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(54) Titre : INHIBITEURS DE LA PROTEASE NS3 DU VHC
 (54) Title: HCV NS3 PROTEASE INHIBITORS

(57) Abrégé/Abstract:

The present invention relates to hepatitis C virus (HCV) NS3 protease inhibitors containing a spirocyclic moiety, uses of such compounds, and synthesis of such compounds.

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(54) Title: HCV NS3 PROTEASE INHIBITORS

(57) Abstract: The present invention relates to hepatitis C virus (HCV) NS3 protease inhibitors containing a spirocyclic moiety, uses of such compounds, and synthesis of such compounds.

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LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 361

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TITLE OF THE APPLICATION

HCV NS3 PROTEASE INHIBITORS

FIELD OF THE INVENTION

5 The present invention relates to hepatitis C virus (HCV) NS3 protease inhibitors containing a spirocyclic moiety, uses of such compounds, and synthesis of such compounds.

BACKGROUND OF THE INVENTION

10 Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals. Current treatments for HCV infection include immunotherapy with recombinant interferon- α alone or in combination with the nucleoside analog ribavirin.

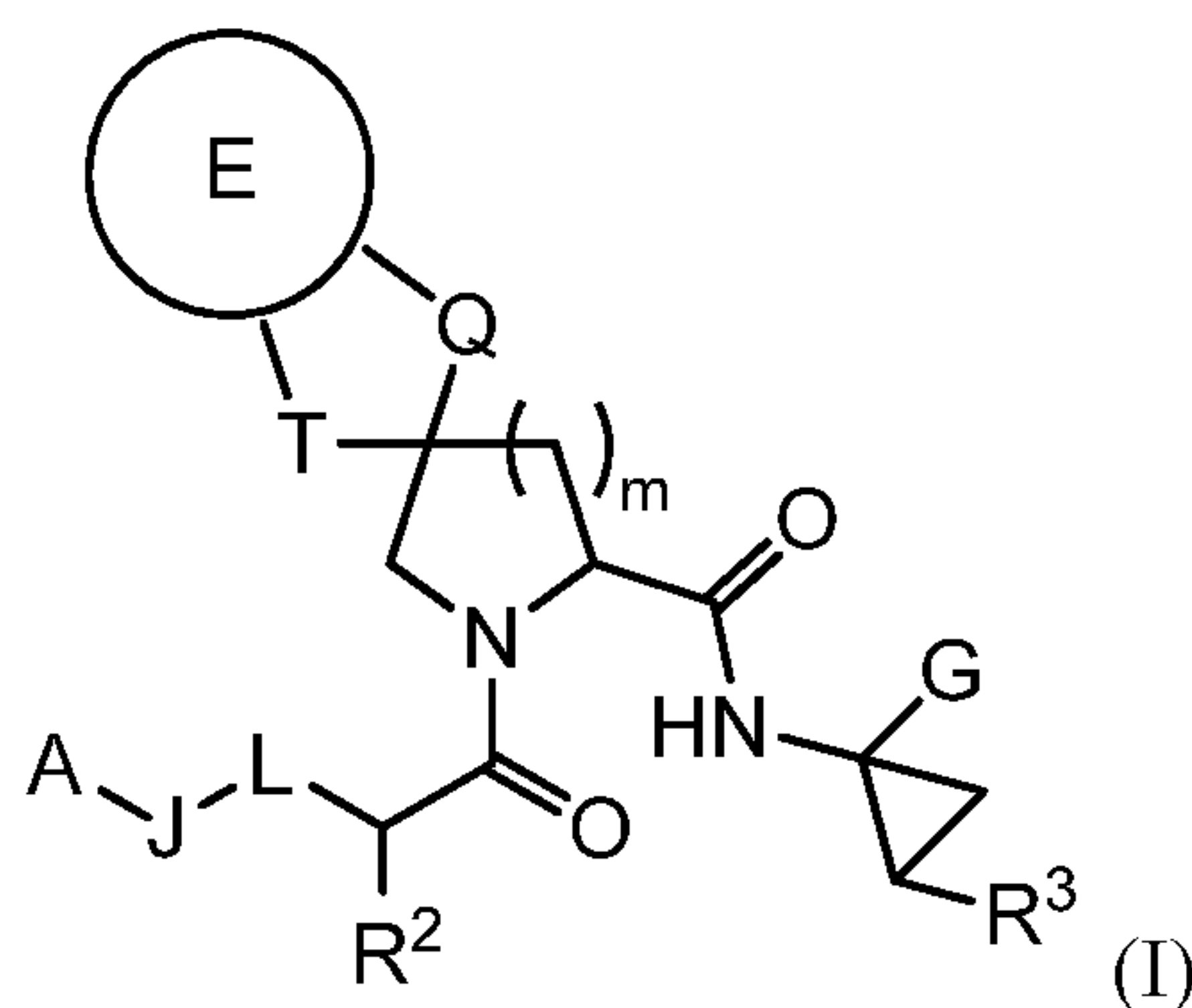
15 Several virally-encoded enzymes are putative targets for therapeutic intervention, including a metalloprotease (NS2-3), a serine protease (NS3, amino acid residues 1-180), a helicase (NS3, full length), an NS3 protease cofactor (NS4A), a membrane protein (NS4B), a zinc metalloprotein (NS5A) and an RNA-dependent RNA polymerase (NS5B).

20 Potential treatments for HCV infection has been discussed in the different references including Balsano, *Mini Rev. Med. Chem.* 8(4):307-318, 2008, Rönn *et al.*, *Current Topics in Medicinal Chemistry* 8:533-562, 2008, Sheldon *et al.*, *Expert Opin. Investig. Drugs* 16(8):1171-1181, 2007, and De Francesco *et al.*, *Antiviral Research* 58:1-16, 2003.

SUMMARY OF THE INVENTION

25 The present invention relates to compounds of formula I or II, and pharmaceutically acceptable salts thereof. These compounds are useful in the inhibition of HCV (hepatitis C virus) NS3 (non-structural 3) protease, the prevention or treatment of one or more of the symptoms of HCV infection, either as compounds or their pharmaceutically acceptable salts, or as pharmaceutical composition ingredients. As pharmaceutical composition ingredients, these compounds may be the primary active therapeutic agent, and, when appropriate, may be combined with other therapeutic agents including but not limited to other HCV antivirals, anti-
30 infectives, immunomodulators, antibiotics or vaccines.

 In a first aspect, the present invention relates to a compound of general Formula I:



or a pharmaceutically acceptable salt thereof, wherein

A is selected from the group consisting of C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₁-C₈ internally substituted alkyl, C₂-C₈ internally substituted alkenyl, C₂-C₈ internally substituted alkynyl, C₃-C₈ cycloalkyl, C₃-C₈ internally substituted cycloalkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, aryl and 7-, 8-, 9- and 10-membered bicyclic groups, wherein

said A Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₈ internally substituted alkyl, C₂-C₈ internally substituted alkenyl, C₂-C₈ internally substituted alkynyl, C₃-C₈ internally substituted cycloalkyl, aryl and bicyclic groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N,

each A aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings and 7-, 8-, 9- and 10-membered bicyclic aromatic rings,

said A is substituted with 0, 1, 2, 3 or 4 substituents R^A;

each R^A is independently selected from the group consisting of H, F, Cl, Br, I, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkyl(NH₂), phenyl, naphthyl, C₃-C₈ cycloalkyl, halo(C₁-C₆ alkoxy), -O(C₁-C₆ alkyl), SH, S(C₁-C₆ alkyl), NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(O)(C₁-C₆ alkyl), -CONH₂, -SO₂NH₂, NO₂, CN, -CF₃, -CHF₂, -CH₂F, -OCHF₂, -OCF₃, -OCH₂F, -SO₂(C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), -SO₂N(C₁-C₆ alkyl)₂, -(C₁-C₆ alkyl)SO₂N(C₁-C₆ alkyl)₂, -NHCOO(C₁-C₆ alkyl), -NHCO(C₁-C₆ alkyl), -NHCONH(C₁-C₆ alkyl), -CO₂(C₁-C₆ alkyl), -C(O)N(C₁-C₆ alkyl)₂, -(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-O-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-S-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-S(O)₂-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), C₁-C₆ internally substituted alkyl, C₁-C₆ internally substituted haloalkyl, C₁-C₆ internally substituted alkyl(NH₂), C₃-C₈ internally

substituted cycloalkyl, halo(C₁-C₆ internally substituted alkoxy), -O(C₁-C₆ internally substituted alkyl), S(C₁-C₆ internally substituted alkyl), -NH(C₁-C₆ internally substituted alkyl), -N(C₁-C₆ internally substituted alkyl)₂, -C(O)(C₁-C₆ internally substituted alkyl), -SO₂(C₁-C₆ internally substituted alkyl), -S(O)(C₁-C₆ internally substituted alkyl), -(C₁-C₆ internally substituted alkyl)S(O)(C₁-C₆ internally substituted alkyl), -S(O)₂(C₁-C₆ internally substituted alkyl), -(C₁-C₆ internally substituted alkyl)S(O)₂(C₁-C₆ internally substituted alkyl), -(C₁-C₆ internally substituted alkyl)N(C₁-C₆ internally substituted alkyl)SO₂(C₁-C₆ internally substituted alkyl), -N(C₁-C₆ internally substituted alkyl)SO₂(C₁-C₆ internally substituted alkyl), -SO₂N(C₁-C₆ internally substituted alkyl)₂, -(C₁-C₆ internally substituted alkyl)SO₂N(C₁-C₆ internally substituted alkyl)₂, -NHCOO(C₁-C₆ internally substituted alkyl), -NHCO(C₁-C₆ internally substituted alkyl), -NHCONH(C₁-C₆ internally substituted alkyl), -CO₂(C₁-C₆ internally substituted alkyl), -C(O)N(C₁-C₆ internally substituted alkyl)₂, -(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₅ internally substituted alkyl)-O-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₅ internally substituted alkyl)-S-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), and -(C₀-C₅ internally substituted alkyl)-S(O)₂-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), wherein

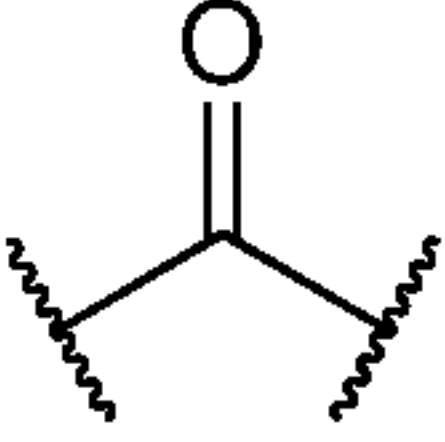
said R^A C₁-C₆ internally substituted alkyl, C₁-C₆ internally substituted haloalkyl, C₁-C₆ internally substituted alkyl(NH₂), C₃-C₈ internally substituted cycloalkyl, halo(C₁-C₆ internally substituted alkoxy), -O(C₁-C₆ internally substituted alkyl), S(C₁-C₆ internally substituted alkyl), -NH(C₁-C₆ internally substituted alkyl), -N(C₁-C₆ internally substituted alkyl)₂, -C(O)(C₁-C₆ internally substituted alkyl), -SO₂(C₁-C₆ internally substituted alkyl), -S(O)(C₁-C₆ internally substituted alkyl), -(C₁-C₆ internally substituted alkyl)S(O)(C₁-C₆ internally substituted alkyl), -S(O)₂(C₁-C₆ internally substituted alkyl), -(C₁-C₆ internally substituted alkyl)S(O)₂(C₁-C₆ internally substituted alkyl), -(C₁-C₆ internally substituted alkyl)N(C₁-C₆ internally substituted alkyl)SO₂(C₁-C₆ internally substituted alkyl), -N(C₁-C₆ internally substituted alkyl)SO₂(C₁-C₆ internally substituted alkyl), -SO₂N(C₁-C₆ internally substituted alkyl)₂, -(C₁-C₆ internally substituted alkyl)SO₂N(C₁-C₆ internally substituted alkyl)₂, -NHCOO(C₁-C₆ internally substituted alkyl), -NHCO(C₁-C₆ internally substituted alkyl), -NHCONH(C₁-C₆ internally substituted alkyl), -CO₂(C₁-C₆ internally substituted alkyl), -C(O)N(C₁-C₆ internally substituted alkyl)₂, -(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₅ internally substituted alkyl)-O-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₅ internally substituted alkyl)-S-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₅ internally substituted alkyl)-S(O)₂-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl),

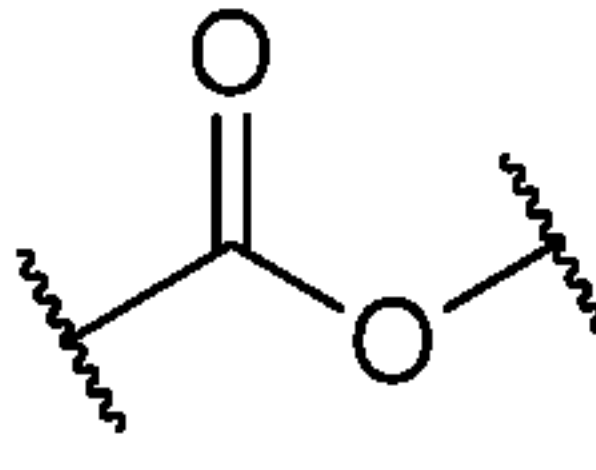
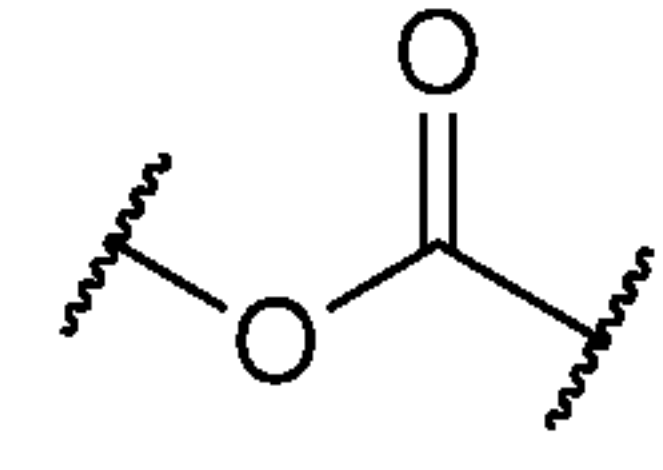
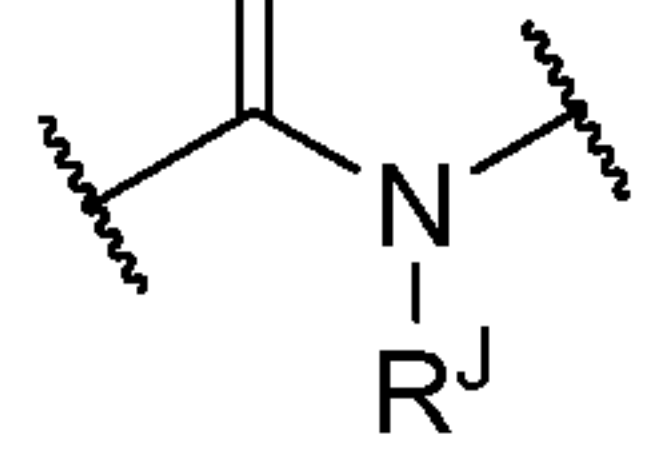
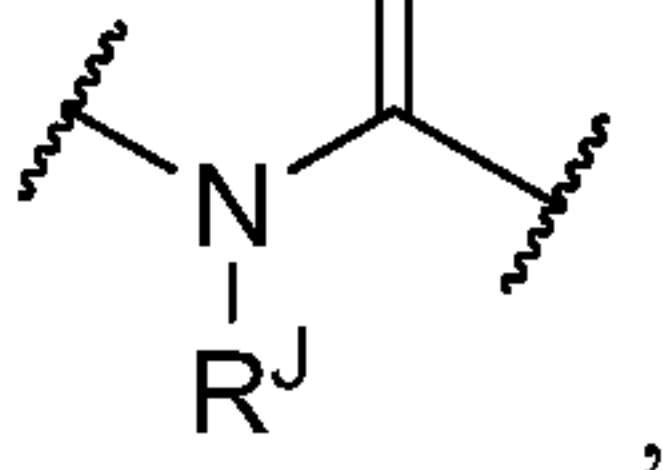
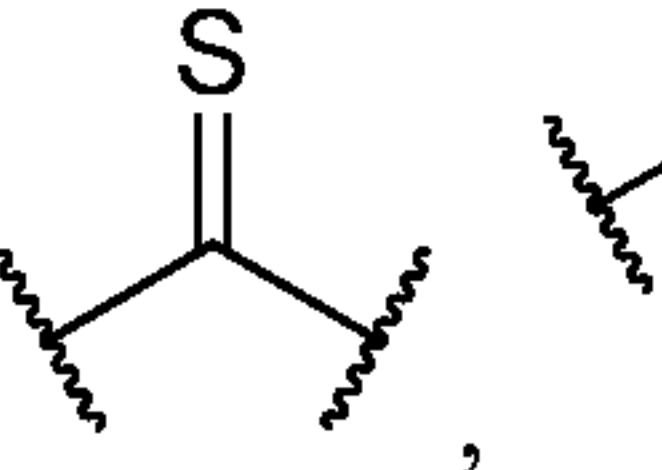
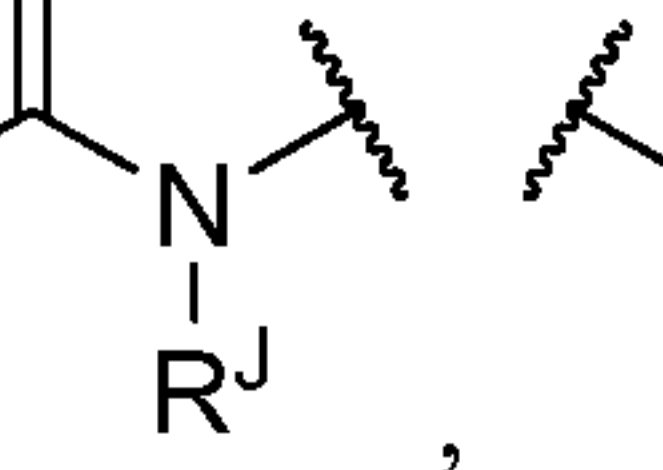
S-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), and -(C₀-C₅ internally substituted alkyl)-S(O)₂-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl) groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N,

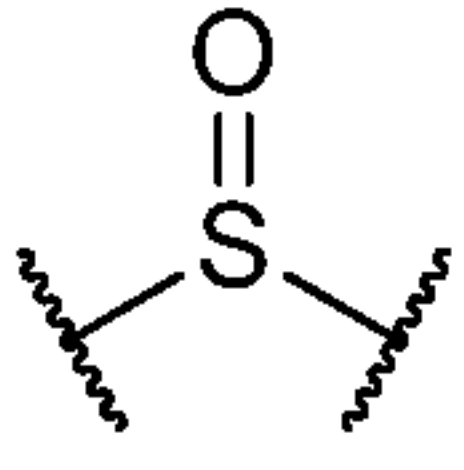
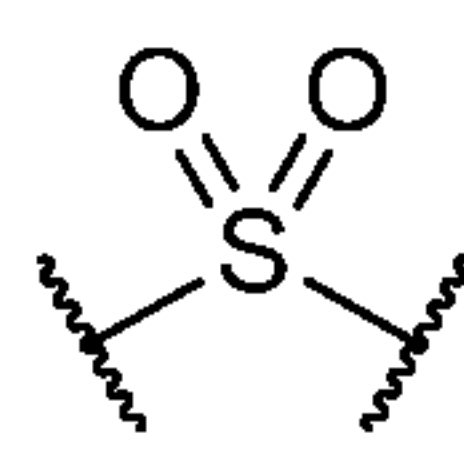
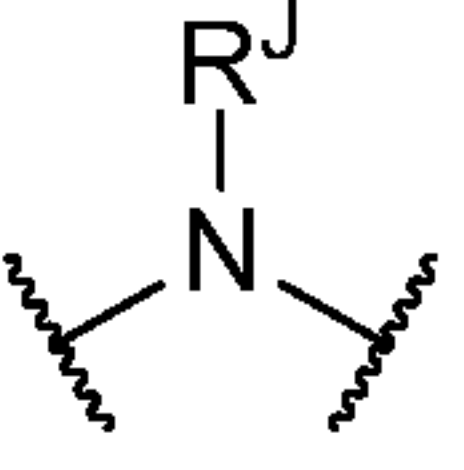
5 two R^A may be taken, together with the atoms to which they are bound, to form a ring having from three to fifteen ring atoms;

R^A and R² may be taken, together with the atoms to which they are bound, to form a ring having from sixteen to twenty-one ring atoms;

10 R^A and R¹ or R⁴ may be taken, together with the atoms to which they are bound, to form a ring having from sixteen to twenty-one ring atoms;

J is selected from the group consisting of a direct bond, C₁-C₈ alkylene, ,

, , , , , ,

, , and , wherein said C₁-C₈ alkylene are substituted by 0, 1, 2 or 3 substituents R^J;

15 R^J is selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆ internally substituted alkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₃-C₆cycloalkyl, C₃-C₆ internally substituted cycloalkyl and aryl, wherein

20 said R^J Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₆ internally substituted alkyl, C₃-C₆ internally substituted cycloalkyl and aryl contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N,

each R^J aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R^J is substituted with 0, 1, 2, 3 or 4 substituents R^A;

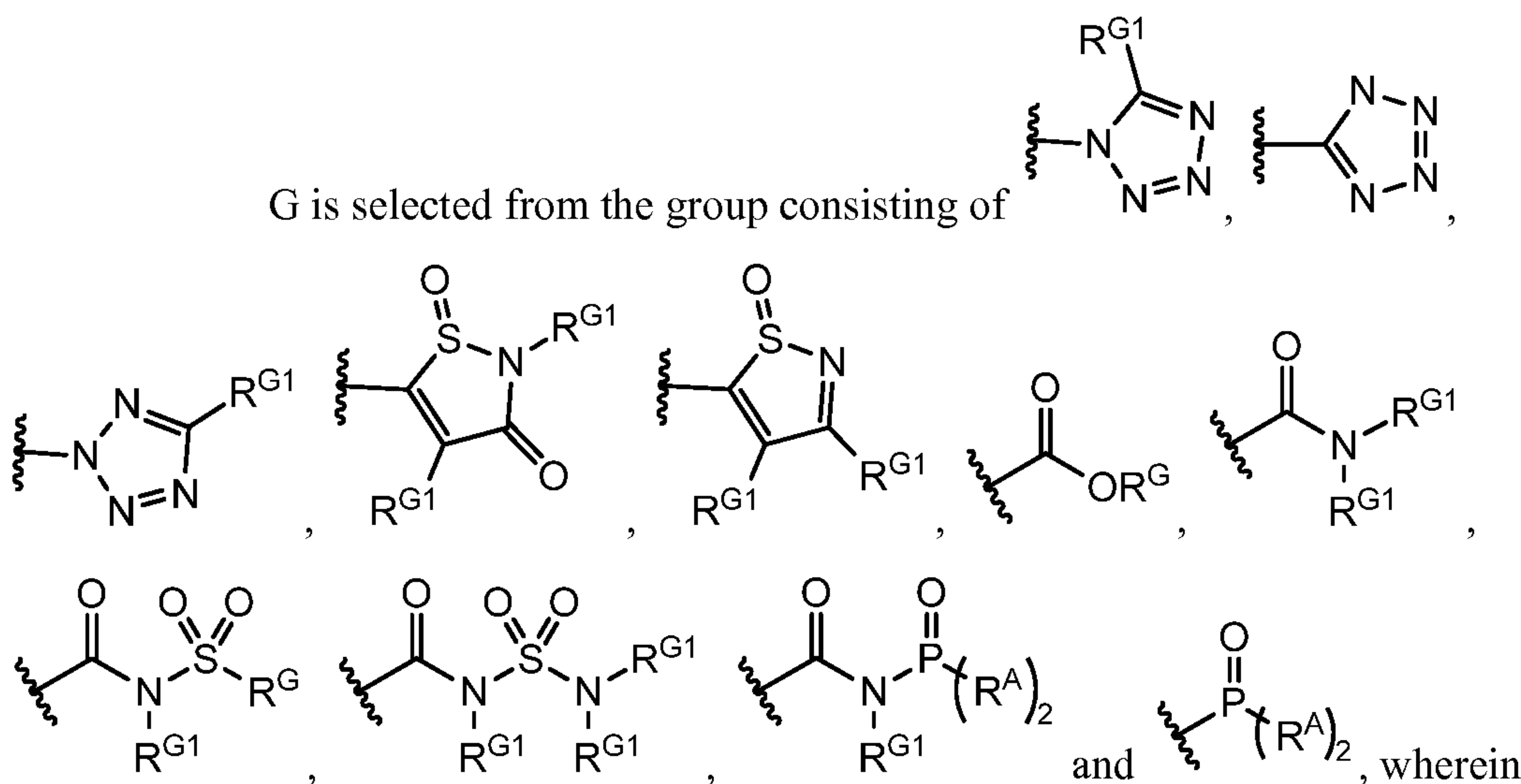
L is selected from the group consisting of (CH₂)₀₋₄, N(R^L), and O;

25 each R^L is independently selected from the group consisting of H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkyl(NH₂), aryl, C₃-C₈ cycloalkyl, halo(C₁-C₆ alkoxy), Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₆ alkyl(aryl) groups, C₁-C₆ internally

substituted alkyl, C₁-C₆ internally substituted haloalkyl, C₁-C₆ internally substituted alkoxy, C₁-C₆ internally substituted alkyl(NH₂), aryl, C₃-C₈ internally substituted cycloalkyl, halo(C₁-C₆ internally substituted alkoxy), and C₁-C₆ internally substituted alkyl(aryl), wherein

5 said R^L Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₆ internally substituted alkyl, C₁-C₆ internally substituted haloalkyl, C₁-C₆ internally substituted alkoxy, C₁-C₆ internally substituted alkyl(NH₂), aryl, C₃-C₈ internally substituted cycloalkyl, halo(C₁-C₆ internally substituted alkoxy), and C₁-C₆ internally substituted alkyl(aryl) groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N,

10 each R^L aryl group is independently selected from the group consisting of 5- and 6-membered aromatic rings,



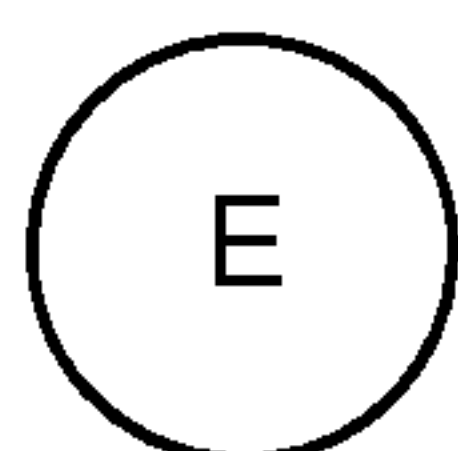
15 R^G is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyl(C₁-C₅)alkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, aryl, aryl(C₁-C₄)alkyl, C₁-C₆ internally substituted alkyl, C₃-C₆ internally substituted cycloalkyl, internally substituted C₃-C₆ cycloalkyl(C₁-C₅)alkyl, and internally substituted aryl(C₁-C₄)alkyl groups, wherein

20 said R^G Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₆ internally substituted alkyl, C₃-C₆ internally substituted cycloalkyl, internally substituted C₃-C₆ cycloalkyl(C₁-C₅)alkyl, aryl, and internally substituted aryl(C₁-C₄)alkyl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N,

each R^G aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

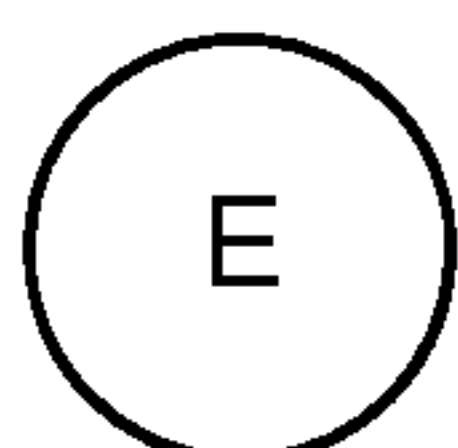
said R^G is substituted with 0, 1 or 2 independently selected R^A substituents,

each R^{G1} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, and benzyl, wherein
 5 each R^{G1} is independently substituted with 0 to 4 substituents R^A,



is selected from the group consisting of:

- 1) aryl rings in which the aryl ring system attaches to Q and T at points that are two independently selected carbon ring atoms,
- 2) C₃-C₈ cycloalkyl rings in which the C₃-C₈ cycloalkyl ring system attaches
 10 to Q and T at points that are two independently selected carbon ring atoms, and
- 3) heterocyclic rings in which the heterocyclic ring system attaches to Q and T at points that are two independently selected ring atoms that are either two carbon ring atoms or one carbon ring atom and one nitrogen ring atom, and the heterocyclic ring system is selected from the group consisting of:
 - 15 a) 5- or 6-membered saturated or unsaturated monocyclic rings with 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O and S,
 - b) 8-, 9- or 10-membered saturated or unsaturated bicyclic rings with
 20 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S, and
 - c) 11- to 15-membered saturated or unsaturated tricyclic rings with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S,



wherein is substituted with 1 substituent R¹ and with 0, 1, 2, 3, 4 or 5
 25 independently selected substituents R⁴;

R¹ is selected from the group consisting of H, halogen atoms, -OH, C₁-C₉ alkyl, C₁-C₉ alkoxy, C₁-C₉ alkyl-C₁-C₉ alkoxy, -CN, -C(O)OH, -C(O)CH₃, -SR^A, -SO₂(C₁-C₉ alkyl), C₃-C₈ cycloalkyl, C₁-C₉ alkyl-C₃-C₈ cycloalkyl, C₃-C₈ cycloalkoxy, C₁-C₉ alkyl-C₃-C₈ cycloalkoxy, C₁-C₉ haloalkyl, -(C₀-C₃ alkyl)-O-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-

S-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S(O)₂-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl),
 -N(R^A)₂, C₁-C₉ alkyl-N(R^A)₂, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₉ internally
 substituted alkyl, C₁-C₉ internally substituted alkoxy, C₁-C₉ internally substituted alkyl-C₁-C₉
 internally substituted alkoxy, -SO₂(C₁-C₉ internally substituted alkyl), C₃-C₈ internally
 5 substituted cycloalkyl, C₁-C₉ internally substituted alkyl-C₃-C₈ internally substituted cycloalkyl,
 C₃-C₈ internally substituted cycloalkoxy, C₁-C₉ alkyl-C₃-C₈ internally substituted cycloalkoxy,
 C₁-C₉ internally substituted haloalkyl, -(C₀-C₃ internally substituted alkyl)-O-(C₀-C₃ internally
 substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₃ internally substituted alkyl)-
 S-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₃ internally
 10 substituted alkyl)-S(O)₂-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted
 cycloalkyl), C₁-C₉ internally substituted alkyl-N(R^A)₂, aryl, naphthyl, -O-aryl and -O-naphthyl
 groups; wherein:

said R¹ C₁-C₉ internally substituted alkyl, C₁-C₉ internally substituted
 alkoxy, C₁-C₉ internally substituted alkyl-C₁-C₉ internally substituted alkoxy, -SO₂(C₁-C₉
 15 internally substituted alkyl), C₃-C₈ internally substituted cycloalkyl, C₁-C₉ internally substituted
 alkyl-C₃-C₈ internally substituted cycloalkyl, C₃-C₈ internally substituted cycloalkoxy, C₁-C₉
 alkyl-C₃-C₈ internally substituted cycloalkoxy, C₁-C₉ internally substituted haloalkyl, -(C₀-C₃
 internally substituted alkyl)-O-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted
 cycloalkyl), -(C₀-C₃ internally substituted alkyl)-S-(C₀-C₃ internally substituted alkyl)-(C₃-C₈
 20 internally substituted cycloalkyl), -(C₀-C₃ internally substituted alkyl)-S(O)₂-(C₀-C₃ internally
 substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), C₁-C₉ internally substituted alkyl-
 N(R^A)₂, aryl, naphthyl, -O-aryl, and -O-naphthyl groups contain 0, 1, 2 or 3 heteroatoms
 independently selected from the group consisting of B, O, S and N,

each R¹ aryl is independently selected from the group consisting of 5- and
 25 6-membered aromatic rings,

said R¹ groups are substituted with 0 to 4 substituents R^A;

R² is selected from the group consisting of C₁-C₉ alkyl, C₂-C₉ alkenyl, C₂-C₉
 alkynyl, C₃-C₈ cycloalkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₉ internally
 substituted alkyl, C₂-C₉ internally substituted alkenyl, C₂-C₉ internally substituted alkynyl, C₃-C₈
 30 internally substituted cycloalkyl and aryl groups, wherein

said R² Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, C₁-C₉ internally substituted
 alkyl, C₂-C₉ internally substituted alkenyl, C₂-C₉ internally substituted alkynyl, C₃-C₈ internally
 substituted cycloalkyl and aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected

from the group consisting of B, O, S and N, and is attached through an atom selected from C and N,

said R² aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

5 said R² is substituted with 0, 1 or 2 independently selected R^A substituents,

R³ is selected from the group consisting of -CH₂CH₃, -CH=CH₂, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, -CH₂CH₂-(bond to R²), -CH=CH-(bond to R²) and a direct bond to R², wherein when R³ is selected from the group consisting of -CH₂CH₂-(bond to R²), -CH=CH-(bond to R²) and a direct bond to R², R² and R³, together with the atoms to which
10 they are bound, form a ring having from fifteen to twenty-one ring atoms and containing 0, 1, 2 or 3 double bonds and 0, 1, 2 or 3 triple bonds;

T is selected from the group consisting of -(CH₂)_q-, -(CH₂)_q-O-(CH₂)_{q1}-, -(CH₂)_q-N(R^A)-(CH₂)_{q1}-, -(CH₂)_q-S-(CH₂)_{q1}-, -(CH₂)_q-C(O)-(CH₂)_{q1}-, -(CH₂)_q-S(O)-(CH₂)_{q1}-, and -(CH₂)_q-S(O)₂-(CH₂)_{q1}-, where q and q1 are each independently selected from the group consisting of 0, 1
15 or 2, and each T is substituted by 0, 1 or 2 groups selected from R^A;

Q is selected from the group consisting of -(CR^A₂)_p-, -(CR^A₂)_p-CR^A=CR^A-(CR^A₂)_{p1}, -(CR^A₂)_p-O-(CR^A₂)_{p1}-, -(CR^A₂)_p-N(R^A)-(CR^A₂)_{p1}-, -(CR^A₂)_p-S-(CR^A₂)_{p1}-, -(CR^A₂)_p-S(O)-(CR^A₂)_{p1}-, and -(CR^A₂)_p-S(O)₂-(CR^A₂)_{p1}-, where p and p1 are independently selected from 0, 1, 2, 3 or 4;

20 each R⁴ is independently selected from the group consisting of H, halogen atoms, -OR^A, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CN, -SR^A, -CO₂R^A, -C(O)N(R^A)₂, -OC(O)N(R^A)₂, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, -(C₀-C₃ alkyl)-O-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S(O)₂-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -SO(R^A), -SO₂(R^A), C₃-C₈ cycloalkyl, C₁-C₆ internally substituted alkyl, C₁-C₆
25 internally substituted alkoxy, -(C₀-C₃ internally substituted alkyl)-O-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₃ internally substituted alkyl)-S-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₃ internally substituted alkyl)-S(O)₂-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), C₃-C₈ internally substituted cycloalkyl and aryl, wherein

30 said R⁴ C₁-C₆ internally substituted alkyl, C₁-C₆ internally substituted alkoxy, -(C₀-C₃ internally substituted alkyl)-O-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₃ internally substituted alkyl)-S-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₃ internally substituted alkyl)-

S(O)₂-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), C₃-C₈ internally substituted cycloalkyl and aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N,

each R⁴ aryl is independently selected from the group consisting of 5- and
5 6-membered aromatic rings,

said R⁴ C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl and aryl groups are substituted with 0 to 4 substituents R^A;

two R⁴ may be taken, together with the atoms to which they are bound, to form a ring; and

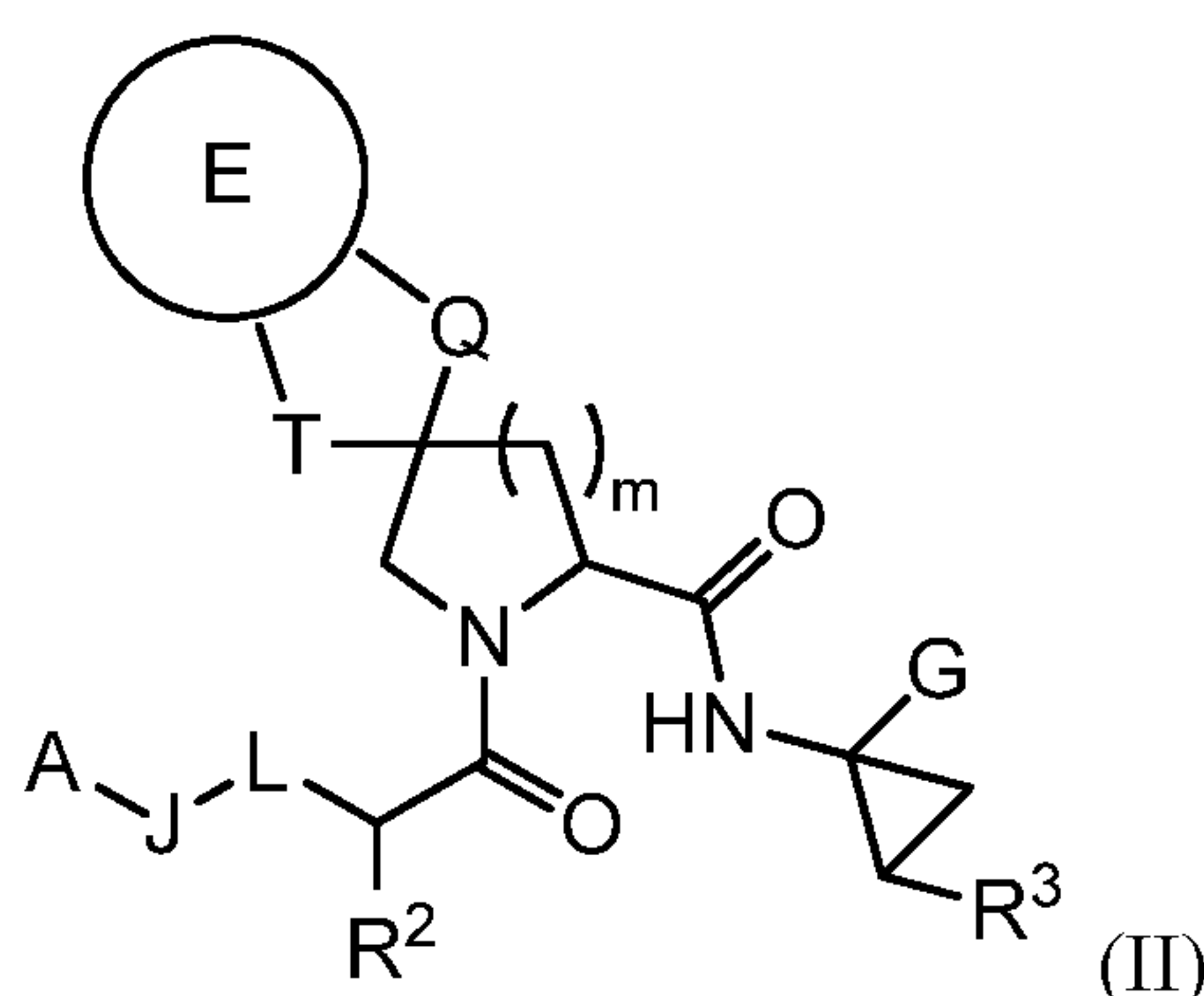
10 m is 0, 1, 2 or 3.

In a subaspect of the first aspect, each R^A can also be independently selected from -NH(C₃-C₈ cycloalkyl), -(C₁-C₅ alkyl)-O-(C₁-C₅ alkyl), and -OC(O)NH-aryl, wherein R^A aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings and 7-, 8-, 9- and 10-membered bicyclic aromatic rings.

15 said R^A internally substituted cycloalkyl can be optionally substituted with 1 or 2 F;

said R¹ -O-(C₀-C₃ internally substituted alkyl)-(C₃-C₉ internally substituted cycloalkyl), -O-(C₀-C₃ internally substituted alkyl)-O-(C₃-C₉ internally substituted cycloalkyl), -O-C₁-C₉ alkyl-aryl, and -O-C₁-C₉ alkyl-O-aryl groups also can contain 0, 1, 2 or 3 heteroatoms
20 independently selected from the group consisting of B, O, S and N; and

said R^L is substituted with 0, 1, 2, 3 or 4 substituents R^A. In a second aspect, the present invention relates to a compound of general Formula II:



or a pharmaceutically acceptable salt thereof, wherein

25 A is a selected from the group consisting of

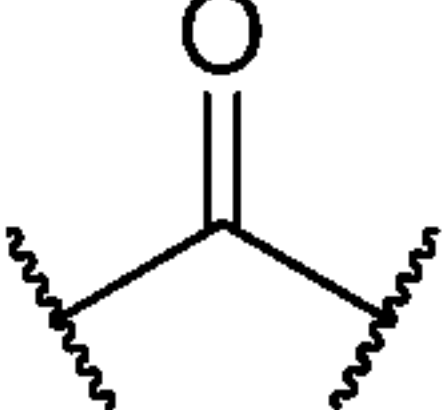
a) C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₈ cycloalkyl, C₆-C₈ bridged cycloalkyl, or C₆-C₈ bridged cycloalkenyl,

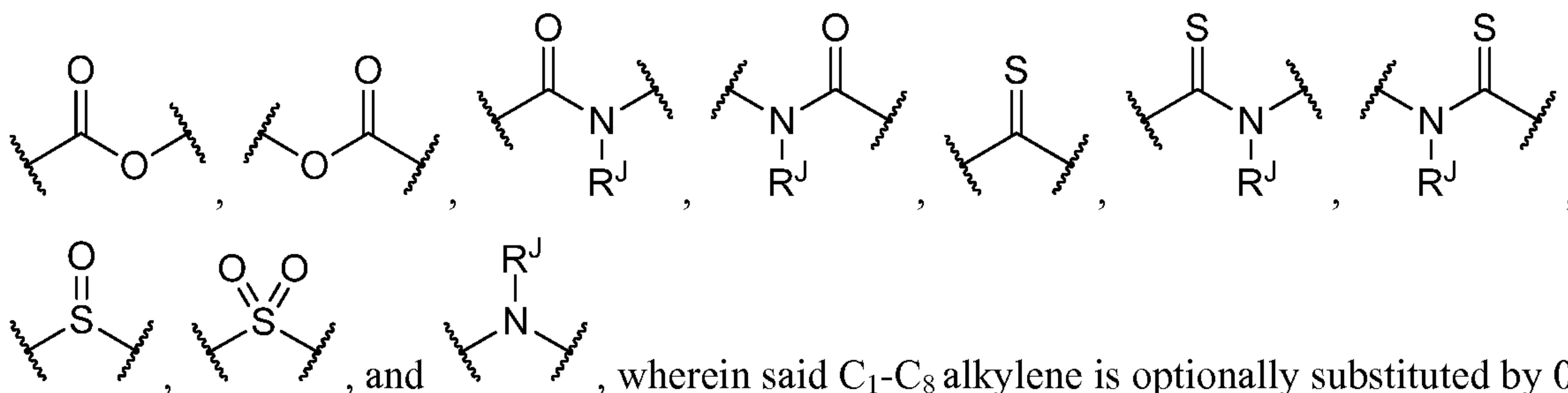
b) substituted C₁-C₈ alkyl, substituted C₂-C₈ alkenyl, substituted C₂-C₈ alkynyl, substituted C₃-C₈ cycloalkyl, substituted C₆-C₈ bridged cycloalkyl, or substituted C₆-C₈ bridged cycloalkenyl, each of which is substituted with 0, 1, 2, 3 or 4 independently selected R^A, and 0 or 1 R^B, provided that at least one R^A substituent, other than H, or an R^B substituent is present;

c) C₁-C₈ haloalkyl, C₃-C₈ halocycloalkyl, or C₁-C₈ haloalkyl substituted with R^B,

d) Aryl, and

e) Het;

J is selected from the group consisting of a direct bond, C₁-C₈ alkylene, ,

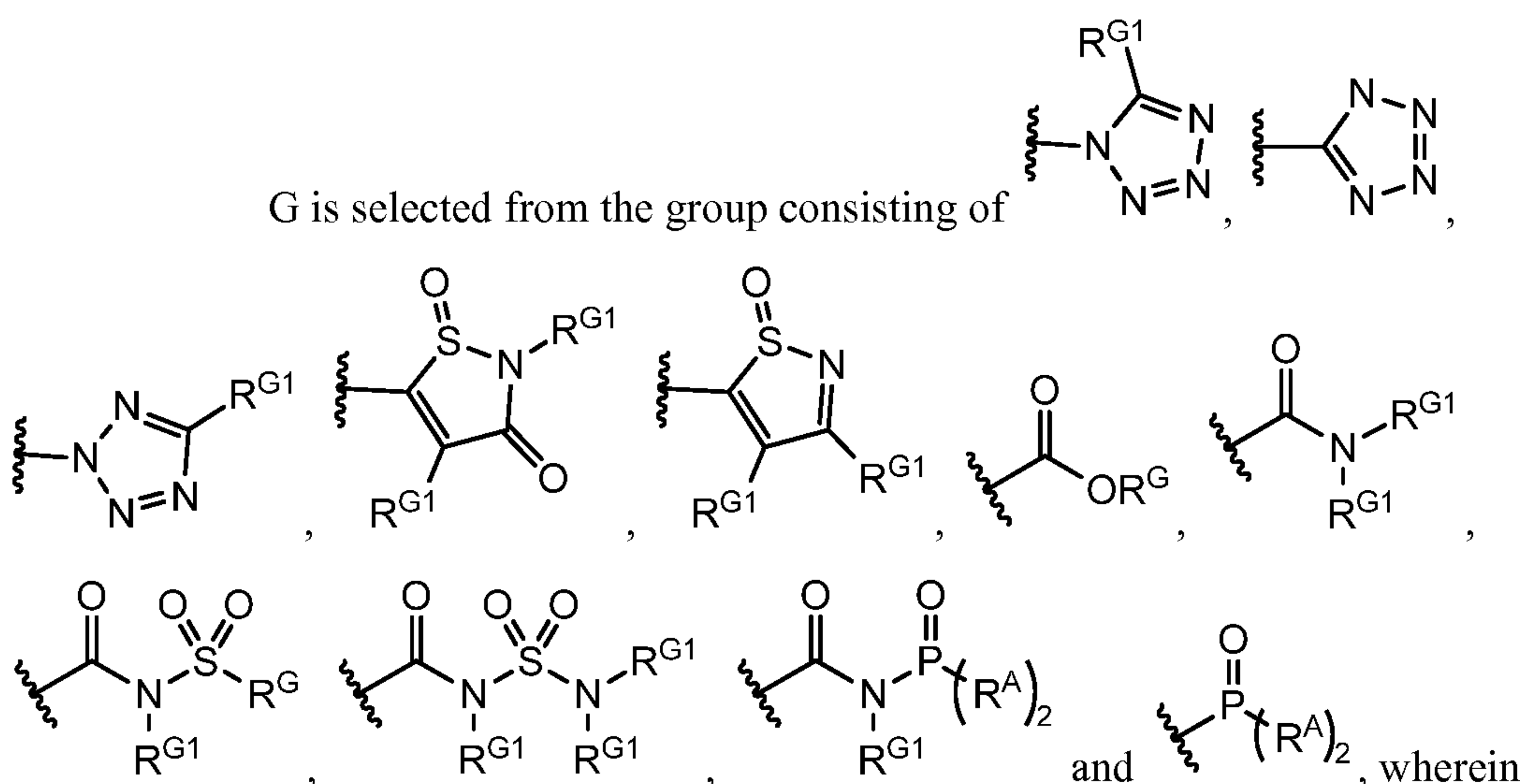


wherein said C₁-C₈ alkylene is optionally substituted by 0, 1, 2 or 3 substituents independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkyl-R^B, C₃-C₆ cycloalkyl, C₁-C₆ alkyl-C₃-C₆ cycloalkyl, Aryl, and Het;

each R^J is selected from the group consisting of hydrogen, C₁-C₆ alkyl, C₁-C₆ alkyl-R^B, C₃-C₆ cycloalkyl, C₁-C₆ alkyl-C₃-C₆ cycloalkyl, Aryl, and Het;

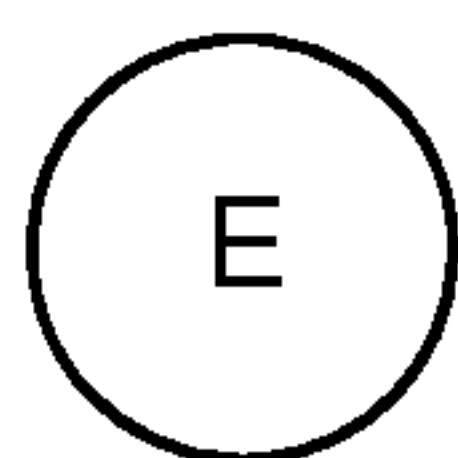
L is selected from the group consisting of (CH₂)₀₋₄, N(R^L), and O;

R^L is selected from the group consisting of H and C₁-C₃ alkyl;



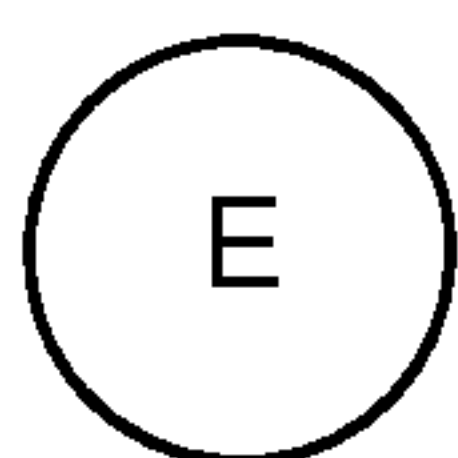
R^G is selected from the group consisting of H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkyl- C_1 - C_5 alkyl, C_1 - C_6 alkyl substituted with R^A , C_3 - C_6 cycloalkyl substituted with R^A , or C_3 - C_6 cycloalkyl- C_1 - C_5 alkyl substituted with R^A ;

each R^{G1} is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, and benzyl;



is selected from the group consisting of:

- 1) an aryl ring attached to Q and T at two independently selected carbon ring atoms, wherein the aryl ring is phenyl or naphthyl,
- 2) a C_3 - C_8 cycloalkyl attached to Q and T at two independently selected carbon ring atoms, and
- 3) a heterocyclic ring attached to Q and T at two independently selected ring atoms that are either two carbon ring atoms or one carbon ring atom and one nitrogen ring atom, wherein the heterocyclic ring is selected from the group consisting of:
 - a) a 5- or 6-membered saturated or unsaturated monocyclic ring with 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O and S,
 - b) a 8-, 9- or 10-membered saturated or unsaturated bicyclic ring with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S,
 - and
 - c) a 11- to 15-membered saturated or unsaturated tricyclic ring with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S,



wherein $\textcircled{\text{E}}$ further contains 1 R^1 substituent and 0, 1, 2, 3, 4 or 5 independently selected R^4 substituents;

each R^1 is selected from the group consisting of hydrogen, halogen, OH, $\text{C}_1\text{-C}_9$ alkyl, $\text{C}_1\text{-C}_6$ alkyl- R^{B} , $\text{C}_1\text{-C}_9$ hydroxylalkyl, $\text{C}_1\text{-C}_9$ alkoxy,

5 $\text{C}_1\text{-C}_9$ alkyl- $\text{C}_1\text{-C}_9$ alkoxy, CN, $\text{C}(\text{O})\text{OH}$, $\text{C}(\text{O})\text{CH}_3$, SR^5 , $\text{SO}_2(\text{C}_1\text{-C}_9 \text{ alkyl})$, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_3\text{-C}_8$ cycloalkyl- $\text{C}_1\text{-C}_9$ alkyl, $\text{C}_1\text{-C}_9$ alkyl- $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_9$ alkyl-O- $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_4$ haloalkyl, $\text{C}_1\text{-C}_5$ haloalkoxy, $-(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-O-}(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-}(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-S-}(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-}(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-S}(\text{O})_2\text{-}(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-}(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $\text{N}(\text{R}^5)_2$, $\text{C}_1\text{-C}_9$ alkyl- $\text{N}(\text{R}^5)_2$, Aryl, and Het;

10 R^2 is selected from the group consisting of $\text{C}_1\text{-C}_9$ alkyl, $\text{C}_2\text{-C}_9$ alkenyl, $\text{C}_2\text{-C}_9$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, Het, and Aryl;

R^3 is selected from the group consisting of $\text{C}_1\text{-C}_9$ alkyl, $\text{C}_2\text{-C}_9$ alkenyl, and $\text{C}_2\text{-C}_9$ alkynyl;

15 T is selected from the group consisting of O, $(\text{CH}_2)_{q_2}$, NH, SO_2 and S, wherein q_2 is 0, 1, 2, 3 or 4;

Q is selected from the group consisting of $-(\text{CR}^{\text{A}}_2)_p-$, $-(\text{CR}^{\text{A}}_2)_p\text{-CR}^{\text{A}}=\text{CR}^{\text{A}}-$, $(\text{CR}^{\text{A}}_2)_{p1}$, $-(\text{CR}^{\text{A}}_2)_p\text{-O-}(\text{CR}^{\text{A}}_2)_{p1}$, $-(\text{CR}^{\text{A}}_2)_p\text{-N}(\text{R}^{\text{A}})\text{-}(\text{CR}^{\text{A}}_2)_{p1}$, $-(\text{CR}^{\text{A}}_2)_p\text{-S-}(\text{CR}^{\text{A}}_2)_{p1}$, $-(\text{CR}^{\text{A}}_2)_p\text{-S}(\text{O})\text{-}(\text{CR}^{\text{A}}_2)_{p1}$, and $-(\text{CR}^{\text{A}}_2)_p\text{-S}(\text{O})_2\text{-}(\text{CR}^{\text{A}}_2)_{p1}$, where p and p1 are independently selected from 0, 1, 2, 3 or 4;

20 provided that $p + p_1 + q_2$ equals 0, 1, 2, 3, or 4;

each R^4 is independently selected from the group consisting of:

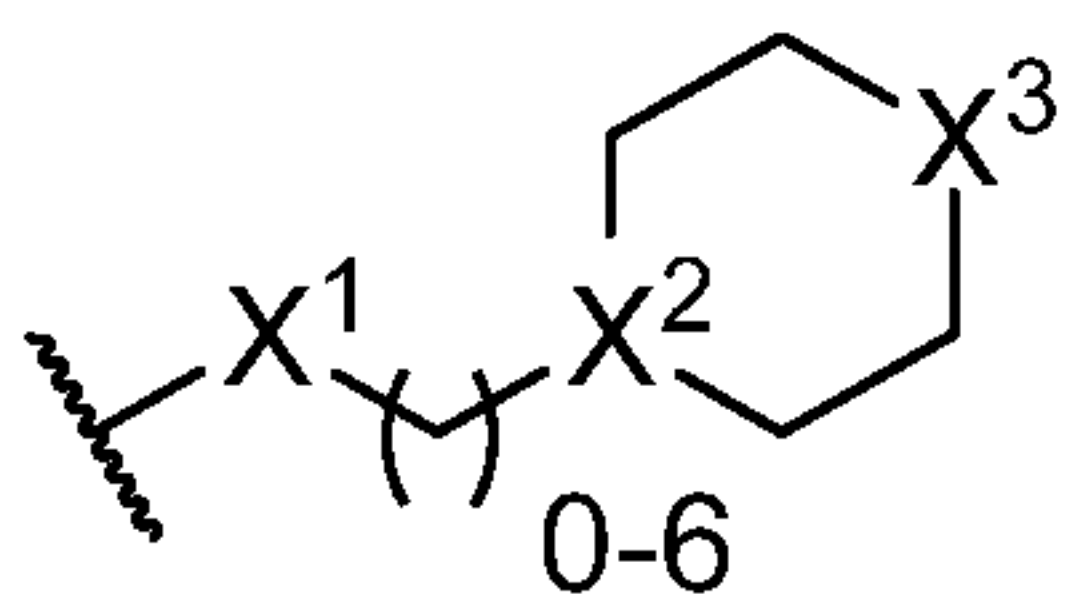
hydrogen, halogen, OH, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkoxy,

$\text{C}_1\text{-C}_6$ alkyl- R^{B} , $\text{C}_1\text{-C}_6$ haloalkyl- R^{B} , $\text{C}_1\text{-C}_6$ alkoxy- R^{B} , $\text{C}_1\text{-C}_6$ haloalkoxy- R^{B} , $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_3\text{-C}_8$ cycloalkyl- $\text{C}_1\text{-C}_9$ alkyl, $\text{C}_1\text{-C}_6$ hydroxyalkyl, O- $\text{C}_1\text{-C}_6$ hydroxyalkyl,

25 O- $\text{C}_1\text{-C}_6$ alkyl- R^{B} , CN, SR^5 , CO_2R^5 , $\text{C}(\text{O})\text{N}(\text{R}^5)_2$, $\text{OC}(\text{O})\text{N}(\text{R}^5)_2$, O-($\text{C}_1\text{-C}_6$)alkyl- OR^5 ,

O-($\text{C}_1\text{-C}_5$ alkyl)-O-($\text{C}_1\text{-C}_3$ alkyl), O-($\text{C}_1\text{-C}_5$ alkyl)-O-($\text{C}_1\text{-C}_3$ alkyl)- R^{B} , $-(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-O-}(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-}(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-S-}(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-}(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$,

-(C₀-C₃ alkyl)-S(O)₂-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), SO(R⁵), SO₂(R⁵), Het, Aryl, and



, wherein X¹ is either CH₂, NH, O, or S; X² is either CH or N; and X³ is either NH, N-R⁵, CH₂, CH-R⁵, O, or S;

provided that two R⁴ groups can join together to form methylene dioxy;

5 each R⁵ is independently selected from the group consisting of:

hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkyl(NH₂), C₆-C₈ bridged cycloalkyl, C₃-C₈ cycloalkyl, and C₃-C₈ halocycloalkyl;

each Aryl is independently phenyl or naphthyl optionally substituted with 1, 2, 3 or 4 R^C substituents;

10 each Het is independently either (a) 4-, 5- or 6-membered saturated or unsaturated monocyclic ring with 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O and S; (b) 8-, 9- or 10-membered saturated or unsaturated bicyclic ring with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S, or (c) 11- to 15-membered saturated or unsaturated tricyclic ring with 1, 2, 3, 4, or 5
15 heteroatom ring atoms independently selected from the group consisting of N, O and S; provided that said Het is optionally substituted with 1, 2, 3 or 4 R^C substituents;

each R^A is independently selected from the group consisting of:

H, F, Cl, Br, I, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkyl(NH₂), C₆-C₈ bridged cycloalkyl, C₃-C₈ cycloalkyl, C₁-C₆ haloalkoxy, C₃-C₈ halocycloalkyl,
20 SH, S(C₁-C₆ alkyl), NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, C(O)(C₁-C₆ alkyl), C(O)(C₃-C₈ cycloalkyl), CONH₂, SO₂NH₂, NO₂, CN, CF₃, CHF₂, CH₂F, OCHF₂, OCF₃, OCH₂F, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)(C₁-C₆ alkyl), SO₂(C₃-C₆ cycloalkyl), -(C₁-C₆ alkyl)S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), SO₂N(C₁-C₆ alkyl)₂, -(C₁-C₆ alkyl)SO₂N(C₁-C₆ alkyl)₂, NHCOO(C₁-C₆ alkyl),
25 NHCO(C₁-C₆ alkyl), NHCONH(C₁-C₆ alkyl), CO₂(C₁-C₆ alkyl), C(O)N(C₁-C₆ alkyl)₂, -(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-O-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-S-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl),
-(C₀-C₅ alkyl)-S(O)₂-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), Aryl, and Het; provided that two R^A groups present on adjacent carbon atoms can together with the adjacent carbon atoms form a C₃-
30 C₆ cycloalkyl;

each R^B is independently either Het or Aryl;

each R^C is independently either hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl or C_1 - C_6 haloalkyl;

alternatively, with respect to A and R^1 , A is either C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, or C_3 - C_8 cycloalkyl, each of which is substituted with R^{A1} , and R^{A1} in combination with R^1 forms a C_3 - C_8 alkylene, a C_3 - C_8 alkenylene, or a C_3 - C_8 alkynylene, each of which may be substituted with 1 or 2 independently selected R^C ;

alternatively, with respect to A and R^2 , A is either C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, or C_3 - C_8 cycloalkyl, each of which is substituted with R^{A1} , and R^{A1} in combination with R^2 form a C_3 - C_8 alkylene, a C_3 - C_8 alkenylene, or a C_3 - C_8 alkynylene, each of which may be substituted 1 or 2 independently selected R^C ;

alternatively, with respect to R^2 and R^3 , R^2 and R^3 form a C_3 - C_8 alkylene, C_3 - C_8 alkenylene, or C_3 - C_8 alkynylene, each of which may be substituted with 1 or 2 independently selected R^C ; and

m is 0, 1, 2 or 3.

The present invention also includes pharmaceutical compositions containing a compound of the present invention and methods of preparing such pharmaceutical compositions. The present invention further includes methods of treating or preventing one or more symptoms of HCV infection.

Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

For the first aspect, wherein the compound is compound of General Formula I:

In a first embodiment of the invention, the compound is a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein

A is selected from the group consisting of C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_8 cycloalkyl, $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, $Si(CH_3)_3$, aryl and 7-, 8-, 9- and 10-membered bicyclic groups, wherein

said A $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, $Si(CH_3)_3$, aryl and bicyclic groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N,

each A aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings and 7-, 8-, 9- and 10-membered bicyclic aromatic rings,

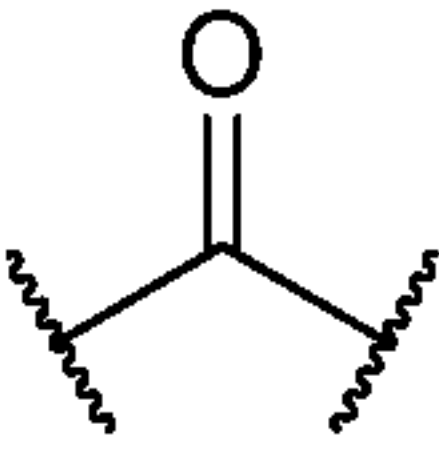
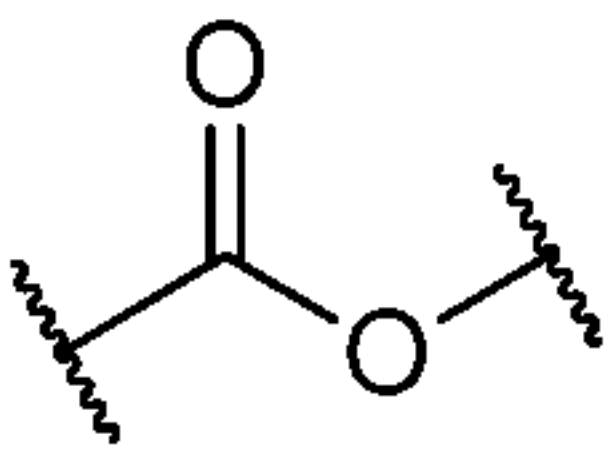
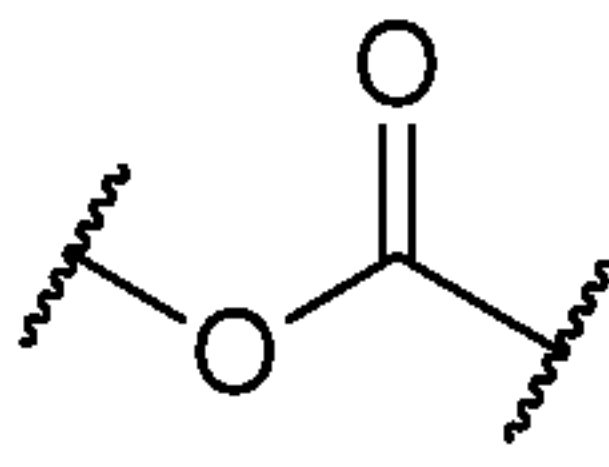
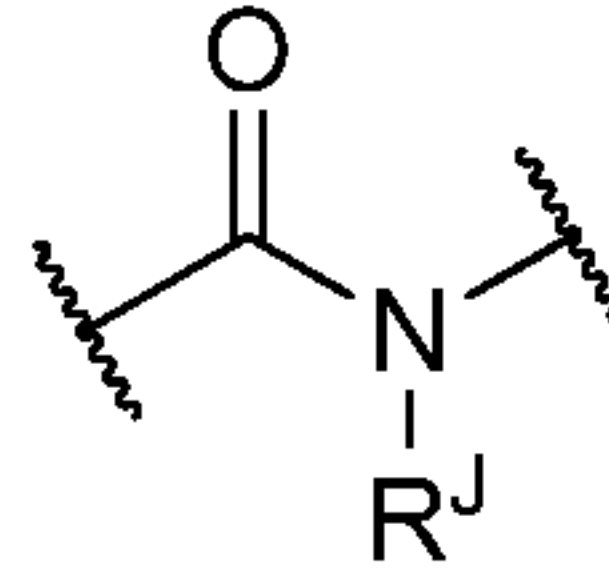
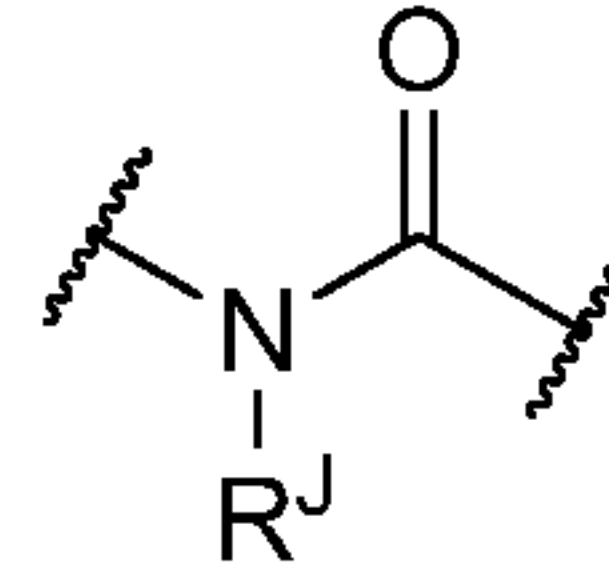
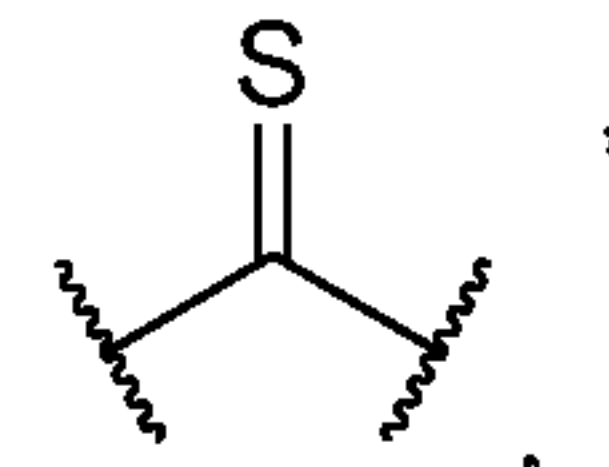
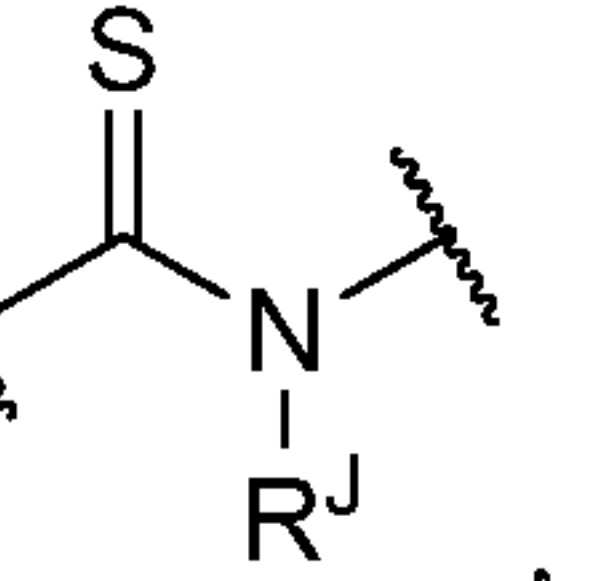
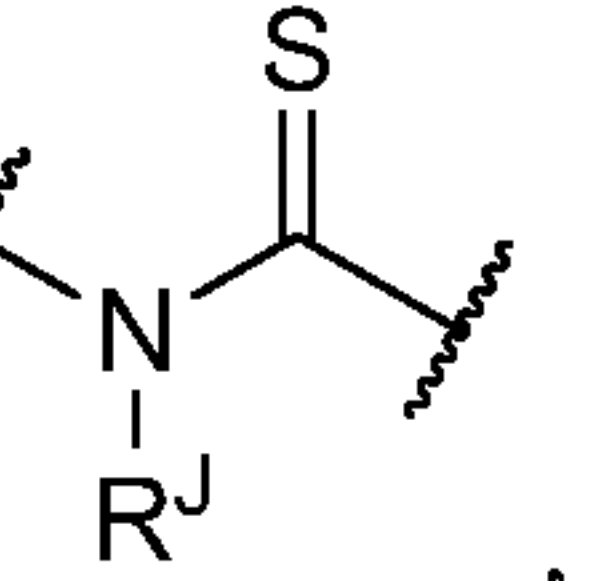
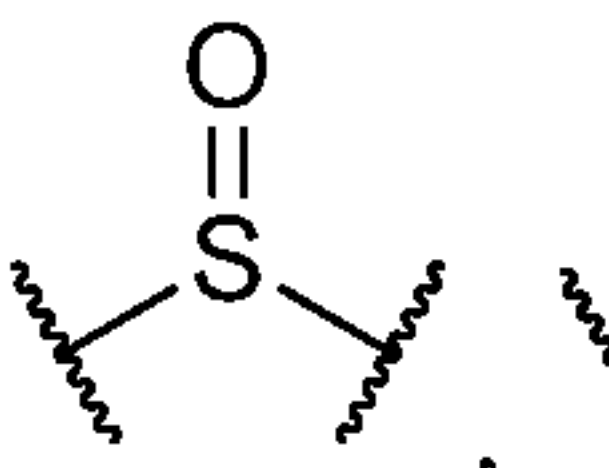
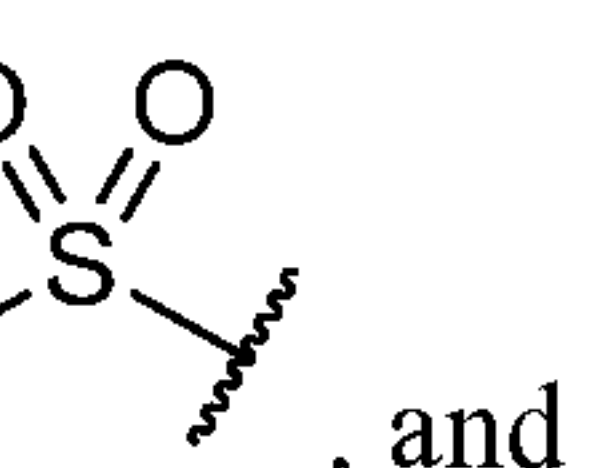
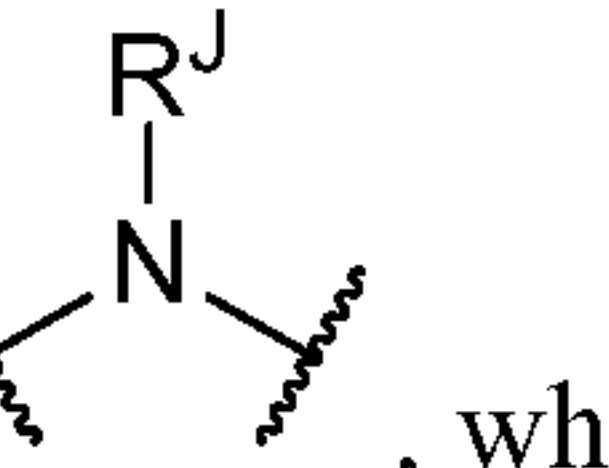
said A is substituted with 0, 1, 2, 3 or 4 substituents R^A;

each R^A is independently selected from the group consisting of H, F, Cl, Br, I, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkyl(NH₂), phenyl, naphthyl, C₃-C₈ cycloalkyl, halo(C₁-C₆ alkoxy), -O(C₁-C₆ alkyl), SH, S(C₁-C₆ alkyl), NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(O)(C₁-C₆ alkyl), -CONH₂, -SO₂NH₂, NO₂, CN, -CF₃, -CHF₂, -CH₂F, -OCHF₂, -OCF₃, -OCH₂F, -SO₂(C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), -SO₂N(C₁-C₆ alkyl)₂, -(C₁-C₆ alkyl)SO₂N(C₁-C₆ alkyl)₂, -NHCOO(C₁-C₆ alkyl), -NHCO(C₁-C₆ alkyl), -NHCONH(C₁-C₆ alkyl), -CO₂(C₁-C₆ alkyl), -C(O)N(C₁-C₆ alkyl)₂, -(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-O-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-S-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), and -(C₀-C₅ alkyl)-S(O)₂-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), wherein

two R^A may be taken, together with the atoms to which they are bound, to form a ring having from three to fifteen ring atoms;

R^A and R² may be taken, together with the atoms to which they are bound, to form a ring having from sixteen to twenty-one ring atoms;

R^A and R¹ or R⁴ may be taken, together with the atoms to which they are bound, to form a ring having from sixteen to twenty-one ring atoms;

J is selected from the group consisting of a direct bond, C₁-C₈ alkylene, , , , , , , , , , , and , wherein said C₁-C₈ alkylene are substituted by 0, 1, 2 or 3 substituents R^J;

R^J is selected from the group consisting of H, C₁-C₆alkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₃-C₆cycloalkyl, and aryl, wherein

said R^J $\text{Si}(R^A)_3$, $\text{Si}(R^A)_2(\text{CH}_3)$, $\text{Si}(R^A)(\text{CH}_3)_2$, $\text{Si}(\text{CH}_3)_3$, and aryl contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N,

each R^J aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

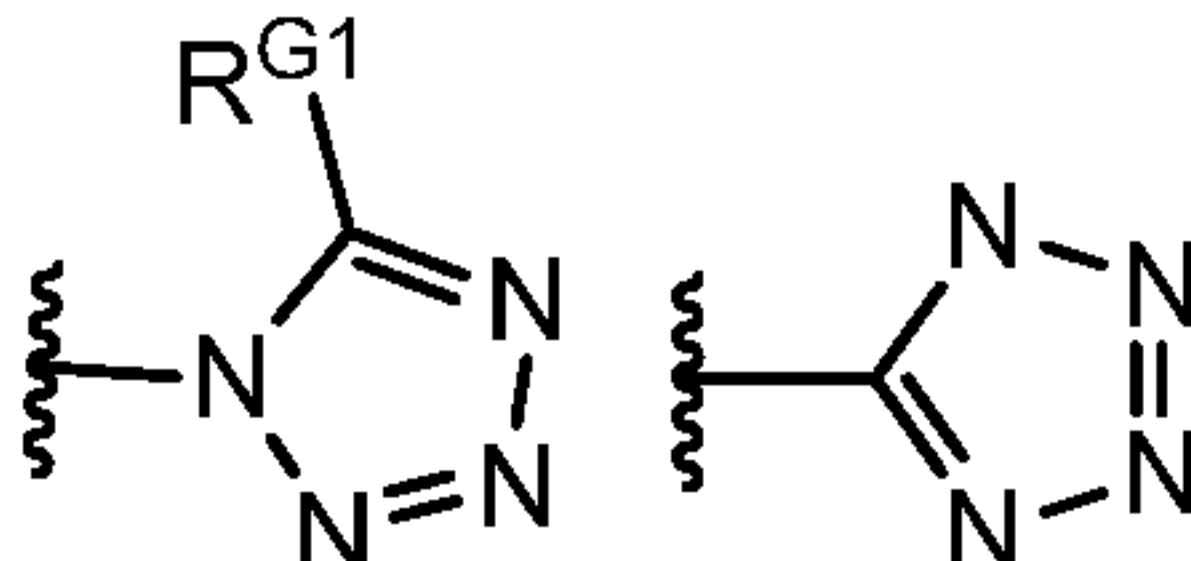
5 said R^J is substituted with 0, 1, 2, 3 or 4 substituents R^A ;

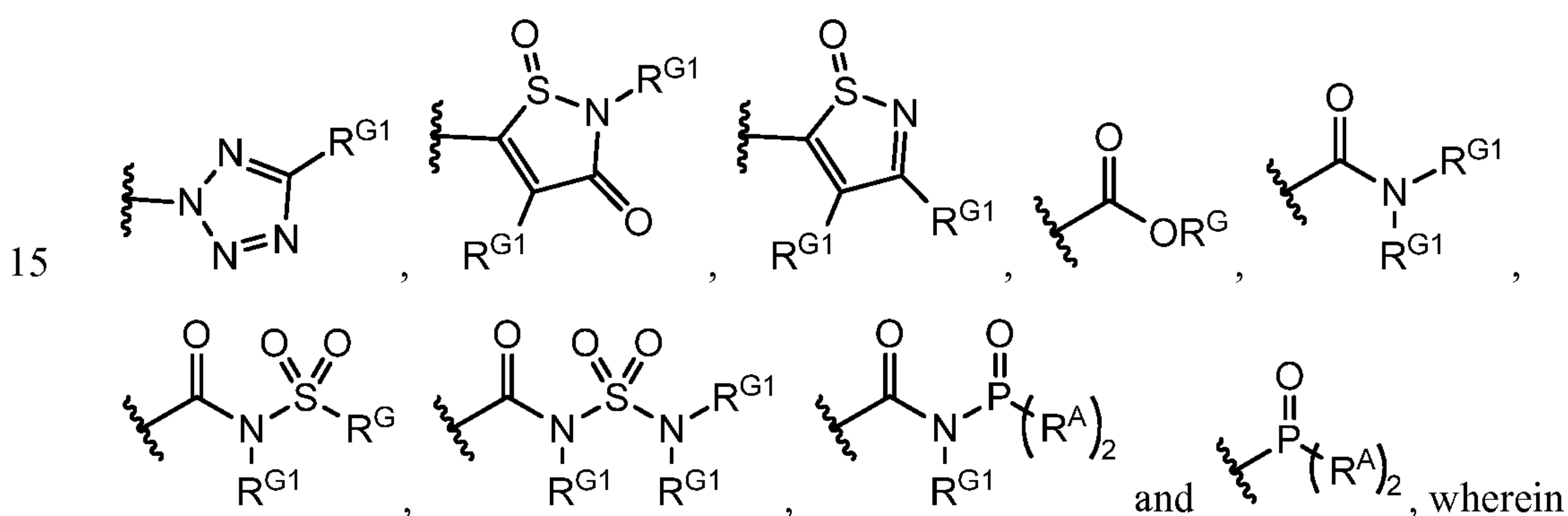
L is selected from the group consisting of $(\text{CH}_2)_{0-4}$, $\text{N}(R^L)$, and O;

each R^L is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl(NH_2), aryl, C_3 - C_8 cycloalkyl, halo(C_1 - C_6 alkoxy), $\text{Si}(R^A)_3$, $\text{Si}(R^A)_2(\text{CH}_3)$, $\text{Si}(R^A)(\text{CH}_3)_2$, $\text{Si}(\text{CH}_3)_3$, and C_1 - C_6 alkyl(aryl) groups, wherein

10 said R^L $\text{Si}(R^A)_3$, $\text{Si}(R^A)_2(\text{CH}_3)$, $\text{Si}(R^A)(\text{CH}_3)_2$, and $\text{Si}(\text{CH}_3)_3$ groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N,

each R^L aryl group is independently selected from the group consisting of 5- and 6-membered aromatic rings,

G is selected from the group consisting of ,



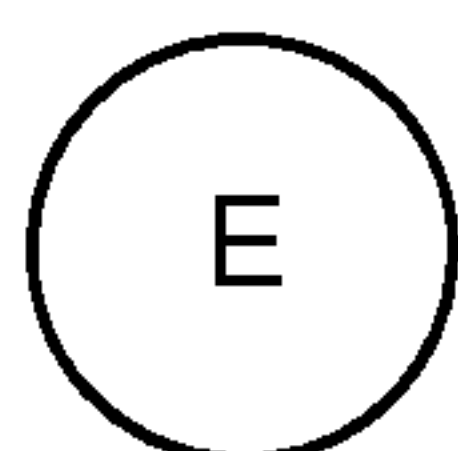
R^G is selected from the group consisting of H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkyl(C_1 - C_5)alkyl, $\text{Si}(R^A)_3$, $\text{Si}(R^A)_2(\text{CH}_3)$, $\text{Si}(R^A)(\text{CH}_3)_2$, $\text{Si}(\text{CH}_3)_3$, aryl, and aryl(C_1 - C_4)alkyl groups, wherein

20 said R^G $\text{Si}(R^A)_3$, $\text{Si}(R^A)_2(\text{CH}_3)$, $\text{Si}(R^A)(\text{CH}_3)_2$, $\text{Si}(\text{CH}_3)_3$, and aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N,

each R^G aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

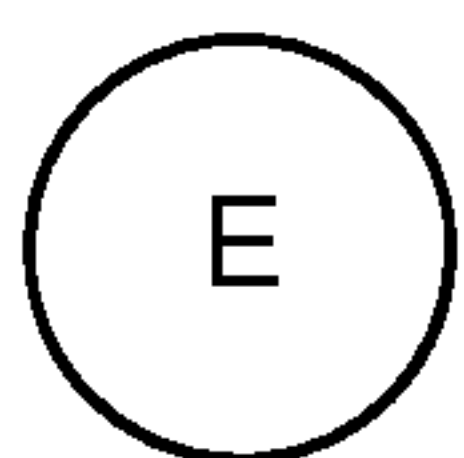
said R^G is substituted with 0, 1 or 2 independently selected R^A substituents,

each R^{G1} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, $Si(CH_3)_3$, and benzyl, wherein
 5 each R^{G1} is independently substituted with 0 to 4 substituents R^A ,



is selected from the group consisting of:

- 1) aryl rings in which the aryl ring system attaches to Q and T at points that are two independently selected carbon ring atoms,
- 2) C_3-C_8 cycloalkyl rings in which the C_3-C_8 cycloalkyl ring system attaches
 10 to Q and T at points that are two independently selected carbon ring atoms, and
- 3) heterocyclic rings in which the heterocyclic ring system attaches to Q and T at points that are two independently selected ring atoms that are either two carbon ring atoms or one carbon ring atom and one nitrogen ring atom, and the heterocyclic ring system is selected from the group consisting of:
 - 15 a) 5- or 6-membered saturated or unsaturated monocyclic rings with 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O and S,
 - b) 8-, 9- or 10-membered saturated or unsaturated bicyclic rings with
 20 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S, and
 - c) 11- to 15-membered saturated or unsaturated tricyclic rings with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S,



wherein E is substituted with 1 substituent R^1 and with 0, 1, 2, 3, 4 or 5
 25 independently selected substituents R^4 ;

R^1 is selected from the group consisting of H, halogen atoms, -OH, C_1-C_9 alkyl, C_1-C_9 alkoxy, C_1-C_9 alkyl- C_1-C_9 alkoxy, -CN, -C(O)OH, -C(O)CH₃, -SR^A, -SO₂(C_1-C_9 alkyl), C_3-C_8 cycloalkyl, C_1-C_9 alkyl- C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_9 alkyl- C_3-C_8 cycloalkoxy, C_1-C_9 haloalkyl, -(C_0-C_3 alkyl)-O-(C_0-C_3 alkyl)-(C_3-C_8 cycloalkyl), -(C_0-C_3 alkyl)-

S-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S(O)₂-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -N(R^A)₂, C₁-C₉ alkyl-N(R^A)₂, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, aryl, naphthyl, -O-aryl and -O-naphthyl groups; wherein:

said R¹ aryl, naphthyl, -O-aryl and -O-naphthyl groups contain 0, 1, 2 or 3
5 heteroatoms independently selected from the group consisting of O, S and N,

each R¹ aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R¹ groups are substituted with 0 to 4 substituents R^A;

R² is selected from the group consisting of C₁-C₉ alkyl, C₂-C₉ alkenyl, C₂-C₉
10 alkynyl, C₃-C₈ cycloalkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, and aryl groups,
wherein

said R² Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, and aryl groups contain 0, 1,
2 or 3 heteroatoms independently selected from the group consisting of O, S and N, and is
attached through an atom selected from C and N,

said R² aryl is independently selected from the group consisting of 5- and
15 6-membered aromatic rings,

said R² is substituted with 0, 1 or 2 independently selected R^A substituents,

R³ is selected from the group consisting of -CH₂CH₃, -CH=CH₂, Si(R^A)₃,
Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, -CH₂CH₂-(bond to R²), -CH=CH-(bond to R²) and a
20 direct bond to R², wherein when R³ is selected from the group consisting of -CH₂CH₂-(bond to
R²), -CH=CH-(bond to R²) and a direct bond to R², R² and R³, together with the atoms to which
they are bound, form a ring having from fifteen to twenty-one ring atoms and containing 0, 1, 2
or 3 double bonds and 0, 1, 2 or 3 triple bonds;

T is selected from the group consisting of -(CH₂)_q-, -(CH₂)_q-O-(CH₂)_{q1}-, -(CH₂)_q-
25 N(R^A)-(CH₂)_{q1}-, -(CH₂)_q-S-(CH₂)_{q1}-, -(CH₂)_q-C(O)-(CH₂)_{q1}-, -(CH₂)_q-S(O)-(CH₂)_{q1}-, and -(CH₂)_q-
S(O)₂-(CH₂)_{q1}-, where q and q1 are each independently selected from the group consisting of 0, 1
or 2, and each T is substituted by 0, 1 or 2 groups selected from R^A;

Q is selected from the group consisting of -(CR^A)₂_p-, -(CR^A)₂_p-CR^A=CR^A-
(CR^A)₂_{p1}-, -(CR^A)₂_p-O-(CR^A)₂_{p1}-, -(CR^A)₂_p-N(R^A)-(CR^A)₂_{p1}-, -(CR^A)₂_p-S-(CR^A)₂_{p1}-, -(CR^A)₂_p-
30 S(O)-(CR^A)₂_{p1}-, and -(CR^A)₂_p-S(O)₂-(CR^A)₂_{p1}-, where p and p1 are independently selected from
0, 1, 2, 3 or 4;

each R⁴ is independently selected from the group consisting of H, halogen atoms,
-OR^A, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CN, -SR^A, -CO₂R^A, -C(O)N(R^A)₂, -OC(O)N(R^A)₂, Si(R^A)₃,

Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, -(C₀-C₃ alkyl)-O-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S(O)₂-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -SO(R^A), -SO₂(R^A), C₃-C₈ cycloalkyl, and aryl, wherein

5 said R^A aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N,

each R^A aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R^A C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl and aryl groups are substituted with 0 to 4 substituents R^A;

10 two R^A may be taken, together with the atoms to which they are bound, to form a ring; and

m is 0, 1, 2 or 3.

In a second embodiment of the invention, the compound is a compound of formula I or a pharmaceutically acceptable salt thereof, wherein

15 A is selected from the group consisting of C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₈ cycloalkyl, aryl and 7-, 8-, 9- and 10-membered bicyclic groups, wherein

said A aryl and bicyclic groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N,

20 each A aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings and 7-, 8-, 9- and 10-membered bicyclic aromatic rings,

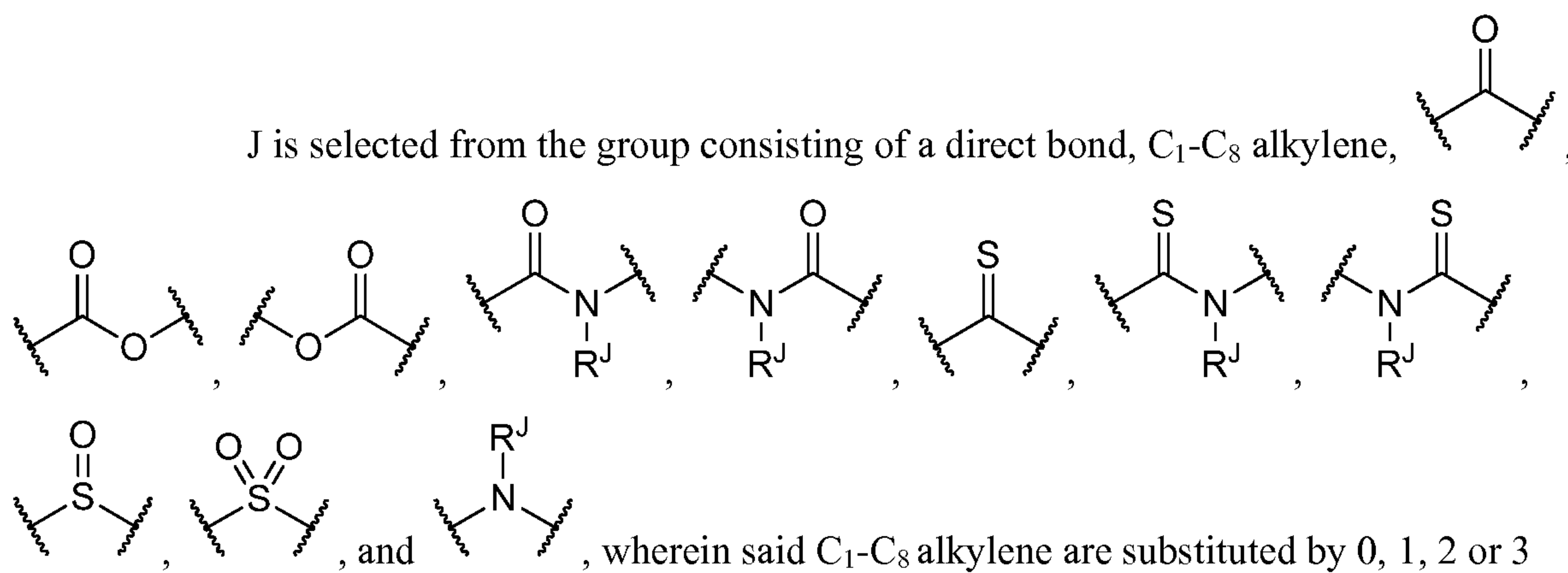
said A is substituted with 0, 1, 2, 3 or 4 substituents R^A;

each R^A is independently selected from the group consisting of H, F, Cl, Br, I, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkyl(NH₂), phenyl, naphthyl, C₃-C₈ cycloalkyl, halo(C₁-C₆ alkoxy), -O(C₁-C₆ alkyl), SH, S(C₁-C₆ alkyl), NH₂, -NH(C₁-C₆ alkyl),
 25 -N(C₁-C₆ alkyl)₂, -C(O)(C₁-C₆ alkyl), -CONH₂, -SO₂NH₂, NO₂, CN, -CF₃, -CHF₂, -CH₂F, -OCHF₂, -OCF₃, -OCH₂F, -SO₂(C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), -SO₂N(C₁-C₆ alkyl)₂, -(C₁-C₆ alkyl)SO₂N(C₁-C₆ alkyl)₂, -NHCOO(C₁-C₆ alkyl), -NHCO(C₁-C₆ alkyl), -NHCONH(C₁-C₆ alkyl),
 30 alkyl), -CO₂(C₁-C₆ alkyl), -C(O)N(C₁-C₆ alkyl)₂, -(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-O-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-S-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), and -(C₀-C₅ alkyl)-S(O)₂-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), wherein

two R^A may be taken, together with the atoms to which they are bound, to form a ring having from three to fifteen ring atoms;

R^A and R^2 may be taken, together with the atoms to which they are bound, to form a ring having from sixteen to twenty-one ring atoms;

5 R^A and R^1 or R^4 may be taken, together with the atoms to which they are bound, to form a ring having from sixteen to twenty-one ring atoms;



10 substituents R^J ;

R^J is selected from the group consisting of H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, and aryl, wherein

said R^J aryl contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N,

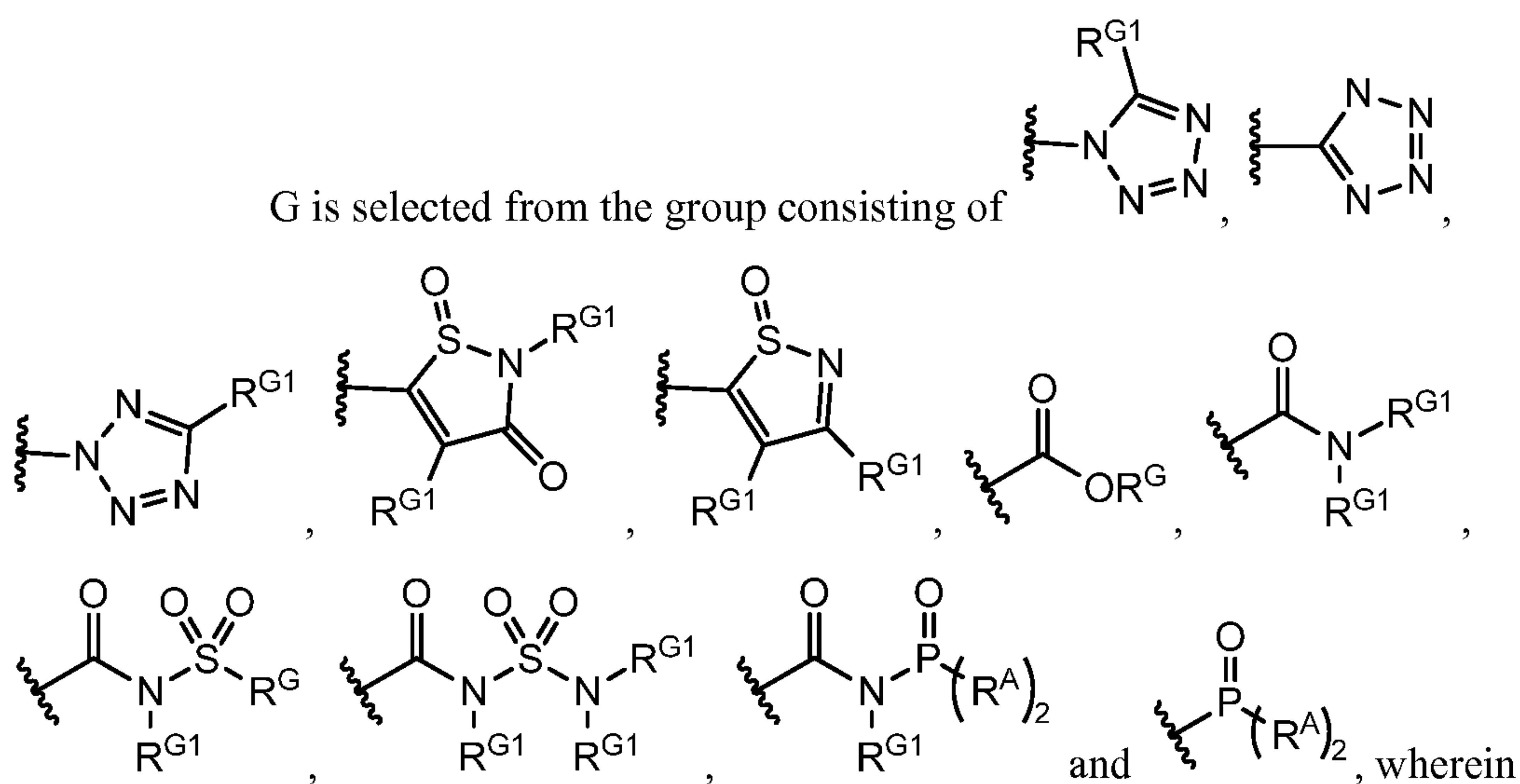
15 each R^J aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R^J is substituted with 0, 1, 2, 3 or 4 substituents R^A ;

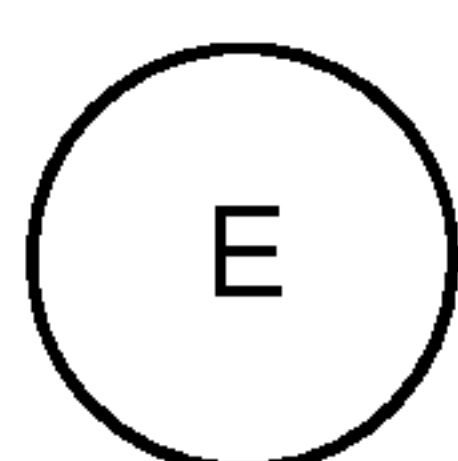
L is selected from the group consisting of $(CH_2)_{0-4}$ and $N(R^L)$;

20 each R^L is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl(NH_2), aryl, C_3 - C_8 cycloalkyl, halo(C_1 - C_6 alkoxy), and C_1 - C_6 alkyl(aryl) groups, wherein

each R^L aryl group is independently selected from the group consisting of 5- and 6-membered aromatic rings,



- R^G is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyl(C₁-C₅)alkyl, aryl, and aryl(C₁-C₄)alkyl groups, wherein said R^G aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N, each R^G aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings, said R^G is substituted with 0, 1 or 2 independently selected R^A substituents, each R^{G1} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, and benzyl, wherein each R^{G1} is independently substituted with 0 to 4 substituents R^A ,

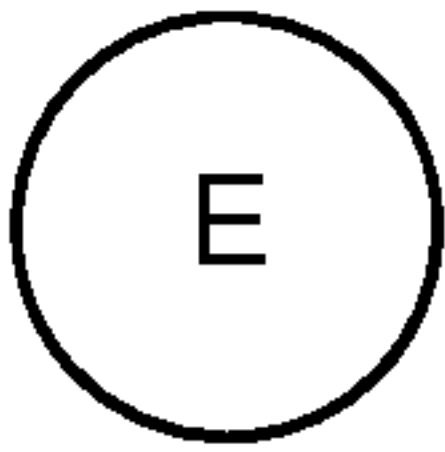


- (E) is selected from the group consisting of:
- 1) aryl rings in which the aryl ring system attaches to Q and T at points that are two independently selected carbon ring atoms,
 - 2) C₃-C₈ cycloalkyl rings in which the C₃-C₈ cycloalkyl ring system attaches to Q and T at points that are two independently selected carbon ring atoms, and
 - 3) heterocyclic rings in which the heterocyclic ring system attaches to Q and T at points that are two independently selected ring atoms that are either two carbon ring atoms or one carbon ring atom and one nitrogen ring atom, and the heterocyclic ring system is selected from the group consisting of:

a) 5- or 6-membered saturated or unsaturated monocyclic rings with 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O and S,

b) 8-, 9- or 10-membered saturated or unsaturated bicyclic rings with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S, and

c) 11- to 15-membered saturated or unsaturated tricyclic rings with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S,

10 wherein  is substituted with 1 substituent R¹ and with 0, 1, 2, 3, 4 or 5 independently selected substituents R⁴;

R¹ is selected from the group consisting of H, halogen atoms, -OH, C₁-C₉ alkyl, C₁-C₉ alkoxy, C₁-C₉ alkyl-C₁-C₉ alkoxy, -CN, -C(O)OH, -C(O)CH₃, -SR^A, -SO₂(C₁-C₉ alkyl), C₃-C₈ cycloalkyl, C₁-C₉ alkyl-C₃-C₈ cycloalkyl, C₃-C₈ cycloalkoxy, C₁-C₉ alkyl-C₃-C₈ cycloalkoxy, C₁-C₉ haloalkyl, -(C₀-C₃ alkyl)-O-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S(O)₂-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -N(R^A)₂, C₁-C₉ alkyl-N(R^A)₂, aryl, naphthyl, -O-aryl and -O-naphthyl groups; wherein:

20 said R¹ aryl, naphthyl, -O-aryl and -O-naphthyl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N,

each R¹ aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R¹ groups are substituted with 0 to 4 substituents R^A;

R² is selected from the group consisting of C₁-C₉ alkyl, C₂-C₉ alkenyl, C₂-C₉ alkynyl, C₃-C₈ cycloalkyl, and aryl groups, wherein

25 said R² aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N, and is attached through an atom selected from C and N,

said R² aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R² is substituted with 0, 1 or 2 independently selected R^A substituents,

30 R³ is selected from the group consisting of -CH₂CH₃, -CH=CH₂, -CH₂CH₂-(bond to R²), -CH=CH-(bond to R²) and a direct bond to R², wherein when R³ is selected from the

group consisting of $-\text{CH}_2\text{CH}_2$ -(bond to R^2), $-\text{CH}=\text{CH}$ -(bond to R^2) and a direct bond to R^2 , R^2 and R^3 , together with the atoms to which they are bound, form a ring having from fifteen to twenty-one ring atoms and containing 0, 1, 2 or 3 double bonds and 0, 1, 2 or 3 triple bonds;

T is selected from the group consisting of $-(\text{CH}_2)_q-$, $-(\text{CH}_2)_q-\text{O}-(\text{CH}_2)_{q1}-$, $-(\text{CH}_2)_q-\text{N}(\text{R}^A)-(\text{CH}_2)_{q1}-$, $-(\text{CH}_2)_q-\text{S}-(\text{CH}_2)_{q1}-$, $-(\text{CH}_2)_q-\text{C}(\text{O})-(\text{CH}_2)_{q1}-$, $-(\text{CH}_2)_q-\text{S}(\text{O})-(\text{CH}_2)_{q1}-$, and $-(\text{CH}_2)_q-\text{S}(\text{O})_2-(\text{CH}_2)_{q1}-$, where q and $q1$ are each independently selected from the group consisting of 0, 1 or 2, and each T is substituted by 0, 1 or 2 groups selected from R^A ;

Q is selected from the group consisting of $-(\text{CR}^A_2)_p-$, $-(\text{CR}^A_2)_p-\text{CR}^A=\text{CR}^A-$, $(\text{CR}^A_2)_{p1}$, $-(\text{CR}^A_2)_p-\text{O}-(\text{CR}^A_2)_{p1}-$, $-(\text{CR}^A_2)_p-\text{N}(\text{R}^A)-(\text{CR}^A_2)_{p1}-$, $-(\text{CR}^A_2)_p-\text{S}-(\text{CR}^A_2)_{p1}-$, $-(\text{CR}^A_2)_p-\text{S}(\text{O})-(\text{CR}^A_2)_{p1}-$, and $-(\text{CR}^A_2)_p-\text{S}(\text{O})_2-(\text{CR}^A_2)_{p1}-$, where p and $p1$ are independently selected from 0, 1, 2, 3 or 4;

each R^4 is independently selected from the group consisting of H, halogen atoms, $-\text{OR}^A$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $-\text{CN}$, $-\text{SR}^A$, $-\text{CO}_2\text{R}^A$, $-\text{C}(\text{O})\text{N}(\text{R}^A)_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^A)_2$, $-(\text{C}_0$ - C_3 alkyl)- $\text{O}-(\text{C}_0$ - C_3 alkyl)-(C_3 - C_8 cycloalkyl), $-(\text{C}_0$ - C_3 alkyl)- $\text{S}-(\text{C}_0$ - C_3 alkyl)-(C_3 - C_8 cycloalkyl), $-(\text{C}_0$ - C_3 alkyl)- $\text{S}(\text{O})_2-(\text{C}_0$ - C_3 alkyl)-(C_3 - C_8 cycloalkyl), $-\text{SO}(\text{R}^A)$, $-\text{SO}_2(\text{R}^A)$, C_3 - C_8 cycloalkyl, and aryl, wherein

said R^4 aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N,

each R^4 aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R^4 C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_8 cycloalkyl and aryl groups are substituted with 0 to 4 substituents R^A ;

two R^4 may be taken, together with the atoms to which they are bound, to form a ring; and

m is 0, 1, 2 or 3.

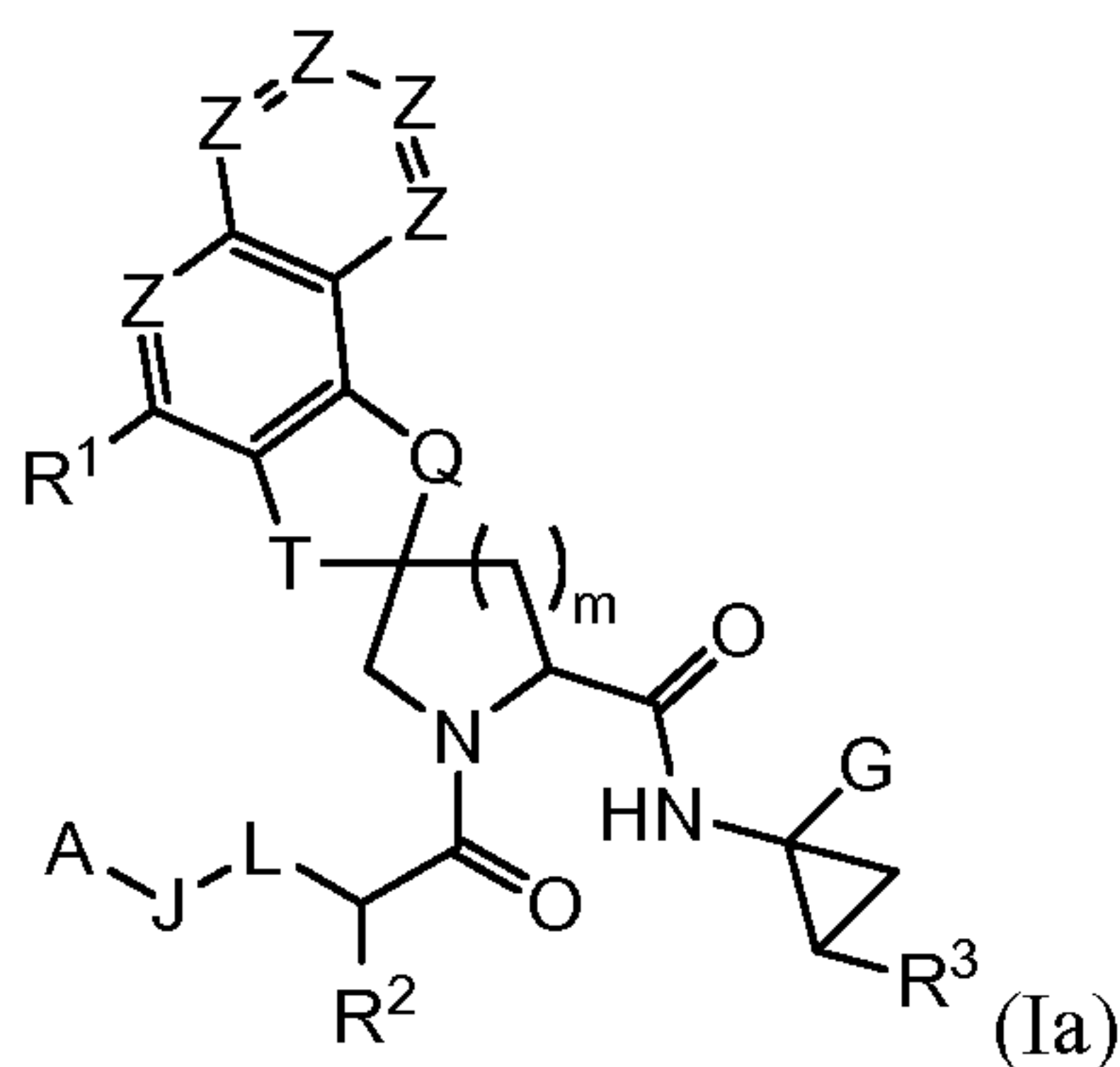
In a third embodiment of the invention, the compound is a compound of formula I or a pharmaceutically acceptable salt thereof, wherein R^A and R^2 are taken, together with the atoms to which they are bound, to form a ring wherein the R^A to R^2 linkage contains from six to nine atoms. In all aspects of this embodiment, all other groups are as provided in the general formula above or in the first through second embodiments.

In a fourth embodiment of the invention, the compound is a compound of formula I or a pharmaceutically acceptable salt thereof, wherein said R^A present on A and R^4 are taken, together with the atoms to which they are bound, to form a ring wherein the R^A to R^4 linkage

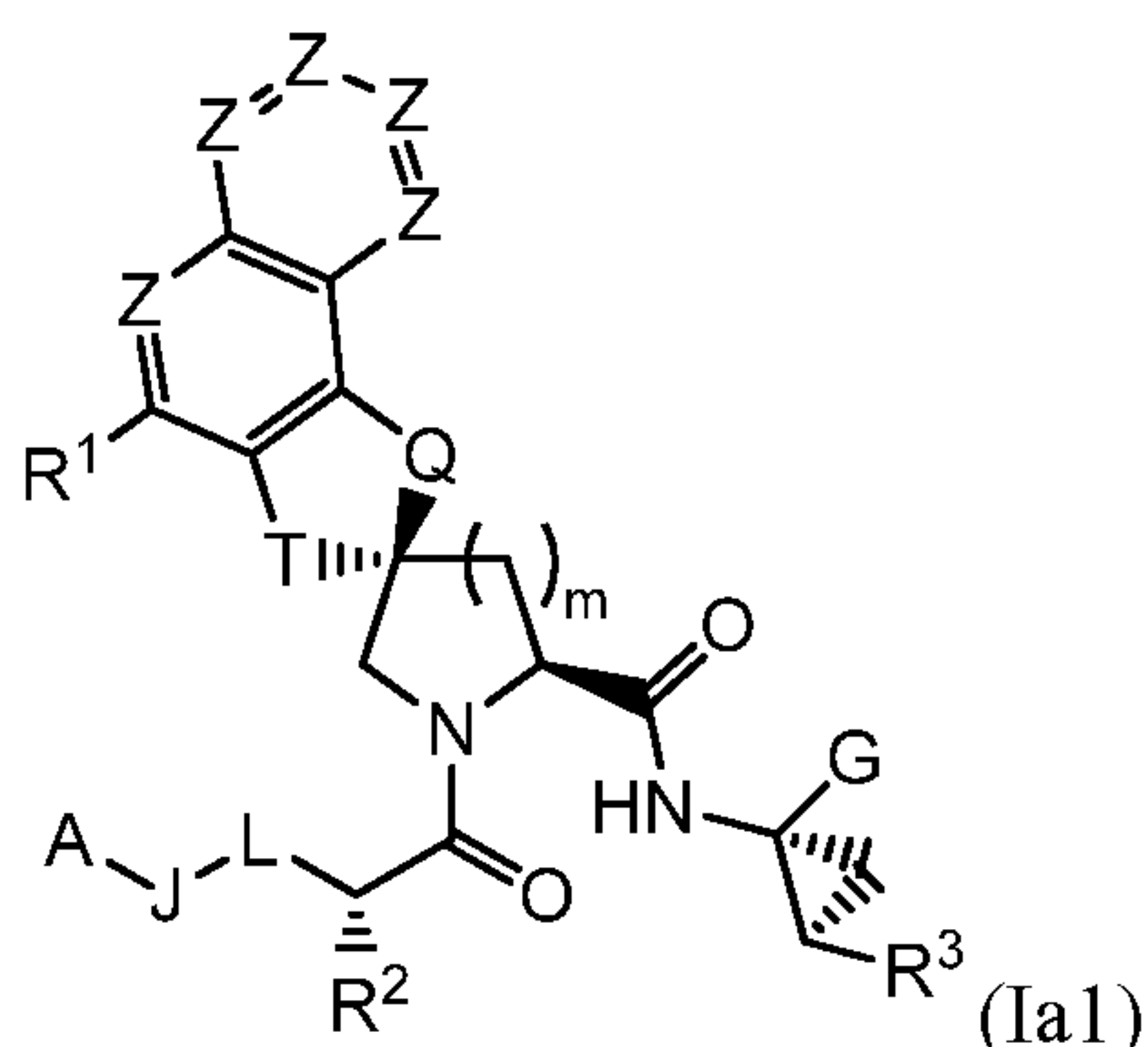
contains from six to nine atoms. In all aspects of this embodiment, all other groups are as provided in the general formula above or in the first through third embodiments.

In a fifth embodiment of the invention, the compound is a compound of formula I or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from the group consisting of $-\text{CH}_2\text{CH}_2-$ (bond to R^2), $-\text{CH}=\text{CH}-$ (bond to R^2) and a direct bond to R^2 , and wherein R^2 and R^3 , together with the atoms to which they are bound, form a ring having from fifteen to twenty-one ring atoms and containing 0, 1, 2 or 3 double bonds and 0, 1, 2 or 3 triple bonds. In a first aspect of this embodiment, R^A and R^1 are taken, together with the atoms to which they are bound, to form a ring wherein the R^A to R^1 linkage contains from six to nine atoms; and R^3 is selected from the group consisting of $-\text{CH}_2\text{CH}_2-$ (bond to R^2), $-\text{CH}=\text{CH}-$ (bond to R^2) and a direct bond to R^2 , and wherein R^2 and R^3 , together with the atoms to which they are bound, form a ring having from fifteen to twenty-one ring atoms and containing 0, 1, 2 or 3 double bonds and 0, 1, 2 or 3 triple bonds. In a second aspect of this embodiment, R^A and R^4 are taken, together with the atoms to which they are bound, to form a ring wherein the R^A to R^4 linkage contains from six to nine atoms; and R^3 is selected from the group consisting of $-\text{CH}_2\text{CH}_2-$ (bond to R^2), $-\text{CH}=\text{CH}-$ (bond to R^2) and a direct bond to R^2 , and wherein R^2 and R^3 , together with the atoms to which they are bound, form a ring having from fifteen to twenty-one ring atoms and containing 0, 1, 2 or 3 double bonds and 0, 1, 2 or 3 triple bonds. In all aspects of this embodiment, all other groups are as provided in the general formula above or in the first through fourth embodiments.

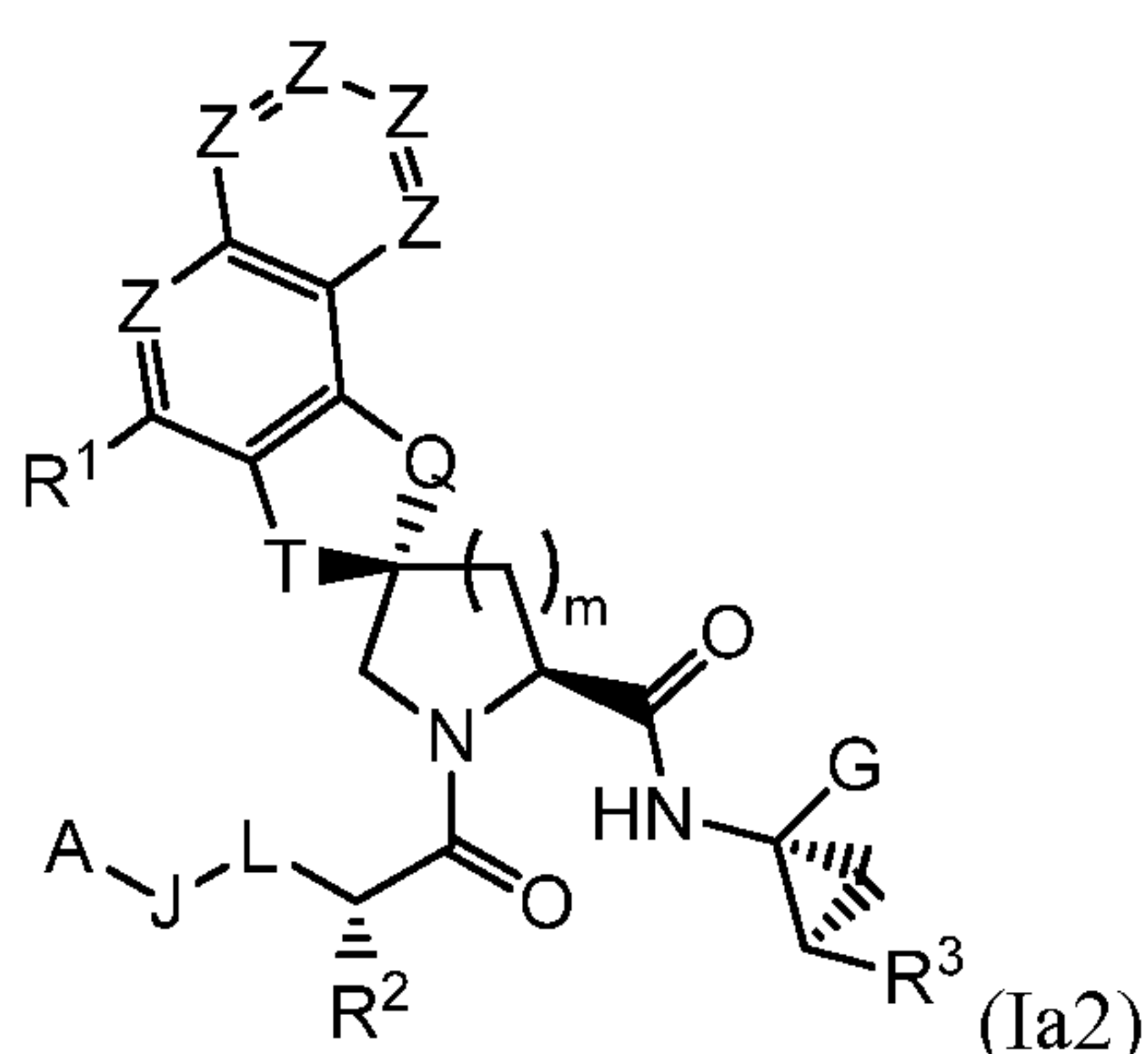
In a sixth embodiment of the invention, the compound is a compound of formula Ia:



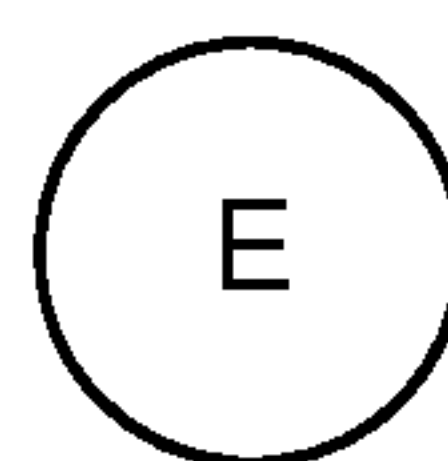
or a pharmaceutically acceptable salt thereof, wherein each Z is independently selected from the group consisting of N and $\text{C}(\text{R}^4)$. In a first aspect of this embodiment, the compound of formula Ia is a compound of formula Ia1:



or a pharmaceutically acceptable salt thereof. In a second aspect of this embodiment, the compound of formula Ia is a compound of formula Ia2:

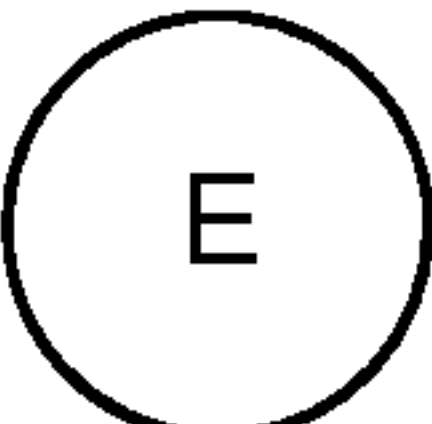


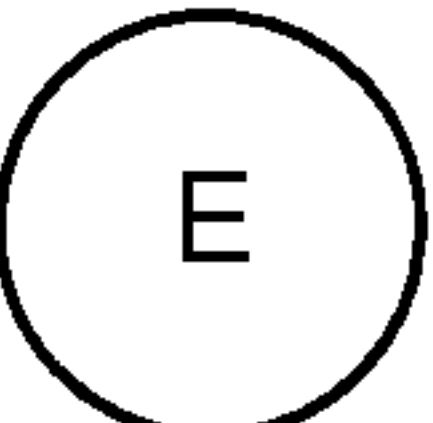
5 or a pharmaceutically acceptable salt thereof. In all aspects of this embodiment, all groups are as provided in the general formula above or in the first through fifth embodiments.

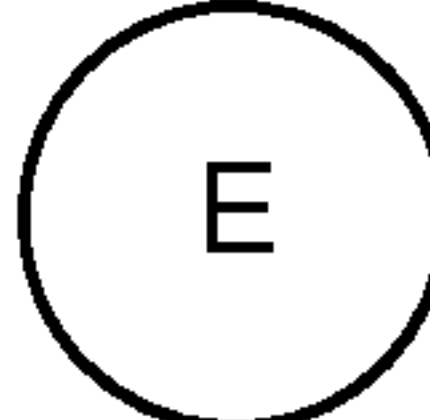


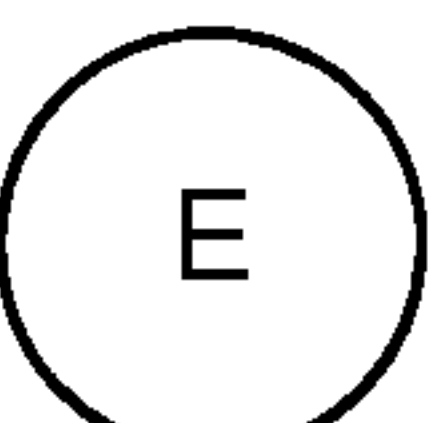
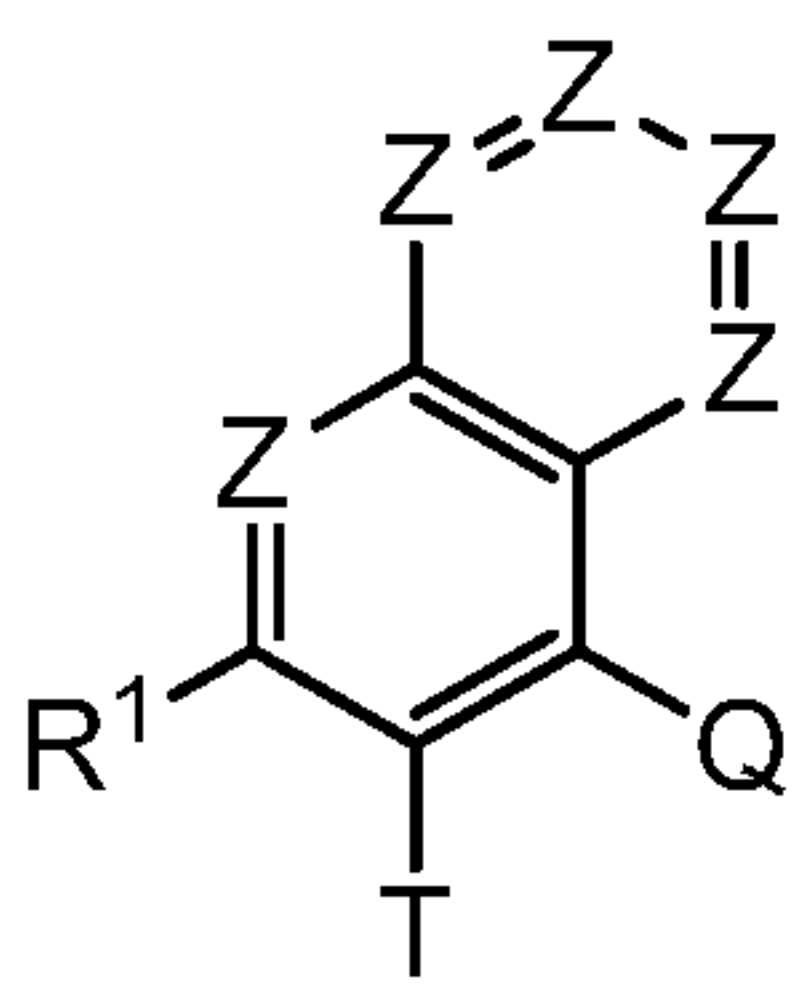
In a seventh embodiment of the invention, **E** is selected from the group consisting of 1) aryl rings in which the aryl ring system attaches to Q and T at points that are two independently selected carbon ring atoms, 2) C₃-C₈ cycloalkyl rings in which the C₃-C₈ cycloalkyl ring system attaches to Q and T at points that are two independently selected carbon ring atoms, and 3) heterocyclic rings in which the heterocyclic ring system attaches to Q and T at points that are two independently selected ring atoms that are either two carbon ring atoms or one carbon ring atom and one nitrogen ring atom, and the heterocyclic ring system is selected from the group consisting of a) 5- or 6-membered saturated or unsaturated monocyclic rings with 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O and S, b) 8-, 9- or 10-membered saturated or unsaturated bicyclic rings with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S, and c) 11- to 15-

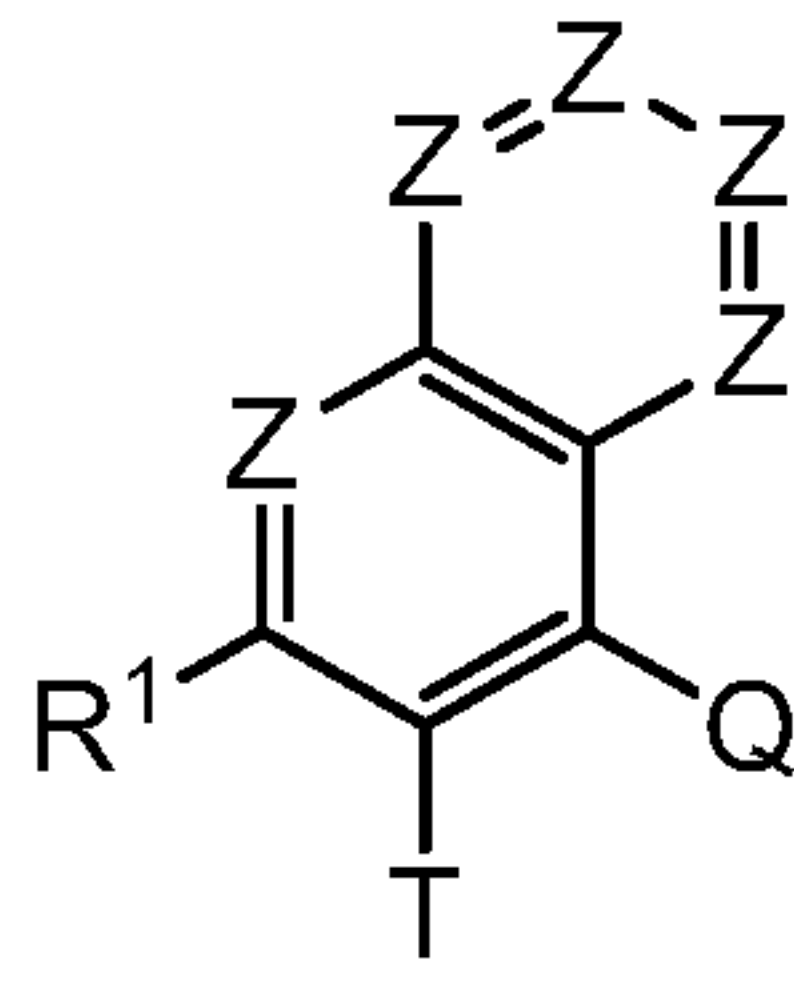
membered saturated or unsaturated tricyclic rings with 1, 2, 3, 4, or 5 heteroatom ring atoms

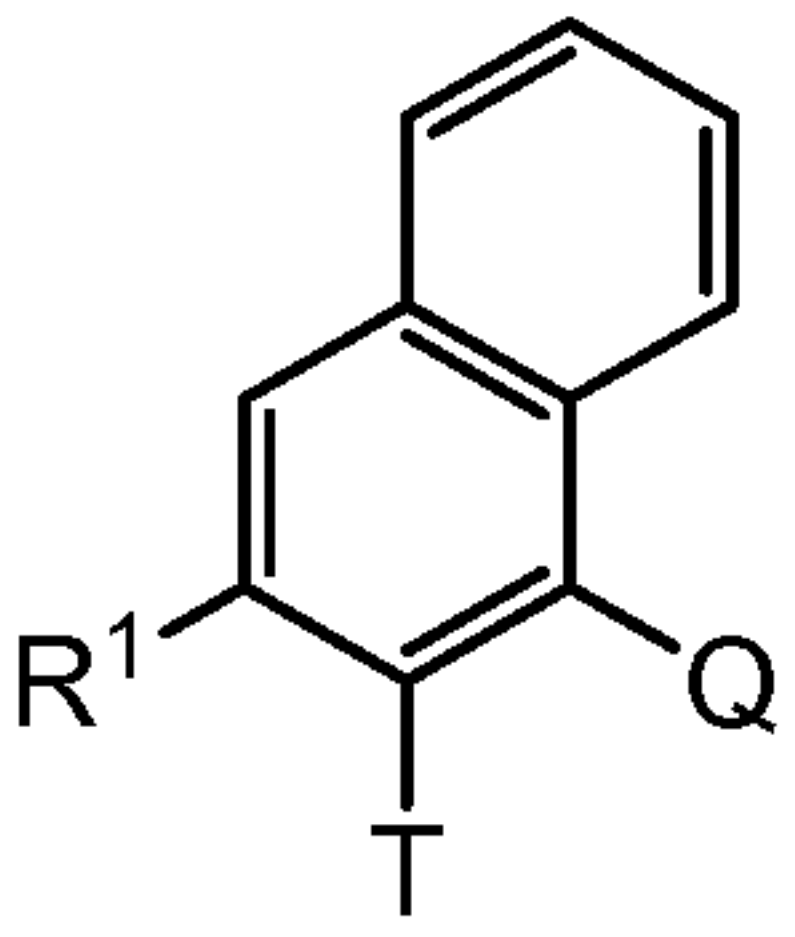
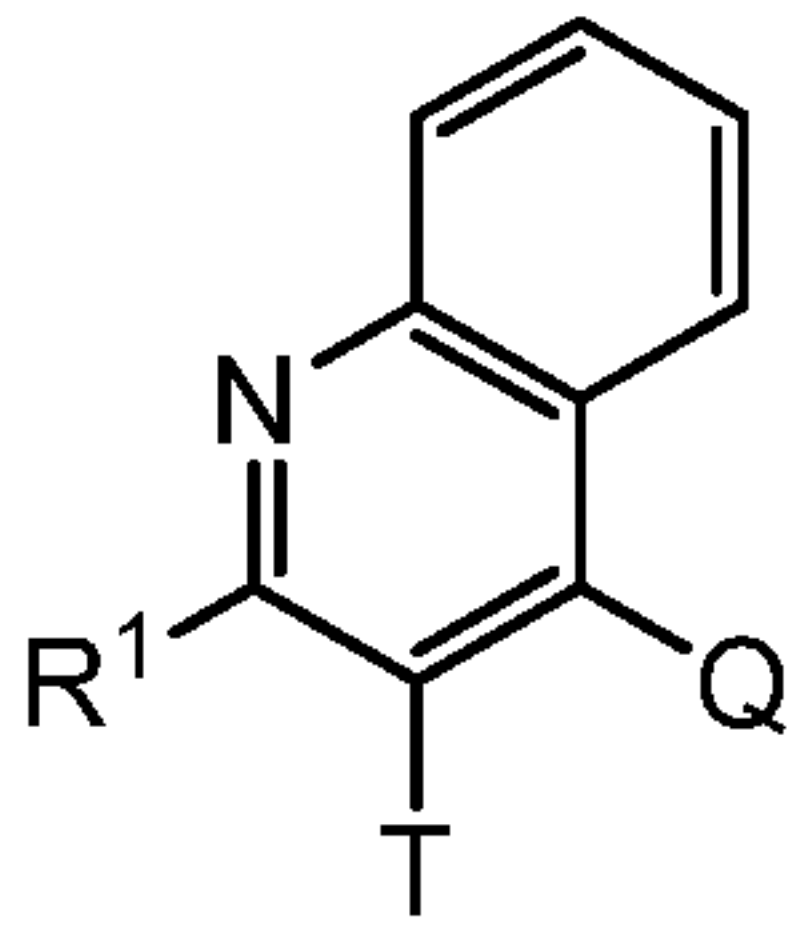
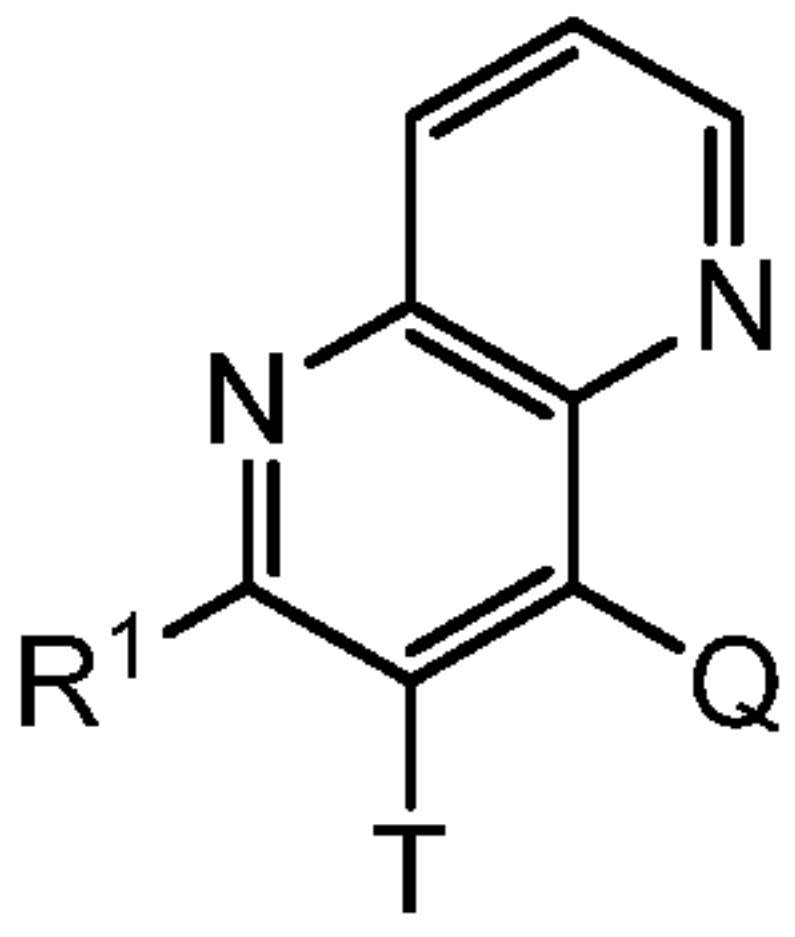
independently selected from the group consisting of N, O and S, wherein  is substituted with 1 substituent R¹ and with 0, 1, 2, 3, 4 or 5 independently selected substituents R⁴. In aspects

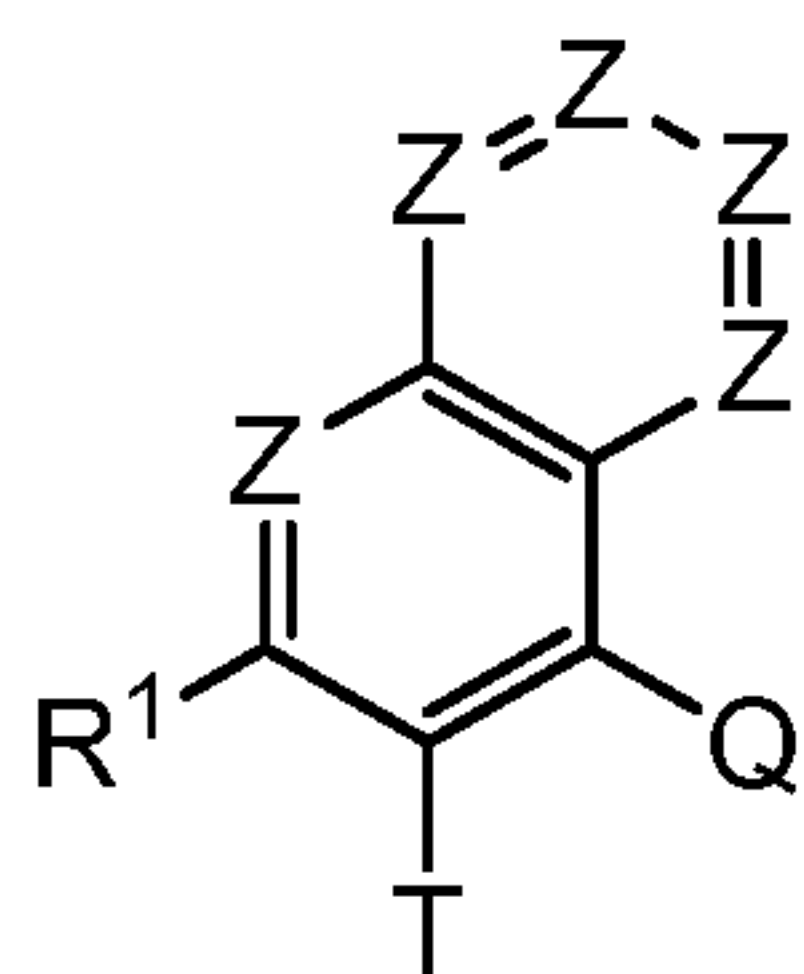
of this embodiment,  is selected from the group consisting of heterocyclic rings in which the heterocyclic ring system attaches to Q and T at points that are two independently selected ring atoms that are two carbon ring atoms, and the heterocyclic ring system is selected from the group consisting of 8-, 9- or 10-membered saturated or unsaturated bicyclic rings with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S,

wherein  is substituted with 1 substituent R¹ and with 0, 1, 2, 3, 4 or 5 independently selected substituents R⁴.

In aspects of this embodiment,  is , wherein each Z is independently selected from the group consisting of N and CH, substituted by 0, 1, 2, or 3 substituents R⁴. In

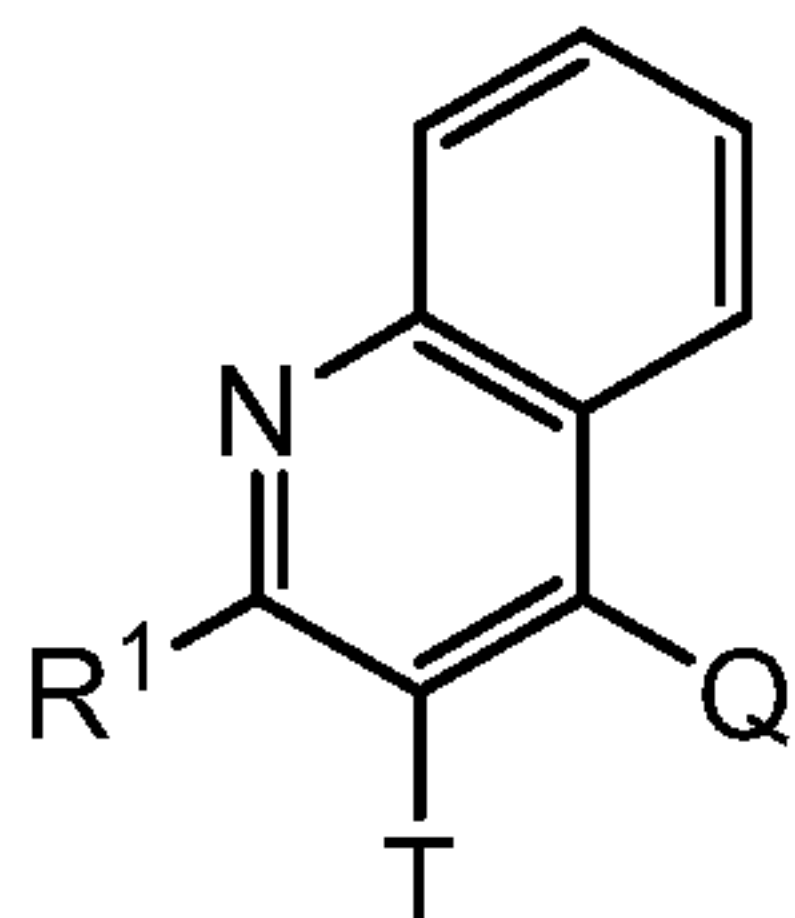
instances of these aspects,  is selected from the group consisting of

,  and , substituted by 0, 1, 2 or 3 substituents R⁴.

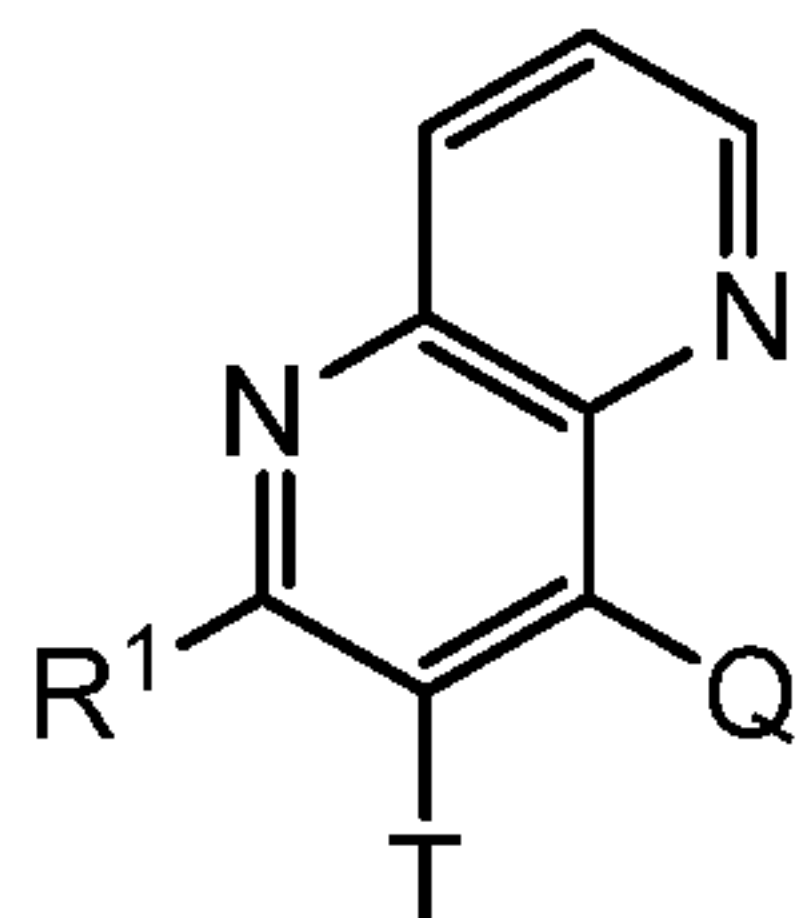


In specific instances of these aspects,

is selected from the group consisting of



and

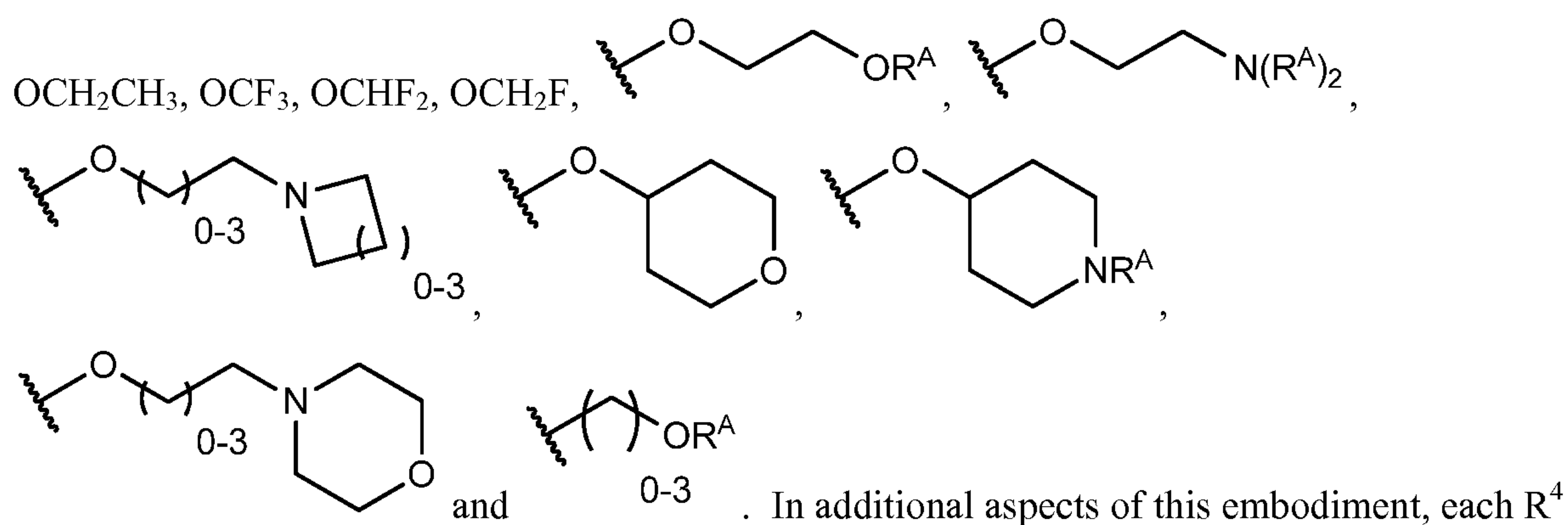


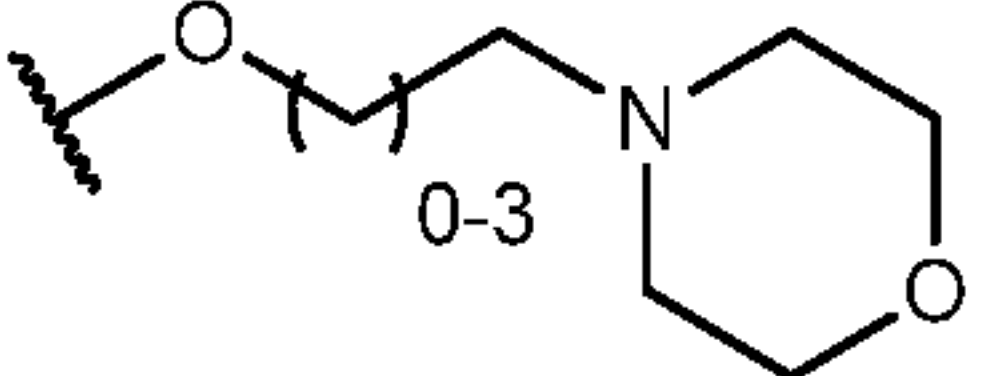
, substituted by 0, 1, 2 or 3 substituents R^4 . In this

embodiment, all other groups are as provided in the general formula above or in the first through sixth embodiments.

- 5 In an eighth embodiment of the invention, each R^4 is independently selected from the group consisting of H, halogen atoms, $-OR^A$, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-CN$, $-SR^A$, $-CO_2R^A$, $-C(O)N(R^A)_2$, $-OC(O)N(R^A)_2$, $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, $Si(CH_3)_3$, $-(C_0-C_3 \text{ alkyl})-O-$
- 10 $(C_0-C_3 \text{ alkyl})-(C_3-C_8 \text{ cycloalkyl})$, $-(C_0-C_3 \text{ alkyl})-S-(C_0-C_3 \text{ alkyl})-(C_3-C_8 \text{ cycloalkyl})$, $-(C_0-C_3 \text{ alkyl})-S(O)_2-(C_0-C_3 \text{ alkyl})-(C_3-C_8 \text{ cycloalkyl})$, $-SO(R^A)$, $-SO_2(R^A)$, C_3-C_8 cycloalkyl, C_1-C_6 internally substituted alkyl, C_1-C_6 internally substituted alkoxy, $-(C_0-C_3 \text{ internally substituted alkyl})-O-(C_0-C_3 \text{ internally substituted alkyl})-(C_3-C_8 \text{ internally substituted cycloalkyl})$, $-(C_0-C_3 \text{ internally substituted alkyl})-S-(C_0-C_3 \text{ internally substituted alkyl})-(C_3-C_8 \text{ internally substituted cycloalkyl})$, $-(C_0-C_3 \text{ internally substituted alkyl})-S(O)_2-(C_0-C_3 \text{ internally substituted alkyl})-(C_3-C_8 \text{ internally substituted cycloalkyl})$, C_3-C_8 internally substituted cycloalkyl and aryl, wherein said
- 15 R^4 C_1-C_6 internally substituted alkyl, C_1-C_6 internally substituted alkoxy, $-(C_0-C_3 \text{ internally substituted alkyl})-O-(C_0-C_3 \text{ internally substituted alkyl})-(C_3-C_8 \text{ internally substituted cycloalkyl})$, $-(C_0-C_3 \text{ internally substituted alkyl})-S-(C_0-C_3 \text{ internally substituted alkyl})-(C_3-C_8 \text{ internally substituted cycloalkyl})$, $-(C_0-C_3 \text{ internally substituted alkyl})-S(O)_2-(C_0-C_3 \text{ internally substituted alkyl})-(C_3-C_8 \text{ internally substituted cycloalkyl})$, C_3-C_8 internally substituted cycloalkyl and aryl
- 20 groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N, each R^4 aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings, said R^4 C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl and aryl groups are substituted with 0 to 4 substituents R^A ; two R^4 may be taken, together with the atoms to which they are bound, to form a ring. In aspects of this embodiment, each R^4 is independently selected
- 25 from the group consisting of H, halogen atoms, $-OR^A$, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-CN$,

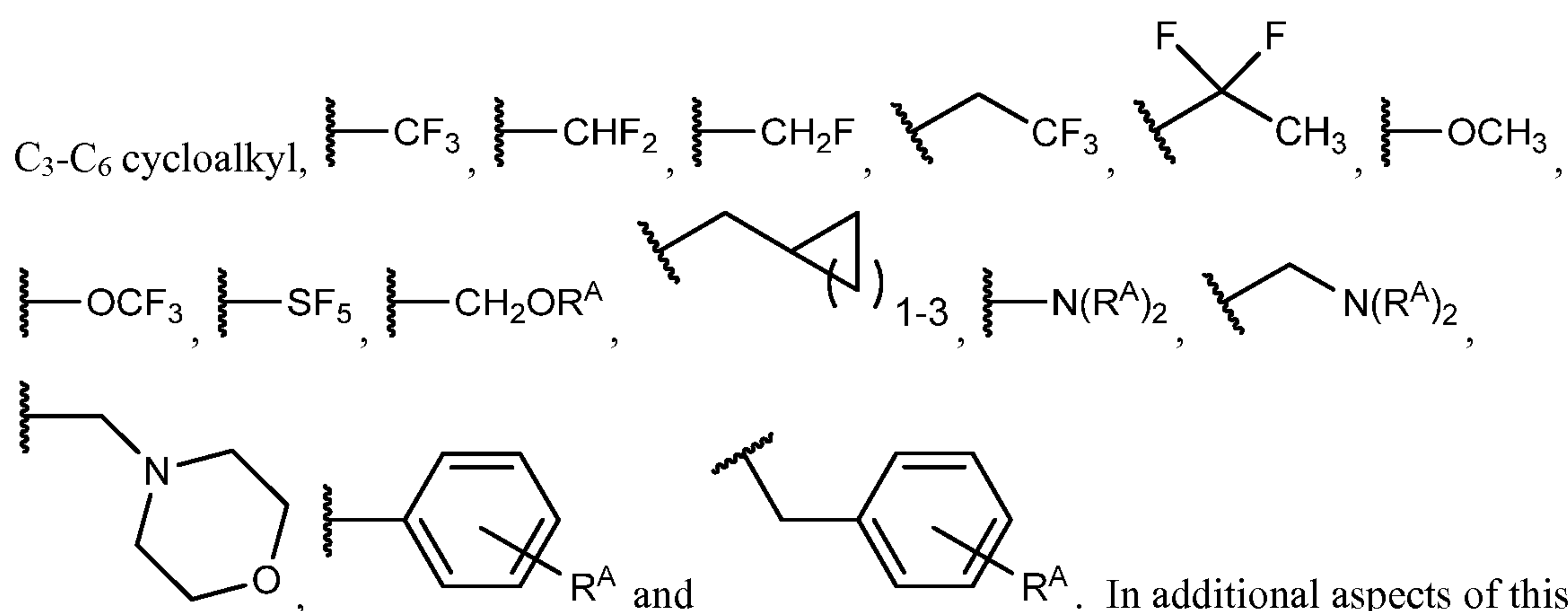
$-\text{SR}^{\text{A}}$, $-\text{CO}_2\text{R}^{\text{A}}$, $-\text{C}(\text{O})\text{N}(\text{R}^{\text{A}})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{\text{A}})_2$, $\text{Si}(\text{R}^{\text{A}})_3$, $\text{Si}(\text{R}^{\text{A}})_2(\text{CH}_3)$, $\text{Si}(\text{R}^{\text{A}})(\text{CH}_3)_2$, $\text{Si}(\text{CH}_3)_3$,
 $-(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-O}\text{-(C}_0\text{-C}_3 \text{ alkyl})\text{-(C}_3\text{-C}_8 \text{ cycloalkyl)}$, $-(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-S}\text{-(C}_0\text{-C}_3 \text{ alkyl})\text{-(C}_3\text{-C}_8$
 cycloalkyl) , $-(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-S}(\text{O})_2\text{-(C}_0\text{-C}_3 \text{ alkyl})\text{-(C}_3\text{-C}_8 \text{ cycloalkyl)}$, $-\text{SO}(\text{R}^{\text{A}})$, $-\text{SO}_2(\text{R}^{\text{A}})$, $\text{C}_3\text{-C}_8$
 cycloalkyl , and aryl, wherein said R^{A} aryl groups contain 0, 1, 2 or 3 heteroatoms independently
5 selected from the group consisting of O, S and N, each R^{A} aryl is independently selected from the
group consisting of 5- and 6-membered aromatic rings, said R^{A} $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_3\text{-C}_8$
 cycloalkyl and aryl groups are substituted with 0 to 4 substituents R^{A} ; two R^{A} may be taken,
together with the atoms to which they are bound, to form a ring. In aspects of this embodiment,
each R^{A} is independently selected from the group consisting of H, halogen atoms, $-\text{OR}^{\text{A}}$, $\text{C}_1\text{-C}_6$
10 alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $-\text{CN}$, $-\text{SR}^{\text{A}}$, $-\text{CO}_2\text{R}^{\text{A}}$, $-\text{C}(\text{O})\text{N}(\text{R}^{\text{A}})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{\text{A}})_2$, $-(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-O}\text{-(C}_0\text{-C}_3$
 $\text{alkyl})\text{-(C}_3\text{-C}_8 \text{ cycloalkyl)}$, $-(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-S}\text{-(C}_0\text{-C}_3 \text{ alkyl})\text{-(C}_3\text{-C}_8 \text{ cycloalkyl)}$, $-(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-}$
 $\text{S}(\text{O})_2\text{-(C}_0\text{-C}_3 \text{ alkyl})\text{-(C}_3\text{-C}_8 \text{ cycloalkyl)}$, $-\text{SO}(\text{R}^{\text{A}})$, $-\text{SO}_2(\text{R}^{\text{A}})$, $\text{C}_3\text{-C}_8 \text{ cycloalkyl}$, and aryl, wherein
said R^{A} aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group
consisting of O, S and N, each R^{A} aryl is independently selected from the group consisting of 5-
15 and 6-membered aromatic rings, said R^{A} $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_3\text{-C}_8 \text{ cycloalkyl}$ and aryl
groups are substituted with 0 to 4 substituents R^{A} ; two R^{A} may be taken, together with the atoms
to which they are bound, to form a ring. In particular aspects of this embodiment, wherein each
 R^{A} is independently selected from the group consisting of H, F, Cl, Br, OH, CN, $\text{C}_1\text{-C}_5$ alkyl, $\text{C}_1\text{-}$
 C_5 alkoxy, substituted by 0, 1, 2, or 3 R^{A} . In aspects of this embodiment, each R^{A} is
20 independently selected from the group consisting of H, F, Cl, Br, OH, CN, $\text{C}_1\text{-C}_5$ alkyl, OCH_3 ,



is selected from the group consisting of H, Cl, OCH_3 , OCF_3 and . In all
25 aspects of this embodiment, all other groups are as provided in the general formula above or in
the first through seventh embodiments.

In a ninth embodiment of the invention, R¹ is selected from the group consisting of H, halogen atoms, -OH, C₁-C₉ alkyl, C₁-C₉ alkoxy, C₁-C₉ alkyl-C₁-C₉ alkoxy, -CN, -C(O)OH, -C(O)CH₃, -SR^A, -SO₂(C₁-C₉ alkyl), C₃-C₈ cycloalkyl, C₁-C₉ alkyl-C₃-C₈ cycloalkyl, C₃-C₈ cycloalkoxy, C₁-C₉ alkyl-C₃-C₈ cycloalkoxy, C₁-C₉ haloalkyl, -(C₀-C₃ alkyl)-O-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S(O)₂-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -N(R^A)₂, C₁-C₉ alkyl-N(R^A)₂, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₉ internally substituted alkyl, C₁-C₉ internally substituted alkoxy, C₁-C₉ internally substituted alkyl-C₁-C₉ internally substituted alkoxy, -SO₂(C₁-C₉ internally substituted alkyl), C₃-C₈ internally substituted cycloalkyl, C₁-C₉ internally substituted alkyl-C₃-C₈ internally substituted cycloalkyl, C₃-C₈ internally substituted cycloalkoxy, C₁-C₉ alkyl-C₃-C₈ internally substituted cycloalkoxy, C₁-C₉ internally substituted haloalkyl, -(C₀-C₃ internally substituted alkyl)-O-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₃ internally substituted alkyl)-S-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₃ internally substituted alkyl)-S(O)₂-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), C₁-C₉ internally substituted alkyl-N(R^A)₂, aryl, naphthyl, -O-aryl and -O-naphthyl groups; wherein said R¹ C₁-C₉ internally substituted alkyl, C₁-C₉ internally substituted alkoxy, C₁-C₉ internally substituted alkyl-C₁-C₉ internally substituted alkoxy, -SO₂(C₁-C₉ internally substituted alkyl), C₃-C₈ internally substituted cycloalkyl, C₁-C₉ internally substituted alkyl-C₃-C₈ internally substituted cycloalkyl, C₃-C₈ internally substituted cycloalkoxy, C₁-C₉ alkyl-C₃-C₈ internally substituted cycloalkoxy, C₁-C₉ internally substituted haloalkyl, -(C₀-C₃ internally substituted alkyl)-O-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₃ internally substituted alkyl)-S-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₃ internally substituted alkyl)-S(O)₂-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), C₁-C₉ internally substituted alkyl-N(R^A)₂, aryl, naphthyl, -O-aryl and -O-naphthyl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N, each R¹ aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings, said R¹ groups are substituted with 0 to 4 substituents R^A. In aspects of this embodiment, R¹ is selected from the group consisting of H, halogen atoms, -OH, C₁-C₉ alkyl, C₁-C₉ alkoxy, C₁-C₉ alkyl-C₁-C₉ alkoxy, -CN, -C(O)OH, -C(O)CH₃, -SR^A, -SO₂(C₁-C₉ alkyl), C₃-C₈ cycloalkyl, C₁-C₉ alkyl-C₃-C₈ cycloalkyl, C₃-C₈ cycloalkoxy, C₁-C₉ alkyl-C₃-C₈ cycloalkoxy, C₁-C₉ haloalkyl, -(C₀-C₃ alkyl)-O-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S-(C₀-C₃ alkyl)-(C₃-C₈

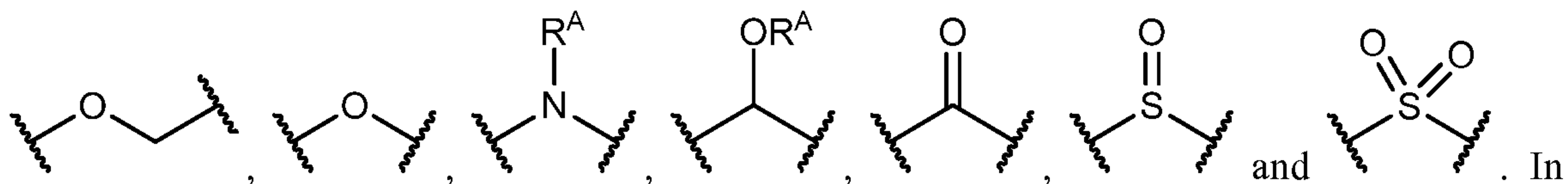
cycloalkyl), $-(C_0-C_3 \text{ alkyl})-S(O)_2-(C_0-C_3 \text{ alkyl})-(C_3-C_8 \text{ cycloalkyl})$, $-N(R^A)_2$, $C_1-C_9 \text{ alkyl}-N(R^A)_2$, $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, $Si(CH_3)_3$, aryl, naphthyl, -O-aryl and -O-naphthyl groups; wherein said R^1 aryl, naphthyl, -O-aryl and -O-naphthyl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N, each R^1 aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings, said R^1 groups are substituted with 0 to 4 substituents R^A . In aspects of this embodiment, R^1 is selected from the group consisting of H, halogen atoms, -OH, C_1-C_9 alkyl, C_1-C_9 alkoxy, C_1-C_9 alkyl- C_1-C_9 alkoxy, -CN, -C(O)OH, -C(O)CH₃, -SR^A, -SO₂(C_1-C_9 alkyl), C_3-C_8 cycloalkyl, C_1-C_9 alkyl- C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_9 alkyl- C_3-C_8 cycloalkoxy, C_1-C_9 haloalkyl, $-(C_0-C_3$ alkyl)-O- $(C_0-C_3$ alkyl)- $(C_3-C_8$ cycloalkyl), $-(C_0-C_3$ alkyl)-S- $(C_0-C_3$ alkyl)- $(C_3-C_8$ cycloalkyl), $-(C_0-C_3$ alkyl)-S(O)₂- $(C_0-C_3$ alkyl)- $(C_3-C_8$ cycloalkyl), $-N(R^A)_2$, C_1-C_9 alkyl- $N(R^A)_2$, aryl, naphthyl, -O-aryl and -O-naphthyl groups; wherein said R^1 aryl, naphthyl, -O-aryl and -O-naphthyl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N, each R^1 aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings, said R^1 groups are substituted with 0 to 4 substituents R^A . In particular aspects of this embodiment, R^1 is selected from the group consisting of H, C_1-C_5 alkyl,



embodiment, R^1 is selected from the group consisting of H, C_1-C_9 alkyl, and aryl groups; wherein said R^1 aryl groups contain 0 or 1 heteroatoms independently selected from the group consisting of O, S and N, each R^1 aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings, said R^1 groups are substituted with 0 to 4 substituents R^A . In all aspects of this embodiment, all other groups are as provided in the general formula above or in the first through eighth embodiments.

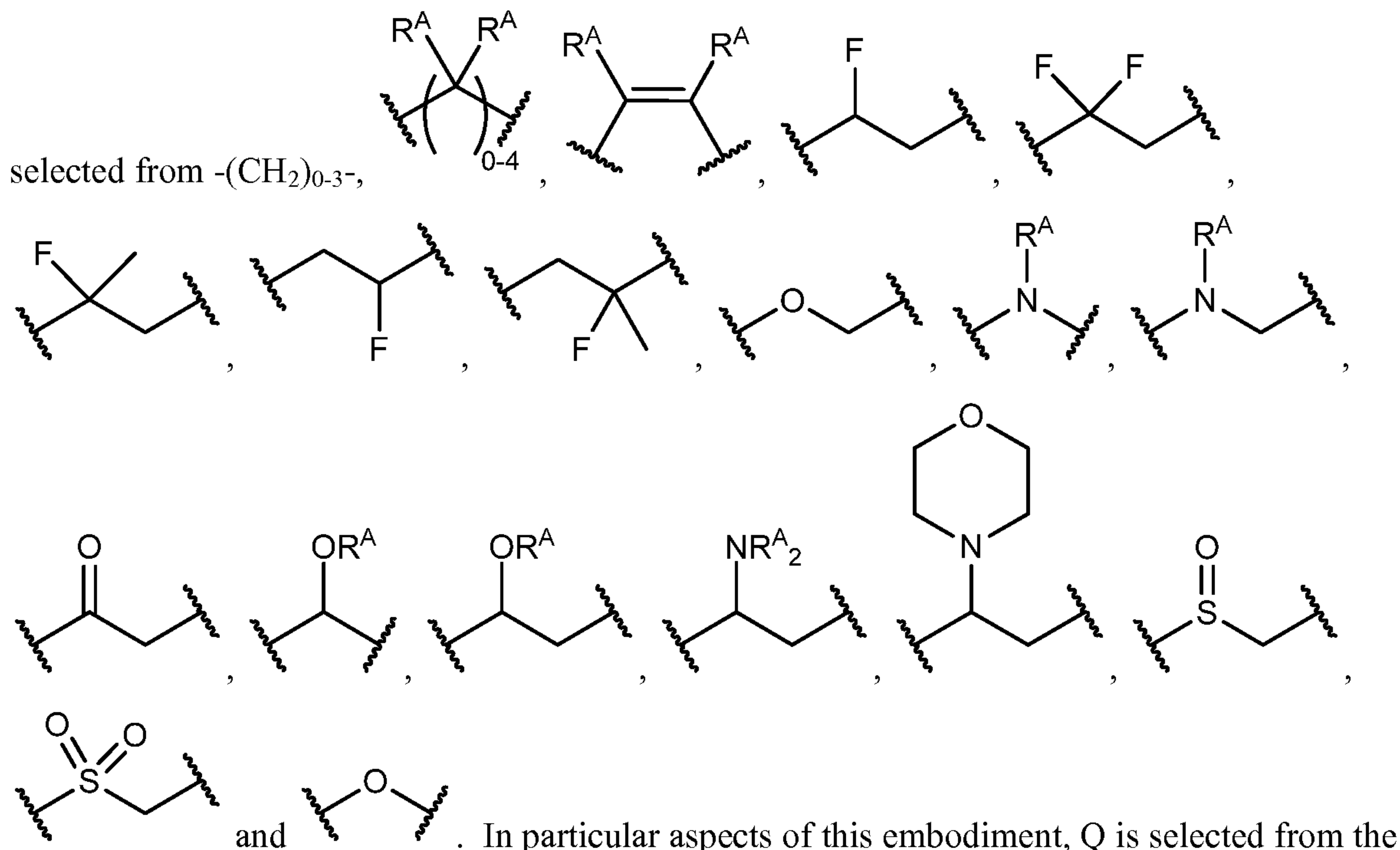
In a tenth embodiment of the invention, T is selected from the group consisting of $-(CH_2)_q-$, $-(CH_2)_q-O-(CH_2)_{q1}-$, $-(CH_2)_q-N(R^A)-(CH_2)_{q1}-$, $-(CH_2)_q-S-(CH_2)_{q1}-$, $-(CH_2)_q-C(O)-$

$(\text{CH}_2)_{q1}$ -, $(\text{CH}_2)_q\text{-S(O)-}(\text{CH}_2)_{q1}$ -, and $(\text{CH}_2)_q\text{-S(O)}_2\text{-}(\text{CH}_2)_{q1}$ -, where q and $q1$ are each independently selected from the group consisting of 0, 1 or 2, and T is substituted by 0, 1 or 2 groups selected from R^A . In aspects of this embodiment, T is selected from $(\text{CH}_2)_{0-3}$ -,

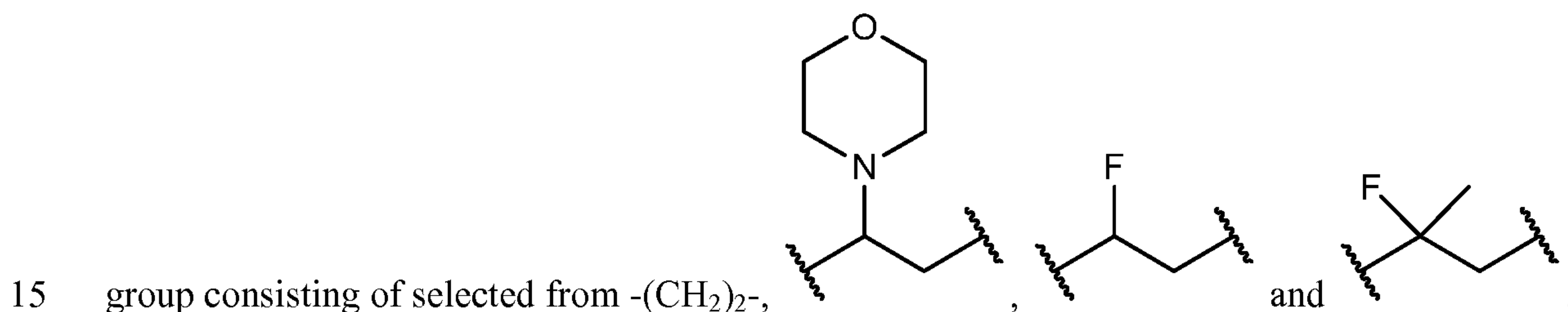


In particular aspects of this embodiment, T is $-\text{O}-$. In all aspects of this embodiment, all groups are as provided in the general formula above or in the first through ninth embodiments.

In an eleventh embodiment of the invention, Q is selected from the group consisting of $(\text{CR}^A_2)_p$ -, $(\text{CR}^A_2)_p\text{-CR}^A=\text{CR}^A\text{-}(\text{CR}^A_2)_{p1}$ -, $(\text{CR}^A_2)_p\text{-O-}(\text{CR}^A_2)_{p1}$ -, $(\text{CR}^A_2)_p\text{-N}(\text{R}^A)\text{-}(\text{CR}^A_2)_{p1}$ -, $(\text{CR}^A_2)_p\text{-S-}(\text{CR}^A_2)_{p1}$ -, $(\text{CR}^A_2)_p\text{-S(O)-}(\text{CR}^A_2)_{p1}$ -, and $(\text{CR}^A_2)_p\text{-S(O)}_2\text{-}(\text{CR}^A_2)_{p1}$ -, where p and $p1$ are independently selected from 0, 1, 2, 3 or 4. In aspects of this embodiment, Q is



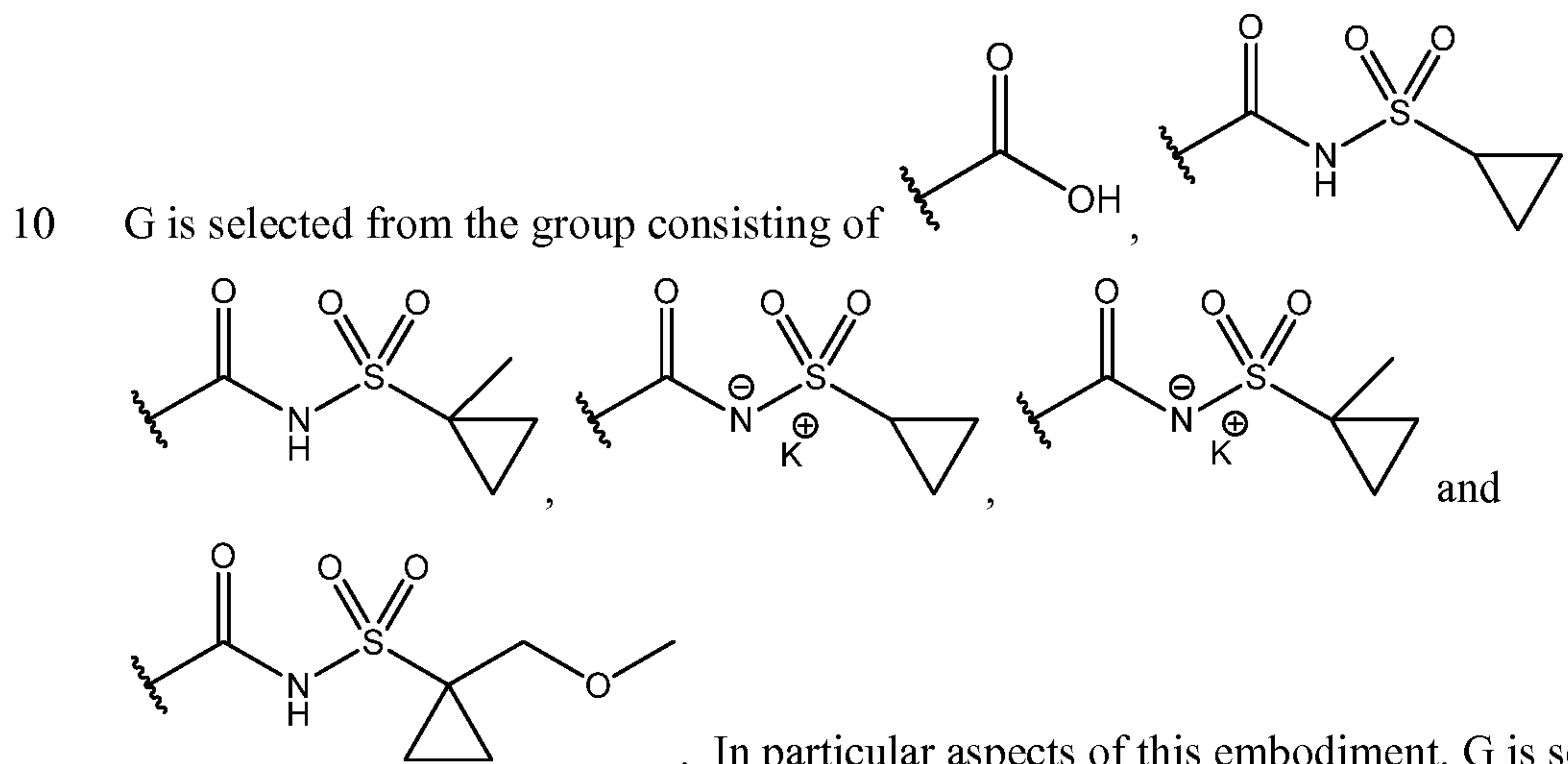
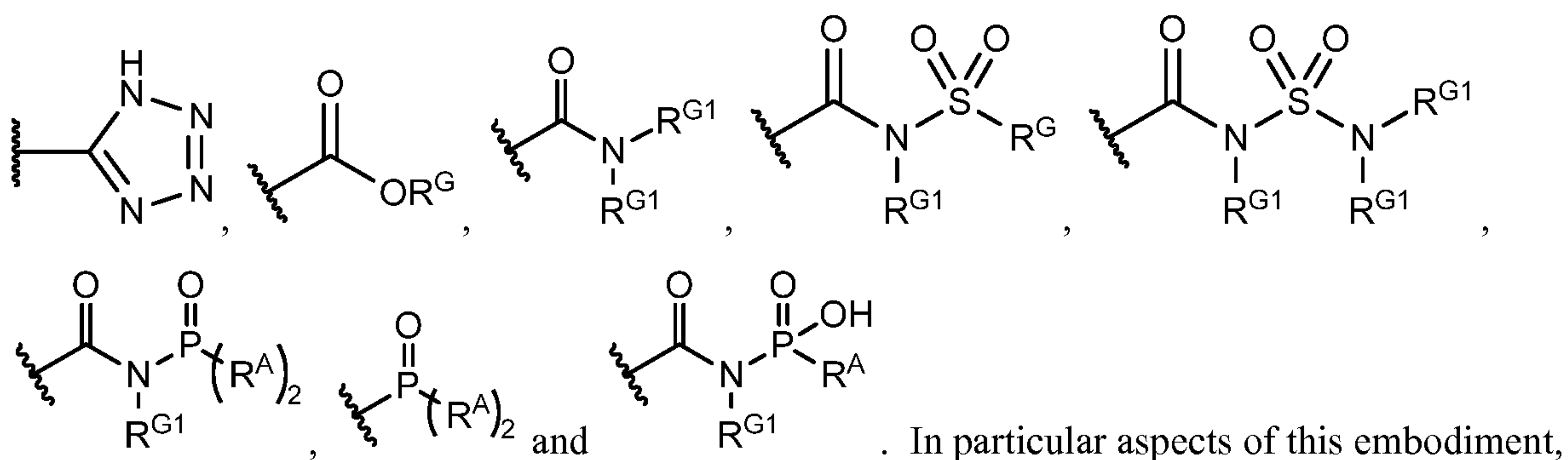
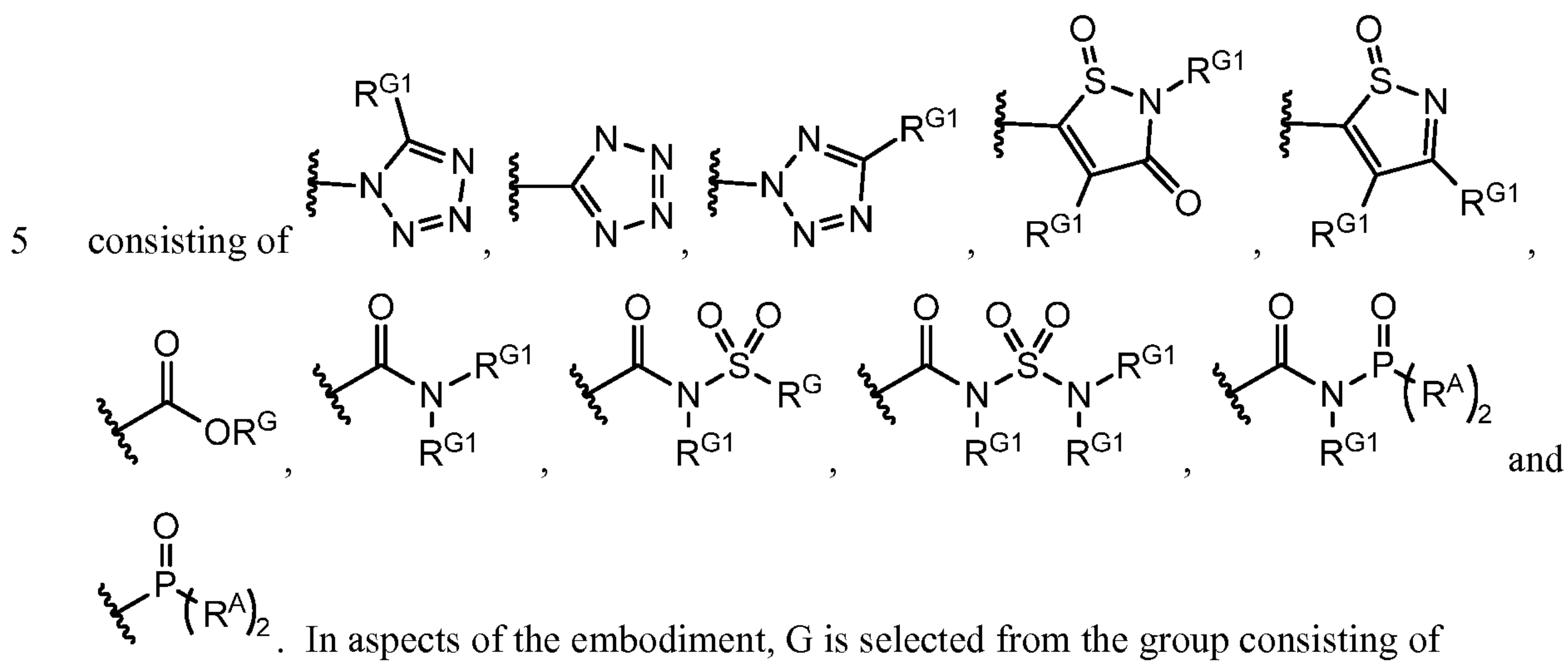
In particular aspects of this embodiment, Q is selected from the

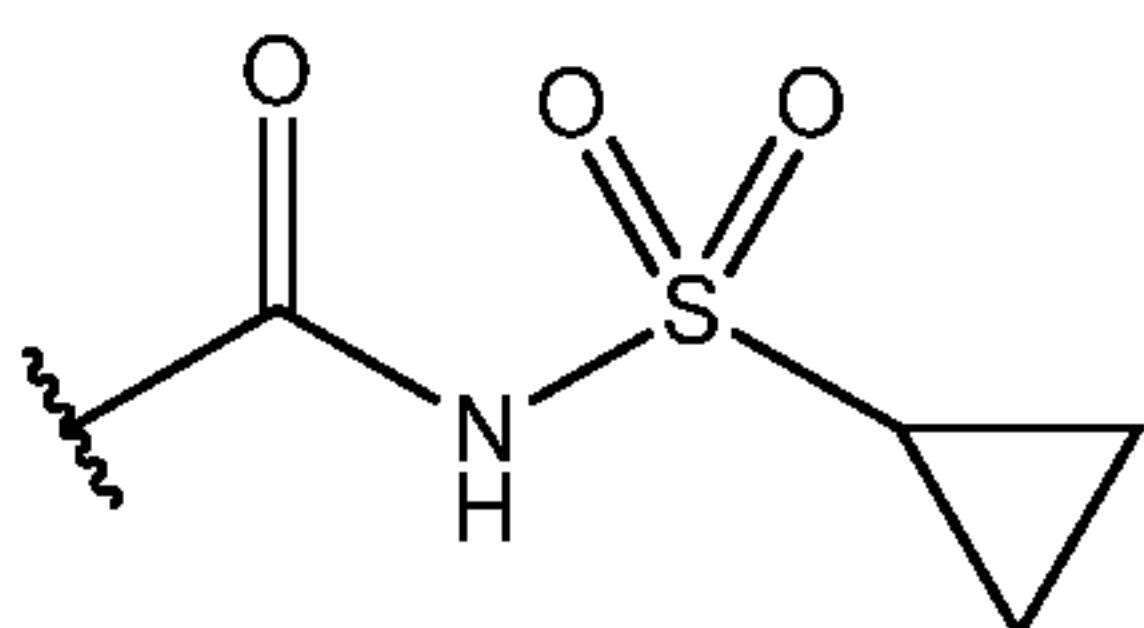
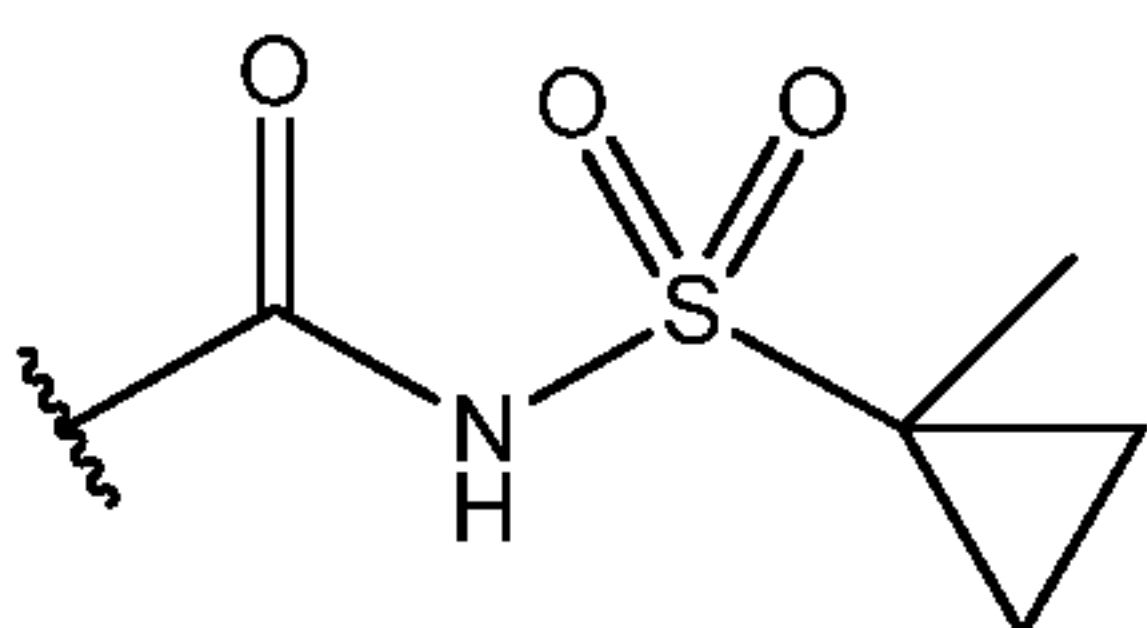


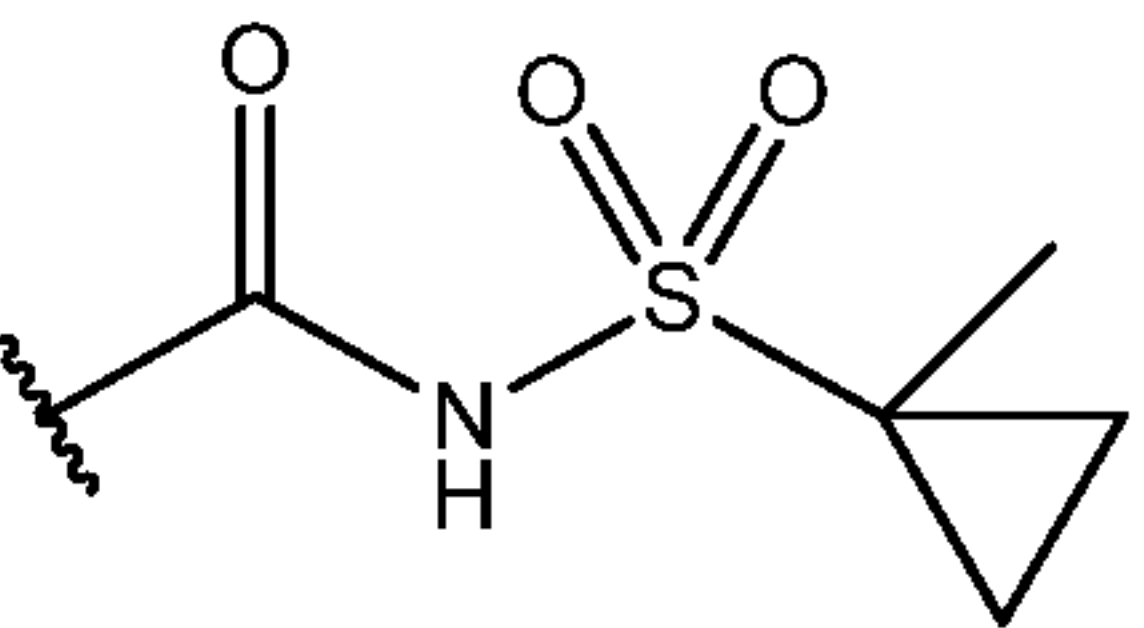
group consisting of selected from $(\text{CH}_2)_2$ -, $(\text{CH}_2)_2$ with F substituent, and $(\text{CH}_2)_2$ with F substituent on a quaternary carbon. In all aspects of this embodiment, all other groups are as provided in the general formula above or in the first through tenth embodiments.

In a twelfth embodiment of the invention, m is 0, 1, 2 or 3. In aspects of this embodiment, m is 1. In all aspects of this embodiment, all other groups are as provided in the general formula above or in the first through eleventh embodiments.

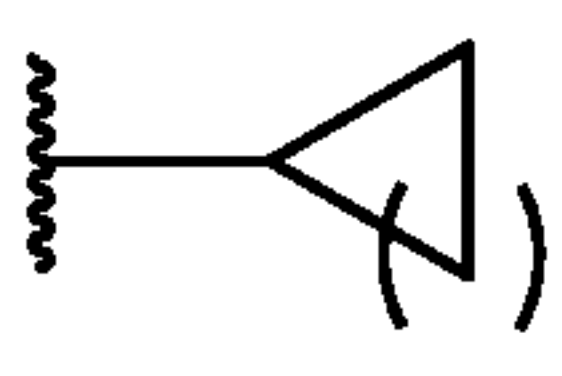
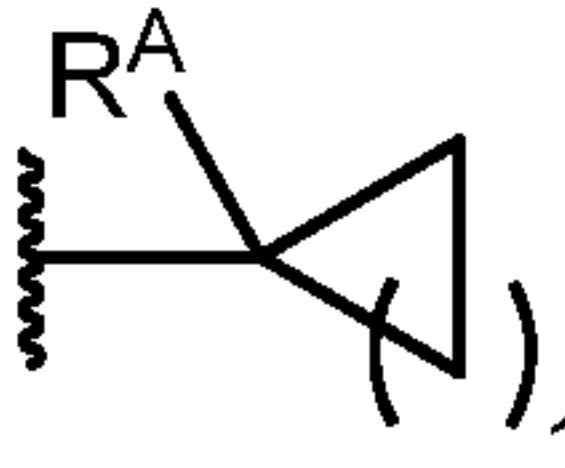
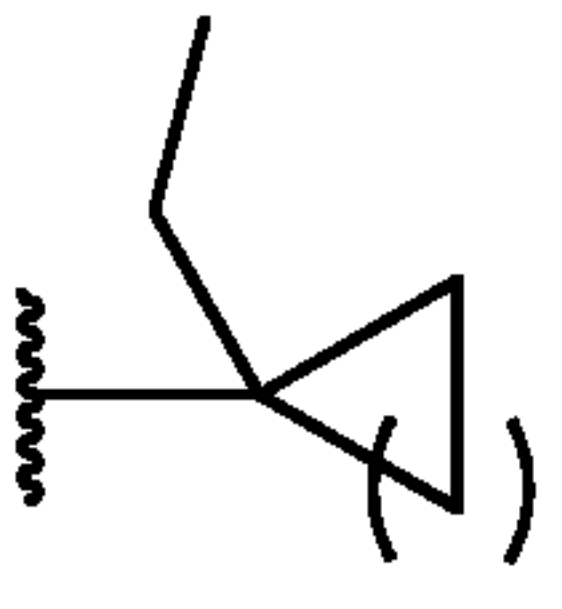
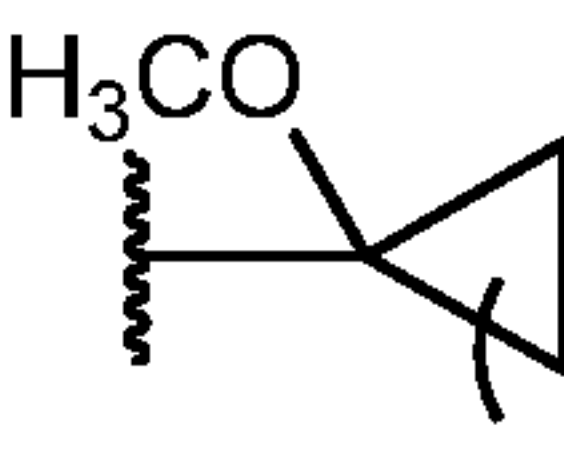
In a thirteenth embodiment of the invention, G is selected from the group

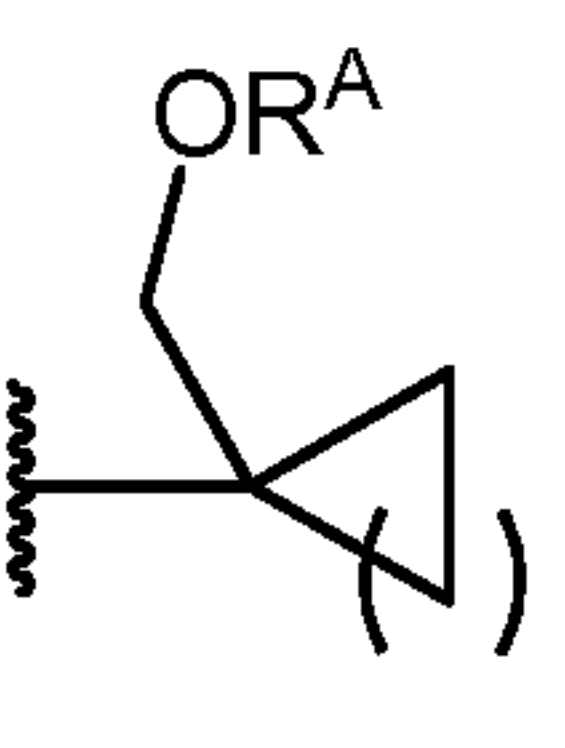
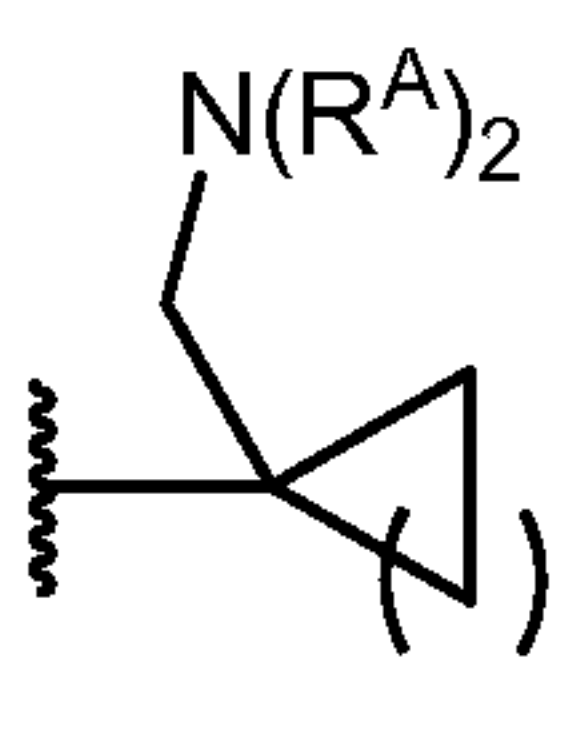
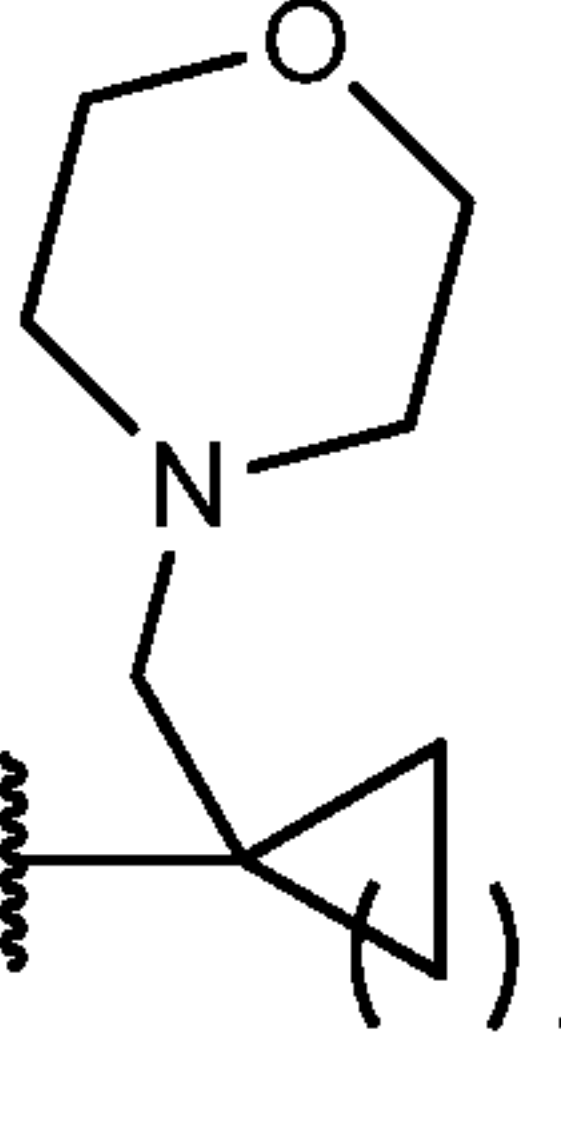


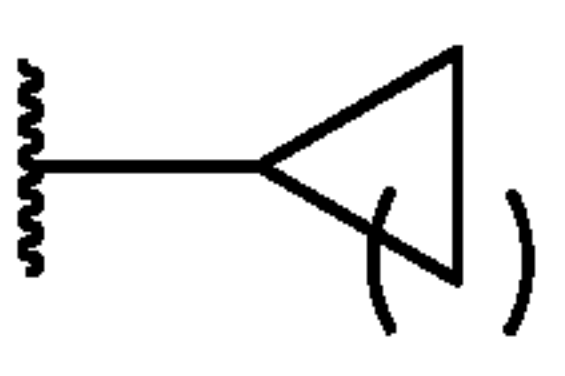
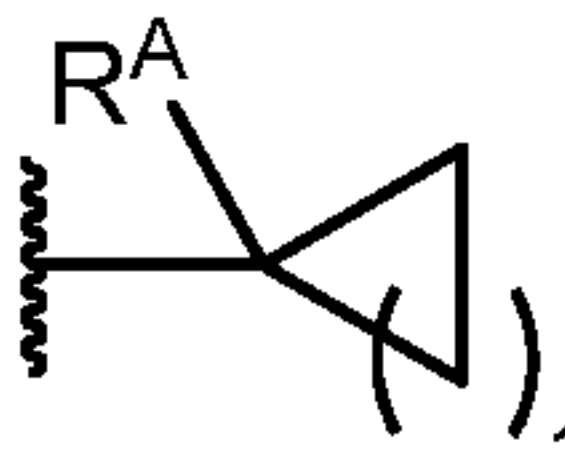
group consisting of  and . In even more particular

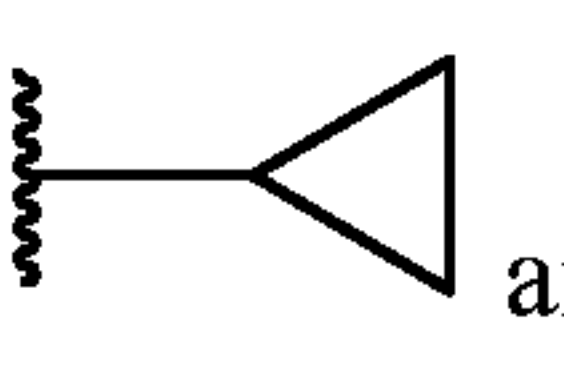
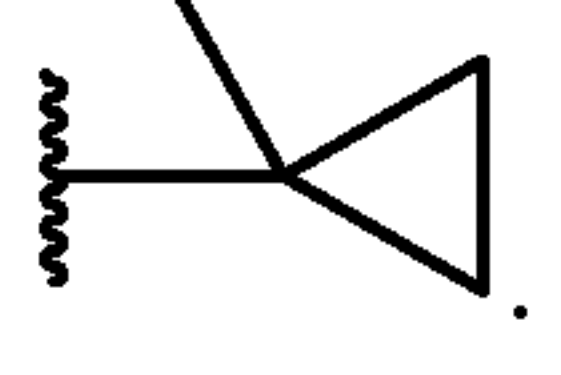
embodiments, G is . In all aspects of this embodiment, all other groups are as provided in the general formula above or in the first through twelfth embodiments.

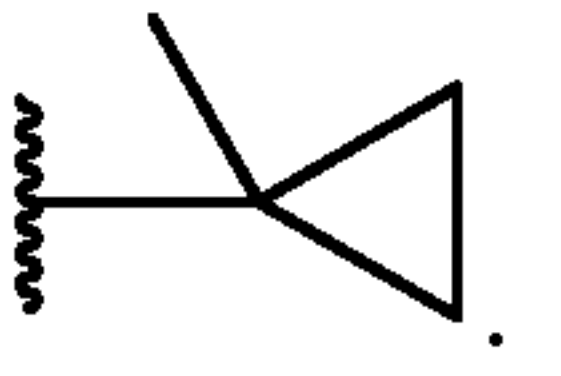
In a fourteenth embodiment of the invention, R^G is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyl(C₁-C₅)alkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, aryl, aryl(C₁-C₄)alkyl, C₁-C₆ internally substituted alkyl, C₃-C₆ internally substituted cycloalkyl, internally substituted C₃-C₆ cycloalkyl(C₁-C₅)alkyl, and internally substituted aryl(C₁-C₄)alkyl groups, wherein said R^G Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₆ internally substituted alkyl, C₃-C₆ internally substituted cycloalkyl, internally substituted C₃-C₆ cycloalkyl(C₁-C₅)alkyl, aryl, and internally substituted aryl(C₁-C₄)alkyl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N, each R^G aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings, said R^G is substituted with 0, 1 or 2 independently selected R^A substituents. In aspects of this embodiment, R^G is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyl(C₁-C₅)alkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, aryl, and aryl(C₁-C₄)alkyl groups, wherein said R^G Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, and aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N, each R^G aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings, said R^G is substituted with 0, 1 or 2 independently selected R^A substituents. In aspects of this embodiment, R^G is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyl(C₁-C₅)alkyl, aryl, and aryl(C₁-C₄)alkyl groups, wherein said R^G aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N, each R^G aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings, said R^G is substituted with 0, 1 or 2 independently selected R^A substituents. R^G is selected from the

group consisting of C₁-C₅ alkyl,  1-3,  1-5,  1-3,  1-3,

 1-3,  1-3 and  1-3. In particular embodiments, R^G is selected

from the group consisting of  1-3 and  1-5. In more particular embodiments,

R^G is selected from the group consisting of  and . In still more particular

5 embodiments, R^G is . In all aspects of this embodiment, all other groups are as provided in the general formula above or in the first through thirteenth embodiments.

In a fifteenth embodiment of the invention, each R^{G1} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, and benzyl, wherein each R^{G1} is independently substituted with 0 to 4 substituents R^A. In particular aspects of this embodiment, each R^{G1} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, and benzyl, wherein each R^{G1} is independently substituted with 0 to 4 substituents R^A. In all aspects of this embodiment, all other groups are as provided in the general formula above or in the first through fourteenth

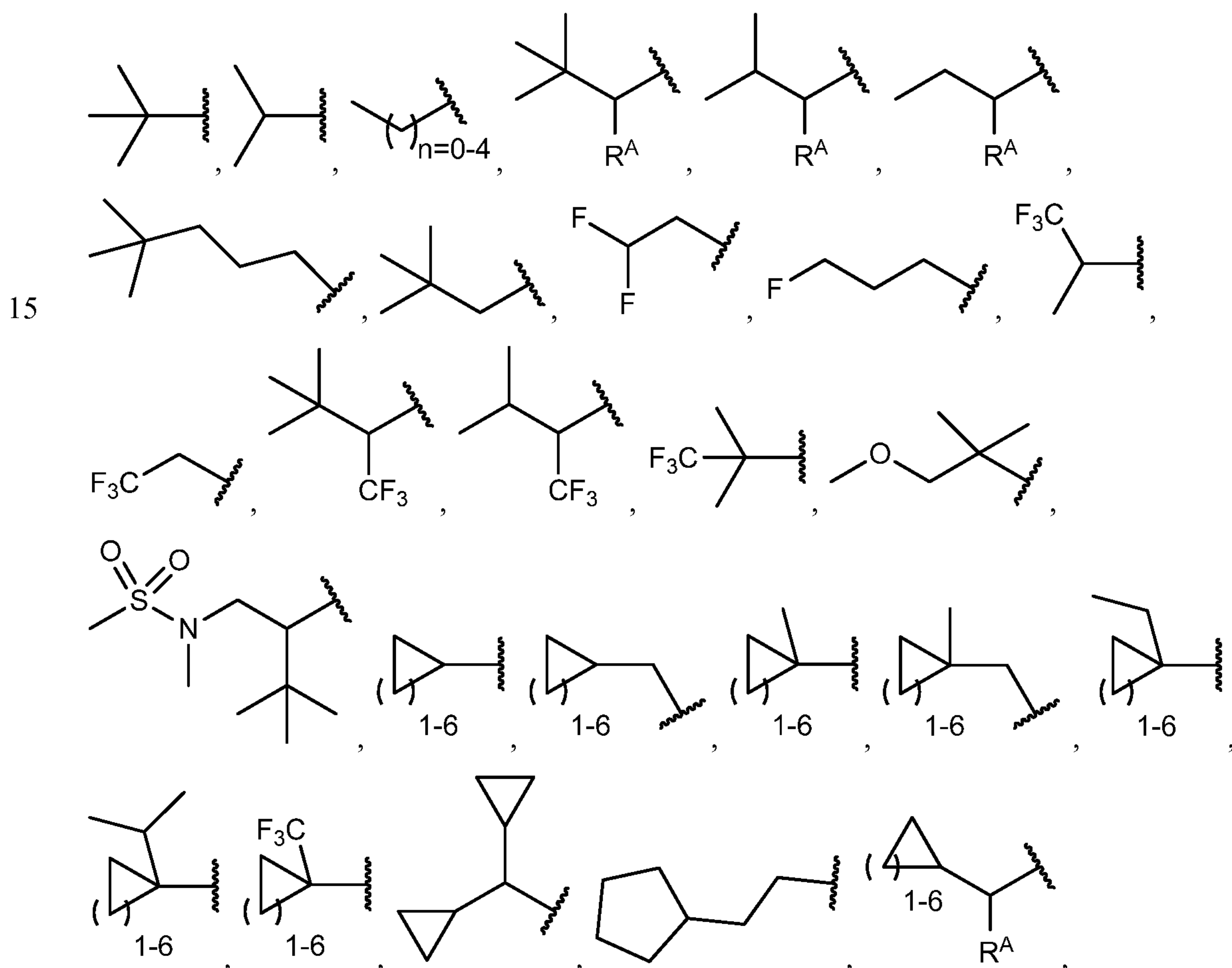
15 In a sixteenth embodiment of the invention, R² is selected from the group consisting of C₁-C₉ alkyl, C₂-C₉ alkenyl, C₂-C₉ alkynyl, C₃-C₈ cycloalkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₉ internally substituted alkyl, C₂-C₉ internally substituted alkenyl, C₂-C₉ internally substituted alkynyl, C₃-C₈ internally substituted cycloalkyl and aryl groups, wherein said R² Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, C₁-C₉ internally substituted alkyl, C₂-C₉ internally substituted alkenyl, C₂-C₉ internally substituted alkynyl, C₃-C₈ internally substituted cycloalkyl and aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the

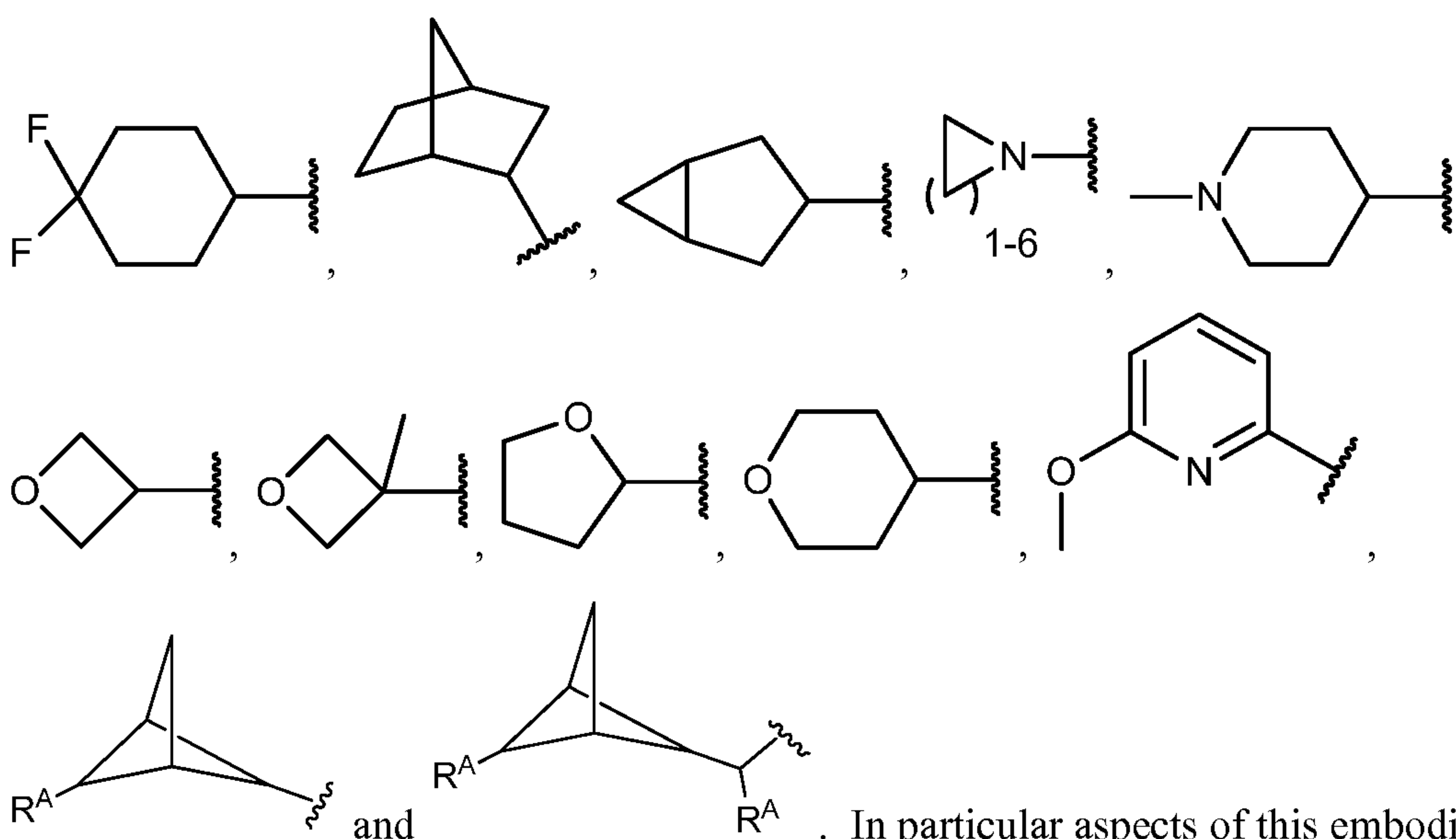
group consisting of B, O, S and N, and is attached through an atom selected from C and N, said R^2 aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings, said R^2 is substituted with 0, 1 or 2 independently selected R^A substituents. In aspects of the embodiments, R^2 is selected from the group consisting of C_1 - C_9 alkyl, C_2 - C_9 alkenyl, C_2 - C_9 alkynyl, C_3 - C_8 cycloalkyl, $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, $Si(CH_3)_3$, and aryl groups, wherein said R^2 $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, and aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N, and is attached through an atom selected from C and N, said R^2 aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings, said R^2 is substituted with 0, 1 or 2 independently selected R^A substituents. In aspects of this embodiment, R^2 is selected from the group consisting of C_1 - C_9 alkyl, C_2 - C_9 alkenyl, C_2 - C_9 alkynyl, C_3 - C_8 cycloalkyl, and aryl groups, wherein said R^2 aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N, and is attached through an atom selected from C and N, said R^2 aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings, said R^2 is substituted with 0, 1 or 2 independently selected R^A substituents. In particular embodiments, R^2 is selected from the group consisting of C_4 - C_9 alkyl. R^2 is C_5 alkyl. In all aspects of this embodiment, all other groups are as provided in the general formula above or in the first through fifteenth embodiments.

In a seventeenth embodiment of the invention, R^3 is selected from the group consisting of $-CH_2CH_3$, $-CH=CH_2$, $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, $Si(CH_3)_3$, $-CH_2CH_2-$ (bond to R^2), $-CH=CH-$ (bond to R^2) and a direct bond to R^2 , wherein when R^3 is selected from the group consisting of $-CH_2CH_2-$ (bond to R^2), $-CH=CH-$ (bond to R^2) and a direct bond to R^2 , R^2 and R^3 , together with the atoms to which they are bound, form a ring having from fifteen to twenty-one ring atoms and containing 0, 1, 2 or 3 double bonds and 0, 1, 2 or 3 triple bonds. In aspects of the embodiment, R^3 is selected from the group consisting of $-CH_2CH_3$, $-CH=CH_2$, $-CH_2CH_2-$ (bond to R^2), $-CH=CH-$ (bond to R^2) and a direct bond to R^2 , wherein when R^3 is selected from the group consisting of $-CH_2CH_2-$ (bond to R^2), $-CH=CH-$ (bond to R^2) and a direct bond to R^2 , R^2 and R^3 , together with the atoms to which they are bound, form a ring having from fifteen to twenty-one ring atoms and containing 0, 1, 2 or 3 double bonds and 0, 1, 2 or 3 triple bonds. In aspects of this embodiment, R^3 is selected from the group consisting of $-CH=CH-$ (bond to R^2) and $-CH-CH-$ (bond to R^2). In particular embodiments, R^3 is $-CH=CH-$ (bond to R^2), wherein R^2 and R^3 form a macrocyclic linkage that contains 1 double bonds. In all aspects of this

embodiment, all other groups are as provided in the general formula above or in the first through sixteenth embodiments.

In an eighteenth embodiment of the invention, A is selected from the group consisting of C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₁-C₈ internally substituted alkyl, C₂-C₈ internally substituted alkenyl, C₂-C₈ internally substituted alkynyl, C₃-C₈ cycloalkyl, C₃-C₈ internally substituted cycloalkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, aryl and 7-, 8-, 9- and 10-membered bicyclic groups, wherein said A Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₈ internally substituted alkyl, C₂-C₈ internally substituted alkenyl, C₂-C₈ internally substituted alkynyl, C₃-C₈ internally substituted cycloalkyl, aryl and bicyclic groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N, each A aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings and 7-, 8-, 9- and 10-membered bicyclic aromatic rings, said A is substituted with 0, 1, 2, 3 or 4 substituents R^A. In aspects of this embodiment, A is selected from the group consisting of





In particular aspects of this embodiment, A is selected from the group consisting of C₁-C₈ alkyl and aryl, wherein said A aryl groups contain 0, 1 or 2 heteroatoms independently selected from the group consisting of O, S and N, each A aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings, said A is substituted with 0, 1 or 2 substituents R^A. In all aspects of this embodiment, all other groups are as provided in the general formula above or in the first through seventeenth embodiments.

In nineteenth embodiment of the invention, each R^A is independently selected from the group consisting of H, F, Cl, Br, I, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkyl(NH₂), phenyl, naphthyl, C₃-C₈ cycloalkyl, halo(C₁-C₆ alkoxy), -O(C₁-C₆ alkyl), SH, S(C₁-C₆ alkyl), NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(O)(C₁-C₆ alkyl), -CONH₂, -SO₂NH₂, NO₂, CN, -CF₃, -CHF₂, -CH₂F, -OCHF₂, -OCF₃, -OCH₂F, -SO₂(C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), -SO₂N(C₁-C₆ alkyl)₂, -(C₁-C₆ alkyl)SO₂N(C₁-C₆ alkyl)₂, -NHCOO(C₁-C₆ alkyl), -NHCO(C₁-C₆ alkyl), -NHCONH(C₁-C₆ alkyl), -CO₂(C₁-C₆ alkyl), -C(O)N(C₁-C₆ alkyl)₂, -(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-O-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-S-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-S(O)₂-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), C₁-C₆ internally substituted alkyl, C₁-C₆ internally substituted haloalkyl, C₁-C₆ internally substituted alkyl(NH₂), C₃-C₈ internally substituted cycloalkyl, halo(C₁-C₆ internally substituted alkoxy), -O(C₁-C₆ internally substituted alkyl), S(C₁-C₆ internally substituted alkyl), -NH(C₁-C₆ internally substituted alkyl), -N(C₁-C₆ internally substituted alkyl)₂, -C(O)(C₁-C₆ internally substituted alkyl), -SO₂(C₁-C₆ internally substituted alkyl), -S(O)(C₁-C₆ internally substituted alkyl), -(C₁-C₆

internally substituted alkyl)S(O)(C₁-C₆ internally substituted alkyl), -S(O)₂(C₁-C₆ internally substituted alkyl), -(C₁-C₆ internally substituted alkyl)S(O)₂(C₁-C₆ internally substituted alkyl), -(C₁-C₆ internally substituted alkyl)N(C₁-C₆ internally substituted alkyl)SO₂(C₁-C₆ internally substituted alkyl), -N(C₁-C₆ internally substituted alkyl)SO₂(C₁-C₆ internally substituted alkyl),

5 -SO₂N(C₁-C₆ internally substituted alkyl)₂, -(C₁-C₆ internally substituted alkyl)SO₂N(C₁-C₆ internally substituted alkyl)₂, -NHCOO(C₁-C₆ internally substituted alkyl), -NHCO(C₁-C₆ internally substituted alkyl), -NHCONH(C₁-C₆ internally substituted alkyl), -CO₂(C₁-C₆ internally substituted alkyl), -C(O)N(C₁-C₆ internally substituted alkyl)₂, -(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₅ internally substituted alkyl)-

10 O-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₅ internally substituted alkyl)-S-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), and -(C₀-C₅ internally substituted alkyl)-S(O)₂-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), wherein said R^A C₁-C₆ internally substituted alkyl, C₁-C₆ internally substituted haloalkyl, C₁-C₆ internally substituted alkyl(NH₂), C₃-C₈ internally substituted cycloalkyl, halo(C₁-C₆ internally substituted alkoxy), -O(C₁-C₆ internally substituted alkyl), S(C₁-C₆ internally substituted alkyl), -NH(C₁-C₆ internally substituted alkyl), -N(C₁-C₆ internally substituted alkyl)₂, -C(O)(C₁-C₆ internally substituted alkyl), -SO₂(C₁-C₆ internally substituted alkyl), -S(O)(C₁-C₆ internally substituted alkyl), -(C₁-C₆ internally substituted alkyl)S(O)(C₁-C₆ internally substituted alkyl), -S(O)₂(C₁-C₆ internally substituted alkyl), -(C₁-C₆ internally substituted alkyl)S(O)₂(C₁-C₆ internally substituted alkyl), -(C₁-C₆ internally substituted alkyl)N(C₁-C₆ internally substituted alkyl)SO₂(C₁-C₆ internally substituted alkyl), -N(C₁-C₆ internally substituted alkyl)SO₂(C₁-C₆ internally substituted alkyl), -SO₂N(C₁-C₆ internally substituted alkyl)₂, -(C₁-C₆ internally substituted alkyl)SO₂N(C₁-C₆ internally substituted alkyl)₂, -NHCOO(C₁-C₆ internally substituted alkyl), -NHCO(C₁-C₆ internally substituted alkyl), -NHCONH(C₁-C₆ internally substituted alkyl), -CO₂(C₁-C₆ internally substituted alkyl), -C(O)N(C₁-C₆ internally substituted alkyl)₂, -(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₅ internally substituted alkyl)-O-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₅ internally substituted alkyl)-S-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), and -(C₀-C₅ internally substituted alkyl)-S(O)₂-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl) groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N, two R^A may be taken, together with the atoms to which they are bound, to form a ring having from three to fifteen ring atoms. In aspects of this

embodiment, each R^A is independently selected from the group consisting of H, F, Cl, Br, I, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkyl(NH₂), phenyl, naphthyl, C₃-C₈ cycloalkyl, halo(C₁-C₆ alkoxy), -O(C₁-C₆ alkyl), SH, S(C₁-C₆ alkyl), NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(O)(C₁-C₆ alkyl), -CONH₂, -SO₂NH₂, NO₂, CN, -CF₃, -CHF₂, -CH₂F, -OCHF₂, -OCF₃, -OCH₂F, -SO₂(C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), -SO₂N(C₁-C₆ alkyl)₂, -(C₁-C₆ alkyl)SO₂N(C₁-C₆ alkyl)₂, -NHCOO(C₁-C₆ alkyl), -NHCO(C₁-C₆ alkyl), -NHCONH(C₁-C₆ alkyl), -CO₂(C₁-C₆ alkyl), -C(O)N(C₁-C₆ alkyl)₂, -(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-O-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-S-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), and -(C₀-C₅ alkyl)-S(O)₂-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), wherein two R^A may be taken, together with the atoms to which they are bound, to form a ring having from three to fifteen ring atoms. In all aspects of this embodiment, all other groups are as provided in the general formula above or in the first through eighteenth embodiments.

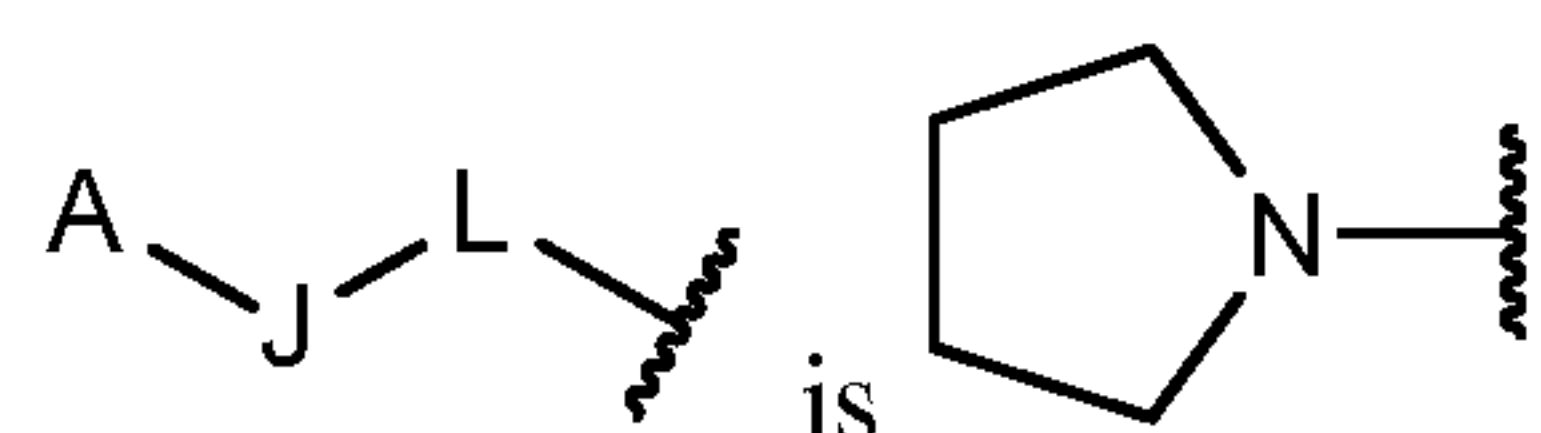
15 In a twentieth embodiment of the invention, L is selected from the group consisting of (CH₂)₀₋₄ and N(R^L). In aspects of the embodiment, L is NH. In all aspects of this embodiment, all other groups are as provided in the general formula above or in the first through nineteenth embodiments.

20 In a twenty-first embodiment of the invention, each R^L is independently selected from the group consisting of H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkyl(NH₂), aryl, C₃-C₈ cycloalkyl, halo(C₁-C₆ alkoxy), Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₆ alkyl(aryl) groups, C₁-C₆ internally substituted alkyl, C₁-C₆ internally substituted haloalkyl, C₁-C₆ internally substituted alkoxy, C₁-C₆ internally substituted alkyl(NH₂), aryl, C₃-C₈ internally substituted cycloalkyl, halo(C₁-C₆ internally substituted alkoxy), and C₁-C₆ internally substituted alkyl(aryl), wherein said R^L Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₆ internally substituted alkyl, C₁-C₆ internally substituted haloalkyl, C₁-C₆ internally substituted alkoxy, C₁-C₆ internally substituted alkyl(NH₂), aryl, C₃-C₈ internally substituted cycloalkyl, halo(C₁-C₆ internally substituted alkoxy), and C₁-C₆ internally substituted alkyl(aryl) groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N, each R^L aryl group is independently selected from the group consisting of 5- and 6-membered aromatic rings. In aspects of the embodiment, each R^L is independently selected from the group consisting of H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkyl(NH₂), aryl, C₃-C₈ cycloalkyl, halo(C₁-C₆ alkoxy), Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, and C₁-C₆ alkyl(aryl) groups, wherein

said R^L $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, and $Si(CH_3)_3$ groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N, each R^L aryl group is independently selected from the group consisting of 5- and 6-membered aromatic rings. In particular aspects of this embodiment, each R^L is independently selected from the group consisting of H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkyl(NH₂), aryl, C₃-C₈ cycloalkyl, halo(C₁-C₆ alkoxy), and C₁-C₆ alkyl(aryl) groups, wherein each R^L aryl group is independently selected from the group consisting of 5- and 6-membered aromatic rings. In all aspects of this embodiment, all other groups are as provided in the general formula above or in the first through twentieth embodiments.

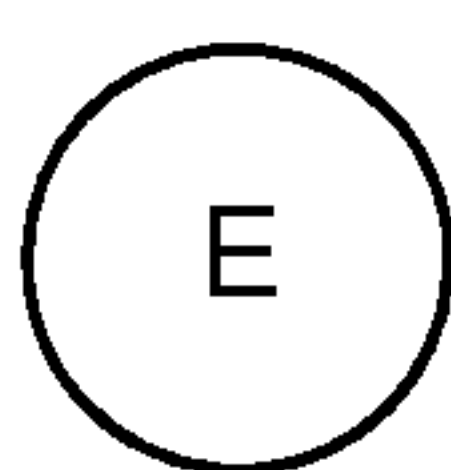
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In a twenty-second embodiment of the invention,



In all aspects of this embodiment, all other groups are as provided in the general formula above or in the first through twenty-first embodiments.

In another embodiment, for the compounds of formula I, each instance of



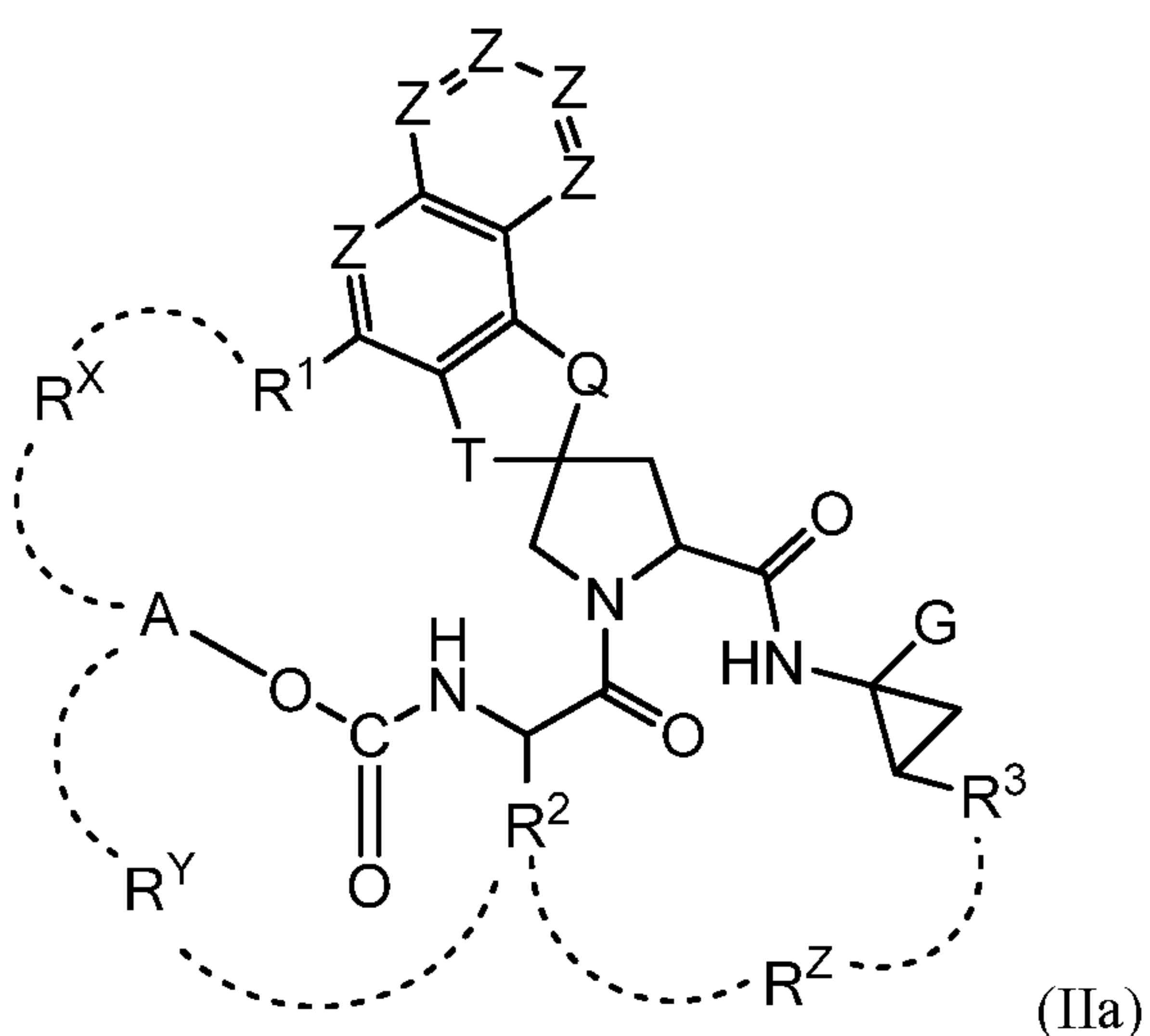
variables E , A , J , L , G , T , Q , Z , R^1 , R^2 , R^3 , R^4 , R^A , R^J , R^L , R^G , R^{G1} and m are each selected independently from each other.

15

For the second aspect, wherein the compound is compound of General Formula II:

In a first (1) embodiment, the compound of Formula II is a compound of Formula

IIa:



20

or a pharmaceutically acceptable salt thereof,

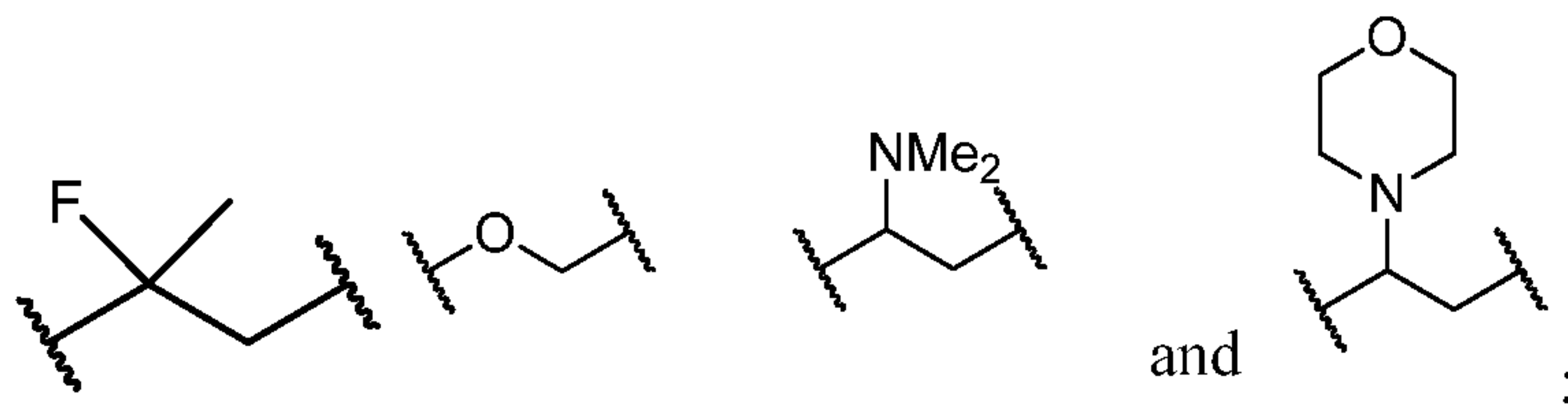
wherein

each Z is independently either N or C-R⁴;

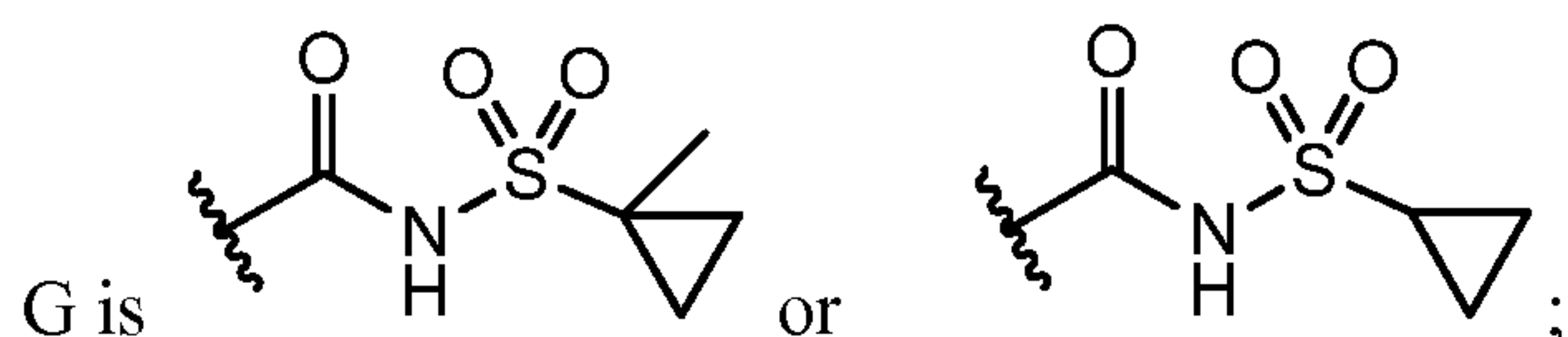
A is selected from the group consisting of:

- 5 a) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₆-C₈ bridged cycloalkyl, or C₆-C₈ bridged cycloalkenyl,
- b) substituted C₁-C₈ alkyl, substituted C₂-C₈ alkenyl, substituted C₂-C₈ alkynyl, substituted C₃-C₈ cycloalkyl, substituted C₆-C₈ bridged cycloalkyl, or substituted C₆-C₈ bridged cycloalkenyl, each of which is substituted with 0, 1, 2, 3 or 4 R^A, and 0 or 1 R^B, provided
- 10 that at least one R^A or R^B substituent is present;
- c) C₁-C₈ haloalkyl, C₃-C₈ halocycloalkyl, or C₁-C₈ haloalkyl substituted with R^B,
- d) Aryl, and
- e) Het;

15 Q is selected from the group consisting of -(CH₂)₂-,  and



T is selected from the group consisting of O, -(CH₂)_{q2}-, NH, SO₂ and S, wherein q₂ is 1 or 2;



20 R¹ is hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl-R^B, Aryl, or Het;

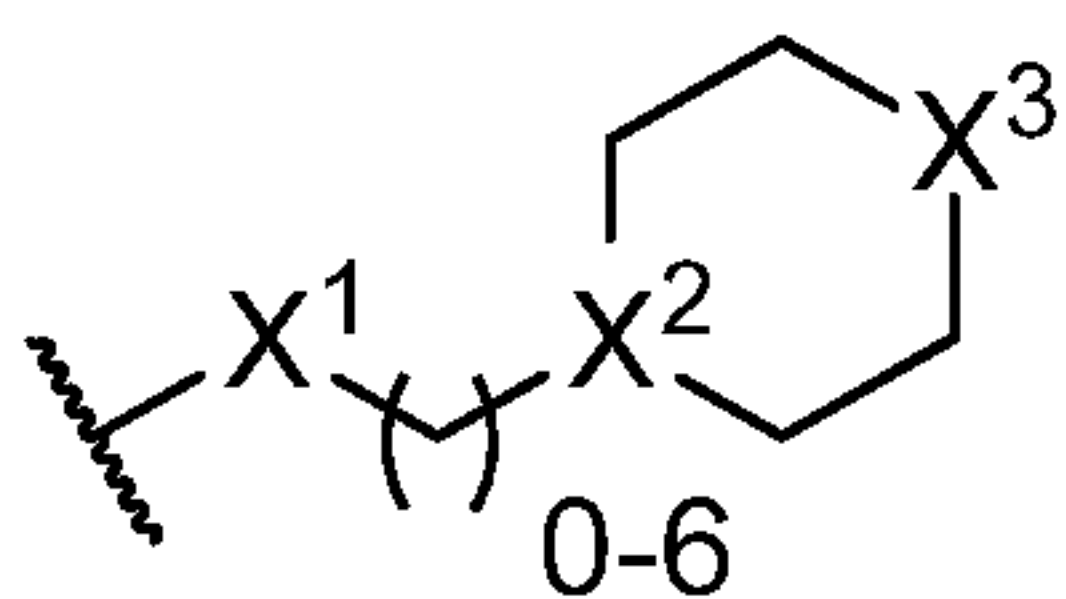
R² is selected from the group consisting of C₁-C₉ alkyl, C₂-C₉ alkenyl, C₂-C₉ alkynyl, C₃-C₈ cycloalkyl, Het, and Aryl;

R³ is selected from the group consisting of C₁-C₉ alkyl, C₂-C₉ alkenyl, and C₂-C₉ alkynyl:

25 each R⁴ is independently selected from the group consisting of:

hydrogen, halogen, OH, C₁-C₆ alkyl, C₁-C₄ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy,

C₁-C₆ alkyl-R^B, C₁-C₆ haloalkyl-R^B, C₁-C₆ alkoxy-R^B, C₁-C₆ haloalkoxy -R^B,
 C₃-C₈ cycloalkyl, C₃-C₈ cycloalkoxy, C₃-C₈ cycloalkyl-C₁-C₉ alkyl, C₁-C₆ hydroxyalkyl,
 O- C₁-C₆ hydroxyalkyl, O- C₁-C₆ alkyl-R^B, CN, O-(C₁-C₅ alkyl)-O-(C₁-C₃ alkyl),
 O-(C₁-C₅ alkyl)-O-(C₁-C₃ alkyl)-R^B, -(C₀-C₃ alkyl)-O-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl),
 5 -(C₀-C₃ alkyl)-S-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S(O)₂-(C₀-C₃ alkyl)-(C₃-C₈
 cycloalkyl), Het, Aryl, and



, wherein X¹ is either CH₂, NH, O, or S; X² is either CH or N; and X³ is
 either NH, N-R⁵, CH₂, CH-R⁵, O, or S;

provided that two R⁴ groups can join together form methylene dioxy;

10 each R^A is independently selected from the group consisting of: F, Cl,
 Br, I, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkyl(NH₂), C₆-C₈ bridged
 cycloalkyl, C₃-C₈ cycloalkyl, C₁-C₆ haloalkoxy, C₃-C₈ halocycloalkyl, SH, S(C₁-C₆ alkyl), NH₂,
 NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, C(O)(C₁-C₆ alkyl), C(O)(C₃-C₈ cycloalkyl), CONH₂, SO₂NH₂,
 NO₂, CN, CF₃, CHF₂, CH₂F, OCHF₂, OCF₃, OCH₂F, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), -(C₁-
 15 C₆ alkyl)S(O)(C₁-C₆ alkyl), SO₂(C₃-C₆ cycloalkyl), -(C₁-C₆ alkyl)S(O)₂(C₁-C₆ alkyl), -(C₁-C₆
 alkyl)N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl),
 SO₂N(C₁-C₆ alkyl)₂, -(C₁-C₆ alkyl)SO₂N(C₁-C₆ alkyl)₂, NHCOO(C₁-C₆ alkyl),
 NHCO(C₁-C₆ alkyl), NHCONH(C₁-C₆ alkyl), CO₂(C₁-C₆ alkyl), C(O)N(C₁-C₆ alkyl)₂,
 -(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-O-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl),
 20 -(C₀-C₅ alkyl)-S-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-S(O)₂-(C₀-C₅ alkyl)-(C₃-C₈
 cycloalkyl), Aryl, and Het; provided that two R^A groups present on adjacent carbon atoms can
 together with the adjacent carbon atoms form a C₃-C₆ cycloalkyl;

each R^B is independently either phenyl or a 5- or 6-membered saturated or
 unsaturated monocyclic ring with 1, or 2 heteroatom ring atoms independently selected from the
 25 group consisting of N, O and S, R^B may be substituted with 1 or 2 independently selected R^C;

each R^C is independently either halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl,
 or C₁-C₆ haloalkyl;

each Aryl is independently phenyl optionally substituted with 1 or 2
 independently selected R^C;

each Het is independently a 4-, 5- or 6-membered saturated or unsaturated monocyclic rings with 1 or 2 heteroatom ring atoms independently selected from the group consisting of N, O and S; provided that said Het is optionally substituted with 1 or 2 independently selected R^C substituents;

5 R^X if present, is a C₃-C₈ alkylene, C₃-C₈ alkenylene, or C₃-C₈ alkynylene, formed between A and R¹,

R^Y if present, is a C₃-C₈ alkylene, C₃-C₈ alkenylene, C₃-C₈ alkynylene, formed between A and R²,

10 R^Z if present, is a C₃-C₈ alkylene, C₃-C₈ alkenylene, or C₃-C₈ alkynylene, formed between R² and R³,

provided that either (a) R^X is present, R^Y is not present and R^Z is not present; (b) R^Y is present, R^X is not present and R^Z is not present; (c) R^Z is present, R^X is not present and R^Y is not present; or (d) R^X and R^Z are present, and R^Y is not present.

15 In a second (2) embodiment R^X is present, R^Y is not present and R^Z is not present, and the other variables are as provided in the first embodiment.

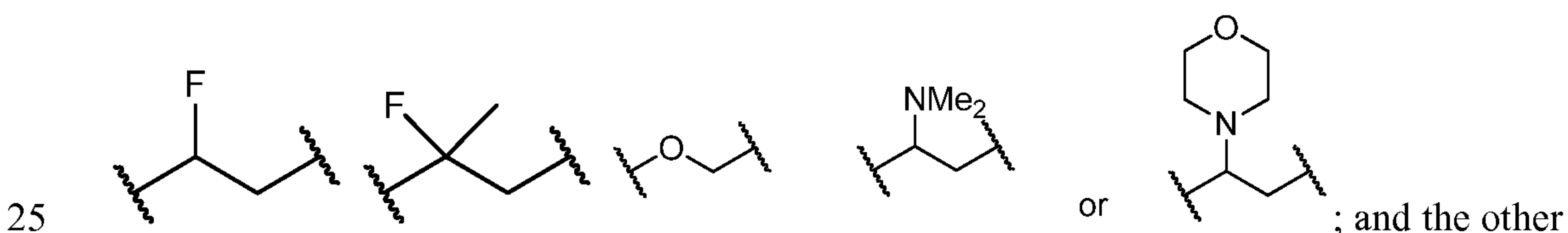
In a third (3) embodiment R^Y is present, R^X is not present and R^Z is not present, and the other variables are as provided in the first embodiment.

In a fourth (4) embodiment R^Z is present, R^X is not present and R^Y is not present; and the other variables are as provided in the first embodiment.

20 In a fifth (5) embodiment R^X and R^Z are present, and R^Y is not present. and the other variables are as provided in the first embodiment.

In a sixth (6) embodiment T is O and the other variables are as provided in general Formula II, or any of embodiments 1 to 5.

In a seventh (7) embodiment Q is either -(CH₂)₂-,



variables are as provided in general Formula II, or any of embodiments 1 to 6.

In an eight (8) embodiment A is selected from the group consisting of

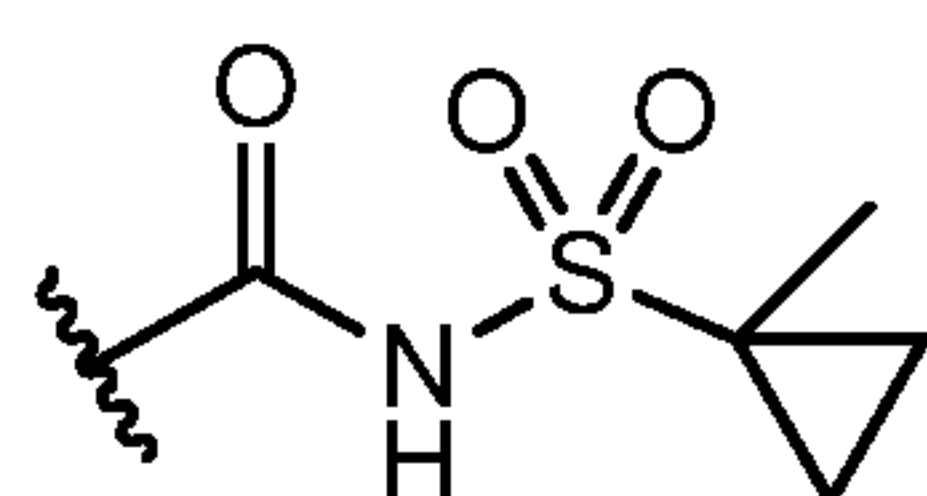
a) C₁-C₆ alkyl, C₃-C₈ cycloalkyl, or C₆-C₈ bridged cycloalkyl,

b) substituted C₁-C₆ alkyl, substituted C₃-C₈ cycloalkyl, or substituted C₆-C₈ bridged cycloalkyl, each of which contains 0 or 1 R^A and 0 or 1 R^B, provided that at least one R^A or R^B substituent is present;

c) Aryl; and

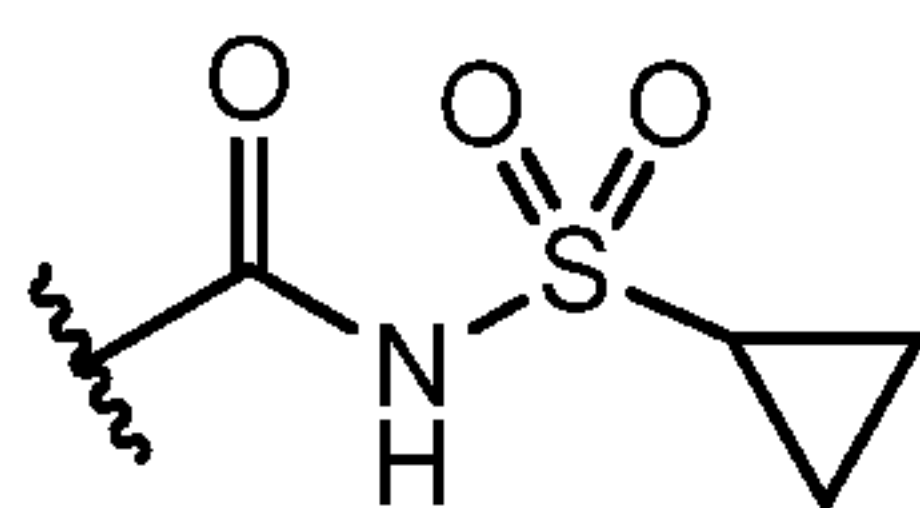
5 d) Het; and the other variables are as provided in general Formula II, or any of embodiments 1 to 7.

In ninth (9) embodiment G is



and the other variables are as provided in general Formula II, or any of
embodiments 1 to 8.

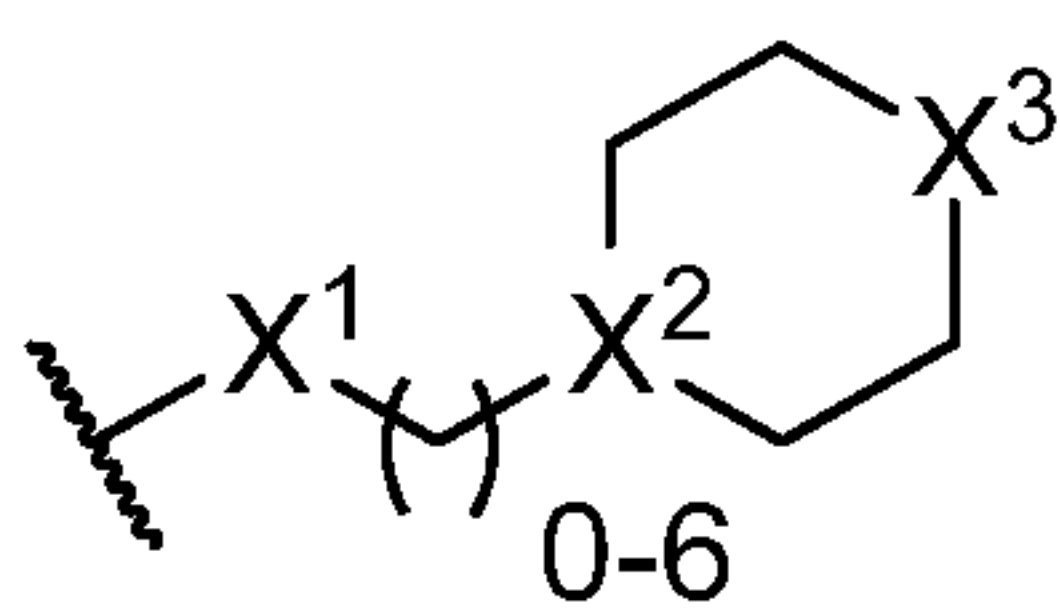
10 In a tenth (10) embodiment G is



and the other variables are as provided in general Formula II, or any of
embodiments 1 to 8.

In an eleventh (11) embodiment R¹ is either hydrogen, C₁-C₆ alkyl, C₃-C₈
cycloalkyl, C₁-C₄ haloalkyl, CF₃, CH₂CF₃, CF₂, CH₃, cyclopropyl, Aryl, or Het; and the other
15 variables are as provided in general Formula II, or any of embodiments 1 to 10.

In a twelfth (12) embodiment each R⁴ is independently selected from the group
consisting of: hydrogen, F, Cl, OH, C₁-C₆ alkyl, C₁-C₂ haloalkyl, CF₃, CH₂-CF₃, CF₂-CH₃,
CF₃, C₁-C₆ alkoxy, C₁-C₄ haloalkoxy, C₁-C₆ alkyl-R^B, C₃-C₈ cycloalkyl, Het, Aryl and



, wherein X¹ is either CH₂, NH, O, or S; X² is either CH or N; and X³ is
20 either NH, N-R⁵, CH₂, CH-R⁵, O, or S; and the other variables are as provided in general
Formula II, or any of embodiments 1 to 11.

In a thirteenth (13) embodiment, each Aryl is independently phenyl optionally
substituted with 1 or 2 independently selected R^C; and the other variables are as provided in
general Formula II, or any of embodiments 1 to 12

25 In a fourteenth (14) embodiment, each Het is independently a 4-, 5- or 6-
membered saturated or unsaturated monocyclic ring with 1 or 2 heteroatom ring atoms
independently selected from the group consisting of N, O and S; provided that said Het is

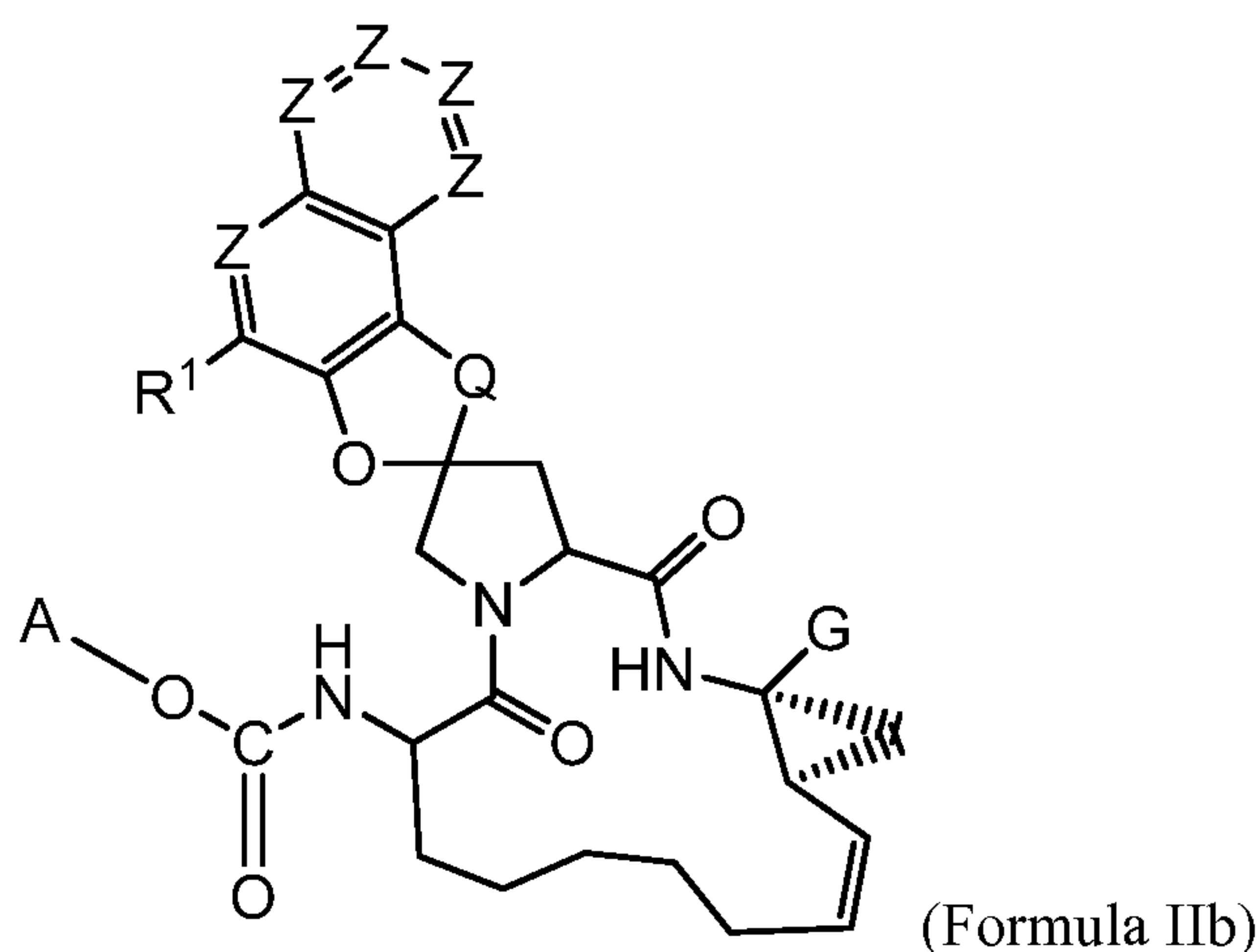
optionally substituted with 1 or 2 independently selected R^C ; and the other variables are as provided in general Formula II, or any of embodiments 1 to 13.

In a fifteenth (15) embodiment each R^A is independently selected from the group consisting of: F, Cl, OH, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_3 - C_8 halocycloalkyl, and C_1 - C_6 haloalkoxy; and the other variables are as provided for in any of embodiments 1 to 14.

In a sixteenth (16) embodiment each R^B is independently either phenyl or 5- or 6-membered saturated or a unsaturated monocyclic ring with 1, or 2 heteroatom ring atoms independently selected from the group consisting of N, O and S, R^B may be substituted with 1 or 2 independently selected R^C ; and the other variables are as provided in general Formula II, or any of embodiments 1 to 15.

In a seventieth (17) embodiment each R^C is independently either halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl or C_1 - C_6 haloalkyl and the other variables are as provided in general Formula II, or any of embodiments 1 to 16.

In an eighteenth (18) embodiment, the compound is a compound of Formula IIa is a compound of Formula IIb:



or a pharmaceutically acceptable salt thereof, wherein

each Z is independently either N or C- R^4 ;

A is a selected from the group consisting of

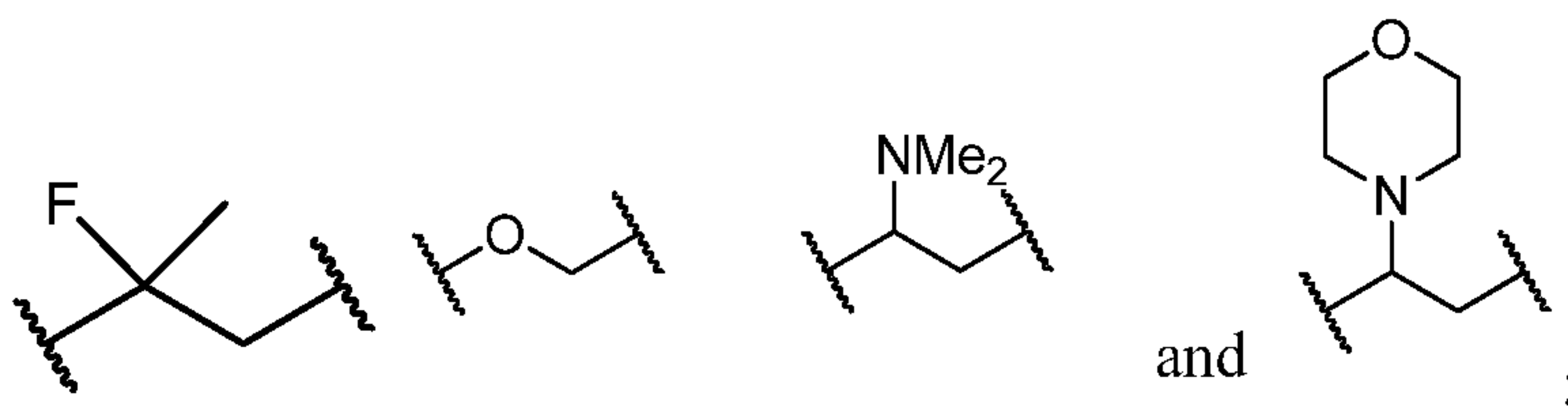
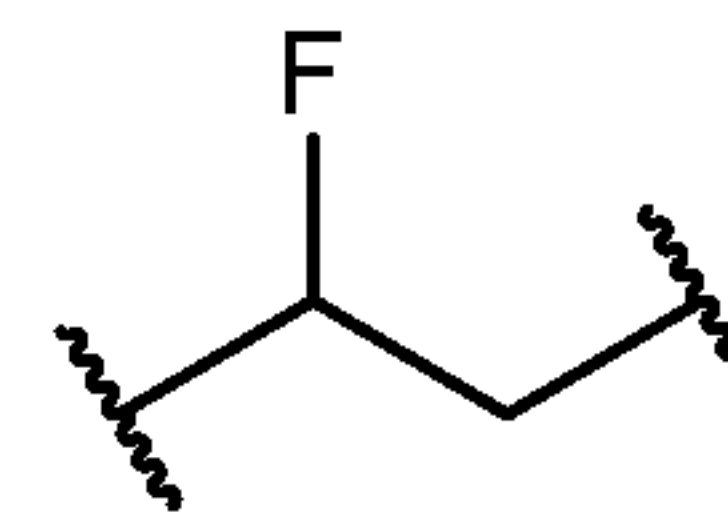
a) C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, or C_6 - C_8 bridged cycloalkyl,

b) substituted C_1 - C_6 alkyl, substituted C_3 - C_8 cycloalkyl, or substituted C_6 - C_8 bridged cycloalkyl, each of which contains 0 or 1 R^A and 0 or 1 R^B , provided that at least one R^A or R^B substituent is present;

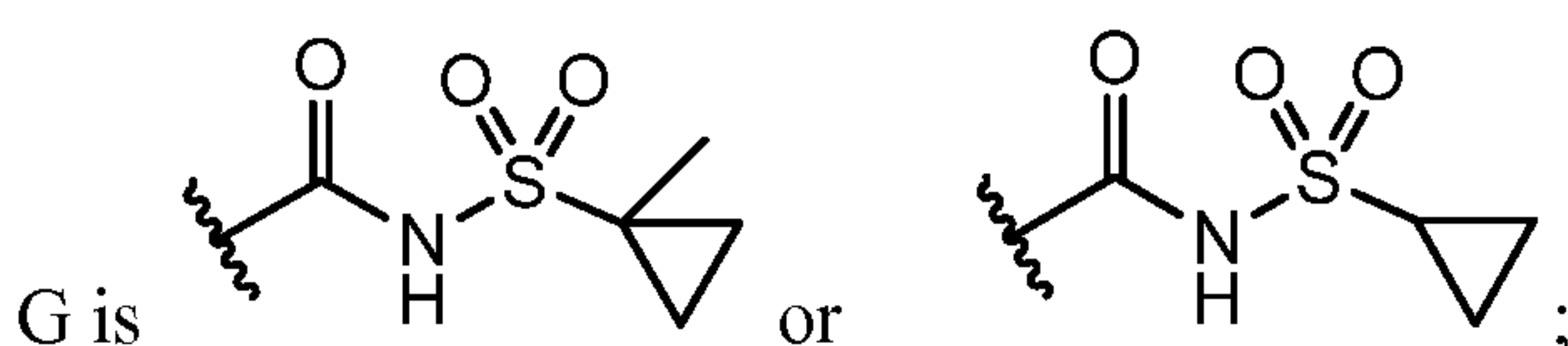
c) Aryl; and

d) Het;

Q is selected from the group consisting of selected from $-(\text{CH}_2)_2-$,



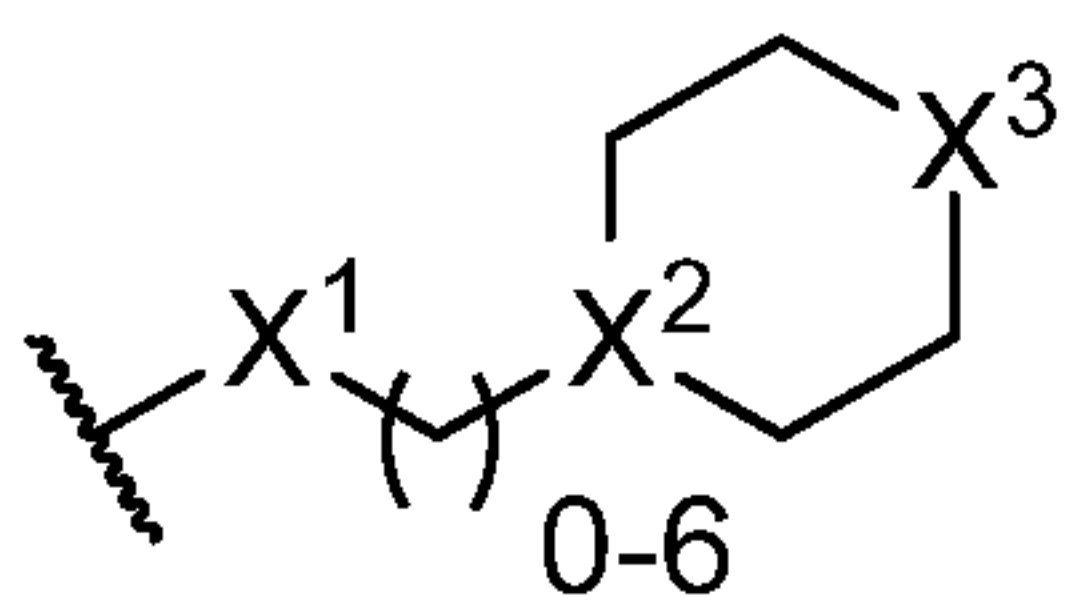
5



R^1 is either hydrogen, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_1 - C_4 haloalkyl, CF_3 , CH_2CF_3 , CF_2 , CH_3 , cyclopropyl, Aryl, or Het;

each R^4 is independently selected from the group consisting of:

10 hydrogen, F, Cl, OH, C_1 - C_6 alkyl, C_1 - C_2 haloalkyl, CF_3 , $\text{CH}_2\text{-CF}_3$, $\text{CF}_2\text{-CH}_3$, CF_3 , C_1 - C_6 alkoxy, C_1 - C_4 haloalkoxy, C_1 - C_6 alkyl- R^B , C_3 - C_8 cycloalkyl, Het, Aryl and



, wherein X^1 is either CH_2 , NH, O, or S; X^2 is either CH or N; and X^3 is either NH, N-R^5 , CH_2 , CH-R^5 , O, or S;

each Aryl is independently phenyl optionally substituted with 1 or 2

15 independently selected R^C ,

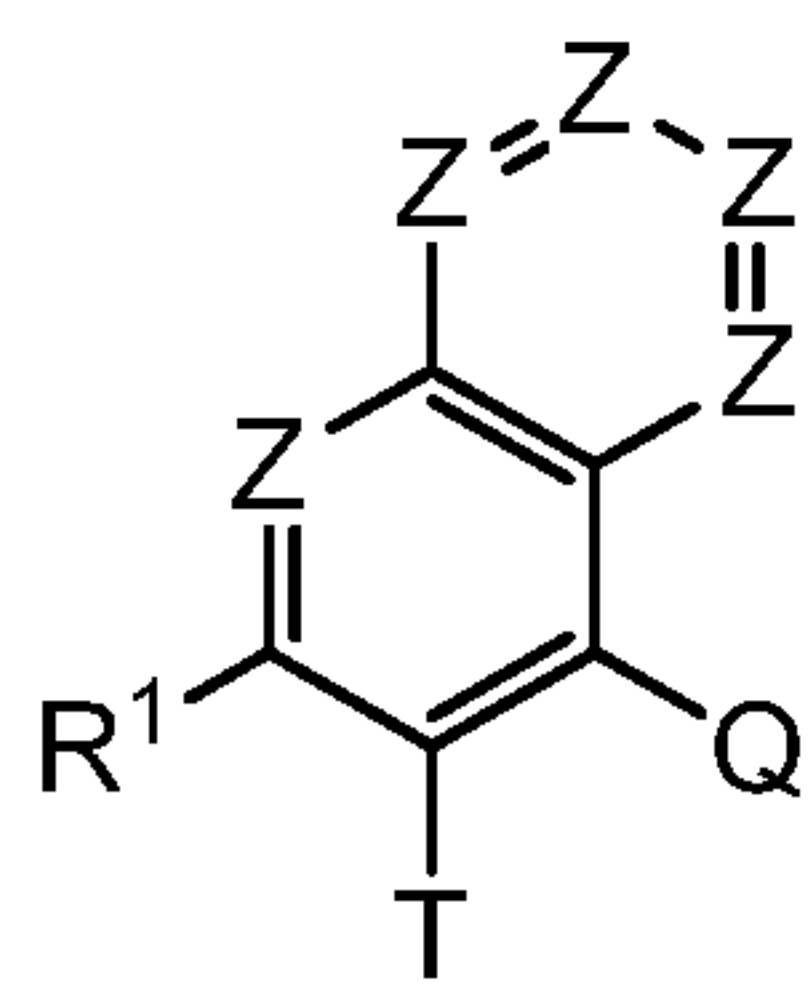
each Het is independently a 4-, 5- or 6-membered saturated or unsaturated monocyclic ring with 1 or 2 heteroatom ring atoms independently selected from the group consisting of N, O and S; provided that said Het is optionally substituted with 1 or 2 independently selected R^C ,

20 each R^A is independently selected from the group consisting of: F, Cl, OH, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_3 - C_8 halocycloalkyl, and C_1 - C_6 haloalkoxy;

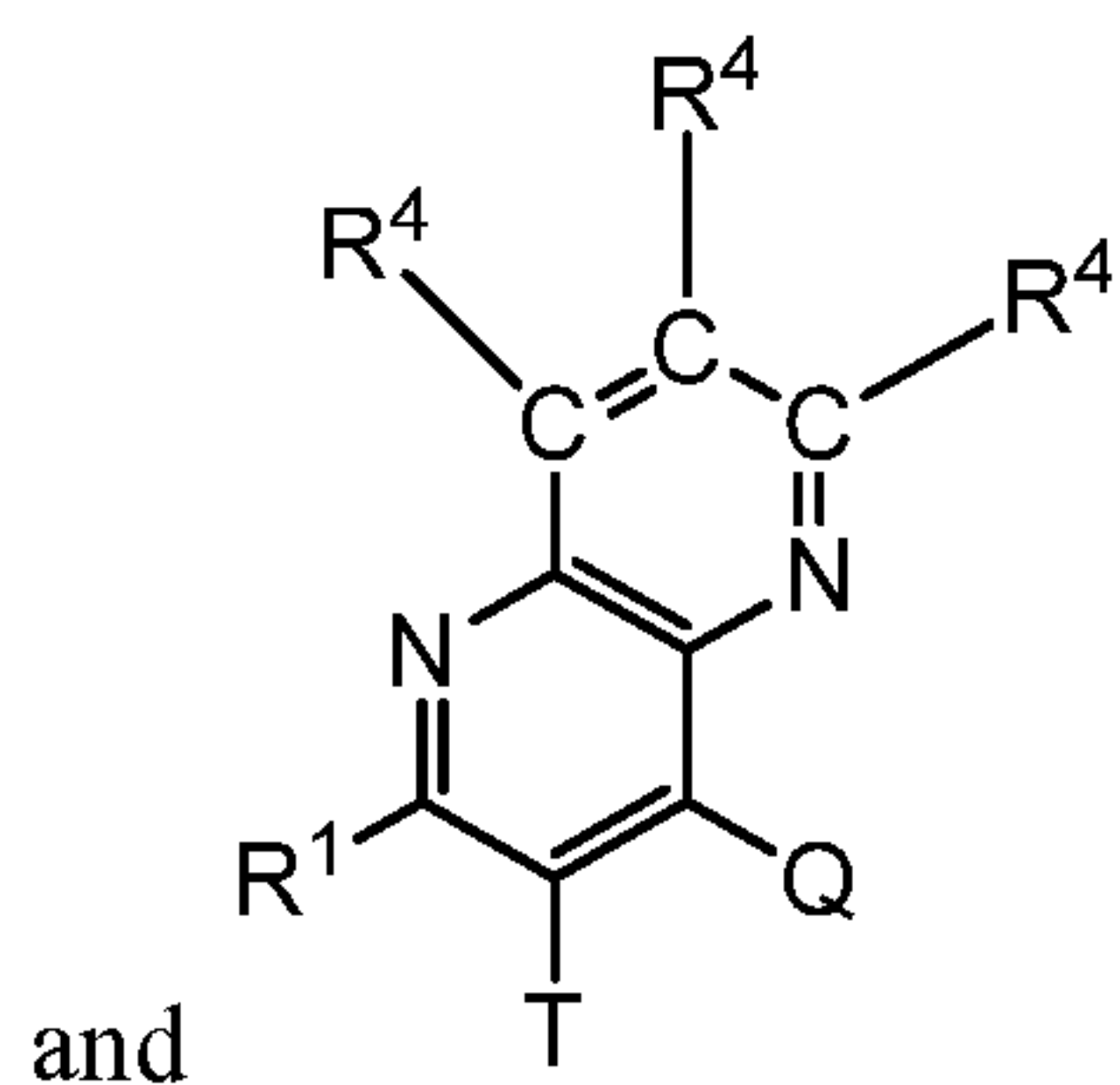
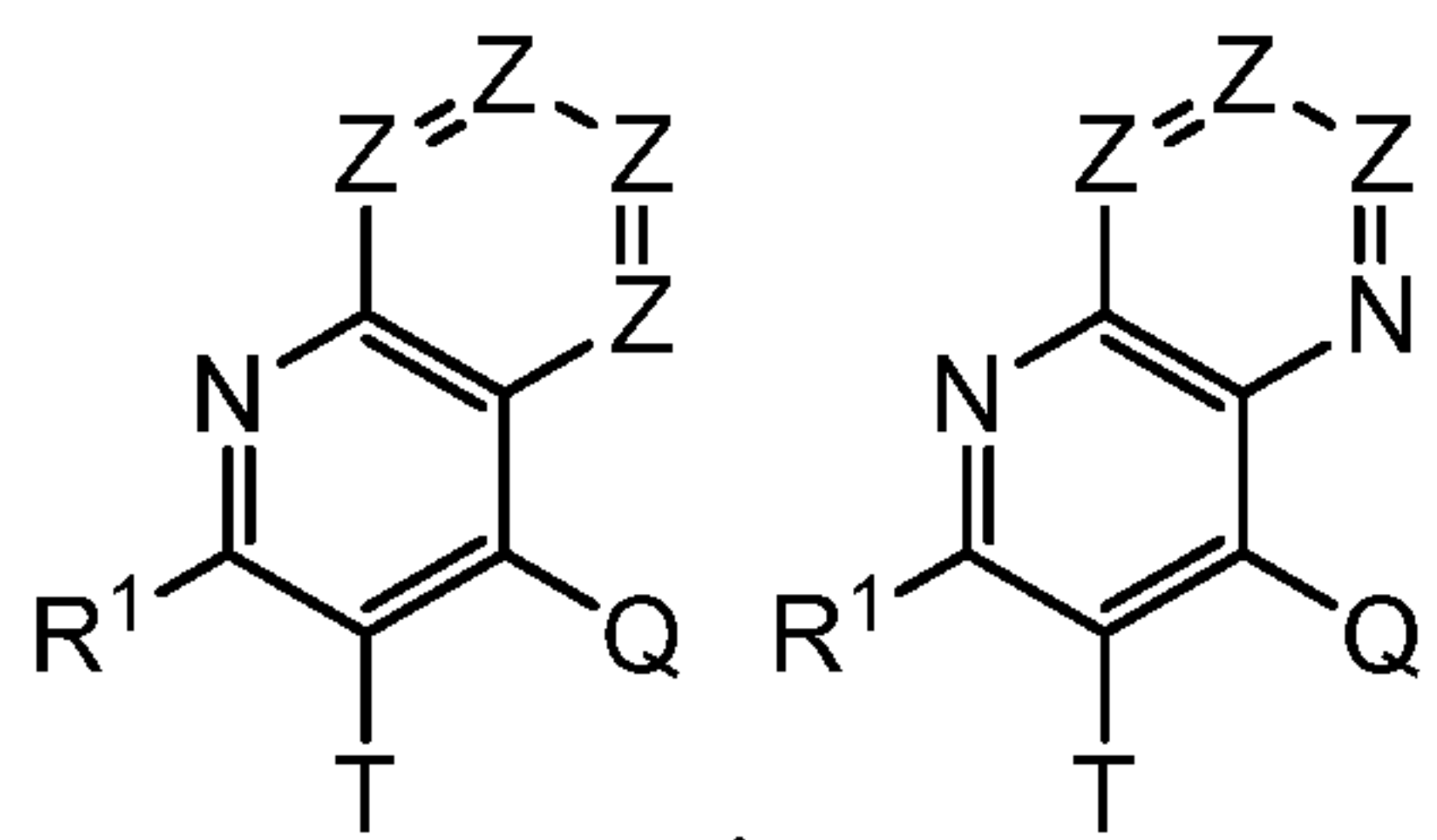
each R^B is independently either phenyl or 5- or 6-membered saturated or a
unsaturated monocyclic ring with 1, or 2 heteroatom ring atoms independently selected from the
group consisting of N, O and S, R^B may be substituted with 1 or 2 independently selected R^C;

each R^C is independently either halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl
5 or C₁-C₆ haloalkyl.

In a ninetieth (19) embodiment,



is selected from the group consisting of;

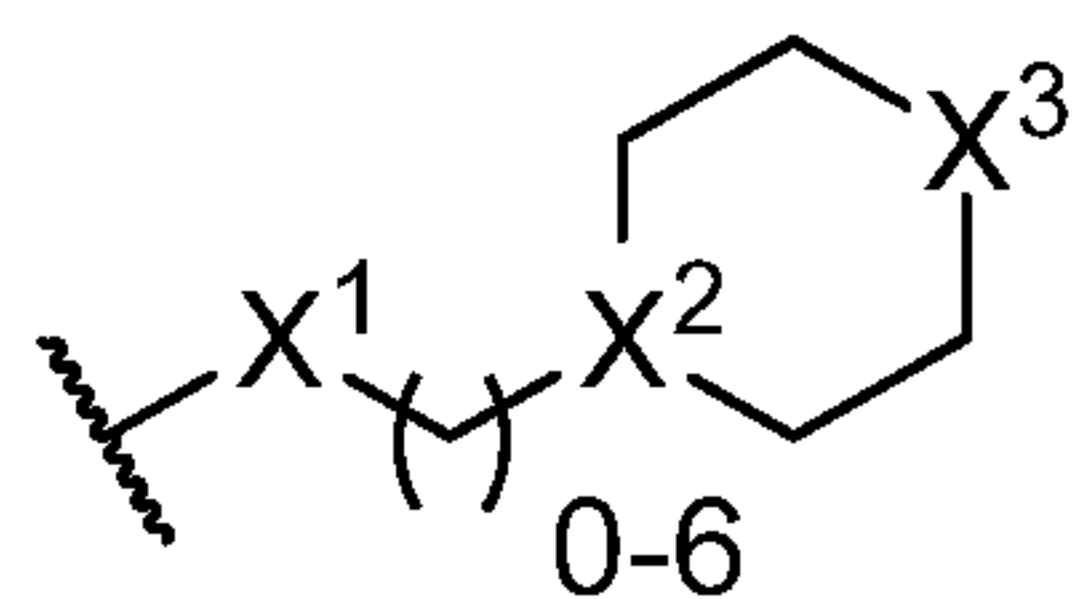


and

wherein each Z is independently either N or C-R⁴,

10 each R⁴ is independently selected from the group consisting of:

hydrogen, F, Cl, OH, C₁-C₆ alkyl, C₁-C₂ haloalkyl, CF₃, CH₂-CF₃, CF₂-CH₃,
CF₃, C₁-C₆ alkoxy, C₁-C₄ haloalkoxy, C₁-C₆ alkyl-R^B, C₃-C₈ cycloalkyl Het, Aryl, and



, wherein X¹ is either CH₂, NH, O, or S; X² is either CH or N; and X³ is
either NH, N-R⁵, CH₂, CH-R⁵, O, or S;

15 each Aryl is independently phenyl optionally substituted with 1 or 2
independently selected R^C;

each Het is independently a 4-, 5- or 6-membered saturated or unsaturated
monocyclic ring with 1 or 2 heteroatom ring atoms independently selected from the group
consisting of N, O and S; provided that said Het is optionally substituted with 1 or 2

20 independently selected R^C;

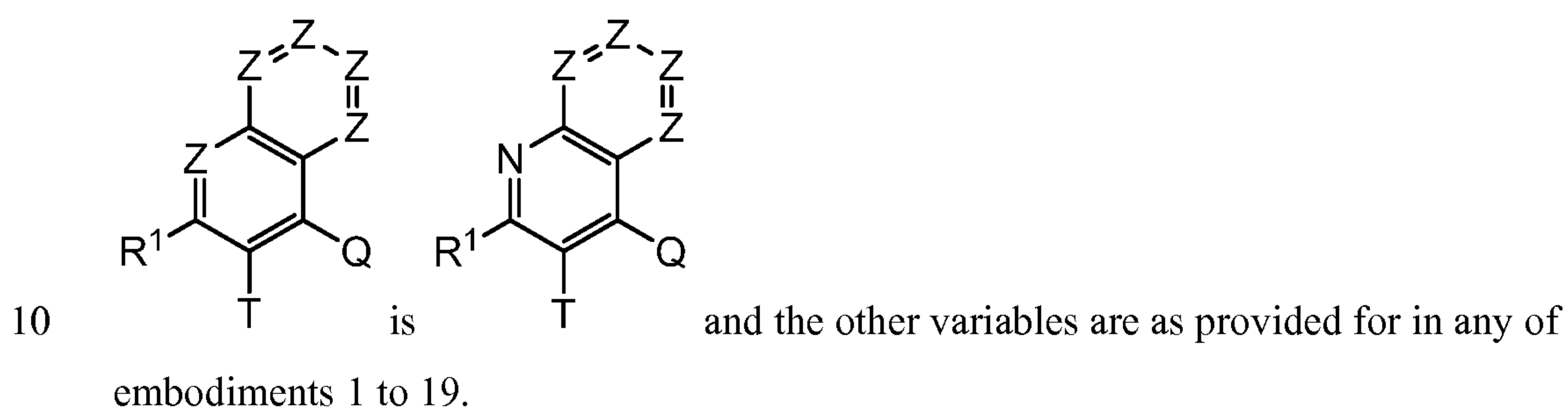
each R^A is independently selected from the group consisting of

F, Cl, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₃-C₈ halocycloalkyl, and C₁-C₆ haloalkoxy;

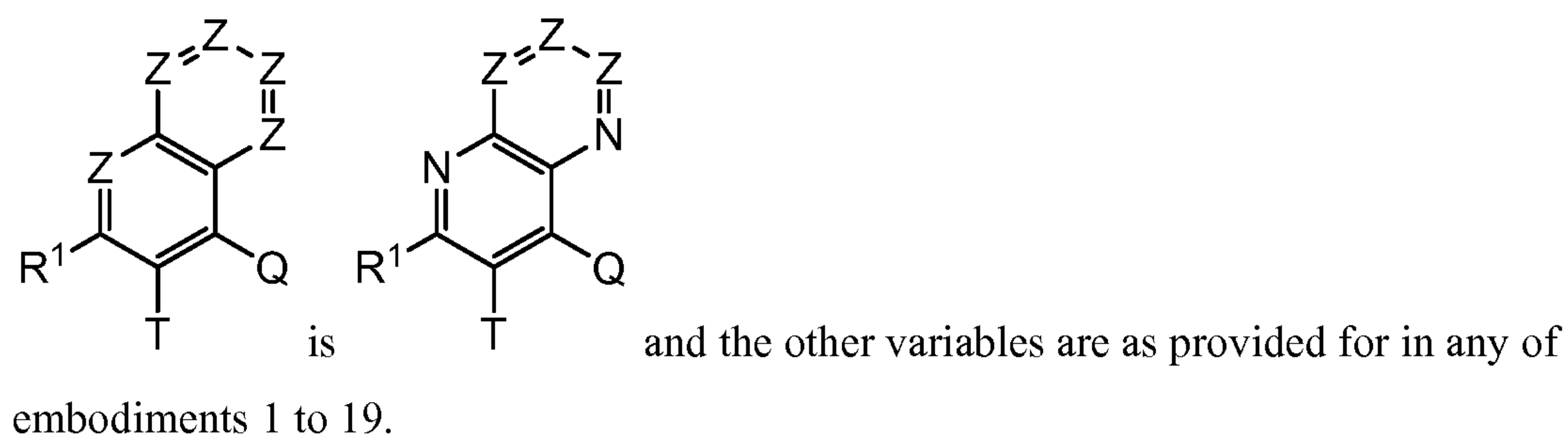
each R^B is independently either phenyl or a 5- or 6-membered saturated or unsaturated monocyclic ring with 1, or 2 heteroatom ring atoms independently selected from the group consisting of N, O and S, wherein R^B may be substituted with 1 or 2 independently selected R^C; and

each R^C is independently either halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl or C₁-C₆ haloalkyl; and the other variables are as provided in any of embodiments 1 to 18.

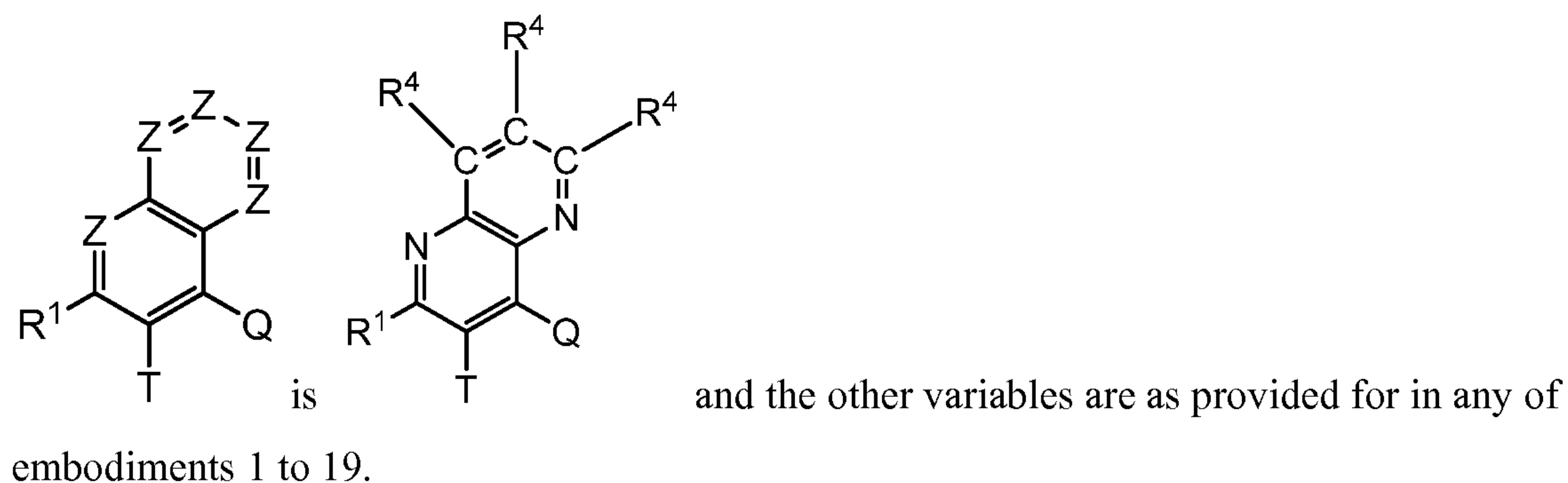
In a twentieth (20) embodiment,



In a twenty first (21) embodiment,

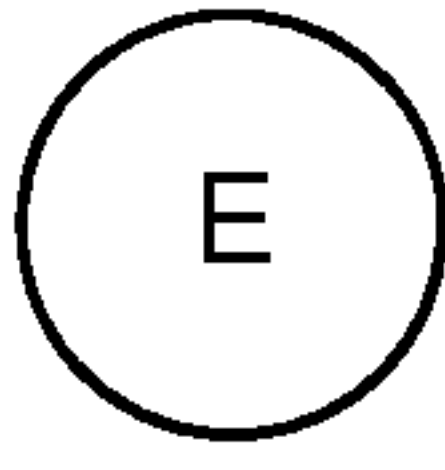


15 In a twenty second embodiment,



20 A particular embodiment referring to a prior embodiment further incorporates all applicable embodiments referred to in the prior embodiment. Applicable embodiments are those consistent with the groups specified in the particular embodiment.

In another embodiment, for the compounds of Formula II, each instance of

variables , A, J, L, G, T, Q, Z, R¹, R², R³, R⁴, R^A, R^J, R^L, R^G, R^{G1} and m are each selected independently from each other.

In another embodiment of the invention, the compound of the invention is selected from the exemplary species depicted in Examples 1 through 527 shown below as I-1 through I-527, and pharmaceutically acceptable salts thereof. In particular aspects of this embodiment, the compound is selected from the group consisting of I-5, I-6, I-12, I-13, I-16, I-33, I-50, I-63, I-66, I-94, I-124, I-161, I-189, I-359 and I-509 and pharmaceutically acceptable salts thereof.

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of a compound of Formula I or II and a pharmaceutically acceptable carrier.

(b) The pharmaceutical composition of (a), further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(c) The pharmaceutical composition of (b), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors, inhibitors of HCV NS4A, inhibitors of HCV NS4B, inhibitors of HCV NS5A and inhibitors of HCV NS5B.

(d) A pharmaceutical combination that is (i) a compound of Formula I or II and (ii) a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents; wherein the compound of Formula I or II and the second therapeutic agent are each employed in an amount that renders the combination effective for inhibiting HCV NS3 protease, or for treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection.

(e) The combination of (d), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(f) A method of inhibiting HCV NS3 protease in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I or II.

(g) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I or II.

(h) The method of (g), wherein the compound of Formula I or II is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(i) The method of (h), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(j) A method of inhibiting HCV NS3 protease in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), or (c) or the combination of (d) or (e).

(k) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), or (c) or the combination of (d) or (e).

The present invention also includes a compound of the present invention for use (i) in, (ii) as a medicament for, or (iii) in the preparation of a medicament for: (a) inhibiting HCV NS3 protease, or (b) treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection. In these uses, the compounds of the present invention can optionally be employed in combination with one or more second therapeutic agents selected from HCV antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(k) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, aspects, classes, sub-classes, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt as appropriate.

In the embodiments of the compound provided above, it is to be understood that each embodiment may be combined with one or more other embodiments, to the extent that such a combination provides a stable compound and is consistent with the description of the embodiments. It is further to be understood that the embodiments of compositions and methods

provided as (a) through (k) above are understood to include all embodiments of the compounds, including such embodiments as result from combinations of embodiments.

The compound may be present in different forms including forms having one of more of the following attributes: salt, hydrate, solvate, crystal structure, and amorphous structure.

5 Specific embodiments of the present invention include a compound of the Examples or made according to the methods therein and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

When any variable (e.g. aryl, heterocycle, R etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also,
10 combinations of substituents or variables are permissible only if such combinations result in stable compounds.

Unless otherwise indicated, or clear from the context in which they appear, the following definitions providing below apply.

As used herein, the term "alkyl" refers to any linear or branched chain alkyl group
15 having a number of carbon atoms in the specified range. The term "C₁₋₆" includes alkyls containing 6, 5, 4, 3, 2, or 1 carbon atoms. Thus, for example, "C₁₋₆ alkyl" (or "C₁-C₆ alkyl") refers to all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. As another example, "C₁₋₄ alkyl" refers to n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. Alkyl groups may be substituted as indicated.

20 As used herein, the term "alkenyl" refers to any linear or branched chain alkyl group having a number of carbon atoms in the specified range and including at least one double bond. Alkenyl groups may be substituted as indicated.

As used herein, the term "alkynyl" refers to any linear or branched chain alkyl group having a number of carbon atoms in the specified range and including at least one triple
25 bond. Alkynyl groups may be substituted as indicated.

As used herein, the term "internally substituted alkyl" refers to any alkyl group containing at least one carbon atom and in which 0, 1, 2 or 3 additional carbon atoms are replaced by heteroatoms independently selected from the group consisting of B, O, S and N. The terms "internally substituted alkenyl" and "internally substituted alkynyl" refer respectively to
30 alkenyl and alkynyl groups containing at least two carbon atoms and in which 0, 1, 2 or 3 additional carbon atoms are replaced by heteroatoms independently selected from the group consisting of B, O, S and N. For example, "C₁₋₆ internally substituted alkyl" (or "C₁-C₆ internally substituted alkyl") includes such groups as -(CH₂)₄BHCH₃, -(CH₂)₃BHCH₂CH₃, -

(CH₂)₂BH(CH₂)₂CH₃, -CH₂BH(CH₂)₃CH₃, -(CH₂)₄OCH₃, -(CH₂)₃OCH₂CH₃,
 -(CH₂)₂O(CH₂)₂CH₃, -CH₂O(CH₂)₃CH₃, -(CH₂)₄SCH₃, -(CH₂)₃SCH₂CH₃, -(CH₂)₂S(CH₂)₂CH₃,
 -CH₂S(CH₂)₃CH₃, -(CH₂)₄NHCH₃, -(CH₂)₃NHCH₂CH₃, -(CH₂)₂NH(CH₂)₂CH₃, and
 -CH₂NH(CH₂)₃CH₃, as well as groups having additional internal substitutions, branched groups
 5 and groups containing fewer carbon atoms. Internally substituted alkyl, internally substituted
 alkenyl and internally substituted alkynyl groups may be substituted as indicated.

The term "alkylene" refers to any linear or branched chain alkylene group (or
 alternatively "alkanediyl") having a number of carbon atoms in the specified range. Thus, for
 example, "-C₁₋₆ alkylene" refers to any of the C₁ to C₆ linear or branched alkylenes. Examples of
 10 alkylenes include -(CH₂)₆-, -(CH₂)₅-, -(CH₂)₄-, -(CH₂)₃-, -(CH₂)₂-, -CH₂- and -CH(CH₃)-.
 Alkylene groups may be substituted as indicated.

The term "alkenylene" refers to any linear or branched chain alkenylene group
 containing a double bond and having a number of carbon atoms in the specified range. The term
 "alkynylene" refers to any linear or branched chain alkenylene group containing a triple bond and
 15 having a number of carbon atoms in the specified range. Thus, for example, "C₂₋₆ alkenylene"
 refers to any of the C₂ to C₆ linear or branched alkenylene and "C₂₋₆ alkynylene" refers to any of
 the C₂ to C₆ linear or branched alkynylene. Alkenylene and alkynylene groups may be
 substituted as indicated.

The term "cycloalkyl" refers to a saturated hydrocarbon containing one ring
 20 having a specified number of carbon atoms. Examples of cycloalkyl include cyclopropyl,
 cyclobutyl, cyclopentyl, and cyclohexyl.

The term "internally substituted cycloalkyl" refers to a saturated hydrocarbon
 containing one ring having a specified number of ring atoms and in which 0, 1, 2 or 3 carbon ring
 atoms are replaced by heteroatoms independently selected from the group consisting of B, O, S
 25 and N.

The term "alkoxy" as used herein, alone or in combination, includes an alkyl
 (alkoxy) or cycloalkyl (cycloalkylalkoxy) group connected to the oxy connecting atom. The
 term "alkoxy" also includes alkyl ether groups, where the term "alkyl" is defined above, and
 "ether" means two alkyl groups with an oxygen atom between them. Examples of suitable
 30 alkoxy groups include methoxy, ethoxy, n-propoxy, *iso*-propoxy, n-butoxy, *sec*-butoxy, *tert*-
 butoxy, methoxymethane (also referred to as 'dimethyl ether'), and methoxyethane (also referred
 to as 'ethyl methyl ether').

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, or biphenyl.

The term "bridged cycloalkyl" refers to a cycloalkyl containing the indicated number of ring hydrocarbons and a C₃-C₅ alkenylene linker joining two non-adjacent carbon atoms of the cycloalkyl ring.

The term "halo" or halogen refers to F, Cl, Br or I. A preferred halogen is F.

The term "haloalkyl," refers an alkyl group wherein one or more of the alkyl group's hydrogen atoms has been replaced with a halogen atom. In one embodiment, a haloalkyl group has from 1 to 6 carbon atoms. In another embodiment, a haloalkyl group is substituted with from 1 to 3 F atoms. Non-limiting examples of haloalkyl groups include -CH₂F, -CHF₂, -CF₃, -CH₂Cl and -CCl₃. The term "C₁-C₆ haloalkyl" refers to a haloalkyl group having from 1 to 6 carbon atoms and at least halogen atom.

The term "haloalkoxy" refers to an alkoxy wherein one or more hydrogen is replaced with halogen.

The term "halocycloalkyl" refers to a cycloalkyl wherein one or more hydrogen is replaced with a halogen.

The term "hydroxyalkyl" refers to an alkyl group wherein one or more of the alkyl group's hydrogen atoms have been replaced with an -OH group. Non-limiting examples of hydroxyalkyl groups include -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH and -CH₂CH(OH)CH₃.

The term heterocycle, heterocyclyl, or heterocyclic, as used herein, represents a stable 4- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. The term heterocycle or heterocyclic includes heteroaryl moieties. In certain embodiments, the heterocyclic group is a heteroaryl group. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl,

isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdiny, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, 5 tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, triazolyl and thienyl.

The term "Het" refers to either (a) 4-, 5- or 6-membered saturated or unsaturated monocyclic ring with 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O and S; (b) 8-, 9- or 10-membered saturated or unsaturated bicyclic ring with 10 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S, or (c) 11- to 15-membered saturated or unsaturated tricyclic ring with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S. In one embodiment the Het is an heteroaryl in another embodiment the Het is a heteroalkyl. The Het may be substituted as indicated.

15 The term "heteroaryl," as used herein, refers to an aromatic monocyclic or multicyclic ring system comprising 5 to 14 ring atoms, wherein from 1 to 4 of the ring atoms is independently O, N or S and the remaining ring atoms are carbon atoms. In one embodiment, a heteroaryl group has 5 to 10 ring atoms. In another embodiment, a heteroaryl group is monocyclic and has 5 or 6 ring atoms. In another embodiment, a heteroaryl group is bicyclic. A 20 heteroaryl group can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein below. In an embodiment, any available nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. The term "heteroaryl" also encompasses a heteroaryl group, as defined above, which is fused to a benzene ring. Non-limiting examples of heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, 25 pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, benzimidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, 30 imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like, and all isomeric forms thereof. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like. In one embodiment, a heteroaryl group is a 5-membered heteroaryl. In another embodiment, a

heteroaryl group is a 6-membered heteroaryl. In another embodiment, a heteroaryl group comprises a 5- to 6-membered heteroaryl group fused to a benzene ring. Unless otherwise indicated, a heteroaryl group is unsubstituted.

The term "heterocycloalkyl" refers to a non-aromatic saturated monocyclic or multicyclic ring system comprising 3 to about 11 ring atoms, wherein from 1 to 4 of the ring atoms are independently O, S, N or Si, and the remainder of the ring atoms are carbon atoms. A heterocycloalkyl group can be joined via a ring carbon, ring silicon atom or ring nitrogen atom. In one embodiment, a heterocycloalkyl group is monocyclic and has from 3 to about 7 ring atoms. In another embodiment, a heterocycloalkyl group is monocyclic has from about 4 to about 7 ring atoms. In another embodiment, a heterocycloalkyl group is bicyclic and has from about 7 to about 11 ring atoms. In still another embodiment, a heterocycloalkyl group is monocyclic and has 5 or 6 ring atoms. In one embodiment, a heterocycloalkyl group is monocyclic. In another embodiment, a heterocycloalkyl group is bicyclic. The nitrogen or sulfur atom of the heterocycloalkyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of monocyclic heterocycloalkyl rings include oxetanyl, piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, delta-lactam, delta-lactone, silacyclopentane, silapyrrolidine. Examples of heterocycloalkyls include azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, imidazoliny, pyrrolidin-2-one, piperidin-2-one, and thiomorpholinyl.

Reference to "saturated" with a respect to a ring, includes fully and partially saturated. Thus a saturated ring includes an aromatic ring and a ring with one or more double bonds.

A moiety that is substituted is one in which one or more hydrogens have been independently replaced with another chemical substituent. As a non-limiting example, substituted phenyls include 2-fluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2,4-fluor-3-propylphenyl. As another non-limiting example, substituted n-octyls include 2,4-dimethyl-5-ethyl-octyl and 3-cyclopentyloctyl. Included within this definition are methylenes (-CH₂-) substituted with oxygen to form carbonyl (-CO-).

Unless otherwise stated, as employed herein, when a moiety is described as "optionally substituted" it is meant that the group optionally has from one or more hydrogens atoms replaced with an indicated substituent. In a general embodiment one to four, one to three, one or two, non-hydrogen substituents are provided. Suitable substituents include, without

limitation, halo, hydroxy, oxo (e.g., an annular -CH- substituted with oxo is -C(O)-), nitro, halohydrocarbyl, hydrocarbyl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyle, arylcarbamoyle, aminoalkyl, acyl, carboxy, hydroxyalkyl, , alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and
 5 ureido groups. Additional substituents, which are themselves not further substituted (unless expressly stated otherwise) are:

- (a) halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino, guanidino, and
- (b) C₁-C₆ alkyl or alkenyl or arylalkyl imino, carbamoyle, azido, carboxamido, mercapto, hydroxy, hydroxyalkyl, alkylaryl, arylalkyl, C₁-C₈ alkyl, SO₂CF₃, CF₃, SO₂m_e, C₁-C₈
 10 alkenyl, C₁-C₈ alkoxy, C₁-C₈ alkoxy-carbonyl, aryloxy-carbonyl, C₂-C₈ acyl, C₂-C₈ acylamino, C₁-C₈ alkylthio, arylalkylthio, arylthio, C₁-C₈alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C₁-C₈ alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C₀-C₆ N-alkylcarbamoyle, C₂-C₁₅ N,N-dialkylcarbamoyle, C₃-C₇ cycloalkyl, aroyl, aryloxy, arylalkyl ether, aryl, aryl fused to a cycloalkyl or heterocycle or another aryl ring, C₃-C₇ heterocycle, or any of these rings fused or
 15 spiro-fused to a cycloalkyl, heterocycle, or aryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above.

Compounds described herein may contain one or more double bonds and may thus give rise to cis/trans isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers unless specifically stated
 20 otherwise.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such
 25 asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. Any formulas, structures or names of compounds described in this specification that do not specify a particular stereochemistry are meant to encompass any and all existing isomers as described above and mixtures thereof in any
 30 proportion. When stereochemistry is specified, the invention is meant to encompass that particular isomer in pure form or as part of a mixture with other isomers in any proportion. The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein.

Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates that are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can
5 be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the
10 pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art. Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

15 As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise. Thus, for example, reference to "a primer" includes two or more such primers, reference to "an amino acid" includes more than one such amino acid, and the like.

The term "substituted" means that one or more hydrogens on the designated atom
20 is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" and "stable structure" are meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a
25 reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic
30 process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization and

the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. The compounds of the invention may be mono, di or tris salts, depending on the number of acid functionalities present in the free base form of the compound. Free bases and salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like.

Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, its corresponding salt may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, trifluoroacetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, para-toluenesulfonic acid, and the like. It will be understood that, as used herein, references to the compounds of the present invention are meant to also include the pharmaceutically acceptable salts.

In the compounds of generic Formula I or II, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula I or II. For example,

different isotopic forms of hydrogen (H) include protium (^1H), deuterium (^2H or D) and tritium (^3H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic Formula I or II can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively.

The term "composition" as used herein is intended to encompass a product comprising specified ingredients and may provide for predetermined amounts or proportions, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. This term in relation to pharmaceutical compositions is intended to encompass a product comprising one or more active ingredients, and an optional carrier comprising inert ingredients, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. In general, pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by combining a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical compositions of the present invention comprise a compound of the invention (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. Exemplary additional therapeutic agents are discussed below. The instant

compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

The term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of one or more pharmaceutically active agents. More than one active agent can be provided by, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of one or more pharmaceutically active agents. The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

In general, pharmaceutical compositions can be prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active compound, which is a compound of general Formula I or II, is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds of the invention, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices.

Pharmaceutical compositions intended for oral use may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1 mg to about 500 mg of the active ingredient and each cachet or capsule preferably containing from about 0.1 mg to about 500 mg of the active ingredient.

Compositions for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate,

calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Other pharmaceutical compositions include aqueous suspensions, which contain the active materials in admixture with excipients suitable for the manufacture of aqueous
5 suspensions. In addition, oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. Oily suspensions may also contain various excipients. The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions, which may also contain excipients such as sweetening and flavoring agents.

10 The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension, or in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably
15 should be preserved against the contaminating action of microorganisms such as bacteria and fungi.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These
20 formulations may be prepared via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

It will also be appreciated that the compounds and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the
25 compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies
30 employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents which are normally administered to treat or prevent a particular

disease, or condition, are known as "appropriate for the disease, or condition, being treated". For example, exemplary additional therapeutic agents include, but are not limited to: interferon, pegylated interferon, α -interferon, pegylated α -interferon, ribavirin, inhibitors of HCV NS5A, inhibitors of HCV NS5B and inhibitors of HCV NS4B. Additional appropriate therapeutic agents or approaches are described generally in The Merck Manual, Seventeenth Edition, Ed. Mark H. Beers and Robert Berkow, Merck Research Laboratories, 1999.

The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably, the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

Accordingly, the present invention additionally provides any one of the aforementioned methods further comprising administering to said patient an amount effective to treat said disease or disorder of at least one additional therapeutic agent, wherein the additional therapeutic agent(s) is/are selected from the group consisting of therapeutic agents known to be useful to treat said disease or disorder.

In one embodiment of this combination therapy method, the additional therapeutic agent(s) is/are selected from the group consisting of interferon, pegylated interferon, α -interferon, pegylated α -interferon, ribavirin, inhibitors of HCV NS5A, inhibitors of HCV NS5B and inhibitors of HCV NS4B.

The terms "administration of" or "administering" a compound should be understood to mean providing a compound of the invention to the individual in need of treatment in a form that can be introduced into that individual's body in a therapeutically useful form and therapeutically useful amount. Examples of different routes of administration include one or more of the following: oral dosage forms, such as tablets, capsules, syrups, suspensions, and the like; injectable dosage forms, such as IV, IM, or IP, and the like; transdermal dosage forms, including creams, jellies, powders, or patches; buccal dosage forms; inhalation powders, sprays, suspensions, and the like; and rectal suppositories.

The terms "effective amount" or "therapeutically effective amount" means the amount of the subject compound sufficient to inhibit HCV replication. Preferably the amount is sufficient to elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

As used herein, the term "treatment" or "treating" means any administration of a compound of the present invention and includes (1) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or (2) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

The compositions containing compounds of the present invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. The term "unit dosage form" is taken to mean a single dose wherein all active and inactive ingredients are combined in a suitable system, such that the patient or person administering the drug to the patient can open a single container or package with the entire dose contained therein, and does not have to mix any components together from two or more containers or packages. Typical examples of unit dosage forms are tablets or capsules for oral administration, single dose vials for injection, or suppositories for rectal administration. This list of unit dosage forms is not intended to be limiting in any way, but merely to represent typical examples of unit dosage forms.

The compositions containing compounds of the present invention may conveniently be presented as a kit, whereby two or more components, which may be active or inactive ingredients, carriers, diluents, and the like, are provided with instructions for preparation of the actual dosage form by the patient or person administering the drug to the patient. Such kits may be provided with all necessary materials and ingredients contained therein, or they may contain instructions for using or making materials or components that must be obtained independently by the patient or person administering the drug to the patient.

When treating or ameliorating a disorder or disease for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 mg to about 100 mg per kg of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. The total daily dosage is from about 1.0 mg to about 2000 mg, preferably from about 0.1 mg to about 20 mg per kg of body weight. In the case of a 70kg adult human, the total daily dose will generally be from about 7 mg to about 1,400 mg. This dosage regimen may be adjusted to provide the optimal therapeutic response. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.005 mg to about 2.5 g of active agent, compounded with an appropriate and convenient amount of carrier material. Unit dosage forms will generally contain between from about 0.005 mg to about 1000 mg of the active ingredient, typically 0.005 mg, 0.01 mg, 0.05 mg, 0.25 mg, 1 mg, 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg or 1000 mg, administered once, twice or three times a day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

The inventive compounds and pharmaceutical compositions of the invention have been found to inhibit the HCV NS3 viral protease. Accordingly, an aspect of this invention is the treatment of HCV infection *in vitro* and of *in vivo* HCV infection in mammals by administering an effective amount of a compound of this invention. The term "mammal" includes humans, as well as other animals, such as, for example, dogs, cats, horses, pigs and cattle. Accordingly, it is understood that the treatment of mammals other than humans refers to the treatment of clinical conditions in non-human mammals that correlate to the above recited conditions.

In another aspect, this invention provides a method of treating a disease or disorder, including those disorders and conditions listed above, in a patient in need of such treating, wherein the method comprises administering to said patient an amount effective to treat

said disease or disorder of a compound of this invention, or a pharmaceutically acceptable salt, solvate or hydrate thereof, or a pharmaceutically acceptable salt or solvate of said prodrug.

The present invention is further directed to a method for that manufacture of a medicament for treating a disease or disorder, including those disorders and conditions listed above, in humans and animals comprising combining a compound of the present invention with one or more additional therapeutic agents, carriers, or diluents.

Compounds of the invention, such as those disclosed below, may be converted to pharmaceutically acceptable salts by suitable methods. For instance, compounds of the Examples described below may be converted to potassium or sodium salts by treatment with stoichiometric amounts of 1 M solutions of aqueous potassium hydroxide or sodium hydroxide in acetonitrile, followed by *in vacuo* concentration. Alternatively, compounds of the Examples bearing basic groups, such as amines, may be converted to acid salts by treatment with stoichiometric amounts of mineral or organic acids.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention.

Several methods for preparing the compounds of this invention are illustrated in the schemes and examples herein. The following examples are provided so that the invention might be more fully understood.

ABBREVIATIONS

^1H NMR	Proton Nuclear Magnetic Resonance spectroscopy
atm	Atmospheres
AcOH	Acetic acid
AlCl_3	Aluminum chloride
aq	Aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BnBr	Benzyl bromide
BBr_3	Boron tribromide
BOC	<i>Tert</i> -Butyloxycarbonyl, Boc
BOC_2O	Di- <i>tert</i> -butyloxycarbonyl

Boc-4-Oxo-PRO-OMe	Boc-4-oxo-L-proline methyl ester
Brosyl	4-bromo benzene sulfonyl
Bu	Butyl, C ₄ H ₉
Bu ₄ NI	Tetra-n-butyl ammonium iodide
BzOH	Benzoic acid
Ca(OH) ₂	Calcium hydroxide
CHCl ₃	Chloroform
CDCl ₃	Deuterated chloroform
CaCO ₃	Calcium carbonate
CDI	Carbonyl diimidazole
CO ₂	Carbon dioxide
Cs ₂ CO ₃	Cesium carbonate
Cu-I	Copper (I) iodide
d	Days
δ	Delta (chemical shift)
DBU	Diazabicycloundecane
DCE	Dichloroethane
DCM	Dichloromethane, methylene chloride
DEOXOFLUOR	Bis(2-methoxyethyl)aminosulfur trifluoride, oxy-DAST
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DIPA	Diisopropyl amine
DIPEA, DIE	Diisopropyl ethyl amine (Hunig's base)
DMAP	4-dimethyl amino pyridine
DMF	Dimethyl formamide
DMP	Dess Martin periodinane
EDC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
Et	Ethyl, C ₂ H ₅
Et ₂ O	Diethylether
EtOAc	Ethyl acetate
EtOH	Ethanol
g	Grams

gt	Genotype
h	Hours
H ₂	Hydrogen gas or atmosphere
HATU	(2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate)
HCl	Hydrochloric acid
HBr	Hydrobromic acid
HPLC	High performance liquid chromatography
Hz	Hertz
MHz	Megahertz
K ₂ CO ₃	Potassium carbonate
KOH	Potassium hydroxide
KOtBu	Potassium <i>tert</i> -butoxide
L	Liter
LC-MS	Liquid chromatography – mass spectroscopy
LDA	Lithium diisopropyl amide
LiCl	Lithium chloride
LiOH·H ₂ O	Lithium hydroxide monohydrate
M	Molar
MCPBA, mCPBA	Meta-chloro-peroxybenzoic acid
Me	Methyl, CH ₃
MeCN, CH ₃ CN	Acetonitrile
MeMgBr	Methylmagnesium bromide
MeOH	Methanol, CH ₃ OH
MeSNa	Sodium methanethiolate, sodium thiomethoxide, CH ₃ SNa
MFSDA	Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate
mg	milligram
MgSO ₄	Magnesium sulfate
MHz	Megahertz
min	Minutes
μl	microliter
mL, ml	milliliter

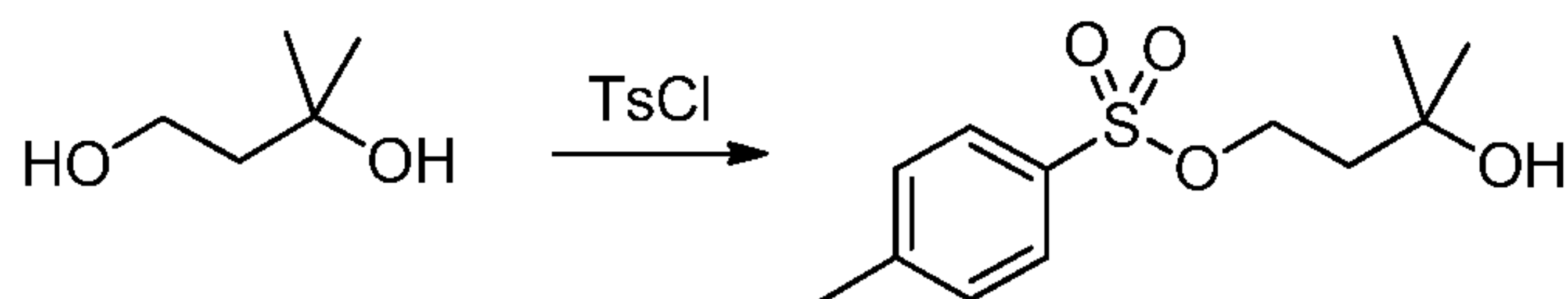
mmole	millimole
MsCl	Methane sulfonyl chloride, mesyl chloride
N	Normal
N ₂	Nitrogen gas
NaBH ₄	Sodium borohydride
Na ₂ S ₂ O ₃	Sodium thiosulfate
Na ₂ SO ₄	Sodium sulfate
Na ₂ SO ₃	Sodium sulfite
NaHSO ₃	Sodium bisulfite
NaBH ₄	Sodium borohydride
NaCO ₃	Sodium carbonate
NaHCO ₃	Sodium bicarbonate
NaKC ₄ H ₄ O ₆	Sodium potassium tartrate
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NH ₄ Cl	Ammonium chloride
NiCl ₂ ·6H ₂ O	Nickel(II) chloride hexahydrate
Pd(OAc) ₂	Palladium acetate
Pd(PPh ₃) ₂ Cl ₂	Tetrakis(triphenylphosphine) Palladium(0) Chloride
Pd(PPh ₃) ₄ , Tetrakis	Tetrakis(triphenylphosphine) Palladium(0)
Pd/C	Palladium on Carbon
Ph	Phenyl
PMB	<i>p</i> -methoxybenzyl
PMB-Cl	<i>p</i> -methoxybenzyl chloride
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone) dipalladium(0)
POBr ₃	Phosphorous oxybromide
PPh ₃	Triphenyl phosphine
PPA	Polyphosphoric acid
RB	Round bottom
RT, rt	Room temperature, approximately 25°C
SCF chromatography	Supercritical fluid chromatography, SCF
SeO ₂	Selenium dioxide

TBAF	Tetrabutyl ammonium fluoride
TBDMS	<i>Tert</i> - butyldimethyl silyl
TBS-OTf	Trifluoromethane sulfonic acid <i>tert</i> -butyldimethylsilyl ester
TBTU	<i>O</i> -(Benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
TEA, Et ₃ N	Triethylamine, N(C ₂ H ₅) ₃
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TsCl	Toluene sulfonyl chloride, tosyl chloride
Zhan Catalyst	1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene[2-isopropoxy)-5- <i>N,N</i> -dimethylaminosulfonyl)phenyl] methylene ruthenium(II)dichloride
sat.	Saturated
SeO ₂	Selenium dioxide
SiO ₂	Silicon dioxide
TMSCF ₃	(Trifluoromethyl)trimethylsilane
TBAF	Tetrabutylammonium fluoride
x	Refers to the number of times a process is iterated (e.g., "washed 3x" = "washed three times")

Intermediates

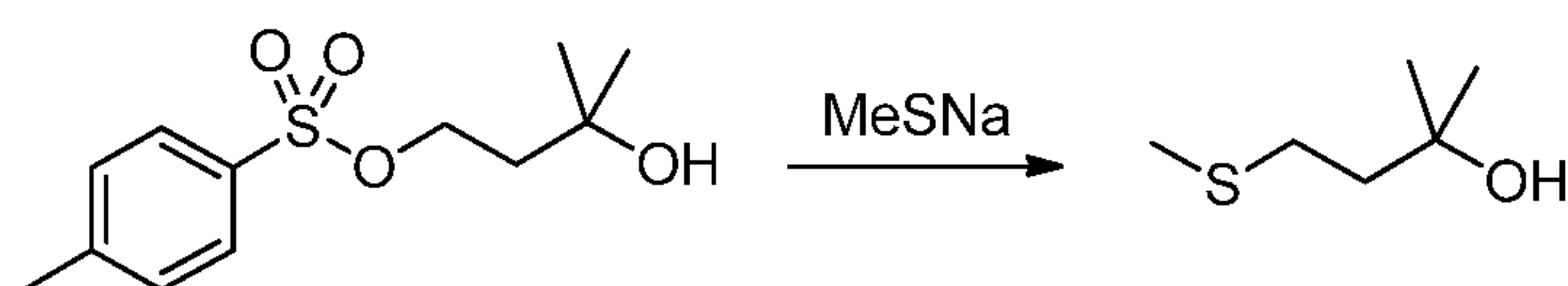
Intermediate 1: 2-Methyl-4-(methylsulfonyl)butan-2-yl 4-nitrophenyl carbonate

Step 1



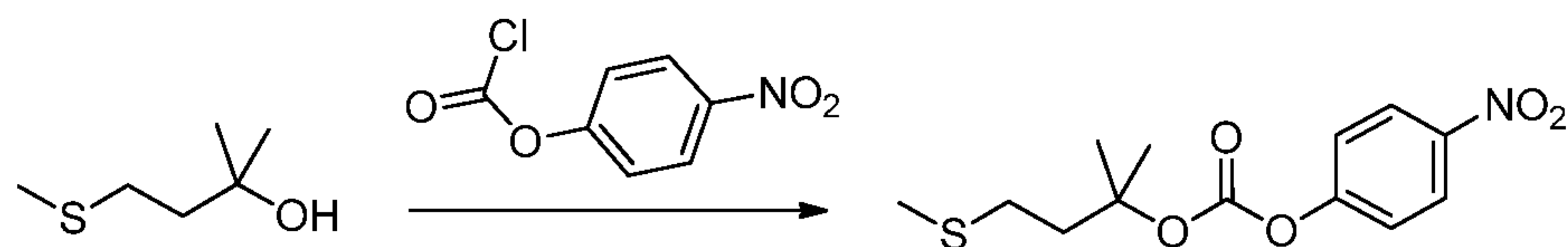
To a solution of 3-methyl-1,3-butanediol (3.72 ml, 35 mmol) in pyridine (30 ml) at 0°C was added TsCl (6.67 g, 35.0 mmol) in pyridine (10 ml) slowly over 10 min, and the mixture was allowed to warm to RT overnight. The mixture was quenched with water and extracted with EtOAc. The combined organic fractions were washed with half brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the product (6.01 g, 67% yield) as oil.

Step 2



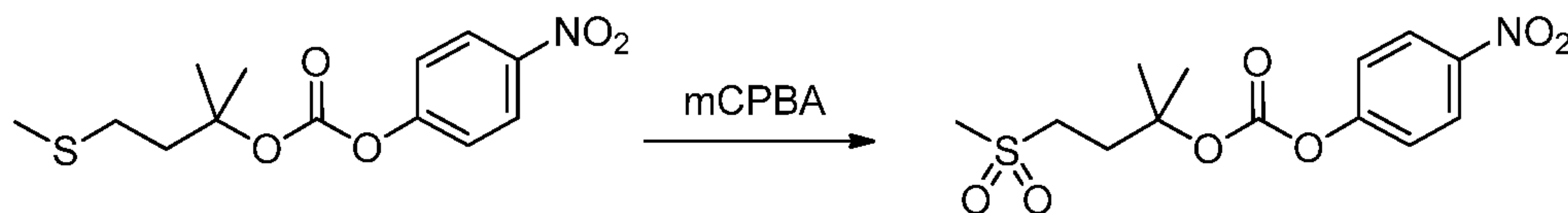
To a solution of the product of Step 1 (1.03 g, 4.00 mmol) in EtOH (10 ml) at RT was added MeSNa (561 mg, 8.00 mmol), and the mixture was warmed to 50°C and stirred for 72 h. The mixture was quenched at RT with water and extracted with DCM. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford the product (510 mg, 95% yield).

Step 3



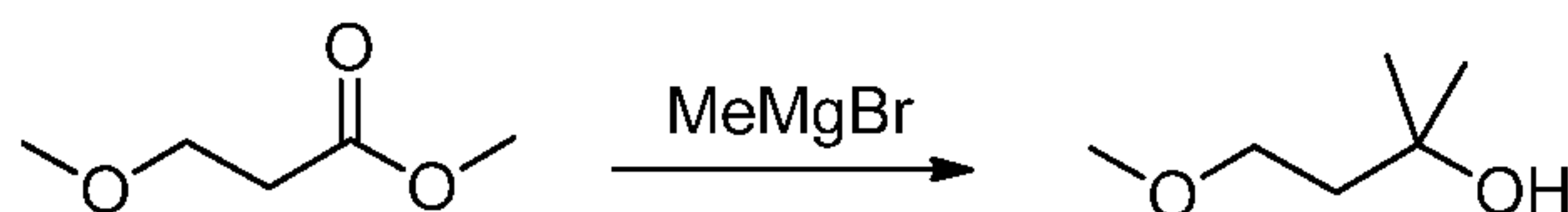
To a solution of the product of Step 2 (510 mg, 3.80 mmol) and pyridine (0.32 ml, 3.99 mmol) in DCE (12 ml) at 0°C was added 4-nitrophenyl chloroformate (766 mg, 3.80 mmol), and the mixture was warmed to 40°C and stirred overnight. The final mixture was diluted at RT with DCM, washed with 1N aq. HCl, saturated NaHCO₃, and brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/DCM 85:15 to 30:70) to give product (902 mg, 79% yield).

Step 4

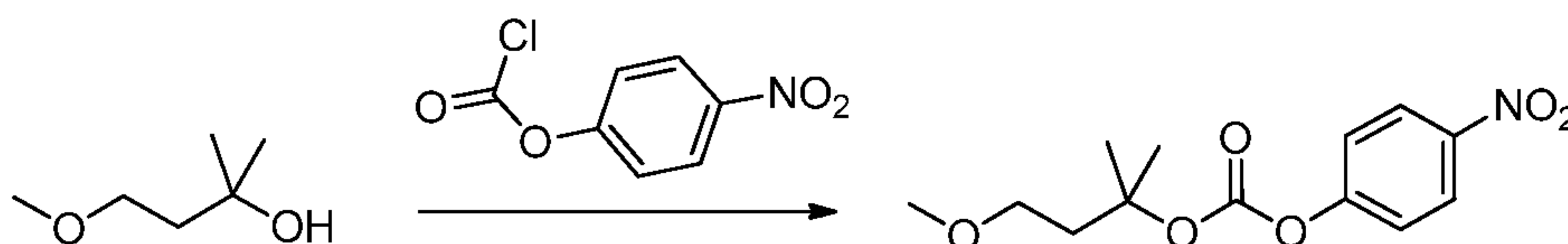


To a solution of the product of Step 3 (300 mg, 1.00 mmol) in DCM (20 ml) at 0°C was added 3-chloroperoxybenzoic acid (618 mg, 2.51 mmol), and the mixture was stirred for 1 h at 0°C then 15 min at RT. The mixture was quenched with sat. aq. NaHCO₃ and extracted with DCM then EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 20:80) to afford 2-methyl-4-(methylsulfonyl)butan-2-yl 4-nitrophenyl carbonate (305 mg, 92% yield) as a white solid. ¹H-NMR (300 MHz, CDCl₃) δ 8.27 (d, J = 9.2 Hz, 2H), 7.36 (d, J = 9.2 Hz, 2H), 3.15-3.21 (m, 2H), 2.96 (s, 3H), 2.32-2.38 (m, 2H), 1.63 (s, 6H).

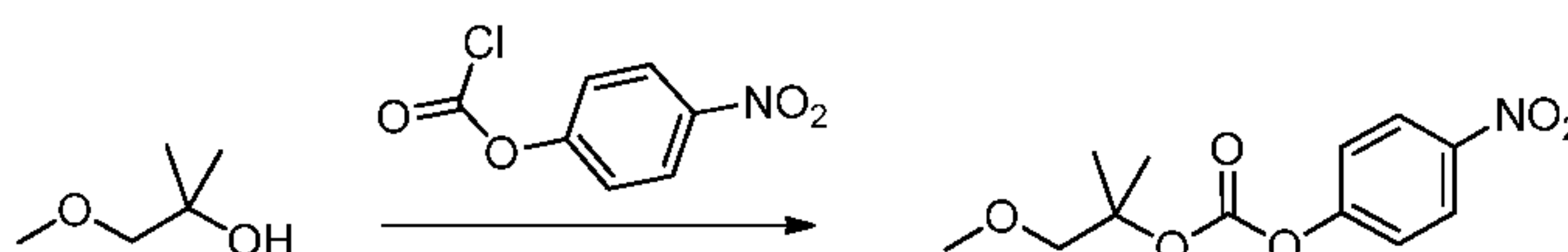
Intermediate 2: 4-methoxy-2-methylbutan-2-yl 4-nitrophenyl carbonate

Step 1

To a solution of 3N MeMgBr in Et₂O (41.7 ml, 125 mmol) and lithium iodide (1.34 g, 10.00 mmol) at 0°C was added methyl 3-methoxypropionate (5.85 ml, 50 mmol) in Et₂O (40 ml), and the mixture was allowed to warm to RT and stirred overnight. The mixture was slowly poured into ice then diluted with sat. aq. NH₄Cl and extracted with Et₂O. The combined organic fractions were washed with sat. aq. NaHCO₃, water, dried over Na₂SO₄, filtered and concentrated *in vacuo* at 0.12atm and 35°C to give the product (1.46 g, 25% yield) as colorless oil.

10 Step 2

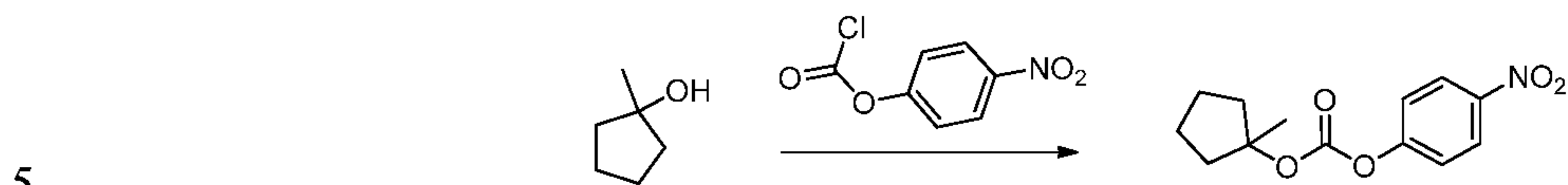
To a solution of the product of Step 1 (1.46 g, 12.3 mmol) and pyridine (1.05 ml, 13.0 mmol) in DCM (40 ml) at 0°C was added 4-nitrophenyl chloroformate (2.49 g, 12.3 mmol), and the mixture was allowed to warm to RT and stirred for 72 h. The final mixture was diluted at RT with DCM, washed with 1N aq. HCl, saturated NaHCO₃, and brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 70:30 then hexanes/DCM 80:20 to DCM) to give 4-methoxy-2-methylbutan-2-yl 4-nitrophenyl carbonate (982 mg, 28% yield). ¹H-NMR (300 MHz, CDCl₃) δ 8.26 (d, J = 9.2 Hz, 2H), 7.35 (d, J = 9.2 Hz, 2H), 3.55 (t, J = 6.4 Hz, 2H), 3.34 (s, 3H), 2.16 (t, J = 6.4 Hz, 2H), 1.58 (s, 6H).

Intermediate 3: 1-methoxy-2-methylpropan-2-yl 4-nitrophenyl carbonate

1-Methoxy-2-methyl-2-propanol (3.50 ml, 30 mmol) was treated with 4-nitrophenyl chloroformate according to conditions similar to the ones described above with respect to Intermediate 2, Step 2 to provide, after purification by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 70:30), 1-methoxy-2-methylpropan-2-yl 4-

nitrophenyl carbonate (7.02 g, 87% yield) as a colorless oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 8.26 (d, $J = 9.2$ Hz, 2H), 7.36 (d, $J = 9.2$ Hz, 2H), 3.56 (s, 3H), 3.43 (s, 3H), 1.57 (s, 6H).

Intermediate 4: Methoxy-2-methylbutan-2-yl 4-nitrophenyl carbonate



1-Methylcyclopentanol (0.60 ml, 6.00 mmol) was treated with 4-nitrophenyl chloroformate according to conditions similar to the ones described in Intermediate 2, Step 2 to provide, after purification by column chromatography over silica gel (eluting with Hexanes/DCM 85:15 to DCM), methoxy-2-methylbutan-2-yl 4-nitrophenyl carbonate (1.03 g, 65% yield) as colorless oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 8.26 (d, $J = 9.2$ Hz, 2H), 7.36 (d, $J = 9.2$ Hz, 2H), 2.19-2.26 (m, 2H), 1.65-1.85 (m, 6H), 1.67 (s, 3H)

10

Intermediate 5: *N*-cyclohexylcyclohexanaminium (2*S*)-2-[(*tert*-butoxycarbonyl)amino]non-8-enoate

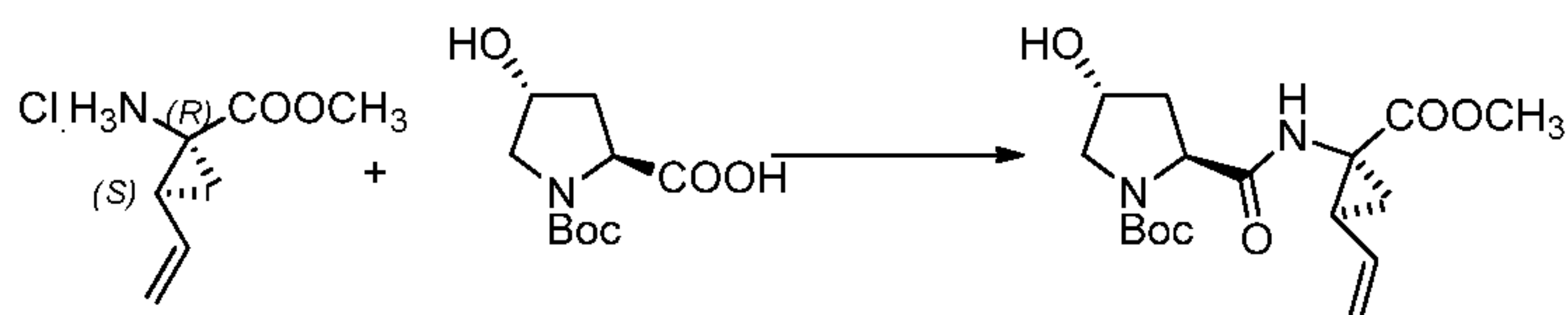


Intermediate 5 was obtained from SYNTH TECH, and Intermediate 5 can be synthesized by known, published procedures, such as those disclosed in Anne-Marie FAUCHER *et al.*, "Synthesis of BILN 2061, an HCV NS3 Protease Inhibitor with Proven Antiviral Effect in Humans," 6(17) ORG. LETT. 2901-2904 (2004). The dicyclohexylamine salt can be readily converted into free acid by treatment with aq. HCl and extraction of the mixture with EtOAc (3x). Subsequently, the organic layers are washed with aq. HCl and brine, dried over MgSO_4 , filtered and concentrated.

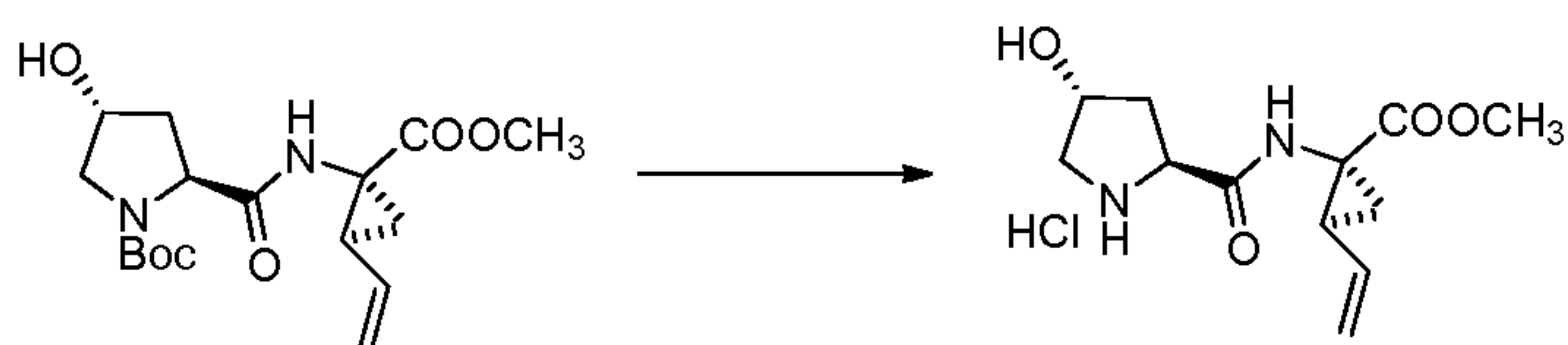
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Intermediate 6: (2*R*,6*S*,13*aS*,14*aR*,16*aS*,*Z*)-methyl 6-[(*tert*-butoxycarbonyl)amino]-2-hydroxy-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13*a*,14,14*a*,15,16,16*a*-hexadecahydrocyclopropa[e]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-14*a*-carboxylate

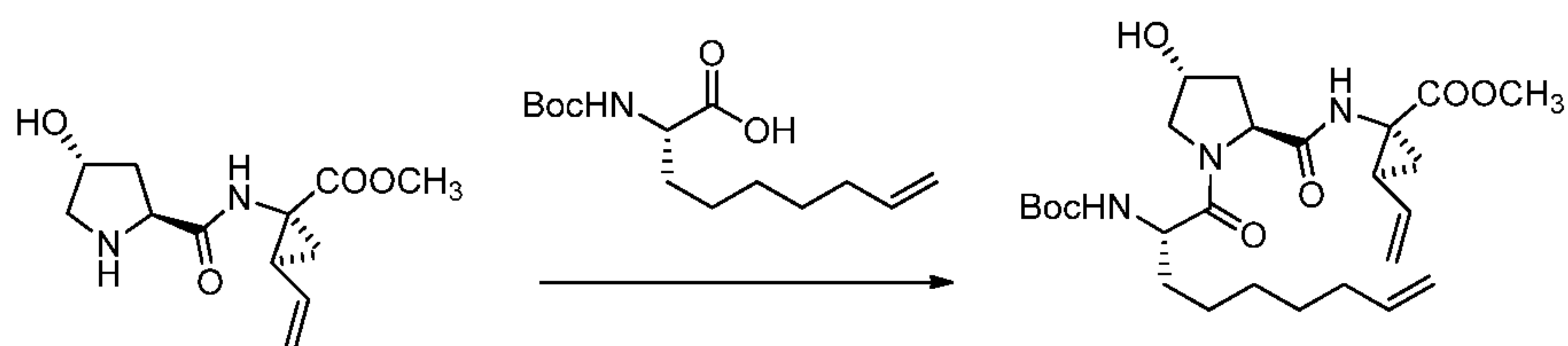
25

Step 1

EDC (8.08 g, 42.2 mmol) and pyridine (5.25 ml, 64.9 mmol) were added to a stirred, RT mixture of the HCl salt of amino ester (6.05 g, 34.1 mmol) and carboxylic acid (7.5 g, 32.4 mmol) in MeCN (75 ml), and the resulting mixture was stirred at RT for 24 h. After the completion of the reaction, the mixture was concentrated under reduced pressure. The residue was diluted with EtOAc (100 ml) and quenched with half-saturated brine (100 ml), and then extracted with EtOAc (3 x 75 ml). The combined organic fractions were dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The product amide was obtained as yellow foam (10.5 g, 91%) and used directly in Step 2.

Step 2

HCl in dioxane 4 N (254 ml, 1016 mmol) was added to a stirred, RT mixture of amide of Step 1 (12.0 g, 33.9 mmol) in DCM (24.0 ml), and the mixture was stirred at RT for 2 h. The reaction mixture was concentrated under reduced pressure to afford a brown solid (10.5 g, ~95 wt% purity, 99%). The product (95 wt%-by ¹H NMR-containing traces of pyridine), was used directly in next step without further purification.

Step 3

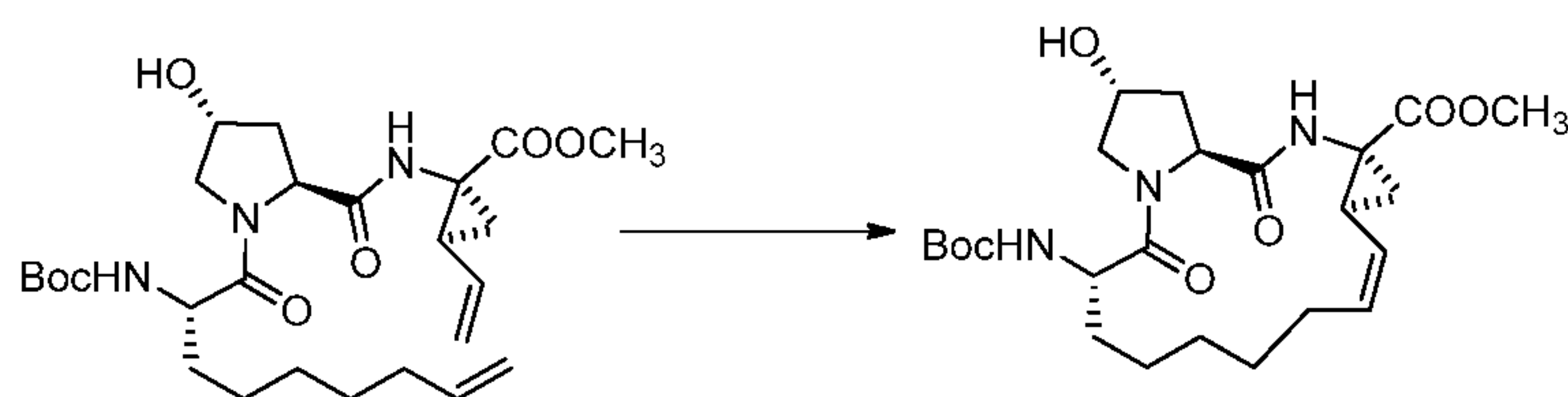
A 1L RB flask was charged with DCM (163 ml), the product of Step 2 (7.10 g, 22.7 mmol) and Hunig's base (3.77 ml, 21.6 mmol) and then allowed to stir 30 min at RT. This solution was designated "Solution A".

Separately, a 500-mL flask under N₂ sweep was charged with DCM (213 ml), (S)-2-((tert-butoxycarbonyl)amino)non-8-enoic acid (6.16 g, 22.7 mmol), TBTU (8.00 g, 24.9 mmol)

and Hunig's Base (3.97 ml, 22.7 mmol) and then allowed to stir 30 min at RT. This solution was designated "Solution B".

Solution B was added to Solution A via cannula over 15 min. The resulting solution was stirred 24 h at RT under a N₂ sweep. The reaction was quenched with 0.5 N HCl (350 ml), then extracted with DCM (100 ml). The combined organic layers washed with saturated NaHCO₃ (250 ml) water (2 x 250 ml) and then brine (100 ml). The organic layers were dried over MgSO₄, then concentrated. The residue was purified by column chromatography on silica gel column (ISCO 220 gram), eluting with 80-100% EtOAc/hexanes to give the product bis-olefin as colorless foam (9.90 g, 86%).

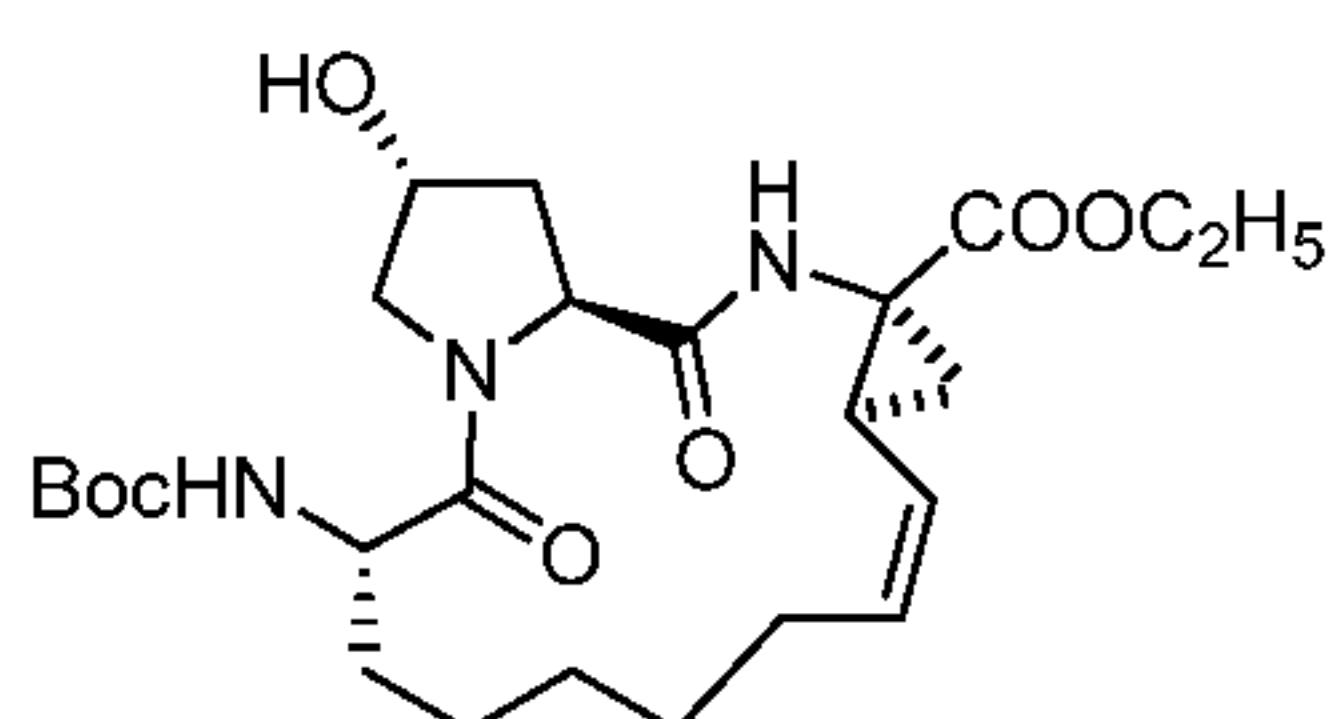
10 Step 4



Grubbs-Hoveyda 1st generation catalyst (0.592 g, 0.985 mmol) was added in one portion to a stirred, RT mixture of DCM (2000 ml) and bis-olefin product of Step 3 (10.0 g, 19.7 mmol) in a 3-necked 5L flask (equipped with condenser and thermocouple) that had been degassed by bubbling with N₂ for 30 min. The flask was vacuum-purged and backfilled with N₂. The mixture was then heated at 40°C for 40 h (monitoring by TLC) until completion. The crude reaction mixture was concentrated. The brown residue was purified by column chromatography on silica gel column (ISCO 220 g), eluting with 50-100% EtOAc/hexanes to give (2R,6S,13aS,14aR,16aS,Z)-methyl 6-((*tert*-butoxycarbonyl)amino)-2-hydroxy-5,16-dioxo-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxylate as brown foam (7.05 g, 74%).

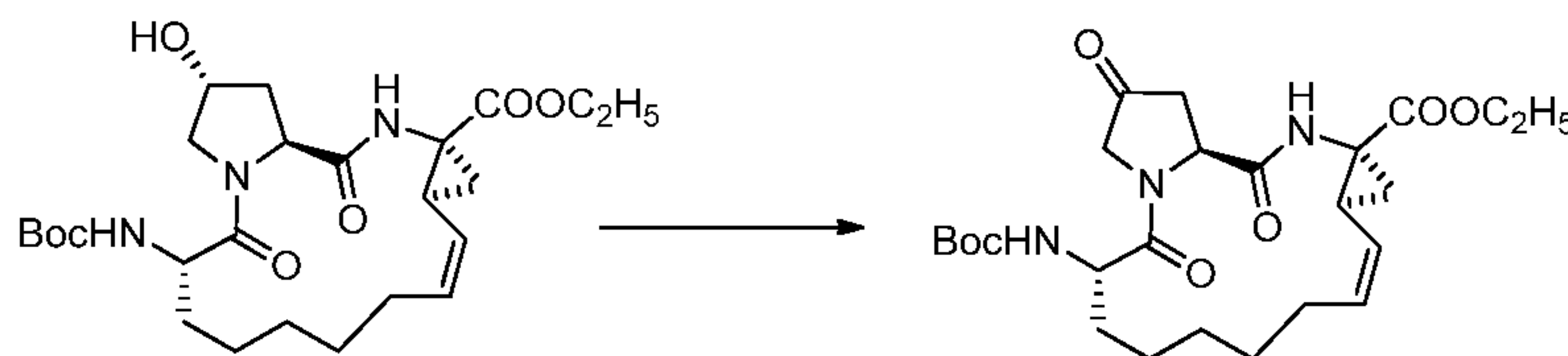
Intermediate 7: Ethyl (6S,12Z,13aS,14aR,16aS)-6-[(*tert*-butoxycarbonyl)amino]-2,5,16-trioxo-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylate

25 Step 1



The product alcohol was synthesized using similar procedure described for the synthesis of Intermediate 6, except ethyl ester was used instead of methyl ester.

Step 2

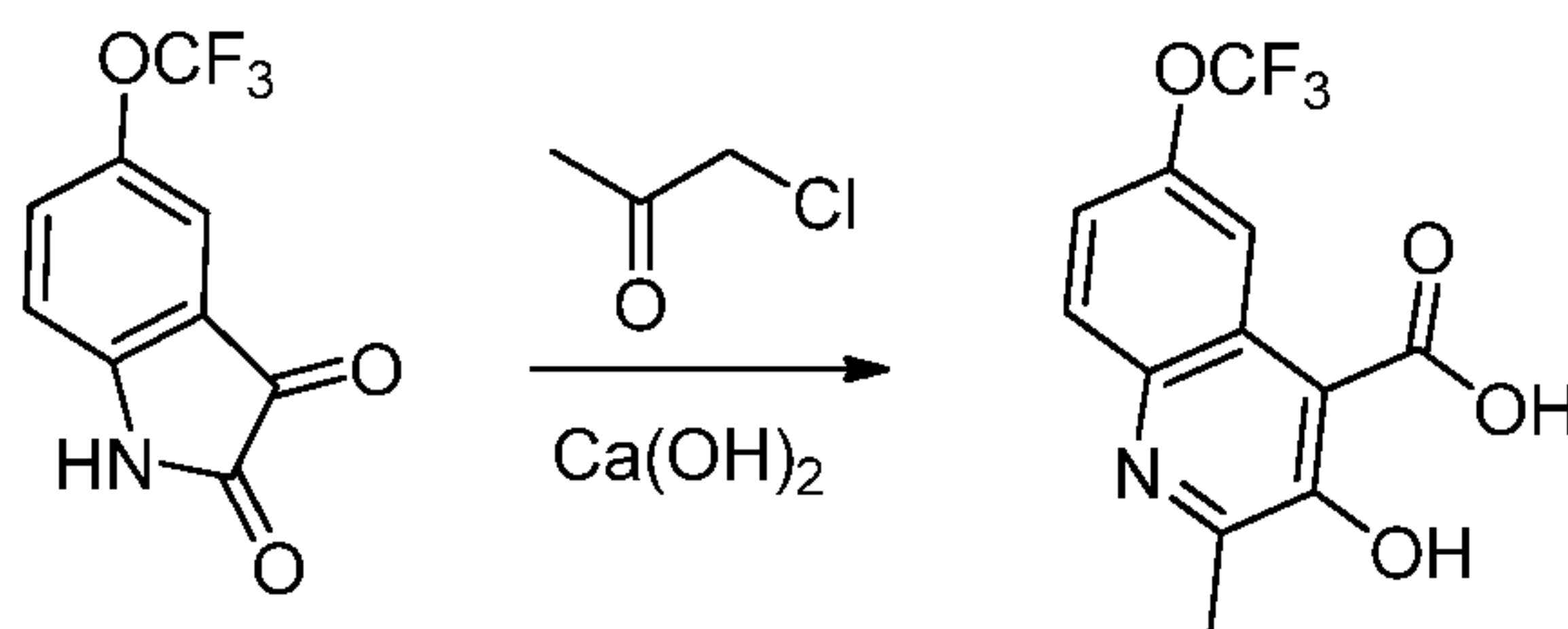


5 A solution of alcohol product of Step 1 (6.00 g, 12.16 mmol) was taken up in DCM (60 ml) and treated with Dess-Martin reagent (5.42 g, 12.4 mmol). The resulting solution was aged at RT for 1 h, until HPLC showed complete conversion of starting material to product. The reaction mixture was quenched with half-sat. NaHCO₃ (120 mL) and stirred for 30 min. The reaction mixture was transferred to a separatory funnel, and the aq. layer was extracted once with
10 50 mL DCM, and then the combined organic layers were washed with 10% Na₂S₂O₃ (100 mL) 2x and brine. The combined organic layers were concentrated, and the crude mixture was purified by silica gel chromatography (EtOAc/hexanes) to yield the Intermediate 7 macrocyclic ketone.

15

EXAMPLES

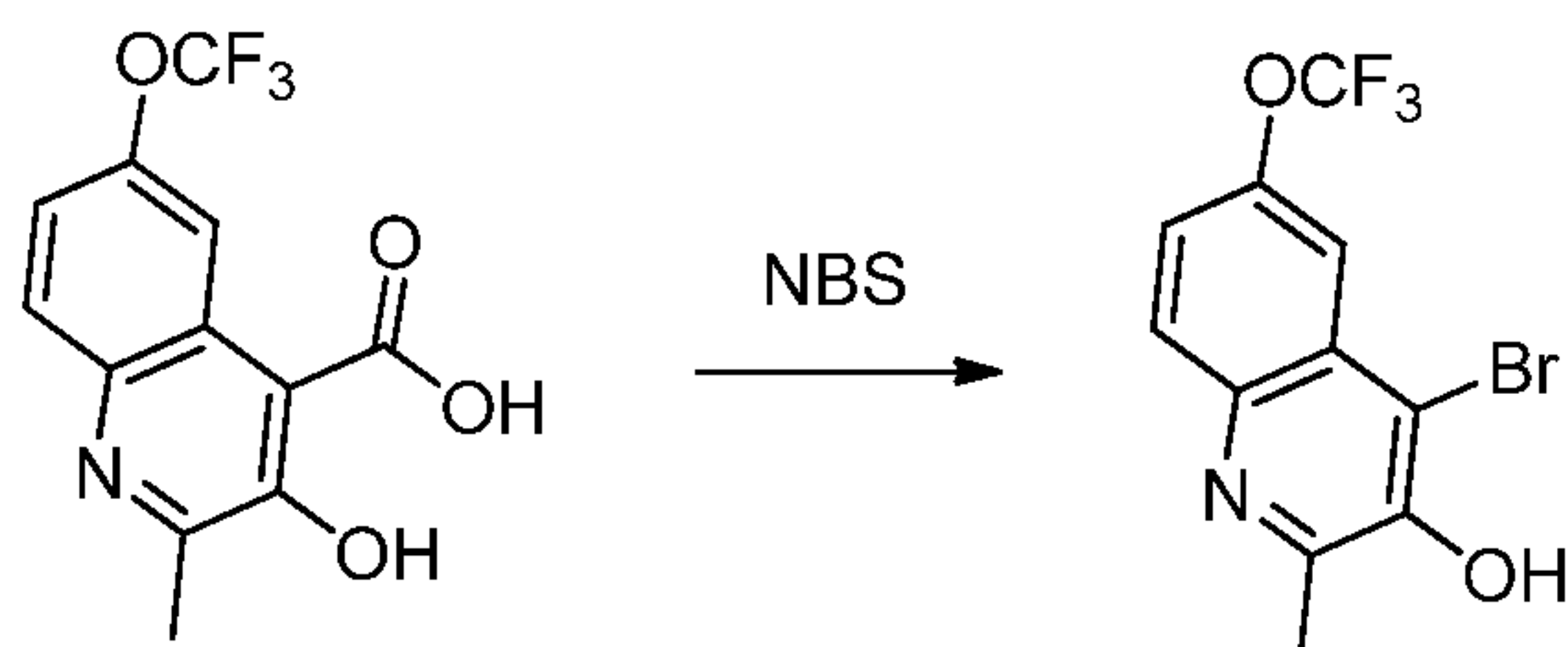
Example 1: *tert*-butyl (2R,6S,13aS,14aR,16aS,Z)-5'-methyl-14a-(1-methylcyclopropyl sulfonylcarbamoyl)-5,16-dioxo-9'-(trifluoromethoxy)-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-6-ylcarbamate (I-1)

20 Step 1

25 A solution of Ca(OH)₂ (38.5 g, 519 mmol) and 5-(trifluoromethoxy)isatin (40 g, 173 mmol) in water (150 ml) was heated at 80°C for 1 h. The heating bath was removed followed by slow addition of chloroacetone (34.5 ml, 433 mmol). The reaction was then heated at 80°C for another 5 h then cooled to RT and quenched with 1N aq. HCl until pH=2. The solid

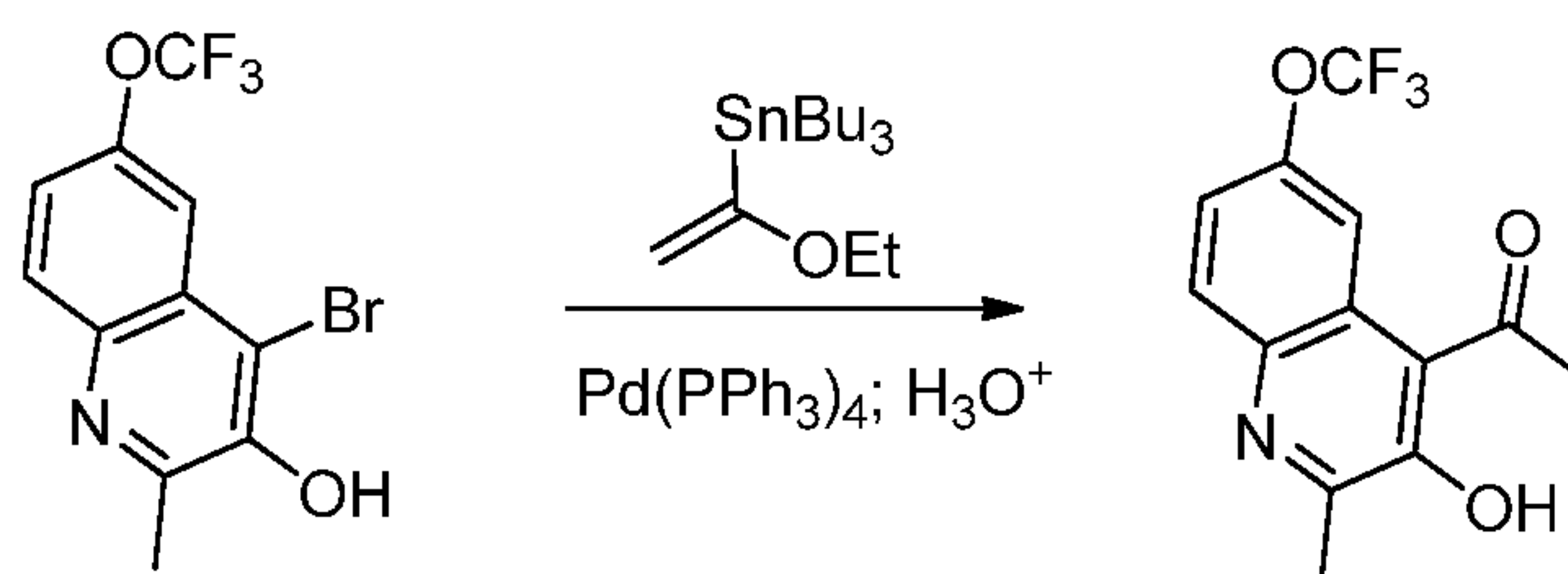
was filtered over fritted disk, washed with water and dried overnight at 50°C under high vacuum to afford the product intermediate (47.0 g, 95% yield) as a slightly yellow solid.

Step 2



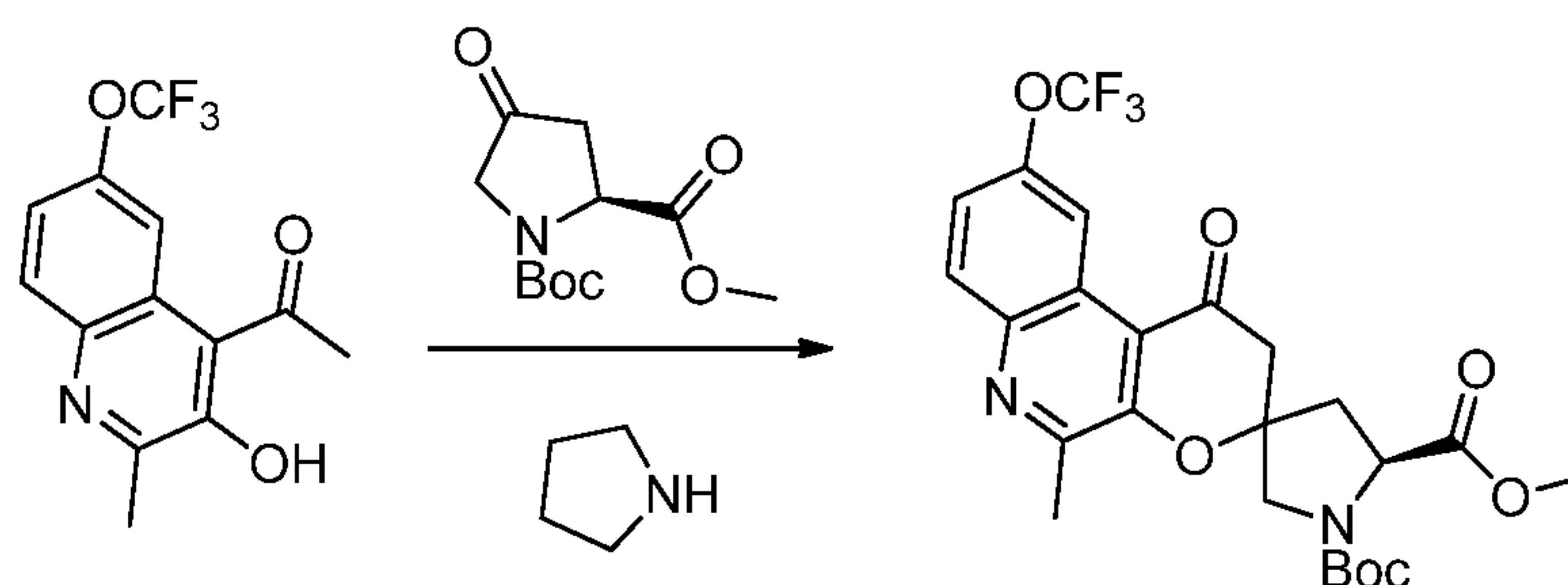
5 To a solution of the product from Step 1 (40 g, 139 mmol) in THF (1000 ml) at RT was added NBS (29.7 g, 167 mmol), and the mixture was stirred for 4 h. The mixture was quenched with saturated brine and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with DCM/EtOAc 99:1 to 60:40) to give the product
10 intermediate (25.0 g, 56% yield) as a red solid.

Step 3



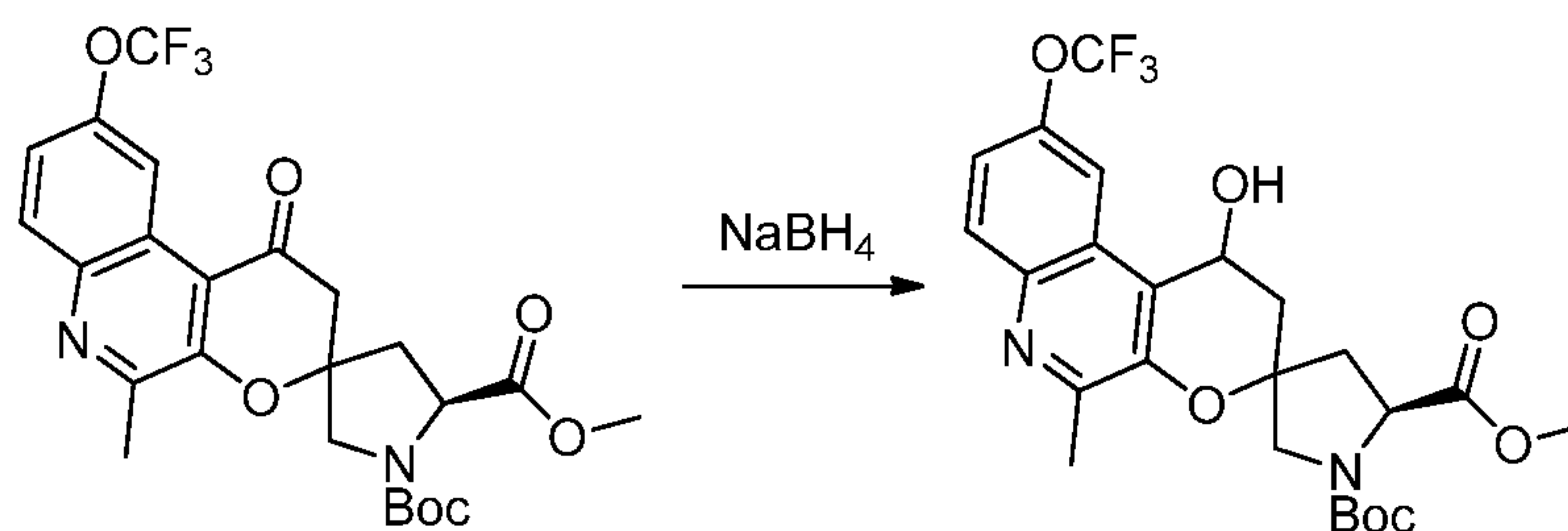
To a solution of the product from Step 2 (20.0 g, 62.1 mmol) and Pd(PPh₃)₄ (7.18 g, 6.21 mmol) in dioxane (240 ml) was added tributyl(1-ethoxyvinyl)tin (52.4 ml, 155 mmol) and
15 the mixture was warmed to 110°C and stirred for 3 h. The reaction was cooled to RT, diluted with 1N aq. HCl (240 ml) and stirred for 90 min. The mixture was then quenched with saturated aq. NaHCO₃ and extracted with EtOAc. The combined organic fractions were washed with saturated brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 60:40) to give
20 the product intermediate (3.40 g, 19%) as a yellow solid.

Step 4



To a solution of the product from Step 3 (2.0 g, 7.01 mmol) in MeOH (30 ml) was added *N*-Boc-4-oxo-L-proline methyl ester (3.41 g, 14.02 mmol), pyrrolidine (0.58 ml, 7.01 mmol), followed by molecular sieves (4 A powder, 2.0 g), and the mixture was heated in a microwave at 105°C for 30 min. The cooled mixture was filtered over fritted disk, washing with MeOH, and then concentrated. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) to afford the product intermediate (2.73 g, 76% yield) as a mixture of diastereoisomers.

Step 5

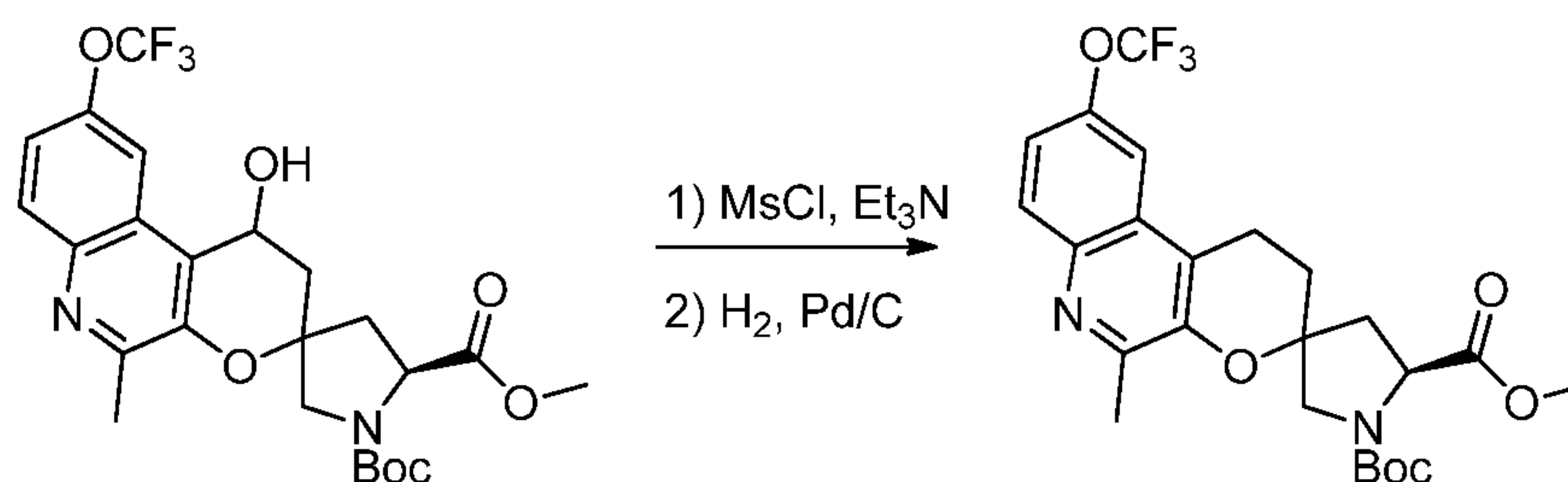


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To a solution of the product from Step 4 (2.20 g, 4.31 mmol) in THF (20 ml) and MeOH (20 ml) at 0°C was added NaBH₄ (196 mg, 5.17 mmol), and the mixture was stirred for 30 min. The mixture was quenched at 0°C with sat. aq. NH₄Cl and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide the product intermediate (2.20 g, 100% yield) as a mixture of diastereoisomers.

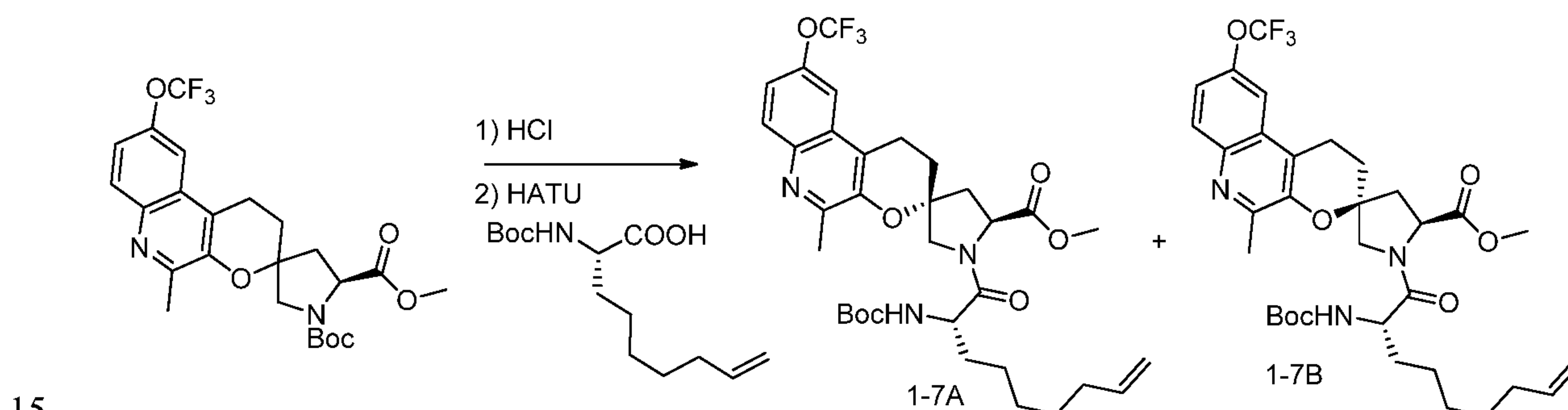
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Step 6



To a solution of the product from Step 5 (2.20 g, 4.29 mmol) in DCM (40 ml) at 0°C was added TEA (2.094 ml, 15.03 mmol) followed by MsCl (0.67 ml, 8.59 mmol), and the mixture was allowed to warm to RT and stirred overnight. More TEA (0.60 ml, 4.29 mmol) and MsCl (0.16 ml, 2.14 mmol) were then added at 0°C, and the reaction was allowed to warm to RT and stirred for 2 h. The mixture was quenched with sat. aq. NaHCO₃ and extracted with DCM. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) to give a crude chloro intermediate (2.20 g, 97% yield) as yellow oil. To a solution of this crude chloro intermediate (2.20 g, 4.15 mmol) in EtOAc (90 ml) at RT was added 10% Pd/C (0.440 g, 0.415 mmol) and the mixture was hydrogenated at 1 atm and RT for 3 h. The mixture was filtered over CELITE, washing with EtOAc and MeOH. The residue was purified by column chromatography over silica gel (eluting with DCM/MeOH 99:1 to 80:20) to give the product intermediate (1.89 g, 92% yield) as a mixture of diastereoisomers.

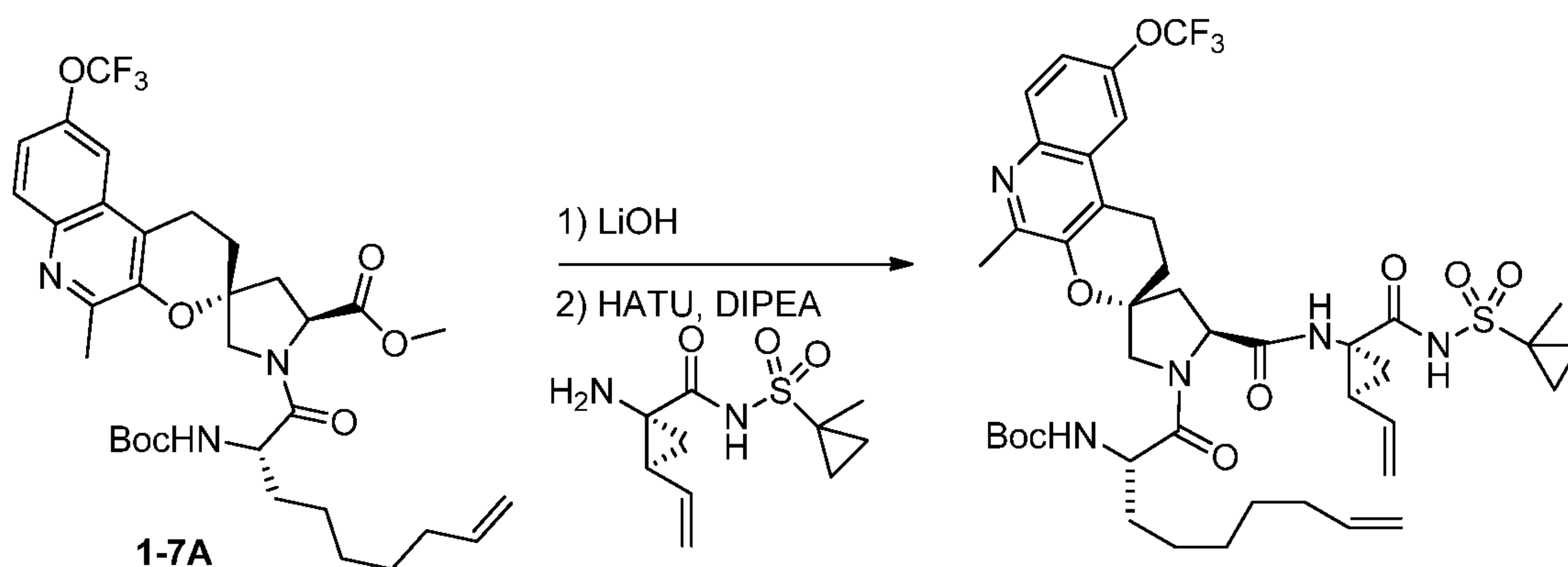
Step 7



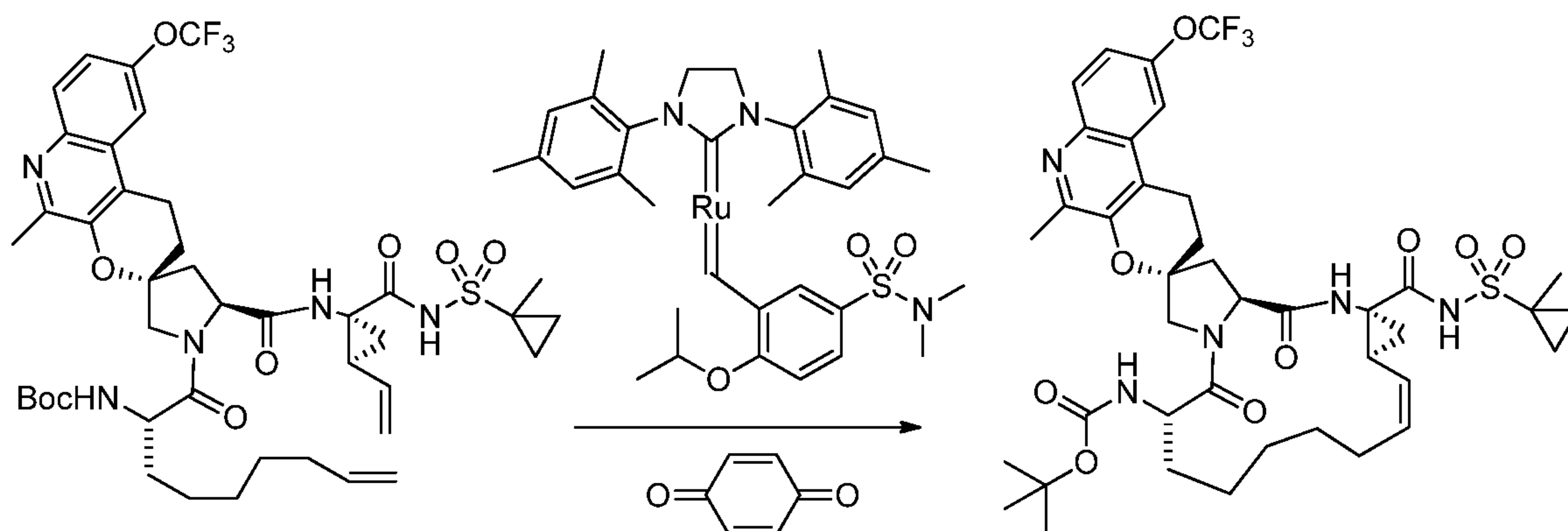
The product from Step 6 (1.10 g, 2.22 mmol) was diluted with 4N HCl in dioxane (22.2 ml, 89 mmol), and the mixture was stirred for 2 h at RT then concentrated *in vacuo* to provide a deprotected amine as HCl salt (1.00 g, 100% yield). To a solution of this deprotected amine as HCl salt (1.00 g, 2.22 mmol), (*S*)-2-(*tert*-butoxycarbonylamino)non-8-enoic acid (1.71 g, 3.78 mmol) and HATU (1.44 g, 3.78 mmol) in DMF (20 ml) at RT was added DIPEA (1.72 ml, 10.1 mmol), and the mixture was stirred at RT overnight. The reaction was further diluted with DMF (5 ml), DCM (20 ml), treated with DIPEA (0.40 ml, 2.3 mmol) and stirred at RT overnight. The final mixture was diluted with water and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) to provide, in order of elution, diastereoisomer 1-7A (660 mg, 40% yield) then diastereoisomer 1-7B (520 mg, 32% yield).

20

25

Step 8

To a solution of diastereoisomer 1-7A from Step 7 (660 mg, 1.02 mmol) in THF (12 ml), MeOH (12.00 ml) and water (8 ml) at RT was added LiOH·H₂O (73.0 mg, 3.05 mmol), and the mixture was warmed to 50°C and stirred for 2 h. MeOH and THF were concentrated *in vacuo*, then the mixture was diluted with 0.5 M aq. HCl until pH=2 and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide a crude acid intermediate (640 mg, 99% yield). To a solution of this crude acid intermediate (640 mg, 1.01 mmol) and (1*R*,2*S*)-1-amino-*N*-(1-methylcyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide (369 mg, 1.51 mmol) in DMF (10 ml) at RT was added HATU (574 mg, 1.51 mmol) followed by DIPEA (0.514 ml, 3.02 mmol), and the mixture was stirred at RT overnight. The mixture was quenched with water and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) to give the product intermediate (770 mg, 79% yield).

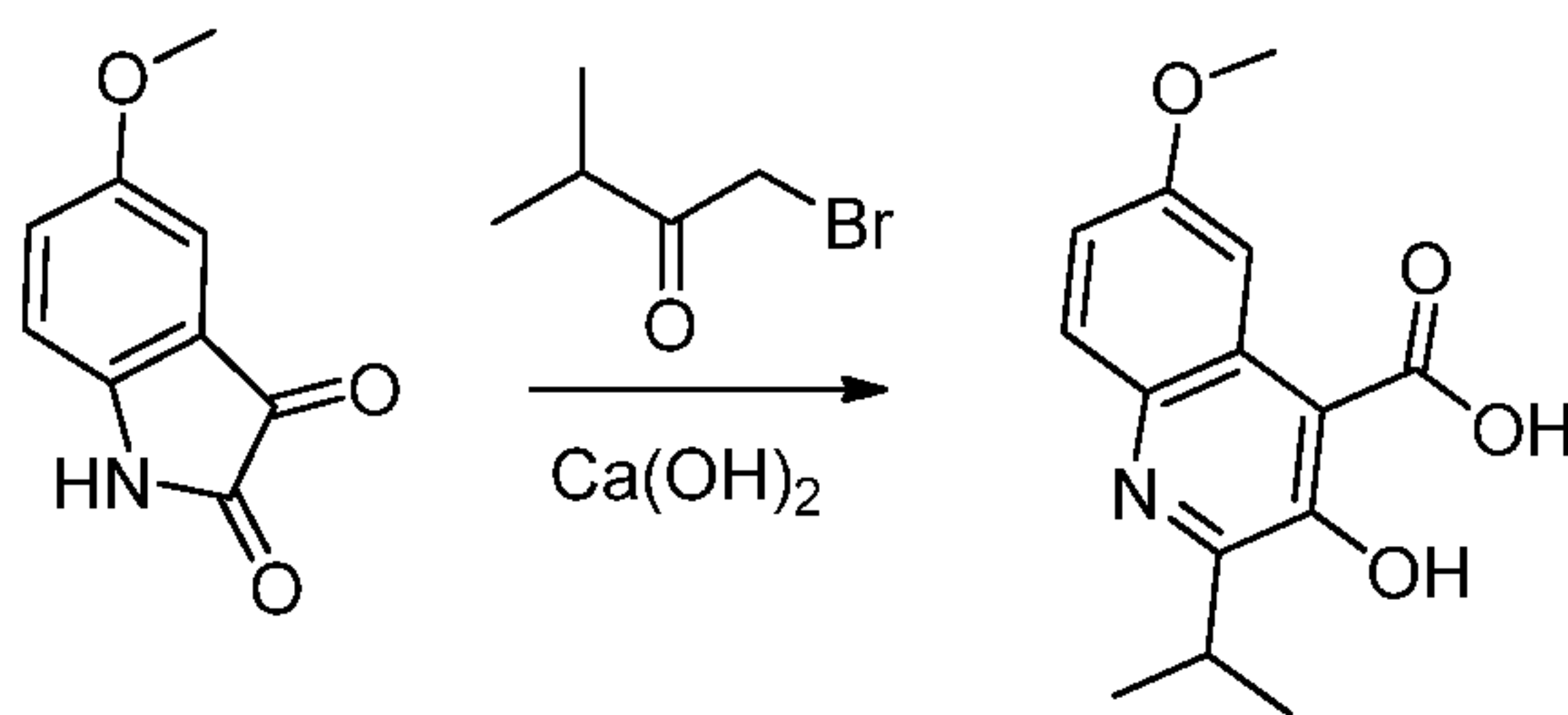
Step 9

A solution of the product from Step 8 (300 mg, 0.348 mmol), 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene[2-(isopropoxy)-5-(*N,N*-

dimethylaminosulfonyl]phenyl]methylenruthenium(II) dichloride (63.8 mg, 0.087 mmol) and 1,4-benzoquinone (11.29 mg, 0.104 mmol) in DCE (150 ml) was degassed, put under N₂, then warmed to 70°C and stirred 4 h. The mixture was quenched at RT with n-butyl vinyl ether (1 ml) and concentrated to dryness. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) to give I-1 (205 mg, 71% yield). ¹H-NMR (400 MHz, CDCl₃) δ 10.10 (s, 1H), 7.96 (d, J = 9.0 Hz, 1H), 7.54 (s, 1H), 7.38 (d, J = 9.0 Hz, 1H), 6.89 (s, 1H), 5.71 (m, 1H), 4.95-5.05 (m, 2H), 4.63 (m, 1H), 4.44 (d, J = 10.8 Hz, 1H), 4.12 (m, 1H), 3.69 (d, J = 10.8 Hz, 1H), 3.00-3.17 (m, 2H), 2.48-2.62 (m, 2H), 2.51 (s, 3H), 2.23-2.44 (m, 4H), 1.72-1.93 (m, 5H), 1.23-1.57 (m, 8H), 1.46 (m, 3H), 1.29 (s, 9H), 0.80 (br s, 2H); LC-MS (M⁺) Calc. for C₄₀H₅₀F₃N₅O₉S 833.9 Found 833.6.

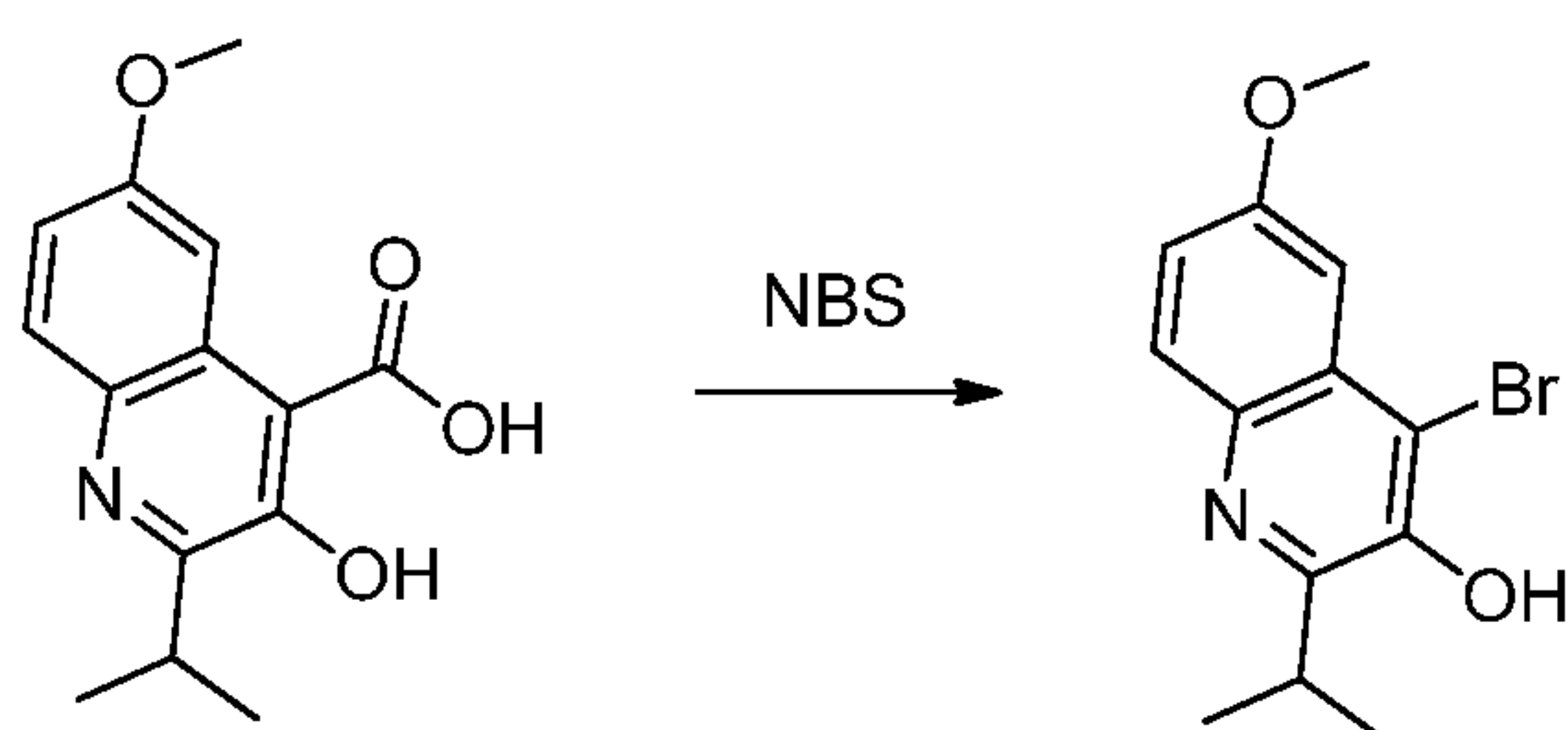
Example 2: tert-Butyl (2R,6S,13aS,14aR,16aS,Z)-5'-isopropyl-9'-methoxy-14a-(1-methylcyclopropylsulfonylcarbonyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-6-ylcarbamate (I-2)

Step 1



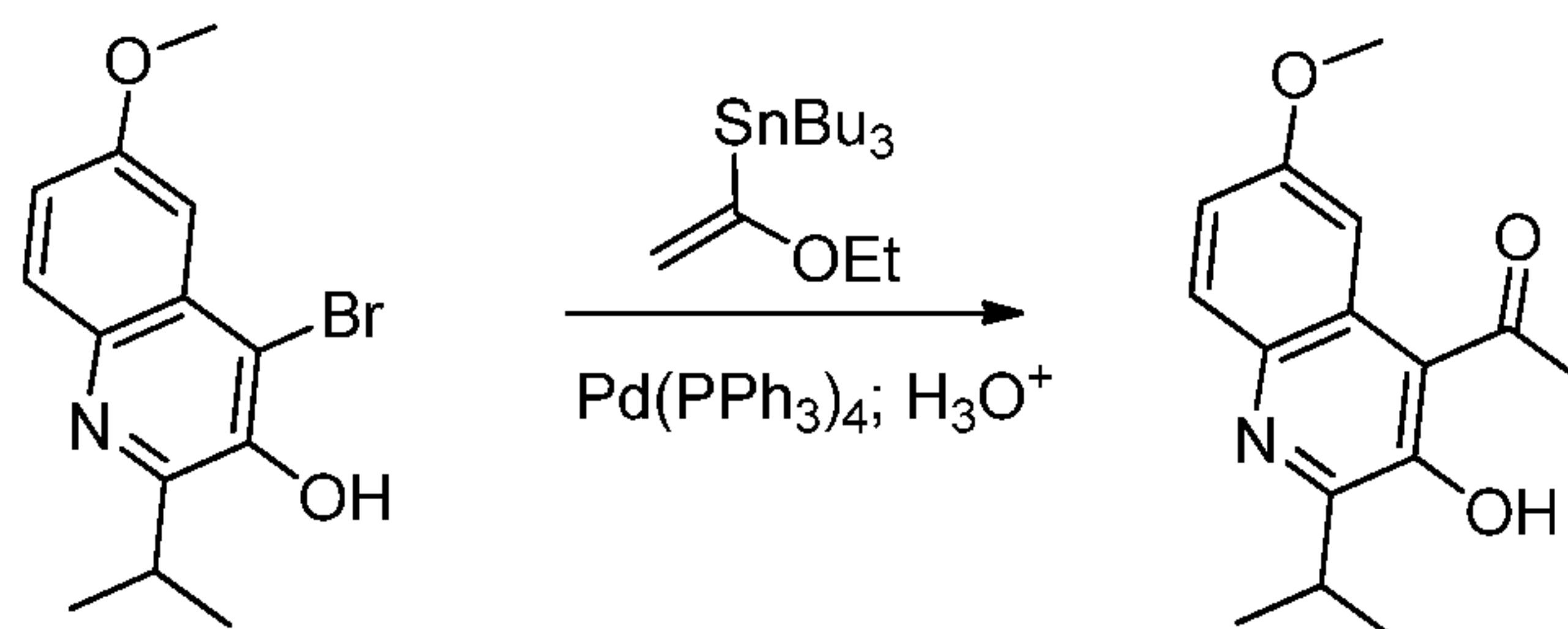
A mixture of 5-methoxyisatin (18 g, 102 mmol) and Ca(OH)₂ (22.6 g, 305 mmol) in water (300 ml) was warmed to 80°C and stirred for 1 h. 1-Bromo-3-methylbutan-2-one (33.5 g, 203 mmol) was then added slowly at 60°C, and the reaction was warmed to 80°C and stirred for 2 h. The mixture was cooled to RT, then diluted with 1 M aq. HCl until pH=2, filtered, rinsing with water then dried under high vacuum at 95°C overnight to give product (20.41 g, 77% yield) as a yellow solid.

Step 2



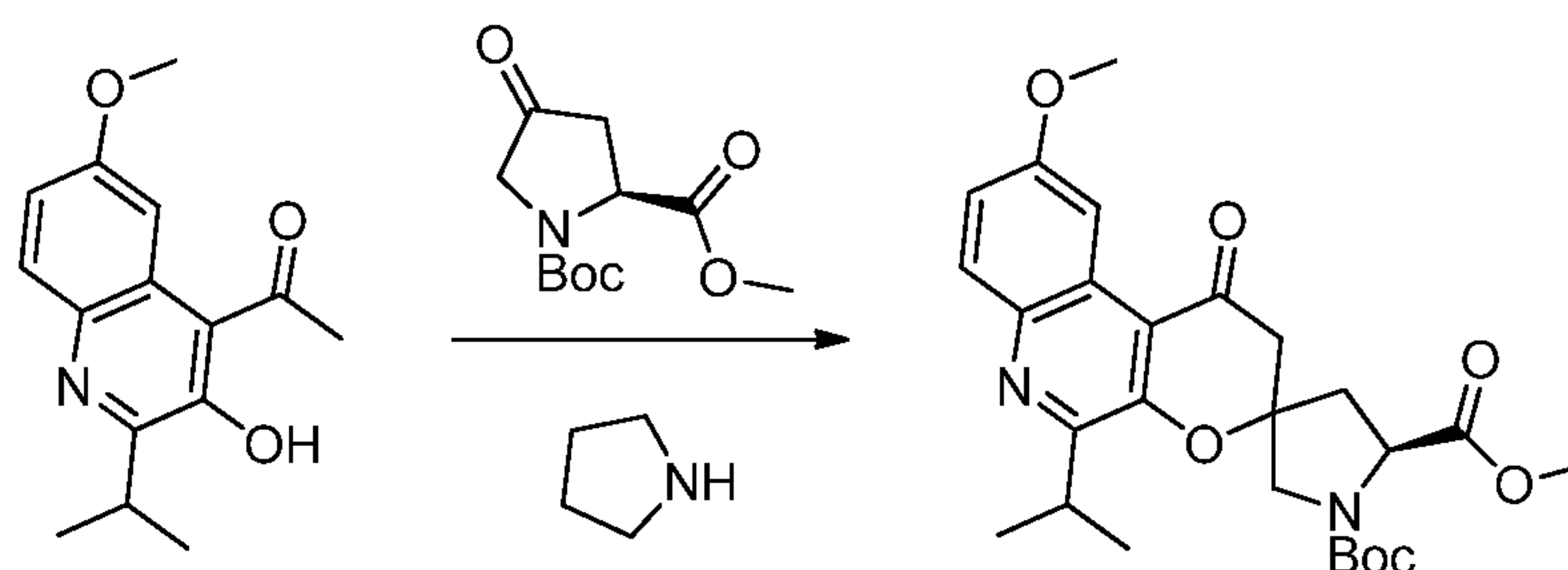
To a suspension of the product from Step 1 (20.4 g, 78 mmol) in THF (250 ml) at RT was added NBS (15.29 g, 86 mmol) portion wise, and the mixture was stirred for 45 min. The mixture was quenched at RT with 5% aq. $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was taken up in DCM (100 ml) and filtered to give a first crop. The filtrate was concentrated *in vacuo* then purified by column chromatography over silica gel (eluting with Hexanes/DCM 80:20 to DCM/EtOAc 95:5) to give a second crop. Both crops were combined to provide intermediate product (20.6 g, 89% yield).

10 Step 3



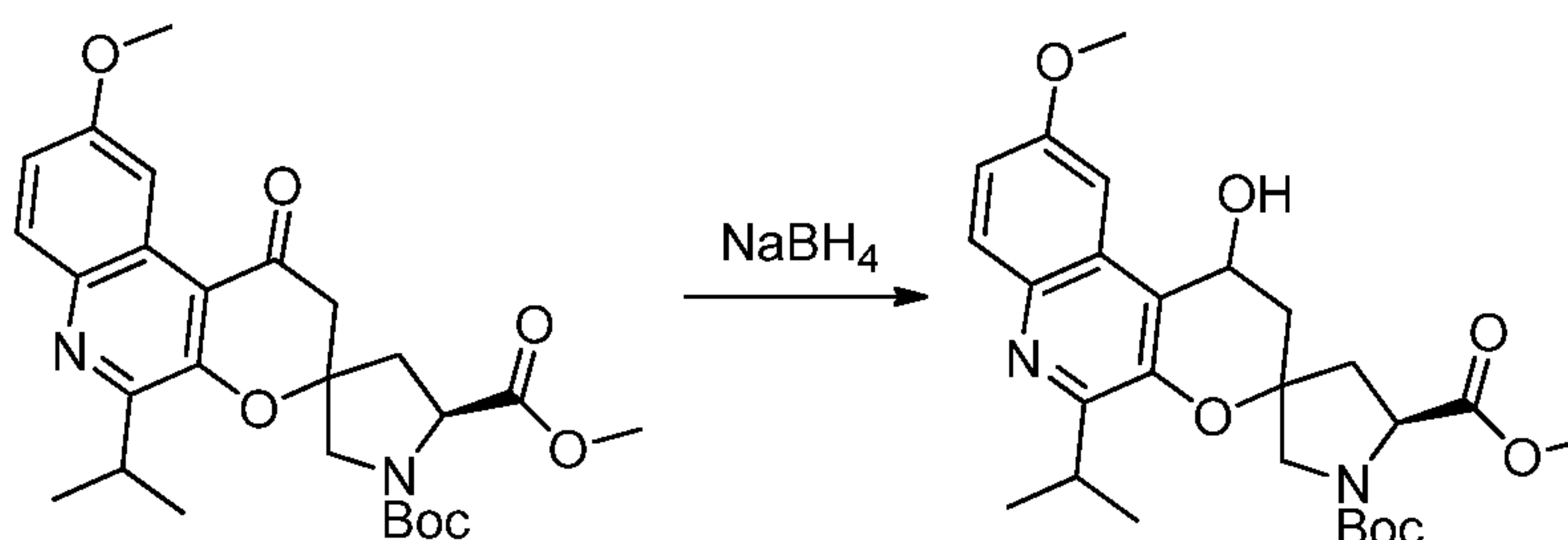
To a solution of the product from Step 2 (20.6 g, 69.5 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (4.01 g, 3.47 mmol) in dioxane (300 ml) at RT was added tributyl(1-ethoxyvinyl)tin (46.9 ml, 139 mmol), and the mixture was warmed to reflux and stirred overnight. The mixture was quenched at RT with 1 N aq. HCl and stirred for 90 min. The reaction was then diluted with water and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 50:50) to give intermediate product (10.53 g, 59% yield) as yellow solid.

20 Step 4



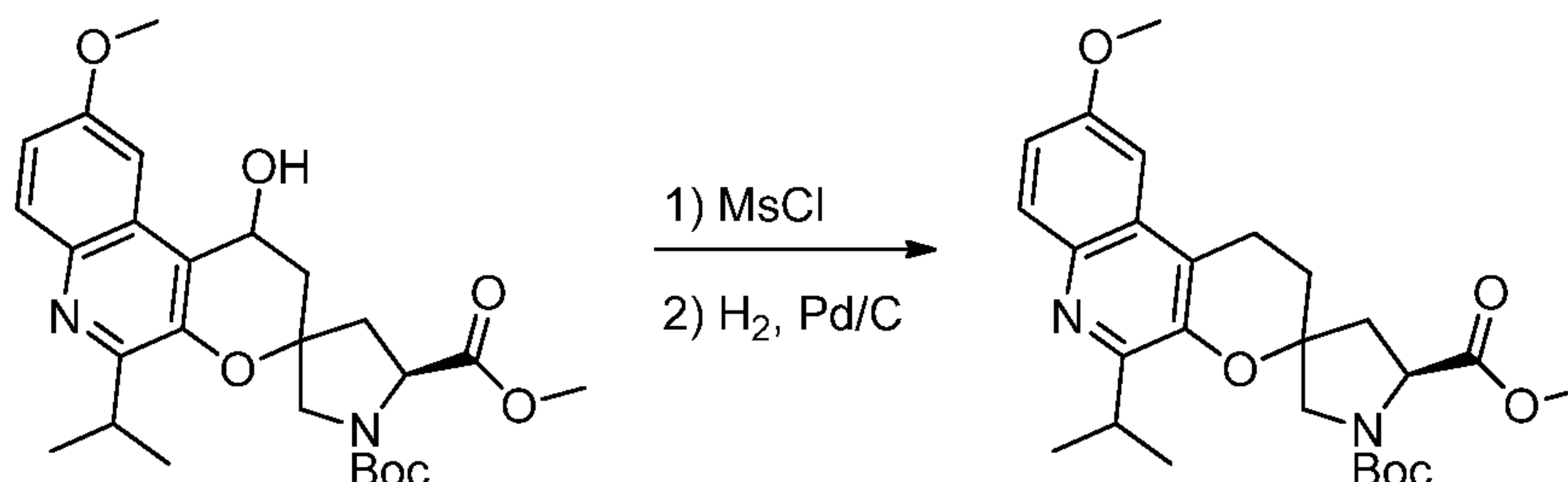
A solution of product from Step 3 (4.30 g, 16.6 mmol), *N*-Boc-4-oxo-L-proline methyl ester (8.07 g, 33.2 mmol) and pyrrolidine (1.33 ml, 16.6 mmol) in MeOH (60 ml) with molecular sieves (4 A powder, 8 g) in a sealed tube was heated in a microwave reactor at 105°C for 90 min. The mixture was cooled, filtered over CELITE and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 30:70) to give a crop of intermediate product (10.53 g) as a mixture of diastereoisomers.

Step 5



To a solution of product from Step 4 (5.26 g, 10.9 mmol) in THF (40 ml) and MeOH (40 ml) at 0°C was added NaBH₄ (0.616 g, 16.3 mmol), and the mixture was allowed to warm to RT and stirred for 1 h. The mixture was quenched at RT with sat. aq. NH₄Cl and extracted with EtOAc. The combined organic fractions were washed with sat. brine then water, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give intermediate product (5.27 g, 100% yield) as a mixture of diastereoisomers.

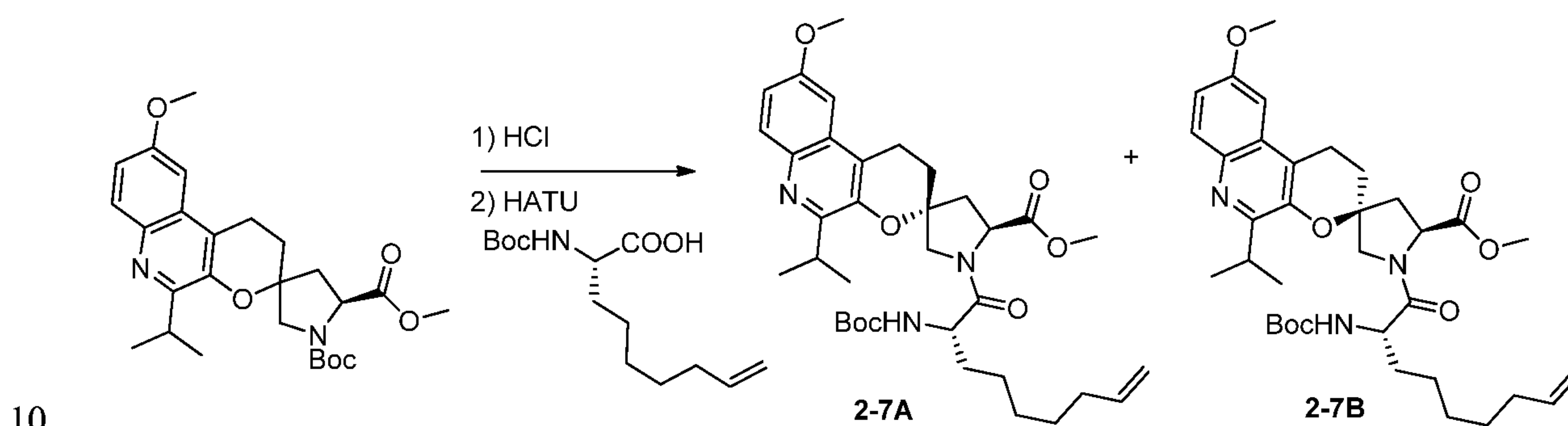
Step 6



To a solution of intermediate product from Step 5 (5.27 g, 10.83 mmol) in DCM (100 ml) at 0°C was added TEA (5.28 ml, 37.9 mmol) then MsCl (1.69 ml, 21.7 mmol), and the

mixture was allowed to warm to RT and stirred overnight. The final mixture was diluted with EtOAc, washed with sat. aq. NaHCO₃, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give a crude chloro intermediate (5.82 g) as yellow foam. A mixture of this crude chloro intermediate (5.82 g, 11.5 mmol) and 10% Pd/C (1.05 g, 0.99 mmol) in EtOAc (100 ml) was hydrogenated at 1 atm for 3 h. The mixture was filtered over CELITE, washing with DCM and MeOH then concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with DCM/MeOH 99:1 to 90:10) to afford intermediate product (5.27 g, 97% yield) as a mixture of diastereoisomers.

Step 7

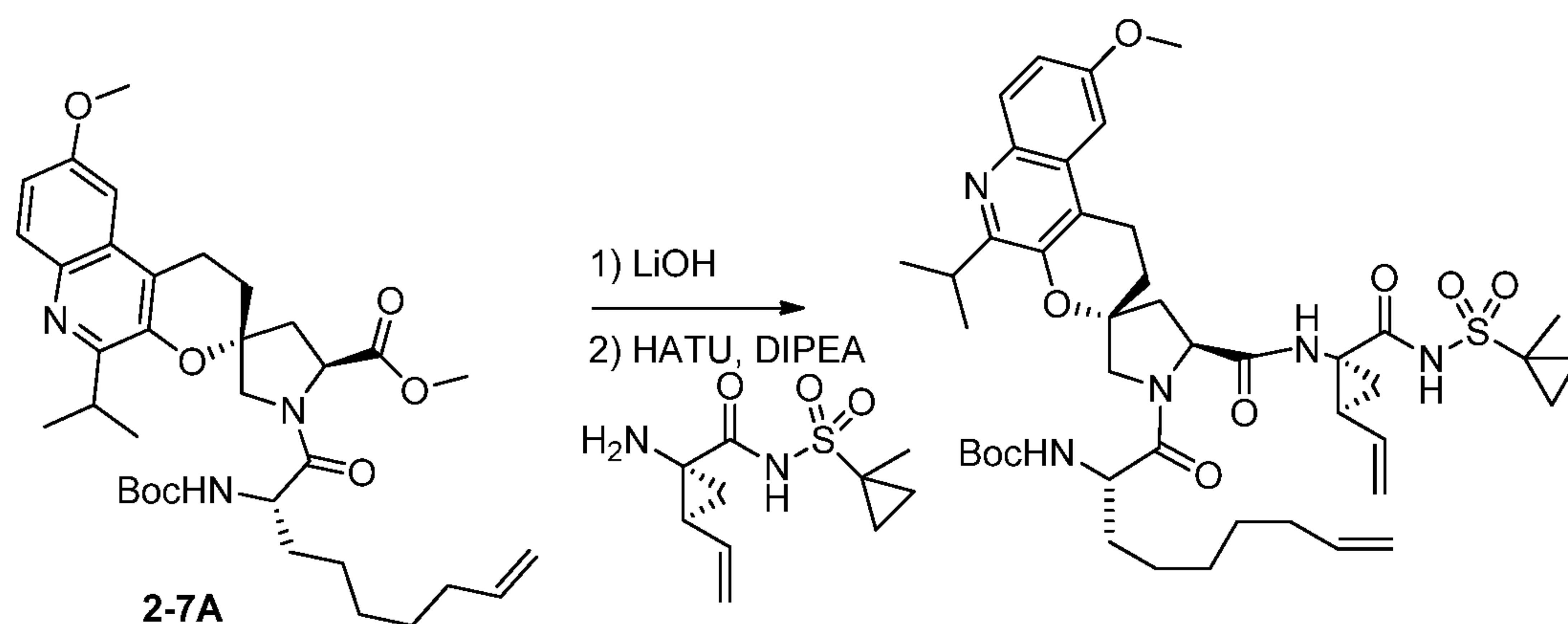


Intermediate product from Step 6 (5.27 g, 11.2 mmol) was diluted with 4 N HCl in dioxane (60 ml, 240 mmol), and the mixture was stirred at RT for 2 h. The mixture was concentrated *in vacuo* to give a deprotected amine as HCl salt (5.06 g, 100% yield). To a solution of this deprotected amine as HCl salt (1.20 g, 2.95 mmol) and (*S*)-2-(*tert*-butoxycarbonylamino)non-8-enoic acid (1.12 g, 4.13 mmol) in DMF (25 ml) at RT was added HATU (1.57 g, 4.13 mmol) followed by DIPEA (2.01 ml, 11.8 mmol), and the mixture was stirred for 1h. More DIPEA (0.5 ml) in DCM (15 ml) was then added, and the reaction was stirred at RT overnight. The final mixture was quenched with water and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 30:70) to provide, in order of elution, diastereoisomer 2-7A (662 mg, 36% yield) followed by diastereoisomer 2-7B (397 mg, 22% yield).

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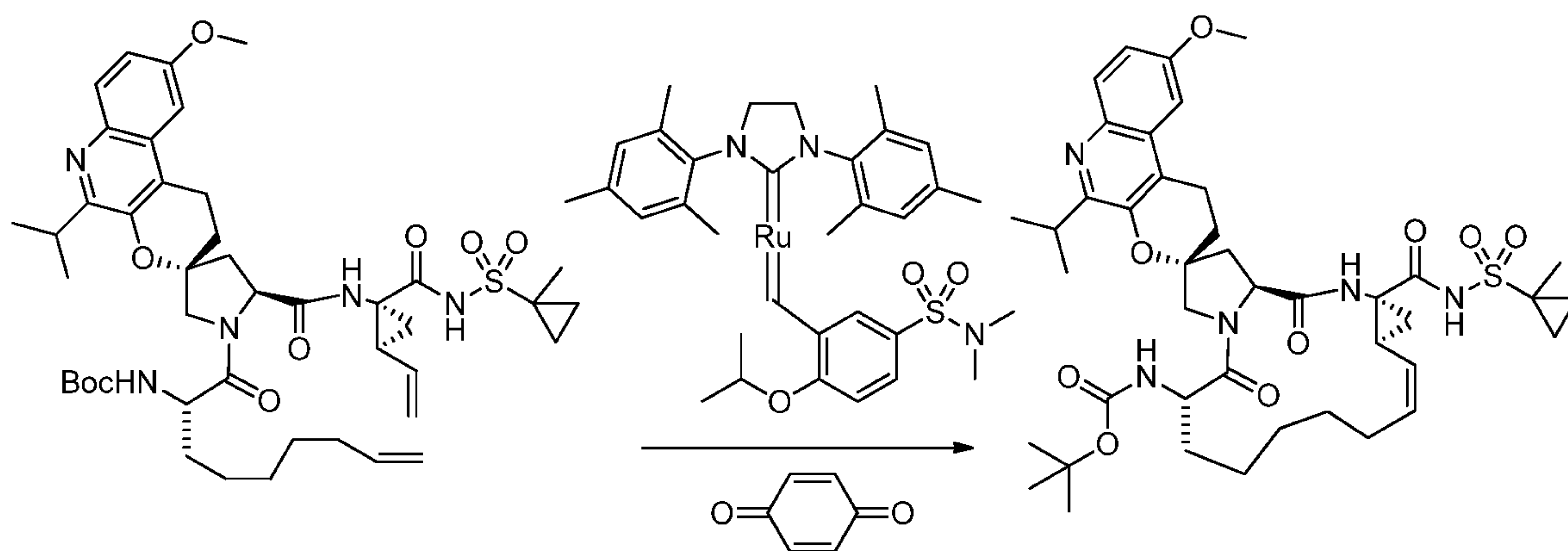
20

Step 8



To a solution of diastereoisomer 2-7A from Step 7 (662 mg, 1.06 mmol) in THF (30 ml), MeOH (30 ml) and water (20 ml) at RT was added LiOH·H₂O (134 mg, 3.18 mmol), and the mixture was warmed to 50°C and stirred for 2h. MeOH and THF were concentrated *in vacuo*, then the mixture was diluted with 0.5 M aq. HCl until pH=2 and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide a crude acid intermediate (570 mg, 88% yield). To a solution of this crude acid intermediate (570 mg, 0.935 mmol) and (1*R*,2*S*)-1-amino-*N*-(1-methylcyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide (297 mg, 1.22 mmol) in DMF (10 ml) at RT was added HATU (462 mg, 1.22 mmol) followed by DIPEA (0.49 ml, 2.80 mmol), and the mixture was stirred 48h at RT. The final mixture was quenched with water and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na₂SO₄ filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (Hexanes/EtOAc 99:1 to EtOAc) to provide intermediate product (660 mg, 84% yield).

15 Step 9

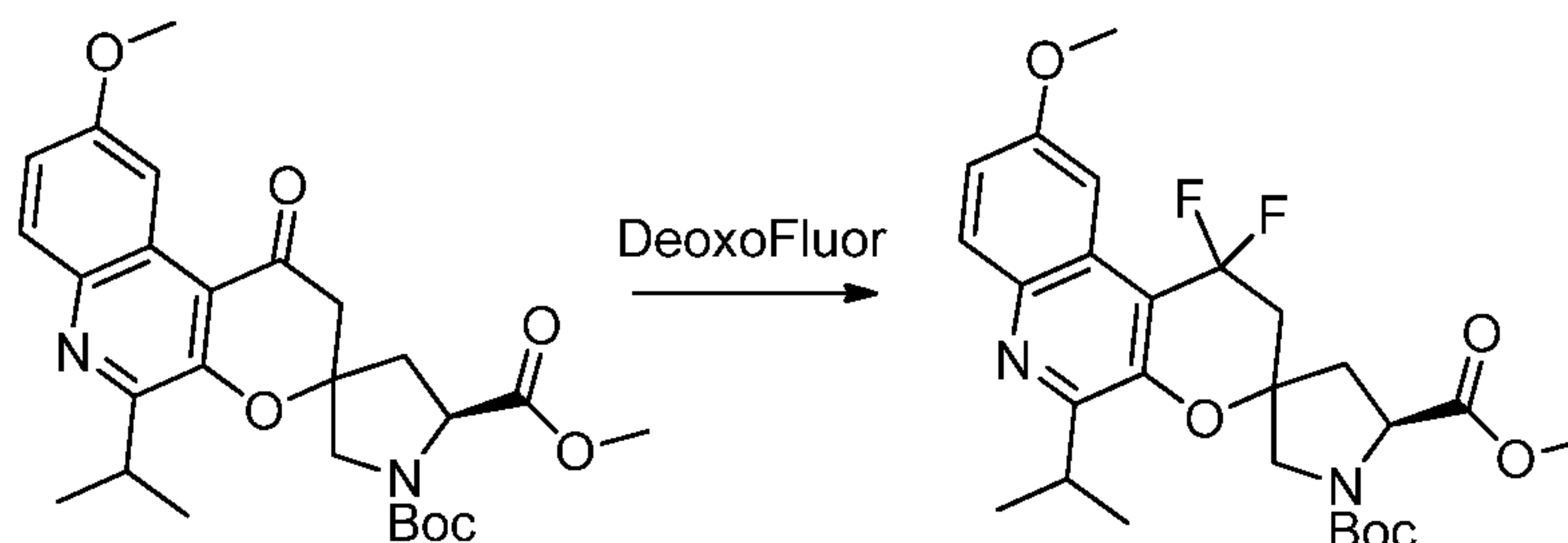


A solution of intermediate product from Step 8 (660 mg, 0.789 mmol), 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene[2-(isopropoxy)-5-(*N,N*-

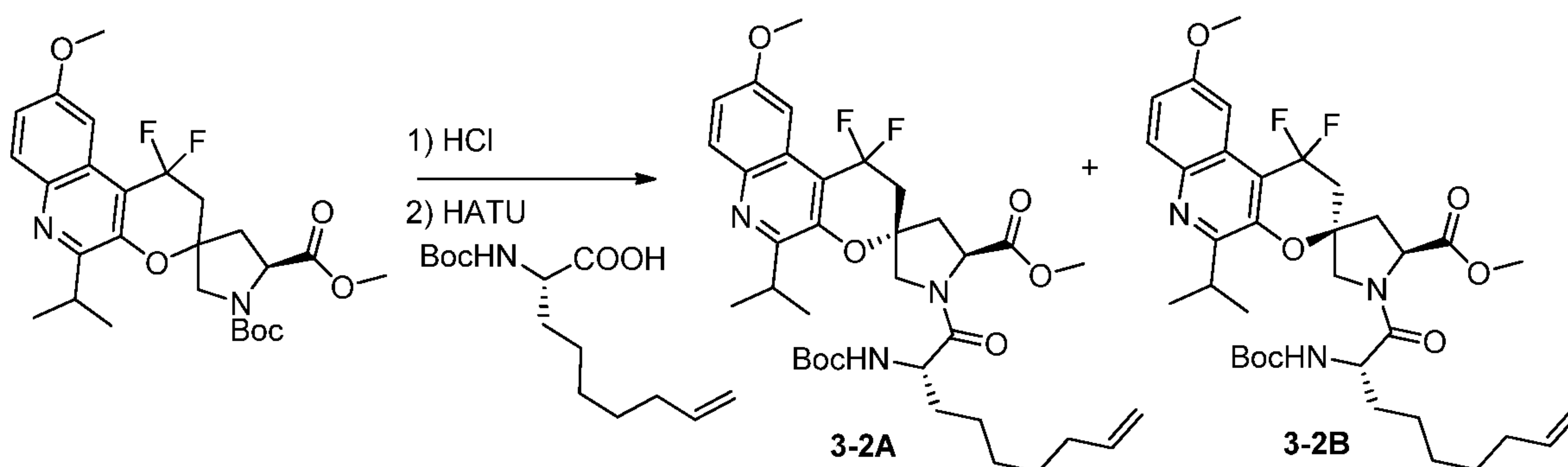
dimethylaminosulfonyl]phenyl]methylenruthenium(II) dichloride (145 mg, 0.197 mmol) and 1,4-benzoquinone (25.6 mg, 0.237 mmol) in DCE (300 ml) was degassed, put under N₂, then warmed to 75°C and stirred for 5h. The mixture was quenched at RT with n-butyl vinyl ether (1 ml) and concentrated to dryness. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) to afford I-2 (550 mg, 86% yield). ¹H-NMR (300 MHz, CDCl₃) δ 10.10 (s, 1H), 7.87 (d, J = 9.0 Hz, 1H), 7.17 (d, J = 9.0 Hz, 1H), 6.94-7.00 (m, 2H), 5.71 (m, 1H), 5.16 (d, J = 7.6 Hz, 1H), 4.99 (m, 1H), 4.59 (m, 1H), 4.36 (d, J = 11.2 Hz, 1H), 4.28 (m, 1H), 3.92 (s, 3H), 3.74 (d, J = 11.2 Hz, 1H), 3.41 (m, 1H), 3.00-3.12 (m, 2H), 2.50-2.60 (m, 2H), 2.21-2.40 (m, 4H), 1.72-2.06 (m, 8H), 1.10-1.55 (m, 11H), 1.47 (s, 3H), 1.31 (s, 9H), 0.80 (br s, 2H); LC-MS (M⁺) Calc. for C₄₂H₅₇NO₉S 808.0 Found 808.2.

Example 3: *tert*-Butyl (2*S*,6*S*,13*aS*,14*aR*,16*aS*,*Z*)-1',1'-difluoro-5'-isopropyl-9'-methoxy-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13*a*,14,14*a*,15,16,16*a*-hexadecahydro-1*H*-spiro[cyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-*c*]quinoline]-6-ylcarbamate (I-3)

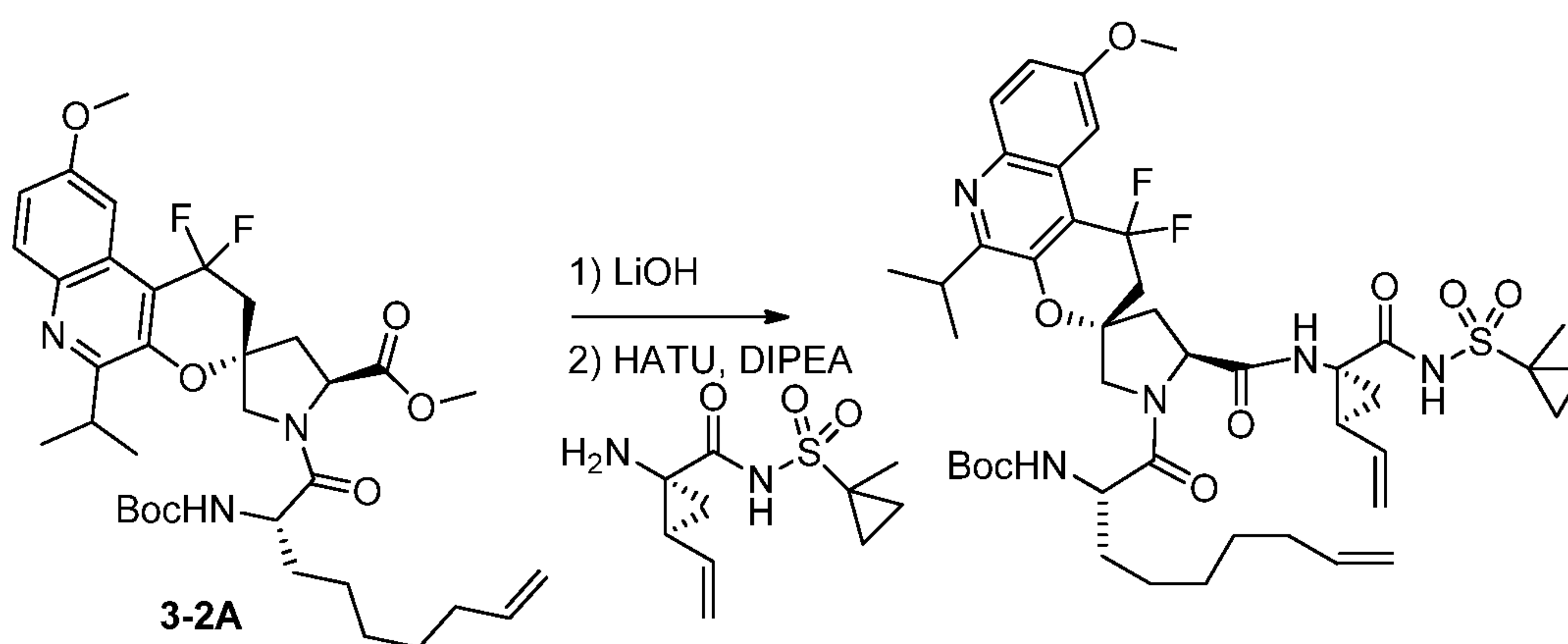
Step 1



To a solution of the intermediate product of Example 2, Step 4 (1.41 g, 2.91 mmol) in DCM (10 ml) was added DEOXOFLUOR (2.68 ml, 14.5 mmol) then EtOH (0.017 ml, 0.29 mmol), and the mixture was warmed to 40°C and stirred overnight. More DEOXOFLUOR (1.10 ml, 5.95 mmol) and EtOH (0.017 ml, 0.29 mmol) were added, and the reaction was stirred at 50°C for 48h. The mixture was poured into sat. aq. NaHCO₃ and DCM, stirred for 60 min, and extracted with DCM and EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 30:70) to give intermediate product (462 mg, 31% yield) as a mixture of diastereoisomers.

Step 2

Intermediate product from Step 1 (462 mg, 0.912 mmol) was diluted with 4N HCl in dioxane (10 ml, 40.0 mmol), and the mixture was stirred at RT for 2h. The mixture was concentrated *in vacuo* to give a deprotected amine as HCl salt (449 mg, 100% yield). To a solution of this deprotected amine as HCl salt (449 mg, 1.01 mmol) and (*S*)-2-(*tert*-butoxycarbonylamino)non-8-enoic acid (344 mg, 1.27 mmol) in DMF (10 ml) at RT was added HATU (482 mg, 1.267 mmol) followed by DIPEA (0.69 ml, 4.06 mmol) and DCM (5 ml) and the mixture was stirred at RT overnight. The mixture was quenched with water and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na₂SO₄ filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 40:60) to give, in order of elution, diastereoisomer 3-2A (418 mg) then diastereoisomer 3-2B (328 mg).

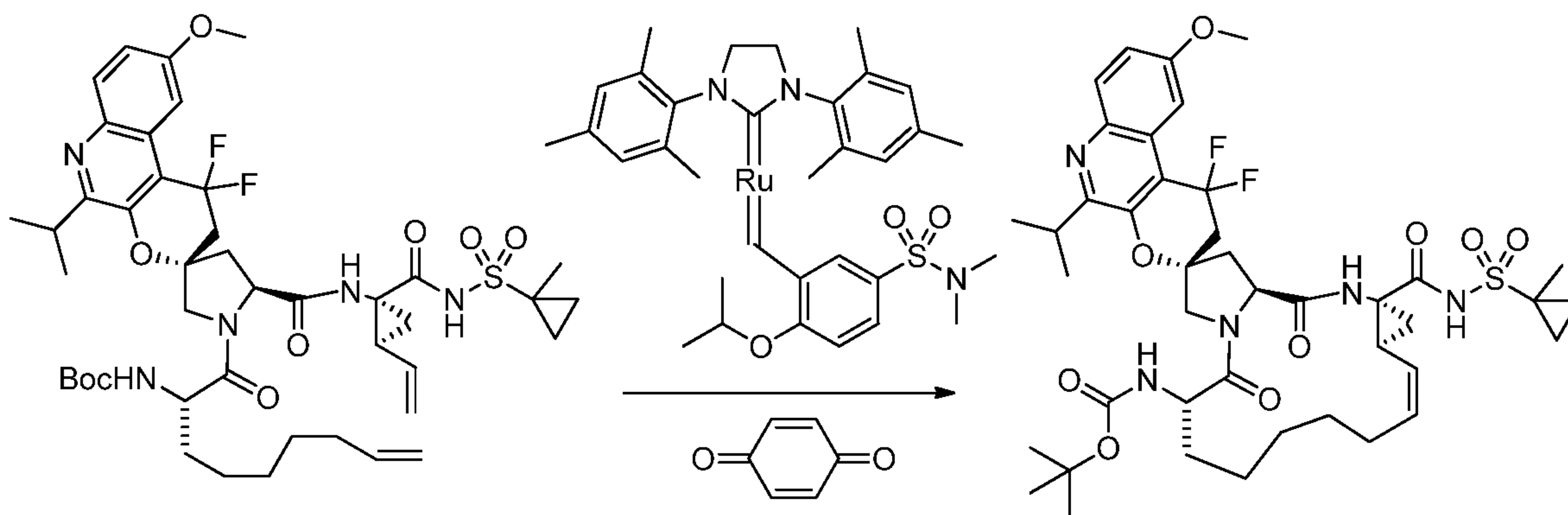
Step 3

15

To a solution of diastereoisomer 3-2A from Step 2 (418 mg, 0.63 mmol) in THF (10 ml), MeOH (10 ml) and water (7 ml) at RT was added LiOH·H₂O (80 mg, 1.90 mmol), and the mixture was warmed to 50°C and stirred for 2h. MeOH and THF were concentrated *in vacuo*, then the mixture was diluted with 0.5 M aq. HCl until pH=2 and extracted with EtOAc.

The combined organic fractions were dried over Na₂SO₄ filtered and concentrated *in vacuo* to give a crude acid intermediate (386 mg, 94% yield). To a solution of this crude acid intermediate (267 mg, 0.413 mmol) and (1*R*,2*S*)-1-amino-*N*-(1-methylcyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide (121 mg, 0.496 mmol) in DMF (7 ml) at RT was added HATU (189 mg, 0.496 mmol) followed by DIPEA (0.21 ml, 1.24 mmol), and the mixture was stirred overnight. The mixture was quenched at RT with water and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 30:70) to afford intermediate product (289 mg, 80% yield).

10 Step 4

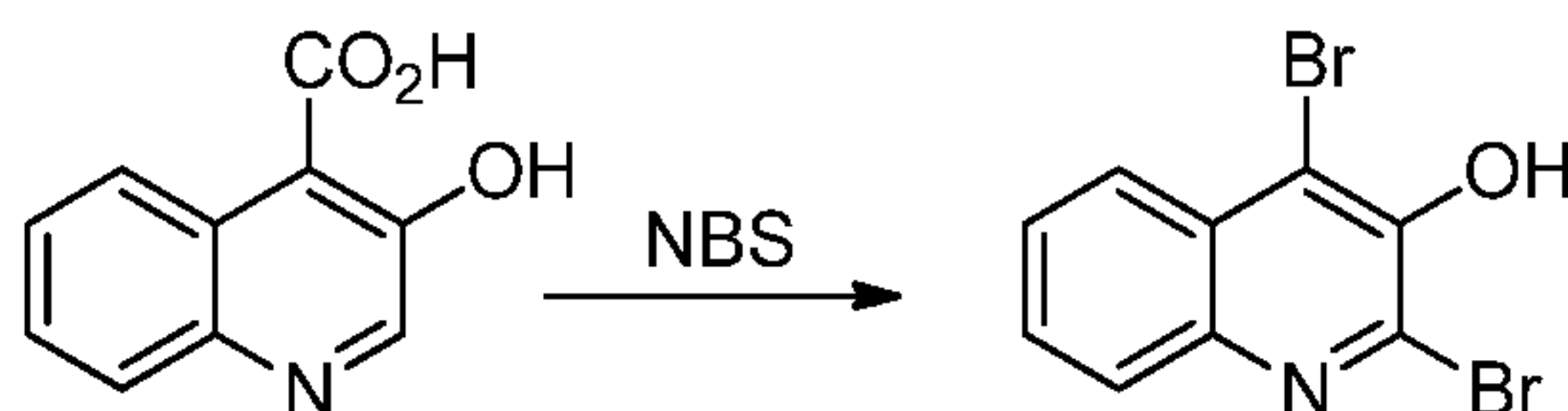


A solution of intermediate product from Step 3 (289 mg, 0.331 mmol), 1,4-benzoquinone (10.75 mg, 0.099 mmol) and 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene[2-(isopropoxy)-5-(*N,N*-dimethylaminosulfonyl)phenyl]methyleneruthenium(II) dichloride (60.8 mg, 0.083 mmol) in DCE (120 ml) at RT was degassed, put under N₂, then warmed to 75°C and stirred 3h. The reaction was quenched at RT with ethyl vinyl ether (1 ml), concentrated *in vacuo*, then purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 30:70) to give I-3 (256 mg, 92% yield). ¹H-NMR (300 MHz, CDCl₃) δ 10.06 (s, 1H), 7.88 (d, J = 9.0 Hz, 1H), 7.49 (s, 1H), 7.22 (d, J = 9.0 Hz, 1H), 6.87 (s, 1H), 5.72 (m, 1H), 4.94-5.05 (m, 2H), 4.59 (m, 1H), 4.50 (d, J = 11.4 Hz, 1H), 4.19 (m, 1H), 3.94 (s, 3H), 3.79 (d, J = 11.4 Hz, 1H), 3.39 (m, 1H), 2.79-2.89 (m, 2H), 2.71 (m, 1H), 2.44-2.58 (m, 2H), 2.31 (m, 1H), 1.72-1.94 (m, 4H), 1.60-1.67 (m, 3H), 1.16-1.50 (m, 12H), 1.47 (s, 3H), 1.28 (s, 9H), 0.81 (br s, 2H); LC-MS (M⁺) Calc. for C₄₂H₅₅F₂N₅O₉S 844.0 Found 844.2.

25 **Example 4: *tert*-Butyl (2*R*,6*S*,13*aS*,14*aR*,16*aS*,*Z*)-14*a*-(1-methylcyclopropylsulfonyl carbamoyl)-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13*a*,14,14*a*,15,16,16*a*-**

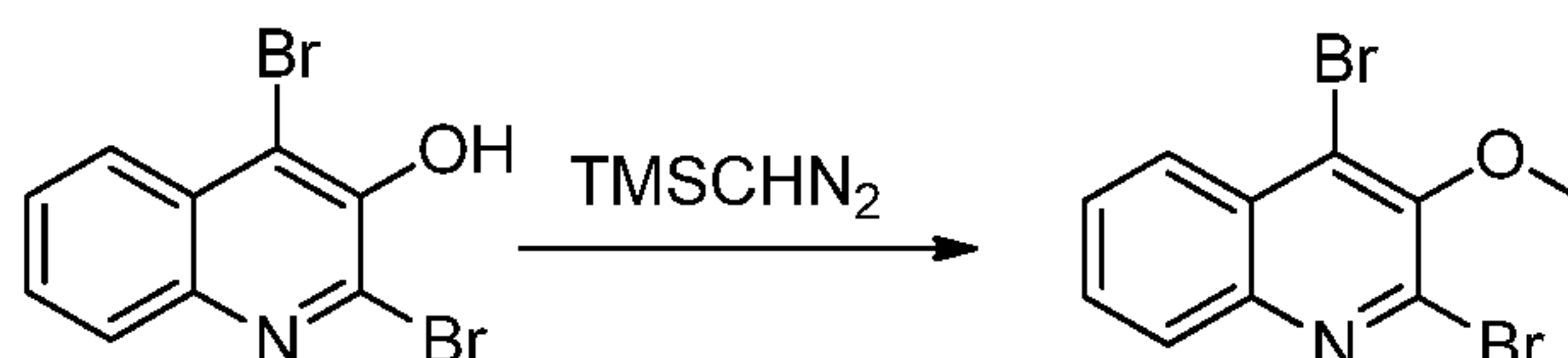
hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-6-ylcarbamate (I-4)

Step 1



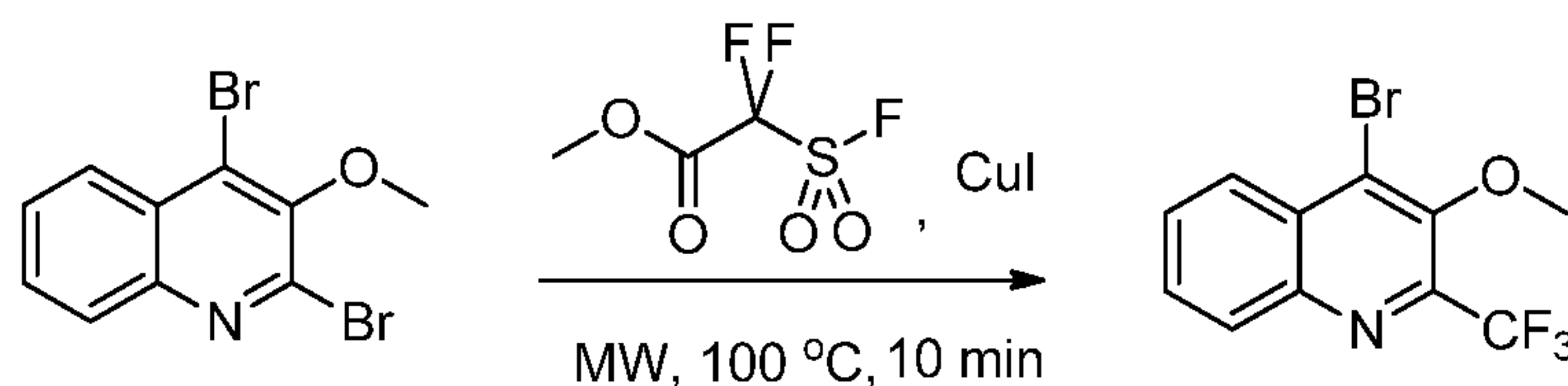
5 A solution of 3-hydroxyquinoline-4-carboxylic acid (10 g, 52.9 mmol) in THF (320 ml) was treated with NBS (17.88 g, 100 mmol) and stirred at RT for 2.5h. The reaction mixture was then extracted with EtOAc and washed with water followed by aq. Na₂S₂O₃ solution. The combined organic layers were dried with Na₂SO₄ and concentrated to afford the intermediate product.

10 Step 2



To a solution of crude product of Step 1 (18.5 g, 61.1 mmol) in MeOH (40 ml). Toluene (200 ml) and (trimethylsilyl)diazomethane (TMSCHN₂; 61.1 ml, 122 mmol) were added at 0°C and stirred. The reaction mixture was warmed to RT and stirred for 30 min. Crude LC-MS showed total consumption of starting material. AcOH (3 ml) was added to the reaction mixture until bubbling stopped. The organics were evaporated, and the crude residue was dissolved in toluene and evaporated to get the crude product as brown solid, which was purified by silica gel column chromatography using (0-5)% EtOAc-Hexanes as mobile phase to get the pure intermediate product (12 g, 37.9 mmol, 62.0% yield).

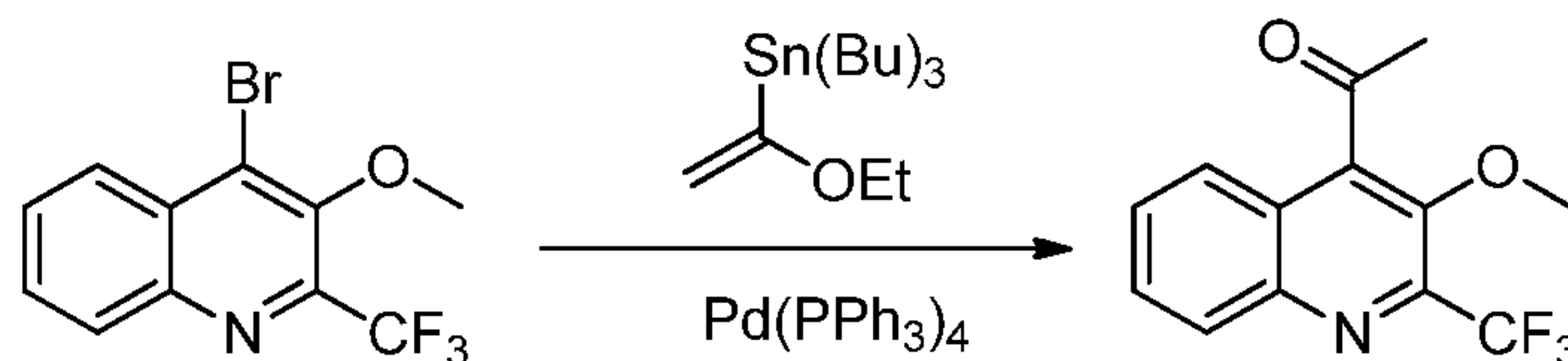
20 Step 3



To a solution of the product of Step 2 (6 g, 18.93 mmol) in DMF (32 ml) was added Cu-I (1.803 g, 9.46 mmol) followed by MFSDA (7.22 ml, 56.8 mmol). The reaction mixture was then heated in microwave at 100°C for 30 min at high absorbance. The reaction was diluted with EtOAc and washed with brine and water. The organics were dried with Na₂SO₄

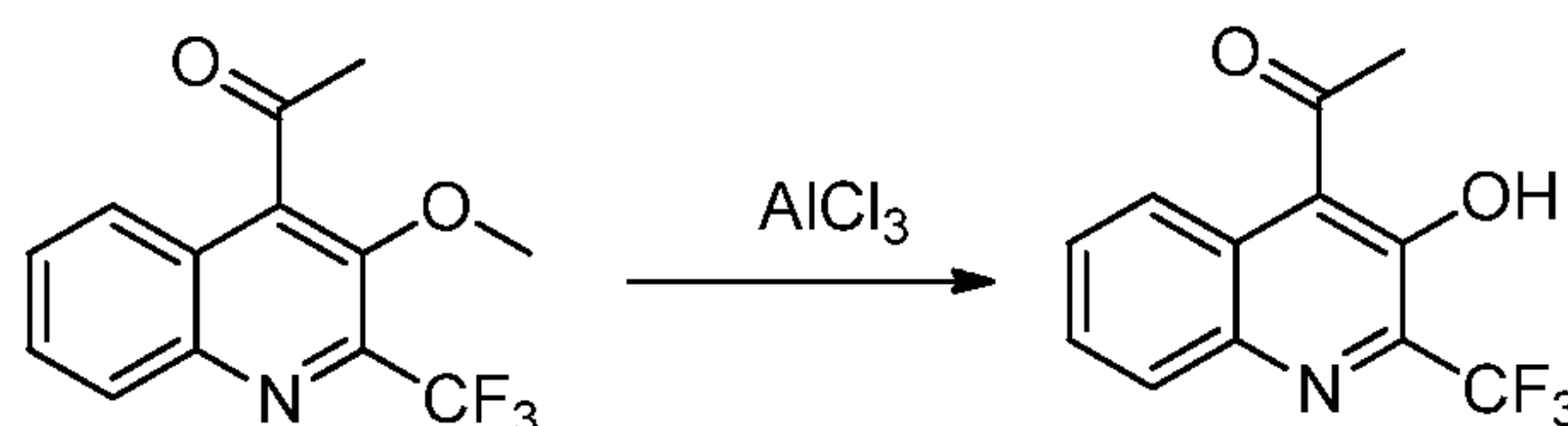
concentrated and purification with 40% hexanes/EtOAc gave intermediate product (2.72 g, 8.89 mmol, 46.9% yield).

Step 4



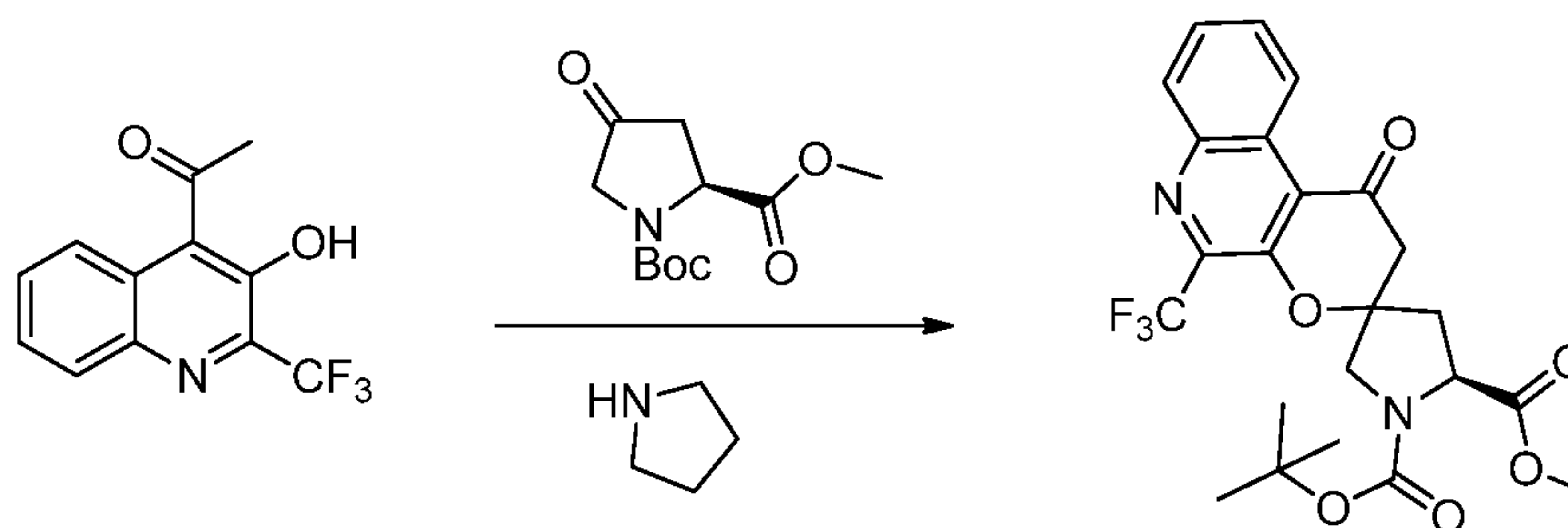
5 A mixture of the product of Step 3 (2.72 g, 8.89 mmol), tributyl(1-ethoxyvinyl)tin (6.00 ml, 17.77 mmol) and Pd(PPh₃)₄ (0.513 g, 0.444 mmol) in dioxane (40 ml) was heated at reflux overnight. The reaction mixture was cooled to RT, added ~10 ml of 1N HCl and stirred at RT for 90 min. The reaction mixture was then diluted with water, extracted 3x with DCM. The combined organic layers were washed with brine, dried over MgSO₄, filtered, concentrated and
10 chromatography eluting with 0-15% EtOAc-hexanes to give product (1.3 g, 4.83 mmol, 54.3% yield).

Step 5



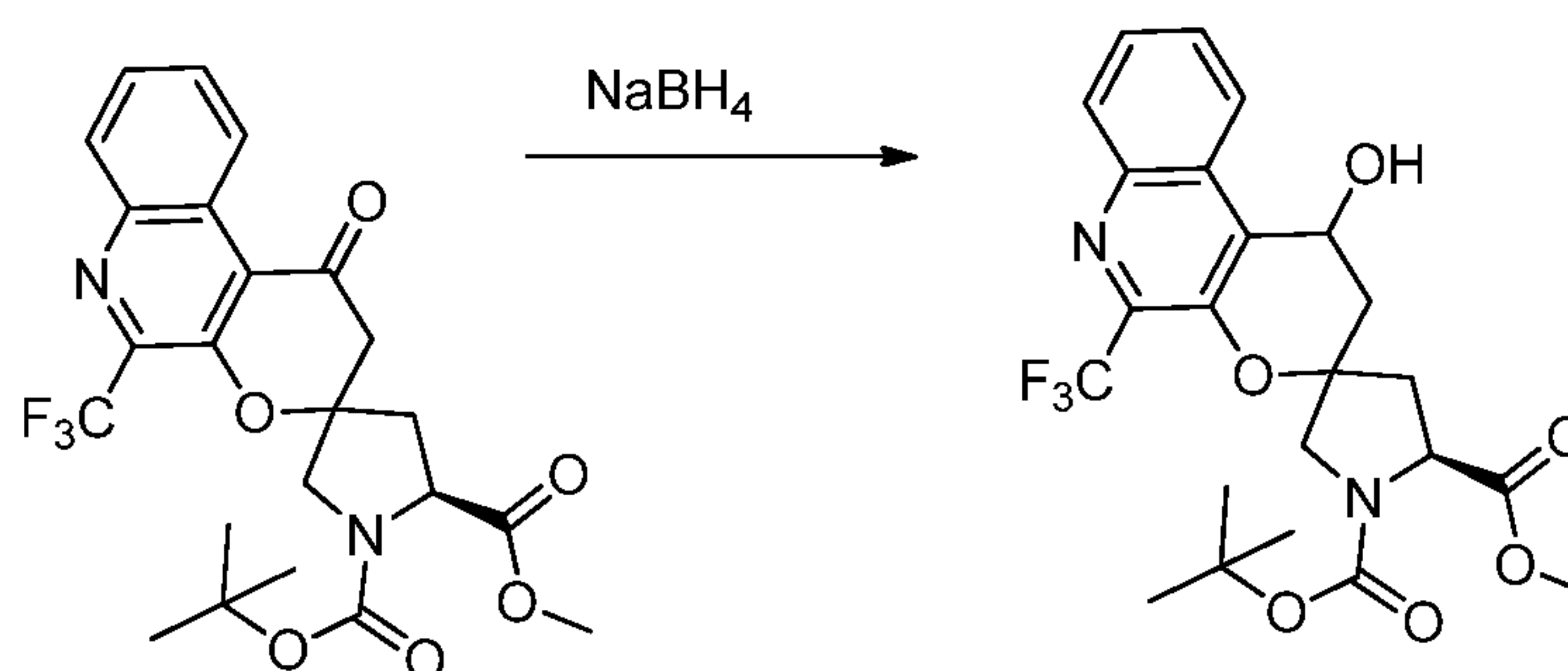
To a solution of the product of Step 5 (1.3 g, 4.83 mmol) in DCM (50 ml) at 0°C
15 was added AlCl₃ (5.79 g, 43.5 mmol) in one rapid portion, and the resulting mixture was allowed to stir at RT overnight. The reaction mixture was quenched with sat. solution of Rochelle's salt (aq.), and the biphasic reaction mixture was stirred at RT for 1 h. The organic phase was separated, and the aq. layer was extracted 3x with DCM. The combined organic layers were then washed with water and brine, filtered, and concentrated. The residue was then purified by
20 column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 60:40) to give the product (310 mg, 1.215 mmol, 25.2% yield).

Step 6



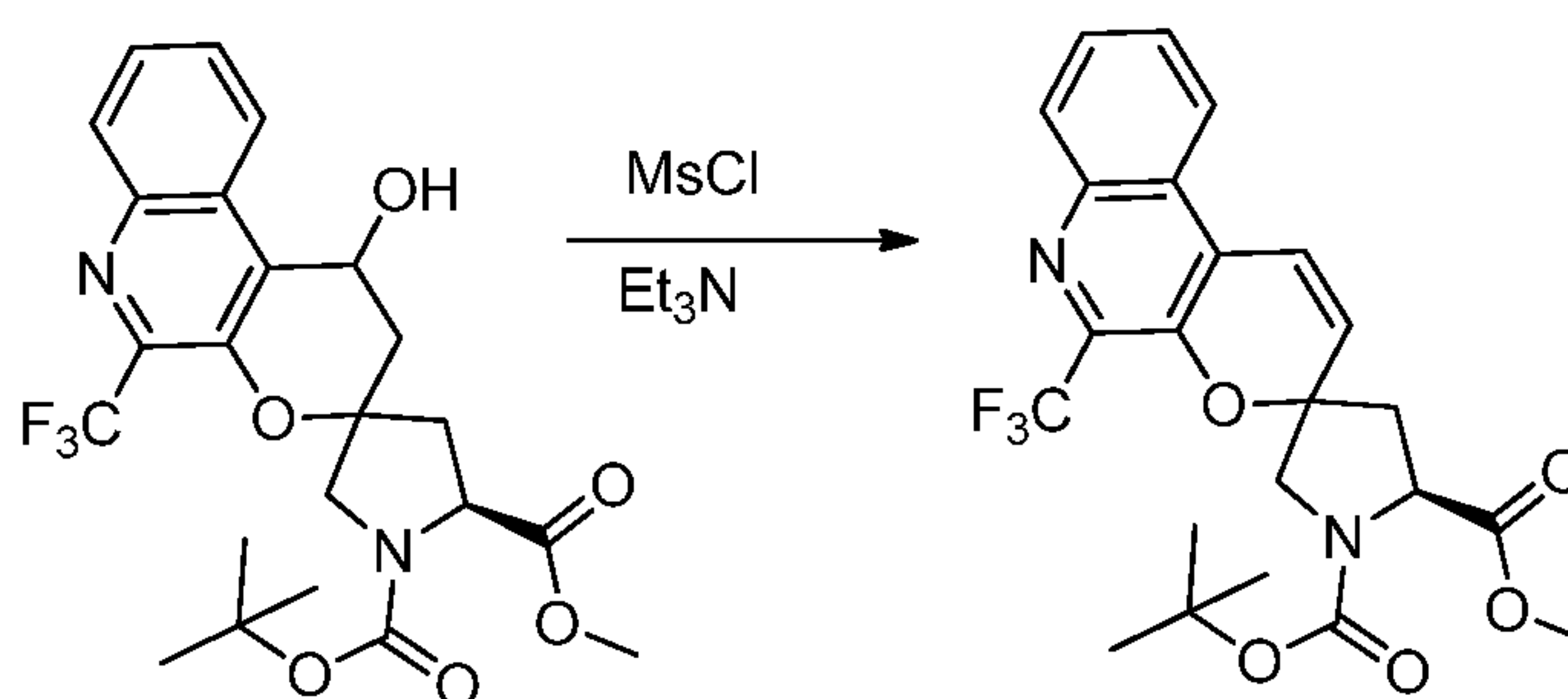
To a solution of the product of Step 5 (0.310 g, 1.215 mmol) in MeOH (4 ml) in a microwave vial was added *N*-Boc-4-oxo-L-proline methyl ester (0.591 g, 2.430 mmol), and pyrrolidine (0.039 ml, 0.486 mmol). To this was then added molecular sieves (4A beads), and the reaction was heated to 105°C and stirred for 30 min in the BIOTOPE INITIATOR microwave reactor on very high absorbance. The reaction was cooled to RT, and the molecular sieves were filtered off. The solvent was evaporated under reduced pressure. The crude orange oil was purified by column chromatography using a silica gel column on an ANA-LOGIX, eluting with hexanes/acetone (0-50%) over the course of 30 min to give the product (565 mg, 1.176 mmol, 97% yield) as a mixture of diastereomers.

10 Step 7



A solution of the product of Step 6 (565 mg, 1.176 mmol) was dissolved in a mixture of THF (10 ml) and MeOH (10 ml). The mixture was cooled to 0°C and stirred for 15 min. NaBH₄ (57.8 mg, 1.529 mmol) was then added to the reaction, and mixture was stirred for 30 min at 0°C. The reaction was then stirred at RT for 1h. The solvent was diluted with EtOAc and quenched with aq. NH₄Cl at RT. The organic fraction was washed with 1 M NaOH, brine, water, dried (Na₂SO₄), filtered, and the solvent was evaporated under reduced pressure. The crude yellow solid product (567 mg, 1.175 mmol, 100% yield) was taken to the next step.

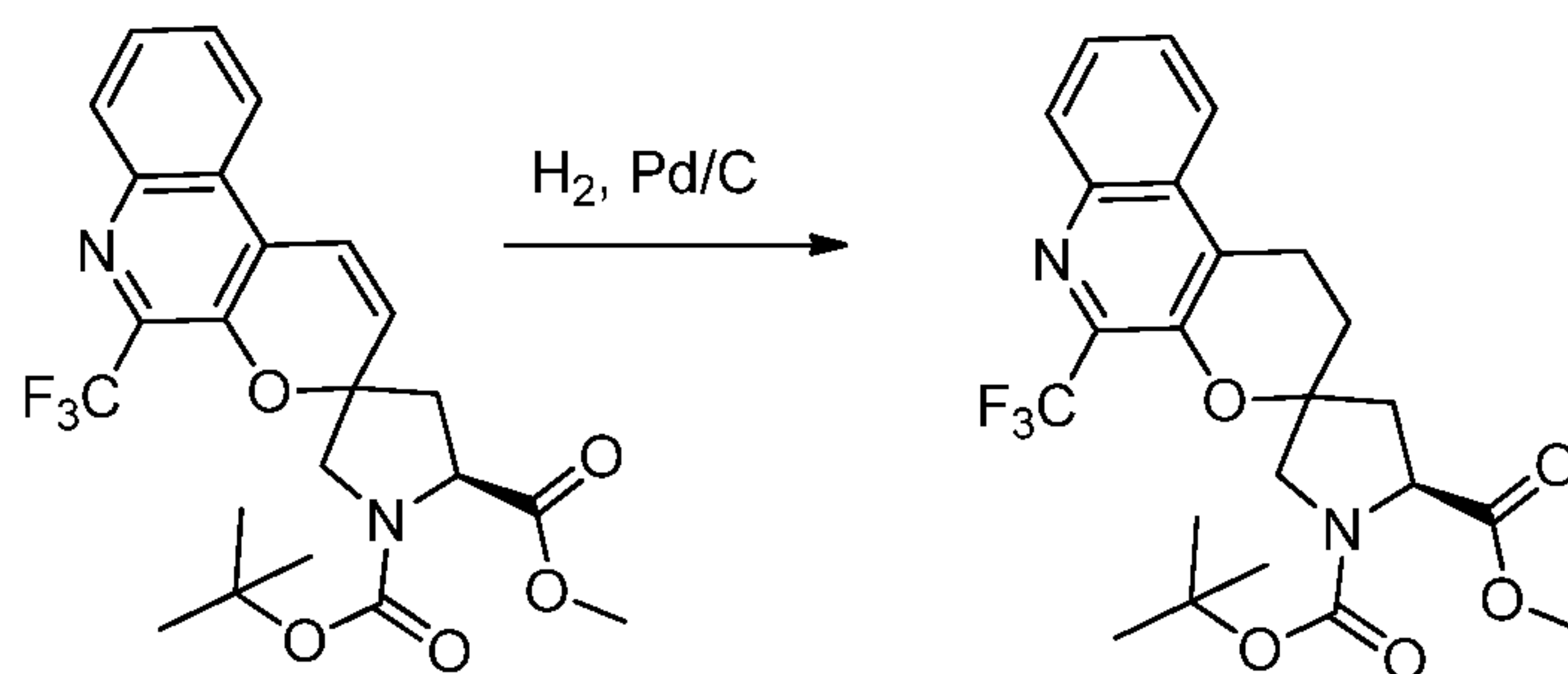
20 Step 8



The product of Step 7 (567 mg, 1.175 mmol) and TEA (0.490 ml, 3.53 mmol) were added to DCM (6 ml). MsCl (0.136 ml, 1.763 mmol) was then added to the solution and

allowed to stir overnight under N₂. The reaction was then quenched with sat. NH₄Cl, and the mixture were extracted with DCM (3 x 10 mL). The combined organic fractions were washed with water and dried (Na₂SO₄), filtered, and the solvent was evaporated under reduced pressure to obtain the product (282 mg, 0.607 mmol, 51.7% yield).

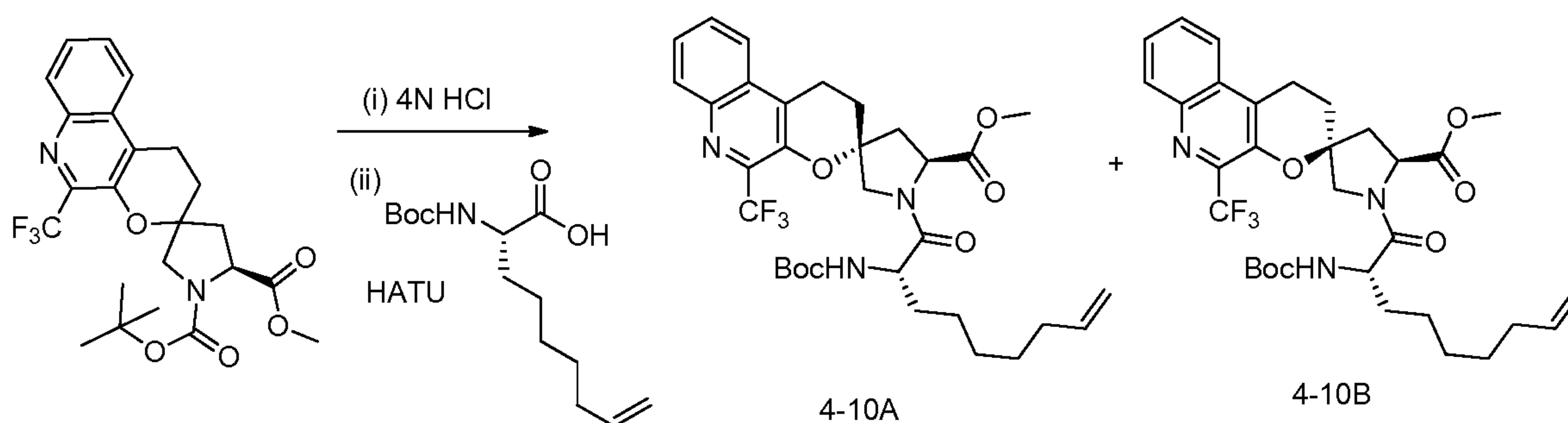
5 Step 9



The product of Step 8 (282 mg, 0.607 mmol) was added to a stirred, cooled RT solution of EtOAc (8 ml). Pd/C (36 mg, 0.034 mmol) was added and after evacuating and back-filling with H₂, the reaction was allowed to stir at RT attached to a H₂-filled balloon for 30 min.

10 The reaction mixture was diluted with DCM (15 mL), and the suspension was filtered through a pad of CELITE. The insoluble's were washed further with DCM, and the filtrate was concentrated *in vacuo* to afford product (280 mg, 0.600 mmol, 99% yield).

Step 10

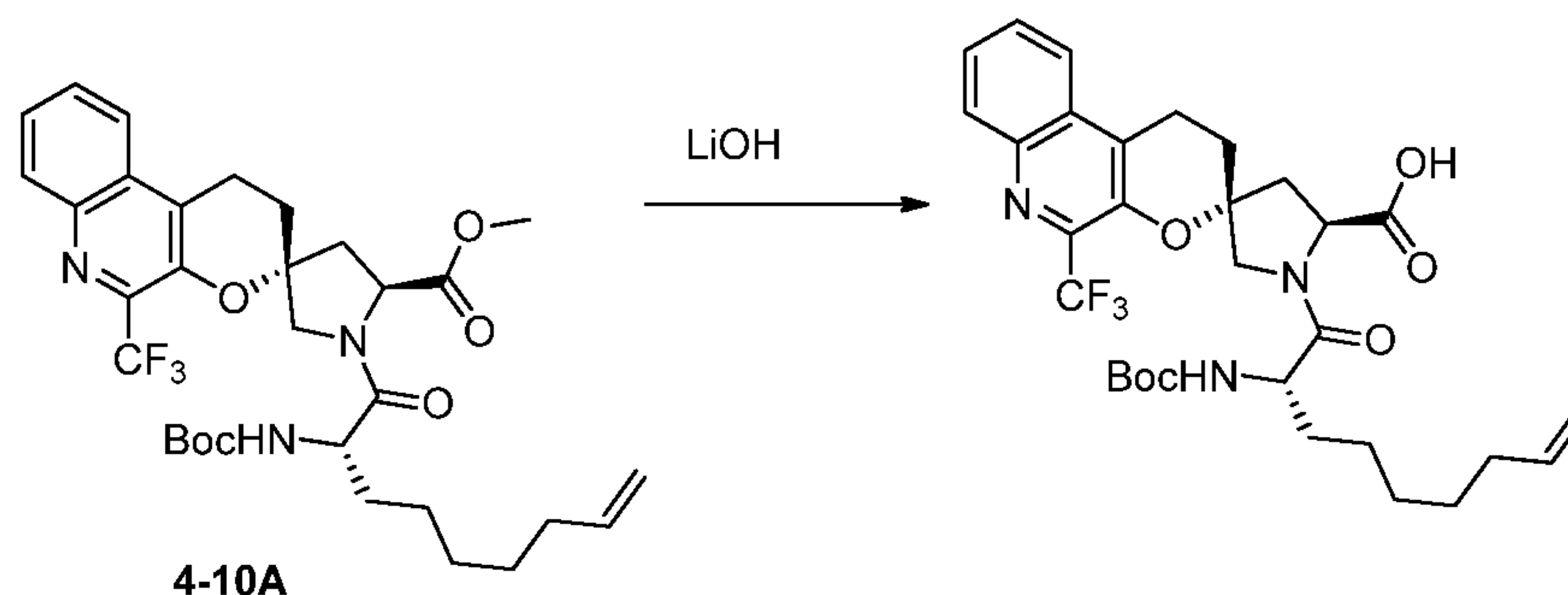


15 A solution of the product of Step 9 (280 mg, 0.600 mmol) in 4N HCl in dioxane (30 ml) was stirred at RT for 1h, evaporated 2x with toluene, 2x with ether to give the amine hydrochloride salt (230 mg, 0.571 mmol, 95% yield) and used as such for the next step. A slurry of amine salt (230 mg, 0.571 mmol), (*S*)-2-(*tert*-butoxycarbonylamino)non-8-enoic acid (388 mg, 0.857 mmol), HATU (326 mg, 0.857 mmol) and TEA (0.239 ml, 1.713 mmol) in DMF (7 ml)

20 was stirred at RT overnight. The reaction mixture was diluted with water, and extracted 3x with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered,

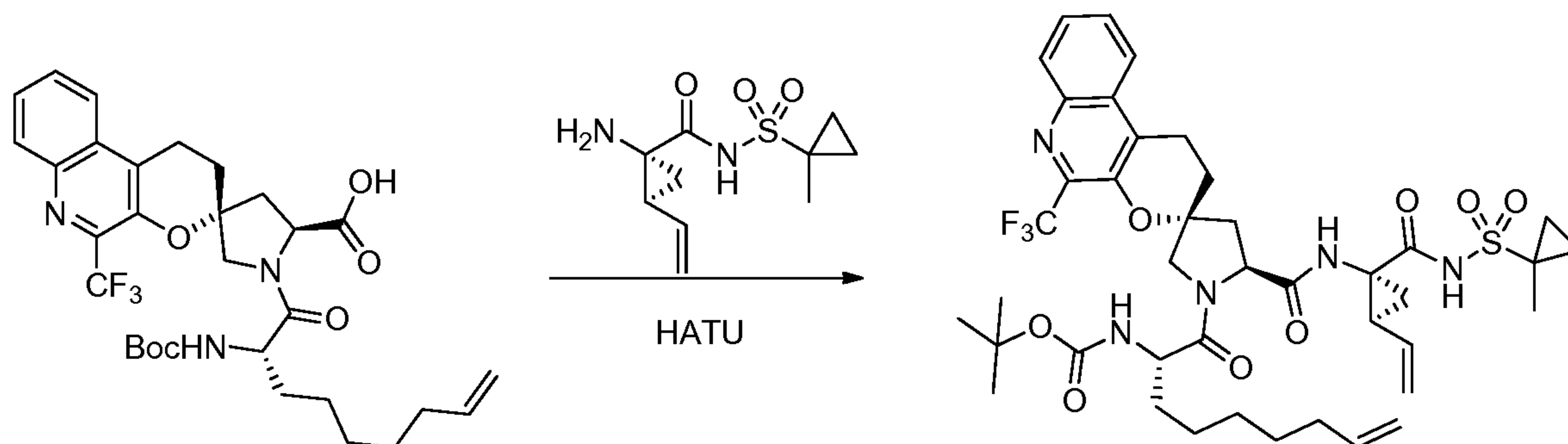
concentrated and chromatographed with 0-50-100% EtOAc-hexanes to give product 4-10A (156 mg, 0.252 mmol, 44.1% yield) and 4-10B (45 mg, 0.073 mmol, 12.72% yield).

Step 11

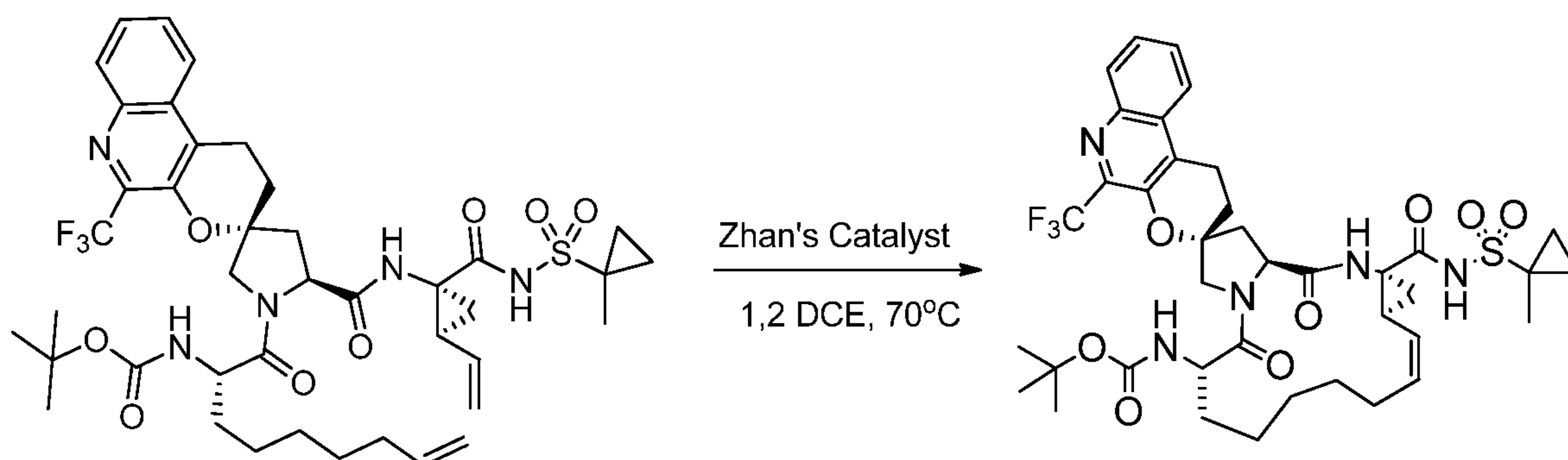


- 5 A mixture of 4-10A (156 mg, 0.252 mmol) and LiOH·H₂O (42.3 mg, 1.007 mmol) in THF (1 ml), MeOH (1 ml) and water (0.7 ml) was stirred at 60°C for 1h. The reaction was then cooled diluted with water, acidified with 1N HCl, extracted 3x with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered and evaporated to dryness to give the crude acid product (130 mg, 0.215 mmol, 85% yield).

10 Step 12

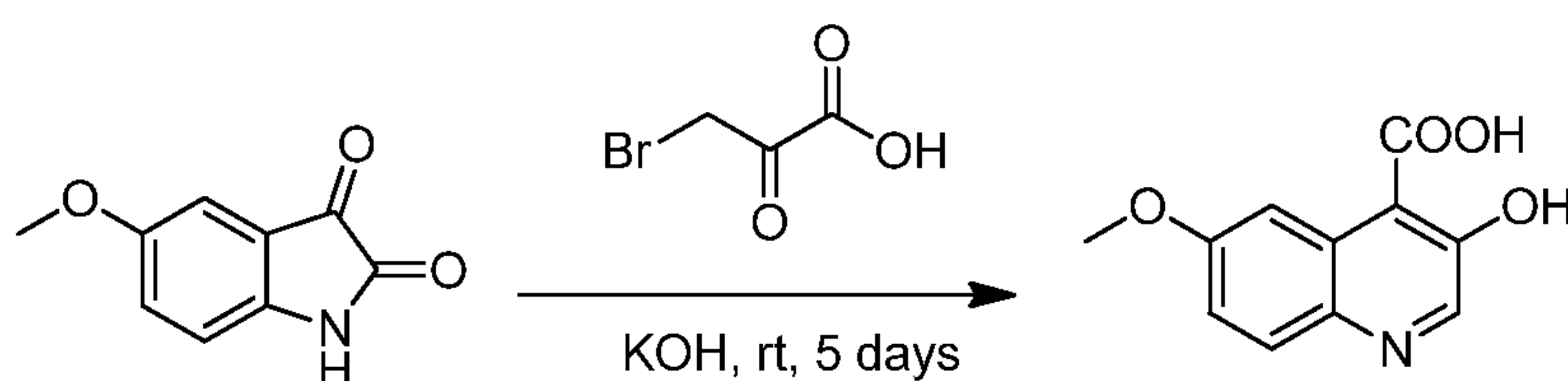


- 15 To a stirred solution of the product of Step 11 (130 mg, 0.215 mmol), (1*R*,2*S*)-1-amino-*N*-(1-methylcyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide (79 mg, 0.322 mmol), and HATU (122 mg, 0.322 mmol) in DMF (2.5 ml) was added TEA (0.09 ml, 0.64 mmol) and stirred. The mixture was stirred at RT overnight. The mixture was diluted with Et₂O (20 mL), washed with water (15 ml), and back extracted with Et₂O (20 ml). The combined organics were dried (Na₂SO₄), filtered, and the solvent was evaporated under reduced pressure. The crude yellow oil was purified by column chromatography eluting with hexanes/EtOAc (0% to 95%) to give the product (82 mg, 0.099 mmol, 45.9% yield) as yellow solid.

Step 13

A solution of the product of Step 12 (86 mg, 0.103 mmol), Zhan's catalyst (18.96 mg, 0.026 mmol) and 1,4-benzoquinone (3.35 mg, 0.031 mmol) in DCE (35 ml) was stirred in an oil-bath kept at $\sim 75^\circ\text{C}$. After the reaction mixture was cooled to RT and quenched with the addition of butyl vinyl ether (0.5 ml), the volatiles were removed *in vacuo*, and the resulting dark green/brown residue was directly purified by column 30% acetone/hexanes (ANALOGIX) to give I-4 (61 mg, 0.076 mmol, 73.4% yield). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 10.06 (s, 1H), 8.13-8.11 (m, 1H), 7.86-7.83 (m, 1H), 7.68-7.63 (m, 2H), 6.68 (br s, 1H), 5.76-5.69 (m, 1H), 5.05-4.99 (m, 2H), 4.60 (dd, $J = 10.0\text{Hz}, 7\text{Hz}$, 1H), 4.44 (d, $J = 13.0\text{ Hz}$, 1H), 4.21-4.16 (m, 1H), 3.71 (d, $J = 11\text{ Hz}$, 1H), 3.32-3.15 (m, 2H), 2.58-2.33 (m, 6H), 1.95-1.76 (m, 4H), 1.6-0.8 (m, 23H). MS $m/e = 804.2$ (MH^+).

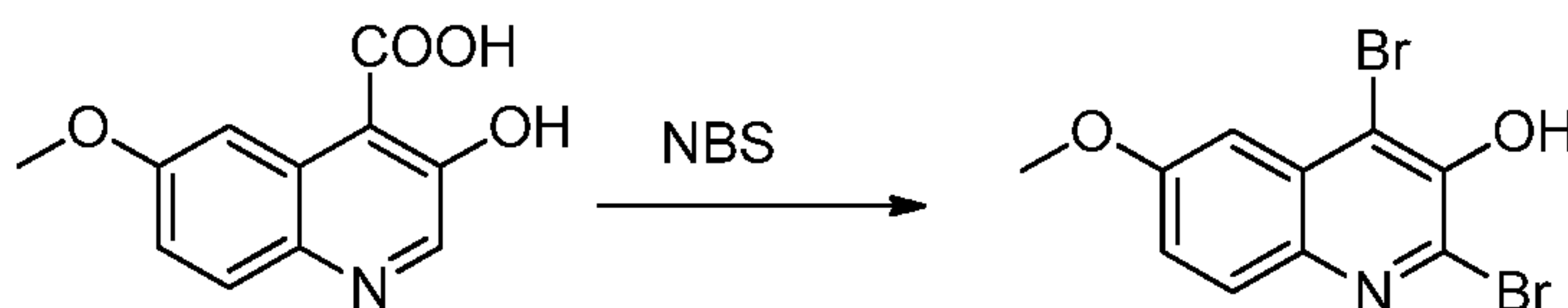
Example 5: *tert*-Butyl (2R,6S,13aS,14aR,16aS,Z)-9'-methoxy-14a-(1-methylcyclopropyl sulfonycarbamoyl)-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-6-ylcarbamate (I-5)

Step 1

A solution of 5-methoxyindoline-2,3-dione (15 g, 85 mmol) in water (150 ml) was treated with KOH (38.0 g, 677 mmol) and heated at 80°C until it completely dissolved. The reaction mixture was cooled and treated with bromopyruvic acid (18.94 g, 113 mmol) and stirred at RT for 5d. The reaction mixture was treated with NaHSO_3 (3.0 g) and slowly acidified with concentrated HCl. The solid product (9.8 g, 44.7 mmol, 52.8% yield) separating out was filtered

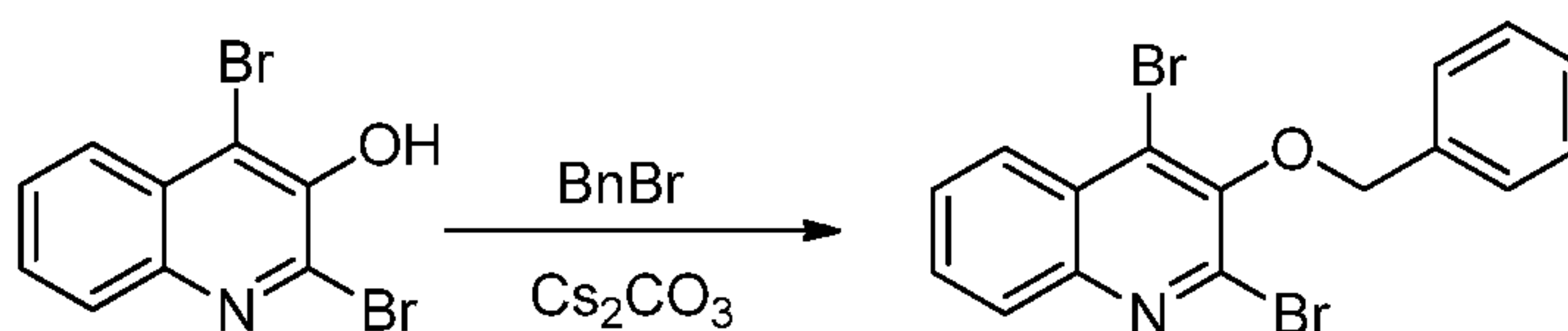
washed thoroughly with water, dried in the oven at 70°C under vacuum overnight and used in the next step.

Step 2



5 A solution of the product of Step 1 (5 g, 22.81 mmol) in THF (200 ml) was treated with NBS (8.94 g, 50.2 mmol) and stirred at RT for 2.5h. The solution was extracted with EtOAc and washed with water and aq. Na₂S₂O₃ solution. The combined organic layers were dried over anhydrous Na₂SO₄ to obtain product (3 g, 9.01 mmol, 39.5% yield).

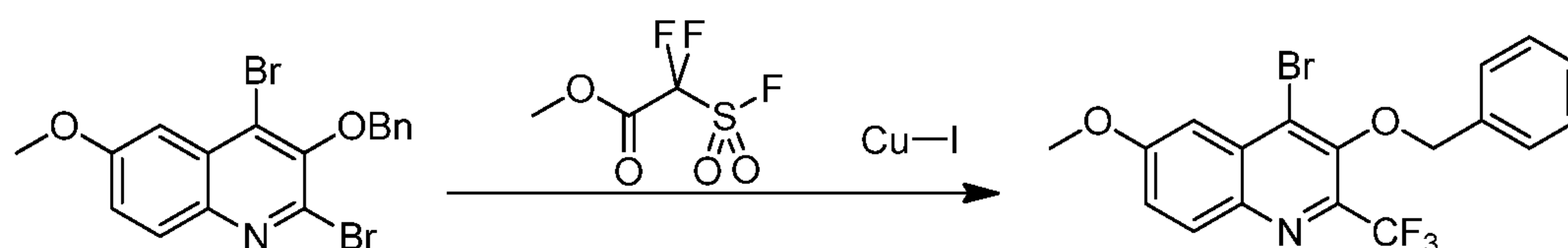
Step 3



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The product of Step 2 (3 g, 9.01 mmol) dissolved in DMF (25 ml) in a N₂-evacuated flask. BnBr (1.393 ml, 11.71 mmol) and Cs₂CO₃ (5.87 g, 18.02 mmol) was added. The reaction was stirred for 2h. The reaction mixture was added to a separatory funnel containing aq. NaHCO₃. The reaction product was extracted with EtOAc. The combined
15 organic fractions were dried (Na₂SO₄) and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with 0% to 30% EtOAc in hexanes over ten column volumes to give the pure product (1.48 g, 38.8% yield).

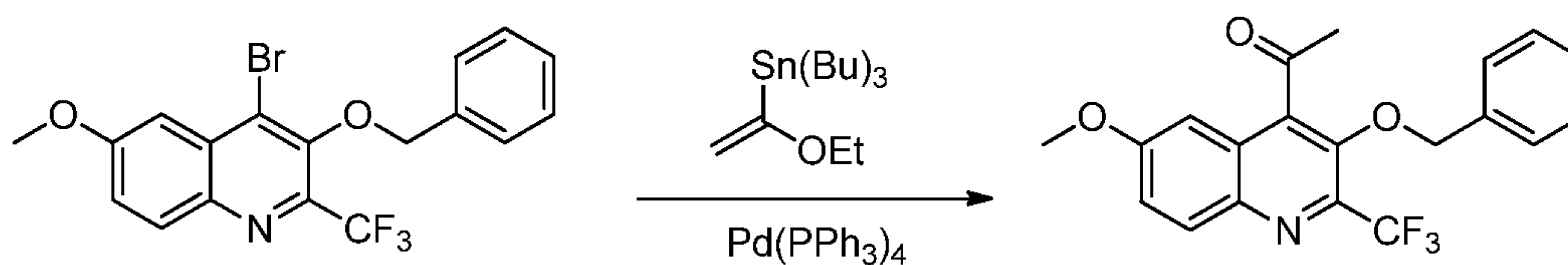
Step 4



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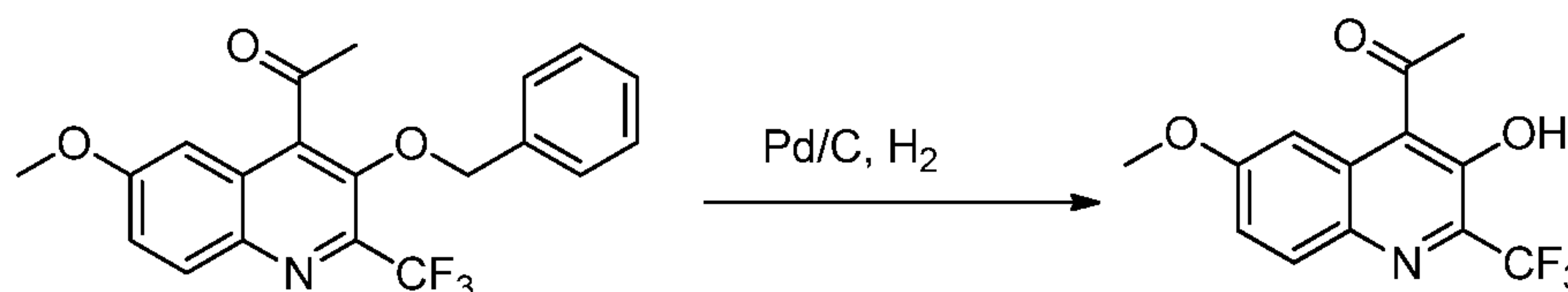
To the product of Step 3 (1.48 g, 3.50 mmol) in DMF (32 ml) was added Cu-I (0.333 g, 1.749 mmol) followed by (MFSDA) methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (1.335 ml, 10.49 mmol). The solution was heated in microwave at 100°C for 30 min at high absorbance. The solution was diluted with EtOAc and washed with brine and water. The solution was then dried with Na₂SO₄ concentrated and purification with chromatography eluting
25 with 0-50% hexanes/DCM gave product (0.48 g, 1.164 mmol, 33.3% yield).

Step 5



A mixture of the product of Step 4 (0.48 g, 1.164 mmol), tributyl(1-ethoxyvinyl)tin (0.787 ml, 2.329 mmol) and Pd(PPh₃)₄ (0.067 g, 0.058 mmol) in dioxane (5 ml) was heated at reflux overnight (oil bath temperature: 119°C). The reaction mixture was cooled, ~10 ml of 1N HCl was added, and the reaction mixture was stirred at RT. The reaction mixture was diluted with water, extracted 3x with DCM. The combined organic layers washed with brine, dried over MgSO₄, filtered, concentrated and chromatographed with 0-15% EtOAc-hexanes to give product (336 mg, 0.895 mmol, 77% yield).

Step 6

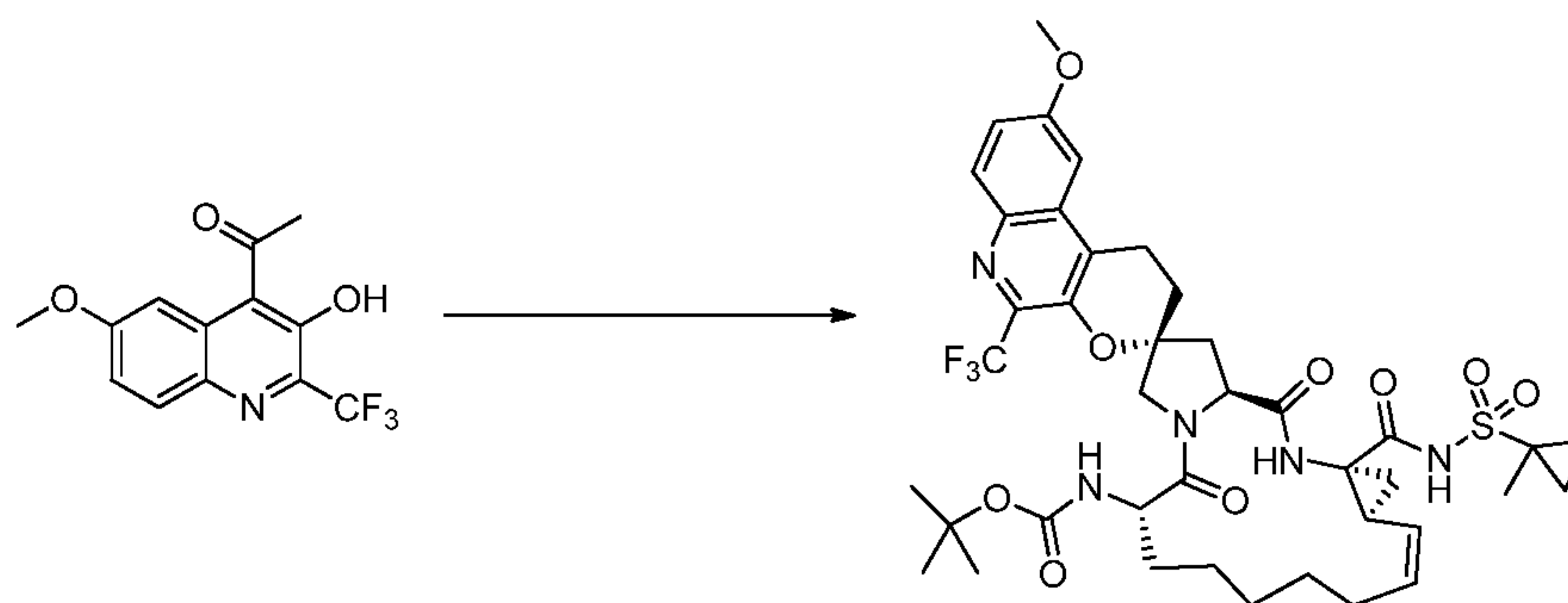


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To activated Pd/C (33.3 mg, 0.313 mmol) was added the product of Step 5 (336 mg, 0.895 mmol) in THF (4 ml). A H₂ balloon was attached, and the reaction mixture was stirred at RT overnight. The reaction mixture was filtered through CELITE and washed with MeOH to obtain the product (225 mg, 0.789 mmol, 88% yield) contaminated with unreacted starting material.

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Step 7-14



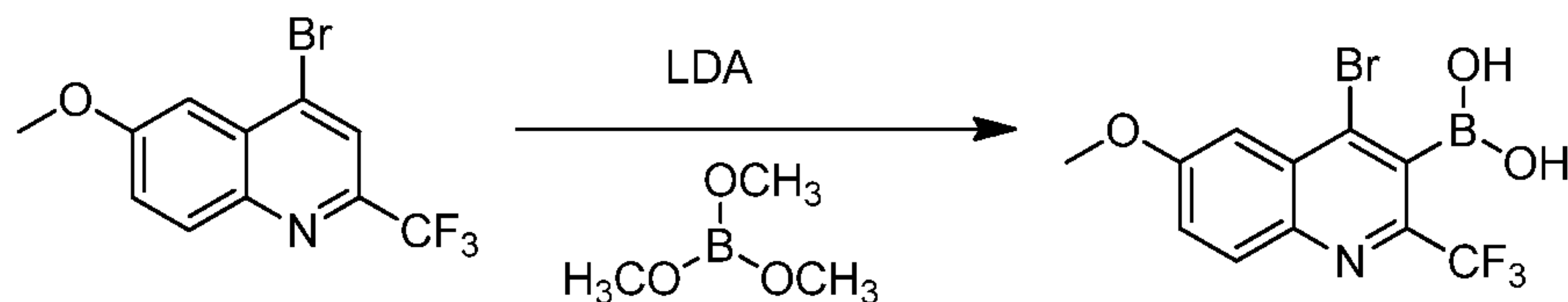
The ketone was treated under the same conditions as used in Example 4 (Steps 6 to 13) to obtain I-5. ¹H-NMR (400 MHz, CDCl₃) δ 10.11 (s, 1H), 8.01-7.99 (d, J = 9.2 Hz, 1H), 7.29-7.26 (m, 1H), 6.99 (d, J = 2.6 Hz, 1H), 6.89 (br s, 1H), 5.74-5.67 (m, 1H), 5.18 (d, J = 8.7Hz, 1H), 4.99 (t, J= 10.0 Hz, 1H), 4.61-4.57 (m, 1H), 4.43 (d, J= 11.0 Hz, 1H), 4.23-4.17 (m,

20

1H), 3.96 (s, 3H), 3.71 (d, J = 11.0Hz, 1H), 3.21-3.09 (m, 2H), 2.61-2.53 (m, 2H), 2.44-2.32 (m, 4H), 1.92-0.8 (m, 27H). ¹⁹F-NMR (400 MHz, CDCl₃) δ -70.14. MS m/e = 834.2 (MH⁺).

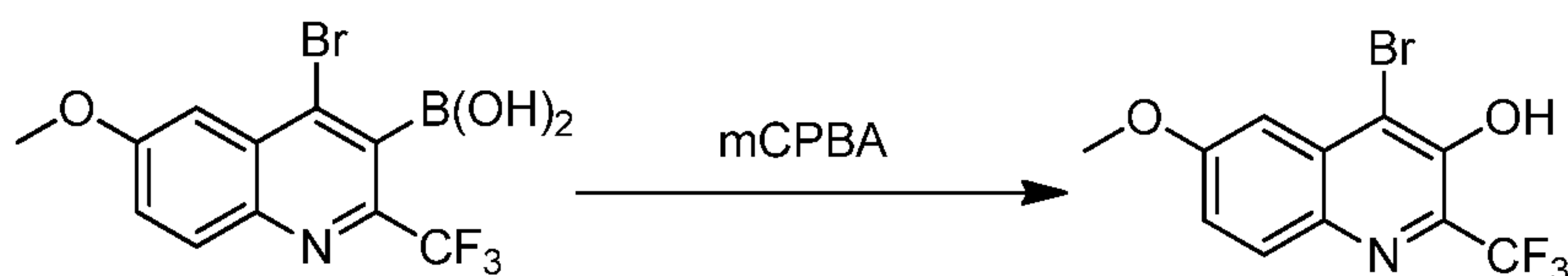
Alternate Procedure for the preparation of the compound of Example 5 (I-5)

5 Step 1

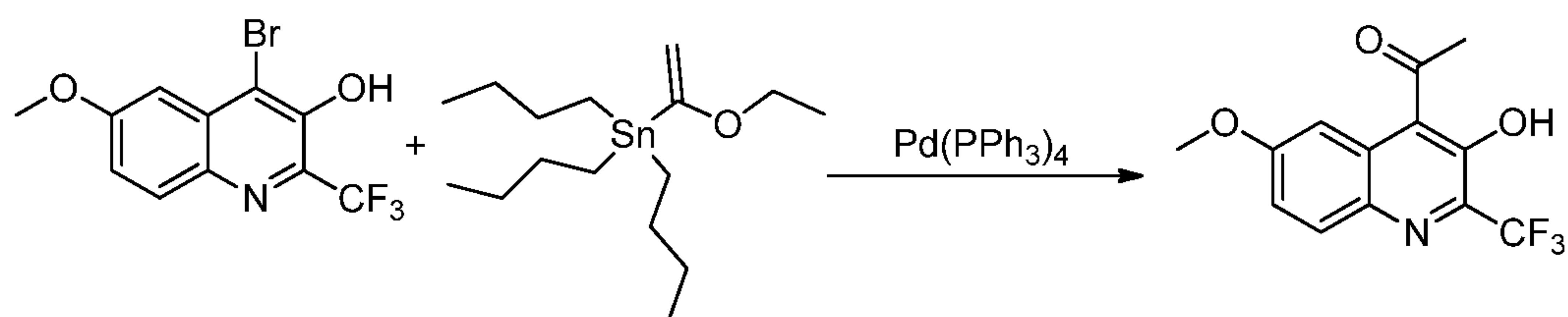


A solution of DIPA (7.16 ml, 50.6 mmol) in 35 mL of THF at -20°C was treated with n-butyl lithium (19.60 ml, 49.0 mmol) and was stirred at -20°C for 20 min and at 0°C for 10 min. The reaction mixture was cooled to -78°C (30 mins) and was treated dropwise with 2-trifluoromethyl-4-bromo-6-methoxy quinoline (5.0 g, 16.34 mmol) in THF (20.00 mL). The reaction mixture was stirred at -78°C for 1h. The reaction mixture was treated with trimethyl borate (14.57 ml, 131 mmol) and stirred at -78°C for 3h. The color of the reaction mixture changed from brown to very dark green (almost black) to green to light green to yellow over 3h. The reaction mixture was quenched with 1N HCl until the system was acidic. The aq. solution was extracted with EtOAc (2X), combined organic layers were washed with water, dried (Na₂SO₄), filtered, concentrated *in vacuo* to obtain the product (5.3 g, 93%) and used in next step. MS m/e = 350.0 (MH⁺).

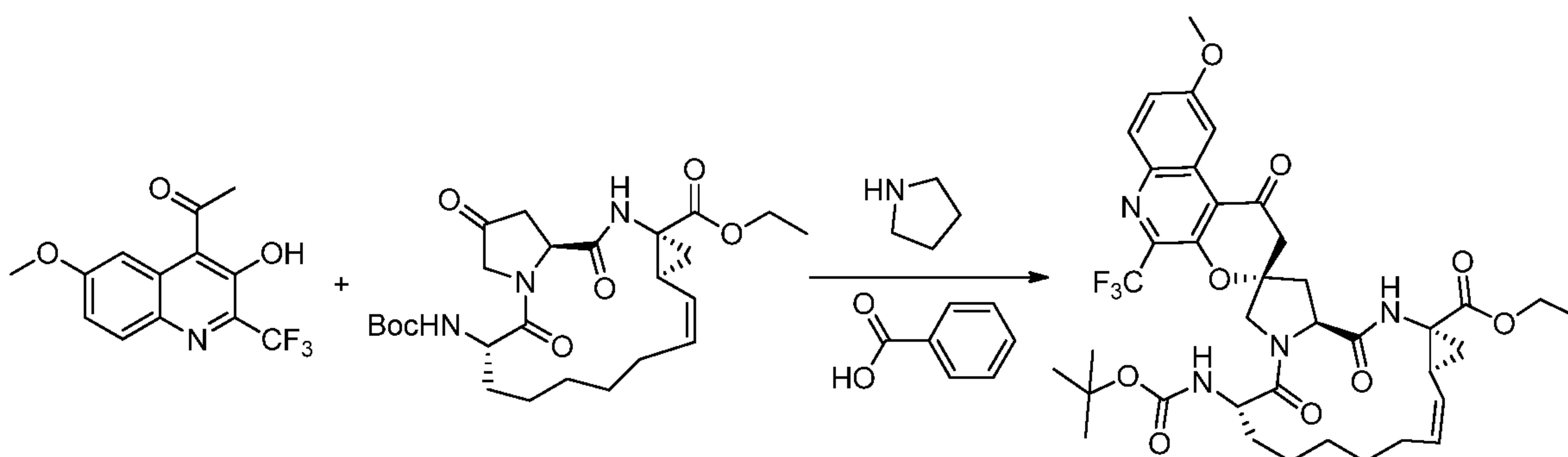
Step 2



To the product from Step 1 (1 g, 2.8 mmol) dissolved in MeCN (5 ml) was added mCPBA (0.773 g, 3.36 mmol), and the reaction mixture was stirred at RT for 1h. The reaction mixture was almost homogeneous after addition of mCPBA and then turned to a slurry. LC-MS after 1h showed ~10% product formation and rest was starting material. Solid NaHCO₃ (0.282 g, 3.36 mmol) was added to the mixture, and the resulting mixture was stirred overnight at RT. LC-MS after over night stirring showed ~90% of product formation with very little starting material. NaHSO₃ (2.040 ml, 1.961 mmol) was added to the mixture and stirred for 1 min. The solid obtained was filtered and washed with 1:1 ACN/H₂O, dried in vacuum to get the product (453 mg, 1.406 mmol, 50.2% yield), which was used in the next step. MS m/e = 322, 324 (MH⁺).

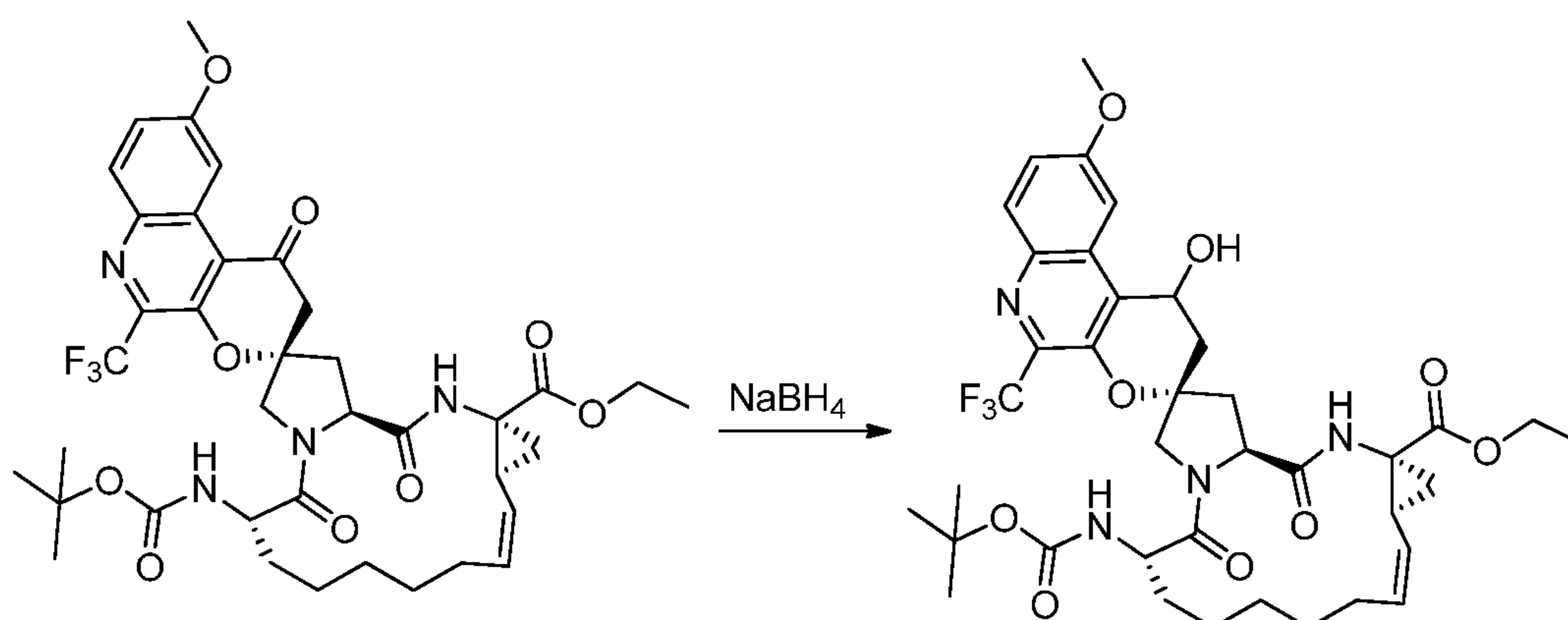
Step 3

A mixture of product from Step 2 (4.42 g, 13.72 mmol), tributyl(1-ethoxyvinyl)tin (9.27 ml, 27.4 mmol) and Tetrakis (1.586 g, 1.372 mmol) in dioxane (46.5 ml) was heated at reflux overnight at 119°C. The reaction mixture was then cooled to RT, and ~35 mL of 1N HCl was added, and the reaction mixture was stirred at RT for ~30 min. LC-MS indicated hydrolysis of vinyl ether. The reaction mixture was diluted with water, extracted 3x with EtOAc, combined organic layer washed with brine, dried over MgSO₄, filtered and concentrated. A lot of solid was obtained. 20 ml of 10% DCM/Hexanes was added to the solid, filtered to get yellow solid, which was the desired product (2.79 g, 9.78 mmol, 71.3% yield). MS m/e = 286.1 (MH⁺).

Step 4

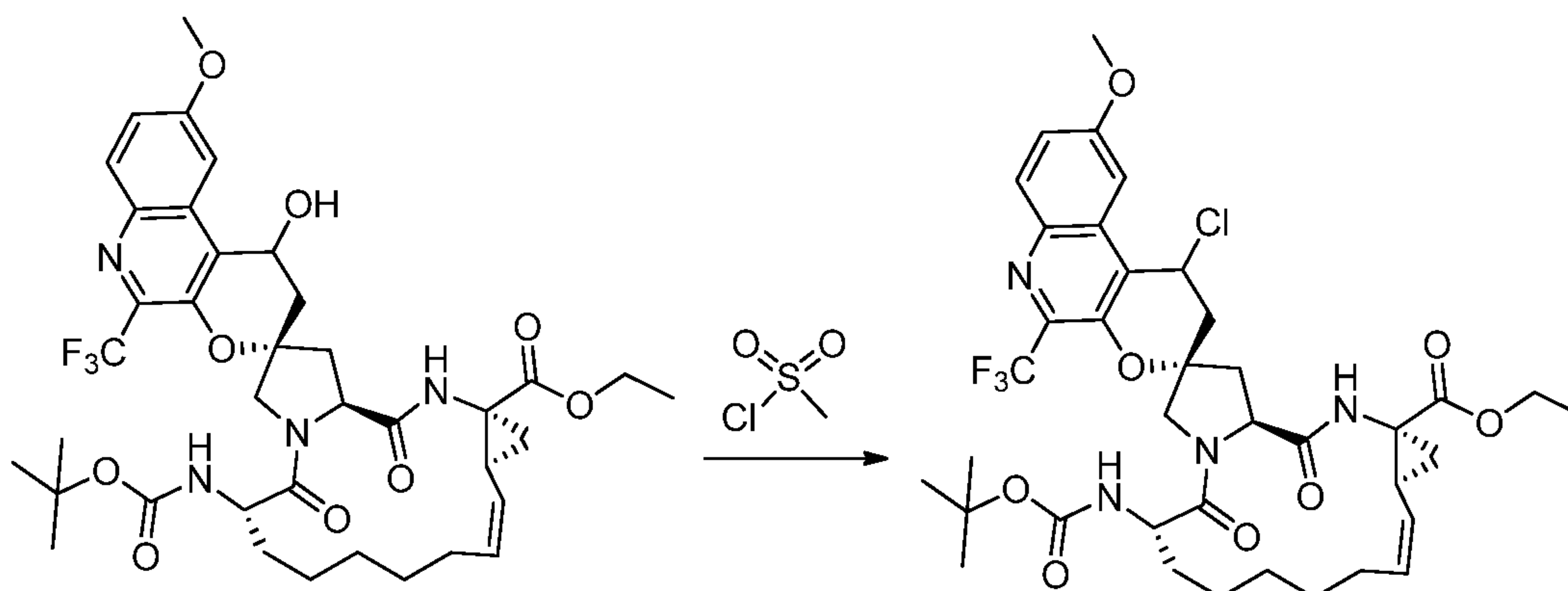
The product from Step 3 (5.25 g, 18.41 mmol), macrocyclic ketone (10 g, 20.34 mmol), benzoic acid (4.5 g, 36.8 mmol), pyrrolidine (0.61 mL, 7.36 mmol) and powdered 4A molecular sieves (1.7 g) were added in dry 2-propanol (108 mL). The reaction mixture was purged with N₂ and heated to 75°C for 20h. LC-MS shows complete consumption of starting quinoline. The reaction mixture was cooled and filtered through a minimum amount of CELITE, and the filter cake was washed well with MeOH and CH₂Cl₂. The wash was concentrated *in vacuo* and purified by silica gel column chromatography using a gradient of 0-100% EtOAc/Hexanes. Further impurities after the column purification were removed by triturating the product with acetone. The solid was collected by filtration and dried under vacuum to provide the product as a free-flowing tan solid (7.0 g, 50% yield). MS m/e = 759.3 (MH⁺).

Step 5

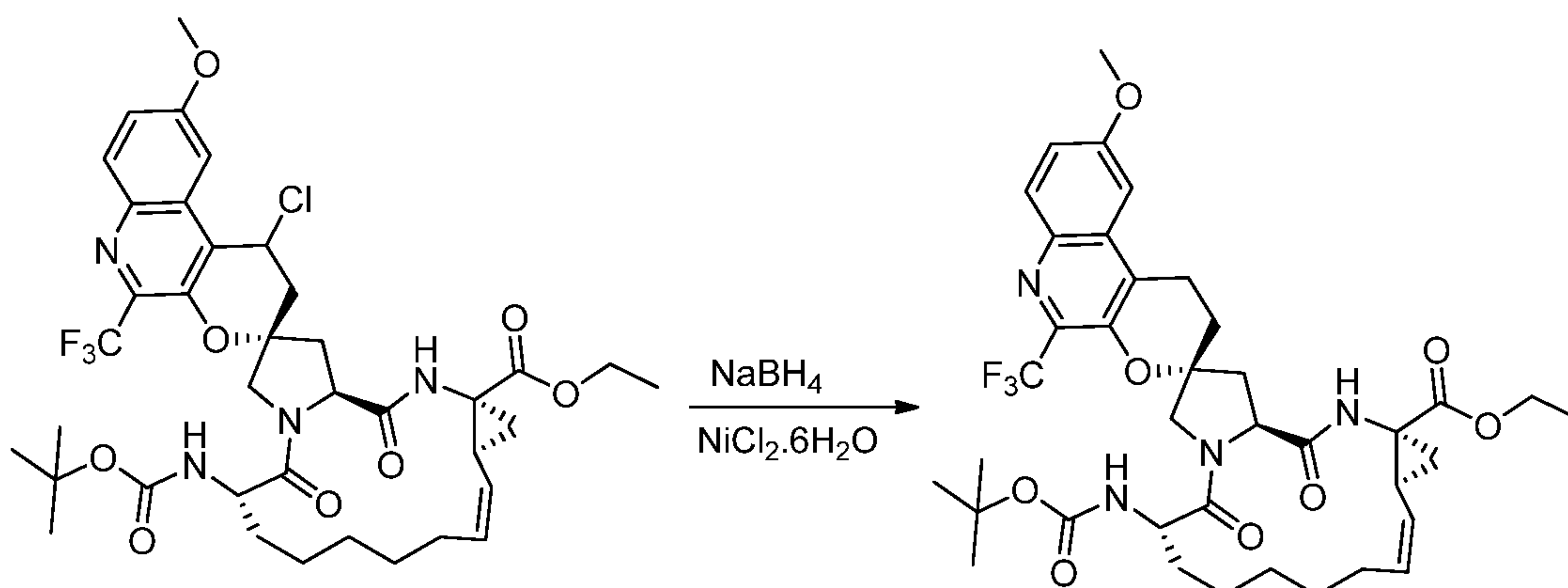


The ketone from Step 4 (5 g, 6.59 mmol) was taken up in MeOH (50 ml)/THF (17 ml) and cooled to 0°C under N₂. NaBH₄ (0.374 g, 9.88 mmol) was then added, and the mixture stirred for 15 min. Upon completion, the reaction was quenched with sat. NH₄Cl solution and diluted with EtOAc. The aq. layer was extracted with EtOAc (3X), and the combined organic extracts were washed with brine, dried over MgSO₄ and concentrated *in vacuo* to obtain the product (5.01 g, 100%). MS m/e = 761.3 (MH⁺).

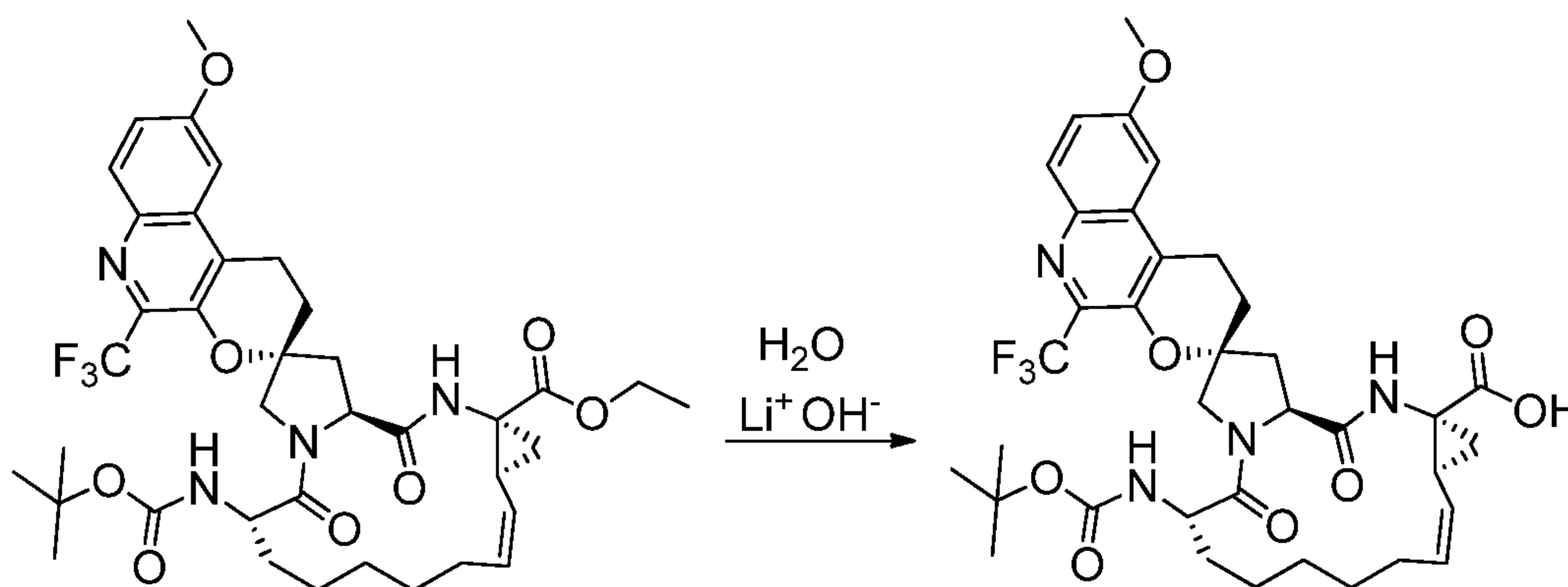
Step 6



The alcohol from Step 5 (5.01 g, 6.59 mmol) was suspended in DCM (65 ml) and cooled to 0°C under N₂. After 15 min, MsCl (1.284 ml, 16.48 mmol) was added, and the reaction mixture was stirred at 0°C for 15 min. TEA (2.76 ml, 19.77 mmol) was added and the resultant mixture was allowed to warm to ambient temperature overnight. LC-MS indicated only about 20% conversion to chloride, so the reaction mixture was cooled to 0°C, and additional MsCl (1.284 ml, 16.48 mmol) and 3eq. of TEA (2.76 ml, 19.77 mmol) were added. LC-MS showed reaction complete. The reaction mixture was diluted with EtOAc, washed with sat. NaHCO₃ solution (2X) and brine. The reaction mixture was dried over MgSO₄, concentrated *in vacuo*, and purified by column chromatography (ISCO system, 50% EtOAc/hexanes) to give product (3.9 g, 5.00 mmol, 76% yield). MS m/e = 779.3 (MH⁺).

Step 7

The chloride from Step 6 (3.9 g, 5.00 mmol) was suspended in MeOH, and NiCl₂·6H₂O (3.57 g, 15.01 mmol) was added. The reaction mixture was allowed for the Ni catalyst to fully dissolve (light green color). The mixture was then cooled to -78°C, and NaBH₄ (0.473 g, 12.51 mmol) was added in one portion. After stirring the light green solution at -78°C for 1h, an aliquot was taken and quenched into HCl-CH₃CN for LC-MS. The LC-MS showed completion. The reaction mixture was quenched by dumping the cold mixture into a stirring mixture of saturated NaHCO₃ (aq) solution (200 mL) and EtOAc (100 mL). The mixture was diluted with EtOAc, and the aq. layer was extracted with EtOAc (3X). The combined organic extracts were washed with sat. NaHCO₃ solution (3X) and brine (1X). The solution was dried over MgSO₄, filtered, and concentrated *in vacuo* to give the product (3.5 g, 4.70 mmol, 94% yield). MS m/e = 745.4 (MH⁺).

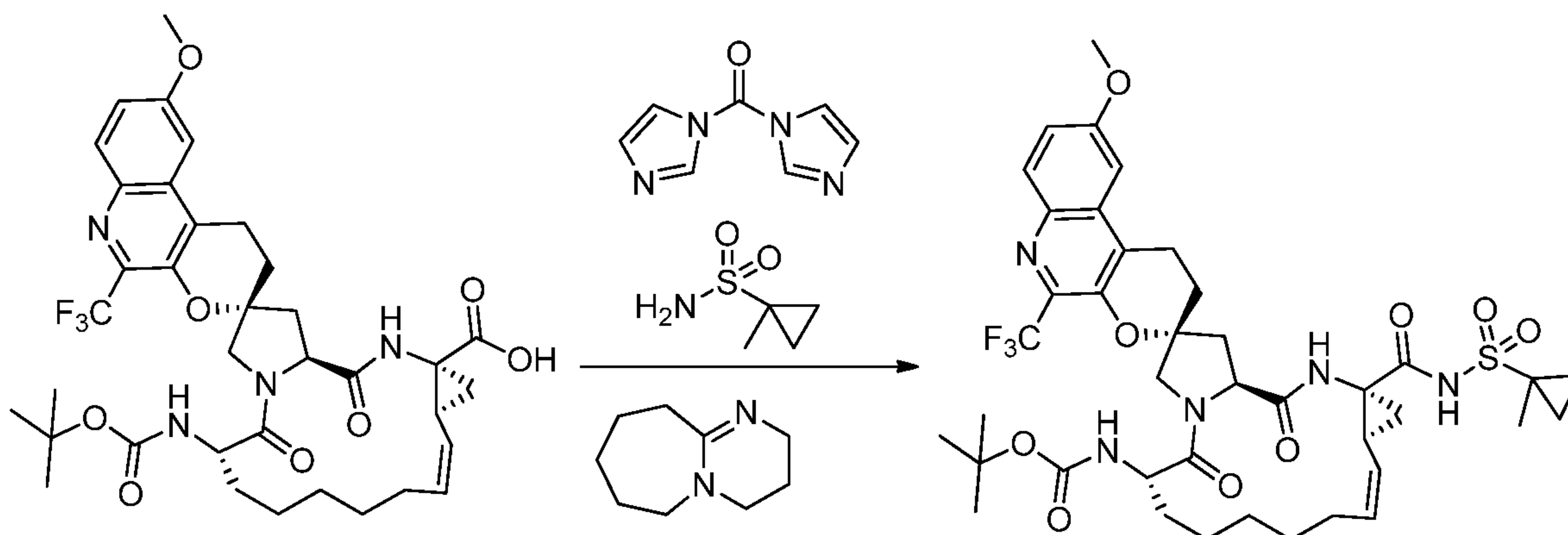
Step 8

The ester from Step 7 (3.5 g, 4.70 mmol) was suspended in MeOH (20 mL)/THF (72 mL), and LiOH·H₂O (1.18 g, 28.2 mmol) was added. The yellow solution was heated to 60°C. LC-MS after 1.5h showed hydrolysis complete, so the solution was acidified to pH 2 with 1N HCl. The reaction mixture was diluted with EtOAc and H₂O. The layers were separated,

and the aq. layer was extracted with EtOAc. The organic layers were combined and washed with brine (4X), ensuring that last brine wash was not acidic. The solution was dried over MgSO₄, concentrated *in vacuo*, and azeotroped with toluene (4X). The resulting white solid was placed under high vacuum and dried to obtain the product (3.37 g, 4.70 mmol, 100% yield). MS m/e =

5 717.4 (MH⁺).

Step 9

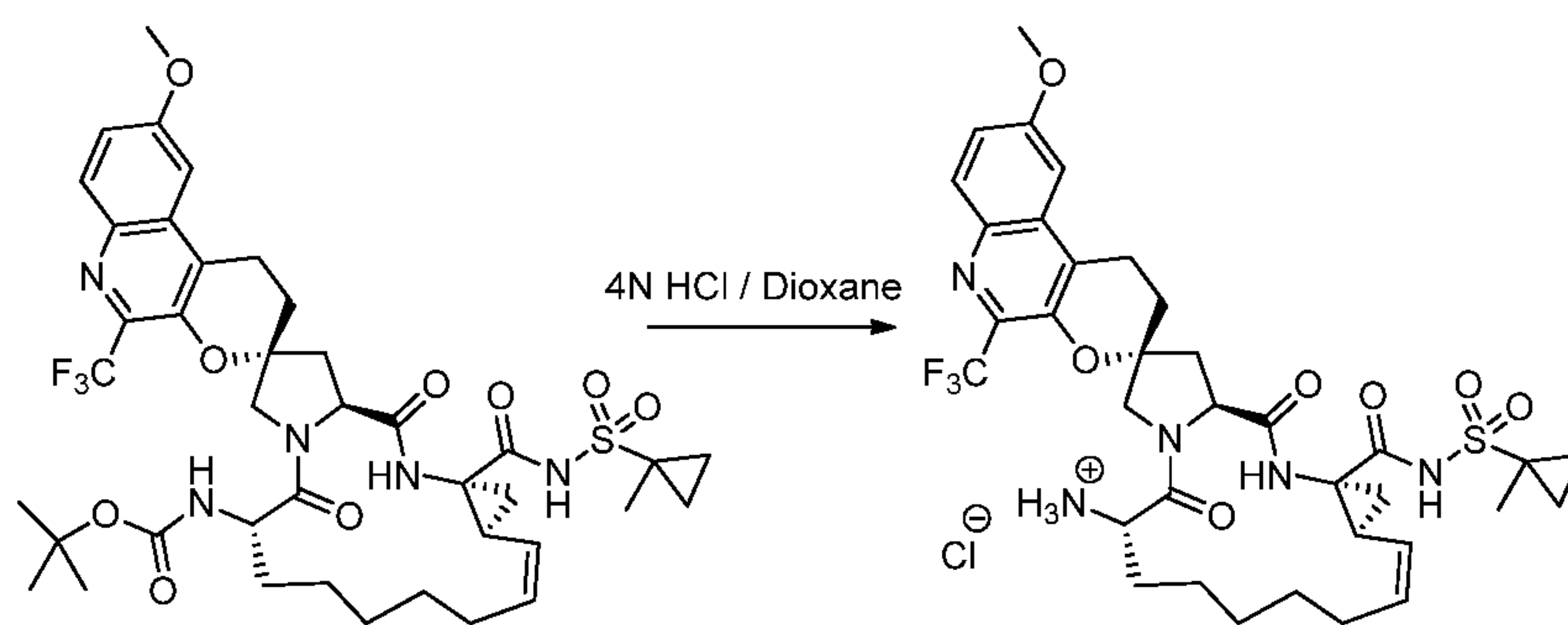


A solution of product from Step 8 (3.37 g, 4.70 mmol) and CDI (1.32 g, 8.14 mmol) in THF (64 ml) was stirred in an oil-bath kept at 70°C for 3h, then cooled to RT. To this was added 1-methylcyclopropane-1-sulfonamide (1.589 g, 11.75 mmol) and DBU (11.75 ml, 11.75 mmol) in THF(1 m), and the mixture was stirred in an oil-bath kept at 50°C for overnight. LC-MS indicated that the major peak is desired product. The reaction mixture was diluted with EtOAc (200 ml), washed with aq. NH₄Cl (2x50 ml), brine, water (2x50 mL) dried over MgSO₄, filtered and concentrated. The residue was first purified by 30% EtOAc/DCM, and then clean

10 fractions were further purified (dry loading with silica gel) with 0-30% EtOAc/hexanes 10 min to 30% hexanes/EtOAc over 20 min 30-75% EtOAc/hexanes over 20 min to give I-5 (2.2 g, 2.64 mmol, 56.1% yield). MS m/e = 834.4 (MH⁺).

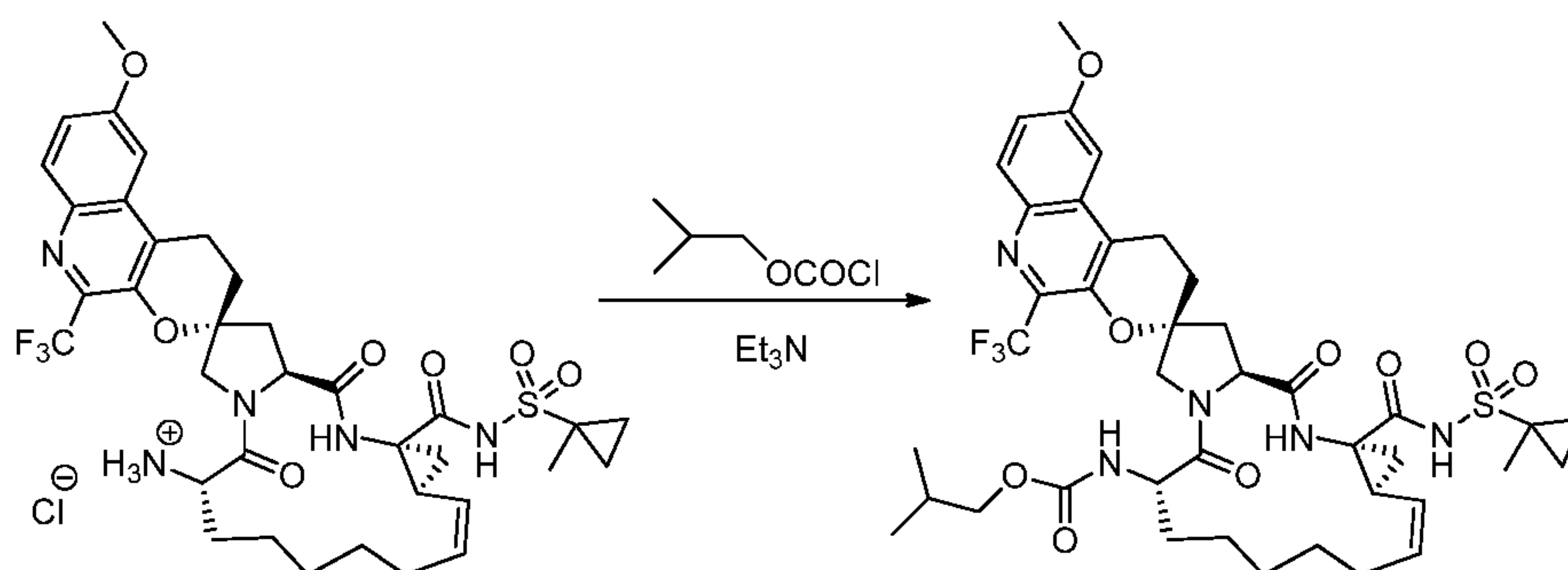
Example 6: Isobutyl ((2R,6S,13aS,14aR,16aS,Z)-9'-methoxy-14a-(((1-methylcyclopropyl) sulfonyl)carbamoyl)-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13a,14,14a, 15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-6)

Step 1



To a solution of I-5 (70 mg, 0.080 mmol) in DCM (1 ml) was added 4 m HCl in dioxane (0.020 ml, 0.080 mmol). The resulting mixture was allowed to stir at RT for 3h. The volatiles were then removed *in vacuo* to furnish crude product as a white solid (62 mg, 0.080 mmol, 100% yield). MS $m/e = 734.2$ (MH^+). This material was used without further purification in the next step.

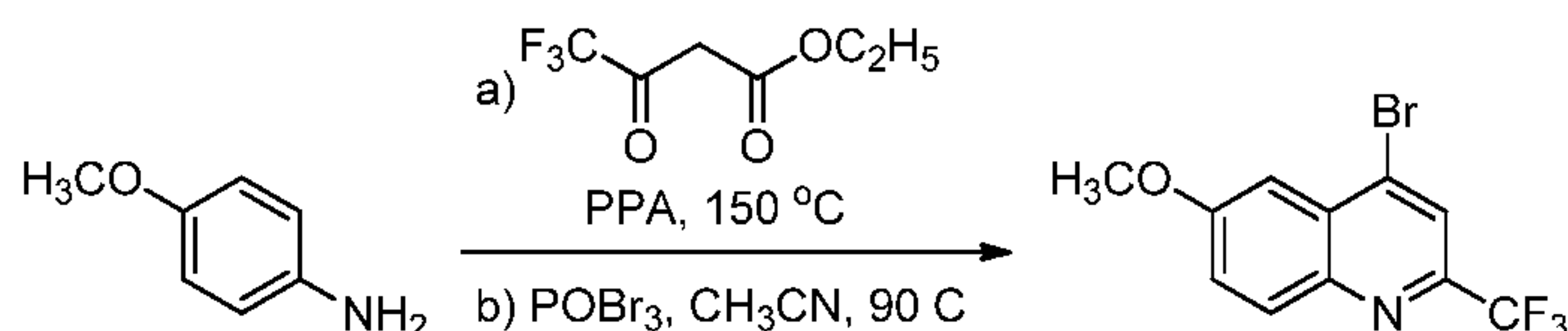
Step 2



A solution of the product of Step 1 (35 mg, 0.045 mmol), TEA (0.019 ml, 0.136 mmol) and isobutyl chloroformate (0.012 ml, 0.091 mmol) in DCM (2 ml) was stirred at RT for 1h. The reaction was then quenched with NH_4Cl and extracted with DCM. The organics were washed 2x with water, brine and dried over Na_2SO_4 . It was then filtered, concentrated and chromatographed with 0-40% acetone-hexanes to give I-6 (25 mg, 0.030 mmol, 66%). MS $m/e = 834.2$ (MH^+). 1H NMR δ (ppm)($CHCl_3-d$): 10.17 (1 H, s), 8.03 (1 H, d, $J = 9.21$ Hz), 7.33-7.28 (2 H, m), 7.04 (1 H, d, $J = 2.66$ Hz), 6.89 (1 H, s), 5.74 (1 H, q, $J = 8.88$ Hz), 5.28 (1 H, d, $J = 8.78$ Hz), 5.03 (1 H, t, $J = 9.45$ Hz), 4.65 (1 H, dd, $J = 9.65, 7.08$ Hz), 4.55 (1 H, d, $J = 11.06$ Hz), 4.22 (1 H, t, $J = 9.47$ Hz), 3.99 (3 H, s), 3.70 (1 H, d, $J = 10.94$ Hz), 3.65-3.55 (2 H, m), 3.24-3.19 (1 H, m), 3.15 (1 H, t, $J = 8.26$ Hz), 2.60 (2 H, dd, $J = 13.53, 7.08$ Hz), 2.49-2.33 (5 H, m), 2.20 (1 H, s), 1.94 (1 H, t, $J = 7.11$ Hz), 1.89-1.72 (4 H, m), 1.42-1.25 (7 H, m), 0.93-0.78 (10 H, m).

Example 7: *tert*-Butyl ((2R,6S,13aS,14aR,16aS,Z)-14a-(((1-methylcyclopropyl)sulfonyl) carbamoyl)-9'-(2-morpholinoethoxy)-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4] diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-7)

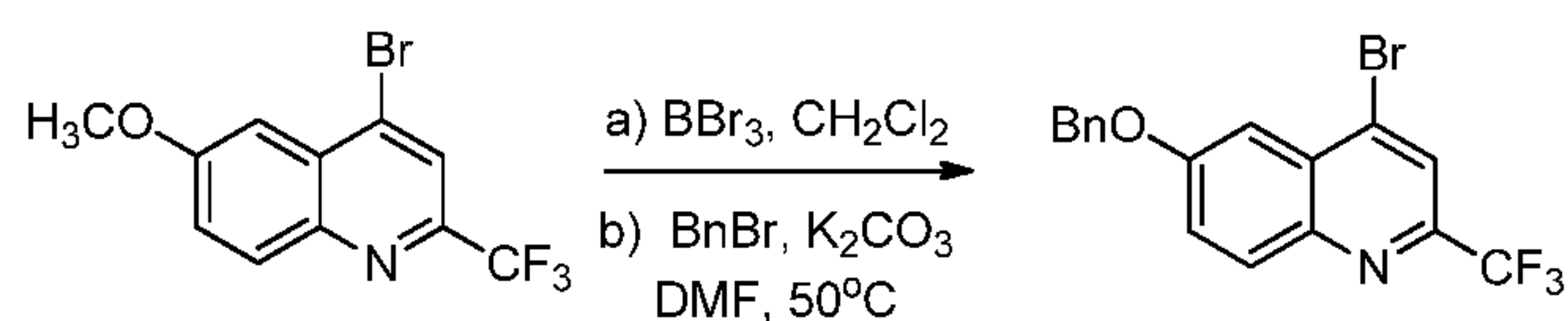
5 Step 1



A solution of trifluoro-3-oxa-butyrate (14.95 g, 81 mmol) and PPA (72 ml) was heated at 100°C and then treated with p-anisidine (10 g, 81 mmol) portion wise. The reaction mixture was further heated to 150°C and stirred for 2h at 150°C. After cooling to RT, the reaction mixture was poured into a beaker containing ice water. After stirring for 20 min, the mixture was filtered, and the resulting solid was washed with water (~3L). The resulting pinkish-purple solid was dried under vacuum to provide 6-methoxy-2-(trifluoromethyl)quinolin-4-ol (11.58 g, 47.6 mmol, 58.6% yield), which was used without purification.

To a solution of above prepared 6-methoxy-2-(trifluoromethyl)quinolin-4-ol (11.55 g, 47.5 mmol) in MeCN (50 ml) was added POBr₃ (16.34 g, 57.0 mmol), and the reaction was stirred at 90°C for 2h. After bringing to RT, the reaction mixture was slowly poured into aq. sat. NaHCO₃ and extracted with EtOAc (200 mL x 2). The aq. fraction was back extracted once with EtOAc, and then the combined organic fractions were washed with brine, dried (MgSO₄), filtered and concentrated under reduced pressure to give 13.6 g crude material. Purification by column chromatography (0-10% EtOAc in hexane) provided intermediate (12.9 g, 42.1 mmol, 89% yield).

Step 2

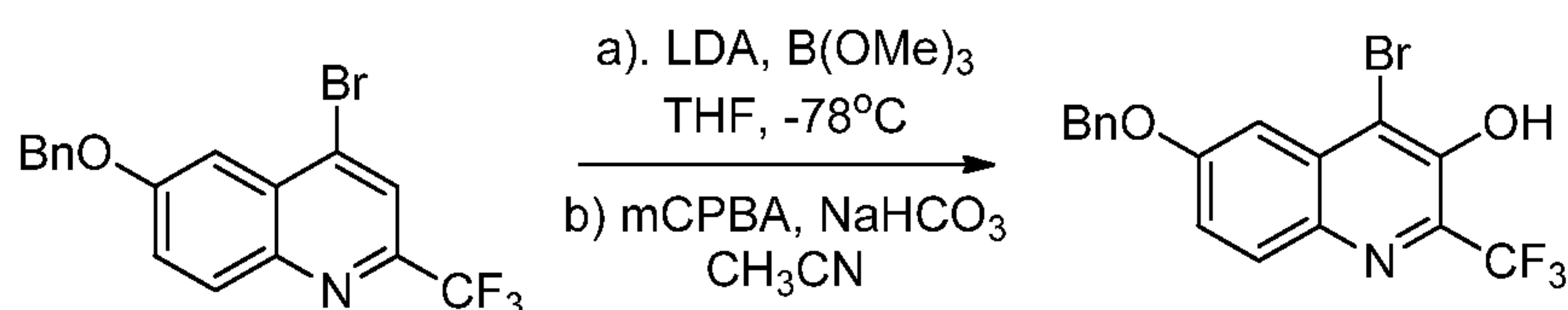


To a solution of the product of Step 1 (12.9 g, 42.1 mmol) in DCM (281 ml) was added BBr₃ (8.12 ml, 84 mmol) at 0°C, and the reaction was stirred for 1h at 0°C and then at RT for 1h. TLC (20% EtOAc in hexane) indicated complete consumption of the starting material. The reaction was carefully poured onto ice-cold solution of sat. NaHCO₃. The NaHCO₃ layer was extracted with EtOAc (600 mL), and the organic layer was washed with brine, dried (MgSO₄), filtered, concentrated *in vacuo* and purified by silica gel chromatography (0-20%

EtOAc in hexane) to provide 4-bromo-2-(trifluoromethyl)quinolin-6-ol (11.65 g, 39.9 mmol, 95% yield).

To a solution of 4-bromo-2-(trifluoromethyl)quinolin-6-ol (11.6 g, 39.7 mmol) in DMF (200 ml) was added K_2CO_3 (8.23 g, 59.6 mmol) followed by benzyl bromide (5.91 ml, 49.6 mmol). The reaction was stirred under N_2 at $50^\circ C$ overnight. After cooling to RT, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by silica gel chromatography (0-5% EtOAc in hexane) to yield product intermediate (12.0 g, 31.4 mmol, 79% yield) as a white solid.

Step 3



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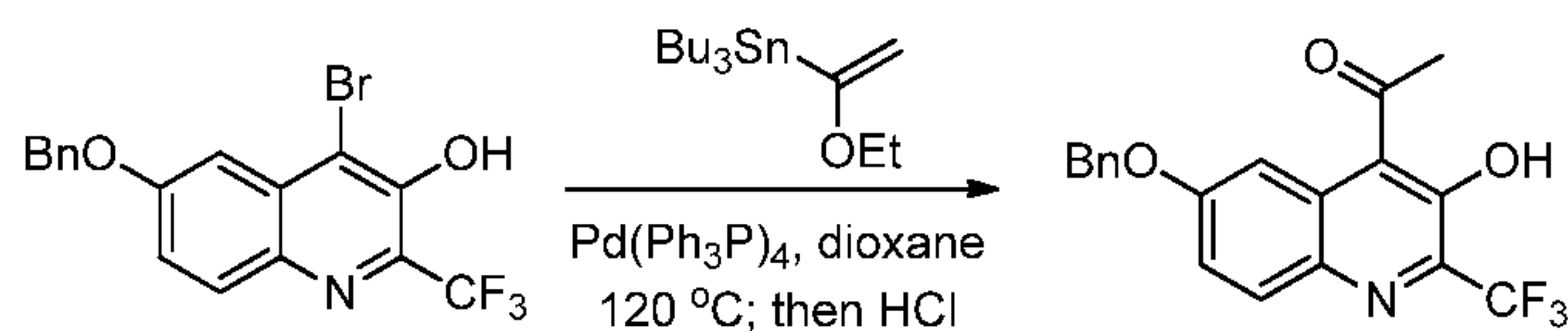
To solution of DIPA (13.76 ml, 97 mmol) in THF (70 ml) at $-20^\circ C$ was added nBuLi (37.7 ml, 94 mmol) under N_2 , and the solution was stirred at $-20^\circ C$ for 20 min and at $0^\circ C$ for 10 min. The reaction mixture was cooled to $-78^\circ C$ and treated with the product of Step 2 (12.00 g, 31.4 mmol) in THF (40.0 ml) dropwise (15-20 min) and stirred at $-78^\circ C$ for 1.5h. The reaction mixture was then treated with trimethyl borate (28.0 ml, 251 mmol) and stirred at $-78^\circ C$ for an additional 3h. LC-MS at this stage indicated complete consumption of the starting material to a peak with desired mass. The reaction mixture was quenched carefully at $-78^\circ C$ with 1N HCl until acidic. The aq. solution was extracted with EtOAc (2x), and the combined organic layers were washed with water, dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide (6-(benzyloxy)-4-bromo-2-(trifluoromethyl)quinolin-3-yl)boronic acid (13.8 g, 32.4 mmol, 103% yield), which was used without purification.

15

(6-(Benzyloxy)-4-bromo-2-(trifluoromethyl)quinolin-3-yl)boronic acid (13.8 g, 32.4 mmol) was taken in MeCN (70 ml), and to this mixture was added mCPBA (8.94 g, 38.9 mmol) followed by $NaHCO_3$ (3.27 g, 38.9 mmol). The reaction was stirred overnight at RT, at which stage LC-MS indicated complete consumption of the starting material. A solution of $NaHSO_3$ (23.60 ml, 22.68 mmol) in 70 mL water was added, and the reaction was stirred for 10-15 min after which the solid was filtered off and washed once with 40 mL MeCN and then several times with water. The solid was collected and dried under vacuum to provide product (9.0 g, 22.60 mmol, 69.8% yield) as a white solid.

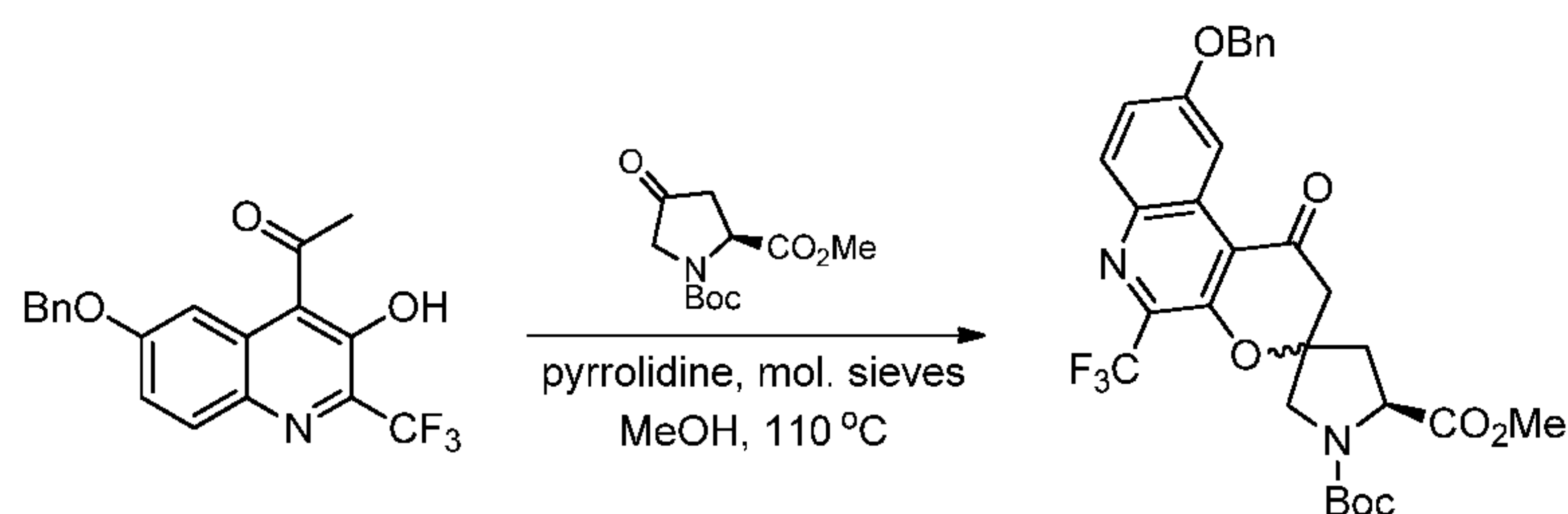
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30 Step 4



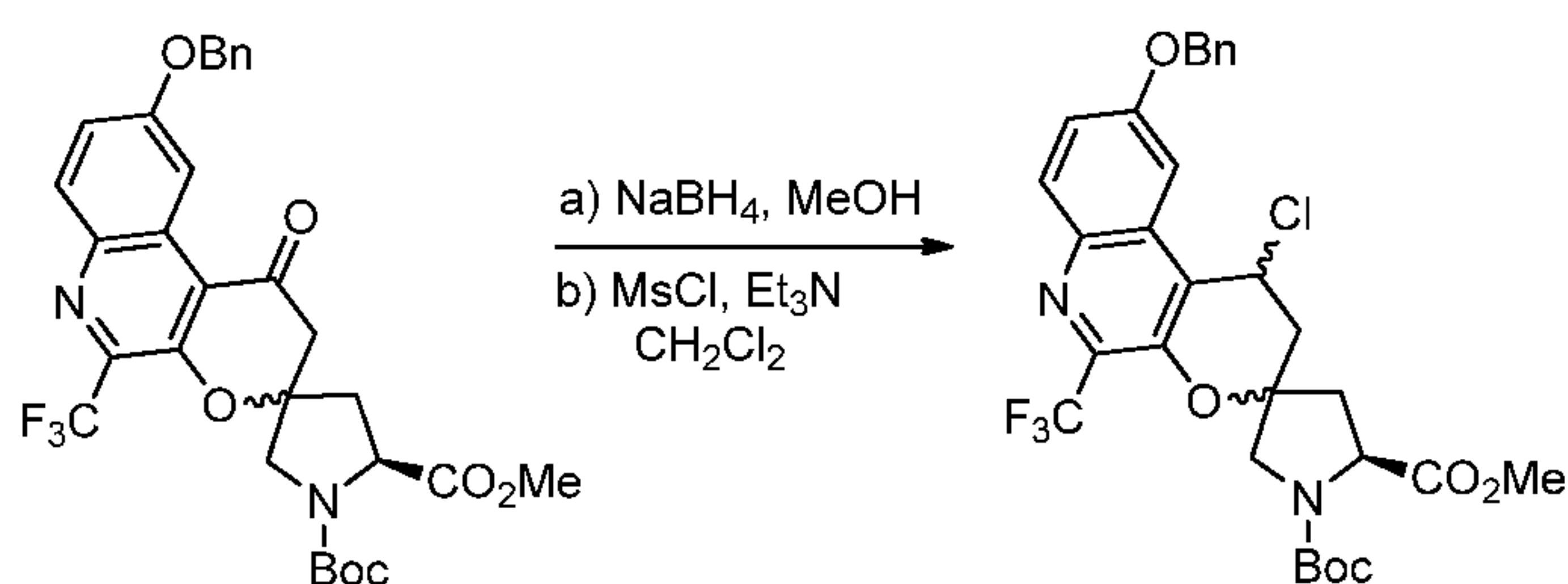
A mixture of the product of Step 3 (9.0 g, 22.60 mmol), tributyl(1-ethoxyvinyl)tin (15.27 ml, 45.2 mmol) and Pd(PPh₃)₄ (2.61 g, 2.260 mmol) in dioxane (75 ml) was heated at 120°C after purging with N₂ for 5 min. Upon complete consumption of the starting material, the reaction was cooled to RT and quenched with ~130 mL 1 M aq. HCl. The reaction was left stirring overnight at RT and then extracted with EtOAc. The combined organic fractions were washed with water and brine, dried (MgSO₄) and concentrated. Purification by column chromatography (0-30% EtOAc in hexane) provided the product of Step 4 (6.9 g, 19.10 mmol, 84% yield).

10 Step 5



The product of Step 4 (6.9 g, 19.10 mmol), commercially available (*S*)-1-*tert*-butyl 2-methyl 4-oxopyrrolidine-1,2-dicarboxylate (9.29 g, 38.2 mmol) and pyrrolidine (0.610 ml, 7.64 mmol) were combined in MeOH (40 ml) in a microwave vial. Molecular sieves (4A beads, 6-7 pieces) were added to the reaction mixture, and the resulting mixture was heated at 105°C for 30 min in a BIOTAGE INITIATOR microwave reactor. After cooling to RT, the reaction was filtered, and the residue was washed with MeOH. The filtrate was concentrated, and the residue was purified by silica gel column chromatography (0-60% EtOAc in hexane) to provide the product of Step 5 (8.8 g, 15.00 mmol, 79% yield) as a mixture of two diastereomers that were not separated at this stage.

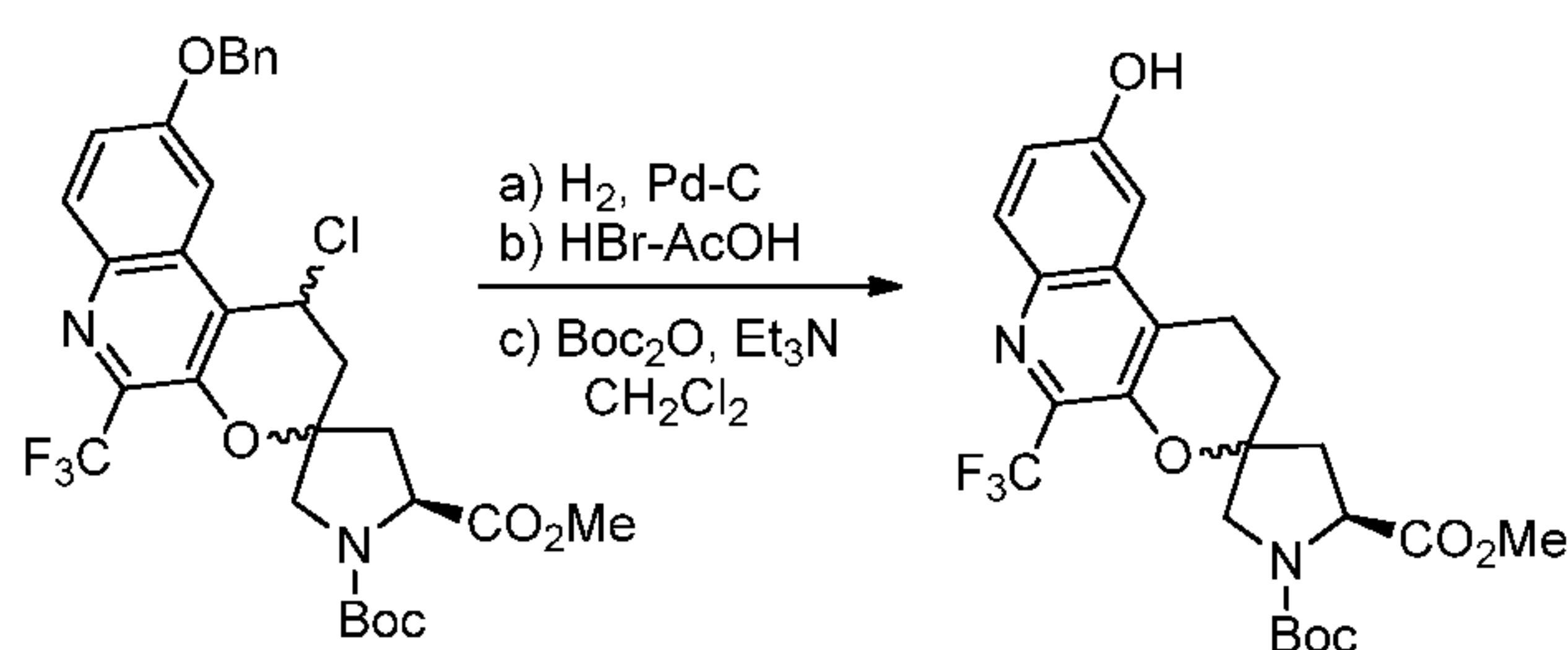
20 Step 6



A solution of the product of Step 5 (2.28 g) in MeOH (40.0 mL) was cooled to 0°C and treated with NaBH₄ (0.57 g, 15.0 mmol). After stirring at 0°C for 1h, the reaction was quenched with aq. NaHCO₃ and extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO₄), filtered, and concentrated under reduced pressure to provide the corresponding hydroxyl compound (8.73 g, 14.83 mmol, 99% yield), which was used without further purification.

To a solution of the above prepared hydroxyl compound (8.73 g, 14.83 mmol) in CH₂Cl₂ (124 ml) was added TEA (5.17 ml, 37.1 mmol) followed by MsCl (2.296 ml, 29.7 mmol) at 0°C. The reaction was allowed to warm to RT and stirred overnight. The reaction was diluted with EtOAc and washed with water and brine. The organic layer was dried (MgSO₄), filtered, and concentrated to give the product of Step 6 in quantitative yield, which was used further without purification.

Step 7

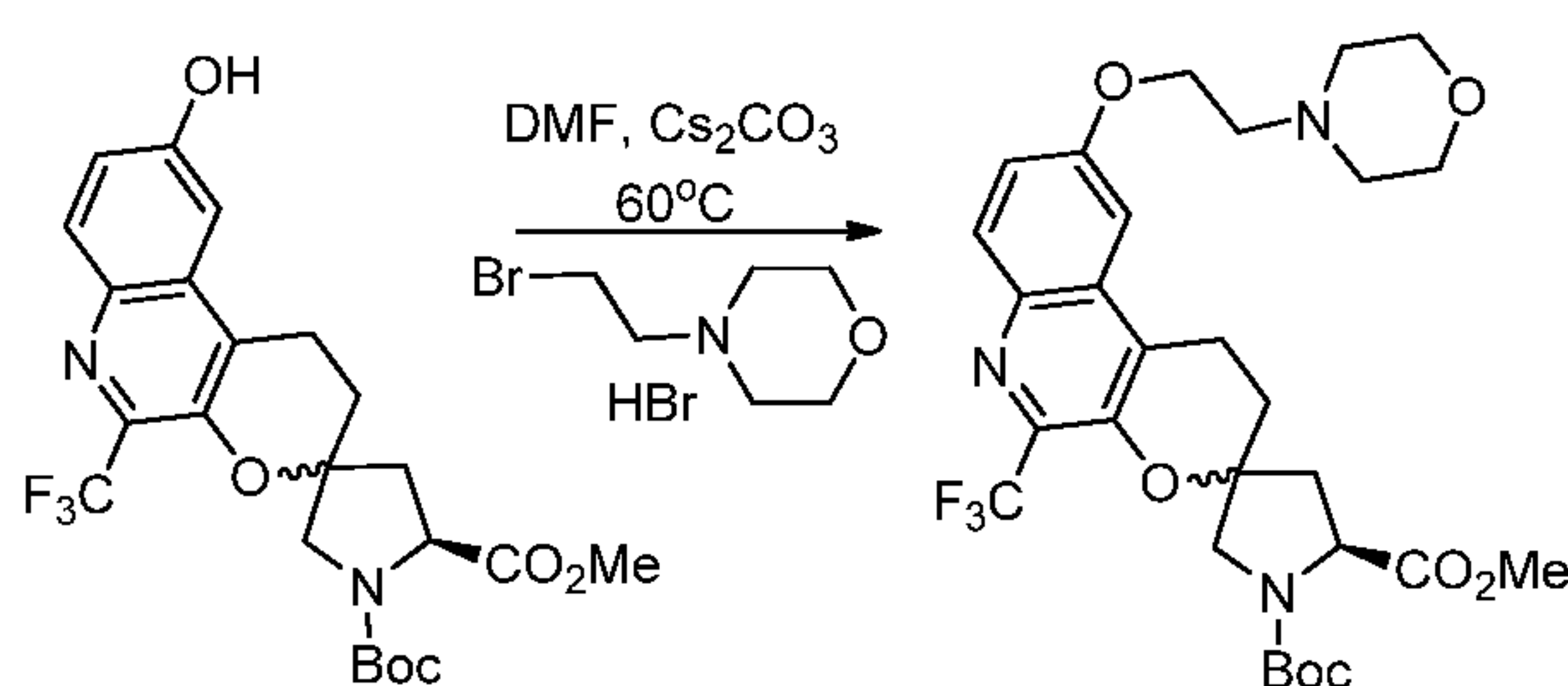


To a solution of the product of Step 6 (9.60 g, 15.82 mmol) in EtOAc (600 mL) was added 10% Pd/C (1.515 g, 1.423 mmol), and the reaction was hydrogenated under a balloon atmosphere for 30 min, at which stage LC-MS indicated complete conversion to the dechlorination product (no debenzylation was observed). The reaction was filtered through CELITE, and the cake was washed with EtOAc. After removing the solvent under reduced pressure, the resulting orange solid was purified by column chromatography (220 g column, 0-60% EtOAc in hexane) to provide the corresponding dechlorinated product (5'S)-1'-tert-butyl 5'-methyl 9-(benzyloxy)-5-(trifluoromethyl)-1,2-dihydrospiro[pyrano[2,3-c]quinoline-3,3'-pyrrolidine]-1',5'-dicarboxylate (6.56 g, 11.46 mmol, 72.4% yield).

A solution of (5'S)-1'-tert-butyl 5'-methyl 9-(benzyloxy)-5-(trifluoromethyl)-1,2-dihydrospiro[pyrano[2,3-c]quinoline-3,3'-pyrrolidine]-1',5'-dicarboxylate (2 g, 3.49 mmol) and HBr in glacial AcOH (20 mL, 177 mmol) was stirred at RT for 4h. After removing the solvent under reduced pressure, the residue was azeotroped 3X with toluene and then dried under vacuum before using the crude.

To the crude from above in DCM (34.5 ml) was added TEA (0.626 ml, 4.49 mmol), and the reaction was stirred for 15 min at RT during which a homogeneous solution was obtained. BOC₂O (1.203 ml, 5.18 mmol) was added, and the reaction was stirred at RT under N₂ for 1h. The reaction was treated with sat. aq. NH₄Cl solution and extracted with DCM. The organic fraction was washed with sat. aq. NH₄Cl solution, water and brine and then dried (MgSO₄), filtered and concentrated to give a brown oily residue. Purification by column chromatography (0-60% acetone in hexane) gave the product of Step 7 (0.95 g, 1.969 mmol, 57.0% yield).

Step 8

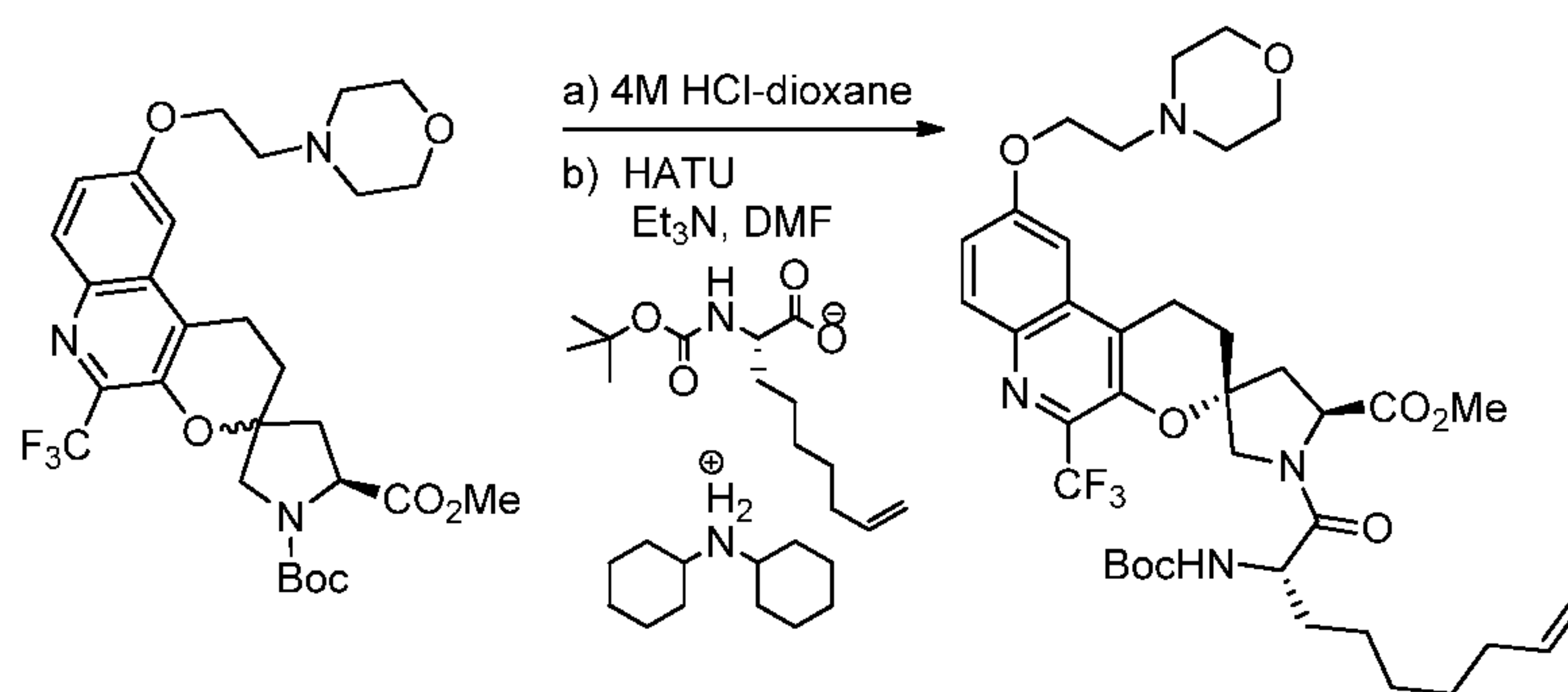


10

A suspension of the product of Step 7 (440 mg, 0.912 mmol), 4-(2-bromoethyl)morpholine HBr salt (502 mg, 1.824 mmol) and Cs₂CO₃ (891 mg, 2.74 mmol) in DMF (9120 μl) was stirred at 55°C for 2h. After bringing to RT, the reaction was diluted with EtOAc and washed with water. The organic fractions were washed with water and brine, dried with Na₂SO₄ and concentrated. The resulting residue was purified by column chromatography (0-60% acetone in hexane) to afford the product of Step 8 (470 mg, 0.789 mmol, 87% yield) as a mixture of diastereomers.

15

Step 9

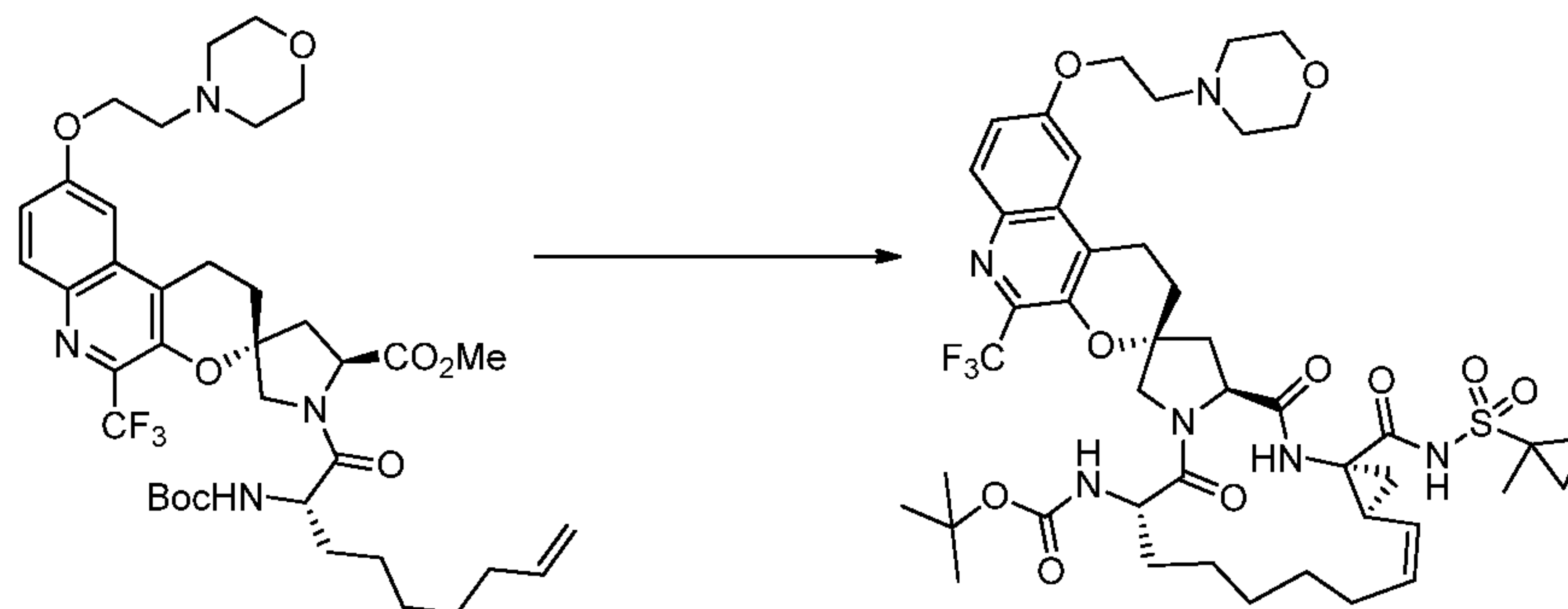


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A solution of the product of Step 8 (470 mg, 0.789 mmol) and 4 m HCl in dioxane (3 mL, 36.5 mmol) was stirred at RT for 2h. The volatiles were removed under reduced pressure, and the residue was azeotroped 3x with toluene. The solid thus obtained was taken in DMF (7.90 mL) and treated with TEA (0.451 mL, 3.24 mmol), dicyclohexylammonium (S)-2-((tert-

butoxycarbonyl)amino)non-8-enoate (715 mg, 1.579 mmol) followed by HATU (600 mg, 1.579 mmol) at RT under N₂. The reaction was stirred at RT overnight and then diluted with EtOAc and washed with water and brine. The organic fraction was dried (MgSO₄), concentrated and purified by silica gel column chromatography (0-50-80% acetone in DCM) to provide the
 5 product of Step 9 (385 mg, 0.514 mmol, 65.1% yield) and its diastereomer.

Step 10

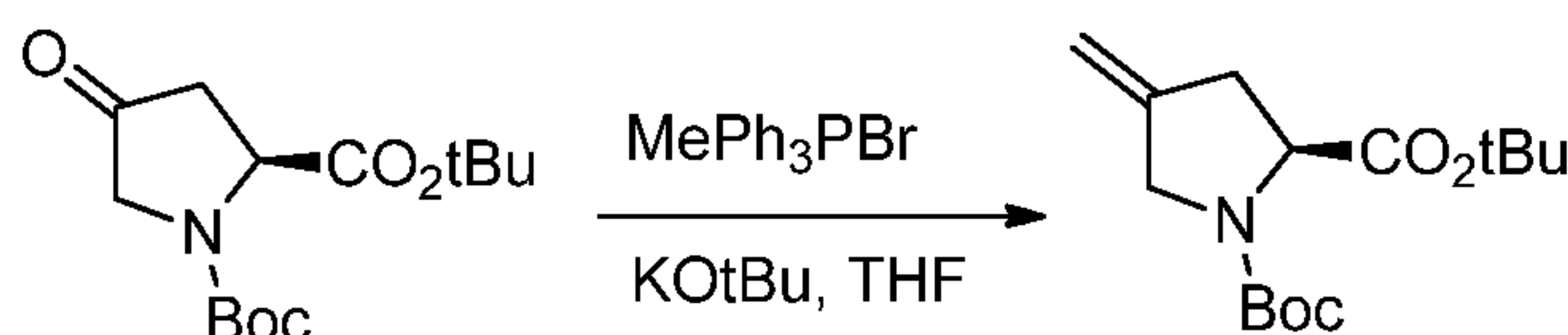


The product of Step 9 was converted to I-7 using the procedures as described in Example 1, Steps 8 and 9.

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Example 8: *tert*-Butyl ((2'*R*,6'*S*,13a'*S*,14a'*R*,16a'*S*,*Z*)-9-methoxy-14a'-(((1-methyl cyclopropyl)sulfonyl)carbamoyl)-5',16'-dioxo-5-(trifluoromethyl)-3',5',6',7',8',9',10',11',13a',14',14a',15',16',16a'-tetradecahydro-1'*H*,2*H*-spiro[[1,4]dioxino[2,3-*c*]quinoline-3,2'-cyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecin]-6'-yl)carbamate (I-8)

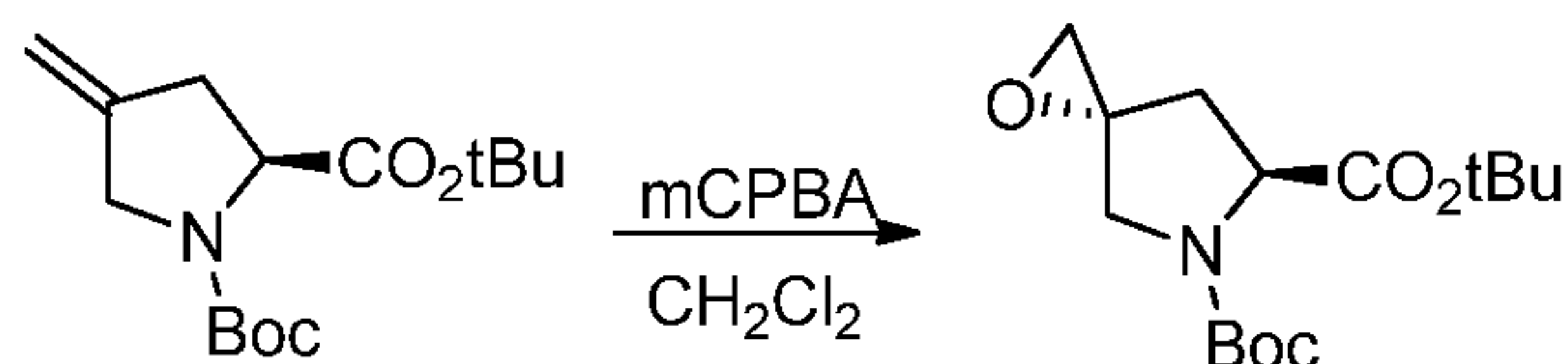
15 Step 1



To a suspension of methyltriphenylphosphonium bromide (16.90 g, 47.3 mmol) in THF (315 ml) was added 1.7 M KOtBu in THF (24.12 ml, 41.0 mmol) in one portion at 0°C under N₂. After the addition, the reaction was removed from the ice bath and stirred at RT for 30
 20 min. The suspension was then cooled to 0°C, and a solution of commercially available (*S*)-di-*tert*-butyl 4-oxopyrrolidine-1,2-dicarboxylate (9 g, 31.5 mmol) in 20 ml THF was dropwise over 5 min. The reaction was stirred at 0°C for 1h and then at RT for 3h. TLC (10% EtOAc in hexanes; CMA stain) showed complete conversion of the starting material to a less polar spot. The reaction was added to a sat. aq. solution of NH₄Cl and then extracted with EtOAc. The
 25 combined organics were dried (MgSO₄), filtered and concentrated to furnish yellow oil, which

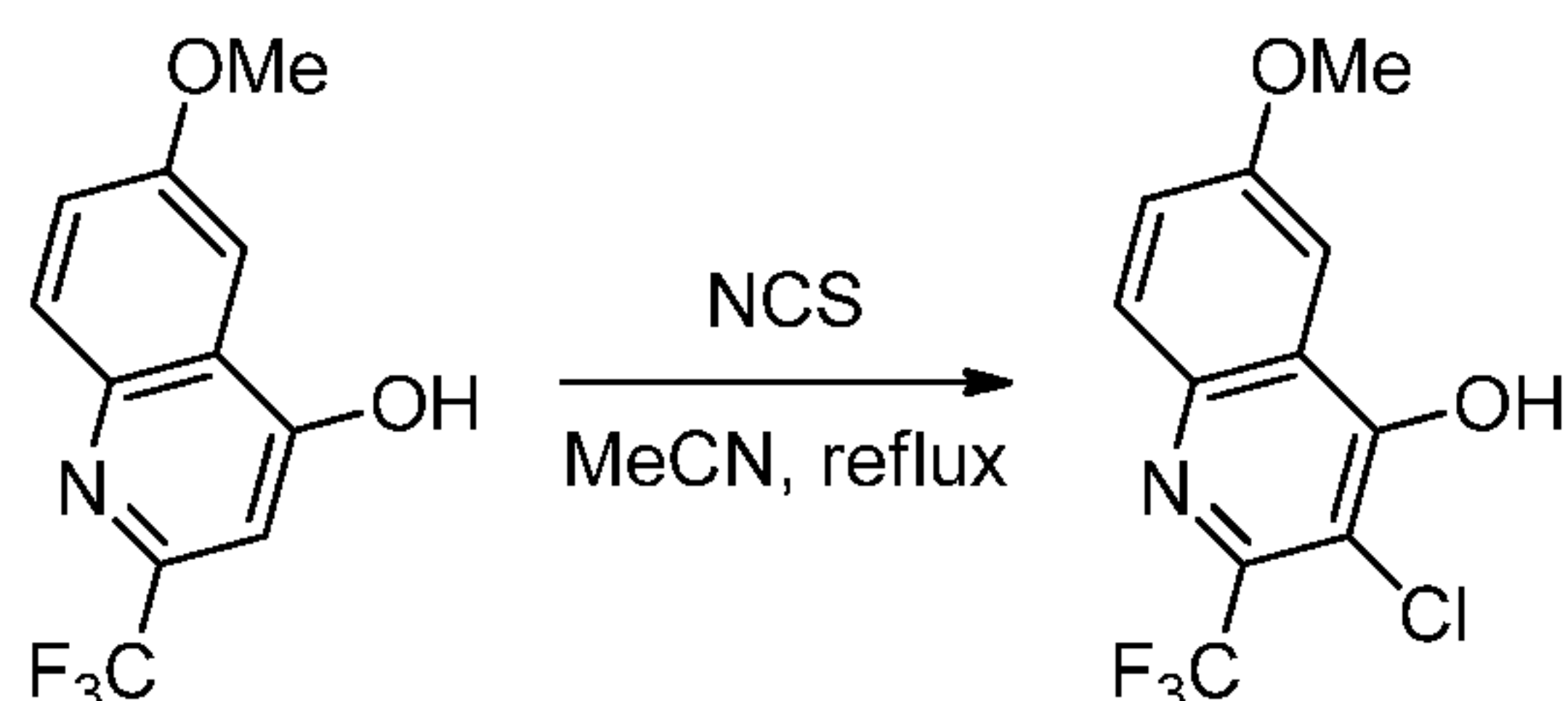
was purified by silica gel column chromatography on an ISCO (REDISEP 120 g, 0-20% EtOAc in hexanes) to provide the product of Step 1 (7.75 g, 27.4 mmol, 87% yield) as colorless oil.

Step 2



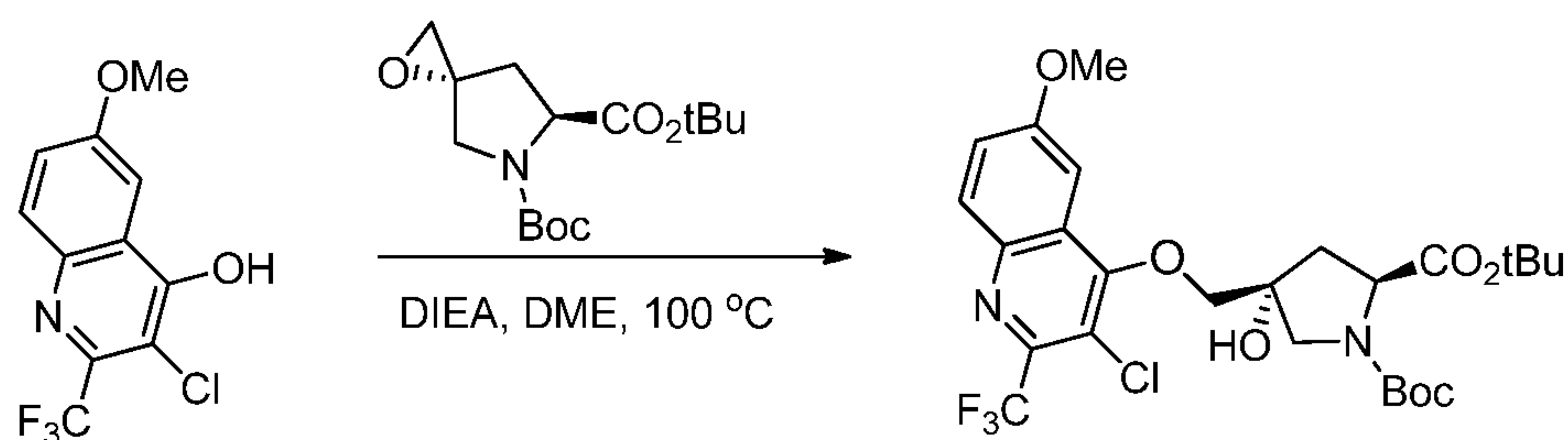
- 5 To a solution of the product of Step 1 (7.75 g, 27.4 mmol) in CH₂Cl₂ (91 ml) at 0°C was added mCPBA (15.32 g, 68.4 mmol). The reaction was stirred at 0°C while being warmed up to RT. TLC (10% EtOAc in hexane) after 2h showed two more polar spots and some unreacted starting material. The reaction was quenched with 10% aq. Na₂SO₃ solution, stirred for 15 min and then extracted with EtOAc. The organic fraction was washed with sat. aq.
- 10 NaHCO₃ and water. The aq. Na₂SO₃ and NaHCO₃ fractions were combined and extracted once with EtOAc. The combined organics were washed with brine, dried (MgSO₄) and concentrated to provide a residue, which was purified by silica gel chromatography (ISCO, 220 g REDISEP column, 0-50% EtOAc in hexane) to provide the product of Step 2 (2.63 g, 32% yield) as the non-polar diastereomer.

15 Step 3



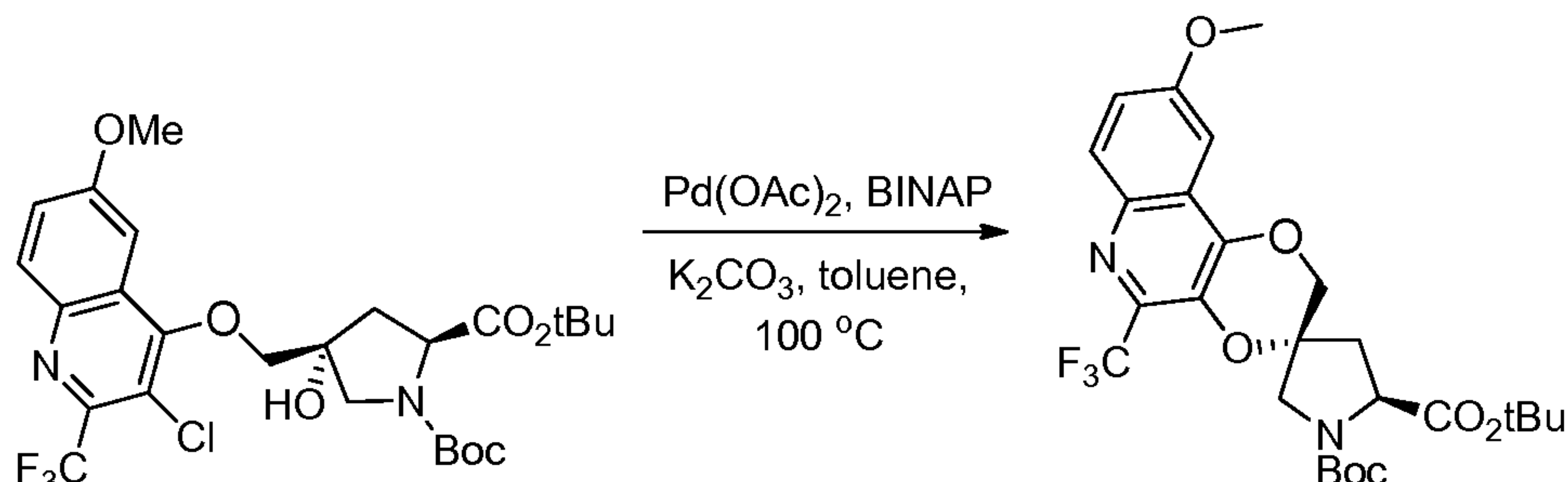
- To a 1L RB flask fitted with a reflux condenser was taken 6-methoxy-2-(trifluoromethyl)quinolin-4-ol (10 g, 41.1 mmol) and MeCN (400 ml) [0.15 m concentration]. This mixture was treated with NCS (6.04 g, 45.2 mmol), and the reaction was stirred at 80°C for
- 20 1h. The solvent was removed under reduced pressure, and the residue was taken up in MeCN and filtered. The solid was washed with ether and then with DCM and dried under vacuum to provide the product of Step 3 (3-chloro-6-methoxy-2-(trifluoromethyl)quinolin-4-ol, 5.0 g).

Step 4



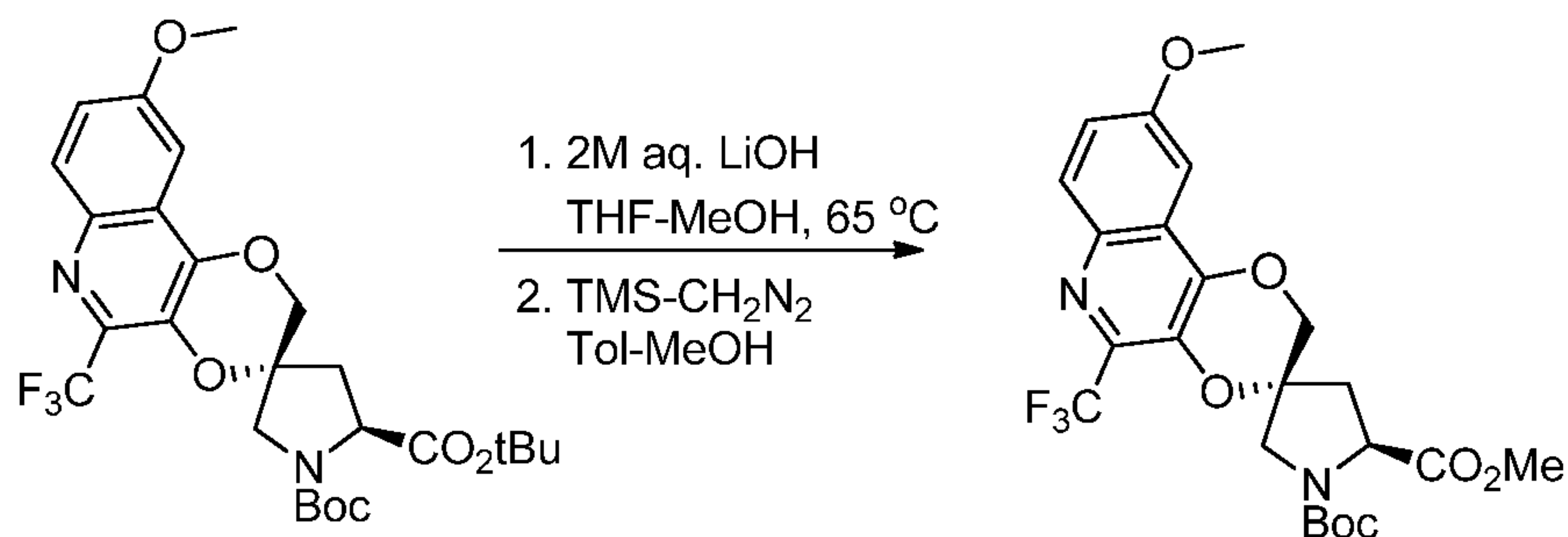
To a solution of the product of Step 2 (1.37 g, 4.58 mmol) in DME (45.8 ml) was added the product of Step 3 (1.525 g, 5.49 mmol) and DIEA (4.00 ml, 22.88 mmol) at RT. The flask was degassed (vacuum/N₂ – 3x) and then stirred at 100°C under N₂ over the weekend. The volatiles were removed under reduced pressure, and the resulting residue was purified by silica gel column chromatography (80 g REDISEP column, 0-40% EtOAc/Hexane) to provide the product of Step 4 (2.3 g, 3.99 mmol, 87% yield).

Step 5



A solution of the product of Step 4 (3.21 g, 5.56 mmol), Pd(OAc)₂ (0.187 g, 0.835 mmol), BINAP (0.624 g, 1.001 mmol), and K₂CO₃ (1.153 g, 8.35 mmol) in toluene (27.8 ml) was degassed (N₂/vacuum) for 5 min and then stirred at 105°C (using a reflux condenser) for 16h under N₂. After bringing to RT, the reaction was diluted with EtOAc, and the insolubles were filtered off. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ISCO, 120 g REDISEP column, 0-40% EtOAc in hexane) to provide the product of Step 5 (2.08 g, 3.85 mmol, 69.2% yield).

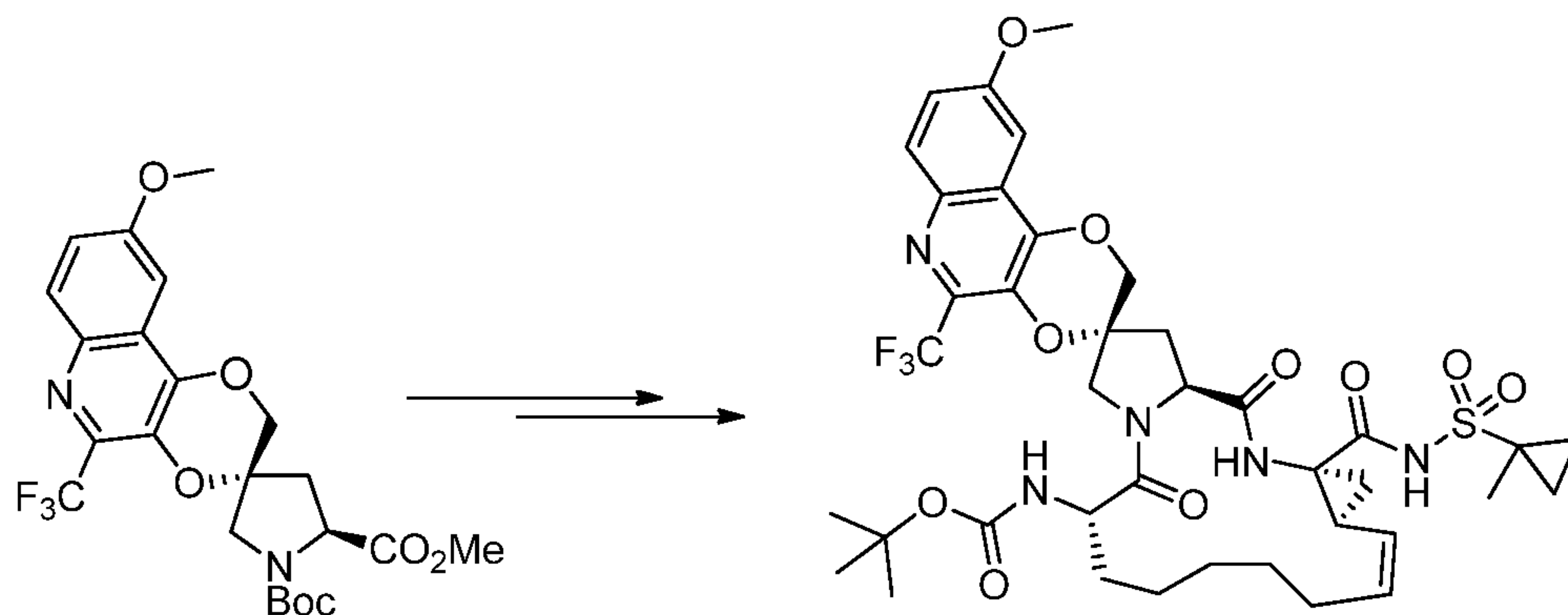
Step 6



To a solution of the product of Step 5 (2.85 g, 5.27 mmol) in a mixture of THF (26.4 ml) and MeOH (26.4 ml) was added 2 m aq. LiOH (26.4 ml, 52.7 mmol), and the reaction was stirred at 65°C for 90 min. The reaction was allowed to come to RT and was quenched with 2 m aq. HCl until pH ~3 and diluted with DCM. The organic layer was separated, washed with
 5 brine and then filtered (MgSO₄) and concentrated to provide (3R,5'S)-1'-(*tert*-butoxycarbonyl)-9-methoxy-5-(trifluoromethyl)-2H-spiro[[1,4]dioxino[2,3-*c*]quinoline-3,3'-pyrrolidine]-5'-carboxylic acid, which was used without purification.

To a solution of (3R,5'S)-1'-(*tert*-butoxycarbonyl)-9-methoxy-5-(trifluoromethyl)-2H-spiro[[1,4]dioxino[2,3-*c*]quinoline-3,3'-pyrrolidine]-5'-carboxylic acid (2.55 g, 5.26 mmol) in
 10 toluene (80 ml) and MeOH (20.00 ml) was added a 2 m solution of trimethylsilyldiazomethane in hexanes, (5.26 ml, 10.53 mmol) at RT. After 10 min of stirring, the volatiles were removed under reduced pressure to provide the product of Step 6 (2.5 g, 5.02 mmol, 95% yield), which was used without purification.

Step 7



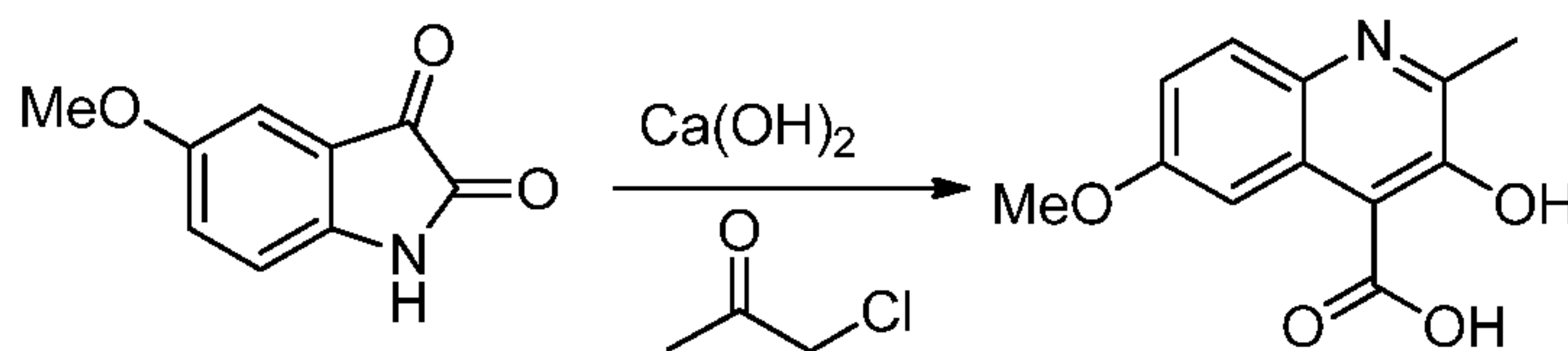
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I-8 was prepared from the product of Step 6 by using the procedures described in Example 7, Steps 9-10.

Example 9: *tert*-Butyl [(2R,6S,12Z,13aS,14aR,16aS)-9'-methoxy-5'-methyl-14a-}[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-*c*]quinolin]-6-yl]carbamate (I-9)

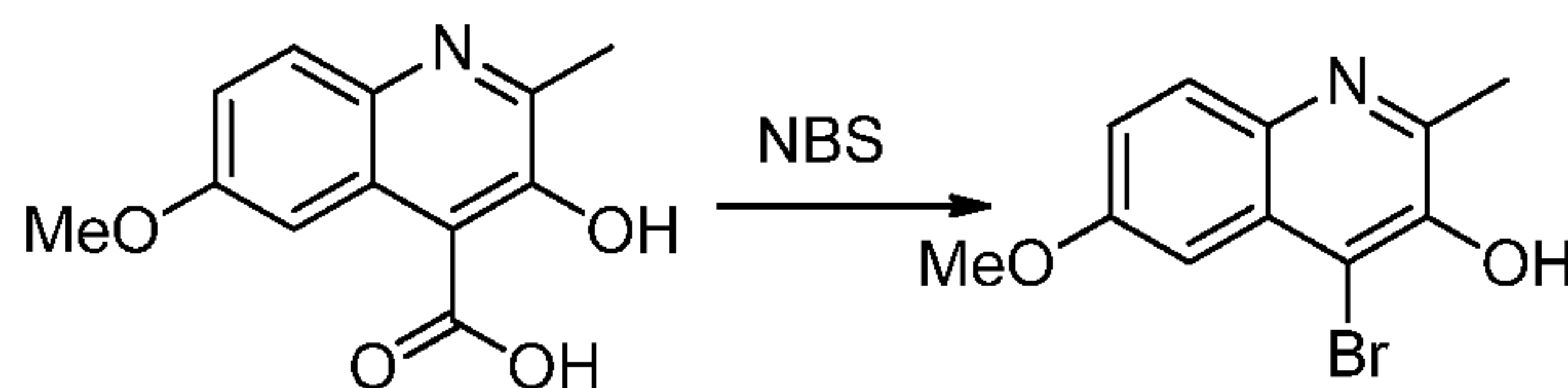
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Step 1



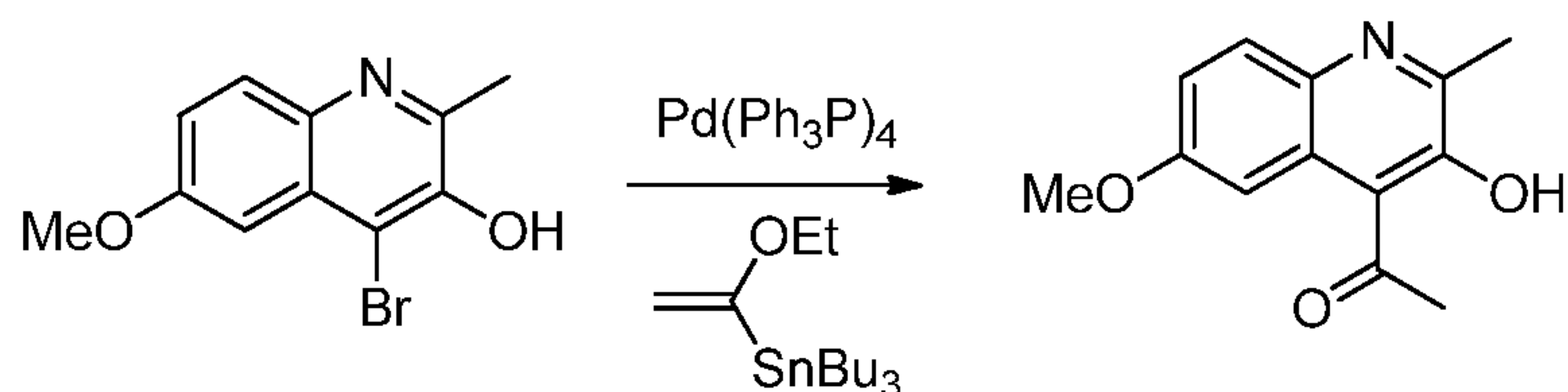
A suspension of 5-methoxyisatin (15 g, 85 mmol) and $\text{Ca}(\text{OH})_2$ (18.82 g, 254 mmol) in water (600 ml) was stirred in an oil-bath kept at 80°C for 1h, added chloroacetone (10.81 ml, 169 mmol), and the thick slurry was stirred for another 4h at 80°C . The mixture was cooled to RT, acidified with concentrated HCl, and the solid was filtered, washed several times with water and finally with ether. The solid was dried in vacuum oven to give 17.7 g of the product of Step 1 as a solid. MS $m/e = 234.2$ (MH^+).

Step 2

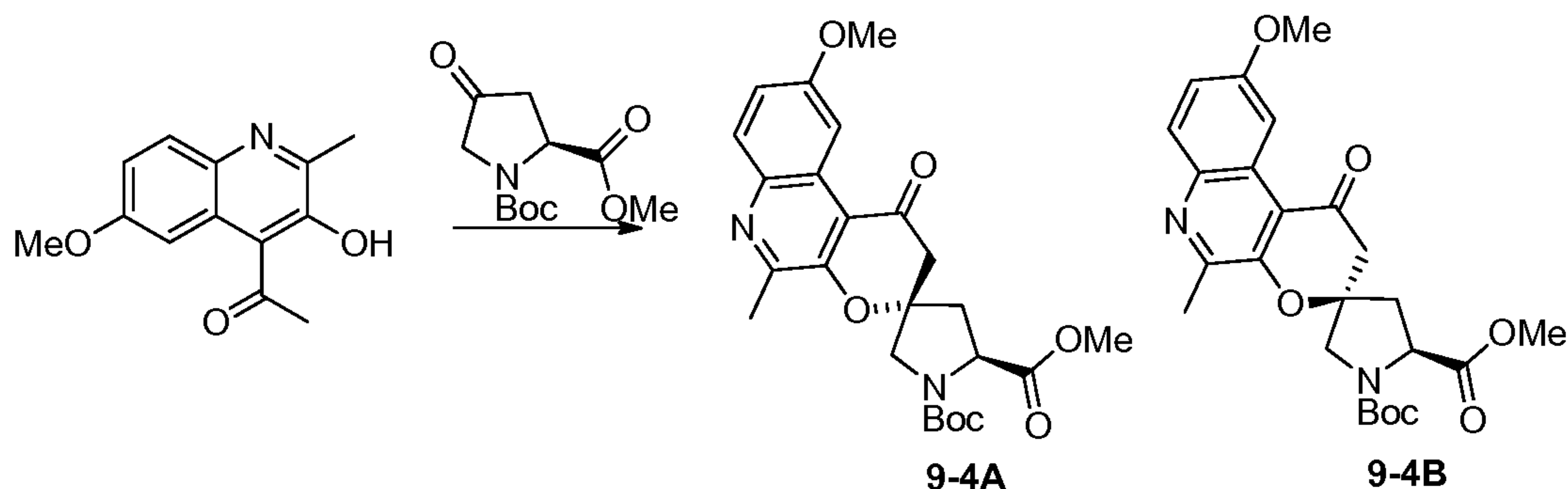


To a suspension of the product of Step 1 (17.6 g, 75 mmol) in DMF (300 ml) at RT was added NBS (13.43 g, 75 mmol) in-portions over a period of 30 min. The mixture was stirred at RT for 3h. The reaction mixture was diluted with aq. $\text{Na}_2\text{S}_2\text{O}_3$ and extracted 3x with EtOAc. The combined organic layer was washed with brine, dried over MgSO_4 , filtered and dried to give a solid. The precipitate remaining in the aq. phase was filtered and dried in vacuum oven. Both solids were combined and taken in about 200 ml of 1:1 MeOH-DCM, and to this was added about 60 g of silica gel. The solvent was evaporated to dryness and the adsorbed crude product was chromatographed eluting with 0- 30-100% EtOAc-DCM to give 13.02 g of the product of Step 2 as yellow colored solid. MS $m/e = 270.0$ (MH^+).

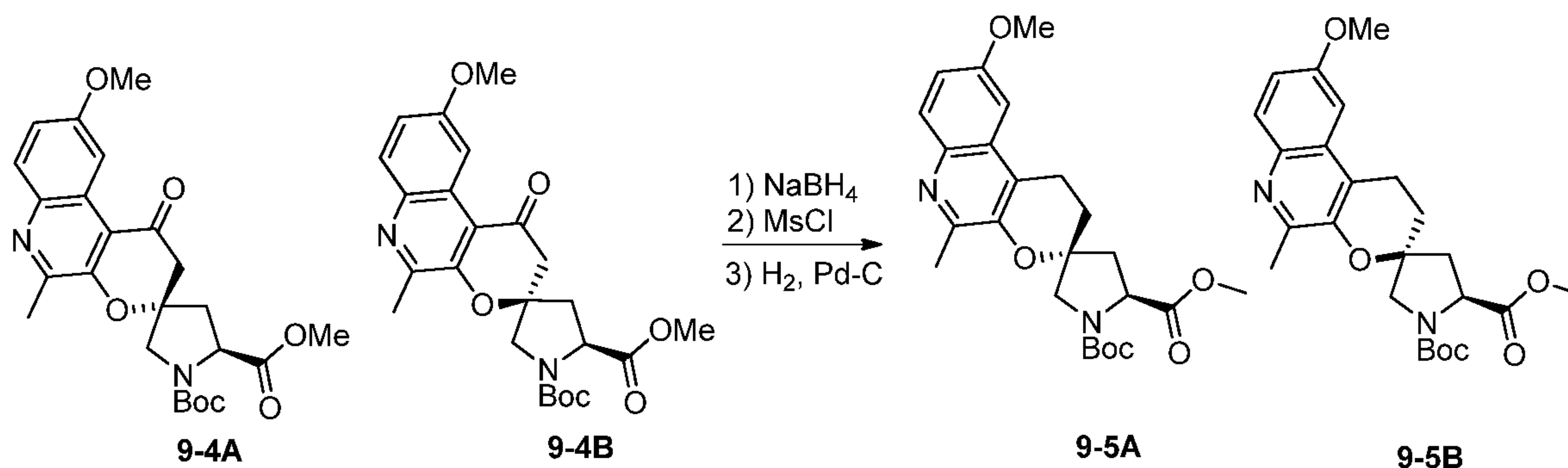
Step 3



A mixture of the product of Step 2 (13.0 g, 48.5 mmol), tributyl(1-ethoxyvinyl)tin (23.39 ml, 69.2 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (2.80 g, 2.424 mmol) in dioxane (200 ml) was heated overnight at reflux. The solution was cooled to RT and stirred with 50 ml of 1N HCl for 1.5h. The reaction mixture was diluted with aq. NaHCO_3 and extracted 3x with DCM. The combined organic layer was washed with brine, dried over MgSO_4 , filtered, concentrated and chromatographed with 0-40-100% EtOAc-hexanes to give 7.19 g of the product of Step 3 as a solid. MS $m/e = 232.0$ (MH^+)

Step 4

A mixture of Boc-4-oxo-Pro-OMe (15.13 g, 62.2 mmol), the product of Step 3 (7.19 g, 31.1 mmol) and pyrrolidine (1.029 ml, 12.44 mmol) in MeOH (200 ml) and 3A
 5 molecular sieves (~25 g, 4-8 mesh) in a sealed tube was stirred in an oil bath kept at 100°C for 1h. The suspension was filtered through a CELITE pad, concentrated and chromatographed with 0-40-100% EtOAc-hexanes to give 4.28 g of 9-4A and 2.87 g of 9-4B. MS for 9-4A m/e = 457.0 (MH⁺). MS for 9-4B m/e = 457.0 (MH⁺).

Step 5

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To a solution of 9-4A and 9-4B (3.2 g, 7.01 mmol) in THF (20 ml) and MeOH (20 ml) at 0°C was added NaBH₄ (0.265 g, 7.01 mmol) and stirred for 10 min at 0°C. It was quenched by the addition of acetone followed by aq. NH₄Cl and extracted 3x with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered, concentrated and
 15 evaporated to dryness to give the crude alcohol, which was used as such.

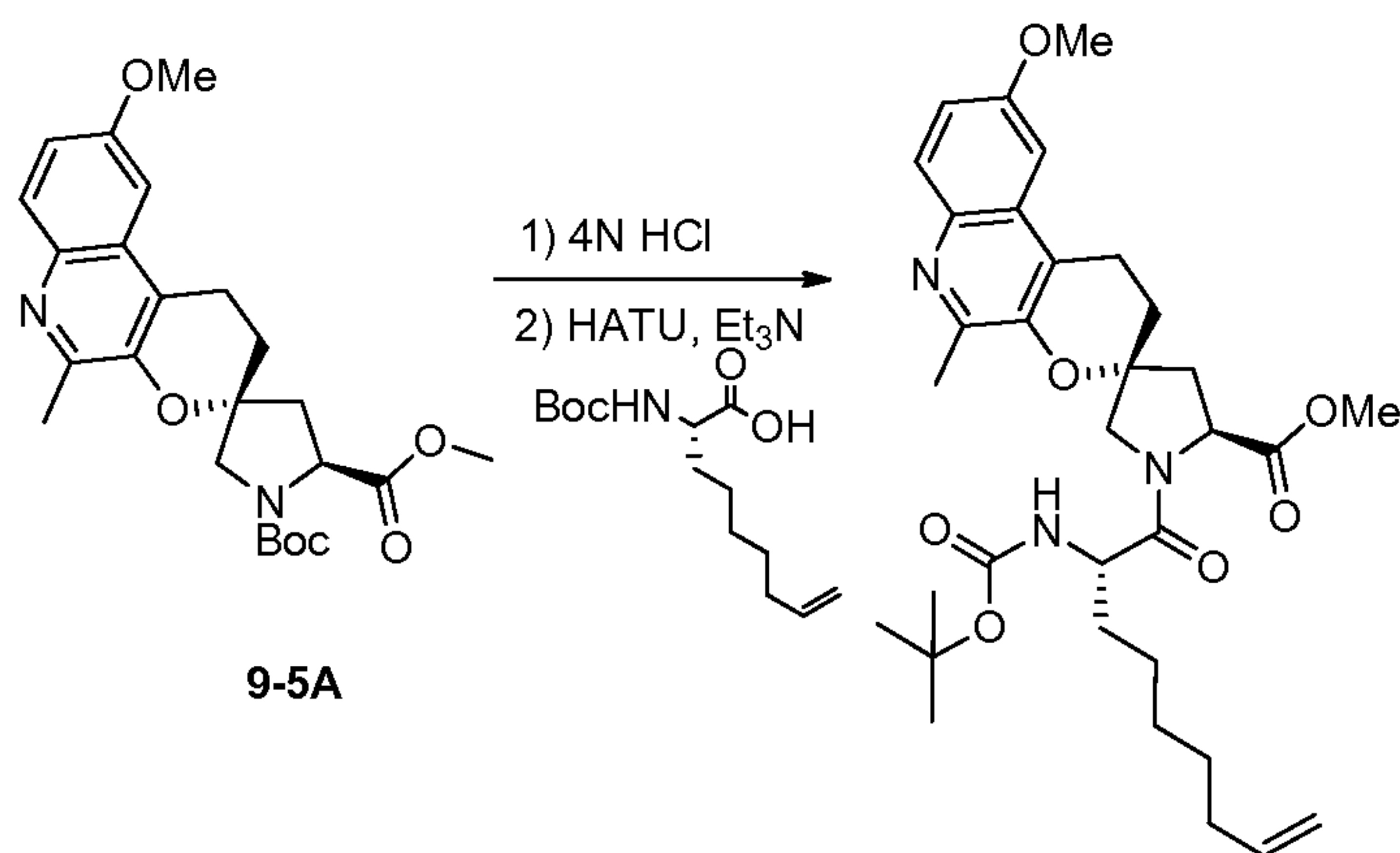
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To a solution of the above product (3.21 g, 7.01 mmol) in DCM (40 ml) at 0°C was added Et₃N (2.93 ml, 21.03 mmol) followed by MsCl (1.093 ml, 14.02 mmol). The mixture was stirred overnight while allowing it to warm to RT. The reaction mixture was diluted with EtOAc, washed 2x with aq. NaHCO₃, brine, dried over MgSO₄, filtered and evaporated to
 20 dryness to give the crude product, which was used as such.

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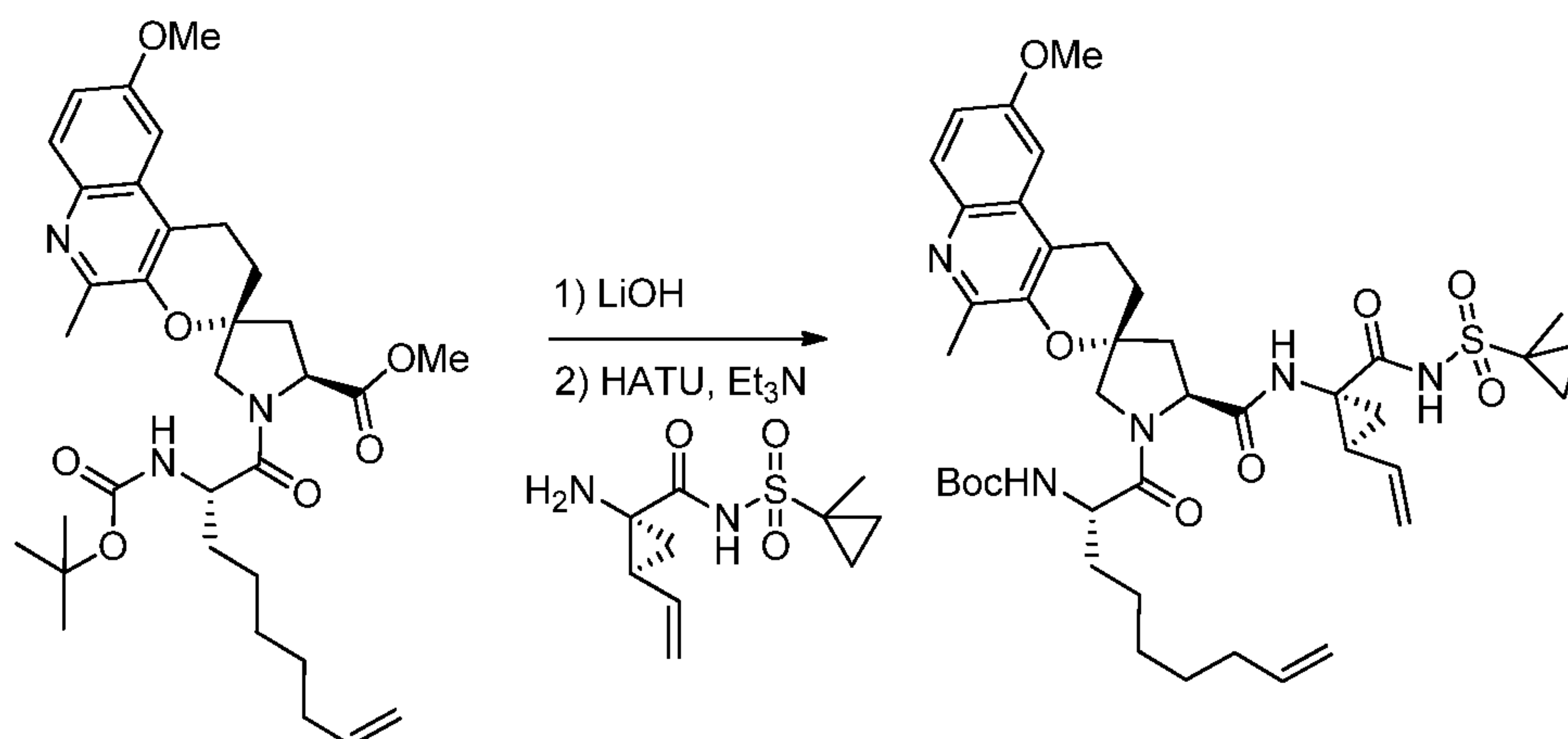
A suspension of the above product (3343 mg, 7.01 mmol) and 10% Pd-C (600 mg) in EtOAc (60 ml) was stirred under a H₂ balloon for 3h. The suspension was filtered through a CELITE pad, washed with MeOH and EtOAc. The filtrate was washed with aq. NaHCO₃, brine, dried over MgSO₄, filtered, concentrated and chromatographed with 0-40-100% EtOAc-hexanes to provide 1.64 g of 9-5A and 9-5B as solid. MS m/e = 443.2 (MH⁺).

Step 6



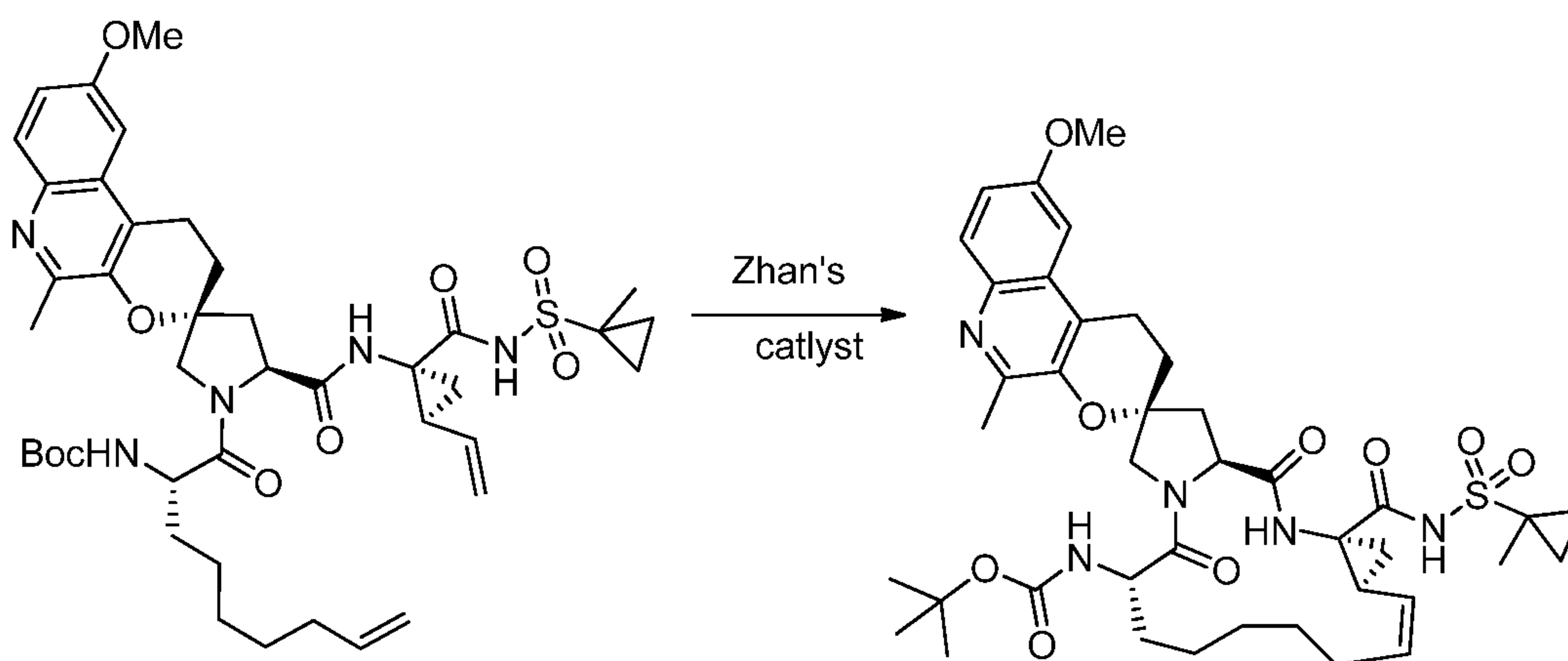
A solution of 9-5A (1.60 g, 3.62 mmol) in 4N HCl dioxane (20 ml) and MeOH (5 ml) was stirred at RT for 2h. The solvent was co-evaporated 2x with toluene and 2x with ether to give the amine as the HCl salt, which was used as such. MS m/e = 343.2 (MH⁺).

To a slurry of the above product (1.371 g, 3.62 mmol) and (S)-2-(*tert*-butoxycarbonylamino)non-8-enoic acid – dicyclohexylamine salt (2.458 g, 5.43 mmol) in DMF (40 ml) at RT was added HATU (2.065 g, 5.43 mmol) followed by TEA (1.514 ml, 10.86 mmol). The mixture was stirred overnight at RT then diluted with water and extracted 3x with EtOAc. The combined organic layer was washed with water, brine, dried over MgSO₄, filtered, concentrated and chromatographed with 0-50-100% EtOAc-hexanes to give 1.57 g of the product of Step 6 as solid. MS m/e = 596.2 (MH⁺).

Step 7

A solution of the product of Step 6 (1.55 g, 2.60 mmol) and LiOH·H₂O (0.437 g, 10.41 mmol) in THF (10 ml), MeOH (10.00 ml) and water (10.00 ml) was stirred in an oil bath kept at 60°C for 1.5h. The solution was diluted with water, acidified with 1N HCl and extracted 3x with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to dryness to give the crude acid, which was used as such. MS m/e = 582.2 (MH⁺).

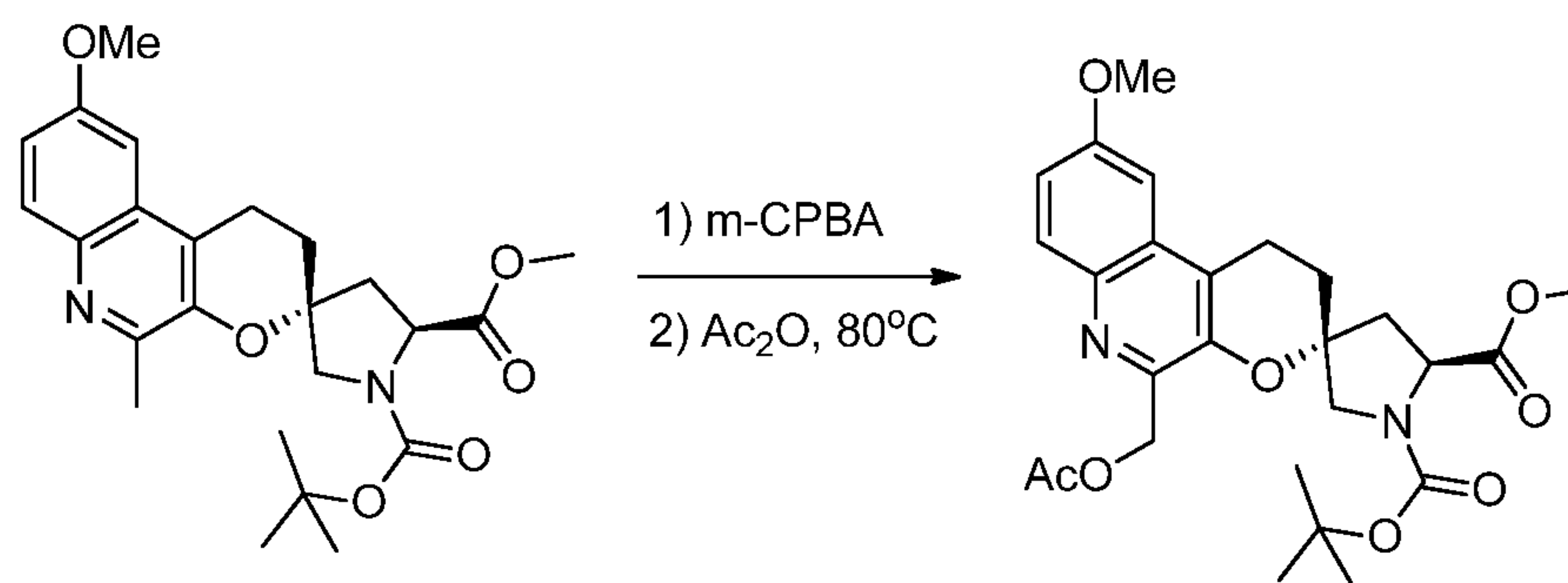
A mixture of the above acid (1.512 g, 2.60 mmol), (1R,2S)-1-amino-N-(1-methylcyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide tosylate salt (1.624 g, 3.90 mmol), HATU (1.483 g, 3.90 mmol) and TEA (1.087 ml, 7.80 mmol) in DMF (20 ml) was stirred overnight at RT. The reaction mixture was diluted with water and extracted 3x with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered, concentrated and chromatographed with 0-30-100% acetone-hexanes to give 2.14 g of the product of Step 7 as solid. MS m/e = 808.4 (MH⁺).

Step 8

A solution of the product of Step 7 (1.07 g, 1.324 mmol), 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene[2-(i-propoxy)-5-(*N,N*-dimethylaminosulfonyl)phenyl]methylene ruthenium(II) dichloride (0.243 g, 0.331 mmol) and 1,4-benzoquinone (0.043 g, 0.397 mmol) in DCE (600 ml) was degassed under vacuum and filled with argon. The mixture was stirred in an oil bath kept at 75°C (bath temp) for 4h then stirred with 0.5 ml of n-butylvinyl ether for 30 min. The solvent was evaporated to dryness, and the residue was chromatographed with 0-40-100% acetone-hexanes to give 800 mg of I-9 as a solid. ¹H-NMR (400 MHz, acetone-d₆) 10.56 (br s, 1H), 8.42 (s, 1H), 7.75 (d, J = 838 Hz, 1H), 7.16-7.13 (m, 2H), 6.04 (d, J = 7.1 Hz, 1H), 5.72-5.66 (m, 1H), 4.99 (t, J = 9.5 Hz, 1H), 4.71 (dd, J = 10.2, 6.9 Hz, 1H), 4.50 (d, J = 11.3 Hz, 1H), 4.11-4.07 (m, 1H), 3.94 (s, 3H), 3.79 (d, J = 10.9 Hz, 1H), 3.77 (s, 1H), 3.20-3.07 (m, 2H), 2.60-2.26 (m, 3H), 2.08-2.04 (m), 1.93-1.86 (m), 1.73 (dd, J = 5.5, 8.1 Hz, 1H), 1.65-1.61 (m, 1H), 1.58-1.54 (m, 2H), 1.48 (s, 9H), 1.46-1.26 (m), 0.89-0.820 (m). MS m/e = 780.2 (MH⁺).

Example 10: tert-butyl ((2R,6S,13aS,14aR,16aS,Z)-5'-(difluoromethyl)-9'-methoxy-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-10)

Step 1



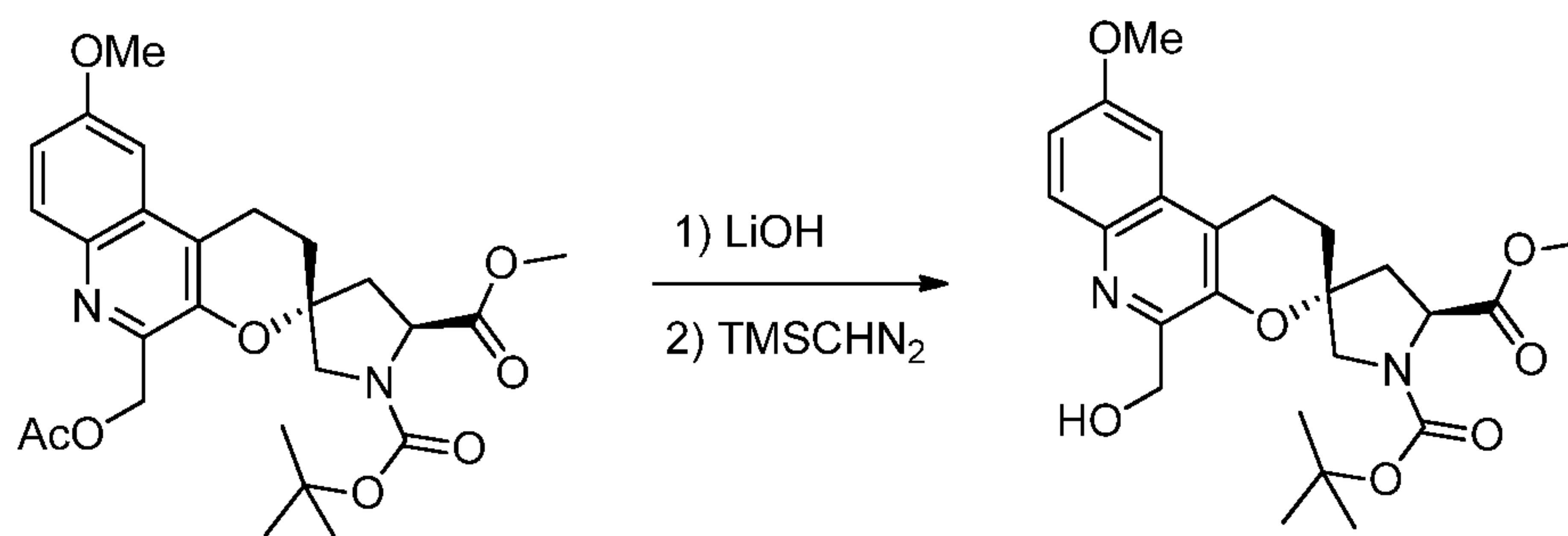
20

To a solution of intermediate 9-5A (the product of Example 9, Step 5) (6.6 g, 14.92 mmol) in DCM (100 ml) at RT was added MCPBA (6.69 g, 29.8 mmol), and the mixture was stirred overnight at RT. The reaction mixture was diluted with aq. K₂CO₃ and aq. Na₂S₂O₃. The DCM was concentrated to about a third volume, and the slurry was extracted 3x with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to dryness to give 6.74 g of the N-oxide intermediate as foam. LC-MS m/e = 459.2 (MH⁺). The crude product was used as such.

25

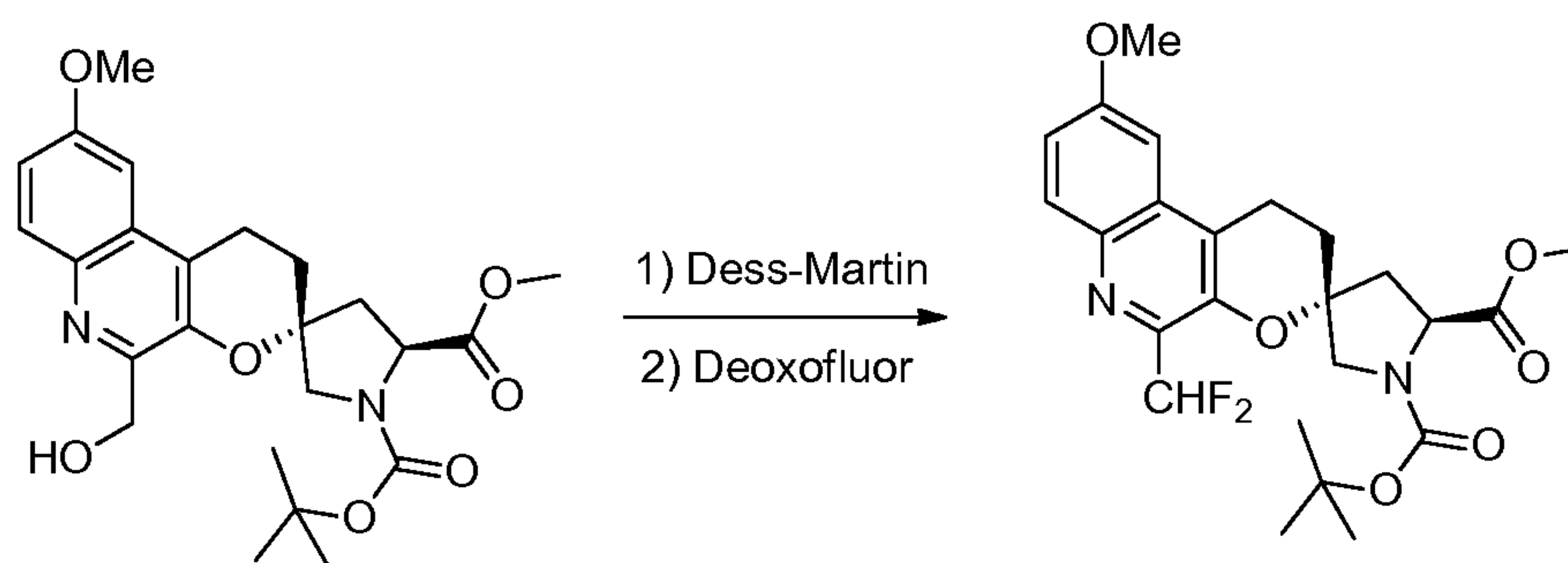
A solution of the crude N-oxide (6.74 g, 14.70 mmol) in acetic anhydride (100 ml, 14.70 mmol) was stirred in an oil-bath kept at 80°C (bath temperature). After stirring for a total of 1.5h, the reaction mixture was cooled to RT then poured into ice-cold water. The slurry was extracted 3x with EtOAc, and the combined organic layer was washed with brine, dried over
 5 MgSO₄, filtered, concentrated and purified by chromatography eluting with 0-50% EtOAc-hexanes to give 5.2 g of the product of Step 1 as a solid: LC-MS m/e = 501.2 (MH⁺).

Step 2



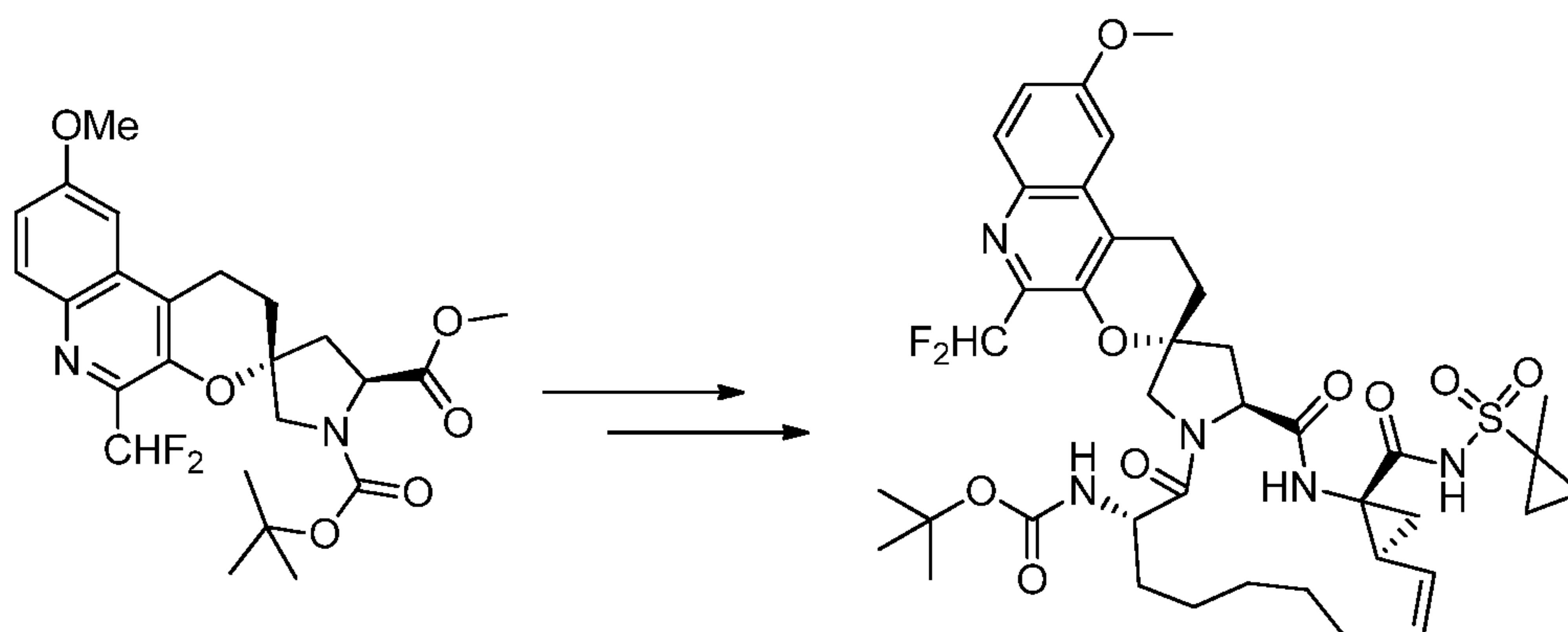
A solution of the product of Step 1 (5.2 g, 10.39 mmol) and LiOH·H₂O (0.785 g, 18.70 mmol) in THF (30 ml), MeOH (30.0 ml) and water (30.0 ml) was stirred at 0°C. The
 10 mixture was stirred for 2h at 0°C and 1h at RT, then another 300 mg of LiOH·H₂O (~0.7 eq.) was added. After stirring for additional 1h at RT, the reaction mixture was diluted with water and acidified with 1N HCl to pH ~ 3. The mixture was extracted 3x with EtOAc, the combined organic layer washed with brine, dried over MgSO₄, filtered and evaporated to dryness to give
 15 4.98 g of product where both the acetate and the methyl ester were hydrolyzed. LC-MS m/e = 445.2 (MH⁺).

To a solution of the acid (1.9 g, 4.27 mmol) in toluene (20 ml) and MeOH (5 ml) at RT was added a 2 m hexane solution of trimethylsilyl diazomethane (4.27 ml, 8.55 mmol). The mixture was stirred at RT for 1h, evaporated to dryness, and the residue was purified by
 20 chromatography eluting with 0-60% EtOAc-hexanes to give 1.56 g of the product of Step 2 as a solid. LC-MS m/e = 459.2 (MH⁺).

Step 3

A solution of the product of Step 2 (1.56 g, 3.40 mmol) and Dess Martin periodinane (2.165 g, 5.10 mmol) in DCM (30 ml) was stirred at RT for 1h, then diluted with ether followed by aq. NaHCO₃ and aq. Na₂S₂O₃. The mixture was stirred for 10 min, and the organic layer was separated. The aq. phase was extracted 2x with EtOAc, and the combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to dryness. The product was purified by chromatography eluting with 0-60% EtOAc-hexanes to give 1.45 g of aldehyde intermediate as a solid. LC-MS m/e = 475.2 (MNa⁺).

To a solution of the aldehyde (1.45 g, 3.18 mmol) in DCM (30 ml) was added bis (2-methoxyethyl)aminosulfur trifluoride (1.757 ml, 9.53 mmol) followed by EtOH (0.037 ml, 0.635 mmol), and the mixture was heated at reflux overnight. LC-MS indicated small amount of unreacted starting material. To the reaction mixture was added another 1eq. of DEOXOFLUOR, and reaction was heated at reflux for another 4h. The reaction mixture was cooled to RT, stirred with aq. NaHCO₃, and the organic layer was separated. The aq. phase was extracted 2x with EtOAc, and the combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to dryness. The crude product was purified by chromatography eluting with 0-60% EtOAc-hexanes to give 1.21 g of the product of Step 3. LC-MS m/e = 501.2 (M+Na)⁺.

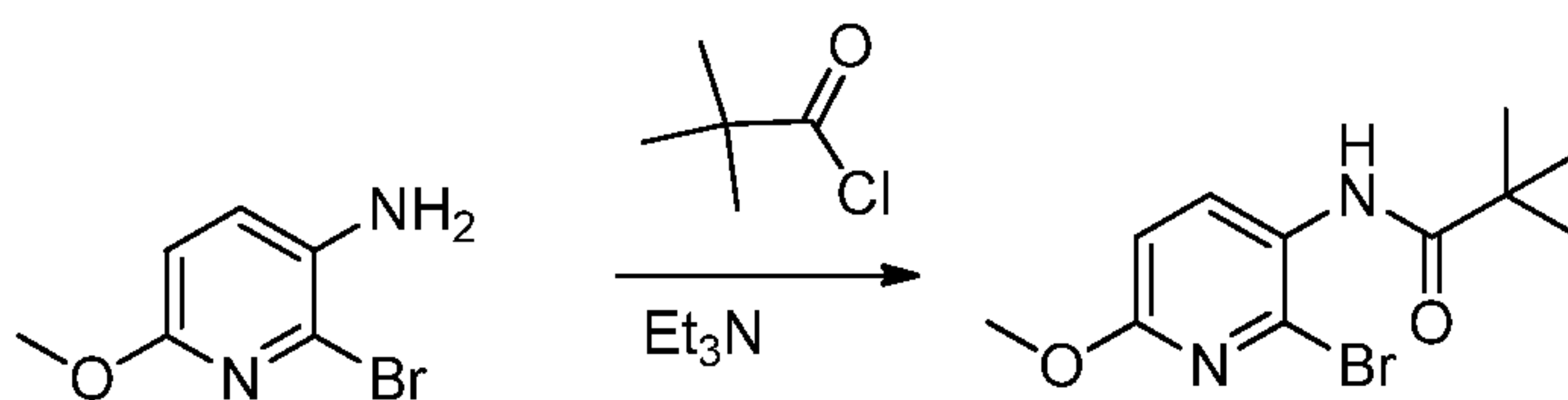
Step 4

20

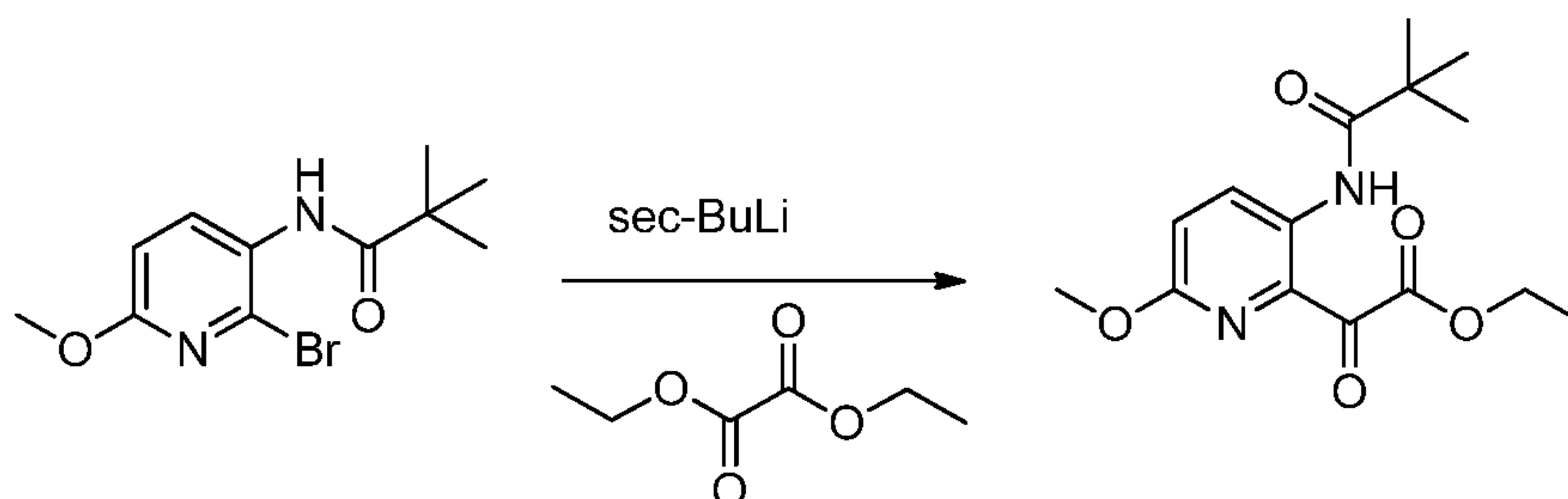
The product of Step 3 was converted to I-10 using a procedure similar to the preparation of Example 9 from the product of Step 5. LC-MS $m/e = m/e = 816.4$ (MH⁺). ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.49 (1H, d, J = 3.6 Hz), 7.90 (1H, d, J = 8.8 Hz), 7.29-7.26 (m, 2H), 6.96 (1H, t, J = 54.6 Hz), 6.01 (1H, d, J = 6.8 Hz), 5.69 (1H, q, J = 8.9 Hz), 5.00 (1H, t, J = 9.6 Hz), 4.67 (1H, t, J = 8.4 Hz), 4.51 (1H, d, J = 11.2 Hz), 4.10 (1H, t, J = 9.0 Hz), 4.00 (3H, s), 3.84 (1H, d, J = 11.2), 3.76 (3H, s), 3.40 (1H, q, J = 6.9 Hz), 3.3-3.20 (2H, m), 2.82 (s, 2H), 2.78 (s, 2H), 2.62-2.41 (m), 2.33 (1H, t, J = 11.6 Hz), 2.21-2.20 (1H, m), 2.14-2.04 (m), 1.90-1.86 (2H, m), 1.74-1.71 (2H, m), 1.65-1.55 (2H, m), 1.49-1.41 (m), 1.37-1.27 (m), 1.13-1.09 (m).

10

Example 11: tert-butyl (2R,6S,13aS,14aR,16aS,Z)-2'-methoxy-6'-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-3,5,6,7,8,9,9',10,10',11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,8'-pyrano[2,3-c][1,5]naphthyridine]-6-ylcarbamate (I-11)

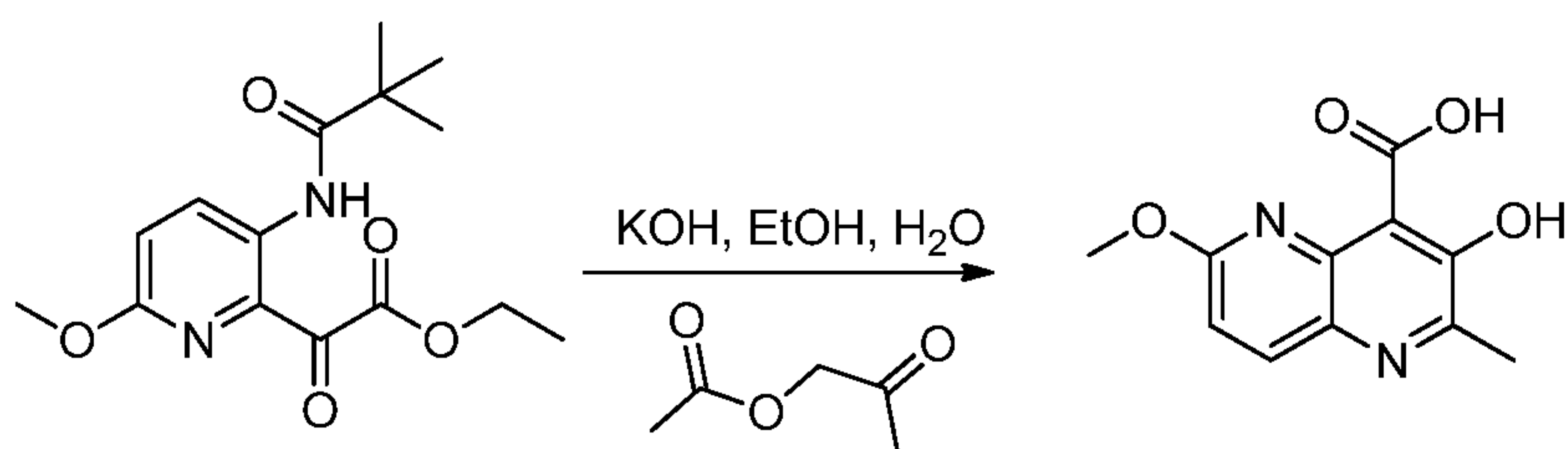
15 Step 1

To a solution of 3-amino-2-bromo-6-methoxypyridine (10.0 g, 49.3 mmol) in DCM (200 ml) at 0°C was added TEA (11.0 ml, 79 mmol) followed by pivaloyl chloride (6.67 ml, 54.2 mmol), and the mixture was allowed to warm to RT and stirred overnight. The mixture was quenched at RT with sat. aq. NH₄Cl and extracted with DCM. The combined organic fractions were washed with sat. aq. NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 20:80) to give the product of Step 1 (13.3 g, 94% yield) as a white solid.

25 Step 2

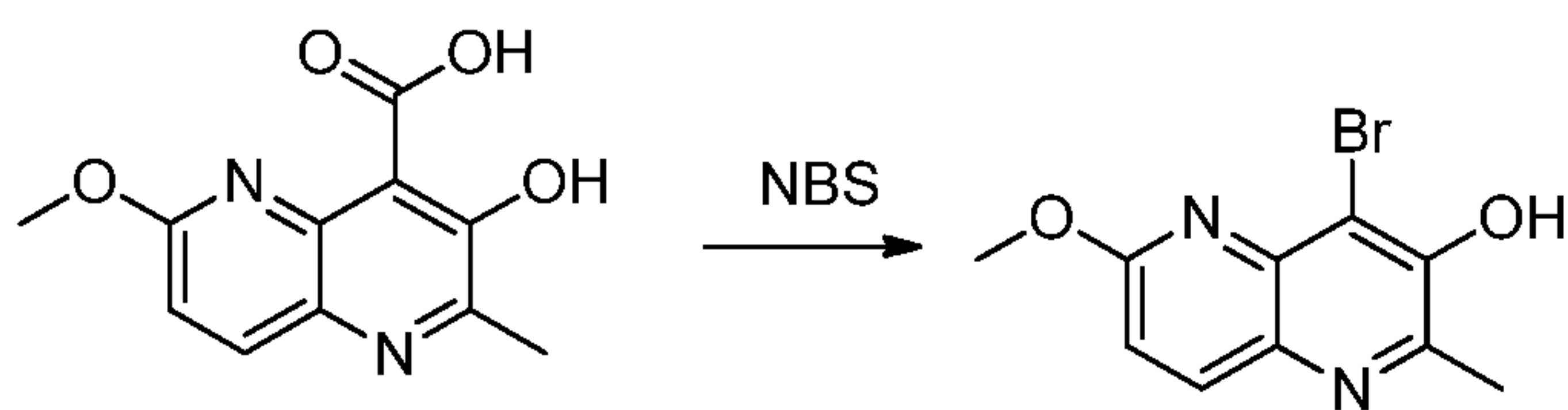
To a solution of the product of Step 1 (13.9 g, 48.3 mmol) in THF (175 ml) at -78°C was added *sec*-butyl lithium 1.4N in hexanes (83 ml, 116 mmol) over 15 min. The mixture was allowed to warm to 0°C after 30 min at -78°C and stirred for 90 min at 0°C. Diethyl oxalate (7.87 ml, 57.9 mmol) was then added to the reaction at -78°C, and the reaction was slowly allowed to warm to RT overnight. The mixture was poured at RT into sat. aq. NH₄Cl and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/DCM 80:20 to DCM) to give the product of Step 2 (6.99 g, 47% yield) as yellow oil.

10 Step 3



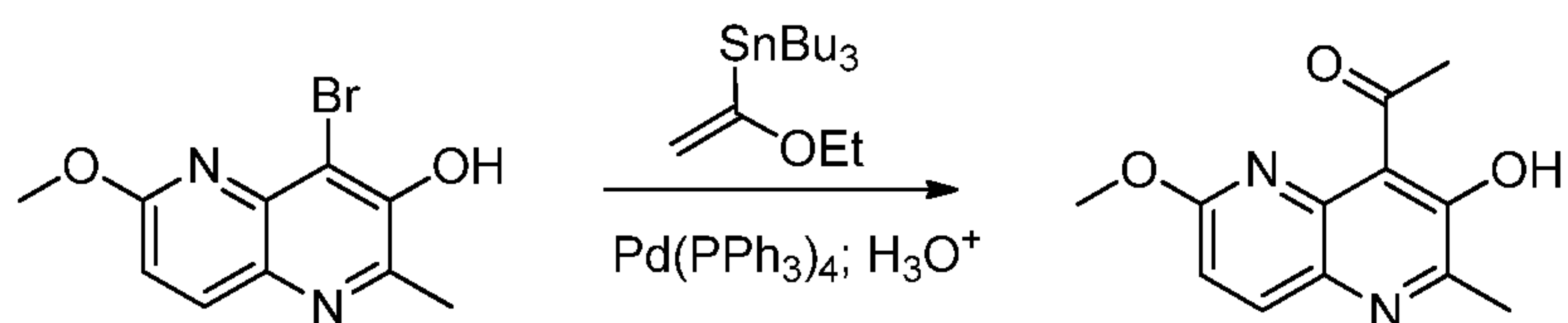
To a solution of the product of Step 2 (10.5 g, 34.1 mmol) in EtOH (70 ml) and water (70 ml) at RT was added 6N KOH (79 ml, 477 mmol), and the mixture was warmed to 90°C and stirred for 1h. Acetoxy-2-propanone (4.05 ml, 37.5 mmol) was then added at 90°C over 3 min, and the reaction was stirred for 1h. The operation was repeated 2x. The mixture was concentrated from EtOH then slowly quenched at 0°C with 1N aq. HCl until pH ~ 4, then filtered and dried *in vacuo* to provide the product of Step 3 (4.81 g, 60% yield).

15 Step 4



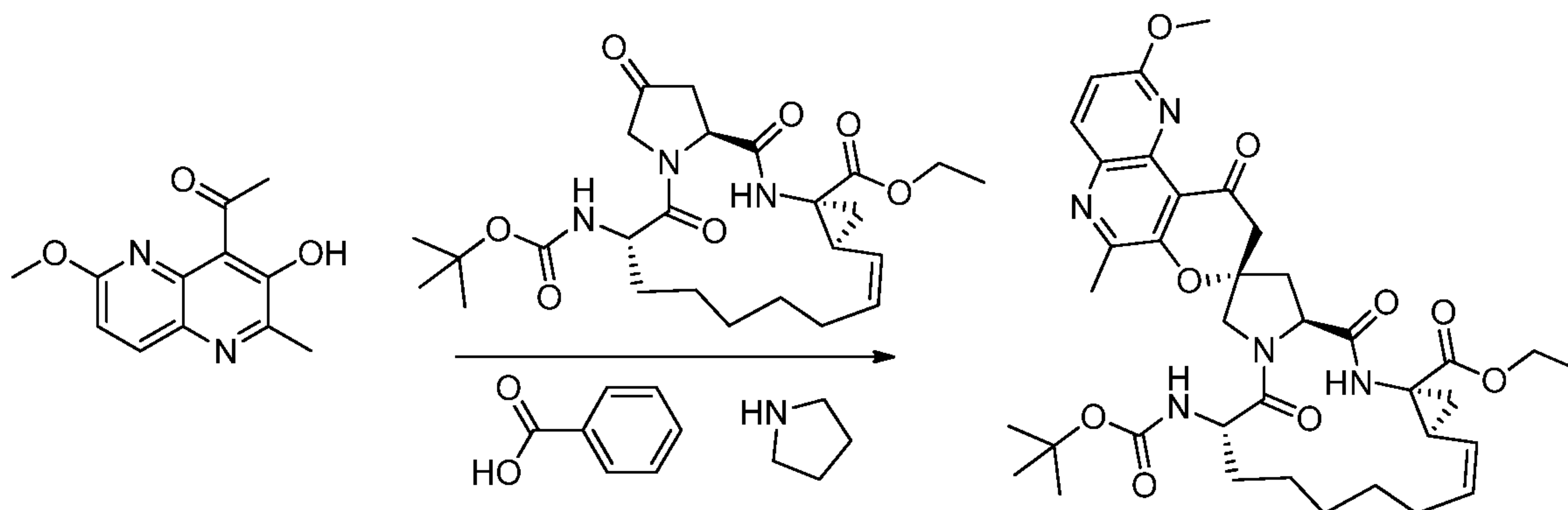
To a solution of the product of Step 3 (5.20 g, 22.2 mmol) in THF (100 ml) at 0°C was added a solution of NBS (3.36 g, 18.9 mmol) in THF (10 ml), and the mixture was stirred for 1h at 0°C then 30 min at RT. The mixture was quenched with 50% brine and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 40:60) to afford the product of Step 4 (5.50 g, 81% yield).

25 Step 5



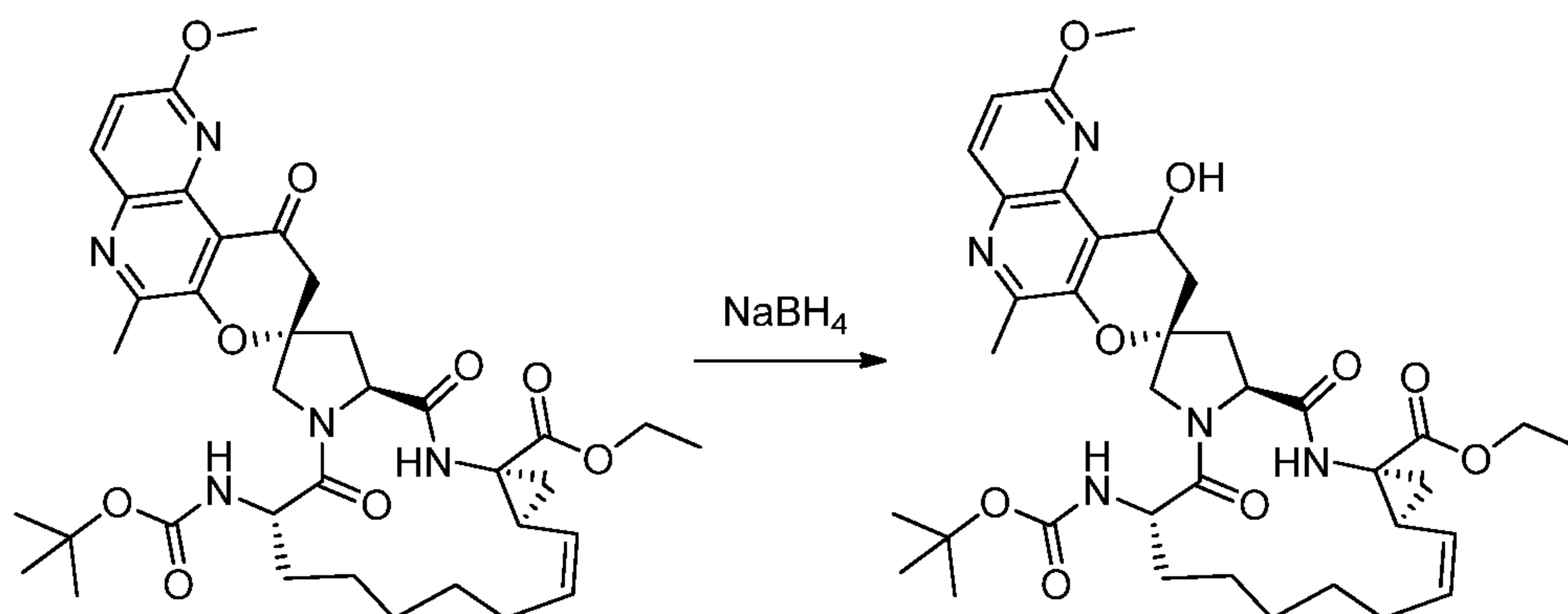
To a solution of the product of Step 4 (5.40 g, 20.1 mmol) and Pd(PPh₃)₄ (0) (1.62 g, 1.40 mmol) in 1,4-dioxane (55 ml) in a sealed tube was added tributyl(1-ethoxyvinyl)tin (17.0 ml, 50.2 mmol), and the mixture was warmed to 110°C and stirred for 3h. More Pd(PPh₃)₄ (400 mg) and tributyl(1-ethoxyvinyl)tin (6 ml) were added, and the reaction was stirred at 110°C for an additional 4h. The final mixture was quenched at 0°C with 1N aq. HCl (60 ml) then stirred at RT for 60 min. The mixture was neutralized at RT with sat. aq. NaHCO₃ (100 ml) and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 60:40) to give the product of Step 5 (2.64 g, purity 70%) as yellow solid.

Step 6



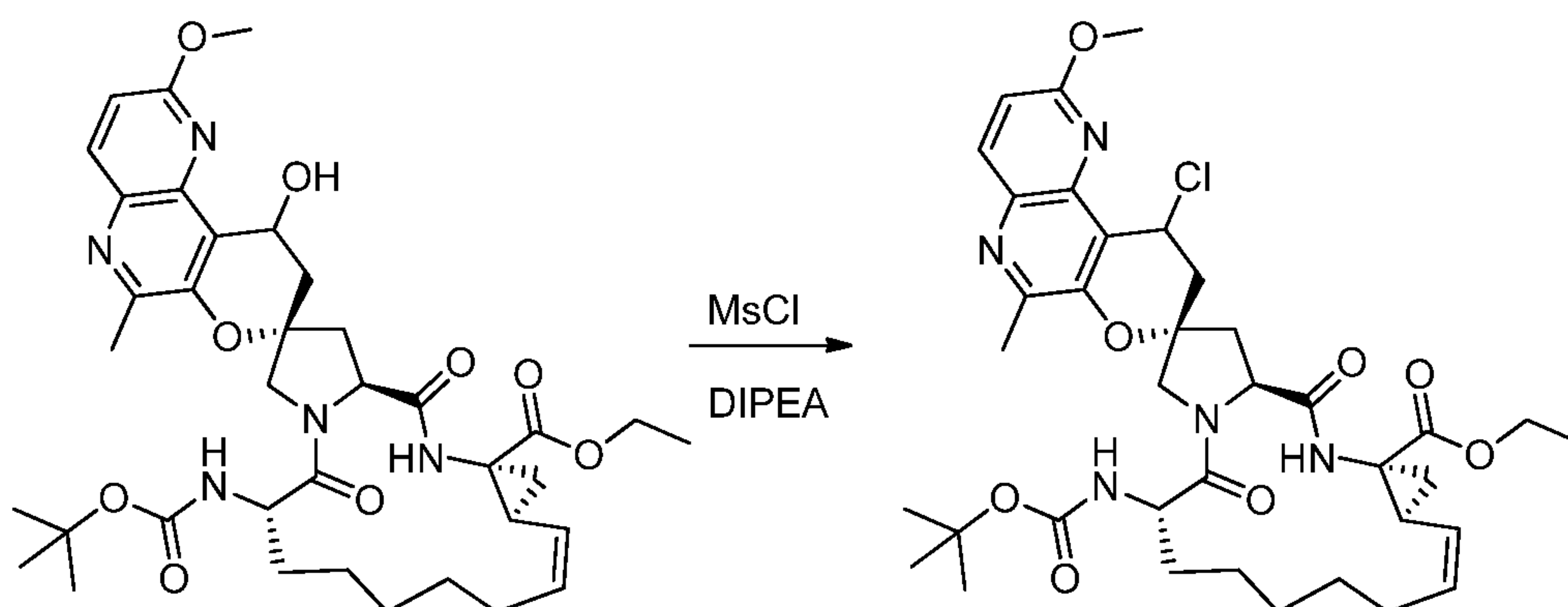
To a solution of the product of Step 5 (500 mg, 2.15 mmol), macrocyclic ketone (1.058 g, 2.153 mmol) and benzoic acid (263 mg, 2.15 mmol) in MeOH (15 ml) was added pyrrolidine (0.069 ml, 0.861 mmol) and 4A molecular sieves (1.0 g), and the mixture was warmed to 55°C and stirred for 72h. The mixture was quenched at RT with sat. aq. NaHCO₃ and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) to give, in order of elution, the product of Step 6 (820 mg, 54% yield), followed by starting intermediate (100 mg).

Step 7



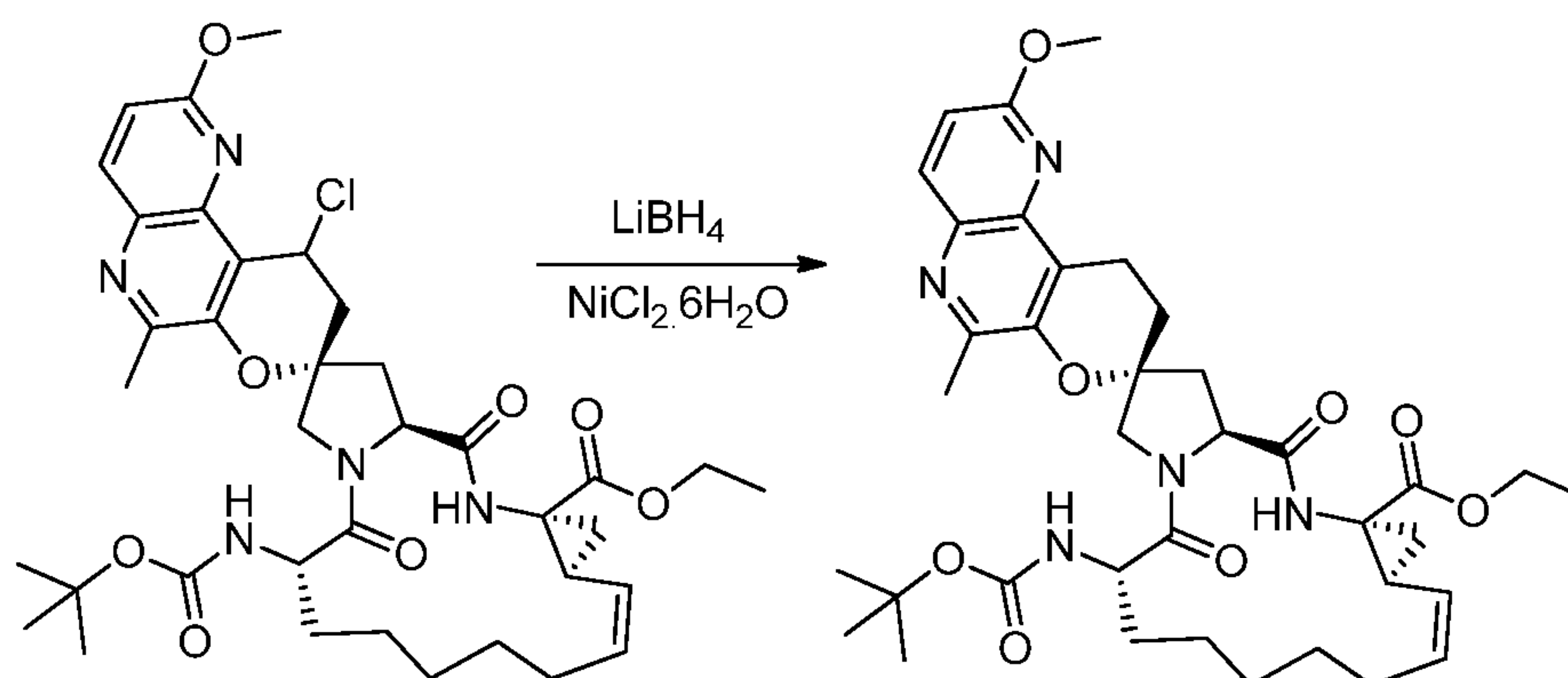
To a solution of the product of Step 6 (540 mg, 0.765 mmol) in THF (6 ml) and MeOH (6 ml) at 0°C was added NaBH₄ (34.7 mg, 0.918 mmol), and the mixture was stirred for 45 min. The mixture was quenched at 0°C with sat. aq. NH₄Cl and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) to give the product of Step 7 (460 mg, 85% yield).

Step 8



To a solution of the product of Step 7 (460 mg, 0.650 mmol) in DCM (15 ml) was added DIPEA (0.45 ml, 2.60 mmol) followed by MsCl (0.101 ml, 1.300 mmol), and the mixture was stirred at RT overnight. The mixture was quenched at RT with aq. NH₄Cl and extracted with DCM. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. A solution of the residue (650 mg) in DMF (5 ml) was treated with LiCl (100 mg, 2.36 mmol), and the mixture was stirred for 1h. The mixture was diluted with 90% brine and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) to give the product of Step 8 (398 mg, 80% purity).

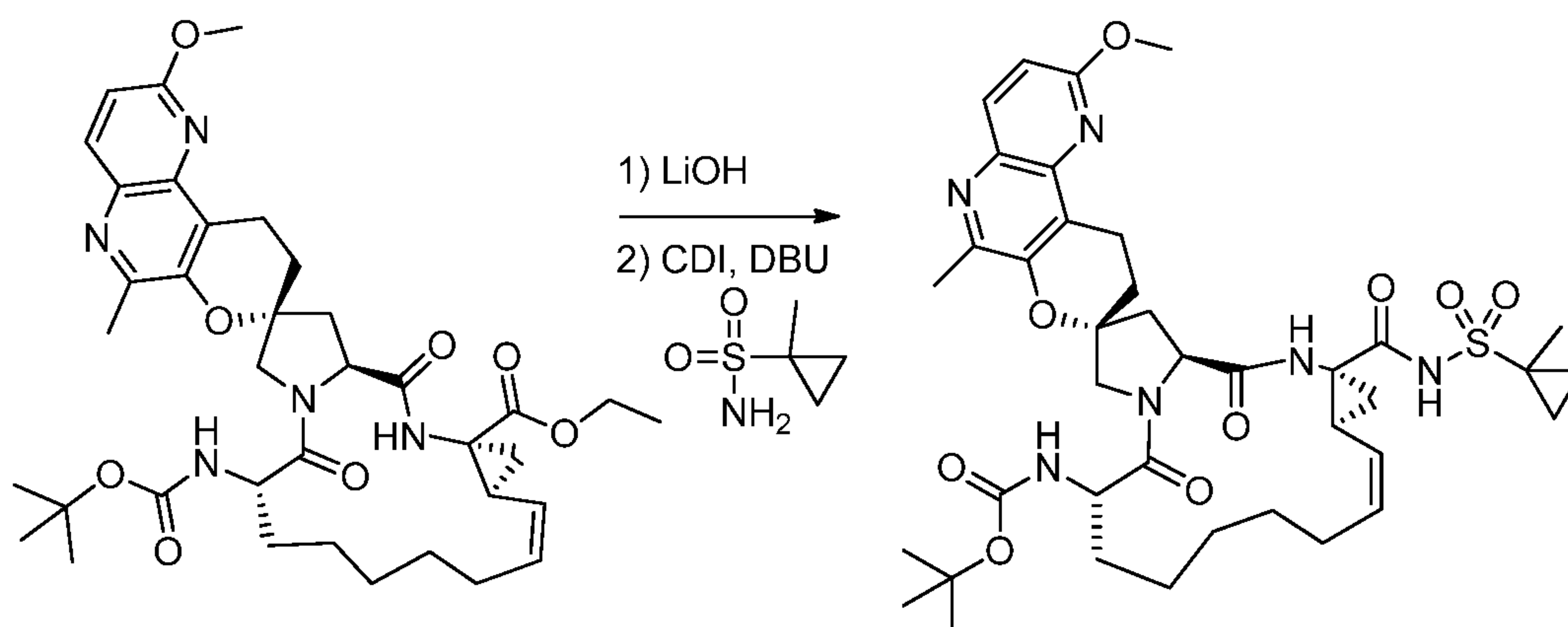
Step 9



To a solution of the product of Step 8 (420 mg, 0.579 mmol) in MeOH (28 ml) at -78°C was added $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (124 mg, 0.521 mmol) then LiBH_4 2N in THF (0.867 ml, 1.74 mmol), and the reaction was stirred for 10 min at -78°C then allowed to warm to 0°C over 1h.

- 5 The reaction was quenched at 0°C with sat. aq. NaHCO_3 and extracted with EtOAc. The combined organic fractions were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 20:80) to give the product of Step 9 (210 mg, 52% yield).

Step 10



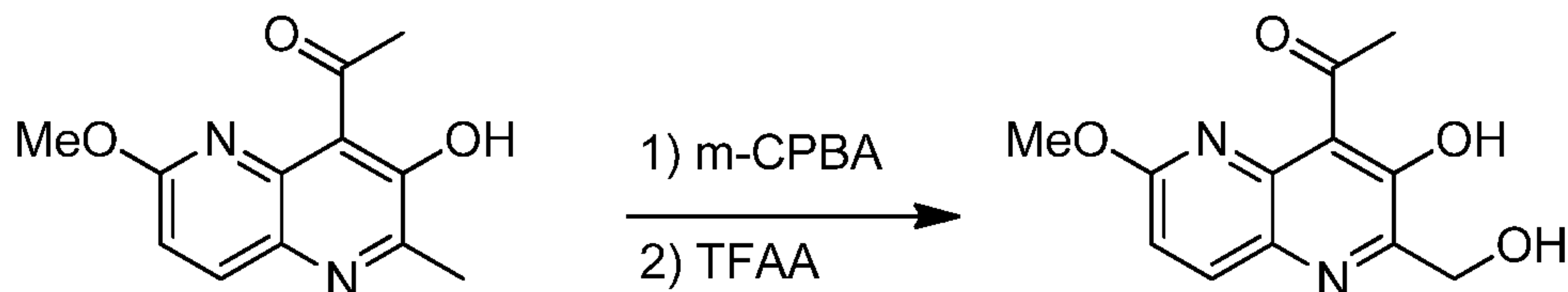
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- To a solution of the product of Step 9 (210 mg, 0.304 mmol) in THF (3 ml), MeOH (3) and water (2.5 ml) was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (21.8 mg, 0.911 mmol), and the reaction was stirred at 50°C for 4h. The mixture was quenched at RT with ice cold 0.3 M aq. HCl until pH \sim 3, and extracted with EtOAc. The combined organic fractions were dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give an intermediate acid (190 mg, 94% yield). To a solution of this intermediate acid (190 mg, 0.286 mmol) in THF (12 ml) was added 1,1'-carbonyldiimidazole (139 mg, 0.859 mmol), and the mixture was warmed to 70°C and stirred for 4h. 1-Methylcyclopropane-1-sulfonamide (193 mg, 1.431 mmol) and DBU (0.216 ml, 1.431 mmol) were then added at RT, and the reaction was warmed to 50°C and stirred for 8h. The
- 15

mixture was quenched at RT with sat. aq. NH_4Cl and extracted with EtOAc. The combined organic fractions were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) to give I-11 (130 mg, 58% yield). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 10.11 (s, 1H), 8.03 (d, $J = 8.8$ Hz, 1H), 6.90-6.95 (m, 3H), 5.72 (m, 1H), 4.95-5.10 (m, 2H), 4.64 (m, 1H), 4.44 (d, $J = 10.8$ Hz, 1H), 4.18 (m, 1H), 4.03 (s, 3H), 4.00-4.10 (m, 1H), 3.41 (d, 1H), 3.20-3.30 (m, 2H), 2.30-2.65 (m, 3H), 2.48 (s, 3H), 2.21 (m, 2H), 1.72-2.00 (m, 5H), 1.15-1.55 (m, 8H), 1.44 (m, 3H), 1.27 (s, 9H), 0.80 (br s, 2H); LC-MS (M^+) Calc. for $\text{C}_{39}\text{H}_{52}\text{N}_6\text{O}_9\text{S}$: 780.9 Found 781.2 ($\text{M}+\text{H}$)⁺.

10 **Example 12: *tert*-Butyl ((2R,6S,13aS,14aR,16aS,Z)-6'-(difluoromethyl)-2'-methoxy-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-3,5,6,7,8,9,9',10,10',11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,8'-pyrano[2,3-c][1,5]naphthyridin]-6-yl)carbamate (I-12)**

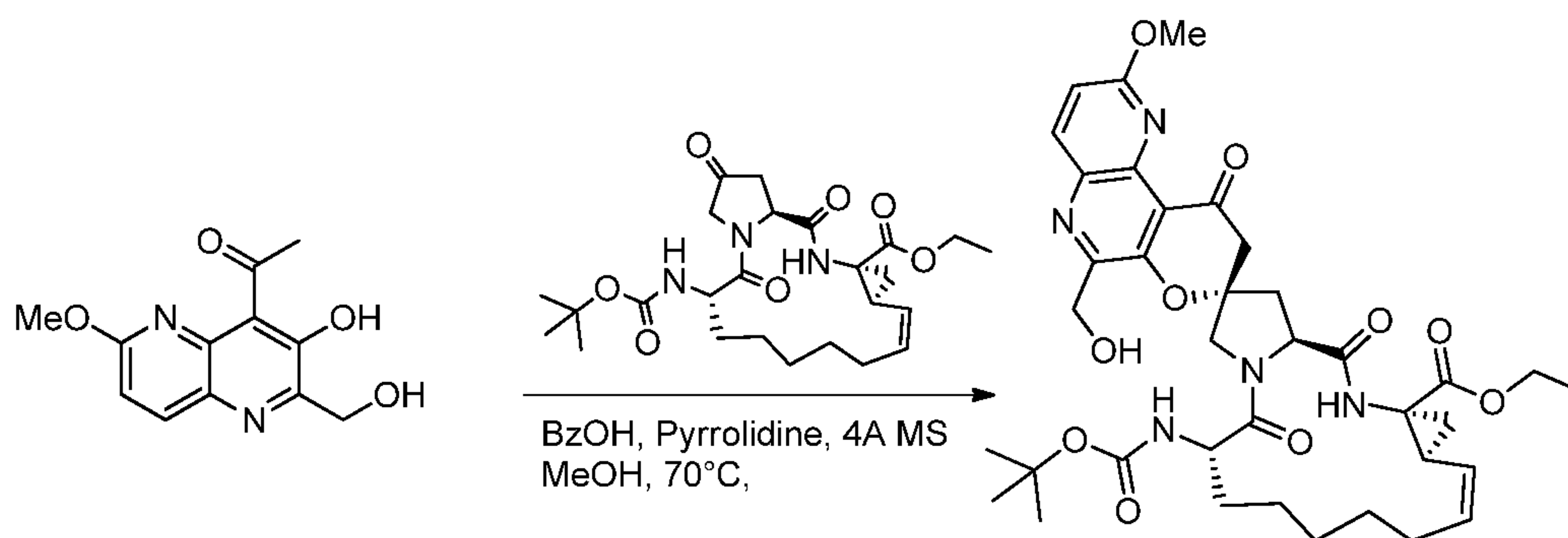
Step 1



15 A mixture of 1-(3-hydroxy-6-methoxy-2-methyl-1,5-naphthyridin-4-yl)ethanone (the product of Example 11, Step 5; 10 g, 43.1 mmol), mCPBA (12.55 g, 56.0 mmol) in DCM (200 ml) was stirred at RT for 3d. The thick slurry was stirred with aq. NaHCO_3 and aq. $\text{Na}_2\text{S}_2\text{O}_3$. The solvent was gently evaporated from the aq. slurry, and the resultant solid was filtered, washed with water followed by ether and dried overnight in a vacuum overnight to give 6.8 g of the N-oxide intermediate as a solid.

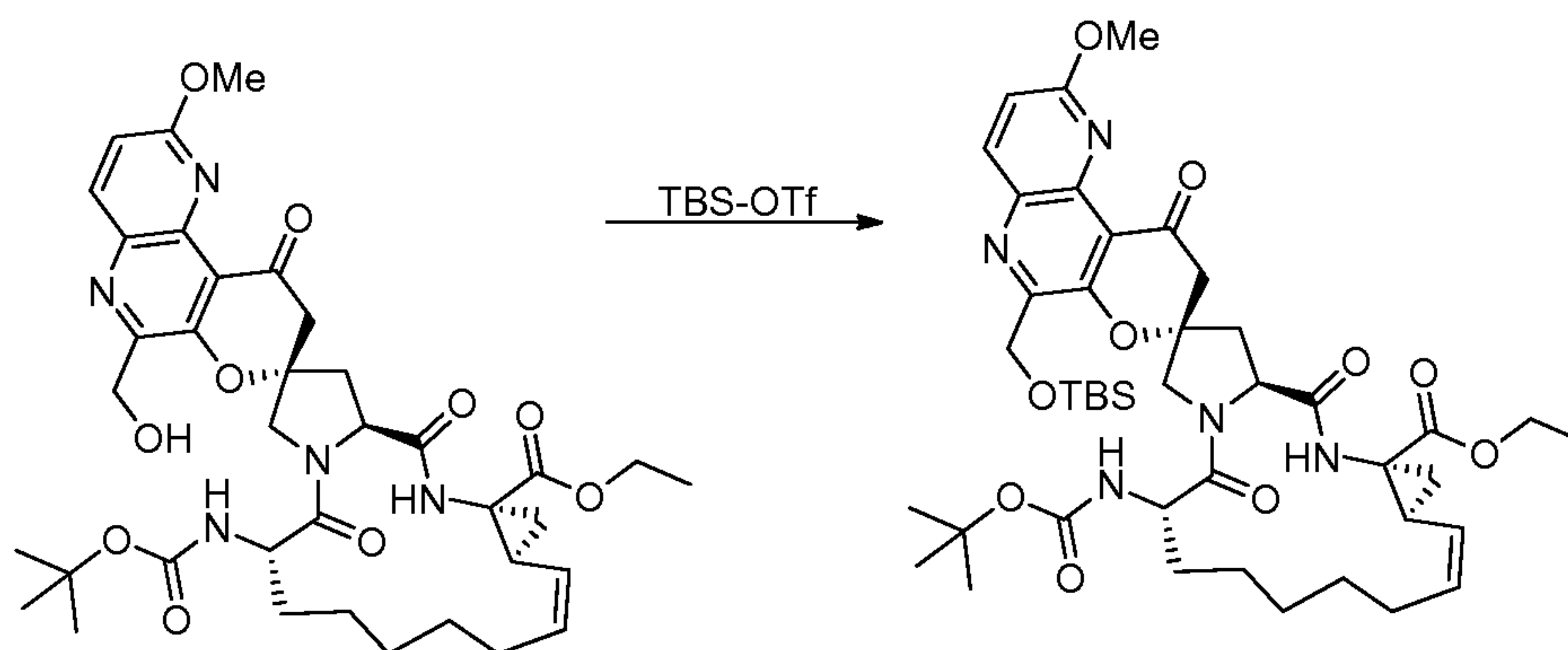
To a flask containing the above solid (6.3 g, 25.4 mmol) was added trifluoroacetic anhydride (100 ml, 708 mmol), and the mixture was heated at reflux. After leaving overnight at RT, the mixture was heated at reflux for another 1h. The reaction mixture was evaporated to dryness. The residue was dissolved in minimum MeOH and diluted with aq. NaHCO_3 . The slurry was filtered and washed with water. The solid was suspended in about 100 ml of 1:1 MeOH-DCM, and to this was added about 30 g of silica gel. The solvent was evaporated to dryness, and the adsorbed crude product was purified by chromatography eluting with 0-3%-5% MeOH-DCM to give 3.35 g of product as a dark solid. LC-MS $m/e = 249.16$ (MH^+).

30 Step 2



A mixture of the product of Step 1 (500 mg, 2.014 mmol), (6S,13aS,14aR,16aS,Z)-ethyl 6-((*tert*-butoxycarbonyl)amino)-2,5,16-trioxo 1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-
 5 a][1,4]diazacyclopentadecine-14a-carboxylate (990 mg, 2.014 mmol), pyrrolidine (0.080 ml, 1.007 mmol), benzoic acid (246 mg, 2.014 mmol), 4A molecular sieves (~1 g) in MeOH (10 ml) in a sealed tube was stirred overnight in an oil-bath kept at ~70°C (bath temperature). The reaction mixture was filtered through a CELITE pad and rinsed with MeOH. The filtrate was concentrated and poured into aq. NaHCO₃. The slurry was extracted 3x with EtOAc, the
 10 combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to dryness. The crude product was purified by chromatography eluting with acetone-hexanes to give 340 mg of product as a solid. Mass spec. m/e observed = 722.36 (M+H)⁺.

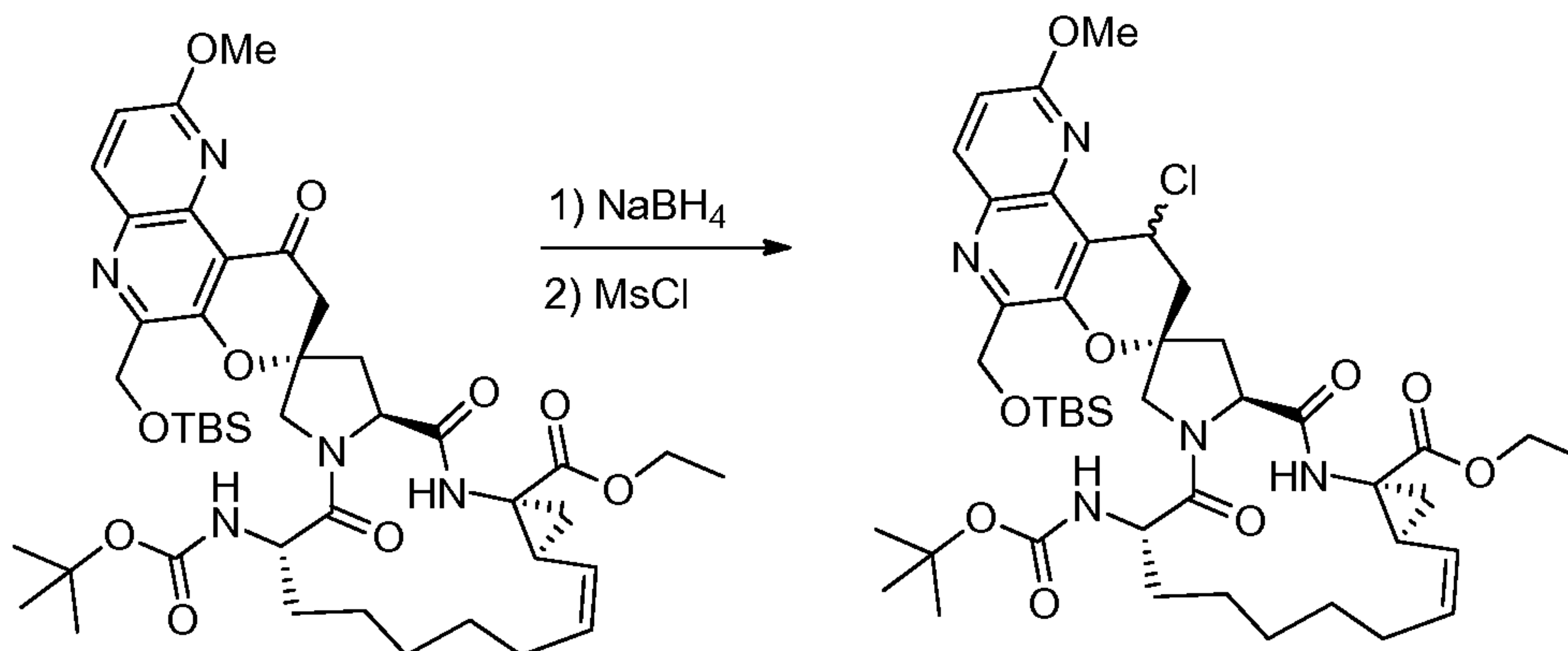
Step 3



To a solution of the product of Step 2 (860 mg, 1.191 mmol) in DCM (10 ml) at 0°C was added Et₃N (0.332 ml, 2.383 mmol) followed by TBS-OTf (0.356 ml, 1.549 mmol), and the mixture was stirred at 0°C. After 2h, added another 0.3eq. of TBS-OTf. The mixture was stirred for additional 30 min then diluted with aq. NaHCO₃. The slurry was extracted 3x with EtOAc, the combined organic layer was washed with brine, dried over MgSO₄, filtered and
 20 evaporated to dryness. The crude product was purified by chromatography eluting with 0-30%

acetone-hexanes to give 570 mg of the product of Step 3 as a solid. LC-MS $m/e = 836.38$ (MH⁺).

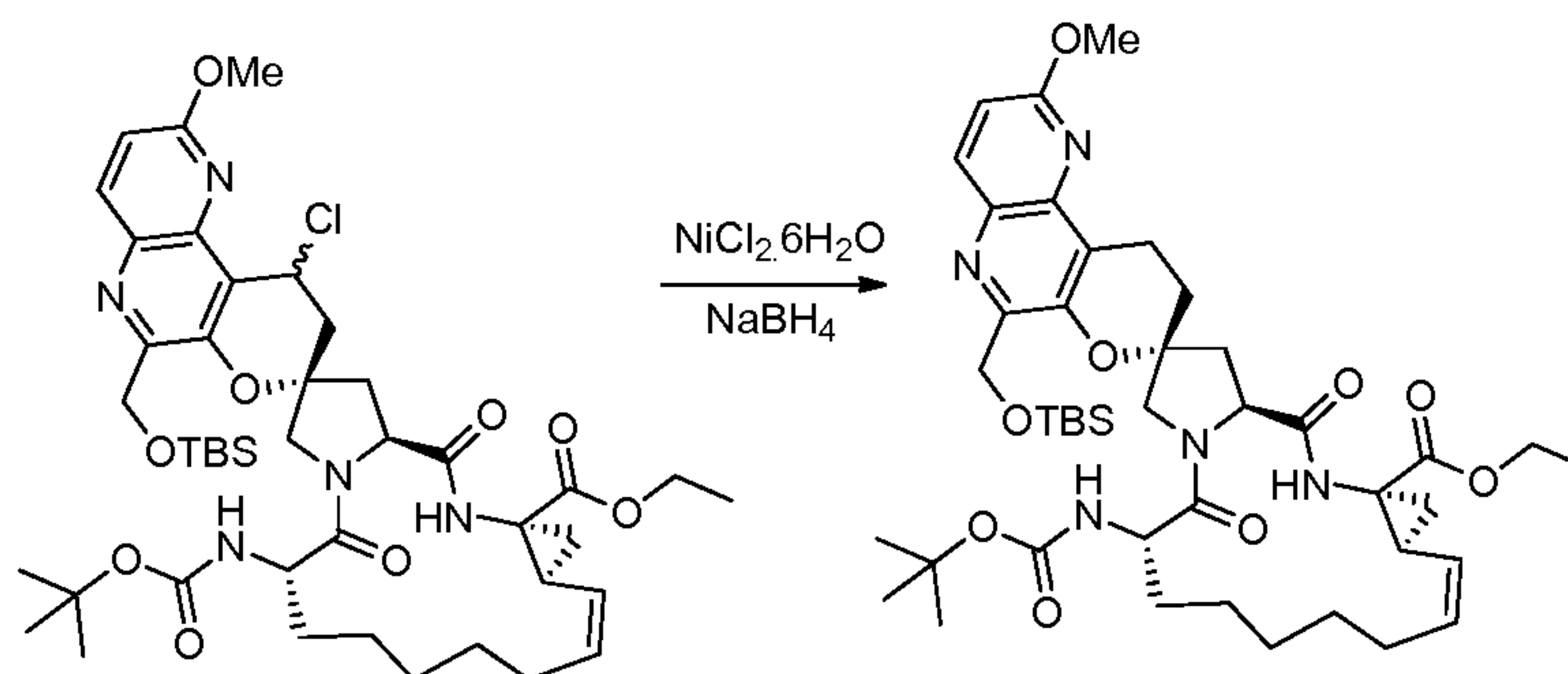
Step 4



5 To a solution of the product of Step 3 (550 mg, 0.658 mmol) in MeOH (4 ml) and THF (1 ml) at 0°C was added NaBH₄ (24.89 mg, 0.658 mmol). The mixture was stirred for 10 min then quenched by the addition of acetone followed by aq. NH₄Cl. The slurry was extracted 3x with EtOAc, and the combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to dryness to give the crude alcohol, which was used as such.

10 To a solution of the alcohol (551 mg, 0.658 mmol) in DCM (7 ml) at 0°C was added Et₃N (0.275 ml, 1.974 mmol) followed by MsCl (0.103 ml, 1.316 mmol) and the mixture was stirred overnight while being allowed to warm to RT. Because LC-MS indicated unreacted starting material, the reaction was cooled again to 0°C, and TEA (0.275 ml, 1.974 mmol) was added, followed by MsCl (0.103 ml, 1.316 mmol) and stirred overnight. The mixture was diluted
15 with EtOAc, washed 2x with aq. NaHCO₃, brine, dried over MgSO₄, filtered and evaporated to dryness to give the crude product. The crude product was purified by chromatography eluting with 0-30% acetone-hexanes to give 328 mg of the product of Step 4 as foam. LC-MS $m/e = 856.35$ (M+H)⁺.

Step 5

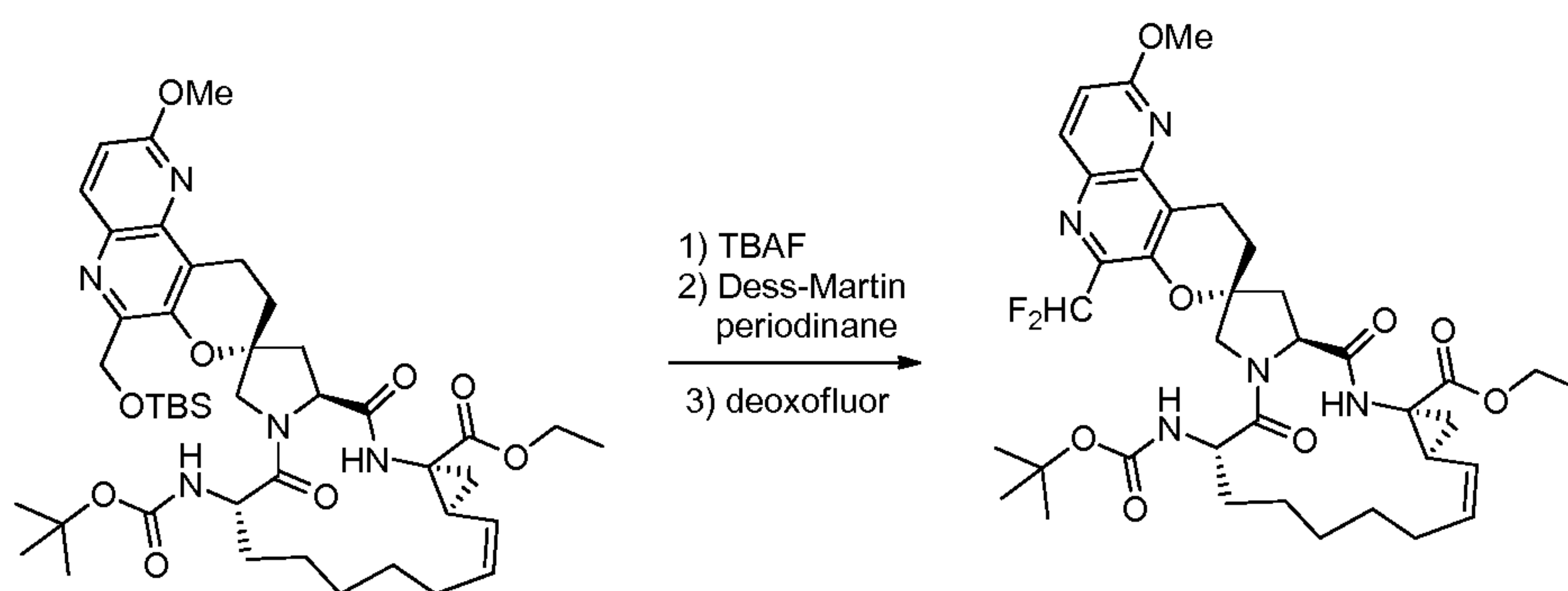


20

A mixture of the product of Step 4 (320 mg, 0.374 mmol) and NiCl₂·6H₂O (266 mg, 1.121 mmol) in MeOH (5 ml) was stirred at RT until the solids dissolved to give a clear solution (~10 min.). The solution was cooled to -78°C, and NaBH₄ (21.20 mg, 0.560 mmol) was added in one portion, and the mixture was stirred at -78°C for 1h then another portion of NaBH₄ (21.20 mg, 0.560 mmol) was added. The mixture was stirred for another 1h at -78°C, then quenched by the addition of aq. NH₄Cl and warmed to RT. The slurry was extracted 3x with EtOAc, the combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to dryness. The crude product was purified by chromatography eluting with 0-40% acetone-hexanes (24 g REDISEP cartridge) to give 128 mg of the product of Step 5 as a solid.

LC-MS m/e = 822.51 (M+H)⁺.

Step 6



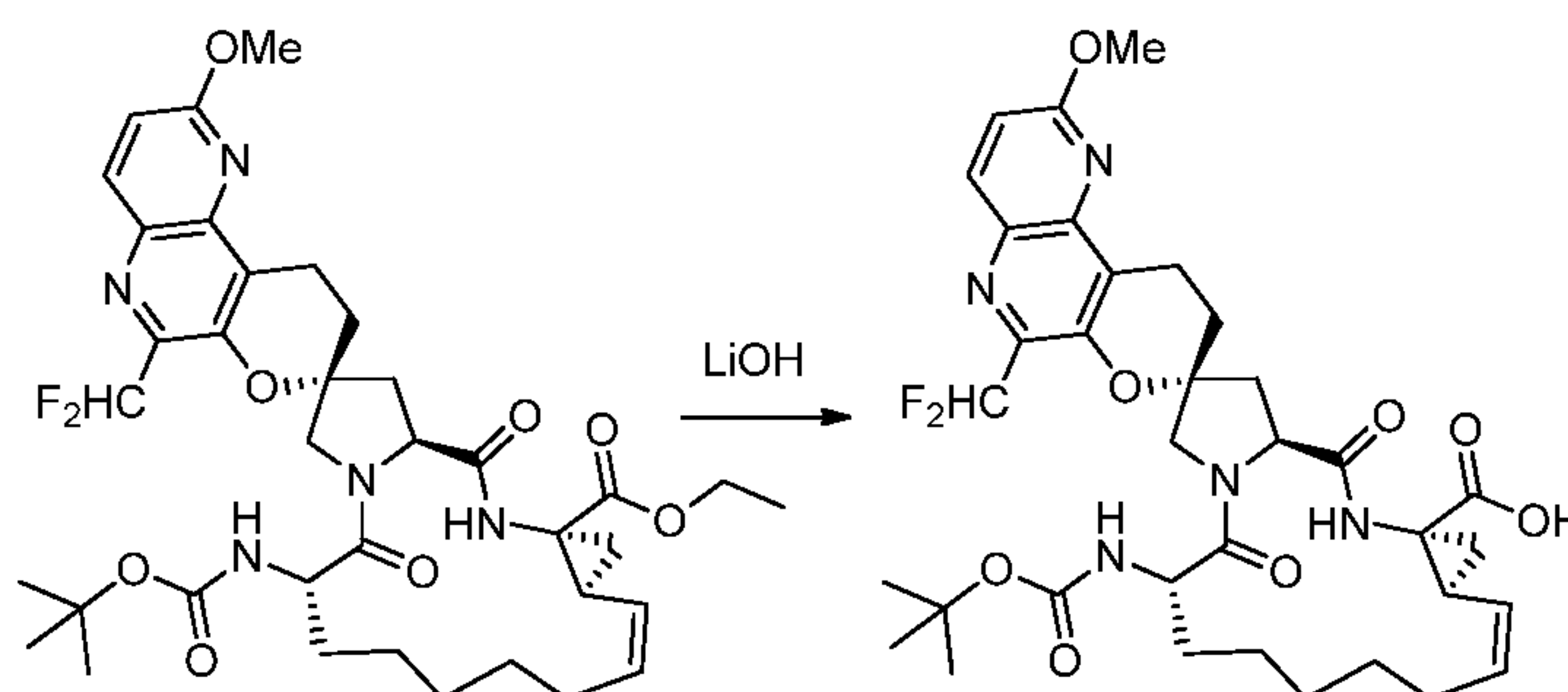
To a solution of the product of Step 5 (128 mg, 0.156 mmol) in THF (2 ml) was added 1 M solution of TBAF (0.311 ml, 0.311 mmol) in THF, and the mixture was stirred at RT for 2h. The reaction mixture was diluted with EtOAc, washed 2x with aq. NH₄Cl, brine, dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by chromatography eluting with 0-40% acetone-hexanes (4 g REDISEP cartridge) to give 98 mg of alcohol intermediate as a solid. LC-MS m/e = 708.37 (MH⁺).

A solution of the above product (98 mg, 0.138 mmol) and Dess-Martin periodinane (88 mg, 0.208 mmol) in DCM (2 ml) was stirred at RT for 1h. The reaction mixture was diluted with aq. Na₂S₂O₃ and aq. NaHCO₃, stirred for few minutes then extracted 3x with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to dryness to give the aldehyde intermediate, which was used as such.

To a solution of the aldehyde (98 mg, 0.139 mmol) in DCM (2 ml) in a sealed tube was added DEOXOFLUOR (0.102 ml, 0.555 mmol) followed by EtOH (1.621 μl, 0.028 mmol), and the mixture was stirred overnight in an oil bath kept at 40°C. The mixture was diluted with EtOAc, washed 2x with aq. NaHCO₃, brine, dried over MgSO₄, filtered and evaporated to

dryness. The residue was purified by chromatography (4 g REDISEP cartridge) eluting with 0-40% acetone-hexanes to give 64 mg of the product of Step 6 as a white solid. LC-MS $m/e = 728.42$ (MH⁺).

Step 7

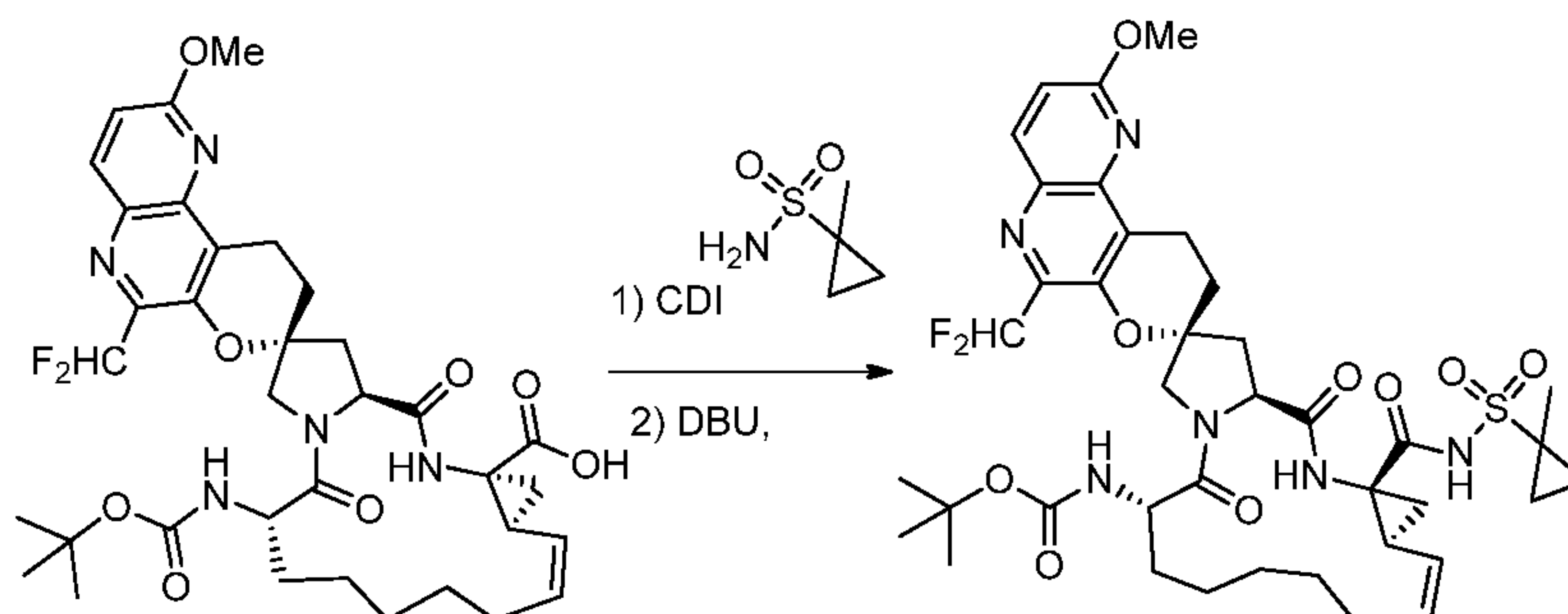


5

A solution of the product of Step 6 (64 mg, 0.088 mmol), LiOH·H₂O (14.76 mg, 0.352 mmol) in THF (0.5 ml), MeOH (0.5 ml) and water (0.5 ml) was stirred in an oil-bath kept at 60°C for 1h then cooled to RT. The reaction mixture was diluted with water, acidified with 1N HCl to pH ~2 and extracted 3x with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to dryness to give 61 mg of the product of Step 7 as a solid. LC-MS $m/e = 644.31$ (M+H)⁺.

10

Step 8



15

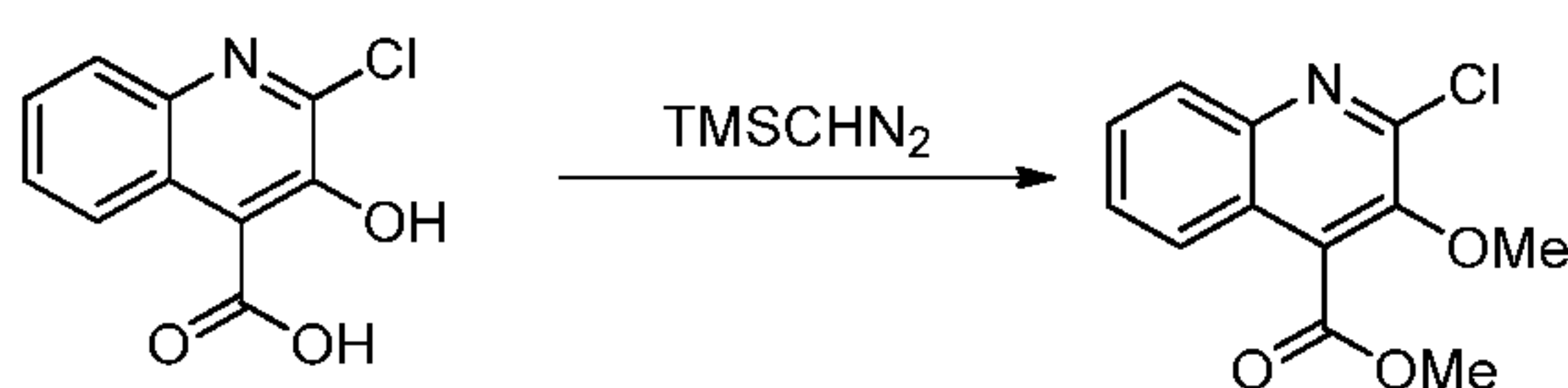
A mixture of the product of Step 7 (40 mg, 0.057 mmol) and CDI (18.54 mg, 0.114 mmol) in THF (2 ml) was stirred in an oil bath kept at 70°C for 2h then cooled to RT. To this was added 1-methylcyclopropane-1-sulfonamide (23.18 mg, 0.171 mmol) followed by DBU (0.026 ml, 0.171 mmol), and the mixture was stirred at 50°C for 3h. Then the reaction mixture was left overnight at RT. The reaction mixture was diluted with water, acidified with 1N HCl and extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to dryness. The crude product was purified by chromatography (4 g REDISEP cartridge) eluting with 0-40% acetone-hexanes to give 38 mg of I-12 as a solid. LC-MS $m/e = 817.46$ (M+H)⁺. ¹H NMR (CDCl₃, 500 MHz) δ (ppm) 8.17 (1 H, d, J = 9.03 Hz),

20

7.07 (1 H, s), 7.02 (1 H, d, J = 9.02 Hz), 6.85 (1 H, t, J = 54.04 Hz), 5.71 (1 H, q, J = 8.98 Hz), 5.09-4.98 (2 H, m), 4.70-4.63 (1 H, m), 4.60 (6 H, s), 4.43 (1 H, d, J = 11.01 Hz), 4.19-4.13 (1 H, m), 4.08 (3 H, m), 3.73 (1 H, d, J = 10.98 Hz), 3.31-3.27 (2 H, m), 2.57 (2 H, dd, J = 13.60, 7.19 Hz), 2.41 (1 H, dd, J = 13.48, 9.62 Hz), 2.36-2.25 (3 H, m), 2.17 (1 H, s), 1.94-1.71 (4 H, m),
 5 1.38-1.19 (m), 0.90-0.78 (m).

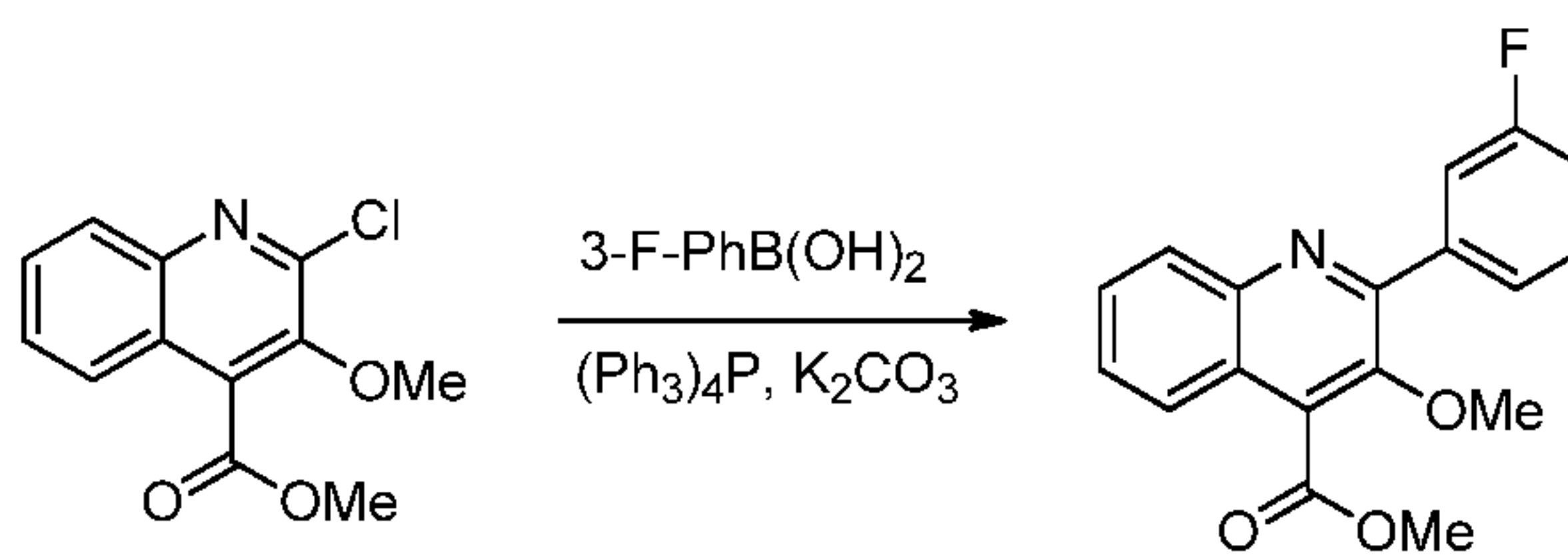
Example 13: tert-Butyl (2R,6S,13aS,14aR,16aS,Z)-5'-(3-fluorophenyl)-14a-(1-methyl cyclopropylsulfonylcarbonyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-6-yl carbamate (I-13)

Step 1



To 2-chloro-3-hydroxy-4-quinolinecarboxylic acid (5 g, 22.36 mmol) in toluene (93 mL)/MeOH (19 mL) was added TMS-diazomethane (33.5 ml, 67.1 mmol) dropwise.
 15 Vigorous bubbling occurred, and the mixture began to warm. An ice bath was used to cool the reaction until addition was complete. After 15 min, reaction was complete by LC-MS. AcOH was then added dropwise until bubbling stopped. The mixture was evaporated to dryness yielding a residue, which was purified by column chromatography on silica gel eluting with EtOAc/Hexanes to give the product of Step 1 (5.21 g, 20.70 mmol, 93% yield) as a colorless
 20 liquid. MS m/e = 252 (MH⁺).

Step 2

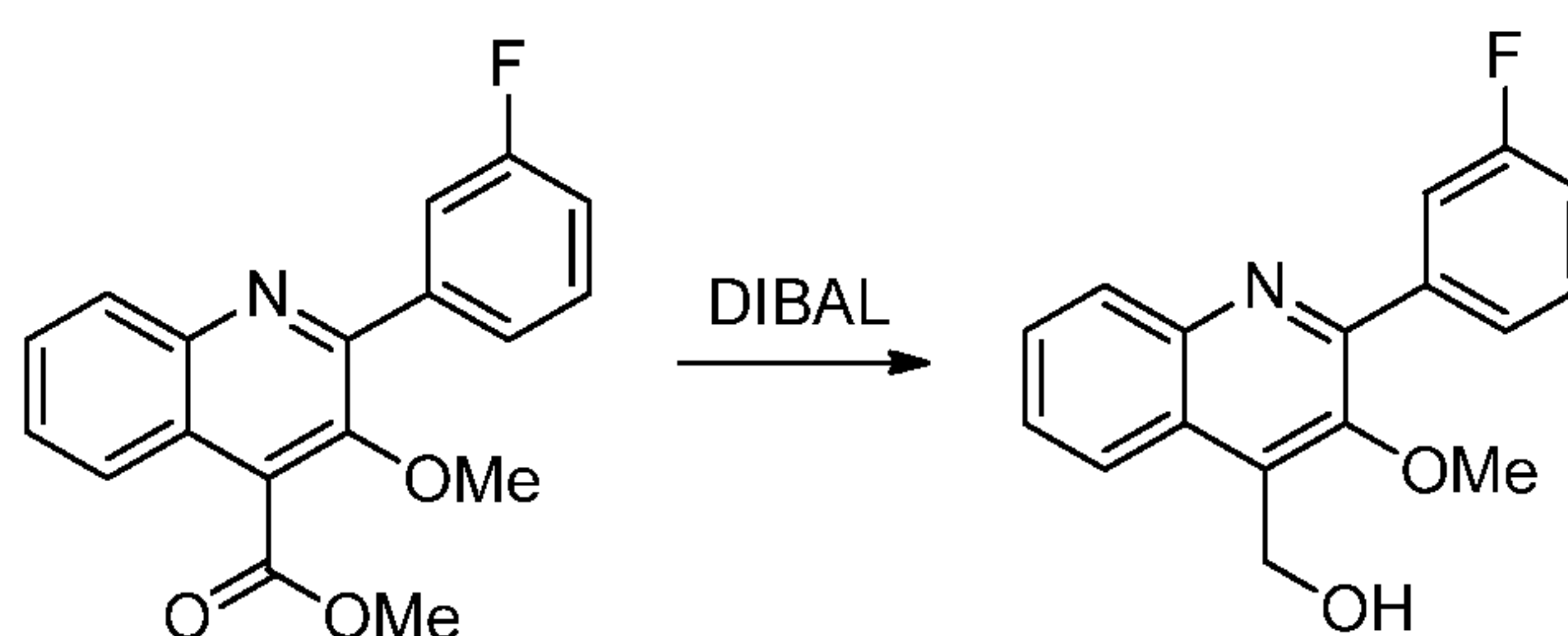


A solution of the product of Step 1 (2 g, 7.95 mmol), Pd(PPh₃)₄ (459 mg, 0.05eq.), 3-fluorophenylboronic acid (1.67 g, 11.92 mmol, 1.5eq.) and K₂CO₃ (4.39 g, 31.8 mmol) in
 25 toluene (20 ml), EtOH (10 ml) and water (5 ml) in a sealed tube was bubbled with argon, and the mixture was stirred in an oil bath kept at ~100°C (bath temperature) for 6h. The reaction mixture was diluted with water and extracted 3x with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered, concentrated and evaporated to dryness.

The residue was purified by column chromatography on silica gel eluting with 100% hexanes to 15% EtOAc in hexanes to give 2.3 g of the product of Step 2 as a resin. MS $m/e = 312.2$ (MH+).

Step 3

5

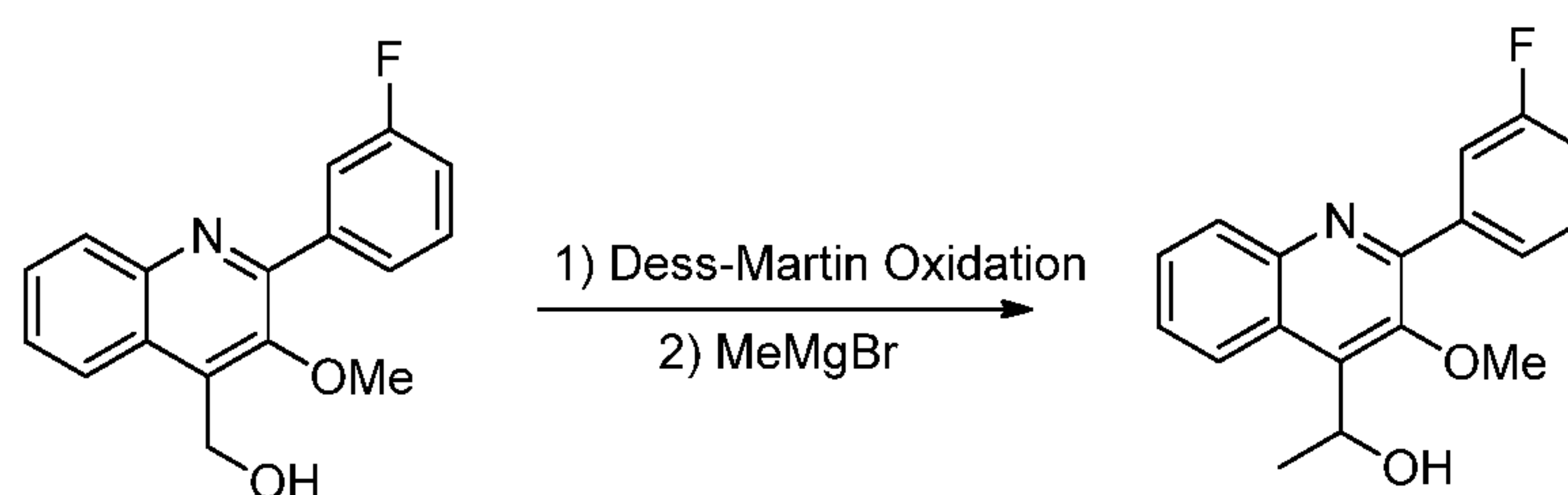


10

To a solution of the product of Step 2 (3.95 g, 12.69 mmol) in 40 ml DCM at -78°C was slowly added 1 M solution of DIBAL-H (30.5 ml, 30.5 mmol) in toluene, then the cooling bath was removed. After stirring at RT for 2.5h, the reaction mixture was quenched by the addition of saturated Na-K-tartrate solution, stirred vigorously for 10 min, added some brine, and the organic layer was separated. The aq. phase was extracted 2x with EtOAc, the combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated to provide the 3.96 g of crude product, which was carried to the next step without any purification. MS: $m/e = 284.2$ (MH+).

Step 4

15

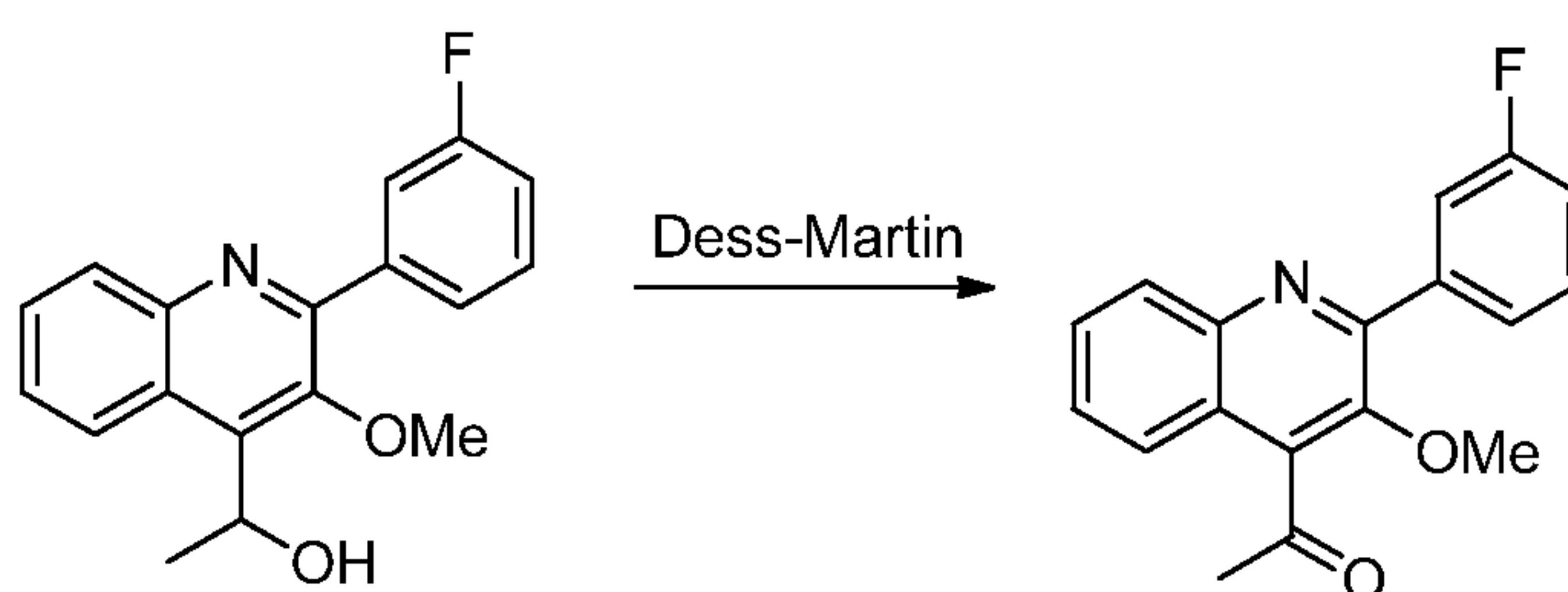


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To a suspension of the product of Step 3 (3.60 g, 12.69 mmol) and NaHCO₃ (3.20 g, 38.1 mmol) in 60 ml DCM at RT was added Dess-Martin periodinane (8.07 g, 19.04 mmol) in one-portion, and the mixture was stirred at RT. TLC at 1h in 30% EtOAc-hexanes indicated some unreacted starting alcohol. To the mixture was added another 1eq. of Dess-Martin reagent, and the stirring was continued at RT. TLC after further 30 min of stirring indicated that the reaction was complete. The reaction mixture was diluted with ether and aq. Na₂S₂O₃ and stirred vigorously for 10 min, and the layers separated. The aq. phase was extracted 2x with ether. The combined organic layers was washed with brine, dried over MgSO₄, filtered and concentrated to provide the crude aldehyde.

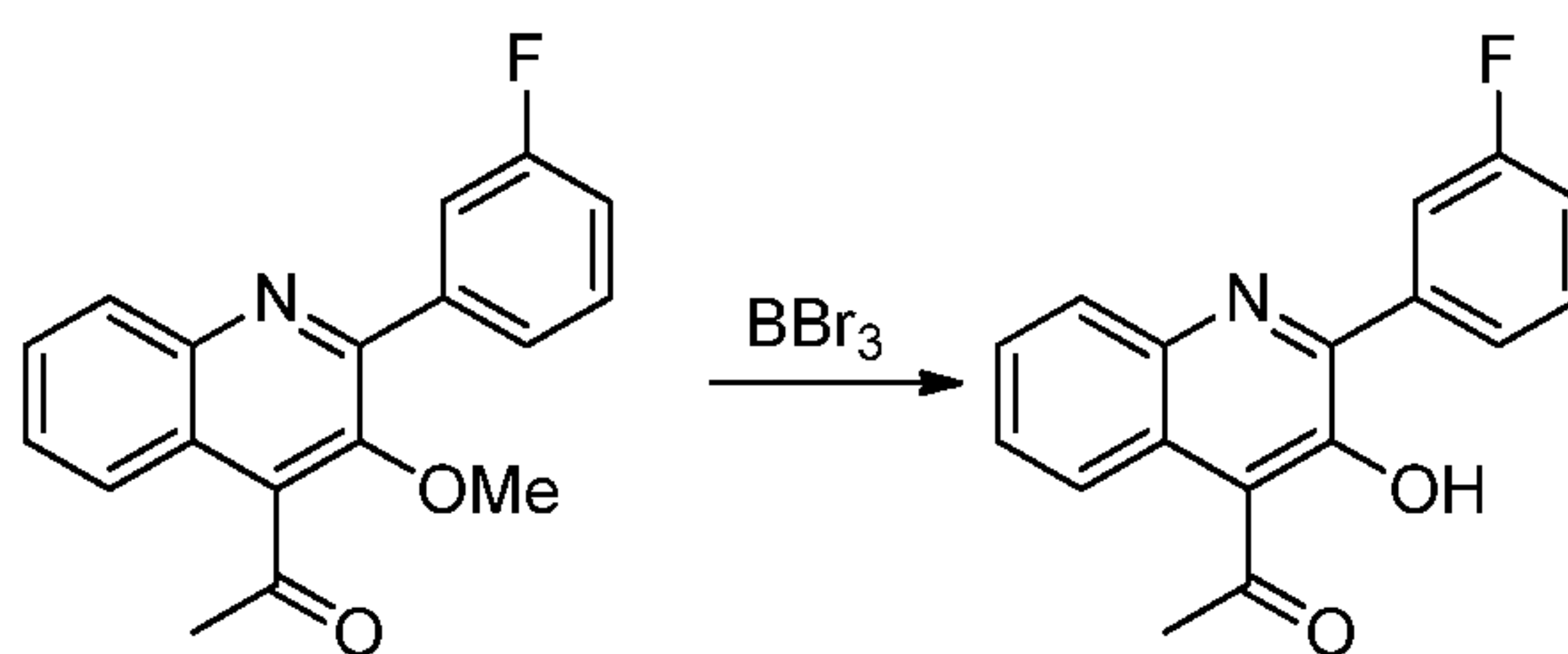
To a solution of the above product (3.57 g, 12.69 mmol) in 60 ml THF at 0°C (the solution appeared cloudy) was added slowly 3 m ether solution of MeMgBr (8.46 ml, 25.4 mmol). The mixture was stirred at 0°C. After 1h of stirring, another 0.5 eq. of MeMgBr was added, and the stirring was continued. The reaction mixture was quenched with aq. NH₄Cl, extracted 3x with EtOAc, combined organic layer washed with brine, dried over MgSO₄ to give the crude product. The crude product was chromatographed with 100% hexanes to 30% EtOAc-hexanes to provide 2.21 g of the product of Step 4 as a solid. MS m/e = 298.2 (MH⁺).

Step 5



To a mixture of the product of Step 4, NaHCO₃ (3.27 g, 38.9 mmol) in DCM (50 ml) at RT was added Dess-Martin periodinane (8.25 g, 19.44 mmol), and the mixture was stirred overnight at RT. TLC after overnight reaction indicated that the reaction is complete. The reaction mixture was diluted with aq. Na₂S₂O₃ and stirred vigorously for about 10 min, and the DCM layer was separated. The aq. phase was extracted 3x with ether, and the combined organic layer was washed with aq. NaHCO₃ followed by brine, dried over MgSO₄, filtered concentrated and purified by chromatography eluting with 0- 10% EtOAc-hexanes to provide 2.75 g of the product of Step 5 as yellow colored crystalline solid. MS m/e = 296.2 (MH⁺).

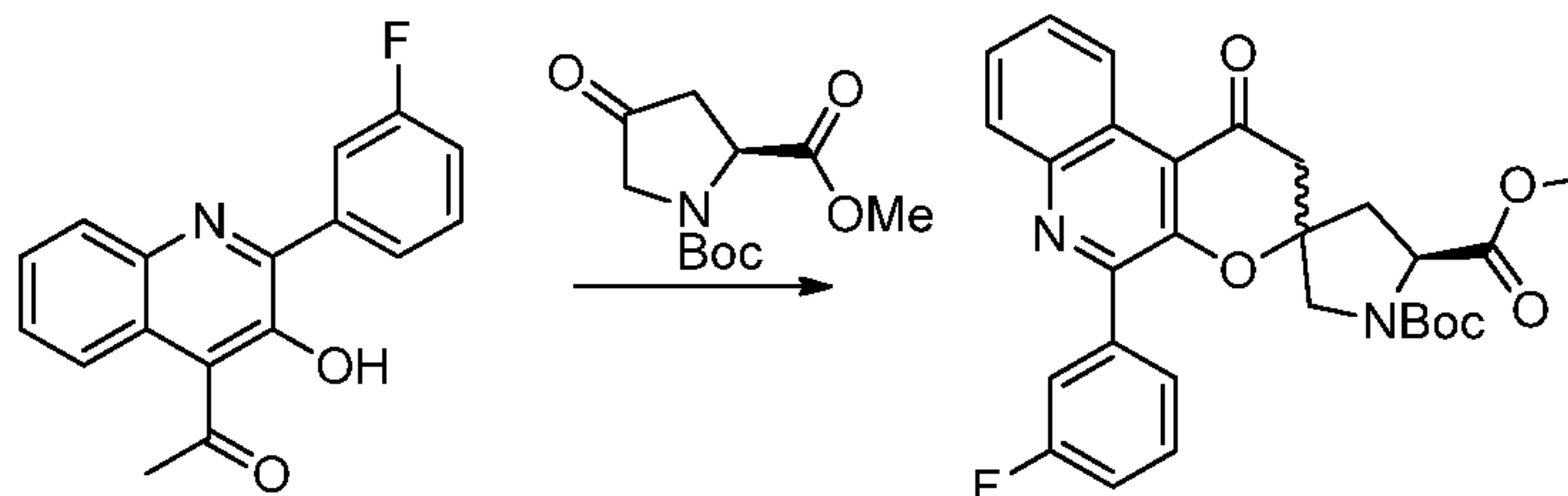
Step 6



To solution of the product of Step 5 (2.75 g, 9.31 mmol) in DCM (50 ml) at 0°C was added BBr₃ (3.52 ml, 37.2 mmol), and the mixture was stirred at RT. LC-MS at 1h indicated that the reaction was complete. The solution was cooled in an ice bath and carefully quenched by the addition of water, and the organic layer was separated. The aq. phase was extracted 3x with DCM, the combined organic layer was washed with brine, dried over MgSO₄, filtered,

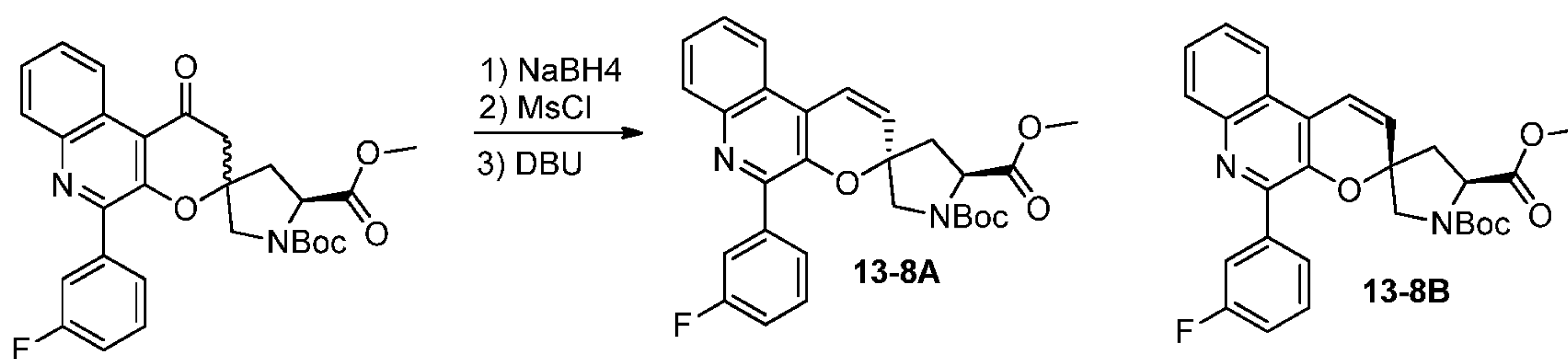
concentrated and purified by chromatography eluting with 0-10% EtOAc in hexanes to provide 1.56 g of the product of Step 6 yellow colored solid. MS $m/e = 282.2$ (MH^+).

Step 7



5 A mixture of the product of Step 6 (1.55 g, 5.51 mmol), Boc-4-Oxo-PRO-OMe (2.68 g, 11.02 mmol), pyrrolidine (0.182 ml, 2.204 mmol) and 3A molecular sieves (4 g, 4-8 mesh) in MeOH (40 ml) in a sealed tube was stirred in an oil-bath kept at 100°C for 8h. The mixture was cooled to RT, filtered through a CELITE pad and evaporated to dryness. The resultant crude product was purified by chromatography eluting with 0-30% EtOAc in hexanes to
10 provide 2.2 g of the product of Step 7 as a mixture of diastereomers. MS $m/e = 507.2$ (MH^+).

Step 8



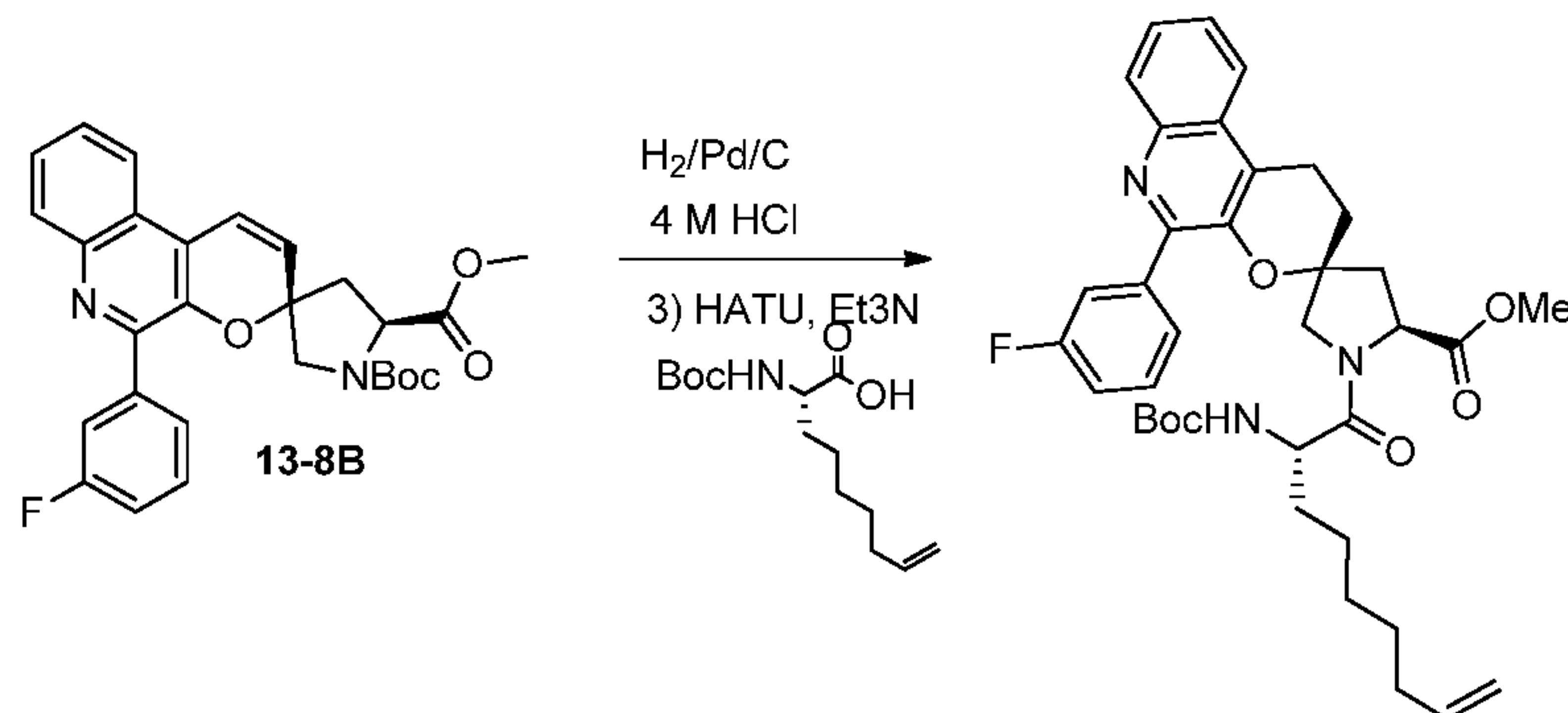
To a solution of the product of Step 7 (2.2 g, 4.34 mmol) in MeOH (10 ml) and THF (10 ml) at RT was added NaBH₄ (0.493 g, 13.03 mmol), and the mixture stirred at RT for
15 45 min. The reaction mixture poured into aq. NH₄Cl solution and extracted 3x with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to dryness to give the 2.25 g of crude alcohol.

To a solution of the above alcohol (1.8 g, 3.54 mmol) in 20 ml DCM at 0°C was added Et₃N (1.973 ml, 14.16 mmol) and MsCl (0.552 ml, 7.08 mmol). The reaction mixture was
20 stirred for 1h at 0°C, then overnight at RT. The reaction mixture was diluted with EtOAc, washed 2x with aq. NaHCO₃, brine, dried over MgSO₄, filtered and evaporated to dryness to give mixture of mesylate and chloride.

To a solution of the above product in DCM (20 ml) at RT was added DBU (1.067 ml, 7.08 mmol), and the mixture was stirred at RT for 36h. The reaction mixture was diluted
25 with EtOAc, washed 2x with water, brine, dried over MgSO₄, filtered, concentrated and purified

by chromatography eluting with 0-30-40% EtOAc-hexanes to give 315 mg of 13-8A and 698 mg of 13-8B. MS for 13-8A $m/e = 491.0$ (MH⁺). MS for 13-8B $m/e = 491.0$ (MH⁺).

Step 9

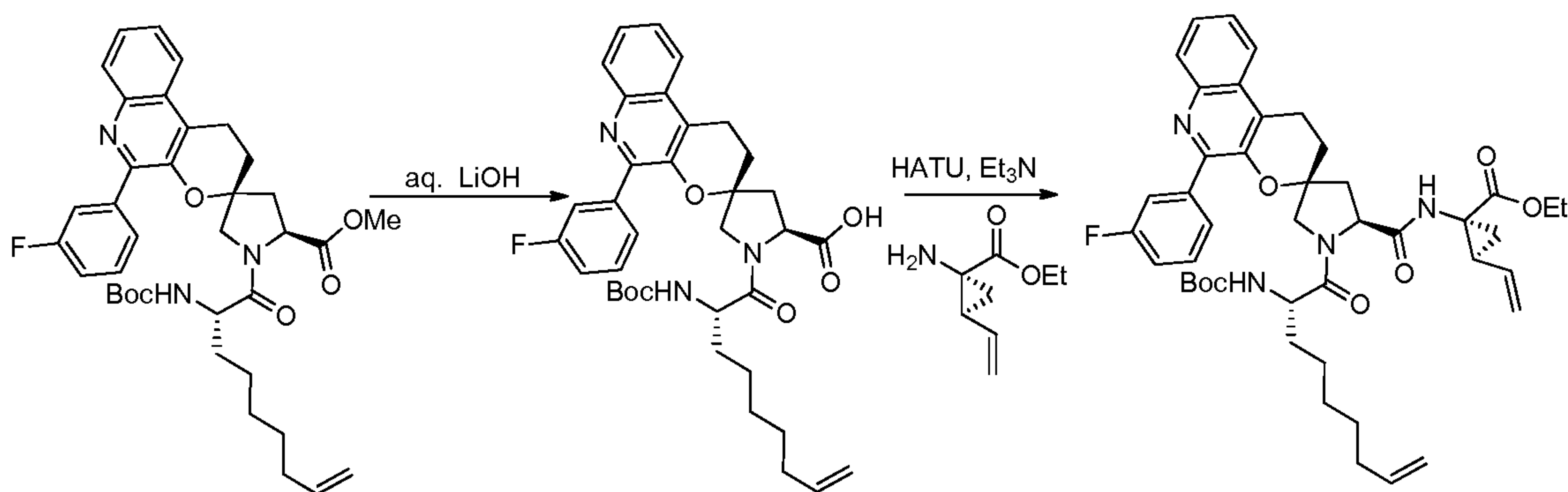


5 A suspension of 13-8B (730 mg, 1.488 mmol) and 10% Pd-C (140 mg) in EtOAc (10 ml) was stirred overnight under a H₂ balloon. The suspension was filtered through a CELITE pad and evaporated to dryness. The residue was chromatographed with 0-40% EtOAc-hexanes to give 630 mg of the reduction product.

A solution of above product (630 mg, 1.279 mmol) in 10 ml of 4N HCl/dioxane and 2 ml of MeOH was stirred at RT for 3h, the solvent was evaporated to dryness, and the residue was co-evaporated with toluene and ether to give crude amine as the HCl salt.

To a mixture of the above product (502 mg, 1.279 mmol), (S)-2-(*tert*-butoxycarbonylamino)non-8-enoic acid-dicyclohexyl amine salt (868 mg, 1.919 mmol) and DIPEA (0.670 ml, 3.84 mmol) in DMF (3 ml) at RT was added HATU (729 mg, 1.919 mmol), and the mixture was stirred at RT. After stirring overnight, the reaction mixture was diluted with EtOAc. The solution was washed 2x with water, brine, dried over MgSO₄, filtered, concentrated and chromatographed with 0-50% EtOAc-hexanes to provide 650 mg of the product of Step 9. MS $m/e = 646.4$ (MH⁺).

Step 10

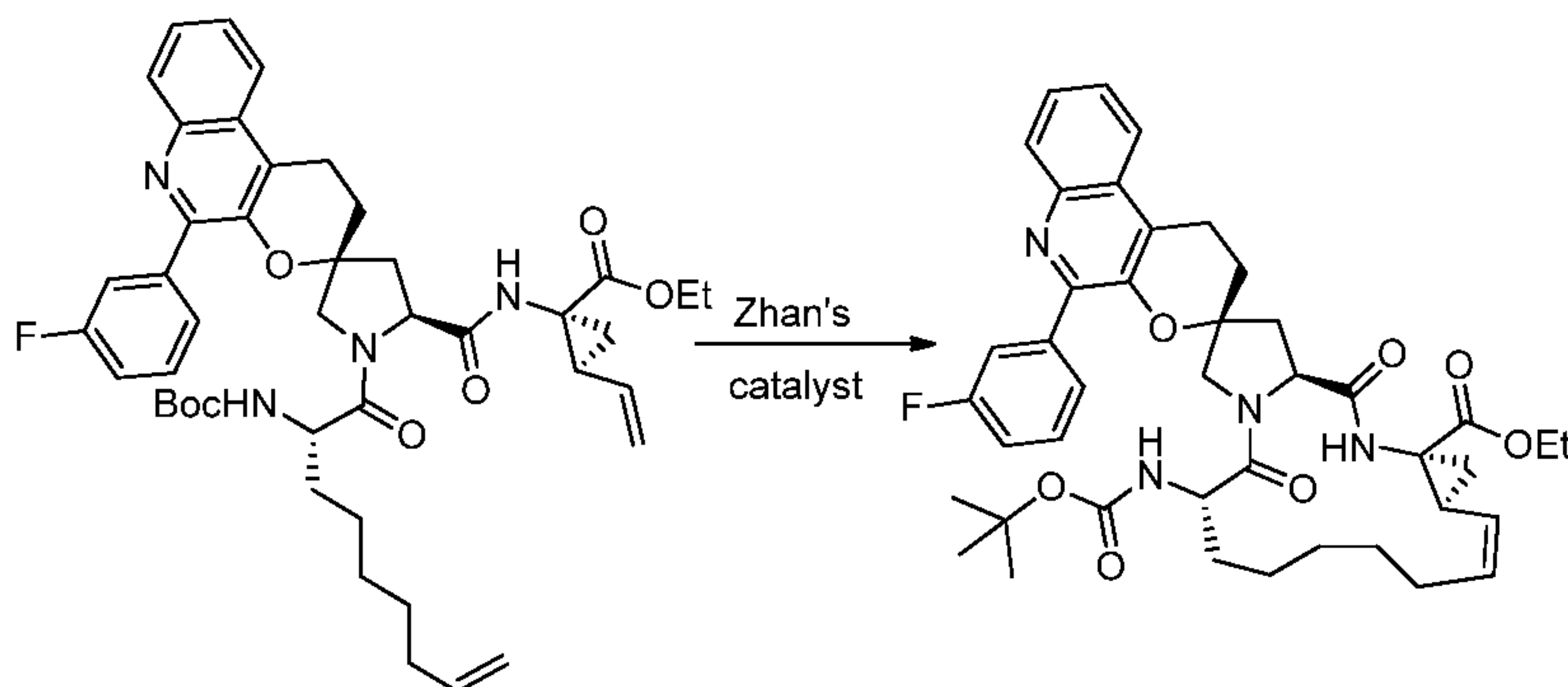


20

A solution of the product of Step 9 (650 mg, 1.007 mmol) and LiOH·H₂O (169 mg, 4.03 mmol) in THF (3 ml), MeOH (3 ml) and water (3 ml) in an RB flask fitted with a condenser was stirred in an oil-bath kept at 60°C. TLC at 1h indicated that the reaction was complete. The reaction mixture was diluted with water, acidified with 1N HCl, and extracted 3x
 5 with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to dryness to give 610 mg of the acid intermediate.

To a solution of the acid intermediate (610 mg, 0.966 mmol) and (1*R*,2*S*)-ethyl 1-amino-2-vinylcyclopropanecarboxylate-hydrochloride salt (278 mg, 1.448 mmol) in DMF (10 ml) at RT was added DIPEA (0.675 ml, 3.86 mmol) followed by HATU (551 mg, 1.448 mmol),
 10 and the mixture was stirred at RT for 2 days. The reaction mixture was diluted with EtOAc, washed 2x with water followed by brine. It was dried over MgSO₄, filtered, concentrated and chromatographed with 0-60% EtOAc-hexanes to provide 630 mg of the product of Step 10 as resin. MS m/e = 769.4 (MH⁺).

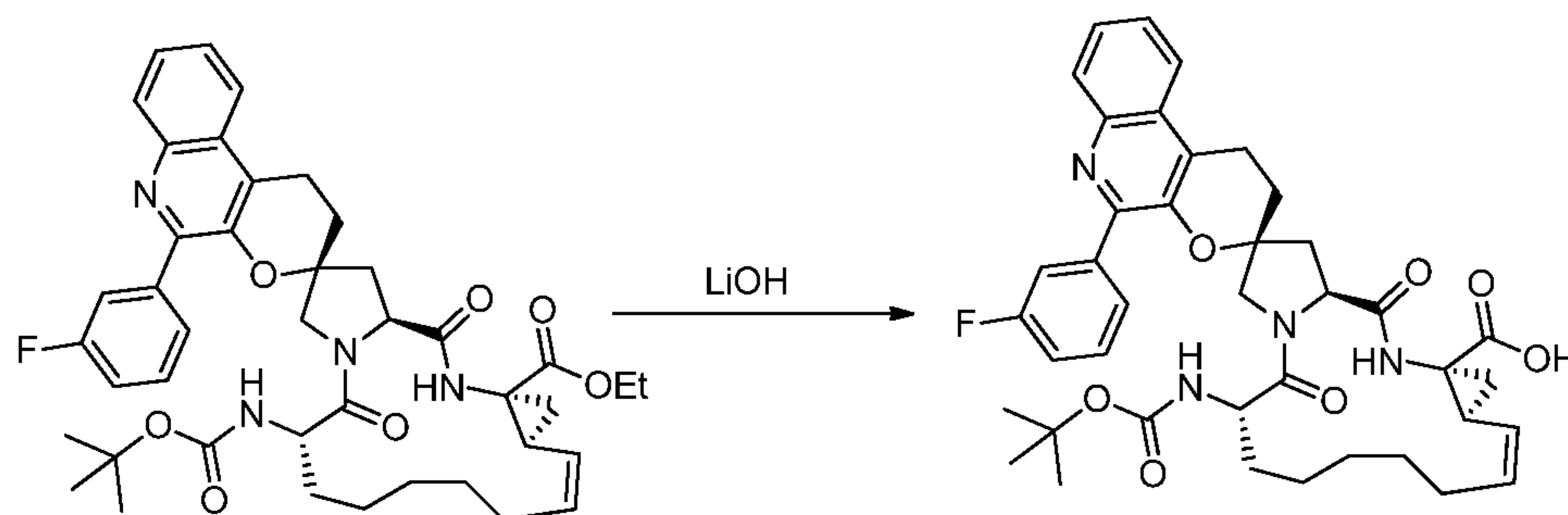
Step 11



15

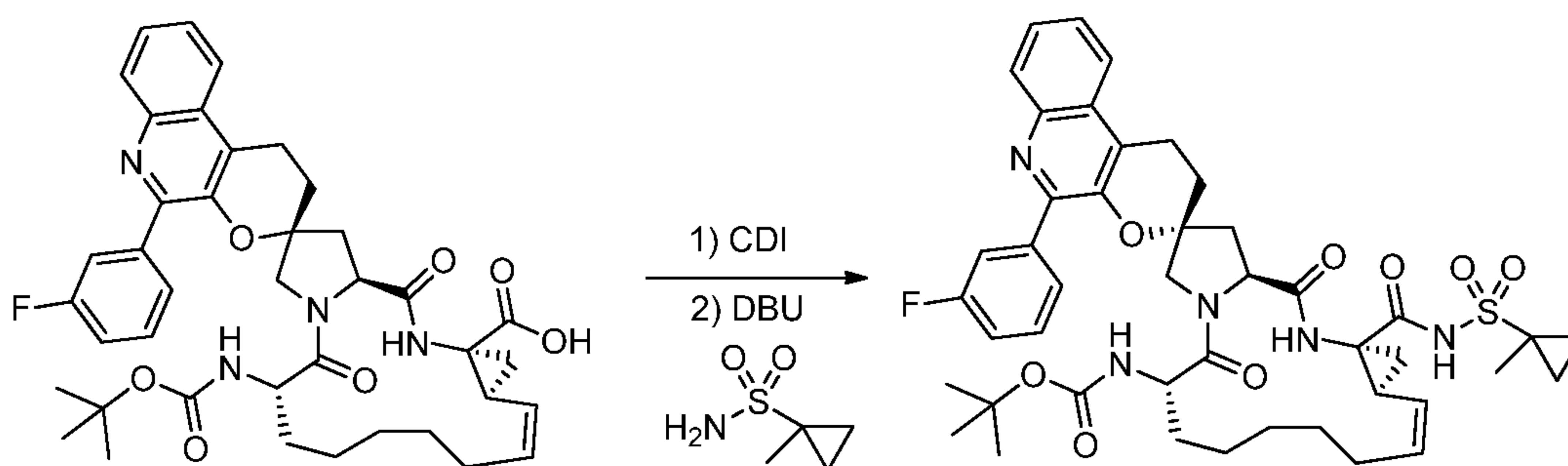
To a solution of the product of Step 10 (220 mg, 0.286 mmol) in DCE (100 ml) at RT was added 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene[2-(isopropoxy)-5-(*N,N*-dimethylaminosulfonyl)phenyl]methyleneruthenium(II) dichloride (52.5 mg, 0.072 mmol) followed by *p*-benzoquinone (9.28 mg, 0.086 mmol). The reaction flask was fitted with a
 20 condenser, degassed under vacuum and stirred in an oil-bath kept at 65°C for 3h. To the reaction mixture was added 0.5 ml of *n*-butyl-vinyl ether; the solvent was evaporated to dryness and chromatographed with 0-60% EtOAc-hexanes to provide 123 mg of the product of Step 11 as a resin. MS m/e = 741.4 (MH⁺).

Step 12



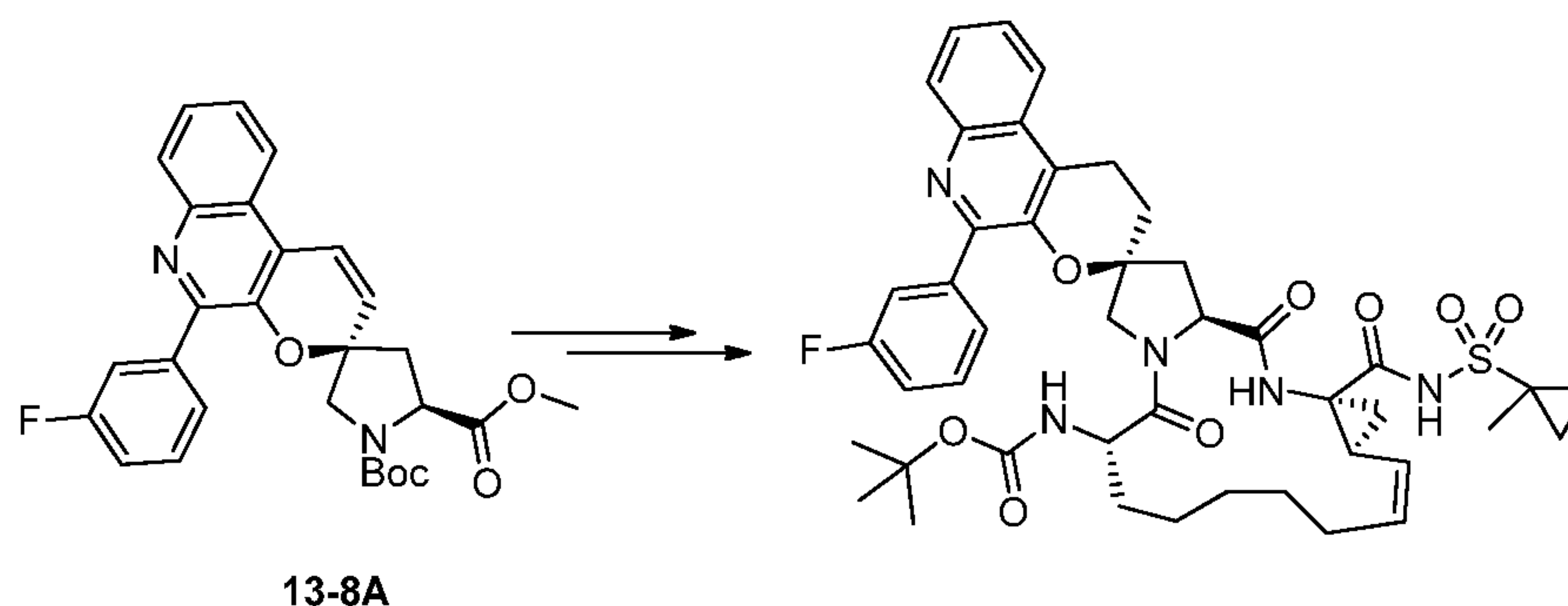
A solution of the product of Step 11 (570 mg, 0.769 mmol) and LiOH·H₂O (129 mg, 3.08 mmol) in THF (2 ml), MeOH (2 ml) and water (2 ml) in an RB flask was stirred in an oil-bath kept at 60°C for 1h, poured into water, acidified with 1N HCl and extracted 3x with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered, concentrated and evaporated to dryness to give 480 mg of the product of Step 12 as a solid. MS m/e = 713.4 (MH⁺).

Step 13



A solution of the product of Step 12 (340 mg, 0.477 mmol) and CDI (155 mg, 0.954 mmol) in THF (5 ml) was heated at reflux for 2h. The solution was cooled to RT, added 1-methylcyclopropane-1-sulfonamide (258 mg, 1.908 mmol) followed by DBU (0.288 ml, 1.908 mmol), and the mixture was stirred at 50°C for 10h then left at RT for 2d. To the reaction mixture was added few drops of AcOH and diluted with EtOAc. The solution was washed 3x with water, brine, dried over MgSO₄, filtered, concentrated and chromatographed with 100% hexanes to 5% MeOH-DCM to provide 390 mg of I-13 as a foam. ¹H-NMR (400 MHz, acetone-d₆) 8.01-7.95 (m, 2H), 7.82 (dt, J = 8.1, 1.2 Hz, 1H), 7.78-7.75 (m, 1H), 7.63-7.57 (m, 2H), 7.38 (dt, J = 6.1, 8.1 Hz, 1H), 7.16 (ddt, J = 1.0, 2.7, 8.7 Hz, 1H), 6.0 (d, J = 7.6 Hz, 1H), 5.72-5.65 (m, 1H), 5.0 (t, J = 9.5 Hz, 1H), 4.68-4.64 (m, 2H), 4.19 (t, J = 9.3 Hz, 1H), 3.87 (d, J = 11.1 Hz, 1H), 3.40-3.26 (m, 3H), 2.61-2.49 (m, 5H), 2.41-2.33 (m, 2H), 2.08-2.04 (m), 1.96-1.86 (m), 1.71 (dd, J = 5.5, 8.0 Hz, 1H), 1.64-1.20 (m), 1.05 (s, 9H), 0.89-0.82 (m). MS m/e = 830.4 (MH⁺).

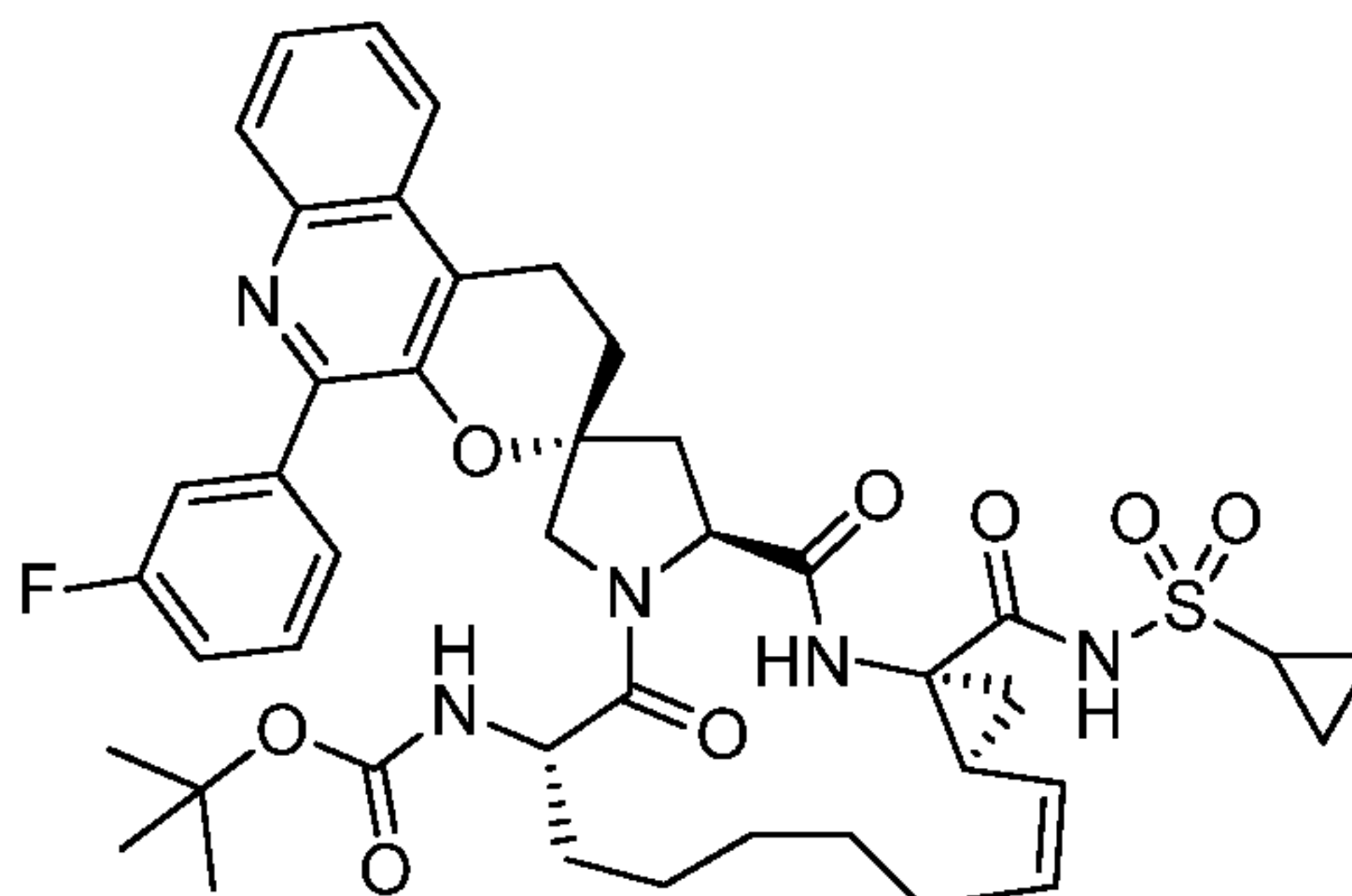
Example 14: *tert*-Butyl (2S,6S,13aS,14aR,16aS,Z)-5'-(3-fluorophenyl)-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-6-ylcarbamate (I-14)



5

I-14 was prepared using a procedure similar to the preparation of I-13 from the procedures of Example 13, Steps 9-13. MS $m/e = 830.4$ (MH^+).

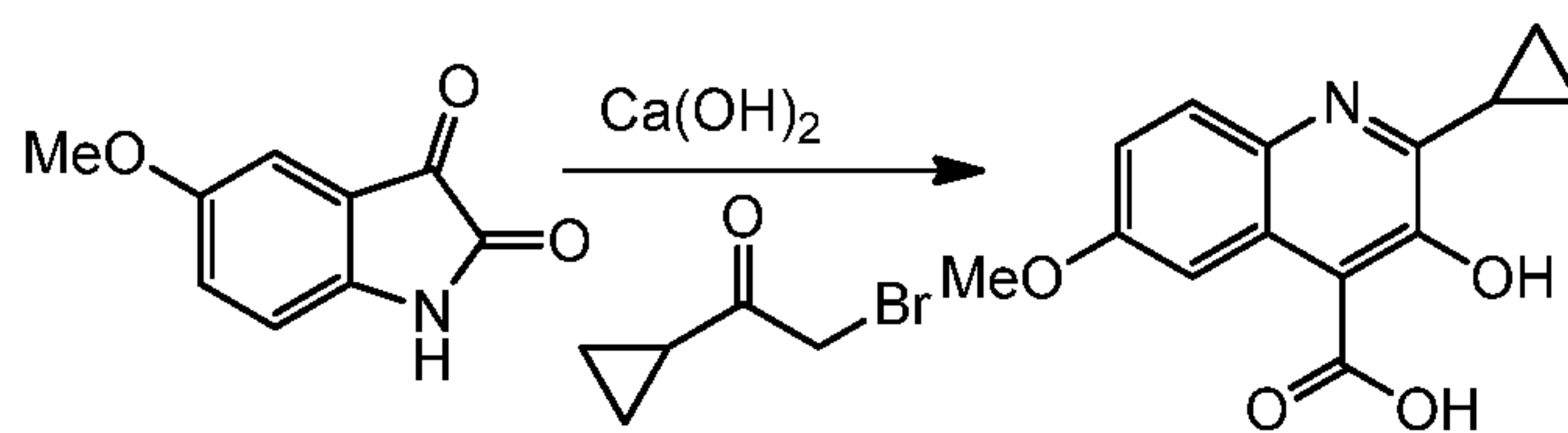
Example 15: *tert*-Butyl (2R,6S,13aS,14aR,16aS,Z)-14a-(cyclopropylsulfonylcarbamoyl)-5'-(3-fluorophenyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-6-ylcarbamate (I-15)



I-15 was prepared from the product of Example 13, Step 12 and cyclopropanesulfonamide using a procedure similar to Example 13, Step 13. MS $m/e = 816.4$ (MH^+).

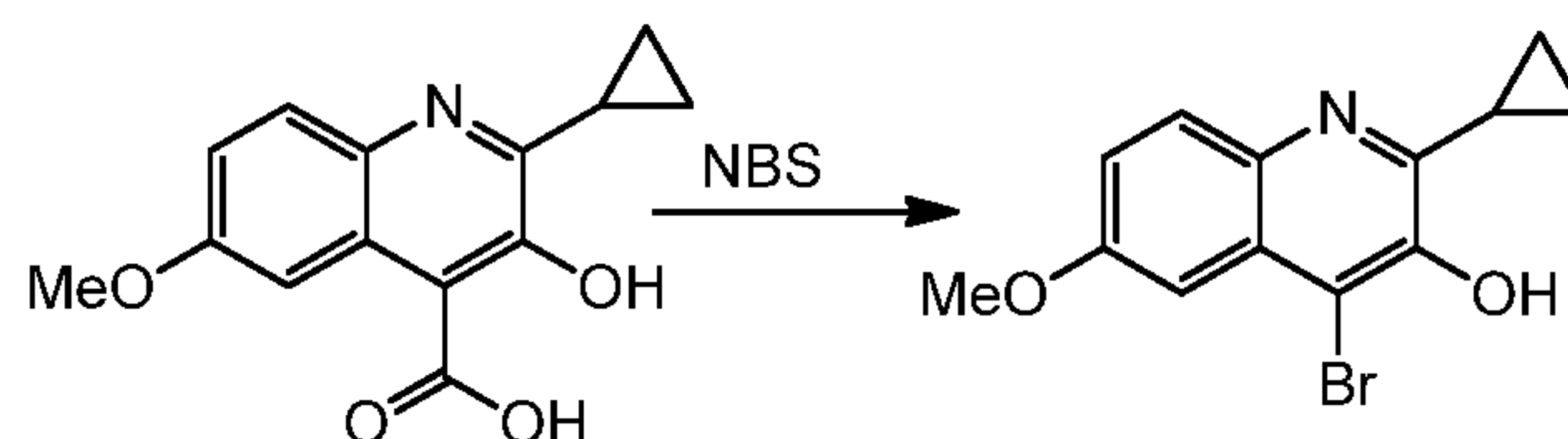
Example 16: *tert*-Butyl (2R,6S,13aS,14aR,16aS,Z)-5'-cyclopropyl-9'-methoxy-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-6-ylcarbamate (I-16)

Step 1



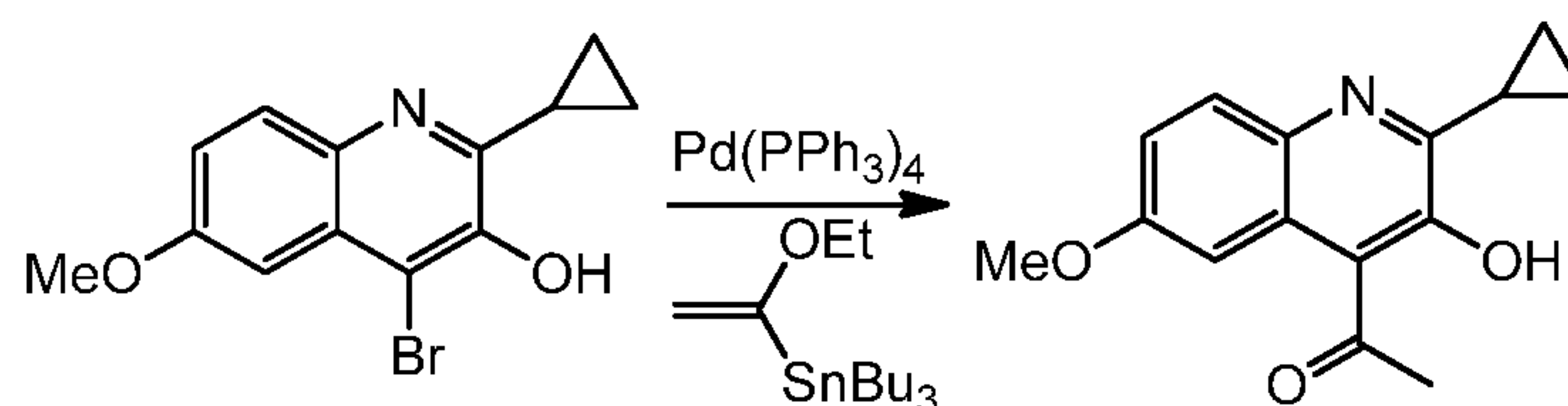
A mixture of 5-methoxyisatin (10 g, 56.4 mmol) and $\text{Ca}(\text{OH})_2$ (12.55 g, 169 mmol) in water (150 ml) was stirred in an oil-bath kept at 80°C for 1h. Then 2-bromo-1-cyclopropylethan-1-one (18.40 g, 113 mmol) was added through the condenser, while the reaction mixture is still being stirred in the oil-bath. The slurry was stirred for 4h, diluted with water and acidified with concentrated HCl. The precipitate was filtered, washed with water, ether and dried overnight in vacuum oven to give 10.54 g of the product of Step 1 as yellow colored solid. MS $m/e = 260.2$ (MH^+).

Step 2

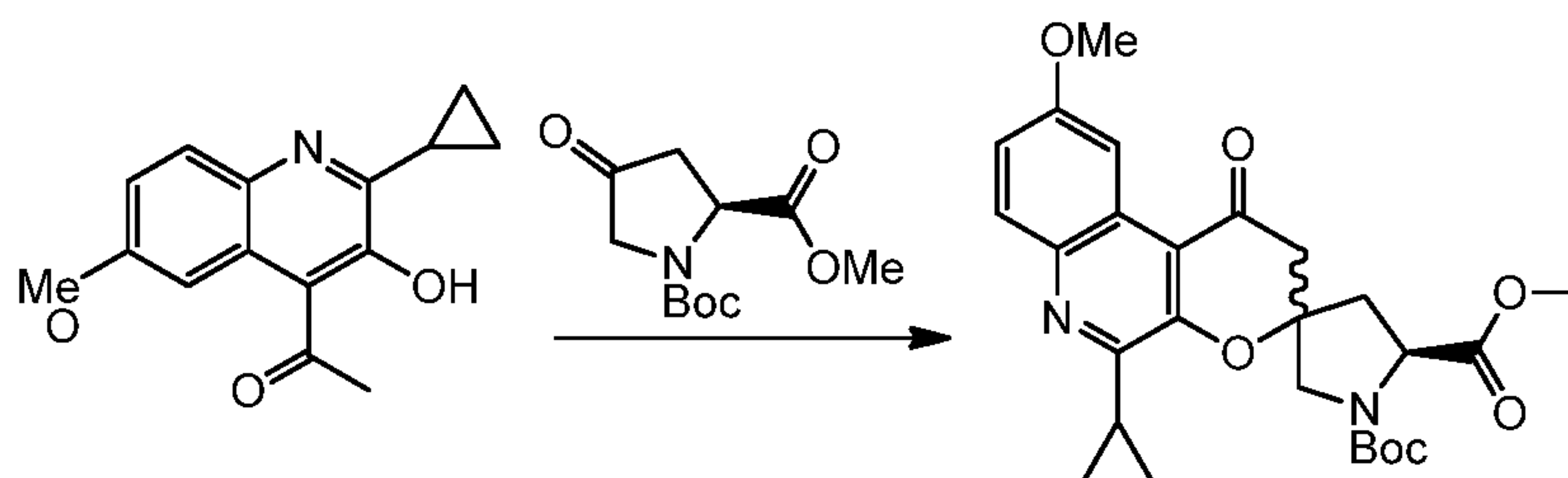


A mixture of the product of Step 1 (10.5 g, 40.5 mmol) and NBS (7.93 g, 44.6 mmol) in THF (150 ml) was stirred at RT for 1h. The reaction mixture was diluted with aq. $\text{Na}_2\text{S}_2\text{O}_3$ and extracted 3x with EtOAc. The combined organic layer was washed with brine, dried over MgSO_4 , filtered, concentrated and chromatographed with 100% hexanes to 100% DCM to provide 9.0 g of the product of Step 2 as yellow colored solid. MS $m/e = 296$ (MH^+).

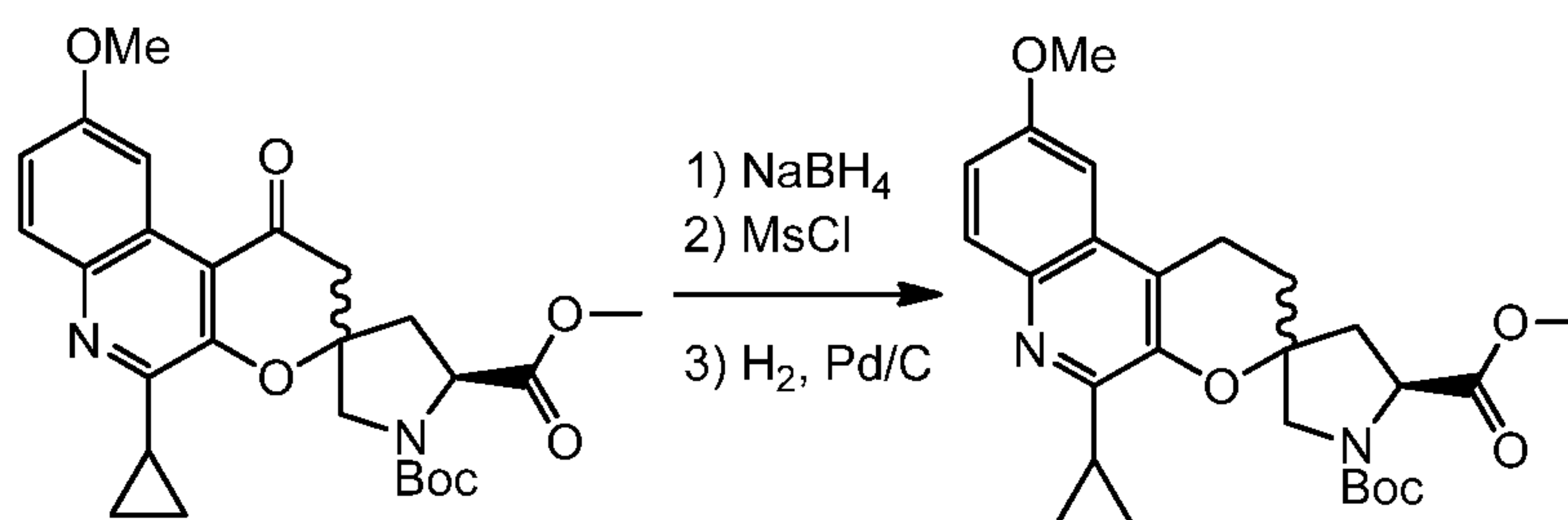
Step 3



A mixture of the product of Step 2 (9 g, 30.6 mmol), tributyl(1-ethoxyvinyl)tin (20 ml, 59.2 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (1.768 g, 1.530 mmol) in dioxane (170 ml) was heated at reflux overnight. The reaction mixture was cooled to RT, added ~200 ml of 1N HCl, and the mixture was stirred at RT for 30 min. The solution was diluted with water and extracted 3x with DCM. The combined organic layer was washed with brine, dried over MgSO_4 , filtered, concentrated and chromatographed with 0-10% EtOAc-hexanes to give 5.74 g of the product of Step 3 as solid. MS $m/e = 258.2$ (MH^+).

Step 4

A mixture of the product of Step 3 (3.5 g, 13.60 mmol), Boc-4-oxo-Pro-OMe (6.62 g, 27.2 mmol), pyrrolidine (0.450 ml, 5.44 mmol) and 3A molecular sieves (~15 g, 4-8 mesh) in MeOH (70 ml) in a sealed tube was stirred in an oil-bath kept at 100°C for 2h. The mixture was filtered through a CELITE pad, rinsed with MeOH, concentrated and chromatographed with 0-30% EtOAc-hexane to provide 3.31 g of the product of Step 4 as a mixture of diastereomers. MS $m/e = 483.2(MH^+)$.

Step 5

10

To a solution of the product of Step 4 (3.3 g, 6.84 mmol) in THF (15 ml) and MeOH (15.00 ml) was added NaBH₄ (0.776 g, 20.52 mmol), and the mixture was stirred at RT for 45 min, poured into aq. NH₄Cl and extracted 3x with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to dryness to give 2.95 g of the crude alcohol as a mixture of diastereomers.

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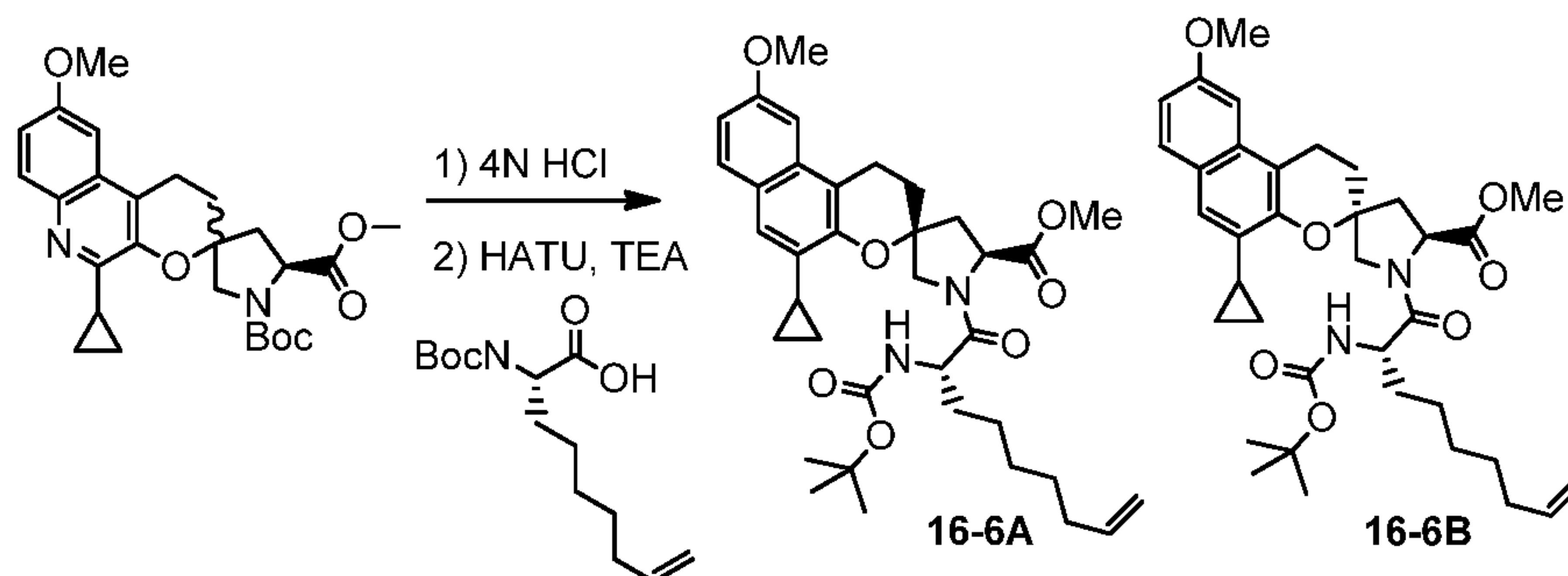
To a solution of the above alcohol (2.97 g, 6.13 mmol) in DCM (40 ml) at 0°C was added TEA (3.42 ml, 24.52 mmol) and MsCl (0.955 ml, 12.26 mmol). The solution was stirred at 0°C for 1h then overnight at RT. The reaction mixture was diluted with ether, washed 2x with water, aq. NaHCO₃ and brine. It was dried over MgSO₄, filtered and evaporated to dryness to give the crude chloride intermediate, which was used as such.

20

The above product was stirred with activated carbon in EtOAc for about 15 min, filtered through a CELITE pad, concentrated and immediately used for this reaction. A suspension of the above product (3.08 g, 6.13 mmol) and 10% Pd/C (500 mg) in EtOAc (50 ml) was stirred under H₂ balloon for 3h. The reaction mixture was filtered through a CELITE pad, rinsed with

MeOH and EtOAc. The filtrate was washed 2x with aq. NaHCO₃, brine, dried over MgSO₄, filtered, concentrated and chromatographed with 0-50% EtOAc-hexanes to provide 1.72 g of the product of Step 5 as a resin. MS m/e = 469.2 (MH⁺).

Step 6



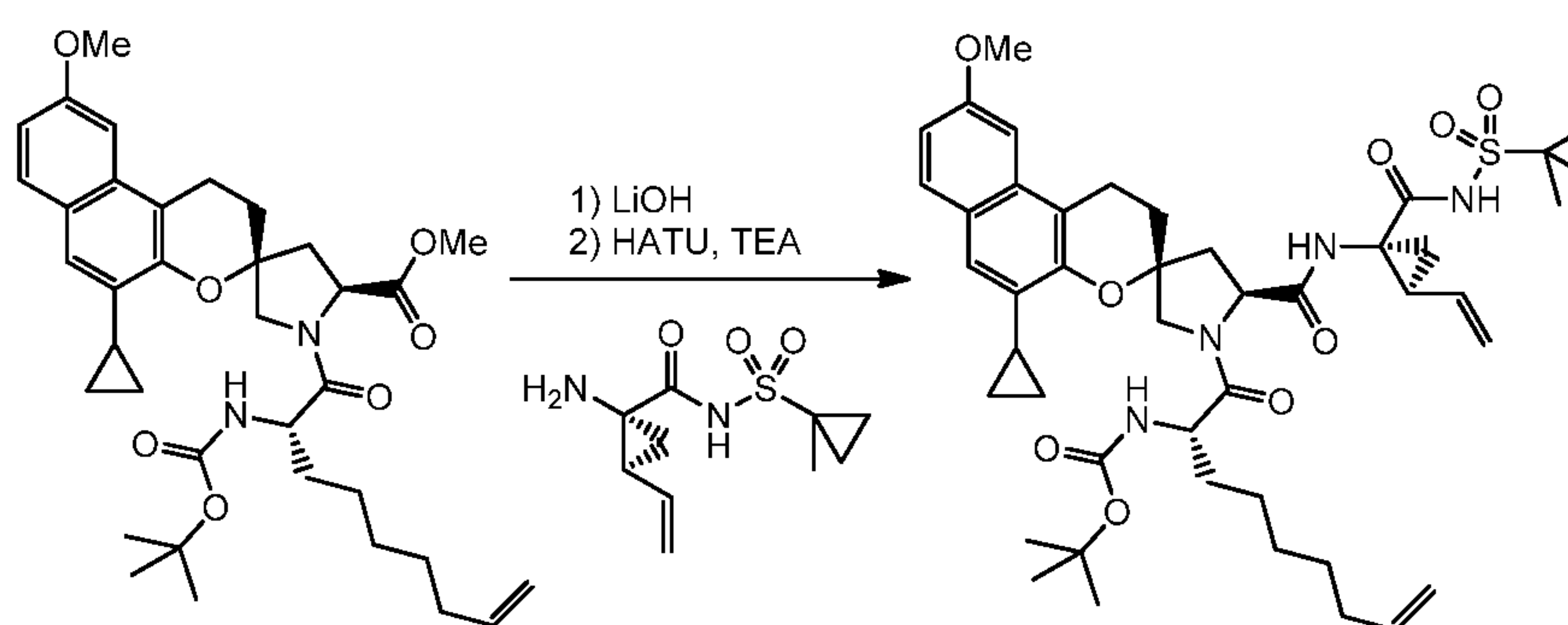
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A solution of the product of Step 5 (1.65 g, 3.52 mmol) in 4N HCl in dioxane (30 ml) was stirred at RT for 1h, co-evaporated 2x with toluene and 2x with ether to give the crude amine as the hydrochloride, which was used as such.

A slurry of the above product (1425 mg, 3.52 mmol), (S)-2-(tert-butoxycarbonylamino)non-8-enoic acid-dicyclohexylamine salt (2390 mg, 5.28 mmol), HATU (2008 mg, 5.28 mmol) and TEA (1.472 ml, 10.56 mmol) in DMF (40 ml) was stirred at RT for 2d. The reaction mixture was diluted with water and extracted 3x with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered, concentrated and chromatographed with 0-50-100% EtOAc-hexanes to give 980 mg of 16-6A and 700 mg of 16-6B. MS for 16-6A m/e = 621.8 (MH⁺). MS for 16-6B m/e = 621.8 (MH⁺).

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Step 7

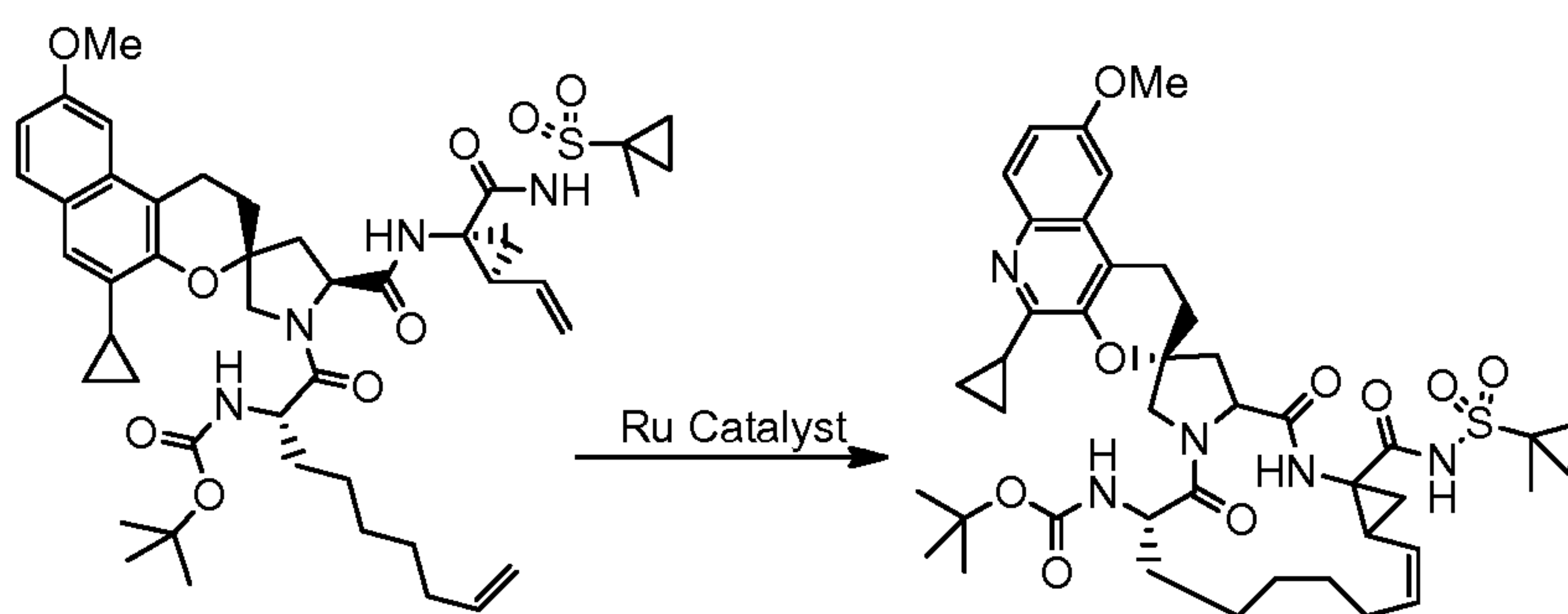


20

A solution of 16-6A (960 mg, 1.544 mmol) and LiOH·H₂O (259 mg, 6.18 mmol) in THF (5 ml), MeOH (5.00 ml) and water (5.00 ml) was stirred in an oil-bath kept at 60°C for 1h. The reaction mixture was cooled to RT, diluted with water, acidified with 1N HCl and extracted 3x with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered, concentrated and evaporated with toluene to give the acid.

A mixture of the above acid (930 mg, 1.530 mmol), (1R,2S)-1-amino-N-(1-methylcyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide (561 mg, 2.295 mmol) HATU (873 mg, 2.295 mmol) and TEA (0.640 ml, 4.59 mmol) in DMF (15 ml) was stirred overnight at RT. The reaction mixture was diluted with water and extracted 3x with EtOAc. The combined
 5 organic layer was washed with brine, dried over MgSO₄, filtered, concentrated and chromatographed with 0-30% acetone-hexanes to give 1.24 g of the product of Step 7. MS m/e = 833.6 (MH⁺).

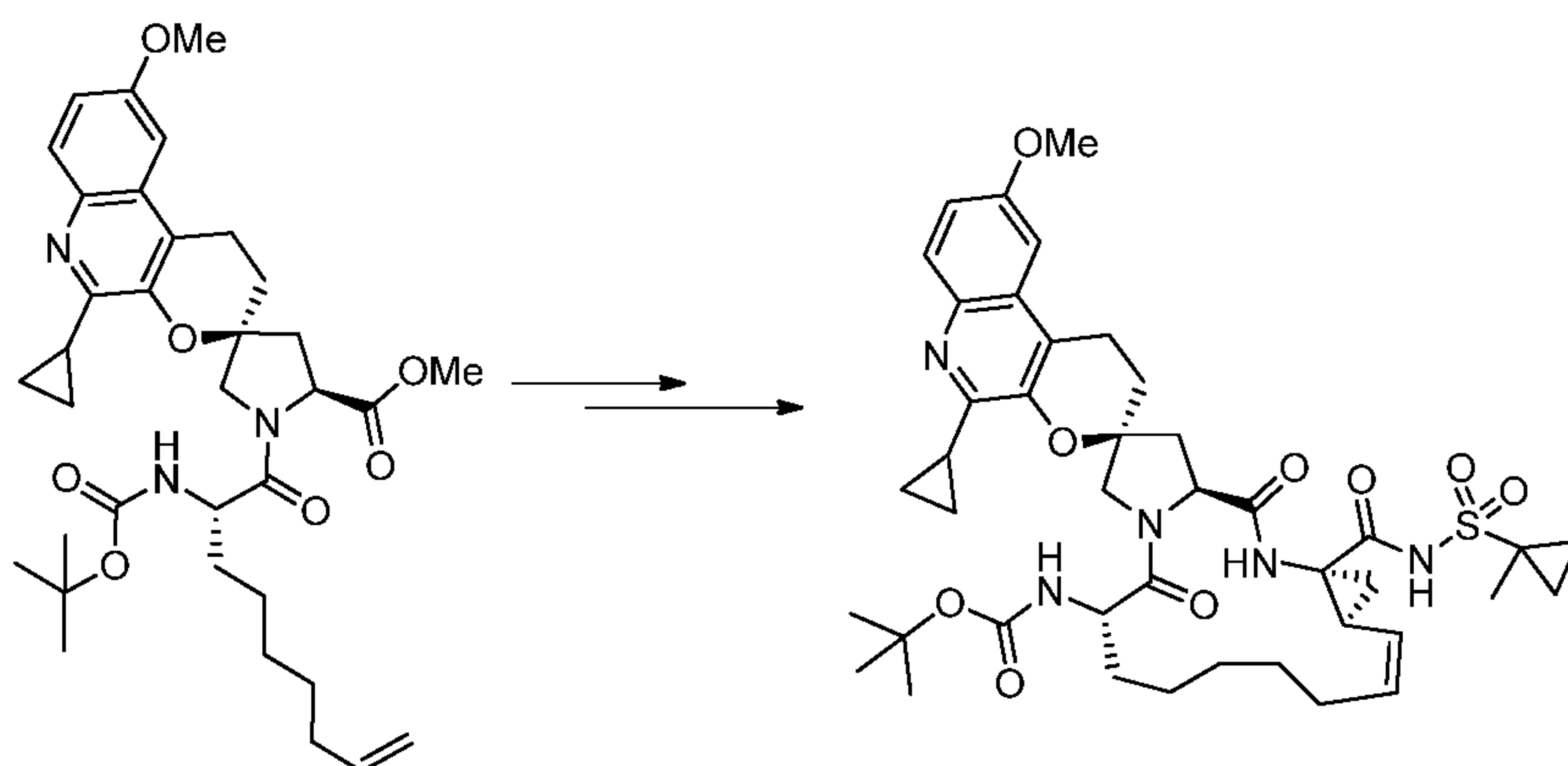
Step 8



10 A solution of the product of Step 7 (1.24 g, 1.487 mmol), Zhan's catalyst (0.273 g, 0.372 mmol) and 1,4-benzoquinone (0.048 g, 0.446 mmol) in DCE (600 ml) was degassed under vacuum and filled under argon atmosphere. The mixture was stirred in an oil-bath kept at 75°C for 4h. To the reaction mixture was added 1 mL of n-butylvinyl ether and stirred at RT for 30 min. The solvent was evaporated to dryness, and the residue was chromatographed with 0-30%
 15 acetone-hexanes to give 990 mg of the compound of I-16 as solid. ¹H-NMR (400 MHz, CDCl₃): 10.09 (s, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.12 (dd, J = 2.4, 9.1 Hz, 1H), 6.94 (d, J = 2.7 Hz, 1H), 6.92 (s, 1H), 5.72-5.65 (m, 1H), 5.16 (d, J = 8.0 Hz, 1H), 4.97 (t, J = 9.5 Hz, 1H), 4.59 (t, J = 8.1 Hz, 1H), 4.45 (d, J = 11.3 Hz, 1H), 4.30-4.24 (m, 1H), 3.90 (s, 3H), 3.75 (d, J = 10.8 Hz, 1H), 3.07-3.03 (m, 2H), 2.57-2.52 (m, 2H), 2.43-2.19 (m), 1.86-1.82 (m), 1.74-1.67 (m), 1.40 (s, 9H),
 20 1.42-1.10 (m), 0.89-0.74 (m). MS m/e = 805.6 (MH⁺).

Example 17: tert-Butyl (2S,6S,13aS,14aR,16aS,Z)-5'-cyclopropyl-9'-methoxy-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-6-ylcarbamate (I-17)

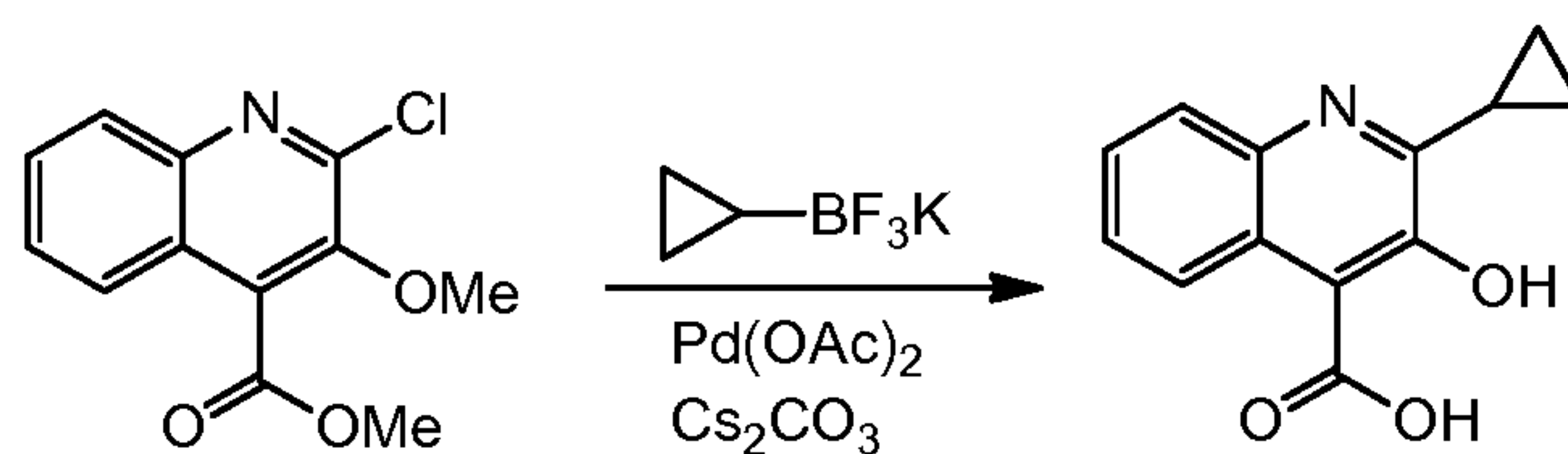
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Intermediate 16-6B (the product of Example 16, Step 6) was converted to I-17 using procedures similar to Example 16, Steps 7-8. MS $m/e = 806.4$ (MH⁺).

5 **Example 18: *tert*-Butyl (2R,6S,13aS,14aR,16aS,Z)-5'-cyclopropyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-6-ylcarbamate (I-18)**

Step 1

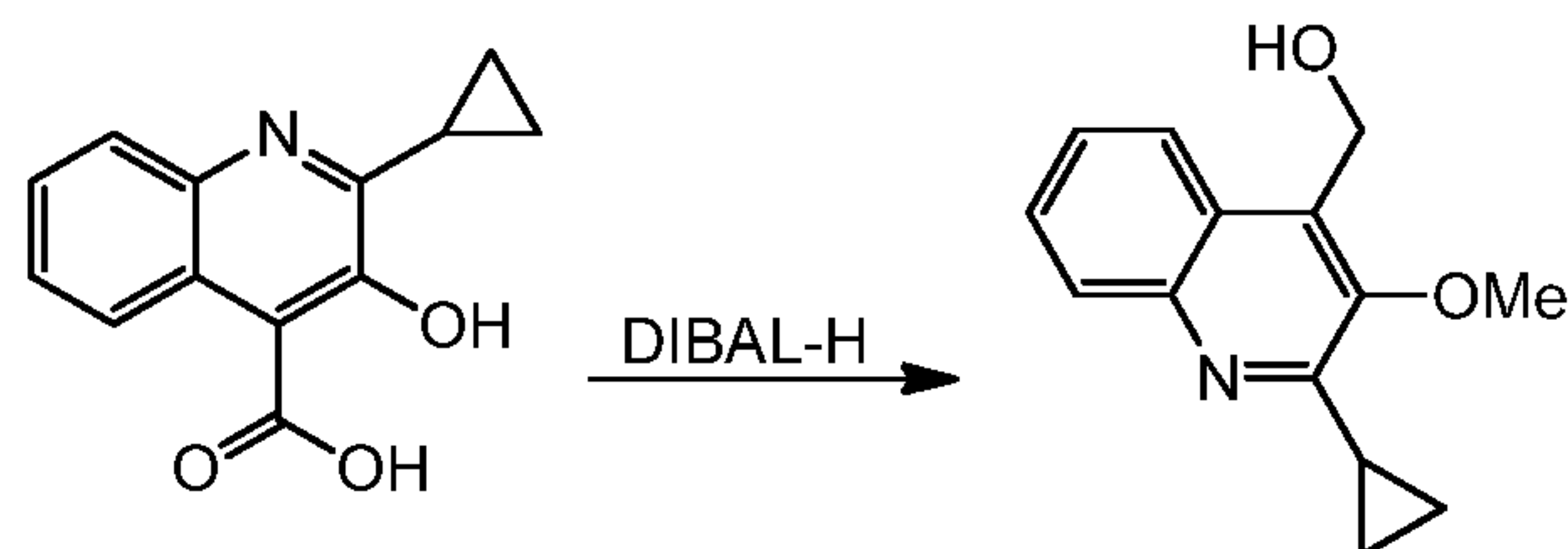


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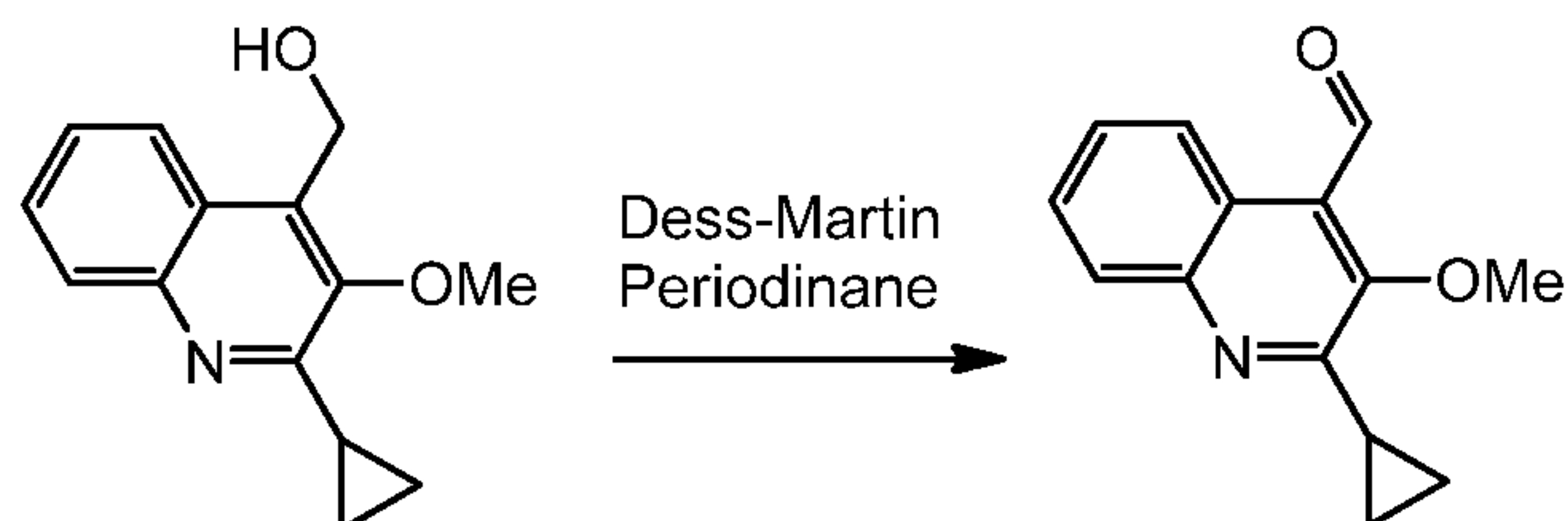
To a pressure vessel with a stir bar was added Cs₂CO₃ (7.77 g, 23.84 mmol), palladium(II) acetate (0.089 g, 0.397 mmol), di(1-adamantyl)-*n*-butylphosphine (available as CATACXIUM A, 0.285 g, 0.795 mmol), cyclopropyl potassium tetrafluoroborate (1.764 g, 11.92 mmol) and a solution of the product of Example 13, Step 1 (2 g, 7.95 mmol) in toluene (28.9 ml) and water (2.89 ml). After bubbling with argon for about 2 min, the vessel was sealed and heated to 100°C. After 16h, the mixture was cooled, water (100 ml) was added, and the mixture was extracted with EtOAc (3x75 ml). The combined organic fractions were washed with brine (1x75 mL), dried with MgSO₄, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/hexanes to give the product of Step 1 (1.9 g, 7.38 mmol, 93% yield) as an amber oil. MS $m/e = 258$ (MH⁺).

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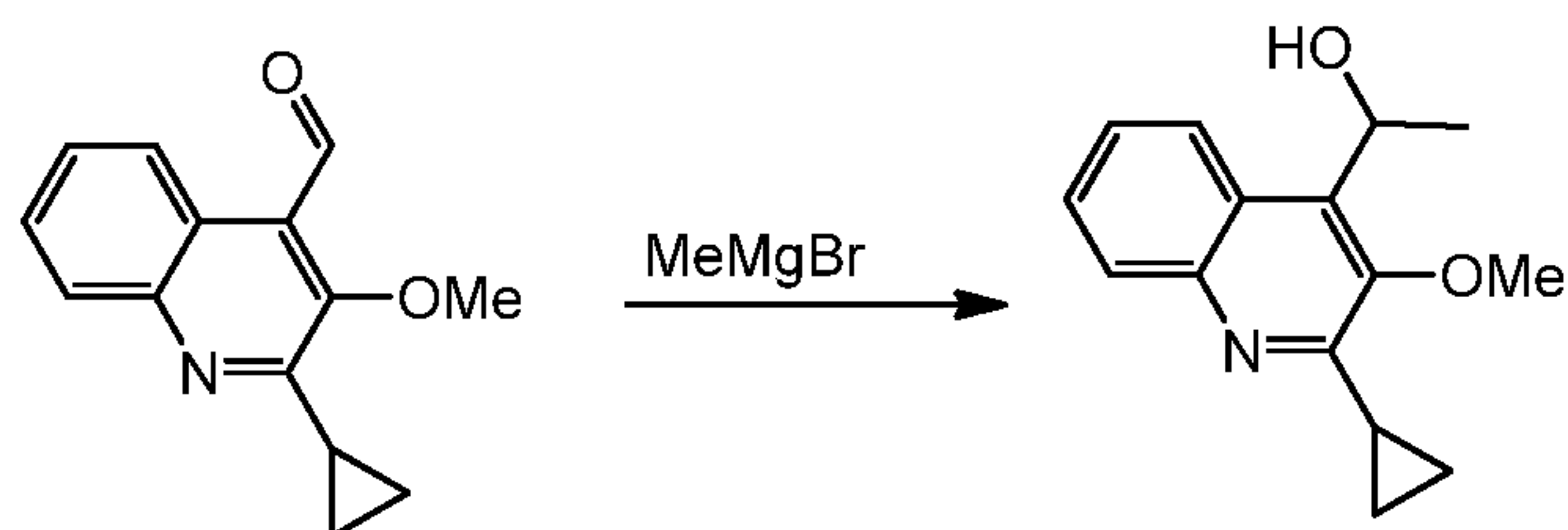
Step 2

DIBAL-H (15.55 ml, 46.6 mmol) was added to a stirred, cooled -78°C mixture of the product of Step 1 (4 g, 15.55 mmol) in DCM (78 mL), and the mixture was stirred for 3h
 5 under N_2 . The reaction mixture was quenched with aq. sodium potassium tartrate, while stirring vigorously. The phases were separated and the aq. phase extracted with EtOAc (3x). The combined organic phases were washed with brine, dried with MgSO_4 , filtered and evaporated to dryness yielding the product of Step 2 (3.31 g, 14.44 mmol, 93% yield). MS $m/e = 230$ (MH^+).

Step 3

10

NaHCO_3 (1.21 g, 14.4 mmol) and Dess-Martin periodinane (12.25 g, 28.9 mmol) were added to the product of Step 2 (3.31 g, 14.44 mmol) in DCM (72.2 ml), and the mixture was stirred overnight under N_2 . When the reaction was complete (by LC-MS), the reaction mixture was poured onto aq. $\text{Na}_2\text{S}_2\text{O}_3$ and aq. 1N NaOH solution and extracted (3x) with DCM. The
 15 combined extracts were washed with brine, dried with MgSO_4 , filtered and evaporated to dryness yielding a residue. The residue was purified by column chromatography on silica gel eluting with EtOAc/Hexanes to give 3.38 g of the product of Step 3 as a yellow oil. MS $m/e = 228$ (MH^+).

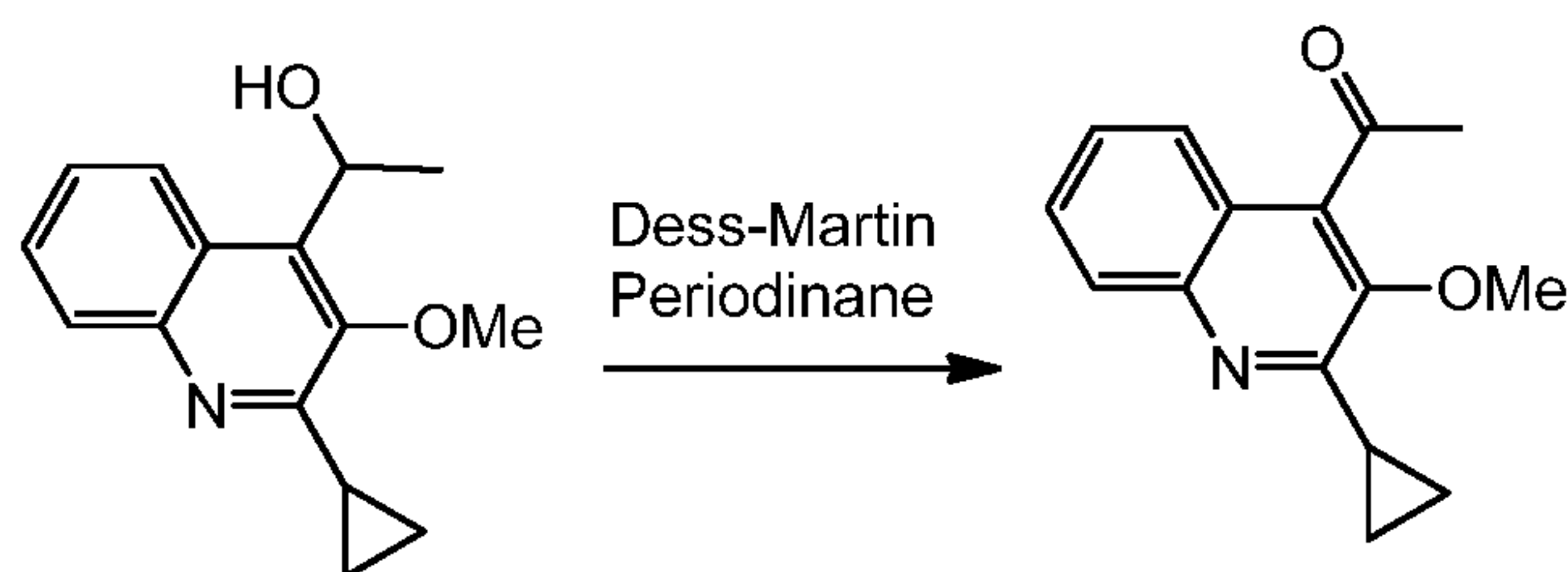
Step 4

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MeMgBr (9.92 ml, 29.7 mmol) was added to a stirred, cooled (-10°C) mixture of the product of Step 3 (3.38 g, 14.87 mmol) in THF, and the mixture was stirred for about 90 min

under N₂. The reaction mixture was quenched with aq. NH₄Cl and extracted with EtOAc (3x). The combined extracts were washed with brine, dried with MgSO₄, filtered and evaporated to dryness yielding the product of Step 4 (3.82 g, 15.70 mmol, 106% yield). MS m/e = 244 (MH⁺).

Step 5

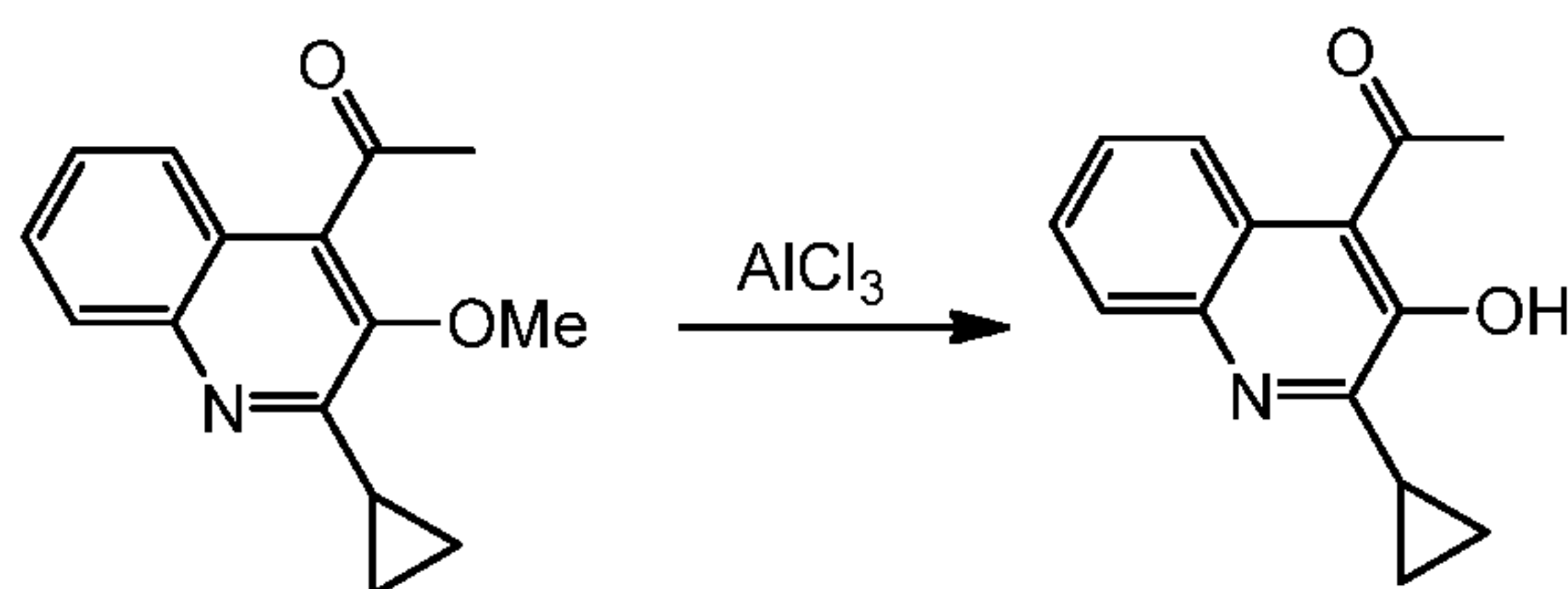


NaHCO₃ (2.67 g, 31.7 mmol) and Dess-Martin periodinane (13.46 g, 31.7 mmol) were added to a stirred mixture of the product of Step 4 (3.86 g, 15.87 mmol) in DCM, and the mixture was stirred overnight under N₂. The reaction mixture was poured onto aq. Na₂S₂O₃ followed by aq. 1N NaOH, which formed a heavy white precipitate. The heavy emulsion was separated from the small amount of clear aq. phase, and the white gloppy mixture was vacuum filtered, and the filtrate (two phases) was partitioned. The aq. part of the filtrate was combined with the aq. phase collected earlier and was extracted (3x) with DCM. The combined organic phases were dried with MgSO₄, filtered and evaporated to dryness. 4.48 g of orange oil was obtained. The residue was purified by column chromatography on silica gel eluting with EtOAc/Hexanes to give the product of Step 5 (2.87 g, 11.89 mmol, 75.0% yield) as a light amber oil. MS m/e = 242 (MH⁺).

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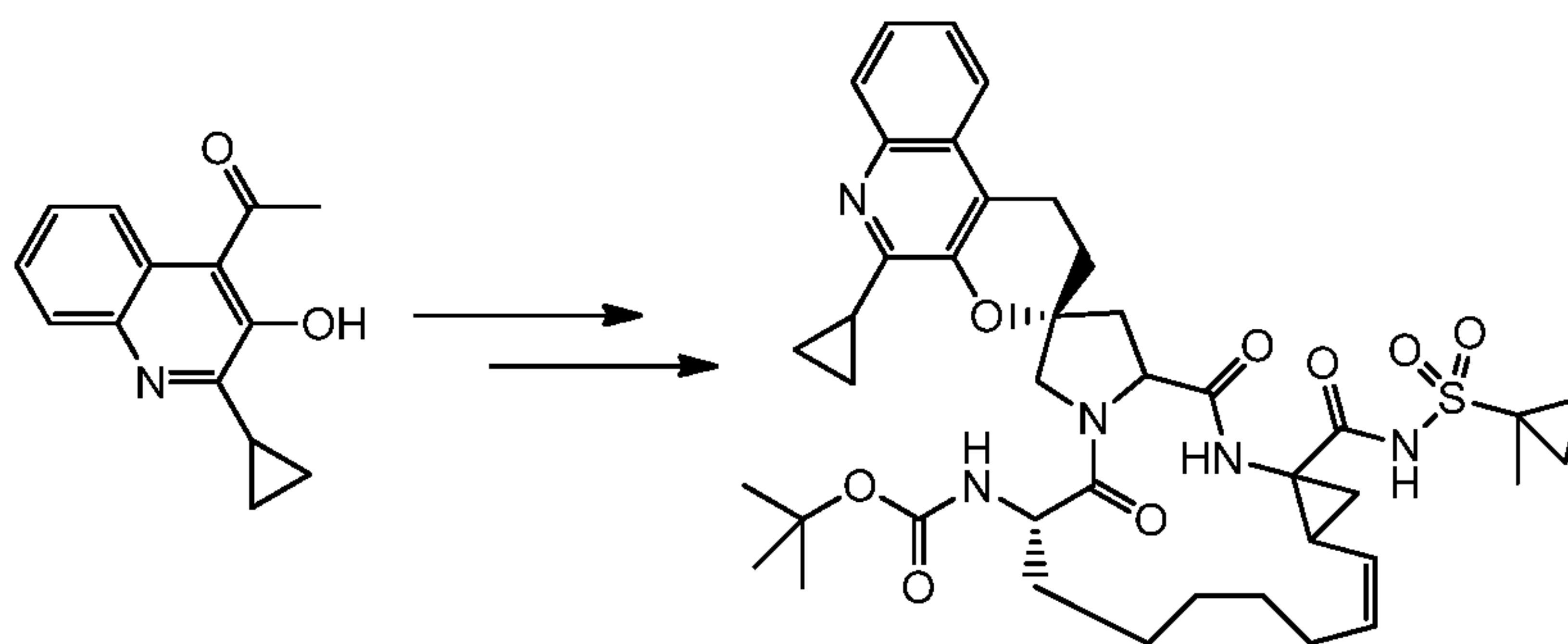
Step 6



AlCl₃ (15.64 g, 117 mmol) was added to a stirred, cooled -10°C solution of the product of Step 5 (2.83 g, 11.73 mmol) in DCM (58.6 ml), and the mixture was stirred under N₂ and warmed to RT. After stirring overnight, the reaction mixture was cooled to -10°C then quenched with aq. Na-K-tartrate. The layers were separated, and the aq. phase was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried with MgSO₄, filtered and evaporated to dryness yielding the product of Step 6 (2.56 g, 11.26 mmol, 96% yield).

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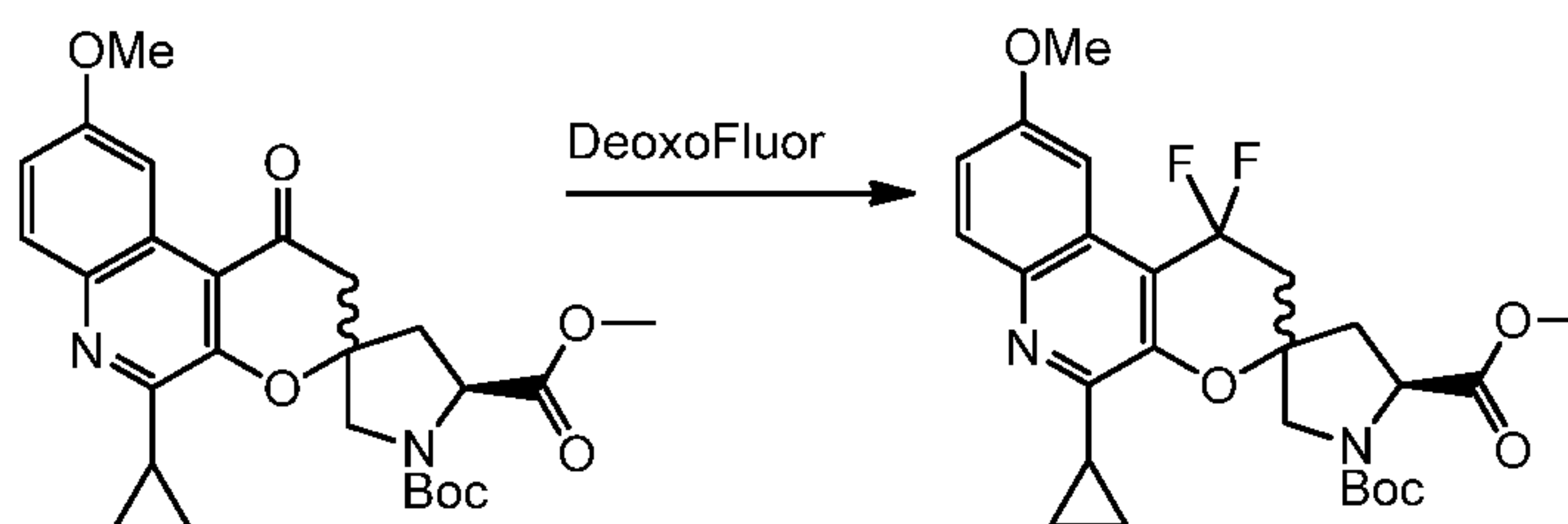
Step 7



The product of Step 6 was converted to I-18 using a procedure similar to Example 16, Steps 4-8. MS $m/e = 776$ (MH⁺).

5 **Example 19: *tert*-Butyl (2S,6S,13aS,14aR,16aS,Z)-5'-cyclopropyl-1',1'-difluoro-9'-methoxy-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-6-ylcarbamate (I-19)**

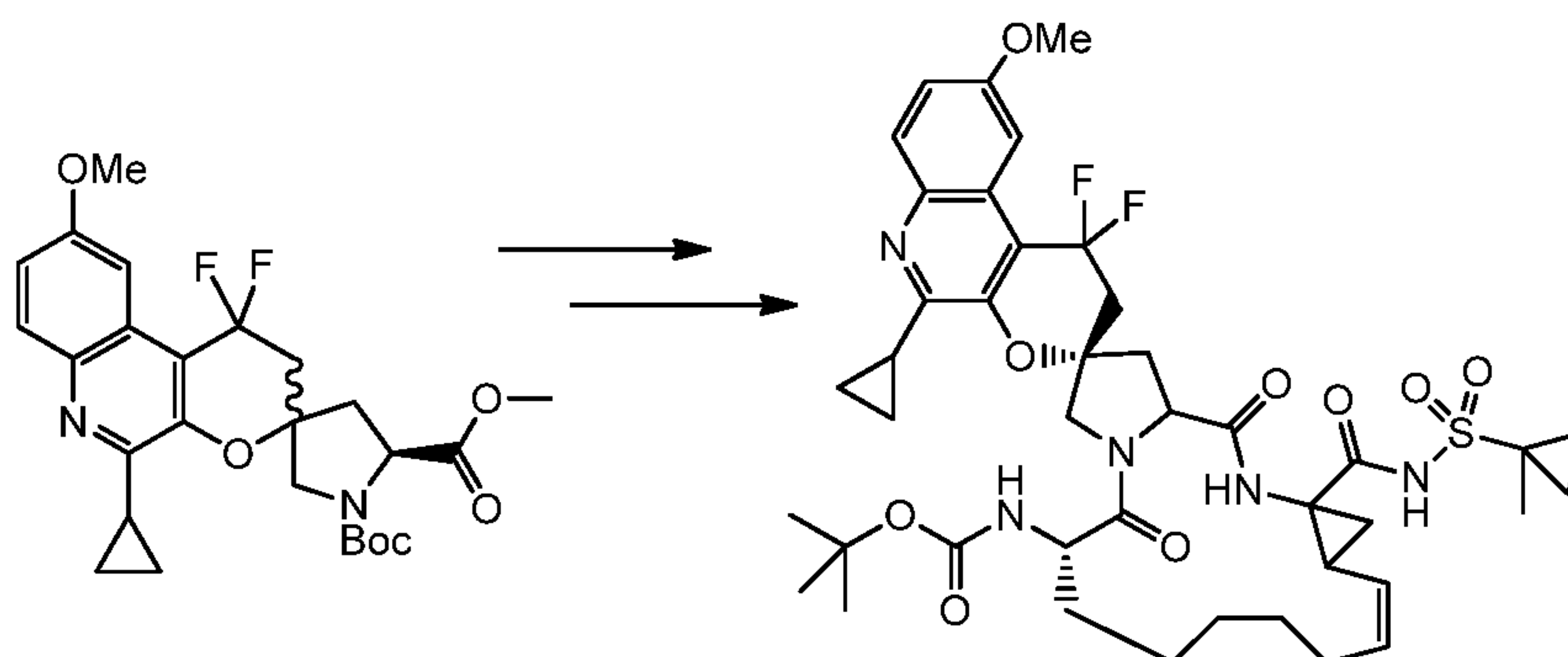
Step 1



10

To a solution of the product of Example 16, Step 4 (3 g, 6.22 mmol) in DCM (30 ml) at RT was added DEOXOFLUOR (5.73 ml, 31.1 mmol) followed by EtOH (0.109 ml, 1.865 mmol), and the mixture was heated at reflux overnight. LC-MS indicated mostly unreacted starting material. To the reaction mixture was added another 10eq. of DEOXOFLUOR and 0.3eq. of EtOH, and the reaction continued. The reaction continued at reflux for 3d. The reaction mixture was slowly poured in to aq. NaHCO₃ and extracted 3x with DCM. The combined organic layer was washed with brine, dried over MgSO₄, filtered, concentrated and chromatographed with 0-30-40% EtOAc-hexanes to provide 1.08 g of the product of Step 1 as solid. MS $m/e = 505.2$ (MH⁺).

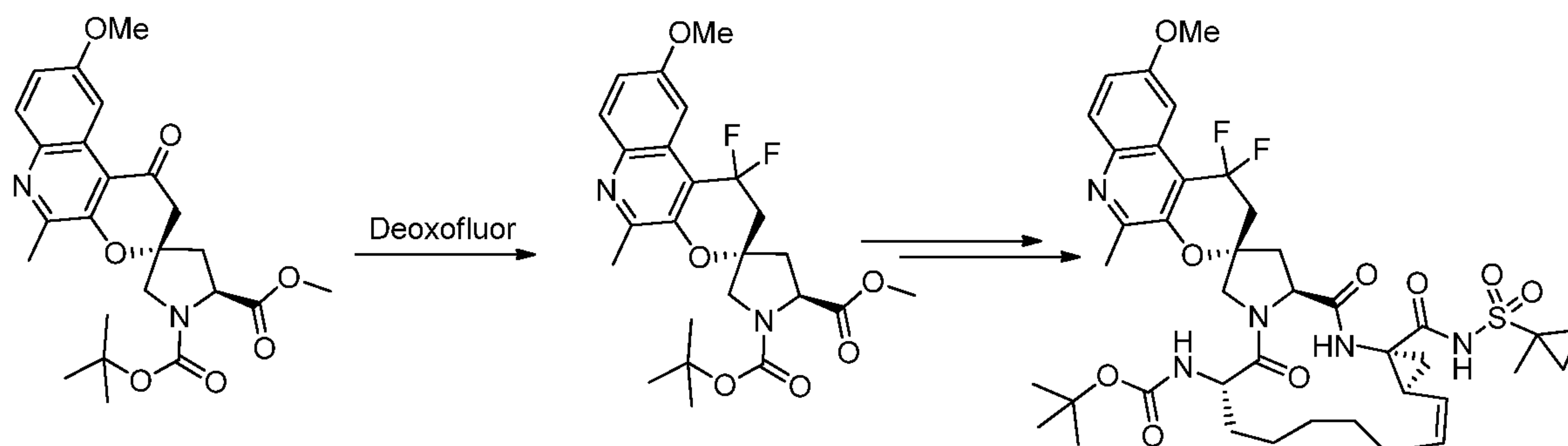
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Step 2

The product of Step 1 was converted to I-19 using a procedure similar to Example 16, Steps 6-8.

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Example 20: tert-Butyl (2S,6S,13aS,14aR,16aS,Z)-1',1'-difluoro-9'-methoxy-5'-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-6-ylcarbamate (I-20)

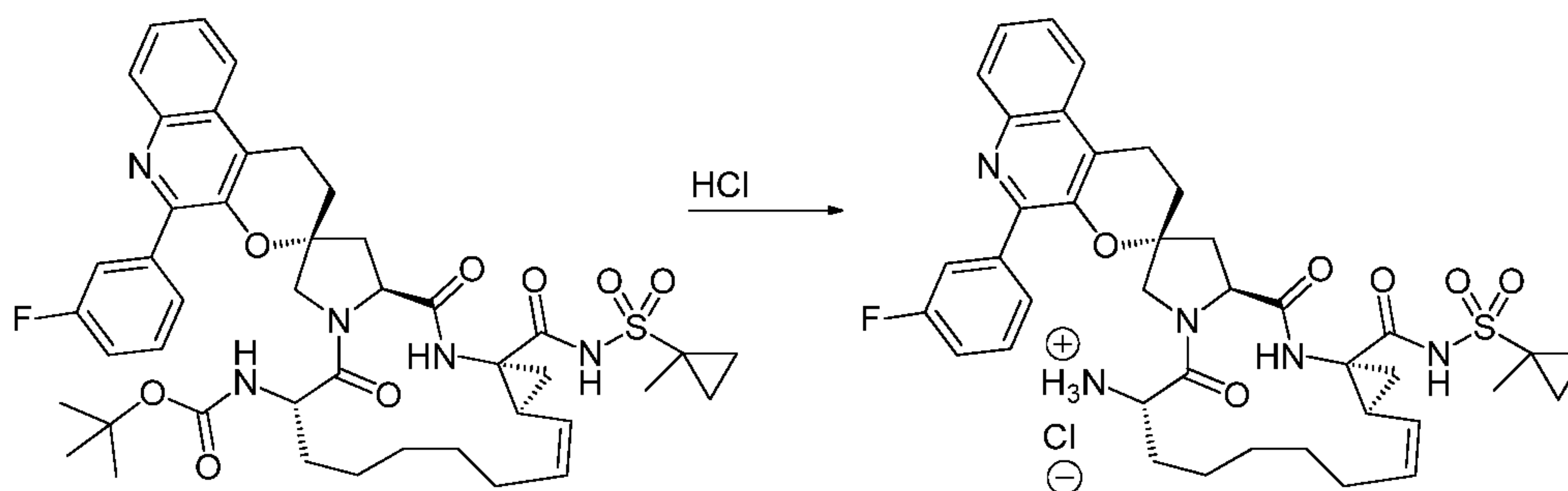


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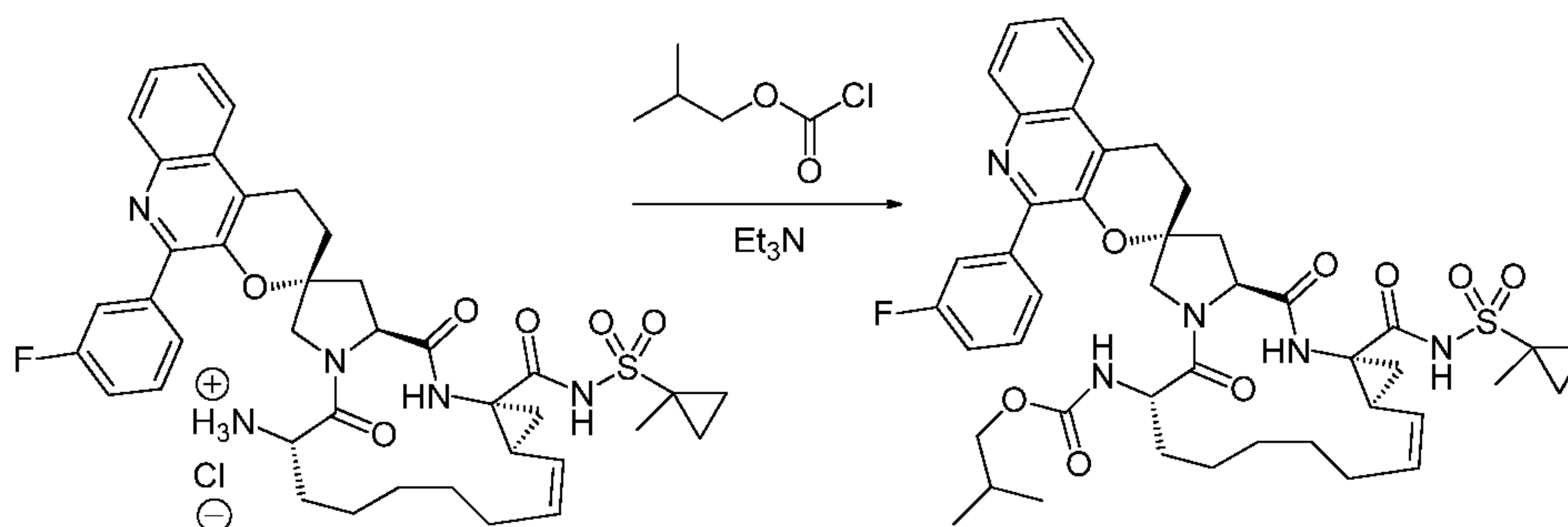
Intermediate 9-4A (the product of Example 9, Step 4) was converted to I-20 using procedures similar to Example 19. MS m/e= 806.4 (MH+).

Example 21: Isobutyl (2R,6S,13aS,14aR,16aS,Z)-5'-(3-fluorophenyl)-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-6-ylcarbamate (I-21)

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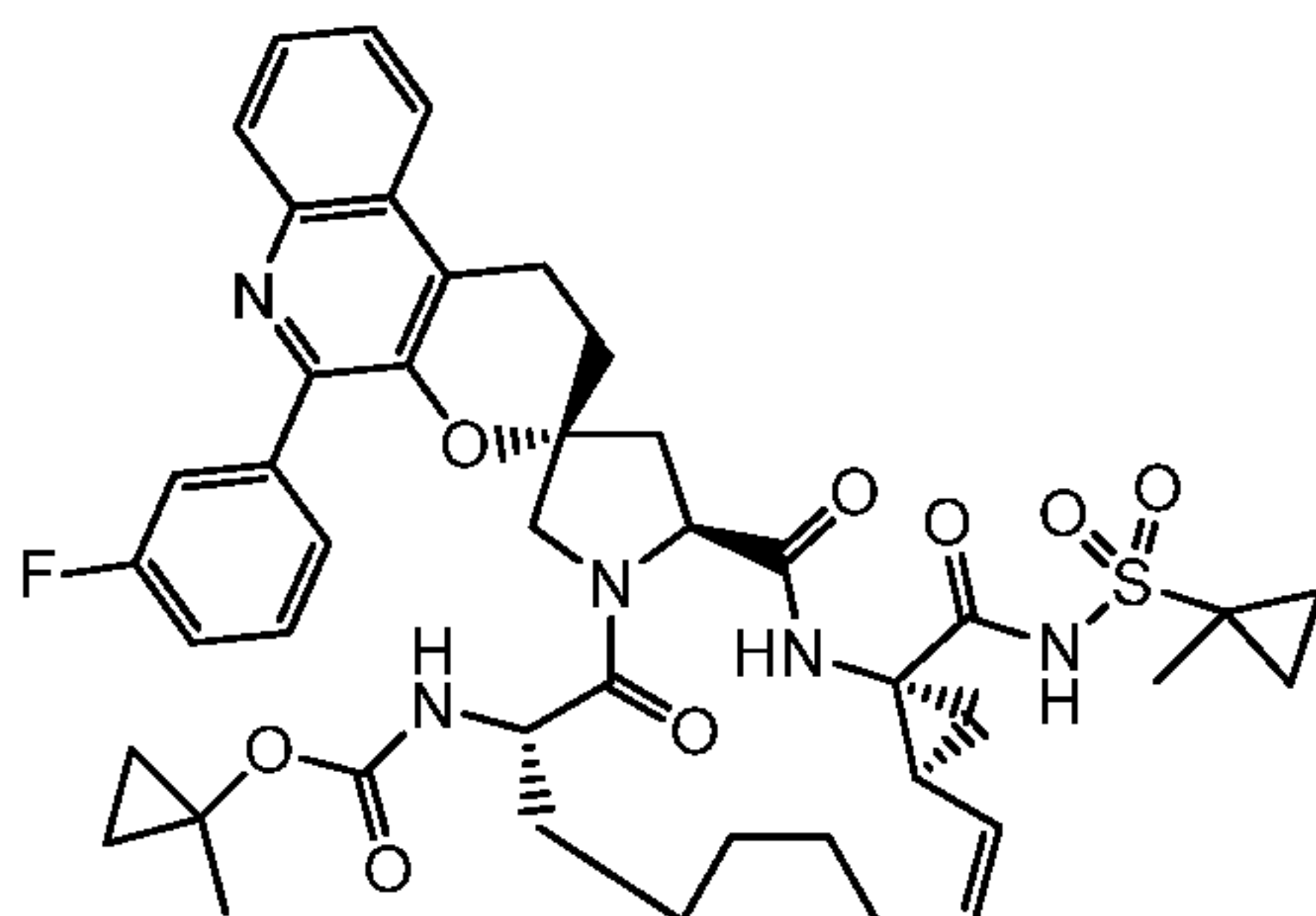
Step 1

To a flask containing I-13 (200 mg, 0.241 mmol) was added 4 ml of 4N HCl/dioxane solution and 1 ml of MeOH, and the mixture was stirred at RT for 2h. The solvent was co-evaporated 2x with toluene and 2x with ether to give 180 mg of the product of Step 1 as HCl salt. MS m/e = 730.2 (MH⁺).

Step 2

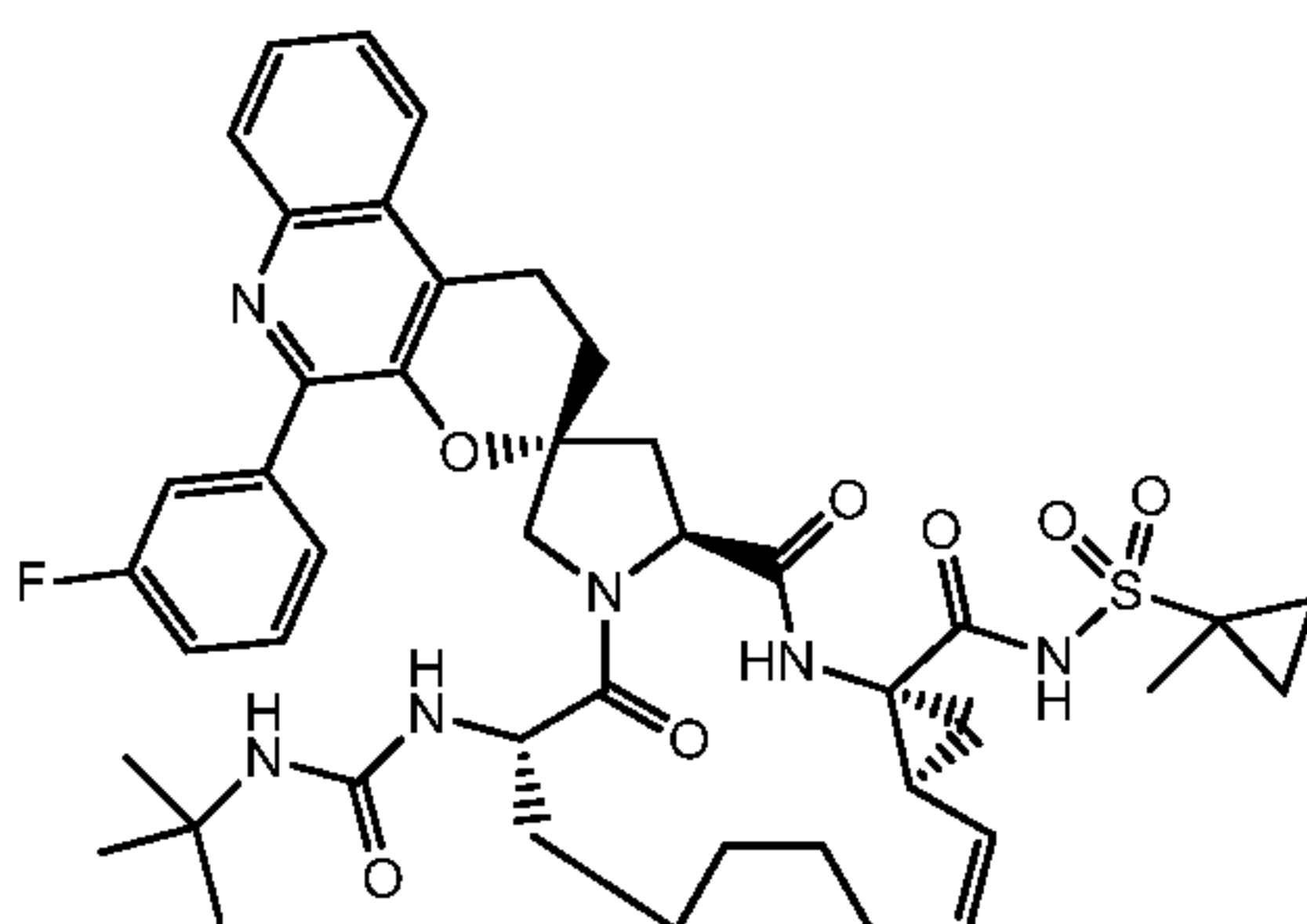
A mixture of the product of Step 1 (50 mg, 0.069 mmol), isobutyl chloroformate (0.018 ml, 0.137 mmol) and TEA (0.038 ml, 0.274 mmol) in DCM (1 ml) was stirred at RT for 2h then diluted with EtOAc. The solution was washed 2x with water, brine, dried over MgSO₄, filtered, concentrated and purified by preparative TLC eluting with 5% MeOH-DCM to give 28 mg of I-21. MS m/e = 830.4 (MH⁺).

15 **Example 22: 1-Methylcyclopropyl (2R,6S,13aS,14aR,16aS,Z)-5'-(3-fluorophenyl)-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-6-ylcarbamate (I-22)**



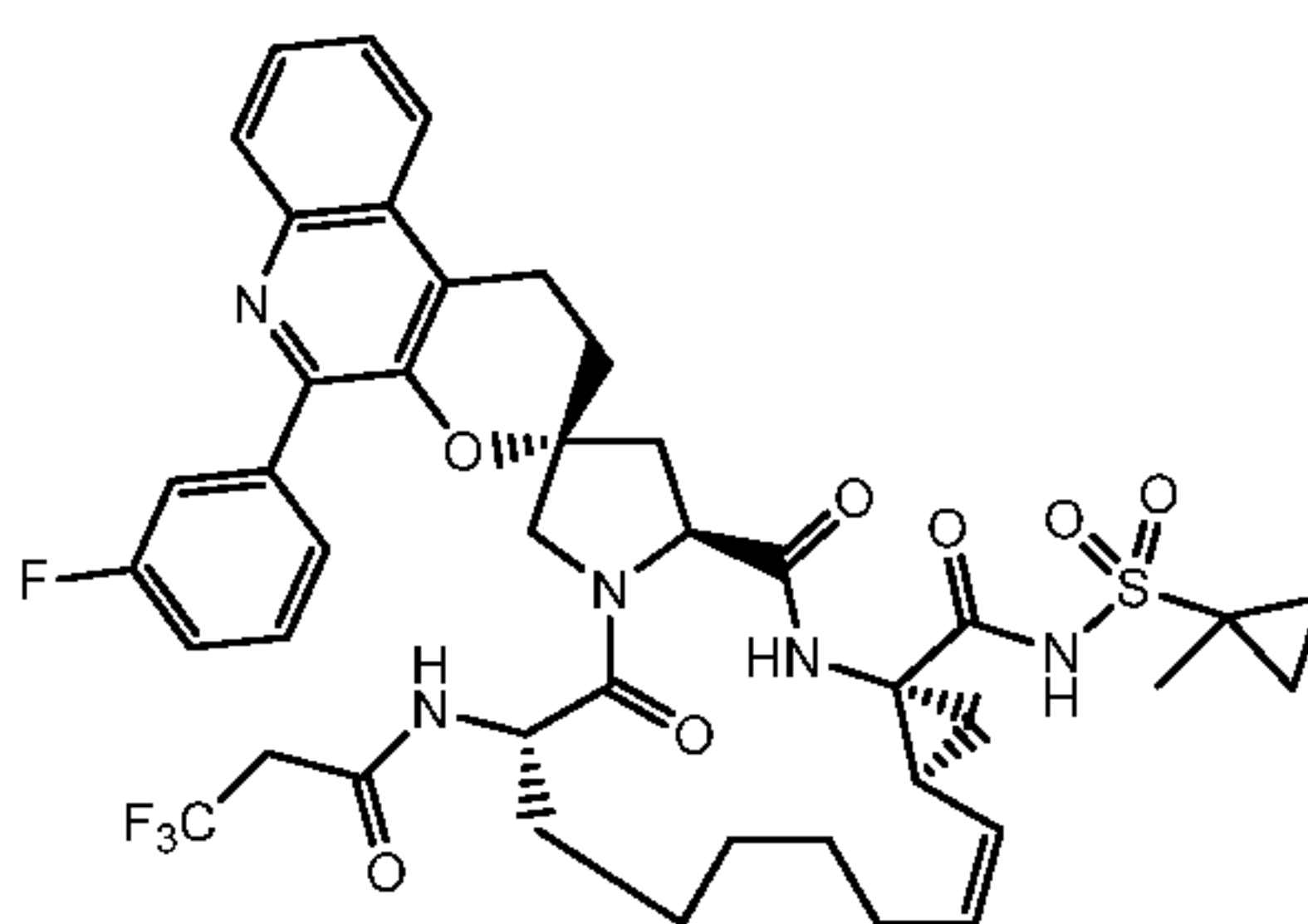
A mixture of the product of Example 21, Step 1 (20 mg, 0.026 mmol), 2,5-dioxopyrrolidin-1-yl 1-methylcyclopropyl carbonate (8.35 mg, 0.039 mmol) and Et₃N (10.91 μl, 0.078 mmol) in DCM (1 ml) was stirred at RT for 4h, then diluted with EtOAc. The solution was washed 2x with water, brine, concentrated and purified by preparative TLC eluting with 5% MeOH-DCM to give 15 mg of I-22. MS m/e = 828.4 (MH⁺).

Example 23: (2R,6S,13aS,14aR,16aS,Z)-6-(3-tert-Butylureido)-5'-(3-fluorophenyl)-N-(1-methylcyclopropylsulfonyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a-carboxamide (I-23)



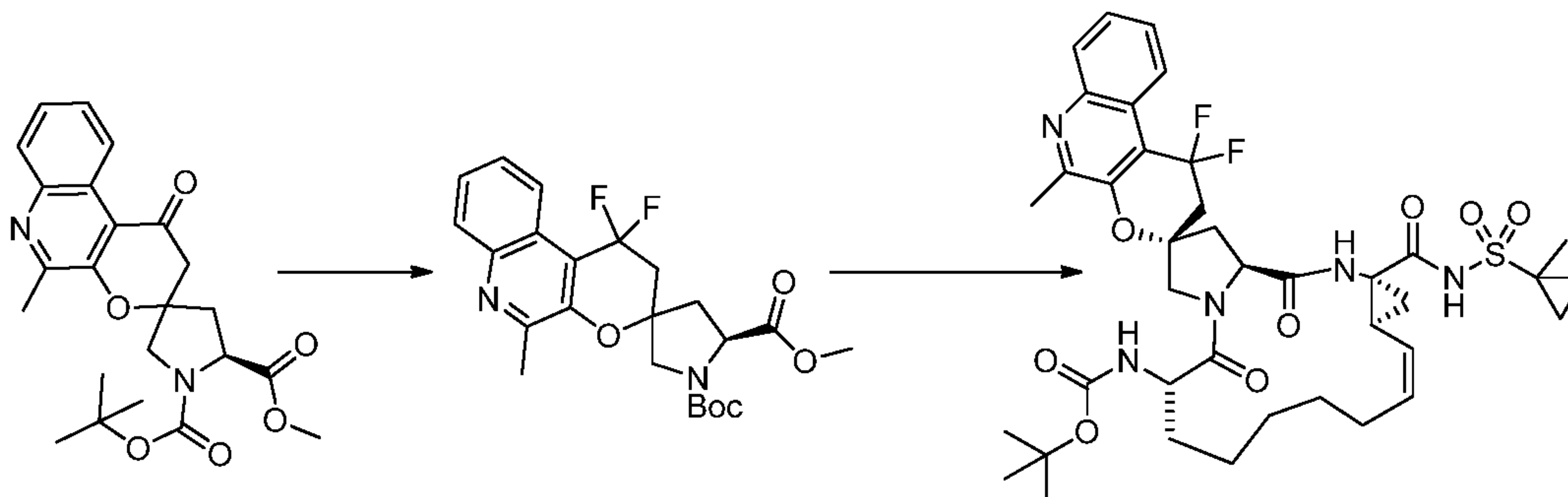
To a solution of the product of Example 21, Step 1 (32.2 mg, 0.042 mmol) in DCM (2 ml) at RT was added Et₃N (0.029 ml, 0.210 mmol) and *tert*-butyl isocyanate (12.49 mg, 0.126 mmol), and the mixture was stirred at RT for 3.5h. To the reaction mixture was added few drops of AcOH, then diluted with EtOAc. The solution was washed 3x with water, brine, dried over MgSO₄, filtered, concentrated and chromatographed with 100% hexanes to 5% MeOH-DCM to provide 34 mg of I-23. MS m/e = 829.4 (MH⁺).

Example 24: (2R,6S,13aS,14aR,16aS,Z)-5'-(3-Fluorophenyl)-N-(1-methylcyclopropyl sulfonyl)-5,16-dioxo-6-(3,3,3-trifluoropropanamido)-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a-carboxamide (I-24)



A mixture of the product of Example 21, Step 1 (20 mg, 0.026 mmol), 3,3,3-trifluoropropionyl chloride (5.38 μ l, 0.052 mmol) and Et₃N (10.91 μ l, 0.078 mmol) in DCM (1 ml) was stirred at RT for 4h. The solution was diluted with EtOAc, washed 2x with water, brine, concentrated and purified by preparative TLC eluting with 5% MeOH-DCM to give 8 mg of I-24. MS m/e = 840.2 (MH⁺).

Example 25: tert-Butyl (2S,6S,13aS,14aR,16aS,Z)-1',1'-difluoro-5'-methyl-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-6-ylcarbamate (I-25)

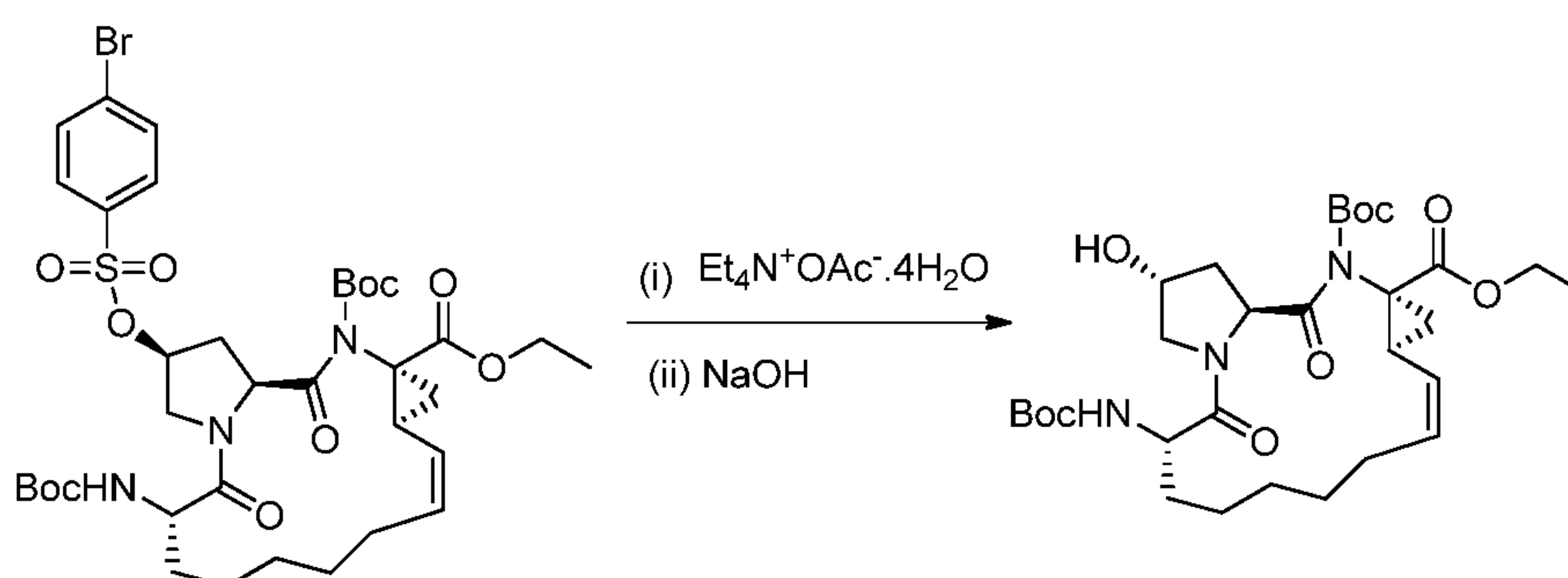


To 1'-*tert*-butyl 5'-methyl (5'*S*)-5-methyl-1-oxo-1,2-dihydro-1'*H*-spiro[pyrano[2,3-*c*]quinoline-3,3'-pyrrolidine]-1',5'-dicarboxylate (180 mg, 0.422 mmol) in DCM (3 ml) was treated with a solution of DEOXOFLUOR (0.233 ml, 1.266 mmol) (0.233 ml, 1.266 mmol) in DCM (1 ml) and EtOH (0.084 mmol, 4.9 μ L) and heated at 50°C. Another 1.8eq. of oxy-DAST and 0.2eq. of EtOH were added and stirred for further 5h. On completion, the solution was poured into saturated NaHCO₃ and after CO₂ evolution ceased, extracted with DCM and dried. The crude reaction mixture was purified by column chromatography with 50% hexanes/EtOAc to give the intermediate as a mixture of diastereomers (50 mg, 0.111 mmol, 26.4% yield). This intermediate was treated with conditions similar to Example 4 (steps 10-13) to give I-25. ¹H-NMR (400 MHz, CDCl₃) δ 10.11 (s, 1H), 8.21 (d, J = 6.66 Hz, 1H), 8.00-7.96 (m, 1H), 7.60-7.53

(m, 2H), 7.02 (br s, 1H), 5.73-5.67 (m, 1H), 5.02-4.98 (m, 1H), 4.91-4.89 (m, 1H), 4.69-4.64 (m, 1H), 4.57 (d, J = 11.0 Hz, 1H), 4.03-3.98 (m, 1H), 3.73 (d, J = 12.0 Hz, 1H), 2.90-0.80 (m, 36H). MS m/e = 786.4 (MH⁺).

5 **Example 26: *tert*-Butyl (2*S*,6*S*,13*aS*,14*aR*,16*aS*,*Z*)-14*a*-(cyclopropylsulfonylcarbamoyl)-5'-methyl-5,16-dioxo-3,5,6,7,8,9,10,11,13*a*,14,14*a*,15,16,16*a*-tetradecahydro-1*H*-spiro [cyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-*c*]quinoline]-6-ylcarbamate (I-26)**

Step 1

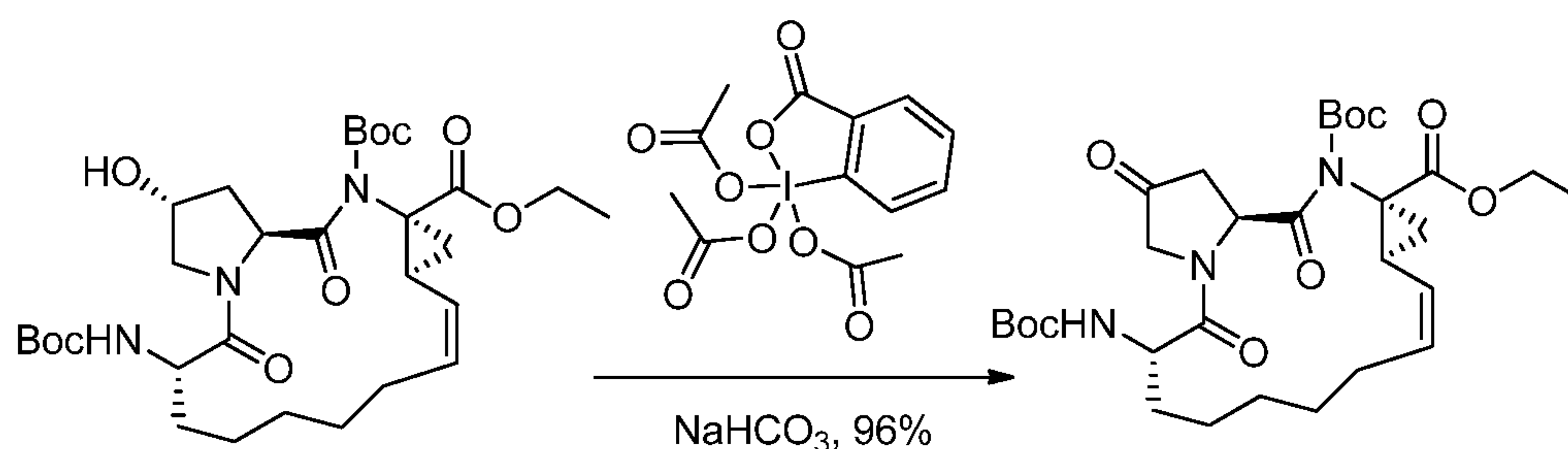


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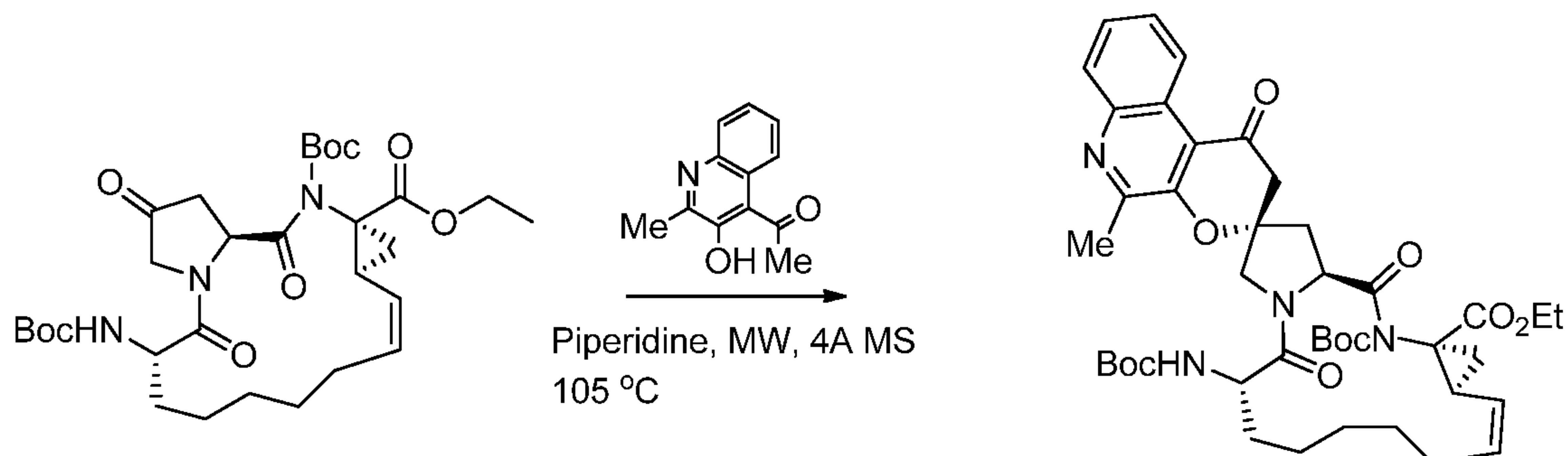
Tetraethylammonium acetate tetrahydrate (1.29 g, 4.92 mmol) was dissolved in benzene (20 ml) equipped with a Dean-Stark trap and heated to reflux overnight. A solution of 15-*tert*-butyl 14*a*-ethyl (2*S*,6*S*,12*Z*,13*aS*,14*aR*,16*aS*)-2-[[4-bromophenyl)sulfonyl]oxy}-6-[(*tert*-butoxycarbonyl)amino]-5,16-dioxo-2,3,6,7,8,9,10,11,13*a*,14,16,16*a*-dodecahydrocyclopropa[*e*] pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-14*a*,15(1*H*,5*H*)-dicarboxylate (2.0 g, 2.461 mmol) in benzene (20 ml) was added to the mixture of tetraethylammonium acetate solution, and the resulting solution was refluxed for 1.5h. The reaction mixture was cooled to the RT, and a solid was formed, which was filtered. The filtrate was evaporated to dryness, and the residue was taken up in MeOH (7 ml) and cooled to 0°C. 1N NaOH solution (6 ml) was slowly added to the mixture, and the resulting mixture was stirred at 0°C for 2h. The reaction mixture was neutralized with 2N HCl (aq.) and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, concentrated, purified by silica gel column chromatography using (0-75%) EtOAc-hexanes as mobile phase, and the product of Step 1 was isolated as white solid.

15

20

Step 2

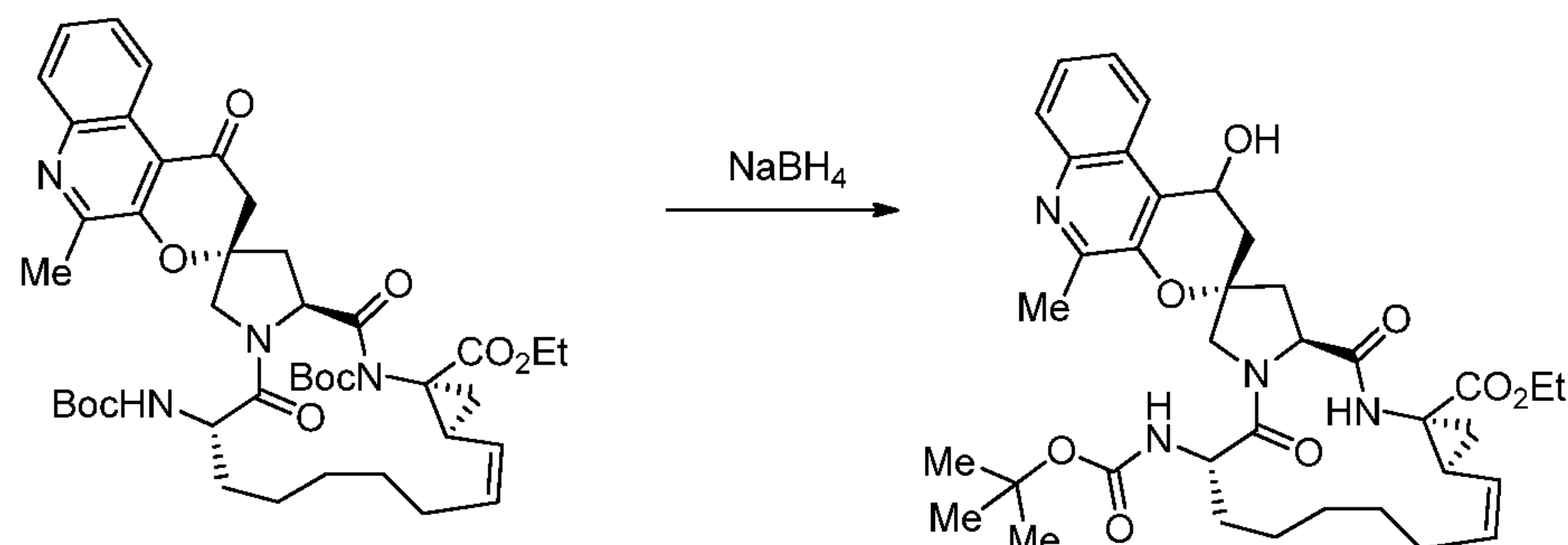
To a suspension of the product of Step 1 (0.76 g, 1.28 mmol) and NaHCO₃ (0.108 g, 1.28 mmol) in DCM (10 ml) at 0°C was added DMP (1.5eq., Aldrich) in one rapid portion. The resulting suspension was stirred for 1h at RT. LC-MS showed only starting alcohol. A second 1.5eq. of DMP (2.17 g, 5.12 mmol) was added at 0°C and left to stir at RT for 1.0h. LC-MS showed product formation. After 3.0h, LC-MS showed starting material to product in 3:2 ratio. To this was added more DMP (1eq.) and left stirring overnight at RT. The crude reaction mixture was then diluted with ether and quenched with 1N aq. NaOH. The aq. layer was then back extracted with ether. The combined organic layers were washed with 1N HCl, water, brine and dried with Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo* to afford the product of Step 2 (0.728 g, 96%) as white foam.

Step 3

The product of Step 2 (272 mg, 0.460 mmol), 2-methyl-3-hydroxy-4-acylquinoline (143 mg, 0.713 mmol) and piperidine (0.027 ml, 0.276 mmol) were combined in MeOH (4 ml) in a microwave vial. To this was then added molecular sieve (250 mg, 4A, powder), and the mixture was heated at 105°C for 30 min at high absorbance. The insoluble were removed *via* filtration, and the insolubles were rinsed further with ether. The combined organic extracts were then washed further with water, 1N aq. NaOH (x2), and brine, dried over Na₂SO₄, filtered and the filtrate concentrated *in vacuo*. Purification by way of column chromatography silica gel (ANALOGIX) using hexanes:EtOAc (2:1) afforded the product of Step 3

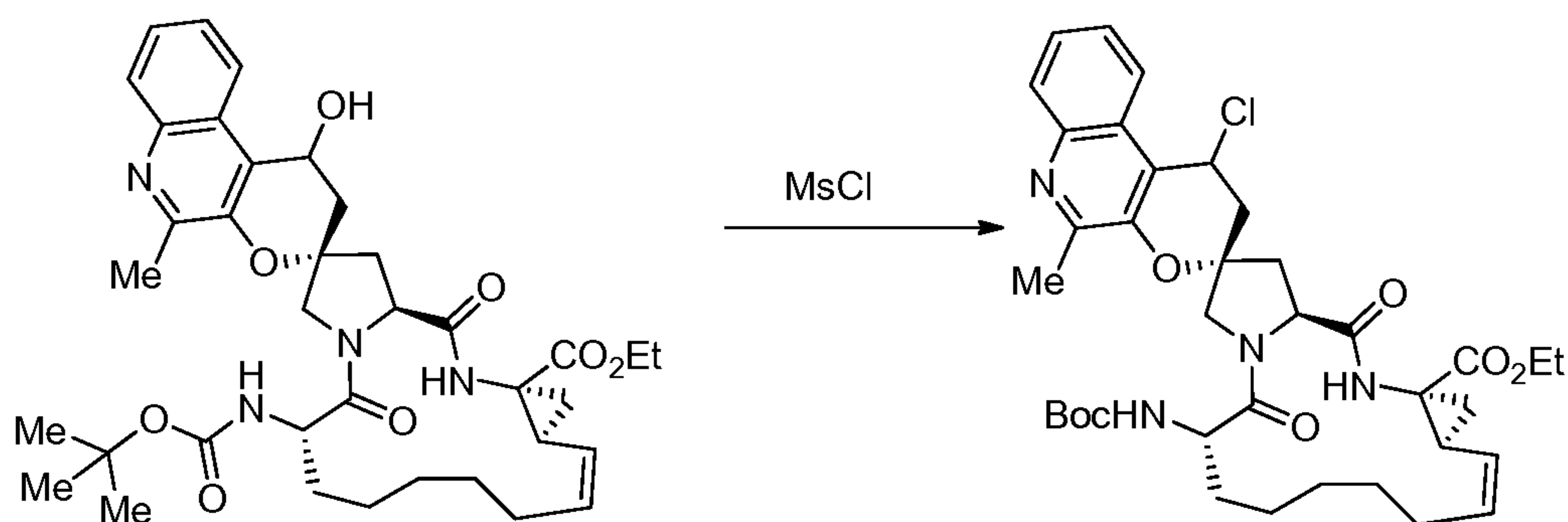
(52 mg, 0.067 mmol, 14.60% yield) was obtained. ^1H NMR indicated a 5:1 mixture of diastereomer with the product shown above being the major isomer.

Step 4



5 To solution of the major product of Step 3 (50 mg, 0.065 mmol) in MeOH (4 ml) was added NaBH_4 (4.88 mg, 0.129 mmol) in one rapid portion. The resulting mixture was then stirred at RT for 1.5h. The volatiles were then removed, and the resulting mixture was partitioned between EtOAc and 1N aq. NaOH. The organic layer was separated and washed further with 10% aq. HCl, 1 N aq. NaOH, water and brine. This was dried over Na_2SO_4 , filtered,
10 and the filtrate concentrated *in vacuo* to furnish the product of Step 4 (0.05 g, 100%).

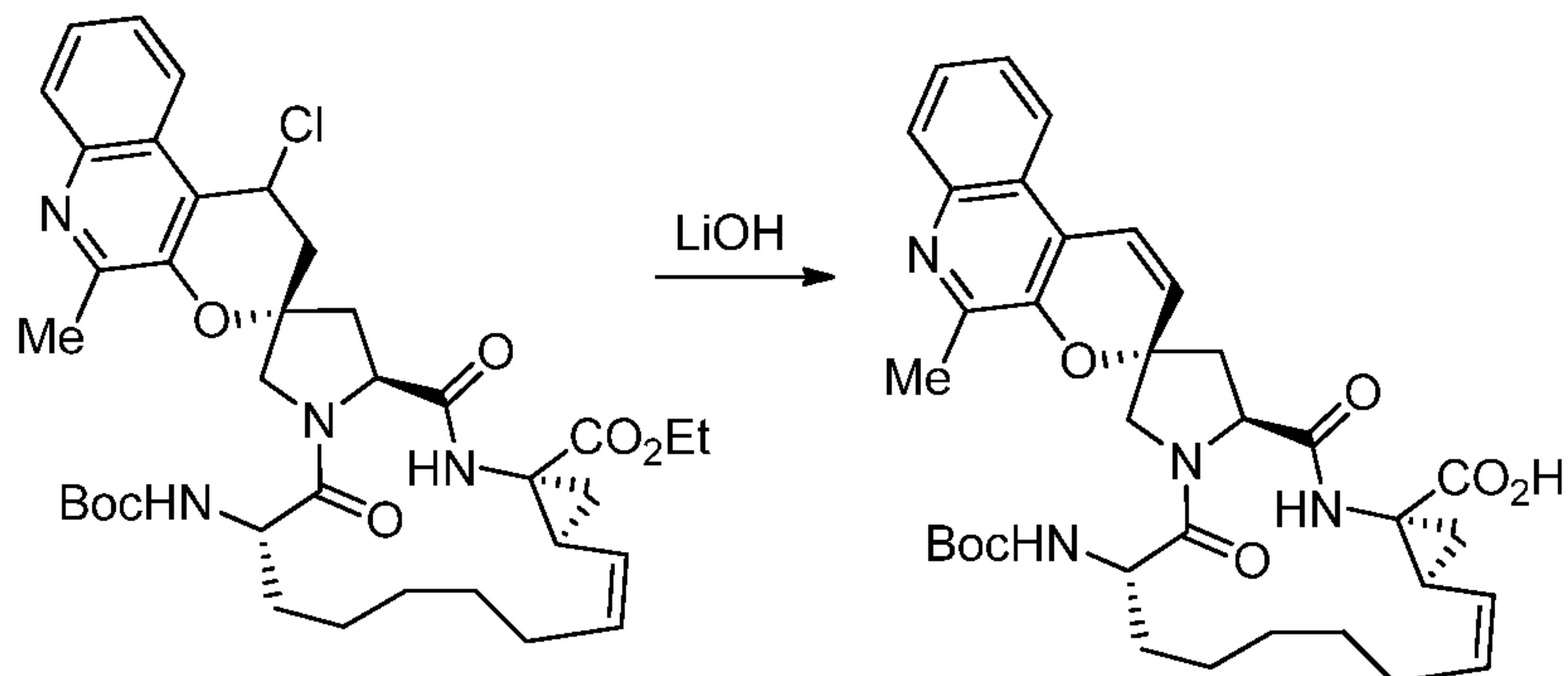
Step 5



To the product of Step 4 (140 mg, 0.180 mmol) in CH_2Cl_2 (4 ml) was added Hunig's base (0.094 ml, 0.541 mmol). MsCl (0.021 ml, 0.270 mmol) was then added dropwise to
15 the reaction mixture. This was then stirred at RT overnight. A small aliquot was withdrawn and analyzed by LC-MS showed formation of the desired product but also the unreacted alcohol. Consequently, another 0.04 mL of MsCl and 0.2 mL of Hunig's base were added, and the mixture was stirred for another 6h. LC-MS of the resulting red solution revealed no more alcohol. Consequently, the volatiles were removed *in vacuo*, and the residue was partitioned between
20 ether and water. The aq. layer was separated and back-extracted with ether. The combined organic extracts were washed further with 1N aq. NaOH, water and brine, dried over Na_2SO_4 , filtered, and the filtrate was concentrated *in vacuo* to afford viscous oil. Purification by way of

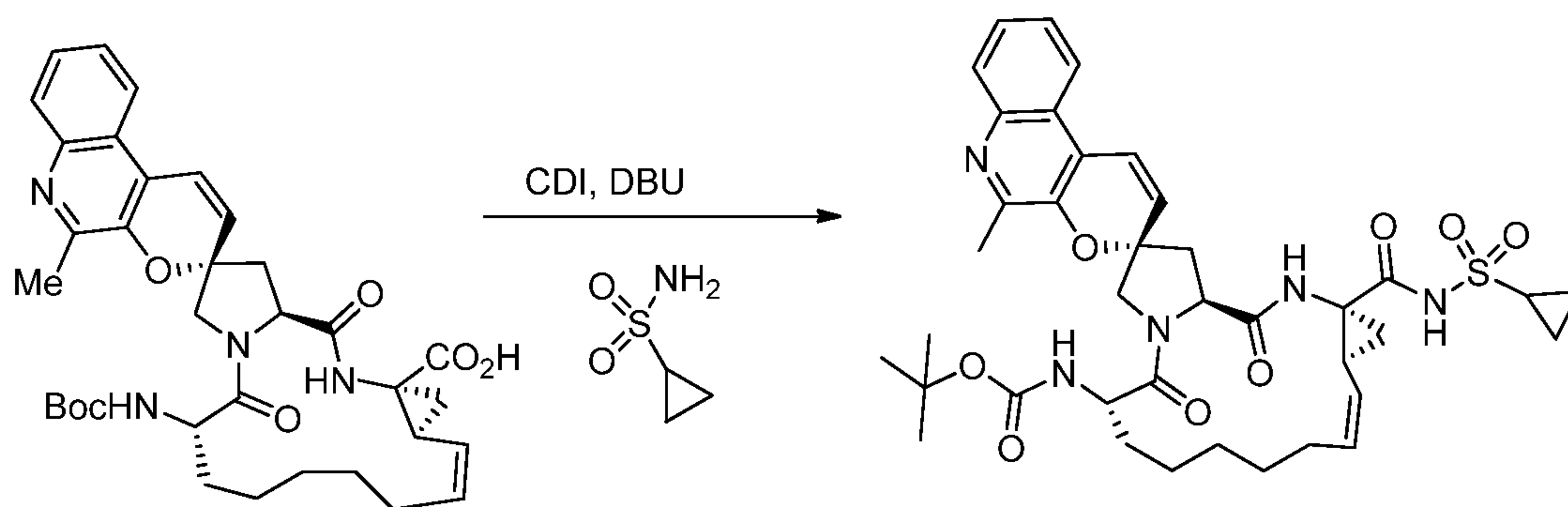
column chromatography (RS-24, 9:1 Hexanes:EtOAc, 2 min to 25 min → 7:3 EtOAc:Hexanes, 5 min) afforded the desired product (105 mg, 0.132 mmol, 73.3% yield) as white foam.

Step 6



5 To a solution of the product of Step 5 (70 mg, 0.101 mmol) in THF (2 ml) and MeOH (1 ml) was added LiOH (0.252 ml, 0.503 mmol). The resulting solution was stirred at RT for 15h. The volatiles were removed *in vacuo*, and the resulting residue was quenched with 0.45 mL of 1N aq. HCl and diluted with EtOAc and water. The aq. layer was separated and back-extracted with EtOAc. The combined organic extracts were then washed further with water and
10 brine, dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo* to furnish crude product (57 mg, 0.090 mmol, 90% yield).

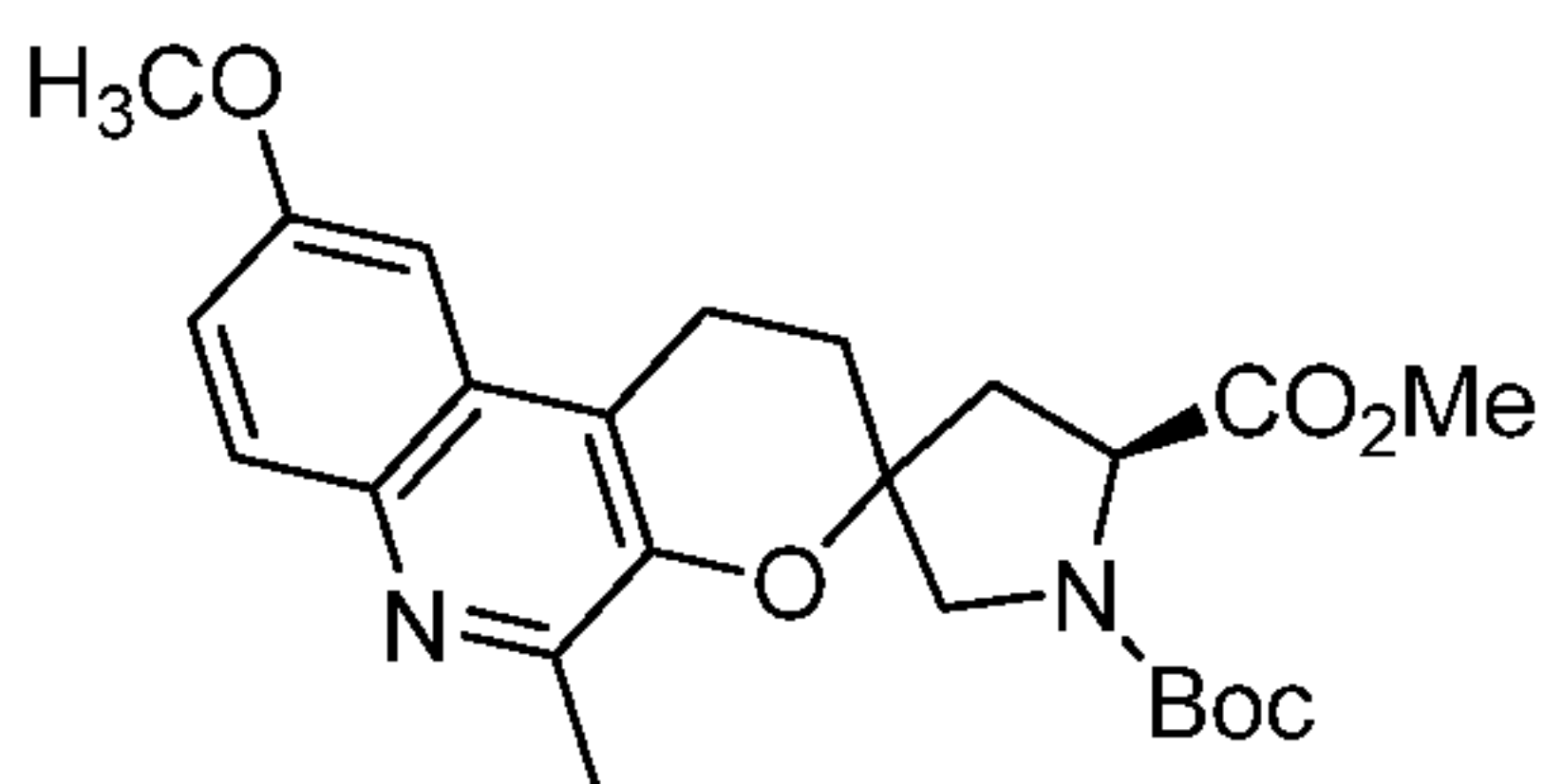
Step 7



15 The product of Step 6 (57 mg, 0.090 mmol) was dissolved in THF (1.5 ml) in a sealed tube. To the reaction mixture was added CDI (29.3 mg, 0.181 mmol), and the reaction was heated to 55°C for 4h. Then, to this was added cyclopropyl sulfonamide (43.8 mg, 0.361 mmol), and then DBU (0.054 ml, 0.361 mmol). The reaction was resealed, stirred, and heated to 55°C for overnight. The reaction was quenched with NH₄Cl and extracted twice with DCM. A preparative TLC purification with 10% MeOH/DCM gave I-26 (49 mg, 0.067 mmol, 73.9%
20 yield). MS m/e = 734.3 (MH⁺).

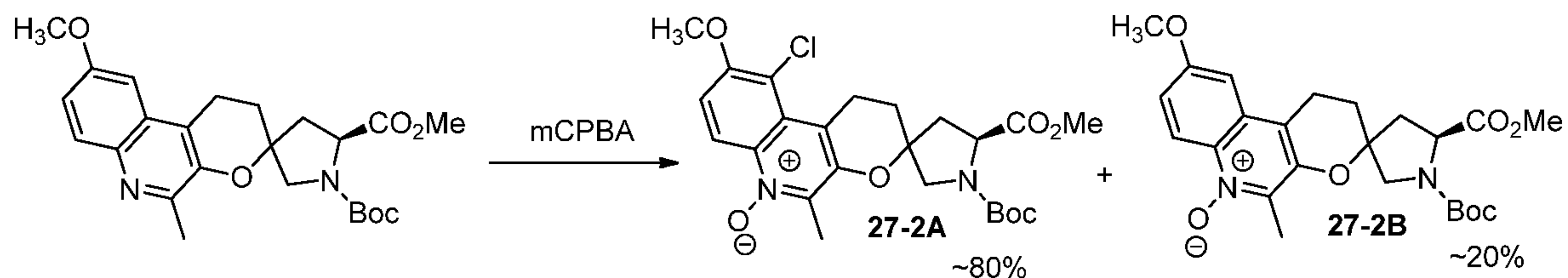
Example 27: *tert*-Butyl (2R,6S,13aS,14aR,16aS,Z)-10'-chloro-5'-(difluoromethyl)-9'-methoxy-14a-(1-methylcyclopropylsulfonylcarbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-6-ylcarbamate (I-27)

5 Step 1



Procedure for the synthesis of the product of Step 1 is the same as the procedure for the synthesis of the products of Example 9, Step 4.

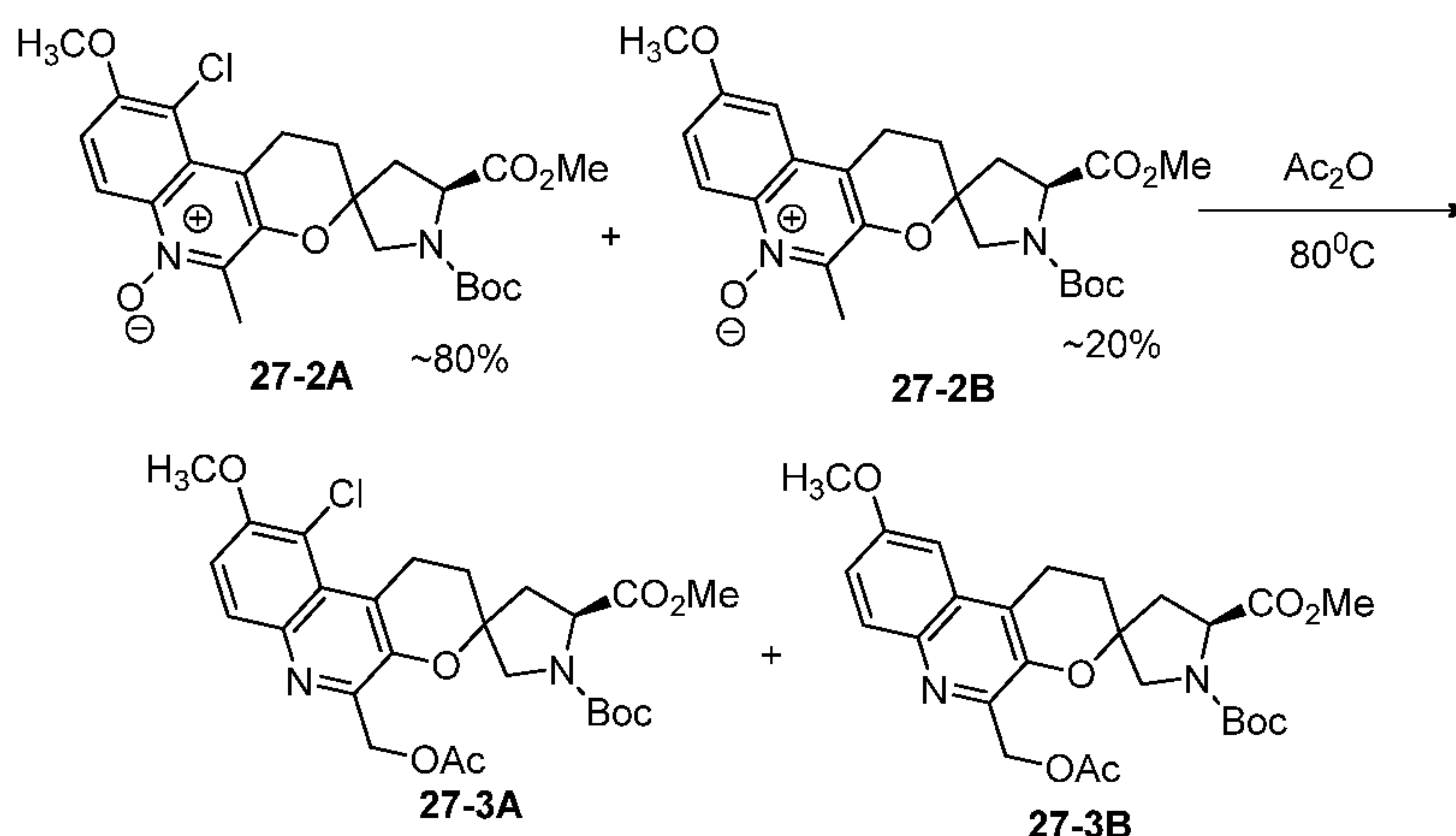
Step 2



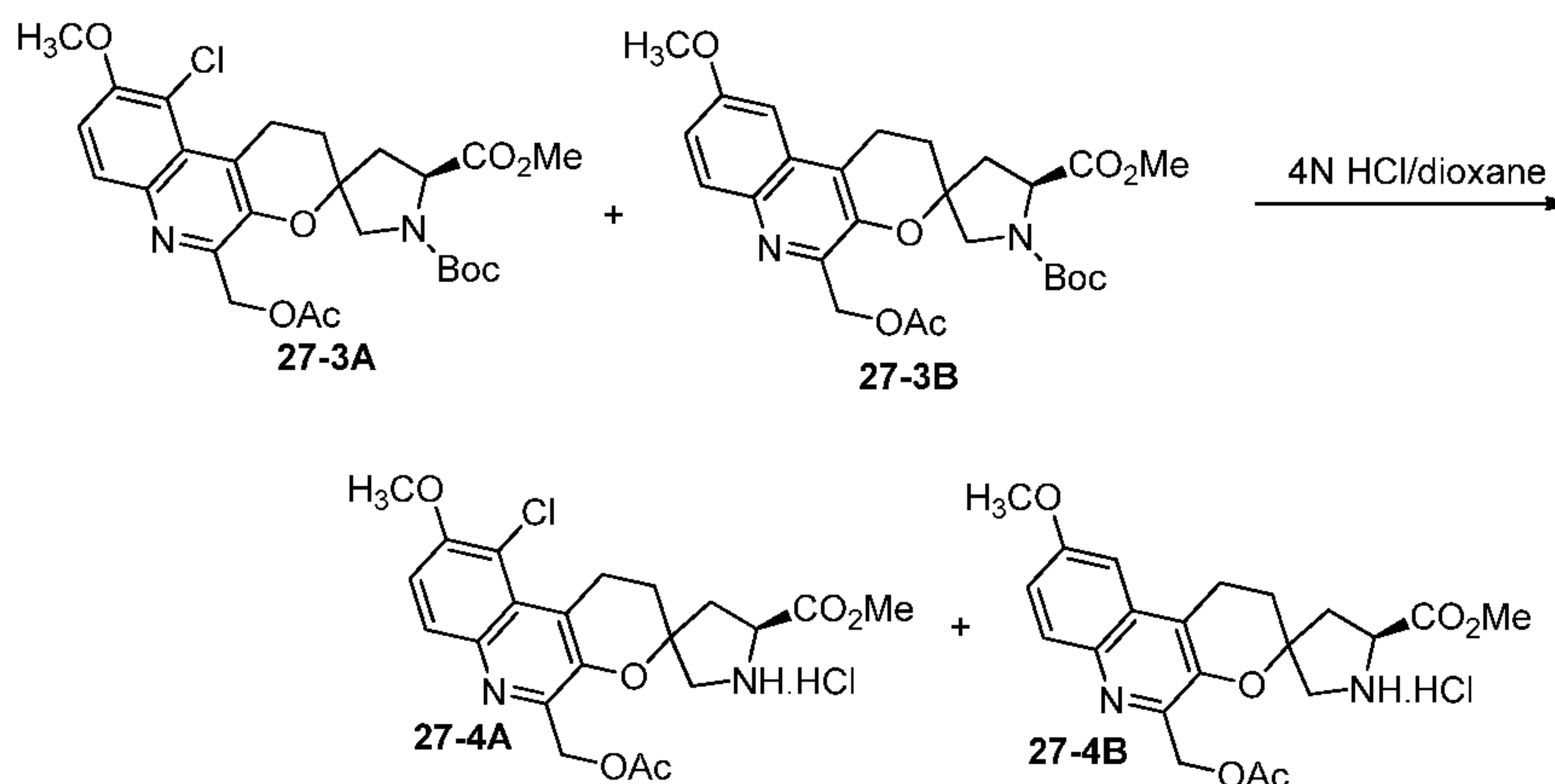
10

The product of Step 1 (0.68 g, 1.537 mmol) was dissolved in chloroform (25 ml) and cooled to 0°C. MCPBA (0.69 g, 3.07 mmol) was added to the mixture, and the resulting mixture was stirred at RT for ~6h. EtOAc (~25 ml) was added, and the mixture was washed with aq. NaHCO₃ (sat.), dried over anhydrous MgSO₄, filtered, and the solvent was evaporated under reduced pressure to give product, which was a mixture of compound 27-2A (~80% by LC-MS) and compound 27-2B (~20% by LC-MS), (0.67 g, 1.368 mmol, 89% yield), and was carried forward.

15

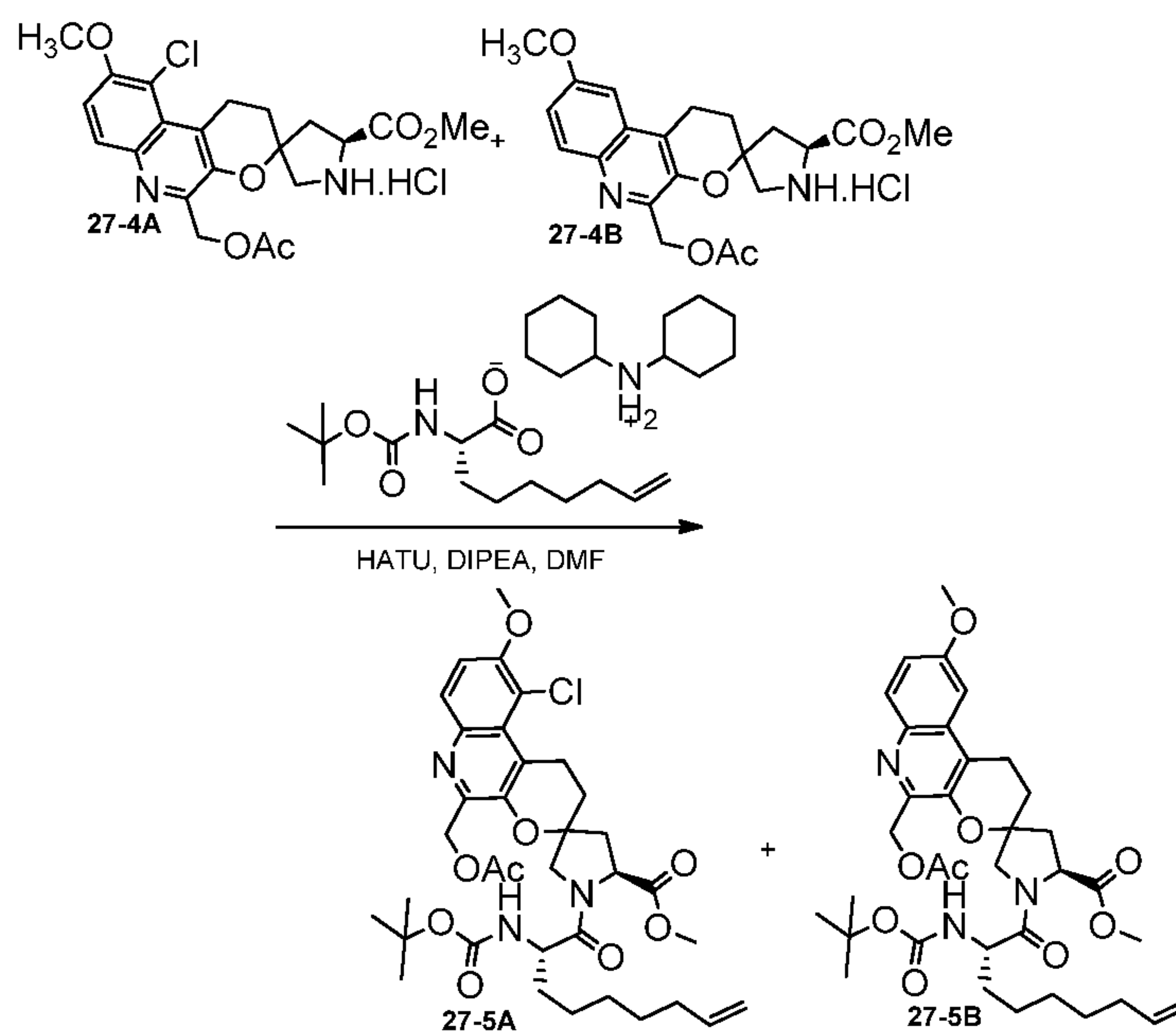
Step 3

The mixture of intermediates 27-2A and 27-2B (0.62 g, 1.258 mmol) was dissolved in acetic anhydride (11.87 ml, 126 mmol) and heated at 80°C for 2h. The reaction mixture was concentrated to remove acetic anhydride. The residue was dissolved in EtOAc, washed with aq. NaHCO₃ (sat.), dried over anhydrous MgSO₄, filtered, concentrated and purified by silica gel column chromatography eluting with (0-80)% EtOAc-DCM, and the product, a mixture of compounds 27-3A and 27-3B, was isolated as yellow oil (0.33 g, 0.62 mmol, 49%).

Step 4

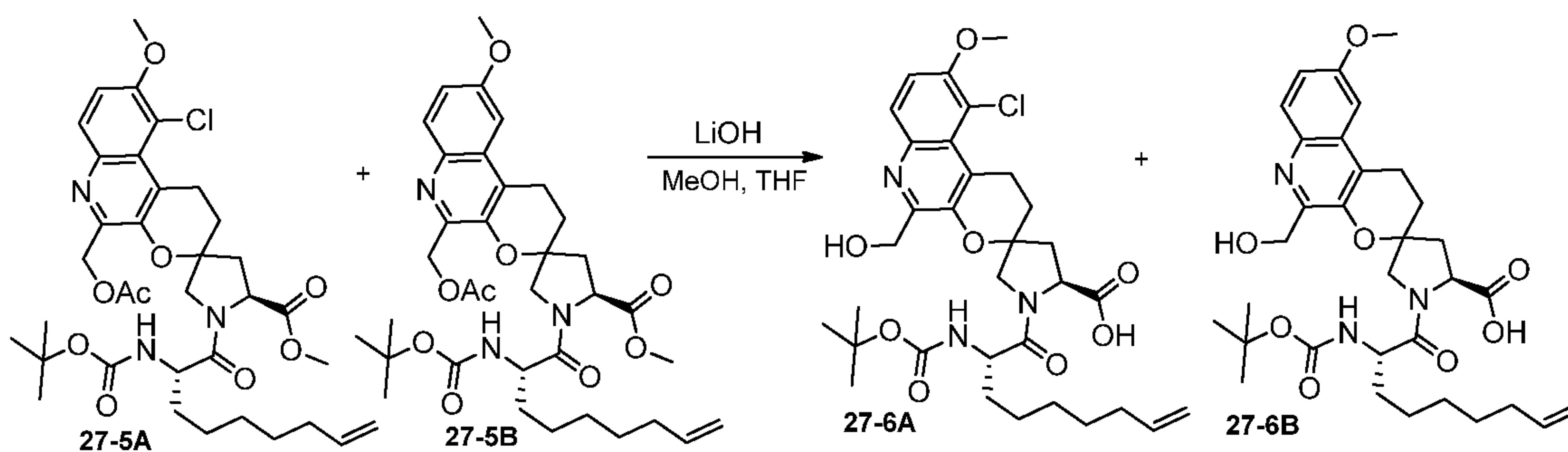
10

A solution of intermediates 27-3A and 27-3B (0.31 g, 0.619 mmol) in 4N HCl in dioxane (10 ml) was stirred at RT for 1h. The reaction mixture was evaporated to dryness to remove excess acid, co-evaporated with toluene (2x) then with Et₂O (2x) to give the product (0.26 g, 0.619 mmol, 96% yield), a mixture of compounds 27-4A and 27-4B, and used as such.

Step 5

To a DMF (7 ml) solution of compounds 27-4A and 27-4B (0.25 g, 0.53 mmol), HATU (0.30 g, 0.53 mmol) and (*S*)-2-(*tert*-butoxycarbonylamino)non-8-enoic acid (0.36 g, 0.79 mmol) was added DIPEA (0.28 ml, 1.59 mmol) at RT, and the resulting yellow solution was stirred at RT overnight.

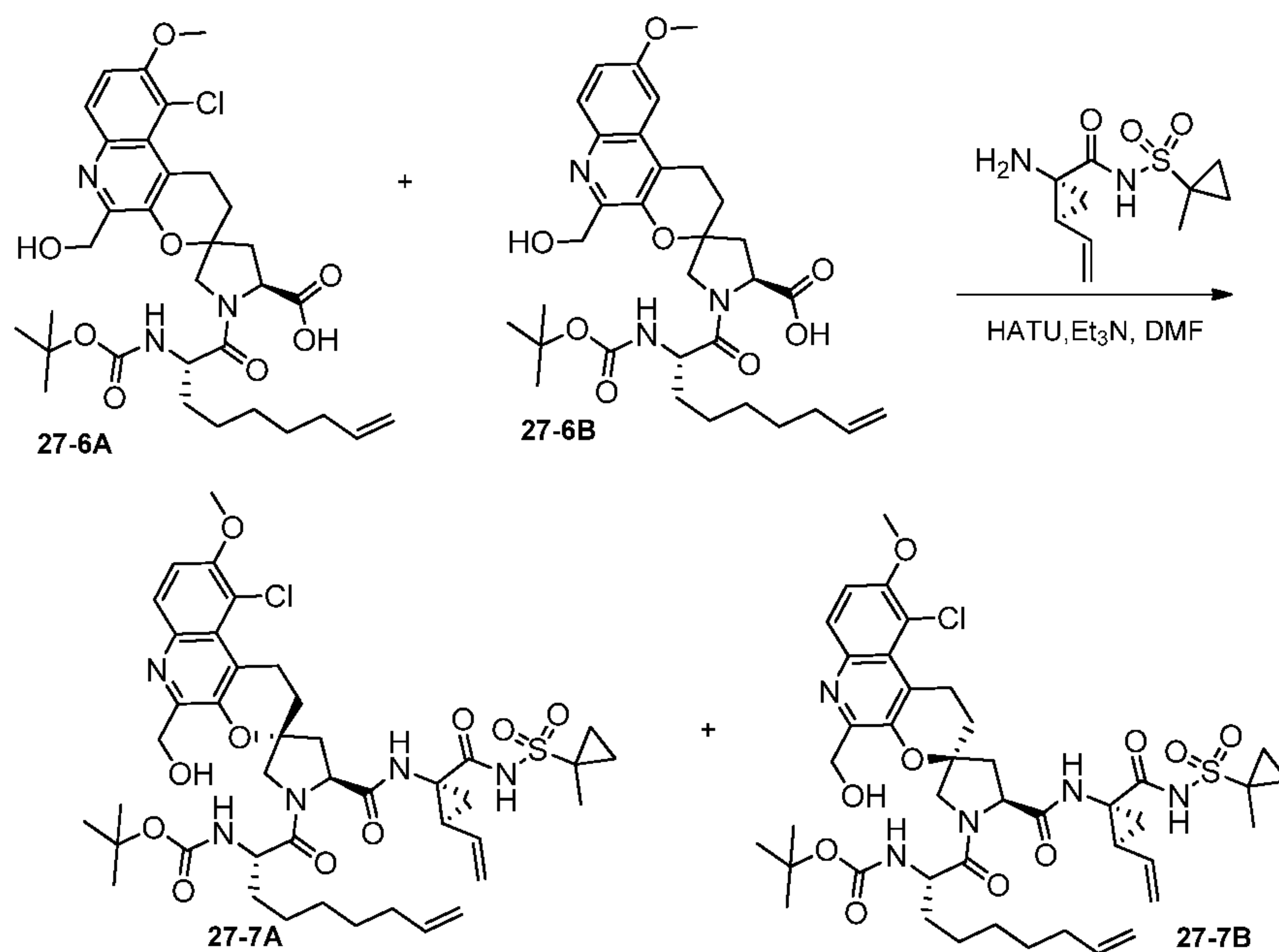
LC-MS of the crude reaction mixture showed complete consumption of starting material. The mixture was cooled, diluted with Et₂O, washed with water (2x), dried over anhydrous MgSO₄, filtered, and the solvent was evaporated under reduced pressure. The crude yellow oil was purified by column chromatography using a silica gel (RS-40) column on an ANALOGIX, eluting with (0-40)% EtOAc-DCM, and the product compounds 27-5A and 27-5B, (0.21 g, 0.31 mmol, 57.5%) was obtained as mixture.

Step 6

Intermediates 27-5A and 27-5B (0.21 g, 0.31 mmol) were dissolved in THF (2.5 ml)/MeOH (2.5 ml), LiOH (2 m aq. solution, 0.763 ml, 1.526 mmol) was added to the mixture,

and the mixture was heated at 60°C for 1h. LC-MS showed complete conversion of starting materials. 1 M HCl (aq.) (0.320 ml) was added to the reaction mixture, and the reaction mixture was diluted with water (20 ml). The mixture was extracted with EtOAc (2x). The combined organic fractions were dried over anhydrous MgSO₄, filtered, and the solvent was evaporated under reduced pressure. The dried mass was co-evaporated with toluene and then with Et₂O to give the product (0.173 g, 0.27 mmol, 90%), mixture of compounds 27-6A and 27-6B.

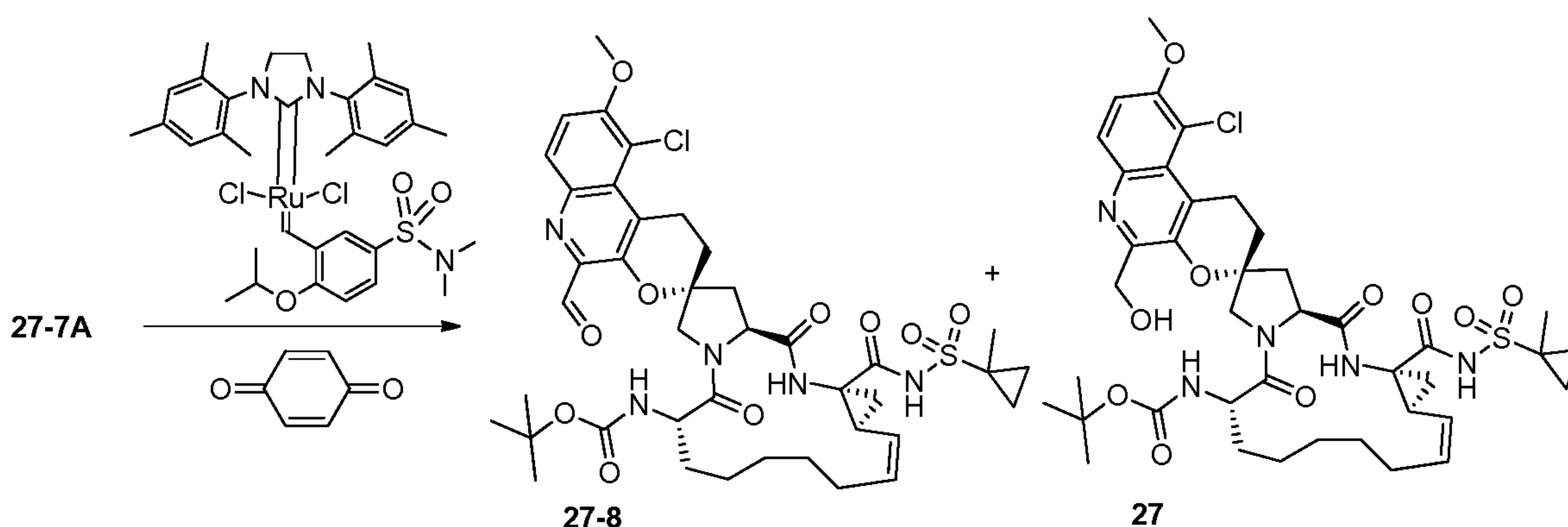
Step 7



To a stirred solution of mixtures of intermediates 27-6A and 27-6B (0.173 g, 0.27 mmol), HATU (0.17 g, 0.41 mmol) and (1R,2S)-1-amino-N-(1-methylcyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide (0.10 g, 0.41 mmol) in DMF (5 ml) was added TEA (0.11 ml, 0.82 mmol) at RT. The resulting mixture was stirred at RT overnight.

LC-MS of the crude reaction mixture showed complete consumption of starting material. The mixture was diluted with Et₂O, washed with water (2x), and the aq. layer was back extracted with Et₂O. The combined organics were dried over anhydrous MgSO₄, filtered, and the solvent was evaporated under reduced pressure. The crude yellow oil was purified by preparative TLC using 40% Acetone-60% Hexanes as mobile phase and the products, compound 27-7A (0.08 g, 0.09 mmol, 34.1%) and compound 27-7B (0.06 g, 0.07 mmol, 25.5%) were isolated. Both isomers of des chloro compounds were not isolated as they were minor products and very little in amount.

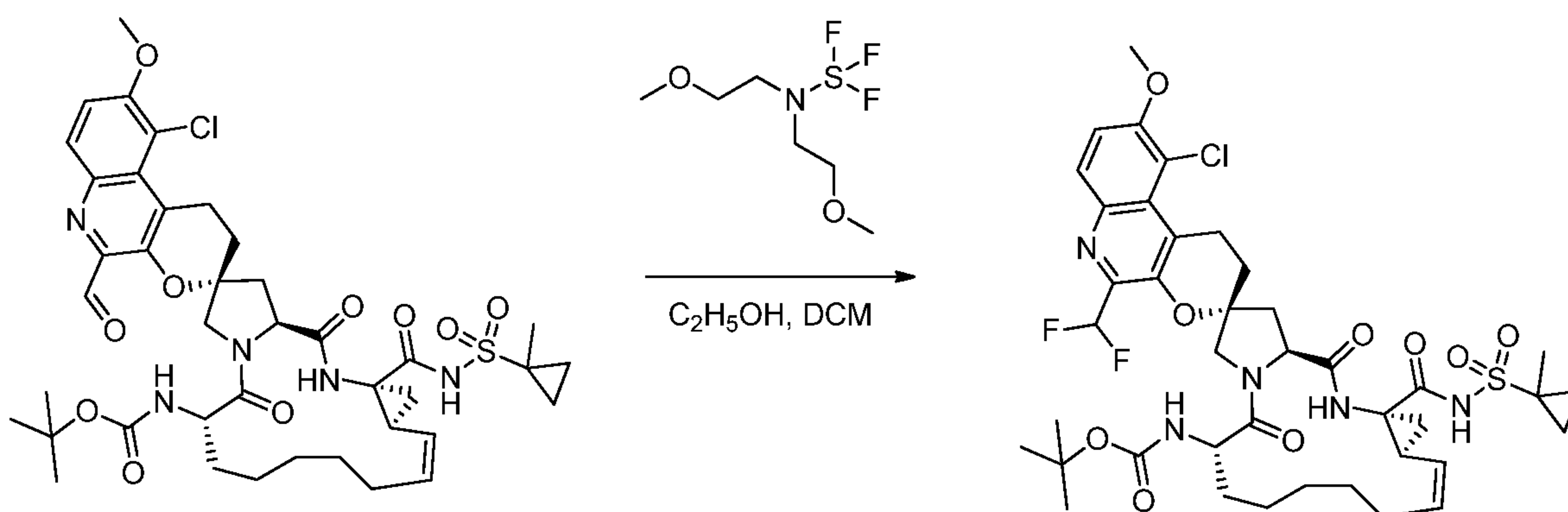
Step 8



Compound 27-7A (0.08 g, 0.09 mmol), Zhan's catalyst (0.017 g, 0.023 mmol), and p-benzoquinone (3.02 mg, 0.028 mmol) were added to a stirred, RT solution of DCE (47 ml). A condenser was added, and the reaction was heated to 65°C for 3h. The crude reaction mixture was cooled to RT and quenched with the addition of butyl vinyl ether (0.5 ml). The volatiles were then removed *in vacuo*, and the resulting dark green/brown residue was directly subjected to purification by way of preparative TLC using 40% Acetone-Hexanes as mobile phase to afford the product as white solid. The product was a mixture of two compounds, which was further purified using silica gel column chromatography (RS 12 g) using (0-75)% EtOAc-DCM as mobile phase and the products, 27-8A (0.01 g, 0.012 mmol, 12.95%) and the compound of I-27 (0.01 g, 0.012 mmol, 12.92%, $M+H^+ = 831$) were isolated. 1H -NMR (400 MHz, $CDCl_3$) δ ppm 10.12 (s, 1H), 7.98-7.92 (m, 1H), 7.36 (t, 1H, 9.6 Hz), 6.99 (s, 1H), 5.75-5.69 (m, 1H), 5.05-4.95 (m, 2H), 4.75-4.60 (m, 3H) 4.48-4.38 (m, 2H), 2.38-2.30 (m, 2H), 2.24-2.11 (m, 2H), Exact mass calculated for $C_{40}H_{52}ClN_5O_{10}S = 829.31$, LC-MS $(M+H)^+ = 830.6$.

15

Example 28: *tert*-Butyl [(2*R*,6*S*,12*Z*,13*aS*,14*aR*,16*aS*)-10'-chloro-5'-(difluoromethyl)-9'-methoxy-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13*a*,14,14*a*,15,16,16*a*-hexadecahydrospiro[cyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-*c*]quinolin]-6-yl]carbamate (I-28)



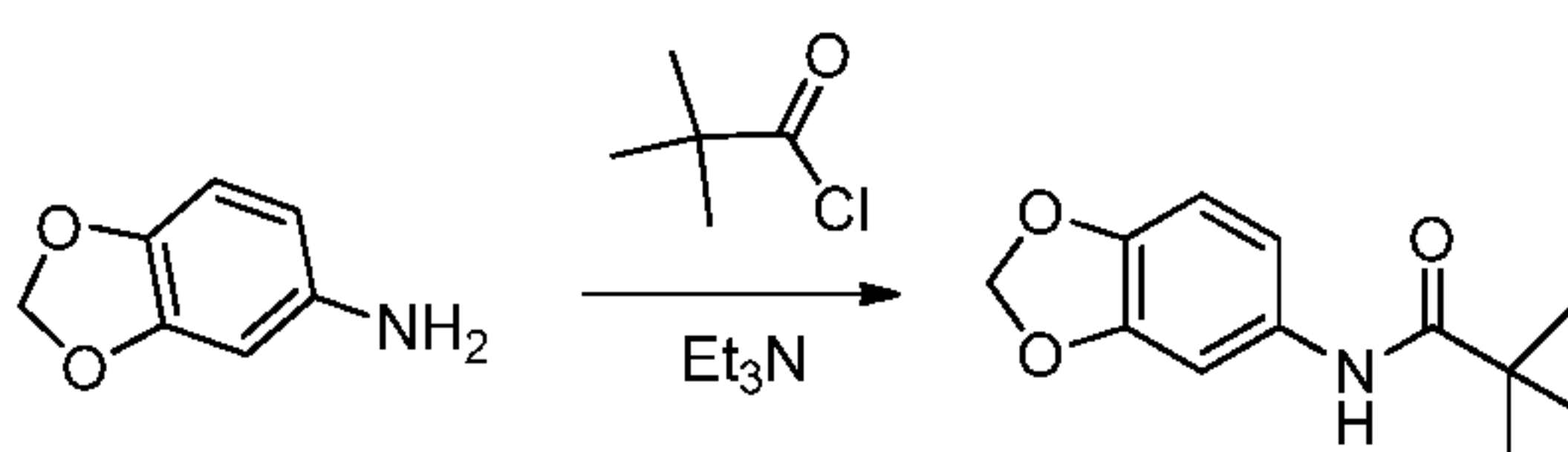
A solution of intermediate 27-8A (Example 27, Step 8; 0.01 g, 0.012 mmol) in CH_2Cl_2 (1 ml) was treated with a solution of DEOXOFLUOR (4.45 μl , 0.024 mmol) in CH_2Cl_2 (0.25 ml) at RT and stirred for 2h. LC-MS showed 19% of product and 74% of starting material.

5 Another 5eq. of DEOXOFLUOR and 0.2eq. of EtOH were added and stirred for 30 min at RT. LC-MS showed increase in product peak. The reaction mixture was stirred at RT overnight. Sat. NaHCO_3 solution (aq.) was added to the mixture and, after CO_2 evolution ceased, extracted with DCM and combined organic layers were dried over anhydrous Na_2SO_4 . The product was purified by preparative TLC using 45% EtOAc - 55% DCM as mobile phase and the product, I-

10 28 (0.002 g, 0.002 mmol, 16.6%) was isolated. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ ppm 10.1 (s, 1H), 8.07 (d, $J = 9.2$ Hz, 2H), 7.40 (d, 1H, 9.6 Hz), 7.03-6.76 (m, 2H), 5.76-5.69 (m, 1H), 4.66-4.61 (m, 1H), 4.48 (d, $J = 12.4$ Hz, 1H), 4.05 (s, 1H), 2.60-2.55 (m, 2H), 2.45-2.21 (m, 4H). Exact mass calculated for $\text{C}_{40}\text{H}_{50}\text{ClF}_2\text{N}_5\text{O}_9\text{S} = 849.3$, LC-MS $(\text{M}+\text{H})^+ = 850.2$.

15 **Example 29: *tert*-butyl (2'R,6'S,13a'S,14a'R,16a'S,Z)-7-cyclopropyl-14a'-(1-methylcyclopropylsulfonylcarbamoyl)-5',16'-dioxo-3',5',6',7',8',9',10,10',11,11',13a',14',14a',15',16',16a'-hexadecahydro-1'H-spiro[[1,3]dioxolo[4,5-f]pyrano[2,3-c]quinoline-9,2'-cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine]-6'-ylcarbamate (I-29)**

Step 1

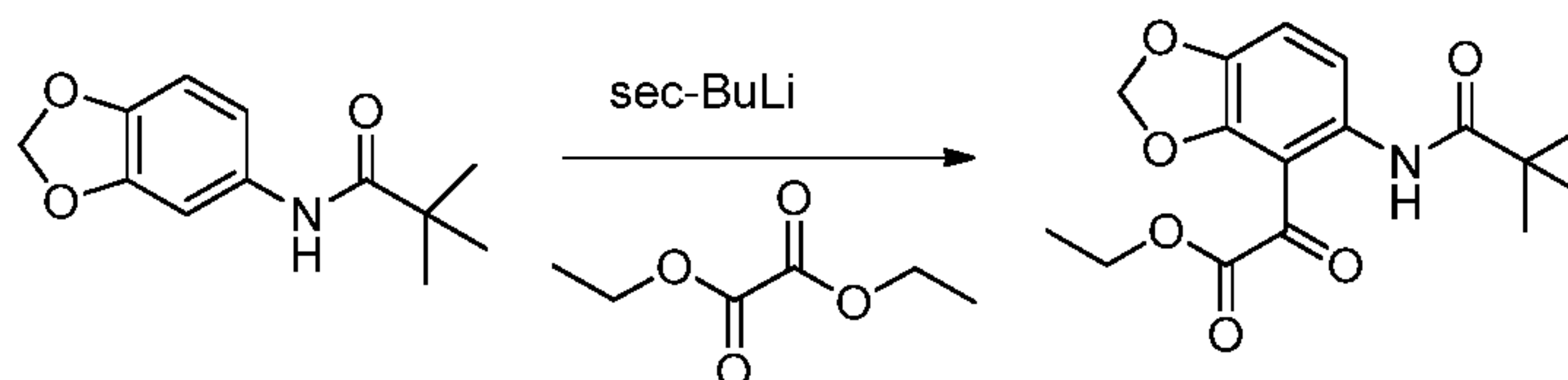


20

To a solution of 3,4-(methylenedioxy)aniline (16.24 g, 118 mmol) in DCM (180 ml) at 0°C was added TEA (24.8 ml, 178 mmol) followed by pivaloyl chloride (14.6 ml, 118 mmol), and the mixture was allowed to warm to RT and stirred overnight. The mixture was quenched at RT with sat. aq. NH_4Cl and extracted with DCM. The combined organic fractions

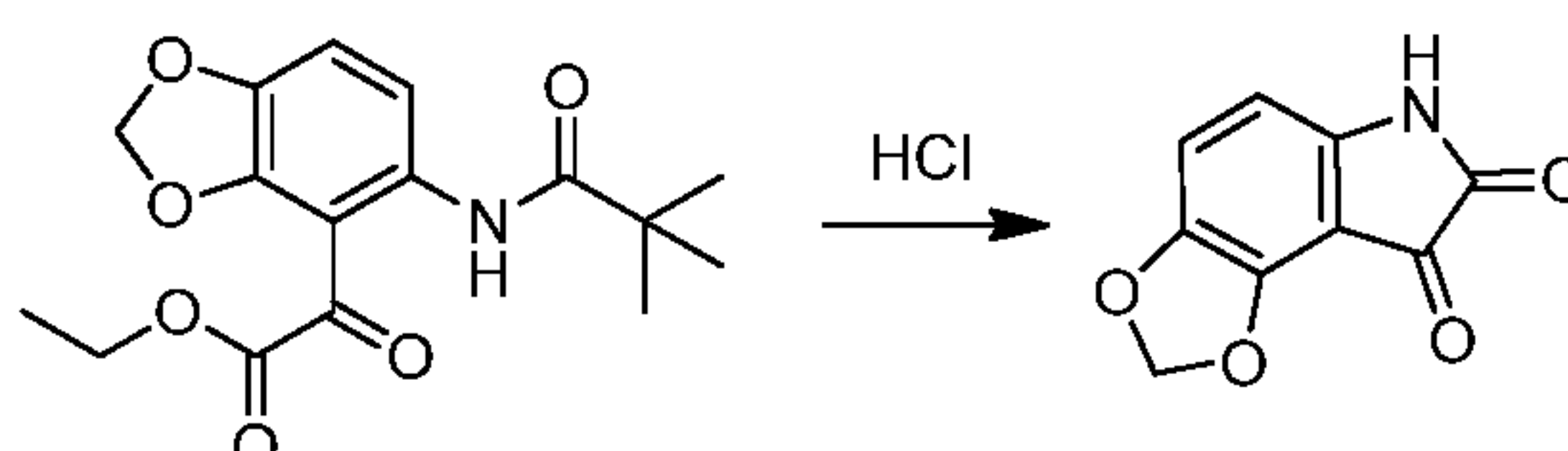
were washed with sat. aq. NaHCO_3 followed by brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 30:70) to give the product of Step 1 (18.31 g, 70% yield) as a light brown solid.

5 Step 2



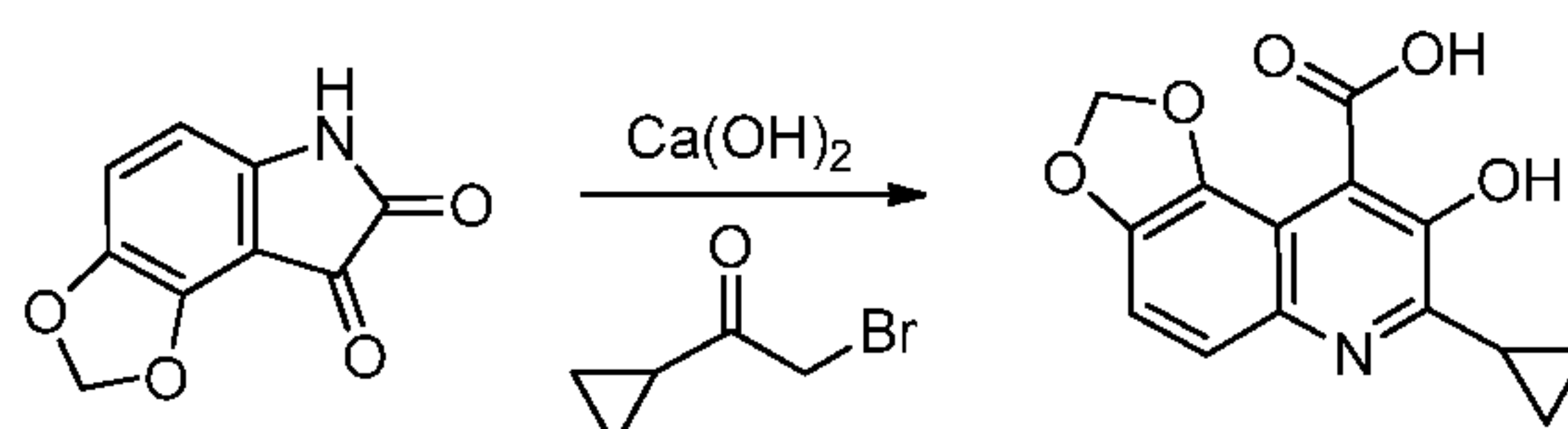
To a solution of the product of Step 1 (15.0 g, 67.8 mmol) in THF (300 ml) at -78°C was added *sec*-butyl lithium (107 ml, 149 mmol) slowly, and the mixture was allowed to warm to 0°C and stirred for 2h. Diethyl oxalate (12.9 g, 88 mmol) in THF (15 ml) was then added at -78°C and the reaction was allowed to warm to RT and stirred for 1h. The mixture was quenched at RT with sat. aq. NH_4Cl and extracted with DCM and EtOAc. The combined organic fractions were washed with sat. brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 60:40) to afford the product of Step 2 (11.8 g, 54% yield) as a yellow solid.

15 Step 3



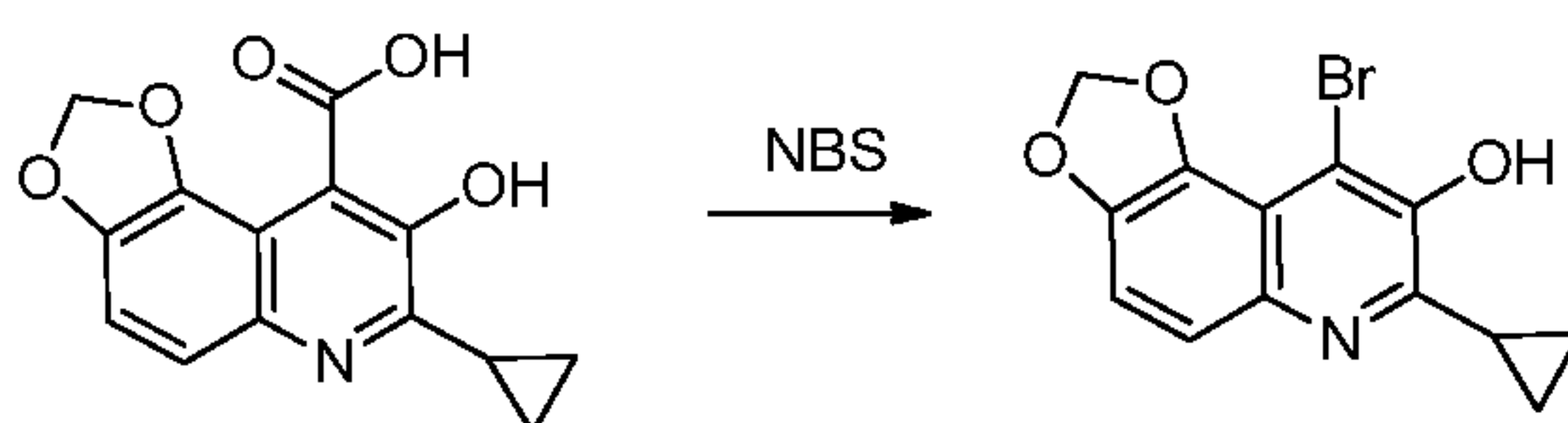
To a solution of the product of Step 2 (14.0 g, 43.6 mmol) in DME (60 ml) was added 12N HCl (50 ml, 43.6 mmol), and the mixture was warmed to 80°C and stirred for 6h. The mixture was cooled to RT, diluted with water, concentrated from DME then cooled over ice overnight. The solid was filtered and dried *in vacuo* to provide the product of Step 3 (6.40 g, 77% yield).

Step 4



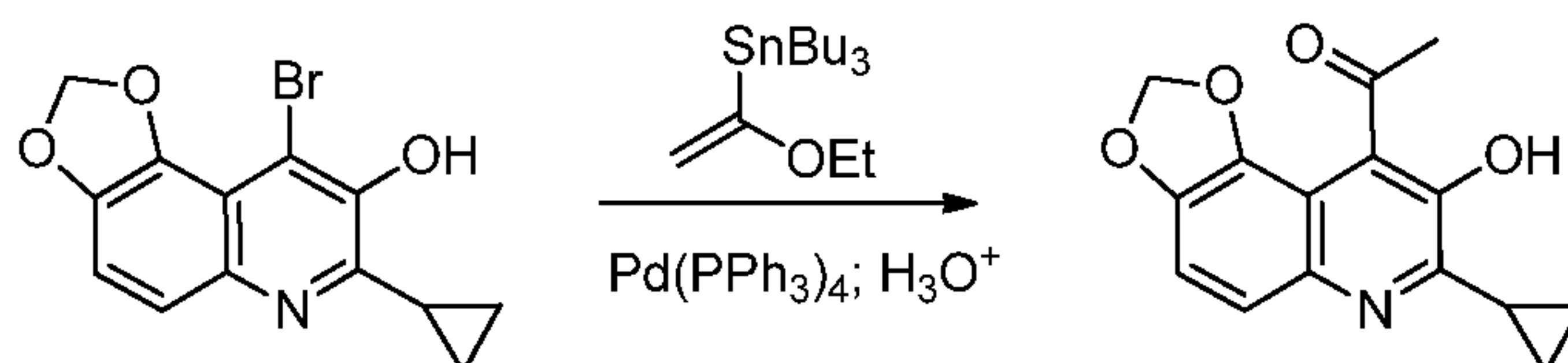
To a solution of the product of Step 3 (6.40 g, 33.5 mmol) in water (150 ml) was added $\text{Ca}(\text{OH})_2$ (7.44 g, 100 mmol), and the mixture was warmed to 80°C and stirred for 1h. 2-Bromo-1-cyclopropylethan-1-one (13.10 g, 80 mmol) was then added at RT and the reaction was warmed to 80°C and stirred for 3.5h. The mixture was cooled to 0°C , ice cold 10% HCl was added slowly, and the reaction was left over ice for 30 min, then the solid was filtered and dried *in vacuo* to provide the product of Step 4 (7.87 g, 86% yield).

Step 5

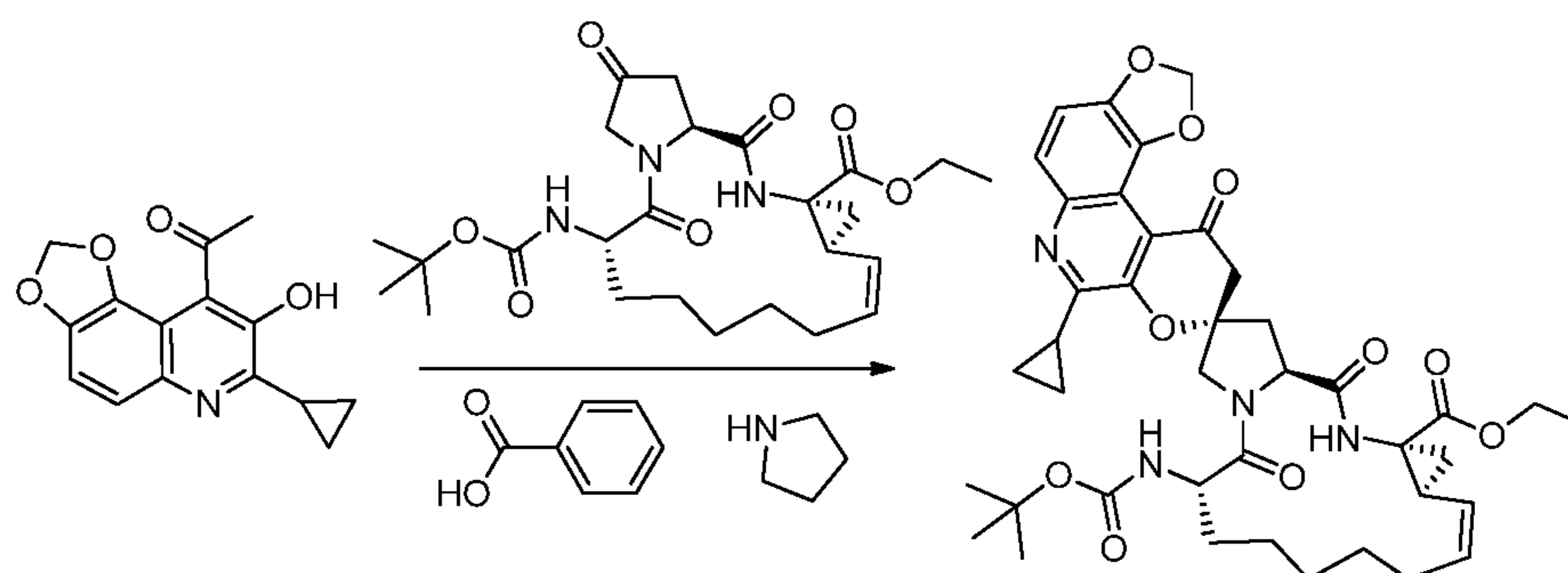


To a solution of the product of Step 4 (7.87 g, 28.8 mmol) in THF (240 ml) at 0°C was added a solution of NBS (4.87 g, 27.4 mmol) in THF (24 ml) slowly, and the mixture was stirred for 1h at 0°C then 9 min at RT. The mixture was poured into sat. brine and extracted with EtOAc. The combined organic fractions were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with DCM/EtOAc 99:1 to 80:20) to give the product of Step 5 (3.26 g, 37% yield).

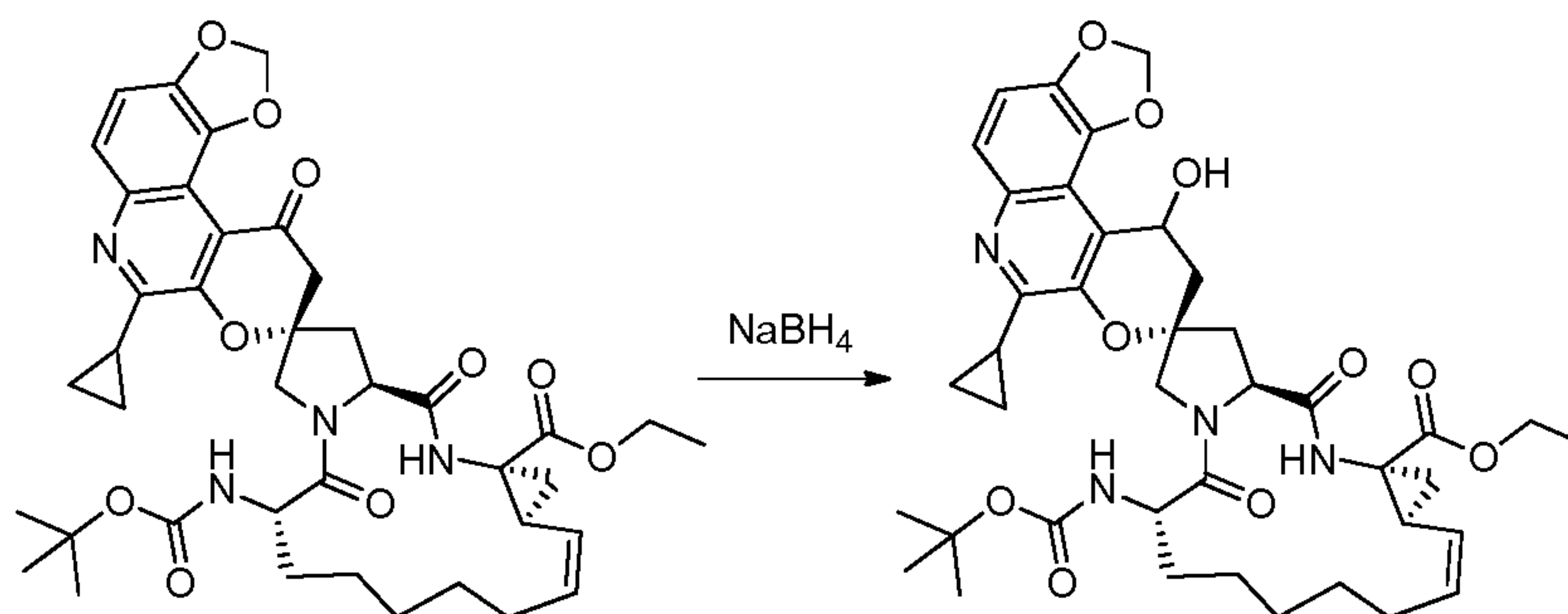
15 Step 6



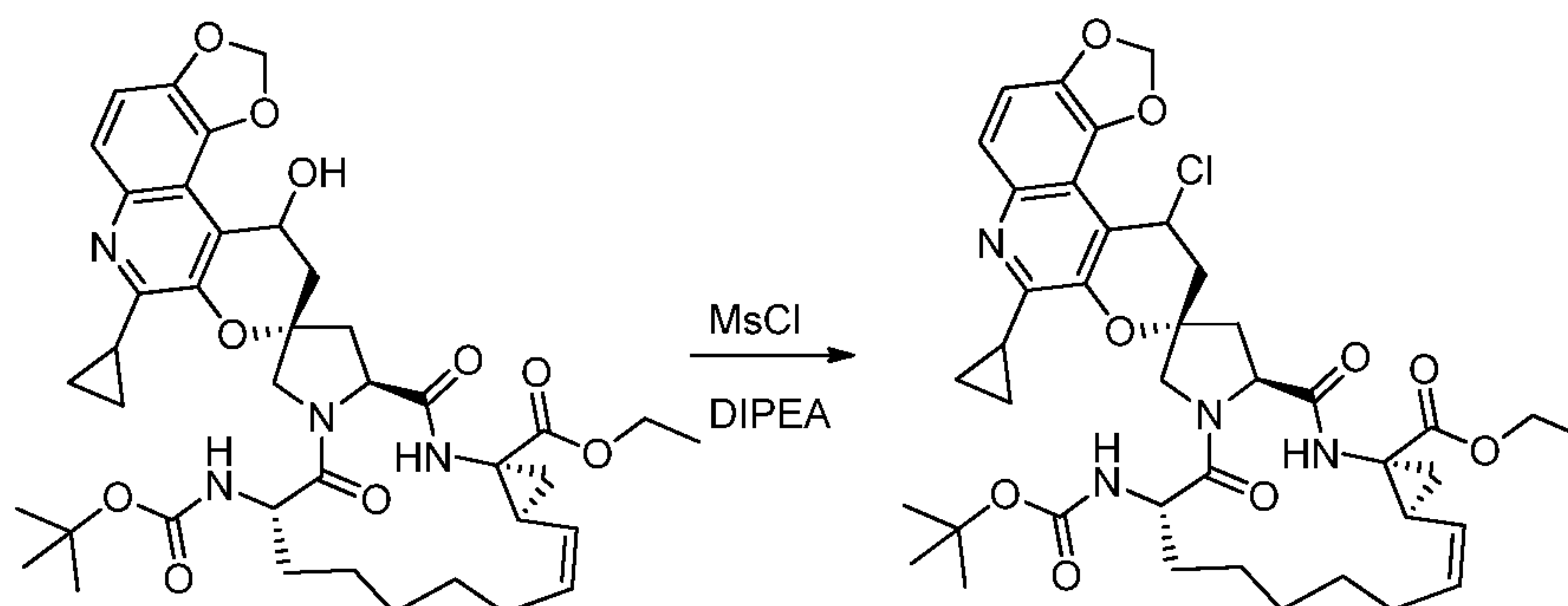
To a solution of the product of Step 5 (2.60 g, 8.44 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (975 mg, 0.844 mmol) in 1,4-dioxane (32 ml) was added tributyl(1-ethoxyvinyl)tin (7.12 ml, 21.1 mmol), and the mixture was warmed to 110°C and stirred for 2h. More $\text{Pd}(\text{PPh}_3)_4$ (150 mg) and tributyl(1-ethoxyvinyl)tin (2 ml) were added, and the reaction was stirred at 110°C for an additional 9h. The final mixture was quenched at RT with 1N aq. HCl (1 ml) and stirred for 1.5h. The mixture was poured into sat. aq. NaHCO_3 and extracted with EtOAc. The combined organic fractions were washed with sat. brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 60:40) to give the product of Step 6 (1.36 g, 59% yield) as a yellow solid.

Step 7

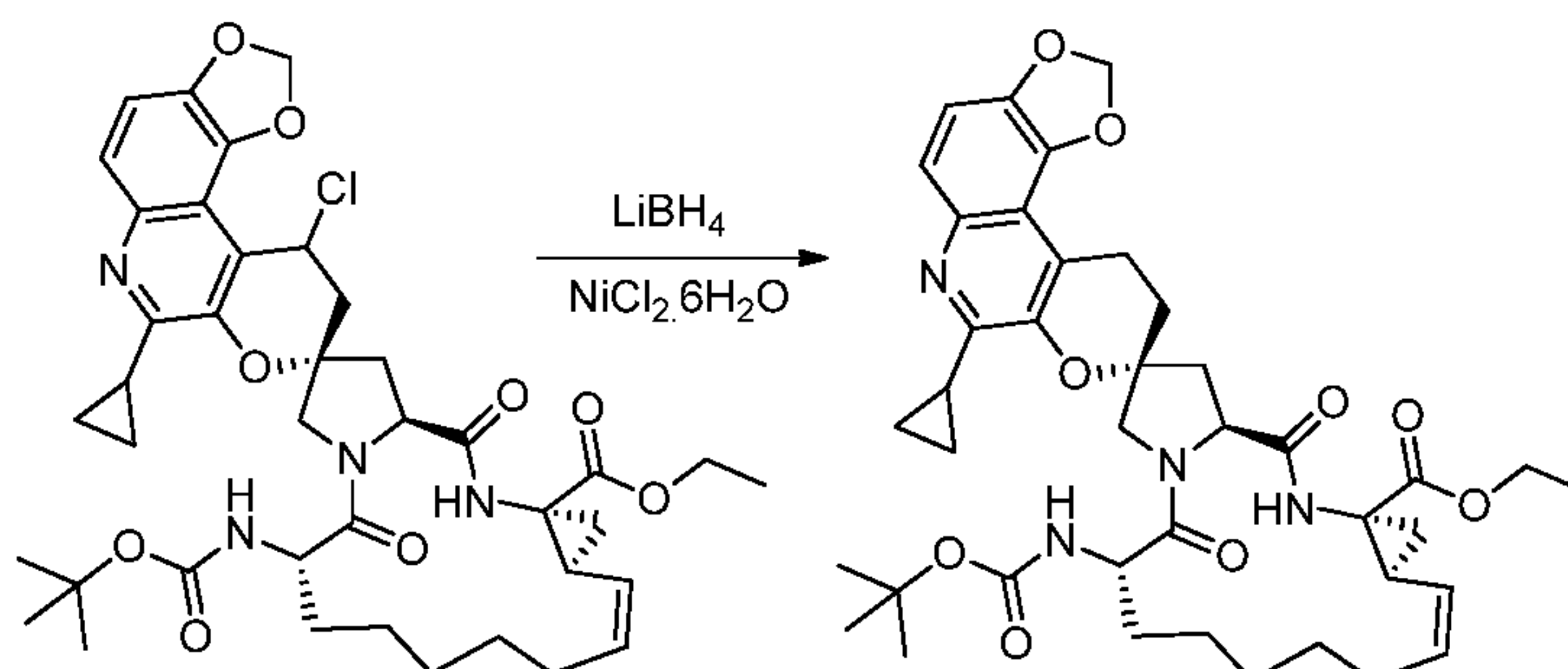
To a solution of the product of Step 6 (293 mg, 1.080 mmol), macrocyclic ketone (531 mg, 1.080 mmol) and benzoic acid (132 mg, 1.080 mmol) in MeOH (9 ml) was added
 5 pyrrolidine (0.0345 ml, 0.432 mmol) and 4A molecular sieves (600 mg), and the mixture was warmed to 60°C and stirred over 72h. The mixture was quenched at RT with sat. aq. NaHCO₃ and brine and extracted with EtOAc. The combined organic fractions were washed with saturated brine and water, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue
 10 was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) to give, in order of elution, the product of Step 7 (360 mg, 45% yield), as a yellow solid, followed by starting material, the product of Step 6 (60 mg).

Step 8

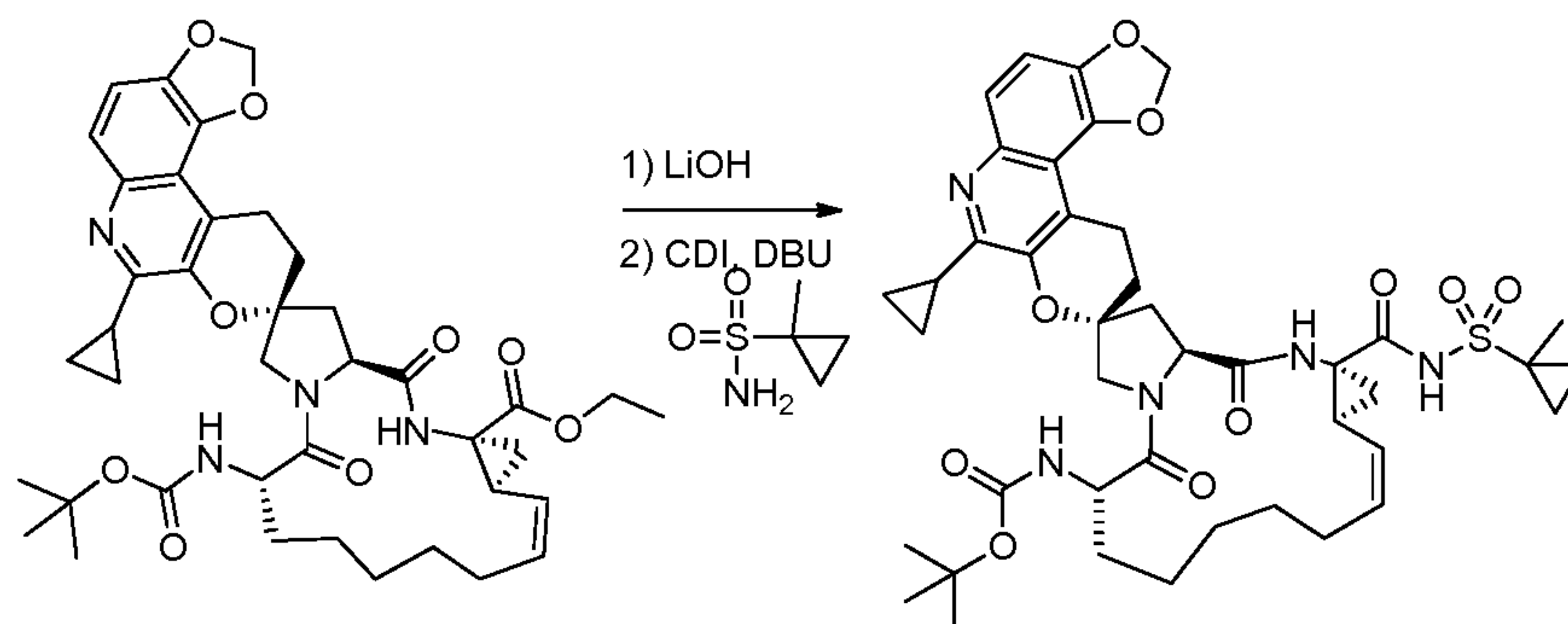
To a solution of the product of Step 7 (330 mg, 0.443 mmol) in THF (3 ml) and
 15 MeOH (3 ml) at 0°C was added NaBH₄ (20.1 mg, 0.532 mmol), and the mixture was stirred for 45 min. The mixture was quenched at 0°C with sat. aq. NH₄Cl and extracted with EtOAc. The combined organic fractions were washed with saturated brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the product of Step 8 (330 mg, 100% yield).

Step 9

To a solution of the product of Step 8 (330 mg, 0.442 mmol) in DCM (10 ml) was added DIPEA (0.231 ml, 1.326 mmol) followed by MsCl (0.055 ml, 0.707 mmol), and the mixture was stirred for 2h. More DIPEA (0.231 ml, 1.326 mmol) and MsCl (0.055 ml, 0.707 mmol) were added, and the reaction was stirred for an additional 2h. LiCl (56.2 mg, 1.326 mmol) followed by DMF (1.0 ml) were then added, and the reaction was stirred overnight. The mixture was quenched at RT with sat. aq. NH₄Cl and extracted with EtOAc. The combined organic fractions were washed with sat. brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide the crude product of Step 9 (340 mg), as crude.

Step 10

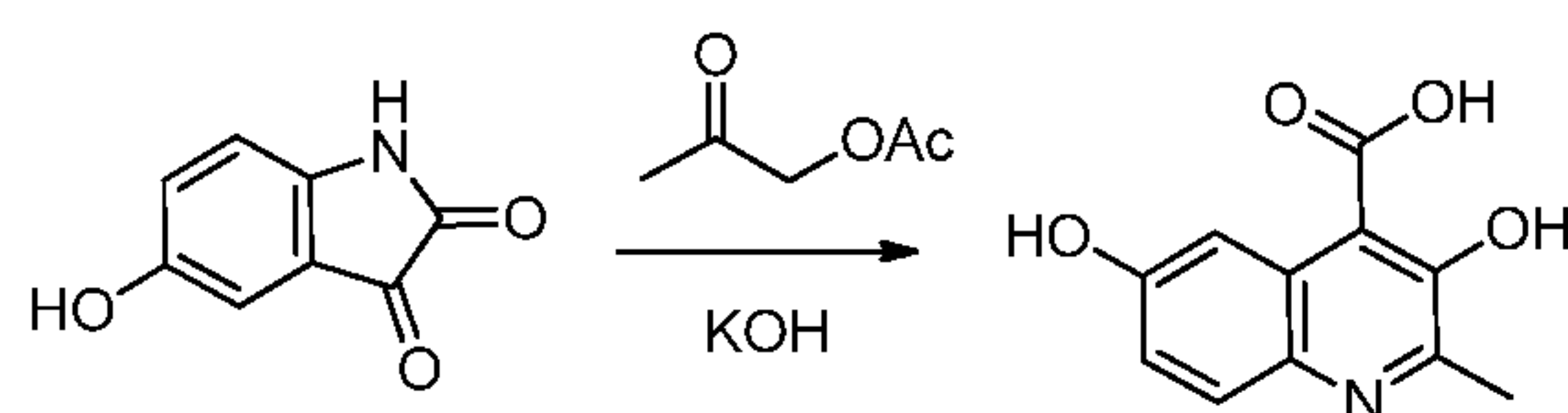
To a solution of the crude product of Step 9 (340 mg, 0.444 mmol) in MeOH (20 ml) at -78°C was added NiCl₂·6H₂O (106 mg, 0.444 mmol) followed by LiBH₄ (0.44 ml, 0.889 mmol) and the mixture was stirred for 1h. More LiBH₄ (0.44 ml, 0.889 mmol) was added at -78°C, and the reaction was stirred for 1h, and then warmed to 0°C for 30 min. The final mixture was quenched at 0°C with sat. aq. NaHCO₃ and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 60:40) to give the product of Step 10 (130 mg, 40% yield) as a white solid.

Step 11

To a solution of the product of Step 10 (120 mg, 0.164 mmol) in THF (3.5 ml), MeOH (3.5 ml) and water (2.5 ml) was added LiOH·H₂O (34.5 mg, 0.821 mmol), and the mixture was warmed to 50°C and stirred for 5h. The mixture was quenched at RT with ice-cold 0.2N aq. HCl and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo* to give an intermediate acid (120 mg, 100% yield). To a solution of this intermediate acid (120 mg, 0.171 mmol) in THF (6 ml) was added carbonyl diimidazole (55.4 mg, 0.341 mmol), and the mixture was warmed to 70°C and stirred vigorously for 4h. More carbonyl diimidazole (20 mg) was added, and the reaction was stirred 1h at 70°C. 1-Methylcyclopropane-1-sulfonamide (92 mg, 0.683 mmol) was then added at RT followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.103 ml, 0.683 mmol), and the reaction was warmed to 50°C and stirred for 9h. The mixture was quenched at RT with sat. aq. NH₄Cl and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 50:50) to give I-29 (70 mg, 50% yield) as a white solid. ¹H-NMR (400 MHz, CDCl₃) δ 10.04 (s, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.76 (s, 1H), 5.71 (m, 1H), 4.95-5.05 (m, 2H), 4.61 (m, 1H), 4.40-4.55 (m, 3H), 4.27 (m, 1H), 4.11 (m, 1H), 3.73 (d, J = 10.8 Hz, 1H), 3.25-3.35 (m, 2H), 2.50-2.60 (m, 2H), 2.30-2.45 (m, 3H), 2.15-2.25 (m, 2H), 1.70-1.95 (m, 4H), 1.20-1.65 (m, 8H), 1.47 (s, 3H), 1.32 (s, 9H), 0.77-0.92 (m, 6H); LC-MS (M⁺) Calc. for C₄₂H₅₃N₅O₁₀S: 819.3 Found 820.0.

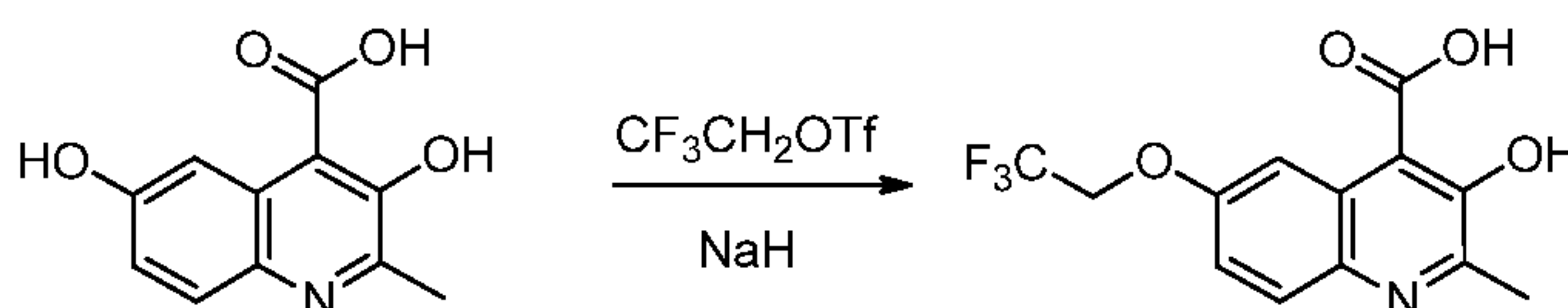
Example 30: tert-butyl ((2R,6S,13aS,14aR,16aS,Z)-5'-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-9'-(2,2,2-trifluoroethoxy)-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-30)

Step 1



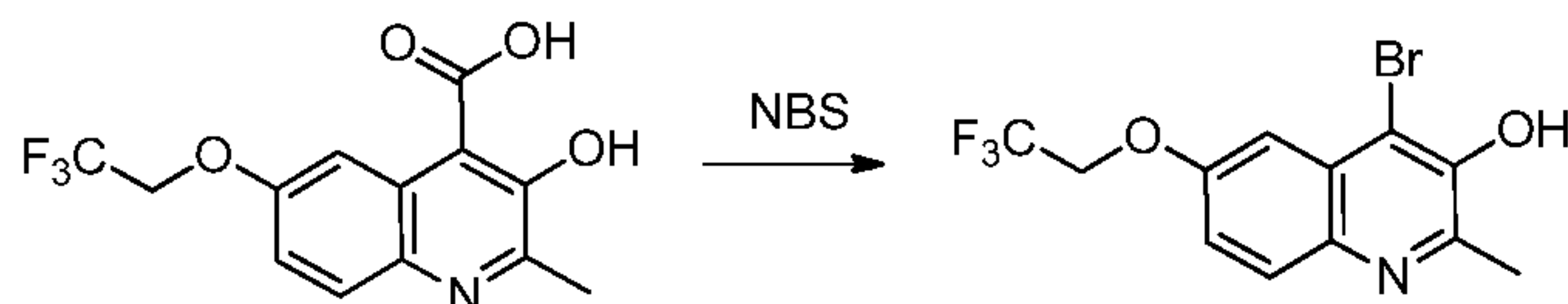
A mixture of 5-hydroxyisatin (9.38 g, 57.5 mmol) and KOH 6N (96 ml, 575 mmol) in water (80 ml) was warmed to 85°C and stirred for 2h. Acetoxy-2-propanone (6.21 ml, 57.5 mmol) was then added 3x (3eq. total), each at 93°C followed by 1h stirring at 93°C. The crude was concentrated from EtOH then slowly quenched at RT with 1N aq. HCl until pH ~ 2, cooled in ice-bath for 15 min. The solid separating out was filtered, rinsed with water and dried under high vacuum to give the product of Step 1 (6.09 g, 48% yield).

Step 2



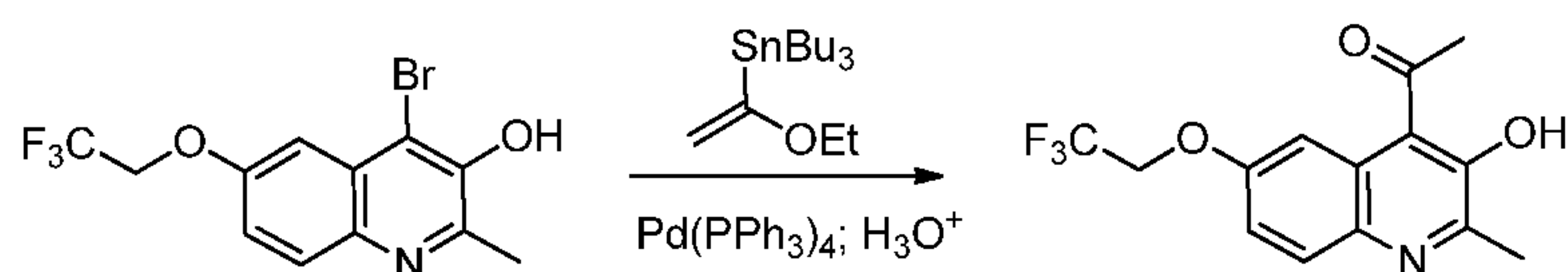
To a solution of the product of Step 1 (3.20 g, 14.6 mmol) in DMF (35 ml) at 0°C was added sodium hydride 60% in hexanes (1.17 g, 29.2 mmol) portion wise followed by DMSO (5 ml), and the mixture was stirred for 30 min. 2,2,2-Trifluoroethyl trifluoromethanesulfonate (2.42 ml, 16.8 mmol) was then added at 0°C, and the reaction was allowed to warm to RT and stirred for 3h. The mixture was quenched at 0°C with 1N HCl until pH ~ 2, diluted with water then filtered, rinsing with water. The product was dried overnight at 80°C under high vacuum to give the product of Step 2 (4.55 g) as yellow solid.

Step 3



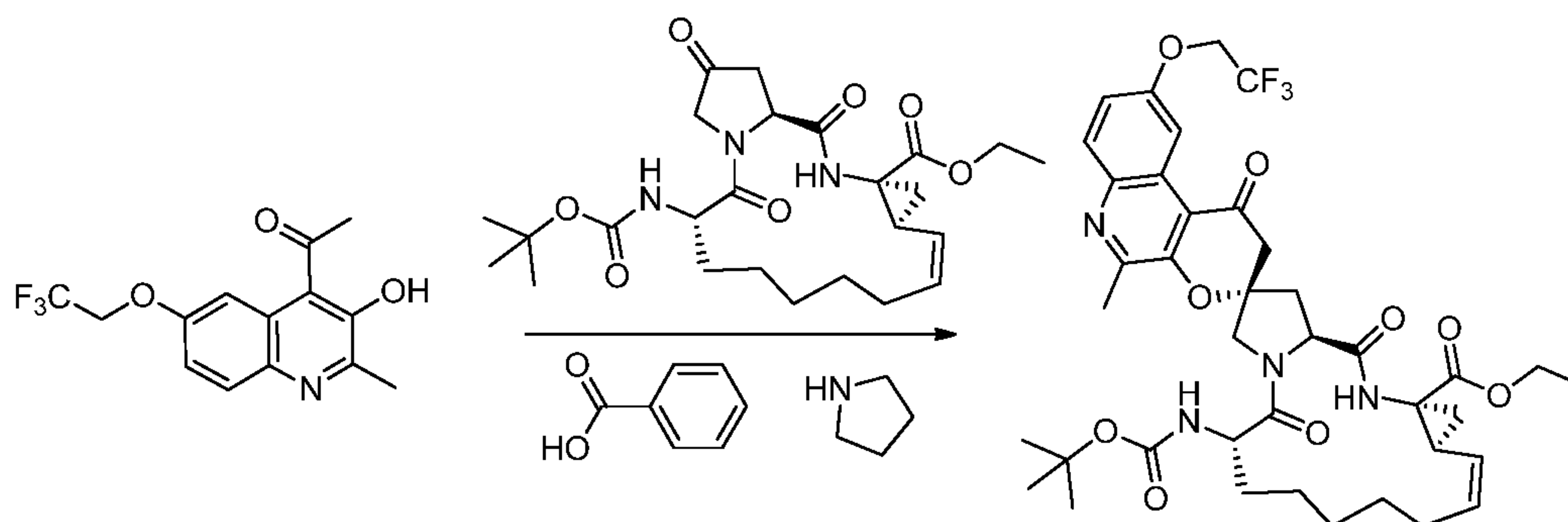
To a solution of the product of Step 2 (4.95 g, 16.4 mmol) in THF (50 ml) at RT was added NBS (3.51 g, 19.7 mmol), and the mixture was stirred for 3h. The mixture was quenched at RT with saturated brine and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The reaction was taken up in DCM, and the solid was filtered to provide a first crop of desired compound. The filtrate was concentrated *in vacuo* and purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 30:70). The resulting purified material was collected with the solid from the first crop to provide the product of Step 3 (2.91 g, 53% yield).

Step 4

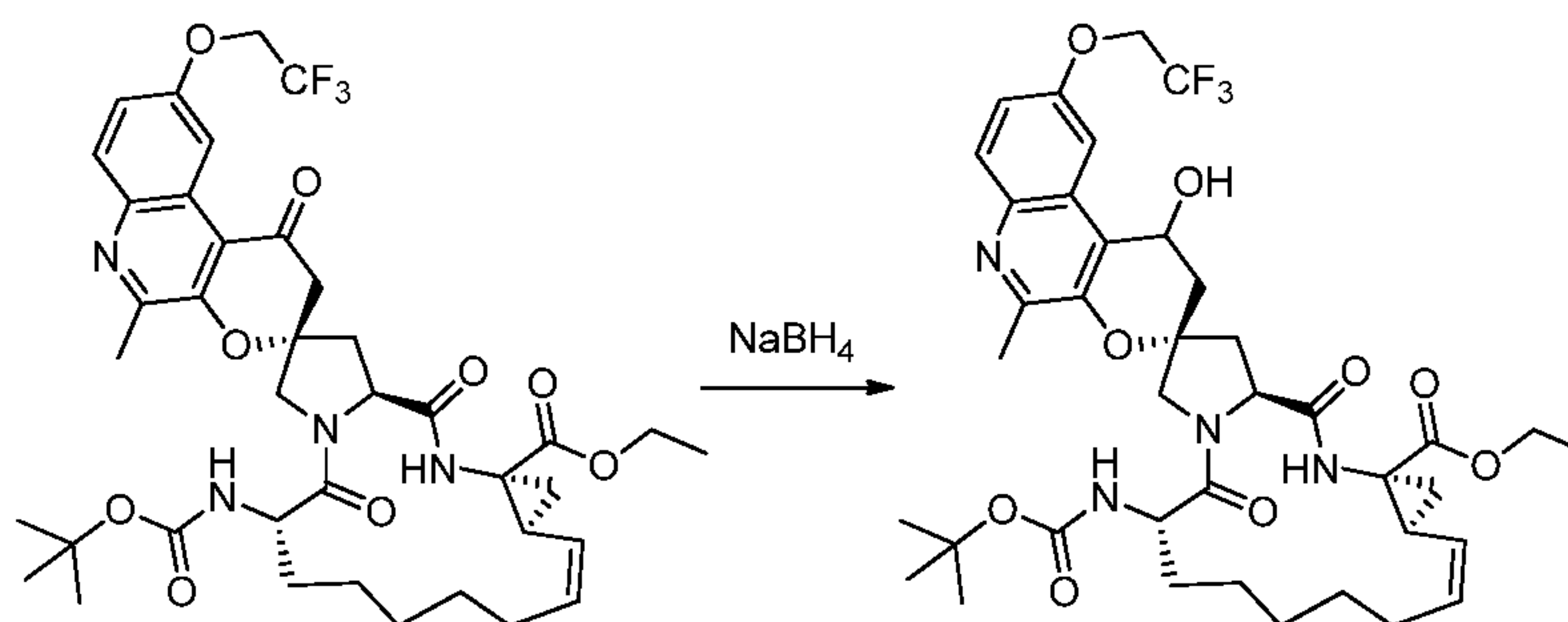


To a solution of the product of Step 3 (3.21 g, 9.55 mmol) and Pd(PPh₃)₄ (1.10 g, 0.955 mmol) in dioxane (40 ml) at RT was added tributyl(1-ethoxyvinyl)tin (7.42 ml, 21.97 mmol), and the mixture was warmed to 110°C and stirred overnight. The mixture was quenched at RT with 1N aq. HCl and stirred for 90 min. The reaction was diluted with sat. aq. NaHCO₃ and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) to give the product of Step 4 (1.29 g, 45% yield) as a brown solid.

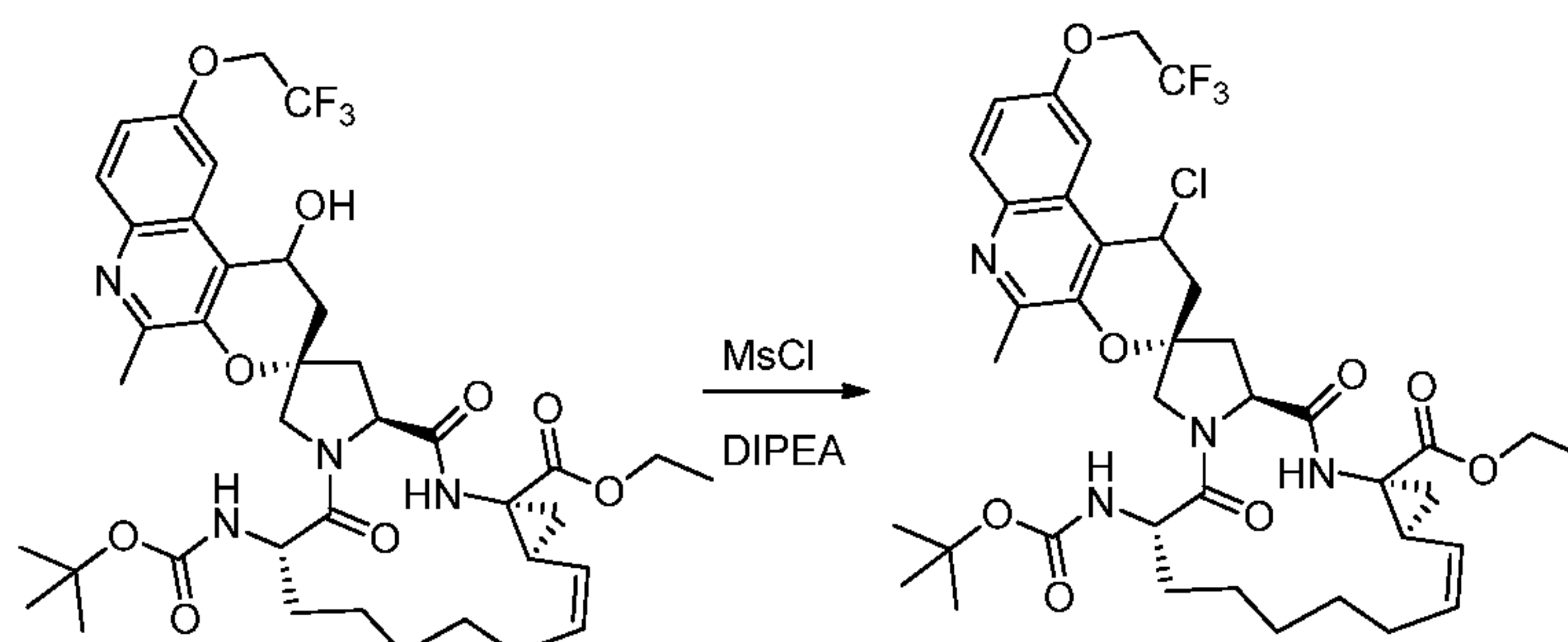
10 Step 5



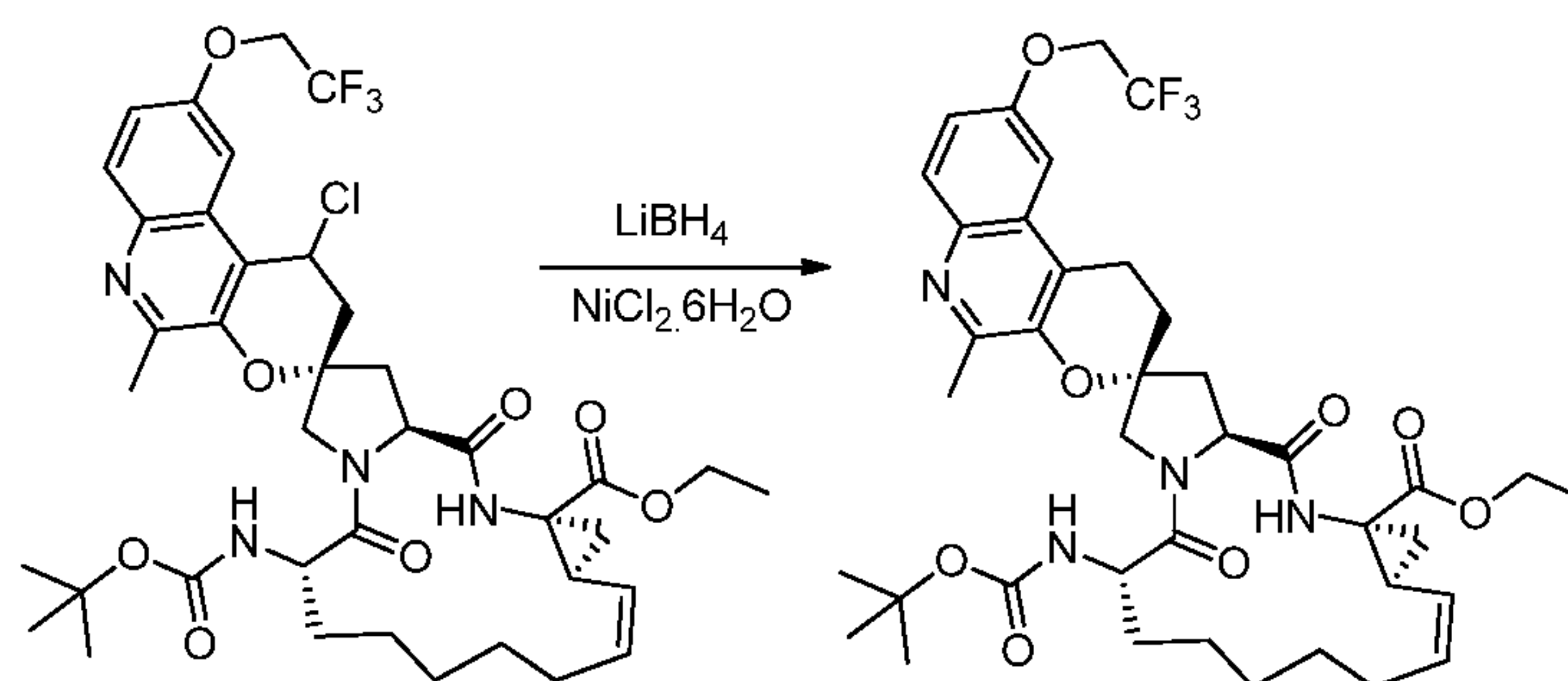
To a solution of the product of Step 4 (500 mg, 1.67 mmol), and macrocyclic ketone (821 mg, 1.671 mmol) and benzoic acid (204 mg, 1.67 mmol) in MeOH (15 ml) at RT was added pyrrolidine (0.053 ml, 0.668 mmol) and 4A molecular sieves (~1 g), and the mixture was warmed to 55°C and stirred for 72h. The mixture was quenched at RT with sat. aq. NaHCO₃ and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) to give the product of Step 5 (875 mg, 68% yield) as yellow foam.

Step 6

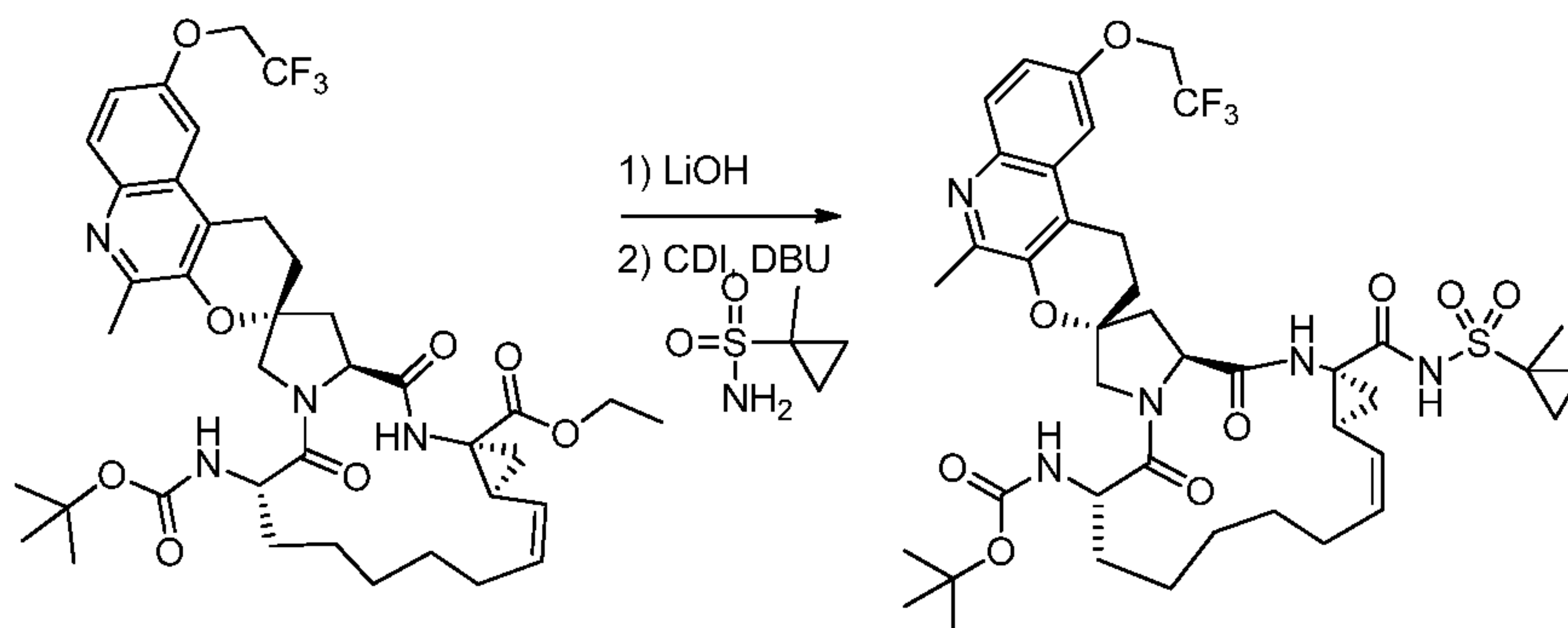
To a solution of the product of Step 5 (875 mg, 1.13 mmol) in THF (6 ml) and MeOH (6 ml) at 0°C was added NaBH₄ (51.4 mg, 1.36 mmol), and the mixture was stirred for 45 min. The mixture was quenched at RT with sat. aq. NH₄Cl and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford the product of Step 6 (880 mg, 100% yield).

Step 7

To a solution of the product of Step 6 (880 mg, 1.14 mmol) and 4-dimethylaminopyridine (1.388 mg, 0.011 mmol) in DCM (25 ml) at -10°C was added DIPEA (0.593 ml, 3.41 mmol), followed by MsCl (0.142 ml, 1.82 mmol) slowly, and the mixture was allowed to warm to RT over 30 min then stirred for 3h. More DIPEA (0.3 ml) and MsCl (0.070 ml) were then added, and the reaction was stirred for another 5h. The final mixture was diluted at RT with EtOAc and sat. aq. NH₄Cl, extracted with EtOAc, washed with brine then dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product of Step 7 (980 mg).

Step 8

To a solution of the product of Step 7 (660 mg, 0.832 mmol) in MeOH (25 ml) at -78°C was added NiCl₂·6H₂O (198 mg, 0.832 mmol) then 2N LiBH₄ in THF (1.66 ml, 3.33 mmol). The reaction was stirred for 15 min then quenched at -78°C with sat. aq. NaHCO₃. The mixture was extracted with EtOAc, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 20:80) to provide the product of Step 8 (309 mg, 49% yield).

Step 9

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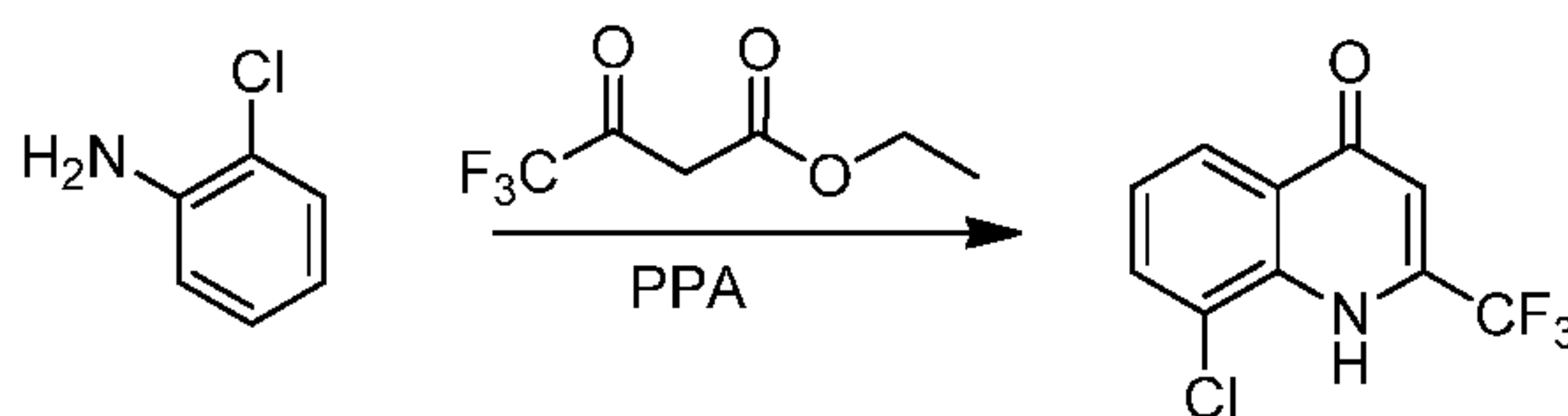
To a solution of the product of Step 8 (361 mg, 0.476 mmol) in THF (10 ml), MeOH (10 ml) and water (7 ml) at RT was added LiOH·H₂O (59.9 mg, 1.427 mmol) and the mixture was warmed to 55°C and stirred for 6h. The mixture was quenched at RT with ice-cold 0.2N aq. HCl and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo* to give an intermediate acid (325 mg, 93% yield). To a solution of this intermediate acid (325 mg, 0.445 mmol) in THF (12 ml) at RT was added carbonyl diimidazole (144 mg, 0.889 mmol), and the mixture was warmed to 70°C and stirred for 4h. 1-Methylcyclopropane-1-sulfonamide (240 mg, 1.779 mmol) and DBU (0.268 ml, 1.779 mmol) were then added at RT, and the reaction was warmed to 50°C and stirred for 3h. The mixture was quenched at RT with sat. aq. NH₄Cl and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 20:80)

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to give I-30 (295 mg, 78% yield) as colorless foam. ¹H-NMR (400 MHz, CDCl₃) δ 10.10 (s, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.22 (d, J = 9.0 Hz, 1H), 7.05 (s, 1H), 6.91 (s, 1H), 5.71 (m, 1H), 4.95-5.05 (m, 2H), 4.61 (m, 1H), 4.40-4.55 (m, 4H), 4.17 (m, 1H), 3.70 (d, J = 10.8 Hz, 1H), 3.00-3.10 (m, 2H), 2.45-2.60 (m, 2H), 2.47 (s, 3H), 2.25-2.40 (m, 4H), 1.65-1.95 (m, 5H), 1.20-1.50 (m, 8H), 1.46 (m, 3H), 1.30 (s, 9H), 0.80 (br s, 2H).

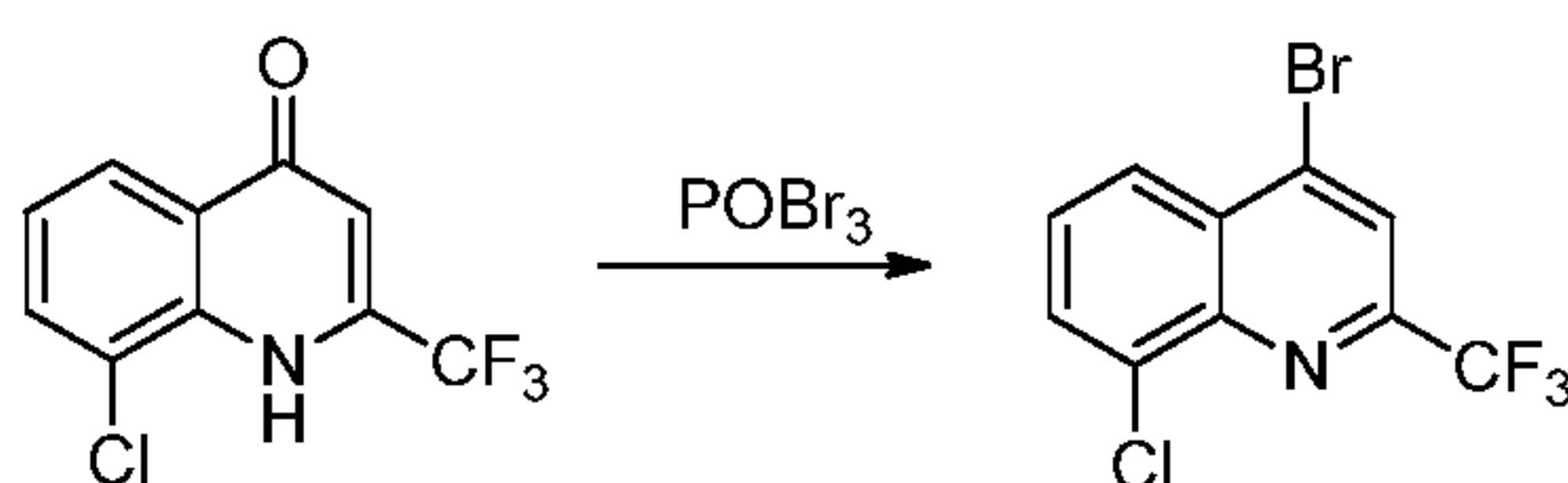
Example 31: *tert*-butyl ((2*R*,6*S*,13*aS*,14*aR*,16*aS*,*Z*)-7'-chloro-14*a*-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13*a*,14,14*a*,15,16,16*a*-hexadecahydro-1*H*-spiro[cyclopropa[e]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-*c*]quinolin]-6-yl)carbamate (I-31)

Step 1



To a well-stirred solution of polyphosphoric acid (70 g) at 100°C was added ethyl 4,4,4-trifluoroacetoacetate (19.6 ml, 133 mmol) dropwise, and the mixture was stirred for 15 min. 2-Chloroaniline (14 ml, 133 mmol) was then added at 100°C dropwise, and the reaction was warmed to 150°C and stirred for 3h. The slurry was slowly poured at RT over ice-cold water then stirred overnight at RT. The mixture was filtered, and the solid was taken up in DCM/MeOH 1:1, concentrated to ~20 ml, then poured into hexanes (700 ml). The resulting solid was filtered, rinsing with hexanes, and dried *in vacuo* to give the product of Step 1 (21.35 g, 65% yield).

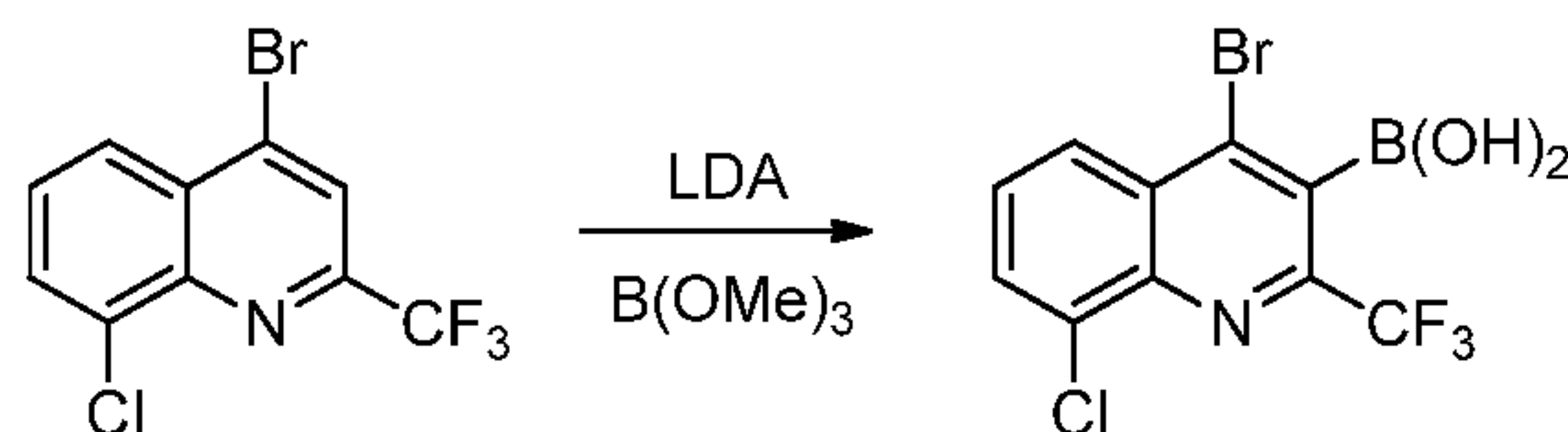
Step 2



To a solution of the product of Step 1 (10 g, 40.4 mmol) in MeCN (250 ml) at RT was added phosphorus oxybromide (13.32 g, 46.4 mmol), and the mixture was warmed to reflux and stirred for 90 min. The mixture was poured at RT into sat. aq. NaHCO₃ and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel

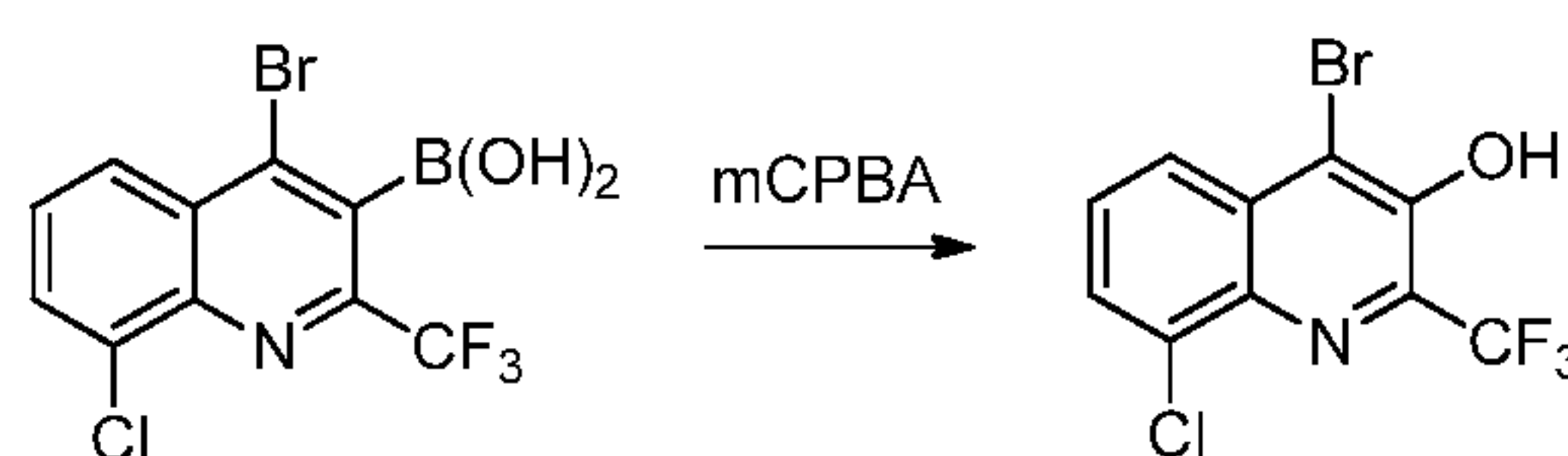
(eluting with Hexanes/EtOAc 99:1 to 50:50) to provide the product of Step 2 (12.5 g, 100% yield) as a white solid.

Step 3



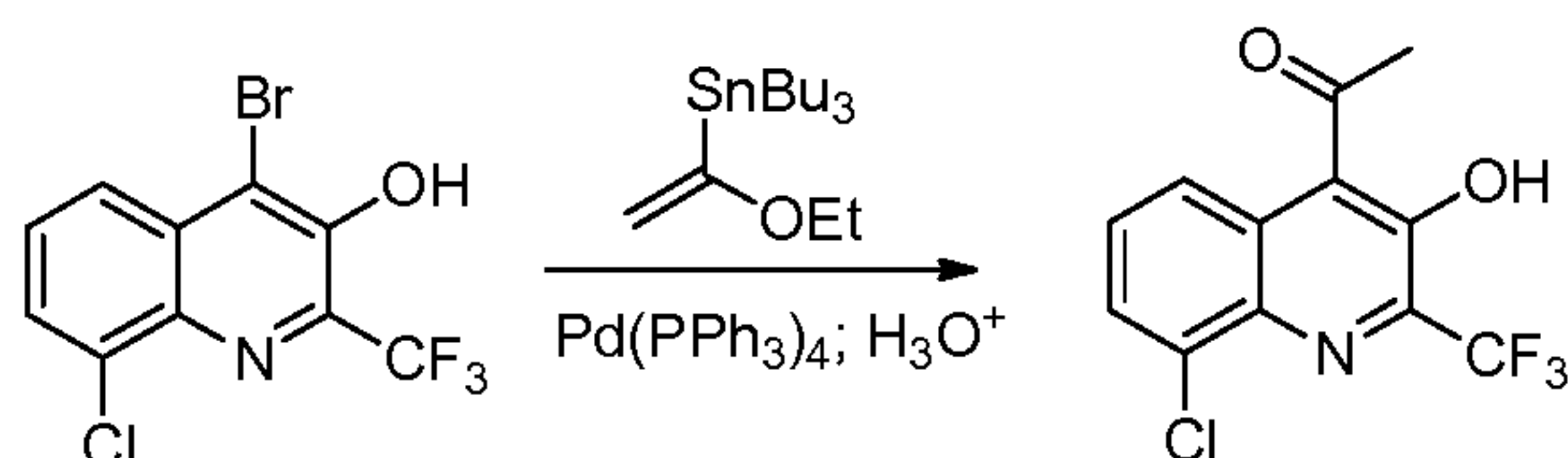
5 To a solution of DIPA (4.06 ml, 28.7 mmol) in THF (25 ml) at -30°C was added n-butyl lithium 2.5N in hexanes (11.04 ml, 27.6 mmol), and the mixture was warmed to 0°C and stirred for 10 min. The product of Step 2 (7.14 g, 23.00 mmol) in THF (20 ml) was then added at -78°C, and the reaction was stirred for 90 min. Trimethylborate (3.85 ml, 34.5 mmol) was then added at -78°C, and the reaction was stirred for 3h. The mixture was quenched at -78°C with sat. aq. NH₄Cl and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 20:80) to give the product of Step 3 (5.47 g, 67% yield) as well as 1.73 g of starting material.

Step 4



15 To the product of Step 3 (4.58 g, 12.9 mmol) was added a 0.103N solution of mCPBA in DCM (144 ml, 14.9 mmol), and the reaction was stirred overnight. The reaction was diluted with EtOAc, poured into sat. aq. NH₄Cl/5% aq. Na₂S₂O₃ 2:1, and extracted with EtOAc. The combined organic fractions were washed with sat. aq. NH₄Cl, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 50:50) to provide the product of Step 4 (3.27 g, 77% yield) as yellow solid.

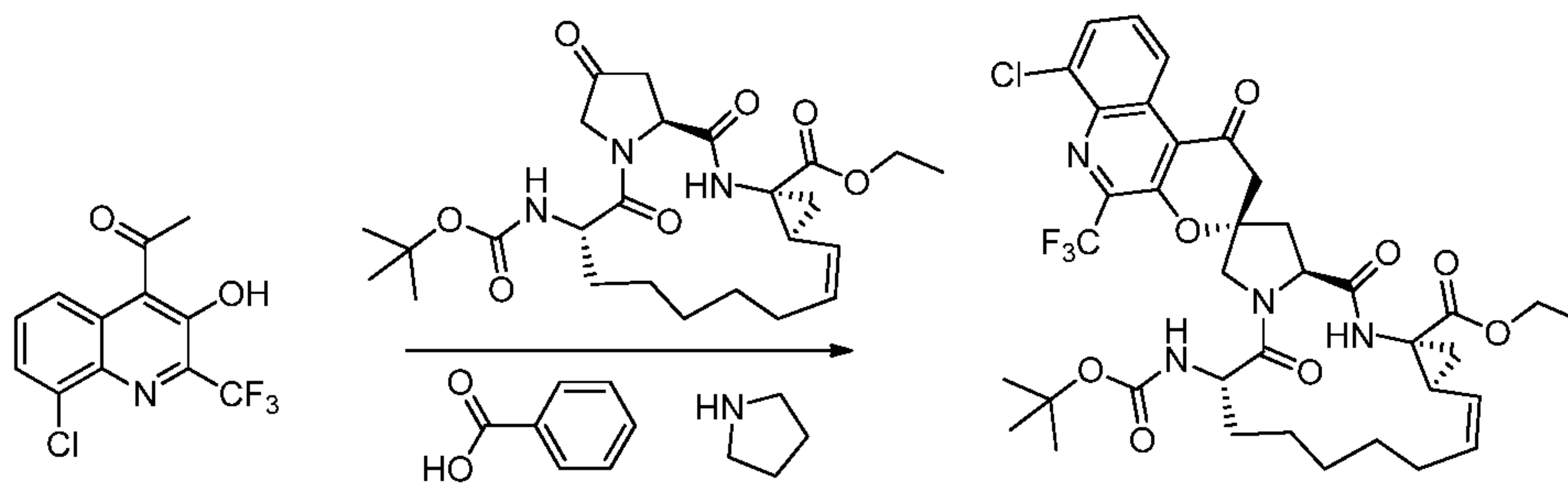
Step 5



25 To a solution of the product of Step 4 (6.13 g, 18.8 mmol) and Pd(PPh₃)₄ (1.085 g, 0.939 mmol) in dioxane (85 ml) at RT was added tributyl(1-ethoxyvinyl)tin (12.7 ml, 37.6

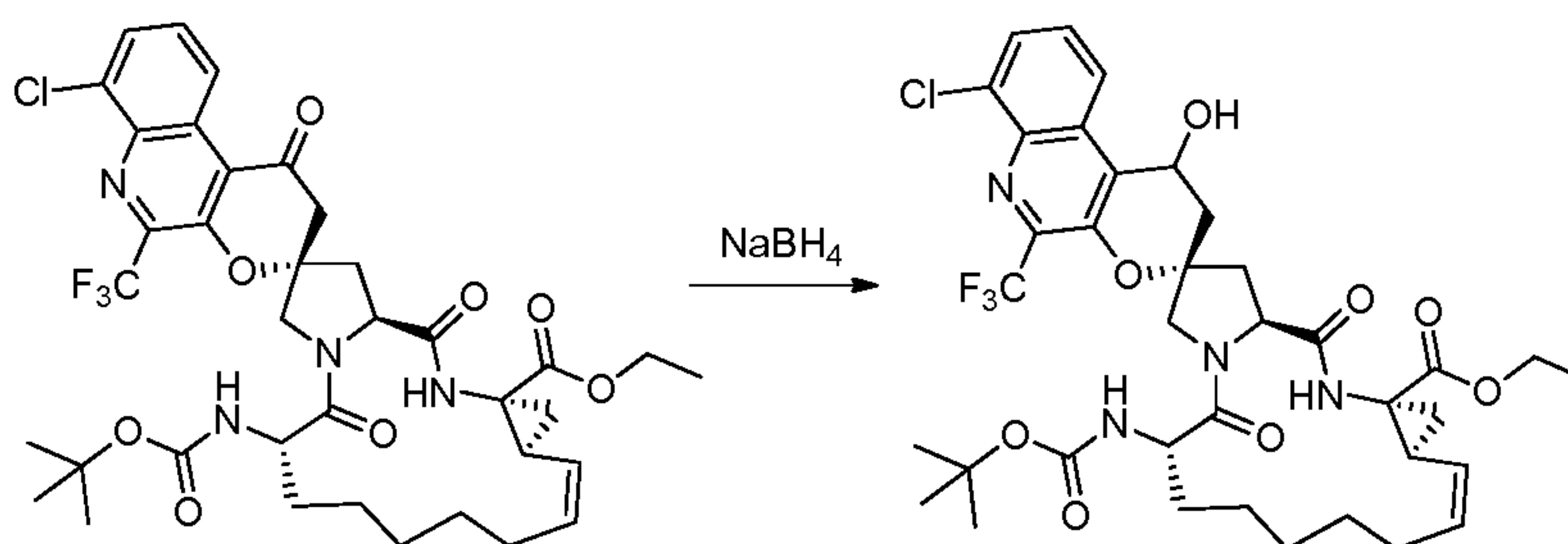
mmol), and the mixture was warmed to 110°C and stirred overnight. The mixture was quenched at RT with 1N aq. HCl (60 ml) and stirred for 3h. The mixture was diluted with water and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 50:50) to afford the product of Step 5 (4.37 g, 80% yield) as yellow solid.

Step 6

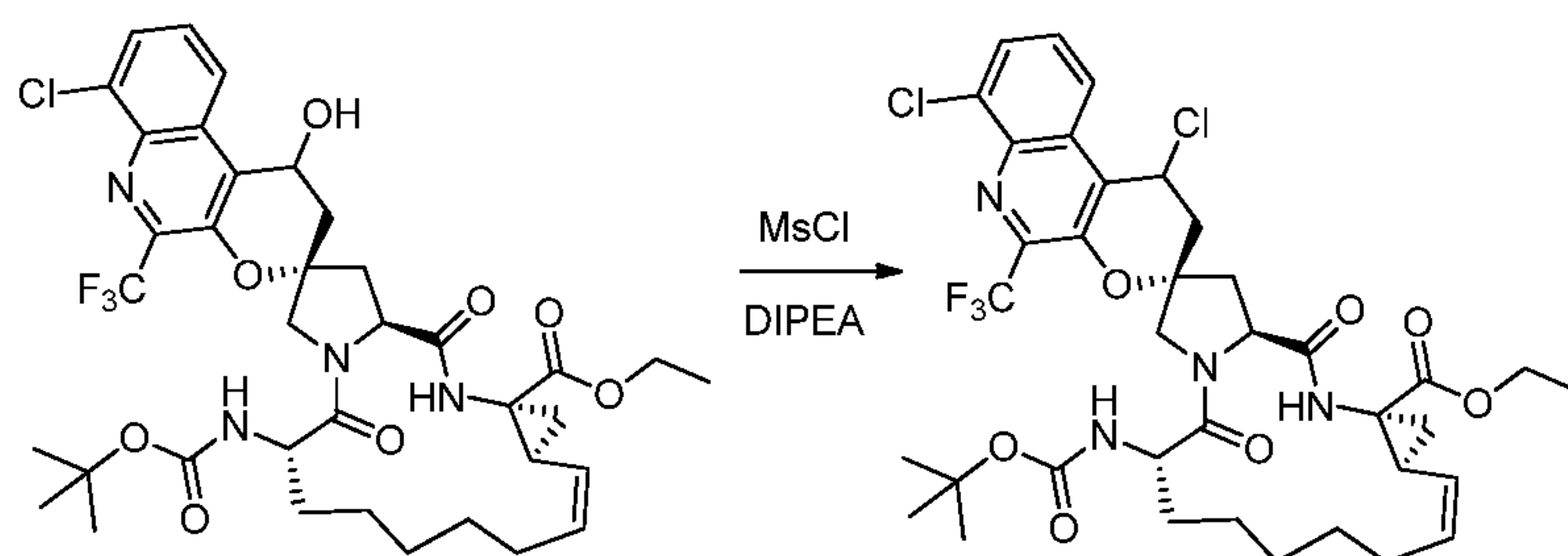


To a solution of the product of Step 5 (450 mg, 1.554 mmol), macrocyclic ketone (764 mg, 1.554 mmol) and benzoic acid (190 mg, 1.554 mmol) in MeOH (12 ml) at RT was added pyrrolidine (0.050 ml, 0.621 mmol) and 4A molecular sieves (~1 g), and the mixture was warmed to 60°C and stirred for 72h. The mixture was quenched at RT with sat. aq. NaHCO₃ and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 40:60) to give the product of Step 6 (799 mg, 67% yield) as yellow foam.

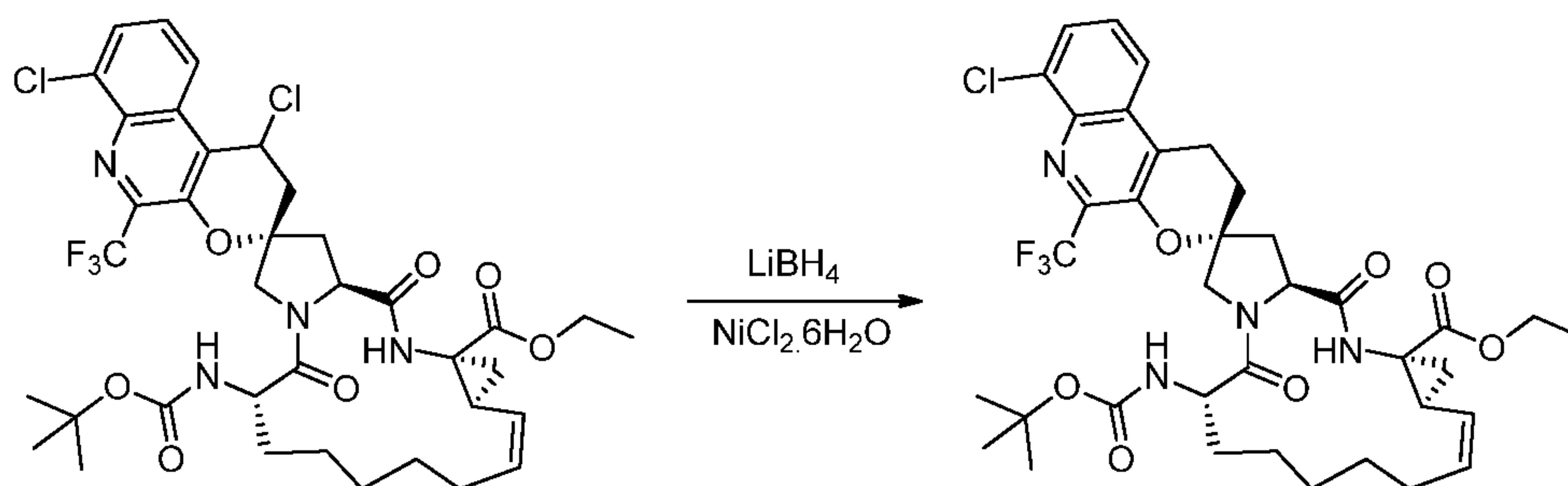
Step 7



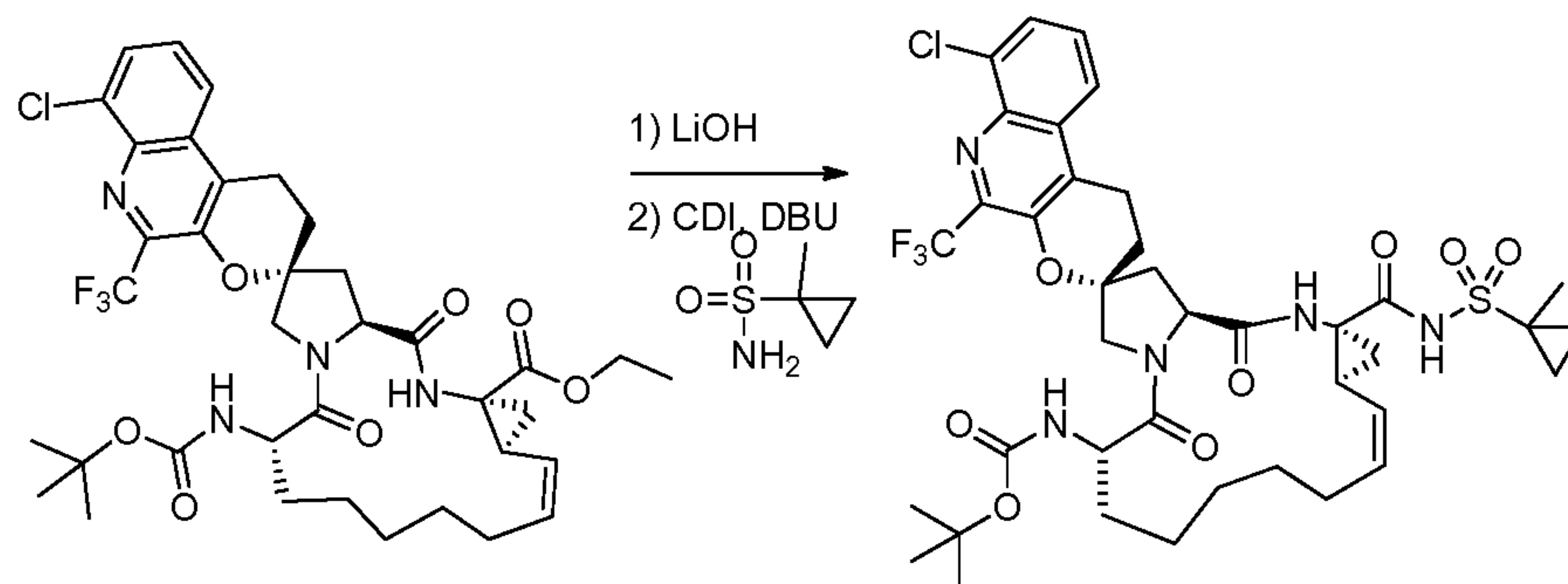
To a solution of the product of Step 6 (799 mg, 1.05 mmol) in THF (6 ml) and MeOH (6 ml) at 0°C was added NaBH₄ (47.5 mg, 1.26 mmol), and the mixture was stirred for 1h. The mixture was quenched at 0°C with sat. aq. NH₄Cl and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide the product of Step 7 (810 mg, 100% yield) as yellow foam.

Step 8

To a solution of the product of Step 7 (222 mg, 0.290 mmol) in DCM (6 ml) at 0°C was added MsCl (0.045 ml, 0.580 mmol) followed by DIPEA (0.202 ml, 1.16 mmol), and the mixture was allowed to warm to RT and stirred overnight. More MsCl (0.020 ml) and DIPEA (0.070 ml) were added, and the mixture was stirred for 6h. The mixture was quenched at RT with sat. aq. NaHCO₃ and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (ISCO 24 g, eluting with Hexanes/EtOAc 99:1 to 30:70) to give the product of Step 8 (139 mg, 61% yield).

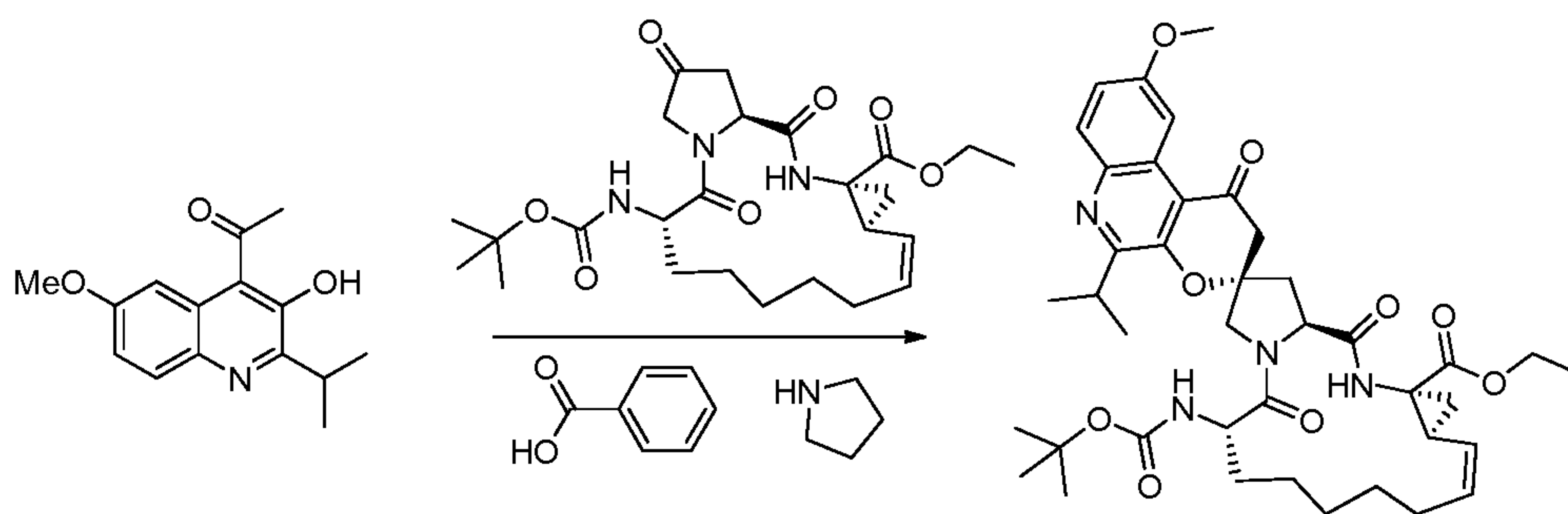
Step 9

To a solution of the product of Step 8 (139 mg, 0.177 mmol) in MeOH (9 ml) at -78°C was added NiCl₂·6H₂O (39.2 mg, 0.165 mmol) then 2N LiBH₄ in THF (0.266 ml, 0.532 mmol). The reaction was allowed to warm to 0°C over 1h then stirred at this temperature for 15 min. The mixture was quenched at 0°C with sat. aq. NaHCO₃ and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 20:80) to give the product of Step 9 (65.6 mg, 49% yield).

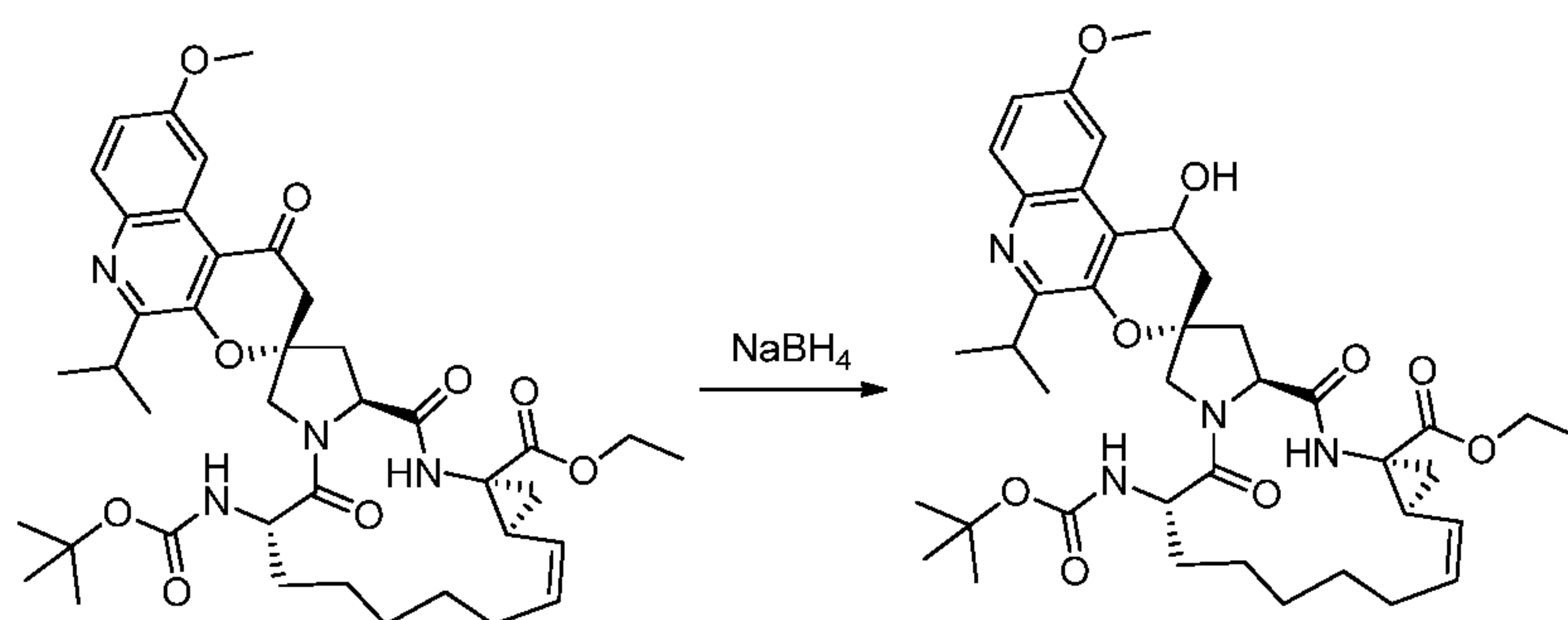
Step 10

To a solution of the product of Step 9 (65.6 mg, 0.088 mmol) in THF (1.2 ml), MeOH (1.2 ml) and water (3 ml) at RT was added LiOH·H₂O (11.0 mg, 0.263 mmol), and the mixture was stirred at 40°C overnight. The mixture was concentrated *in vacuo* then quenched at RT with ice-cold 0.2N aq. HCl and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo* to give an intermediate acid (63.4 mg, 100% yield). To a solution of this intermediate acid (63.4 mg, 0.088 mmol) in THF (2.5 ml) at RT was added carbonyl diimidazole (28.5 mg, 0.176 mmol), and the mixture was warmed to 70°C and stirred for 5h. 1-Methylcyclopropane-1-sulfonamide (47.5 mg, 0.352 mmol) and DBU (0.053 ml, 0.352 mmol) were then added at RT, and the reaction was warmed to 50°C and stirred for 8h. The mixture was quenched at RT with sat. aq. NH₄Cl and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) then preparative TLC over silica gel (eluting with Hexanes/Acetone 6:4) to afford I-31 (7.8 mg, 11% yield) as a white solid. ¹H-NMR (400 MHz, CDCl₃) δ 10.11 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.58 (t, J = 8.4 Hz, 1H), 6.84 (s, 1H), 5.72 (m, 1H), 4.95-5.07 (m, 2H), 4.62 (m, 1H), 4.46 (m, 1H), 4.13 (m, 1H), 3.70 (d, J = 10.8 Hz, 1H), 3.15-3.35 (m, 2H), 2.45-2.65 (m, 2H), 2.25-2.40 (m, 4H), 1.65-1.95 (m, 5H), 1.20-1.50 (m, 8H), 1.48 (m, 3H), 1.25 (s, 9H), 0.82 (br s, 2H); LC-MS (M⁺) Calc. for C₃₉H₄₇ClF₃N₅O₈S 837.3 Found 782.0 (M+H-tBu)+.

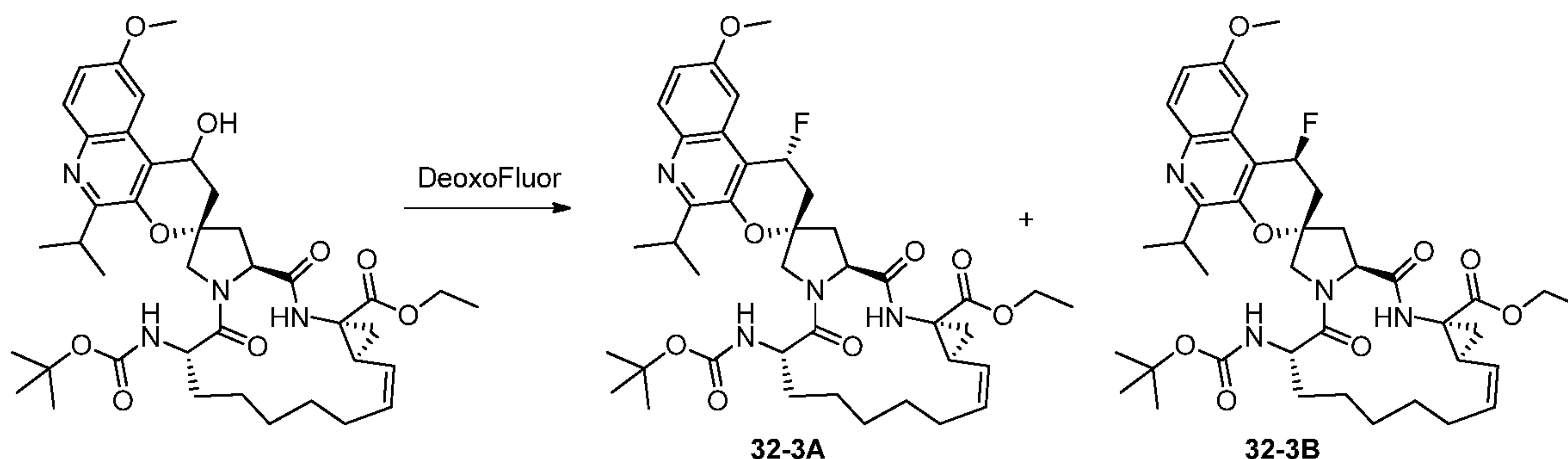
Example 32: tert-butyl ((1'R,2S,6S,13aS,14aR,16aS,Z)-1'-fluoro-5'-isopropyl-9'-methoxy-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-32)

Step 1

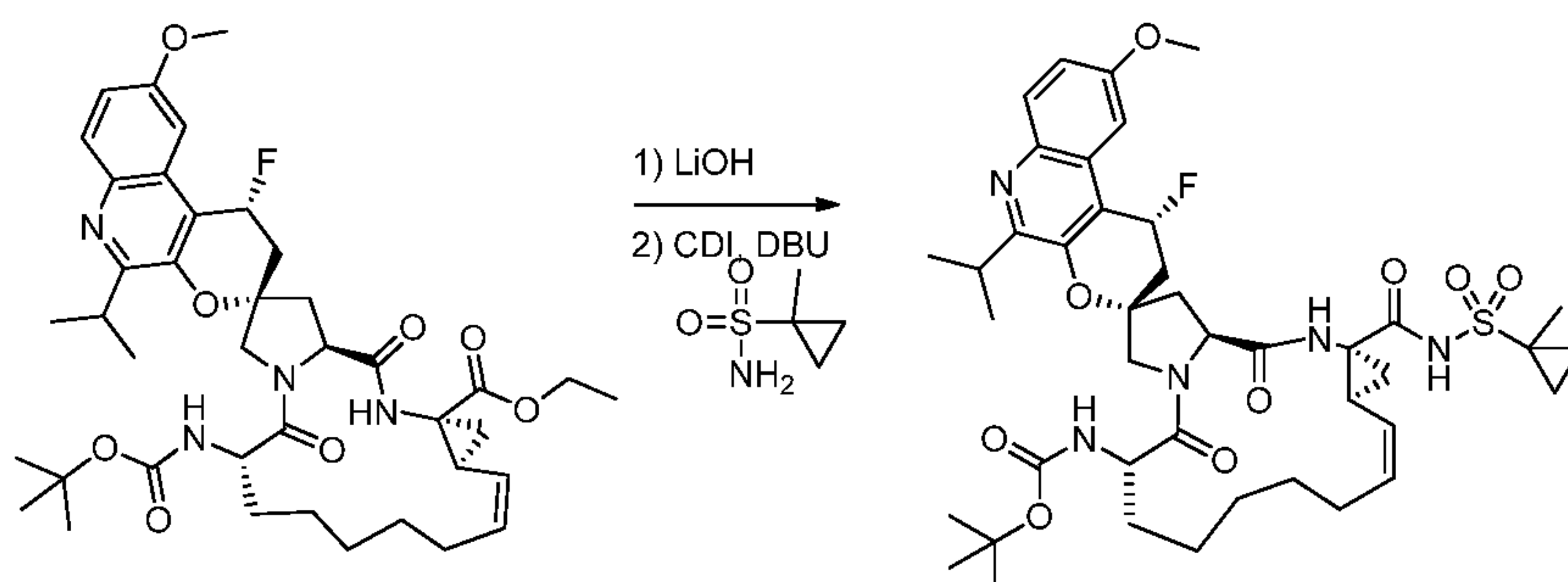
To a solution of the product of Example 2, Step 3 (325 mg, 1.25 mmol), macrocyclic ketone (616 mg, 1.25 mmol) and benzoic acid (153 mg, 1.25 mmol) in MeOH (10 ml) at RT was added pyrrolidine (0.040 ml, 0.50 mmol) and molecular sieves (4A, ~1 g), and the mixture was warmed to 60°C and stirred for 72h. The mixture was quenched at RT with sat. aq. NaHCO₃ and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 40:60) to give the product of Step 1 (686 mg, 75% yield) as yellow foam.

Step 2

To a solution of the product of Step 1 (686 mg, 0.94 mmol) in THF (5 ml) and MeOH (5 ml) at 0°C was added NaBH₄ (42.5 mg, 1.12 mmol), and the mixture was stirred for 1h. The mixture was quenched at 0°C with sat. aq. NH₄Cl and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide the product of Step 2 (671 mg, 98% yield) as yellow foam.

Step 3

To a solution of the product of Step 2 (671 mg, 0.91 mmol) in DCM (9 ml) at 0°C was added DEOXOFLUOR (0.20 ml, 1.10 mmol) and EtOH (0.005 ml), and the mixture was
 5 allowed to warm to RT and stirred overnight. The mixture was quenched at RT with sat. aq. NaHCO₃ and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to 50:50) to give, in order of elution, intermediate 32-3A (301 mg, 45% yield) followed by intermediate 32-3B (241 mg, 36% yield).

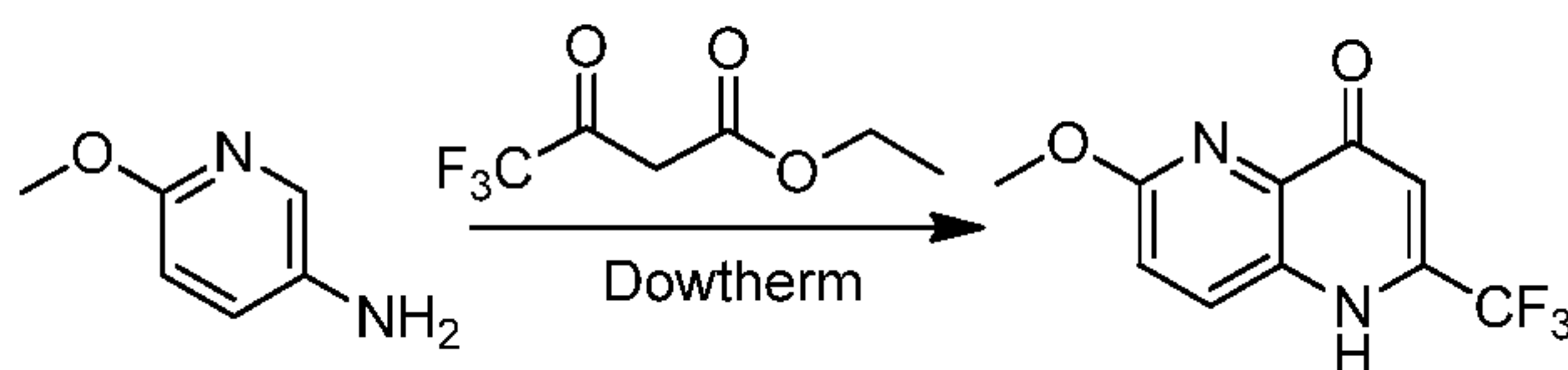
10 Step 4

To a solution of intermediate 32-3A from Step 3 (301 mg, 0.408 mmol) in THF (5 ml), MeOH (5 ml) and water (3 ml) at RT was added LiOH·H₂O (51.4 mg, 1.23 mmol), and the mixture was stirred at RT overnight. More LiOH·H₂O (15 mg) was added, and the reaction was
 15 stirred another 2h at RT. The mixture was concentrated *in vacuo* then quenched at RT with ice-cold 0.2N aq. HCl and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo* to give an intermediate acid (263 mg, 91% yield). To a solution of this intermediate acid (263 mg, 0.371 mmol) in THF (10 ml) at RT was added carbonyl diimidazole (120 mg, 0.742 mmol), and the mixture was warmed to 70°C and stirred for
 20 6h. 1-methylcyclopropane-1-sulfonamide (201 mg, 1.48 mmol) and DBU (0.22 ml, 1.48 mmol) were then added at RT, and the reaction was warmed to 50°C and stirred for 8h. The mixture

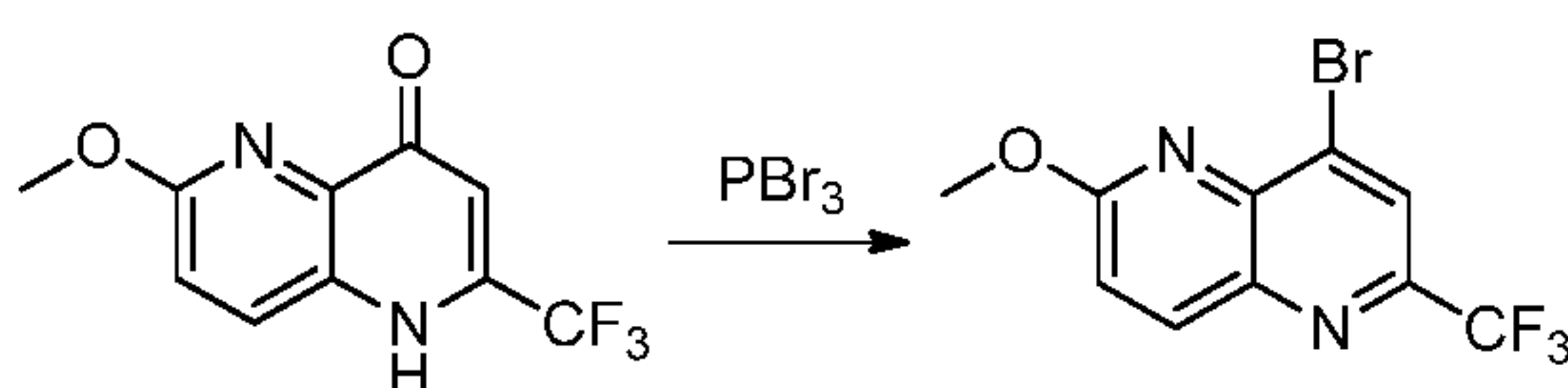
was quenched at RT with sat. aq. NH_4Cl and extracted with EtOAc. The combined organic fractions were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/Acetone 99:1 to 50:50) to afford I-32 (231 mg, 75% yield) as a white solid. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 10.02 (s, 1H), 7.90 (d, $J = 10.0$ Hz, 1H), 7.20 (m, 2H), 6.86 (s, 1H), 6.13 and 6.00 (br s, 1H), 5.71 (m, 1H), 5.17 (m, 1H), 5.01 (m, 1H), 4.50 (m, 1H), 4.36 (m, 1H), 3.94 (s, 3H), 3.99 (d, $J = 11.2$ Hz, 1H), 3.43 (m, 1H), 2.50-2.75 (m, 2H), 2.44 (m, 1H), 2.30 (m, 1H), 1.72-1.95 (m, 4H), 1.50-1.70 (m, 2H), 1.20-1.50 (m, 8H), 1.43 (s, 3H), 1.39 (s, 9H), 0.80 (br s, 2H); LC-MS (M^+) Calc. for $\text{C}_{42}\text{H}_{56}\text{FN}_5\text{O}_9\text{S}$ 825.38 Found 826.2 $[\text{M}+\text{H}]^+$.

10

Example 33: *tert*-butyl ((2S,6S,13aS,14aR,16aS,Z)-10'-fluoro-2'-methoxy-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-6'-(trifluoromethyl)-3,5,6,7,8,9,9',10,10',11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,8'-pyrano[2,3-c][1,5]naphthyridin]-6-yl)carbamate (I-33)

15 Step 1

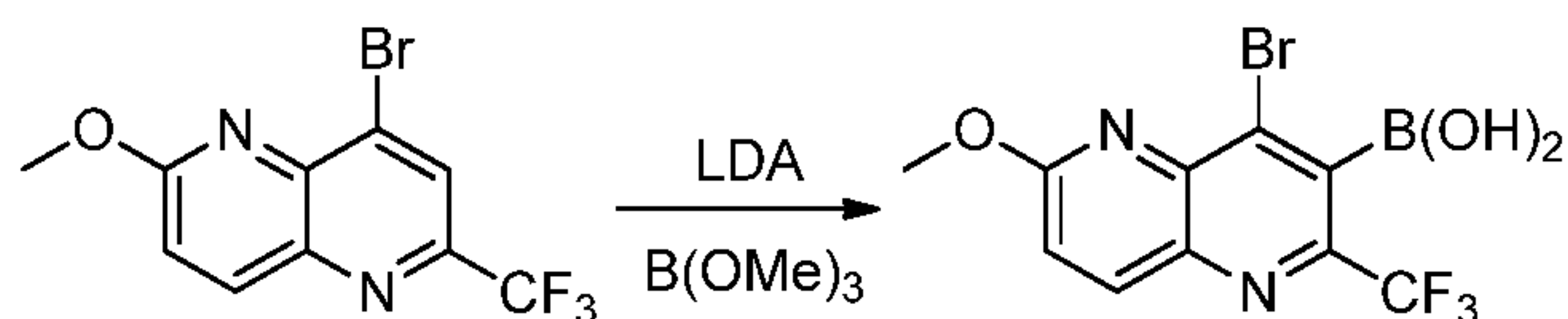
To a solution of 5-amino-2-methoxypyridine (25 g, 201 mmol) in DOWTHERM (250 ml) at RT was added ethyl 4,4,4-trifluoroacetoacetate (32.6 ml, 222 mmol), and the mixture was warmed to reflux (250°C) and stirred for 7h. The mixture was allowed to cool to RT overnight, then filtered over fritted disk, rinsing with hexanes to provide a crude solid. The filtrate solution was purified by column chromatography over silica gel, eluting with hexanes, to remove DOWTHERM. The crude solid was then added to the same column followed by purification through elution from hexanes to hexanes/EtOAc 10:90, to give the product of Step 1 (18.3 g, 37%).

25 Step 2

To a solution of the product of Step 1 (13.2 g, 54.1 mmol) in DMF (100 ml) at 0°C was slowly added PBr_3 (6.10 ml, 64.9 mmol), and the mixture was warmed to 40°C over 1h then stirred overnight at this temperature. The mixture was quenched at 0°C with water (50 ml),

and NaHCO₃ was added slowly until pH ~7. The mixture was filtered over fritted disk, rinsing with water and the resulting solid was dried *in vacuo* to give the product of Step 2 (12.7 g, 77%) as white solid.

Step 3

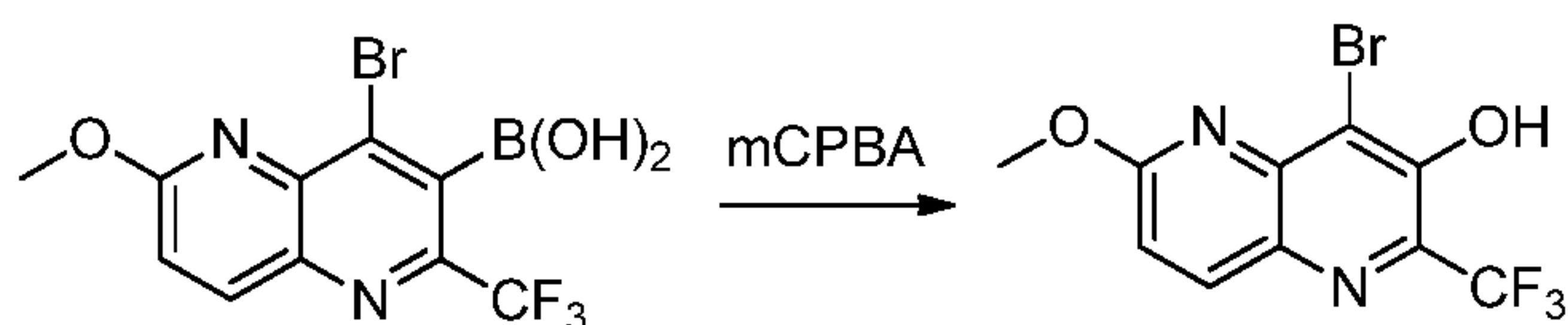


5

To a solution of the product of Step 2 (15.9 g, 51.8 mmol) in THF (200 ml) at -78°C was added 1.8 M LDA in hexanes (115 ml, 207 mmol) slowly over 30 min, and the mixture was stirred at -78°C for 2h. Trimethylborate (46.3 ml, 414 mmol) was added, and the reaction was stirred for 2h at -78°C, then allowed to warm to RT overnight. The final mixture was poured at 0°C over ice-cold 1N aq. HCl (200 ml) and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford the crude product of Step 3 (22.7 g).

10

Step 4



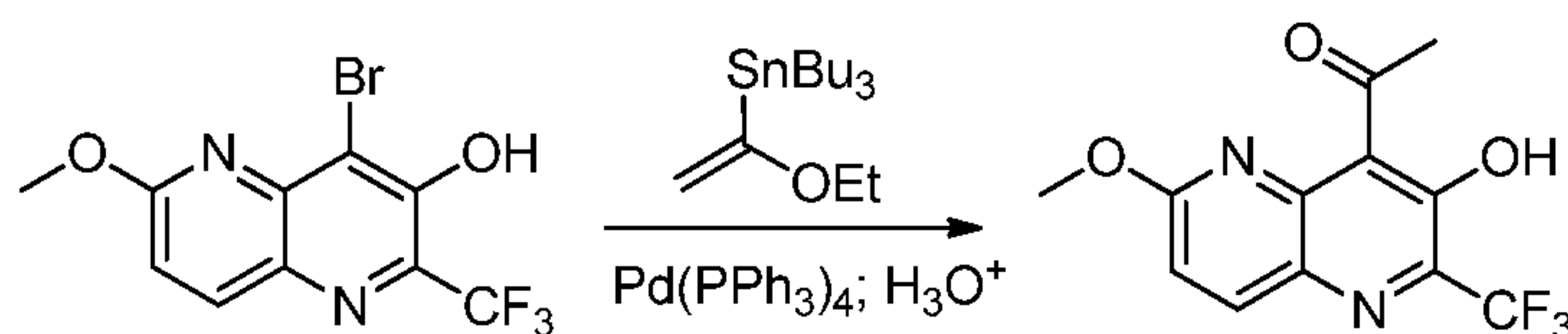
15

To a solution of the crude product of Step 3 (18.2 g, 51.8 mmol) in MeCN (400 ml) at RT was added 70% mCPBA (13.40 g, 78 mmol), and the mixture was stirred for 15 min. Solid NaHCO₃ (6.53 g, 78 mmol) was then added at RT, and the reaction was stirred overnight. The mixture was quenched at RT with water (200 ml), treated with NaHSO₃ (3.77 g, 36.2 mmol) and extracted with EtOAc. The combined organic fractions were washed with sat. aq. NaHCO₃, dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide crude 1. The combined aq. layers were slowly acidify to pH=4-5 with concentrated HCl, exacted with EtOAc, dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide crude 2. Crudes 1 and 2 were combined and purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to Hexanes/EtOAc 20:80 then DCM to DCM/EtOAc 50:50). The purified fractions were diluted with EtOAc, washed with sat. aq. NaHCO₃/brine 1:1, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the product of Step 4 (8.7 g, 51%).

20

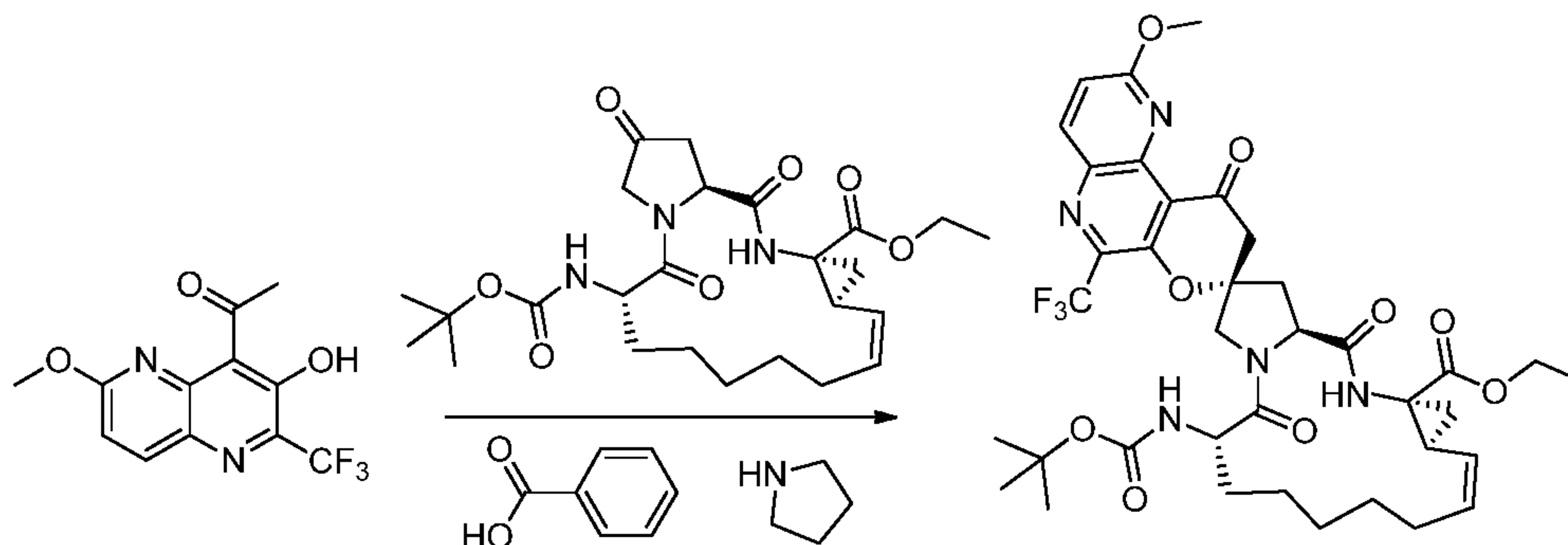
25

Step 5

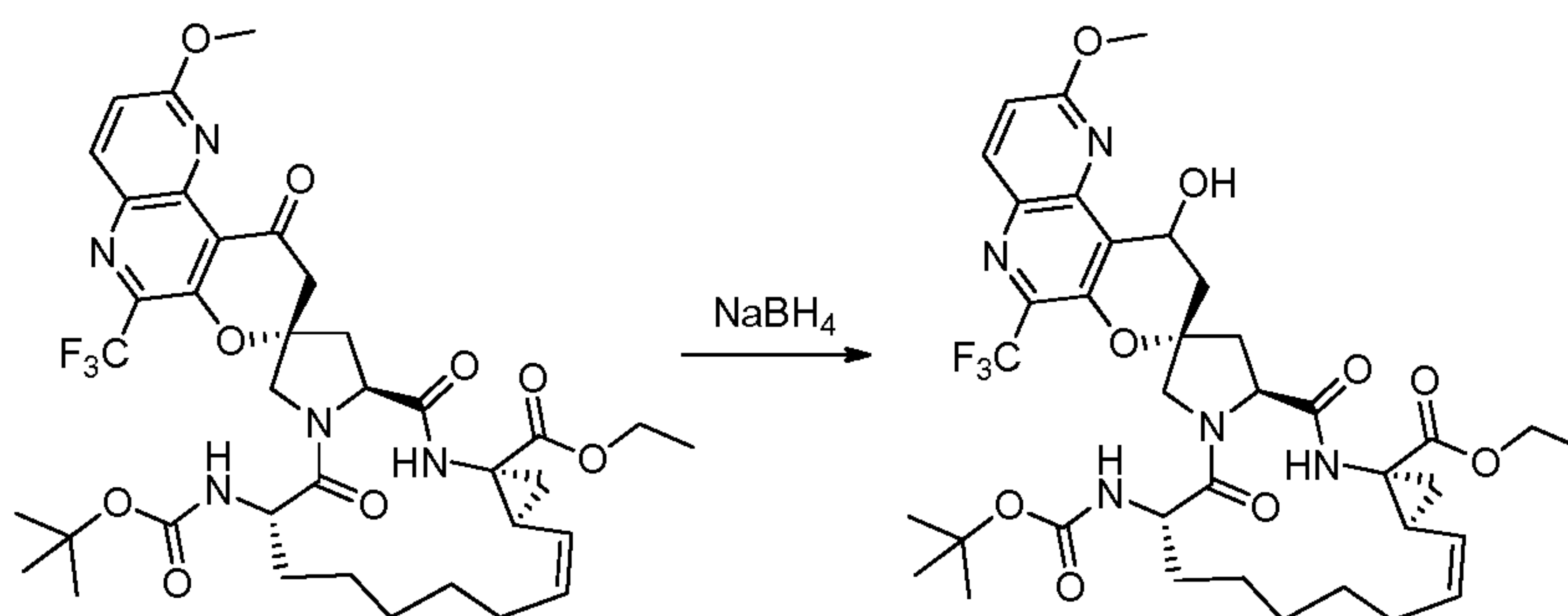


To a solution of the product of Step 4 (3.30 g, 10.2 mmol) and Pd(PPh₃)₄ (1.18 g, 1.02 mmol) in 1,4-dioxane (30 ml) at RT was added tributyl(1-ethoxyvinyl)tin (10.4 ml, 30.6 mmol), and the mixture was warmed to 110°C and stirred overnight. The mixture was quenched at 0°C with 1N aq. HCl (100 ml) and stirred at RT for 1h. The mixture was neutralized with sat. aq. NaHCO₃ until pH ~7 and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes to Hexanes/EtOAc 50:50) to give the product of Step 5 (2.07 g, 71%).

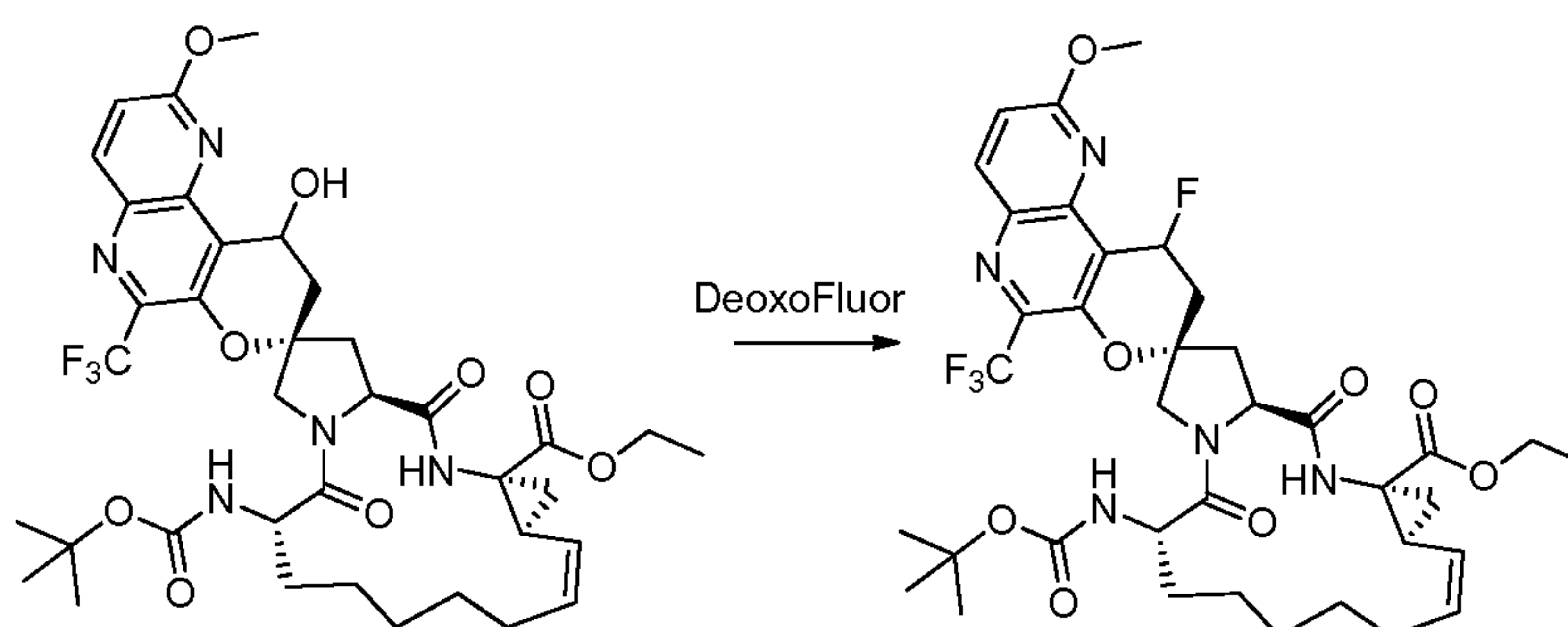
10 Step 6



To a solution of the product of Step 5 (520 mg, 1.82 mmol), macrocyclic ketone (893 mg, 1.82 mmol) and benzoic acid (222 mg, 1.82 mmol) in MeOH (12 ml) at RT was added pyrrolidine (0.145 ml, 1.82 mmol) and molecular sieves (4A, ~1 g), and the mixture was warmed to 65°C and stirred for 48h. The mixture was quenched at RT with sat. aq. NaHCO₃ and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) to give, in order of elution, starting material (131 mg) followed by the crude product of Step 6 (664 mg, 48% yield).

Step 7

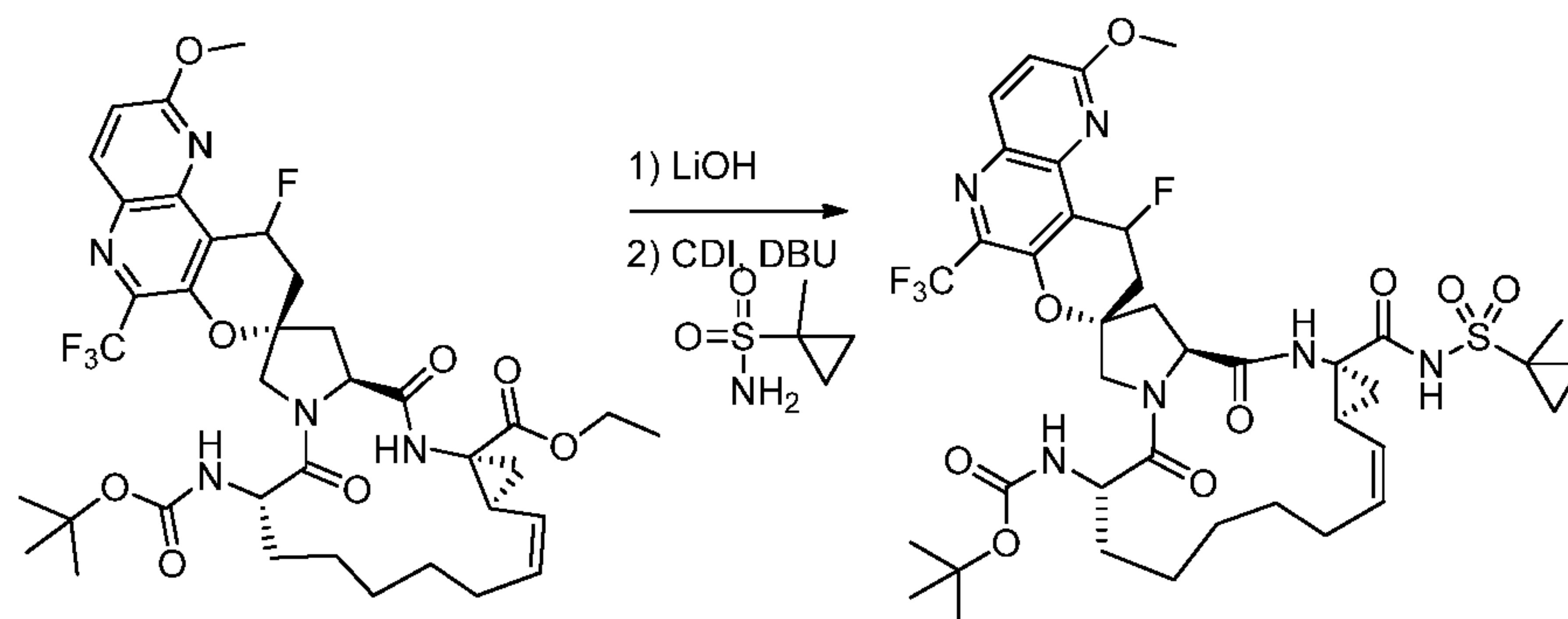
To a solution of the crude product of from Step 6 (664 mg, 0.87 mmol) in THF (5 ml) and MeOH (5 ml) at 0°C was added NaBH₄ (39.7 mg, 1.05 mmol), and the mixture was stirred for 1h. The mixture was quenched at 0°C with sat. aq. NH₄Cl and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) to give the product of Step 7 (228 mg, 34% yield) as yellow foam.

Step 8

10

To a solution of the product of Step 7 (228 mg, 0.299 mmol) in DCM (4 ml) at 0°C was added DEOXOFLUOR (0.066 ml, 0.359 mmol) and EtOH (0.005 ml), and the mixture was allowed to warm to RT and stirred overnight. The mixture was quenched at RT with sat. aq. NaHCO₃ and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/EtOAc 99:1 to EtOAc) to give the product of Step 8 (66.9 mg, 29% yield) as a ~1:1 mixture of diastereoisomers at the benzylic fluoride.

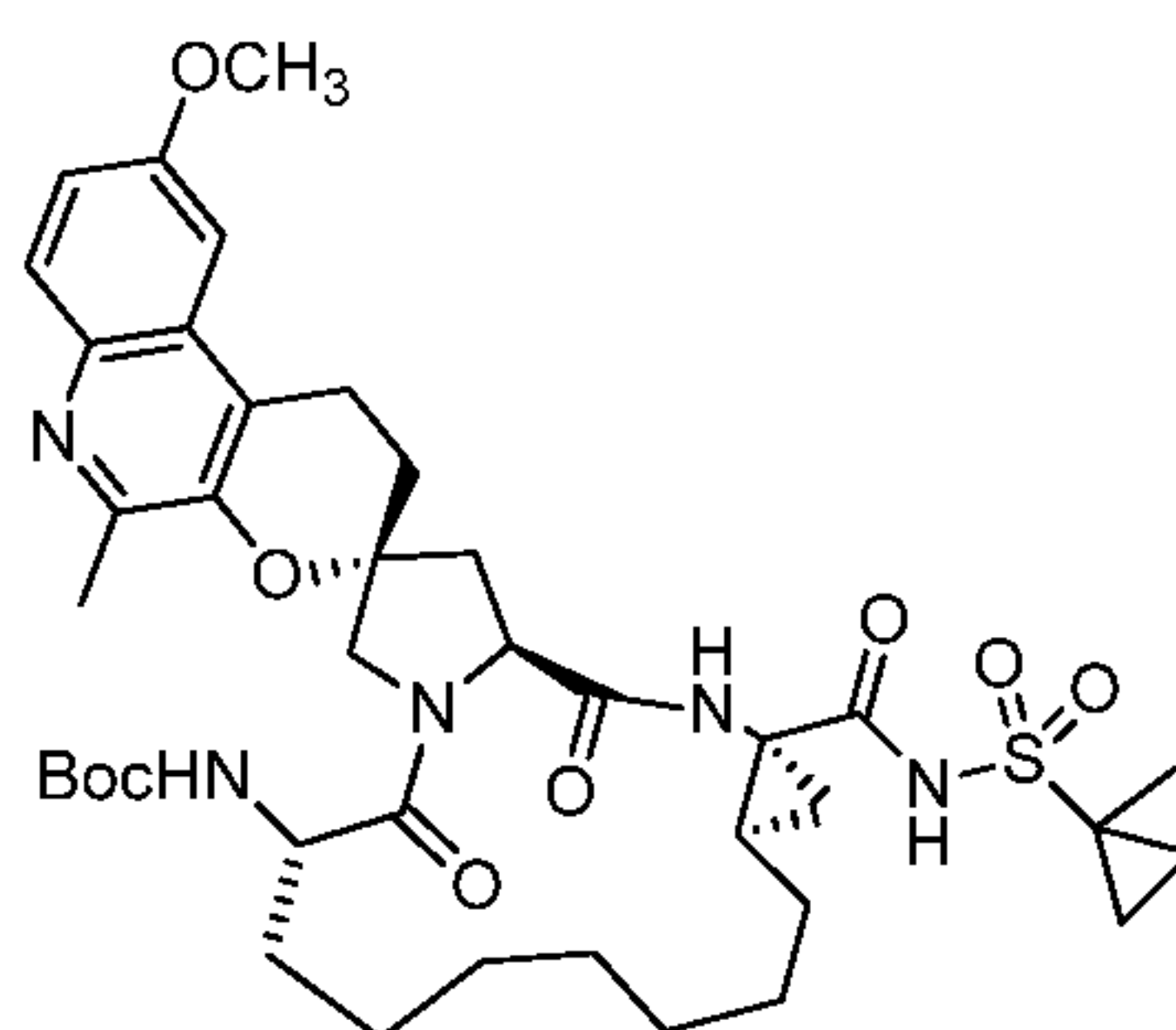
15

Step 9

To a solution of the product of Step 8 (66.9 mg, 0.088 mmol) in THF (1.2 ml), MeOH (1.2 ml) and water (0.7 ml) was added LiOH·H₂O (18.38 mg, 0.438 mmol), and the mixture was stirred at RT overnight. The mixture was concentrated *in vacuo* then quenched at RT with ice-cold 0.2N aq. HCl and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo* to give an intermediate acid (68.5 mg).

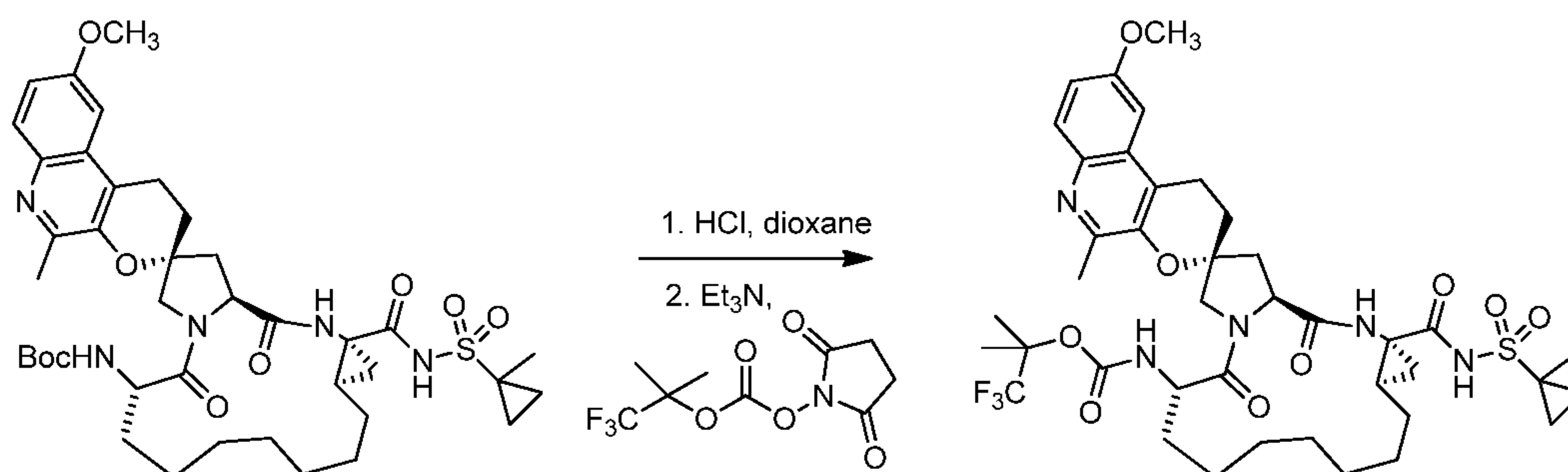
To a solution of this intermediate acid (68.5 mg, 0.093 mmol) in THF (2.5 ml) at RT was added carbonyl diimidazole (30.2 mg, 0.186 mmol), and the mixture was warmed to 70°C and stirred for 6h. 1-Methylcyclopropane-1-sulfonamide (50.3 mg, 0.372 mmol) and DBU (0.056 ml, 0.372 mmol) were then added at RT, and the reaction was warmed to 45°C and stirred overnight. The mixture was quenched at RT with sat. aq. NH₄Cl and extracted with EtOAc. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel (eluting with Hexanes/acetone 99:1 to 50:50) to give I-33 (33.9 mg, 43% yield) as a ~1:1 mixture of diastereoisomers at the benzylic fluoride, as colorless oil. ¹H-NMR (400 MHz, CDCl₃) δ 10.15 and 10.07 (s, 1H), 8.21 (d, 1H), 7.08 (d, 1H), 6.88 (s, 1H), 6.55 and 6.43 (br d, 1H), 5.70 (m, 1H), 5.26 (d, 1H), 4.95-5.05 (m, 2H), 4.72 (m, 1H), 4.45-4.65 (m, 2H), 4.36 (m, 1H), 4.07 (m, 1H), 3.90 and 3.74 (d, 1H), 2.25-2.75 (m, 5H), 1.60-1.95 (m, 6H), 1.15-1.55 (m, 8H), 1.57 (m, 3H), 1.39 (s, 9H), 0.80 (br s, 2H); LC-MS (M⁺) Calc. for C₃₉H₄₈F₄N₆O₉S 852.31 Found 853.2.

Example 34: *tert*-Butyl ((2R,6S,13aR,14aR,16aS)-9'-methoxy-5'-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,12,13,13a,14,14a,15,16,16a-octadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-34)



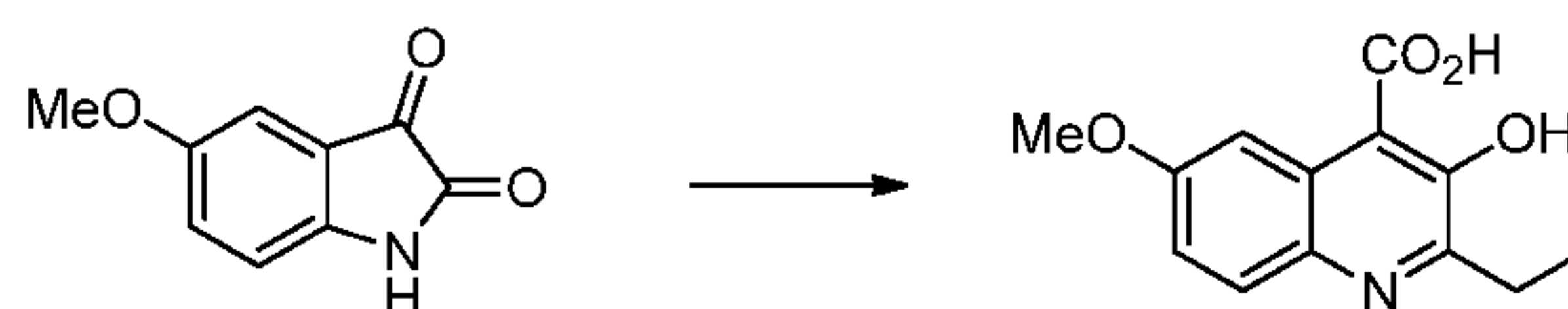
A suspension of I-9 (260 mg, 0.333 mmol), 10% Pd/C (26 mg) in EtOAc (6 ml) was stirred under a H₂ balloon. LC-MS at 4h indicated no product formation. The mixture was filtered through a CELITE pad, evaporated to dryness and once again stirred with 60 mg of 10% Pd/C in 5 ml of MeOH under H₂ balloon for 5h. The reaction mixture was filtered through a CELITE pad and evaporated to dryness. The crude product was purified by SFC chromatography followed by silica-gel chromatography eluting with 0-40-100% acetone-hexanes to give 54 mg of I-34. LC-MS: m/e = 782.2 (MH⁺).

10 **Example 35: 1,1,1-trifluoro-2-methylpropan-2-yl ((2R,6S,13aR,14aR,16aS)-9'-methoxy-5'-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,12,13,13a,14,14a,15,16,16a-octadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-35)**

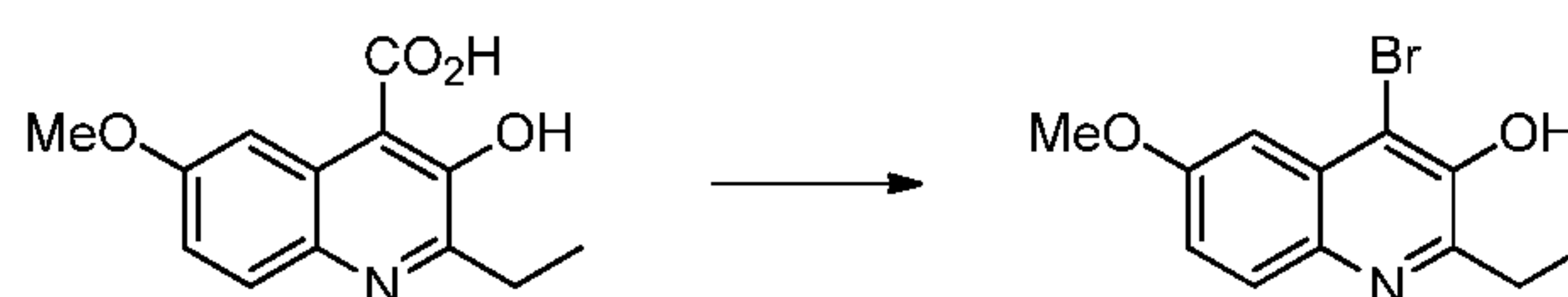


15 I-34 was converted to I-35 using procedures similar to that of Example 20. LC-MS: m/e = 836.2 (MH⁺).

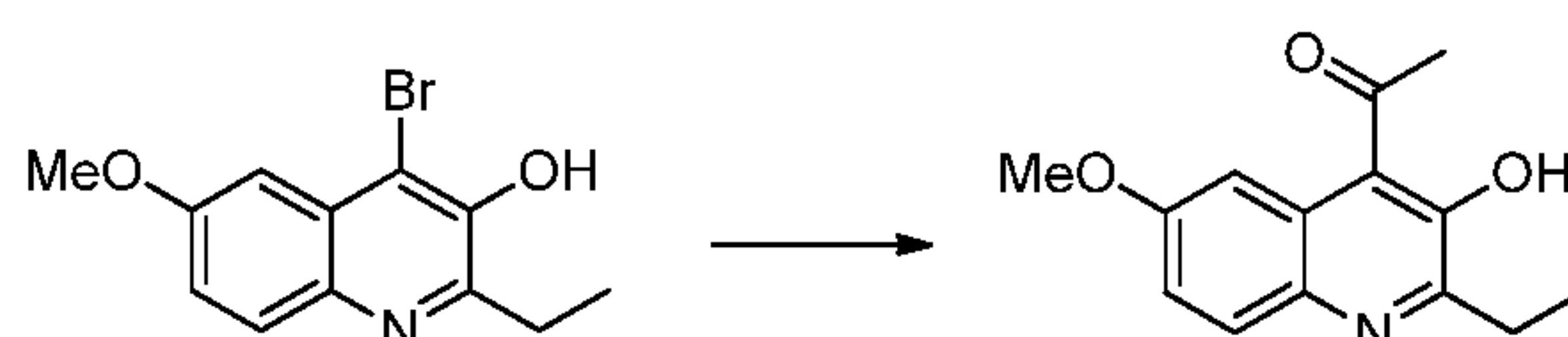
20 **Example 36: Neopentyl ((1'R,2S,6S,13aS,14aR,16aS,Z)-5'-ethyl-1'-fluoro-9'-methoxy-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-36)**

Step 1

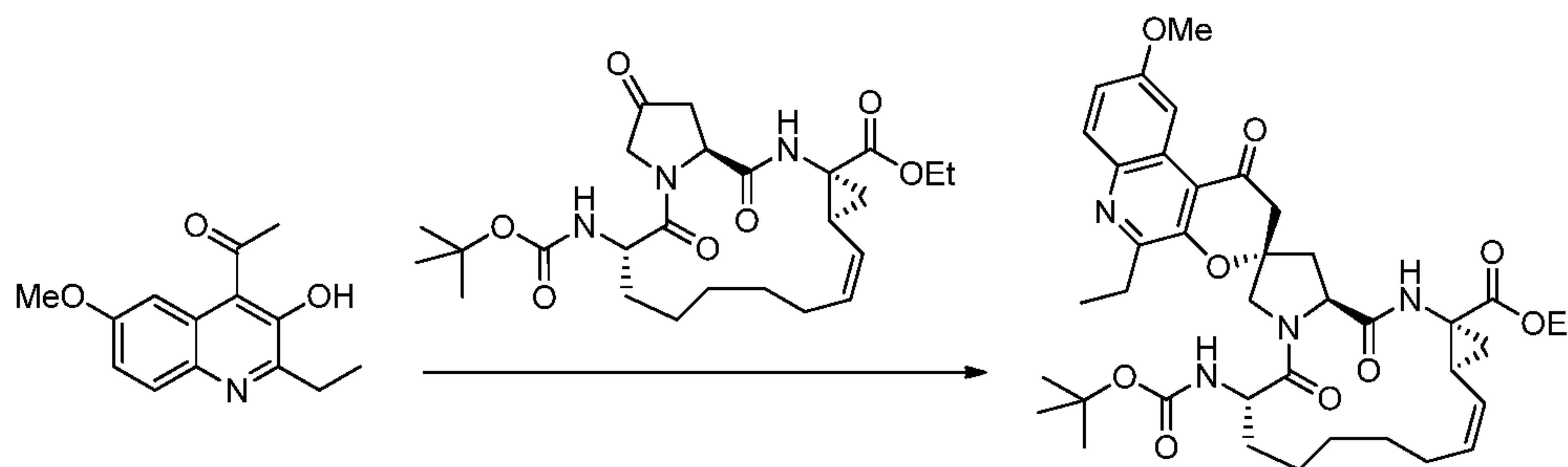
A solution of 5-methoxy isatin (7 g) in 150 ml of water was treated with $\text{Ca}(\text{OH})_2$ (6.65 g) and heated at 80°C for 1h. The reaction mixture was treated with 2-bromobutanone (11.93 g) and stirred at 80°C for 6h. The reaction mixture was cooled to RT and acidified with concentrated HCl until the aq. layer turns acidic. The precipitated solid was filtered dried extensively to give the product of Step 1 (7.4 g, 76%) as a white solid.

Step 2

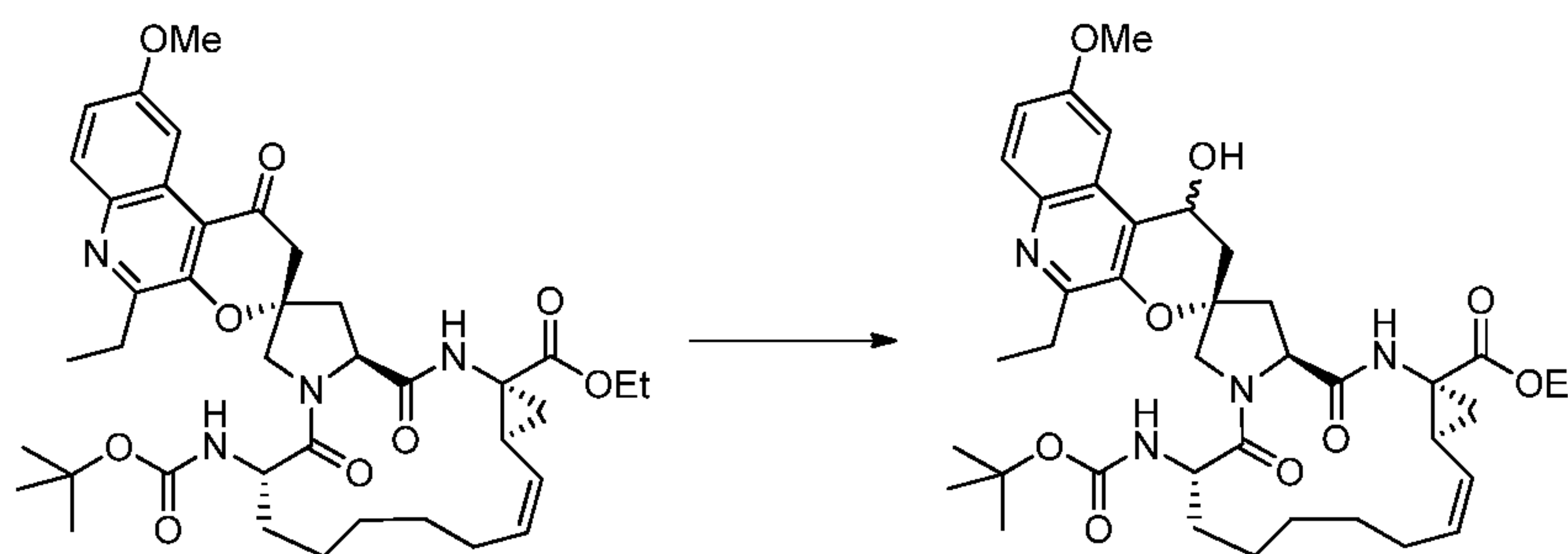
A solution of the product of Step 1 (6.08 g, 24.59 mmol) in THF (60 ml) was treated with NBS (4.38 g, 24.59 mmol) at RT and stirred for 1h. TLC with 45% EtOAc/Hexanes. The solvent was removed by evaporation, EtOAc was added, and the resulting solution was washed with water and brine, and the solvent was removed to give 5.99 g crude brown solid. After TLC with 25% EtOAc/Hexanes, the crude solid was purified on ANALOGIX with 120 g REDISEP column eluting with 0-60% EtOAc/Hexanes. 4.93 g of the product of Step 2 (71%) was isolated as light brown solid.

Step 3

A solution of the product of Step 2 (4.92 g, 17.44 mmol) in dioxane (98 ml) was treated with tributyl(1-ethoxyvinyl)tin (11.78 ml, 34.9 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (1.224 g, 1.744 mmol) and heated in an oil bath at 115°C under N_2 atmosphere for 3h. The reaction mixture was cooled and treated with aq. HCl (1 m, 100 ml) and stirred at RT for 1h. The reaction mixture was made basic with 125 ml sat. NaHCO_3 and extracted into EtOAc. After TLC with 5% EtOAc/DCM, the crude solid was purified on ANALOGIX with 220 g REDISEP column eluting with 0-15% EtOAc/DCM. 3.69 g of the product of Step 3 (86%) was isolated as pale greenish yellow solid.

Step 4

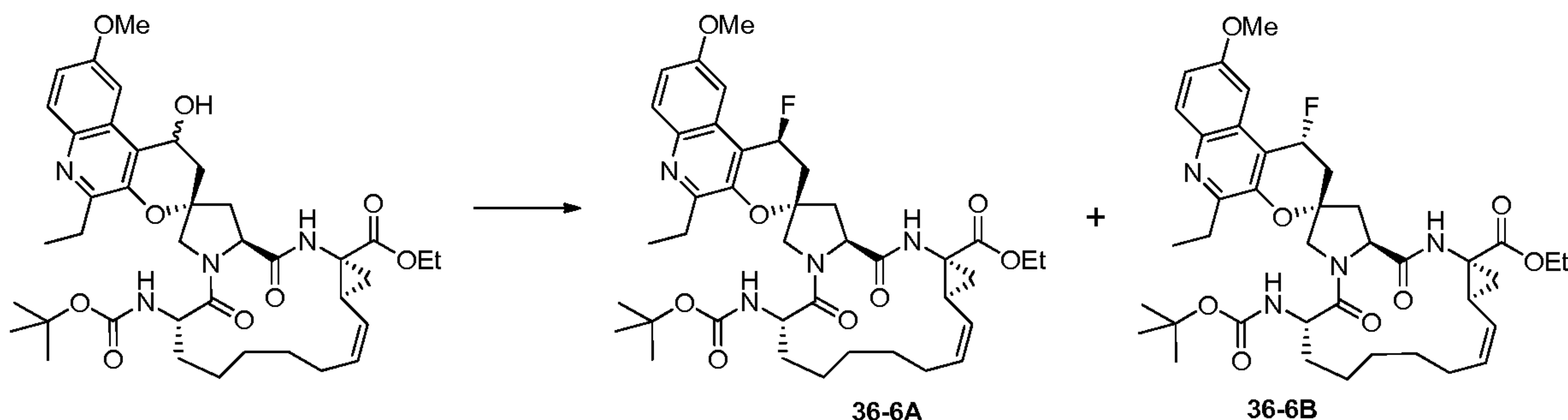
A reaction tube was charged with benzoic acid (149 mg, 1.221 mmol), the product of Step 3 (329 mg, 1.343 mmol) and molecular sieves (600 mg). The tube was sealed, and a solution of ethyl (6*S*,12*Z*,13*aS*,14*aR*,16*aS*)-6-[(*tert*-butoxycarbonyl)amino]-2,5,16-trioxo-1,2,3,6,7,8,9,10,11,13*a*,14,15,16,16*a*-tetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-14*a*(5*H*)-carboxylate (600 mg, 1.221 mmol) in MeOH (4882 μ l) was added followed by addition of pyrrolidine (40.8 μ l, 0.488 mmol). The mixture was stirred (oil bath at 55°C) overnight. TLC (40% EtOAc in DCM) showed a small amount of starting material left. The mixture was diluted with DCM (50 ml), and the solids were removed by filtration. The filtrate was concentrated in a ROTAVAP, and the residue was dissolved in EtOAc (100 ml). The organic layer was washed with half-saturated NaHCO₃ (20 ml), and brine (20 ml), dried over MgSO₄, filtered and concentrated in a ROTAVAP. The residue was purified on a gold cap REDISEP (120 g) silica gel column (gradient: 0-40% EtOAc in DCM) to give the product of Step 4 (470 mg, 0.654 mmol, 53.6% yield) as a white powder.

Step 5

A RB flask was charged with a solution of the product of Step 4 (450 mg, 0.626 mmol) in dry THF (4695 μ l) and MeOH (1565 μ l). The mixture was cooled in ice-water bath and treated with NaBH₄ (26.1 mg, 0.689 mmol). After 30 min, TLC showed complete reaction. The reaction was quenched at 0°C by addition of aq. sat. NH₄Cl (5 ml) and stirred for 15 min. The mixture was diluted with EtOAc (50 ml) and water (5 ml). Upon separation, the organic layer was washed with aq. half-sat. NaHCO₃ (10 ml), and brine (10 ml), dried over MgSO₄, filtered

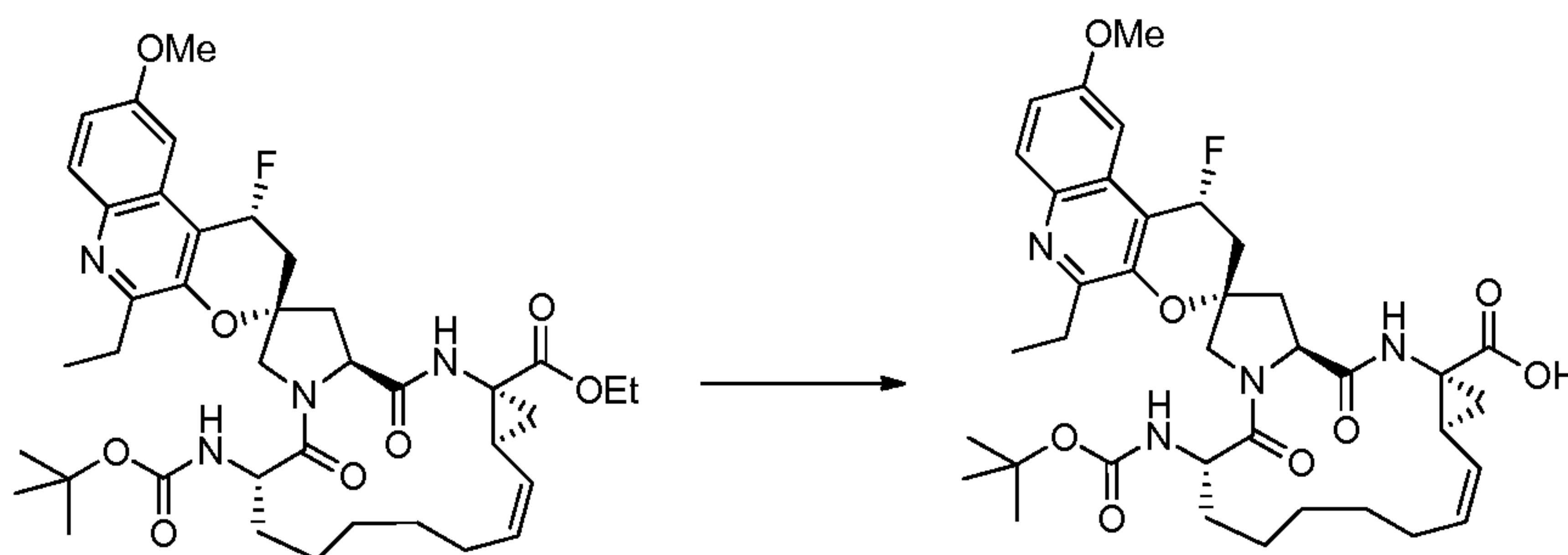
and concentrated in a ROTAVAP to give the crude product of Step 5 (455 mg, 0.631 mmol, 101% yield) as a white powder. The crude was used as it is.

Step 6



5 A RB flask was charged with a solution of diastereomeric alcohol products of Step 5 (360 mg, 0.499 mmol) in dry DCM (9988 μ l). The solution was cooled in ice-water bath and treated with DEOXOFLUOR (184 μ l, 0.999 mmol). LC-MS and TLC showed no starting material after 1h. The reaction was quenched by careful addition of aq. sat. NaHCO_3 (15 ml). The product was extracted into EtOAc (50 ml). The organic layer was dried over MgSO_4 ,
 10 filtered and concentrated in a ROTAVAP. The residue was purified on a gold cap REDISEP (40 g) silica gel column (gradient: 0 to 60% EtOAc in DCM) to give the corresponding diastereomeric products. 36-6B less polar (110 mg, 0.152 mmol, 30.5% yield); 36-6A more polar (140 mg, 0.194 mmol, 38.8% yield).

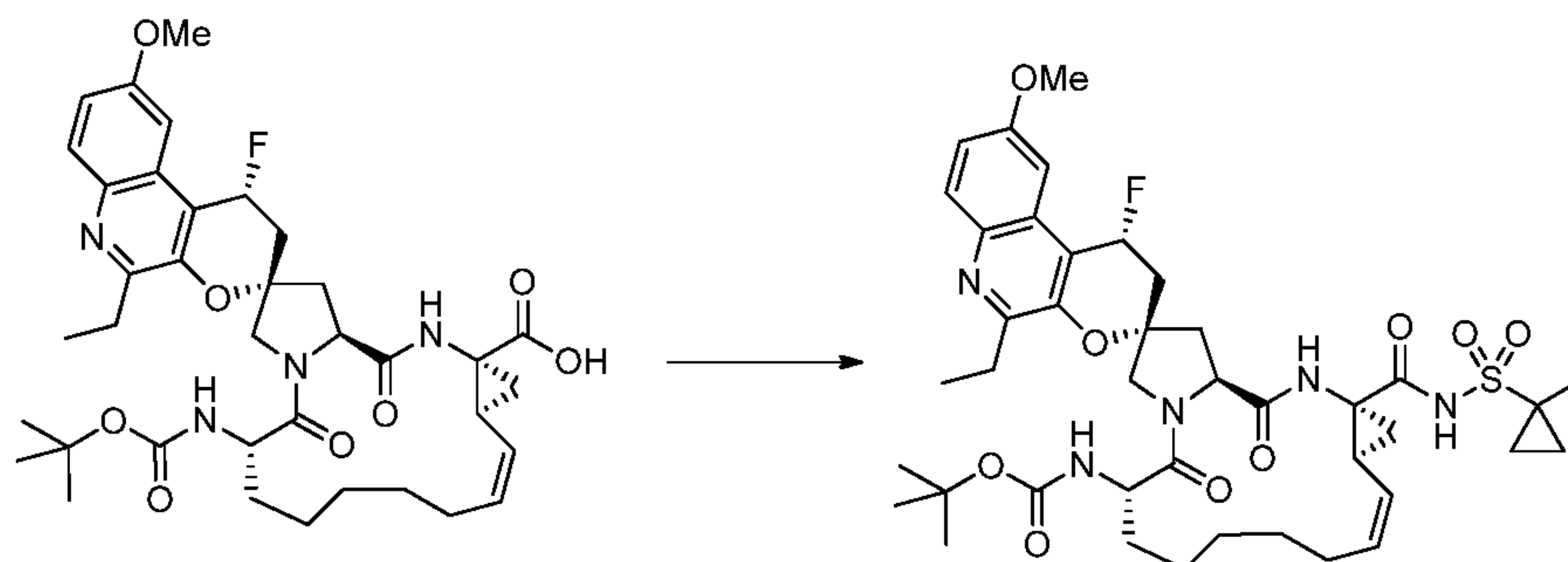
Step 7



15 A RB flask was charged with ethyl ester 36-6B (140 mg, 0.194 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (40.6 mg, 0.968 mmol). THF (3 ml), MeOH (1 ml) and water (1 ml) were added, and the mixture was heated (oil bath at 40°C) and monitored by LC-MS. After 4h, the reaction was quenched by addition of aq. 0.5 M HCl (10 ml). The product was extracted into EtOAc (2x 20 ml). The combined organic layers were washed with brine (5 ml), dried over MgSO_4 , filtered
 20 and concentrated in a ROTAVAP to give the crude product of Step 7 (133 mg, 0.191 mmol, 99%

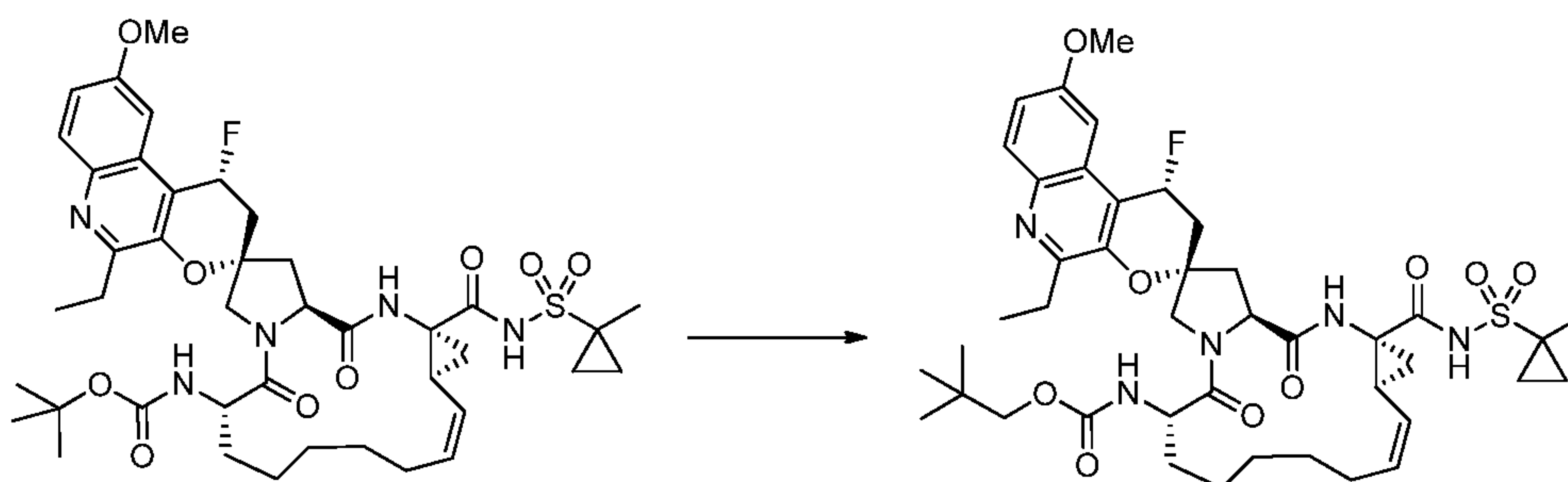
yield) as a white powder. The product was azeotropically dried with toluene (3x 5 ml) and used without further purification.

Step 8



- 5 A reaction tube was charged with CDI (56.0 mg, 0.345 mmol) and sealed. A solution of carboxylic acid product of Step 7 (120 mg, 0.173 mmol) in dry THF (1727 μ l) was added by syringe. The tube was heated (oil bath at 75°C) for 3h. After cooling to RT, a solution of 1-methylcyclopropane-1-sulfonamide (70.0 mg, 0.518 mmol) in dry THF (1 ml) and DBU (77 μ l, 0.518 mmol) were successively added. The tube was heated (oil bath at 55°C) overnight.
- 10 LC-MS showed very little starting material left. The mixture was diluted with EtOAc (20 ml) and washed with aq. sat. NH₄Cl (2x 5 ml) and brine (5 ml), dried over MgSO₄, filtered and concentrated in a ROTAVAP. The residue was purified on a gold cap REDISEP (24 g) silica gel column (gradient: 0 to 40% acetone in hexanes) to give the product of Step 8 (94 mg, 0.116 mmol, 67.0% yield) as a white powder.

15 Step 9

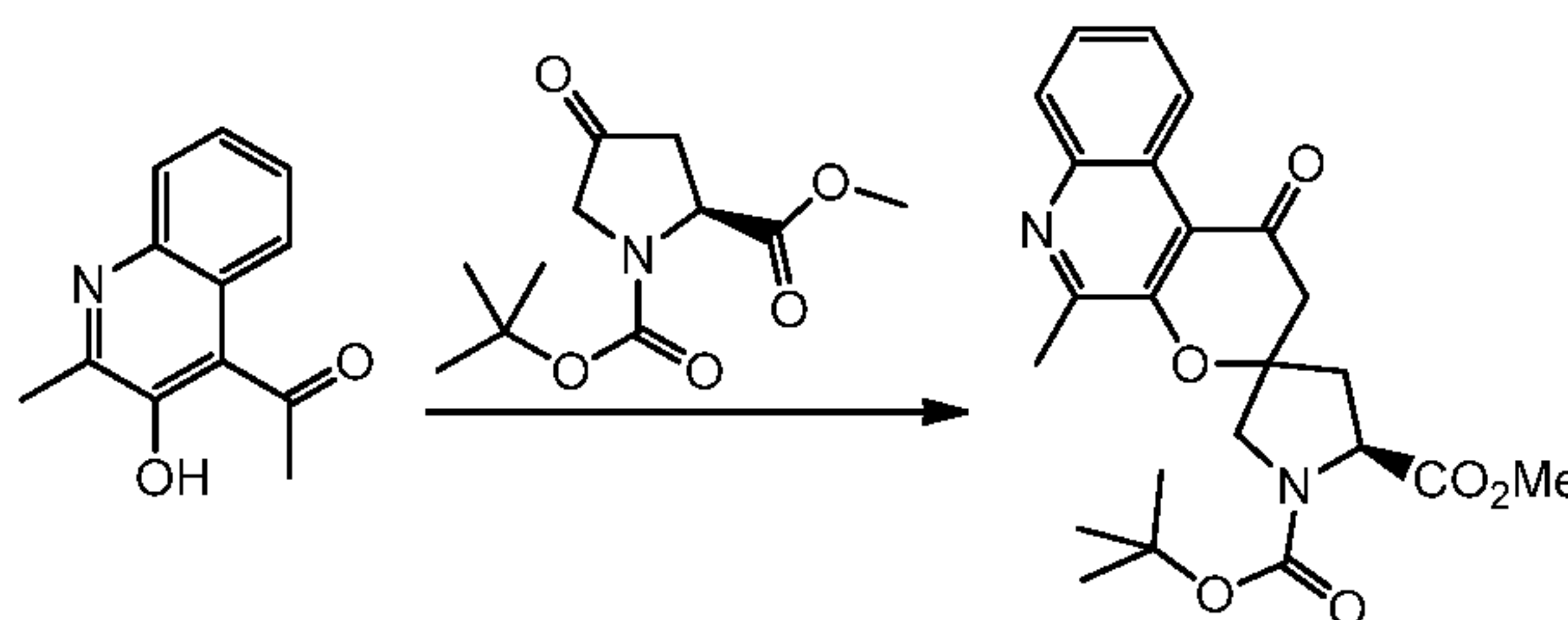


- The N-Boc protected product of Step 8 (87 mg, 0.107 mmol) was dissolved in 4 ml solution in dioxane of HCl (5 ml, 20.00 mmol). The reaction mixture was stirred and monitored by LC-MS. After 2h, there was no more starting material left. The mixture was concentrated to dryness to give the crude amine hydrochloride (81 mg, 0.108 mmol, 101% yield) as a white powder. No further purification was carried out.
- 20

A RB flask was charged with a solution of amine hydrochloride (80 mg, 0.107 mmol) in dry DCM (2 ml) and cooled in an ice-water bath followed by addition of neopentyl chloroformate (0.032 ml, 0.214 mmol) and DIPEA (0.074 ml, 0.428 mmol). The mixture was stirred and monitored by LC-MS. After 2h, no more starting material was left. The solution was purified on a gold cap REDISEP (12 g) silica gel column (gradient: 0 to 40% acetone in hexanes) to give I-36 (75 mg, 0.091 mmol, 85% yield) as a white powder.

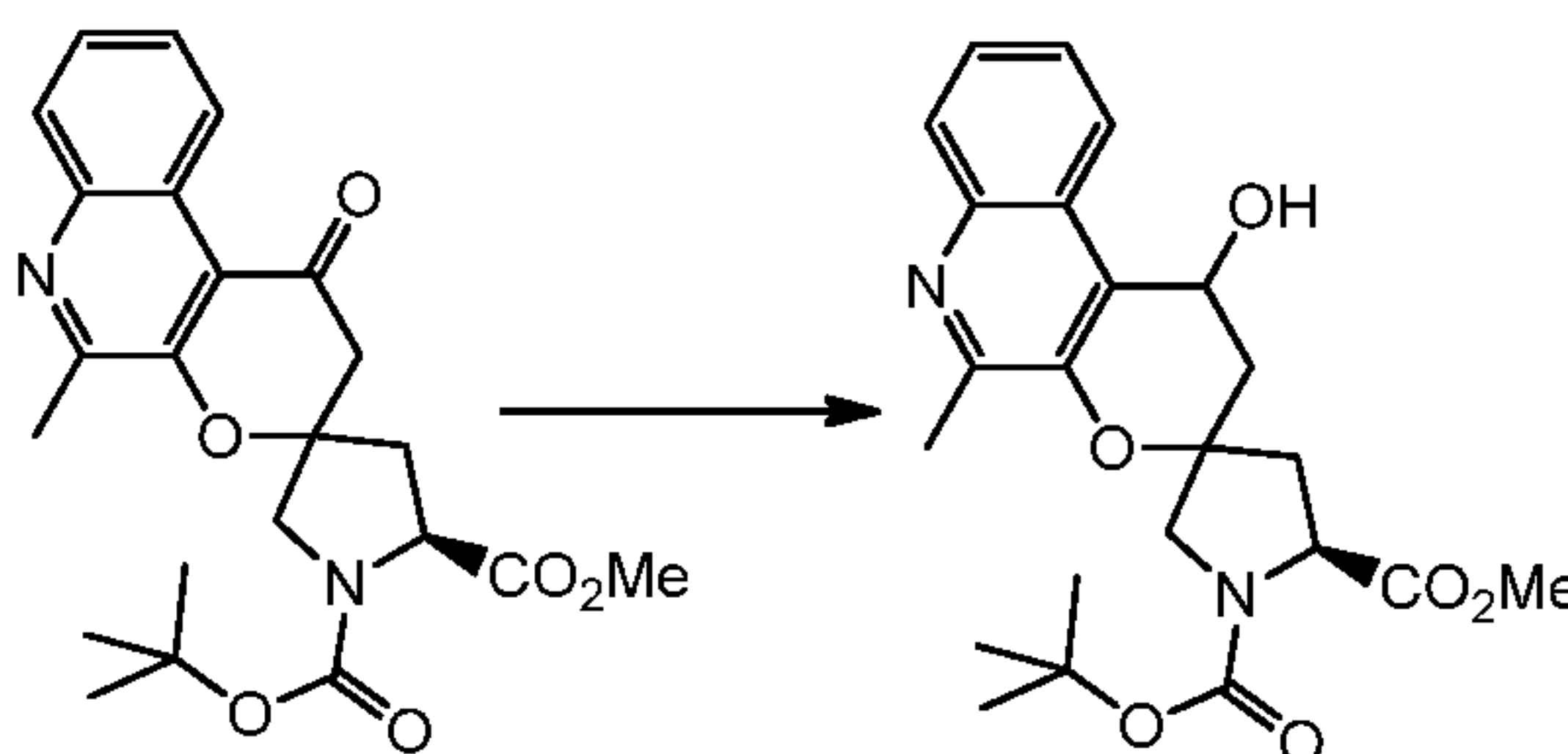
Example 37: tert-butyl ((2R,6S,13aS,14aR,16aS,Z)-5'-(hydroxymethyl)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-37)

Step 1



N-Boc-4-oxo-L-proline methyl ester (1209 mg, 4.97 mmol) and 1-(3-hydroxy-2-methylquinolin-4-yl)ethanone (500 mg, 2.485 mmol) dissolved in MeOH (4970 μ l), pyrrolidine (82 μ l, 0.994 mmol), 3A sieves were added, and the mixture was heated at 105°C in the microwave for 35 min at very high absorbance. The mixture was cooled to RT and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give the product of Step 1 (1.07 g, 75% yield) as a yellow oil.

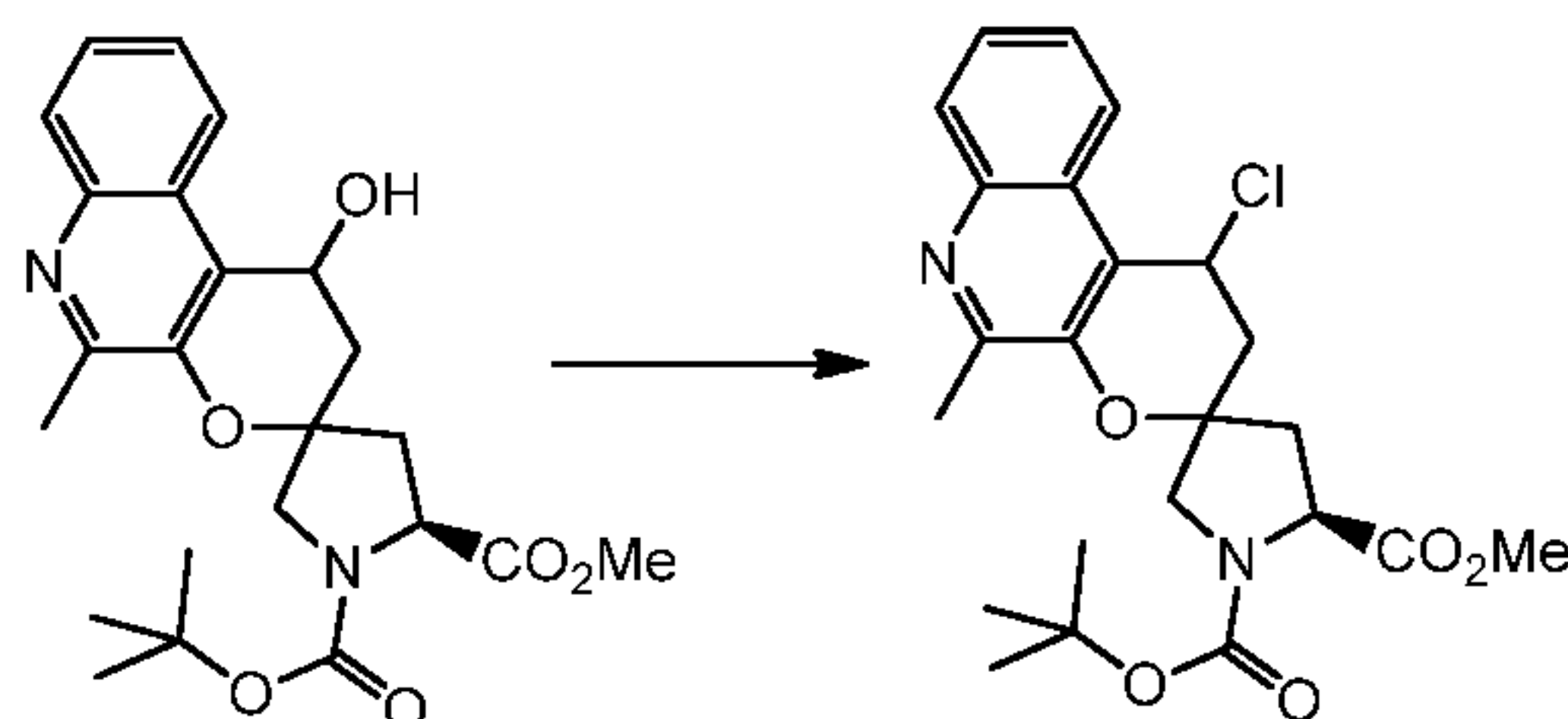
Step 2



The product of Step 1 (800 mg, 1.876 mmol) was dissolved in MeOH (9379 μ l)/THF (9379 μ l), cooled to 0°C, NaBH₄ (71.0 mg, 1.876 mmol) was added, and the mixture stirred for 15 min. The mixture was concentrated, the residue dissolved in EtOAc (100 ml), and the mixture was washed with aq. NH₄Cl (sat., 3x 30 mL), dried (MgSO₄), filtered, and

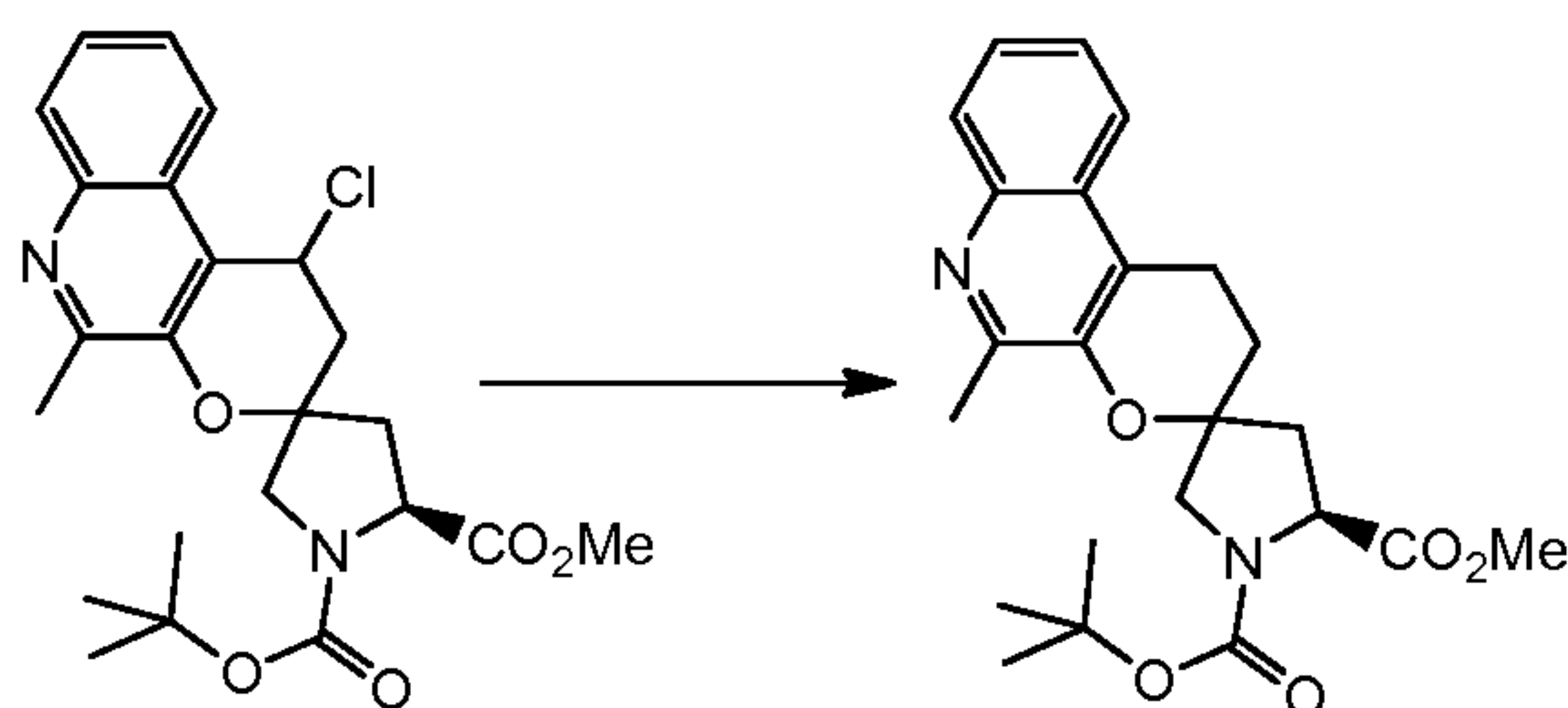
the solvent was evaporated under reduced pressure to give the product of Step 2 (700 mg, 1.634 mmol, 87% yield).

Step 3



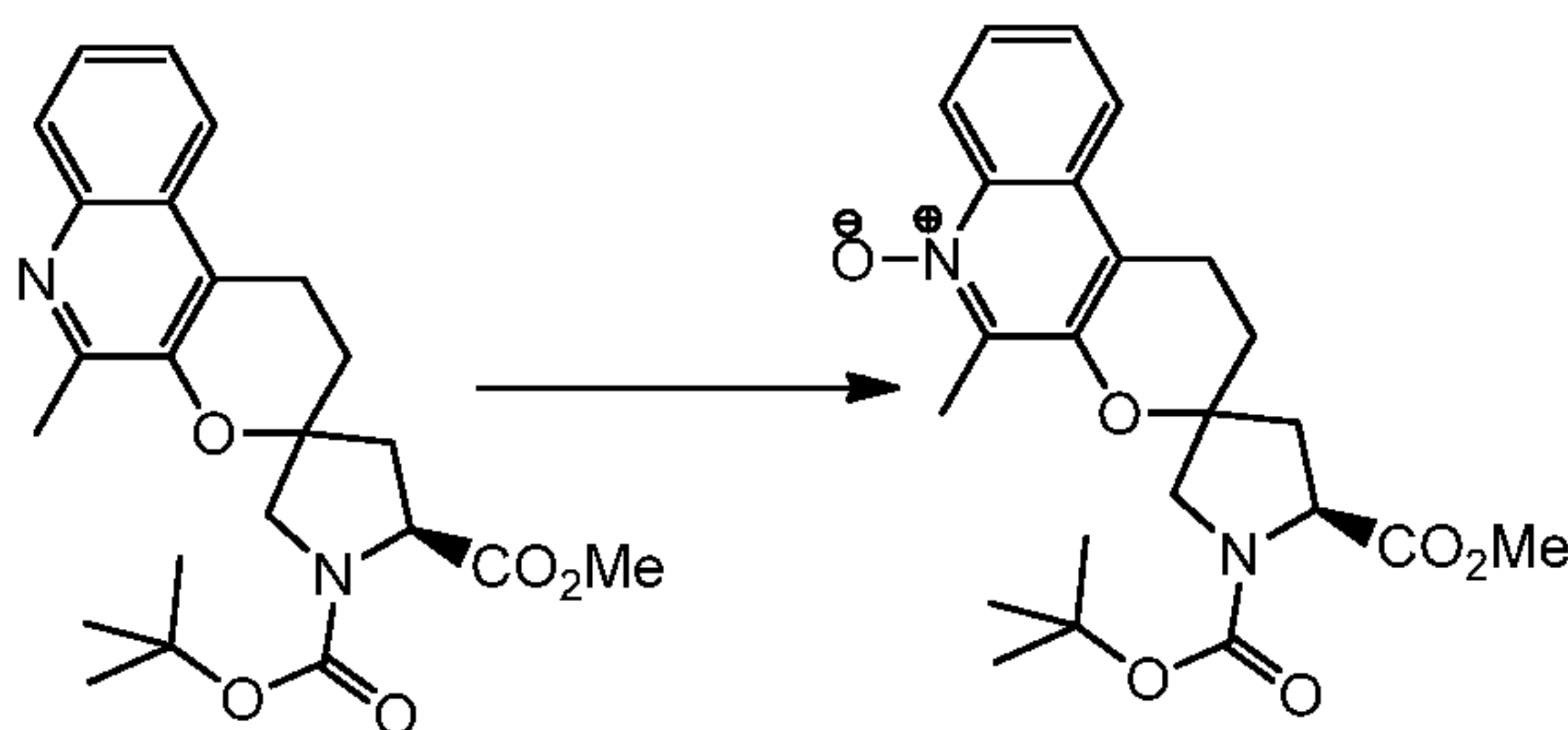
5 The product of Step 2 (700 mg, 1.634 mmol) was dissolved in DCM (10.900 ml), TEA (0.911 ml, 6.53 mmol), then MsCl (0.255 ml, 3.27 mmol) were added. The mixture was stirred overnight. EtOAc (100 ml) was added, and the mixture was washed with aq. NH₄Cl (sat., 2x 50 mL), dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure to give the product of Step 3 (730 mg, 1.633 mmol, 100% yield) as a yellow oil.

10 Step 4



15 The product of Step 3 (730 mg, 1.633 mmol) was dissolved in EtOAc (16.300 ml), 10% Pd/C (174 mg, 0.163 mmol) was added, and the mixture put under H₂ atmosphere (1atm) and stirred for 1h. The solid was removed by filtration, additional EtOAc (100 ml) was added to the filtrate, and the mixture was washed with aq. NaHCO₃ (sat., 2x 50 mL), dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give the product of Step 4 (510 mg, 1.236 mmol, 76% yield) as a colorless foam.

Step 5

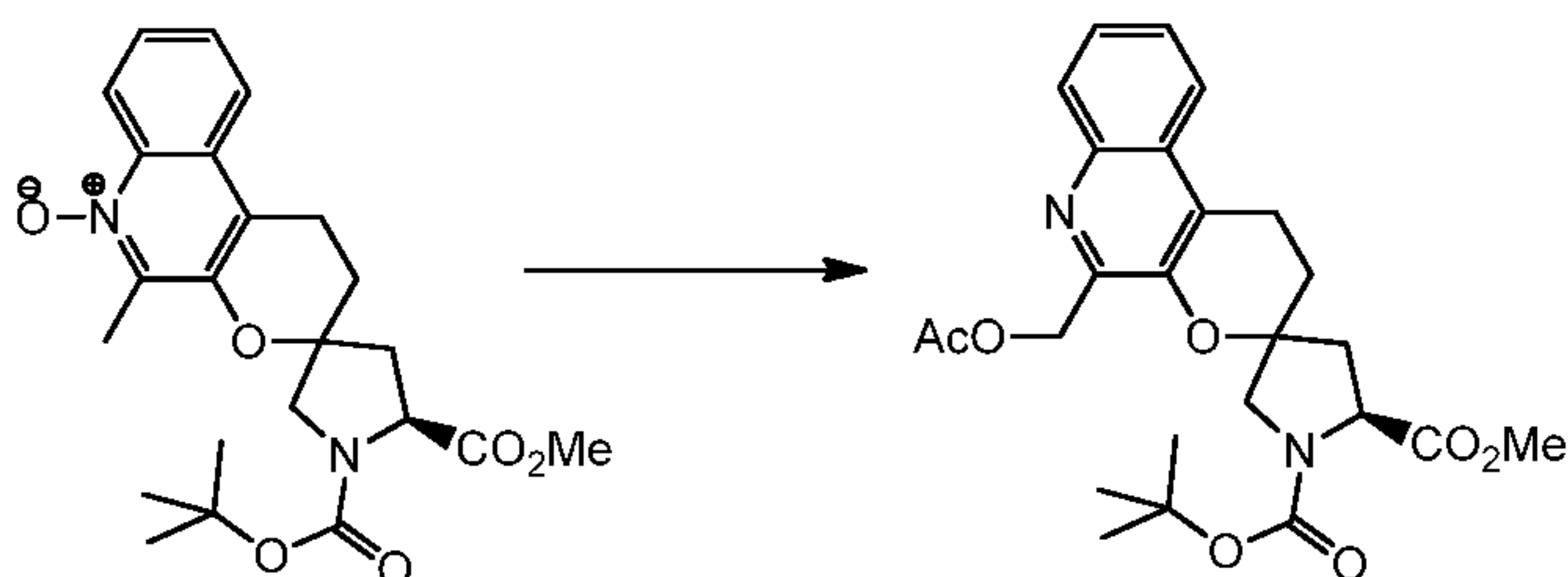


20

The product of Step 4 (100 mg, 0.242 mmol) was dissolved in chloroform (1.212 mL), mCPBA (109 mg, 0.485 mmol) was added, and the mixture stirred overnight. EtOAc (50 ml) was added, and the mixture was washed with aq. NaHCO₃ (sat., 3x 30 mL), dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure to give the product of Step 5

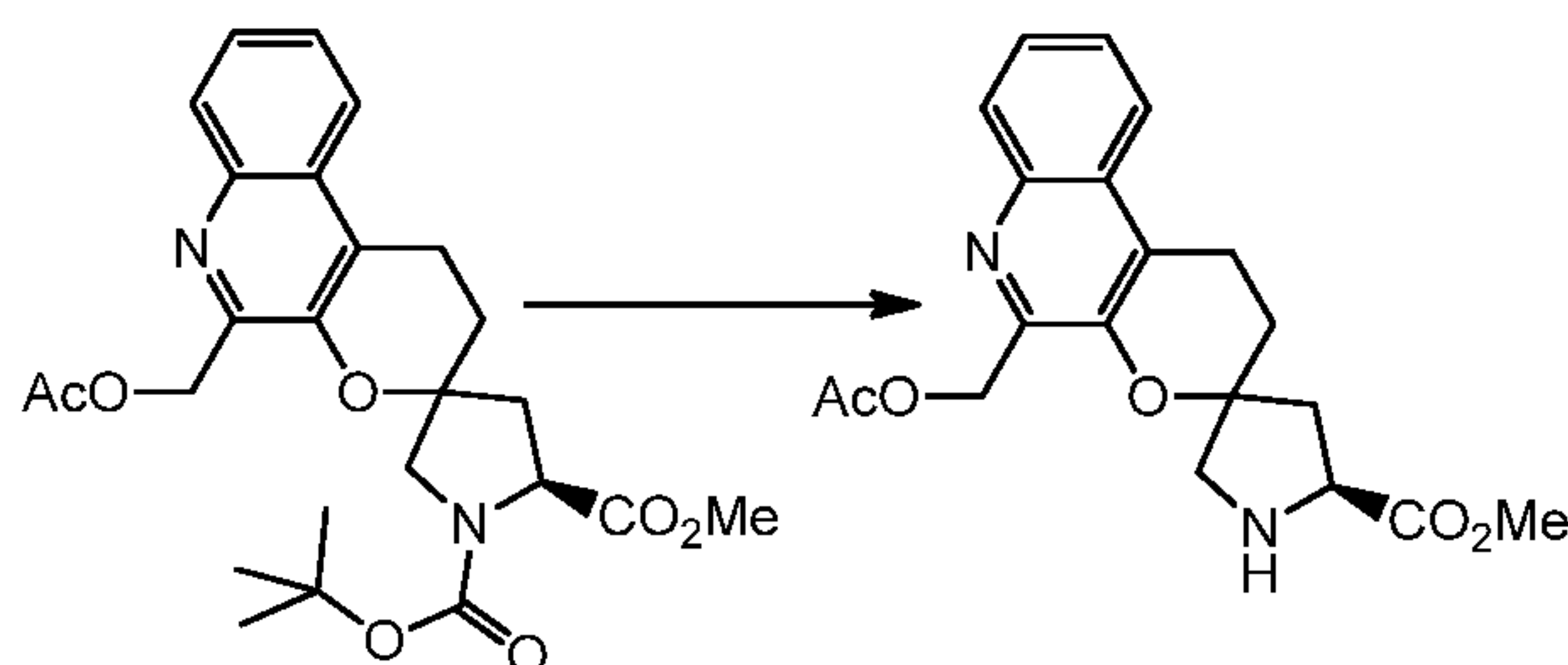
5 (used crude in next step).

Step 6



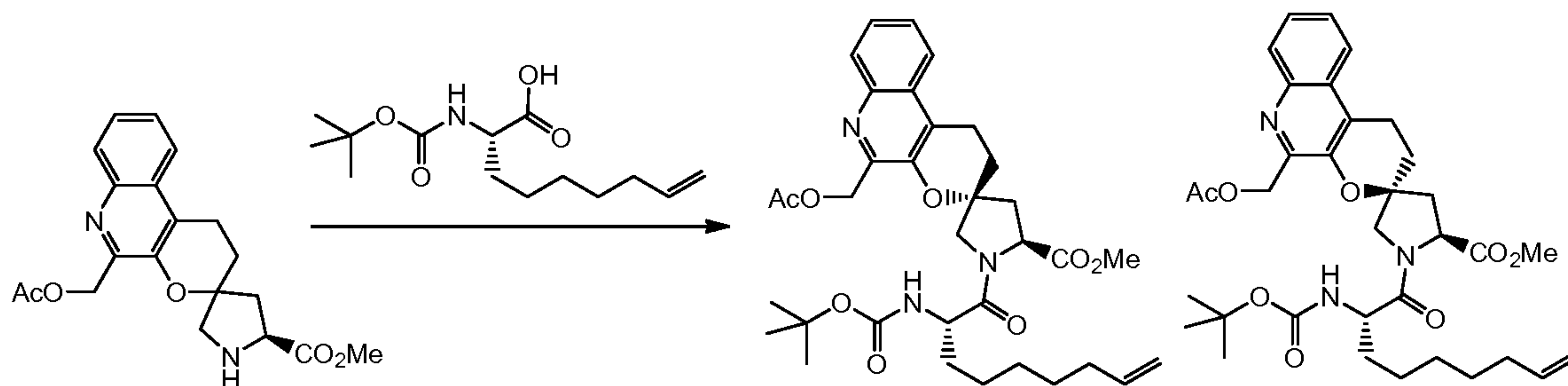
The product of Step 5 (100 mg, 0.233 mmol) was dissolved in acetic anhydride (2202 μ l, 23.34 mmol) heated at 80°C for 2h, the mixture was then concentrated. The residue was dissolved in EtOAc, washed with NaHCO₃ (sat.), dried (MgSO₄), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give the product of Step 6 (80 mg, 0.170 mmol, 72.9% yield) as colorless oil.

Step 7



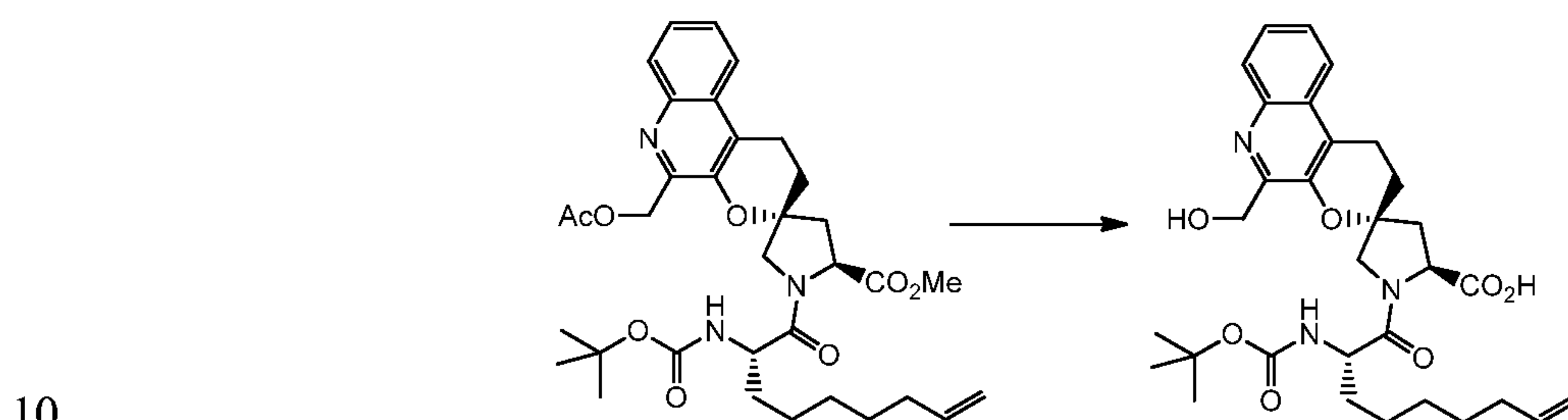
15 The product of Step 6 (80 mg, 0.170 mmol) was dissolved in HCl in dioxane (2125 μ l, 8.50 mmol), stirred for 1h. The mixture was concentrated to give the product of Step 7 (used crude in the next step).

Step 8



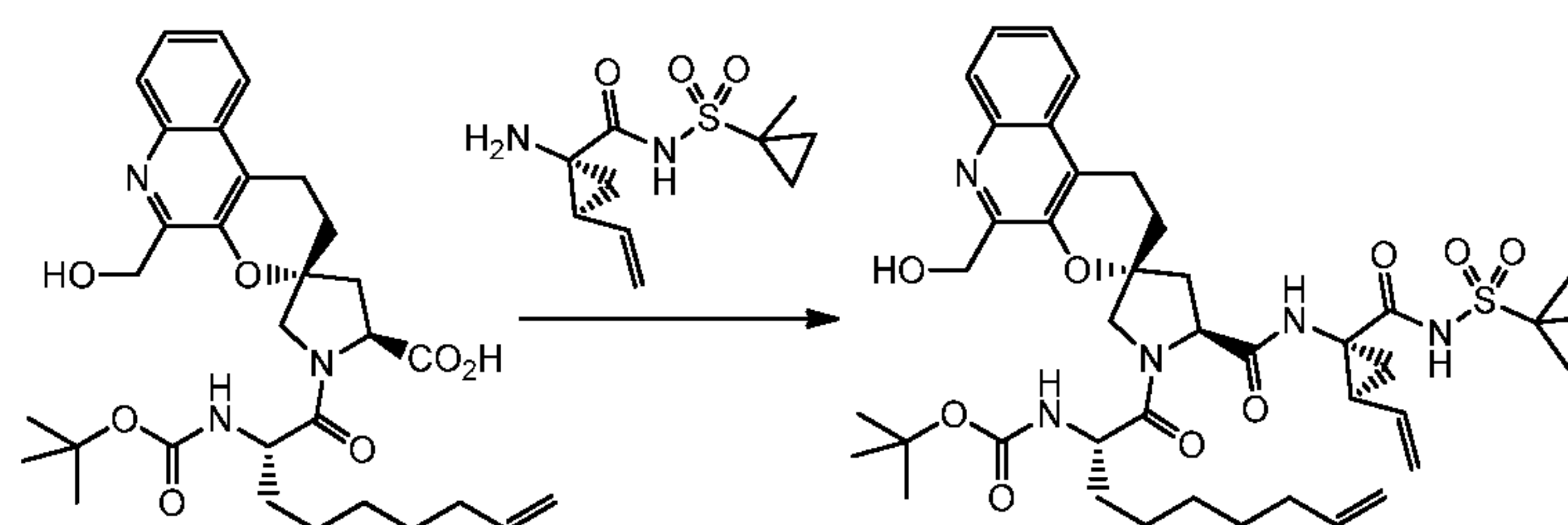
The product of Step 7 (154 mg, 0.340 mmol) was dissolved in DMF (1701 μ l), (*S*)-2-(*tert*-butoxycarbonylamino)non-8-enoic acid dicyclohexylamine salt (69.2 mg, 0.170 mmol), DIPEA (119 μ l, 0.680 mmol), and HATU (129 mg, 0.340 mmol) were added, and the mixture stirred overnight. Et₂O (100 ml) was added, and the mixture was washed with aq. NH₄Cl (sat., 3x 30 mL), dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give in order of elution; product 37-8A (41 mg, 0.066 mmol, 38.6% yield) and product 37-8B (15 mg, 0.024 mmol, 14.14% yield) as colorless oils.

Step 9



The product of Step 8, 37-8A, (41 mg, 0.066 mmol) was dissolved in THF (506 μ l)/MeOH (506 μ l), to this LiOH (164 μ l, 0.329 mmol) was added, and the mixture heated at 60°C for 1h, the mixture was cooled to RT and acidified to pH 4, the mixture was extracted with EtOAc (2x 10 mL). The combined organic fractions were dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure to give the product of Step 9 (36 mg, 0.063 mmol, 96% yield).

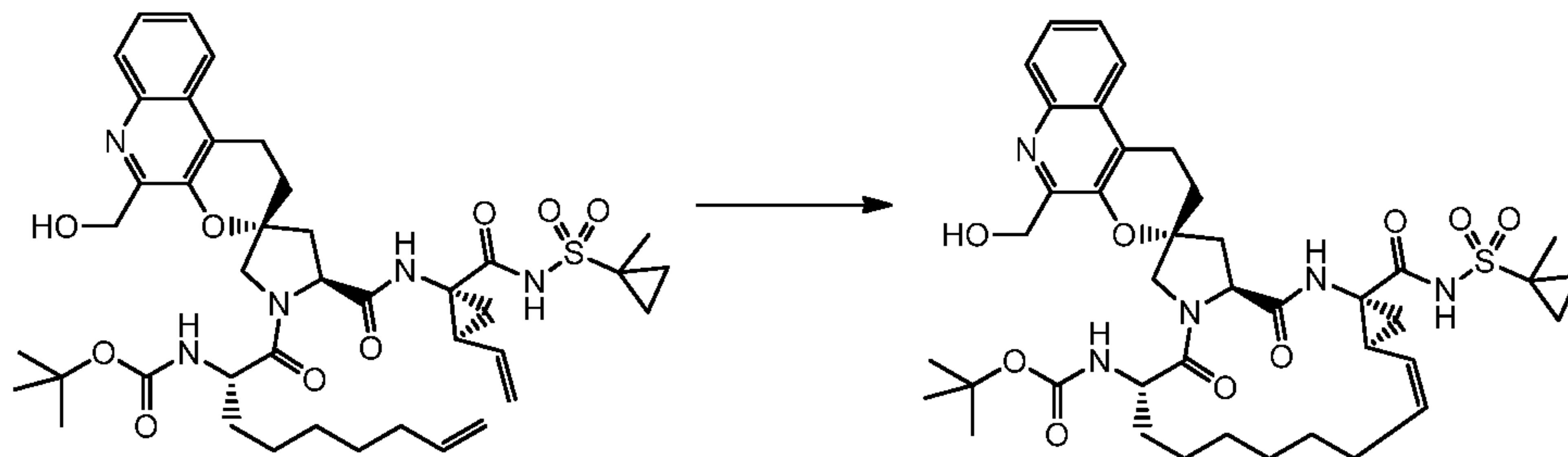
Step 10



The product of Step 9 (36 mg, 0.063 mmol) was dissolved in DMF (2114 μ l), (1*R*,2*S*)-1-amino-*N*-(1-methylcyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide (46.5 mg, 0.190 mmol), DIPEA (22.15 μ l, 0.127 mmol), and HATU (48.2 mg, 0.127 mmol) added, and the mixture stirred overnight. EtOAc (50 ml) was added, and the mixture was washed with aq. NH₄Cl (sat., 2x 25 mL), dried (MgSO₄), filtered, and the solvent was evaporated under reduced

pressure. The crude product was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give the product of Step 10 (23 mg, 0.029 mmol, 45.7% yield) as colorless oil.

Step 11

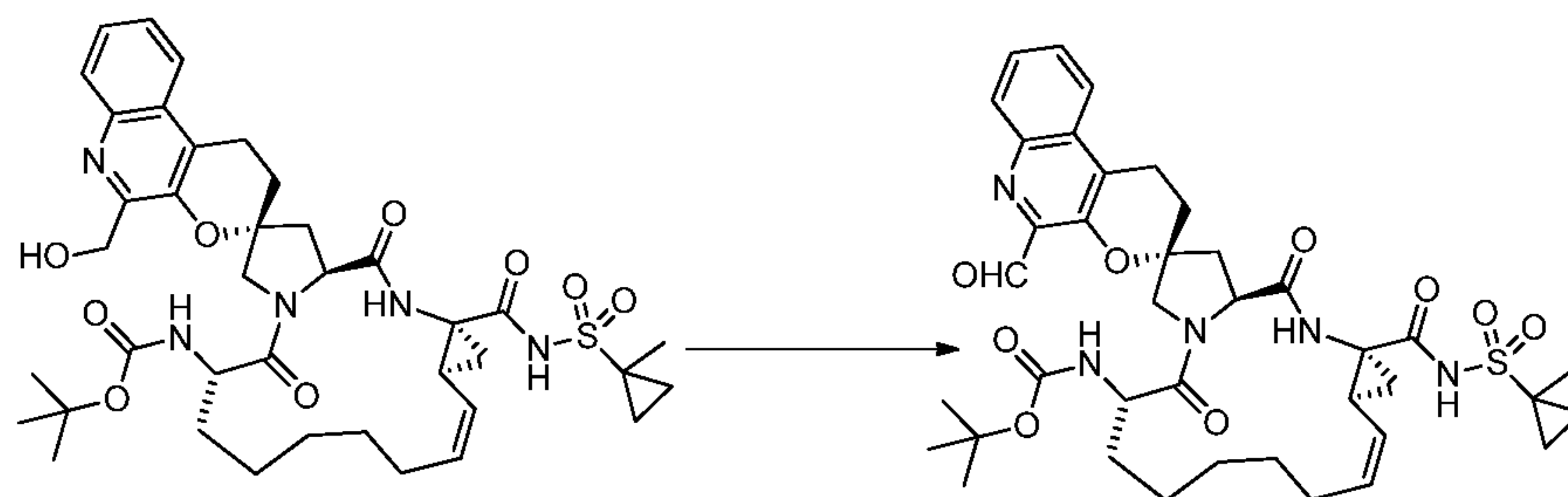


5 The product of Step 10 (23 mg, 0.029 mmol) was dissolved in DCE (14.500 ml), Zhan's catalyst (5.31 mg, 7.24 μ mol) and 1,4-benzoquinone (0.939 mg, 8.69 μ mol) were added, the mixture was heated at 65°C for 2h. The mixture was cooled to RT; butylvinylether was added, and, after 30 min, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give I-37 (10
10 mg, 0.013 mmol, 45.1% yield). ¹H-NMR (400 MHz, CDCl₃) δ 8.01 (d, J = 8.1 Hz, 1H), 7.81-7.76 (m, 1H), 7.66-7.60 (m, 1H), 7.60-7.52 (m, 2H), 6.95 (m, 1H), 6.02 (m, 1H), 5.83-5.68 (m, 3H), 5.43-5.32 (m, 2H), 5.03-5.49 (m, 5H), 4.75 (m, 1H), 4.62 (m, 1H), 4.47-4.42 (m, 1H), 4.12-4.04 (m, 1H), 3.78-3.62 (m, 4H), 3.19-3.13 (m, 2H), 2.6-0.8 multiplets comprising remaining peaks. MS: m/e = 766.2 (100) (MH⁺).

15

Example 38: tert-butyl ((2R,6S,13aS,14aR,16aS,Z)-14a-(((1-methylcyclopropyl)sulfonyl) carbamoyl)-5'-(morpholinomethyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-38)

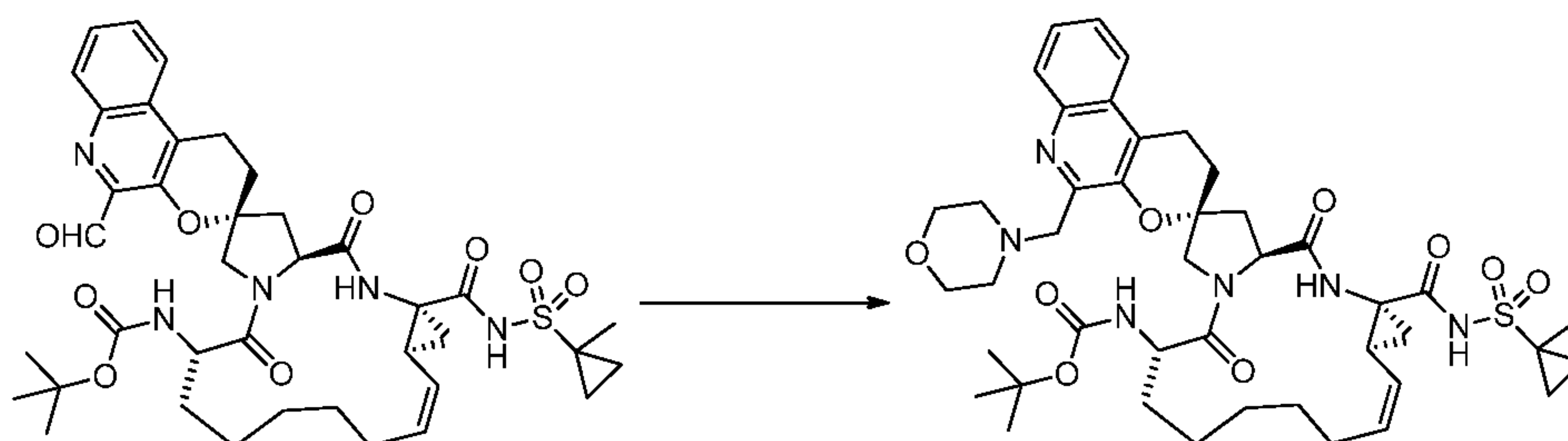
20 Step 1



I-37 (80 mg, 0.104 mmol) was dissolved in DCM (1045 μ l) cooled to 0°C, NaHCO₃ (8.77 mg, 0.104 mmol) then Dess-Martin periodinane (89 mg, 0.209 mmol) were

added. The mixture was stirred for 1h, aq. NaHCO₃ (20 ml) was added, and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic fractions were dried (MgSO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give the product of Step 1 (30 mg, 0.039 mmol, 37.6% yield) as yellow oil.

Step 2

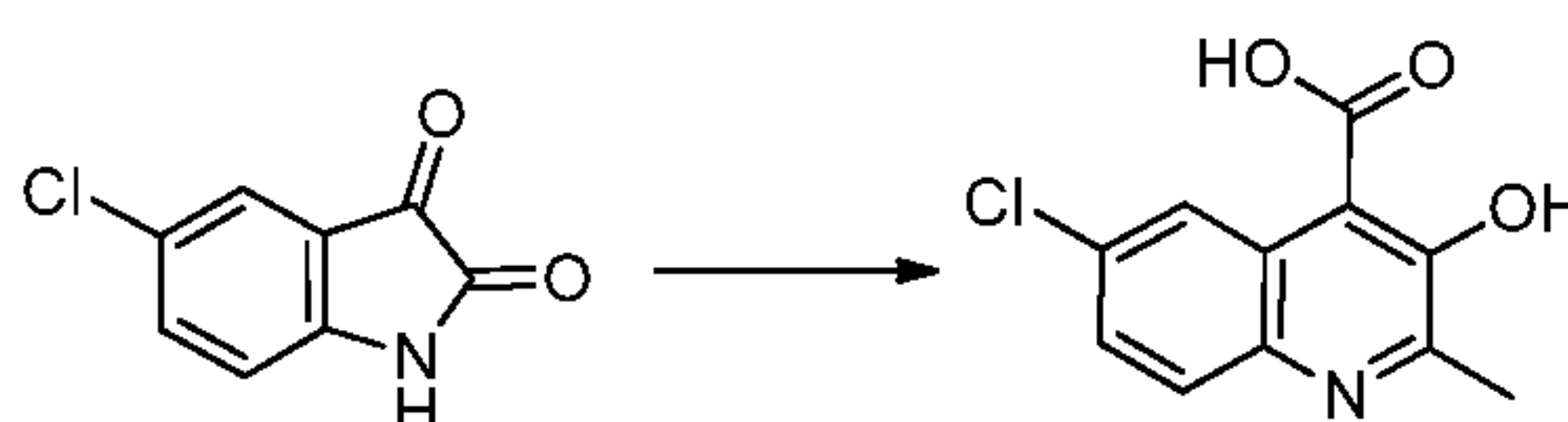


The product of Step 1 (30 mg, 0.039 mmol) was dissolved in DCE (785μl), morpholine (13.69μl, 0.157 mmol) was added, and the mixture was cooled to 0°C. Sodium triacetoxyborohydride (33.3 mg, 0.157 mmol) was added, and the mixture was stirred overnight. Aq. NaHCO₃ (20 ml) was added, and the mixture was extracted with EtOAc (3x 20 mL). The combined organic fractions were dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/MeOH to give I-38 (5 mg, 5.99μmol, 15.25% yield) as colorless solid. ¹H-NMR (400 MHz, CDCl₃) δ 8.03 (d, J = 9.3 Hz, 1H), 7.8-7.76 (m, 1H), 7.58-7.51 (m, 2H), 6.73 (m, 1H), 5.72 (q, j + 10.5 hz, 1H), 5.07-4.97 (m, 2H), 4.76 (m, 1H), 4.40 (d, J = 10.9 Hz, 1H), 4.25 (m, 1H), 3.90 (d, J = 13.1 Hz, 1H), 3.76-3.59 (m, 7H), 3.54 (d, J = 12.5 Hz, 1H), 3.49-3.44 (m, 3H), 3.17 (m, 2H), 2.61-2.24 and 1.6-0.8 multiplets comprising remaining peaks. MS: m/e = 835 (100) (MH⁺).

20

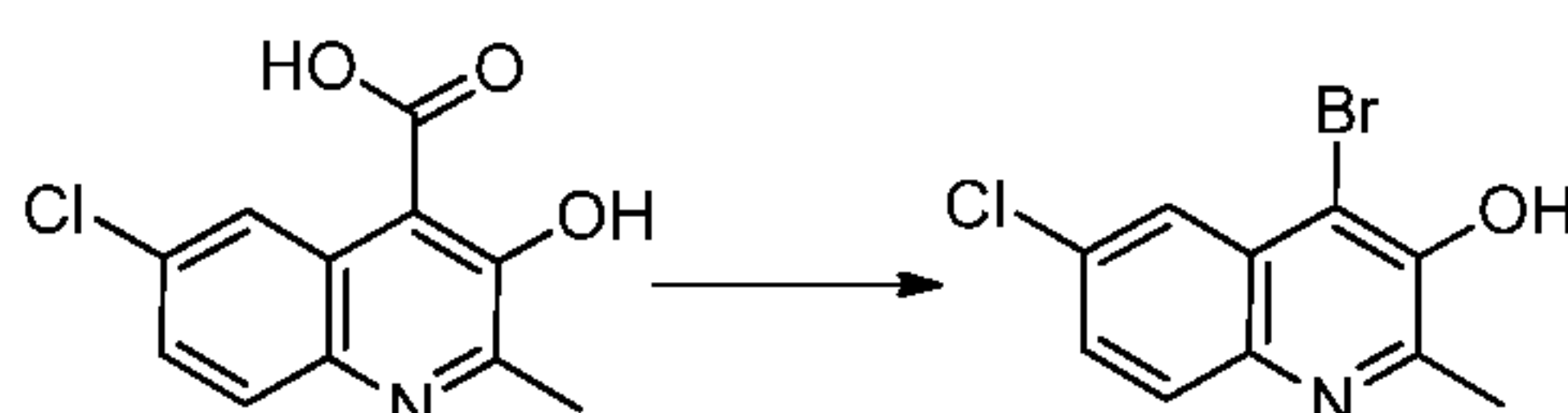
Example 39: *tert*-Butyl ((2R,6S,13aS,14aR,16aS,Z)-9'-chloro-5'-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-39)

25 Step 1



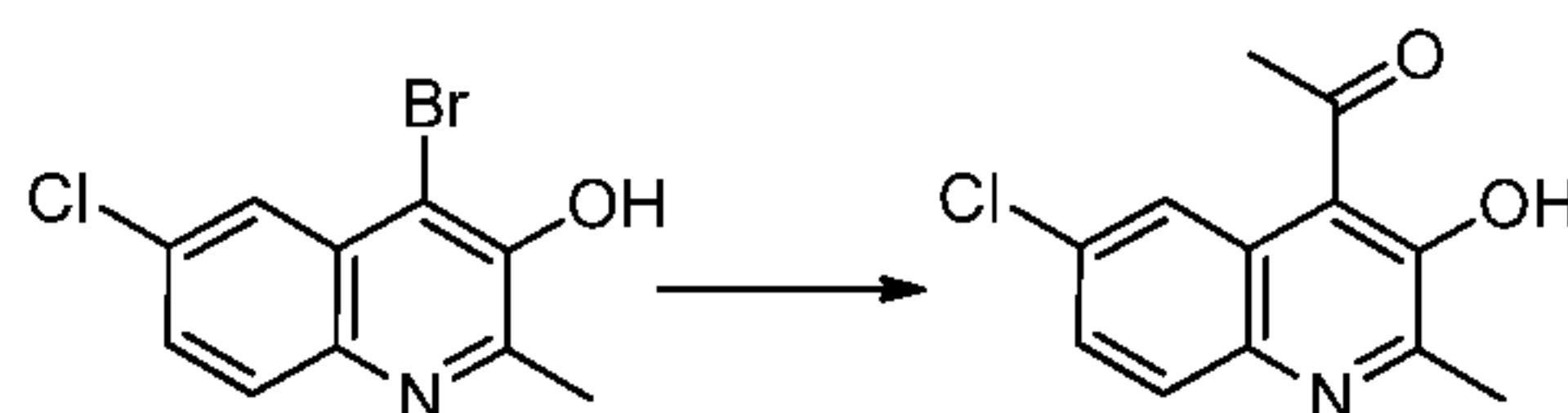
5-Chloroisatin (25 g, 138 mmol) was suspended in water (344 ml), $\text{Ca}(\text{OH})_2$ (30.6 g, 413 mmol) was added, and the mixture heated at 80°C for 1h. Chloroacetone (27.4 ml, 344 mmol) was added slowly, and the mixture stirred at 80°C for 1.5h. The mixture was cooled to 0°C , AcOH (47.3 ml, 826 mmol) added, and the resulting solid collected by filtration, washing with water (2x 200 ml), to give the product of Step 1 (32 g, 135 mmol, 98% yield) as yellow solid.

Step 2



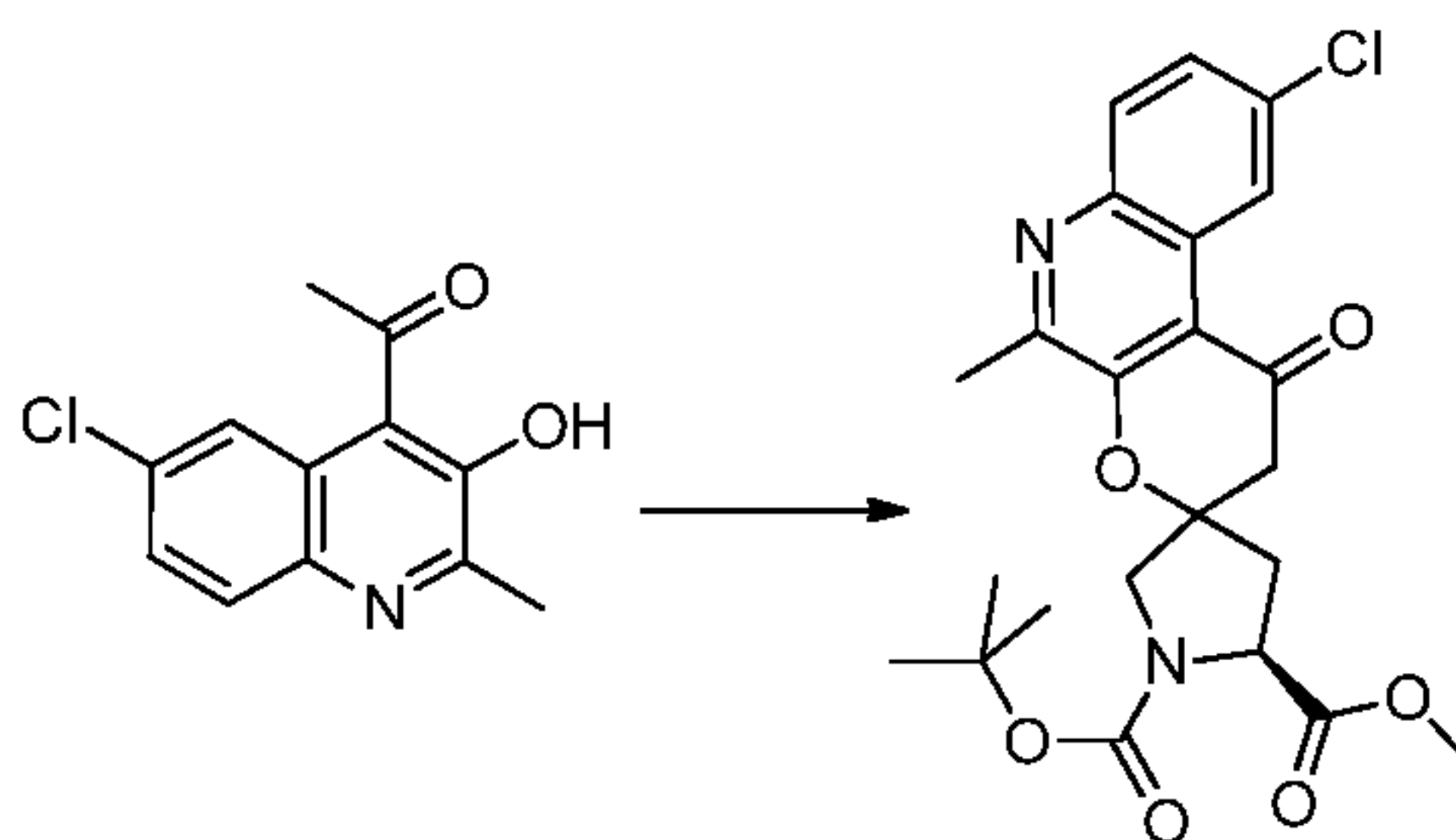
The product of Step 1 (5 g, 21.04 mmol) was suspended in THF (105 ml), NBS (3.74 g, 21.04 mmol) was added, and the mixture stirred for 30 min. The mixture was concentrated under reduced pressure. The residue was triturated with DCM (100 ml), and the solid collected by filtration to give the product of Step 2 (3.682 g, 13.51 mmol, 64.2% yield).

Step 3



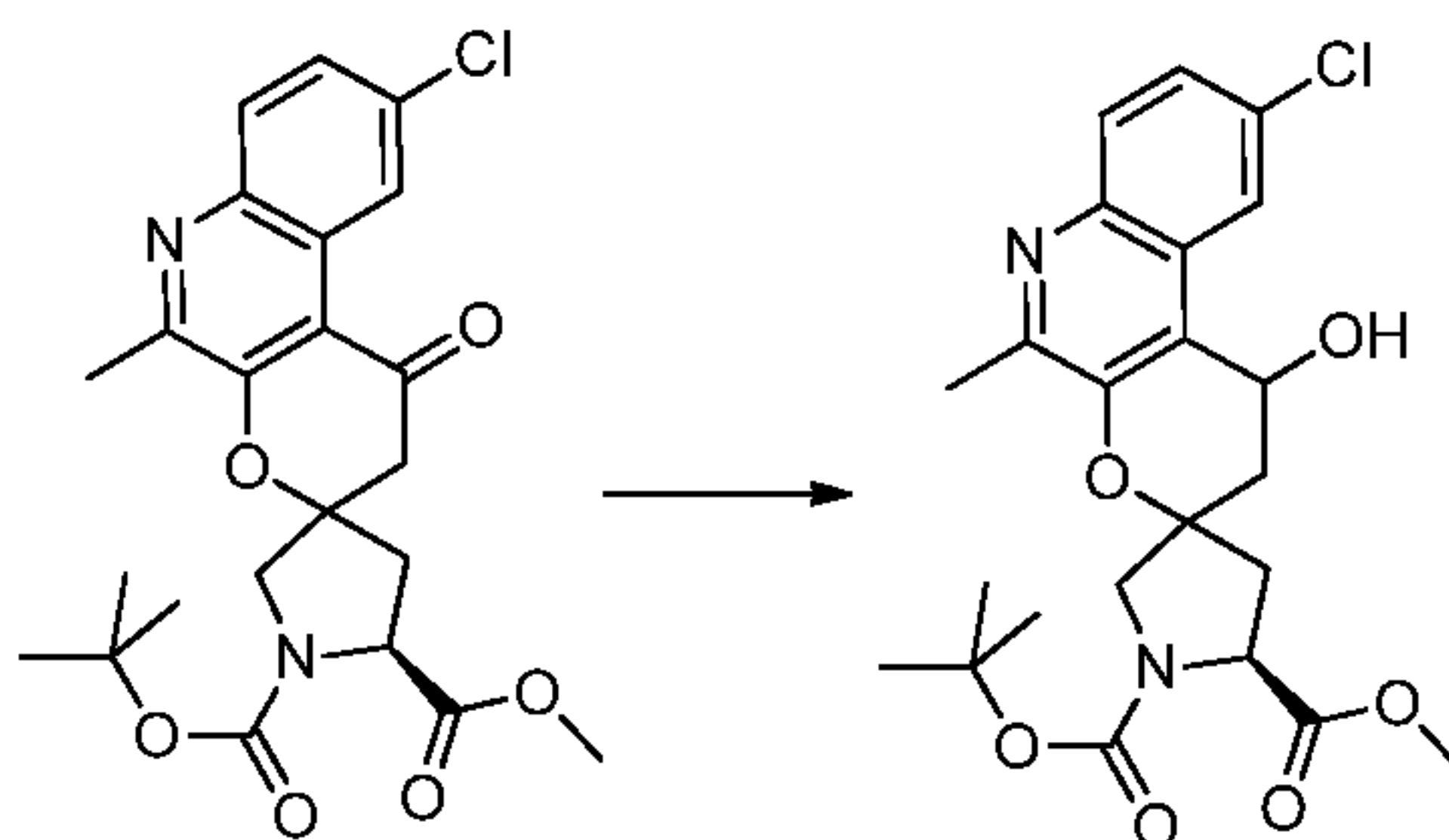
The product of Step 2 (3.682 g, 13.51 mmol) was dissolved in dioxane (54.0 ml), tributyl(1-ethoxyvinyl)tin (9.12 ml, 27.0 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.781 g, 0.676 mmol) added, and the mixture was heated at 107°C in a sealed tube overnight. After cooling to RT, 1N HCl (54 ml) was added, and the mixture stirred for 30 min. Aq. NaHCO_3 was added, and the mixture was extracted with EtOAc (6x 150 mL). The combined organic fractions were dried (MgSO_4), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give the product of Step 3 (2.38 g, 10.10 mmol, 74.7% yield) as a yellow solid.

Step 4



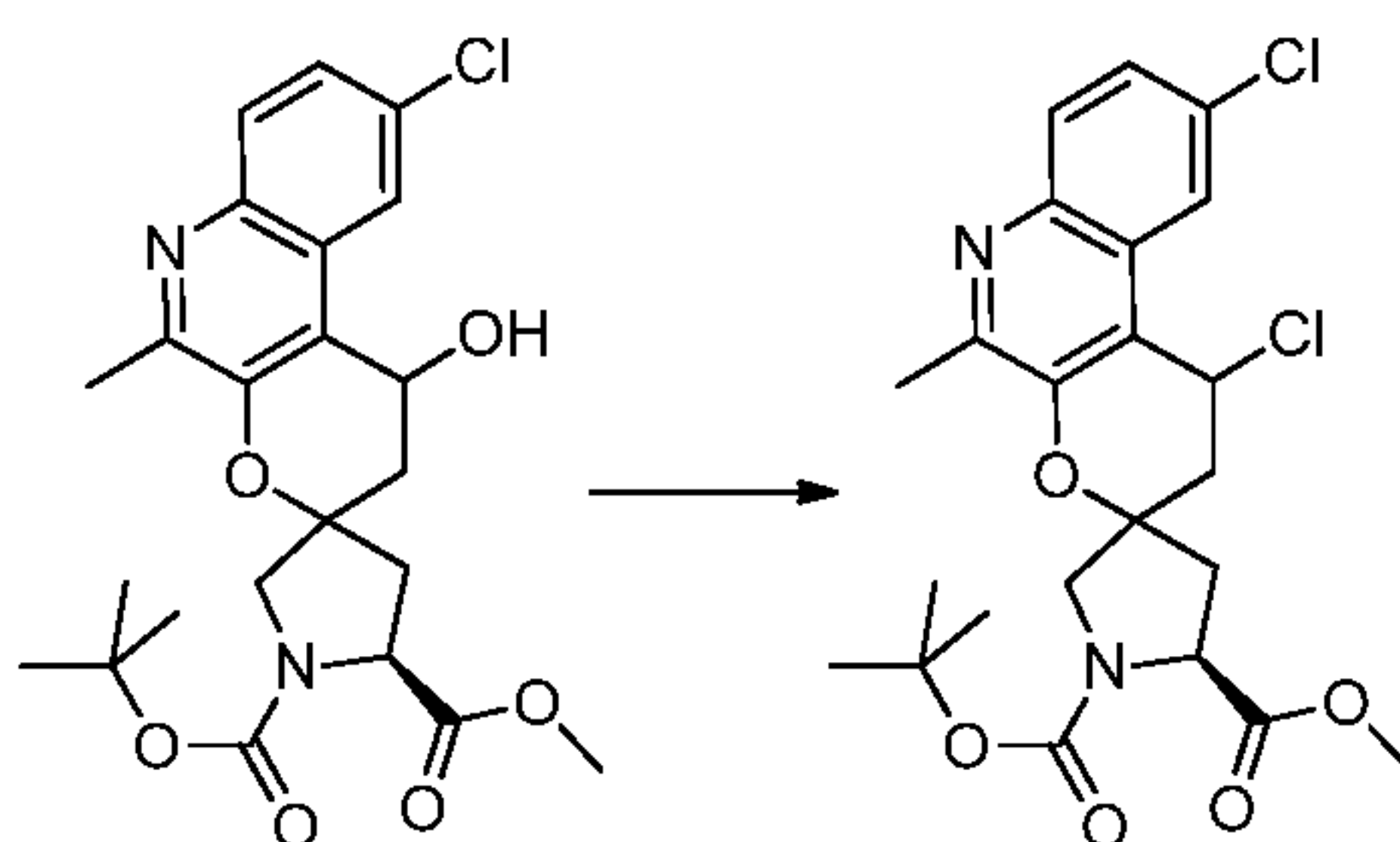
The product of Step 3 (2.38 g, 10.10 mmol) was dissolved in MeOH (67.3 ml), *N*-Boc-4-oxo-L-proline methyl ester (4.91 g, 20.20 mmol) then pyrrolidine (0.334 ml, 4.04 mmol) was added. The mixture was heated at 105°C for 1h. The mixture was cooled to RT and dry-loaded onto silica gel. The residue was purified by column chromatography on silica gel, eluting
5 with EtOAc/hexane to give the product of Step 4 (3.78 g, 8.20 mmol, 81% yield) as a yellow solid.

Step 5



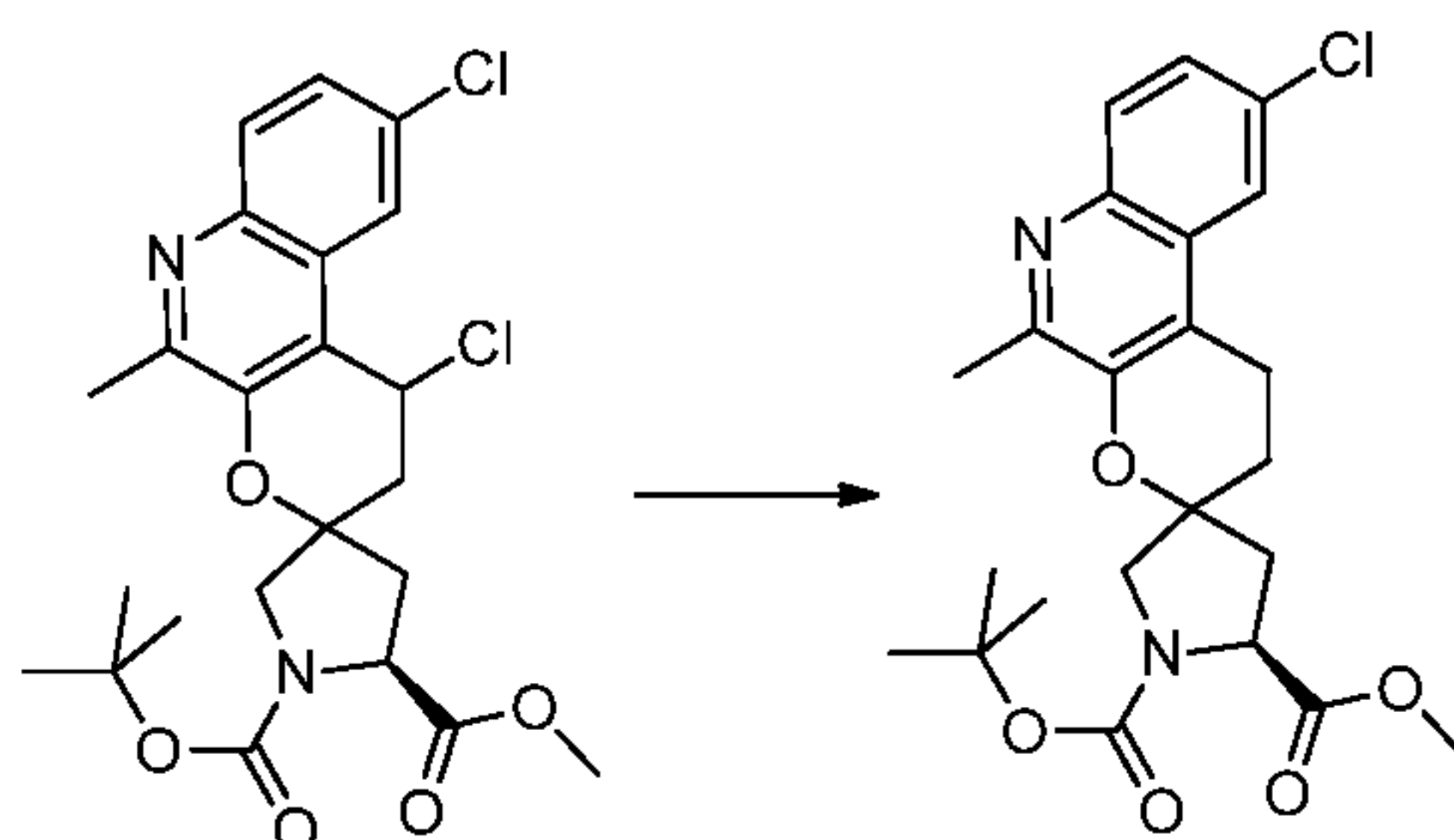
The product of Step 4 (3.78 g, 8.20 mmol) was dissolved in THF (27.3 ml)/MeOH
10 (27.3 ml) and cooled to 0°C. NaBH₄ (0.310 g, 8.20 mmol) was added, and the mixture was stirred for 30 min. The mixture was concentrated under reduced pressure, and dissolved in EtOAc/NaHCO₃ (sat., 300 ml each). The aqueous layer was extracted with EtOAc (300 ml). The combined organic layers were dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure to give the product of Step 5 (3.8 g, 8.21 mmol, 100% yield), used crude in next
15 step.

Step 6



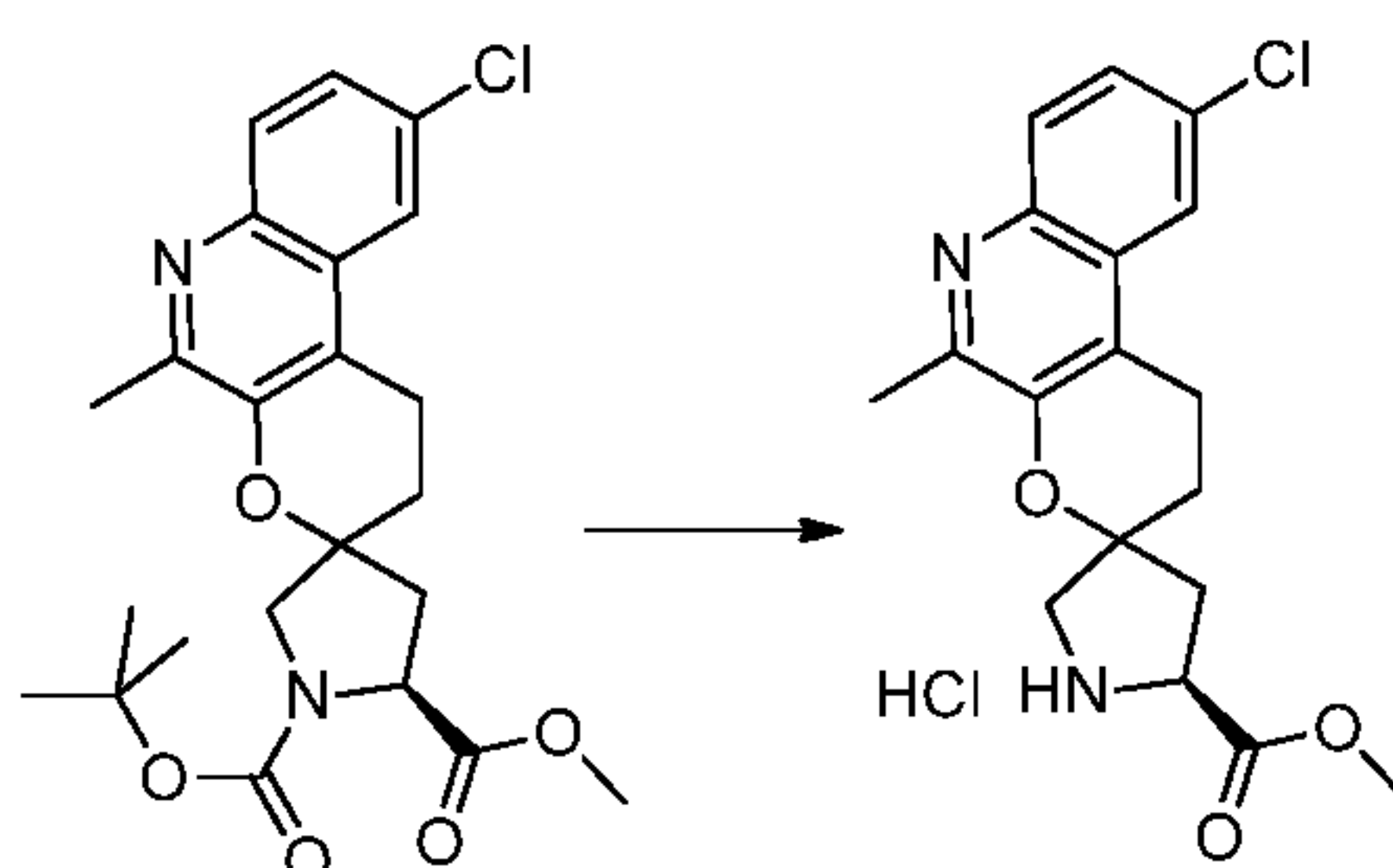
The product of Step 5 (3.8 g, 8.21 mmol) was dissolved in DCM (54.7 ml), cooled to 0°C, TEA (4.58 ml, 32.8 mmol) then MsCl (1.279 ml, 16.42 mmol) were added, and the
20 mixture stirred overnight. DCM (200 ml) was added, and the mixture was washed with aq. NH₄Cl (sat., 2x 100 mL), dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with EtOAc/hexane to give the product of Step 6 (3.22 g, 6.69 mmol, 81% yield) as yellow foam.

Step 7



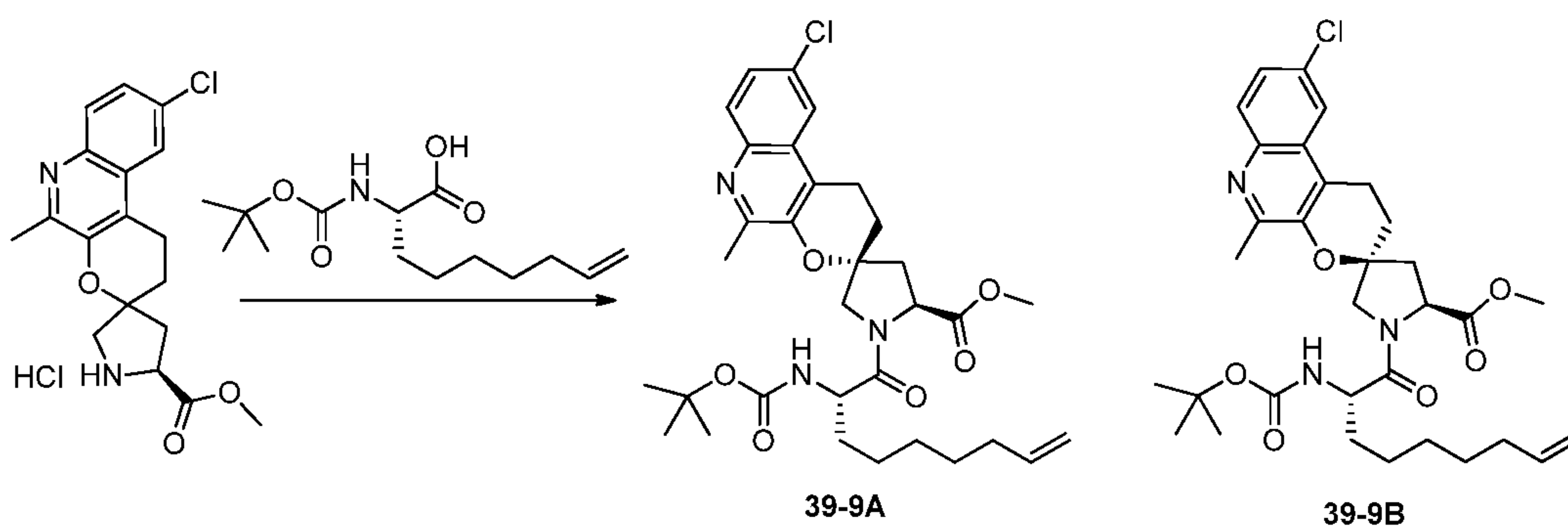
The product of Step 6 (1.56 g, 3.24 mmol) was dissolved in EtOAc (32.4 ml), 10% Pd/C (0.345 g, 0.324 mmol) was added, and the mixture was stirred under 1 atm of H₂ for 25 min. The catalyst removed by filtration (washing with MeOH), and the filtrates were concentrated under reduced pressure to give the product of Step 7 (1.45 g, 3.24 mmol, 100% yield).

Step 8



The product of Step 7 (2.91 g, 6.51 mmol) was dissolved in HCl (4 m in dioxane) (65.1 ml, 260 mmol) and stirred for 2h. The mixture was concentrated under reduced pressure to give the product of Step 8 (2.258 g, 6.51 mmol, 100% yield).

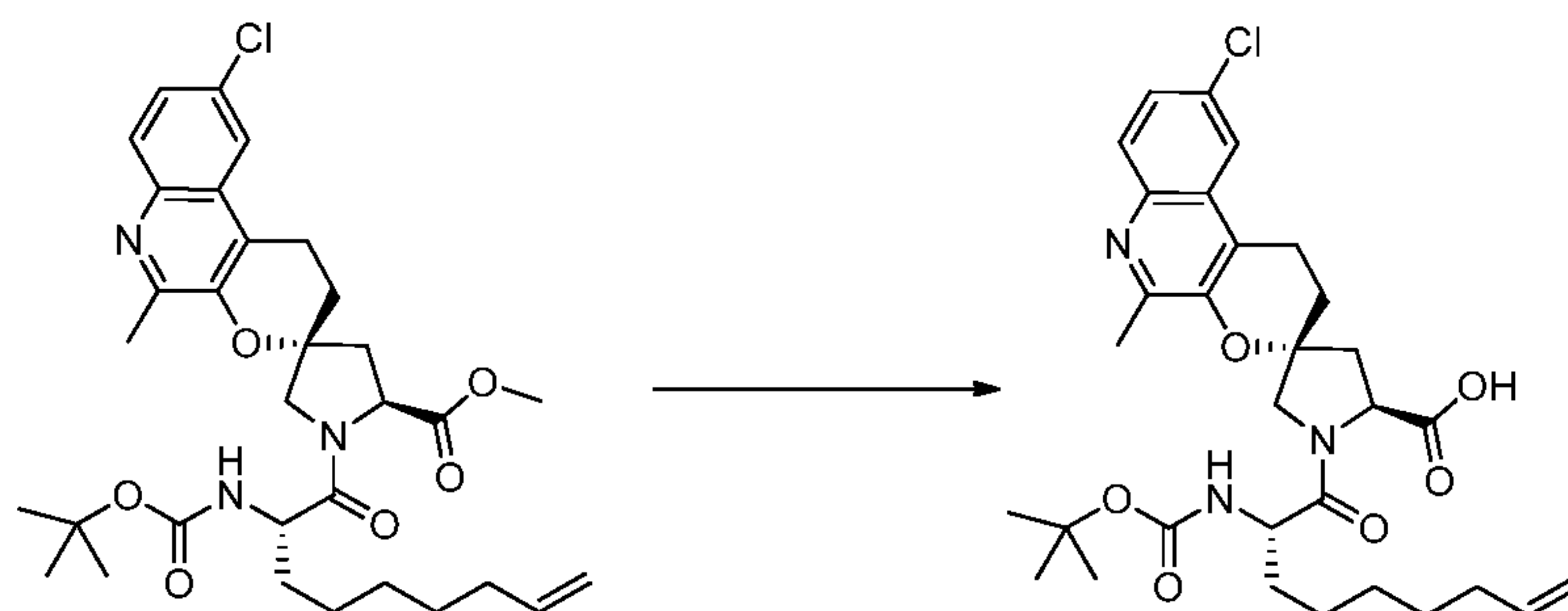
Step 9



The product of Step 8 (2.258 g, 6.51 mmol) was dissolved in DMF (65.1 ml), (*S*)-2-((*tert*-butoxycarbonyl)amino)non-8-enoic acid dicyclohexylamine salt (4.42 g, 9.77 mmol), DIPEA (5.69 ml, 32.6 mmol) and HATU (3.71 g, 9.77 mmol) added, stirred overnight. EtOAc (500 ml) was added, and the mixture was washed with aq. NH₄Cl (sat., 2x 200 mL), dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was

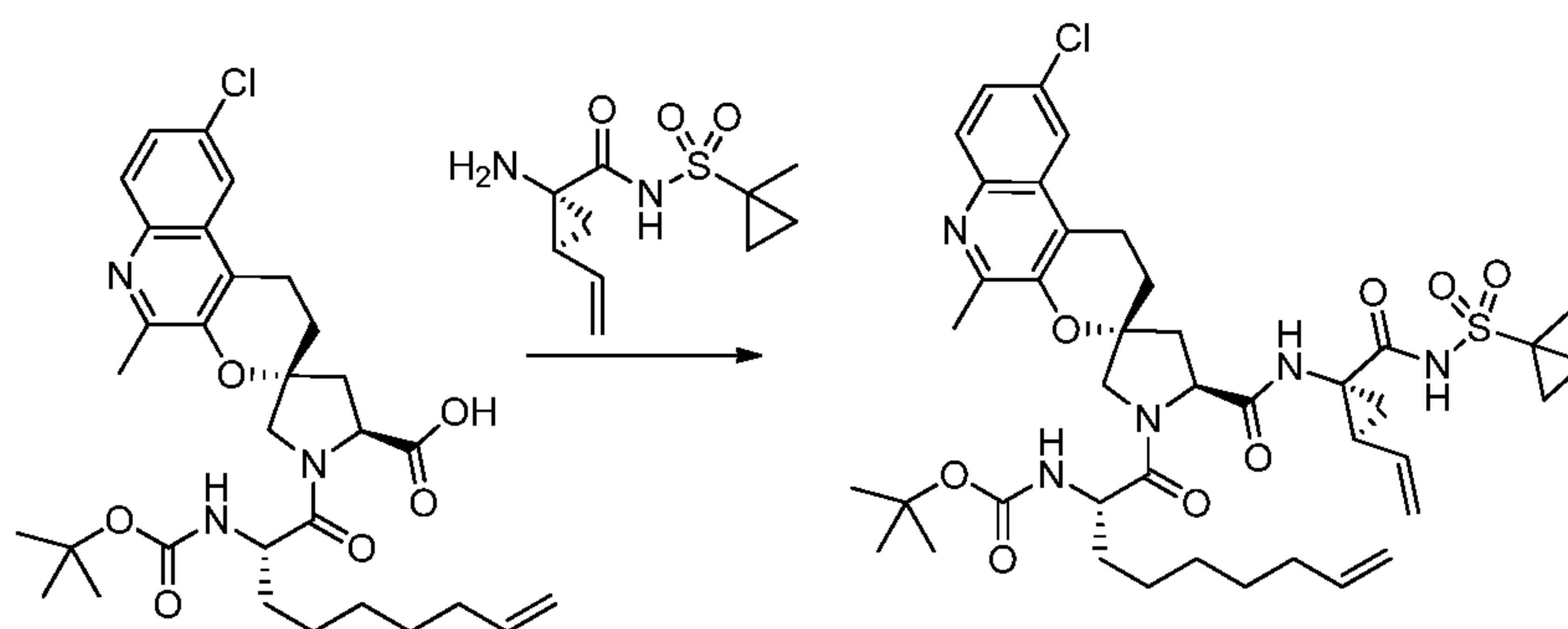
dissolved in ether (400 ml), washed with water (200 ml), dried (MgSO_4), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give (after re-chromatography of mixed fractions) compound 39-9A (1.4 g, 2.333 mmol, 35.8% yield) and compound 39-9B (0.8 g, 1.333 mmol, 20.47% yield) in order of elution as yellow oils.

Step 10



Compound 39-9A (1.4 g, 2.333 mmol) was dissolved in THF (7.78 ml)/MeOH (7.78 ml), LiOH (5.83 ml, 11.66 mmol) was added, and the mixture heated at 60°C for 30 min. The mixture was cooled to RT, water (50 ml) was added, and the mixture acidified to pH = 5 with 1N HCl, the mixture was extracted with EtOAc (2x 100 mL). The combined organic fractions were washed with water (1x 50 mL), dried (MgSO_4), filtered, and the solvent was evaporated under reduced pressure to give the product of Step 10 (1.367 g, 2.332 mmol, 100% yield).

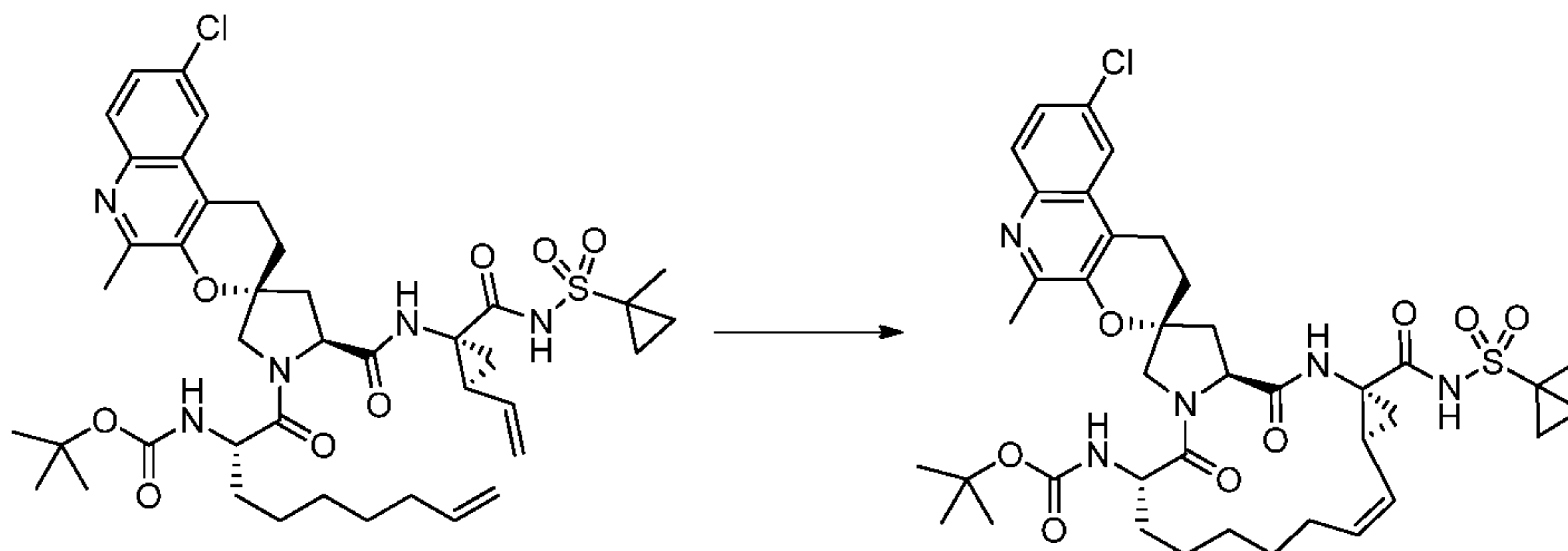
Step 11



The product of Step 10 (1.367 g, 2.332 mmol) was dissolved in DMF (23.32 ml), (1R,2S)-1-amino-N-(1-methylcyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide (0.855 g, 3.50 mmol), DIPEA (0.815 ml, 4.66 mmol), and HATU (1.330 g, 3.50 mmol) added, stirred overnight. Aq. NH_4Cl (50 ml) was added, and the mixture was extracted with Et_2O (3x 50 mL). The combined organic fractions were washed with water (1x 50 mL), dried (MgSO_4), filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by

column chromatography on silica gel, eluting with EtOAc/hexane to give the product of Step 11 (1.337 g, 1.646 mmol, 70.6% yield) as colorless foam.

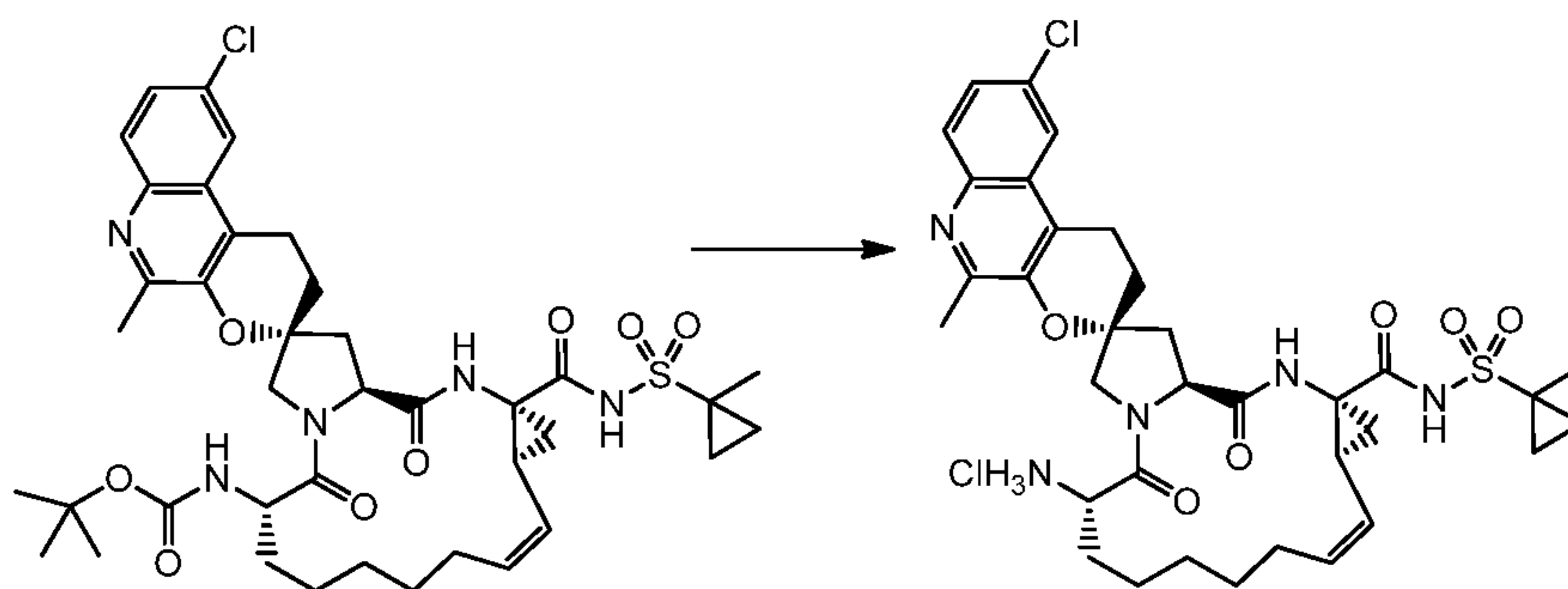
Step 12



5 The product of Step 11 (700 mg, 0.862 mmol) was dissolved in DCE (359.00 mL), Zhan's catalyst (158 mg, 0.215 mmol) and 1,4-benzoquinone (27.9 mg, 0.258 mmol) added, and the mixture was heated at 75°C for 30 min, when TLC showed complete conversion. The mixture was cooled to RT, butyl vinyl ether was added, and the mixture stirred for 30 min, the mixture was then concentrated under reduced pressure. The residue was purified by column
 10 chromatography on silica gel, eluting with EtOAc/hexane to give I-39 (484 mg, 0.617 mmol, 71.6% yield) as orange foam. ¹H-NMR (400 MHz, CDCl₃) δ 10.06 (m, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.72 (m, 1H), 7.47-7.44 (m, 1H), 6.68 (m, 1H), 5.72 (q, J = 10.4 Hz, 1H), 5.29 (m, 3H), 5.01 (t, J = 8.33, 1H), 4.94 (d, J = 7.3 Hz, 1H), 4.62 (t, J = 8.9 Hz, 1H), 4.46 (d, J = 11.7 Hz, 1H), 4.17-4.08 (1H, m), 3.68 (d, J = 10.6 Hz, 1H), 3.13-3.03 (m, 2H), 1.93 (m, 1H), 1.87-1.73 (m,
 15 3H), 2.61-2.24 and 1.6-0.8 multiplets comprising remaining peaks. MS: m/e = 784.2 (100) (MH⁺).

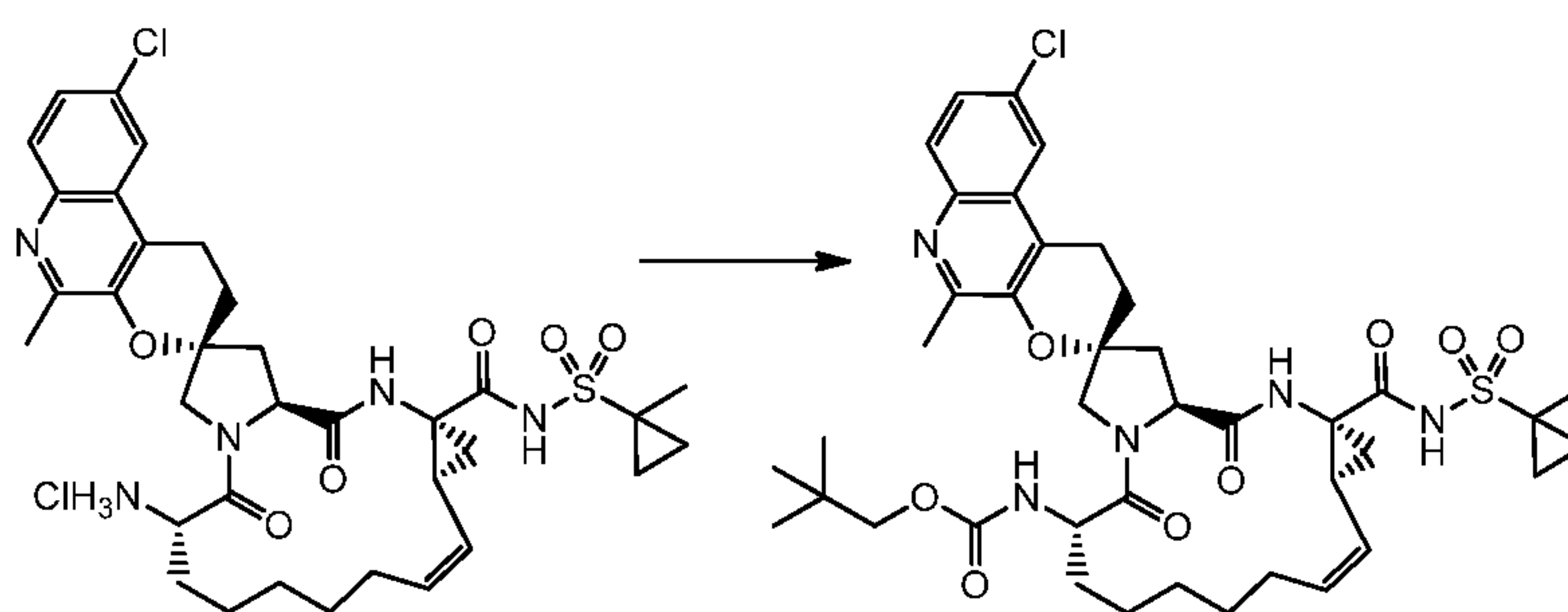
Example 40: Neopentyl ((2R,6S,13aS,14aR,16aS,Z)-9'-chloro-5'-methyl-14a-(((1-methyl cyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-40)

Step 1



I-39 (440 mg, 0.561 mmol) was dissolved in DCM (5.61 mL), HCl (4 m in dioxane, 4.91 mL, 19.63 mmol) was added, and the mixture stirred for 1h. The mixture was concentrated under reduced pressure to give the product of Step 1 (420 mg, 0.583 mmol, 104% yield) as beige solid.

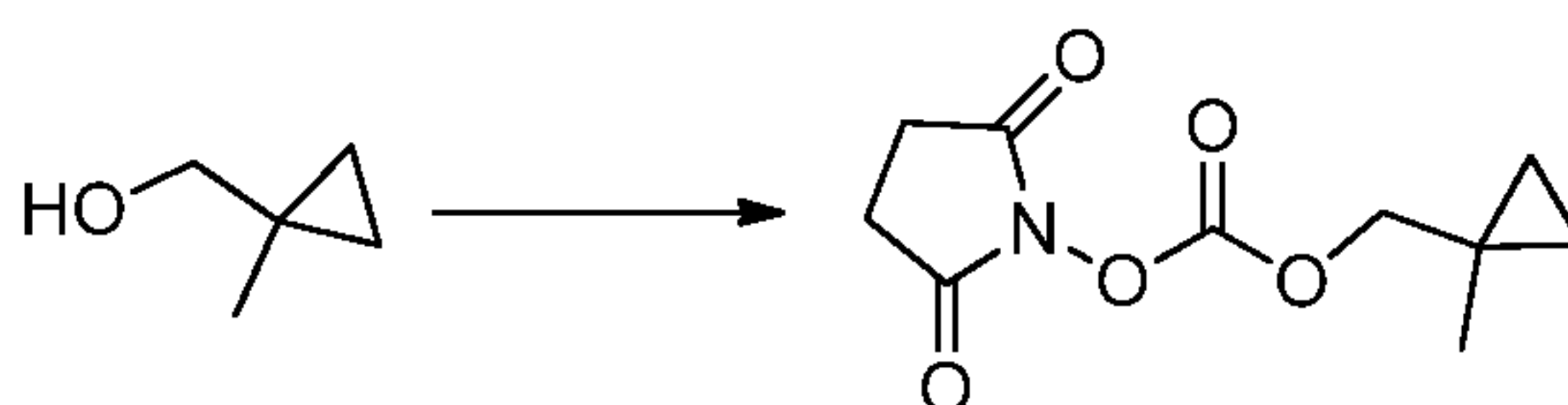
Step 2



The product from Step 1 (50 mg, 0.069 mmol) was suspended in DCM (694 μ l), cooled to 0°C, neopentyl chloroformate (20.90 mg, 0.139 mmol) and TEA (29.0 μ l, 0.208 mmol) added, and the mixture stirred at RT for 1h. TLC showed complete conversion, and the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give I-40 (36 mg, 0.045 mmol, 65.0% yield) as a colorless solid. MS: m/e = 798.3 (100) (MH⁺).

Example 41: (1-methylcyclopropyl)methyl ((2R,6S,13aS,14aR,16aS,Z)-9'-chloro-5'-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-41)

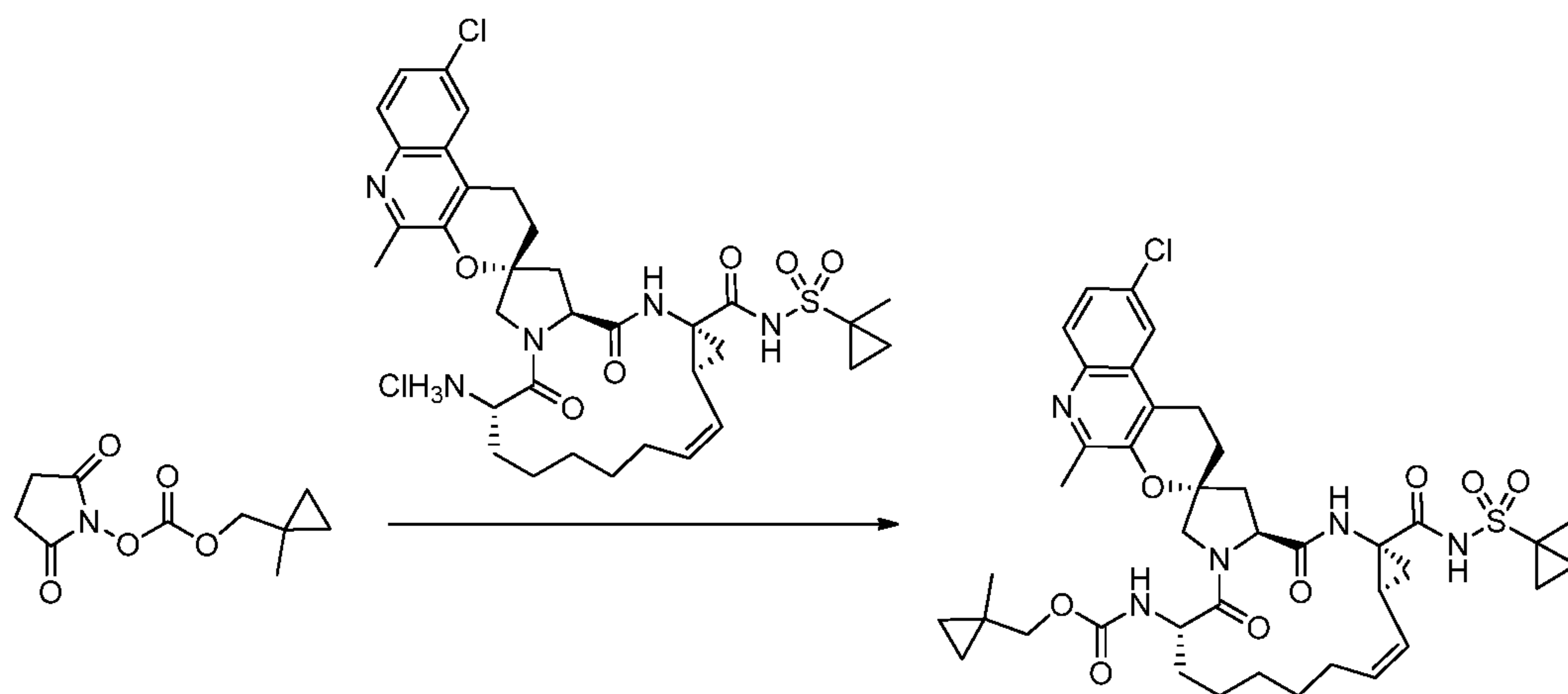
Step 1



20

1-Methylcyclopropanemethanol (1.127 ml, 11.61 mmol) was dissolved in MeCN (38.7 ml), *N,N'*-disuccinimidyl carbonate (3.87 g, 15.09 mmol) then TEA (4.85 ml, 34.8 mmol) added, and the mixture was stirred overnight. The mixture was concentrated to one-third volume, and then treated with aq. NaHCO₃ (50 ml). After 5 min, the solution was extracted with EtOAc (3x 50 ml), dried (MgSO₄), and concentrated to give the product of Step 1 (2.73 g, 12.02 mmol, 103% yield).

Step 2

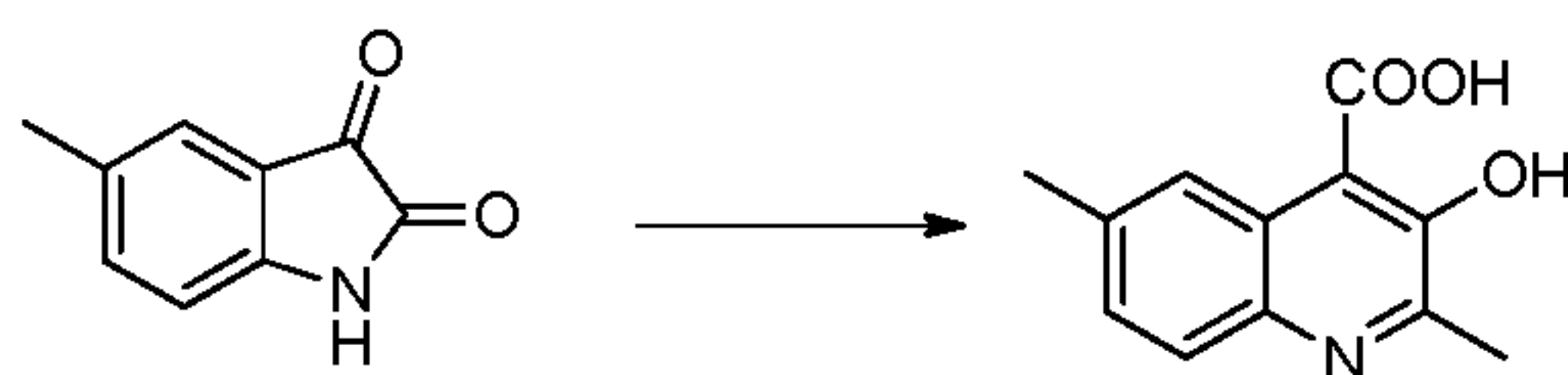


The product of Step 1 (34.7 mg, 0.153 mmol) and the product of Example 40, Step 1 (50 mg, 0.069 mmol) were dissolved in DCM (694 μl) and cooled to 0°C. TEA (29.0 μl, 0.208 mmol) was added, and the mixture stirred for 1h. TLC showed complete conversion, and the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with EtOAc/hexane to give I-41 (40 mg, 0.050 mmol, 72.4% yield) as colorless oil. MS: *m/e* = 796.2 (100) (MH⁺).

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Example 42: *tert*-Butyl (1aR,3aS,3'R,9S,16aS,Z)-5',9'-dimethyl-1a-(1-methylcyclopropyl sulfonylcarbamoyl)-3,8-dioxo-1a,1',2,2',3,3a,4,6,8,9,10,11,12,13,14,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-5,3'-pyrano[2,3-c]quinoline]-9-ylcarbamate (I-42)

20 Step 1

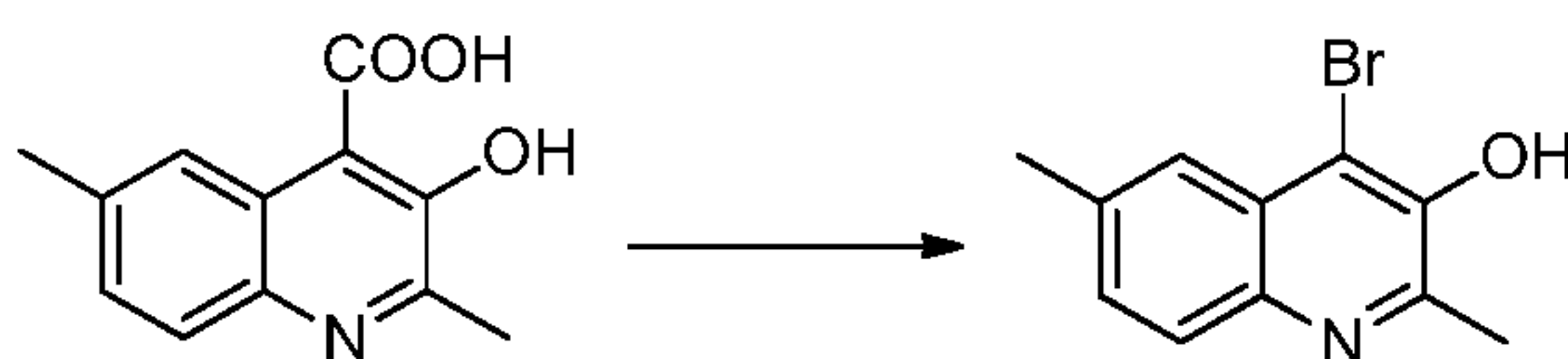


A solution of 5-methylisatin (10.00 g, 62.1 mmol) in water (150 mL) was treated with Ca(OH)₂ (13.8 g, 186 mmol) and heated at 80°C for 1h. The reaction mixture was then

treated with chloroacetone (14.35 g, 12.37 mL) and heated additionally for 6h. It was cooled to RT and acidified with aq. HCl. The solid separating out was filtered, dried and used as is (yield 12.3 g).

Step 2

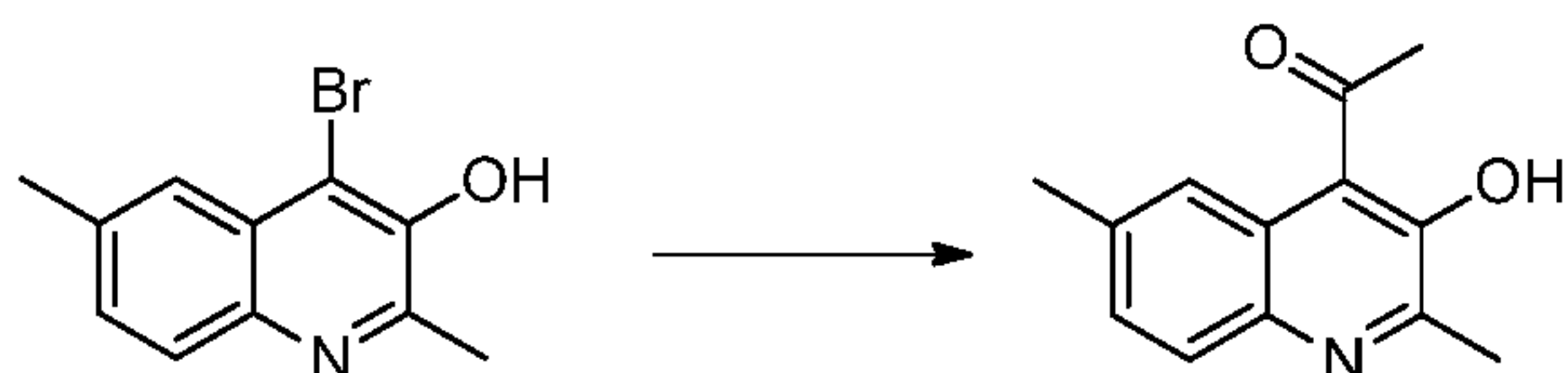
5



A suspension of the product of Step 1 (7.00 g, 32.2 mmol) in THF (75 mL) was treated with NBS (7.17 g, 40.3 mmol) and stirred at RT for 4h. The reaction mixture diluted with EtOAc (600 mL) and washed with water (2 x 300 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated *in vacuo* and purified by silica gel chromatography (EtOAc/Hexanes) to yield bromide product of Step 2 (3.5 g, 43%).

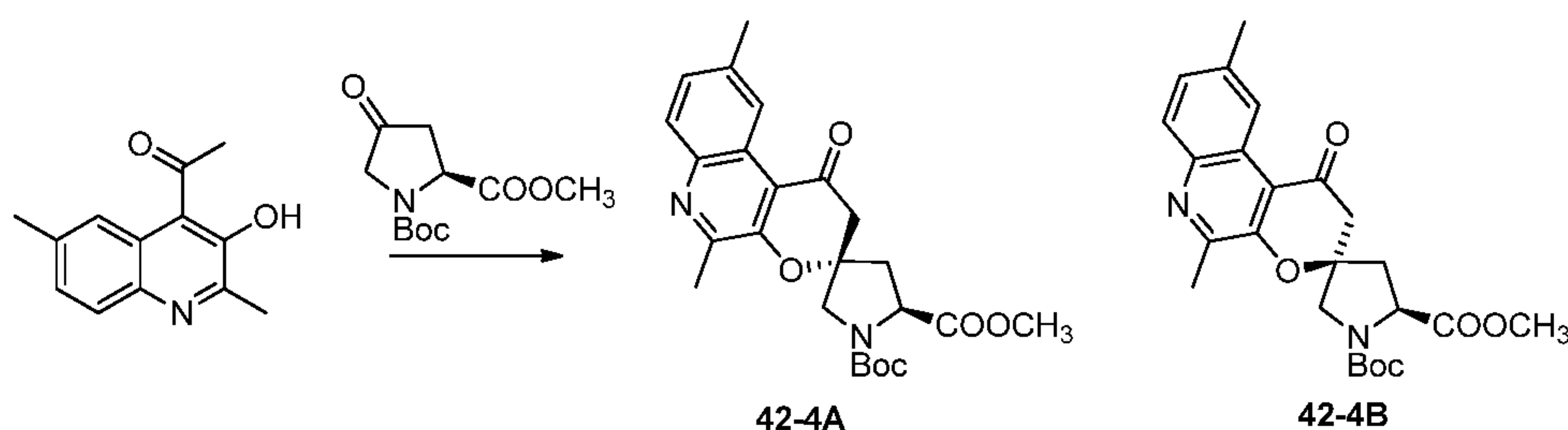
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Step 3



A solution of the bromide product of Step 2 (3.3 g, 13.09 mmol) in dry dioxane (50.0 mL) under N₂ was treated with tributyl(1-ethoxyvinyl)stannane (8.84 mL, 9.45 mmol), Pd(PPh₃)₄ (1.5 g, 1.3 mmol) and heated at reflux for 4h. The reaction mixture was cooled to RT and reacted with aq. HCl (1 m, 20 mL) and stirred at RT for 45 min. It was neutralized with a solution of sat. aq. NaHCO₃ and extracted into EtOAc. The combined organic layers were dried (MgSO₄), filtered, concentrated *in vacuo* and purified by silica gel chromatography to yield desired ketone product of Step 3 (1.4 g, 50%).

15

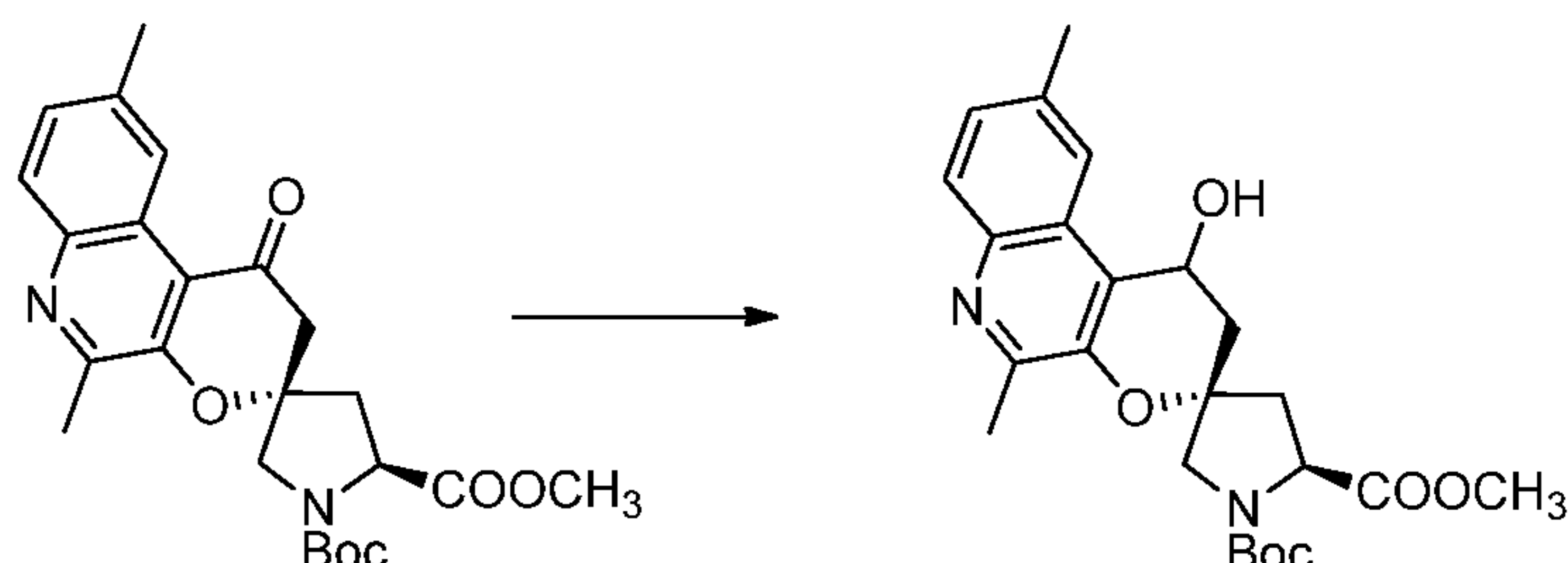
20 Step 4

A solution of ketone product of Step 3 (700 mg, 3.25 mmol) and 4-oxo-proline (1.5 g, 6.50 mmol) in MeOH (10 mL) was treated with powdered 4A molecular sieves (2.5 g) and pyrrolidine (136 μL, 1.62 mmol) and heated in a microwave at 105°C for 30 min. The reaction mixture was cooled to RT. A similar scale reaction was repeated, and the crude

25

reactions were combined. The combined reaction mixtures were filtered, concentrated *in vacuo* and purified by silica gel chromatography (EtOAc/Hexanes) to yield two diastereomers 42-4A (1.3 g) and 42-4B (730 mg).

Step 5

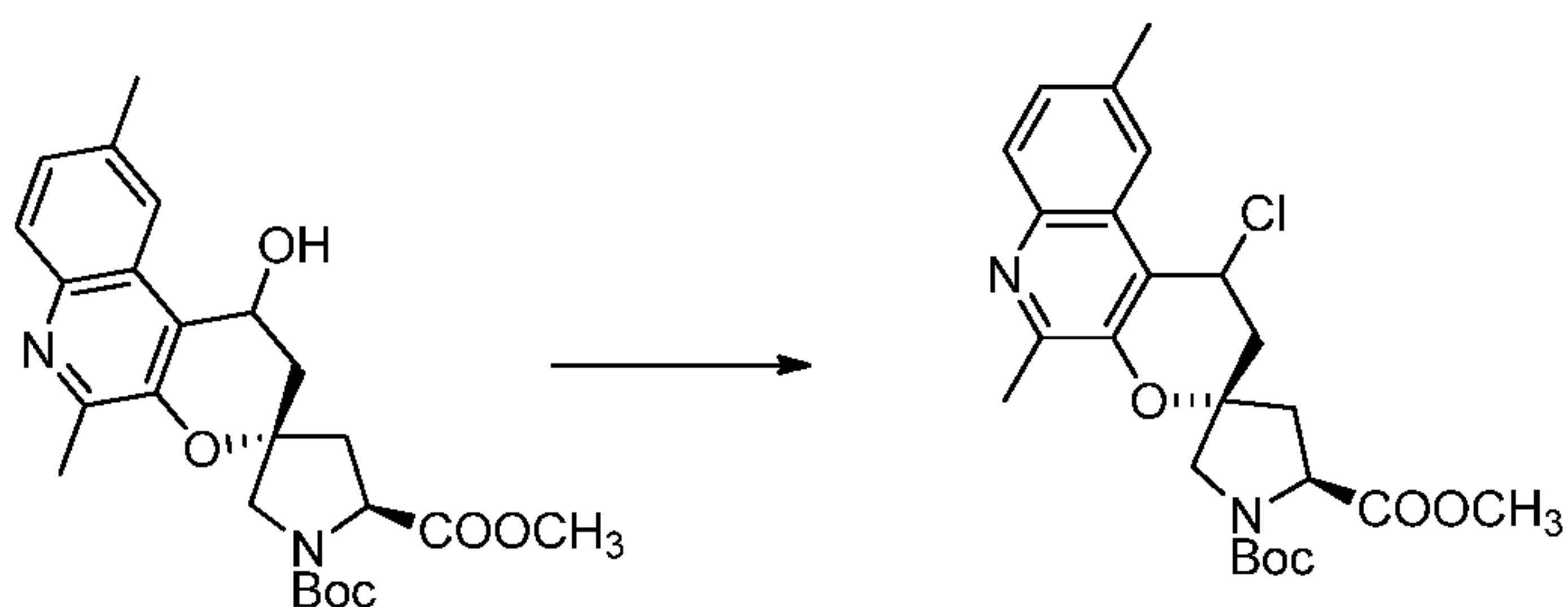


5

A solution of ketone 42-4A (1.30 g, 2.95 mmol) in MeOH (20 mL) was cooled to 0°C and treated with NaBH₄ (112 mg, 2.95 mmol). The reaction mixture was stirred at RT for 15 min and quenched with a solution of sat. aq. NaHCO₃. The reaction mixture was extracted with EtOAc (450 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated *in vacuo* and purified by chromatography (SiO₂, EtOAc/Hexanes) to yield the reduced alcohol product of Step 5 (1 g, 77%), colorless foam as a mixture of diastereomers.

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Step 6

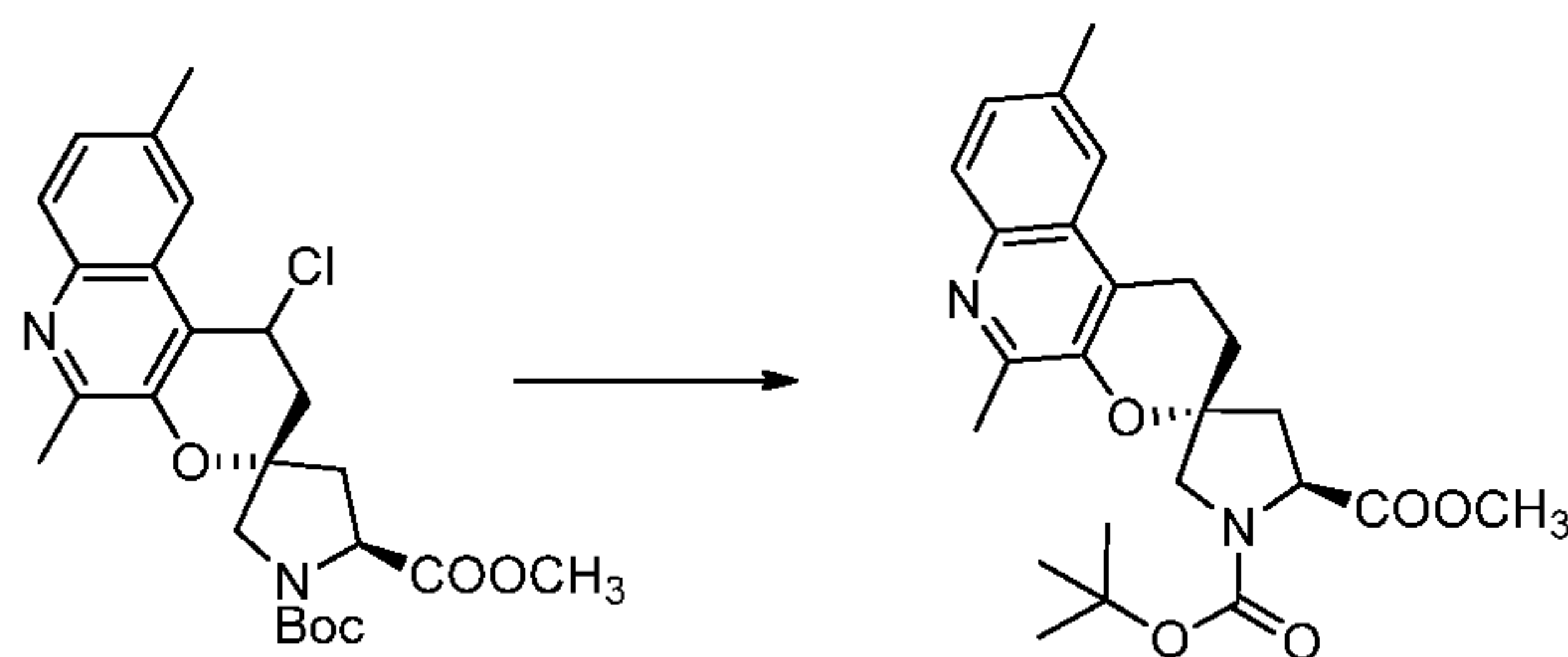


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A solution of the product of Step 5 (1.00 g, 2.26 mmol) in DCM (20.0 mL) at 0°C was treated with TEA (0.813 mL) and MsCl (0.352 mL) and stirred overnight when the ice bath slowly warmed up to RT. The reaction mixture was diluted with a solution of sat. aq. NaHCO₃, and the reaction mixture was extracted with EtOAc (300 mL). The combined organic layer were dried (MgSO₄), filtered concentrated *in vacuo* and used in the next step without further purification (1.1 g).

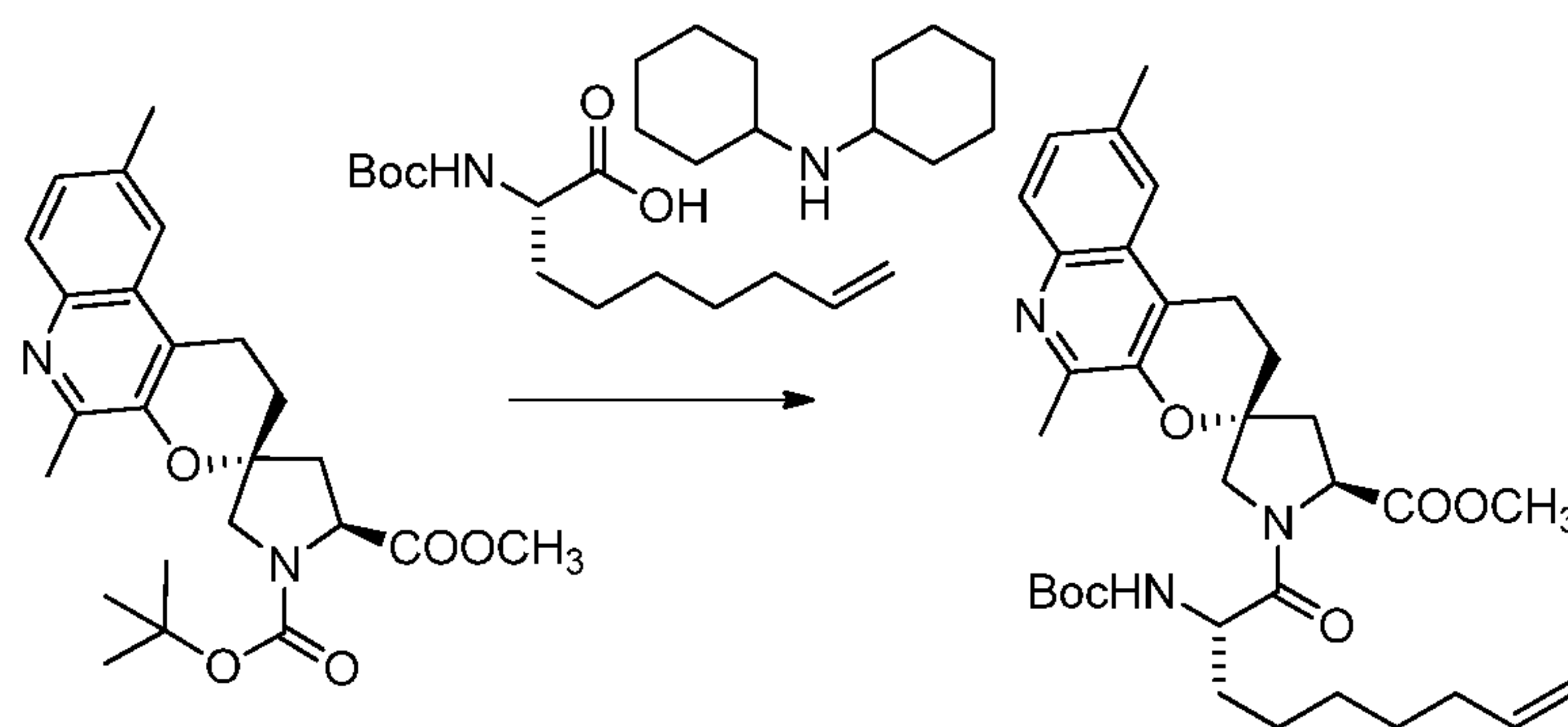
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Step 7



A solution of the product of Step 6 (1.1 g, 2.4 mmol) in EtOAc (40 mL) was treated with Pd/C (10% wt) and hydrogenated with H₂ using balloon pressure. The reaction mixture was stirred at RT for 1.5h and filtered through CELITE. The filtrate was concentrated *in vacuo* and purified by silica gel chromatography (CH₂Cl₂/MeOH) to yield reduced product of Step 7 (1.0 g, 98%).

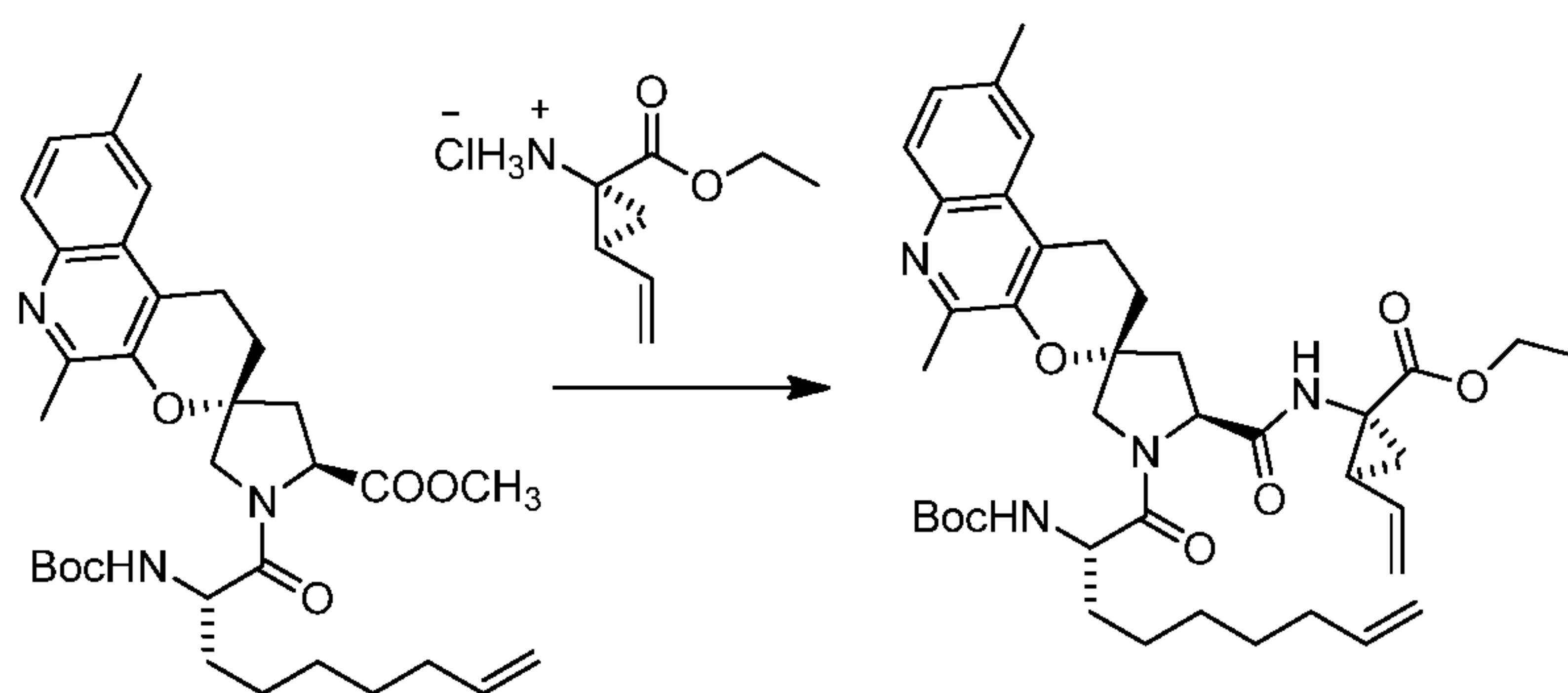
Step 8



A solution of the product of Step 7 (1.00 g, 2.35 mmol) in DCM (20 mL) was treated with trifluoroacetic acid (20 mL) and stirred at RT for 1h. The reaction mixture was concentrated *in vacuo*. The residue was taken in dry dioxane (20 mL) and concentrated *in vacuo*. The residue was treated with ether, when the amine salt precipitated out, which was filtered, dried and used as is.

A solution of (2*S*)-2-((*tert*-butoxycarbonyl)amino)non-8-enoic acid (1.165 g, 2.57 mmol), amine salt (1.3 g, 2.34 mmol), HATU (1.34 g, 3.51 mmol) in DMF and DCM (20 mL each) was treated with Hunig's base (1.2 g, 1.6 mL, 9.36 mmol) and stirred at RT for 12h. The reaction mixture was diluted with EtOAc (300 mL) and washed with water and a solution of sat. aq. NaHCO₃. The combined organic layers were dried (MgSO₄), filtered, concentrated *in vacuo*, and purified by silica gel chromatography to yield the product of Step 8 as colorless foam (1.1 g, 81%).

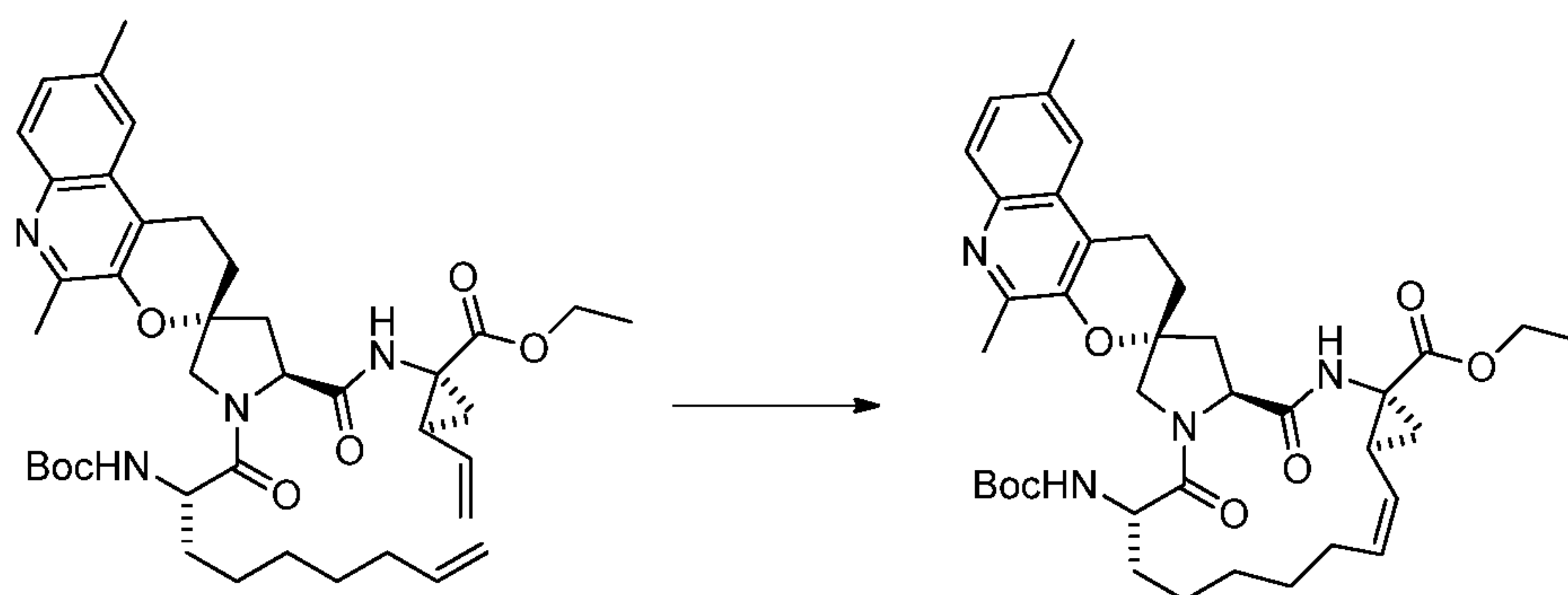
Step 9



A solution of the product of Step 8 (1.10 g, 1.897 mmol) in MeOH (8.00 mL), water (4.00 mL) and THF (15 mL) was treated with aq. LiOH solution (2 m, 2.85 mL) and heated at 60°C for 1h. The reaction mixture was cooled to RT and acidified with aq. HCl (1 m, 5 mL) and extracted into EtOAc (250 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated *in vacuo* and used as it is.

A solution of acid (1.10 g, 1.95 mmol) in DMF and DCM (5.00 mL each) was treated with (1R,2S)-1-(ethoxycarbonyl)-2-vinylcyclopropanaminium chloride (745 mg, 3.89 mmol), HATU (1.1 g, 2.92 mmol) and Hunig's base (1.70 mL, 9.71 mmol) and stirred at RT for 12h. The reaction mixture was diluted with aq. NaHCO₃ and extracted into EtOAc. The combined organic layers were dried (MgSO₄), filtered, concentrated *in vacuo* and purified by chromatography (SiO₂, EtOAc/Hexanes) to yield the coupled product of Step 9 as a colorless foam (1.00 g, 73%).

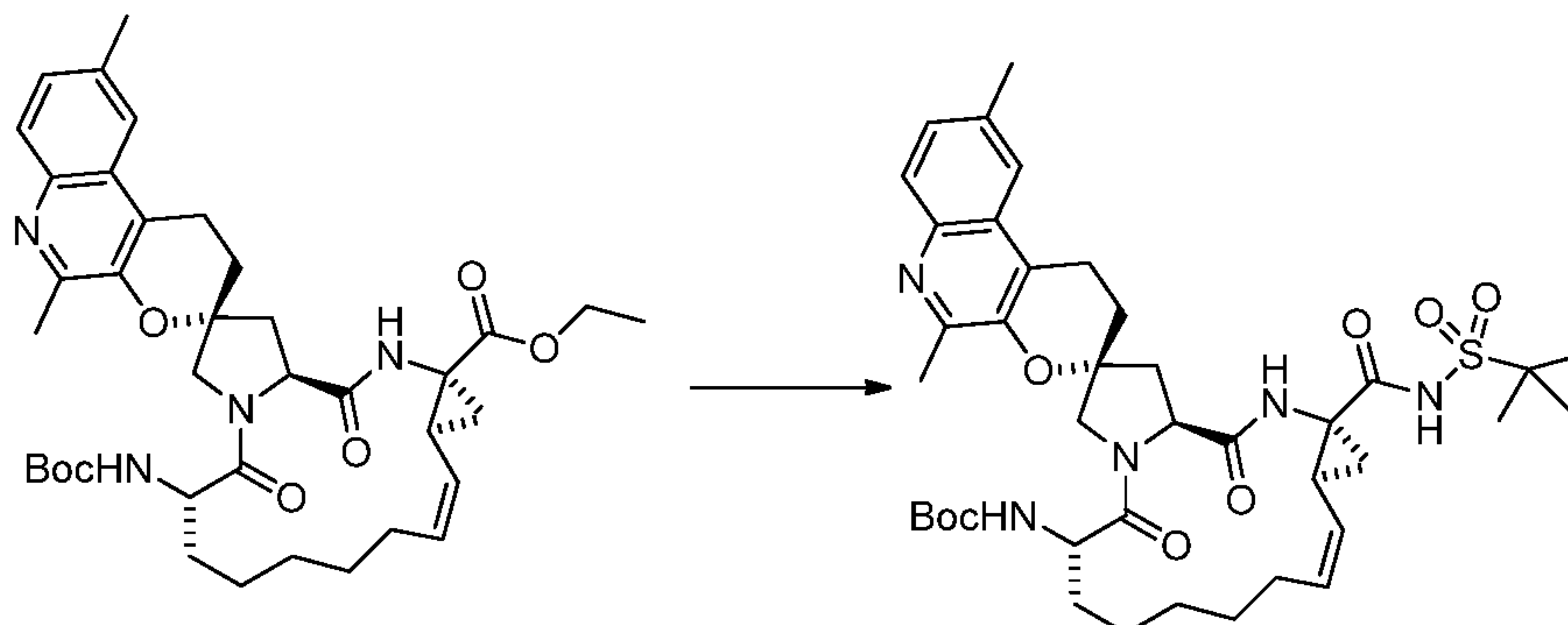
Step 10



A solution of the diene product of Step 9 (1.00 g, 1.42 mmol) in DCE (400 mL) was degassed and treated with Zhan's catalyst (261 mg, 0.356 mmol), benzoquinone (0.427 mmol, 46 mg) and heated at 65°C for 3h. The disappearance of starting material was followed by TLC. On complete consumption of starting material as indicated by TLC, the reaction mixture was quenched with methylvinyl ether (1.00 mL), concentrated *in vacuo* and purified by

silicagel chromatography (Hexanes, EtOAc) to yield the cyclized product of Step 10 (963 mg, 68%).

Step 11

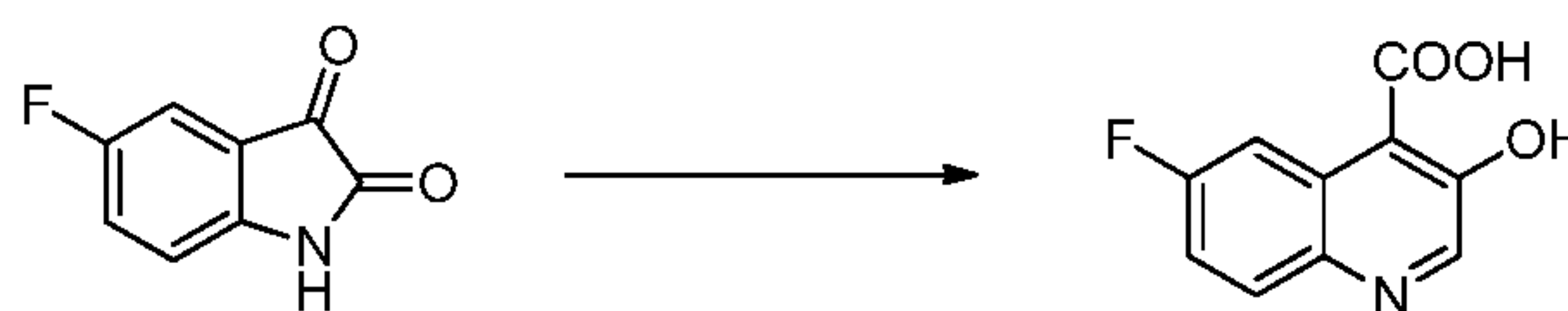


5 A solution of the cyclized product of Step 10 (650 mg, 0.963 mmol) in MeOH (8.00 mL), water (5.0 mL) and THF (8.0 mL) was treated with aq. LiOH (2.5 mL, 2 M, 4.82 mmol) and stirred at RT overnight. The reaction mixture was diluted with aq. HCl to make acidic and extracted into EtOAc (250 mL). The combined organic layers were dried (MgSO₄), filtered concentrated *in vacuo* and used as is.

10 A solution of acid (100 mg, 0.155 mmol) in THF (3 mL) was treated with carbonyl diimidazole (50 mg, 0.31 mmol) and heated at 70°C for 2h. The reaction mixture was cooled to RT and treated with methylcyclopropyl sulfonamide (42 mg) and DBU (46 μl) and heated at 50°C. The reaction was heated at 50°C for 4h and once again treated with methylcyclopropylsulfonamide and DBU in the same amounts. The reaction mixture was stirred
15 at RT for 24h and concentrated *in vacuo* and purified by silica gel chromatography to yield I-42 as colorless solid (89 mg).

Example 43: *tert*-Butyl (1aR,3aS,3'R,9S,16aS,Z)-9'-fluoro-5'-methyl-1a-(1-methylcyclopropylsulfonycarbonyl)-3,8-dioxo-1a,1',2,2',3,3a,4,6,8,9,10,11,12,13,14,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-5,3'-pyrano[2,3-c]quinoline]-9-ylcarbamate (I-43)

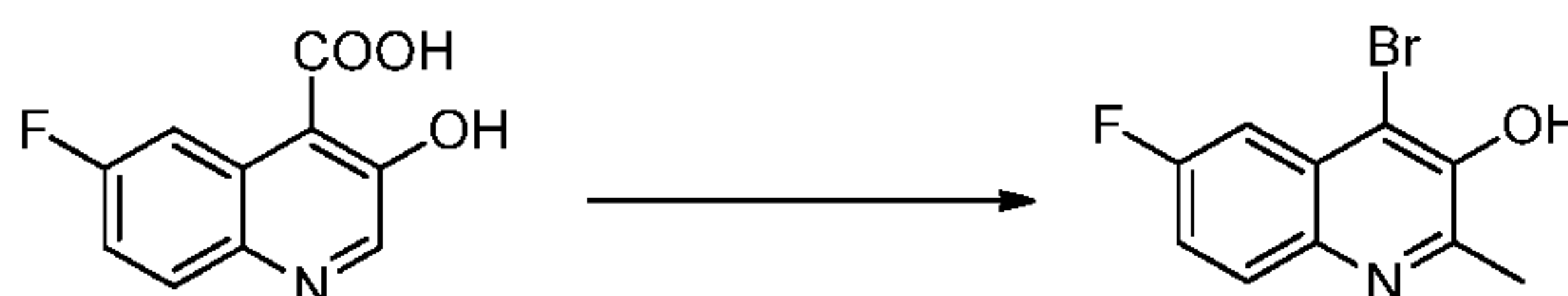
Step 1



25 A slurry of 5-fluoroisatin (10.1 g, 61.2 mmol) in water (150 ml) was treated with Ca(OH)₂ (13.60 g, 184 mmol) and heated at 80°C for 1h. The slurry was then treated with

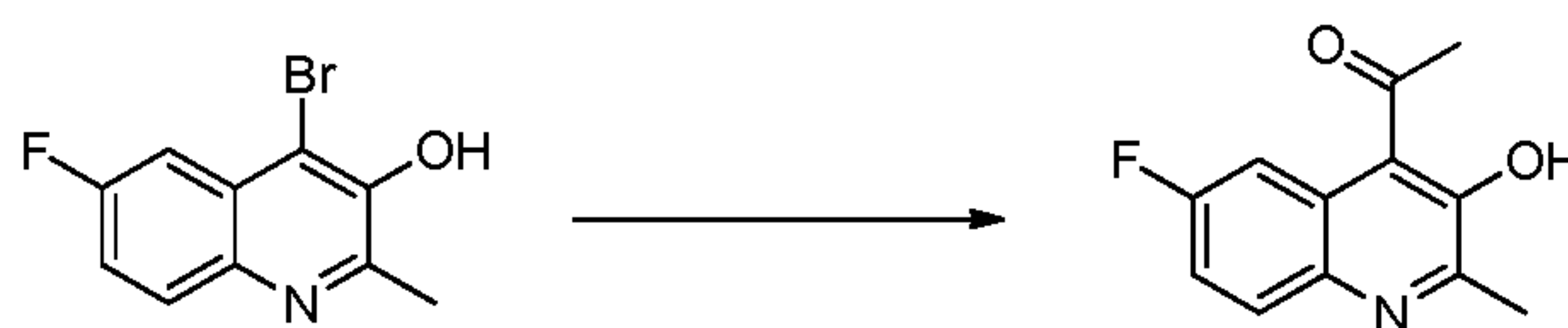
chloroacetone (12.18 ml, 153 mmol), when the slurry stopped stirring forming a concrete-like mass. The mass was broken up with a spatula, and more water was added (~200 ml). It was further heated at same temperature for additional 6h. The reaction mixture was cooled to RT and acidified with aq. HCl (250 ml, 1N). The solid separating out was filtered, washed with water and dried under vacuum to yield the product of Step 1 (11.8 g, 87%) as a pale yellow solid used in the next step without further purification.

5 Step 2



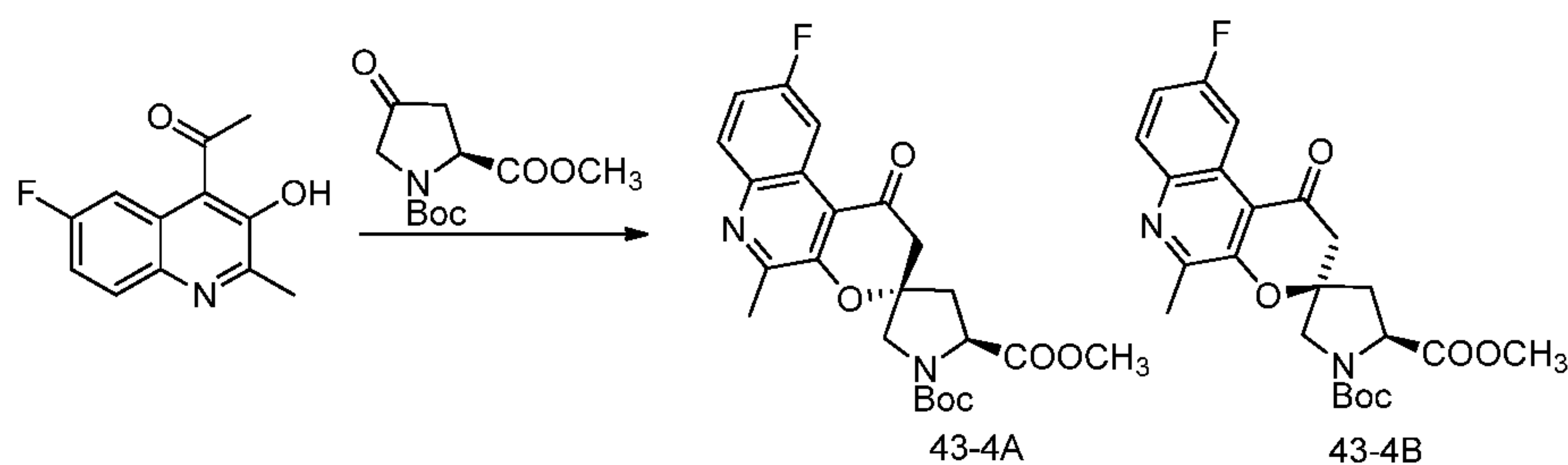
A solution of the product of Step 1 (5.9 g, 26.6 mmol) in DMF (100 ml) was treated with NBS (5.68 g, 31.9 mmol) at RT and stirred for 16h. The reaction mixture was diluted with EtOAc, and the organic layer was washed with water and brine. The organic layer was concentrated *in vacuo* to yield a brown solid (6 g). The crude mixture was directly adsorbed on silica gel and purified chromatography (EtOAc/Hexanes) to yield the product of Step 2 (1.05 g) as pale yellow solid.

15 Step 3



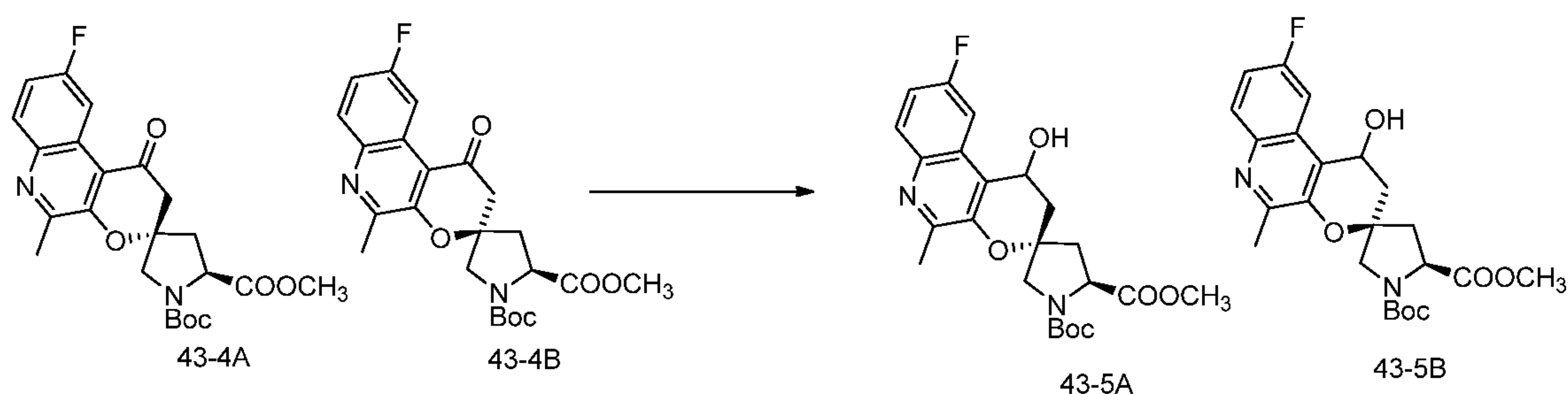
A solution of the product of Step 2 (2.4 g, 9.37 mmol) in dioxane (48 mL) was treated with tributyl(1-ethoxyvinyl)tin (6.33 mL, 18.74 mmol), Pd(PPh₃)₂Cl₂ (0.658 g, 0.937 mmol) and heated in an oil bath at 115°C under N₂ atmosphere for 3h. The reaction mixture was cooled to RT, treated with aq. HCl (1 m, 48 mL) and stirred at RT for 1h. The reaction mixture was made basic with a solution of sat. NaHCO₃ and extracted into EtOAc. The combined organic layer was dried (MgSO₄), filtered, concentrated *in vacuo* and purified by silica gel chromatography (acetone/Hexanes, 0-25%) to isolate ketone the product of Step 3 (1.49 g) as a pale yellow solid.

25 Step 4



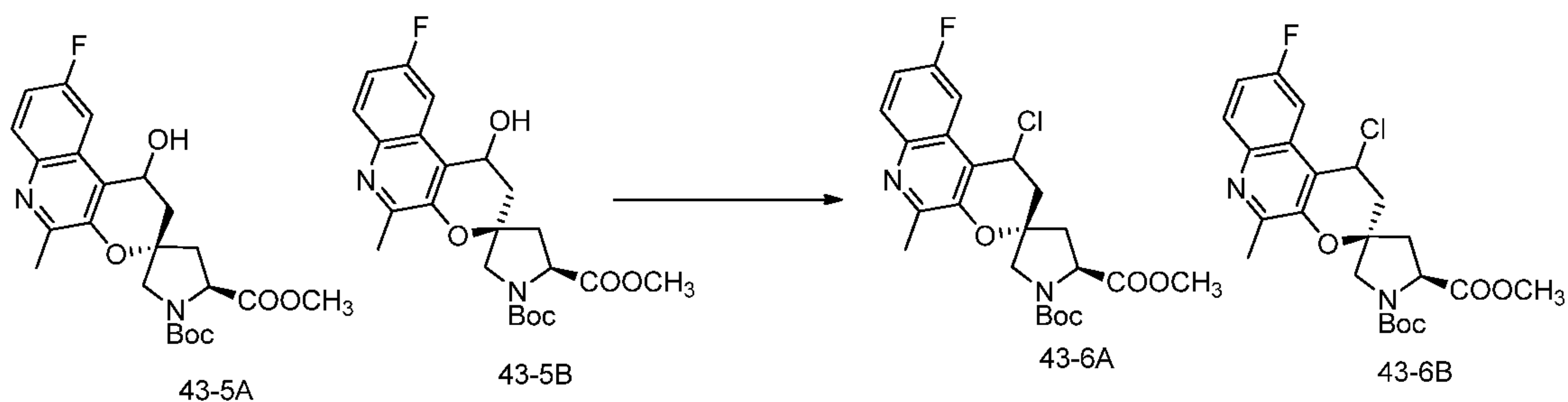
A solution of the product of Step 3 (693 mg, 3.16 mmol) in MeOH (14 ml) was treated with 1-*tert*-butyl-2-methyl(2S)-4-oxopyrrolidine-1,2-dicarboxylate (1.54 g, 6.32 mmol) and pyrrolidine (0.261 ml, 3.16 mmol) in a microwave tube. To this was then added powdered 4A molecular sieves 693 mg, and the reaction was heated to 105°C in microwave reactor for 35 min. Analysis of TLC (30% EtOAc/Hexanes) indicated complete consumption of starting material and formation of two new products corresponding to 43-4A and 43-4B. The reaction was repeated 3x, and the crude material (7.0 g) were combined and purified by silica gel chromatography to yield an inseparable mixture of 43-4A and 43-4B (3.22 g, 76%).

10 Step 5



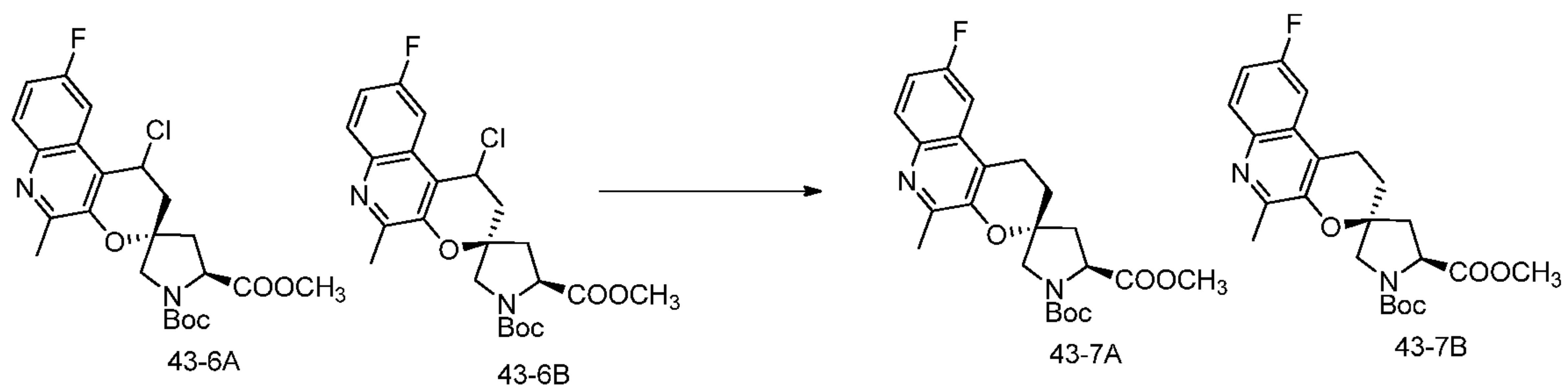
A solution of 43-4A and 43-4B (1.96 g, 4.40 mmol) in MeOH (40 ml) was cooled to 0°C and treated with NaBH₄ (166 mg, 4.40 mmol) over 1 min and stirred for 30 min at 0°C. TLC (50% EtOAc/Hexanes) indicated complete consumption of starting material. The reaction was stirred for 45 min total and quenched with sat. aq. NaHCO₃ solution. It was extracted with EtOAc, and the combined organic layers were washed with brine, dried (MgSO₄), filtered, concentrated *in vacuo* and purified by silica gel chromatography (EtOAc/Hexanes) to yield 43-5A and 43-5B (1.77 g) as colorless foam.

Step 6



A solution of 43-5A and 43-5B (1.77 g, 3.95 mmol) in DCM (35 ml) was cooled in an ice bath and treated with Et₃N (1.652 ml, 11.85 mmol) then MsCl (0.616 ml, 7.90 mmol). The reaction mixture was allowed to slowly warm to RT and stirred overnight. TLC with 50% EtOAc/Hexanes indicated complete consumption of starting material. The reaction mixture was diluted with EtOAc and washed with sat. aq. NaHCO₃, water, brine and filtered through anhydrous Na₂SO₄. The filtrate was concentrated to dryness and purified by silica gel chromatography to yield chlorides 43-6A and 43-6B (1.74 g, 95%) as a pale yellow solid.

Step 7

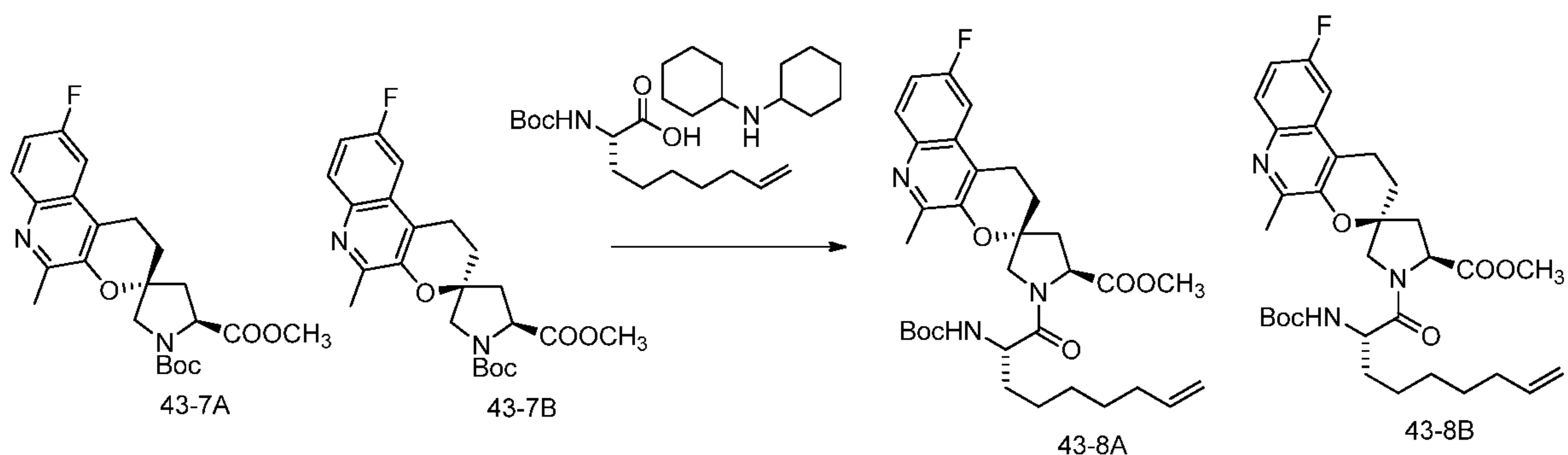


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A solution of 43-6A and 43-6B (1.74 g, 3.74 mmol) in EtOAc (35 mL) was treated with Pd/C (10%, 199 mg) and hydrogenated with balloon pressure. The reaction mixture was stirred at RT for 2h. It was diluted with MeOH to dissolve precipitate formed and filtered. The filtered cake was washed with excess MeOH, and the filtrate was concentrated *in vacuo* to yield reduced products 43-7A and 43-7B (1.75 g) as a colorless solid.

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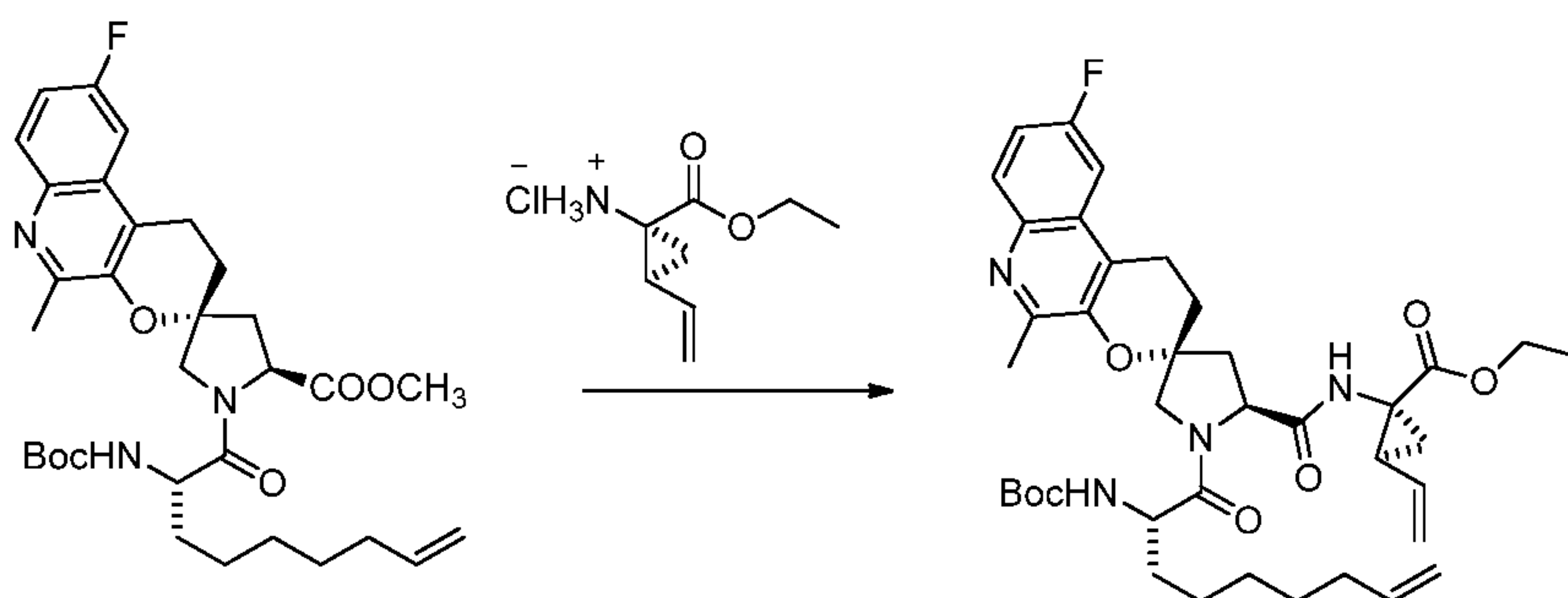
Step 8



A solution of 43-7A and 43-7B (1.74 g, 4.04 mmol) in 4 M HCl in dioxane (5 ml) was stirred at RT for 1.25h. The reaction mixture was concentrated *in vacuo* to yield amine salts (1.61 g) as orange solid that were used in next reaction without further purification.

5 A solution of amine salts (1.61 g, 4.87 mmol) in DCM (16 ml) and DMF (16 ml) was treated with DIPEA (2.55 ml, 14.62 mmol), dicyclohexylammonium (*S*)-2-(*tert*-butoxycarbonylamino)non-8-enoate (2.65 g, 5.85 mmol) and HATU (2.25 g, 5.85 mmol) and stirred at RT for 16h. The reaction mixture was diluted with EtOAc (300 mL) and washed with water and a solution of sat. aq. NaHCO₃. The combined organic layers were dried (MgSO₄),
 10 filtered, concentrated *in vacuo*, and purified by silica gel chromatography to separate the two diastereomers 43-8A and 43-8B yielding desired diastereomer 43-8A (1.42 g) as colorless foam.

Step 9

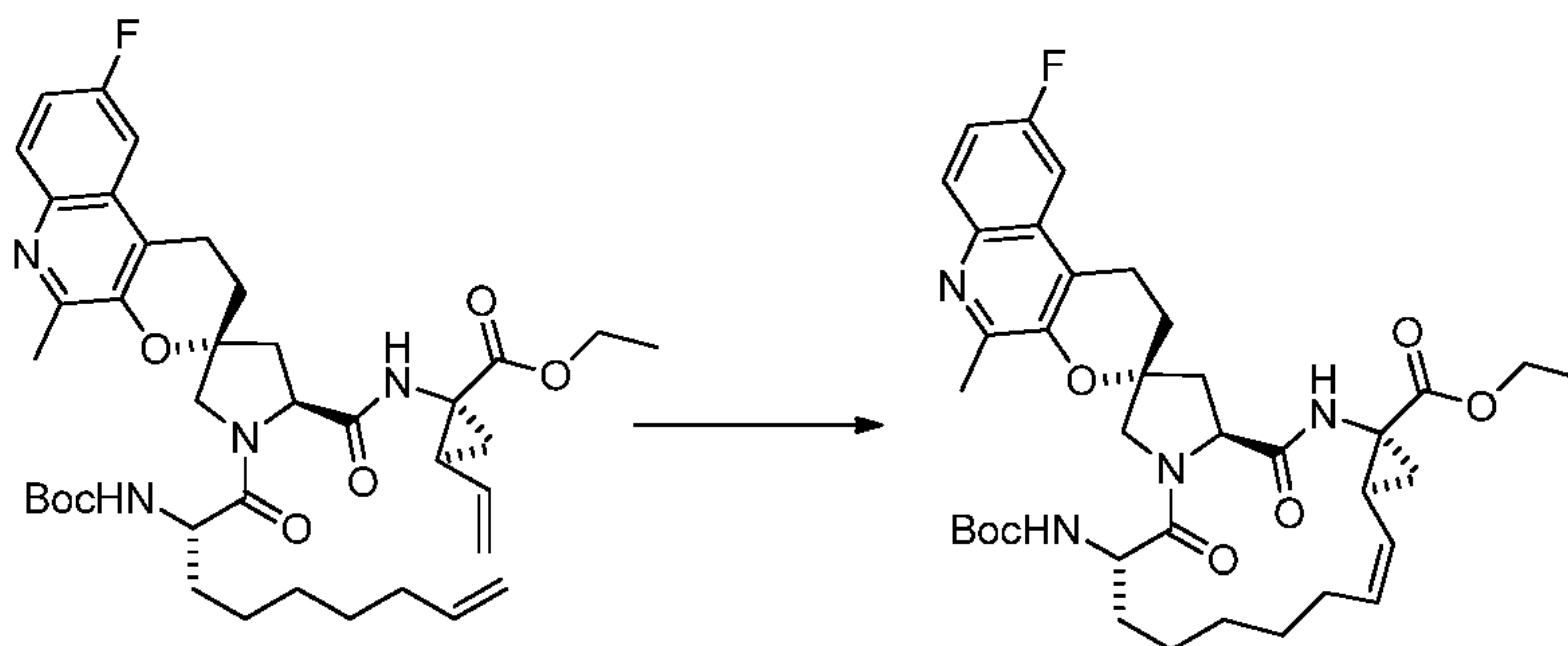


A solution of 43-8A (1.42 g, 2.43 mmol) in MeOH (11 ml) and THF (16.50 ml) was treated with a 2 M aq. solution of LiOH (3.64 ml, 7.28 mmol) and heated at 60-65°C for 1h. Analysis of TLC (50% EtOAc/Hexanes) indicated all starting material was consumed. The reaction mixture was acidified with 1N HCl (8.0 mL) and extracted with EtOAc. The combined extracts, were washed with brine and filtered through Na₂SO₄. The filtrate was concentrated *in vacuo* to yield carboxylic acid as pale yellow foam (1.46 g).

20 A solution of acid (1.39 g, 2.43 mmol) in DMF (14 ml) and DCM (14 ml) was treated with DIPEA (2.33 ml, 13.35 mmol), HATU (1.20 g, 3.16 mmol), (1R,2S)-1-(ethoxycarbonyl)-2-vinylcyclopropanaminium chloride (0.93 g, 4.86 mmol) and stirred at RT for

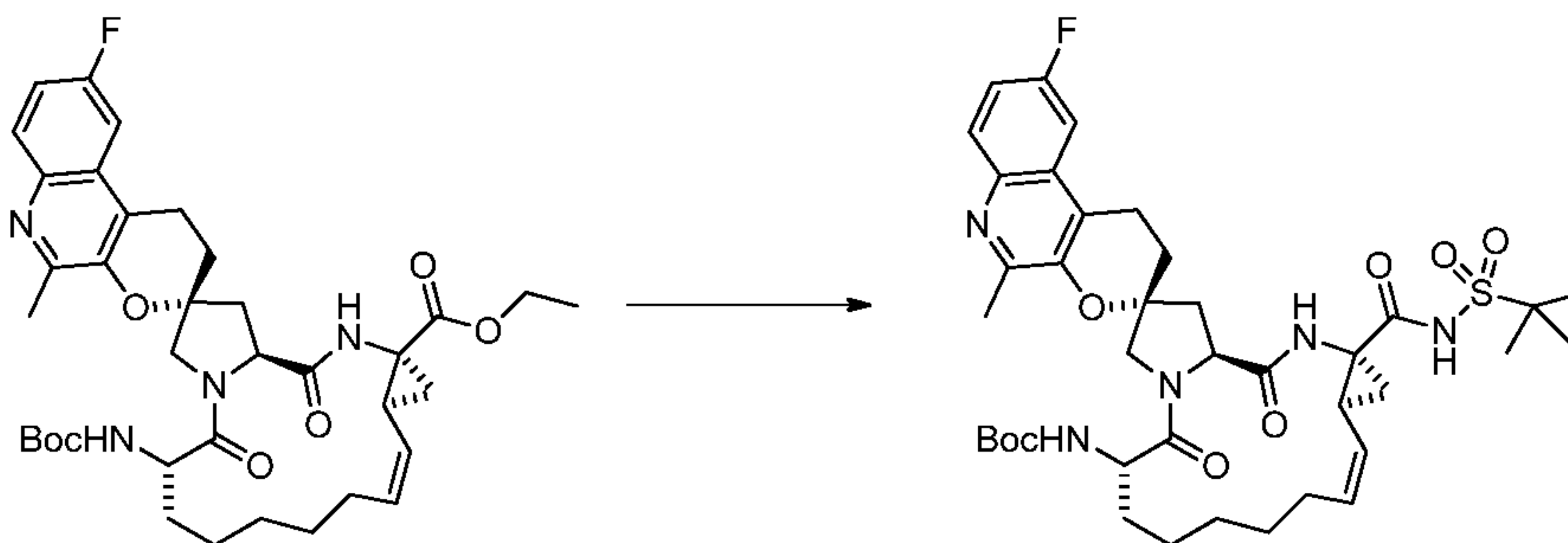
15h. The reaction mixture was concentrated *in vacuo* and diluted with EtOAc. The combined organic layers were washed with water, 0.5N aq. HCl, brine and filter through anhydrous Na₂SO₄. The filtrate was concentrated *in vacuo* and purified by silica gel chromatography (EtOAc/Hexanes) to yield the product of Step 9 as a colorless solid (1.6 g).

5 Step 10



A solution of the product of Step 9 (800 mg, 1.132 mmol) in DCE (400 ml) was degassed, treated with Zhan's catalyst (208 mg, 0.283 mmol), benzoquinone (36.7 mg, 0.340 mmol) and heated at 75°C for 4h. The disappearance of starting material was followed by TLC (60% EtOAc/Hexanes). On complete consumption of starting material, the reaction mixture was cooled to RT and quenched with methylvinyl ether and stirred for 10 min. The reaction mixture was concentrated *in vacuo* and purified by silica gel chromatography to yield the product of Step 10 as a tan colored solid (357 mg, 47%).

15 Step 11

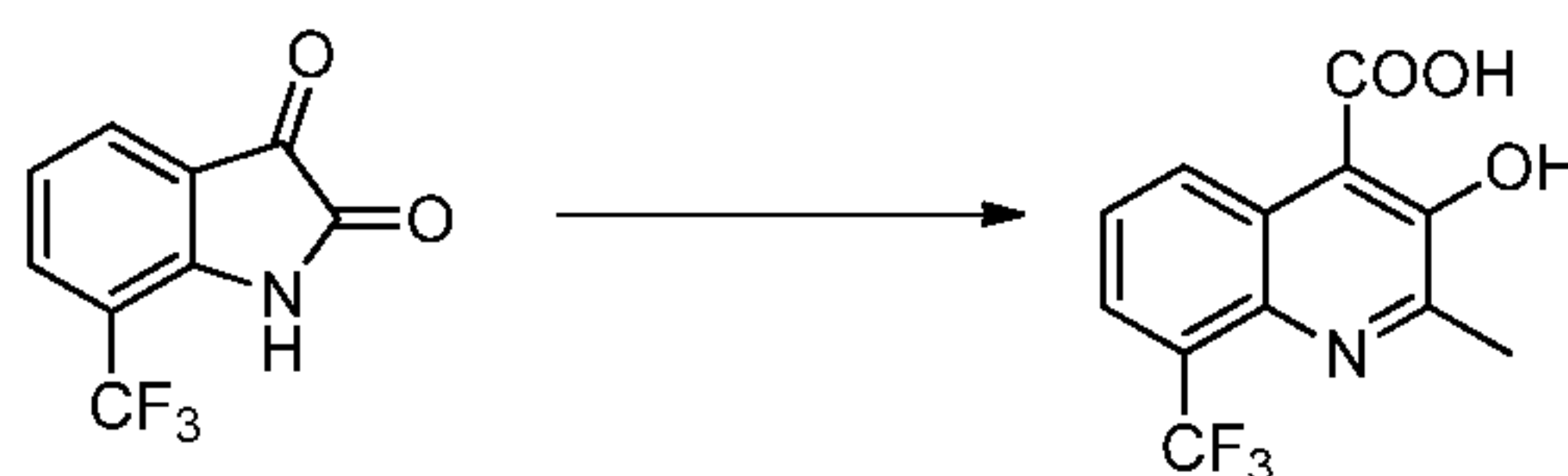


A solution of the product of Step 10 (357 mg, 0.526 mmol) in MeOH (2.0 ml) and THF (3.00 ml) was cooled to 0°C and treated with a solution of 2 m aq. LiOH (1.32 ml, 2.63 mmol). The reaction was allowed to warm to RT and stirred overnight. Analysis of TLC with 60% EtOAc/Hexanes indicated all the starting material was consumed. The reaction mixture was acidified with aqueous 1N HCl (4.00 mL) and concentrated to dryness. The crude mixture was used as is.

A solution of acid (0.342 g, 0.526 mmol) in THF (7 mL) was treated with carbonyl diimidazole (0.171 g, 1.052 mmol) and heated at 70°C in a sealed tube for 2h. The reaction mixture was cooled to RT and treated with 1-methylcyclopropane-1-sulfonamide (0.284 g, 2.104 mmol) and DBU (0.315 mL, 2.104 mmol) and further heated at 50°C for 12h. The reaction mixture was cooled to RT and diluted with EtOAc. The organic layer was washed with 0.5 M aqueous HCl, water, brine and filtered through anhydrous Na₂SO₄. The filtered EtOAc layer was concentrated *in vacuo*, and the residue was purified by silica gel chromatography twice using EtOAc/Hexanes and EtOAc/DCM to yield I-43 as a colorless solid.

Example 44: tert-Butyl (1aR,3aS,3'R,9S,16aS,Z)-5'-methyl-1a-(1-methylcyclopropylsulfonylcarbamoyl)-3,8-dioxo-7'-(trifluoromethyl)-1a,1',2,2',3,3a,4,6,8,9,10,11,12,13,14,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-5,3'-pyrano[2,3-c]quinoline]-9-ylcarbamate (I-44)

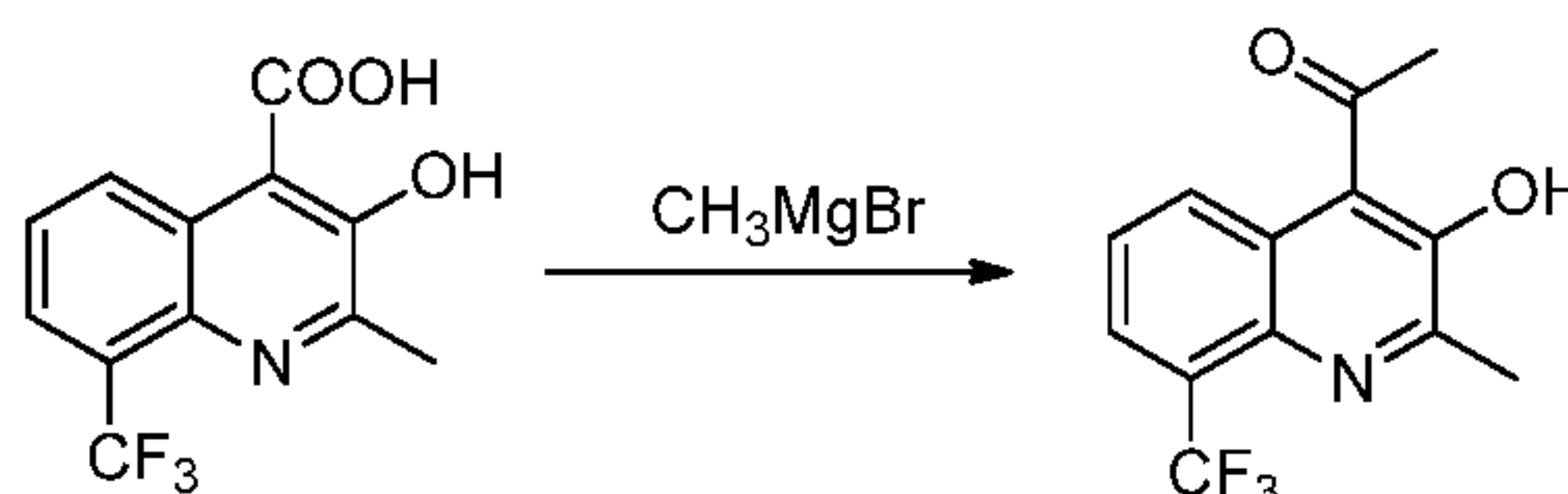
Step 1



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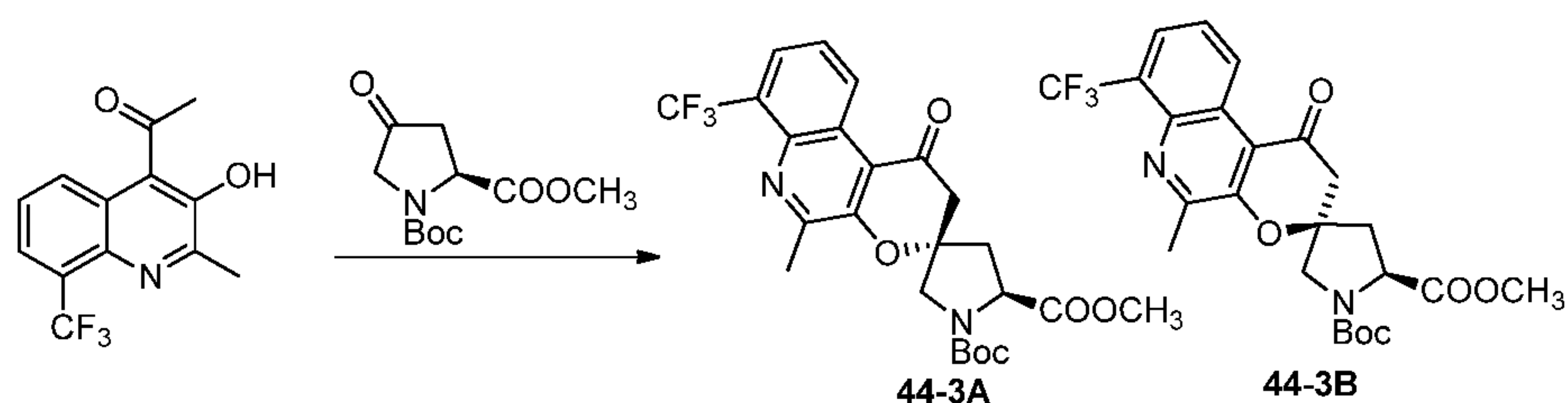
A slurry of 7-trifluoroisatin in water was treated with Ca(OH)₂ and heated at 80°C for 1h. The reaction was then treated with chloroacetone and further heated at 80°C for 6h. The reaction mixture was cooled to RT and acidified with aq. HCl (250 ml, 1N). The solid separating out was filtered, washed with water and dried under vacuum to yield the product of Step 1.

20 Step 2



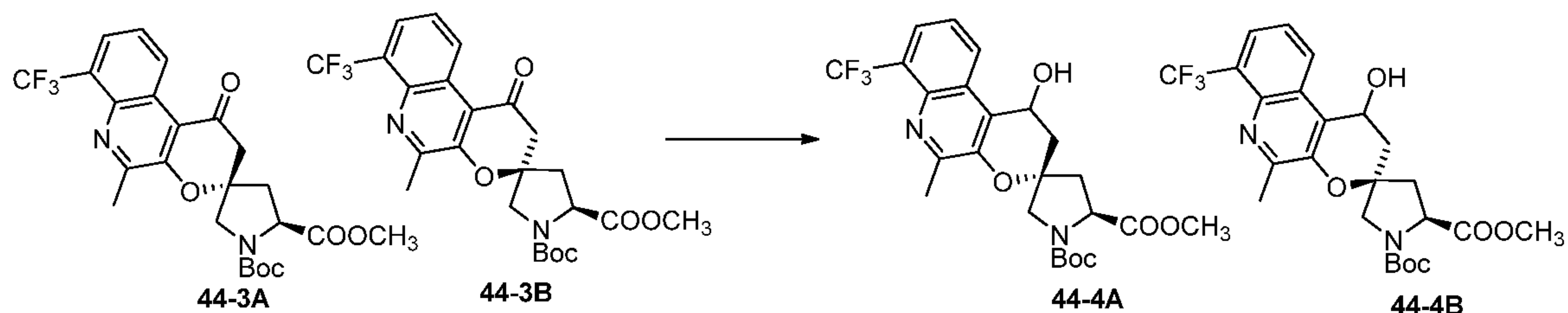
A solution of the product of Step 1 in dry THF was treated with TEA and a solution of MeMgBr in ether. The reaction mixture was heated for 4h and cooled to 0°C and quenched with MeOH and aq. NH₄Cl solution. The reaction mixture was diluted with aq. HCl and extracted with EtOAc. The combined organic layers were dried (MgSO₄), filtered, concentrated *in vacuo* and purified by silica gel chromatography to yield the product of Step 2 as a pale yellow solid.

Step 3



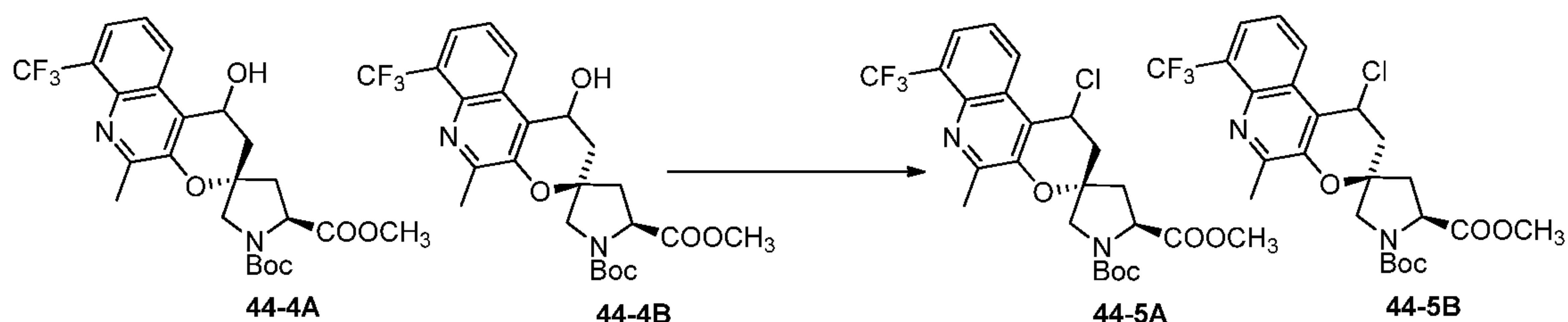
A solution of the product of Step 2 (1.11 g, 4.12 mmol) in MeOH (22 ml) was treated with 1-*tert*-butyl-2-methyl(2S)-4-oxopyrrolidine-1,2-dicarboxylate (2.01 g, 8.25 mmol) and pyrrolidine (0.341 ml, 4.12 mmol) in a sealed tube. To this was added molecular sieves (1.11 g, 4A powder), and the reaction was heated to 105°C and stirred for 12h in a sealed tube. The reaction was cooled to RT, and analysis of TLC (EtOAc/Hexanes 2:3) indicated complete consumption of starting material. The reaction mixture was filtered, concentrated *in vacuo* and purified by silica gel chromatography (Hexanes, EtOAc) to yield condensed products 44-3A and 44-3B as inseparable mixture (2.5 g, 76%).

10 Step 4



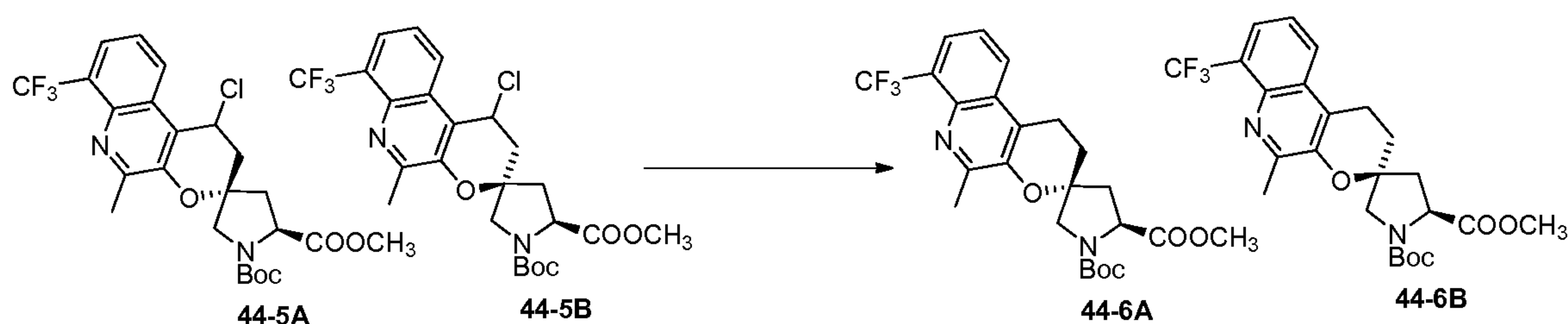
A solution of 44-3A and 44-3B (2.24 g, 4.53 mmol) in MeOH (40 ml) was cooled to 0°C and treated with NaBH₄ (0.686 g, 18.12 mmol) over 10 min and stirred for 45 min at 0°C. The reaction was allowed to warm to RT and stirred for an additional 30 min. Analysis of TLC (EtOAc/Hexanes 3:2) indicated complete consumption of starting material. The reaction mixture was concentrated *in vacuo*, and the residue was taken in EtOAc. The organic layer was washed with 0.5 M NaOH solution (2X), water and brine. The combined organic layers were dried (MgSO₄), filtered, concentrated *in vacuo* and purified by silica gel chromatography to yield reduced alcohols 44-4A and 44-4B (1.47 g, 65%).

20 Step 5



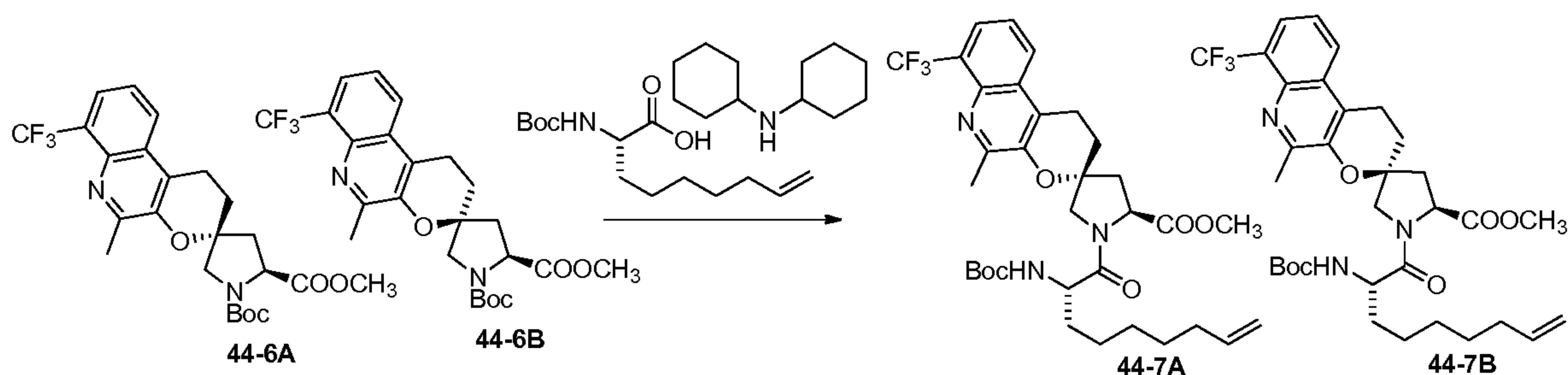
A solution of alcohols 44-4A and 44-4B (1.25 g, 2.52 mmol) in DCM (25 ml) was treated with Et₃N (0.877 ml, 6.29 mmol) then MsCl (0.392 ml, 5.04 mmol) and stirred at RT for 5h. Analysis of reaction mixture using TLC (EtOAc/Hexanes, 35%) indicated complete consumption of starting material. The reaction mixture was diluted with EtOAc and washed with sat. aq. NaHCO₃, water, brine and filtered through anhydrous Na₂SO₄. The filtrate was concentrated *in vacuo* and residue purified by silica gel chromatography to yield 44-5A and 44-5B (1.74 g, 95%) as a pale yellow solid.

Step 6



A solution of chlorides 44-5A and 44-5B (970 mg, 1.89 mmol) in EtOAc (20 mL) was treated with Pd/C (10% 100 mg) and hydrogenated with balloon pressure at RT for 4h. On completion of the reaction as indicated by TLC (EtOAc/Hexanes 35%), the reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to yield 44-6A and 44-6B (850 mg) as off-white foam.

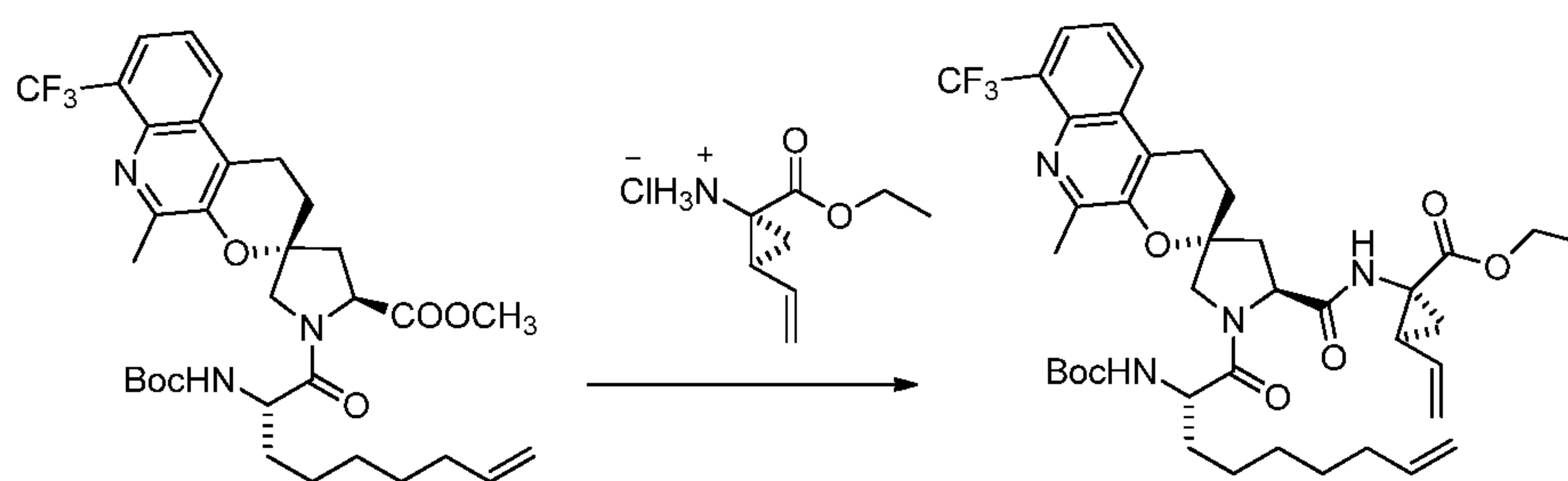
Step 7



A solution of compounds 44-6A and 44-6B (950 mg, 1.977 mmol) in DCM (3.05 ml) was cooled to 0°C and treated with trifluoroacetic acid (3.05 ml, 39.5 mmol) and allowed to warm to RT. The reaction was stirred for 1h, when TLC (EtOAc/Hexanes 45%) indicated complete consumption of starting material. The reaction mixture was concentrated *in vacuo*, and excess TFA was chased out with toluene and then dioxane to give 1.6 g of brownish yellow oil. The mixture was taken in EtOAc and washed with sat. NaHCO₃, then 50% water/sat. NaHCO₃, brine and dried over Na₂SO₄. The EtOAc layer was filtered, and the filtrate was concentrated *in vacuo* to yield deprotected amine that was used in next reaction without further purification.

A solution of amine salts (730 mg, 1.92 mmol) in DCM (10 ml) and DMF (10 ml) were treated with DIPEA (1.00 ml, 5.76 mmol), dicyclohexylammonium (S)-2-(*tert*-butoxycarbonylamino)non-8-enoate (1.04 g, 2.30 mmol) and HATU (876 mg, 2.30 mmol) and stirred at RT for 15h. The reaction mixture was diluted with EtOAc (300 mL) and washed with water and aq. NaHCO₃. The combined organic layers were dried (Na₂SO₄), filtered, concentrated *in vacuo*, and purified by silica gel chromatography to separate the two diastereomers 44-7A and 44-7B yielding desired diastereomer 44-7A as a colorless foam (426 mg, 47%).

Step 8



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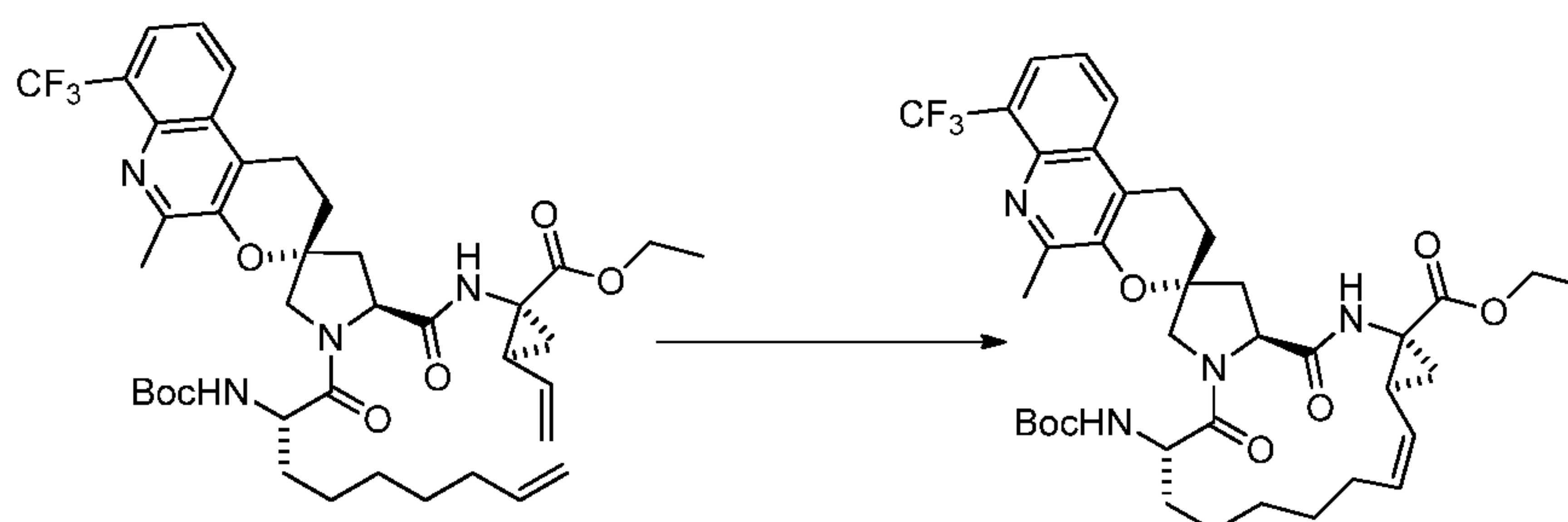
A solution of 44-7A (423 mg, 0.668 mmol) in MeOH (3.38 ml) and THF (5.07 ml) was treated with 2 M aq. solution of LiOH (1.00 ml, 2.00 mmol) and heated to 60-65°C for 1h. The reaction mixture was acidified with 1N HCl (2.0 mL) and extracted with EtOAc. The combined extracts, were washed with brine and filtered through Na₂SO₄. The filtrate was concentrated *in vacuo* to yield carboxylic acid as a light khaki solid (406 mg).

15

A solution of acid (403 mg, 0.650 mmol) in DMF (4 ml) and DCM (4 ml) was treated with Hunig's base (0.510 ml, 2.93 mmol), HATU (321 mg, 0.845 mmol), (1R,2S)-1-(ethoxycarbonyl)-2-vinylcyclopropanaminium chloride (249 mg, 1.301 mmol) and stirred at RT for 24h. The reaction mixture was concentrated *in vacuo* and diluted with EtOAc. The combined organic layers were washed with water, 0.5N aq. HCl, brine and filter through anhydrous Na₂SO₄. The filtrate was concentrated *in vacuo* and purified by silica gel chromatography to yield the product of Step 8 as a colorless solid (444 mg).

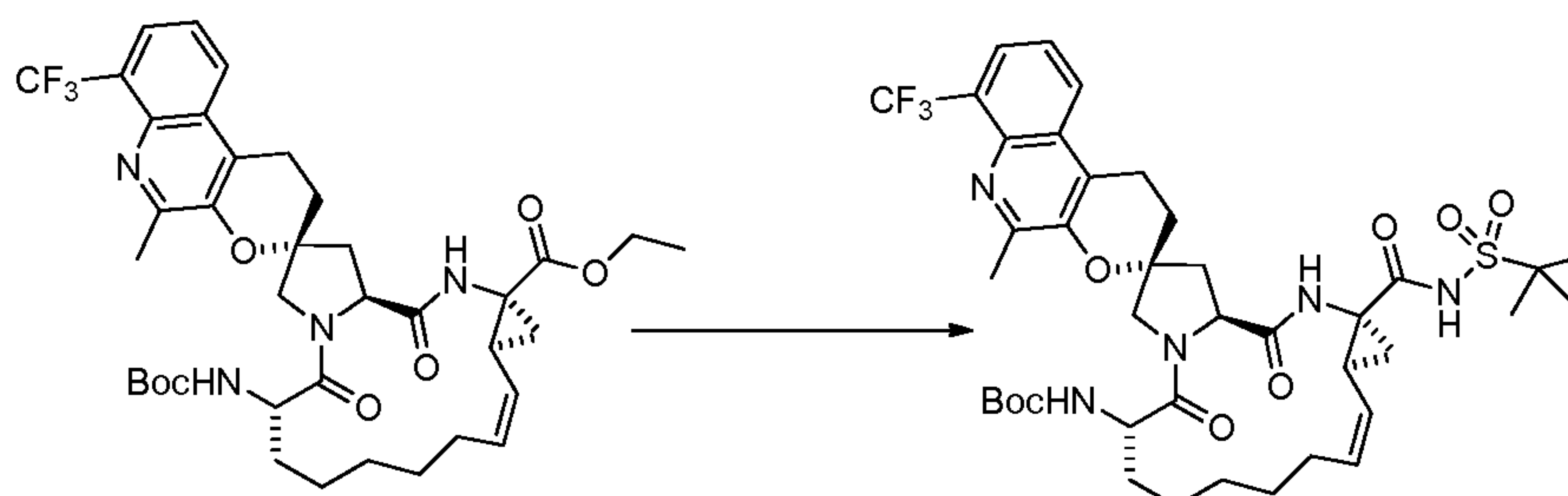
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Step 9



A solution of the product of Step 8 (433 mg, 0.572 mmol) in DCE (170 ml) was degassed, treated with Zhan's catalyst (105 mg, 0.143 mmol), benzoquinone (18.6 mg, 0.172 mmol) and heated at 65°C for 3h. The disappearance of starting material was followed by TLC (60% EtOAc/Hexanes). On complete consumption of starting material, the reaction mixture was cooled to RT and quenched with methylvinyl ether. The reaction mixture was concentrated *in vacuo* and purified by silica gel chromatography to yield the product of Step 9 as a brown colored solid (208 mg, 50%).

Step 10



10

A solution of the product of Step 9 (205 mg, 0.281 mmol) in MeOH (1.6 ml) and THF (2.4 ml) was cooled to 0°C and treated with 2 m aq. solution of LiOH (0.703 ml, 1.406 mmol). The reaction was allowed to warm to RT and stirred overnight. Analysis of TLC with 60%EtOAc/Hexanes indicated all the starting material was consumed. The reaction mixture was acidified with aqueous 0.5N HCl (3.00 mL) and extracted into EtOAc. The combined organic layers were dried, filtered and concentrated *in vacuo* to yield crude acid (201 mg) as a brown solid.

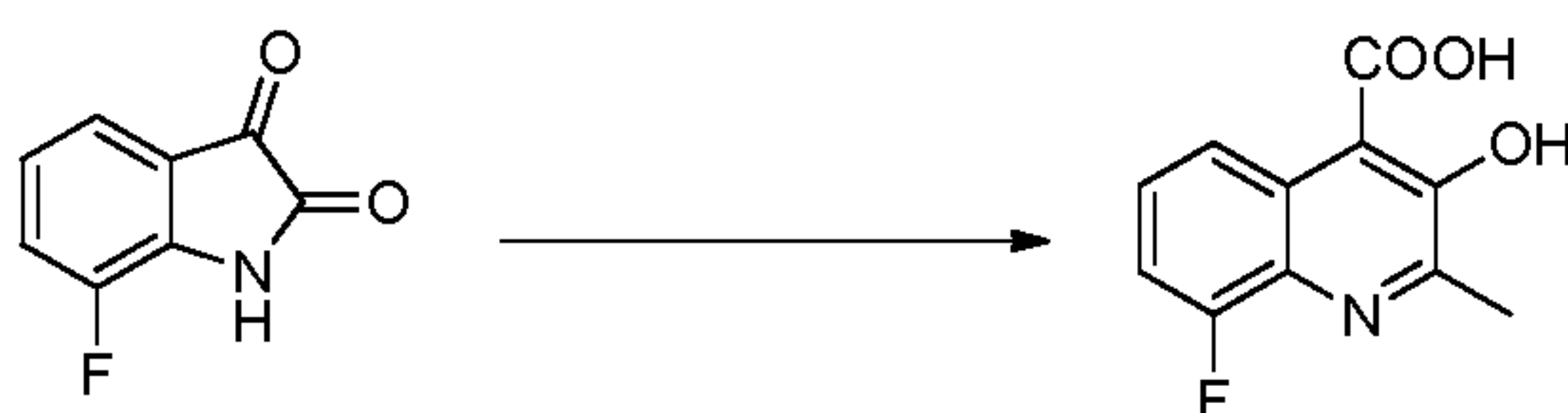
A solution of acid (75 mg, 0.107 mmol) in THF (2 mL) was treated with carbonyl diimidazole (34.7 mg, 0.214 mmol) and heated at 70°C for 2h. The reaction mixture was cooled to RT and treated with 1-methylcyclopropane-1-sulfonamide (57.9 mg, 0.428 mmol) and DBU (0.064 mL, 0.428 mmol) and heated at 50°C for 12h. The reaction mixture was cooled to RT and diluted with EtOAc. The organic layer was separated and washed with 0.5 m HCl, water, brine

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and filtered through anhydrous Na_2SO_4 . The filtered EtOAc layer was concentrated *in vacuo* and purified by silica gel using EtOAc/Hexanes to yield I-44 (60 mg) as a colorless solid.

Example 45: tert-Butyl (1aR,3aS,3'R,9S,16aS,Z)-7'-fluoro-5'-methyl-1a-(1-methylcyclopropylsulfonylcarbamoyl)-3,8-dioxo-1a,1',2,2',3,3a,4,6,8,9,10,11,12,13,14,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-5,3'-pyrano[2,3-c]quinoline]-9-ylcarbamate (I-45)

Step 1



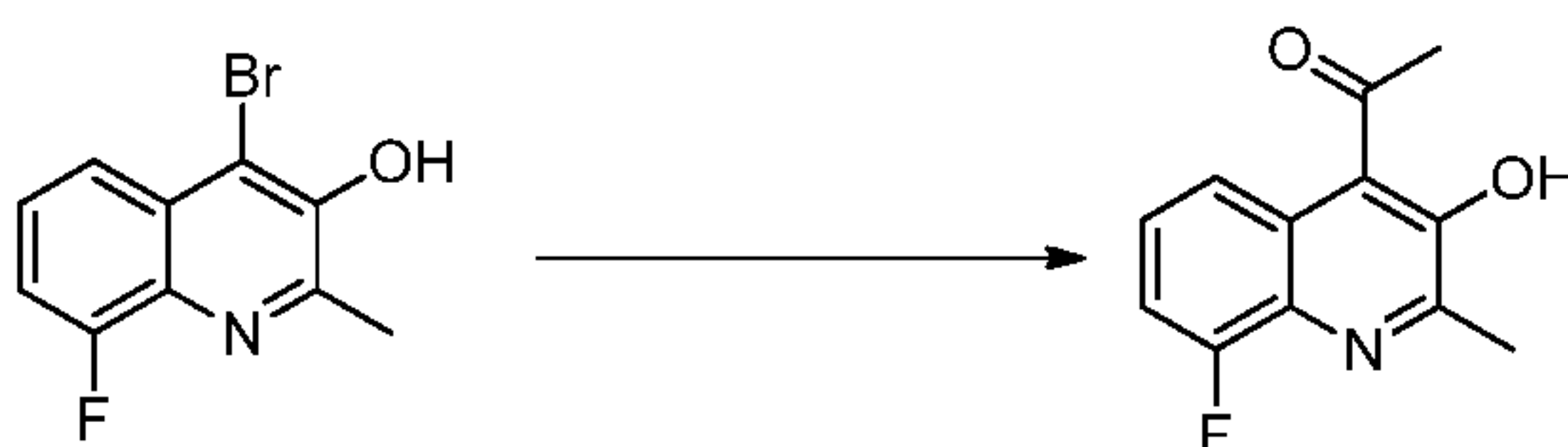
10 A slurry of 7-fluoroisatin in water was treated with $\text{Ca}(\text{OH})_2$ and heated at 80°C for 1h. The reaction was then treated with chloroacetone and further heated at 80°C for 6h. The reaction mixture was cooled to RT and acidified with aq. HCl (250 ml, 1N). The solid separating out was filtered, washed with water and dried under vacuum to yield the product of Step 1.

Step 2



15 A suspension of the product of Step 1 (7.00 g, 31.6 mmol) in THF (100 mL) was treated with NBS (6.76 g, 38.0 mmol) and stirred at RT for 16h. The reaction mixture diluted with EtOAc and washed with water. The combined organic layer were dried (Na_2SO_4), filtered, concentrated *in vacuo* and purified by silica gel chromatography (EtOAc/Hexanes) to yield the product of Step 2 (4.5 g, 56%) as a brownish yellow solid.

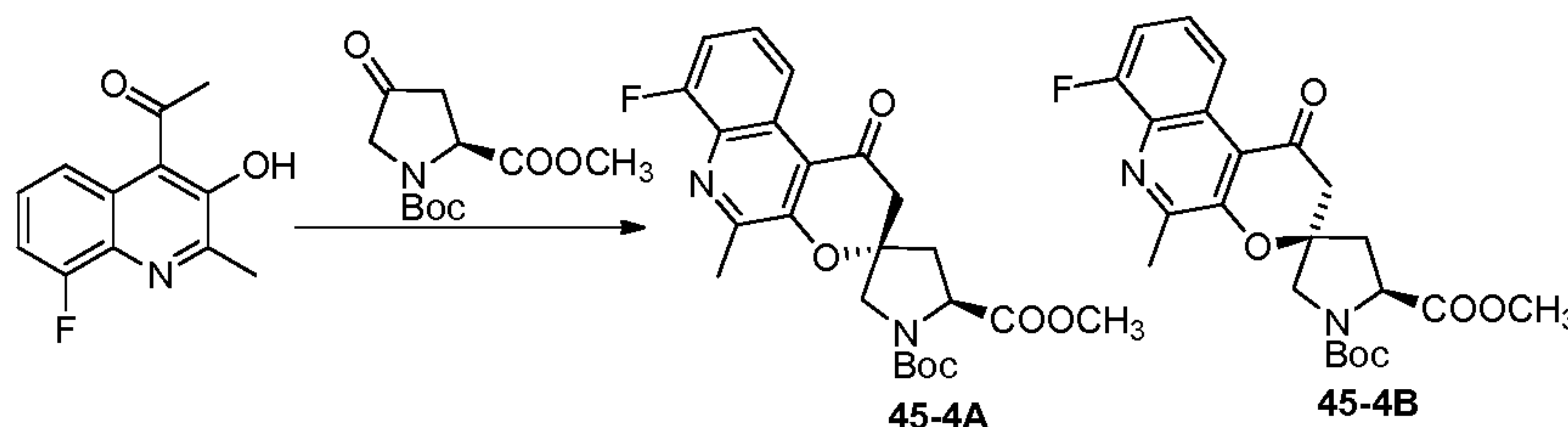
Step 3



25 A solution of the product of Step 2 (2.00 g, 7.81 mmol) in dry dioxane (40.0 mL) was treated with tributyl(1-ethoxyvinyl)stannane (5.28 mL, 15.62 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.548 g, 0.78 mmol) and heated at reflux for 4h. The reaction mixture was cooled to RT and reacted with 1 M aq HCl (40 mL) and stirred at RT for 45 min. The reaction mixture was neutralized with sat.

aq. NaHCO₃ solution and extracted into EtOAc. The combined organic layers were dried (Na₂SO₄), filtered, concentrated *in vacuo* and purified by silica gel chromatography to yield desired the product of Step 3 (755 mg, 44%).

Step 4

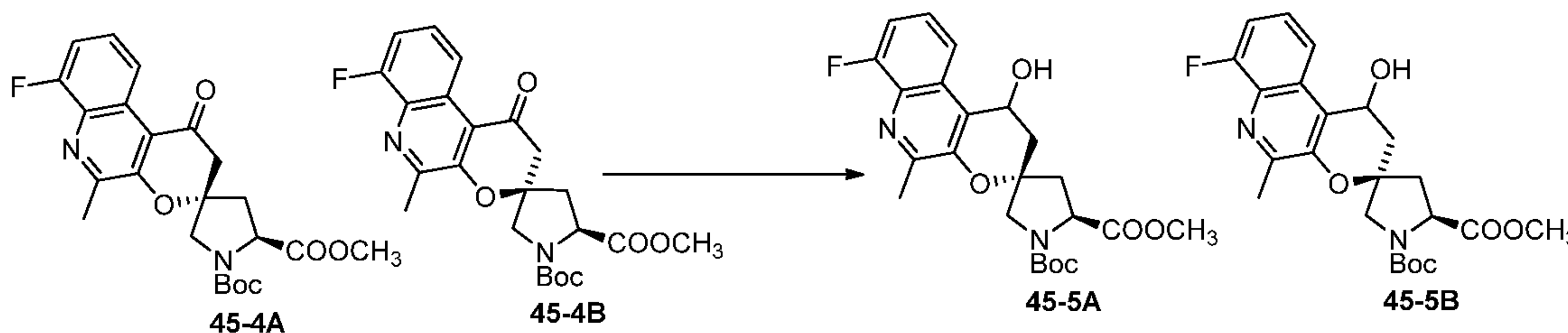


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A solution of the product of Step 3 (750 mg, 3.42 mmol) in MeOH (15 ml) was treated with (S)-1-*tert*-butyl 2-methyl 4-oxopyrrolidine-1,2-dicarboxylate (1.66 g, 6.84 mmol) and pyrrolidine (0.283 ml, 3.42 mmol) in a sealed tube. To this was added molecular sieves (750 mg, 4A powder), and the reaction was heated to 105°C and stirred for 12h in a sealed tube. The reaction was cooled to RT, and analysis of TLC (EtOAc/Hexanes 30%) indicated complete consumption of starting material. The reaction mixture was filtered, concentrated *in vacuo* and purified by silica gel chromatography (Hexanes/ EtOAc) to yield condensed products 45-4A and 45-4B as inseparable mixture (1.08 g, 71%).

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Step 5

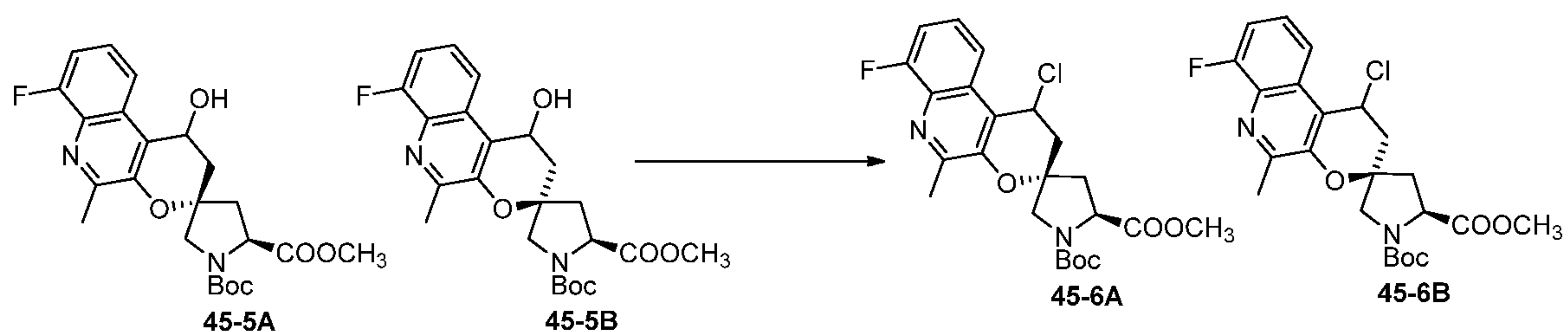


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A solution of ketones 45-4A and 45-4B (1.08 g, 2.42 mmol) in MeOH (20 ml) was cooled to 0°C and treated with NaBH₄ (92 mg, 2.42 mmol) over 1 min and stirred for 30 min at 0°C. Analysis of TLC (EtOAc/Hexanes 1:1) indicated complete consumption of starting material. The reaction mixture was quenched with sat. aq. NaHCO₃, concentrated *in vacuo*, and residue was taken in EtOAc. The organic layer was washed with water and brine. The combined organic layers were dried, filtered, concentrated *in vacuo* and purified by silica gel chromatography to yield reduced alcohols 45-5A and 45-5B (878 mg, 81%).

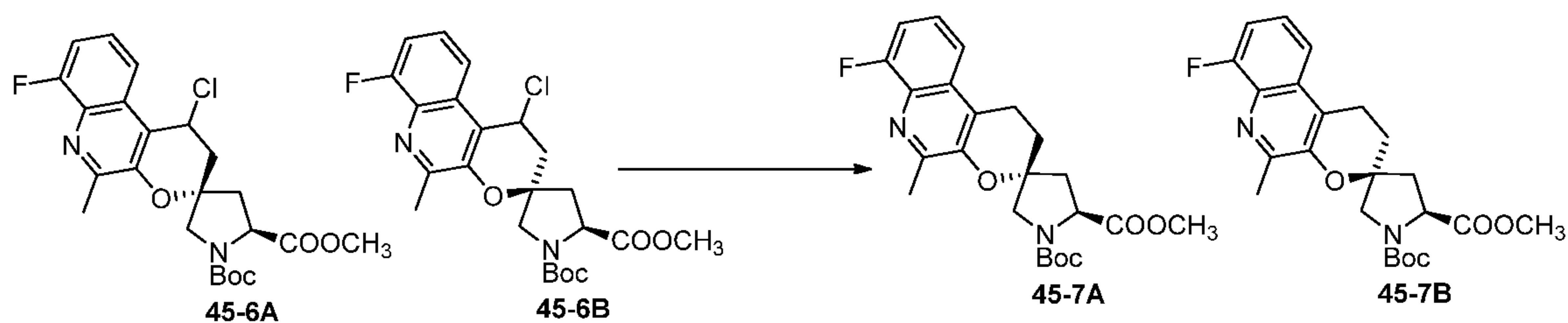
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Step 6



A solution of 45-5A and 45-5B (875 mg, 1.96 mmol) in DCM (17 ml) was treated with Et₃N (0.82 ml, 5.88 mmol) then MsCl (0.305 ml, 3.92 mmol) and stirred at RT for 5h. Analysis of reaction mixture using TLC (EtOAc/Hexanes, 50%) indicated complete consumption of starting material. The reaction mixture was diluted with EtOAc and washed with sat. aq. NaHCO₃ solution, water, brine and filtered through anhydrous Na₂SO₄. The filtrate was concentrated *in vacuo* and residue was purified by silica gel chromatography to yield 45-6A and 45-6B (752 mg, 83%) as a pale yellow solid.

Step 7

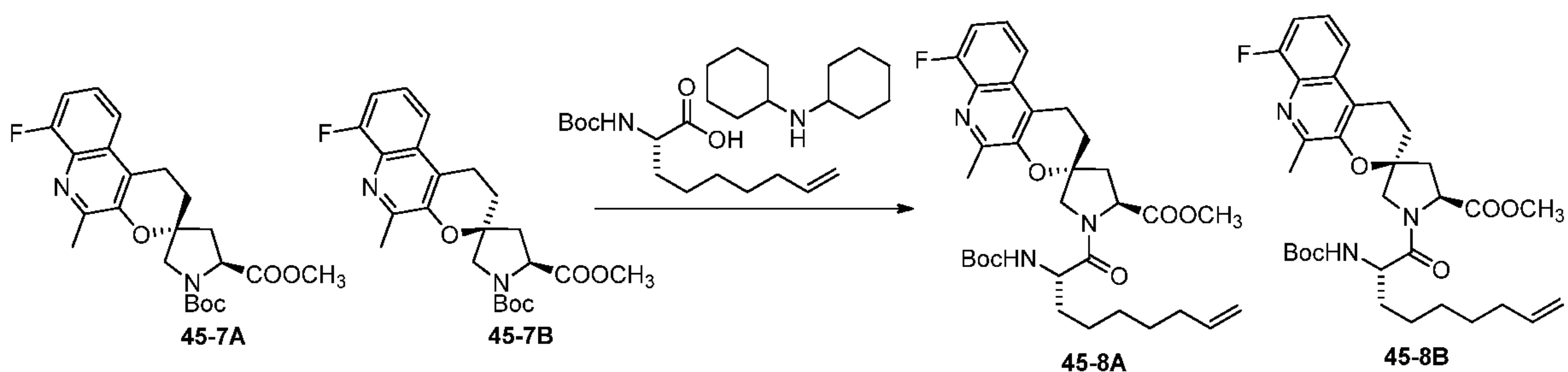


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A solution of chlorides 45-6A and 45-6B (749 mg, 1.61 mmol) in EtOAc (15 mL) was treated with Pd/C (10% 86 mg) and hydrogenated with balloon pressure RT for 4h. On completion of the reaction as indicated by TLC (EtOAc/Hexanes 50%), the reaction mixture was diluted with MeOH, filtered, and the filtrate was concentrated *in vacuo* to yield 45-7A and 45-7B (709 mg) as a yellow orange solid.

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Step 8



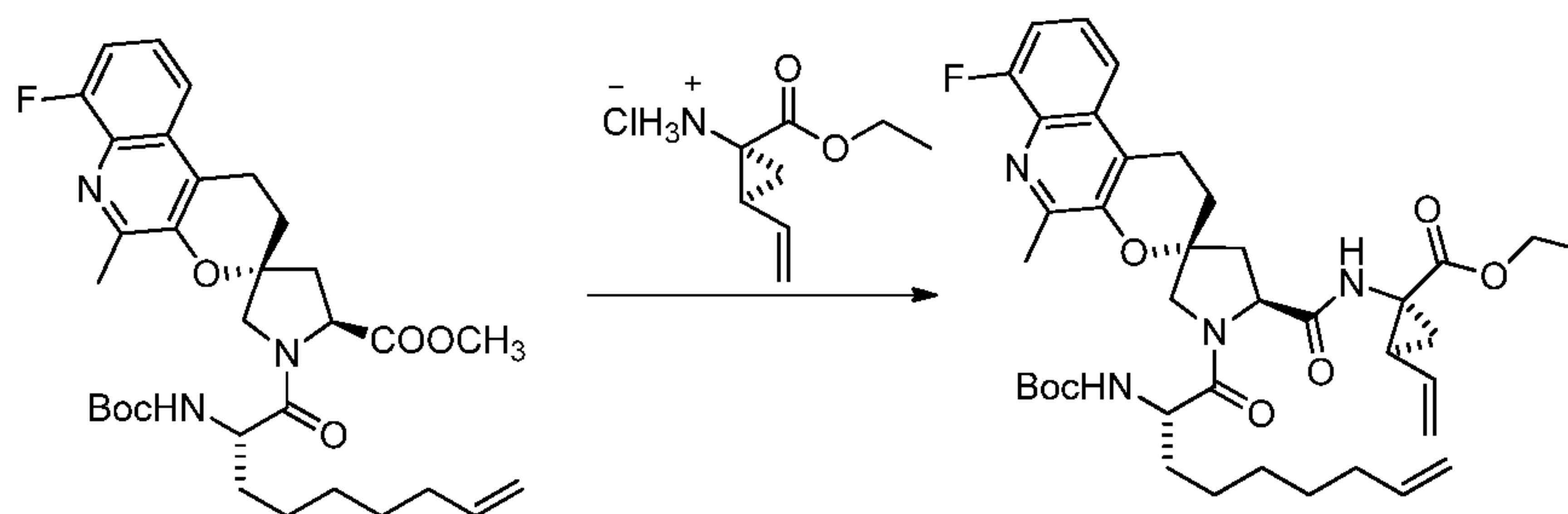
A solution of compounds 45-7A and 45-7B (943 mg, 2.19 mmol) in DCM (3.38 ml) was cooled to 0°C and treated with trifluoroacetic acid (3.38 ml, 43.8 mmol) and allowed to warm to RT. The reaction was stirred for 1h, when TLC (EtOAc/Hexanes 50%) indicated

20

complete consumption of starting material. The reaction mixture was concentrated *in vacuo*. The mixture was taken in EtOAc and washed with sat. NaHCO₃ solution, then 50% water/sat. NaHCO₃, brine and dried over Na₂SO₄. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to yield deprotected anime (694 mg) that was used in next reaction without
5 further purification.

A solution of amine (691 mg, 2.10 mmol) in DCM (7 ml) and DMF (7 ml) was treated with Hunig's base (1.1 ml, 6.28 mmol), dicyclohexylammonium (S)-2-(*tert*-butoxycarbonylamino)non-8-enoate (1.14 g, 2.51 mmol) and HATU (954 mg, 2.51 mmol) and stirred at RT for 20h. The reaction mixture was diluted with EtOAc (300 mL) and washed with
10 water and aq. NaHCO₃. The combined organic layers were dried (Na₂SO₄), filtered, concentrated *in vacuo*, and purified by silica gel chromatography to separate the two diastereomers 45-8A and 45-8B yielding desired diastereomer 45-8A as a colorless foam (505 mg, 41%).

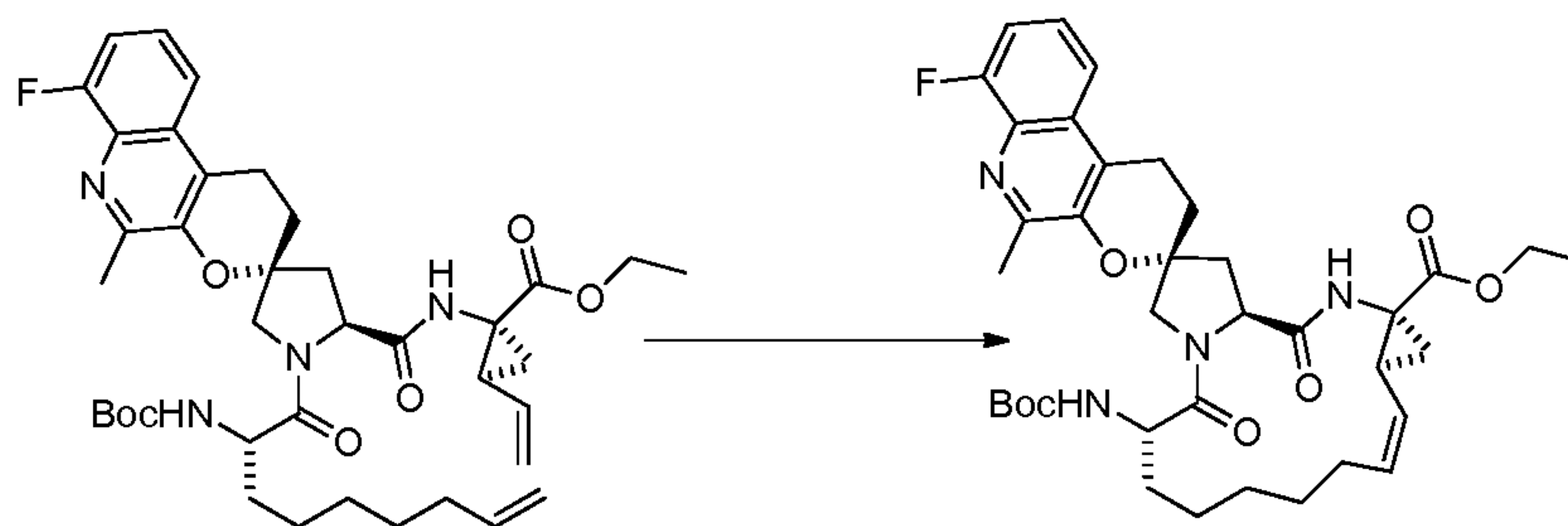
Step 9



A solution of 45-8A (503 mg, 0.862 mmol) in MeOH (3.5 ml) and THF (5.25 ml) was treated with 2 M aq. solution of LiOH (1.30 ml, 2.59 mmol) and heated at 60-65°C for 1h. The reaction mixture was acidified with 1N HCl (3.0 mL) and extracted with EtOAc. The combined extracts were washed with brine and filtered through Na₂SO₄. The filtrate was
20 concentrated *in vacuo* to yield carboxylic acid as white foam (491 mg).

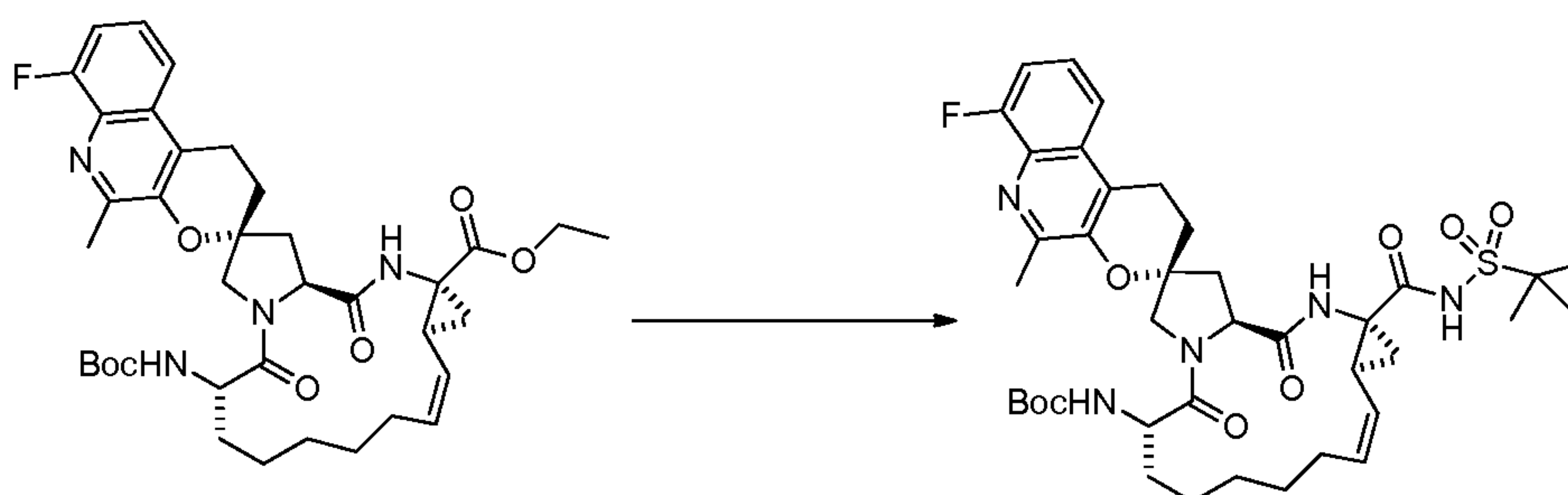
A solution of acid (484 mg, 0.850 mmol) in DMF (4 ml) and DCM (4 ml) was treated with Hunig's base (0.666 ml, 3.82 mmol), HATU (420 mg, 1.11 mmol), (1R, 2S)-1-(ethoxycarbonyl)-2-vinylcyclopropanaminium chloride (326 mg, 1.70 mmol) and stirred at RT for 15h. The reaction mixture was concentrated *in vacuo* and diluted with EtOAc. The
25 combined organic layers were washed with water, 0.5N aq. HCl, brine and filtered through anhydrous Na₂SO₄. The filtrate was concentrated *in vacuo* and purified by silica gel chromatography to yield the product of Step 9 as colorless solid (580 mg).

Step 10



A solution of the product of Step 9 (577 mg, 0.816 mmol) in DCE (180 ml) was degassed, treated with Zhan's catalyst (150 mg, 0.204 mmol), benzoquinone (26.5 mg, 0.245 mmol) and heated at 65°C for 1h. The disappearance of starting material was followed by TLC (60% EtOAc/Hexanes). On complete consumption of starting material, the reaction mixture was cooled to RT and quenched with methylvinyl ether (2.0 mL). The reaction mixture was concentrated *in vacuo* and purified by silica gel chromatography to yield the product of Step 10 as a brown colored solid (263 mg, 48%).

Step 11



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A solution of the product of Step 10 (262 mg, 0.386 mmol) in MeOH (2.0 ml) and THF (3.0 ml) was cooled to 0°C and treated with 2 m aq. solution of LiOH (0.965 ml, 1.93 mmol). The reaction was allowed to warm to RT and stirred for 22h. Analysis of TLC with 60% EtOAc/Hexanes indicated all the starting material was consumed. The reaction mixture was acidified with aqueous 0.5N HCl (3.00 mL) and extracted into EtOAc. The combined organic layers were dried, filtered and concentrated *in vacuo* to yield crude acid (229 mg) as grayish brown solid.

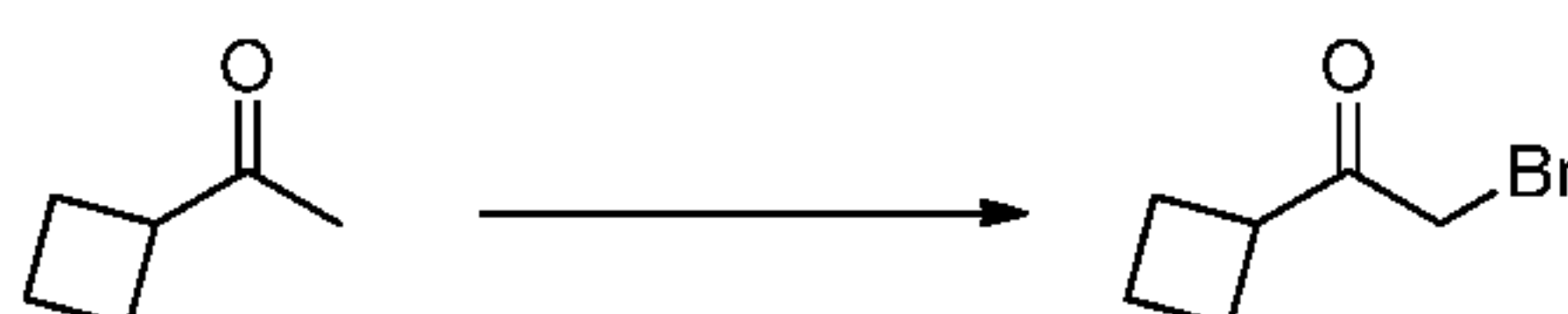
A solution of acid (100 mg, 0.154 mmol) in THF (2 mL) was treated with carbonyl diimidazole (49.8 mg, 0.307 mmol) and heated at 70°C for 2h. The reaction mixture was cooled to RT and treated with 1-methylcyclopropane-1-sulfonamide (83 mg, 0.615 mmol) and DBU (92µl, 0.615 mmol) and heated at 50°C for 12h. The reaction mixture was cooled to RT and diluted with EtOAc. The organic layer was separated and washed with 0.5 m HCl, water,

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brine and filtered through anhydrous Na_2SO_4 . The filtered EtOAc layer was concentrated *in vacuo* and purified by silica gel using EtOAc/Hexanes to yield I-45 (134 mg).

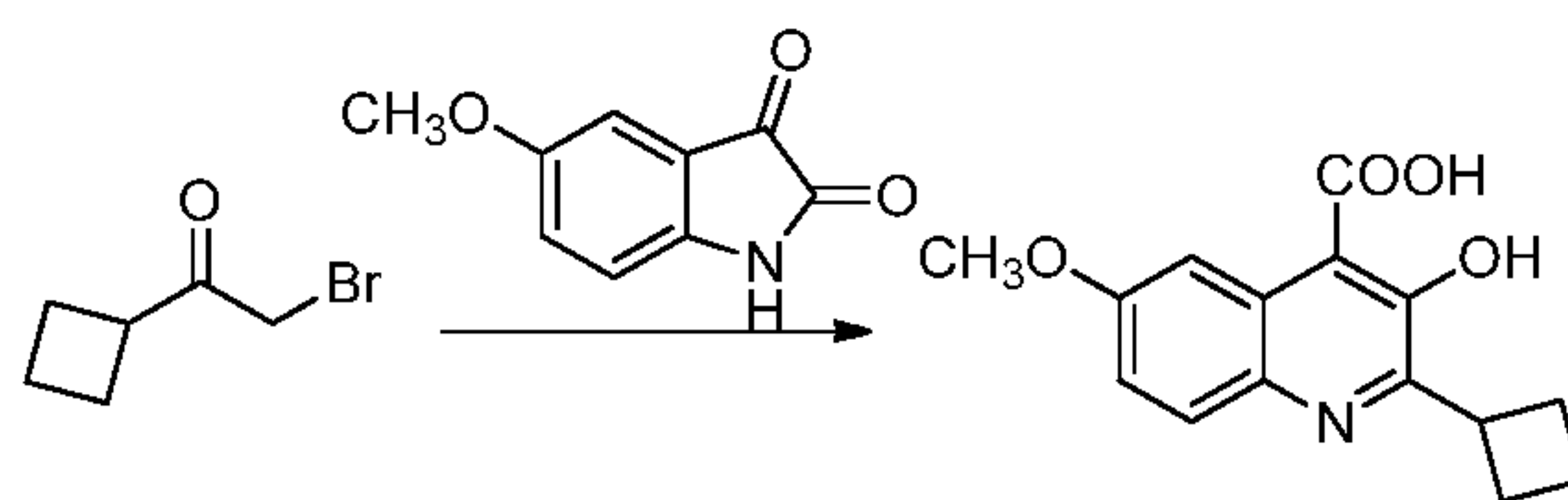
Example 46: *tert*-Butyl (1aR,3aS,3'R,9S,16aS,Z)-5'-cyclobutyl-9'-methoxy-1a-(1-methylcyclopropylsulfonylcarbamoyl)-3,8-dioxo-1a,1',2,2',3,3a,4,6,8,9,10,11,12,13,14,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-5,3'-pyrano[2,3-c]quinoline]-9-ylcarbamate (I-46)

Step 1



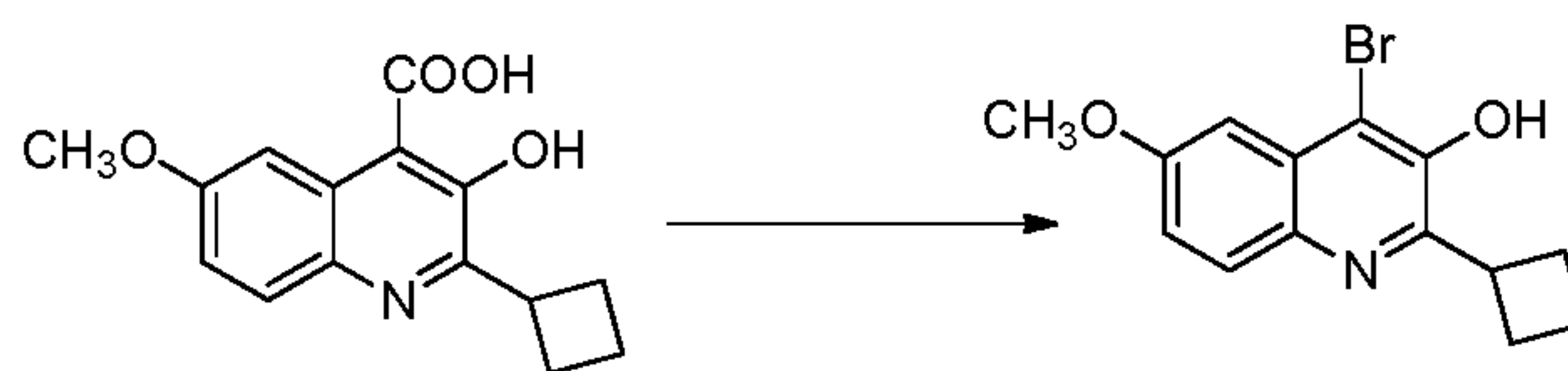
A solution of 1-cyclobutylethanone (5.0 g, 50.1 mmol) in MeOH (50 mL) was treated with bromine (10.0 g, 62.6 mmol) at 0°C and stirred 1h at RT. The reaction mixture was extracted in ether (150 mL) washed with aq. $\text{Na}_2\text{S}_2\text{O}_3$. The combined organic layer were dried (MgSO_4), filtered, concentrated *in vacuo* and distilled under reduced pressure to yield the product of Step 1 as colorless oil (5.6 g, 51%) that turns brown on standing.

Step 2



A solution of 5-methoxy-1H-indole-2,3-dione (2.5 g, 14.11 mmol) in water (20.0 mL) was treated with $\text{Ca}(\text{OH})_2$ (3.14 g, 42.3 mmol) and heated at 80°C for 1h. The reaction mixture was treated with the product of Step 1 (5.00 g, 28.2 mmol) and heated at reflux for additional 8h. The reaction mixture was cooled and treated with aq. HCl to precipitate the desired product of Step 2 (3.86 g, 99%), which was filtered and used without further purification.

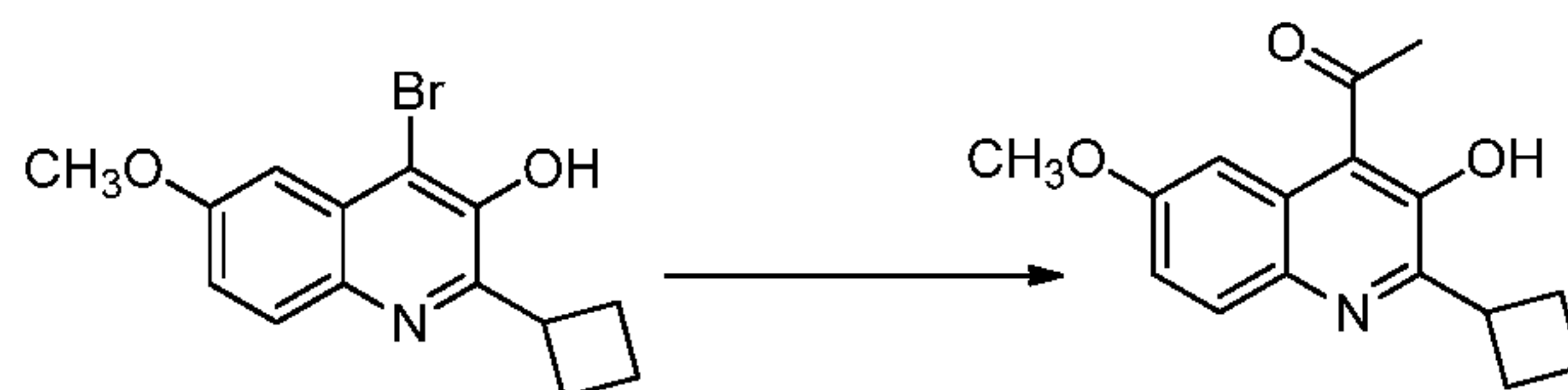
Step 3



A suspension of the product of Step 2 (3.8 g, 13.9 mmol) in THF (40 mL) and dioxane (50 mL) was treated with NBS (3.13 g, 13.90 mmol) and stirred at RT for 1h. The reaction mixture was diluted with EtOAc (300 mL) and washed with water. The combined

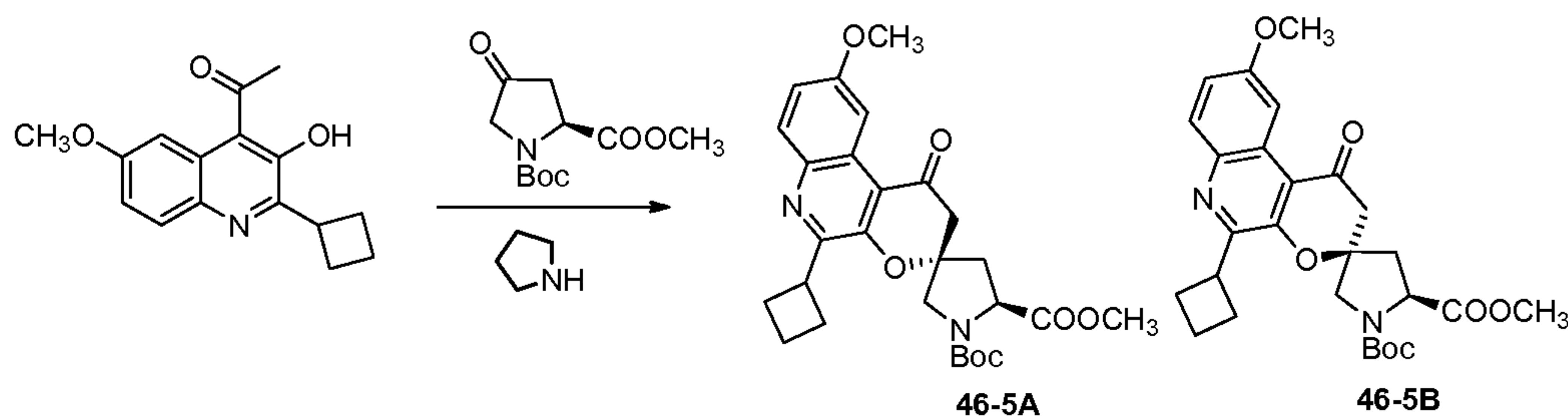
organic layer were dried (MgSO₄), filtered, concentrated *in vacuo* and purified by silica gel chromatography (EtOAc/Hexanes) to yield the product of Step 3 (1.7 g, 40%).

Step 4



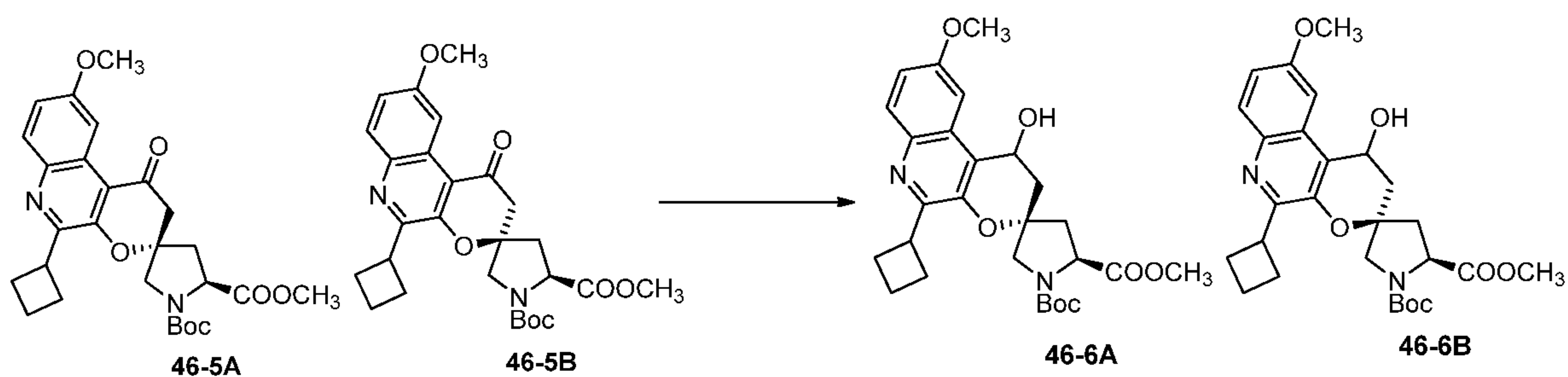
5 A solution of the product of Step 3 (1.6 g, 5.19 mmol) in dry dioxane (30.0 mL) was treated with tributyl(1-ethoxyvinyl)stannane (4.51 g, 12.98 mmol), Pd(PPh₃)₂Cl₂ (0.342 g, 0.779 mmol) and heated at reflux for 4h. The reaction mixture was cooled to RT and reacted with aq. HCl (30 mL) and stirred at RT for 45 min. The reaction mixture was neutralized with sat. aq. NaHCO₃ and extracted into EtOAc. The combined organic layers were dried (MgSO₄),
10 filtered, concentrated *in vacuo* and purified by silica gel chromatography to yield desired product of Step 4 (800 mg, 57%).

Step 5



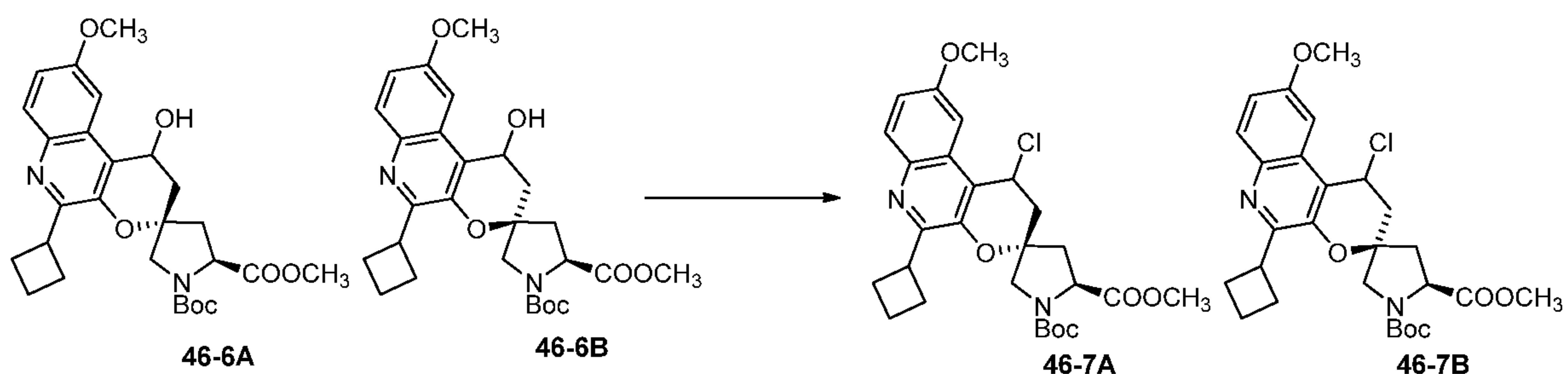
15 A solution of the product of Step 4 (800 mg, 2.95 mmol) and Boc-4-oxo-proline methyl ester (1.44 g, 5.90 mmol) in MeOH (10 mL) was treated with powdered 4A molecular sieves (2.0 g) and pyrrolidine (120 μl, 1.17 mmol) and heated in a microwave at 105°C for 30 min. The reaction mixture was cooled to RT. The reaction mixture was filtered, concentrated *in vacuo* and purified by silica gel chromatography using EtOAc/Hexanes to yield cyclized products 46-5A and 46-5B as inseparable mixture of diastereomers (total yield, 674 mg).

20 Step 6



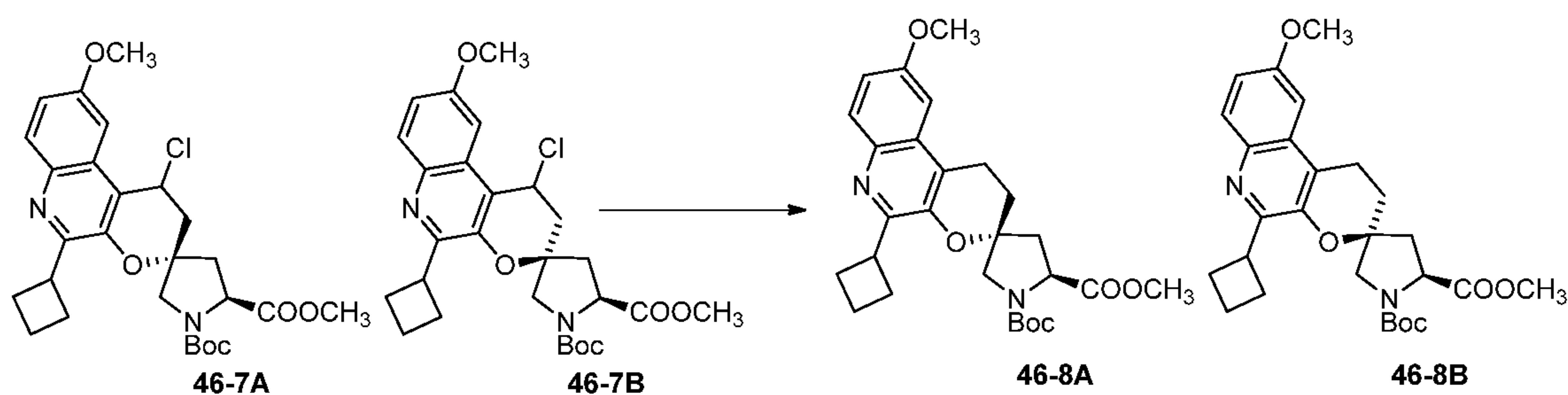
A solution of 46-5A and 46-5B (674 mg, 1.36 mmol) were dissolved in MeOH (10 mL) and cooled to 0°C. To this mixture was added NaBH₄ (51.4 mg, 1.36 mmol) and stirred at 0°C for 20 min. The reaction mixture was diluted with aq. NaHCO₃ and was extracted into EtOAc (250 mL). The combined organic layer were dried (MgSO₄), filtered, concentrated *in vacuo* and purified by silica gel chromatography using EtOAc/Hexanes to yield reduced products 46-6A and 46-6B as mixture (556 mg, 82%).

Step 7



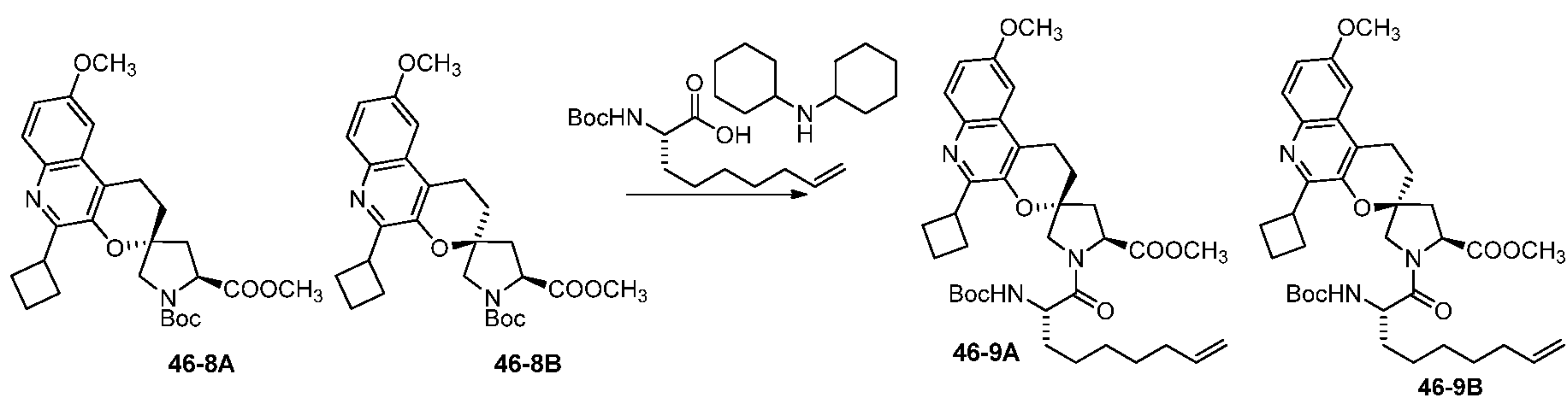
A solution of 46-6A and 46-6B (556 mg, 1.12 mmol) in DCM (10 mL) was cooled to 0°C and treated with Et₃N (0.403 mL, 282 mg) and MsCl (0.267 mL, 255 mg) and stirred overnight when the ice bath slowly warmed-up to RT. The ice bath was removed, and the reaction mixture was allowed to stir at RT. The reaction mixture was quenched with aq. NaHCO₃, and extracted into EtOAc. The combined organic layer was dried, (MgSO₄), filtered, and concentrated *in vacuo*. The residue containing 46-7A and 46-7B was used as is (crude yield 610 mg).

Step 8



A solution of 46-7A and 46-7B (crude 610 mg) were taken in EtOAc (25 mL) and treated with Pd/C (10%, 126 mg) and hydrogenated for 0.5h at 1atm. On completion of the reaction as indicated by TLC, the reaction mixture was filtered through a plug of CELITE. The solid cake was washed with DCM and concentrated *in vacuo*. The crude mixture was purified by silica gel chromatography (DCM, MeOH) to yield reduced products 46-8A and 46-8B (580 mg).

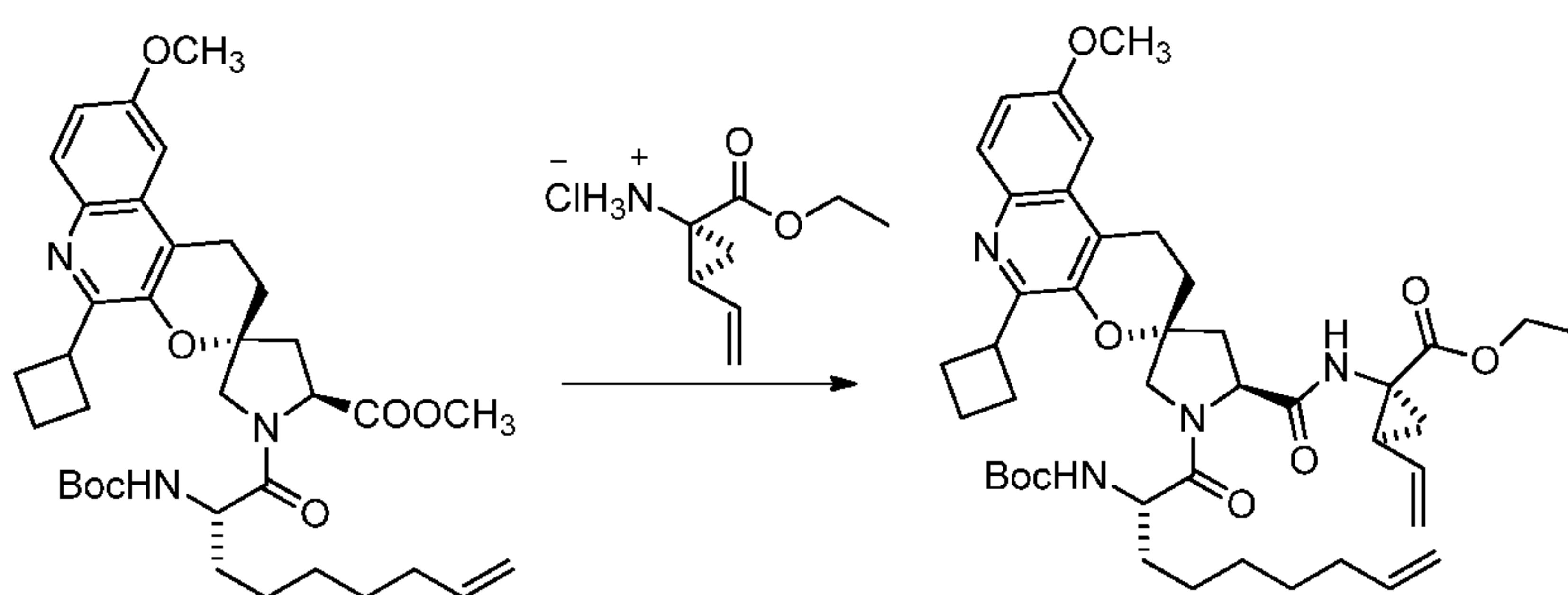
Step 9



A solution of Boc-protected compounds 46-8A and 46-8B (600 g, 1.24 mmol) in 4 m HCl in dioxane (15 mL) was stirred at RT for 1h. The reaction mixture was concentrated *in vacuo*. The residue obtained was used without further purification.

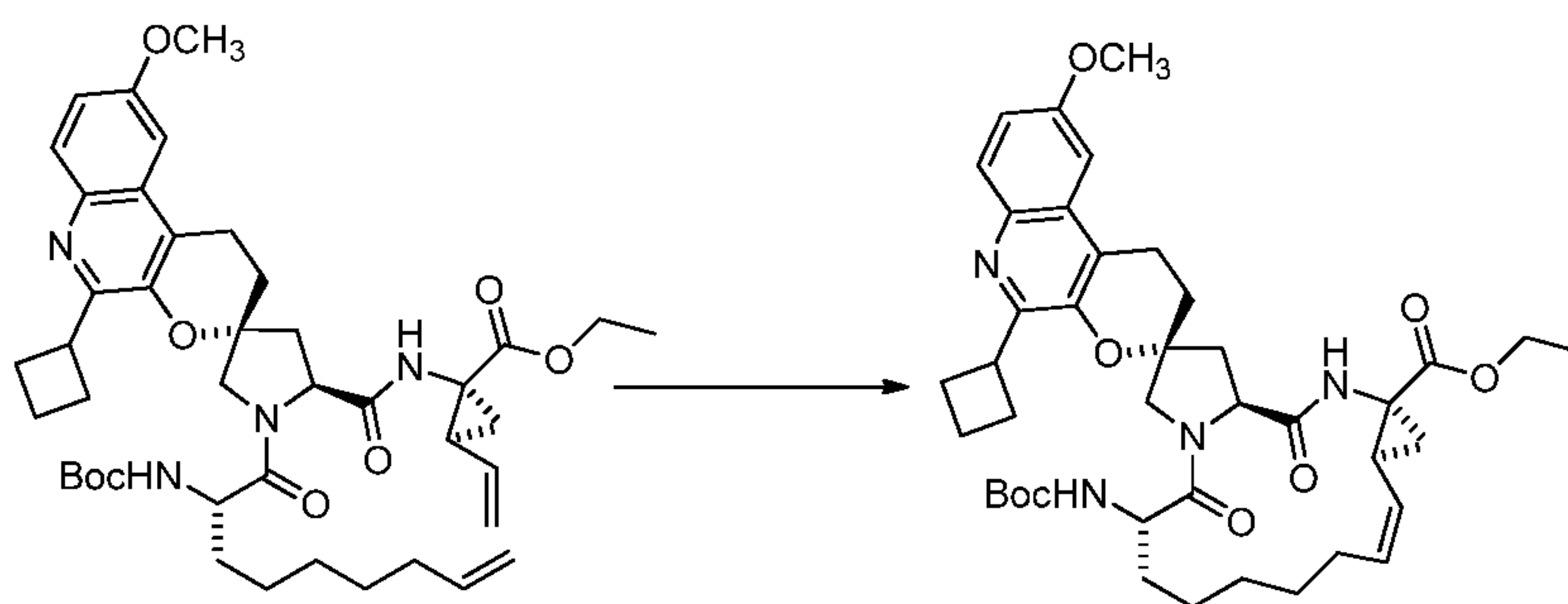
5 A solution of acid (773 mg, 1.71 mmol), amine salt (550 mg, 1.31 mmol), HATU (749 mg, 1.97 mmol) in DMF and DCM (5 mL each) was treated with Hunig's base (679 mg, 5.25 mmol) and stirred at RT for 12h. The reaction mixture was diluted with EtOAc (250 mL) and washed with water and aq. NaHCO₃. The combined organic layers were dried (MgSO₄), filtered, concentrated *in vacuo*, and purified by silica gel chromatography to separate two
10 diastereomers 46-9A (400 mg) and 46-9B (201 mg) as colorless foam.

Step 10

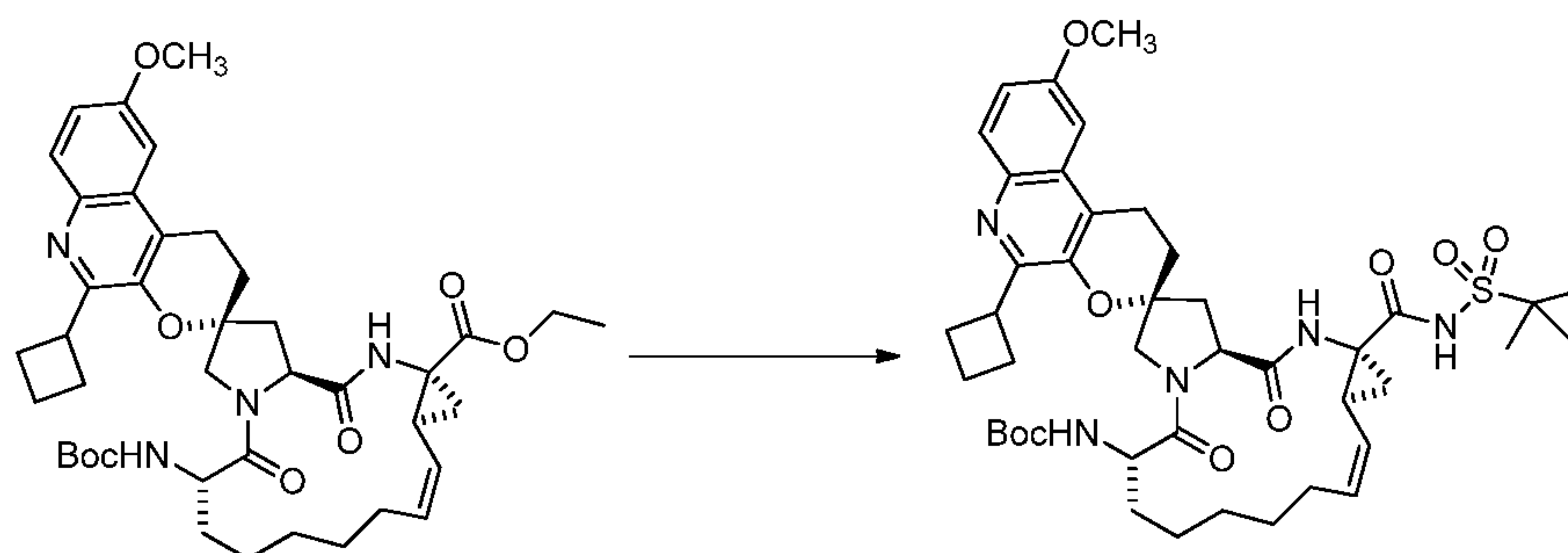


A solution of 46-9A (400 mg, 0.629 mmol) in MeOH, water, and THF (5.0 mL each) was treated with LiOH and stirred at 70°C for 1h. The reaction mixture was acidified with
15 aq. HCl (1 m) and extracted into EtOAc (250 mL). The organic layers were dried (MgSO₄), filtered concentrated *in vacuo* and used as is.

A solution of acid (300 g, 0.482 mmol) in DMF and DCM (5.00 mL each) was treated with amine salt (139 mg, 0.724 mmol), HATU (275 mg, 0.724 mmol) and Hunigs base (249 mg, 1.93 mmol) and stirred at RT for 12h. The reaction mixture was diluted with aq.
20 NaHCO₃ and extracted into EtOAc. The combined organic layers were dried (MgSO₄), filtered concentrated *in vacuo* and purified by chromatography (SiO₂, EtOAc/Hexanes) to yield coupled product of Step 10 as a colorless foam (340 mg, 93%).

Step 11

A solution of the product of Step 10 (340 mg, 0.45 mmol) in DCE (100 mL) was degassed and treated with Zhan's catalyst (82 mg, 0.112 mmol) and benzoquinone (14.5 mg, 0.134 mmol) and heated at 70°C for 2.2h. The disappearance of starting material was followed by TLC. On complete consumption of starting material as indicated by TLC, the reaction mixture was quenched with methylvinyl ether (1.00 mL), concentrated *in vacuo* and purified by silica gel chromatography (Hexanes, EtOAc) to yield the product of Step 11 cyclized product. (233 mg, 72%).

10 Step 12

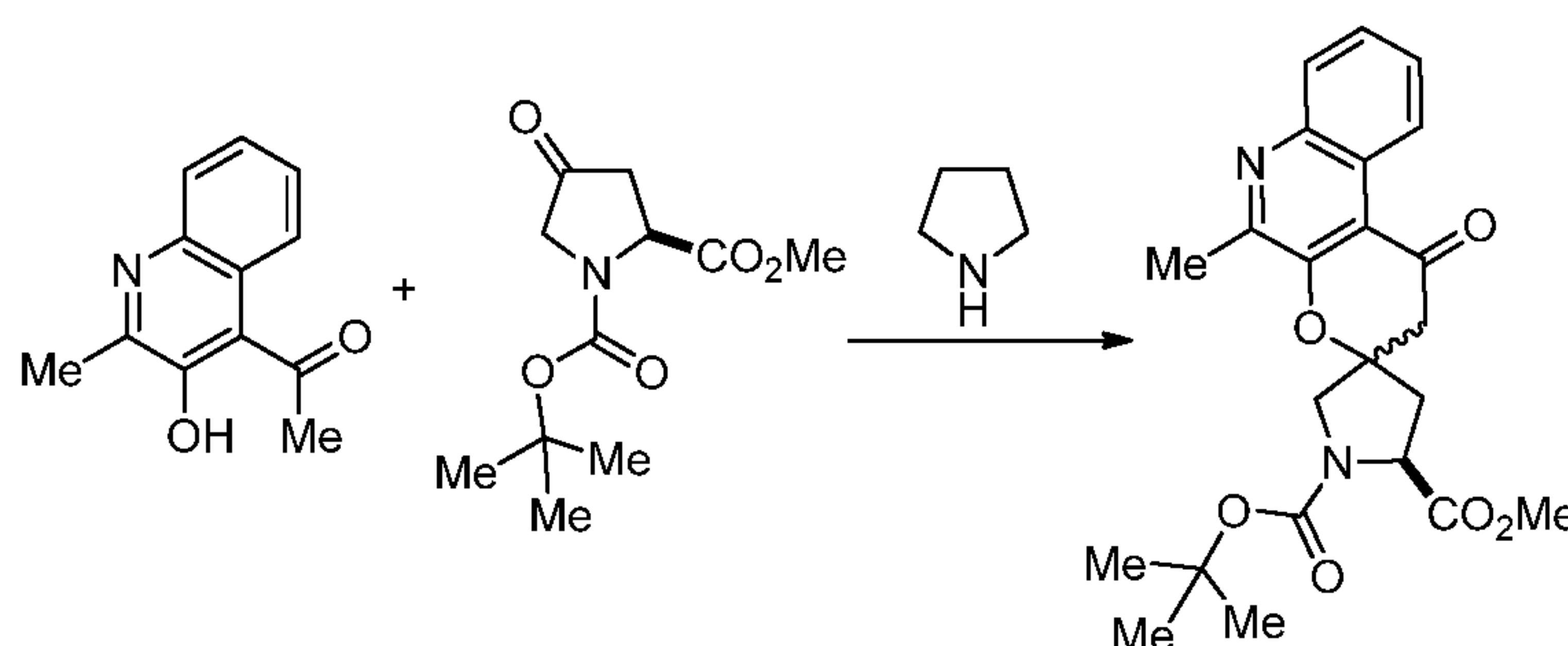
A solution of the product of Step 11 (230 mg, 0.315 mmol) in MeOH (3.0 ml), THF (3.0 ml) and water (3.00 mL) was treated with LiOH (38 mg, 1.57 mmol). The reaction mixture was stirred at RT overnight. Analysis of TLC (EtOAc/Hexanes, 60%) indicated all the starting material was consumed. The reaction mixture was acidified with 1 M HCl (2.00 mL) and extracted into EtOAc. The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to yield crude acid (313 mg).

A solution of acid (220 mg, 0.313 mmol) in THF (4 mL) was treated with carbonyl diimidazole (102 mg, 0.626 mmol) and heated at 70°C for 2h. The reaction mixture was cooled to RT and treated with 1-methylcyclopropane-1-sulfonamide (169 mg, 1.25 mmol) and DBU (191 mg, 1.25 mmol) and heated at 70°C for 12h. The reaction mixture was cooled to RT and diluted with EtOAc and treated with 1 mL of AcOH. The organic layer was separated

and washed with water, brine, dried (MgSO₄) and filtered. The filtered EtOAc layer was concentrated *in vacuo* and purified by silica gel using EtOAc/Hexanes to yield I-46 (213 mg, 68%).

5 **Example 47: *tert*-Butyl ((2R,6S,13aS,14aR,16aS,Z)-5'-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-47)**

Step 1

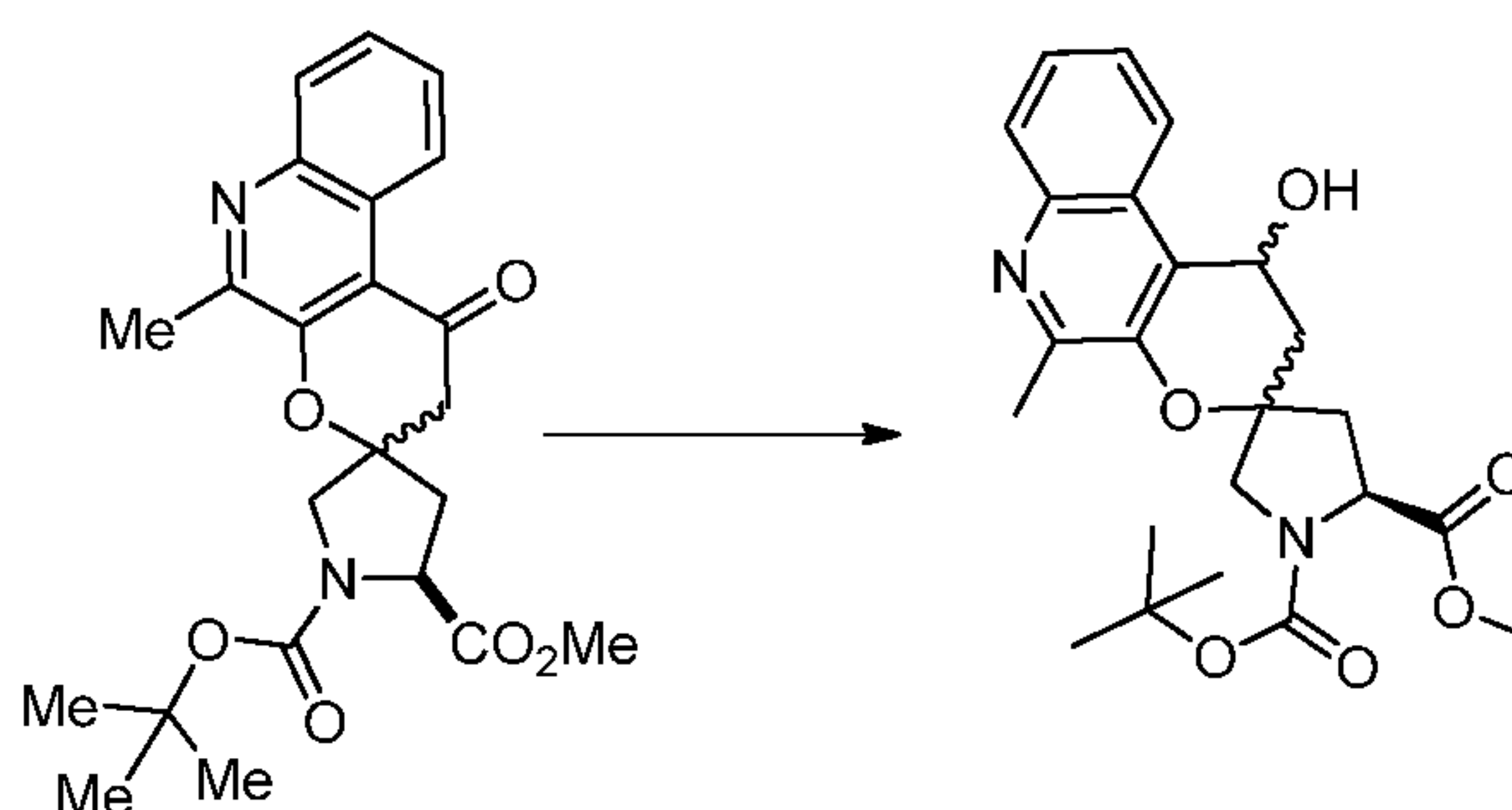


10

Boc- γ -keto-L-proline methyl ester (9.67 g, 39.8 mmol), 2-methyl-3-hydroxy-4-acylquinoline (5 g, 24.85 mmol) and pyrrolidine (0.822 ml, 9.94 mmol) were combined in MeOH (62.1 ml) in a sealed tube. To this was added dry molecular sieves, and the mixture was heated at 105°C for 60 min. The mixture was filtered and concentrated. The residue was purified by

15 column chromatography on silica gel eluting with EtOAc/isohexane (0-80%) to give a mixture of the product of Step 1 (10.22 g, 23.96 mmol, 96% yield) as a yellow solid.

Step 2

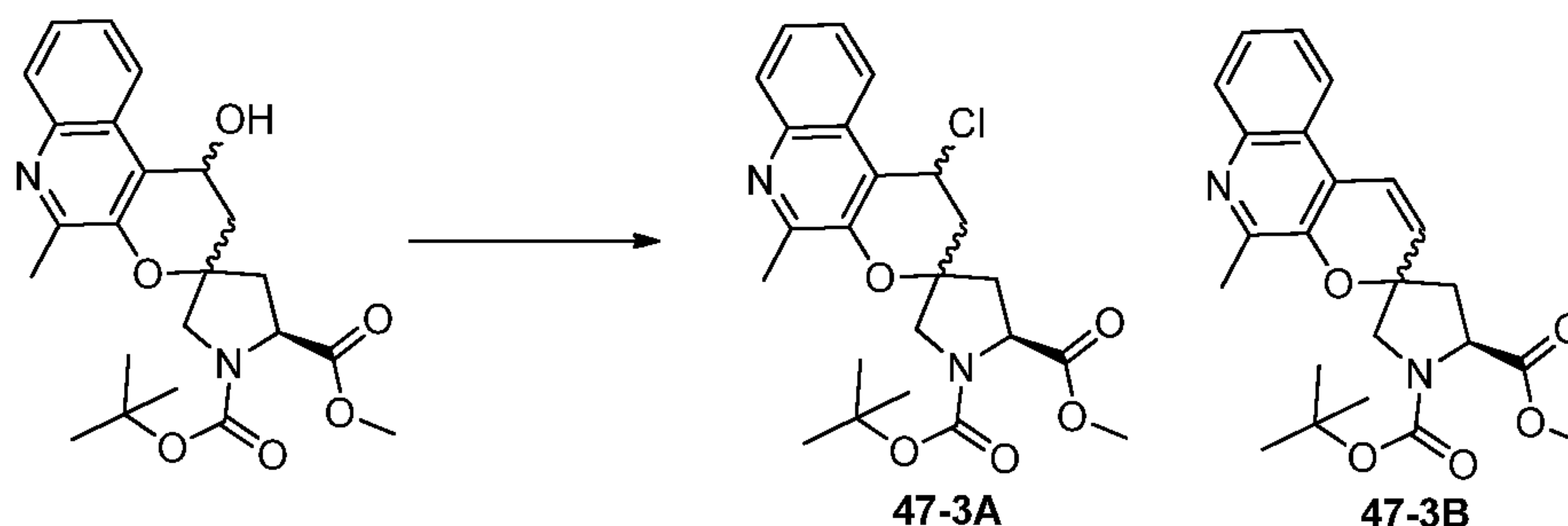


The product of Step 1 (10.22 g, 23.96 mmol) was dissolved in THF (59.9 ml) and

20 MeOH (59.9 ml). The mixture was cooled to 0°C. NaBH₄ (0.92 g, 24.32 mmol) was added portionwise, and the mixture was stirred for 15 min at 0°C. The reaction was then stirred at RT for 1h. The mixture was quenched and stirred with aq. NH₄Cl (100 ml) and EtOAc (200 ml) at

0°C for 30 min. The aq. layer was separated and extracted with EtOAc (100 ml). The combined organic fractions were washed with brine (50 ml), dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with EtOAc/DCM (0-80%) to give the product of Step 2 (13.07 g, 27.8 mmol, 116% yield) as an off-white solid.

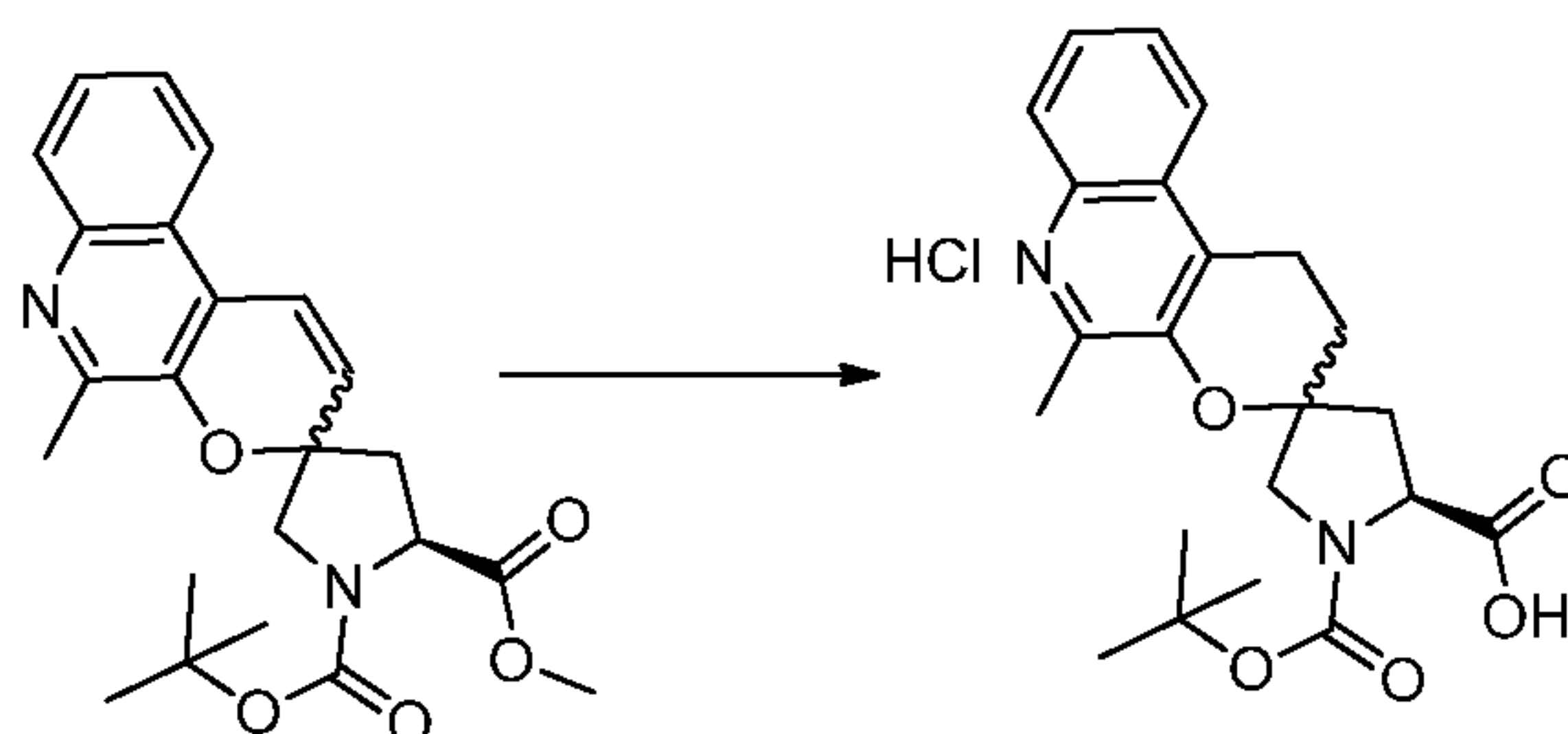
Step 3



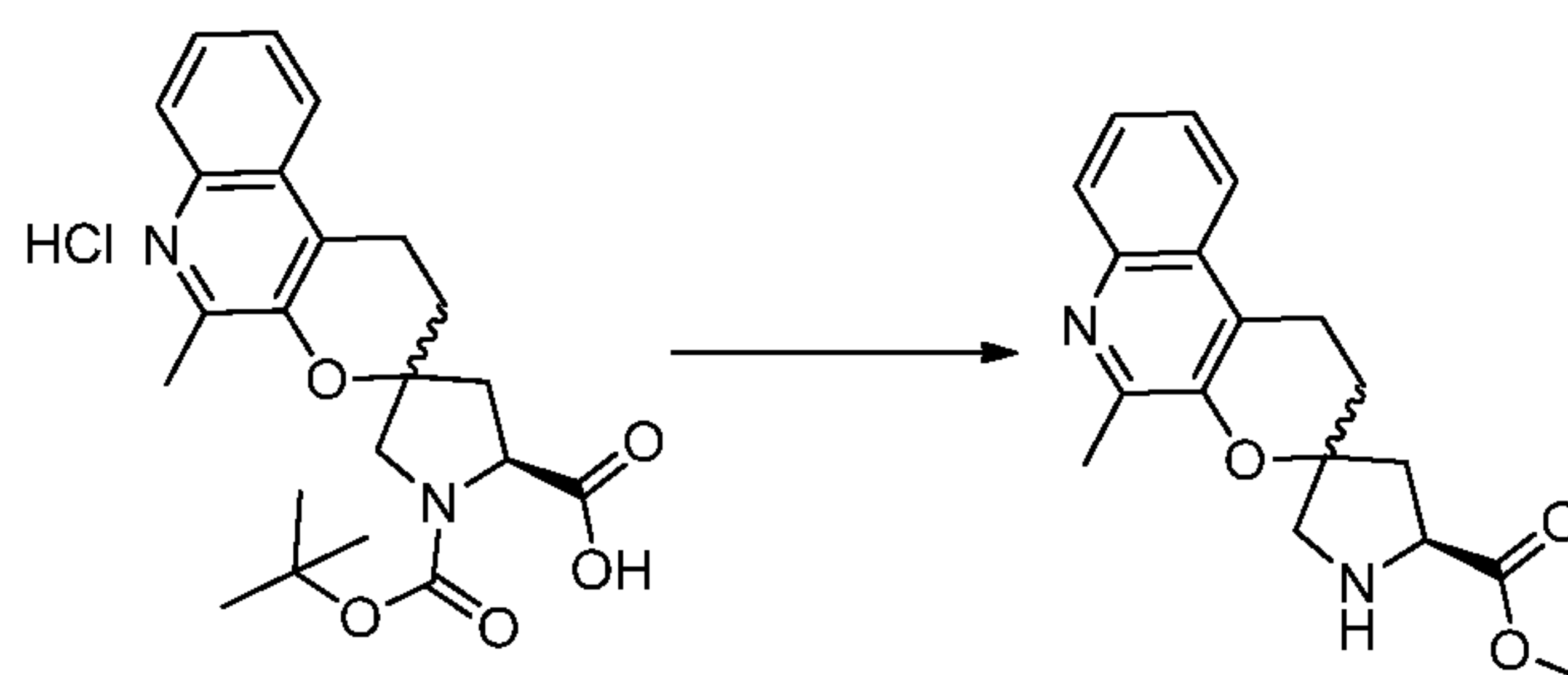
MsCl (3.54 ml, 45.8 mmol) was added to a mixture of the product of Step 2 (13.07 g, 30.5 mmol) and TEA (8.48 ml, 61.0 mmol) in DCM (200 ml) at RT, and the resulting solution was stirred overnight at RT.

Aq. NH₄Cl (sat., 100 mL) was added, and the mixture was extracted with DCM (100 mL). The organic fraction was separated, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with EtOAc/hexanes (0% to 100%) to give compound 47-3A (8.37 g, 18.73 mmol, 61.4% yield) as a light-yellow solid along with small amounts 47-3B.

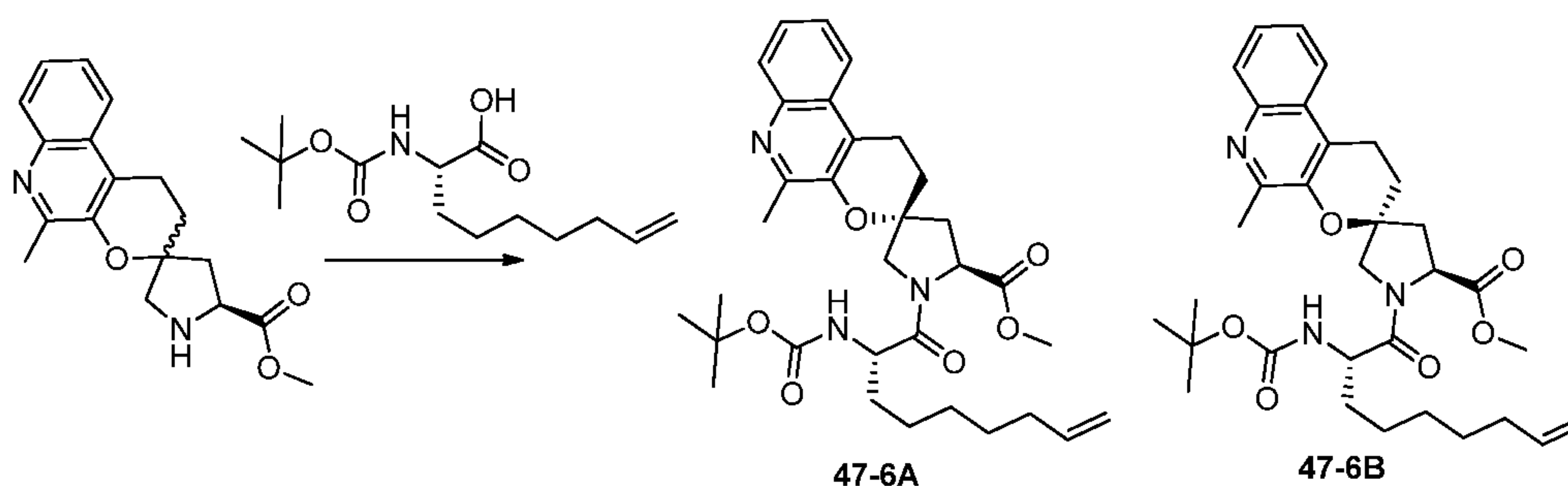
Step 4



A solution of compound 47-3B (8.37 g, 18.73 mmol) in EtOAc (187 ml) was hydrogenated over Pd/C (0.997 g, 0.936 mmol) at RT under an H₂ balloon overnight. The mixture was filtered. The insolubles were washed with EtOAc and MeOH. The filtrates were evaporated under reduced pressure to give the product of Step 4 (8.19 g, 18.24 mmol, 97% yield) as yellow solids.

Step 5

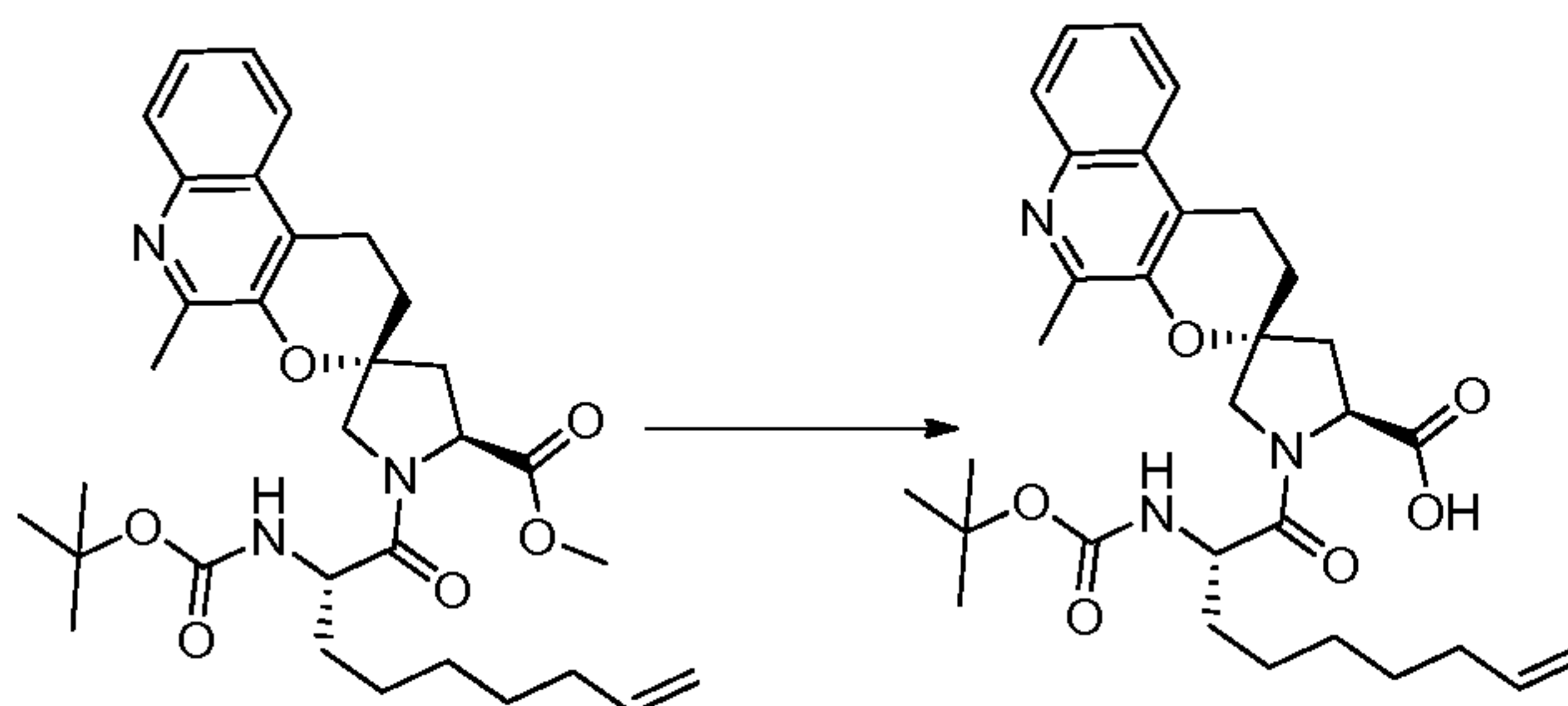
TFA (61.2 mL, 794 mmol) was added to a solution of the product of Step 4 (8.19 g, 19.86 mmol) in DCM (120 mL) at RT and stirred for 2h. The solution was concentrated. The residue was diluted with DCM and washed with aq. NaHCO₃. The aq. layer was separated and extracted with DCM. The organic layers were combined, dried (MgSO₄), filtered and the solvent was evaporated under reduced pressure to give the product of Step 5 (5.4 g, 17.29 mmol, 87% yield) as yellow foam.

Step 6

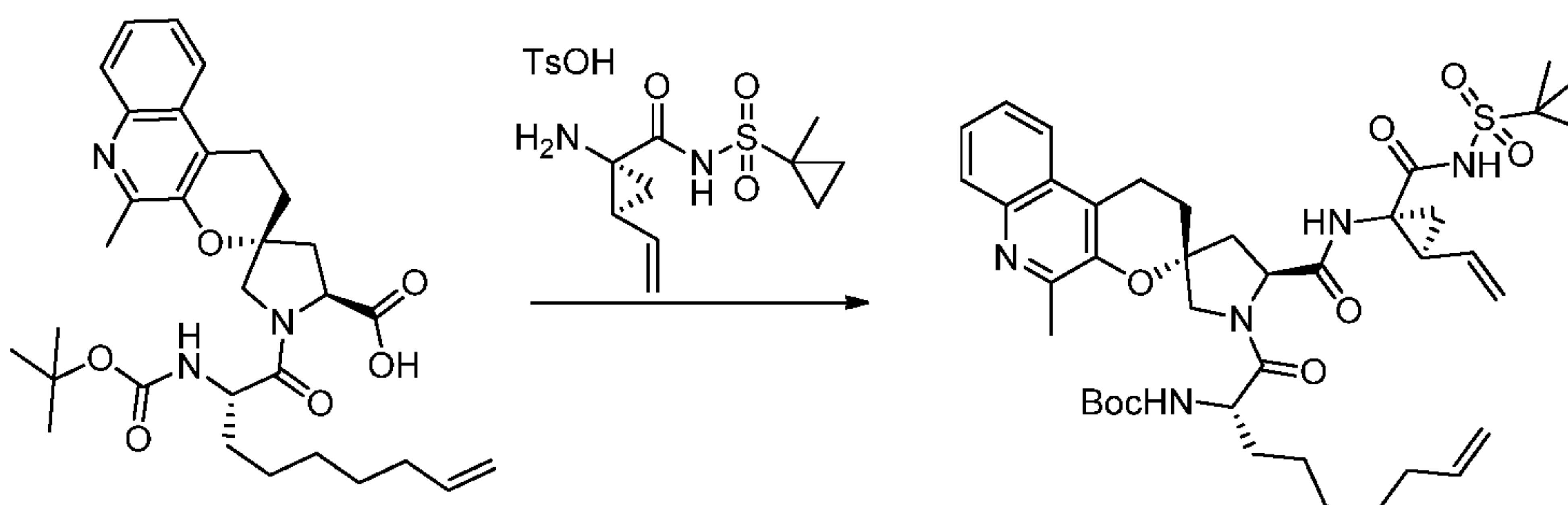
10

The product of Step 5 (5.4 g, 17.29 mmol), the dihexyl amine salt of (S)-2-(tert-butoxycarbonylamino)non-8-enoic acid (11.74 g, 25.9 mmol), and HATU (13.15 g, 34.6 mmol) were dissolved in DMF (200 ml). To this solution was added DIEA (5.71 ml, 34.6 mmol). The reaction was stirred at RT overnight. The mixture was diluted with water and extracted with Et₂O. The combined organics were washed with brine (250 mL), dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with EtOAc/isohexane (0-100%) to give first compound 47-6A (3.44 g, 6.08 mmol, 35.2% yield) as off-white foam and then compound 47-6B (3.18 g, 5.62 mmol, 32.5% yield) as tan foam.

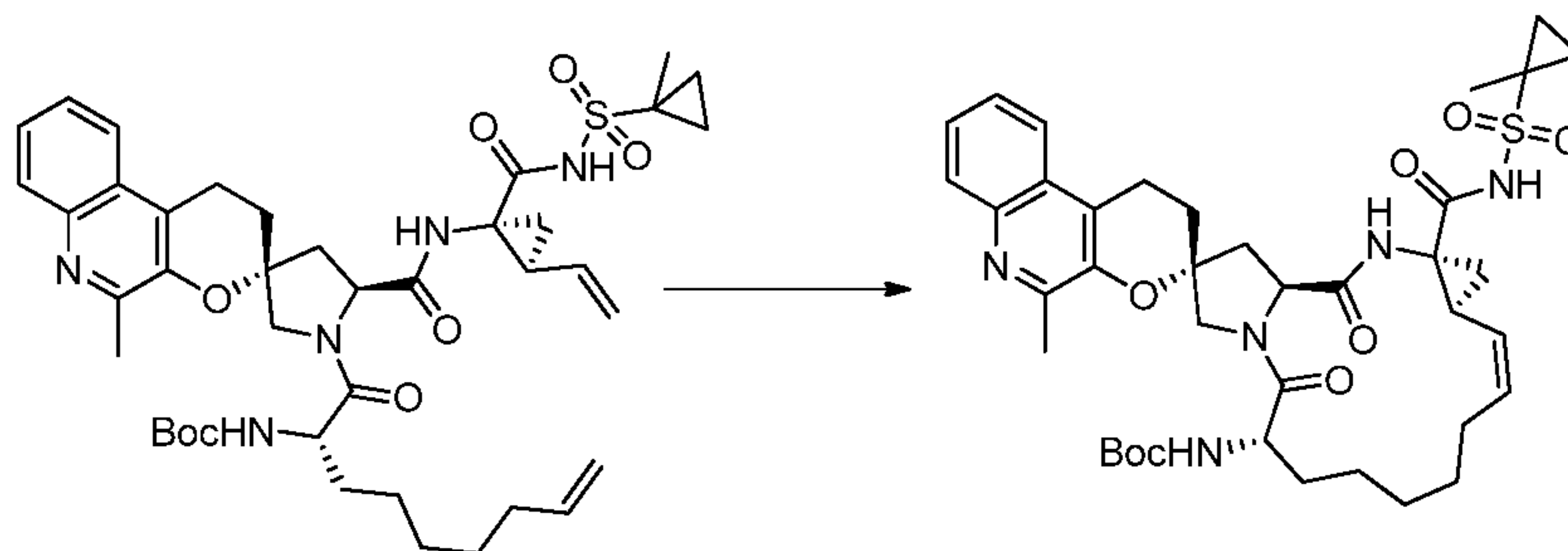
15

Step 7

Compound 47-6A (1.71 g, 3.02 mmol) was dissolved in THF (15.00 mL) and MeOH (15 mL). NaOH (10% aq., 15 mL, 41.3 mmol) was added and stirred at RT for 2.5h. The mixture was diluted with brine, acidified with 10% HCl (15.01 ml) to pH 3-5, and extracted with EtOAc. The aq. layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO₄), filtered, and concentrated to give the product of Step 7 (1.68 g).

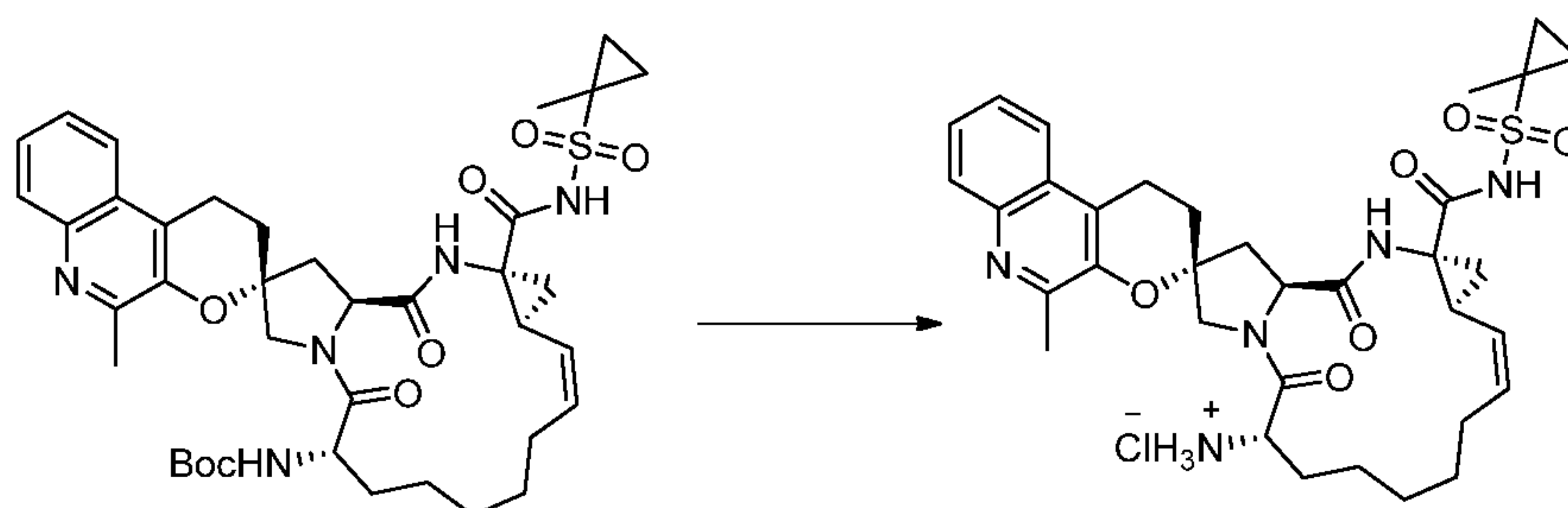
Step 8

A mixture of the product of Step 7 (1.68 g, 3.05 mmol), (1R,2S)-1-amino-N-(1-methylcyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide 4-methylbenzenesulfonate (1.903 g, 4.57 mmol), HATU (1.853 g, 4.87 mmol), and TEA (1.698 ml, 12.18 mmol) in DMF (30.5 ml) was stirred for 4h at RT. The mixture was diluted with EtOAc (300 ml), washed with water and brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by column chromatography on silica gel eluting with MeOH-DCM 0- 6% to give the product of Step 8 (2.36 g, 3.03 mmol, 100% yield) as off-white foam.

Step 9

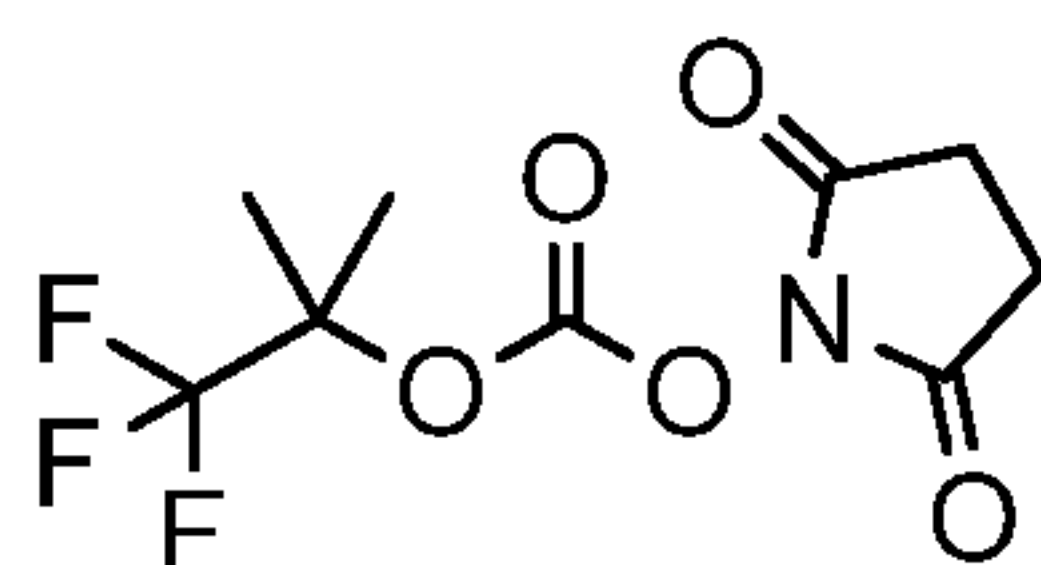
A solution of the product of Step 8 (0.99 g, 1.273 mmol), Zhan's catalyst (0.196 g, 0.267 mmol), and p-benzoquinone (0.055 g, 0.509 mmol) in DCE (509 ml) was heated at 65°C for 7h. The solution was cooled to RT, quenched with butyl vinyl ether (5 mL) and stirred for 15 min. Then it was washed with aq. NH₄Cl (sat.), dried (MgSO₄), filtered, and concentrated. The residue was purified by column chromatography on silica gel eluting with 0- 60% acetone/hexanes to give the product of Step 9 (600 mg, 0.800 mmol, 62.9% yield) as a brown resin. LC-MS MH⁺: 750.

Step 10



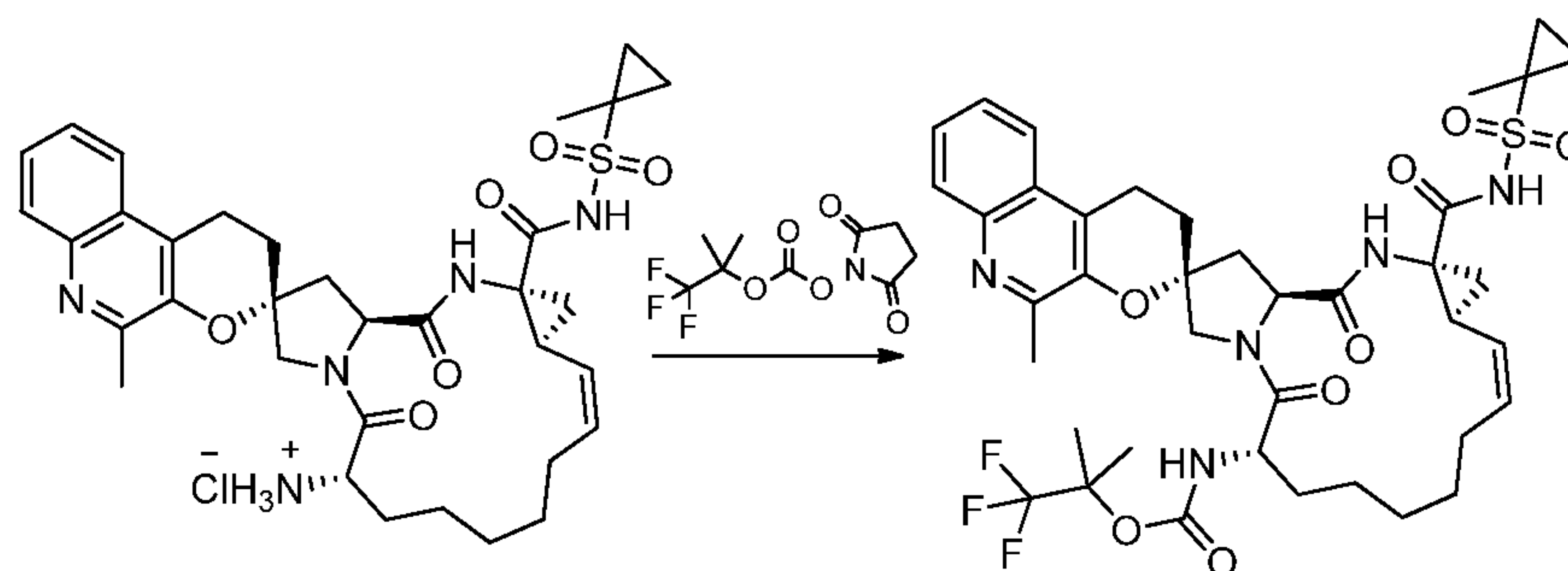
To a flask containing the product of Step 9 (600 mg, 0.800 mmol) was added HCl in dioxane (20 ml, 80 mmol), and the mixture was stirred at RT for 1.5h. The mixture was triturated with 100 ml hexane and allowed to settle. The clear solvent was decanted. The residue was evaporated 3x with toluene to give the crude product of Step 10 (627 mg, 0.914 mmol, 114% yield) as a tan solid. This material was used for next step reaction without further purification.

Step 11



To a mixture of 2-trifluoromethyl-2-propanol (1.84 g, 14.36 mmol) and N,N'-disuccinimidyl carbonate (5.52 g, 21.55 mmol) in MeCN (71.8 ml) was added TEA (6.01 ml, 43.1 mmol). The resulting solution was stirred overnight at RT. The solution was diluted with EtOAc, washed with brine, dried, and evaporated to dryness to give the product of Step 11 (2.17 g, 8.06 mmol, 56.1% yield) as a tan solid.

Step 12

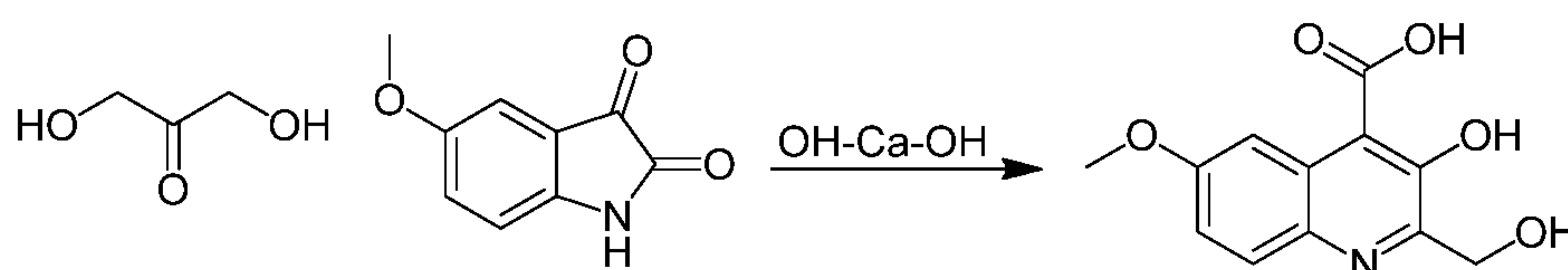


To a suspension of the product of Step 10 (59 mg, 0.086 mmol) and the product of Step 11 (93 mg, 0.344 mmol) in DCM (1.5 ml) was added TEA (0.060 ml, 0.430 mmol). The mixture was stirred at RT overnight. It was diluted with DCM, washed with aq. NH_4Cl ,
 5 concentrated, and separated by preparative TLC with 5% MeOH/DCM to give I-47 (24.7 mg, 35.7%) as a white solid. LC-MS MH^+ : 804.

Similar protocols were used for preparing derivatives of the product of Step 10 as amides and sulfonamides by the treatment with acid chlorides and sulfonyl chlorides. Alternatively, the product of Step 10 may be coupled with acids to yield amides using standard
 10 peptide coupling agents. Similarly, treatment of amine salts with TEA and isocyanates allows formation of ureas that may be purified in a similar manner.

Example 48: Neopentyl ((2R,6S,13aS,14aR,16aS,Z)-9'-methoxy-14a-(((1-methyl cyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-5'-(2,2,2-trifluoroethyl)-1',2',3,5,6,7,8,9,10,11, 13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4] diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-48)

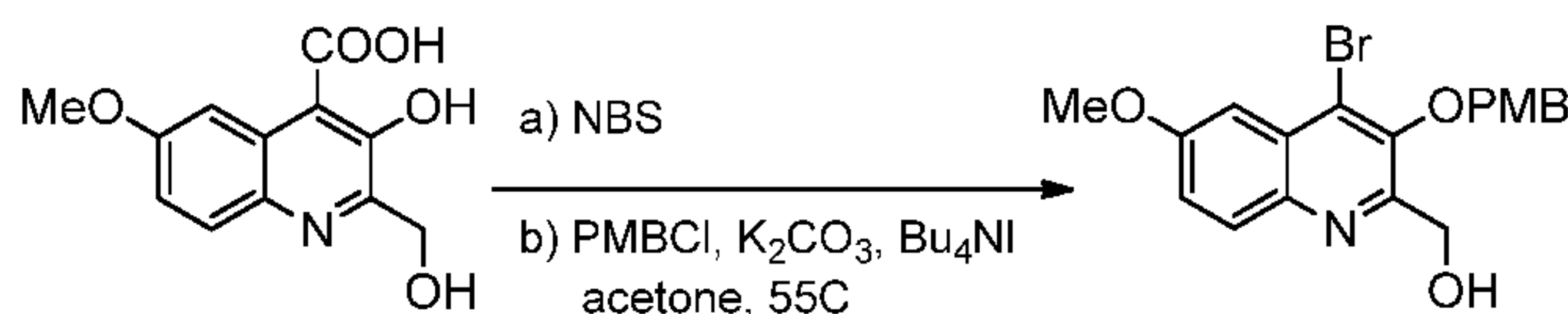
Step 1



To 5-methoxyisatin (30 g, 169 mmol) in water (1000 ml) was added $\text{Ca}(\text{OH})_2$
 20 (37.6 g, 508 mmol), and the mixture was heated to 80°C while stirring under N_2 for 1h. 1,3-Dihydroxyacetone (30.5 g, 339 mmol) was then added, and the mixture was stirred for another 3h. After allowing the mixture to cool to about 50°C , 80 ml of concentrated aq. HCl was added, and the mixture was stirred overnight. The mixture was cooled in a freezer to near 0°C , then the solid collected by vacuum filtration. The solid was dried in a vacuum oven at 70°C for 7h, then

at RT over 2d. The product of Step 1 (41.15 g, 165 mmol, 98% yield) was obtained as a reddish brown solid.

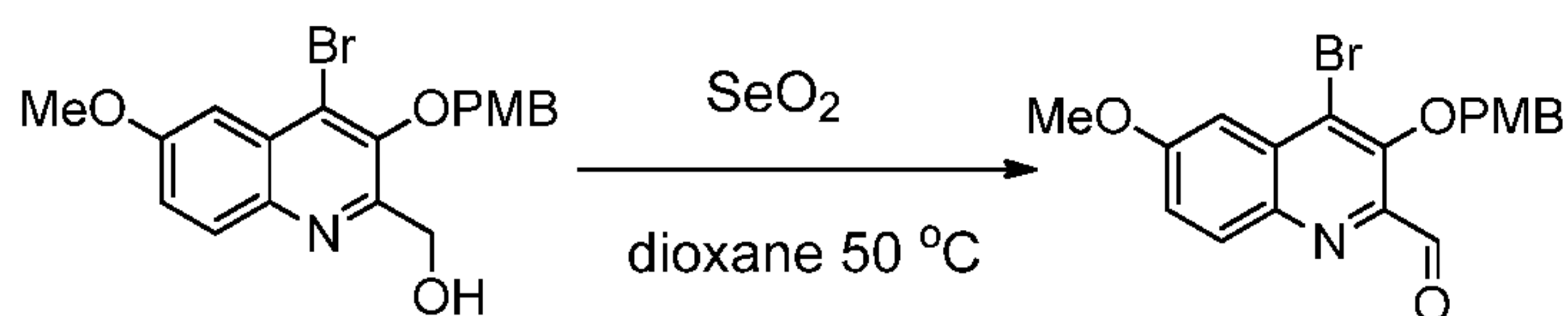
Step 2



5 NBS (23.40 g, 131 mmol) was added in portions to a stirred, cooled -10°C mixture of the product of Step 1 (32.77 g, 131 mmol) in THF over 1.5h. The mixture was stirred for 1h at -10°C under N₂. The reaction mixture was poured onto aq. Na₂S₂O₃ and extracted (3x) with EtOAc. The combined extracts were washed with brine, dried with MgSO₄, filtered and evaporated to dryness. The crude product was dry-loaded onto silica gel and purified in two
10 batches (EtOAc/hexanes, 0-60%). 17.9 g of bromide was obtained (47.9% yield).

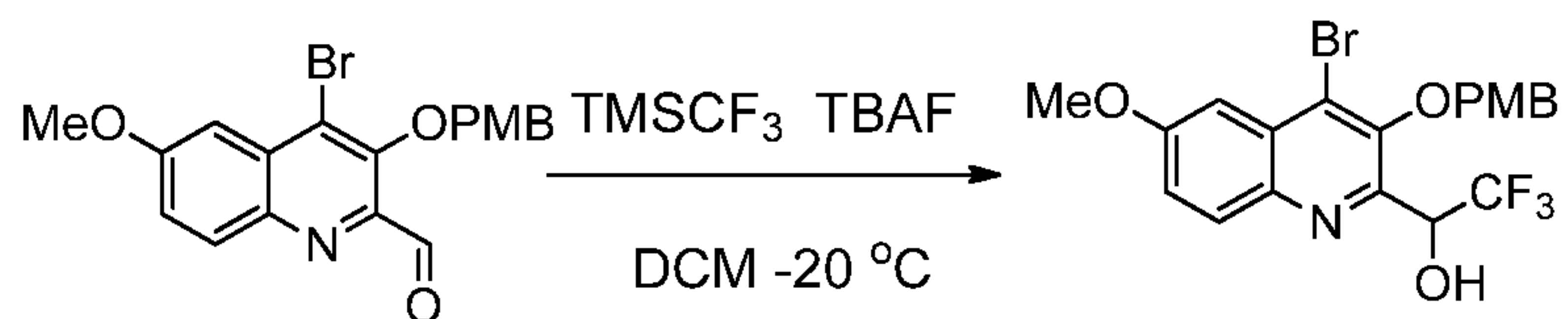
The product of bromide (10.79 g, 38 mmol), K₂CO₃ (15.75 g, 114 mmol) and Bu₄NI (4.21 g, 11.39 mmol) were slurried in acetone (108 mL). PMB-Cl (6.21 mL, 45.6 mmol) was added, and the mixture was heated at 55°C for 1h. The reaction was then cooled, poured into water (100 mL) and EtOAc (400 mL), and the layers were separated. The organic layers
15 was washed with brine (100 mL), dried over MgSO₄ and concentrated to an orange solid. The material was purified on silica gel using a gradient of 0-30% EtOAc in hexane to give 11.5 g of the product of Step 2 in 75% yield.

Step 3



20 The product of Step 2 (6.0 g, 14.84 mmol) was dissolved in dioxane (95 mL), SeO₂ (1.65 g, 14.84 mmol) was added, and the slurry was heated to 50°C for 1h. After cooling, the inorganic solids were filtered off and washed with EtOAc. The filtrate was concentrated to yield 5.0 g pure product of Step 3 in 84% yield.

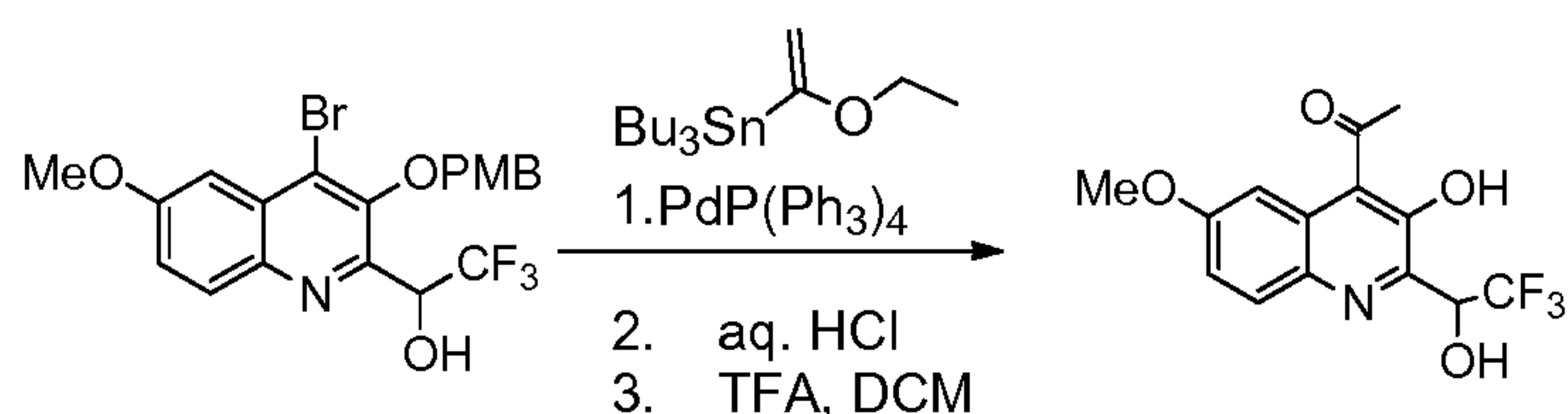
Step 4



25

To a solution of the product of Step 3 (3.2 g, 7.95 mmol) in DCM (60 mL) was added CsF (1.2 g, 19.5 mmol) and molecular sieves (1 g, 4A). The mixture was cooled to -20°C and aged 20 min. TMSCF₃ (4.0 mL, 7.95 mmol, 2.0 M THF) was added, and after no reaction was observed, additional TMSCF₃ (2.0 mL, 4.0 mmol, 2.0 M THF) and TBAF (4.0 mL, 4.0 mmol, 1.0 M THF) were added concurrently dropwise, resulting in complete conversion to product. The mixture was warmed to RT and filtered, washing with DCM. The filtrate was washed with saturated NH₄Cl and purified on silica gel using a gradient of 0-40% EtOAc in hexane to give 3.3 g desired product of Step 4 in 88% yield.

Step 5



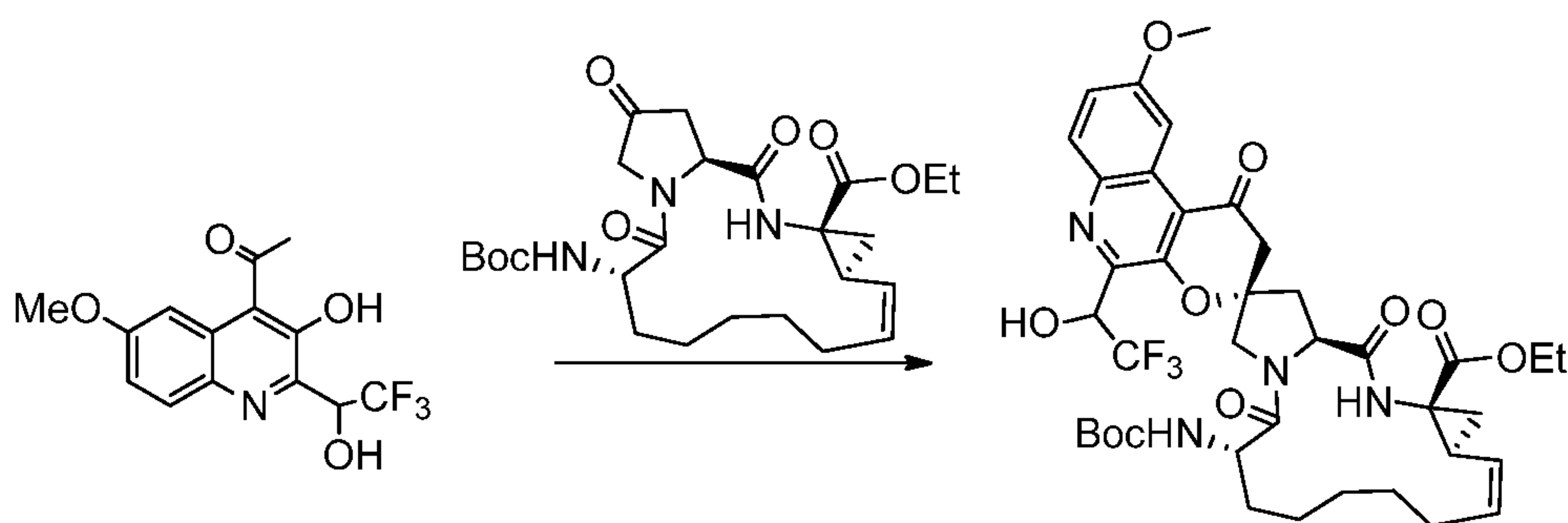
10

A flask containing a solution of the product of Step 4 (2.8 g, 5.93 mmol) and tributyl(1-ethoxyvinyl)tin (4.28 g, 11.86 mmol) in dioxane (56 mL) was 3x evacuated and backfilled with N₂ to remove oxygen. Pd(PPh₃)₄ (685 mg, 0.593 mmol) was added, and the degas sequence was repeated. The reaction was heated at 105°C for 16h, giving complete conversion to the enol intermediate. The reaction was then cooled to RT and aged with aq. HCl (20 mL, 2N) for 4h to unmask the ketone. The mixture was then poured into sat. NaHCO₃ (50 mL) and EtOAc (50 mL), the aq. was separated, and the organic was washed with brine, dried over MgSO₄ and concentrated to an oil, which contained both PMB- and des-PMB product. Tin reagent was removed by a silica column using 0-25% EtOAc in hexane, and the resulting solid was slurried in DCM and aged with TFA (0.914 mL, 11.86 mmol) for 1h. After flushing 3x with DCM, NaHCO₃ was added to obtain pH ~5. The organic was dried over MgSO₄ and purified by silica column using 0-40% EtOAc in hexane to give 1.2 g of the product of Step 5 in 64% yield.

15

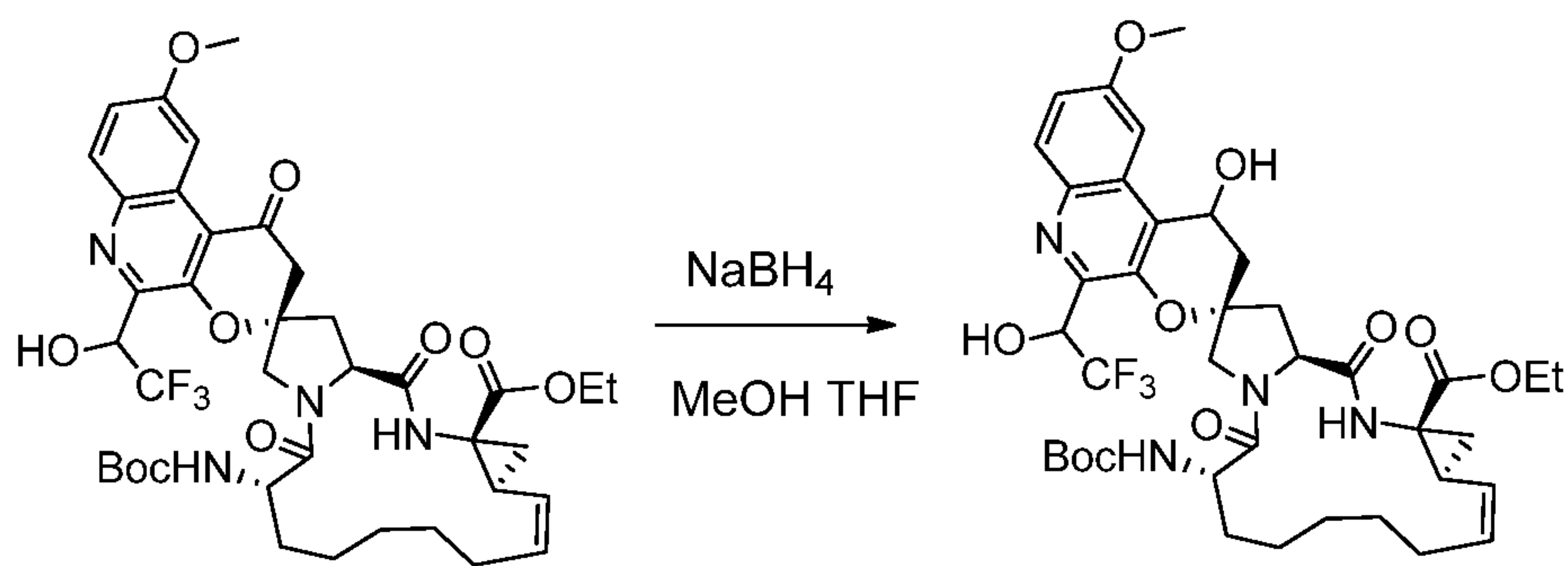
20

Step 6



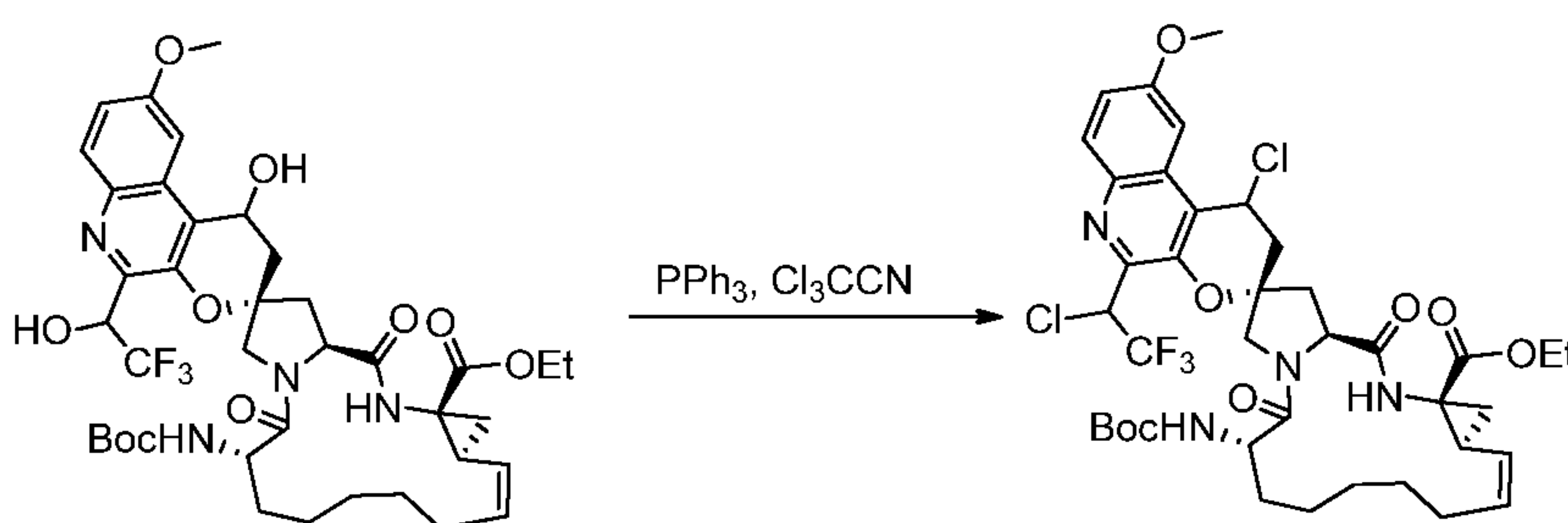
The product of Step 5 (1.2 g, 3.81 mmol), macrocyclic ketone (1.87 g, 3.81 mmol), benzoic acid (0.456 g, 3.81 mmol), pyrrolidine (160 μ l, 1.90 mmol) and molecular sieves (1.7 g, 4A) were combined in MeOH (24 mL) and heated to 70°C for 19h. The mixture was filtered over SOLKA FLOC and washed with MeOH. The filtrate was concentrated, dissolved in EtOAc, washed with NaHCO₃ and then brine, and concentrated to a brown foam that was purified on silica using 10-80% EtOAc in hexane to afford 1.24 g of the product of Step 6 in 41% yield.

Step 7



The product of Step 6 (1.24 g, 1.57 mmol) was dissolved in THF (10 mL) and MeOH (5 mL) and cooled to 0°C. NaBH₄ (65 mg, 1.73 mmol) was added in portions over 3 min, effecting vigorous gas evolution. After 15 min, the reaction was determined complete and sat. NH₄Cl (10 mL) was slowly added. After a 5 min age, the reaction was poured into EtOAc (40 mL) and water (10 mL). The organic layer was dried over MgSO₄ and concentrated to 1.21 g of the product of Step 7 in 97% yield.

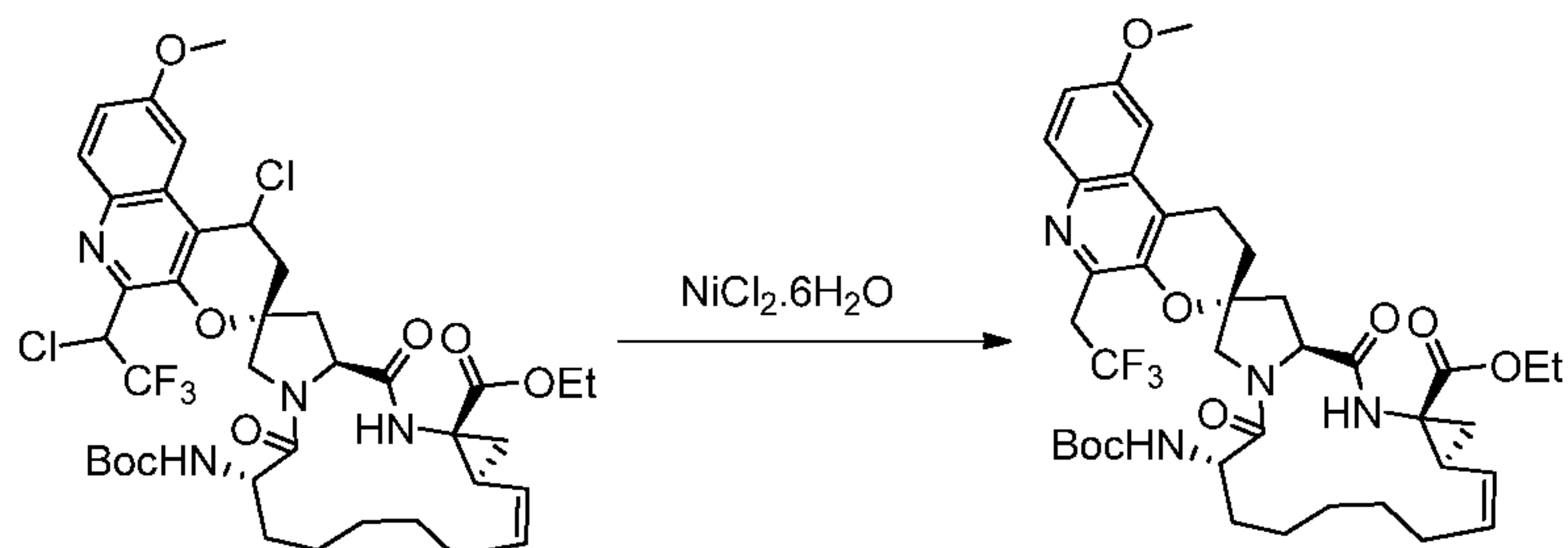
Step 8



To a solution of the product of Step 7 (1.21 g, 1.53 mmol) in THF (12 mL) was added Cl₃CCN (0.54 mL, 5.35 mmol) and then PPh₃ (1.40 g, 5.35 mmol) in portions with an exotherm to 30°C. The resulting mixture was heated at 60°C for several hours. After cooling, the mixture was filtered and washed with THF. The filtrate was concentrated and purified by

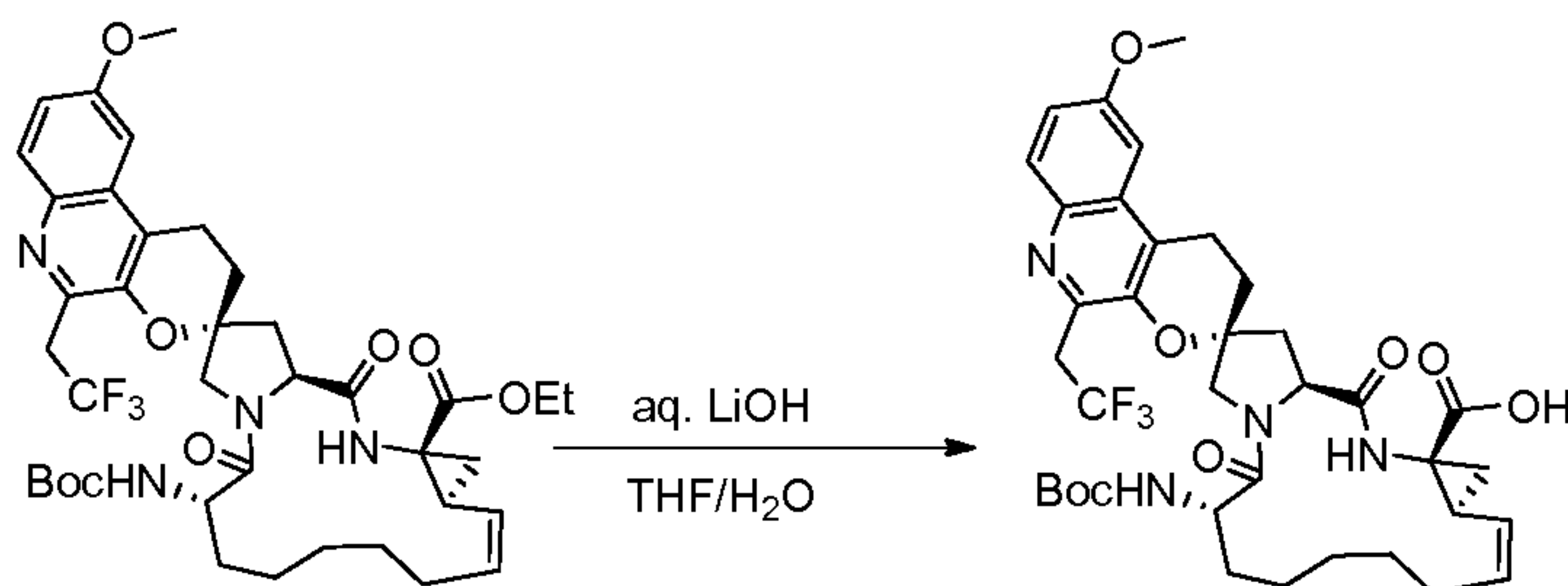
silica gel chromatography using 5-60% EtOAc/hexane to give 600 mg of the product of Step 8 in 47% yield.

Step 9



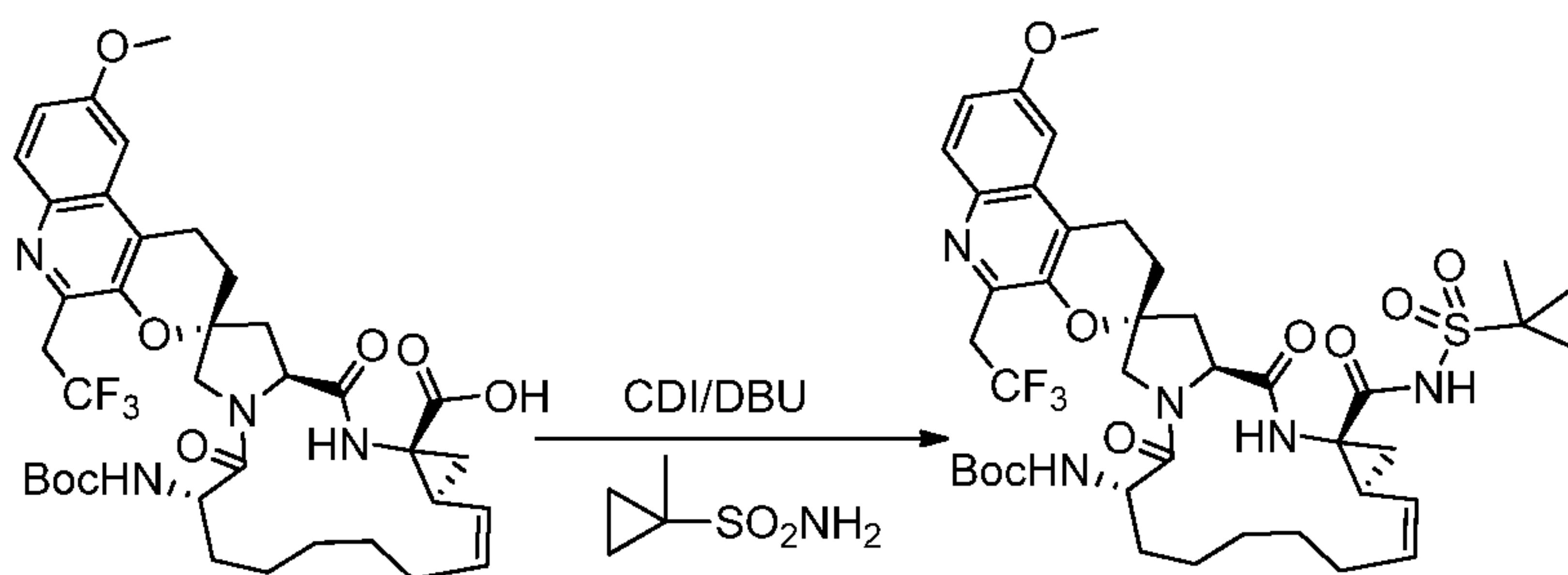
- 5 The product of Step 8 (600 mg 0.725 mmol) was dissolved in MeOH (12 mL) and degassed with subsurface N₂ spurge for 15 min. NiCl₂·6H₂O (517 mg, 2.17 mmol) was added, and after it dissolved, the reaction was cooled to -78°C. NaBH₄ (110 mg, 2.90 mmol) was added, and the mixture was stirred for 1h. After quenching with NaHCO₃, the reaction was poured into EtOAc and water, adding brine to clear the emulsion. The layers were separated, and the aq.
- 10 layer was extracted once with EtOAc. The combined organic was washed with brine, dried over MgSO₄ and concentrated to 520 mg solid, which was purified on silica with 5-60% EtOAc/hexane to yield 330 mg of the product of Step 9 in 60% yield.

Step 10



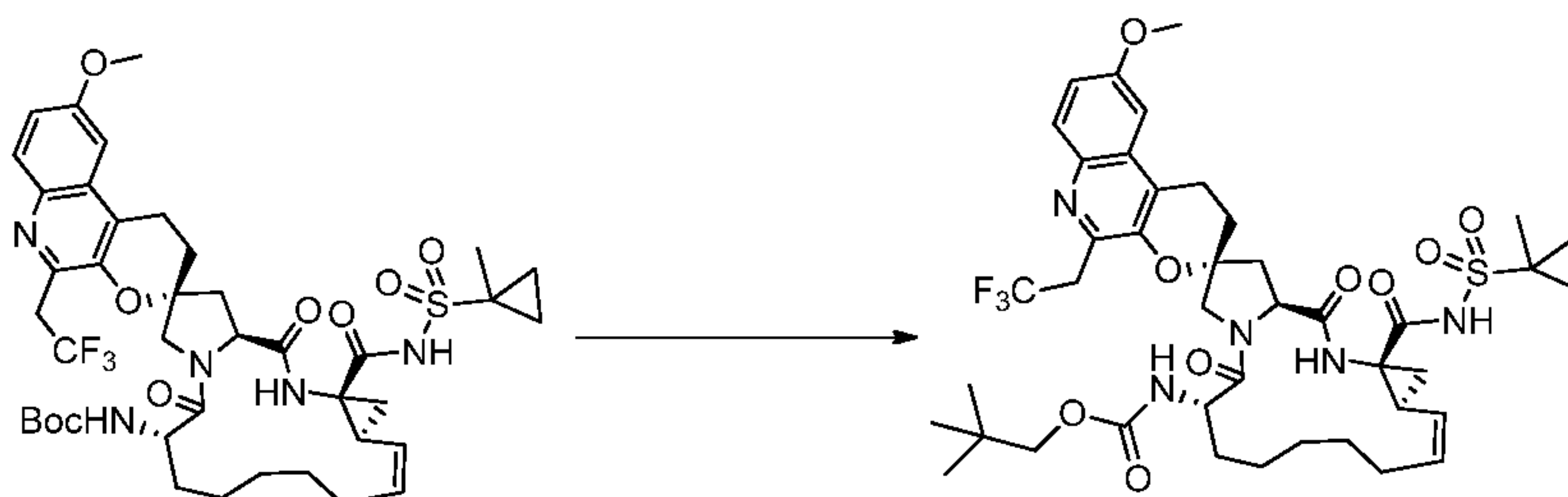
- 15 A solution of the product of Step 9 (330 mg, 0.435 mmol) in THF (3 mL), MeOH (1.5 mL) and water (1.5 mL) was treated with LiOH and heated at 45°C for 1h, and then cooled, and acidified to pH 4 with HCl (0.8 mL, 2N) and poured into EtOAc and water. The aq. layer was extracted with EtOAc, and the combined organics were washed twice with brine, dried over MgSO₄ and azeotroped with toluene to give 280 mg of the product of Step 10 in 88% yield.

20 Step 11



A solution of the product of Step 10 (220 mg, 0.301 mmol) and CDI (98 mg, 0.602 mmol) in THF (2 mL) was heated at 70°C for 2h. 1-Methylcyclopropane-1-sulfonamide (122 mg, 0.903 mmol) and DBU (136µl, 0.903 mmol) were then added, and the reaction was aged at 50°C for 45 min. The reaction was cooled and poured into EtOAc and NH₄Cl. The layers were separated, and the organic was washed with brine, dried over MgSO₄, concentrated and purified on silica with 0-10% MeOH/DCM to obtain 200 mg of the product of Step 11 in 78% yield.

Step 12



10

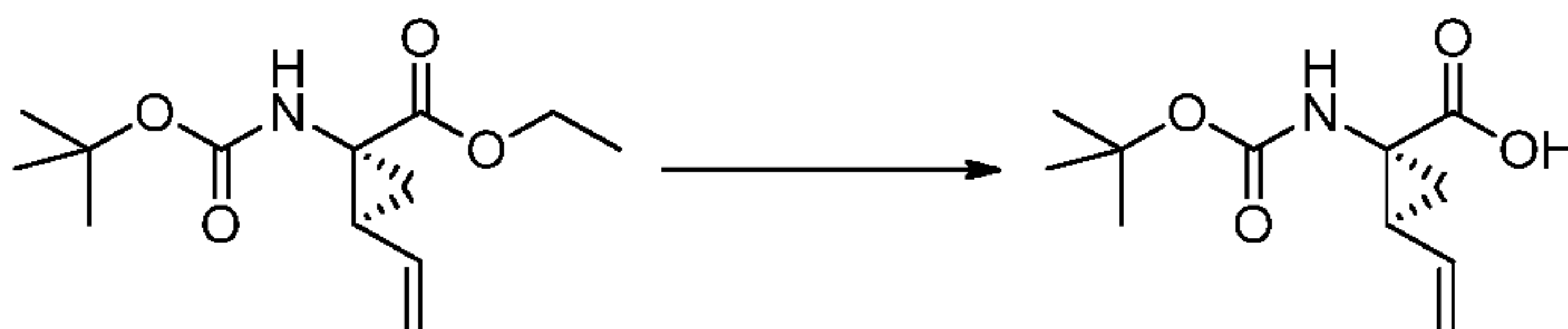
The product of Step 11 (192 mg, 0.226 mmol) was stirred for 45 min in a dioxane solution of HCl (5 mL, 20 mmol, 4N), at which point the solvent was removed and the solid was dried under vacuum to give 178 mg deprotected amine salt in 100% yield.

The amine salt (42 mg, 0.054 mmol) in DCM (1 mL) was cooled to 0°C, and neopentyl chloroformate (16µl, 0.107 mmol) was added, followed by DiPEA (28µl, 0.161 mmol). The reaction was stirred for 20 min and then purified directly on silica column with a gradient of 0-60% acetone in hexane to give 24 mg of I-48 in 52% yield. Mass spec. observed mass 862.71 (M+1) ¹H NMR δ (ppm)(Acetone-d₆): 10.58 (1 H, s), 8.52 (1 H, s), 7.86 (1 H, d, J = 8.93 Hz), 7.24 (2 H, s), 6.37 (1 H, s), 5.71 (1 H, d, J = 10.05 Hz), 5.02 (1 H, t, J = 9.21 Hz), 4.74 (1 H, m), 4.53 (1 H, d, J = 10.80 Hz), 4.14 (1 H, m), 3.99 (4 H, m), 3.95-3.79 (2 H, m), 3.69-3.63 (2 H, m), 3.60-3.51 (2 H, m), 3.29-3.14 (3 H, m), 2.84-2.81 (8 H, m), 2.65-2.61 (bm), 2.57-2.52 (m), 2.43-2.34 (bm), 2.11 (bm), 1.89 (3 H, bs), 1.74-1.22 (bm), 0.87 (12 H, m).

20

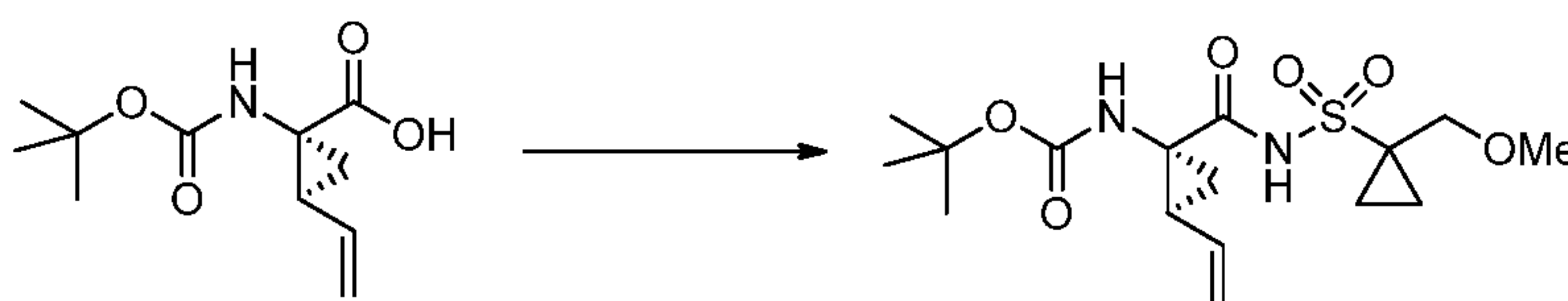
Example 49: *tert*-Butyl ((2R,6S,13AS,14AR,16AS,Z)-9'-methoxy-14a-(((1-(methoxymethyl)cyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13A,14,14A,15,16,16A-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-A][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-49)

5 Step 1



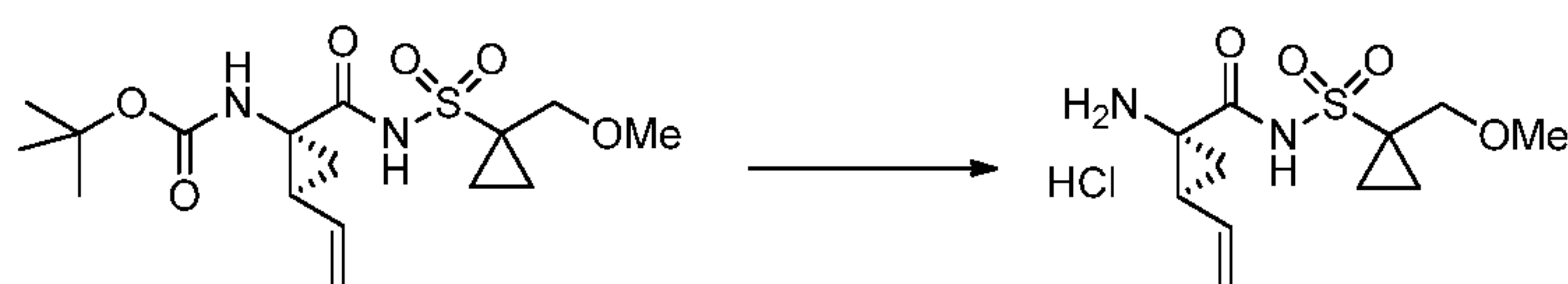
To a THF solution (58.8 mL) of (1R,2S)-ethyl 1-((*tert*-butoxycarbonyl)amino)-2-vinylcyclopropanecarboxylate (3.0 g, 11.76 mmol) was added a solution of LiOH·H₂O (2.465 g, 58.8 mmol) in water (58.8 mL) over a period of 10 min. The resultant mixture was heated at 65°C for 16h, then was concentrated to half its volume and the pH adjusted to 2-3 with 1 m (aq.) HCl. The mixture was extracted with DCM (3x 100 mL) and the combined organic extracts dried over MgSO₄, filtered, and concentrated *in vacuo* to afford 2.7 g of the product of Step 1, which was used without further purification.

15 Step 2



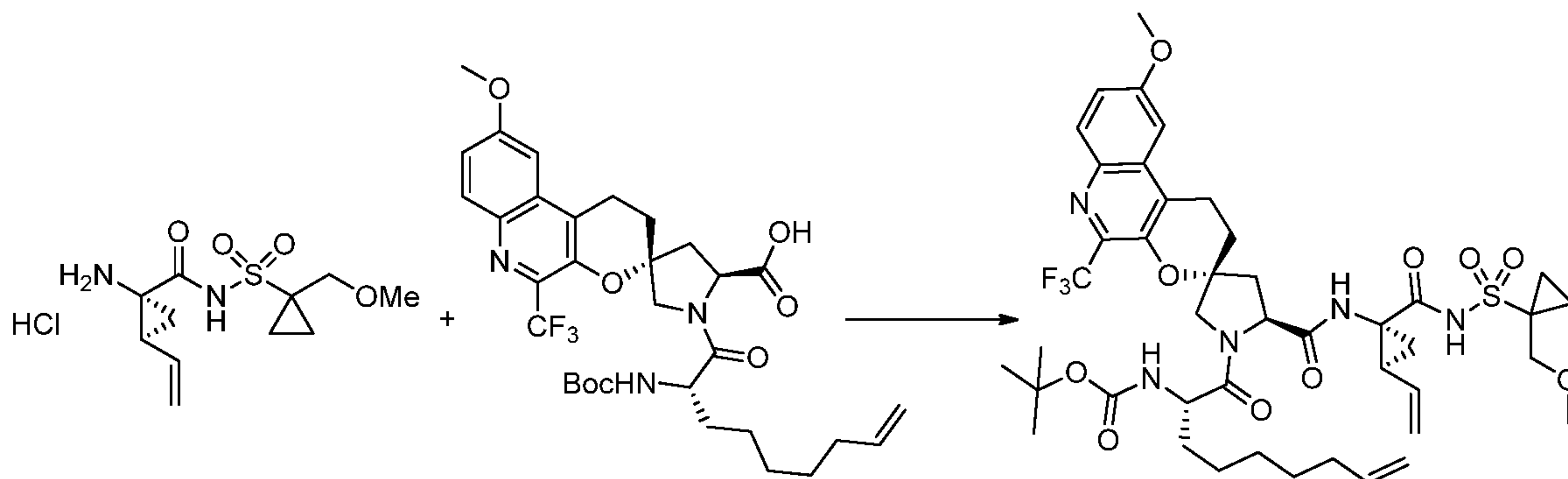
To a THF solution (22 mL) of the product from Step 1 was added N,N'-carbonyldiimidazole (1.070 g, 6.60 mmol), and the resultant mixture heated at 85°C for 2h. The mixture was cooled to ambient temperature, and a THF solution (11 mL) of 1-(methoxymethyl)cyclopropane-1-sulfonamide (1.454 g, 8.80 mmol) was added, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (1.316 mL, 8.80 mmol). The resultant mixture was heated at 75°C for 16h, then 1 m (aq.) HCl (10 mL) and H₂O (50 mL) was added. The product was extracted with EtOAc (200 mL), and the organic extract washed sequentially with 1 m HCl/H₂O (1:2, 50 mL) and brine (50 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using a gradient of 0-30% EtOAc/CH₂Cl₂ as eluent to afford 1.13 g of the indicated product of Step 2.

25 Step 3



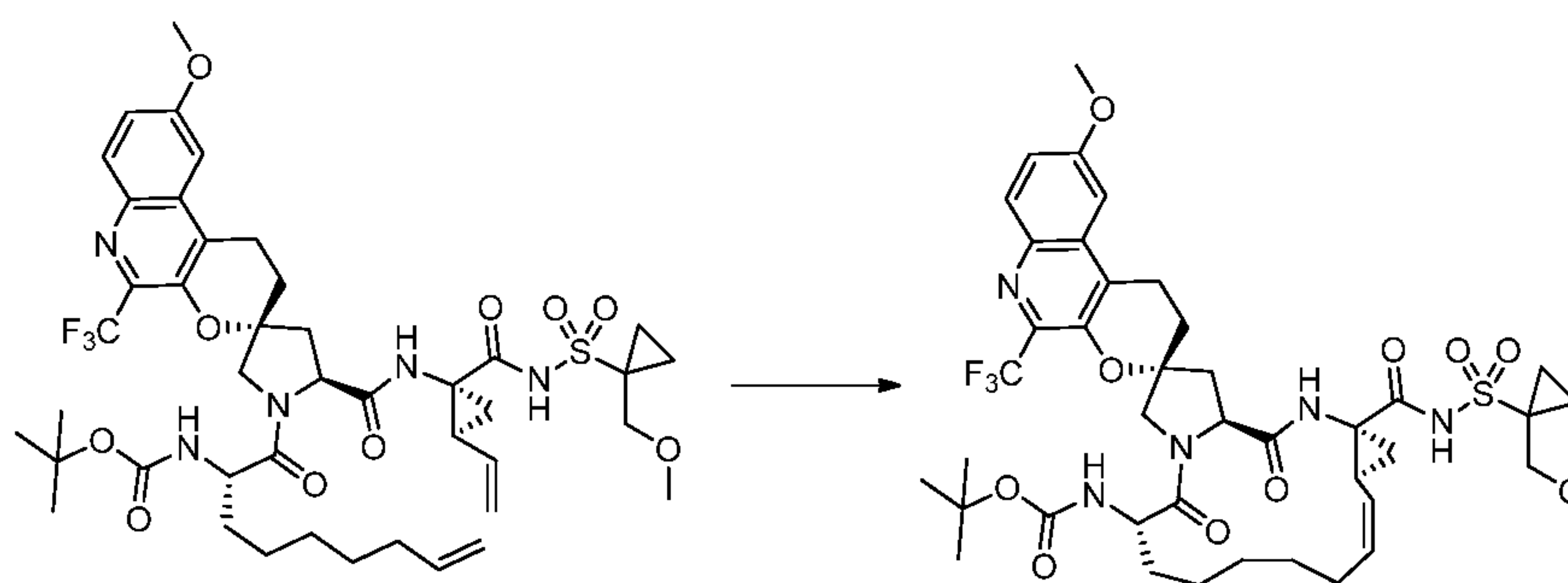
To the product from Step 2 (1.1 g, 2.94 mmol) was added 4 m HCl in dioxane (10 mL, 40 mmol), and the resultant mixture stirred for 1h. The mixture was concentrated *in vacuo* to afford 920 mg of the product of Step 3, which was used without further purification.

5 Step 4



To a DMF solution (10 mL) of acid obtained similarly to the product of Example 4, Step 11 (805 mg, 1.266 mmol) was added the product from Step 3 (590 mg, 1.9 mmol), HATU (722 mg, 1.9 mmol), and TEA (0.53 mL, 3.8 mmol). The resultant mixture was stirred at ambient temperature for 14h, diluted with EtOAc, and the organic layer washed sequentially with H₂O (3X) and brine (1X), dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using a gradient of 0-100% EtOAc/Hexanes as eluent to obtain 1.123 g of the product of Step 4. *m/z* = 892.4 (M+H).

Step 5

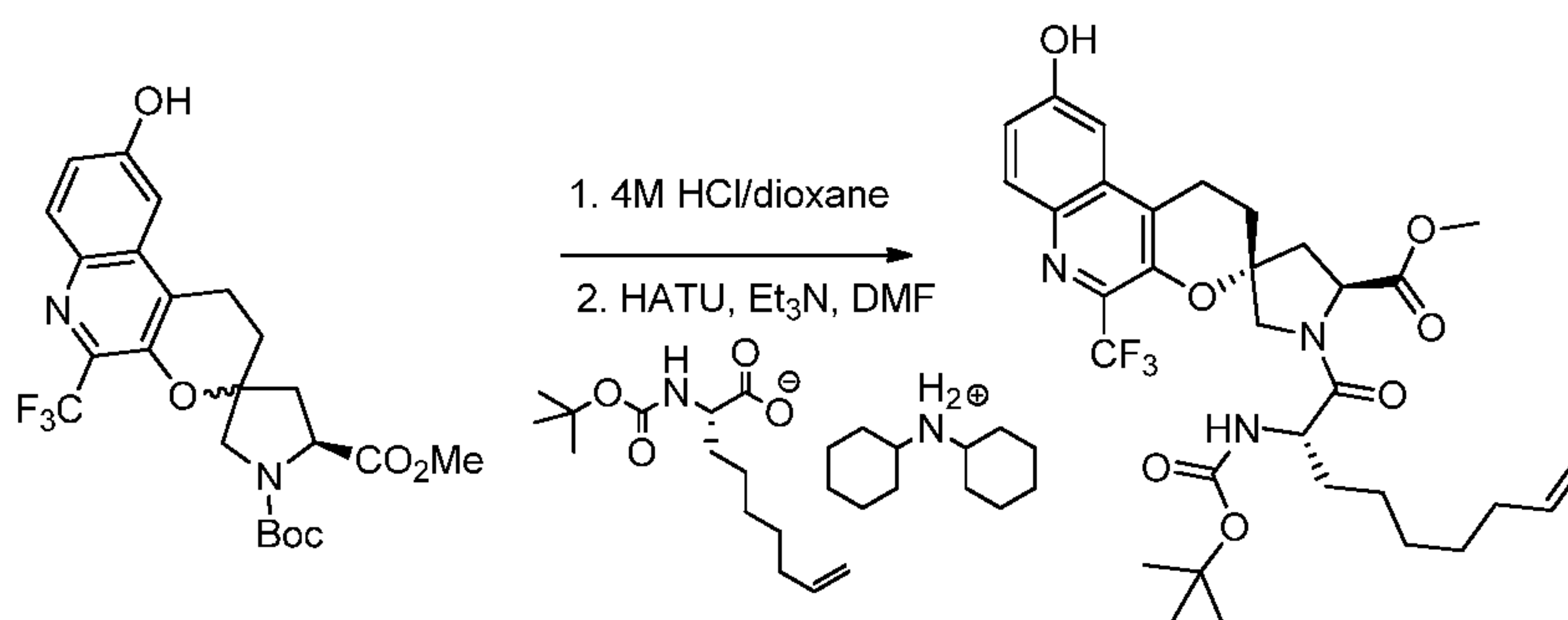


To a DCE solution (434 mL) of the product from Step 4 (1.123 g, 1.259 mmol) was added 1,4-benzoquinone (40.8 mg, 0.378 mmol) and Zhan's catalyst (231 mg, 0.315 mmol). The mixture was evacuated/flushed with N₂ 5x and heated at 75°C under a stream of N₂ for 3.5h then at 80°C for 30 min. The mixture was cooled to ambient temperature and quenched by the

addition of 0.4 mL of butyl vinyl ether. After stirring at ambient temperature for 20 min, the mixture was concentrated *in vacuo* and purified by silica gel column chromatography using a gradient of 0-50% Acetone/Hexanes as eluent. The product was further purified by SFC chromatography to provide 359 mg of I-49. ¹H NMR δ (ppm)(CHCl₃-d): 10.08 (1 H, br s), 8.04 (1 H, d, J = 9.22 Hz), 7.36-7.26 (1 H, m), 7.04 (1 H, s), 6.85 (1 H, s), 5.74 (1 H, d, J = 10.07 Hz), 5.21 (1 H, d, J = 8.44 Hz), 5.06 (1 H, s), 4.64 (1 H, s), 4.44 (1 H, d, J = 10.88 Hz), 4.25 (1 H, s), 4.00 (3 H, s), 3.76 (2 H, t, J = 13.86 Hz), 3.71-3.61 (1 H, m), 3.36 (3 H, s), 3.26-3.10 (2 H, m), 2.57 (2 H, t, J = 9.09 Hz), 2.48 (1 H, t, J = 11.62 Hz), 2.38 (2 H, m), 1.96-1.83 (4 H, m), 1.77 (1 H, d, J = 11.98 Hz), 1.68 (1 H, m), 1.61-1.43 (4 H, m), 1.30 (12 H, s), 1.08 (2 H, s), 0.93-0.83 (2 H, m). *m/z* = 864.4 (M+H).

Example 50: *tert*-Butyl ((2*R*,6*S*,13*aS*,14*aR*,16*aS*,*Z*)-14*a*-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-9'-(3-morpholinopropoxy)-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13*a*,14,14*a*,15,16,16*a*-hexadecahydro-1*H*-spiro[cyclopropa[e]pyrrolo[1,2-
a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-*c*]quinolin]-6-yl)carbamate (I-50)

Step 1

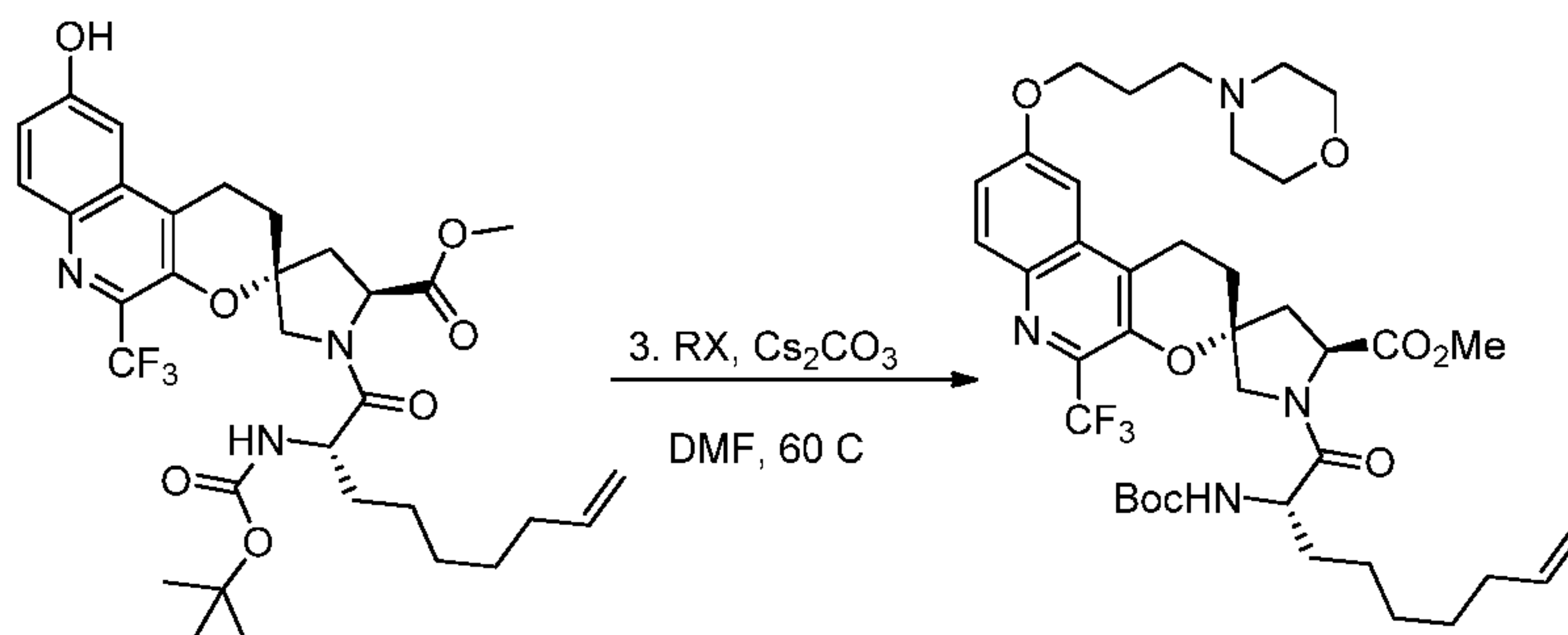


A solution of the product of Example 7, Step 7 (520 mg, 1.078 mmol) and 4 m HCl in dioxane (4 mL, 16.00 mmol) was stirred at RT for 2h. The volatiles were removed under reduced pressure, and the residue was azeotroped 3x with toluene. The solid thus obtained was used without purification.

The solid thus obtained was taken in DMF (10.75 mL) and treated with TEA (0.451 mL, 3.24 mmol), dicyclohexylammonium (S)-2-(*tert*-butoxycarbonylamino)non-8-enoate (973 mg, 2.149 mmol) followed by HATU (817 mg, 2.149 mmol) at RT. The reaction was stirred at RT for 2h, at which stage LC-MS showed complete consumption of the starting material. The reaction was quenched with aq. NaHCO₃ and extracted with EtOAc. The organics

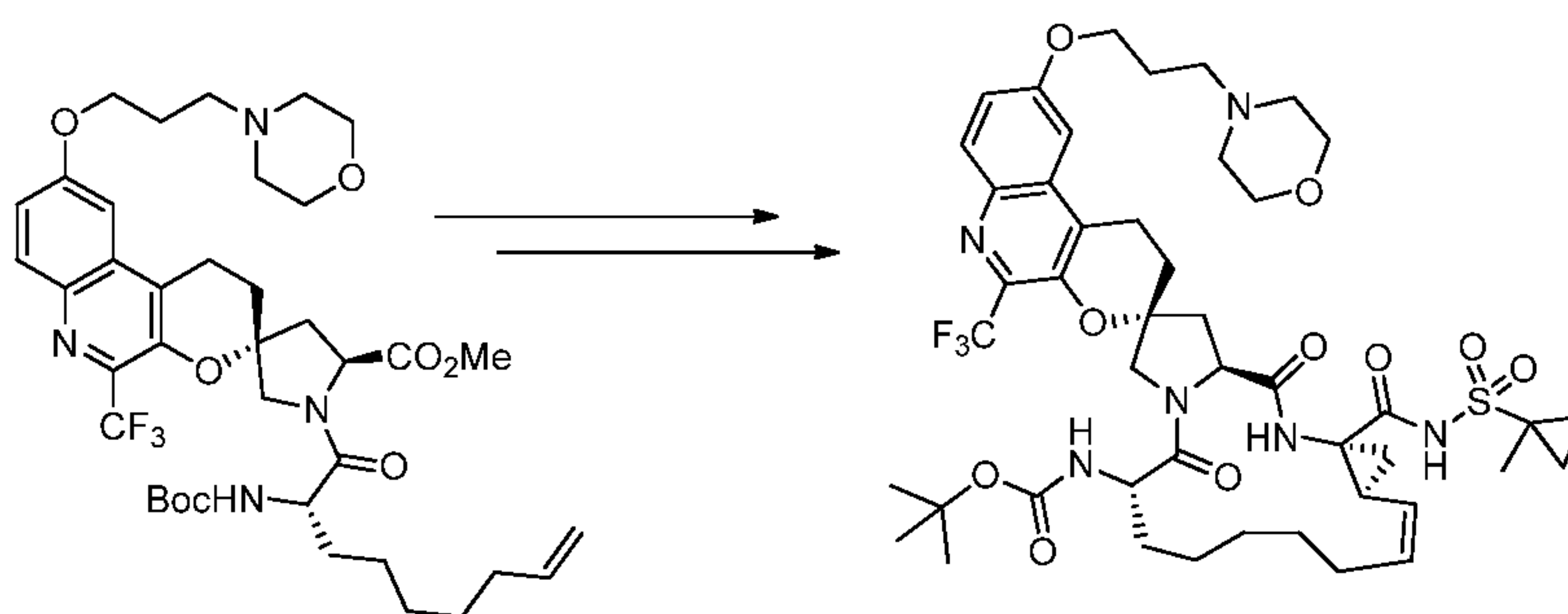
were dried (MgSO₄), concentrated and purified by silica gel column chromatography (0-60-100% EtOAc in hexane) to provide the indicated product of Step 1 and its diastereomer.

Step 2



- 5 The product of Step 2 was prepared from the product of Step 1 by the procedure described in Example 7, Step 8, in which the 4-(2-bromoethyl)morpholine HBr salt was replaced with 4-(3-chloropropyl)morpholine hydrochloride.

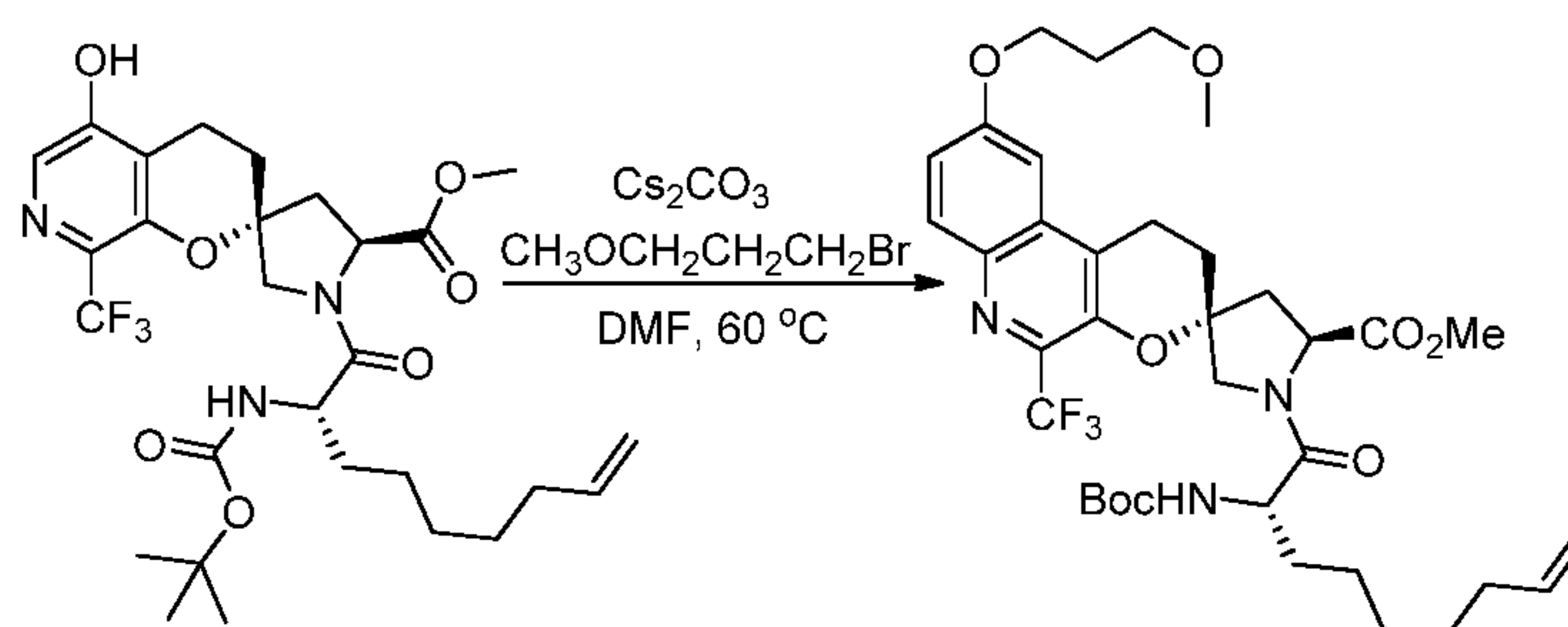
Step 3



- 10 The product of Step 2 was converted to I-50 by the procedures described in Example 7, Steps 9-11.

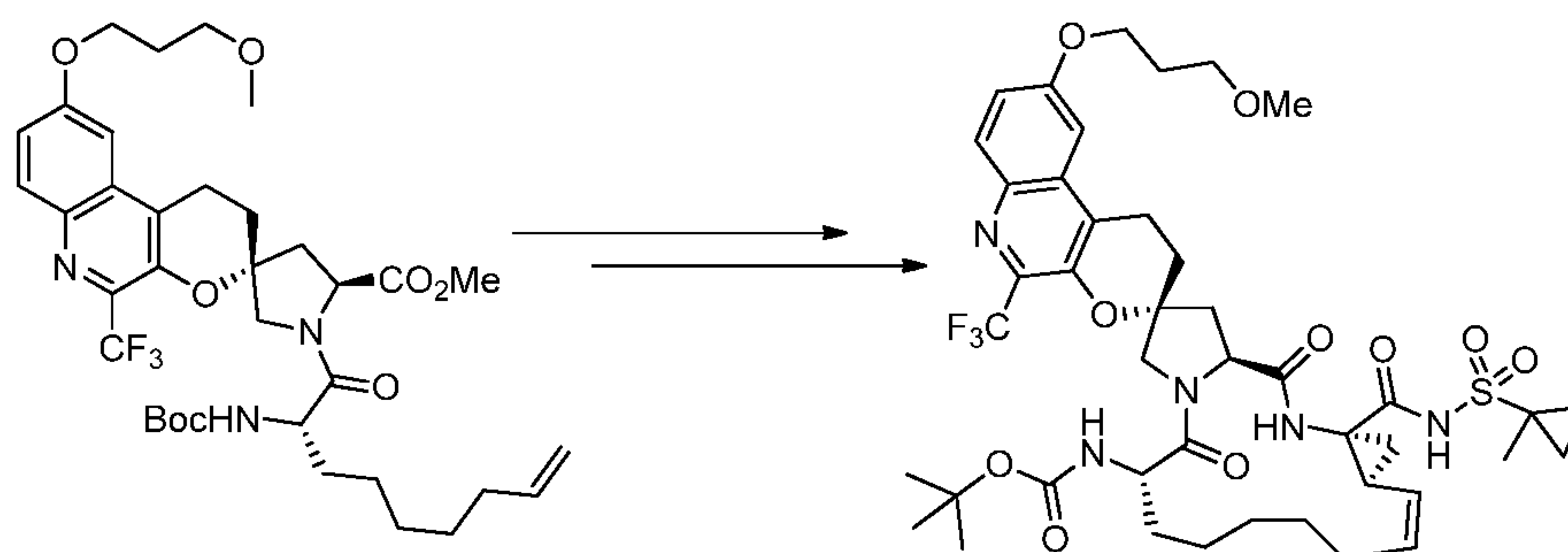
15 **Example 51: tert-Butyl ((2R,6S,13aS,14aR,16aS,Z)-9'-(3-methoxypropoxy)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-51)**

Step 1



The product of Step 1 was prepared from the product of Example 50, Step 1 by the procedure described in Example 50, Step 2, in which 4-(3-chloropropyl)morpholine hydrochloride was replaced with 1-bromo-3-methoxy propane.

5 Step 2

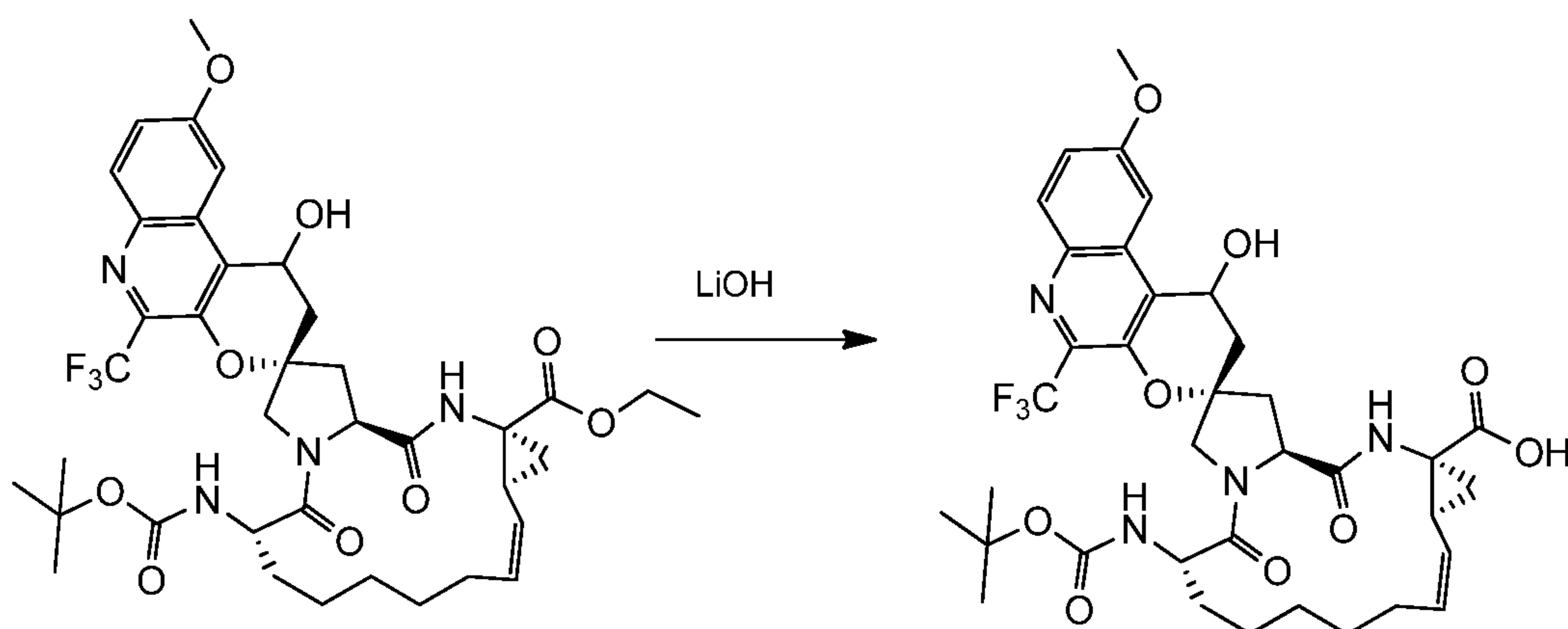


The product of Step 1 was converted to I-51 using the procedures described in Example 7, Steps 9-11.

10 **Example 52: *tert*-Butyl ((1'*R*,2*S*,6*S*,13*aS*,14*aR*,16*aS*,*Z*)-9'-methoxy-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-1'-((((1-methylcyclopropyl)sulfonyl)carbamoyl)oxy)-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13*a*,14,14*a*,15,16,16*a*-hexadecahydro-1*H*-spiro[cyclopropa[e]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-*c*]quinolin]-6-yl)carbamate (I-52);** and

15 **Example 53: *tert*-Butyl ((1'*R*,2*S*,6*S*,13*aS*,14*aR*,16*aS*,*Z*)-9'-methoxy-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-1'-((((1-methylcyclopropyl)sulfonyl)carbamoyl)oxy)-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13*a*,14,14*a*,15,16,16*a*-hexadecahydro-1*H*-spiro[cyclopropa[e]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-*c*]quinolin]-6-yl)carbamate (I-53)**

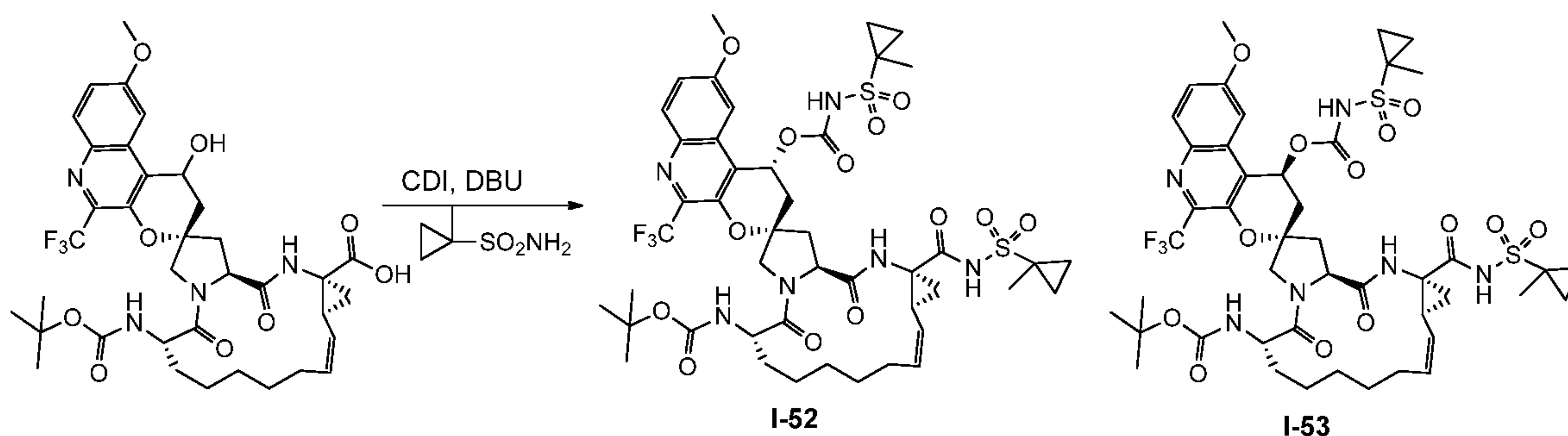
20 Step 1



To a solution of the product of Example 5, alternate procedure Step 5 (380 mg, 0.499 mmol) in THF (4.5 ml), MeOH (2.0 ml) and H₂O (2.0 ml) was added the LiOH (72 mg, 3.0 mmol) at RT. It was stirred at RT for 5.5h. The LC-MS shows the hydrolysis was completed.

- 5 The reaction mixture was cooled to 0°C, and acidified to pH = 2~3 with 1N HCl, and diluted with EtOAc (30 ml). The layers were separated and the aq. layer was extracted again with EtOAc (15 ml x2). The organic layers were combined and washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo* to give (2S,6S,13aS,14aR,16aS,Z)-6-((tert-butoxycarbonyl)amino)-1'-hydroxy-9'-methoxy-5,16-dioxo-5'-(trifluoromethyl)-
- 10 1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a-carboxylic acid (the product of Step 1) as a white solid. The product was azeotroped with toluene (2x10 ml) and kept under vacuum overnight. This product was carried on to next step without further purification. *m/z*= 733.3 (M+1).

15 Step 2



- A solution of the product of Step 1 (380 mg, 0.519 mmol) and CDI (160 mg, 0.985 mmol) in THF (4.5 ml) was stirred in an oil-bath at 70°C for 3h, then cooled to RT. To this reaction mixture was added 1-methylcyclopropane-1-sulfonamide (175 mg, 1.296 mmol) and DBU in THF (1 ml) (1.296 ml, 1.296 mmol), and the mixture was stirred in an oil-bath at 46°C
- 20

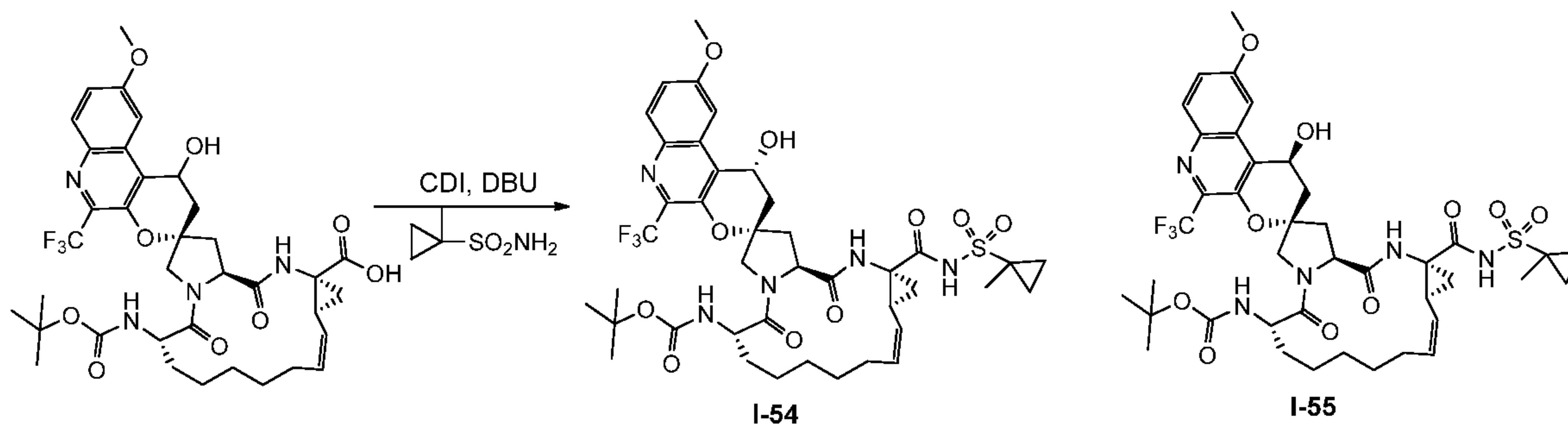
for 2.2h. The LC-MS indicates that the major is desired product. The reaction mixture was diluted with EtOAc (40 ml), washed with aq. NH₄Cl (2x6 ml), brine, dried over MgSO₄, filtered, concentrated. The residue was purified by column chromatography on silica gel (40 g, gold column), eluting with 100% hexane for 200 ml, gradient to 40% of acetone to give the mixture of
 5 the compounds of Examples 52 and 53, which were separated by Gilson (the column is C18, 19x150 mm; eluting with MeCN/water + 0.1% formic acid (gradient 40% of MeCN to 100% MeCN). Freeze drying gave I-52 and I-53 as white solids.

Example 52: ¹H NMR δ (ppm)(CDCl₃): 10.01 (1 H, s), 8.02 (1 H, d, J = 9.25 Hz), 7.30 (1 H, s), 7.09 (1 H, s), 6.90 (1 H, s), 6.49 (1 H, s), 5.73 (1 H, q, J = 8.85 Hz), 5.15 (1 H, s),
 10 5.00 (1 H, t, J = 9.39 Hz), 4.62 (1 H, d, J = 11.10 Hz), 4.49 (1 H, s), 4.32 (1 H, s), 3.96 (3 H, s), 3.87 (1 H, d, J = 11.65 Hz), 2.66 (3 H, d, J = 14.80 Hz), 2.47 (2 H, d, J = 15.75 Hz), 2.34 (1 H, t, J = 12.26 Hz), 2.17 (2 H, d, J = 19.79 Hz), 1.86 (2 H, s), 1.81 (1 H, s), 1.71 (1 H, s), 1.41 (11 H, s), 1.38-1.24 (9 H, m), 0.86 (4 H, s), 0.61 (1 H, s), 0.40 (1 H, s). *m/z* = 1011.2 [M+1].

Example 53: ¹H NMR δ (ppm)(CDCl₃): 10.22 (1 H, s), 8.95 (1 H, s), 8.05 (1 H, t, J = 9.20 Hz), 7.37-7.27 (2 H, m), 7.08 (1 H, s), 7.03 (1 H, s), 6.65 (1 H, s), 5.75 (1 H, q, J = 8.87 Hz), 5.16 (1 H, d, J = 8.85 Hz), 5.07 (1 H, t, J = 9.37 Hz), 4.69 (1 H, t, J = 8.07 Hz), 4.52 (1 H, d, J = 12.45 Hz), 4.24 (1 H, t, J = 10.01 Hz), 3.98 (3 H, s), 3.83 (1 H, d, J = 12.29 Hz), 2.75-2.66 (3 H, m), 2.70-2.54 (3 H, m), 2.49 (1 H, q, J = 8.83 Hz), 1.98 (1 H, t, J = 7.01 Hz), 1.89 (1 H, s), 1.85 (3 H, d, J = 12.90 Hz), 1.27 (4 H, d, J = 15.05 Hz), 1.06 (9 H, s), 1.01 (1 H, s), 0.96-0.75 (4
 20 H, m). *m/z* = 1011.2 [M+1].

**Example 54: *tert*-Butyl [(1'*R*,2*S*,6*S*,12*Z*,13*aS*,14*aR*,16*aS*)-1'-hydroxy-9'-methoxy-14a-}[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-
 25 a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-*c*]quinolin]-6-yl]carbamate (I-54);** and

**Example 55: *tert*-Butyl [(1'*S*,2*S*,6*S*,12*Z*,13*aS*,14*aR*,16*aS*)-1'-hydroxy-9'-methoxy-14a-}[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-
 a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-*c*]quinolin]-6-yl]carbamate (I-55)**



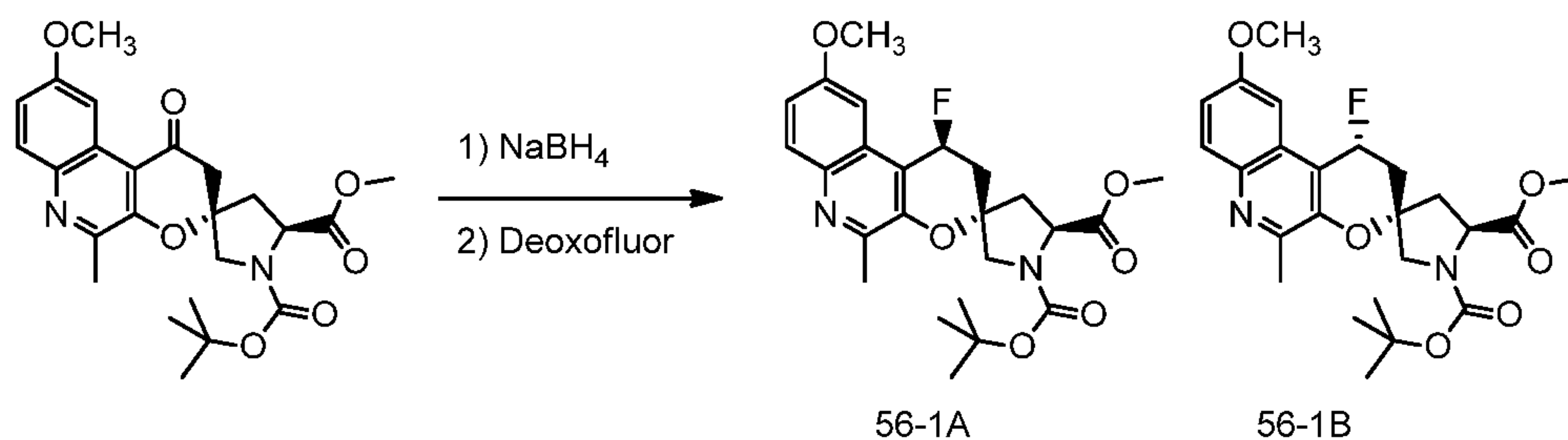
A solution of the product of Examples 52 and 53, Step 1 (250 mg, 0.341 mmol) and CDI (83 mg, 0.512 mmol) in THF (4.5 ml) was stirred in an oil-bath kept at 70°C for 3h, then cooled to RT. To this was added 1-methylcyclopropane-1-sulfonamide (92 mg, 0.682 mmol) and DBU in THF (1 ml) (0.853 ml, 0.853 mmol), and the mixture was stirred in an oil-bath kept at 46°C for 2.2h. The reaction mixture was diluted with EtOAc (40 ml), washed with aq. NH₄Cl (2x 4 ml), brine, dried over MgSO₄, filtered, concentrated. The residue was purified by column chromatography on silica gel (40 g, gold column, dry loading), eluting with 100% hexane for 400 ml, gradient to 60% of acetone to give the mixture of I-54 and I-55 along with a mixture of bis-sulfonamides. The mixture of I-54 and I-55 were separated by HPLC (C18, 19x150 mm; eluting with MeCN/water + 0.1% formic acid (gradient 50% of MeCN to 100% MeCN).

Example 54: ¹H NMR (500 MHz, CDCl₃) δ (ppm): 10.31-10.18 (1 H, m), 8.04 (1 H, d, J = 9.20 Hz), 7.38 (1 H, s), 7.32 (2 H, t, J = 10.07 Hz), 5.71 (1 H, d, J = 9.91 Hz), 5.37 (1 H, s), 5.23 (1 H, d, J = 8.49 Hz), 4.98 (1 H, t, J = 9.48 Hz), 4.50 (2 H, d, J = 11.01 Hz), 4.36 (1 H, s), 4.15 (1 H, q, J = 7.20 Hz), 4.01 (3 H, s), 3.89-3.76 (1 H, m), 2.72 (2 H, s), 2.57 (6 H, s), 2.51-2.37 (4 H, m), 2.07 (1 H, s), 1.93-1.82 (3 H, m), 1.72 (1 H, d, J = 11.63 Hz), 1.41-1.22 (6 H, m), 1.03 (1 H, s), 0.80 (2 H, s), 0.10 (1 H, s). *m/z* = 850.3 [M+1].

Example 55: ¹H NMR (500 MHz, CDCl₃) δ (ppm): 10.23 (1 H, s), 8.03 (1 H, d, J = 9.16 Hz), 7.30 (3 H, d, J = 4.81 Hz), 7.09 (1 H, s), 5.76 (1 H, q, J = 8.88 Hz), 5.40 (1 H, s), 5.34 (1 H, d, J = 8.56 Hz), 5.05 (1 H, t, J = 9.36 Hz), 4.70 (1 H, t, J = 8.17 Hz), 4.56 (1 H, d, J = 12.07 Hz), 4.24-4.11 (2 H, m), 3.98 (3 H, s), 3.86 (1 H, d, J = 12.06 Hz), 2.79 (4 H, s), 2.69-2.54 (4 H, m), 2.50 (2 H, s), 2.37 (1 H, q, J = 8.64 Hz), 2.08 (1 H, s), 1.95 (1 H, t, J = 6.99 Hz), 1.91-1.81 (4 H, m), 1.37 (2 H, s), 1.38-1.26 (8 H, m), 1.21 (9 H, s), 0.98-0.81 (4 H, m), 0.10 (1 H, s). *m/z* = 850.3 [M+1].

Example 56: *tert*-Butyl ((1'*R*,2*S*,6*S*,13*aS*,14*aR*,16*aS*,*Z*)-1'-fluoro-9'-methoxy-5'-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13*a*,14,14*a*,15,16,16*a*-hexadecahydro-1*H*-spiro[cyclopropa[e]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-*c*]quinolin]-6-yl)carbamate (I-56)

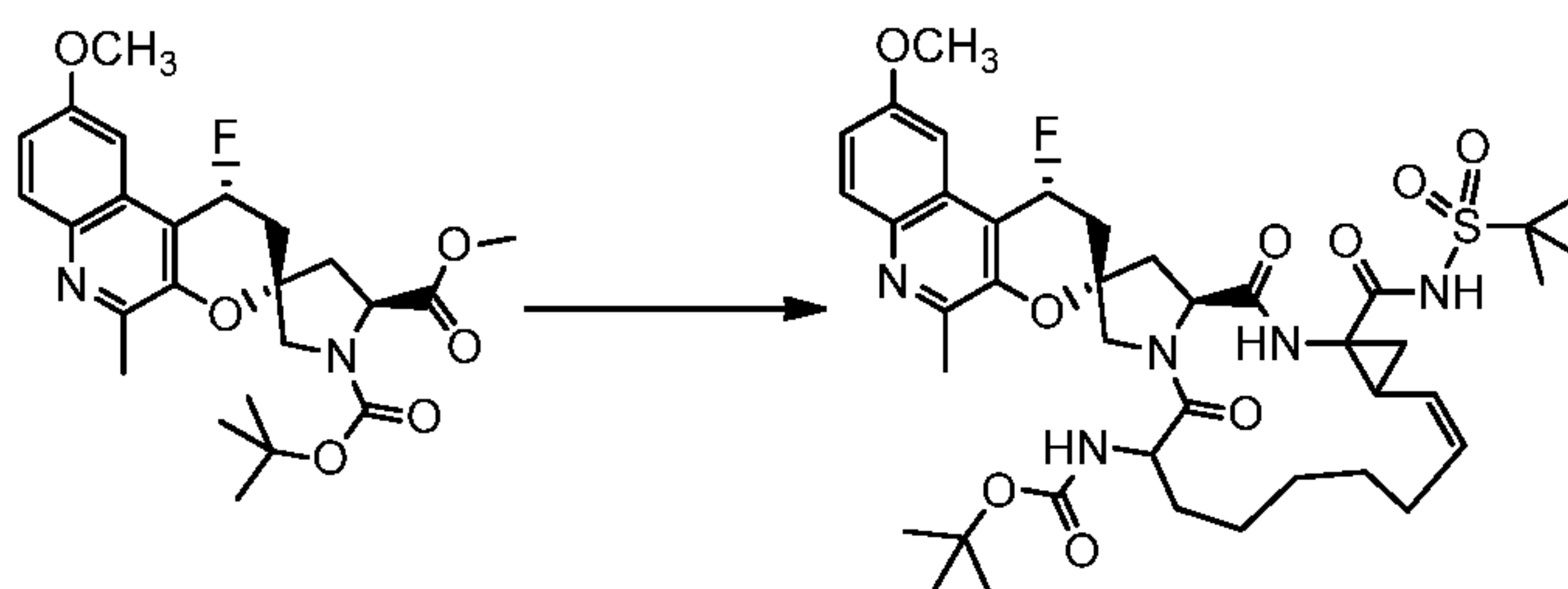
5 Step 1



To a solution of compound 9-4A prepared by Example 9, Steps 1-4 (1.5 g, 3.29 mmol) in MeOH (10 ml) and THF (10 ml) at 0°C was added NaBH₄ (0.124 g, 3.29 mmol). The mixture was stirred at 0°C for 10 min then quenched by the addition of aq. NH₄Cl. The slurry
10 was extracted 3x with EtOAc, and the combined organic layer was washed with brine, dried over MgSO₄, filtered and evaporated to dryness to give a mixture of diastereomeric alcohols. The crude products were azeotroped with toluene and used as such.

To a solution of the crude mixture (1508 mg, 3.29 mmol) in DCM (20 ml) at 0°C was added DEOXOFLUOR (0.607 ml, 3.29 mmol). The ice-bath was removed, and the mixture
15 was stirred at RT for 2.5h. The reaction mixture was stirred with aq. NaHCO₃, and the organic layer was separated. The aq. phase was extracted 2x with DCM. The combined organic layer was washed with brine, dried over MgSO₄, filtered, concentrated and purified by chromatography eluting with 0-40% EtOAc-hexanes to give 560 mg of 56-1A and 450 mg of 56-1B. LC-MS m/e = 461.2 (MH⁺) for 56-1A. LC-MS m/e = 461.2 (MH⁺) for 56-1B.

20 Step 2

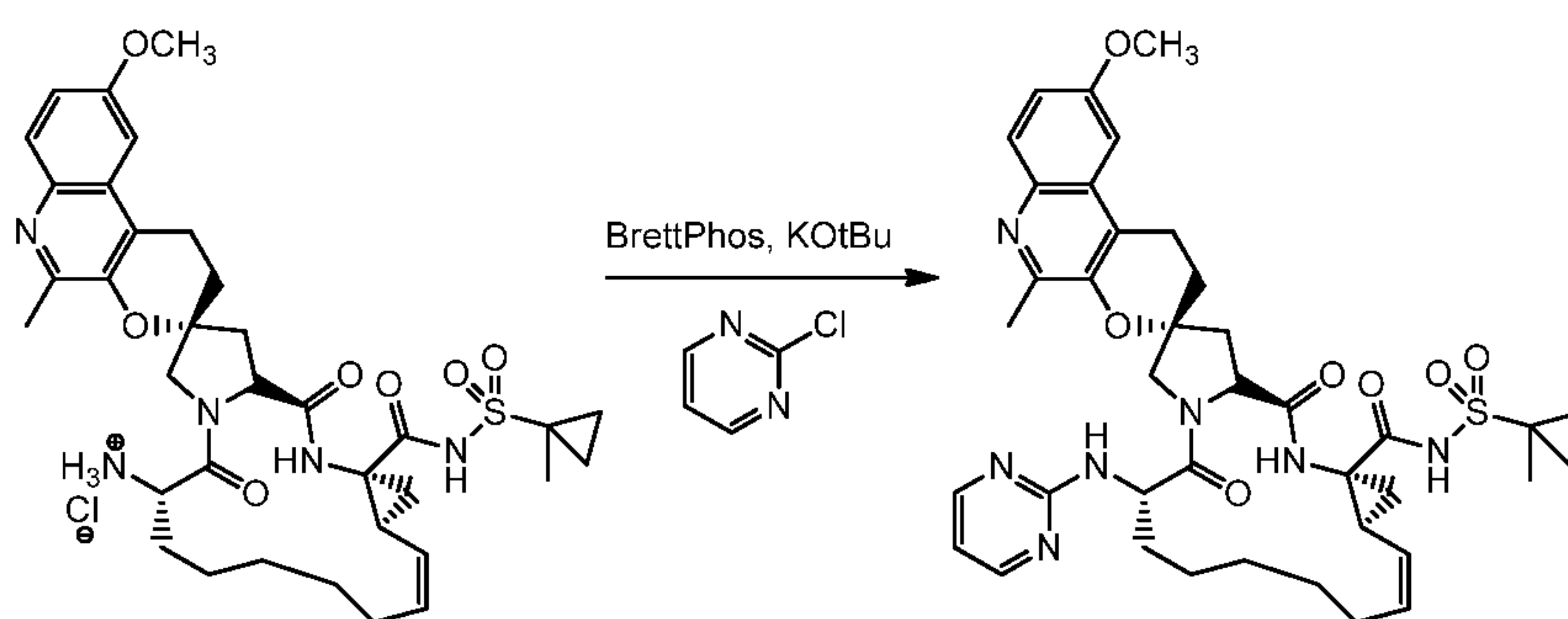


Compound 56-1B was converted to I-56 using a procedure similar to the procedures of Example 9. ¹H NMR (400 MHz, acetone-d₆) 10.47 (s, 1H), 8.30 (s, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.37 (s, 1H), 7.20 (d, J = 9.2 Hz, 1H), 6.36 (s, 1H), 6.23 (s, 1H), 6.18 (d, J = 8.0

Hz, 1H), 5.72 (q, J = 8.2 Hz, 1H), 5.00 (t, J = 9.2 Hz, 1H), 4.72 (d, J = 10.8 Hz, 1H), 4.63-4.59 (m, 1H), 4.26 (t, J = 8.0 Hz, 1H), 4.00 (d, J = 10.8 Hz, 1H), 3.96 (s, 3H), 3.75 (s, 3H), 2.94-2.55 (m), 2.45 (s, 3H), 2.28-2.22 (m), 2.07-1.88 (m), 1.72-1.68 (m, 1H), 1.61-1.30 (m), 0.87 (m, 2H). MS m/e = 798.2 (MH⁺).

5

Example 57: (2R,6S,13aS,14aR,16aS,Z)-9'-methoxy-5'-methyl-N-((1-methylcyclopropyl)sulfonyl)-5,16-dioxo-6-(pyrimidin-2-ylamino)-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a-carboxamide (I-57)



10

To a solution of (2R,6S,12Z,13aS,14aR,16aS)-9'-methoxy-5'-methyl-14a-[[[(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-aminium chloride (obtained by treatment of I-9 with 4 m HCl in dioxane for 30 min and concentration *in vacuo*; 50 mg, 0.070 mmol) in dioxane (500 μl) was added chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2'-4'-6'-tri-*i*-propyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II) (BrettPhos indoline precatalyst, 11.15 mg, 0.014 mmol) sodium *tert*-butoxide (18.78 mg, 0.195 mmol) and 2-chloroquinoline (16 mg, 0.144 mmol), and the mixture heated to 80°C while stirring under N₂ overnight. The reaction mixture was filtered then purified by preparative HPLC Reverse phase (C-18), eluting with acetonitrile/water + 0.1% formic acid, to yield I-57 (7.4 mg, 9.76 μmol, 13.99% yield) as a off white solid.

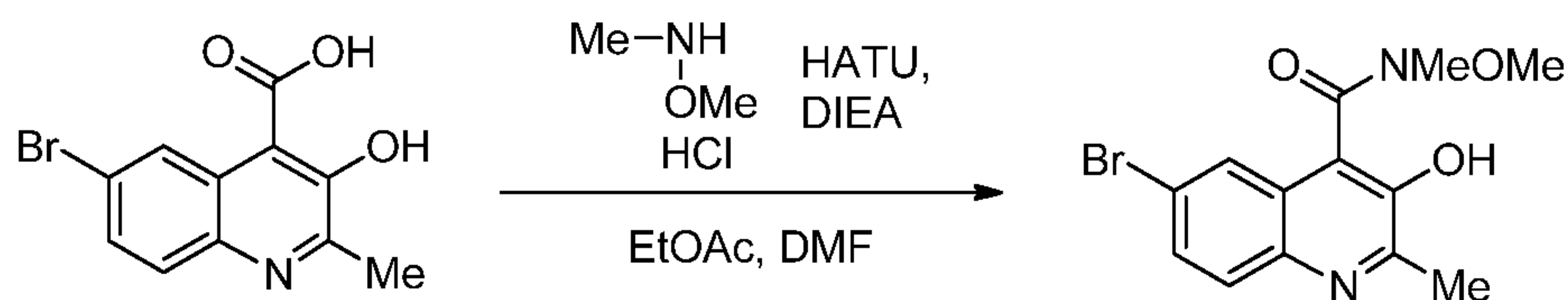
15

20

Example 58: *tert*-Butyl ((2R,6S,13aS,14aR,16aS,Z)-9'-hydroxy-5'-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-58)

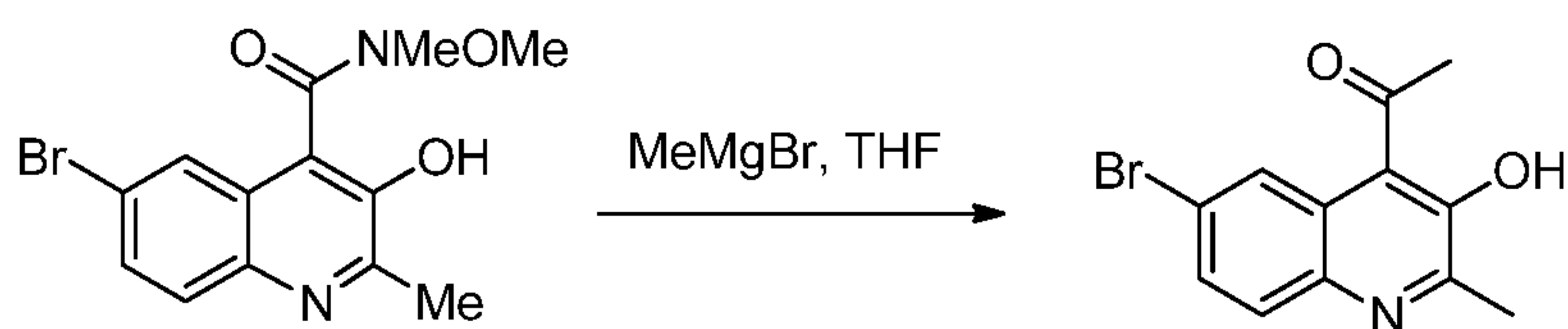
25

Step 1



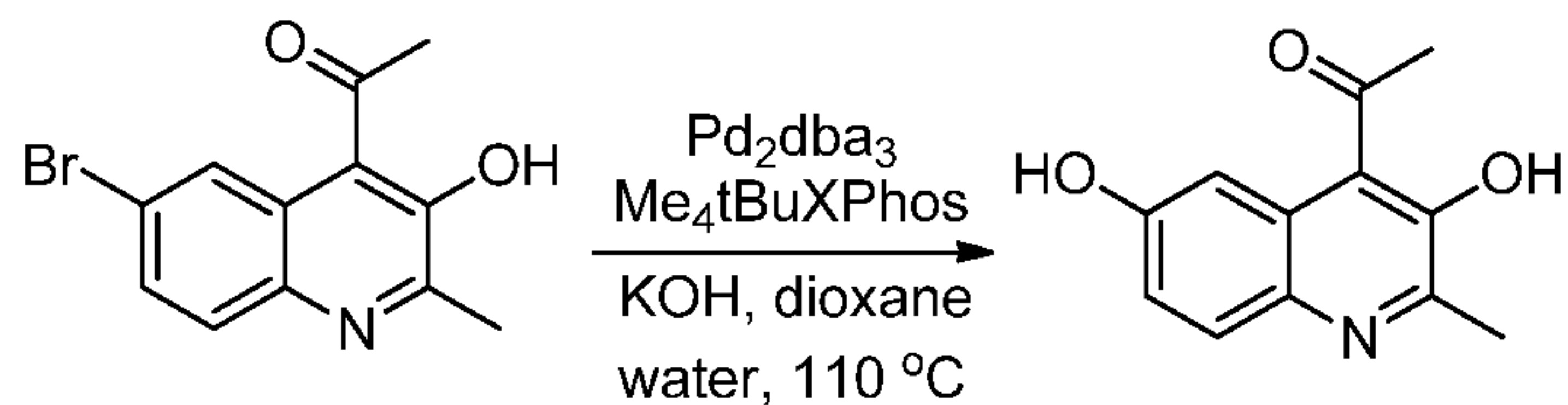
To a mixture of 6-bromo-3-hydroxy-2-methylquinoline-4-carboxylic acid (5.27 g, 18.68 mmol; prepared from 5-bromoindoline-2,3-dione using the procedure described in Step 1 for the synthesis of Example 1). N,O-dimethyl hydroxylamine hydrochloride (2.369 g, 24.29 mmol) and Hunig's base (6.04 g, 46.7 mmol) in EtOAc (72 ml) and DMF (8.00 ml) was added HATU (10.66 g, 28.0 mmol) at RT. The reaction was heated to 50°C and stirred 16h. LC-MS indicated complete conversion to a product with desired mass. The reaction was quenched with water and extracted several times with EtOAc. The organics were washed with water and brine, dried (Na₂SO₄) and concentrated. Purification by silica gel column chromatography (ISCO 220 g column, 0-30% acetone in hexane) provided the desired compound (4.25 g, 13.07 mmol, 70.0 % yield) as a yellow solid.

Step 2



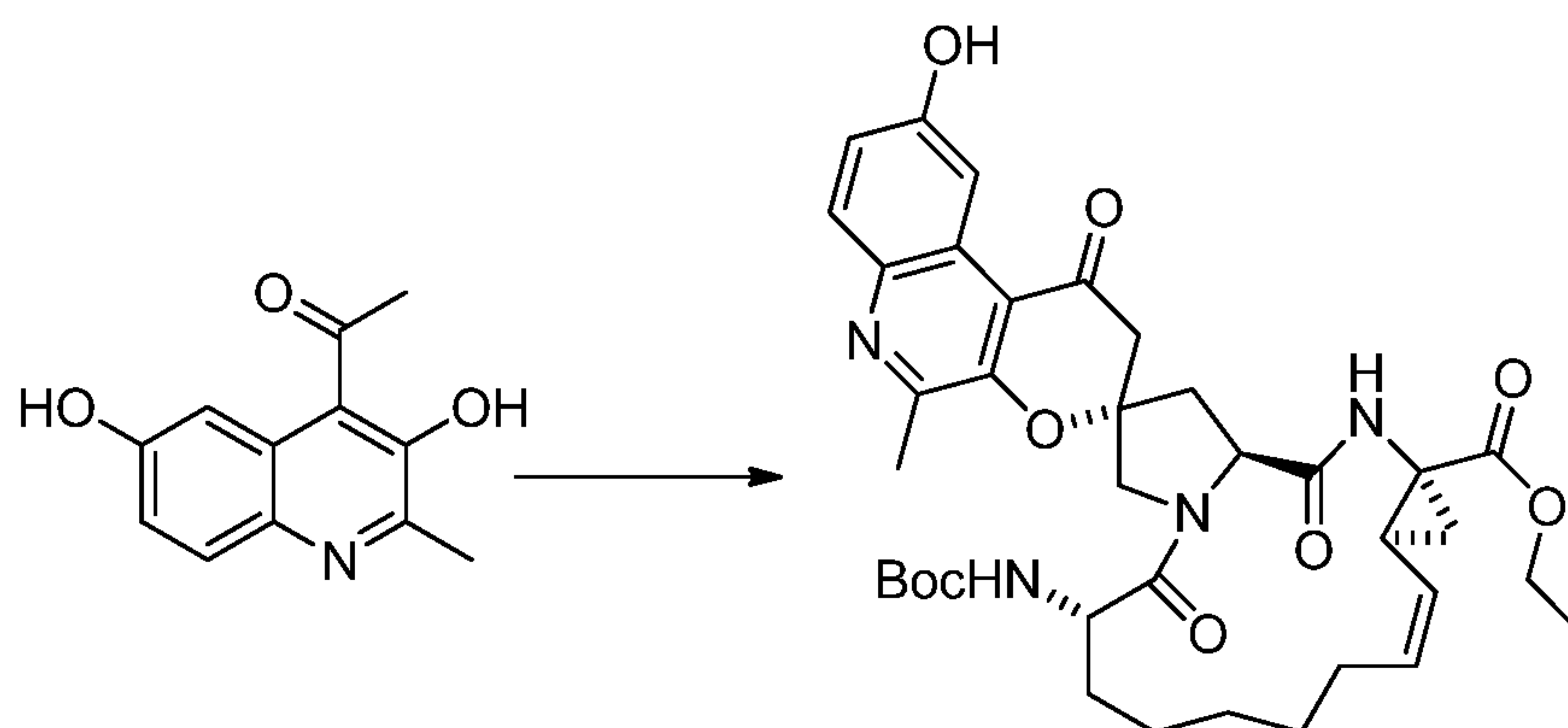
To a solution of the product obtained from Step 1 (4.2 g, 12.92 mmol) in THF (120 ml) at 0°C was added MeMgBr (12.92 ml, 38.8 mmol; 3 m in ether), and the reaction was stirred overnight after gradually allowing it to come to RT. LC-MS indicated approximately 75% conversion to the desired product. After cooling, the reaction to 0°C, 1.0eq. of MeMgBr was added; no change after 2h. The reaction was carefully quenched with sat. aq. NH₄Cl solution and extracted with EtOAc. The combined organic fractions were, dried (MgSO₄), filtered, concentrated under *vacuo* and purified by column chromatography (0-50% EtOAc in hexane) to provide 1-(6-bromo-3-hydroxy-2-methylquinolin-4-yl)ethanone (2.5 g, 8.92 mmol, 69.1% yield) as a yellow solid.

Step 3



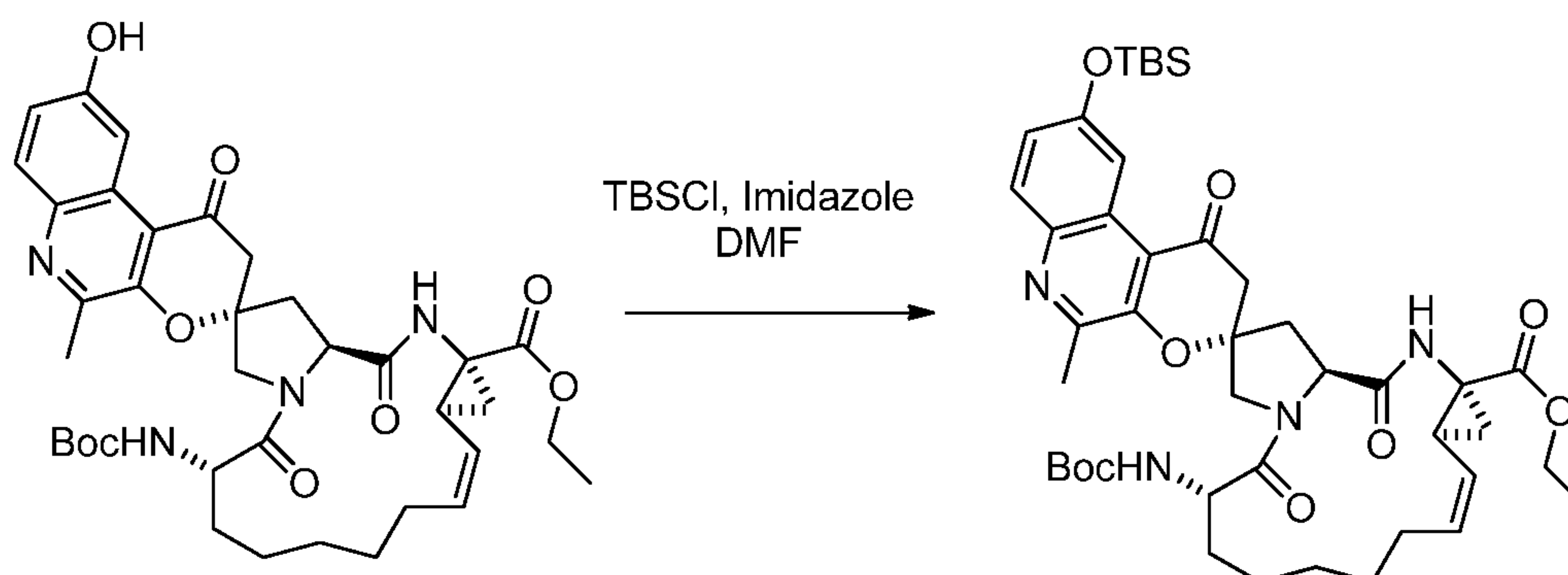
In a sealed tube were placed 1-(6-bromo-3-hydroxy-2-methylquinolin-4-yl)ethanone (2.0 g, 7.14 mmol, obtained from Step 2), KOH (1.202 g, 21.42 mmol), Pd₂(dba)₃ (0.327 g, 0.357 mmol), Me₄tBuXPhos [CAS: 857356-94-6; bis(1,1, dimethylethyl[3,4,5,6-tetramethyl-2',4',6'-tris(1-methylethyl)[1,1'-biphenyl]-2-yl]phosphine (0.343 g, 0.714 mmol),
 5 dioxane (20 ml) and degassed water (20 ml). The reaction was heated at 110°C for 2h, at which stage LC-MS indicated complete conversion to the desired product. After cooling to RT, the reaction was transferred into a beaker and carefully acidified with 1N HCl, stirred for 5 min and then carefully basified by addition of solid NaHCO₃ (effervesence observed - slow addition is crucial). The mixture was then extracted several times with EtOAc until all the product was in
 10 the organic fractions. The combined organics were washed with brine, dried over Na₂SO₄ and concentrated. Purification by column chromatography (0-40% acetone in hexane) provided the product of Step 3 (1.0 g, 64.5% yield).

Step 4



15 The product of Step 4 was prepared from the product of Step 3 using the procedures described in Example 30, Step 5.

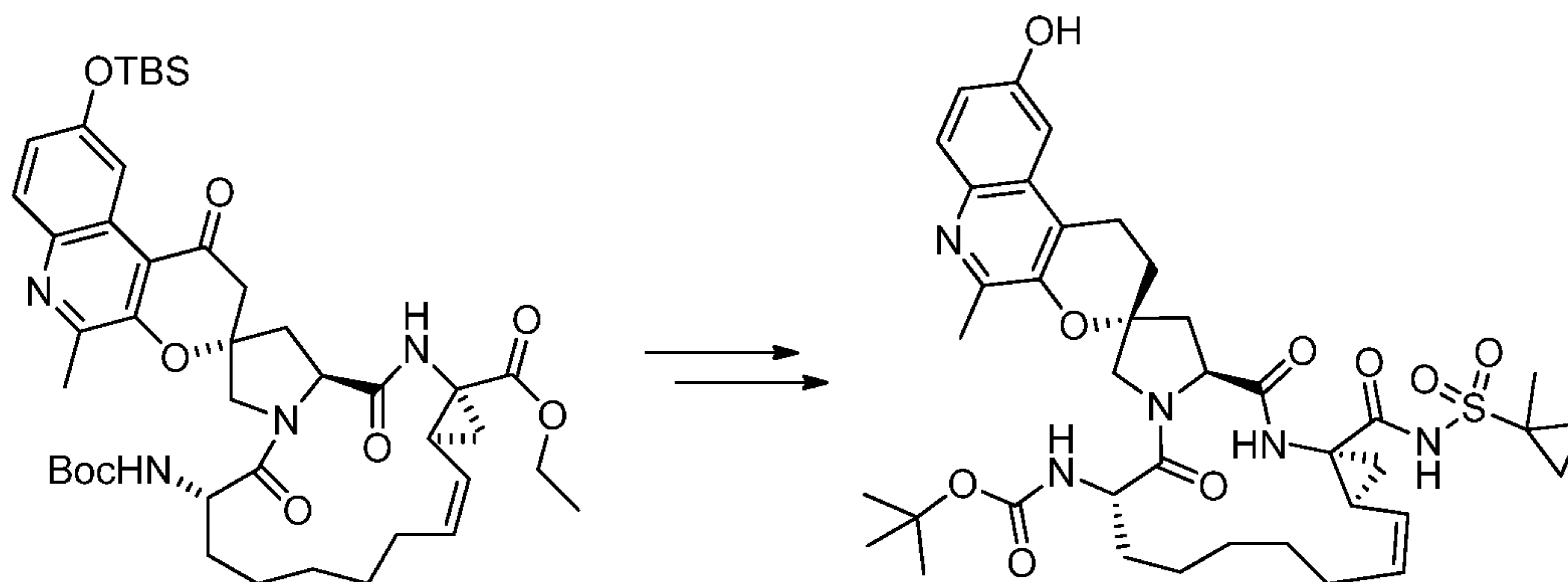
Step 5



20 To a solution of the product of Step 4 (230 mg, 0.333 mmol) in DMF (3330μl) was added imidazole (68.0 mg, 0.999 mmol) followed by *tert*-butyldimethylchlorosilane (100

mg, 0.666 mmol). The reaction was stirred overnight under N₂ at RT and then diluted with EtOAc and washed with water and brine. The combined organic fractions were dried (MgSO₄), concentrated and purified by column chromatography (0-100% EtOAc in hexane) to provide the product of Step 5 (250 mg, 0.311 mmol, 93% yield).

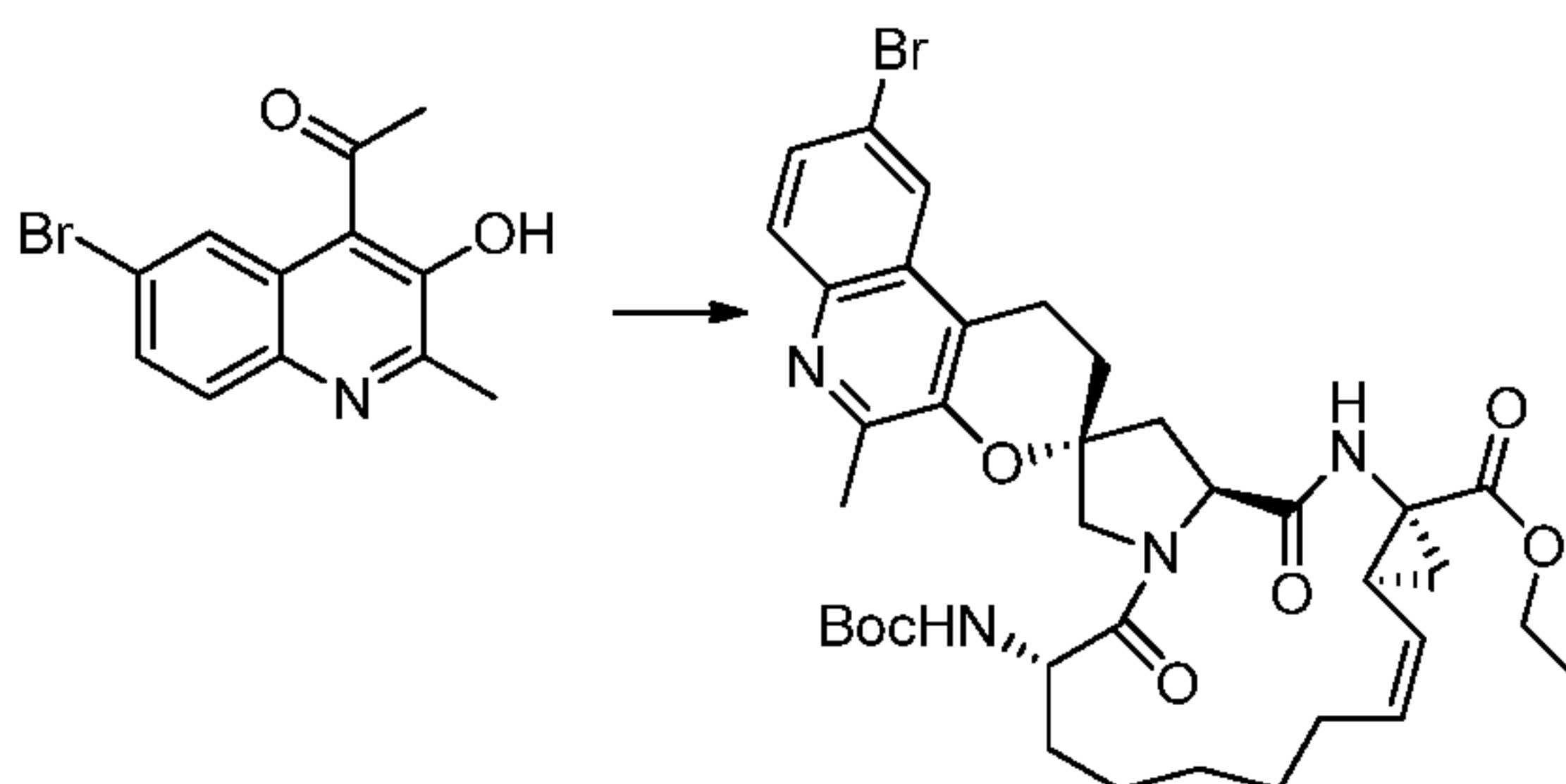
5 Step 6



The product of Step 5 was converted into I-58 using the procedures described in Example 30, Steps 6-9.

10 **Example 59: *tert*-Butyl ((2R,6S,13aS,14aR,16aS,Z)-9'-cyano-5'-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-59)**

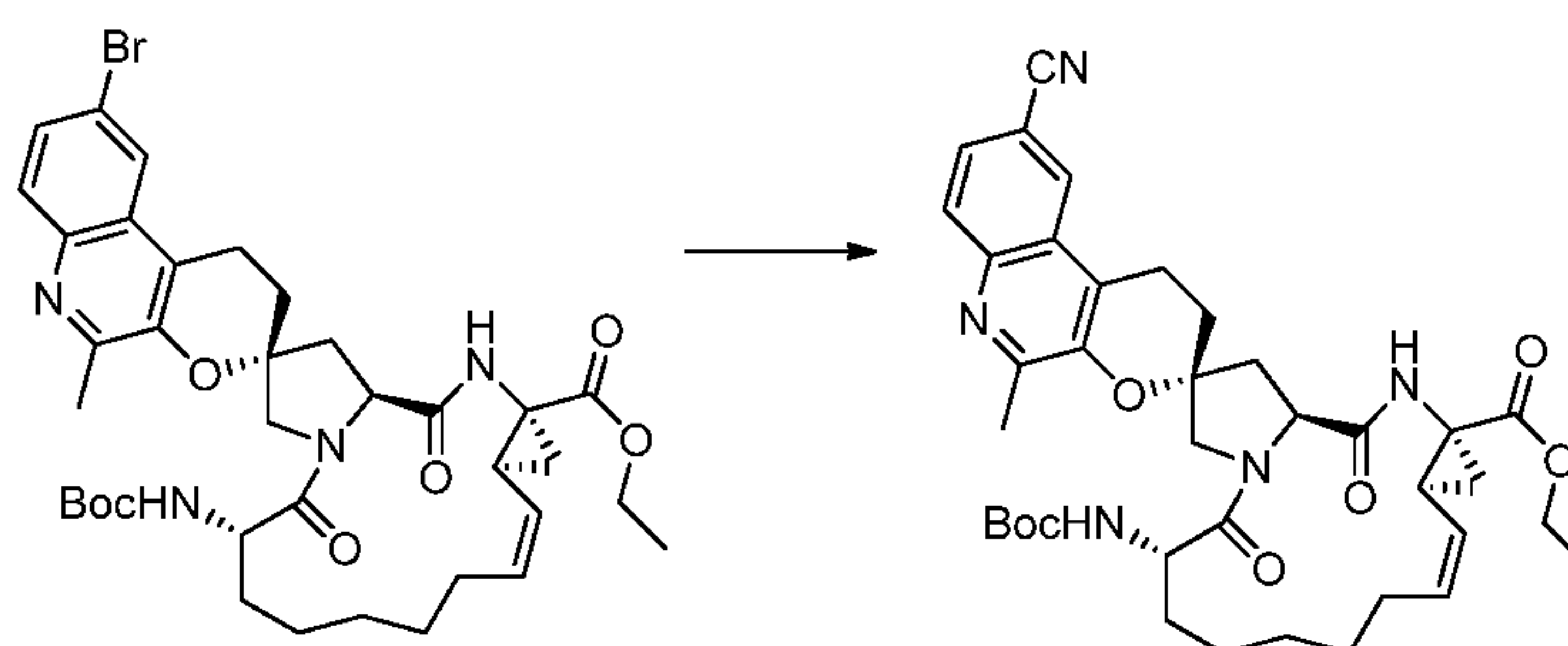
Step 1



15

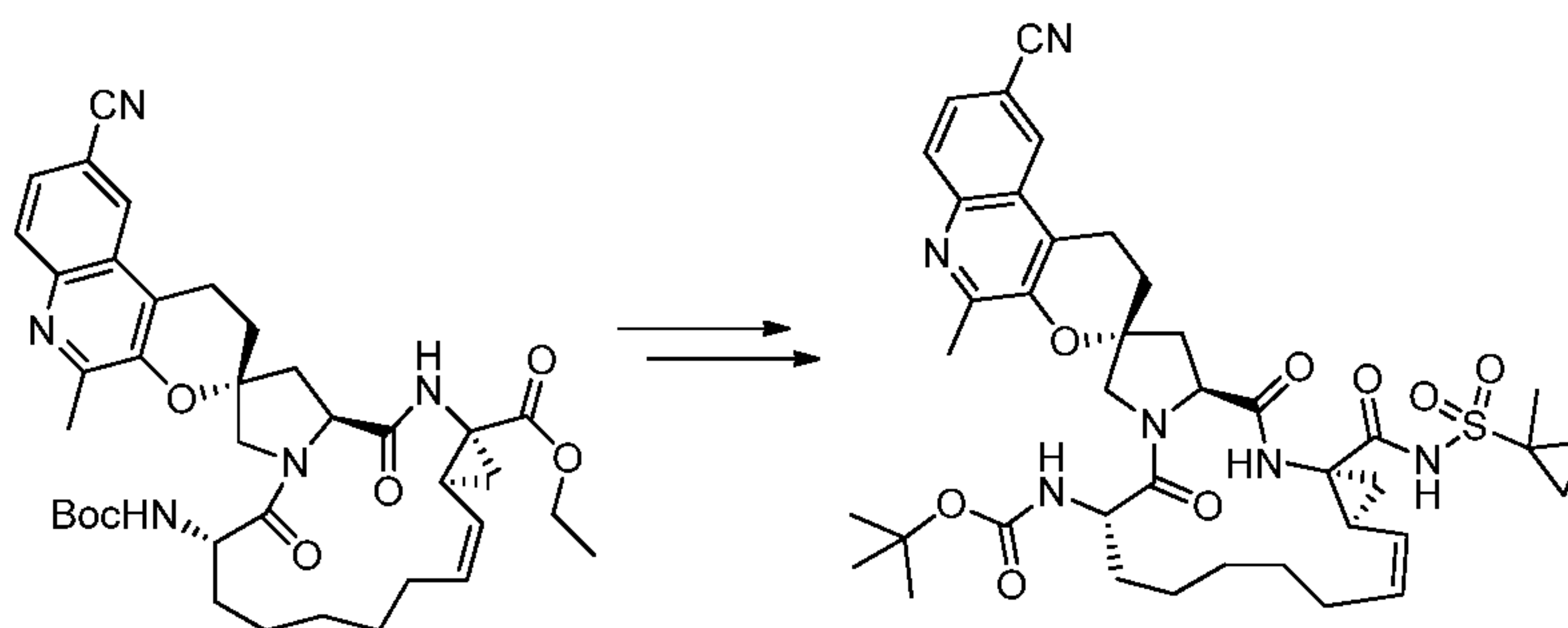
The product of Step 1 was prepared from *i*-(6-bromo-3-hydroxy-2-methylquinolin-4-yl)ethanone using the procedures described in Example 30, Steps 5-8

Step 2



To a solution of the product of Step 1 (47 mg, 0.064 mmol) in DMF (1 mL) was added zinc cyanide (9.70 mg, 0.083 mmol) followed by Pd(Ph₃P)₄ (11.01 mg, 9.53 μmol). The reaction was stirred at 100°C for 16h, cooled to RT and then diluted with EtOAc and washed with water and brine. The combined organic fractions were dried (MgSO₄), concentrated and purified by column chromatography (0-100% EtOAc in hexane) to provide the product of Step 2 (37 mg, 0.054 mmol, 85% yield).

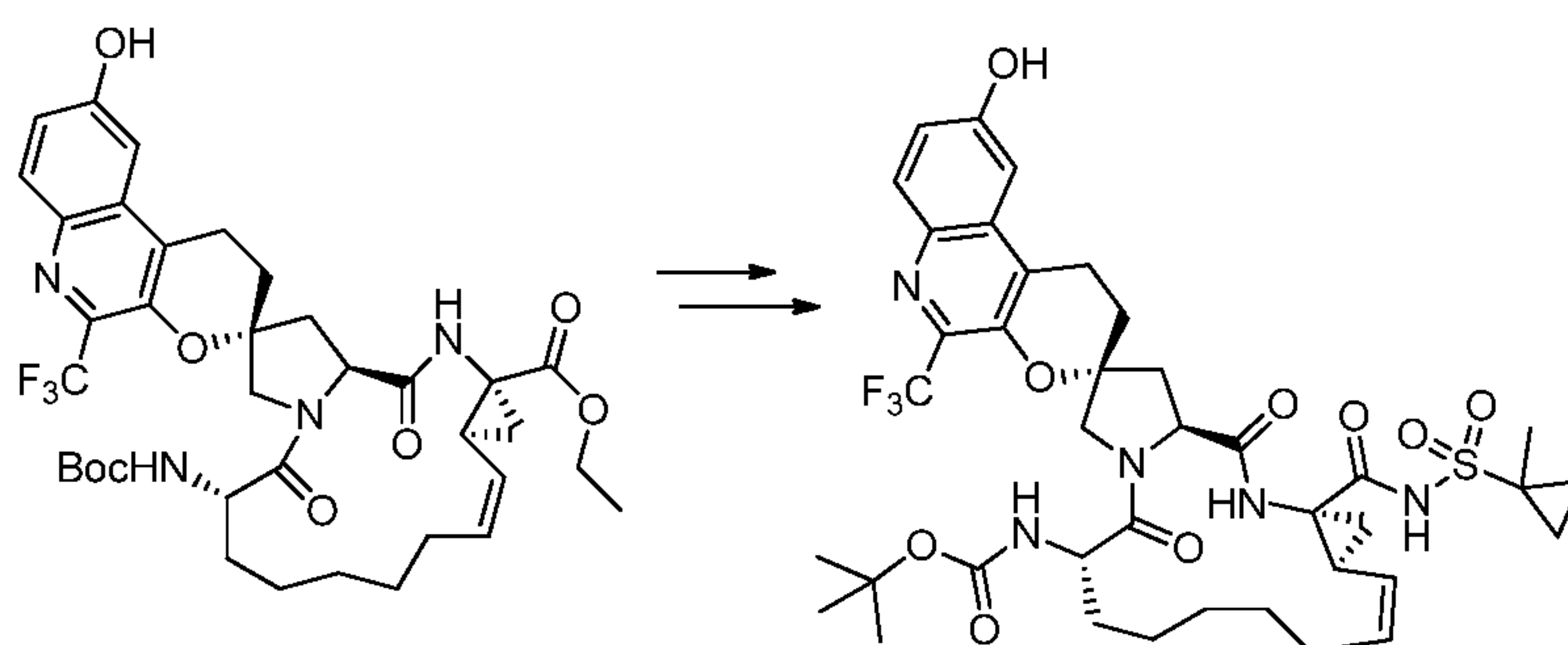
Step 3



The product of Step 2 was converted into I-59 using the procedures described in Example 30, Step 9.

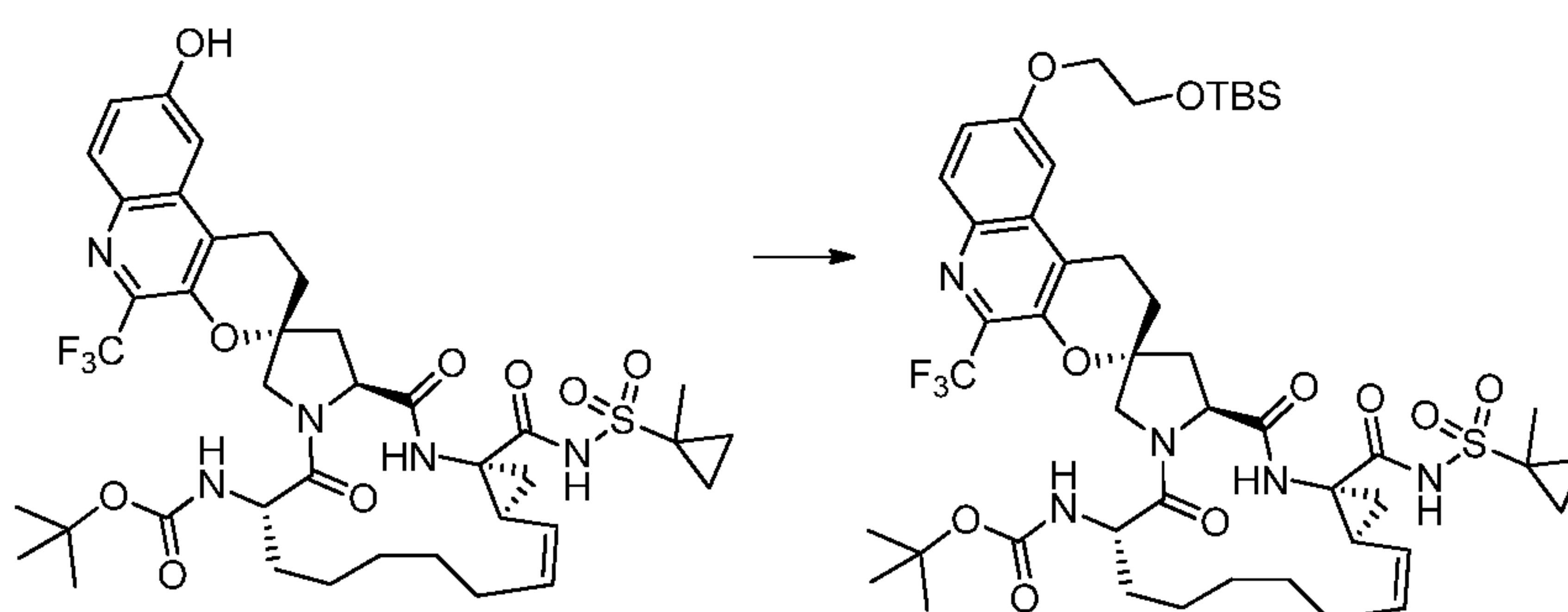
Example 60: *tert*-Butyl ((2R,6S,13aS,14aR,16aS,Z)-9'-(2-hydroxyethoxy)-14a-(((1-methyl cyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13a, 14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4] diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-60)

Step 1



The product of Example 50, Step 1 was converted into the product of Step 1 by using the procedures described in Example 30, Step 9.

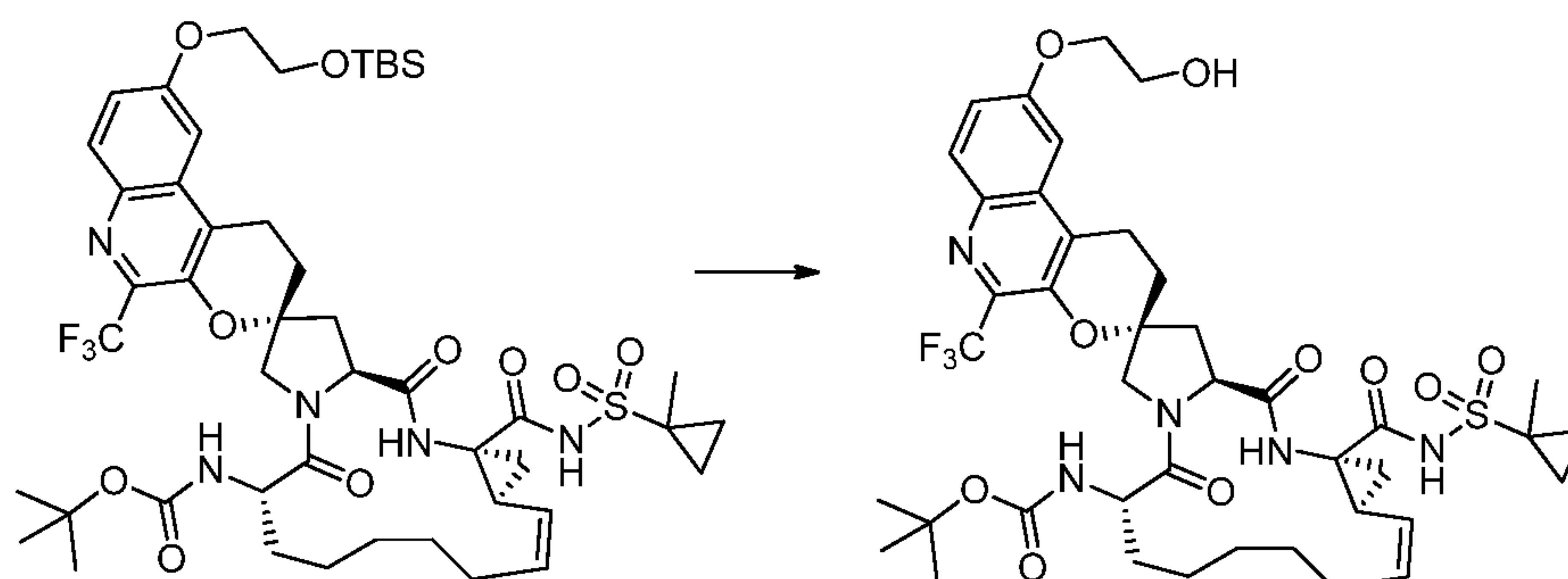
Step 2



5

To a solution of the product of Step 1 (205 mg, 0.250 mmol) in DMF (2.500 mL) was added (2-bromoethoxy)(*tert*-butyl)dimethylsilane (90 mg, 0.375 mmol) followed by Cs₂CO₃ (163 mg, 0.500 mmol) at RT. The reaction was stirred at 65°C for 8h and then allowed to cool to RT. After diluting with EtOAc, the reaction was washed with water and brine. The organic fraction was dried (Na₂SO₄), filtered, concentrated and purified (ISCO, 24 g silica gel column, 0-60% EtOAc in hexane) to provide the product of Step 2 (180 mg, 0.184 mmol, 73.6% yield).

Step 3

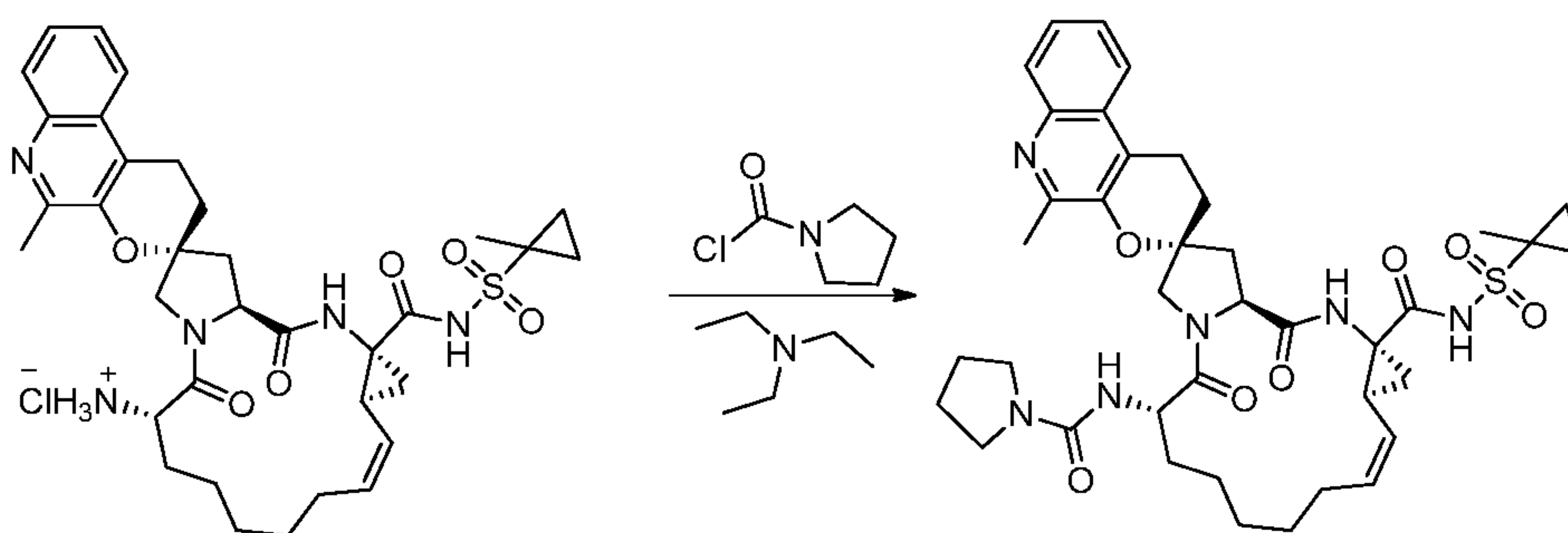


To a solution of the product of Step 2 (175 mg, 0.179 mmol) in THF (4 mL) was added TBAF (0.53 mL, 0.537 mmol) at RT. The reaction was stirred under an atmosphere of N₂ for 1h, at which stage LC-MS indicated complete conversion to the desired product. The

reaction was quenched with sat. aq. NH₄Cl solution and washed with EtOAc. The organic fractions were combined, dried (Na₂SO₄), filtered and concentrated to give an oily residue, which was purified by silica gel chromatography (24 g REDISEP column, 0-80% acetone in hexane) to provide I-60 (145 mg, 0.168 mmol, 94% yield) as a white solid.

5

Example 61: (2R,6S,12Z,13aS,14aR,16aS)-5'-methyl-N-[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-6-[(pyrrolidin-1-ylcarbonyl)amino]-1,1',2',6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a(5H)-carboxamide (I-61)



10

To a suspension of the product of Example 47, Step 10 (11 mg, 0.016 mmol) in DCM (0.5 ml) were added Et₃N (0.011 ml, 0.080 mmol) and 1-pyrrolidinecarbonyl chloride (5.31 μl, 0.048 mmol). The mixture was stirred at RT overnight. It was diluted with DCM, washed with aq. NH₄Cl, concentrated and separated by preparative thin layer chromatography with 5% MeOH/DCM to give I-61 (10 mg, 0.013 mmol, 84% yield) as a white solid. LC-MS MH⁺: 747.

15

Example 62: tert-Butyl ((2S,6S,13aS,14aR,16aS,Z)-9'-methoxy-1'-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-5'-(trifluoromethyl)-3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-tetradecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-62);

20

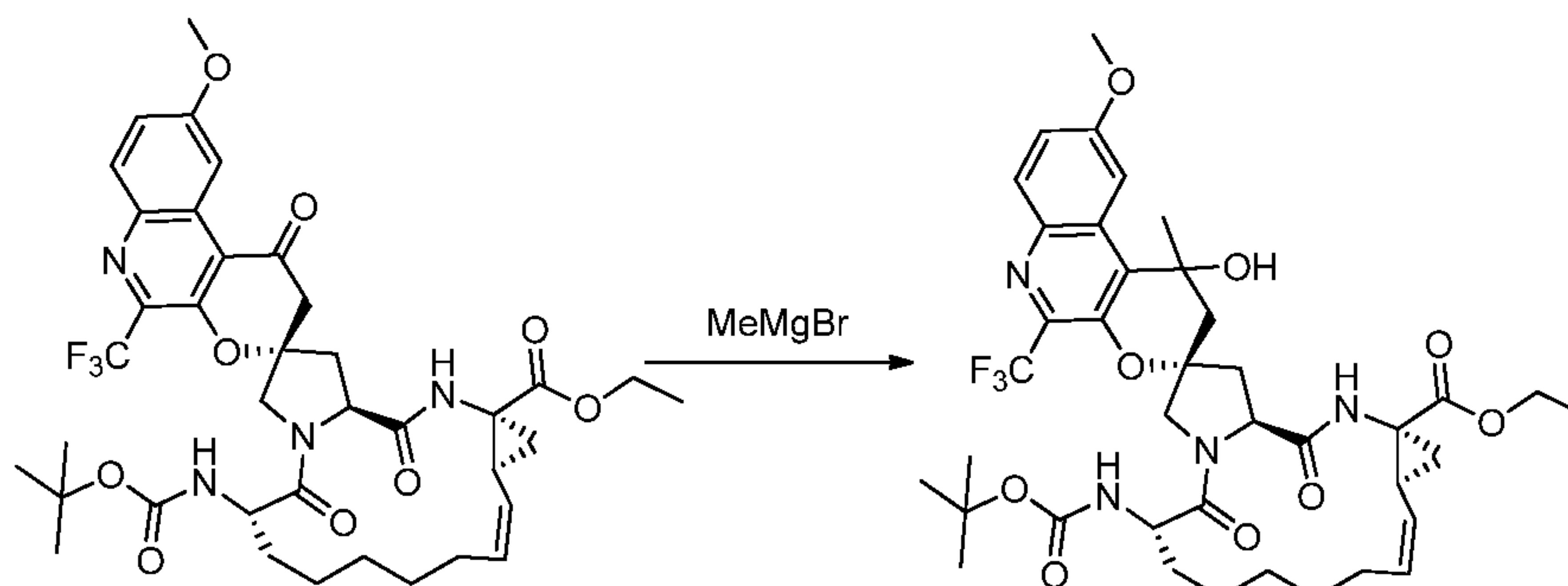
Example 63: tert-Butyl ((1'R,2S,6S,13aS,14aR,16aS,Z)-1'-fluoro-9'-methoxy-1'-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-63); and

25

Example 64: tert-Butyl ((1'S,2S,6S,13aS,14aR,16aS,Z)-1'-fluoro-9'-methoxy-1'-methyl-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,

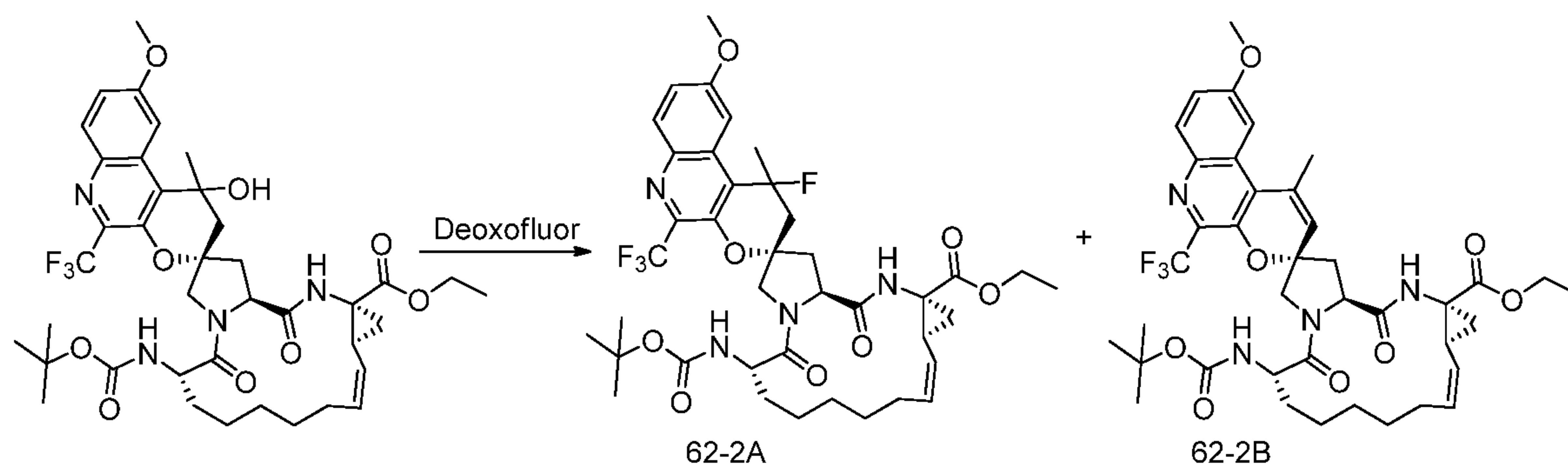
9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-64)

Step 1



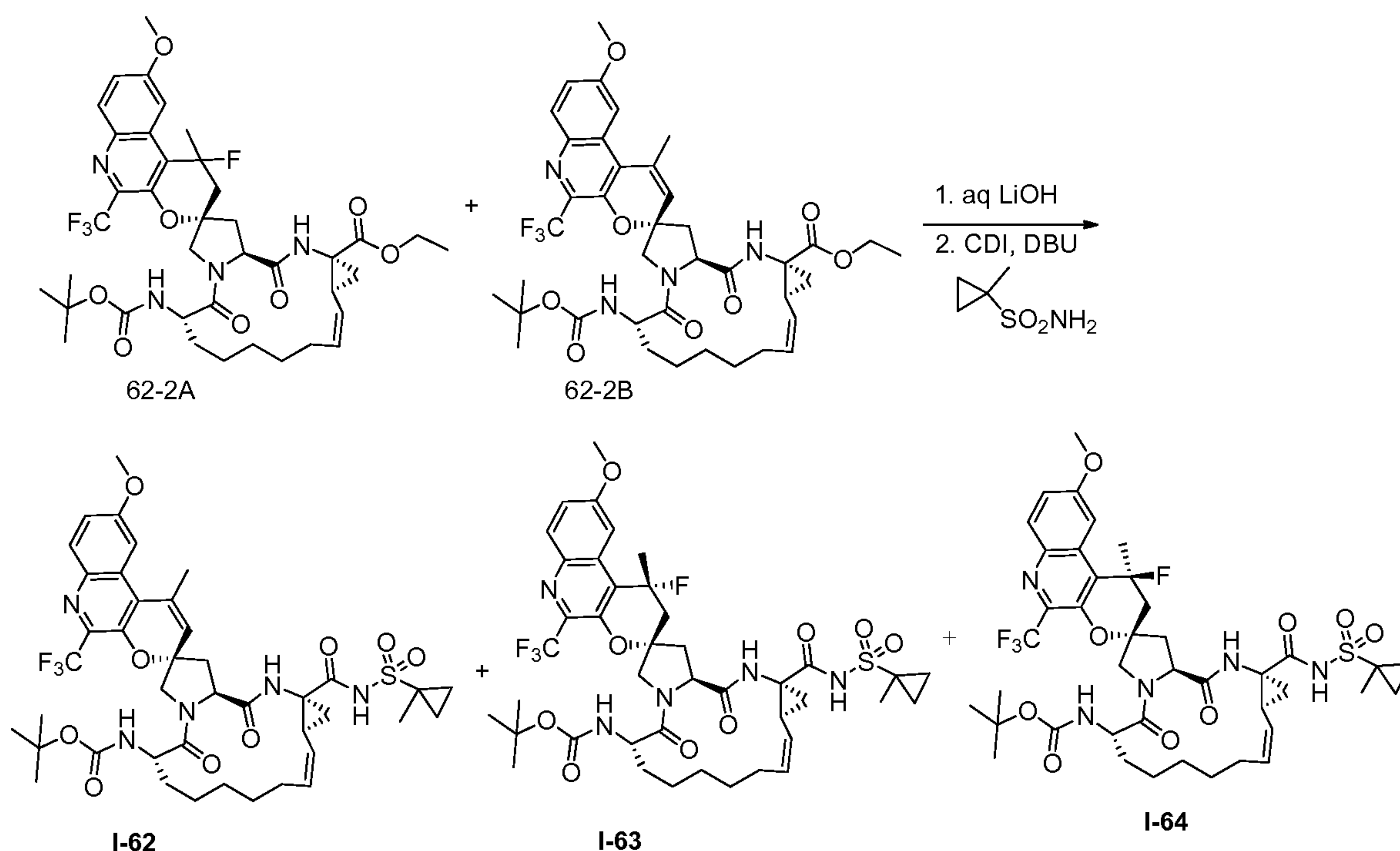
- 5 To the solution of (2S,6S,13aS,14aR,16aS,Z)-ethyl 6-((*tert*-butoxycarbonyl amino)-9'-methoxy-1',5,16-trioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15, 16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a-carboxylate (2923 mg, 3.85 mmol) in THF(26 ml) was added 1.4 m of MeMgBr solution in THF (11.01 ml, 15.41 mmol) at -25°C and stirred at -25°C for 20 min.
- 10 TLC and LC-MS indicated that the major was product (about 50%) and starting material. Then the reaction was quenched with 1N HCl to pH=5-6 (about 12 ml 1N HCl), and diluted with EtOAc (40 ml). The layers were separated, and the aq. layer was extracted again with EtOAc (25 ml x2). The organic layers were combined and washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel
- 15 (120 g, gold column), eluting with 100% hexane for 400 ml, gradient to 35% of acetone to give 1430 mg of starting material and 1130 mg of (2S,6S,13aS,14aR,16aS,Z)-ethyl 6-((*tert*-butoxycarbonyl)amino)-1'-hydroxy-9'-methoxy-1'-methyl-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a-carboxylate as a light yellow
- 20 solid. $m/z=775.4$ (M+1)

Step 2



To a solution of the product of Step 1 (731 mg, 0.143 mmol) in DCM (18 ml) at 0°C was added DEOXOFLUOR (0.209 ml, 1.132 mmol) and EtOH (0.013 ml), and the mixture was stirred at 0°C for 30 min. The reaction was quenched with aq. NaHCO₃ (15 ml). The layers were separated, and the aq. layer was extracted again with DCM (3x30 ml). The combined organic layer were dried over MgSO₄, filtered, evaporated to dryness under reduced pressure. The residue was purified by column chromatography using silica gel column (80 g, gold column), eluting with 100% hexane for 400 ml, gradient to 60% of EtOAc to give the mixture of (2S,6S,13aS,14aR,16aS,Z)-ethyl 6-((*tert*-butoxycarbonyl)amino)-1'-fluoro-9'-methoxy-1'-methyl-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a-carboxylate ($m/z=777.3$ (M+1)) and (2S,6S,13aS,14aR,16aS,Z)-ethyl 6-((*tert*-butoxycarbonyl)amino)-9'-methoxy-1'-methyl-5,16-dioxo-5'-(trifluoromethyl)-3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-tetradecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a-carboxylate ($m/z=757.3$ (M+1)) as a white solid (the LC- MS indicate the ratio about 62-2A/62-2B = 4/1).

Step 3



The reaction mixture of 62-2A and 62-2B (275 mg, which about 80% of 62-2A and 20% of 62-2B) was suspended in THF (4.5 ml), MeOH (1.5 ml) and H₂O (1.1 ml) and the LiOH (56.0 mg, 2.336 mmol) was added. It was stirred at RT for 7.5 h. The LC-MS shows the hydrolysis was complete. It was acidified to pH = 2~3 with 1N HCl solution (about 1.9 ml of 1N HCl) at 0°C, and diluted with EtOAc (30 ml). The layers were separated, and the aq. layer was extracted again with EtOAc (30 mlx1). The organic layers were combined and washed with brine (4x6 ml), dried over MgSO₄, filtered, and concentrated *in vacuo*. The concentrated layer was azeotroped with toluene (2X) and kept under vacuum overnight to give 256 mg of the mixture of acids which were used without purification.

A reaction mixture of (2S,6S,13aS,14aR,16aS,Z)-6-((*tert*-butoxycarbonyl)amino)-1'-fluoro-9'-methoxy-1'-methyl-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a-carboxylic acid and (2S,6S,13aS,14aR,16aS,Z)-6-((*tert*-butoxycarbonyl)amino)-9'-methoxy-1'-methyl-5,16-dioxo-5'-(trifluoromethyl)-3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-tetradecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a-carboxylic acid (269 mg), CDI (114 mg, 0.704 mmol) in THF (4.5 ml) was stirred in an oil-bath at 70°C for 3h, then it was cooled to RT. To this reaction mixture was added 1-methylcyclopropane-1-sulfonamide (95 mg, 0.704 mmol) and DBU in THF (1 m) (0.932 ml, 0.932 mmol), and the mixture was stirred in an oil-bath at

46°C for 2.2h. The reaction mixture was diluted with EtOAc (40 ml), washed with aq. NH₄Cl (2x4 ml), brine, dried over MgSO₄, filtered, concentrated. The residue was purified by column chromatography on silica gel (40 g, gold column), eluting with 100% hexane for 200 ml, gradient to 40 % of acetone to give mixture of fluorides, which were separated by supercritical fluid chromatography to yield:

Example 62: ¹H NMR δ (ppm)(CHCl₃): 10.13 (1 H, s), 8.05 (1 H, d, J = 9.23 Hz), 7.49 (1 H, s), 7.37-7.26 (2 H, m), 6.95 (1 H, s), 5.91 (1 H, s), 5.75 (1 H, q, J = 8.80 Hz, 5.24 (1 H, s), 5.04 (1 H, t, J = 9.29 Hz), 4.61 (2 H, t, J = 13.23 Hz), 4.21 (1 H, s), 3.99 (3 H, s), 3.64 (1 H, d, J = 11.38 Hz), 2.80 (1 H, d, J = 12.09 Hz), 2.61 (1 H, s), 2.55 (3 H, s), 2.48 (1 H, d, J = 12.05 Hz), 2.39 (1 H, q, J = 8.72 Hz), 1.94 (3 H, s), 1.91-1.73 (4 H, m), 1.41 (1 H, s), 1.30 (18 H, d, J = 13.55 Hz), 1.18 (1 H, s), 1.12 (3 H, s), 0.95-0.80 (5 H, m). *m/z* = 846.3 (M+1).

Example 63: ¹H NMR δ (ppm)(CHCl₃): 10.01 (1 H, s), 8.07 (1 H, d, J = 9.18 Hz), 7.60 (1 H, s), 7.35 (1 H, d, J = 9.21 Hz), 7.30 (1 H, s), 6.85 (1 H, s), 5.72 (1 H, q, J = 8.82 Hz), 5.30 (1 H, d, J = 8.60 Hz), 5.00 (1 H, t, J = 9.35 Hz), 4.62 (1 H, d, J = 10.99 Hz), 4.47 (1 H, t, J = 8.33 Hz), 4.35 (1 H, t, J = 9.61 Hz), 4.01 (3 H, s), 3.85 (1 H, d, J = 11.10 Hz), 2.82 (1 H, dd, J = 21.99, 14.86 Hz), 2.66 (1 H, s), 2.66-2.55 (3 H, m), 2.55-2.40 (1 H, m), 2.37 (1 H, q, J = 8.72 Hz), 2.08 (1 H, s), 2.08-1.98 (2 H, m), 1.93-1.82 (4 H, m), 1.83-1.73 (4 H, m), 1.39 (9 H, s), 1.33 (5 H, s), 1.29 (3 H, s), 0.96-0.77 (4 H, m). *m/z* = 866.2 [M+1].

Example 64: ¹H NMR δ (ppm)(CHCl₃): 10.17 (1 H, s), 8.11-8.02 (1 H, m), 7.60 (1 H, s), 7.38-7.26 (2 H, m), 7.05 (1 H, s), 5.75 (1 H, q, J = 8.88 Hz), 5.08-5.00 (2 H, m), 4.68 (1 H, t, J = 8.43 Hz), 4.62-4.39 (4 H, m), 4.01 (4 H, s), 3.72 (1 H, d, J = 11.84 Hz), 2.84-2.51 (6 H, m), 2.41-2.29 (1 H, m), 2.13-1.98 (4 H, m), 1.95 (2 H, t, J = 7.37 Hz), 1.91-1.69 (7 H, m), 1.38 (3 H, d, J = 18.32 Hz), 1.31 (9 H, s), 1.24 (1 H, d, J = 7.55 Hz), 1.19 (9 H, s), 0.96-0.83 (6 H, m). *m/z* = 866.2 [M+1].

25

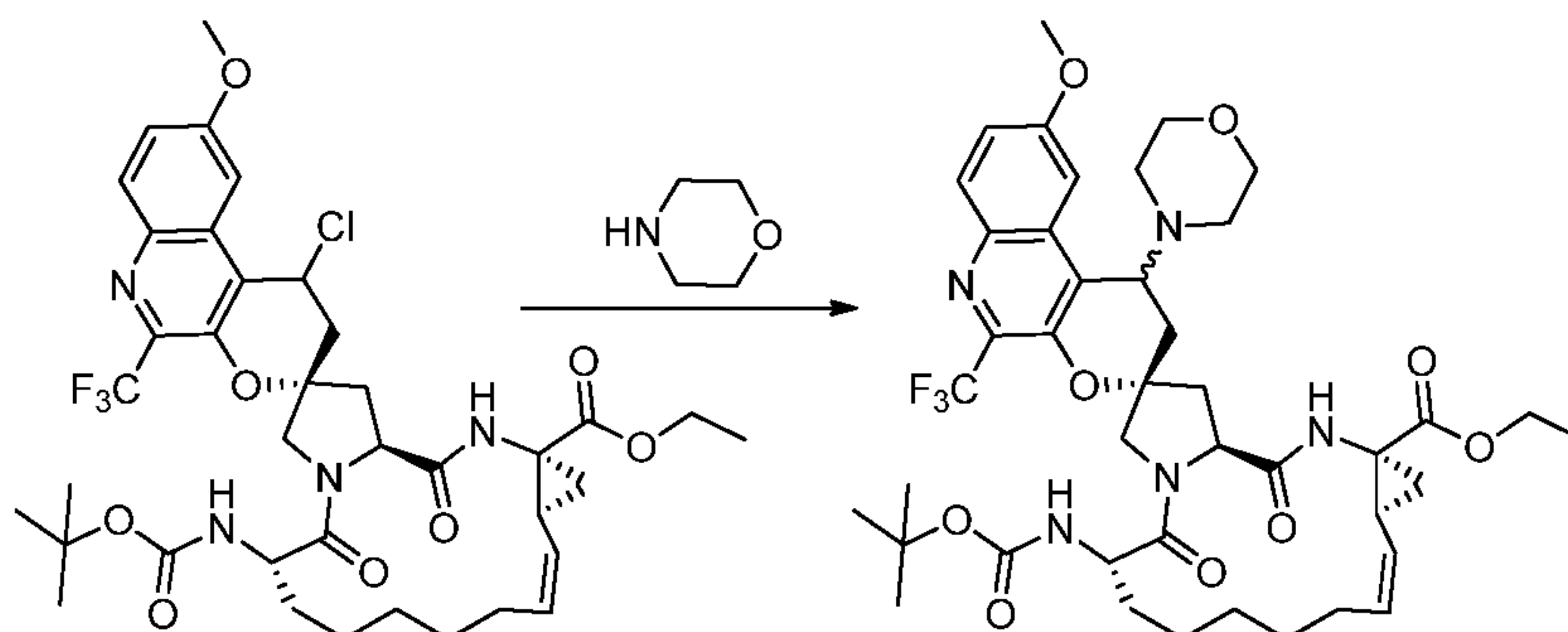
Example 65: *tert*-Butyl((1'S,2R,6S,13aS,14aR,16aS,Z)-9'-methoxy-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-1'-morpholino-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-65);

30 and

Example 66: *tert*-Butyl((1'R,2R,6S,13aS,14aR,16aS,Z)-9'-methoxy-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-1'-morpholino-5,16-dioxo-5'-(trifluoromethyl)-

1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-66)

Step 1

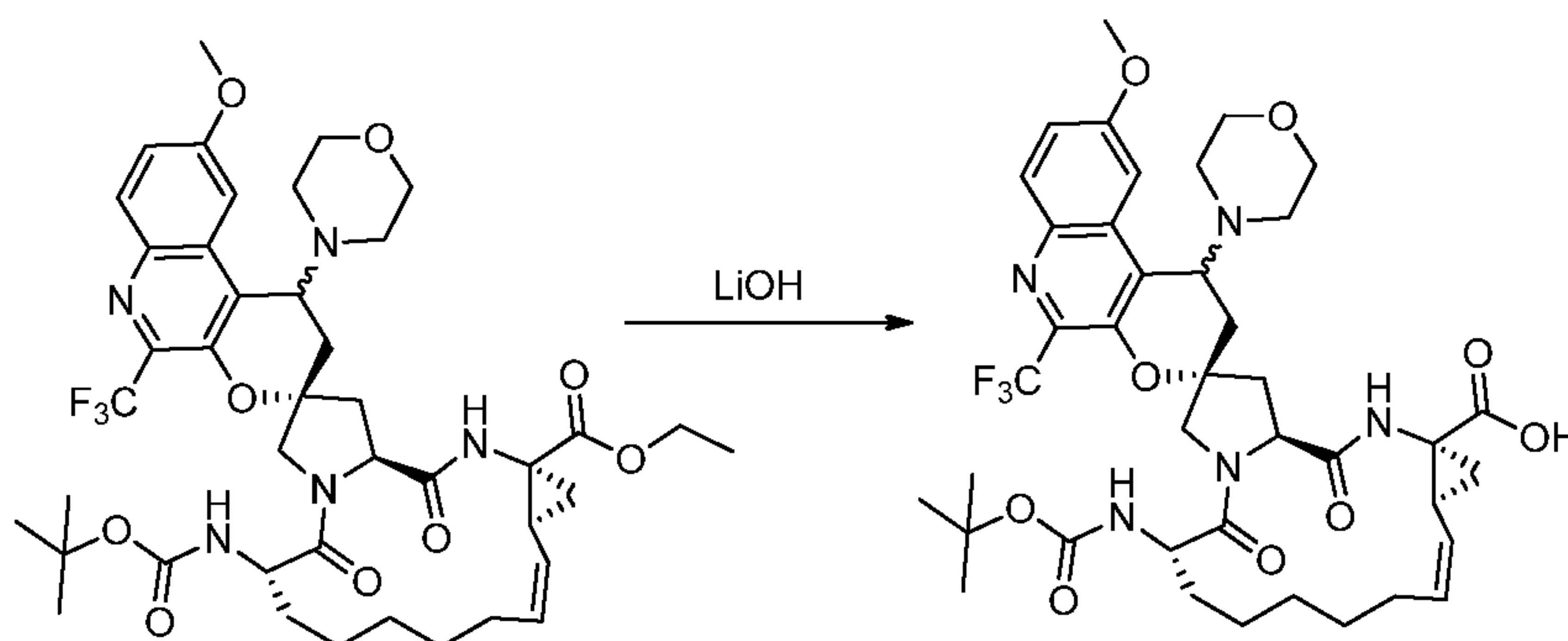


5 The reaction mixture of ethyl (2*S*,6*S*,12*Z*,13*aS*,14*aR*,16*aS*)-6-[(*tert*-butoxycarbonyl)amino]-1'-chloro-9'-methoxy-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',6,7,8,9,10,11,13*a*,14,15,16,16*a*-tetradecahydrospiro[cyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-*c*]quinoline]-14*a*(5*H*)-carboxylate (176 mg, 0.226 mmol) and sodium iodide (67.7 mg, 0.452 mmol) in 1.00 ml of morpholine in a microwave vial

10 was stirred for 24h at RT. The LC-MS indicated the reaction almost complete. It was evaporated under reduced pressure to remove excess morpholine, diluted with EtOAc (15 ml) and water (5 ml). The layers were separated, and the aq. layer was extracted again with EtOAc (15 mlx2). The organic layers were combined and washed with brine (3 ml), dried over MgSO₄, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by

15 column chromatography on silica gel (24 g, gold column, dry loading), eluting with 100% hexane for 300 ml, gradient to 40% of EtOAc to yield the product of Step 1 (*m/z*= 830.3 (M+1)), as a light yellow solid.

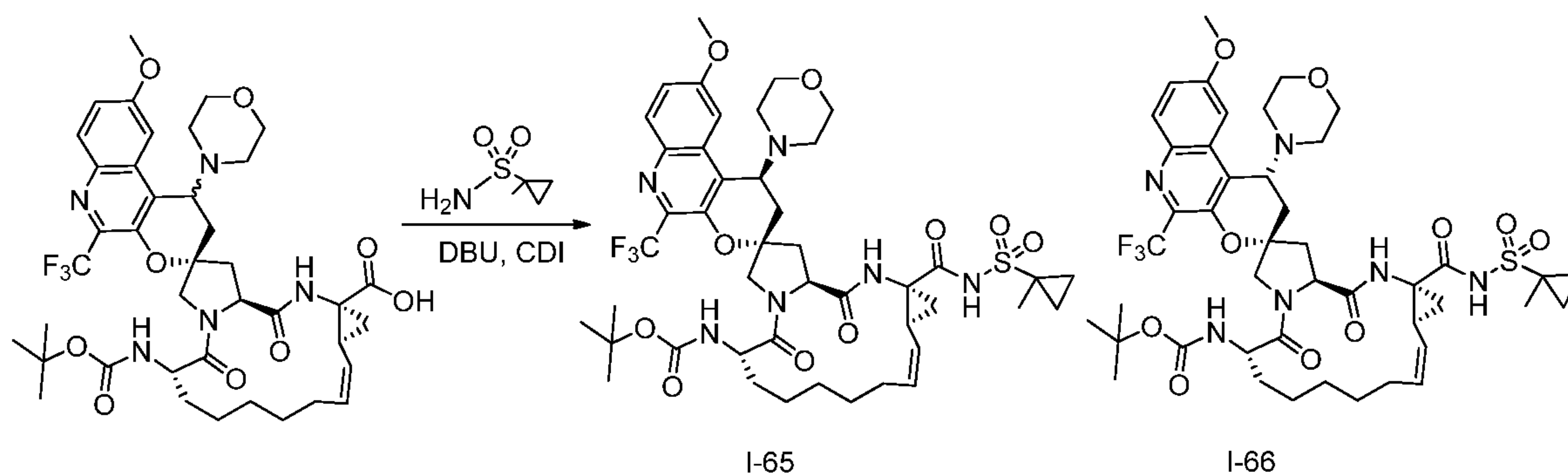
Step 2



20 To the reaction mixture of the product of Step 1 (110 mg, 0.133 mmol) in THF (2.0 ml), MeOH (1.0 ml) and H₂O (0.7 ml) was added the LiOH (38.1 mg, 1.591 mmol) at RT. It

was stirred at RT for 5.5h. The LC-MS shows the hydrolysis was complete. It was acidified to pH = 2~3 with 1N HCl solution (about 1.2 ml of 1N HCl) at 0°C, and diluted with EtOAc (30 ml). The layers were separated, and the aq. layer was extracted again with EtOAc(10 mlx1). The organic layers were combined and washed with brine (4x3 ml), dried over MgSO₄, filtered, and was evaporated under reduced pressure. The resulting concentrate was azeotroped with toluene (2X) and kept under vacuum overnight to give 104 mg of the product of Step 2 (*m/z*= 802.08 (M+1)), as a white solid that was used without further purification.

Step 3



A solution of the product of Step 2 (98 mg, 0.122 mmol) and CDI (41.6 mg, 0.257 mmol) in THF (2.0 ml) was stirred in an oil-bath kept at 70°C for 3h, then cooled to RT. To this reaction mixture was added 1-methylcyclopropane-1-sulfonamide (49.6 mg, 0.367 mmol) and DBU in THF (1 ml) (0.428 ml, 0.428 mmol), and the mixture was stirred in an oil-bath kept at 50°C for 2.5h. LC-MS indicated that the reaction almost completed. The reaction mixture was diluted with EtOAc (30 ml), washed with aq. NH₄Cl (2x4 ml), brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by column chromatography on silica gel (12 g, gold column, dry loading), eluting with 100% hexane for 200 ml, gradient to 45% of acetone/hexanes to *tert*-butyl ((2R,6S,13aS,14aR,16aS,Z)-9'-methoxy-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-1'-morpholino-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (*m/z*= 919.80 (M+1)), as a white solid.

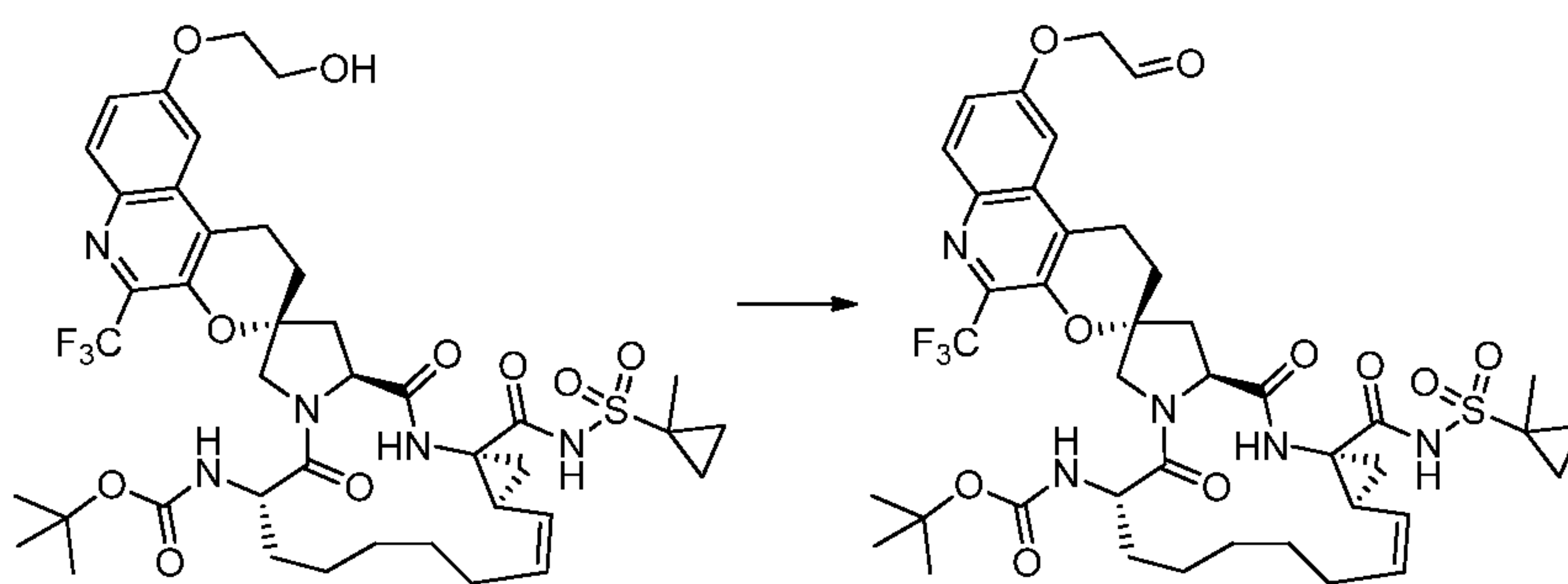
The isomeric mixture of *tert*-butyl ((2R,6S,13aS,14aR,16aS,Z)-9'-methoxy-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-1'-morpholino-5,16-dioxo-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate was separated and purified with 50%MeOH (0.2% diethylamine)/CO₂, 70 ml/min, 100bar, on an IC column (30x250 mm) to obtain I-65 and I-66.

Example 65: $^1\text{H NMR } \delta$ (ppm)(CHCl_3): $^1\text{H NMR } \delta$ (ppm)($\text{CHCl}_3\text{-d}$): 10.10 (1 H, s), 8.02 (1 H, d, $J = 9.14$ Hz), 7.83 (1 H, s), 7.35-7.27 (3 H, m), 6.97 (1 H, s), 5.73 (1 H, q, $J = 8.87$ Hz), 5.28 (1 H, d, $J = 8.96$ Hz), 5.01 (1 H, t, $J = 9.31$ Hz), 4.78 (1 H, d, $J = 11.39$ Hz), 4.63 (1 H, s), 4.54-4.44 (2 H, m), 4.35 (1 H, t, $J = 10.01$ Hz), 4.02 (4 H, s), 3.90 (1 H, t, $J = 11.39$ Hz), 3.73 (4 H, s), 3.68 (4 H, s), 3.51 (1 H, q, $J = 7.12$ Hz), 3.44 (1 H, q, $J = 7.13$ Hz), 3.08-3.00 (3 H, m), 2.70-2.33 (12 H, m), 2.28 (1 H, dd, $J = 13.77, 5.73$ Hz), 1.95-1.81 (5 H, m), 1.76 (7 H, t, $J = 22.15$ Hz), 1.33 (12 H, s), 1.32-1.20 (7 H, m), 0.99 (1 H, d, $J = 6.65$ Hz), 0.94-0.75 (7 H, m), 0.09 (1 H, s). $m/z = 919.70$ [M+1].

Example 66: $^1\text{H NMR } \delta$ (ppm)(CHCl_3): $^1\text{H NMR } \delta$ (ppm)($\text{CHCl}_3\text{-d}$): 10.10 (1 H, s), 8.02 (1 H, d, $J = 9.14$ Hz), 7.83 (1 H, s), 7.35-7.27 (3 H, m), 6.97 (1 H, s), 5.73 (1 H, q, $J = 8.87$ Hz), 5.28 (1 H, d, $J = 8.96$ Hz), 5.01 (1 H, t, $J = 9.31$ Hz), 4.78 (1 H, d, $J = 11.39$ Hz), 4.63 (1 H, s), 4.54-4.44 (2 H, m), 4.35 (1 H, t, $J = 10.01$ Hz), 4.02 (4 H, s), 3.90 (1 H, t, $J = 11.39$ Hz), 3.73 (4 H, s), 3.68 (4 H, s), 3.51 (1 H, q, $J = 7.12$ Hz), 3.44 (1 H, q, $J = 7.13$ Hz), 3.08-3.00 (3 H, m), 2.70-2.33 (12 H, m), 2.28 (1 H, dd, $J = 13.77, 5.73$ Hz), 1.95-1.81 (5 H, m), 1.76 (7 H, t, $J = 22.15$ Hz), 1.33 (12 H, s), 1.32-1.20 (7 H, m), 0.99 (1 H, d, $J = 6.65$ Hz), 0.94-0.75 (7 H, m), 0.09 (1 H, s). $m/z = 919.70$ [M+1].

Example 67: *tert*-Butyl ((2R,6S,13aS,14aR,16aS,Z)-14a-(((1-methylcyclopropyl)sulfonyl)carbamoyl)-5,16-dioxo-9'-(2-(piperidin-1-yl)ethoxy)-5'-(trifluoromethyl)-1',2',3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-1H-spiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl)carbamate (I-67)

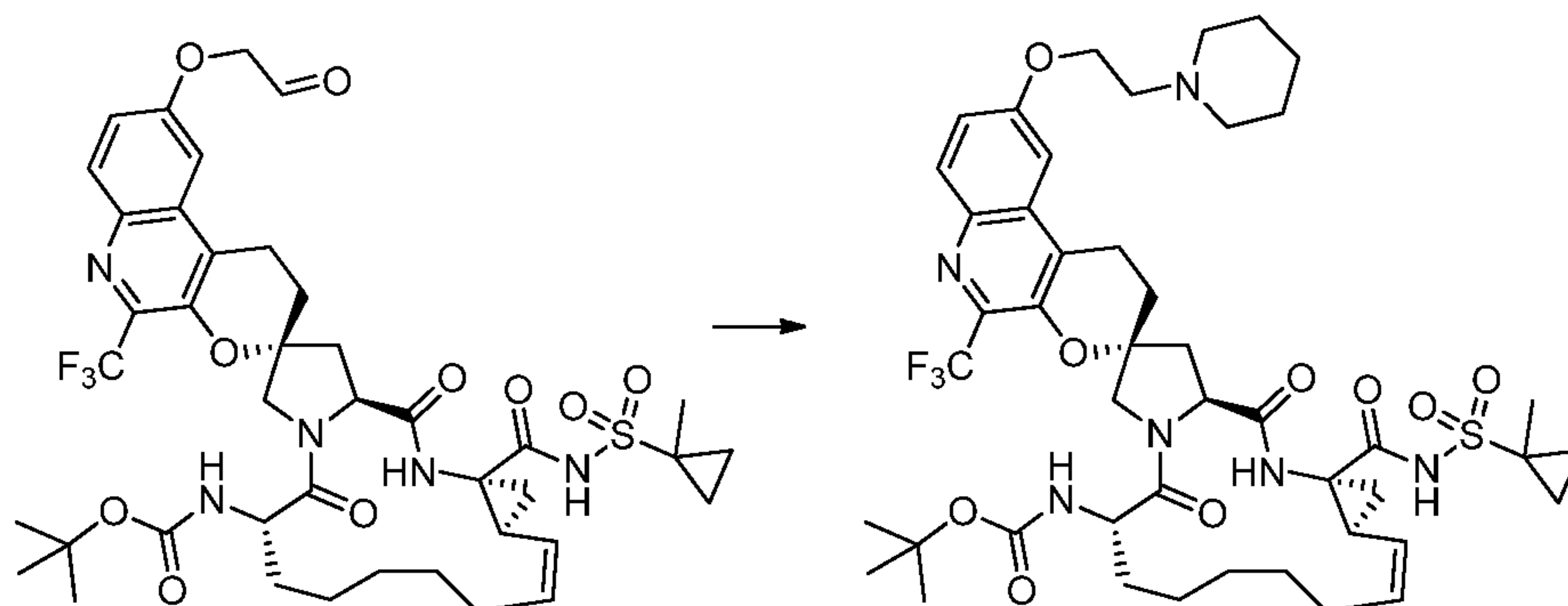
Step 1



To a solution of the compound of Example 60 (145 mg, 0.168 mmol) in CH_2Cl_2 (3.357 mL) was added Dess-Martin periodinane (85 mg, 0.201 mmol) at RT. The reaction was stirred 2h, at which stage LC-MS indicated complete consumption of the starting material (a new peak corresponding to the mass of the product dihydrate was observed by LC-MS). The reaction was quenched with 10% aq. $\text{Na}_2\text{S}_2\text{O}_3$ solution and sat. aq. NaHCO_3 solution and stirred for 15

min at RT. After separating the organic fraction, the aq. layer was washed twice with CH₂Cl₂. The combined organic fractions were washed with sat. aq. NaHCO₃ followed by brine. The organic fraction was dried (Na₂SO₄), filtered, concentrated to give the product of Step 1 (142 mg, 0.165 mmol, 98% yield) as a white solid, which was used without purification.

5 Step 2



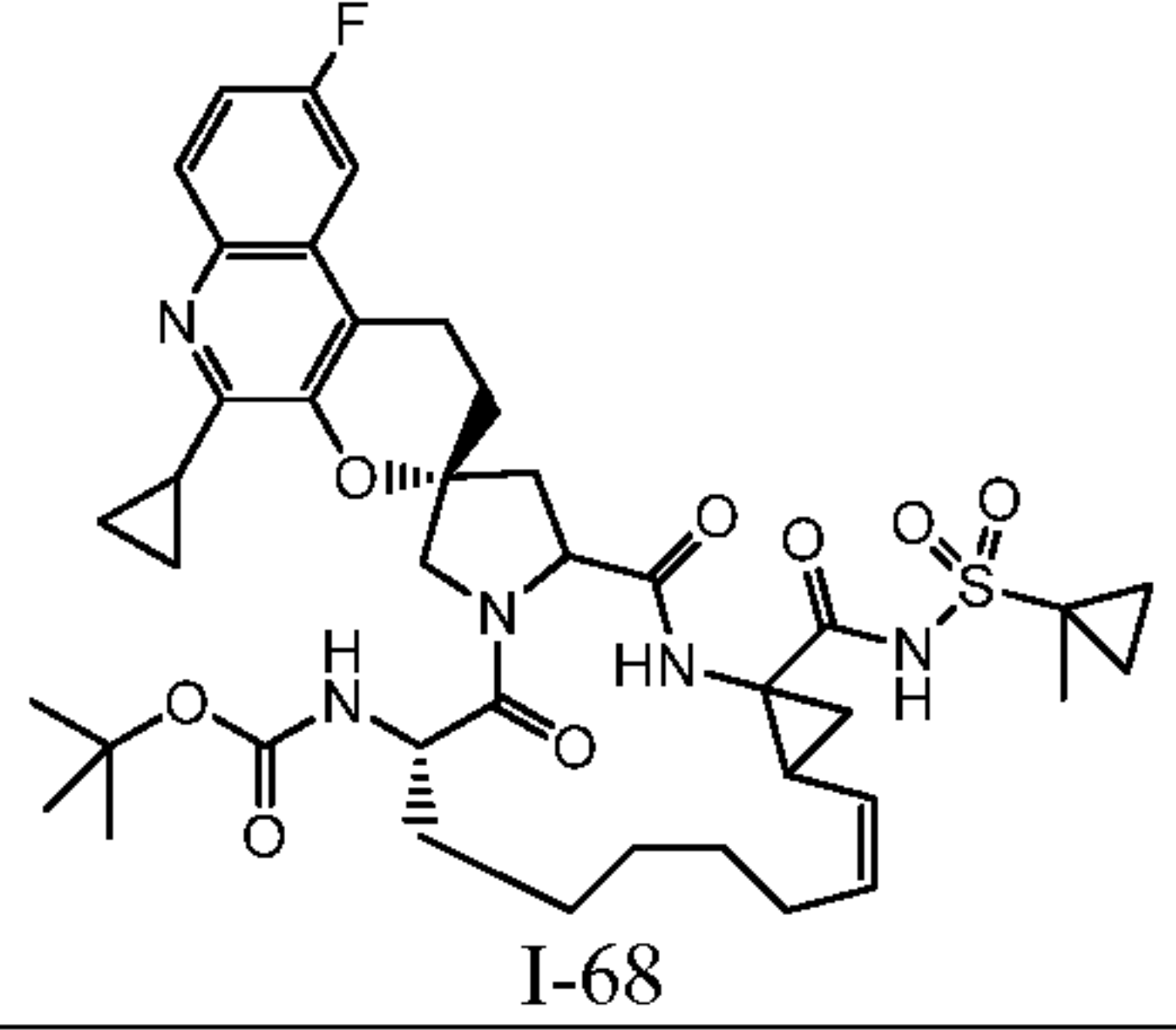
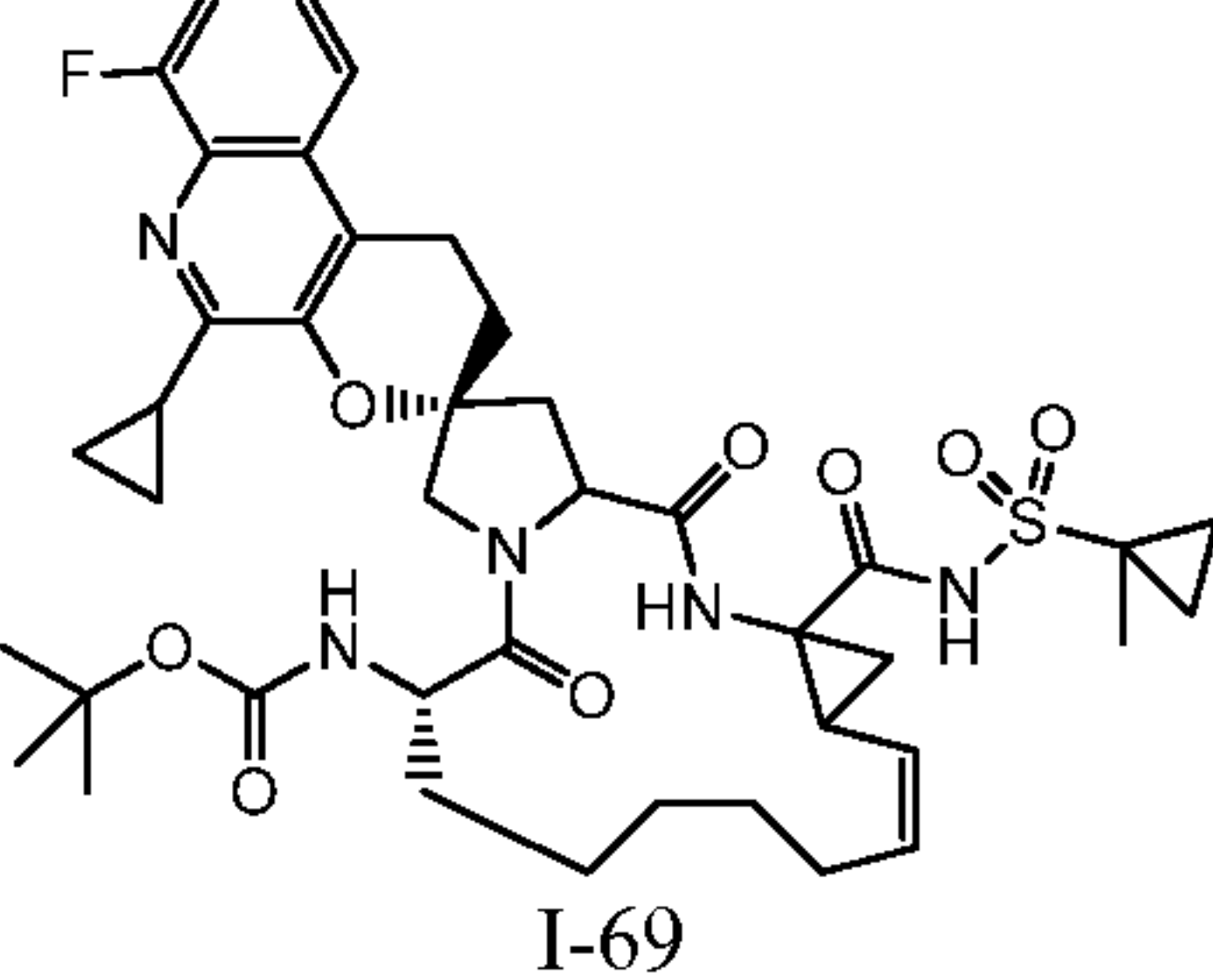
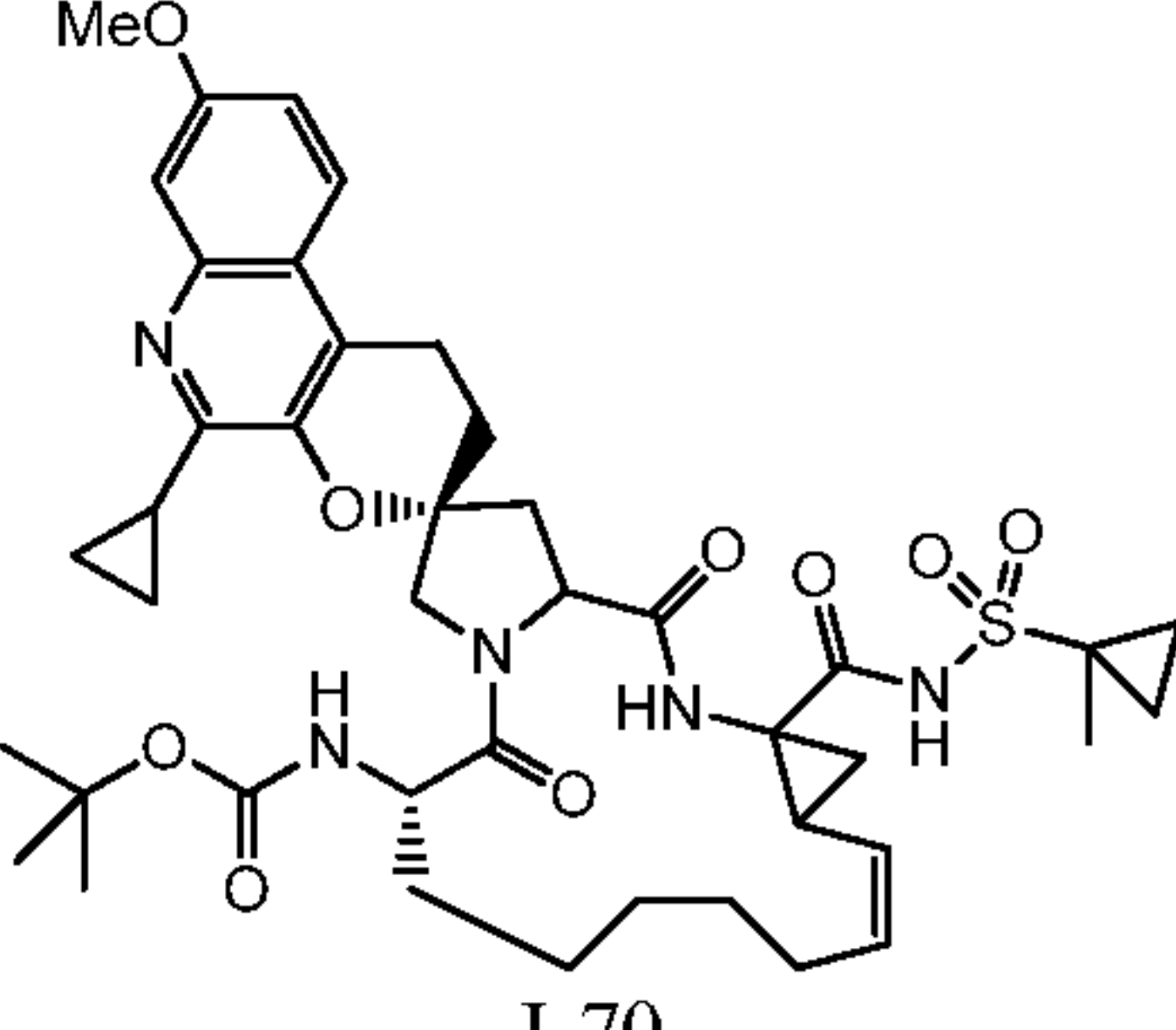
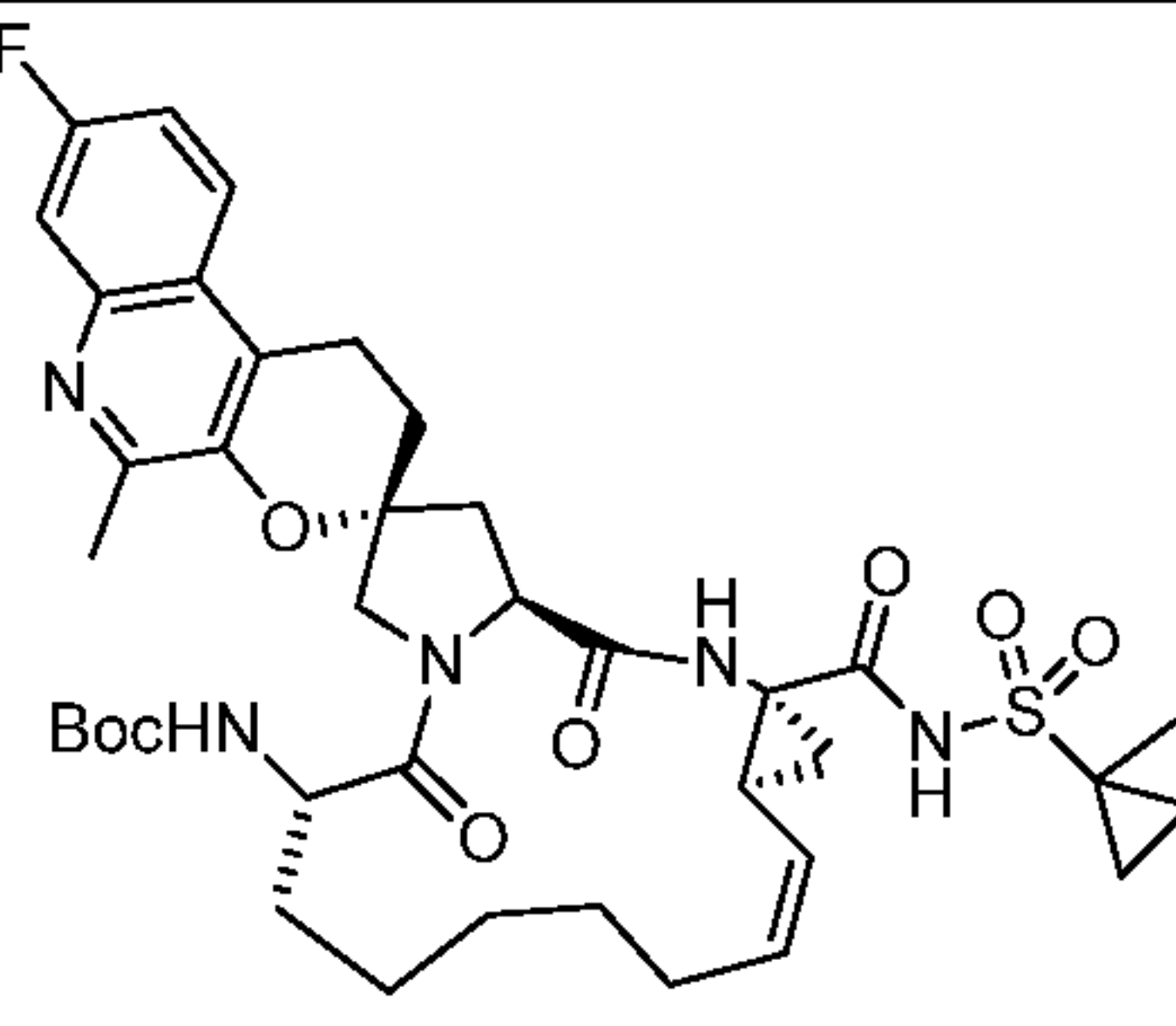
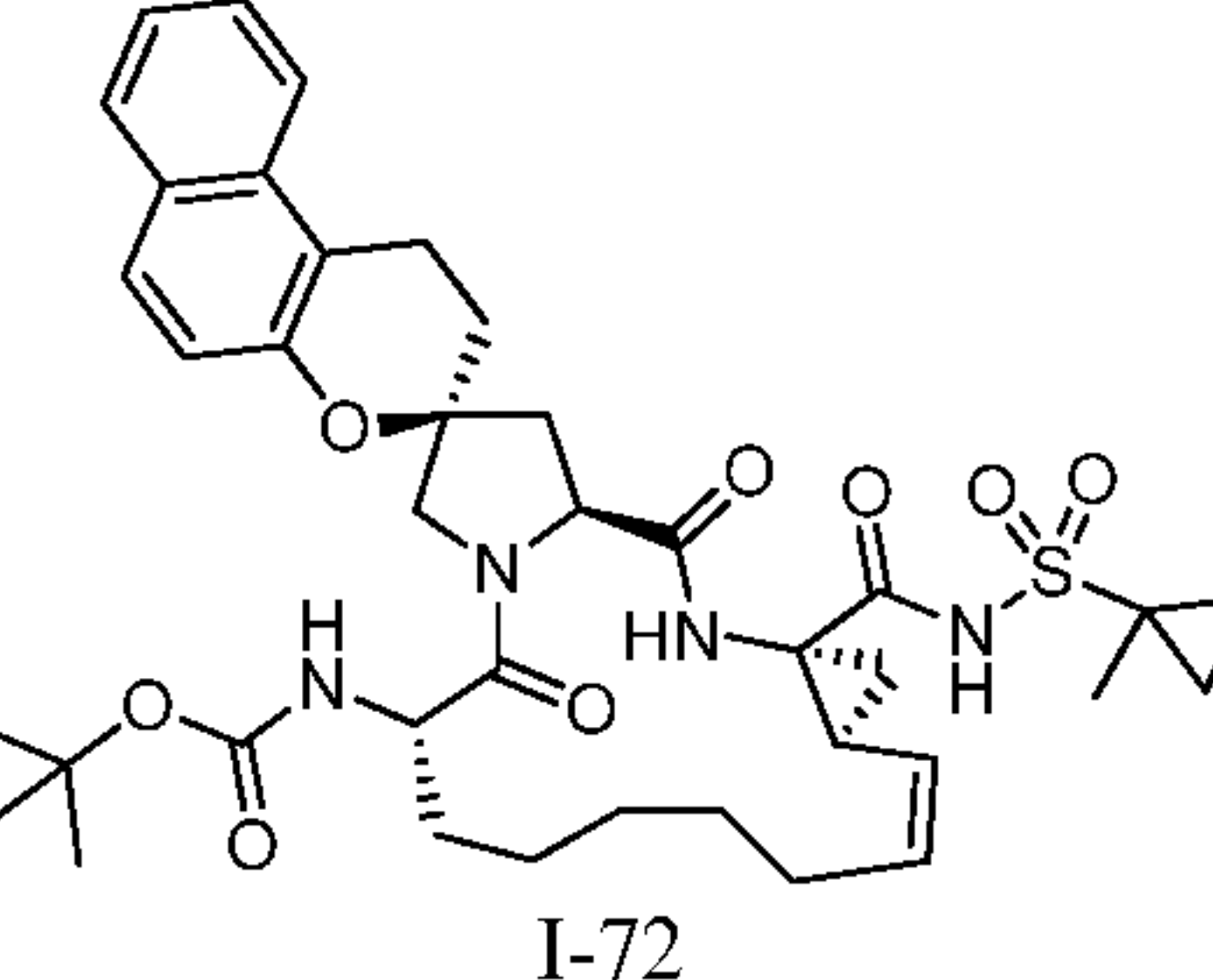
To a solution of the product of Step 1 (50 mg, 0.058 mmol) in DCE (2.5 mL) was added piperidine (0.029 mL, 0.290 mmol) at RT. The reaction was stirred for 15 min and then was treated with 0.05 mL AcOH followed by sodium triacetoxyborohydride (24.59 mg, 0.116 mmol) at RT. The reaction was stirred at RT for 16h and then diluted with CH₂Cl₂ and washed twice with sat. aq. NaHCO₃ followed by brine. The organic fraction was dried (Na₂SO₄), filtered, concentrated and purified by silica gel column chromatography (0-60-100% acetone in hexane) to provide I-67 (20 mg, 0.021 mmol, 37.0% yield).

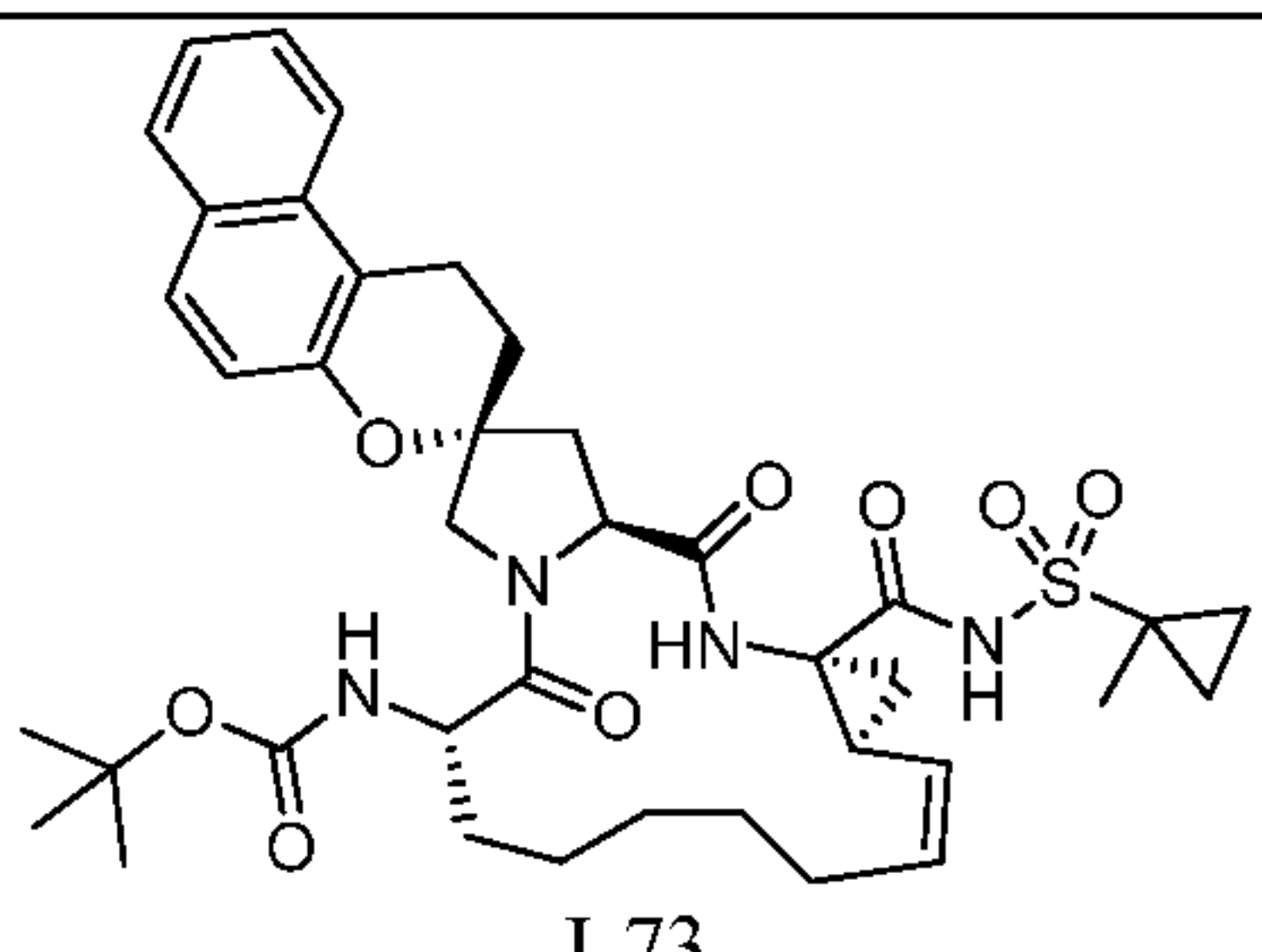
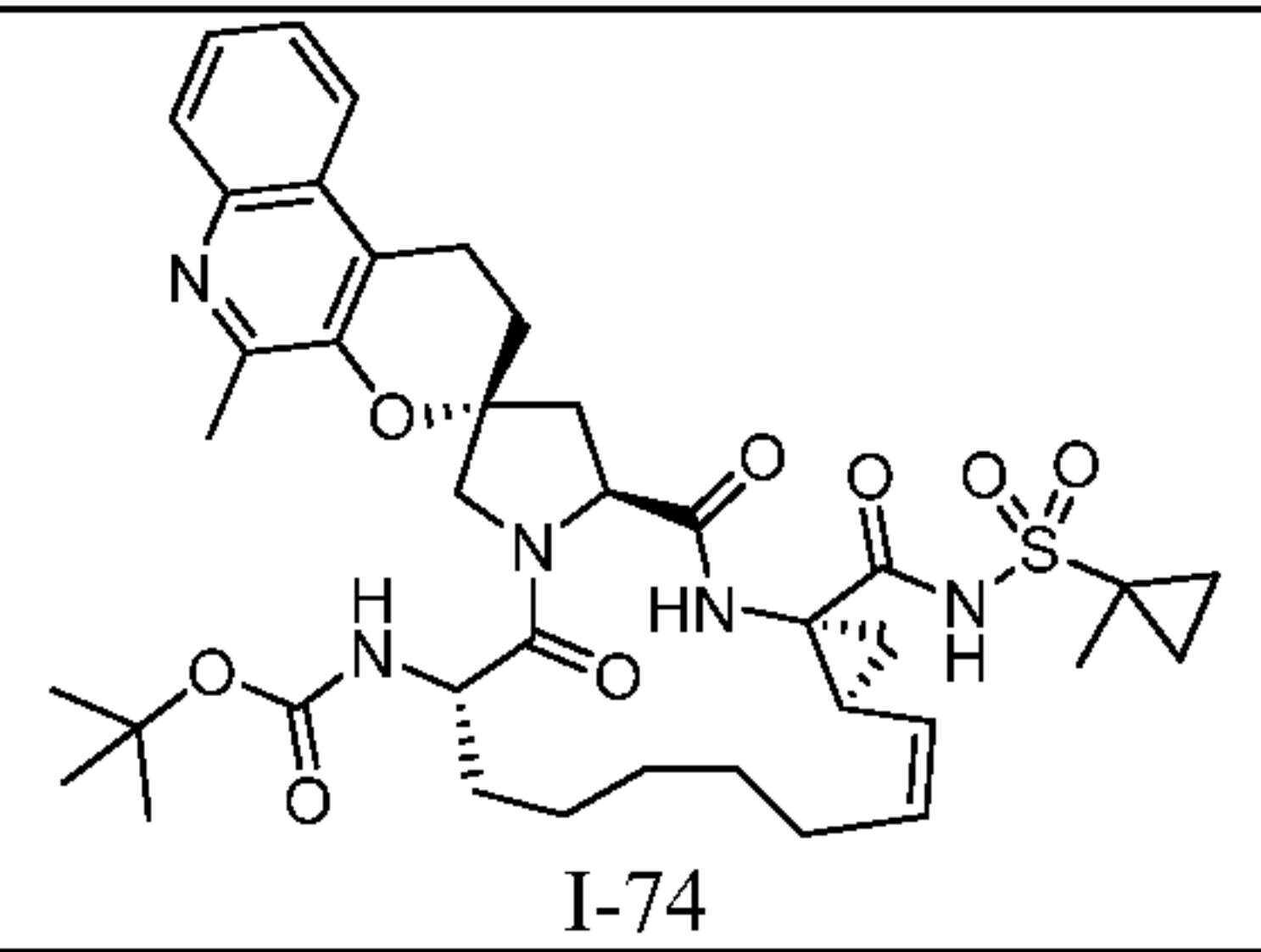
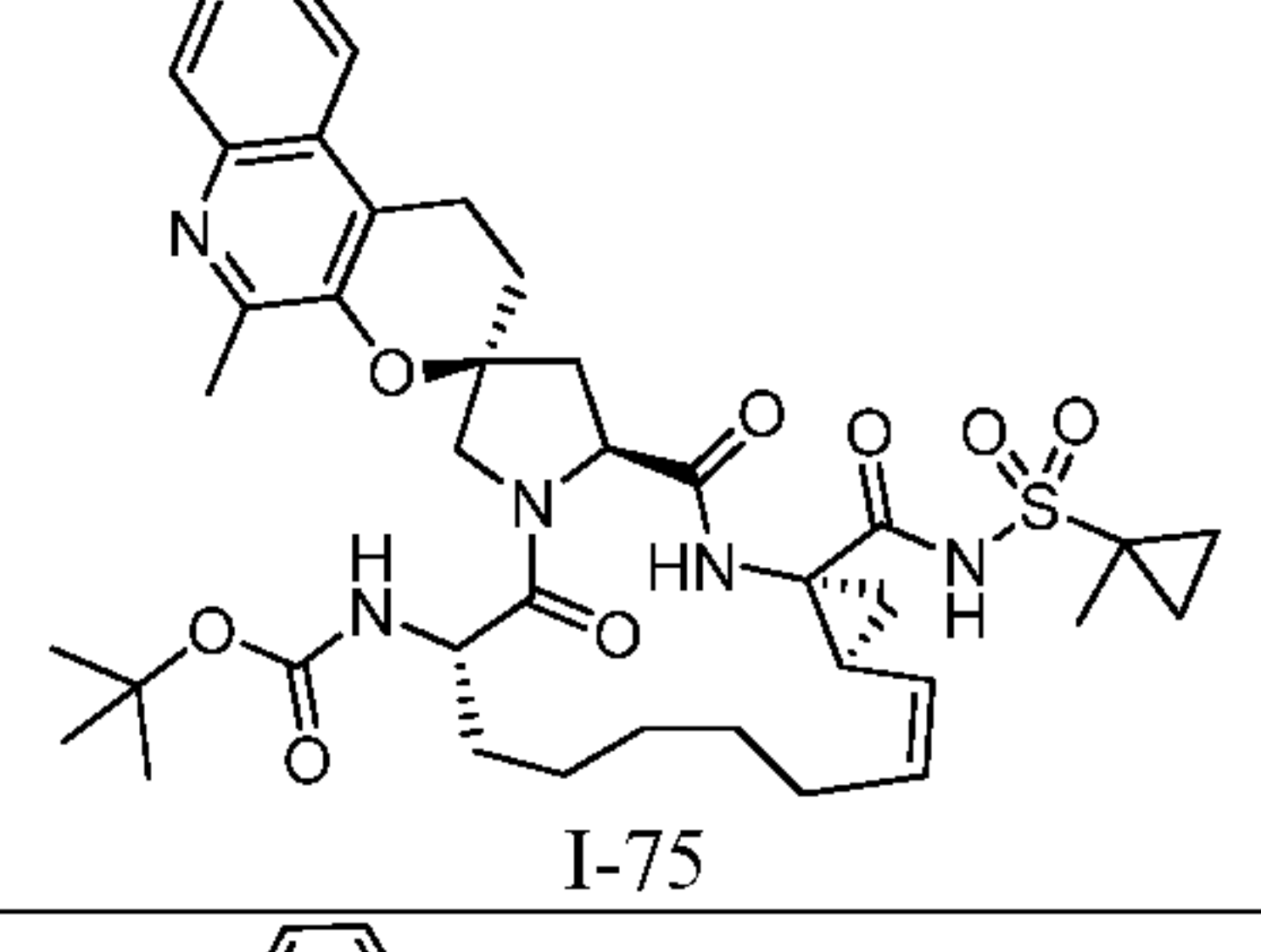
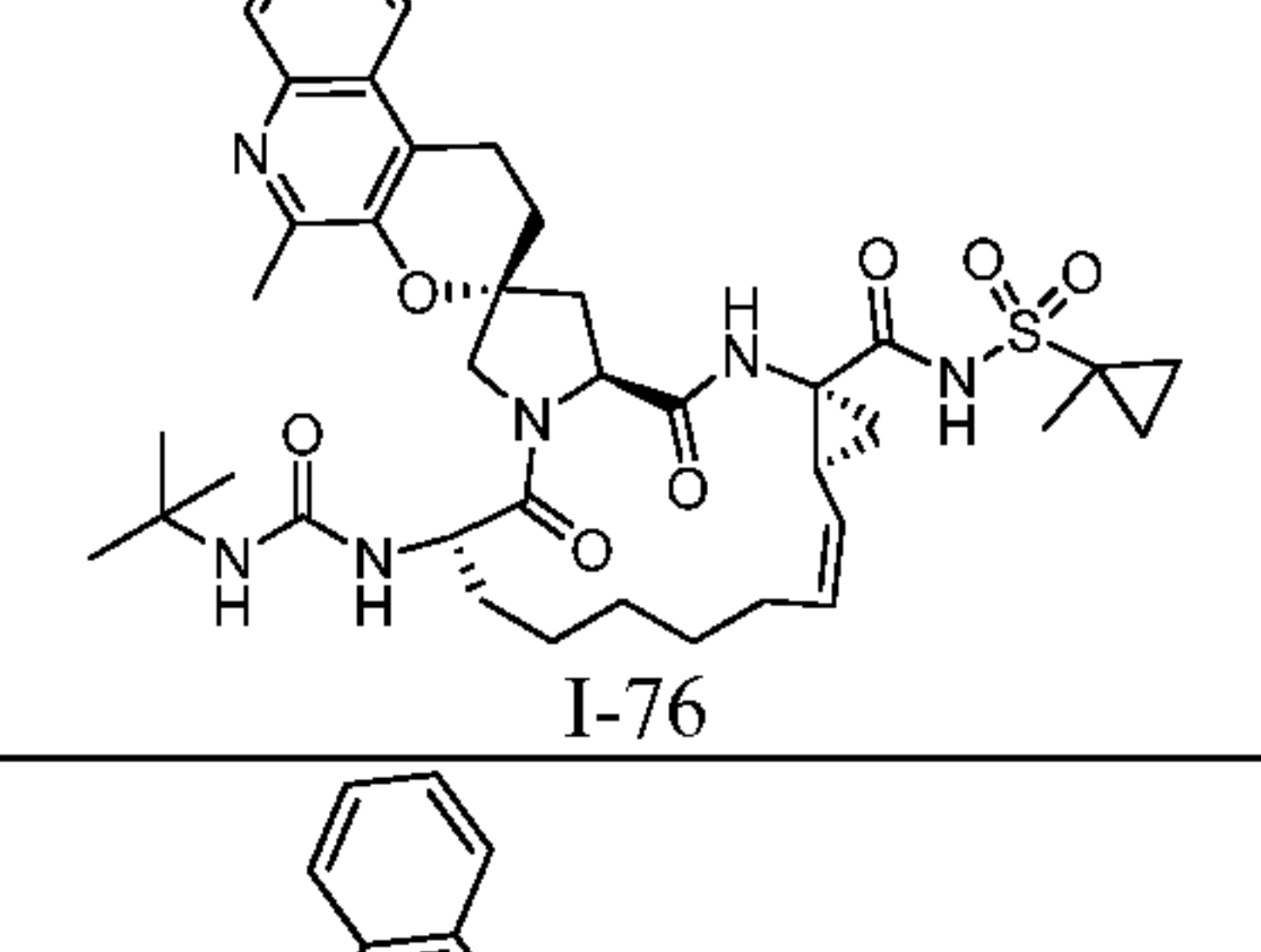
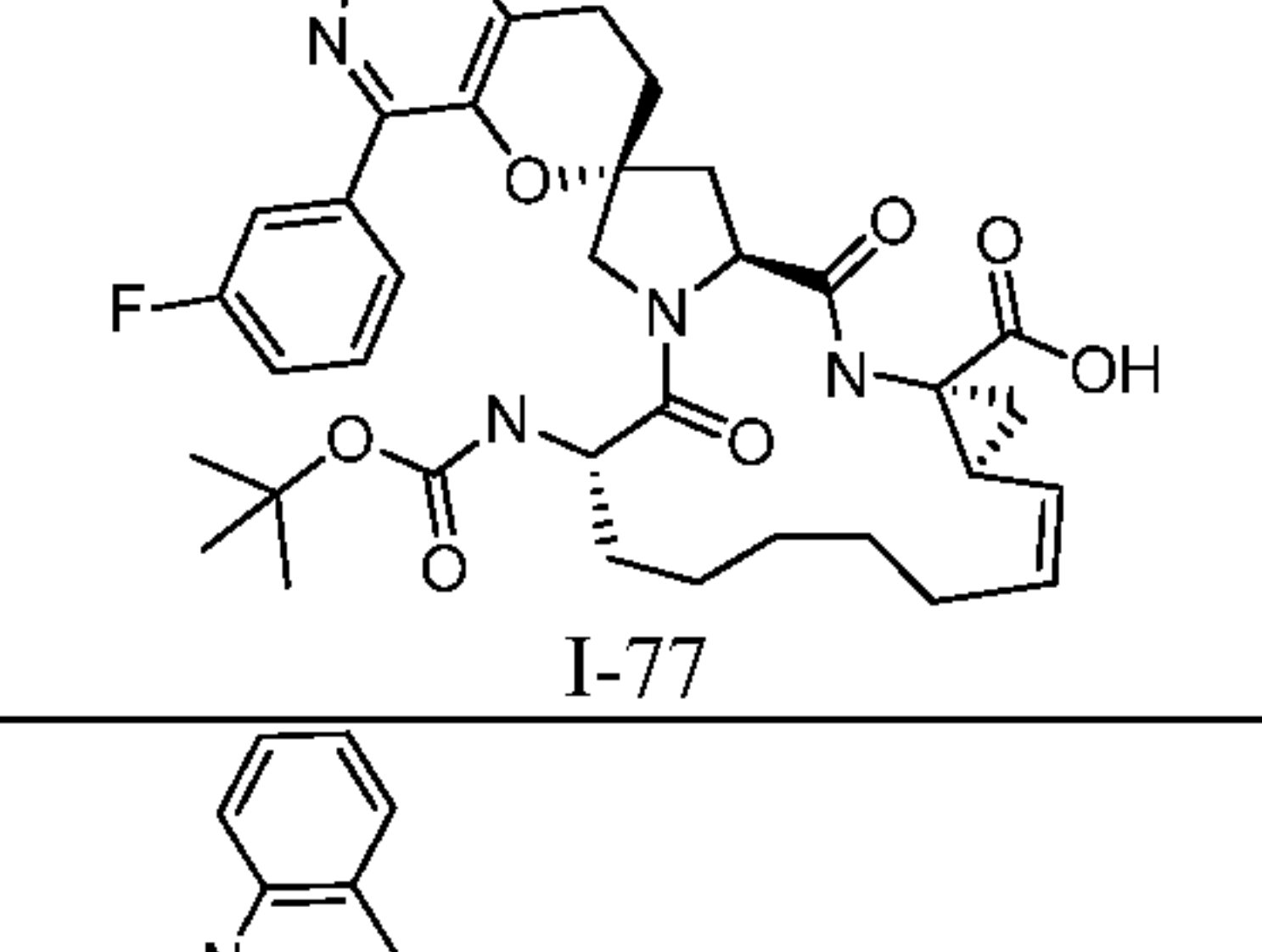
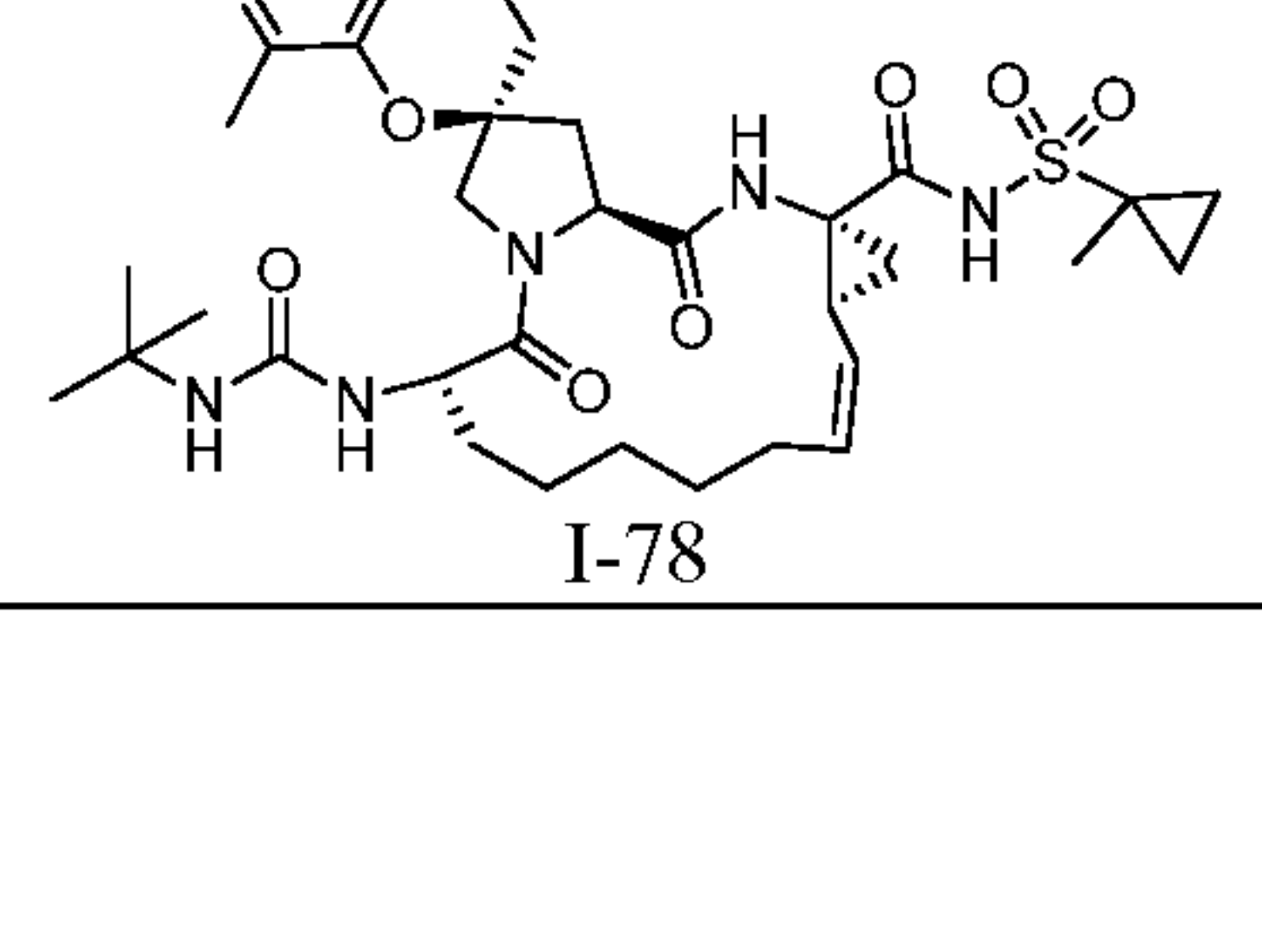
15 Examples 68-526

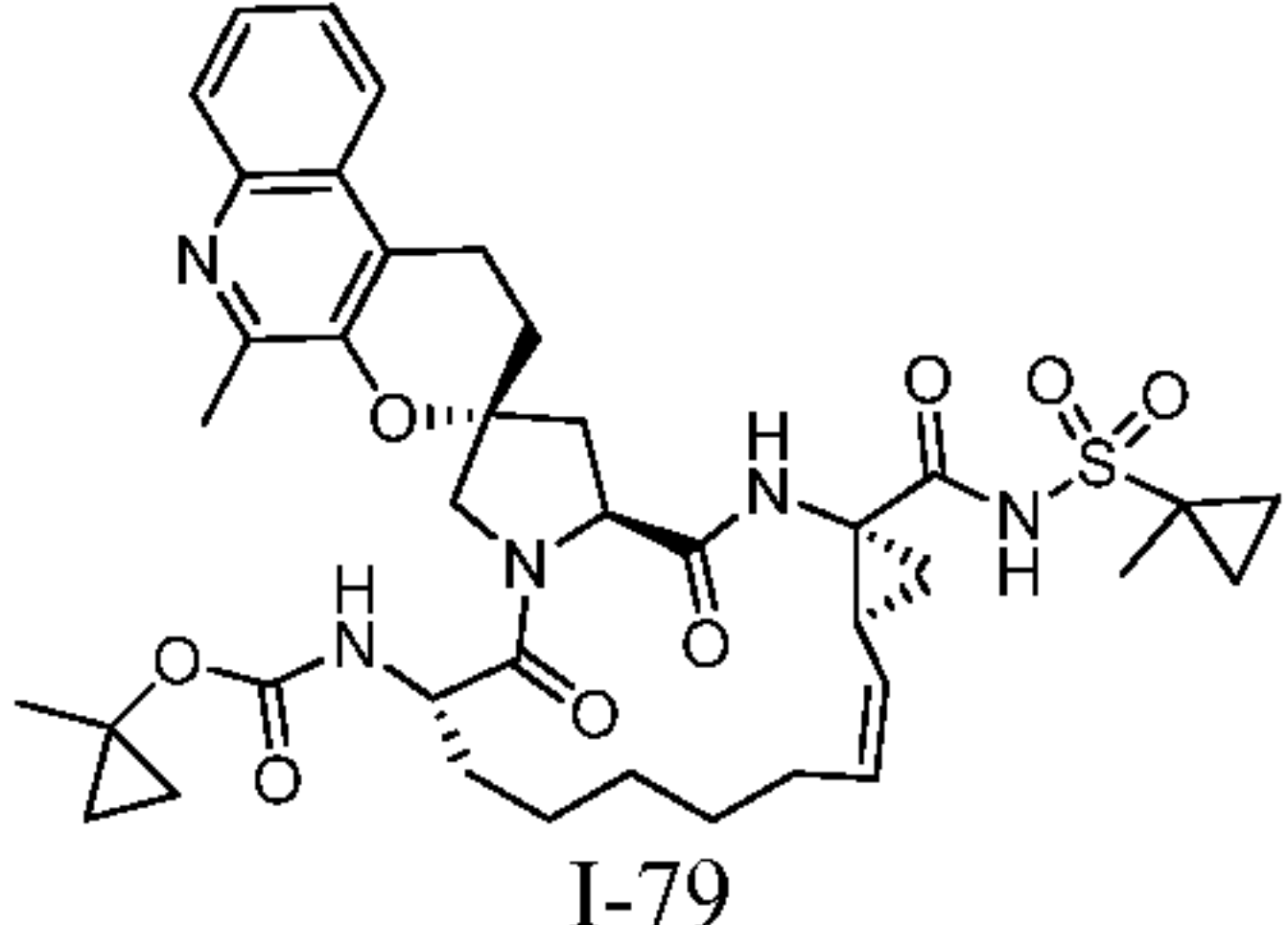
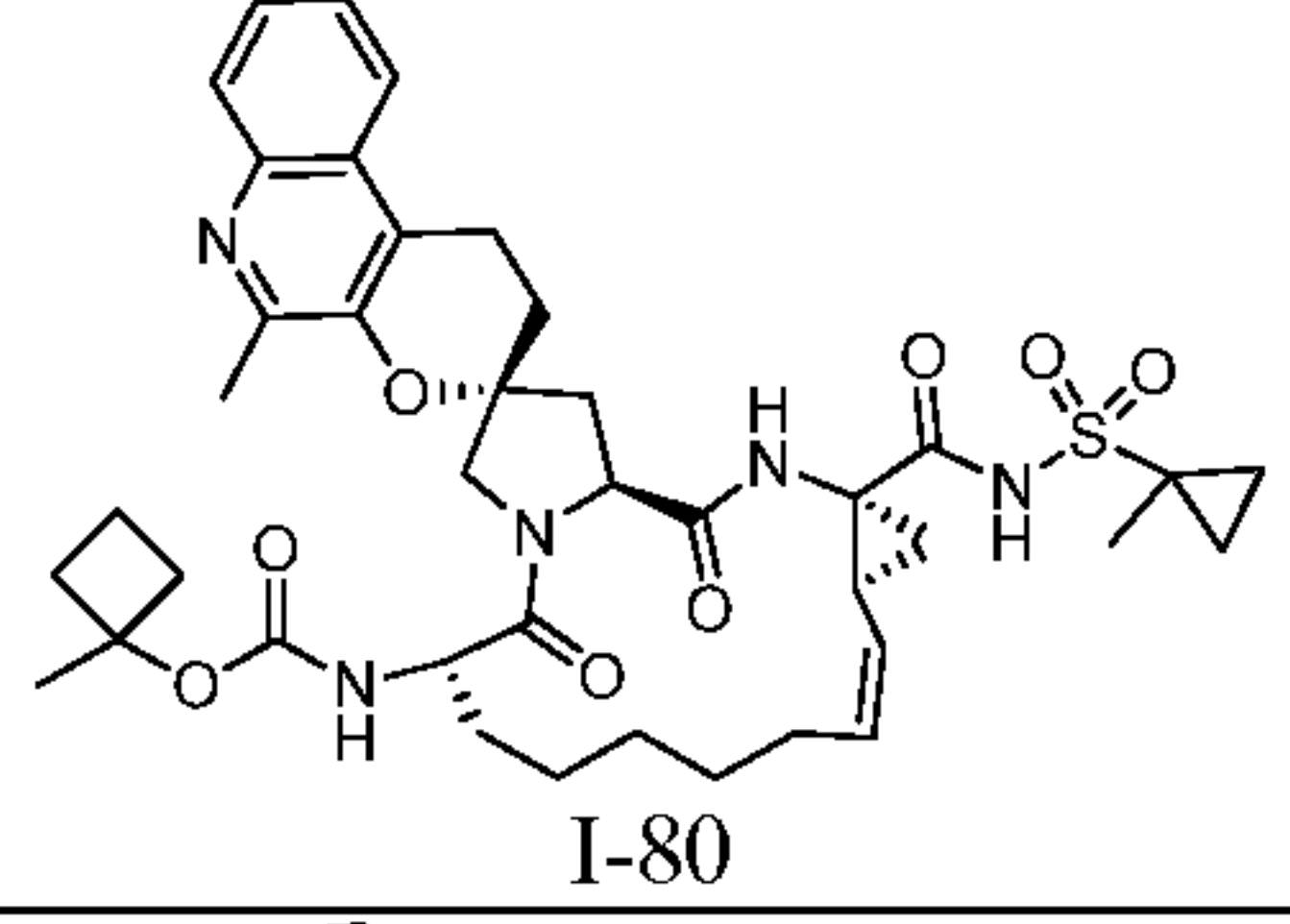
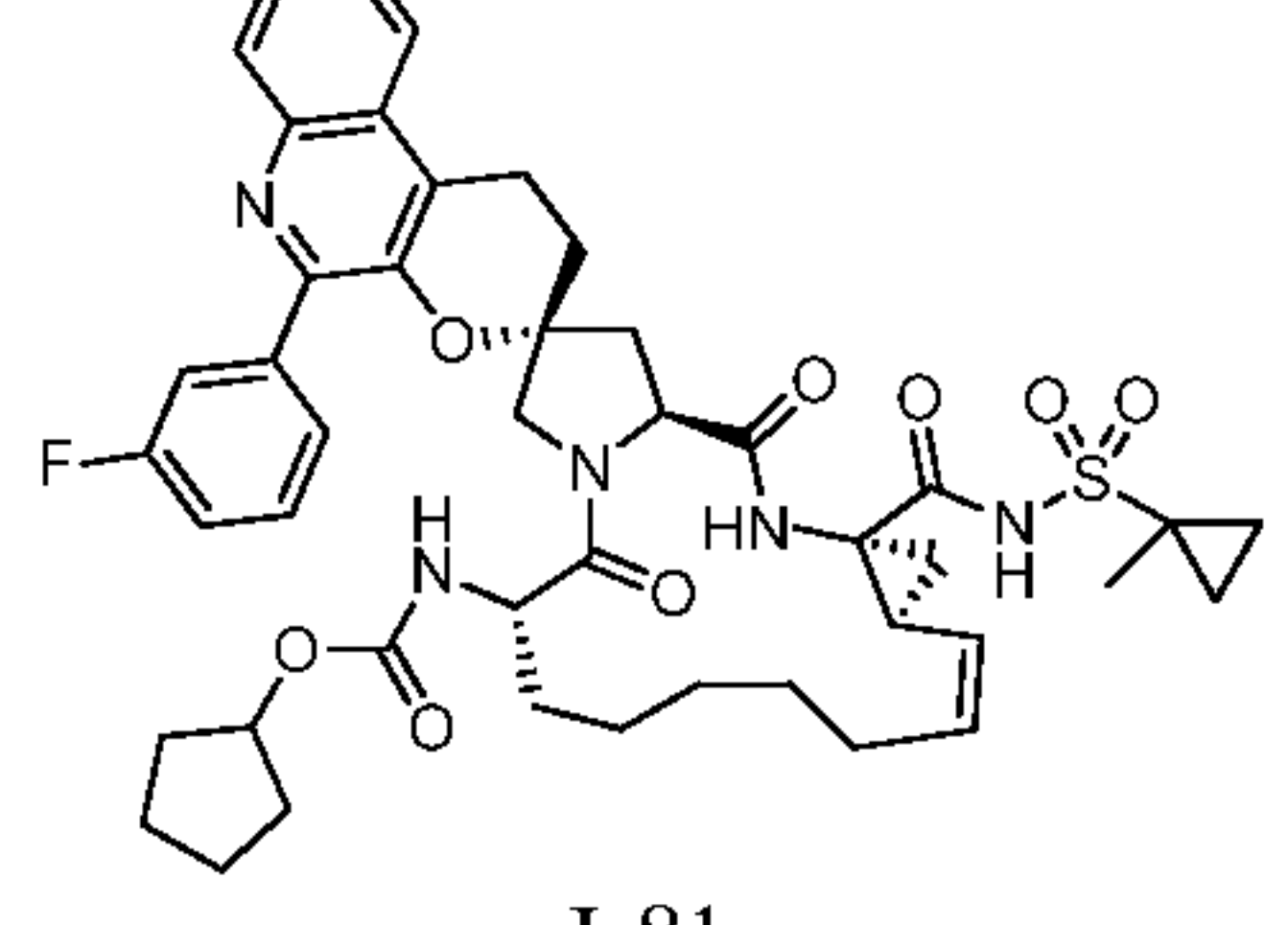
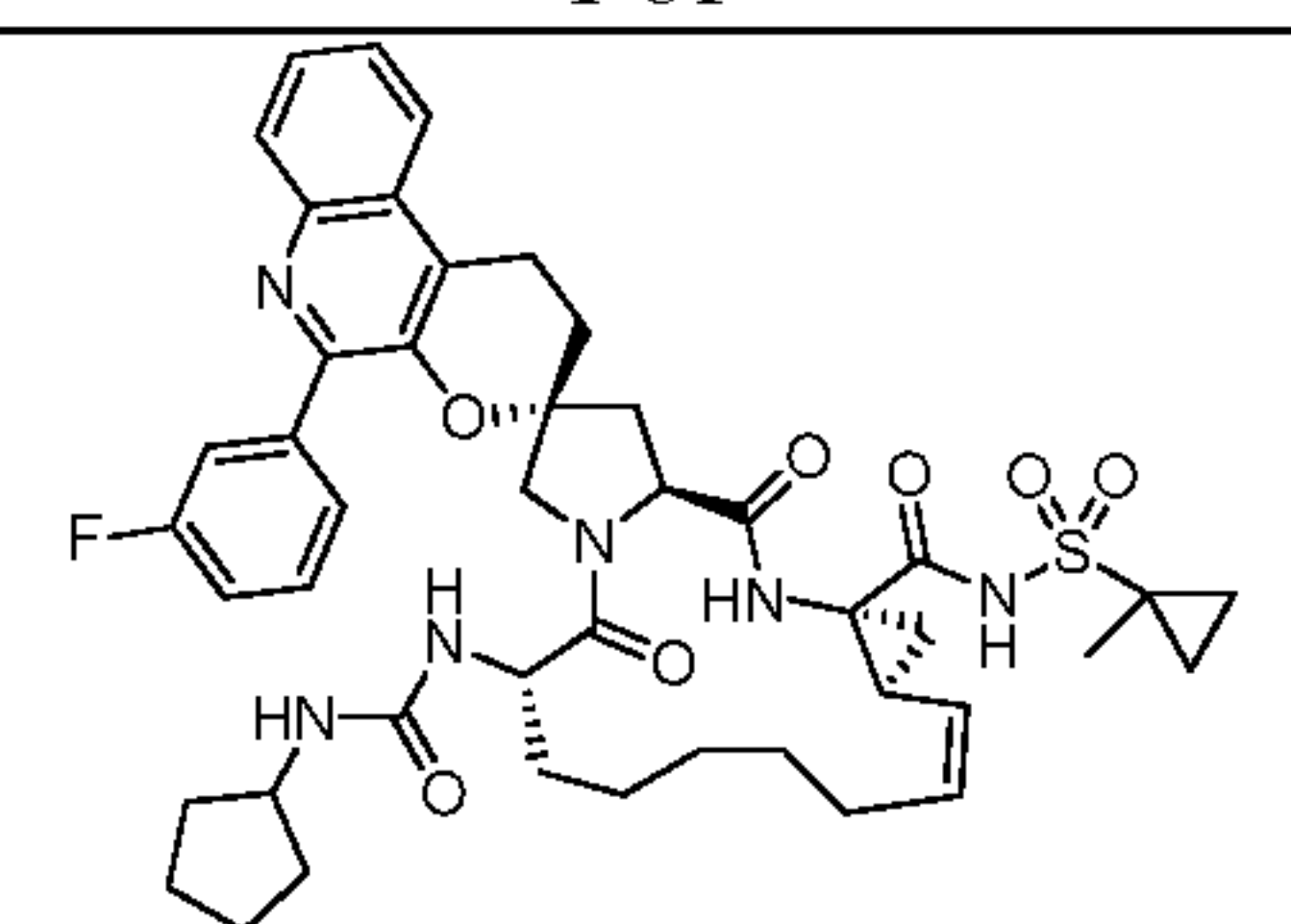
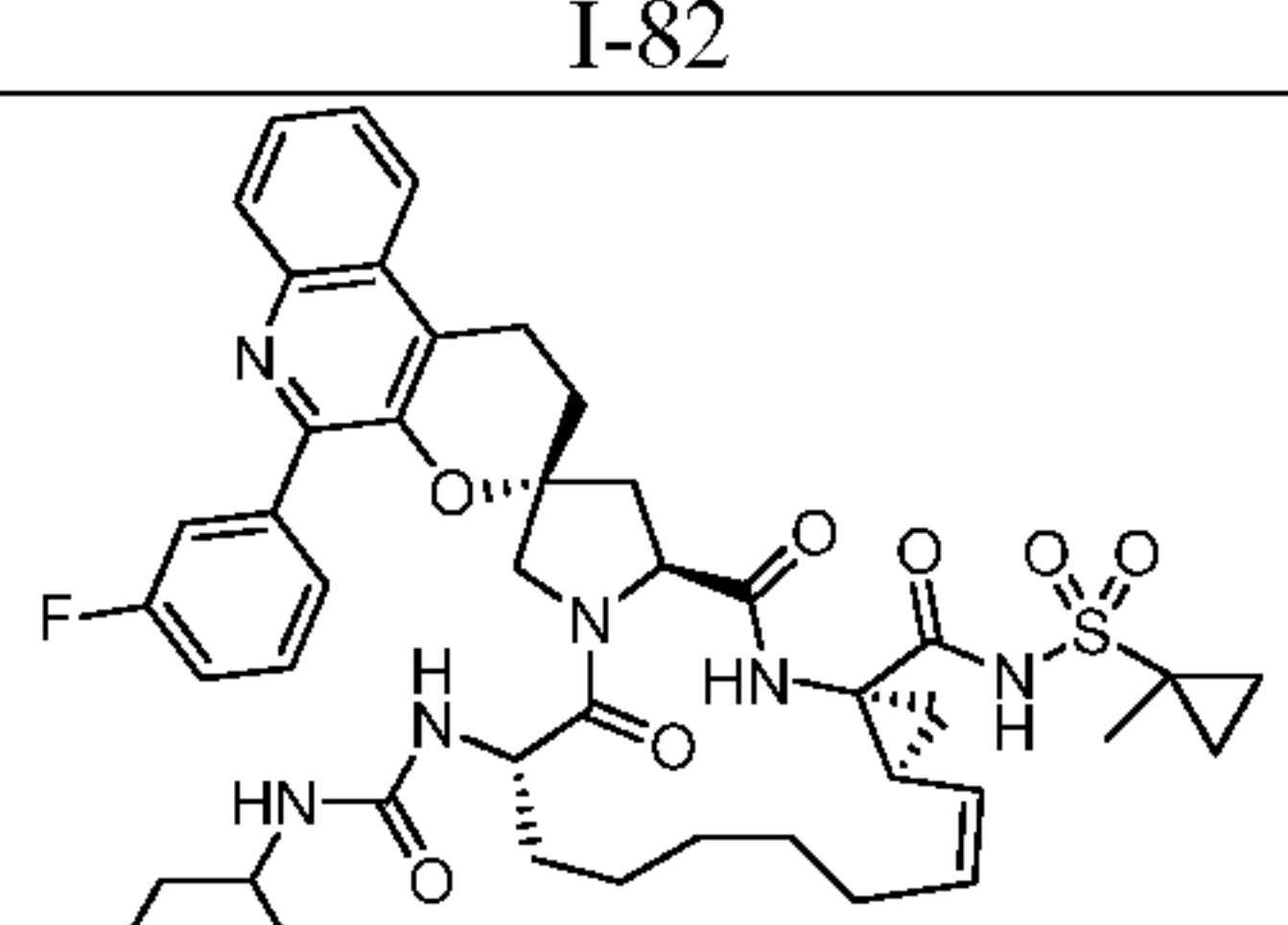
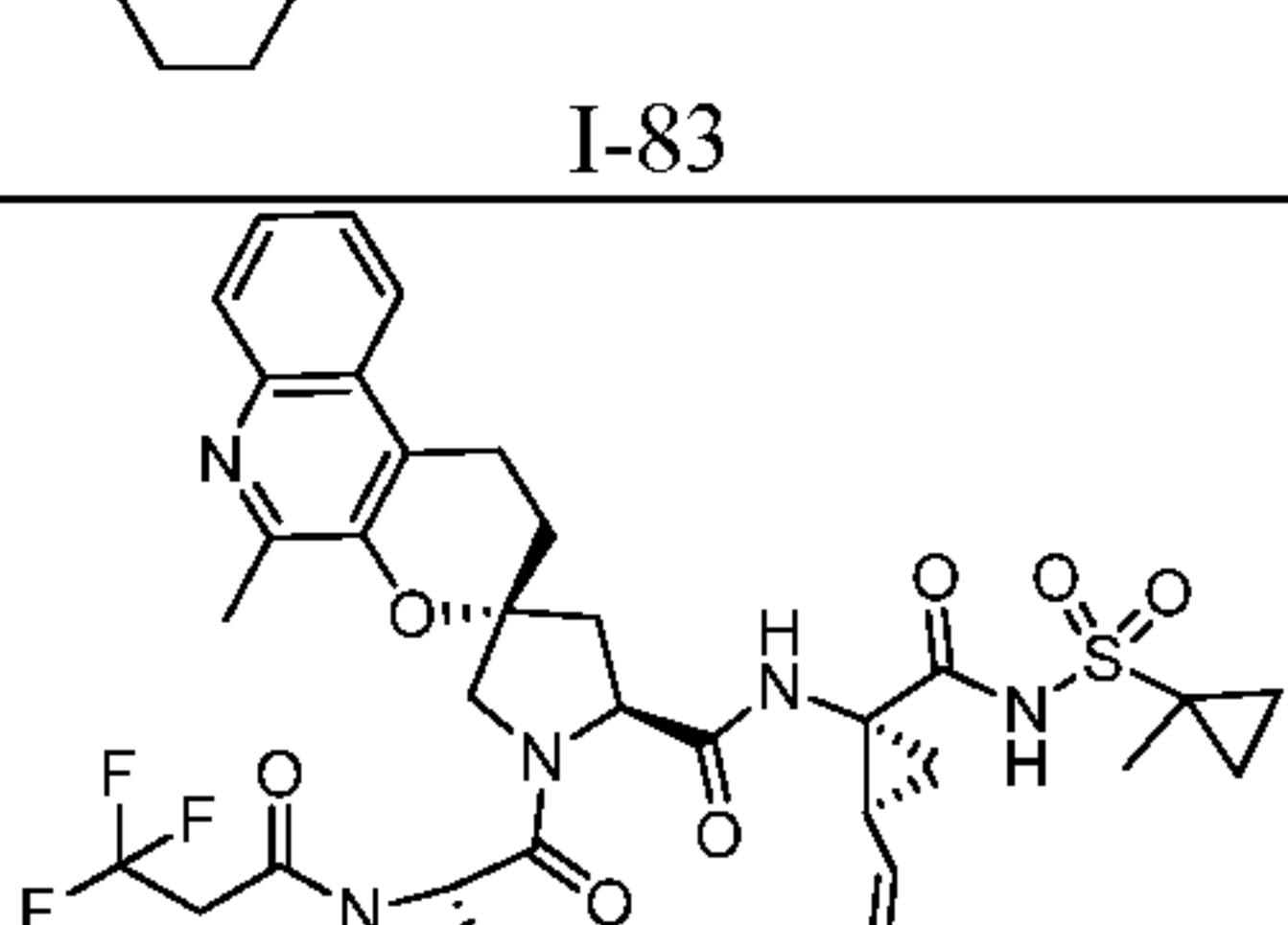
Table 1 illustrates additional HCV protease inhibitors. Reference to "Proc." indicates the Example describing the general procedure employed to produce the compound. The procedure was modified as needed. By using the appropriate procedures or combination of procedures and the appropriate intermediates, the compounds of Examples 68-526 were prepared, as shown in Table 1 below. All compounds prepared from racemic intermediates were separated from resulting diastereomers using reverse or normal phase column chromatography following macrocycle formation or after the final step.

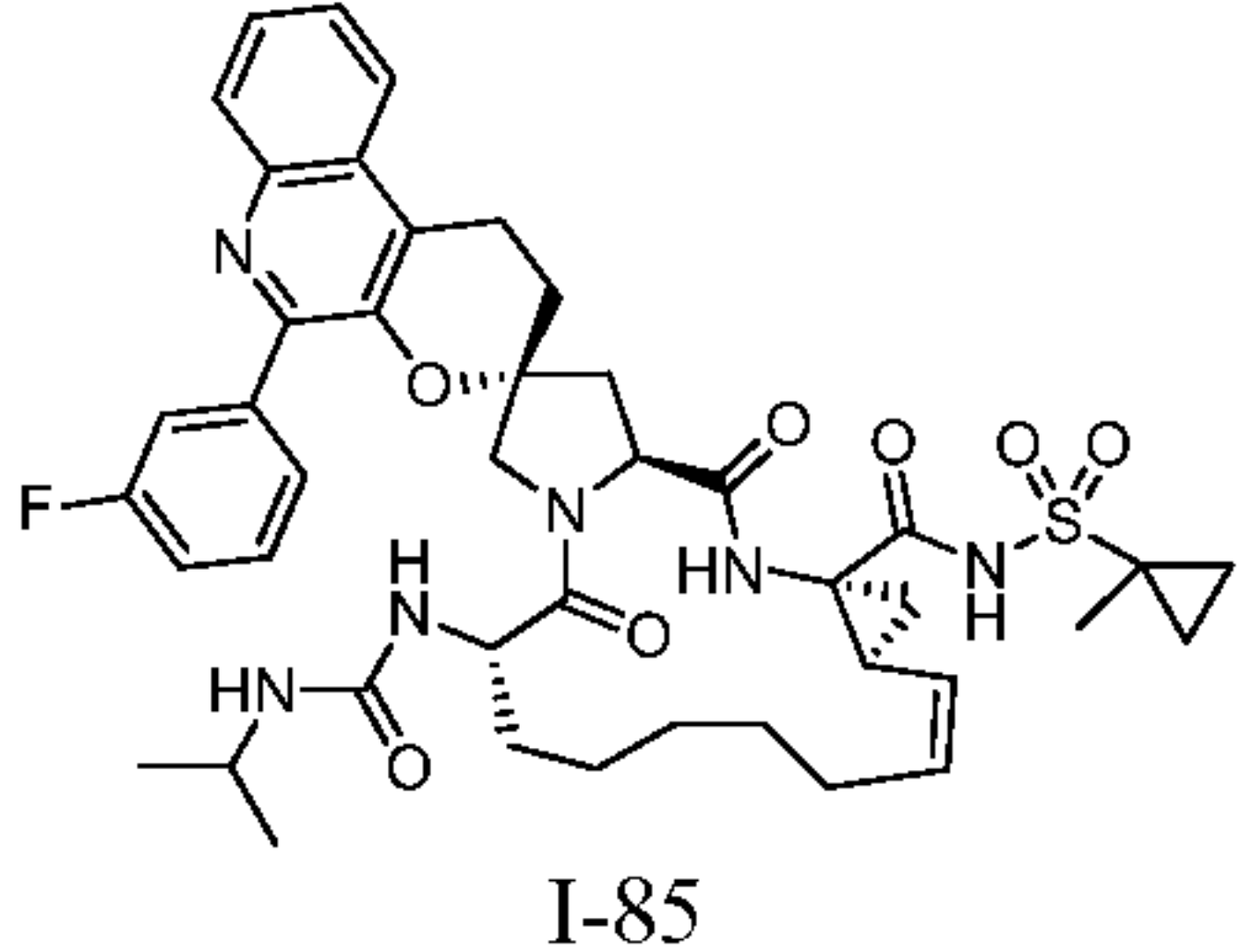
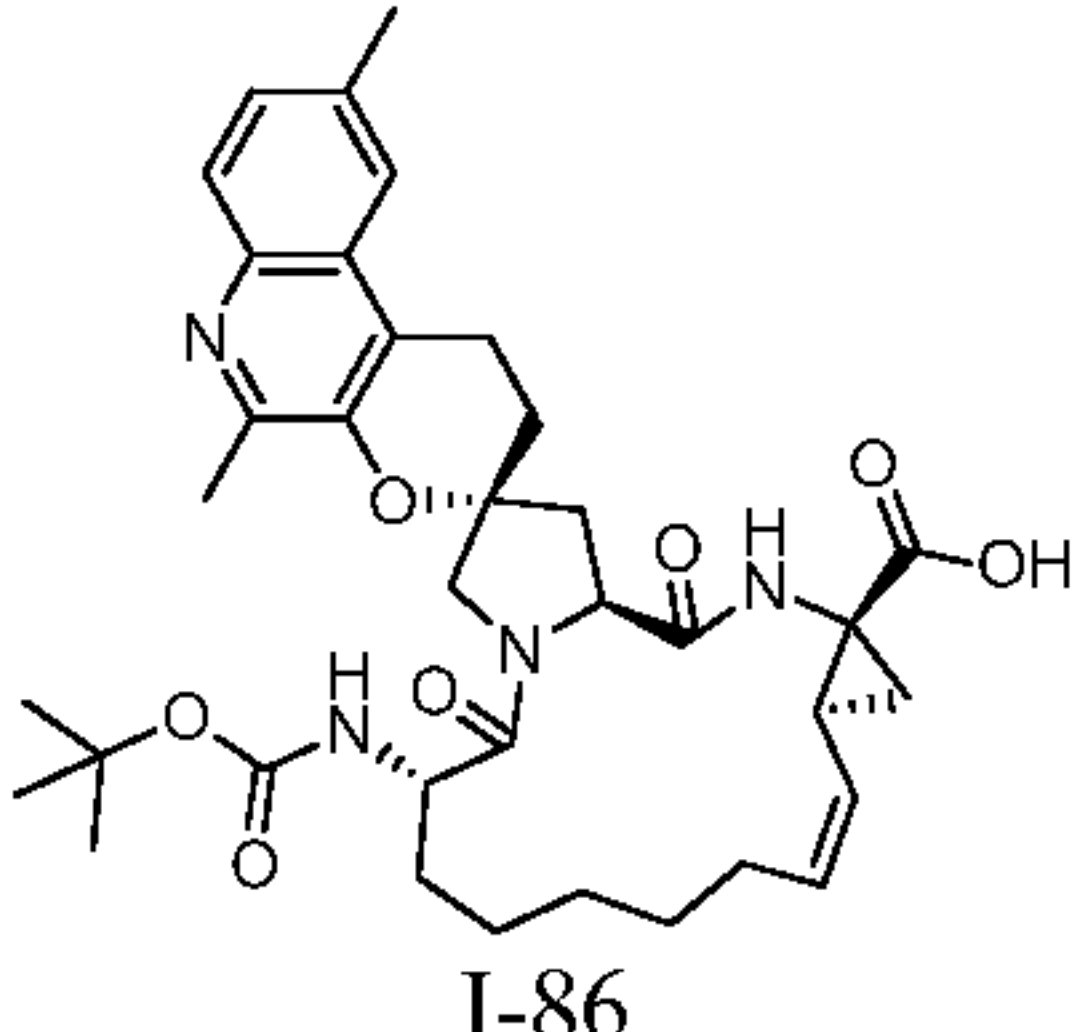
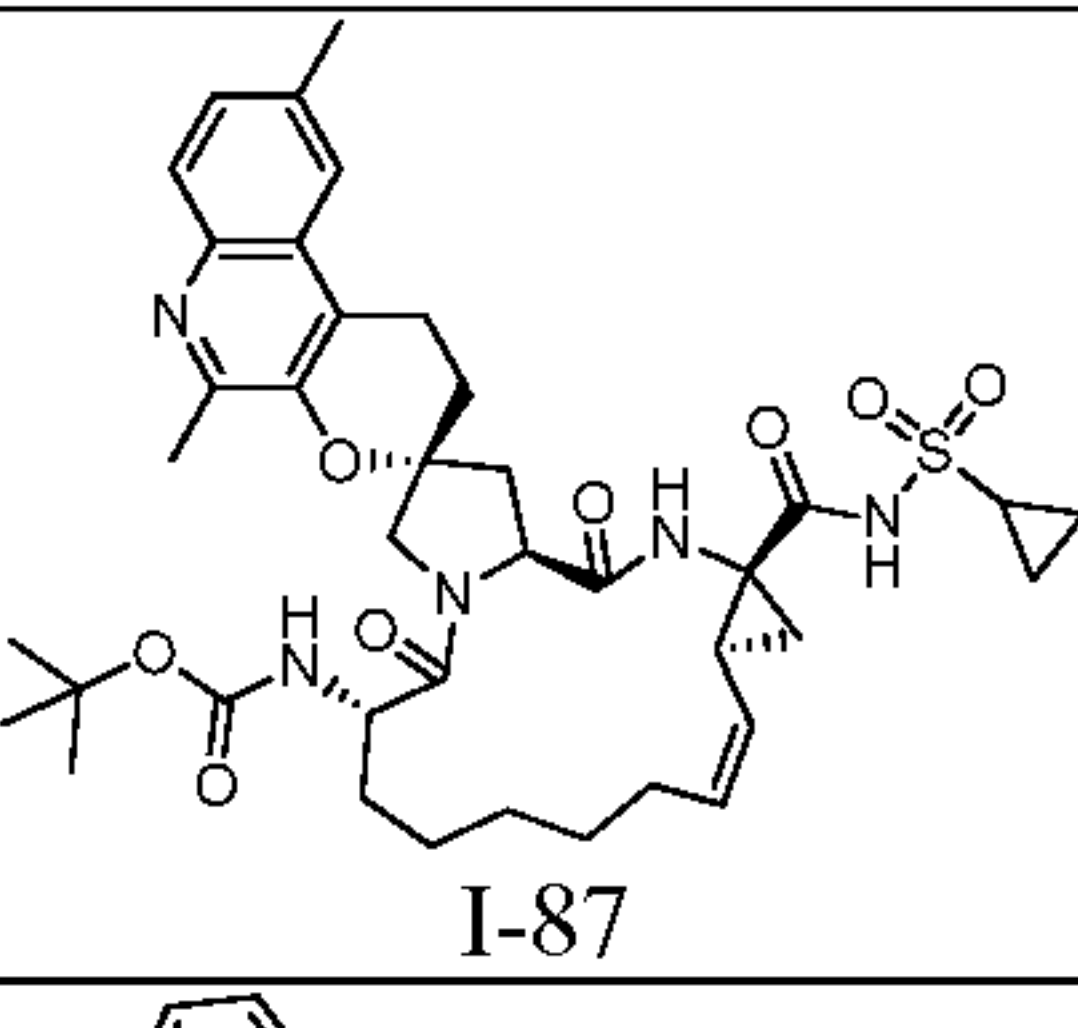
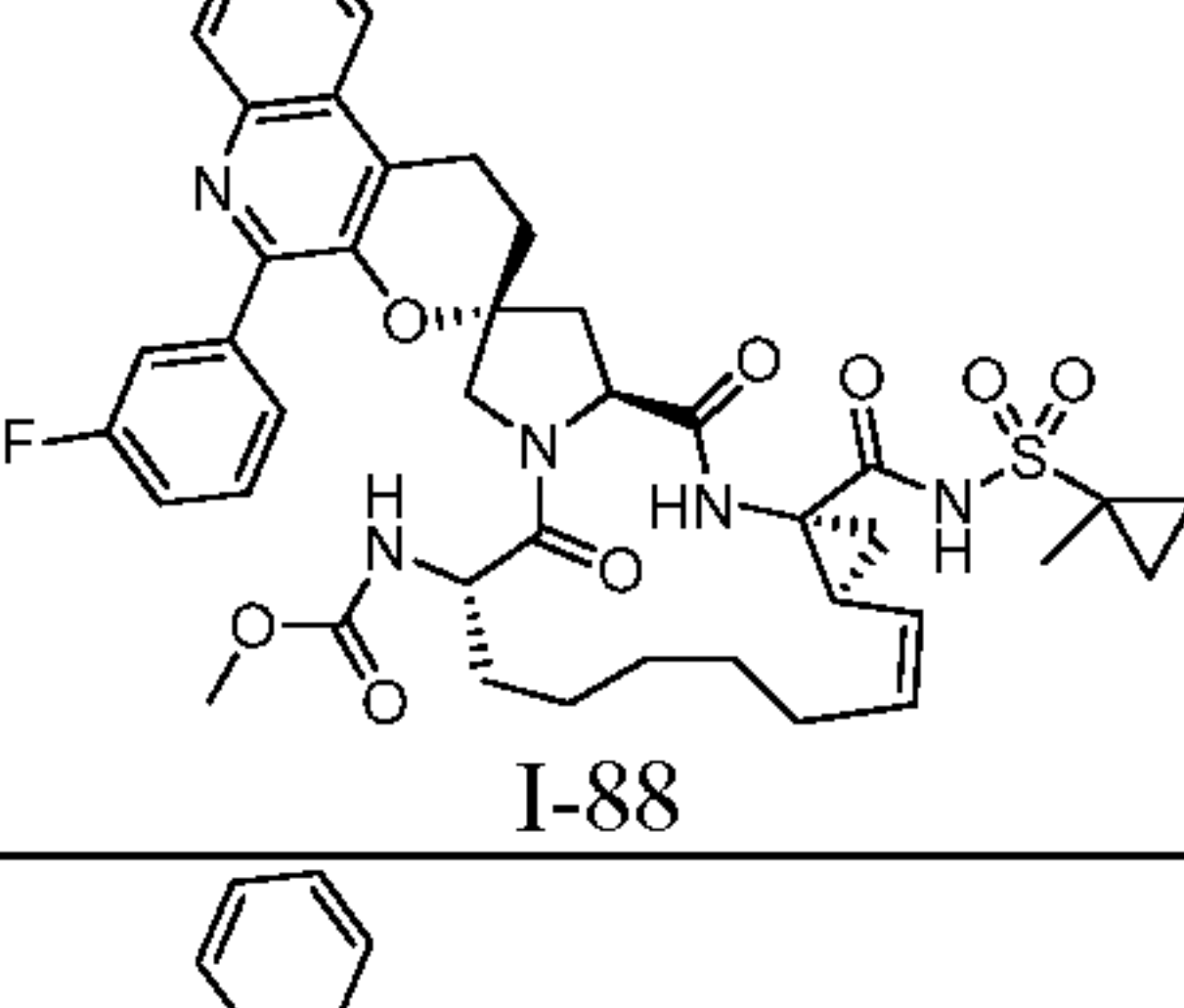
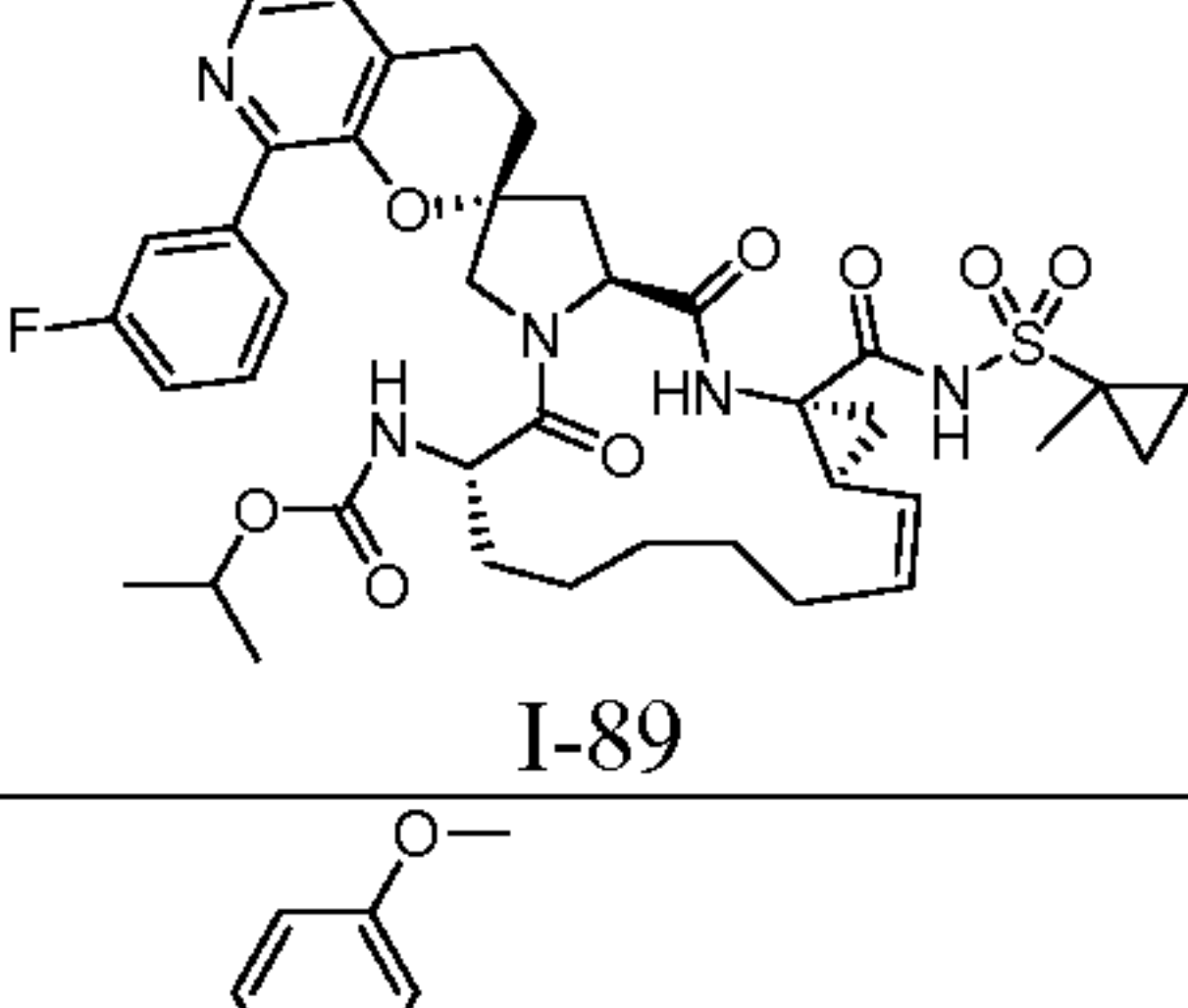
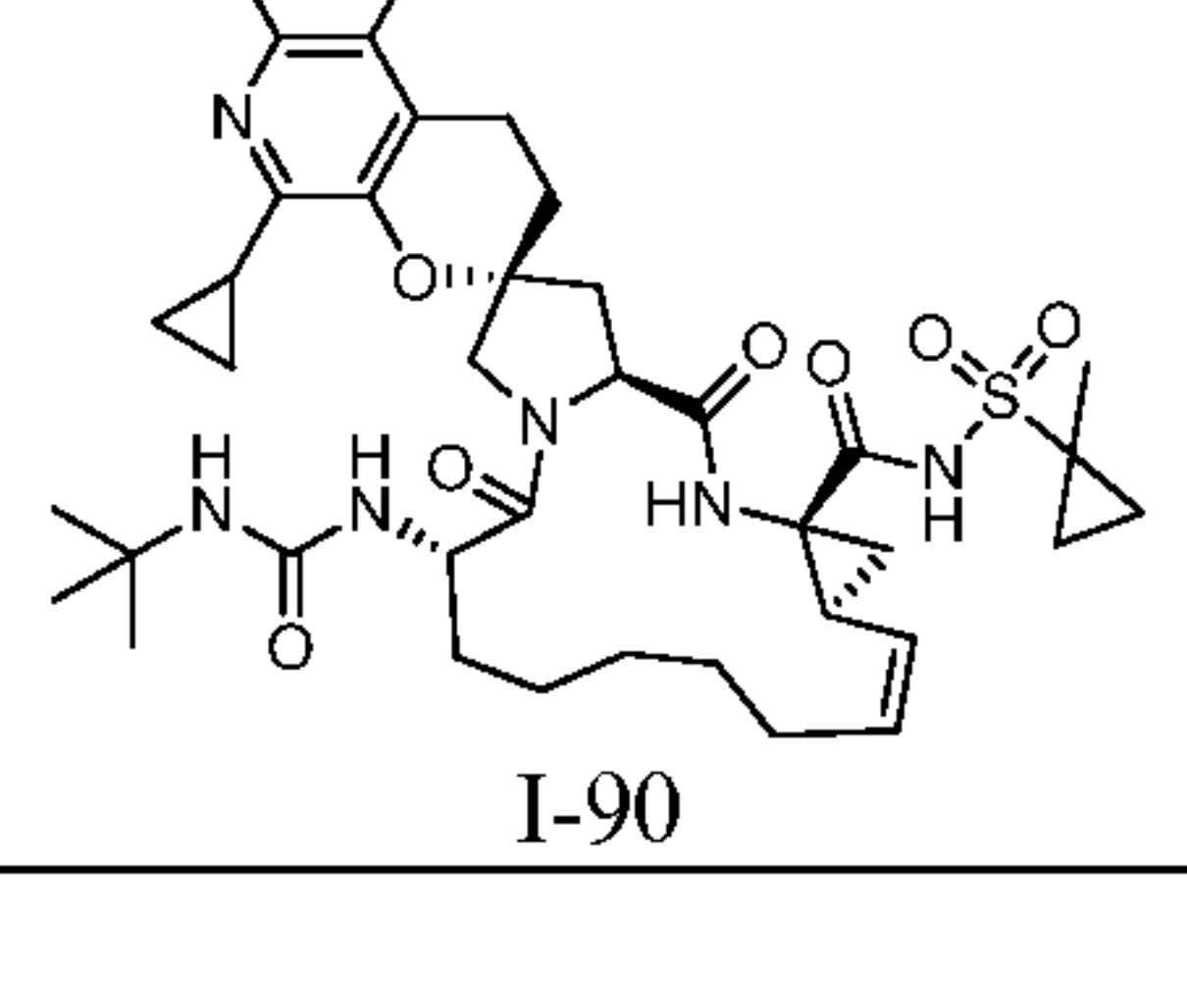
Table 1: Compounds of Examples 68-526

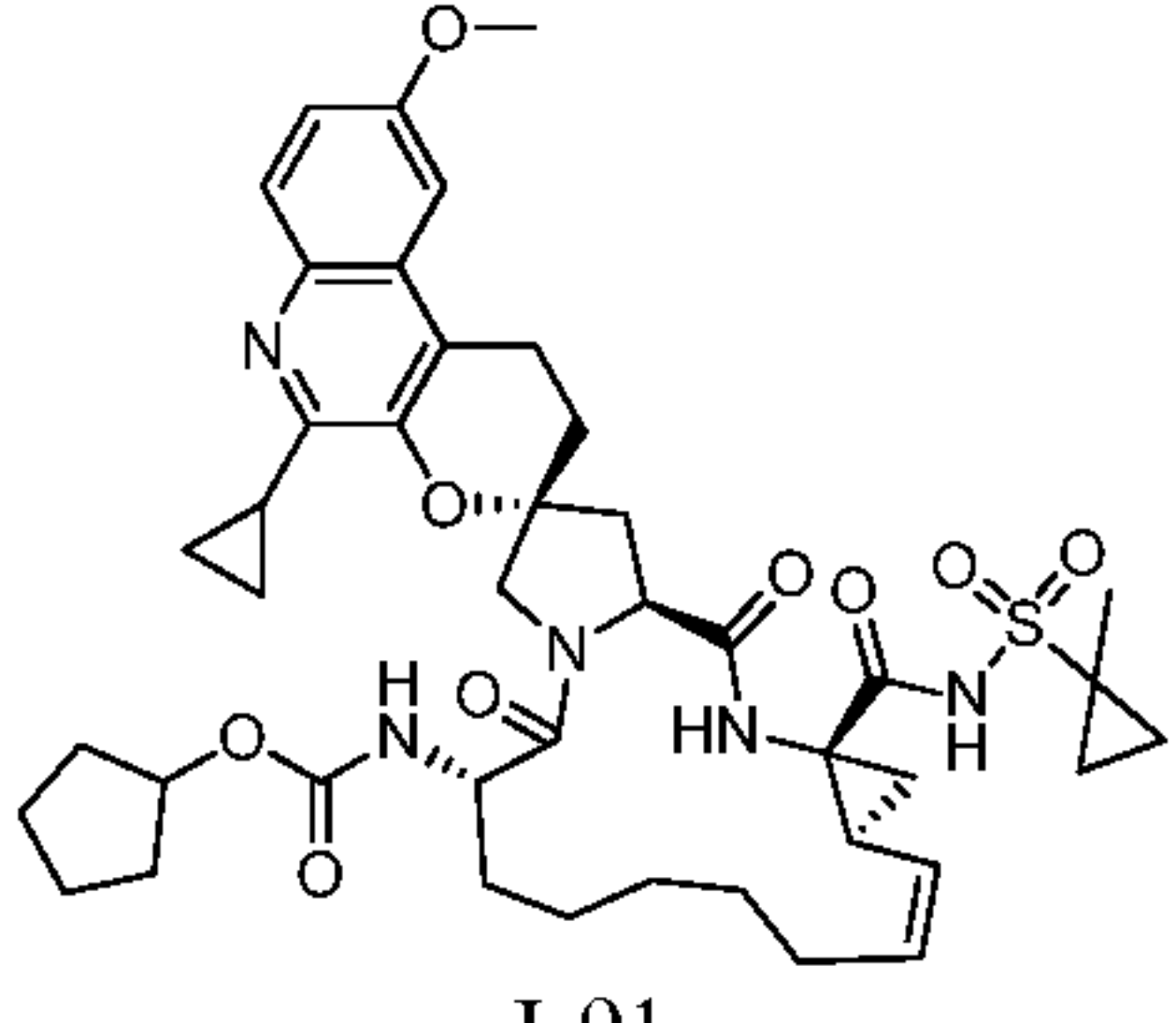
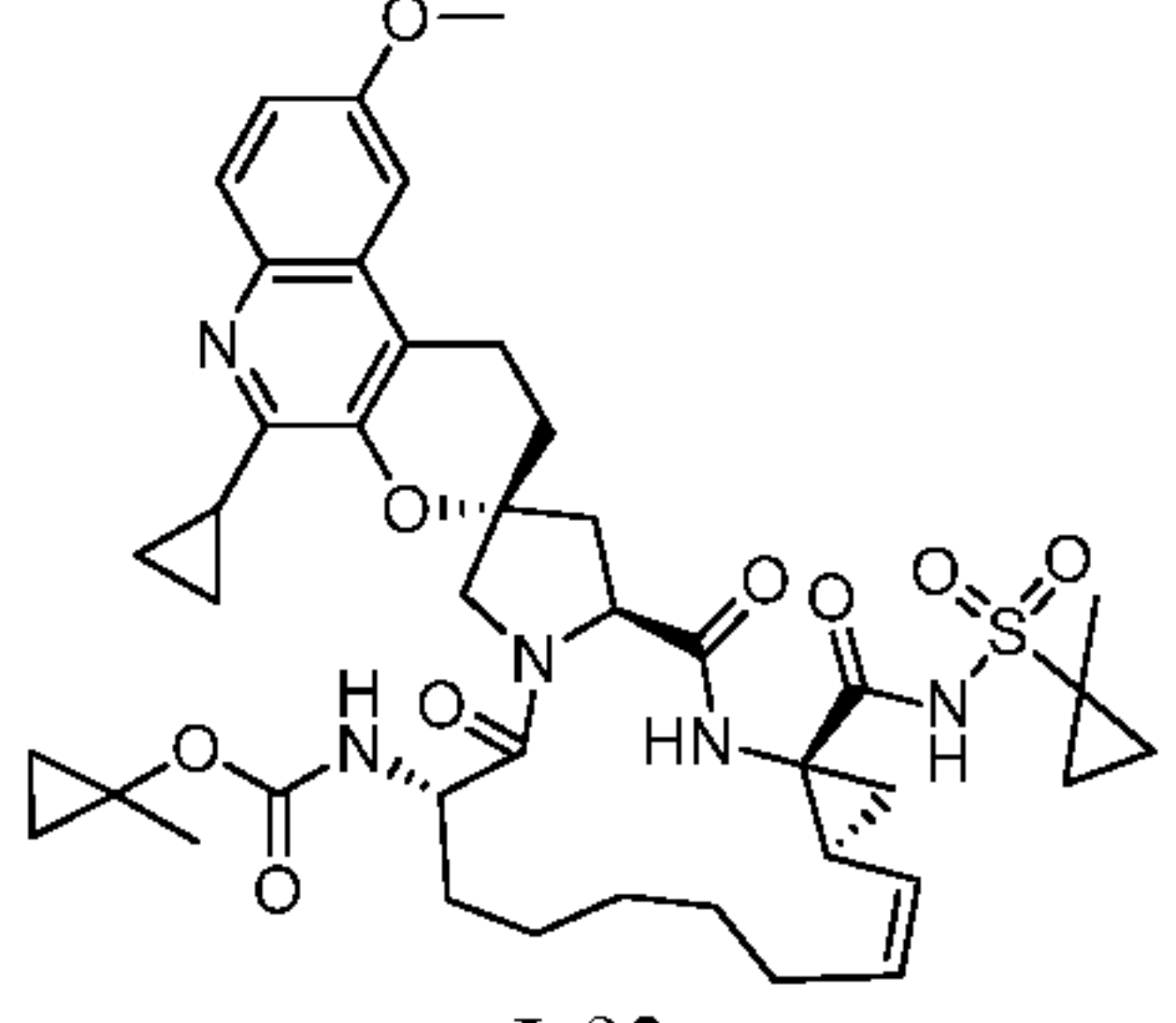
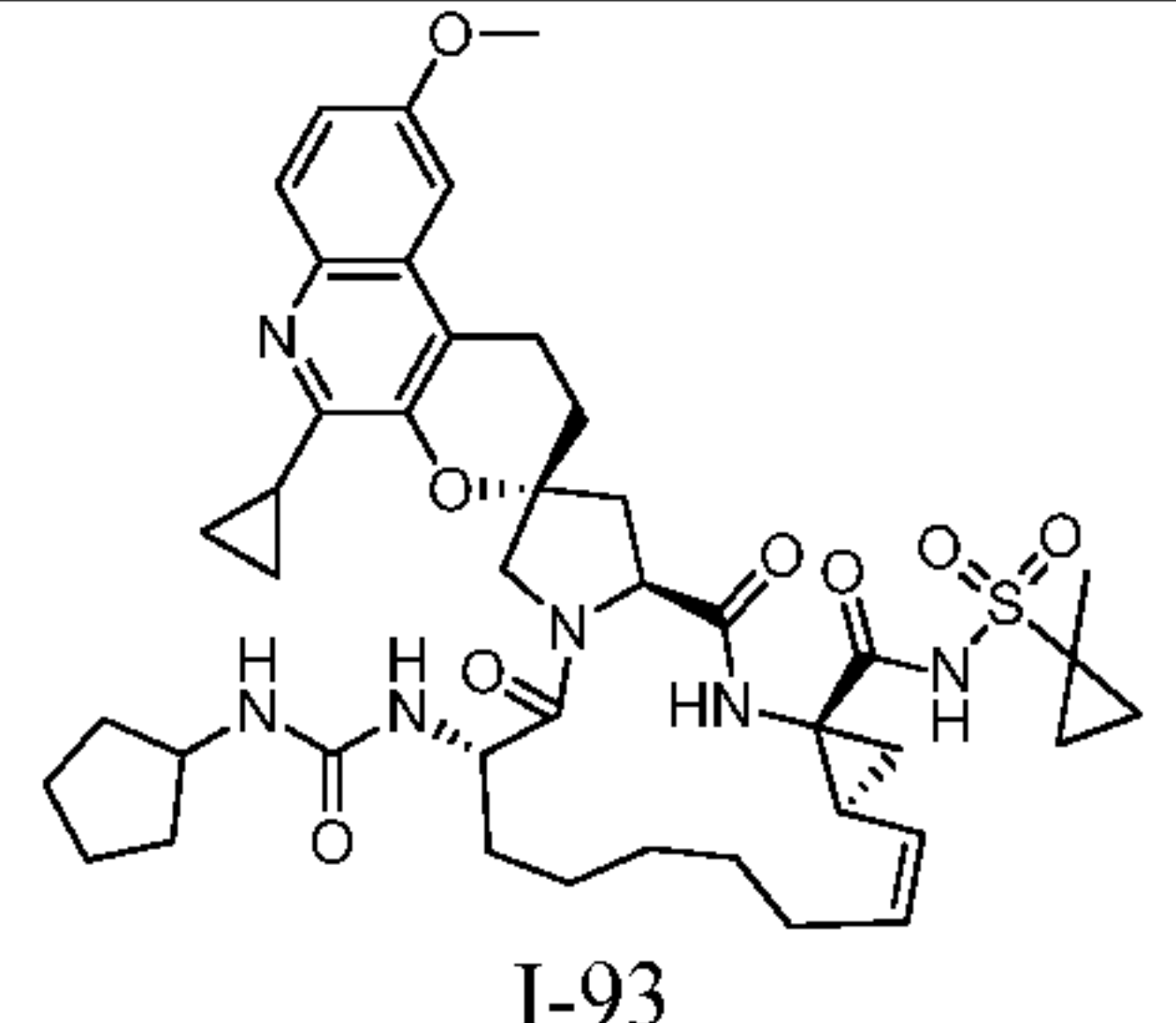
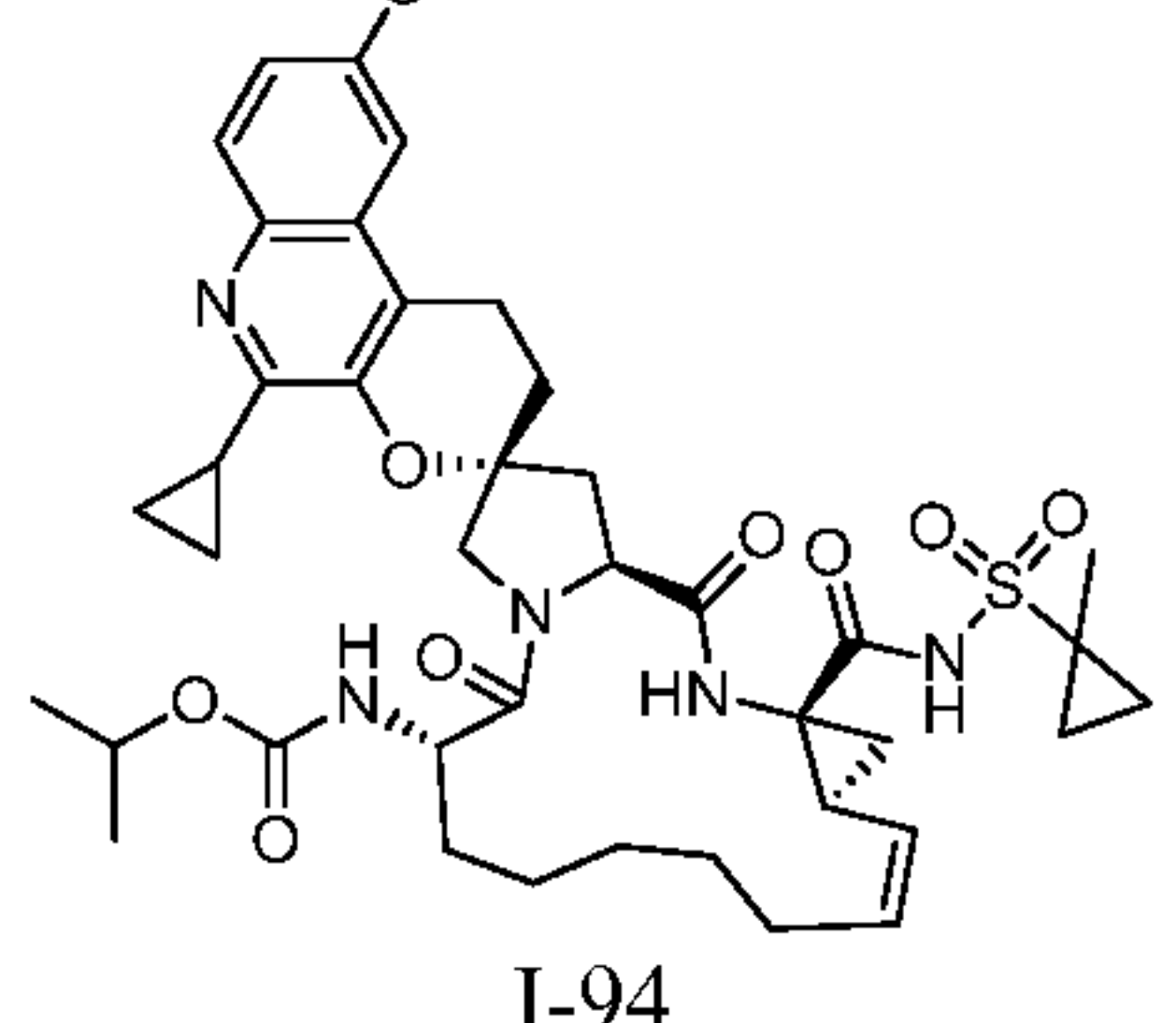
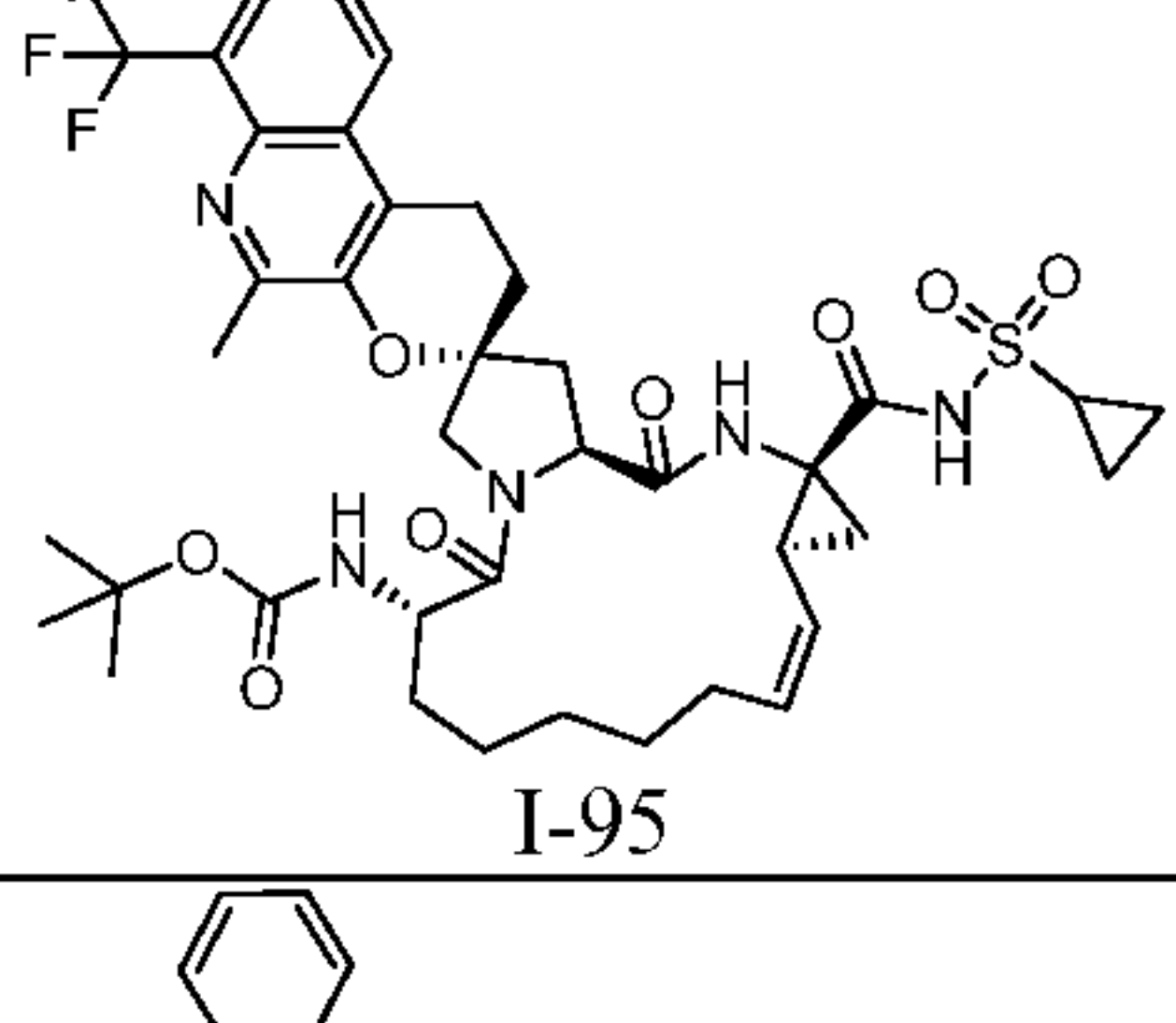
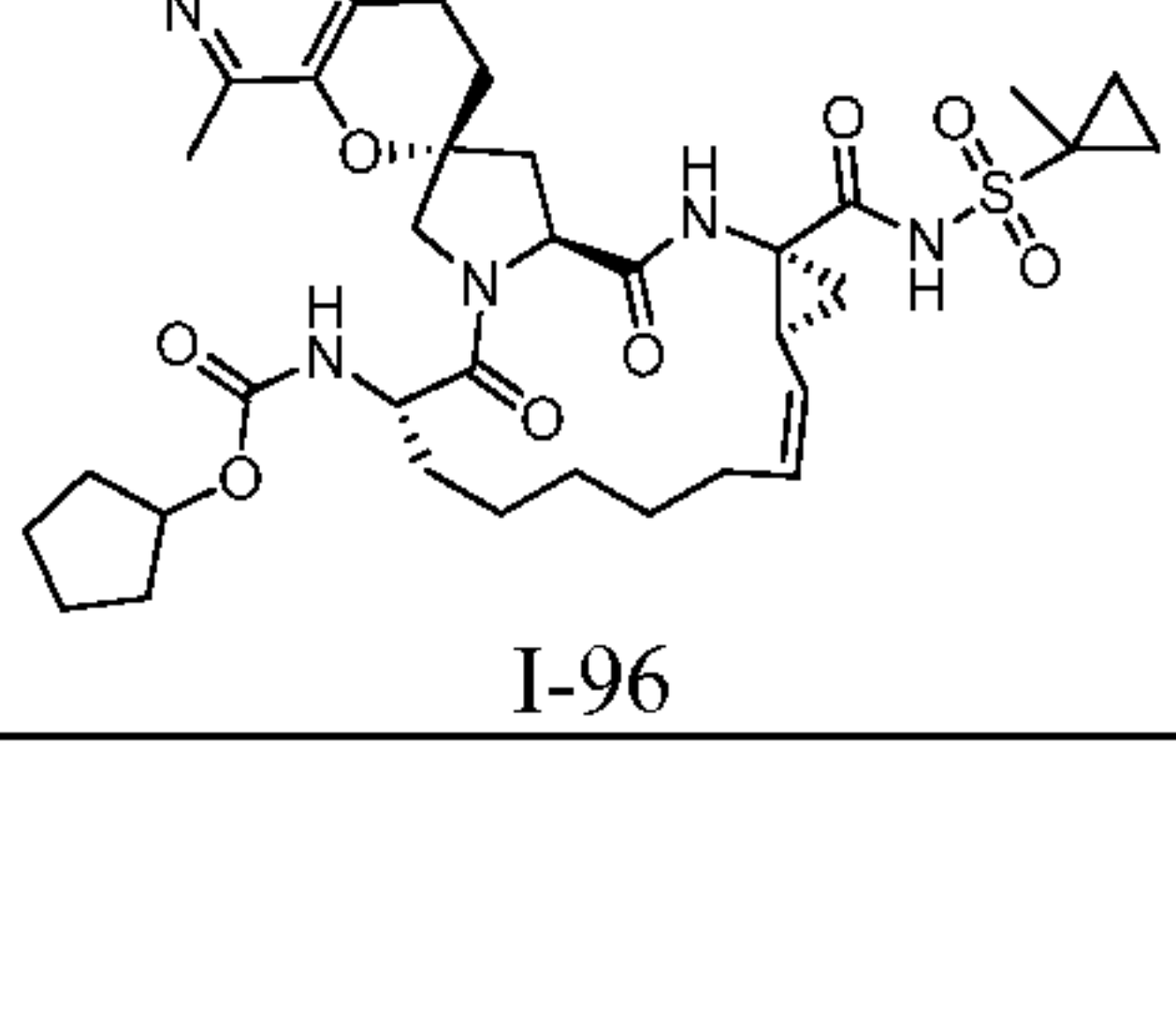
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
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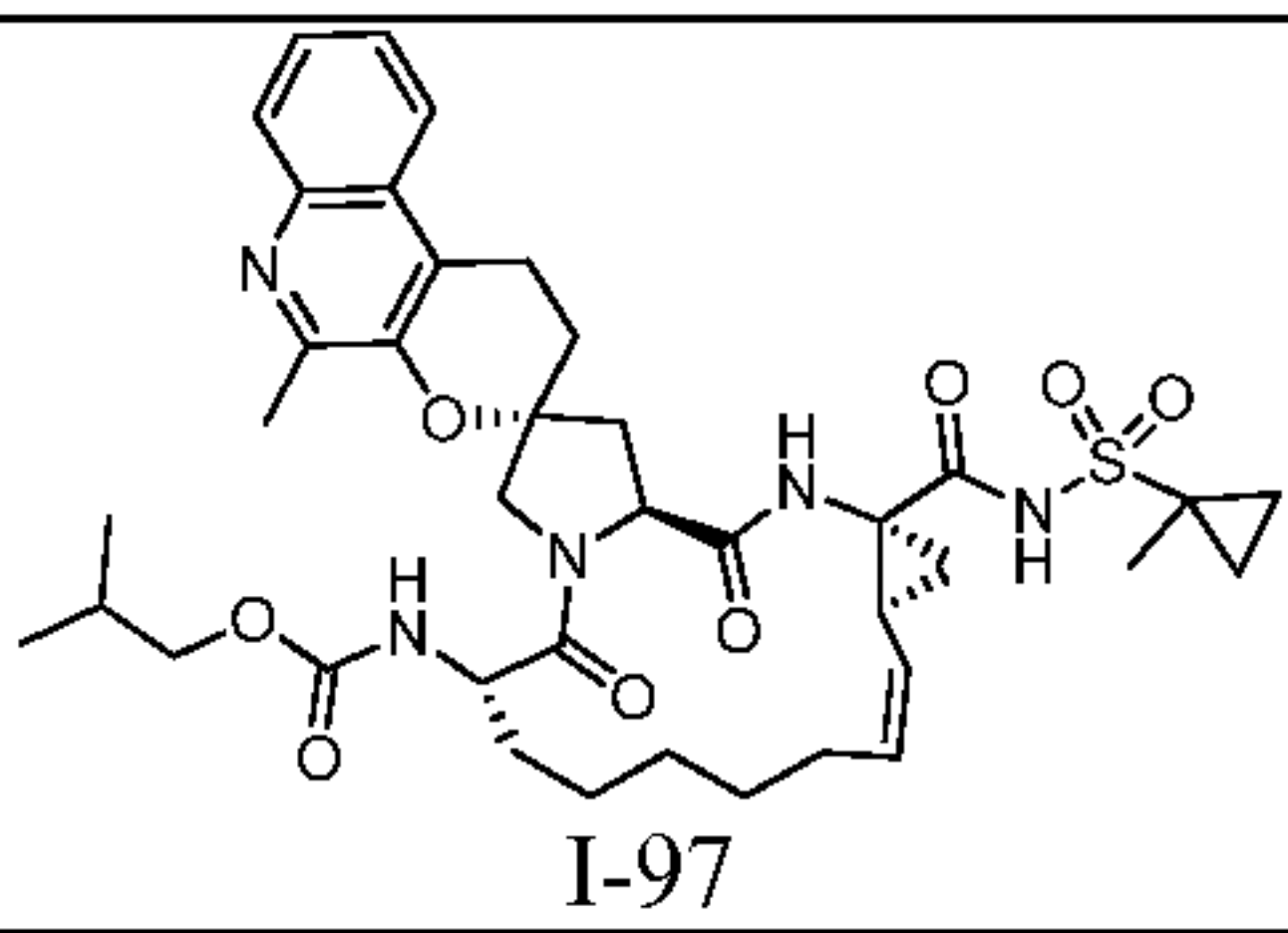
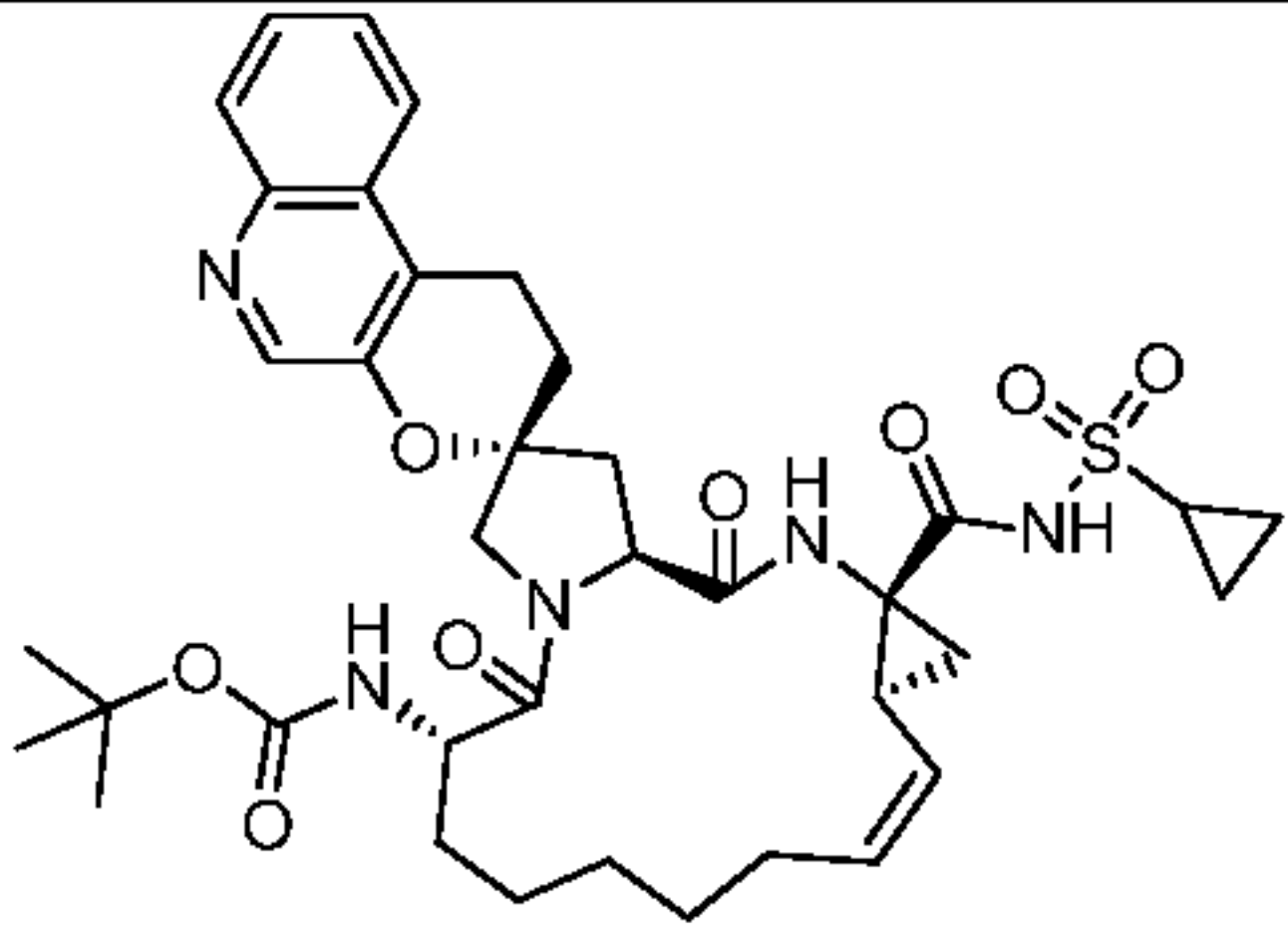
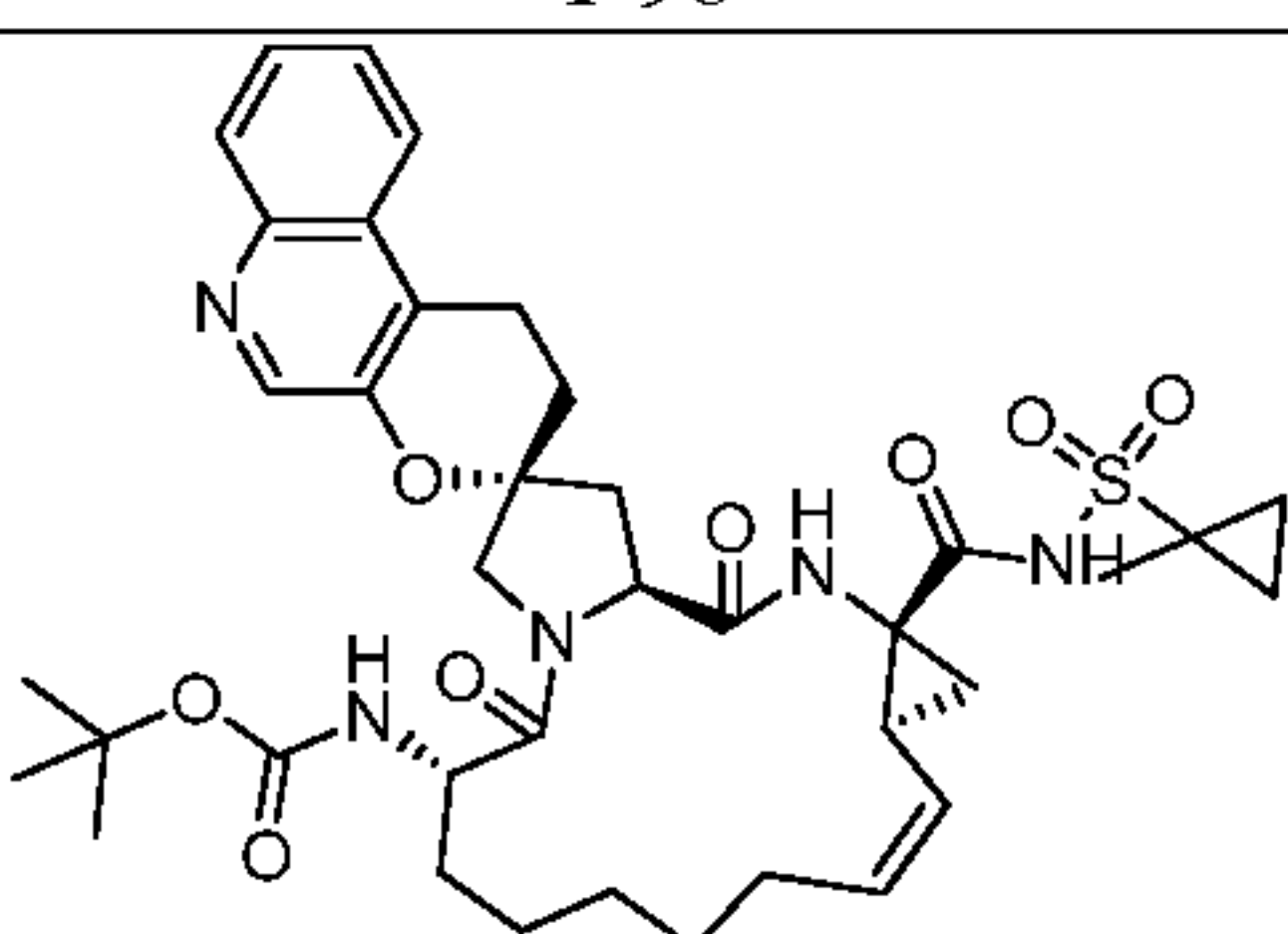
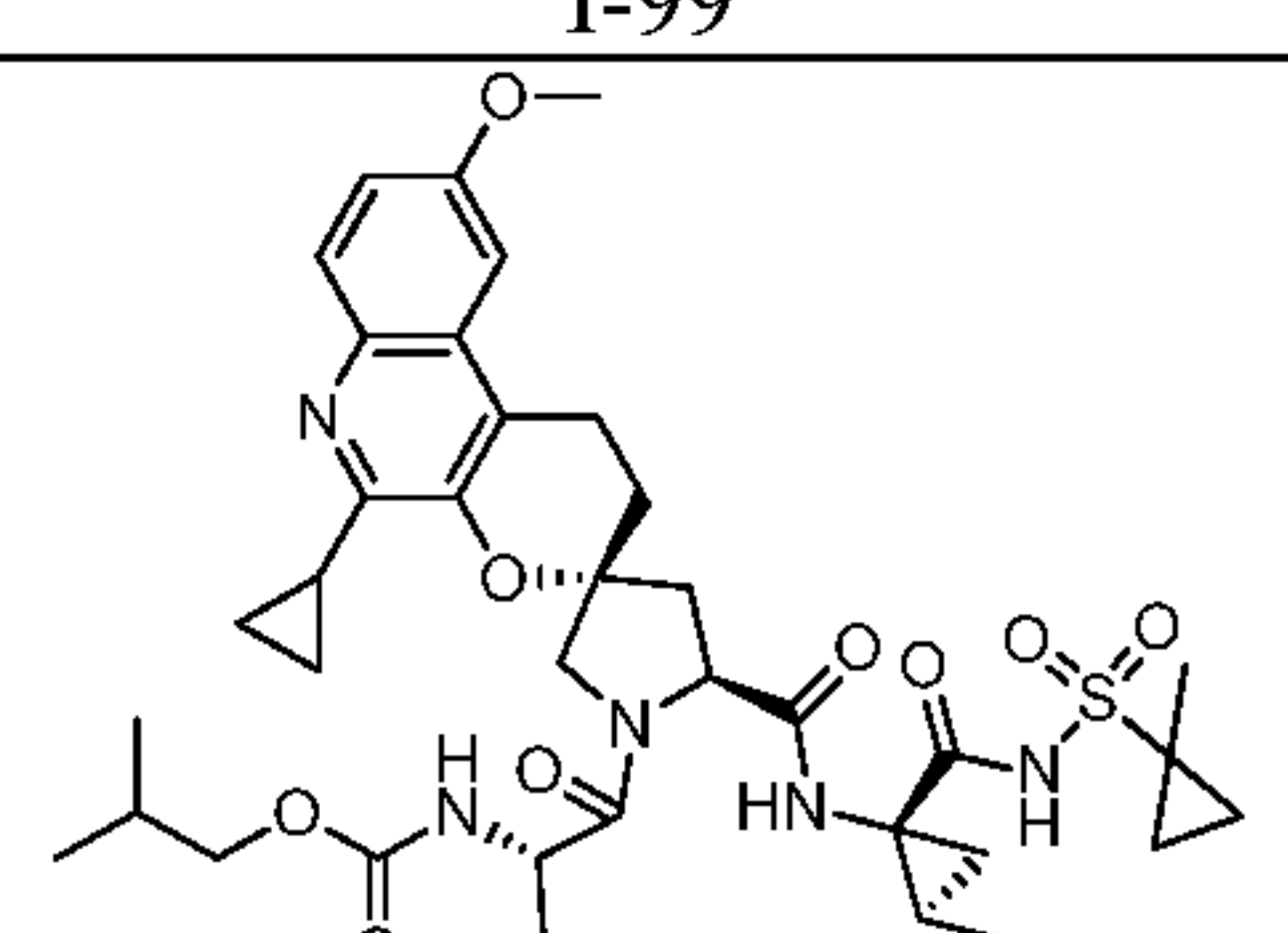
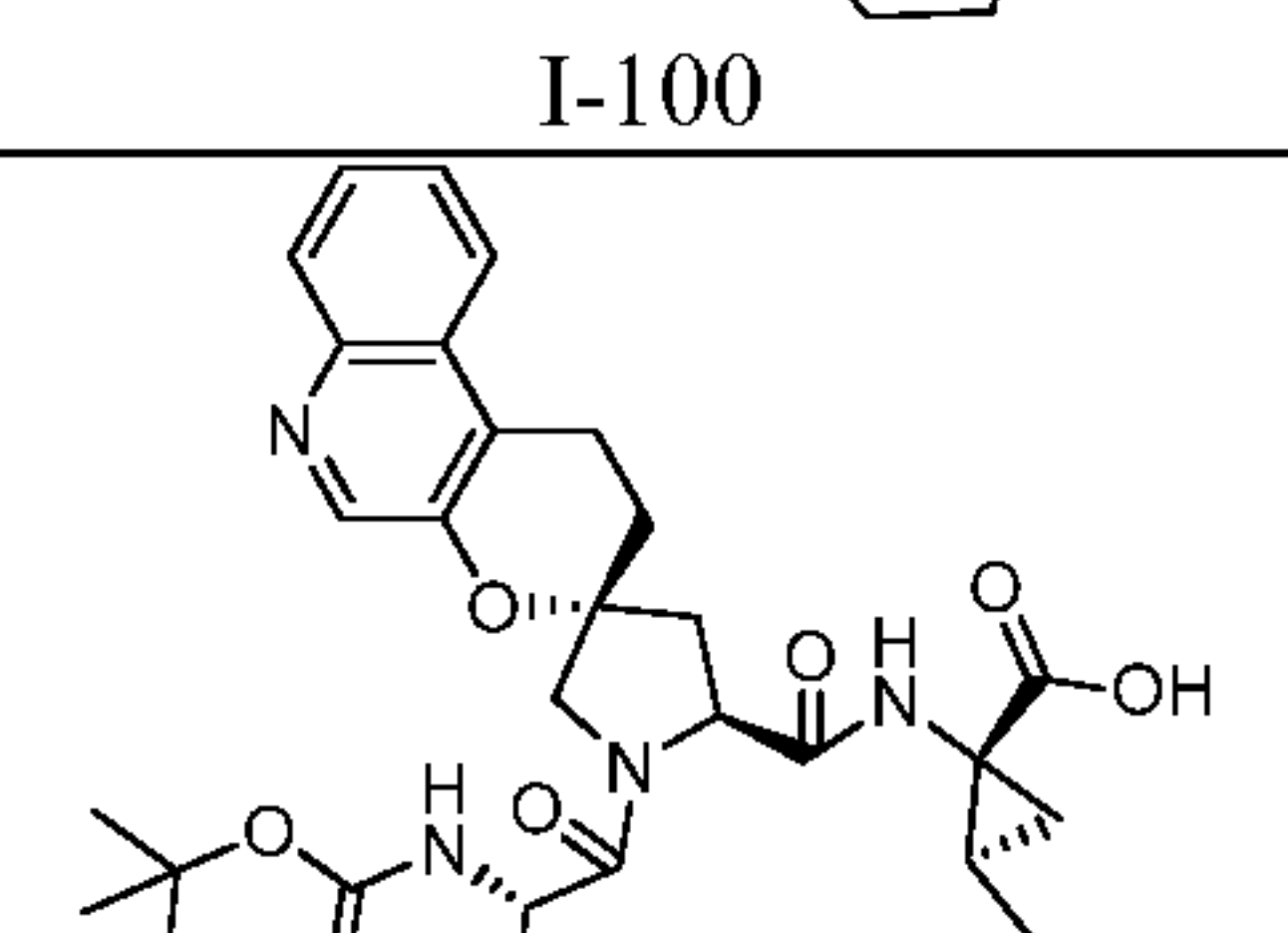
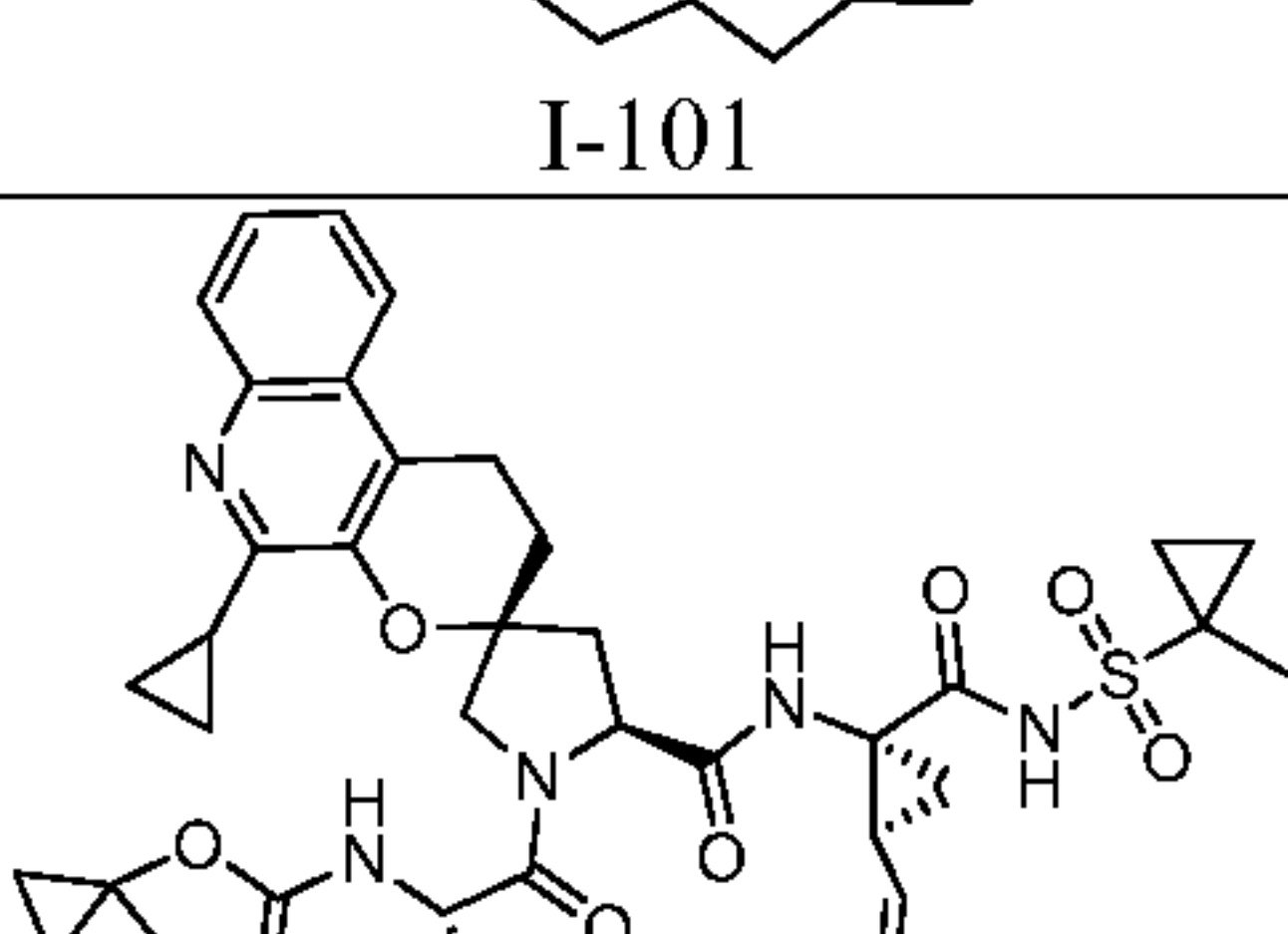
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
68	 I-68	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i>)-5'-cyclopropyl-9'-fluoro-14a-{{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	794
69	 I-69	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i>)-5'-cyclopropyl-7'-fluoro-14a-{{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1,35	794
70	 I-70	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i>)-5'-cyclopropyl-8'-methoxy-14a-{{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16	806
71	 I-71	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13a <i>S</i> ,14a <i>R</i> ,16a <i>S</i>)-8'-fluoro-5'-methyl-14a-{{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	768.2
72	 I-72	<i>tert</i> -butyl [(3 <i>S</i> ,6' <i>S</i> ,12' <i>Z</i> ,13a' <i>S</i> ,14a' <i>R</i> ,16a' <i>S</i>)-14a'-{{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5',16'-dioxo-1,1',2,5',6',7',8',9',10',11',13a',14',14a',15',16',16a'-hexadecahydrospiro[benzo[<i>f</i>]chromene-3,2'-cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine]-6'-yl]carbamate	9	773.2

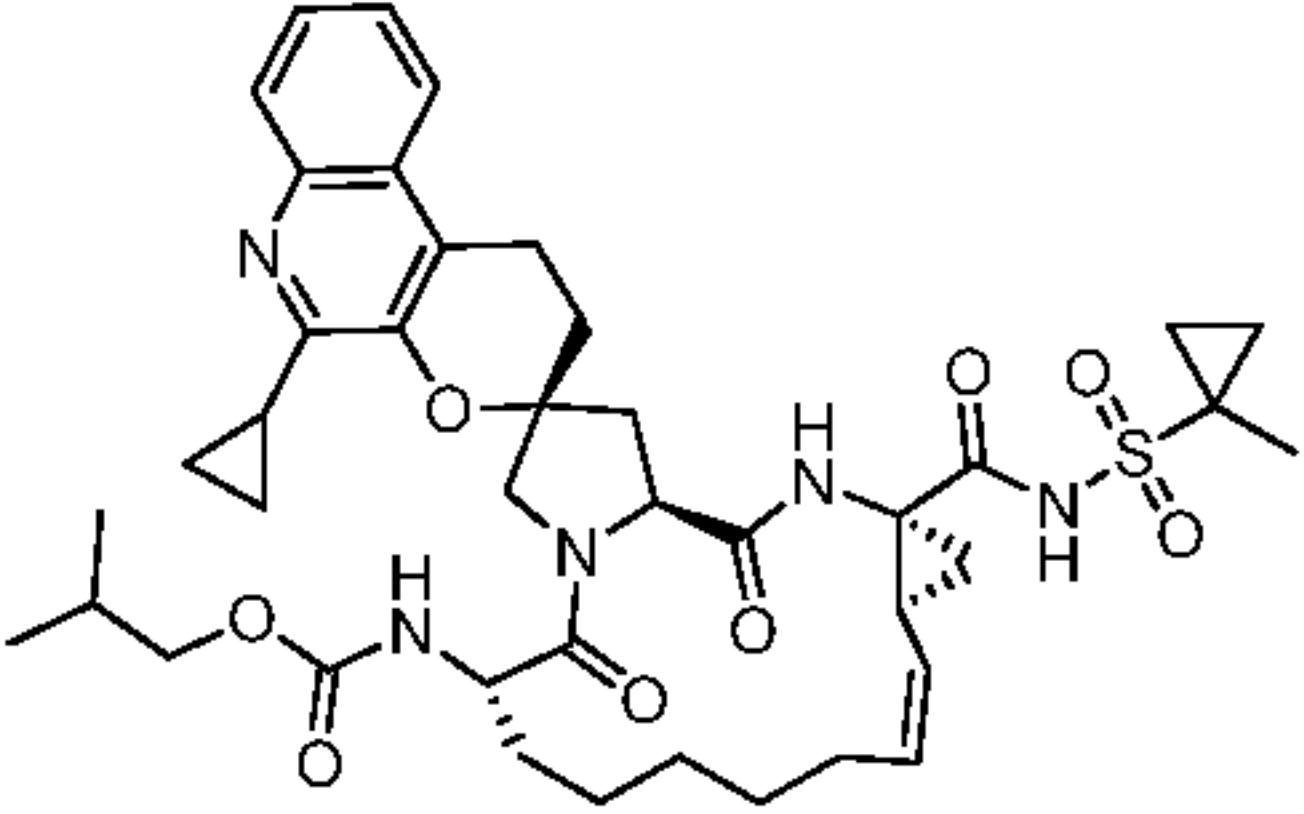
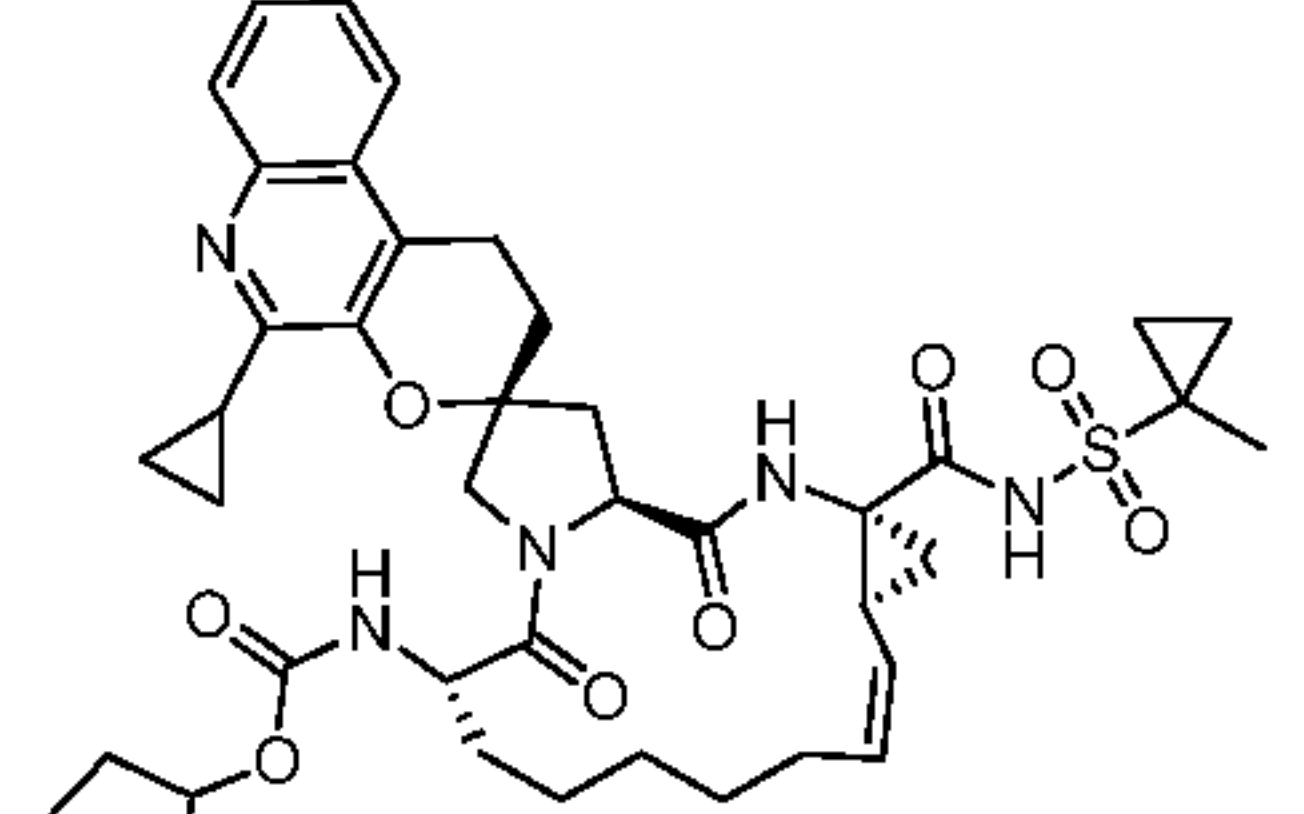
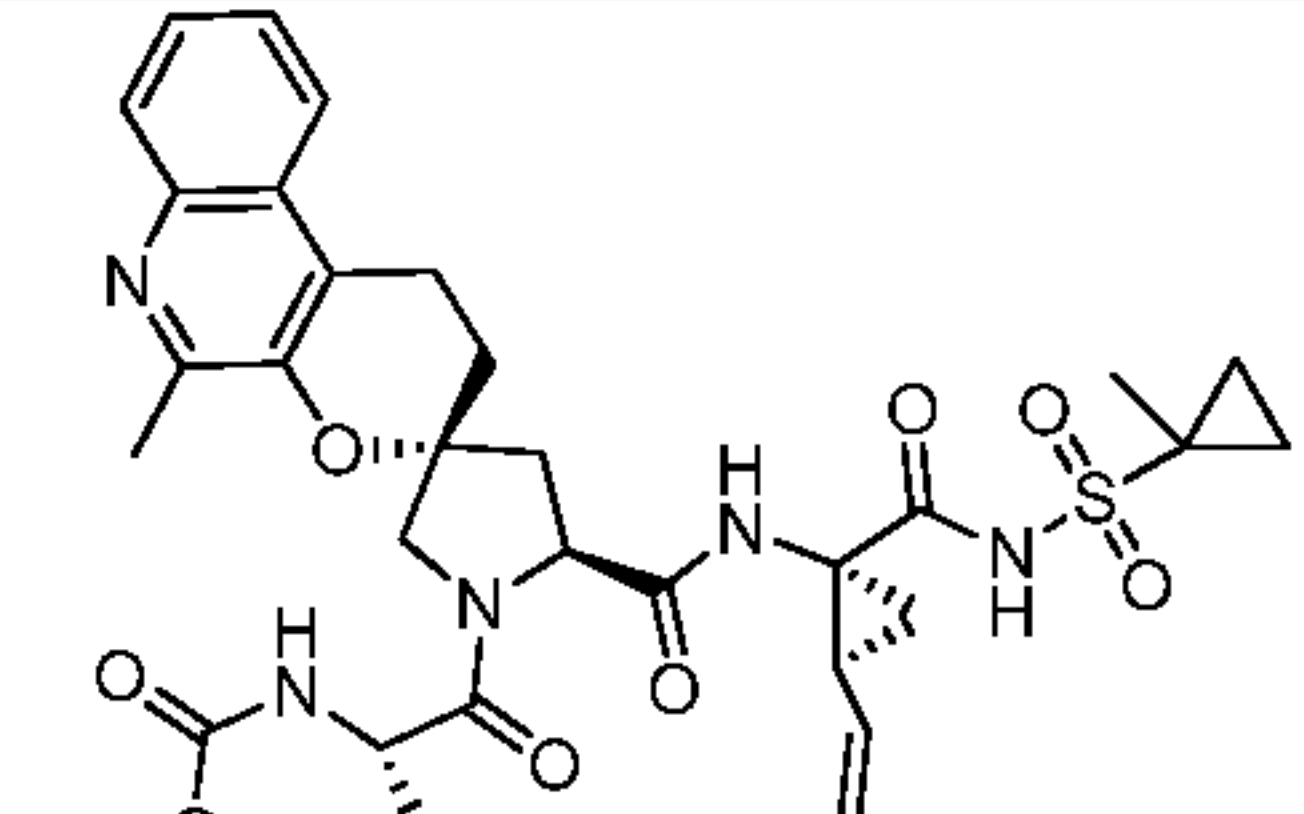
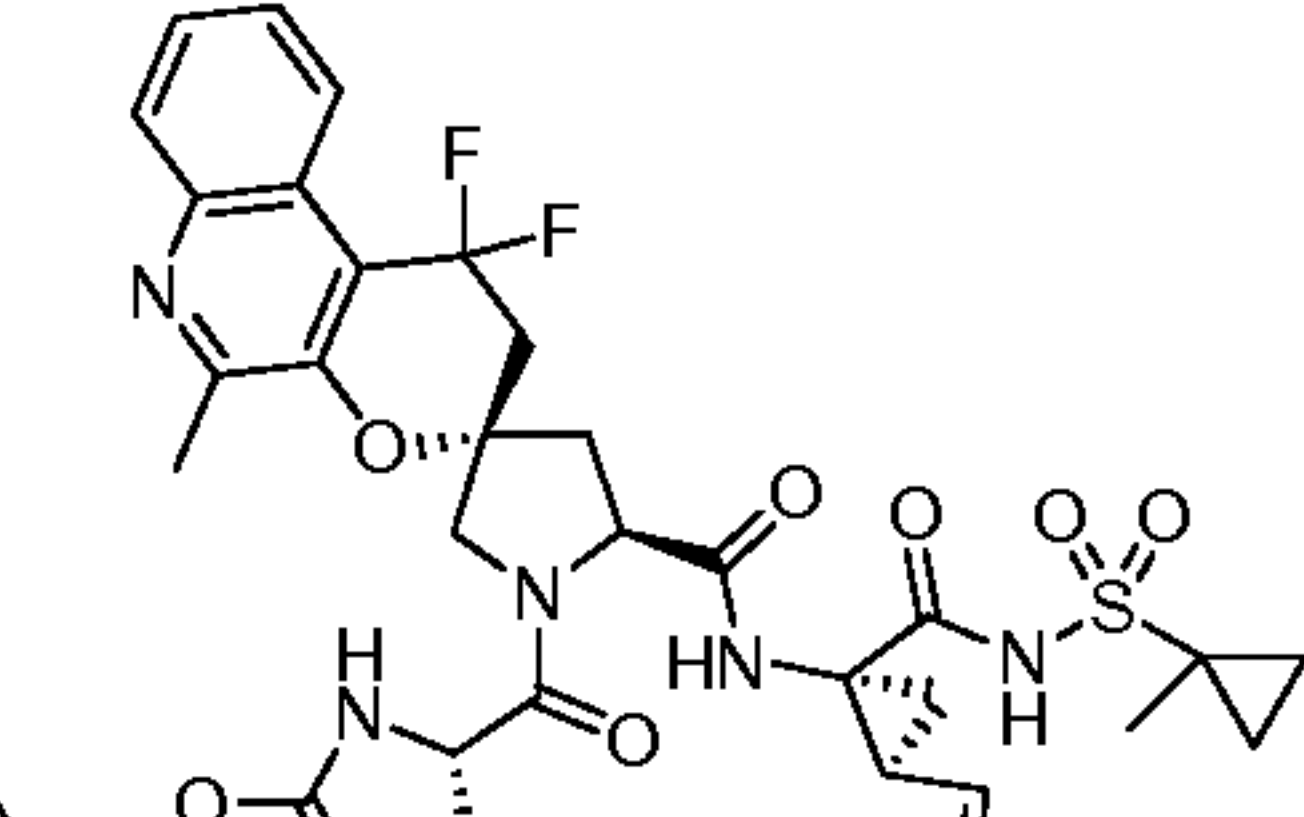
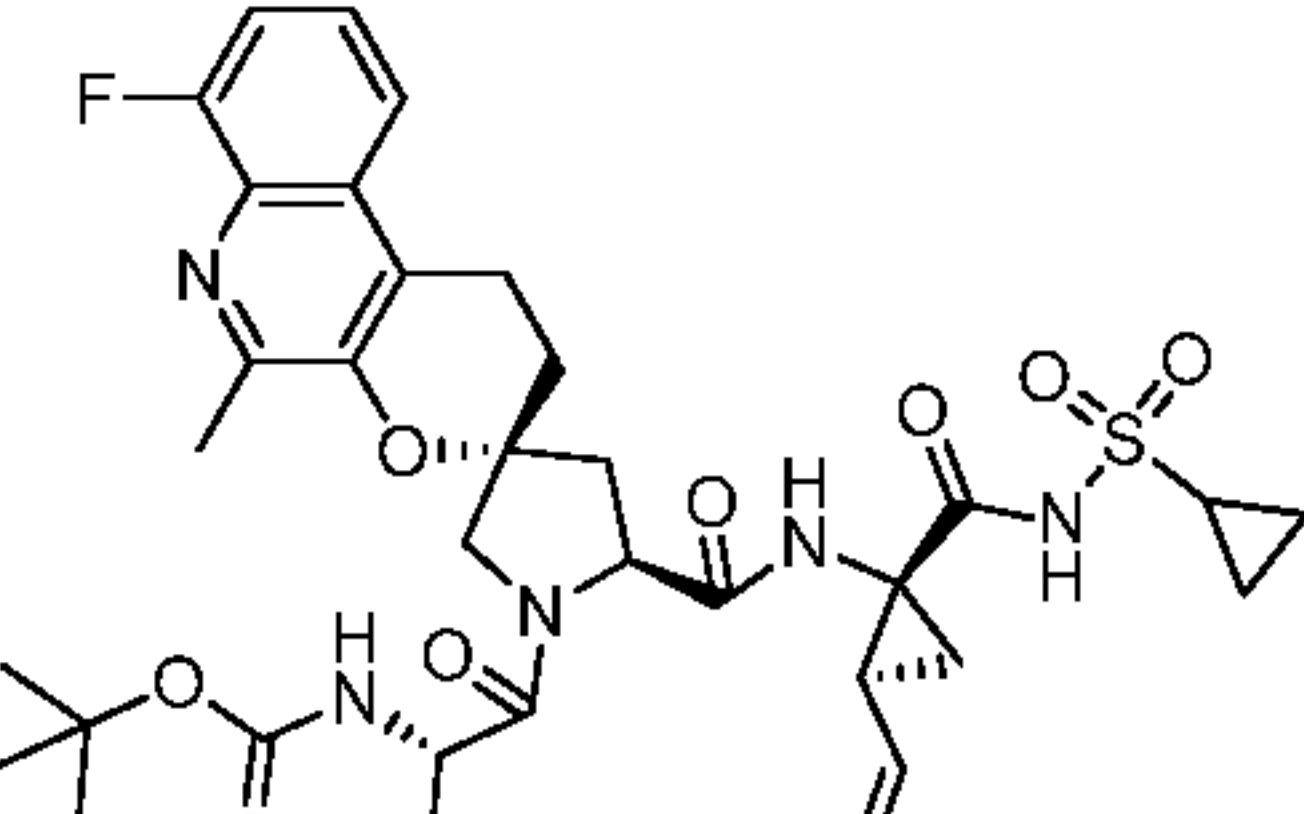
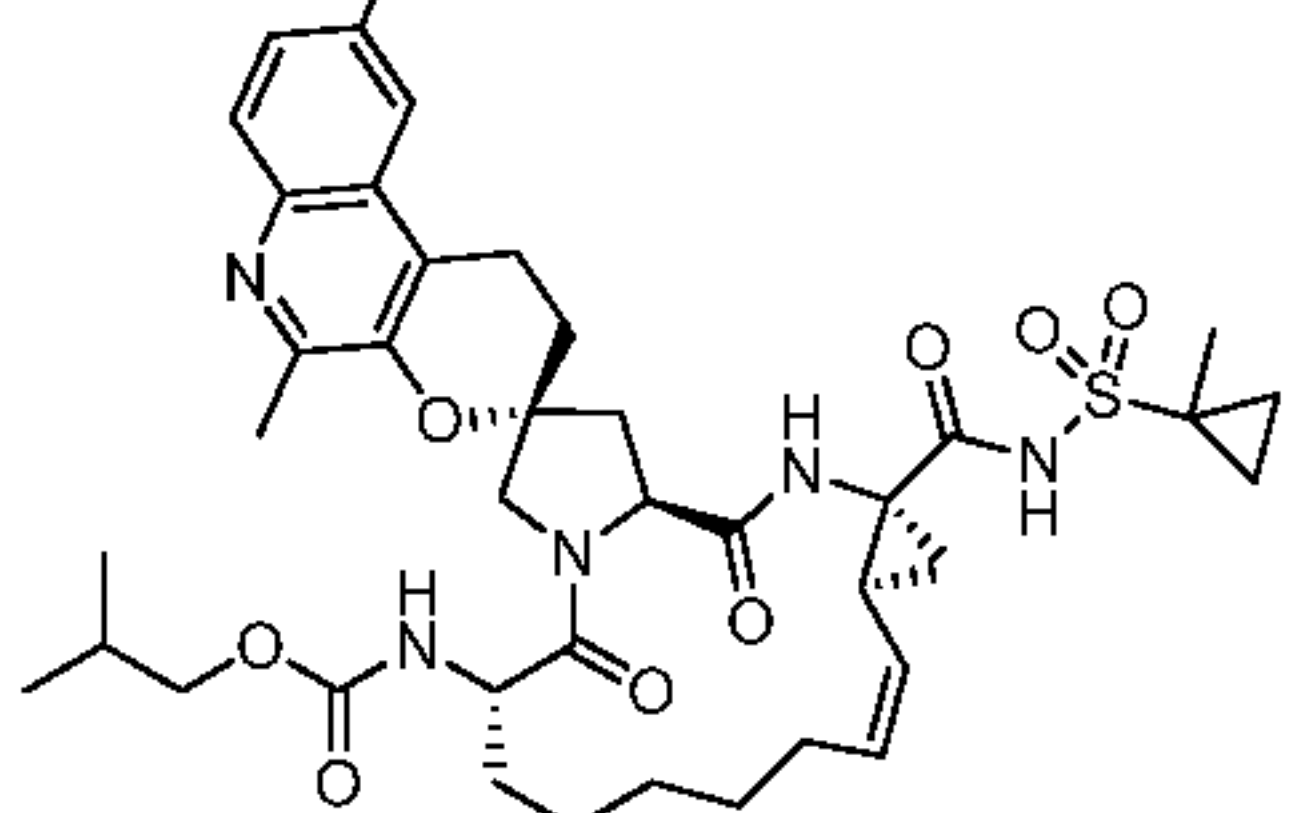
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
73	 I-73	<i>tert</i> -butyl [(3 <i>R</i> ,6' <i>S</i> ,12' <i>Z</i> ,13 <i>a</i> ' <i>S</i> ,14 <i>a</i> ' <i>R</i> ,16 <i>a</i> ' <i>S</i>)-14 <i>a</i> '-[[1-(1-methylcyclopropyl)sulfonyl]carbamoyl]-5',16'-dioxo-1,1',2,5',6',7',8',9',10',11',13 <i>a</i> ',14',14 <i>a</i> ',15',16',16 <i>a</i> '-hexadecahydrospiro[benzo[<i>f</i>]chromene-3,2'-cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecin]-6'-yl]carbamate	9	773.2
74	 I-74	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>a</i> ' <i>S</i> ,14 <i>a</i> ' <i>R</i> ,16 <i>a</i> ' <i>S</i>)-5'-methyl-14 <i>a</i> '-[[1-(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ',14,14 <i>a</i> ',15,16,16 <i>a</i> '-hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	750.3
75	 I-75	<i>tert</i> -butyl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>a</i> ' <i>S</i> ,14 <i>a</i> ' <i>R</i> ,16 <i>a</i> ' <i>S</i>)-5'-methyl-14 <i>a</i> '-[[1-(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ',14,14 <i>a</i> ',15,16,16 <i>a</i> '-hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	750.3
76	 I-76	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>a</i> ' <i>S</i> ,14 <i>a</i> ' <i>R</i> ,16 <i>a</i> ' <i>S</i>)-6-[(<i>tert</i> -butylcarbamoyl)amino]-5'-methyl- <i>N</i> -[[1-(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ',14,15,16,16 <i>a</i> '-tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> '(5 <i>H</i>)-carboxamide	47	749.2
77	 I-77	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>a</i> ' <i>S</i> ,14 <i>a</i> ' <i>R</i> ,16 <i>a</i> ' <i>S</i>)-6-[(<i>tert</i> -butoxycarbonyl)amino]-5'-(3-fluorophenyl)-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ',14,15,16,16 <i>a</i> '-tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> '(5 <i>H</i>)-carboxylic acid	13	713.4
78	 I-78	(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>a</i> ' <i>S</i> ,14 <i>a</i> ' <i>R</i> ,16 <i>a</i> ' <i>S</i>)-6-[(<i>tert</i> -butylcarbamoyl)amino]-5'-methyl- <i>N</i> -[[1-(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ',14,15,16,16 <i>a</i> '-tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> '(5 <i>H</i>)-carboxamide	23	749.4

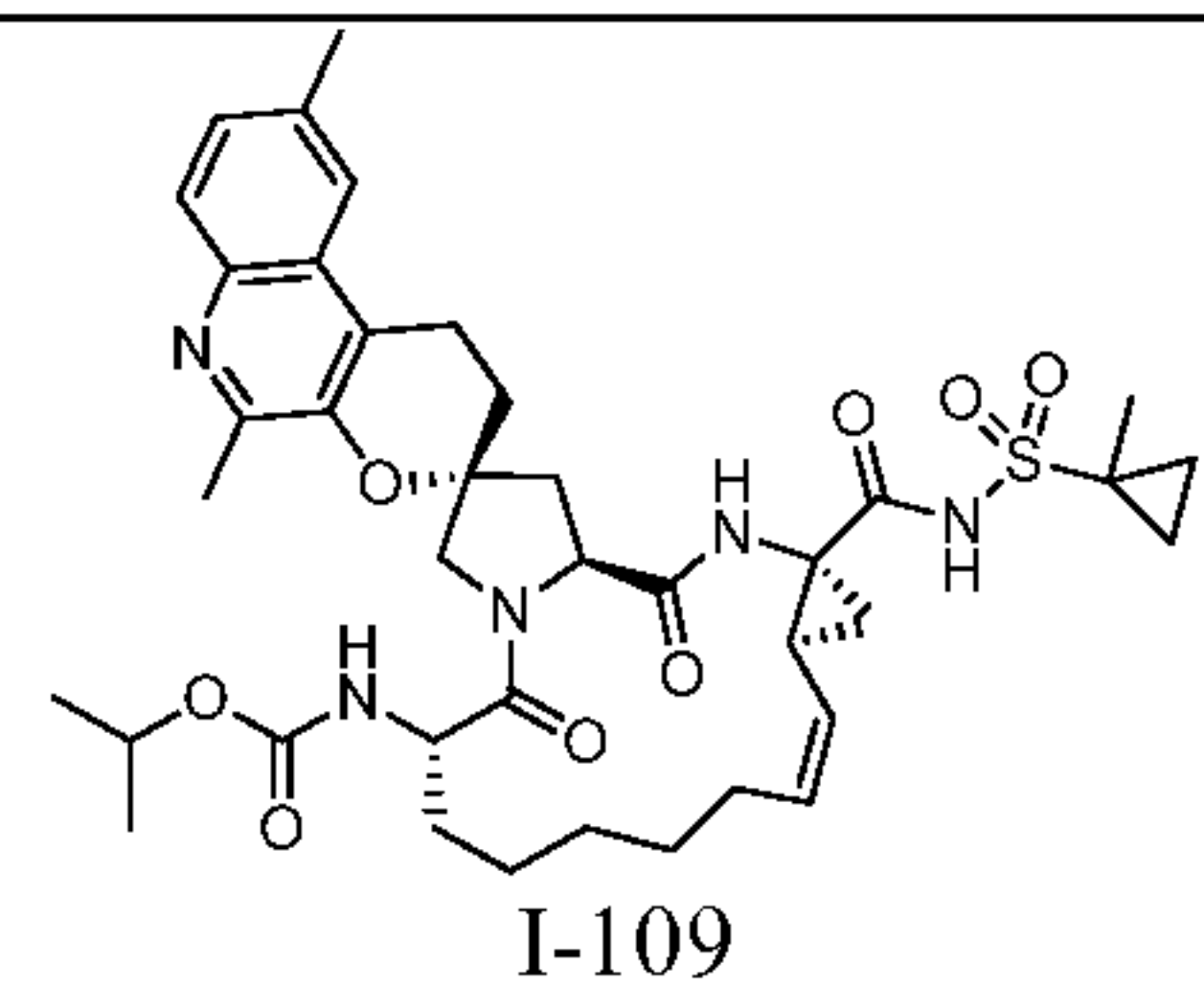
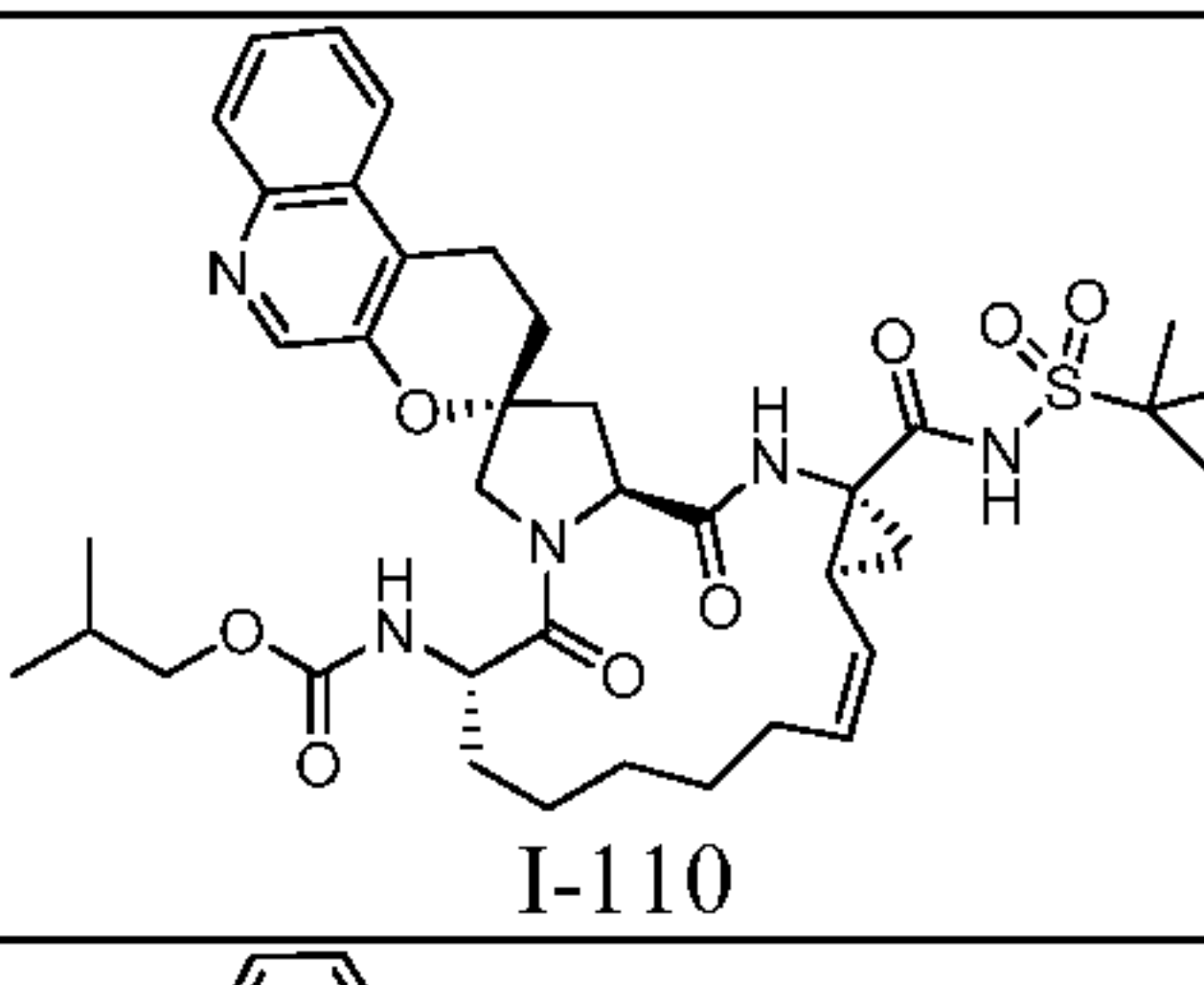
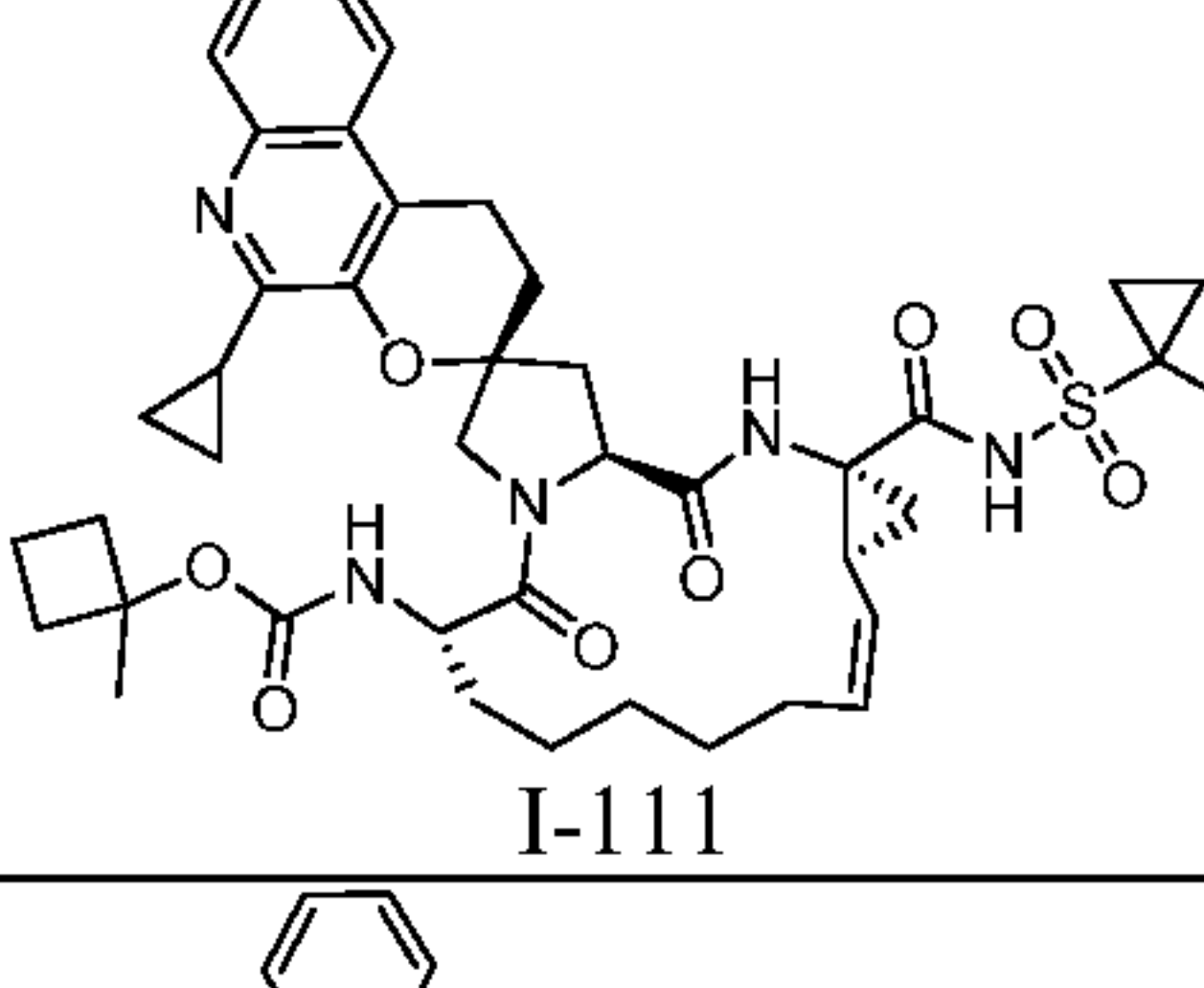
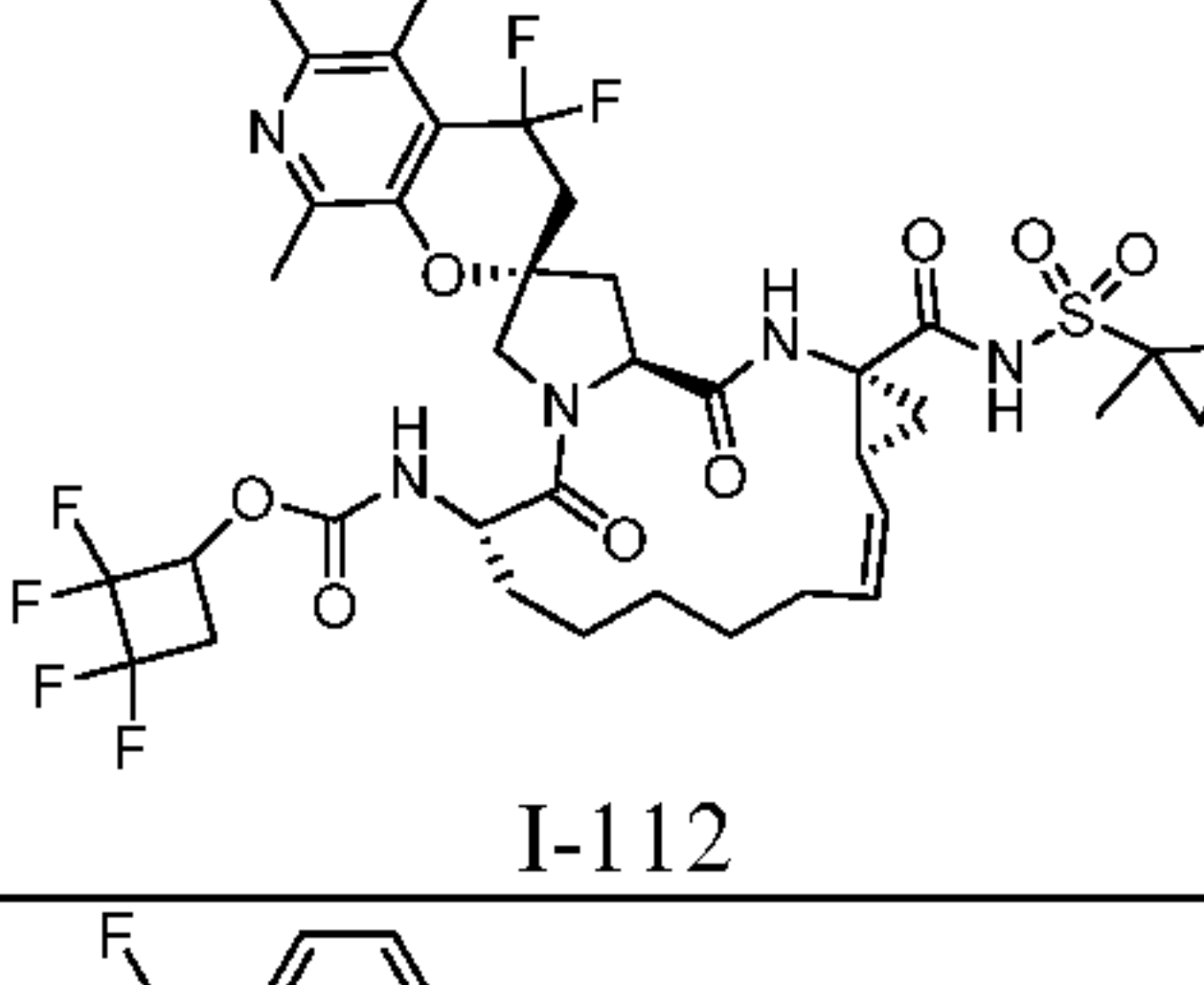
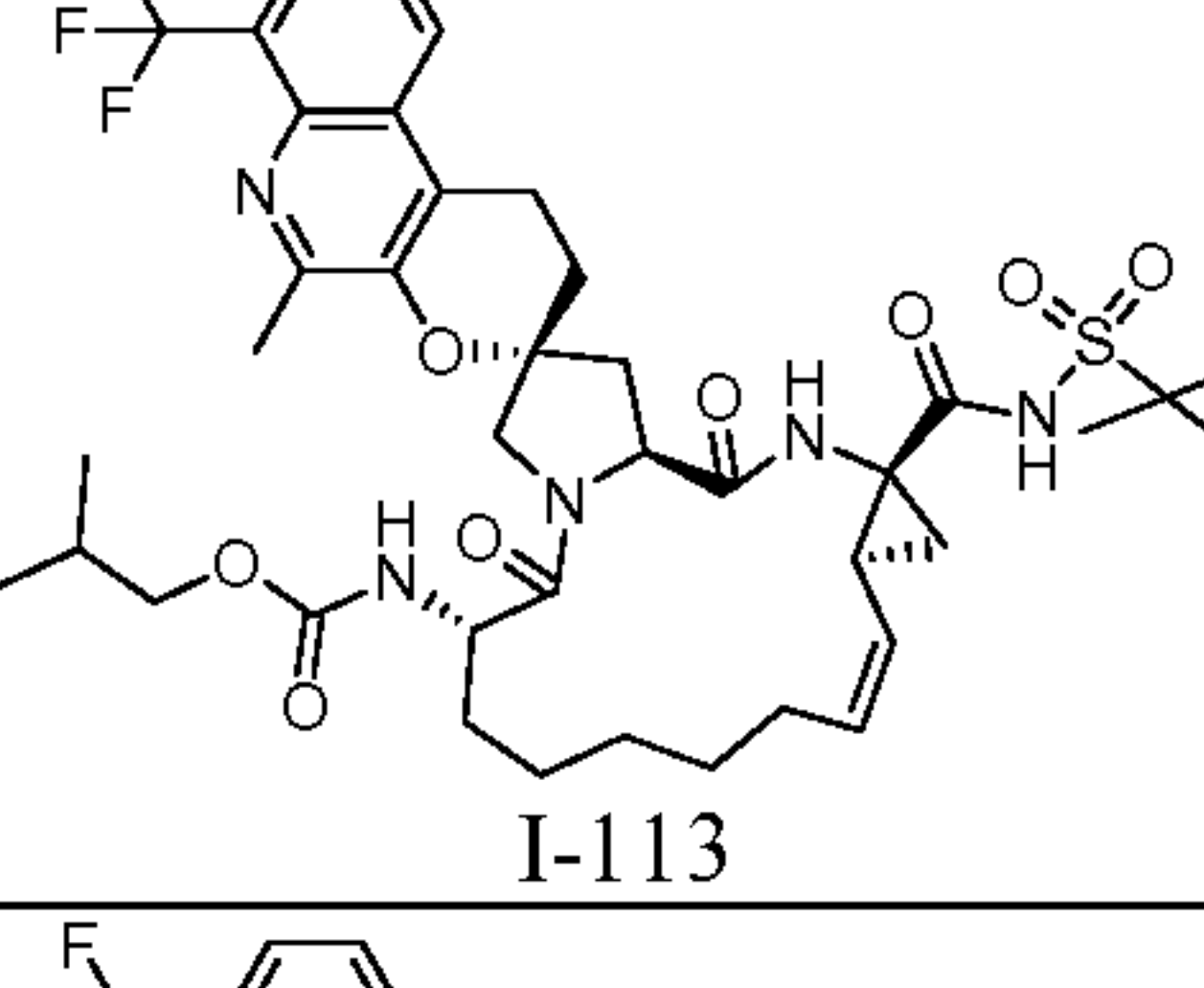
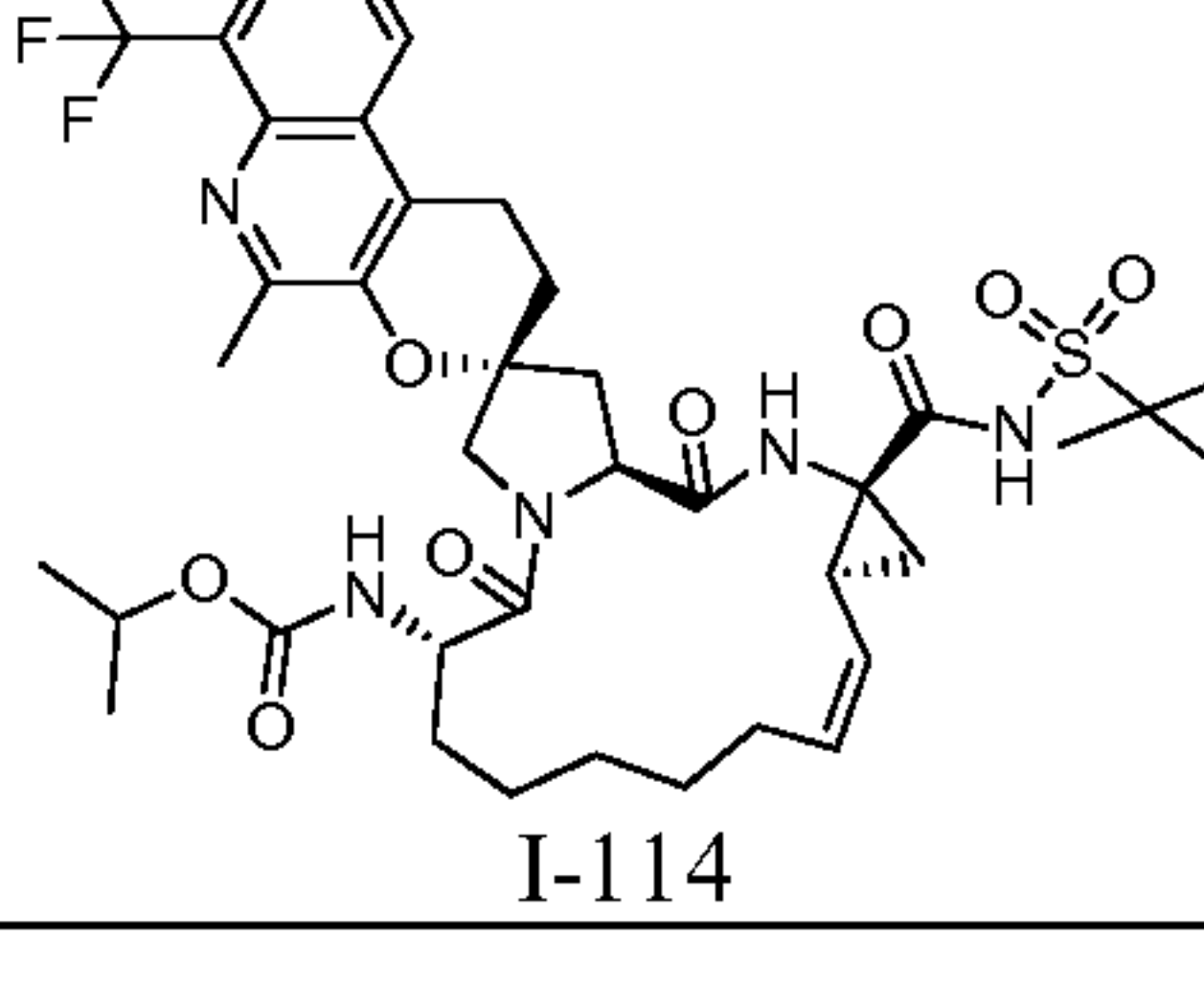
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
79	 I-79	1-methylcyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	748.4
80	 I-80	1-methylcyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	35	762.4
81	 I-81	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(3-fluorophenyl)-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	13	842.4
82	 I-82	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(cyclopentylcarbamoyl)amino]-5'-(3-fluorophenyl)- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	13	841.2
83	 I-83	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(cyclohexylcarbamoyl)amino]-5'-(3-fluorophenyl)- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	13	855.2
84	 I-84	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-6-[(3,3,3-trifluoropropanoyl)amino]-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	24	760.4

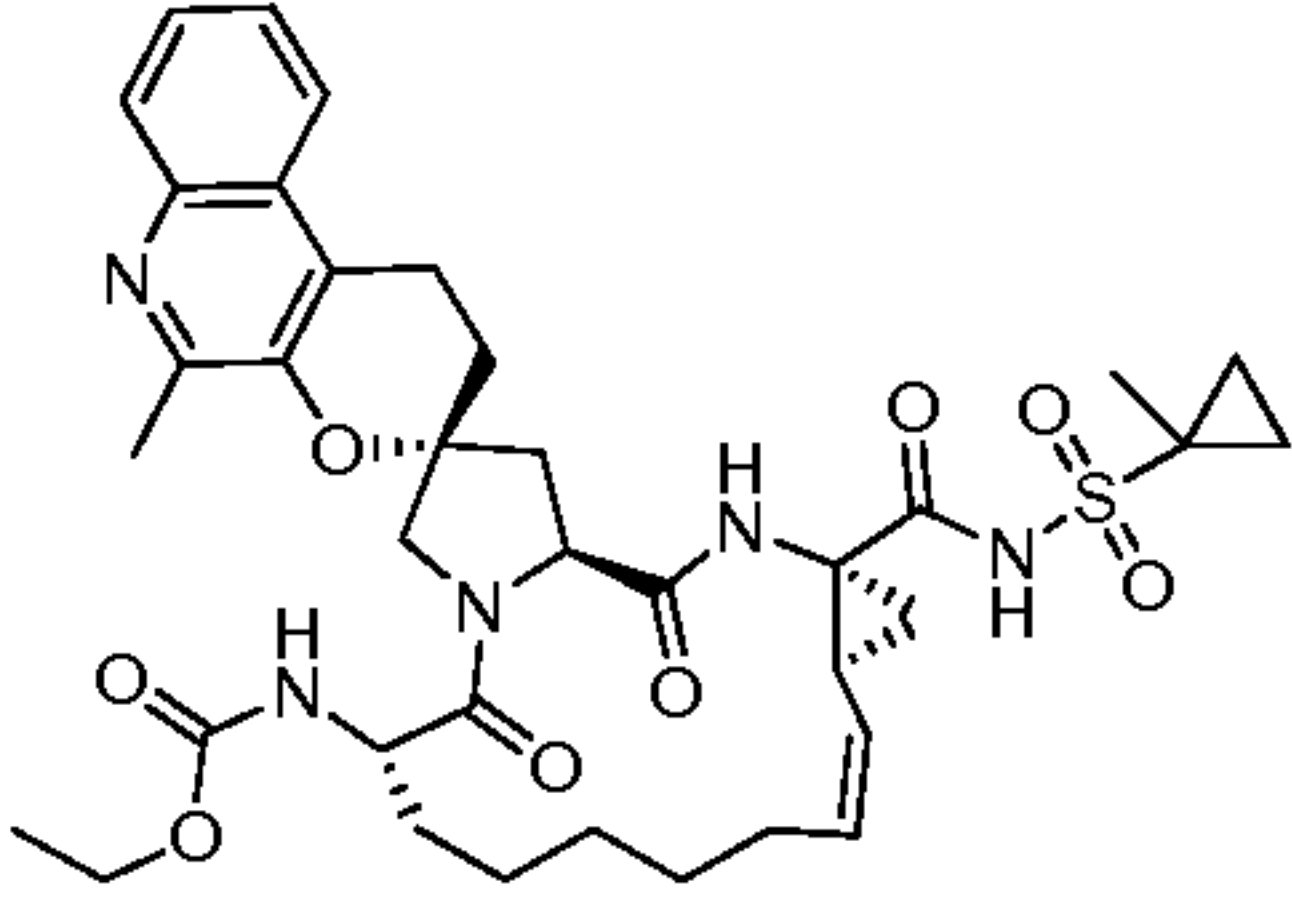
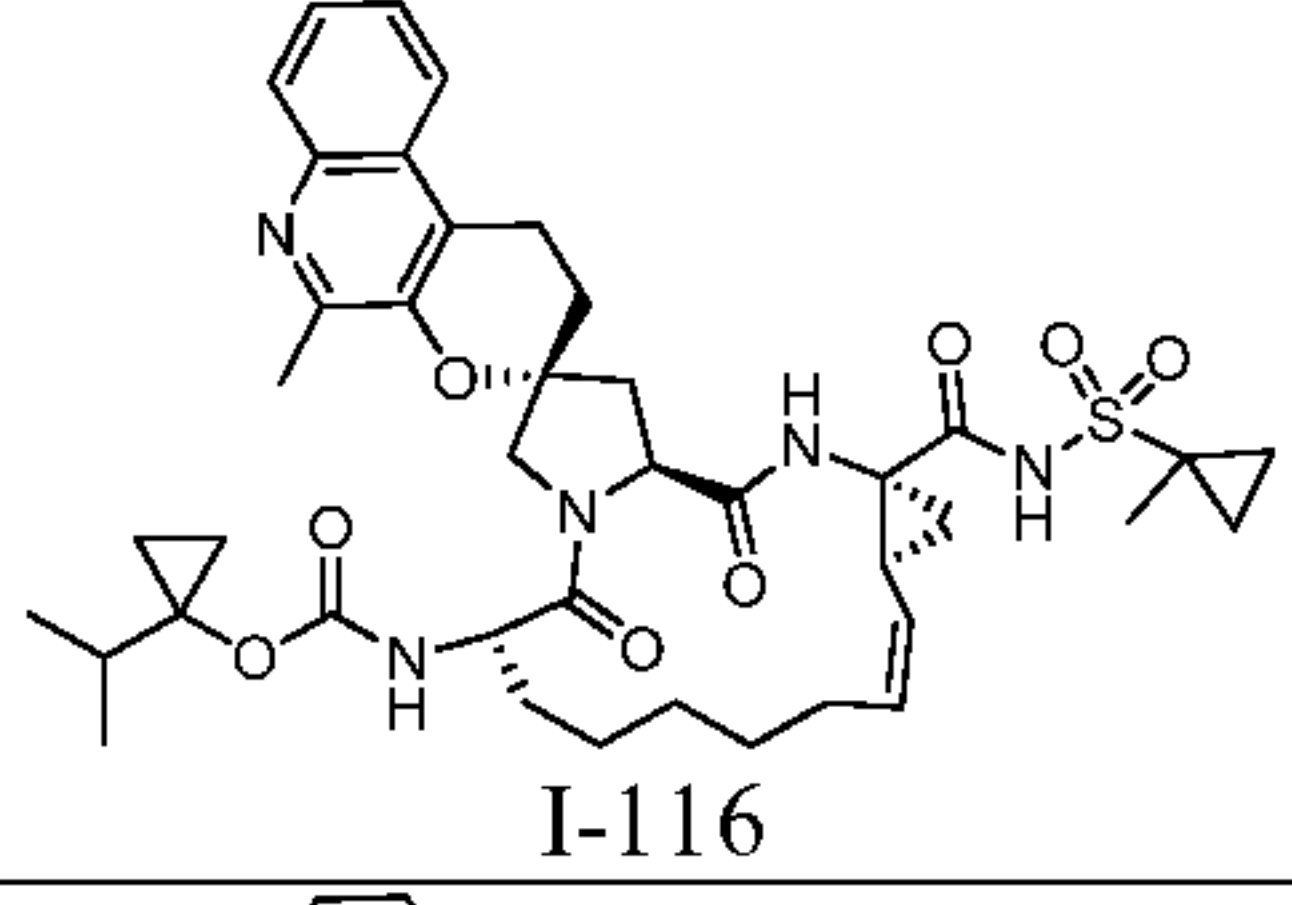
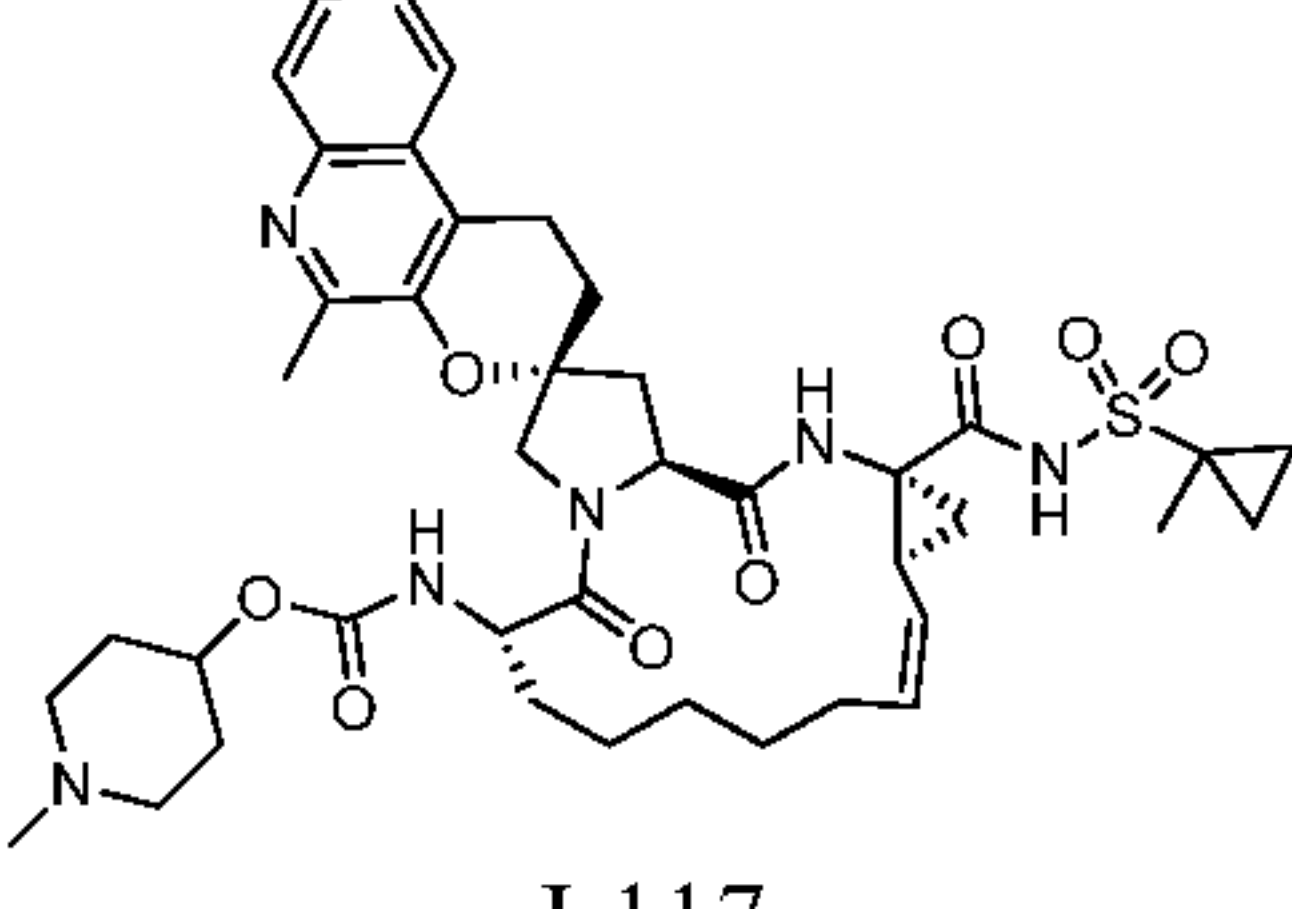
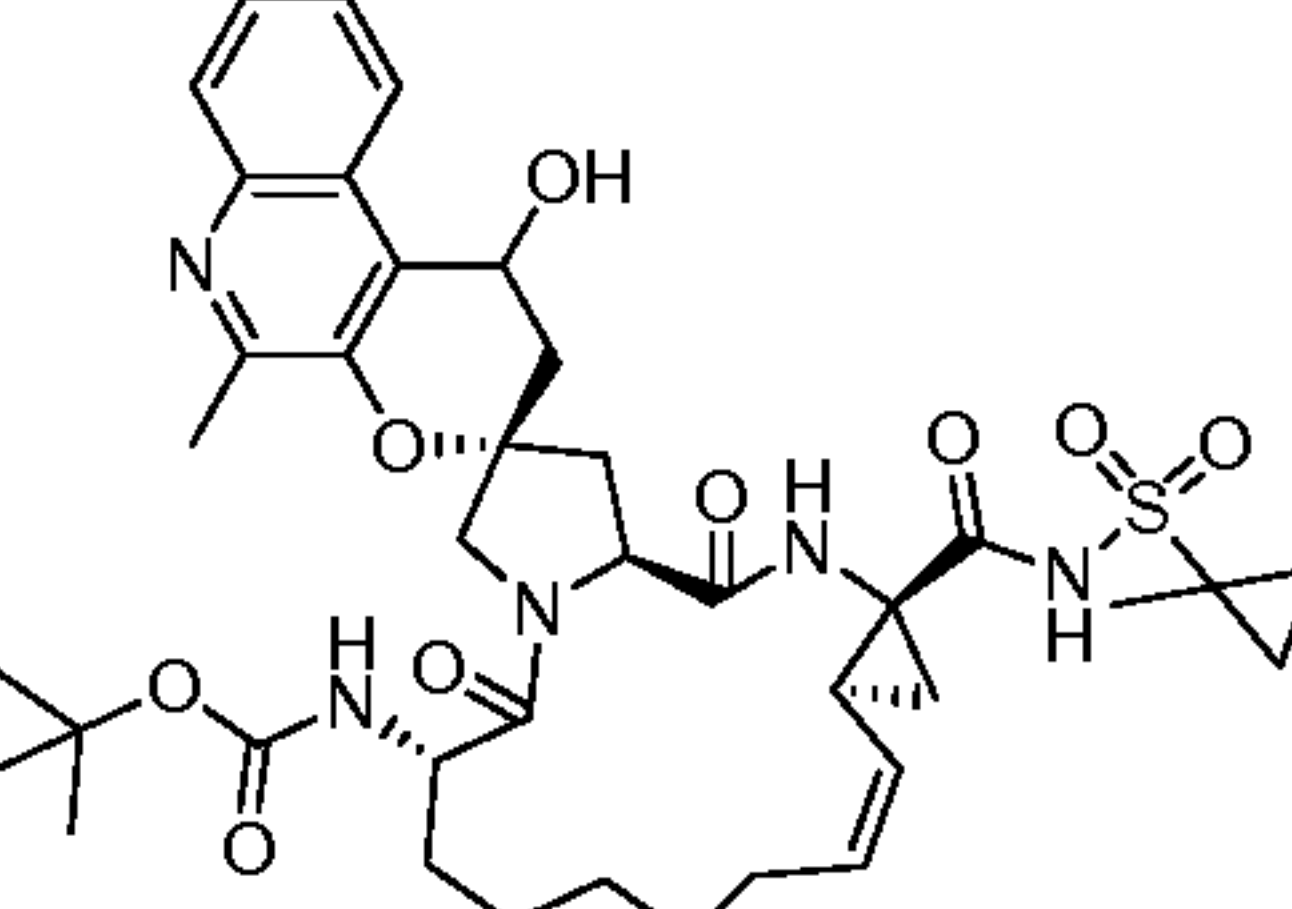
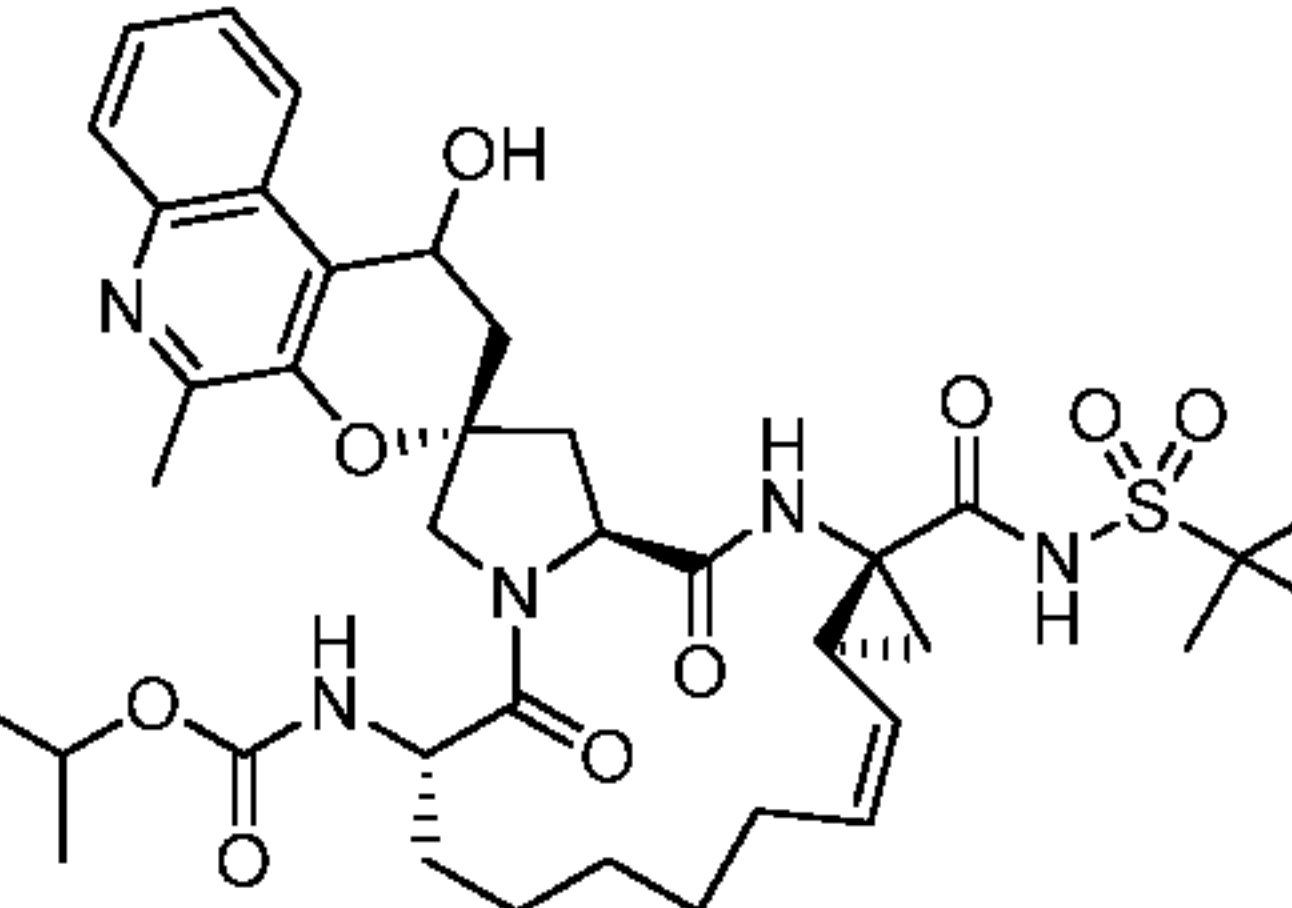
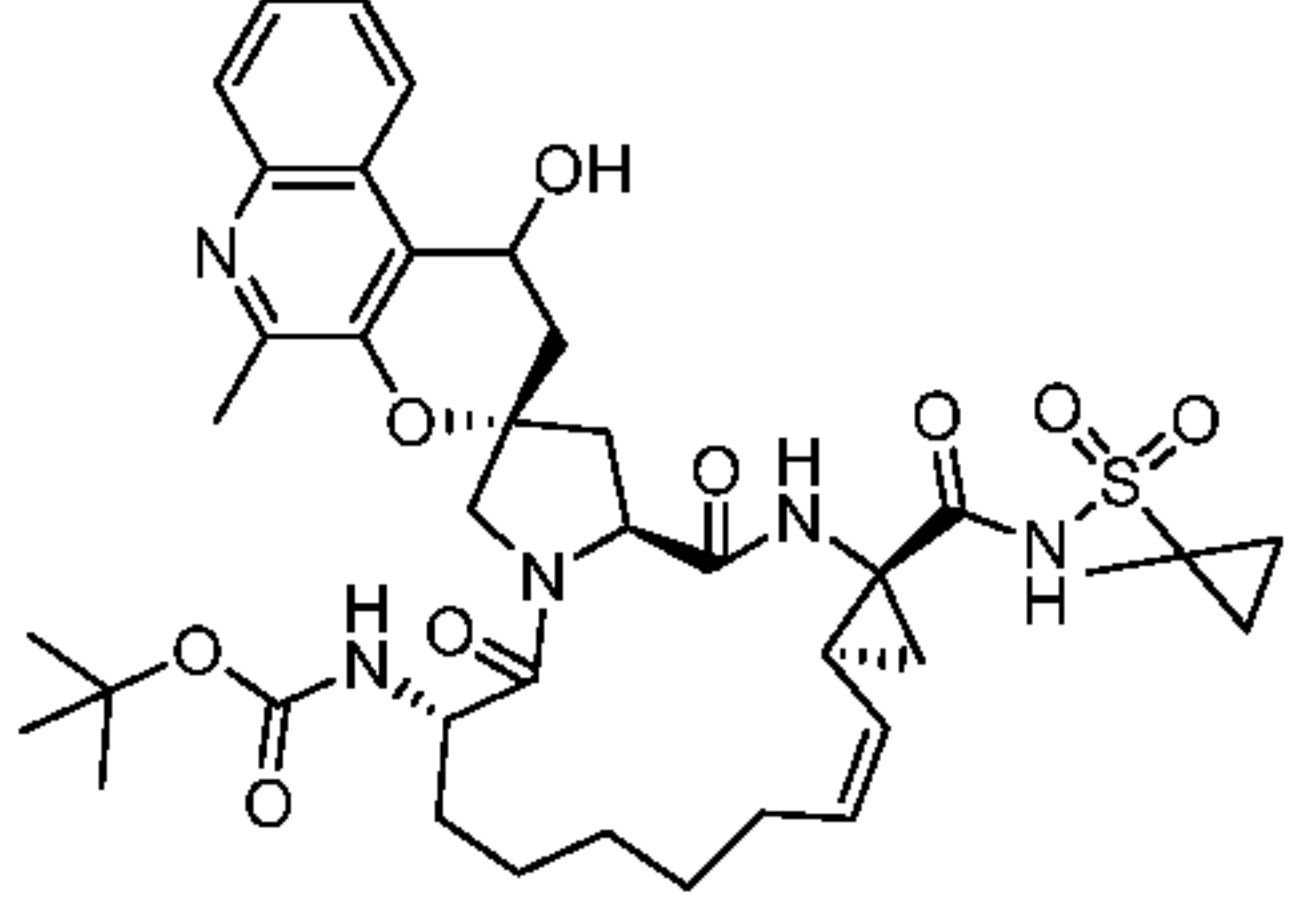
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
85	 I-85	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(3-fluorophenyl)- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-6-[(propan-2-ylcarbamoyl)amino]-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	13	815.2
86	 I-86	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(<i>tert</i> -butoxycarbonyl)amino]-5',9'-dimethyl-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxylic acid	42	647.5
87	 I-87	<i>tert</i> -butyl {(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-14 <i>a</i> -[(cyclopropylsulfonyl)carbamoyl]-5',9'-dimethyl-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl} carbamate	42	750.5
88	 I-88	methyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(3-fluorophenyl)-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl} carbamate	13	788.4
89	 I-89	propan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(3-fluorophenyl)-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl} carbamate	13	817.2
90	 I-90	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(<i>tert</i> -butylcarbamoyl)amino]-5'-cyclopropyl-9'-methoxy- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	16	805.4

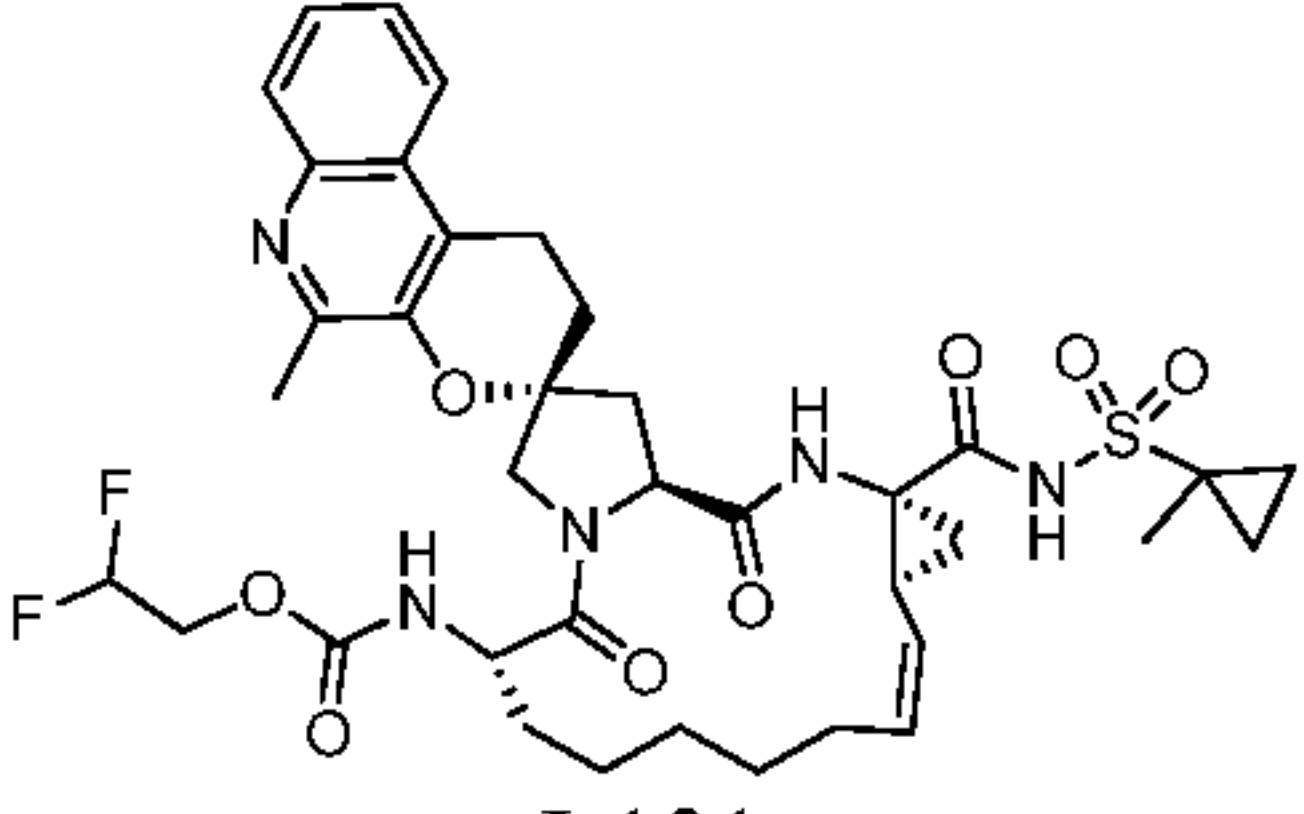
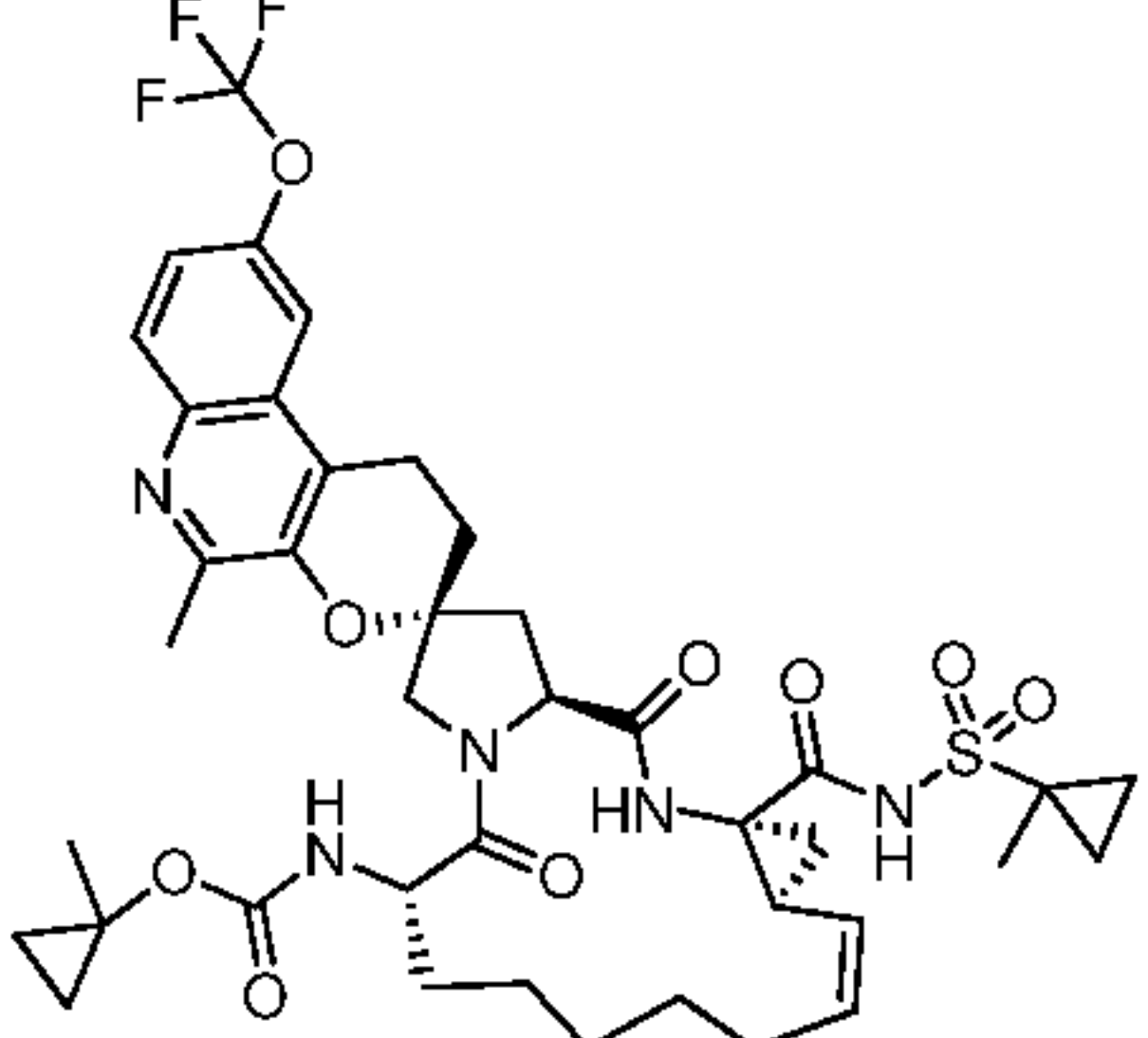
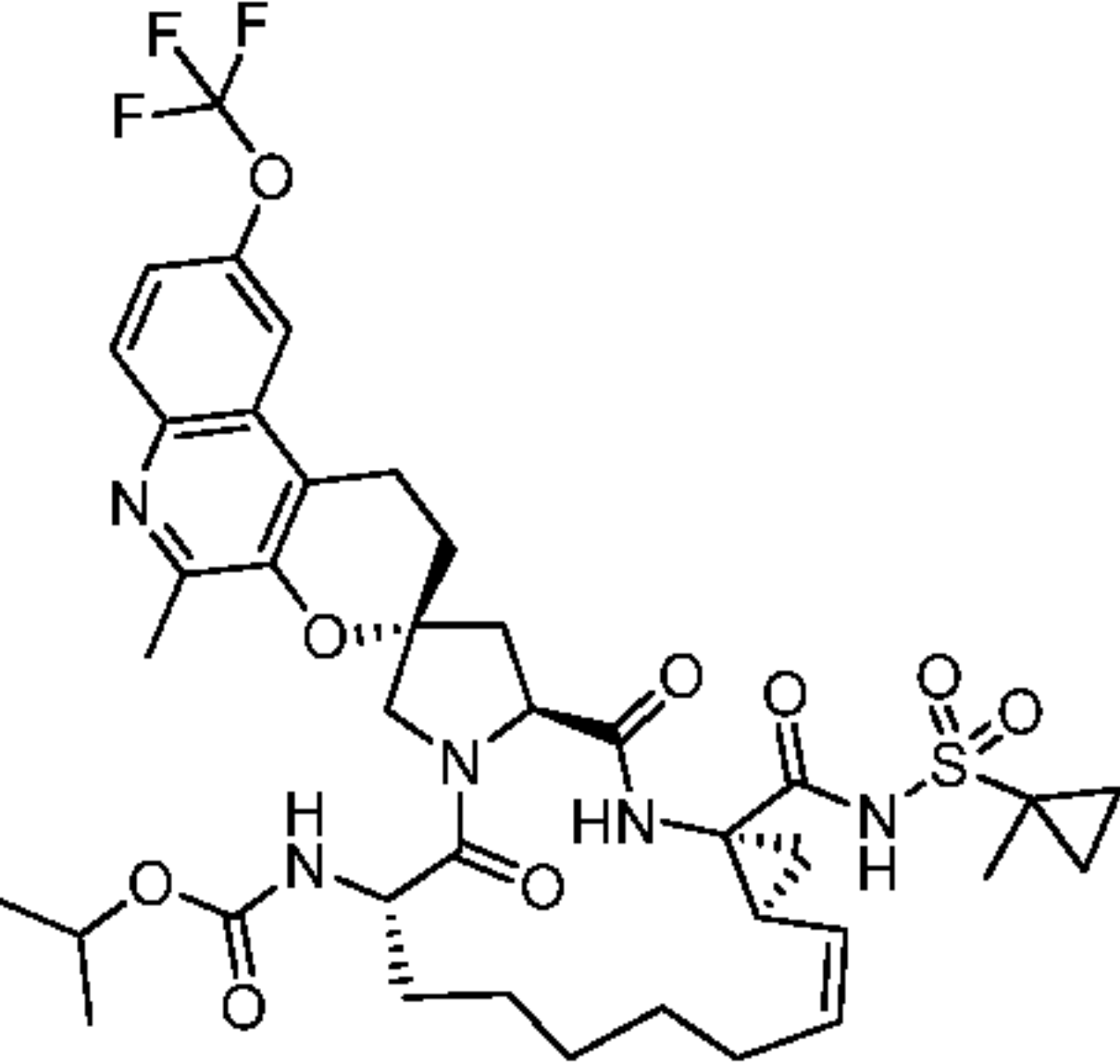
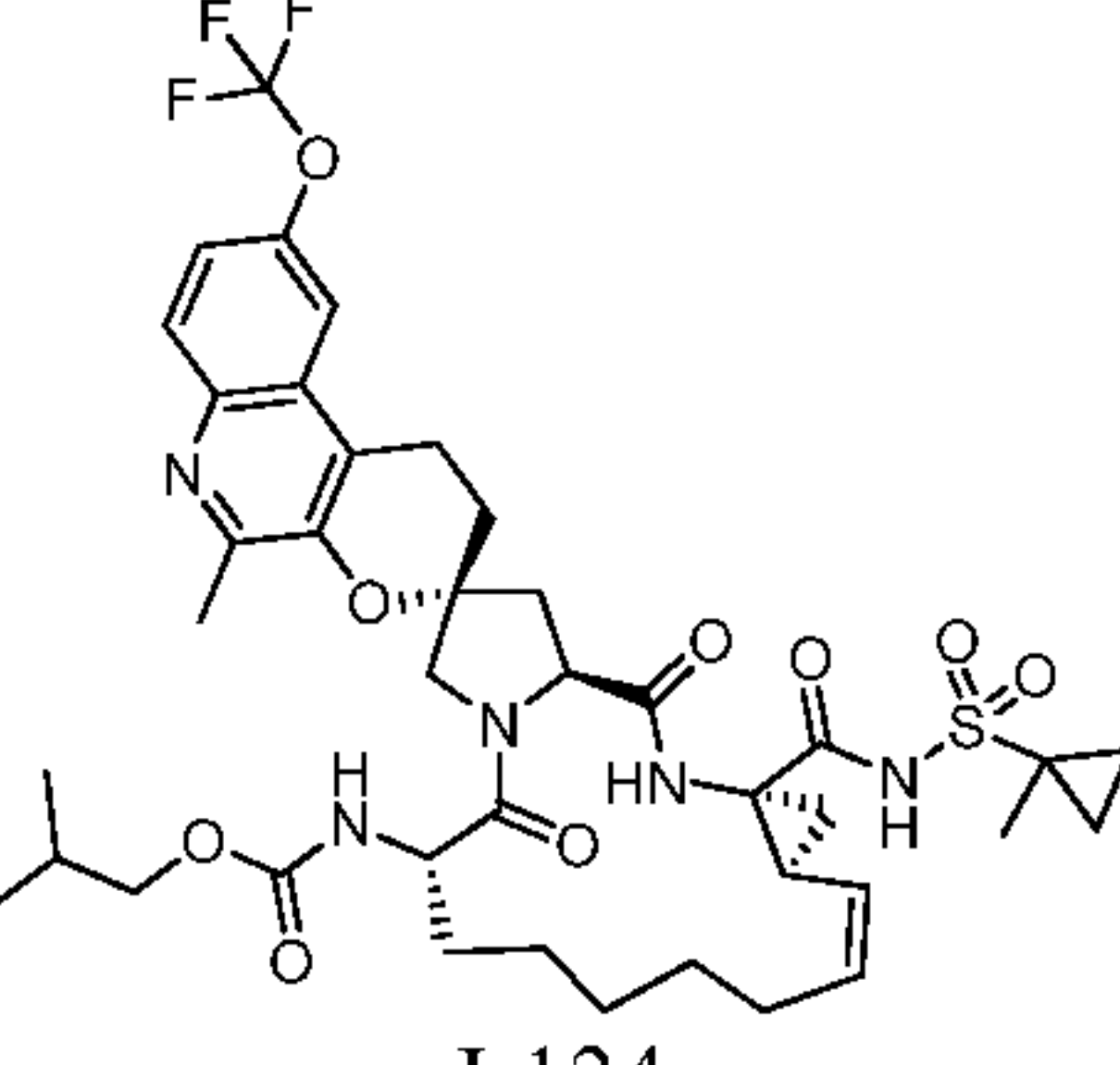
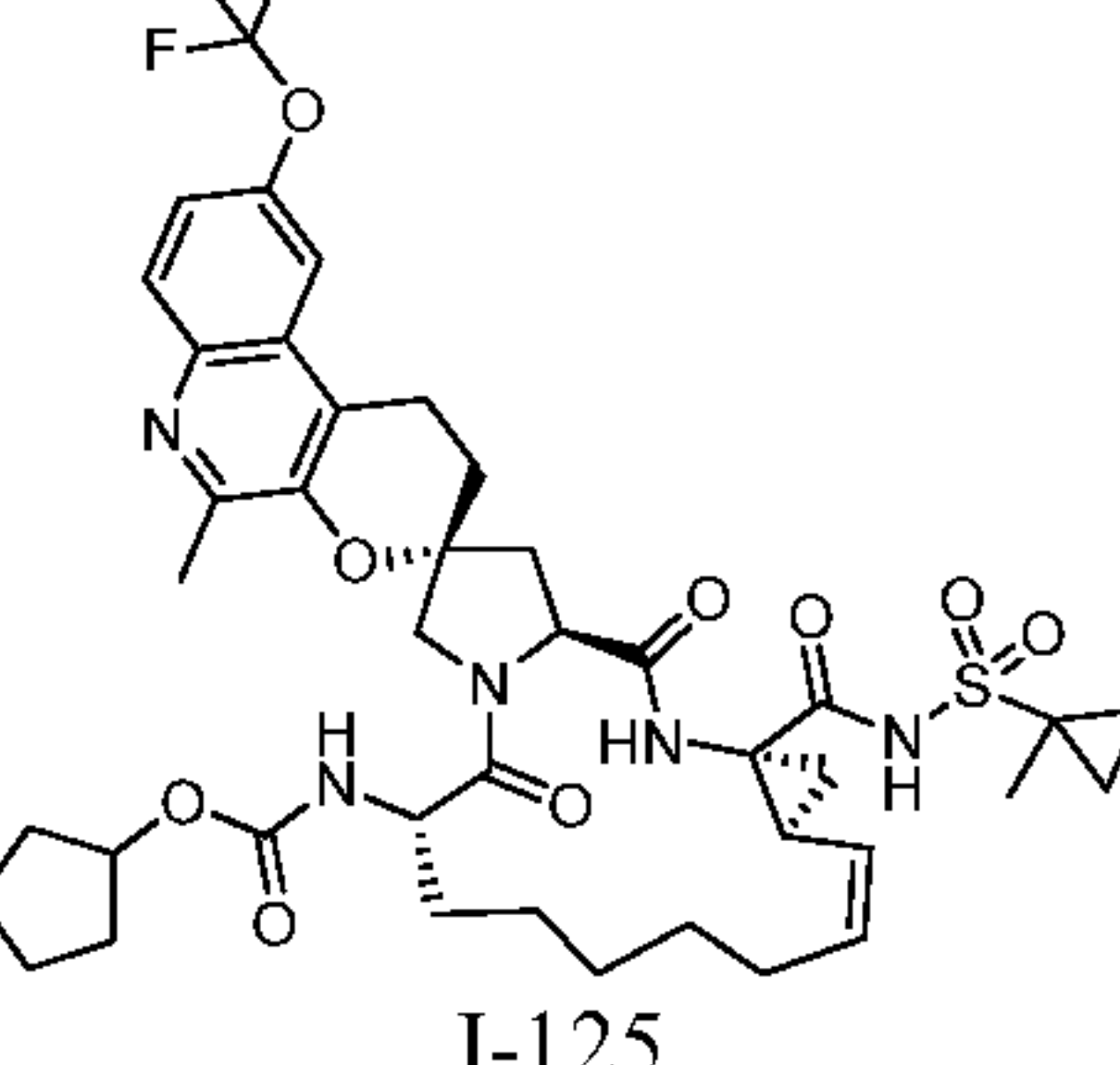
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
91	 I-91	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16	818.5
92	 I-92	1-methylcyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16	804.4
93	 I-93	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(cyclopentylcarbamoyl)amino]-5'-cyclopropyl-9'-methoxy- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	16	817.4
94	 I-94	propan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16, 528	792.4
95	 I-95	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-14a-[(cyclopropylsulfonyl)carbamoyl]-5'-methyl-5,16-dioxo-7'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	44	804.2
96	 I-96	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	761.8

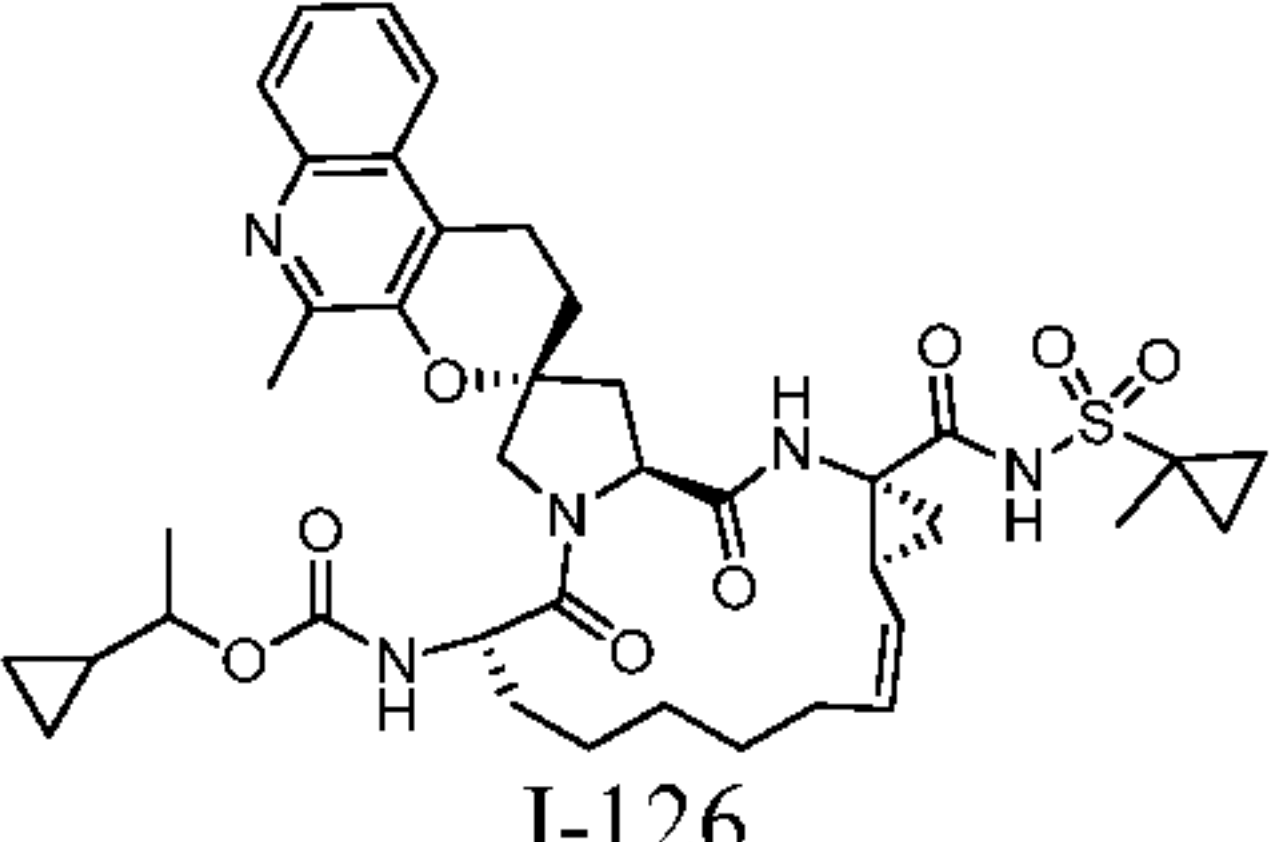
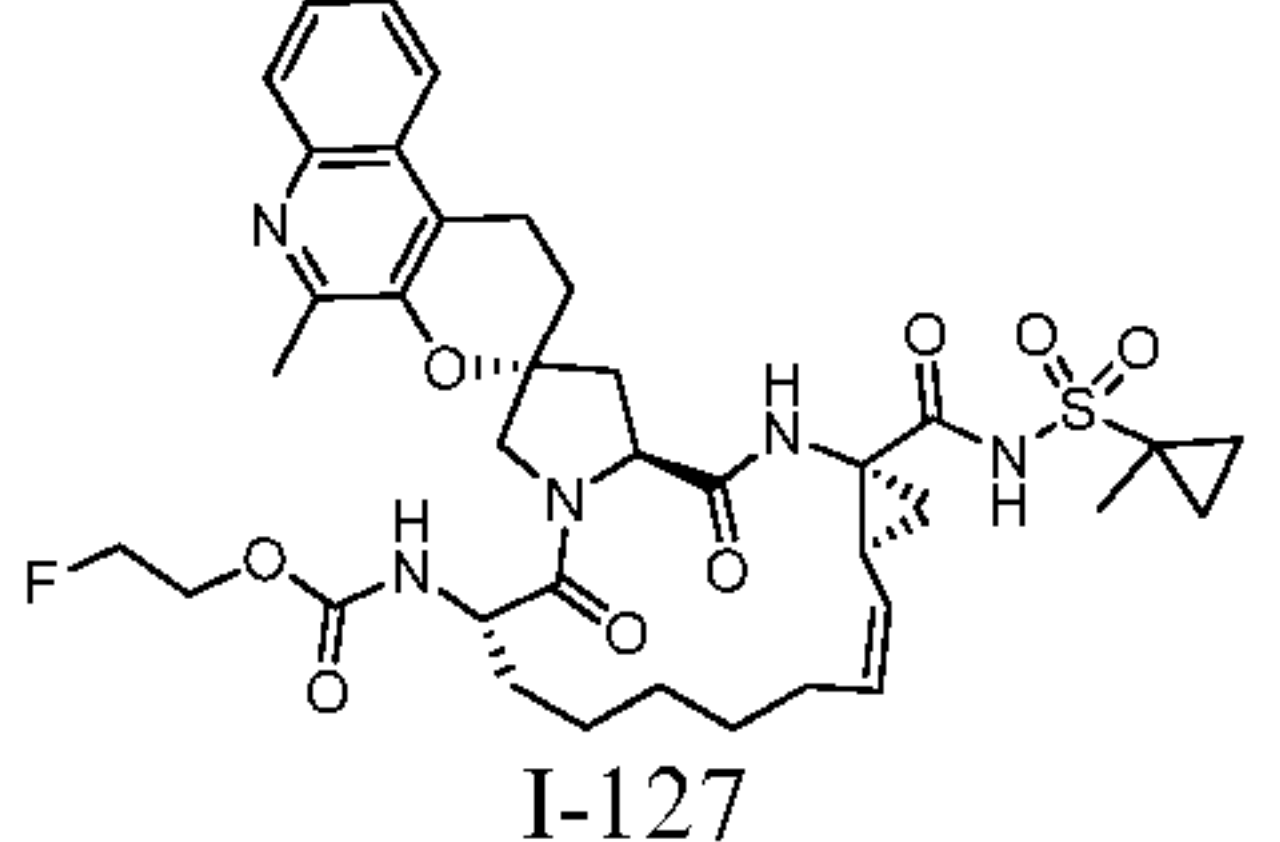
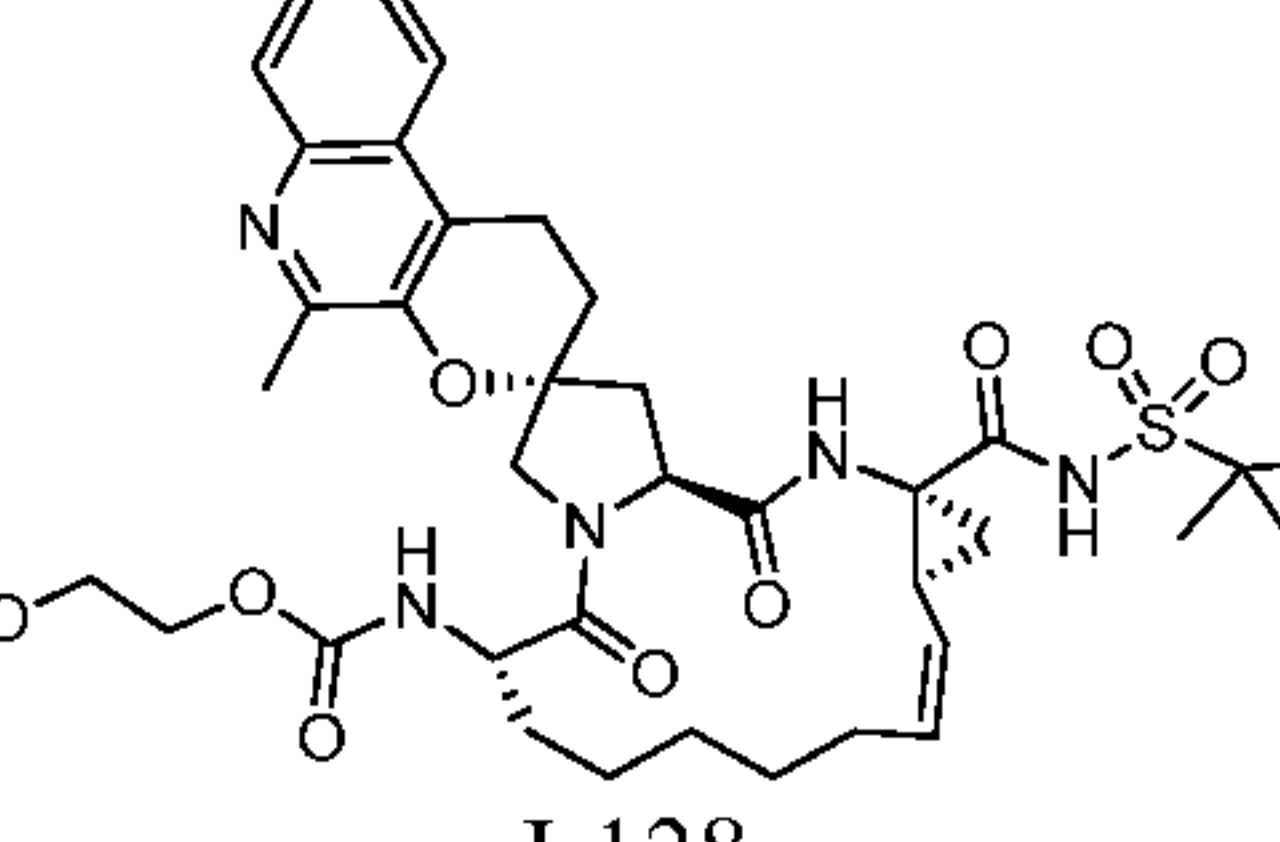
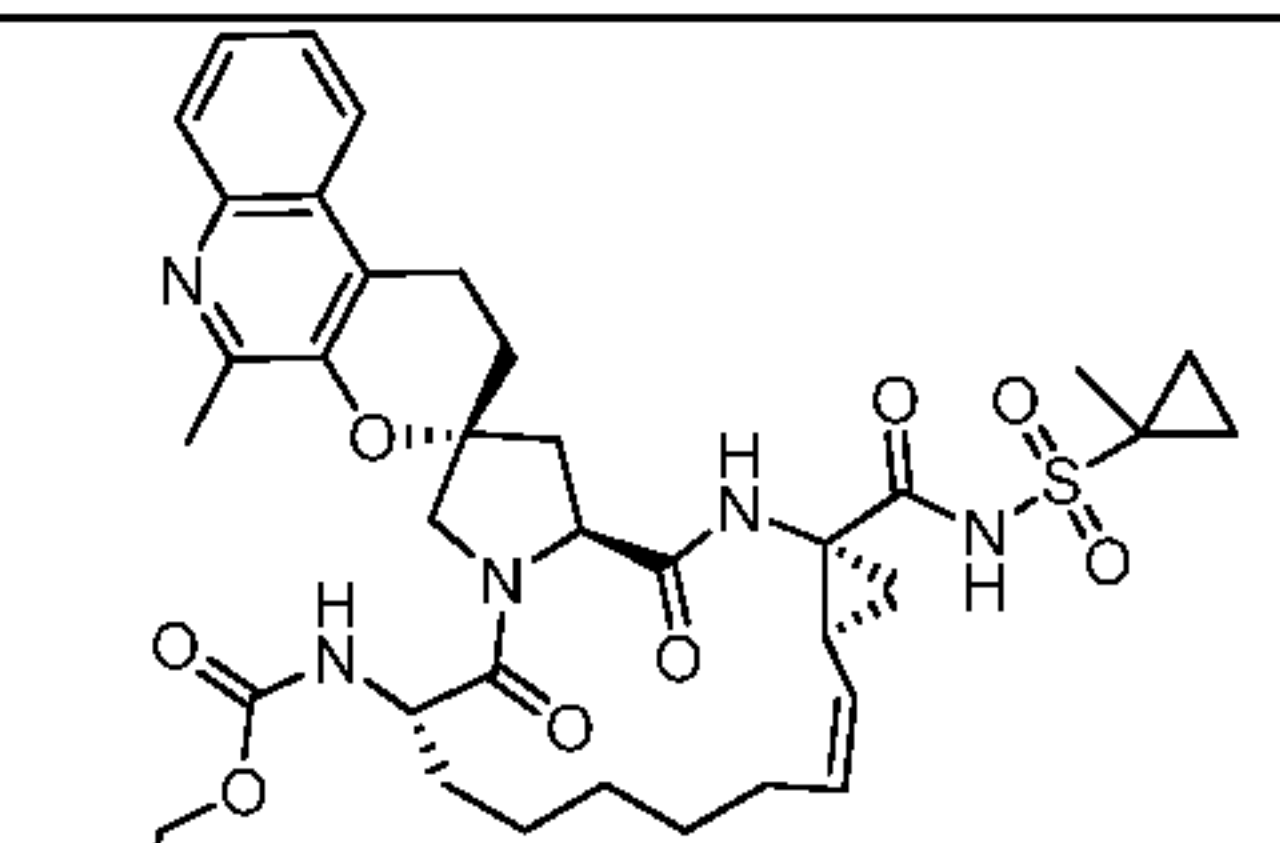
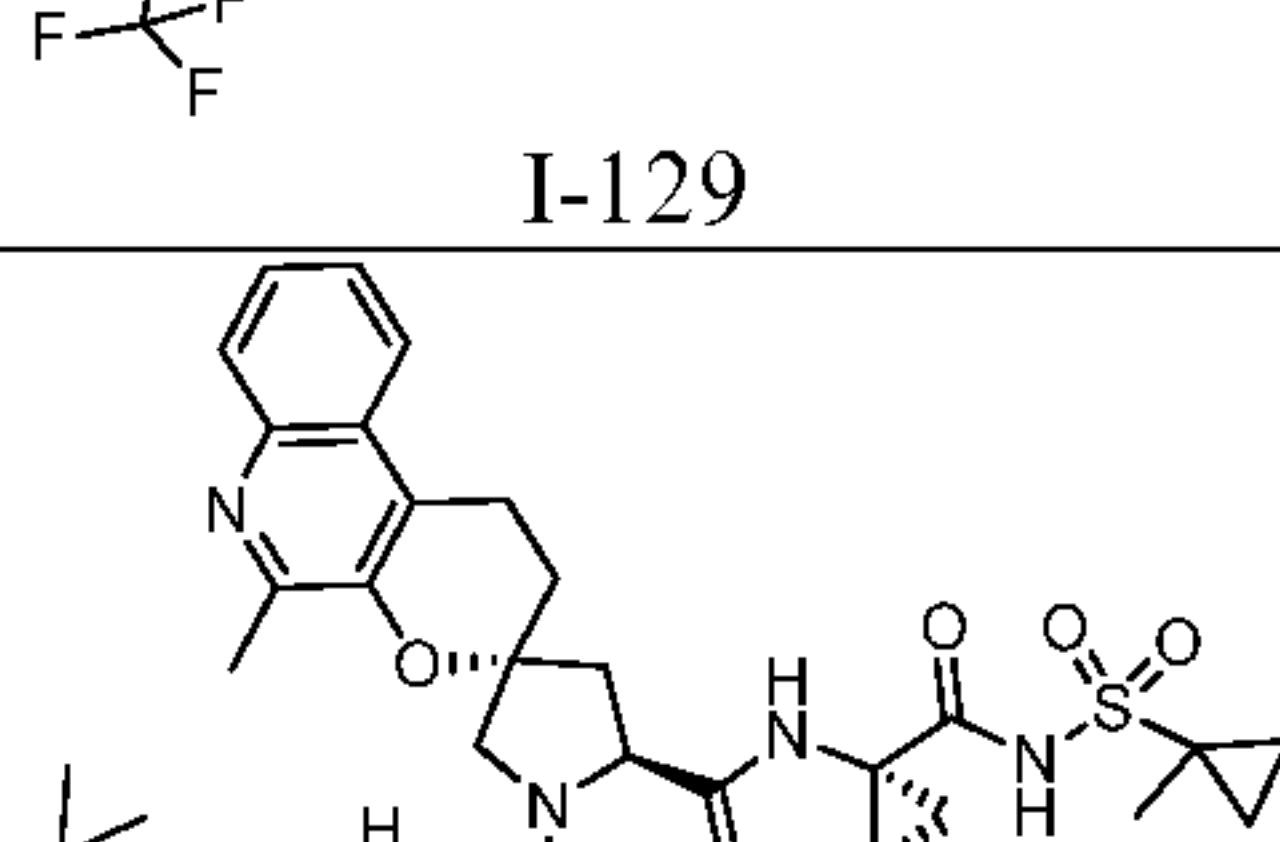
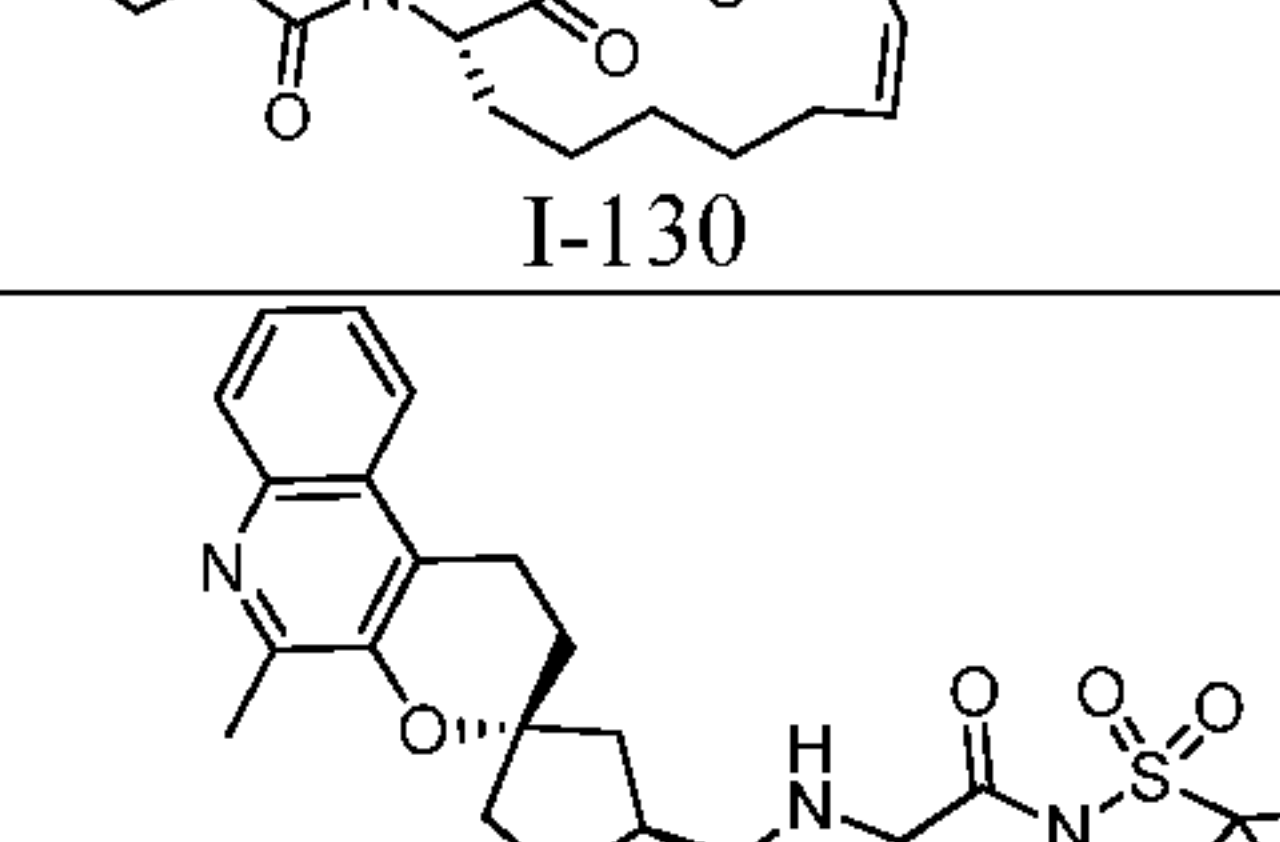
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
97	 I-97	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-[[1-(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	750.4
98	 I-98	<i>tert</i> -butyl {(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-14a-[(cyclopropylsulfonyl)carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl} carbamate	9	766.4
99	 I-99	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-14a-[[1-(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	736.4
100	 I-100	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-9'-methoxy-14a-[[1-(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16	806.2
101	 I-101	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(<i>tert</i> -butoxycarbonyl)amino]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxylic acid	9	--
102	 I-102	1-methylcyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-14a-[[1-(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	773.8

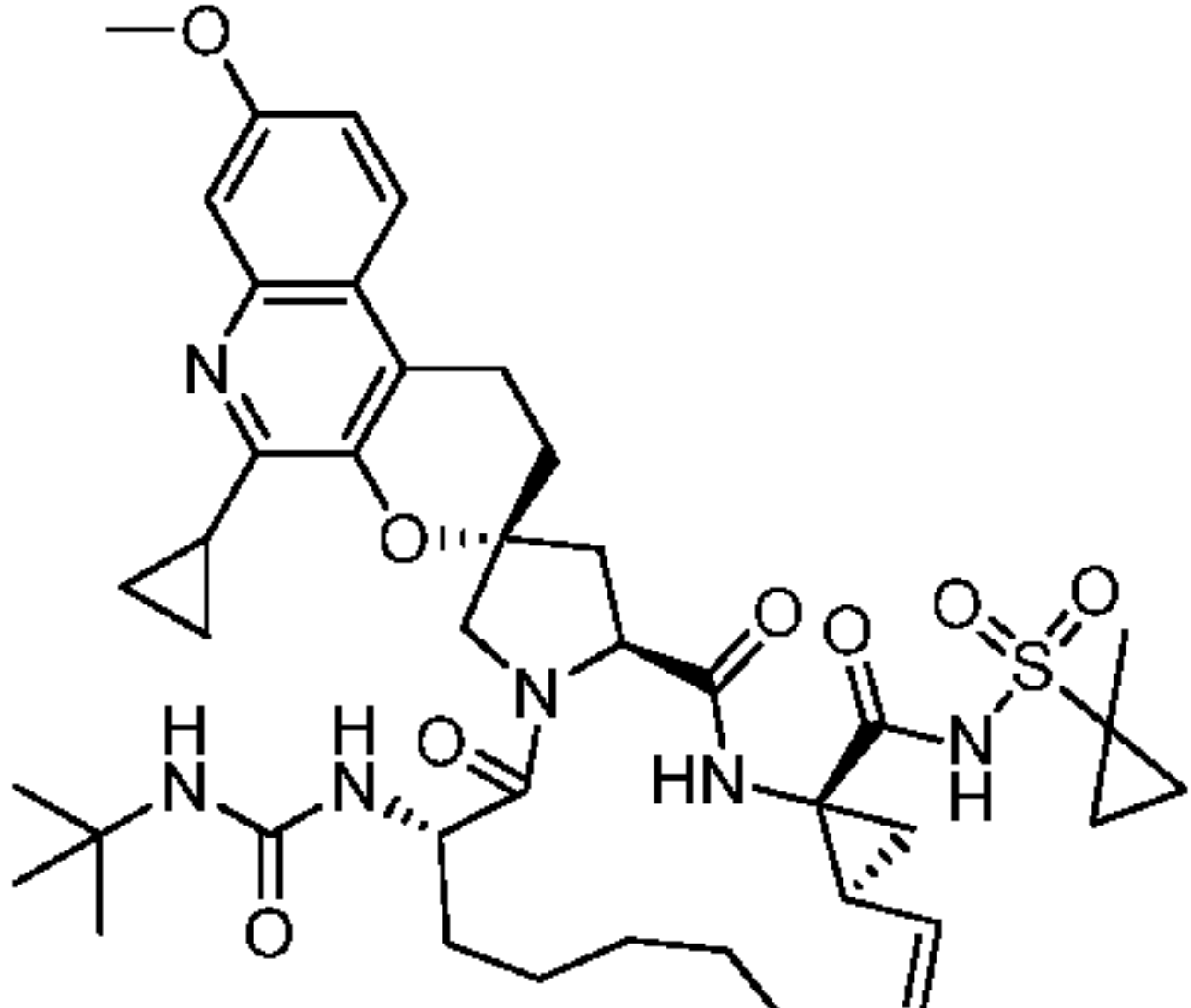
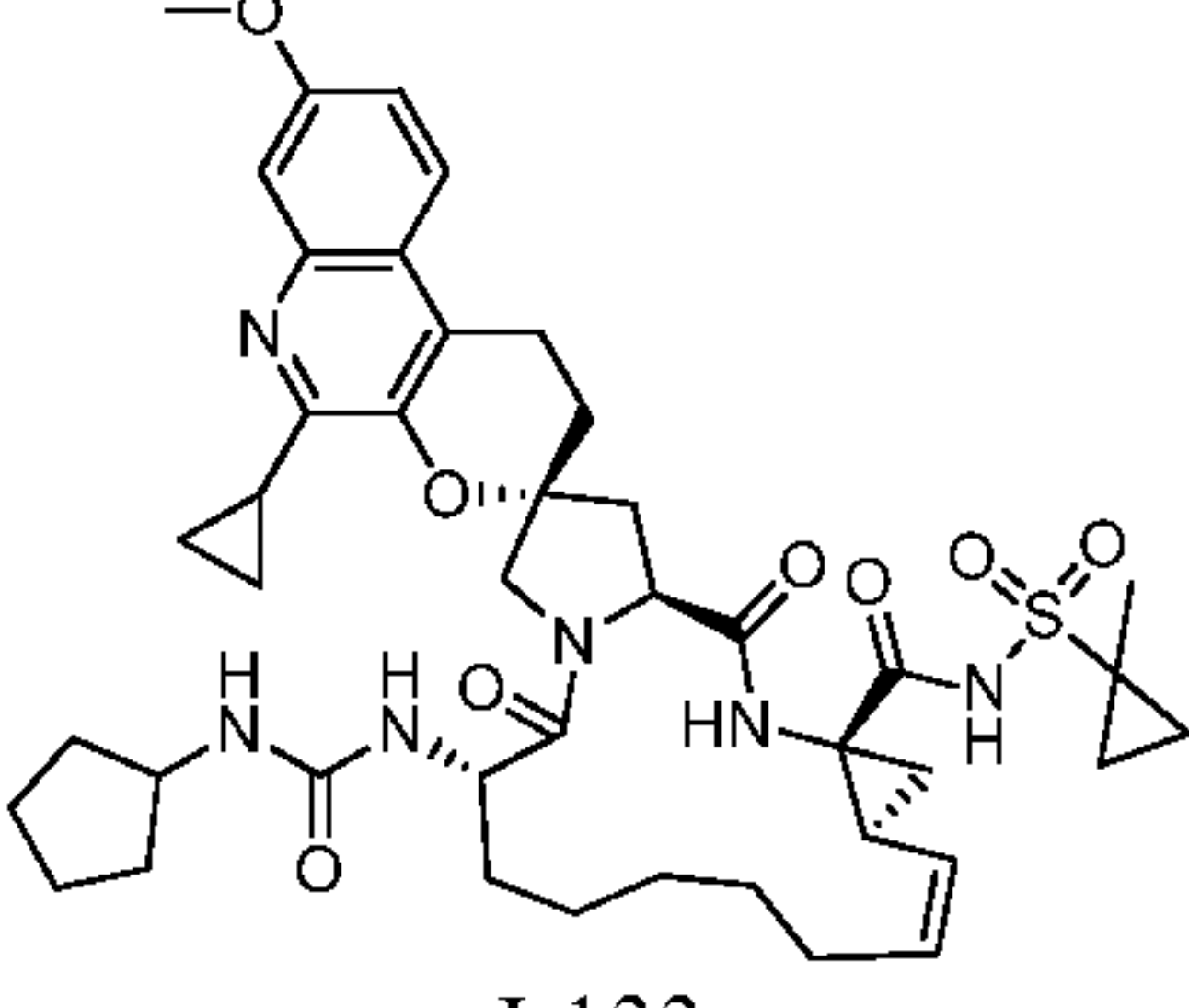
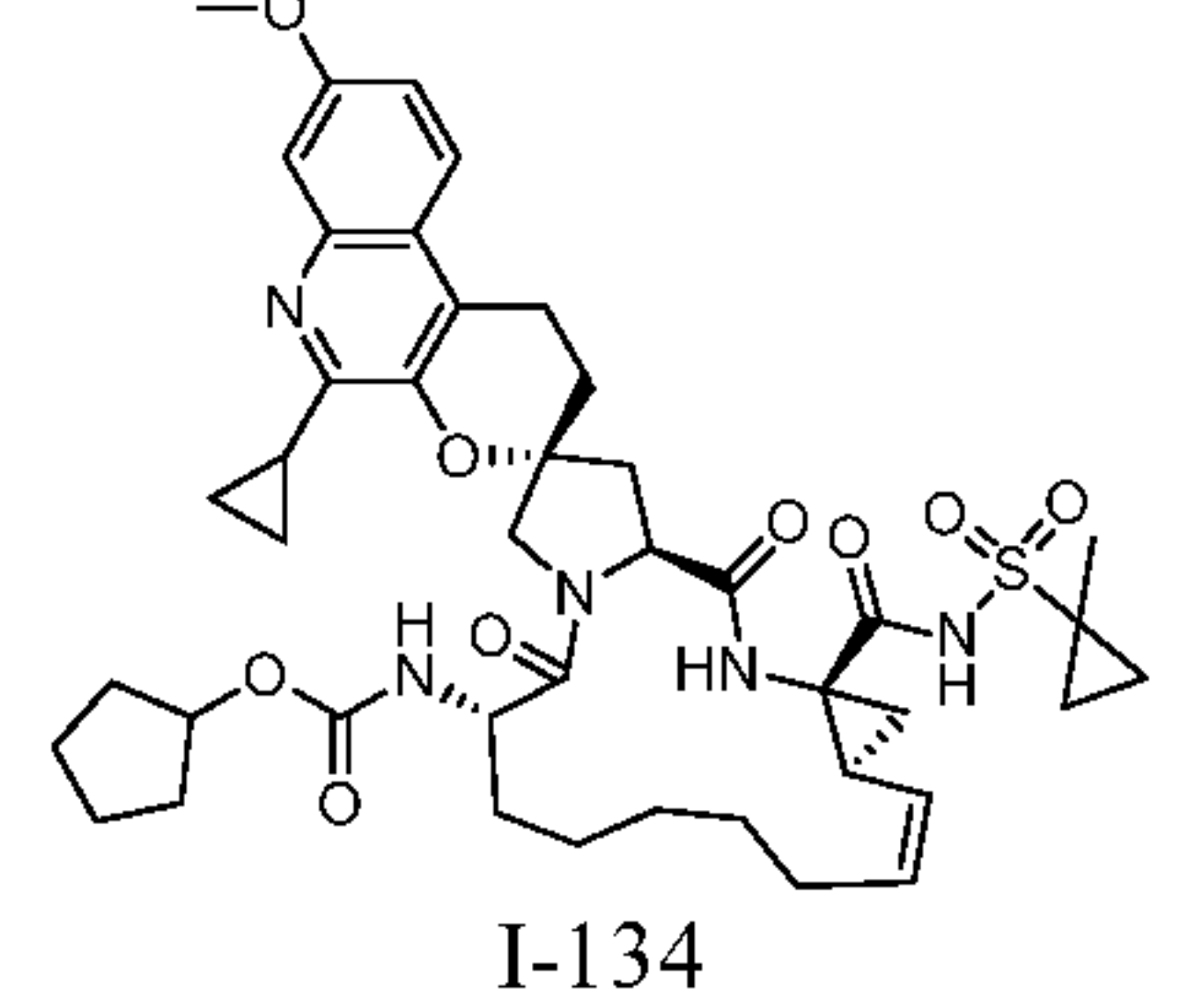
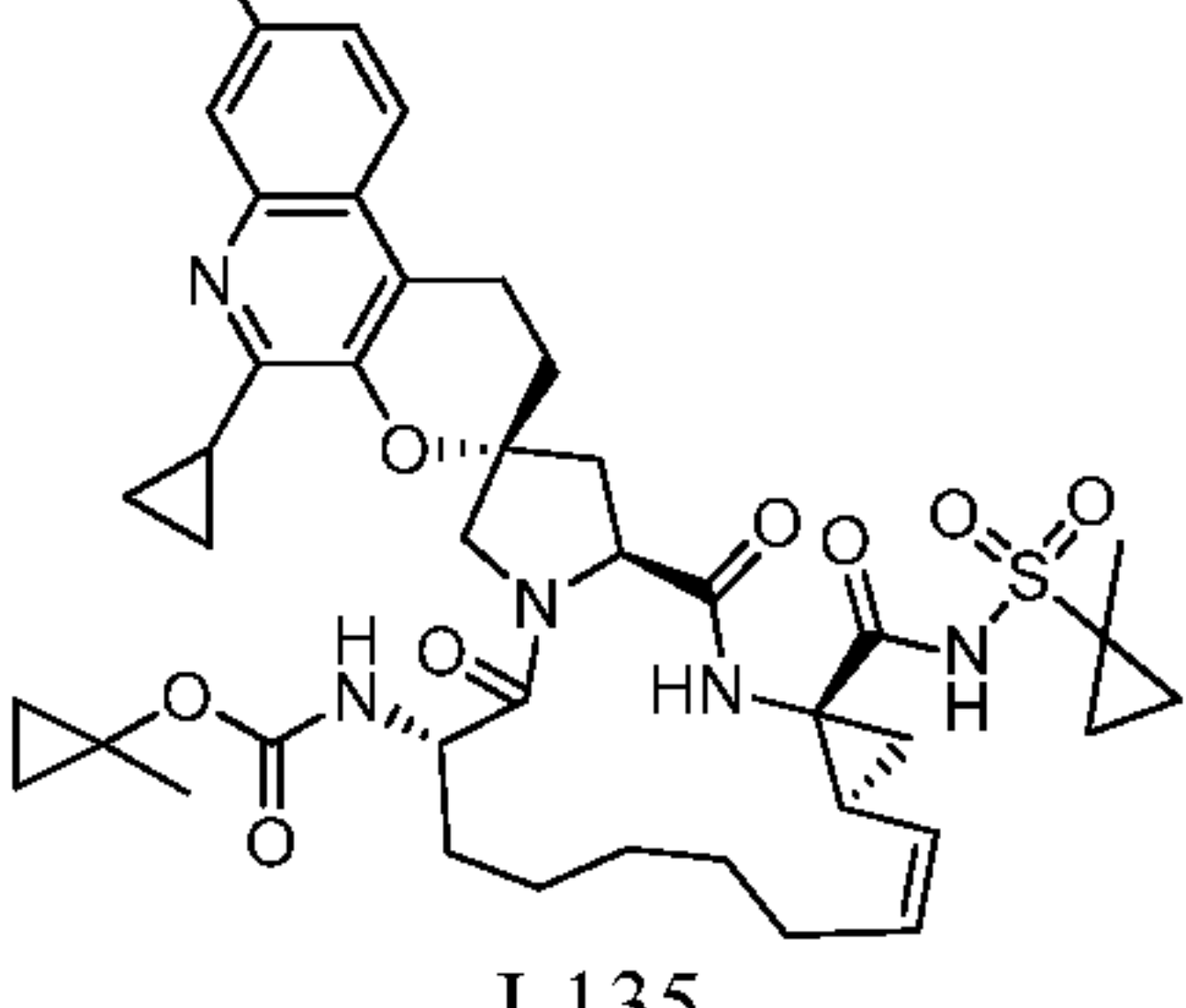
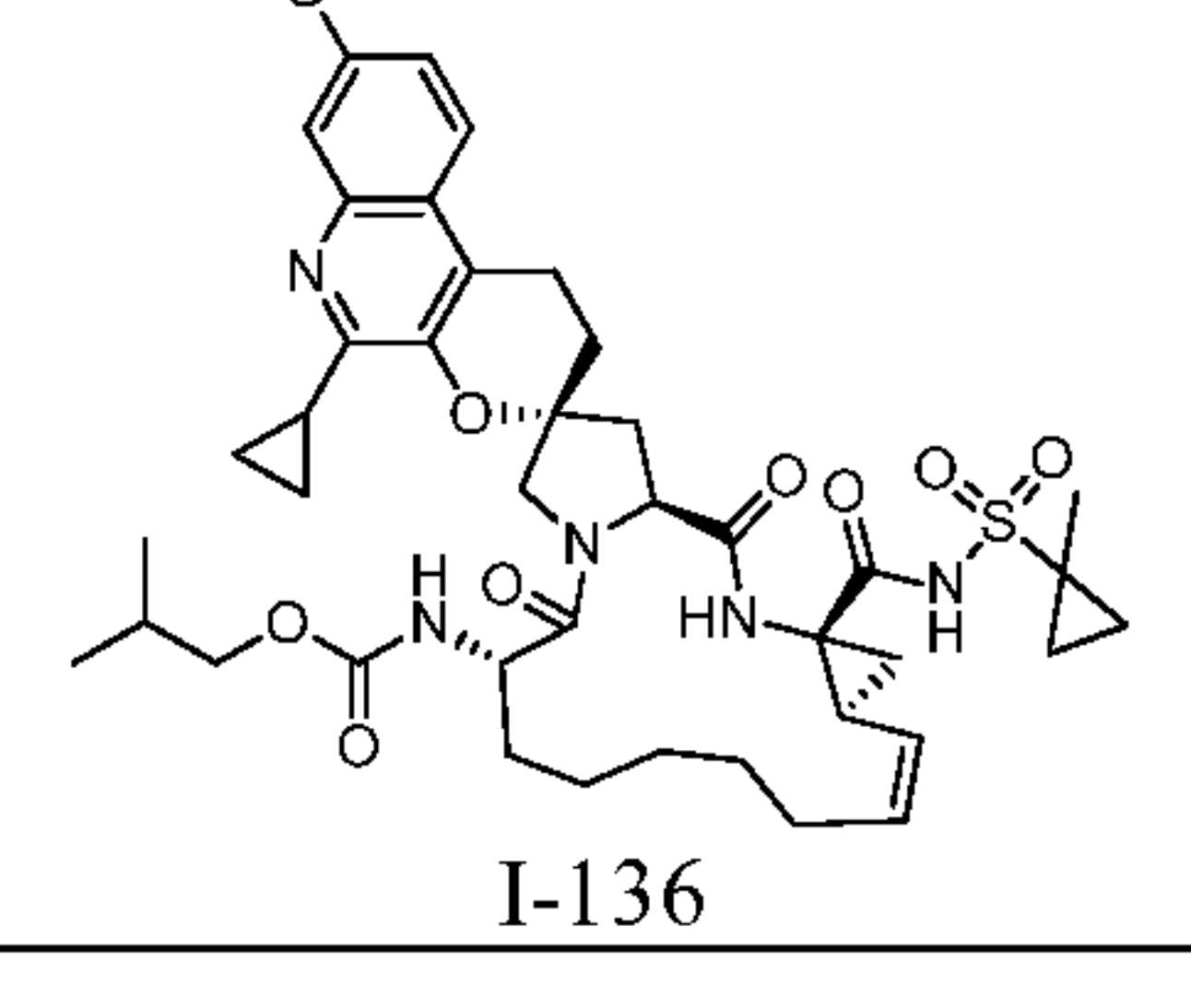
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
103	 I-103	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	775.6
104	 I-104	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	4	787.8
105	 I-105	propan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 6	736.2
106	 I-106	2-methylpropyl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1',1'-difluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	19, 21	786.2
107	 I-107	<i>tert</i> -butyl {(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-14a-[(cyclopropylsulfonyl)carbamoyl]-7'-fluoro-5'-methyl-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl} carbamate	45	753.8
108	 I-108	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5',9'-dimethyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	42	764.5

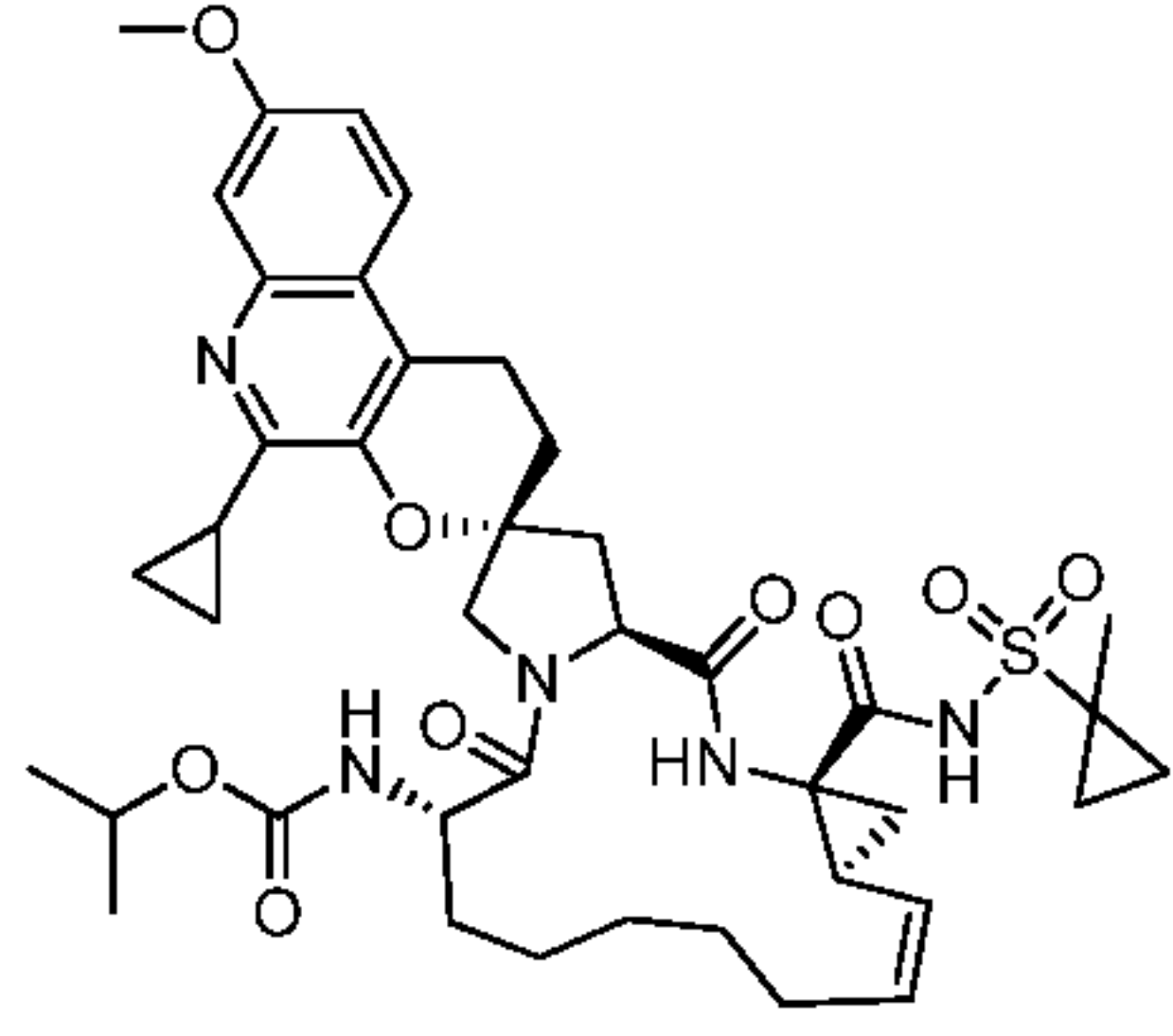
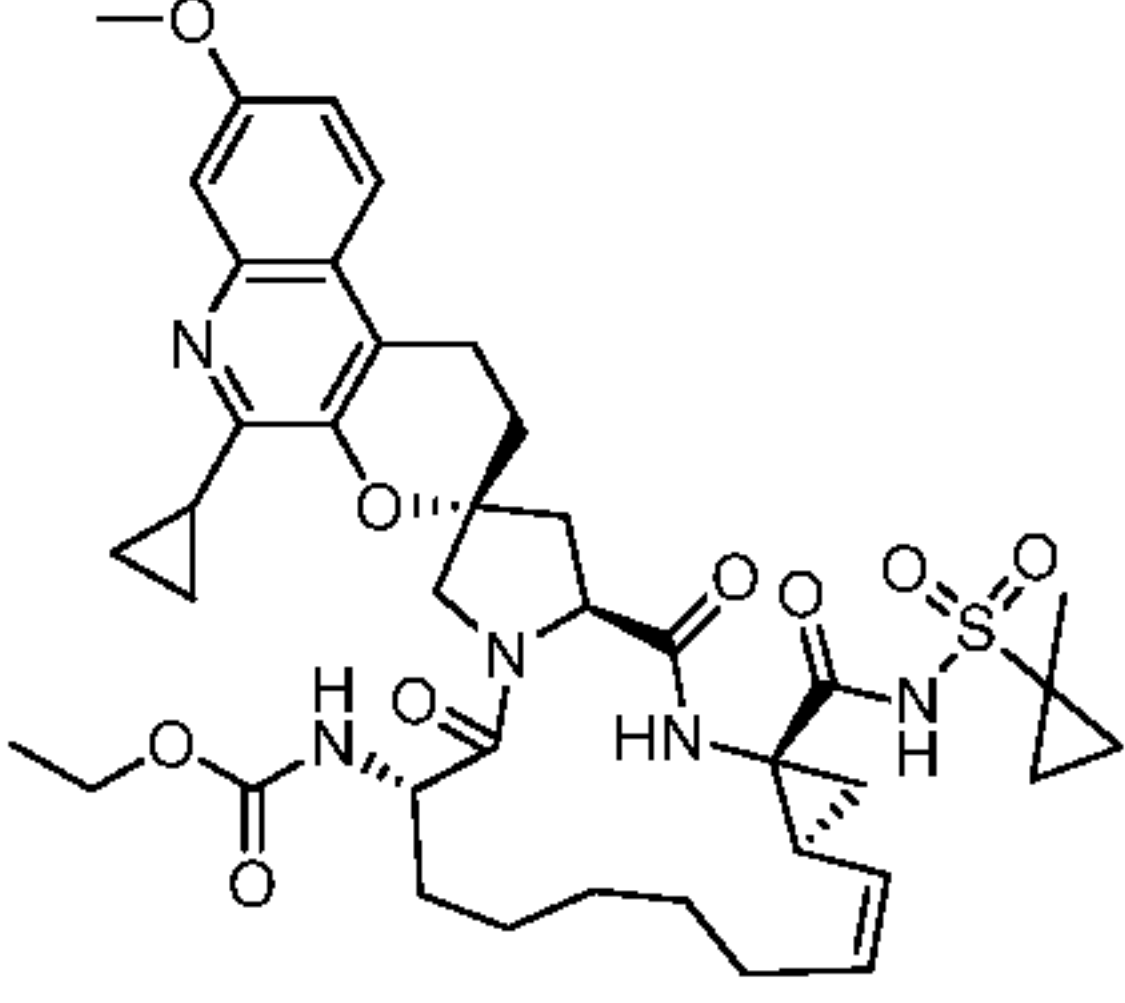
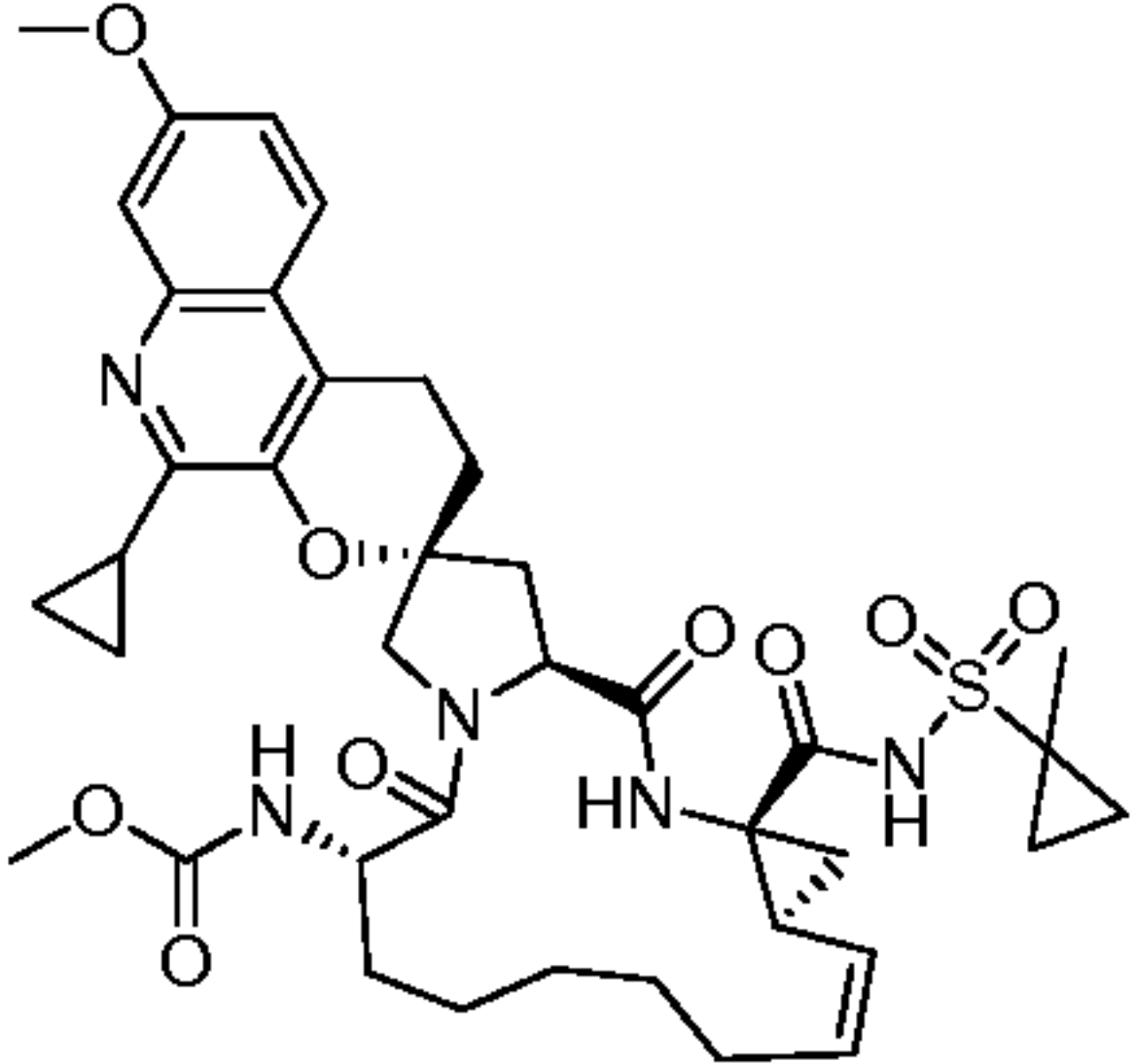
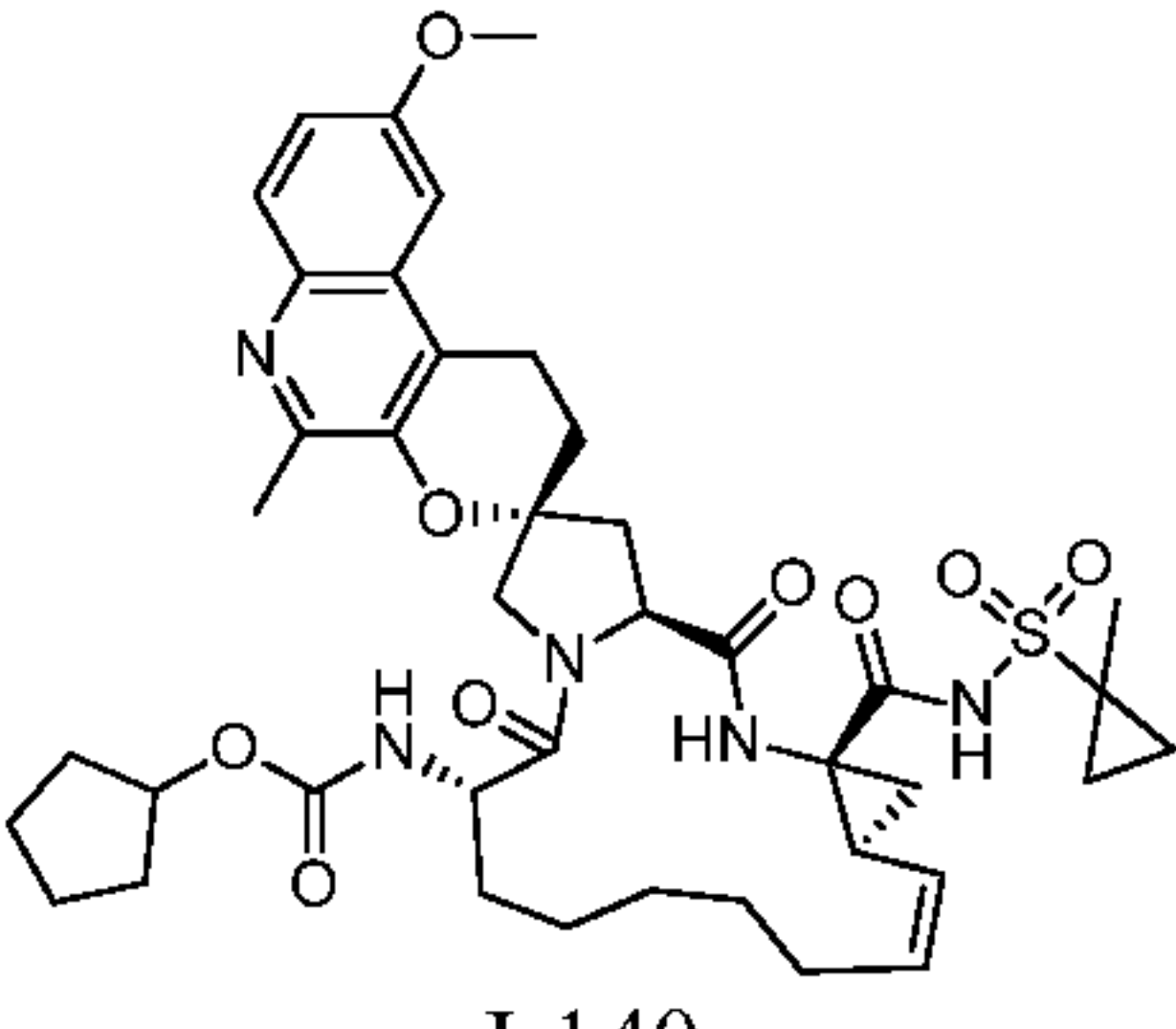
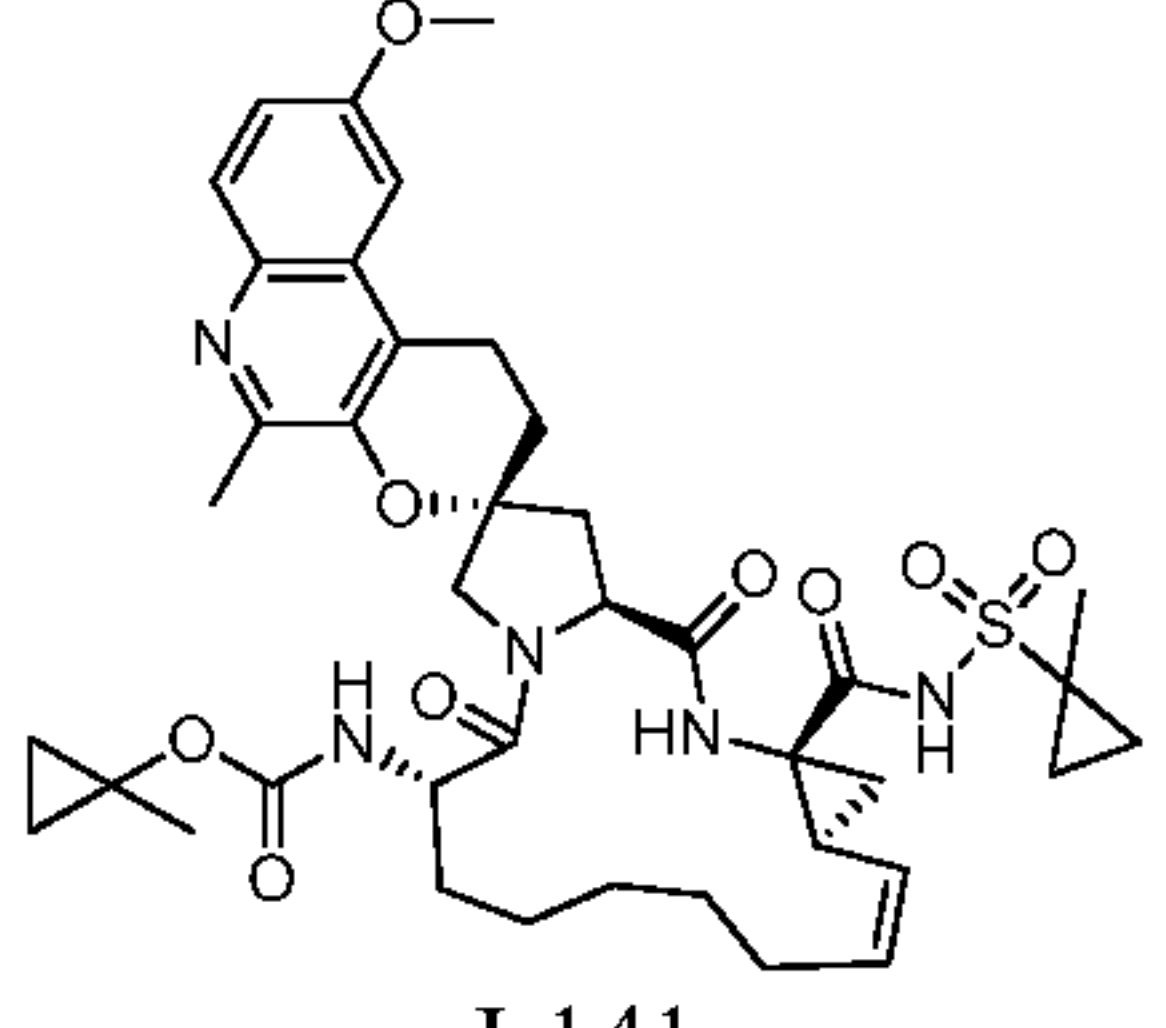
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
109	 I-109	propan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5',9'-dimethyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	42	750.5
110	 I-110	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	--
111	 I-111	1-methylcyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	787.8
112	 I-112	2,2,3,3-tetrafluorocyclobutyl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1',1'-difluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	19, 35	856.2
113	 I-113	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-7'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	44	818.2
114	 I-114	propan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-7'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	44	804.2

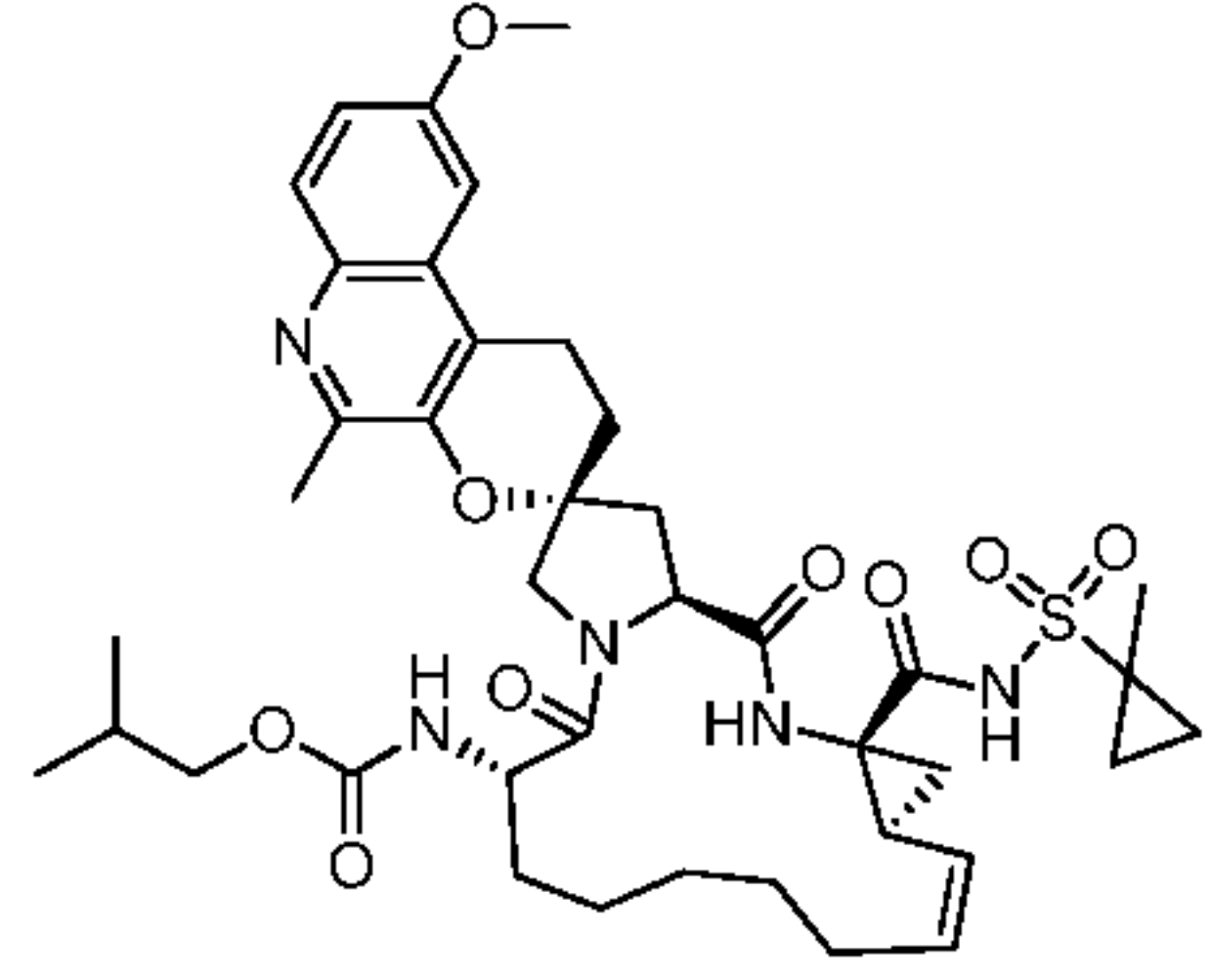
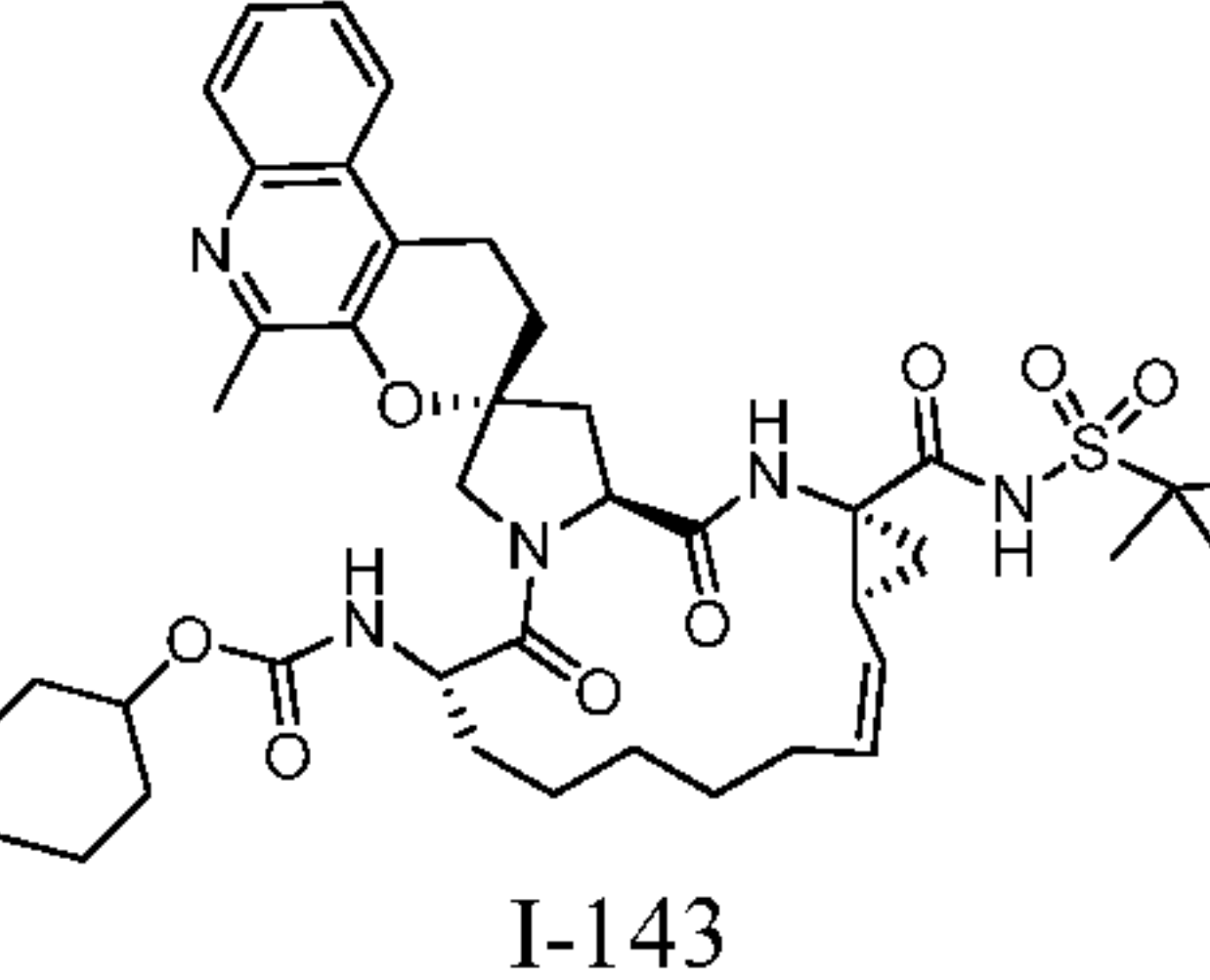
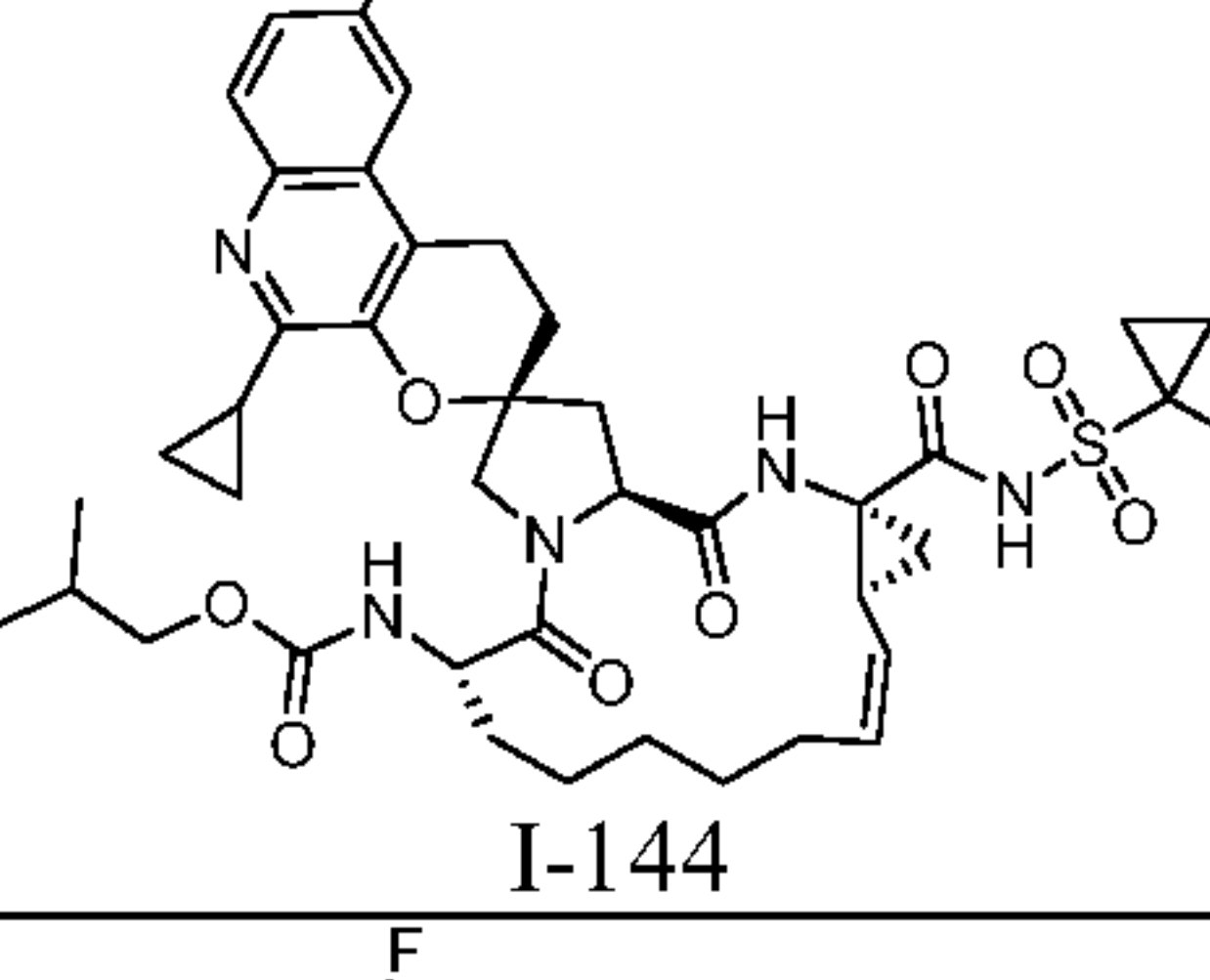
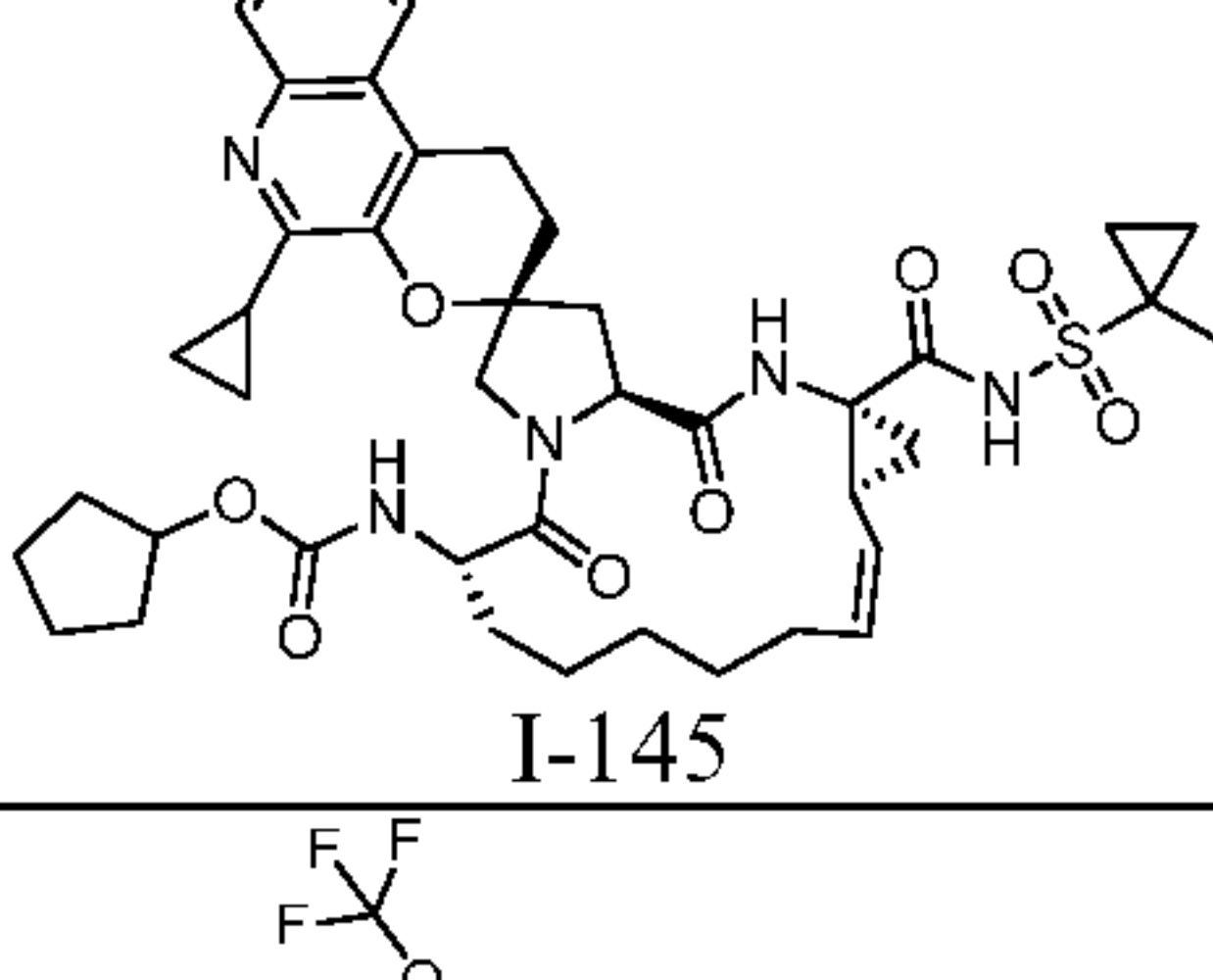
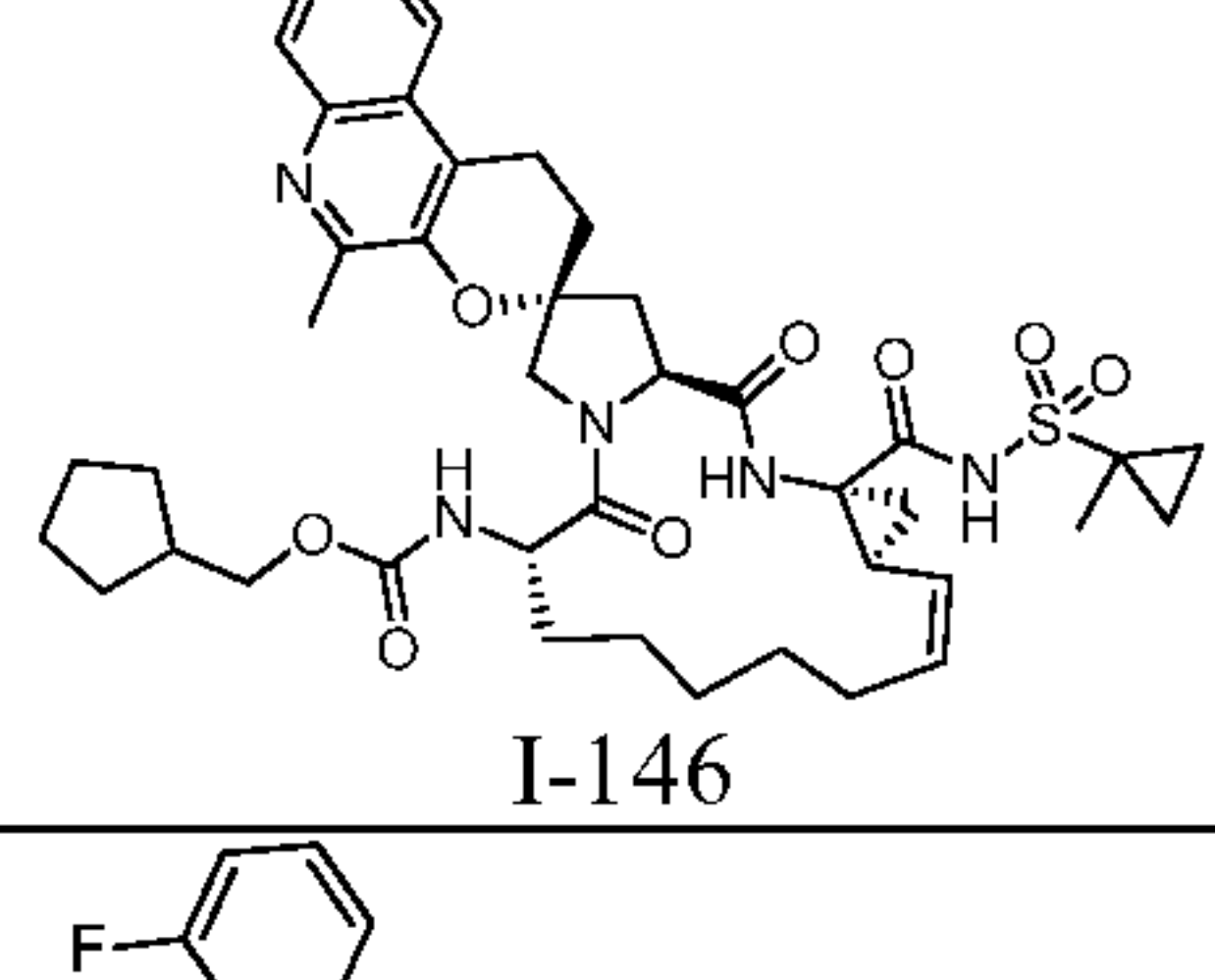
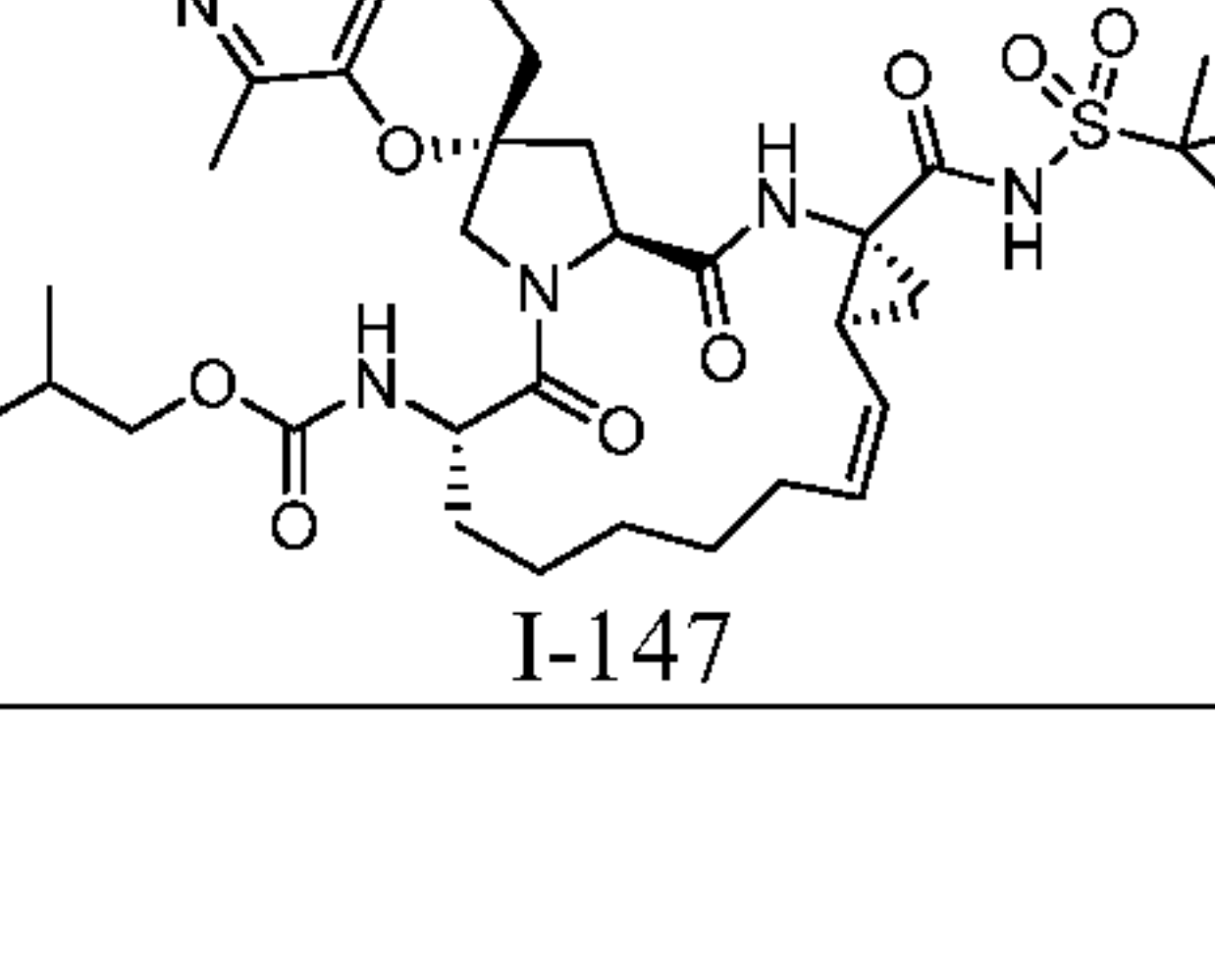
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
115	 I-115	ethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl} carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl] carbamate	1, 35	722.4
116	 I-116	1-(propan-2-yl)cyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl} carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl] carbamate	1, 35	776.4
117	 I-117	1-methylpiperidin-4-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl} carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl] carbamate	1, 35	790.8
118	 I-118	<i>tert</i> -butyl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-hydroxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl} carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl] carbamate	9	766.5
119	 I-119	propan-2-yl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-hydroxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl} carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl] carbamate	9	752.5
120	 I-120	<i>tert</i> -butyl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-hydroxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl} carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl] carbamate	9	766.5

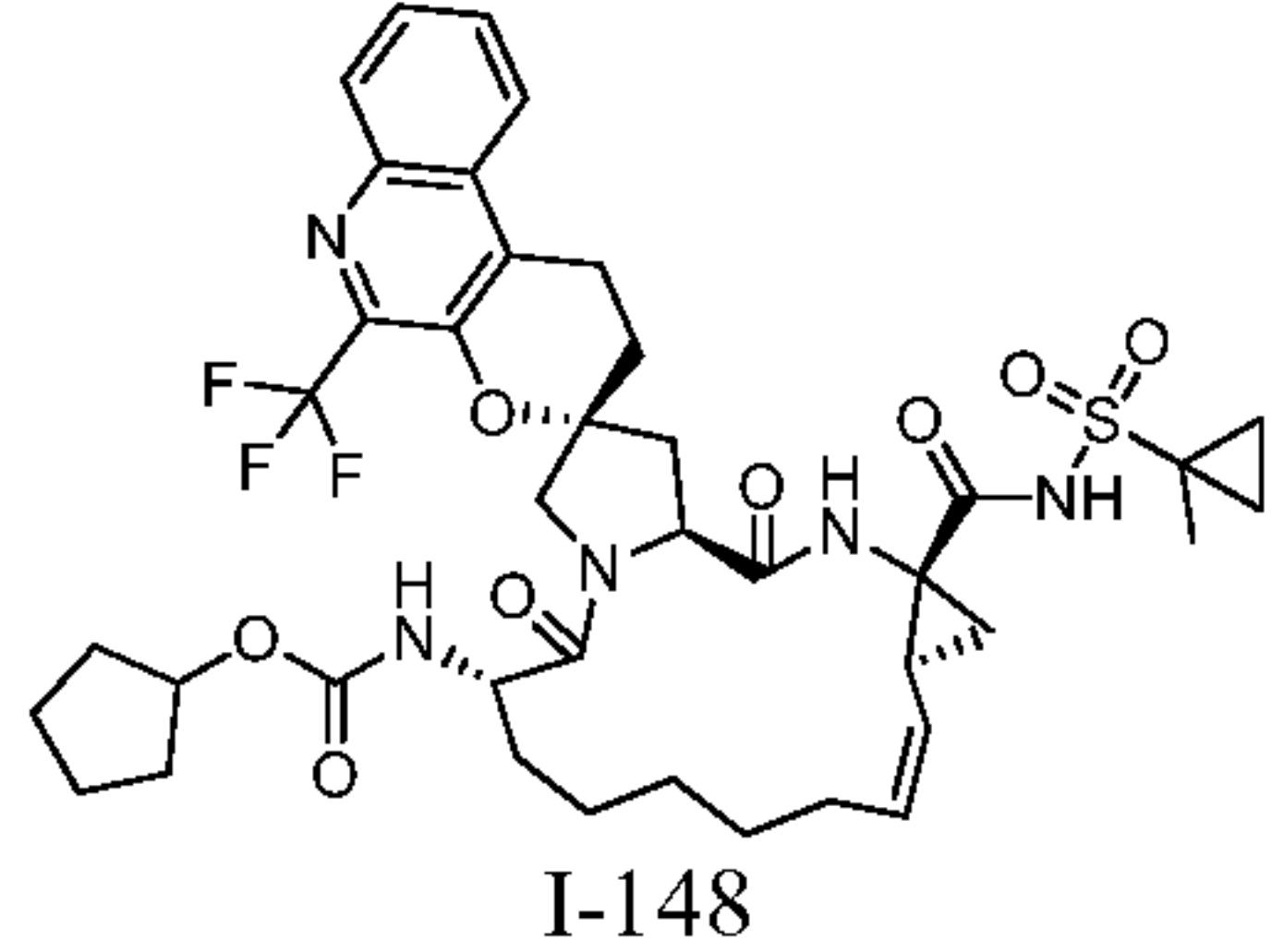
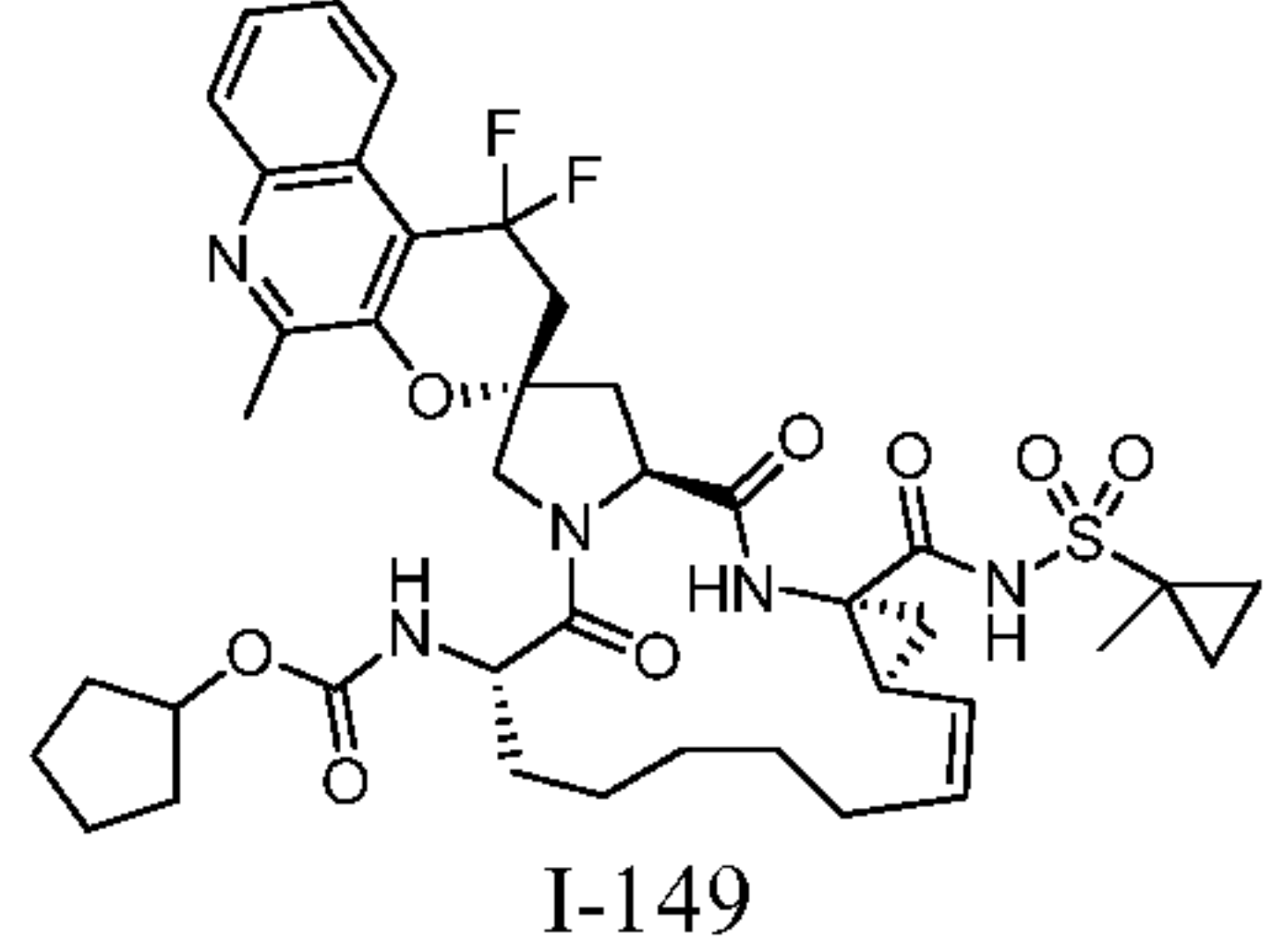
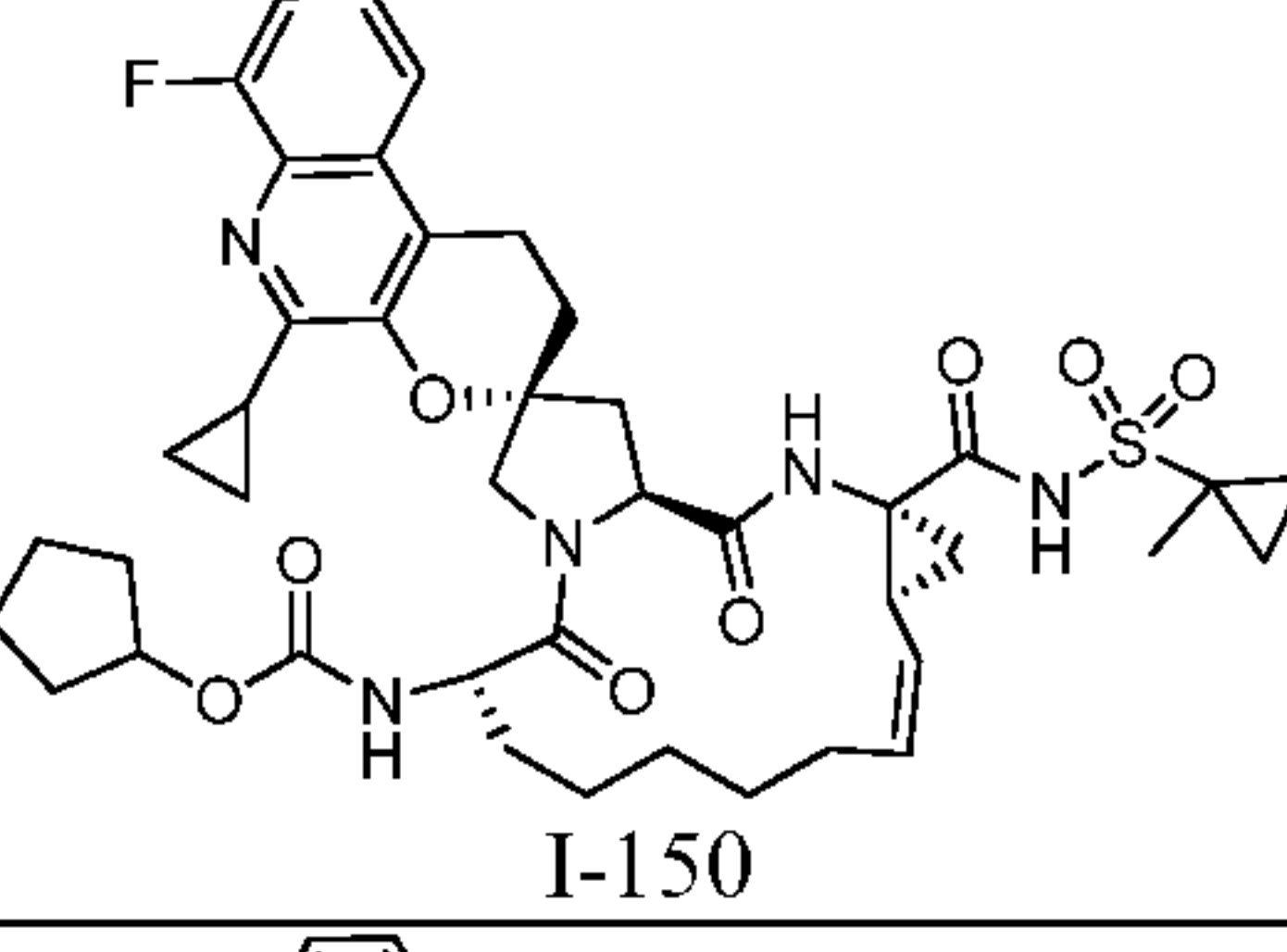
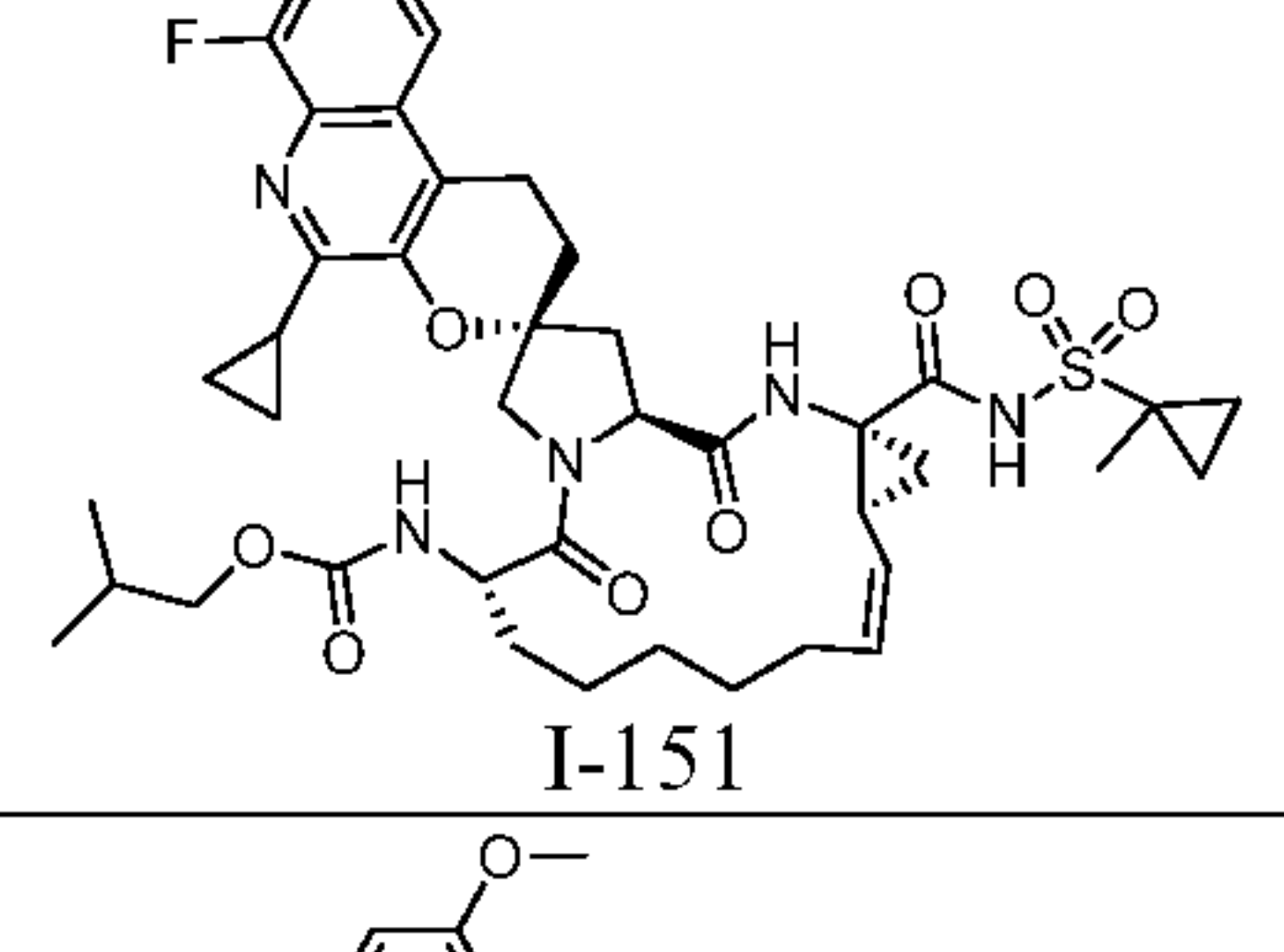
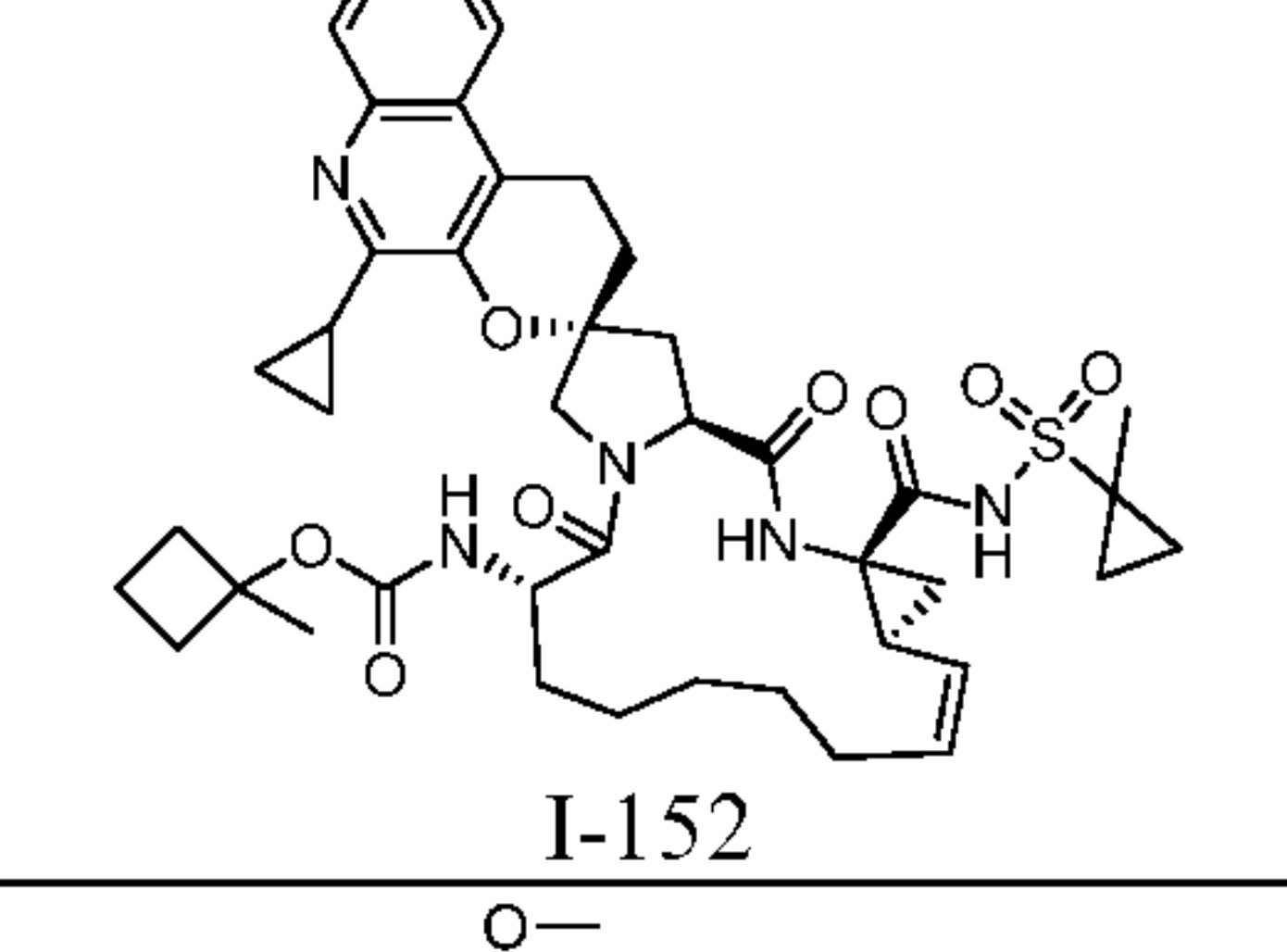
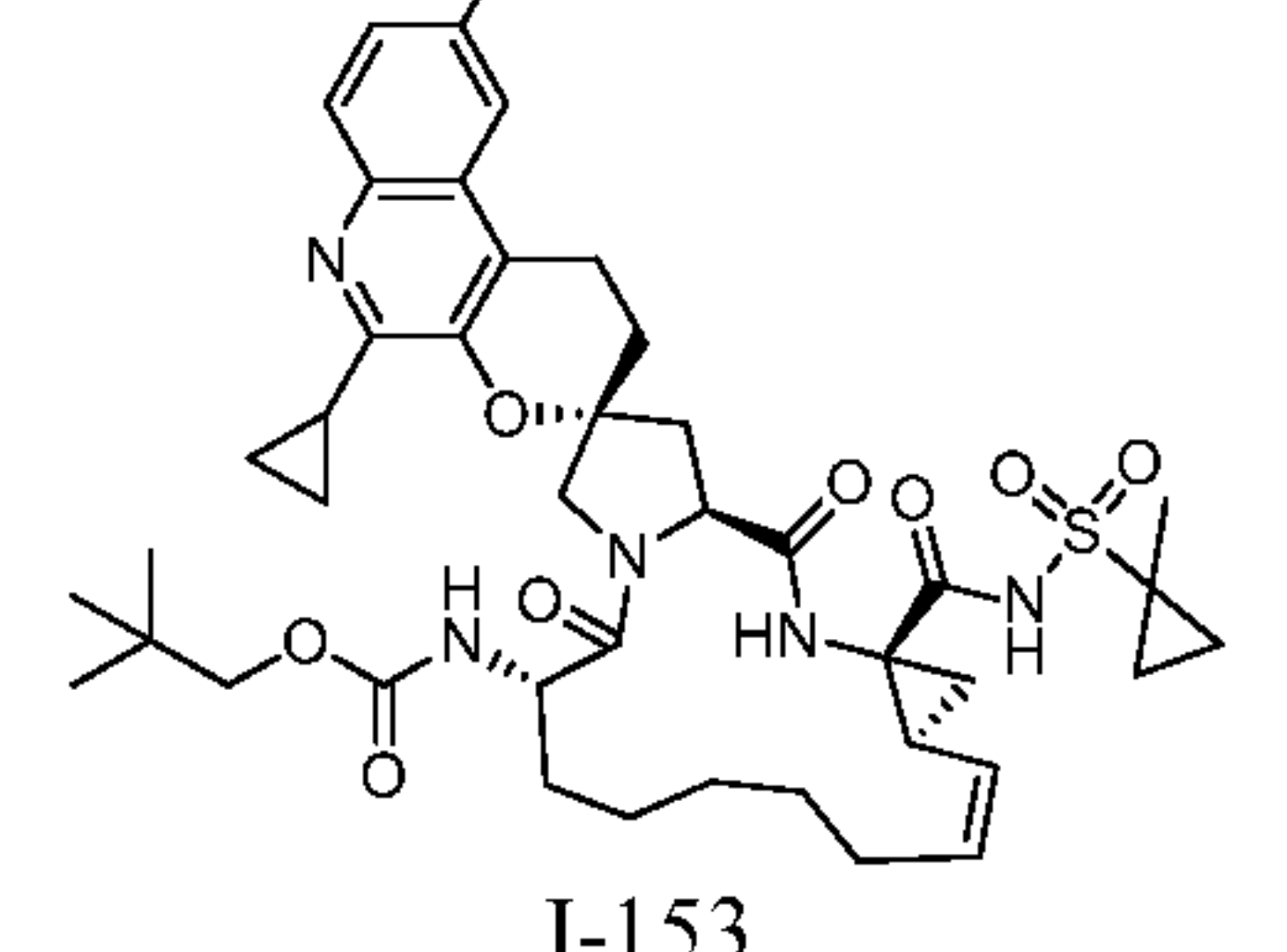
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
121	 I-121	2,2-difluoroethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	757.7
122	 I-122	1-methylcyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	832.2
123	 I-123	propan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	820.2
124	 I-124	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 528	834.2
125	 I-125	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	846.2

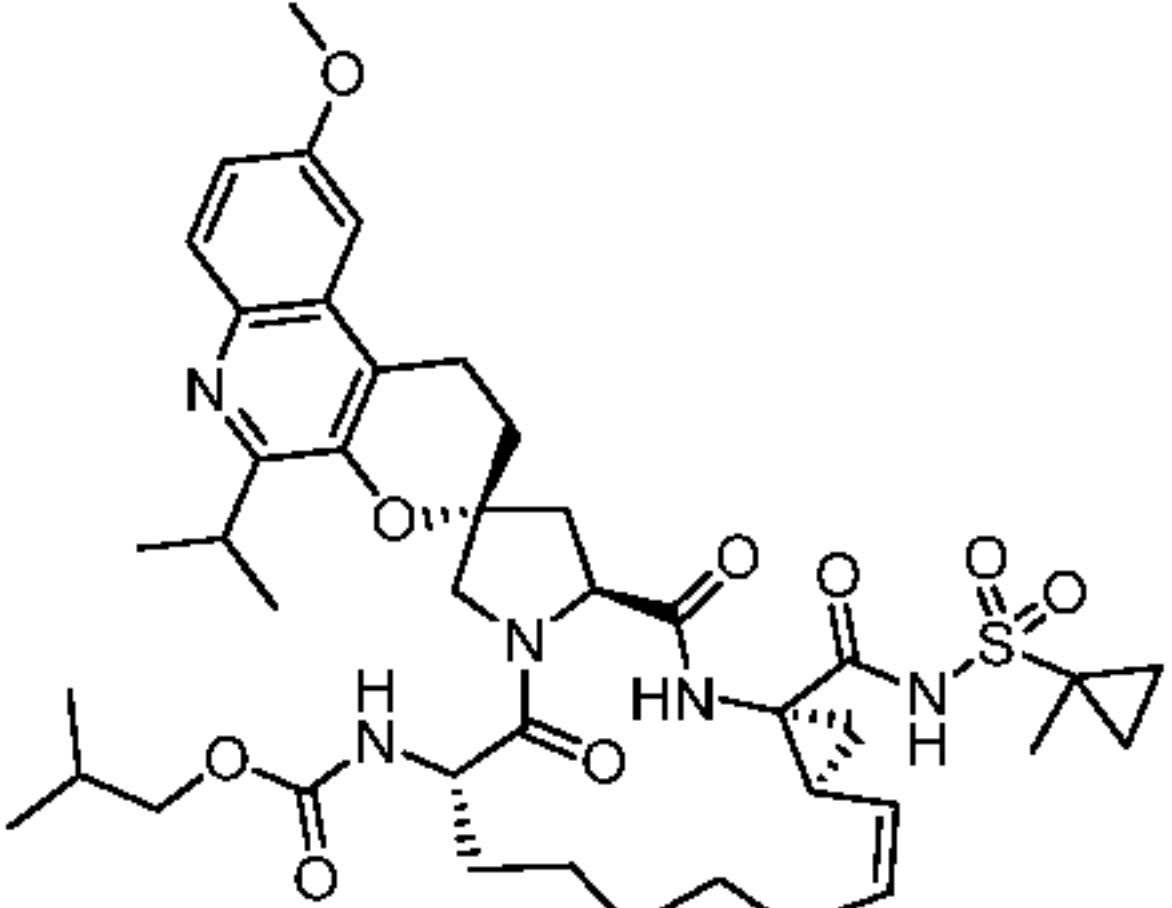
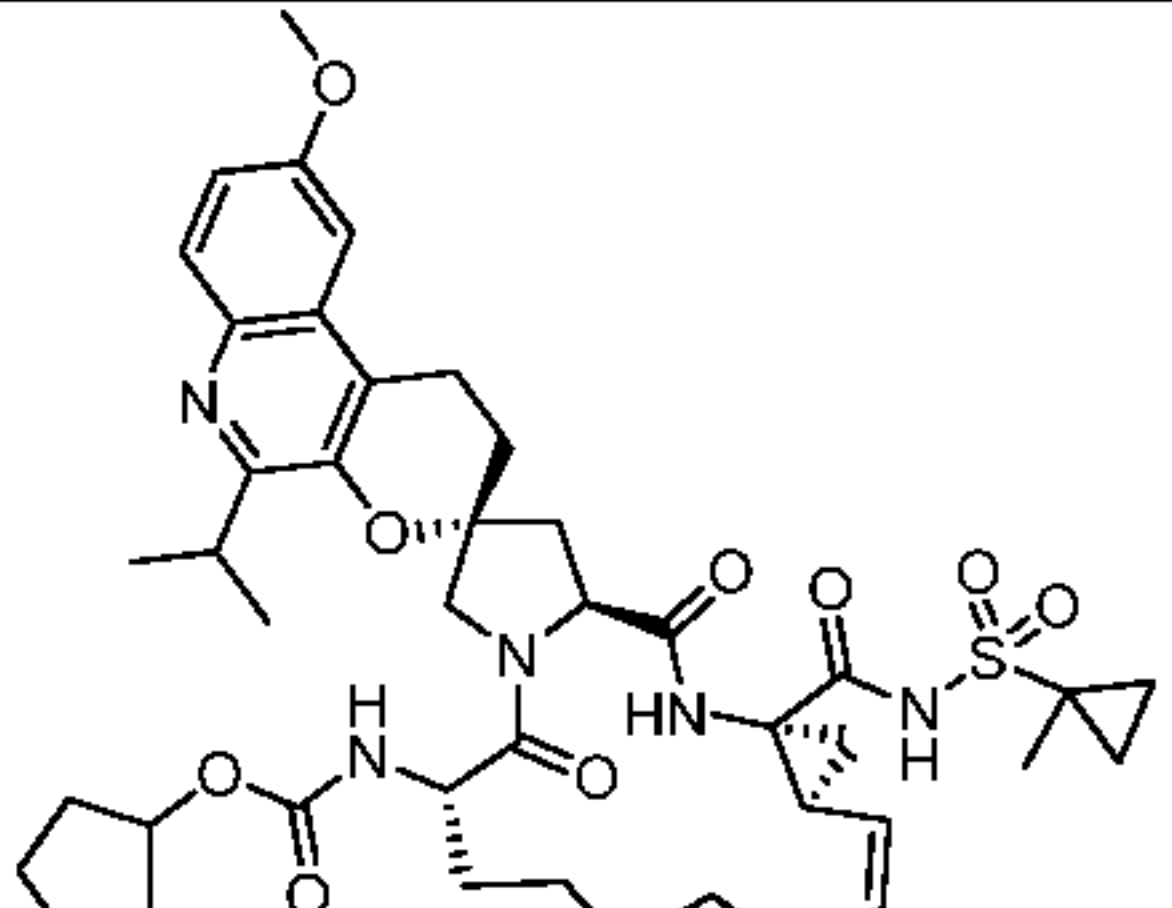
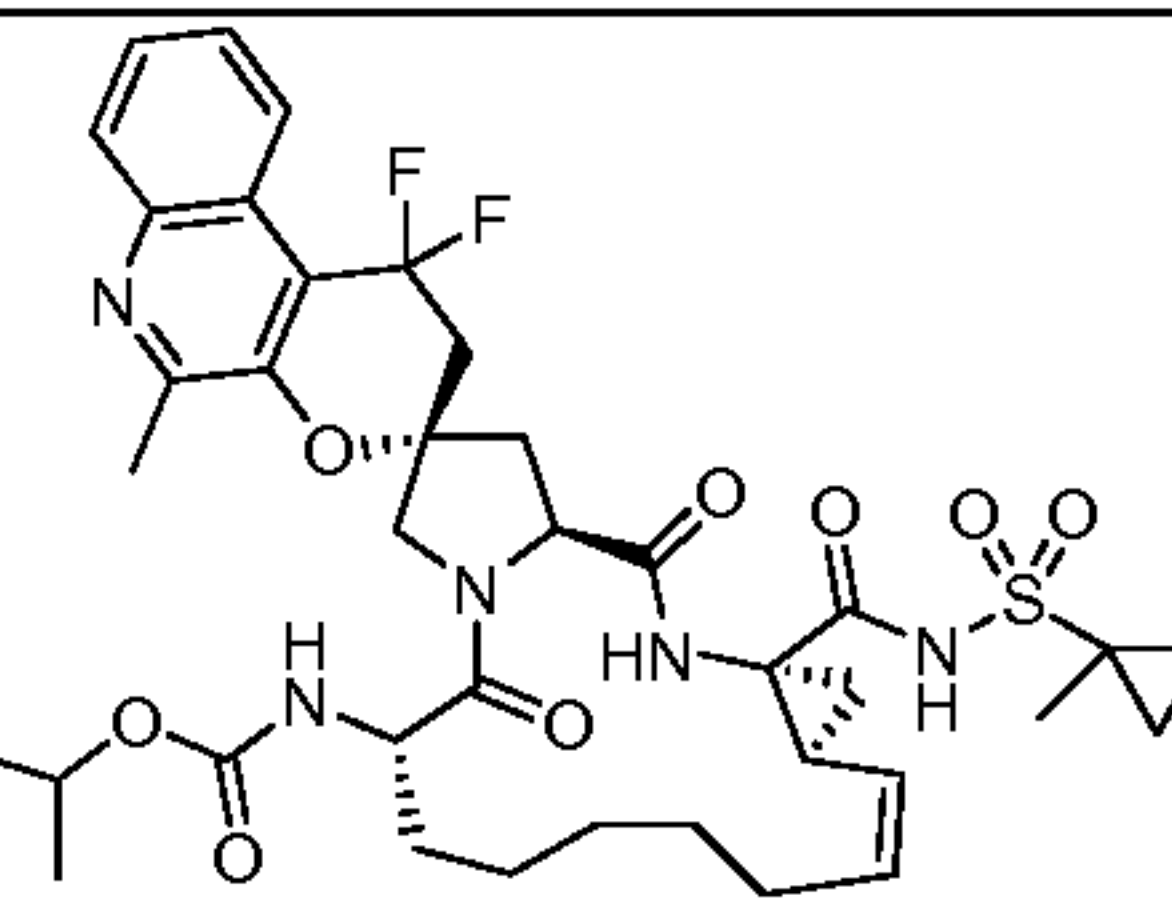
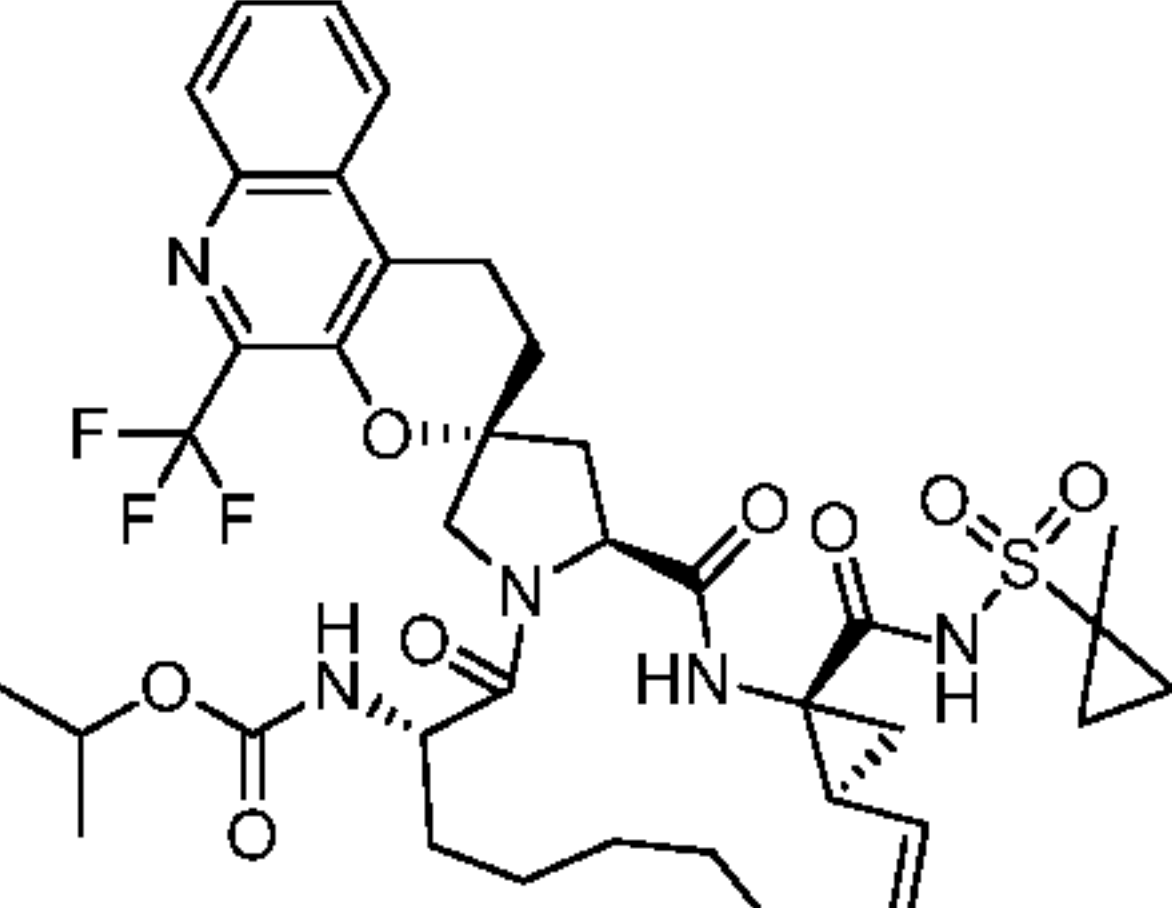
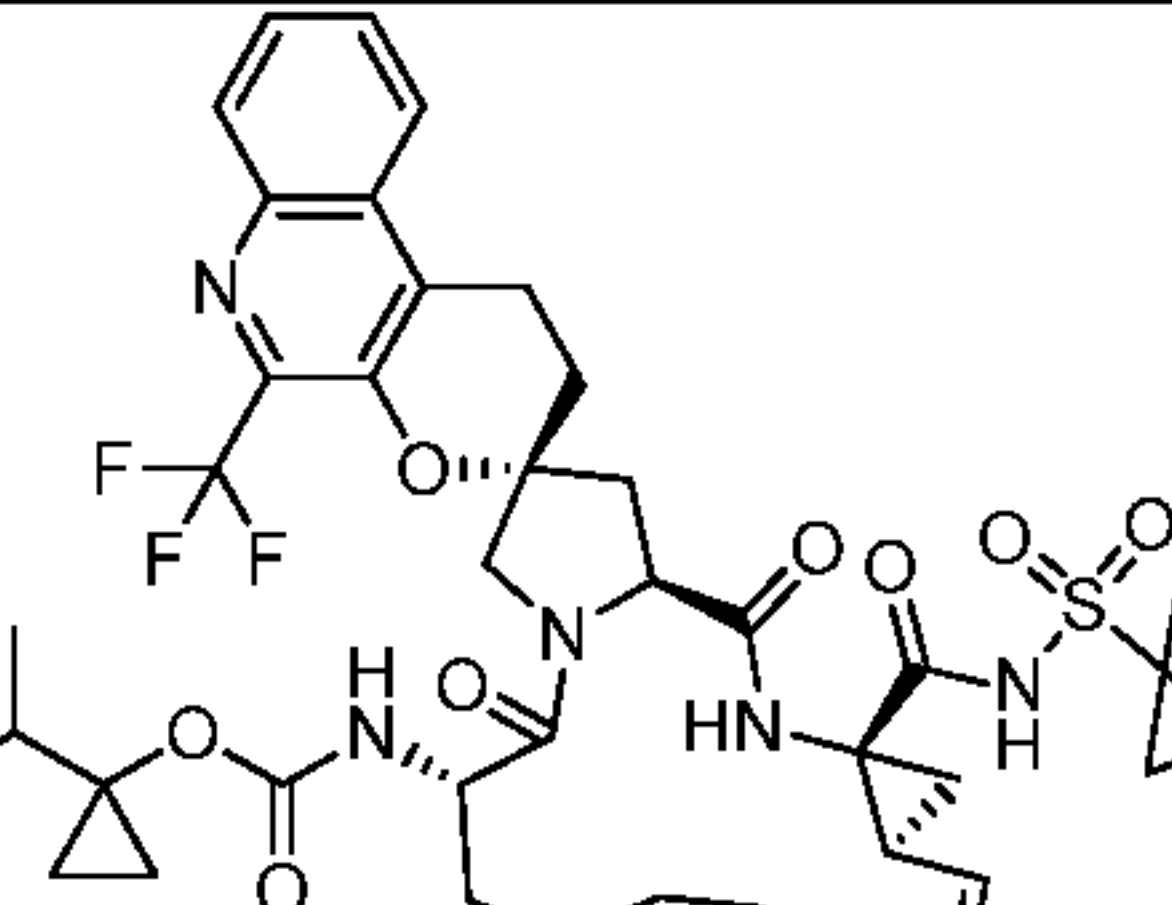
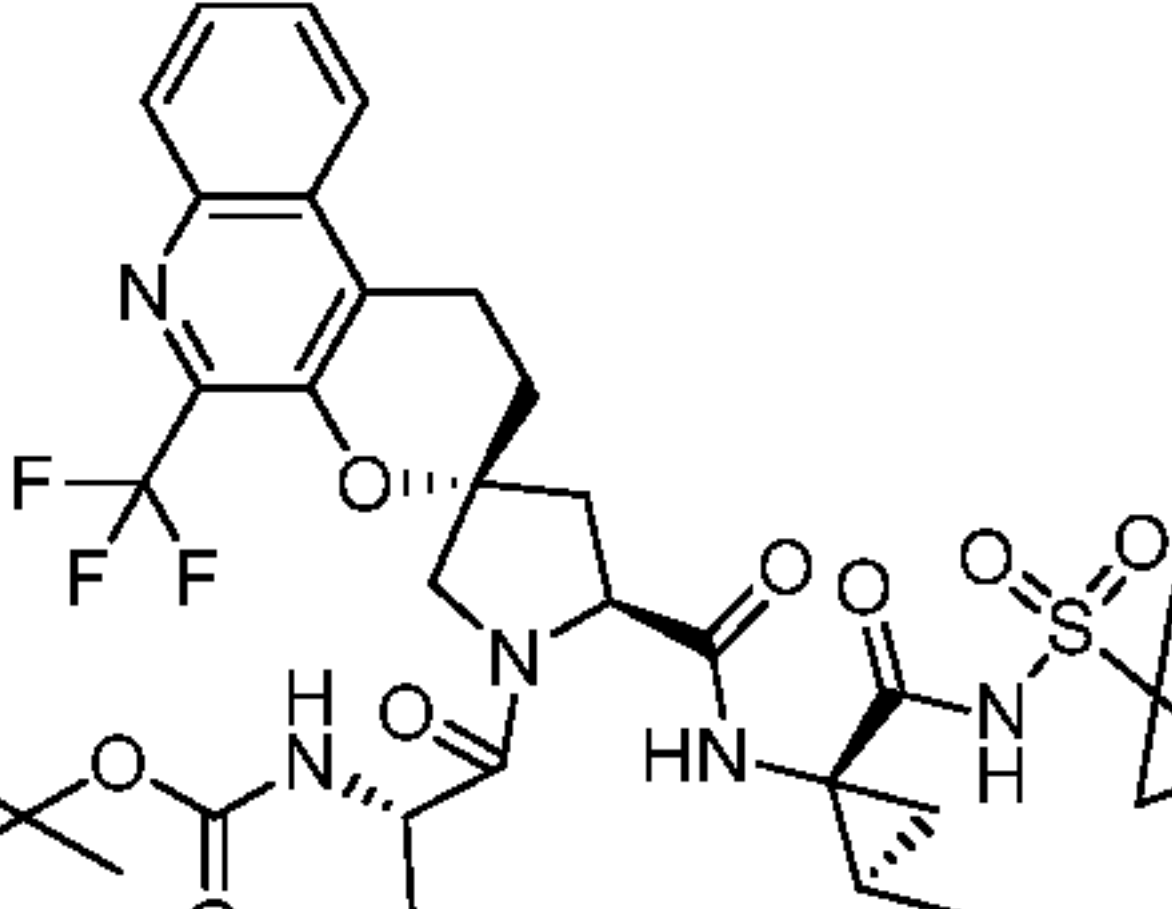
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
126	 I-126	1-cyclopropylethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	761.7
127	 I-127	2-fluoroethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	739.7
128	 I-128	2-methoxyethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	751.8
129	 I-129	2,2,2-trifluoroethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 6	776.2
130	 I-130	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	763.8
131	 I-131	1,1'-bi(cyclopropyl)-1-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	773.7

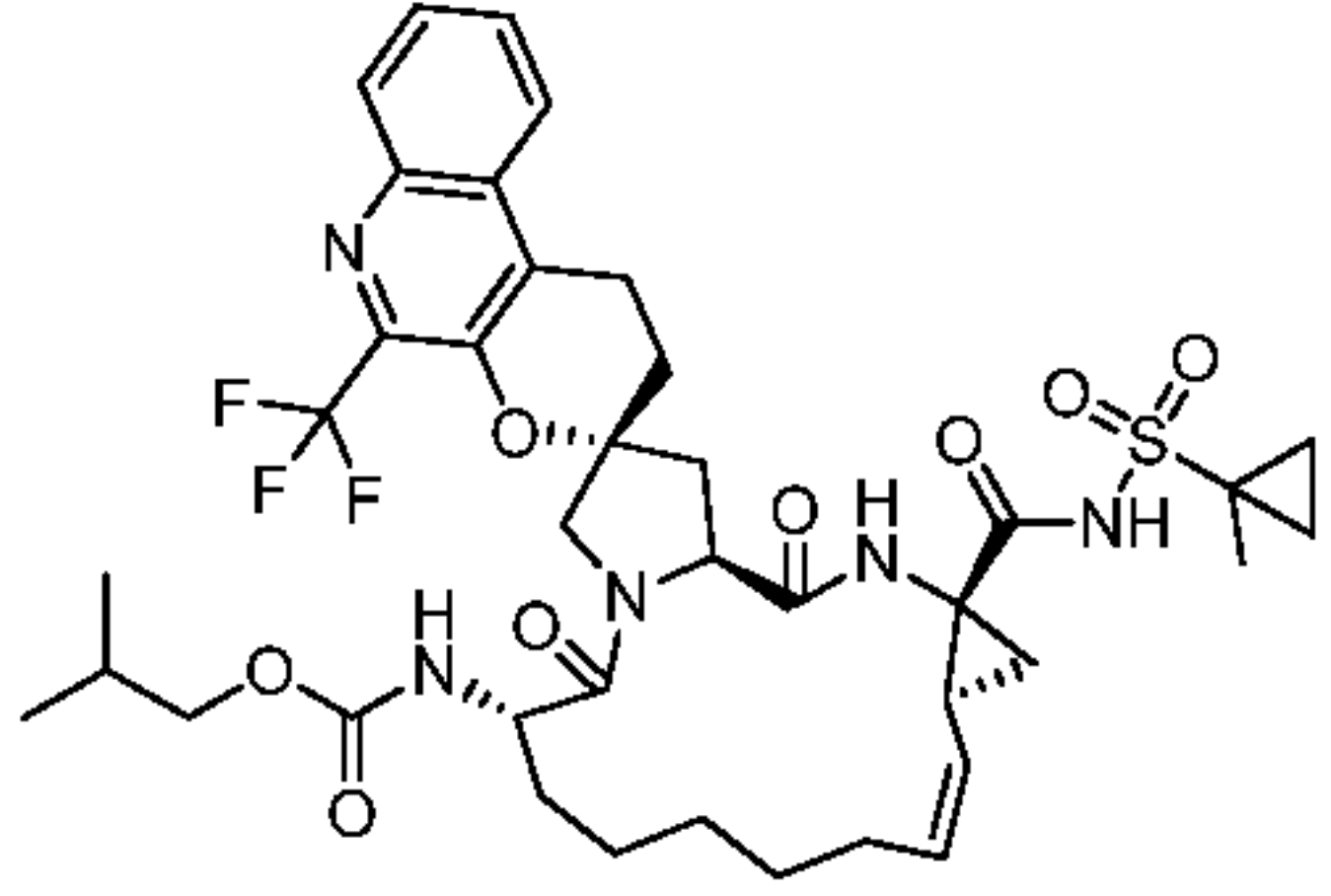
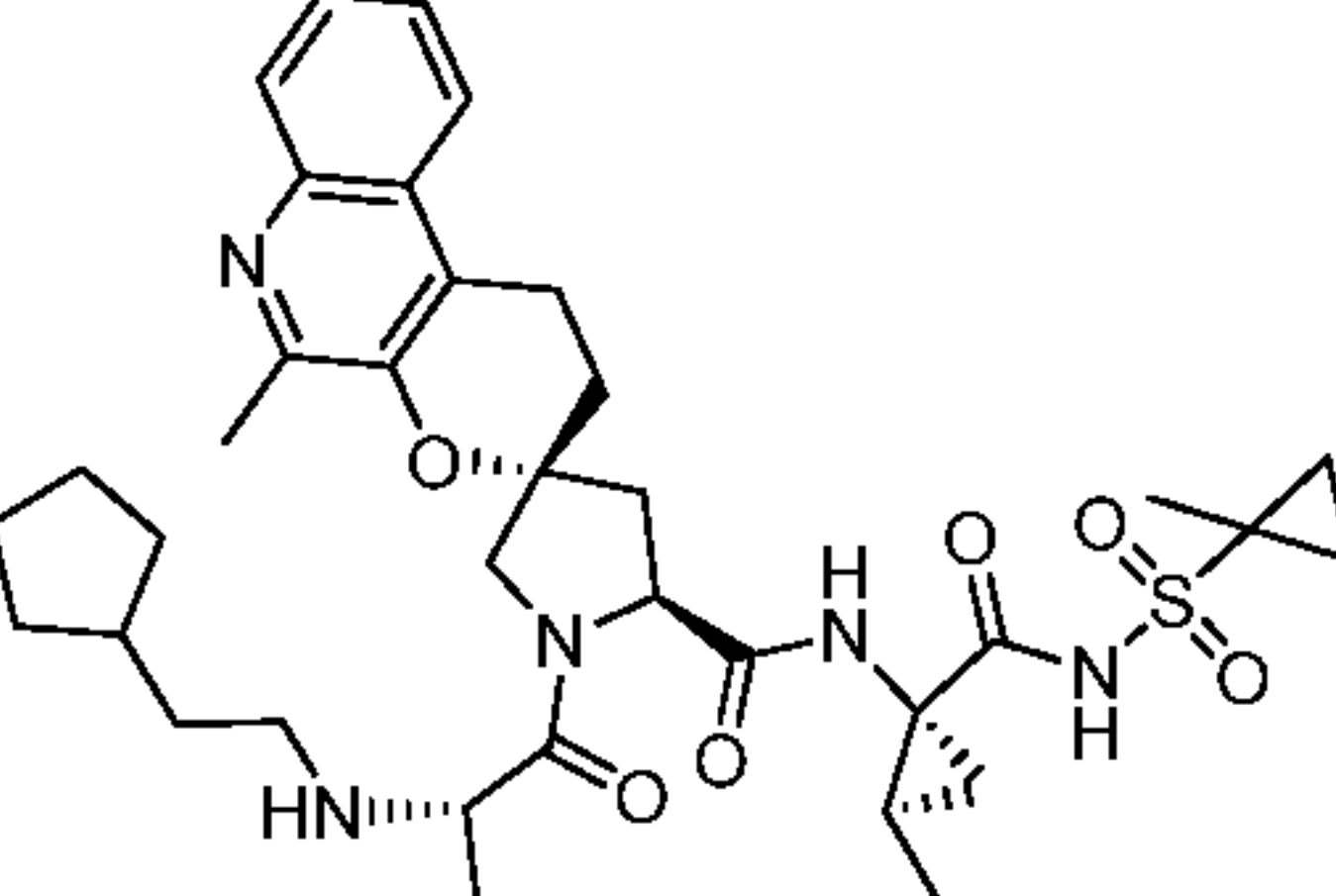
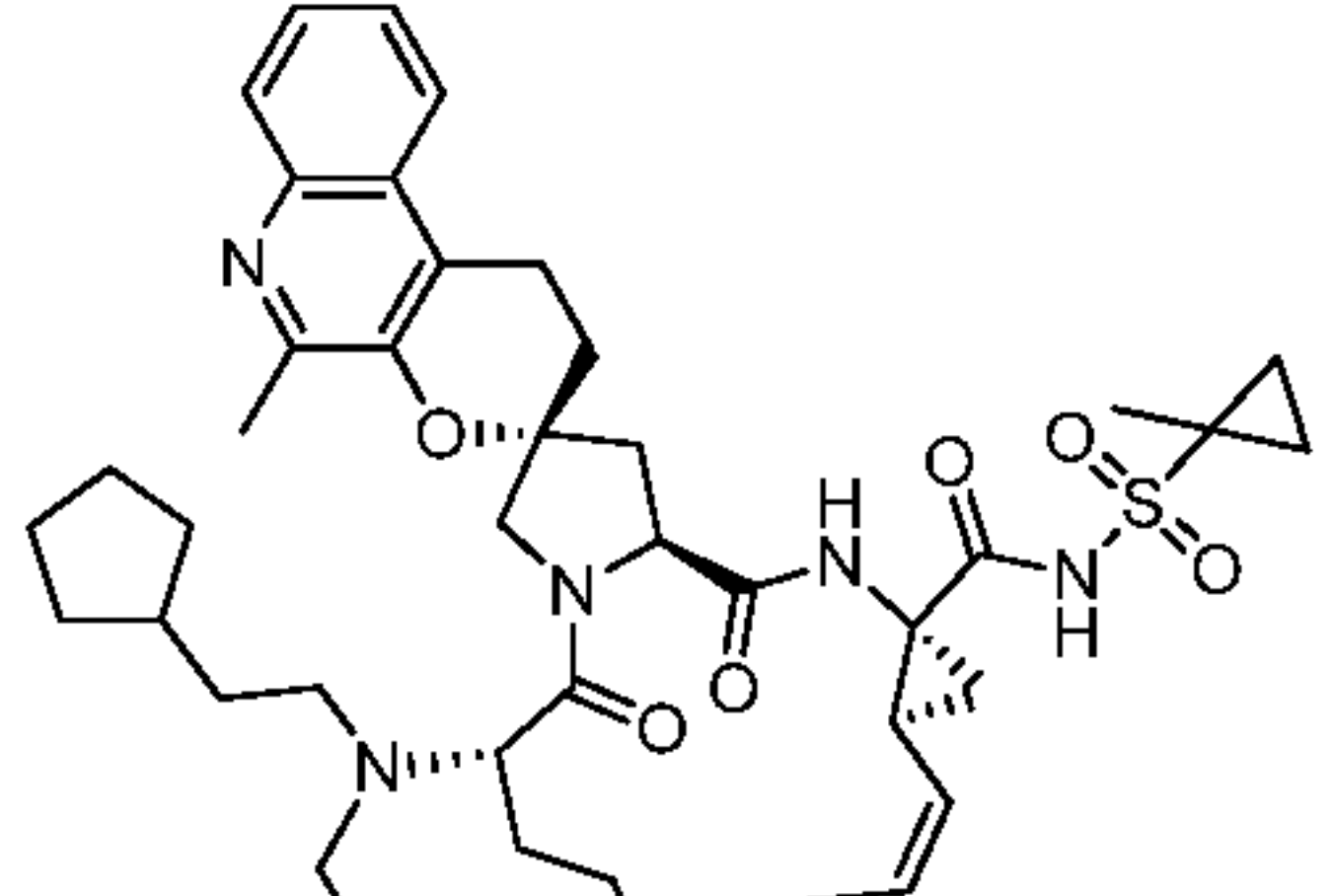
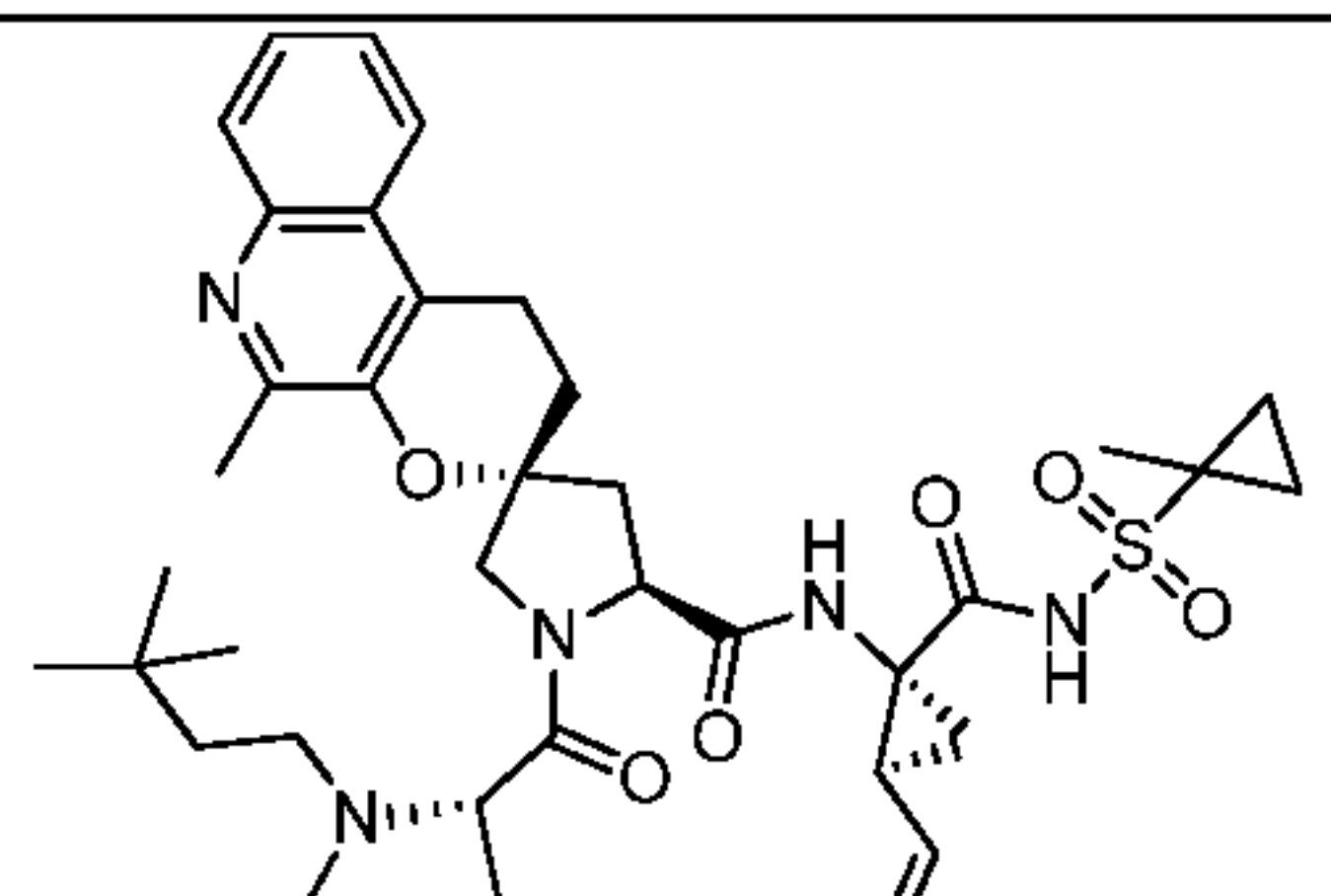
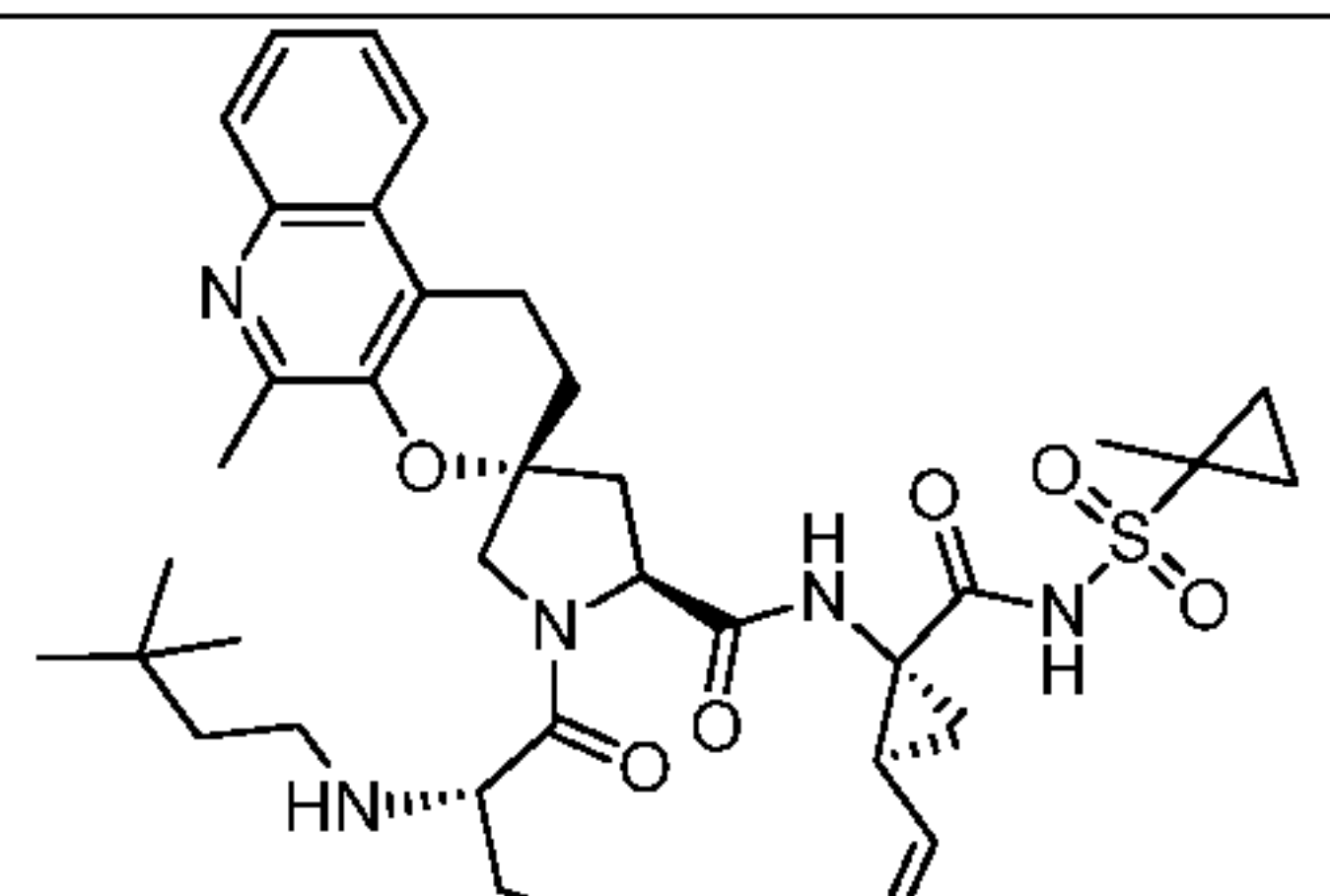
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
132	 I-132	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(<i>tert</i> -butylcarbamoyl)amino]-5'-cyclopropyl-8'-methoxy- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	16	805.2
133	 I-133	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(cyclopentylcarbamoyl)amino]-5'-cyclopropyl-8'-methoxy- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	16	817.2
134	 I-134	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-8'-methoxy-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16	818.4 (K+ salt)
135	 I-135	1-methylcyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-8'-methoxy-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16	804.4 (K+ salt)
136	 I-136	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-8'-methoxy-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16	806.2 (K+ salt)

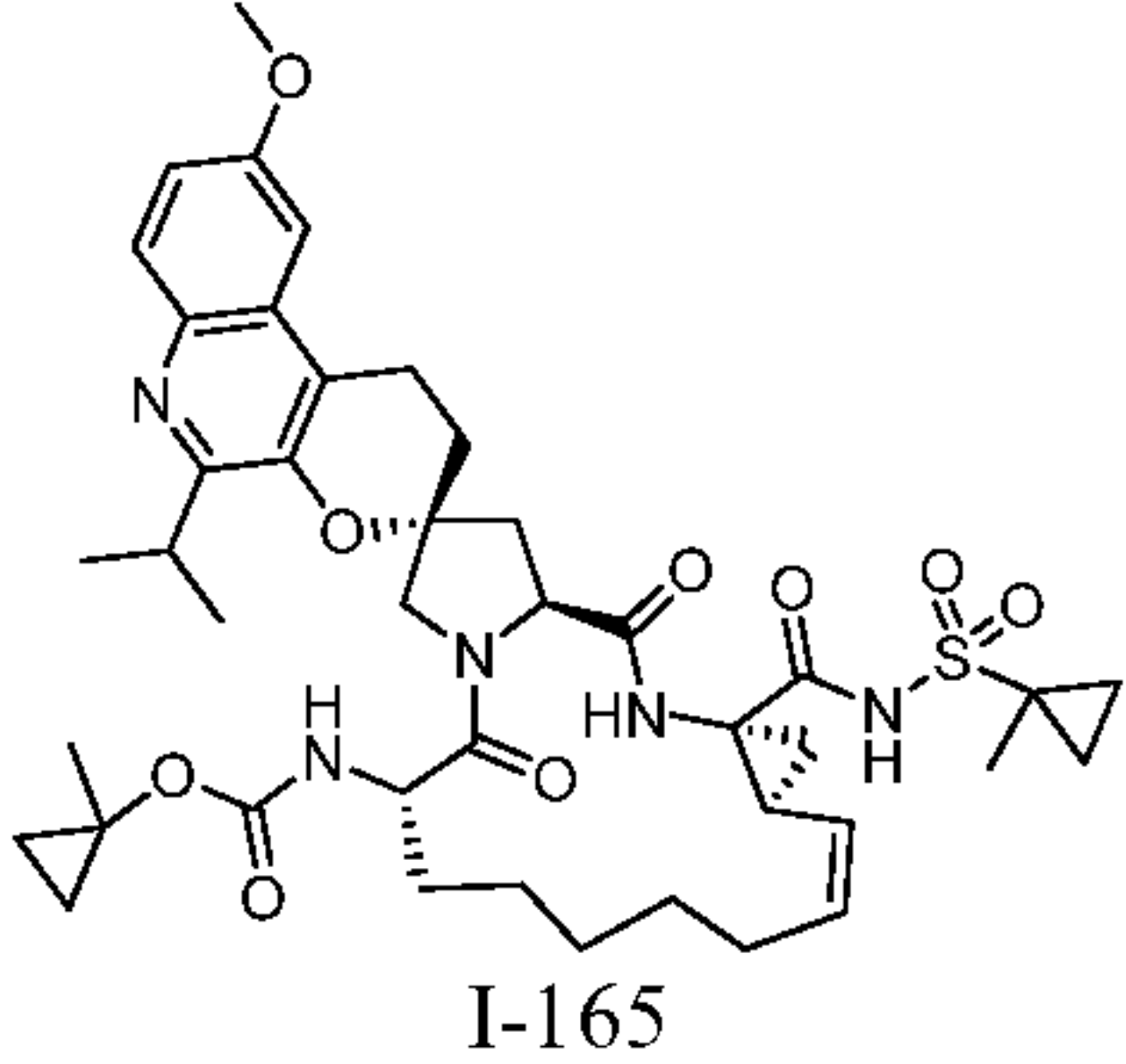
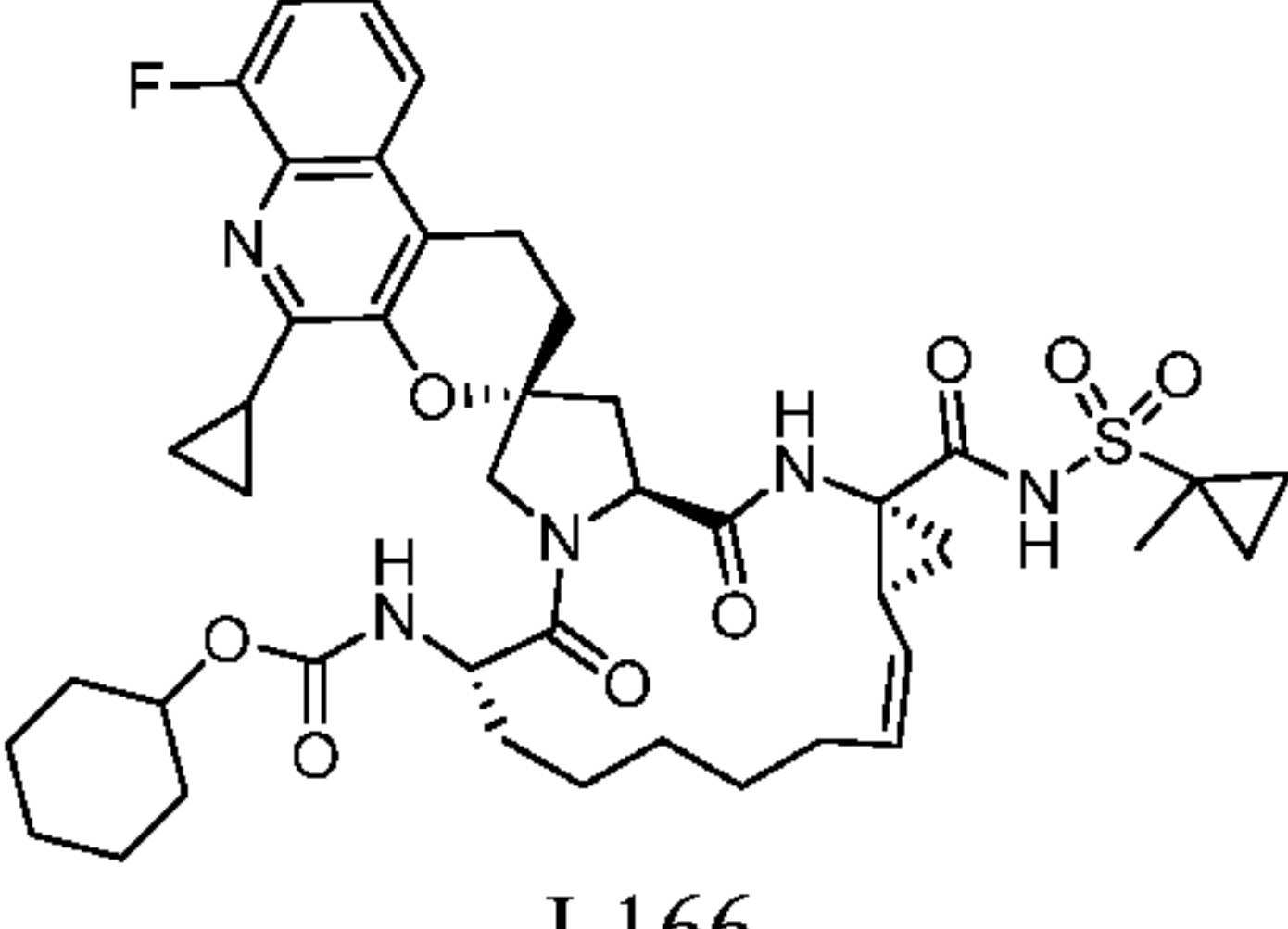
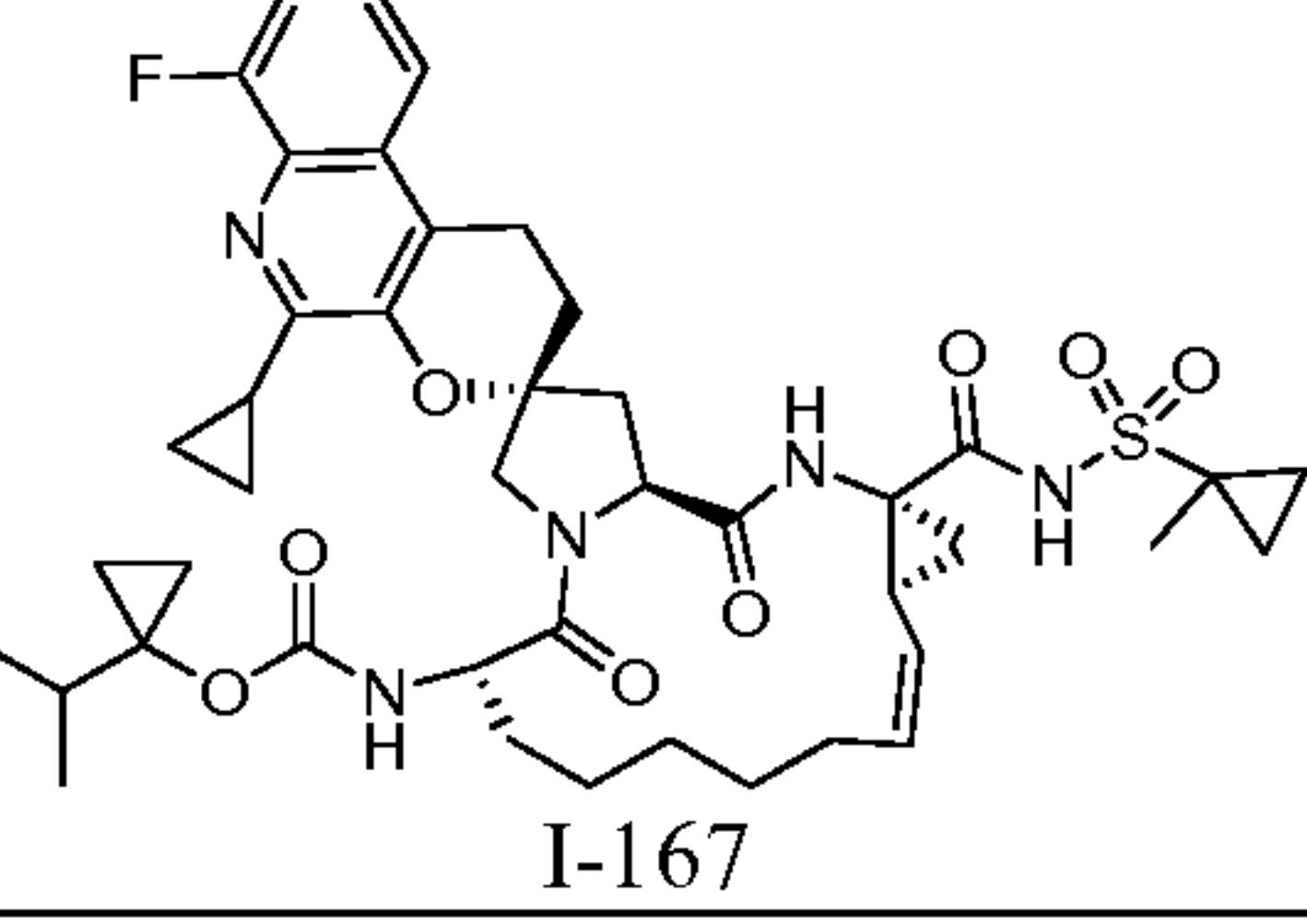
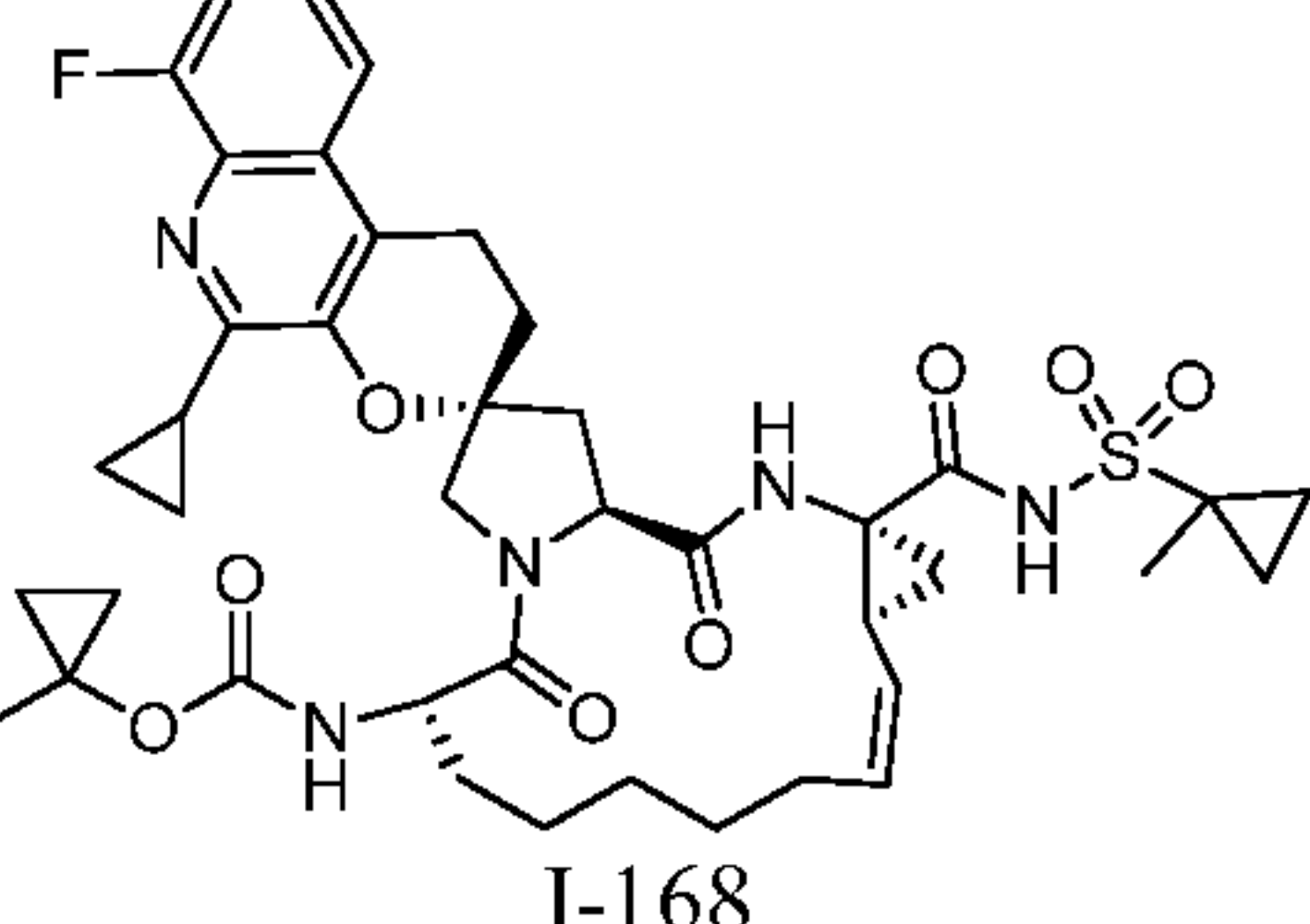
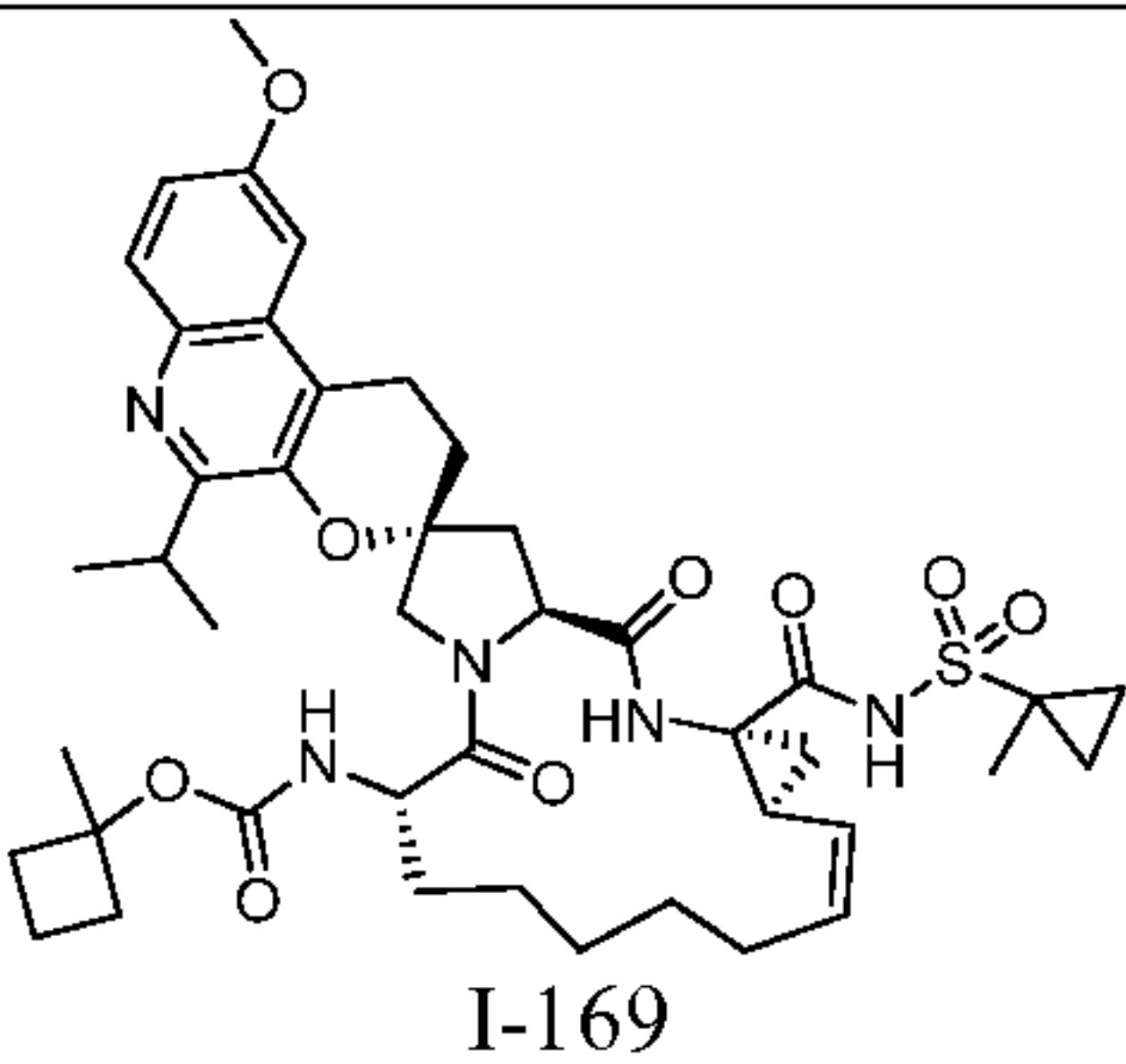
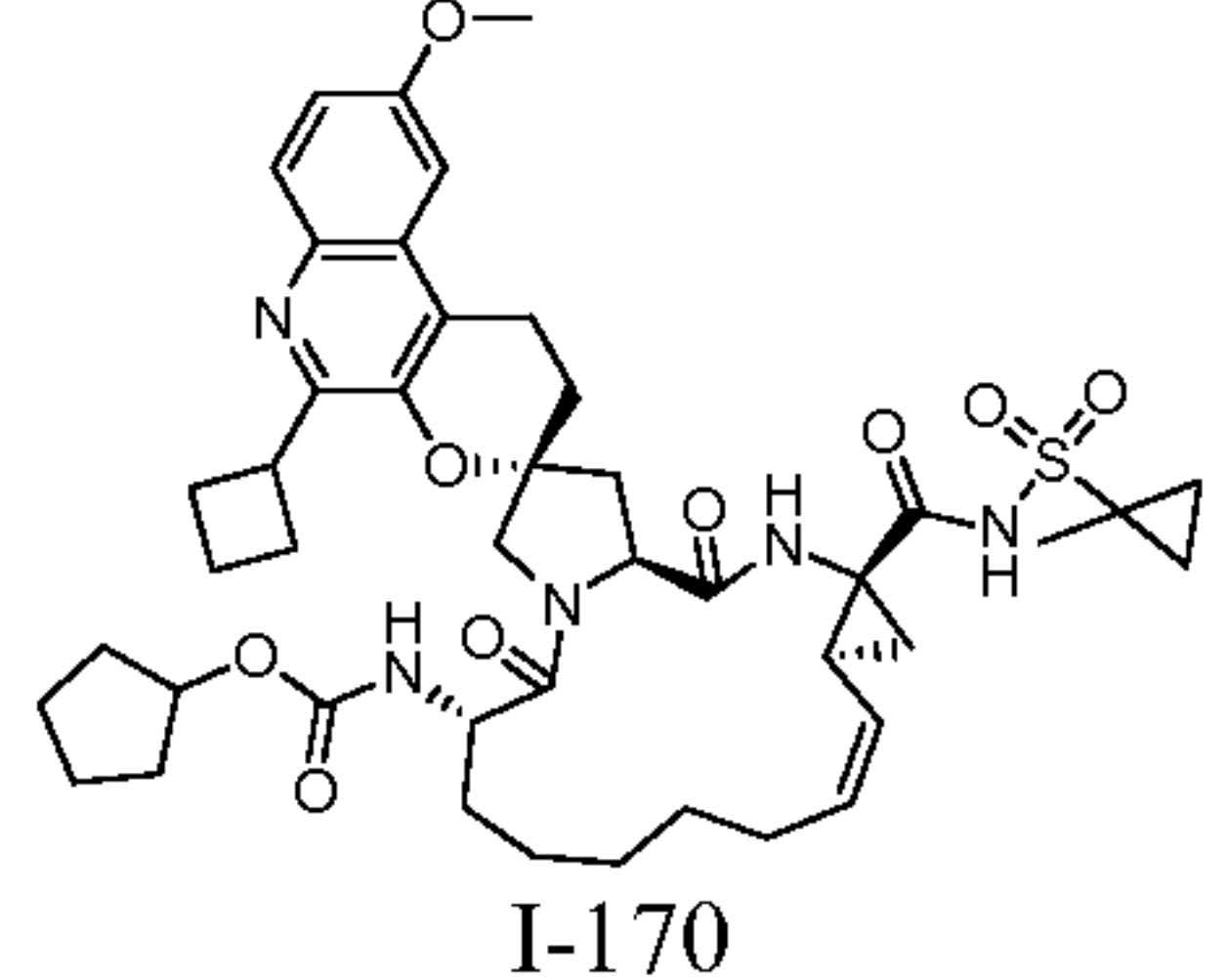
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
137	 I-137	propan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-8'-methoxy-14a- {[1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16	791.6
138	 I-138	ethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-8'-methoxy-14a- {[1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16	777.7
139	 I-139	methyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-8'-methoxy-14a- {[1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16	763.7
140	 I-140	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a- {[1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	792.2 (K+ salt)
141	 I-141	1-methylcyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a- {[1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	778.2

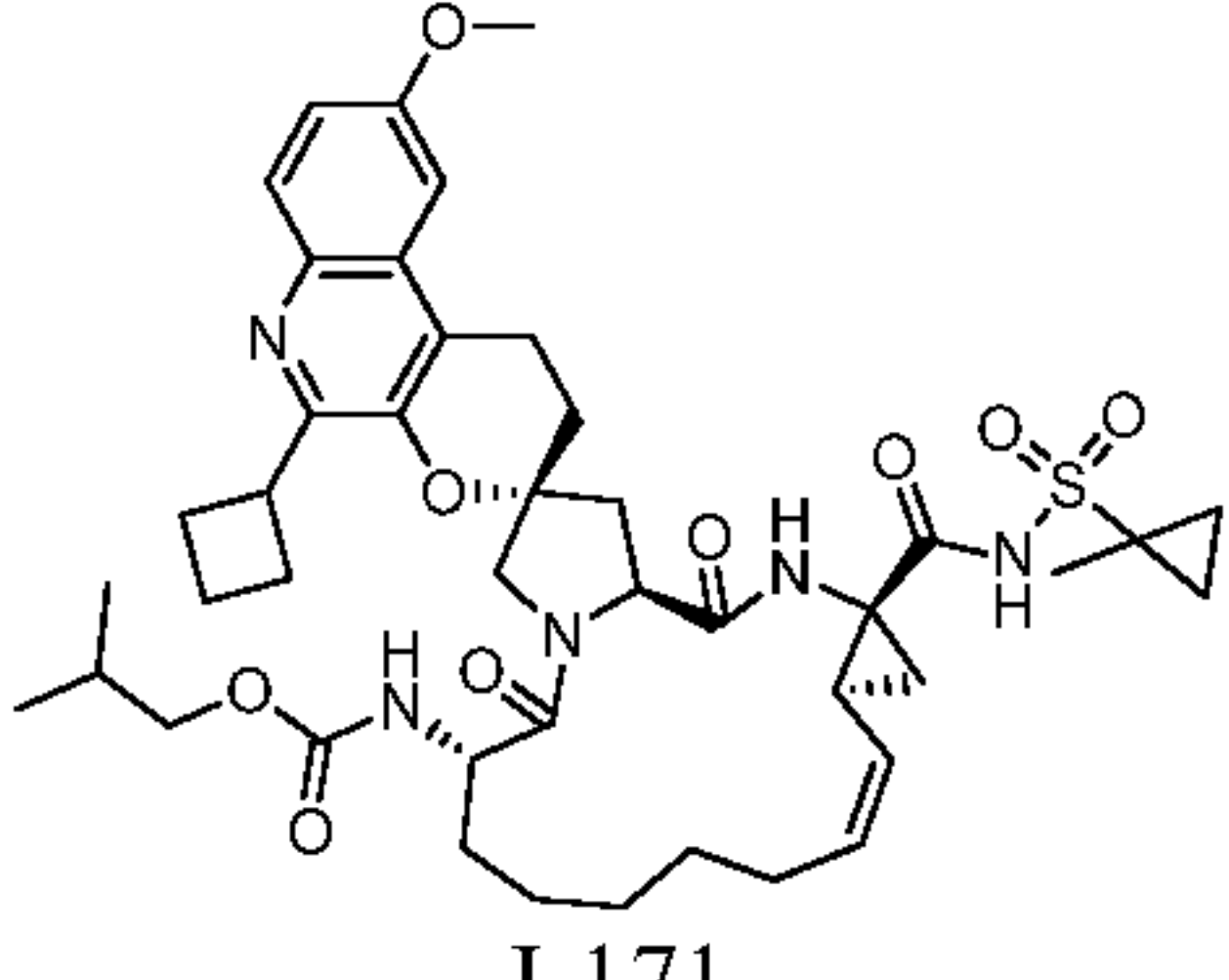
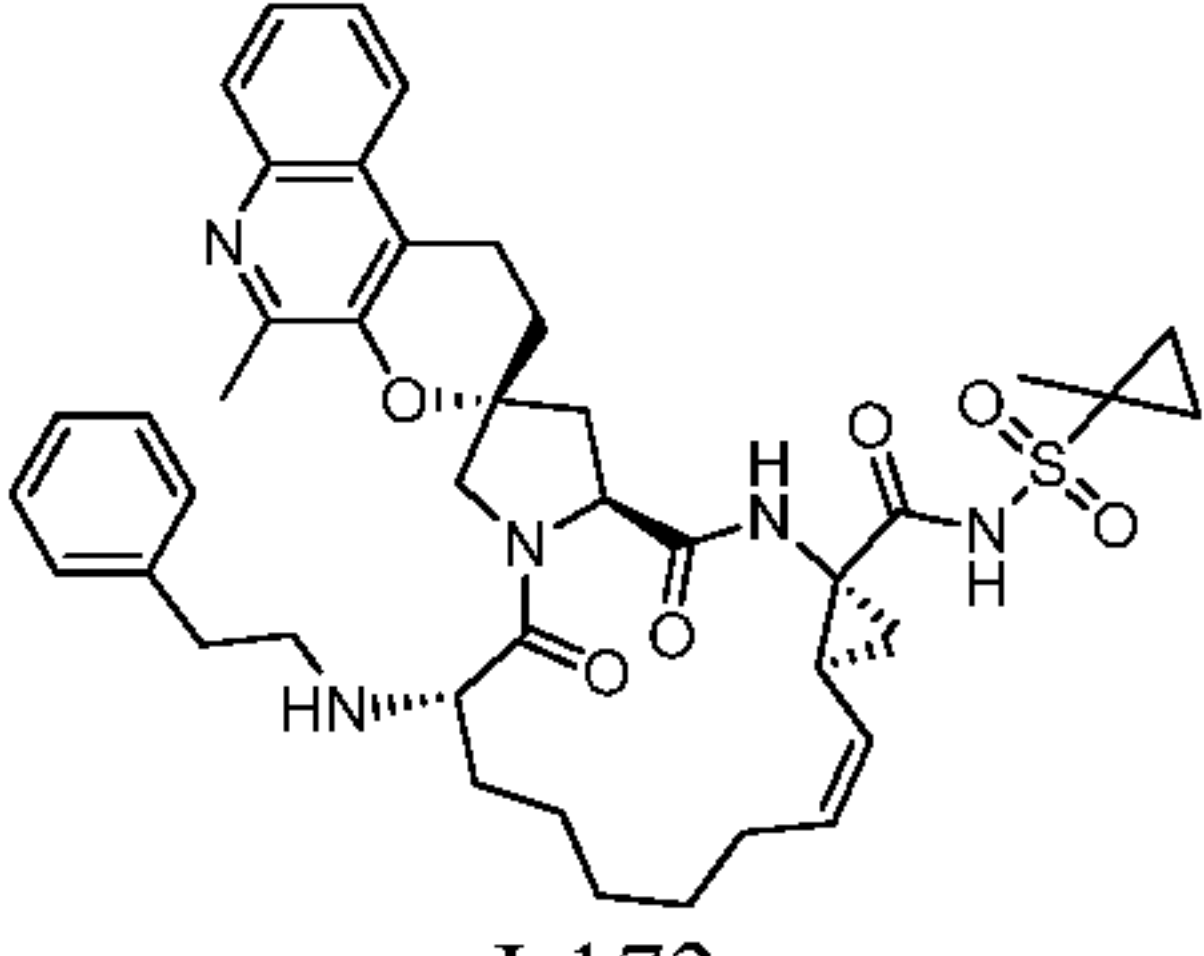
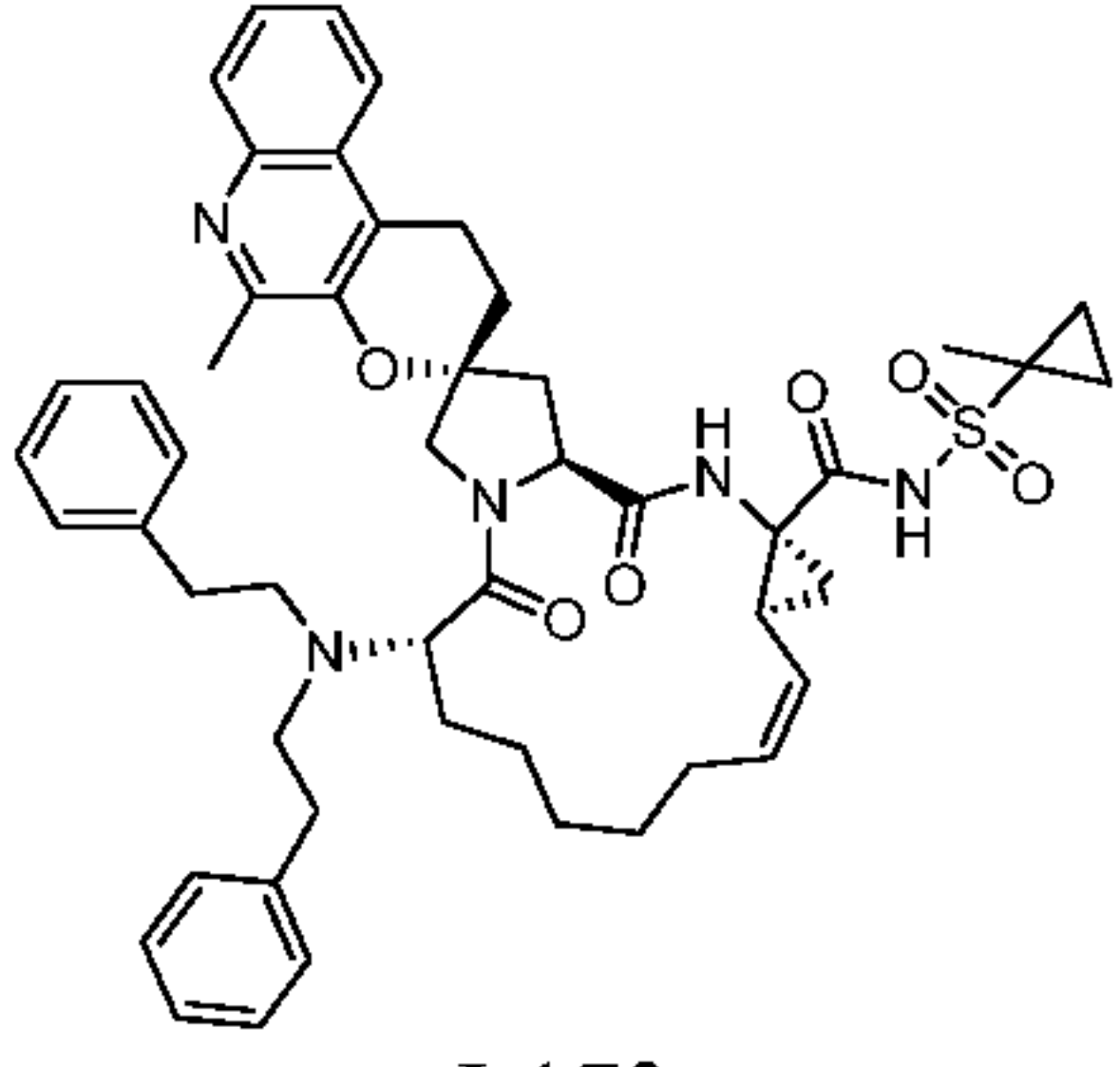
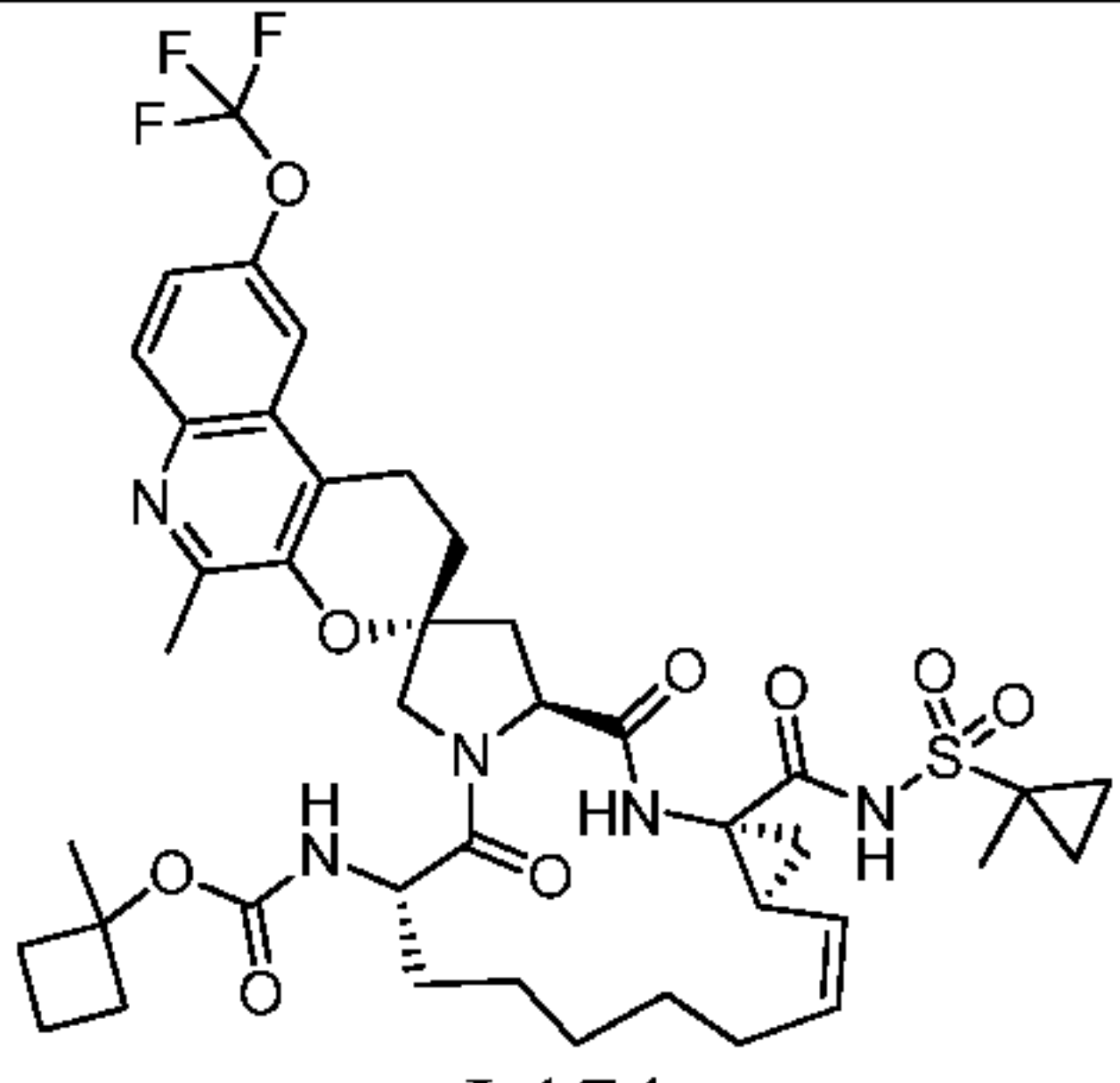
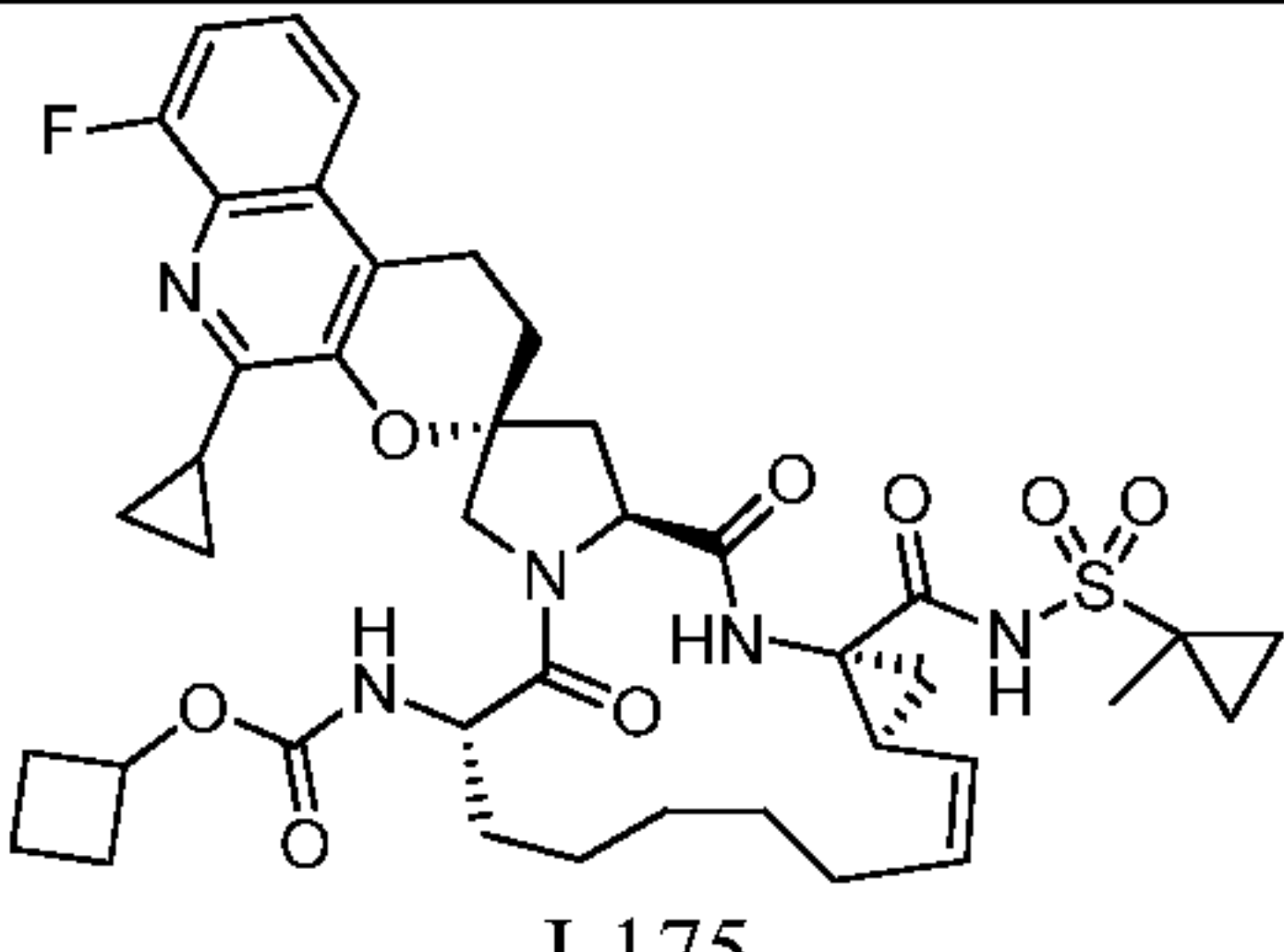
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
142	 I-142	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	780.2
143	 I-143	cyclohexyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	776.6 (K+ salt)
144	 I-144	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-9'-fluoro-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16	793.7
145	 I-145	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-9'-fluoro-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16	805.7
146	 I-146	cyclopentylmethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	860.2
147	 I-147	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-7'-fluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	45	768.2

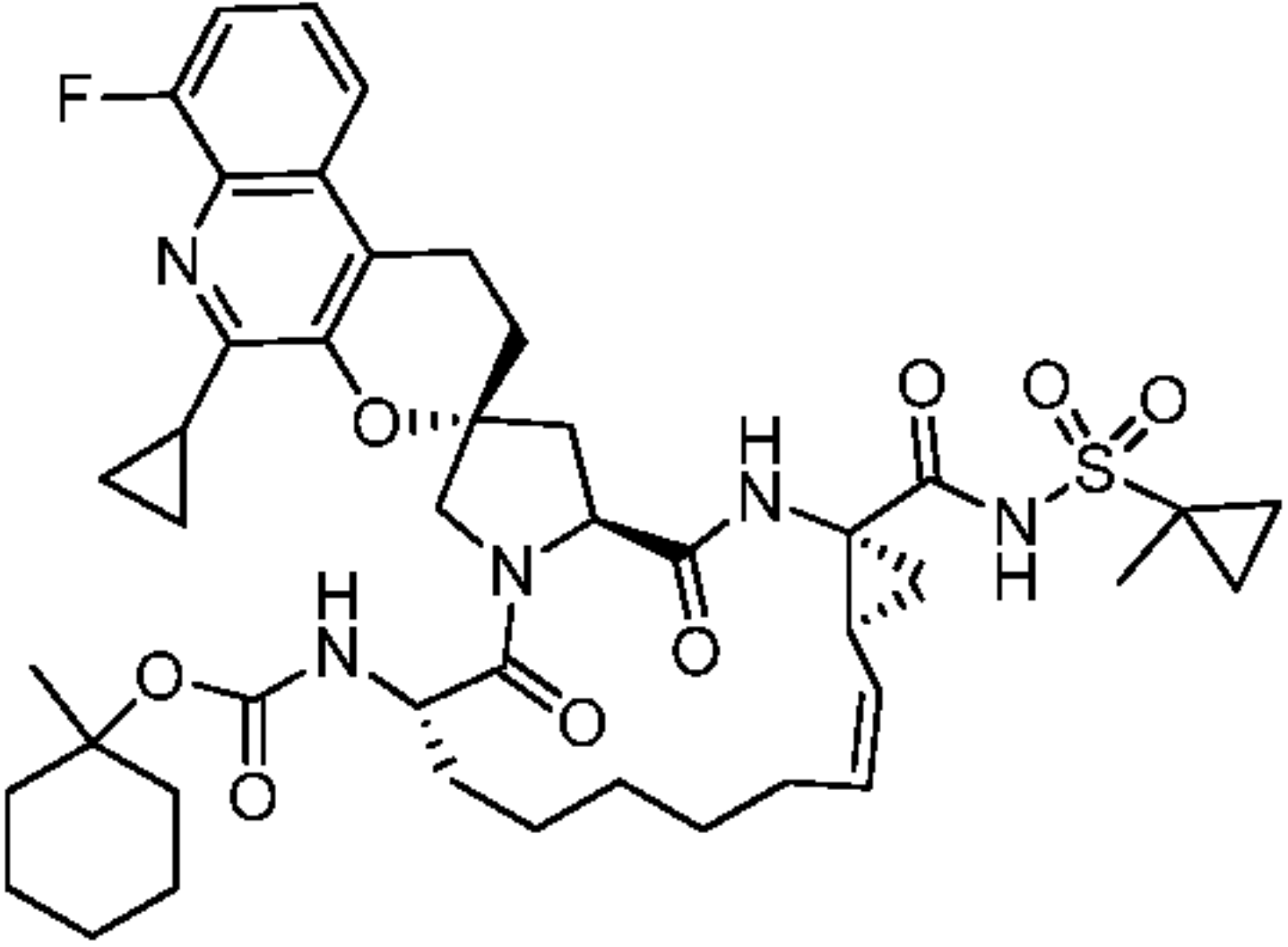
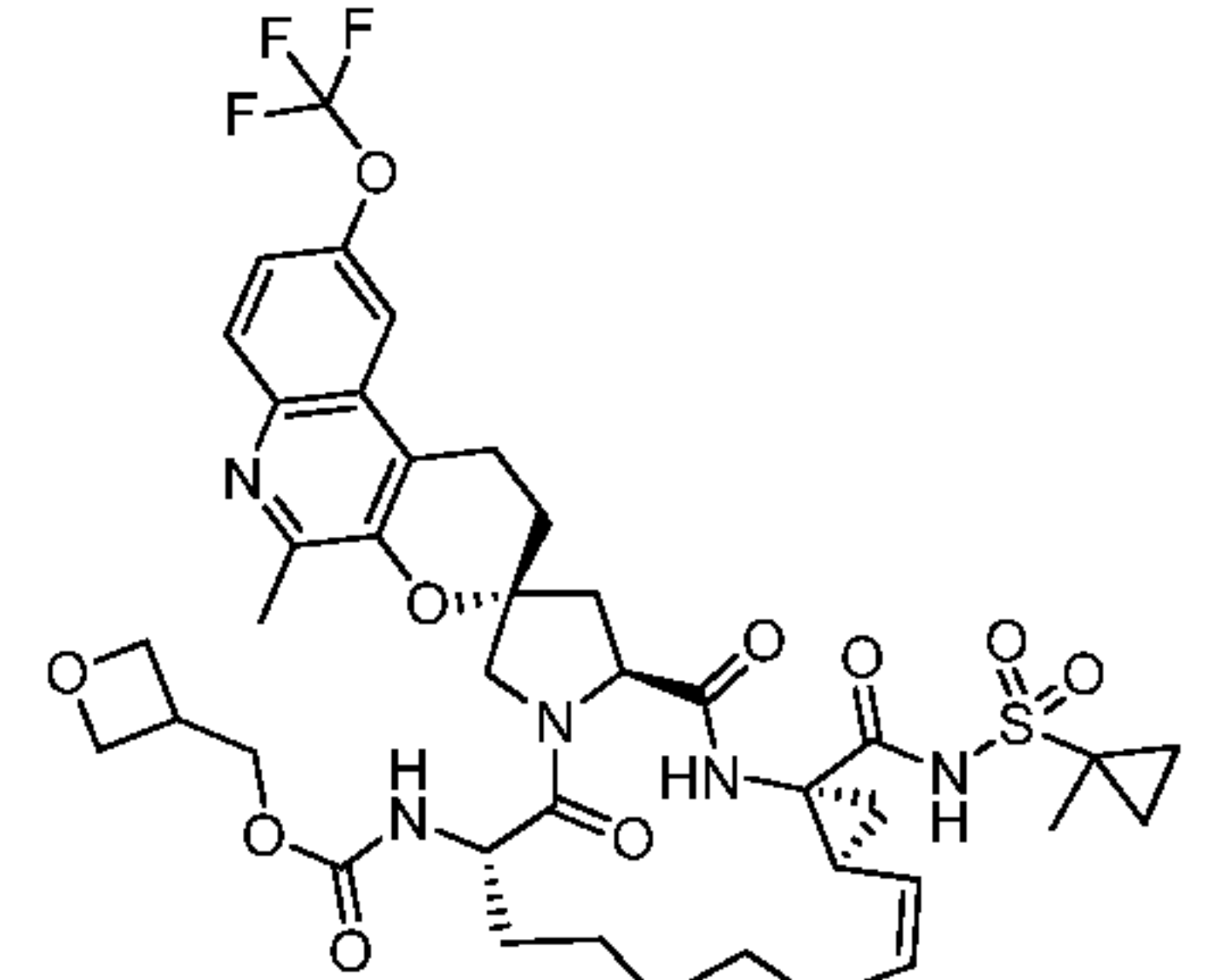
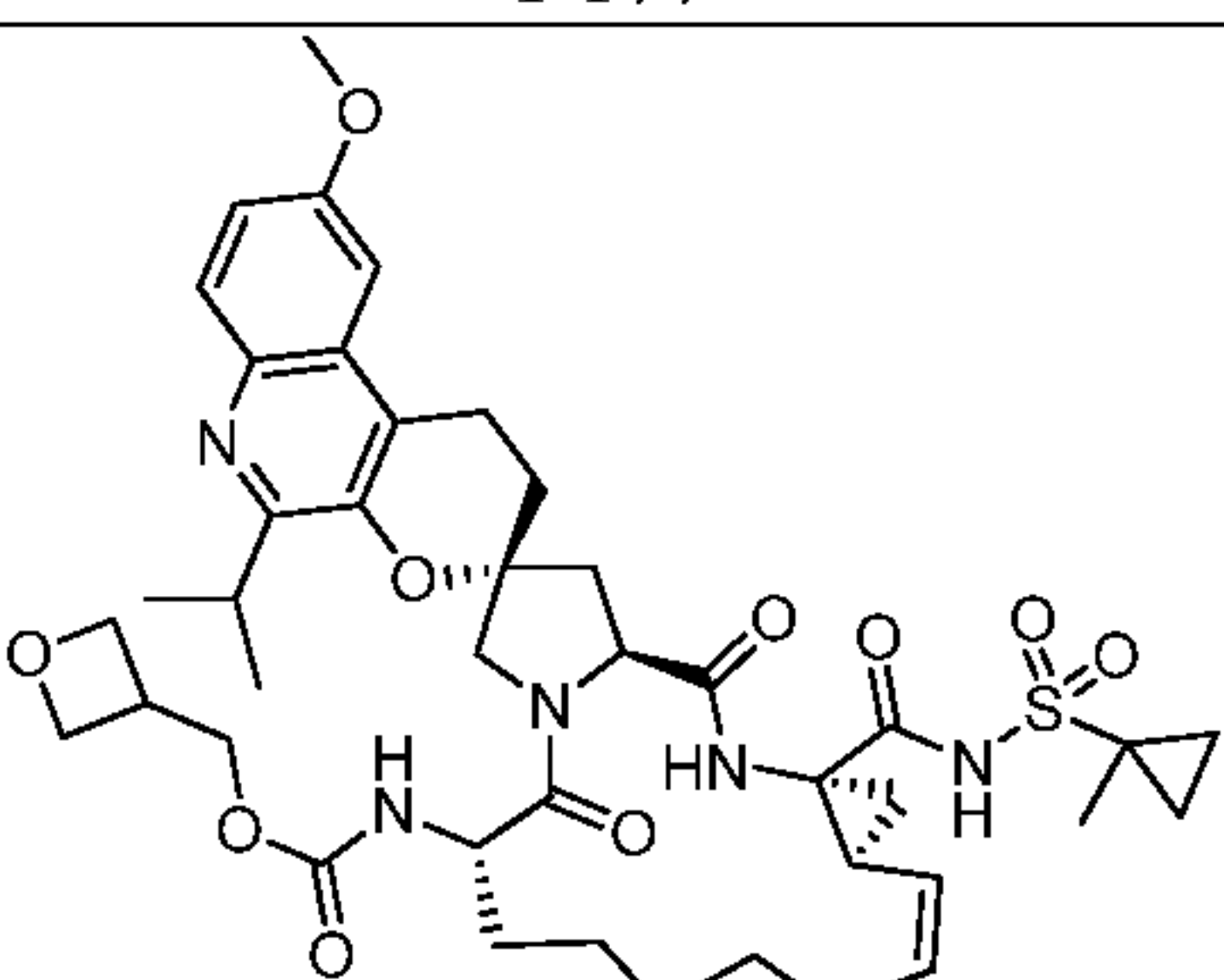
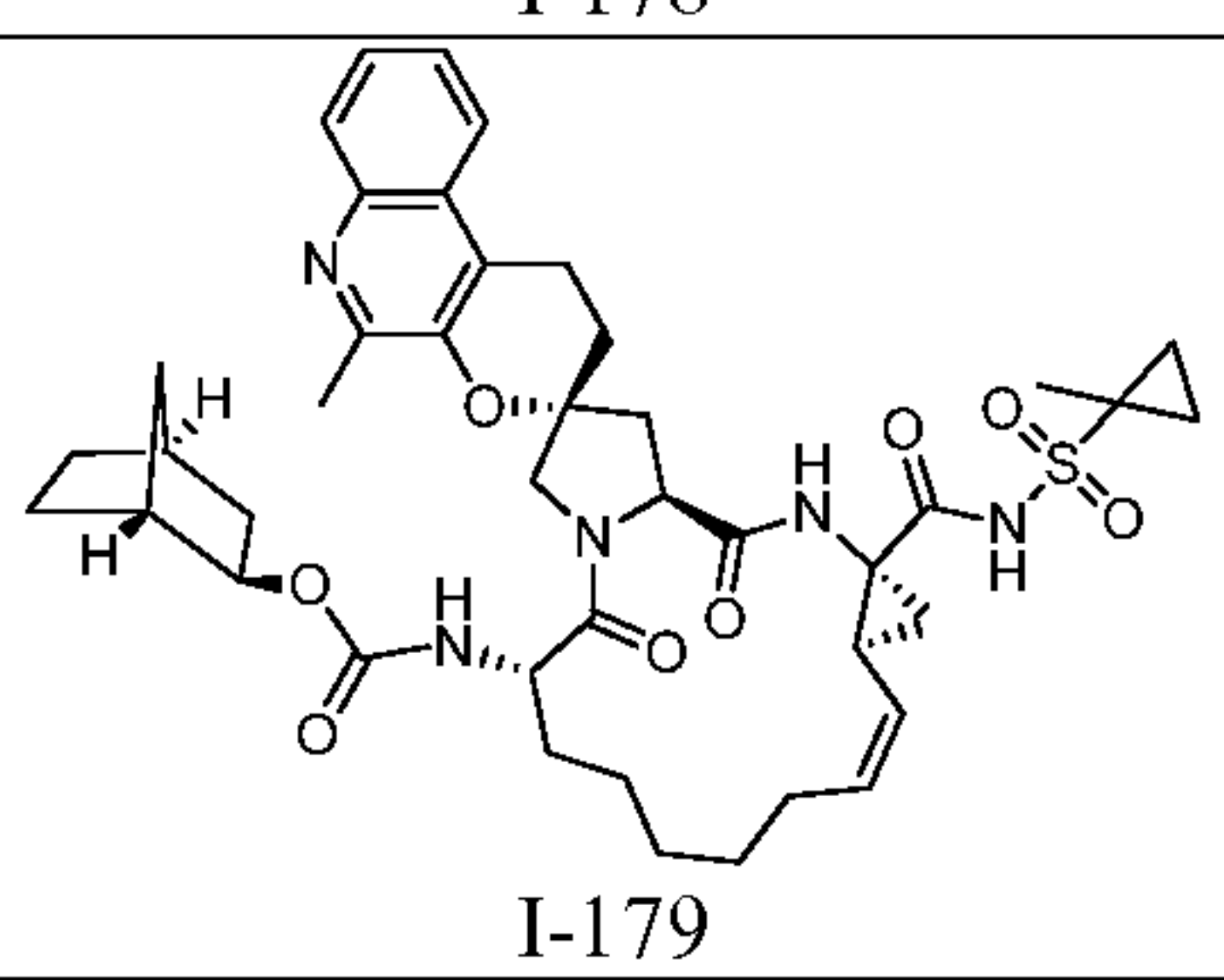
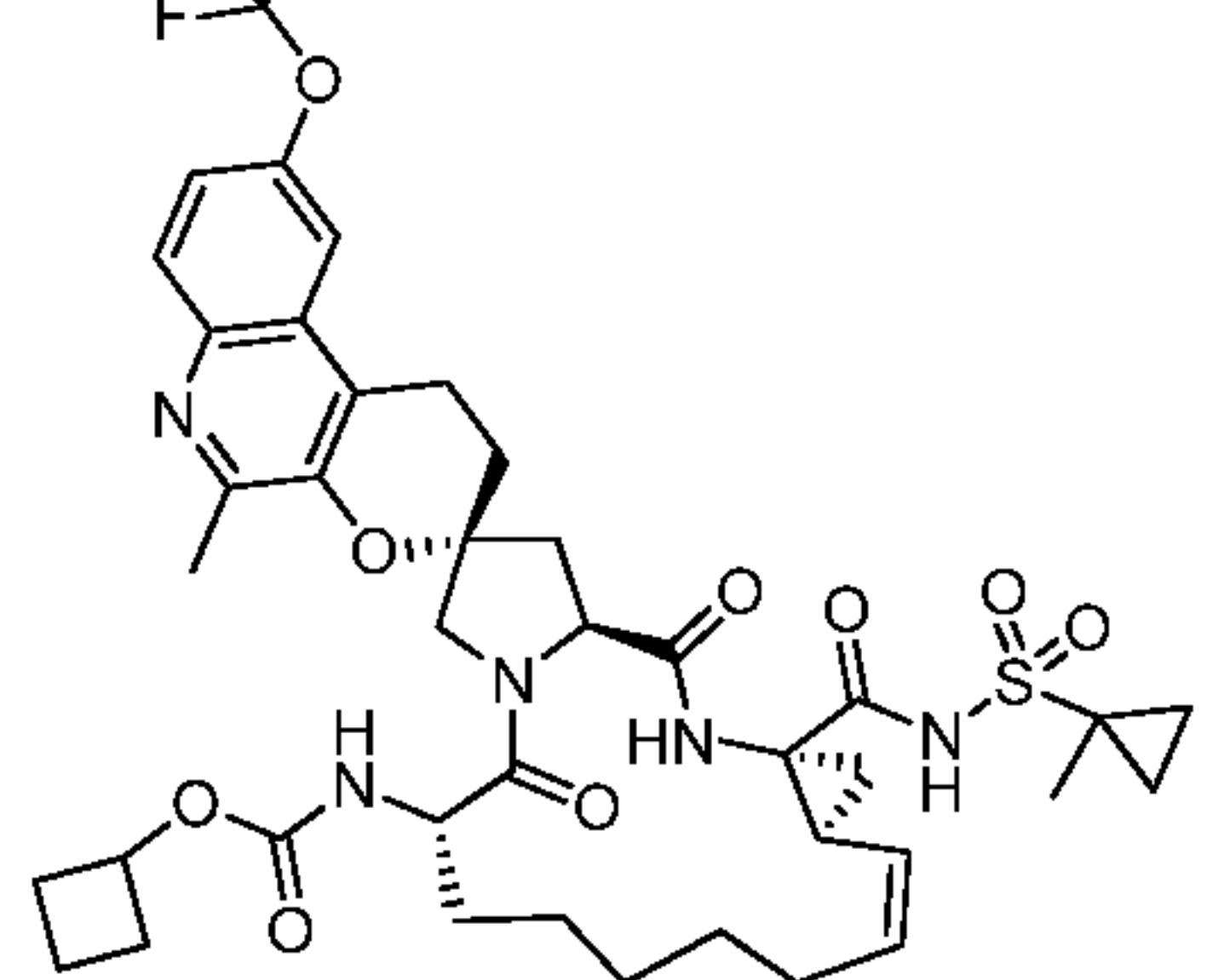
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
148	 I-148	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-14a- -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16- dioxo-5'-(trifluoromethyl)- 1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> - hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	4, 35	816.6 (K+ salt)
149	 I-149	cyclopentyl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1',1'- difluoro-5'-methyl-14a- -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16- dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> - hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	20, 35	798.6
150	 I-150	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'- cyclopropyl-7'-fluoro-14a- -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16- dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> - hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	805.6
151	 I-151	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'- cyclopropyl-7'-fluoro-14a- -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16- dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> - hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	794.4 (K+ salt)
152	 I-152	1-methylcyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)- 5'-cyclopropyl-9'-methoxy-14a- -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16- dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> - hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16	817.6 (K+ salt)
153	 I-153	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)- 5'-cyclopropyl-9'-methoxy-14a- -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16- dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> - hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16	819.6 (K+ salt)

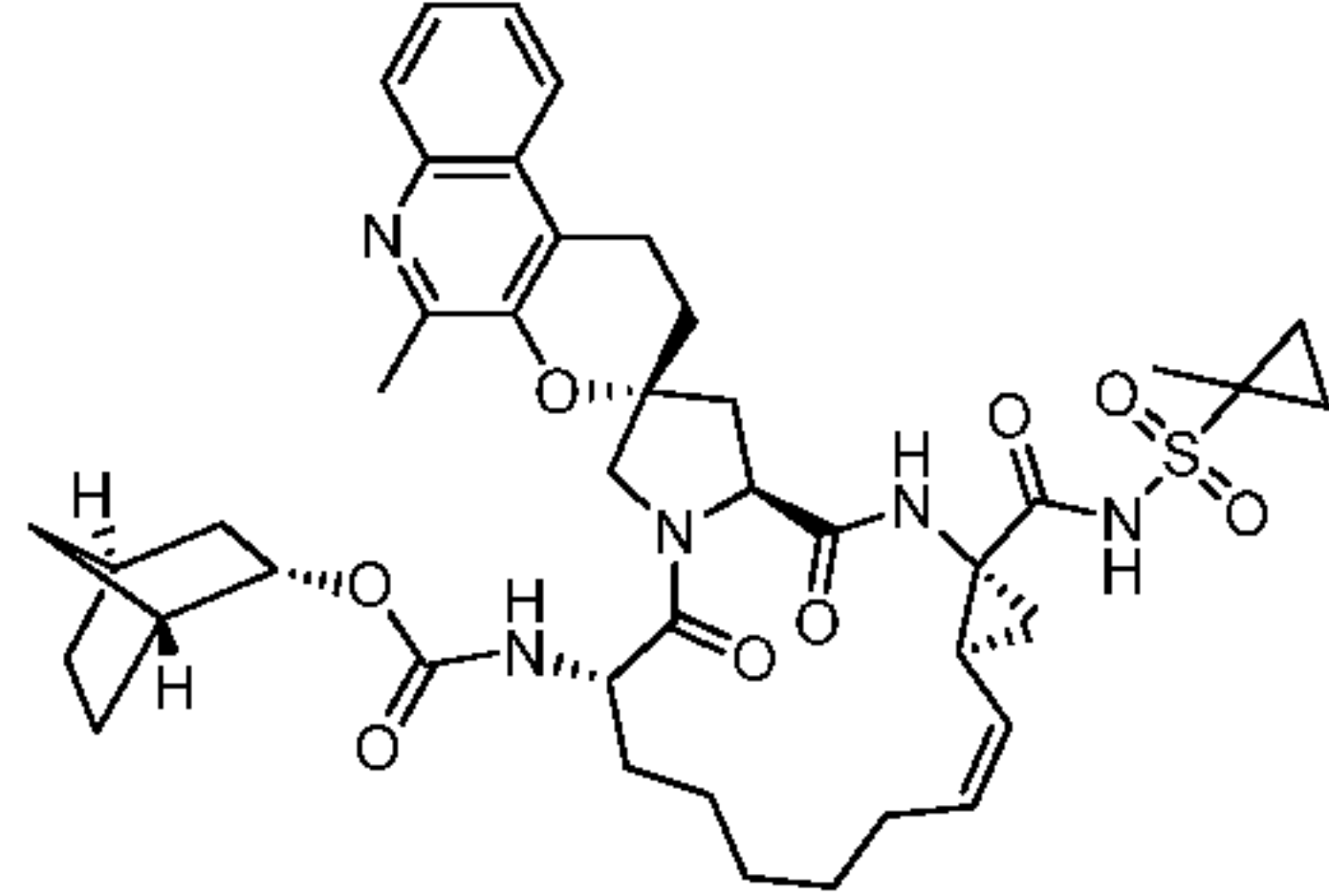
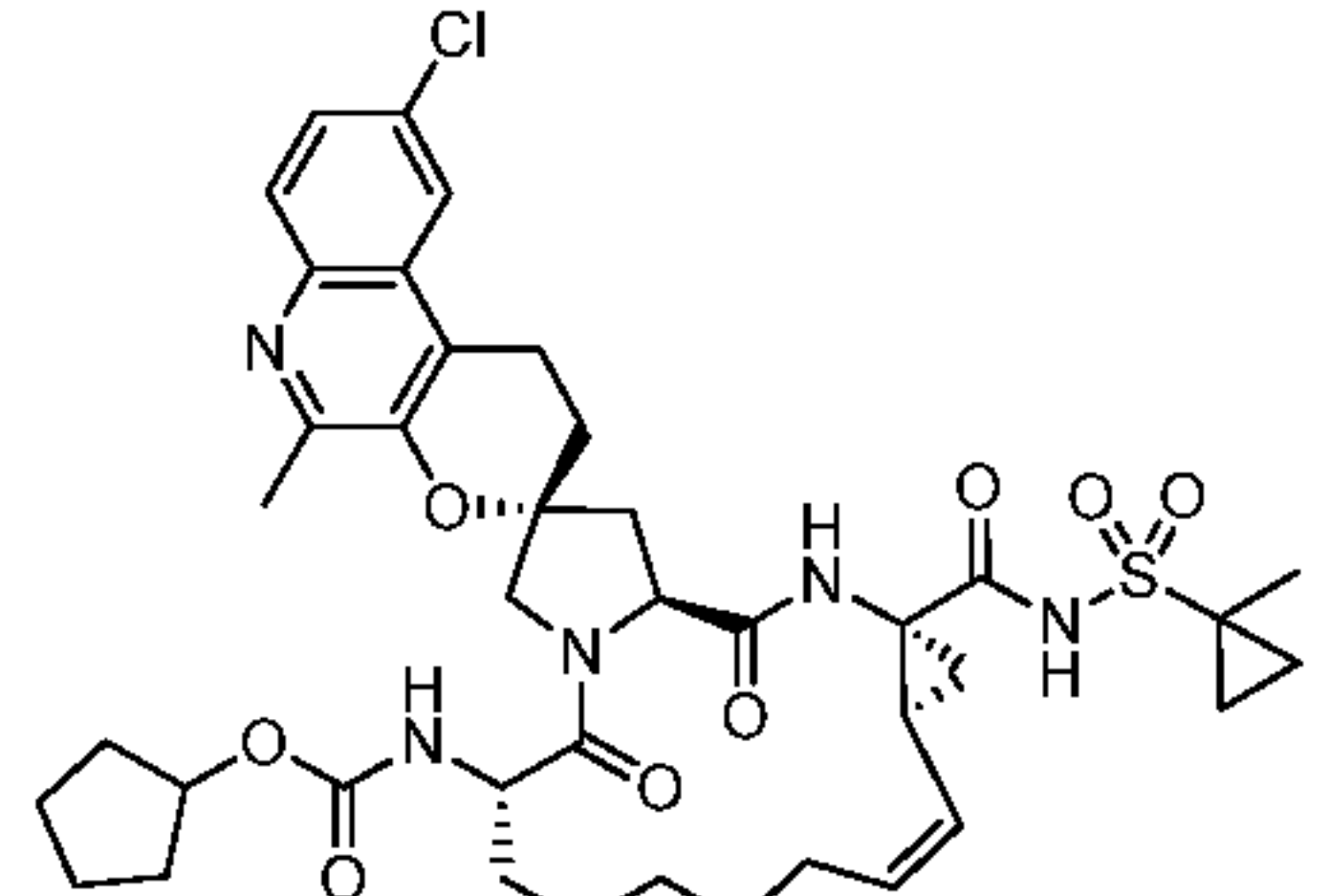
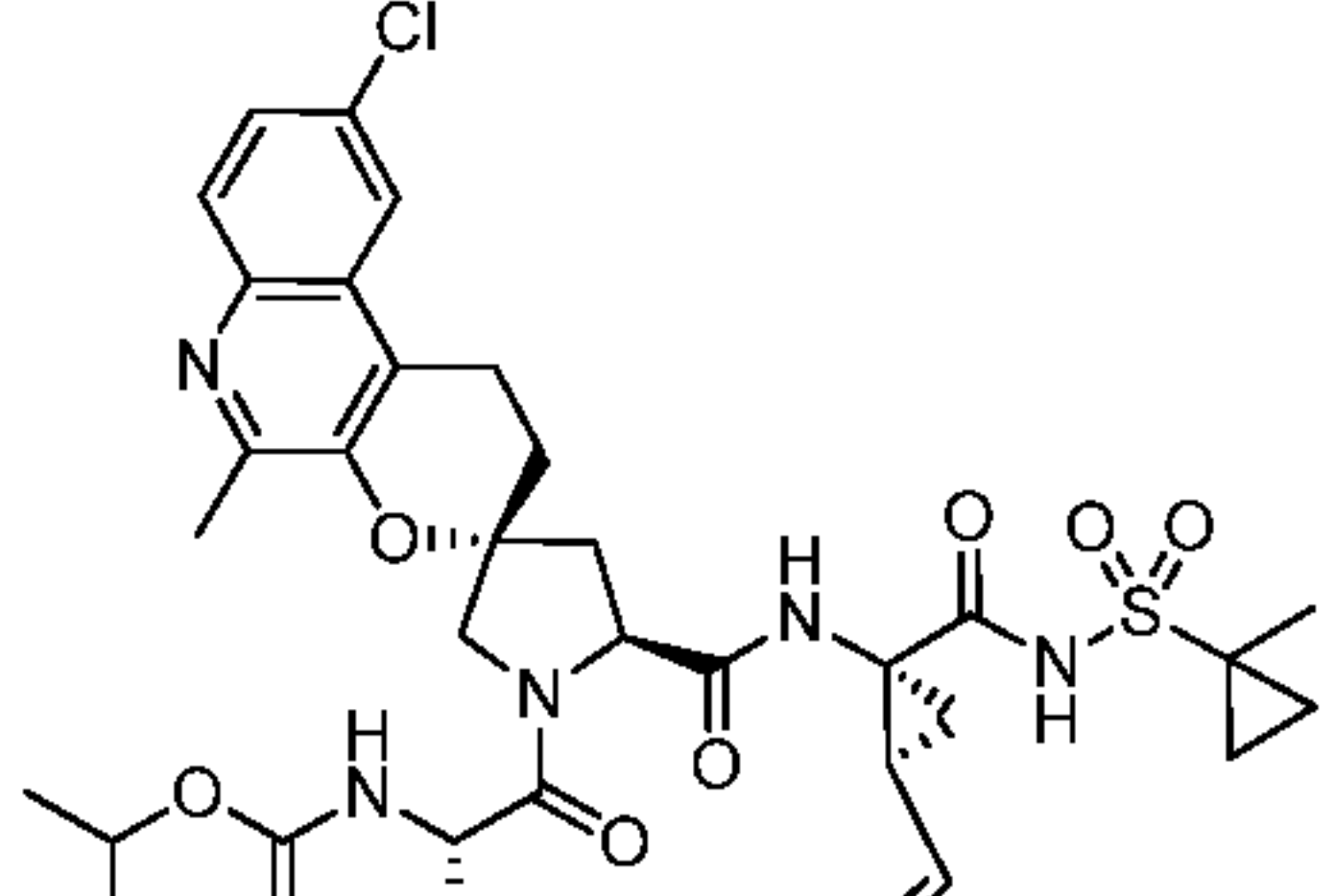
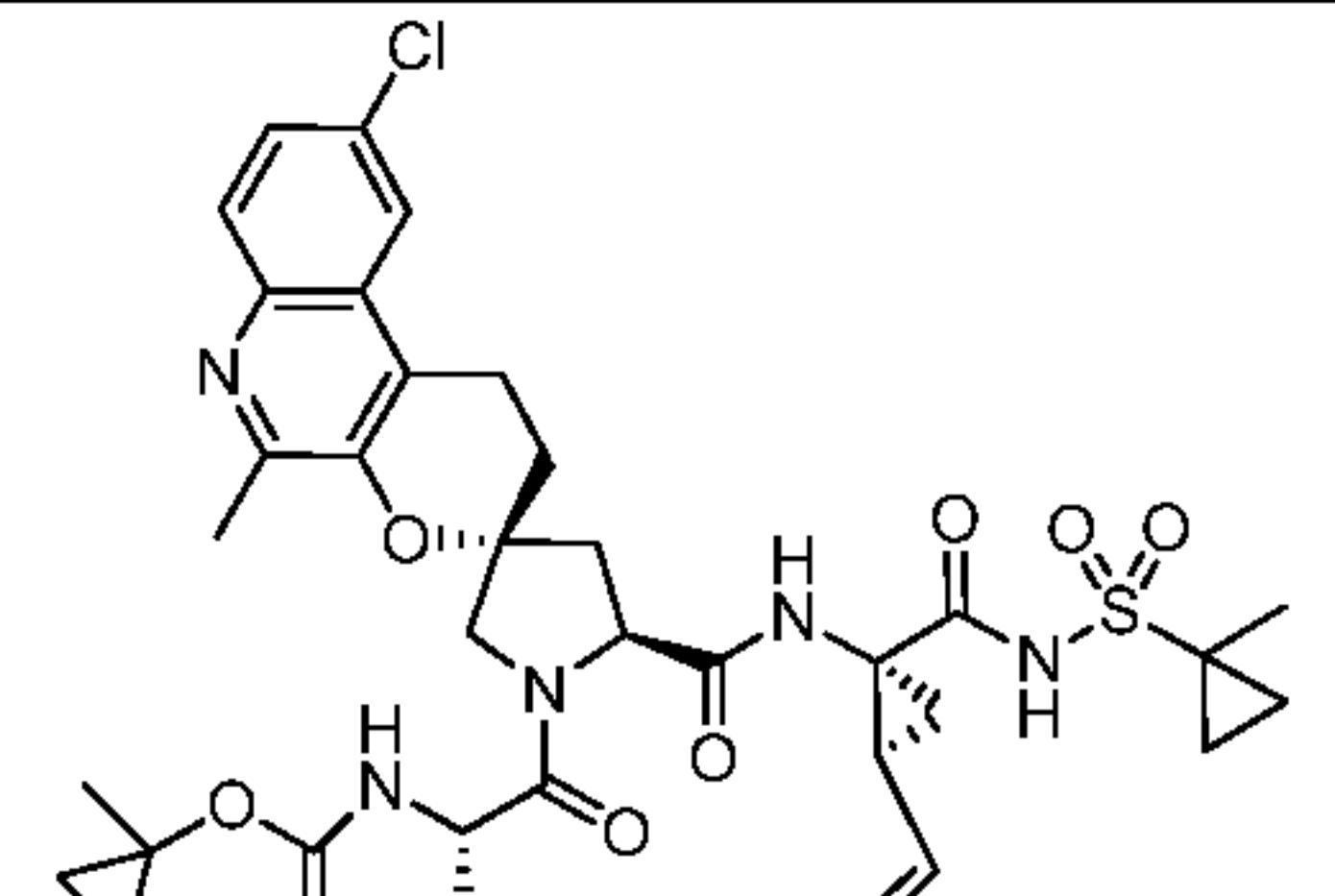
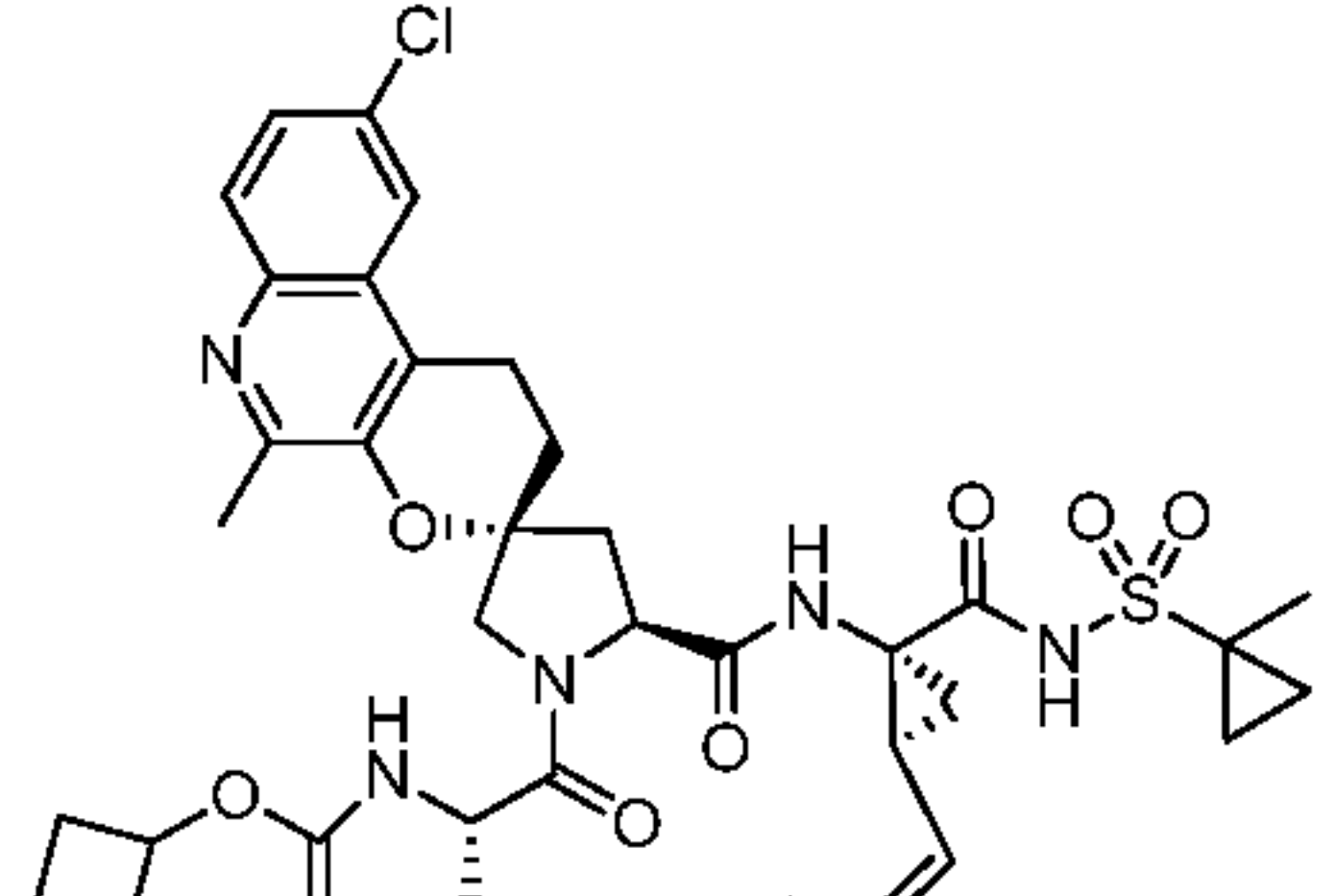
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
154	 I-154	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	2	808.2
155	 I-155	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	2	820.2
156	 I-156	propan-2-yl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1',1'-difluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	20, 35	772.6
157	 I-157	propan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	4, 35	790.4
158	 I-158	1-(propan-2-yl)cyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	4, 35	830.4
159	 I-159	1-methylcyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	4, 35	802.4

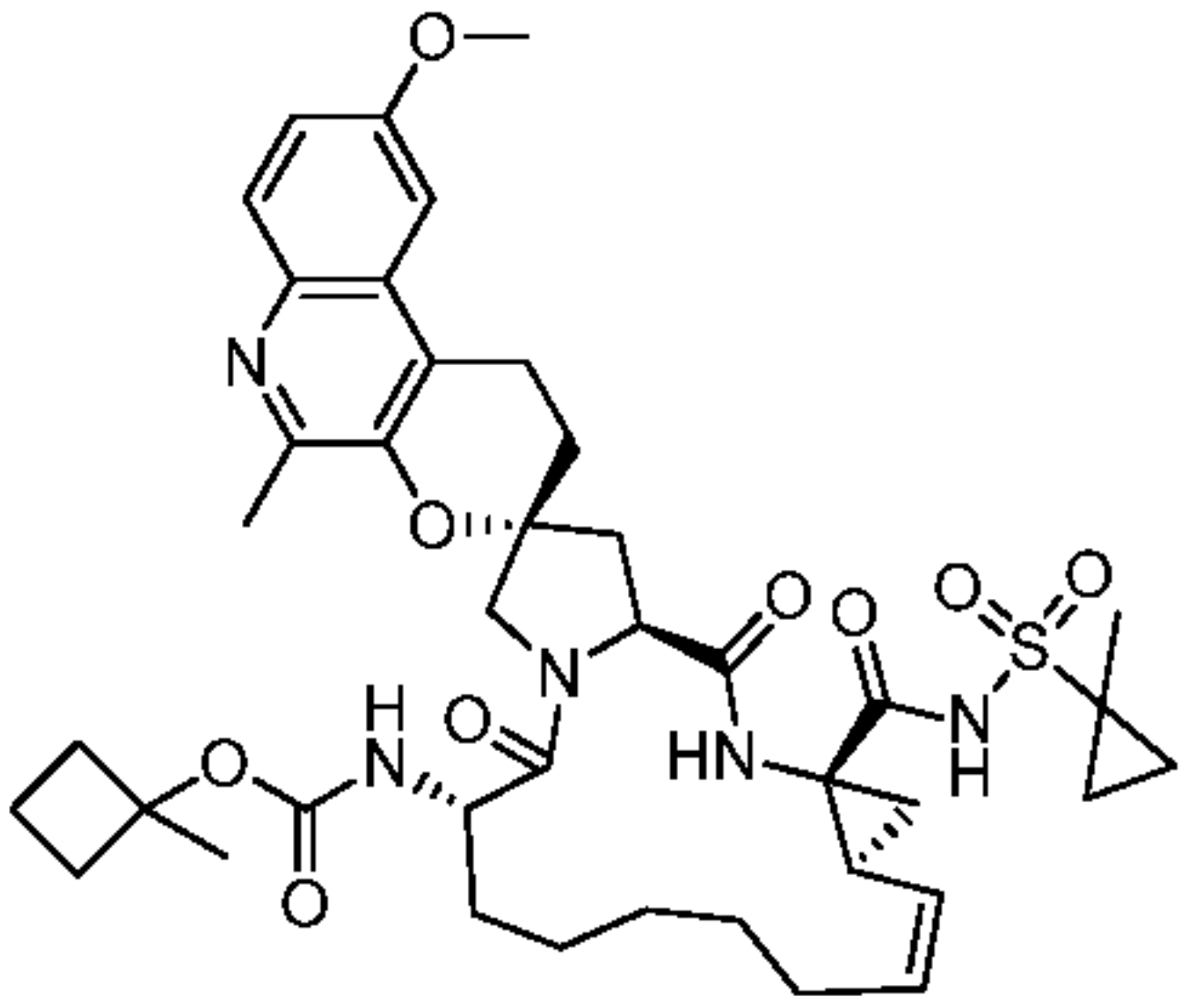
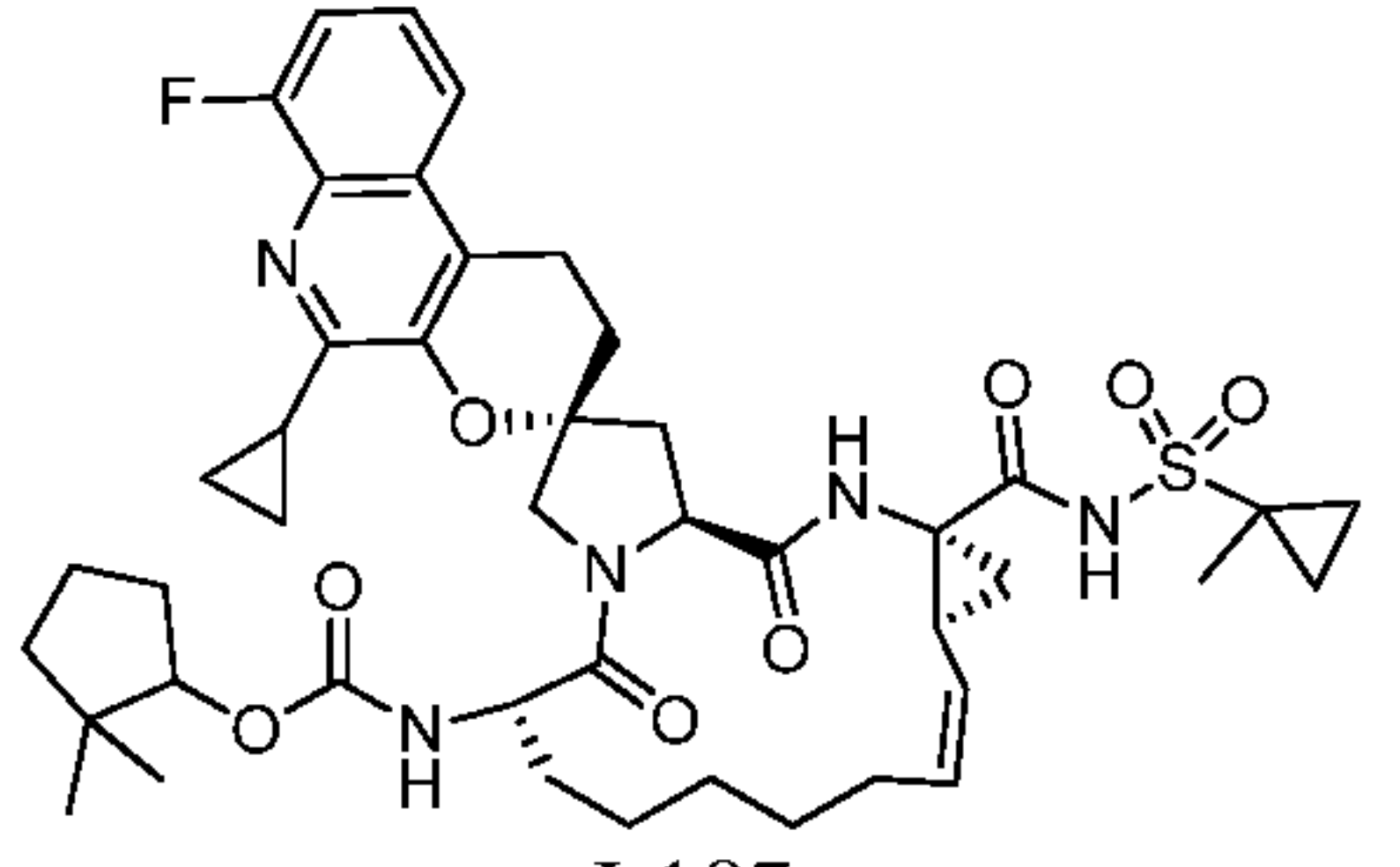
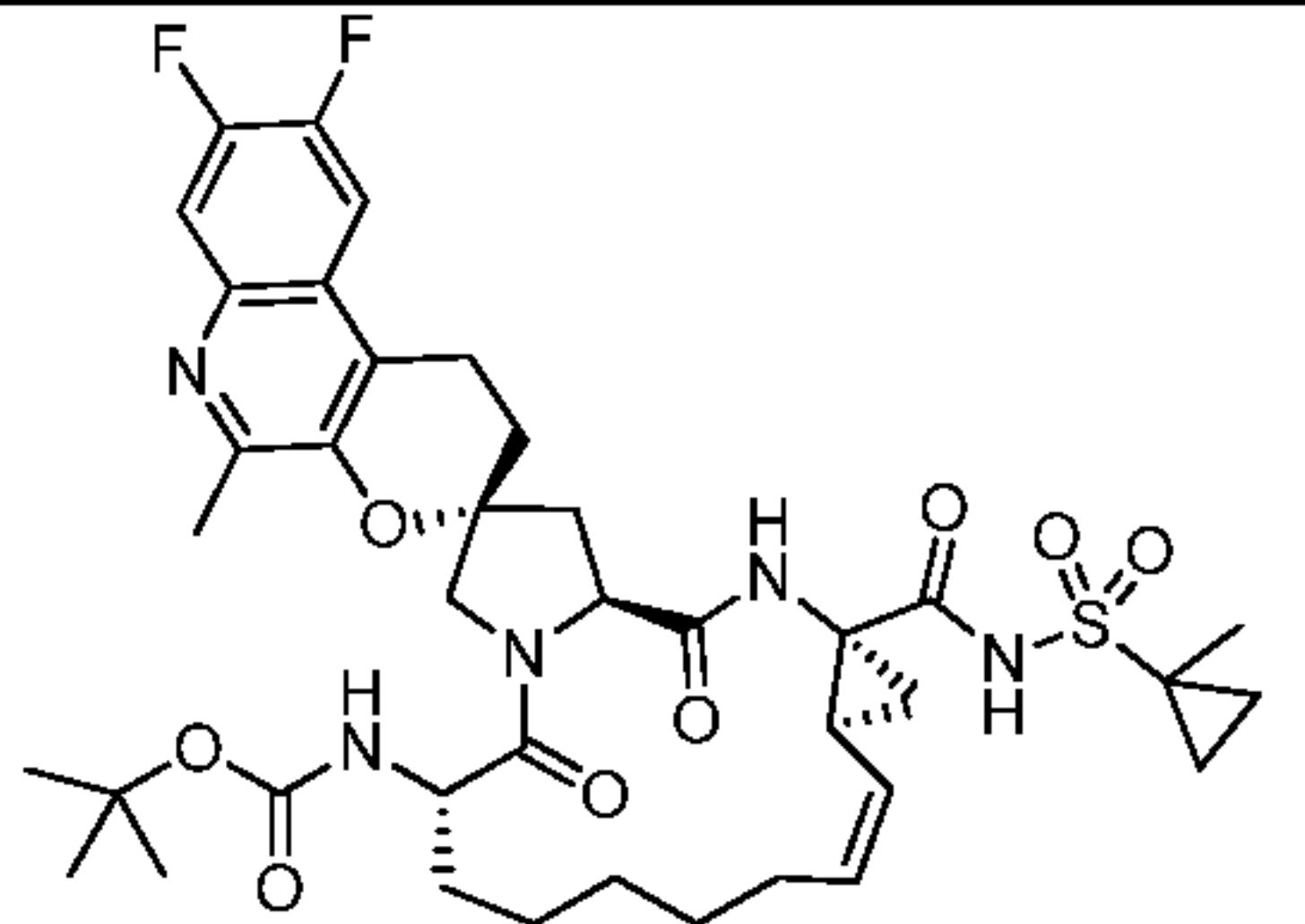
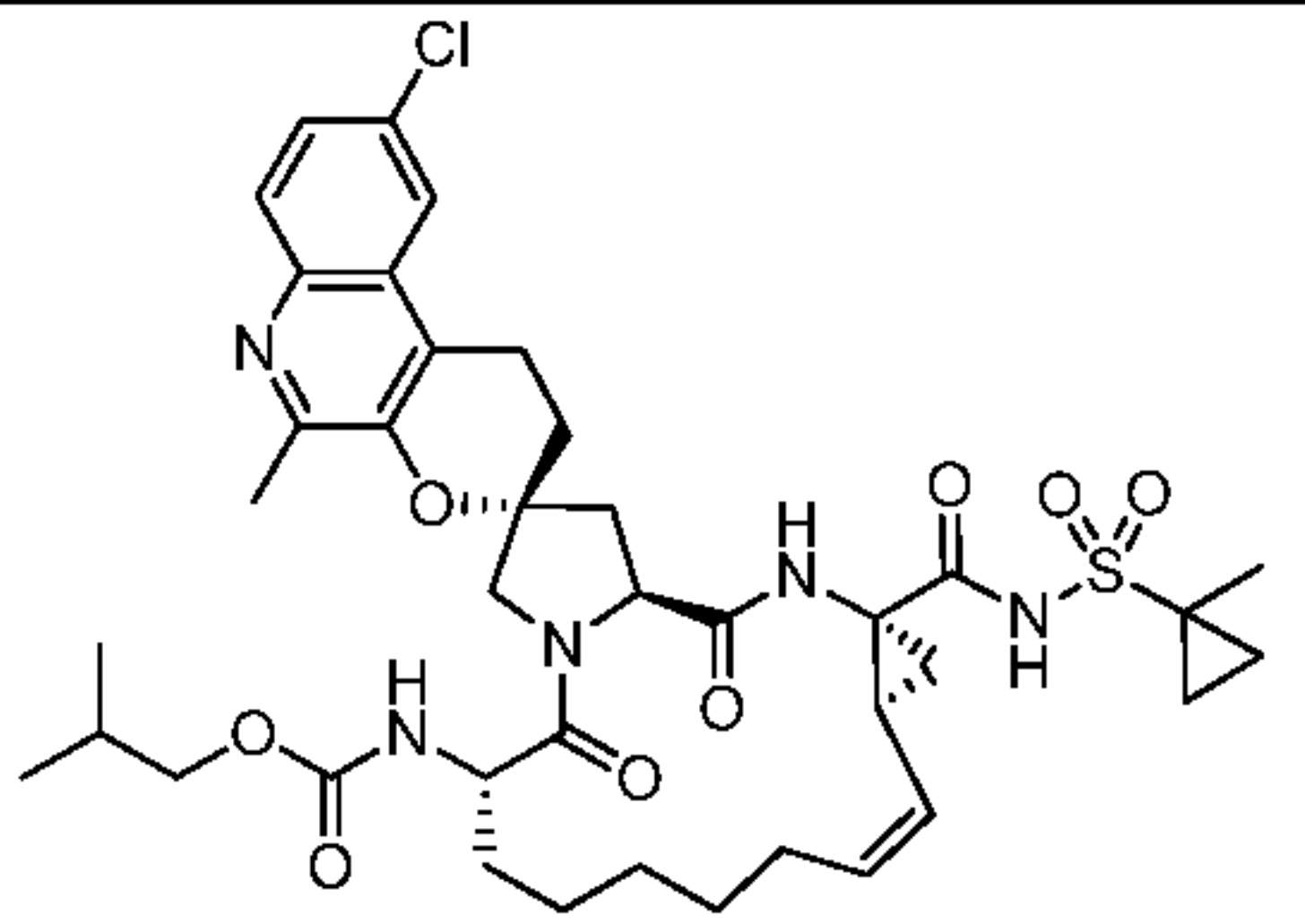
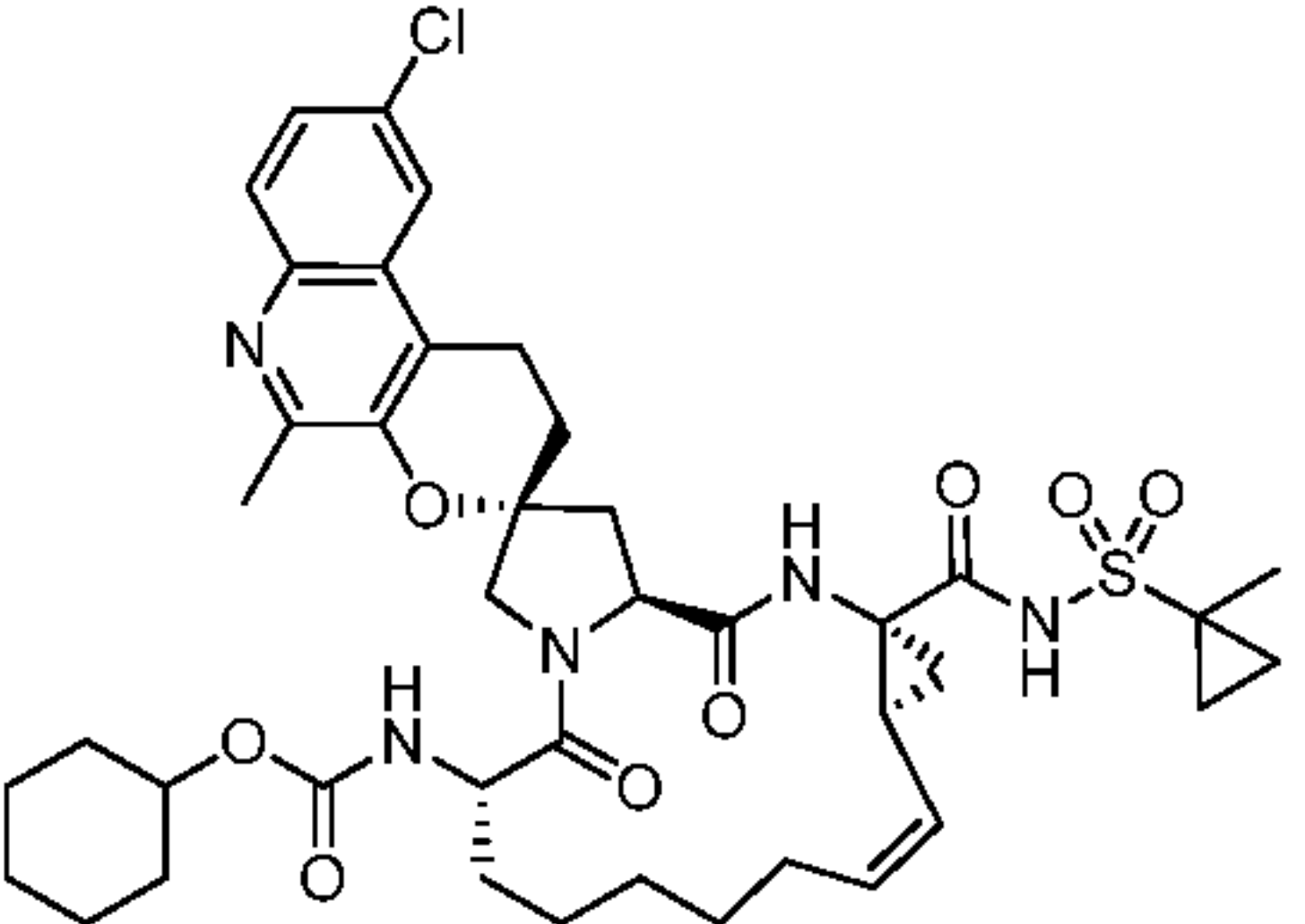
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
160	 I-160	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-14a- {[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16- dioxo-5'-(trifluoromethyl)- 1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> - hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	4, 35	804.4 (K+ salt)
161	 I-161	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(2- cyclopentylethyl)amino]-5'-methyl- <i>N</i> -[(1- methylcyclopropyl)sulfonyl]-5,16-dioxo- 1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> - tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	57	745.5
162	 I-162	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[bis(2- cyclopentylethyl)amino]-5'-methyl- <i>N</i> -[(1- methylcyclopropyl)sulfonyl]-5,16-dioxo- 1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> - tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	57	841.5
163	 I-163	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[bis(3,3- dimethylbutyl)amino]-5'-methyl- <i>N</i> -[(1- methylcyclopropyl)sulfonyl]-5,16-dioxo- 1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> - tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	57	817.5
164	 I-164	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(3,3- dimethylbutyl)amino]-5'-methyl- <i>N</i> -[(1- methylcyclopropyl)sulfonyl]-5,16-dioxo- 1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> - tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	57	733.5

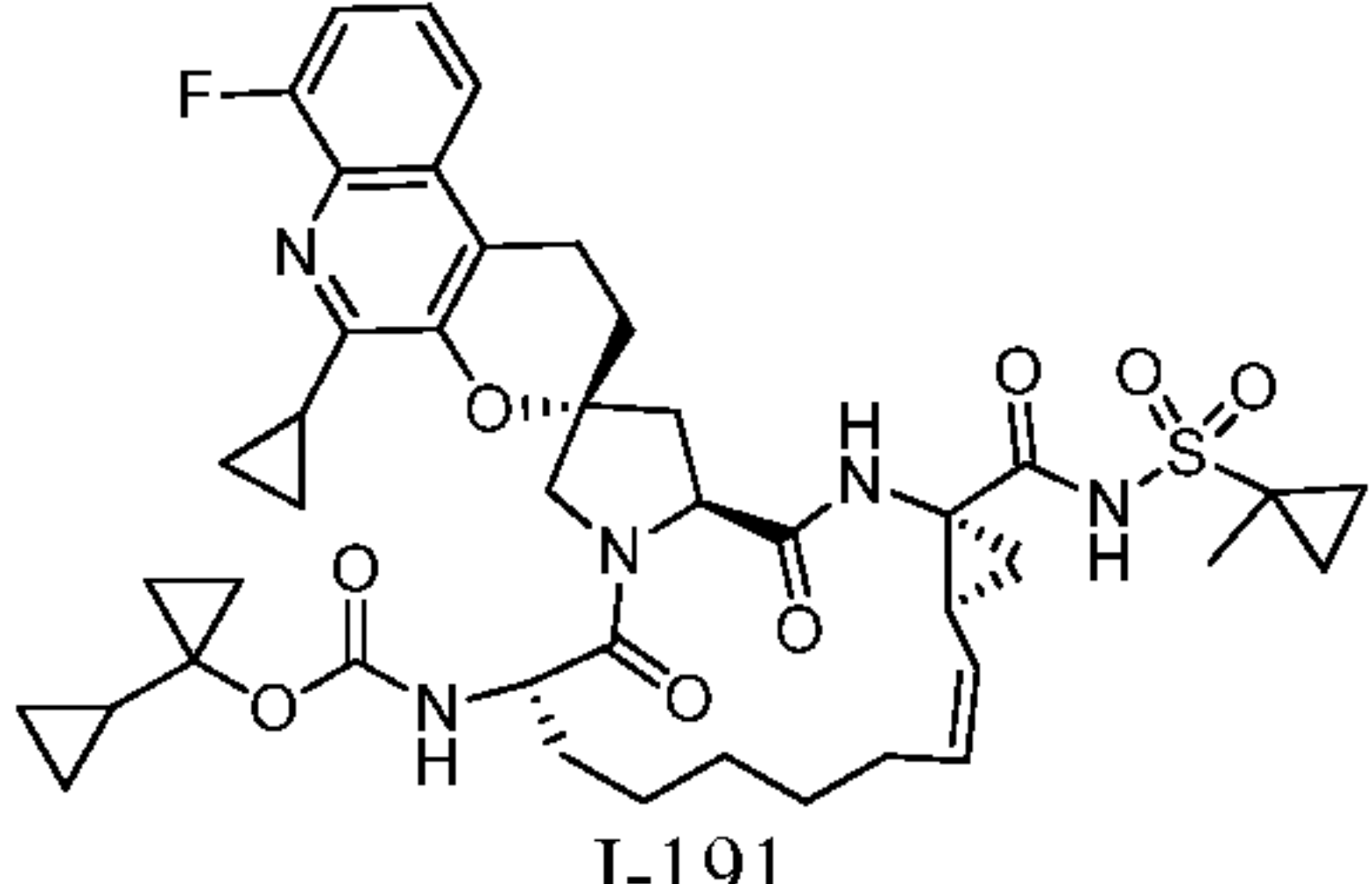
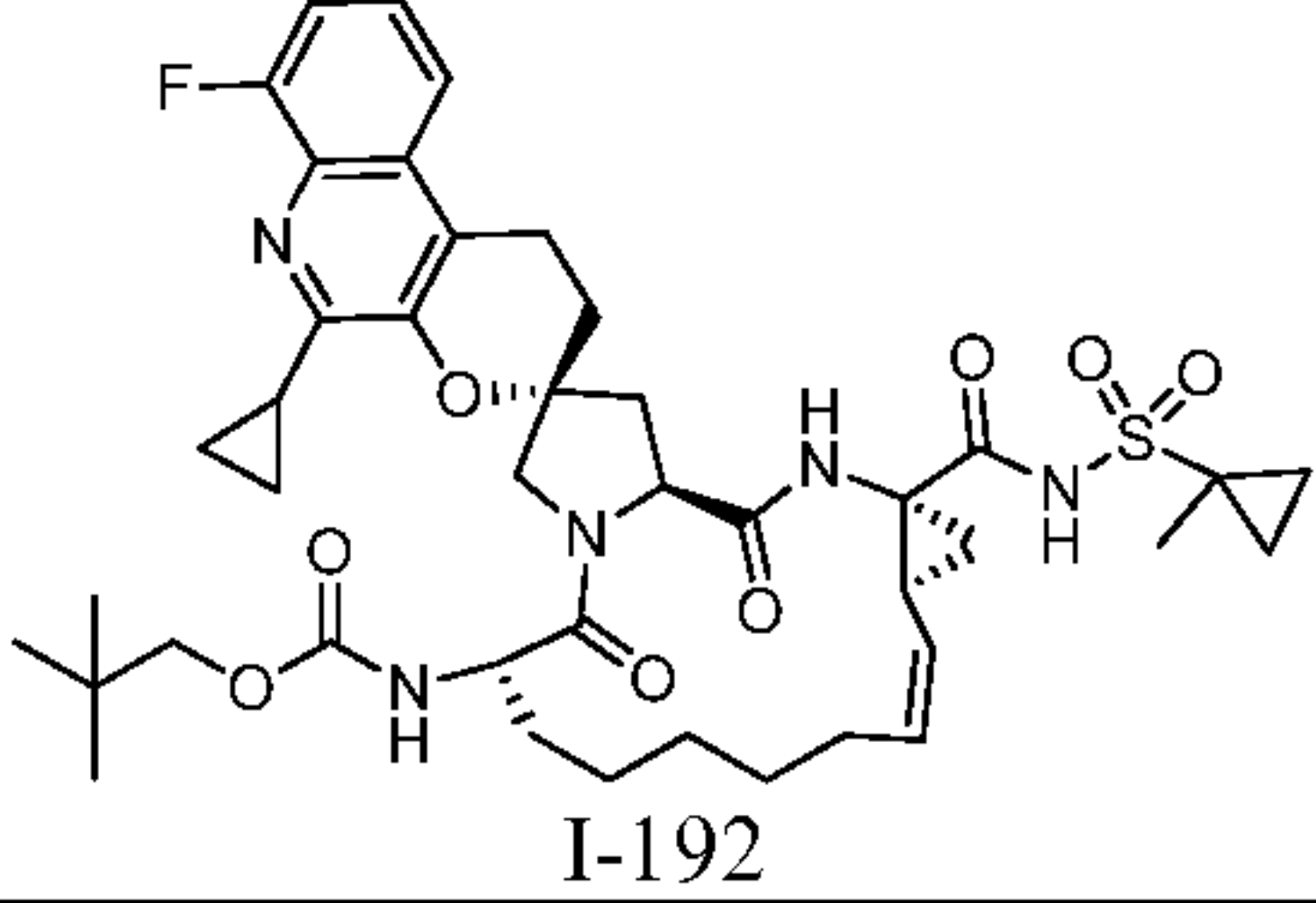
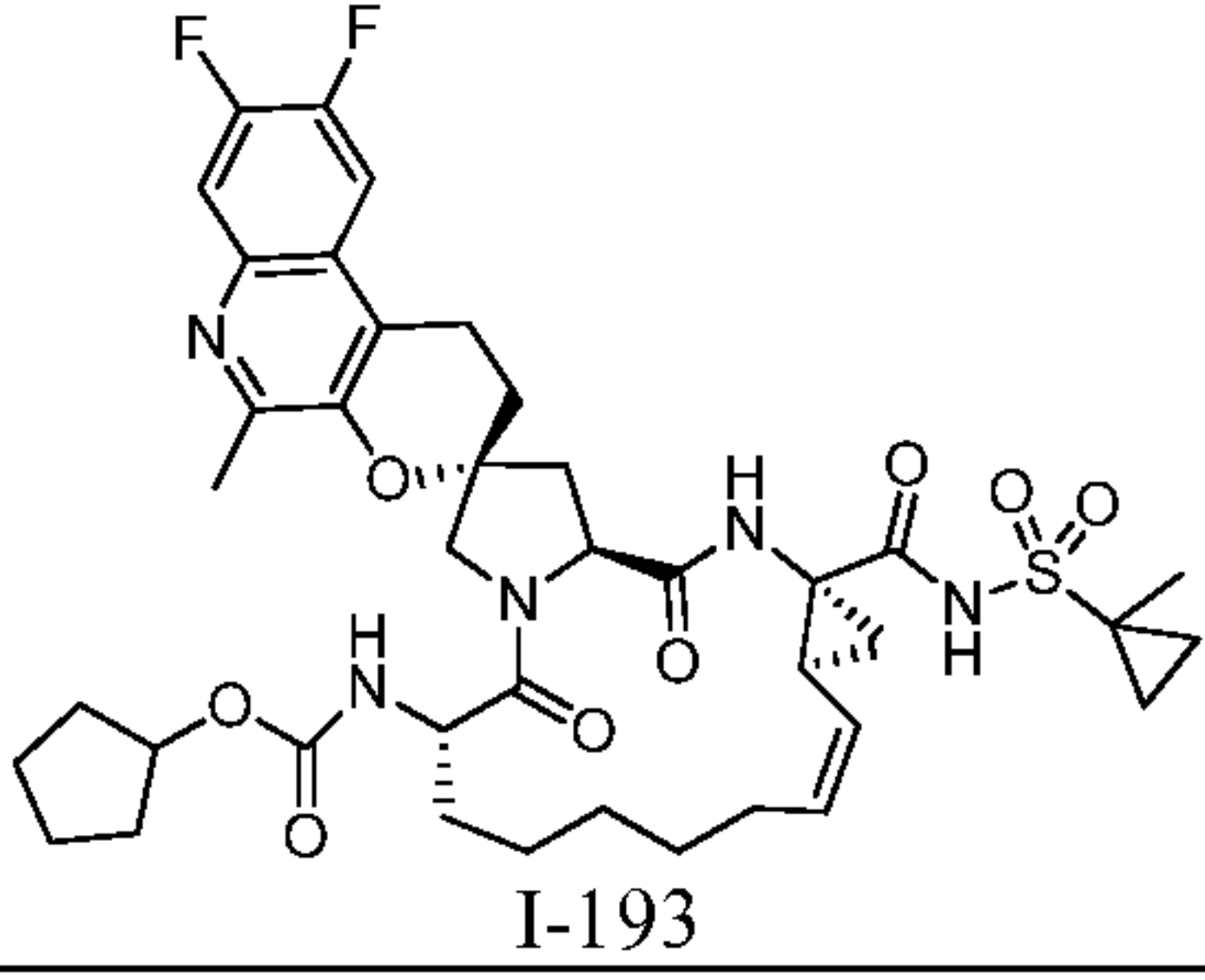
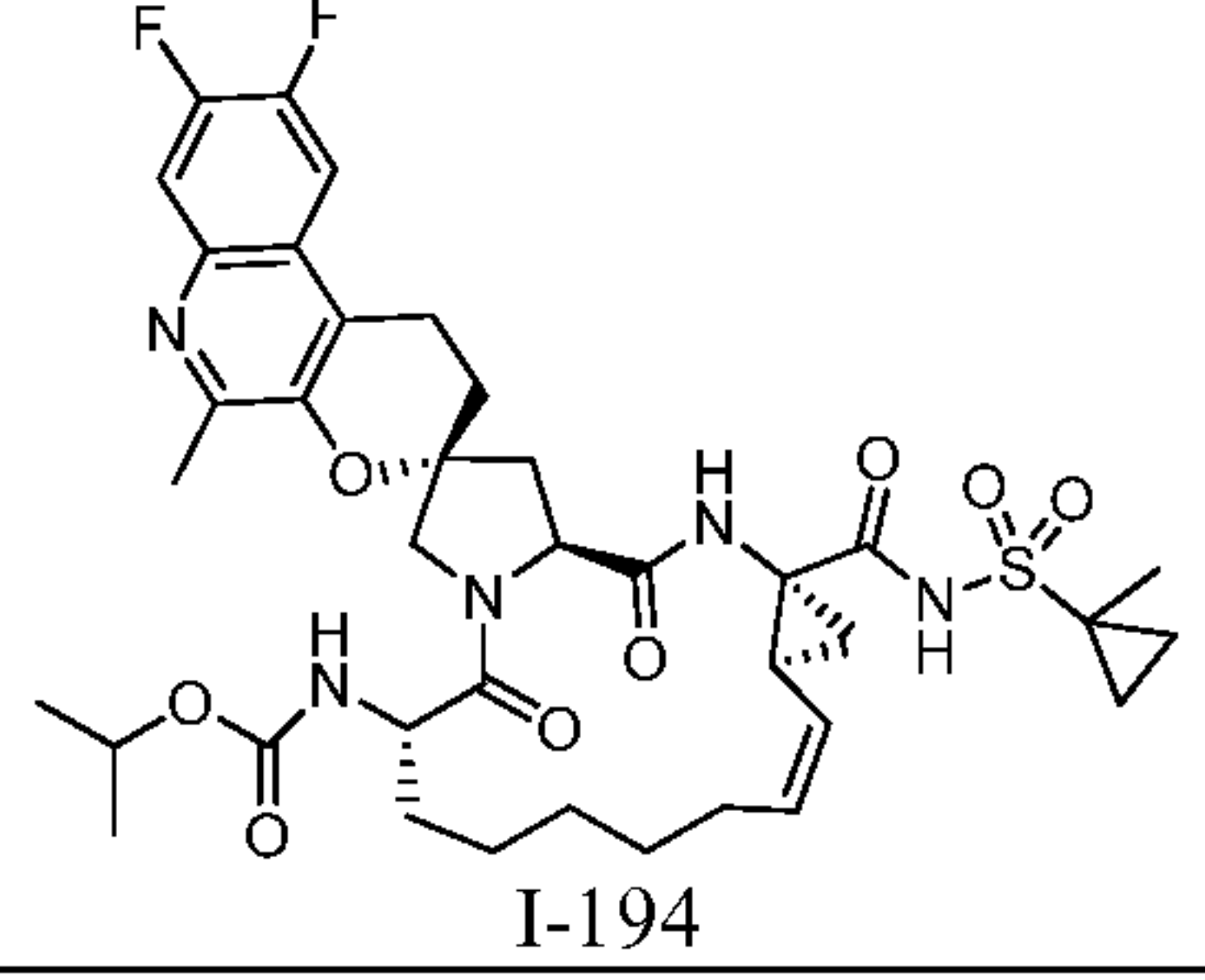
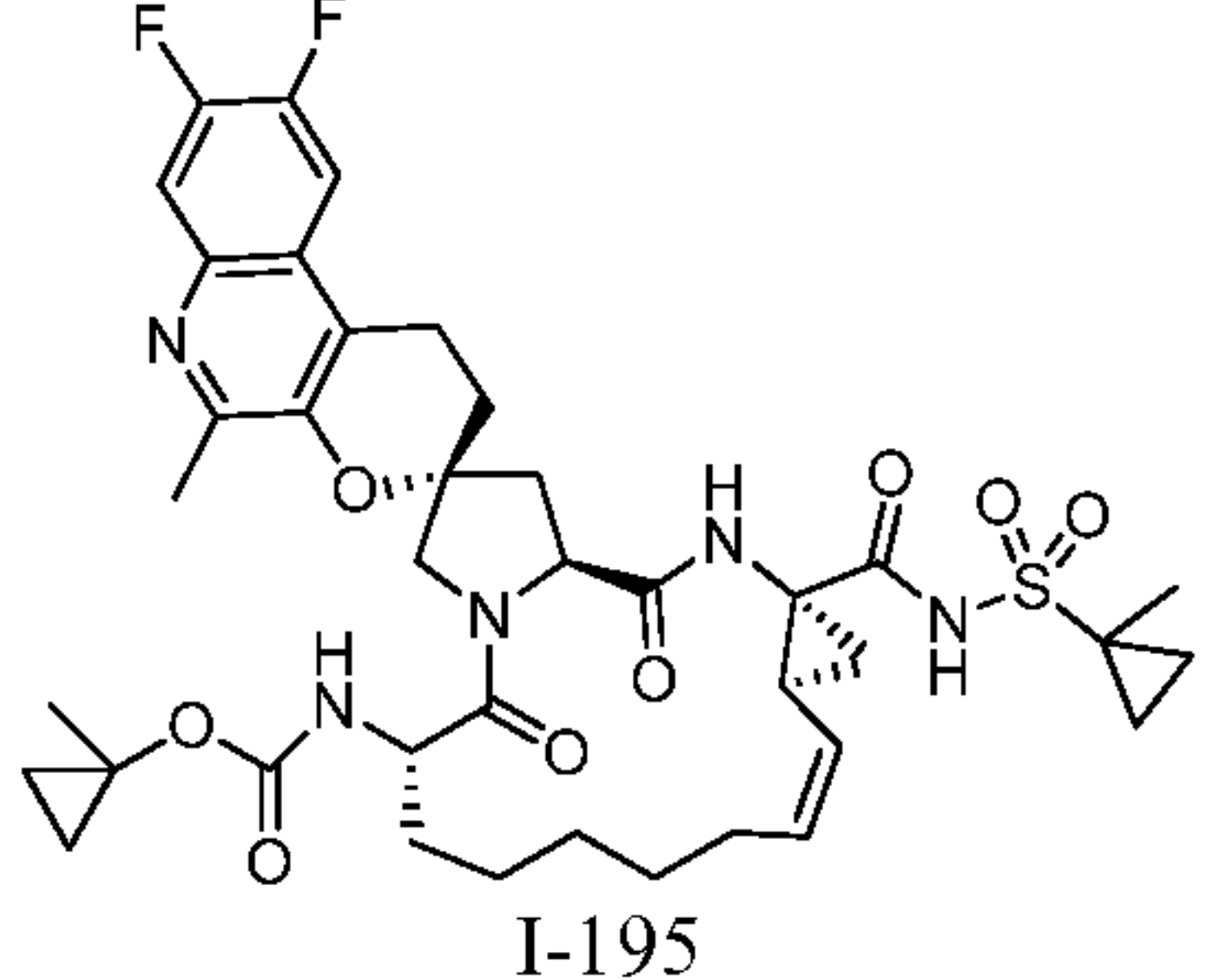
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
165	 I-165	1-methylcyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	2	806.2
166	 I-166	cyclohexyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-7'-fluoro-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	820.4
167	 I-167	1-(propan-2-yl)cyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-7'-fluoro-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	820.4
168	 I-168	1-methylcyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-7'-fluoro-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	792.4
169	 I-169	1-methylcyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	2	820.2
170	 I-170	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclobutyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	46	832.6

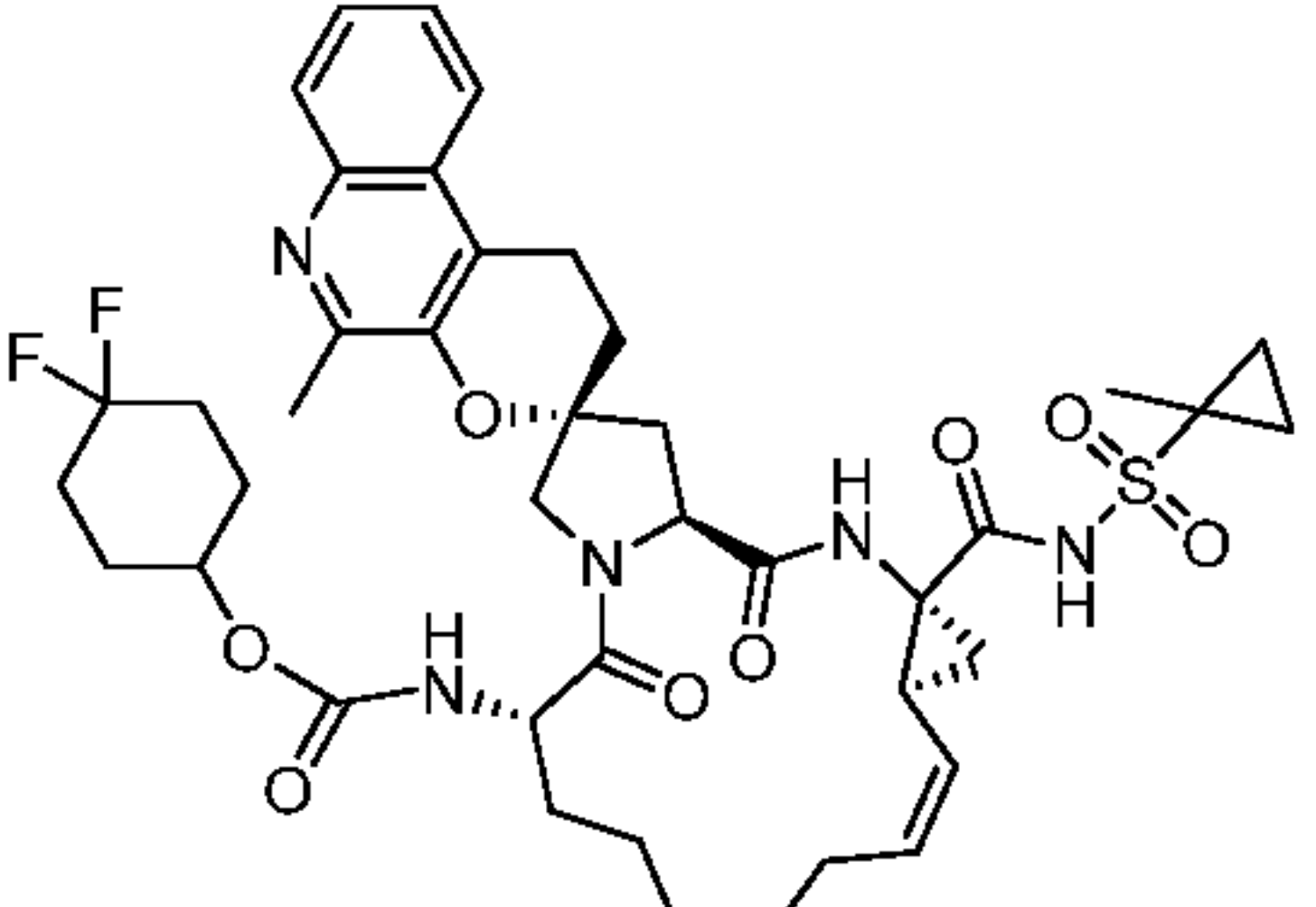
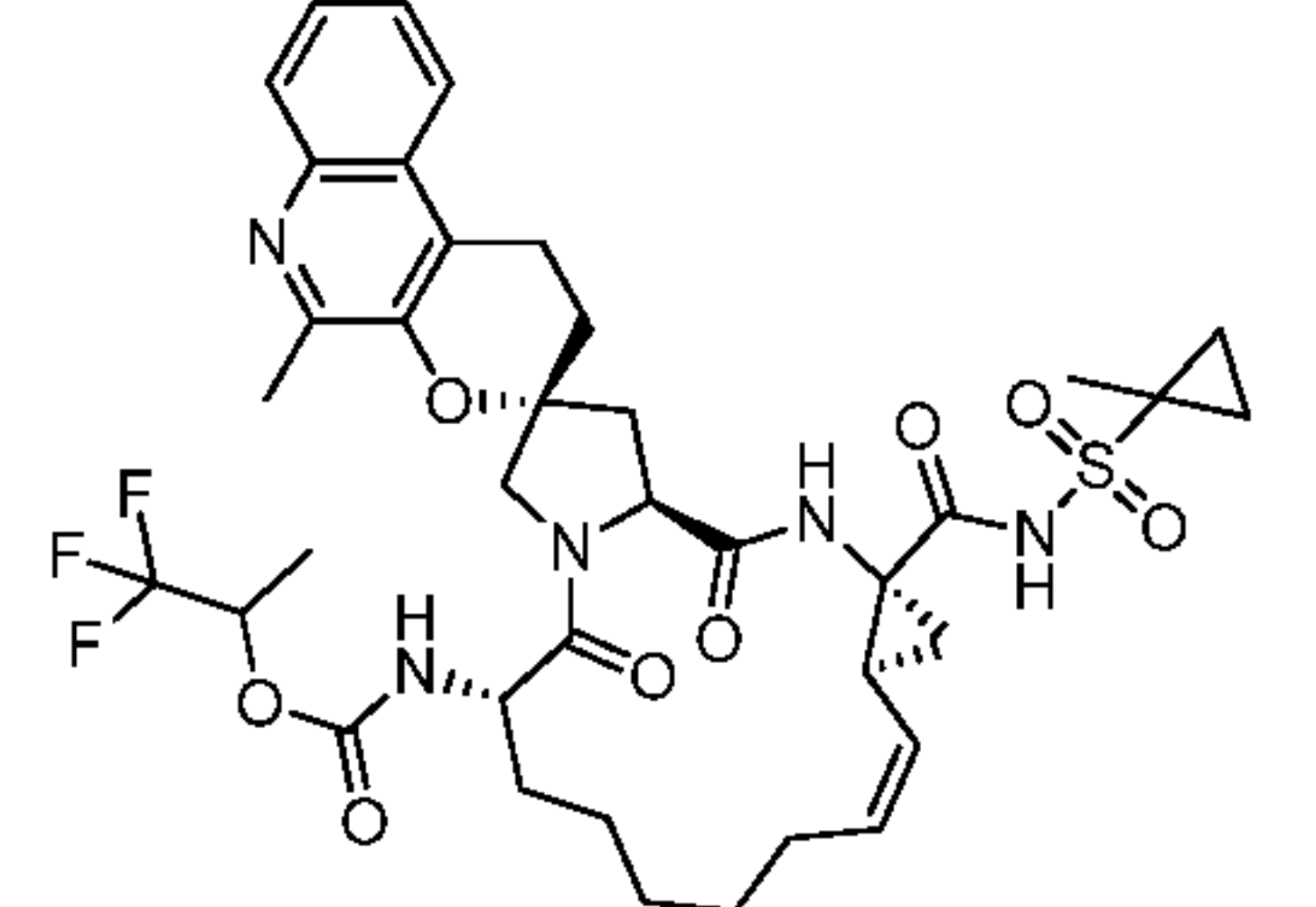
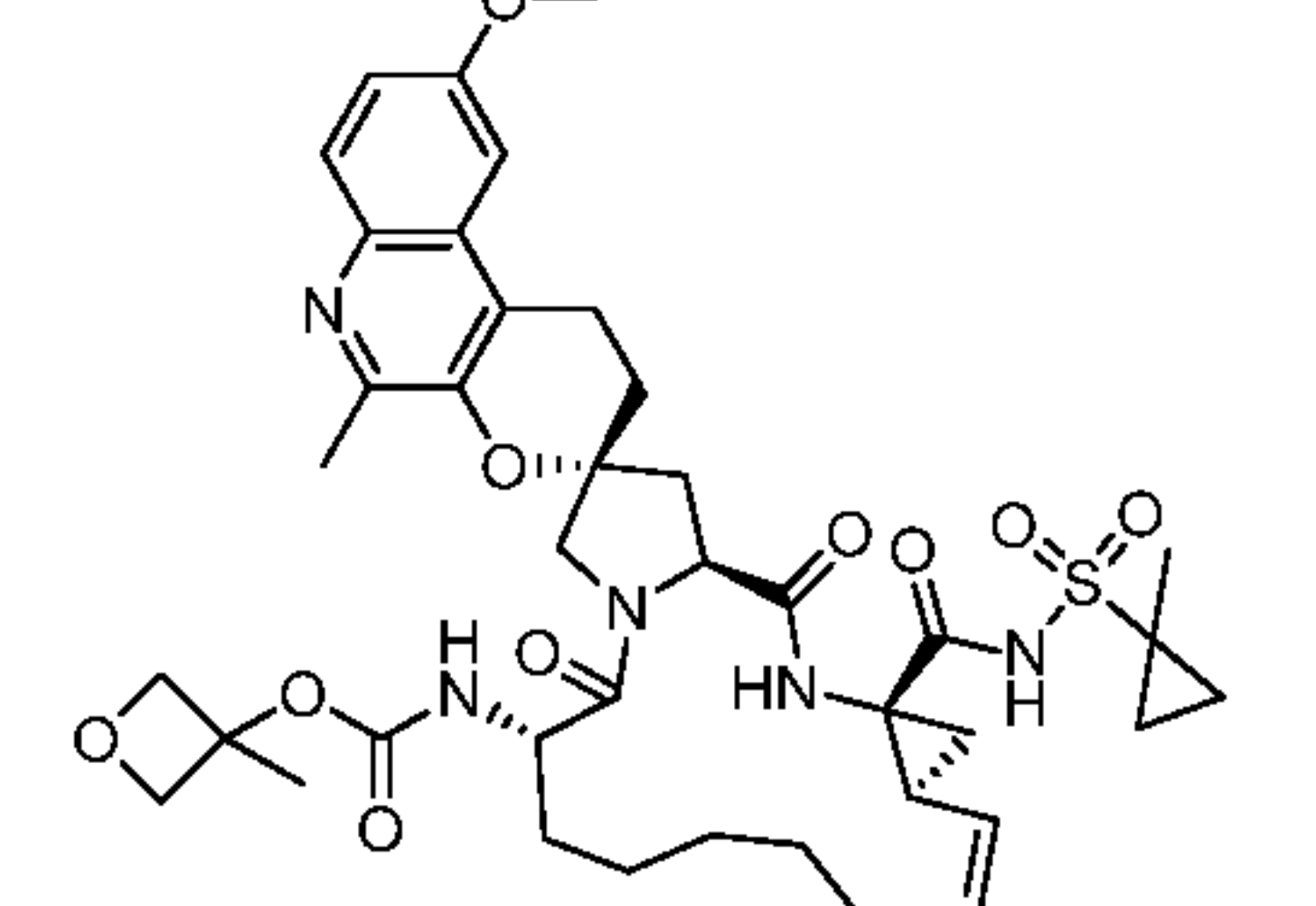
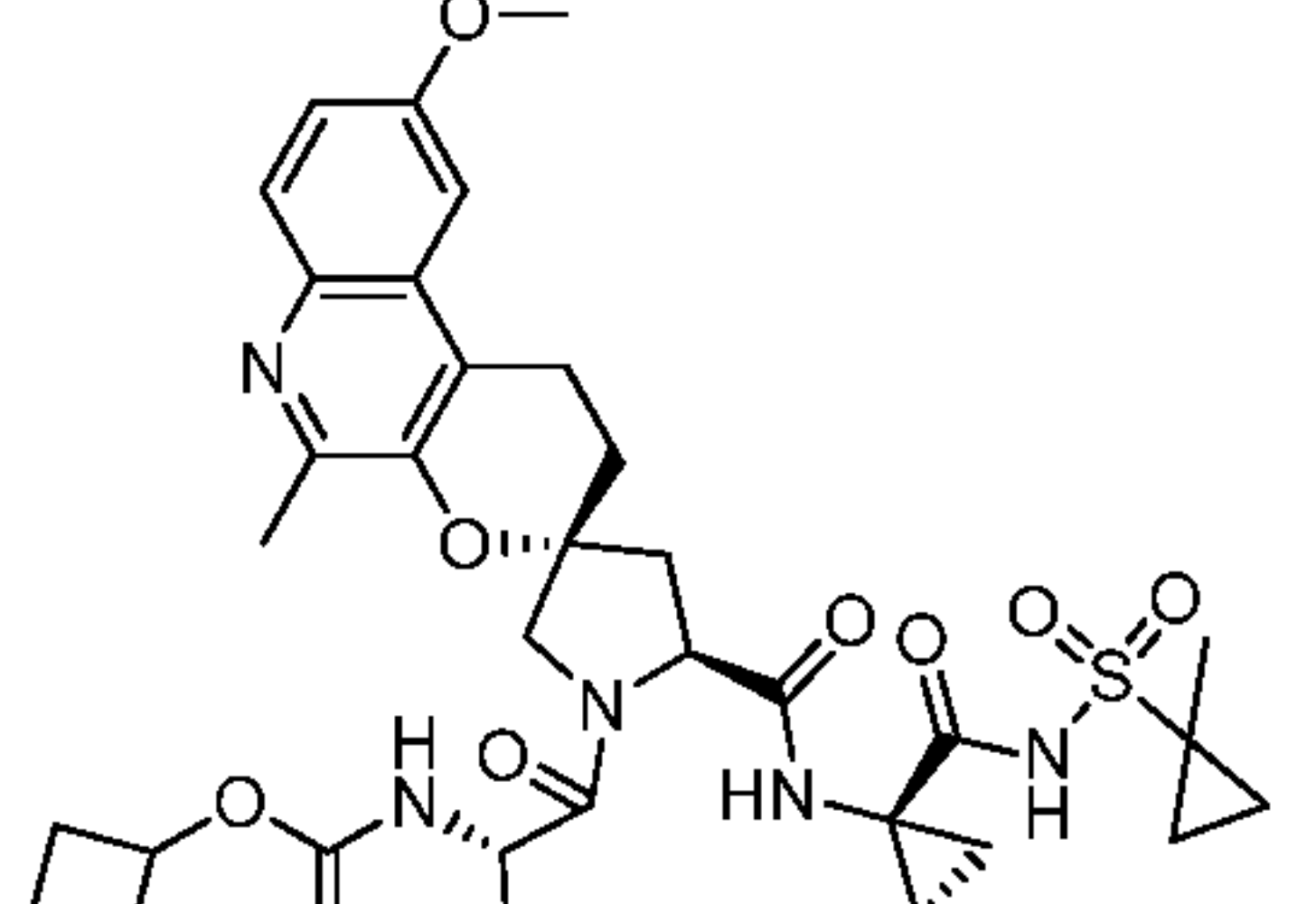
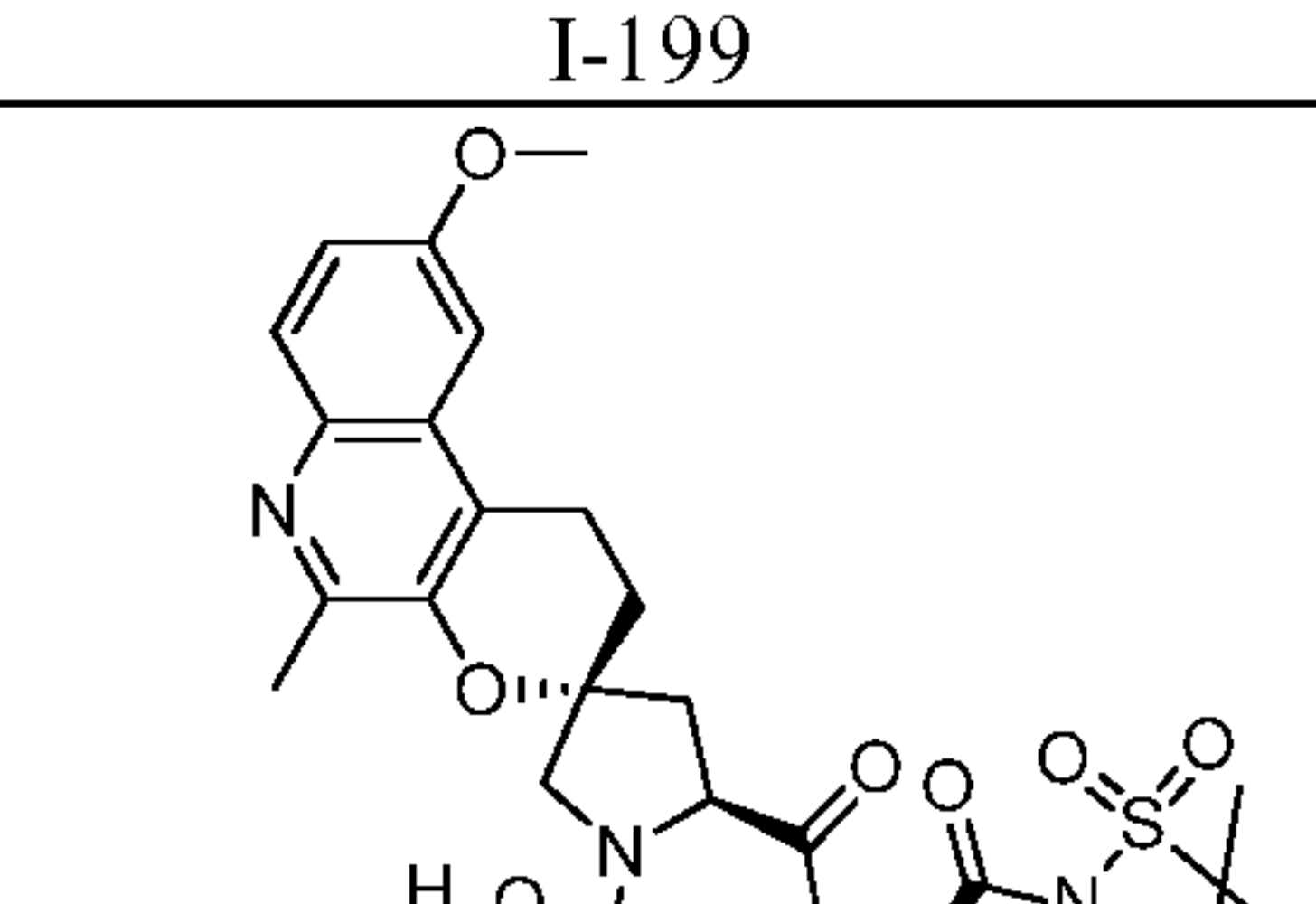
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
171	 I-171	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclobutyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	46	820.6
172	 I-172	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-6-[(2-phenylethyl)amino]-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	57	753.5
173	 I-173	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[bis(2-phenylethyl)amino]-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	57	857.5
174	 I-174	1-methylcyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	846.2
175	 I-175	cyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-7'-fluoro-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	792.4

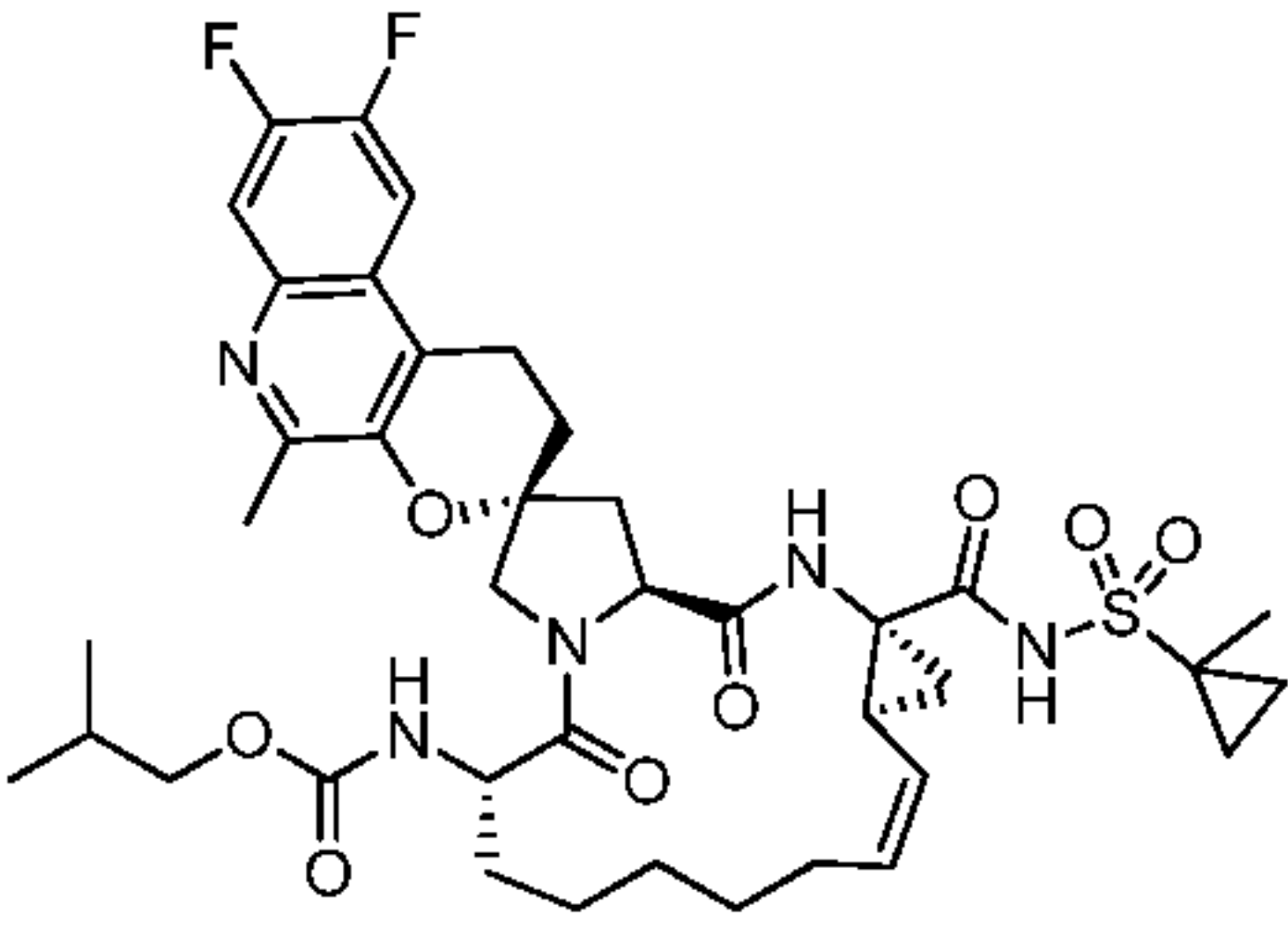
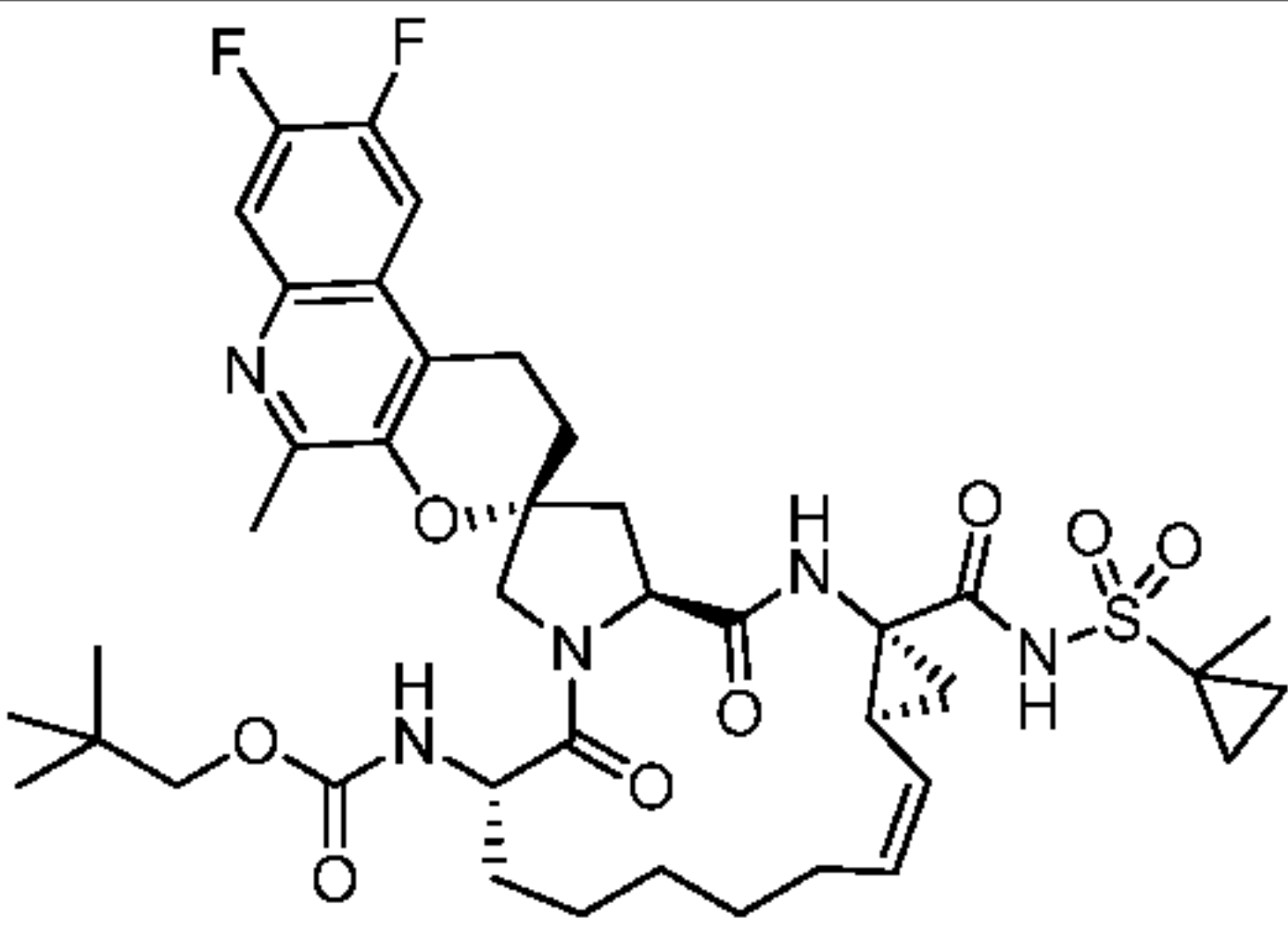
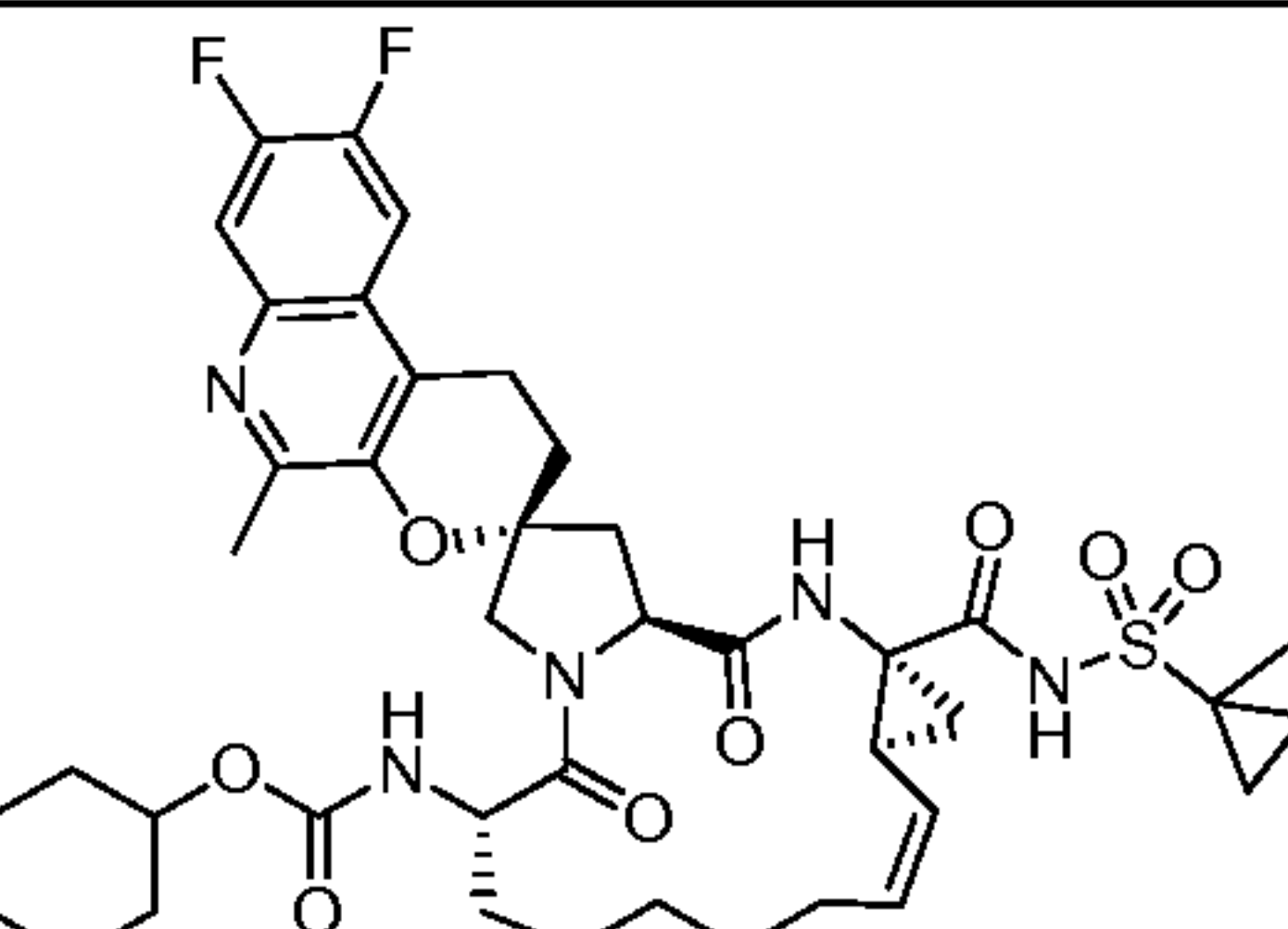
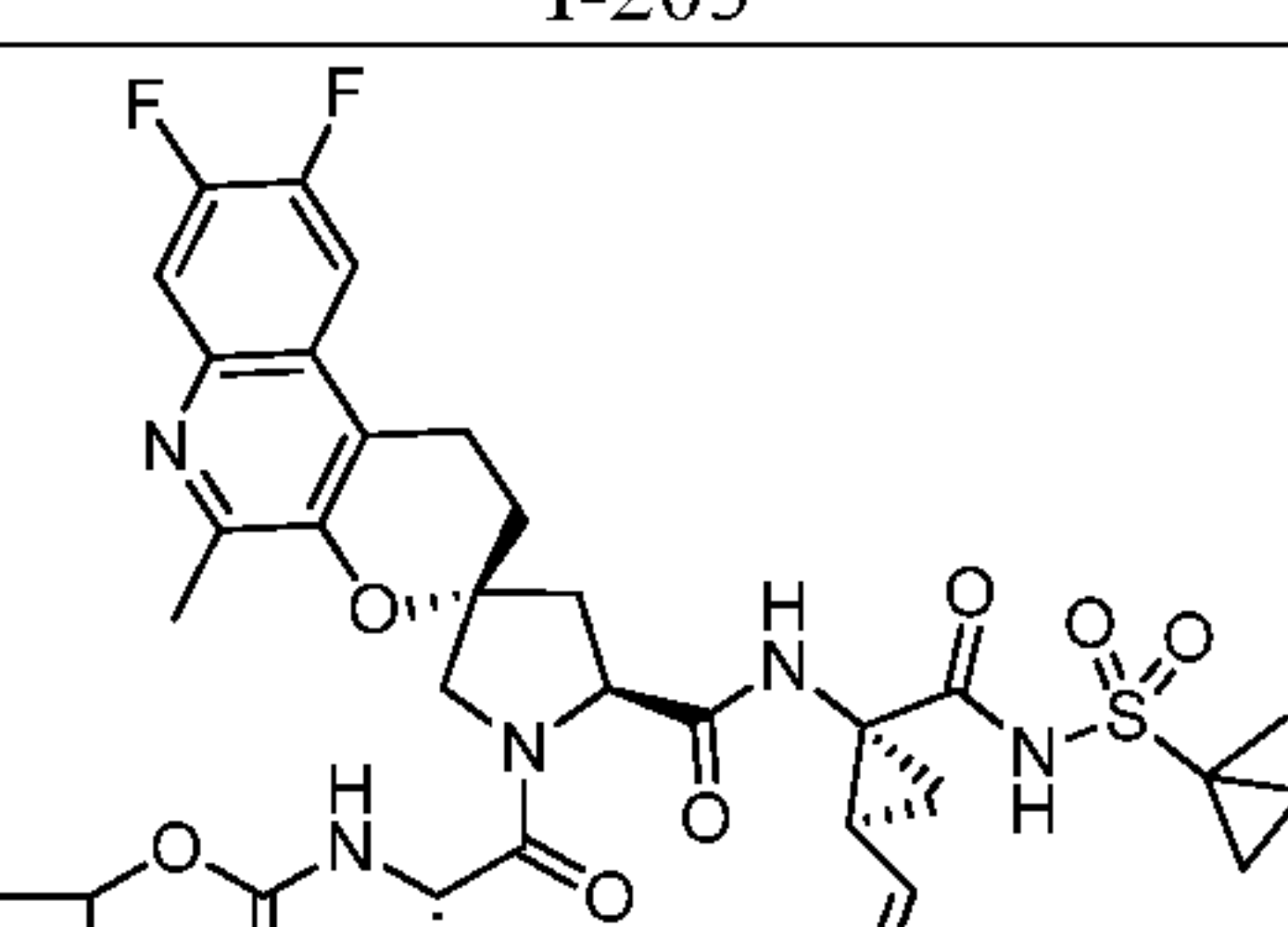
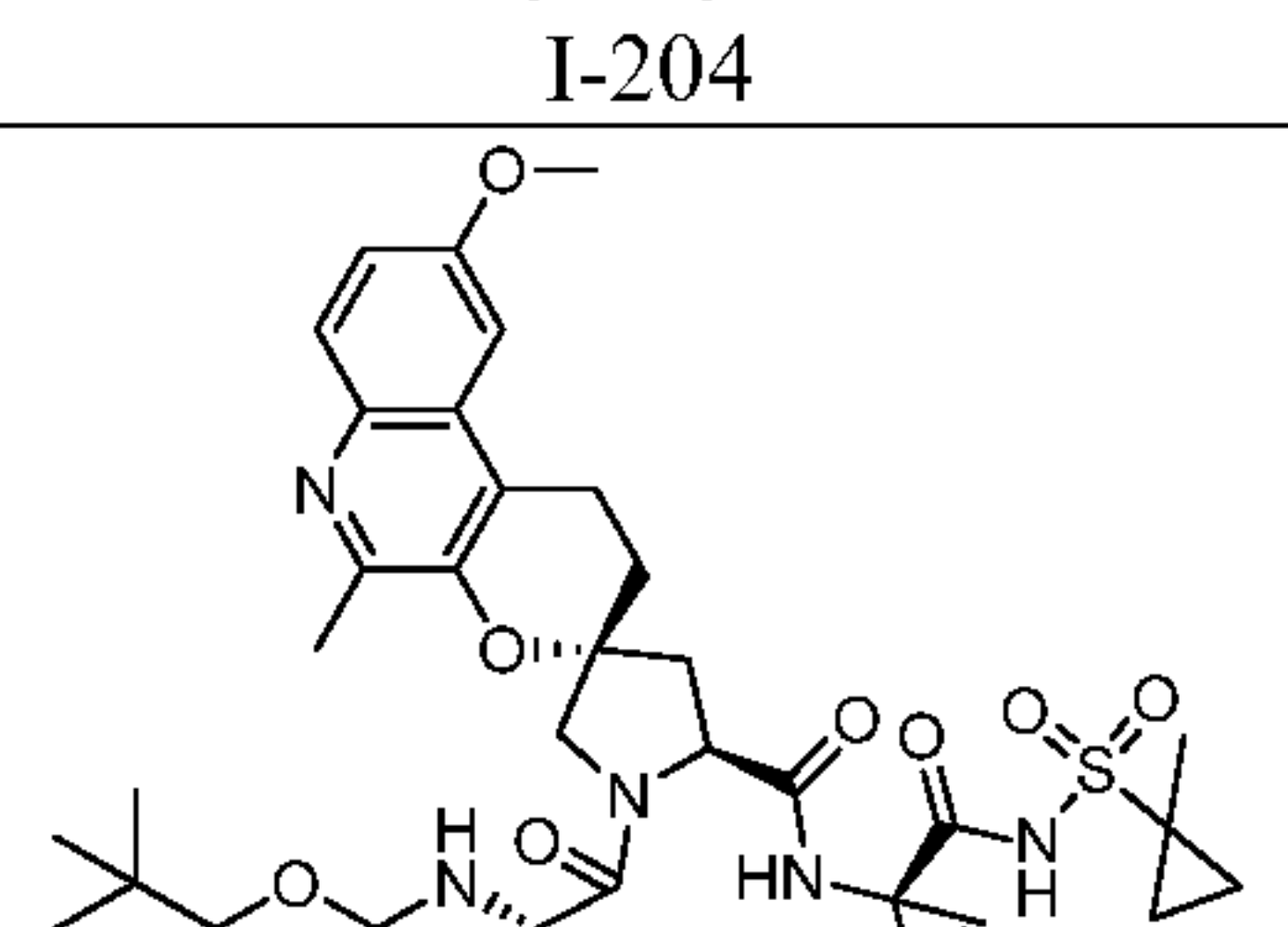
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
176	 I-176	1-methylcyclohexyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-7'-fluoro-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	834.4
177	 I-177	oxetan-3-ylmethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	848.2
178	 I-178	oxetan-3-ylmethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	2	822.2
179	 I-179	(1 <i>R</i> ,2 <i>R</i> ,4 <i>S</i>)-bicyclo[2.2.1]hept-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	787.5
180	 I-180	cyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	832.2

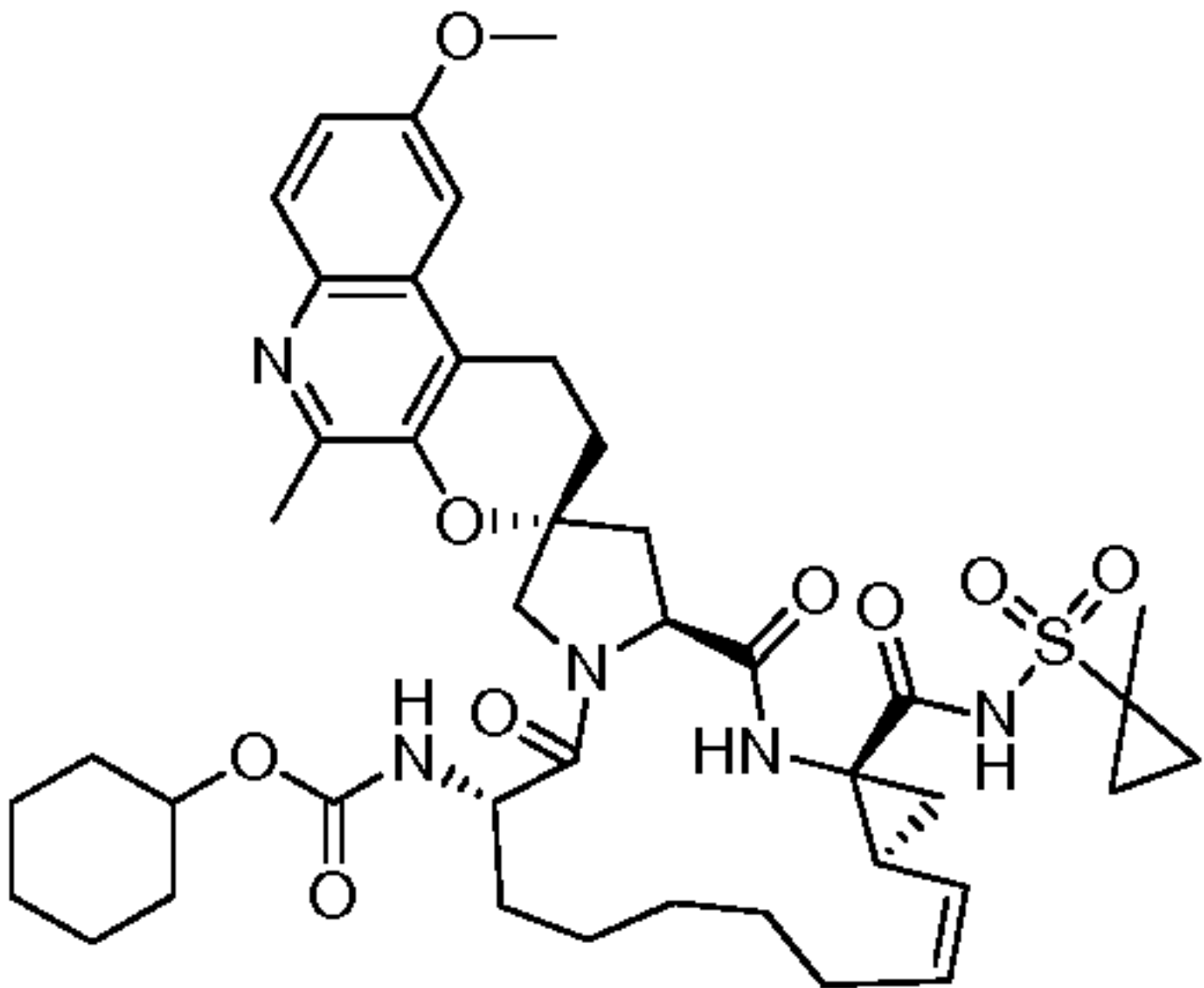
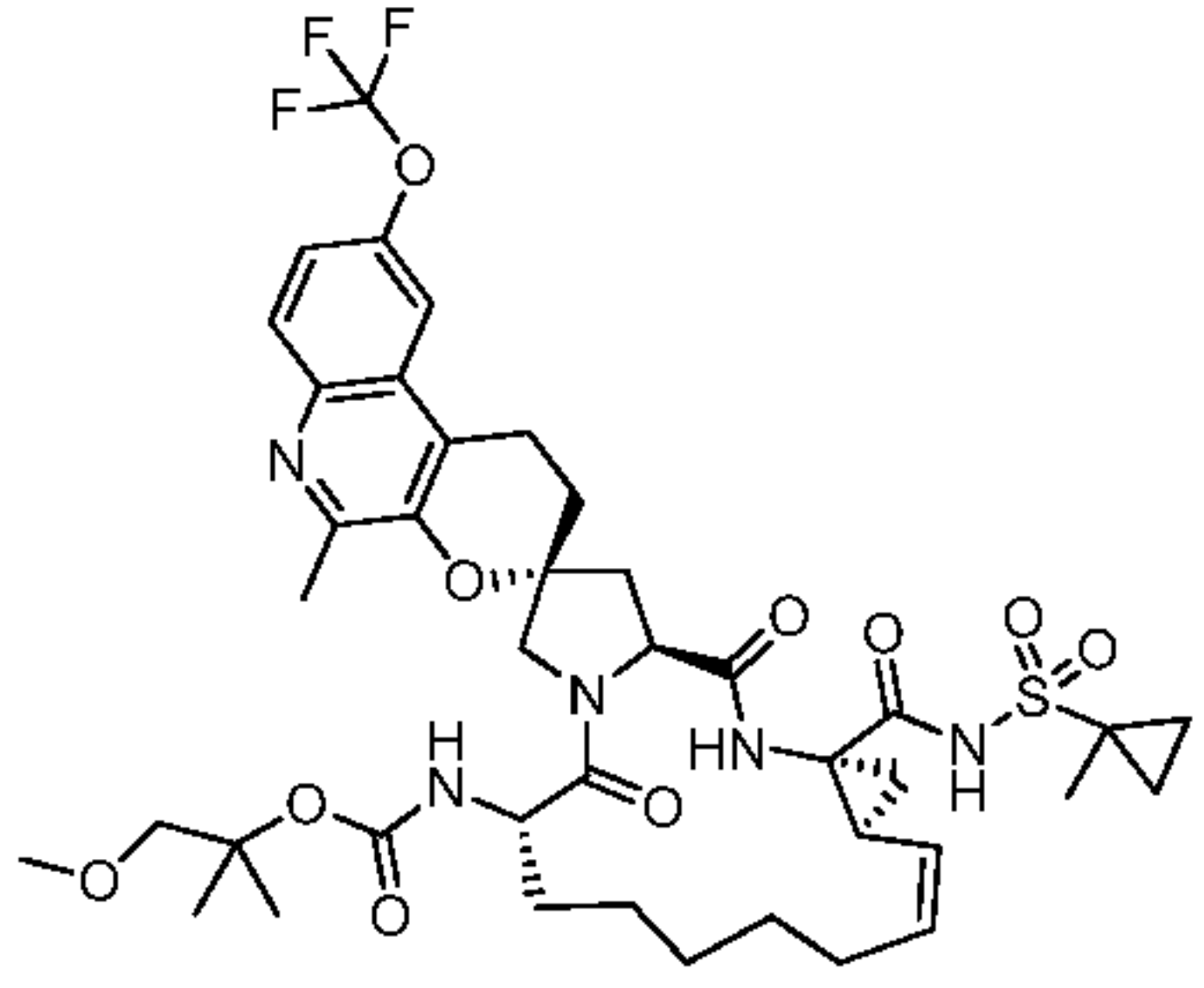
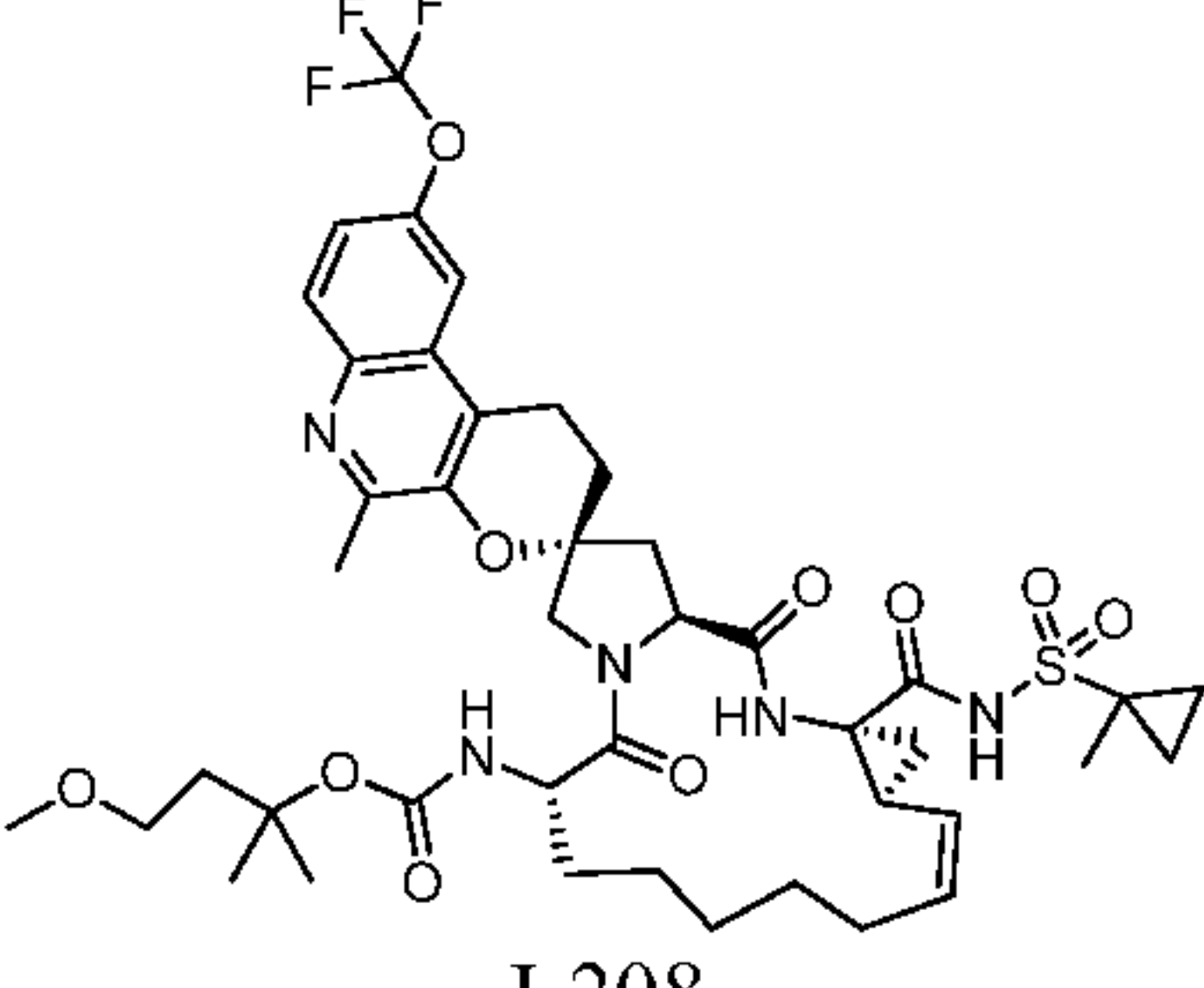
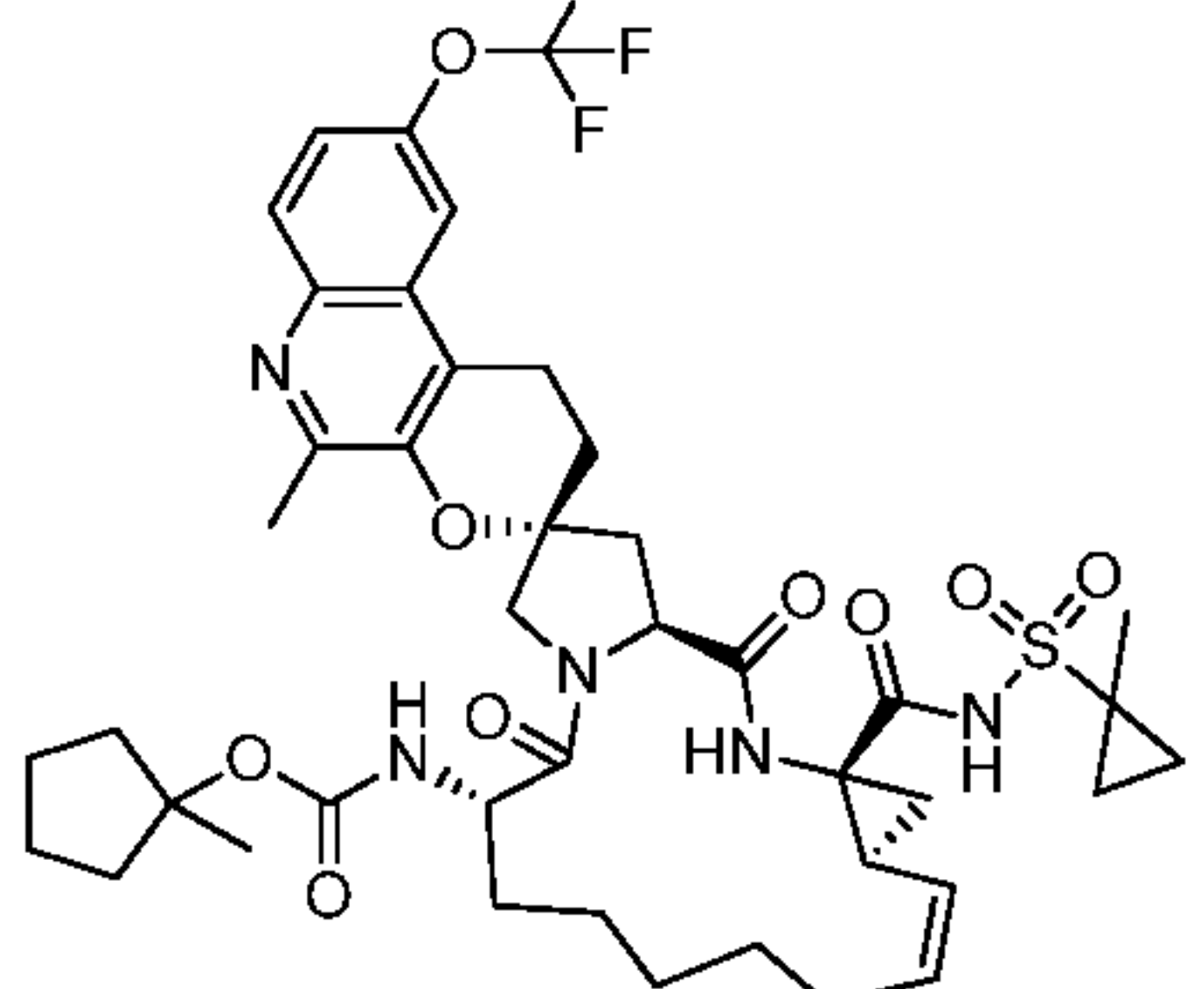
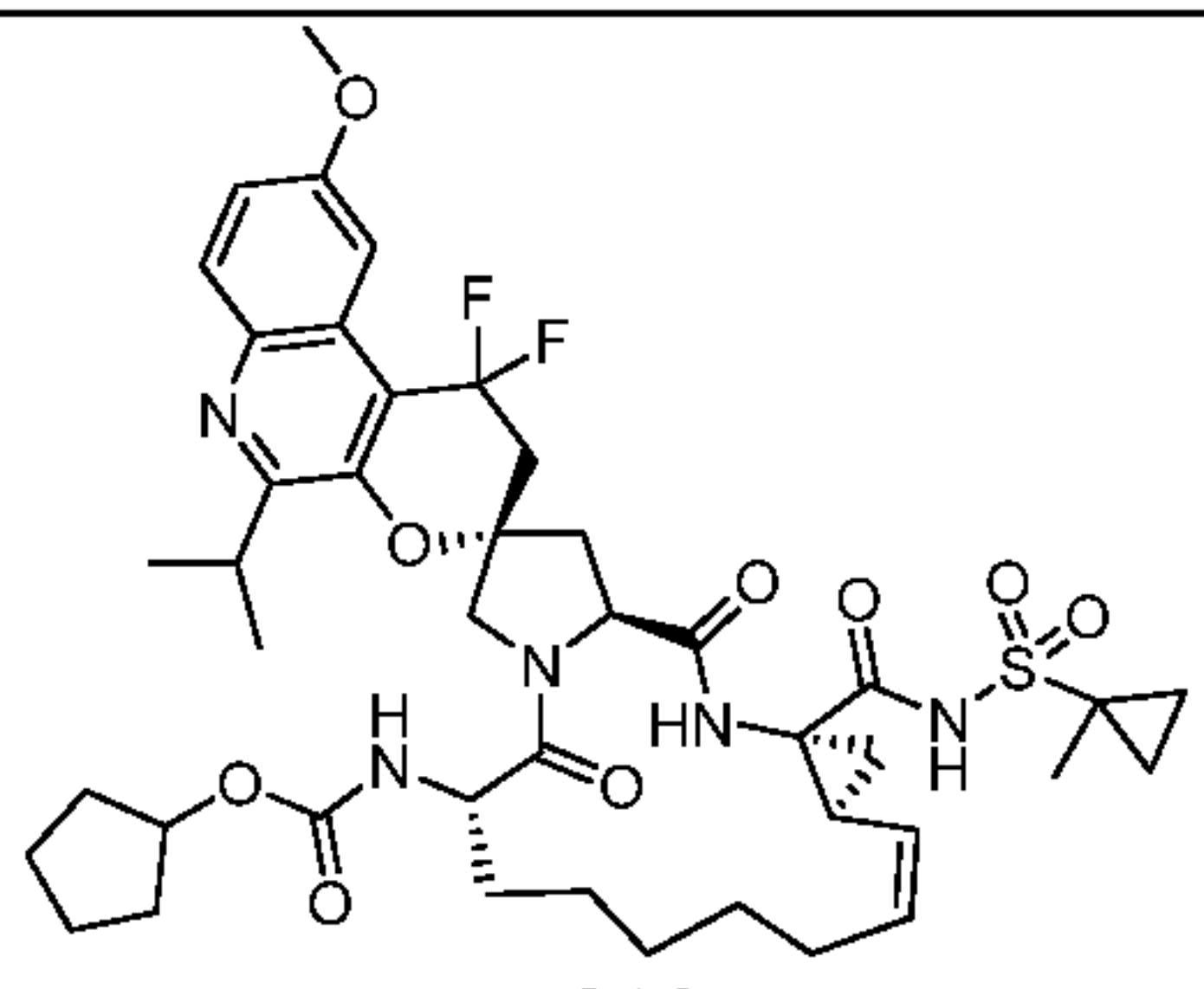
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
181	 I-181	(1 <i>R</i> ,2 <i>S</i> ,4 <i>S</i>)-bicyclo[2.2.1]hept-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	787.5
182	 I-182	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39	796.3 (K+ salt)
183	 I-183	propan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39	770.2 (K+ salt)
184	 I-184	1-methylcyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39	782.2 (K+ salt)
185	 I-185	cyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39	782.2 (K+ salt)

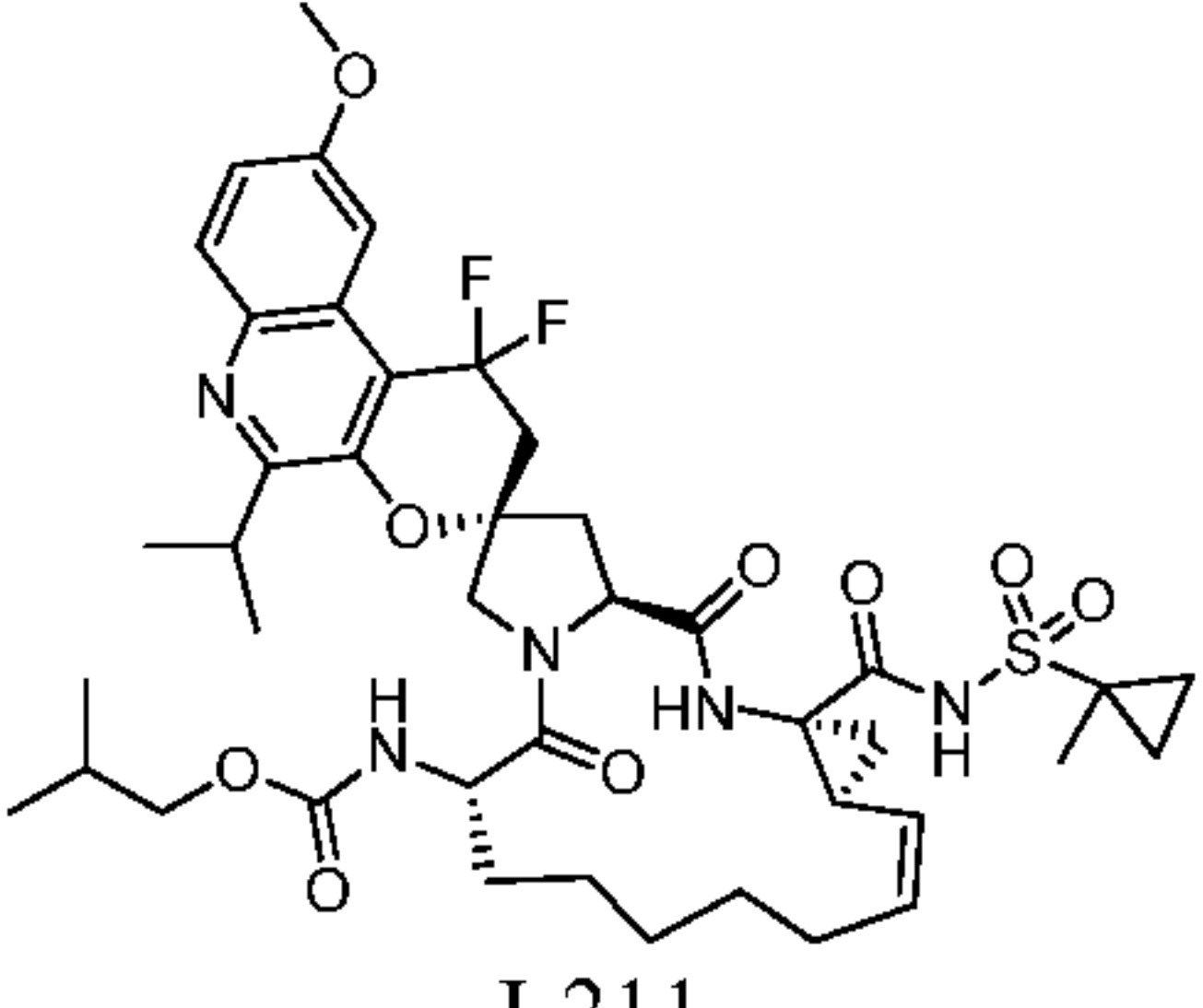
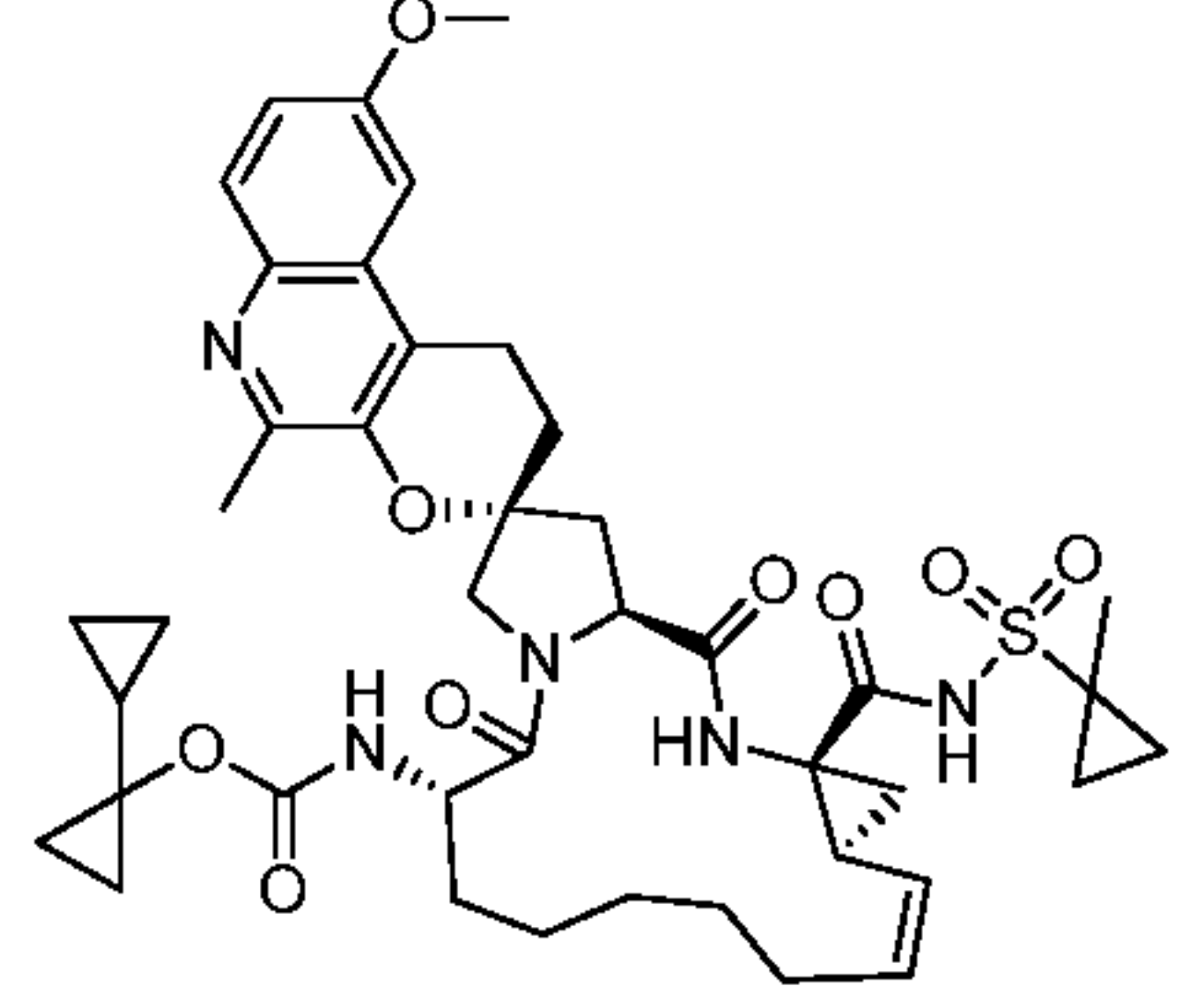
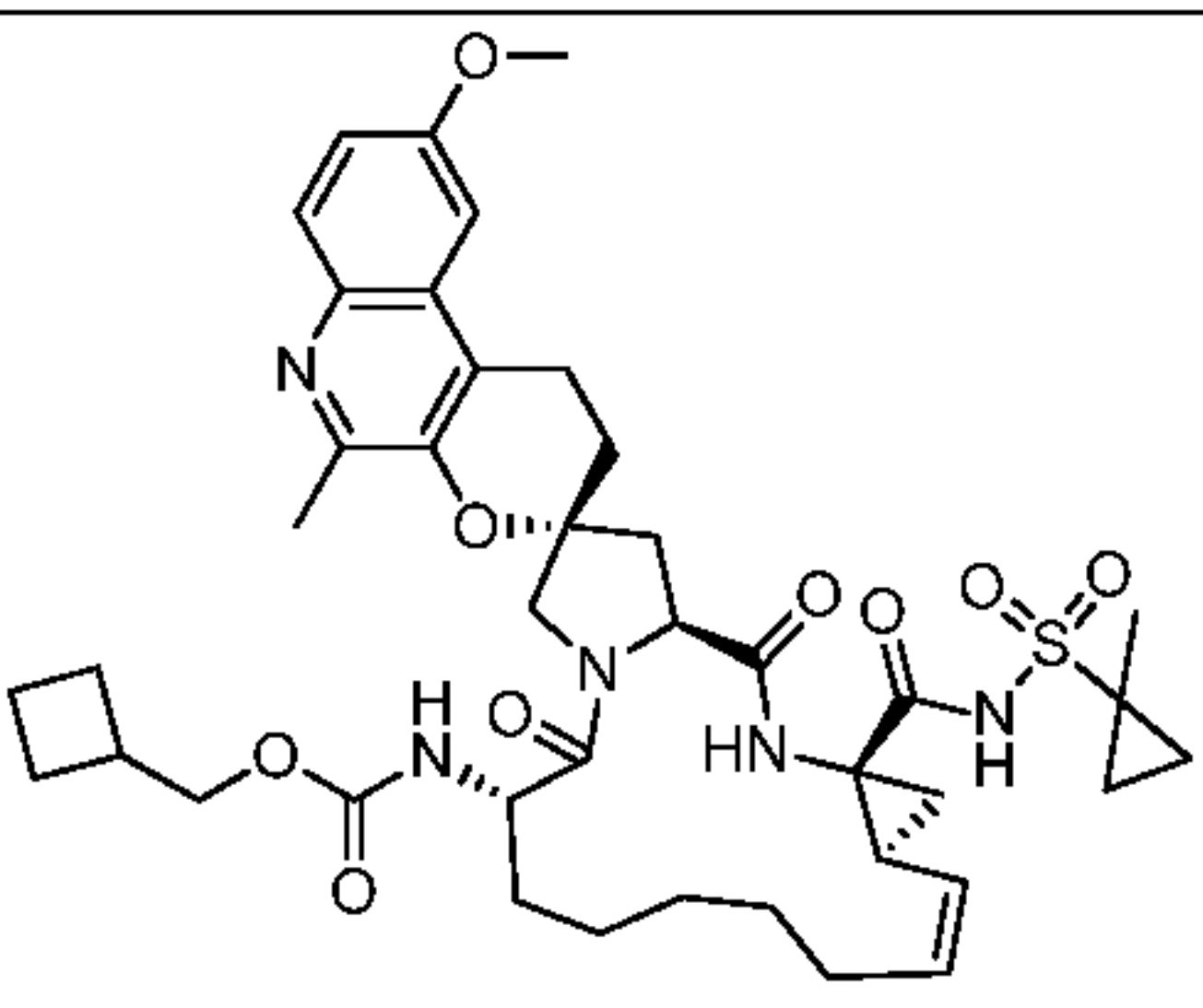
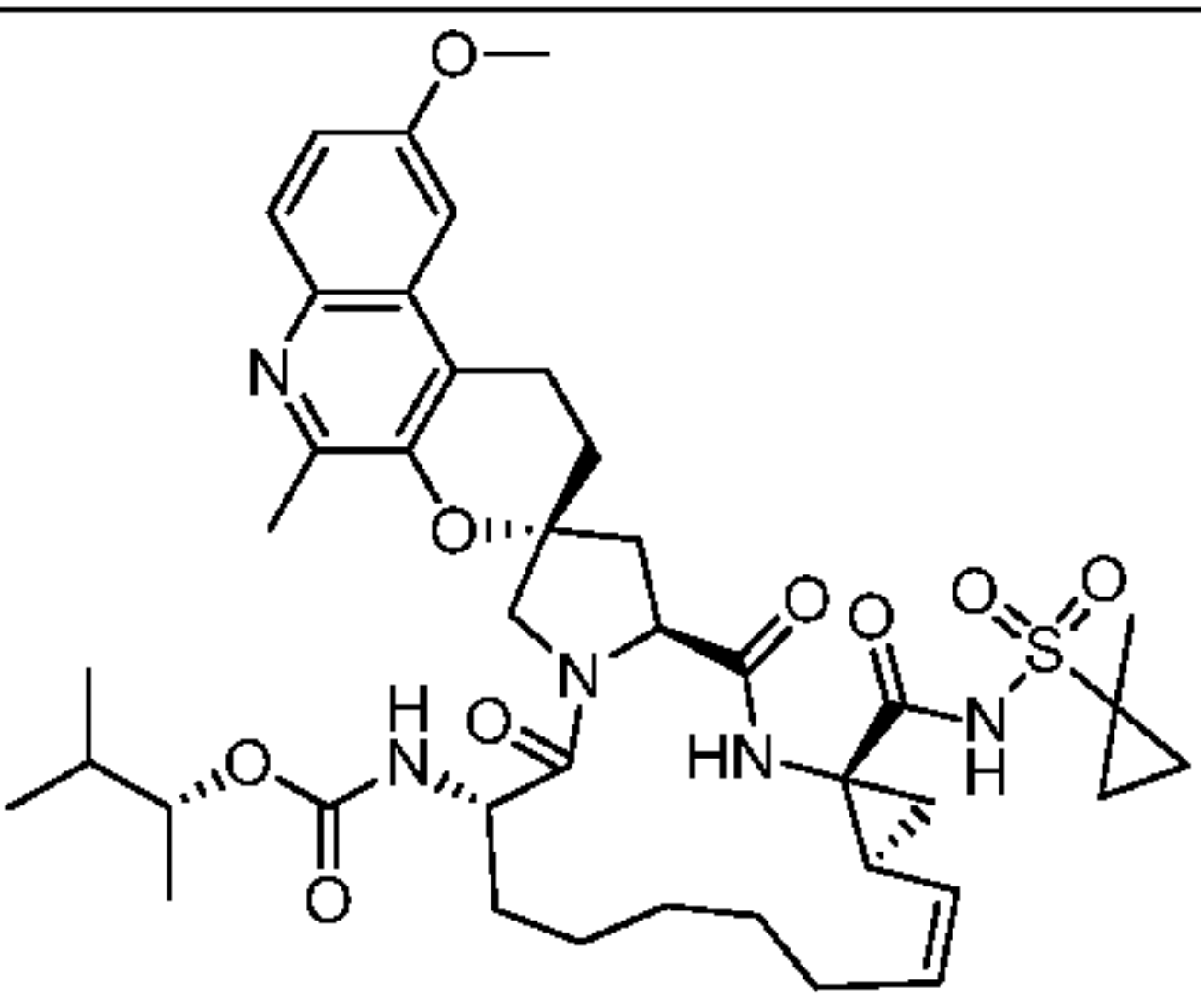
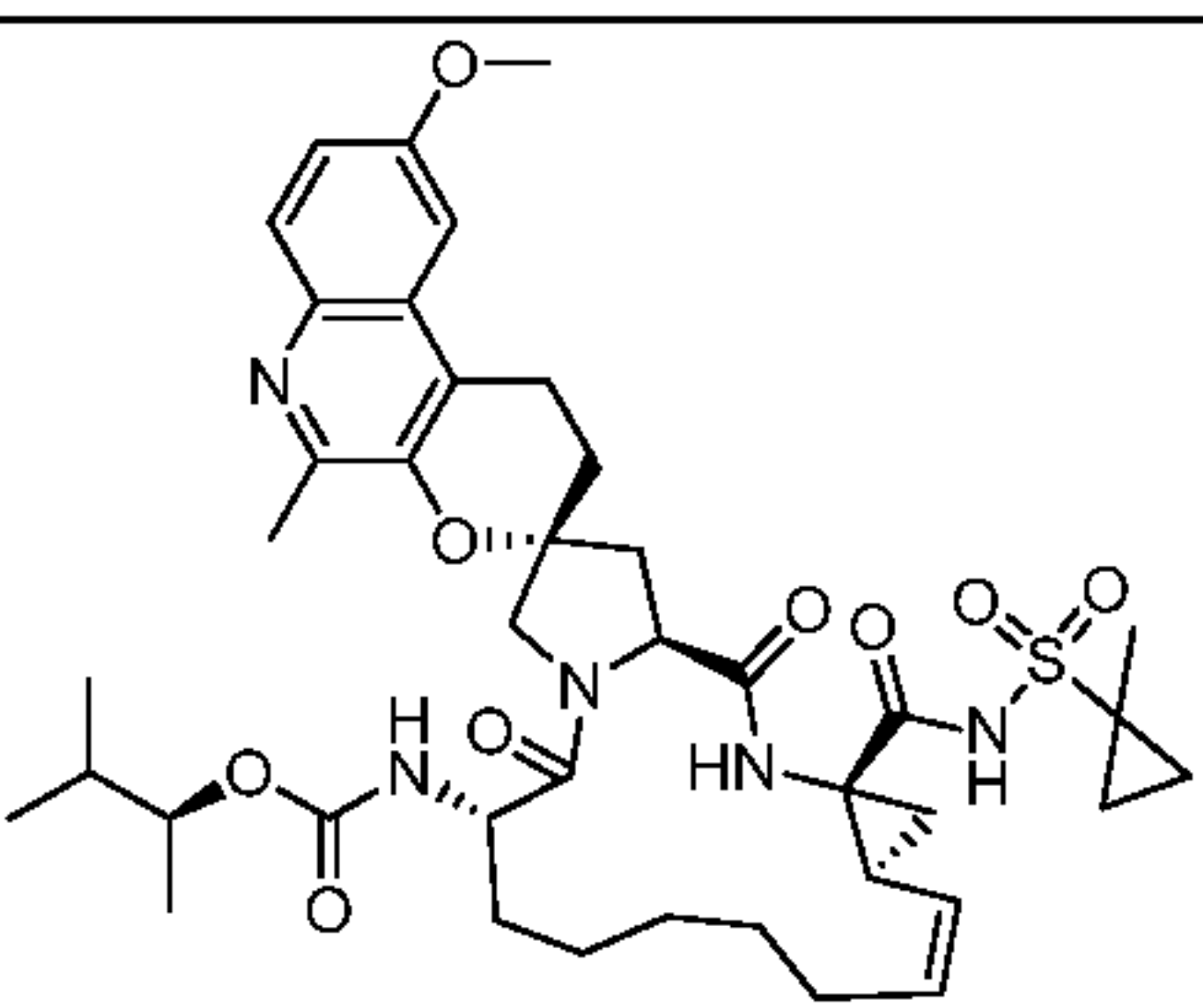
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
186	 I-186	1-methylcyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	792.4 (K+ salt)
187	 I-187	2,2-dimethylcyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-7'-fluoro-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	834
188	 I-188	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8',9'-difluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	786.2
189	 I-189	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39, 528	784.2 (K+ salt)
190	 I-190	cyclohexyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39	810.2 (K+ salt)

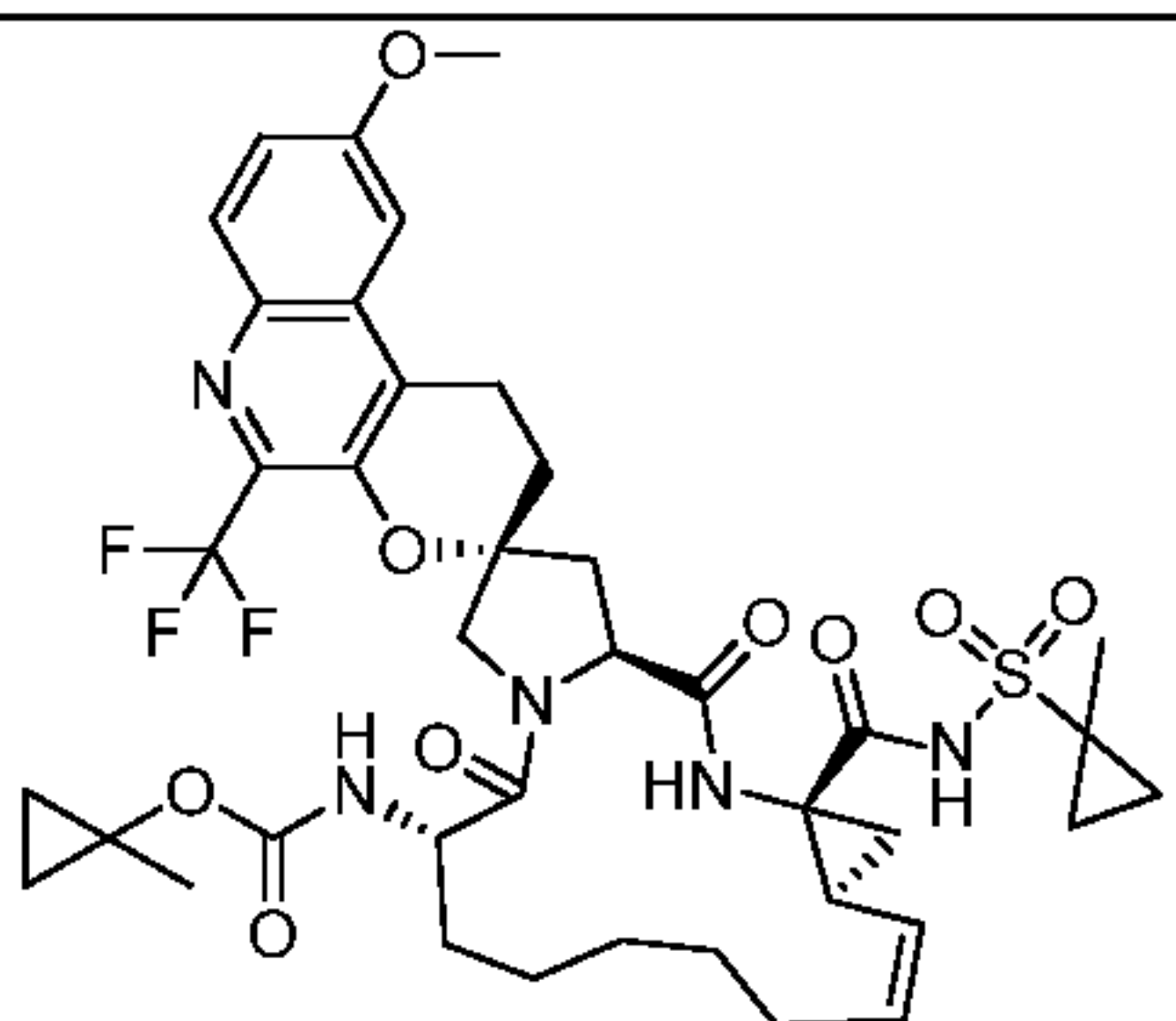
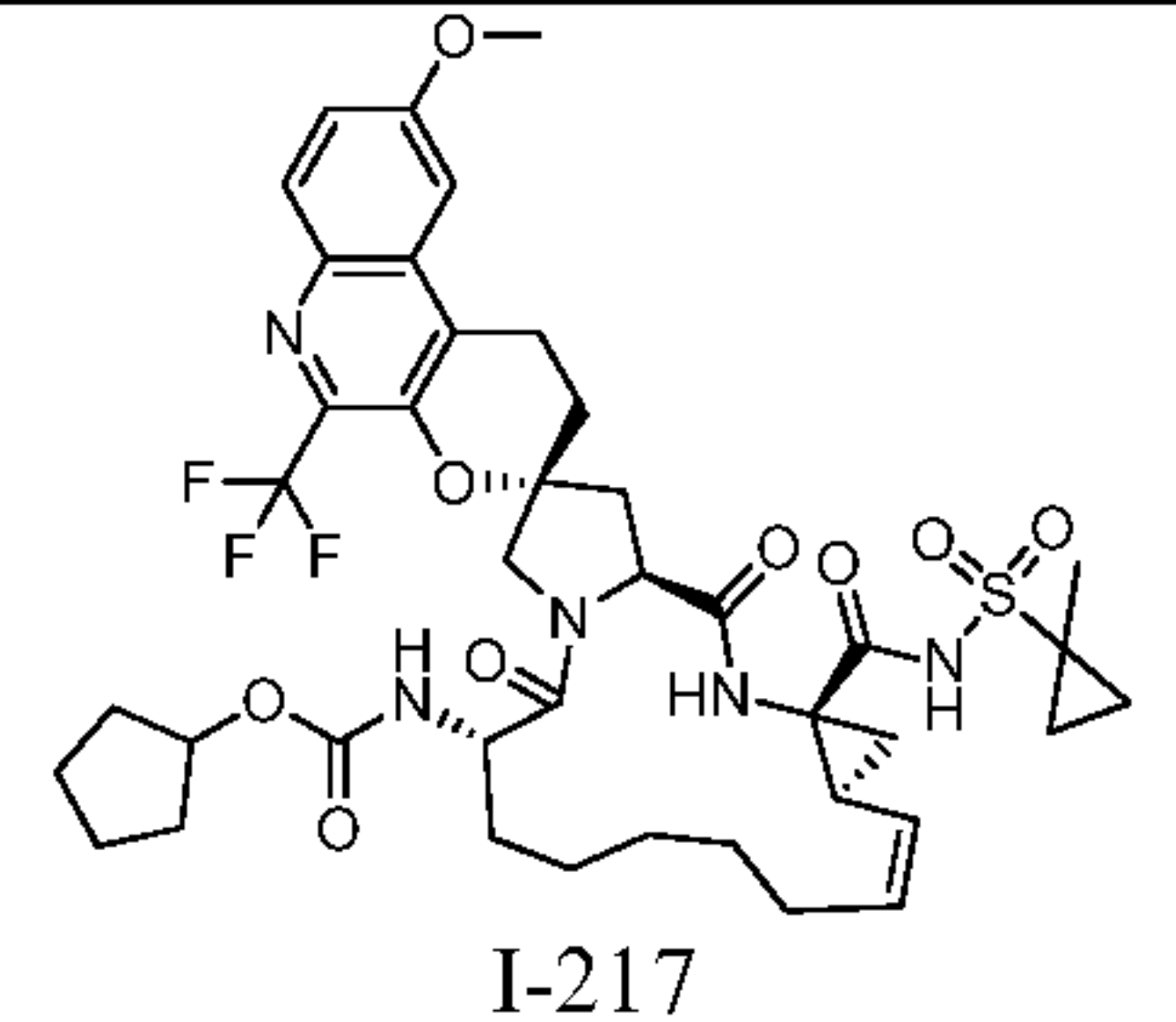
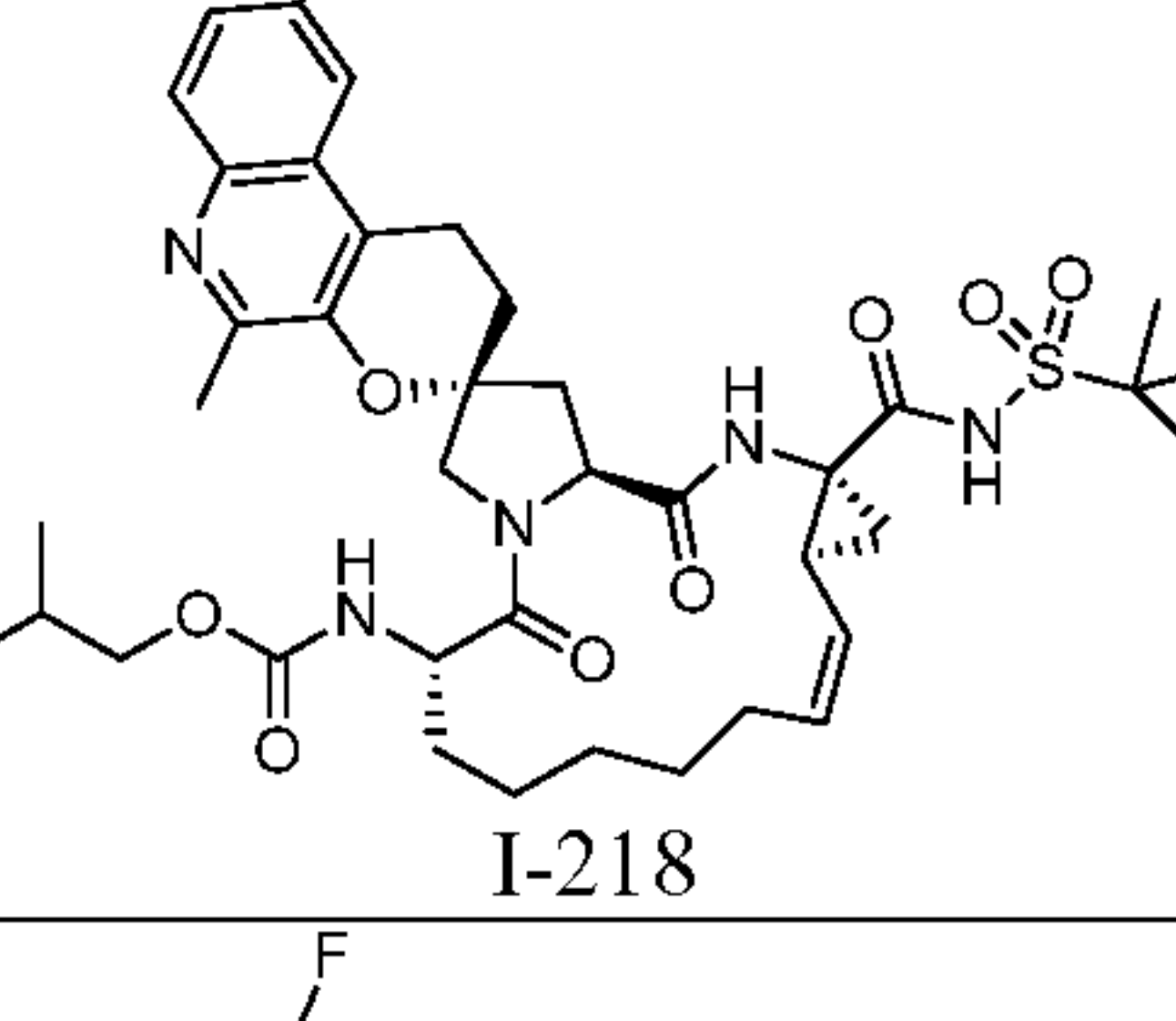
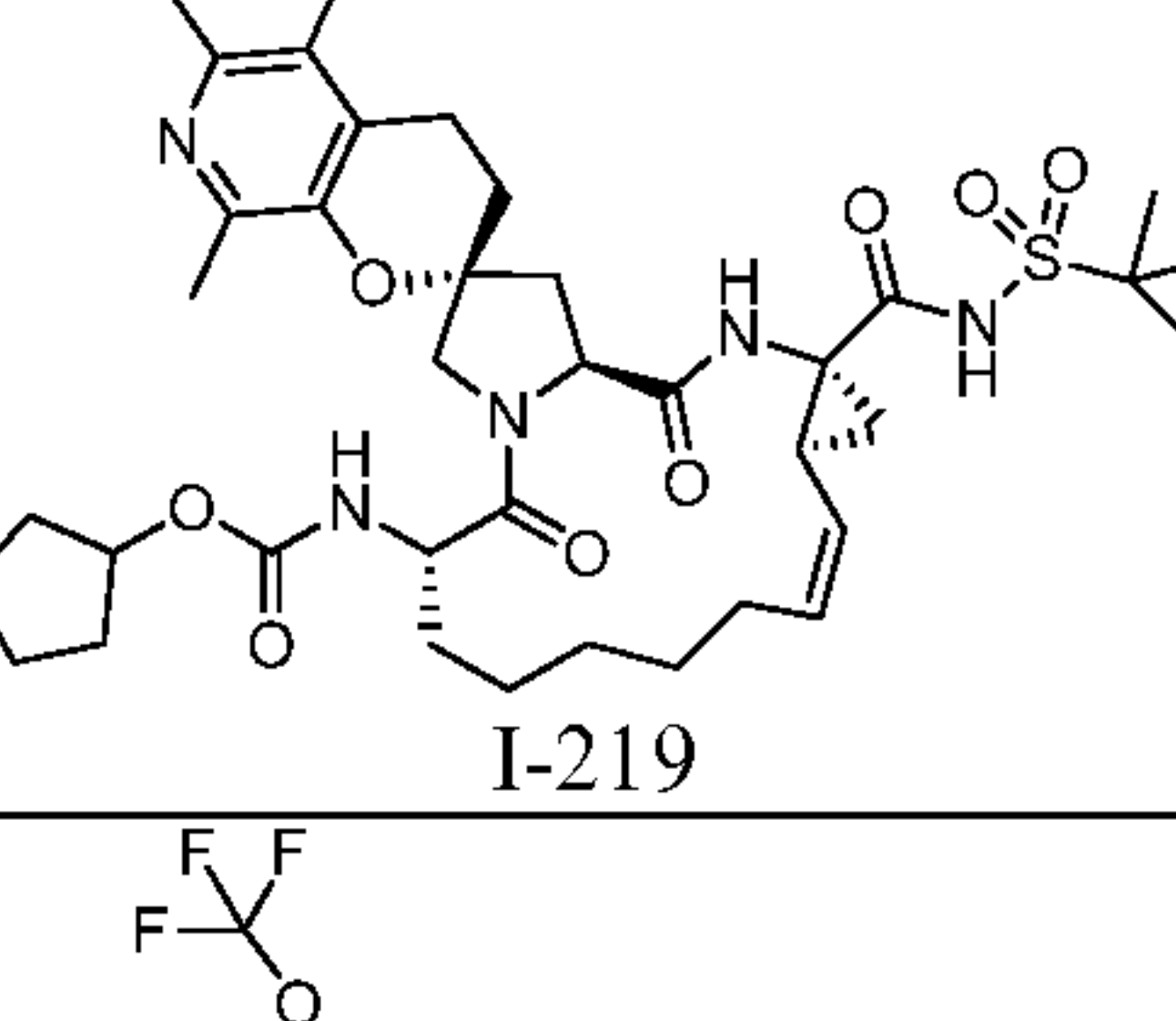
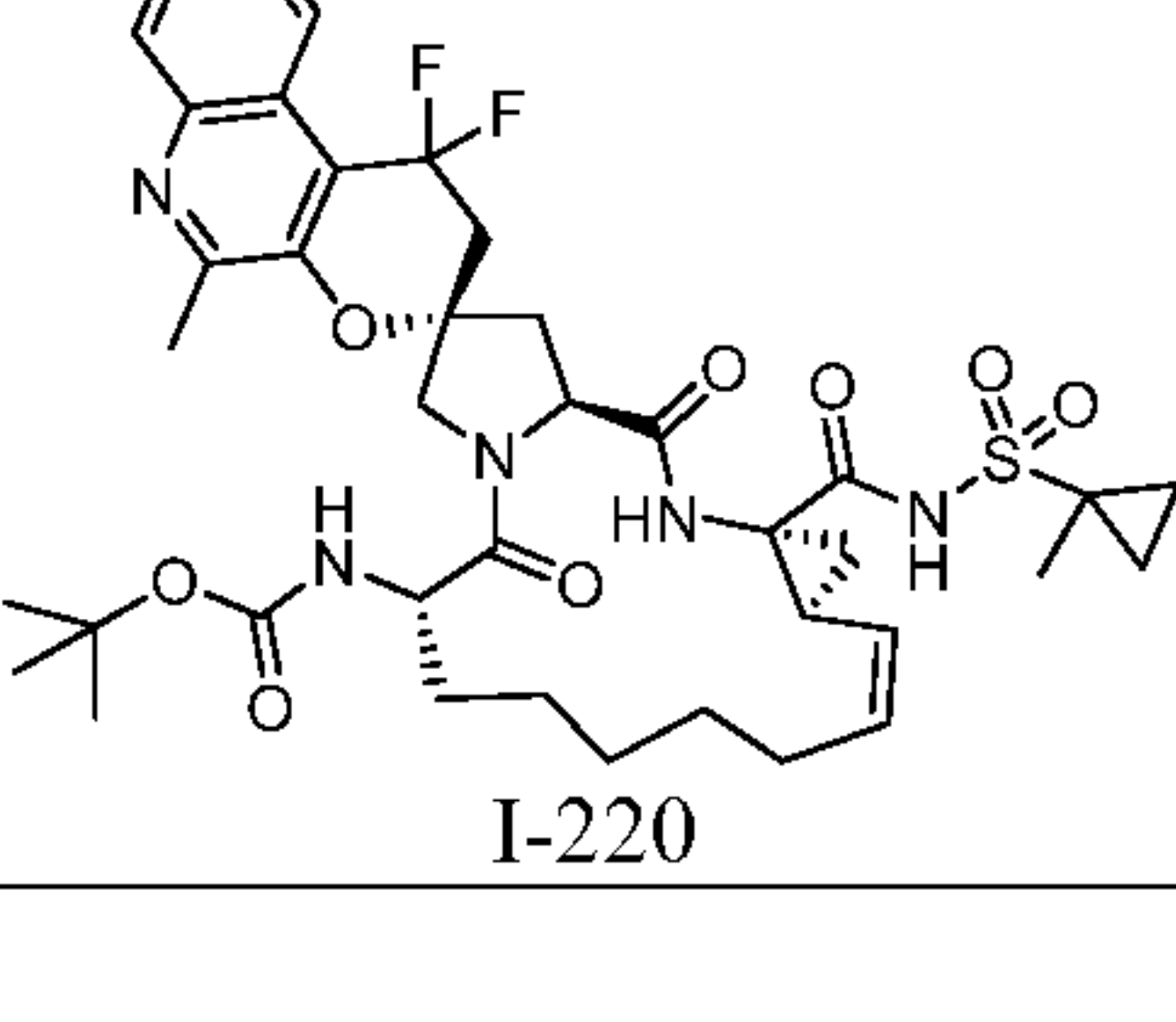
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
191	 I-191	1,1'-bi(cyclopropyl)-1-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-7'-fluoro-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	818
192	 I-192	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-7'-fluoro-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	45	808
193	 I-193	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8',9'-difluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	799.2 (K+ salt)
194	 I-194	propan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8',9'-difluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	772.2 (K+ salt)
195	 I-195	1-methylcyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8',9'-difluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	784.2 (K+ salt)

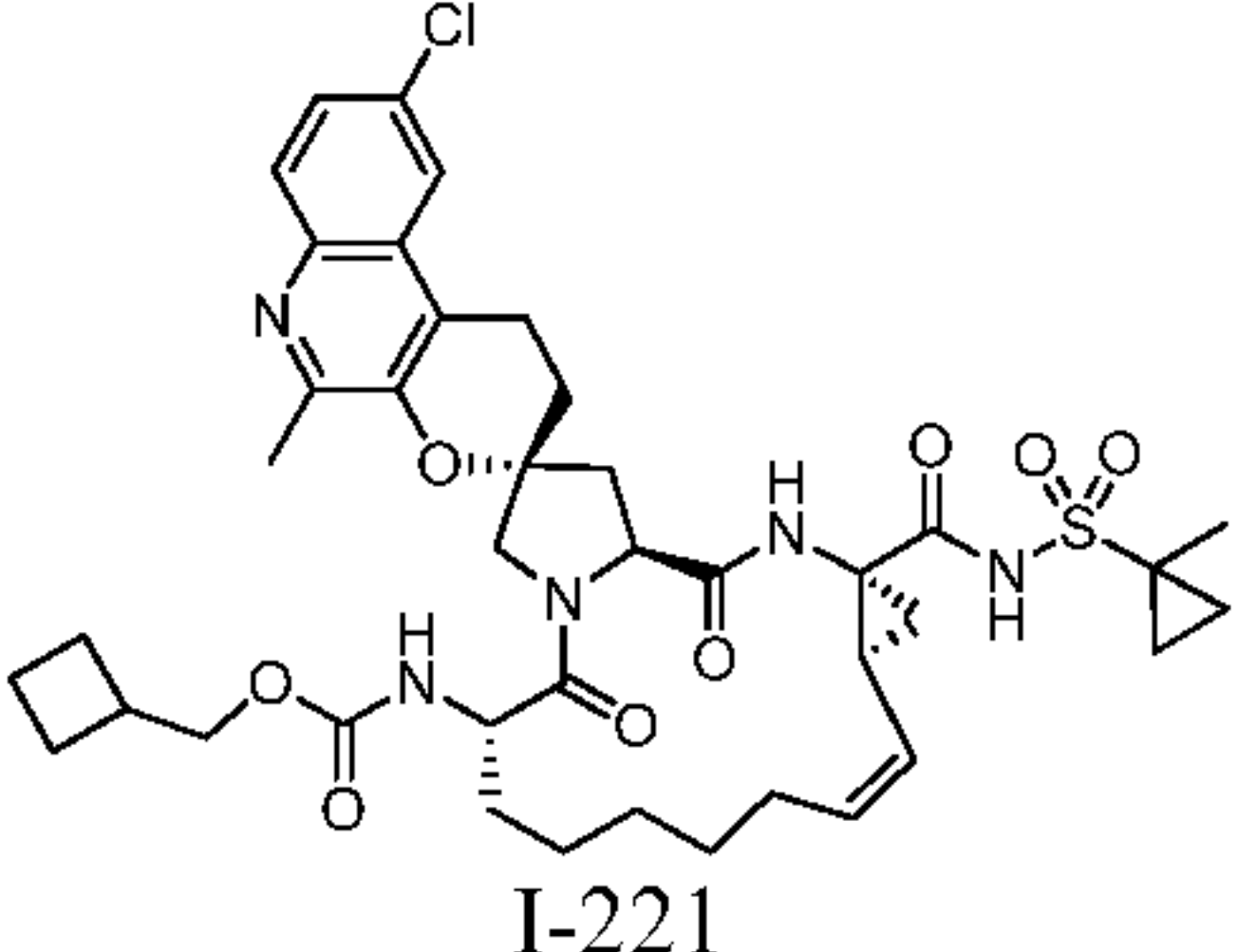
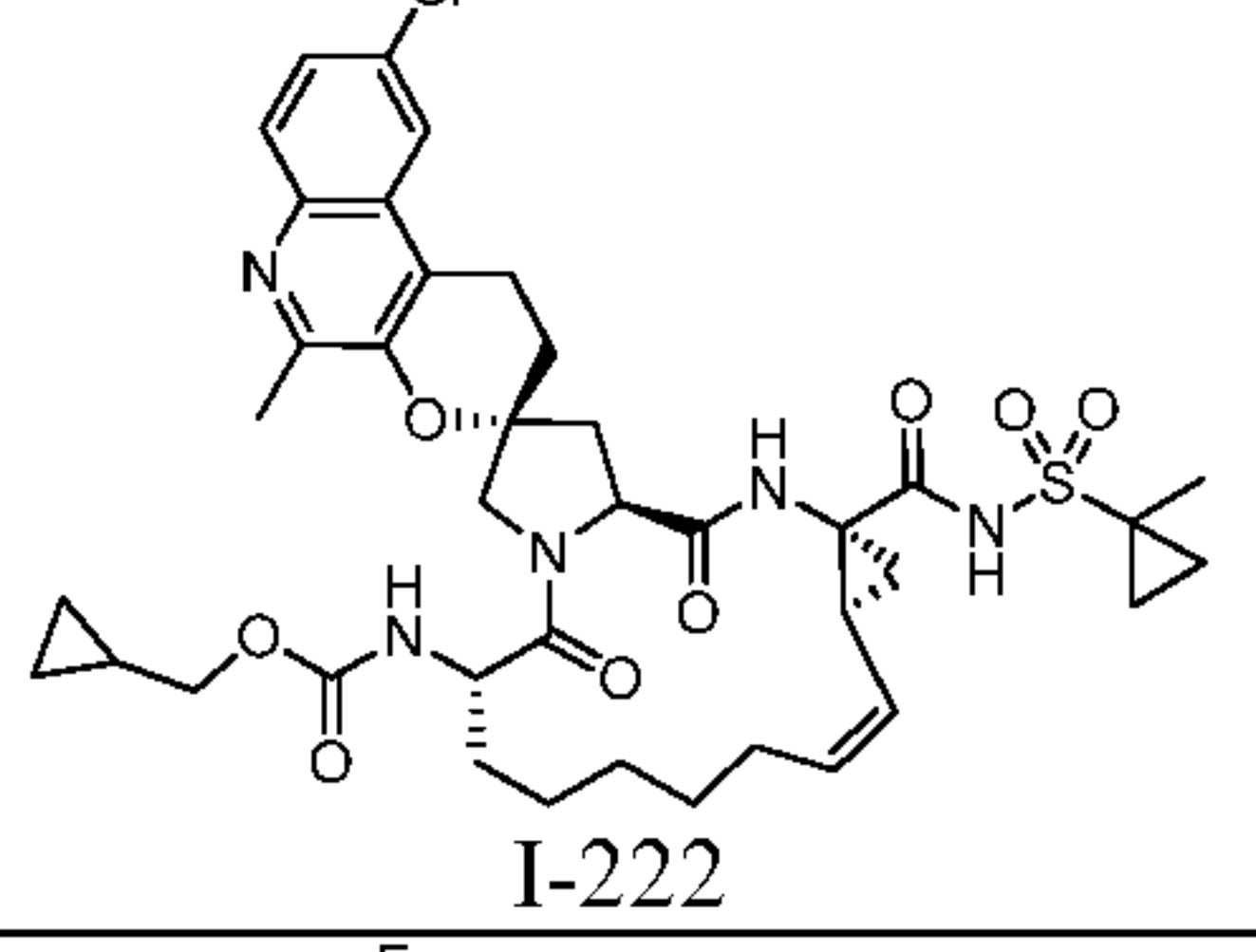
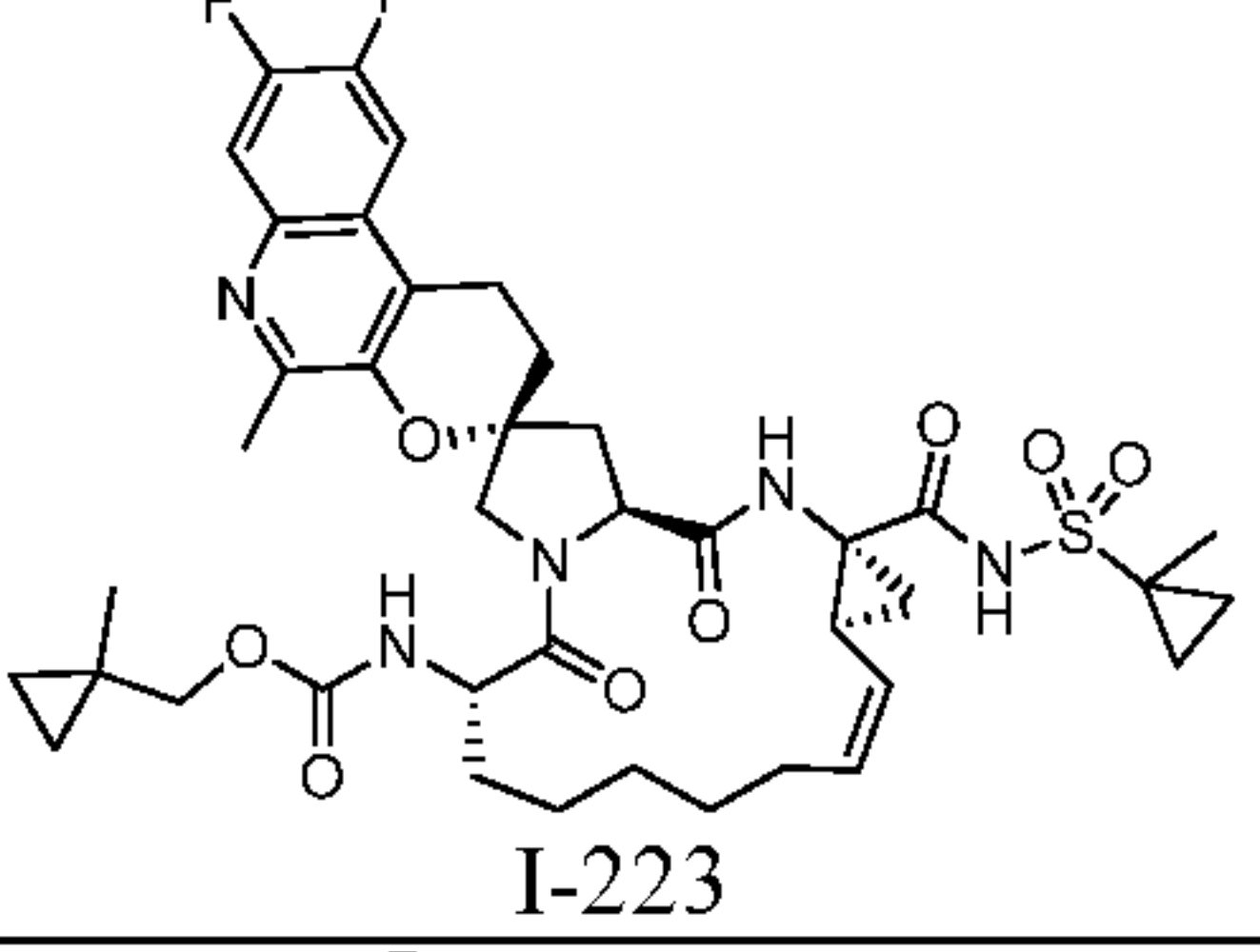
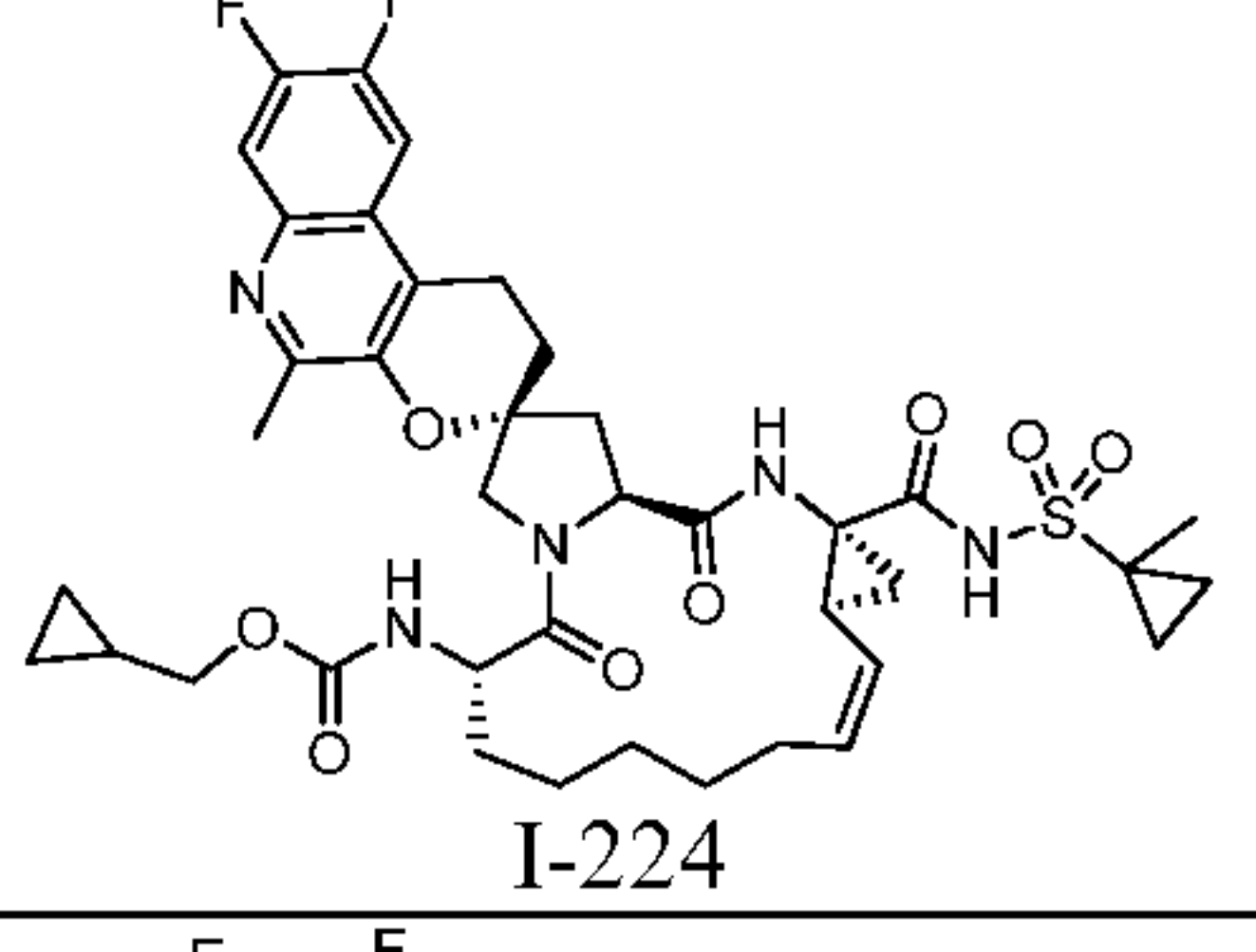
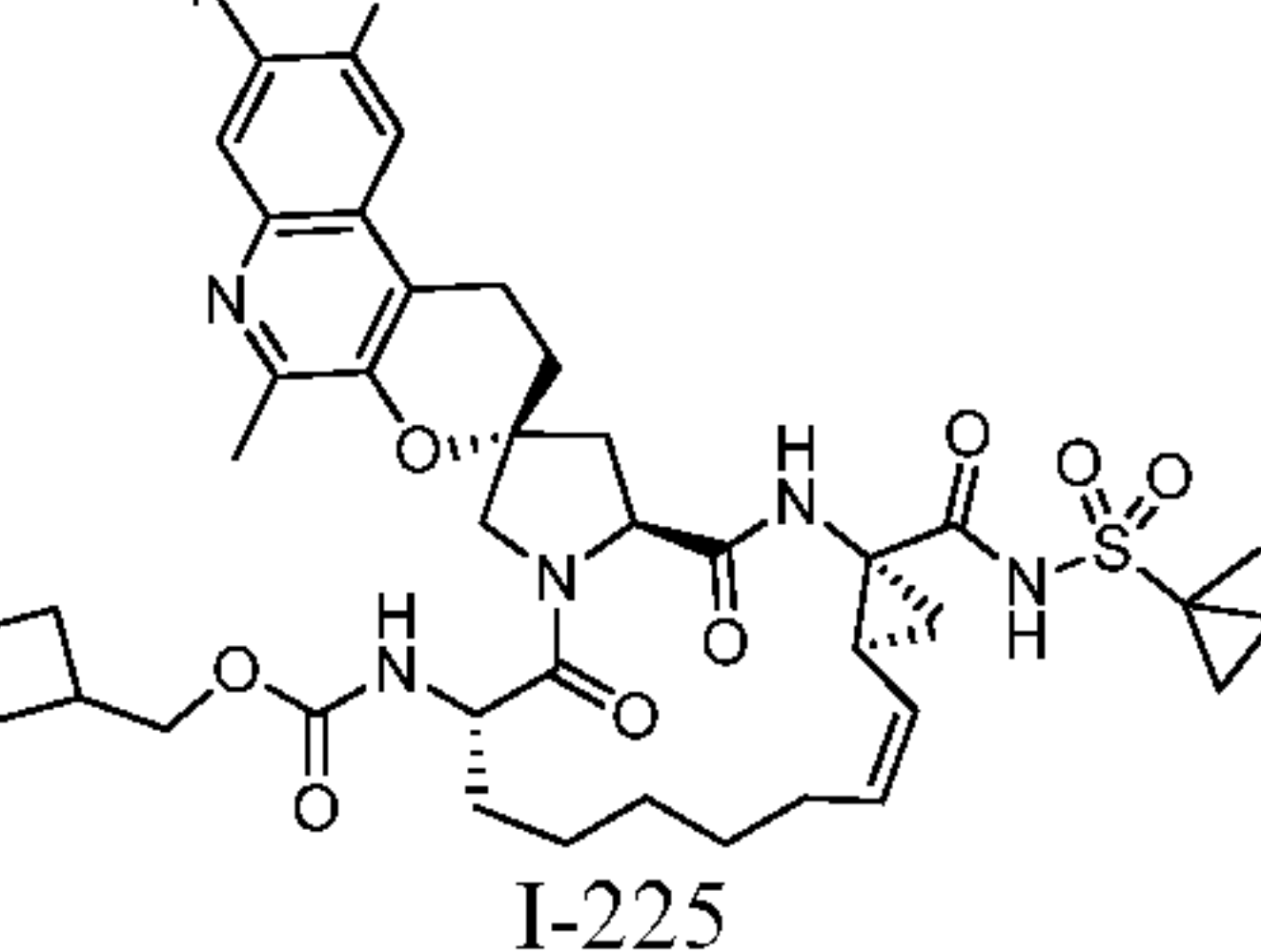
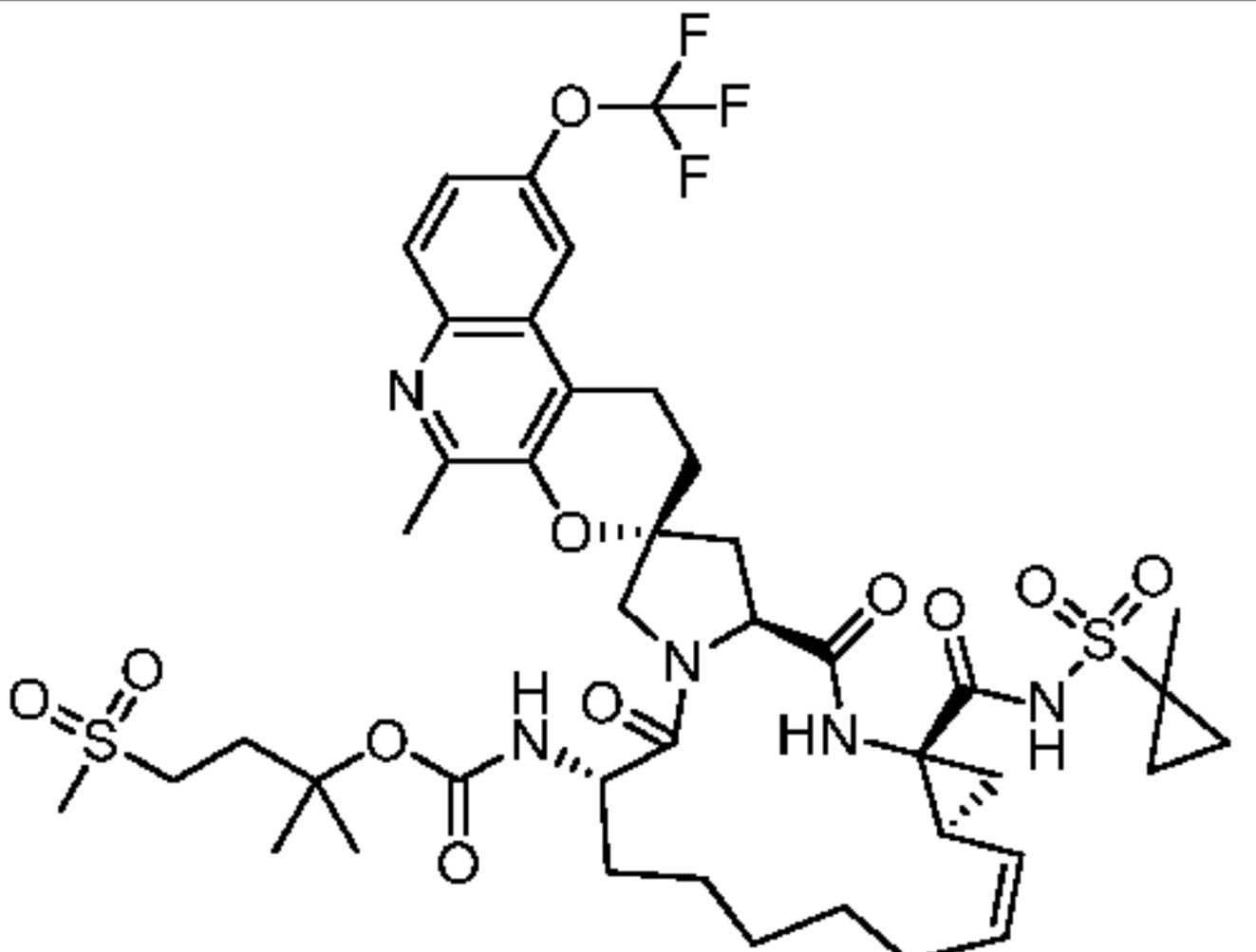
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
196	 I-196	4,4-difluorocyclohexyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	812.5
197	 I-197	1,1,1-trifluoropropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	790.3
198	 I-198	3-methyloxetan-3-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	794.2
199	 I-199	cyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	778.2 (K+ salt)
200	 I-200	2-methylcyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	806.2 (K+ salt)

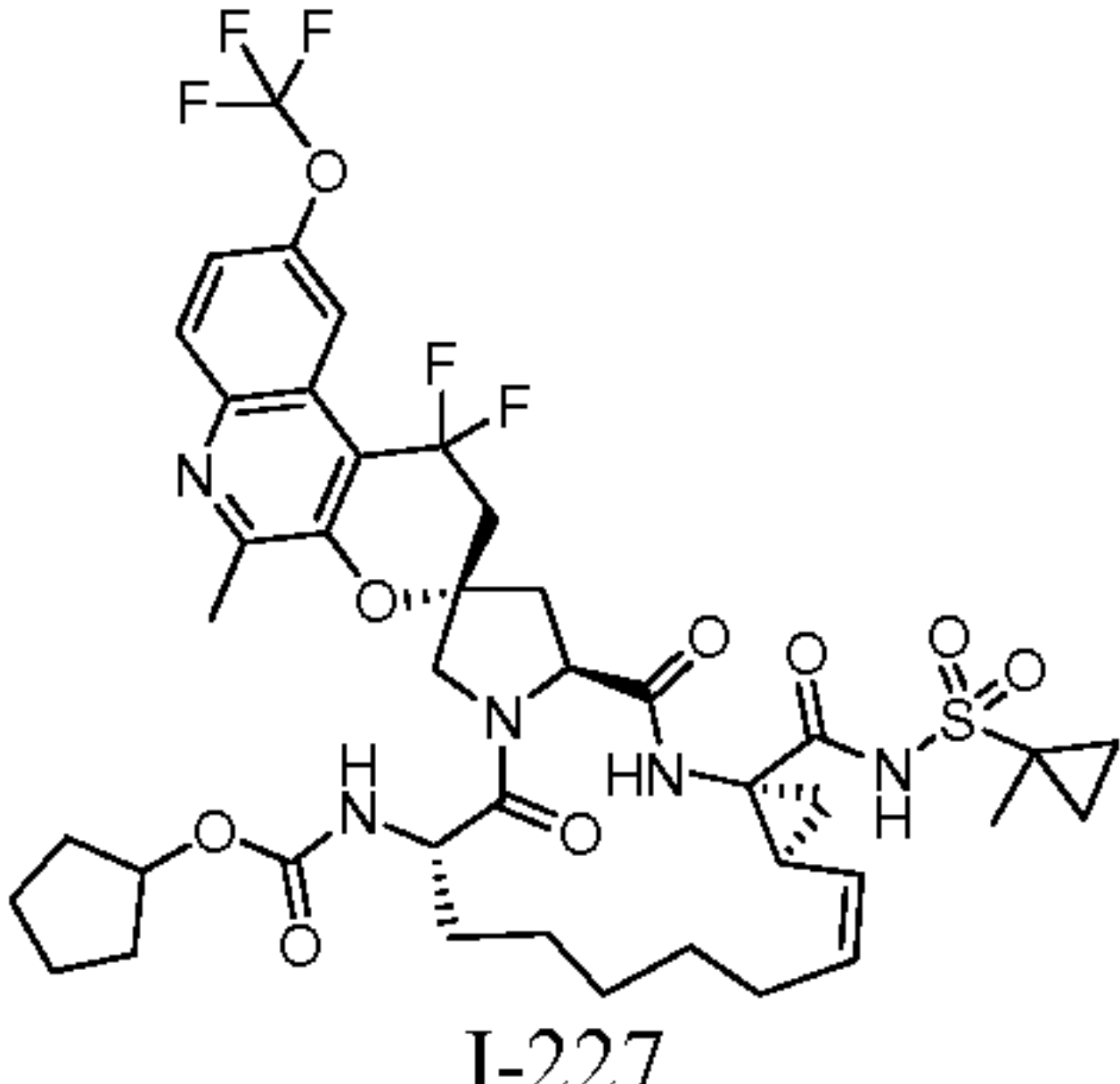
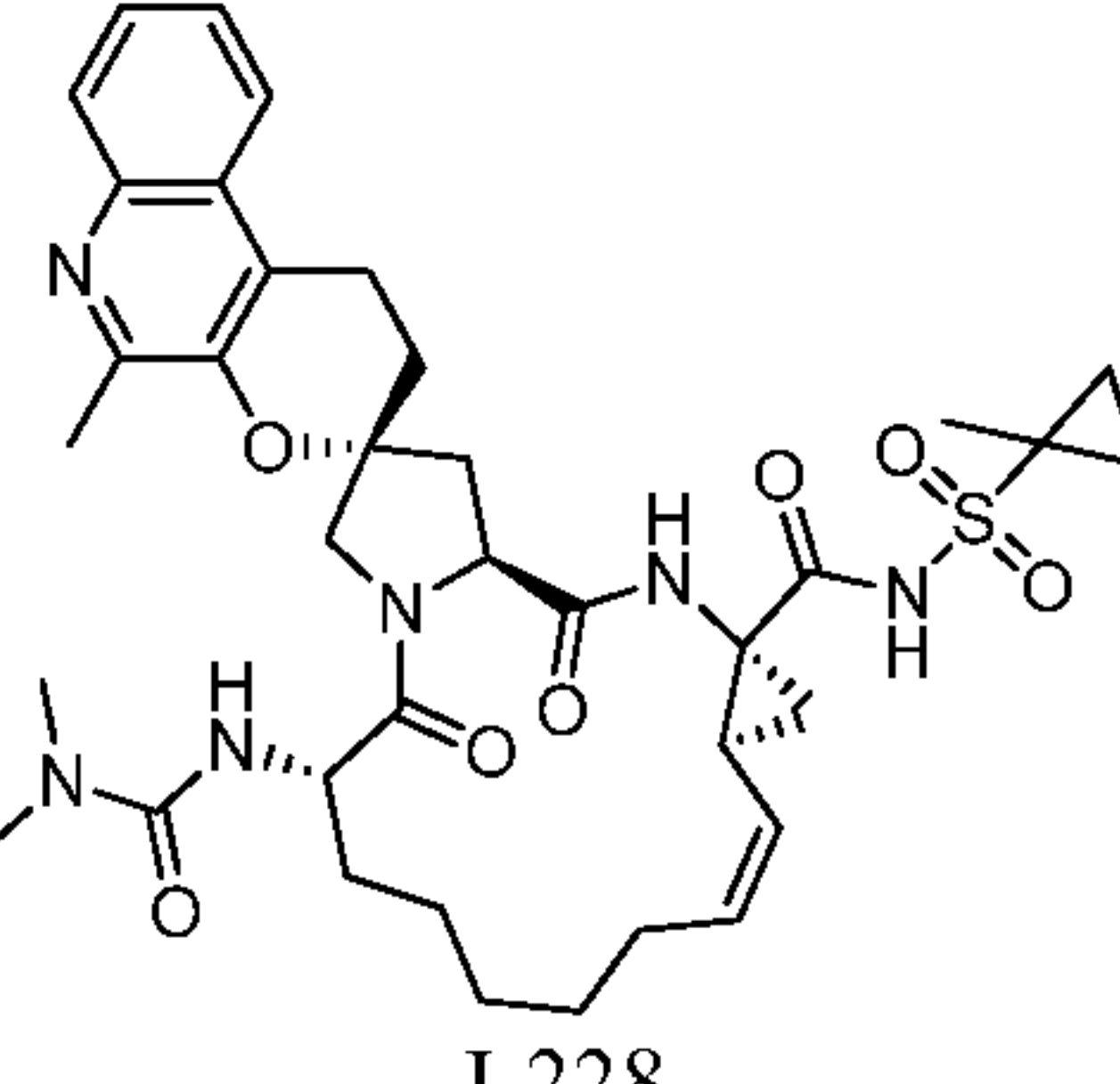
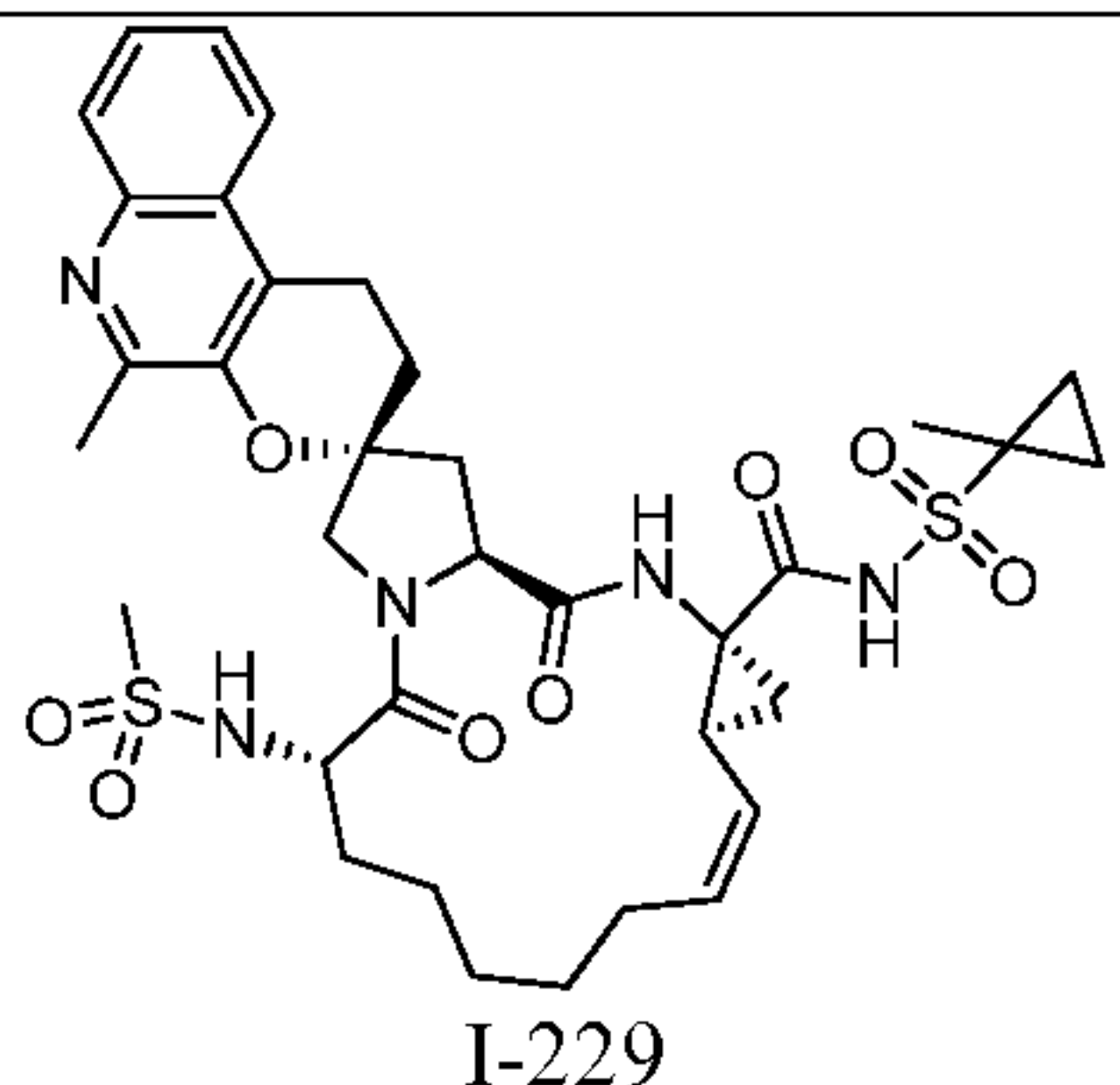
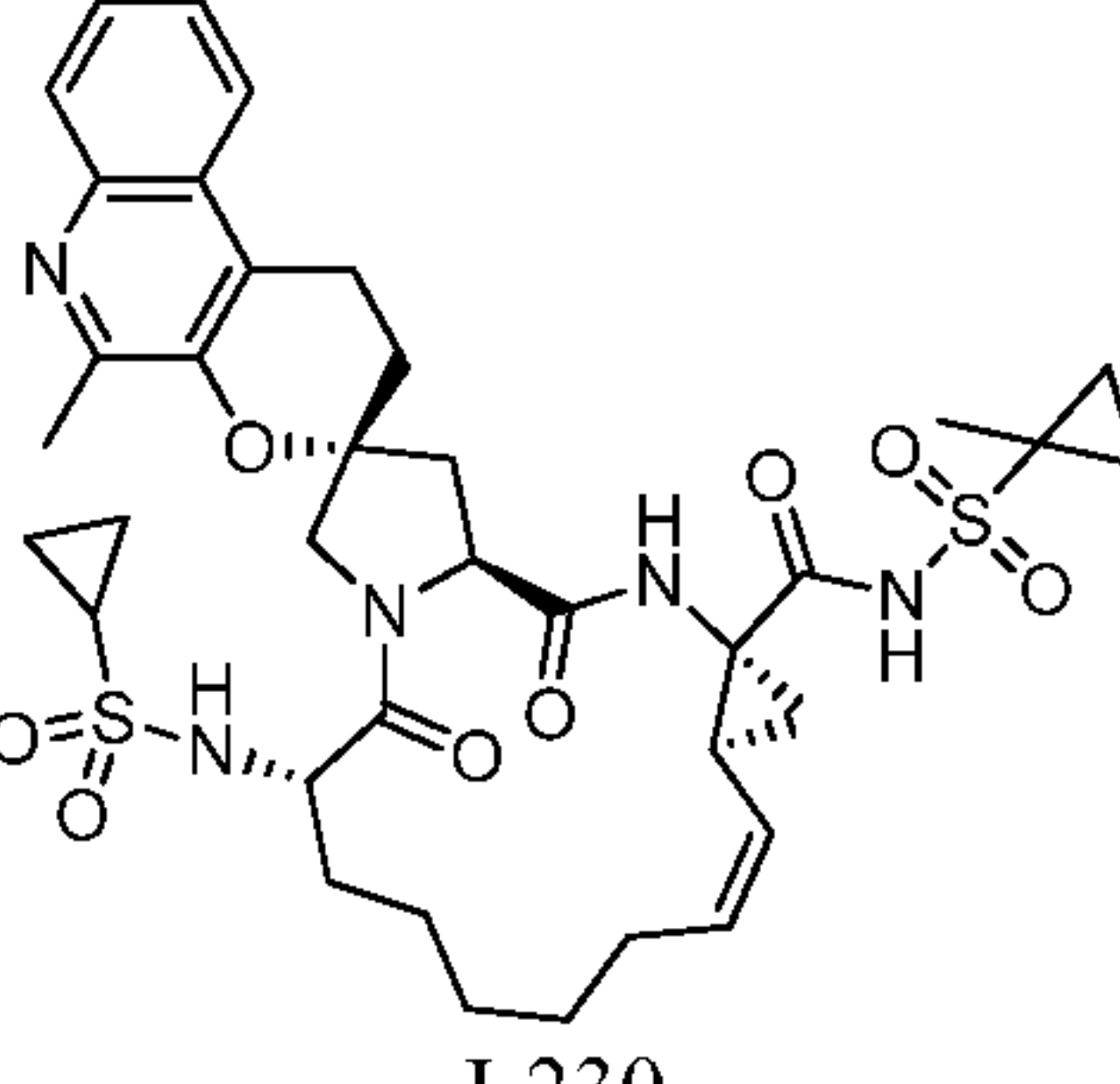
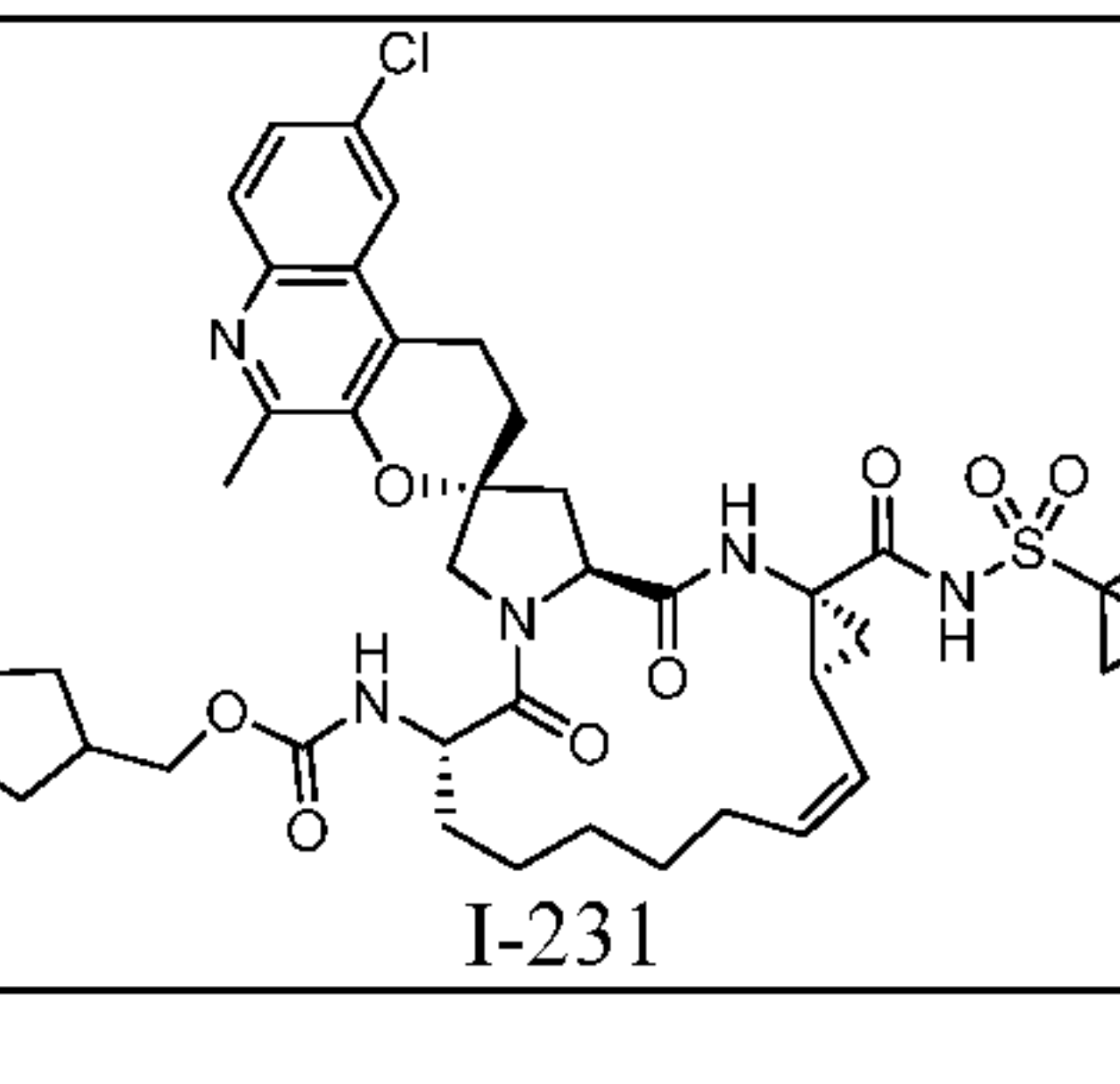
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
201	 I-201	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8',9'-difluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	786.2 (K+ salt)
202	 I-202	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8',9'-difluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	800.2 (K+ salt)
203	 I-203	cyclohexyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8',9'-difluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	812.2 (K+ salt)
204	 I-204	cyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8',9'-difluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	784.2 (K+ salt)
205	 I-205	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	794.2 (K+ salt)

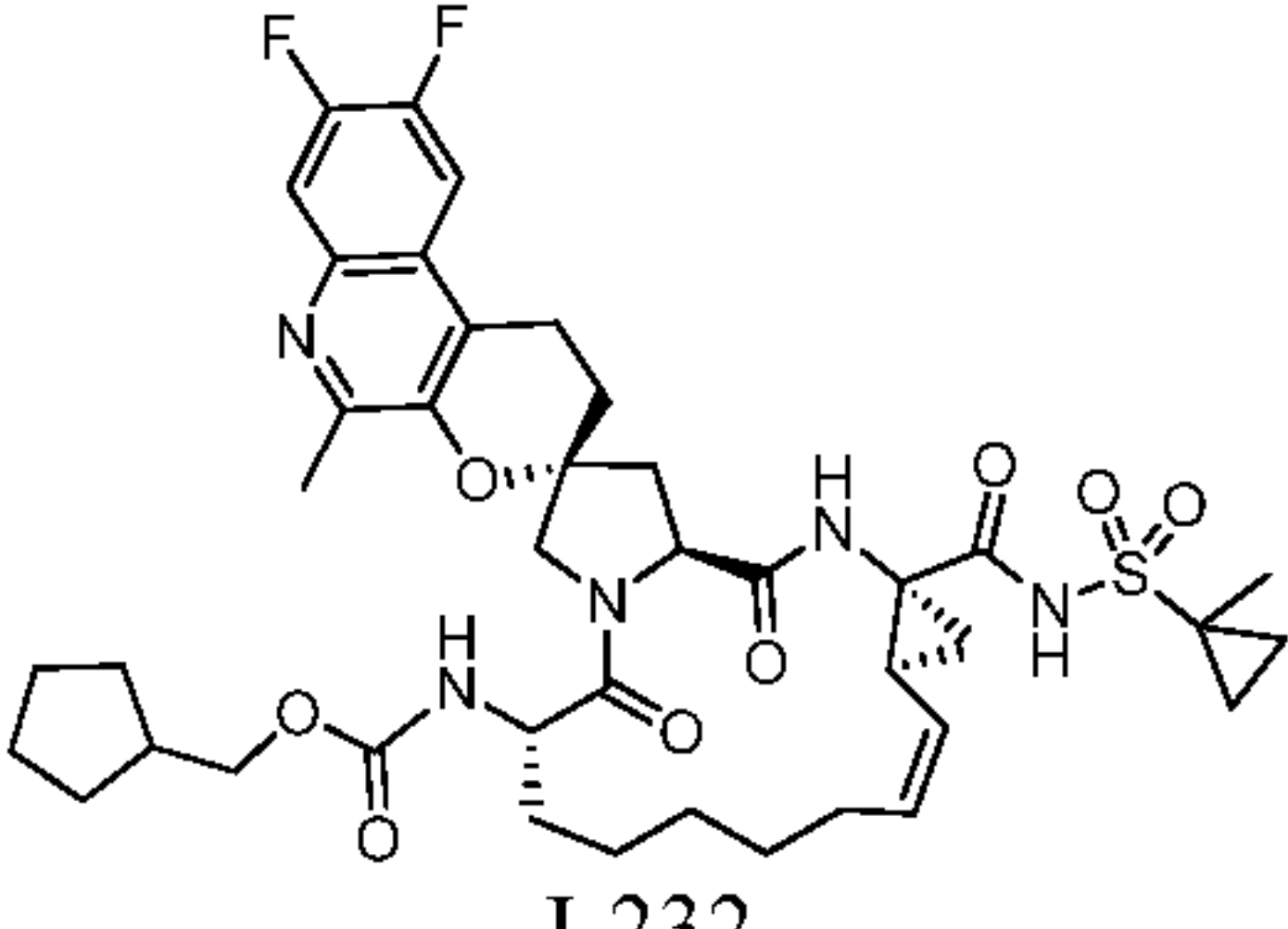
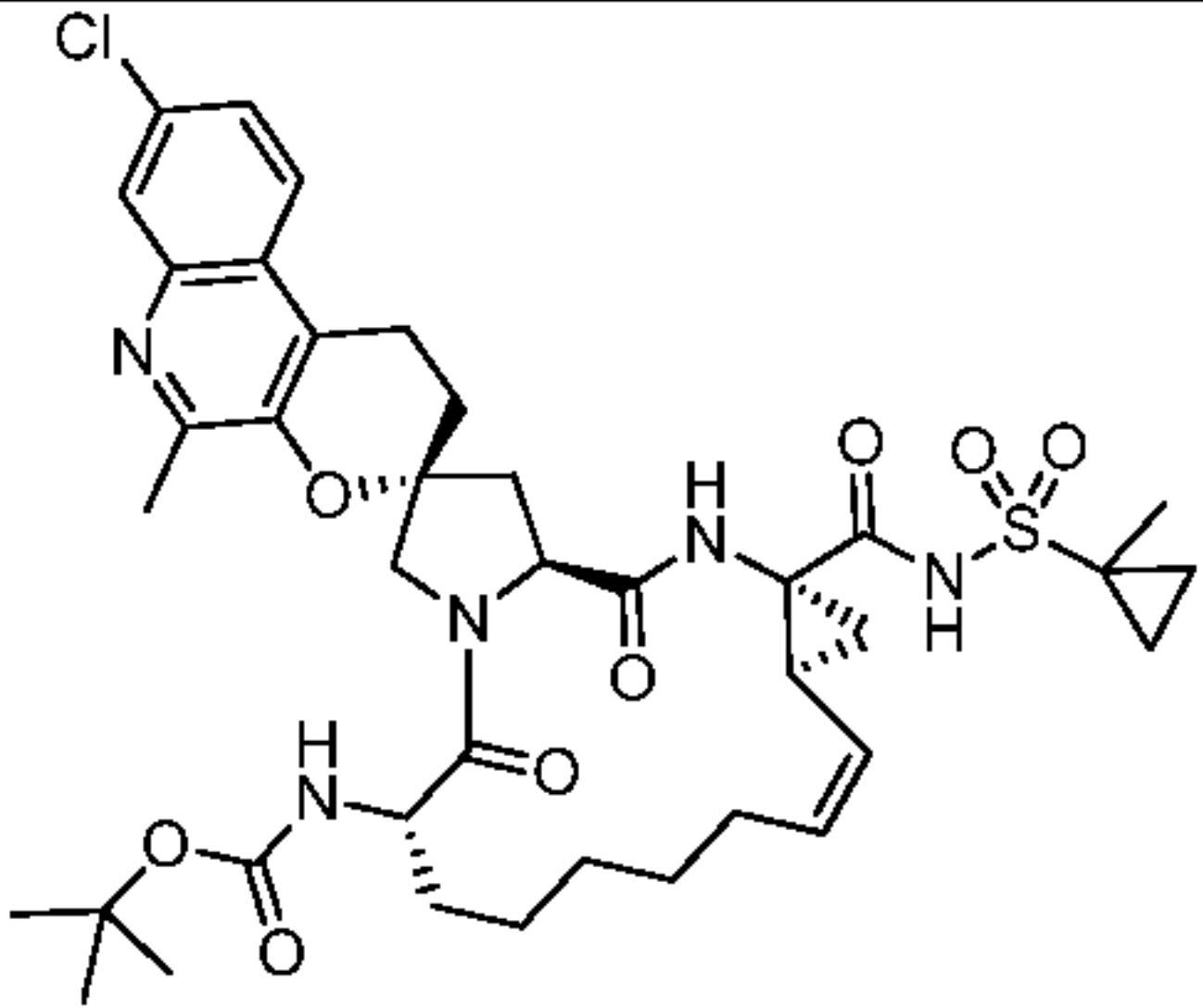
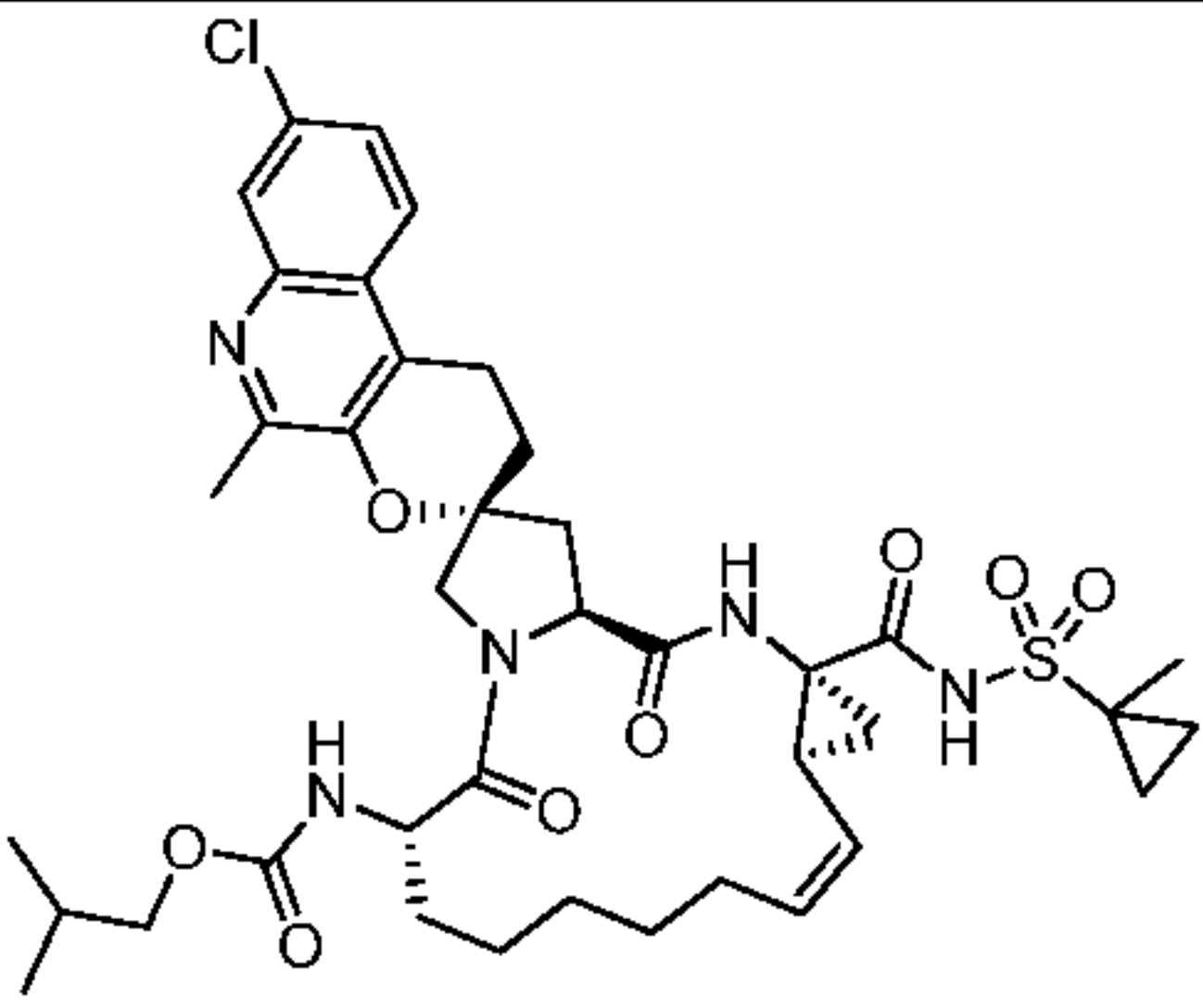
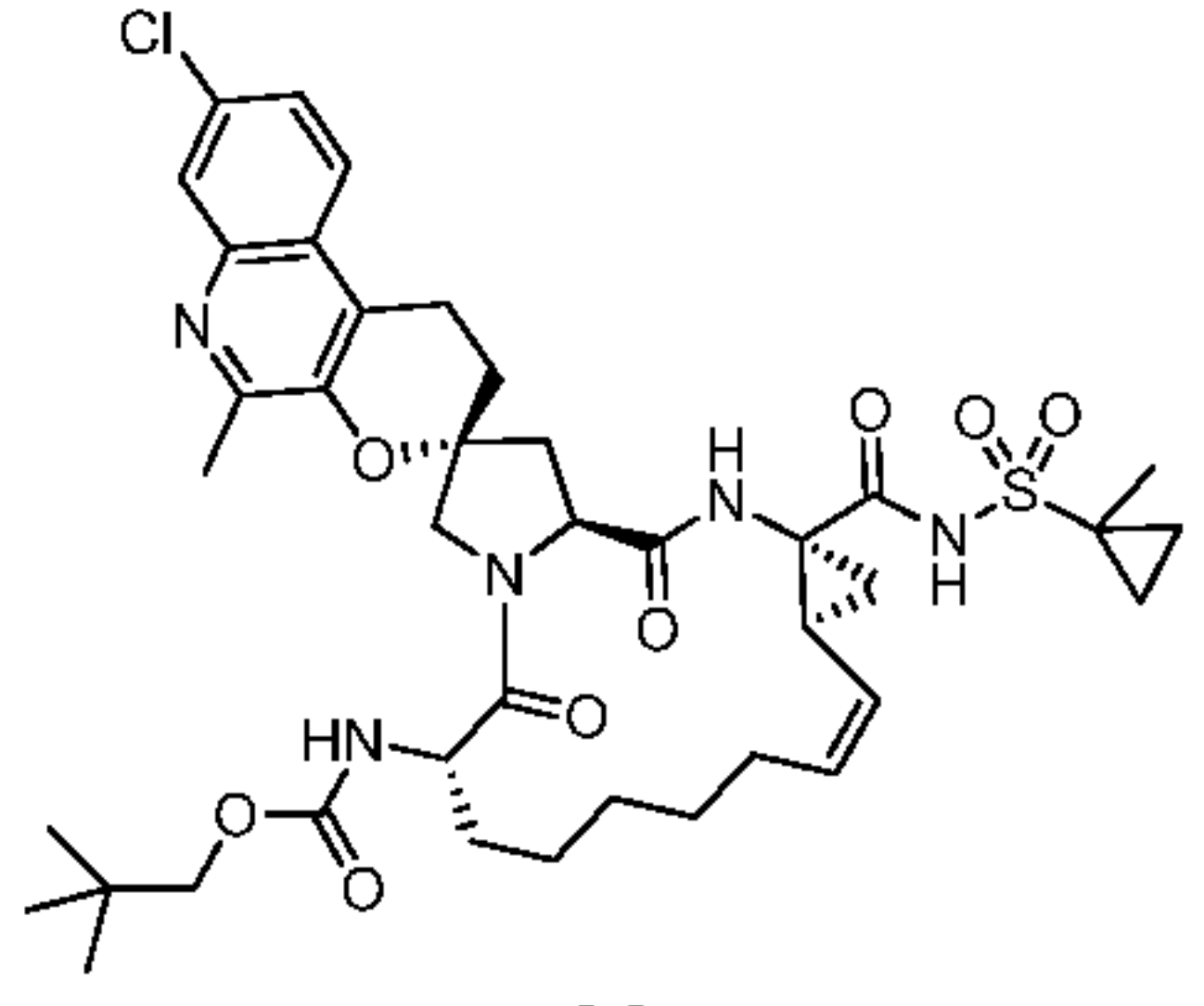
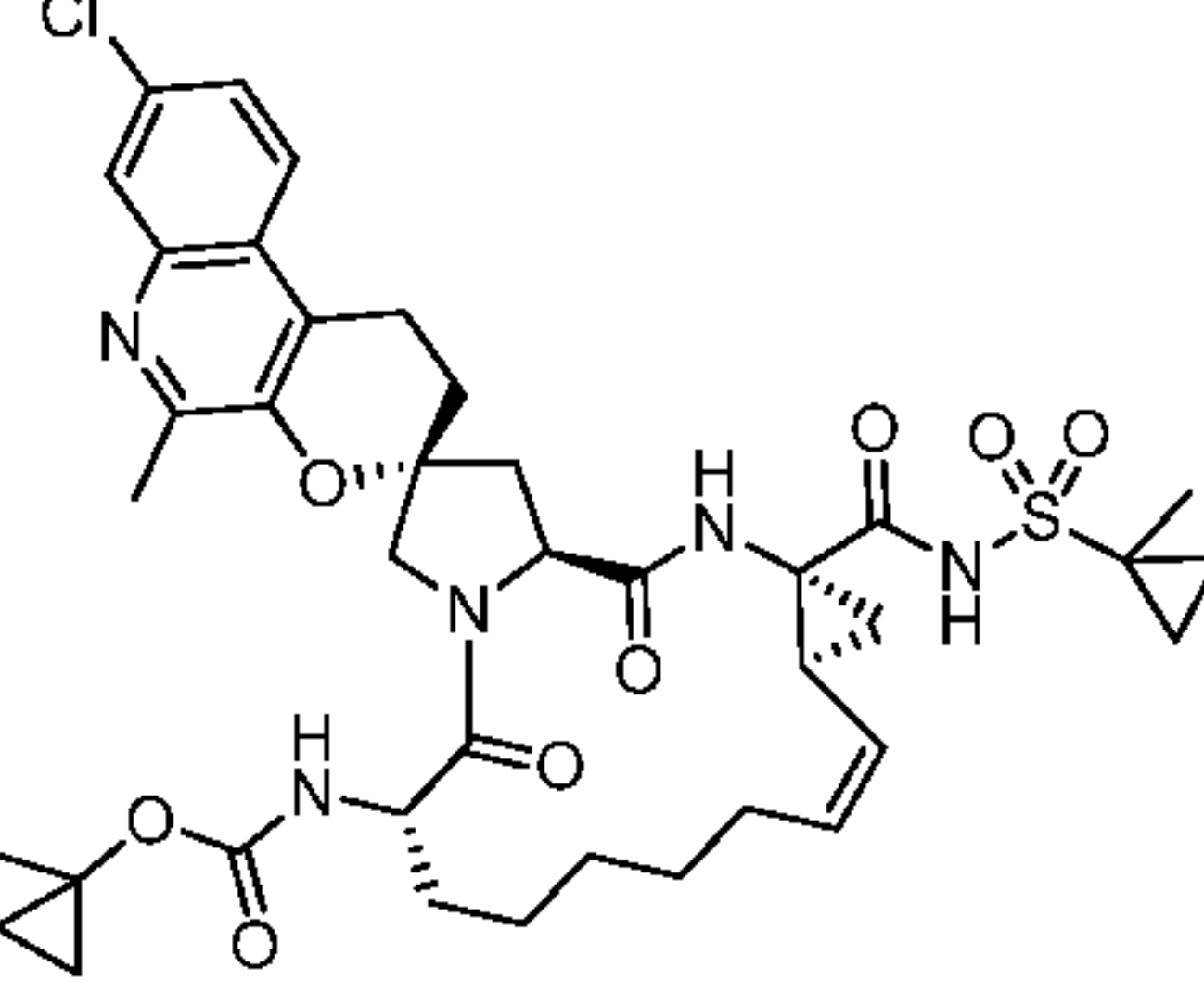
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
206	 I-206	cyclohexyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	9	806.2 (K+ salt)
207	 I-207	1-methoxy-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	1	864.2
208	 I-208	4-methoxy-2-methylbutan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	1	878.2
209	 I-209	1-methylcyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	1	860.2
210	 I-210	cyclopentyl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1',1'-difluoro-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	3	856.2

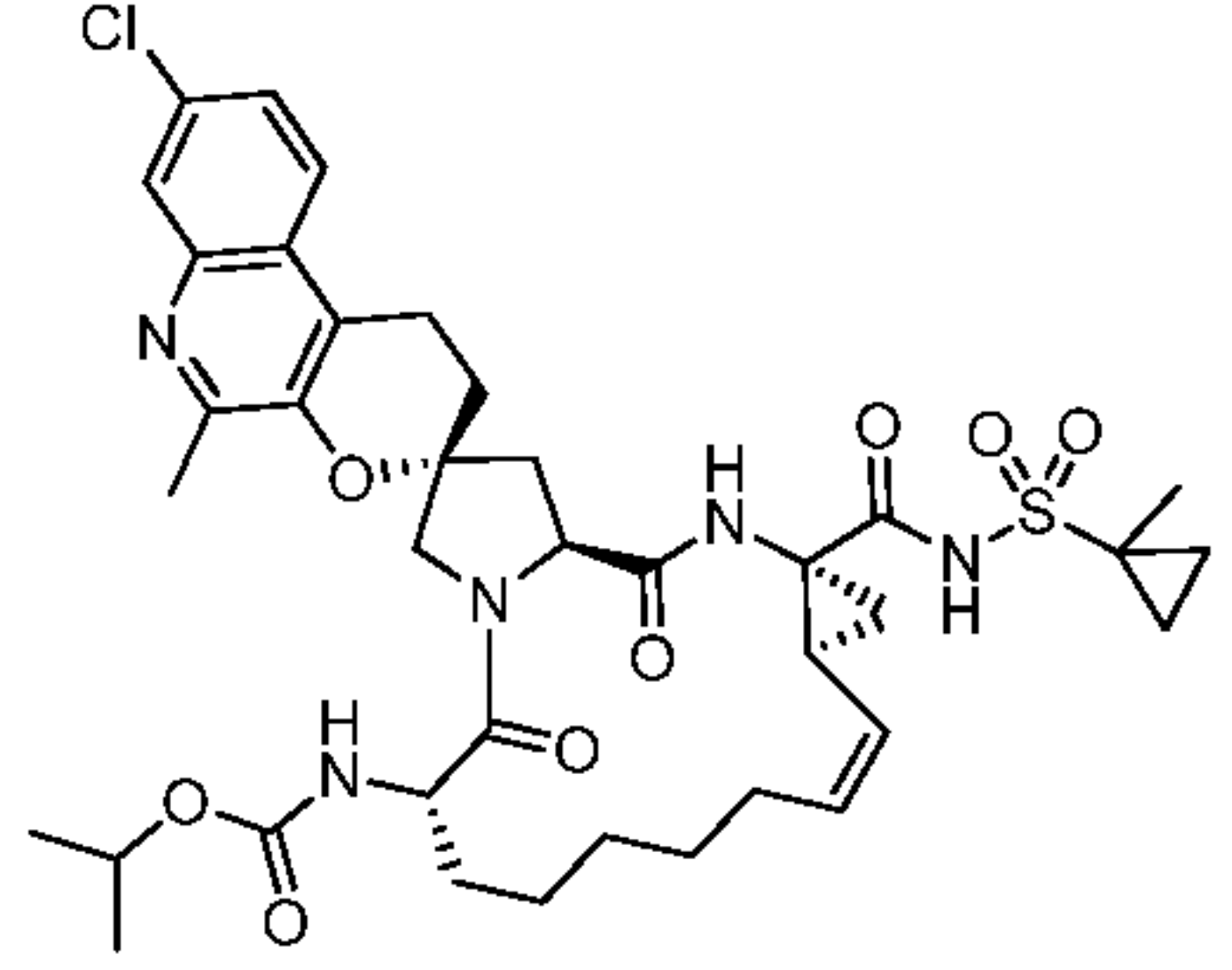
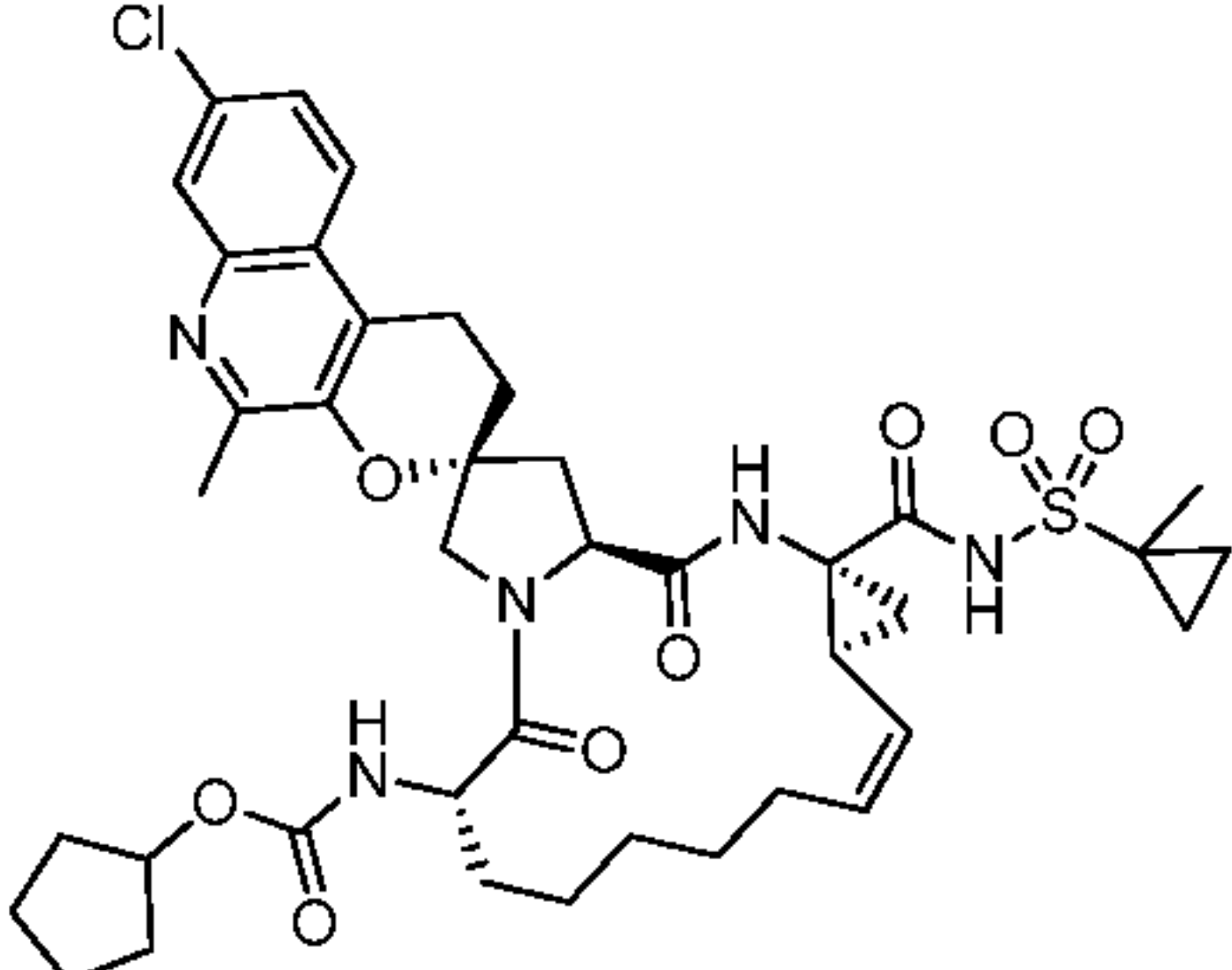
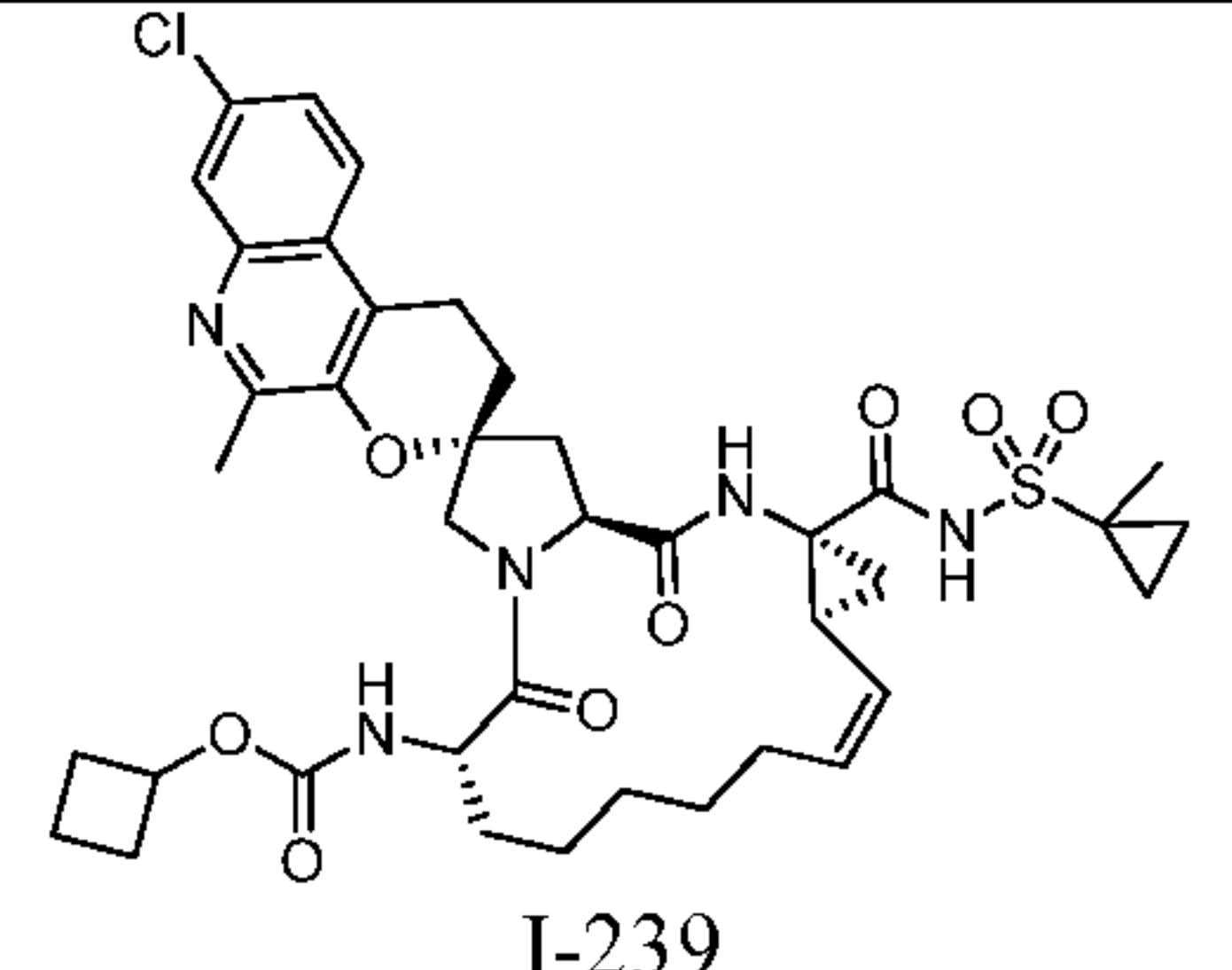
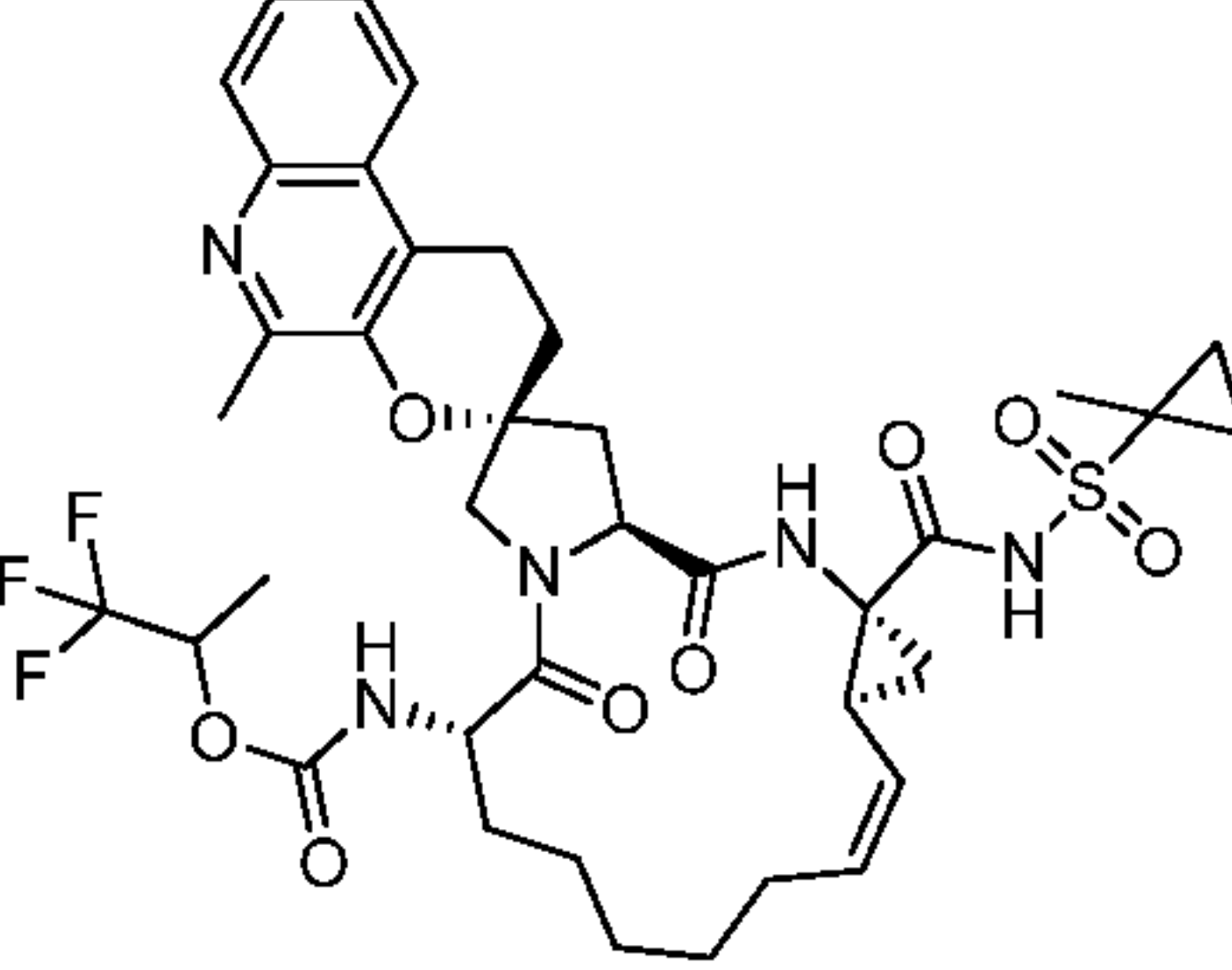
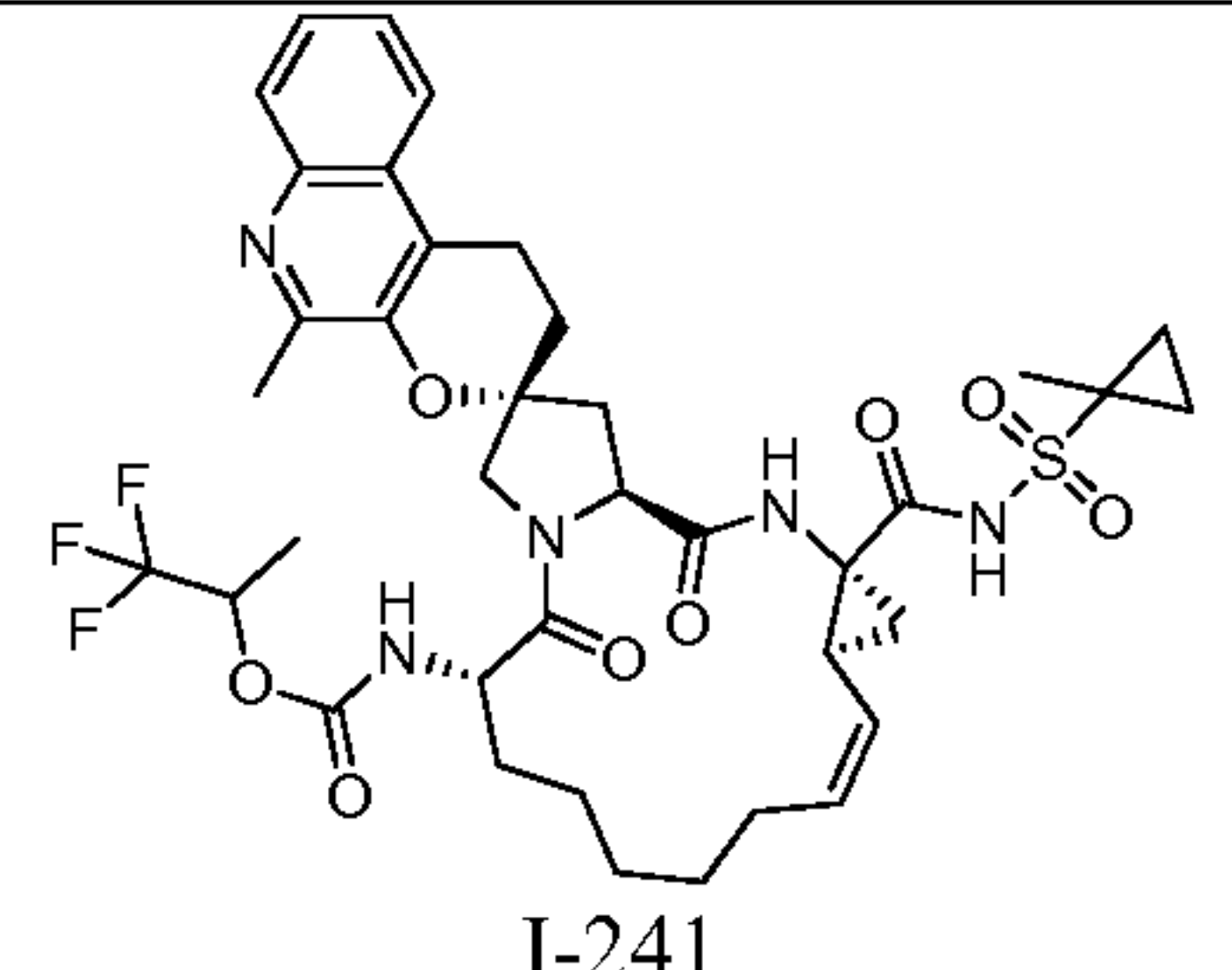
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
211	 I-211	2-methylpropyl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1',1'-difluoro-9'-methoxy-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	3	844.2
212	 I-212	1,1'-bi(cyclopropyl)-1-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	804.2 (K+ salt)
213	 I-213	cyclobutylmethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	792.2 (K+ salt)
214	 I-214	(2 <i>R</i>)-3-methylbutan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	794.2 (K+ salt)
215	 I-215	(2 <i>S</i>)-3-methylbutan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	794.2 (K+ salt)

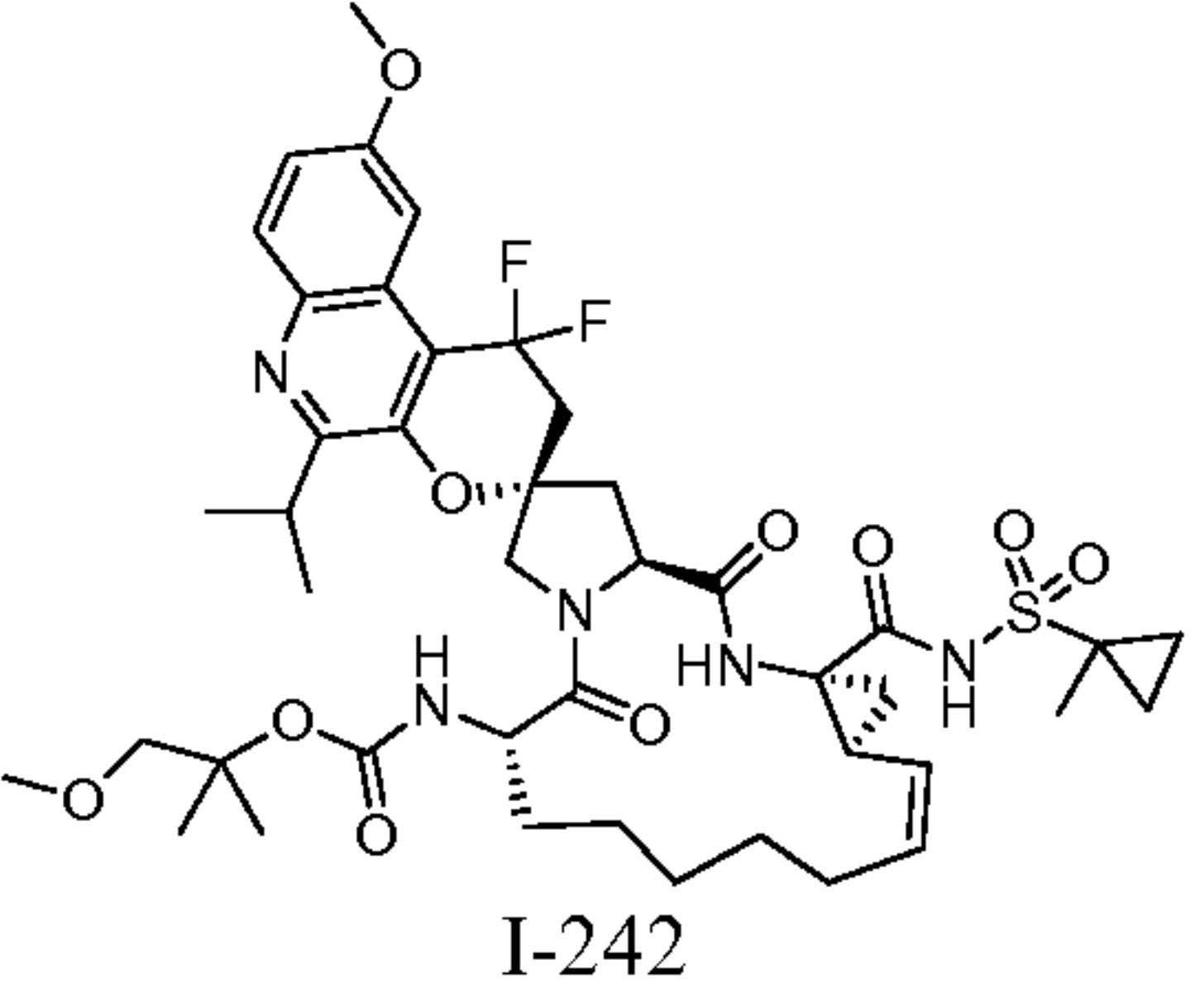
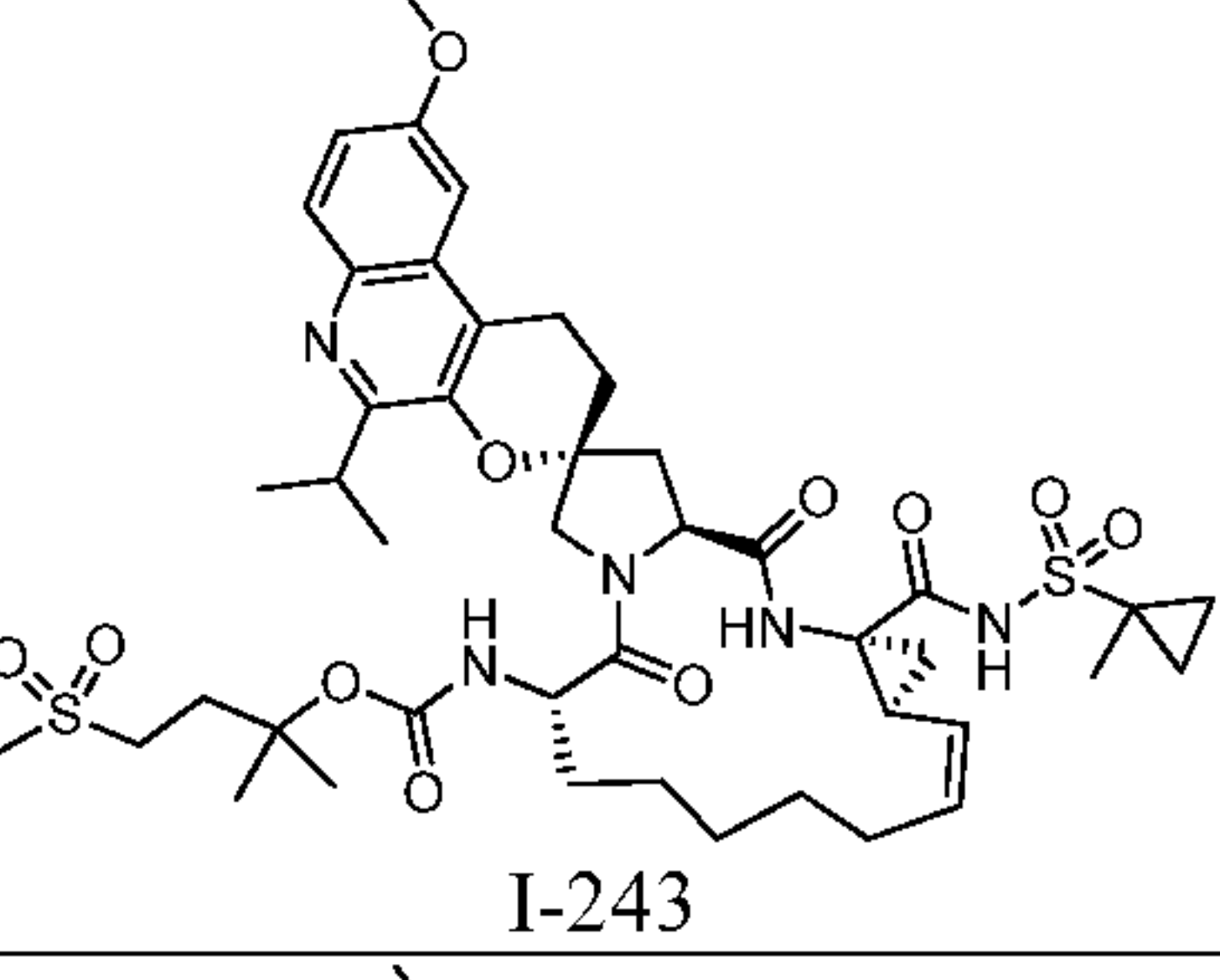
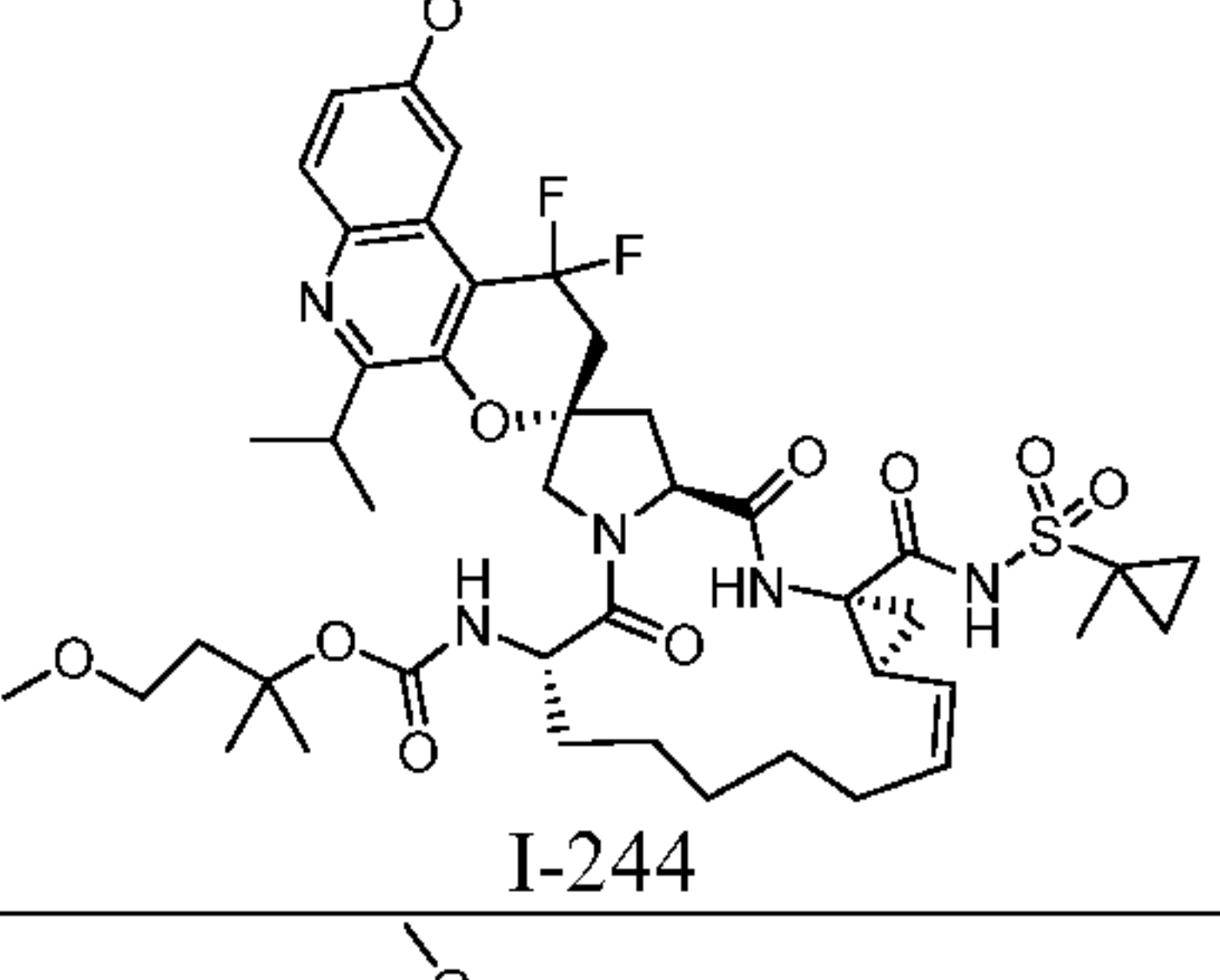
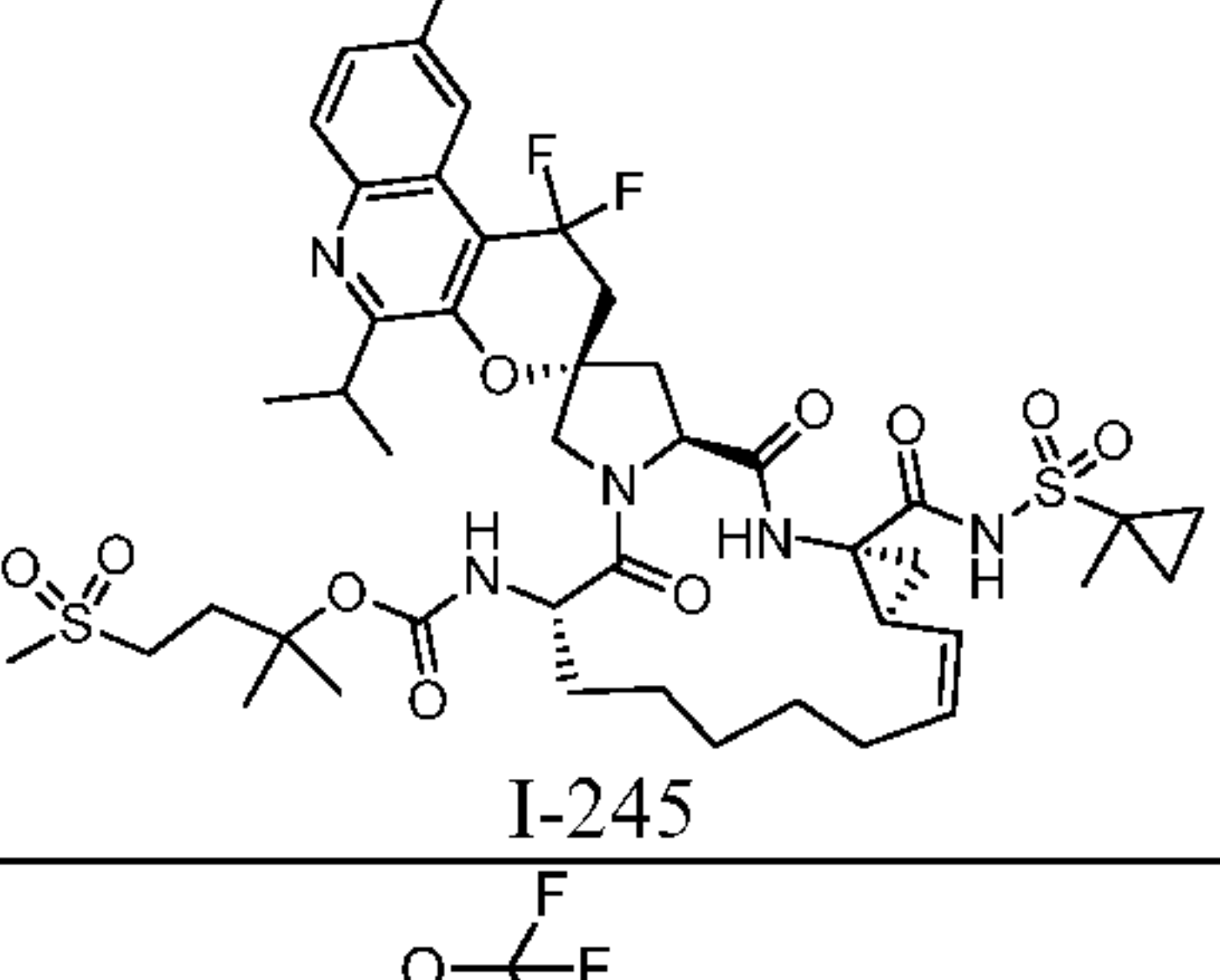
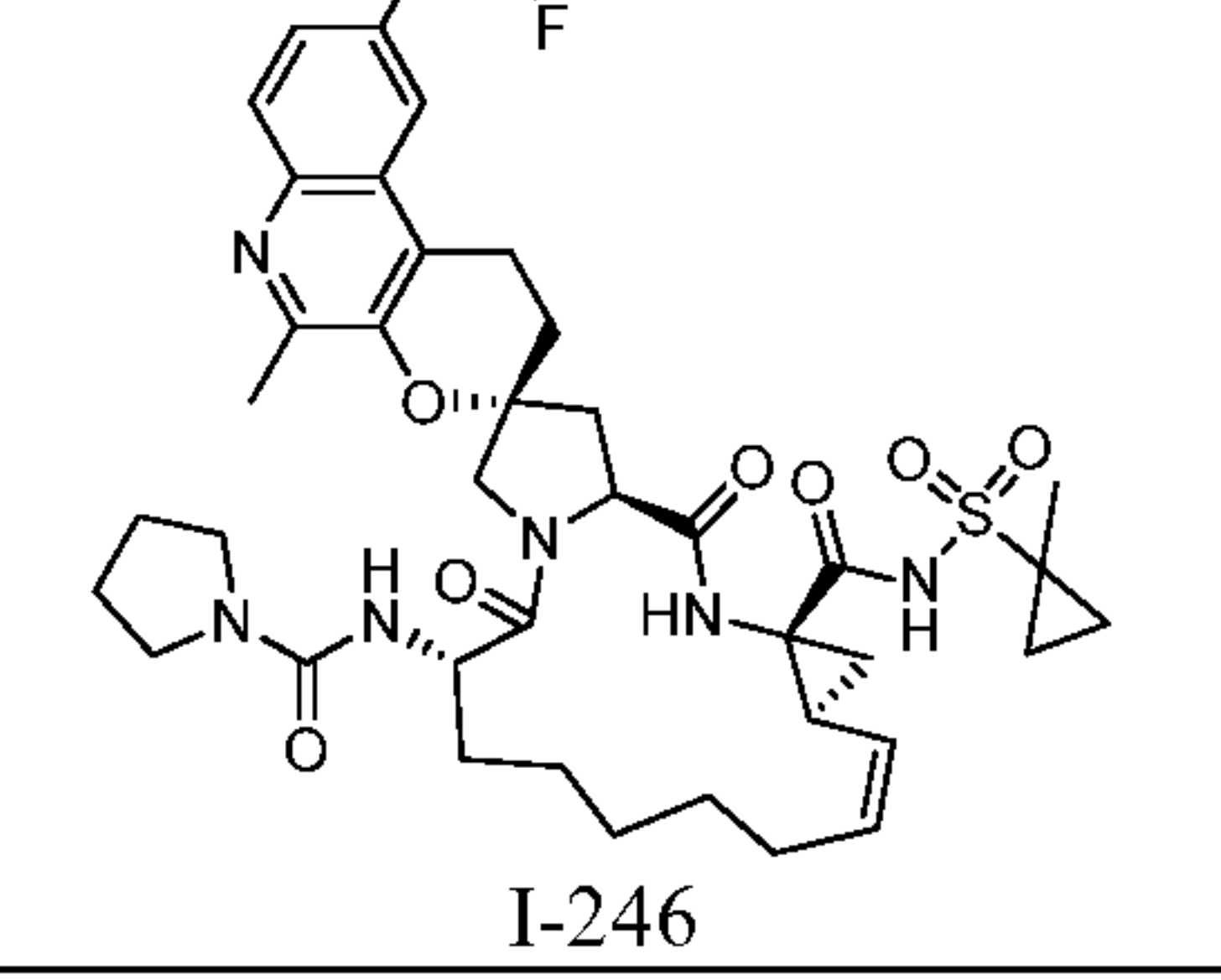
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
216	 I-216	1-methylcyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5, 35	832.2
217	 I-217	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5, 35	846.3
218	 I-218	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-fluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	768.2
219	 I-219	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-fluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	780.2
220	 I-220	<i>tert</i> -butyl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1',1'-difluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	870.2

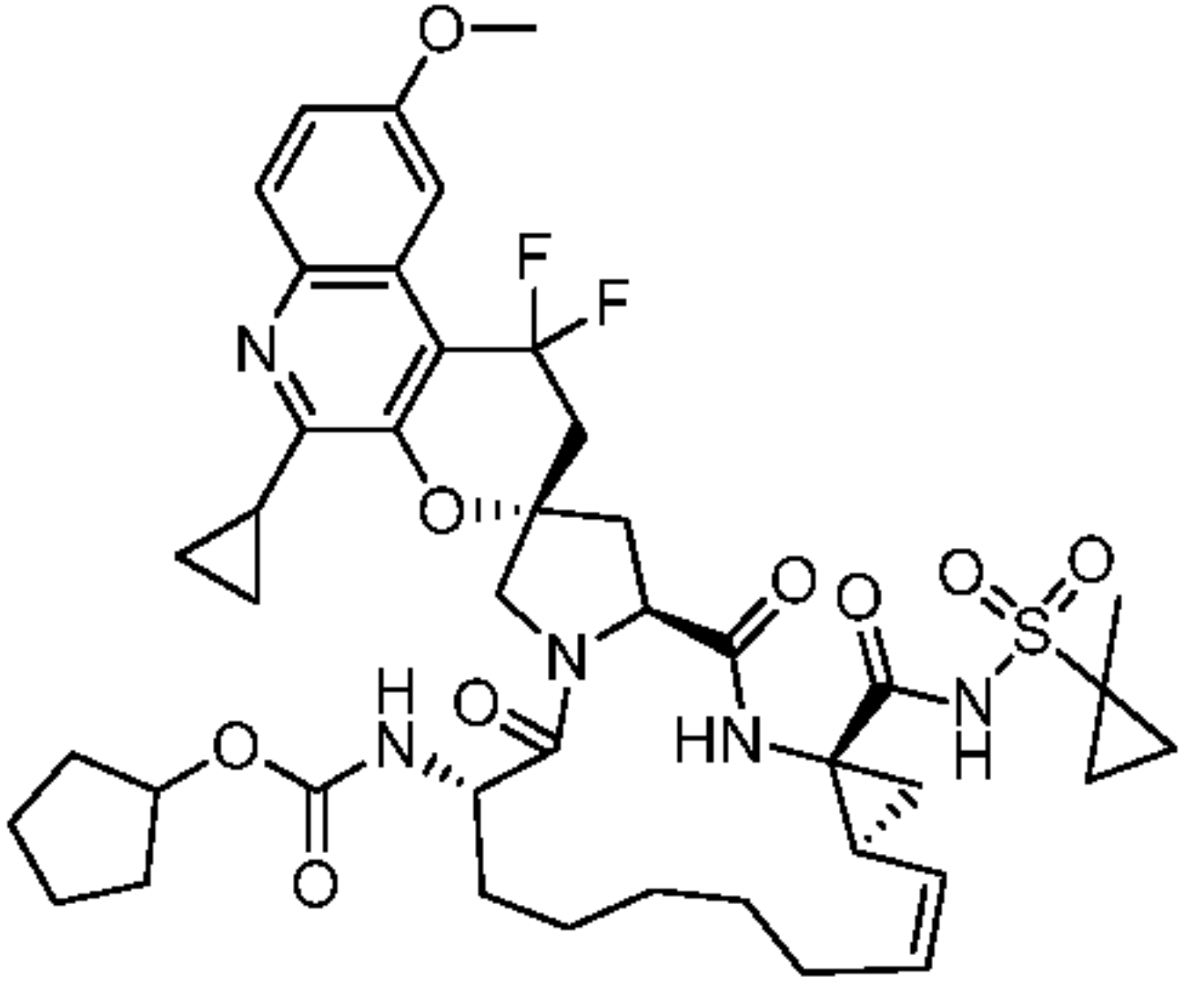
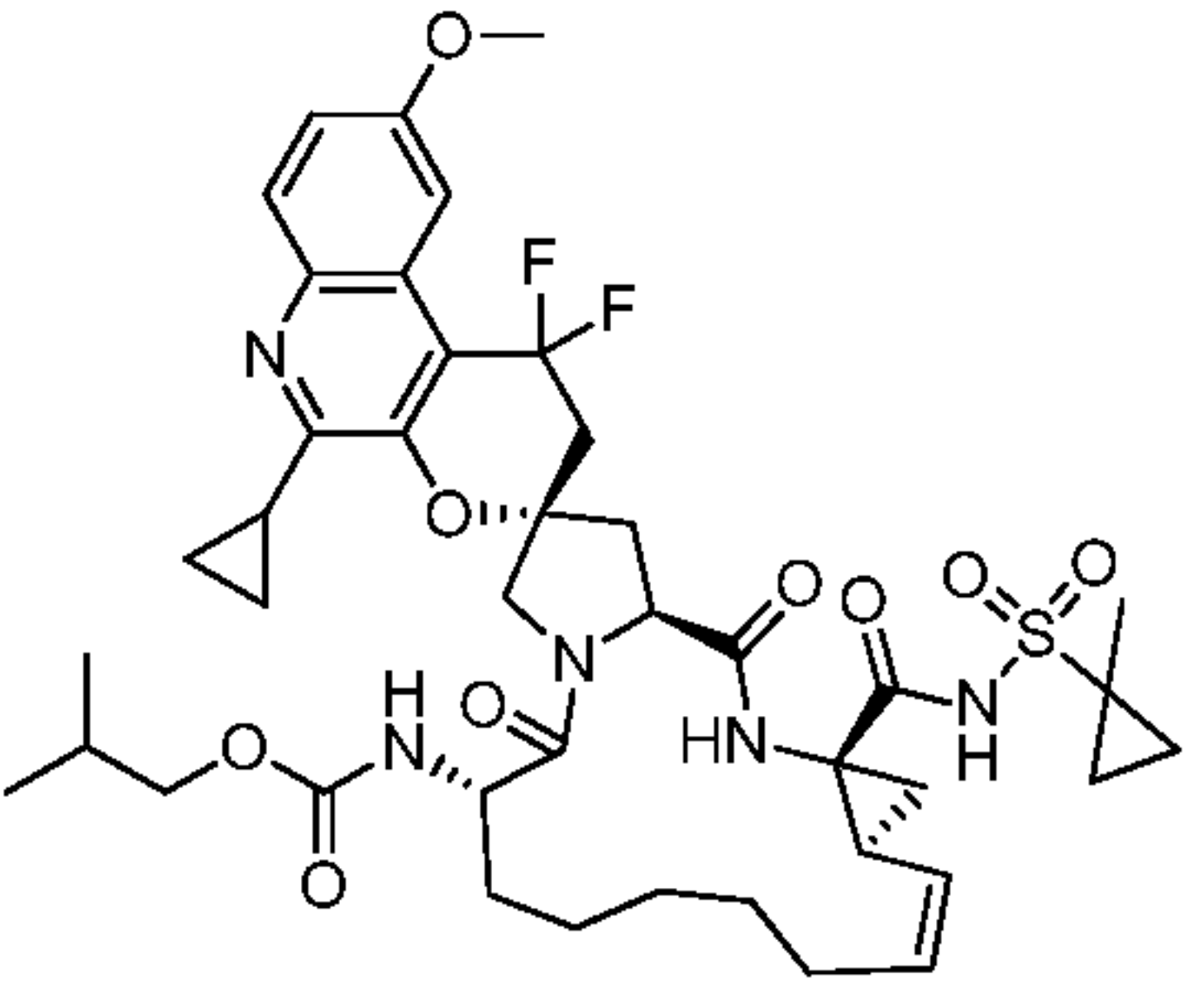
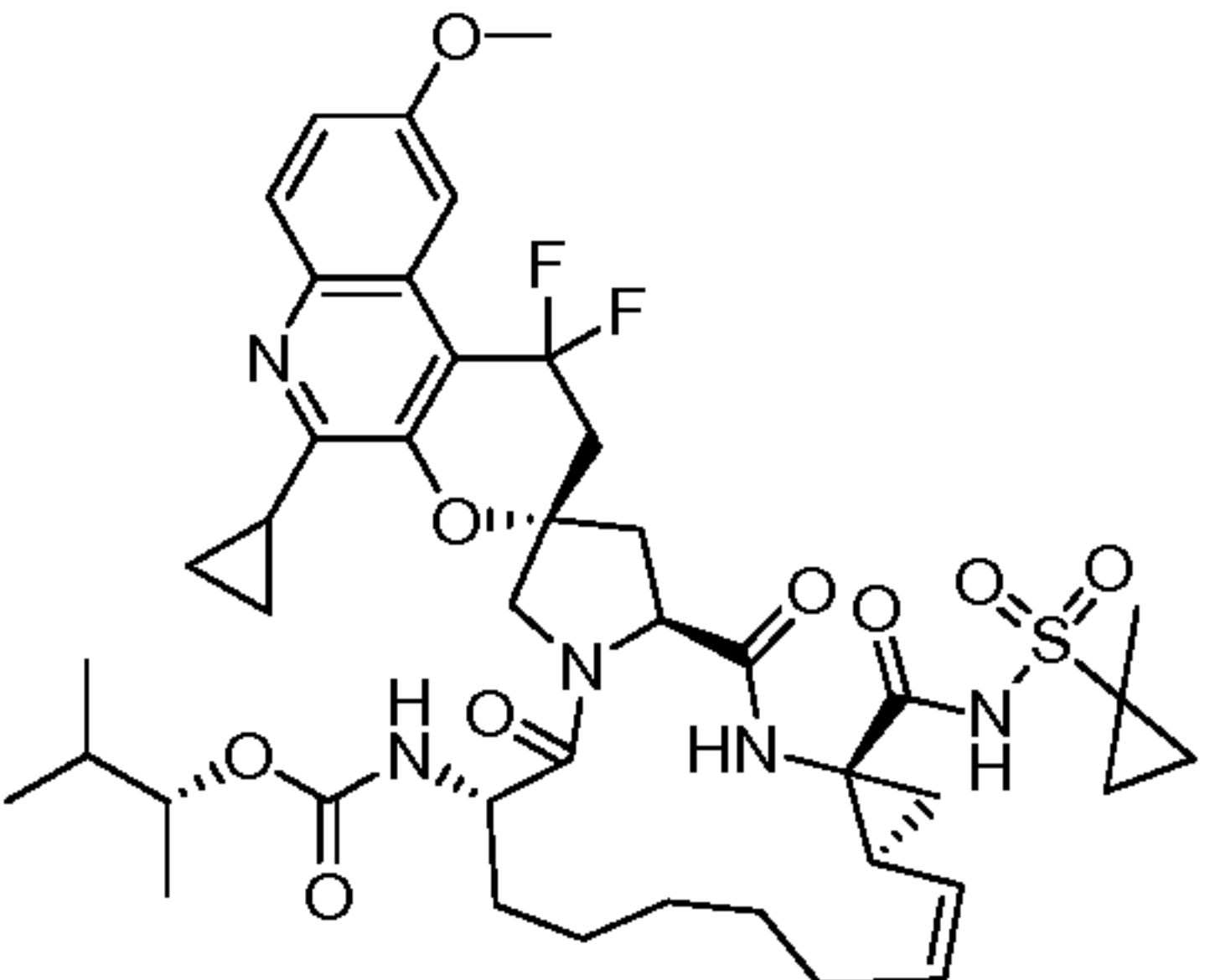
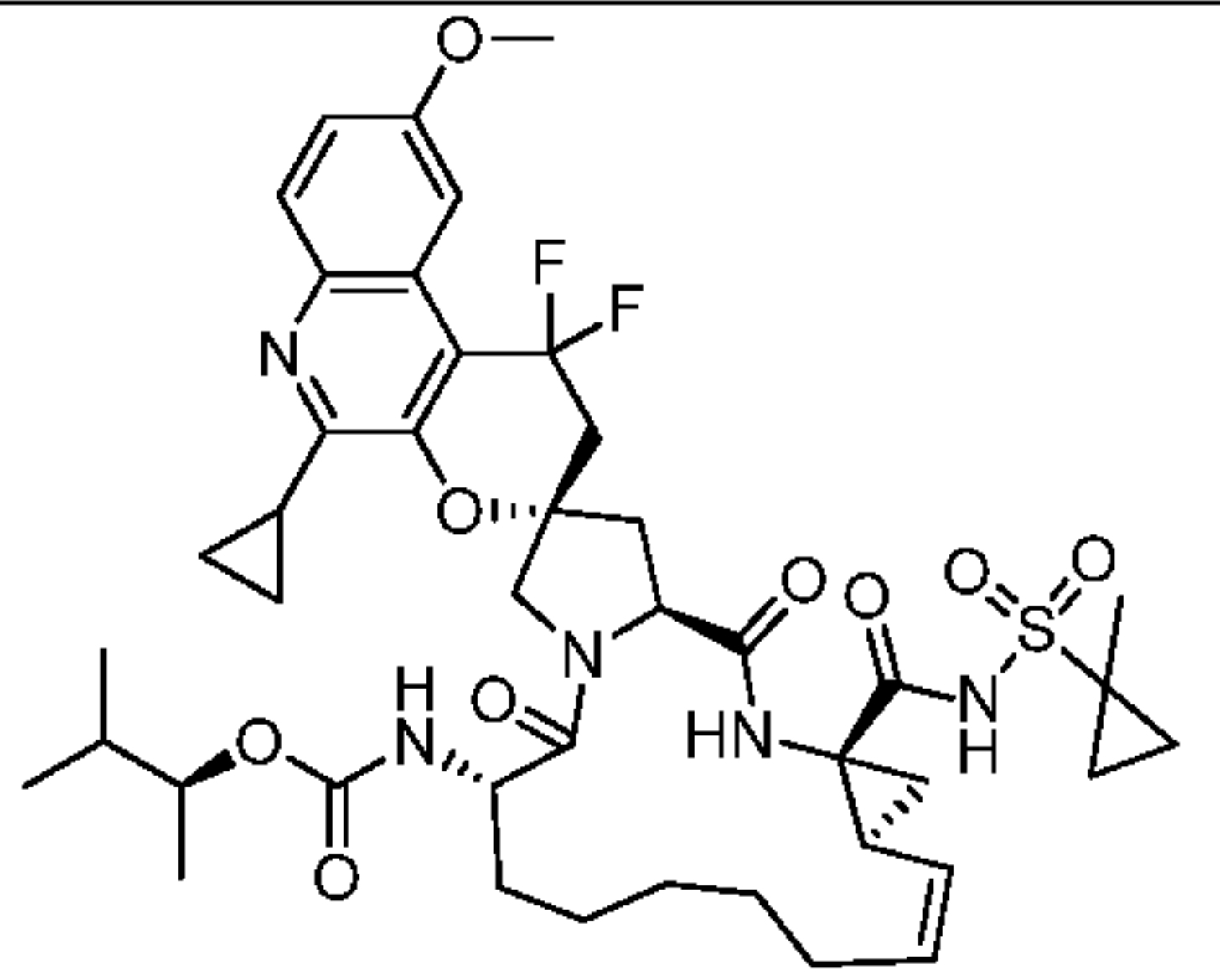
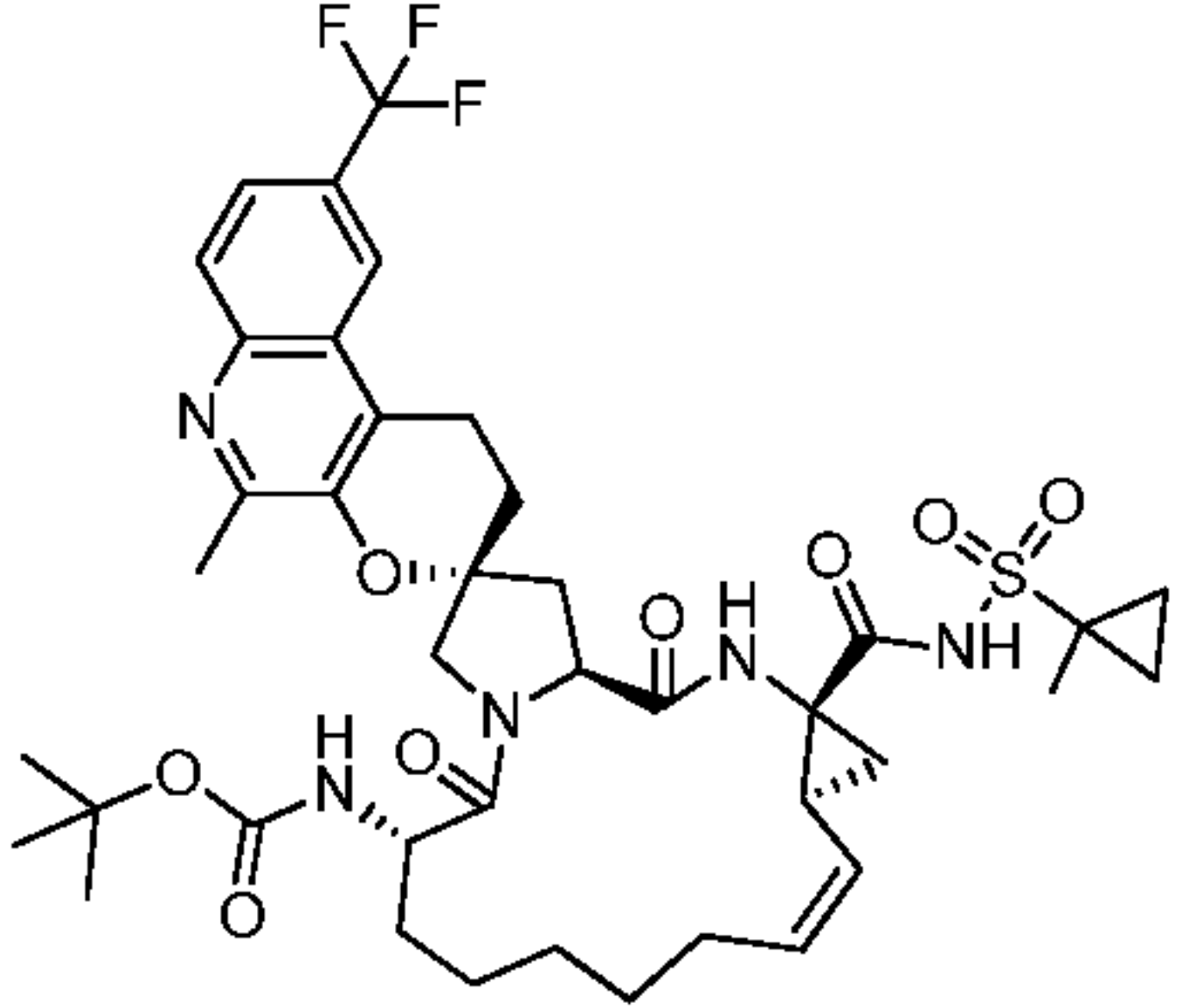
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
221	 I-221	cyclobutylmethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-5'-methyl-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39	796.2
222	 I-222	cyclopropylmethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-5'-methyl-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39	782.2 (K+ salt)
223	 I-223	(1-methylcyclopropyl)methyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8',9'-difluoro-5'-methyl-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	798.2
224	 I-224	cyclopropylmethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8',9'-difluoro-5'-methyl-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	784.2
225	 I-225	cyclobutylmethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8',9'-difluoro-5'-methyl-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	798.2
226	 I-226	2-methyl-4-(methylsulfonyl)butan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	926.2 (K+ salt)

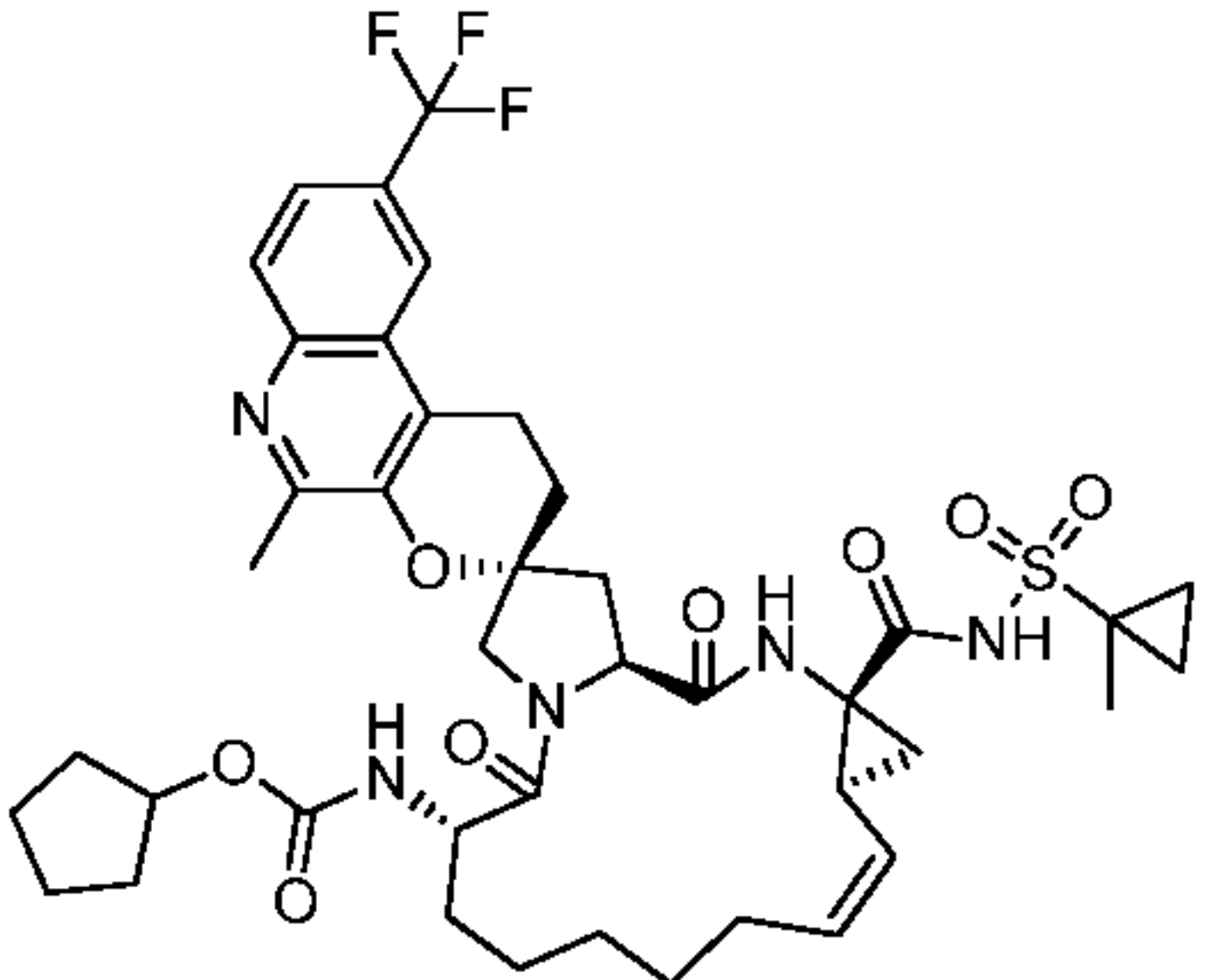
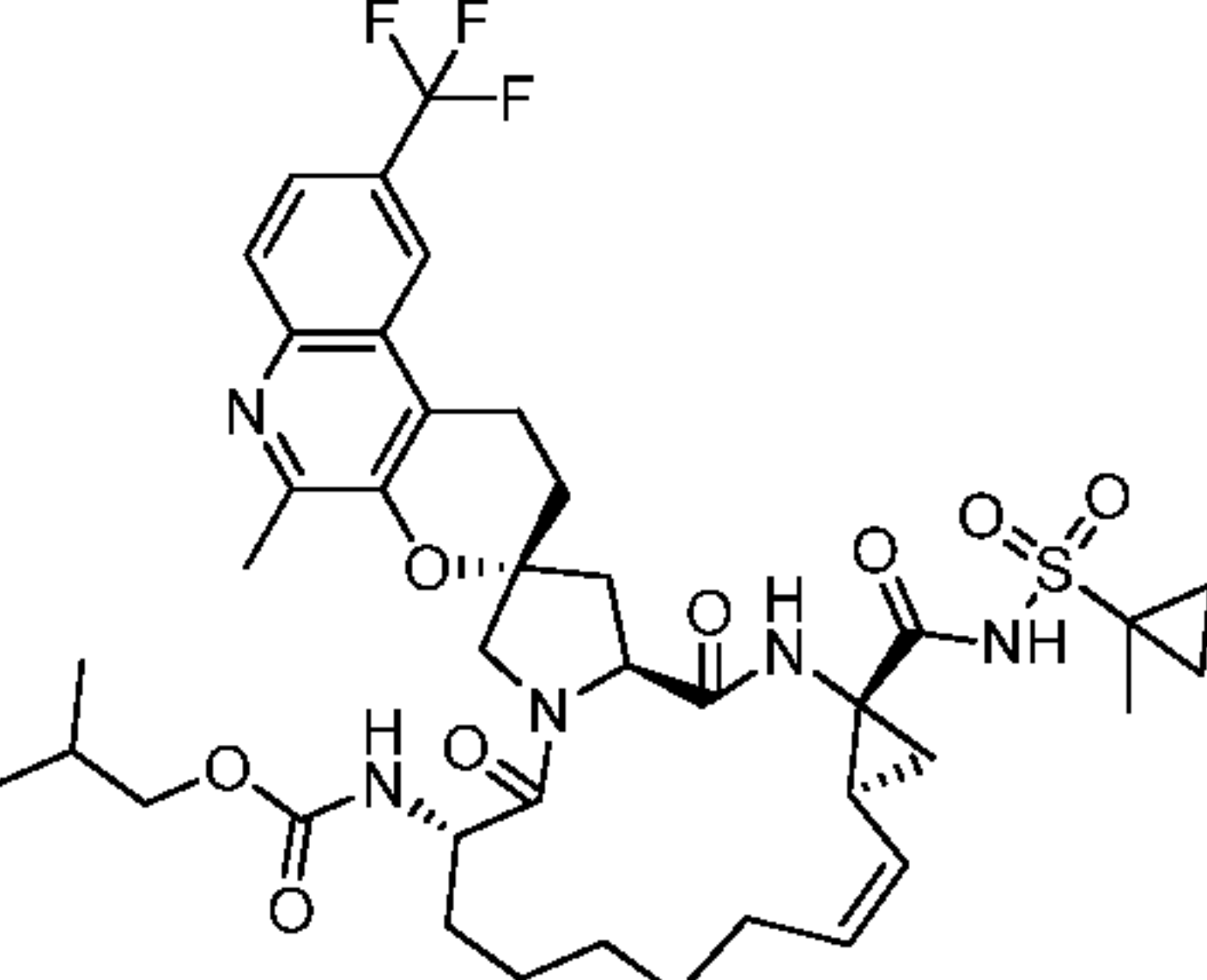
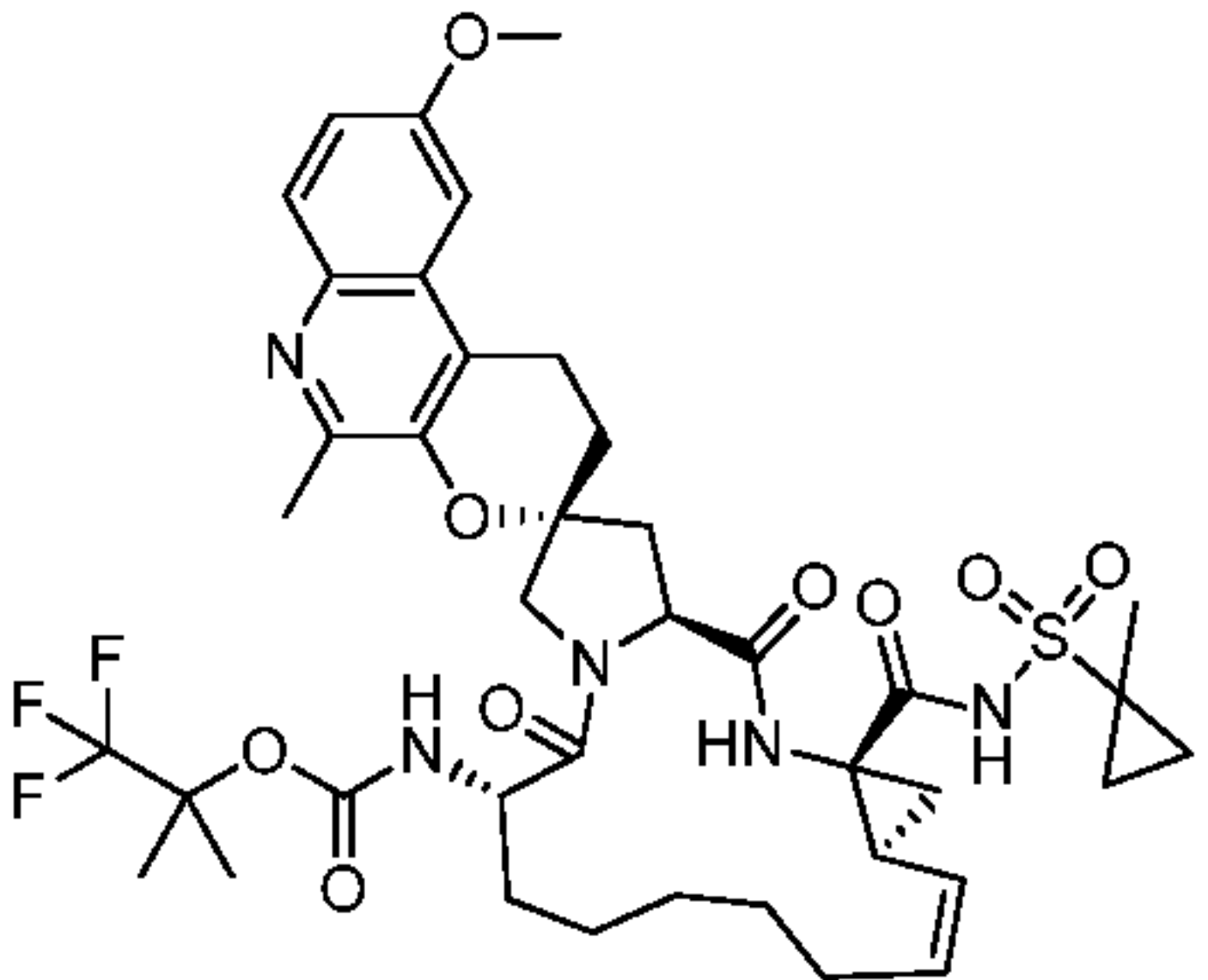
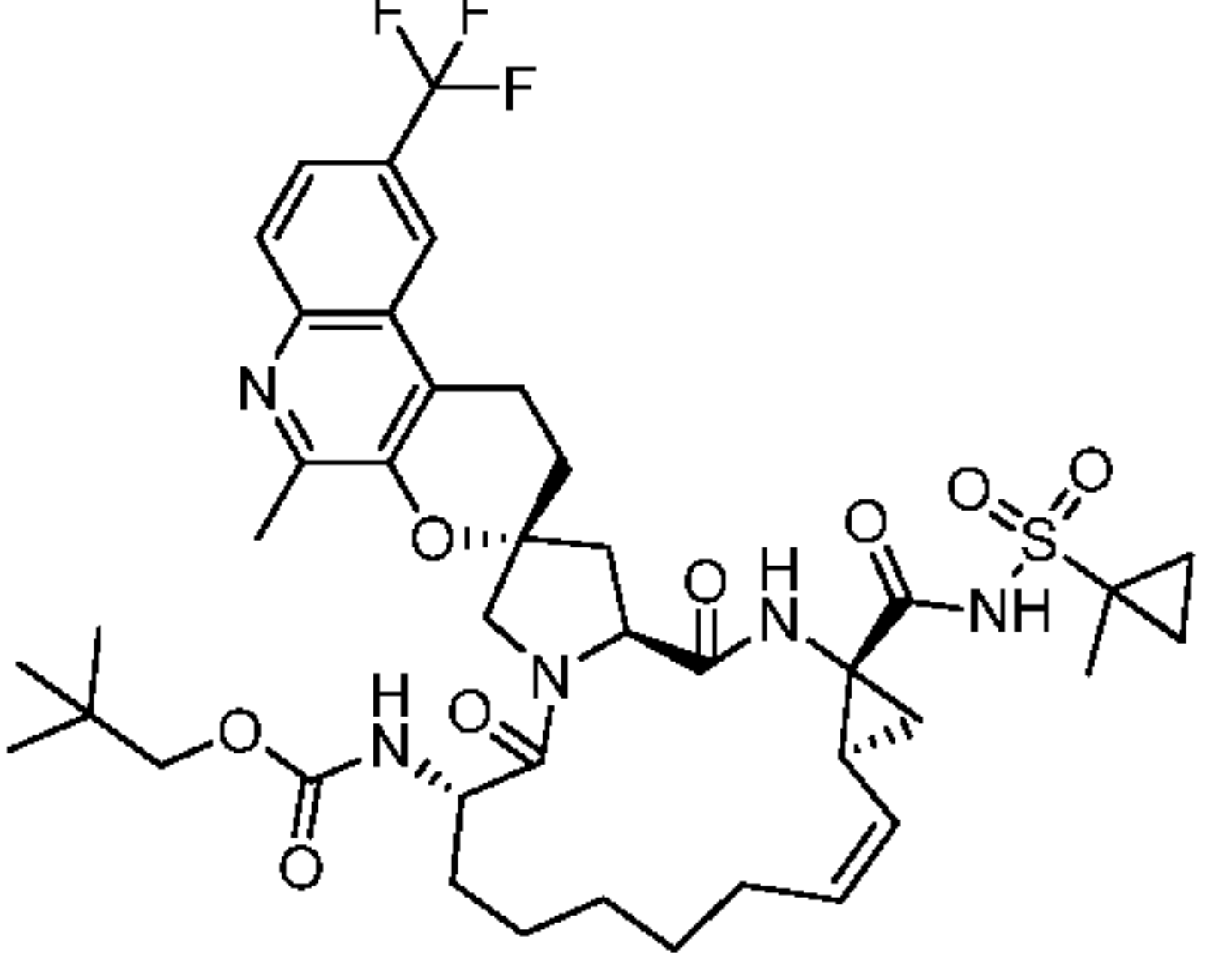
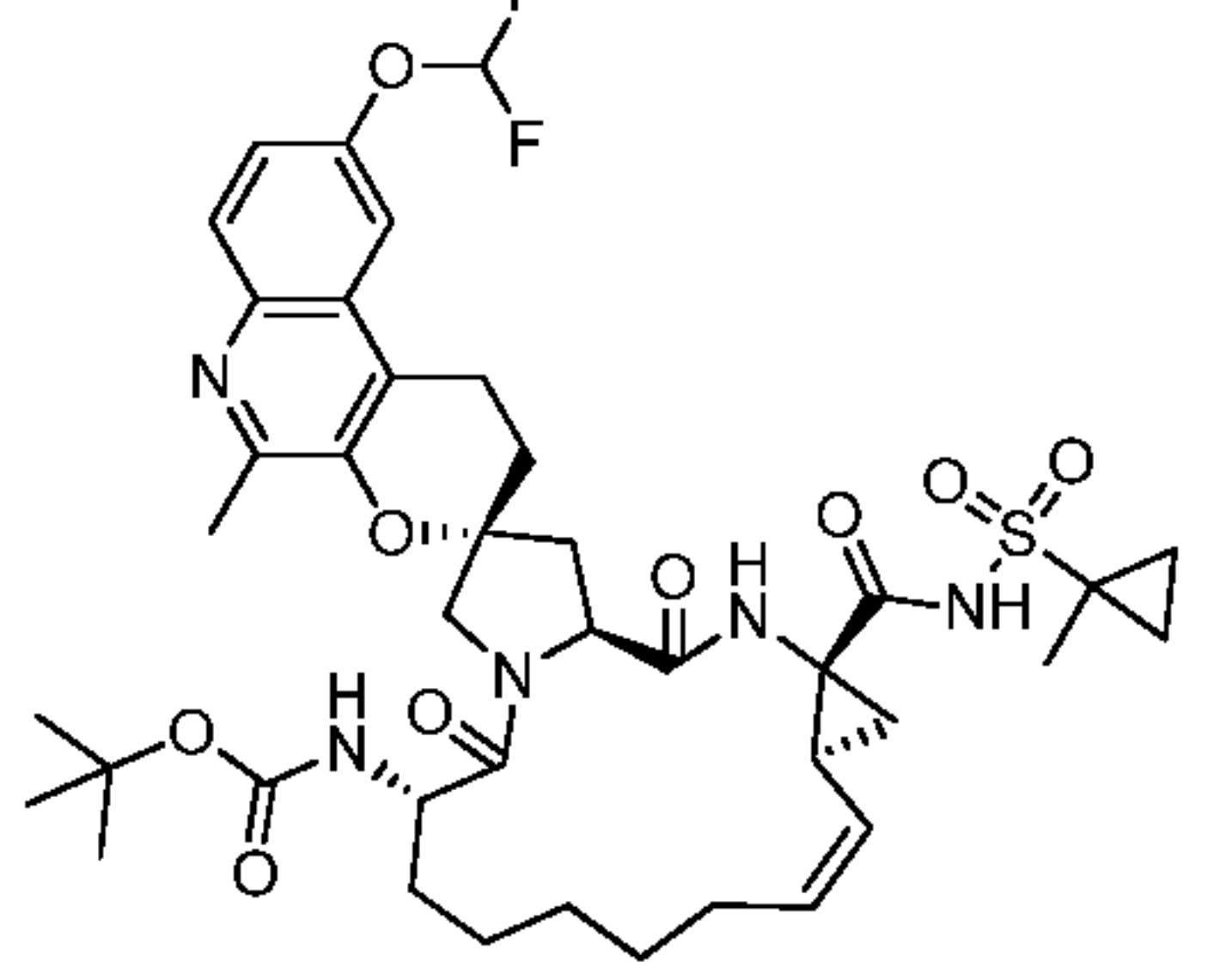
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
227	 I-227	cyclopentyl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1',1'-difluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	882.2 (K+ salt)
228	 I-228	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(dimethylcarbamoyl)amino]-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	61	721.4
229	 I-229	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-6-[(methylsulfonyl)amino]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	47	728.4
230	 I-230	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(cyclopropylsulfonyl)amino]-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	47	--
231	 I-231	cyclopentylmethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39	810.2

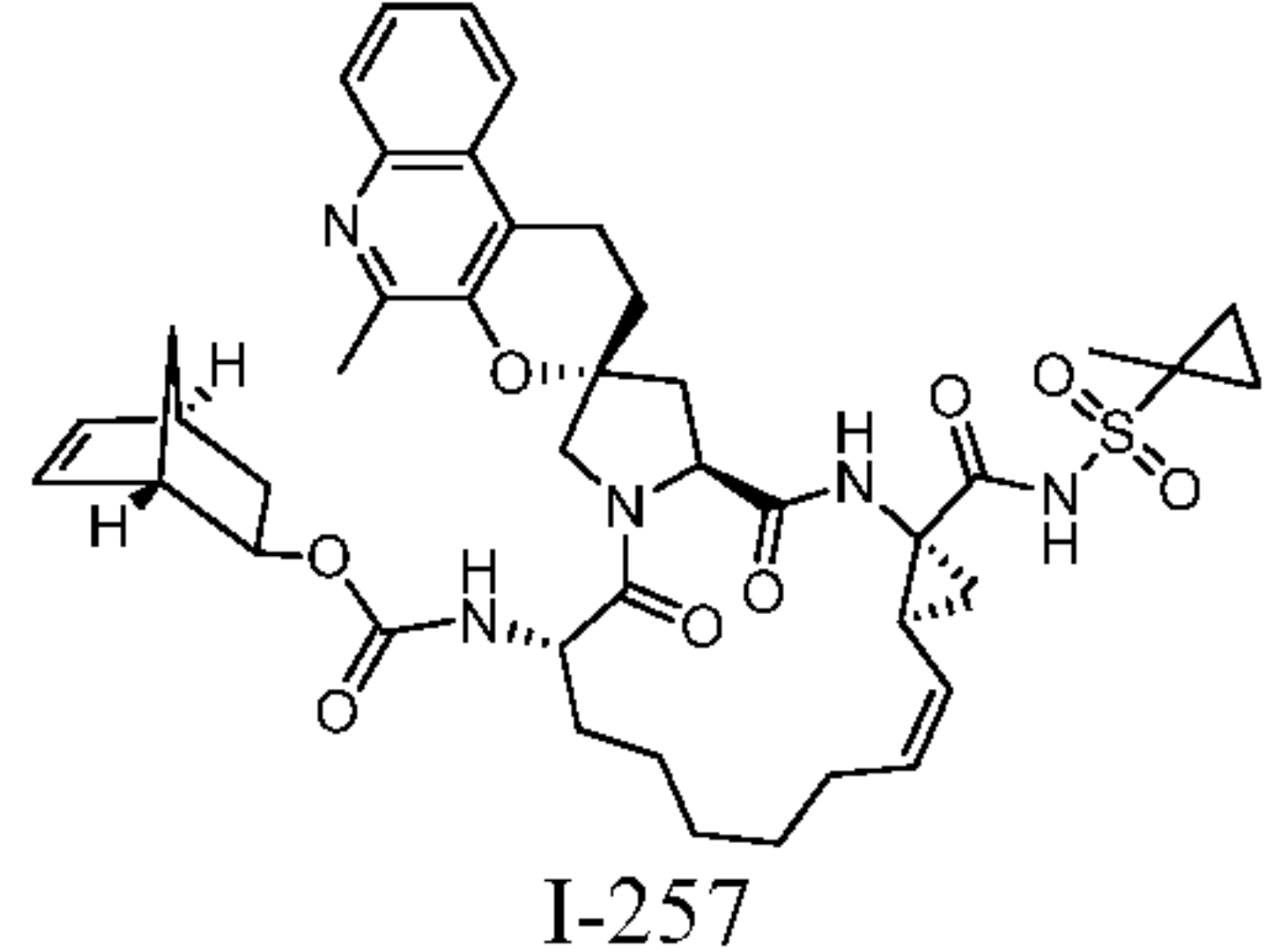
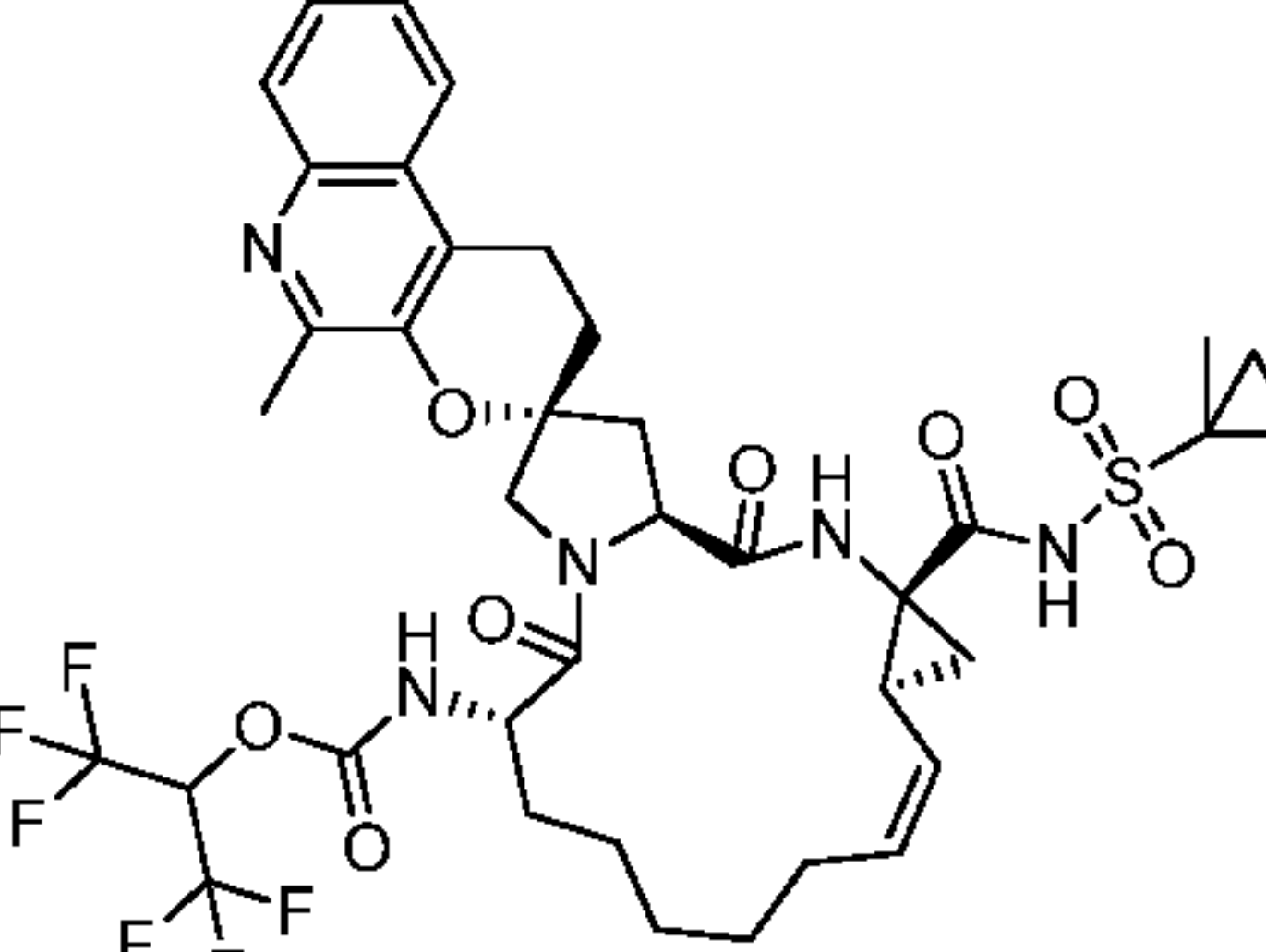
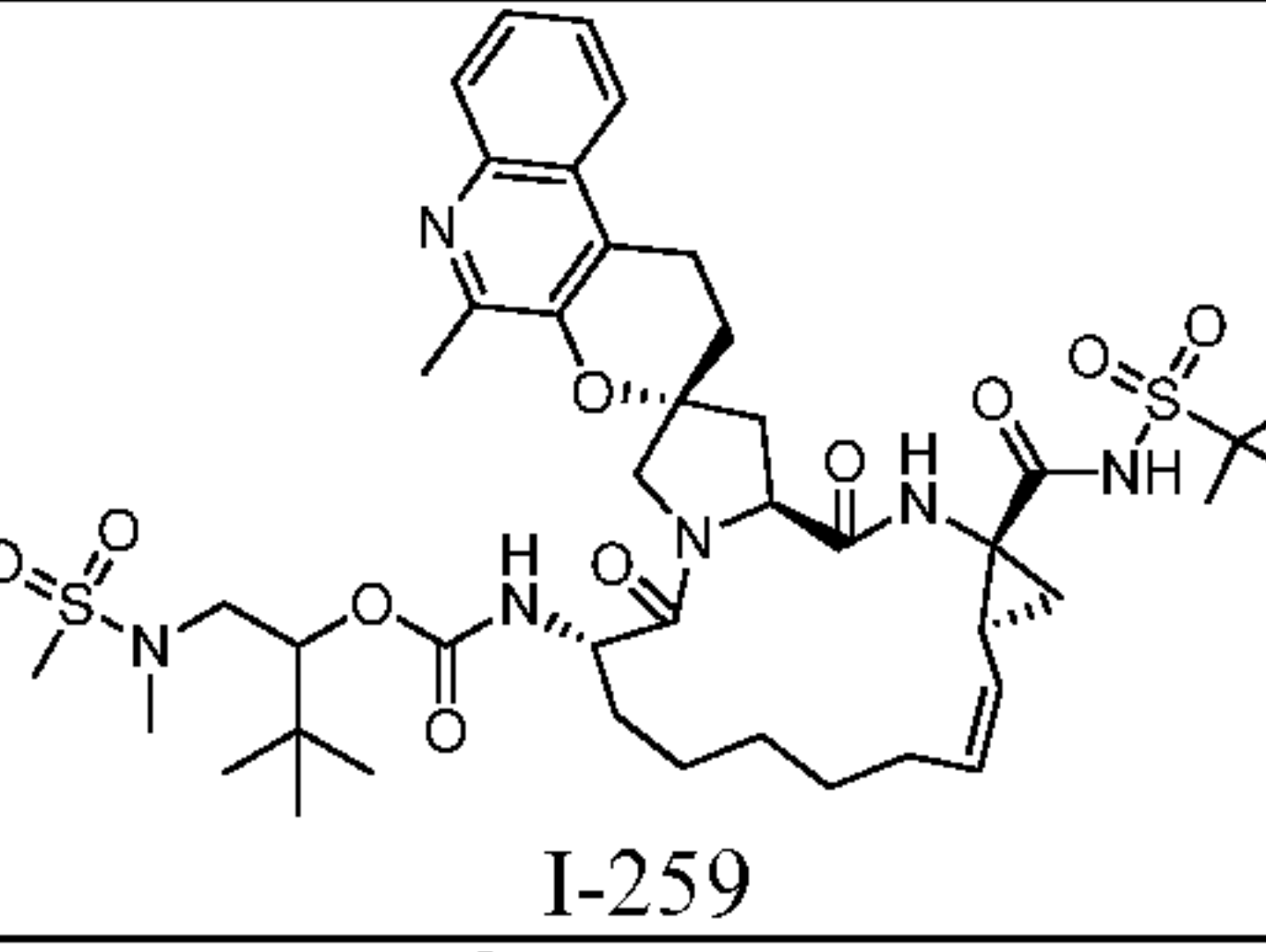
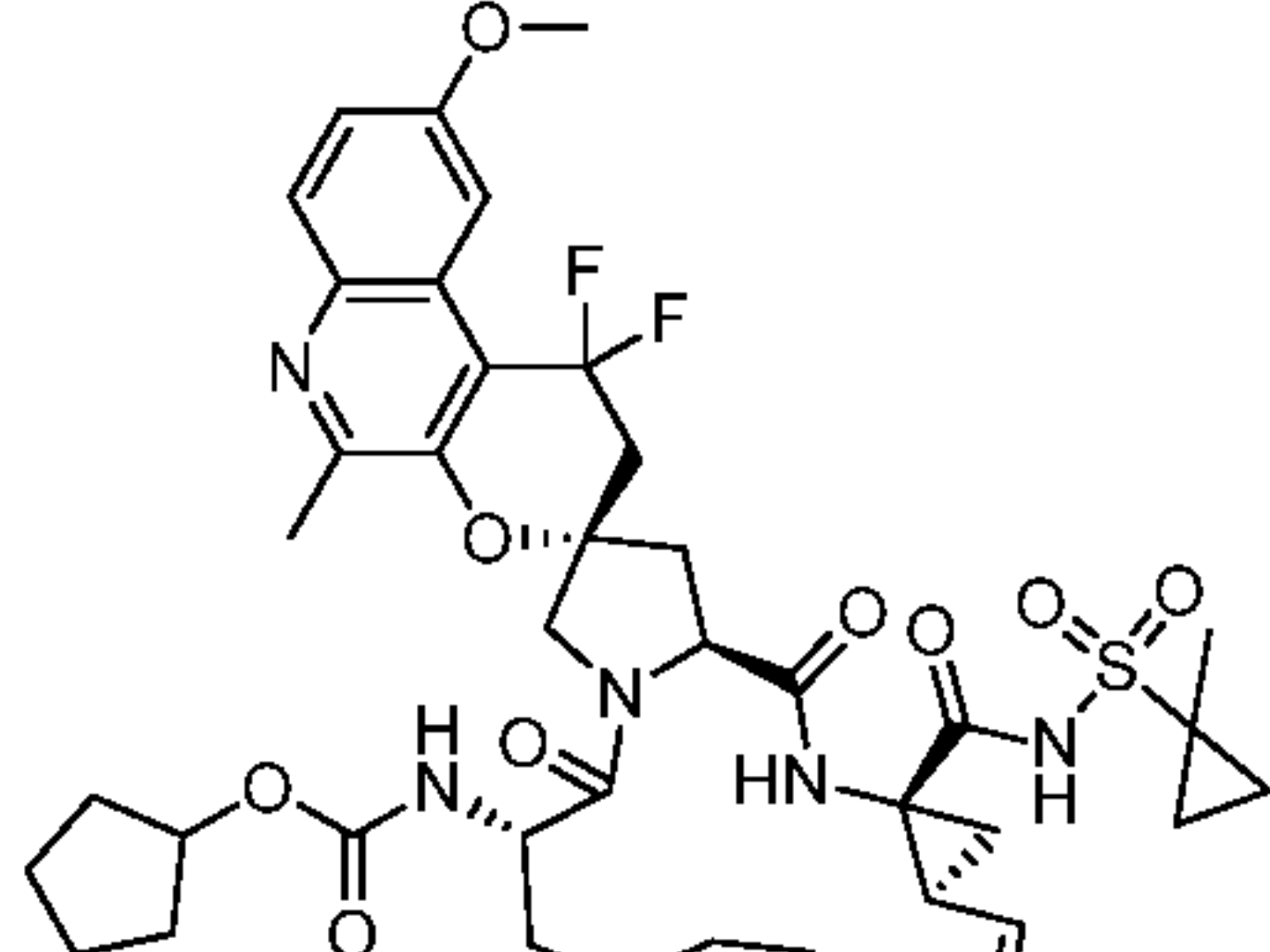
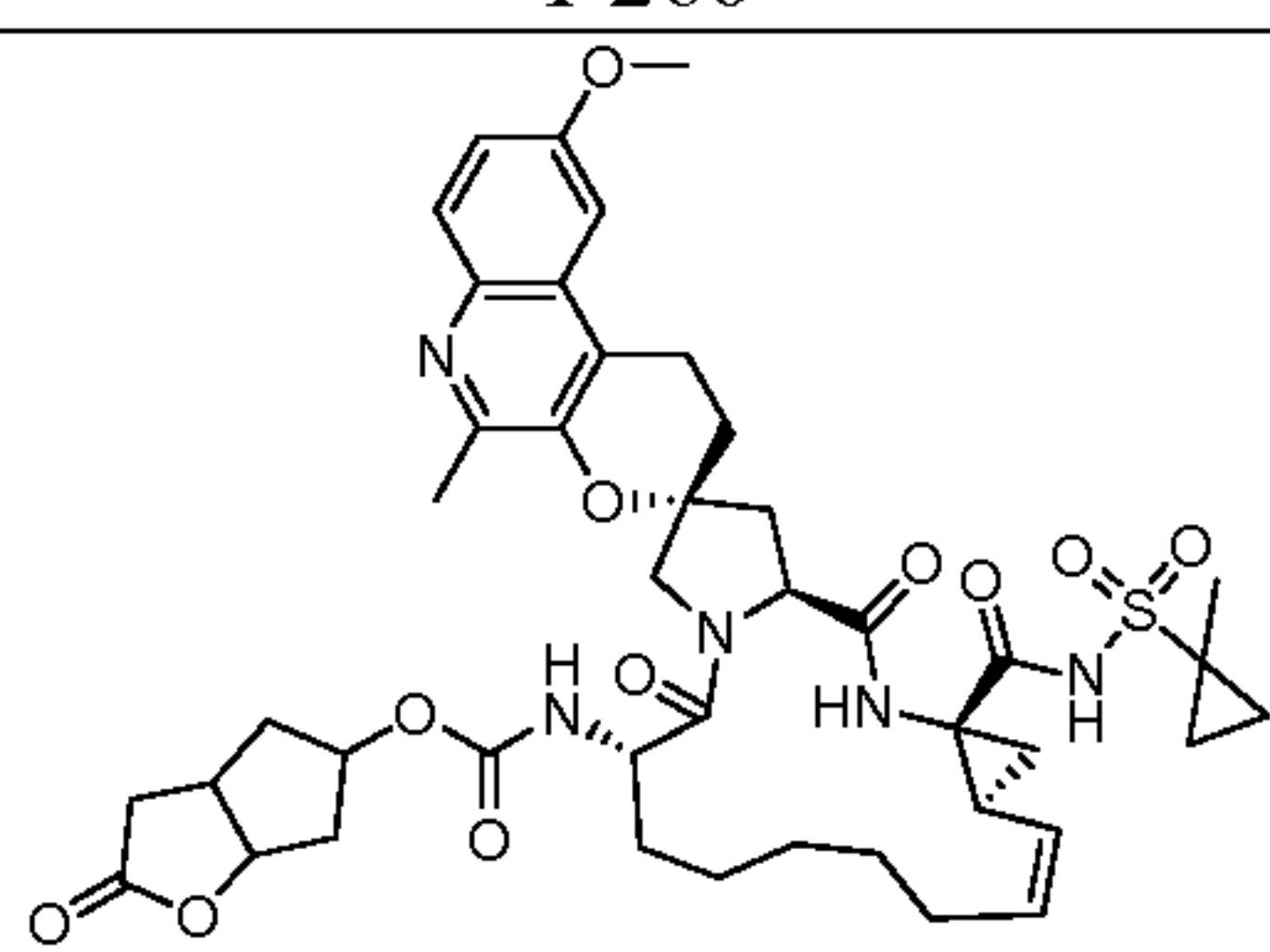
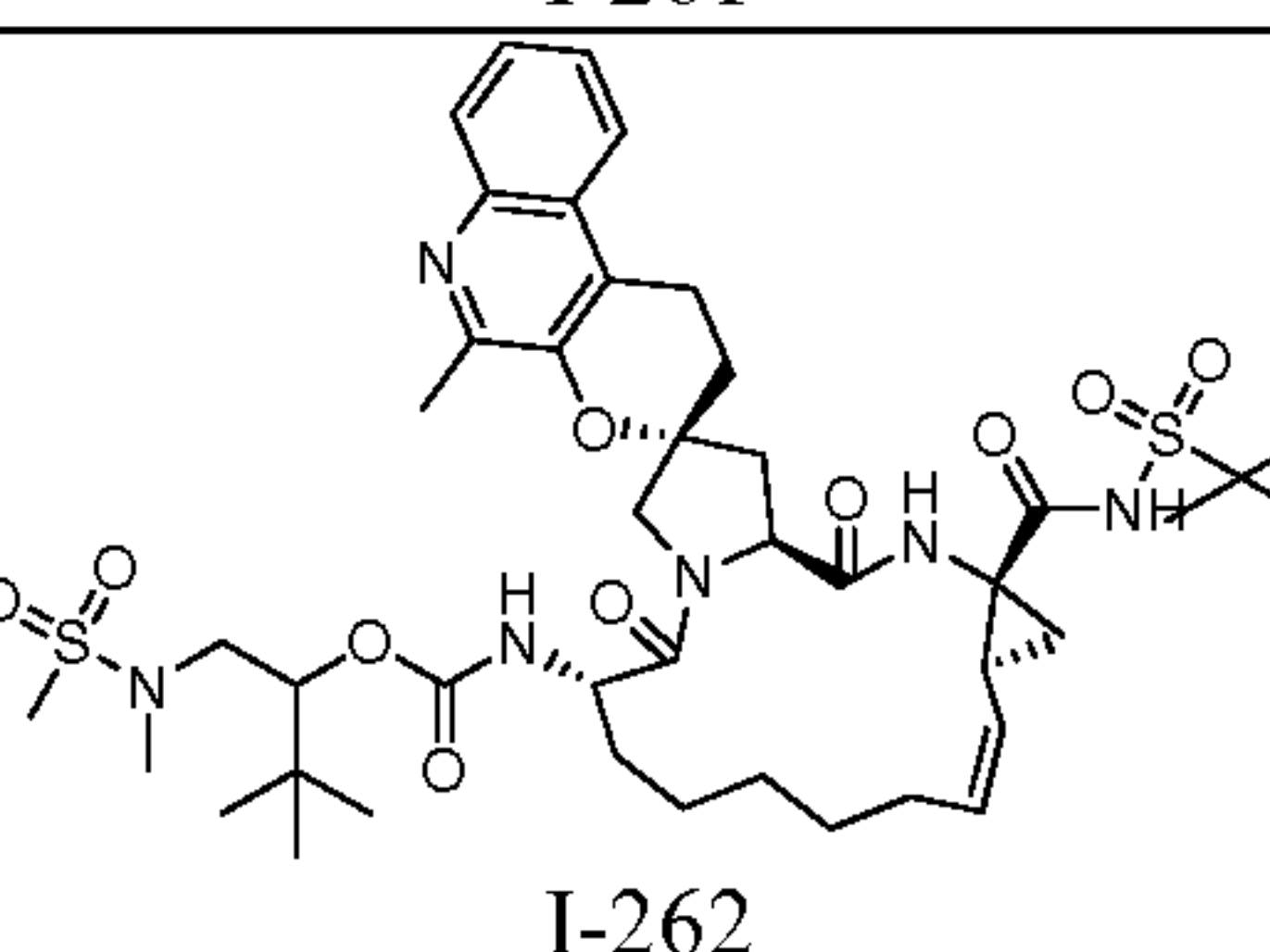
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
232	 I-232	cyclopentylmethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8',9'-difluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropano[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	812.2
233	 I-233	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8'-chloro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropano[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39	784.2
234	 I-234	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8'-chloro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropano[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39	784.2 (K+ salt)
235	 I-235	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8'-chloro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropano[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39	798.2 (K+ salt)
236	 I-236	1-methylcyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8'-chloro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropano[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39	782.2 (K+ salt)

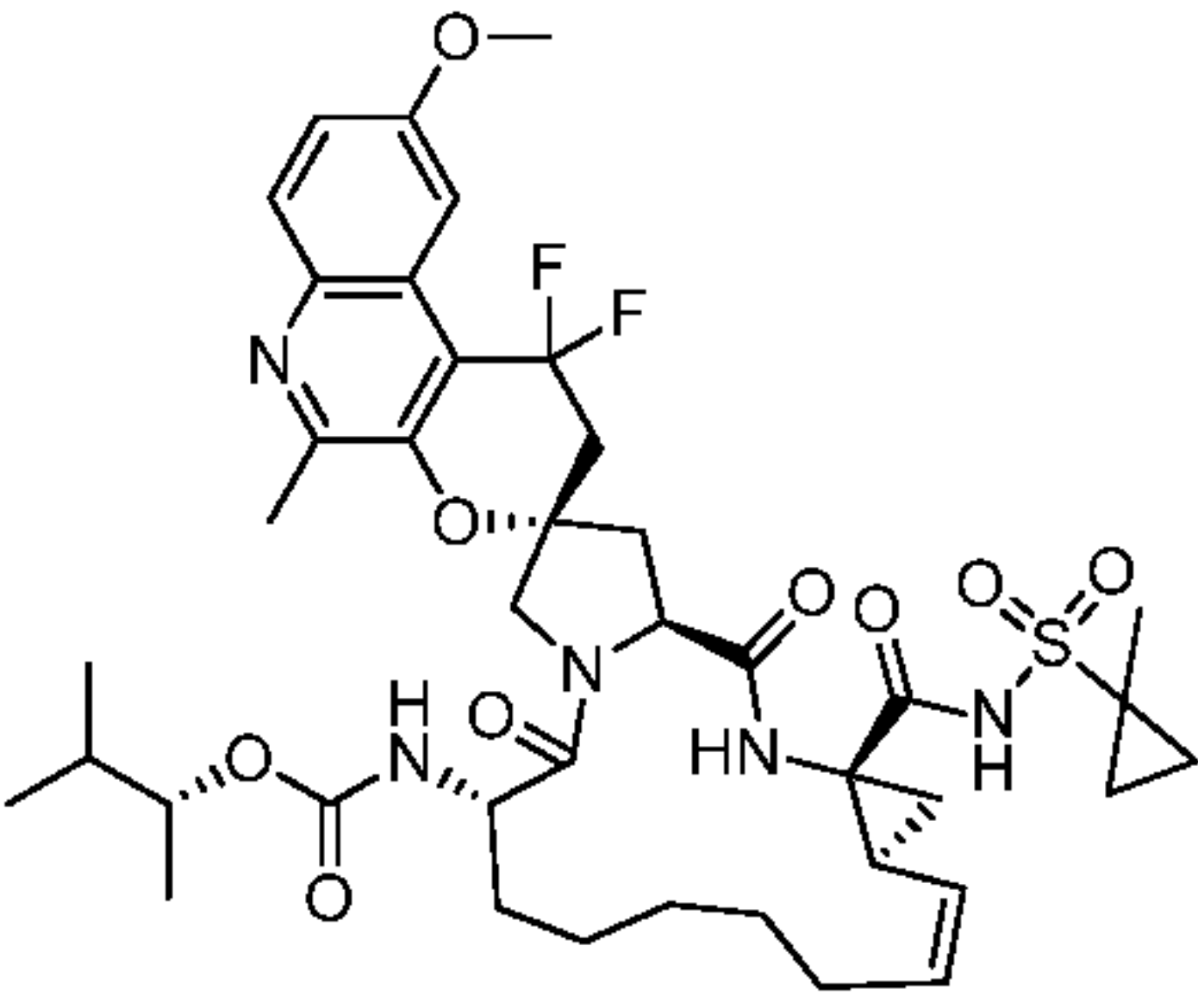
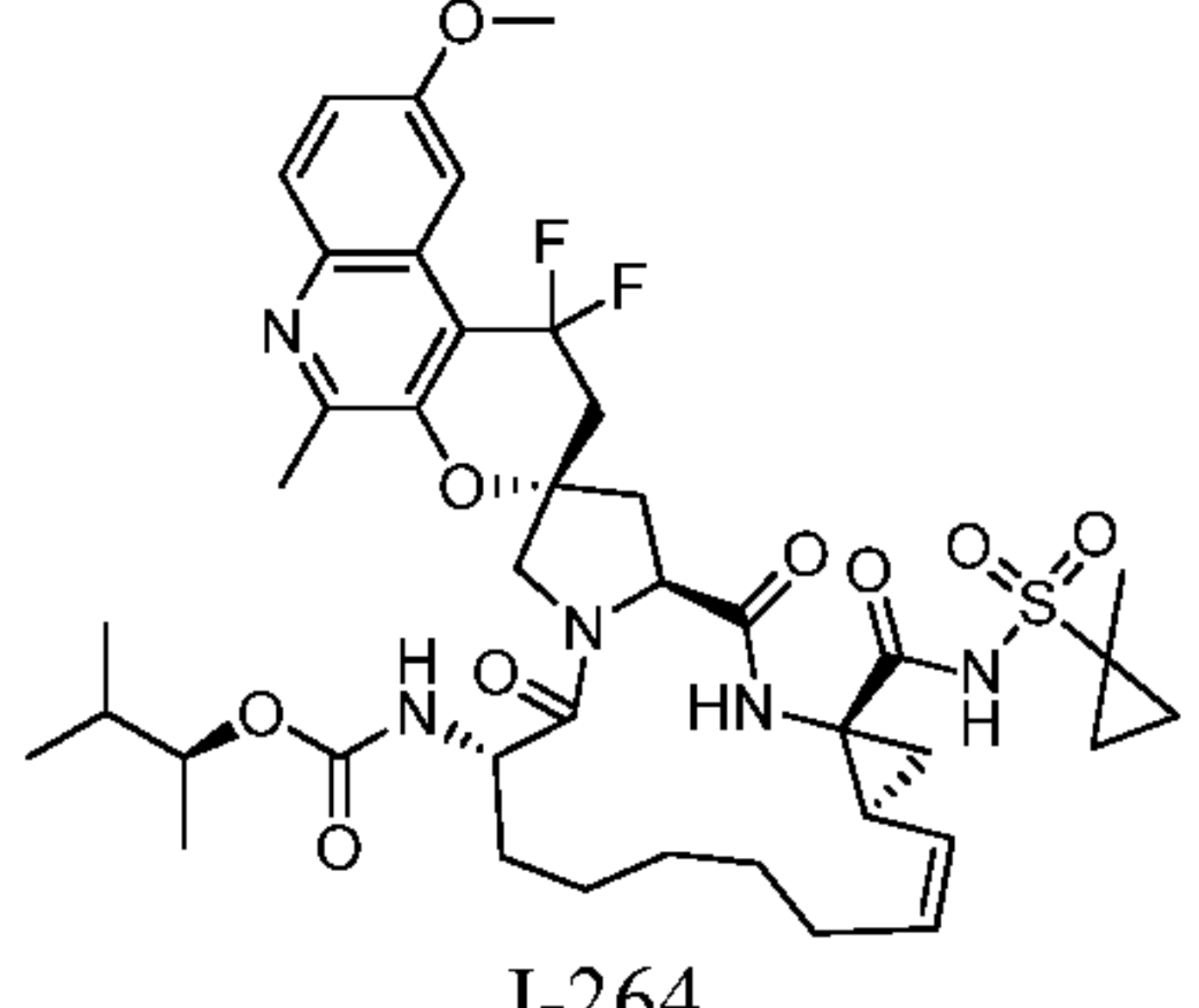
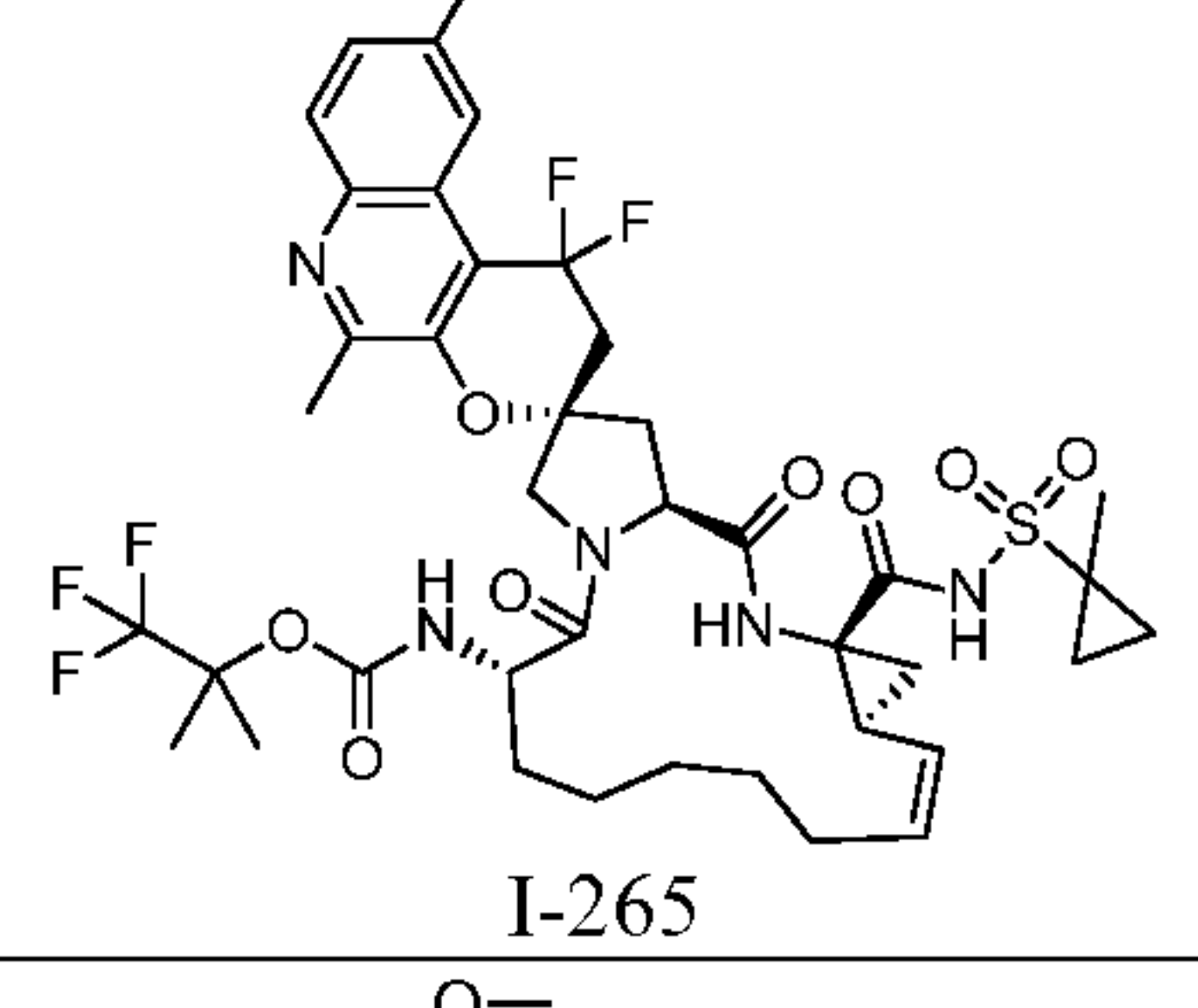
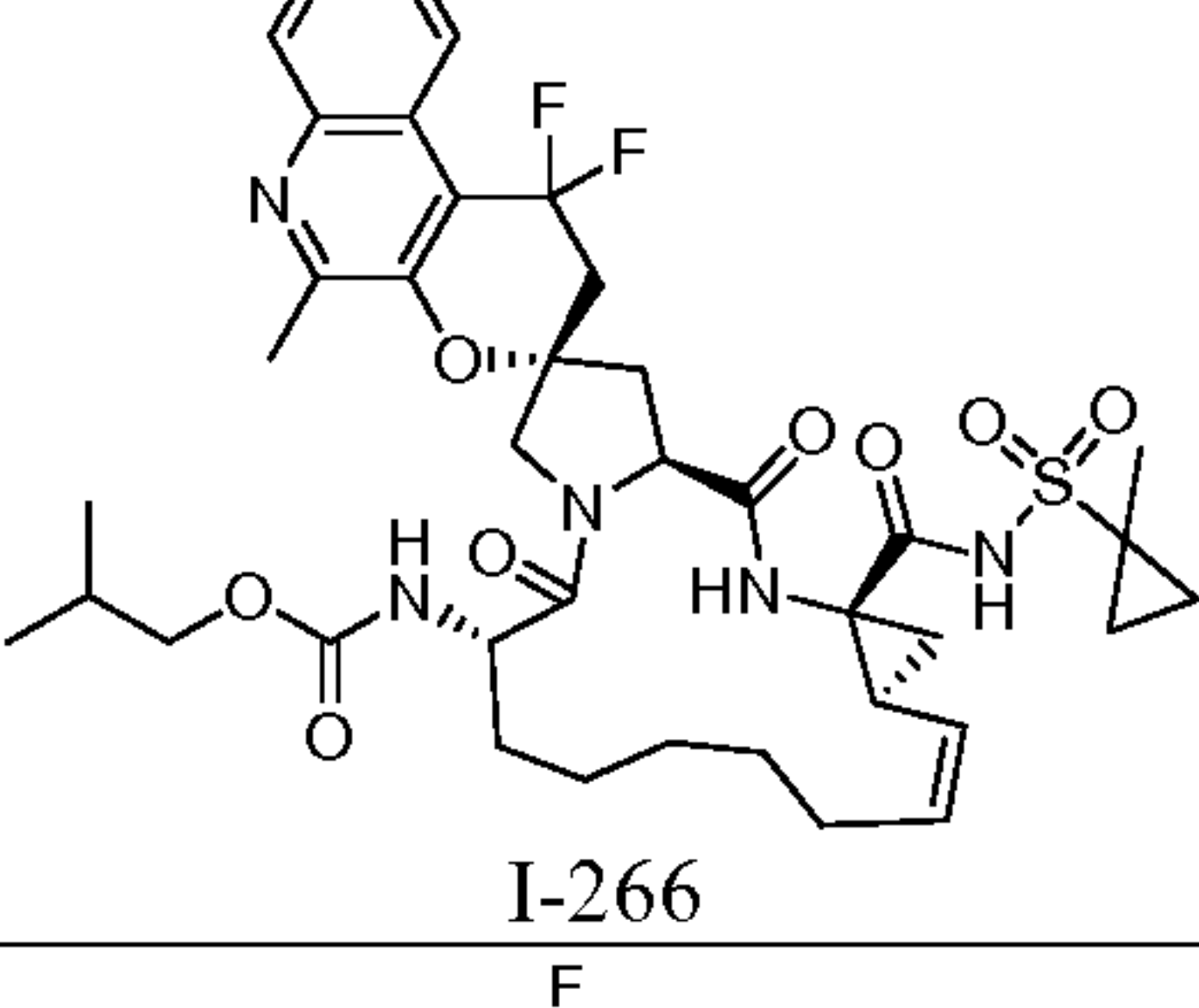
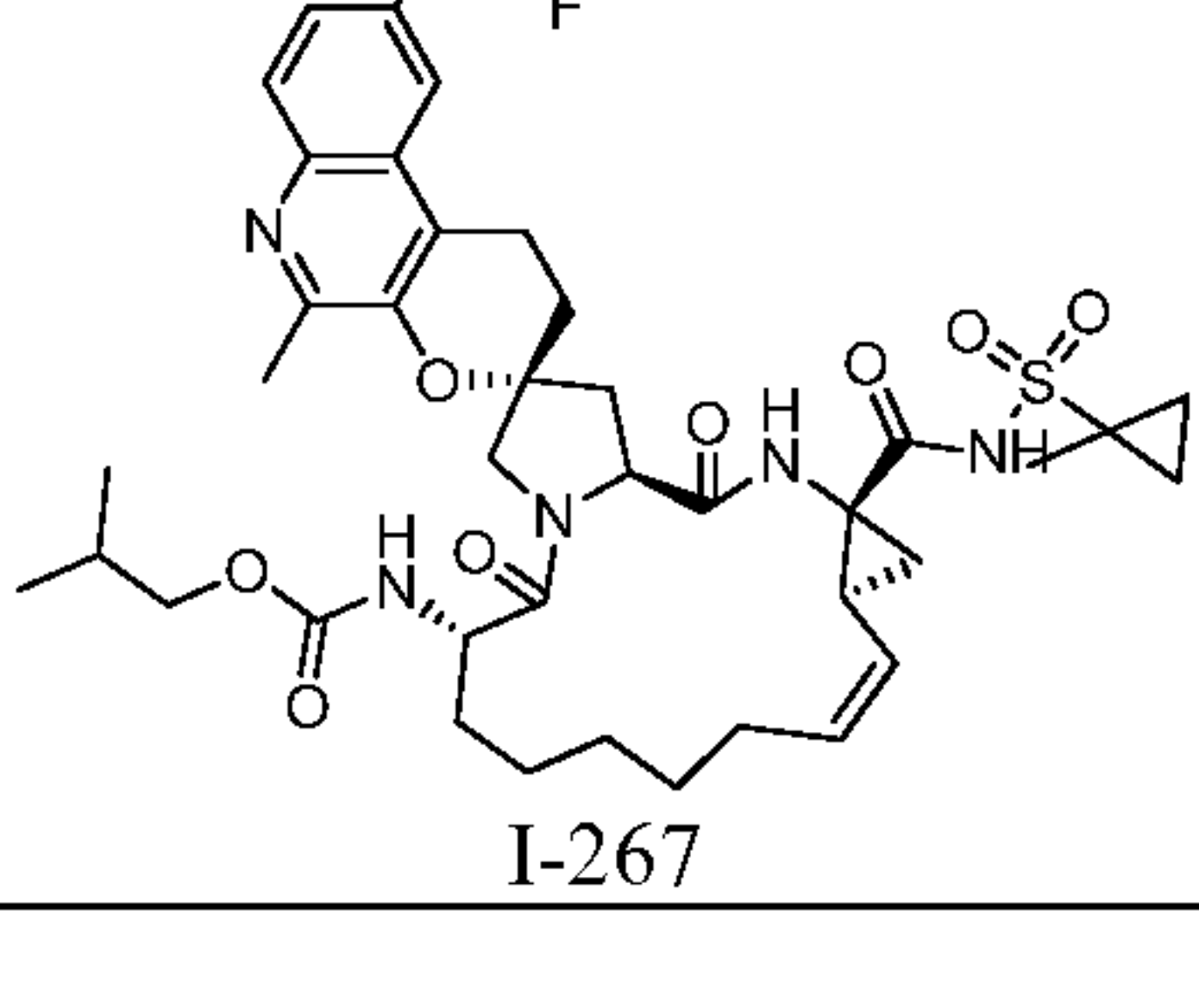
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
237	 I-237	propan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8'-chloro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39	770.2
238	 I-238	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8'-chloro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39	796.2
239	 I-239	cyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8'-chloro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39	782.2
240	 I-240	1,1,1-trifluoropropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	790.5
241	 I-241	1,1,1-trifluoropropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	790.5

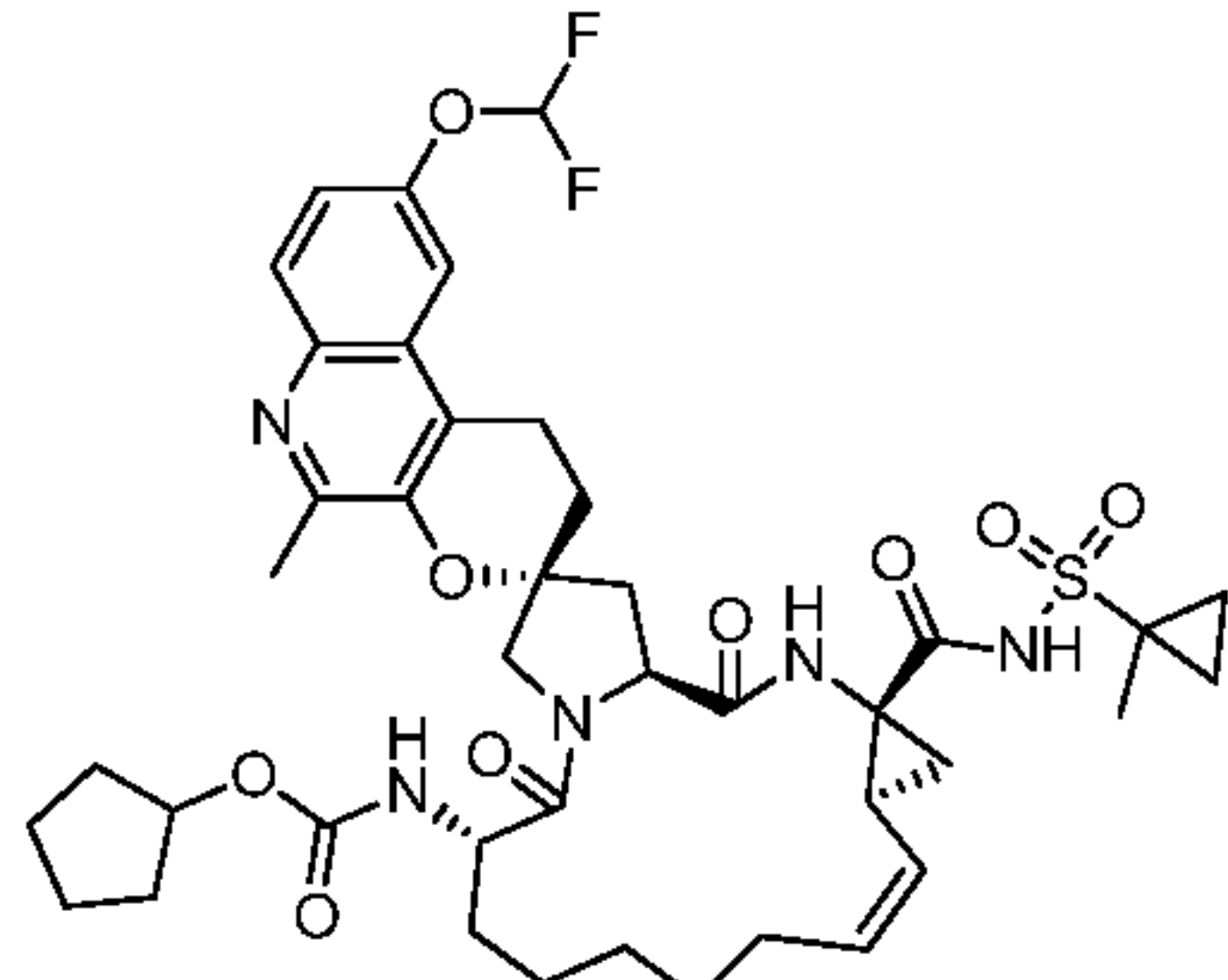
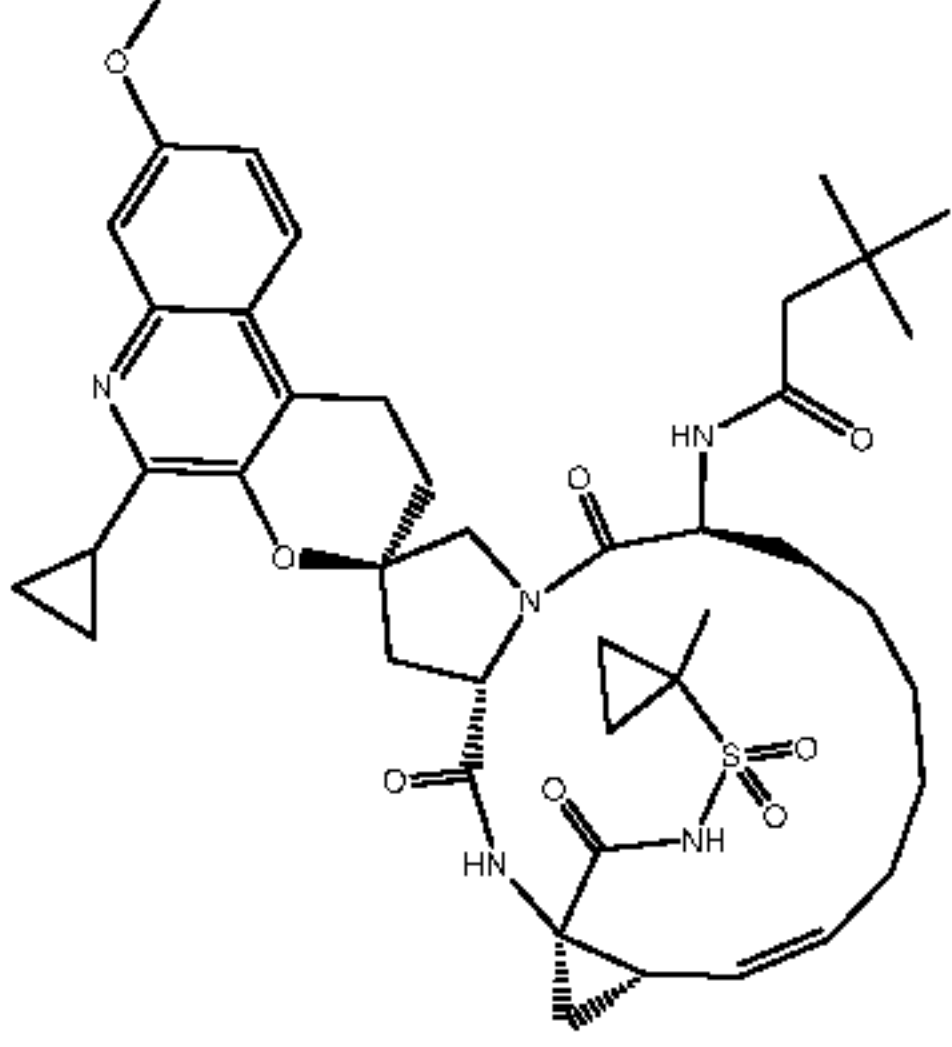
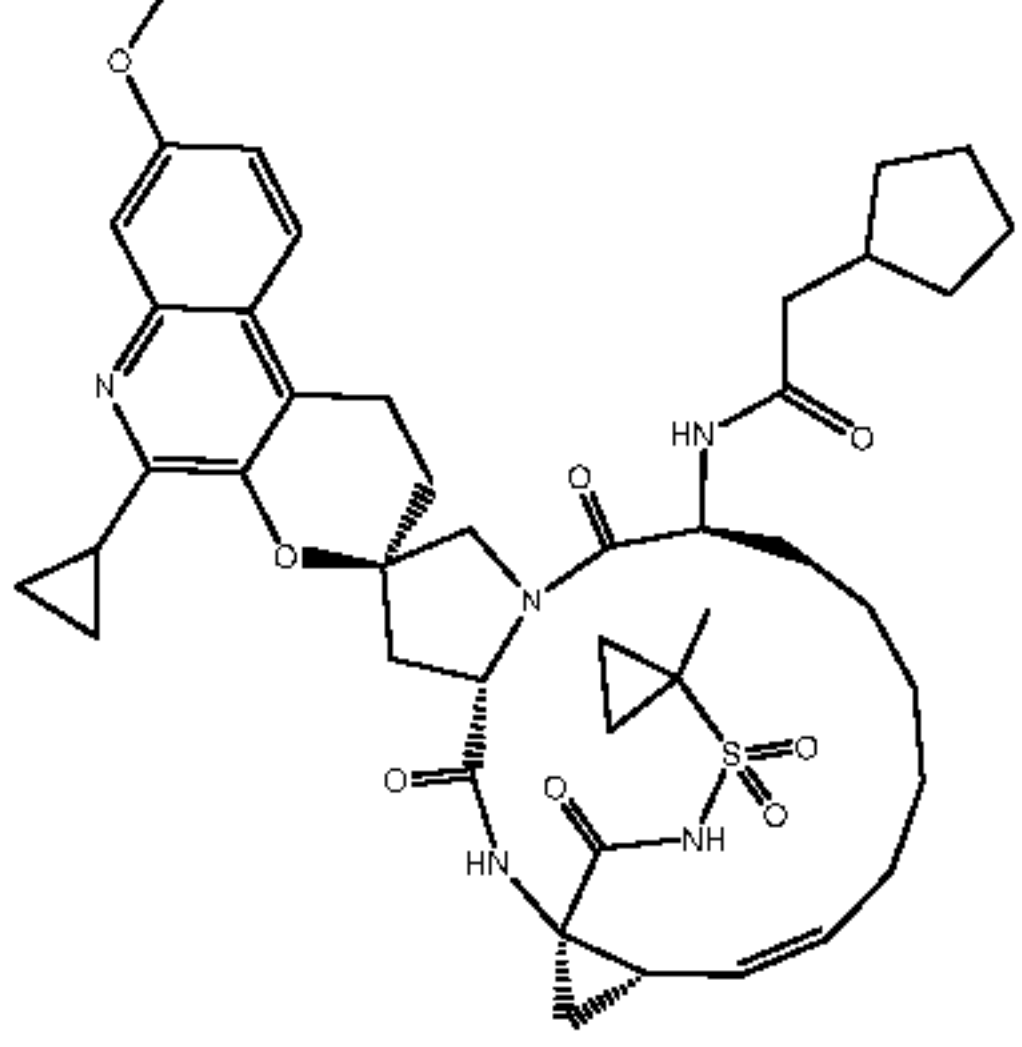
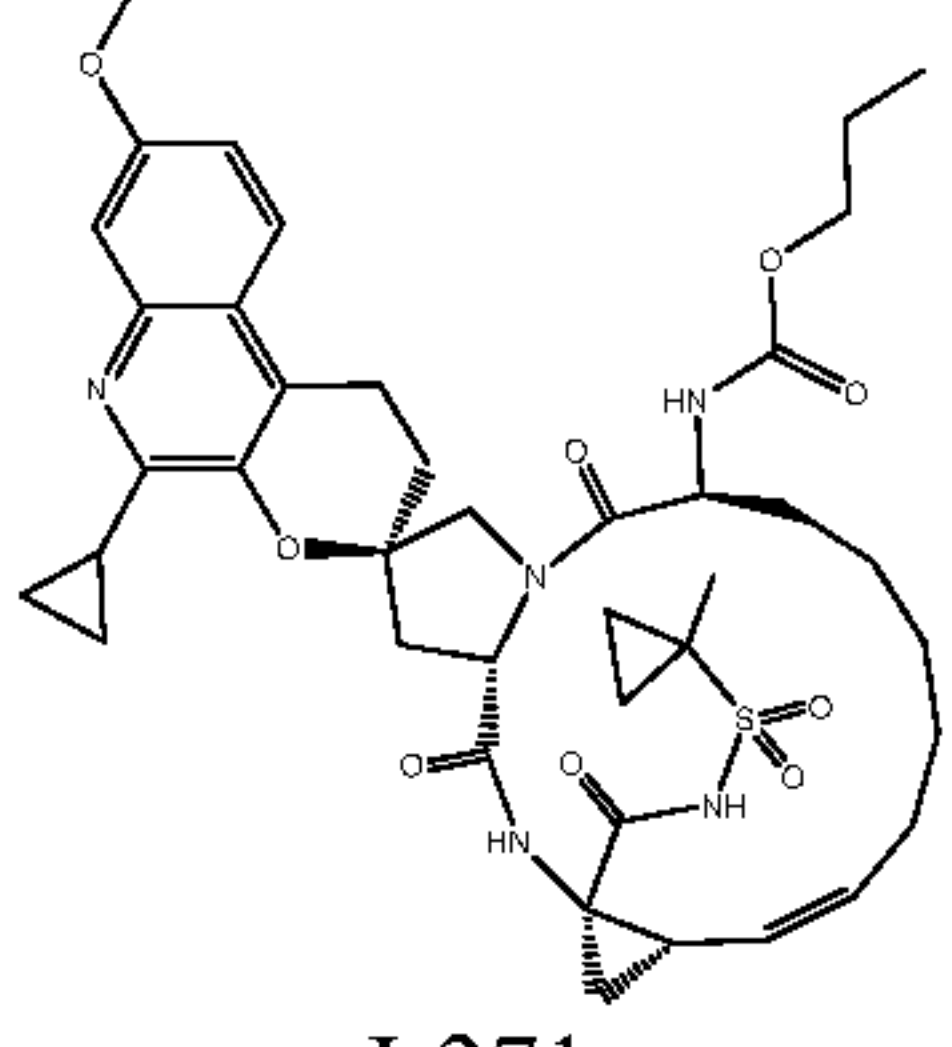
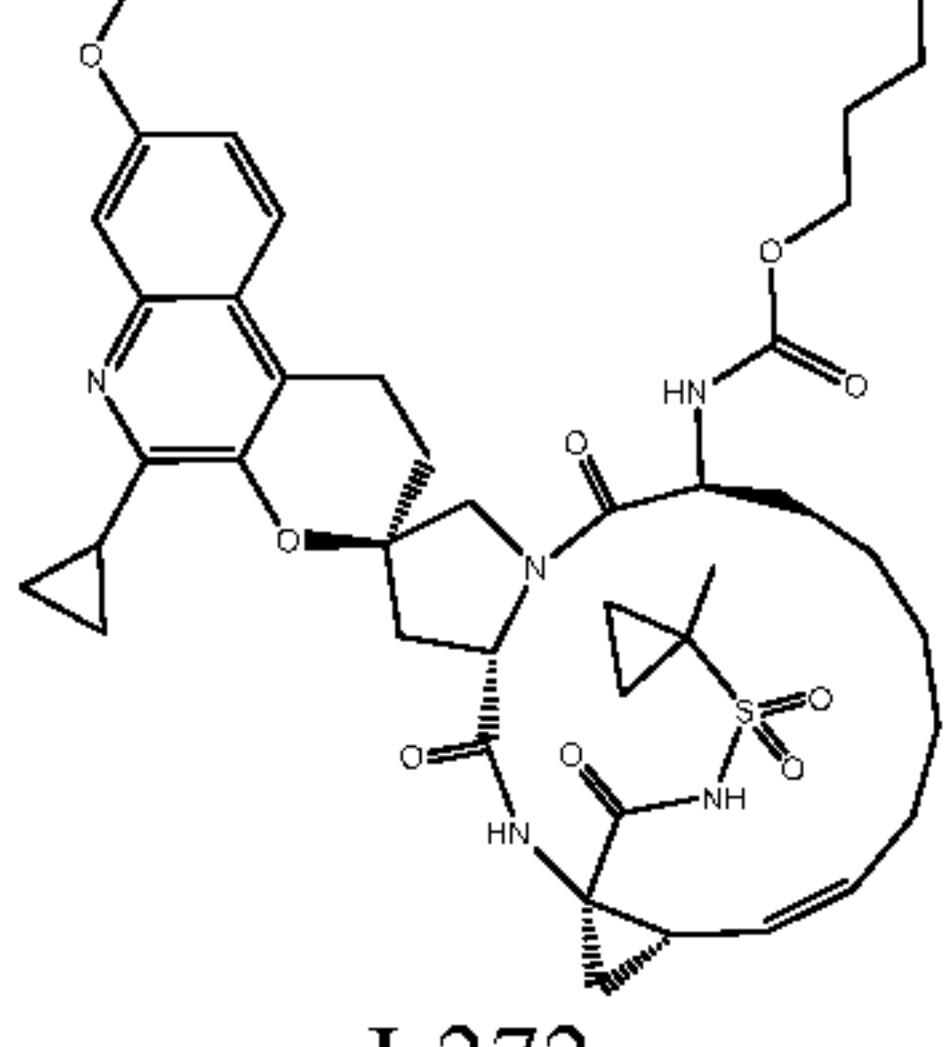
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
242	 I-242	1-methoxy-2-methylpropan-2-yl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1',1'-difluoro-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	3	874.2
243	 I-243	2-methyl-4-(methylsulfonyl)butan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	2	900.2 (K+ salt)
244	 I-244	4-methoxy-2-methylbutan-2-yl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1',1'-difluoro-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	2	888.2
245	 I-245	2-methyl-4-(methylsulfonyl)butan-2-yl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1',1'-difluoro-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	2	936.2 (K+ salt)
246	 I-246	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-6-[(pyrrolidin-1-ylcarbonyl)amino]-9'-(trifluoromethoxy)-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	1	830.7

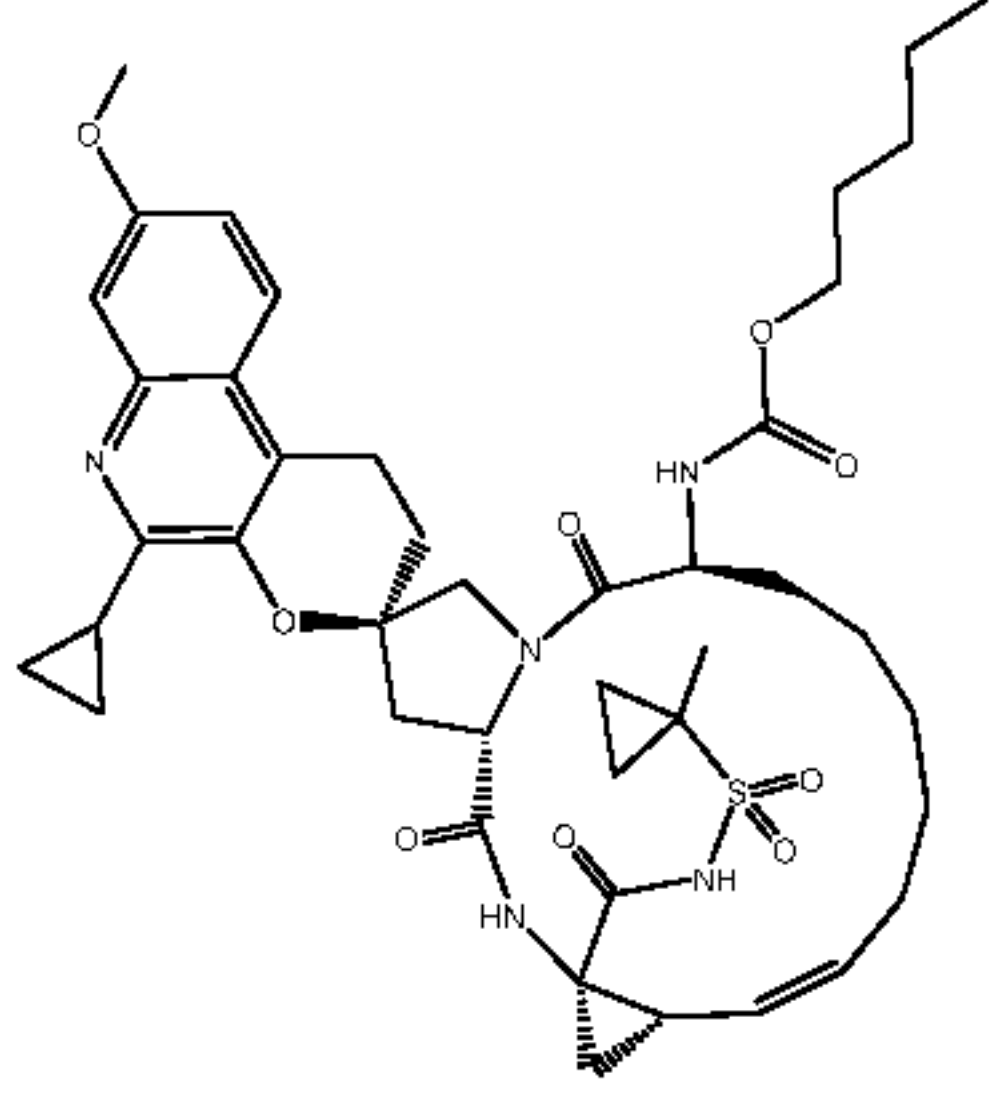
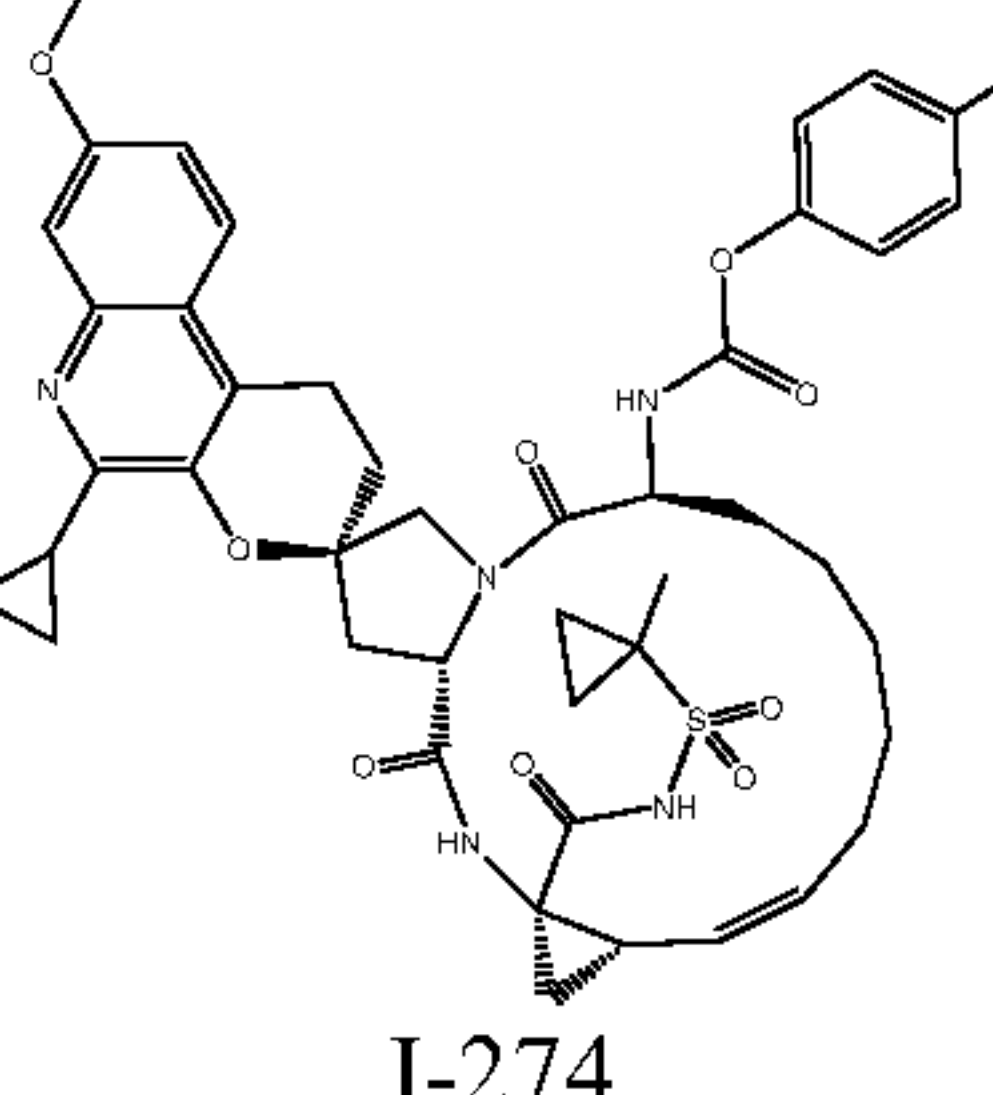
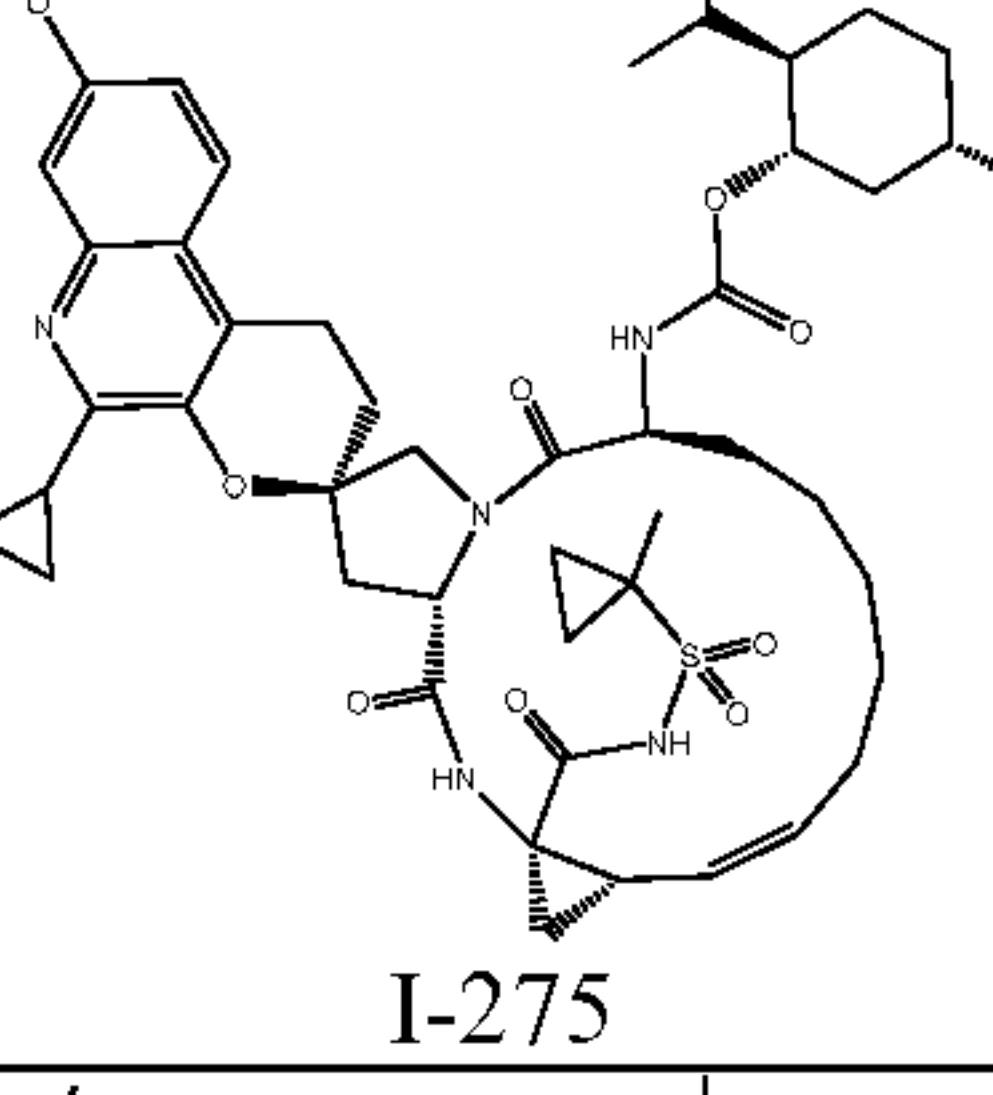
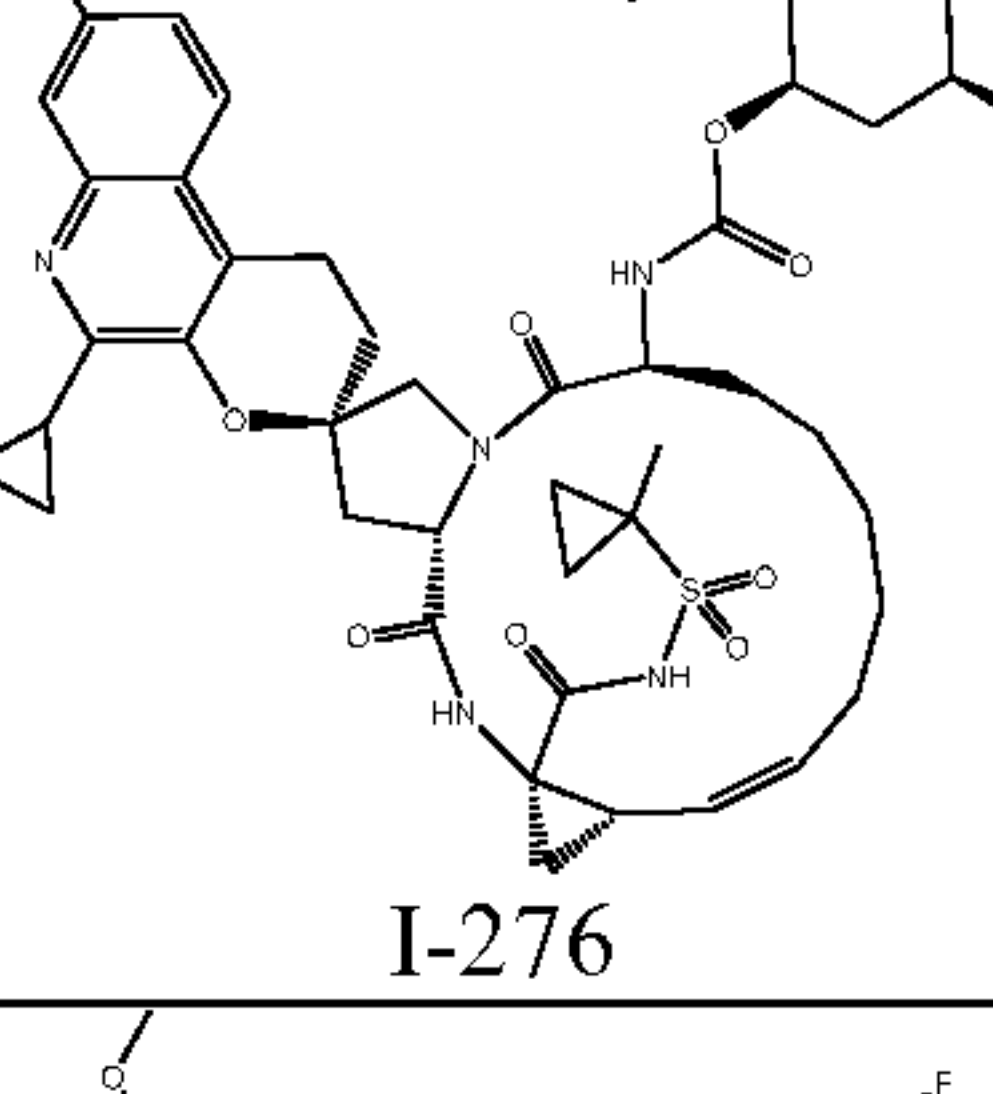
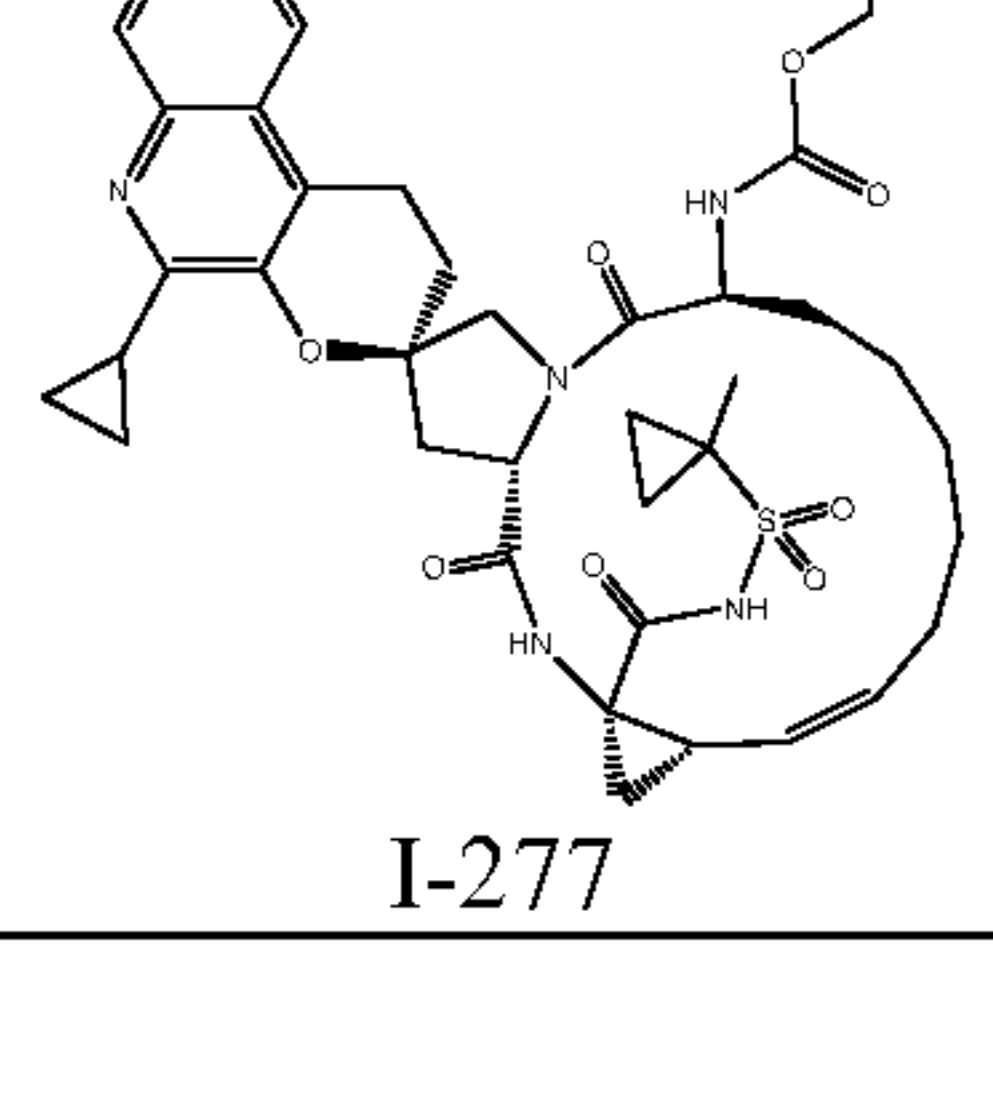
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
247	 <p>I-247</p>	cyclopentyl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-1',1'-difluoro-9'-methoxy-14a-[[[(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	19	854.2
248	 <p>I-248</p>	2-methylpropyl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-1',1'-difluoro-9'-methoxy-14a-[[[(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	19	842.2 (K+ salt)
249	 <p>I-249</p>	(2 <i>R</i>)-3-methylbutan-2-yl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-1',1'-difluoro-9'-methoxy-14a-[[[(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	19	856.2 (K+ salt)
250	 <p>I-250</p>	(2 <i>S</i>)-3-methylbutan-2-yl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-1',1'-difluoro-9'-methoxy-14a-[[[(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	19	856.2
251	 <p>I-251</p>	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-[[[(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-9'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	44	817.4

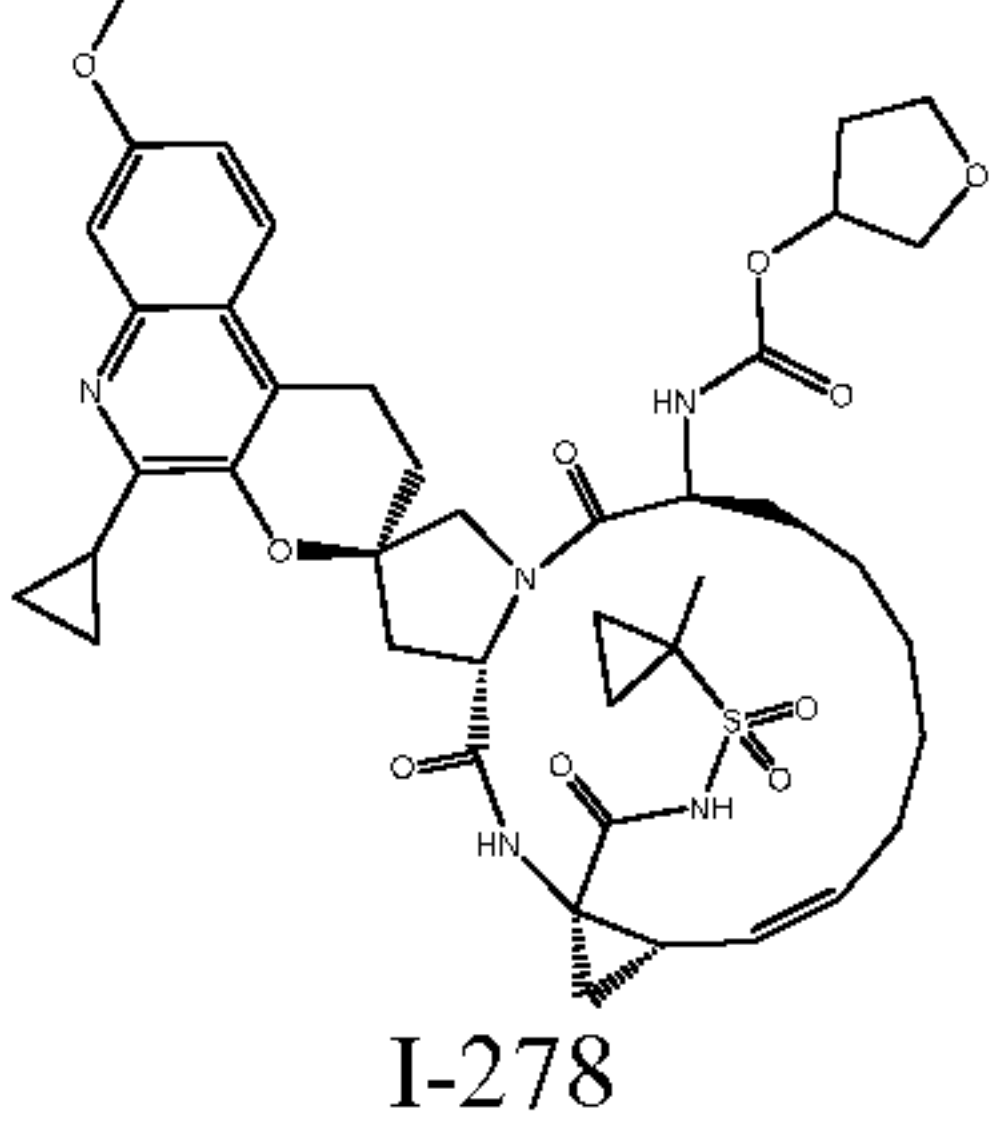
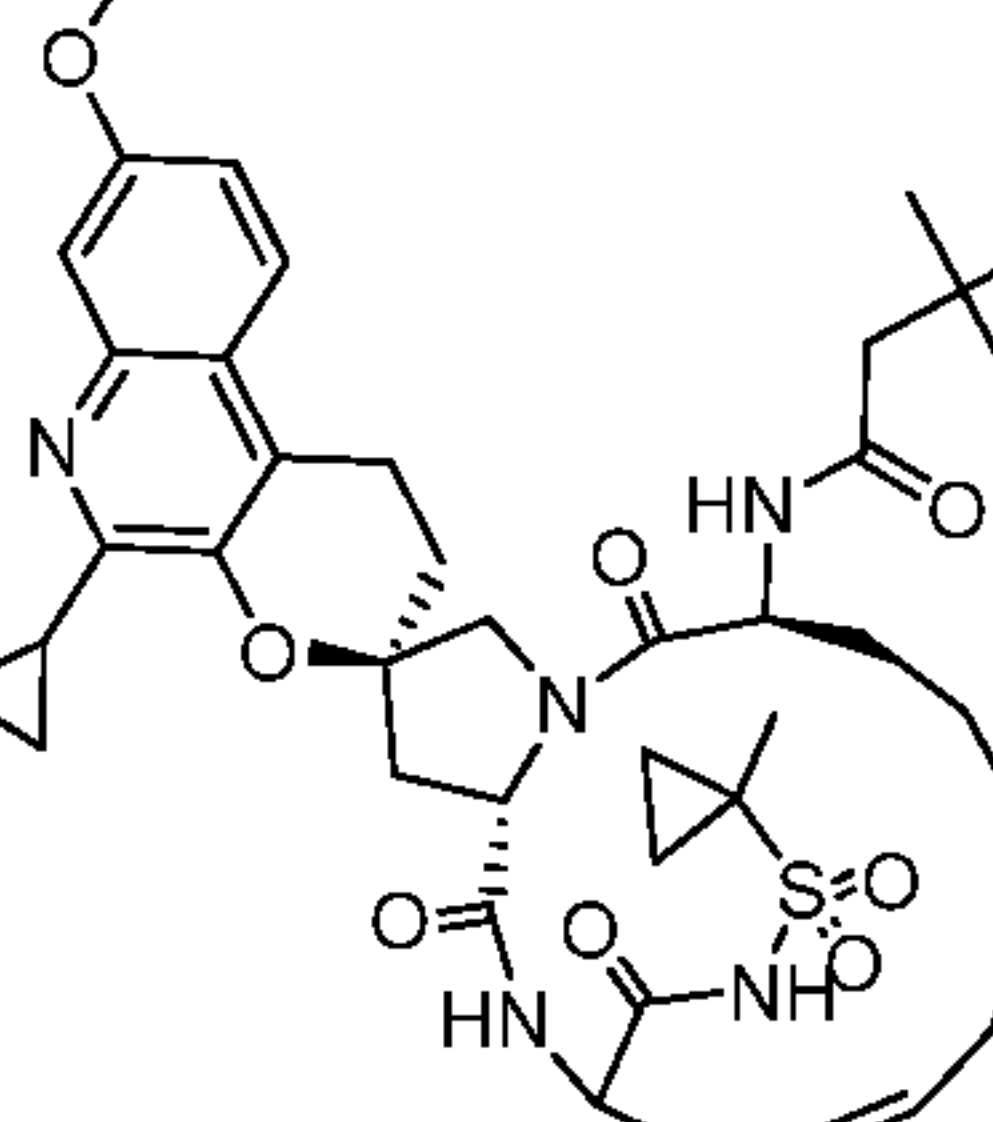
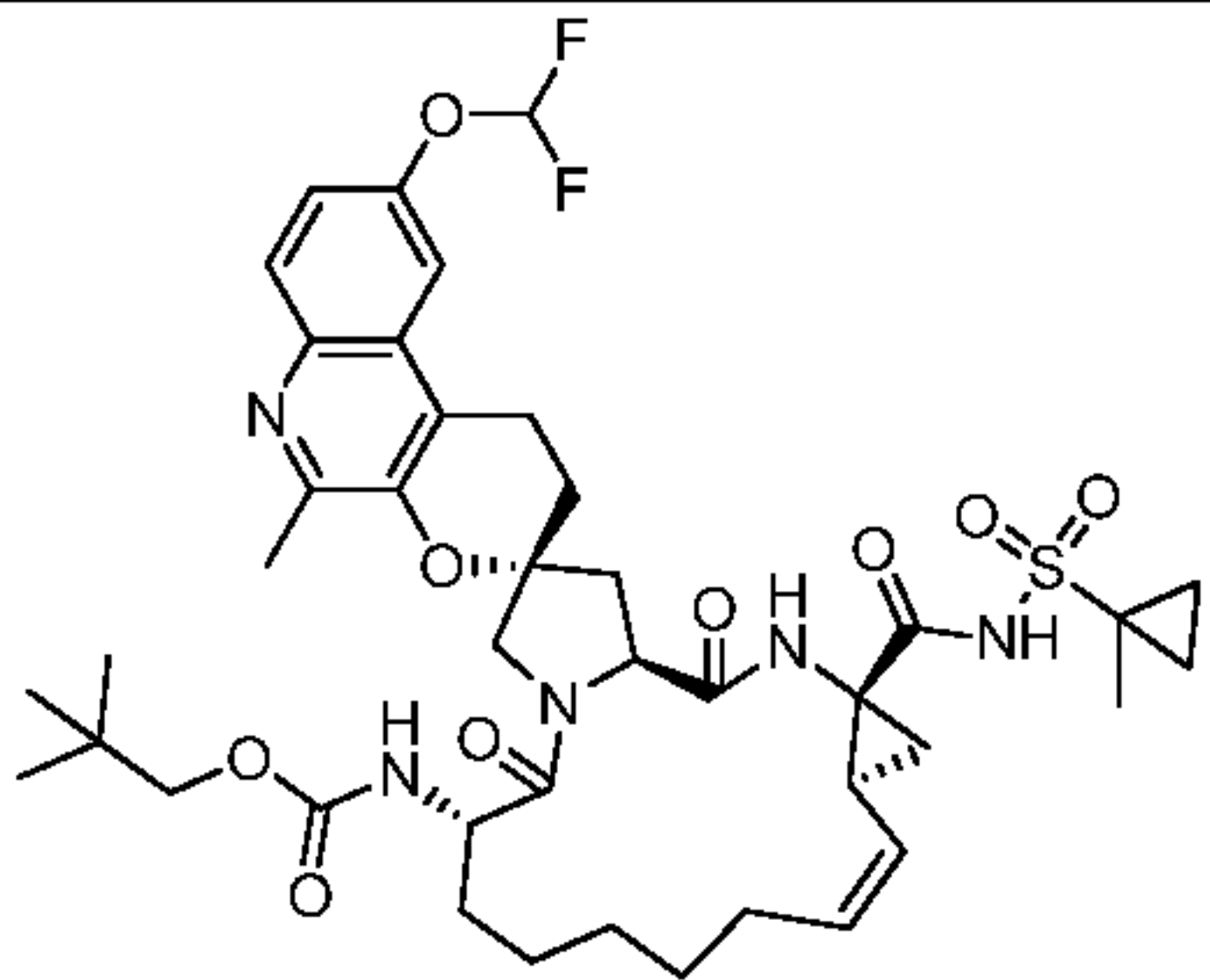
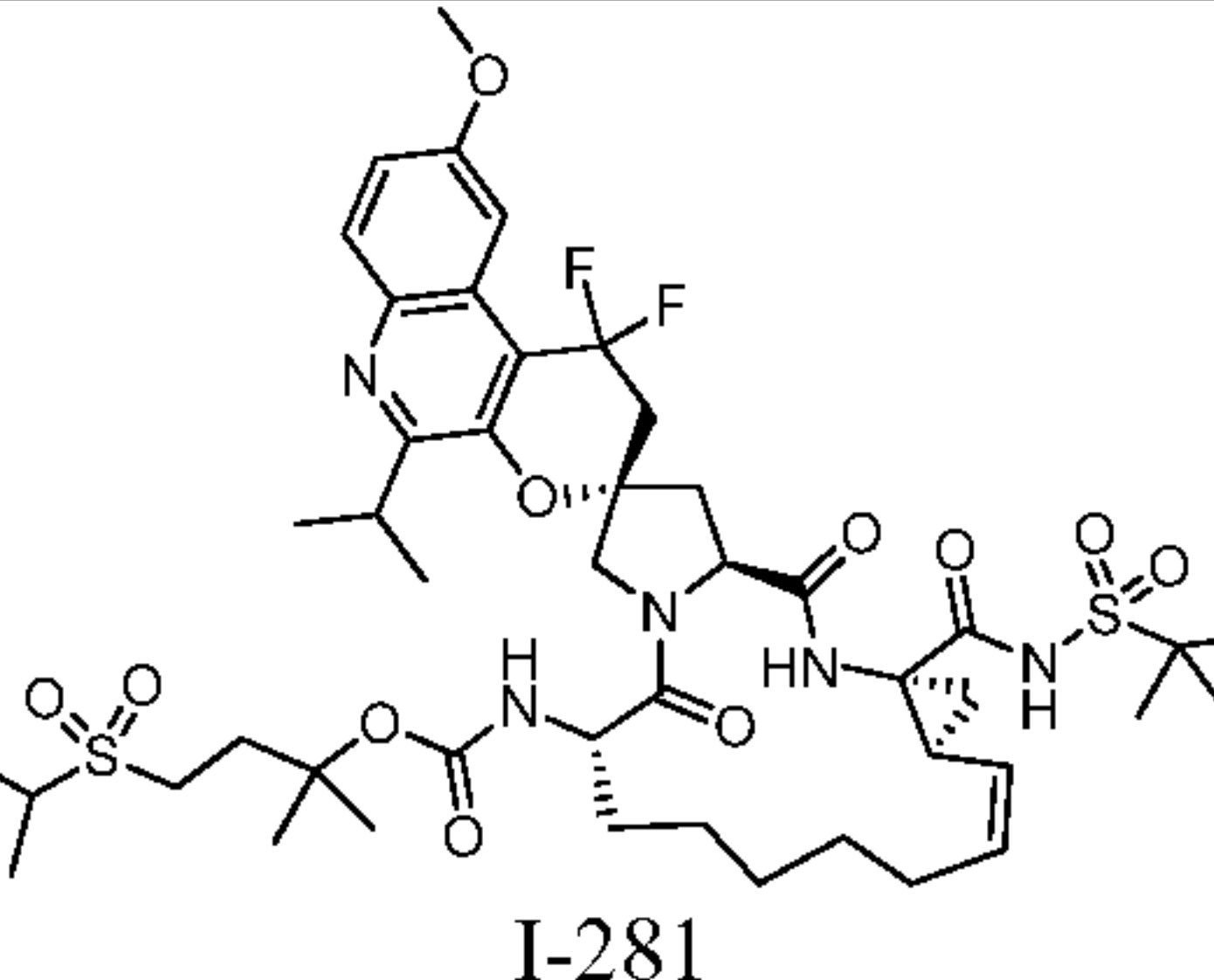
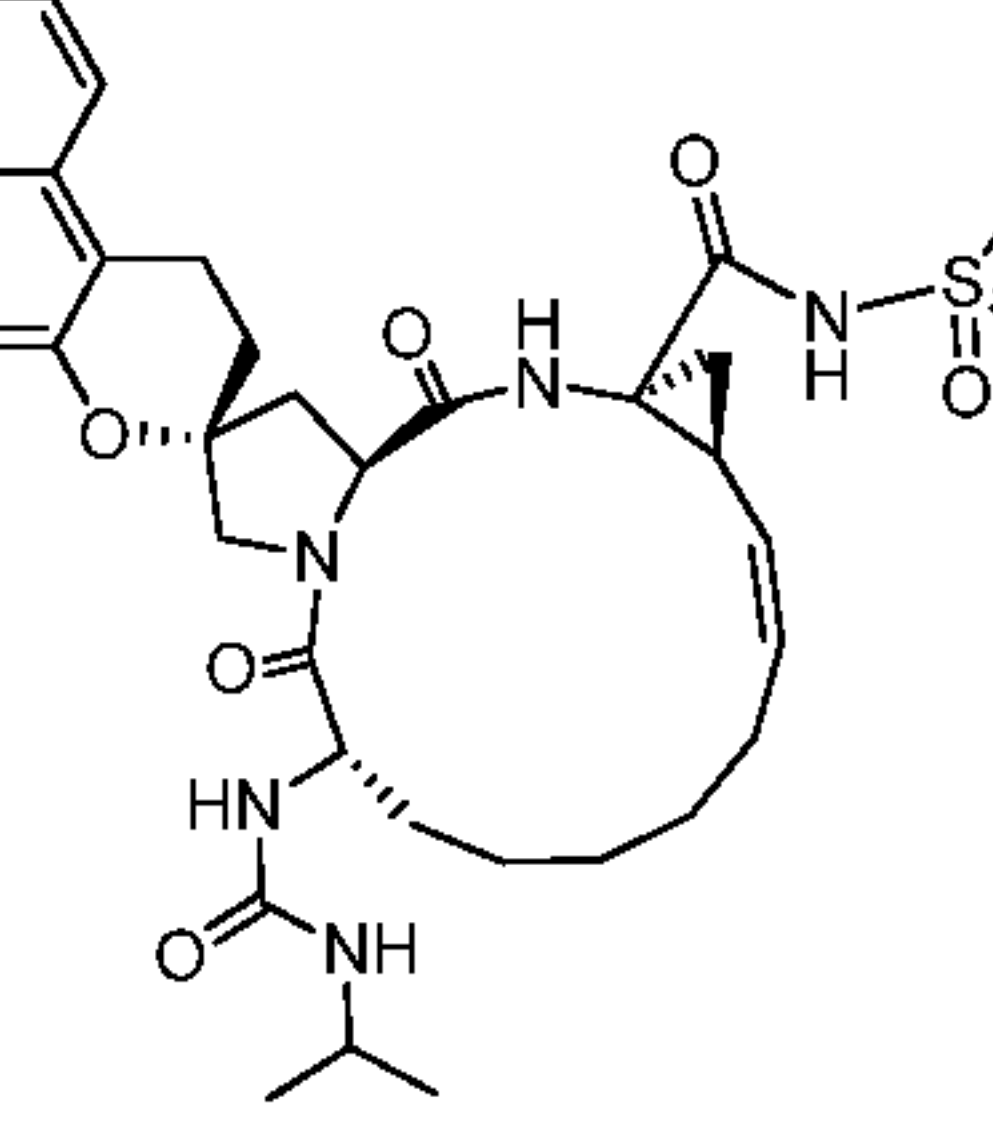
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
252	 I-252	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-9'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	44	--
253	 I-253	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-9'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	44	818.5
254	 I-254	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	834.2 (K+ salt)
255	 I-255	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-9'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	44	832.5
256	 I-256	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-(difluoromethoxy)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	816.5

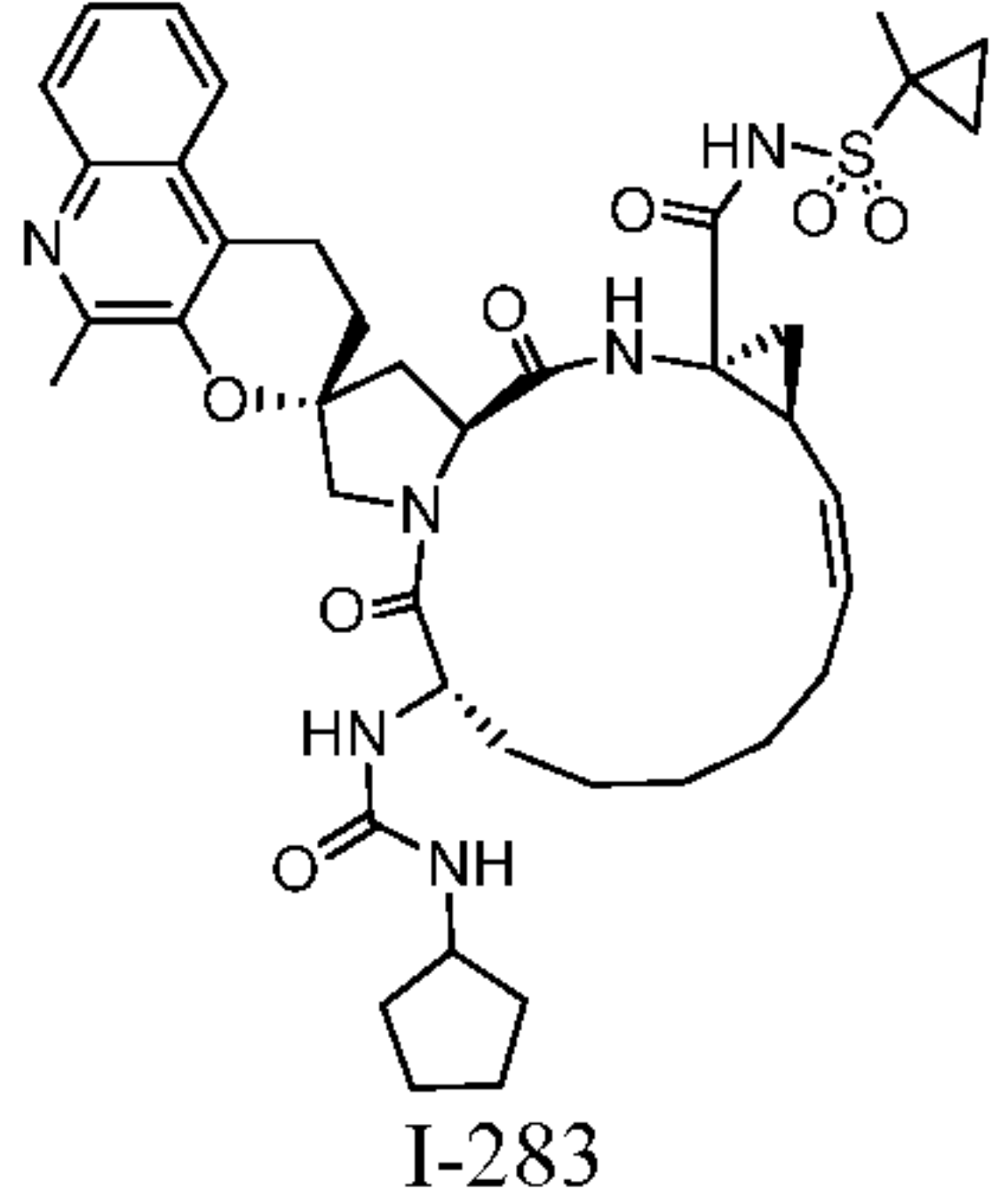
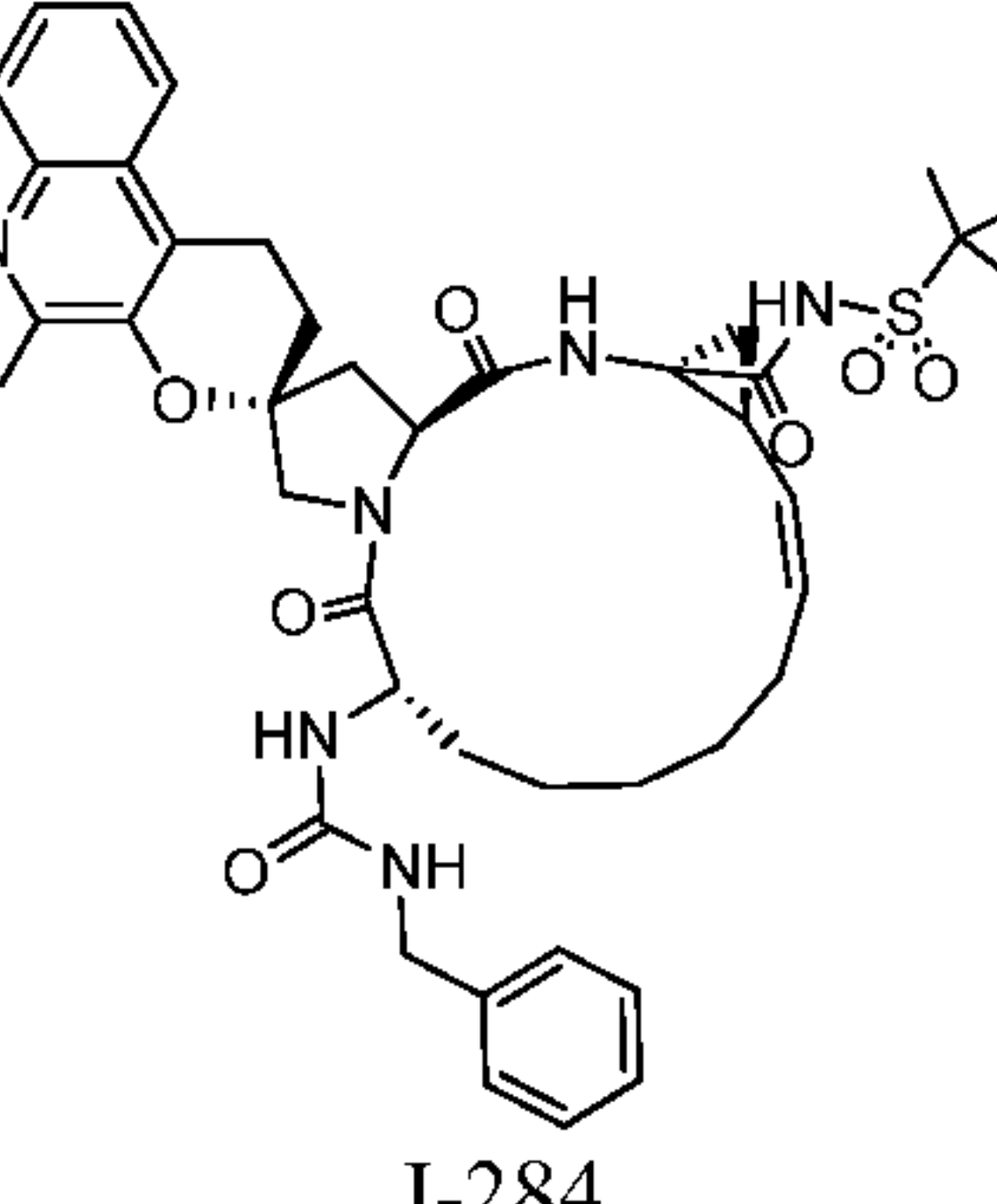
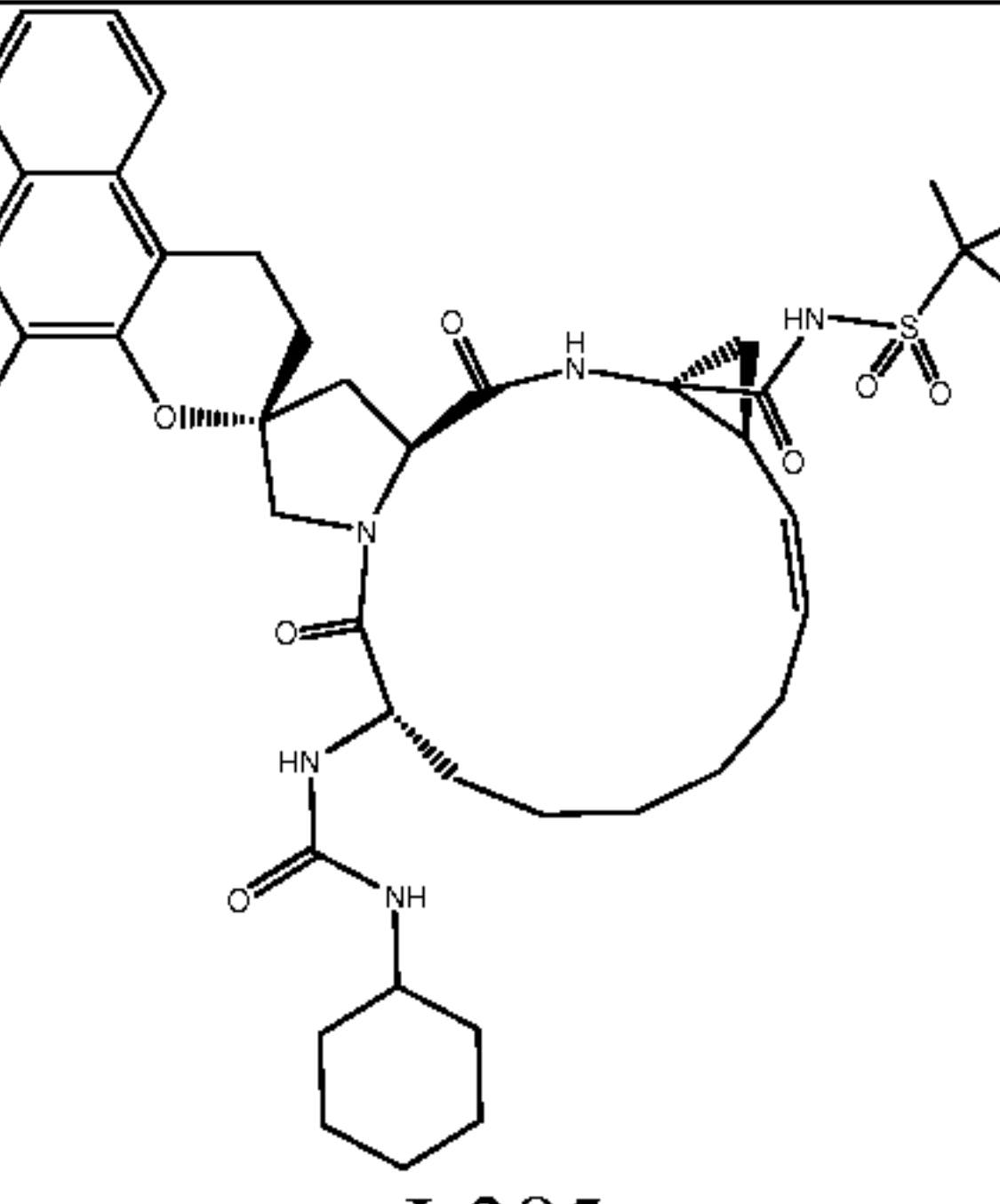
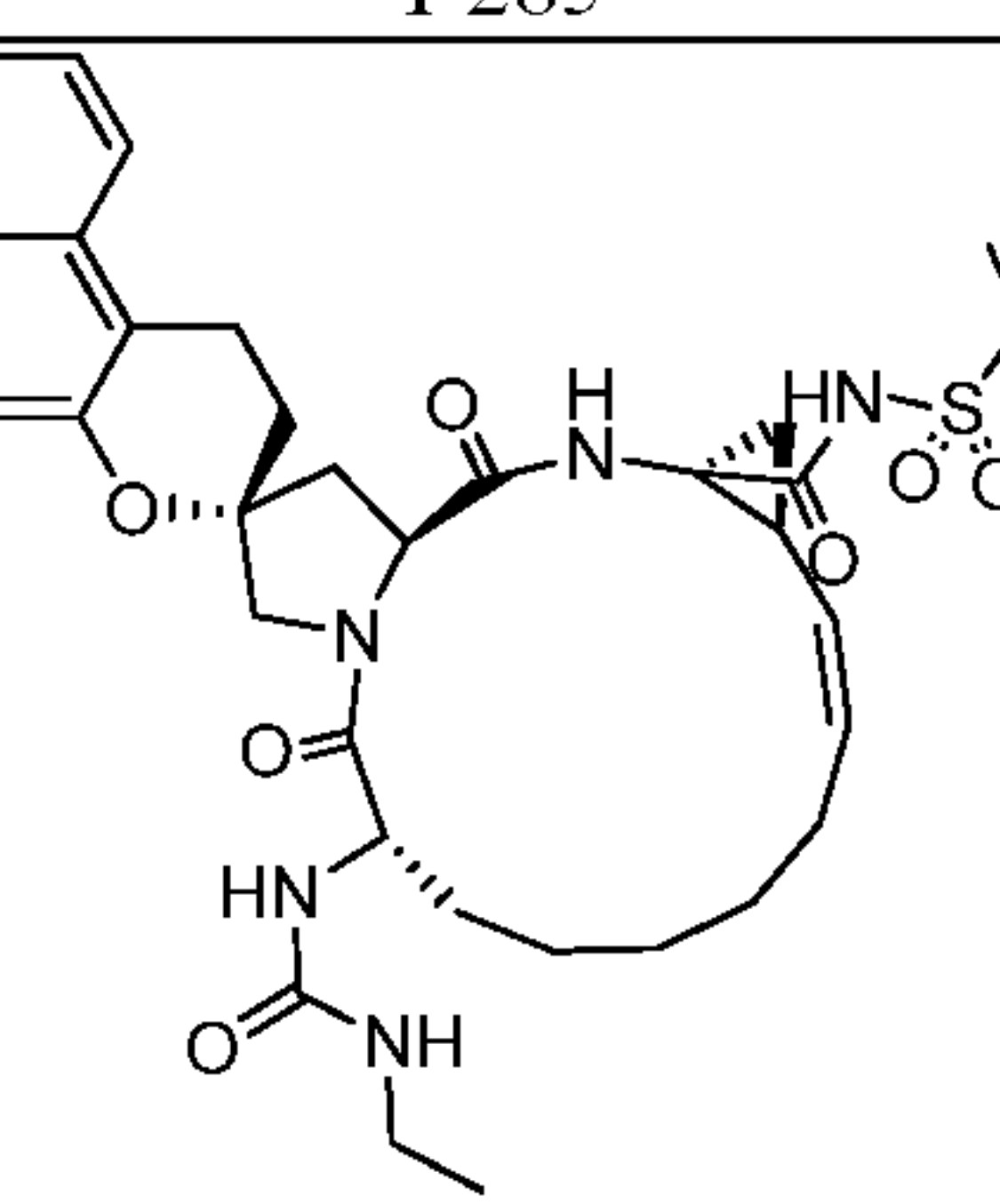
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
257	 I-257	(1 <i>S</i> ,4 <i>S</i>)-bicyclo[2.2.1]hept-5-en-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	786.4
258	 I-258	1,1,1,3,3,3-hexafluoropropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	--
259	 I-259	3,3-dimethyl-1-[methyl(methylsulfonyl)amino]butan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	885.4
260	 I-260	cyclopentyl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1',1'-difluoro-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	20	828.2
261	 I-261	2-oxohexahydro-2 <i>H</i> -cyclopenta[<i>b</i>]furan-5-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	848.2
262	 I-262	3,3-dimethyl-1-[methyl(methylsulfonyl)amino]butan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 35	885.4

Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
263		(2R)-3-methylbutan-2-yl [(2S,6S,12Z,13aS,14aR,16aS)-1',1'-difluoro-9'-methoxy-5'-methyl-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	20	830.2 (K+ salt)
264		(2S)-3-methylbutan-2-yl [(2S,6S,12Z,13aS,14aR,16aS)-1',1'-difluoro-9'-methoxy-5'-methyl-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	20	830.2 (K+ salt)
265		1,1,1-trifluoro-2-methylpropan-2-yl [(2S,6S,12Z,13aS,14aR,16aS)-1',1'-difluoro-9'-methoxy-5'-methyl-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	20	870.2 (K+ salt)
266		2-methylpropyl [(2S,6S,12Z,13aS,14aR,16aS)-1',1'-difluoro-9'-methoxy-5'-methyl-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	20	816.2 (K+ salt)
267		2-methylpropyl [(2R,6S,12Z,13aS,14aR,16aS)-9'-(difluoromethoxy)-5'-methyl-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	44	816.4

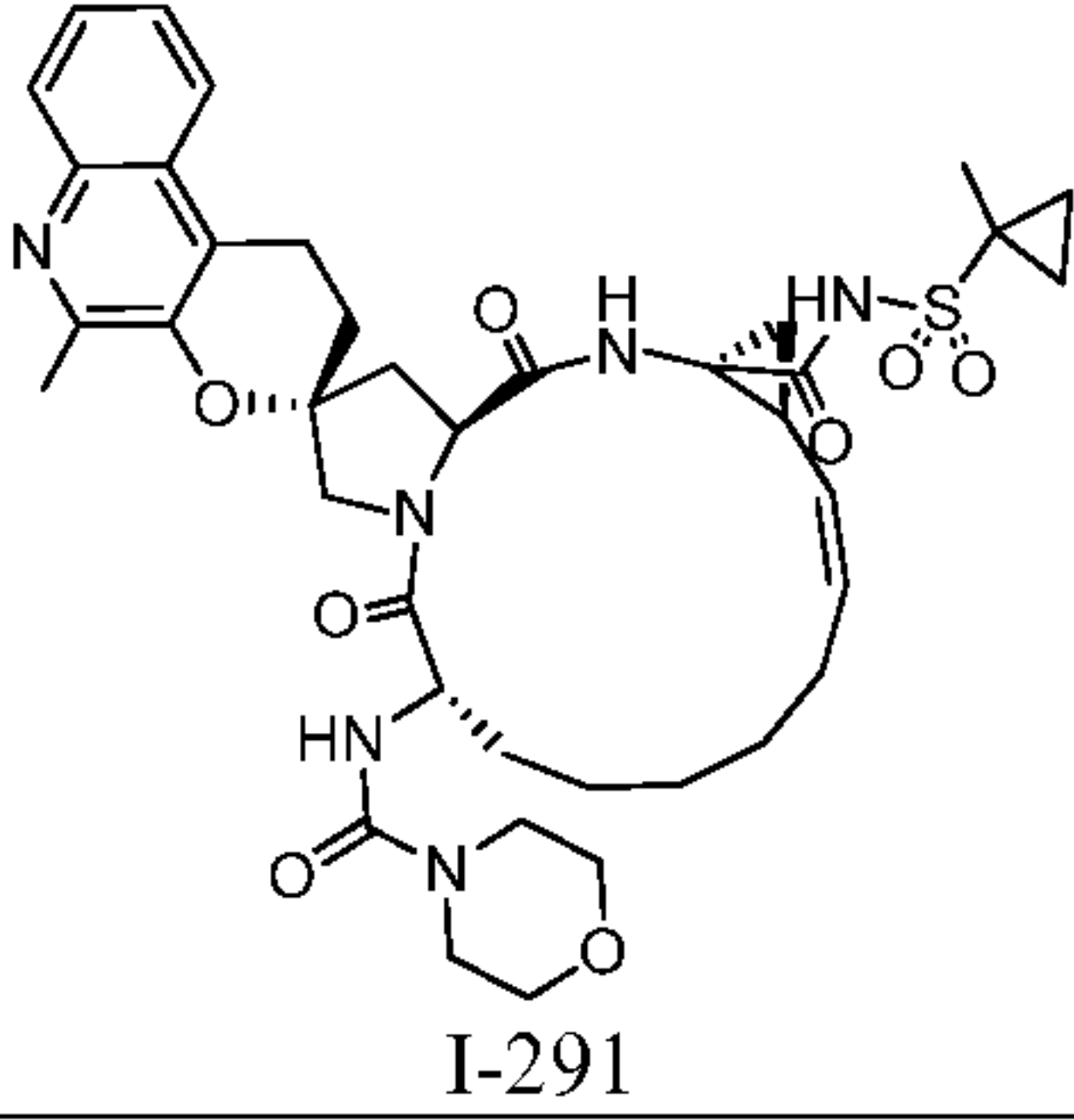
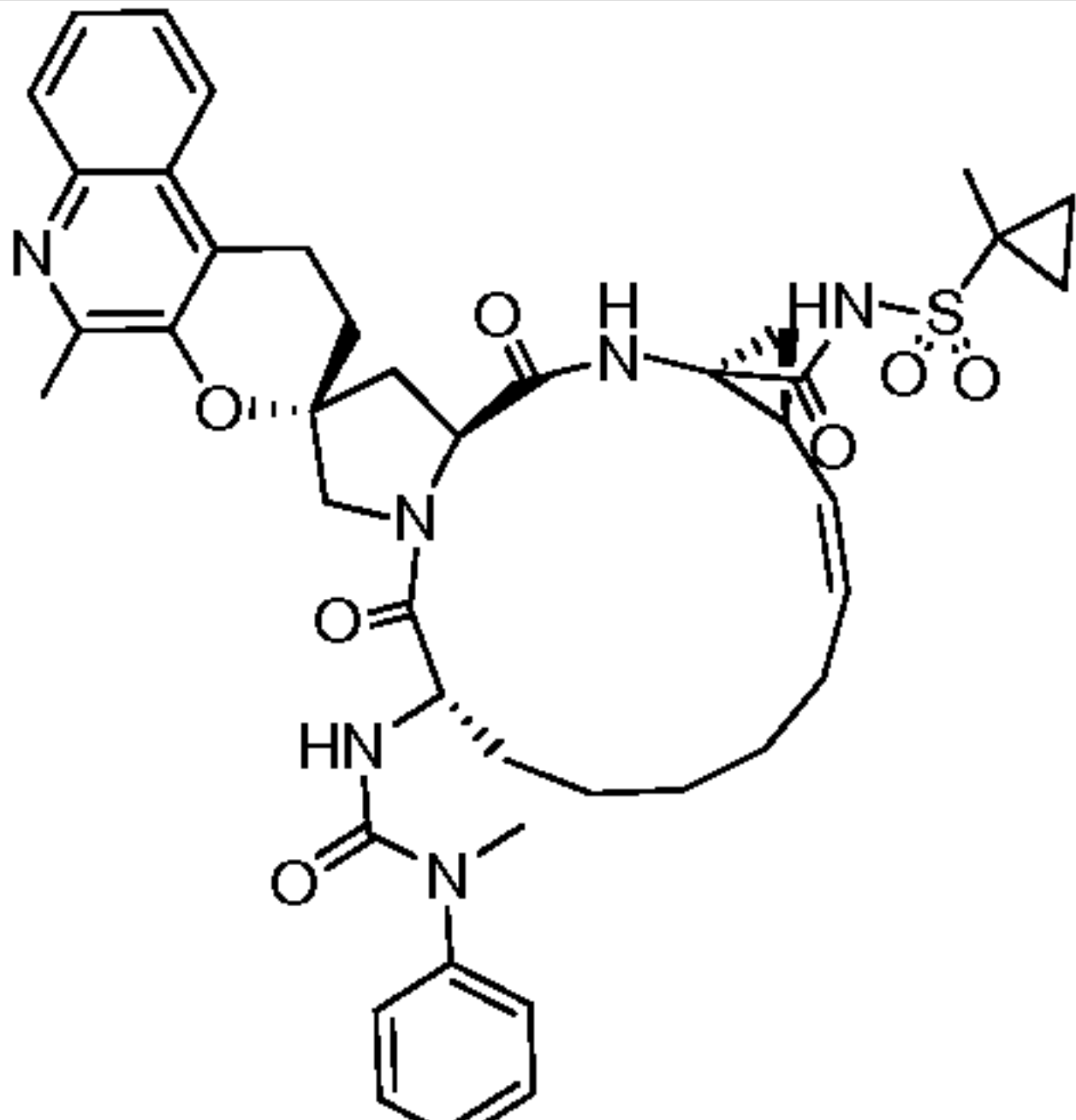
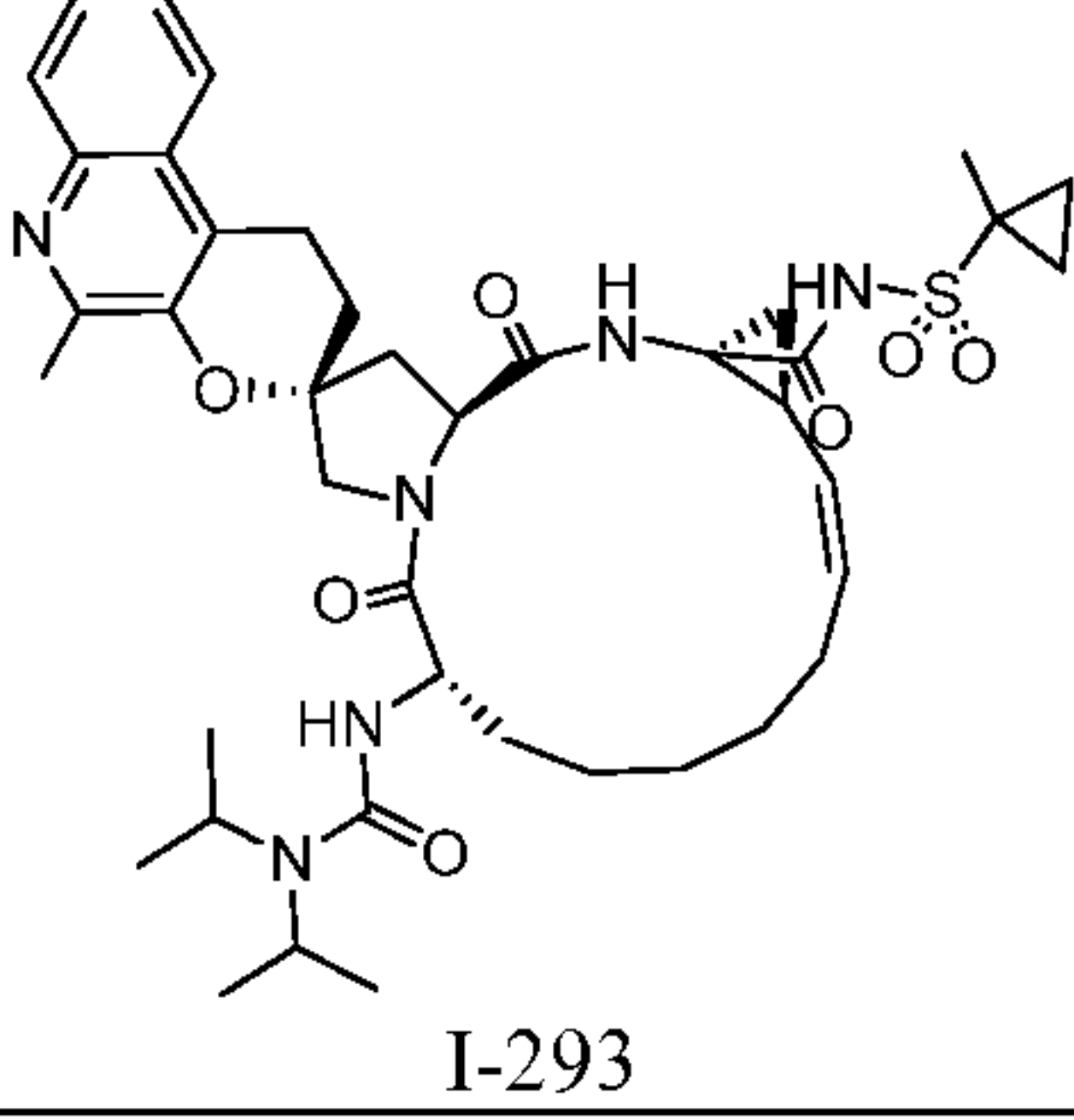
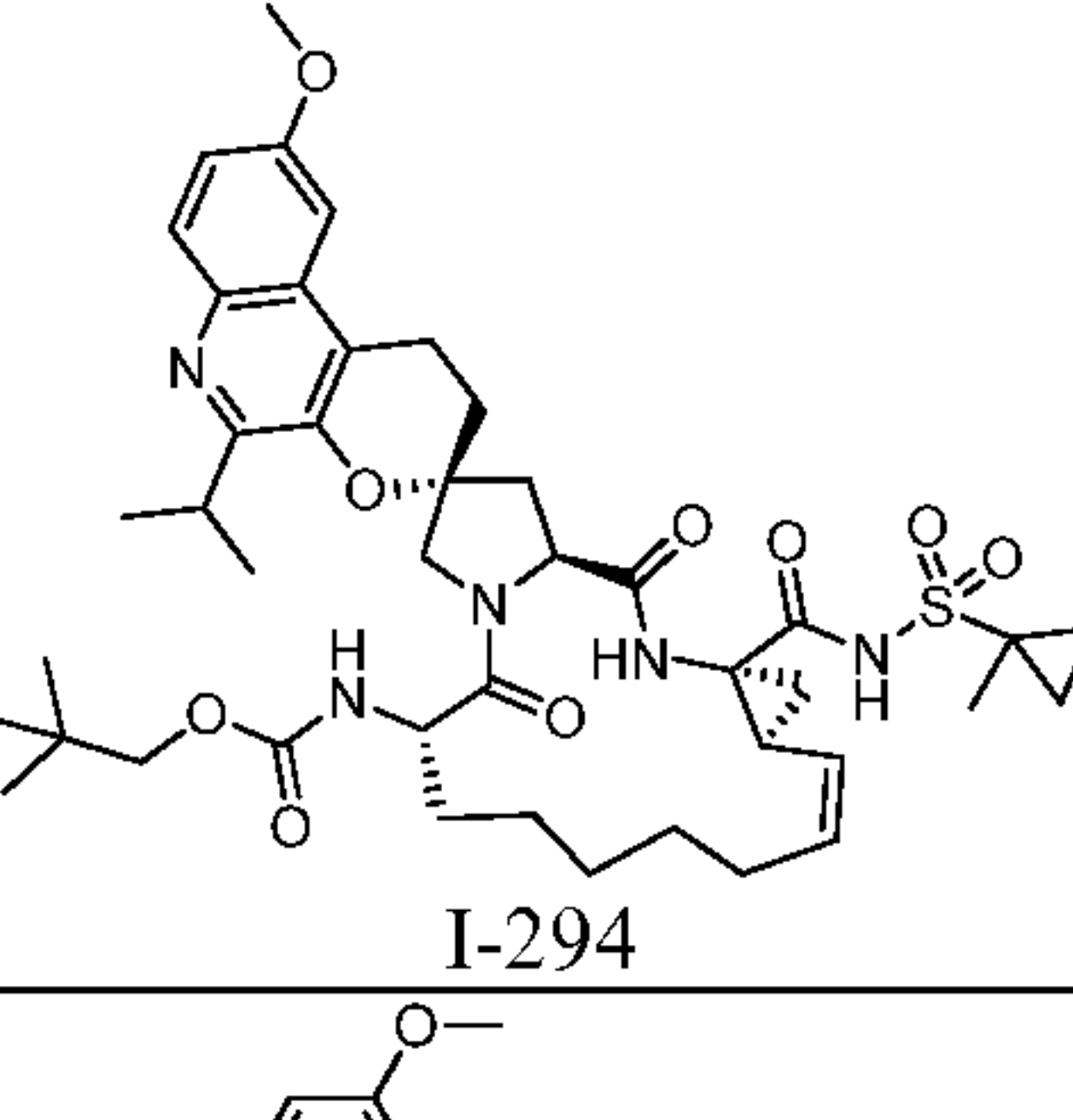
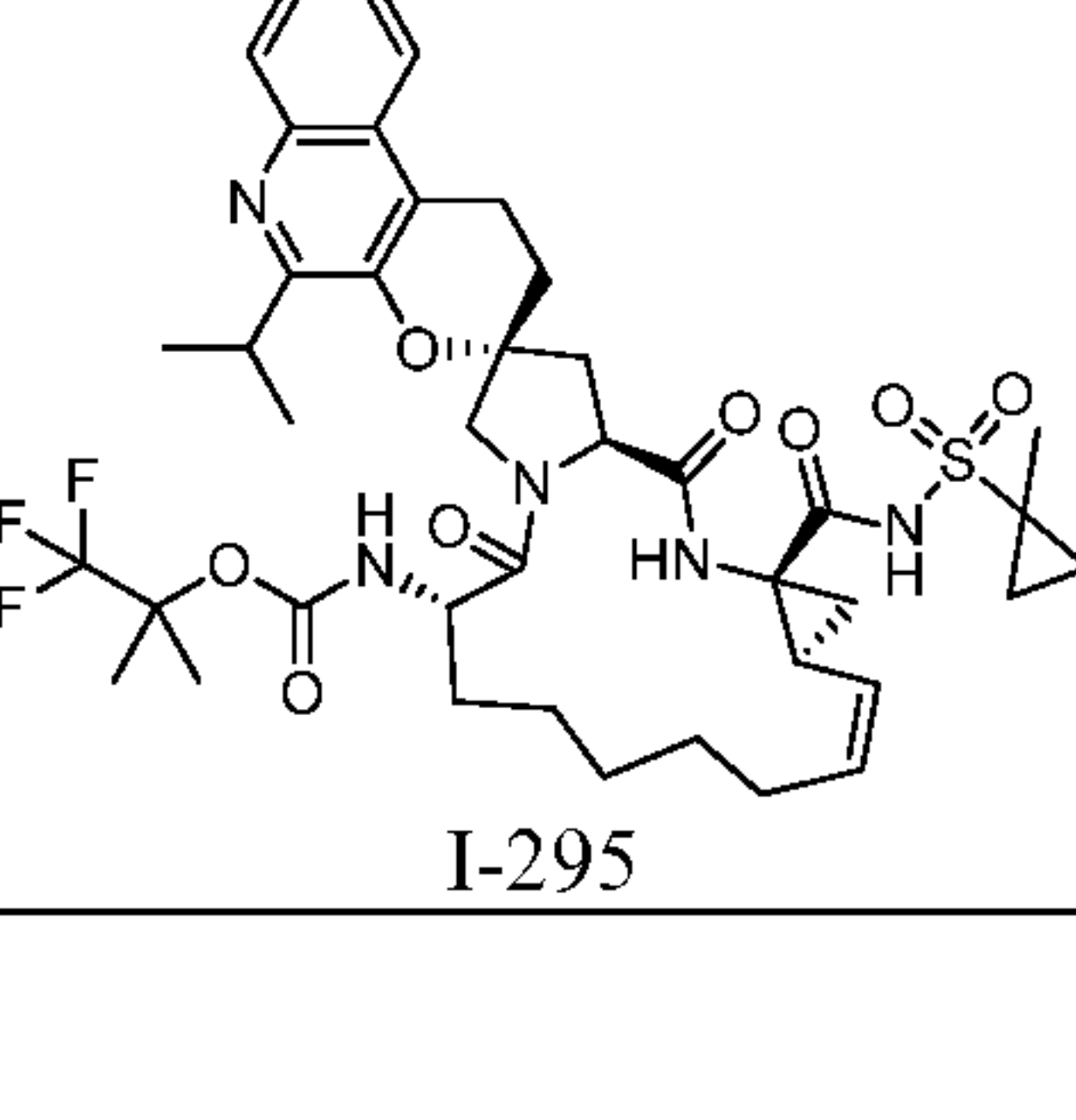
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
268	 I-268	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-(difluoromethoxy)-5'-methyl-14a- {[1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	--
269	 I-269	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-6-[(3,3-dimethylbutanoyl)amino]-8'-methoxy- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	9	804.61 (HCOOH salt)
270	 I-270	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(cyclopentylacetyl)amino]-5'-cyclopropyl-8'-methoxy- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	9	--
271	 I-271	propyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-8'-methoxy-14a- {[1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	792.55 (HCOOH salt)
272	 I-272	butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-8'-methoxy-14a- {[1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	806.56 (HCOOH salt)

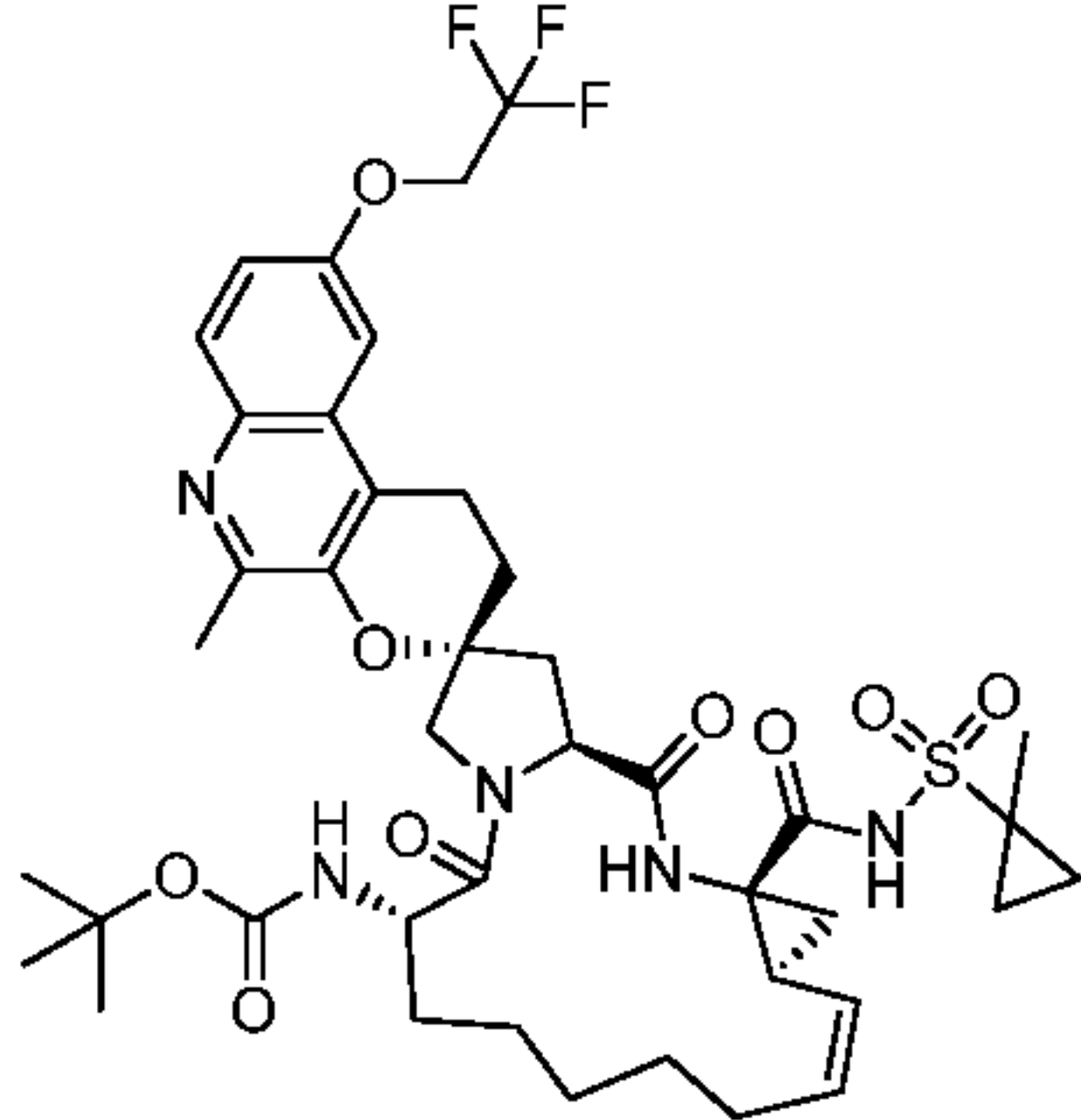
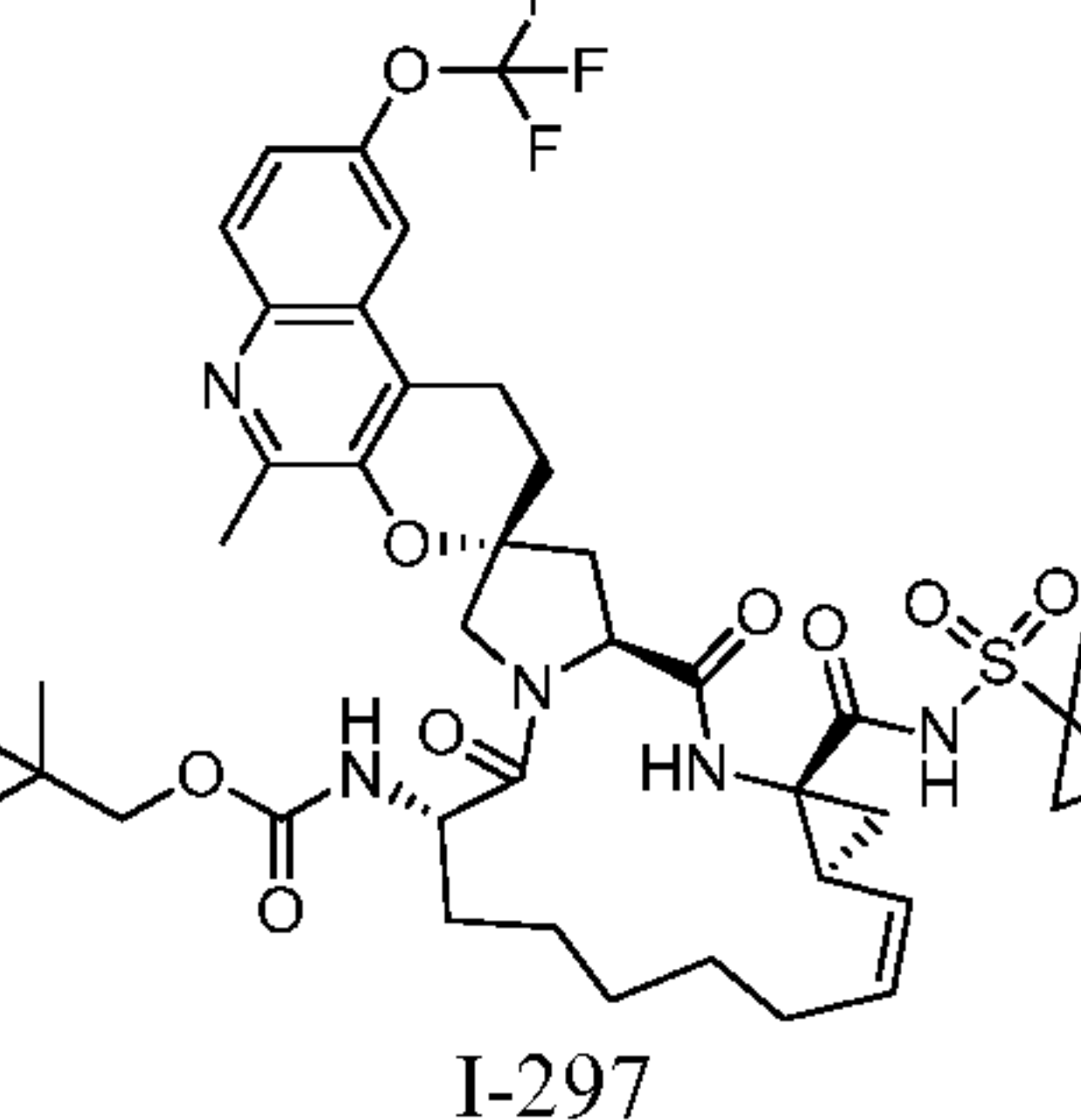
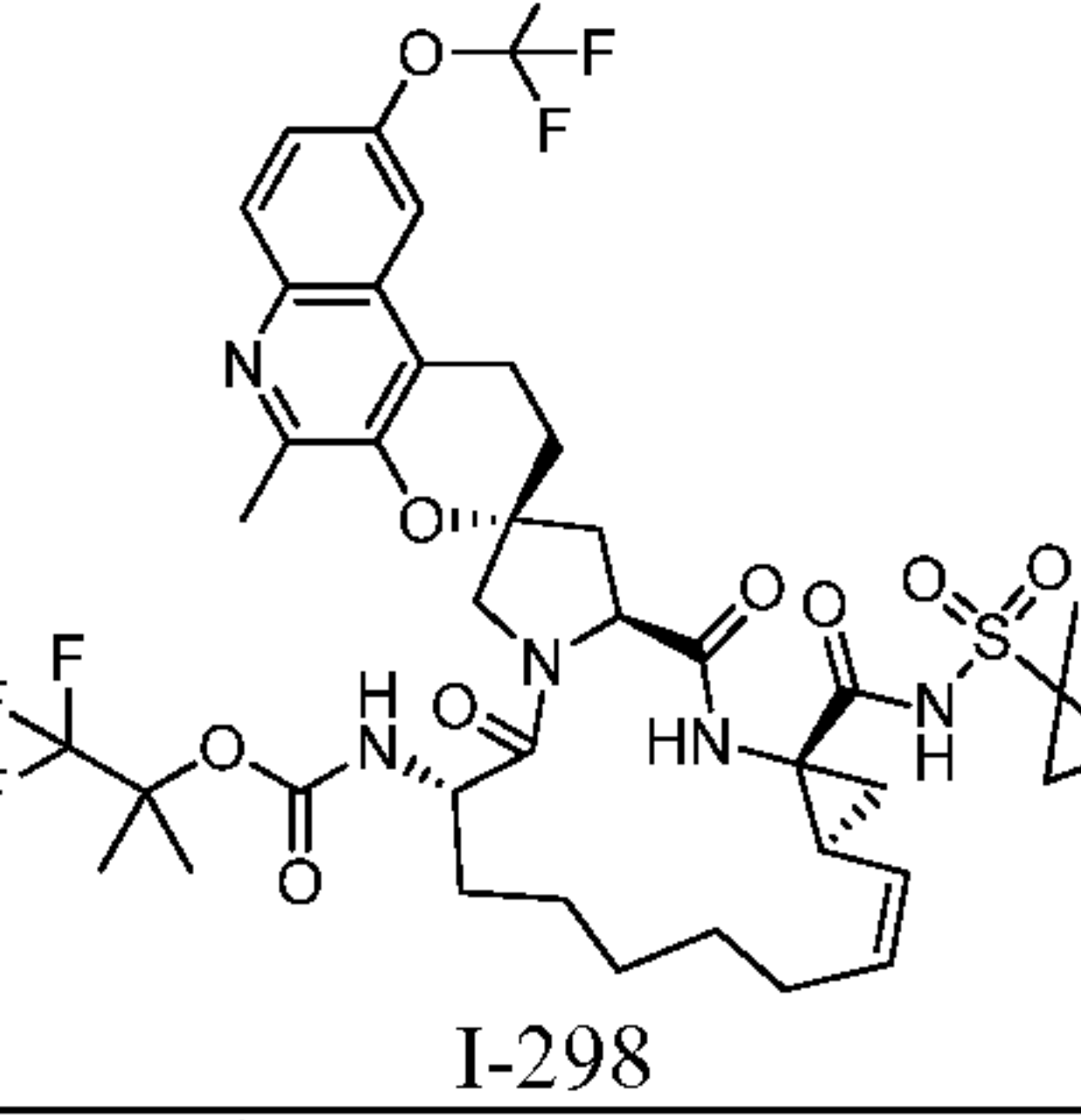
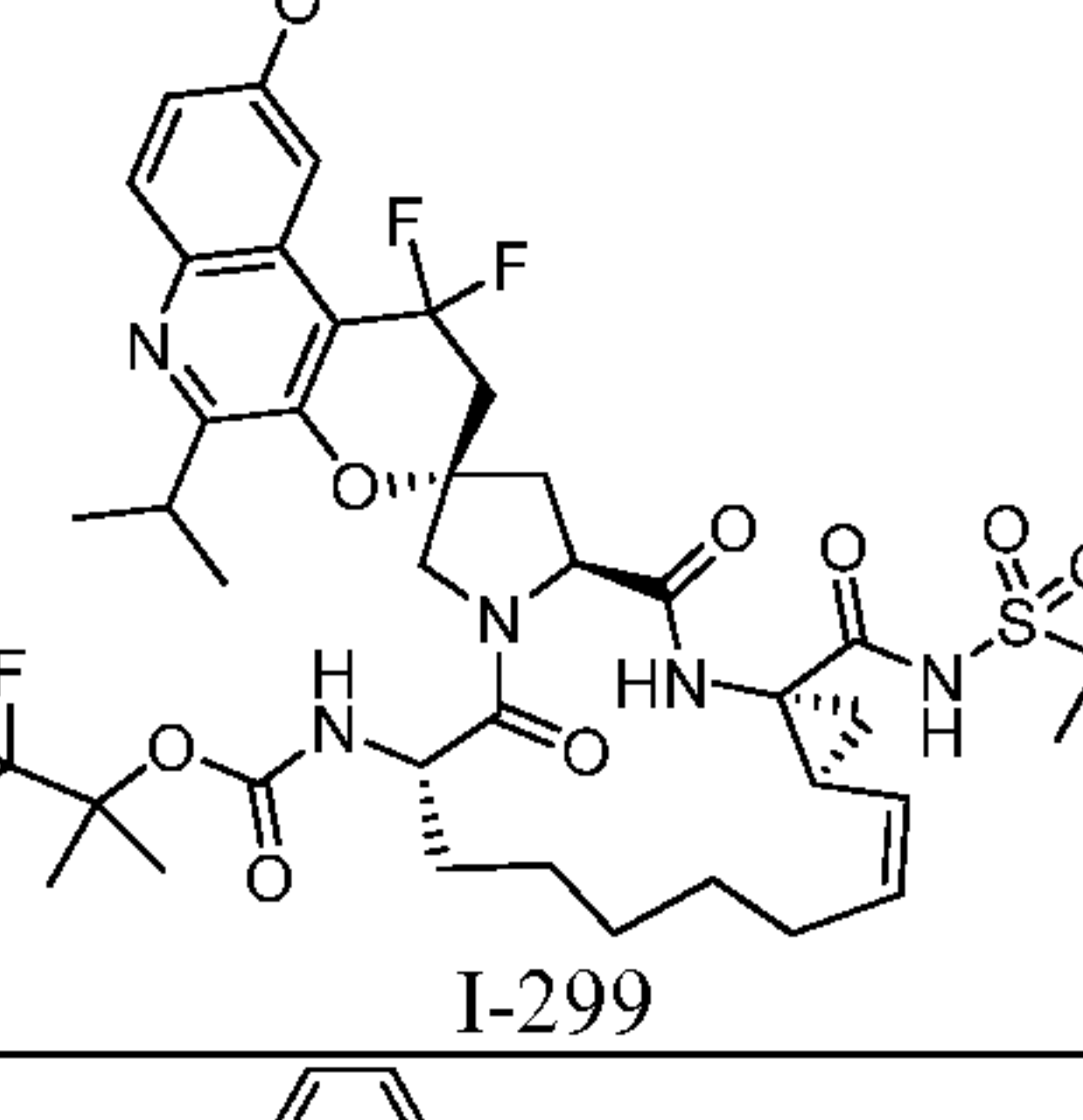
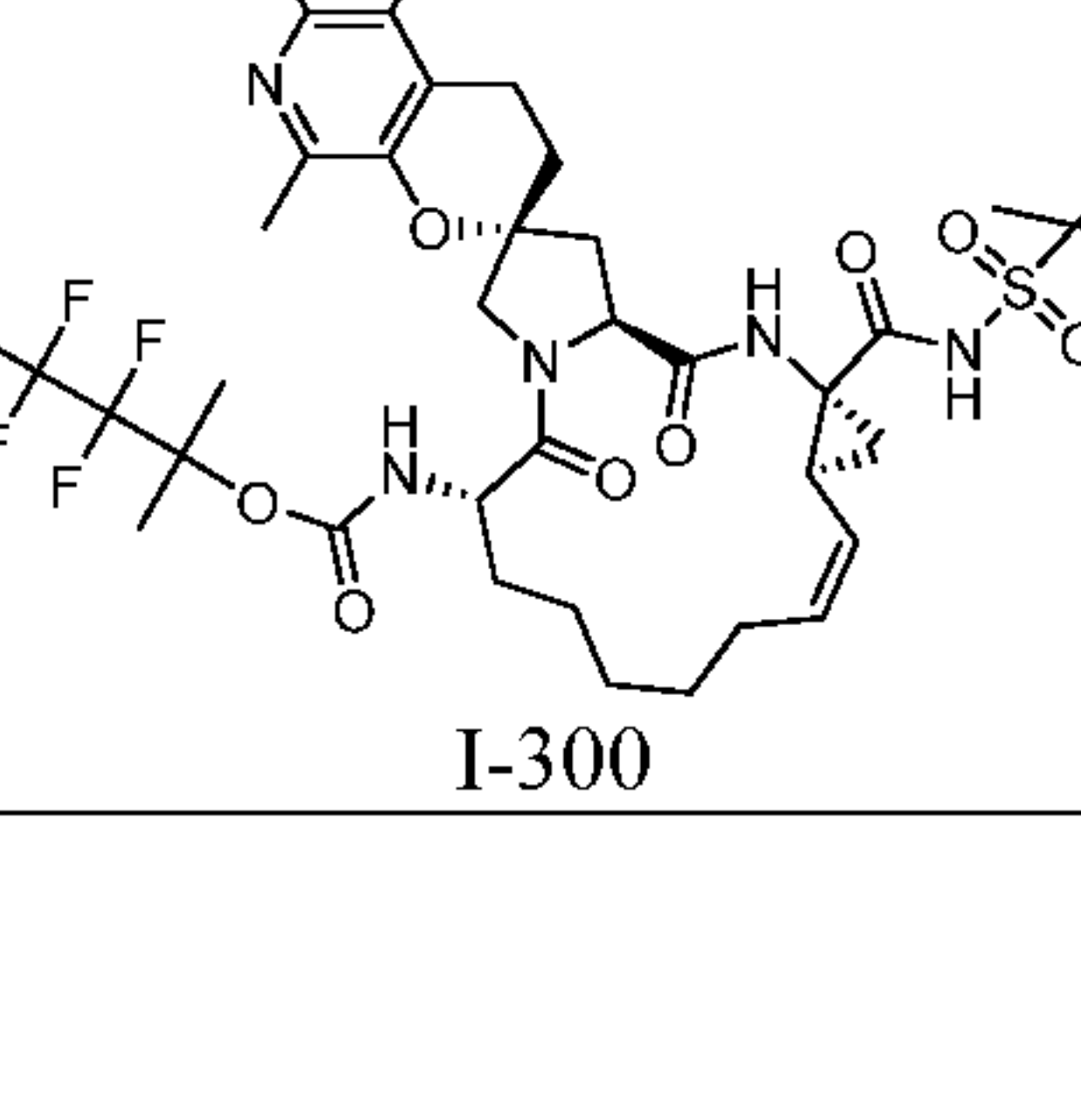
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
273	 I-273	pentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-8'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	820.58 (HCOOH salt)
274	 I-274	4-methylphenyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-8'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	840.59 (HCOOH salt)
275	 I-275	(1 <i>S</i> ,2 <i>R</i> ,5 <i>S</i>)-5-methyl-2-(propan-2-yl)cyclohexyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-8'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	888.67 (HCOOH salt)
276	 I-276	(1 <i>R</i> ,2 <i>S</i> ,5 <i>R</i>)-5-methyl-2-(propan-2-yl)cyclohexyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-8'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	888.7 (HCOOH salt)
277	 I-277	2-fluoroethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-8'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	796.51 (HCOOH salt)

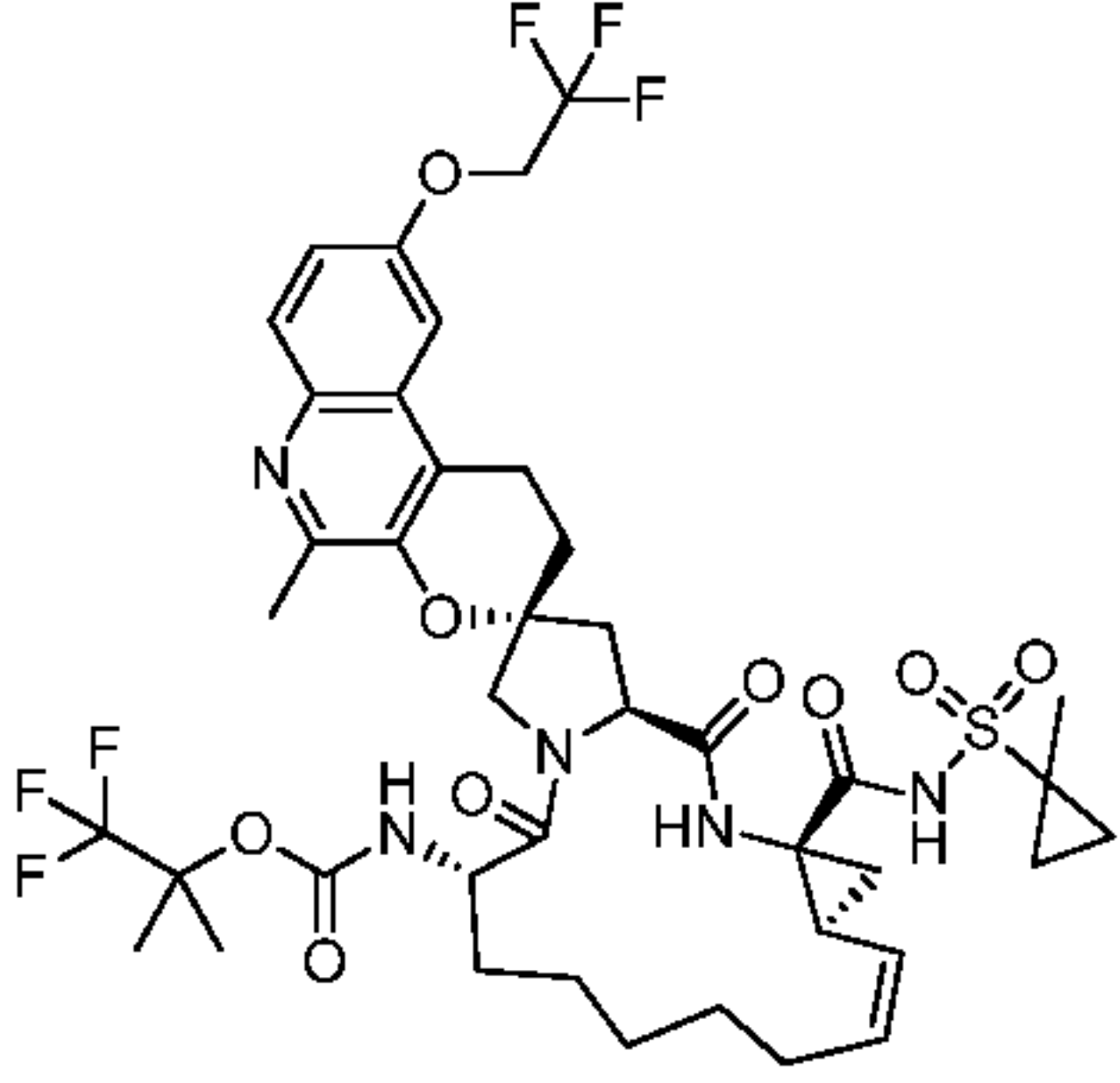
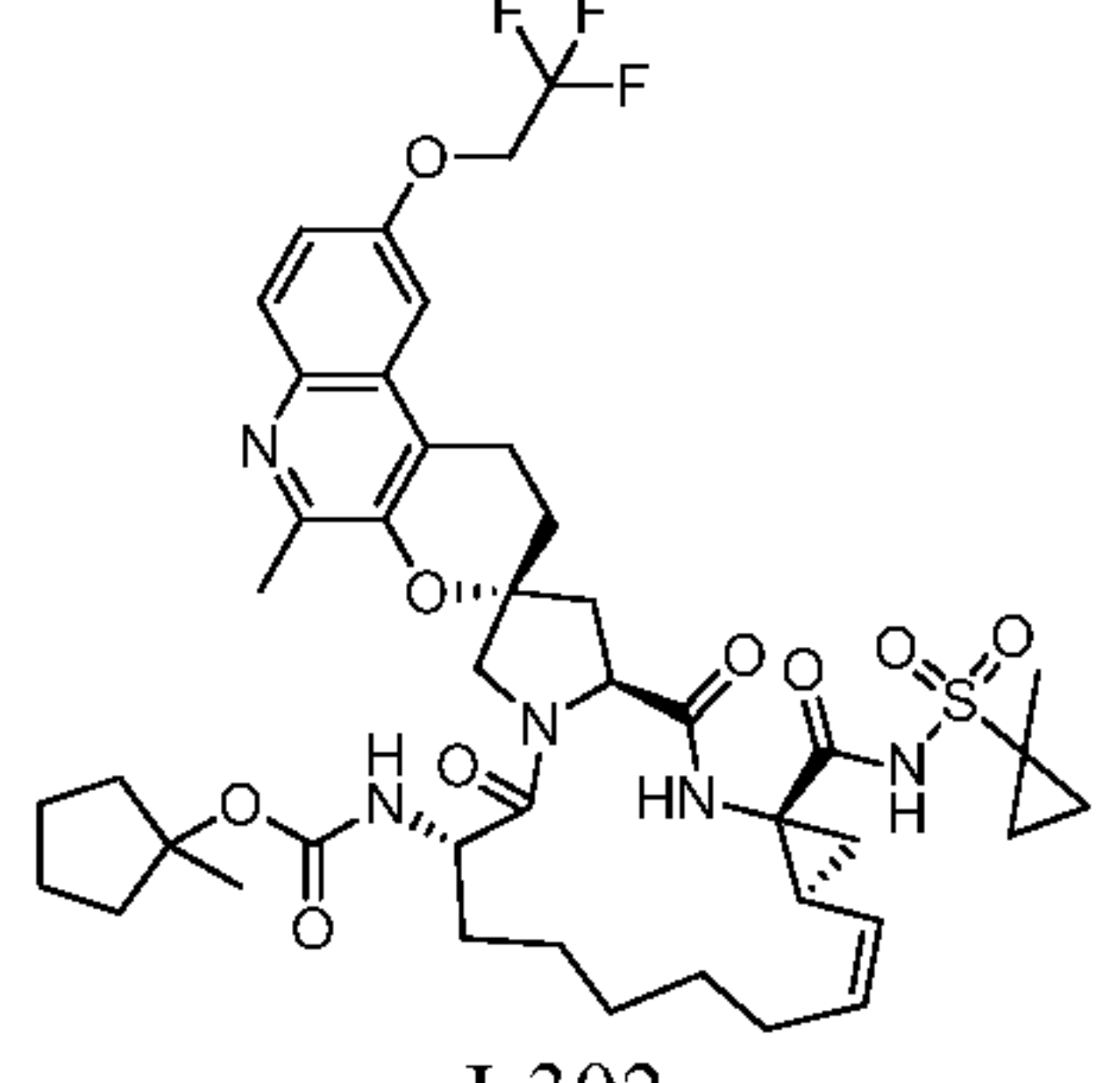
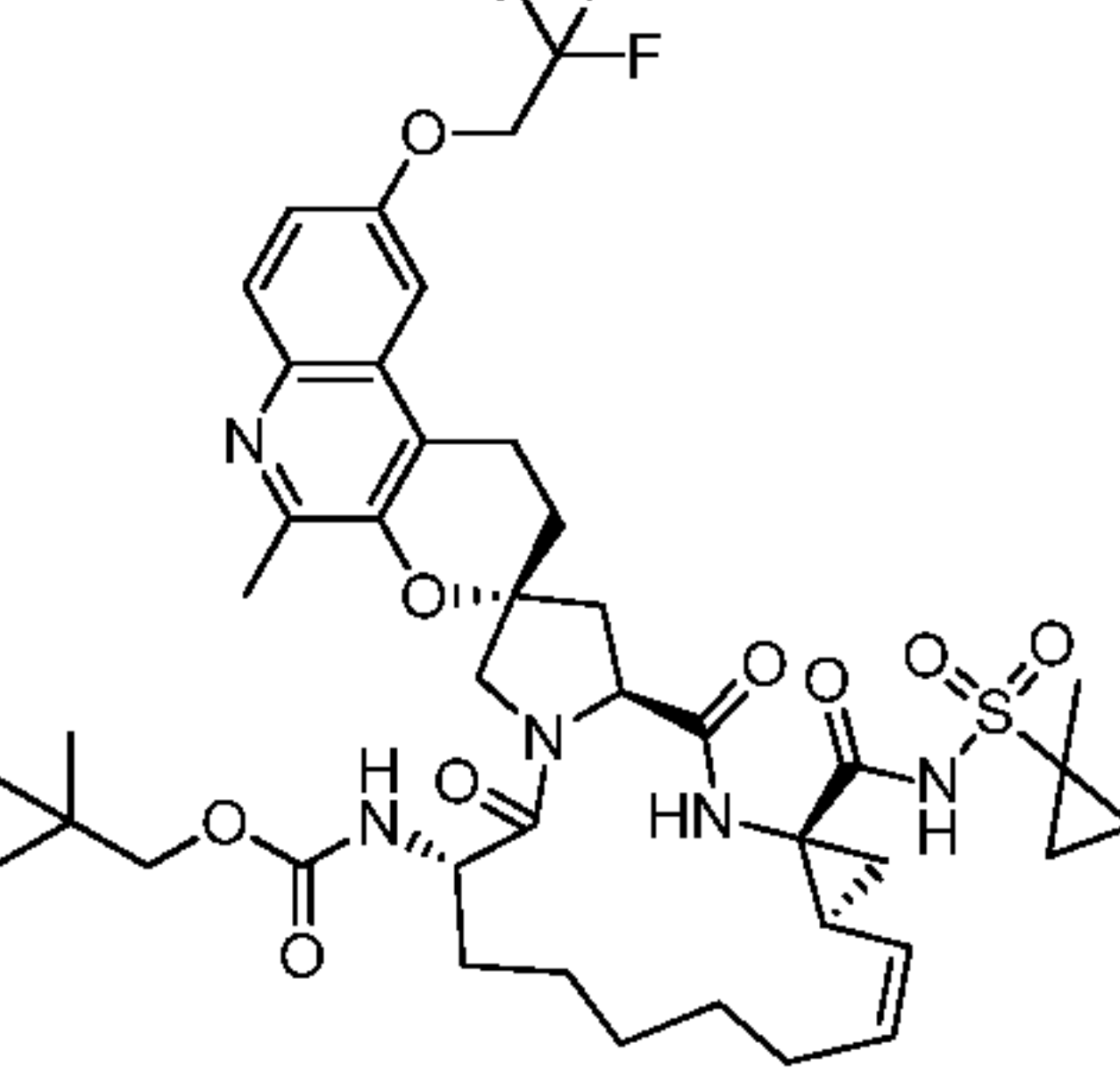
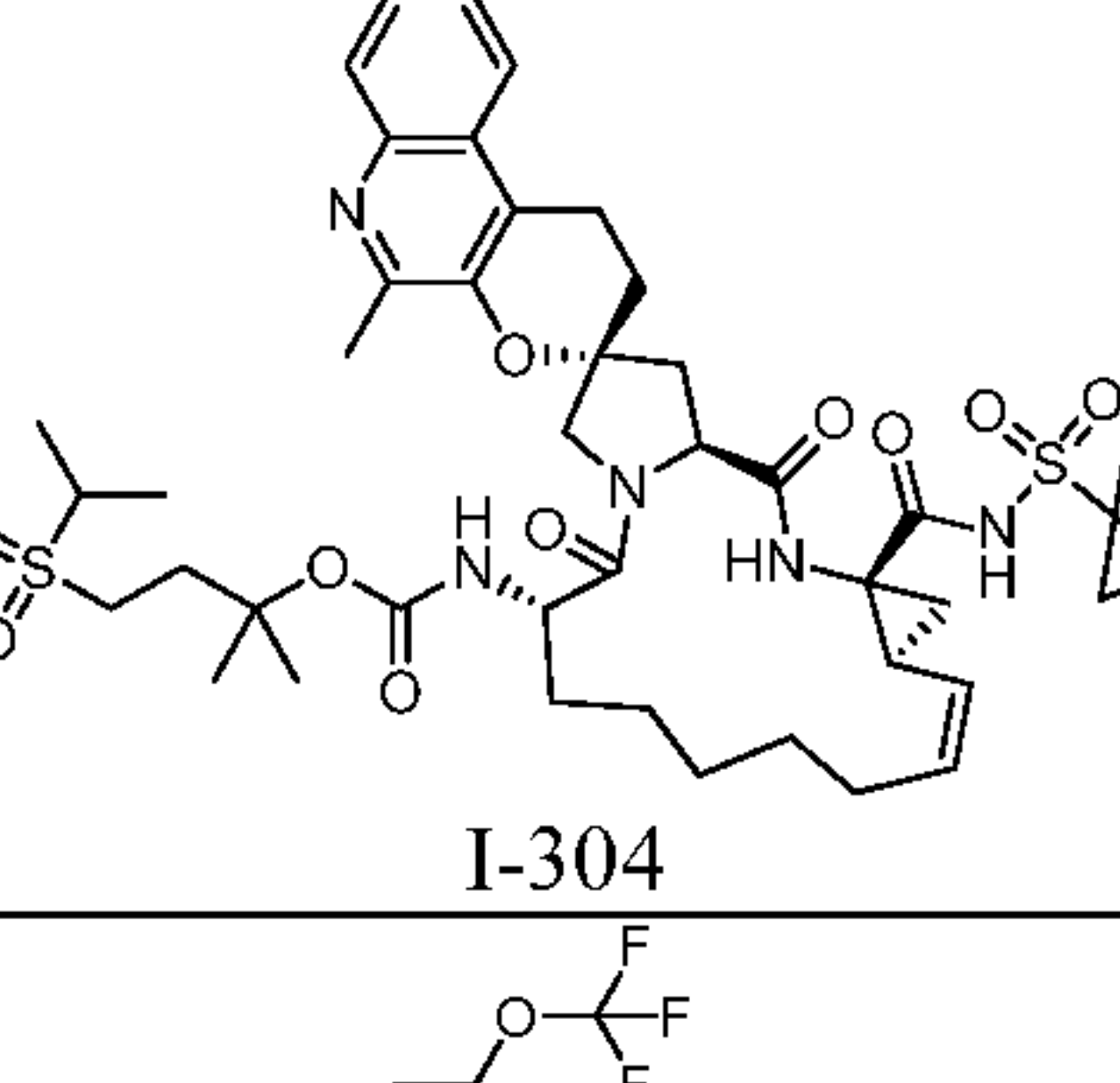
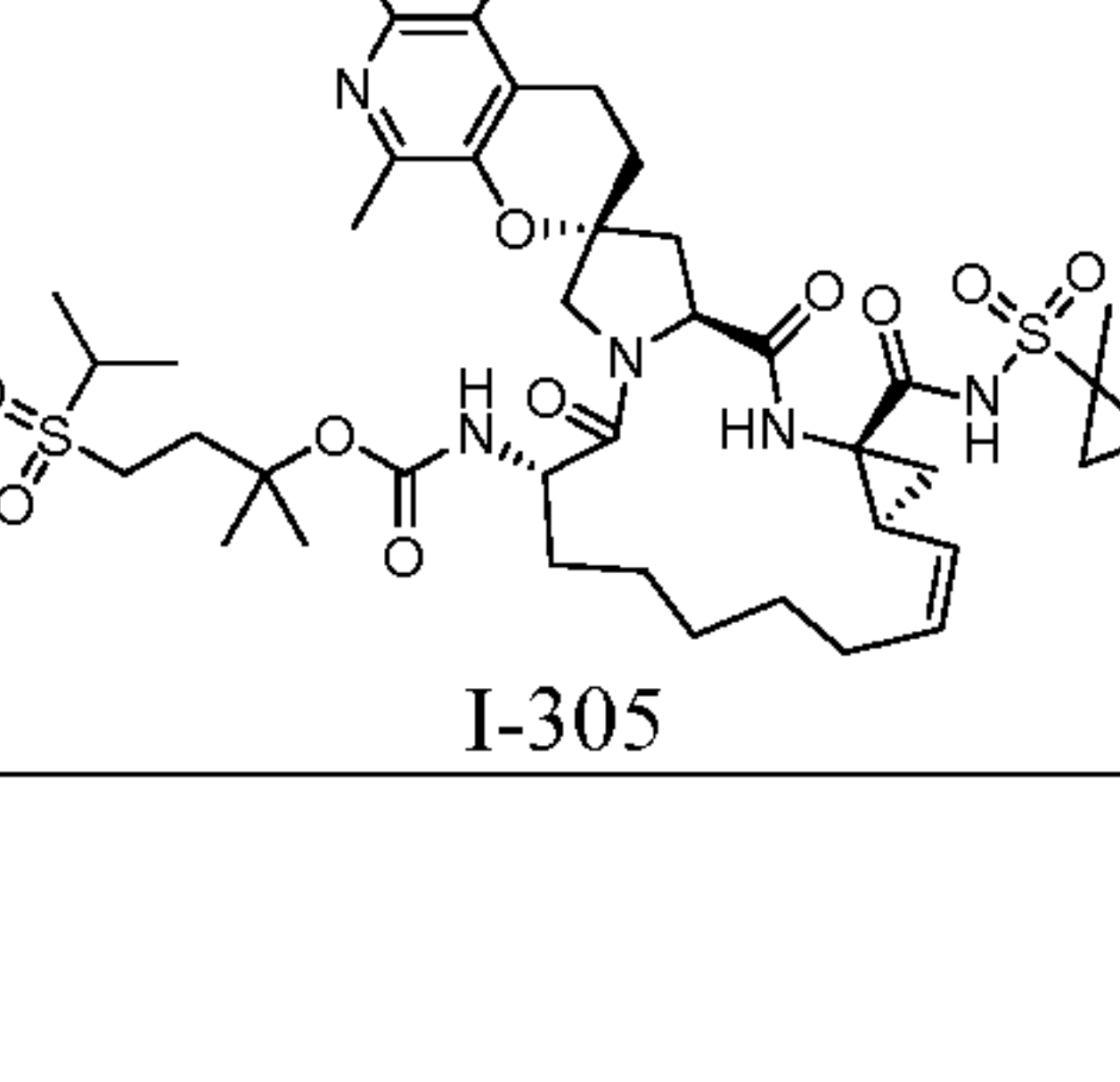
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
278	 I-278	tetrahydrofuran-3-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-8'-methoxy-14a- {[1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	820.53 (HCOOH salt)
279	 I-279	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-6-[(3,3-dimethylbutanoyl)amino]-8'-methoxy- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	9	820.59 (HCOOH salt)
280	 I-280	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-(difluoromethoxy)-5'-methyl-14a- {[1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	830.5
281	 I-281	2-methyl-4-(propan-2-ylsulfonyl)butan-2-yl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1',1'-difluoro-9'-methoxy-14a- {[1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	2	963.6
282	 I-282	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-6-[(propan-2-ylcarbamoyl)amino]-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	47	735.47 (HCOOH salt)

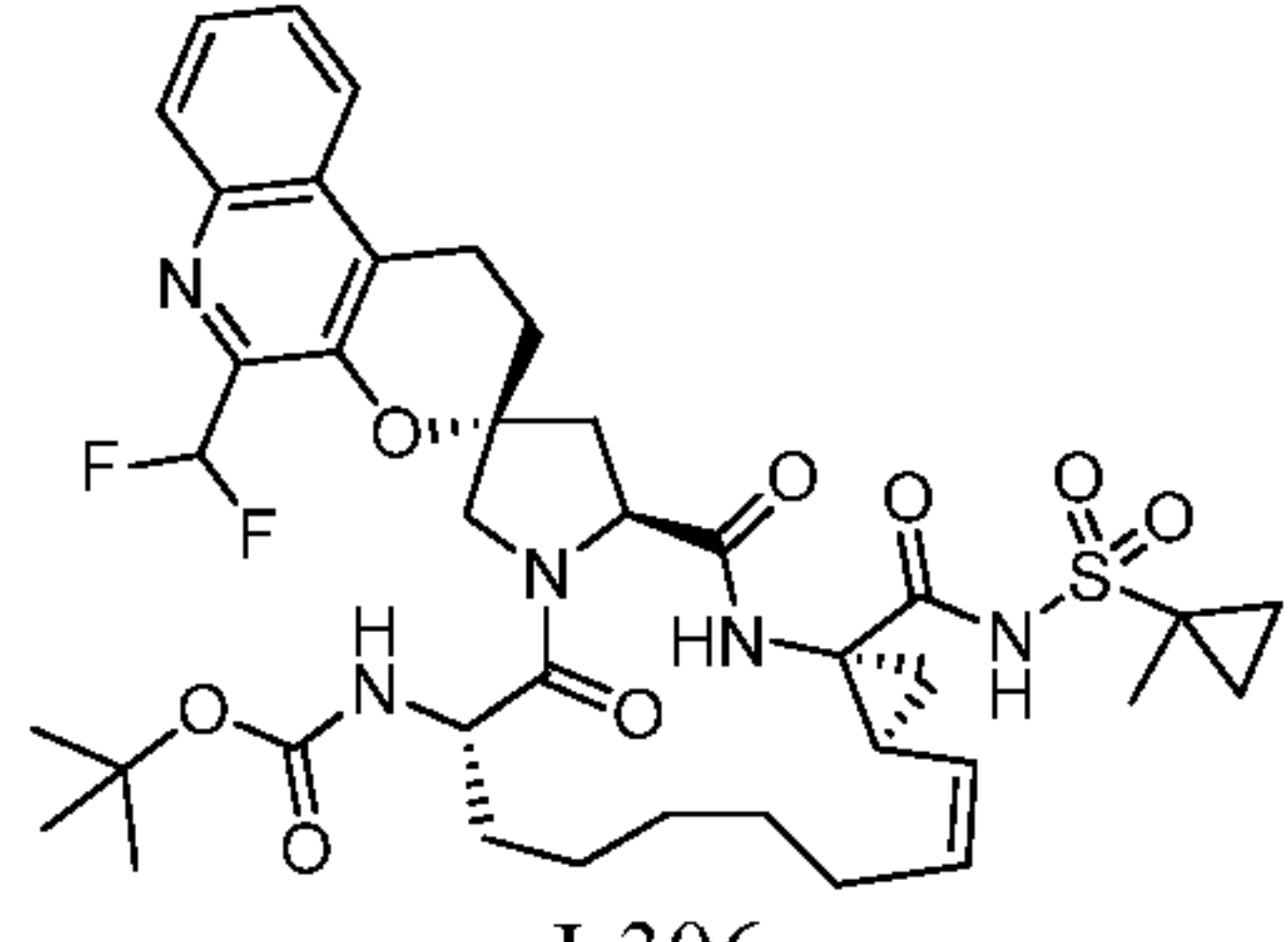
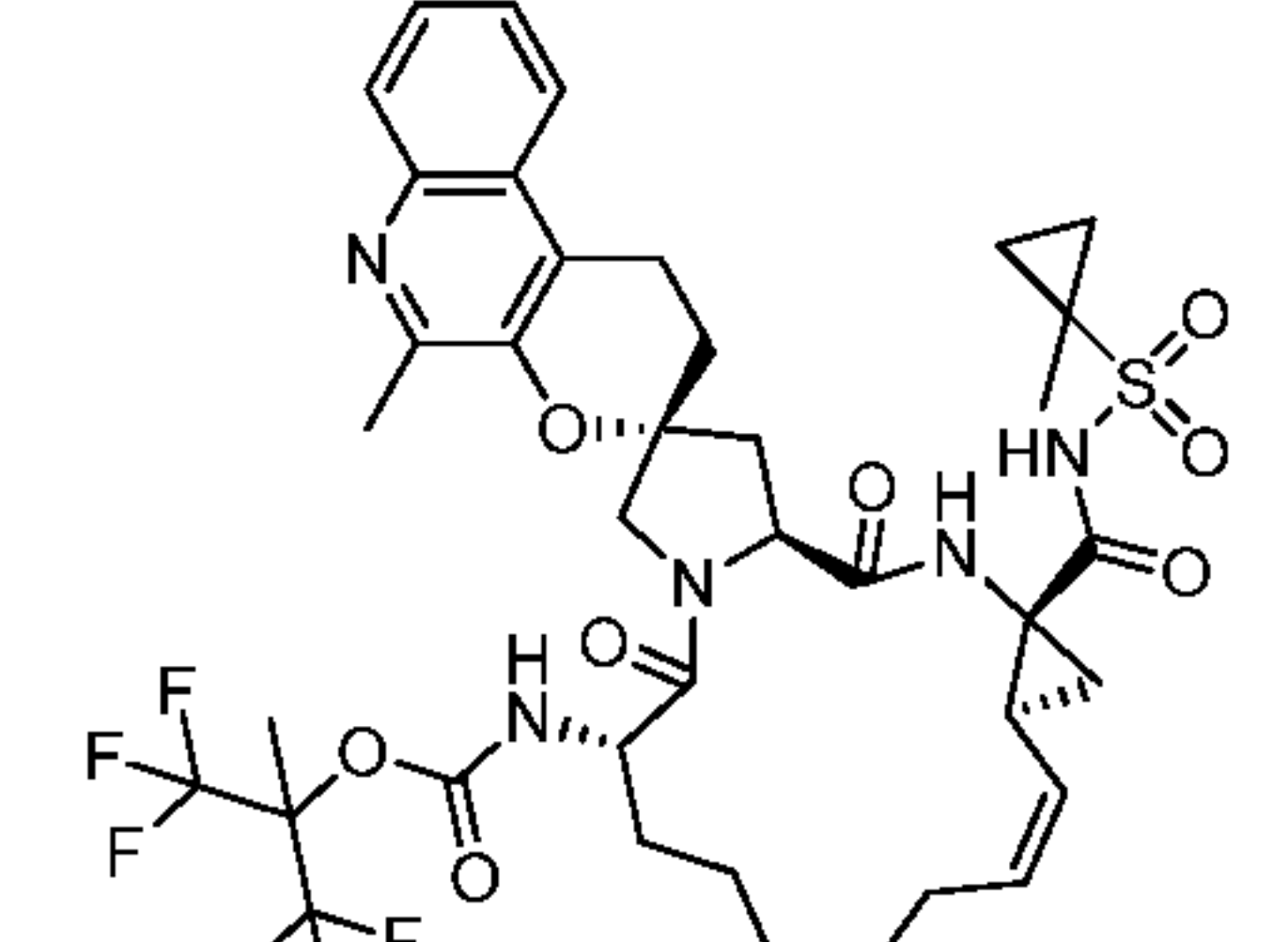
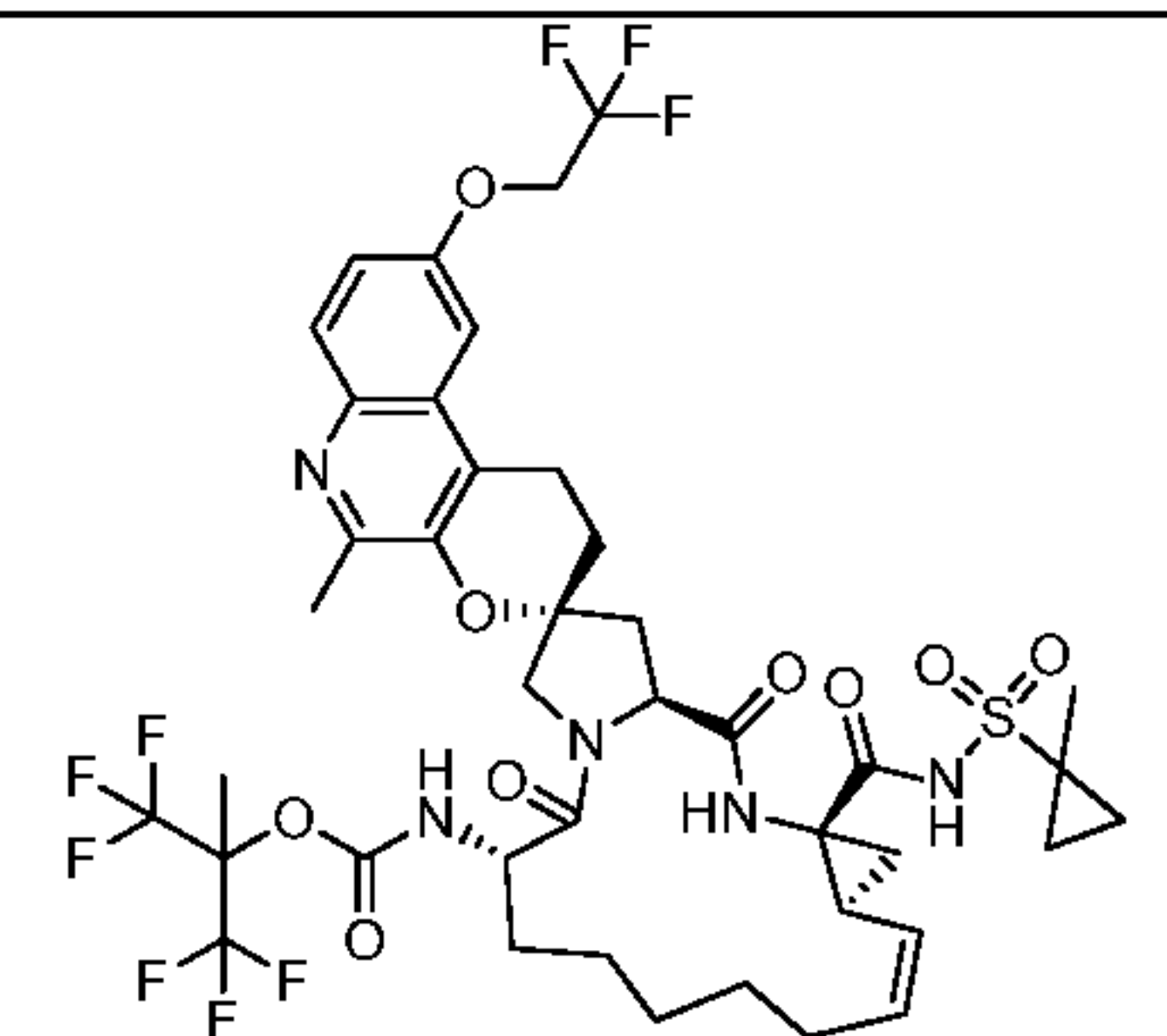
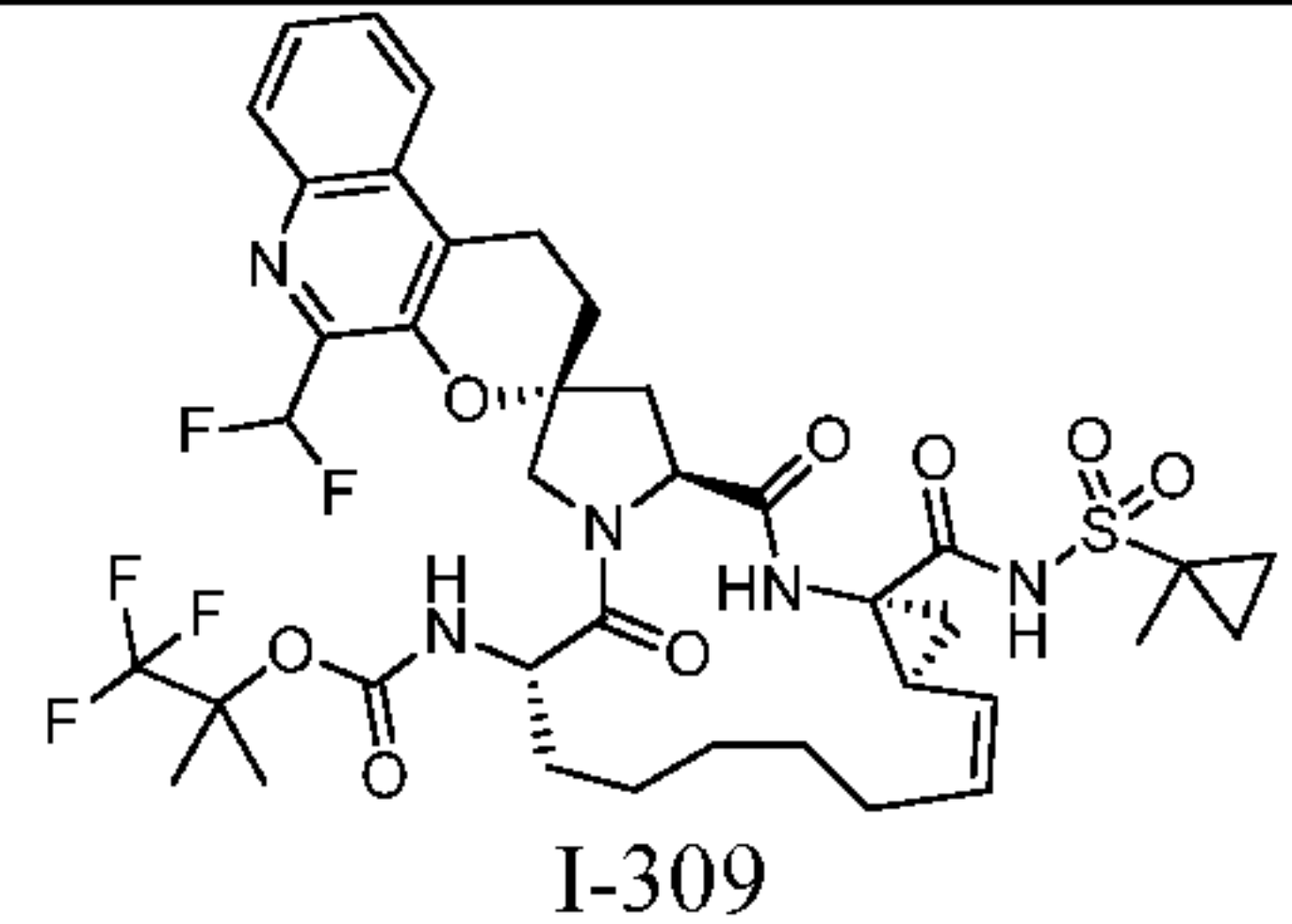
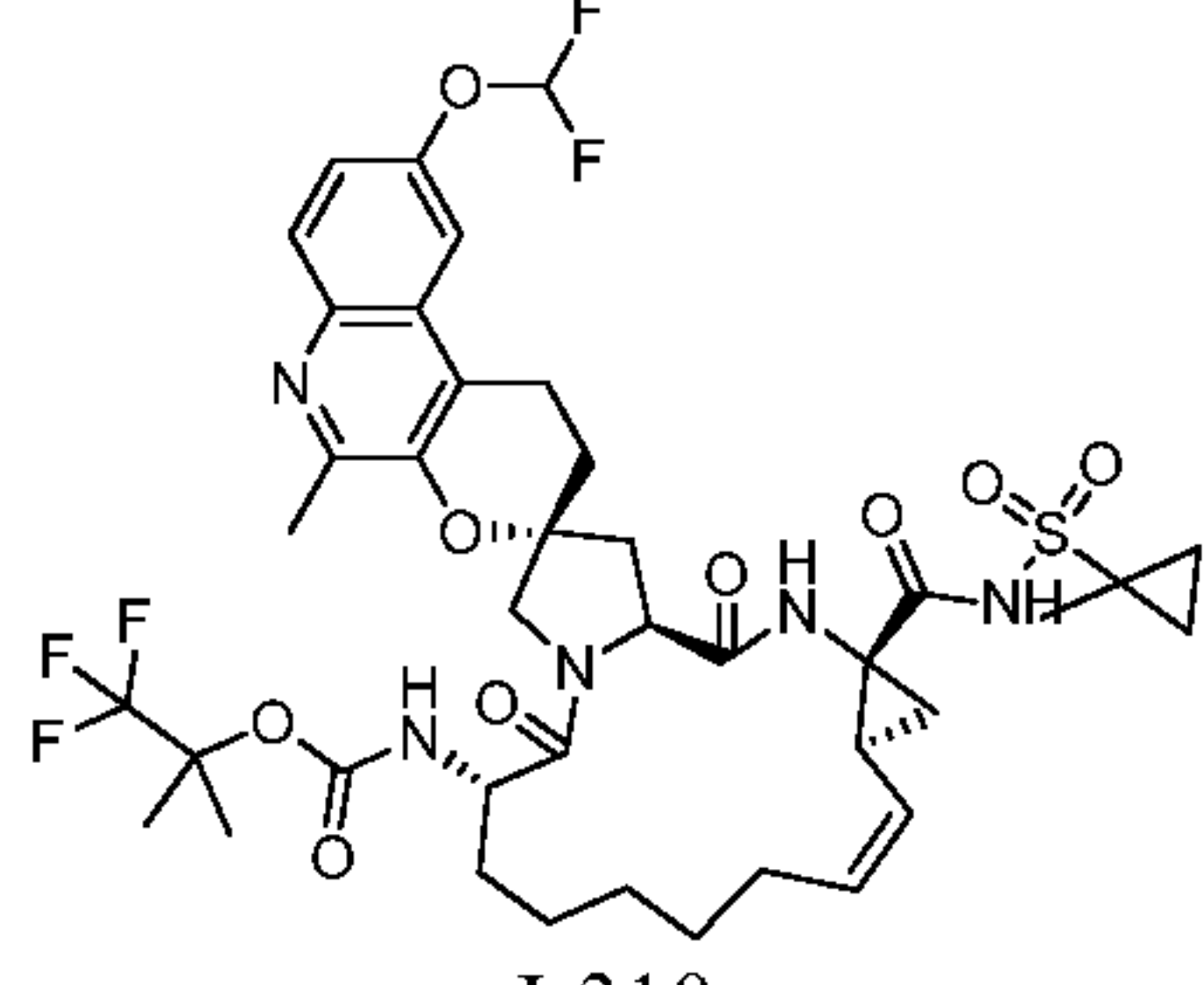
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
283	 <p>I-283</p>	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(cyclopentylcarbamoyl)amino]-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	47	761.51 (HCOOH salt)
284	 <p>I-284</p>	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(benzylcarbamoyl)amino]-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	47	783.47 (HCOOH salt)
285	 <p>I-285</p>	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(cyclohexylcarbamoyl)amino]-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	47	775.5 (HCOOH salt)
286	 <p>I-286</p>	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(ethylcarbamoyl)amino]-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	47	721.43

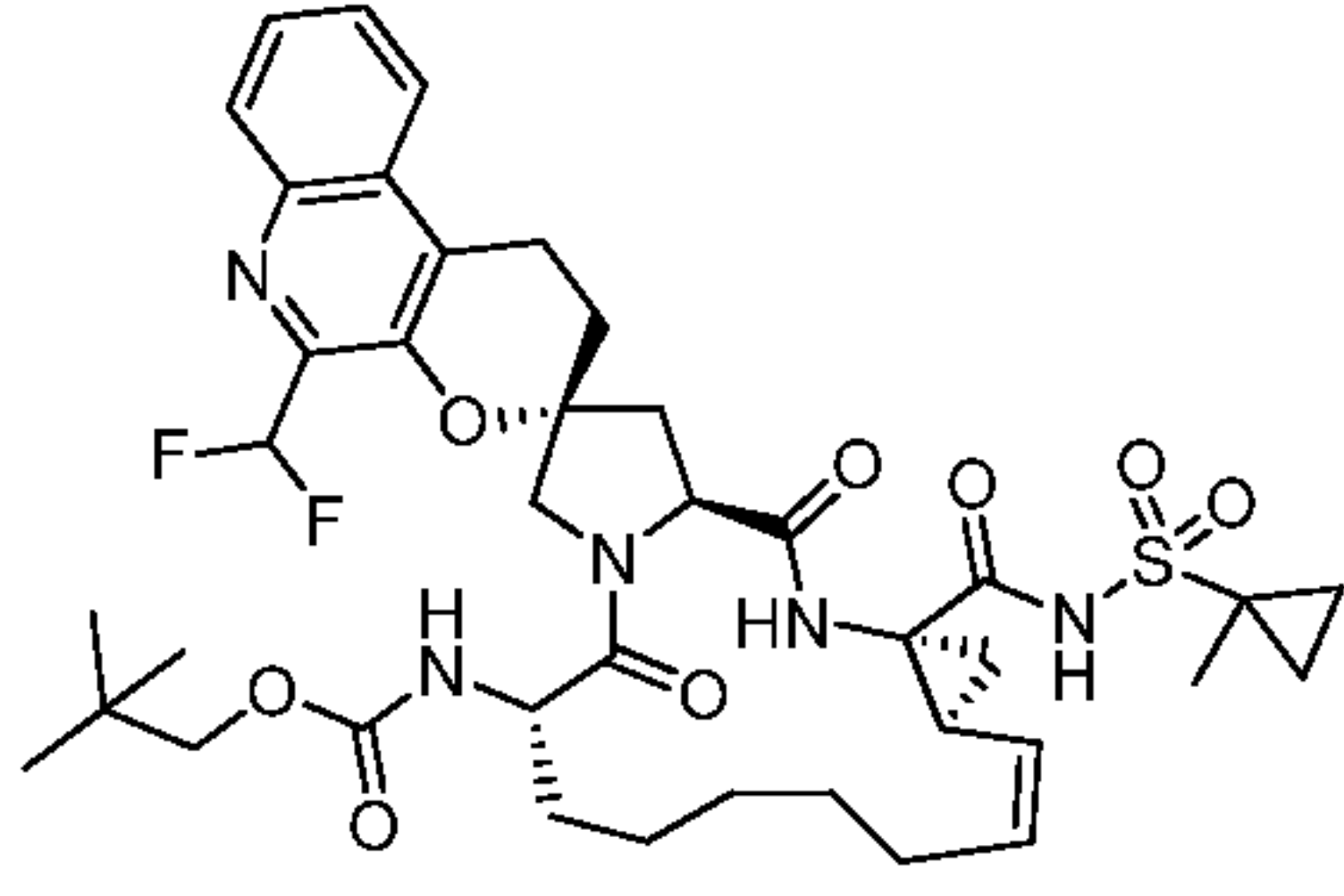
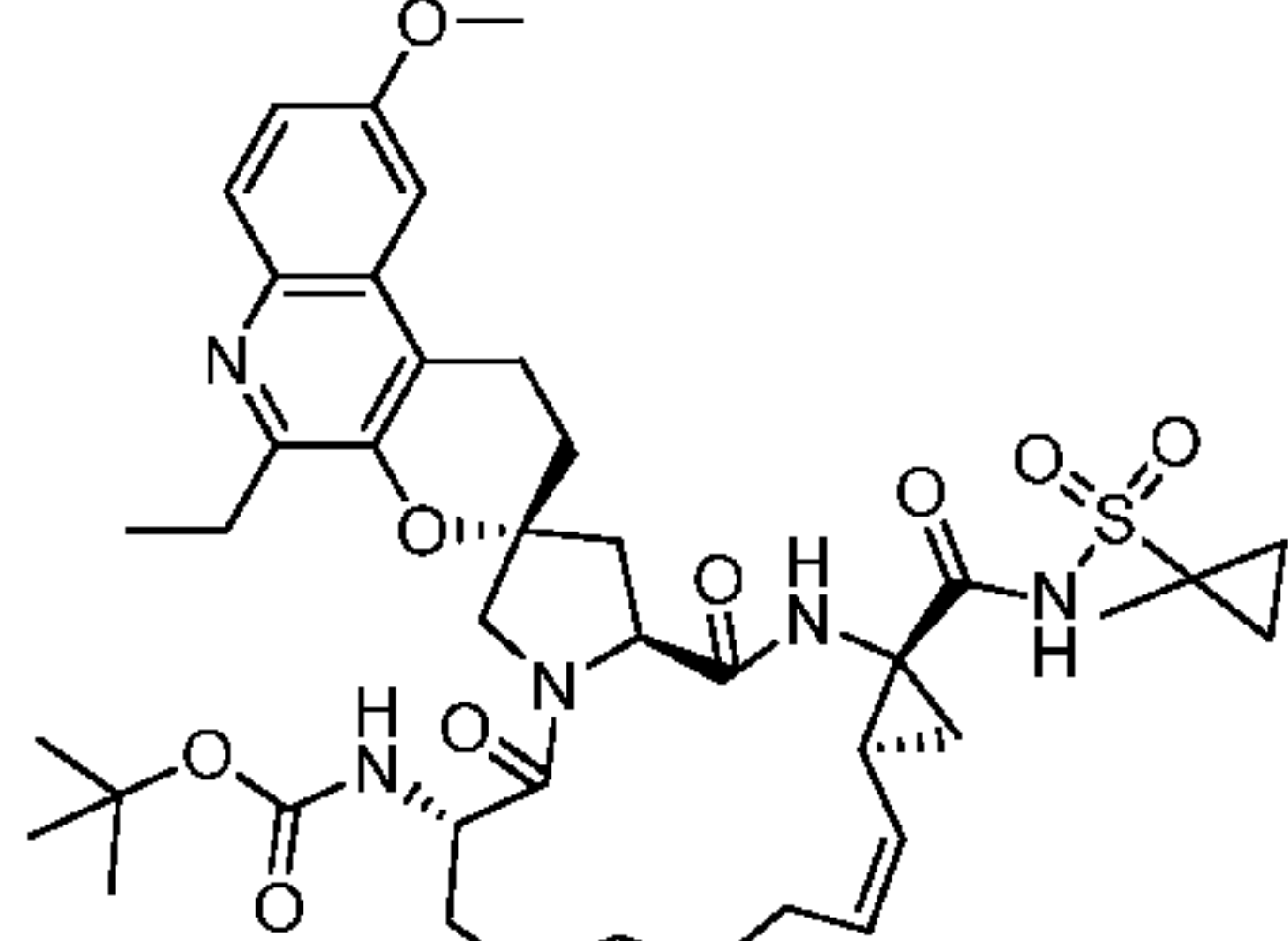
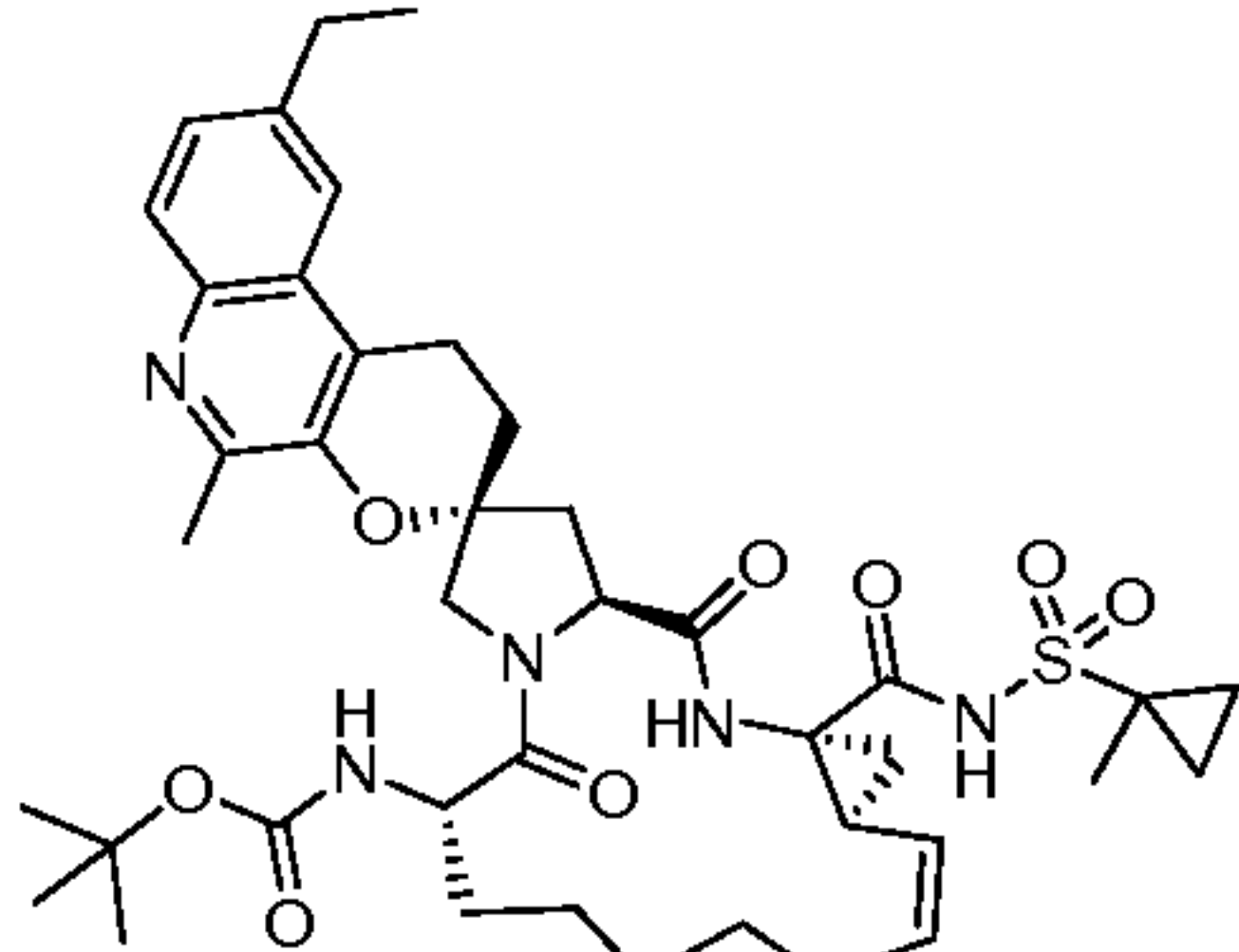
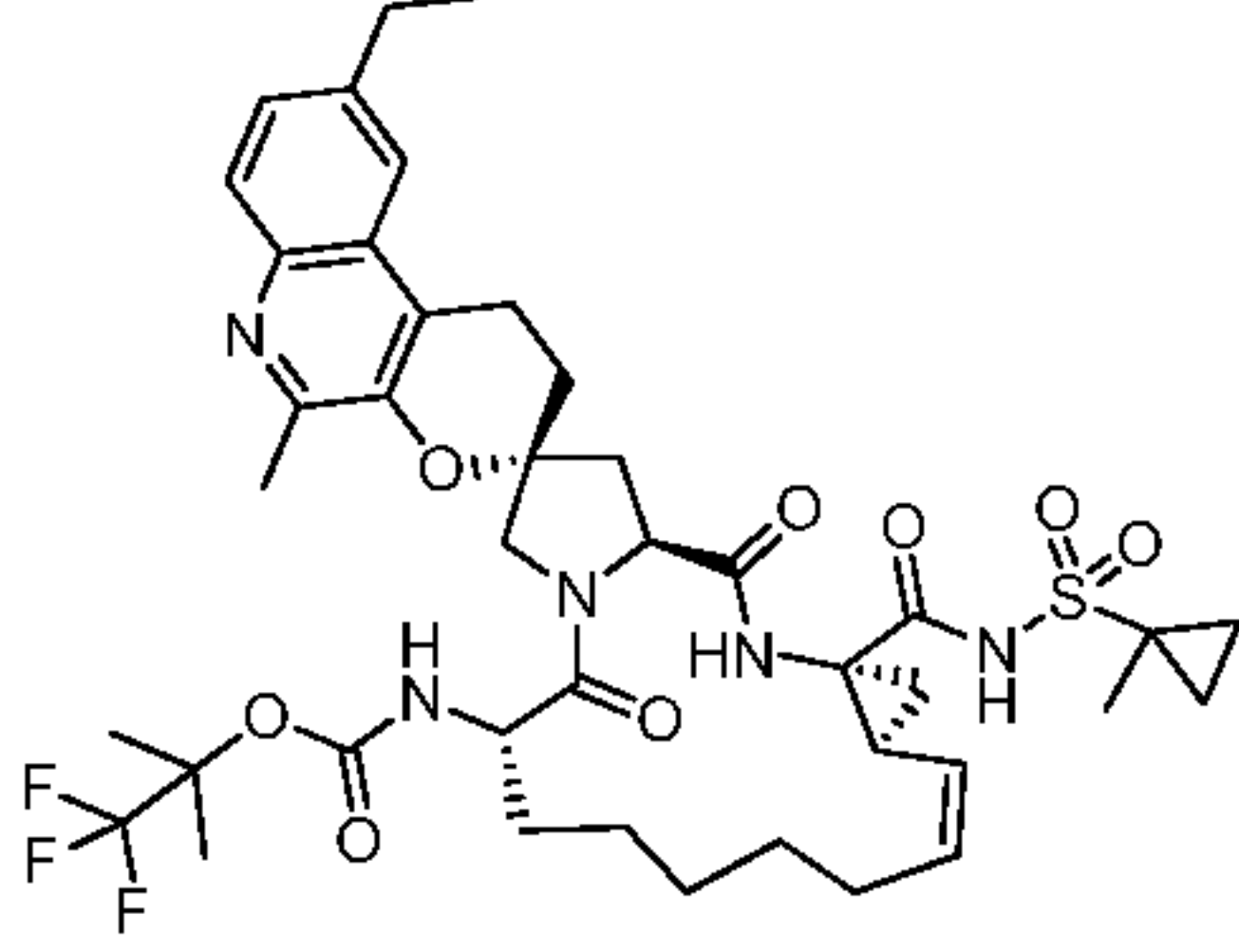
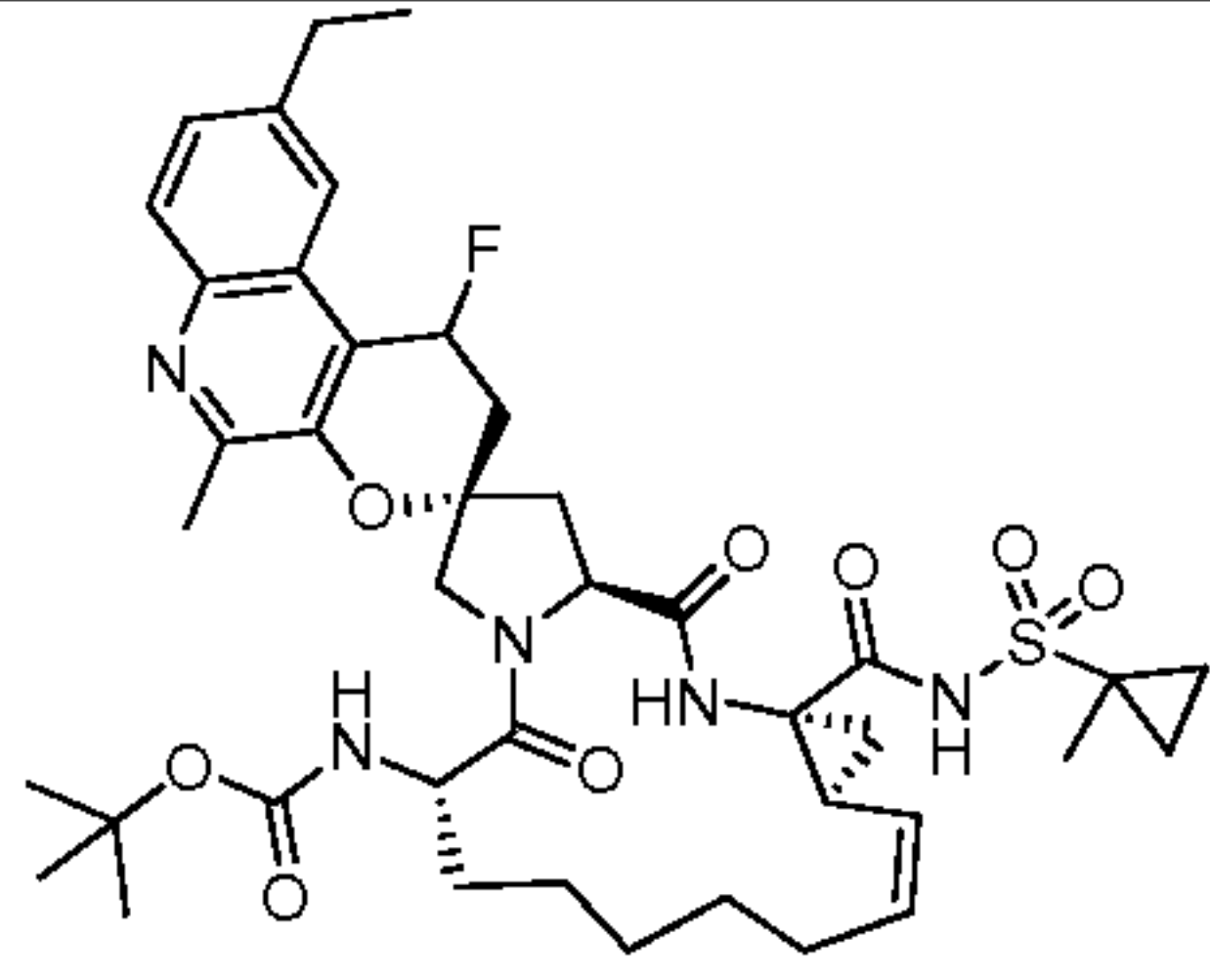
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
287	<p>I-287</p>	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(butylcarbamoyl)amino]-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	47	749.48 (HCOOH salt)
288	<p>I-288</p>	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-6-{[(2-phenylethyl)carbamoyl]amino}-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	47	797.51 (HCOOH salt)
289	<p>I-289</p>	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(diethylcarbamoyl)amino]-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	61	49.5 (HCOOH salt)
290	<p>I-290</p>	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-6-[(piperidin-1-ylcarbonyl)amino]-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	61	761.51 (HCOOH salt)

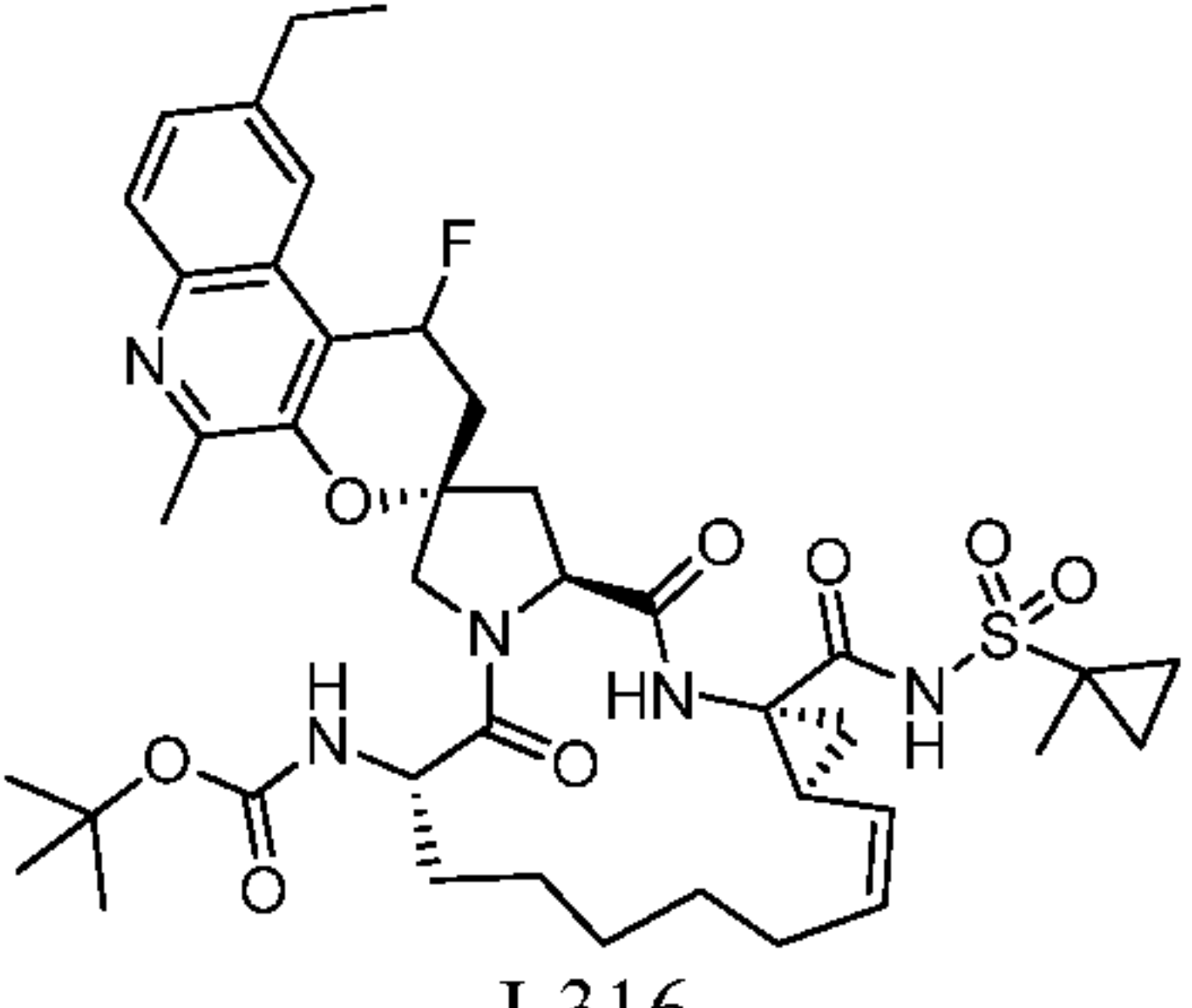
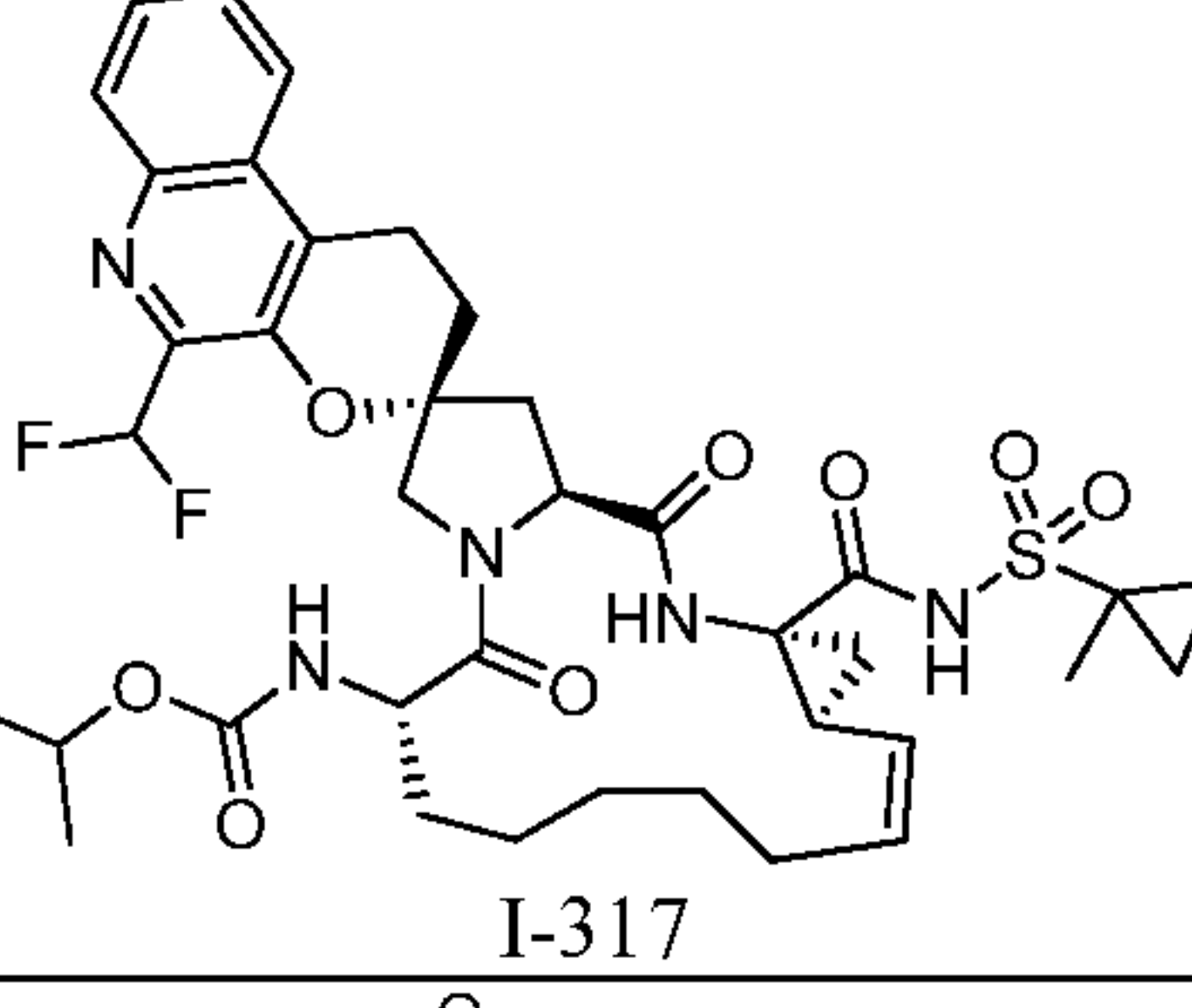
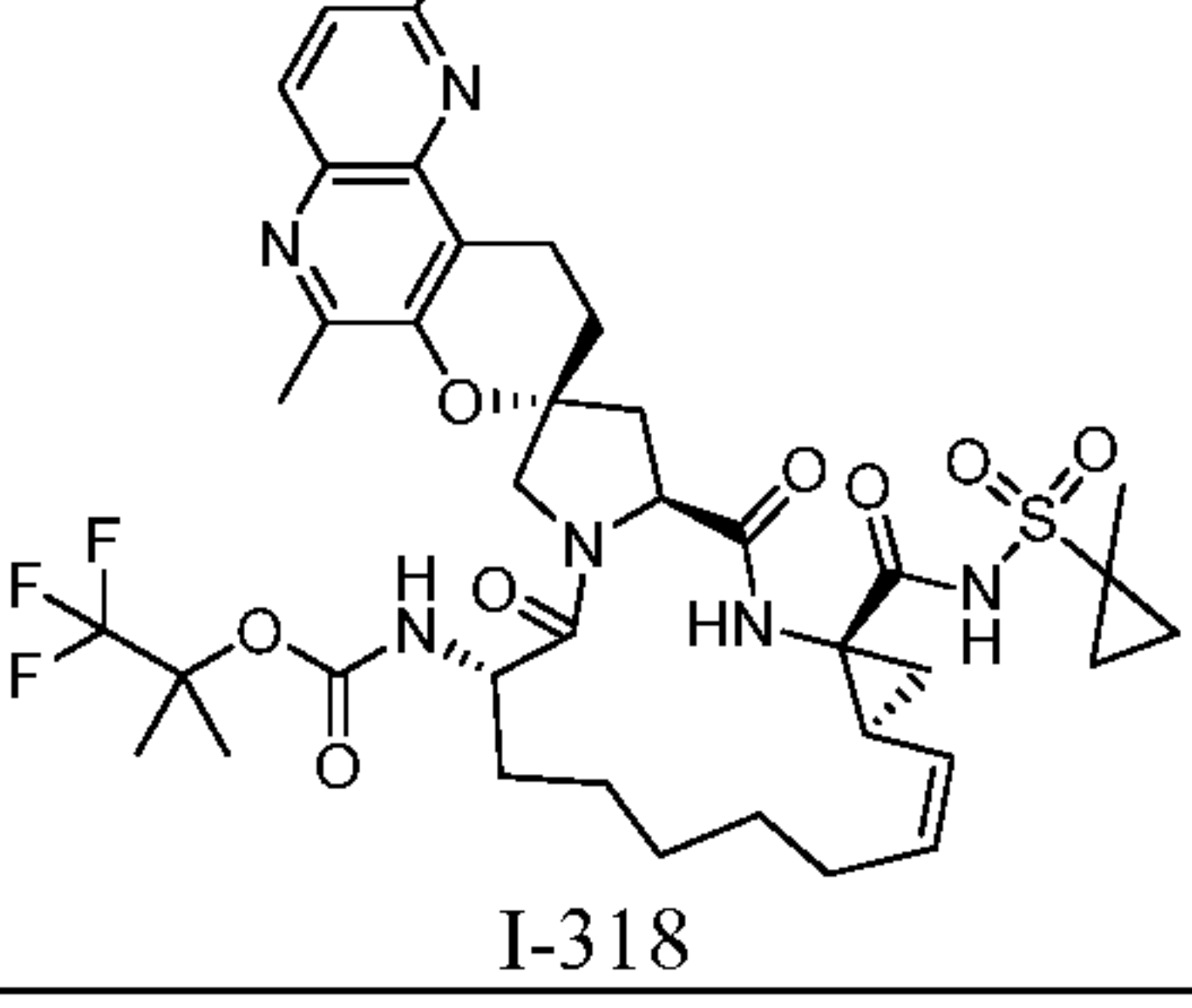
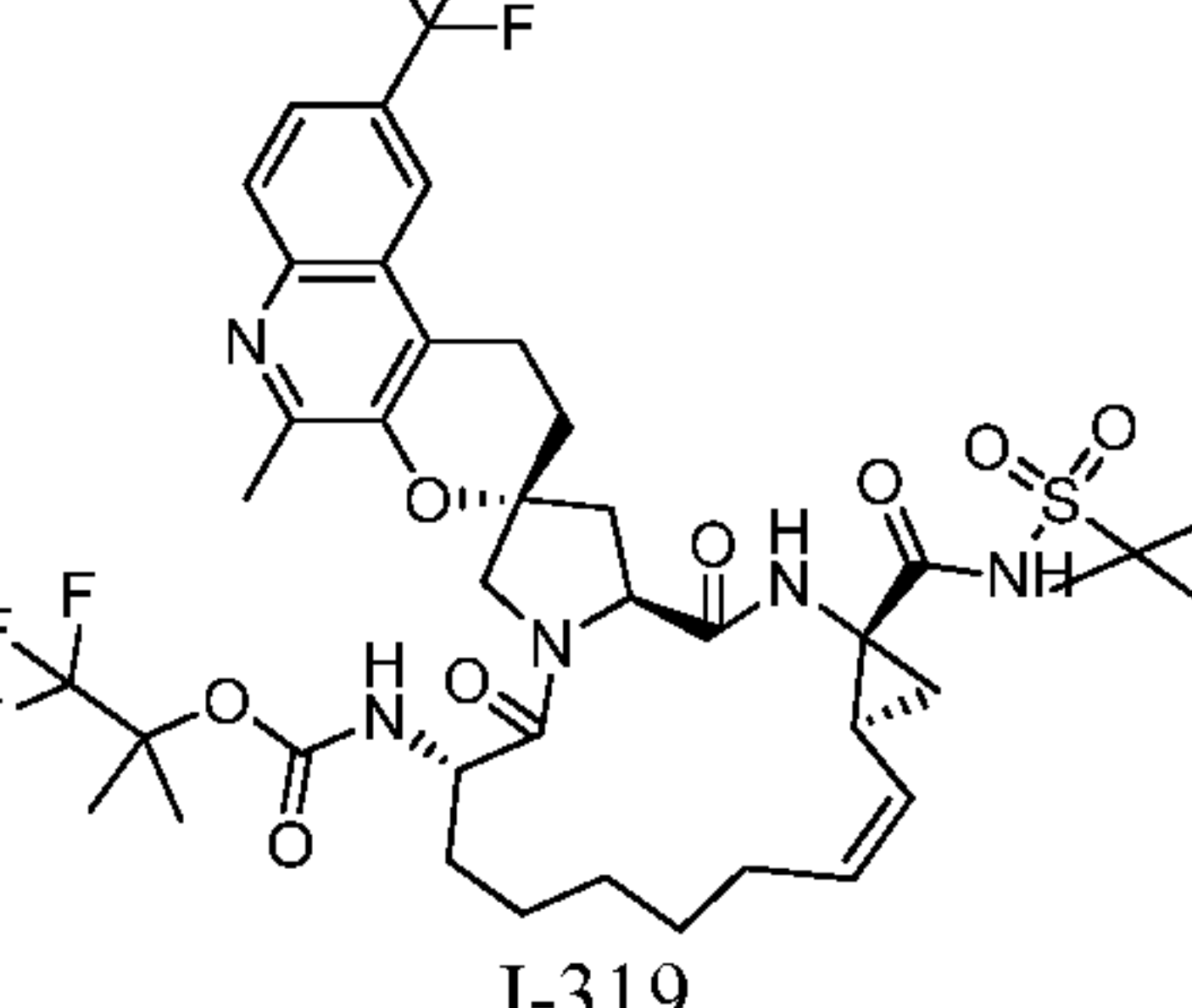
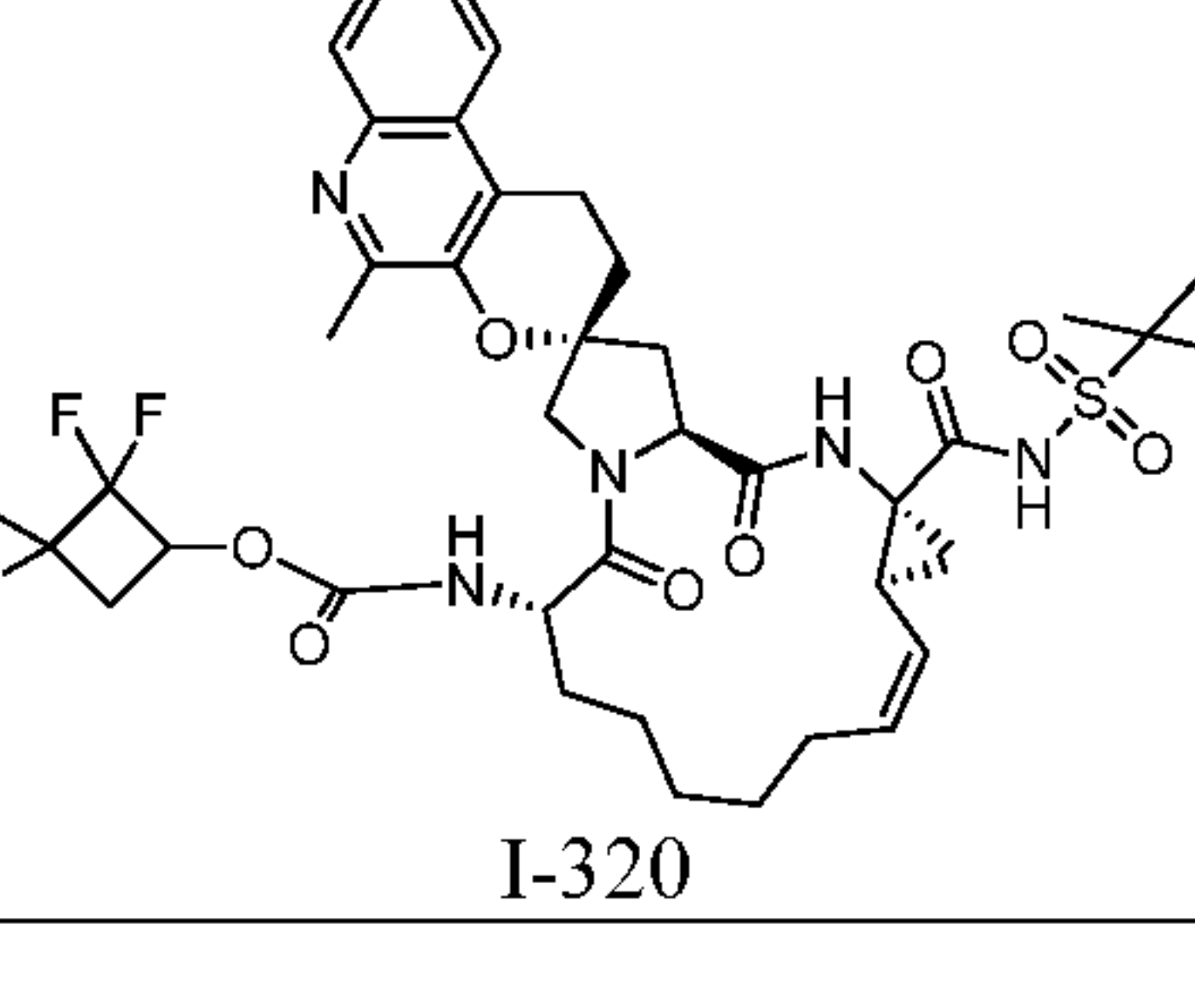
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
291		(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-6-[(morpholin-4-ylcarbonyl)amino]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	61	763.47 (HCOOH salt)
292		(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-6-[[methyl(phenyl)carbamoyl]amino]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	61	783.46 (HCOOH salt)
293		(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[[di(propan-2-yl)carbamoyl]amino]-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	61	777.51 (HCOOH salt)
294		2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	2	821.8
295		1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	2	861.7

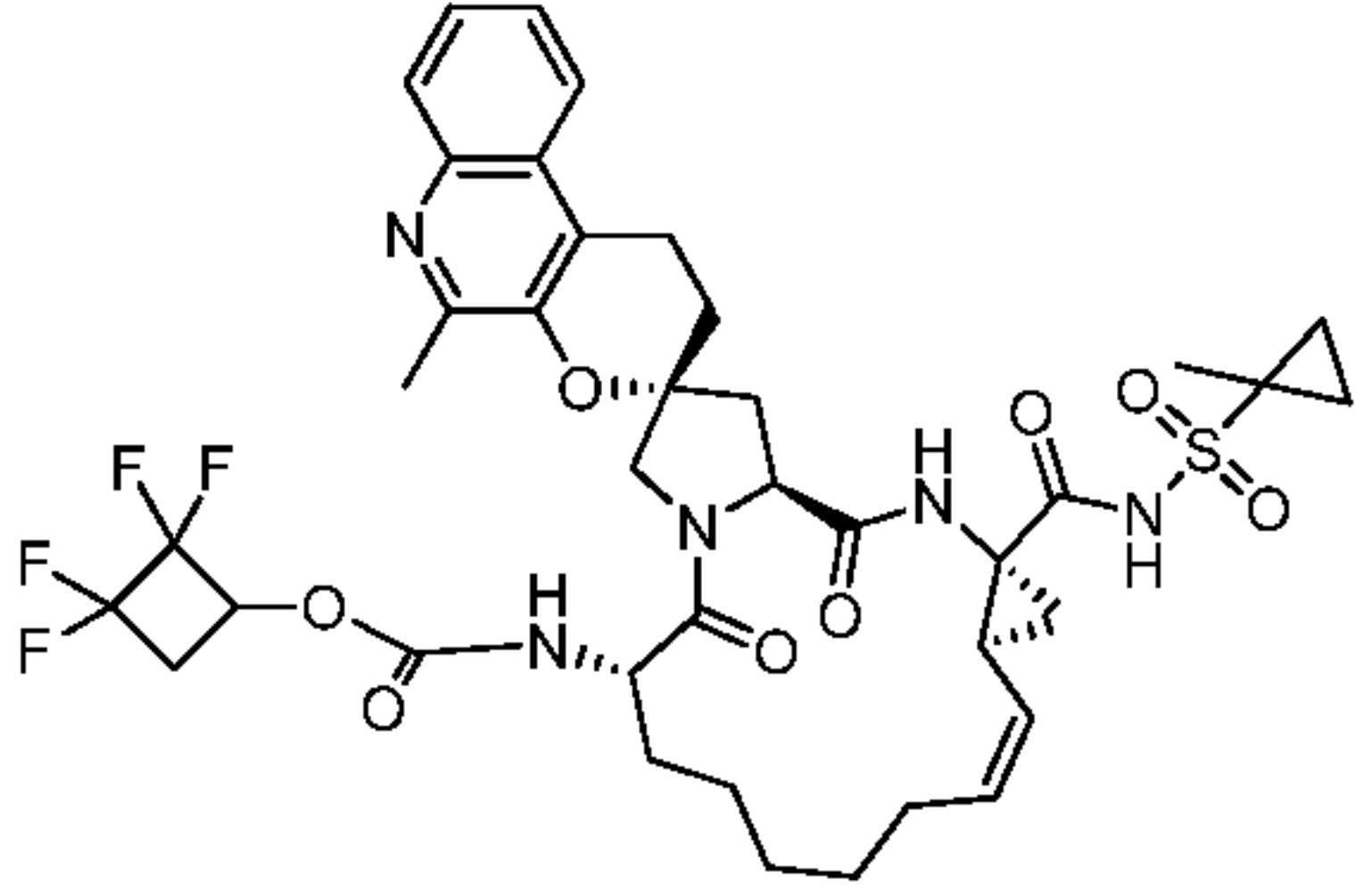
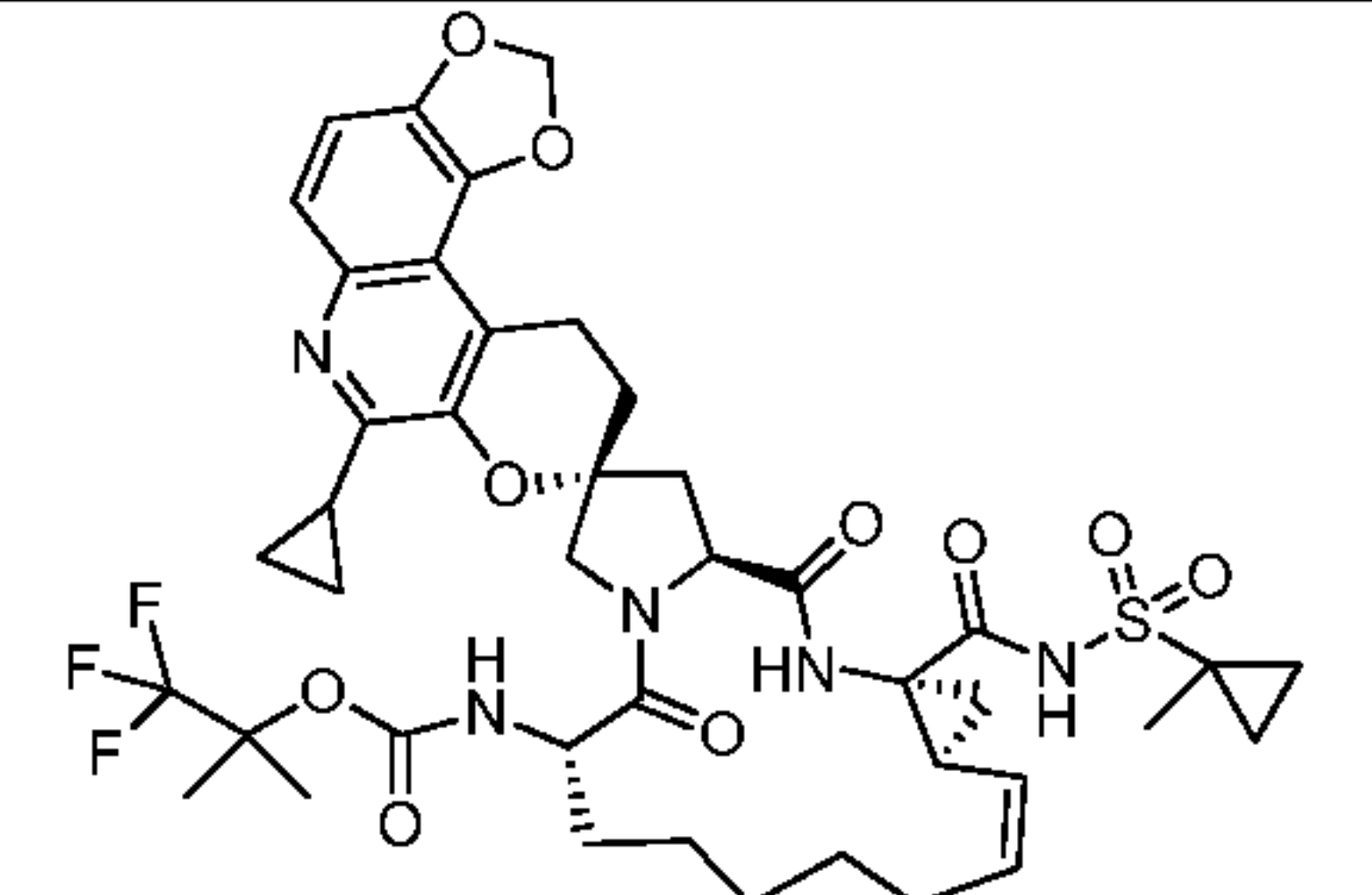
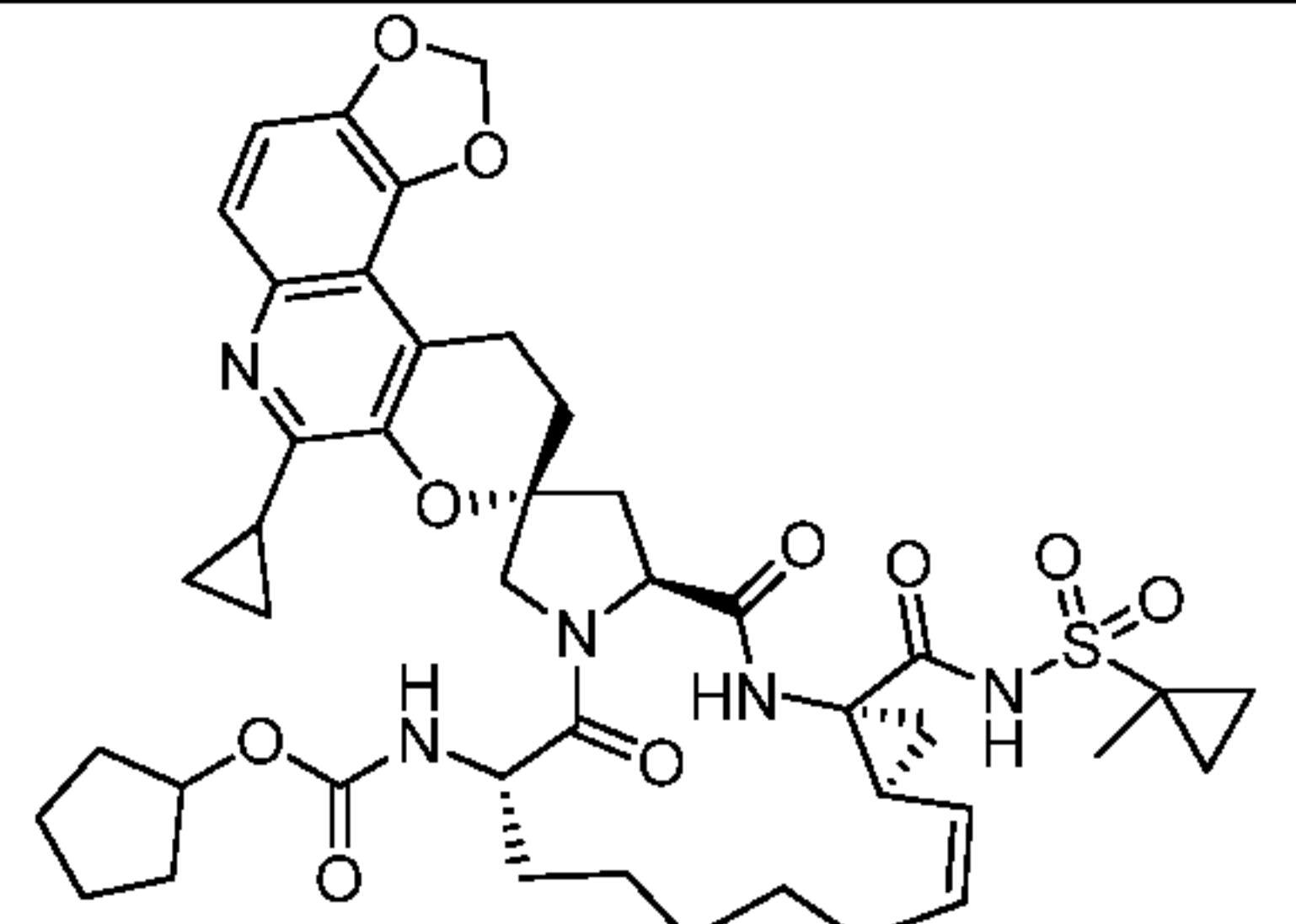
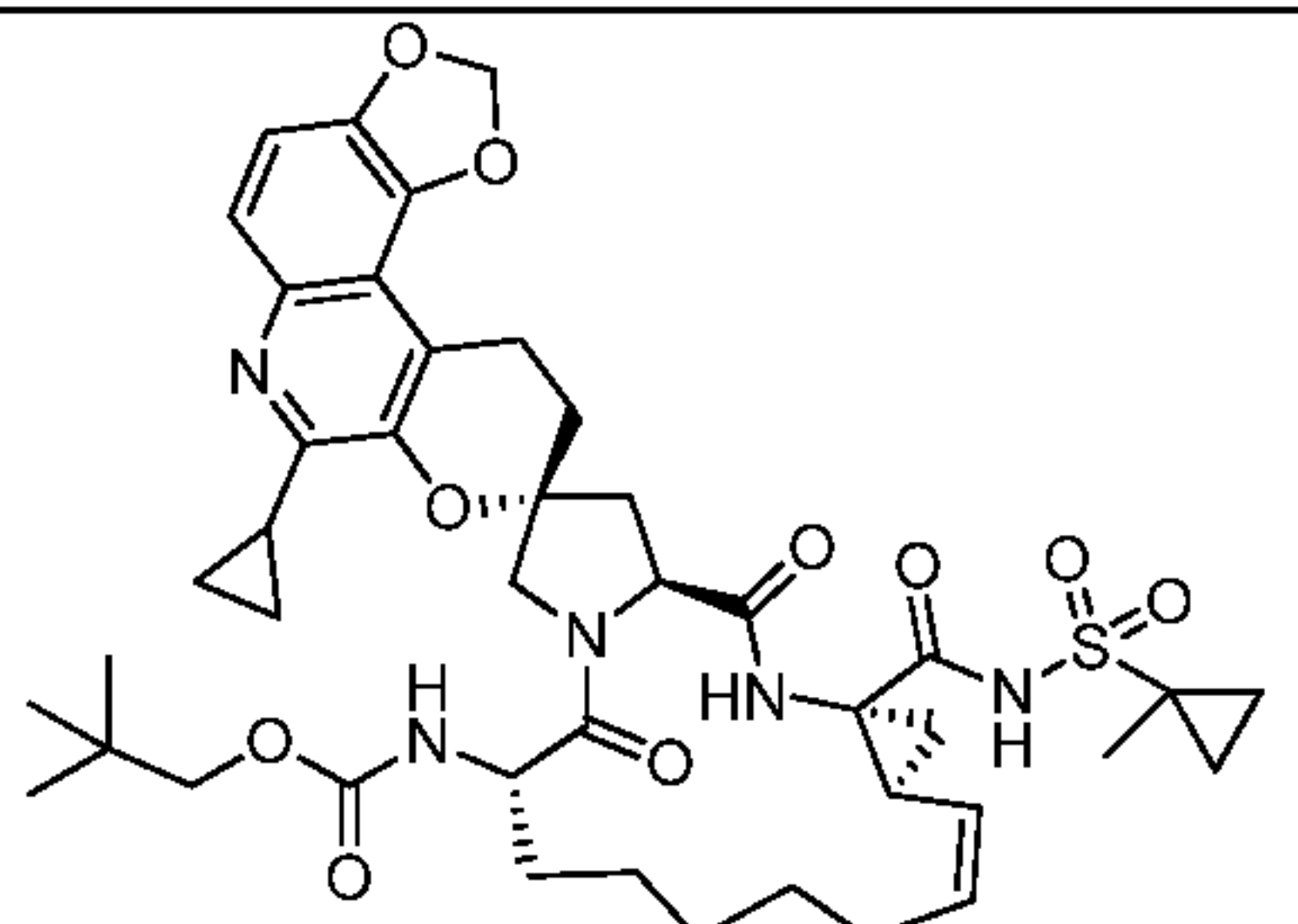
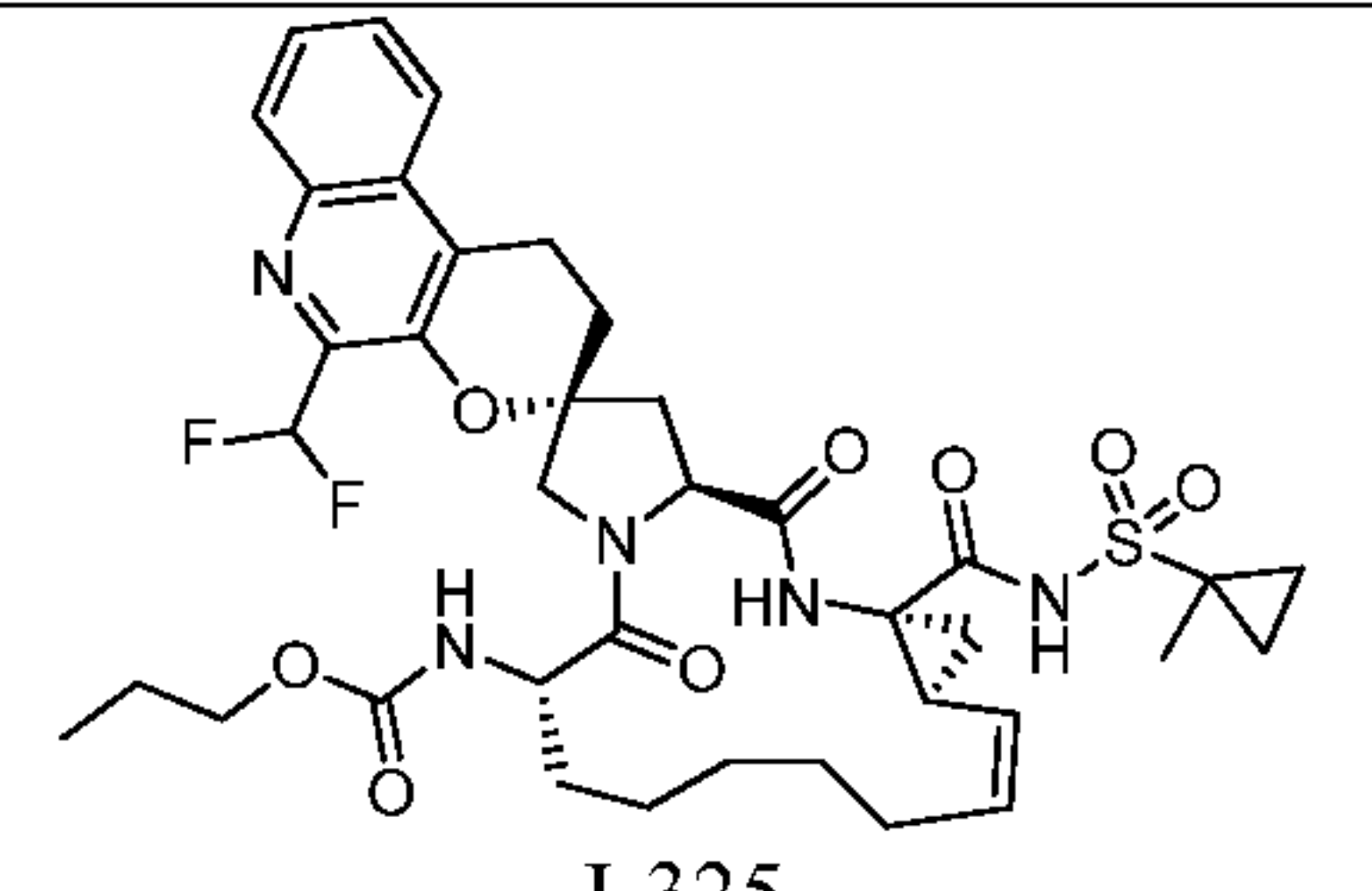
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
296		<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-9'-(2,2,2-trifluoroethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	30	847.7
297		2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	847.8
298		1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	887.6
299		1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1',1'-difluoro-9'-methoxy-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	2	897.6 (K+ salt)
300		3,3,4,4,4-pentafluoro-2-methylbutan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	854.5

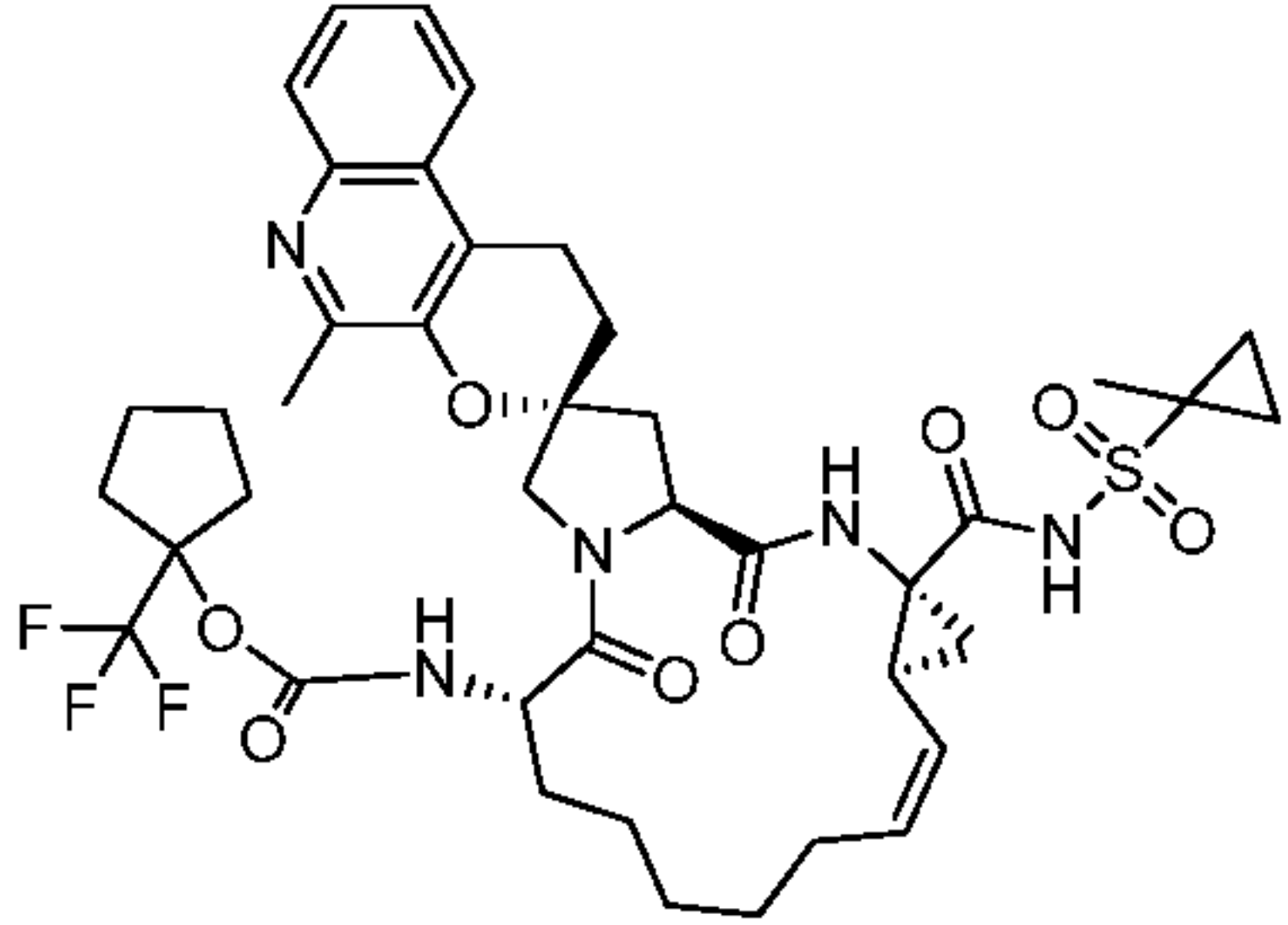
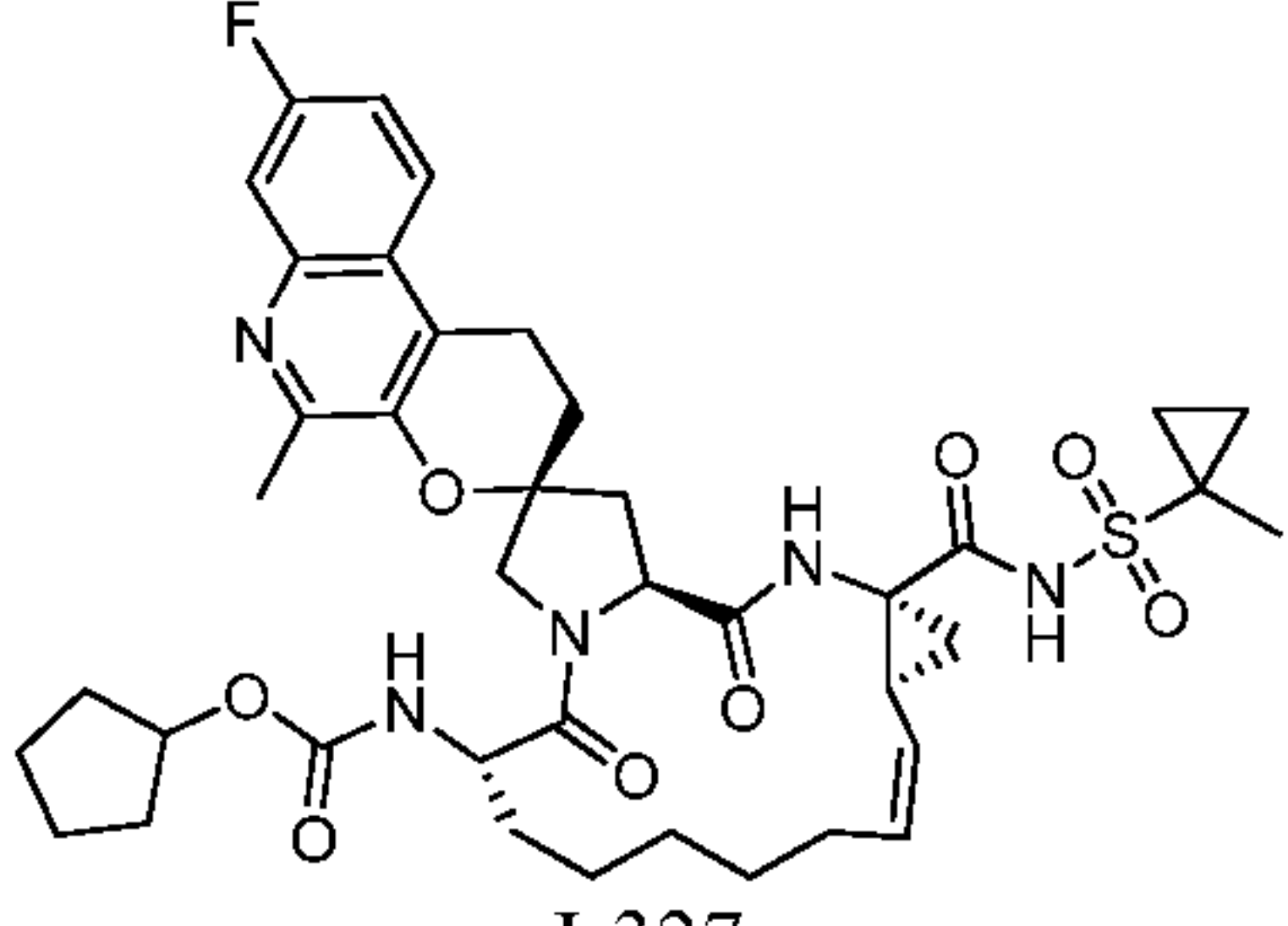
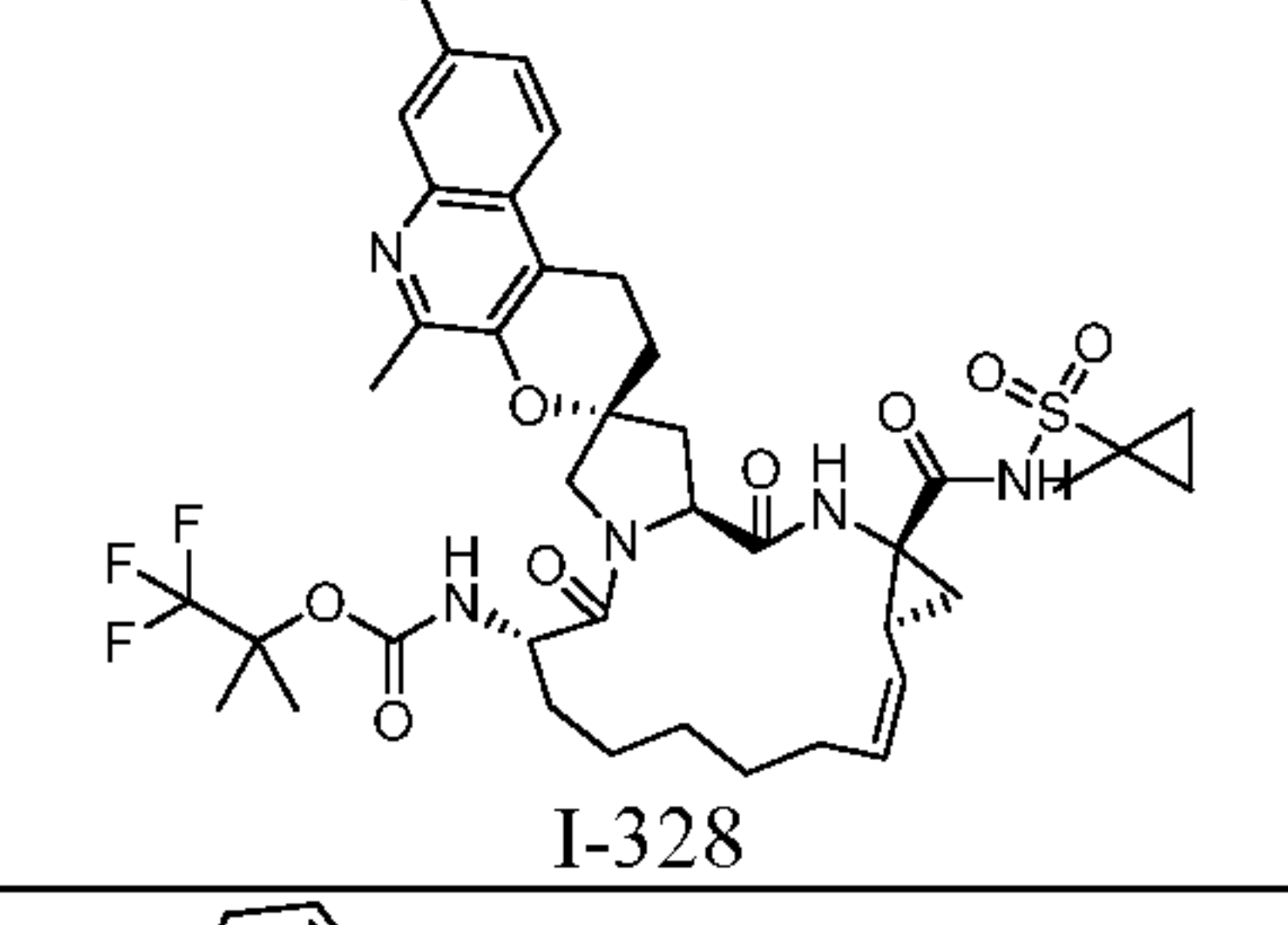
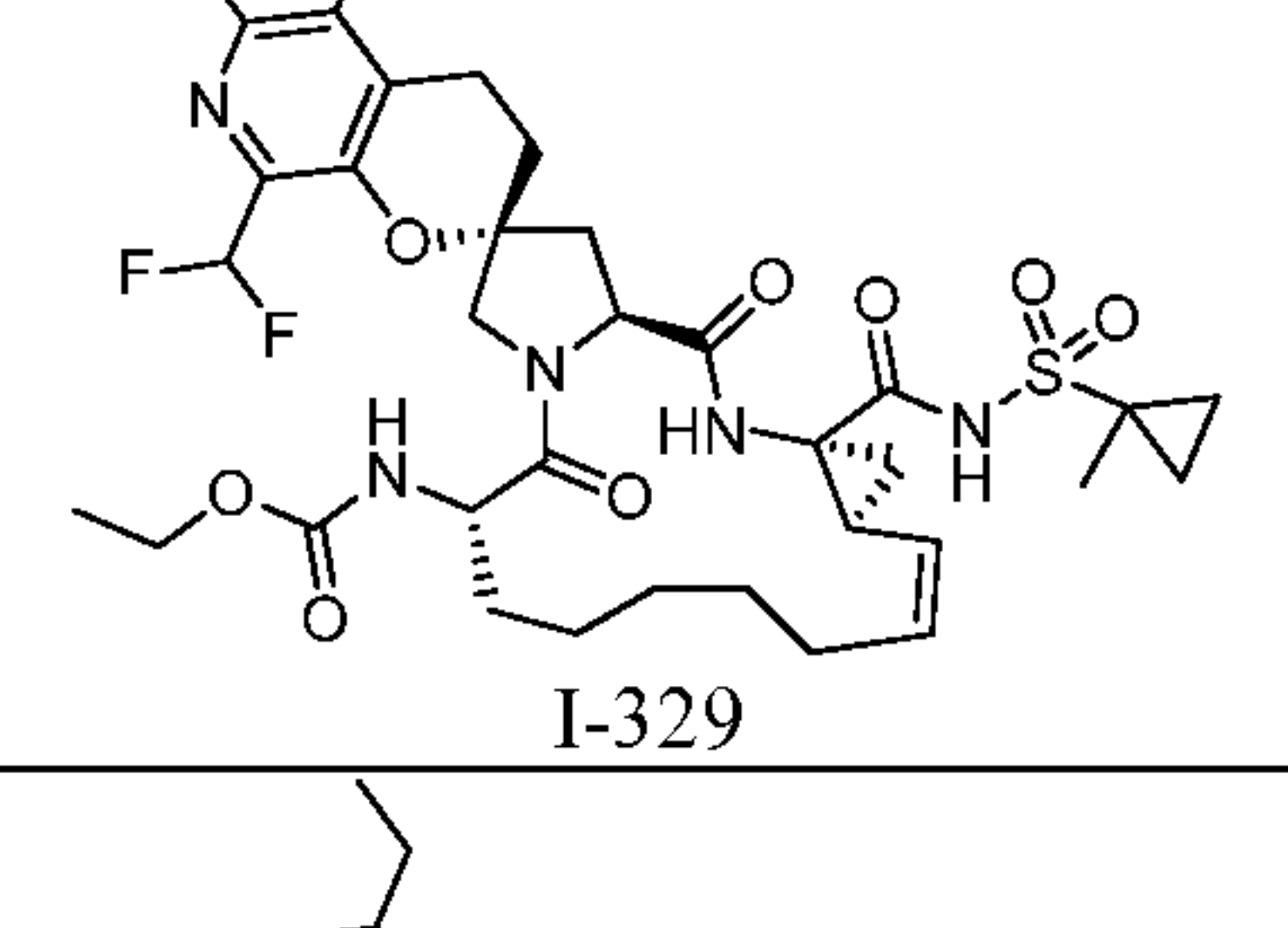
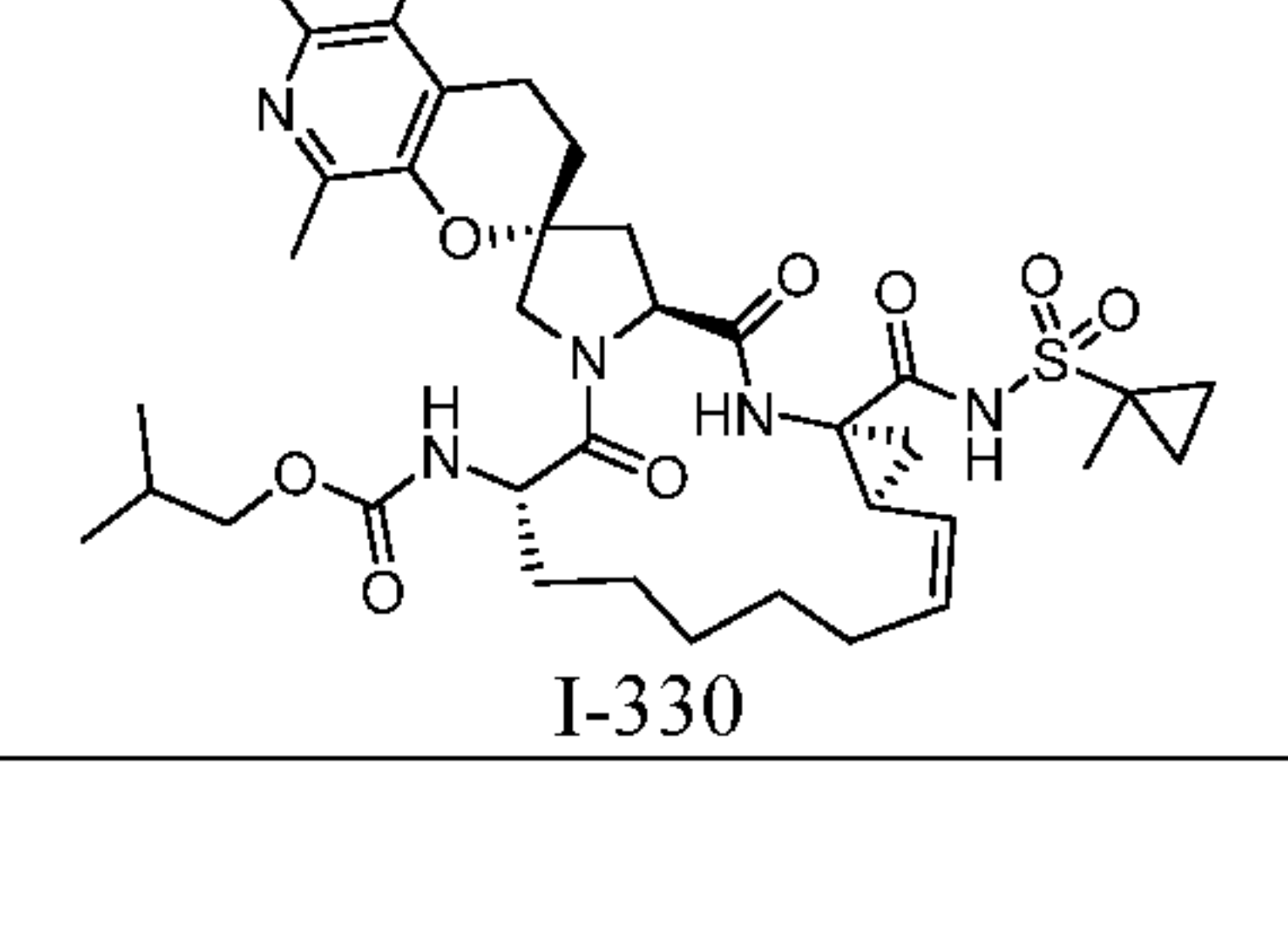
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
301	 I-301	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-9'-(2,2,2-trifluoroethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	30	901.6
302	 I-302	1-methylcyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-9'-(2,2,2-trifluoroethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	30	873.6
303	 I-303	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-9'-(2,2,2-trifluoroethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	30	861.7
304	 I-304	2-methyl-4-(propan-2-ylsulfonyl)butan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	869.7
305	 I-305	2-methyl-4-(propan-2-ylsulfonyl)butan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-9'-(trifluoromethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	954.6

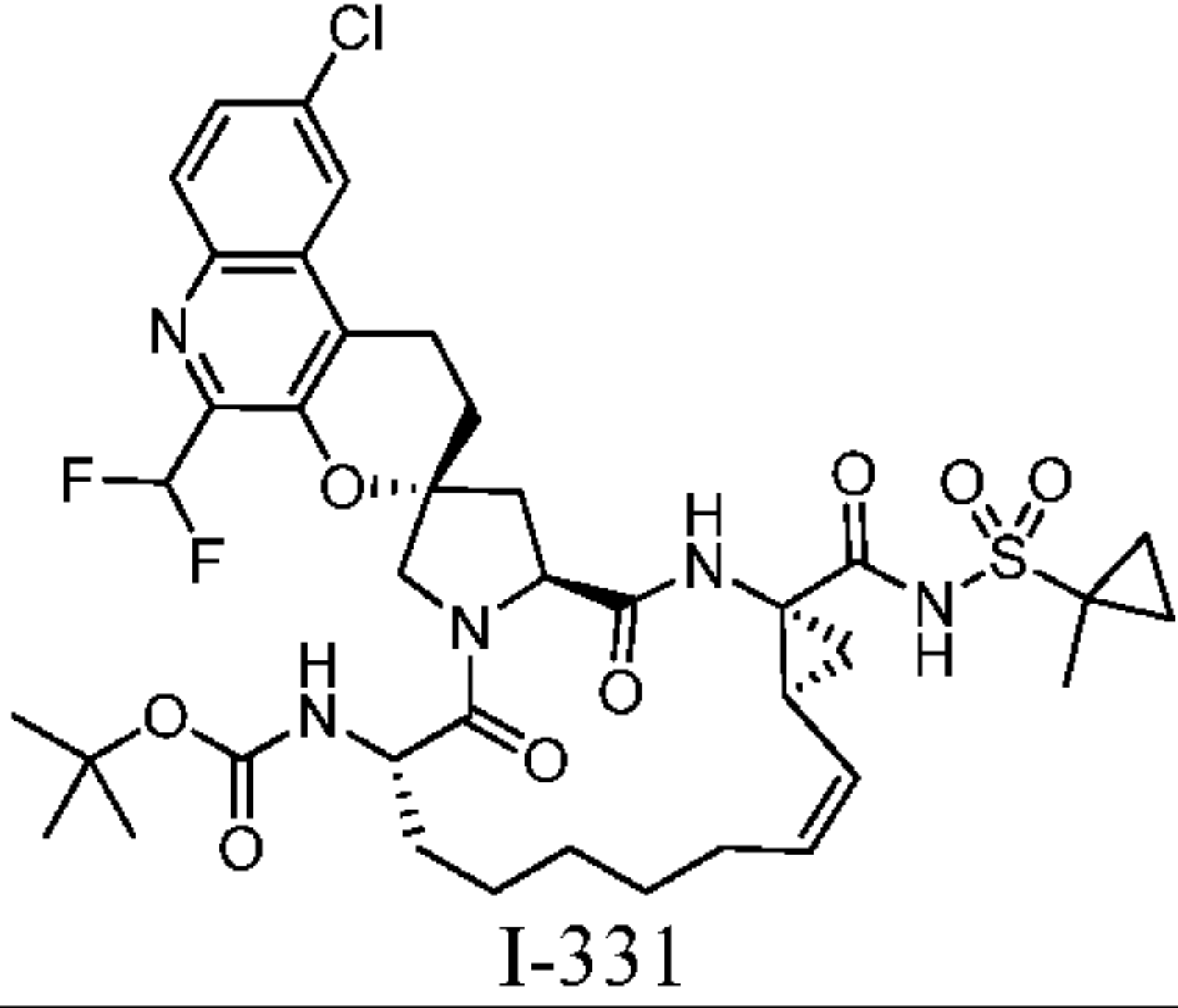
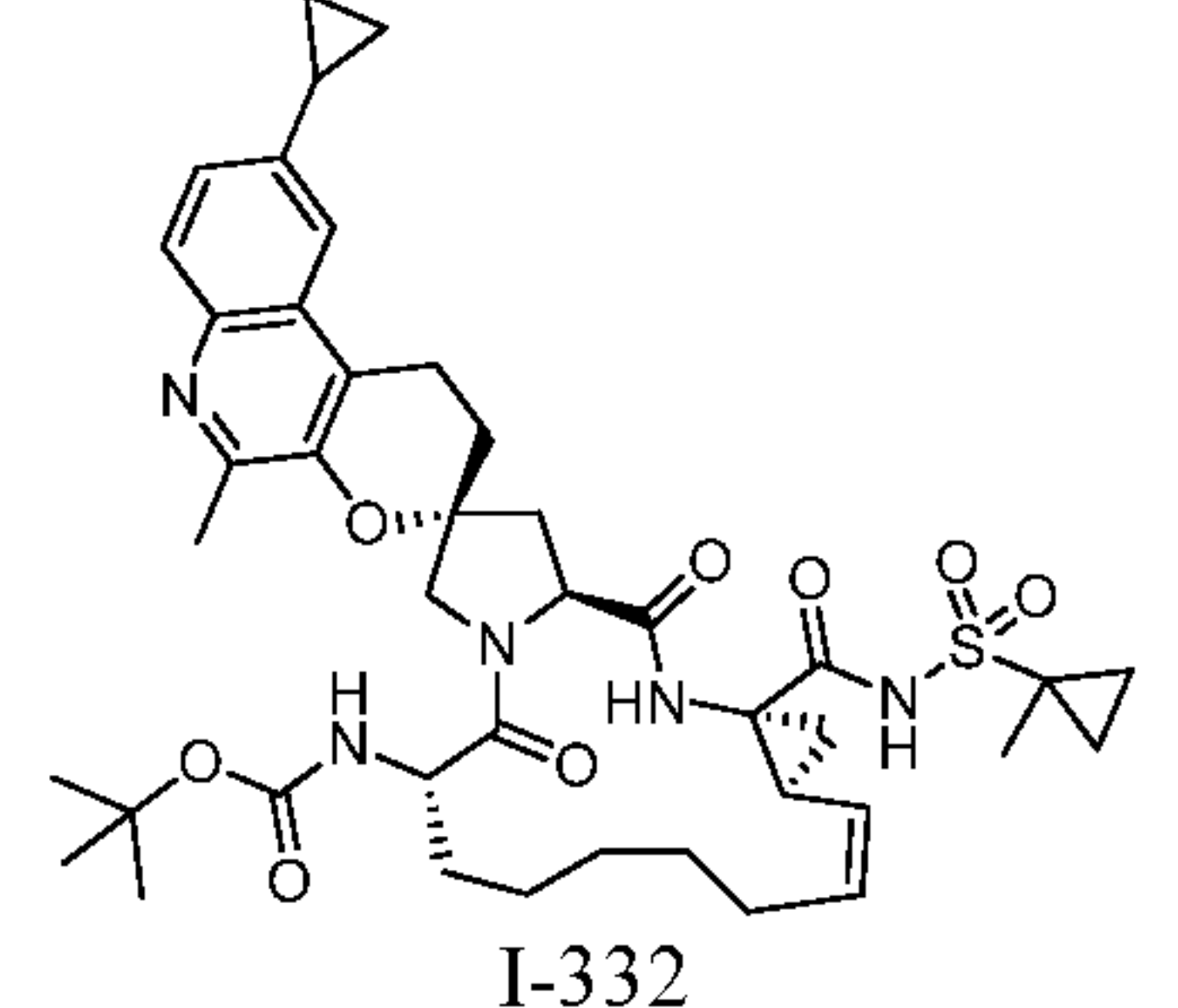
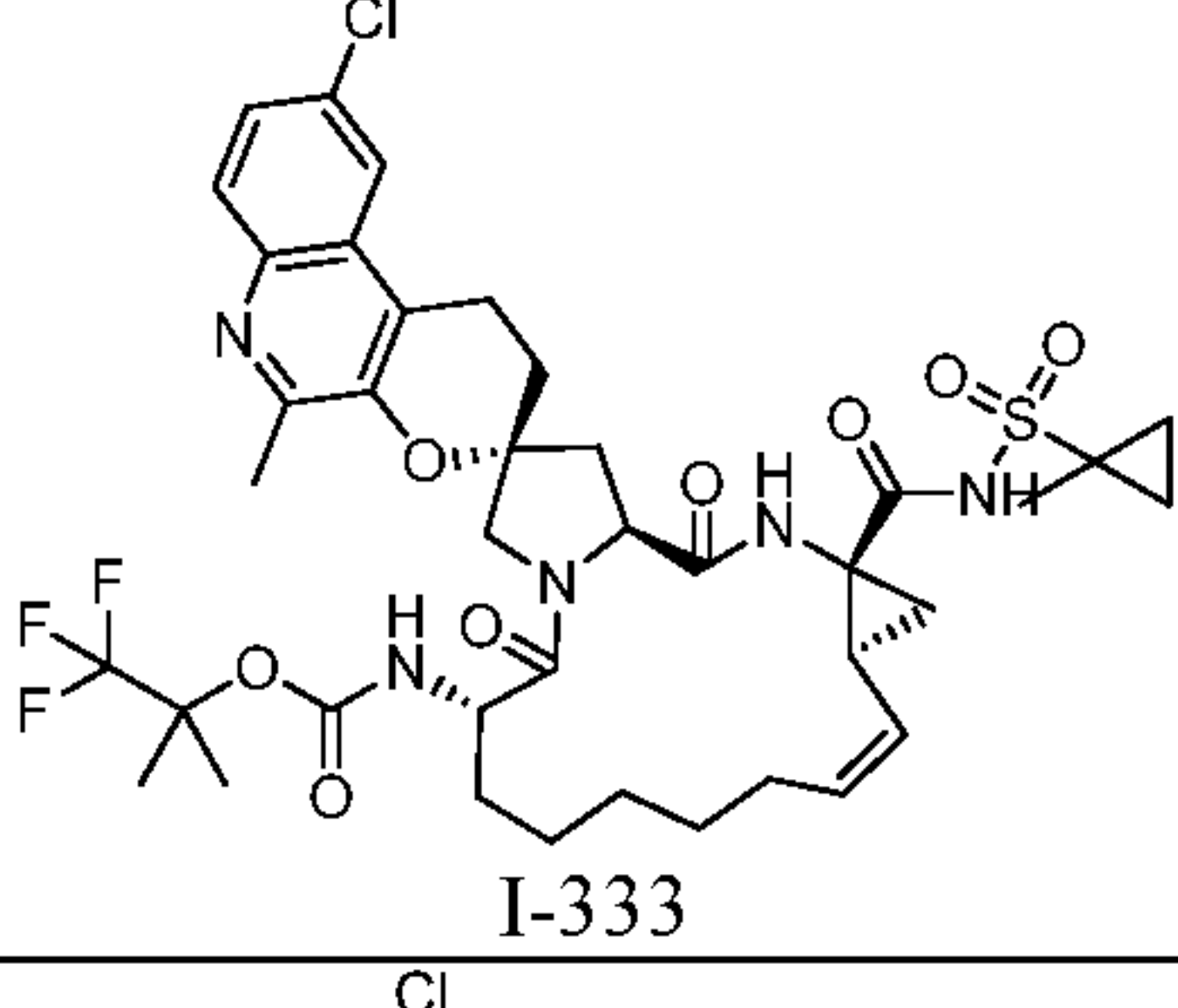
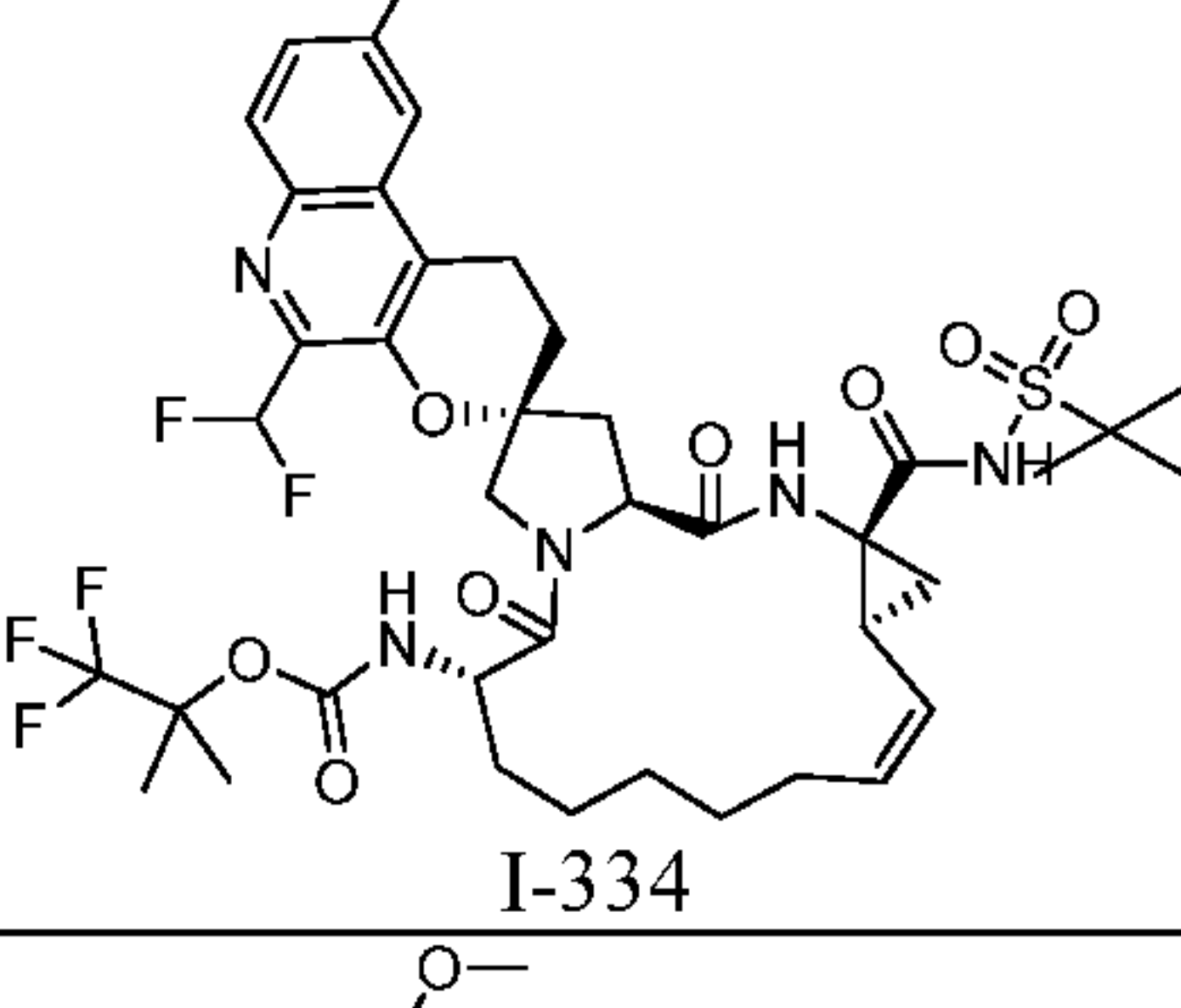
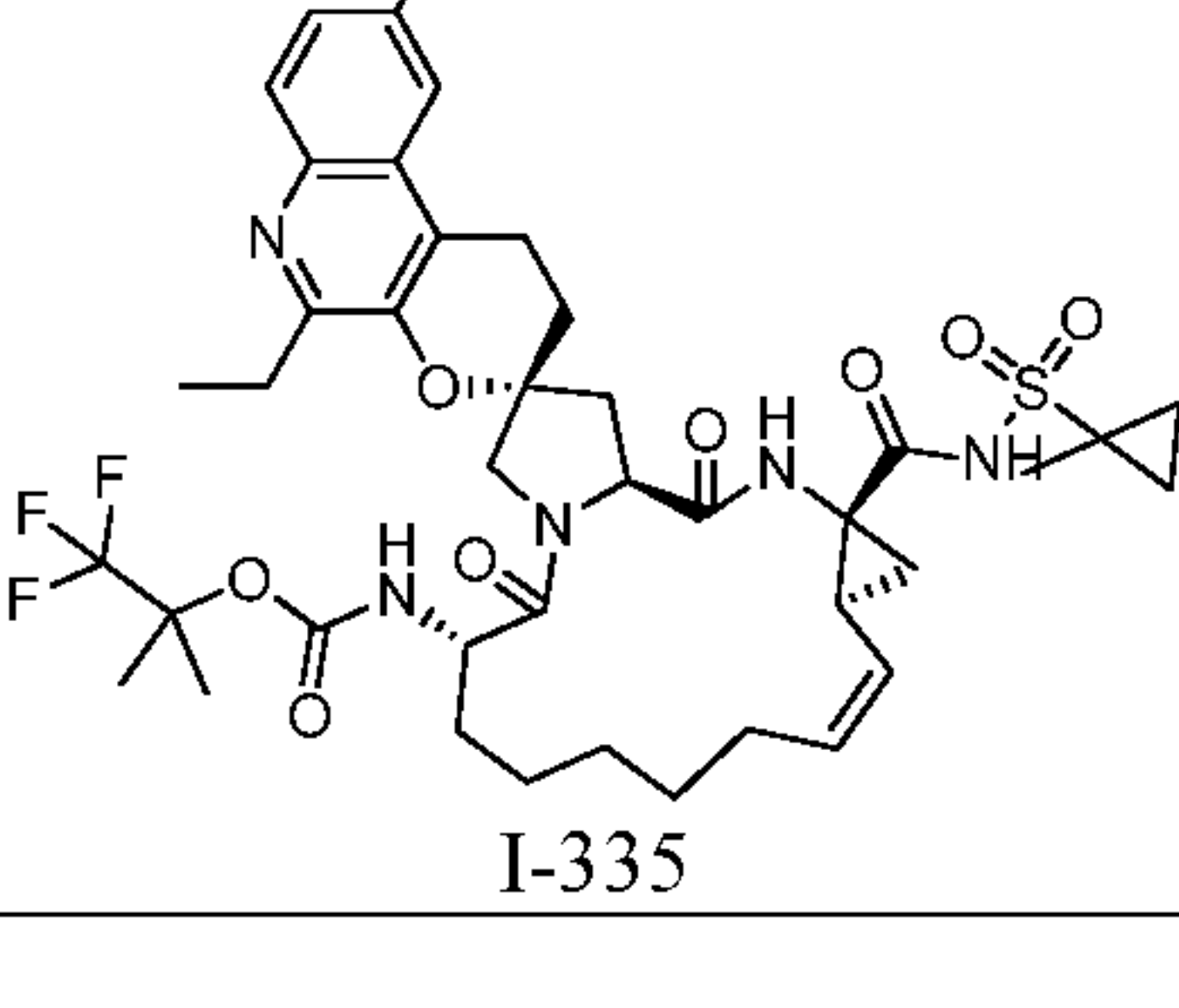
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
306	 I-306	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(difluoromethyl)-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10	786.2
307	 I-307	1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	--
308	 I-308	1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-9'-(2,2,2-trifluoroethoxy)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	30	955.5
309	 I-309	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(difluoromethyl)-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10, 35	840
310	 I-310	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-(difluoromethoxy)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	--

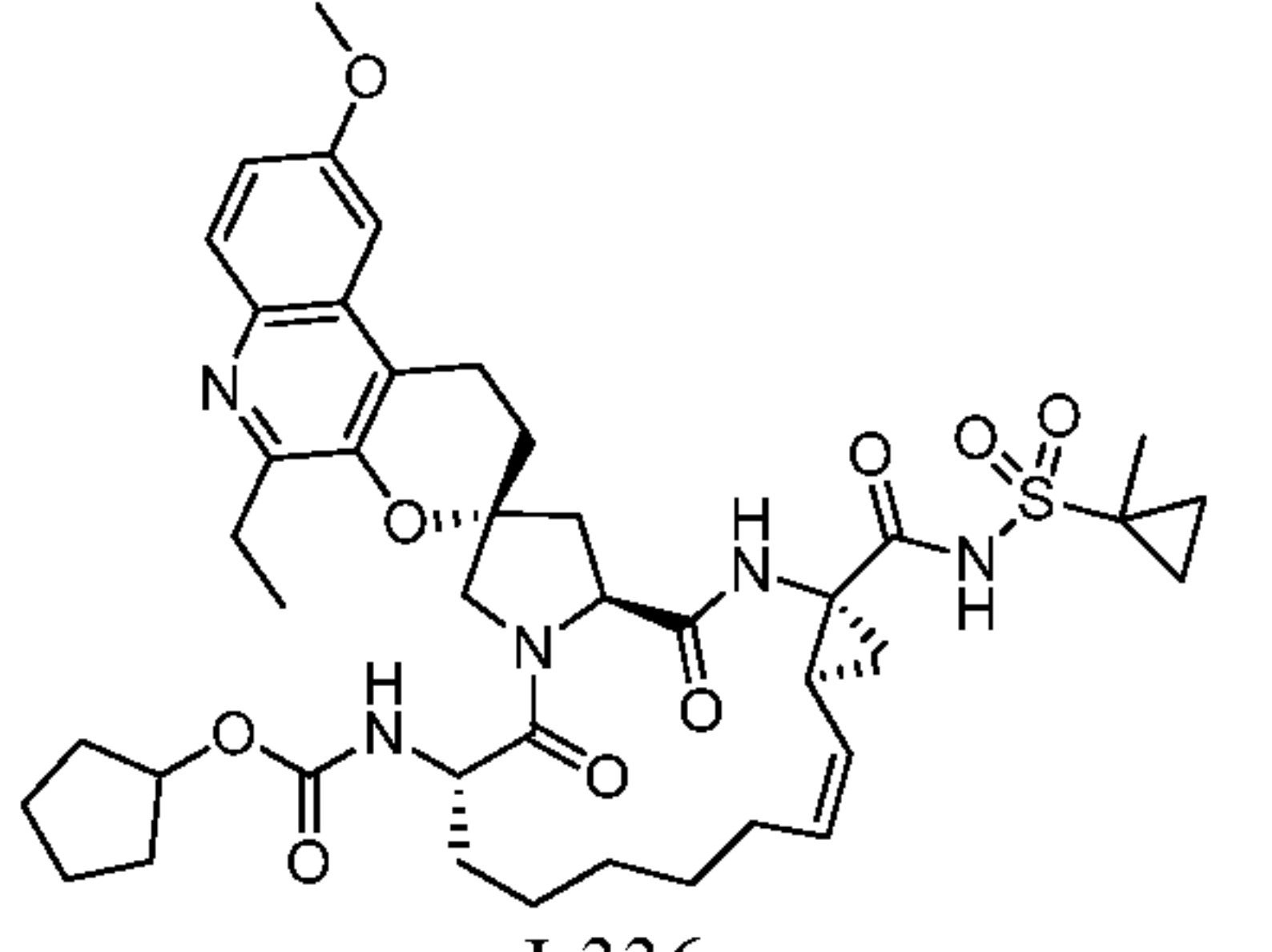
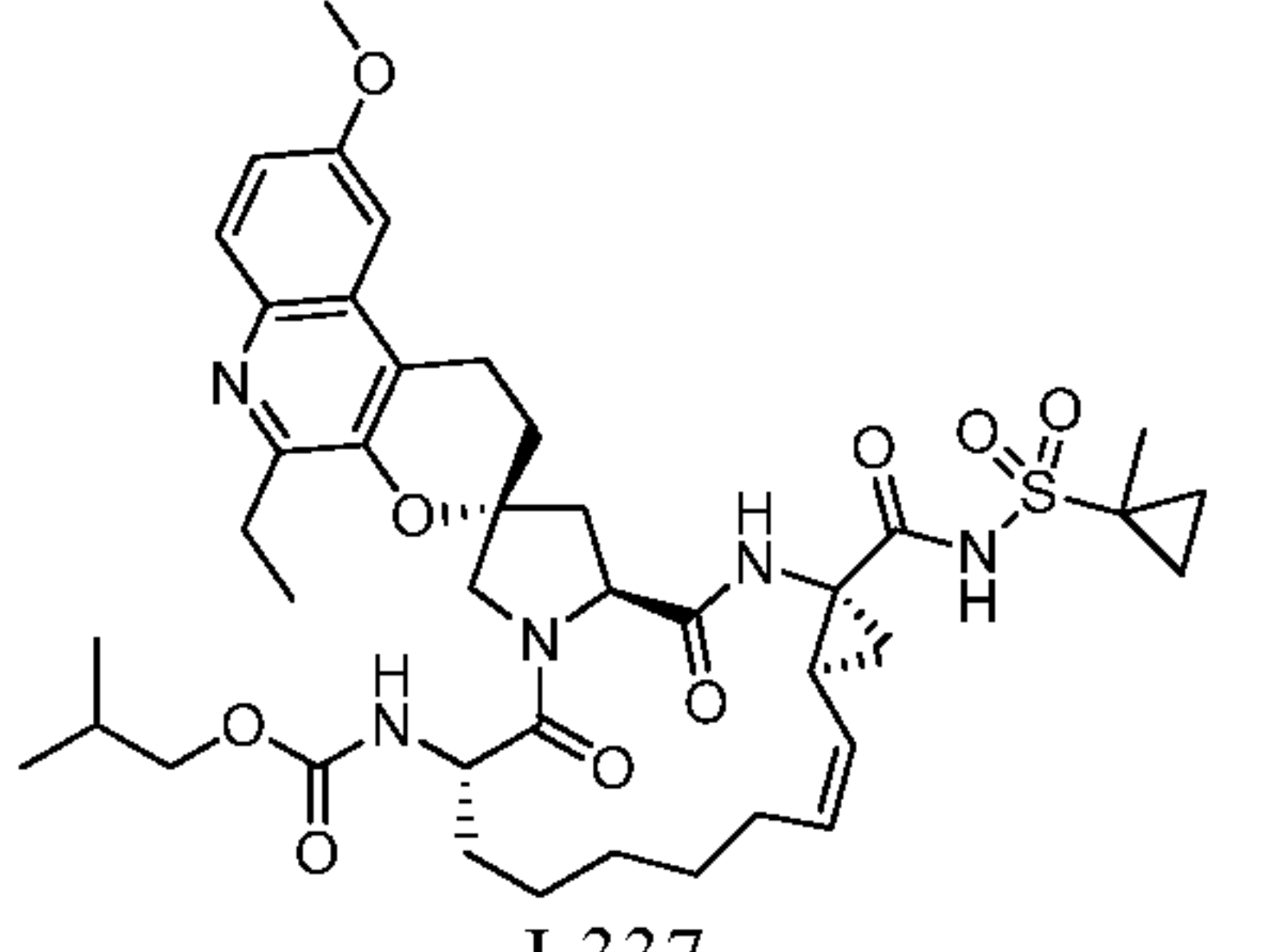
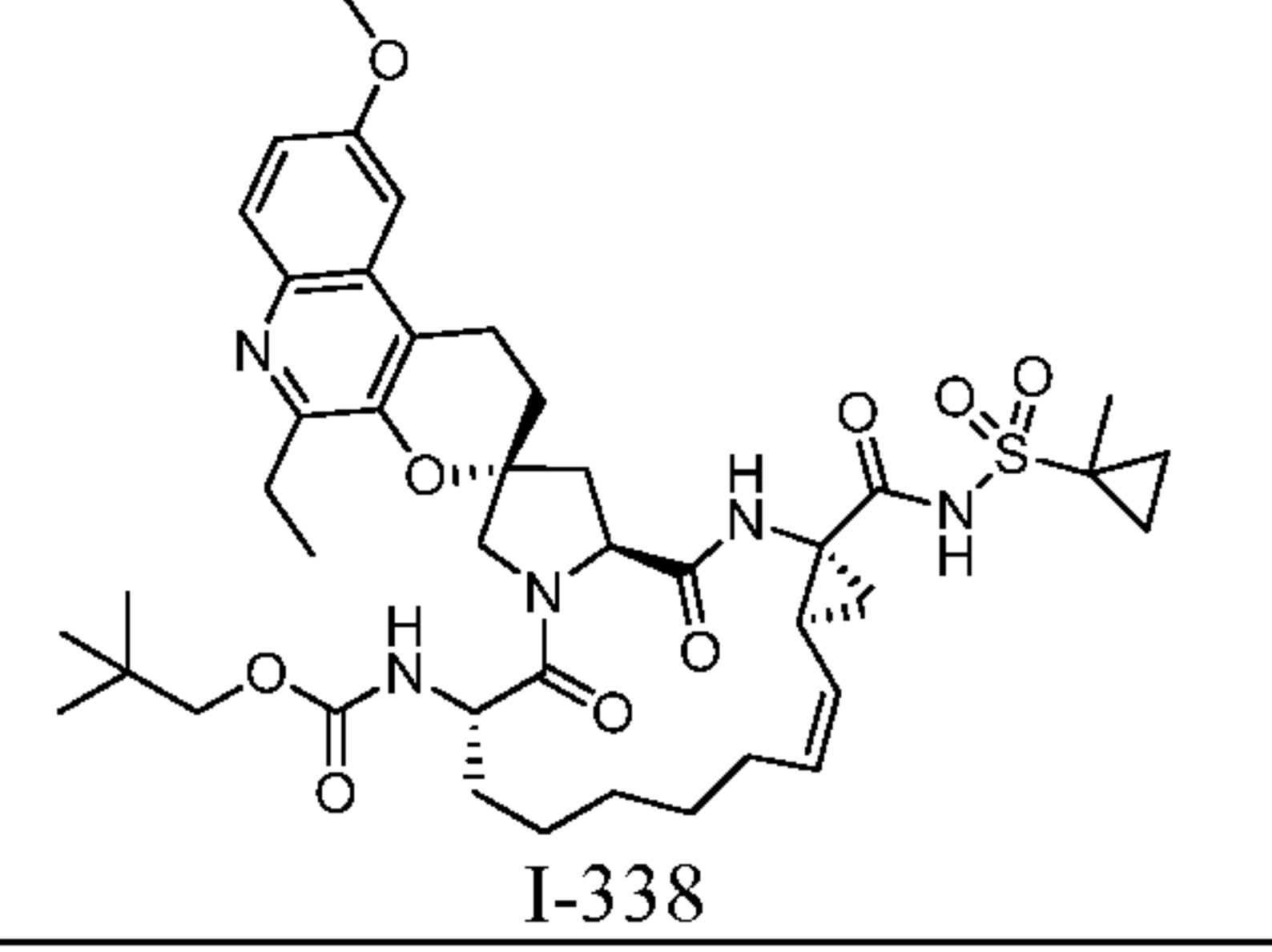
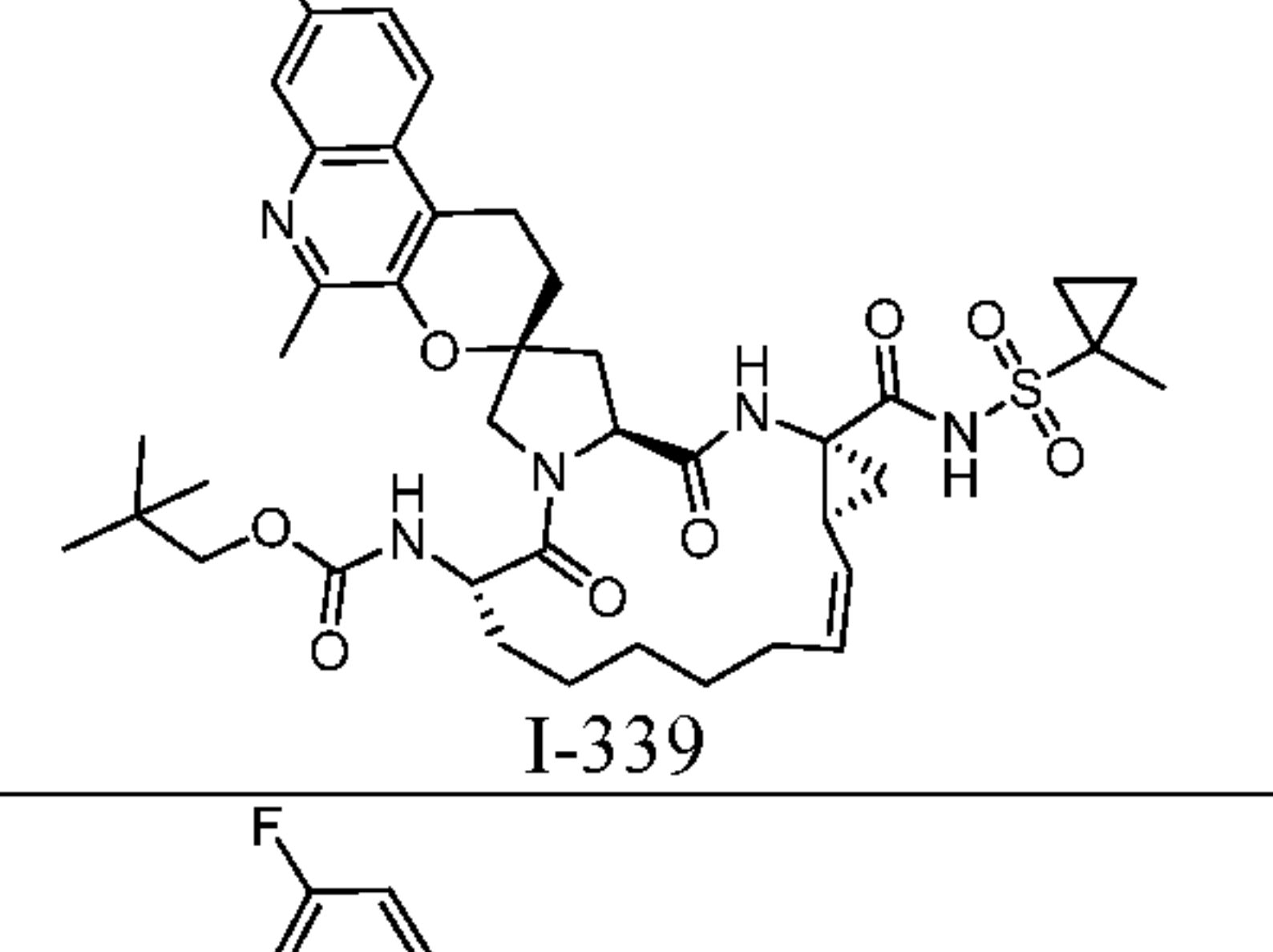
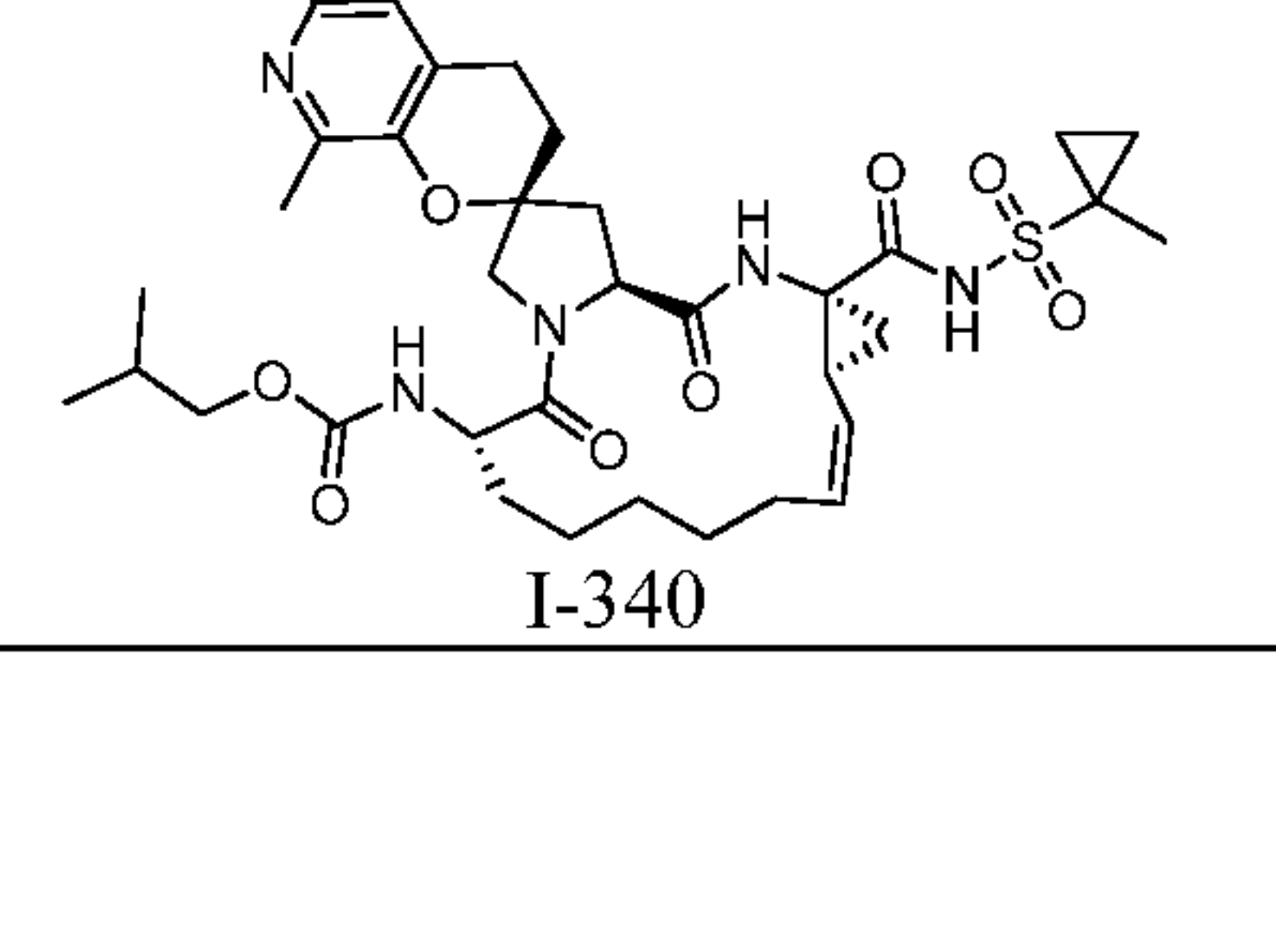
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
311	 I-311	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(difluoromethyl)-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10, 35	800.2
312	 I-312	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-9'-methoxy-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	--
313	 I-313	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-ethyl-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	30	778.2
314	 I-314	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-ethyl-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	30	832.2
315	 I-315	<i>tert</i> -butyl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-ethyl-1'-fluoro-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	32	796.2

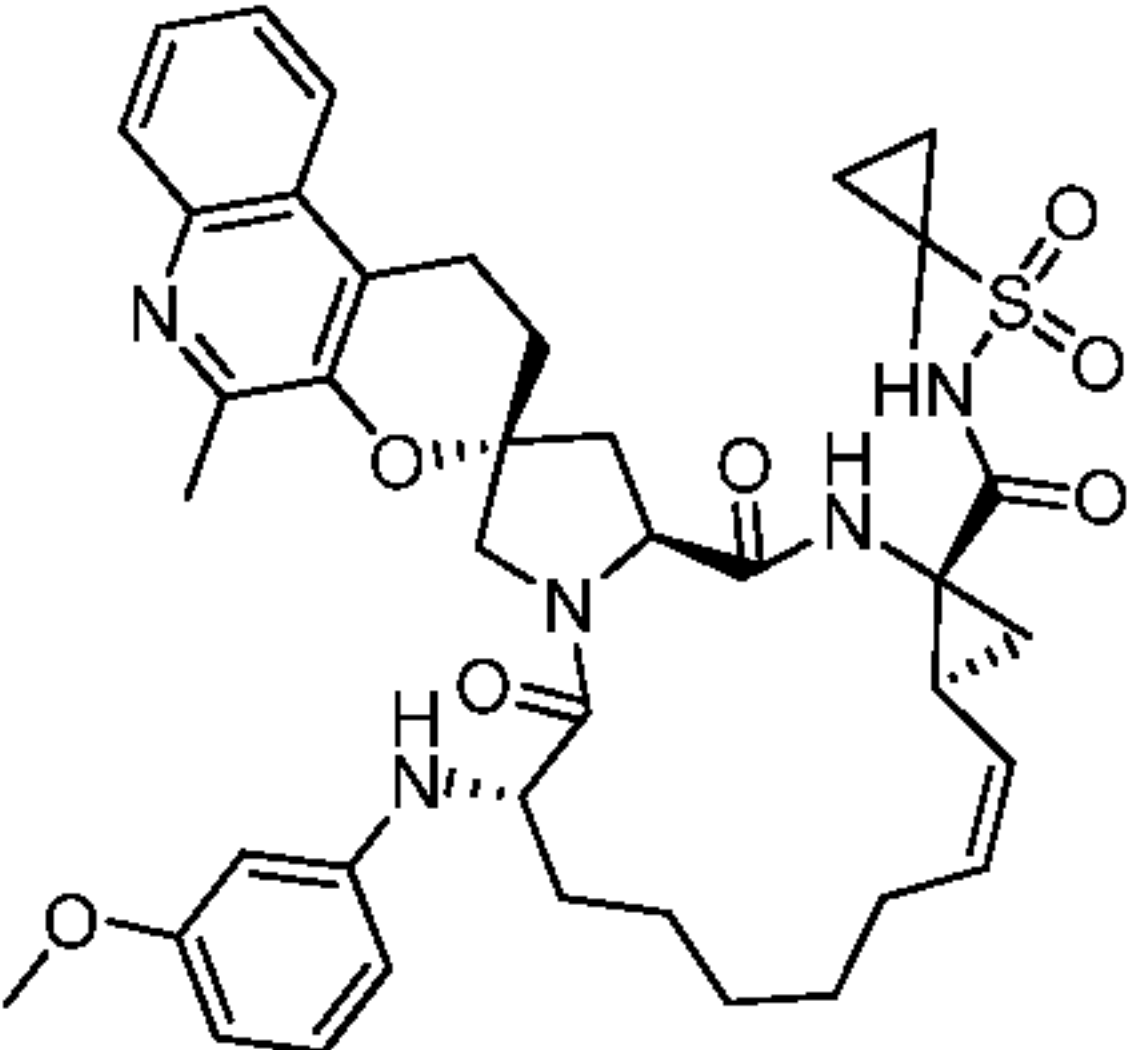
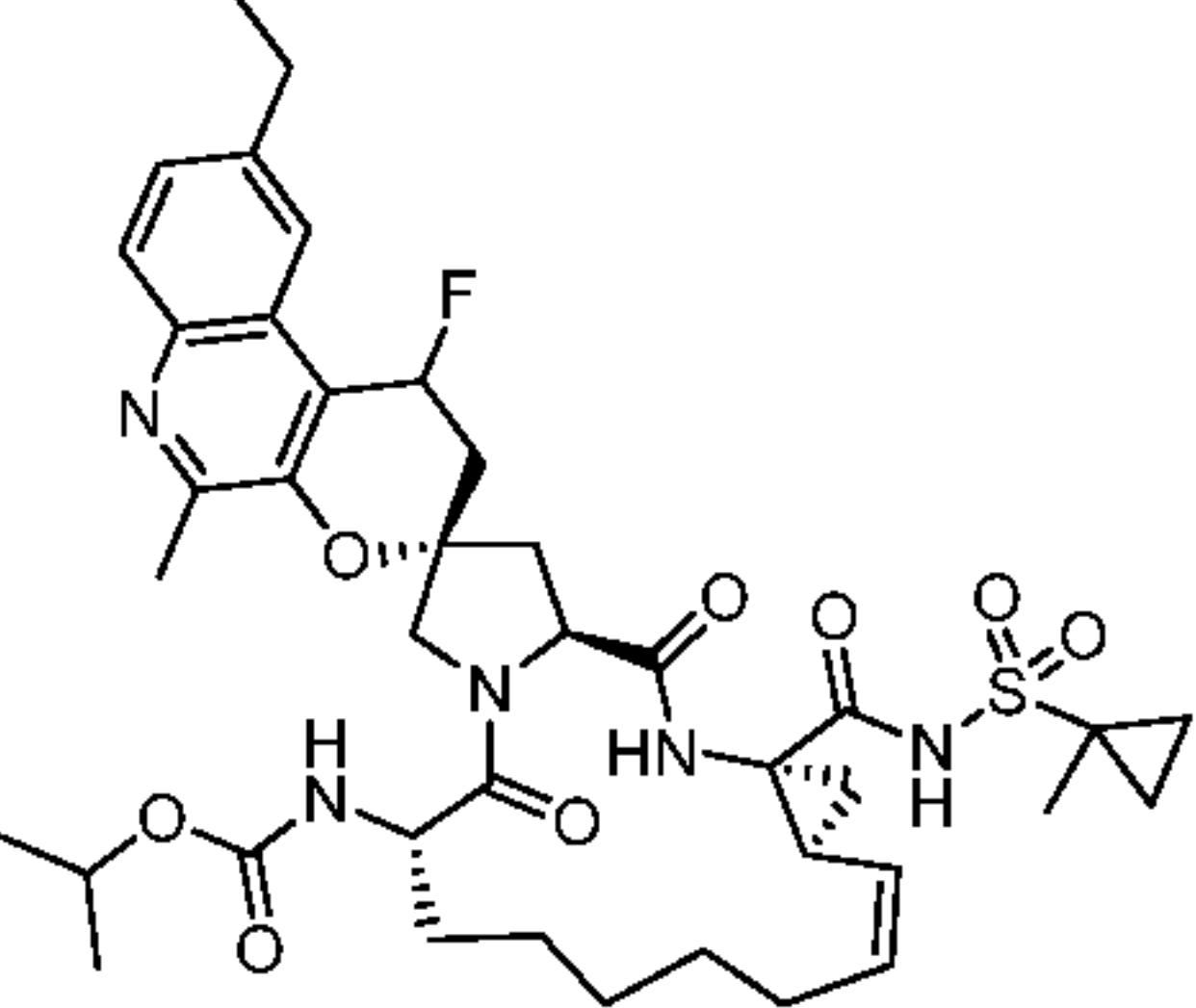
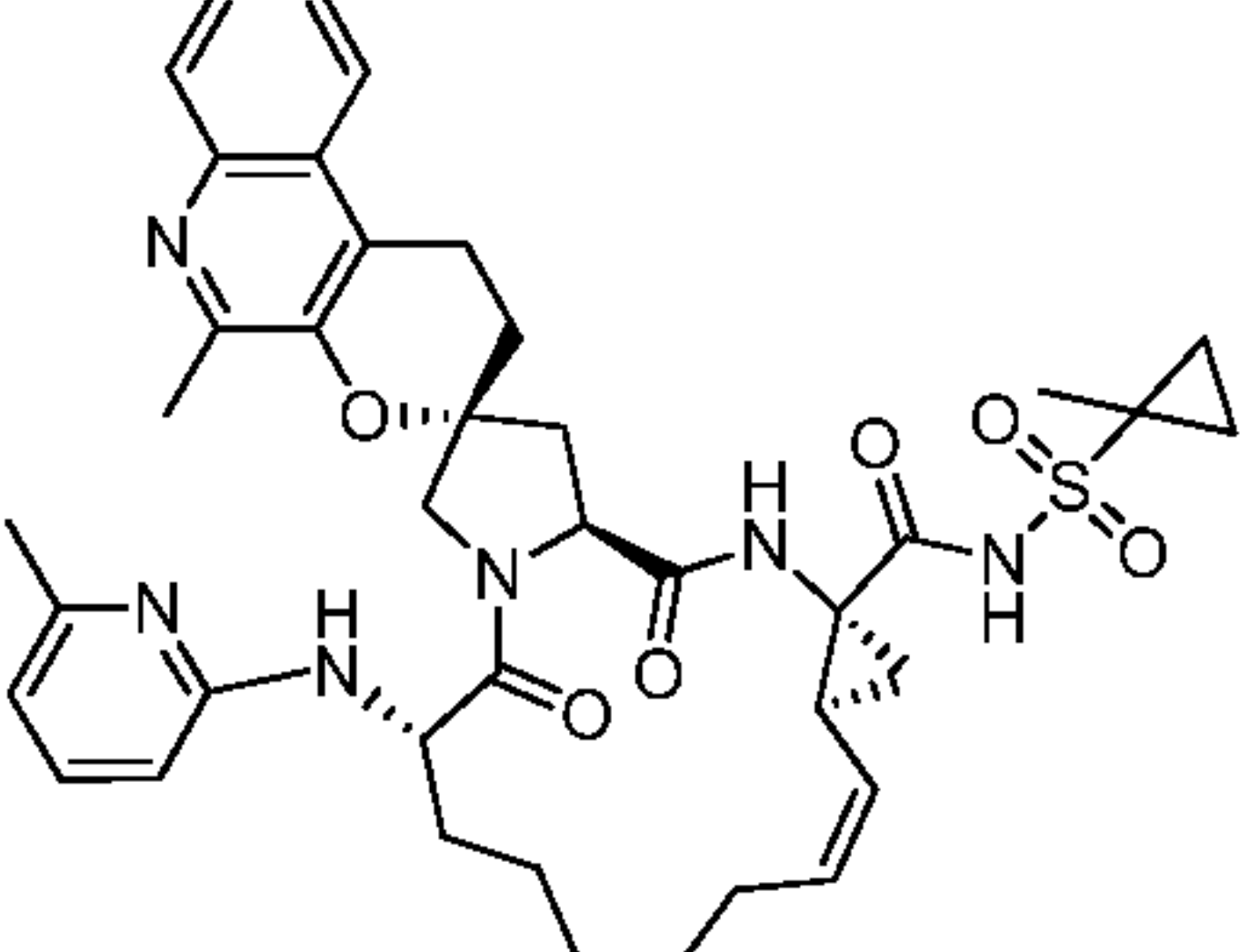
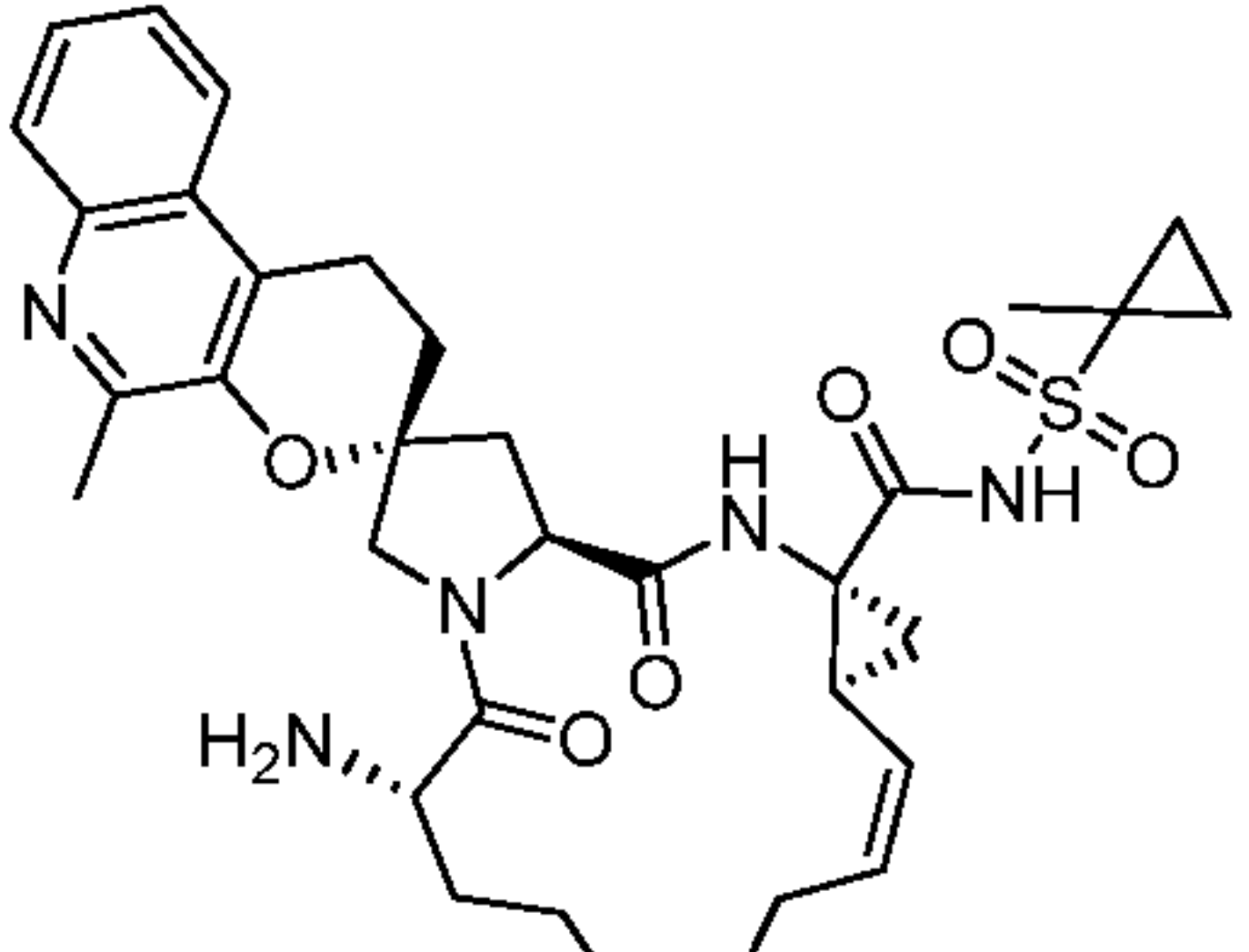
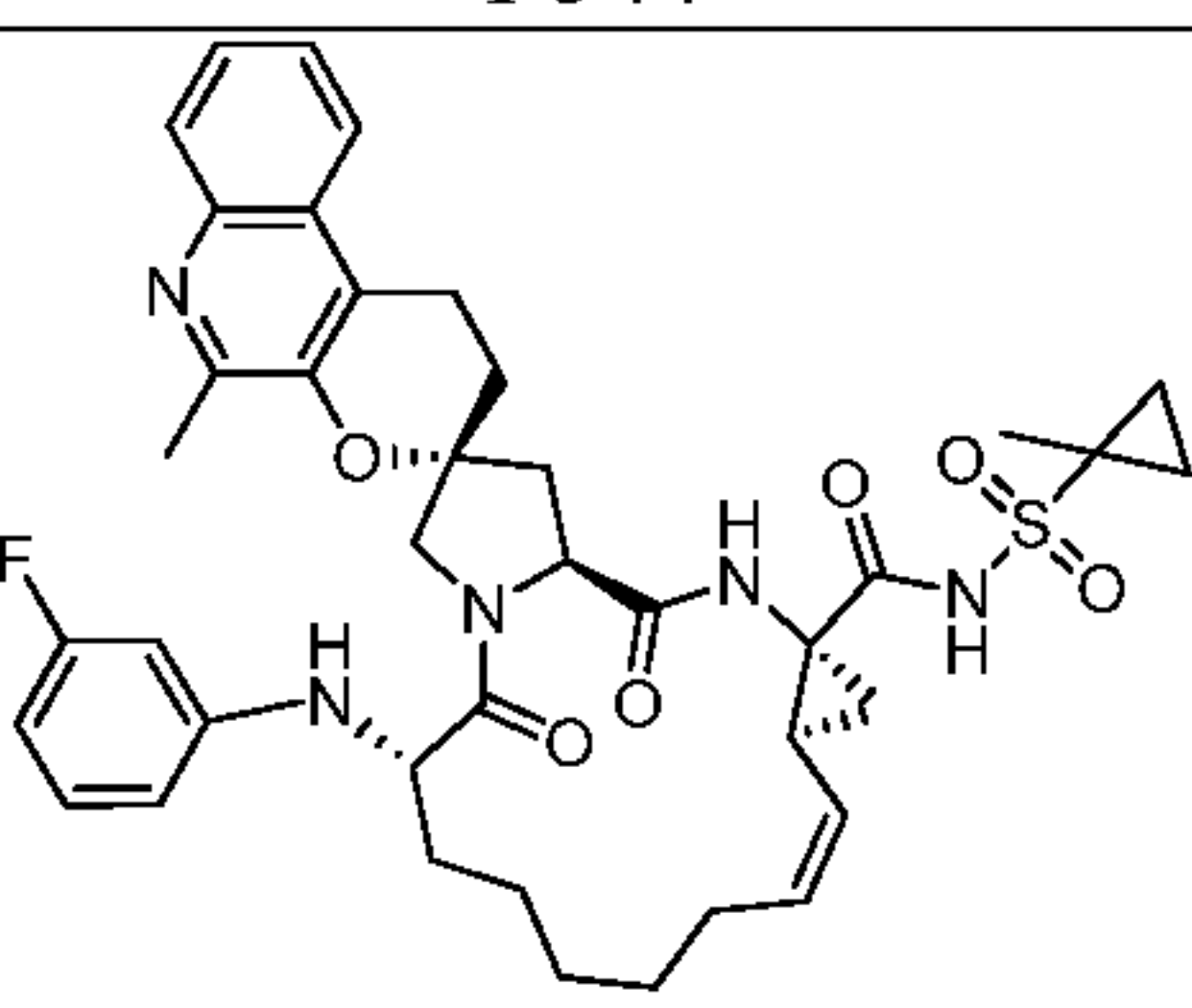
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
316	 I-316	<i>tert</i> -butyl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-ethyl-1'-fluoro-5'-methyl-14a-[[1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	32	796.2
317	 I-317	propan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(difluoromethyl)-14a-[[1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10, 35	772.1
318	 I-318	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-2'-methoxy-6'-methyl-14a-[[1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,5,6,7,8,9,9',10,10',11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,8'-pyrano[2,3- <i>c</i>][1,5]naphthyridin]-6-yl]carbamate	11	835.2
319	 I-319	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-[[1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-9'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	44	888.5
320	 I-320	2,2,3,3-tetrafluorocyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-[[1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	820.4

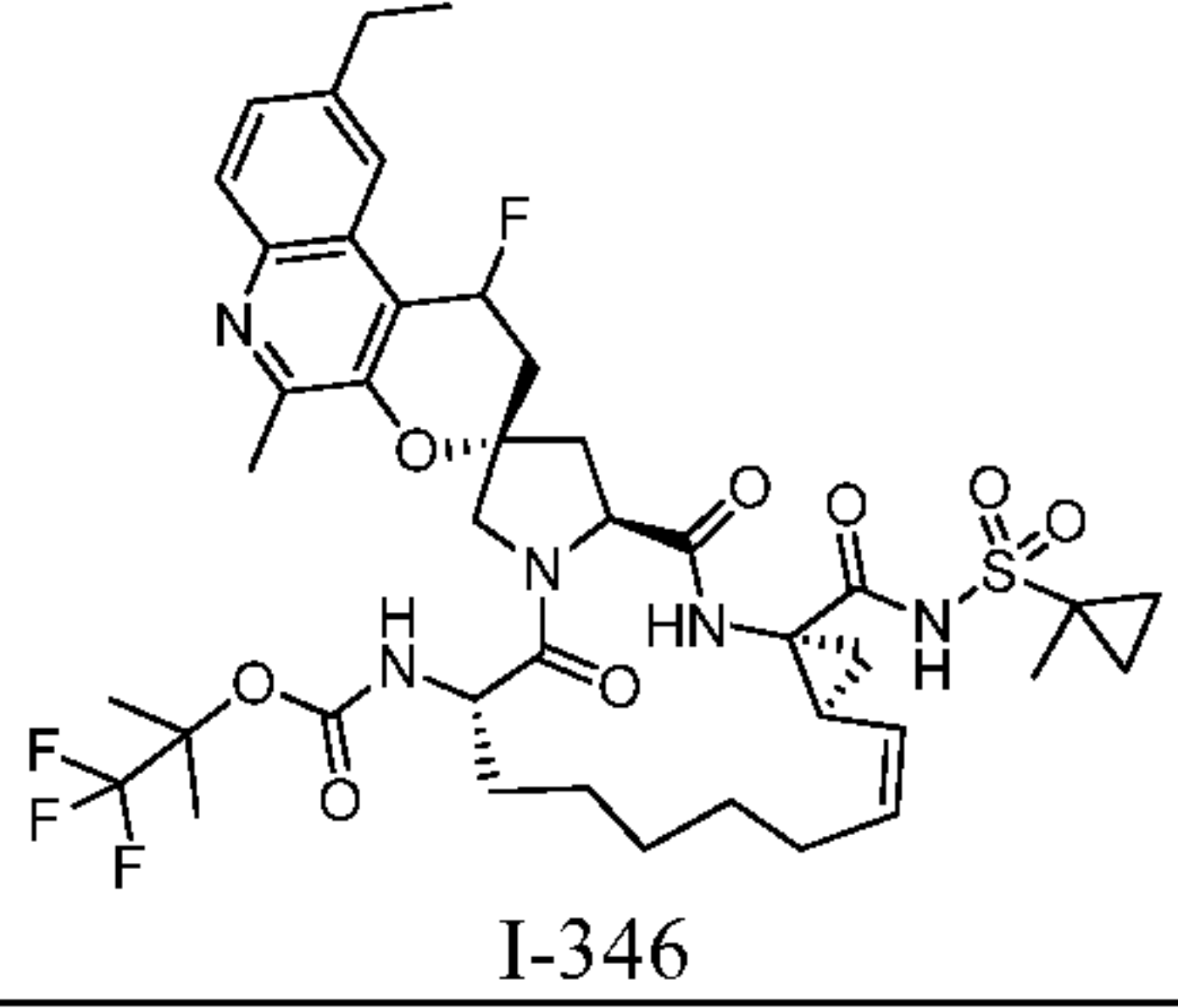
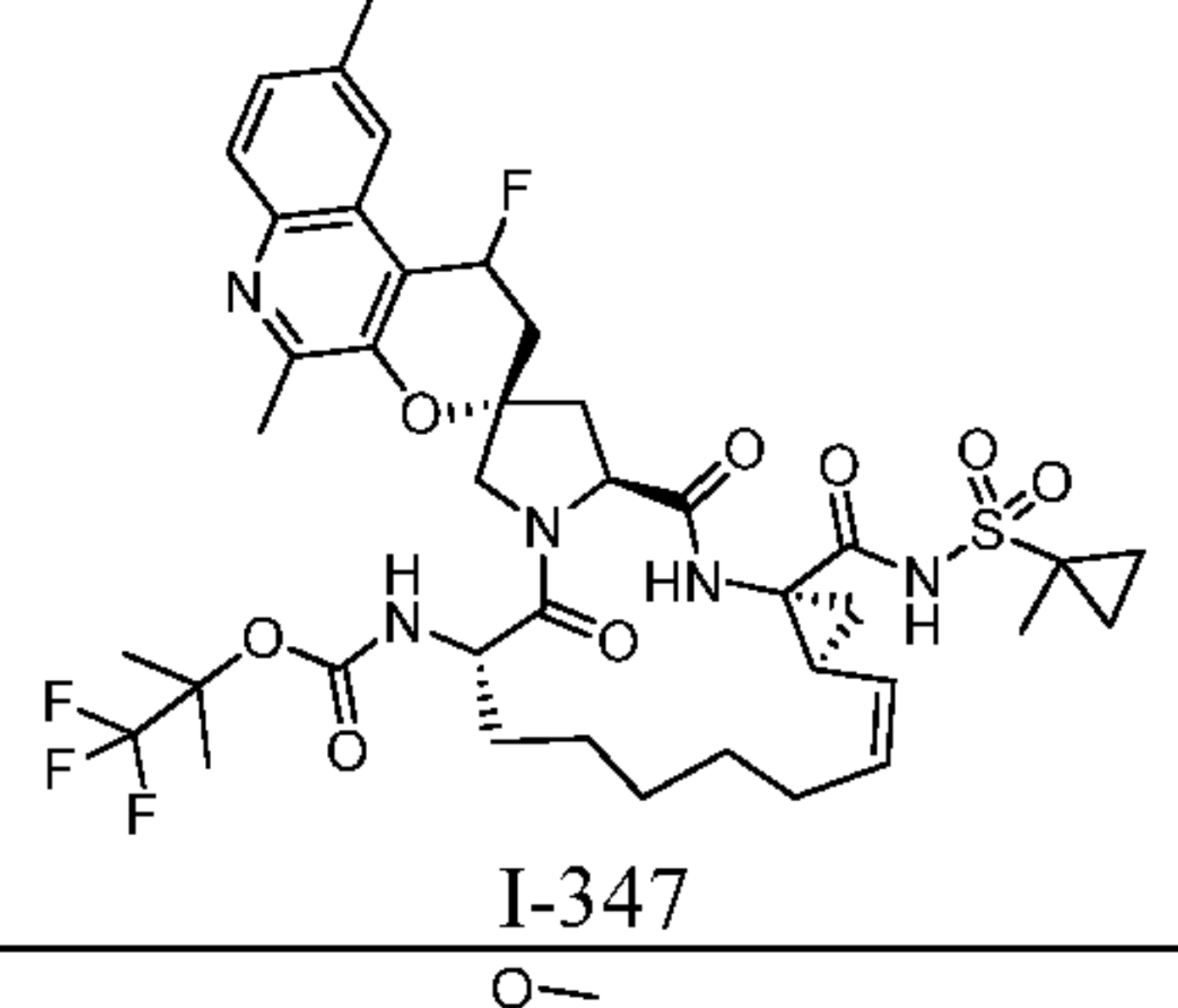
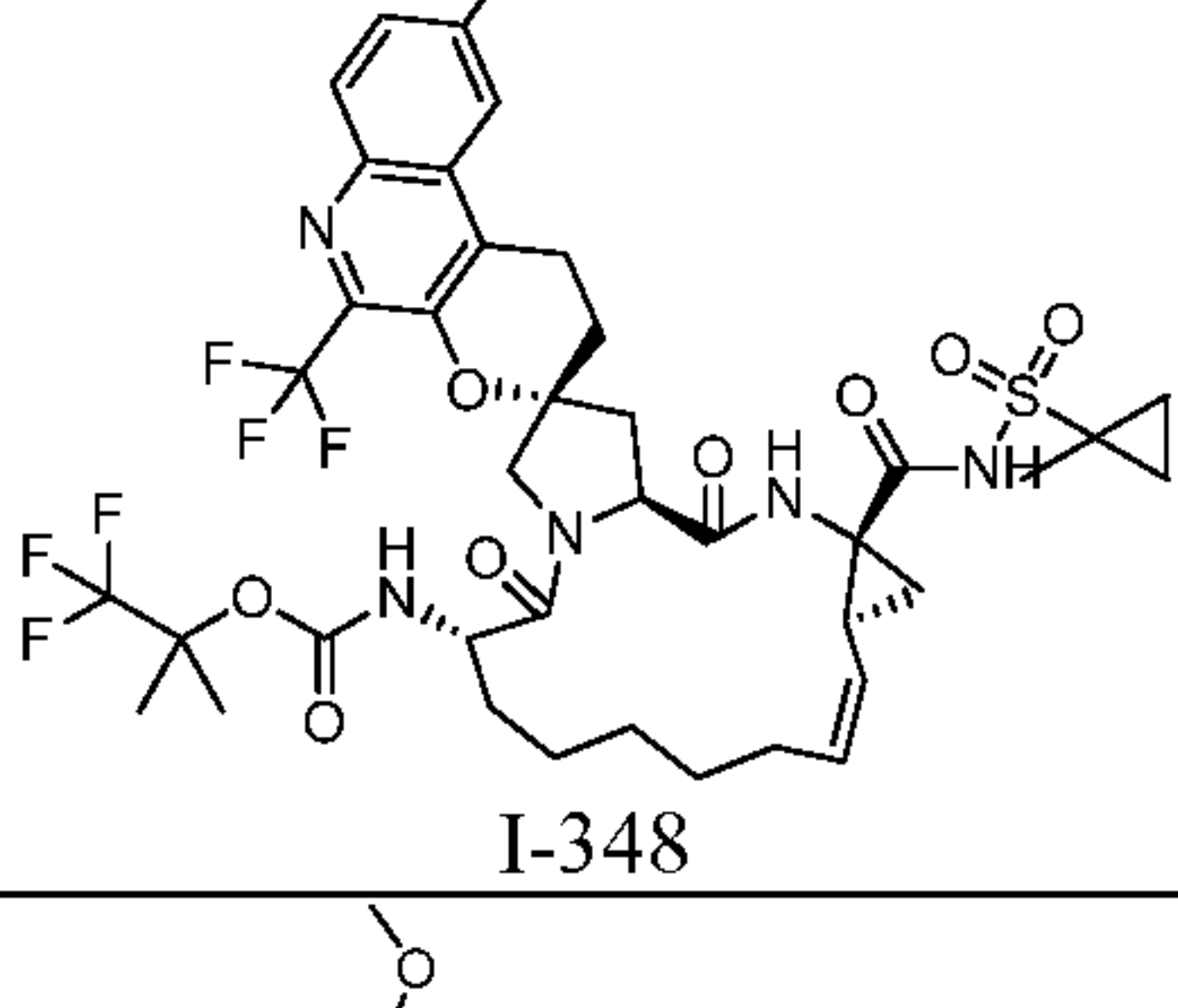
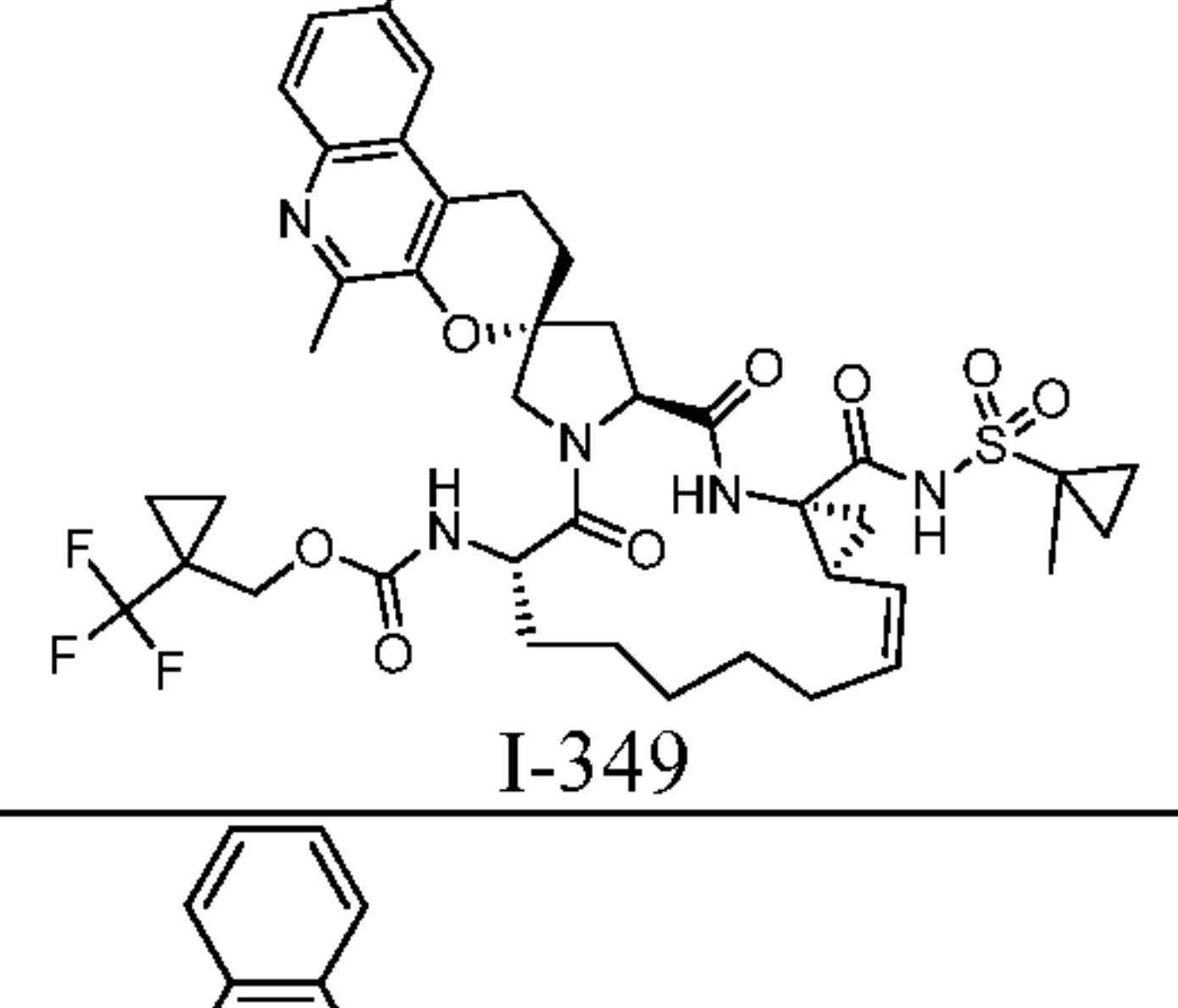
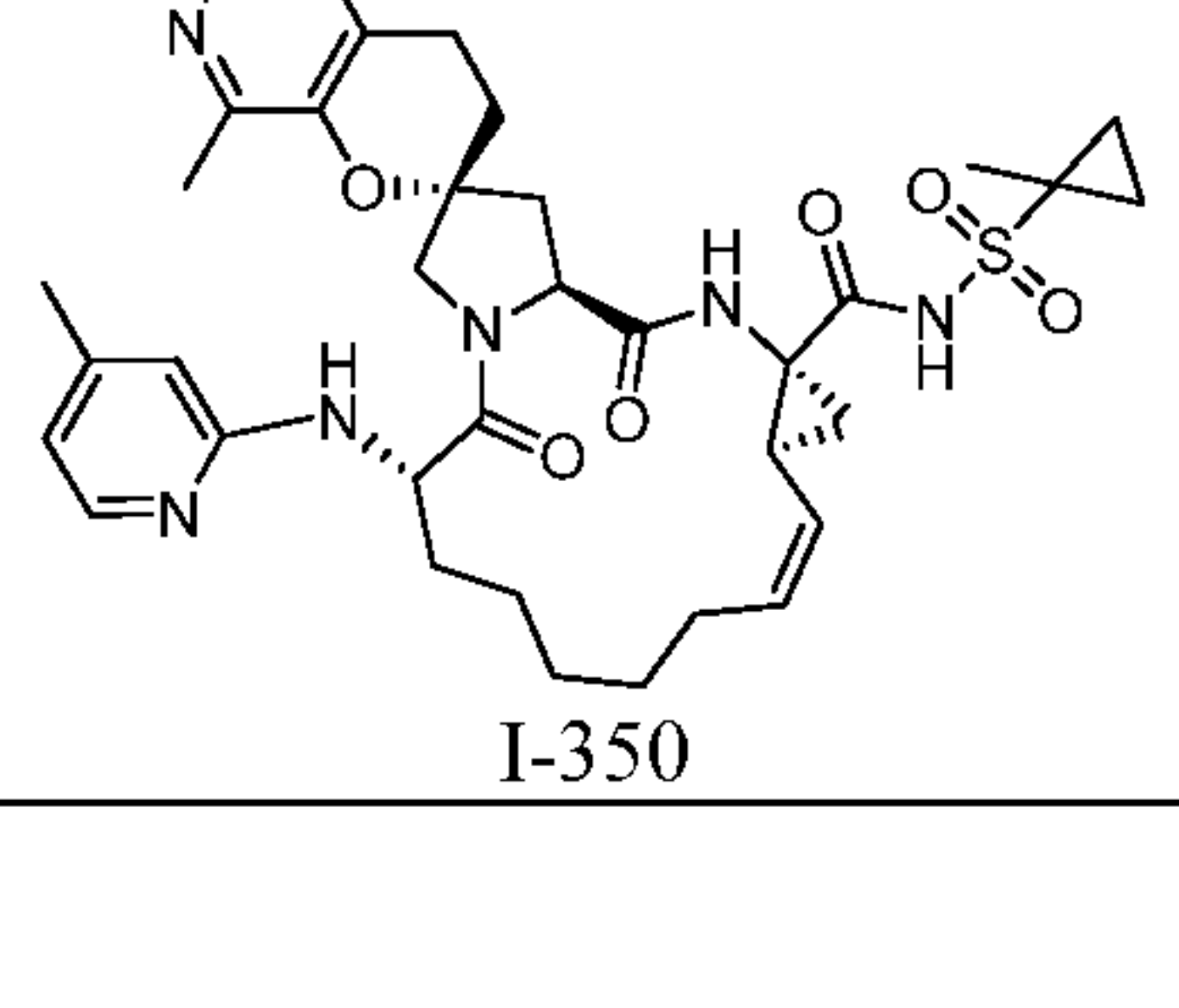
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
321	 I-321	2,2,3,3-tetrafluorocyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-[[1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	820.4
322	 I-322	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-7'-cyclopropyl-14a-[[1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,5,6,7,8,9,10,10',11,11',13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,9'-[1,3]dioxolo[4,5- <i>f</i>]pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	29	873.6
323	 I-323	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-7'-cyclopropyl-14a-[[1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,5,6,7,8,9,10,10',11,11',13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,9'-[1,3]dioxolo[4,5- <i>f</i>]pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	29	831.7
324	 I-324	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-7'-cyclopropyl-14a-[[1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,5,6,7,8,9,10,10',11,11',13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,9'-[1,3]dioxolo[4,5- <i>f</i>]pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	29	833.6
325	 I-325	propyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(difluoromethyl)-14a-[[1-methylcyclopropyl)sulfonyl]carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10, 35	772.2

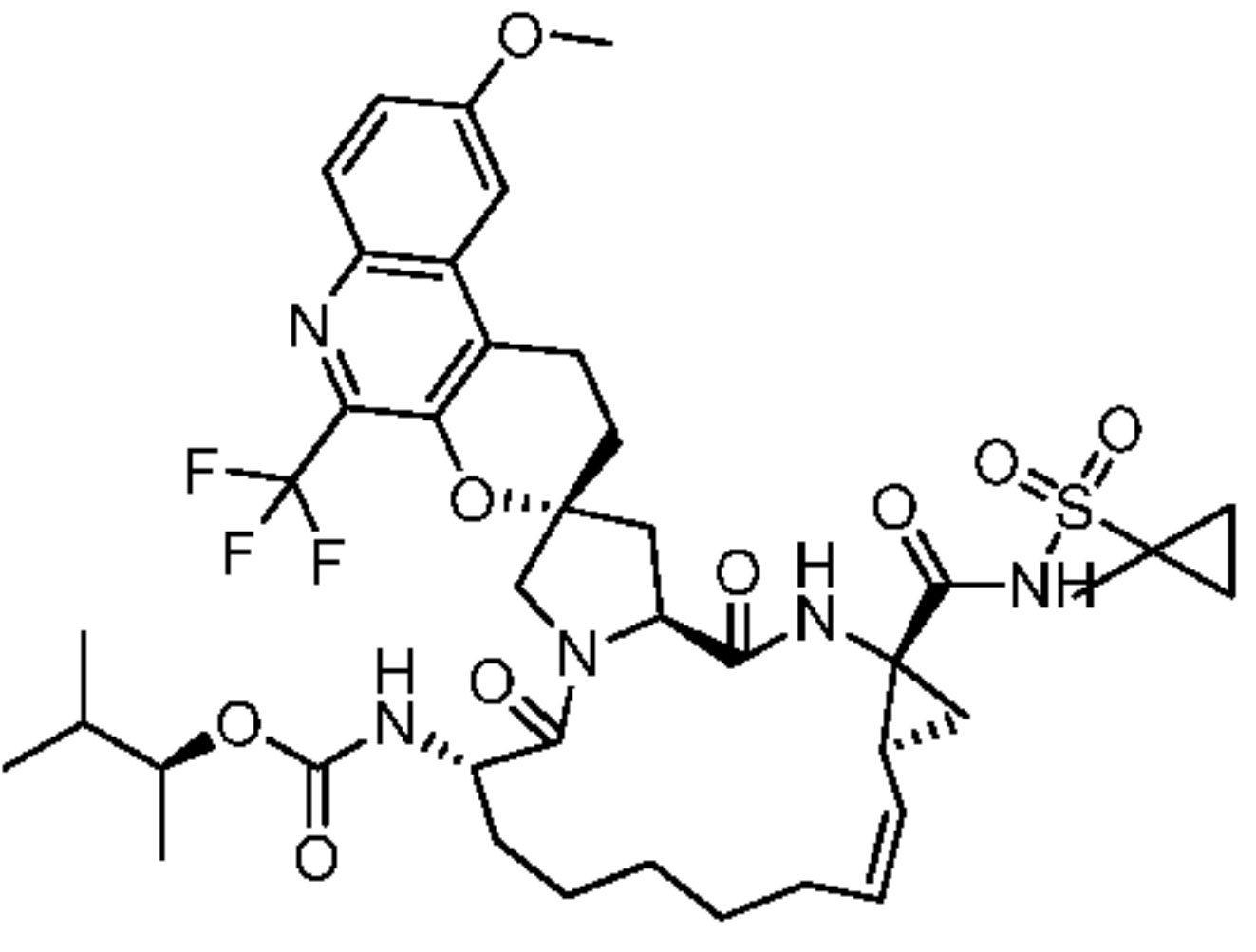
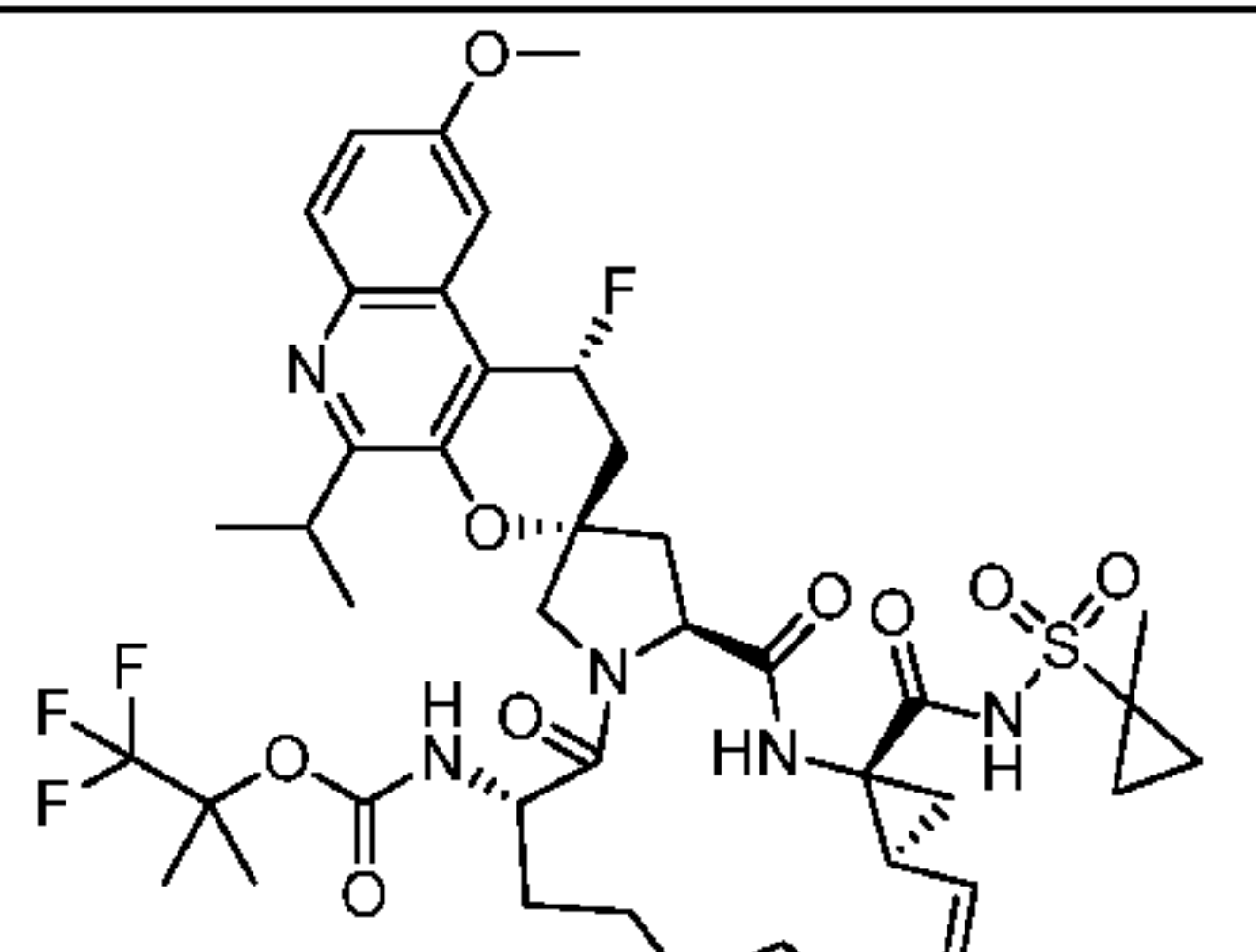
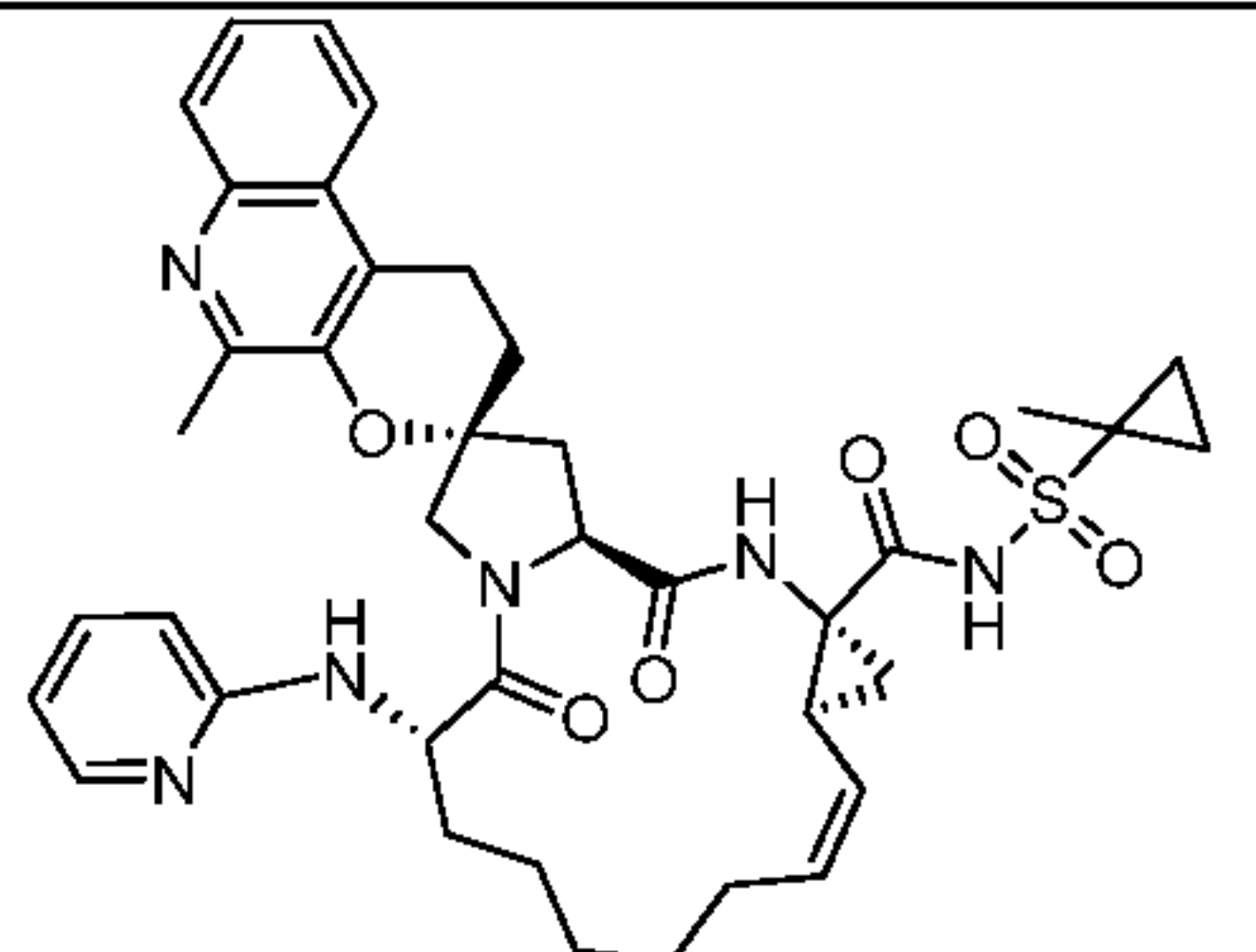
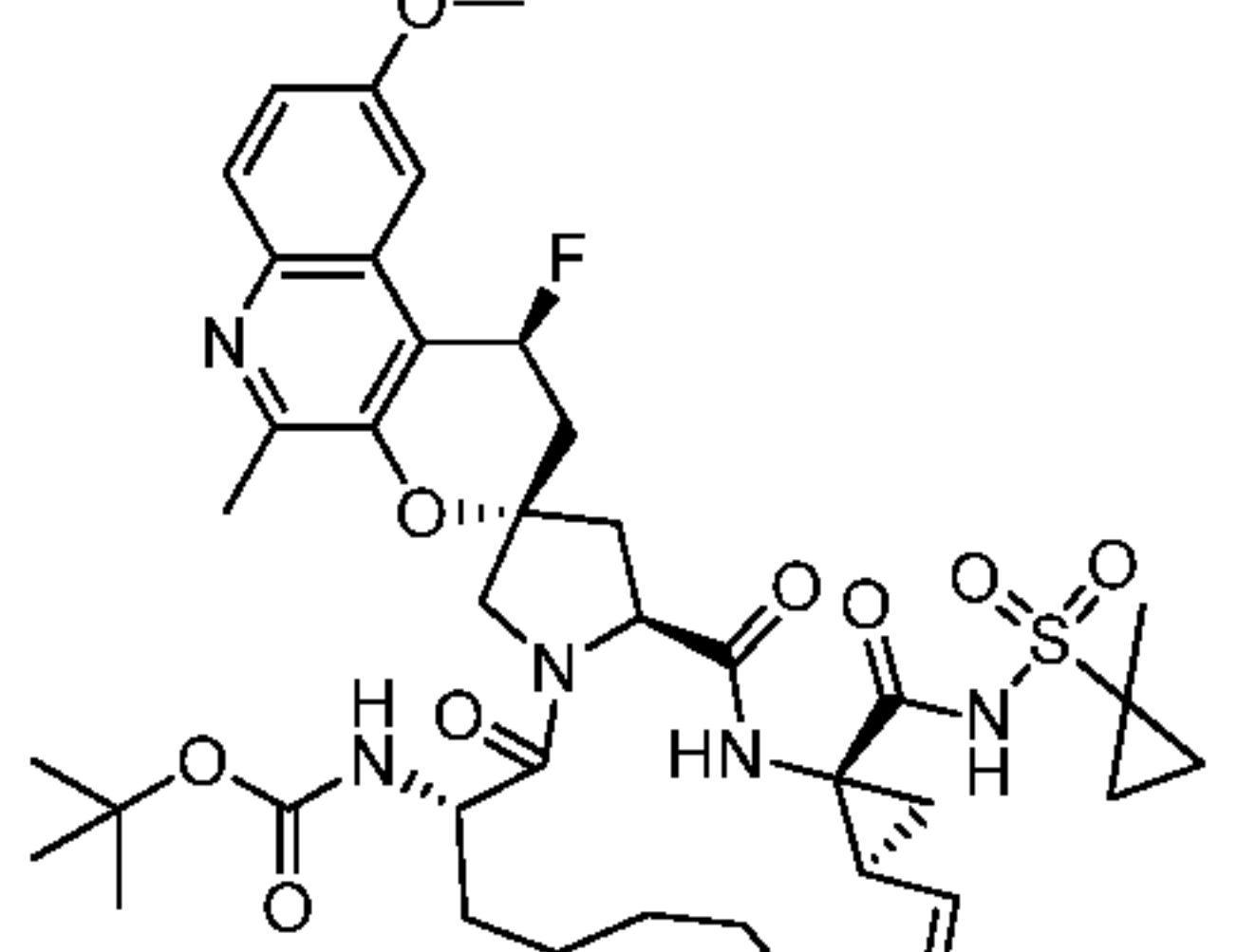
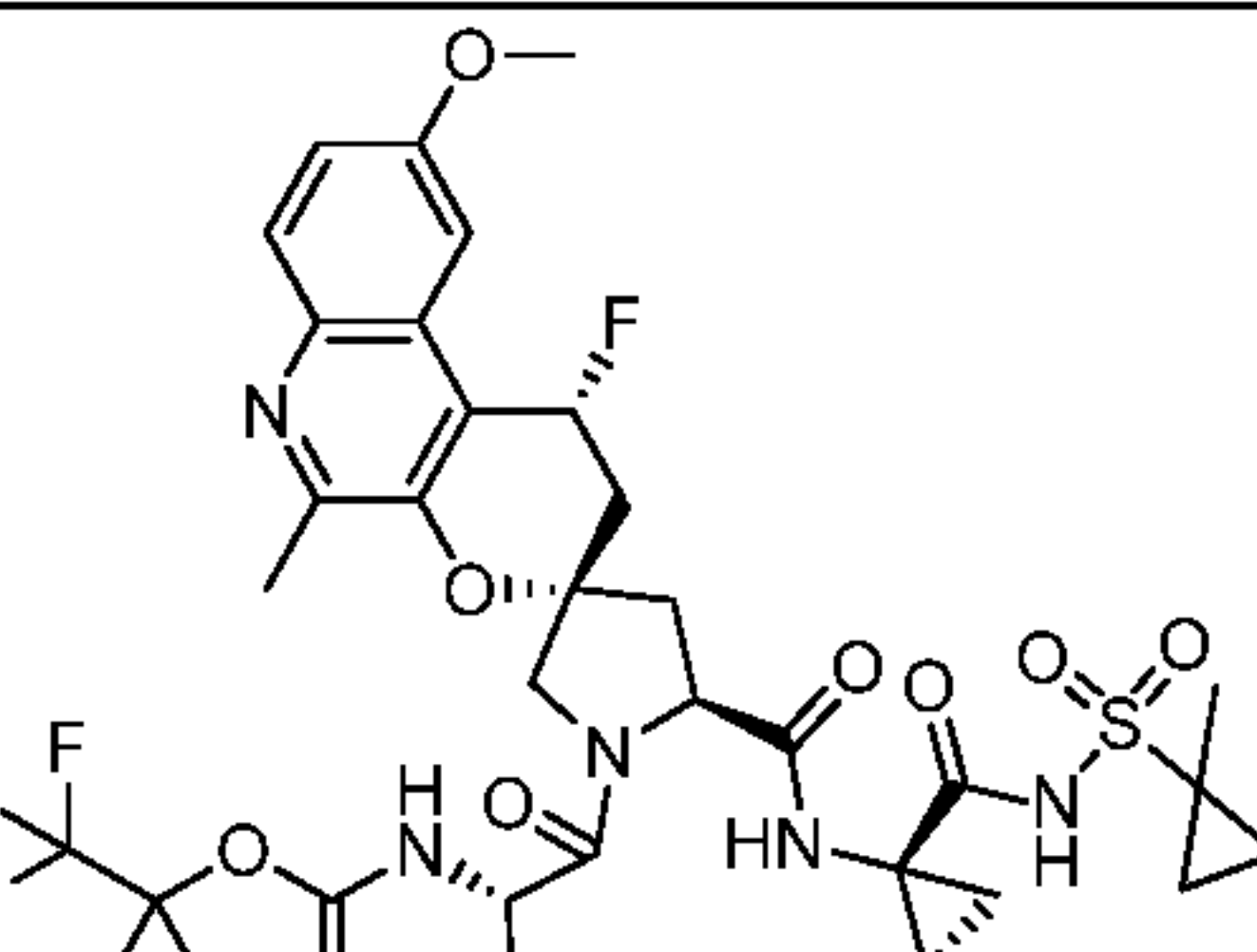
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
326	 I-326	1-(trifluoromethyl)cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	830.5
327	 I-327	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8'-fluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	780.2 (K+ salt)
328	 I-328	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8'-fluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	822.5
329	 I-329	ethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(difluoromethyl)-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10, 35	758.2
330	 I-330	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-ethyl-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	30	778.2

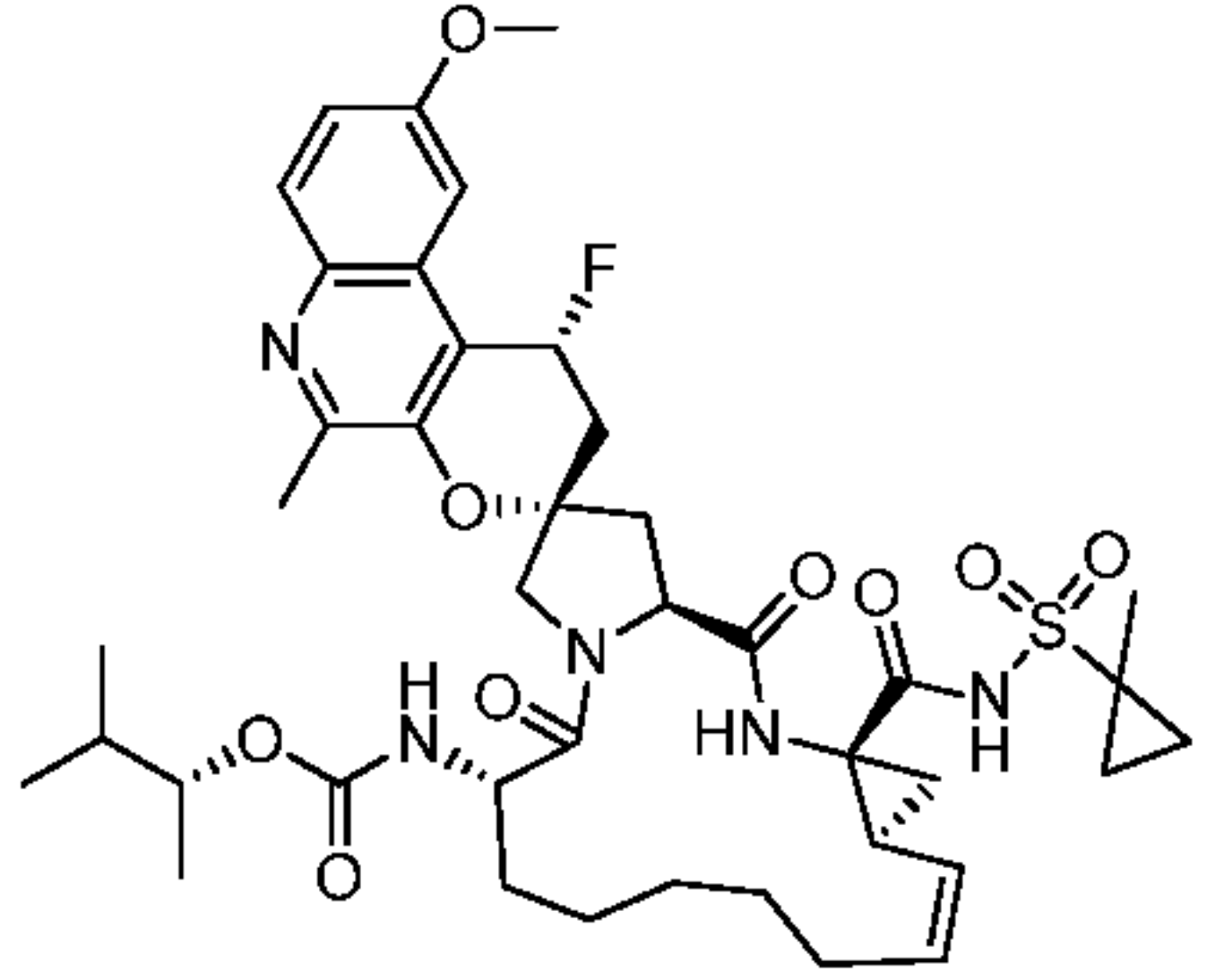
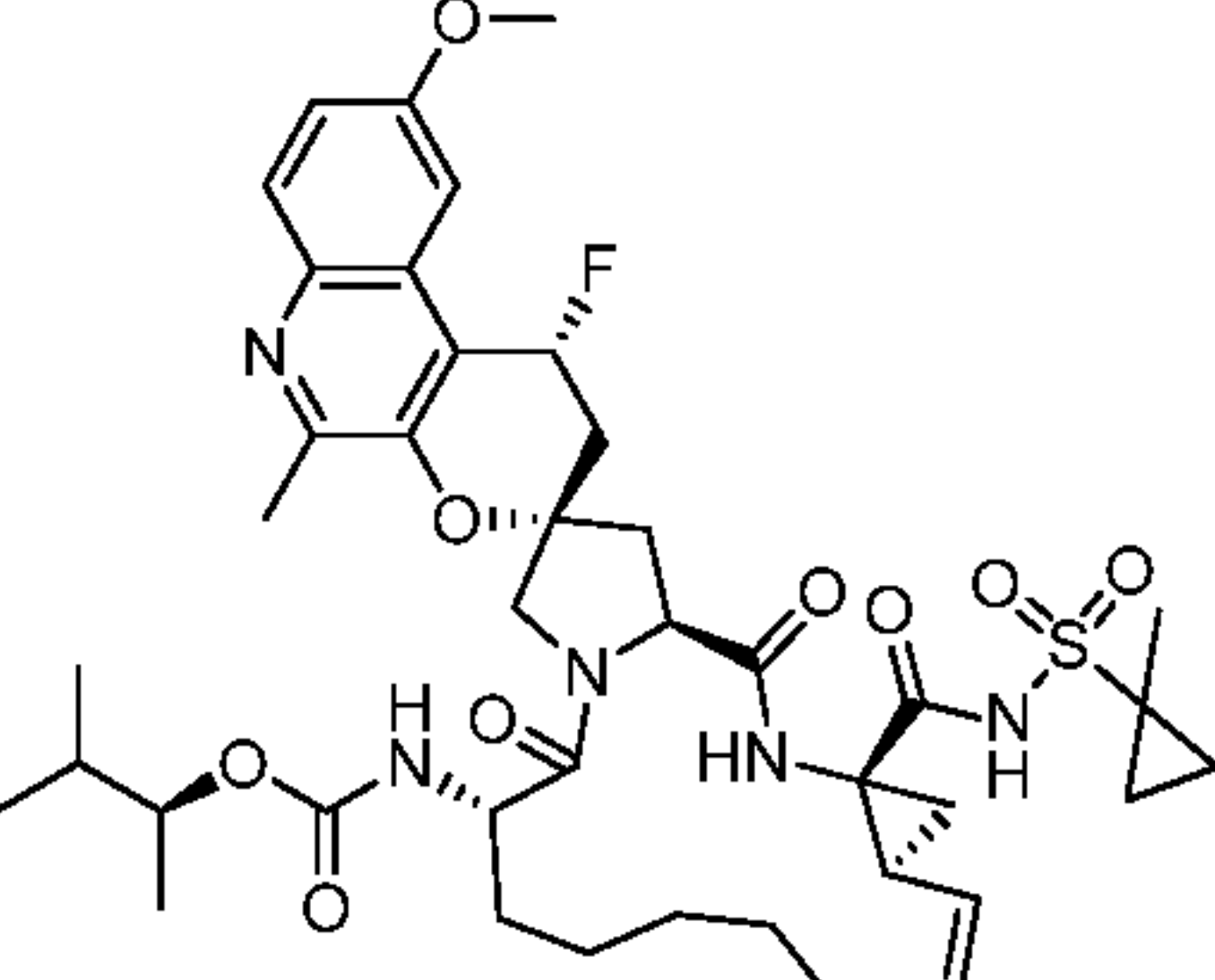
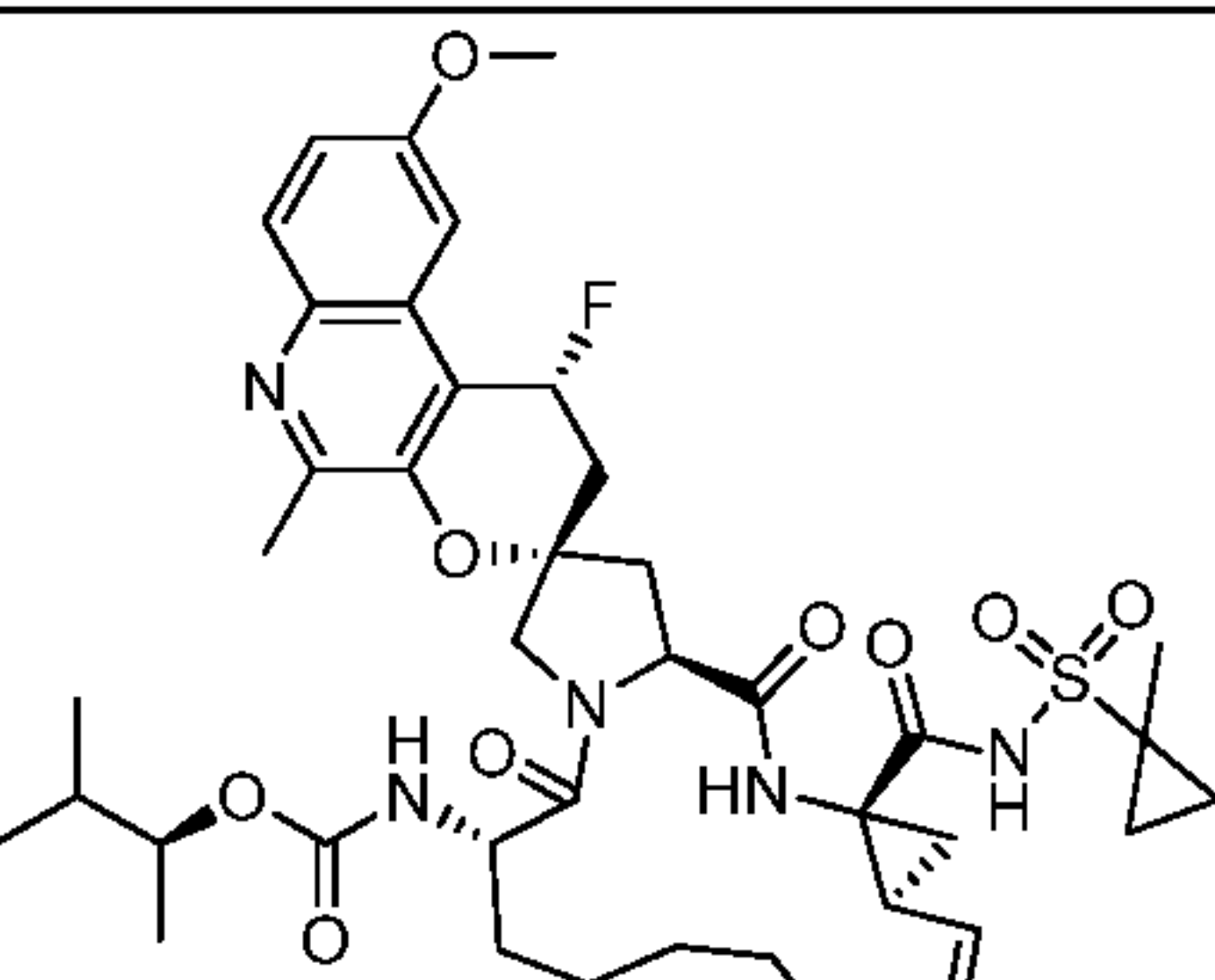
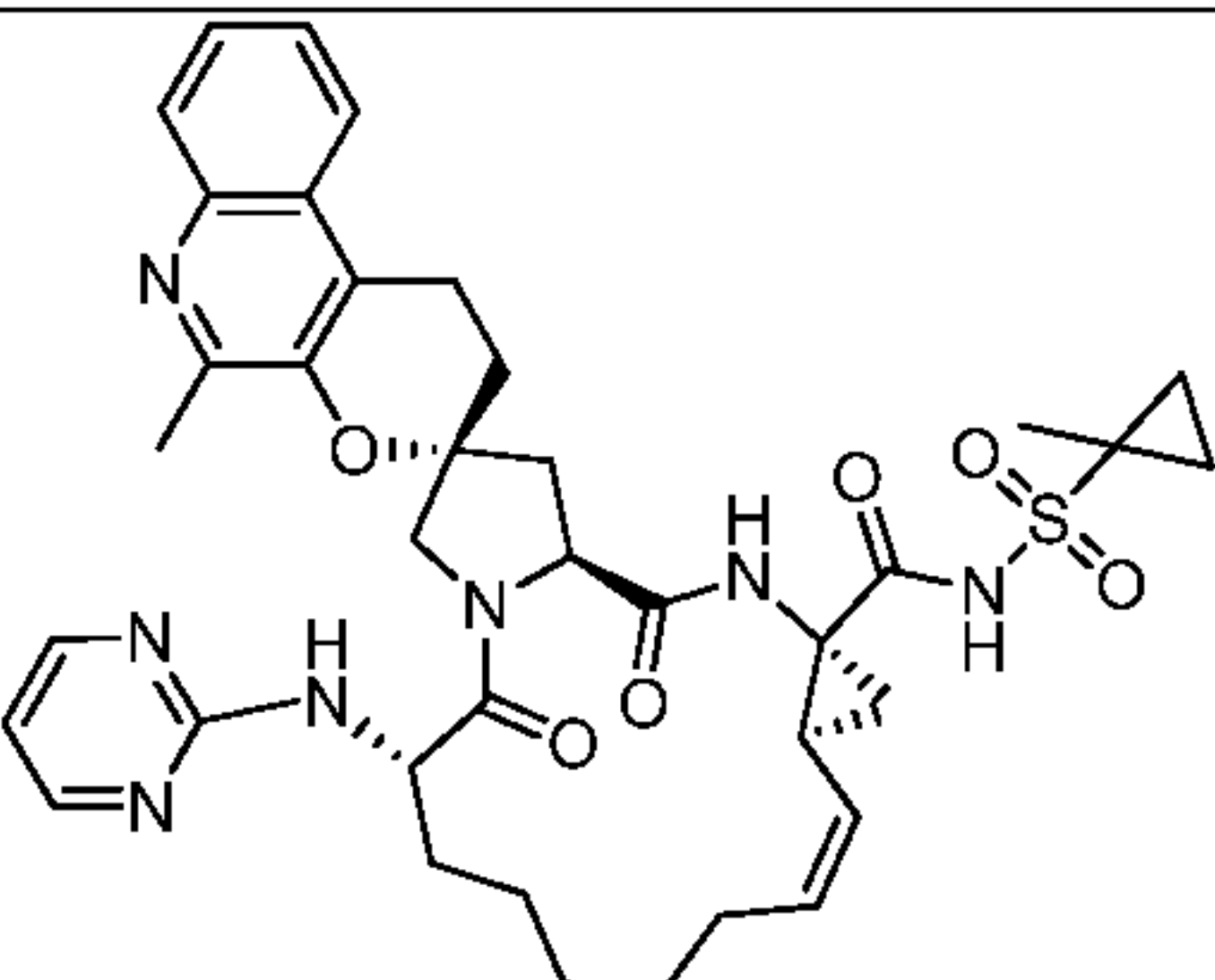
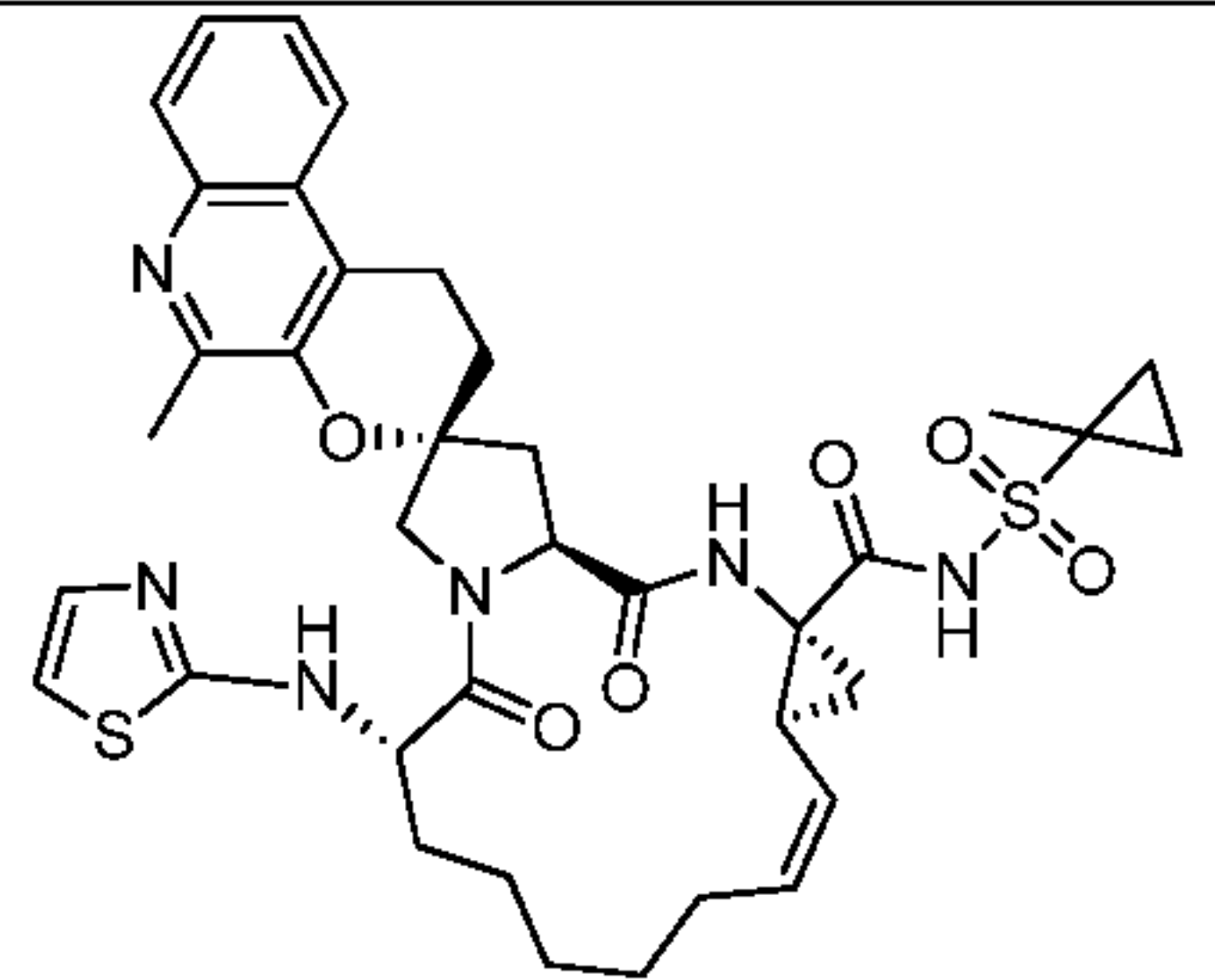
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
331	 I-331	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-5'-(difluoromethyl)-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10	764
332	 I-332	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-cyclopropyl-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1	790.2
333	 I-333	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	39	838
334	 I-334	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-5'-(difluoromethyl)-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10	874.2
335	 I-335	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	848.0

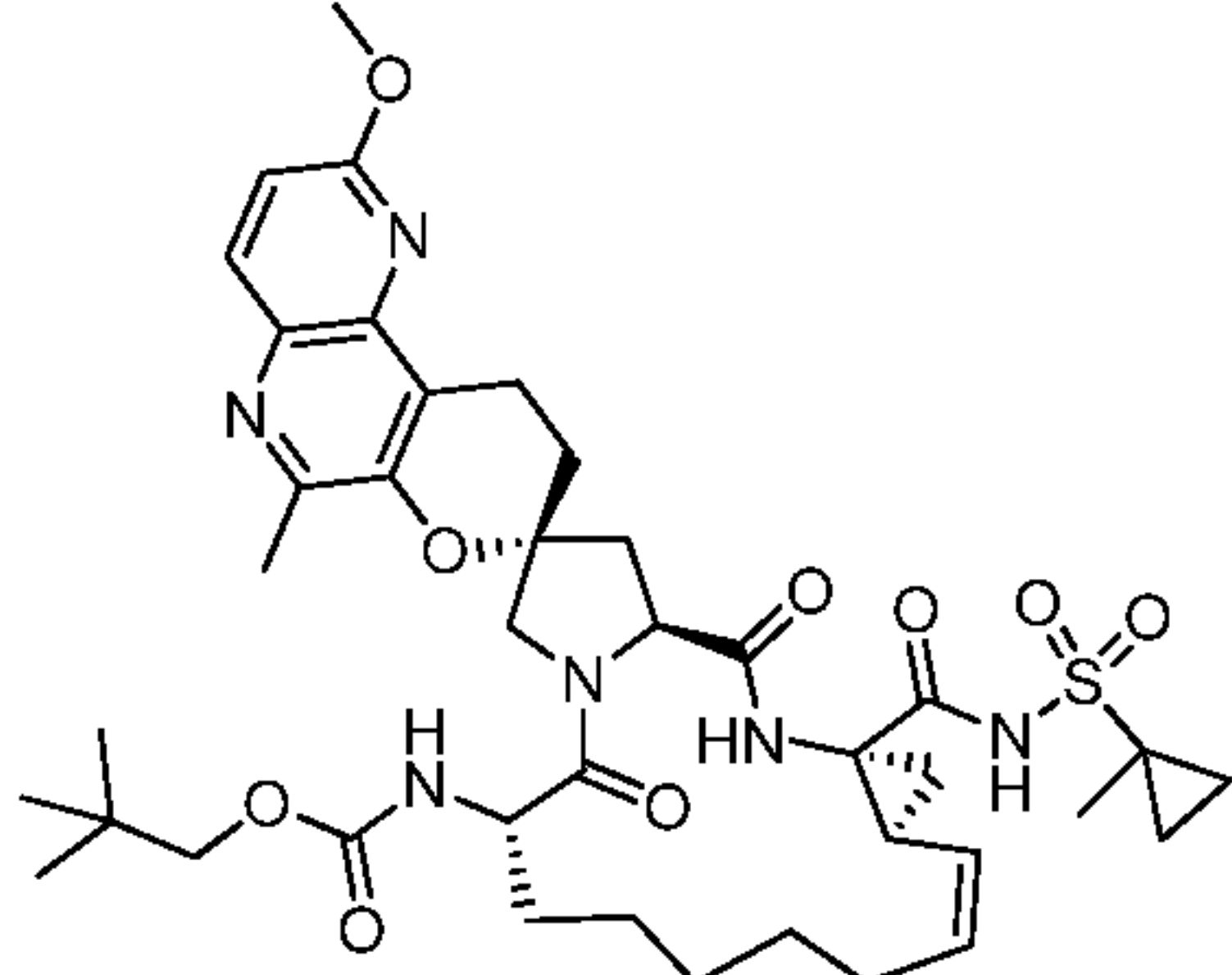
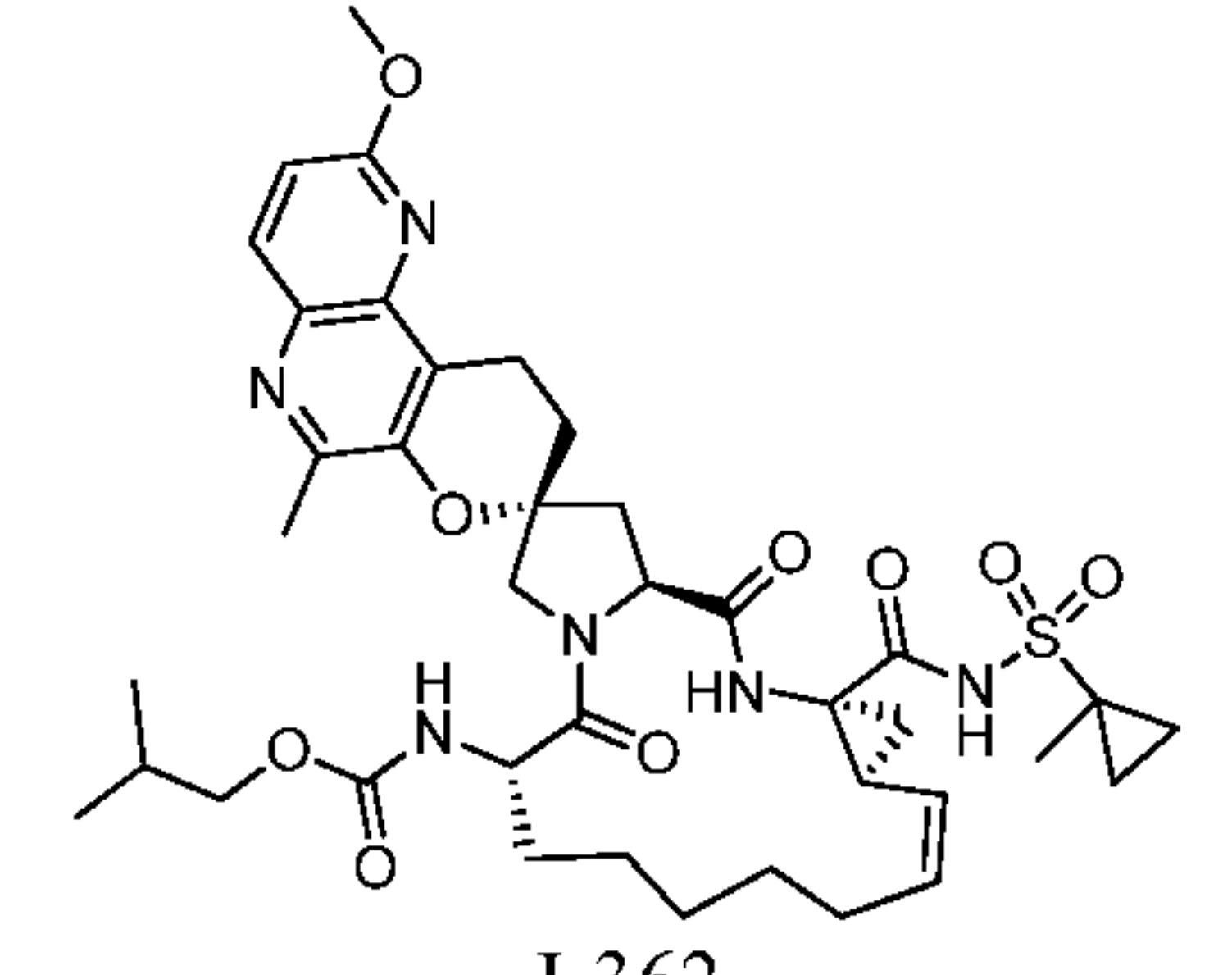
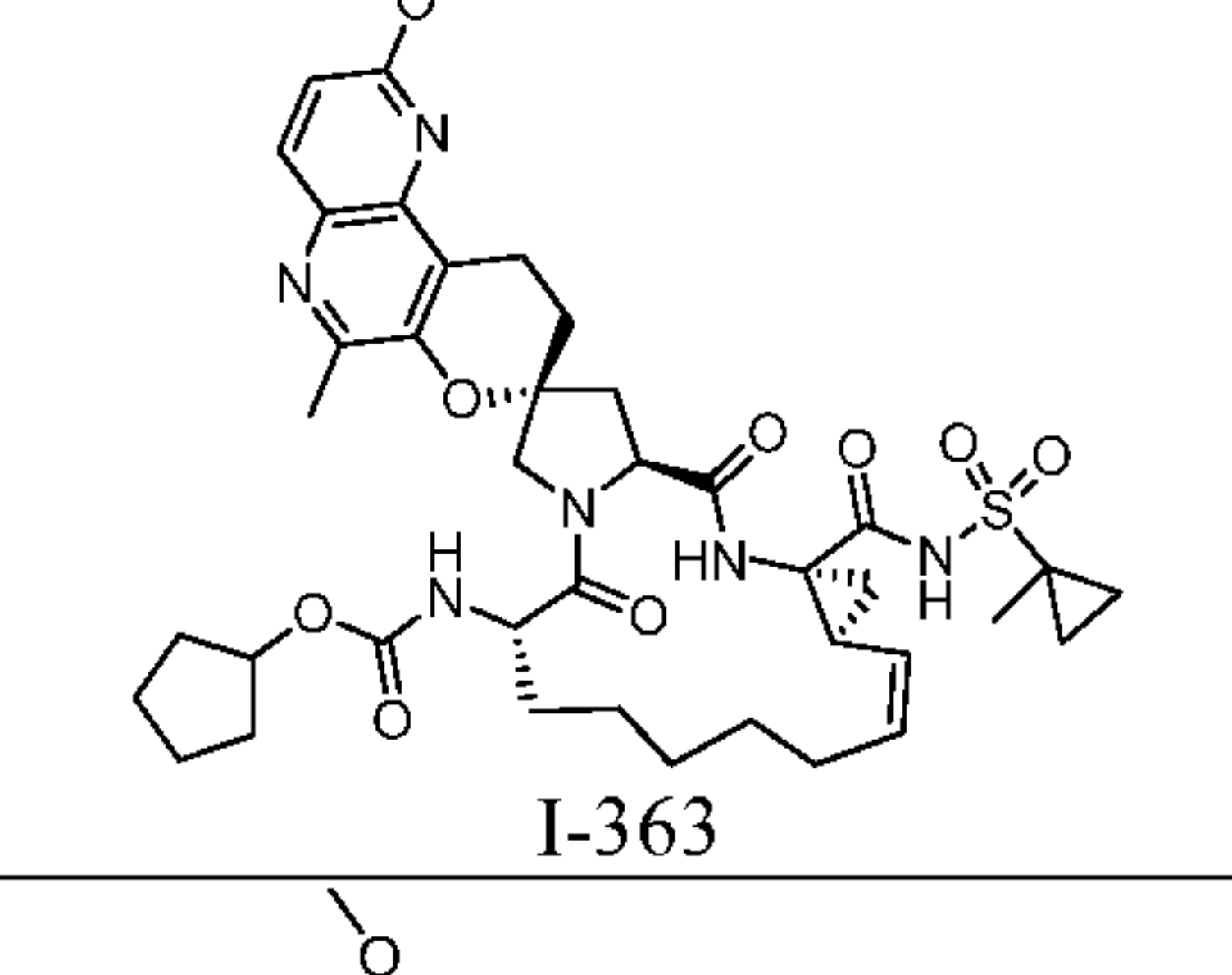
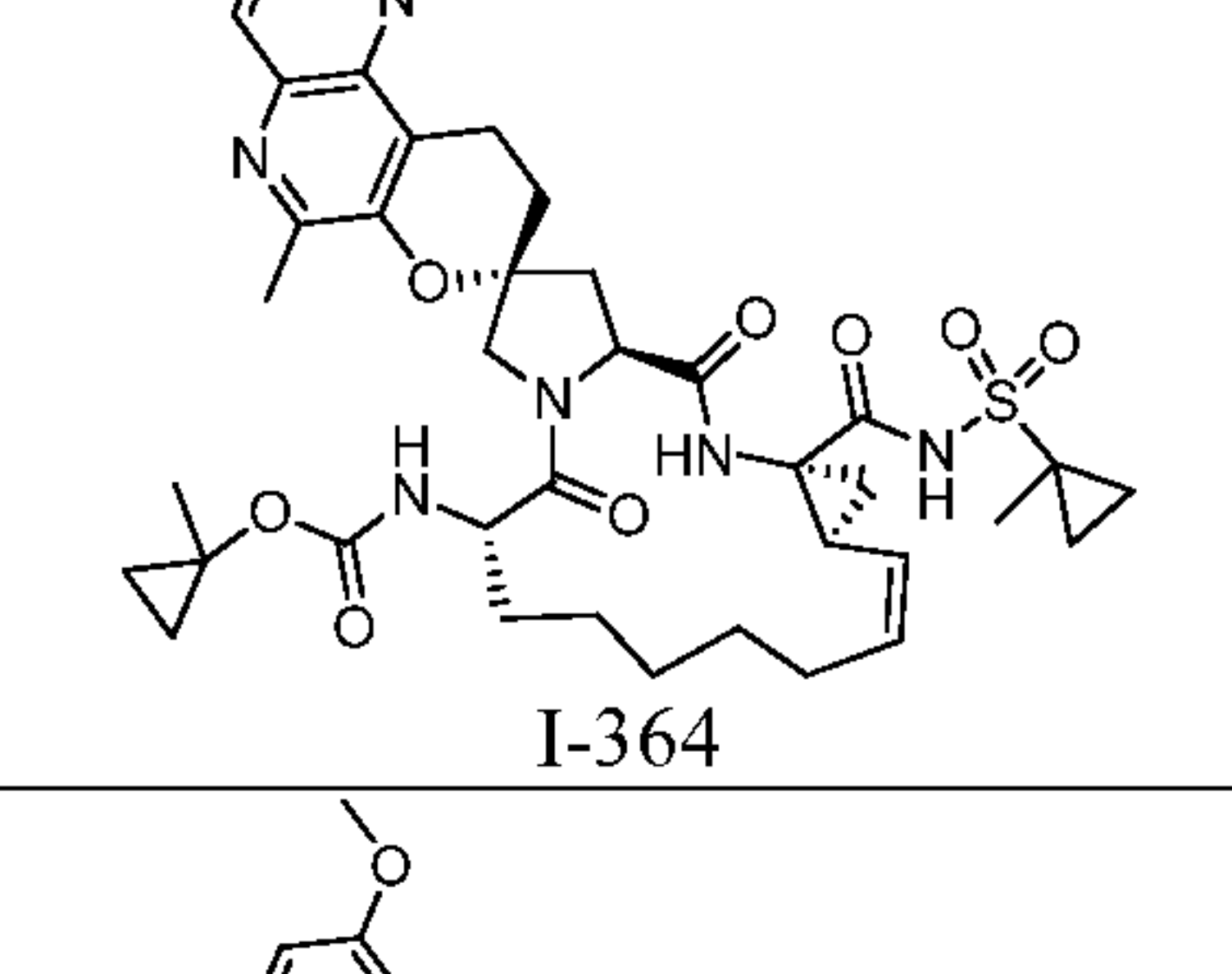
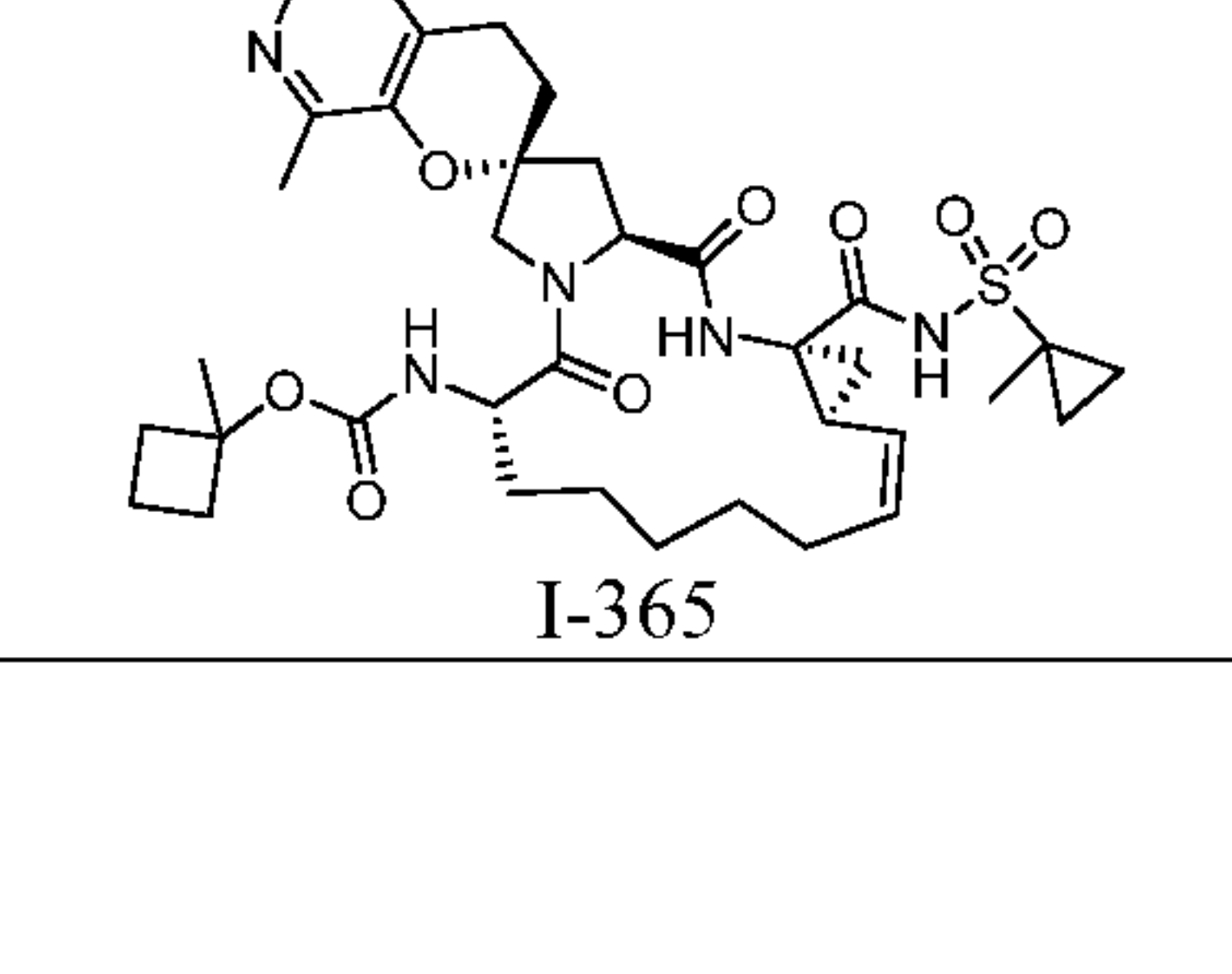
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
336	 I-336	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	806.5
337	 I-337	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	794
338	 I-338	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	808.38
339	 I-339	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8'-fluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	782.2
340	 I-340	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8'-fluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	48	768.1

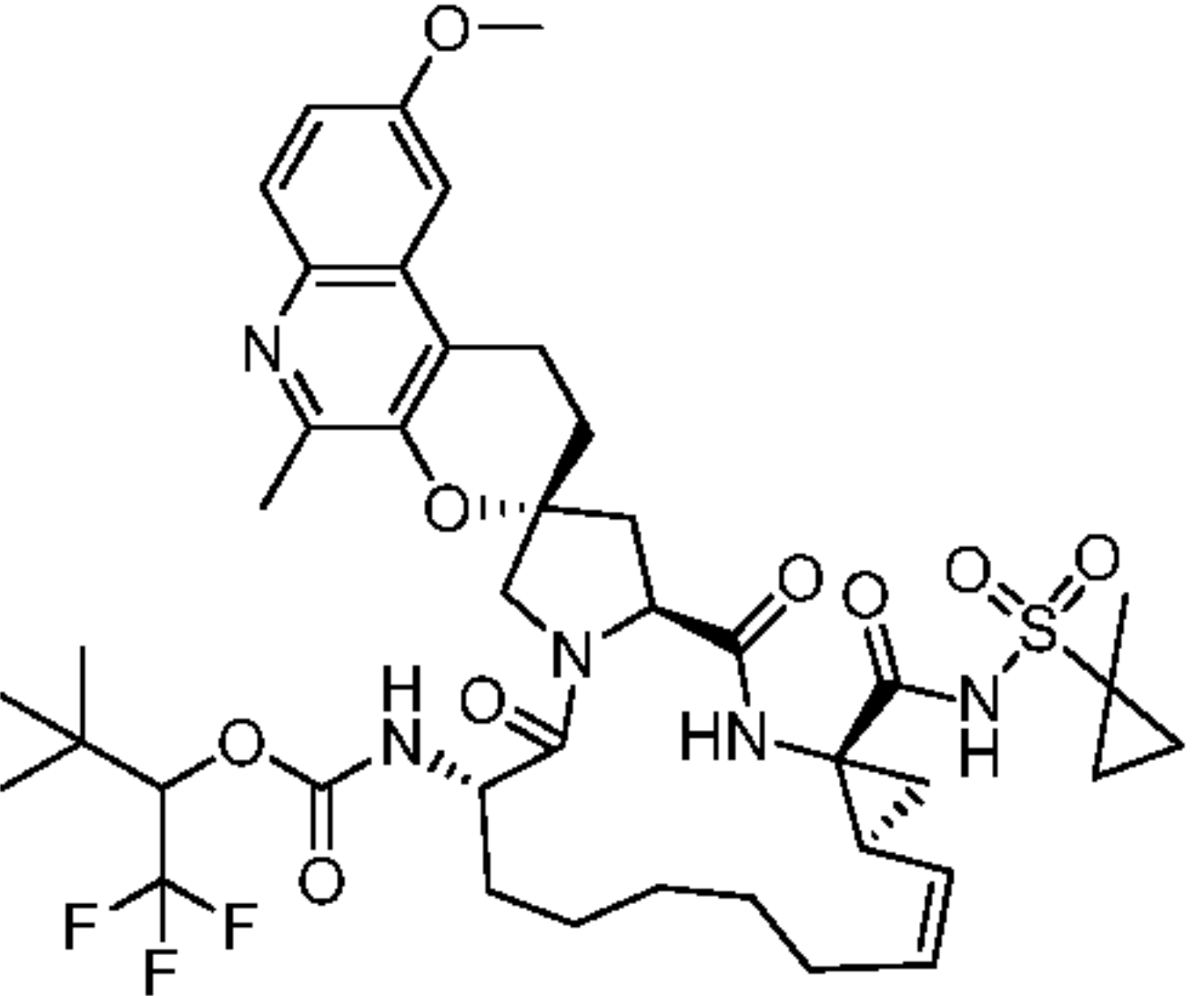
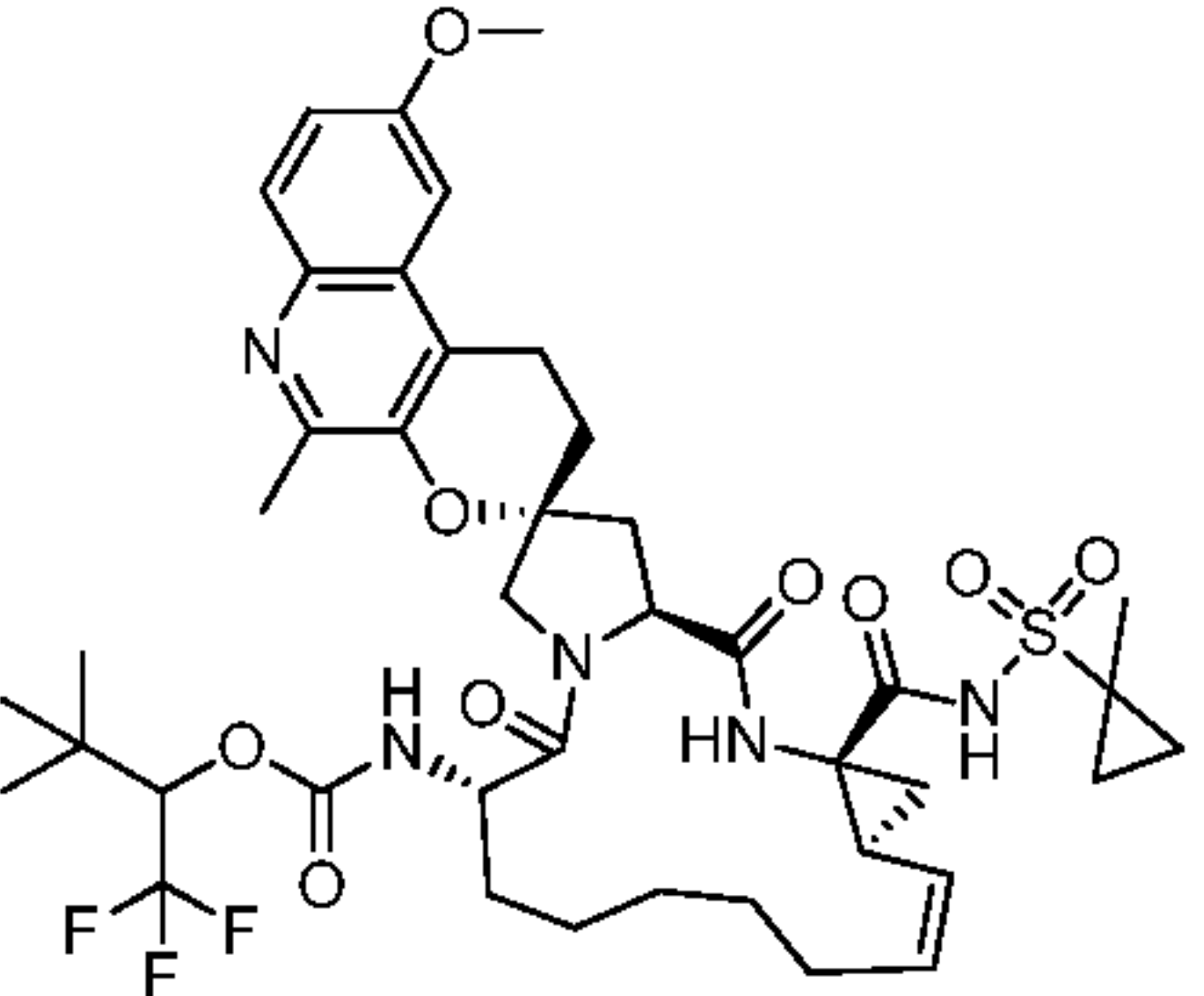
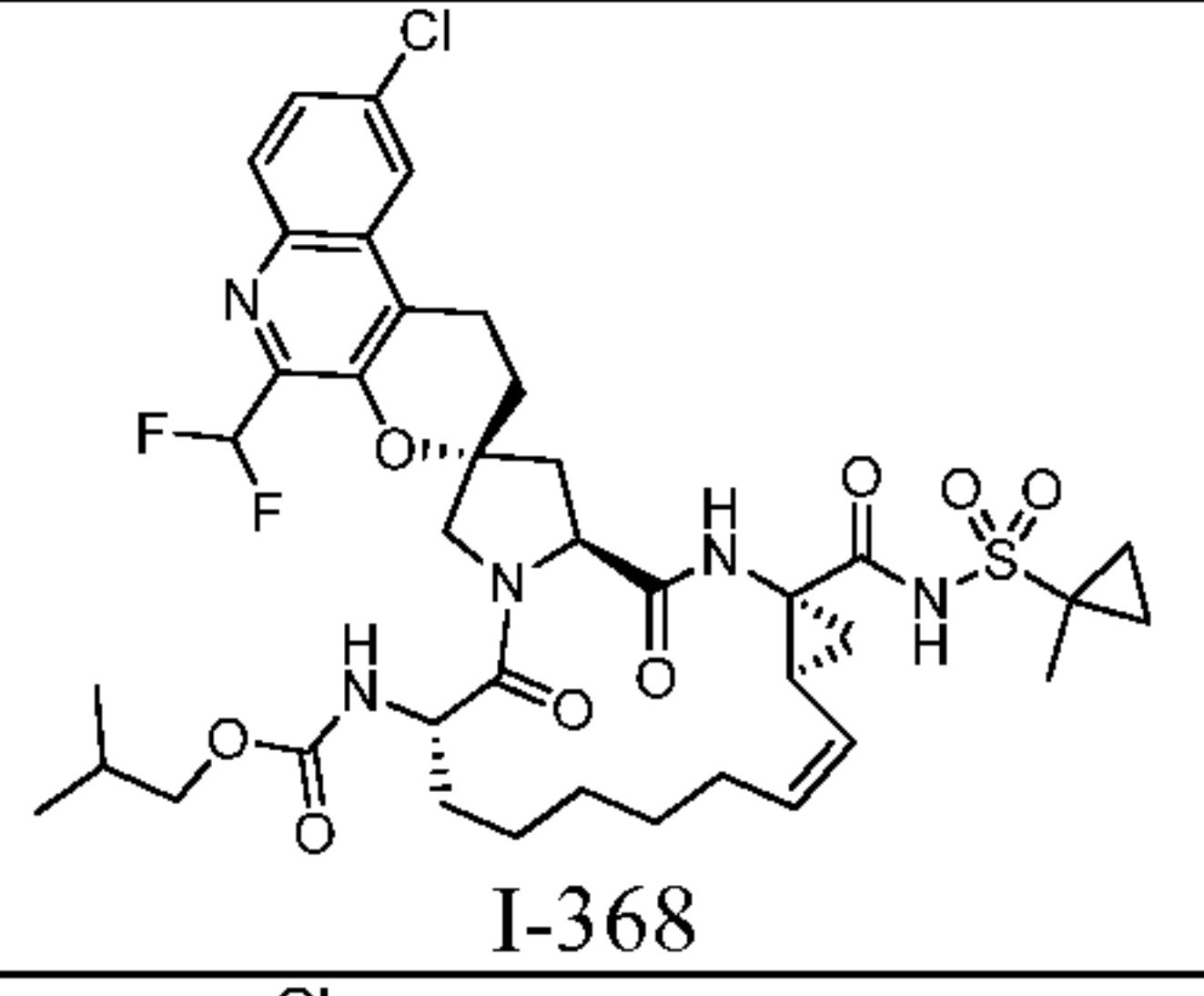
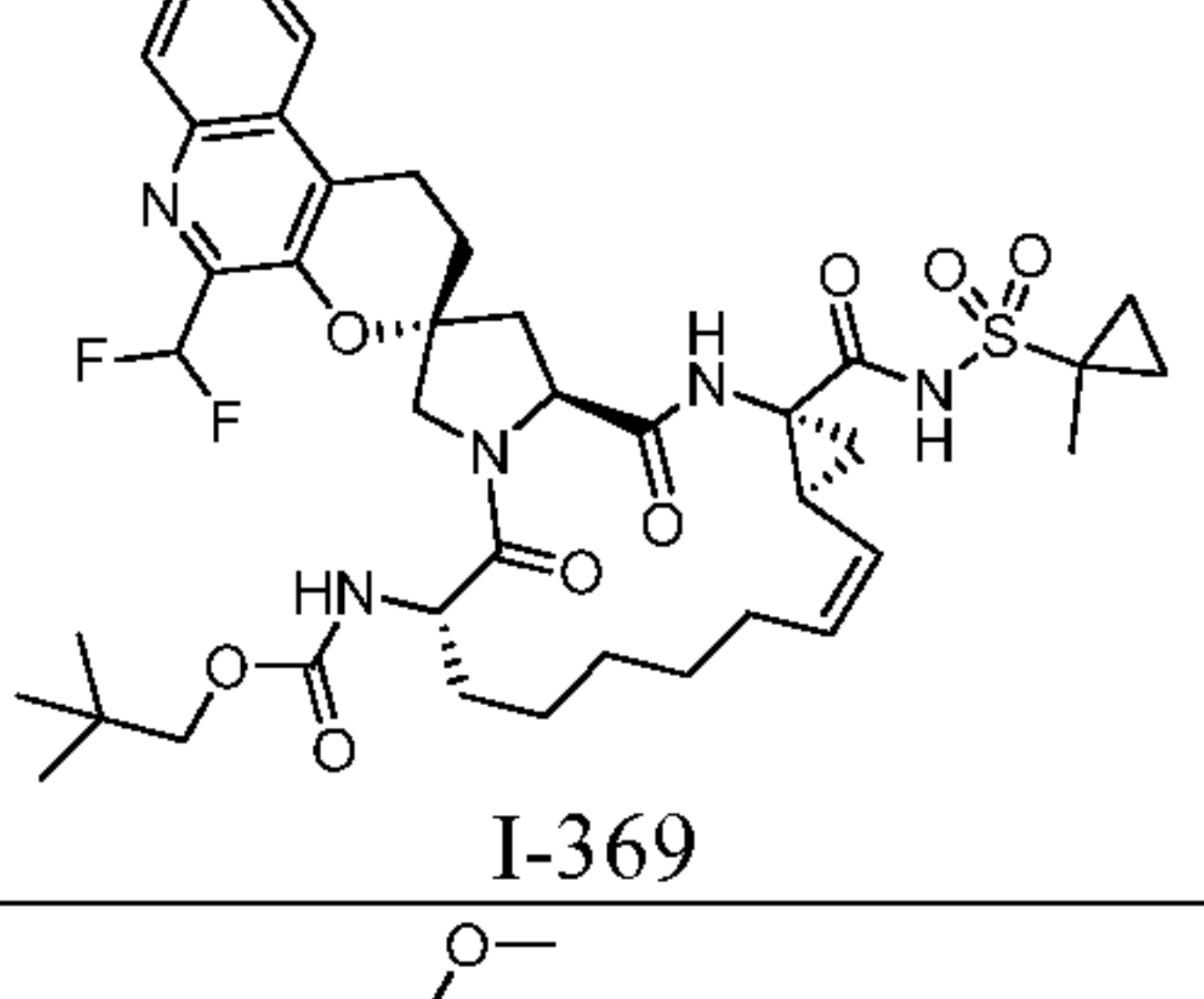
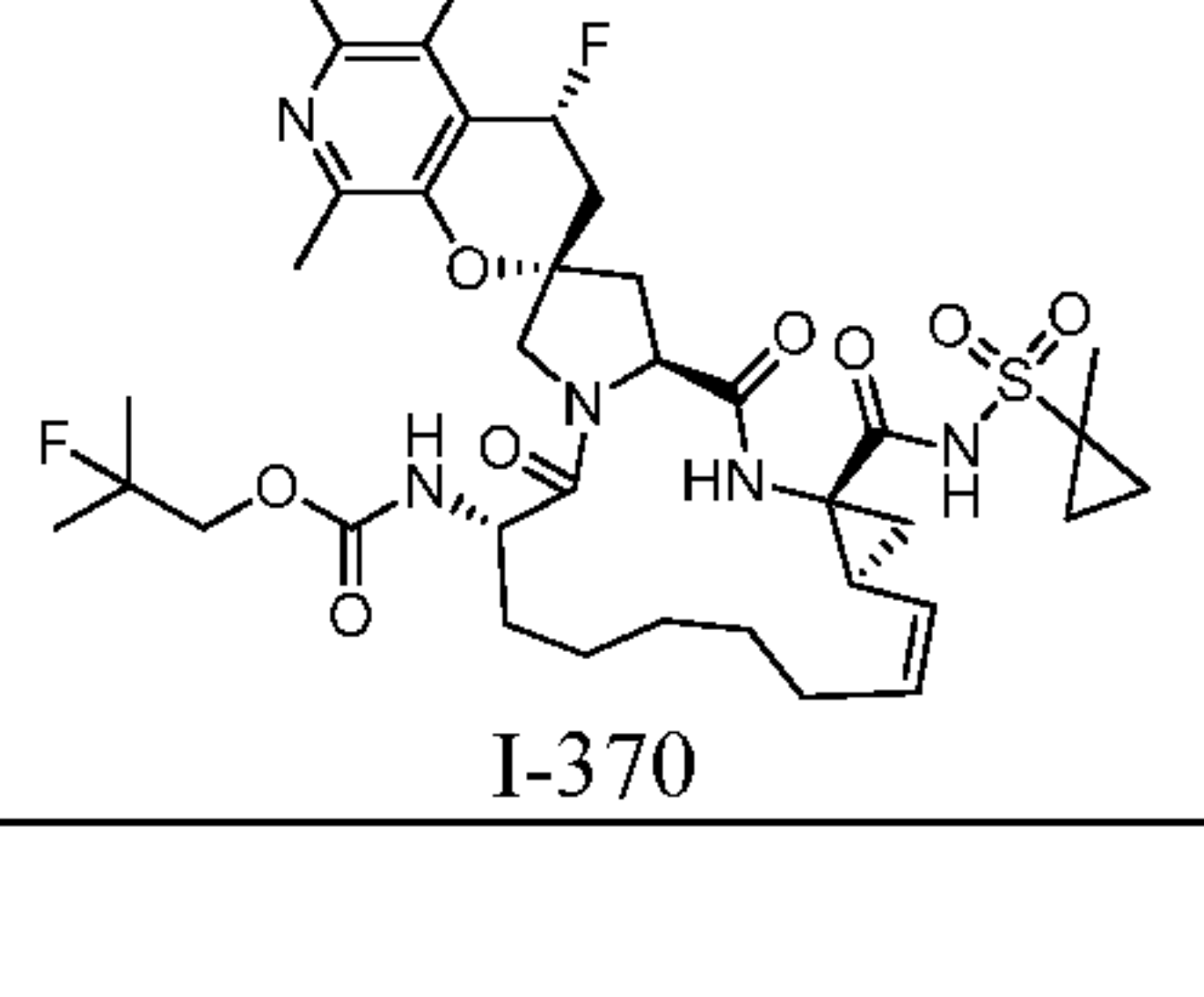
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
341	 I-341	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(3-methoxyphenyl)amino]-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	57	756.4
342	 I-342	propan-2-yl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-ethyl-1'-fluoro-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	32	796.6
343	 I-343	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-6-[(6-methylpyridin-2-yl)amino]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	57	741.4
344	 I-344	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-amino-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	47	650.4
345	 I-345	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(3-fluorophenyl)amino]-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	57	744

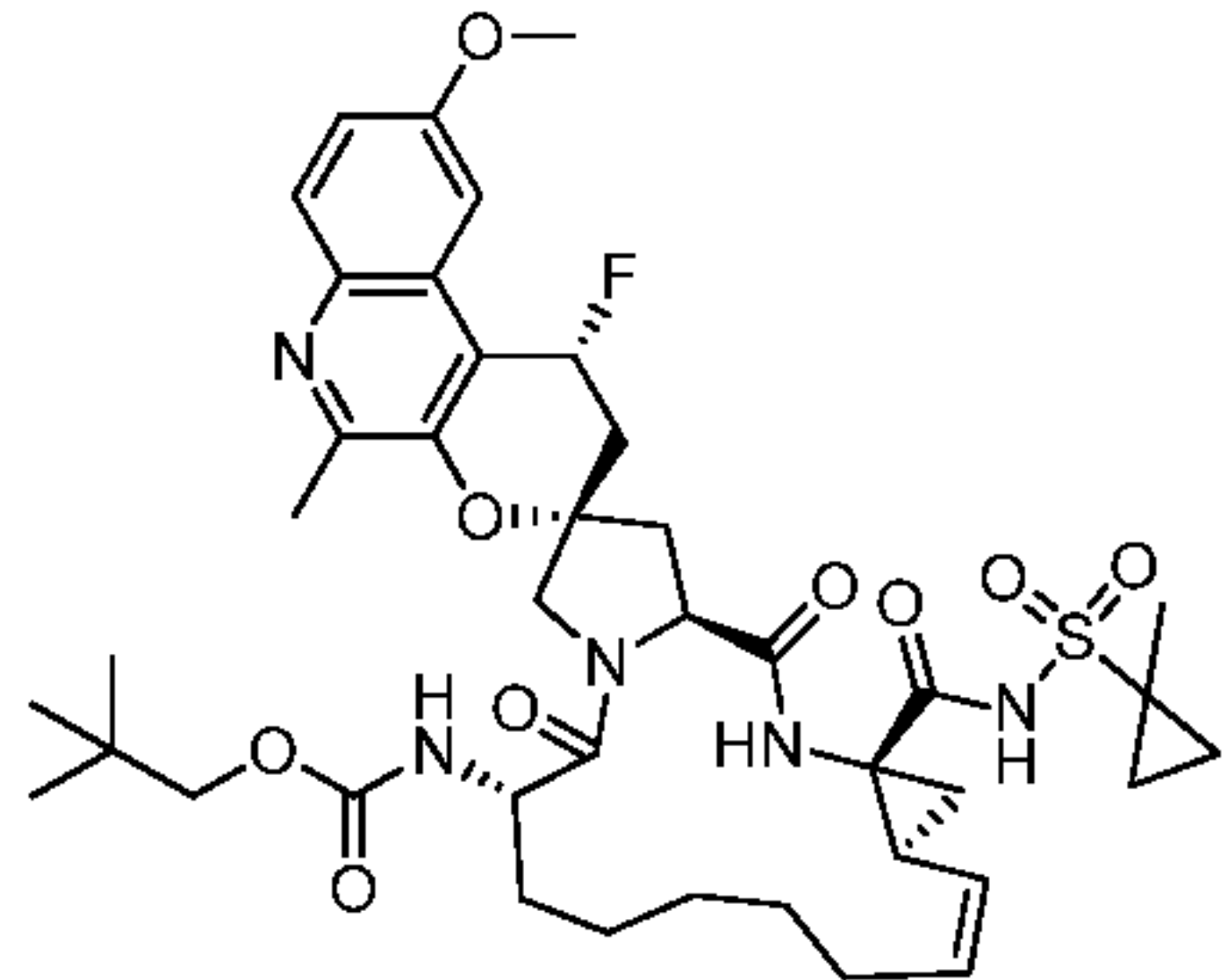
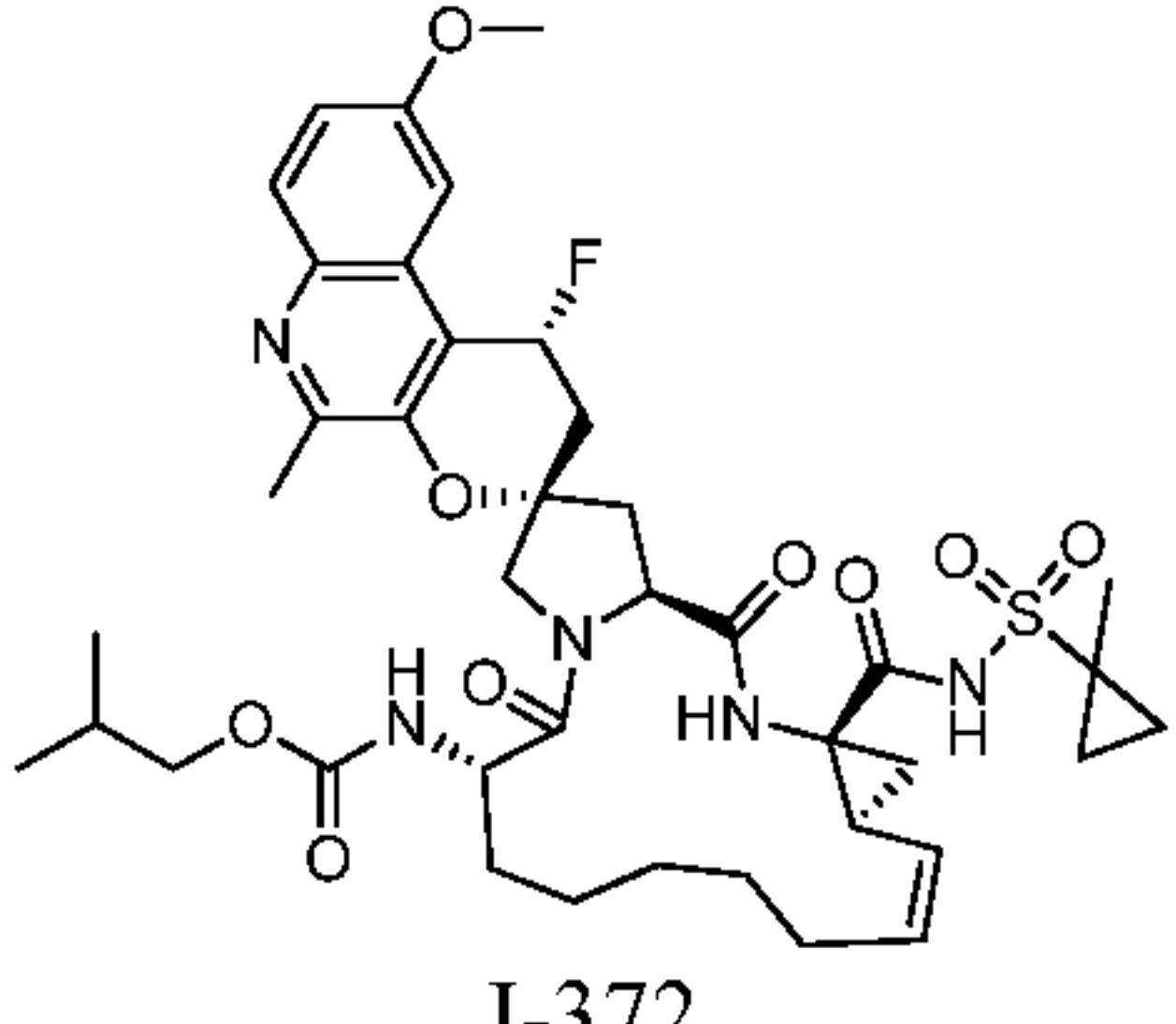
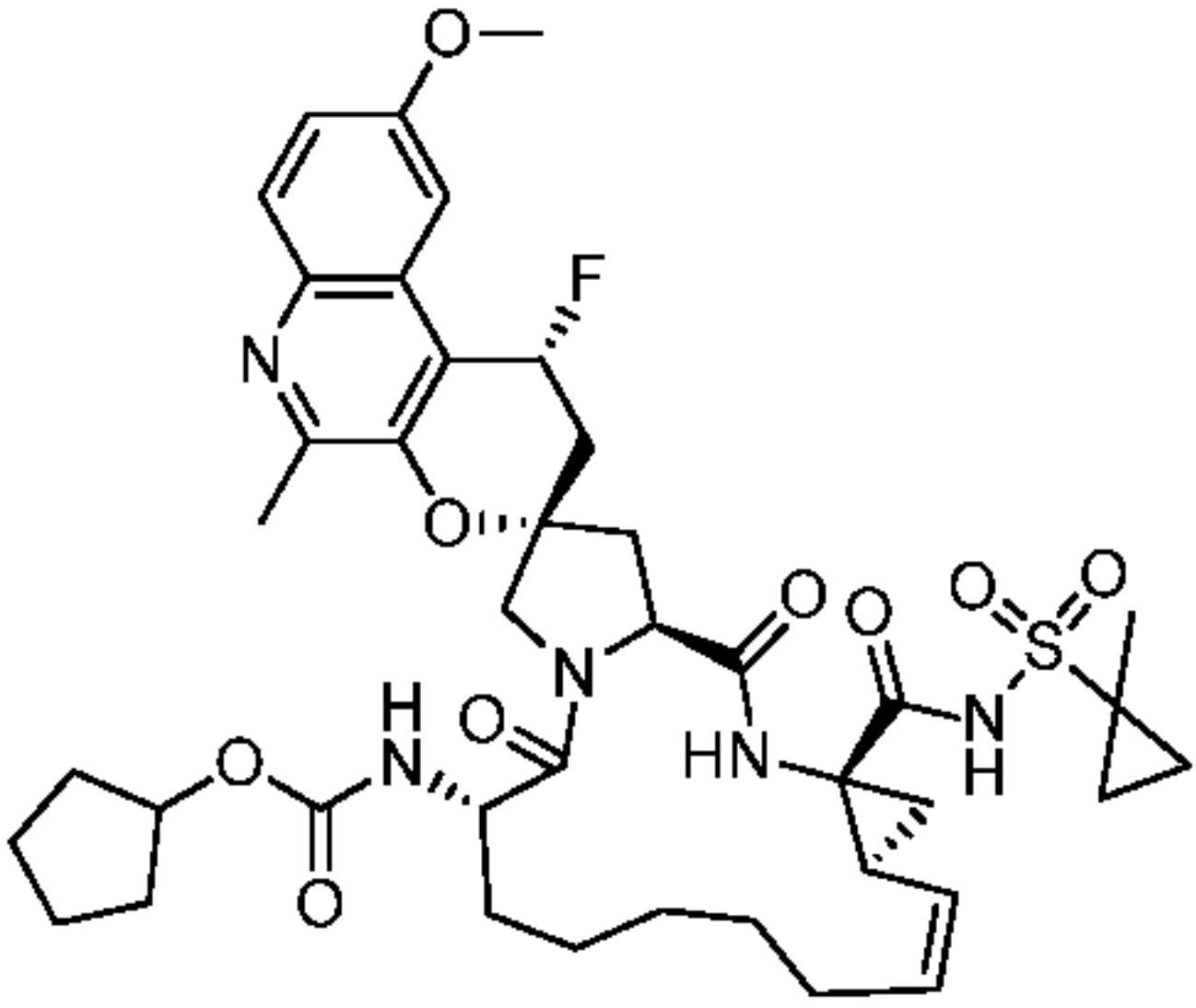
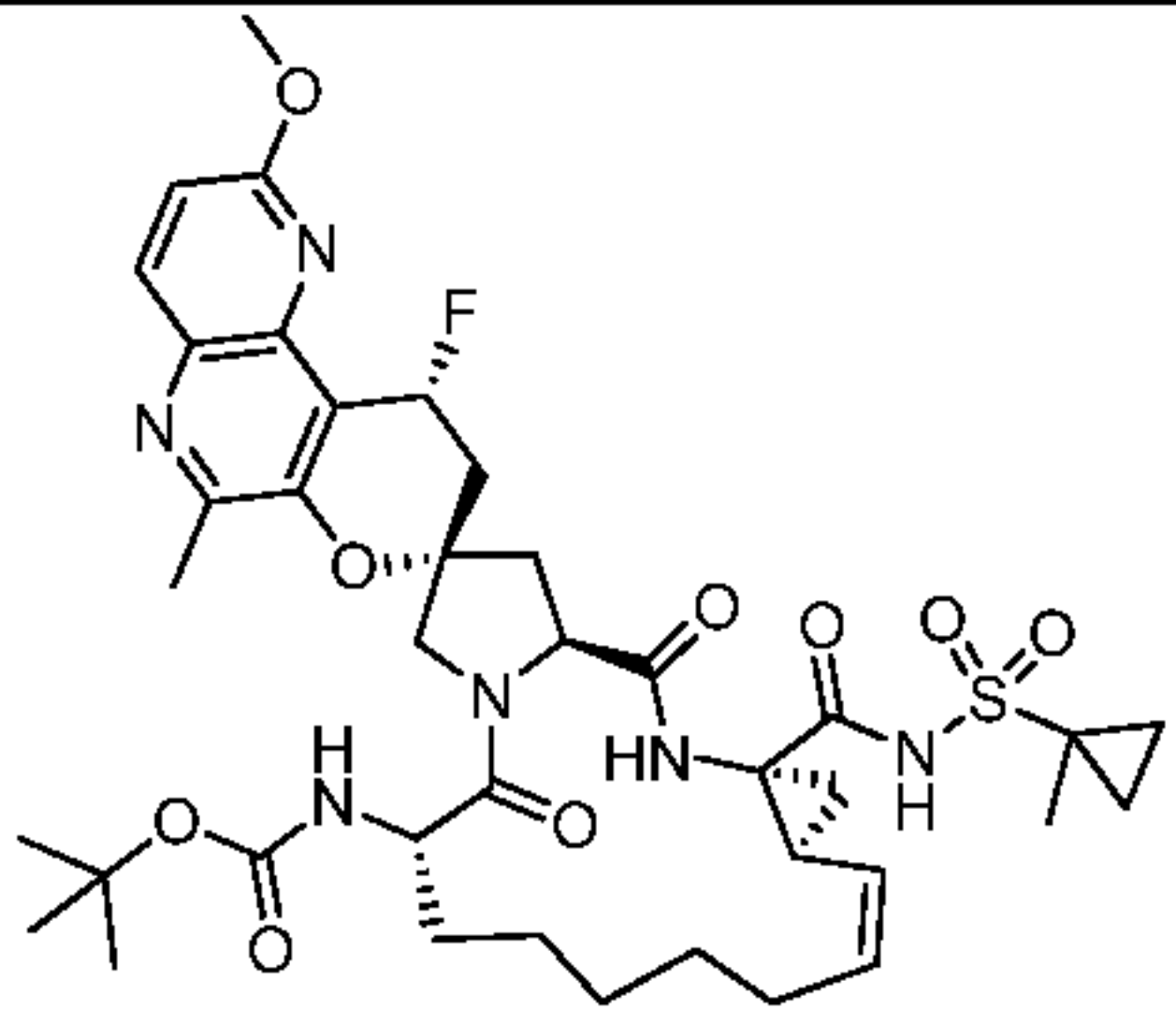
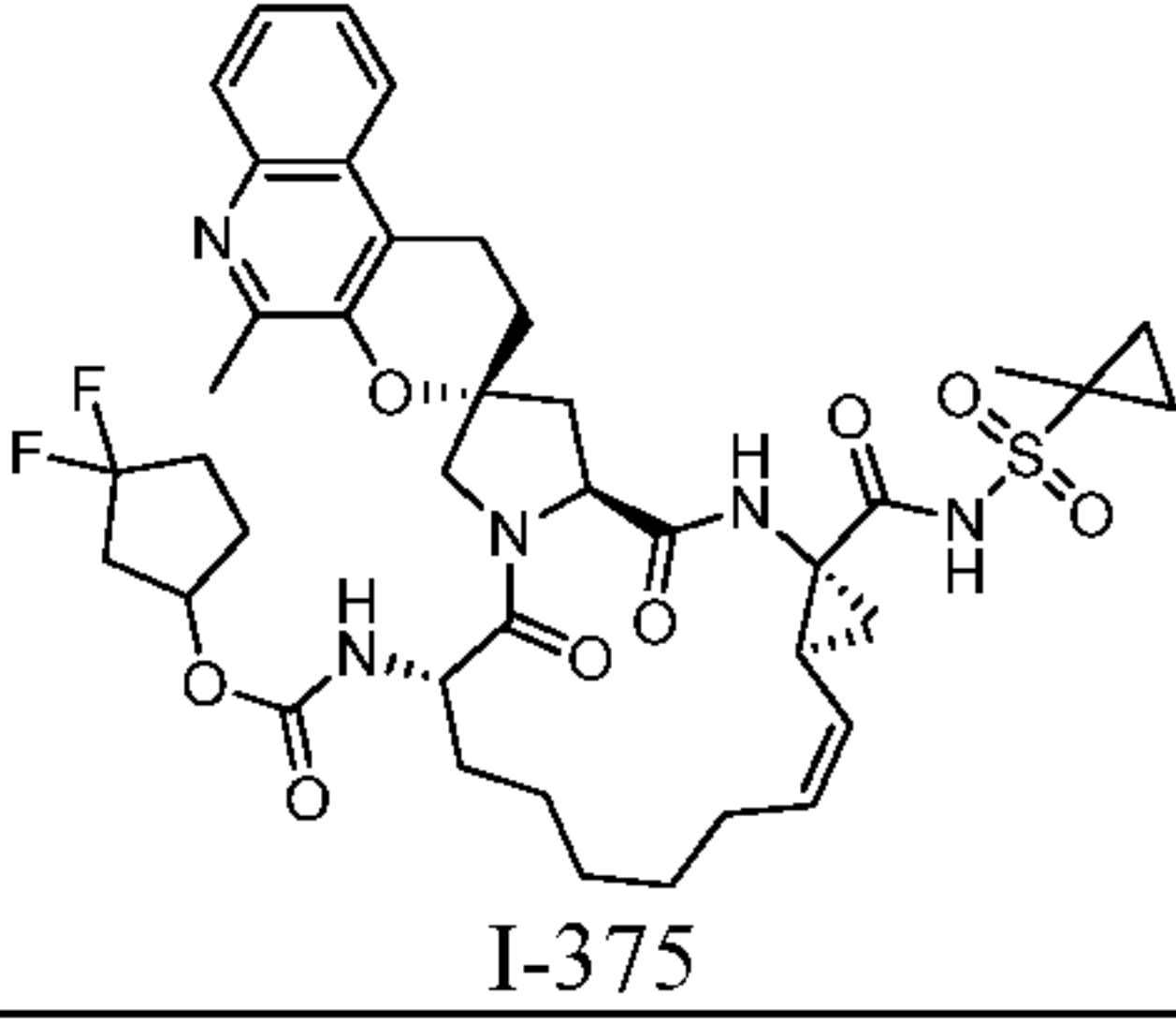
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
346	 I-346	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-ethyl-1'-fluoro-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	32	850.1
347	 I-347	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-ethyl-1'-fluoro-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	32	850.1
348	 I-348	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5, 35	888 (K+ salt)
349	 I-349	[1-(trifluoromethyl)cyclopropyl]methyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	846 (K+ salt)
350	 I-350	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-6-[(4-methylpyridin-2-yl)amino]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	57	740.4

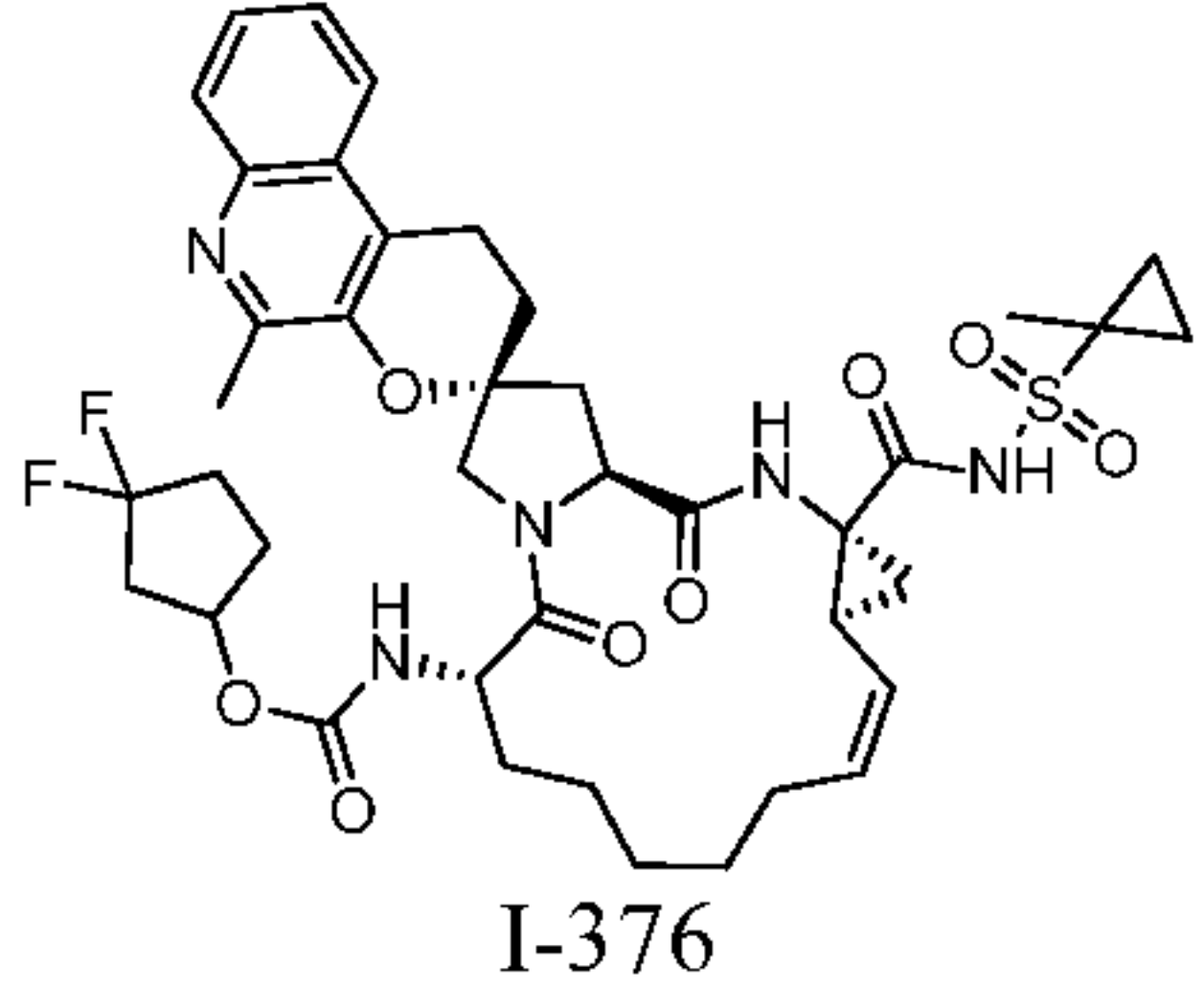
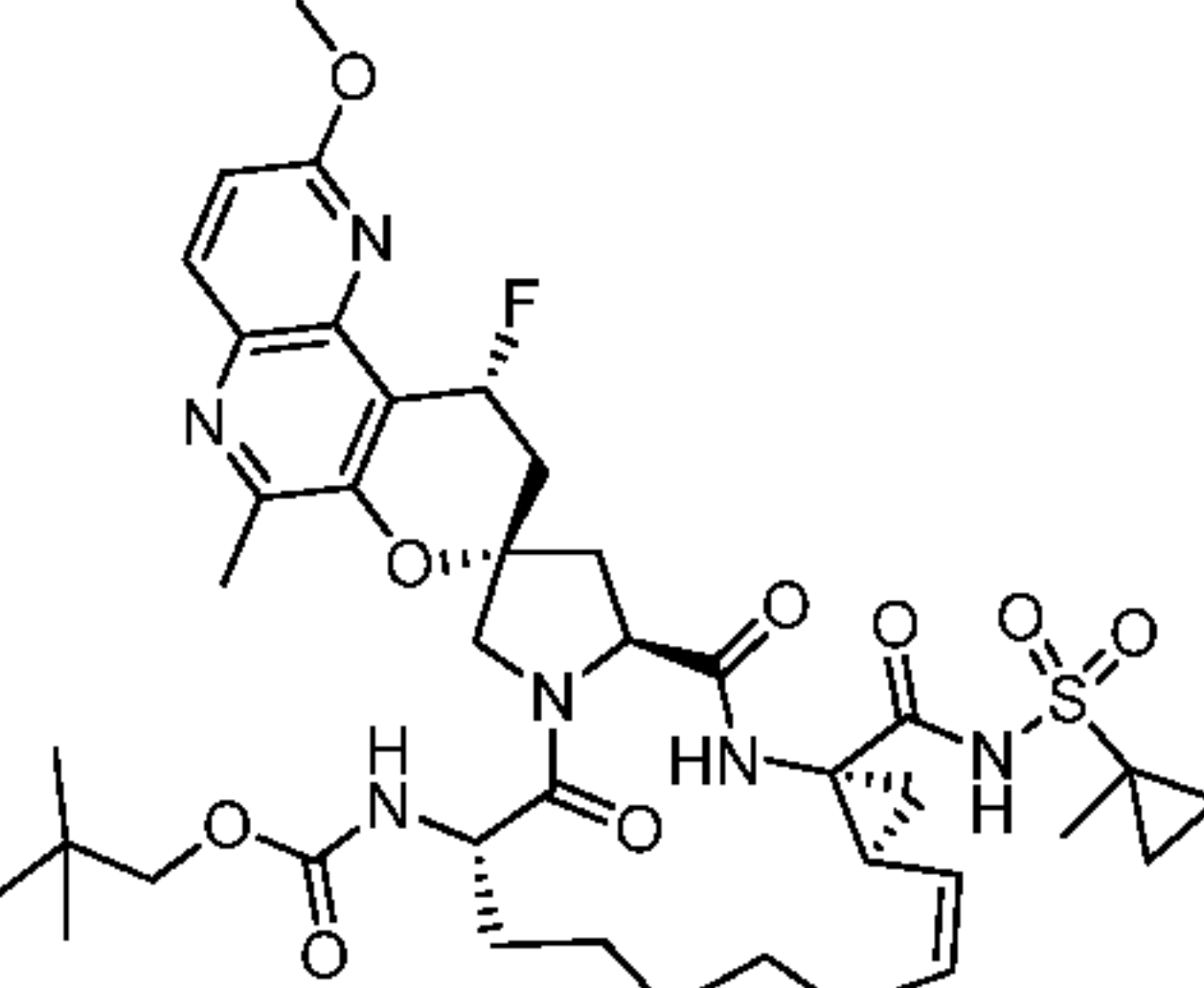
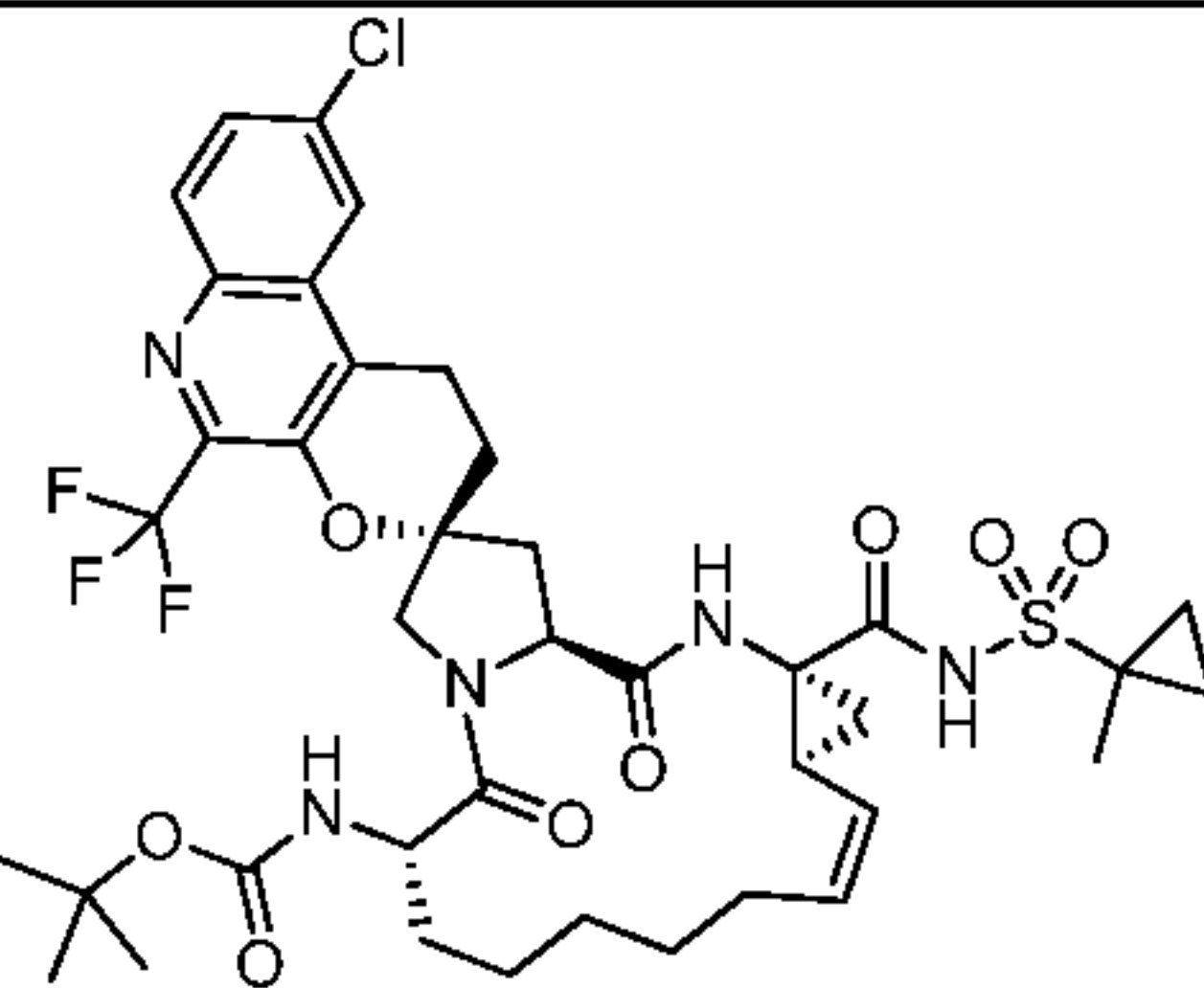
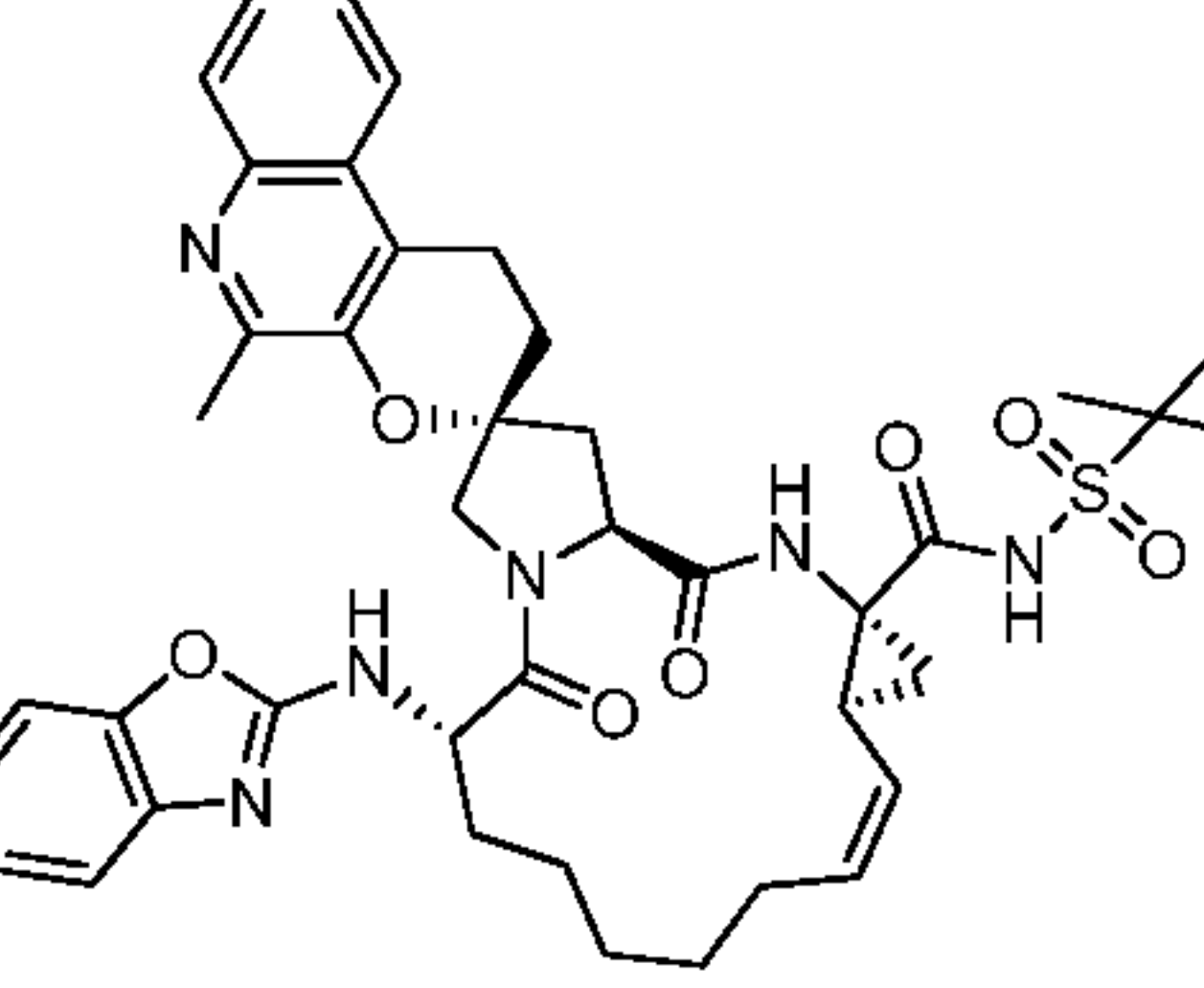
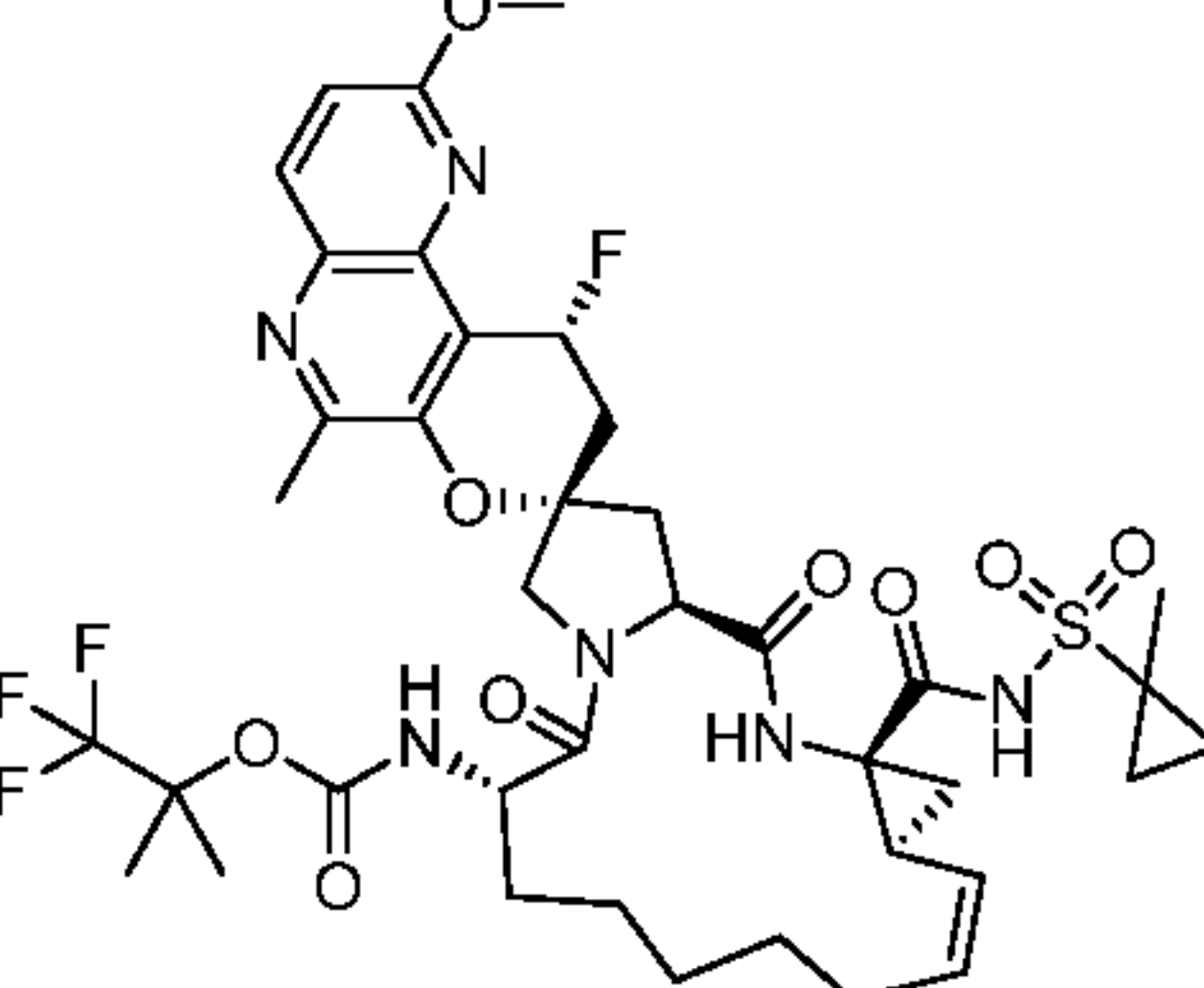
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
351	 I-351	(2S)-3-methylbutan-2-yl [(2R,6S,12Z,13aS,14aR,16aS)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	5, 35	848.2 (K+ salt)
352	 I-352	1,1,1-trifluoro-2-methylpropan-2-yl [(1'R,2S,6S,12Z,13aS,14aR,16aS)-1'-fluoro-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	2, 56	880.2 (K+ salt)
353	 I-353	(2R,6S,12Z,13aS,14aR,16aS)-5'-methyl-N-[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-6-(pyridin-2-ylamino)-1,1',2',6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a(5H)-carboxamide	57	727.3
354	 I-354	tert-butyl [(1'S,2S,6S,12Z,13aS,14aR,16aS)-1'-fluoro-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	56	798.2
355	 I-355	1,1,1-trifluoro-2-methylpropan-2-yl [(1'R,2S,6S,12Z,13aS,14aR,16aS)-1'-fluoro-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	56	853.2 (K+ salt)

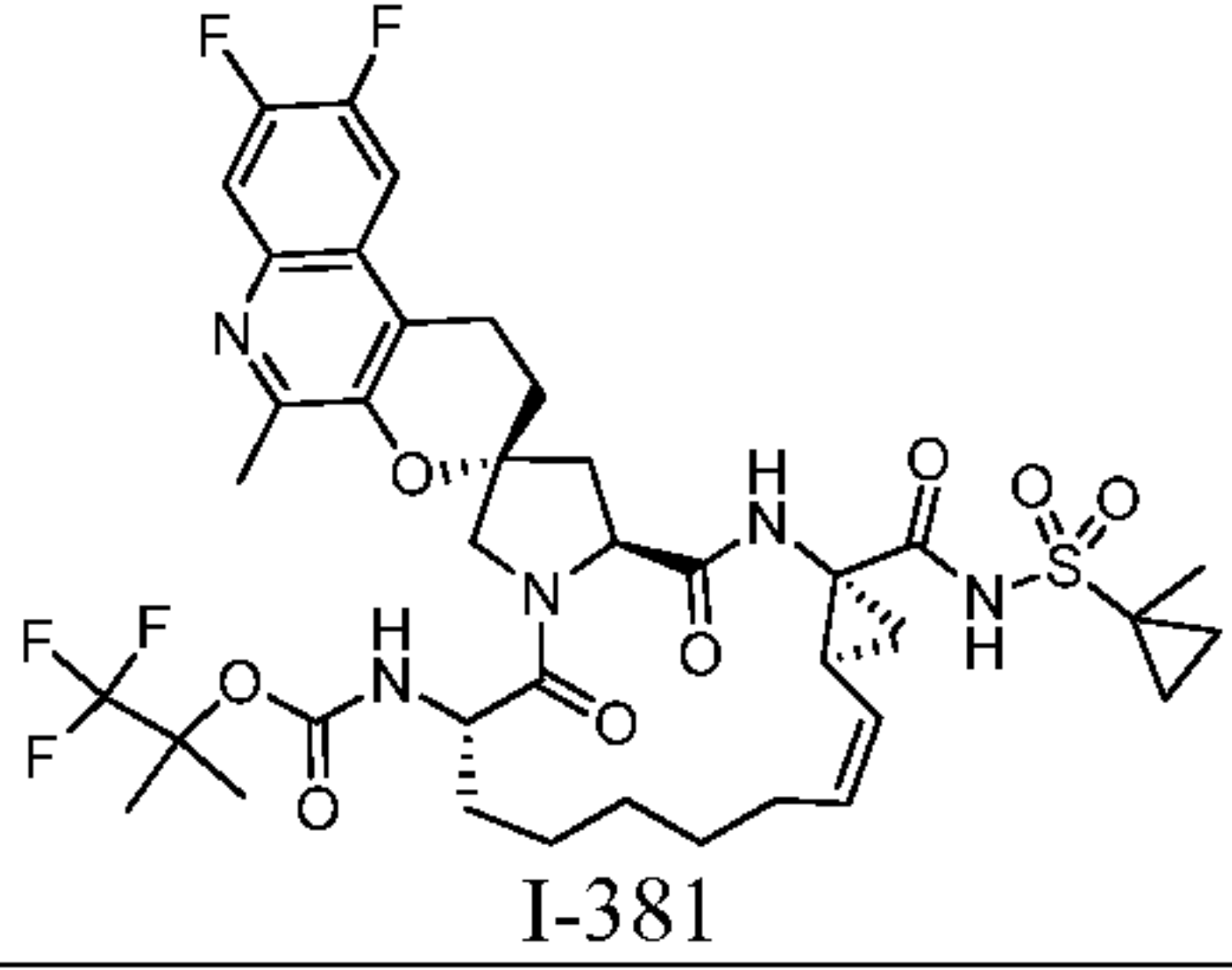
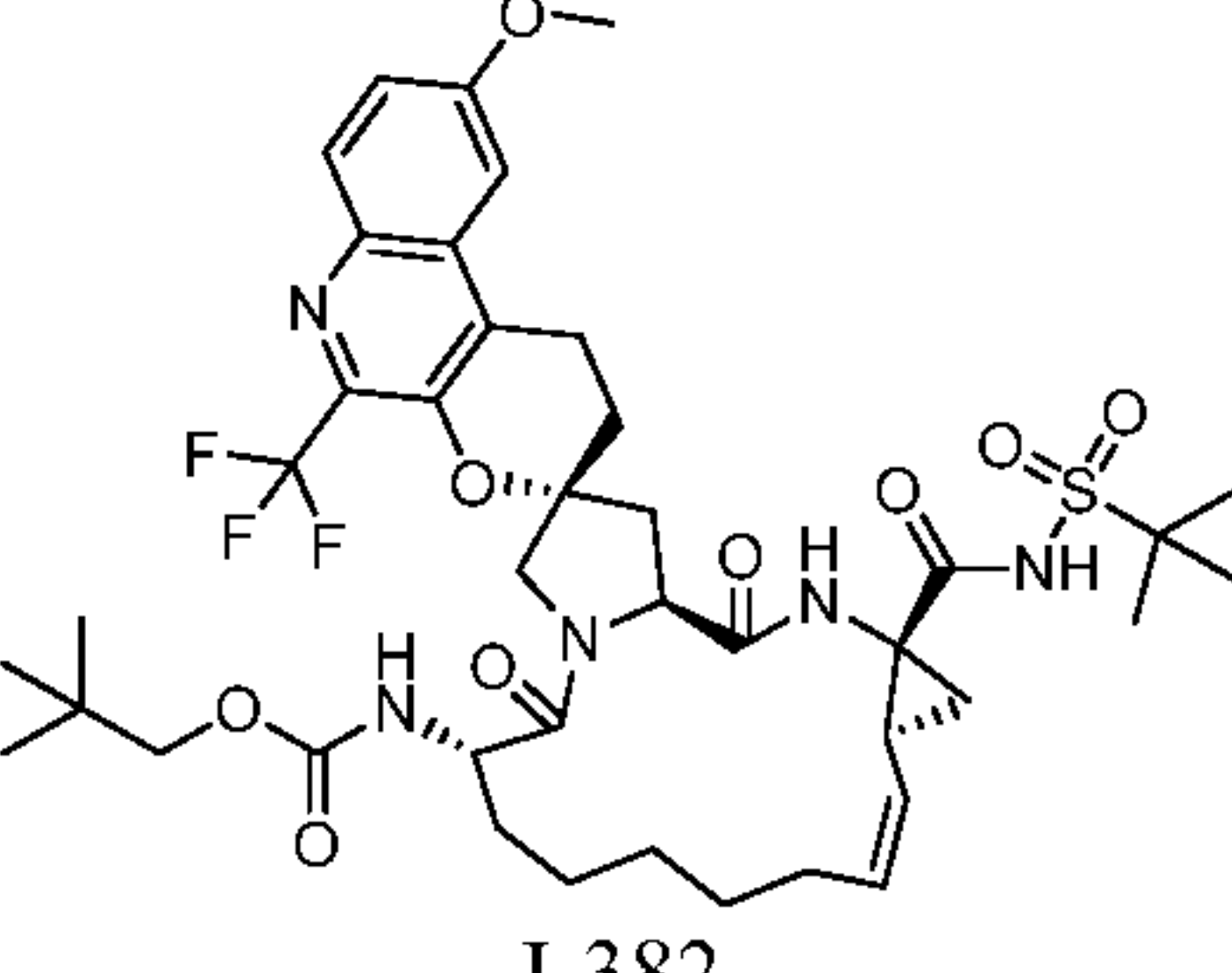
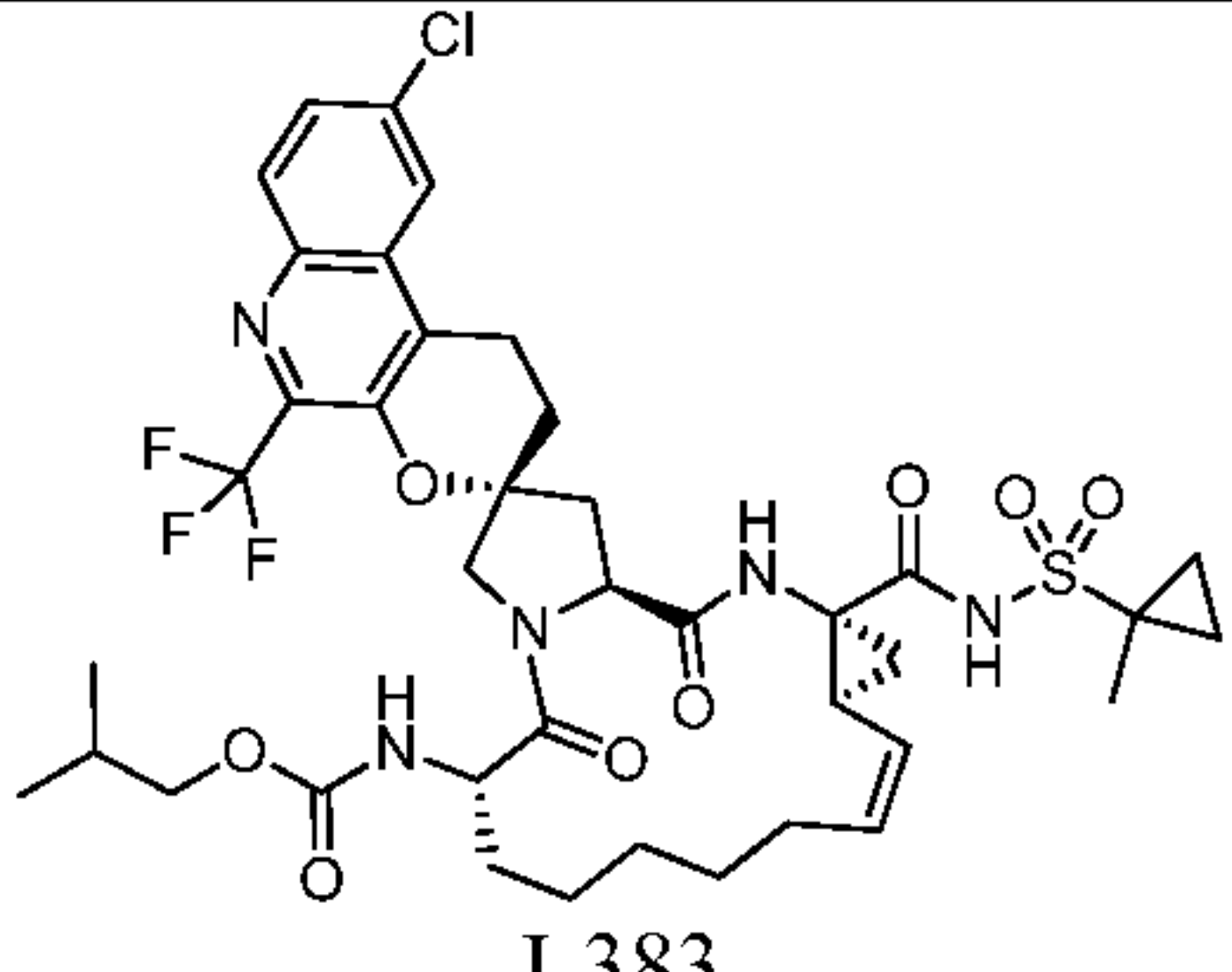
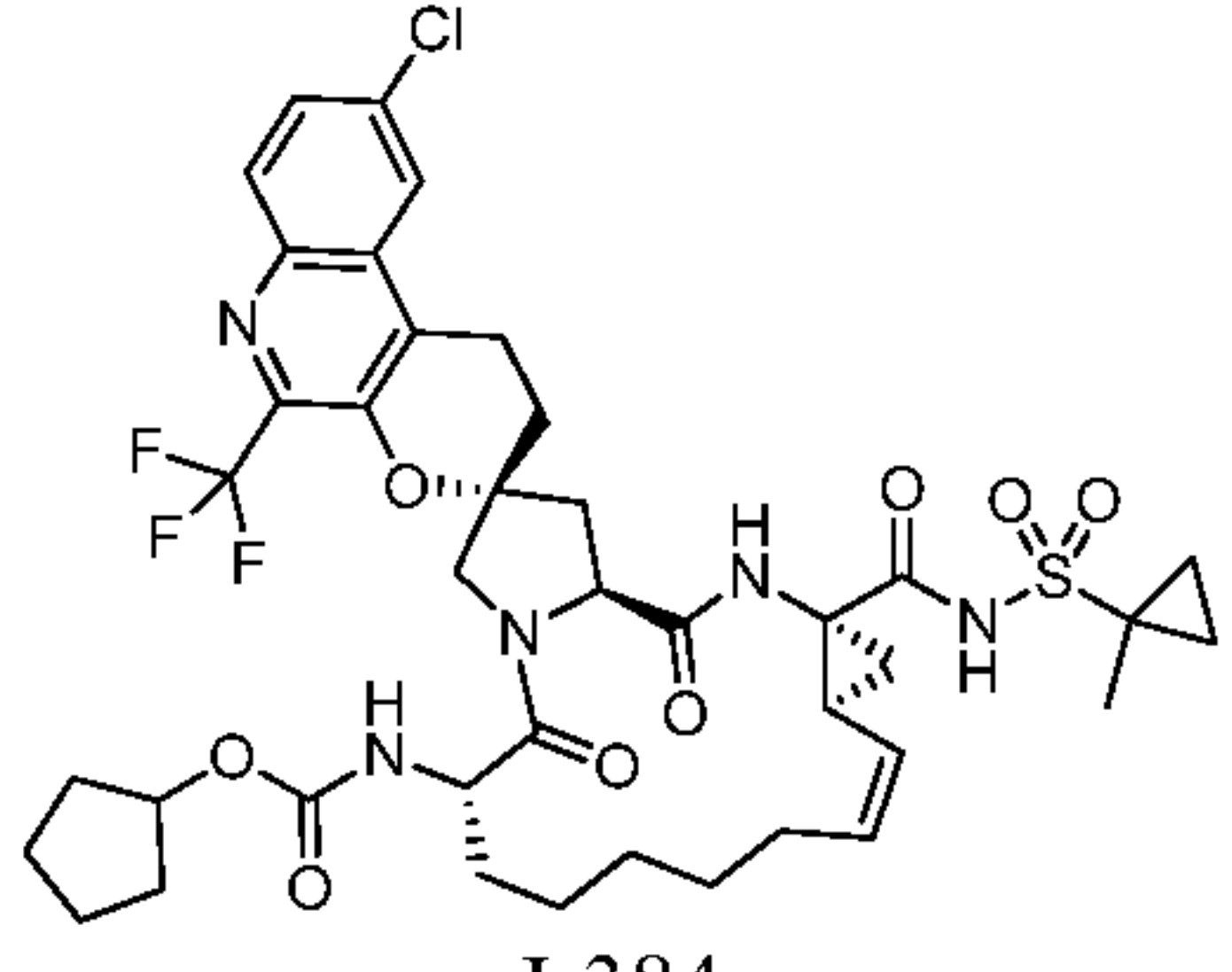
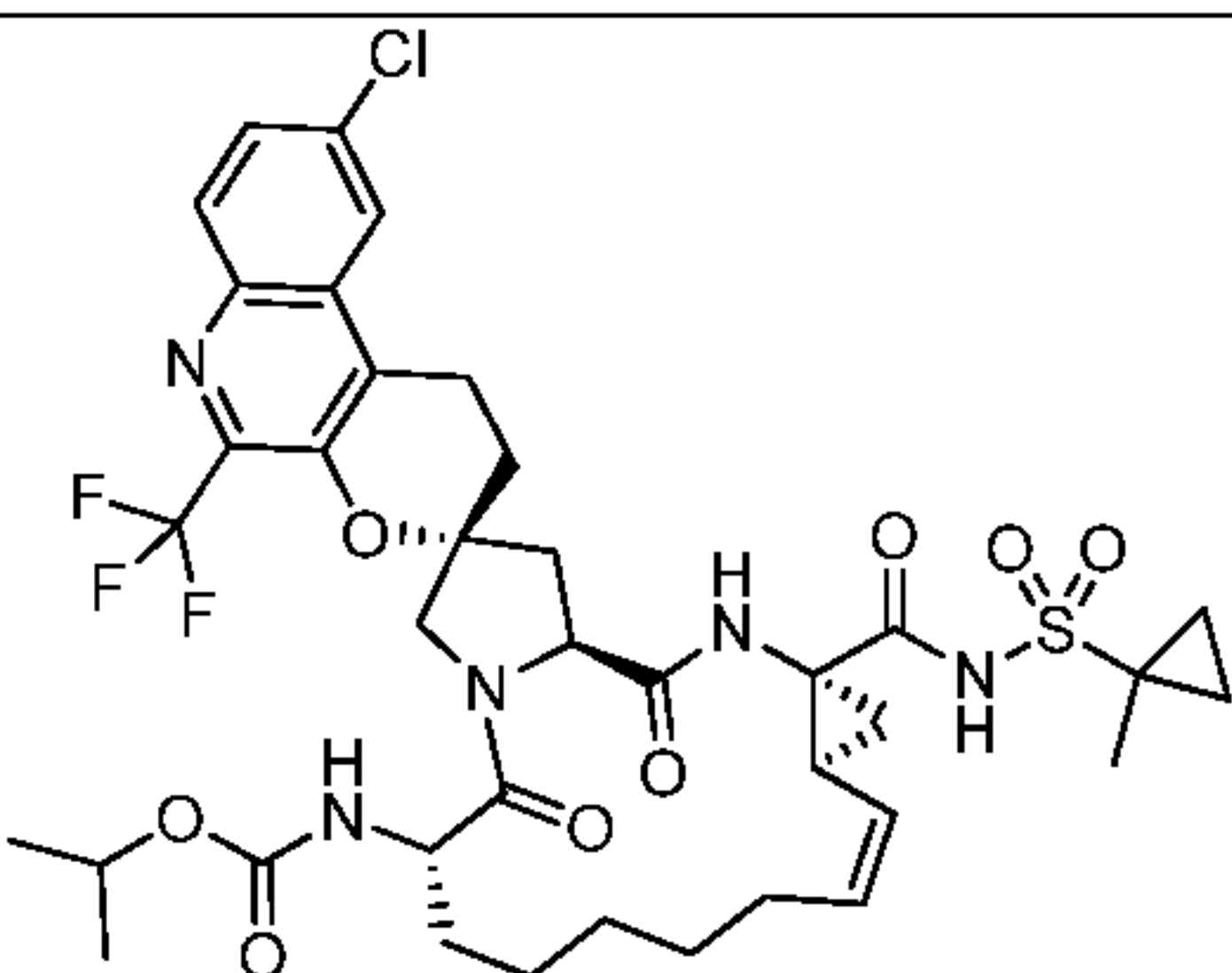
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
356	 I-356	(2R)-3-methylbutan-2-yl [(1'R,2S,6S,12Z,13aS,14aR,16aS)-1'-fluoro-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	56	812.2 (K+ salt)
357	 I-357	(2S)-3-methylbutan-2-yl [(1'R,2S,6S,12Z,13aS,14aR,16aS)-1'-fluoro-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	56	812.2 (K+ salt)
358	 I-358	(2S)-3-methylbutan-2-yl [(1'R,2S,6S,12Z,13aS,14aR,16aS)-1'-fluoro-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	57	812.5
359	 I-359	(2R,6S,12Z,13aS,14aR,16aS)-5'-methyl-N-[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-6-(pyrimidin-2-ylamino)-1,1',2',6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a(5H)-carboxamide	56, 528	727.4
360	 I-360	(2R,6S,12Z,13aS,14aR,16aS)-5'-methyl-N-[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-6-(1,3-thiazol-2-ylamino)-1,1',2',6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a(5H)-carboxamide	57	733.4

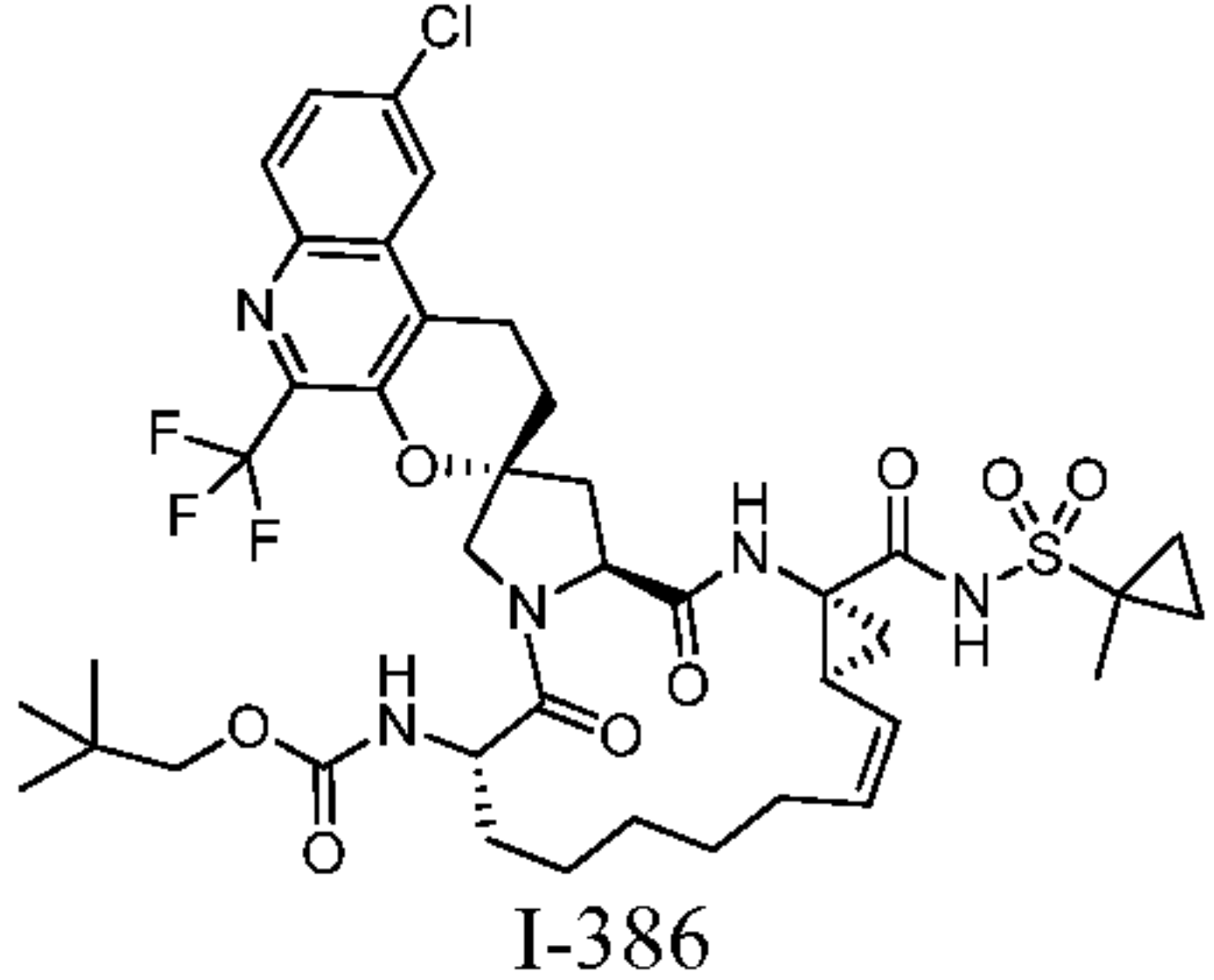
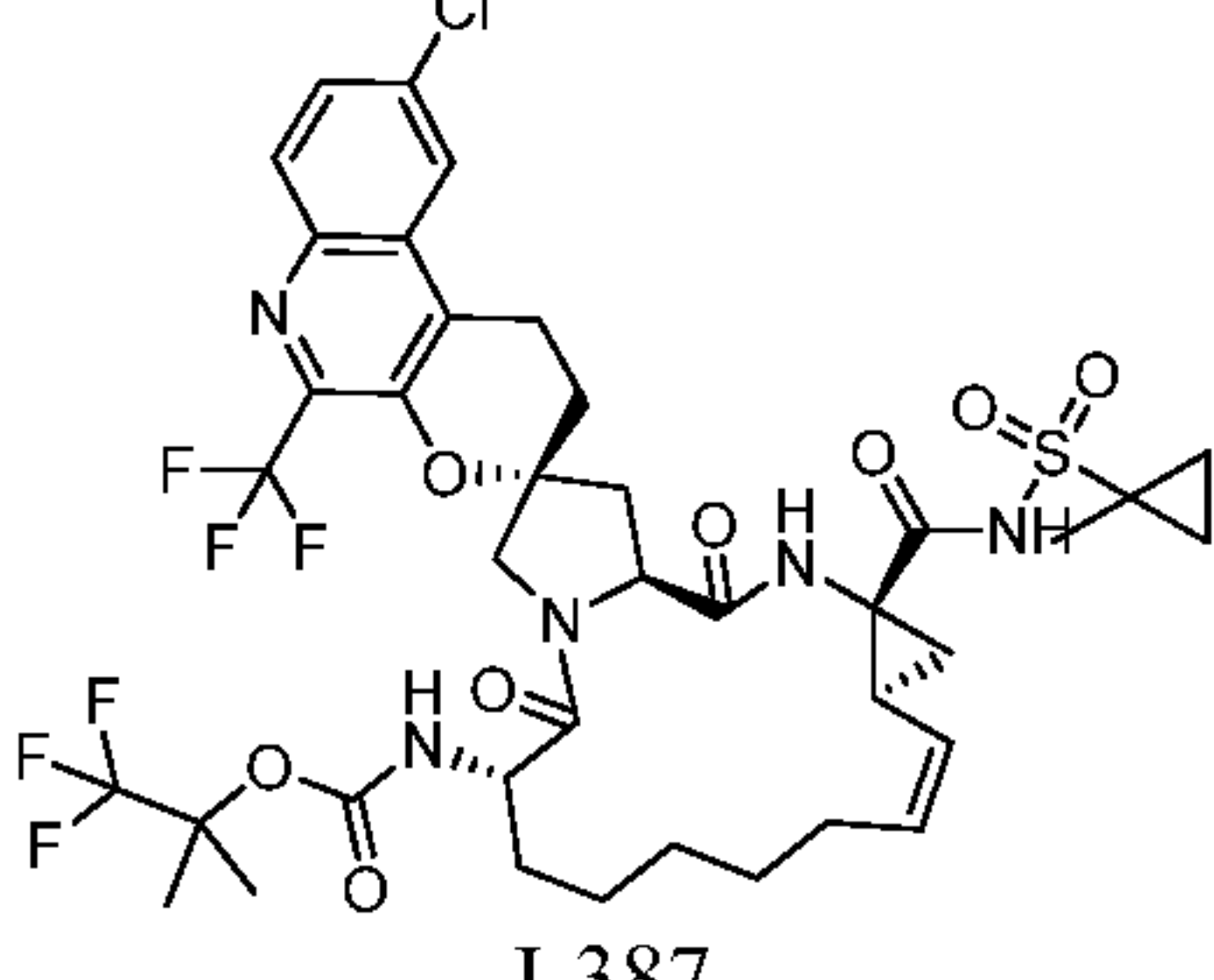
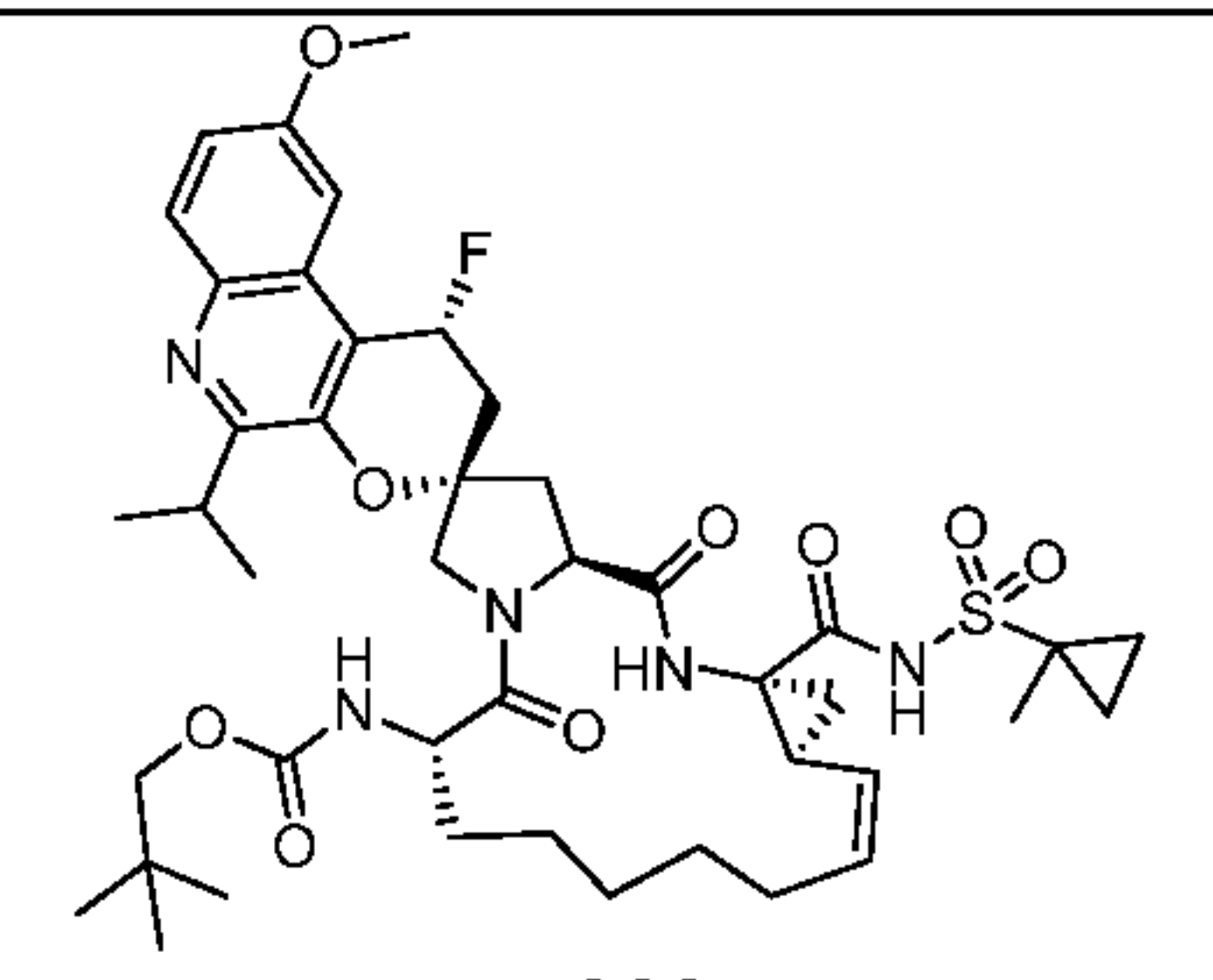
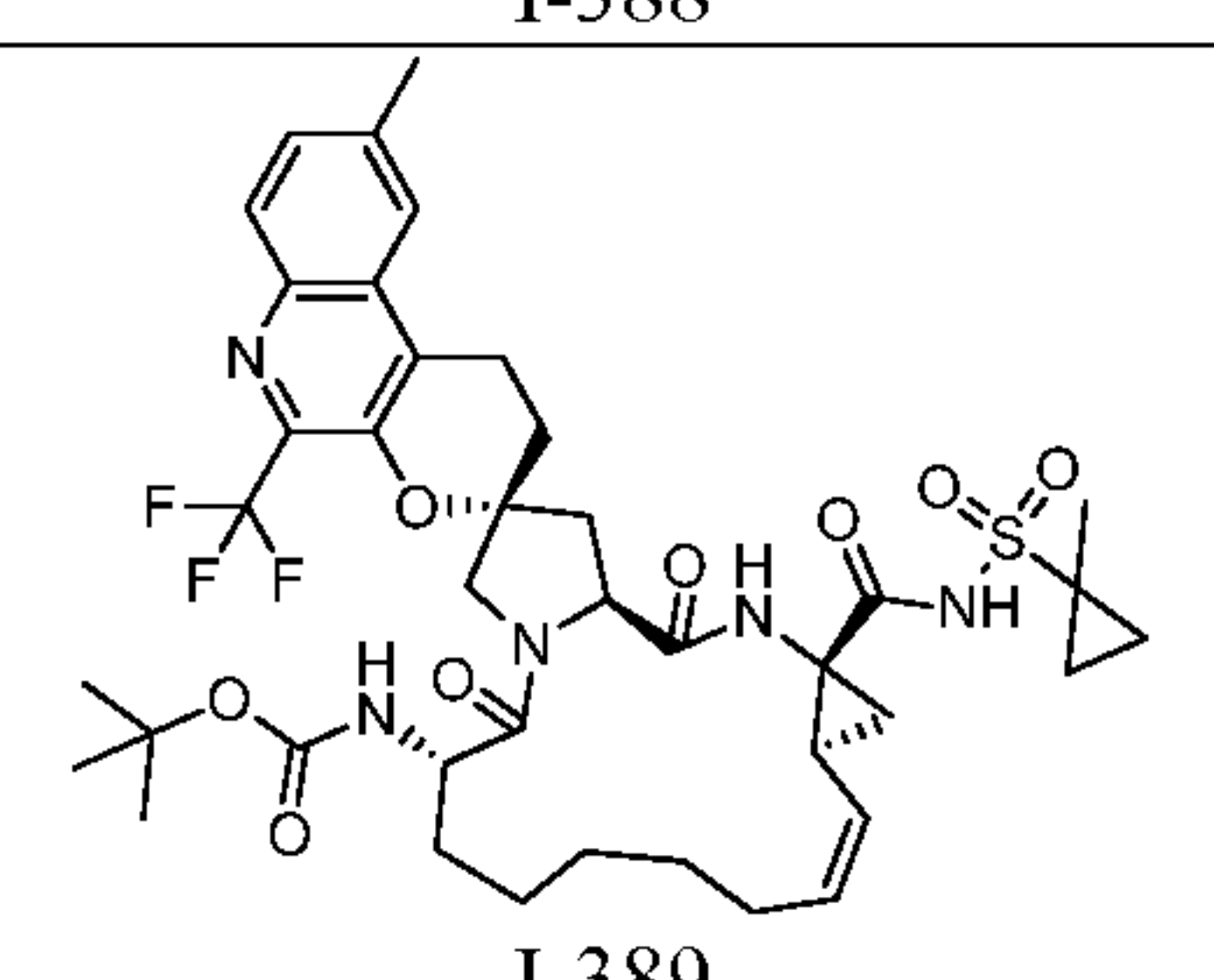
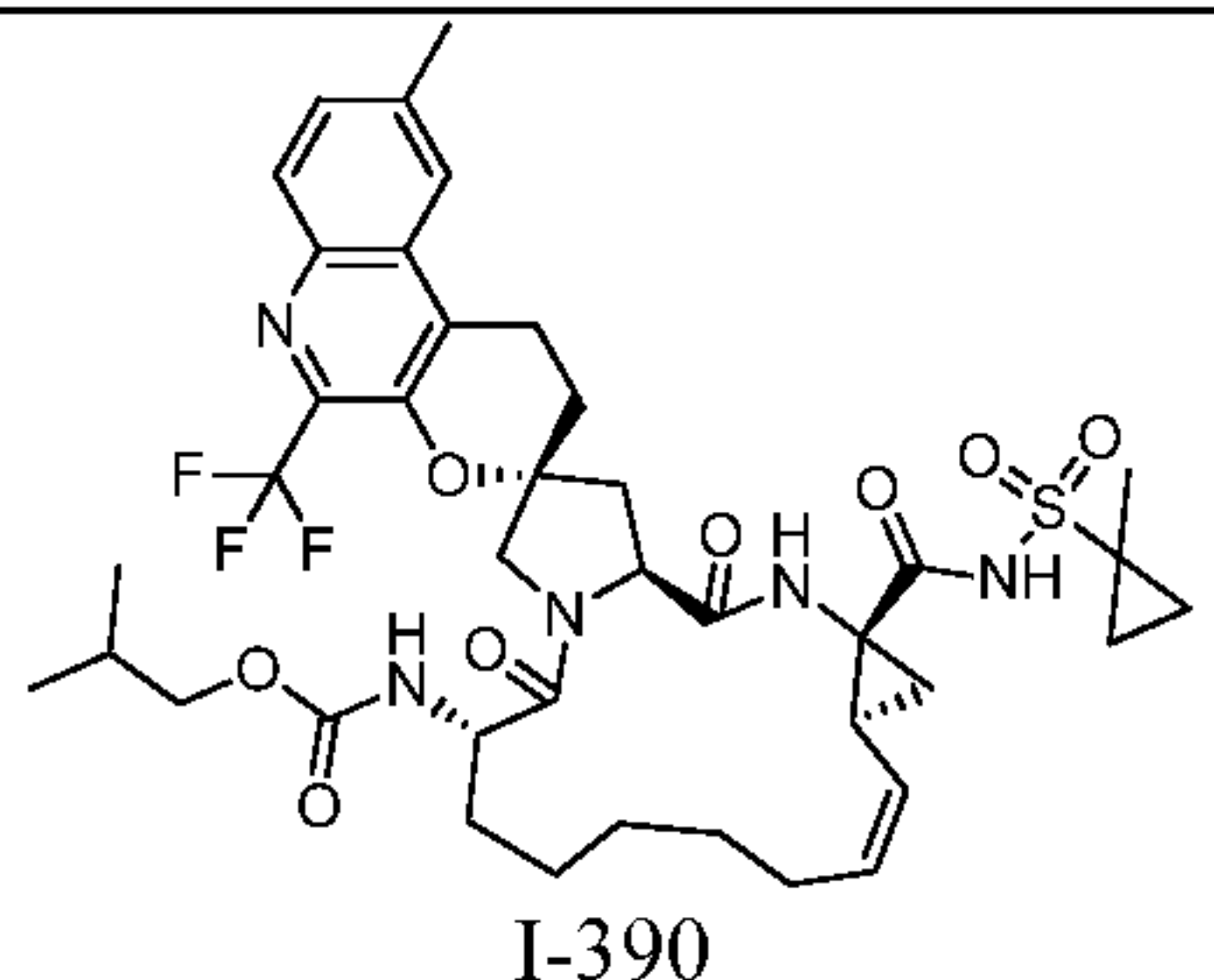
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
361	 I-361	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-2'-methoxy-6'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,5,6,7,8,9,9',10,10',11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,8'-pyrano[2,3- <i>c</i>][1,5]naphthyridin]-6-yl]carbamate	11	795.2
362	 I-362	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-2'-methoxy-6'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,5,6,7,8,9,9',10,10',11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,8'-pyrano[2,3- <i>c</i>][1,5]naphthyridin]-6-yl]carbamate	11	781.2
363	 I-363	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-2'-methoxy-6'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,5,6,7,8,9,9',10,10',11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,8'-pyrano[2,3- <i>c</i>][1,5]naphthyridin]-6-yl]carbamate	11	793.2
364	 I-364	1-methylcyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-2'-methoxy-6'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,5,6,7,8,9,9',10,10',11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,8'-pyrano[2,3- <i>c</i>][1,5]naphthyridin]-6-yl]carbamate	11	779.2
365	 I-365	1-methylcyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-2'-methoxy-6'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,5,6,7,8,9,9',10,10',11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,8'-pyrano[2,3- <i>c</i>][1,5]naphthyridin]-6-yl]carbamate	11	793.2

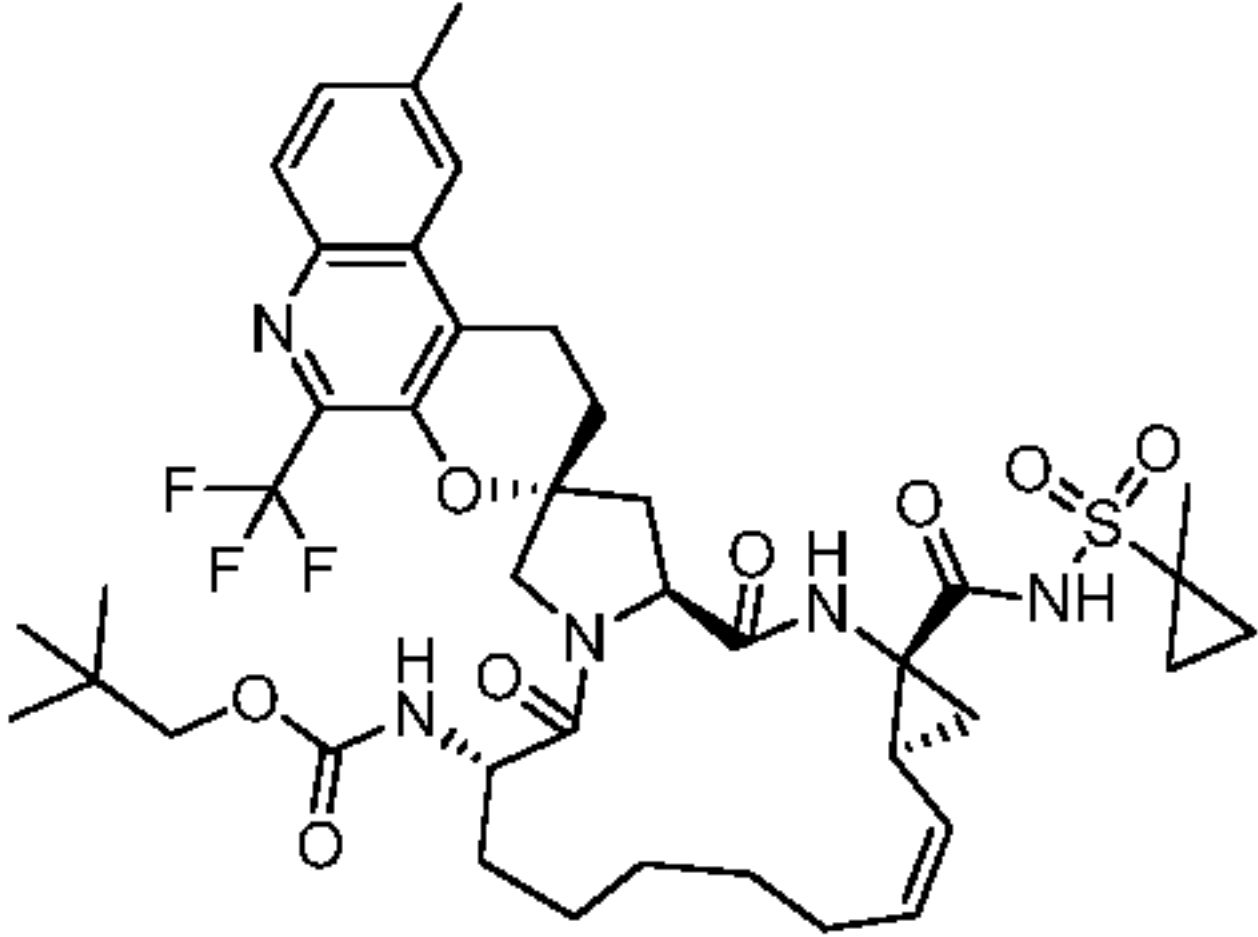
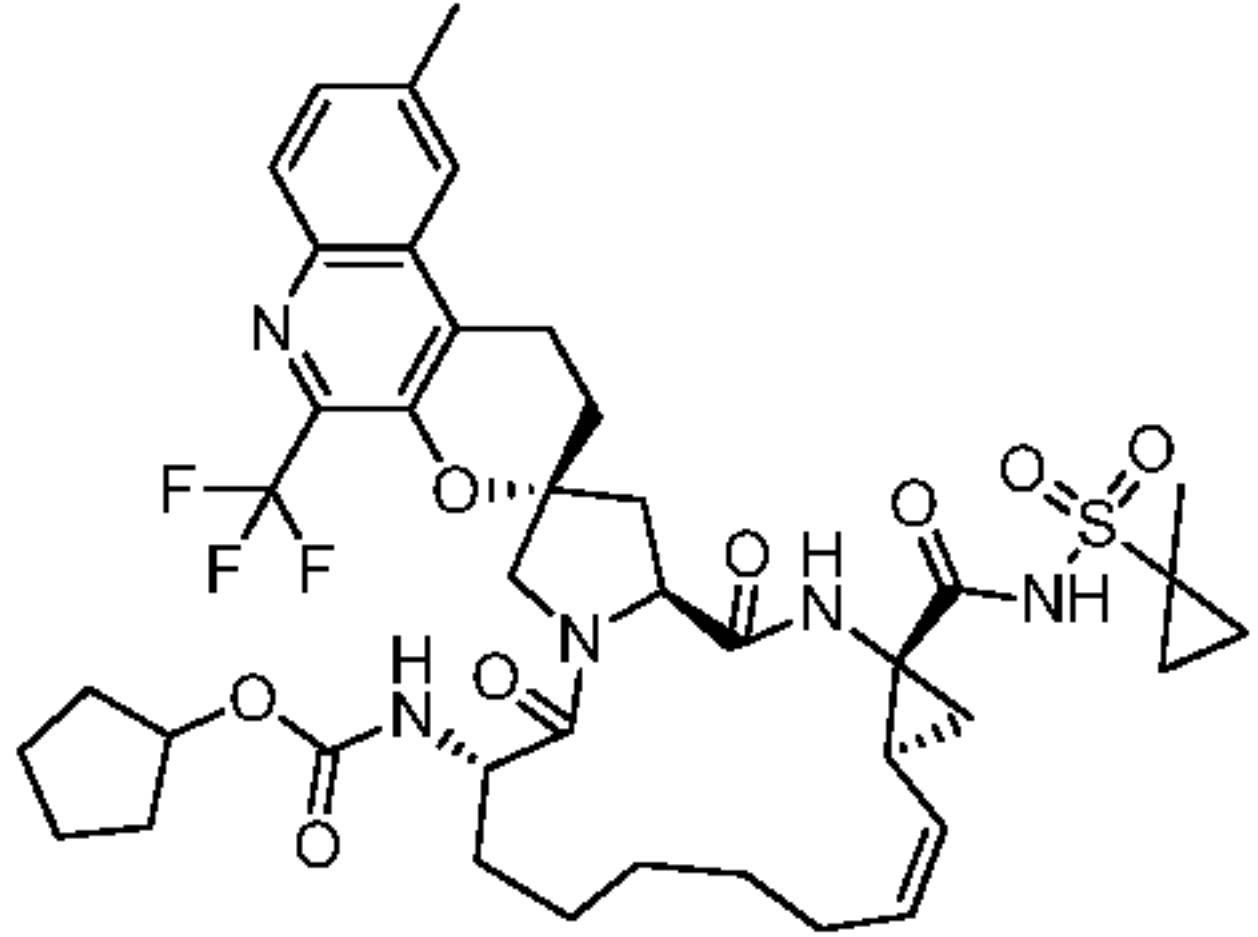
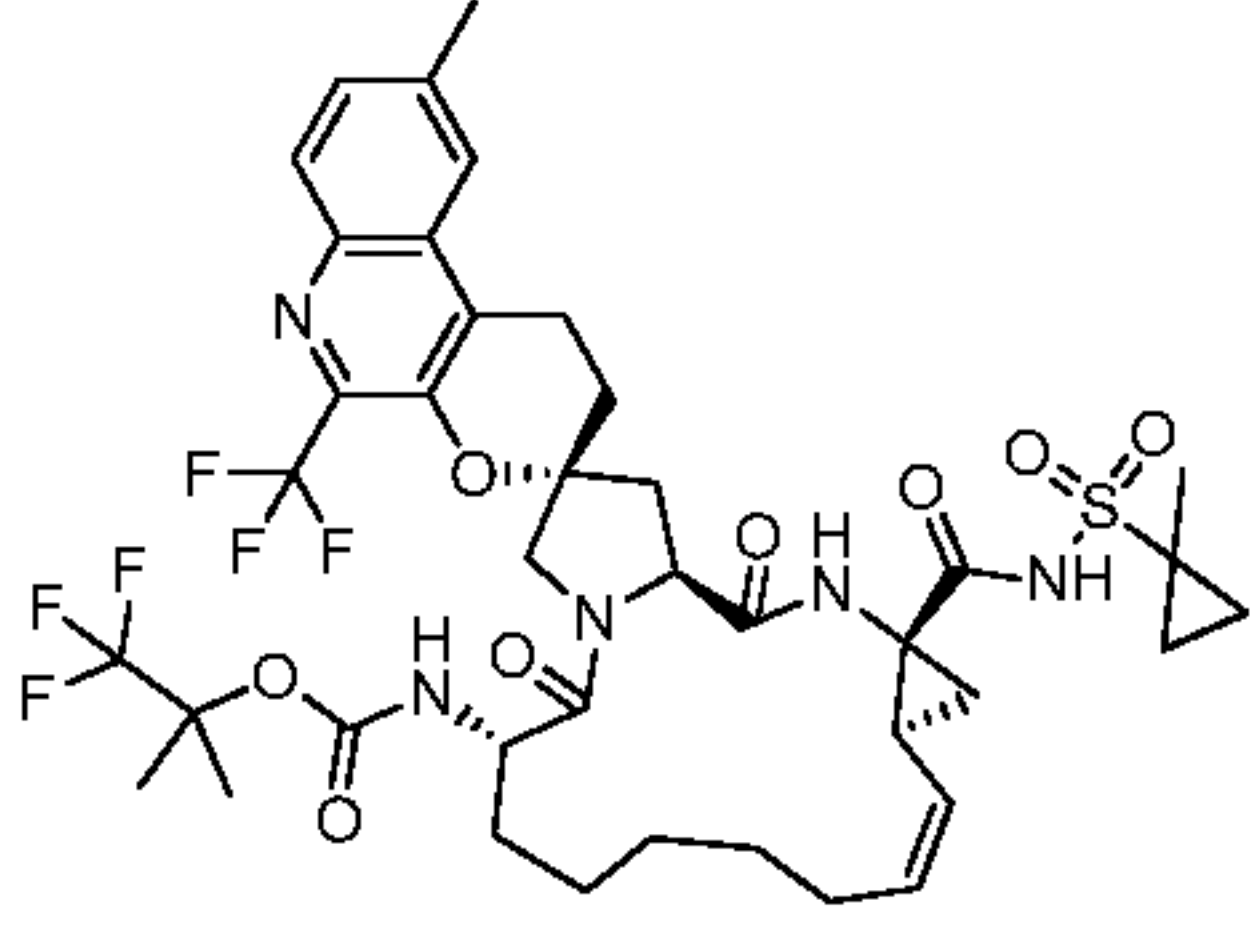
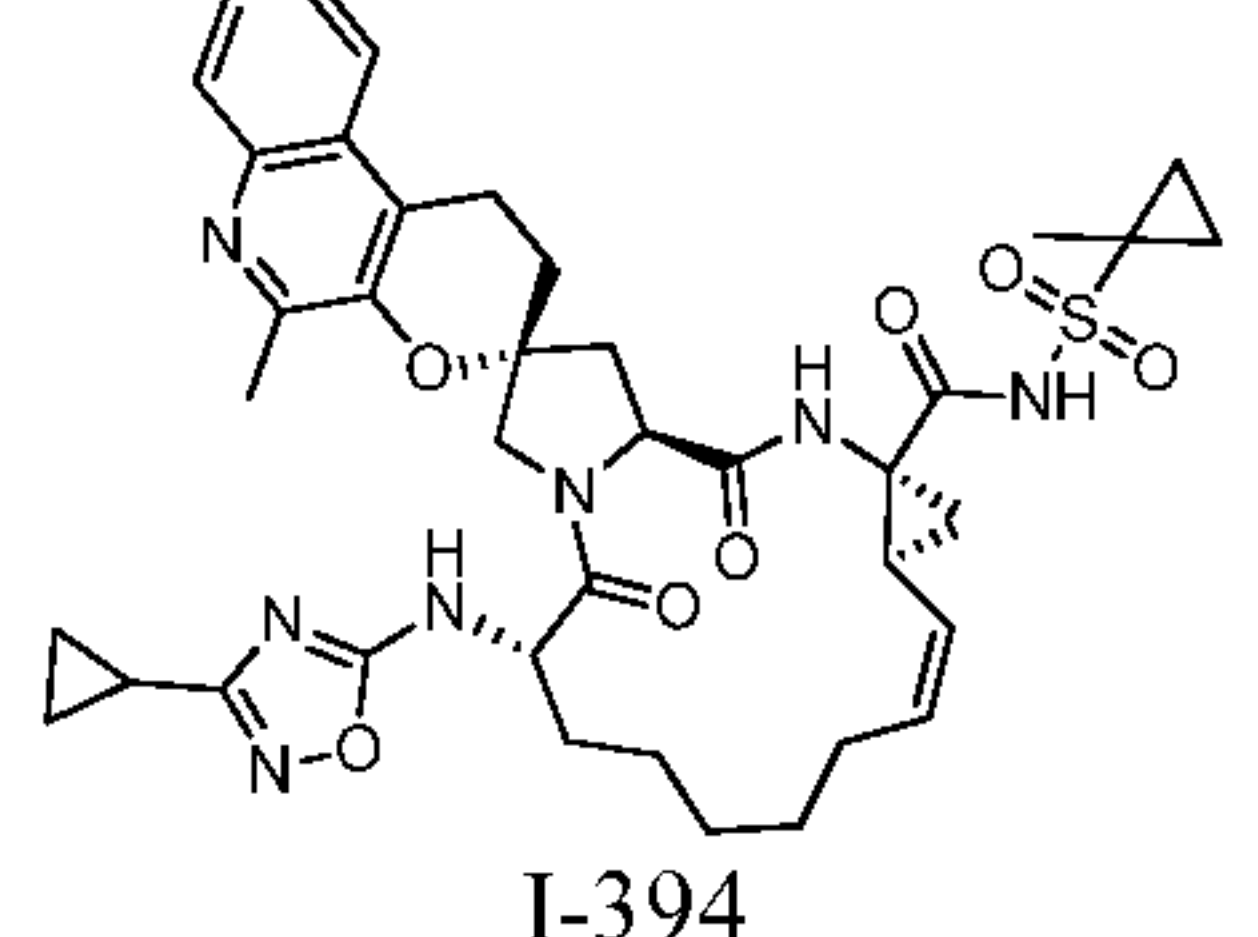
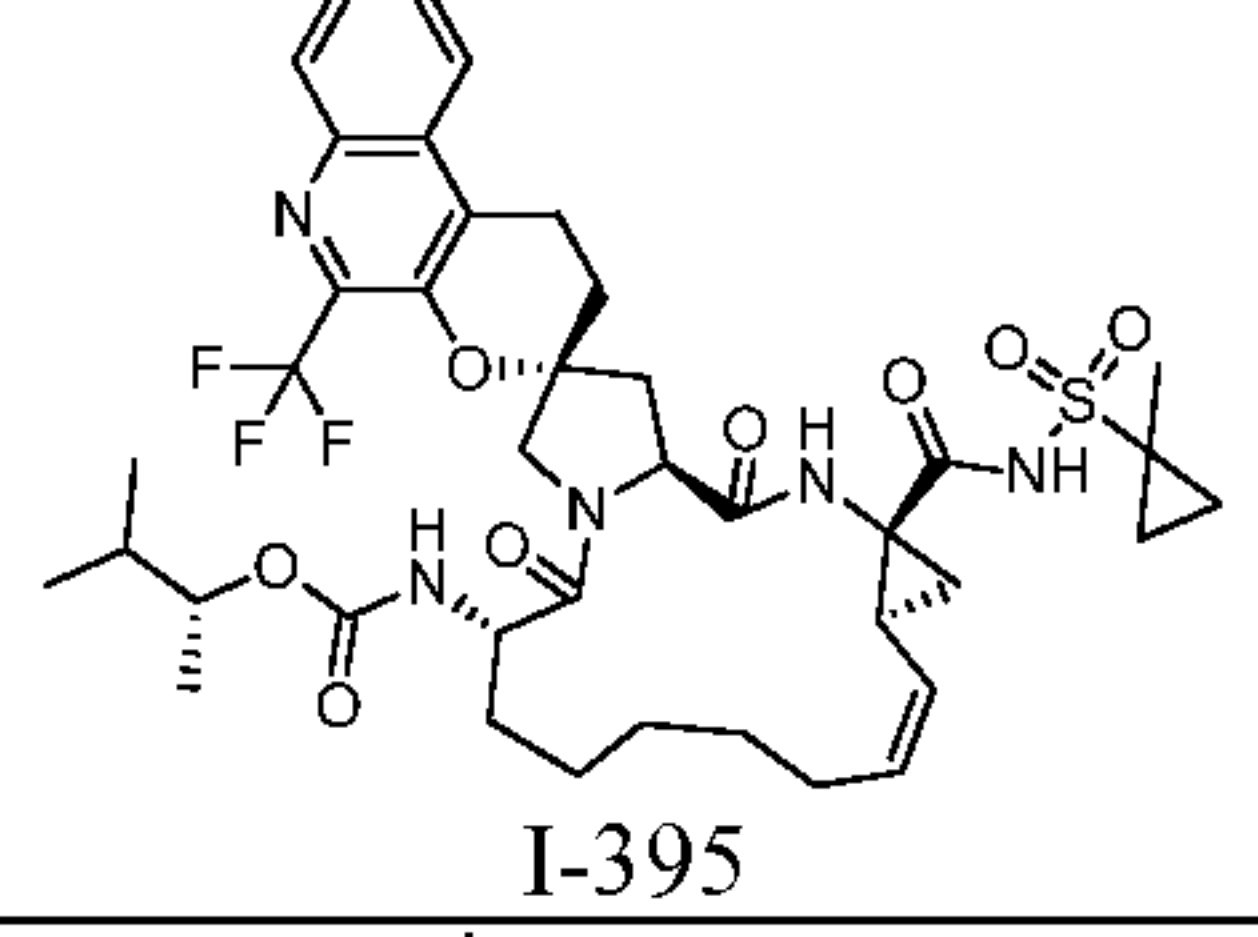
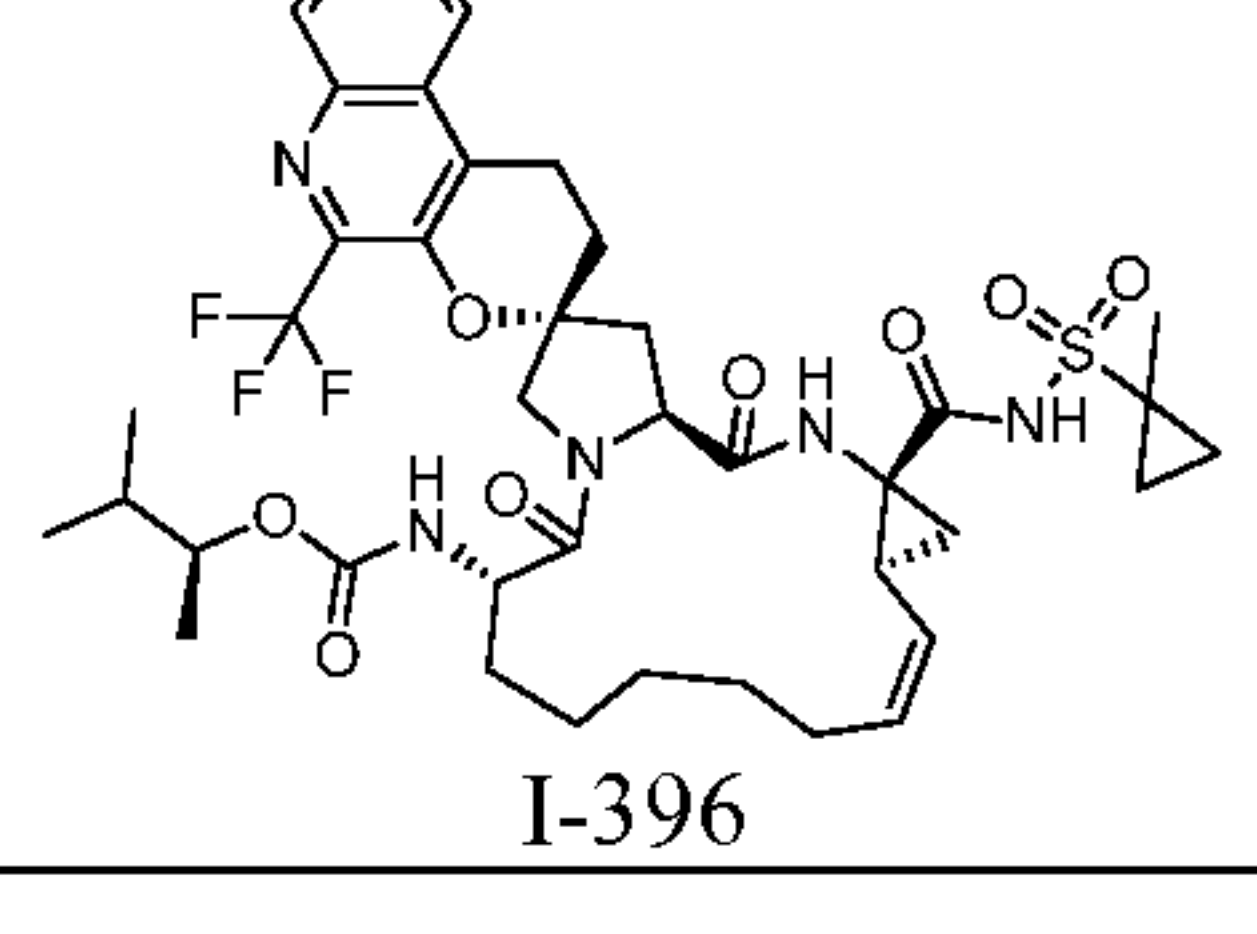
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
366	 <p>I-366</p>	1,1,1-trifluoro-3,3-dimethylbutan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	862
367	 <p>I-367</p>	1,1,1-trifluoro-3,3-dimethylbutan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	862.2
368	 <p>I-368</p>	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-5'-(difluoromethyl)-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10	820
369	 <p>I-369</p>	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-5'-(difluoromethyl)-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10	834
370	 <p>I-370</p>	2-fluoro-2-methylpropyl [(1' <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-fluoro-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	56	816 (K+ salt)

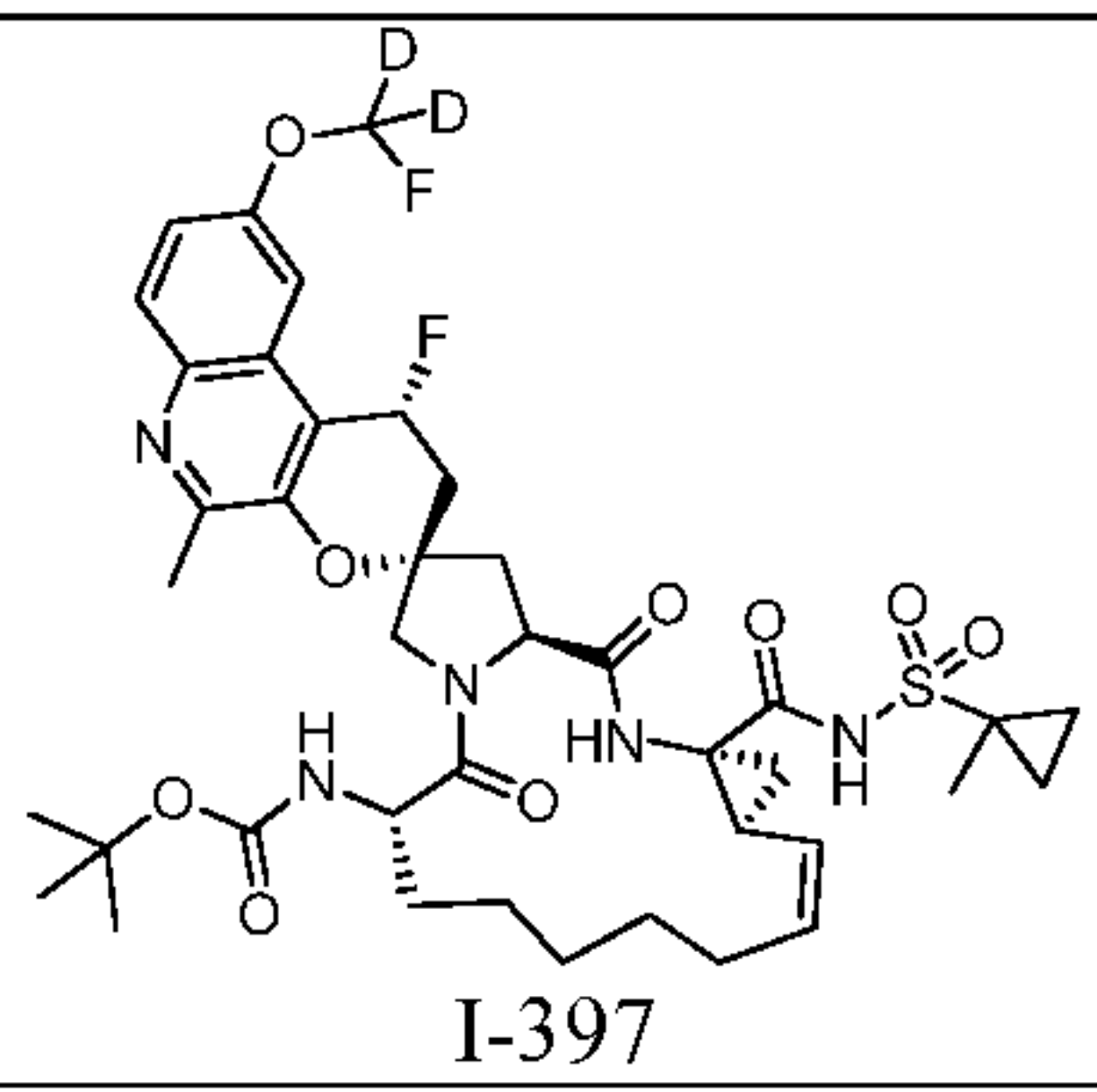
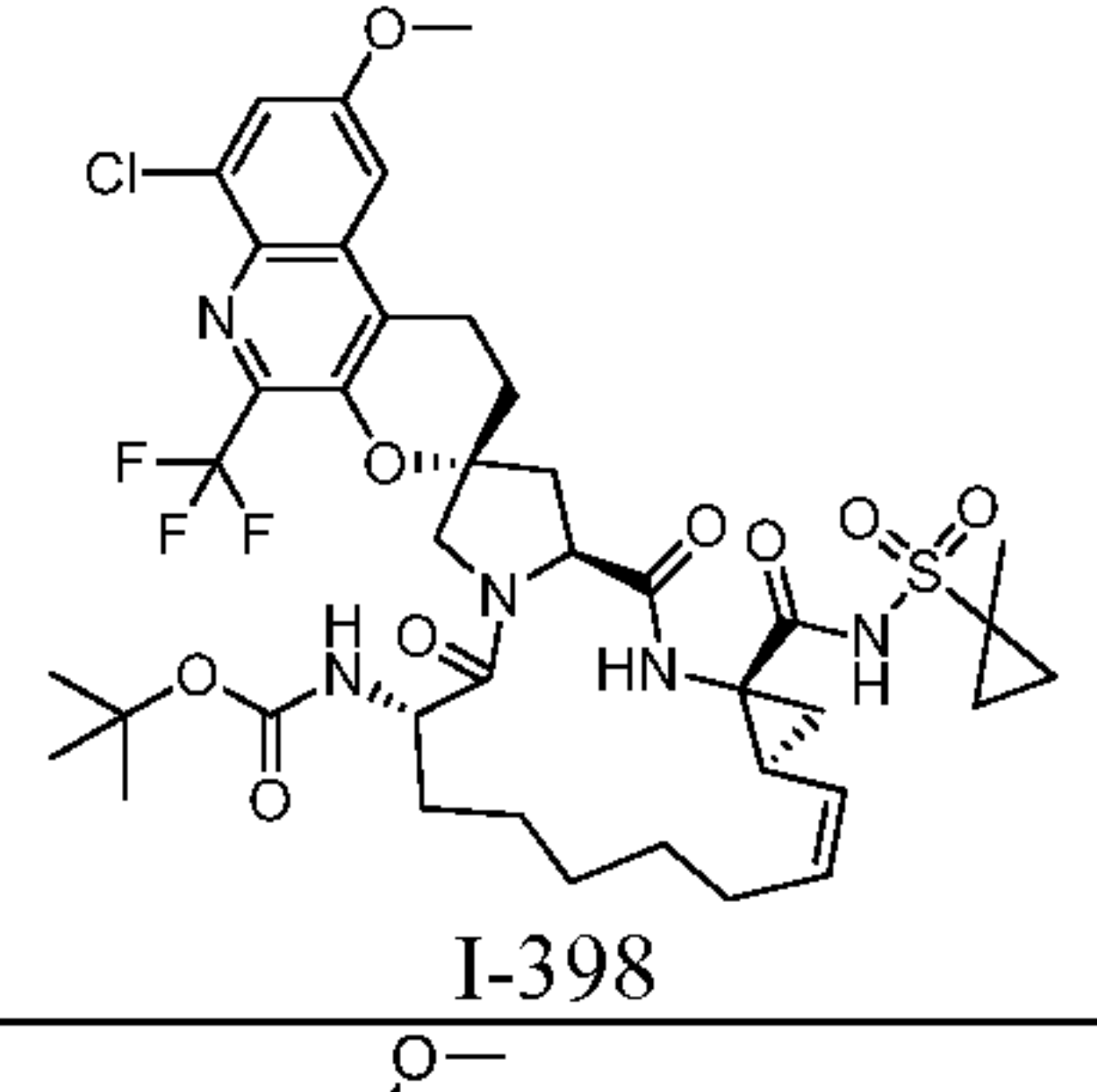
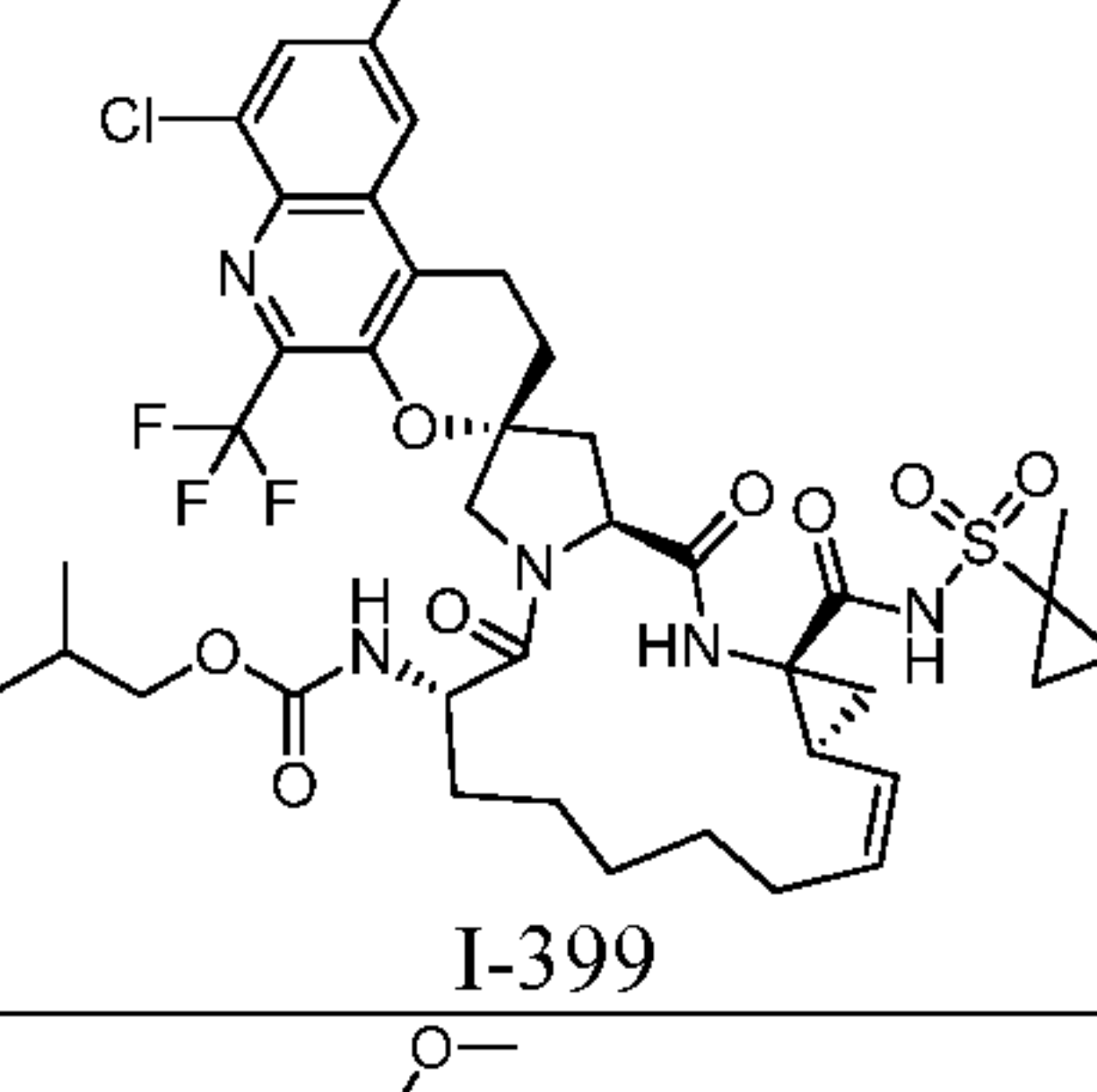
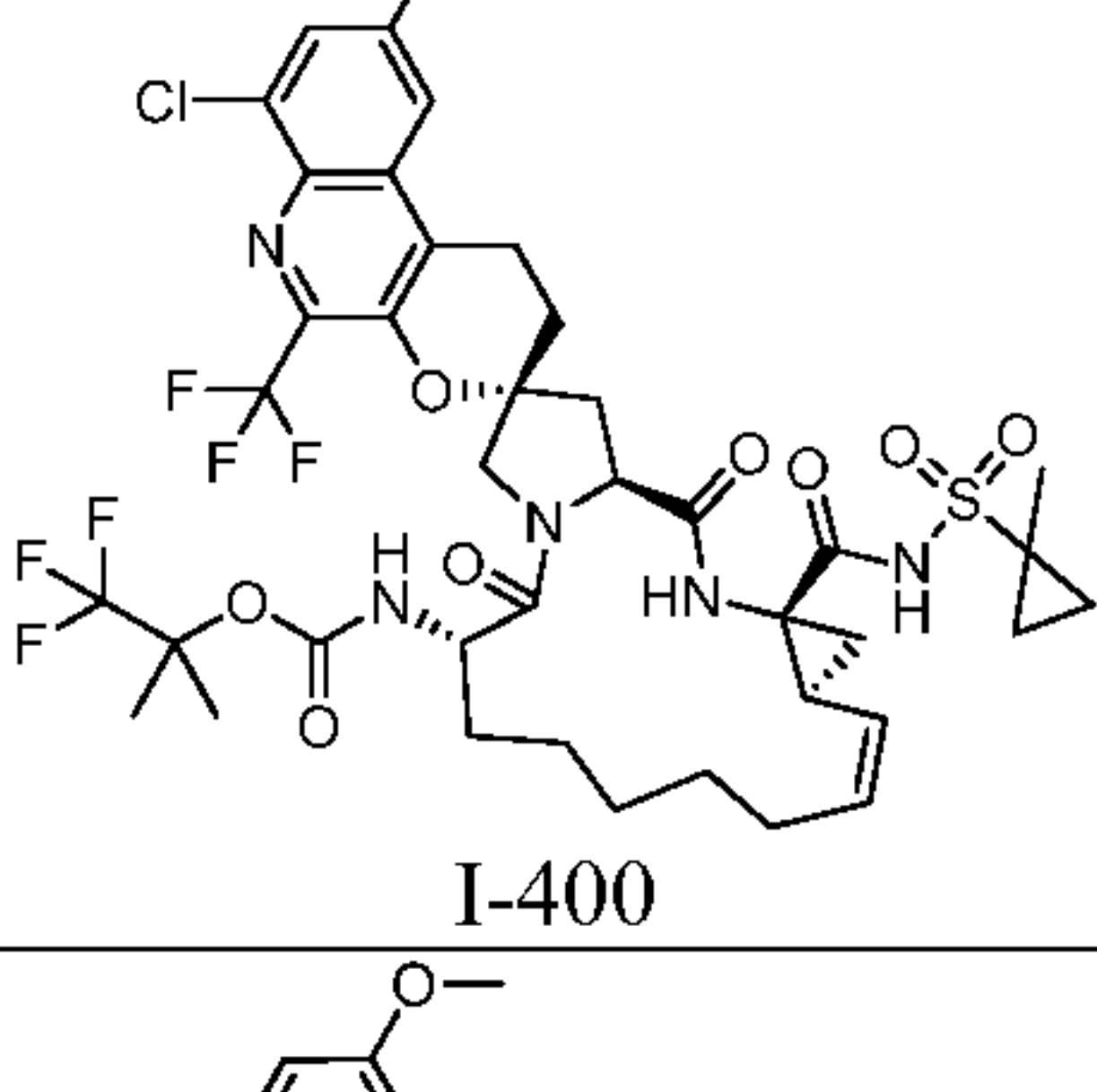
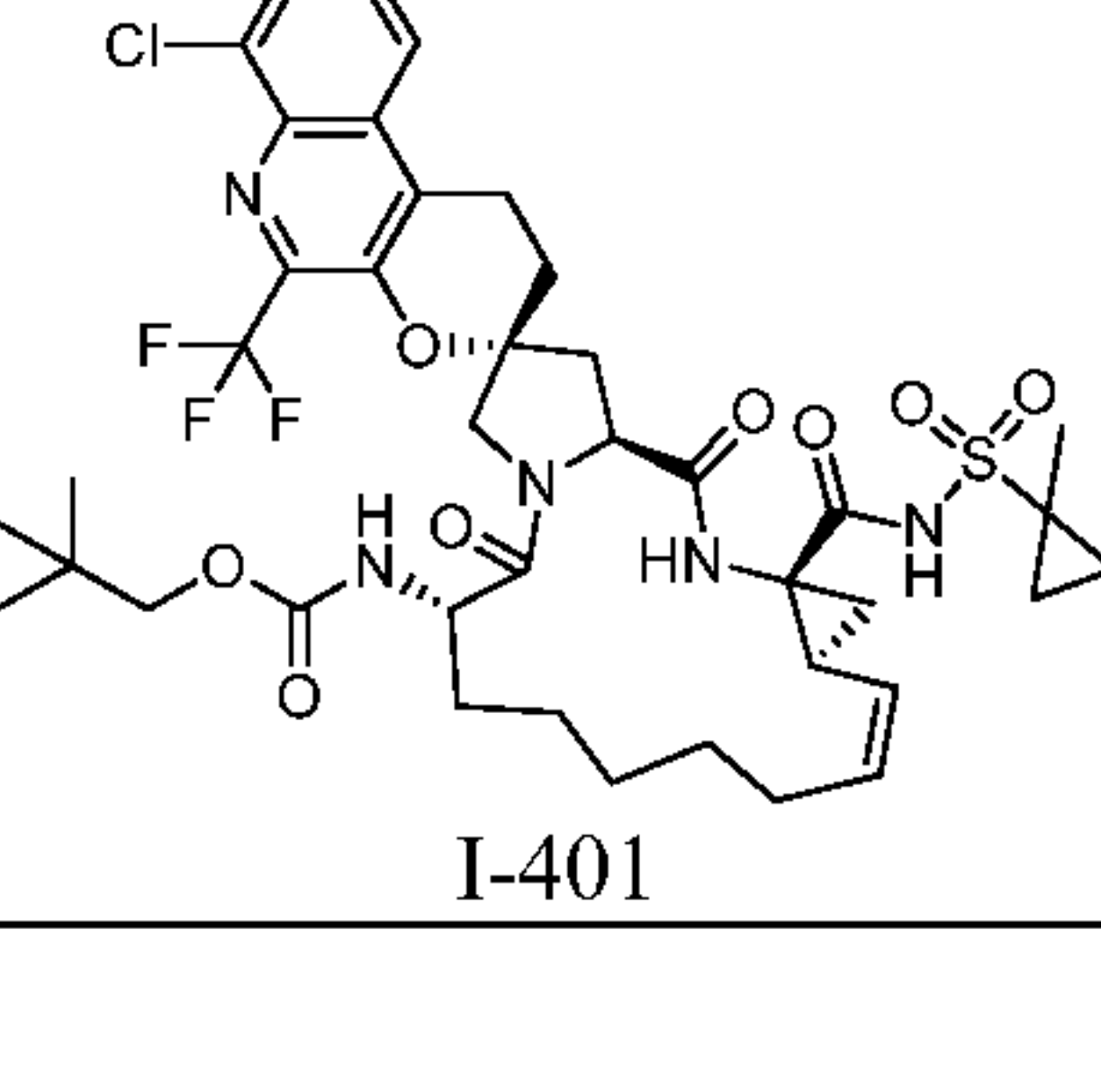
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
371	 I-371	2,2-dimethylpropyl [(1 <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-fluoro-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl} carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	56	812.2 (K+ salt)
372	 I-372	2-methylpropyl [(1 <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-fluoro-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl} carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	56	798.2 (K+ salt)
373	 I-373	cyclopentyl [(1 <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-fluoro-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl} carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	56	810.2 (K+ salt)
374	 I-374	<i>tert</i> -butyl [(2 <i>S</i> ,6 <i>S</i> ,10' <i>R</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-10'-fluoro-2'-methoxy-6'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl} carbamoyl}-5,16-dioxo-1,5,6,7,8,9,9',10,10',11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,8'-pyrano[2,3- <i>c</i>][1,5]naphthyridin]-6-yl]carbamate	33	799.2
375	 I-375	3,3-difluorocyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl} carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	798.5

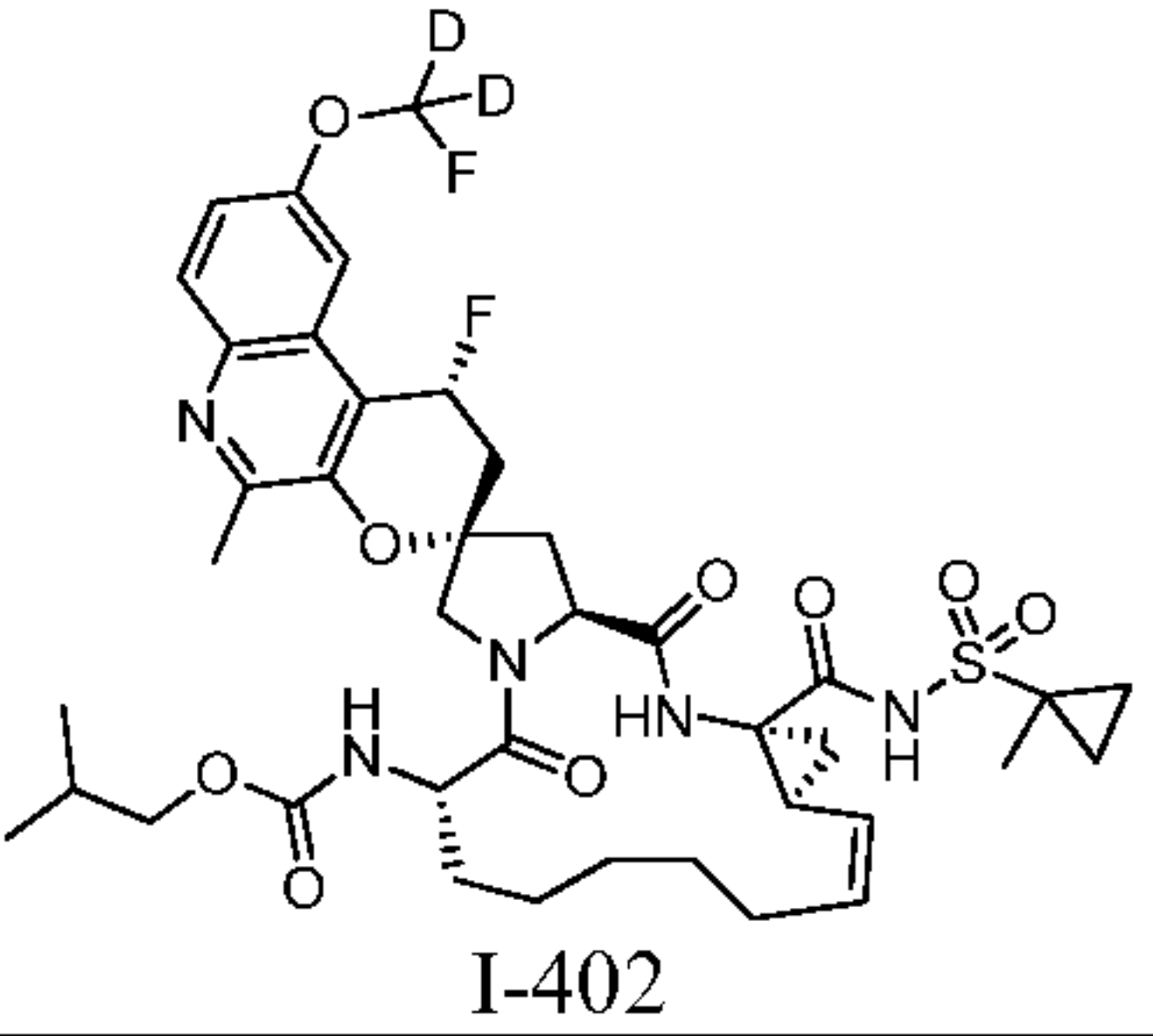
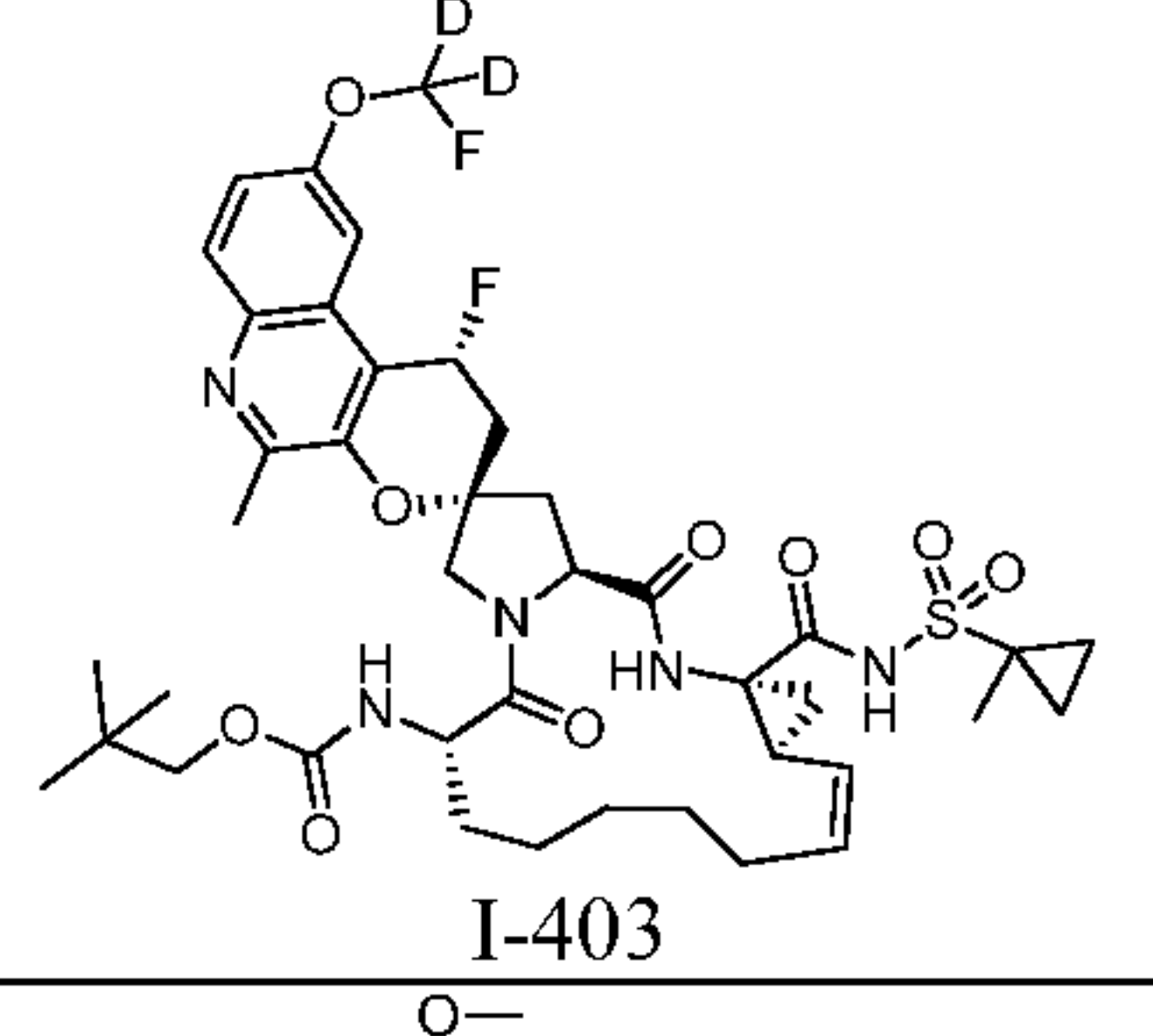
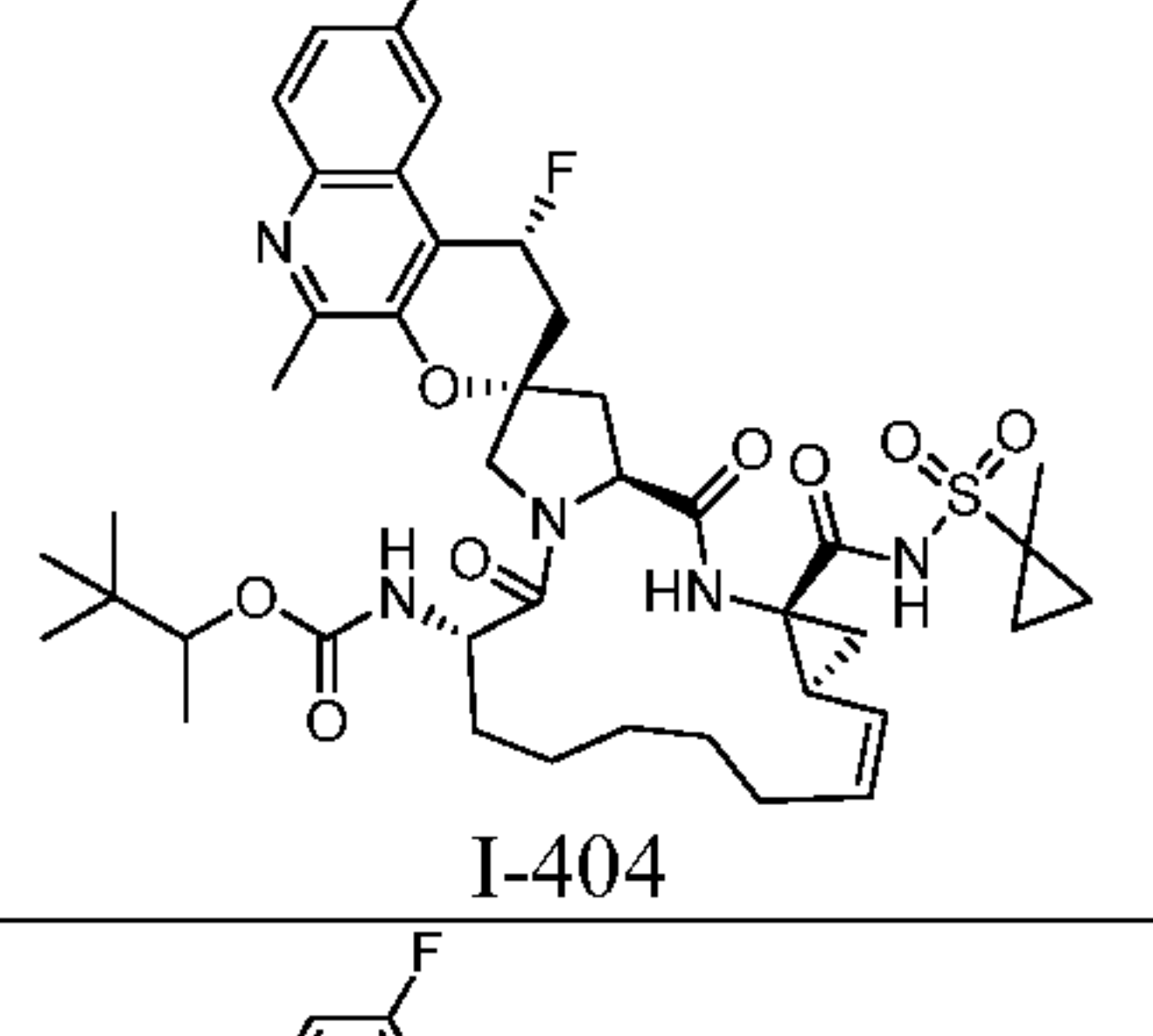
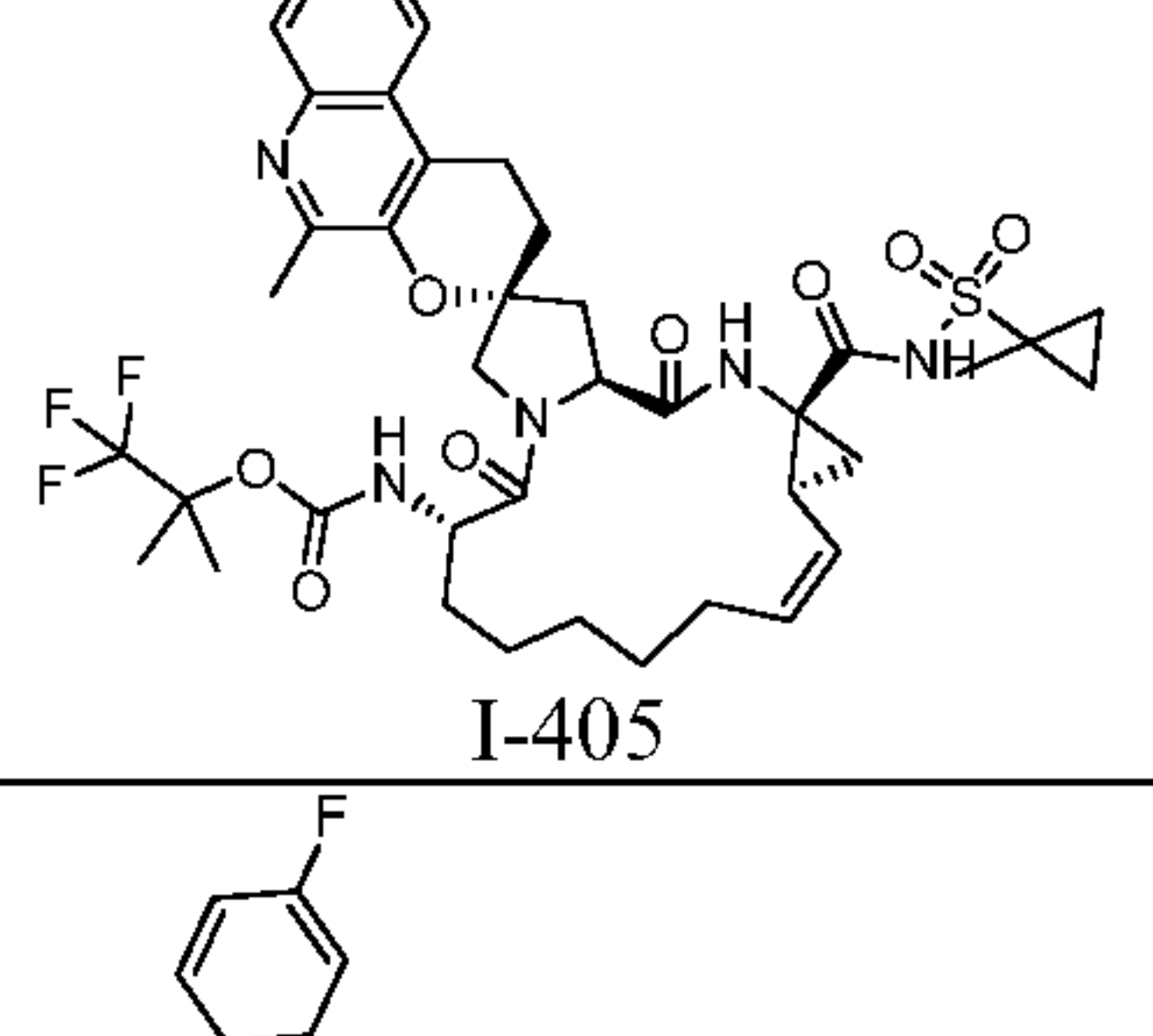
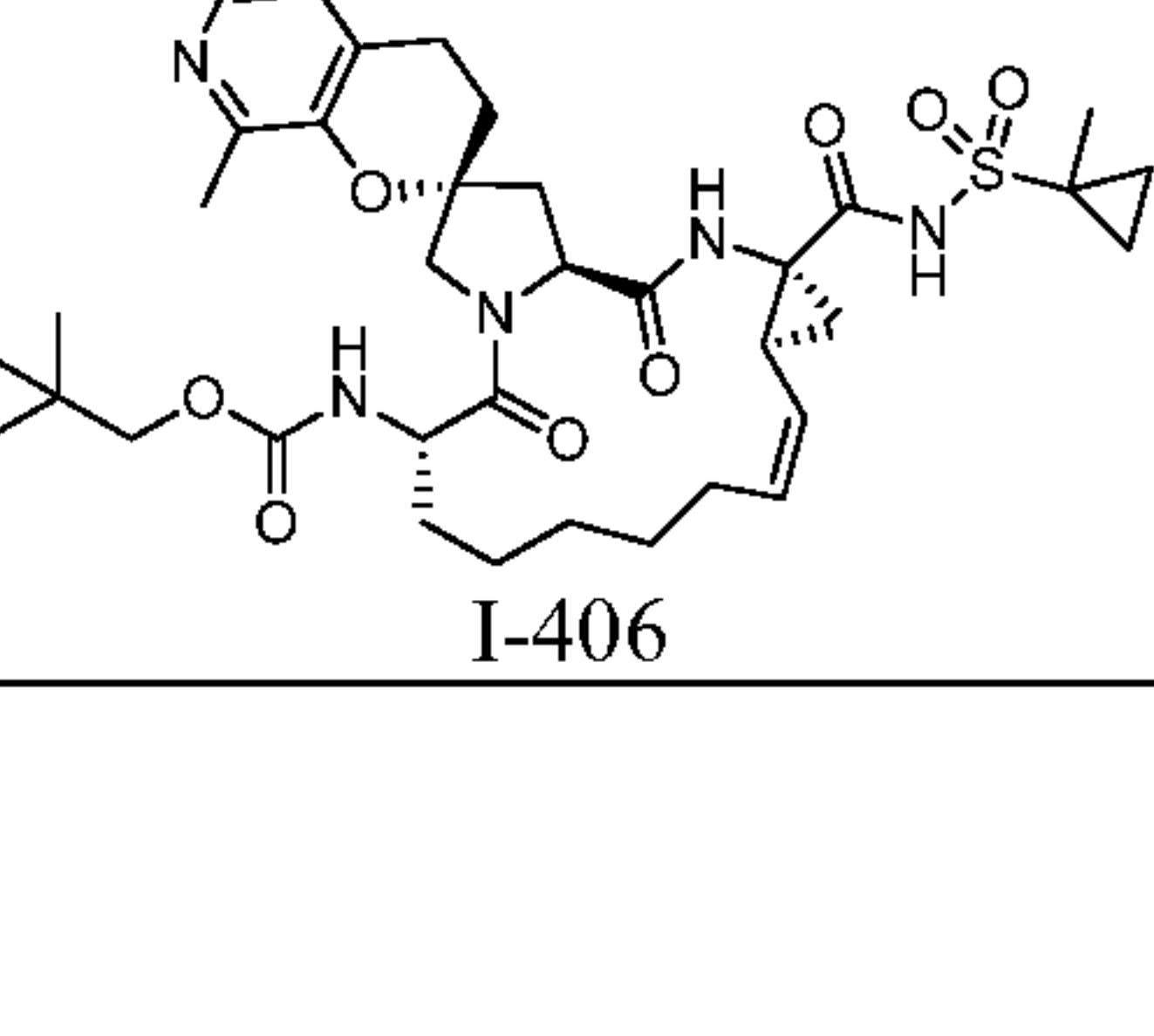
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
376	 I-376	3,3-difluorocyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	798.5
377	 I-377	2,2-dimethylpropyl [(2 <i>S</i> ,6 <i>S</i> ,10' <i>R</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-10'-fluoro-2'-methoxy-6'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,5,6,7,8,9,9',10,10',11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,8'-pyrano[2,3- <i>c</i>][1,5]naphthyridin]-6-yl]carbamate	33	813.2
378	 I-378	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5	782
379	 I-379	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-(1,3-benzoxazol-2-ylamino)-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	57	766.4
380	 I-380	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>S</i> ,6 <i>S</i> ,10' <i>R</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-10'-fluoro-2'-methoxy-6'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,5,6,7,8,9,9',10,10',11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,8'-pyrano[2,3- <i>c</i>][1,5]naphthyridin]-6-yl]carbamate	33	853.2 (K+ salt)

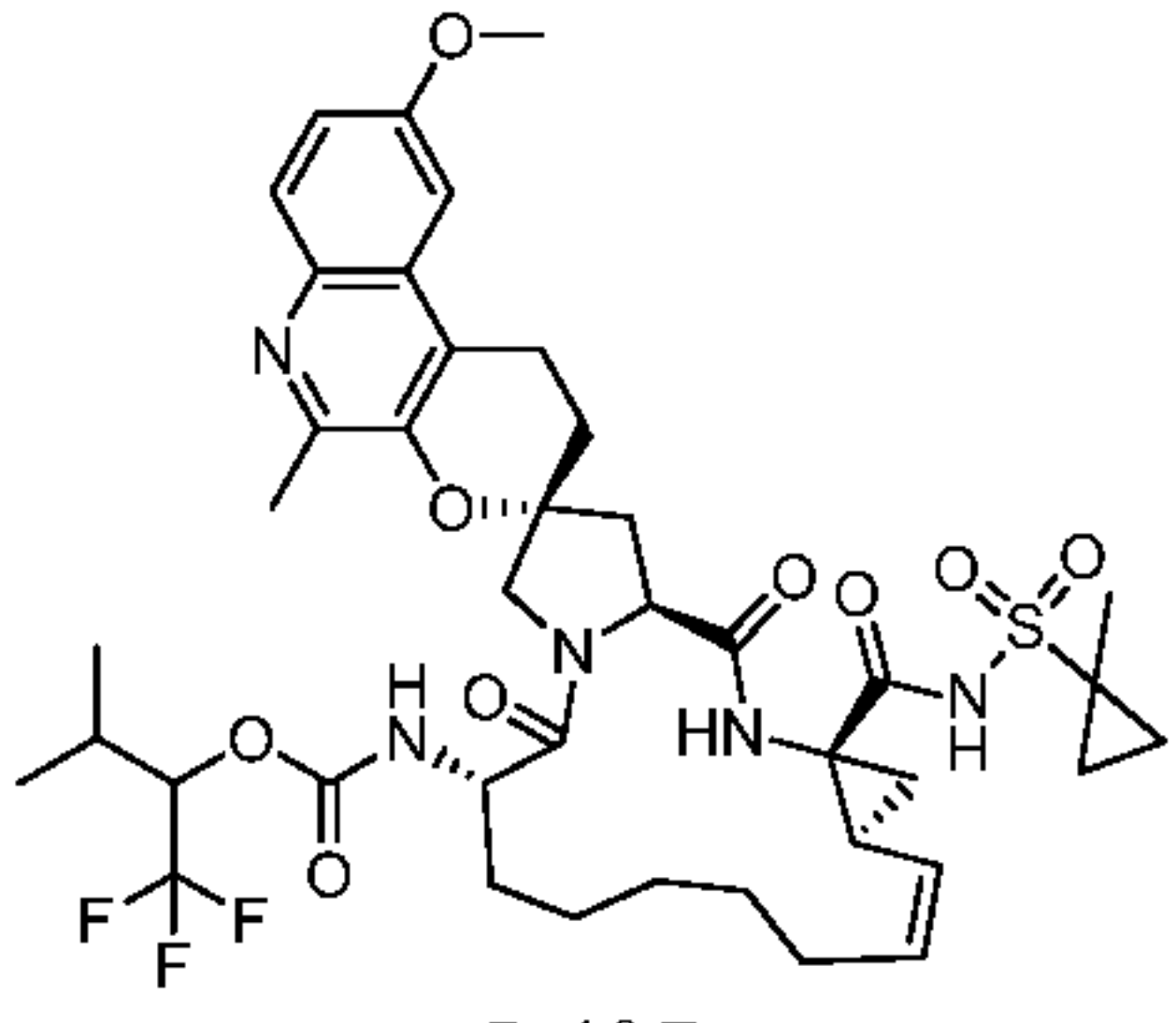
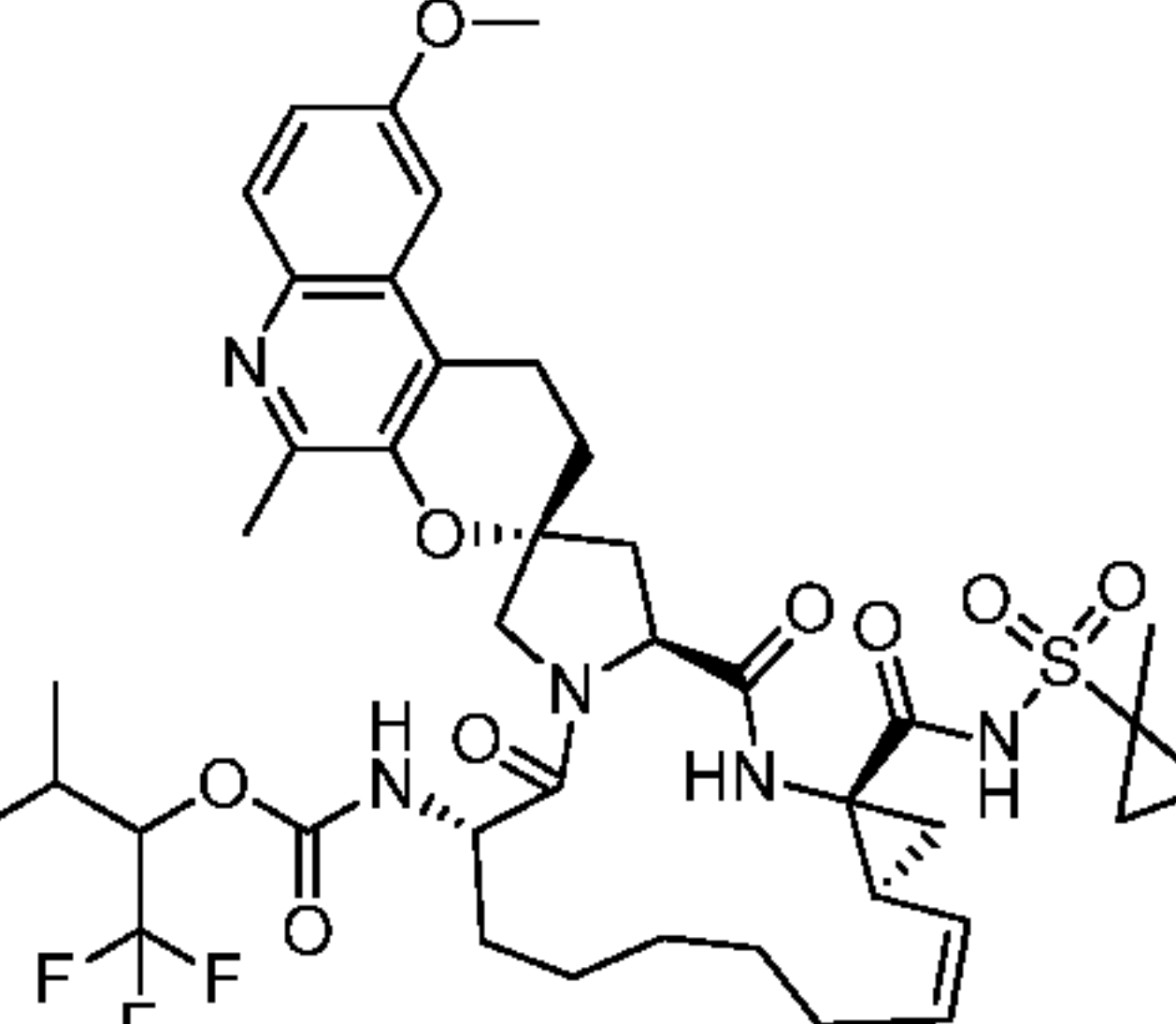
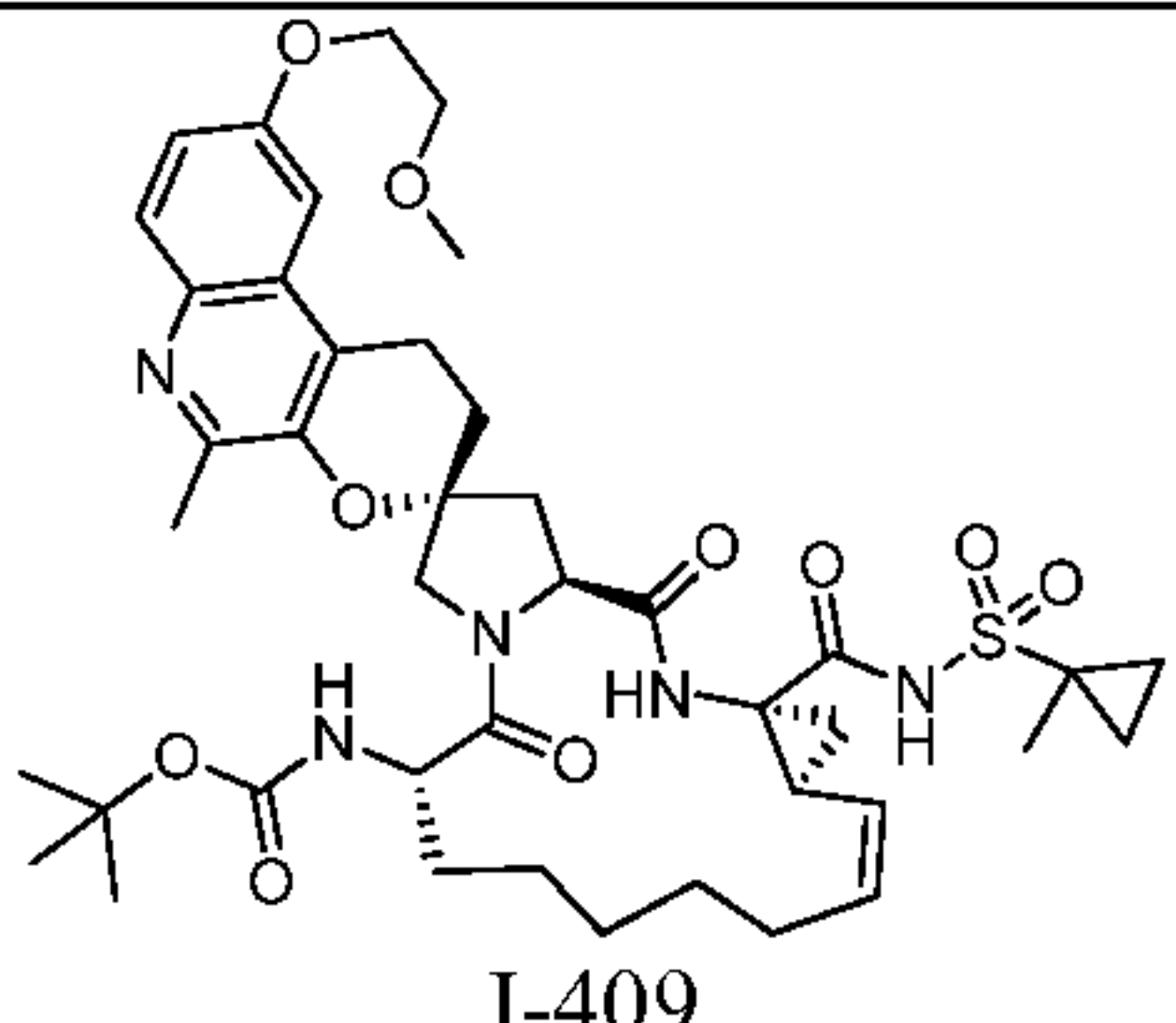
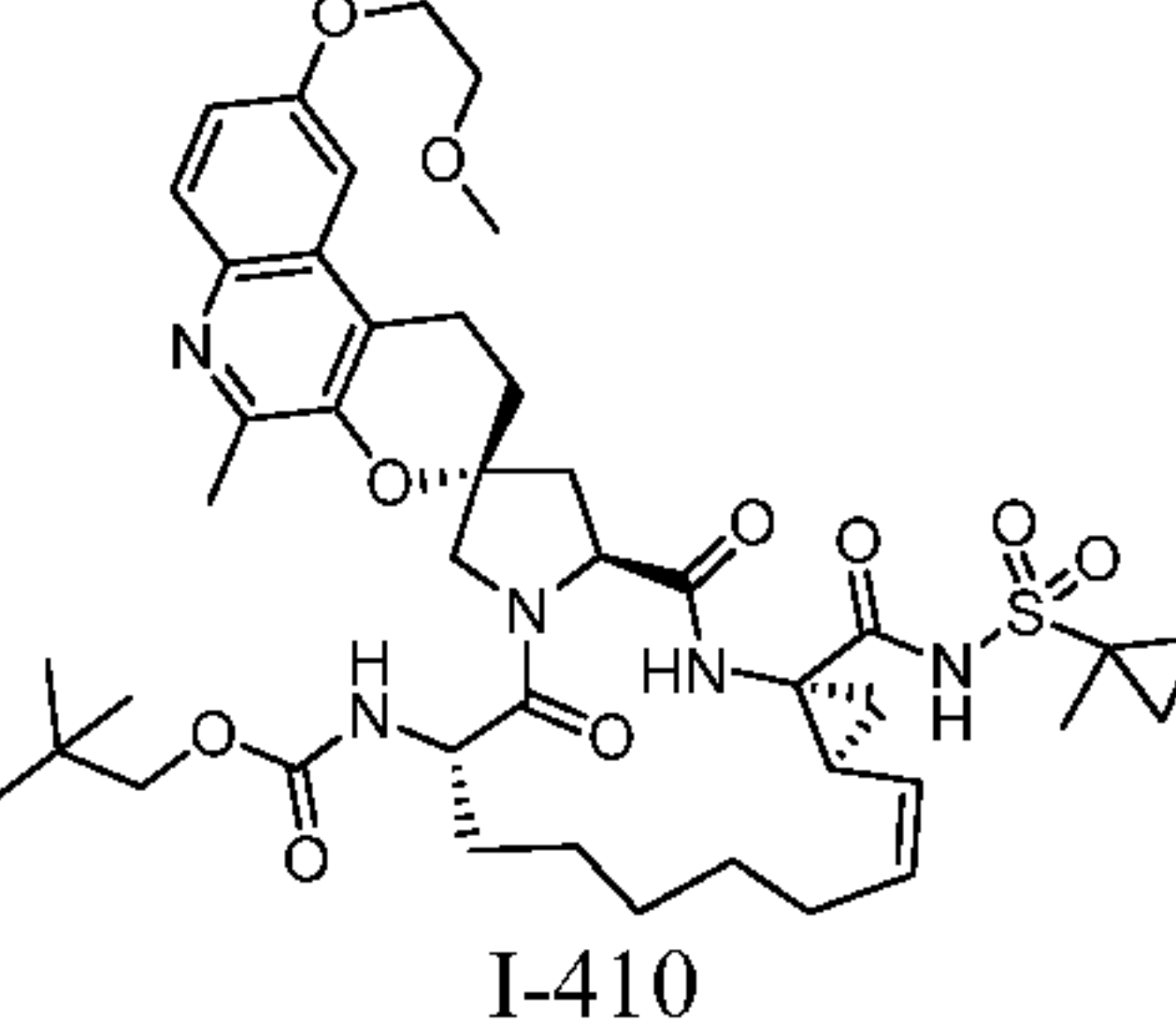
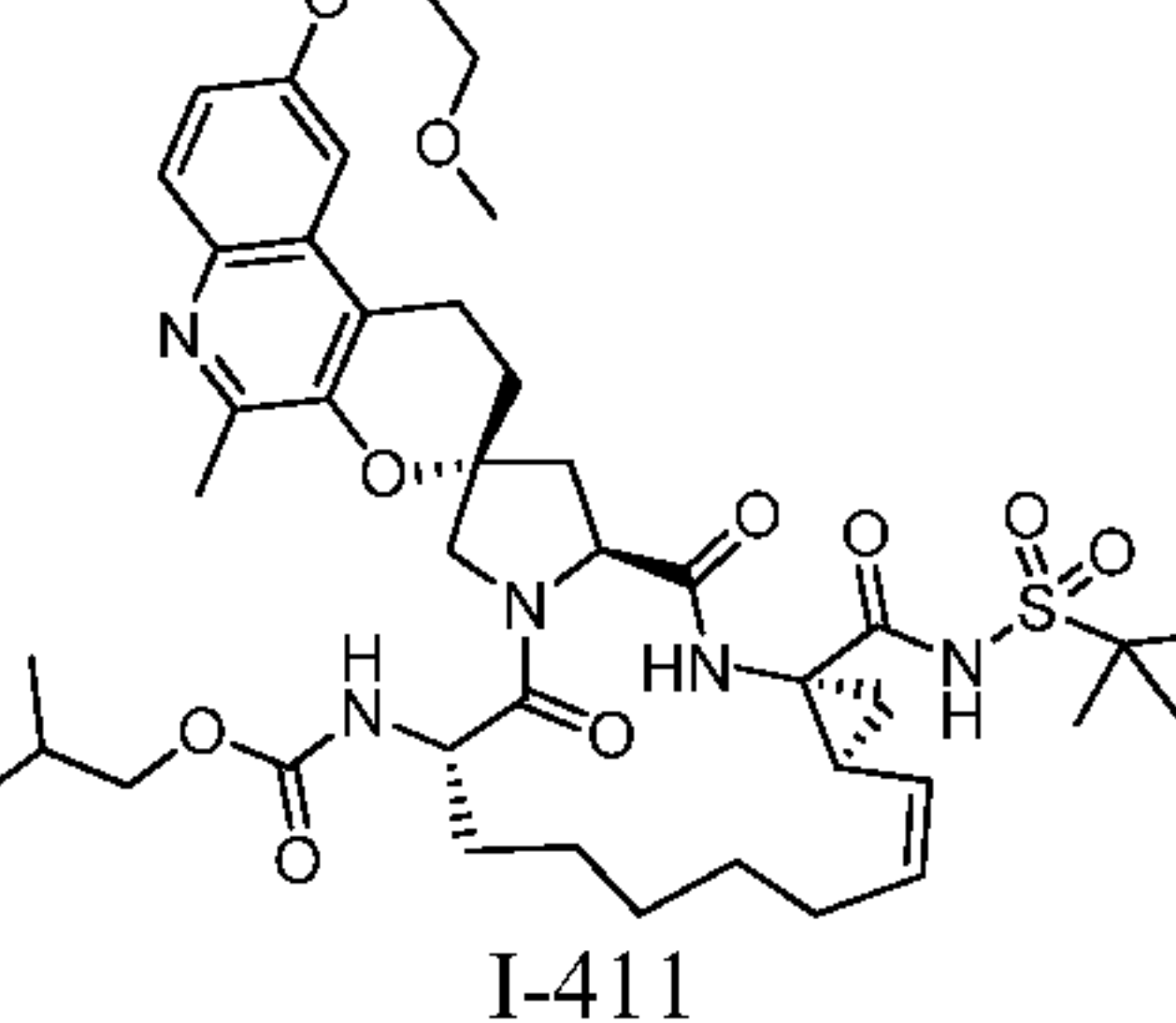
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
381	 I-381	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-8',9'-difluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	44	840
382	 I-382	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5, 35	848 (K+ salt)
383	 I-383	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5	839
384	 I-384	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5	850
385	 I-385	propan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5	824

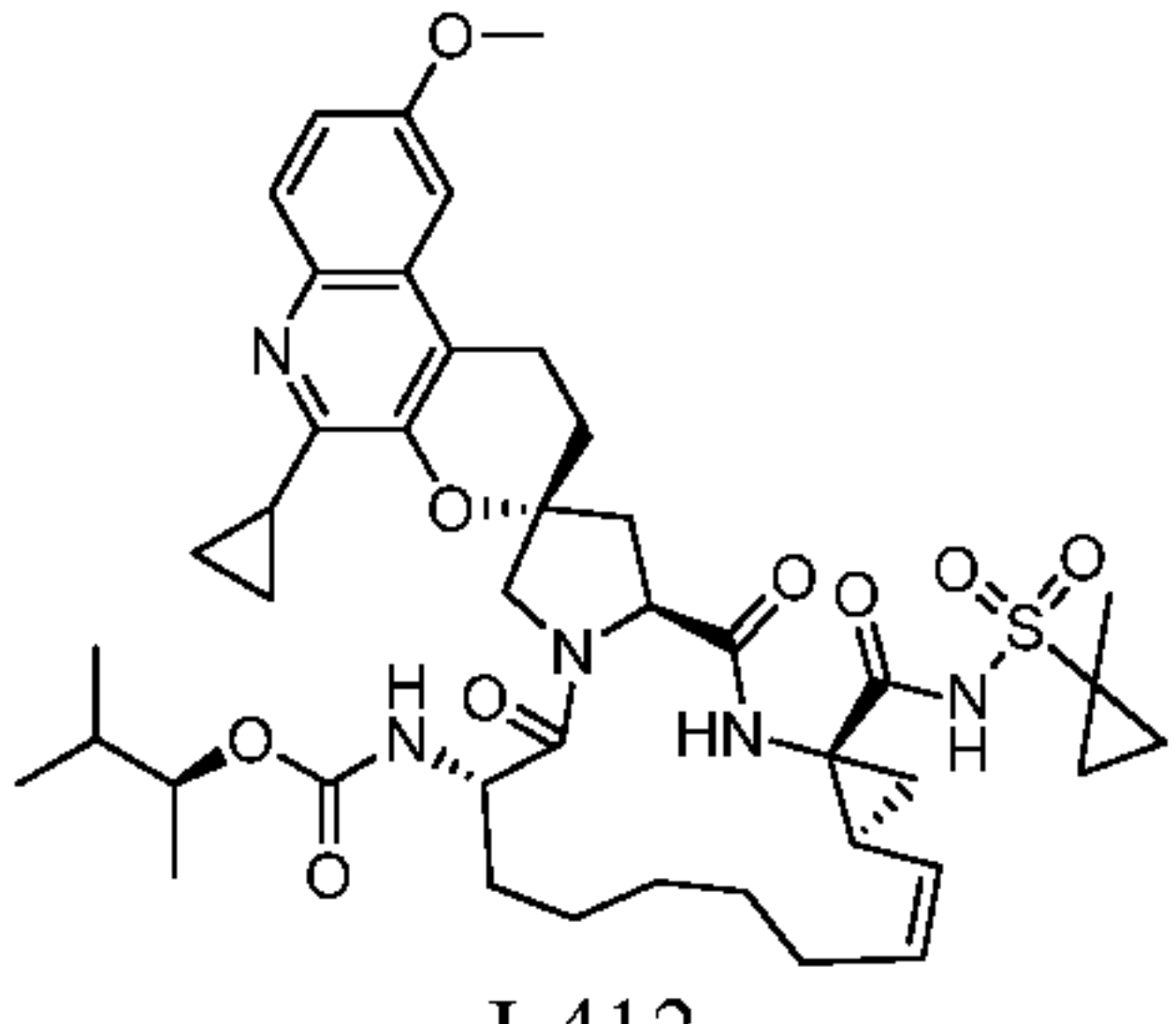
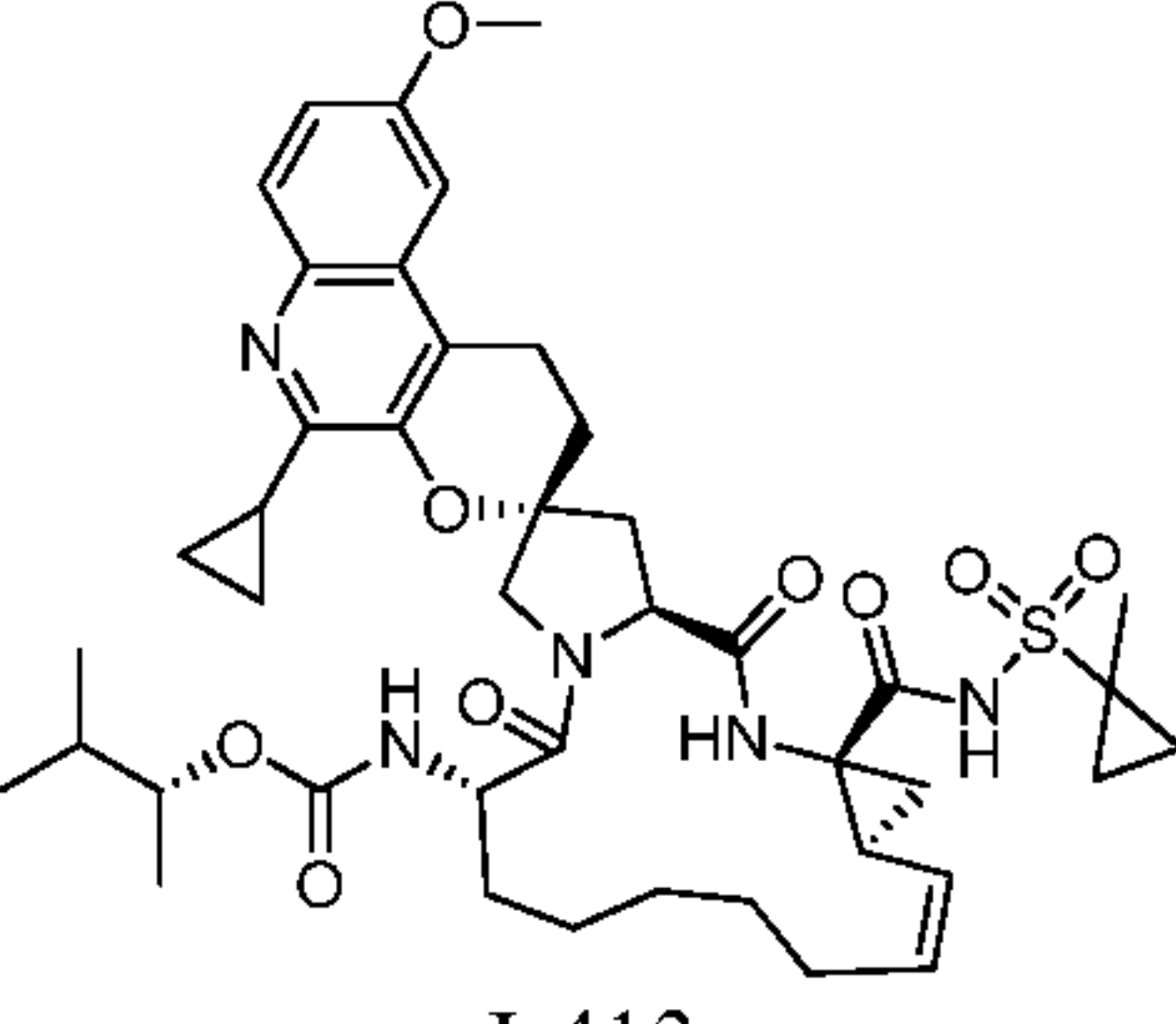
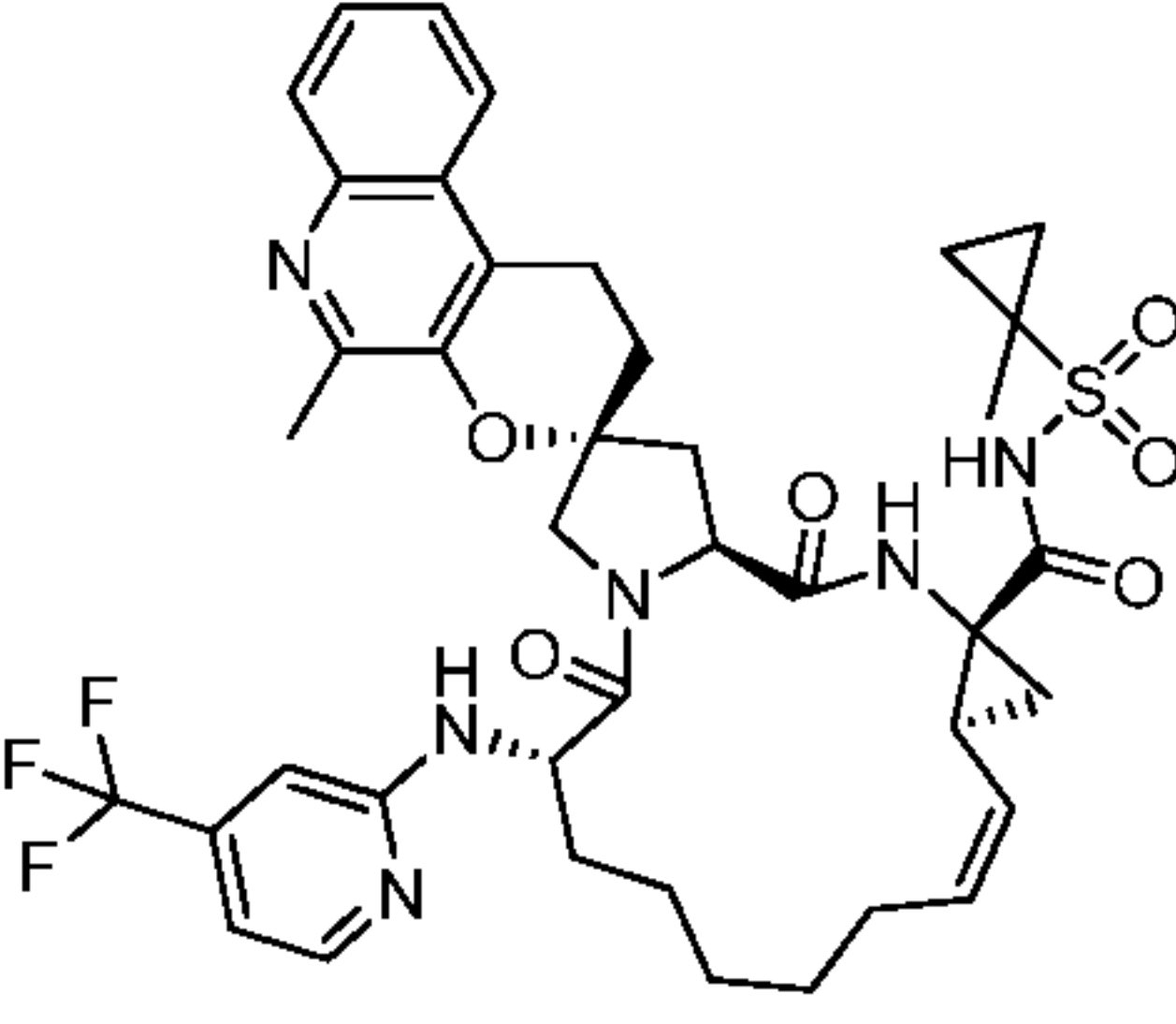
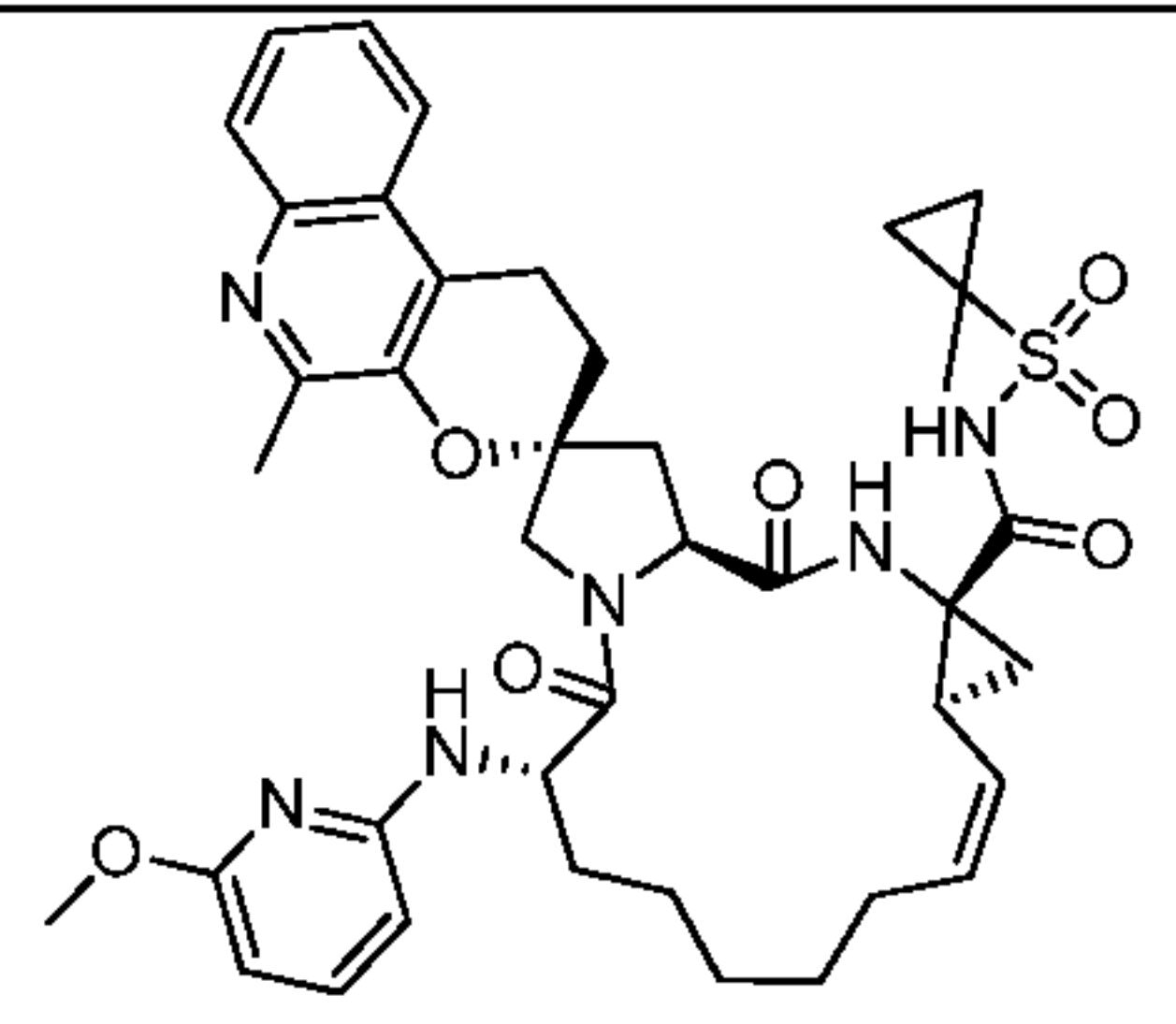
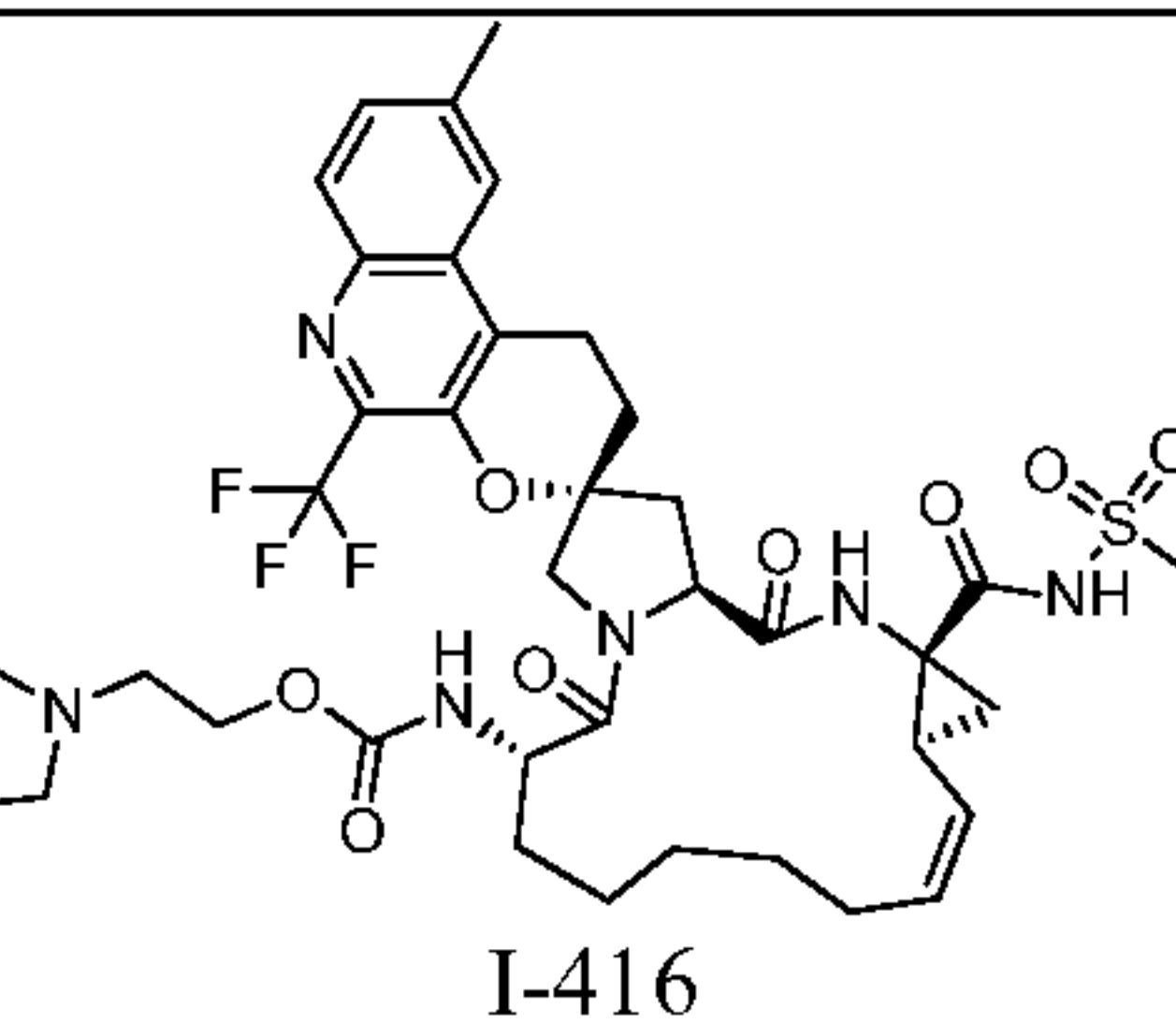
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
386	 I-386	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5	852
387	 I-387	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-chloro-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5	891.8
388	 I-388	2,2-dimethylpropyl [(1' <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-fluoro-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	32	840.2
389	 I-389	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	31	841.1
390	 I-390	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	31	818.2

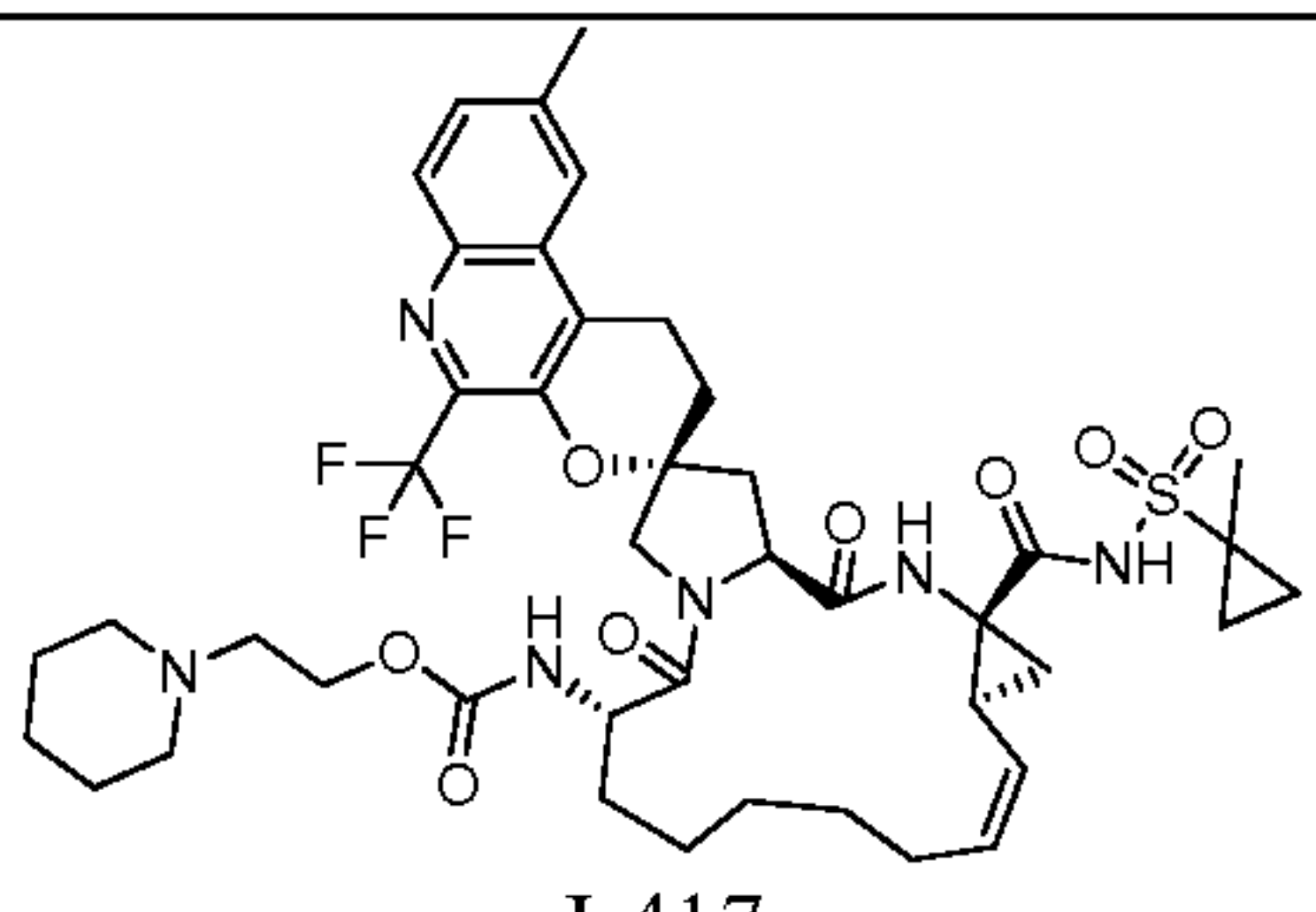
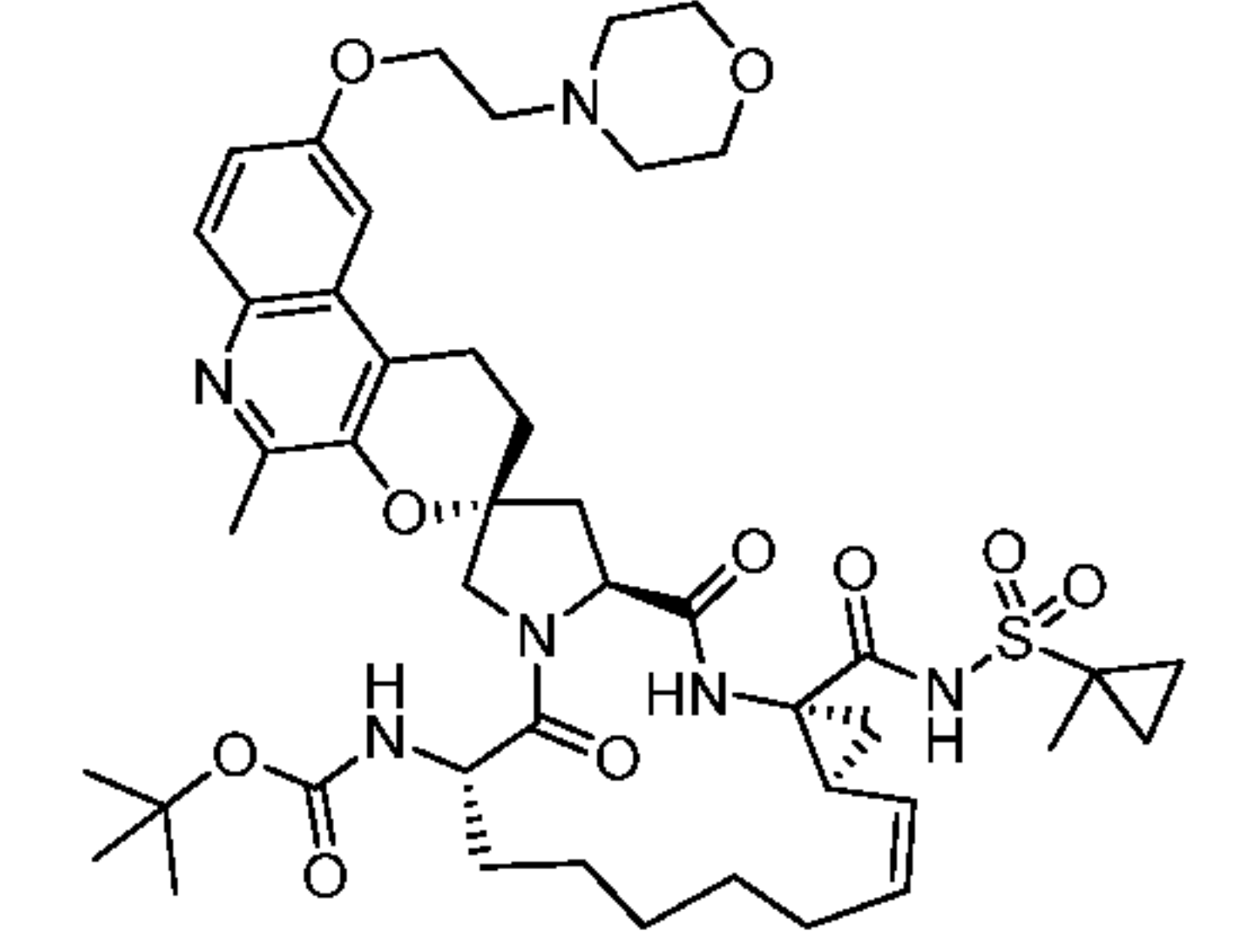
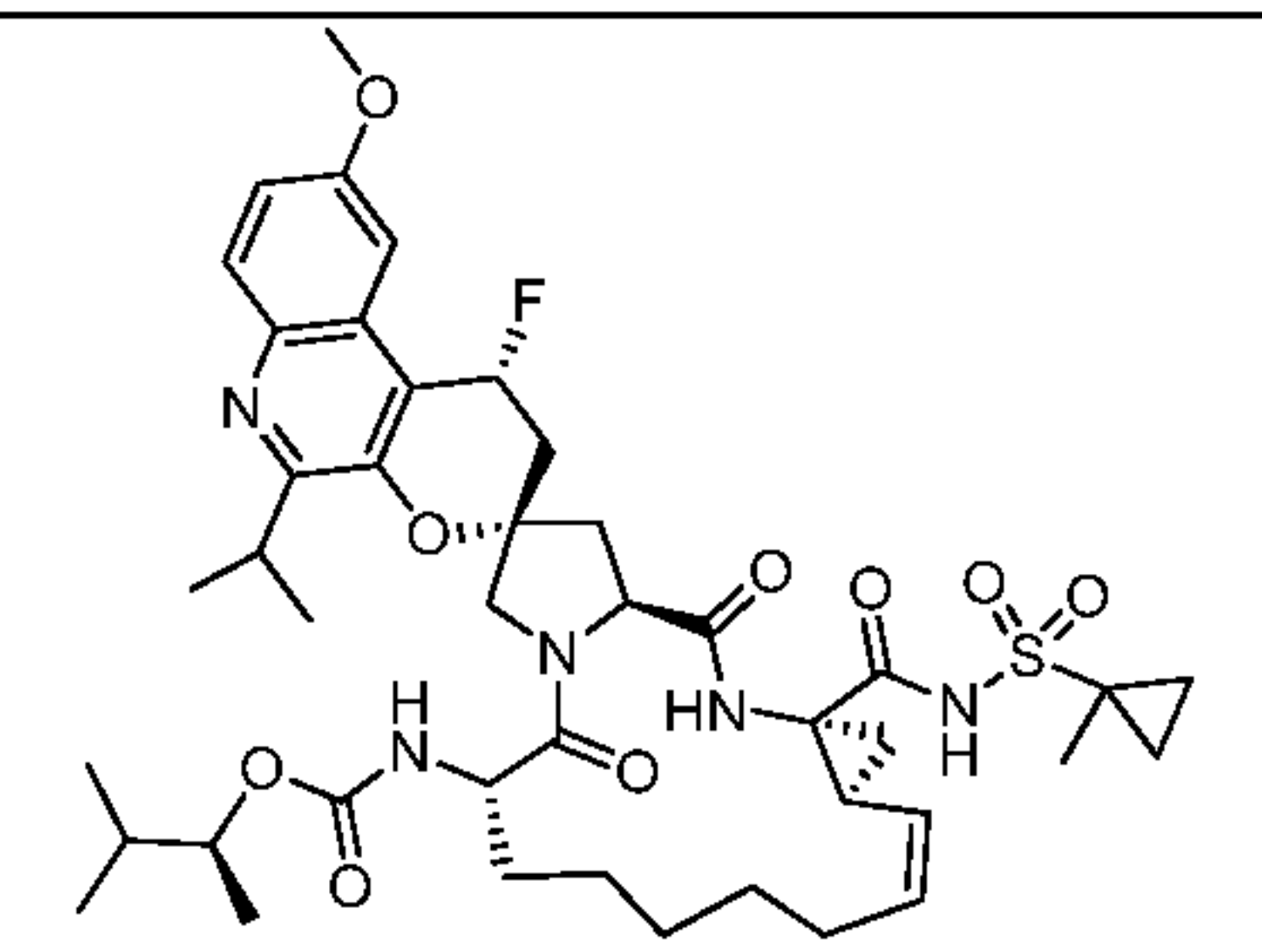
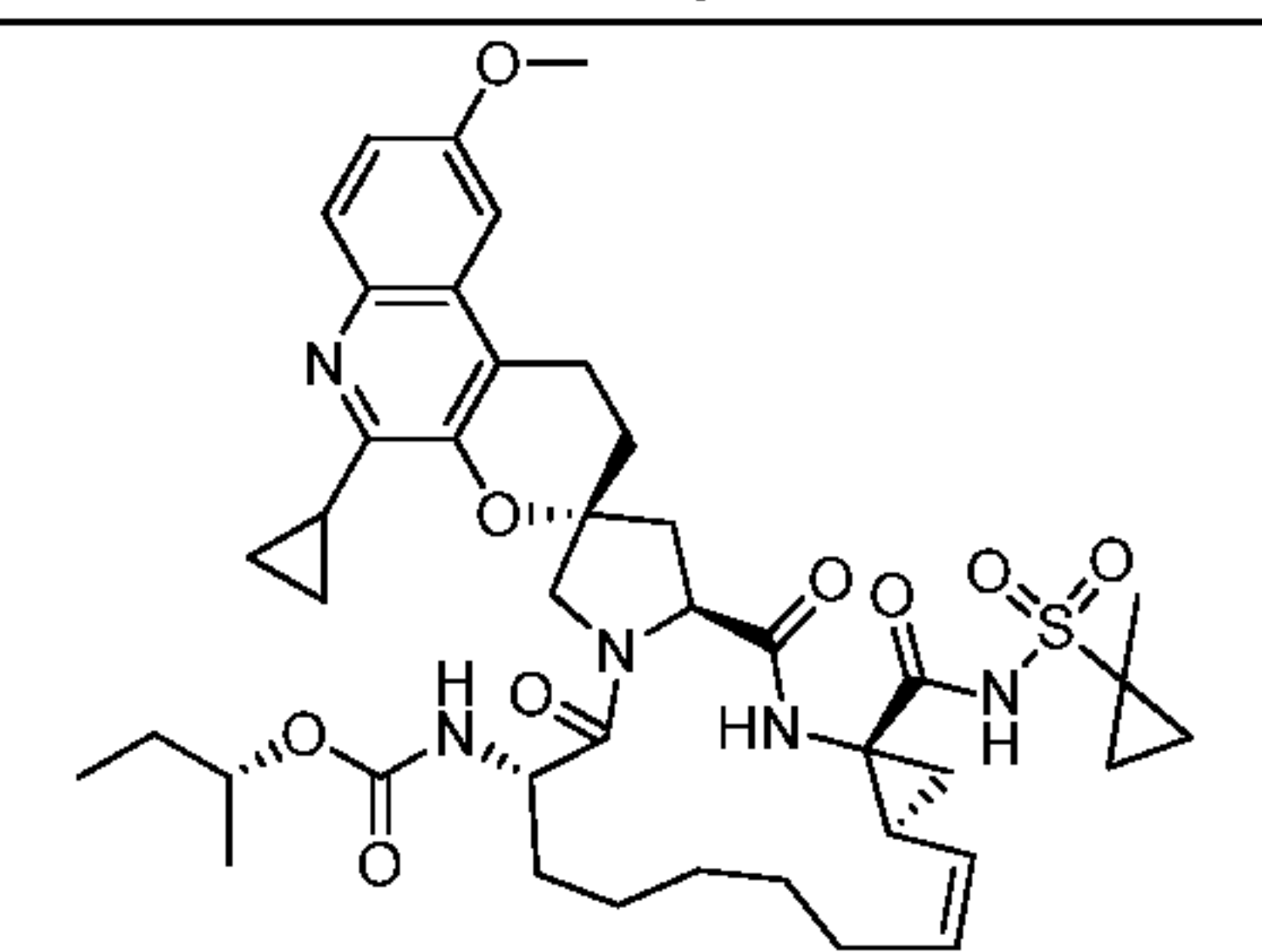
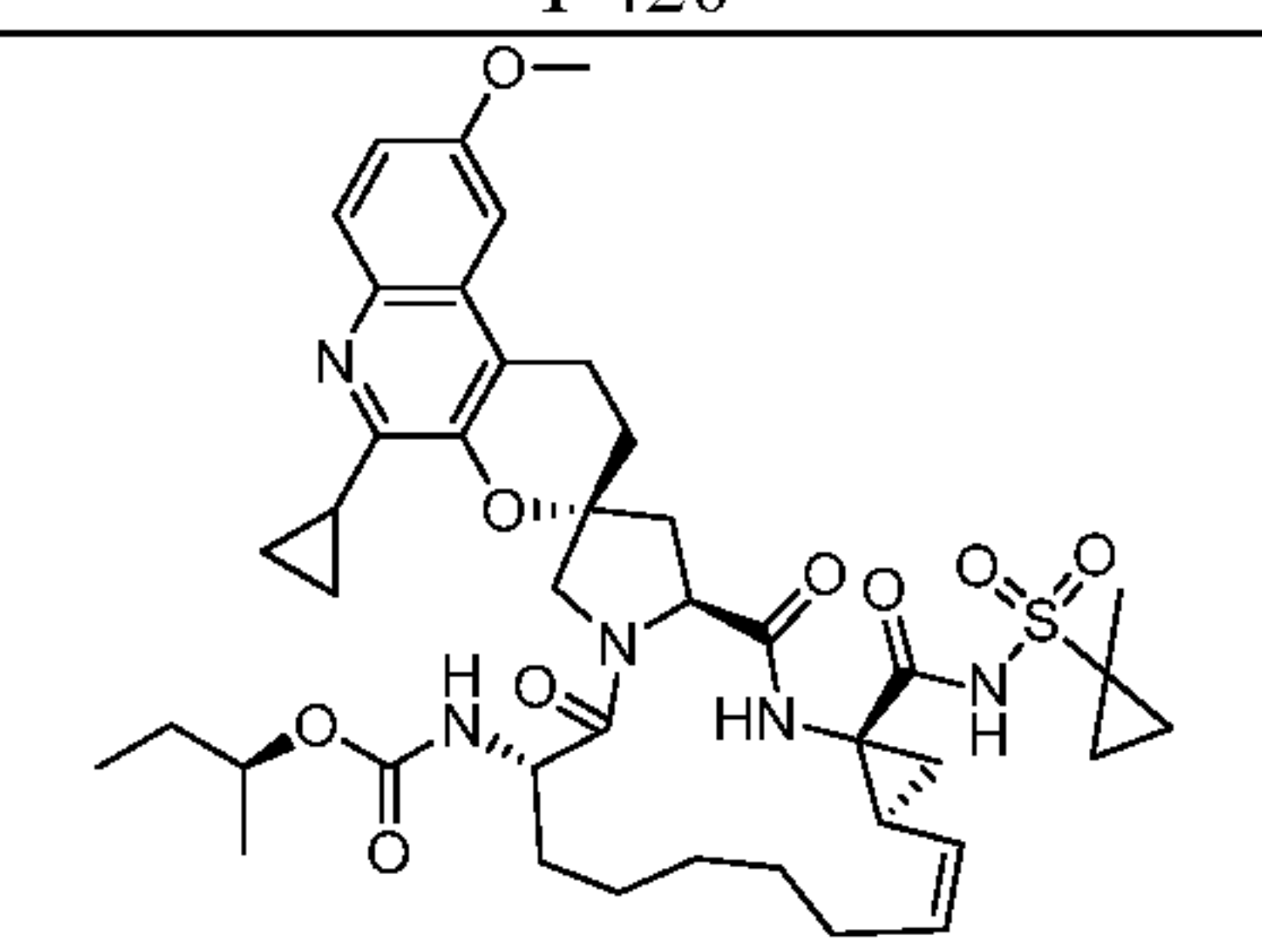
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
391	 I-391	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	31	832.2
392	 I-392	cyclopentyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	31	830.2
393	 I-393	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	31	872.1
394	 I-394	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)amino]-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	57	758
395	 I-395	(2 <i>R</i>)-3-methylbutan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	31	832.2
396	 I-396	(2 <i>S</i>)-3-methylbutan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	31	832.2

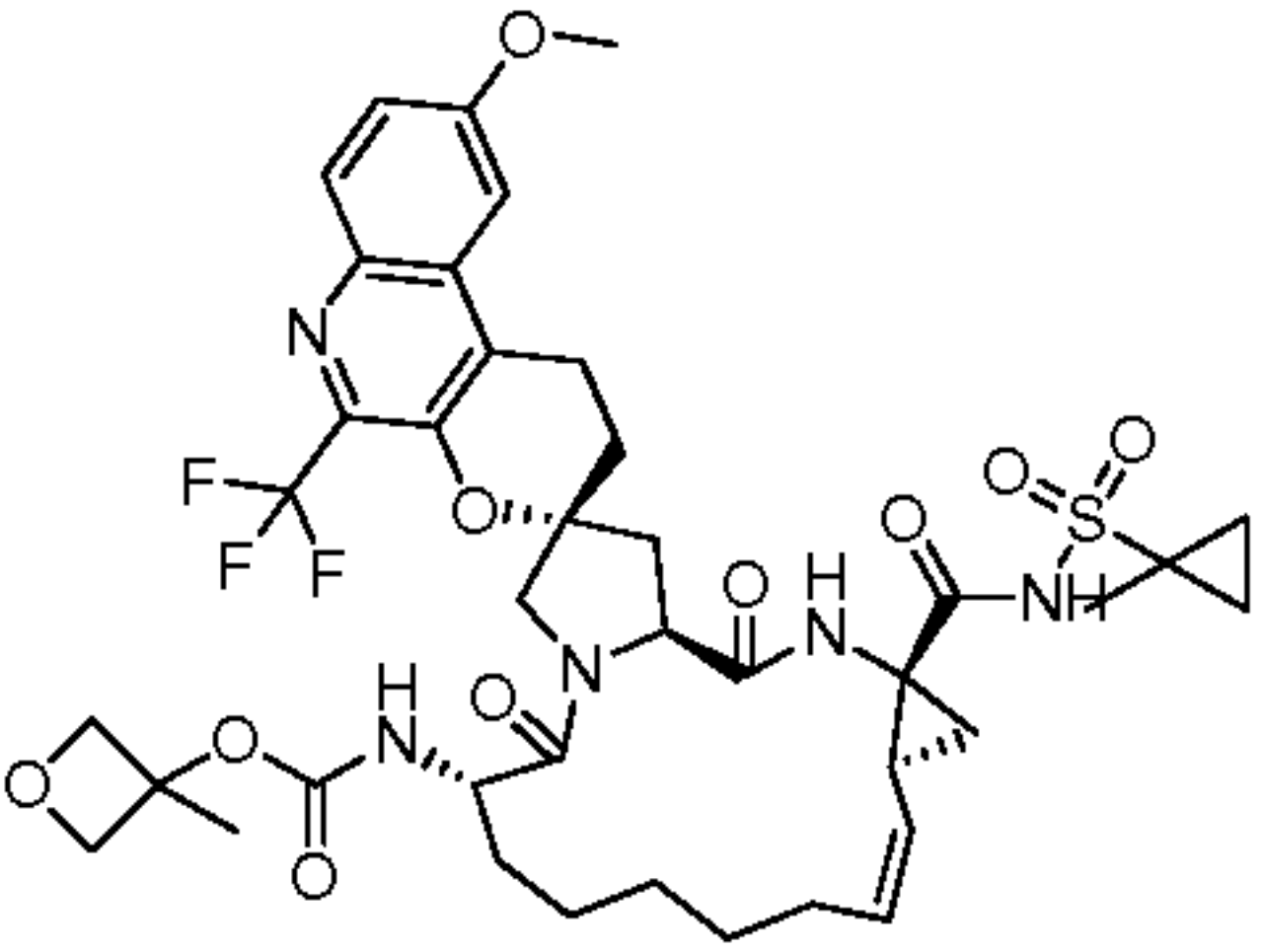
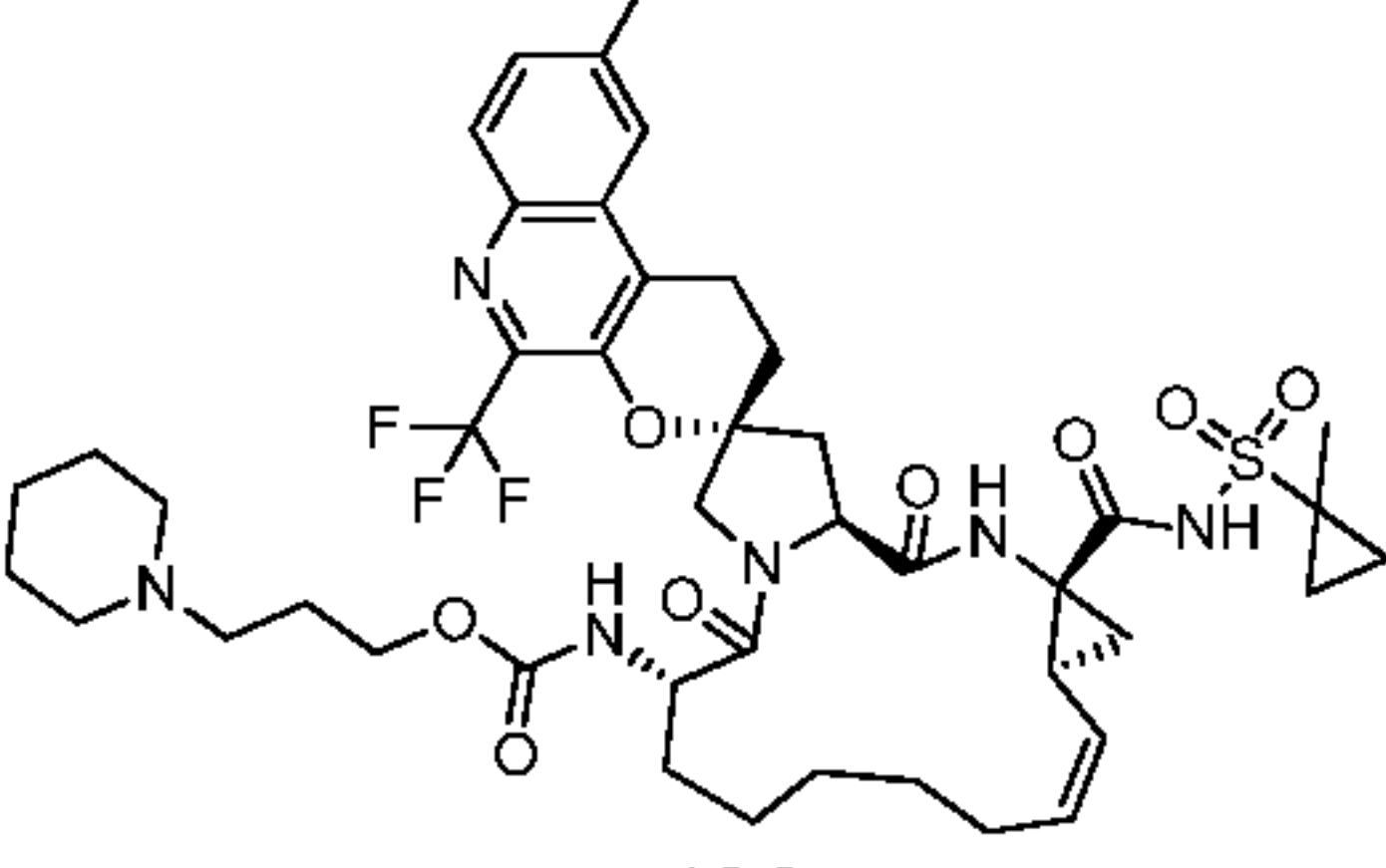
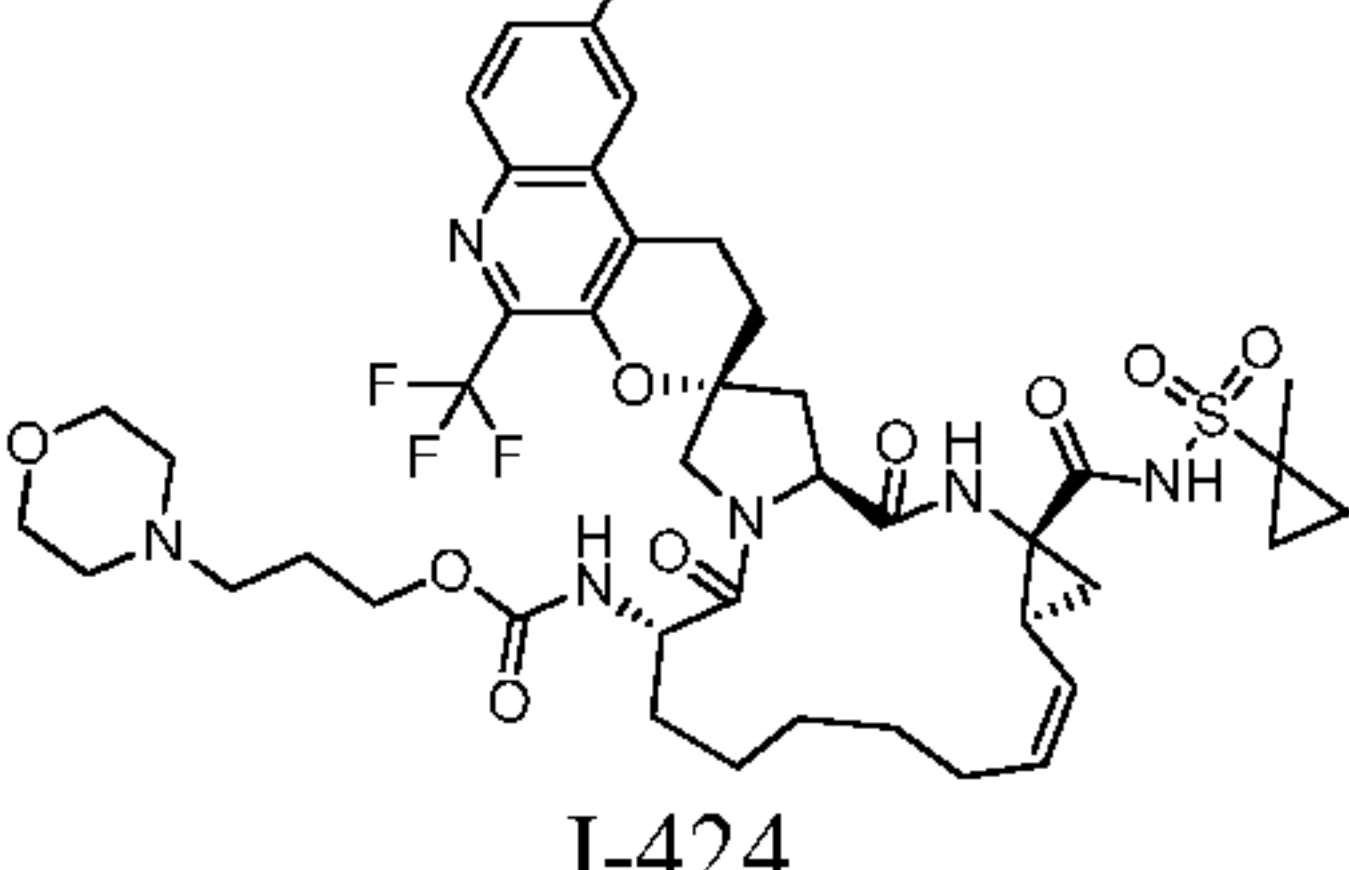
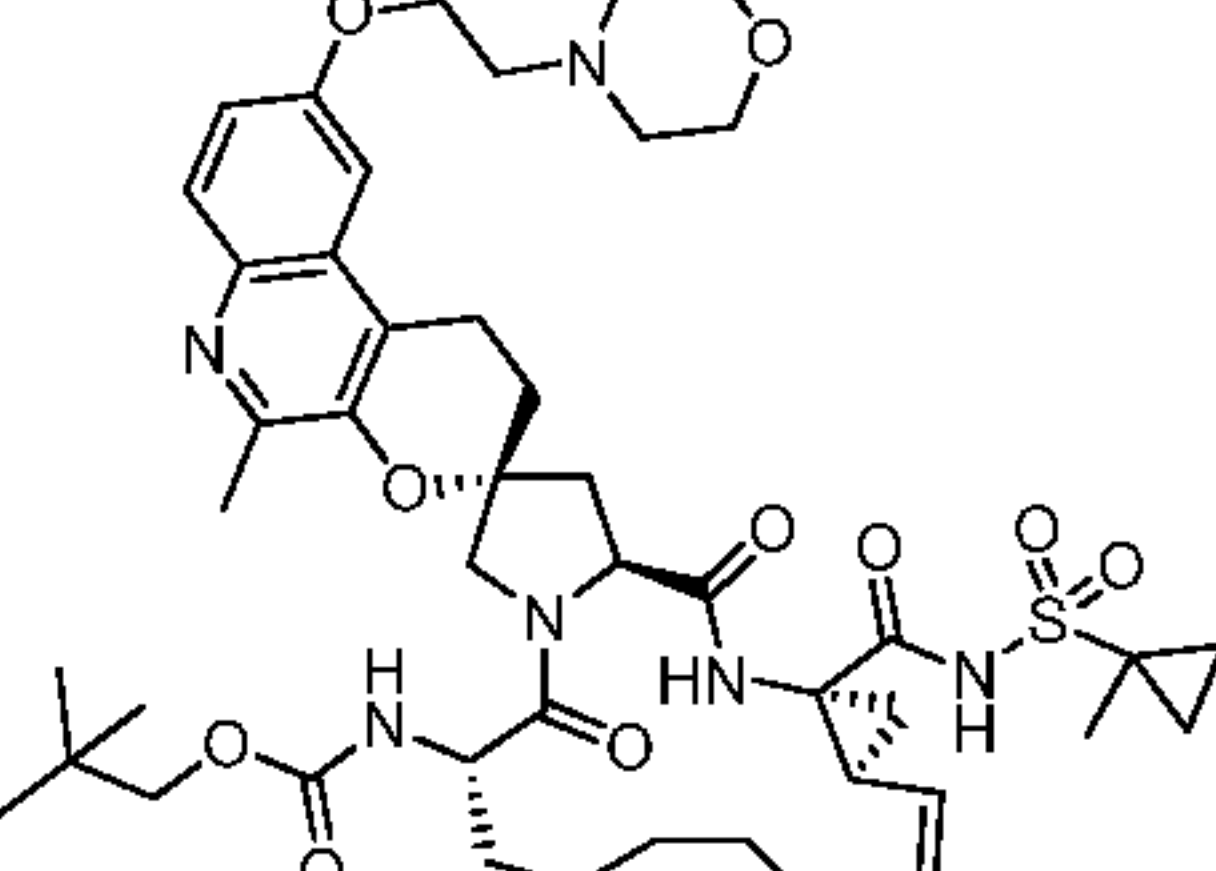
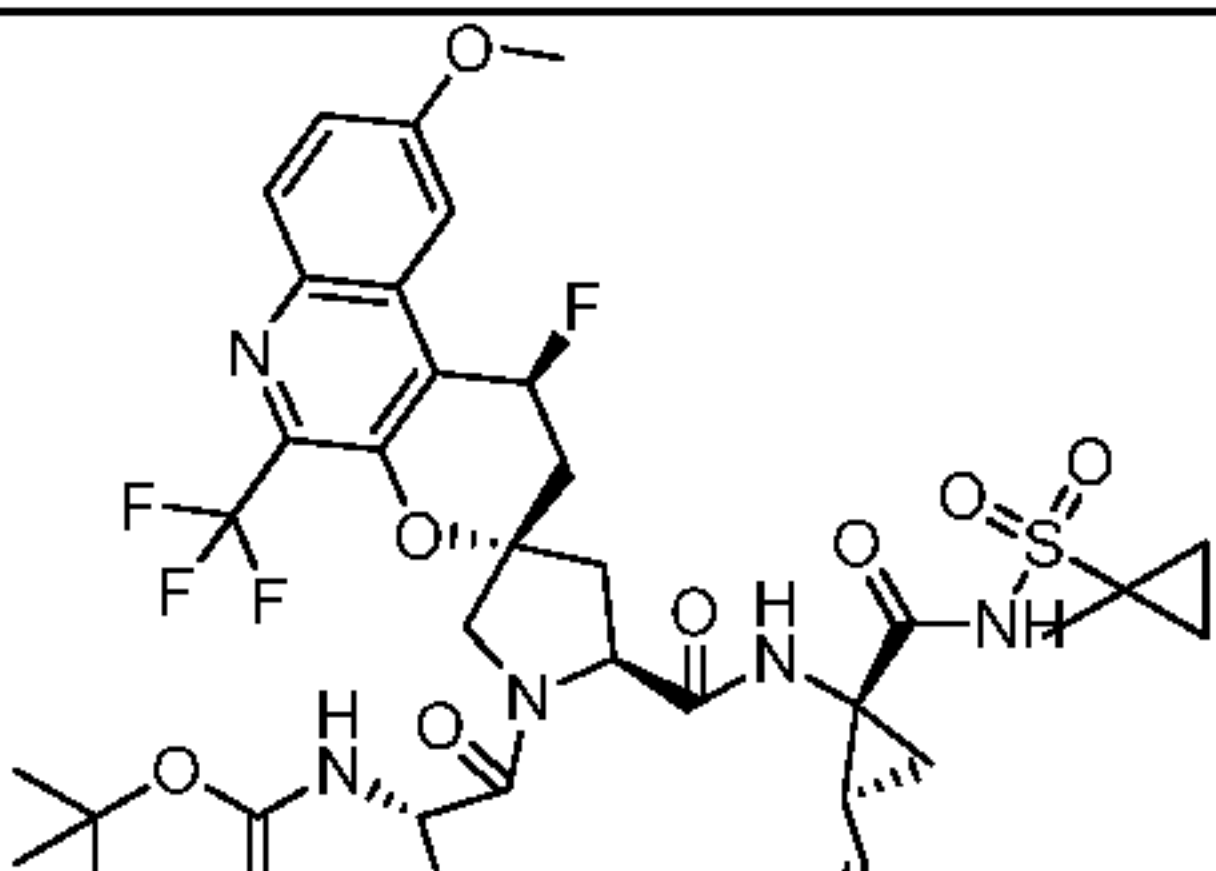
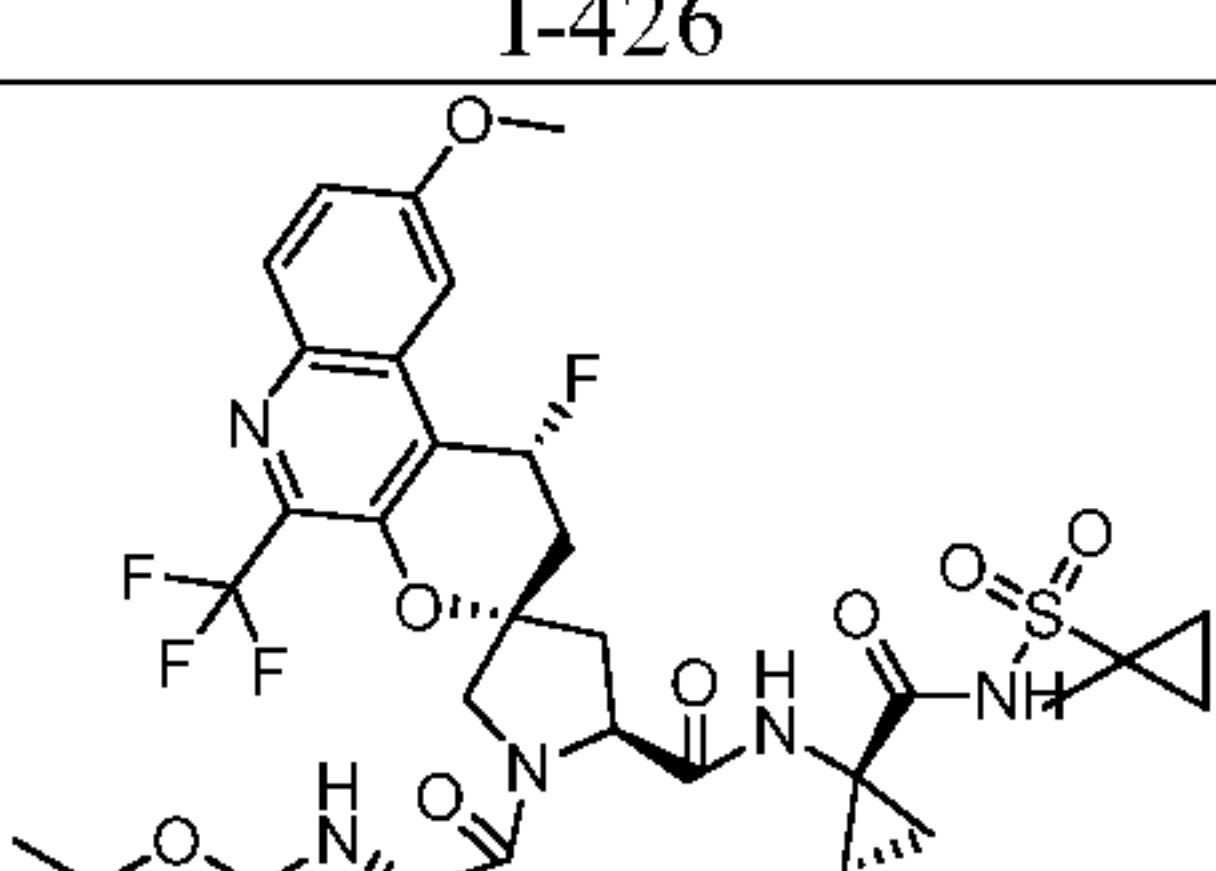
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
397	 I-397	<i>tert</i> -butyl [(1' <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-fluoro-9'-{[fluoro(² H ₂)methyl]oxy}-5'-methyl-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	58, 7, 50, 32	818.2
398	 I-398	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-7'-chloro-9'-methoxy-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	6	812
399	 I-399	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-7'-chloro-9'-methoxy-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	6	868
400	 I-400	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-7'-chloro-9'-methoxy-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	6	922
401	 I-401	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-7'-chloro-9'-methoxy-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	6	882

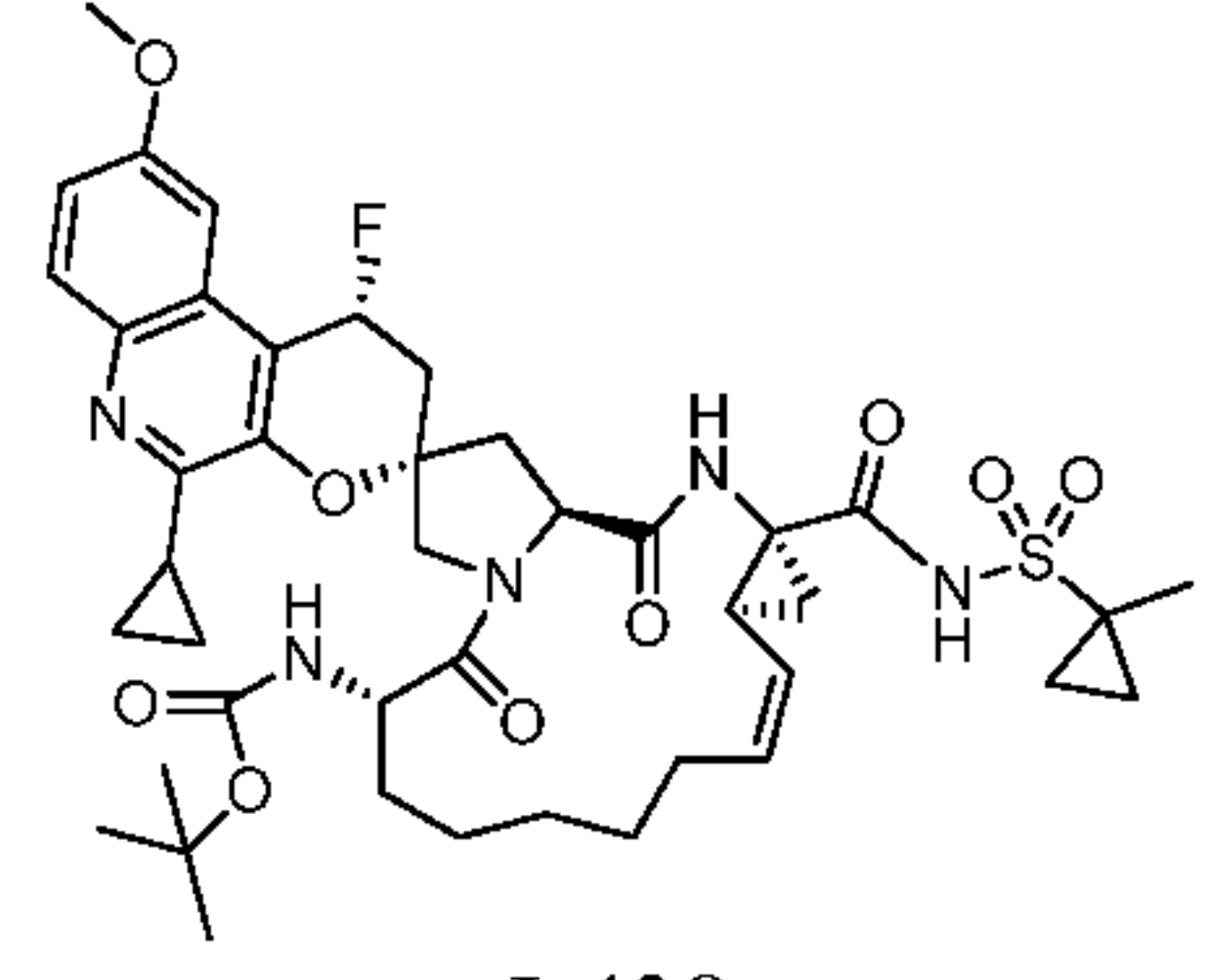
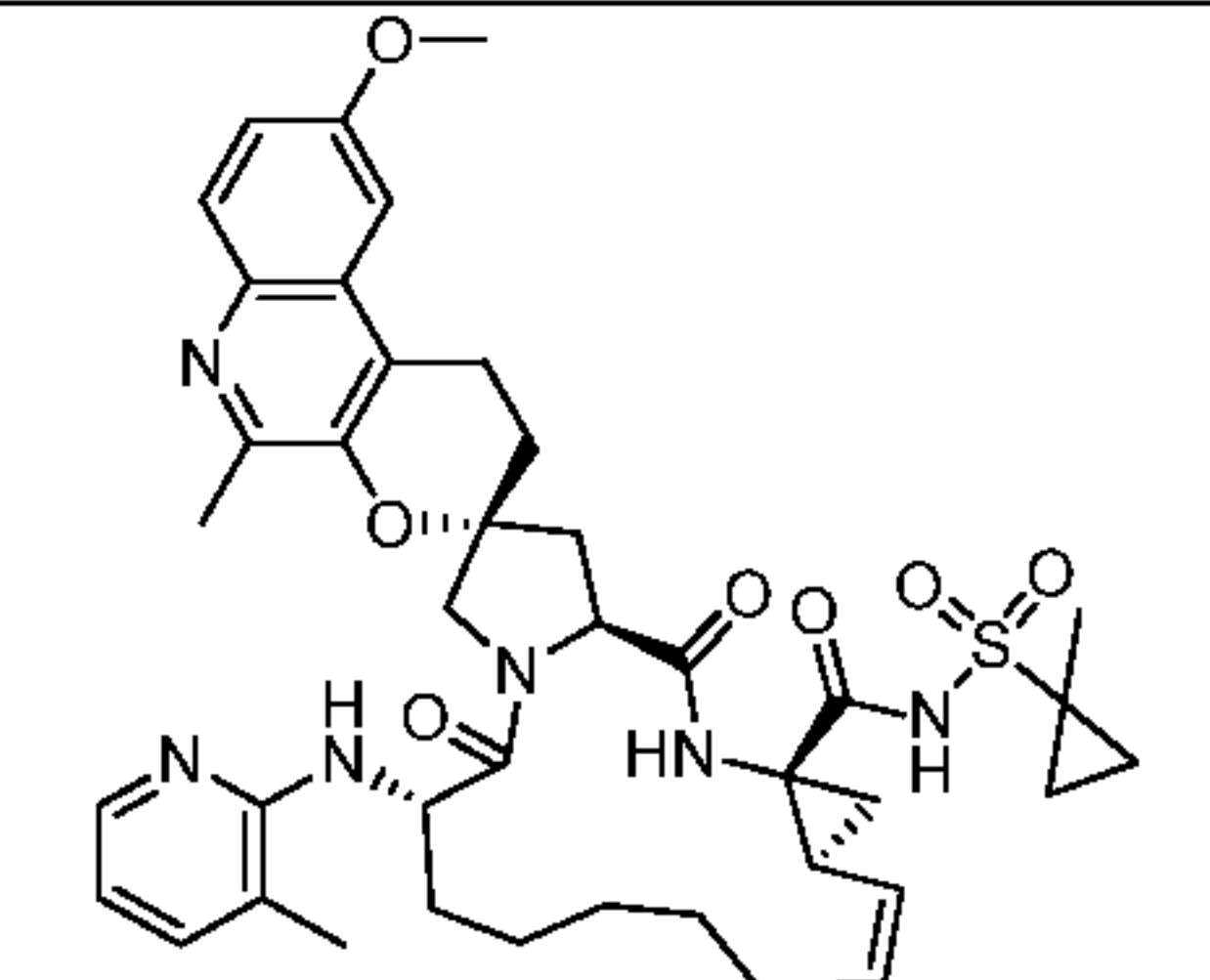
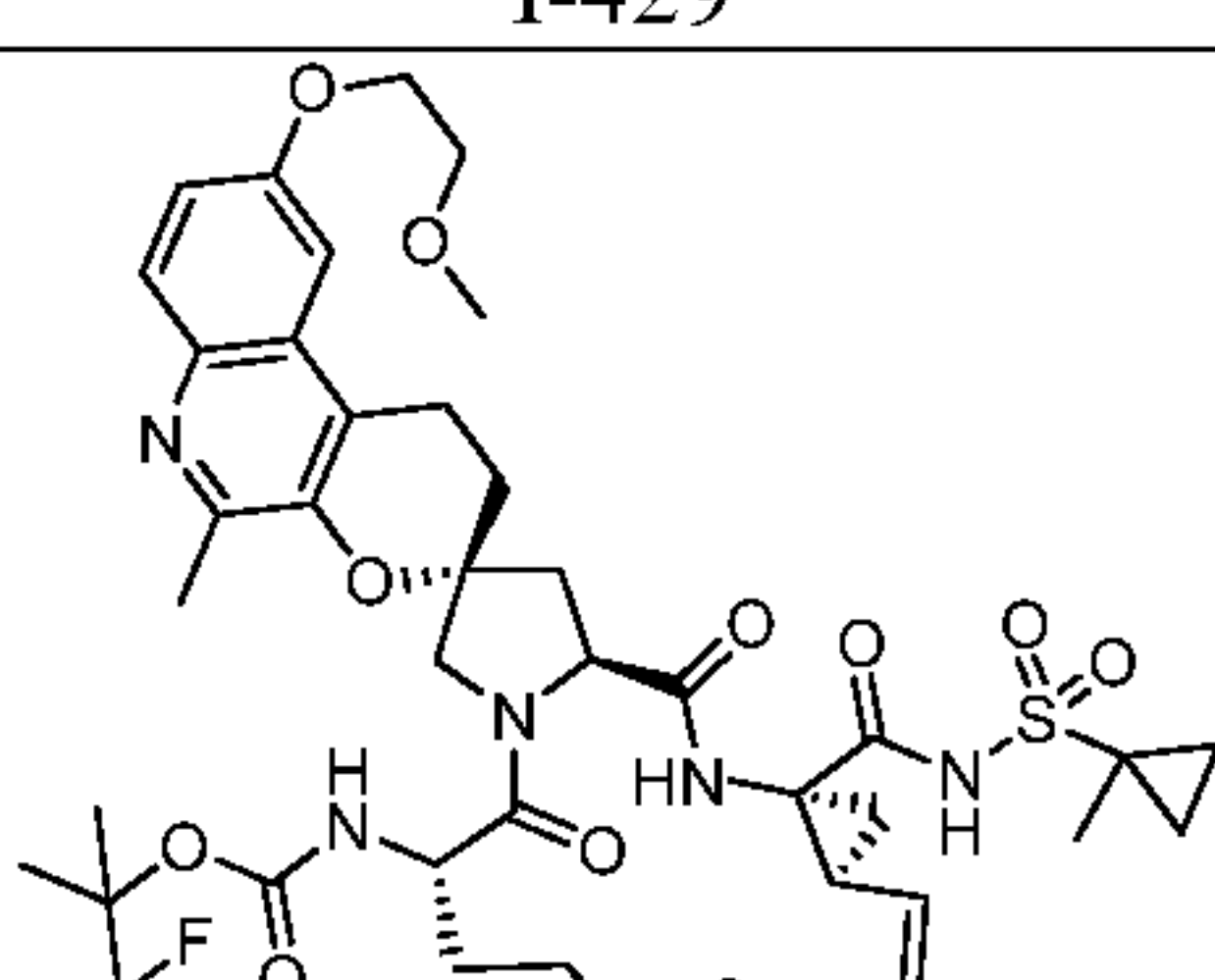
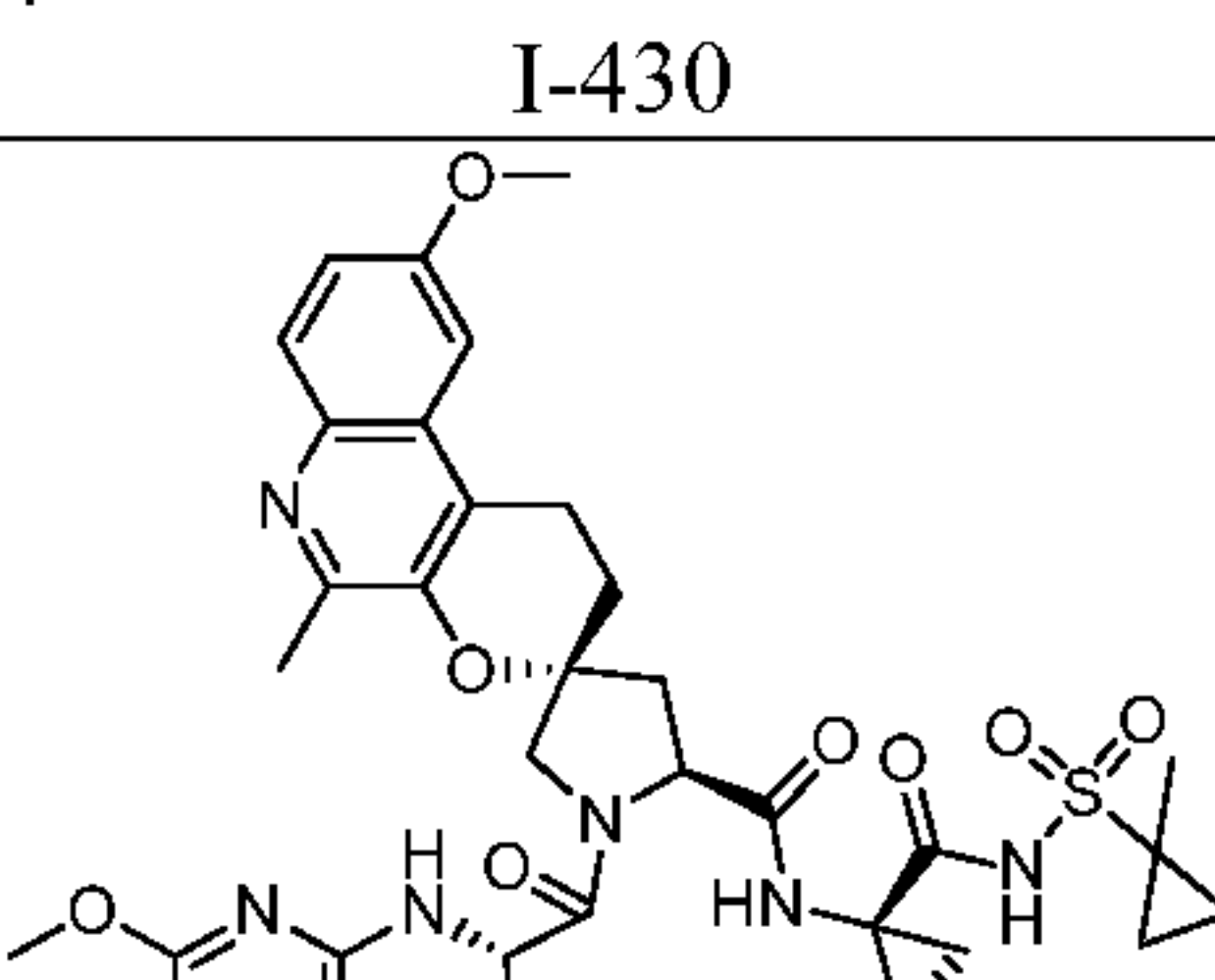
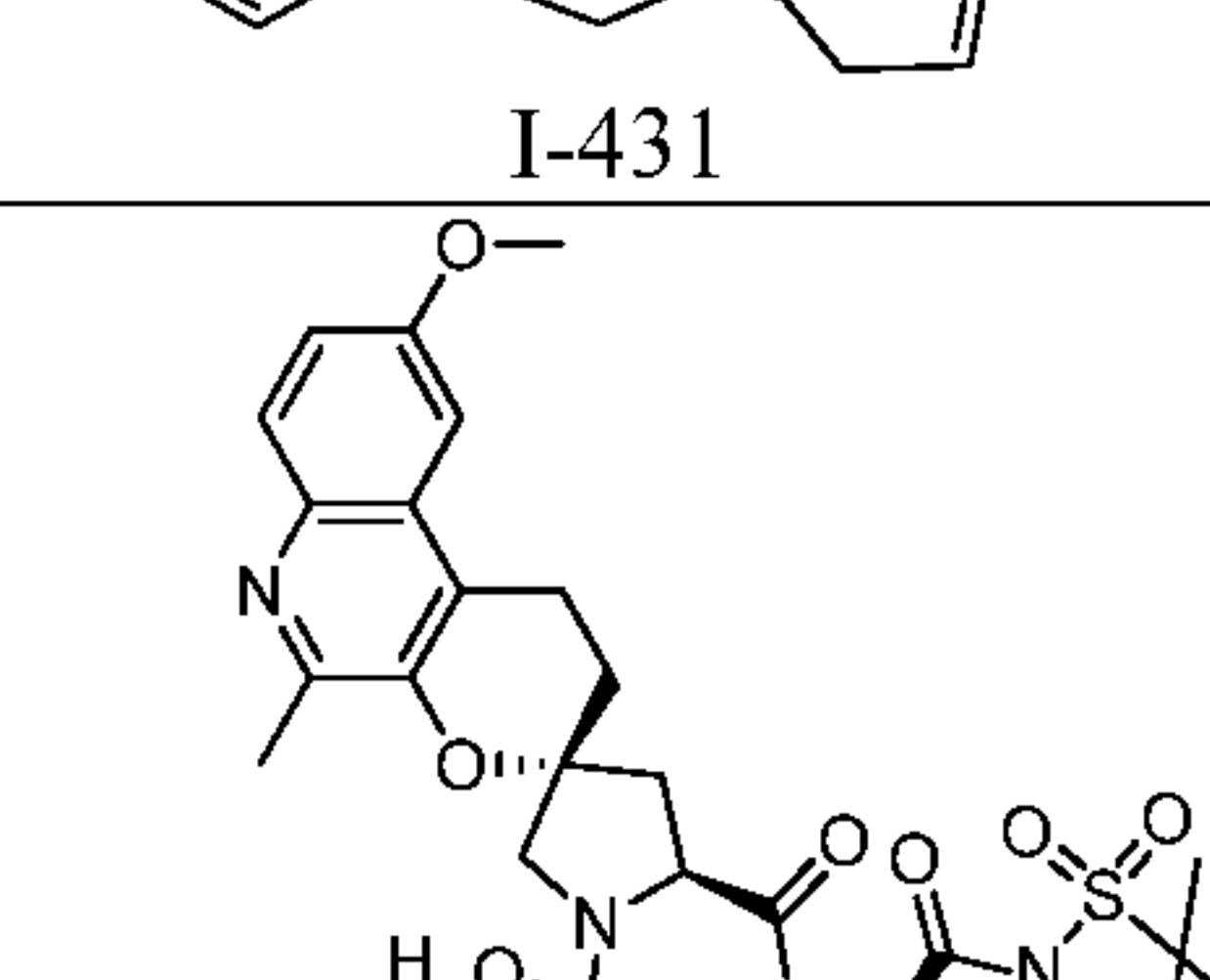
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
402	 I-402	2-methylpropyl [(1 <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-fluoro-9'-{[fluoro(² H ₂)methyl]oxy}-5'-methyl-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	56, 7, 50, 32	818.2 (K+ salt)
403	 I-403	2,2-dimethylpropyl [(1 <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-fluoro-9'-{[fluoro(² H ₂)methyl]oxy}-5'-methyl-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	58, 7, 50, 32	832.2 (K+ salt)
404	 I-404	3,3-dimethylbutan-2-yl [(1 <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-fluoro-9'-methoxy-5'-methyl-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	58, 7	826.2
405	 I-405	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-fluoro-5'-methyl-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	822.0
406	 I-406	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-fluoro-5'-methyl-14a-[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	43	782.0

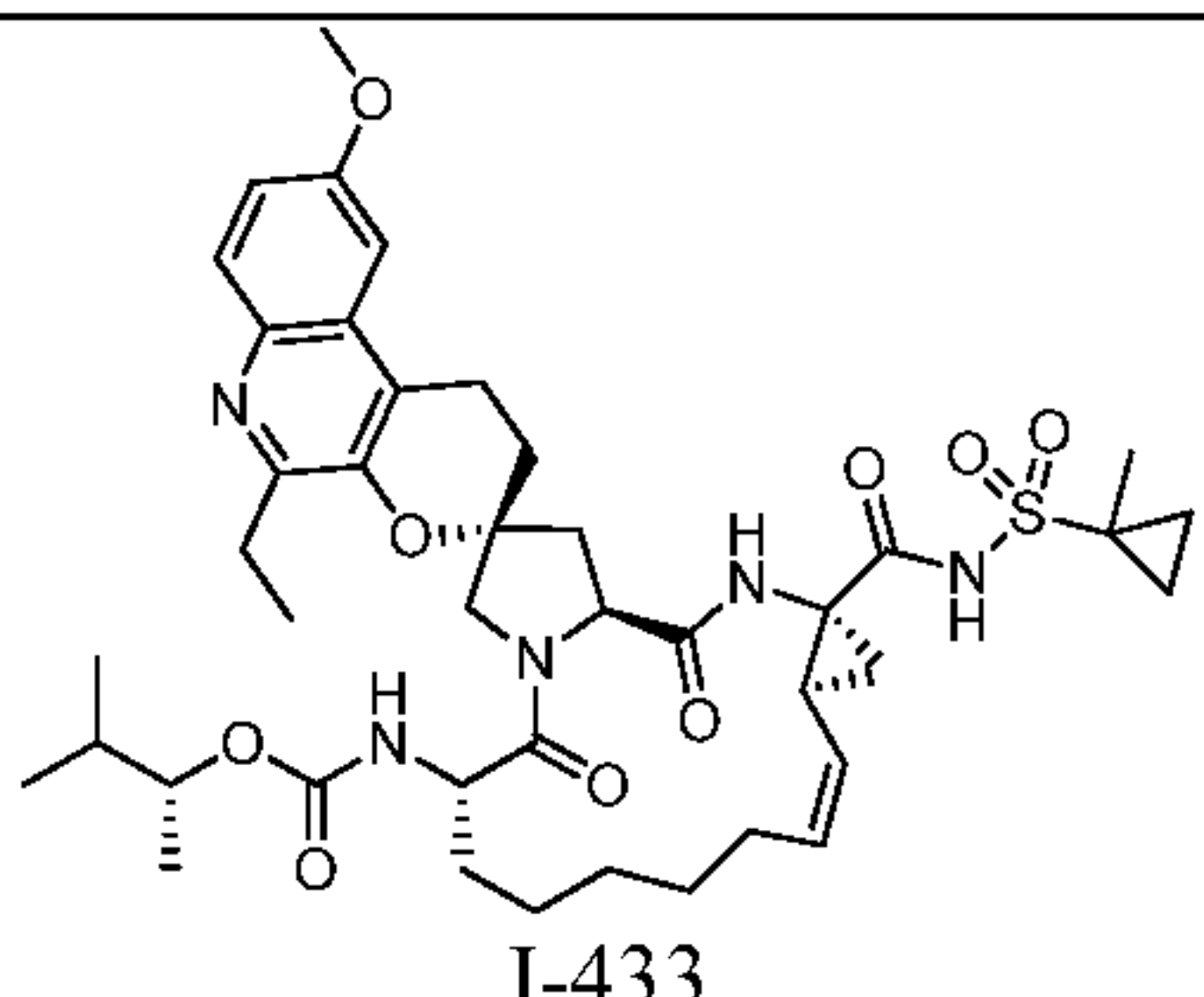
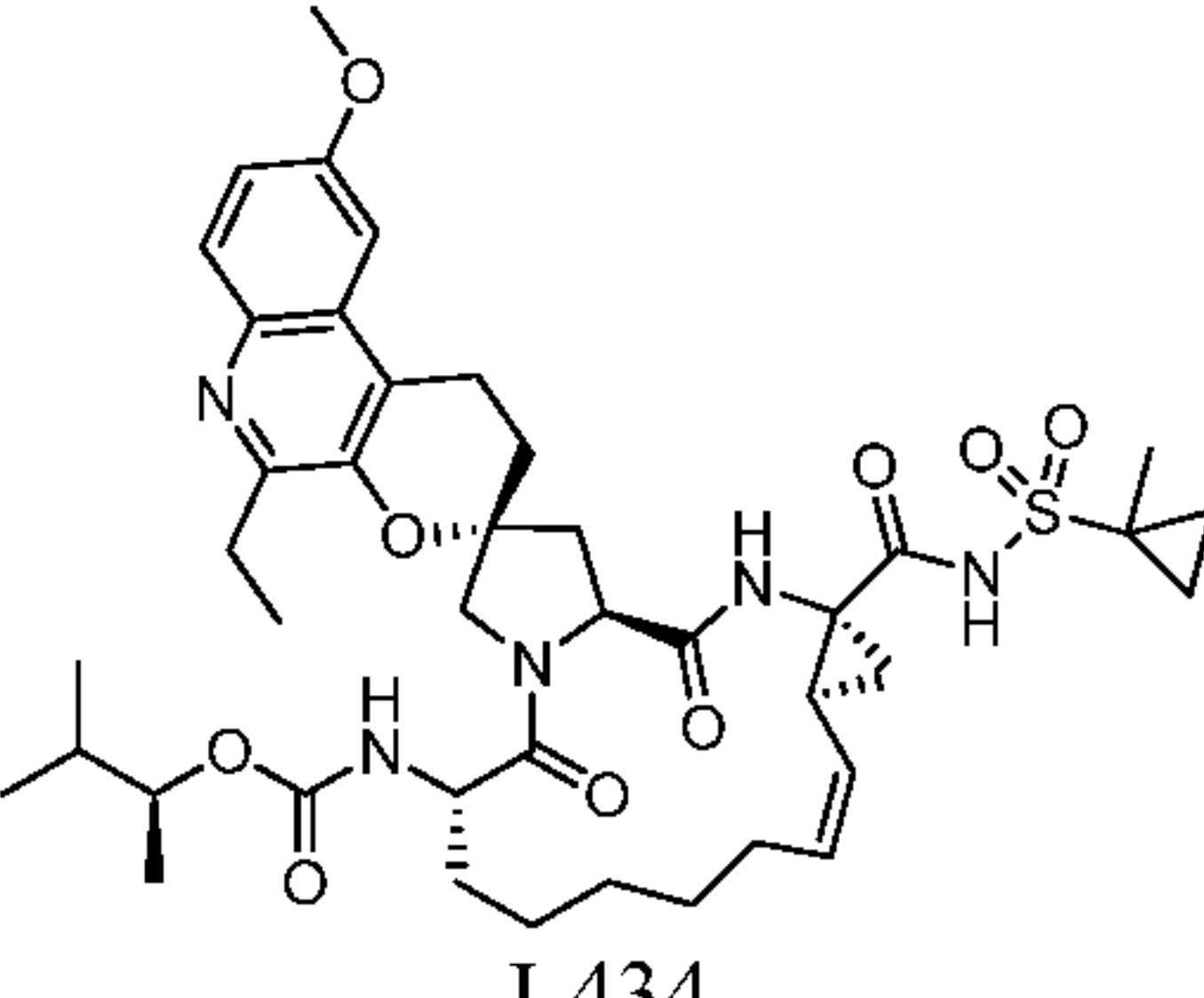
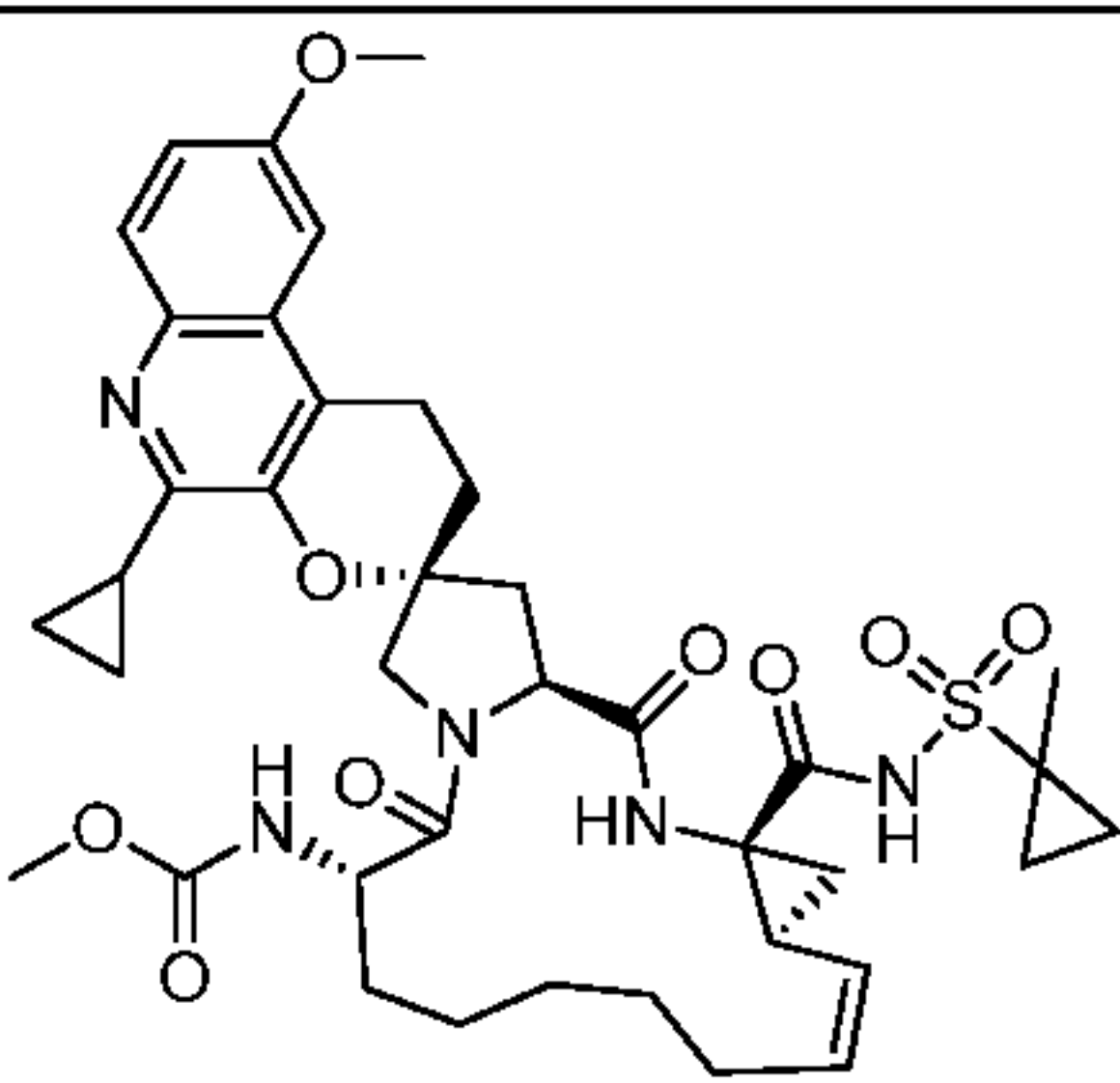
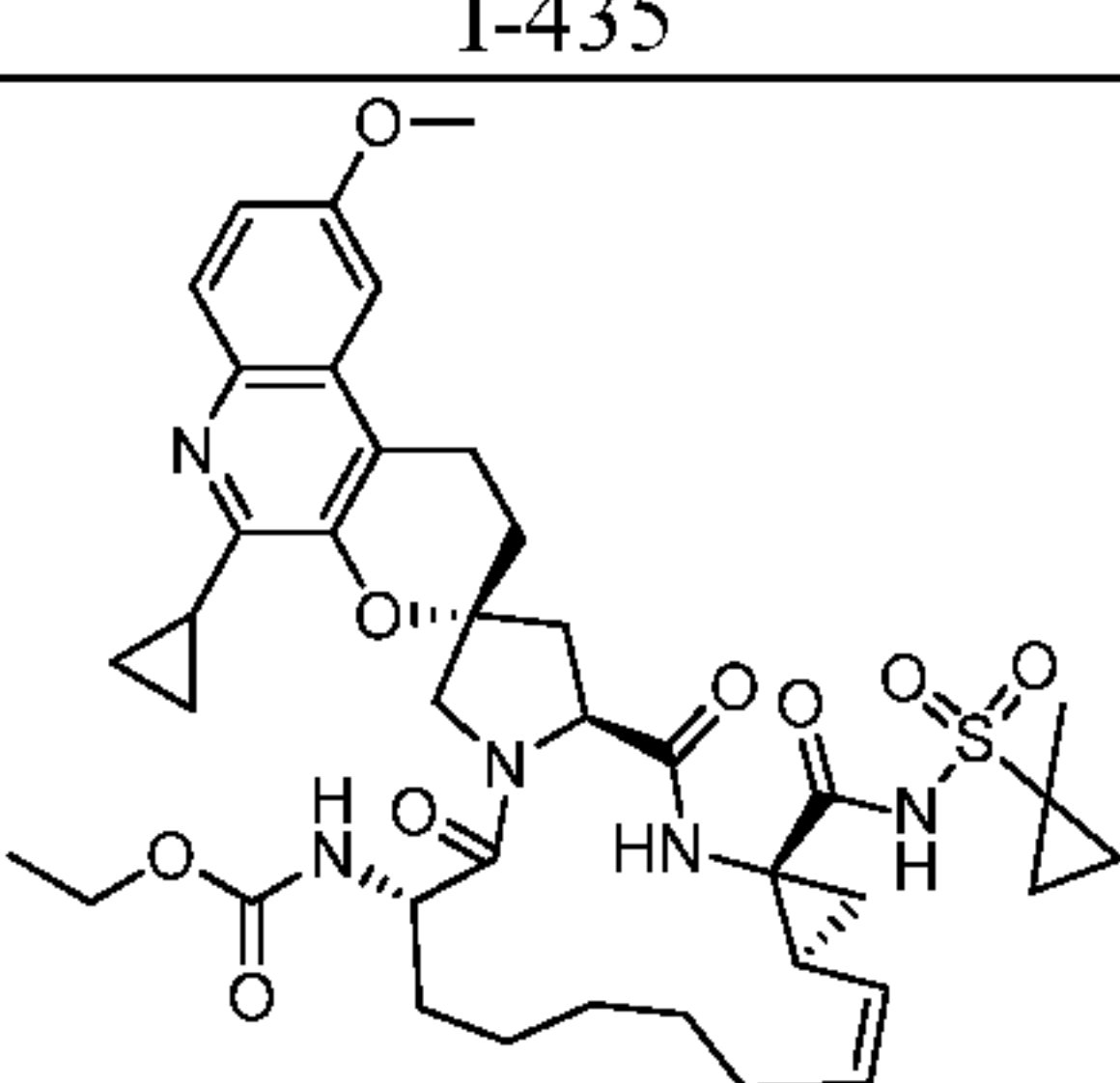
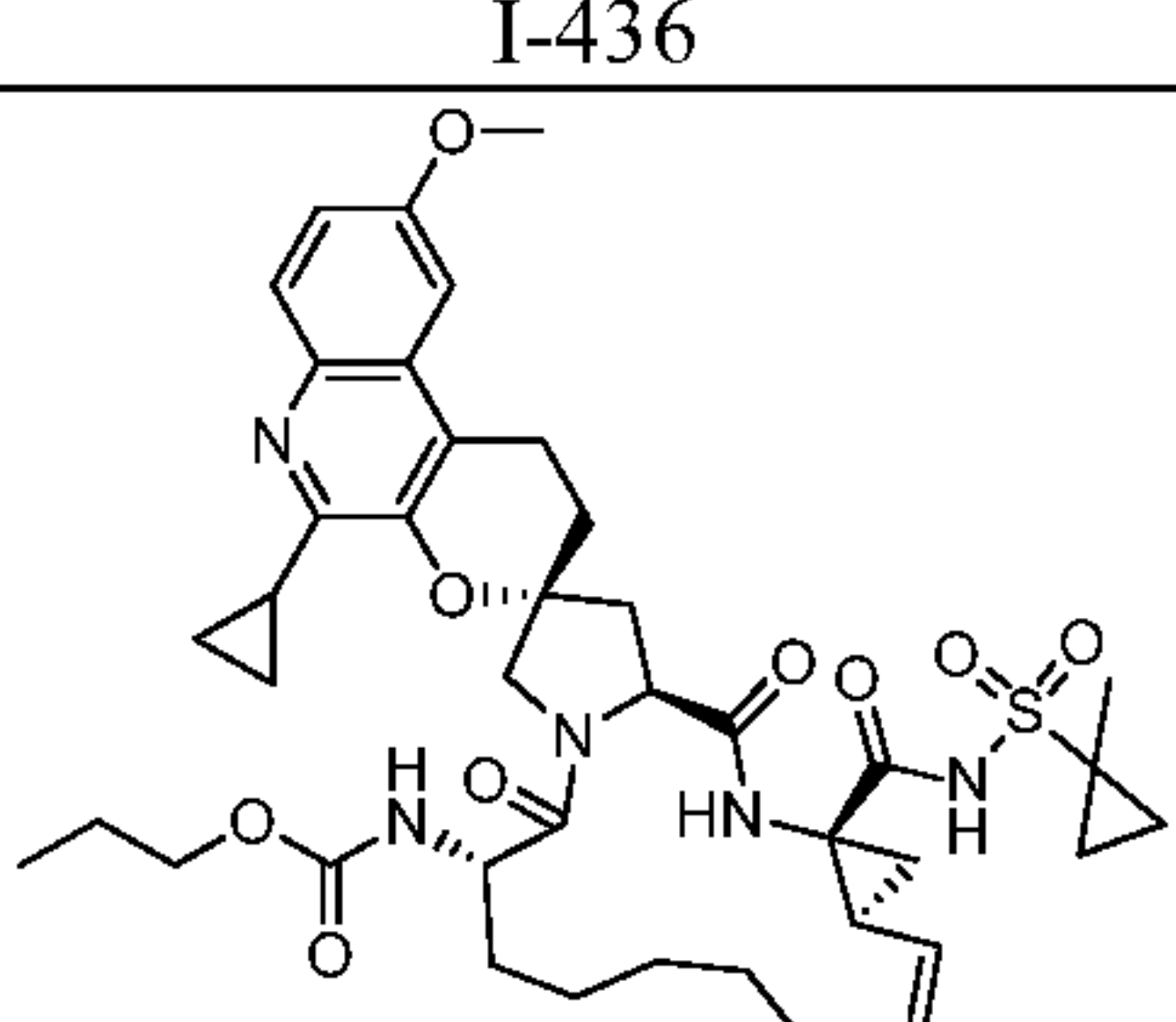
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
407	 I-407	1,1,1-trifluoro-3-methylbutan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	848 (K+ salt)
408	 I-408	1,1,1-trifluoro-3-methylbutan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	9	848 (K+ salt)
409	 I-409	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-(2-methoxyethoxy)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 7, 50, 51	824.2
410	 I-410	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-(2-methoxyethoxy)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 7, 50, 51, 6	838.2
411	 I-411	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-(2-methoxyethoxy)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 7, 50, 51, 6	824.2

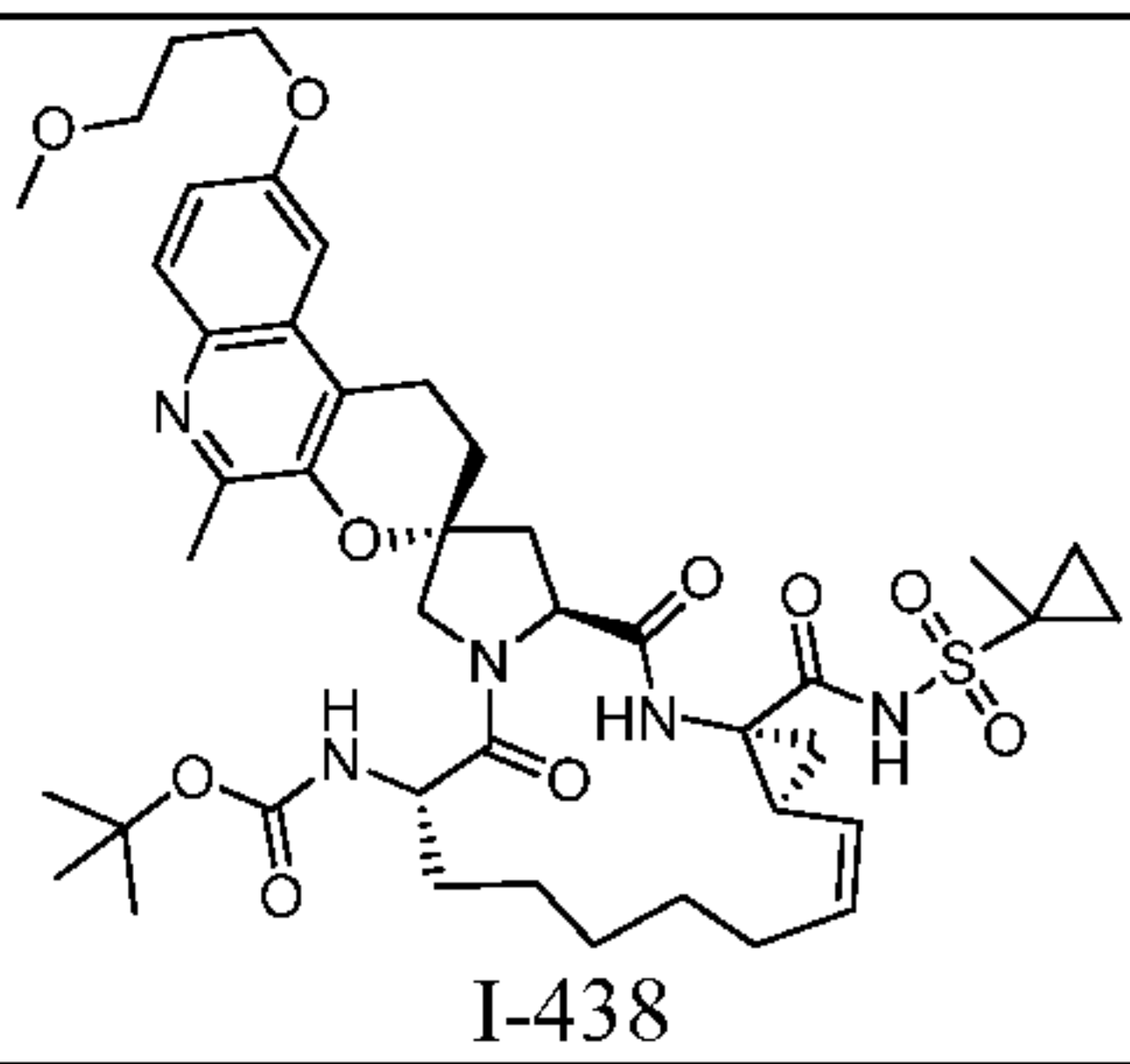
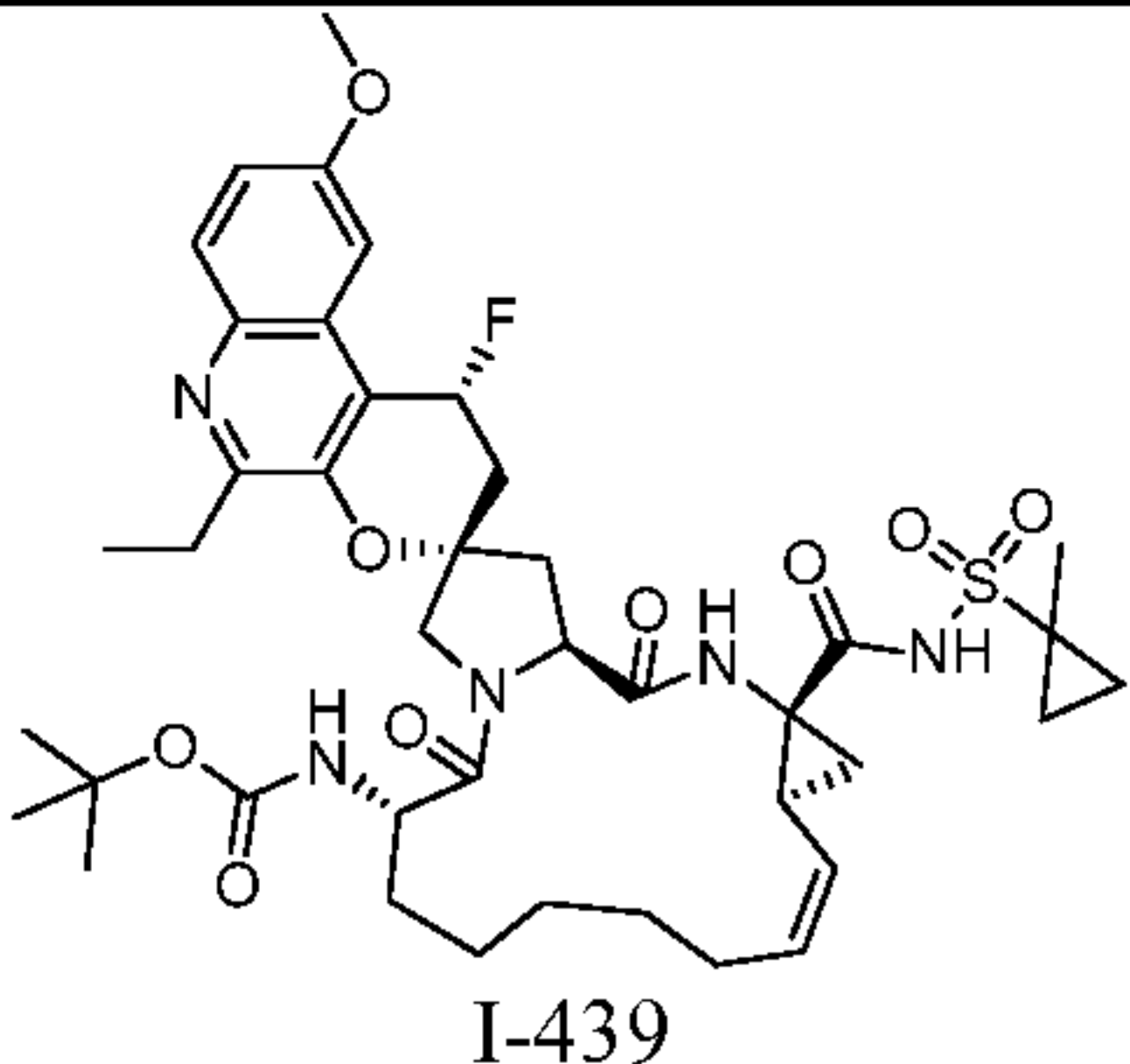
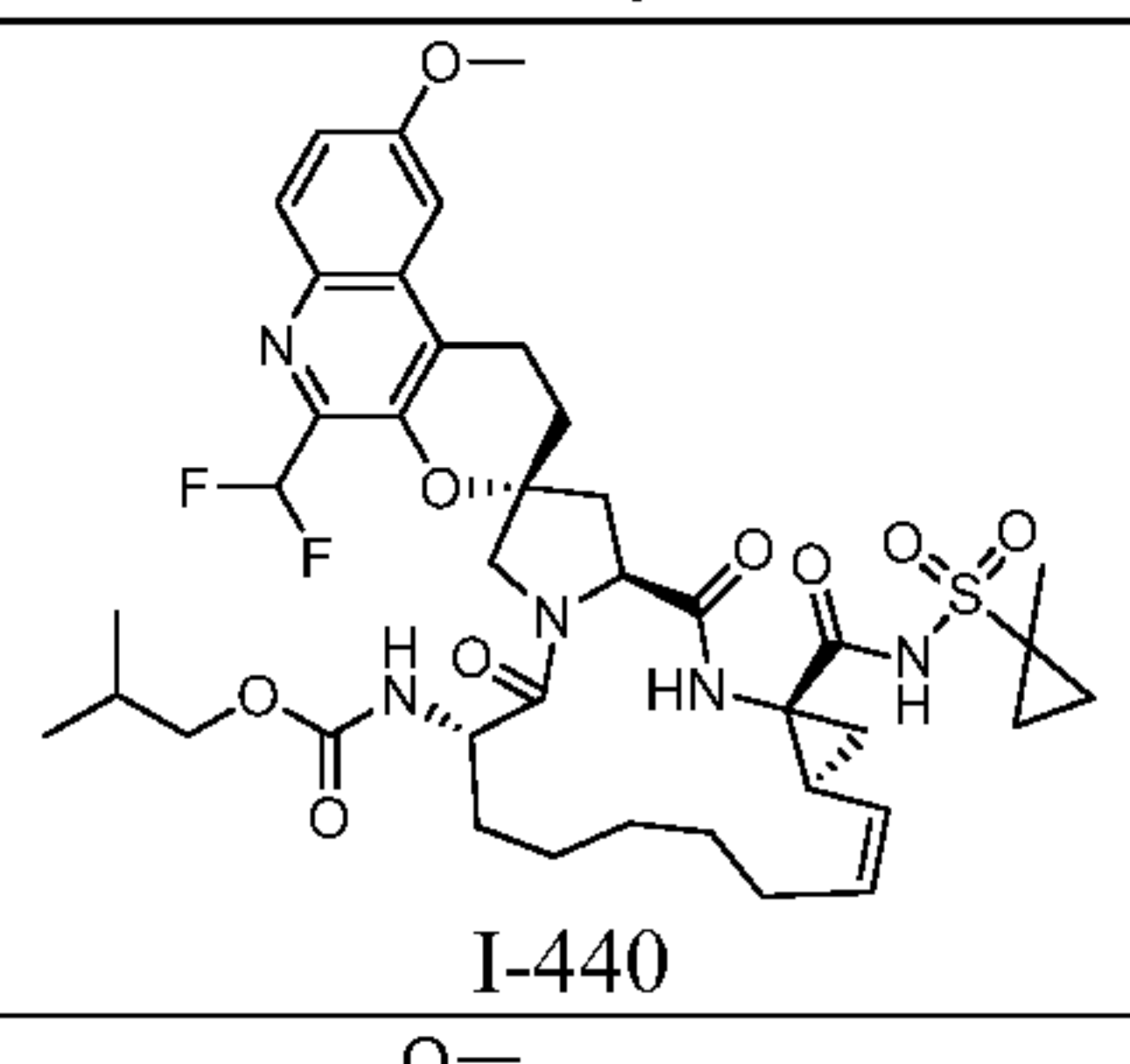
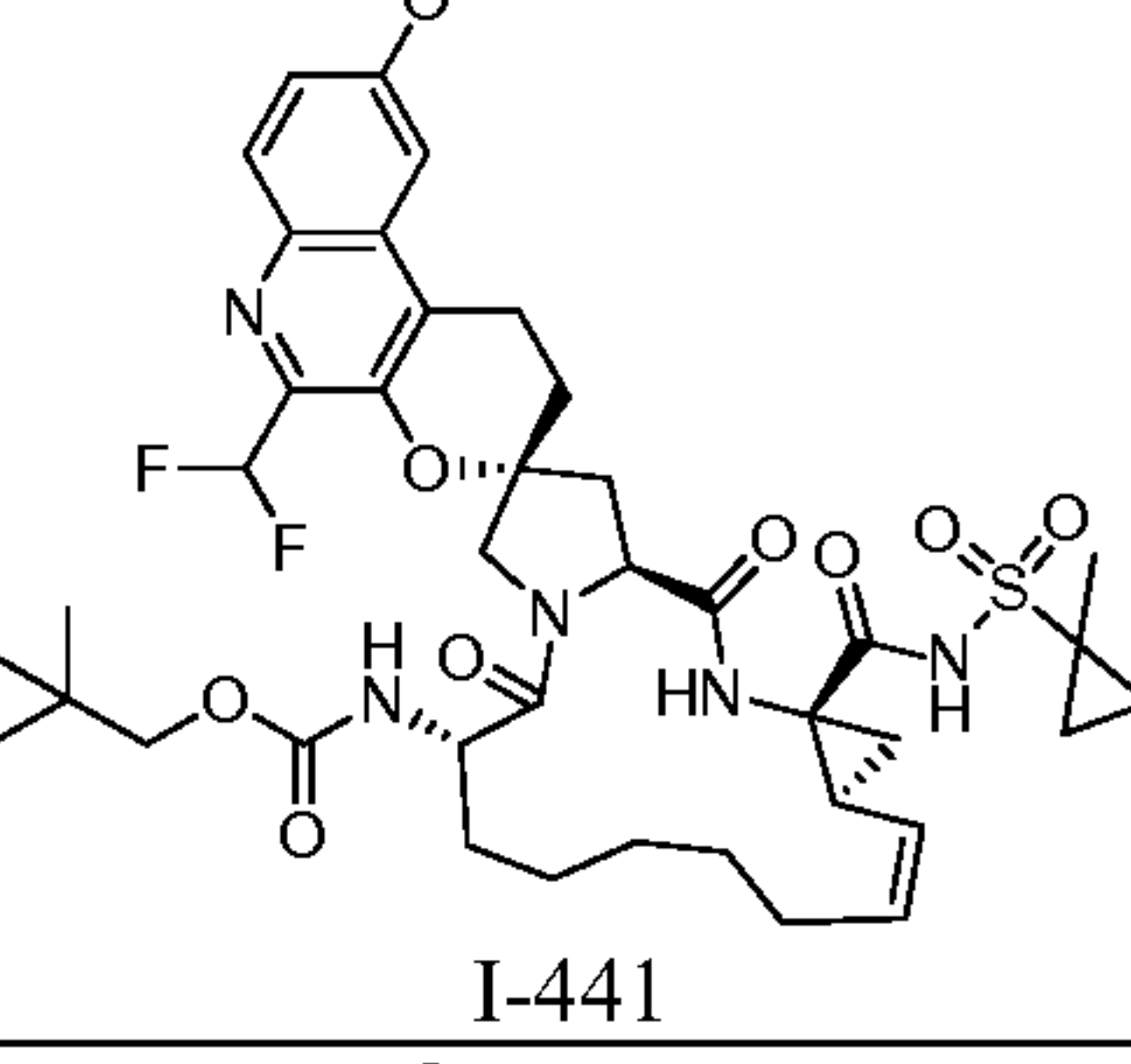
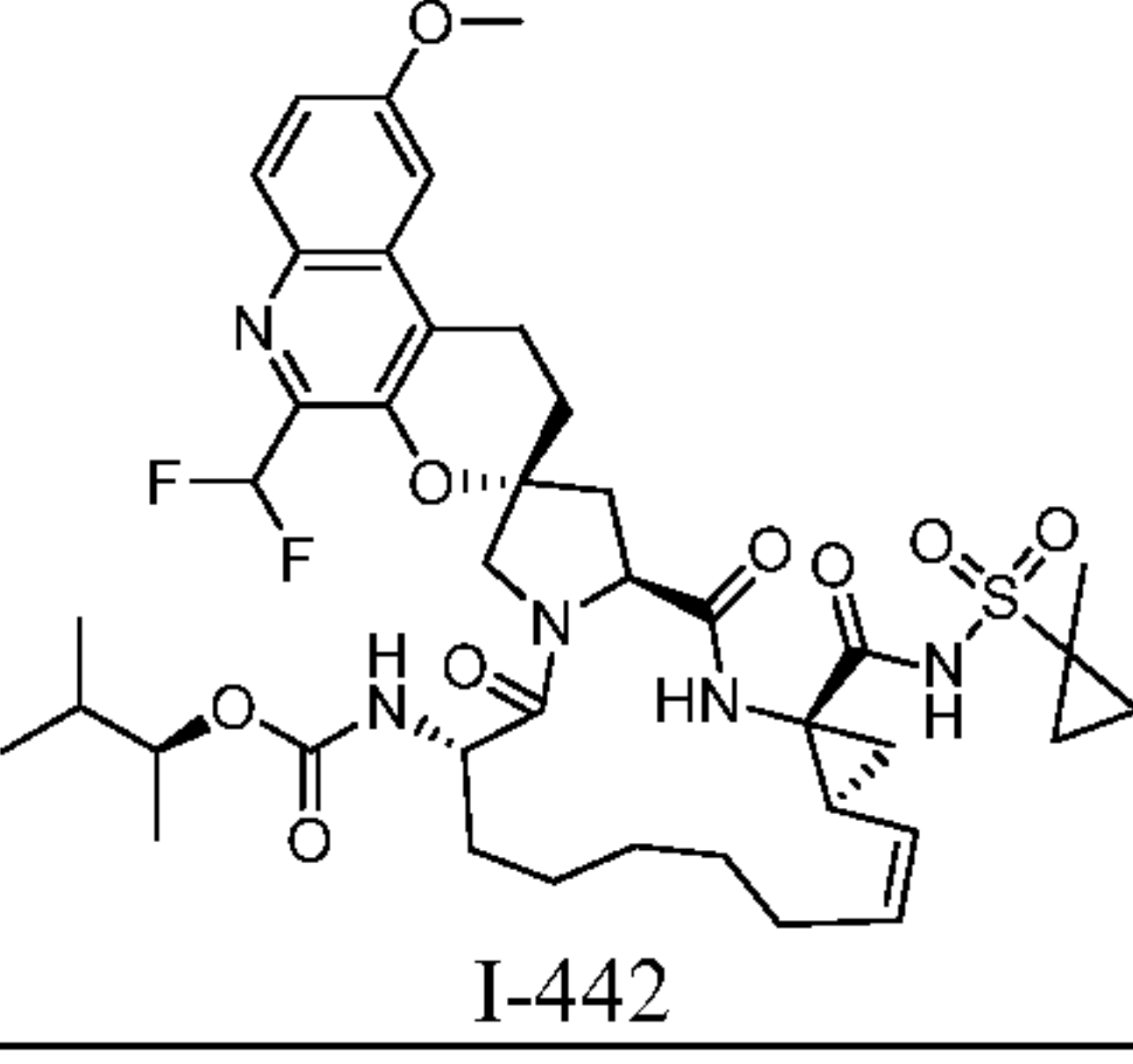
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
412	 I-412	(2S)-3-methylbutan-2-yl [(2R,6S,12Z,13aS,14aR,16aS)-5'-cyclopropyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	16	820.2 (K+ salt)
413	 I-413	(2R)-3-methylbutan-2-yl [(2R,6S,12Z,13aS,14aR,16aS)-5'-cyclopropyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	16	820.2 (K+ salt)
414	 I-414	(2R,6S,12Z,13aS,14aR,16aS)-5'-methyl-N-[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-6-{{4-(trifluoromethyl)pyridin-2-yl}amino}-1,1',2',6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a(5H)-carboxamide	57	794.4
415	 I-415	(2R,6S,12Z,13aS,14aR,16aS)-6-[(6-methoxypyridin-2-yl)amino]-5'-methyl-N-[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a(5H)-carboxamide	57	756.4
416	 I-416	2-(pyrrolidin-1-yl)ethyl [(2R,6S,12Z,13aS,14aR,16aS)-9'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	31	859.2

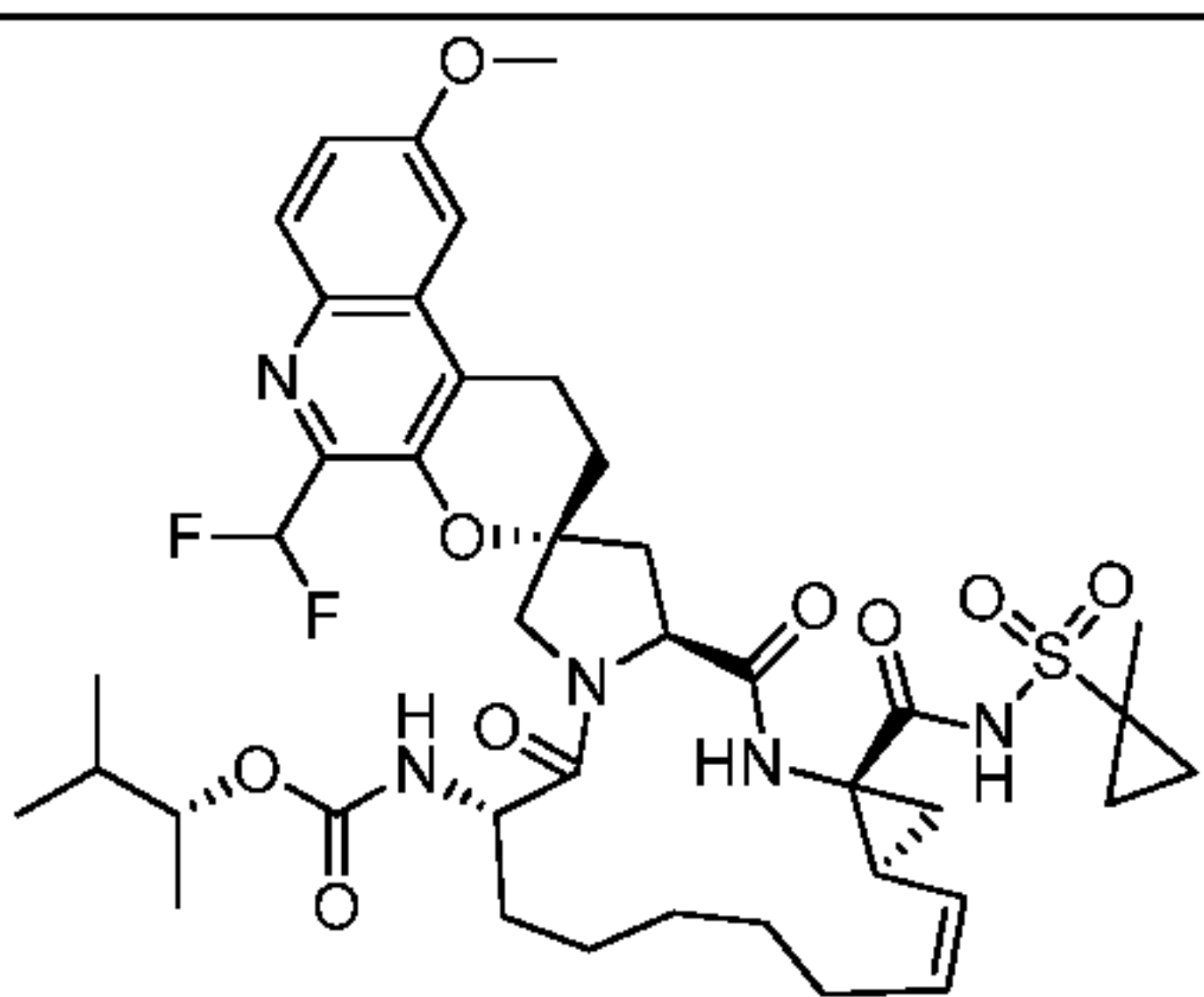
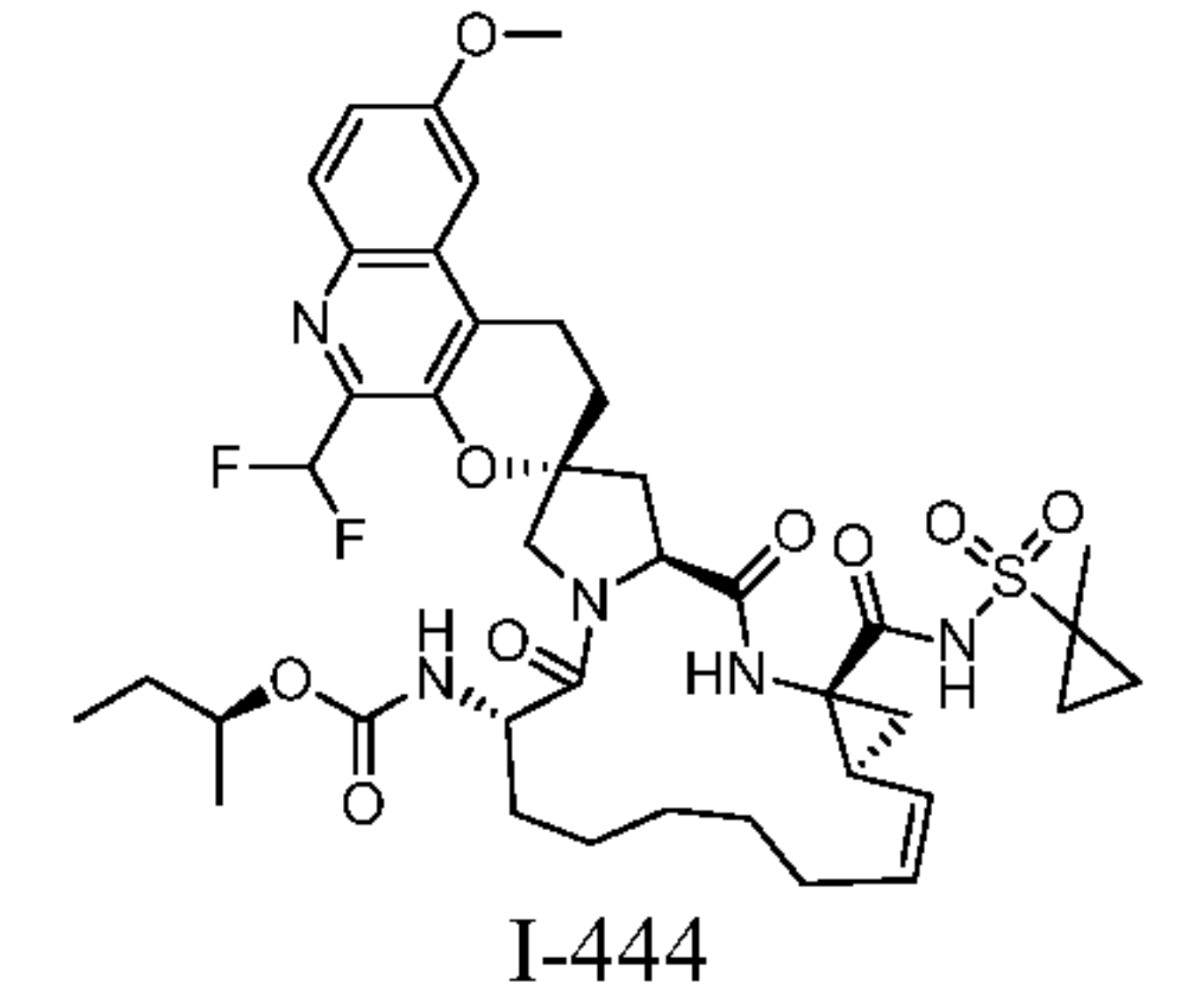
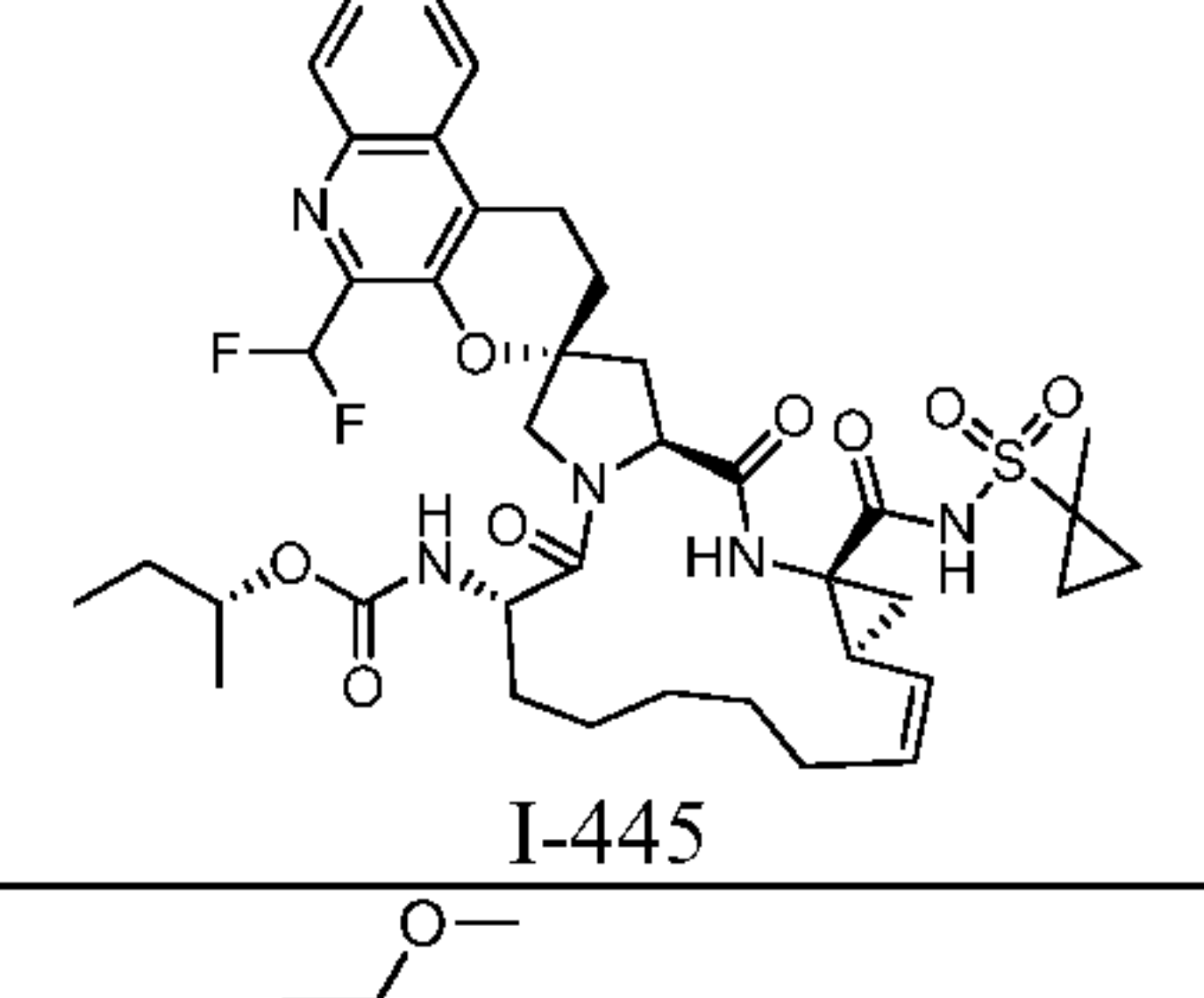
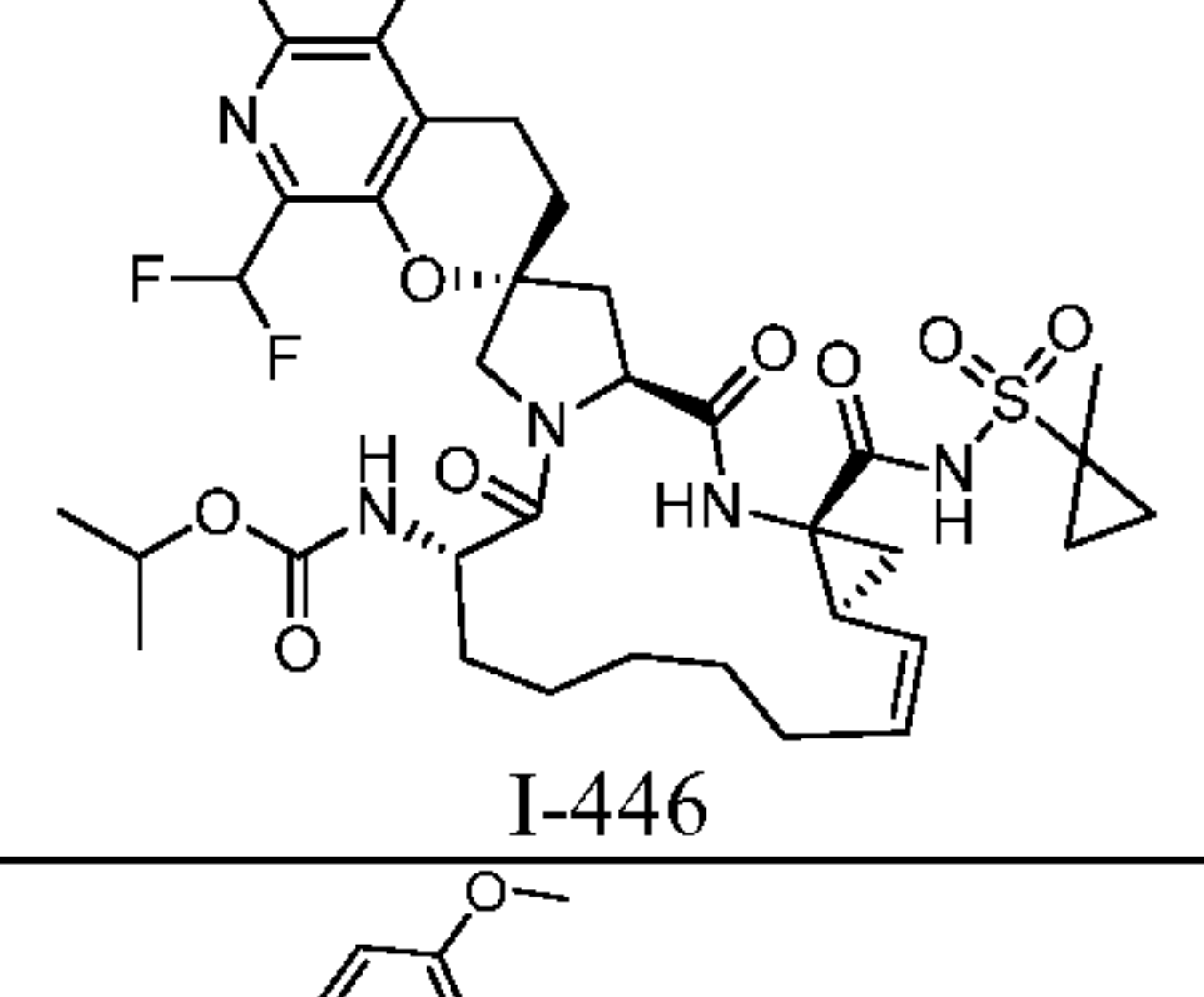
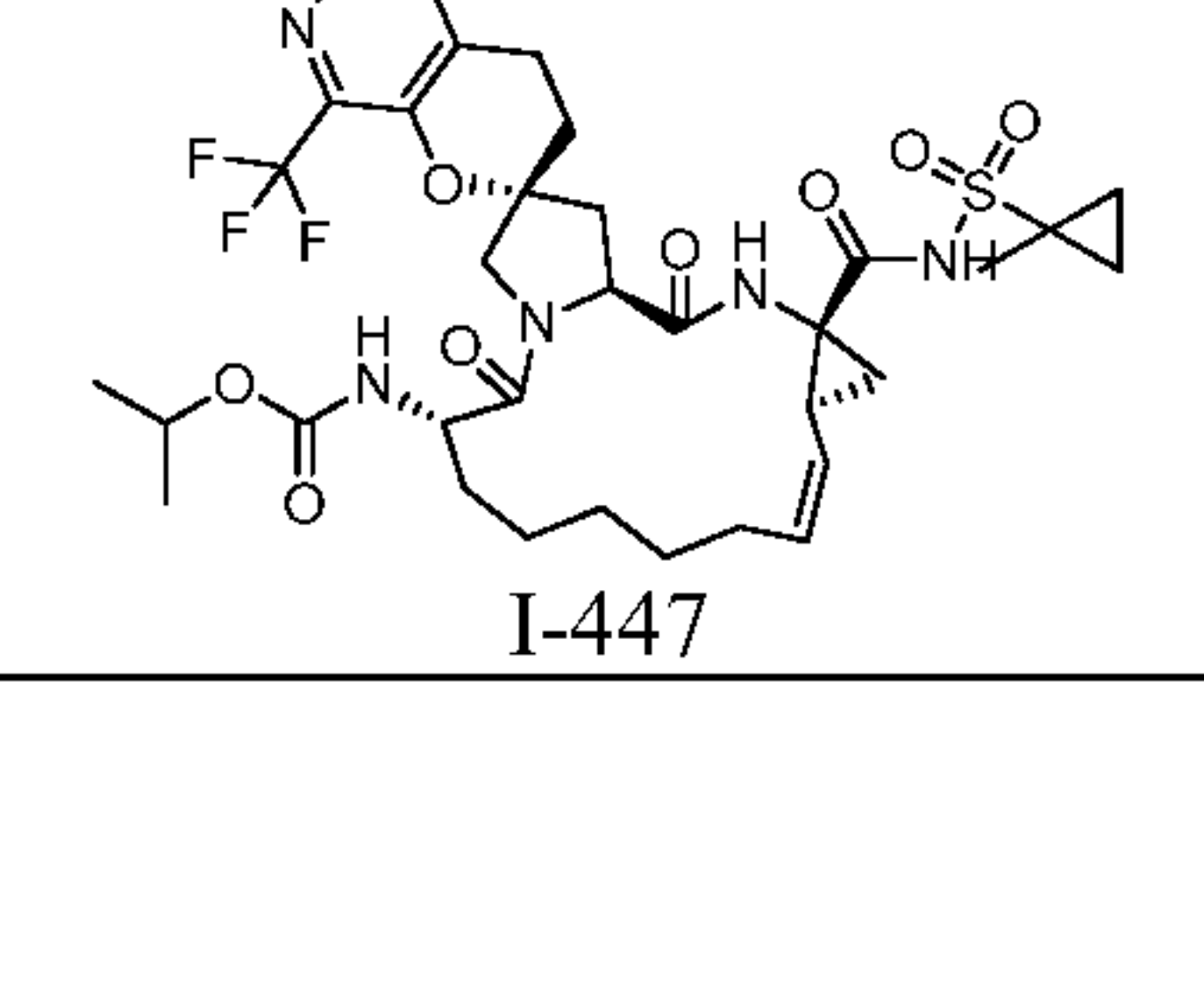
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
417	 I-417	2-(piperidin-1-yl)ethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	31	873.2
418	 I-418	<i>tert</i> -butyl {(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-9'-[2-(morpholin-4-yl)ethoxy]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl} carbamate	58, 50	879.3
419	 I-419	(2 <i>S</i>)-3-methylbutan-2-yl [(1' <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-fluoro-9'-methoxy-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(propan-2-yl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	3	840.2 (K+ salt)
420	 I-420	(2 <i>R</i>)-butan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-9'-methoxy-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16	806.2 (K+ salt)
421	 I-421	(2 <i>S</i>)-butan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-9'-methoxy-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	16	806.3

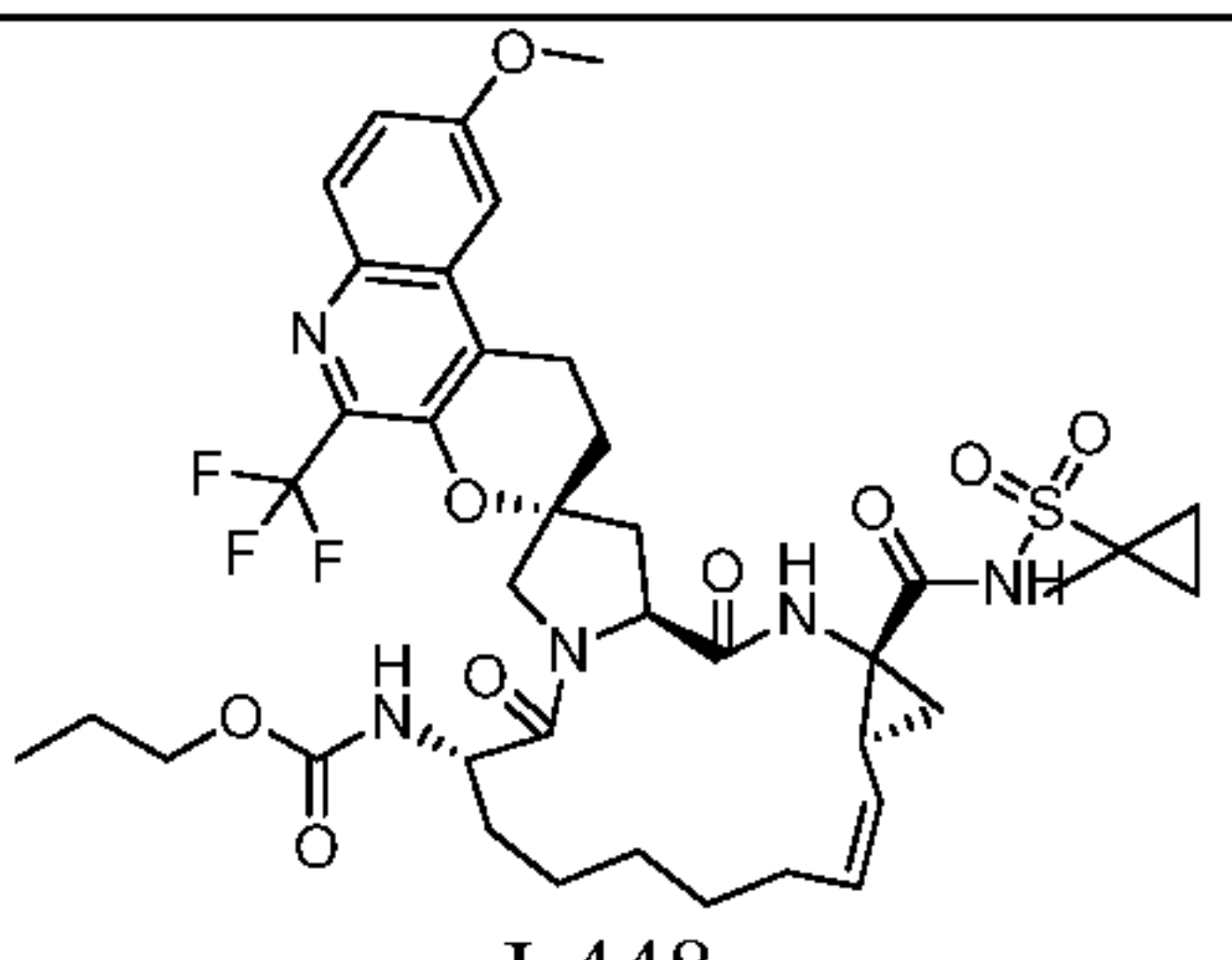
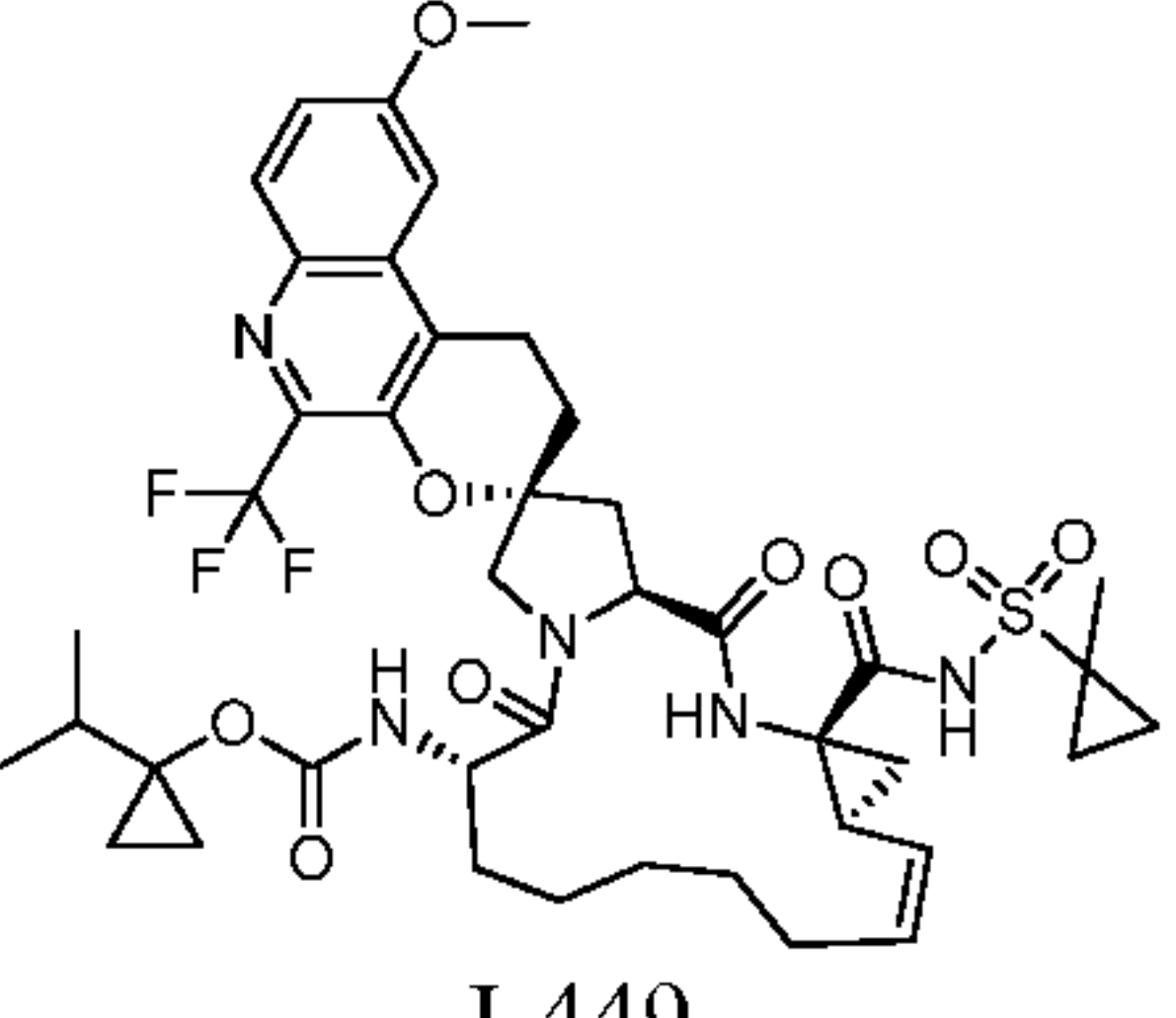
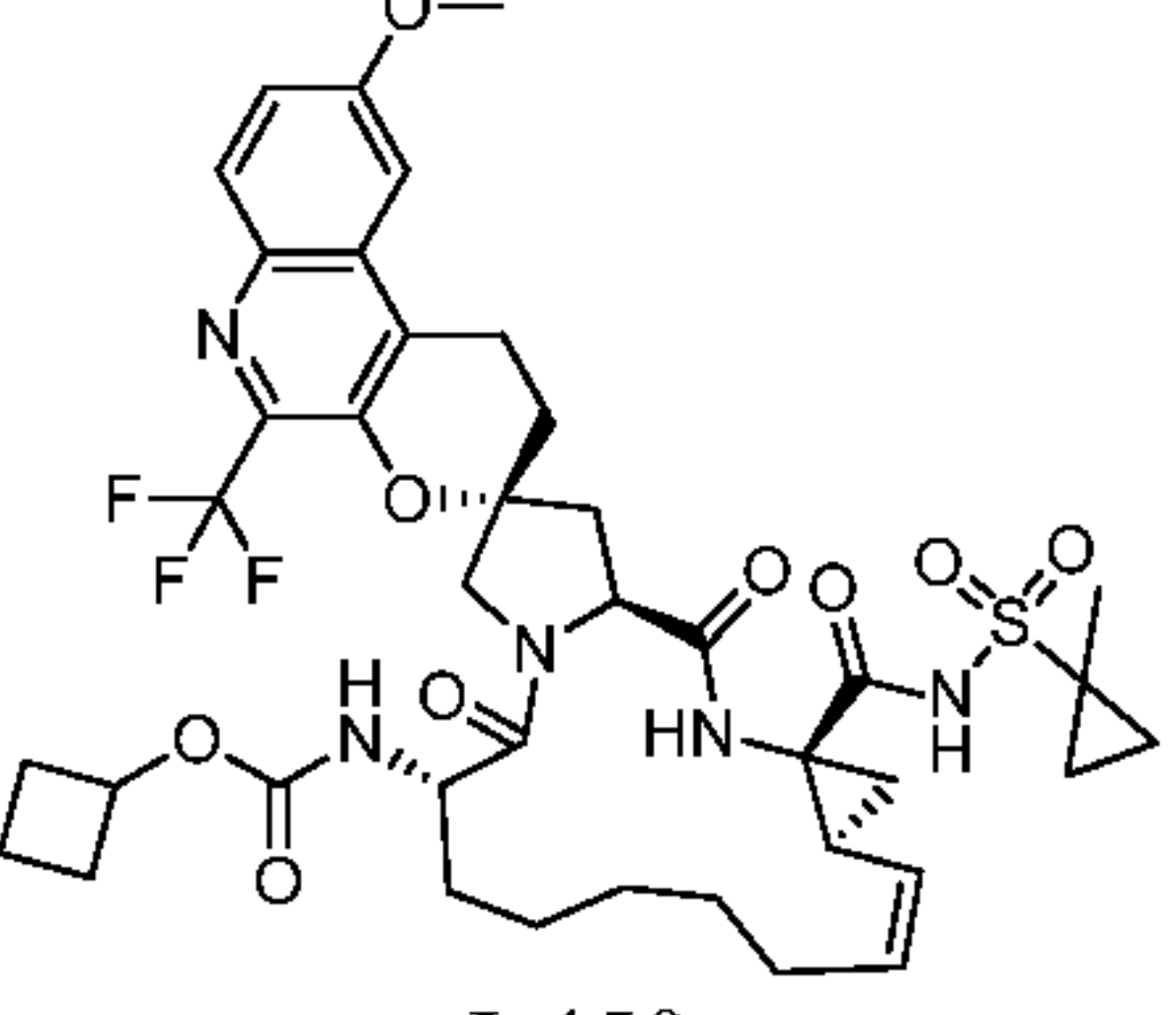
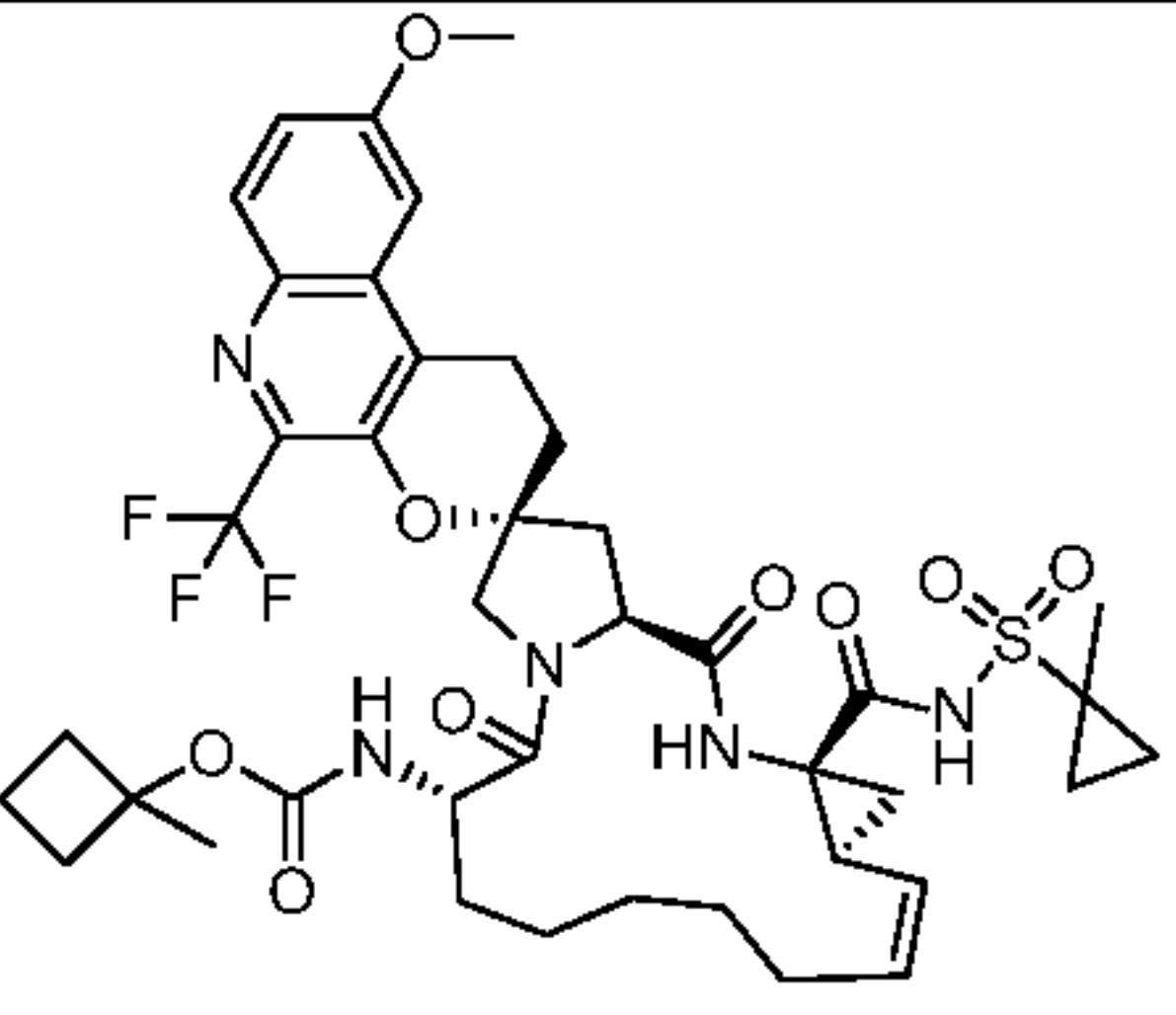
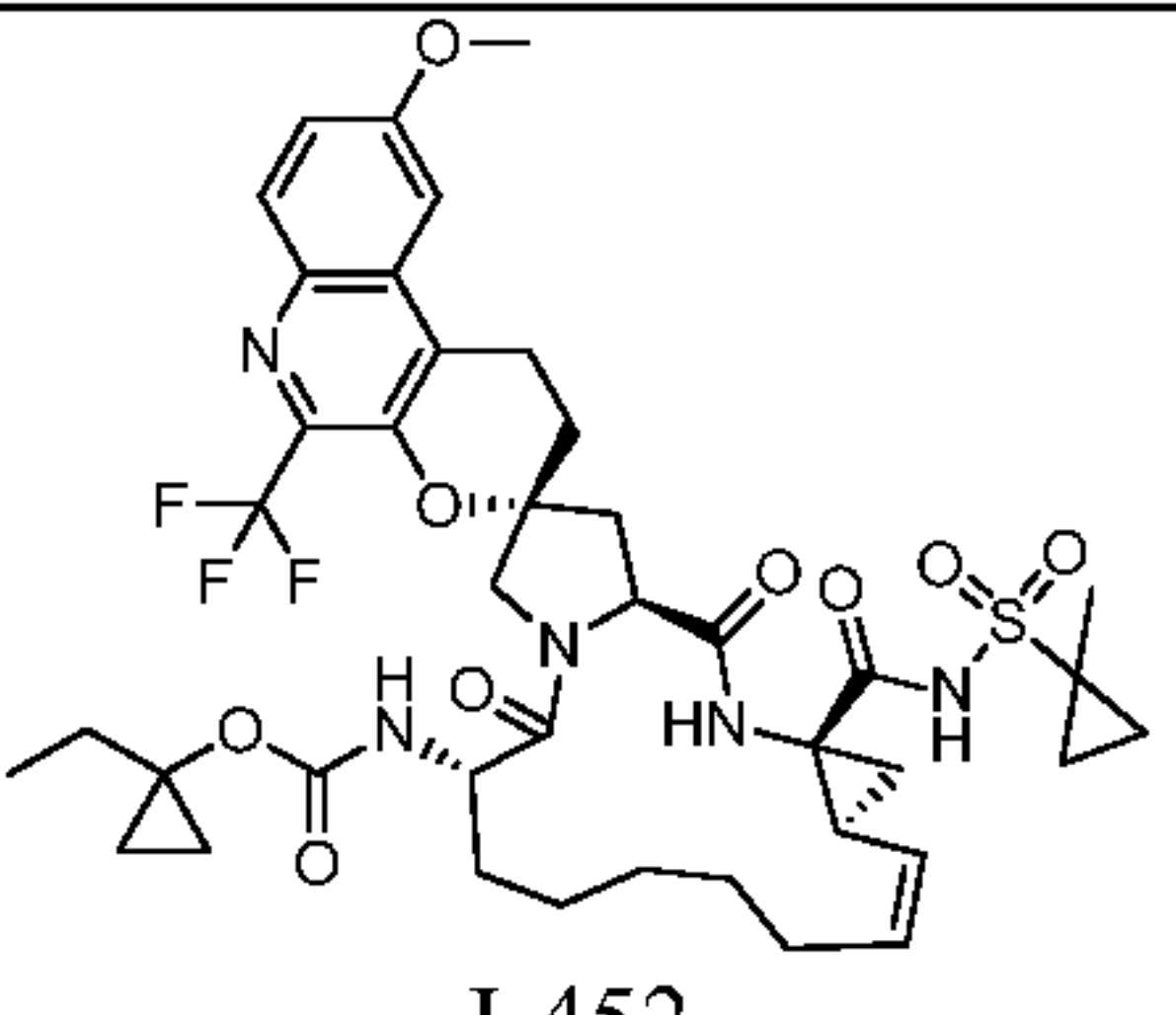
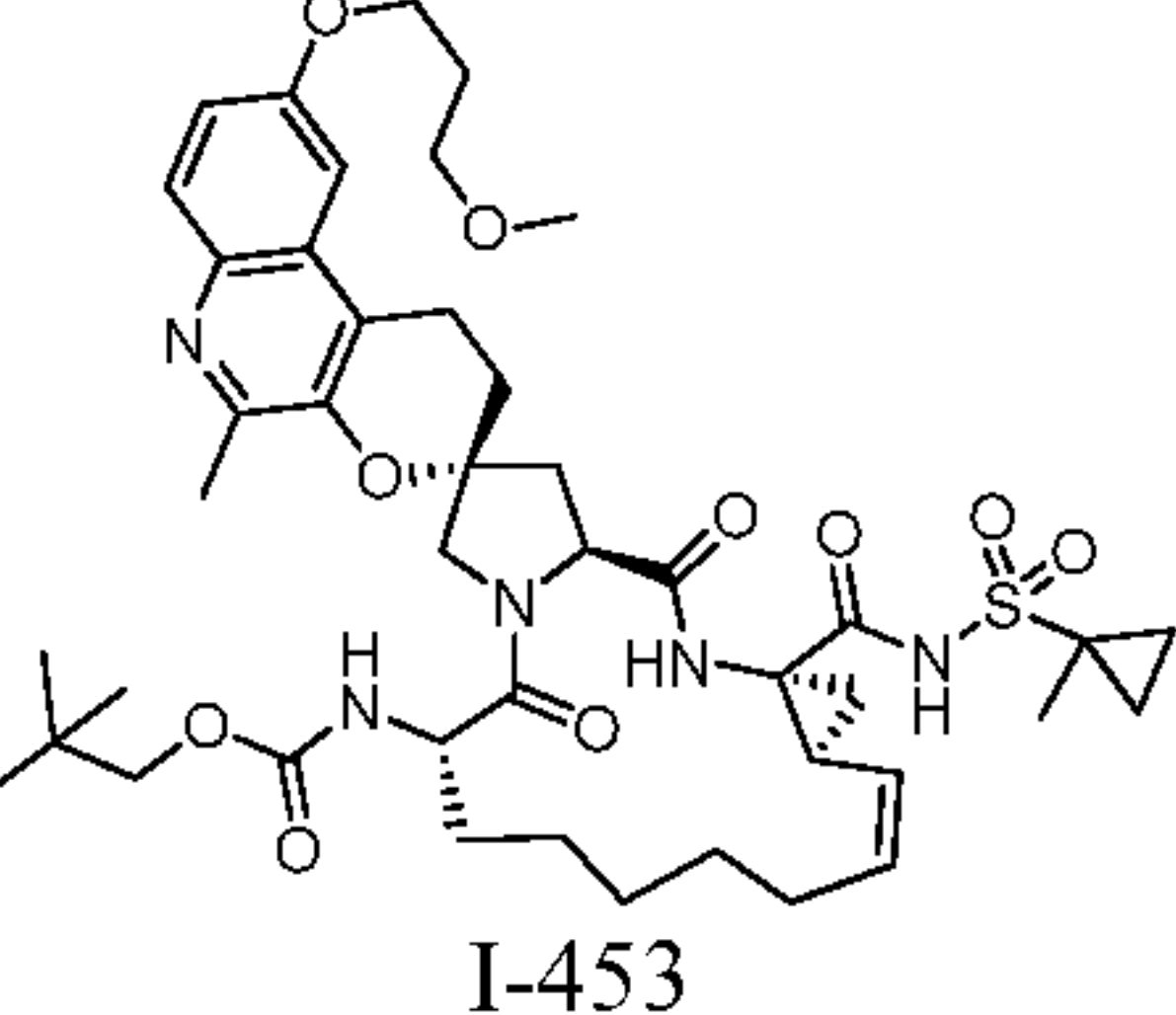
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
422	 I-422	3-methyloxetan-3-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	5, 35	848.2 (K+ salt)
423	 I-423	3-(piperidin-1-yl)propyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	31	887.2
424	 I-424	3-(morpholin-4-yl)propyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	31	889.2
425	 I-425	2,2-dimethylpropyl {(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-9'-[2-(morpholin-4-yl)ethoxy]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl} carbamate	58, 50	893.2
426	 I-426	<i>tert</i> -butyl [(1' <i>S</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-fluoro-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	32	874.4
427	 I-427	<i>tert</i> -butyl [(1' <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-fluoro-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	32	852.29

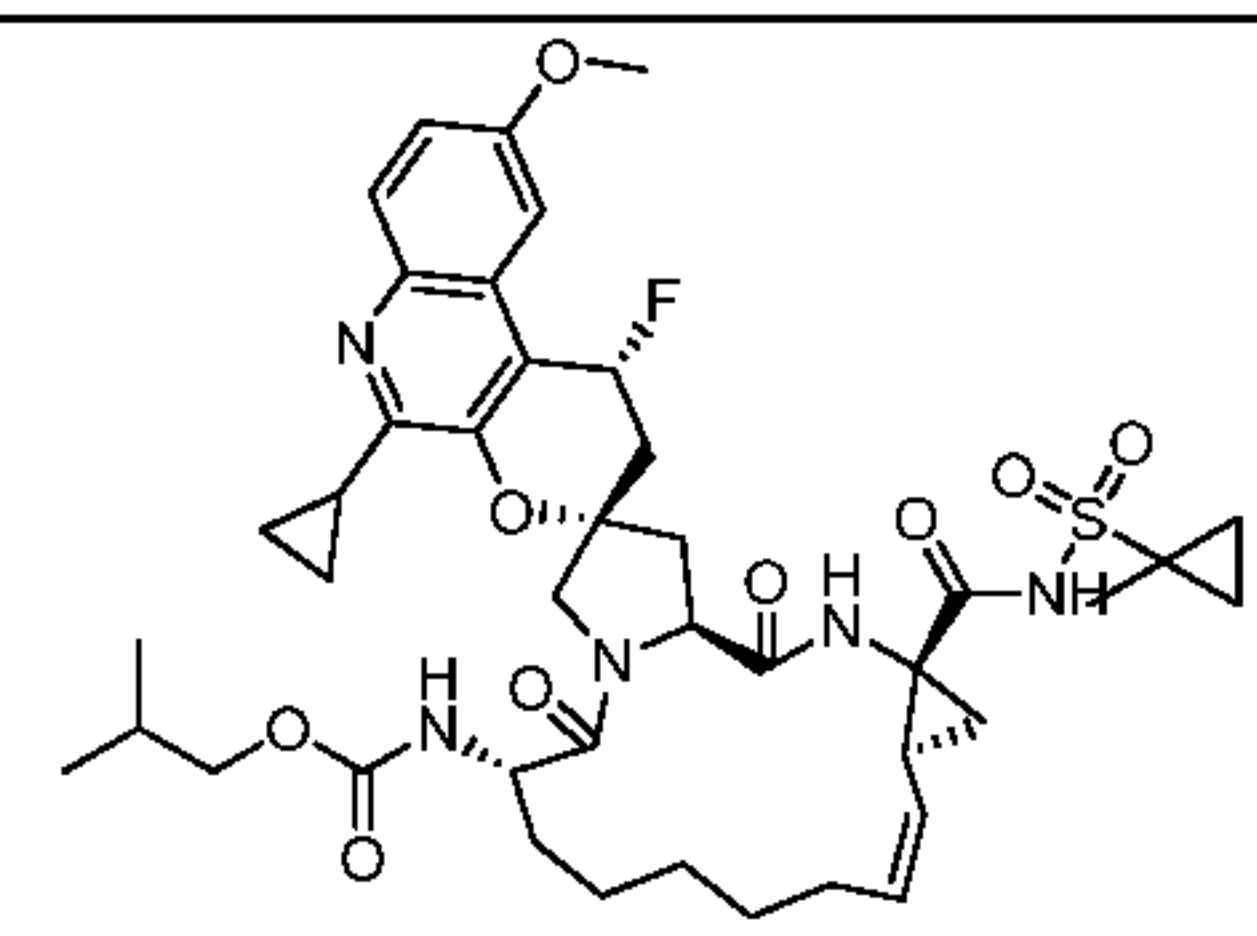
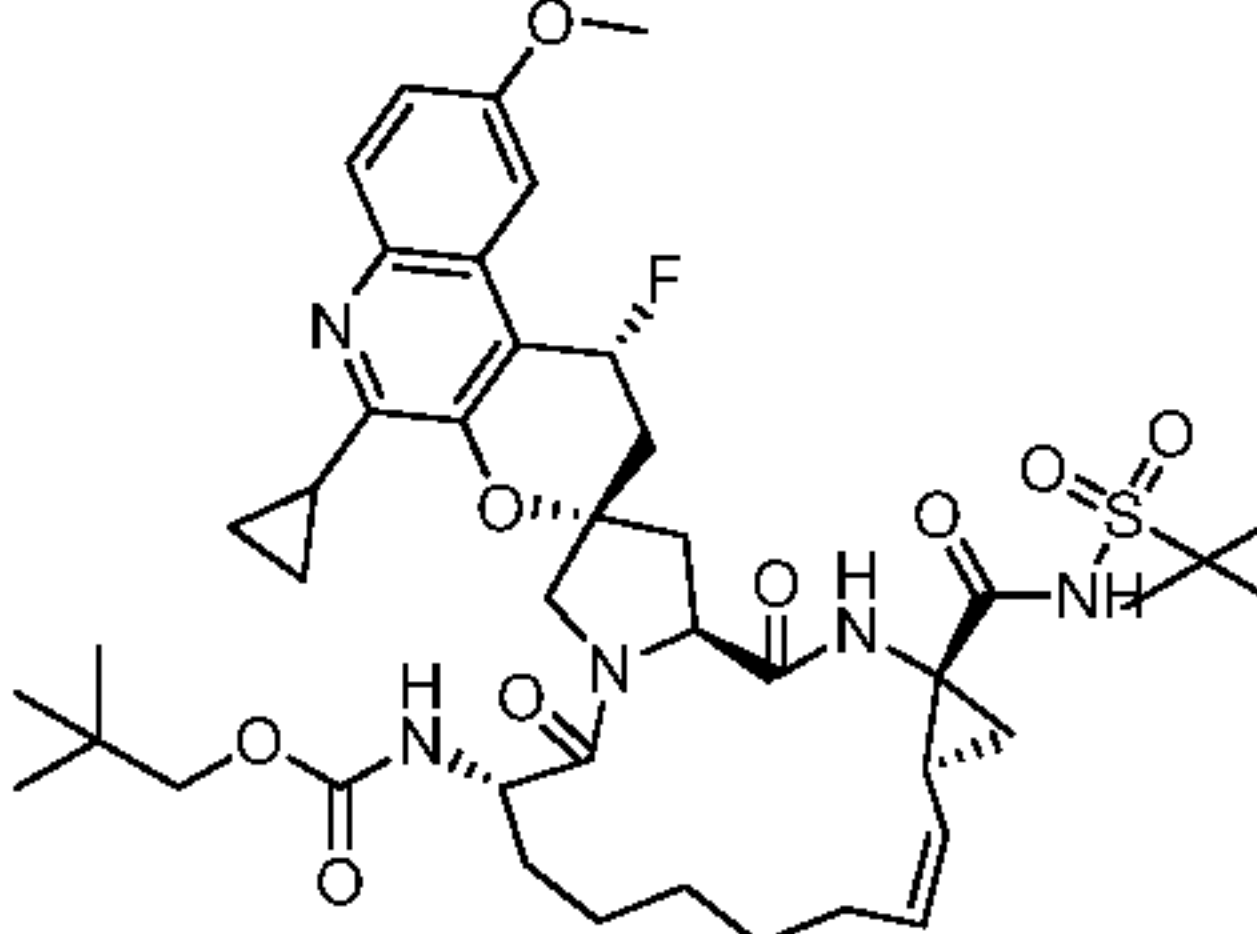
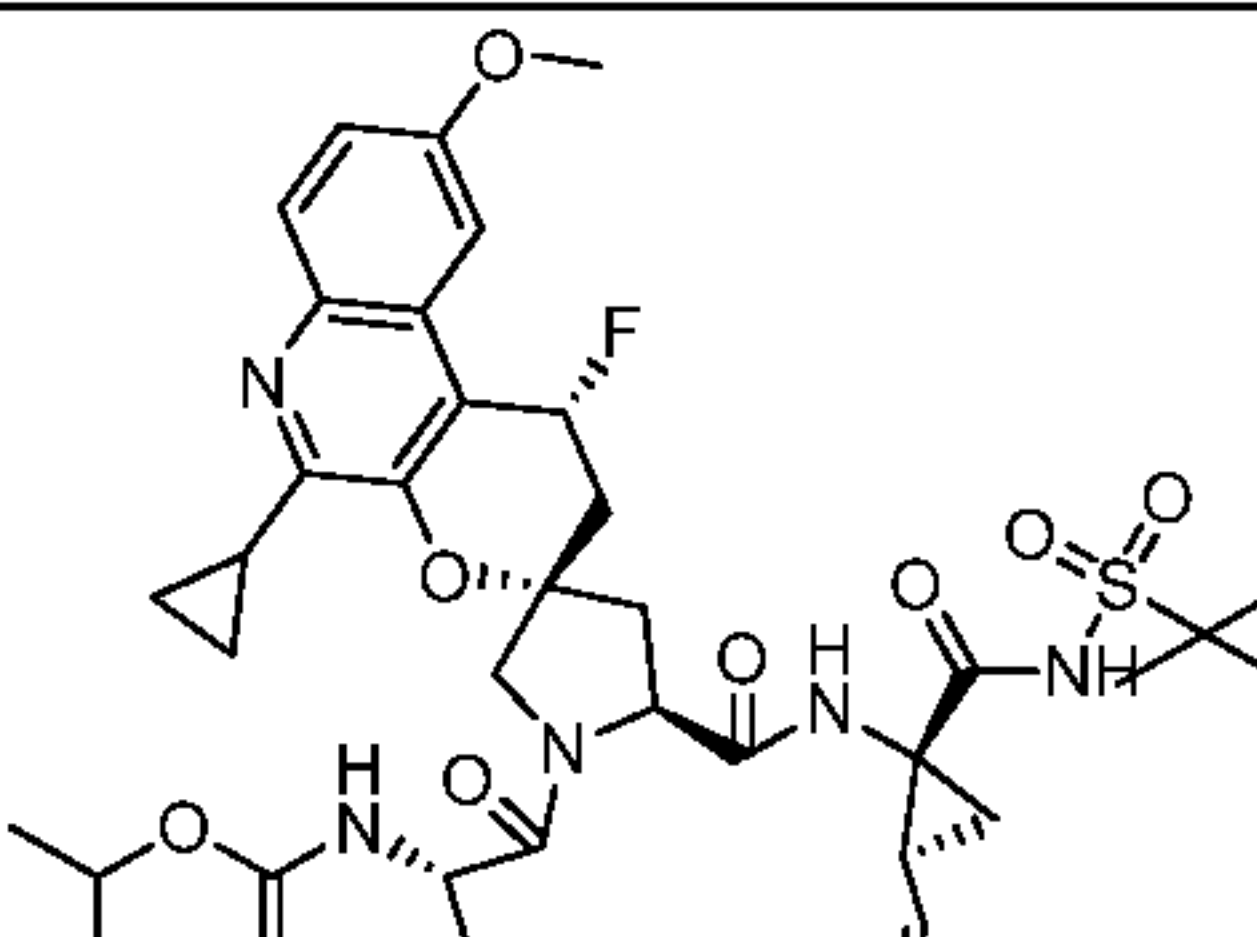
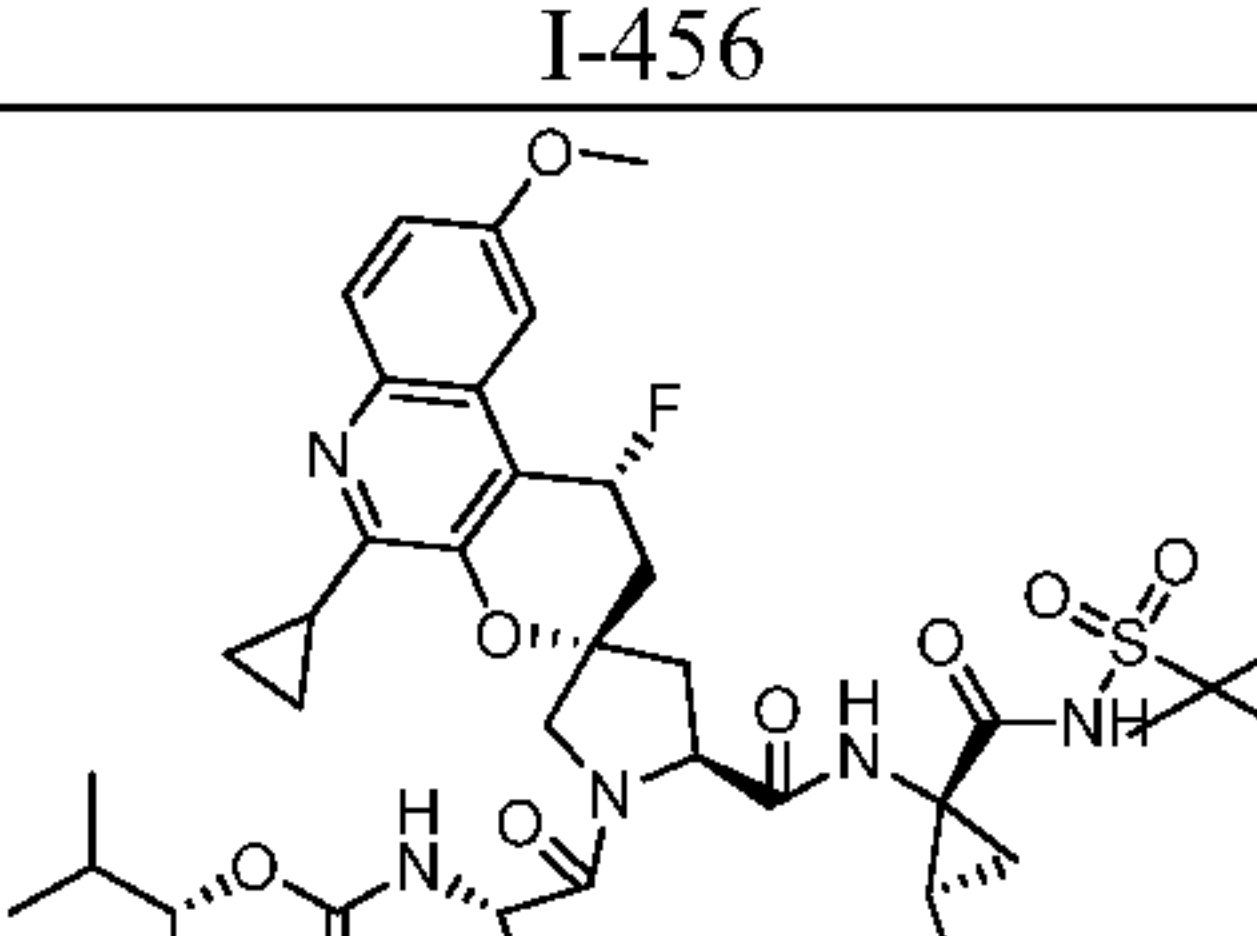
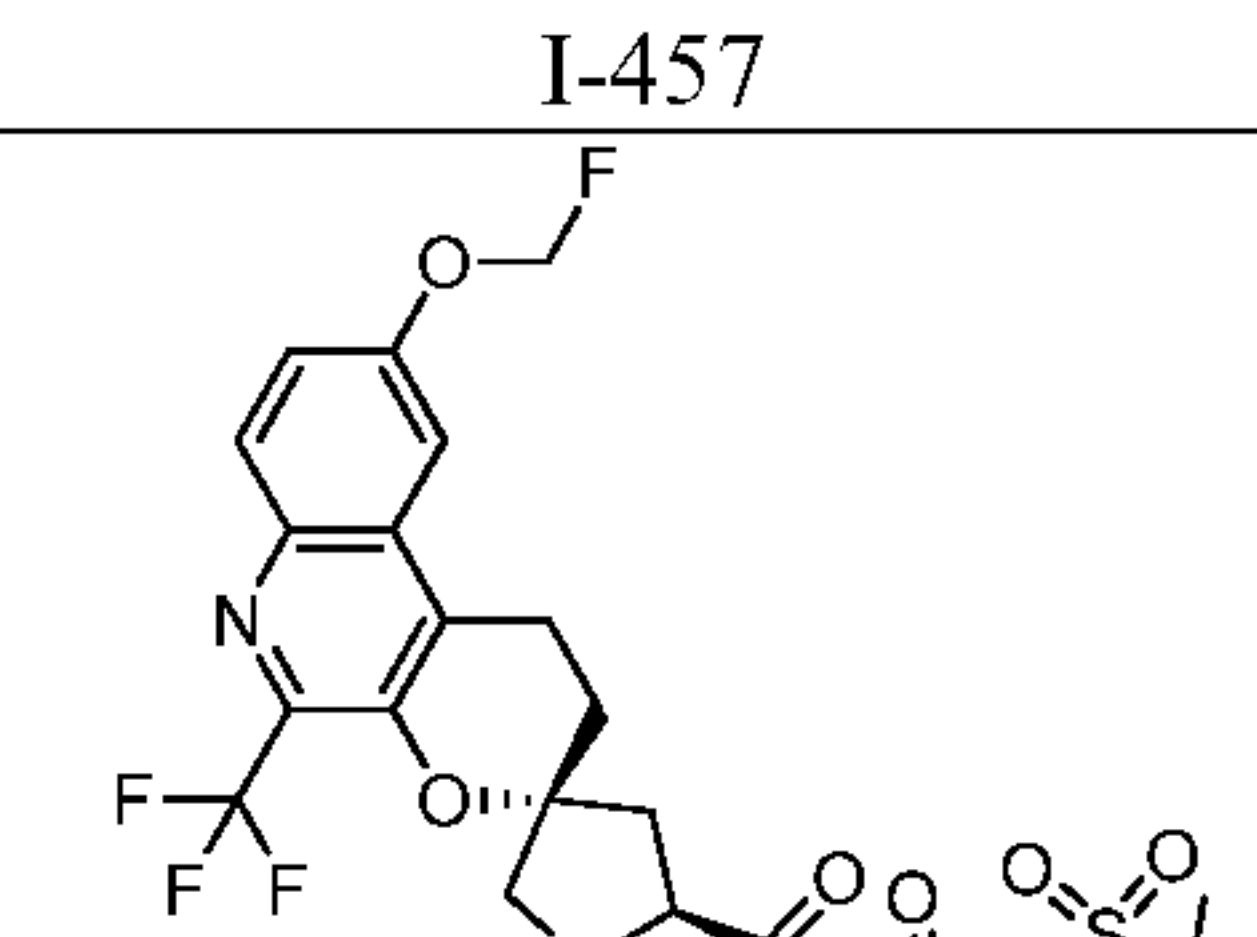
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
428	 I-428	<i>tert</i> -butyl [(1' <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-1'-fluoro-9'-methoxy-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	32	824.2
429	 I-429	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-6-[(3-methylpyridin-2-yl)amino]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	57	771.2
430	 I-430	1,1,1-trifluoro-2-methylpropan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-(2-methoxyethoxy)-5'-methyl-14a-{(1-methylcyclopropyl)sulfonyl}carbamoyl]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 7, 50, 51, 35	878.1
431	 I-431	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-6-[(6-methoxypyridin-2-yl)amino]-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	57	787.2
432	 I-432	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-6-[(4-methoxypyridin-2-yl)amino]-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	57	787.2

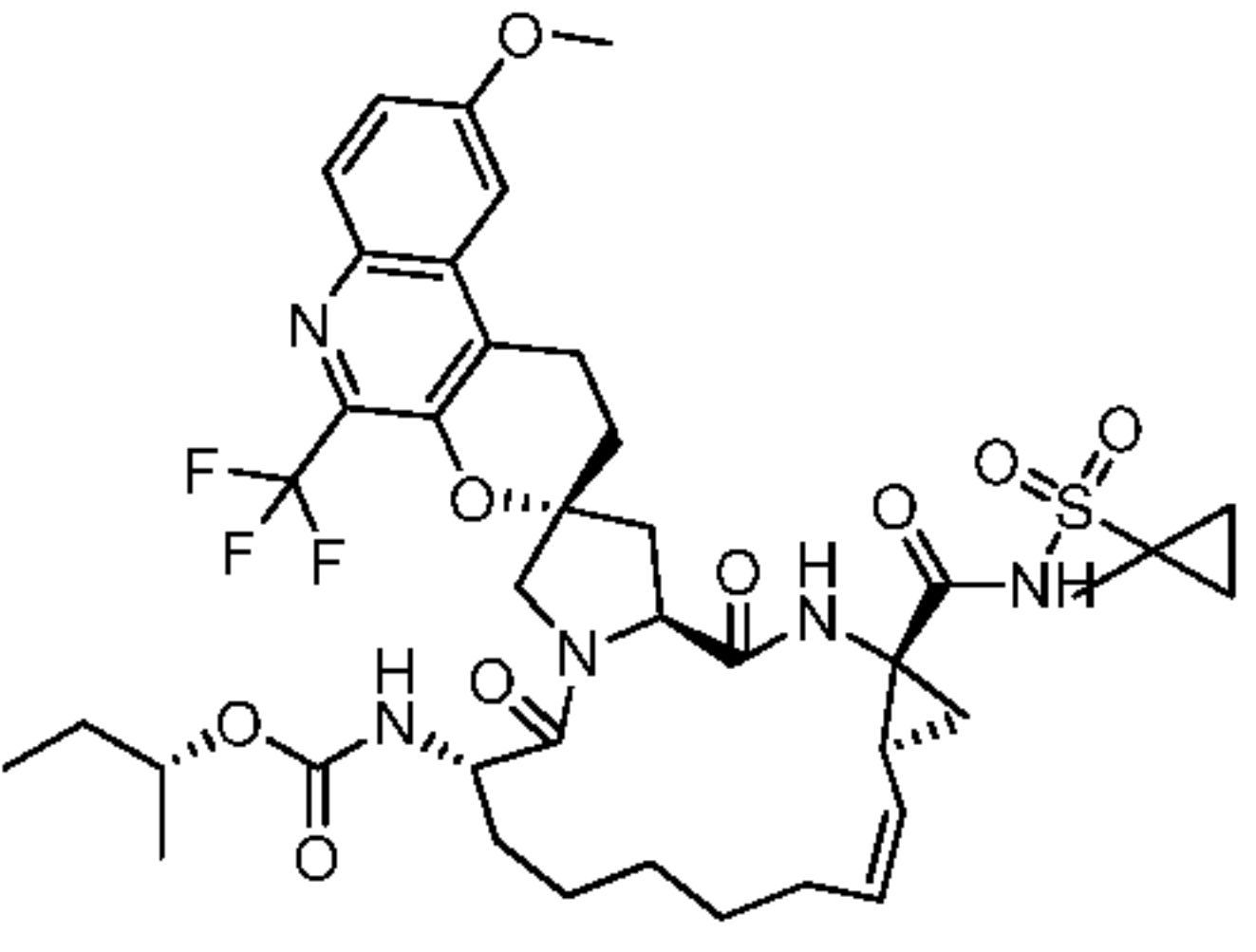
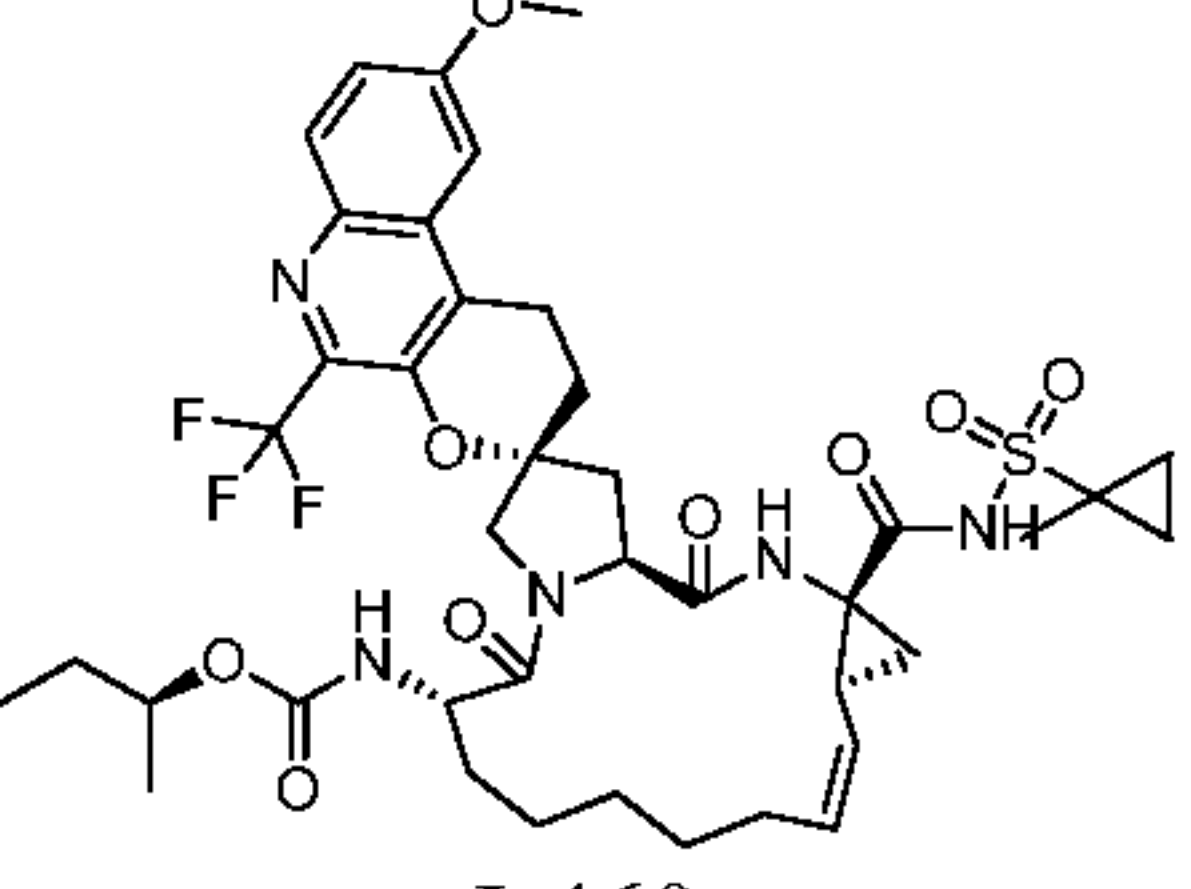
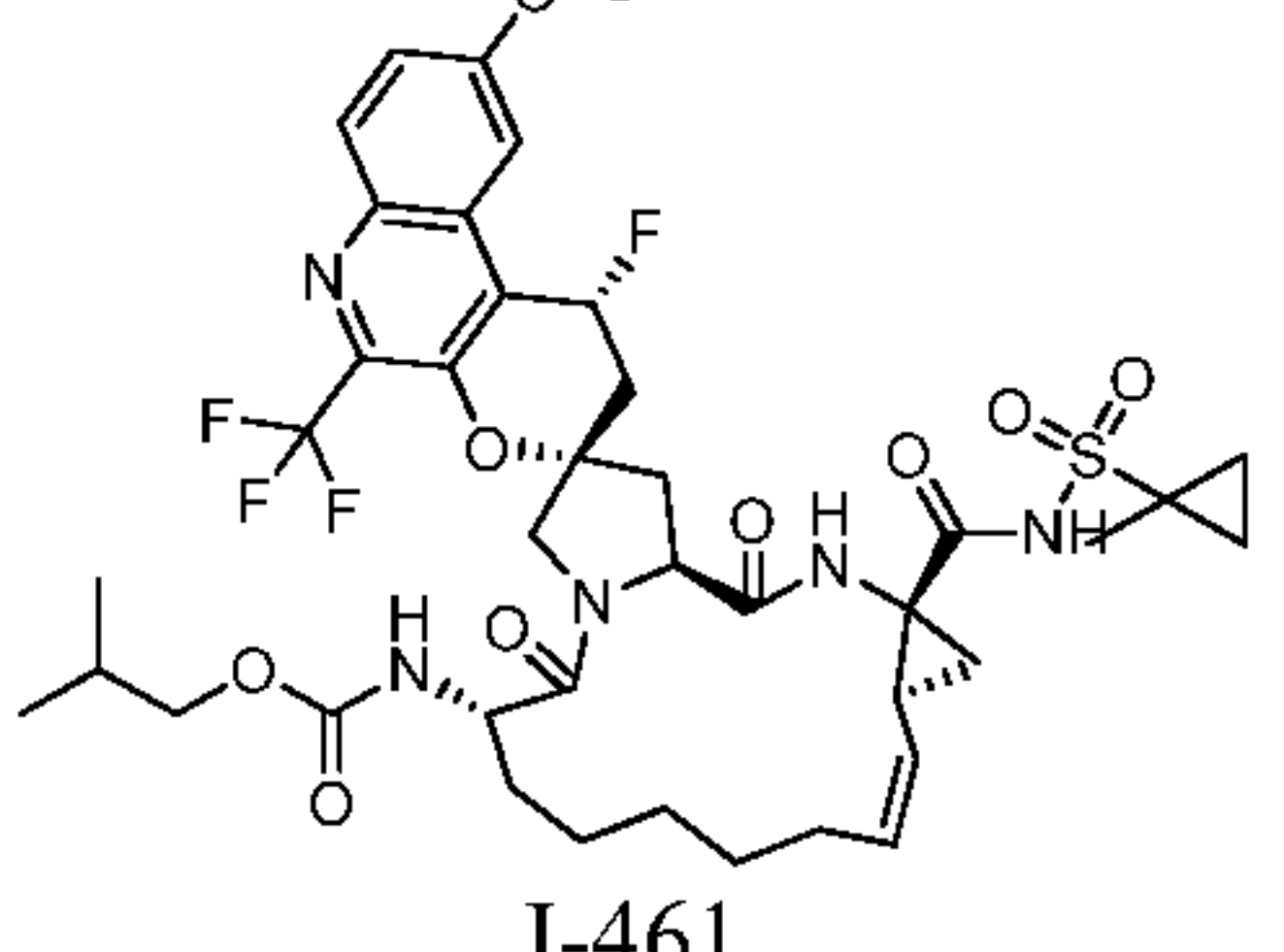
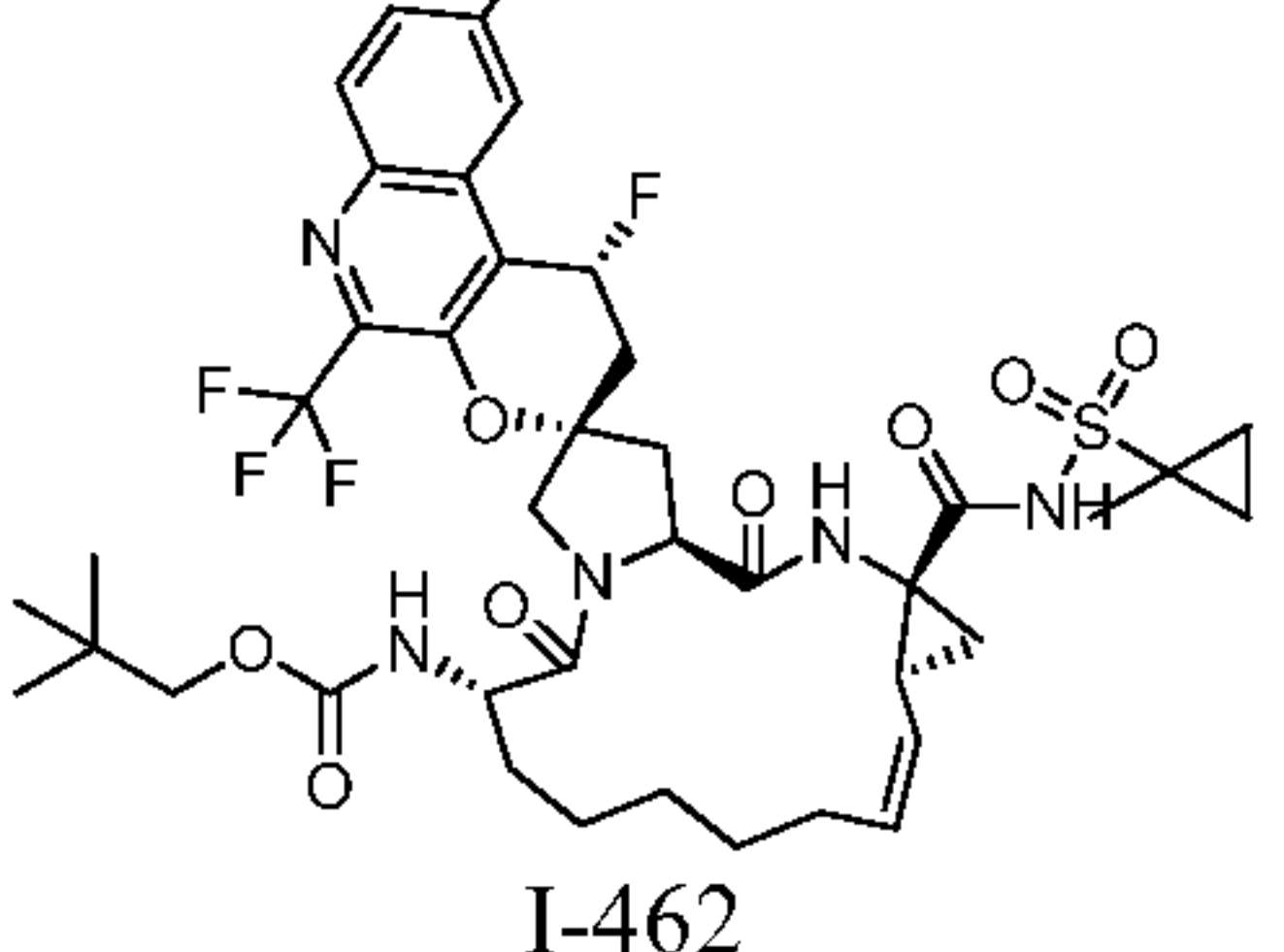
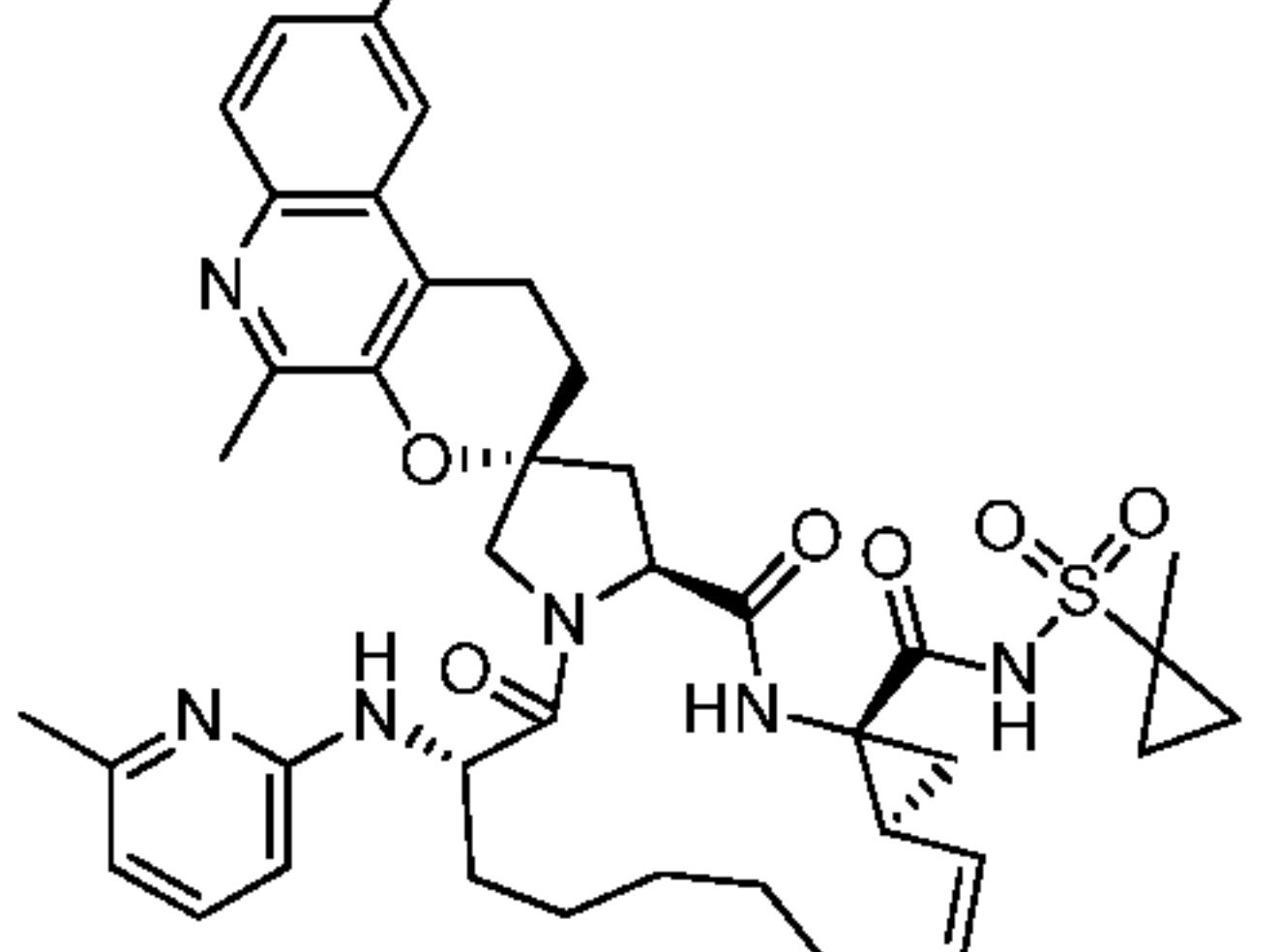
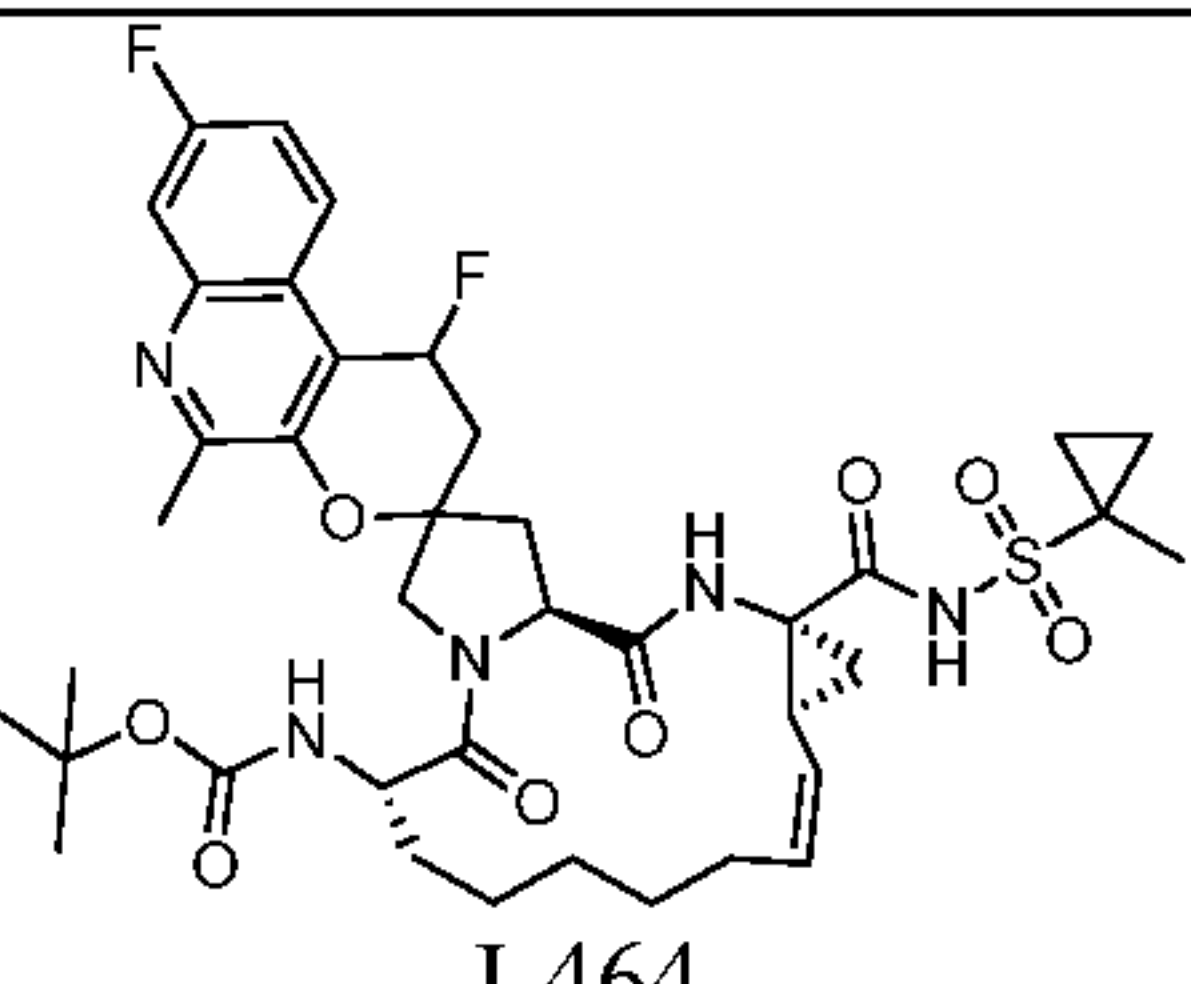
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
433		(2R)-3-methylbutan-2-yl [(2R,6S,12Z,13aS,14aR,16aS)-5'-ethyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	2, 31	808.4
434		(2S)-3-methylbutan-2-yl [(2R,6S,12Z,13aS,14aR,16aS)-5'-ethyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	2, 31	808.2
435		methyl [(2R,6S,12Z,13aS,14aR,16aS)-5'-cyclopropyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	17	764.2 (K+ salt)
436		ethyl [(2R,6S,12Z,13aS,14aR,16aS)-5'-cyclopropyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	17	778.2 (K+ salt)
437		propyl [(2R,6S,12Z,13aS,14aR,16aS)-5'-cyclopropyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	17	792.2 (K+ salt)

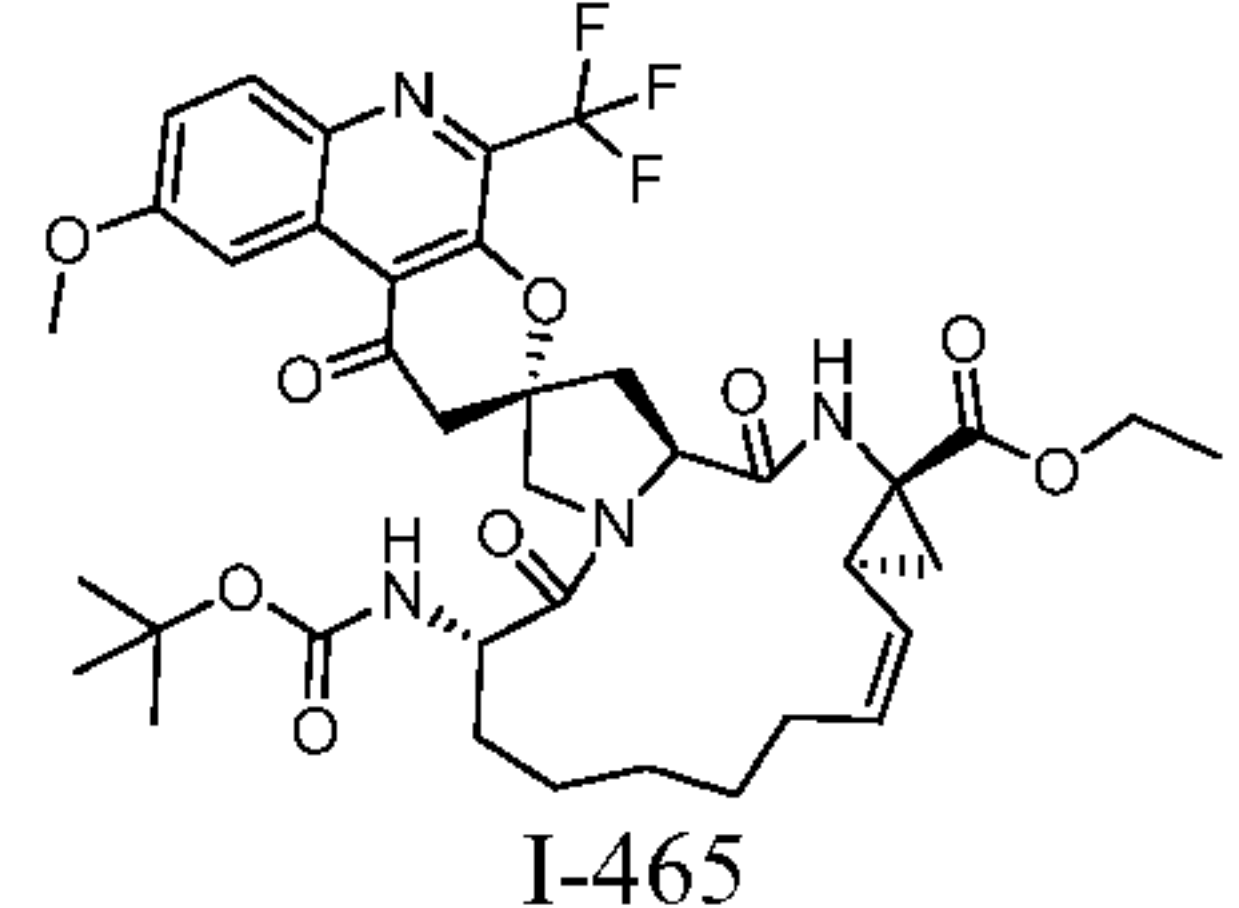
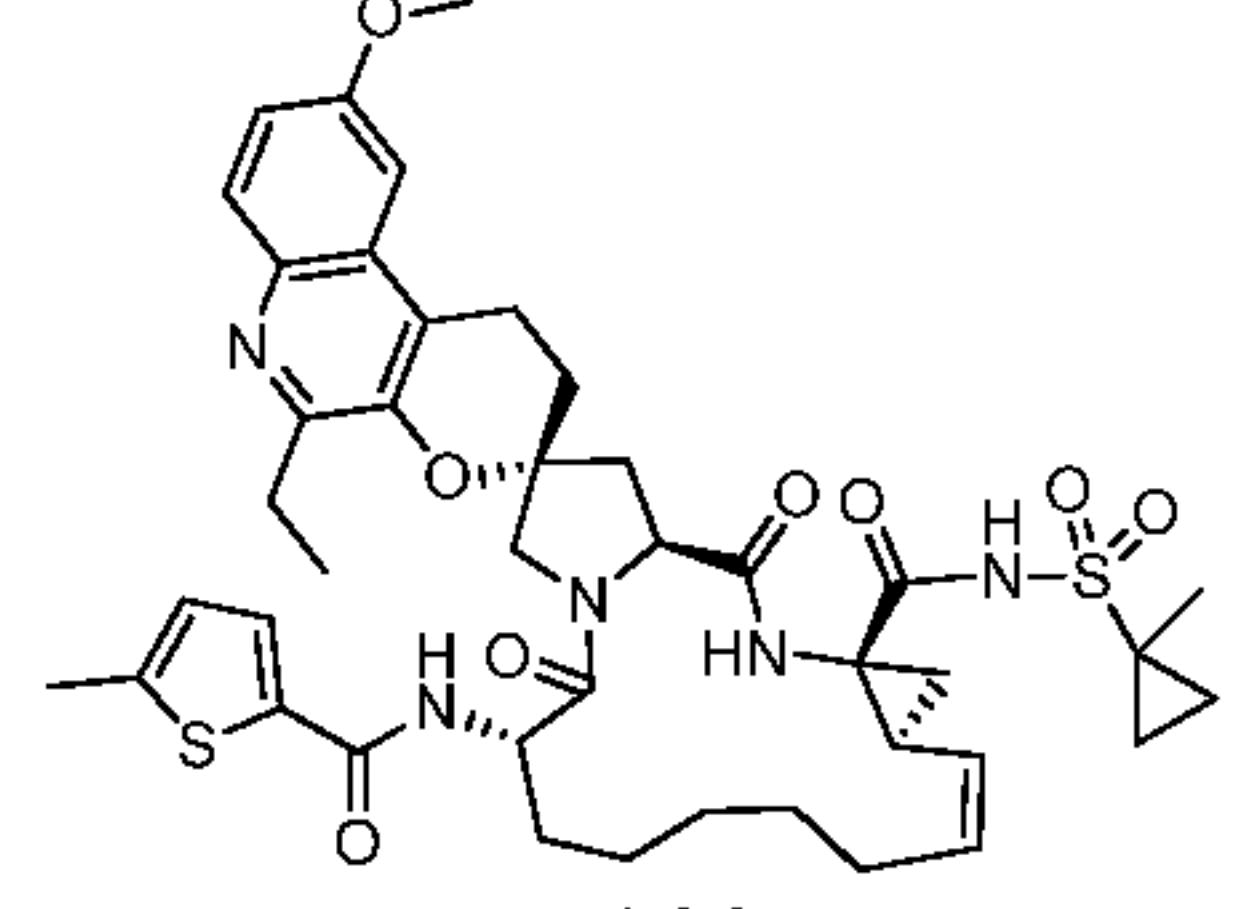
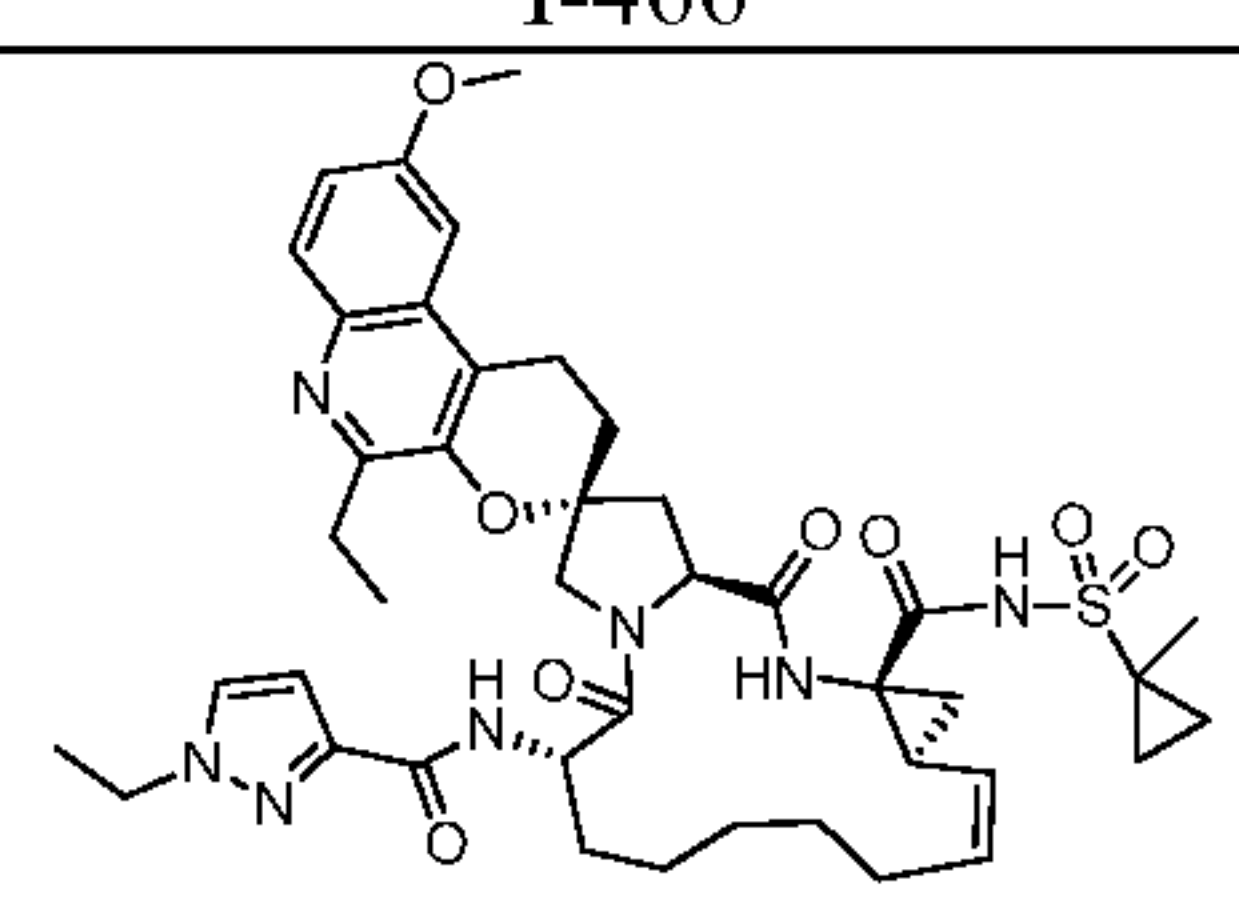
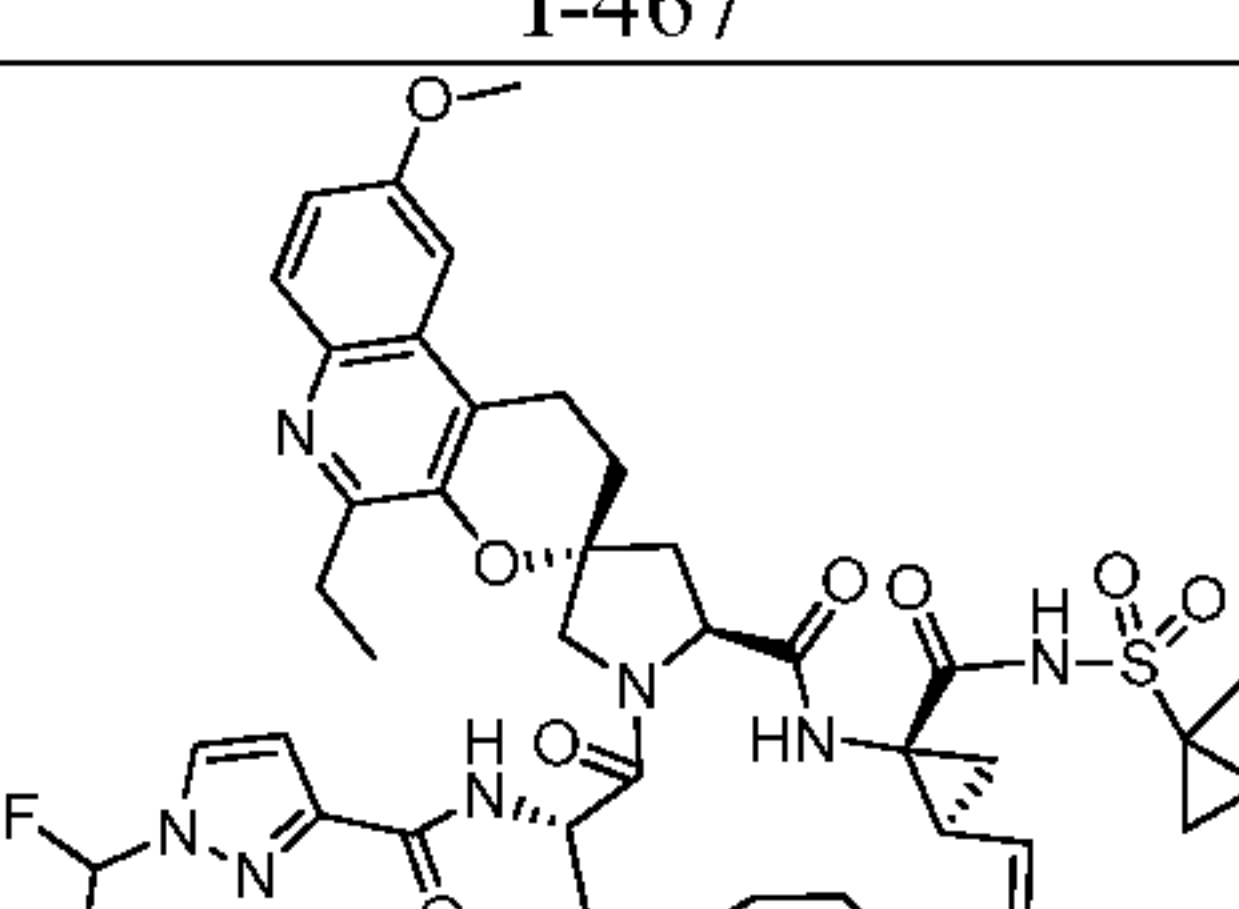
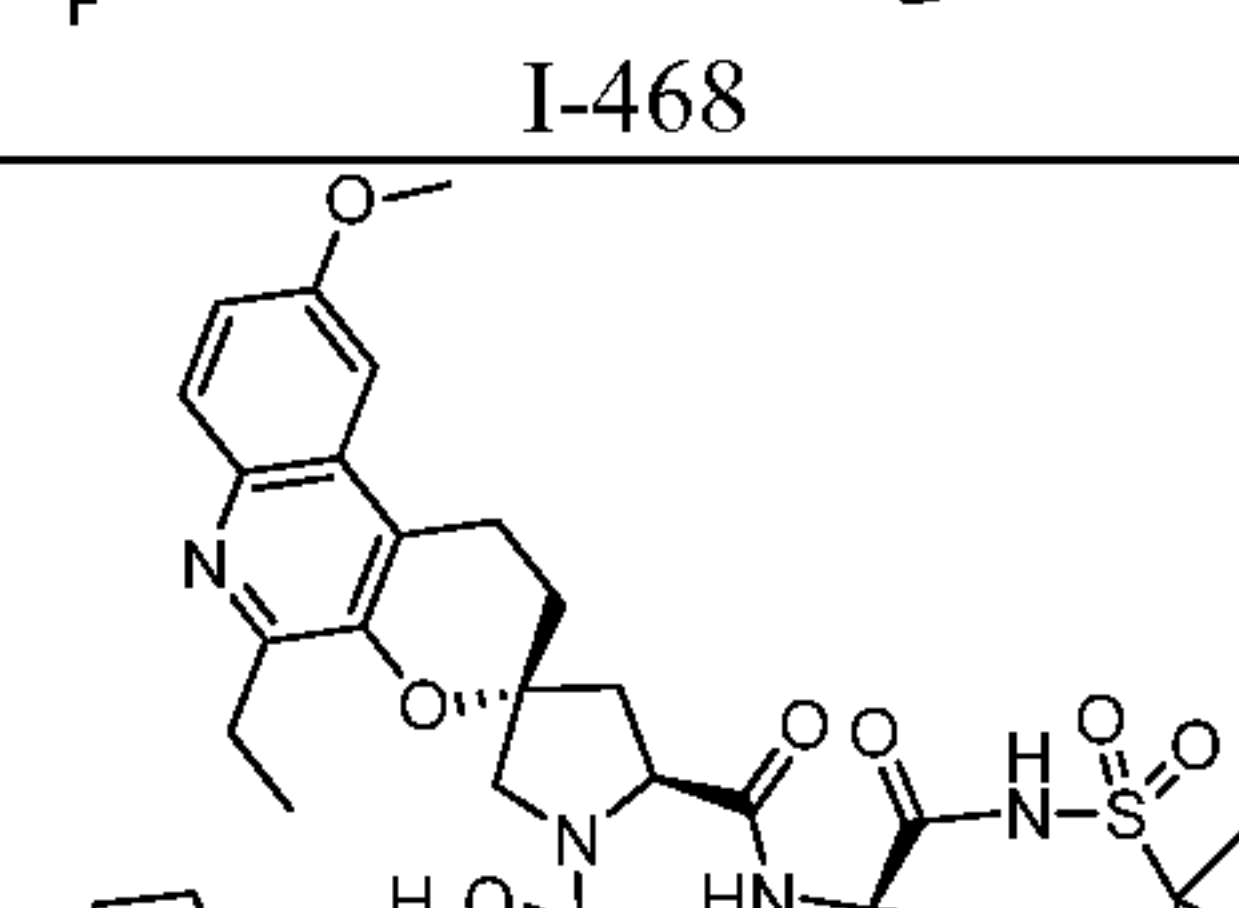
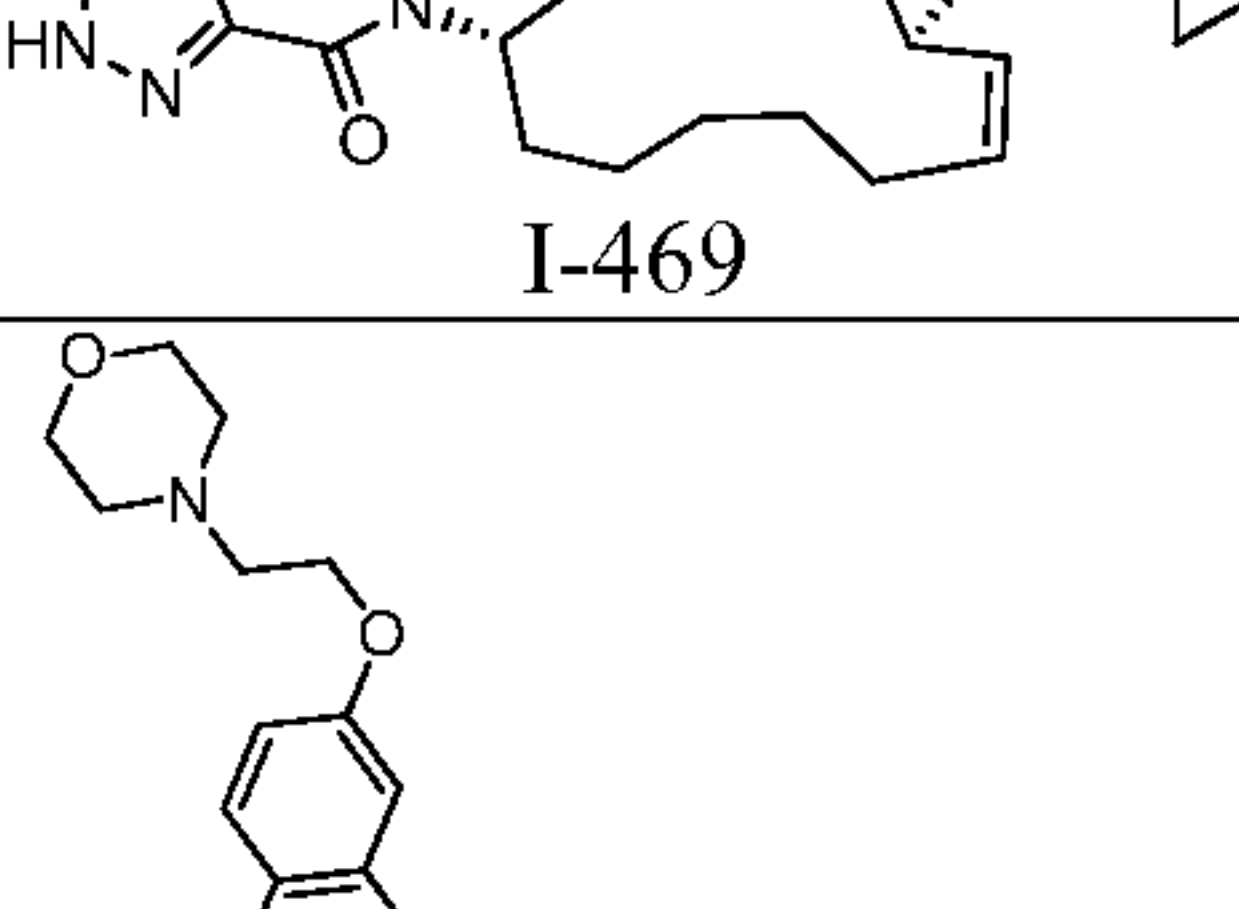
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
438	 I-438	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-(3-methoxypropoxy)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 7, 50 51	838.4
439	 I-439	<i>tert</i> -butyl [(1' <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-1'-fluoro-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	36	812.2
440	 I-440	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(difluoromethyl)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10	816.2 (K+ salt)
441	 I-441	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(difluoromethyl)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10	830.5
442	 I-442	(2 <i>S</i>)-3-methylbutan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(difluoromethyl)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10	830.2 (K+ salt)

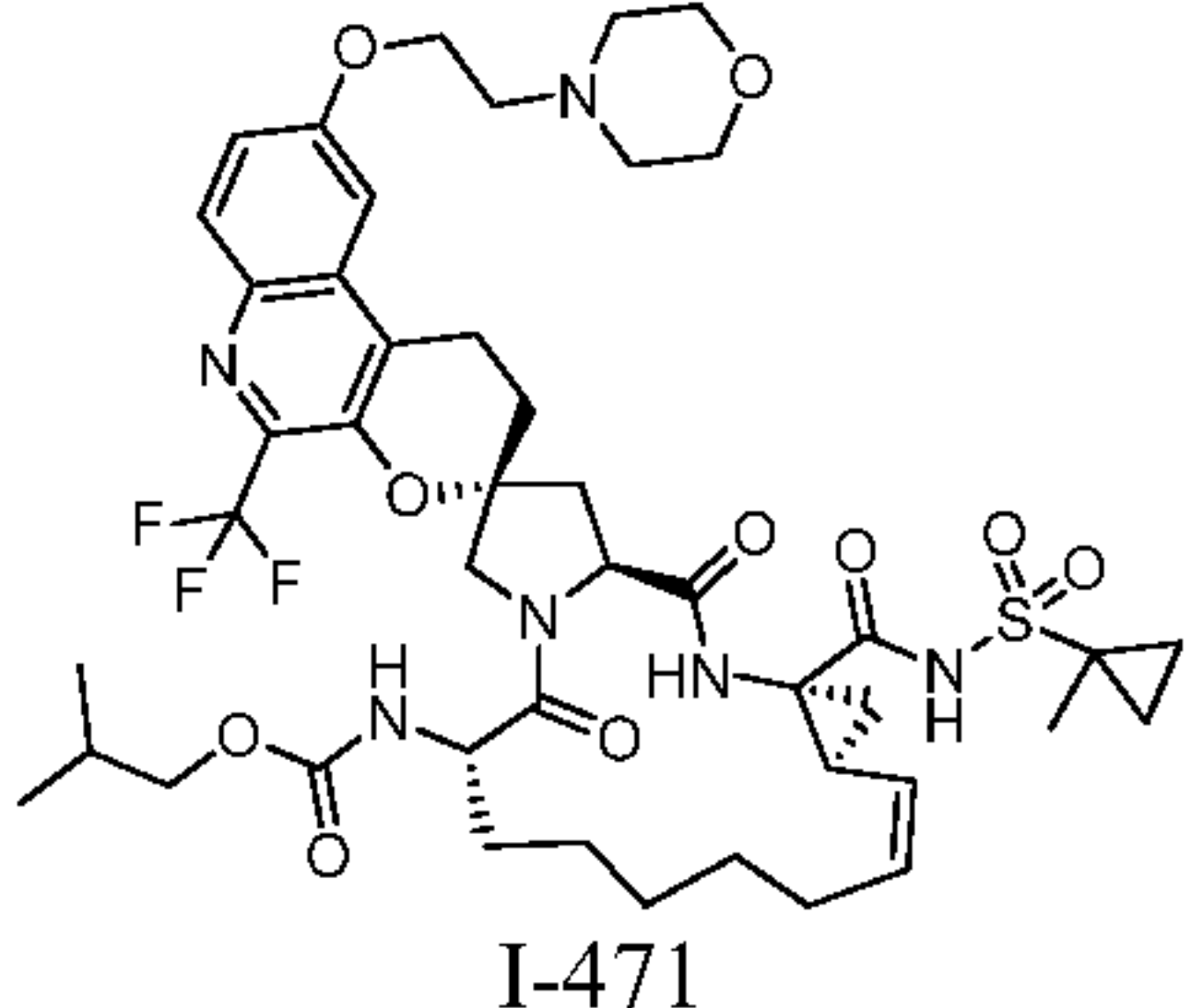
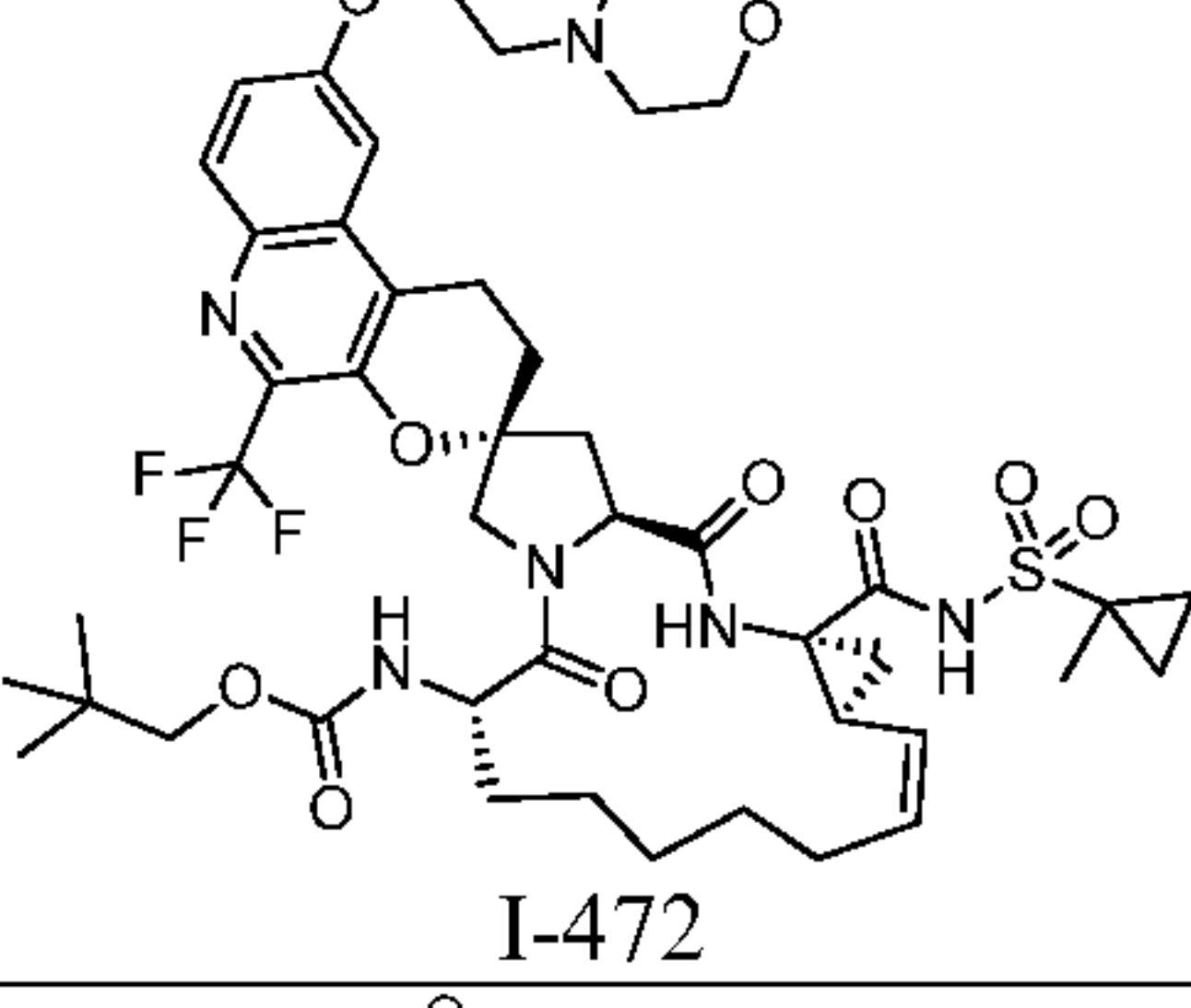
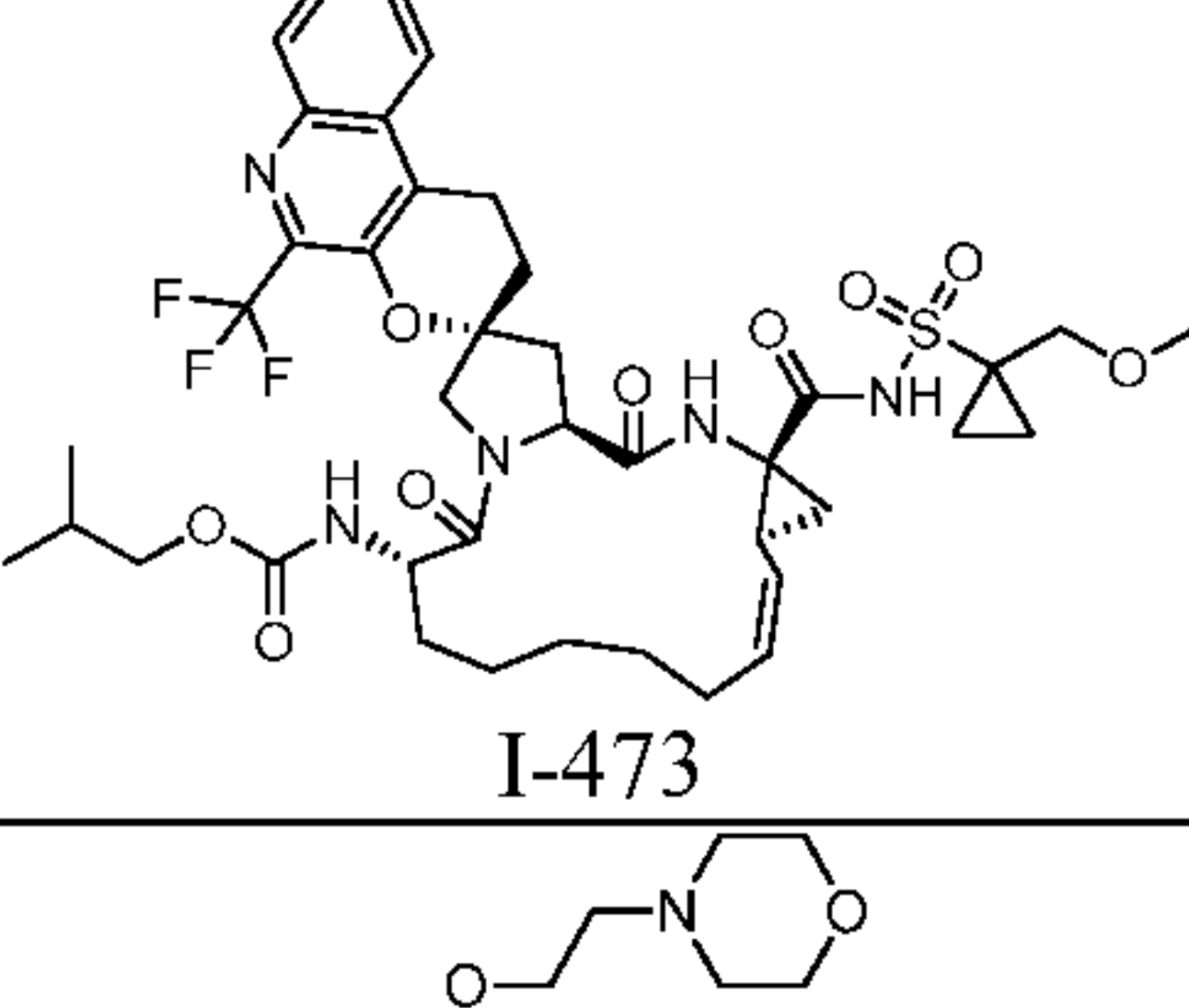
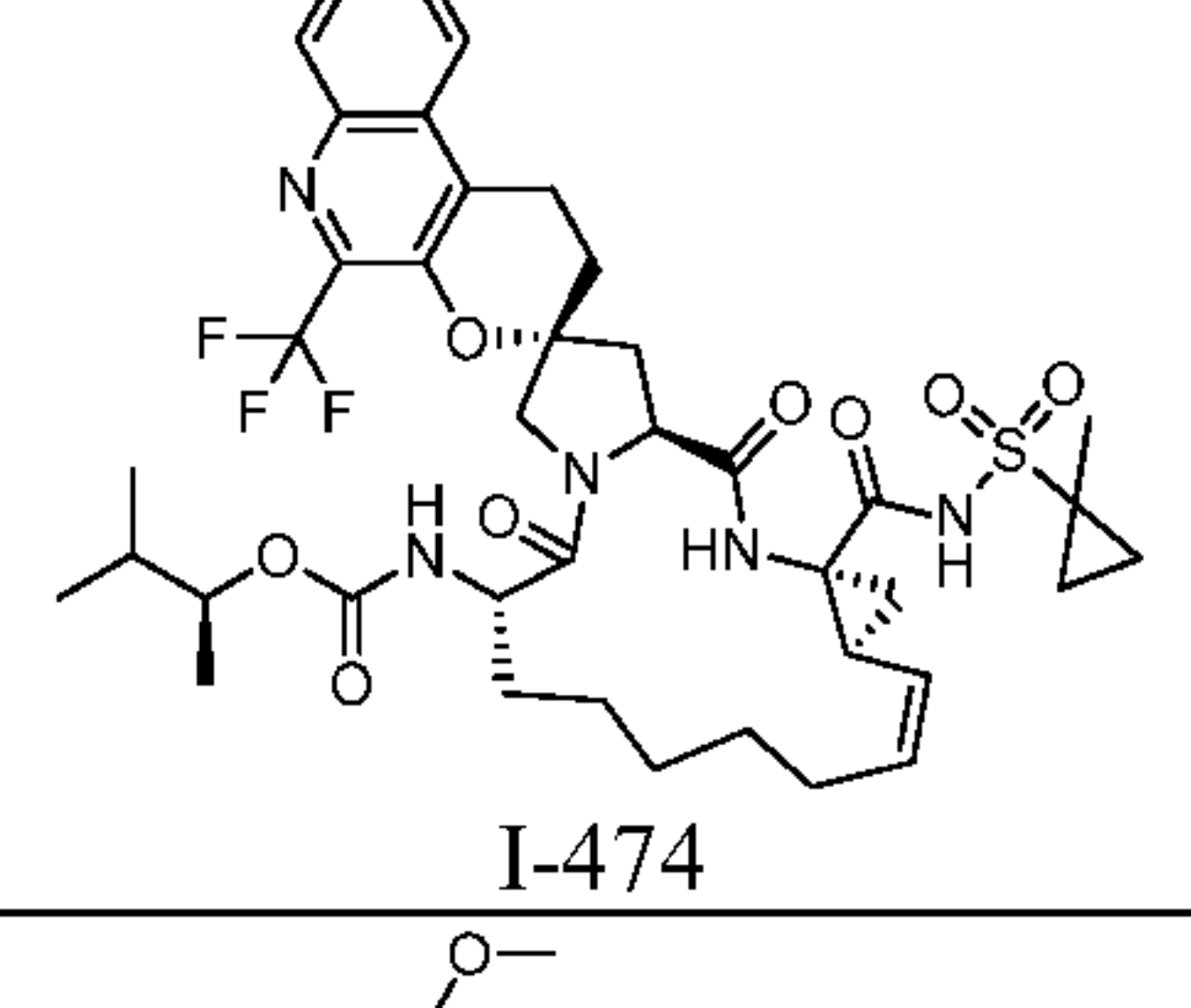
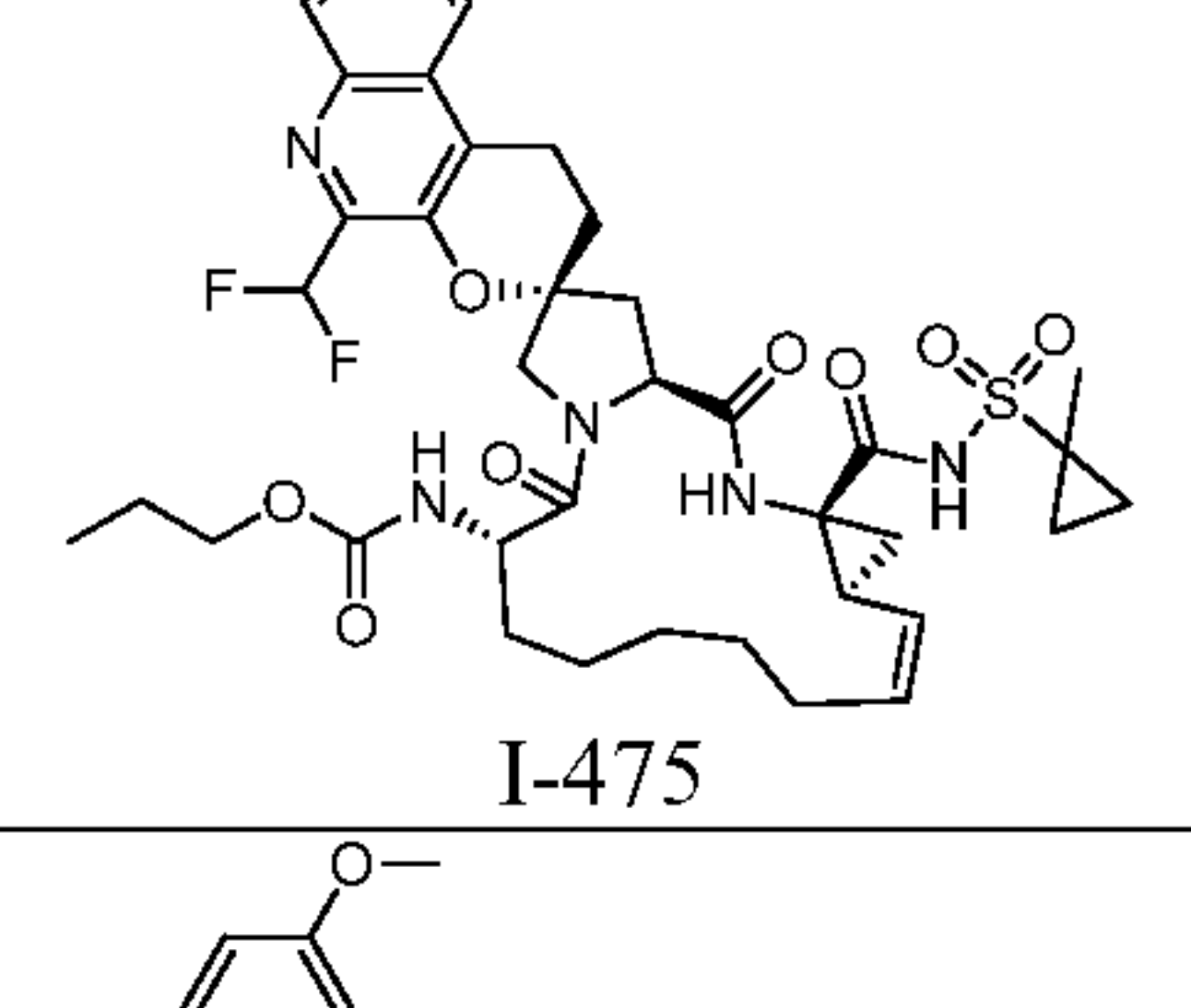
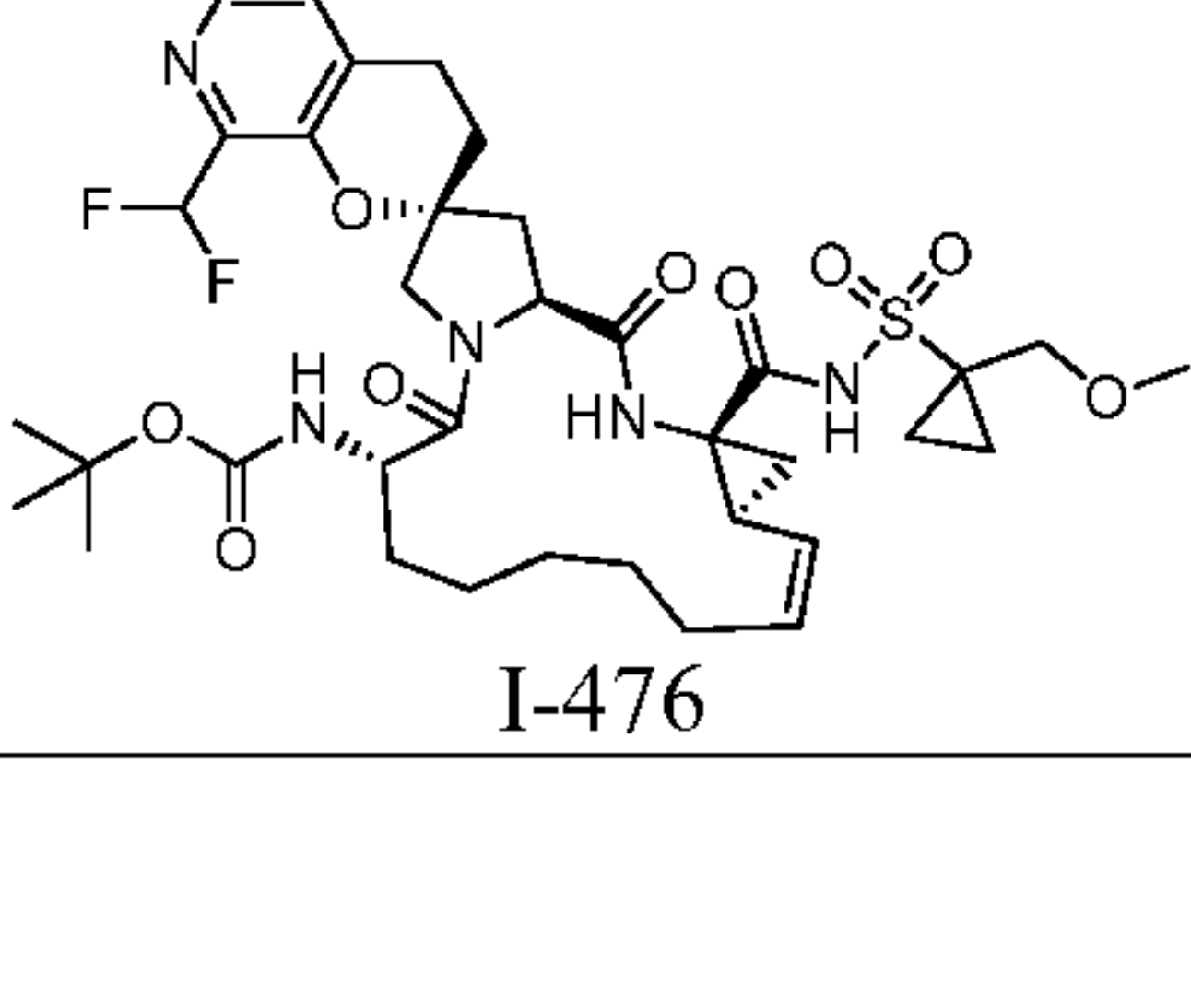
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
443	 I-443	(2R)-3-methylbutan-2-yl [(2R,6S,12Z,13aS,14aR,16aS)-5'-(difluoromethyl)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl} carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	10	830.2 (K+ salt)
444	 I-444	(2S)-butan-2-yl [(2R,6S,12Z,13aS,14aR,16aS)-5'-(difluoromethyl)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl} carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	10	816.2 (K+ salt)
445	 I-445	(2R)-butan-2-yl [(2R,6S,12Z,13aS,14aR,16aS)-5'-(difluoromethyl)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl} carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	10	816.2 (K+ salt)
446	 I-446	propan-2-yl [(2R,6S,12Z,13aS,14aR,16aS)-5'-(difluoromethyl)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl} carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	10	802.2
447	 I-447	propan-2-yl [(2R,6S,12Z,13aS,14aR,16aS)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl} carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	5, 35	820.8

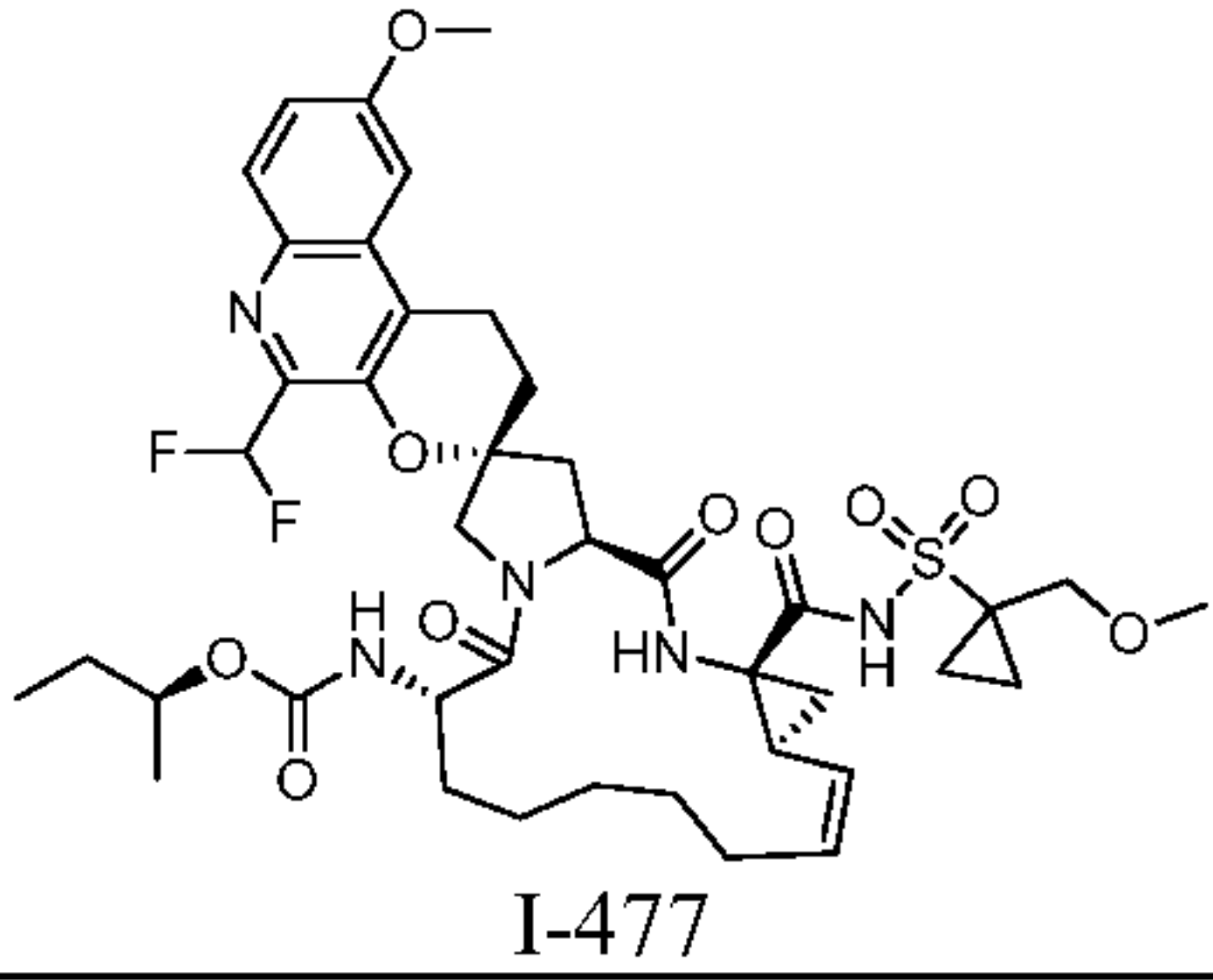
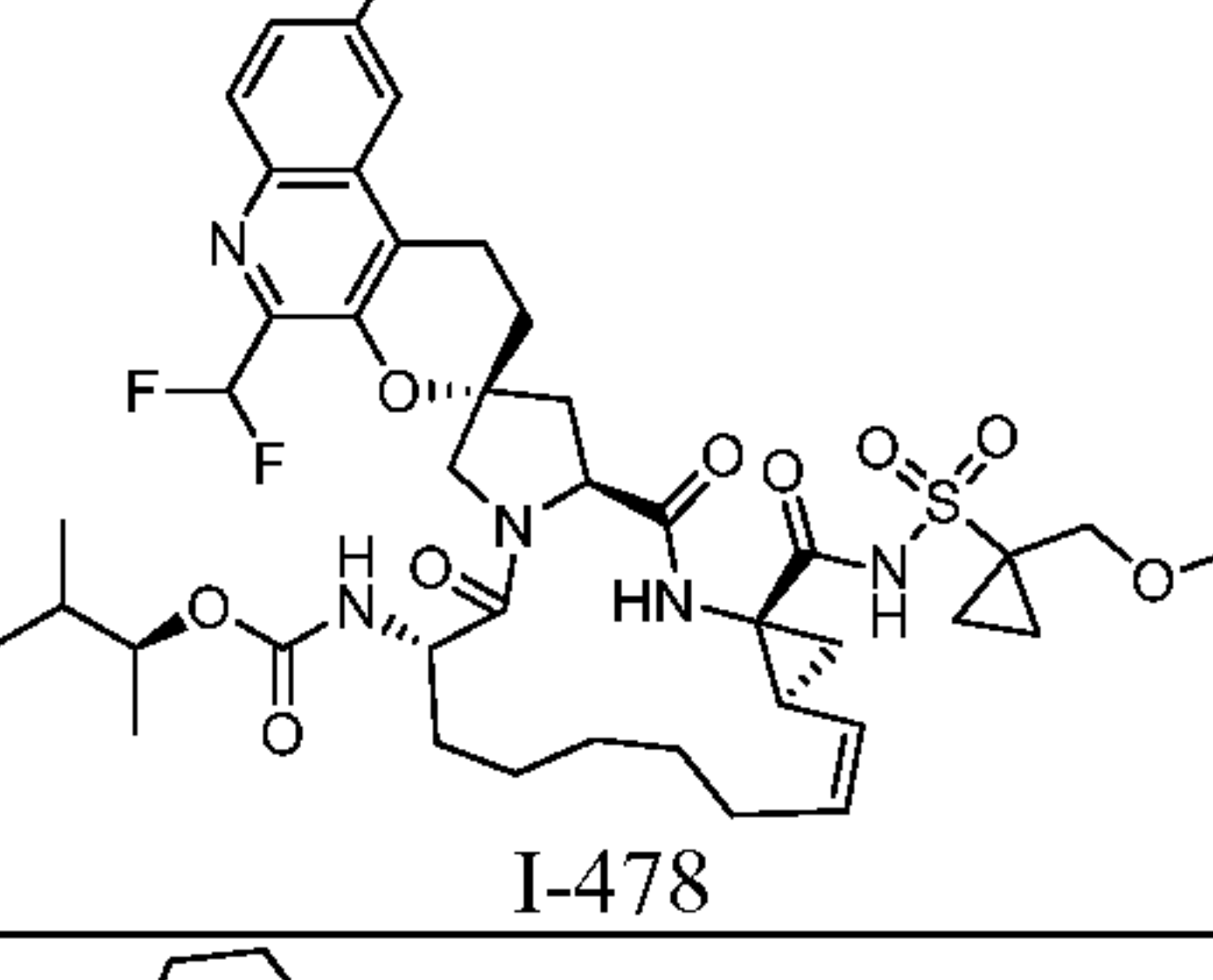
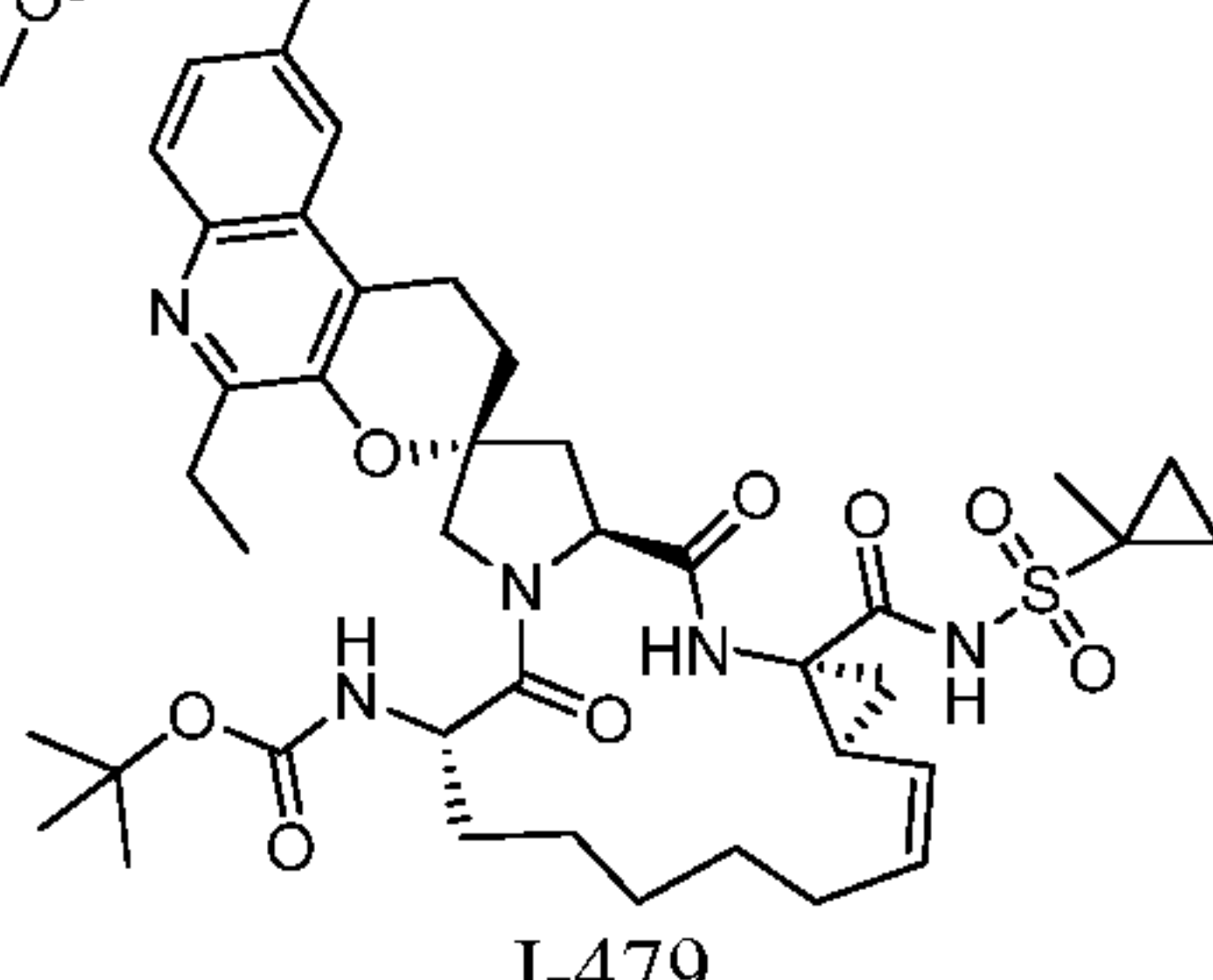
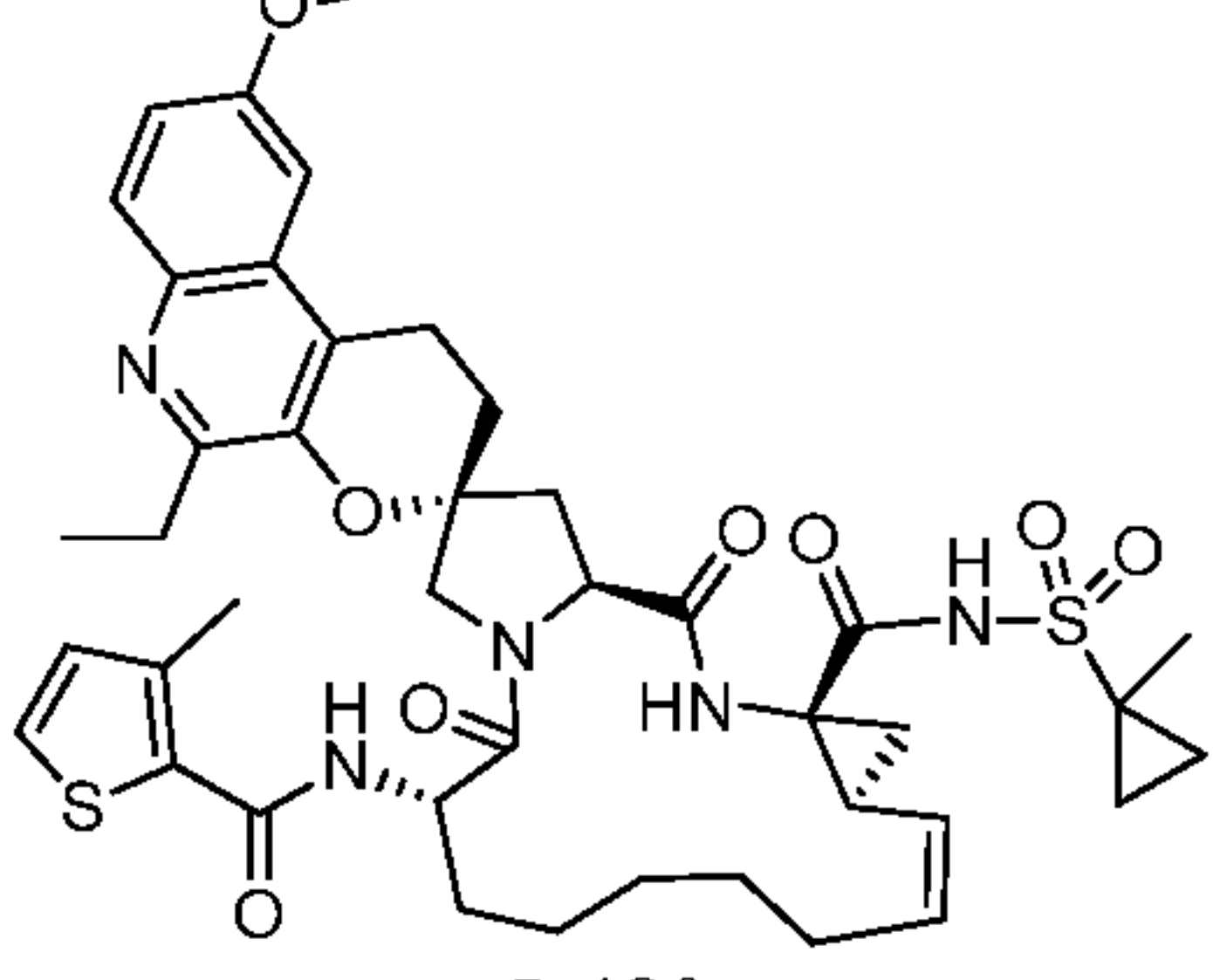
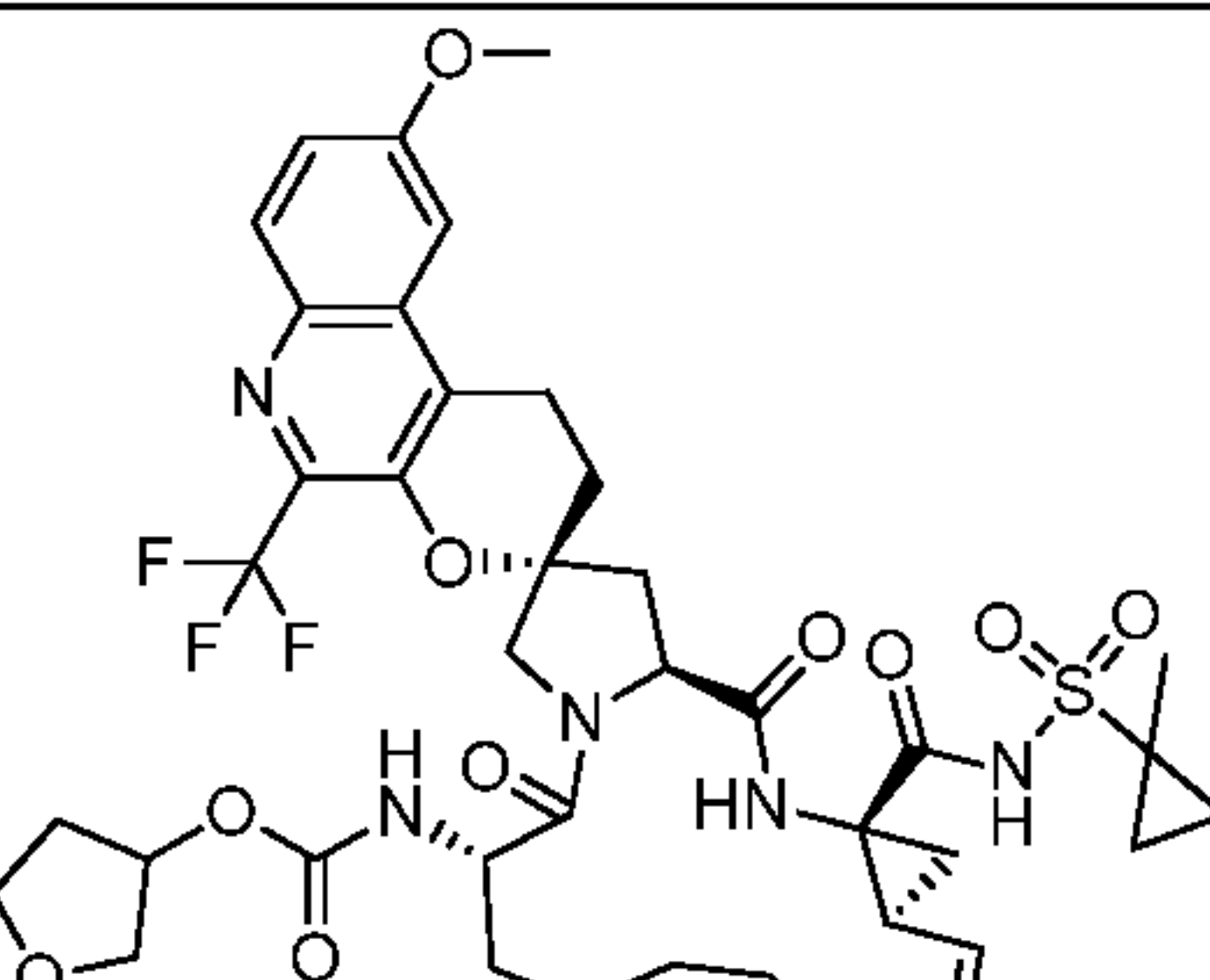
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
448	 I-448	propyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5, 35	820.3
449	 I-449	1-(propan-2-yl)cyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5, 35	860.34
450	 I-450	cyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5, 35	832.3
451	 I-451	1-methylcyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5, 35	846.5
452	 I-452	1-ethylcyclopropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5, 35	846.6
453	 I-453	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-(3-methoxypropoxy)-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	1, 7, 50, 51, 6	852.4

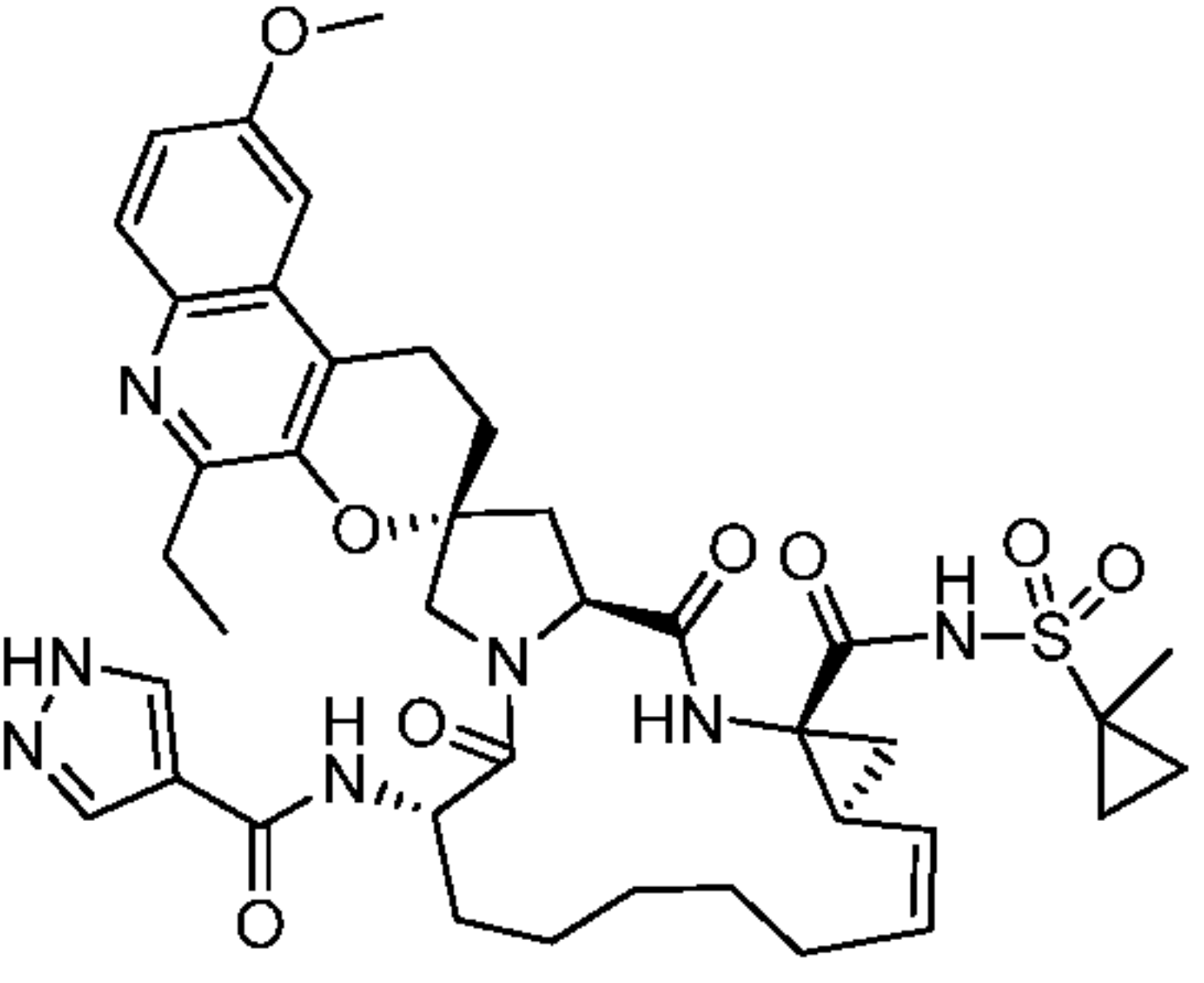
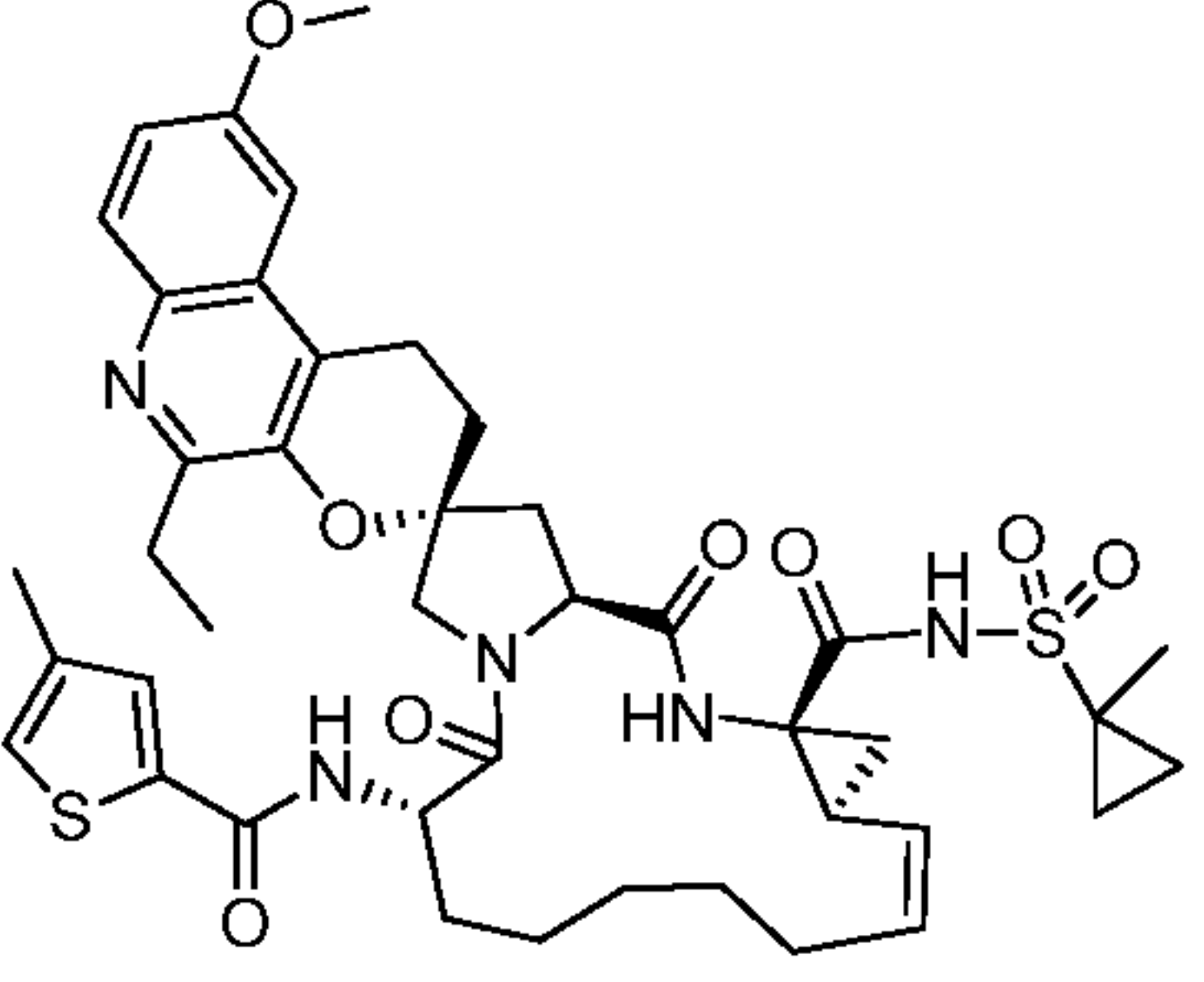
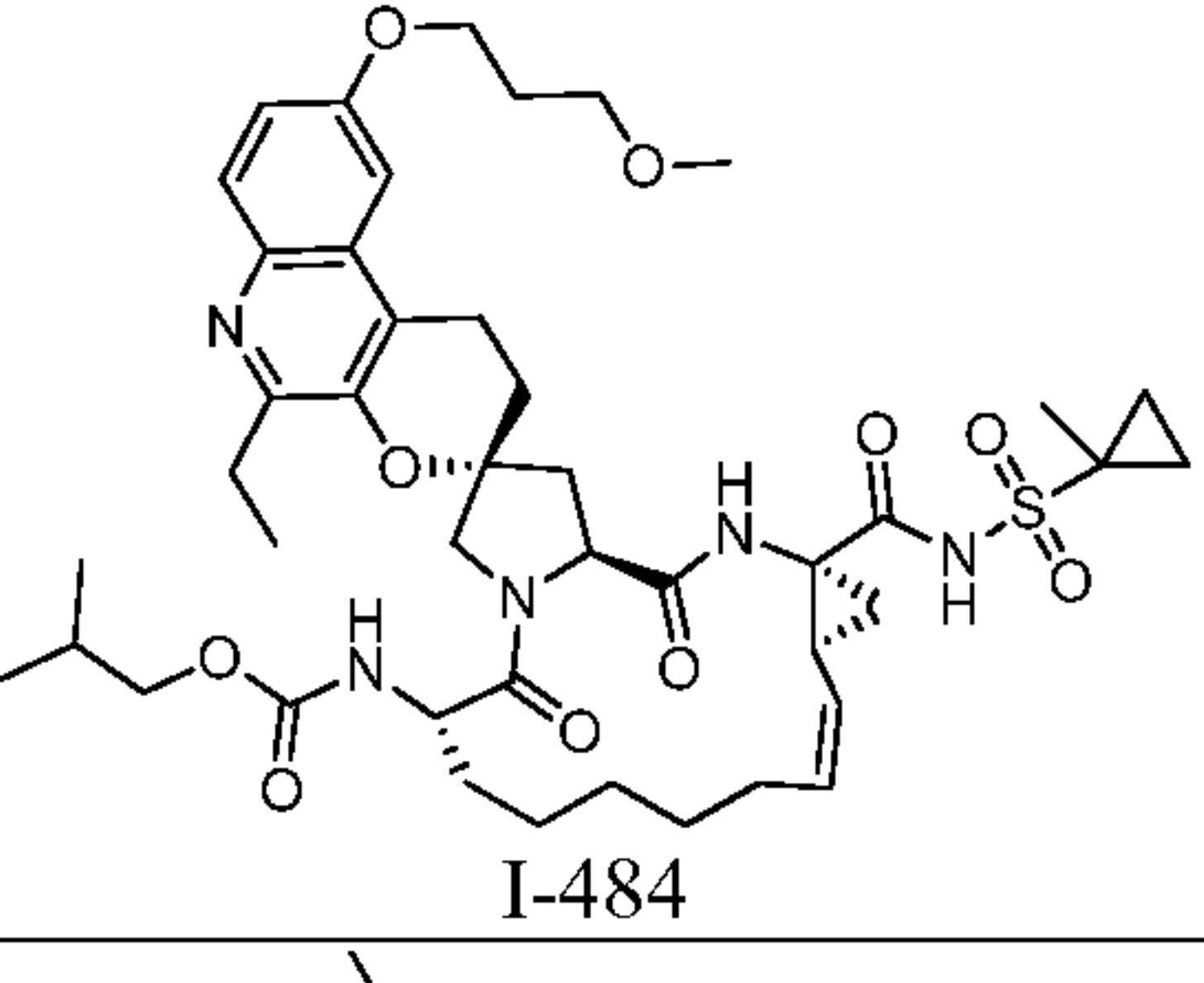
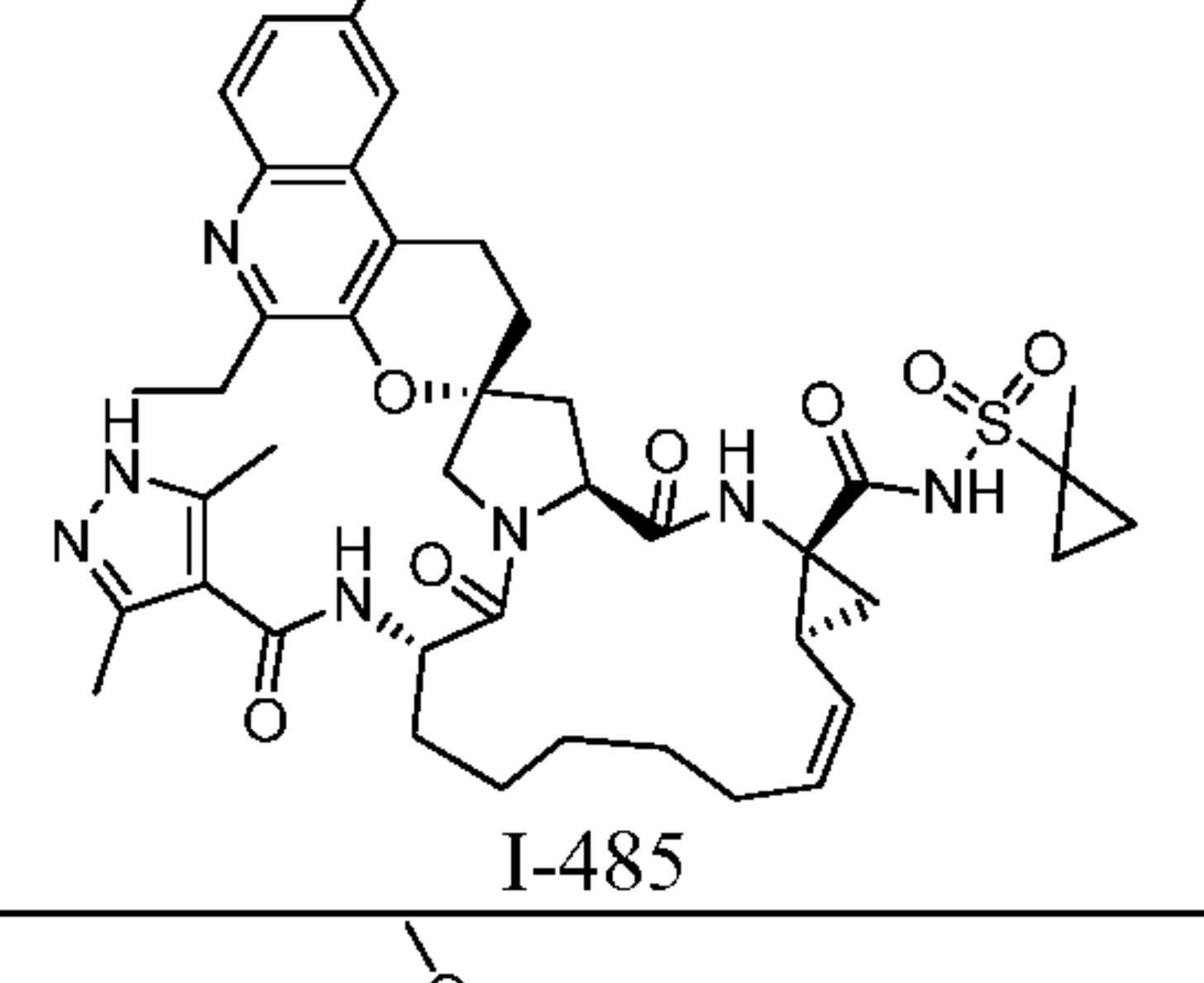
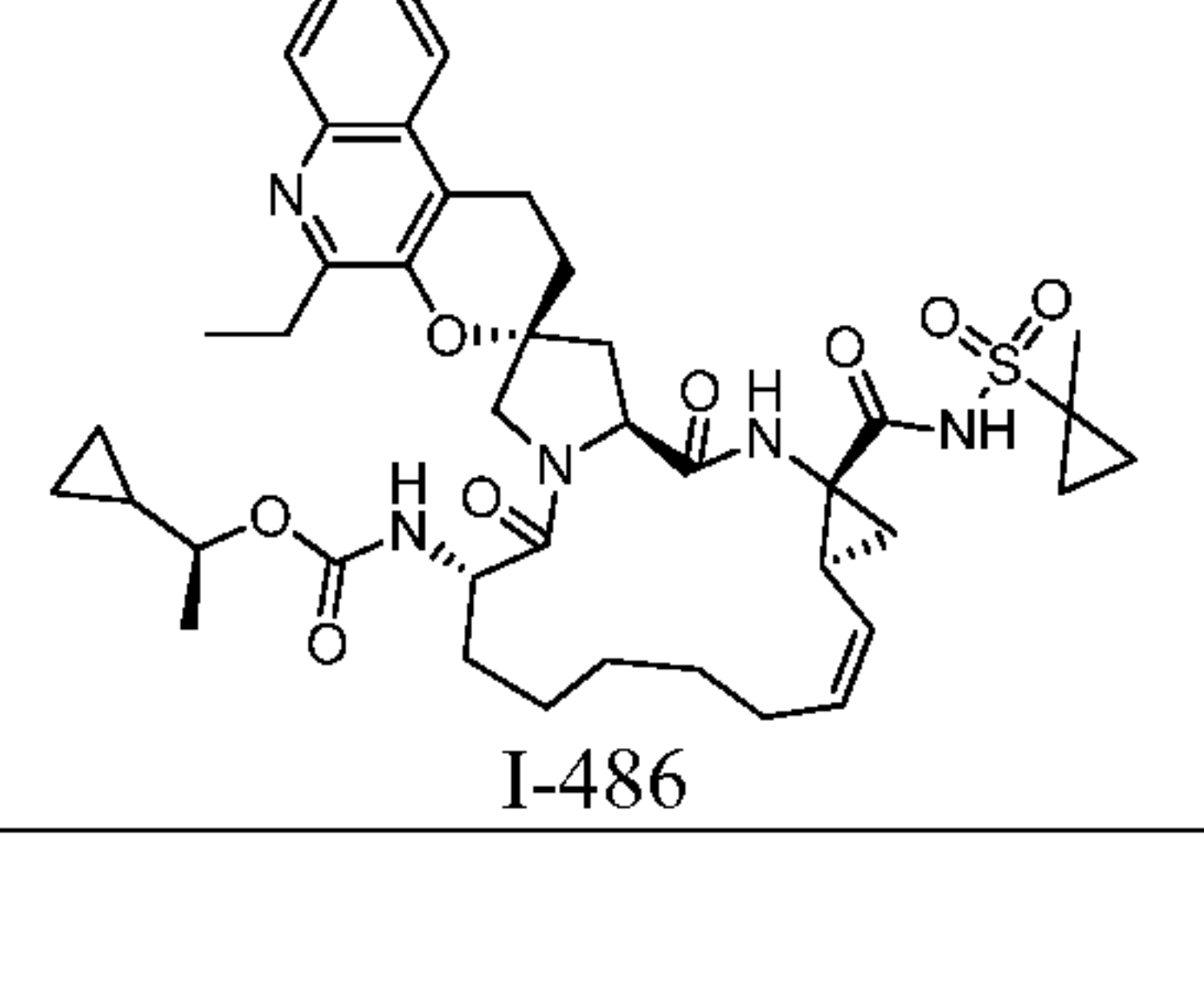
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
454	 I-454	2-methylpropyl [(1 <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-1'-fluoro-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	17	824.2 (K+ salt)
455	 I-455	2,2-dimethylpropyl [(1 <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-1'-fluoro-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	17	838.2 (K+ salt)
456	 I-456	propan-2-yl [(1 <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-1'-fluoro-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	17	810.2 (K+ salt)
457	 I-457	(2 <i>R</i>)-3-methylbutan-2-yl [(1 <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-cyclopropyl-1'-fluoro-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	17	838.2 (K+ salt)
458	 I-458	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-(fluoromethoxy)-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	7	852.4

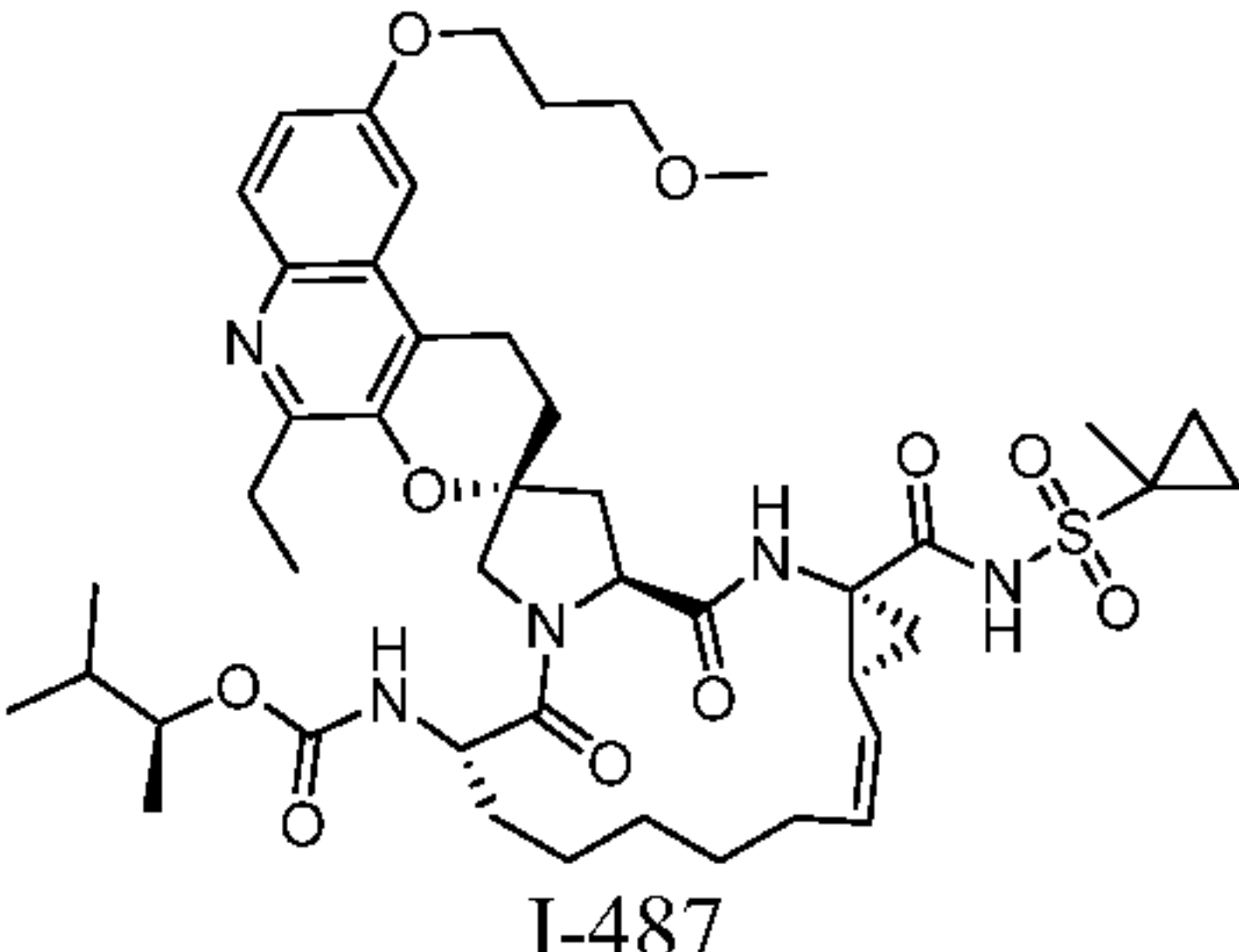
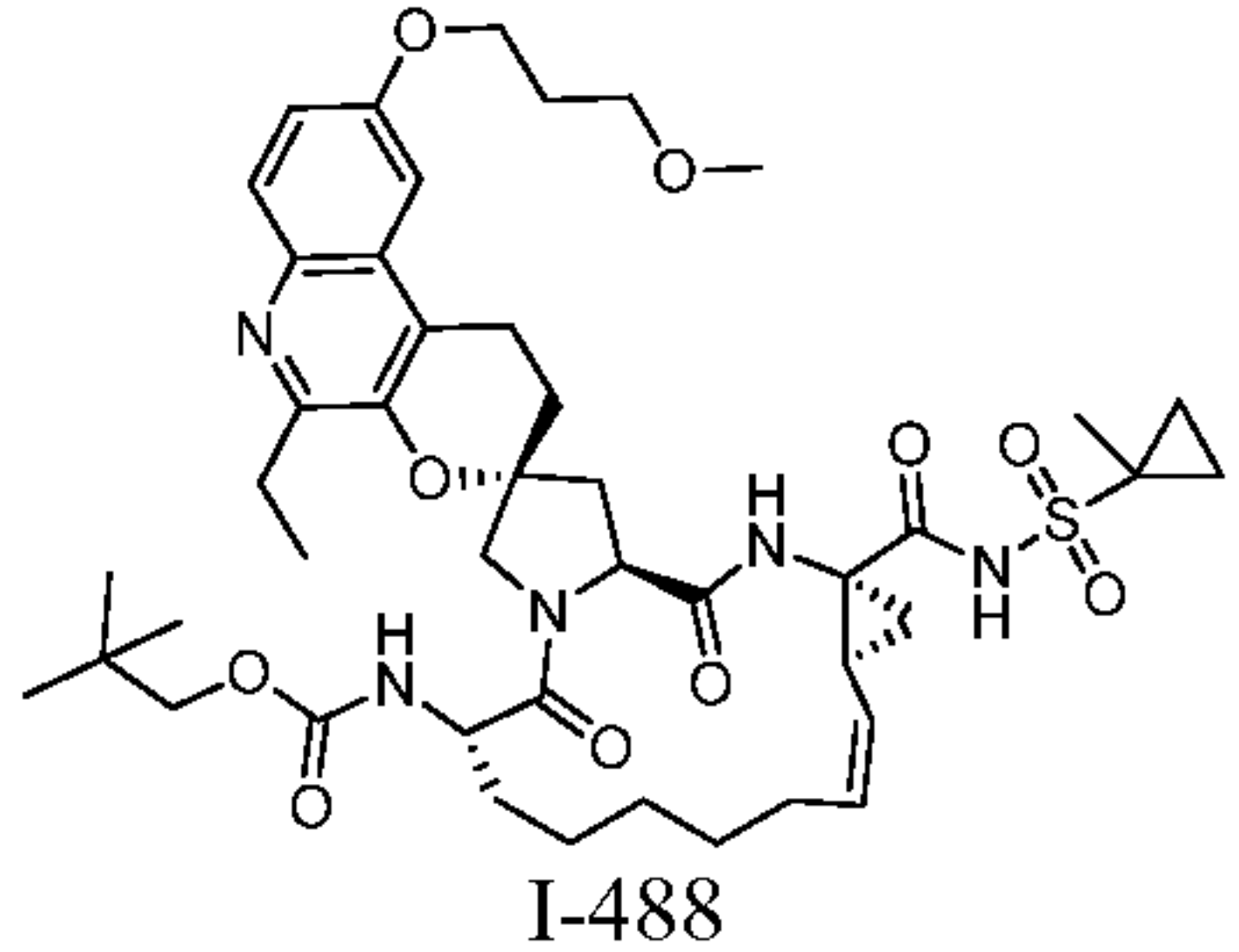
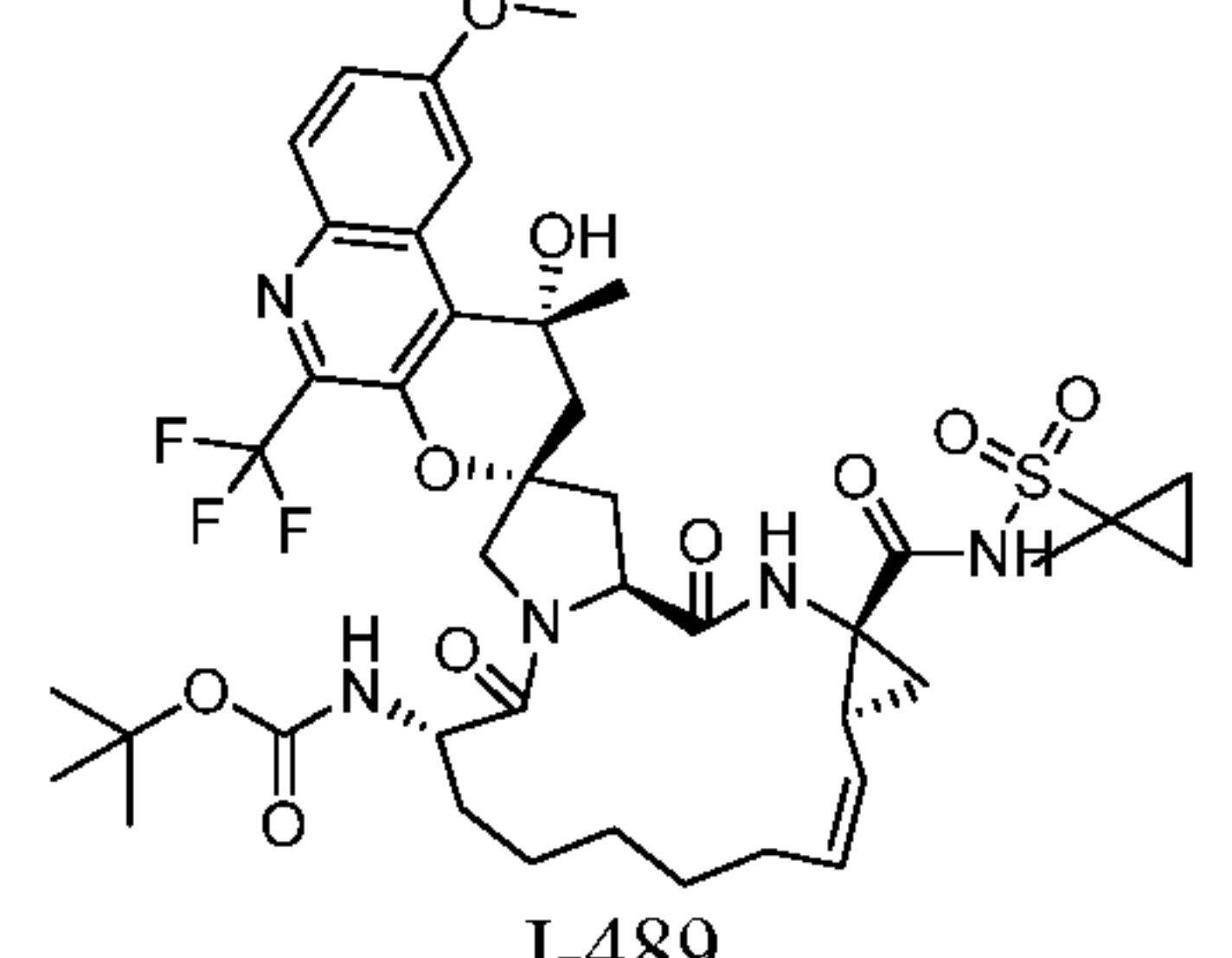
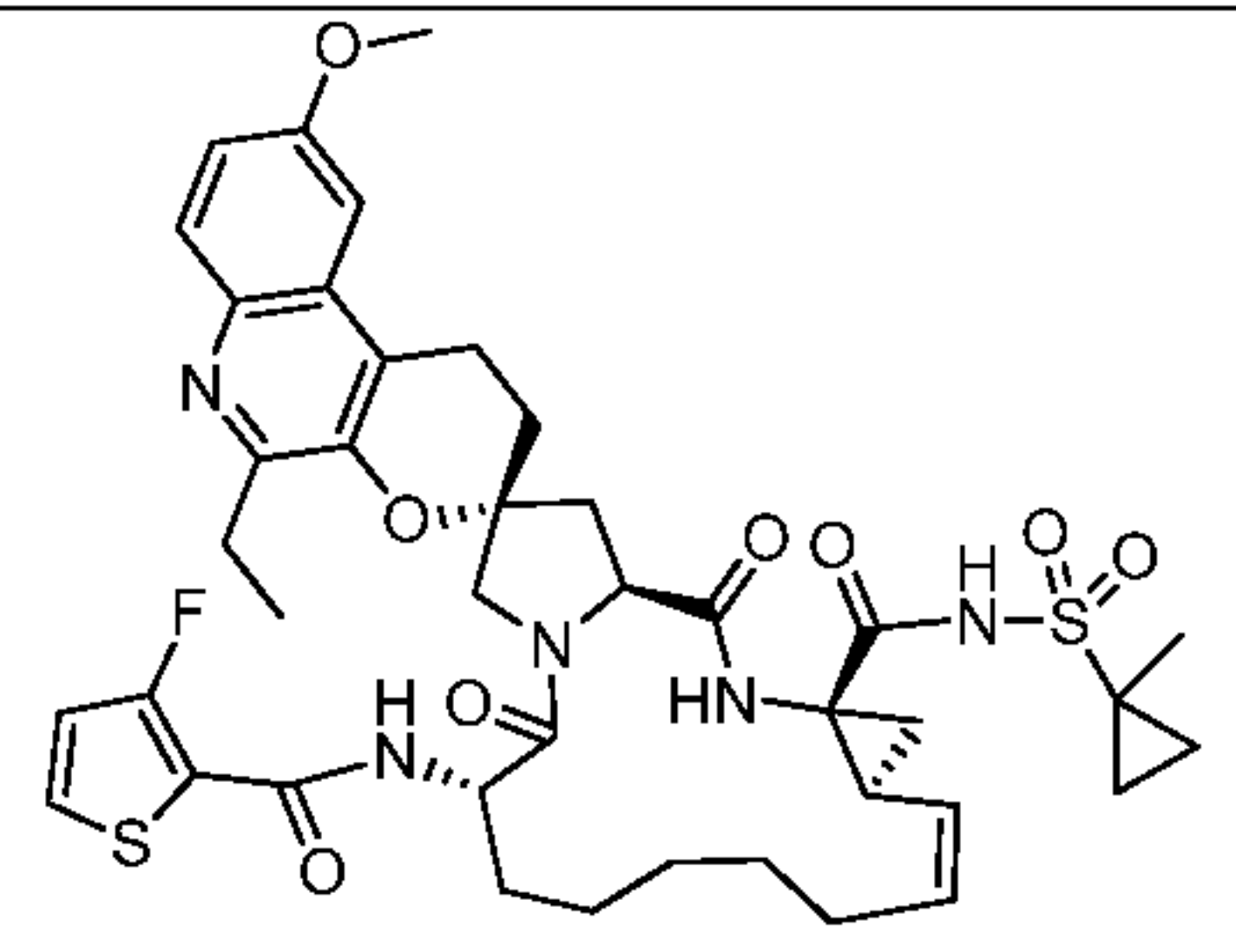
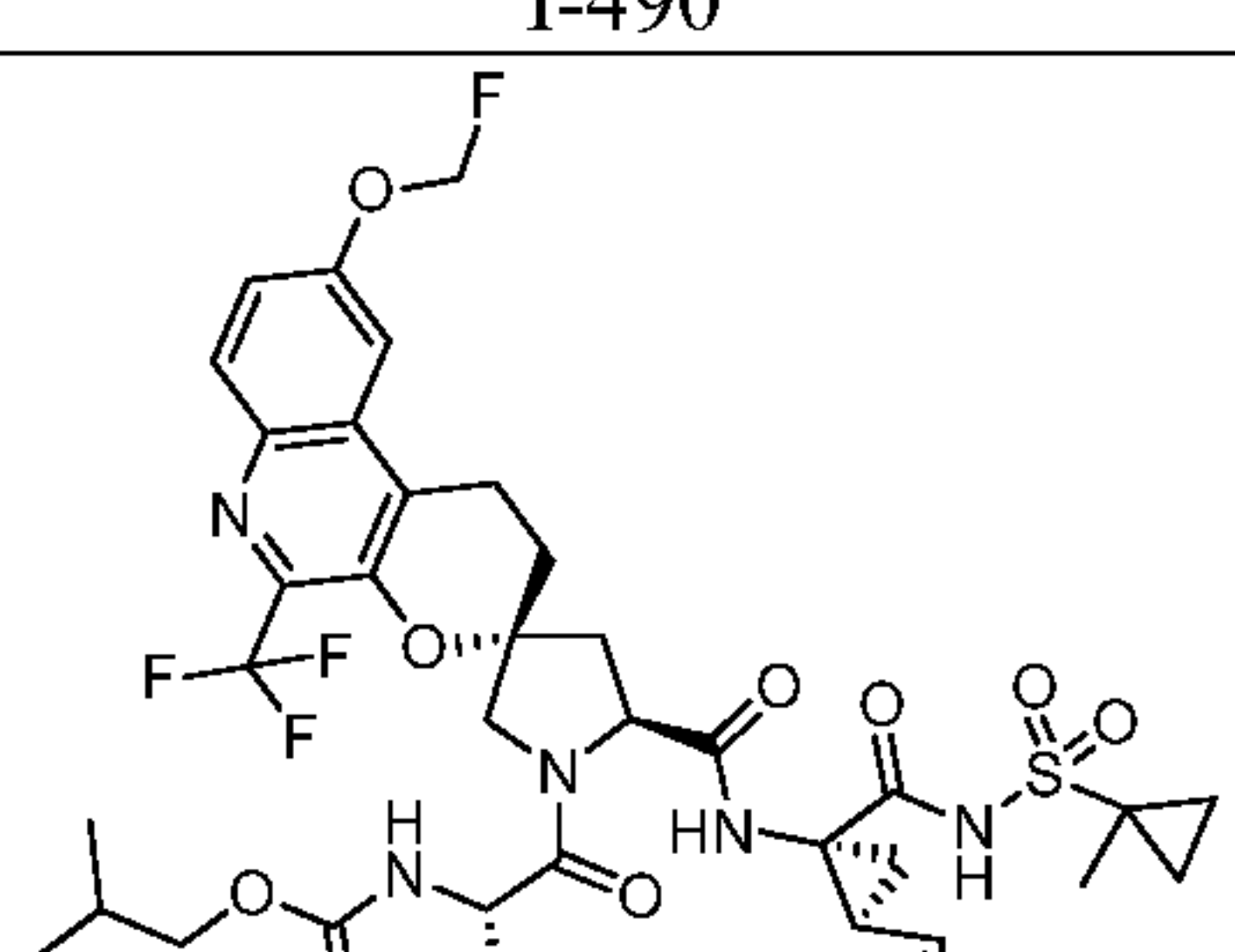
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
459	 I-459	(2 <i>R</i>)-butan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5, 35	834.8 (K+ salt)
460	 I-460	(2 <i>S</i>)-butan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5, 35	834.8 (K+ salt)
461	 I-461	2-methylpropyl [(1' <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-fluoro-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	3, 35	852.26
462	 I-462	2,2-dimethylpropyl [(1' <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-fluoro-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5, 35	866
463	 I-463	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-5'-methyl- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-6-[(6-methylpyridin-2-yl)amino]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	57	771.3
464	 I-464	<i>tert</i> -butyl [(6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1',8'-difluoro-5'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	25	786.2

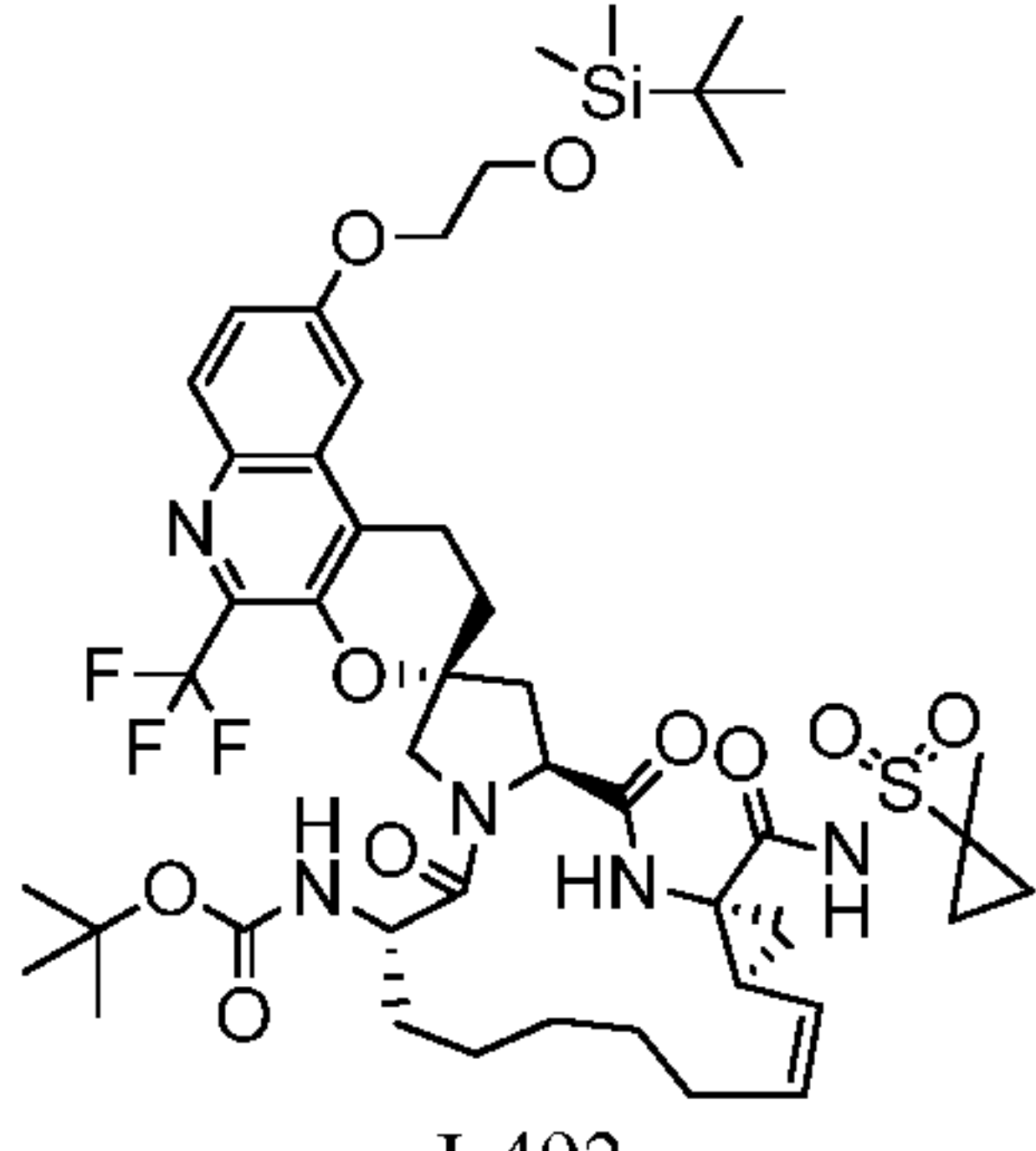
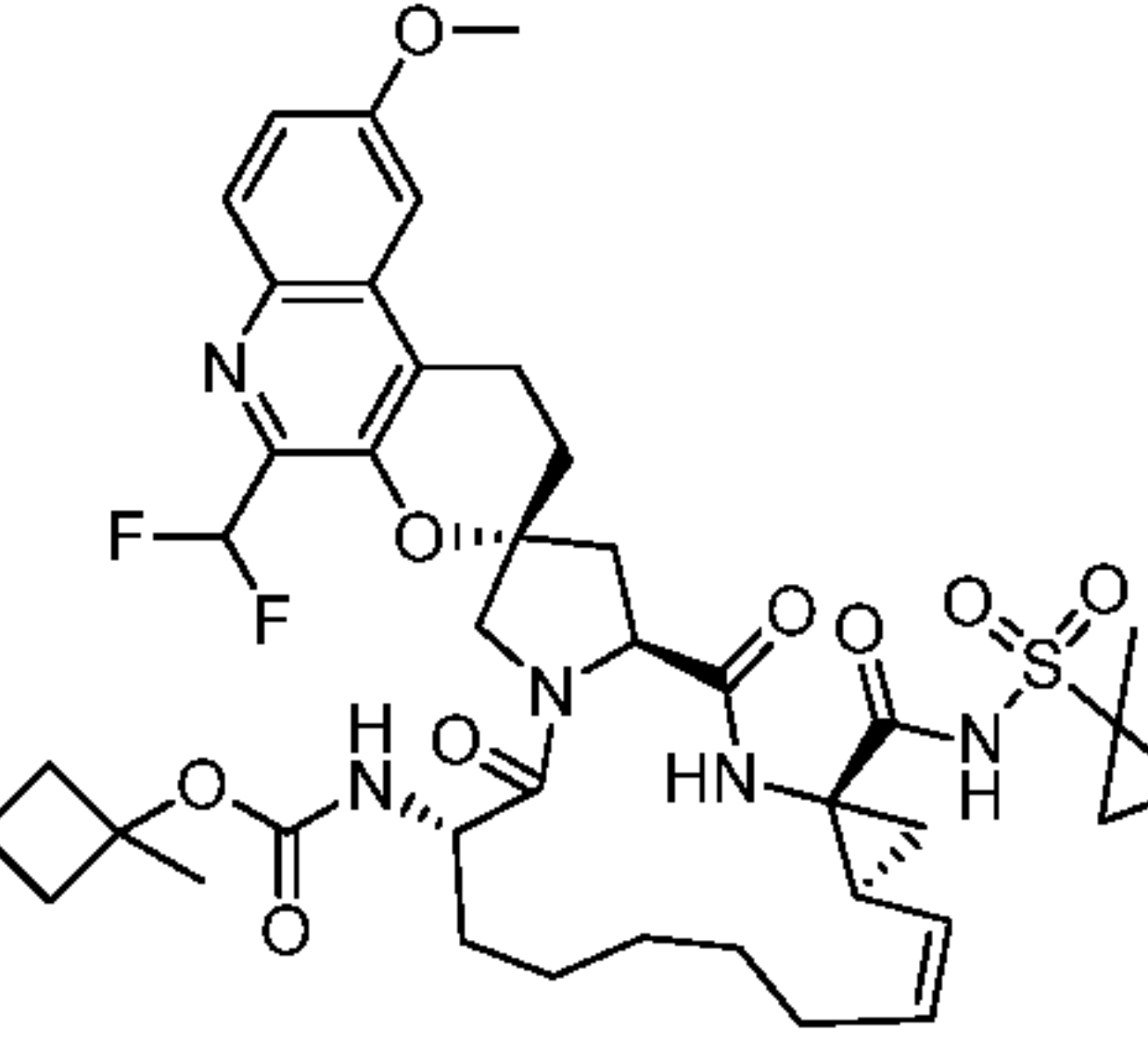
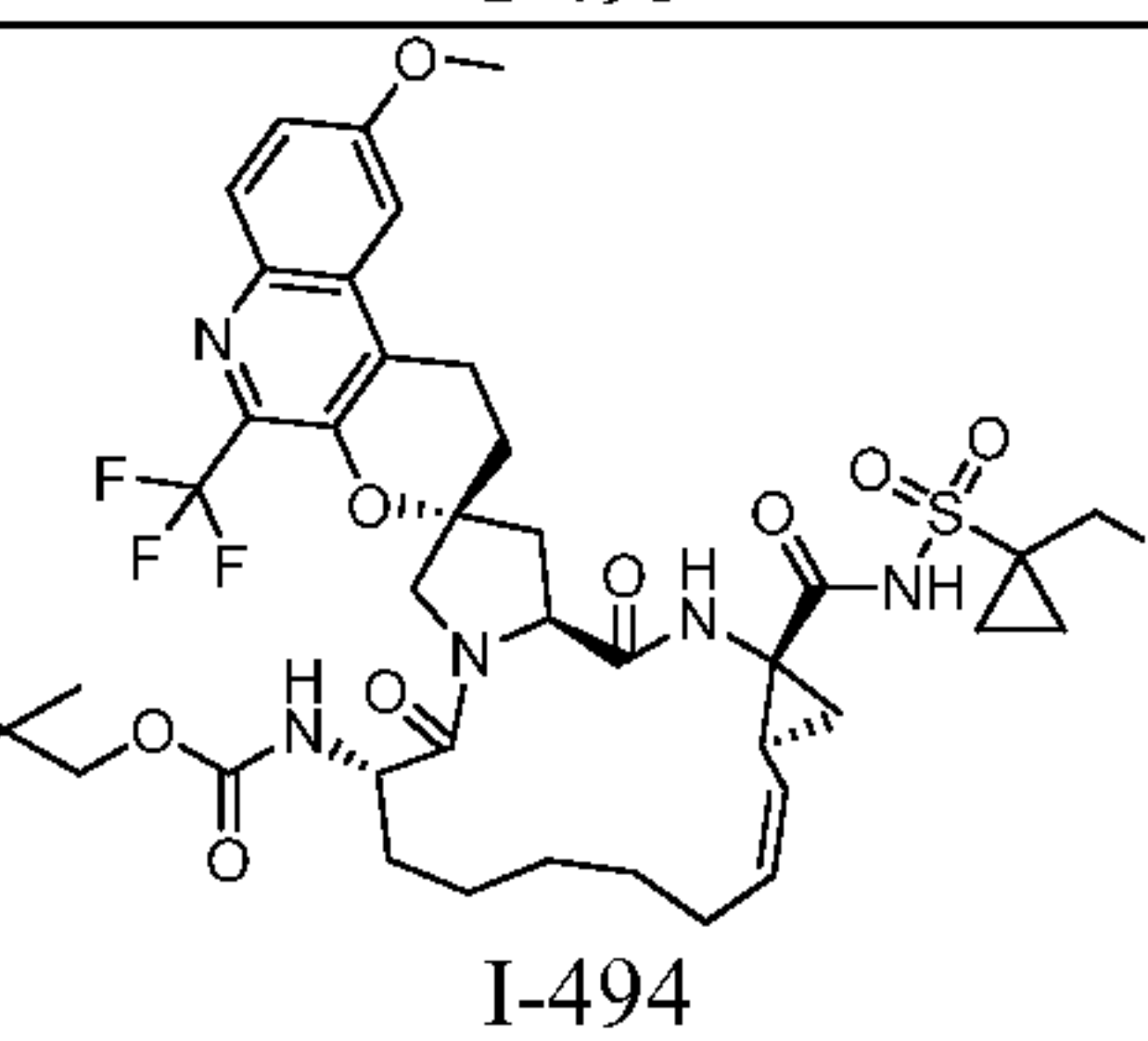
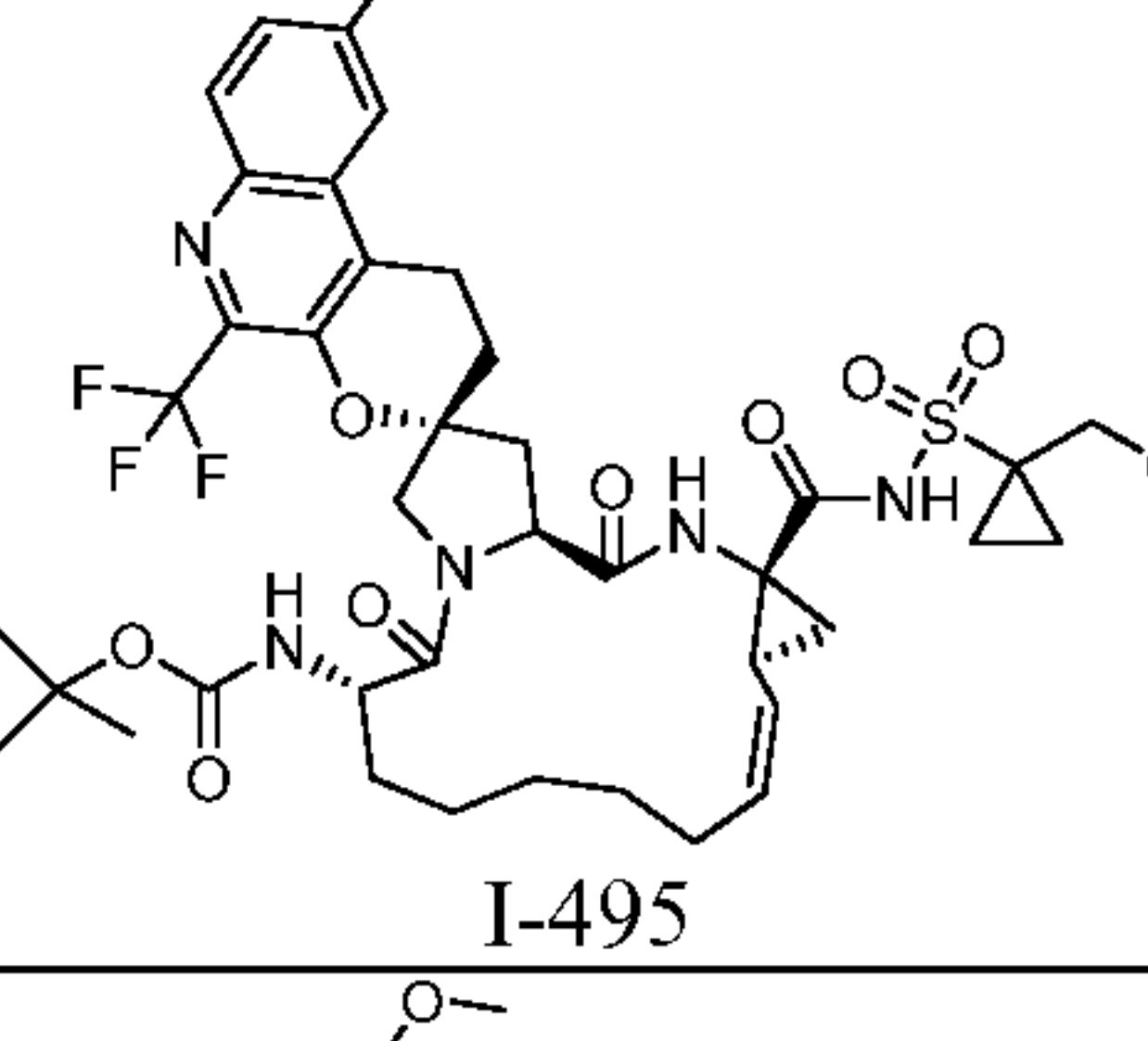
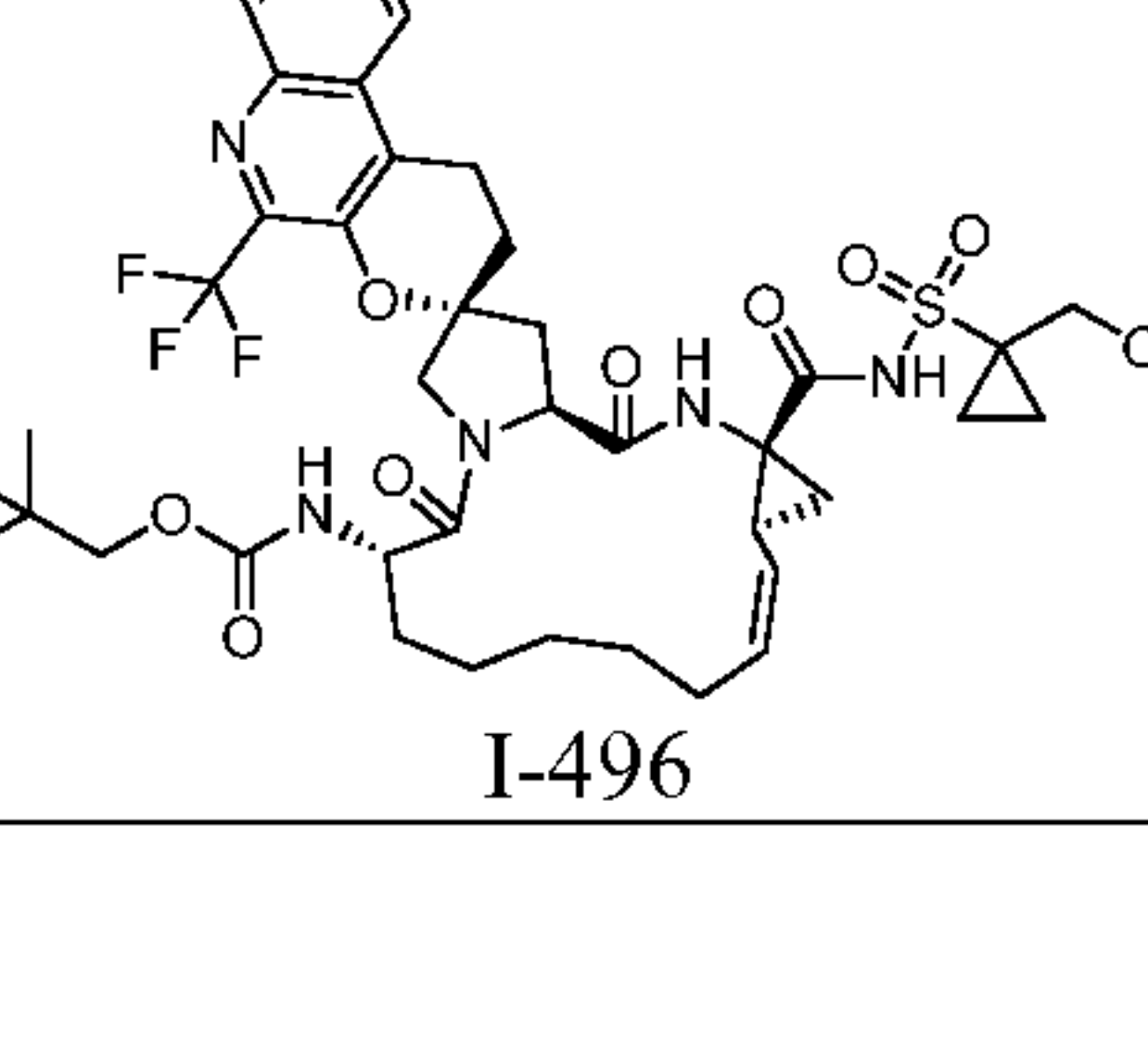
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
465		ethyl (2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(<i>tert</i> -butoxycarbonyl)amino]-9'-methoxy-1',5,16-trioxo-5'-(trifluoromethyl)-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxylate	5	--
466		(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-9'-methoxy- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-6-[[5-methylthiophen-2-yl)carbonyl]amino]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	47	818.35
467		(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-6-[[1-ethyl-1 <i>H</i> -pyrazol-3-yl)carbonyl]amino]-9'-methoxy- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	47	816.34
468		(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-([1-(difluoromethyl)-1 <i>H</i> -pyrazol-3-yl)carbonyl]amino)-5'-ethyl-9'-methoxy- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	47	838.03
469		(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-9'-methoxy- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-6-[(1 <i>H</i> -pyrazol-3-yl)carbonyl]amino]-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	47	788.06
470		<i>tert</i> -butyl {(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-14 <i>a</i> -[[[(1-methylcyclopropyl)sulfonyl]carbamoyl]-9'-[2-(morpholin-4-yl)ethoxy]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl} carbamate	56, 30, 51	893.29

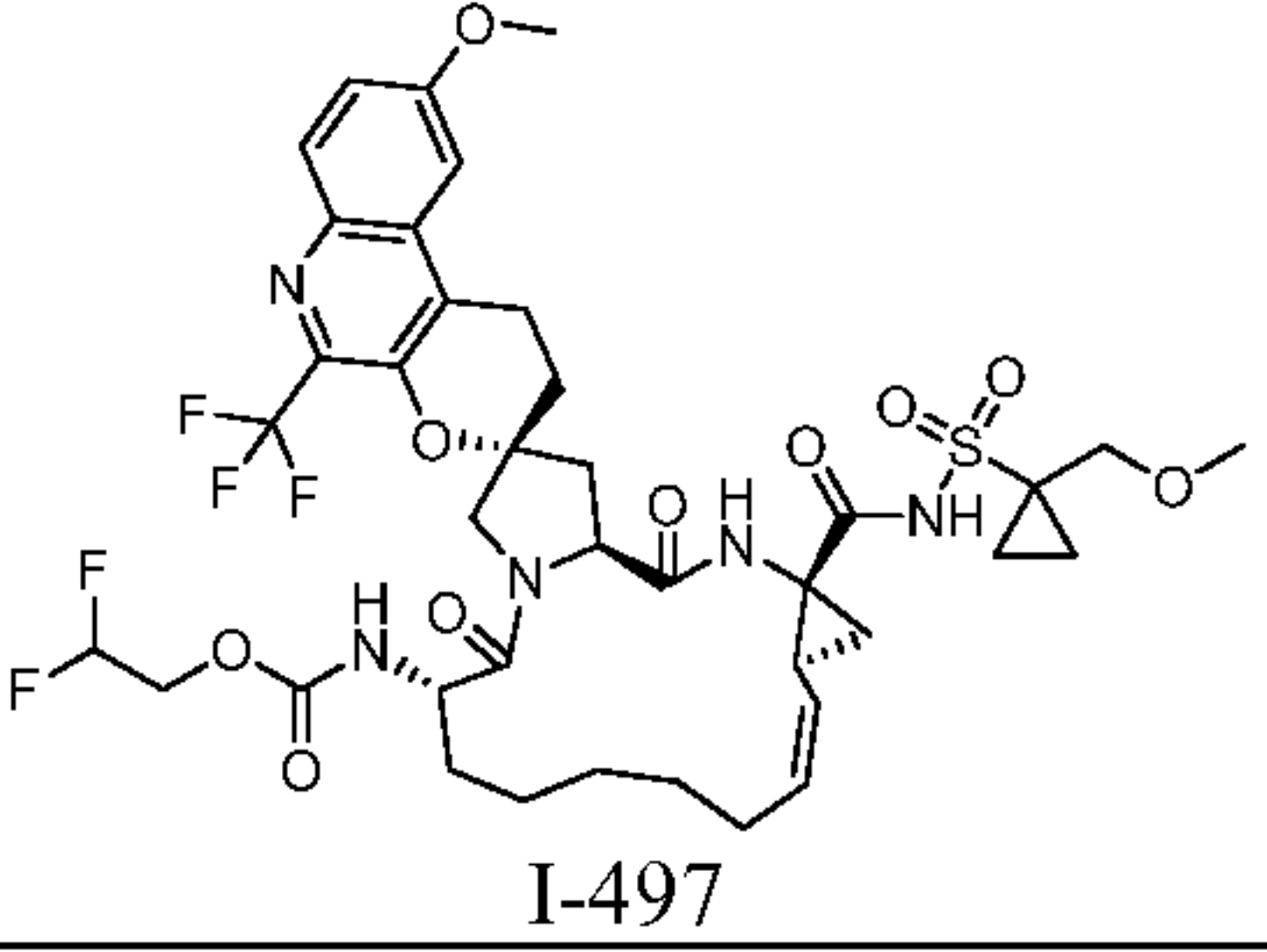
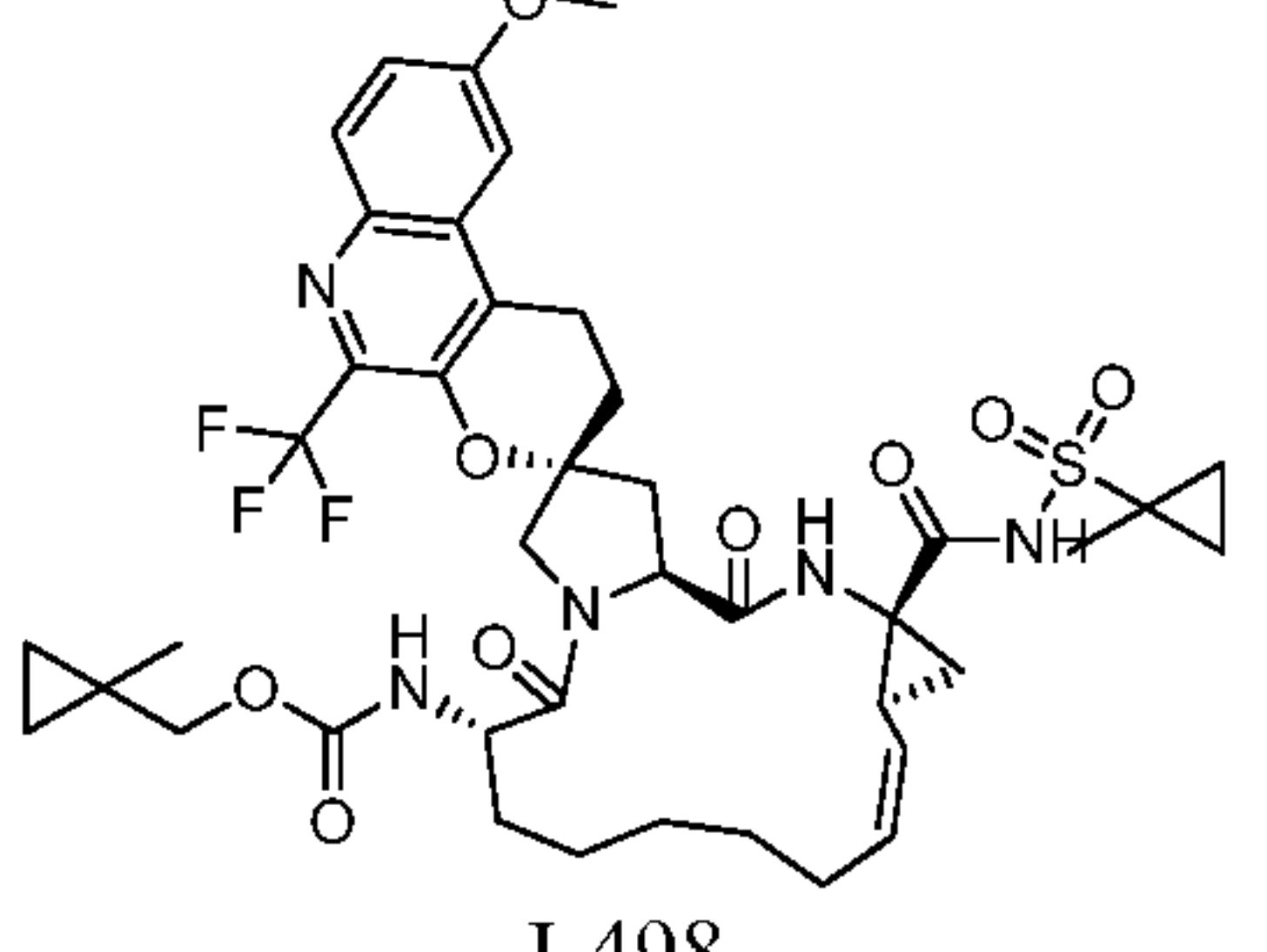
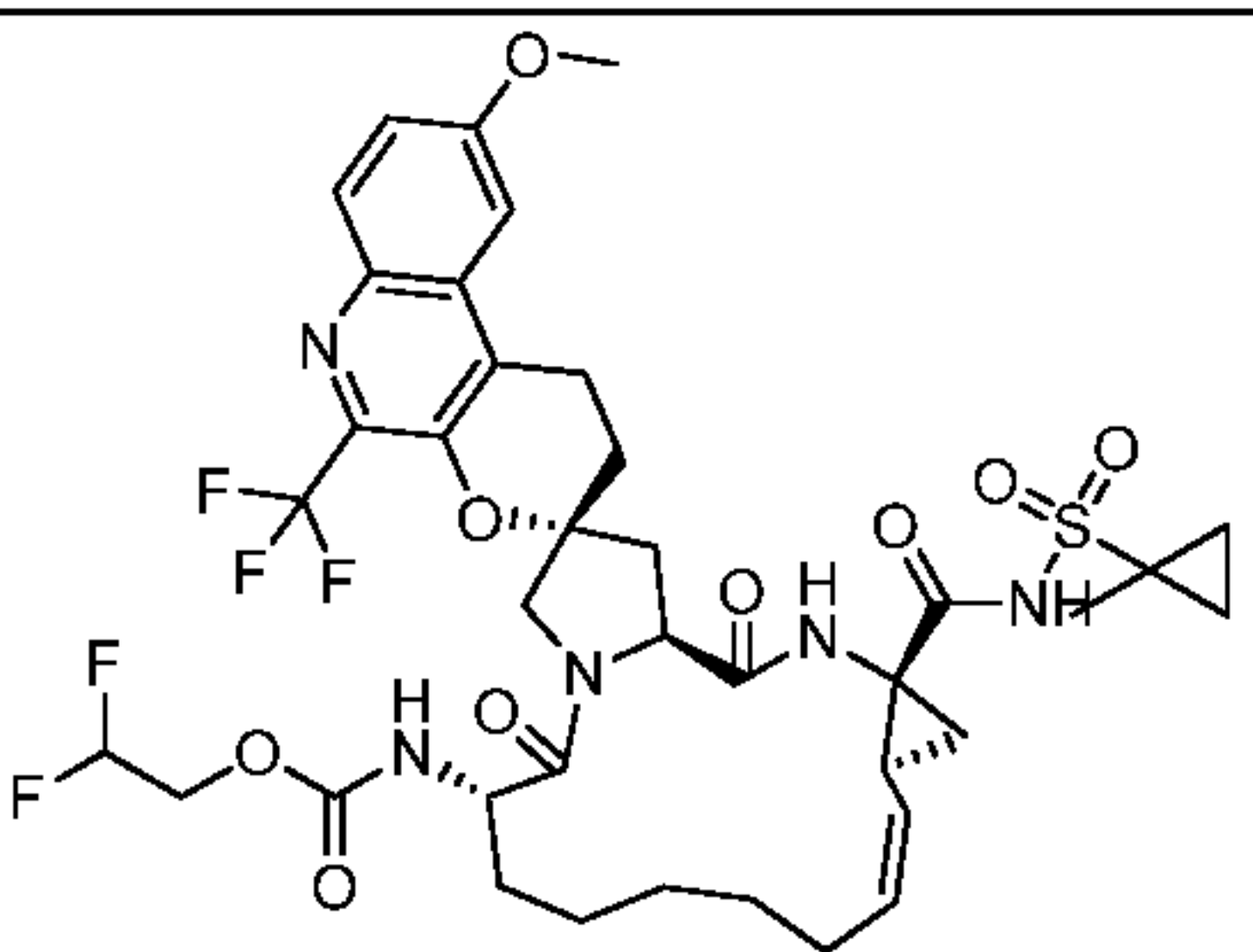
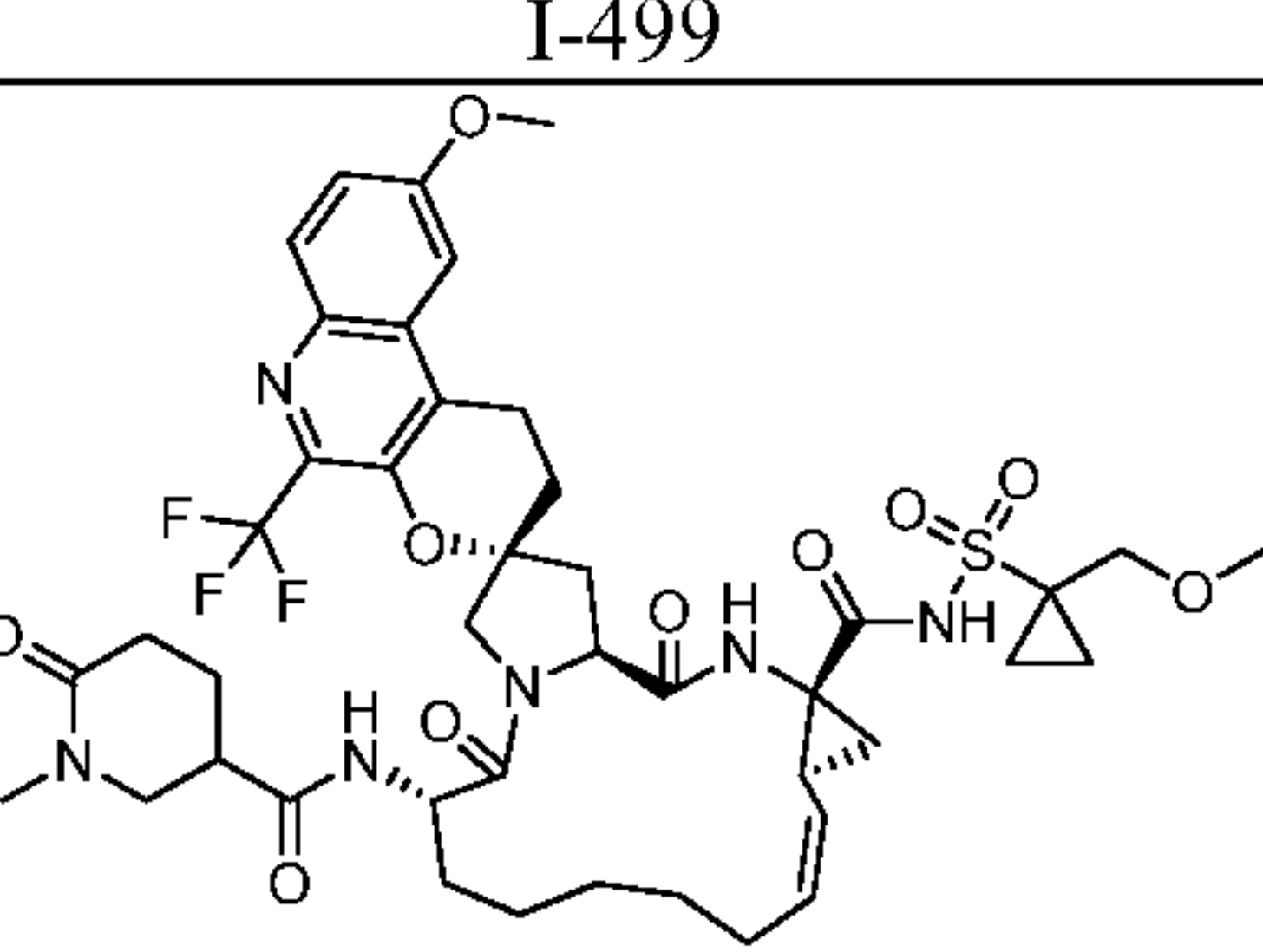
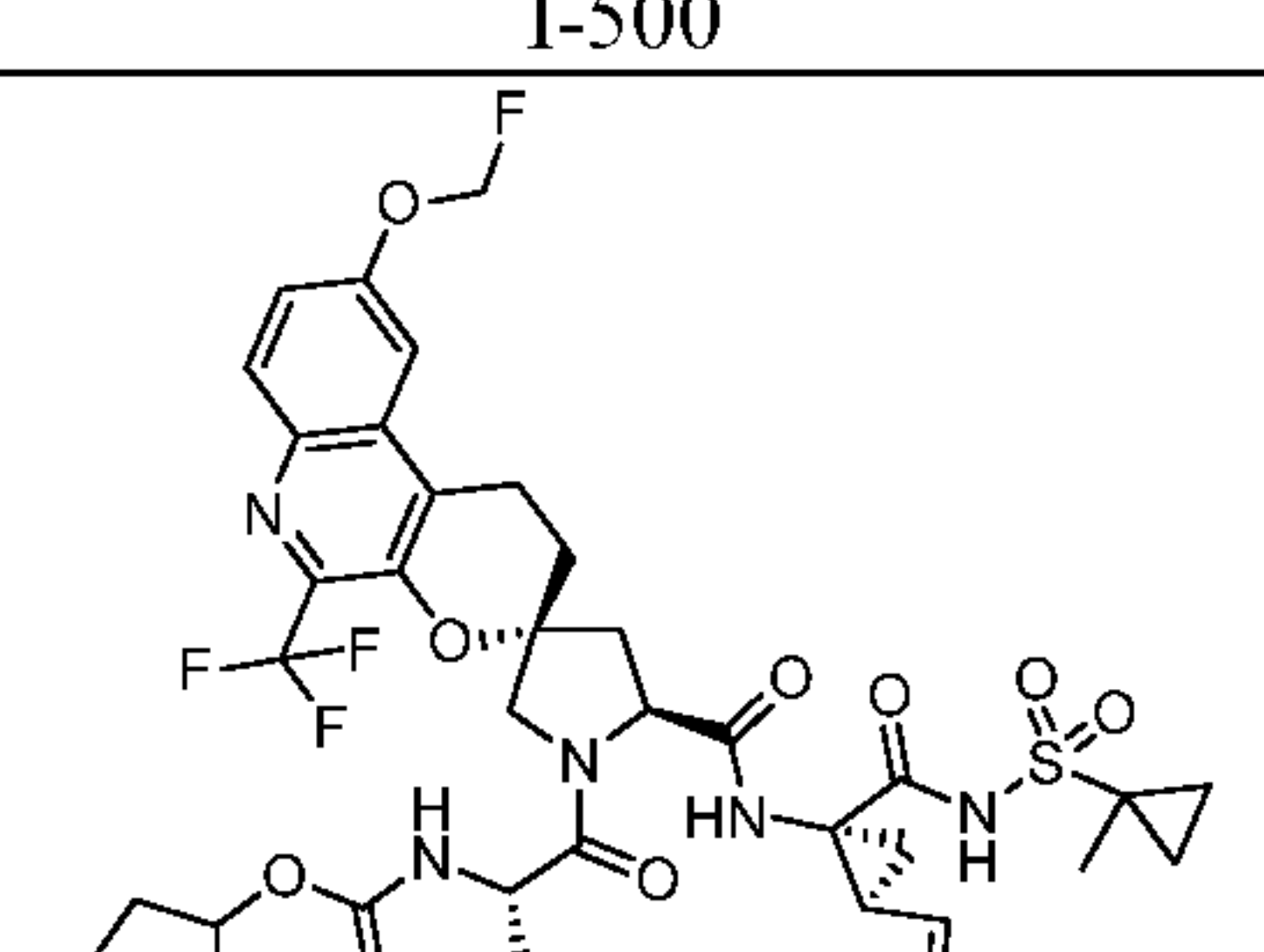
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
471	 I-471	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-14a- {[(1-methylcyclopropyl)sulfonyl]carbamoyl}-9'-[2- (morpholin-4-yl)ethoxy]-5,16-dioxo-5'- (trifluoromethyl)- 1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> - hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	7	933.59 (HCl salt)
472	 I-472	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)- 14a- {[(1-methylcyclopropyl)sulfonyl]carbamoyl}- 9'-[2-(morpholin-4-yl)ethoxy]-5,16-dioxo-5'- (trifluoromethyl)- 1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> - hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	7	947.42 (HCl salt)
473	 I-473	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'- methoxy-14a-({[1- (methoxymethyl)cyclopropyl]sulfonyl} carbamoyl)- 5,16-dioxo-5'-(trifluoromethyl)- 1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> - hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47, 6	864.3
474	 I-474	(2 <i>S</i>)-3-methylbutan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-14a- {[(1-methylcyclopropyl)sulfonyl]carbamoyl}-9'-[2- (morpholin-4-yl)ethoxy]-5,16-dioxo-5'- (trifluoromethyl)- 1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> - hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	7	947.48
475	 I-475	propyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'- (difluoromethyl)-9'-methoxy-14a- {[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16- dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> - hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10	802.41 (K+ salt)
476	 I-476	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'- (difluoromethyl)-9'-methoxy-14a- {[(1-methoxymethyl)cyclopropyl]sulfonyl} carbamoyl)- 5,16-dioxo- 1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> - hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10	846.33

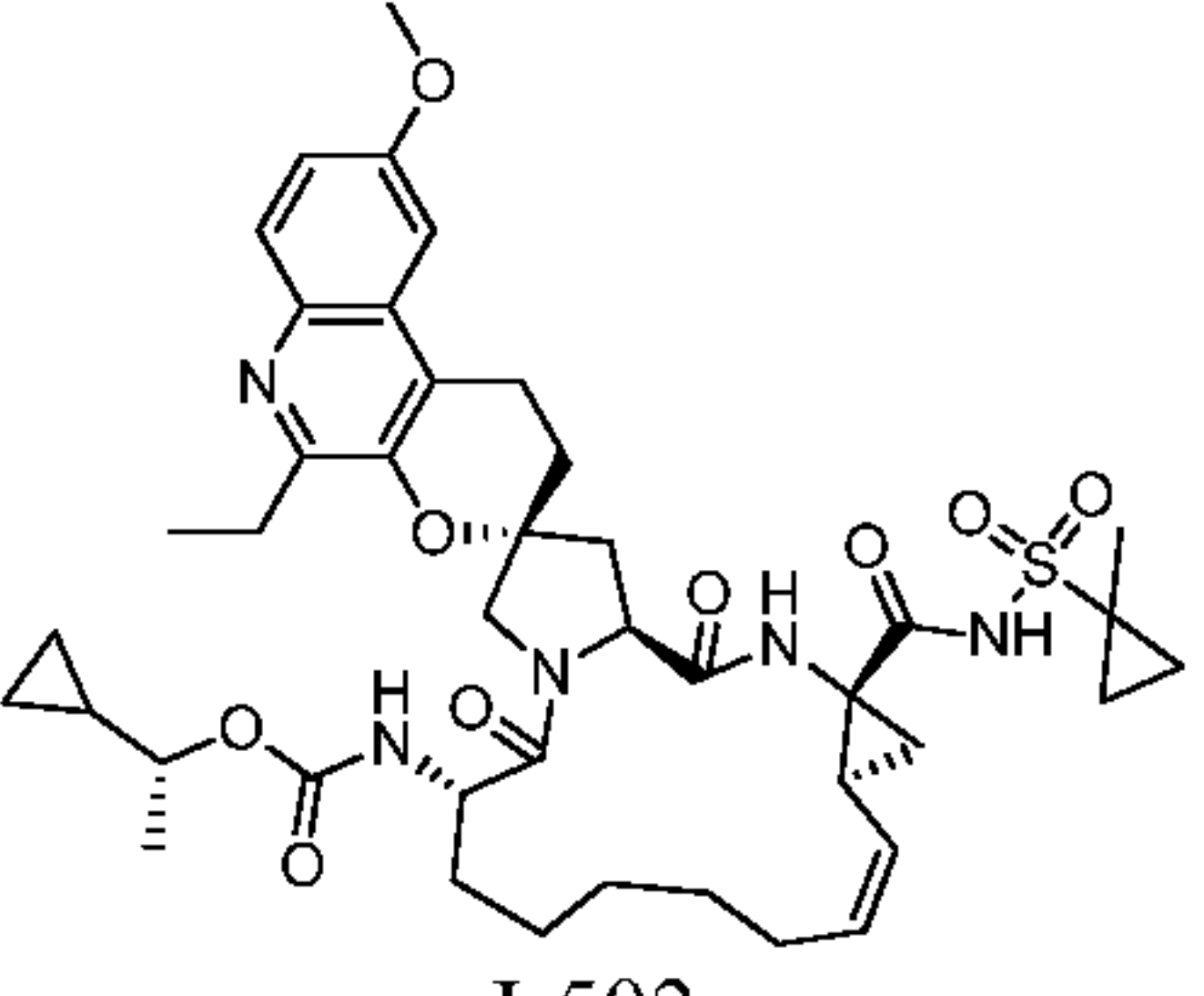
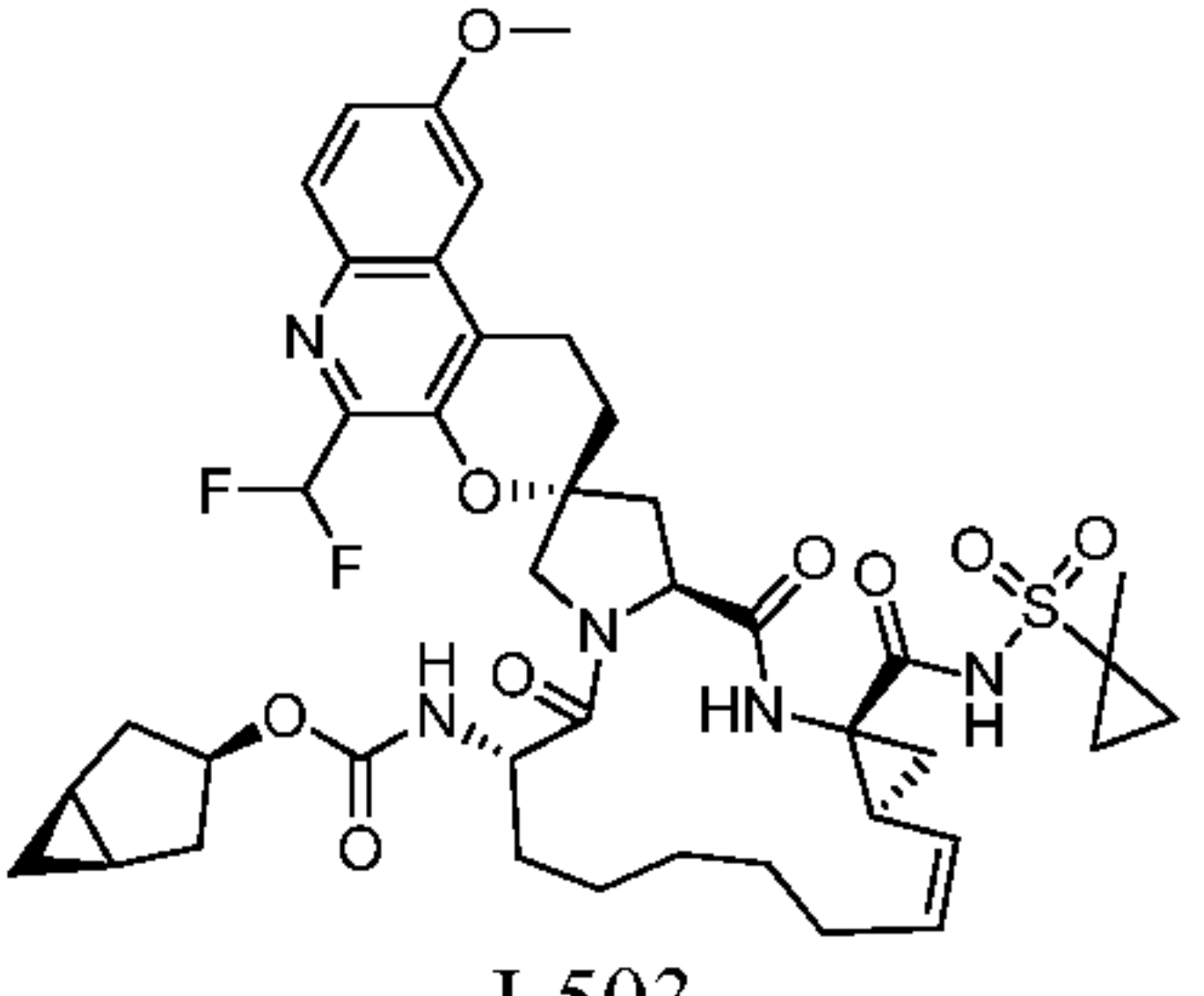
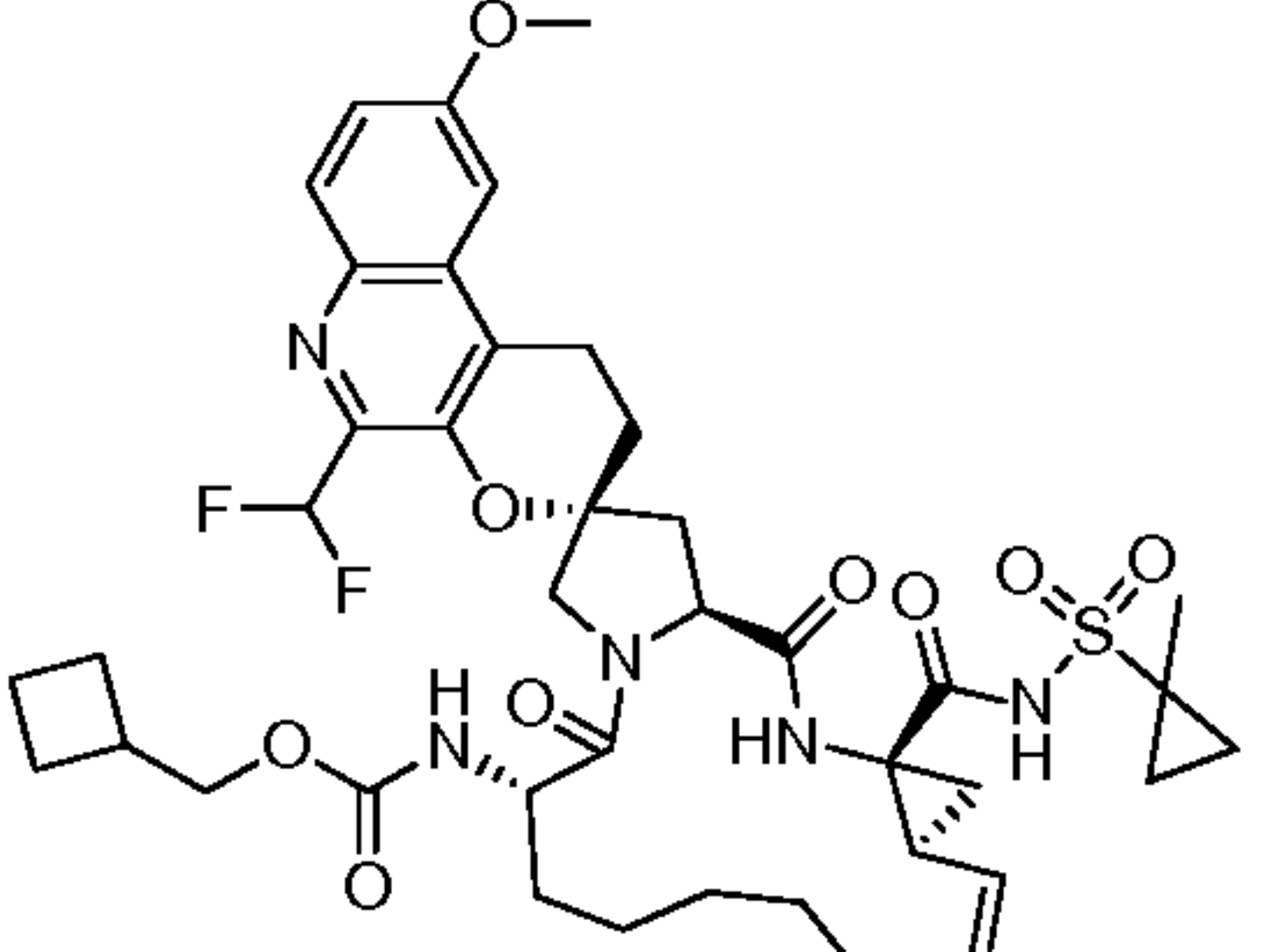
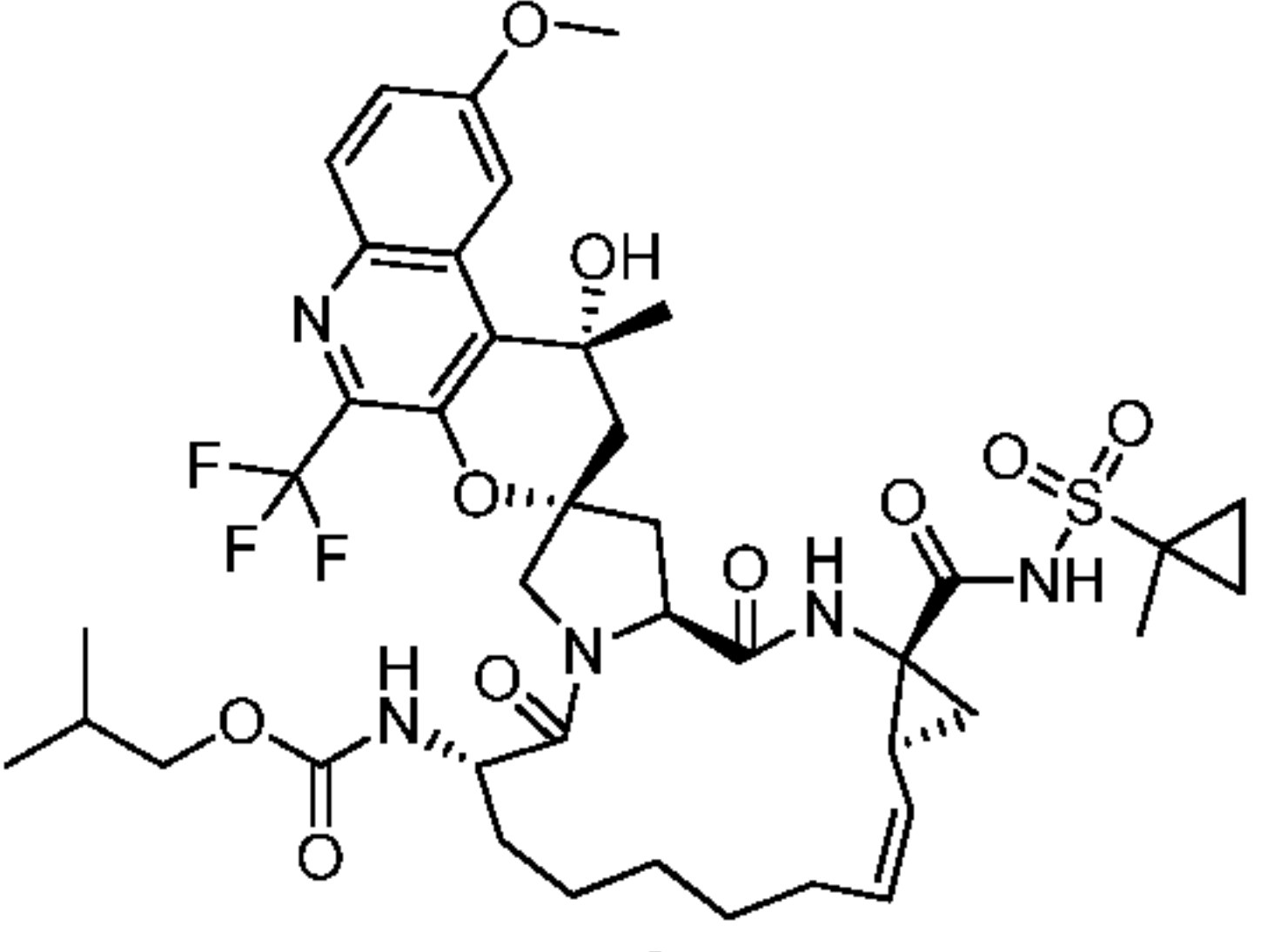
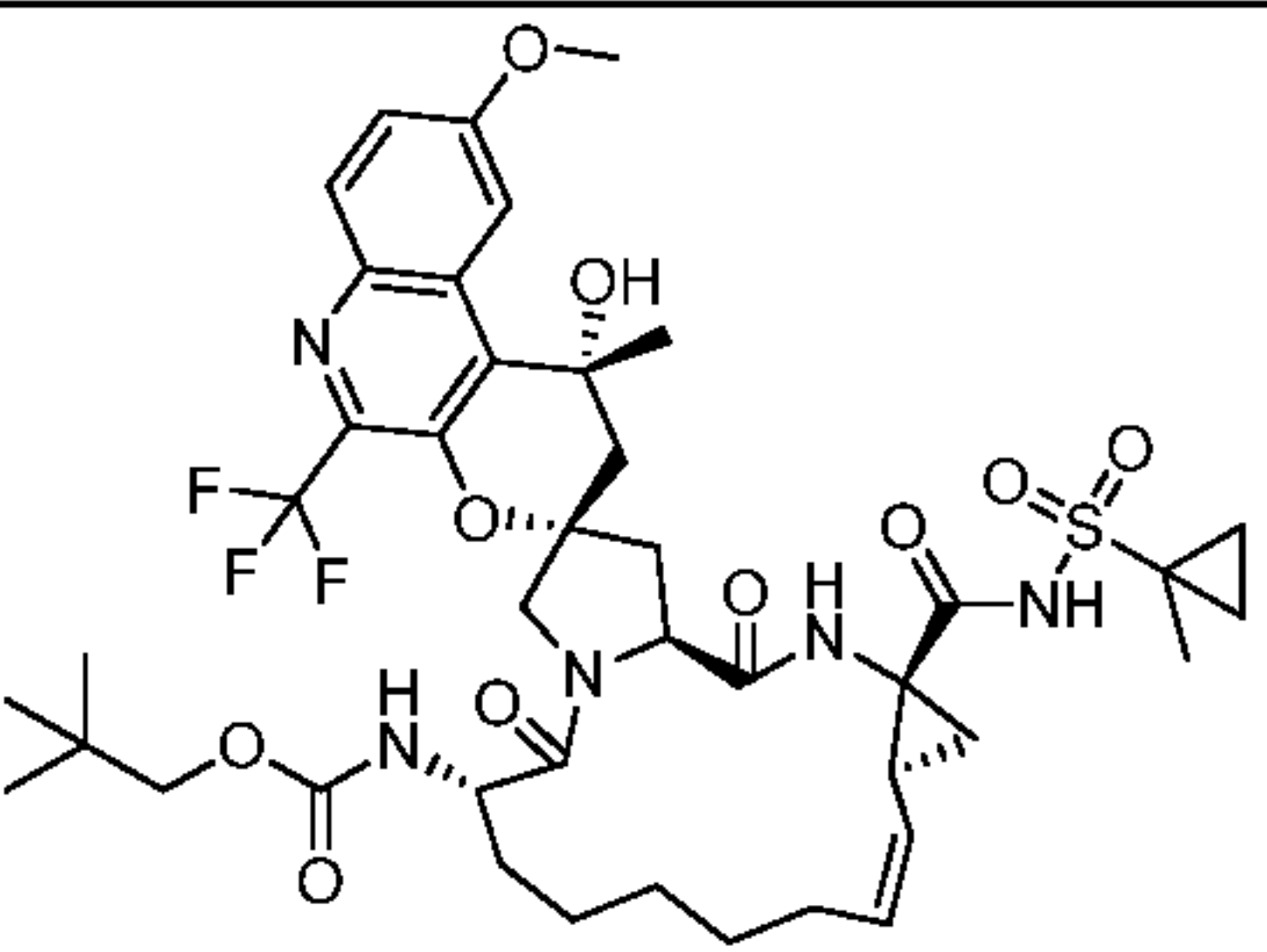
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
477		(2S)-butan-2-yl [(2R,6S,12Z,13aS,14aR,16aS)-5'-(difluoromethyl)-9'-methoxy-14a-({[1-(methoxymethyl)cyclopropyl]sulfonyl} carbamoyl)-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	10	846.38 (K+ salt)
478		(2S)-3-methylbutan-2-yl [(2R,6S,12Z,13aS,14aR,16aS)-5'-(difluoromethyl)-9'-methoxy-14a-({[1-(methoxymethyl)cyclopropyl]sulfonyl} carbamoyl)-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	10	860.38
479		tert-butyl [(2R,6S,12Z,13aS,14aR,16aS)-5'-ethyl-9'-(3-methoxypropoxy)-14a-({[1-(1-methylcyclopropyl)sulfonyl] carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	56, 30, 51	852.25
480		(2R,6S,12Z,13aS,14aR,16aS)-5'-ethyl-9'-methoxy-N-[(1-methylcyclopropyl)sulfonyl]-6-{{[(3-methylthiophen-2-yl)carbonyl]amino}-5,16-dioxo-1,1',2',6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a(5H)-carboxamide	47	818.27
481		tetrahydrofuran-3-yl [(2R,6S,12Z,13aS,14aR,16aS)-9'-methoxy-14a-({[1-(1-methylcyclopropyl)sulfonyl] carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	5, 35	848.27 (K+ salt)

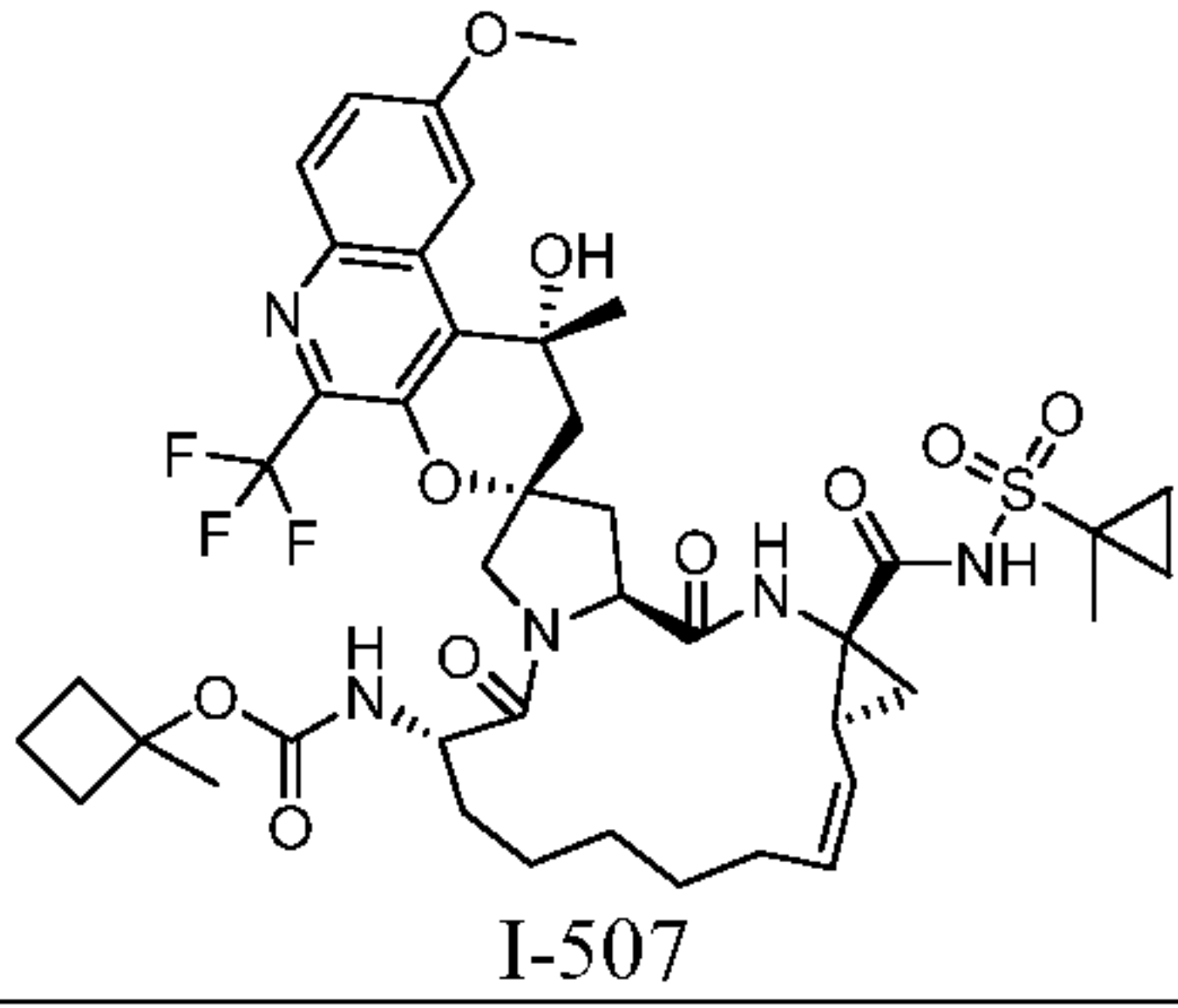
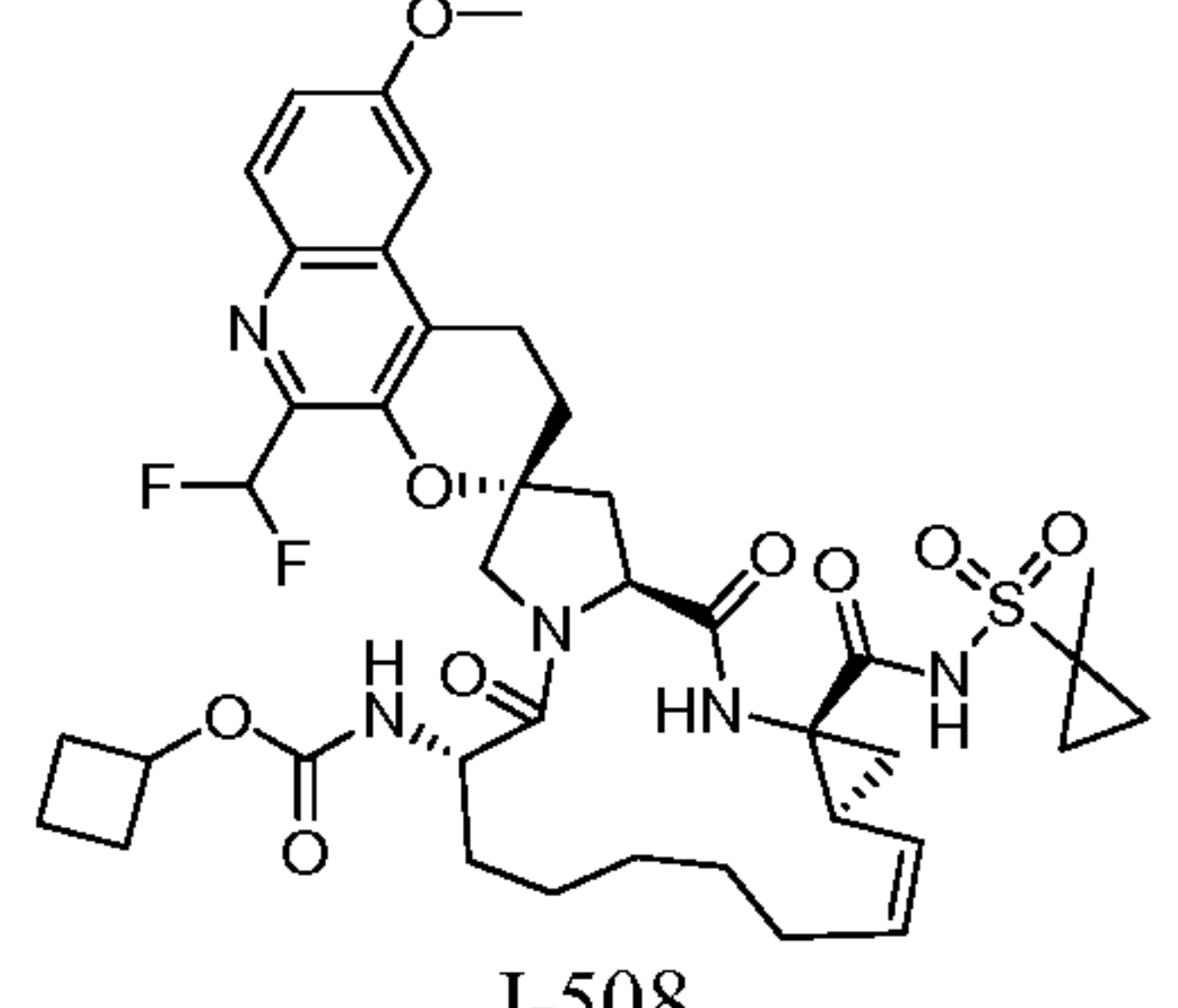
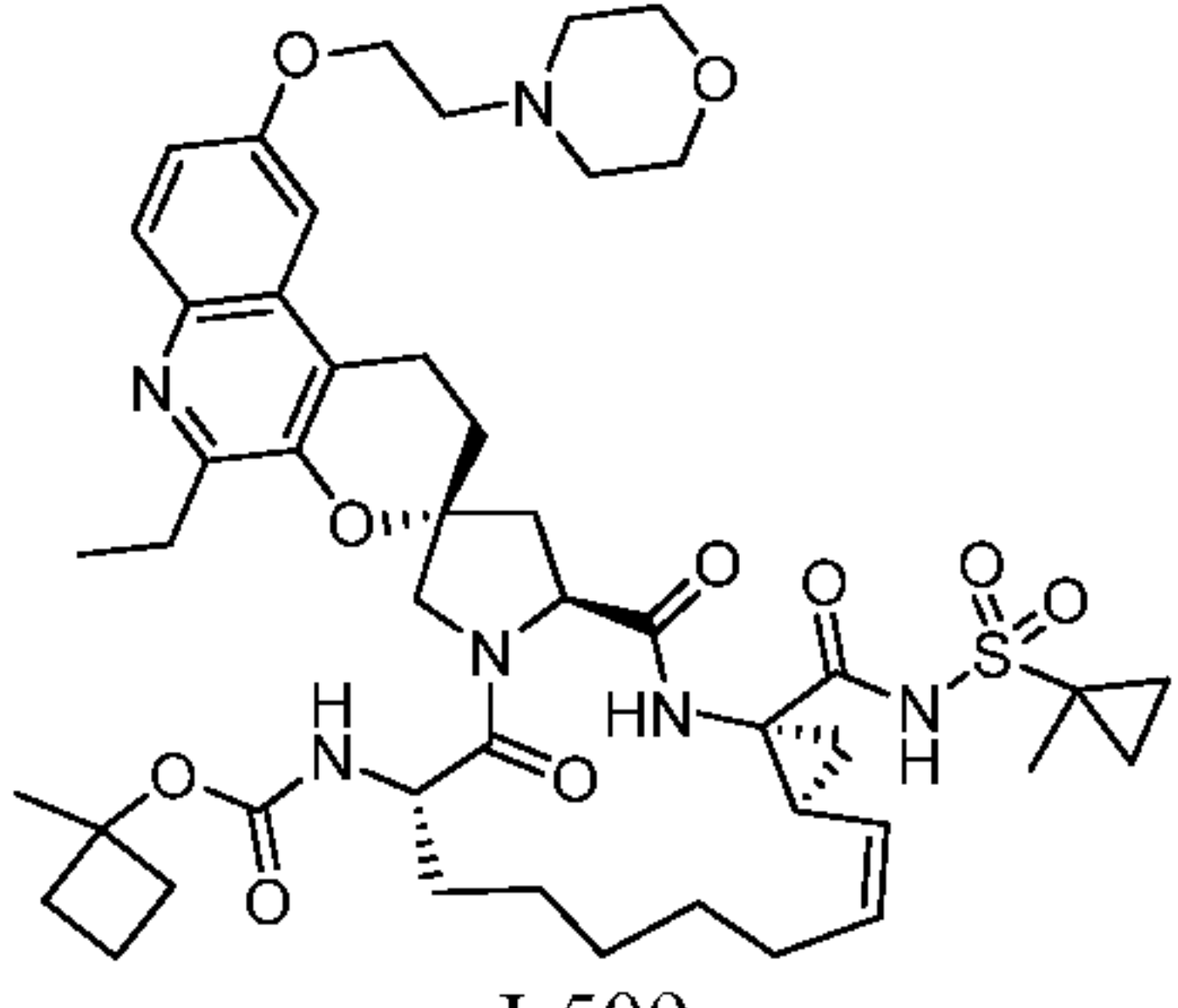
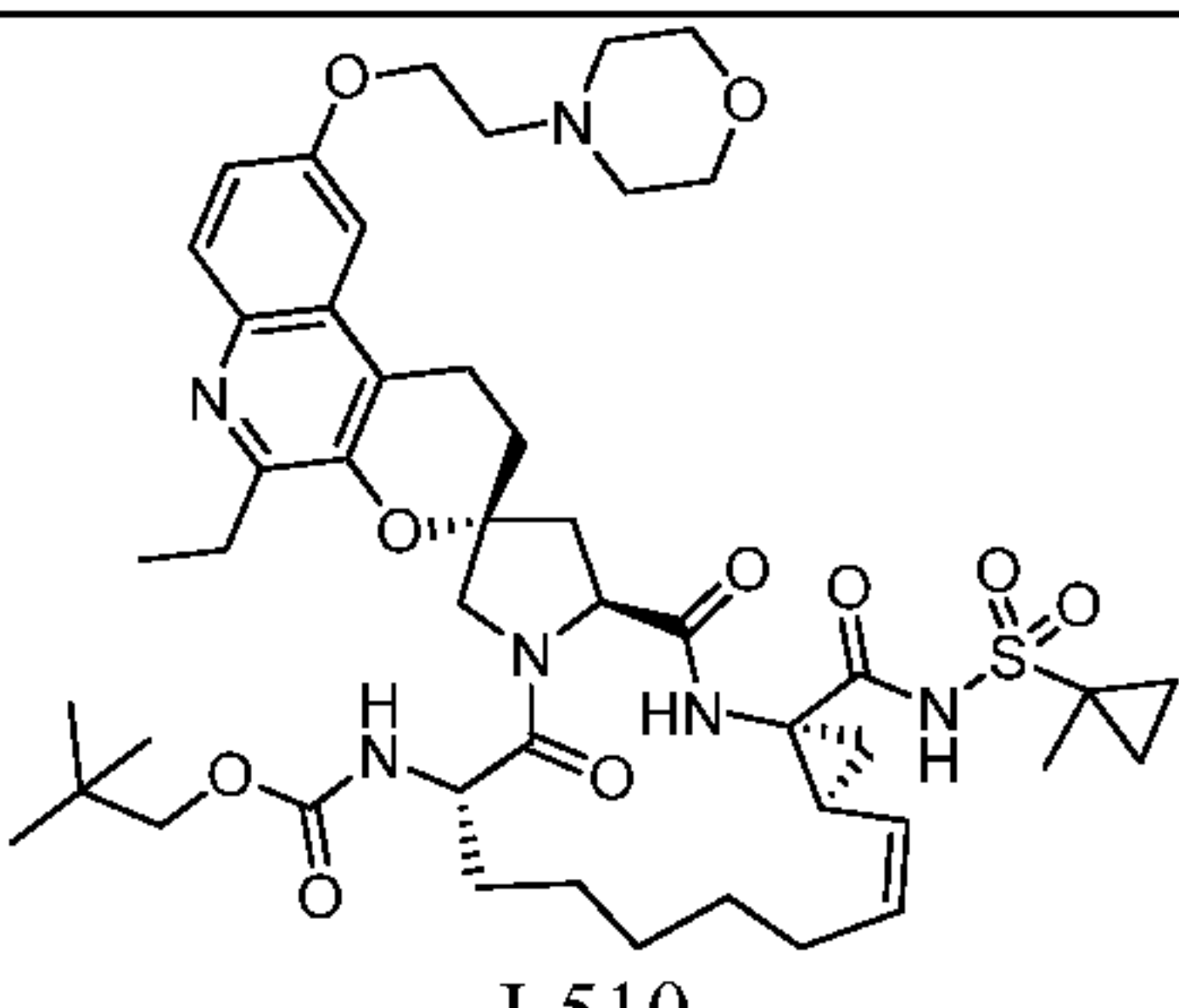
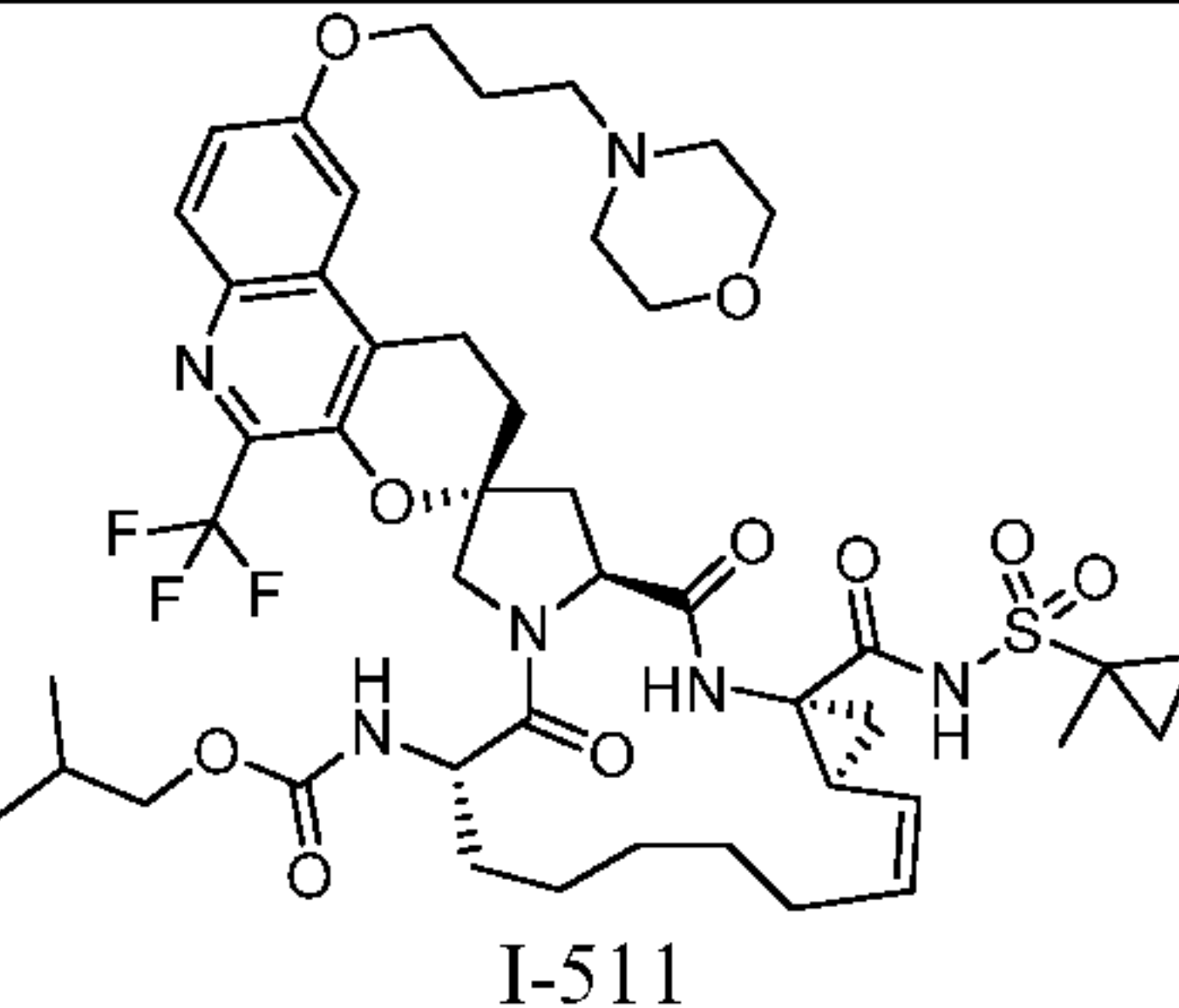
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
482	 I-482	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-9'-methoxy- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-6-[(1 <i>H</i> -pyrazol-4-ylcarbonyl)amino]-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	47	788.24
483	 I-483	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-9'-methoxy- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-6-[[4-methylthiophen-2-yl)carbonyl]amino]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	47	818.27
484	 I-484	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-9'-(3-methoxypropoxy)-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	56, 30, 51, 6	852.5 (K+ salt)
485	 I-485	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[[3,5-dimethyl-1 <i>H</i> -pyrazol-4-yl)carbonyl]amino]-5'-ethyl-9'-methoxy- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	2, 47	816.4
486	 I-486	(1 <i>S</i>)-1-cyclopropylethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-9'-methoxy-14 <i>a</i> -{[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	2, 47	806.4

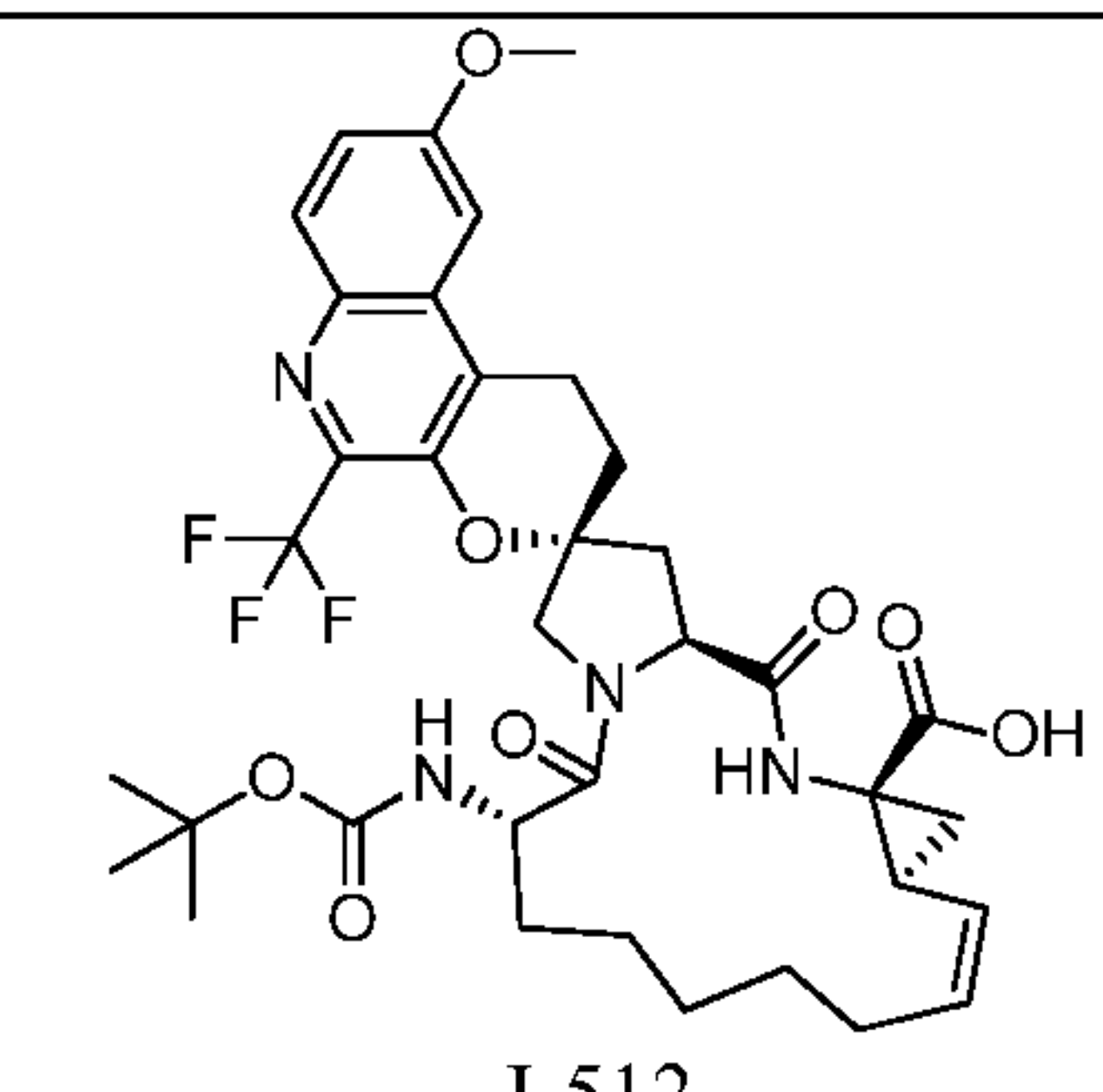
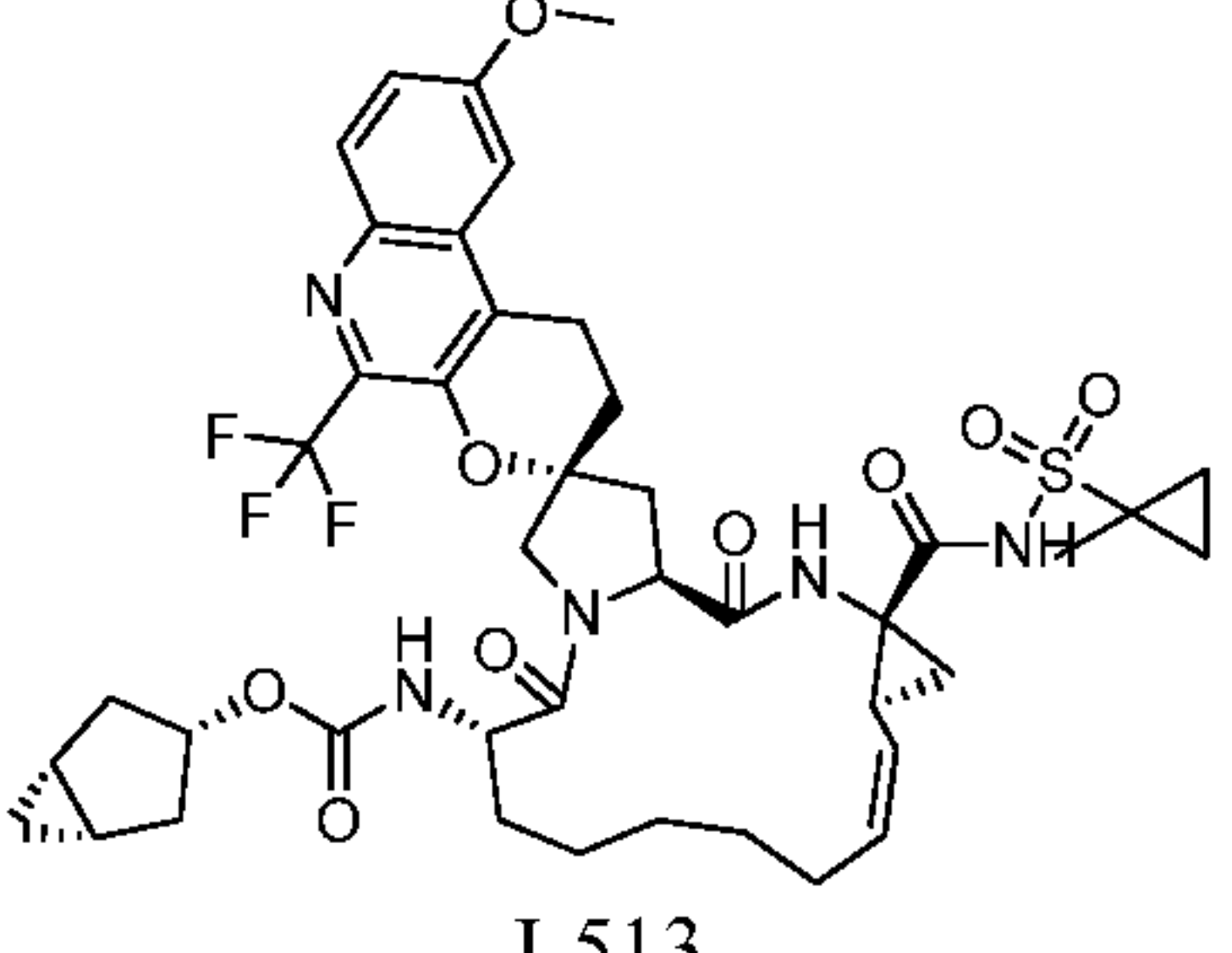
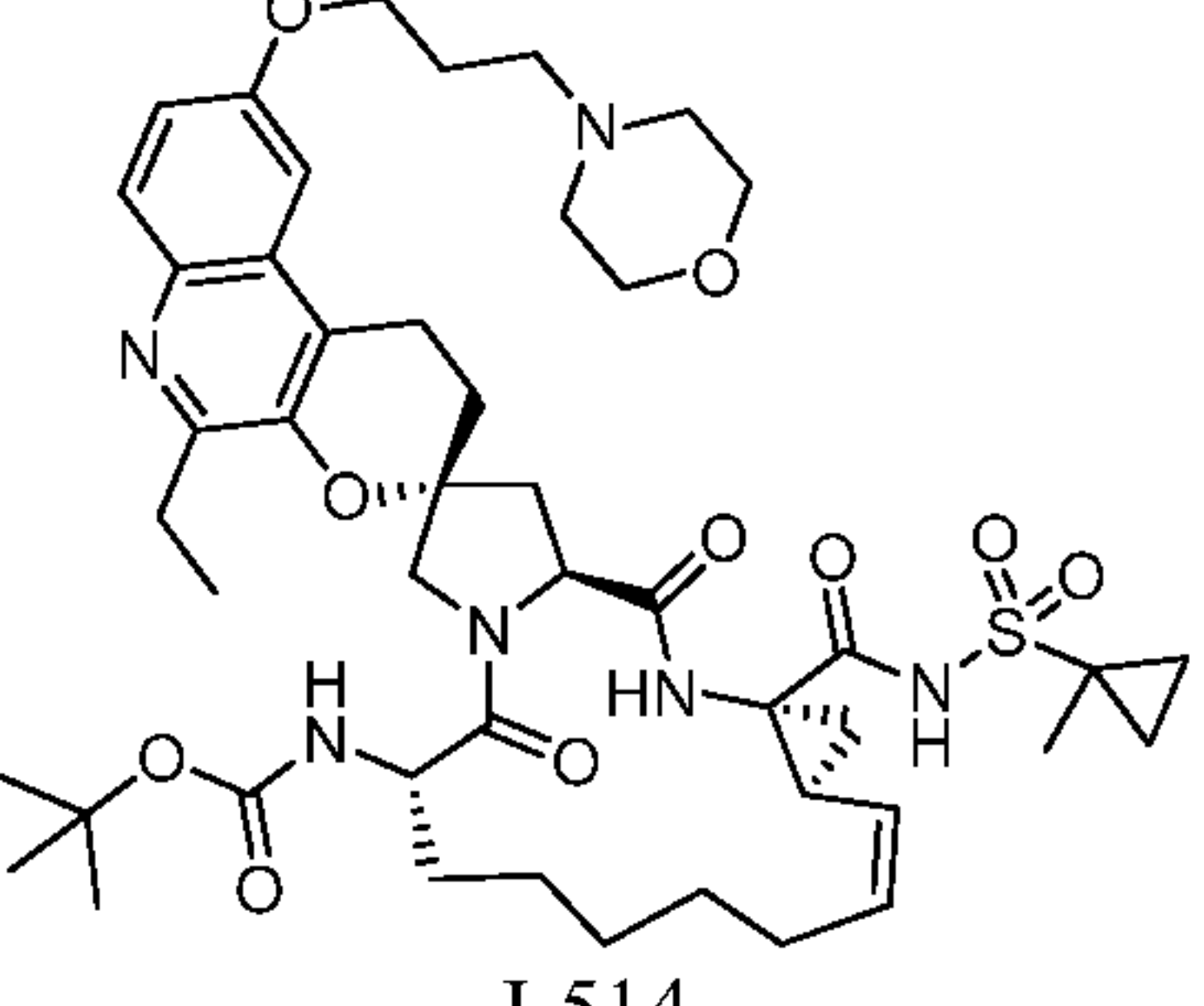
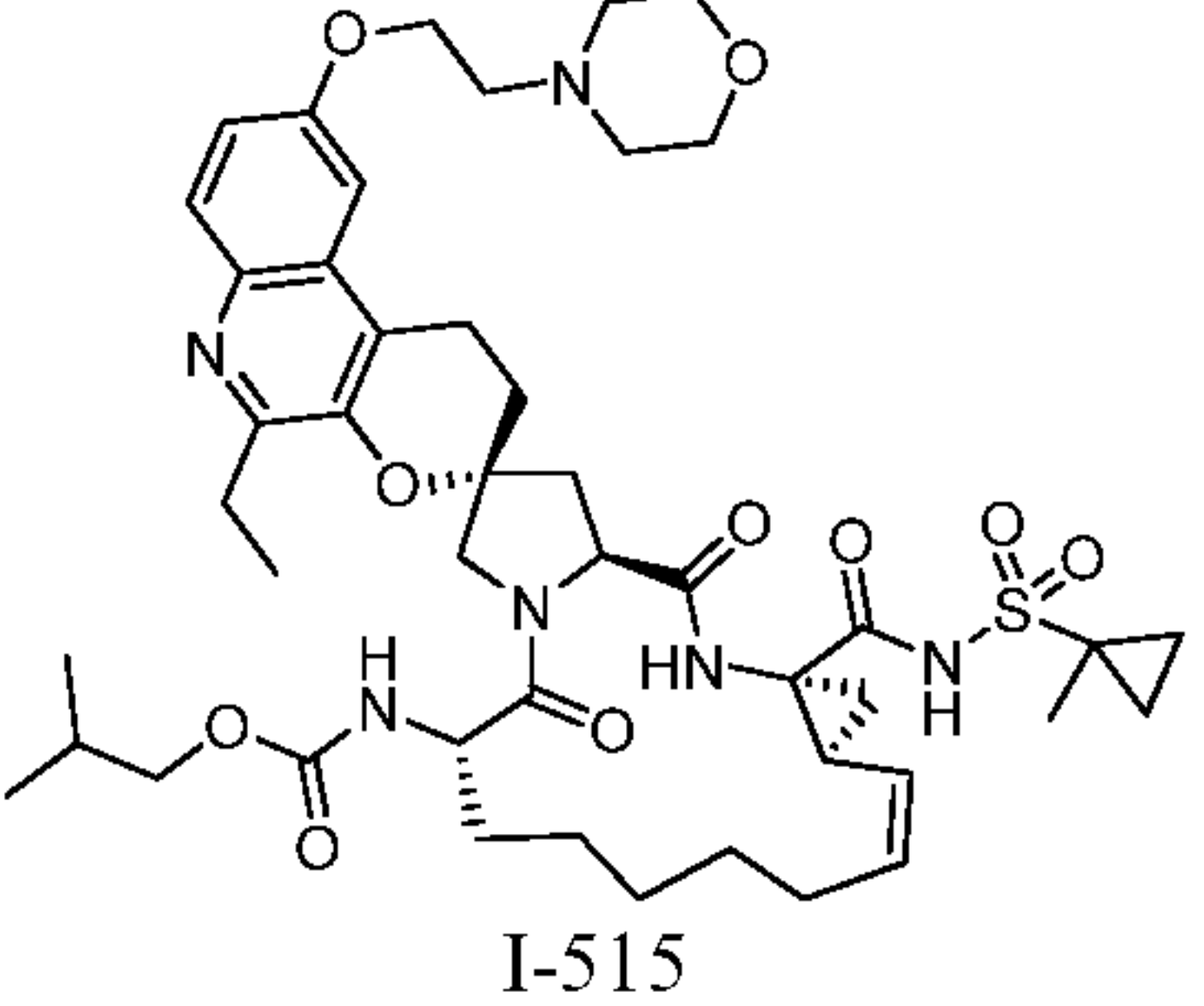
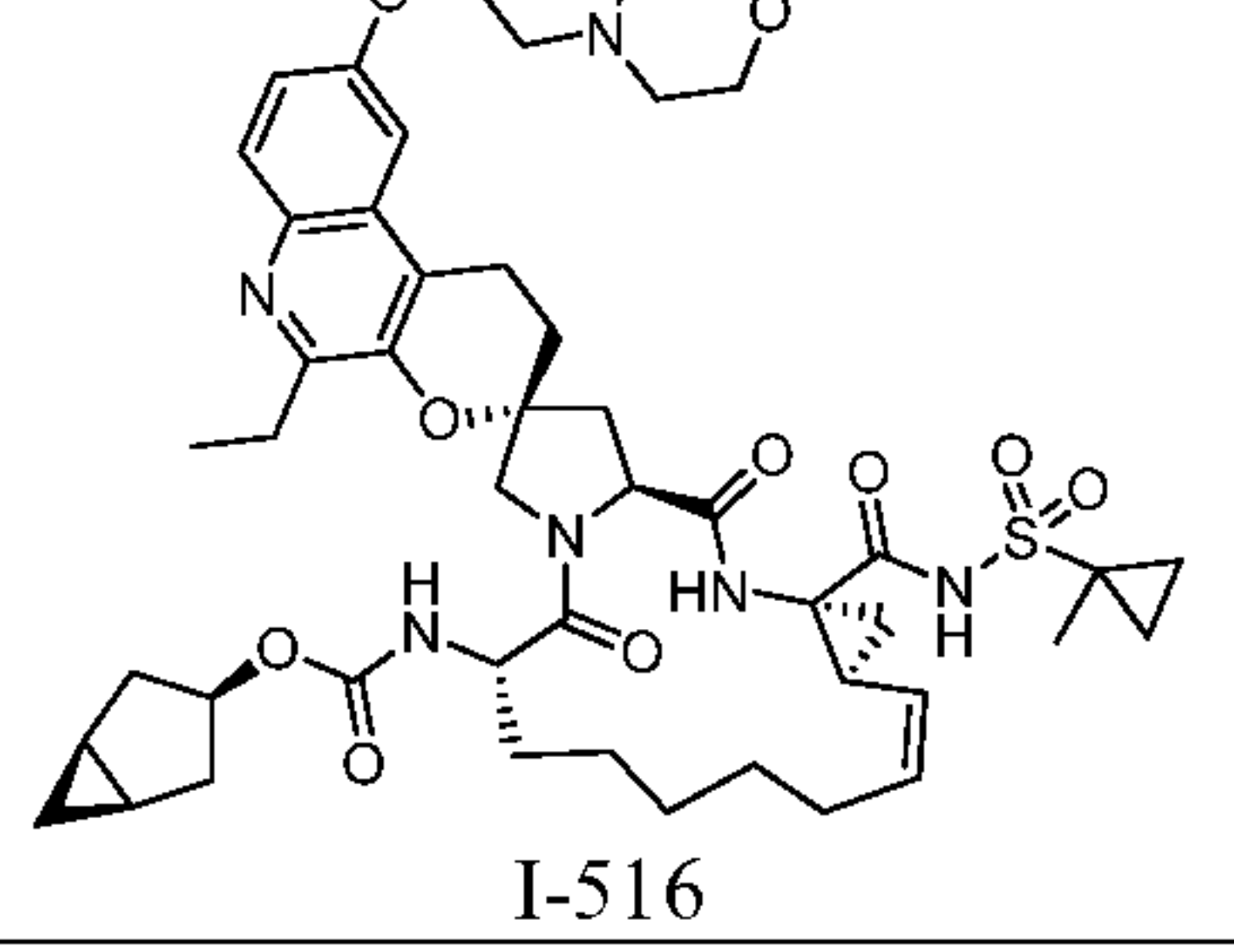
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
487	 I-487	(2S)-3-methylbutan-2-yl [(2R,6S,12Z,13aS,14aR,16aS)-5'-ethyl-9'-(3-methoxypropoxy)-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	56, 30, 51, 35	866.5 (K+ salt)
488	 I-488	2,2-dimethylpropyl [(2R,6S,12Z,13aS,14aR,16aS)-5'-ethyl-9'-(3-methoxypropoxy)-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	56, 30, 51, 6	866.5 (K+ salt)
489	 I-489	tert-butyl [(1'R,2S,6S,12Z,13aS,14aR,16aS)-1'-hydroxy-9'-methoxy-1'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	62	865.3
490	 I-490	(2R,6S,12Z,13aS,14aR,16aS)-5'-ethyl-6-{{(3-fluorothiophen-2-yl)carbonyl}amino}-9'-methoxy-N-[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-1,1',2',6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinoline]-14a(5H)-carboxamide	47	822.23
491	 I-491	2-methylpropyl [(2R,6S,12Z,13aS,14aR,16aS)-9'-(fluoromethoxy)-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-2,3'-pyrano[2,3-c]quinolin]-6-yl]carbamate	7, 50, 6	852.4 (K+ salt)

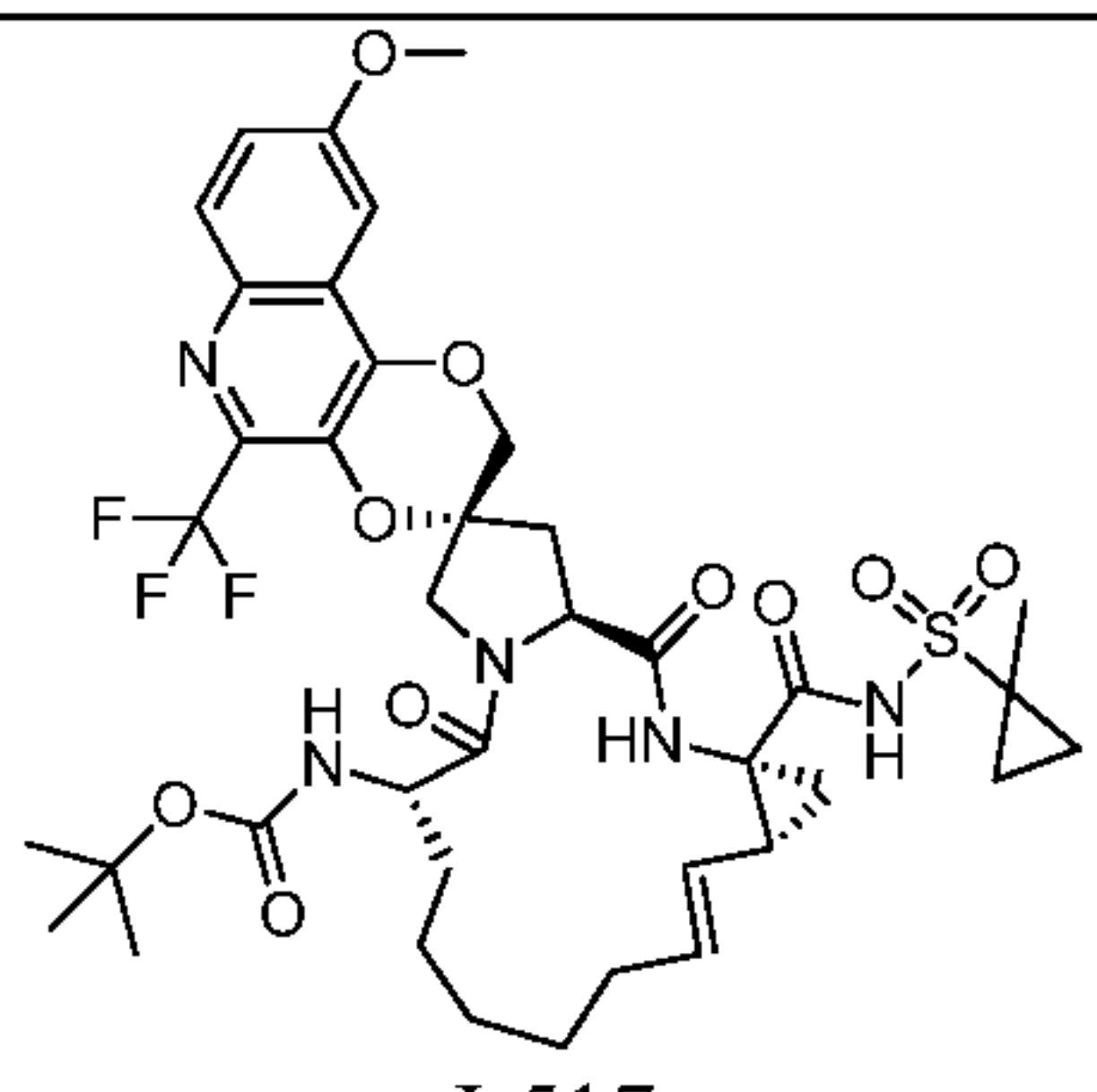
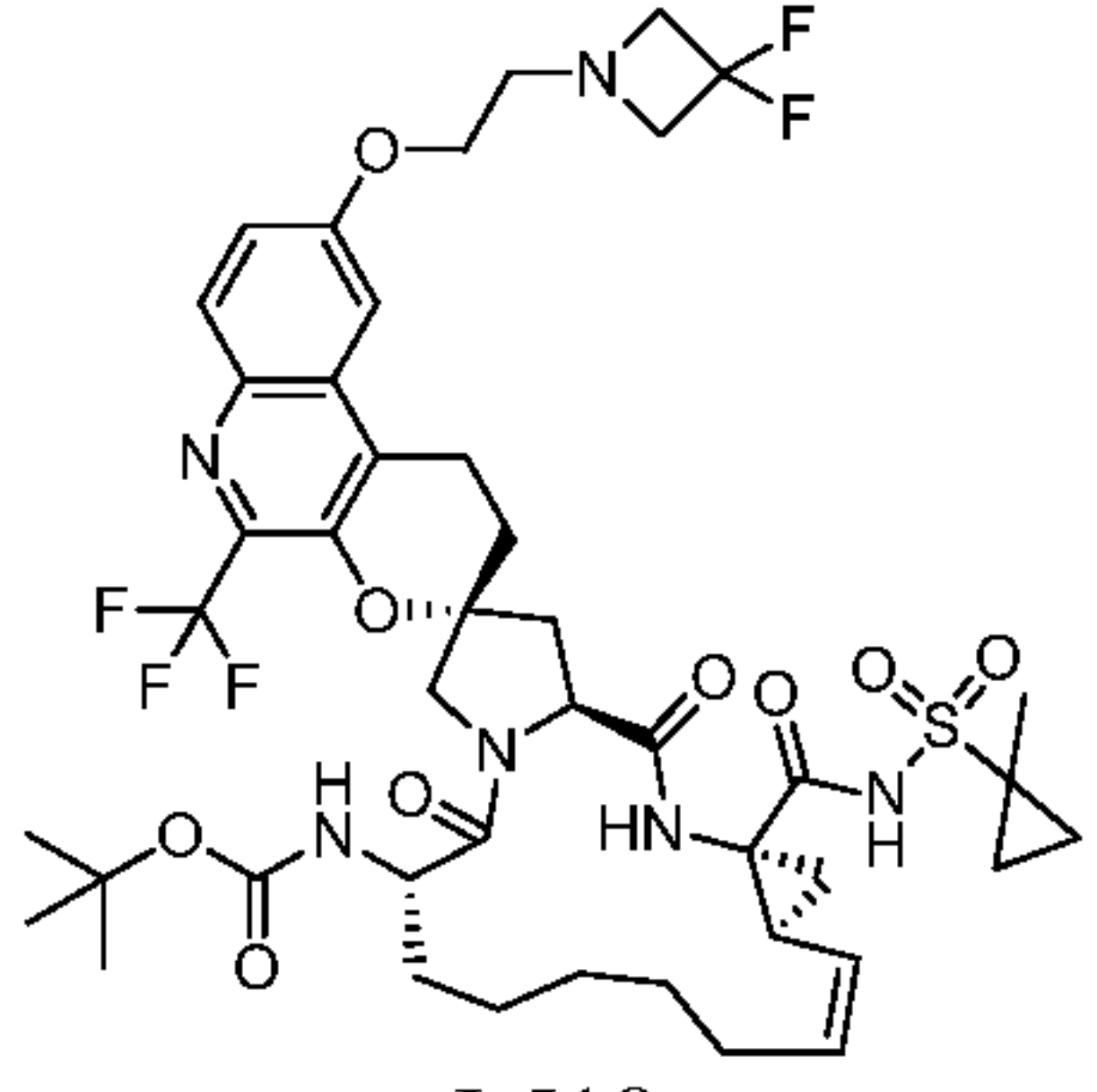
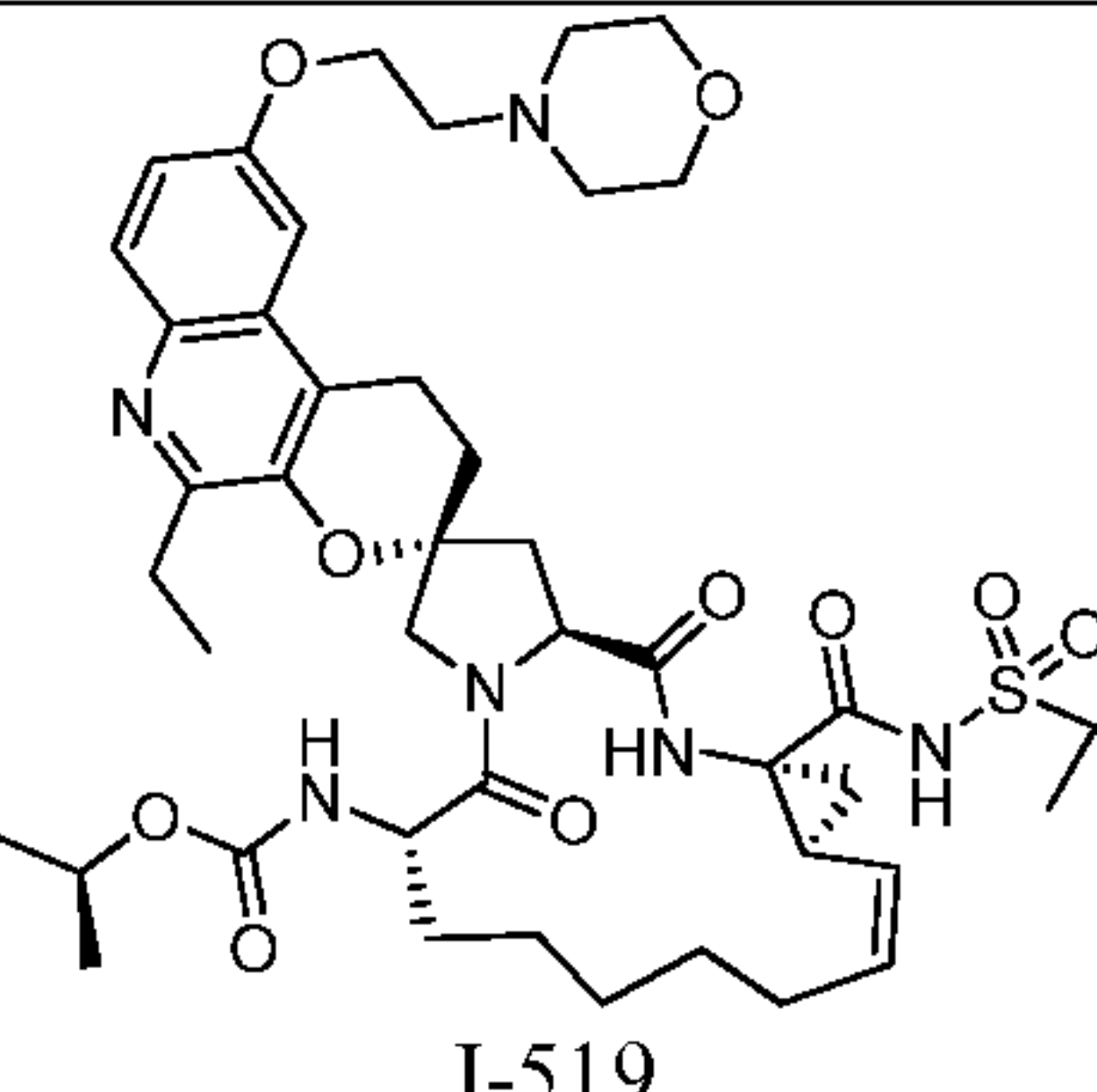
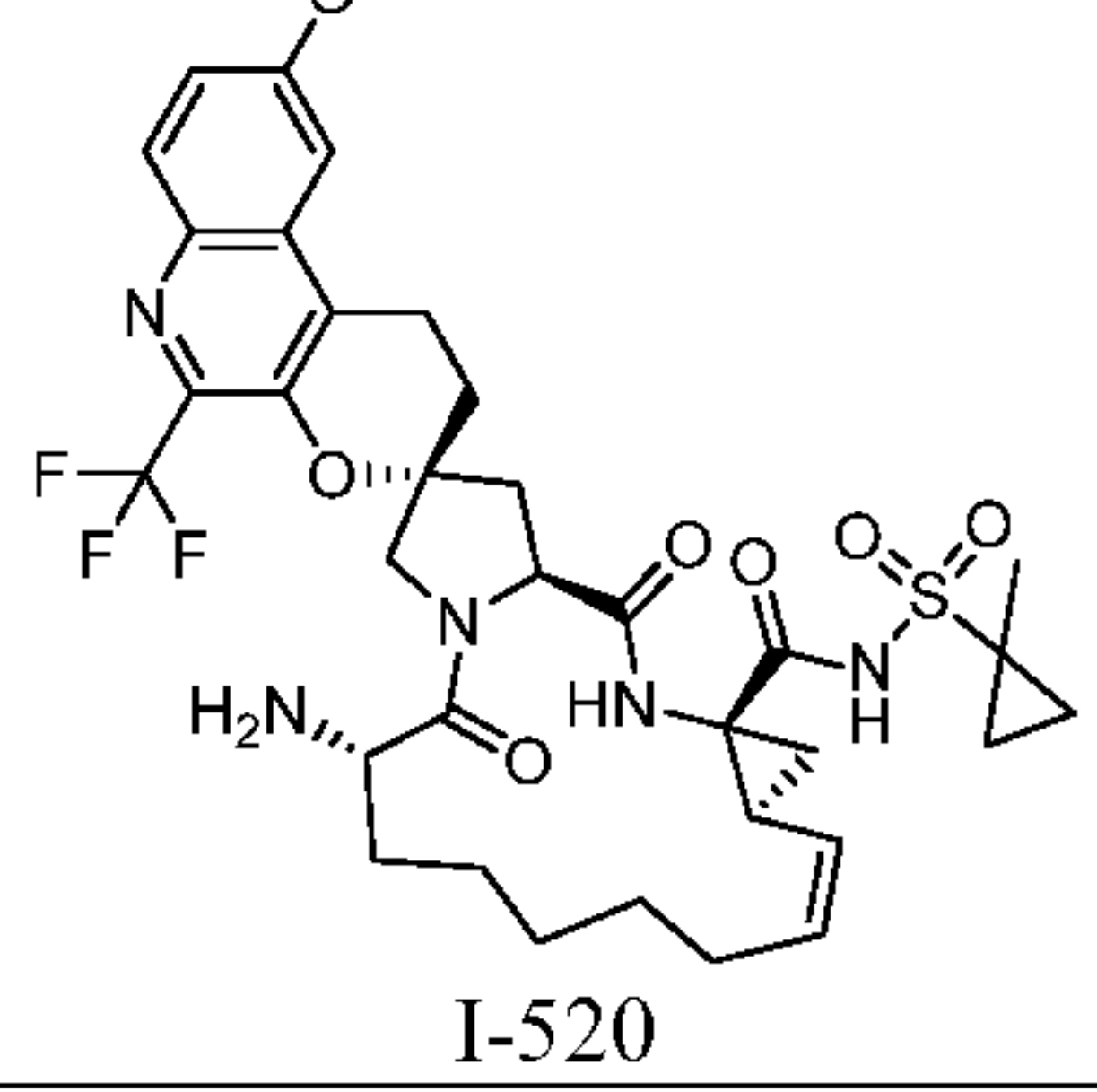
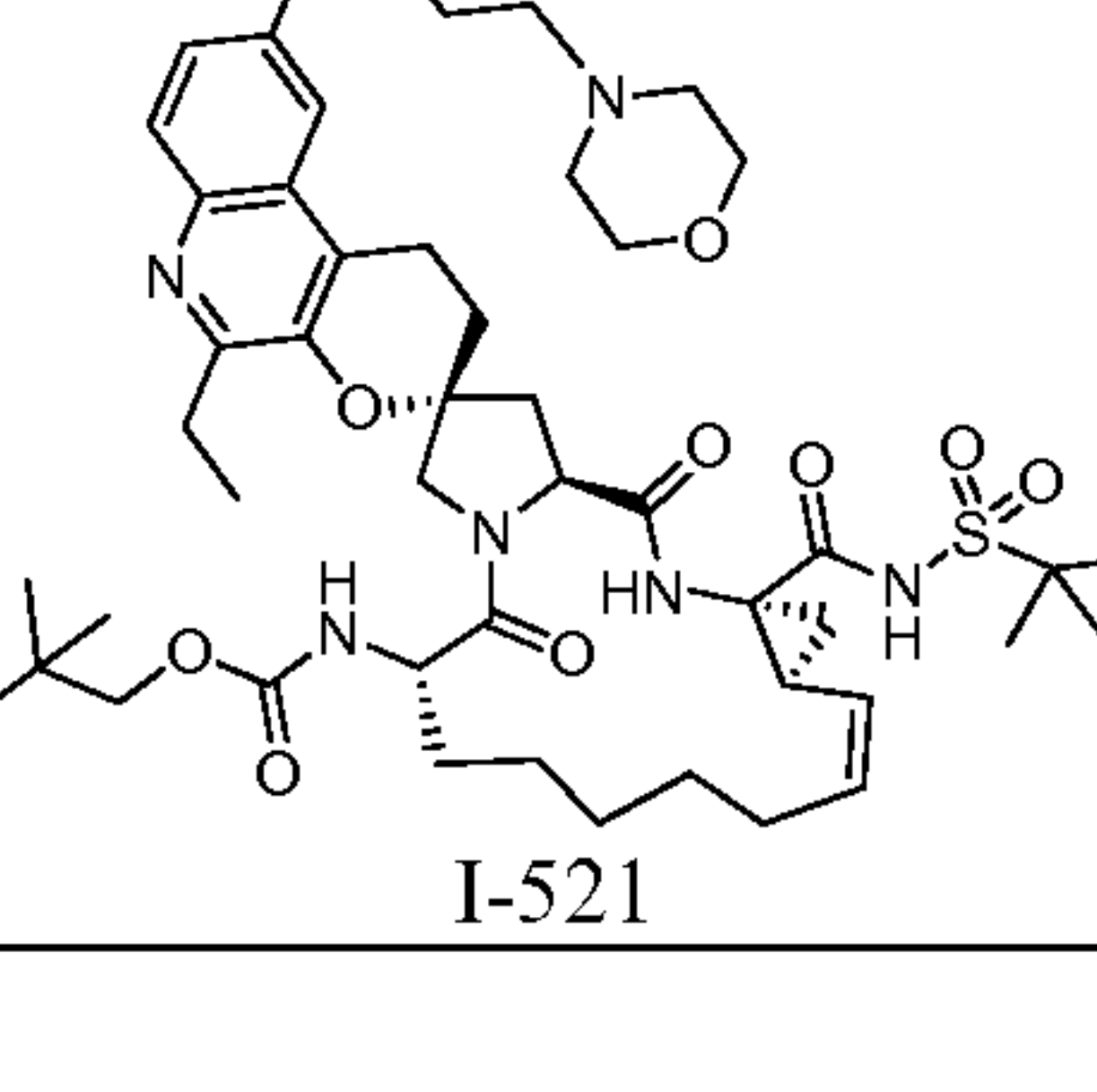
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
492	 I-492	<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-(2-{{ <i>tert</i> -butyl(dimethyl)silyl}oxy}ethoxy)-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	60	978.4
493	 I-493	1-methylcyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(difluoromethyl)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10	828.33 (K+ salt)
494	 I-494	(1-methylcyclopropyl)methyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-(methoxymethyl)cyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	49, 41	876.4
495	 I-495	1-methylcyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-(methoxymethyl)cyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	49, 41	876.4
496	 I-496	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-(methoxymethyl)cyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	49, 41	878.4

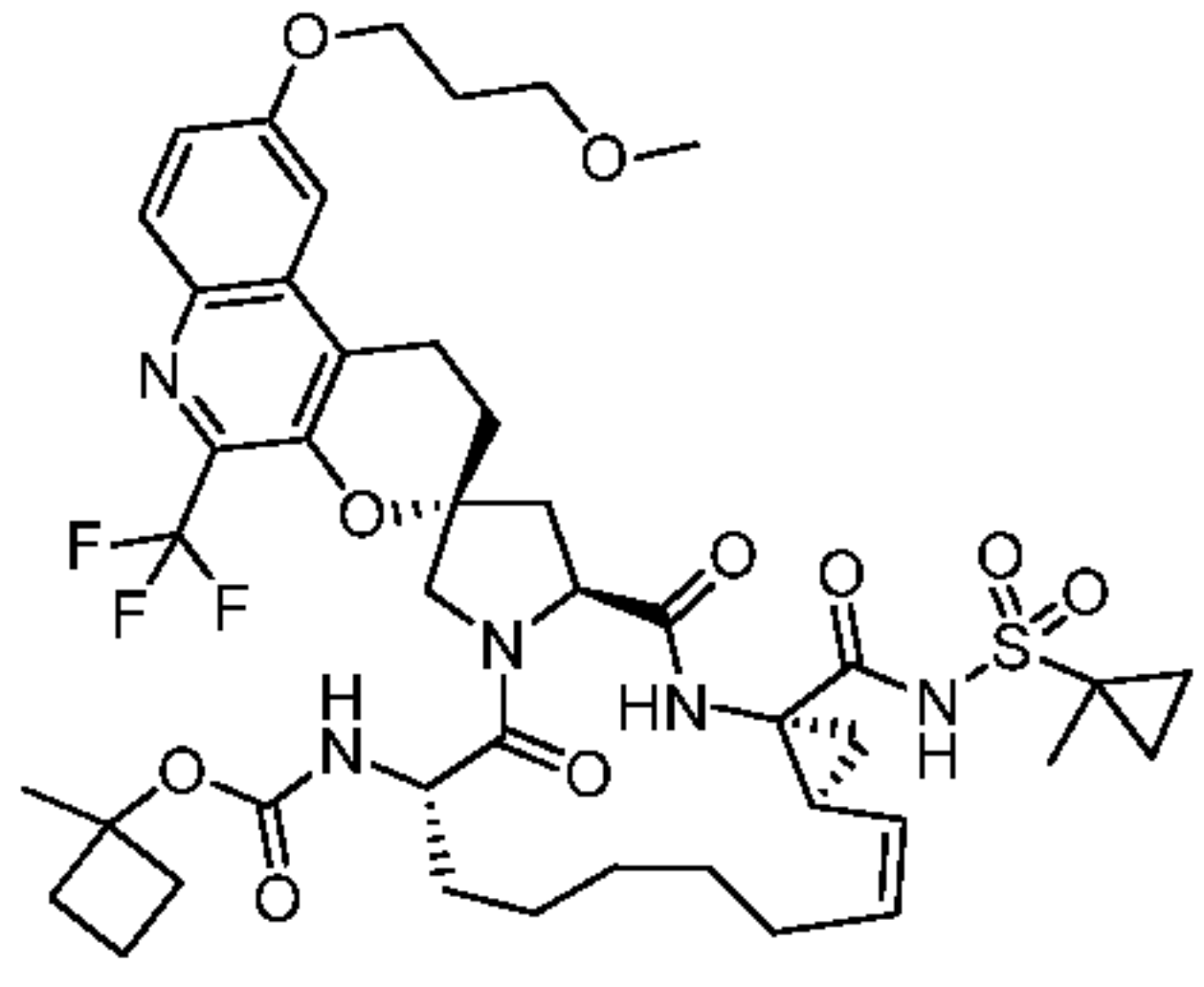
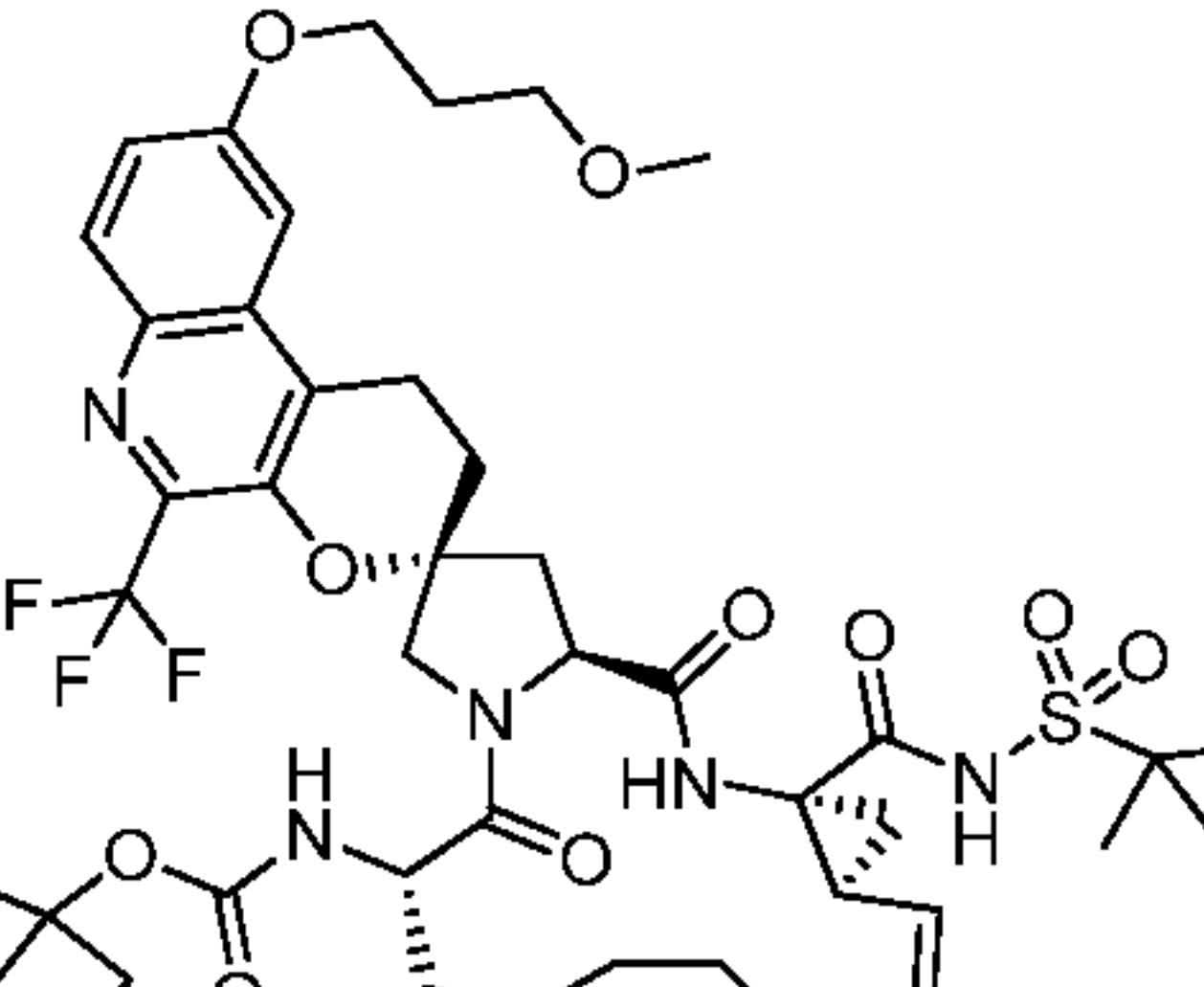
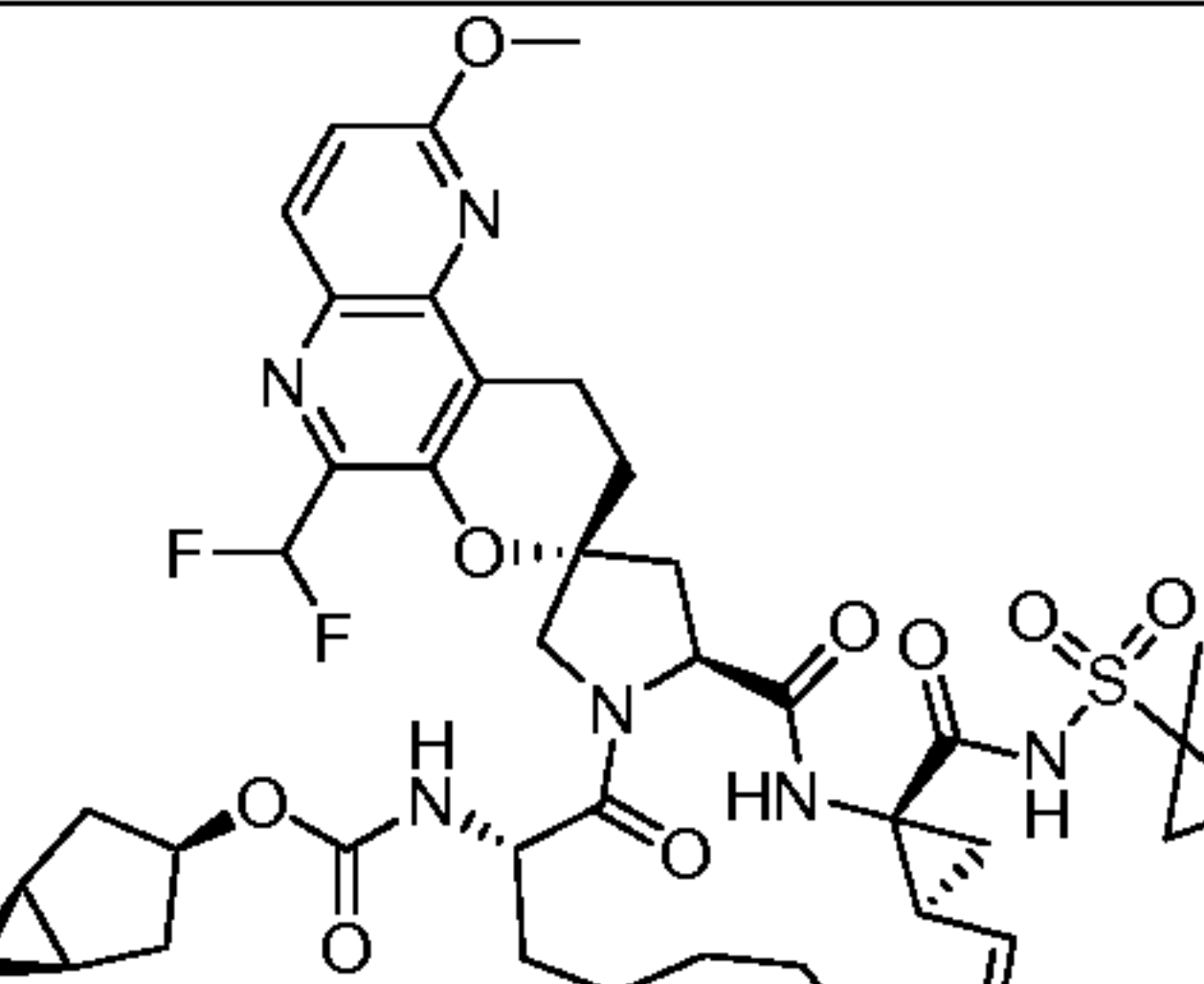
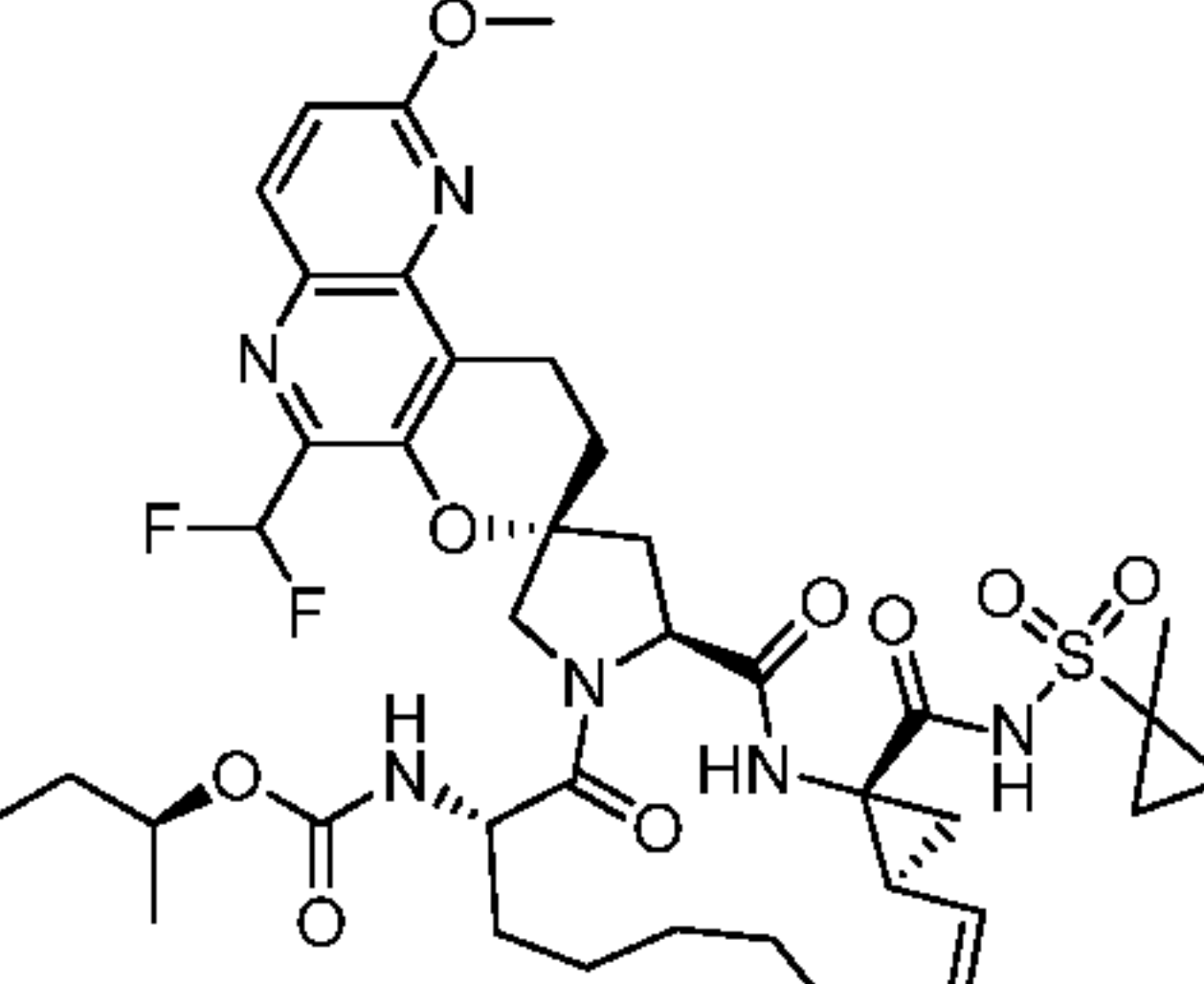
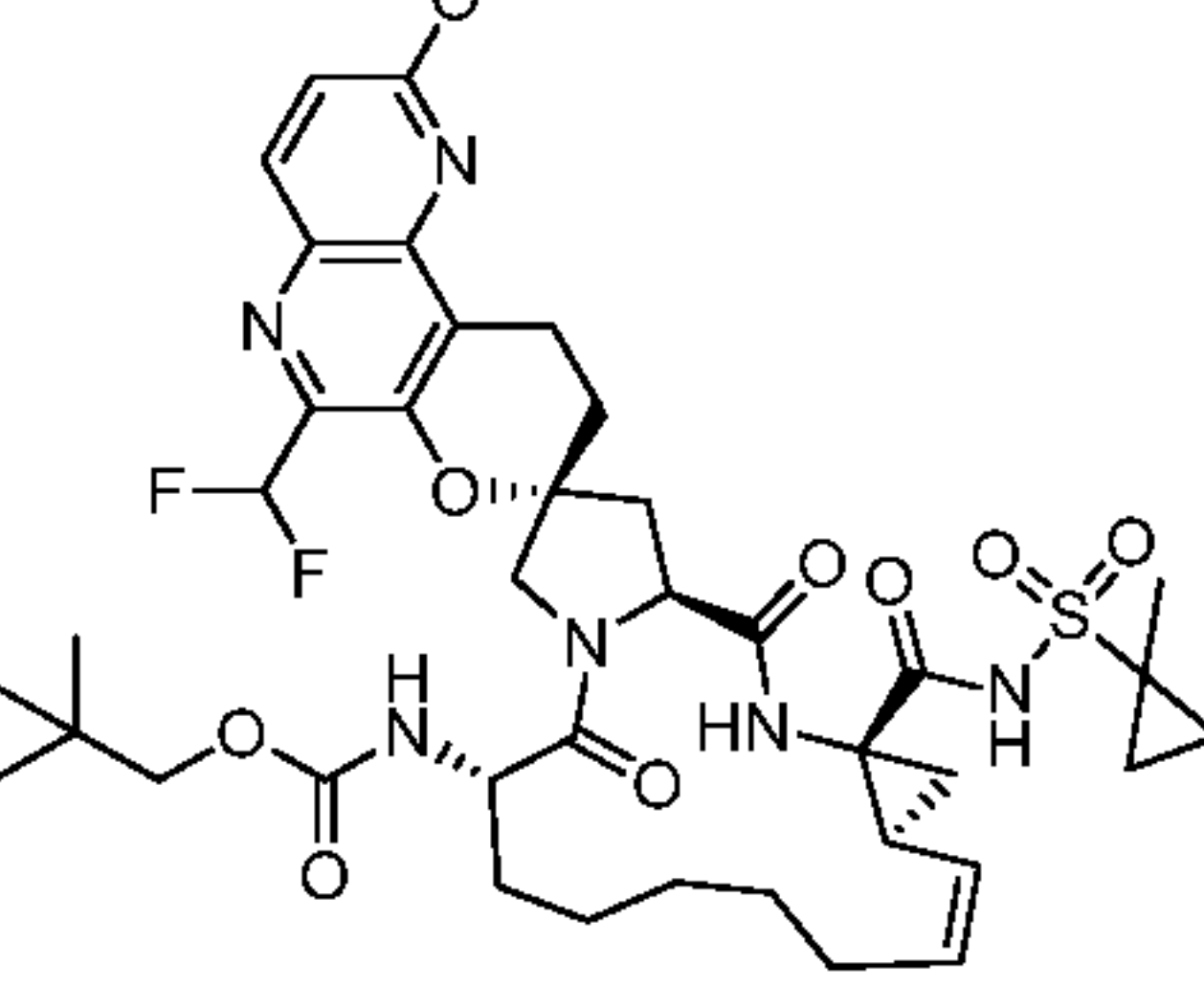
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
497	 I-497	2,2-difluoroethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-({[1-(methoxymethyl)cyclopropyl]sulfonyl}carbamoyl)-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	49, 41	872.3
498	 I-498	(1-methylcyclopropyl)methyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-({[1-(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5, 41	846.3 (K+ salt)
499	 I-499	2,2-difluoroethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-({[1-(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5, 41	842.3 (K+ salt)
500	 I-500	(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy- <i>N</i> -{[1-(methoxymethyl)cyclopropyl]sulfonyl}-6-({[1-(1-methyl-6-oxopiperidin-3-yl)carbonyl]amino}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	49	903.3
501	 I-501	(1 <i>R</i> ,5 <i>S</i>)-bicyclo[3.1.0]hex-3-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-(fluoromethoxy)-14a-({[1-(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	7, 50, 35	876.28 (K+ salt)

Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
502	 I-502	(1 <i>R</i>)-1-cyclopropylethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	47	806.4
503	 I-503	(1 <i>R</i> ,3 <i>r</i> ,5 <i>S</i>)-bicyclo[3.1.0]hex-3-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(difluoromethyl)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10	840.28 (K+ salt)
504	 I-504	cyclobutylmethyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(difluoromethyl)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10	828.29 (K+ salt)
505	 I-505	2-methylpropyl [(1' <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-hydroxy-9'-methoxy-1'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	62	865.2
506	 I-506	2,2-dimethylpropyl [(1' <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-hydroxy-9'-methoxy-1'-methyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	62	879.3

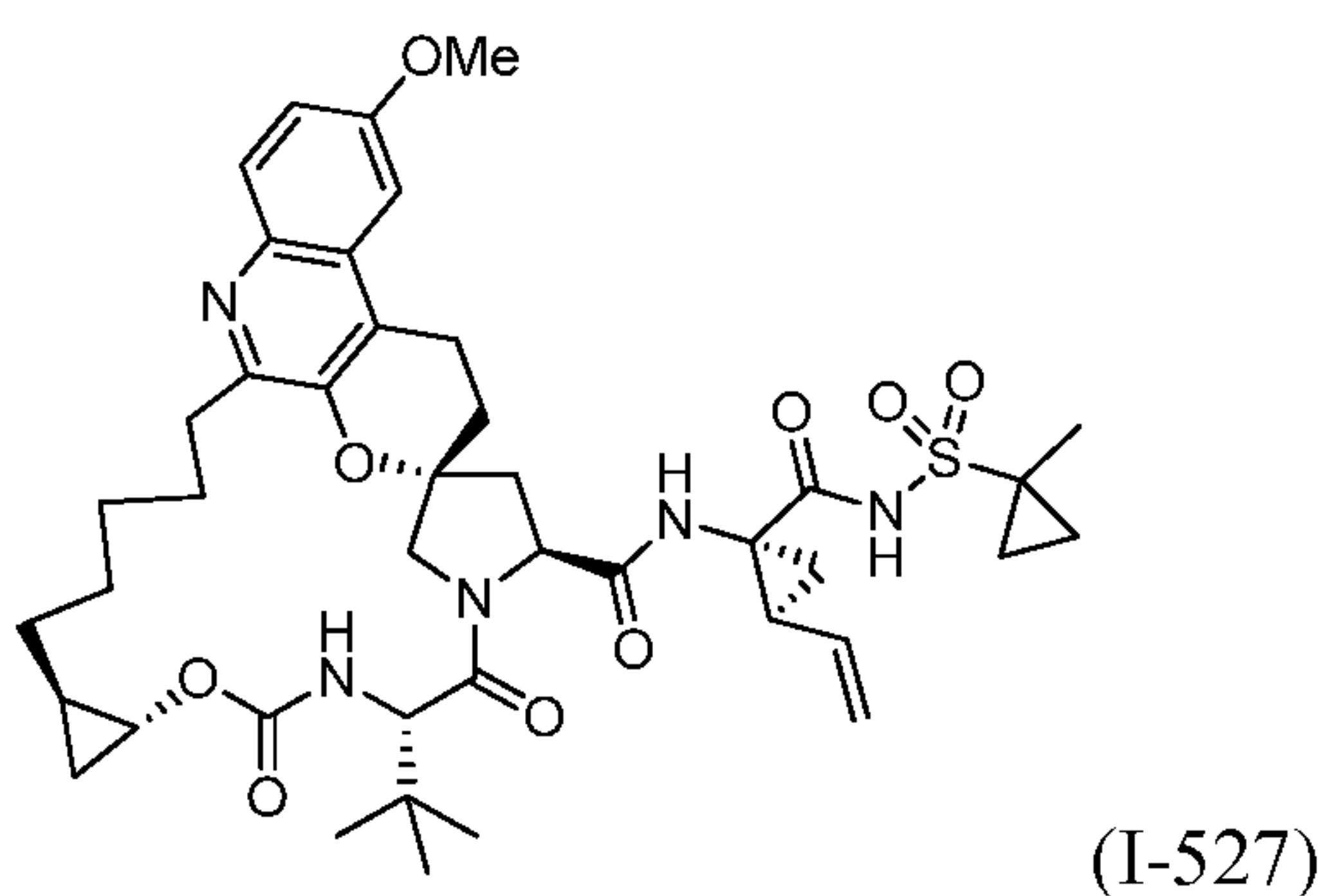
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
507	 I-507	1-methylcyclobutyl [(1 <i>R</i> ,2 <i>S</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-1'-hydroxy-9'-methoxy-1'-methyl-14a- {[(1-methylcyclopropyl)sulfonyl]carbamoyl}]-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	62	876.2
508	 I-508	cyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-(difluoromethyl)-9'-methoxy-14a- {[(1-methylcyclopropyl)sulfonyl]carbamoyl}]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	10	814.31 (K+ salt)
509	 I-509	1-methylcyclobutyl {(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-14a- {[(1-methylcyclopropyl)sulfonyl]carbamoyl}-9'-[2-(morpholin-4-yl)ethoxy]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl} carbamate	56, 30, 51, 528	905.36 (K+ salt)
510	 I-510	2,2-dimethylpropyl {(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-14a- {[(1-methylcyclopropyl)sulfonyl]carbamoyl}-9'-[2-(morpholin-4-yl)ethoxy]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl} carbamate	56, 30, 51, 6	907.58 (K+ salt)
511	 I-511	2-methylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-14a- {[(1-methylcyclopropyl)sulfonyl]carbamoyl}-9'-[3-(morpholin-4-yl)propoxy]-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	7, 50	947.32

Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
512		(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-[(<i>tert</i> -butoxycarbonyl)amino]-9'-methoxy-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxylic acid	5	716.2
513		(1 <i>R</i> ,3 <i>r</i> ,5 <i>S</i>)-bicyclo[3.1.0]hex-3-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	5, 41	858.3
514		<i>tert</i> -butyl {(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-9'-[3-(morpholin-4-yl)propoxy]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl} carbamate	56, 30, 51, 6	907.4
515		2-methylpropyl {(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-9'-[2-(morpholin-4-yl)ethoxy]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl} carbamate	56, 30, 51, 6	893.39 (HCl salt)
516		(1 <i>R</i> ,3 <i>r</i> ,5 <i>S</i>)-bicyclo[3.1.0]hex-3-yl {(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbamoyl}-9'-[2-(morpholin-4-yl)ethoxy]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl} carbamate	56, 30, 51, 6	917.46 (HCl salt)

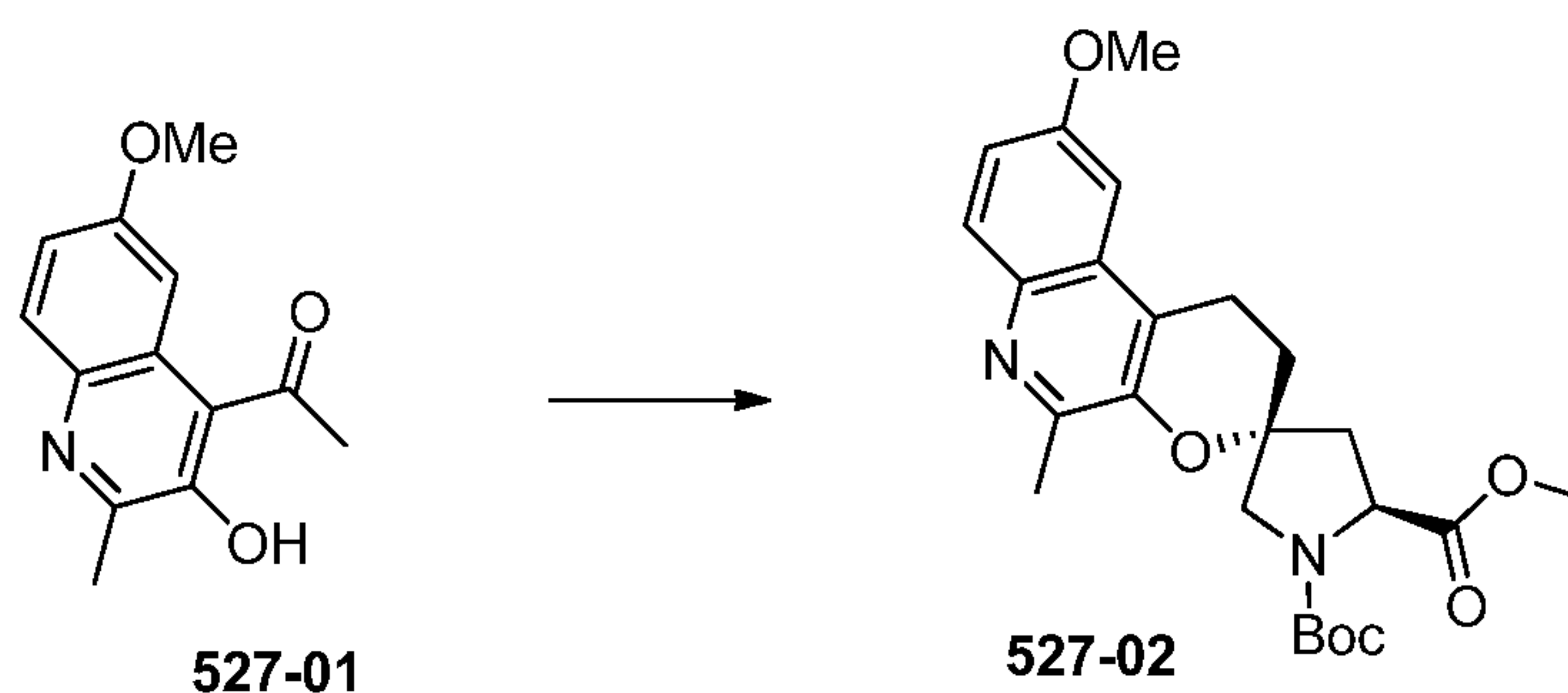
Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
517		<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>E</i> ,13 <i>aR</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-methoxy-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(trifluoromethyl)-1,5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-[1,4]dioxino[2,3- <i>c</i>]quinolin]-6-yl]carbamate	8	836.5
518		<i>tert</i> -butyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-[2-(3,3-difluoroazetidin-1-yl)ethoxy]-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	67	939.4
519		(2 <i>S</i>)-3-methylbutan-2-yl {(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-9'-[2-(morpholin-4-yl)ethoxy]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl} carbamate	56, 30, 51, 35	907.6 (HCl salt)
520		(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6-amino-9'-methoxy- <i>N</i> -[(1-methylcyclopropyl)sulfonyl]-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinoline]-14 <i>a</i> (5 <i>H</i>)-carboxamide	6	--
521		2,2-dimethylpropyl {(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-5'-ethyl-14a-{{(1-methylcyclopropyl)sulfonyl}carbonyl}-9'-[3-(morpholin-4-yl)propoxy]-5,16-dioxo-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl} carbamate	56, 30, 51, 35	921.68 (HCl salt)

Ex. No.	Structure	Name	Proc.	LR-MS (M+H)
522	 I-522	1-methylcyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-(3-methoxypropoxy)-14a- {[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	51	904.4 (K+ salt)
523	 I-523	1-methylcyclobutyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-9'-(3-methoxypropoxy)-14a- {[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-5'-(trifluoromethyl)-1,1',2',5,6,7,8,9,10,11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,3'-pyrano[2,3- <i>c</i>]quinolin]-6-yl]carbamate	51	892.38 (K+ salt)
524	 I-524	(1 <i>R</i> ,3 <i>r</i> ,5 <i>S</i>)-bicyclo[3.1.0]hex-3-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6'-(difluoromethyl)-2'-methoxy-14a- {[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,5,6,7,8,9,9',10,10',11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,8'-pyrano[2,3- <i>c</i>][1,5]naphthyridin]-6-yl]carbamate	12	841.45
525	 I-525	(2 <i>S</i>)-butan-2-yl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6'-(difluoromethyl)-2'-methoxy-14a- {[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,5,6,7,8,9,9',10,10',11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,8'-pyrano[2,3- <i>c</i>][1,5]naphthyridin]-6-yl]carbamate	12	817.46
526	 I-526	2,2-dimethylpropyl [(2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)-6'-(difluoromethyl)-2'-methoxy-14a- {[(1-methylcyclopropyl)sulfonyl]carbamoyl}-5,16-dioxo-1,5,6,7,8,9,9',10,10',11,13 <i>a</i> ,14,14 <i>a</i> ,15,16,16 <i>a</i> -hexadecahydrospiro[cyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-2,8'-pyrano[2,3- <i>c</i>][1,5]naphthyridin]-6-yl]carbamate	12	831.46

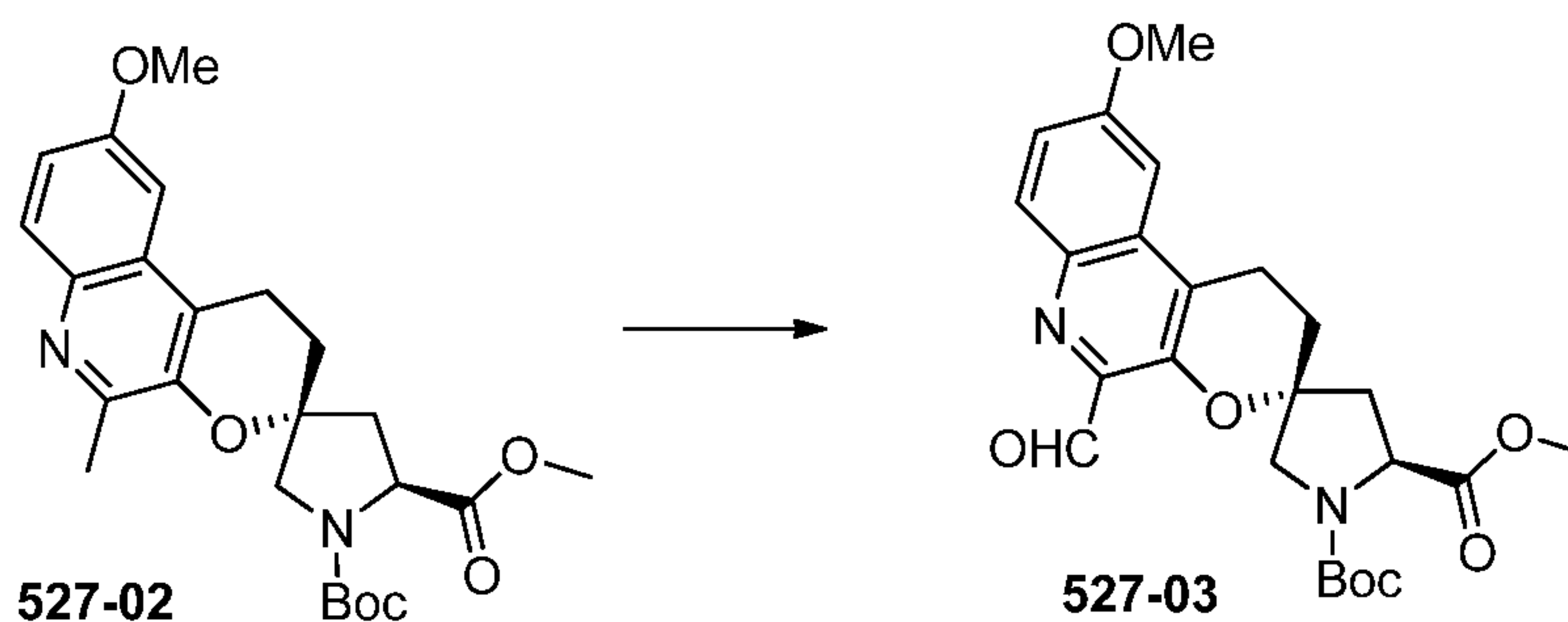
Example 527:



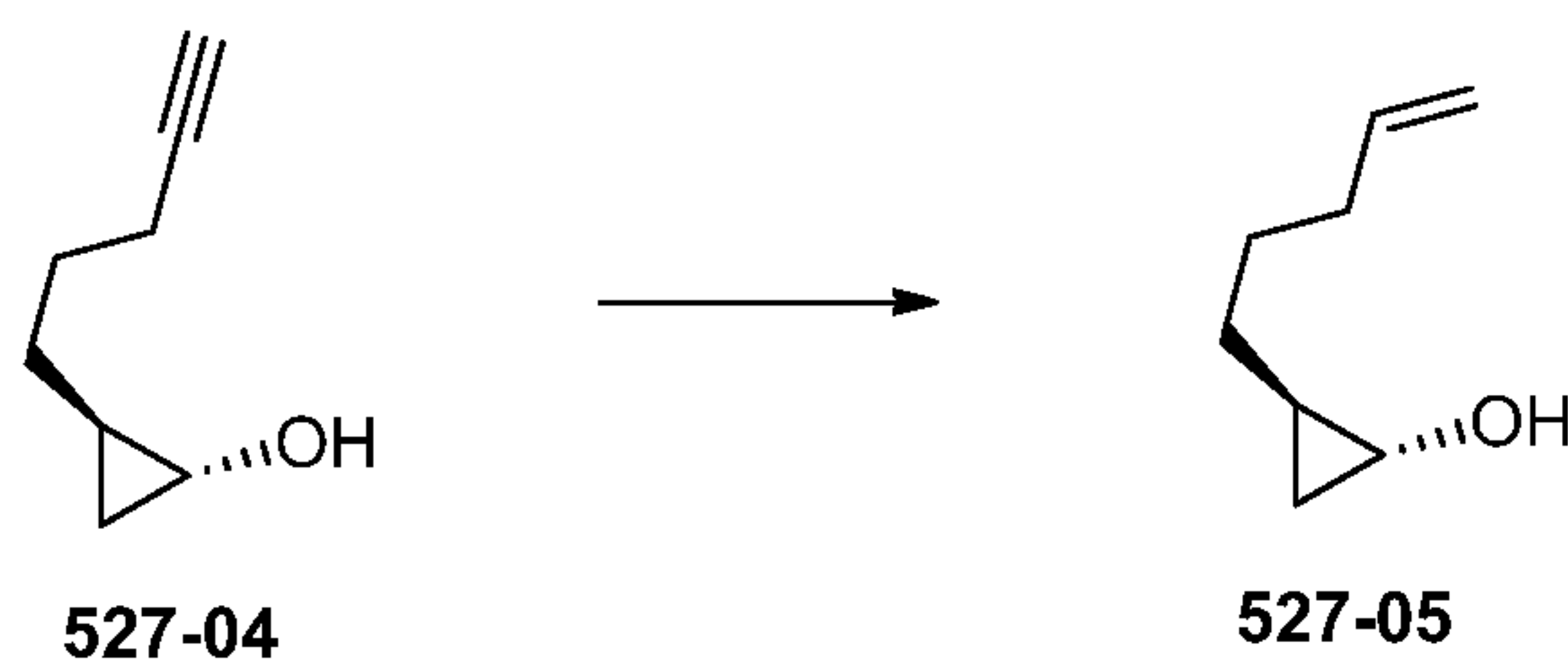
Experimental Procedures:



2-Methyl-3-hydroxy-4-acetyl-6-methoxyquinoline (**527-01**) was synthetically manipulated following previously described procedures to obtain the required spirocyclic intermediate **527-02**.



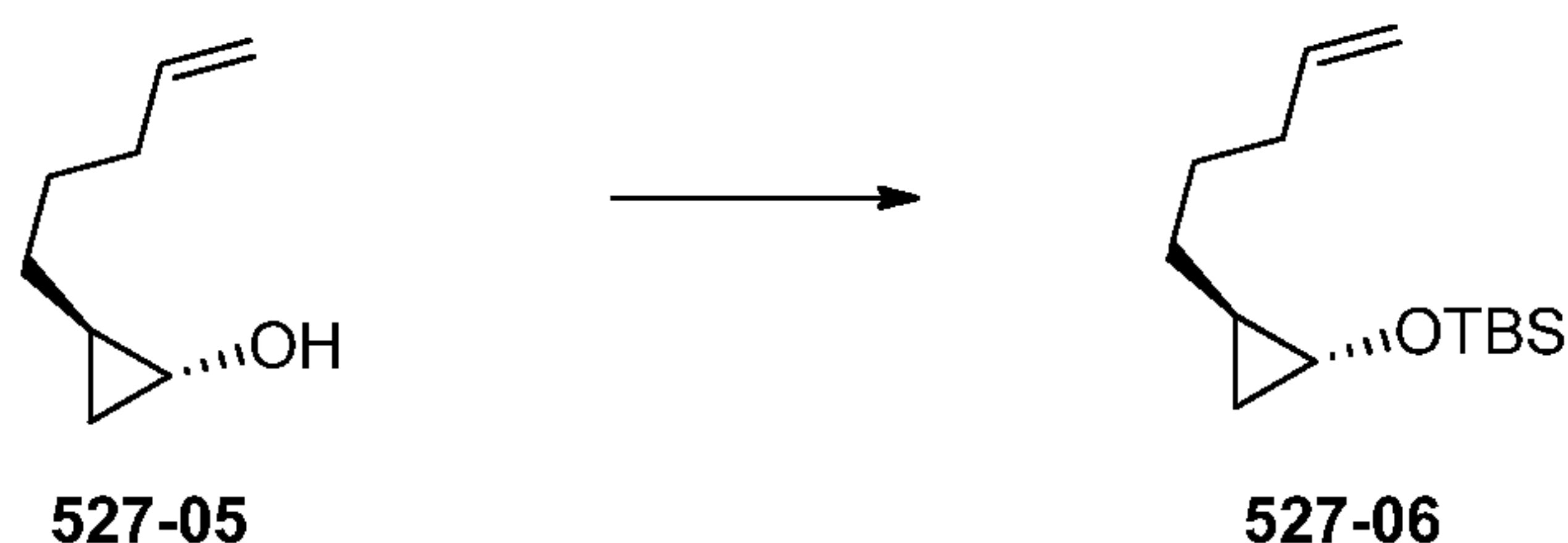
The 2-methylquinoline intermediate **527-02** was synthetically manipulated using previously described procedures to obtain the required 2-formylquinoline intermediate **527-03**.



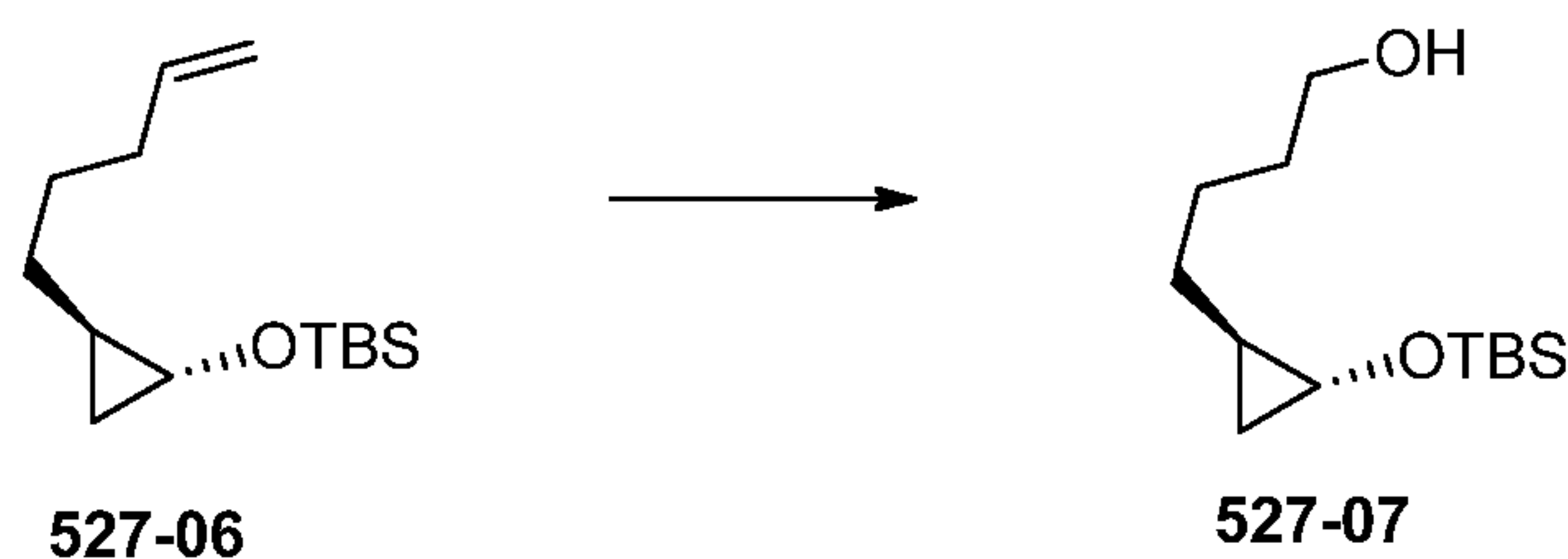
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A solution of (1R,2R)-2-(pent-4-yn-1-yl)cyclopropanol (**527-04**) (2 g, 16.11 mmol) in methanol (64.4 ml) was treated with quinoline (1.908 ml, 16.11 mmol) and Lindlar

Catalyst (0.428 g, 0.201 mmol). The mixture was hydrogenated at room temp (ballon pressure). After 2 h TLC showed a complete reaction. The solids were removed by filtration and the filtrate was concentrated to almost dryness in rotavap. The residue was taken into ether (100 mL) and washed with aq 1 m HCl (2 x 25 mL) and brine (20 mL), dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was adsorbed on silica gel and purified on a gold cap Redisep (80 g) silica gel column using dichloromethane to elute the column. The product **527-05** (740 mg, 5.75 mmol, 35.7 % yield) was obtained as a colorless oil.

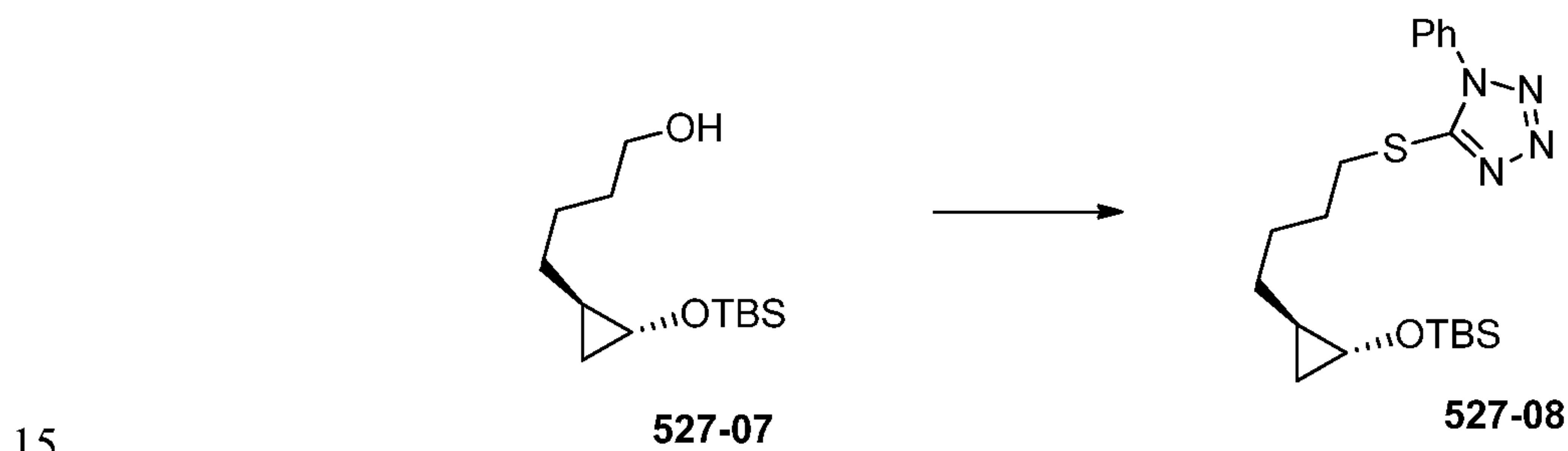


A round-bottom flask was charged with a solution of alcohol **527-05** (470 mg, 3.72 mmol) in dry 2-methyl-THF (1.49 ml). The solution was cooled in ice-water bath and treated with 2,6-lutidine (1084 μ l, 9.31 mmol), imidazole (63.4 mg, 0.931 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (898 μ l, 3.91 mmol). The cooling bath was removed after 10 min and the mixture was stirred at room temp overnight. The mixture was diluted with ethyl ether (50 mL). The organic layer was washed with aq 1 m HCl (2 x 20 mL), aq saturated sodium bicarbonate (20 mL) and brine (20 mL), dried over magnesium sulfate, filtered and concentrated in rotavap to give the crude product **527-06** (920 mg, 3.83 mmol, 103 % yield) as a colorless oil. No further purification was carried out.

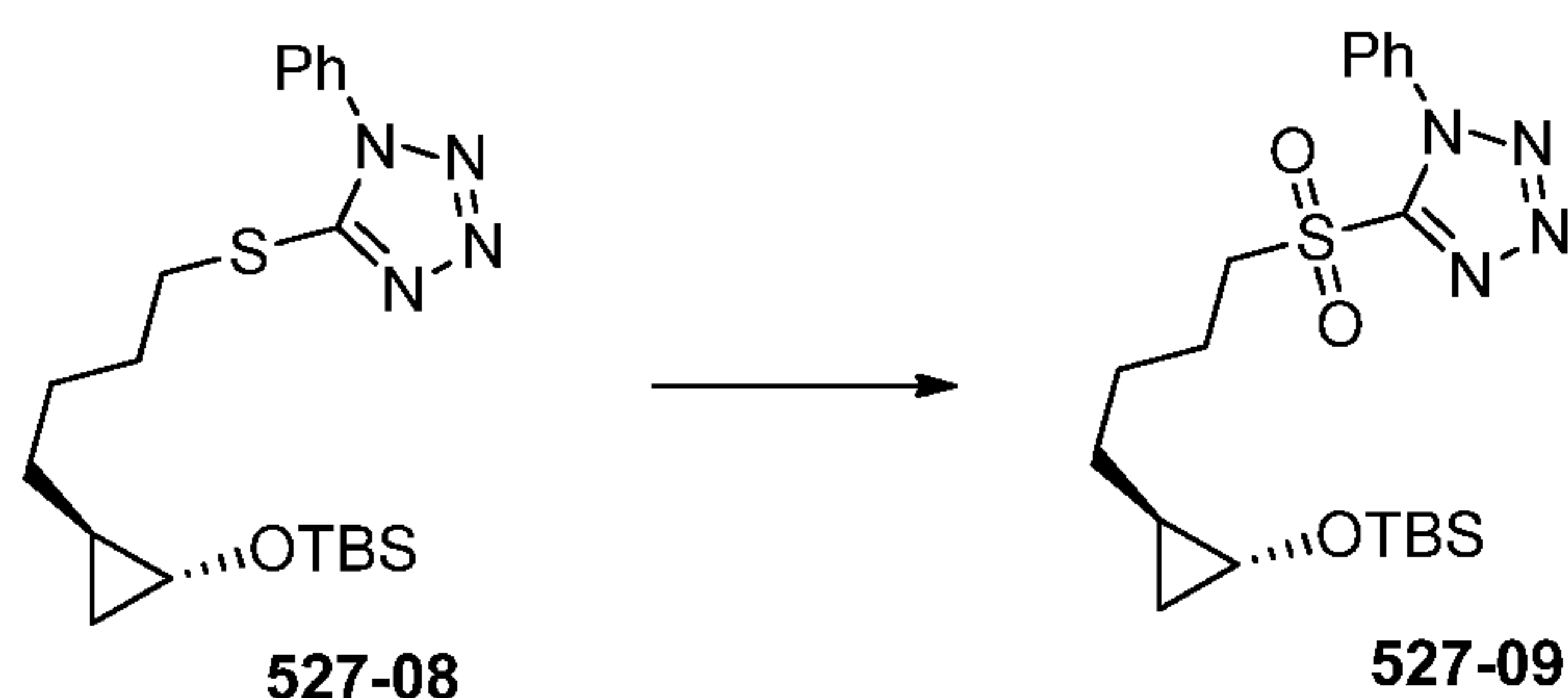


A round-bottom flask was charged with a solution of alkene **527-06** (900 mg, 3.74 mmol) in acetone (1.87 ml) and Water (1.87 ml). More Acetone (18.7 mL) was added followed by potassium osmate(VI) dihydrate (69.0 mg, 0.187 mmol). After 5 min sodium periodate (4003 mg, 18.71 mmol) was added. A thick slurry was formed after 5 min and stirring was continued for 3 h. TLC (20% ethyl acetate in hexanes) showed no more alkene was left. The solids were removed by filtration. The filter cake was washed with acetone (20 mL). The filtrate was cooled in ice-water bath. 5% Aq sodium thiosulfate (40 mL) was slowly added. Stirring was continued

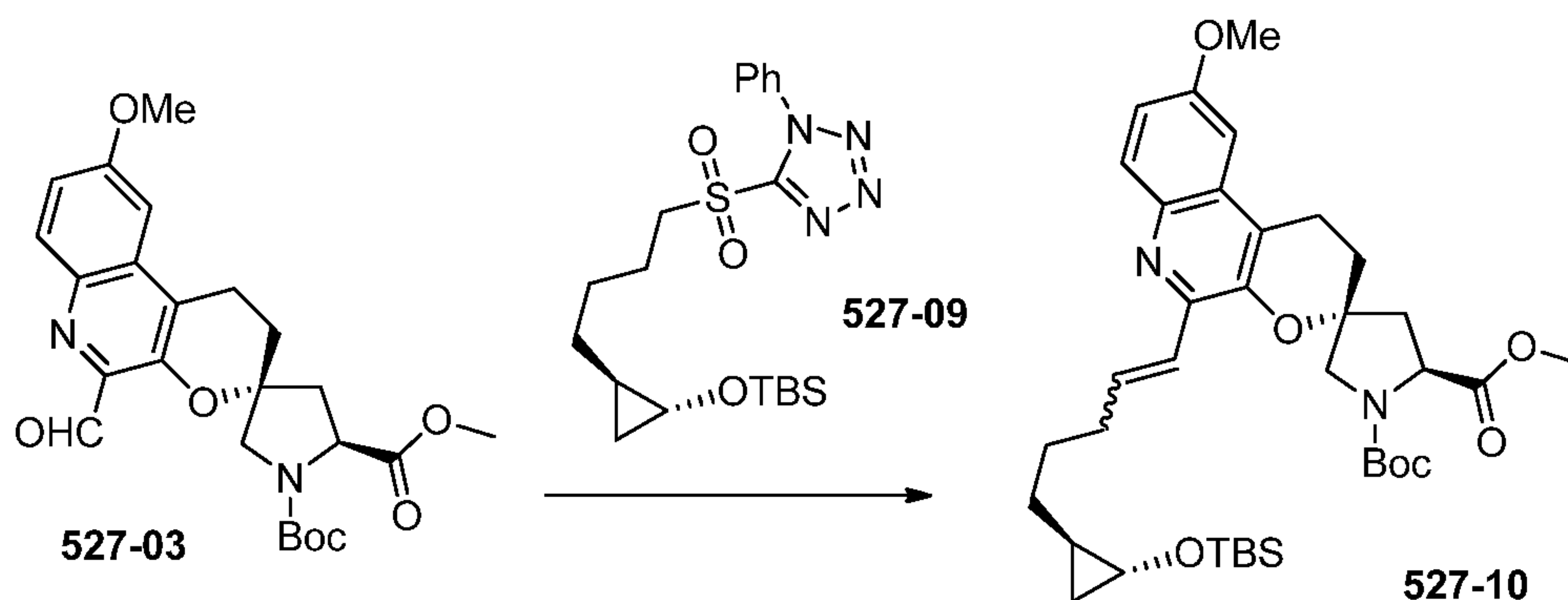
for 10 min. The mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with 5% aq sodium thiosulfate (20 mL) and brine (20 mL), dried over magnesium sulfate, filtered and concentrated to almost dryness. The residual acetone was co-evaporated with toluene (2 x 10 mL) to give the crude aldehyde intermediate as a colorless oil
 5 which was used without further purification. The aldehyde intermediate was dissolved in 2-methyl-THF (20 mL) and methanol (2 mL). The solution was cooled in ice water bath and treated with sodium borohydride (212 mg, 5.61 mmol). Stirring was continued for 30 min. The mixture was treated with aq saturated ammonium chloride (20 mL) and stirred for 10 min. Water (20 mL) was added and the mixture was extracted with ethyl acetate (50 mL). The aq layer was acidified
 10 with aq 1 M HCl (pH 1) and extracted with ethyl acetate (50 mL). The combined organic extracts were washed with brine (20 mL), dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was adsorbed on silica gel and purified on a gold cap Redisep (80 g) silica gel column (gradient: 0 to 100 % ethyl acetate in hexanes) to give the product **527-07** (570 mg, 2.332 mmol, 62.3 % yield) as a colorless oil.



A round-bottom flask was charged with alcohol **527-07** (0.57 g, 2.332 mmol), triphenylphosphine (0.917 g, 3.50 mmol) and 1-phenyl-1h-tetrazole-5-thiol (0.499 g, 2.80 mmol). Dry 2-methylTHF (23.32 ml) was added at 0 °C follow by slow addition of DIAD (0.5270 ml, 3.50 mmol). The mixture was gradually warmed to room temp and stirred for 3 h. The mixture
 20 was diluted with ethyl acetate (80 mL) and washed with half-saturated sodium bicarbonate (2 x 25 mL), water (25 mL) and brine (20 mL), dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was adsorbed on silica gel and purified on a gold cap Redisep (120 g) silica gel column (gradient: 0 to 30% ethyl acetate in hexanes) to give the product **527-08** (830 mg, 2.051 mmol, 88 % yield) as a colorless oil.

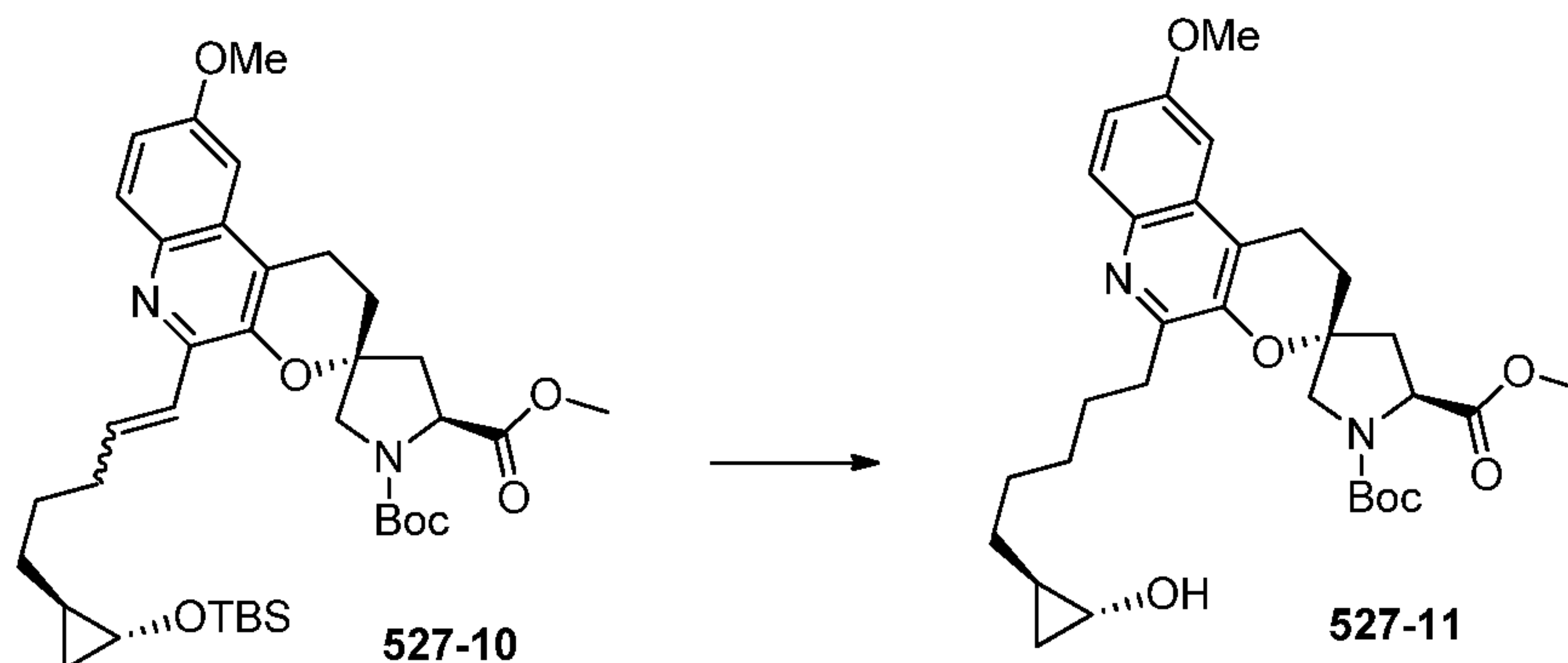


A round-bottom flask was charged with a solution of sulfide **527-08** (0.825 g, 2.039 mmol) in CH_2Cl_2 (20.39 ml). The solution was cooled in ice-water bath and treated with 75% m-CPBA (1.876 g, 8.16 mmol). The cooling bath was removed after 10 min and the mixture
 5 was stirred at room temp. After 6 h LCMS showed complete conversion. The reaction mixture was cooled and quenched with 10% aq sodium thiosulfate (20 mL), stirred for 5 min followed by addition of aq saturated sodium bicarbonate (20 mL). The mixture was stirred for 5 min and extracted with ethyl acetate (2 x 40 mL). The combined organic layers were washed with 10% aq potassium carbonate (2 x 15 mL) and brine (15 mL), dried over magnesium sulfate, filtered and
 10 concentrated in rotavap. The residue was adsorbed on silica gel and purified on a Redisep (80 g) silica gel column (gradient: 0 to 25 % ethyl acetate in hexanes) to give the product **527-09** (810 mg, 1.855 mmol, 91 % yield) a colorless oil.

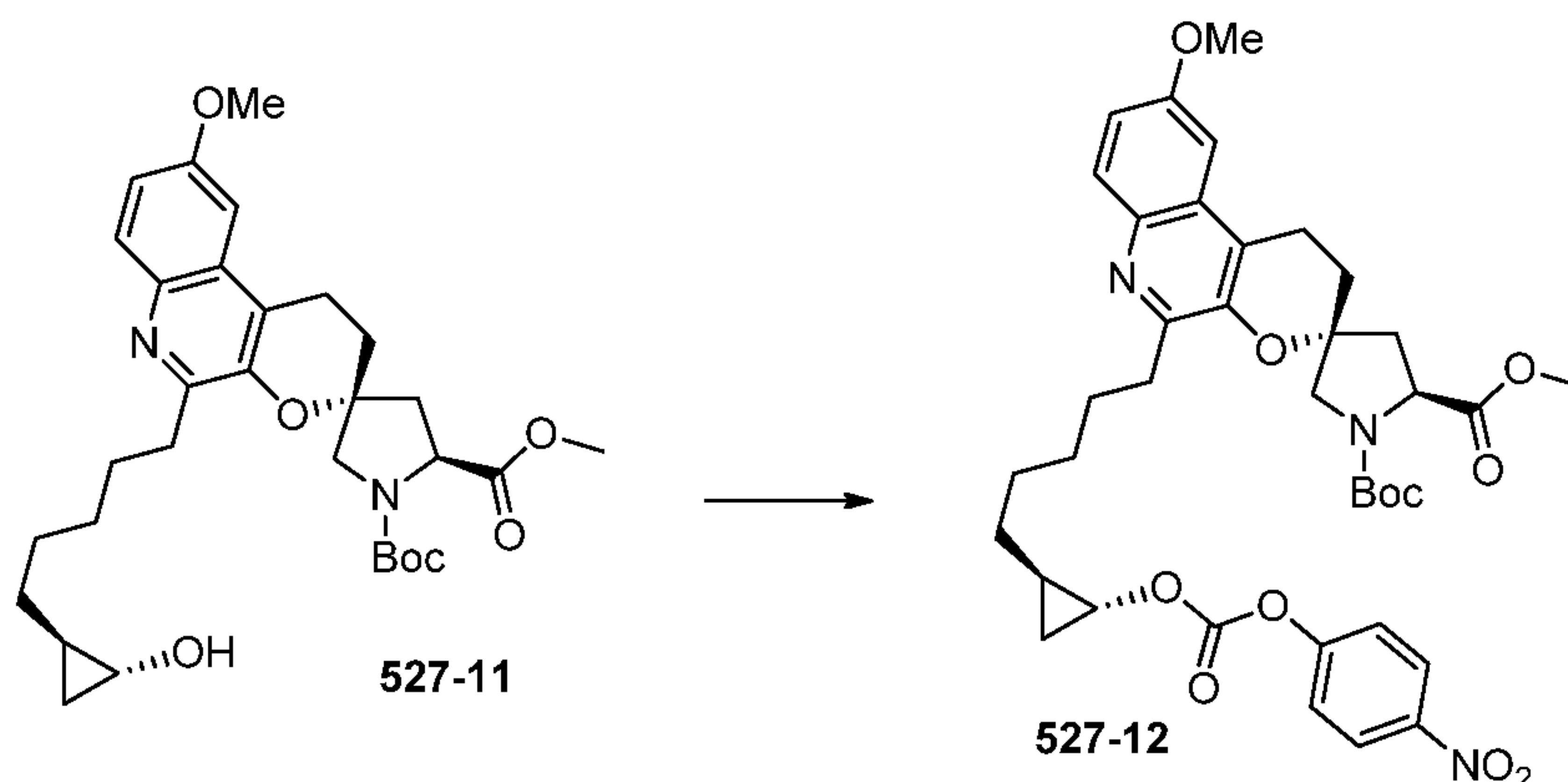


A solution of sulfone **527-09** (800 mg, 1.831 mmol) in dry 2-methyl-THF (6104
 15 μl) was cooled in acetone-dry ice bath and treated with 1 M potassium hexamethyldisilazide (1831 μl , 1.831 mmol). The resulting yellow solution was stirred for 45 min followed by addition of aldehyde **527-03** (697 mg, 1.526 mmol) in dry 2-methylTHF (1 mL). The mixture was gradually warmed to room temp and stirred overnight. The reaction was quenched by addition of water (5 mL) and stirred for 5 min. Aq 1 M HCl (1 mL) was added and the product was extracted
 20 into ethyl acetate (20 mL). Upon separation the organic layer was washed with brine (5 mL), dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was adsorbed on

silica gel and purified on a Redisep (12 g) silica gel column (gradient: 0 to 70 % ethyl acetate in hexanes) to give the product **527-10** (610 mg, 0.915 mmol, 59.9 % yield) as a colorless oil.

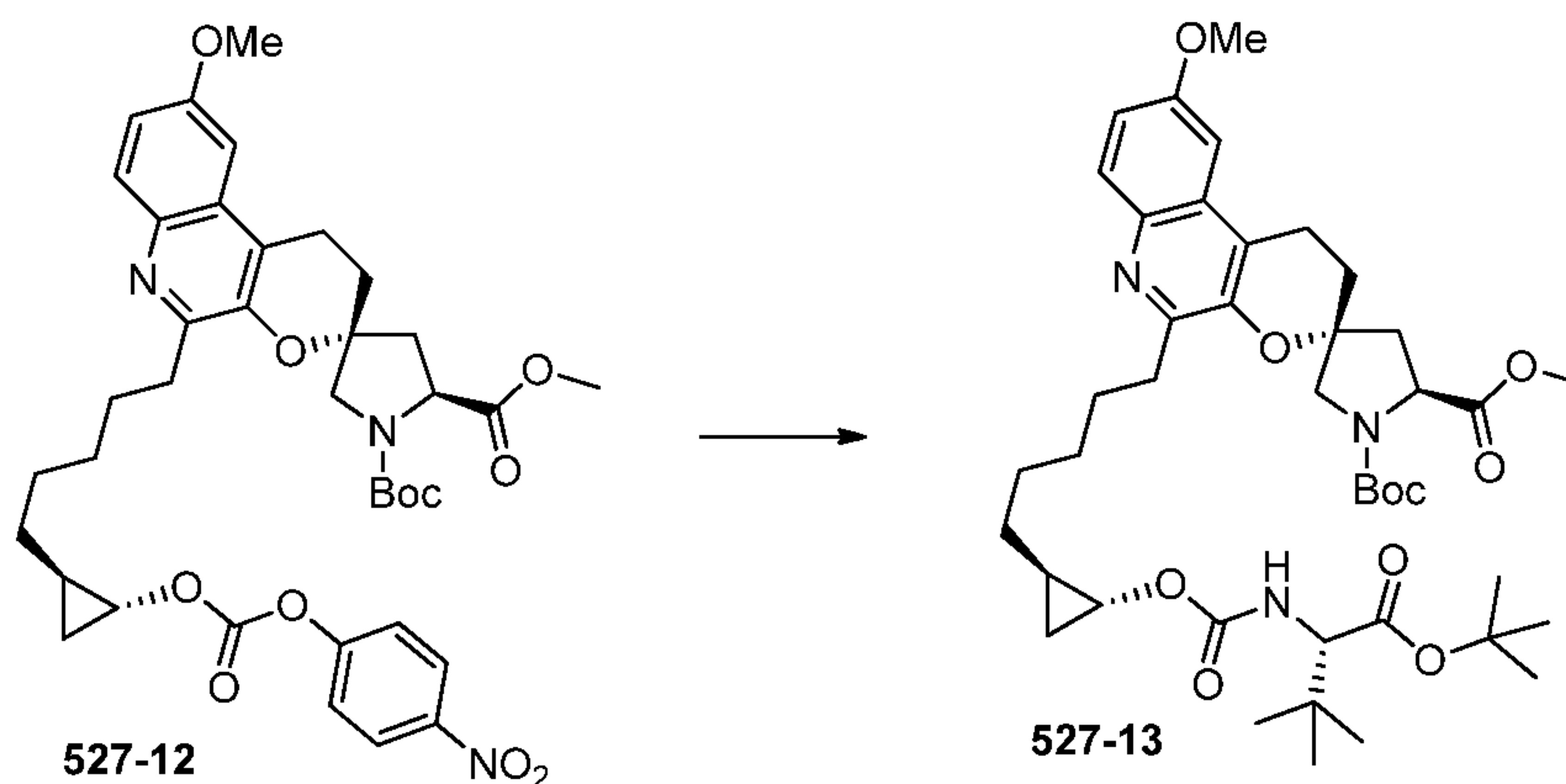


A round-bottom flask was charged with a solution of **527-10** (0.57 g, 0.855 mmol) in 2-methyl-THF (8.55 ml). 10% palladium on carbon (30 mg, 0.028 mmol) was added and the mixture was hydrogenated at room temp (ballon pressure). After 3 h LCMS showed complete hydrogenation of the double bond. The solids were removed by filtration (celite) and the filtrate was treated with 1 M TBAF (1.709 ml, 1.709 mmol) at room temp. At 1 h LCMS showed no more of the silylether present. The mixture was diluted with ethyl acetate (80 mL) and washed with aq saturated sodium bicarbonate (20 mL), and brine (20 mL), dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was adsorbed on silica gel and purified on a gold cap Redisep (80 g) silica gel column (gradient: 0 to 60% acetone in hexanes) to give the product **527-11** (420 mg, 0.757 mmol, 89 % yield) as a colorless foam.

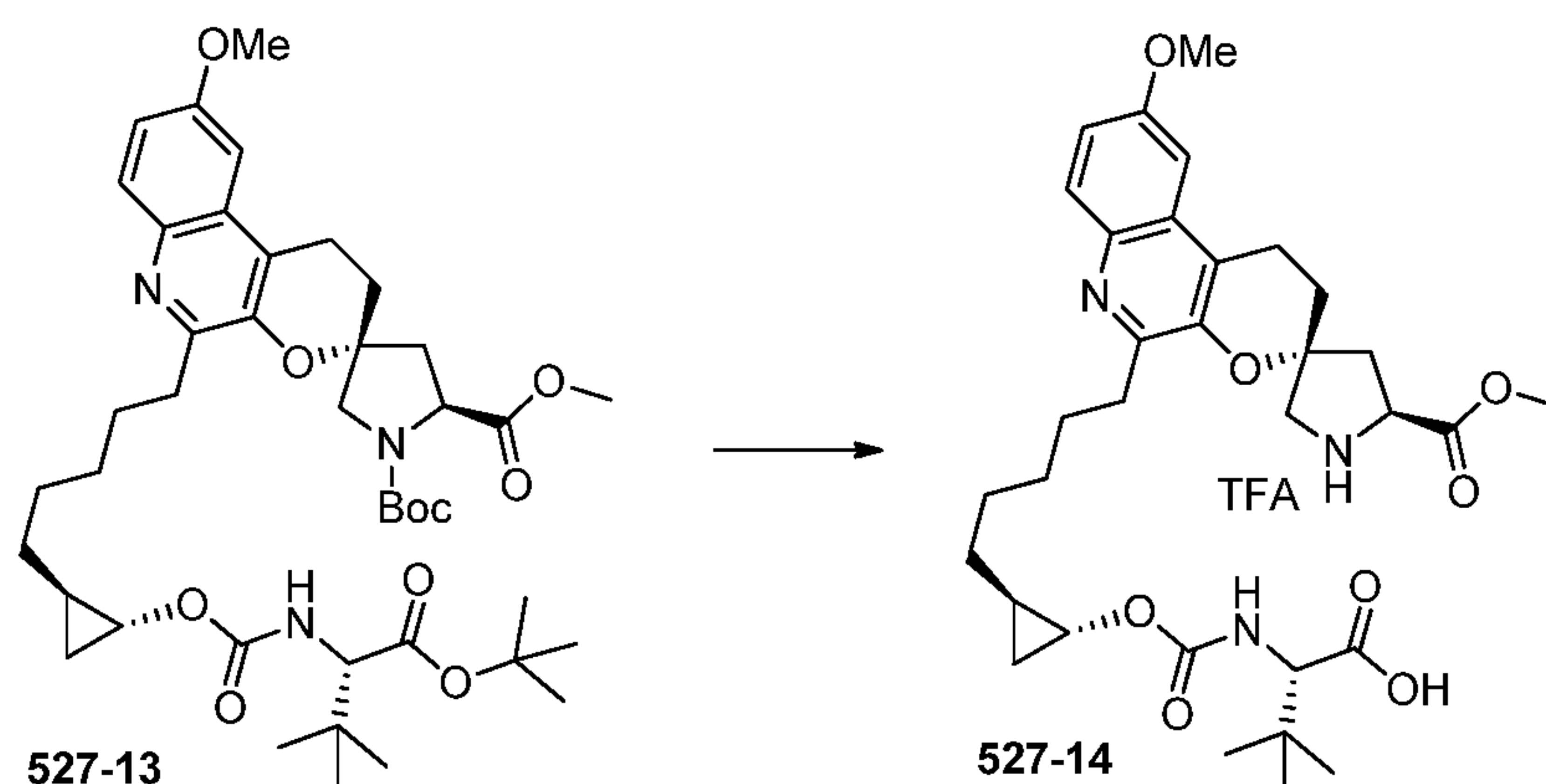


A reaction tube was charged with **527-11** (0.42 g, 0.757 mmol) and 4-nitrophenyl chloroformate (0.382 g, 1.893 mmol). Acetonitrile (3.03 ml) was added to dissolve solids followed by addition of pyridine (0.306 ml, 3.79 mmol). The reaction mixture was stirred at room temperature until no more starting material was left. LCMS showed no more starting material left after 2 h. The mixture was diluted with ethyl acetate (300 mL) and washed with aq

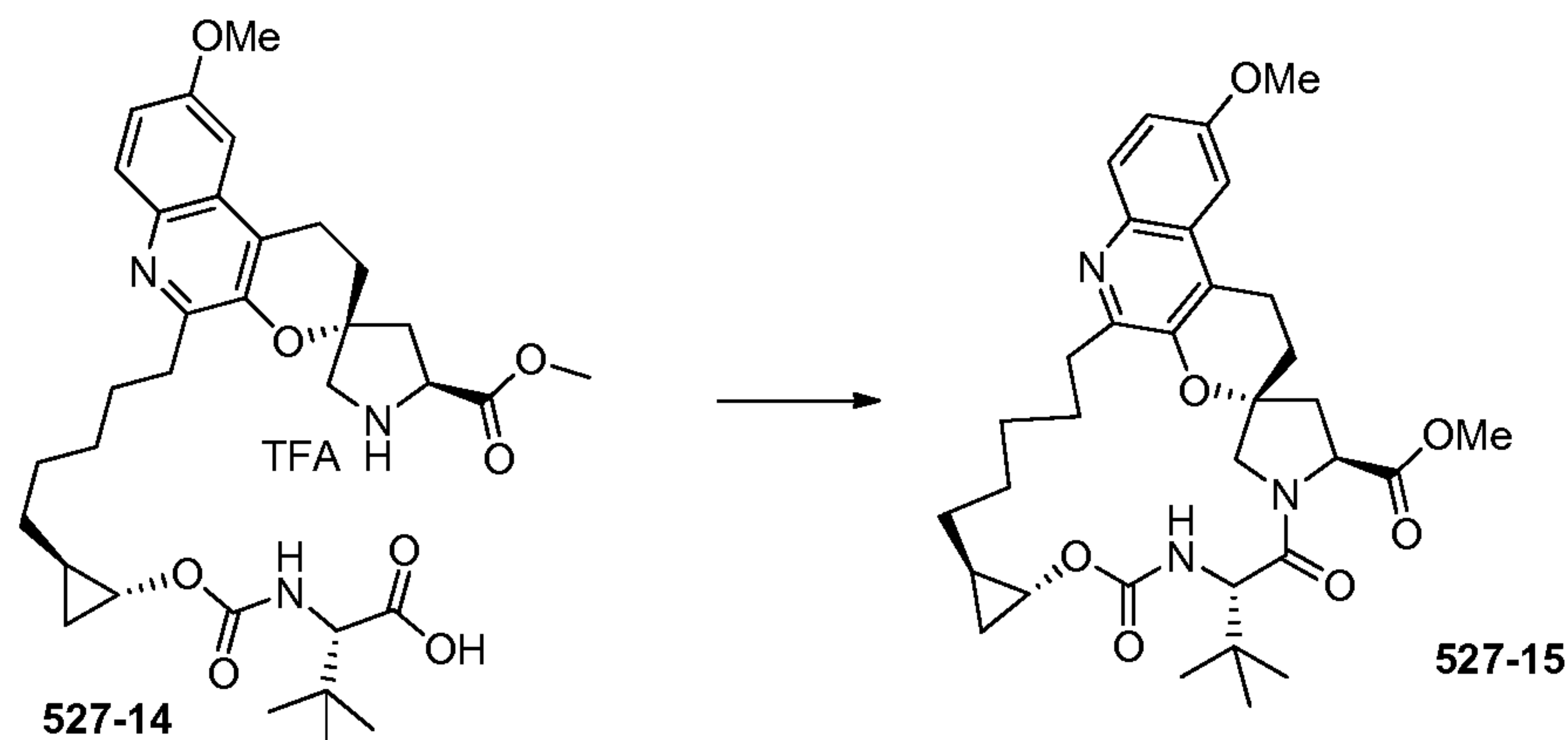
0.5 m HCl (2 x 30 mL). The organic layer was washed with aq saturated sodium bicarbonate (30 mL), brine (30 mL), dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was adsorbed on silica gel and purified on a gold cap Redisep (80 g) silica gel column (gradient: 0 to 60 % ethyl acetate in hexanes) to give the product **527-12** (469 mg, 0.652 mmol, 5 86 % yield) as a colorless foam.



A round-bottom flask was charged with mixed carbonate **527-12** (230 mg, 0.320 mmol) and amine hydrochloride (S)-tert-butyl 2-amino-3,3-dimethylbutanoate hydrochloride (107 mg, 0.479 mmol). The mixture was dissolved in dry acetonitrile (3195 μ l) followed by addition of Hunig's Base (223 μ l, 1.278 mmol). The mixture was stirred overnight. A solution of DMAP (7.81 mg, 0.064 mmol) in THF (0.3 mL) was added and the mixture was stirred overnight. LCMS showed about 20% starting material left and the mixture was kept at 5 °C over weekend. LCMS showed about 7% starting material left. The mixture was diluted with ethyl acetate (30 mL) and washed with 0.5 m HCl (5 mL), aq saturated sodium bicarbonate (5 mL) and 15 brine (5 mL), dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was adsorbed on silica gel and purified on a gold cap Redisep (40 g) silica gel column (gradient: 0 to 50% acetone in hexanes) to give the product **527-13** (185 mg, 0.241 mmol, 75 % yield) as a colorless foam.

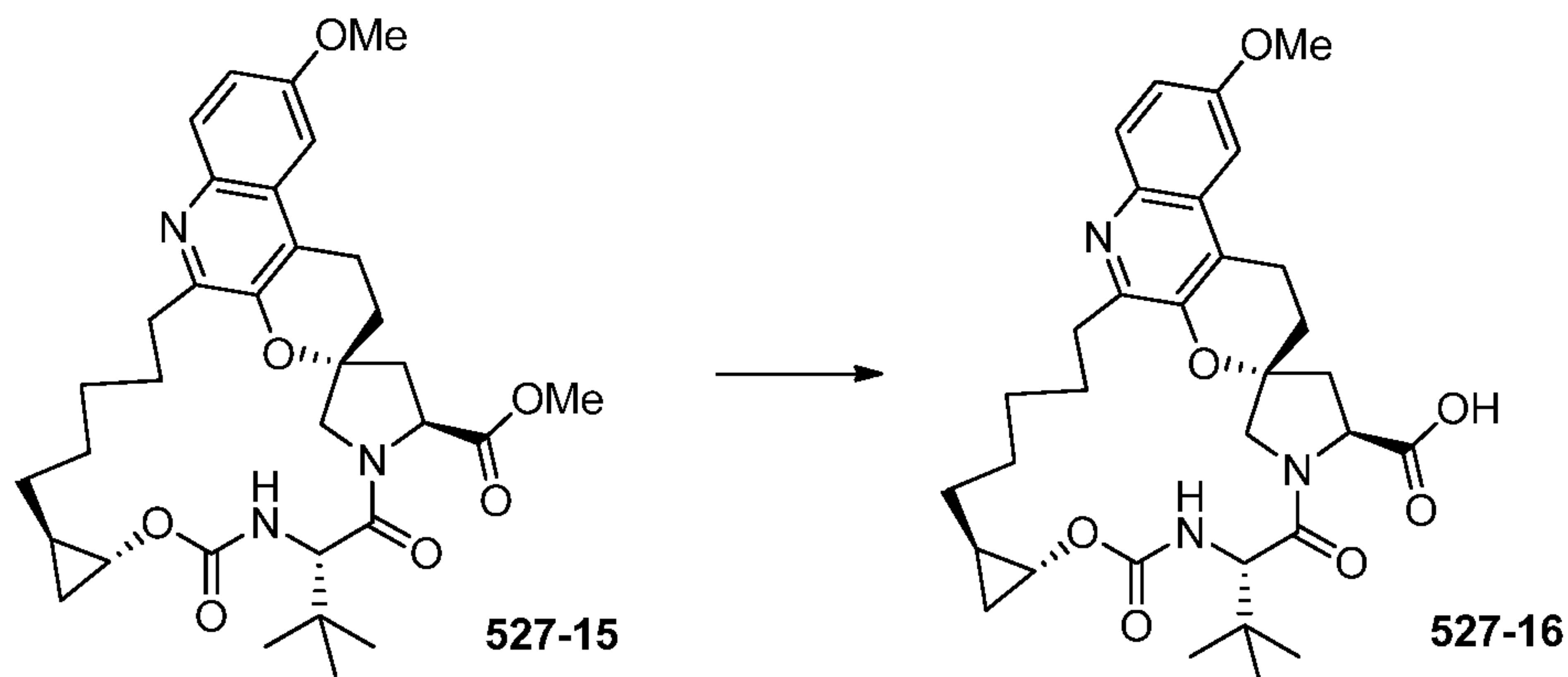


The intermediate **527-13** (0.18 g, 0.234 mmol) was dissolved in CH₂Cl₂ (3 ml) and treated with TFA (3 mL). The resulting solution was stirred at room temp until complete deprotection of the N-Boc and t-butylester moieties was attained. After 4h LCMS showed
 5 complete reaction. The mixture was concentrated in rotavap to give the product **527-14** (175 mg, 0.241 mmol, 103 % yield) as a slightly yellow oil. The product was dried azeotropically with toluene (2 x 3 mL). No further purification was carried out.

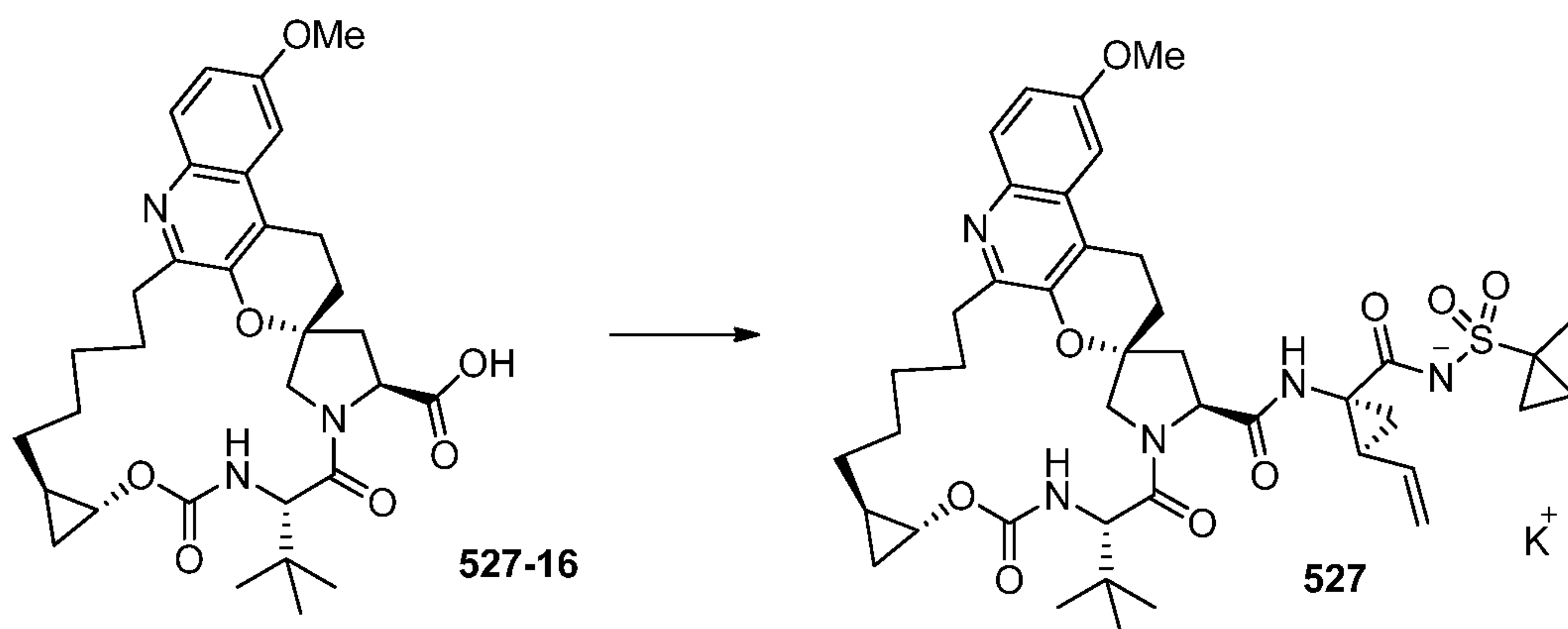


A round-bottom flask was charged with HATU (0.178 g, 0.4527 mmol) and dry
 10 DMF (2.342 ml). The resulting solution was cooled in an ice-water bath and Hunig's Base (0.205 ml, 1.171 mmol) was added followed by slow addition of a solution of amino acid **527-14** (0.17 g, 0.234 mmol) in dry DMF (7.03 ml) over 15 min (syringe pump). The reaction was stirred overnight (temp from 0 to 25 °C). The reaction mixture was concentrated to almost dryness in rotavap (high vacuum pump) and the residue was diluted with ethyl acetate (30 mL). The mixture
 15 was washed with aq 0.5 M HCl (5 mL), half-saturated sodium bicarbonate (2 x 5 mL) and brine (5 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was adsorbed on silica gel and purified on a gold cap Redisep (40 g) silica

gel column (gradient: 0 to 50 % acetone in hexanes) to give the product **527-15** (124 mg, 0.209 mmol, 89 % yield) as a white powder.



A round-bottom flask was charged with methyl ester **527-15** (120 mg, 0.202 mmol) and lithium hydroxide (24.20 mg, 1.011 mmol). 2-Methyl-THF (3 ml), MeOH (0.5 ml) and Water (0.5 ml) were added and the mixture was stirred at room temp. LCMS at 3 h showed complete reaction. The reaction was treated with dichloromethane (10 mL) and water (10 ml). Aq 1 m HCl was added until acidic pH (aprox 1.5 mL). Layers were separated. Aq layer was extracted with dichloromethane (10 mL) and ethyl acetate (10 mL). The combined organic extracts were washed with brine (5 mL), dried over magnesium sulfate, filtered and concentrated to give the product **527-16** (111 mg, 0.191 mmol, 95 % yield) as a white powder. No further purification was carried out for the product.



A round bottom flask was charged with acid **527-16** (40 mg, 0.069 mmol), (1R,2S)-1-amino-N-((1-methylcyclopropyl)sulfonyl)-2-vinylcyclopropanecarboxamide 4-methylbenzenesulfonate (57.5 mg, 0.138 mmol) and HATU (52.5 mg, 0.138 mmol). The mixture was dissolved in dry DMF (0.5 ml) followed by addition of Hunig'sBase (60.3 μ l, 0.345 mmol). The mixture was stirred overnight. The DMF was removed in rotavap using high-vacuum and the

residue was treated with ethyl acetate (15 mL). The organic layer was washed with aq 0.5 m HCl (3 mL), half-saturated sodium bicarbonate (2 x 3 mL) and brine (3 mL), dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was adsorbed on silica gel and purified on a gold cap Redisep (12 g) silica gel column (gradient: 0 to 60 % acetone in hexanes) to give the product 527 (45 mg, 0.056 mmol, 81 % yield) as a white powder. The product 527 (45 mg, 0.056 mmol, 81 % yield) was dissolved in acetonitrile (3 mL) and cooled in ice-water bath. A 0.5 m soln of potassium hydroxide (112 μ l, 0.56 mmol) was added and the mixture was stirred for 5 min. The mixture was concentrated to dryness in rotavap and dried under vacuum to give the potassium salt of 527 (47.3 mg, 0.056 mmol, 81 % yield) as a white powder.

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Example 528: Additional Synthesis

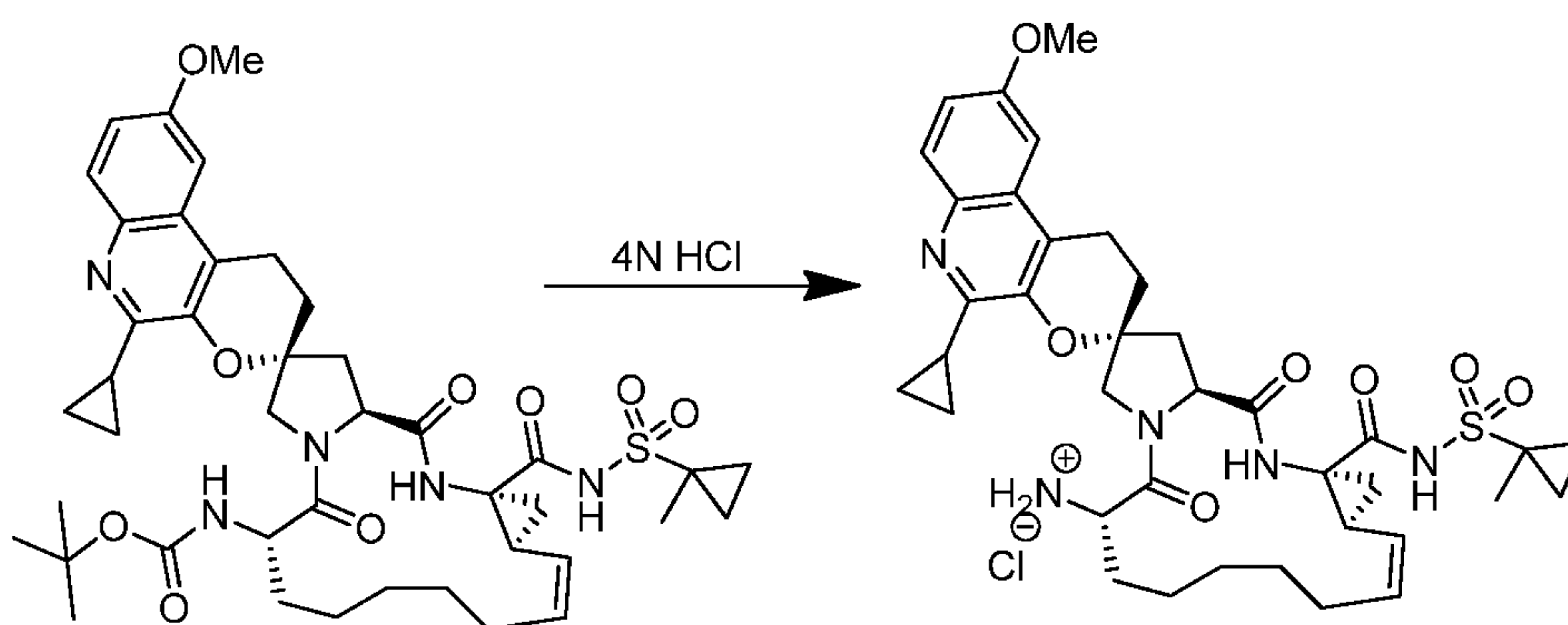
Additional examples of synthesizing different compounds are provided below.

These example further illustrate different synthesis techniques that can employed for compounds described herein.

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Synthesis of I-94

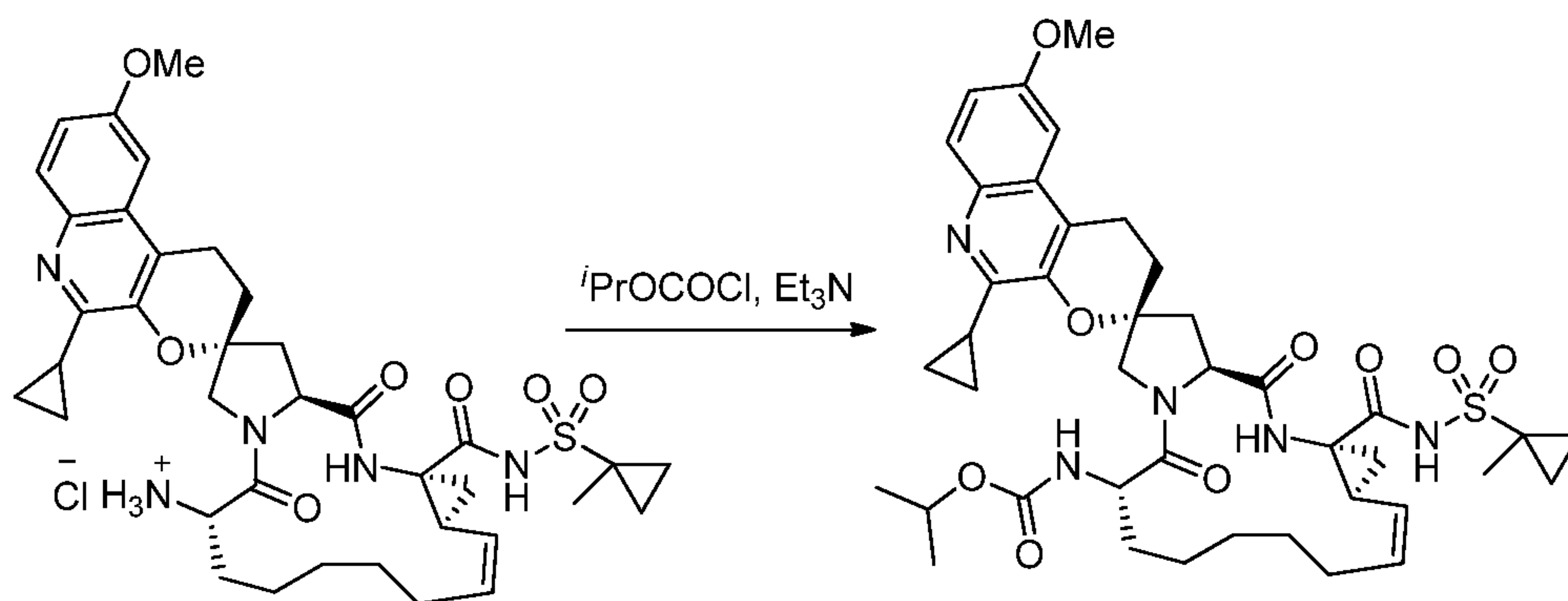
Step 1



A solution of I-16 (200 mg, 0.248 mmol) in 3 ml of 4 N HCl in dioxane was stirred at rt for 2 hr, and concentrated. The residue was evaporated twice with toluene and twice with ether to give the crude product of step 1 as a hydrochloride salt. MS m/e = 706.4 (MH⁺).

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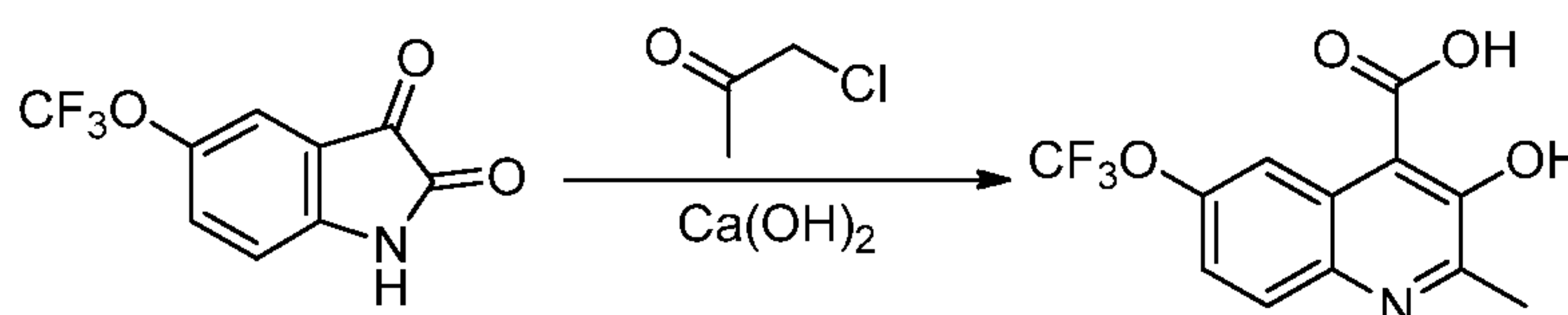
Step 2



A solution of product of step 1 (20 mg, 0.027 mmol), Et₃N (0.011 ml, 0.081 mmol) and isopropyl chloroformate (7.40 μl, 0.054 mmol) in 1 mL dichloromethane was stirred at rt for 2 hr, diluted with EtOAc, washed 2x with water, brine, concentrated and purified by preparative
5 TLC eluting with 5% MeOH-DCM to give I-94 MS m/e = 792.4 (MH⁺).

Synthesis of I-124

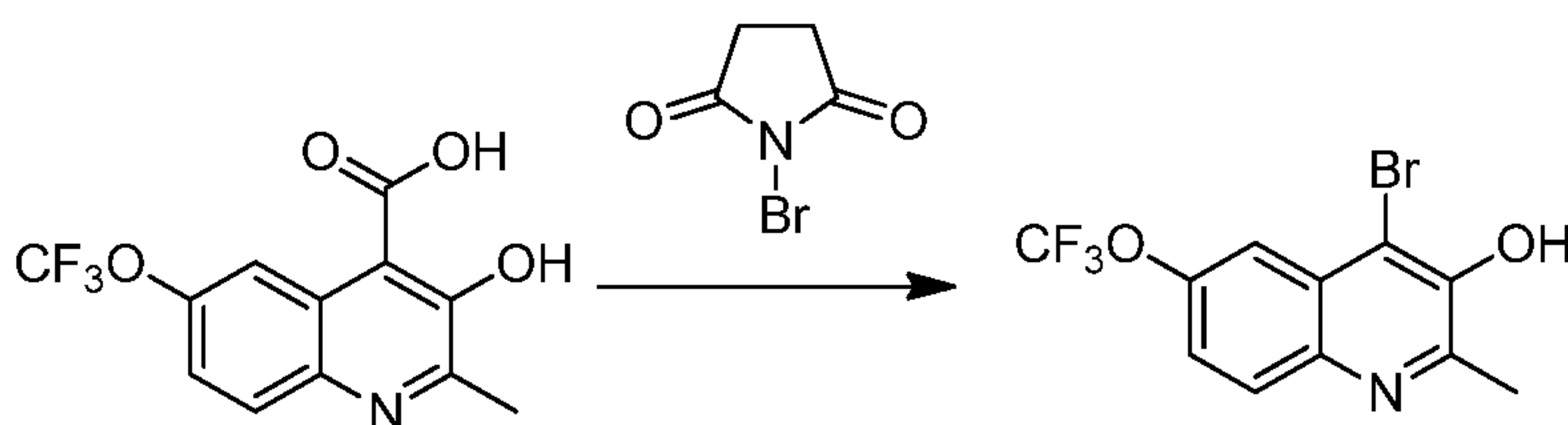
Step 1



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To a mixture of Ca(OH)₂ (38.5 g, 519 mmol) and 5-trifluoroisatin (40 g, 173 mmol) at room temperature was added water (150 ml) and the mixture was allowed to warm to 80 °C and stirred for 1 h. It was removed from bath and chloroacetone (34.5 ml, 433 mmol) was then added cautiously (very exothermic) and the reaction was left at room temperature for a
15 while, then allowed to warm to 80 °C and stirred for 5 hr. 1N HCl was added adjusting the pH =2. The solid separating out was filtered and dried over house vacuum. It was dried at 50 °C under vacuum pump for several hours until no water was present to yield product of step 1 (yield 95%)

Step 2

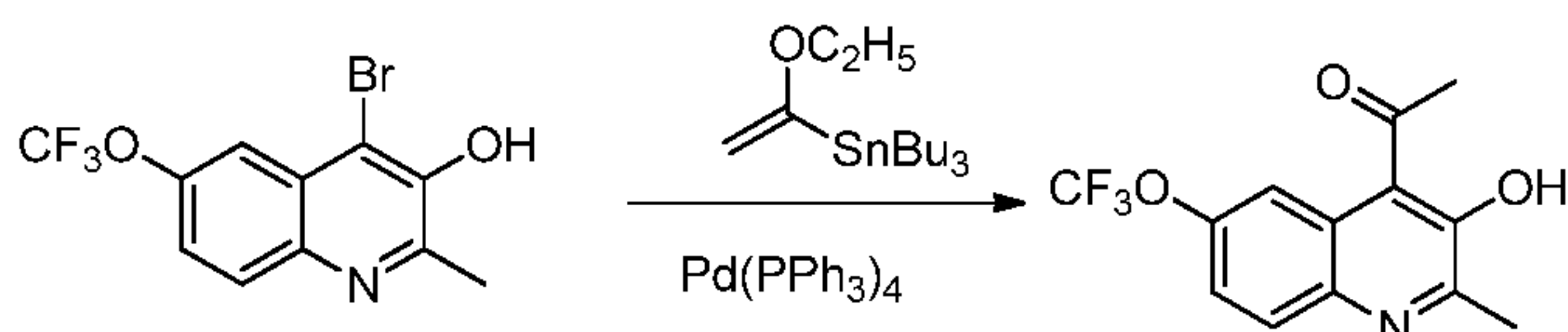


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The product of step 1 (40 g, 139 mmol) in THF (1000 ml) at room temperature was treated with NBS (29.7 g, 167 mmol) and the mixture was stirred for 4 h. The mixture was

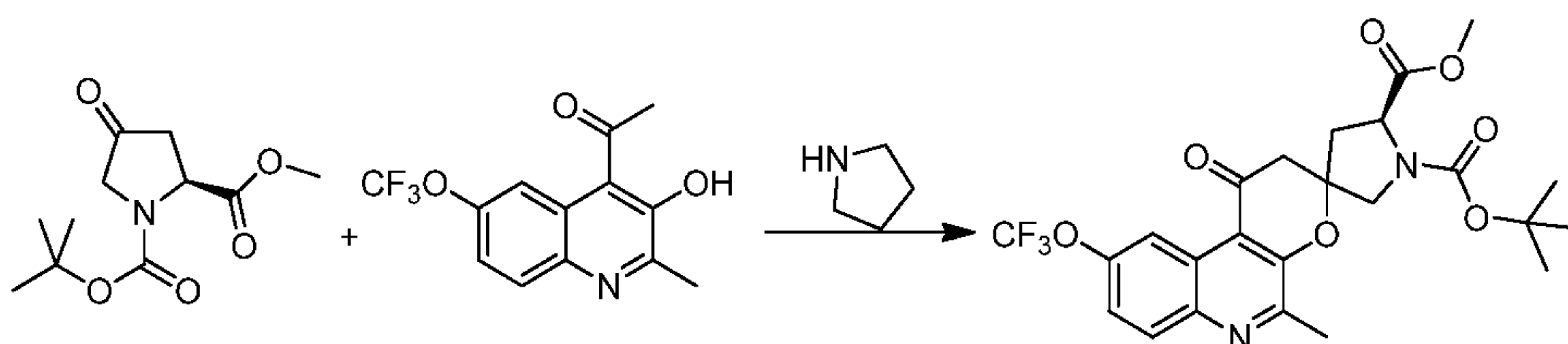
quenched at room temperature with saturated brine and extracted with EtOAc. The combined organic fractions were dried over Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by column chromatography several times over silica gel (Isco 330 g, eluting with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$) to give bromide as a red solid in a combined yield of 56%

5 *Step 3*



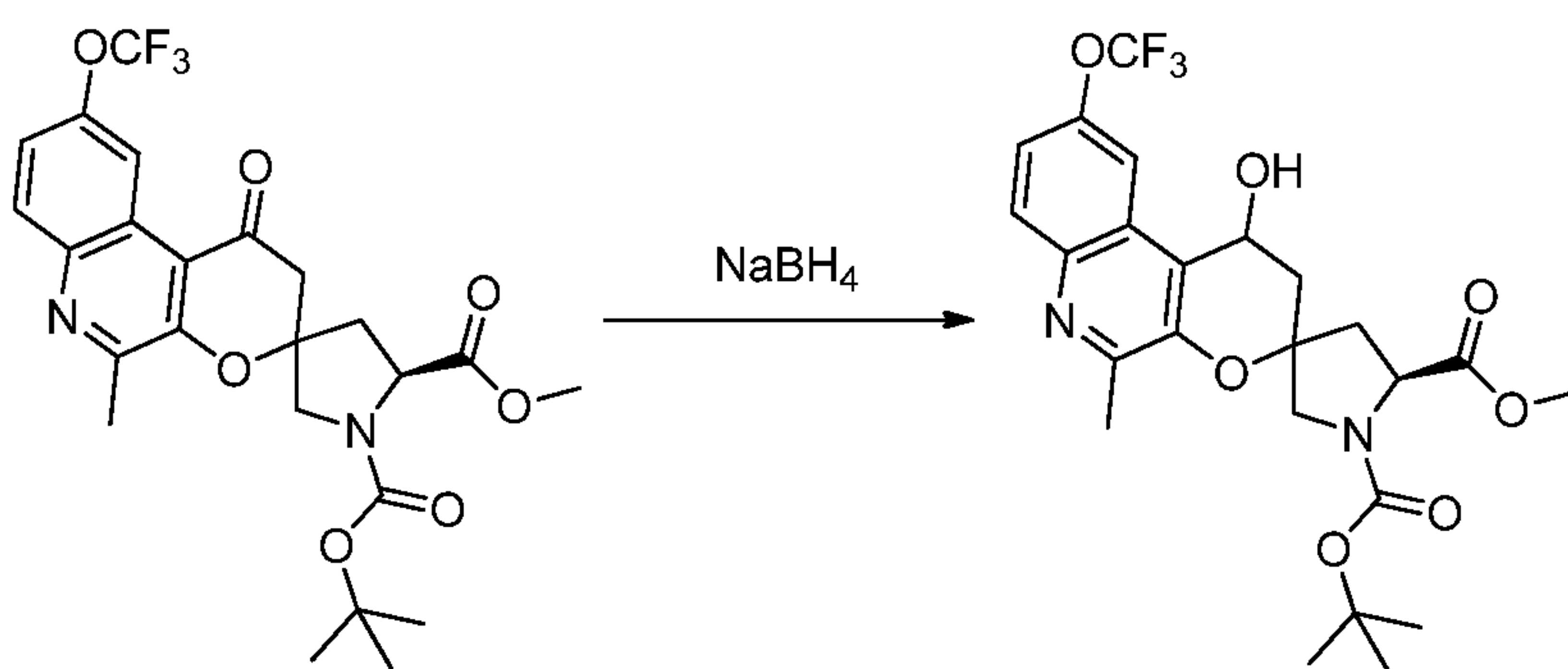
The product of step 2 (20 g, 62.1 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (7.18 g, 6.21 mmol) in dioxane (240 ml) at room temperature was added tributyl(1-ethoxyvinyl)tin (52.4 ml, 155 mmol) and the mixture was allowed to warm to 110°C and stirred for 3 h. The mixture was treated with 10 240 ml of 1N HCl and stirred for 90 min at room temperature. The mixture was quenched at room temperature with saturated aqueous NaHCO_3 and extracted with EtOAc. The combined organic fractions were washed with saturated brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. The crude mixture was taken in hexanes and washed with acetonitrile. The hexane layer was concentrated in vacuo and the crude residue was purified by silica gel chromatography 15 twice to yield 3.4 g product of step 3 as a yellow solid

Step 4



To a solution of ketone of step 3 (2.0 g, 7.01 mmol) in MeOH (30 ml) at room temperature was added BOC-4-Oxo-Pro-OMe (3.41 g, 14.02 mmol), pyrrolidine (0.580 ml, 7.01 mmol), followed by molecular sieves (4A powder, 2.0 g) and the mixture was warmed to 105°C 20 using microwave- high absorbance and stirred for 30 min. The mixture was filtered washing the cake with MeOH. The filtrate was concentrated in vacuo and the residue was purified by column chromatography over silica gel (Isco 120 g, eluting with Hexanes/EtOAc) to yield 2.73 g (76%) of product of step 4 as a yellow solid as a mixture of diastereomers.

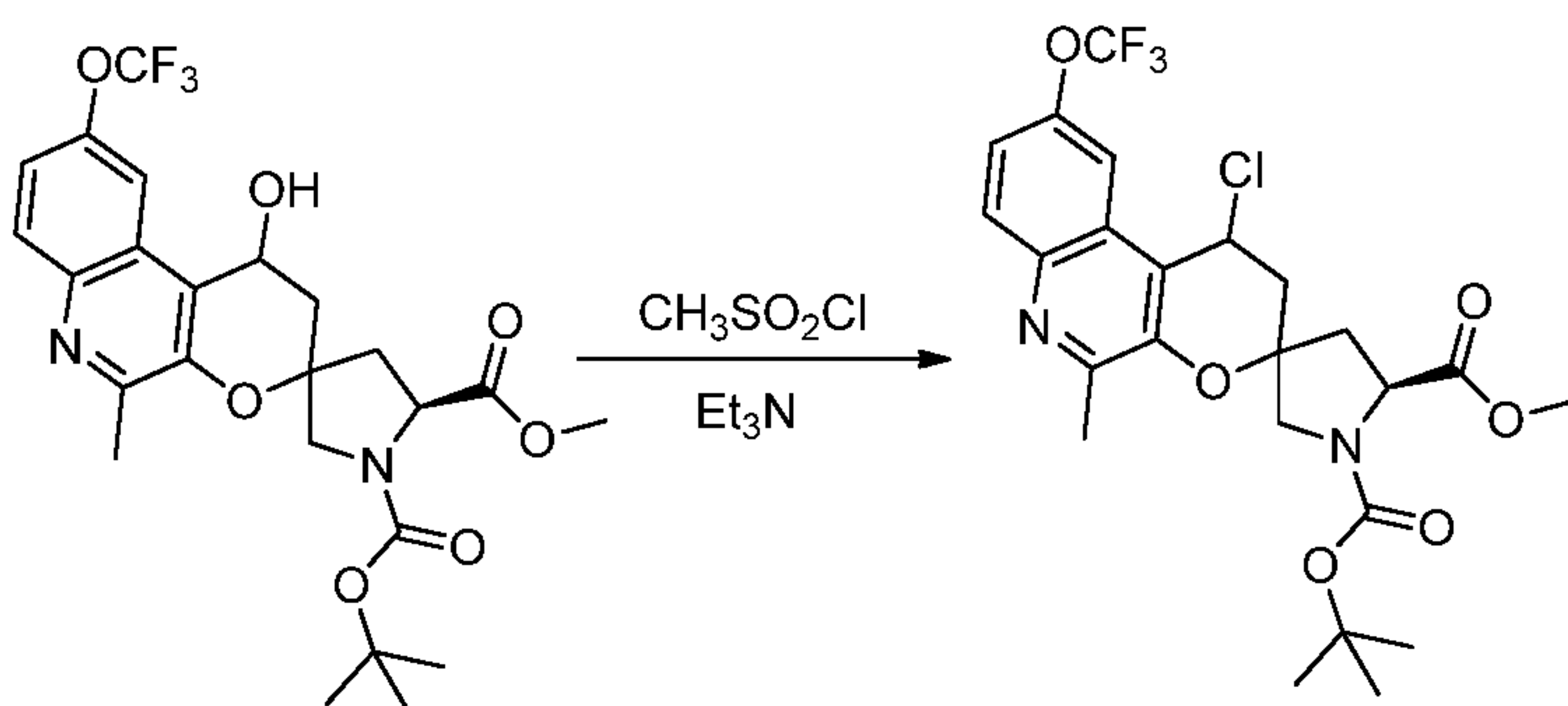
25 *Step 5*



To a solution of diastereomeric products from step 4 (2.2 g, 4.31 mmol) in THF (20 ml) and MeOH (20 ml) at 0 °C was added NaBH₄ (0.196 g, 5.17 mmol) and stirred at that temperature for 30 min. On complete consumption of the starting material, the mixture was

5 quenched at 0 °C with saturated aqueous NH₄Cl solution and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo to yield a colorless solid in 100% yield.

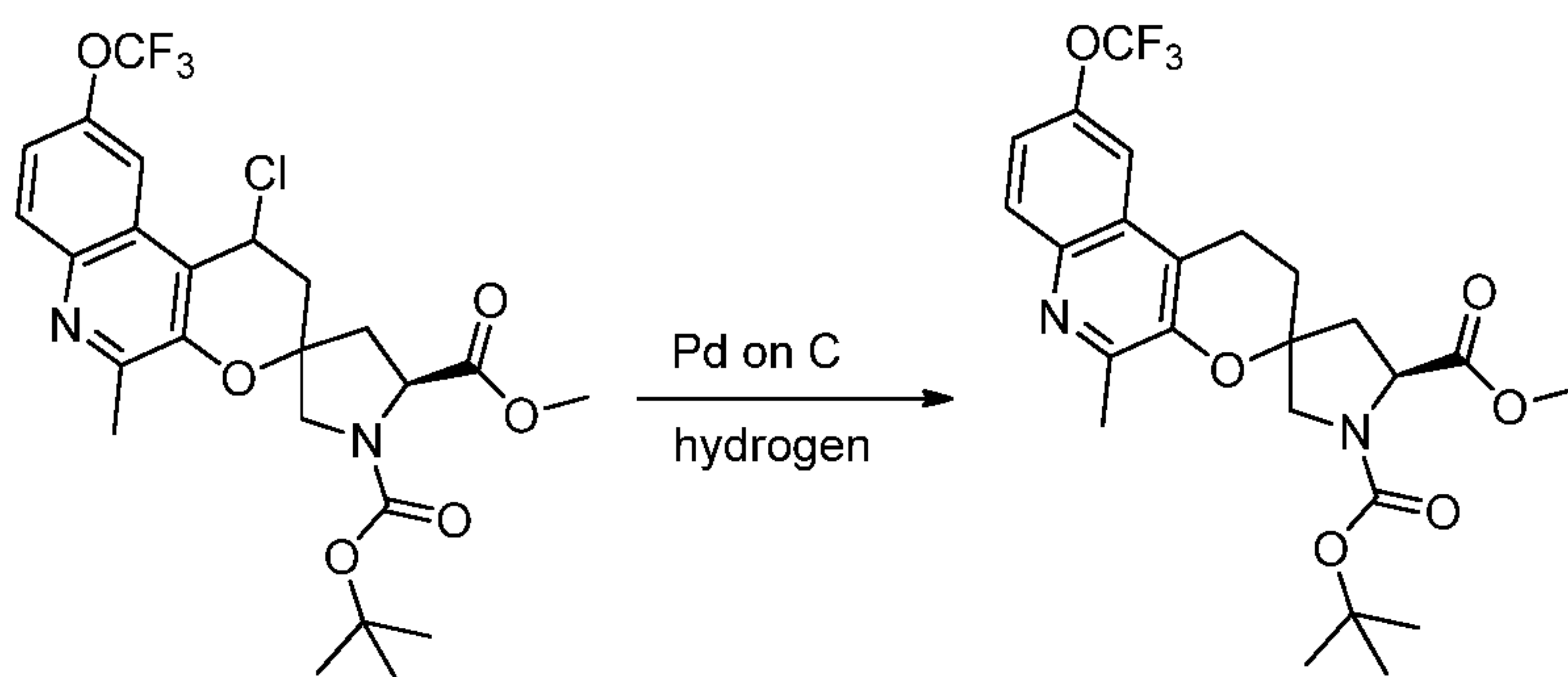
Step 6



To a solution of product of step 6 (2.2 g, 4.29 mmol) in CH₂Cl₂ (40 ml) at 0 °C was added Et₃N (2.094 ml, 15.03 mmol) followed by CH₃SO₂Cl (0.667 ml, 8.59 mmol) and the mixture was allowed to warm to room temperature stirring overnight. Analysis of reaction mixture with LCMS indicated presence of unreacted starting material. It was cooled to 0 °C and

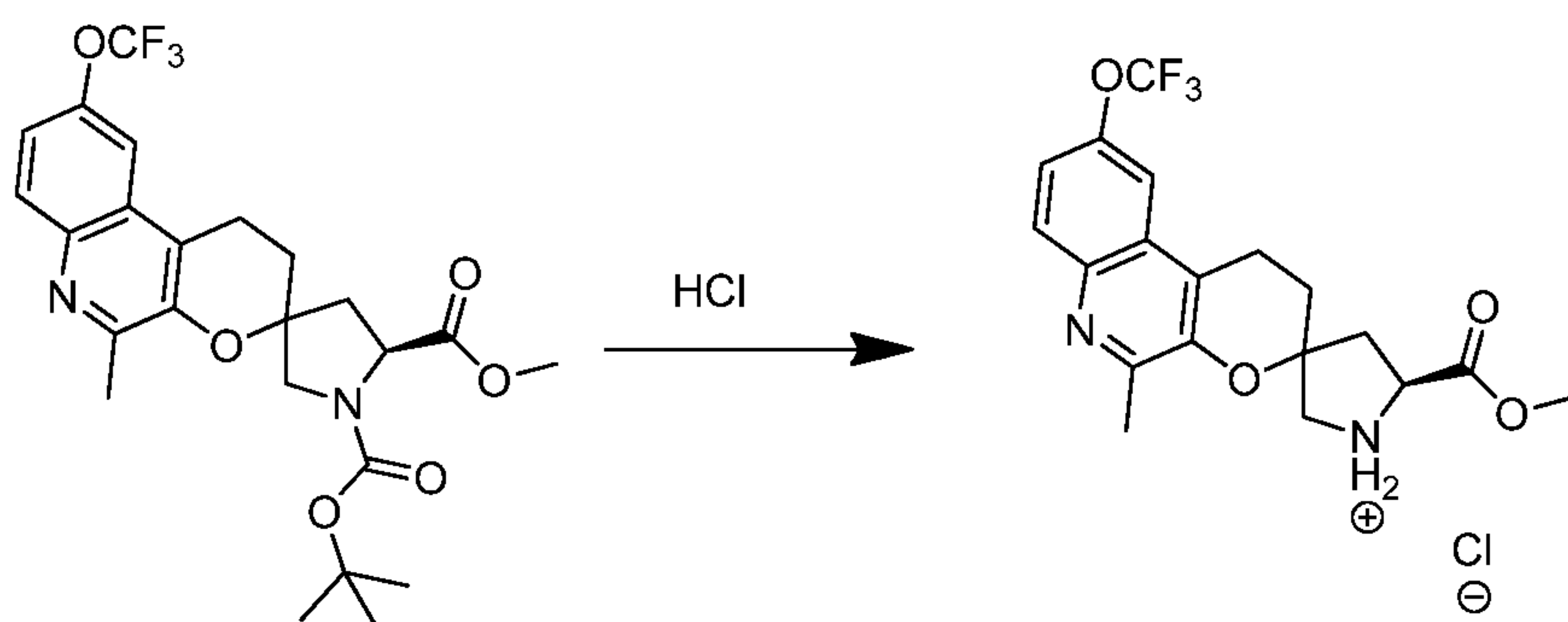
15 additional Et₃N (1eq., 0.6 ml, 4.29 mmol) and CH₃SO₂Cl (0.5 eq., 2.14 mmol, 0.16 ml) was added and the reaction was stirred at room temperature for 2 hrs. The reaction mixture was quenched at room temperature with saturated aqueous sodium bicarbonate and extracted with CH₂Cl₂. The combined organic fractions were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography over silica gel (Isco 120 g, eluting with Hexanes/EtOAc) to give chloride as a yellow oil. (2.2 g, 90%)

20 *Step 7*



To a solution of product of step 6 (2.44 g, 4.60 mmol) in EtOAc (100 ml) at room temperature was added 5% palladium on carbon (0.489 g, 0.460 mmol) and the mixture was degassed and backfilled with hydrogen balloon at room temperature and stirred for 3 h. On complete consumption of starting material as indicated by TLC and LC-MS, the mixture was filtered over Celite, washing the cake with EtOAc and MeOH. The residue was purified by column chromatography over silica gel (Isco 120 g, eluting with MeOH/DCM) to give reduced product as yellow foam in 92% yield.

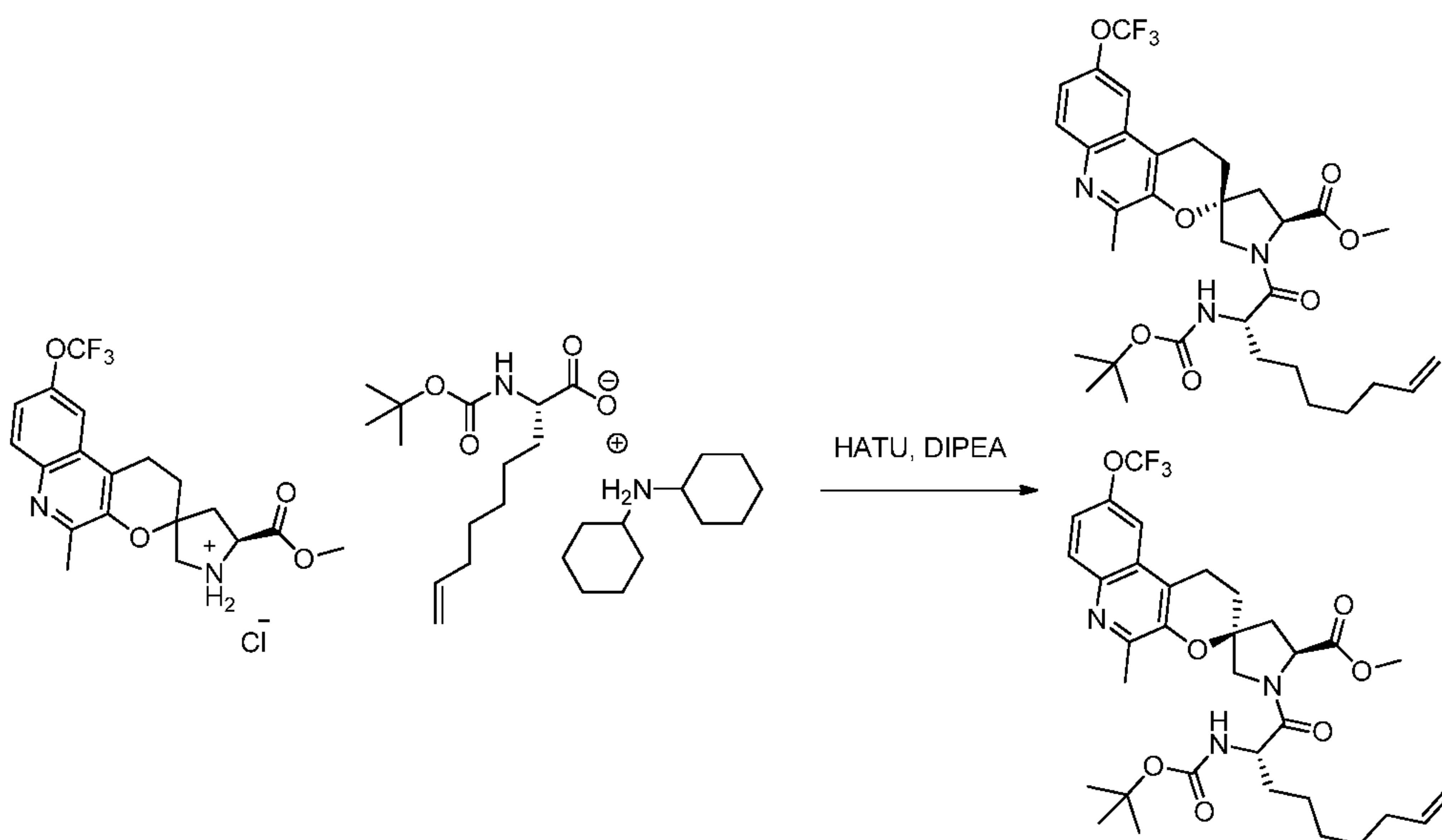
Step 8



10

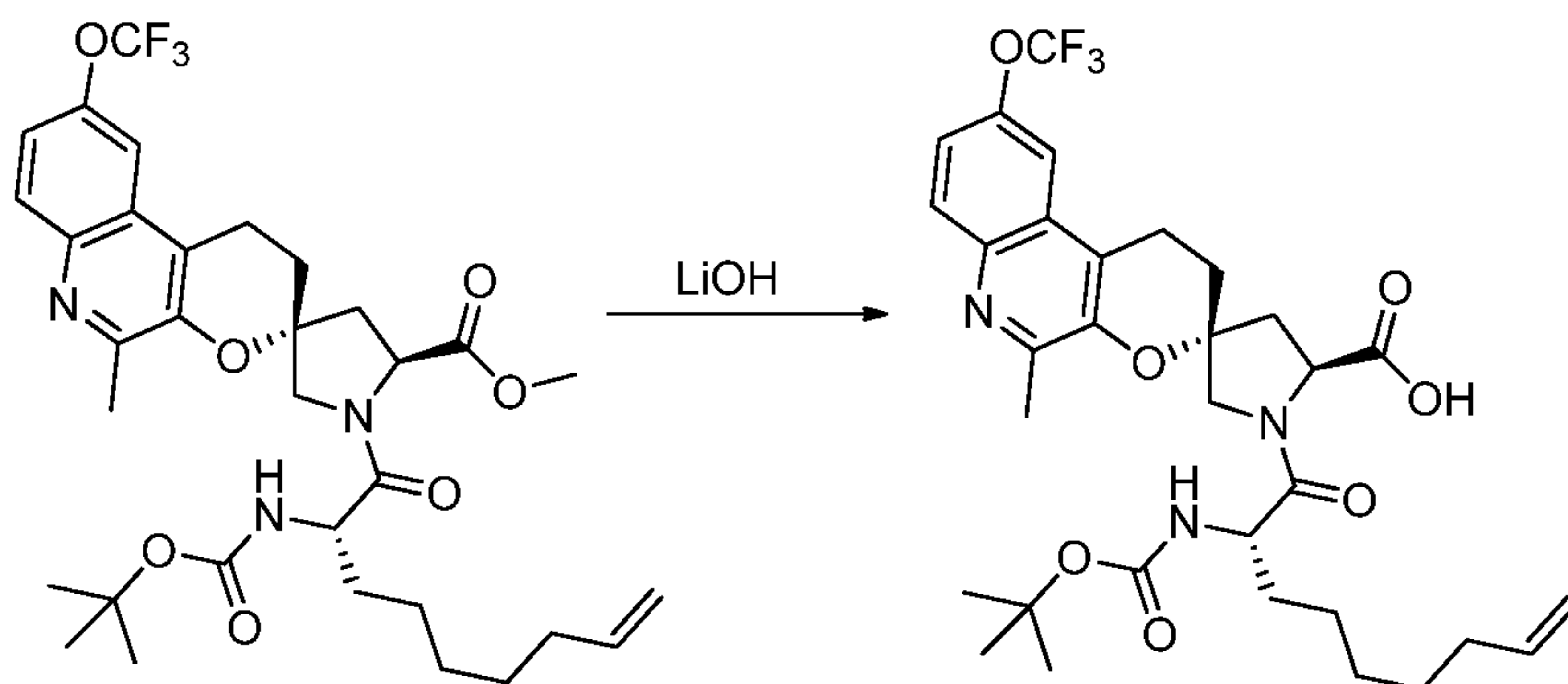
To a solution of product of step 7 (1.1 g, 2.216 mmol) was added 4 N HCl in dioxane (22.16 ml, 89 mmol) at RT and the mixture was stirred for 2 h. The reaction mixture was concentrated. The crude mixture was coevaporated with toluene 3-4 times until dry of all solvents. (Yield = 100%)

15 *Step 9*



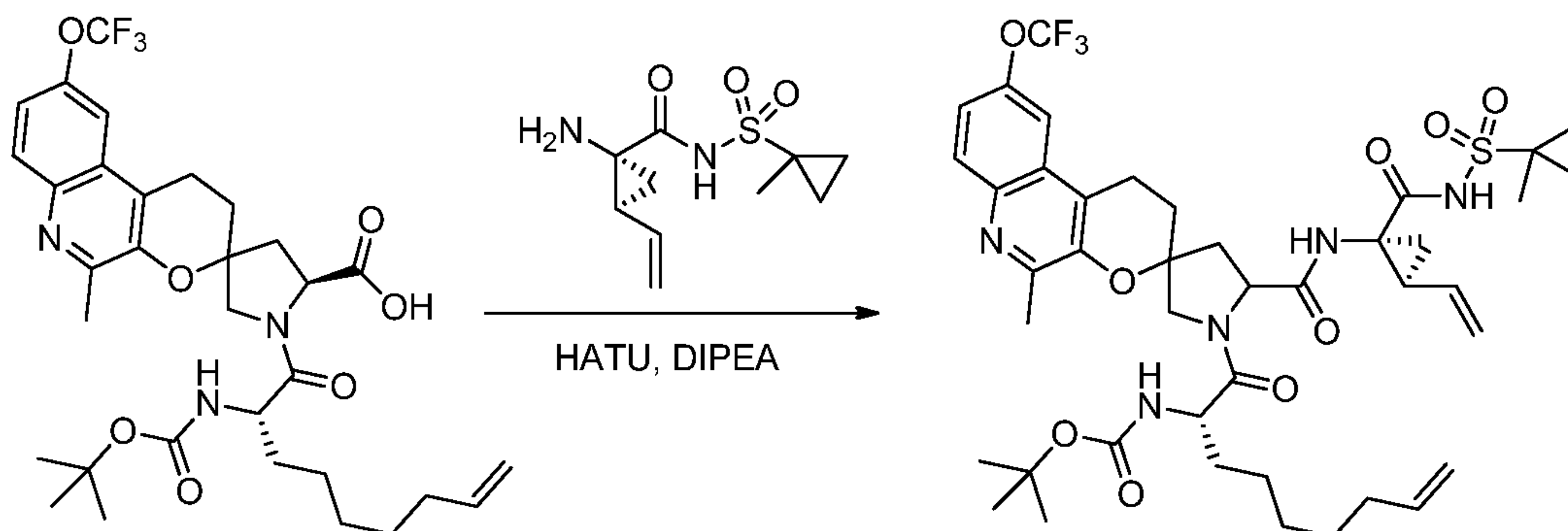
To a solution of product of step 8 (1.0 g, 2.52 mmol), acid salt (1.713 g, 3.78 mmol) and HATU (1.439 g, 3.78 mmol) in DMF (20 ml) at room temperature was added DIPEA (1.716 ml, 10.09 mmol) and the mixture was stirred at room temperature overnight. The reaction was cloudy and not homogenous. Additional 5 ml DMF, 20 ml DCM and 0.4 ml Hunigs base and allow stirring at room temperature overnight. The mixture was diluted at room temperature with water and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography over silica gel via a slow gradient (Isco 120 g, eluting with Hexanes/EtOAc) to give two diastereomers of coupled of product in 40 and 32%

Step 10

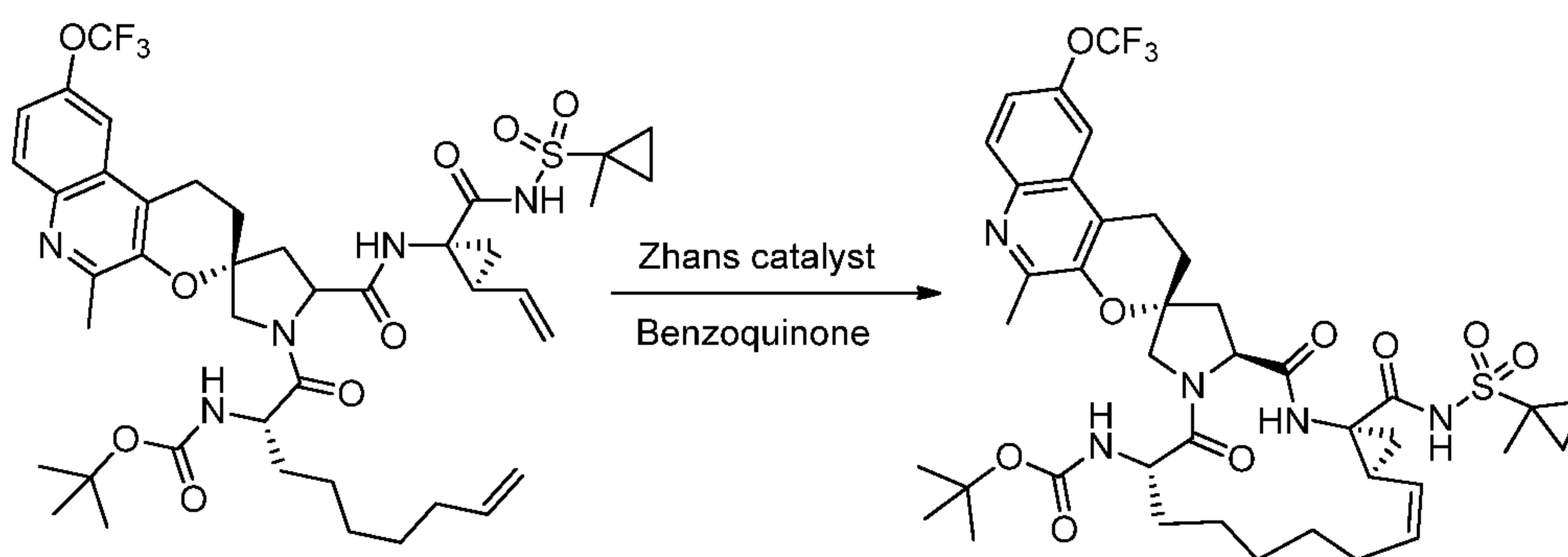


To a solution of nonpolar diastereomer from step 9 (660 mg, 1.016 mmol) in THF (12 ml), MeOH (12.00 ml) and H₂O (8 ml) at RT was added LiOH (73.0 mg, 3.05 mmol) and the mixture was allowed to warm to 50 °C and stirred for 2 h. LCMS of the reaction mixture indicated complete consumption of starting material. The mixture was quenched at room

temperature by concentrating MeOH and THF then adding a solution of 0.5 M aqueous HCl until pH=2. The mostly aqueous solution was then extracted with EtOAc several times. The combined organic layers were dried with Na₂SO₄, filtered and concentrated in vacuo. The crude was used as it is in next step (Yield= 99%)

5 *Step 11*

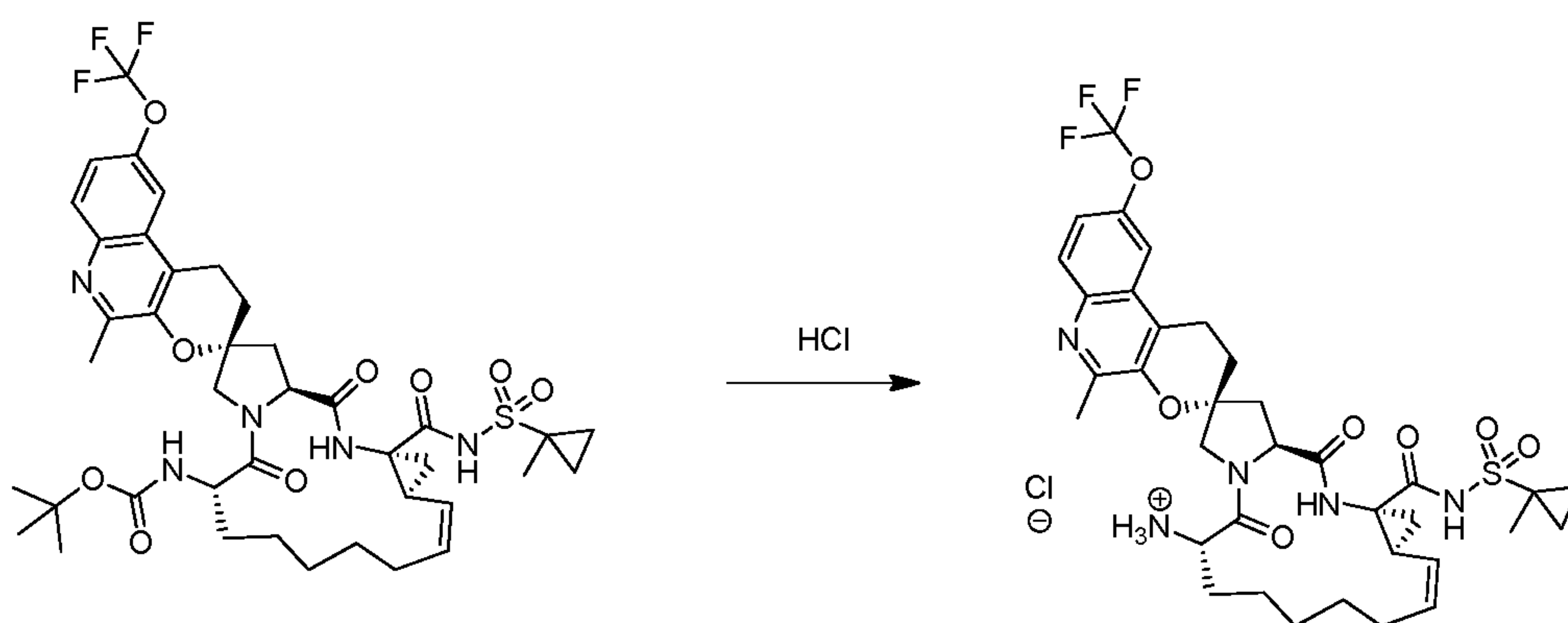
To a solution of product of step 10 (640 mg, 1.007 mmol) and amine (369 mg, 1.510 mmol) in DMF (10 ml) at room temperature was added HATU (574 mg, 1.510 mmol) followed by Hunigs base (0.514 ml, 3.02 mmol) and the mixture was stirred at RT overnight. The mixture was diluted with water and extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography over silica gel (Isco 80 g, eluting with Hexanes/EtOAc) to give in order product in 89% yield.

10 *Step 12*

To a solution of product of step 10 (300 mg, 0.348 mmol), 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene[2-(i-propoxy)-5-(n,n-dimethylaminosulfonyl)phenyl]methyleneruthenium(ii) dichloride (63.8 mg, 0.087 mmol) and 1,4-benzoquinone (11.29 mg, 0.104 mmol) in DCE (150 ml) at room temperature was degassed, put under nitrogen, then warmed to 70°C and stirred 3 h. LCMS indicated ~10% SM remaining, allow to stir additional hour at 70°C. The mixture was quenched at room temperature with 1 ml

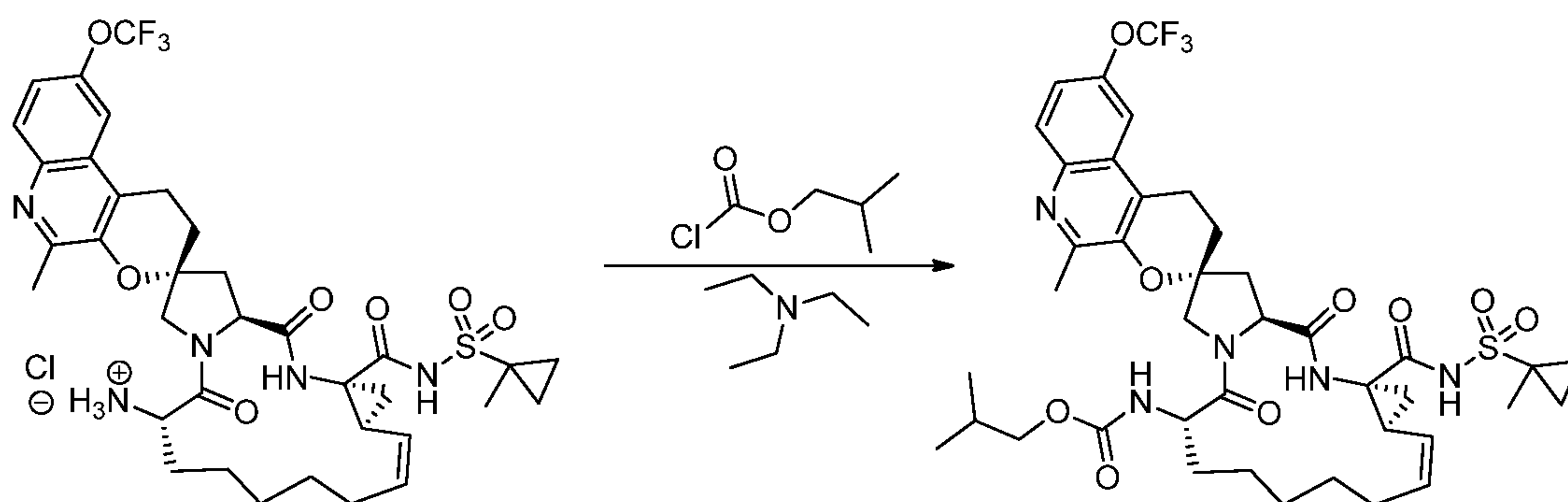
butyl vinyl ether and concentrated to dryness. The residue was purified by column chromatography over silica gel (Isco 40 g, eluting with Hexanes/EtOAc) to give in order of elution product containing 10% of uncyclized starting material. It was treated with 51 mg Zhan's catalyst and 10 mg 1,4-Benzoquinone and heat to 70°C for 2 hrs. LCMS indicated all SM
 5 consumed. The mixture was quenched at room temperature with 1 ml butyl vinyl ether and concentrated to dryness. The residue was combined with 0316331-0051-02 (~80 mg additional material) and purified by column chromatography over silica gel (Isco 80 g, eluting with Hexanes/EtOAc) to give product in 71%

Step 13



A solution of product of step 11 (200 mg, 0.240 mmol) in 4 M HCl in dioxane (10 ml, 40.0 mmol) was stirred at RT for 2 h. LCMS indicated complete consumption of starting material. The reaction mixture was concentrated to dryness to yield amine salt at 100%

Step 14



To a solution of product of step 13 (15 mg, 0.019 mmol) in DCM (2 ml) at room temperature was added triethylamine (10.86 μ l, 0.078 mmol) followed by isobutyl chloroformate (5.07 μ l, 0.039 mmol) and the mixture was stirred for 1 h under nitrogen. LCMS indicated reaction was complete. The mixture was quenched at room temperature with water and extracted
 20 with CH_2Cl_2 and dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 361

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THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

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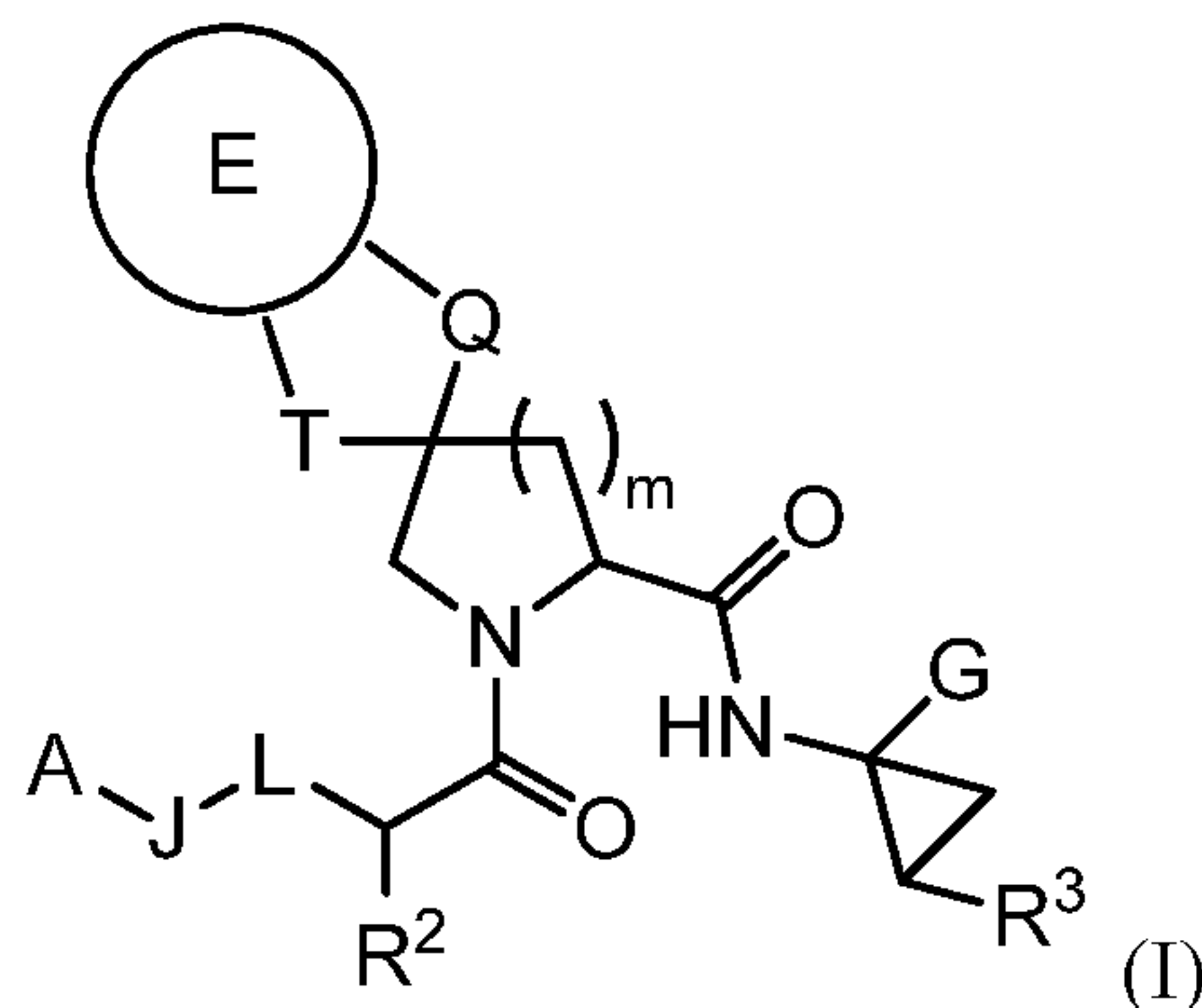
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NOM DU FICHER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

WHAT IS CLAIMED IS:

1. A compound of formula I:



- 5 or a pharmaceutically acceptable salt thereof, wherein

A is selected from the group consisting of C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₁-C₈ internally substituted alkyl, C₂-C₈ internally substituted alkenyl, C₂-C₈ internally substituted alkynyl, C₃-C₈ cycloalkyl, C₃-C₈ internally substituted cycloalkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, aryl and 7-, 8-, 9- and 10-membered bicyclic groups,

- 10 wherein

said A Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₈ internally substituted alkyl, C₂-C₈ internally substituted alkenyl, C₂-C₈ internally substituted alkynyl, C₃-C₈ internally substituted cycloalkyl, aryl and bicyclic groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N,

- 15 each A aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings and 7-, 8-, 9- and 10-membered bicyclic aromatic rings,

said A is substituted with 0, 1, 2, 3 or 4 substituents R^A;

- 20 each R^A is independently selected from the group consisting of H, F, Cl, Br, I, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkyl(NH₂), phenyl, naphthyl, C₃-C₈ cycloalkyl, halo(C₁-C₆ alkoxy), -O(C₁-C₆ alkyl), SH, S(C₁-C₆ alkyl), NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -NH(C₃-C₈ cycloalkyl), -C(O)(C₁-C₆ alkyl), -CONH₂, -SO₂NH₂, NO₂, CN, -CF₃, -CHF₂, -CH₂F, -OCHF₂, -OCF₃, -OCH₂F, -(C₁-C₅ alkyl)-O-(C₁-C₅ alkyl), -SO₂(C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), -SO₂N(C₁-C₆ alkyl)₂, -(C₁-C₆ alkyl)SO₂N(C₁-C₆ alkyl)₂, -NHCOO(C₁-C₆ alkyl), -NHCO(C₁-C₆ alkyl), -NHCONH(C₁-C₆ alkyl), -CO₂(C₁-C₆ alkyl), -C(O)N(C₁-C₆ alkyl)₂, -(C₀-
- 25

C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-O-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-S-
 (C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-S(O)₂-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl),
 -OC(O)NH-aryl, C₁-C₆ internally substituted alkyl, C₁-C₆ internally substituted haloalkyl, C₁-C₆
 internally substituted alkyl(NH₂), C₃-C₈ internally substituted cycloalkyl, halo(C₁-C₆ internally
 5 substituted alkoxy), -O(C₁-C₆ internally substituted alkyl), S(C₁-C₆ internally substituted alkyl),
 -NH(C₁-C₆ internally substituted alkyl), -N(C₁-C₆ internally substituted alkyl)₂, -C(O)(C₁-C₆
 internally substituted alkyl), -SO₂(C₁-C₆ internally substituted alkyl), -S(O)(C₁-C₆ internally
 substituted alkyl), -(C₁-C₆ internally substituted alkyl)S(O)(C₁-C₆ internally substituted alkyl),
 -S(O)₂(C₁-C₆ internally substituted alkyl), -(C₁-C₆ internally substituted alkyl)S(O)₂(C₁-C₆
 10 internally substituted alkyl), -(C₁-C₆ internally substituted alkyl)N(C₁-C₆ internally substituted
 alkyl)SO₂(C₁-C₆ internally substituted alkyl), -N(C₁-C₆ internally substituted alkyl)SO₂(C₁-C₆
 internally substituted alkyl), -SO₂N(C₁-C₆ internally substituted alkyl)₂, -(C₁-C₆ internally
 substituted alkyl)SO₂N(C₁-C₆ internally substituted alkyl)₂, -NHCOO(C₁-C₆ internally
 substituted alkyl), -NHCO(C₁-C₆ internally substituted alkyl), -NHCONH(C₁-C₆ internally
 15 substituted alkyl), -CO₂(C₁-C₆ internally substituted alkyl), -C(O)N(C₁-C₆ internally substituted
 alkyl)₂, -(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₅
 internally substituted alkyl)-O-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted
 cycloalkyl), -(C₀-C₅ internally substituted alkyl)-S-(C₀-C₅ internally substituted alkyl)-(C₃-C₈
 internally substituted cycloalkyl), and -(C₀-C₅ internally substituted alkyl)-S(O)₂-(C₀-C₅
 20 internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), wherein

each R^A aryl is independently selected from the group consisting of 5- and 6-
 membered aromatic rings and 7-, 8-, 9- and 10-membered bicyclic aromatic rings,

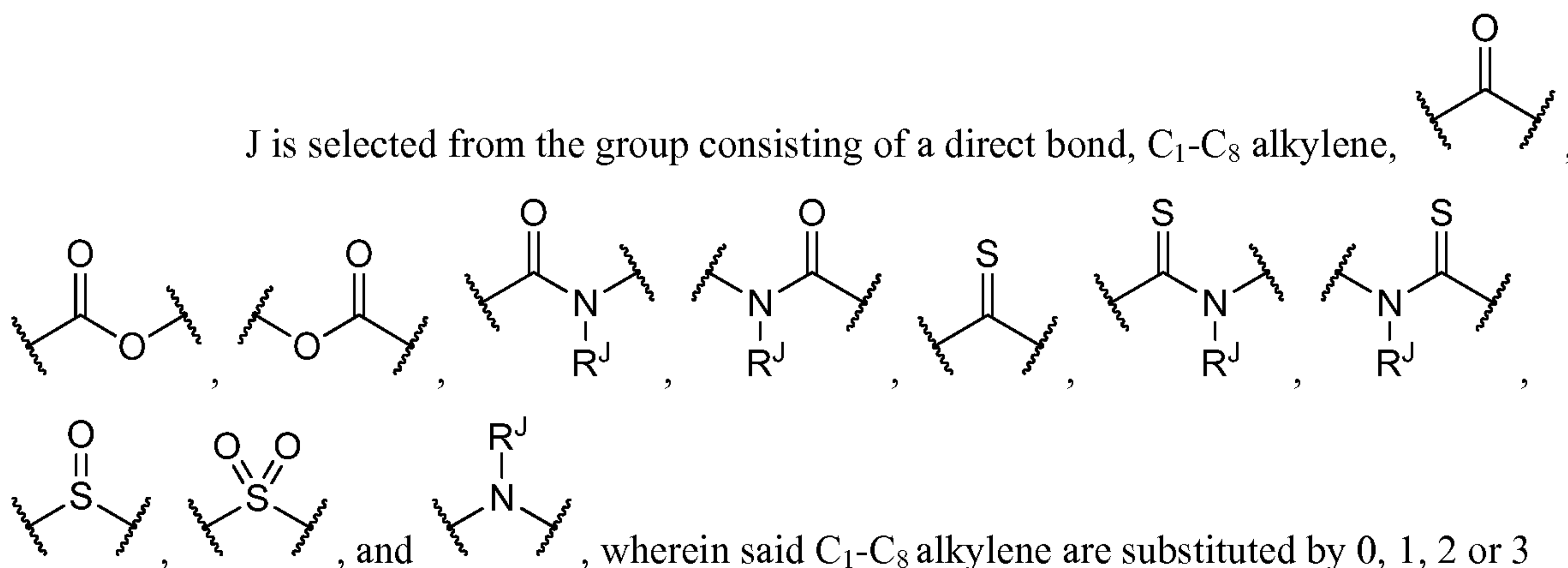
said R^A C₁-C₆ internally substituted alkyl, C₁-C₆ internally substituted haloalkyl,
 C₁-C₆ internally substituted alkyl(NH₂), C₃-C₈ internally substituted cycloalkyl, halo(C₁-C₆
 25 internally substituted alkoxy), -O(C₁-C₆ internally substituted alkyl), S(C₁-C₆ internally
 substituted alkyl), -NH(C₁-C₆ internally substituted alkyl), -N(C₁-C₆ internally substituted
 alkyl)₂, -C(O)(C₁-C₆ internally substituted alkyl), -SO₂(C₁-C₆ internally substituted alkyl),
 -S(O)(C₁-C₆ internally substituted alkyl), -(C₁-C₆ internally substituted alkyl)S(O)(C₁-C₆
 internally substituted alkyl), -S(O)₂(C₁-C₆ internally substituted alkyl), -(C₁-C₆ internally
 30 substituted alkyl)S(O)₂(C₁-C₆ internally substituted alkyl), -(C₁-C₆ internally substituted
 alkyl)N(C₁-C₆ internally substituted alkyl)SO₂(C₁-C₆ internally substituted alkyl), -N(C₁-C₆
 internally substituted alkyl)SO₂(C₁-C₆ internally substituted alkyl), -SO₂N(C₁-C₆ internally
 substituted alkyl)₂, -(C₁-C₆ internally substituted alkyl)SO₂N(C₁-C₆ internally substituted alkyl)₂,

-NHCOO(C₁-C₆ internally substituted alkyl), -NHCO(C₁-C₆ internally substituted alkyl),
 -NHCONH(C₁-C₆ internally substituted alkyl), -CO₂(C₁-C₆ internally substituted alkyl),
 -C(O)N(C₁-C₆ internally substituted alkyl)₂, -(C₀-C₅ internally substituted alkyl)-(C₃-C₈
 5 internally substituted cycloalkyl), -(C₀-C₅ internally substituted alkyl)-O-(C₀-C₅ internally
 substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₅ internally substituted alkyl)-
 S-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), and -(C₀-C₅
 internally substituted alkyl)-S(O)₂-(C₀-C₅ internally substituted alkyl)-(C₃-C₈ internally
 substituted cycloalkyl) groups contain 0, 1, 2 or 3 heteroatoms independently selected from the
 group consisting of B, O, S and N,

10 said internally substituted cycloalkyl is optionally substituted with 1 or 2 F, two R^A
 may be taken, together with the atoms to which they are bound, to form a ring having from three
 to fifteen ring atoms;

R^A and R² may be taken, together with the atoms to which they are bound, to form
 a ring having from sixteen to twenty-one ring atoms;

15 R^A and R¹ or R⁴ may be taken, together with the atoms to which they are bound,
 to form a ring having from sixteen to twenty-one ring atoms;



20 substituents R^J;

R^J is selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆ internally
 substituted alkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₃-C₆cycloalkyl, C₃-C₆
 internally substituted cycloalkyl and aryl, wherein

25 said R^J Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₆ internally
 substituted alkyl, C₃-C₆ internally substituted cycloalkyl and aryl contain 0, 1, 2 or 3 heteroatoms
 independently selected from the group consisting of B, O, S and N,

each R^J aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R^J is substituted with 0, 1, 2, 3 or 4 substituents R^A ;

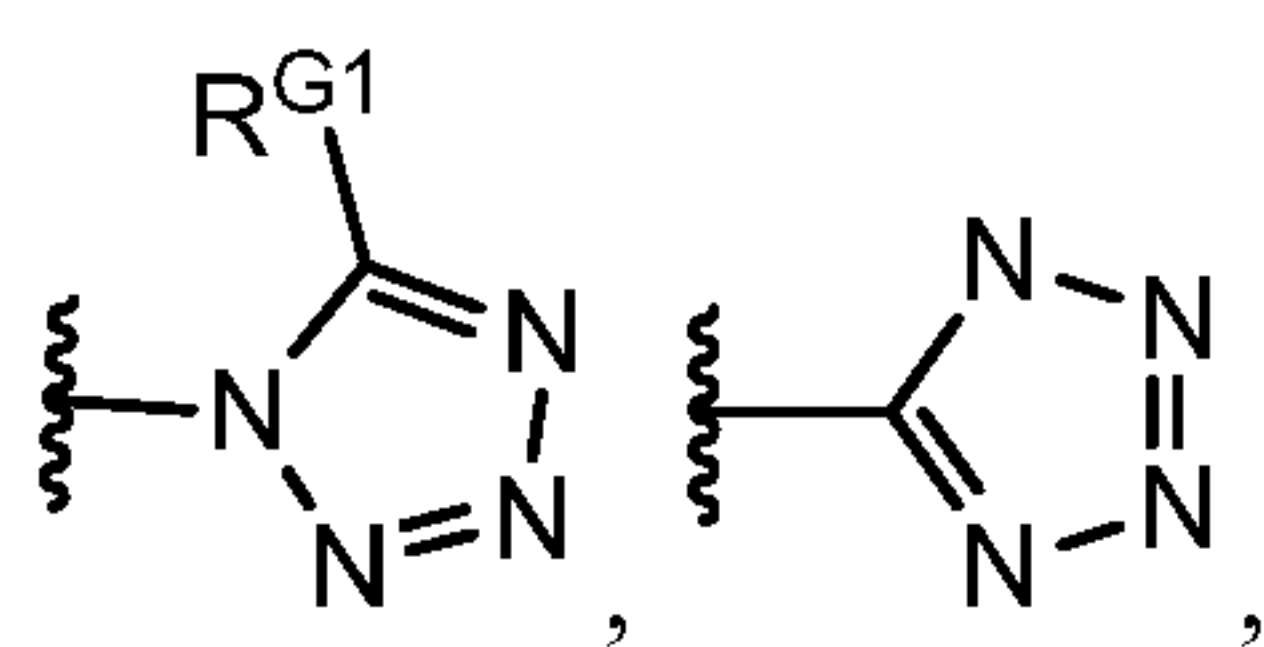
L is selected from the group consisting of $(CH_2)_{0-4}$, $N(R^L)$, and O;

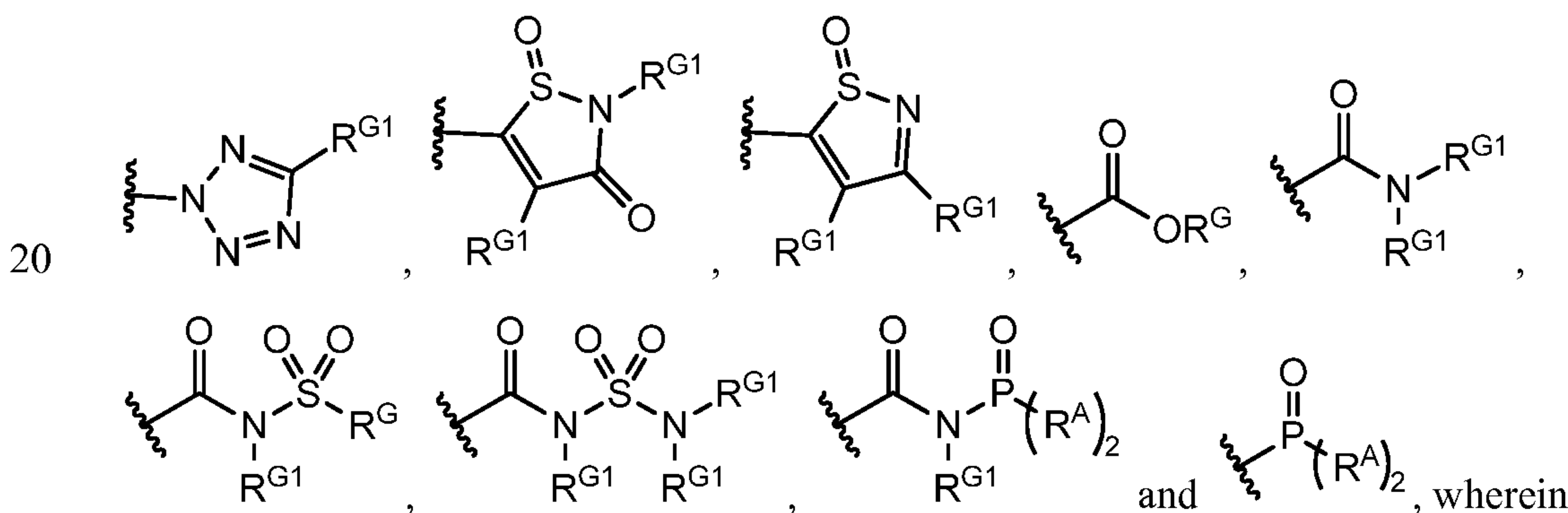
5 each R^L is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl(NH_2), aryl, C_3 - C_8 cycloalkyl, halo(C_1 - C_6 alkoxy), $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, $Si(CH_3)_3$, C_1 - C_6 alkyl(aryl) groups, C_1 - C_6 internally substituted alkyl, C_1 - C_6 internally substituted haloalkyl, C_1 - C_6 internally substituted alkoxy, C_1 - C_6 internally substituted alkyl(NH_2), aryl, C_3 - C_8 internally substituted cycloalkyl, halo(C_1 - C_6 internally substituted alkoxy), and C_1 - C_6 internally substituted alkyl(aryl), wherein

10 said R^L $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, $Si(CH_3)_3$, C_1 - C_6 internally substituted alkyl, C_1 - C_6 internally substituted haloalkyl, C_1 - C_6 internally substituted alkoxy, C_1 - C_6 internally substituted alkyl(NH_2), aryl, C_3 - C_8 internally substituted cycloalkyl, halo(C_1 - C_6 internally substituted alkoxy), and C_1 - C_6 internally substituted alkyl(aryl) groups contain 0, 1, 2
15 or 3 heteroatoms independently selected from the group consisting of B, O, S and N,

each R^L aryl group is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R^L is substituted with 0, 1, 2, 3 or 4 substituents R^A ;

G is selected from the group consisting of 



R^G is selected from the group consisting of H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkyl(C_1 - C_5)alkyl, $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, $Si(CH_3)_3$, aryl, aryl(C_1 - C_4)alkyl, C_1 - C_6 internally substituted alkyl, C_3 - C_6 internally substituted cycloalkyl,

internally substituted C₃-C₆ cycloalkyl(C₁-C₅)alkyl, and internally substituted aryl(C₁-C₄)alkyl groups, wherein

said R^G Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₆

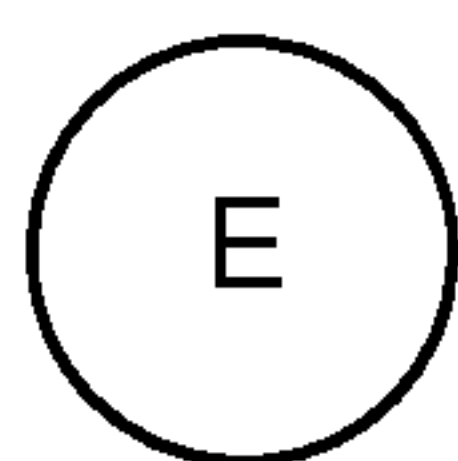
internally substituted alkyl, C₃-C₆ internally substituted cycloalkyl, internally substituted C₃-C₆ cycloalkyl(C₁-C₅)alkyl, aryl, and internally substituted aryl(C₁-C₄)alkyl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N,

each R^G aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R^G is substituted with 0, 1 or 2 independently selected R^A

10 substituents,

each R^{G1} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, and benzyl, wherein each R^{G1} is independently substituted with 0 to 4 substituents R^A,



is selected from the group consisting of:

15 1) aryl rings in which the aryl ring system attaches to Q and T at points that are two independently selected carbon ring atoms,

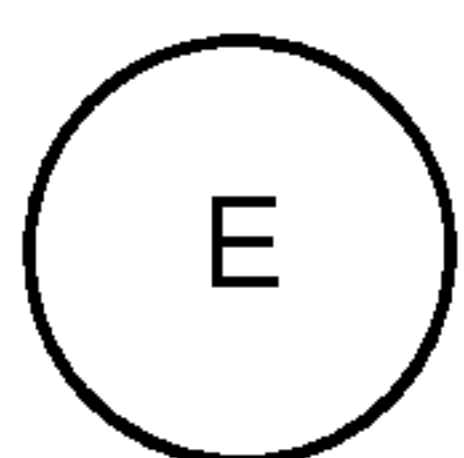
2) C₃-C₈ cycloalkyl rings in which the C₃-C₈ cycloalkyl ring system attaches to Q and T at points that are two independently selected carbon ring atoms, and

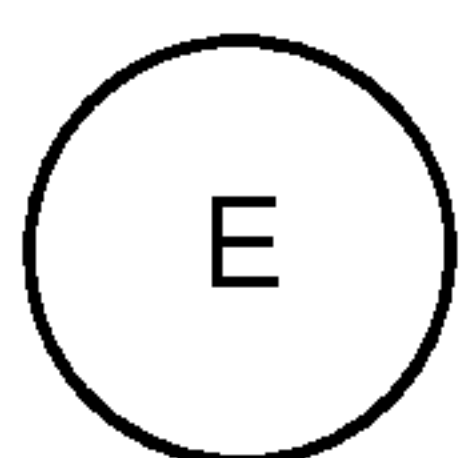
3) heterocyclic rings in which the heterocyclic ring system attaches to Q and T at points that are two independently selected ring atoms that are either two carbon ring atoms or one carbon ring atom and one nitrogen ring atom, and the heterocyclic ring system is selected from the group consisting of:

25 a) 5- or 6-membered saturated or unsaturated monocyclic rings with 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O and S,

b) 8-, 9- or 10-membered saturated or unsaturated bicyclic rings with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S, and

30 c) 11- to 15-membered saturated or unsaturated tricyclic rings with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S,



wherein  is substituted with 1 substituent R¹ and with 0, 1, 2, 3, 4 or 5 independently selected substituents R⁴;

R¹ is selected from the group consisting of H, halogen atoms, -OH, C₁-C₉ alkyl, C₁-C₉ alkoxy, C₁-C₉ alkyl-C₁-C₉ alkoxy, -CN, -C(O)OH, -C(O)CH₃, -SR^A, -SO₂(C₁-C₉ alkyl), C₃-C₈ cycloalkyl, C₁-C₉ alkyl-C₃-C₈ cycloalkyl, C₃-C₈ cycloalkoxy, C₁-C₉ alkyl-C₃-C₈ cycloalkoxy, C₁-C₉ haloalkyl, -(C₀-C₃ alkyl)-O-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S(O)₂-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -N(R^A)₂, C₁-C₉ alkyl-N(R^A)₂, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₉ internally substituted alkyl, C₁-C₉ internally substituted alkoxy, C₁-C₉ internally substituted alkyl-C₁-C₉ internally substituted alkoxy, -SO₂(C₁-C₉ internally substituted alkyl), C₃-C₈ internally substituted cycloalkyl, C₁-C₉ internally substituted alkyl-C₃-C₈ internally substituted cycloalkyl, C₃-C₈ internally substituted cycloalkoxy, C₁-C₉ alkyl-C₃-C₈ internally substituted cycloalkoxy, C₁-C₉ internally substituted haloalkyl, -(C₀-C₃ internally substituted alkyl)-O-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -O-(C₀-C₃ internally substituted alkyl)-(C₃-C₉ internally substituted cycloalkyl), -O-(C₀-C₃ internally substituted alkyl)-O-(C₃-C₉ internally substituted cycloalkyl), -(C₀-C₃ internally substituted alkyl)-S-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₃ internally substituted alkyl)-S(O)₂-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), C₁-C₉ internally substituted alkyl-N(R^A)₂, aryl, naphthyl, -O-aryl, -O-C₁-C₉ alkyl-aryl, , -O-C₁-C₉ alkyl-O-aryl, and -O-naphthyl groups; wherein:

said R¹ C₁-C₉ internally substituted alkyl, C₁-C₉ internally substituted alkoxy, C₁-C₉ internally substituted alkyl-C₁-C₉ internally substituted alkoxy, -SO₂(C₁-C₉ internally substituted alkyl), C₃-C₈ internally substituted cycloalkyl, C₁-C₉ internally substituted alkyl-C₃-C₈ internally substituted cycloalkyl, C₃-C₈ internally substituted cycloalkoxy, C₁-C₉ alkyl-C₃-C₈ internally substituted cycloalkoxy, C₁-C₉ internally substituted haloalkyl, -(C₀-C₃ internally substituted alkyl)-O-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₃ internally substituted alkyl)-S-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), -(C₀-C₃ internally substituted alkyl)-S(O)₂-(C₀-C₃ internally substituted alkyl)-(C₃-C₈ internally substituted cycloalkyl), C₁-C₉ internally substituted alkyl-N(R^A)₂, aryl, naphthyl, -O-aryl and -O-naphthyl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N,

each R¹ aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R¹ groups are substituted with 0 to 4 substituents R^A;

R² is selected from the group consisting of C₁-C₉ alkyl, C₂-C₉ alkenyl, C₂-C₉ alkynyl, C₃-C₈ cycloalkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₁-C₉ internally substituted alkyl, C₂-C₉ internally substituted alkenyl, C₂-C₉ internally substituted alkynyl, C₃-C₈ internally substituted cycloalkyl and aryl groups, wherein

said R² Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, C₁-C₉ internally substituted alkyl, C₂-C₉ internally substituted alkenyl, C₂-C₉ internally substituted alkynyl, C₃-C₈ internally substituted cycloalkyl and aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N, and is attached through an atom selected from C and N,

said R² aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R² is substituted with 0, 1 or 2 independently selected R^A substituents,

R³ is selected from the group consisting of -CH₂CH₃, -CH=CH₂, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, -CH₂CH₂-(bond to R²), -CH=CH-(bond to R²) and a direct bond to R², wherein when R³ is selected from the group consisting of -CH₂CH₂-(bond to R²), -CH=CH-(bond to R²) and a direct bond to R², R² and R³, together with the atoms to which they are bound, form a ring having from fifteen to twenty-one ring atoms and containing 0, 1, 2 or 3 double bonds and 0, 1, 2 or 3 triple bonds;

T is selected from the group consisting of -(CH₂)_q-, -(CH₂)_q-O-(CH₂)_{q1}-, -(CH₂)_q-N(R^A)-(CH₂)_{q1}-, -(CH₂)_q-S-(CH₂)_{q1}-, -(CH₂)_q-C(O)-(CH₂)_{q1}-, -(CH₂)_q-S(O)-(CH₂)_{q1}-, and -(CH₂)_q-S(O)₂-(CH₂)_{q1}-, where q and q1 are each independently selected from the group consisting of 0, 1 or 2, and each T is substituted by 0, 1 or 2 groups selected from R^A;

Q is selected from the group consisting of -(CR^A)₂_p-, -(CR^A)₂_p-CR^A=CR^A-(CR^A)₂_{p1}-, -(CR^A)₂_p-O-(CR^A)₂_{p1}-, -(CR^A)₂_p-N(R^A)-(CR^A)₂_{p1}-, -(CR^A)₂_p-S-(CR^A)₂_{p1}-, -(CR^A)₂_p-S(O)-(CR^A)₂_{p1}-, and -(CR^A)₂_p-S(O)₂-(CR^A)₂_{p1}-, where p and p1 are independently selected from 0, 1, 2, 3 or 4;

each R⁴ is independently selected from the group consisting of H, halogen atoms, -OR^A, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CN, -SR^A, -CO₂R^A, -C(O)N(R^A)₂, -OC(O)N(R^A)₂, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, -(C₀-C₃ alkyl)-O-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S(O)₂-(C₀-C₃ alkyl)-(C₃-C₈

cycloalkyl), $-\text{SO}(\text{R}^{\text{A}})$, $-\text{SO}_2(\text{R}^{\text{A}})$, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_6$ internally substituted alkyl, $\text{C}_1\text{-C}_6$ internally substituted alkoxy, $-(\text{C}_0\text{-C}_3$ internally substituted alkyl)- O - $(\text{C}_0\text{-C}_3$ internally substituted alkyl)- $(\text{C}_3\text{-C}_8$ internally substituted cycloalkyl), $-(\text{C}_0\text{-C}_3$ internally substituted alkyl)- S - $(\text{C}_0\text{-C}_3$ internally substituted alkyl)- $(\text{C}_3\text{-C}_8$ internally substituted cycloalkyl), $-(\text{C}_0\text{-C}_3$ internally substituted alkyl)- $\text{S}(\text{O})_2$ - $(\text{C}_0\text{-C}_3$ internally substituted alkyl)- $(\text{C}_3\text{-C}_8$ internally substituted cycloalkyl), $\text{C}_3\text{-C}_8$ internally substituted cycloalkyl and aryl, wherein

said R^4 $\text{C}_1\text{-C}_6$ internally substituted alkyl, $\text{C}_1\text{-C}_6$ internally substituted alkoxy, $-(\text{C}_0\text{-C}_3$ internally substituted alkyl)- O - $(\text{C}_0\text{-C}_3$ internally substituted alkyl)- $(\text{C}_3\text{-C}_8$ internally substituted cycloalkyl), $-(\text{C}_0\text{-C}_3$ internally substituted alkyl)- S - $(\text{C}_0\text{-C}_3$ internally substituted alkyl)- $(\text{C}_3\text{-C}_8$ internally substituted cycloalkyl), $-(\text{C}_0\text{-C}_3$ internally substituted alkyl)- $\text{S}(\text{O})_2$ - $(\text{C}_0\text{-C}_3$ internally substituted alkyl)- $(\text{C}_3\text{-C}_8$ internally substituted cycloalkyl), $\text{C}_3\text{-C}_8$ internally substituted cycloalkyl and aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N,

each R^4 aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R^4 $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_3\text{-C}_8$ cycloalkyl and aryl groups are substituted with 0 to 4 substituents R^{A} ;

two R^4 may be taken, together with the atoms to which they are bound, to form a ring; and

m is 0, 1, 2 or 3.

2. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein

A is selected from the group consisting of $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_2\text{-C}_8$ alkenyl, $\text{C}_2\text{-C}_8$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{Si}(\text{R}^{\text{A}})_3$, $\text{Si}(\text{R}^{\text{A}})_2(\text{CH}_3)$, $\text{Si}(\text{R}^{\text{A}})(\text{CH}_3)_2$, $\text{Si}(\text{CH}_3)_3$, aryl and 7-, 8-, 9- and 10-membered bicyclic groups, wherein

said A $\text{Si}(\text{R}^{\text{A}})_3$, $\text{Si}(\text{R}^{\text{A}})_2(\text{CH}_3)$, $\text{Si}(\text{R}^{\text{A}})(\text{CH}_3)_2$, $\text{Si}(\text{CH}_3)_3$, aryl and bicyclic groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N,

each A aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings and 7-, 8-, 9- and 10-membered bicyclic aromatic rings,

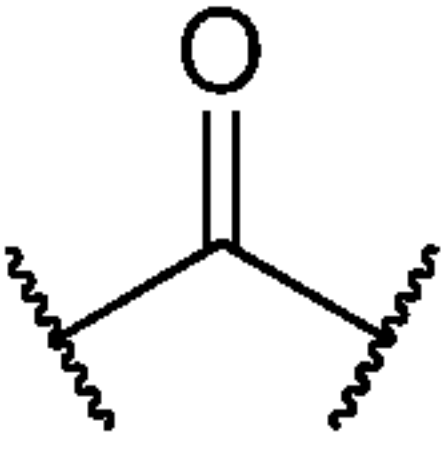
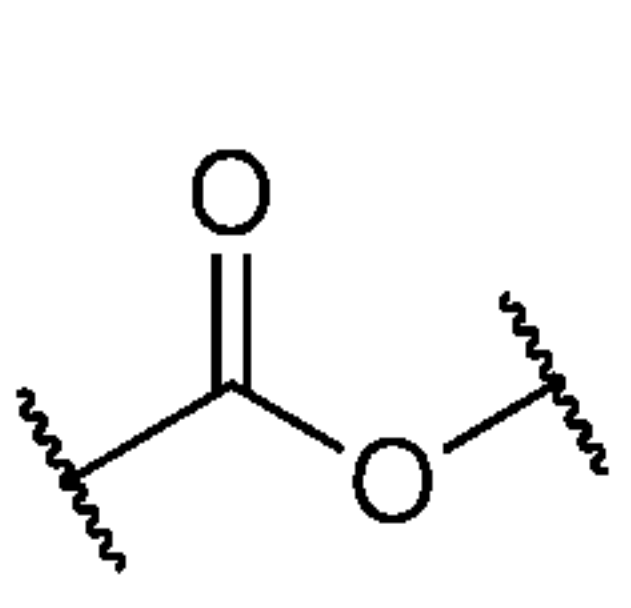
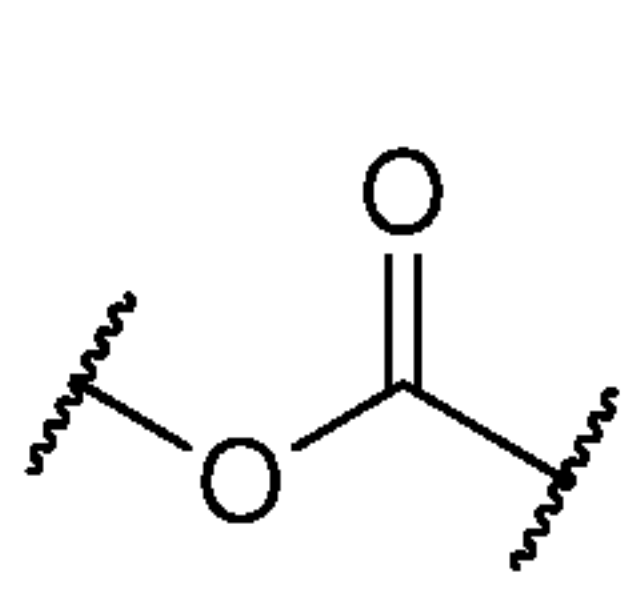
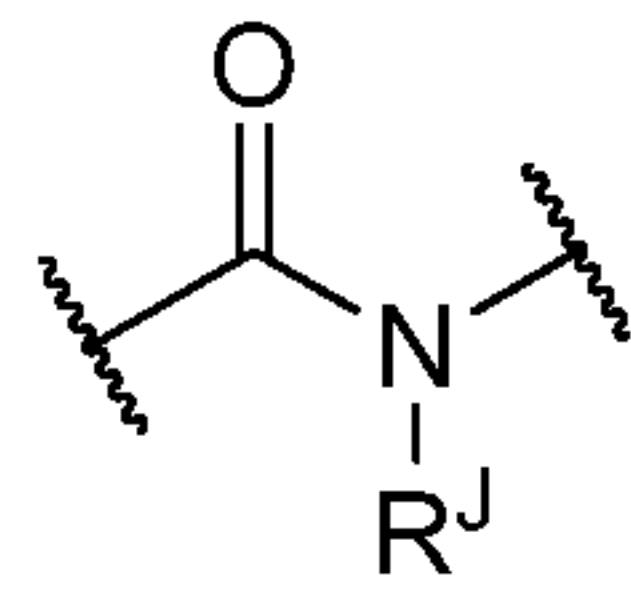
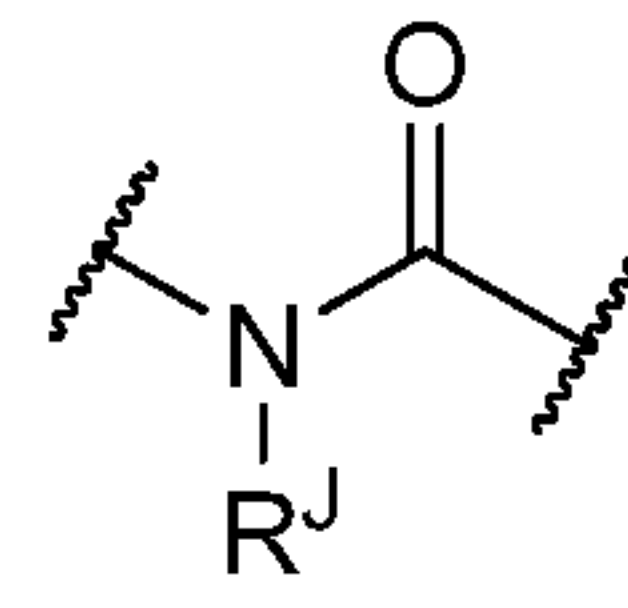
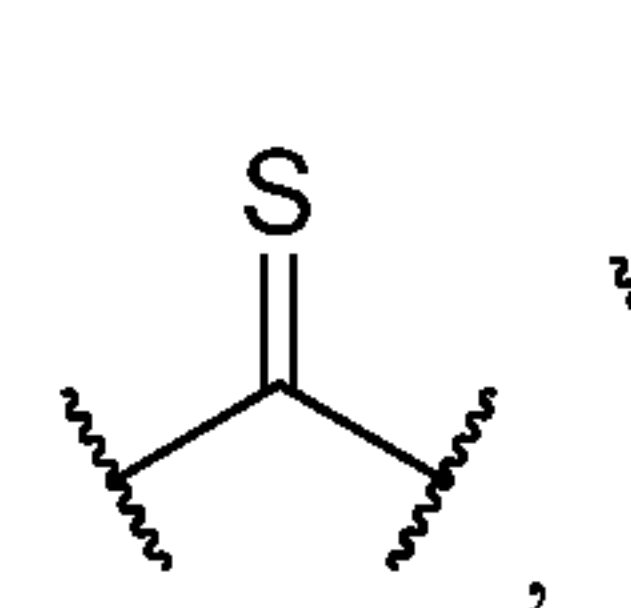
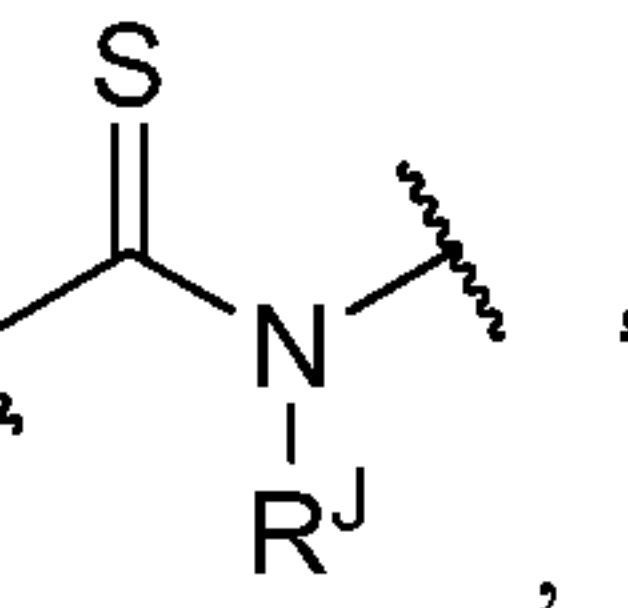
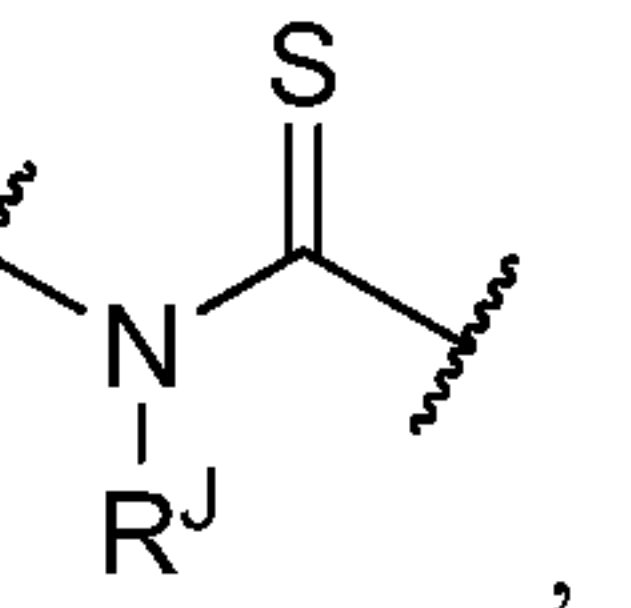
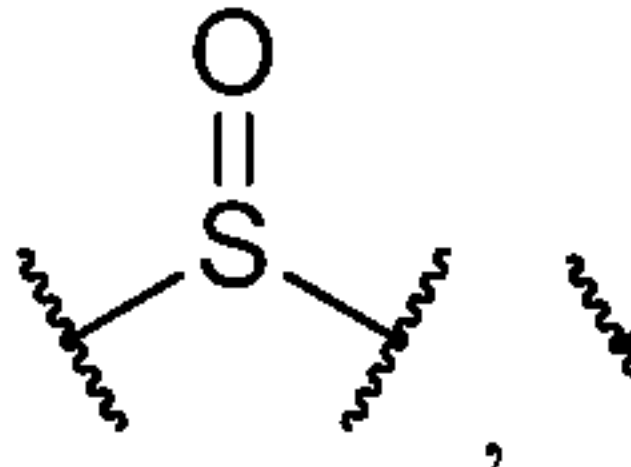
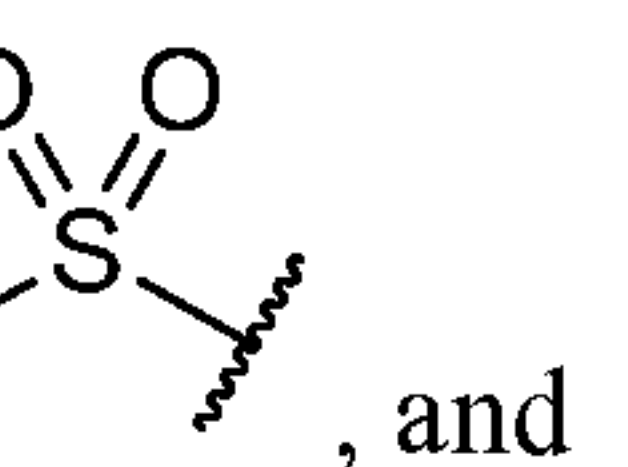
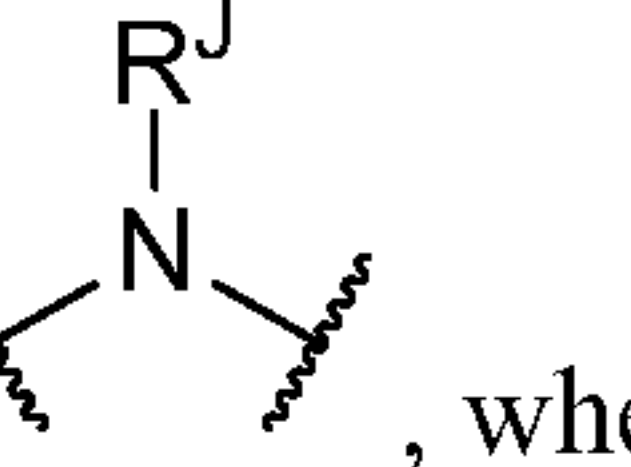
said A is substituted with 0, 1, 2, 3 or 4 substituents R^{A} ;

each R^A is independently selected from the group consisting of H, F, Cl, Br, I, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkyl(NH₂), phenyl, naphthyl, C₃-C₈ cycloalkyl, halo(C₁-C₆ alkoxy), -O(C₁-C₆ alkyl), SH, S(C₁-C₆ alkyl), NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(O)(C₁-C₆ alkyl), -CONH₂, -SO₂NH₂, NO₂, CN, -CF₃, -CHF₂, -CH₂F, -OCHF₂, -OCF₃, -OCH₂F, -SO₂(C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), -SO₂N(C₁-C₆ alkyl)₂, -(C₁-C₆ alkyl)SO₂N(C₁-C₆ alkyl)₂, -NHCOO(C₁-C₆ alkyl), -NHCO(C₁-C₆ alkyl), -NHCONH(C₁-C₆ alkyl), -CO₂(C₁-C₆ alkyl), -C(O)N(C₁-C₆ alkyl)₂, -(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-O-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-S-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), and -(C₀-C₅ alkyl)-S(O)₂-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), wherein

two R^A may be taken, together with the atoms to which they are bound, to form a ring having from three to fifteen ring atoms;

R^A and R^2 may be taken, together with the atoms to which they are bound, to form a ring having from sixteen to twenty-one ring atoms;

R^A and R^1 or R^4 may be taken, together with the atoms to which they are bound, to form a ring having from sixteen to twenty-one ring atoms;

J is selected from the group consisting of a direct bond, C₁-C₈ alkylene, , , , , , , , , , , and , wherein said C₁-C₈ alkylene are substituted by 0, 1, 2 or 3 substituents R^J ;

R^J is selected from the group consisting of H, C₁-C₆alkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, C₃-C₆cycloalkyl, and aryl, wherein

said R^J Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, and aryl contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N,

each R^J aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

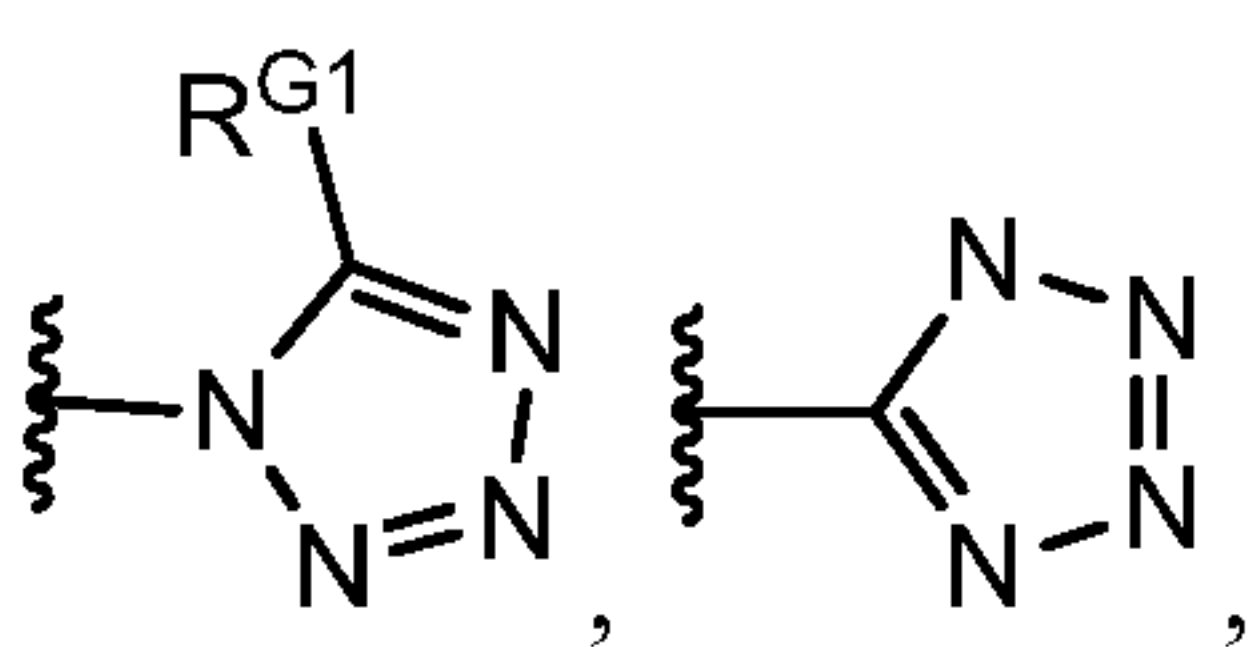
said R^J is substituted with 0, 1, 2, 3 or 4 substituents R^A ;

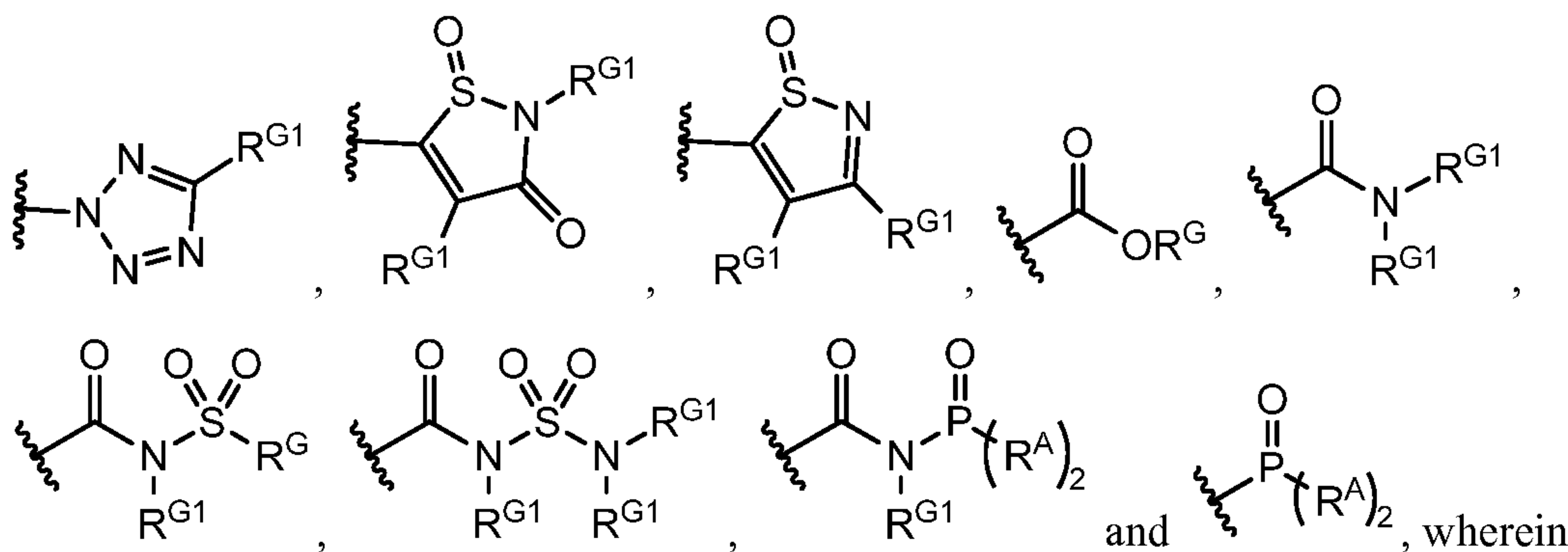
L is selected from the group consisting of $(CH_2)_{0-4}$ and $N(R^L)$;

each R^L is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl(NH_2), aryl, C_3 - C_8 cycloalkyl, halo(C_1 - C_6 alkoxy),
 5 $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, $Si(CH_3)_3$, and C_1 - C_6 alkyl(aryl) groups, wherein

said R^L $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, and $Si(CH_3)_3$ groups contain
 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N,

each R^L aryl group is independently selected from the group consisting of
 5- and 6-membered aromatic rings,

10 G is selected from the group consisting of 



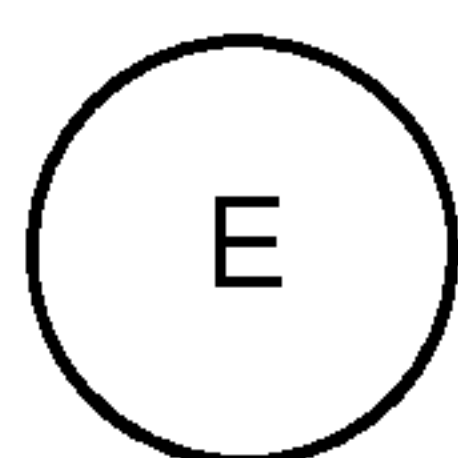
R^G is selected from the group consisting of H, C_1 - C_6 alkyl, C_3 - C_6
 cycloalkyl, C_3 - C_6 cycloalkyl(C_1 - C_5)alkyl, $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, $Si(CH_3)_3$, aryl,
 15 and aryl(C_1 - C_4)alkyl groups, wherein

said R^G $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, $Si(CH_3)_3$, and aryl
 groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S
 and N,

each R^G aryl is independently selected from the group consisting of
 20 5- and 6-membered aromatic rings,

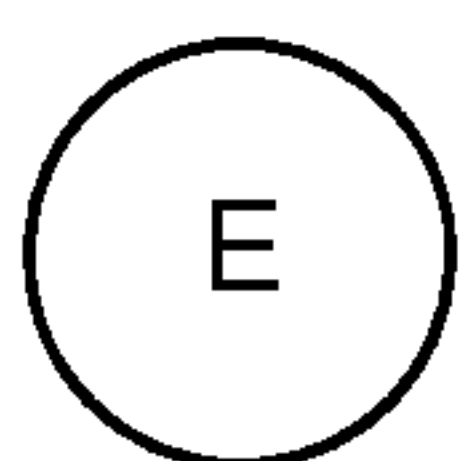
said R^G is substituted with 0, 1 or 2 independently selected R^A
 substituents,

each R^{G1} is independently selected from the group consisting of H, C_1 - C_6
 alkyl, C_3 - C_7 cycloalkyl, $Si(R^A)_3$, $Si(R^A)_2(CH_3)$, $Si(R^A)(CH_3)_2$, $Si(CH_3)_3$, and benzyl, wherein
 25 each R^{G1} is independently substituted with 0 to 4 substituents R^A ,



is selected from the group consisting of:

- 1) aryl rings in which the aryl ring system attaches to Q and T at points that are two independently selected carbon ring atoms,
- 2) C₃-C₈ cycloalkyl rings in which the C₃-C₈ cycloalkyl ring system attaches to Q and T at points that are two independently selected carbon ring atoms, and
- 3) heterocyclic rings in which the heterocyclic ring system attaches to Q and T at points that are two independently selected ring atoms that are either two carbon ring atoms or one carbon ring atom and one nitrogen ring atom, and the heterocyclic ring system is selected from the group consisting of:
 - a) 5- or 6-membered saturated or unsaturated monocyclic rings with 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O and S,
 - b) 8-, 9- or 10-membered saturated or unsaturated bicyclic rings with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S, and
 - c) 11- to 15-membered saturated or unsaturated tricyclic rings with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S,



wherein is substituted with 1 substituent R¹ and with 0, 1, 2, 3, 4 or 5 independently selected substituents R⁴;

R¹ is selected from the group consisting of H, halogen atoms, -OH, C₁-C₉ alkyl, C₁-C₉ alkoxy, C₁-C₉ alkyl-C₁-C₉ alkoxy, -CN, -C(O)OH, -C(O)CH₃, -SR^A, -SO₂(C₁-C₉ alkyl), C₃-C₈ cycloalkyl, C₁-C₉ alkyl-C₃-C₈ cycloalkyl, C₃-C₈ cycloalkoxy, C₁-C₉ alkyl-C₃-C₈ cycloalkoxy, C₁-C₉ haloalkyl, -(C₀-C₃ alkyl)-O-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S(O)₂-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -N(R^A)₂, C₁-C₉ alkyl-N(R^A)₂, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, aryl, naphthyl, -O-aryl and -O-naphthyl groups; wherein:

said R¹ aryl, naphthyl, -O-aryl and -O-naphthyl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N,

each R¹ aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R¹ groups are substituted with 0 to 4 substituents R^A;

R² is selected from the group consisting of C₁-C₉ alkyl, C₂-C₉ alkenyl, C₂-C₉ alkynyl, C₃-C₈ cycloalkyl, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, and aryl groups, wherein

said R² Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, and aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N, and is attached through an atom selected from C and N,

said R² aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R² is substituted with 0, 1 or 2 independently selected R^A substituents,

R³ is selected from the group consisting of -CH₂CH₃, -CH=CH₂, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, -CH₂CH₂-(bond to R²), -CH=CH-(bond to R²) and a direct bond to R², wherein when R³ is selected from the group consisting of -CH₂CH₂-(bond to R²), -CH=CH-(bond to R²) and a direct bond to R², R² and R³, together with the atoms to which they are bound, form a ring having from fifteen to twenty-one ring atoms and containing 0, 1, 2 or 3 double bonds and 0, 1, 2 or 3 triple bonds;

T is selected from the group consisting of -(CH₂)_q-, -(CH₂)_q-O-(CH₂)_{q1}-, -(CH₂)_q-N(R^A)-(CH₂)_{q1}-, -(CH₂)_q-S-(CH₂)_{q1}-, -(CH₂)_q-C(O)-(CH₂)_{q1}-, -(CH₂)_q-S(O)-(CH₂)_{q1}-, and -(CH₂)_q-S(O)₂-(CH₂)_{q1}-, where q and q1 are each independently selected from the group consisting of 0, 1 or 2, and T is substituted by 0, 1 or 2 groups selected from R^A;

Q is selected from the group consisting of -(CR^A₂)_p-, -(CR^A₂)_p-CR^A=CR^A-(CR^A₂)_{p1}-, -(CR^A₂)_p-O-(CR^A₂)_{p1}-, -(CR^A₂)_p-N(R^A)-(CR^A₂)_{p1}-, -(CR^A₂)_p-S-(CR^A₂)_{p1}-, -(CR^A₂)_p-S(O)-(CR^A₂)_{p1}-, and -(CR^A₂)_p-S(O)₂-(CR^A₂)_{p1}-, where p and p1 are independently selected from 0, 1, 2, 3 or 4;

each R⁴ is independently selected from the group consisting of H, halogen atoms, -OR^A, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CN, -SR^A, -CO₂R^A, -C(O)N(R^A)₂, -OC(O)N(R^A)₂, Si(R^A)₃, Si(R^A)₂(CH₃), Si(R^A)(CH₃)₂, Si(CH₃)₃, -(C₀-C₃ alkyl)-O-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S(O)₂-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -SO(R^A), -SO₂(R^A), C₃-C₈ cycloalkyl, and aryl, wherein

said R⁴ aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N,

each R⁴ aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R⁴ C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl and aryl groups are substituted with 0 to 4 substituents R^A;

5 two R⁴ may be taken, together with the atoms to which they are bound, to form a ring; and

m is 0, 1, 2 or 3.

3. The compound according to claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein

10 A is selected from the group consisting of C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₈ cycloalkyl, aryl and 7-, 8-, 9- and 10-membered bicyclic groups, wherein

said A aryl and bicyclic groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N,

15 each A aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings and 7-, 8-, 9- and 10-membered bicyclic aromatic rings,

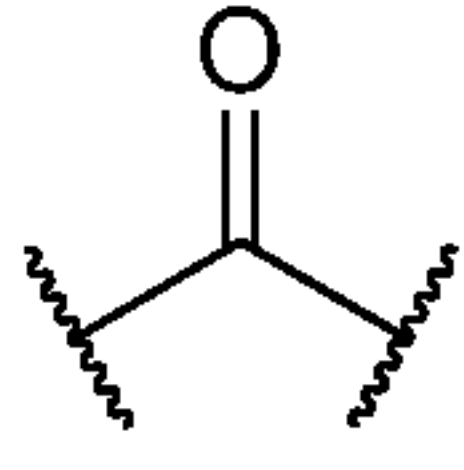
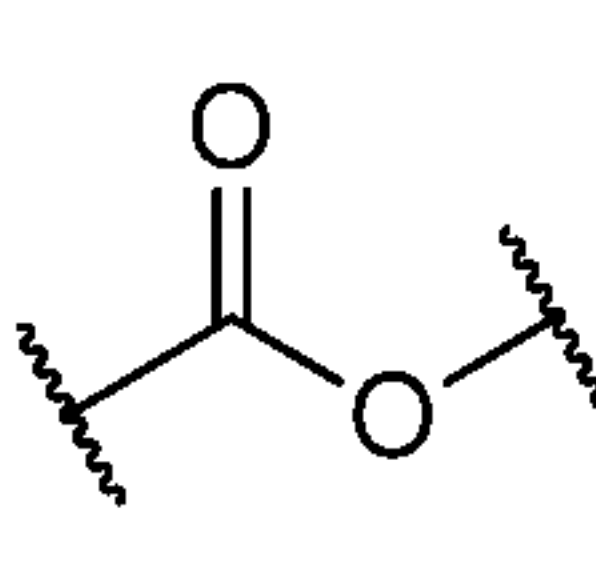
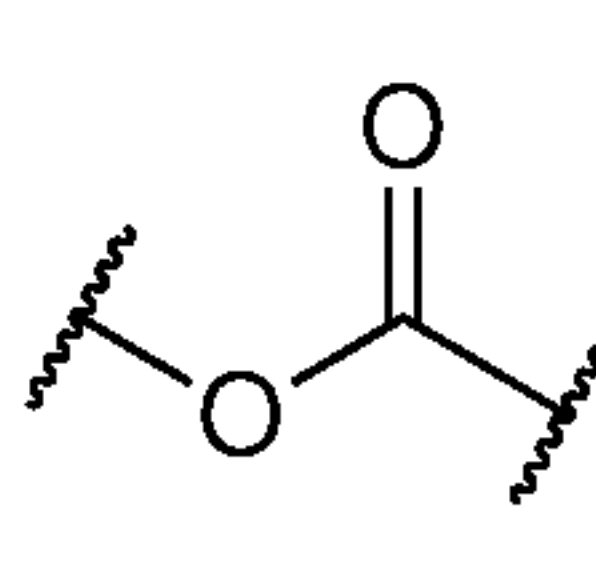
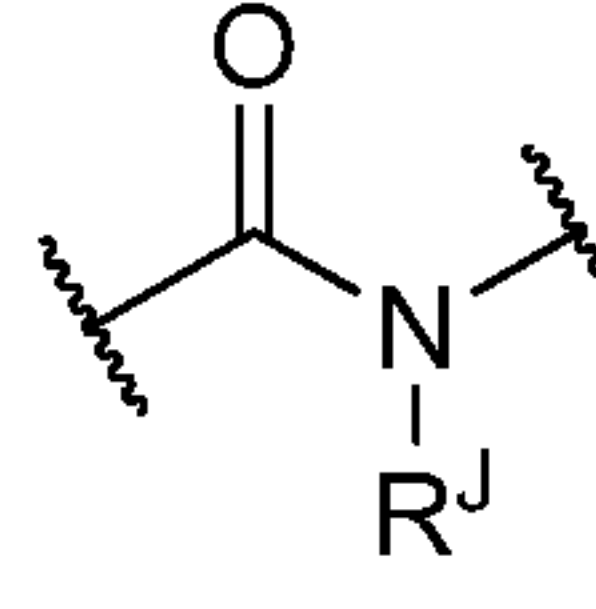
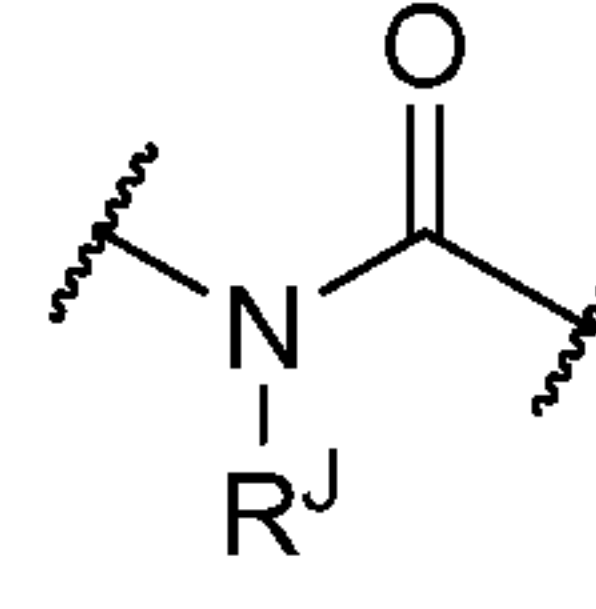
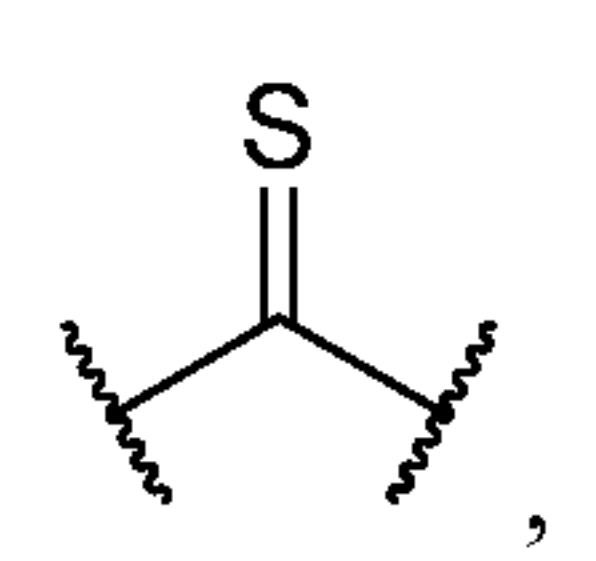
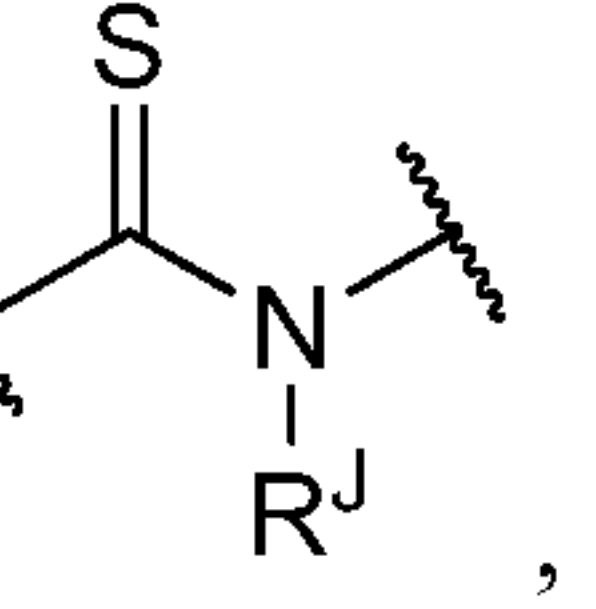
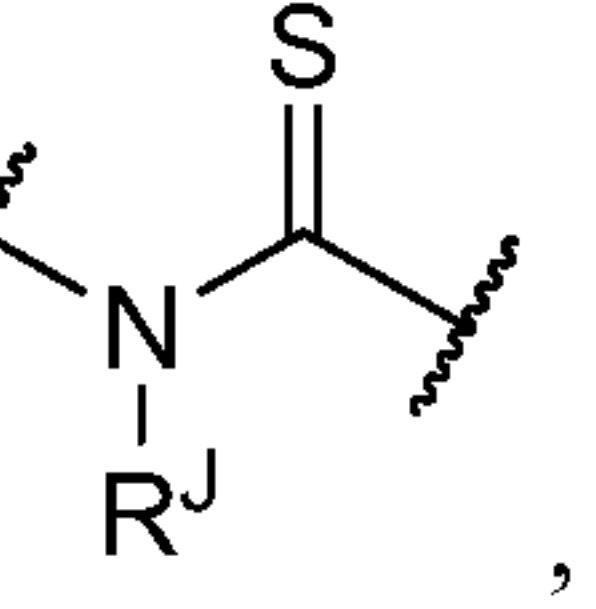
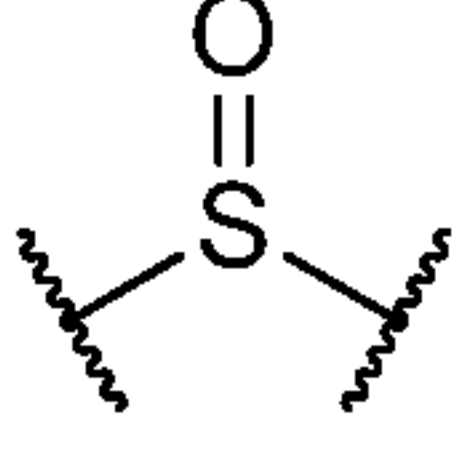
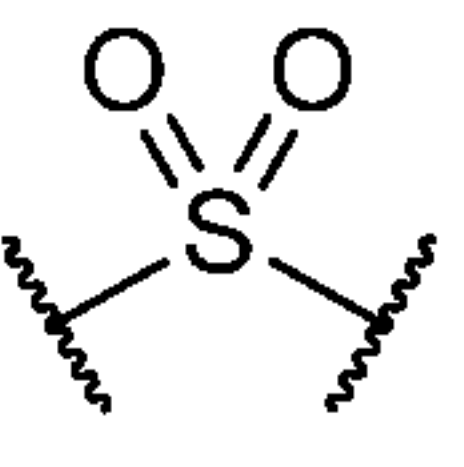
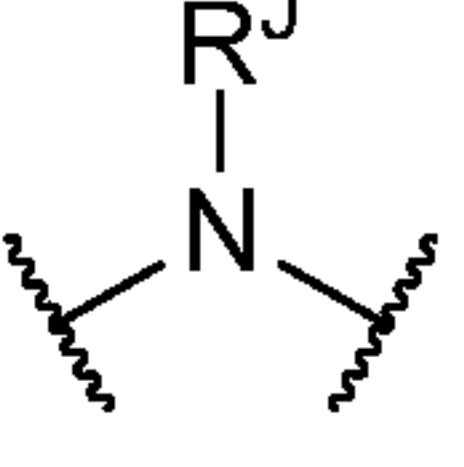
said A is substituted with 0, 1, 2, 3 or 4 substituents R^A;

each R^A is independently selected from the group consisting of H, F, Cl, Br, I, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkyl(NH₂), phenyl, naphthyl, C₃-C₈ cycloalkyl, halo(C₁-C₆ alkoxy), -O(C₁-C₆ alkyl), SH, S(C₁-C₆ alkyl), NH₂, -NH(C₁-C₆ alkyl),
 20 -N(C₁-C₆ alkyl)₂, -C(O)(C₁-C₆ alkyl), -CONH₂, -SO₂NH₂, NO₂, CN, -CF₃, -CHF₂, -CH₂F, -OCHF₂, -OCF₃, -OCH₂F, -SO₂(C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), -SO₂N(C₁-C₆ alkyl)₂, -(C₁-C₆ alkyl)SO₂N(C₁-C₆ alkyl)₂, -NHCOO(C₁-C₆ alkyl), -NHCO(C₁-C₆ alkyl), -NHCONH(C₁-C₆ alkyl),
 25 alkyl), -CO₂(C₁-C₆ alkyl), -C(O)N(C₁-C₆ alkyl)₂, -(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-O-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-S-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), and -(C₀-C₅ alkyl)-S(O)₂-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), wherein

two R^A may be taken, together with the atoms to which they are bound, to form a ring having from three to fifteen ring atoms;

30 R^A and R² may be taken, together with the atoms to which they are bound, to form a ring having from sixteen to twenty-one ring atoms;

R^A and R^1 or R^4 may be taken, together with the atoms to which they are bound, to form a ring having from sixteen to twenty-one ring atoms;

J is selected from the group consisting of a direct bond, C_1 - C_8 alkylene, , , , , , , , , , , and , wherein said C_1 - C_8 alkylene are substituted by 0, 1, 2 or 3 substituents R^J ;

R^J is selected from the group consisting of H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, and aryl, wherein

said R^J aryl contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of B, O, S and N,

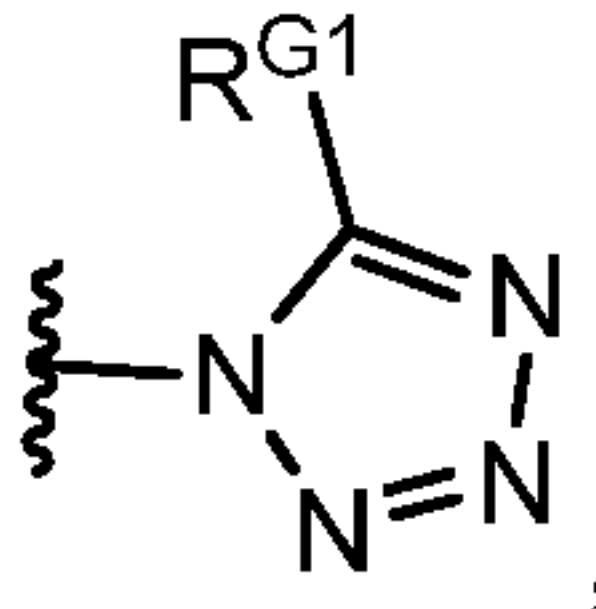
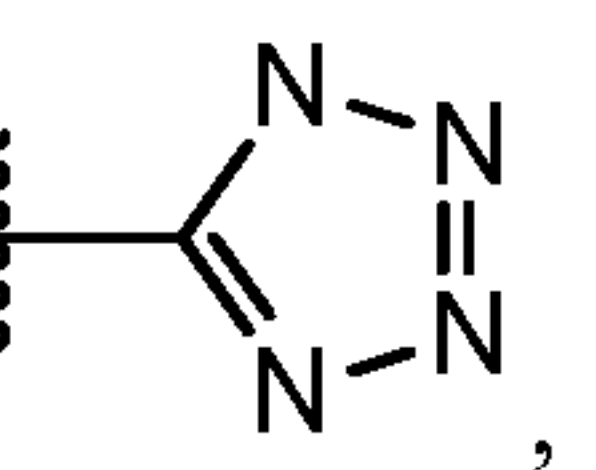
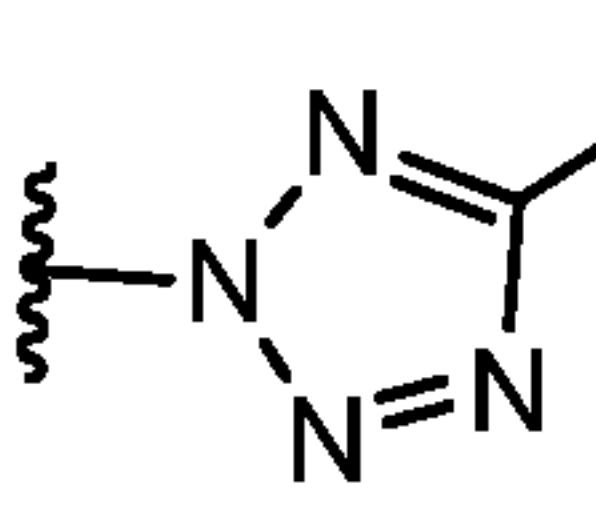
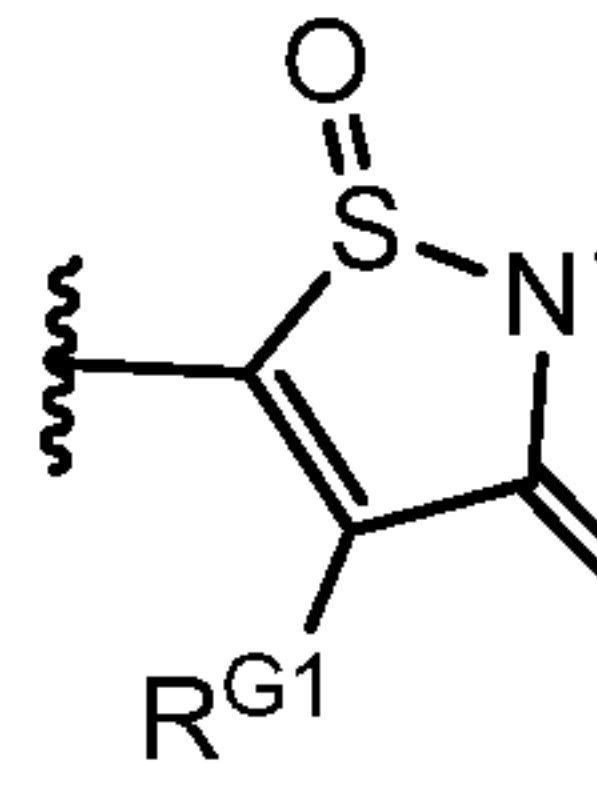
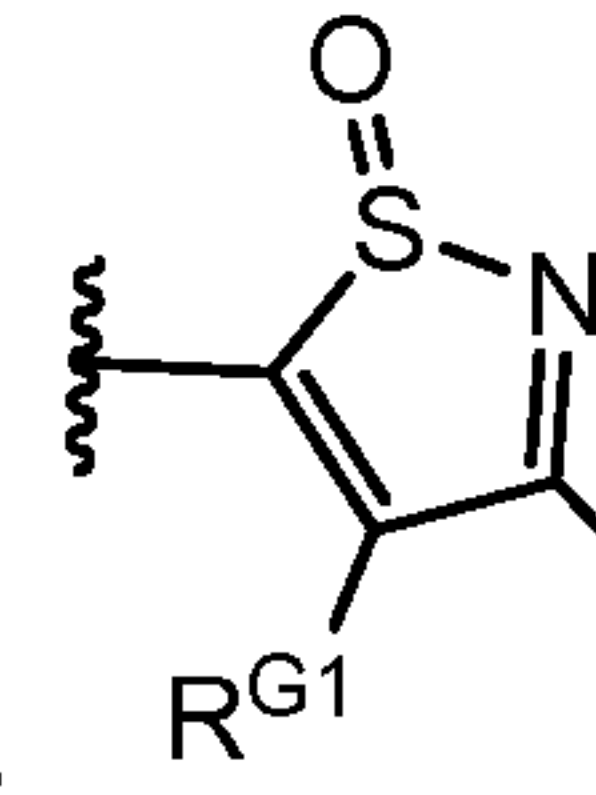
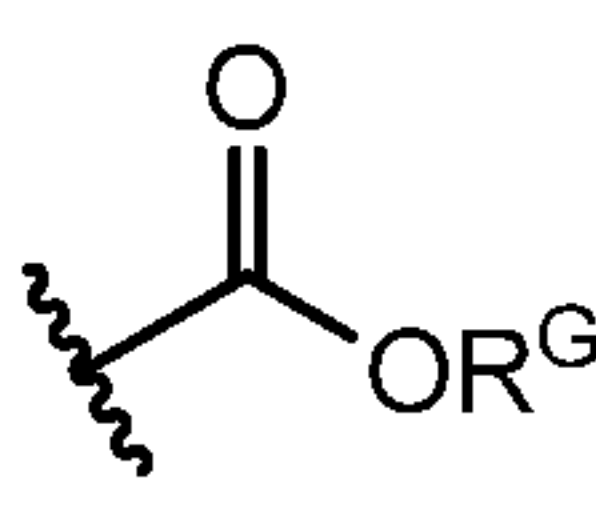
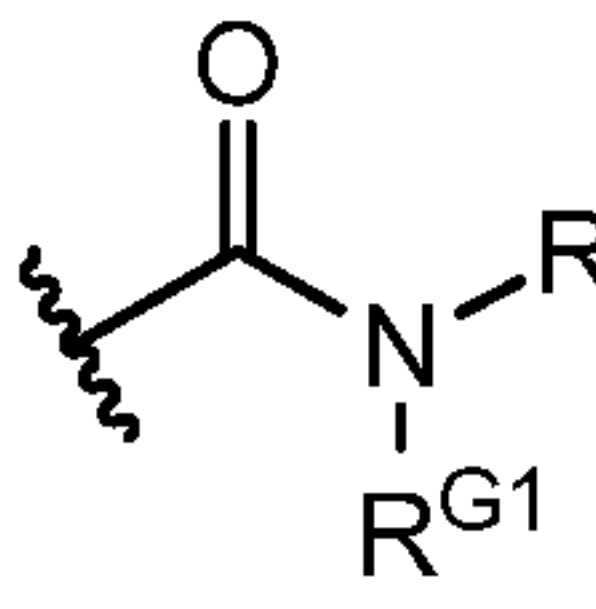
each R^J aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

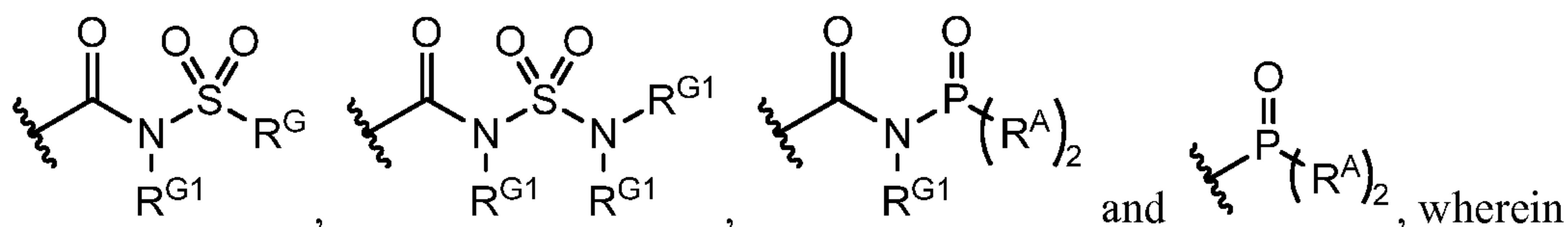
said R^J is substituted with 0, 1, 2, 3 or 4 substituents R^A ;

L is selected from the group consisting of $(CH_2)_{0-4}$ and $N(R^L)$;

each R^L is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkyl(NH_2), aryl, C_3 - C_8 cycloalkyl, halo(C_1 - C_6 alkoxy), and C_1 - C_6 alkyl(aryl) groups, wherein

each R^L aryl group is independently selected from the group consisting of 5- and 6-membered aromatic rings,

G is selected from the group consisting of , , , , , , and ,



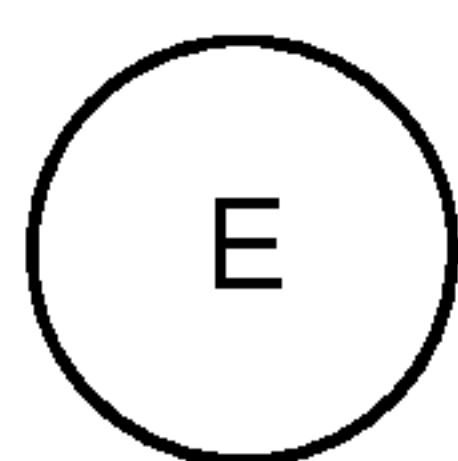
R^G is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyl(C₁-C₅)alkyl, aryl, and aryl(C₁-C₄)alkyl groups, wherein

5 said R^G aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N,

each R^G aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R^G is substituted with 0, 1 or 2 independently selected R^A substituents,

10 each R^{G1} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, and benzyl, wherein each R^{G1} is independently substituted with 0 to 4 substituents R^A ,



is selected from the group consisting of:

1) aryl rings in which the aryl ring system attaches to Q and T at points that are two independently selected carbon ring atoms,

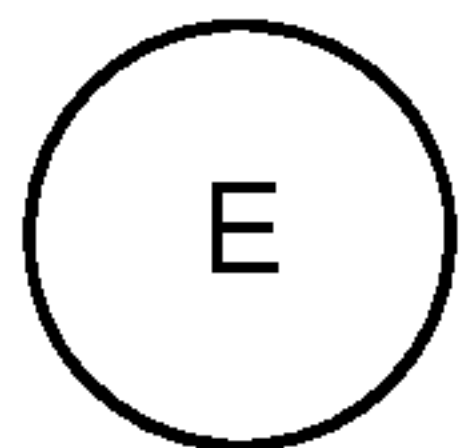
2) C₃-C₈ cycloalkyl rings in which the C₃-C₈ cycloalkyl ring system attaches to Q and T at points that are two independently selected carbon ring atoms, and

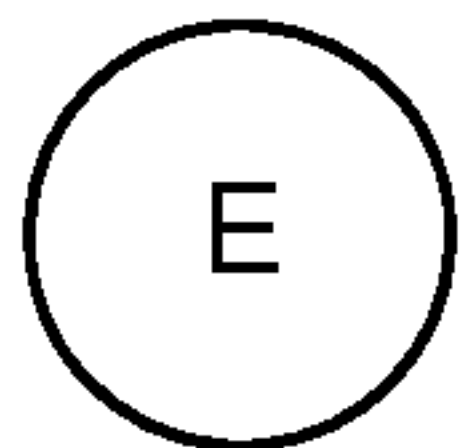
3) heterocyclic rings in which the heterocyclic ring system attaches to Q and T at points that are two independently selected ring atoms that are either two carbon ring atoms or one carbon ring atom and one nitrogen ring atom, and the heterocyclic ring system is selected from the group consisting of:

a) 5- or 6-membered saturated or unsaturated monocyclic rings with 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O and S,

25 b) 8-, 9- or 10-membered saturated or unsaturated bicyclic rings with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S, and

c) 11- to 15-membered saturated or unsaturated tricyclic rings with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S,



wherein  is substituted with 1 substituent R¹ and with 0, 1, 2, 3, 4 or 5 independently selected substituents R⁴;

R¹ is selected from the group consisting of H, halogen atoms, -OH, C₁-C₉ alkyl, C₁-C₉ alkoxy, C₁-C₉ alkyl-C₁-C₉ alkoxy, -CN, -C(O)OH, -C(O)CH₃, -SR^A, -SO₂(C₁-C₉ alkyl), C₃-C₈ cycloalkyl, C₁-C₉ alkyl-C₃-C₈ cycloalkyl, C₃-C₈ cycloalkoxy, C₁-C₉ alkyl-C₃-C₈ cycloalkoxy, C₁-C₉ haloalkyl, -(C₀-C₃ alkyl)-O-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S(O)₂-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -N(R^A)₂, C₁-C₉ alkyl-N(R^A)₂, aryl, naphthyl, -O-aryl and -O-naphthyl groups; wherein:

said R¹ aryl, naphthyl, -O-aryl and -O-naphthyl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N,

each R¹ aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R¹ groups are substituted with 0 to 4 substituents R^A;

R² is selected from the group consisting of C₁-C₉ alkyl, C₂-C₉ alkenyl, C₂-C₉ alkynyl, C₃-C₈ cycloalkyl, and aryl groups, wherein

said R² aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N, and is attached through an atom selected from C and N,

said R² aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

said R² is substituted with 0, 1 or 2 independently selected R^A substituents,

R³ is selected from the group consisting of -CH₂CH₃, -CH=CH₂, -CH₂CH₂-(bond to R²), -CH=CH-(bond to R²) and a direct bond to R², wherein when R³ is selected from the group consisting of -CH₂CH₂-(bond to R²), -CH=CH-(bond to R²) and a direct bond to R², R² and R³, together with the atoms to which they are bound, form a ring having from fifteen to twenty-one ring atoms and containing 0, 1, 2 or 3 double bonds and 0, 1, 2 or 3 triple bonds;

T is selected from the group consisting of -(CH₂)_q-, -(CH₂)_q-O-(CH₂)_{q1}-, -(CH₂)_q-N(R^A)-(CH₂)_{q1}-, -(CH₂)_q-S-(CH₂)_{q1}-, -(CH₂)_q-C(O)-(CH₂)_{q1}-, -(CH₂)_q-S(O)-(CH₂)_{q1}-, and -(CH₂)_q-

$S(O)_2-(CH_2)_{q1}$ -, where q and $q1$ are each independently selected from the group consisting of 0, 1 or 2, and T is substituted by 0, 1 or 2 groups selected from R^A ;

Q is selected from the group consisting of $-(CR^A_2)_p$ -, $-(CR^A_2)_p-CR^A=CR^A-$
 $(CR^A_2)_{p1}$ -, $-(CR^A_2)_p-O-(CR^A_2)_{p1}$ -, $-(CR^A_2)_p-N(R^A)-(CR^A_2)_{p1}$ -, $-(CR^A_2)_p-S-(CR^A_2)_{p1}$ -, $-(CR^A_2)_p-$
 5 $S(O)-(CR^A_2)_{p1}$ -, and $-(CR^A_2)_p-S(O)_2-(CR^A_2)_{p1}$ -, where p and $p1$ are independently selected from 0, 1, 2, 3 or 4;

each R^4 is independently selected from the group consisting of H, halogen atoms, $-OR^A$, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-CN$, $-SR^A$, $-CO_2R^A$, $-C(O)N(R^A)_2$, $-OC(O)N(R^A)_2$, $-(C_0-C_3$
 10 $alkyl)-O-(C_0-C_3 alkyl)-(C_3-C_8 cycloalkyl)$, $-(C_0-C_3 alkyl)-S-(C_0-C_3 alkyl)-(C_3-C_8 cycloalkyl)$, $-(C_0-C_3 alkyl)-S(O)_2-(C_0-C_3 alkyl)-(C_3-C_8 cycloalkyl)$, $-SO(R^A)$, $-SO_2(R^A)$, $C_3-C_8 cycloalkyl$, and aryl, wherein

said R^4 aryl groups contain 0, 1, 2 or 3 heteroatoms independently selected from the group consisting of O, S and N,

each R^4 aryl is independently selected from the group consisting of 5- and
 15 6-membered aromatic rings,

said R^4 C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl and aryl groups are substituted with 0 to 4 substituents R^A ;

two R^4 may be taken, together with the atoms to which they are bound, to form a ring; and

20 m is 0, 1, 2 or 3.

4. The compound according to any one of claim 1 to claim 3, or a pharmaceutically acceptable salt thereof, wherein R^A and R^2 are taken, together with the atoms to which they are bound, to form a ring wherein the R^A to R^2 linkage contains from six to nine atoms.

25 5. The compound according to any one of claim 1 to claim 4, or a pharmaceutically acceptable salt thereof, wherein R^A and R^1 are taken, together with the atoms to which they are bound, to form a ring wherein the R^A to R^1 linkage contains from six to nine atoms.

30 6. The compound according to any one of claim 1 to claim 4, or a pharmaceutically acceptable salt thereof, wherein R^A and R^4 are taken, together with the atoms to

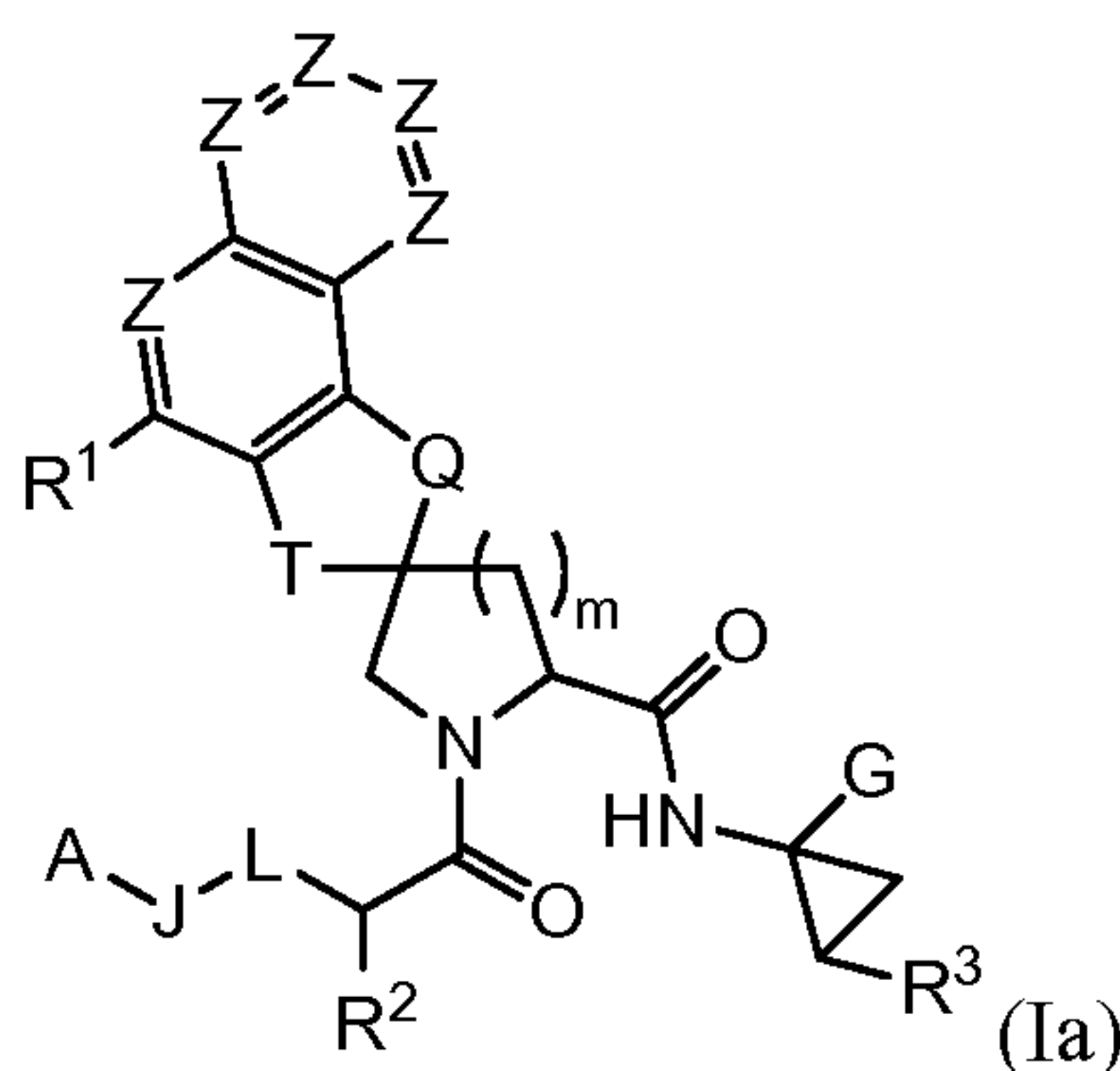
which they are bound, to form a ring wherein the R^A to R⁴ linkage contains from six to nine atoms.

7. The compound according to any one of claim 1 to claim 6, or a pharmaceutically acceptable salt thereof, wherein R³ is selected from the group consisting of -CH₂CH₂-(bond to R²), -CH=CH-(bond to R²) and a direct bond to R², and wherein R² and R³, together with the atoms to which they are bound, form a ring having from fifteen to twenty-one ring atoms and containing 0, 1, 2 or 3 double bonds and 0, 1, 2 or 3 triple bonds.

8. The compound according to any one of claim 1 to claim 7, wherein R^A and R¹ are taken, together with the atoms to which they are bound, to form a ring wherein the R^A to R¹ linkage contains from six to nine atoms; and R³ is selected from the group consisting of -CH₂CH₂-(bond to R²), -CH=CH-(bond to R²) and a direct bond to R², and wherein R² and R³, together with the atoms to which they are bound, form a ring having from fifteen to twenty-one ring atoms and containing 0, 1, 2 or 3 double bonds and 0, 1, 2 or 3 triple bonds.

9. The compound according to any one of claim 1 to claim 7, wherein R^A and R⁴ are taken, together with the atoms to which they are bound, to form a ring wherein the R^A to R⁴ linkage contains from six to nine atoms; and R³ is selected from the group consisting of -CH₂CH₂-(bond to R²), -CH=CH-(bond to R²) and a direct bond to R², and wherein R² and R³, together with the atoms to which they are bound, form a ring having from fifteen to twenty-one ring atoms and containing 0, 1, 2 or 3 double bonds and 0, 1, 2 or 3 triple bonds.

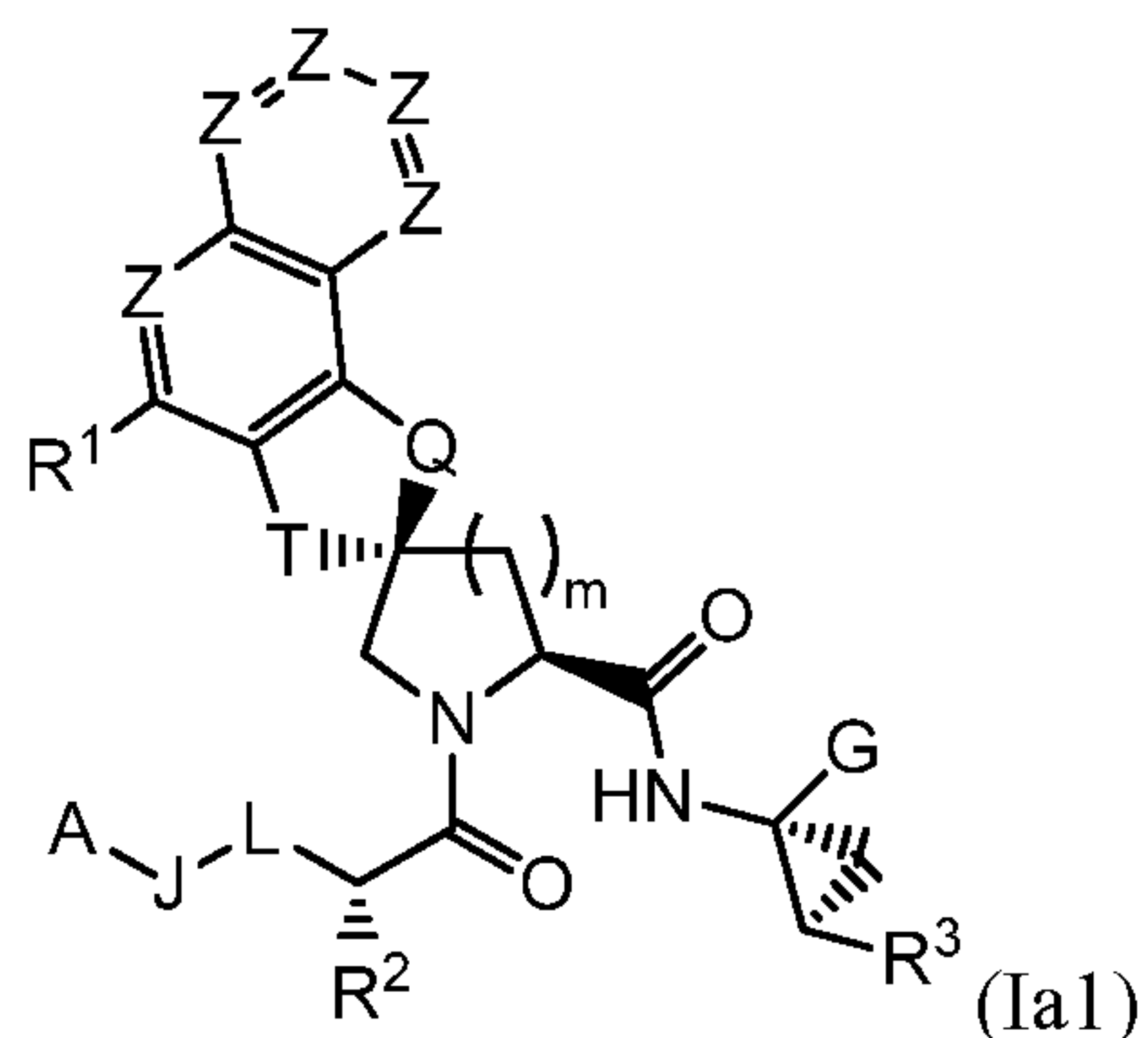
10. The compound according to any one of claim 1 to claim 9, wherein the compound is a compound of formula Ia:



or a pharmaceutically acceptable salt thereof, wherein

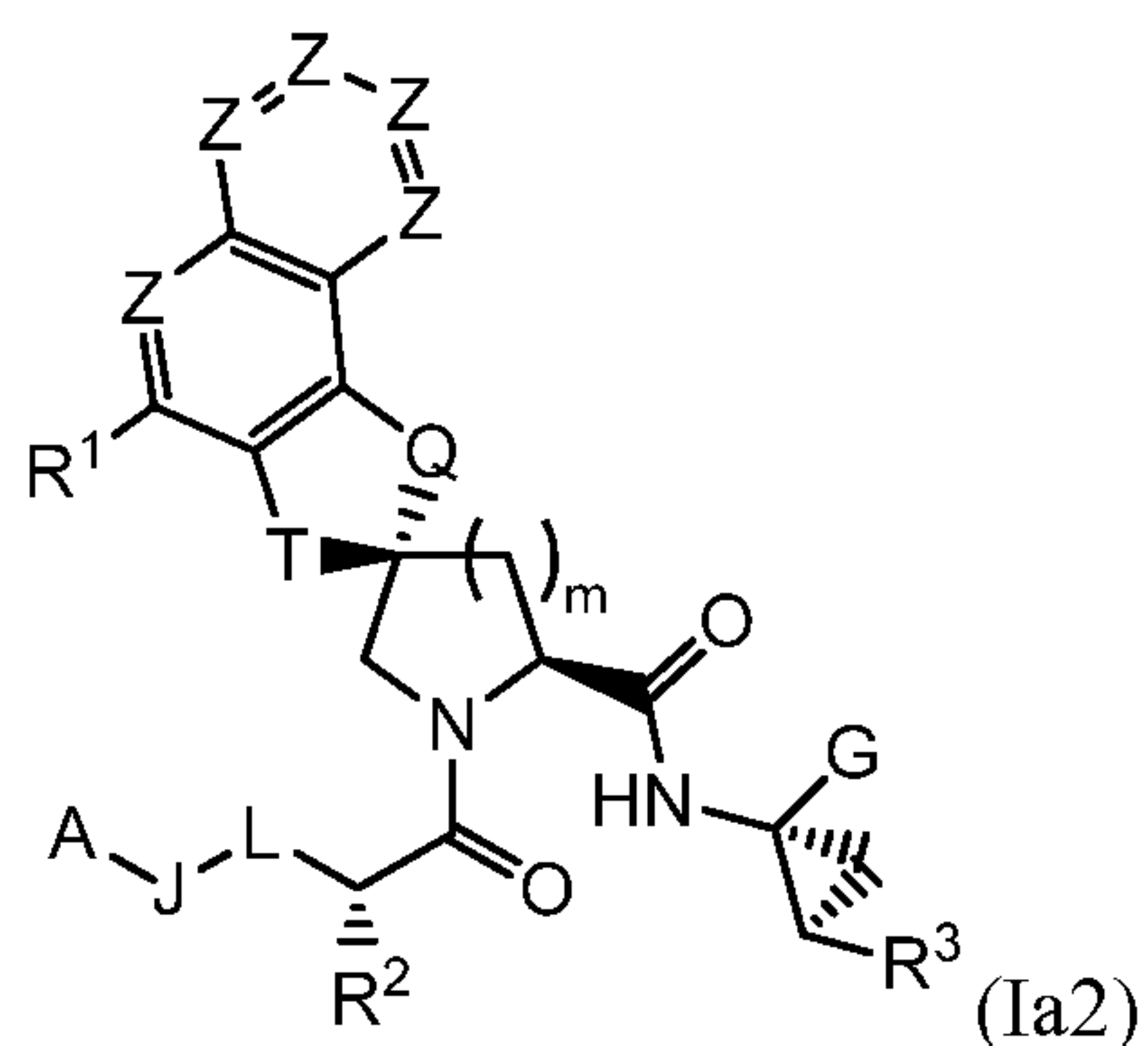
each Z is independently selected from the group consisting of N and C(R⁴).

11. The compound according to claim 10, wherein the compound of formula Ia is a compound of formula Ia1:



or a pharmaceutically acceptable salt thereof.

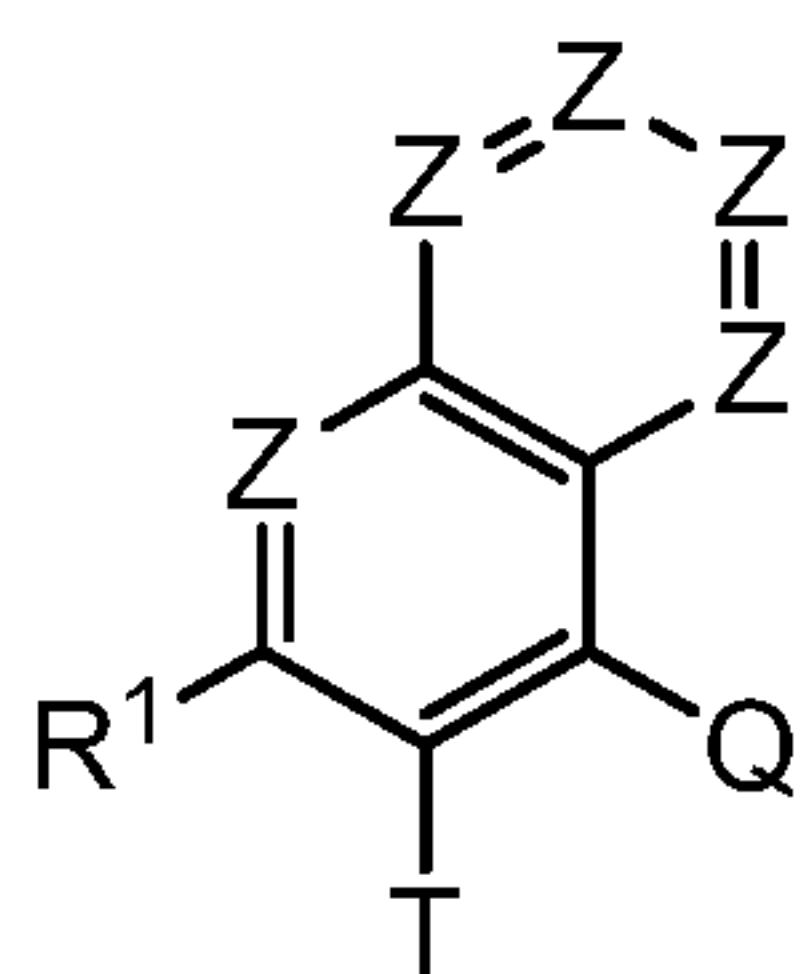
5 12. The compound according to claim 10, wherein the compound of formula Ia is a compound of formula Ia2:



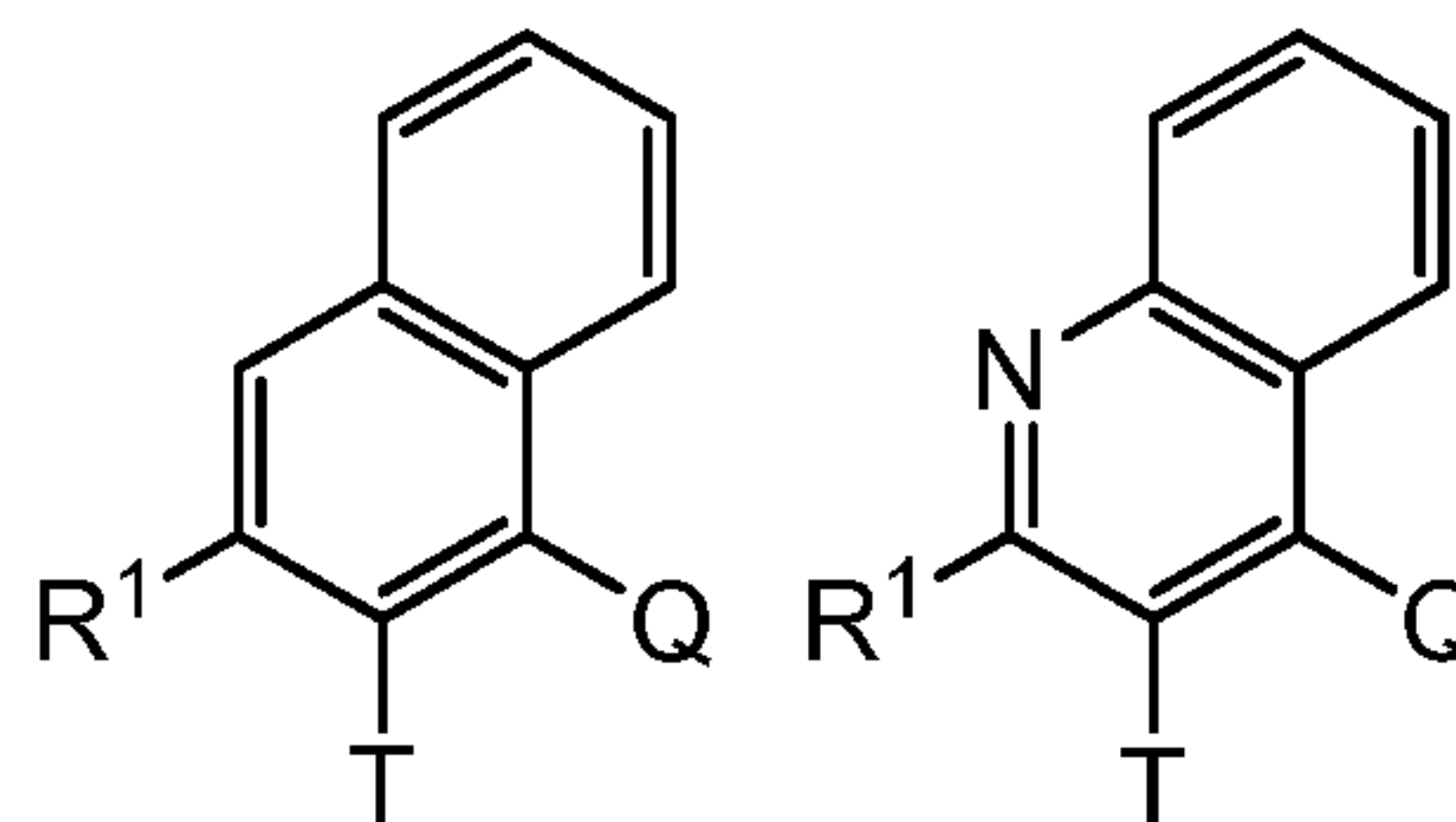
or a pharmaceutically acceptable salt thereof.

10 13. The compound according to any one of claim 10 to claim 12, wherein each Z is independently selected from N and CH.

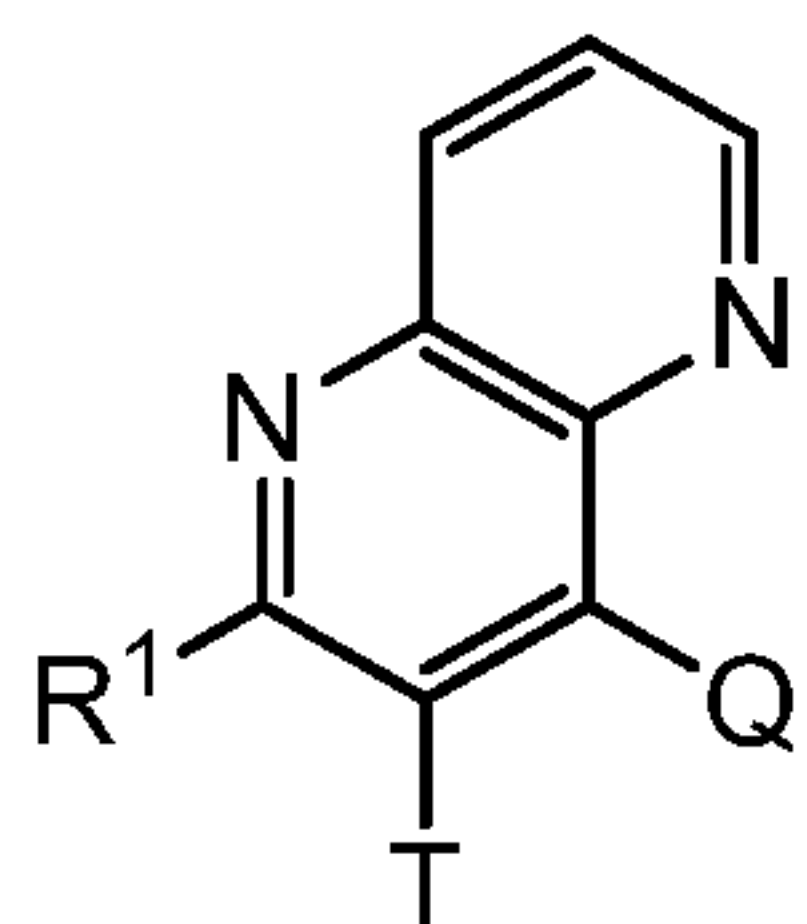
14. The compound according to any one of claim 10 to claim 13, wherein



is selected from the group consisting of



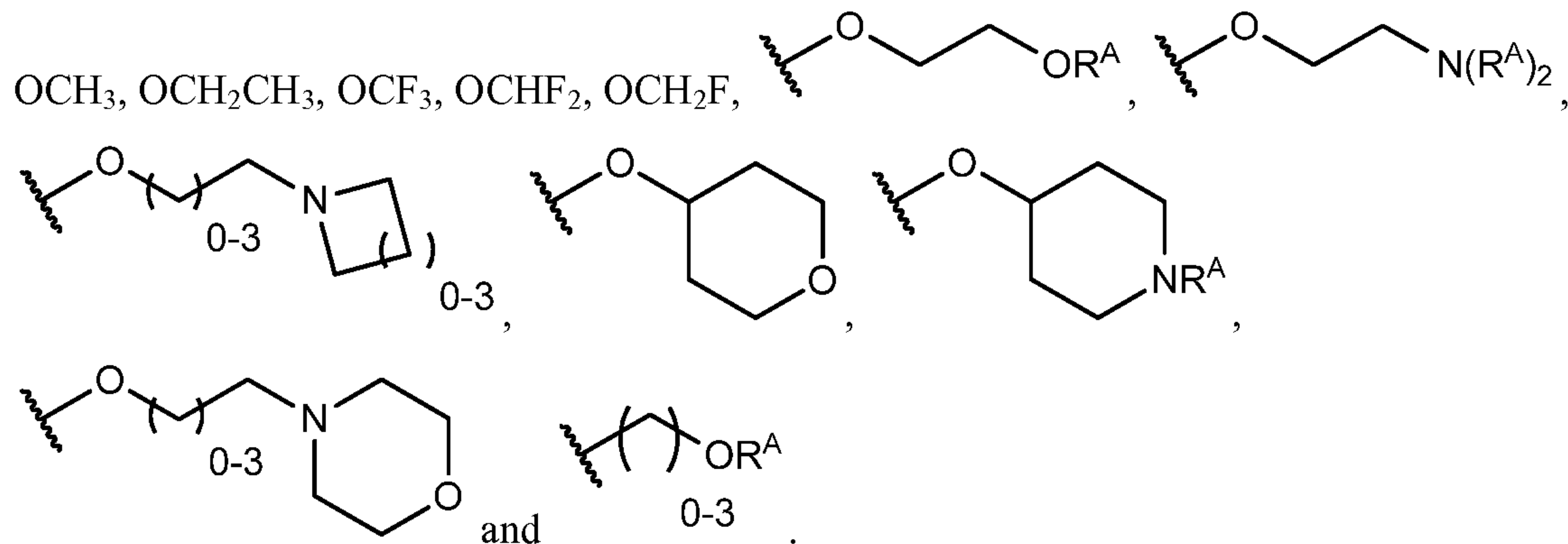
and



, substituted by 0, 1, 2 or 3 substituents R^4 .

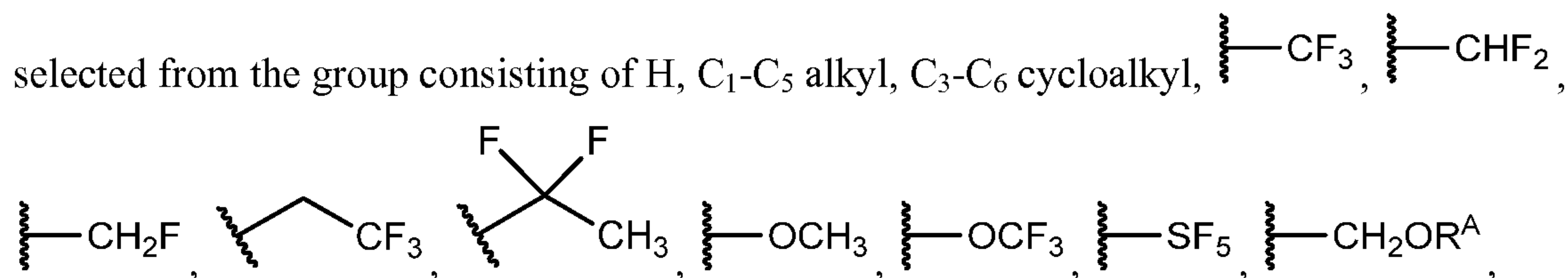
15. The compound according to any one of claim 1 to claim 14, wherein each R^4 is independently selected from the group consisting of H, F, Cl, Br, OH, CN, C_1 - C_5 alkyl, C_1 - C_5 alkoxy, substituted by 0, 1, 2, or 3 R^A .

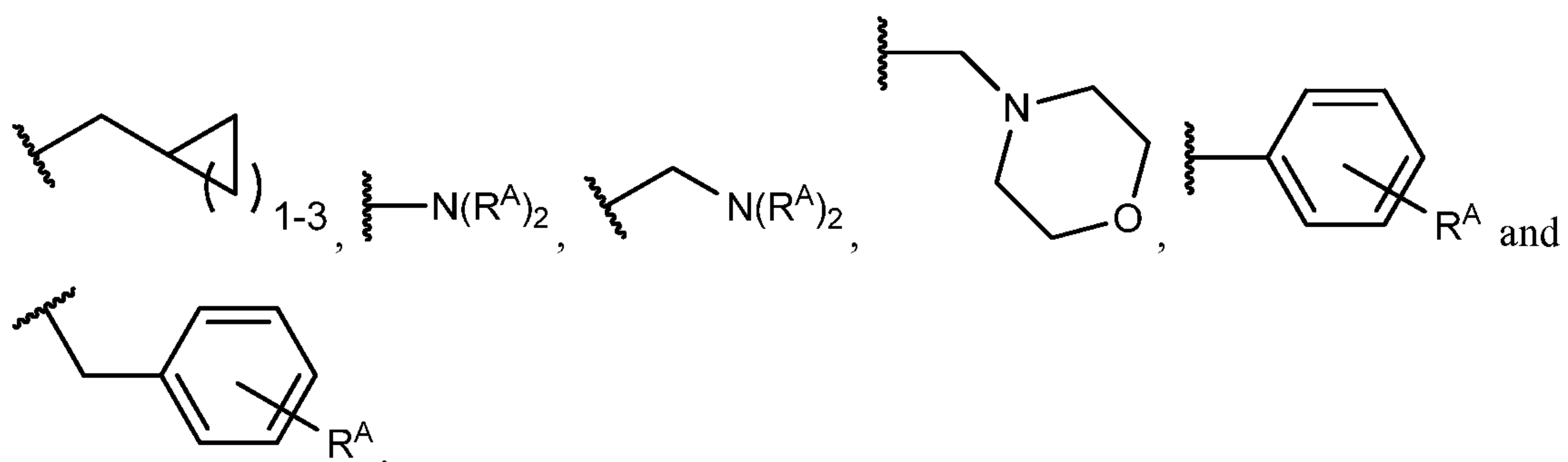
16. The compound according to any one of claim 1 to claim 15, wherein each R^4 is independently selected from the group consisting of H, F, Cl, Br, OH, CN, C_1 - C_5 alkyl,



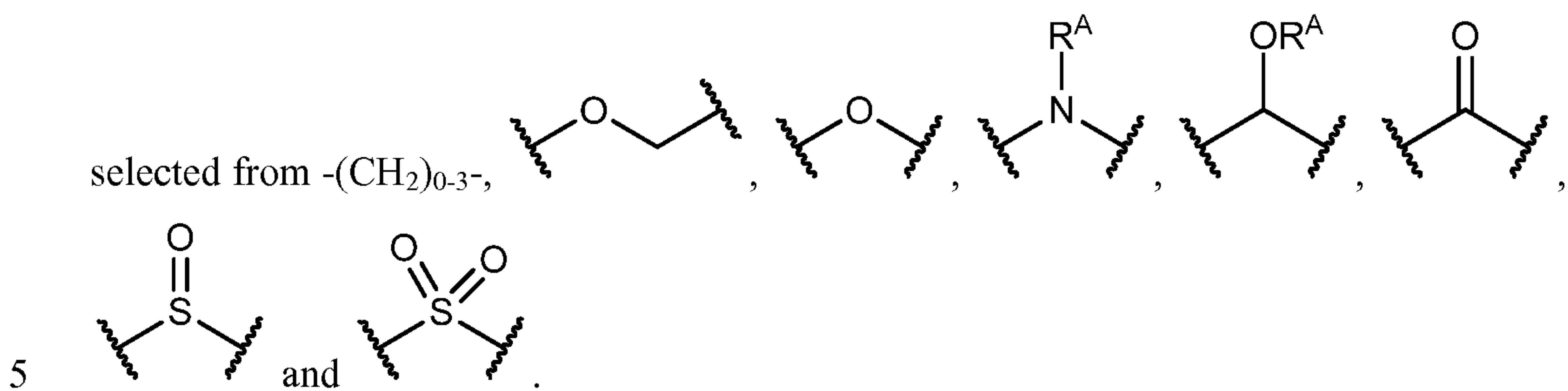
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17. The compound according to any one of claim 1 to claim 16, wherein R^1 is

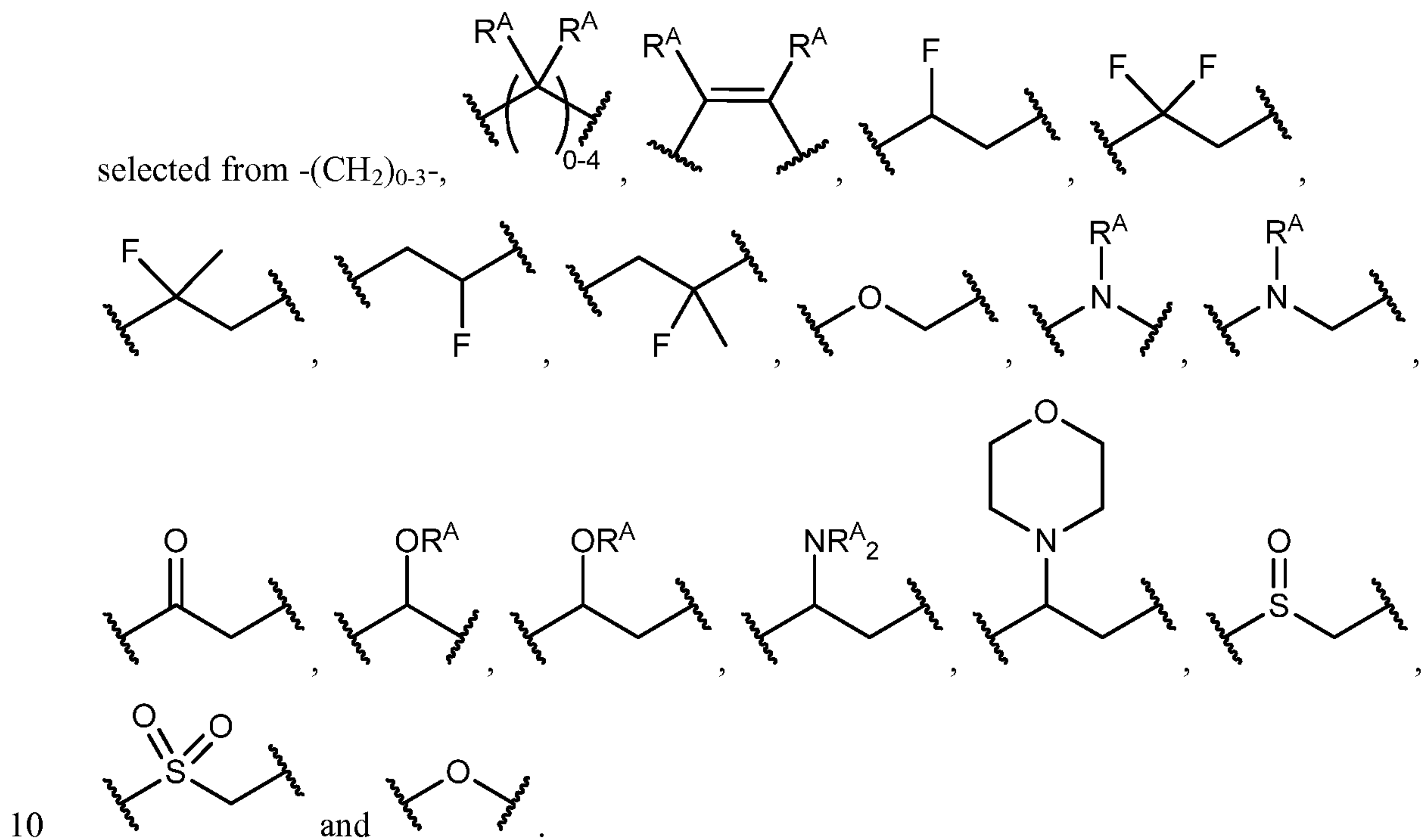




18. The compound according to any one of claim 1 to claim 17, wherein T is



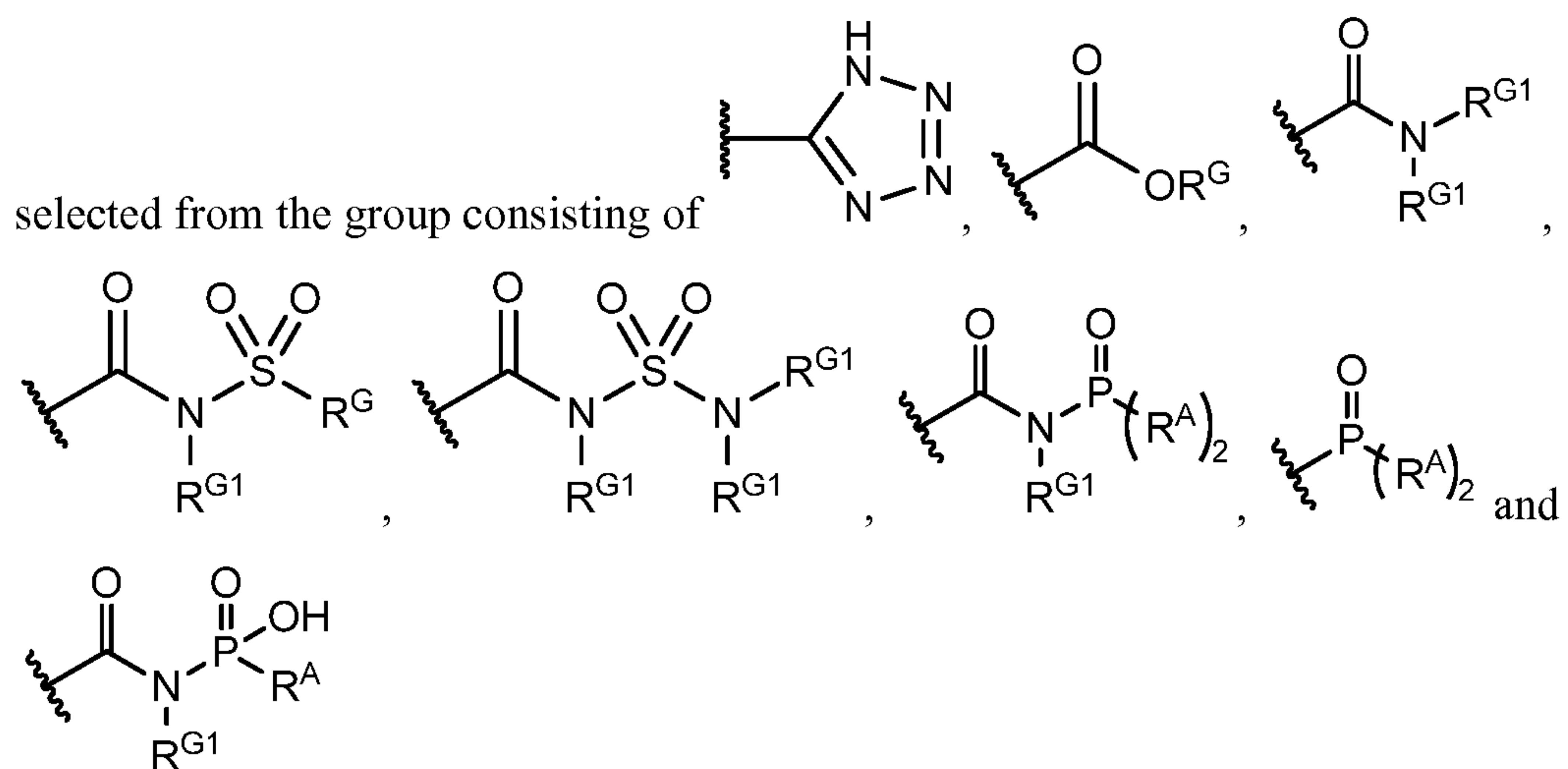
19. The compound according to any one of claim 1 to claim 18, wherein Q is



20. The compound according to any one of claim 1 to claim 19, wherein m is

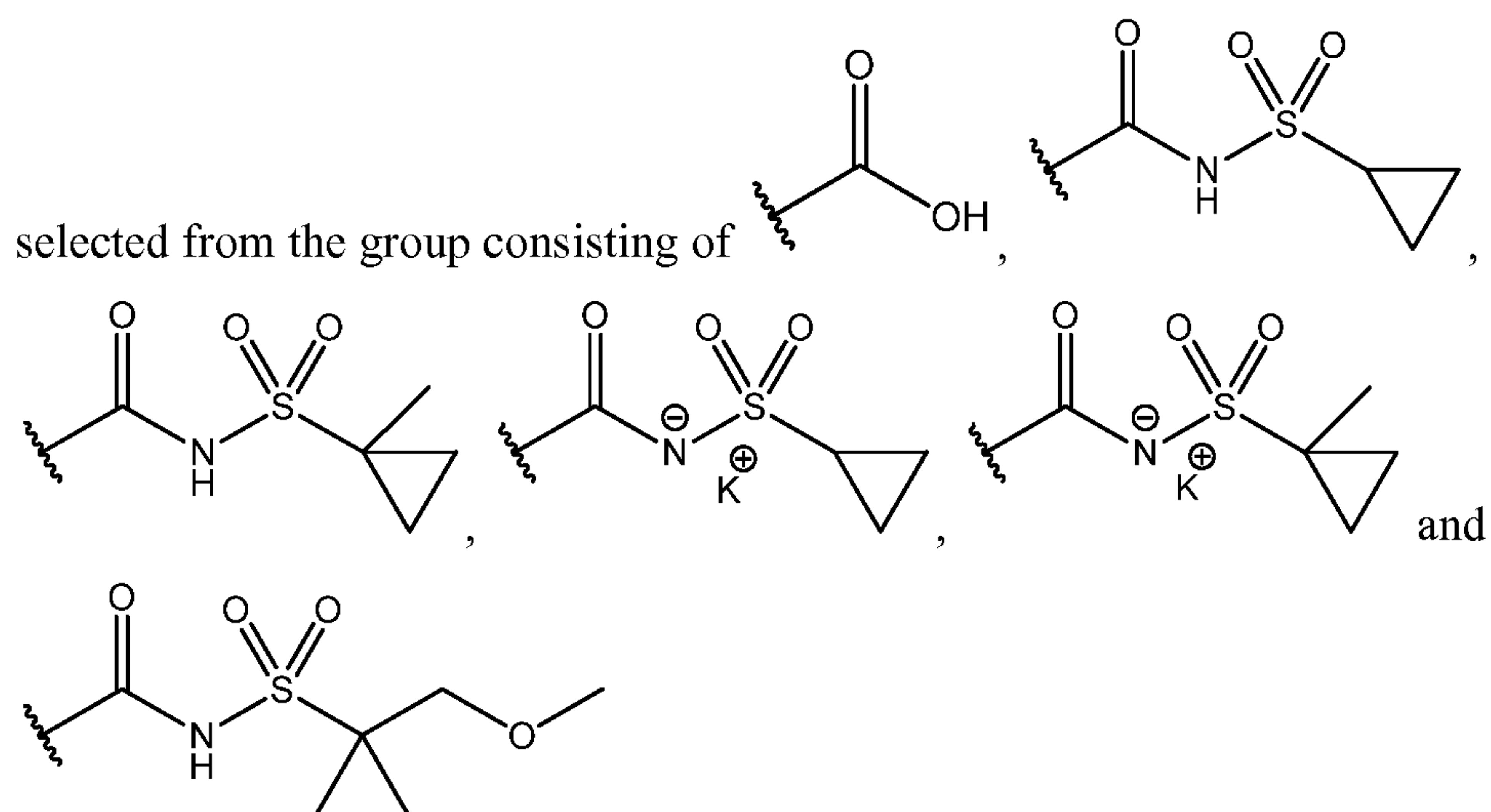
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21. The compound according to any one of claim 1 to claim 20, wherein G is

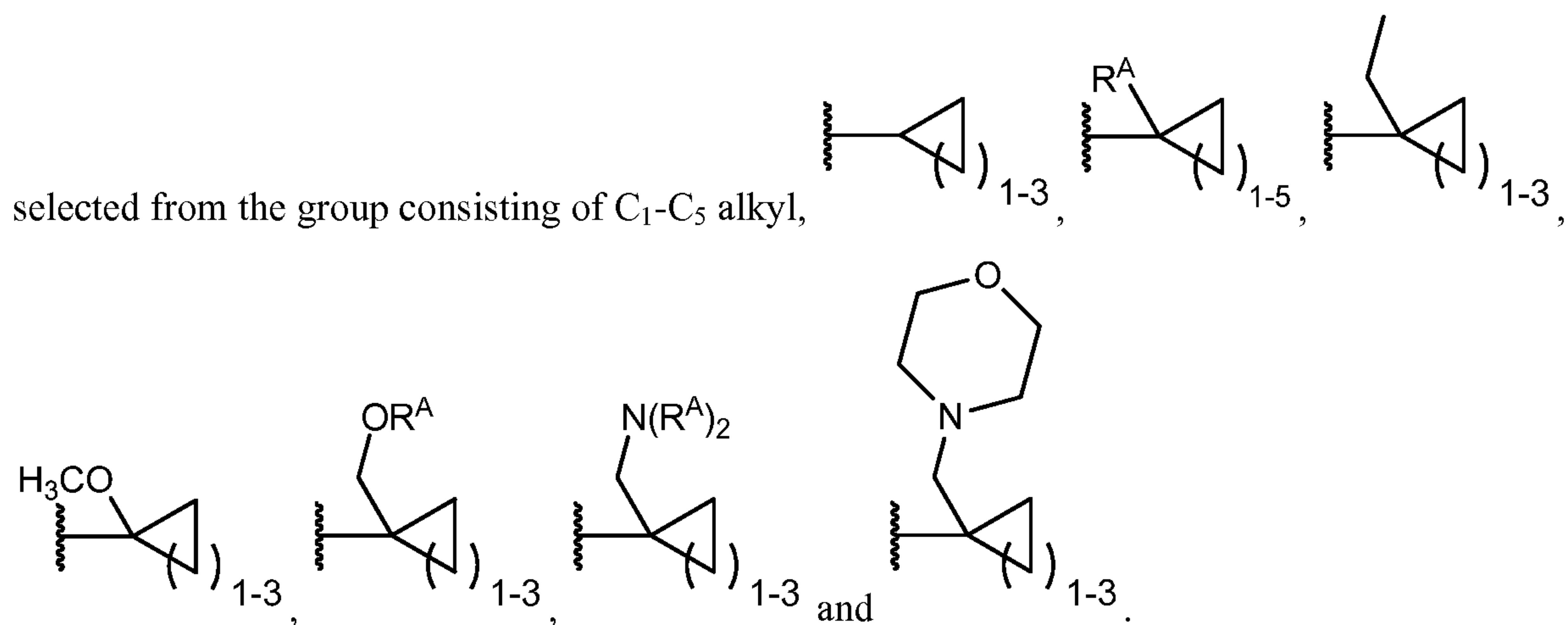


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22. The compound according to any one of claim 1 to claim 21, wherein G is



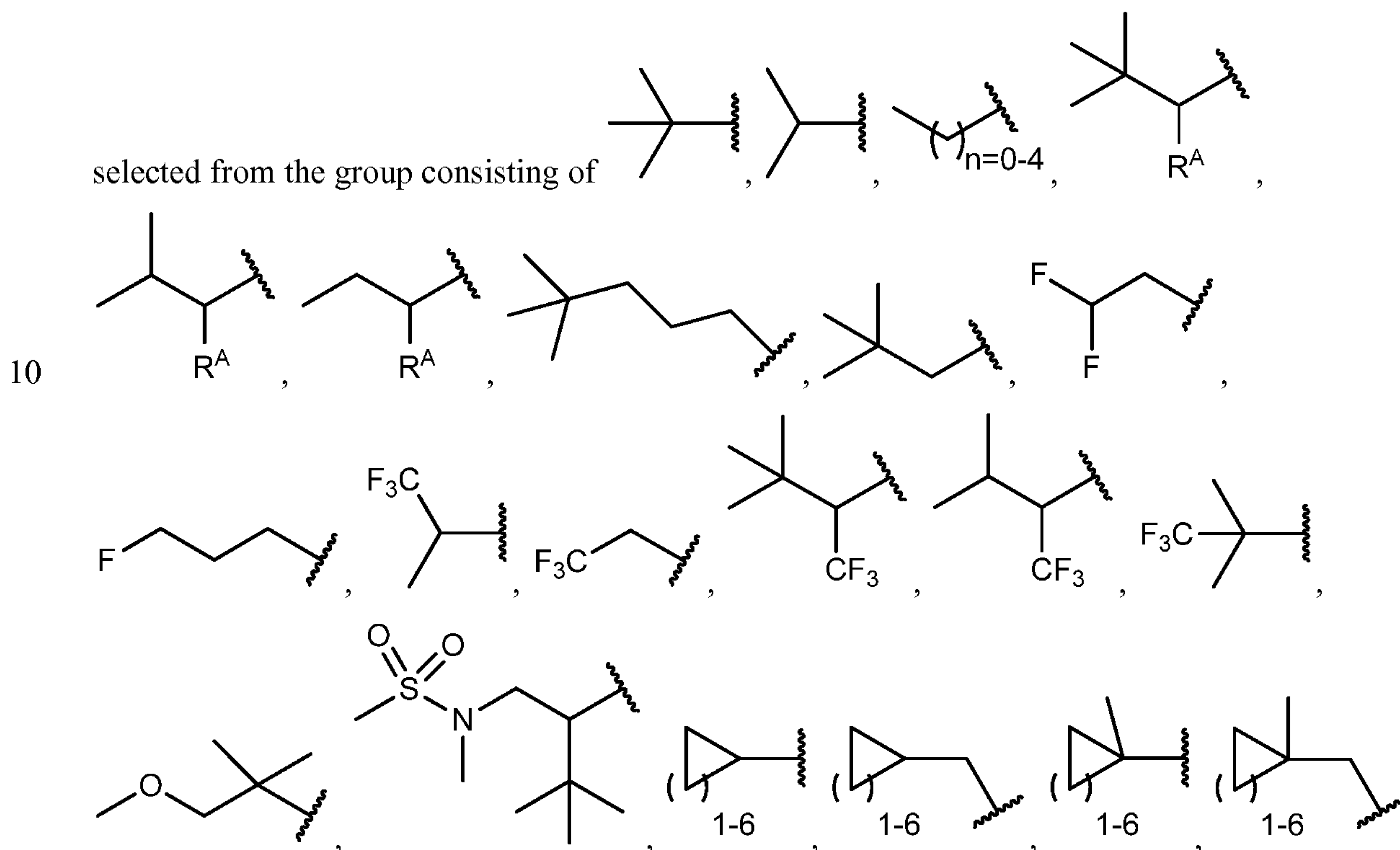
23. The compound according to any one of claim 1 to claim 21, wherein R^G is

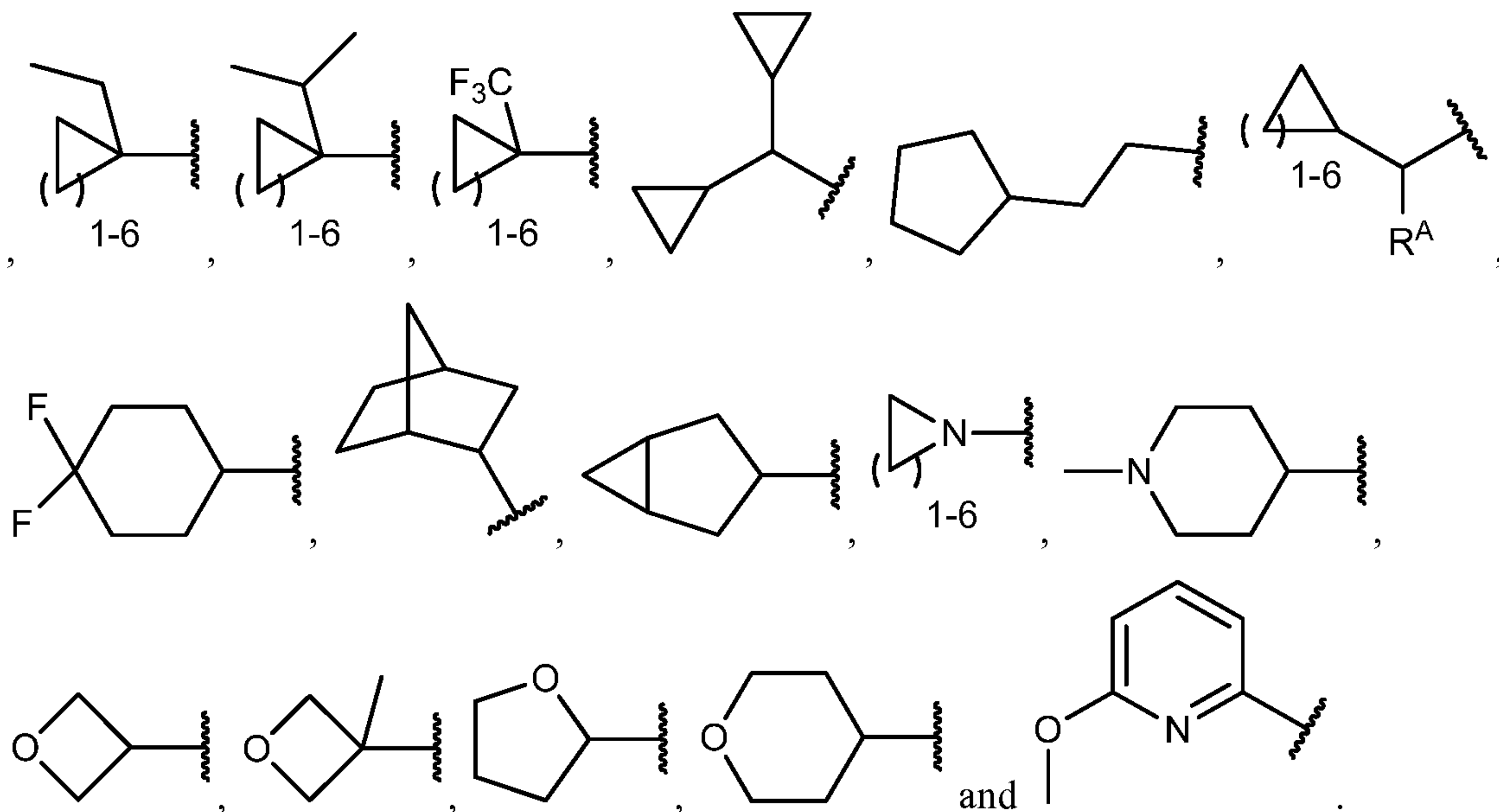


24. The compound according to any one of claim 1 to claim 23, wherein R² is
5 selected from the group consisting of C₄-C₉ alkyl.

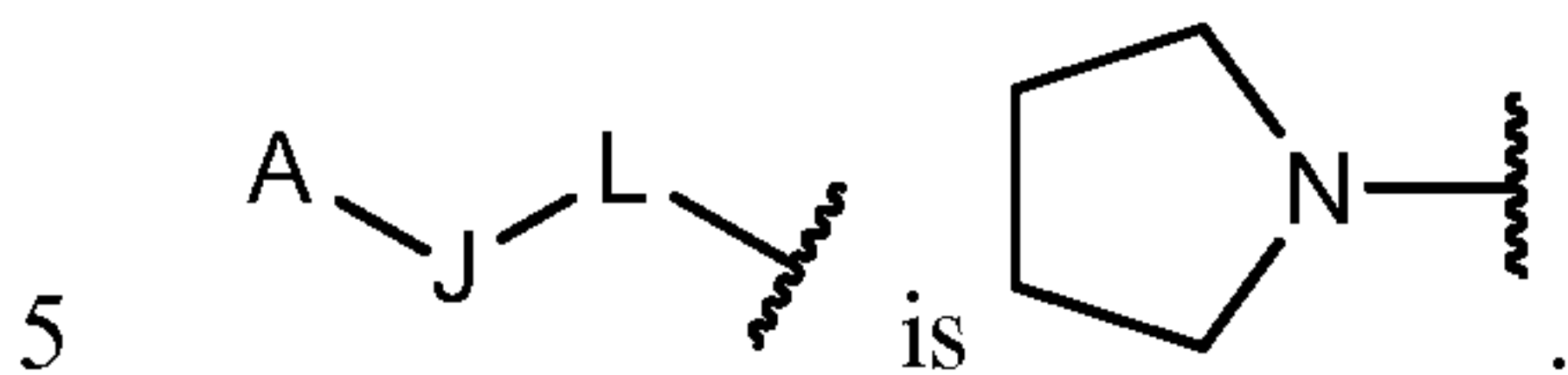
25. The compound according to any one of claim 1 to claim 24, wherein R³ is selected from the group consisting of -CH=CH-(bond to R²) and -CH-CH-(bond to R²).

26. The compound according to any one of claim 1 to claim 25, wherein A is

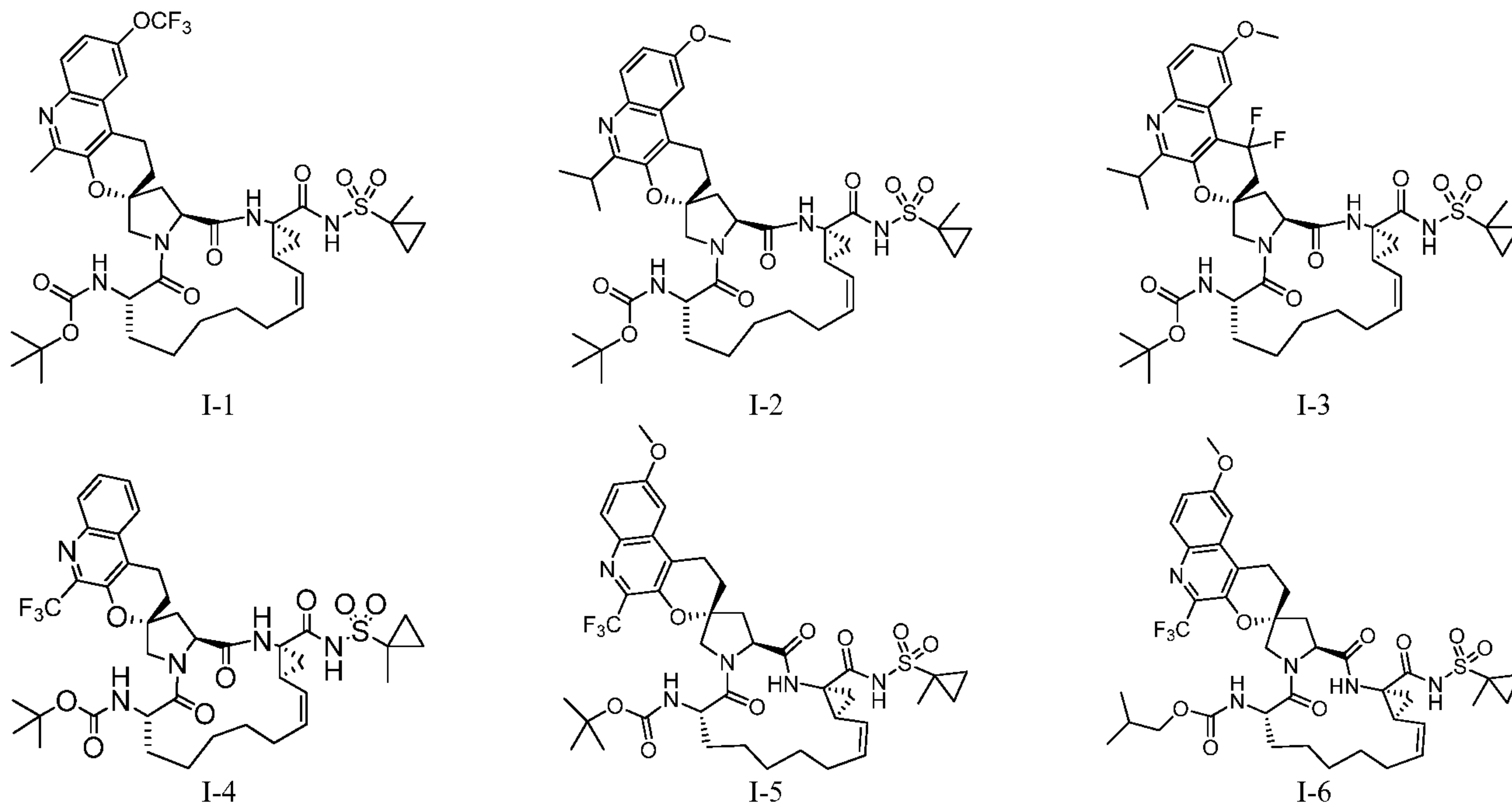


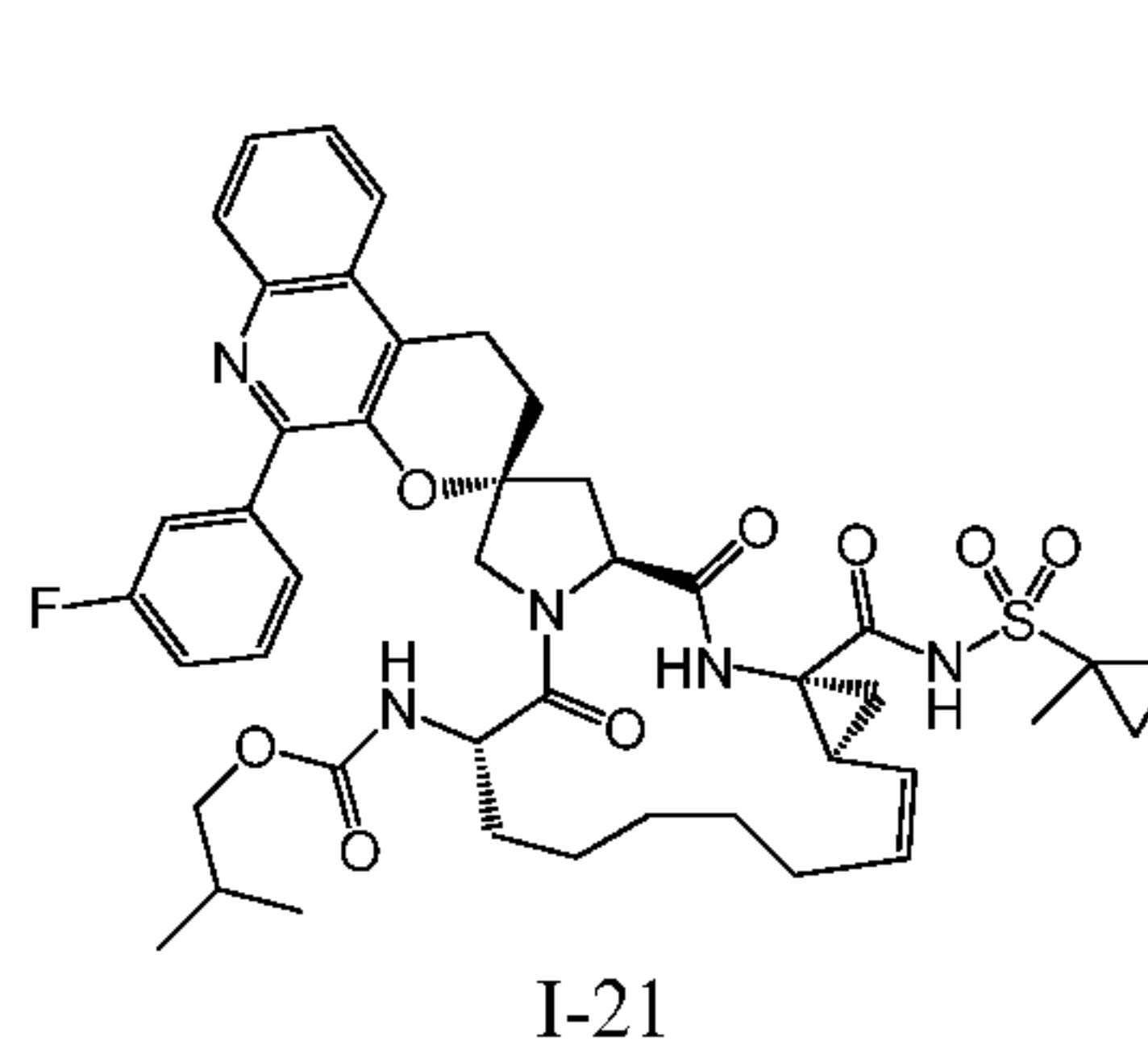
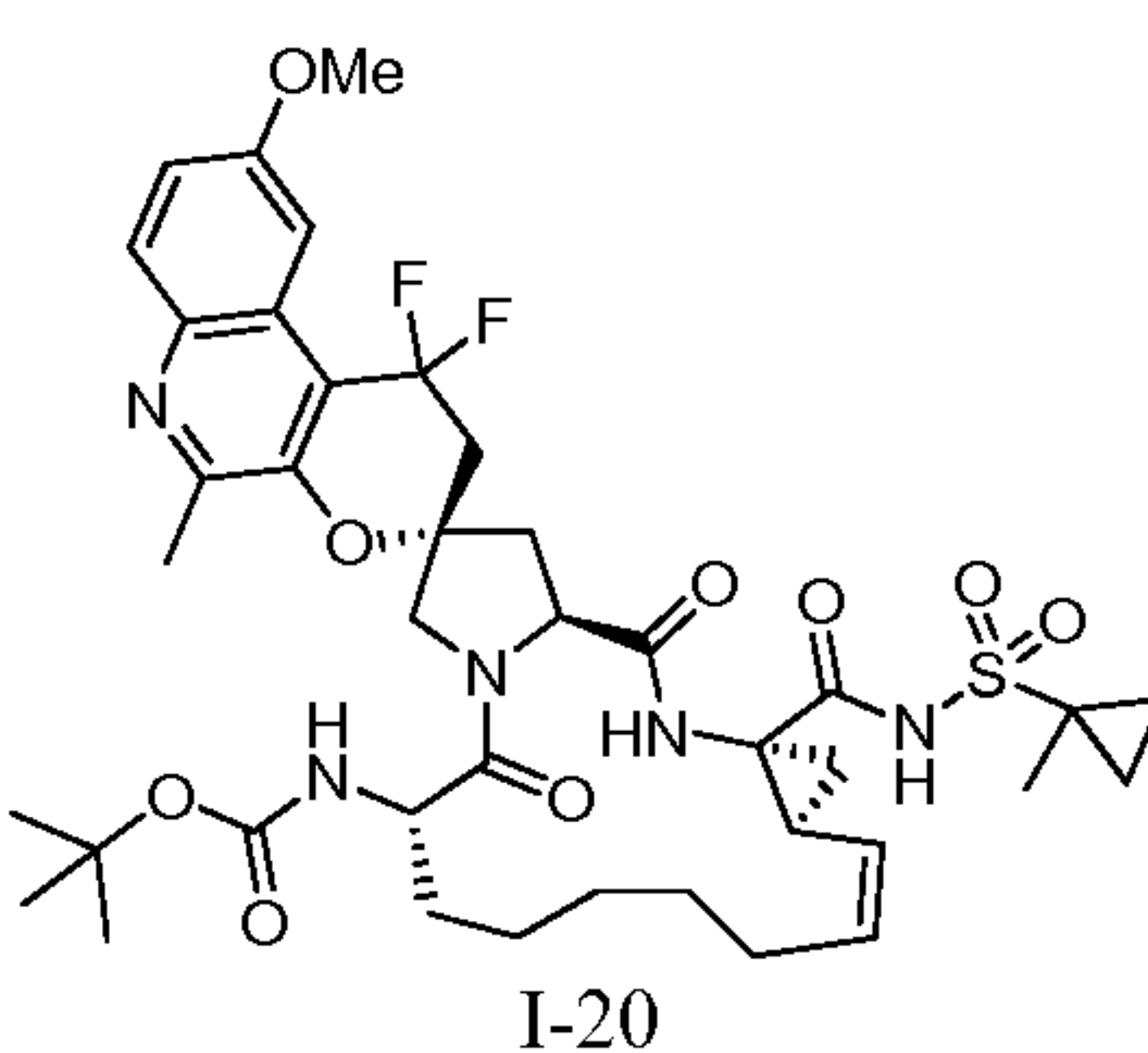
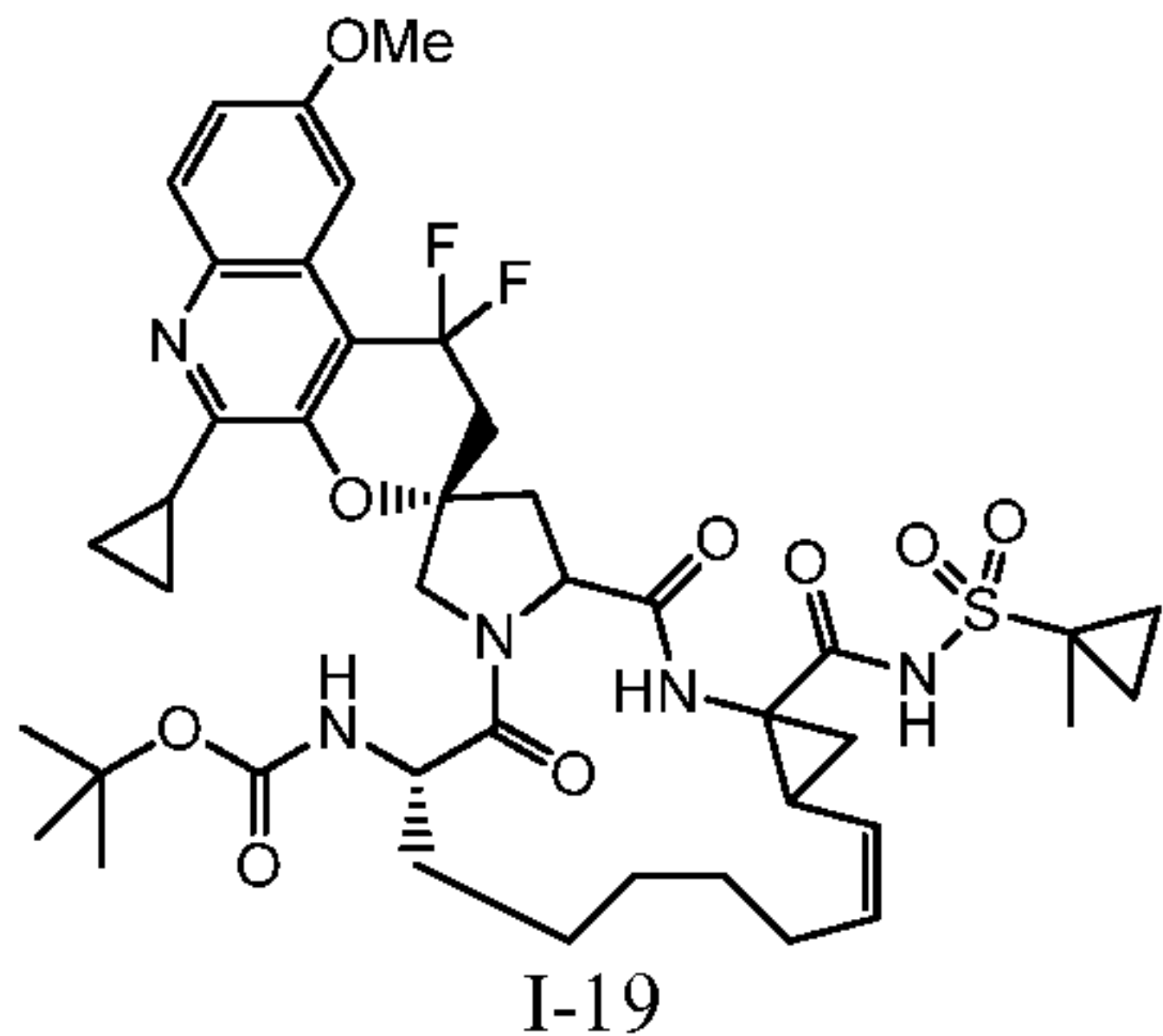
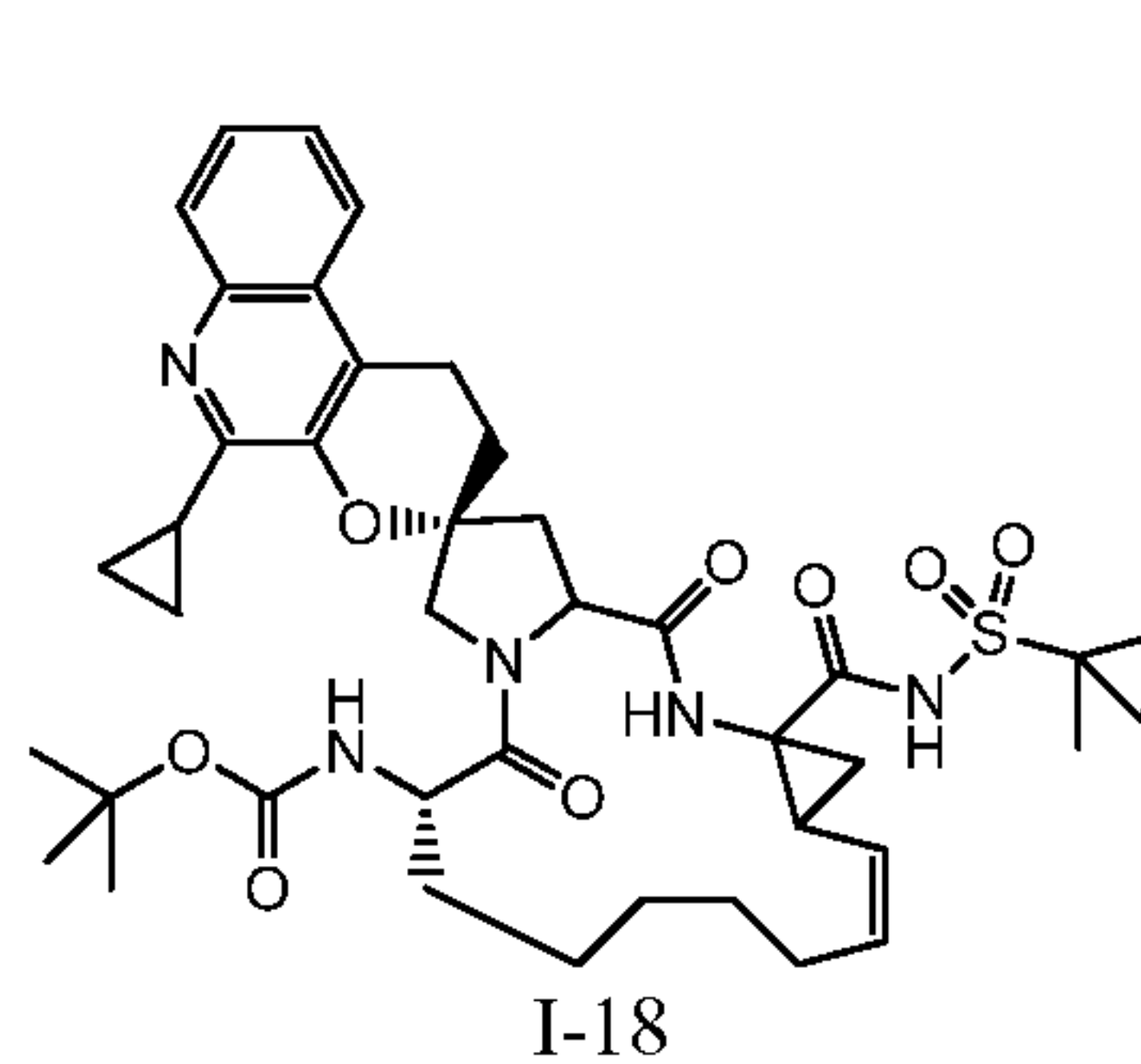
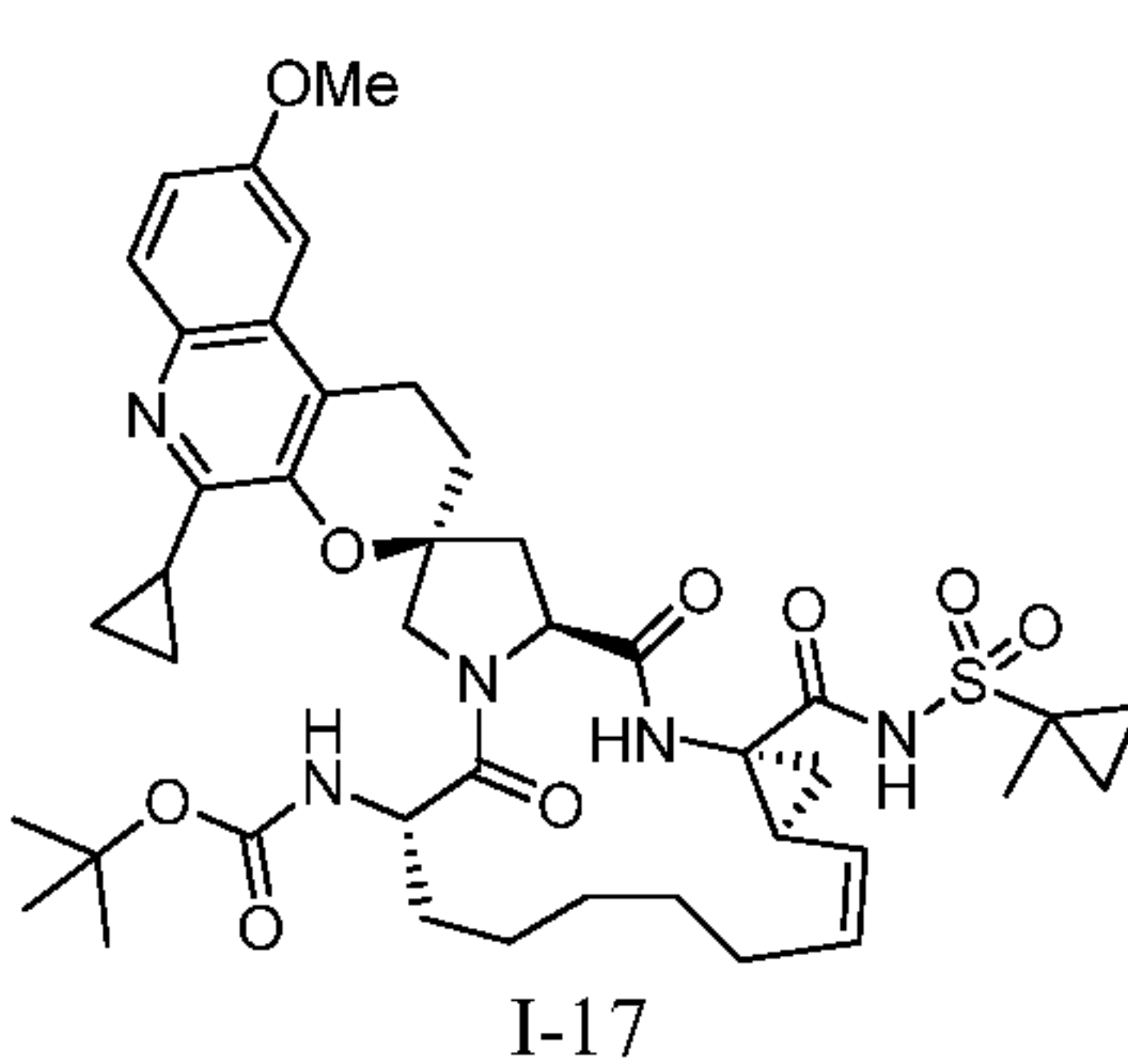
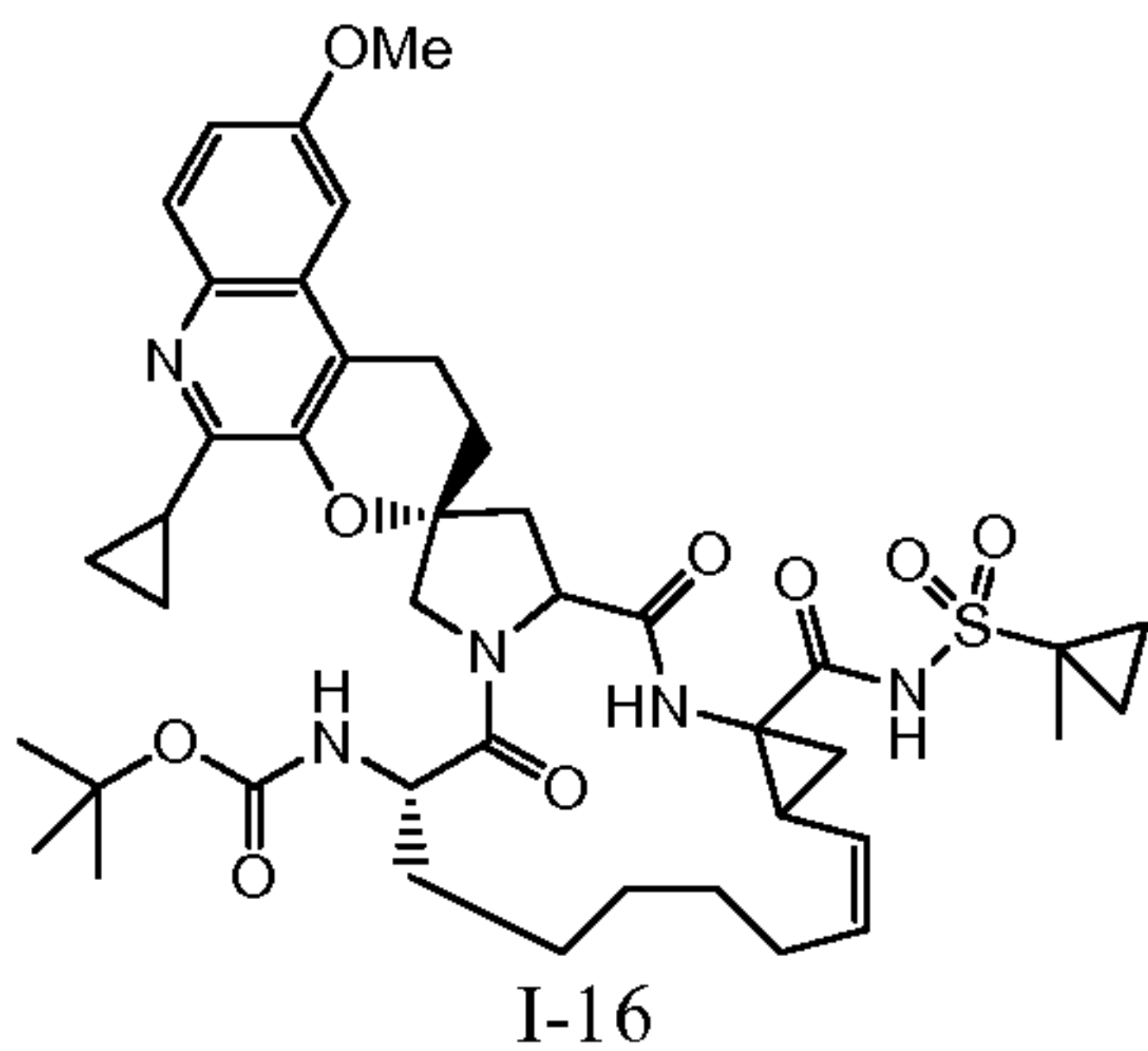
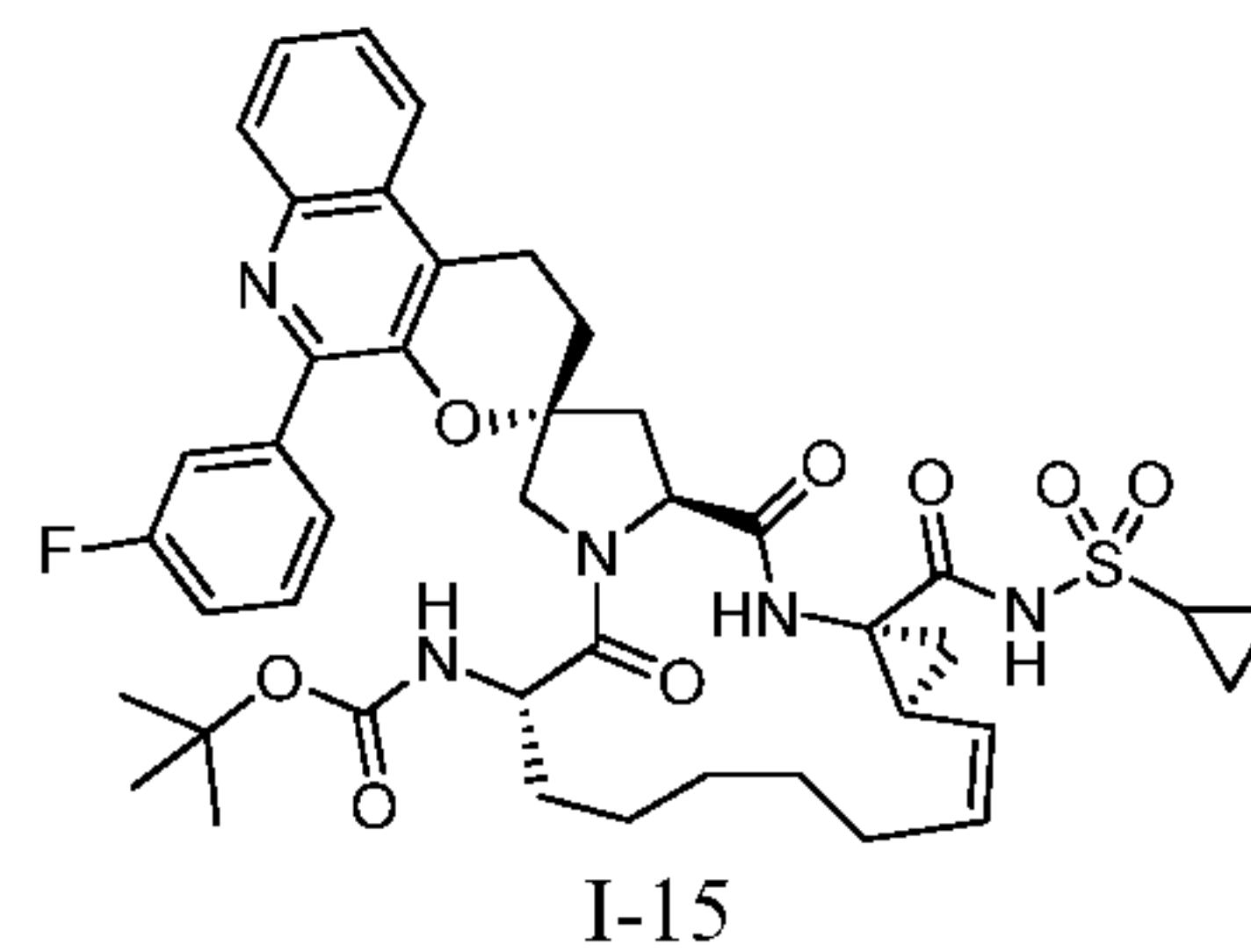
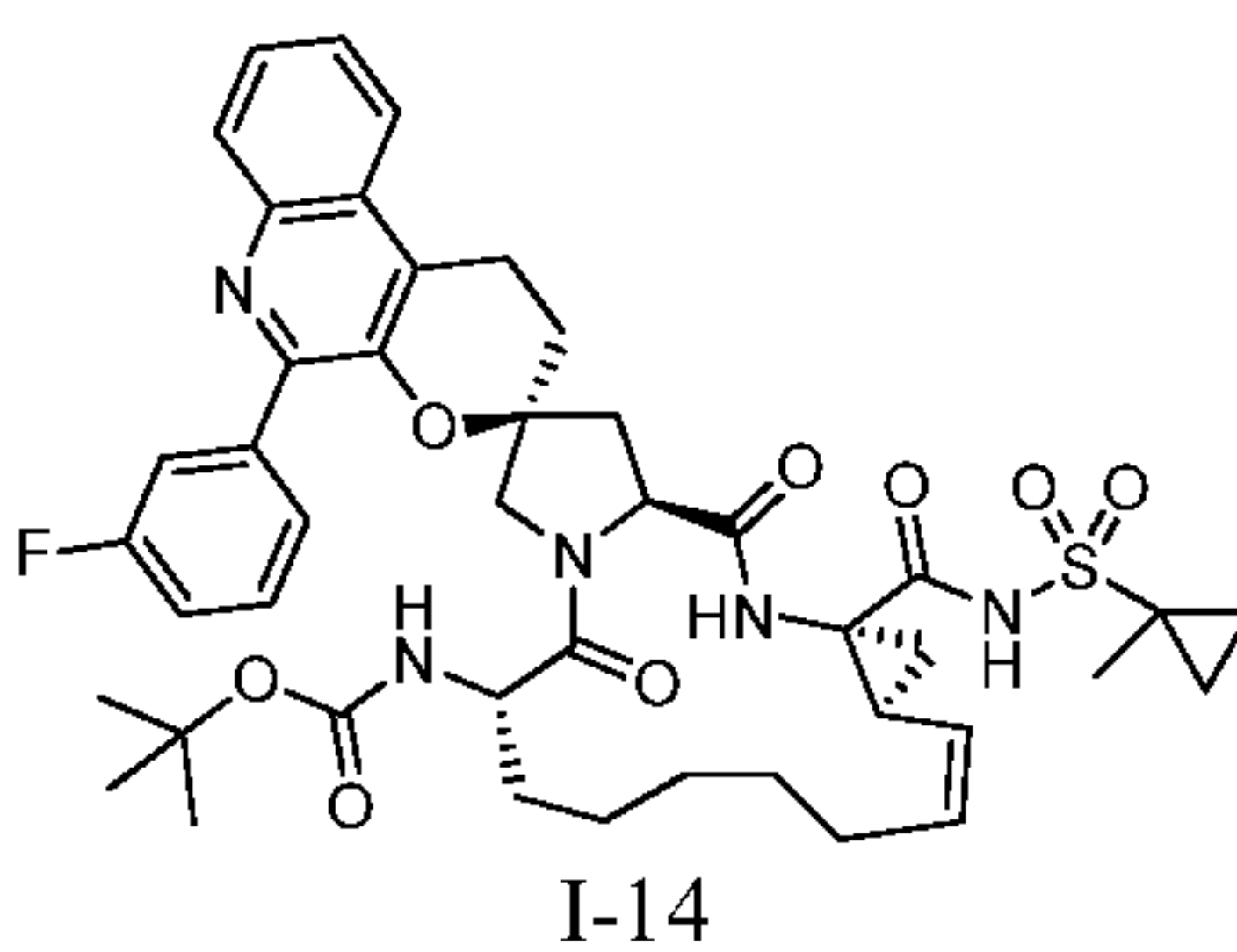
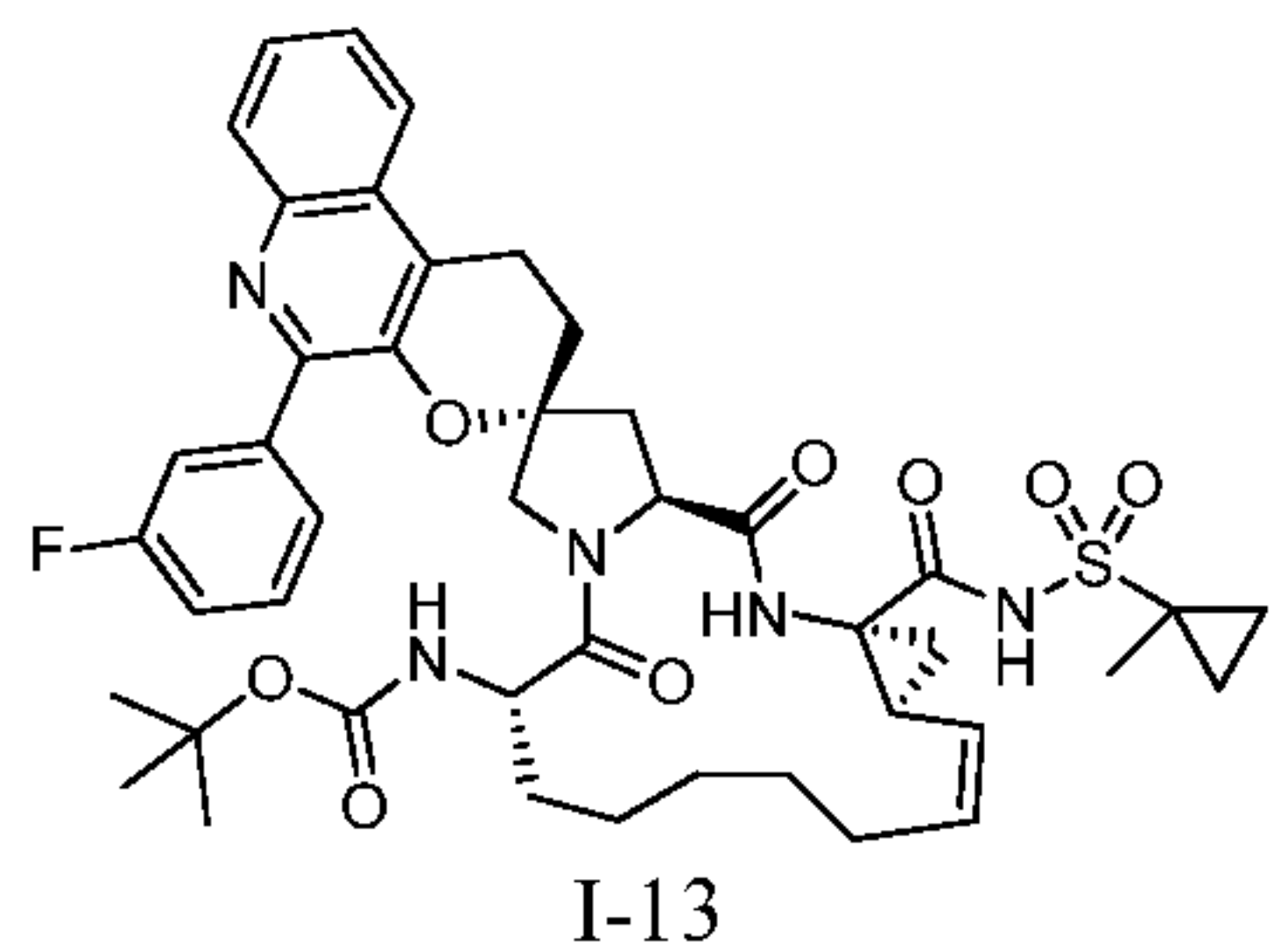
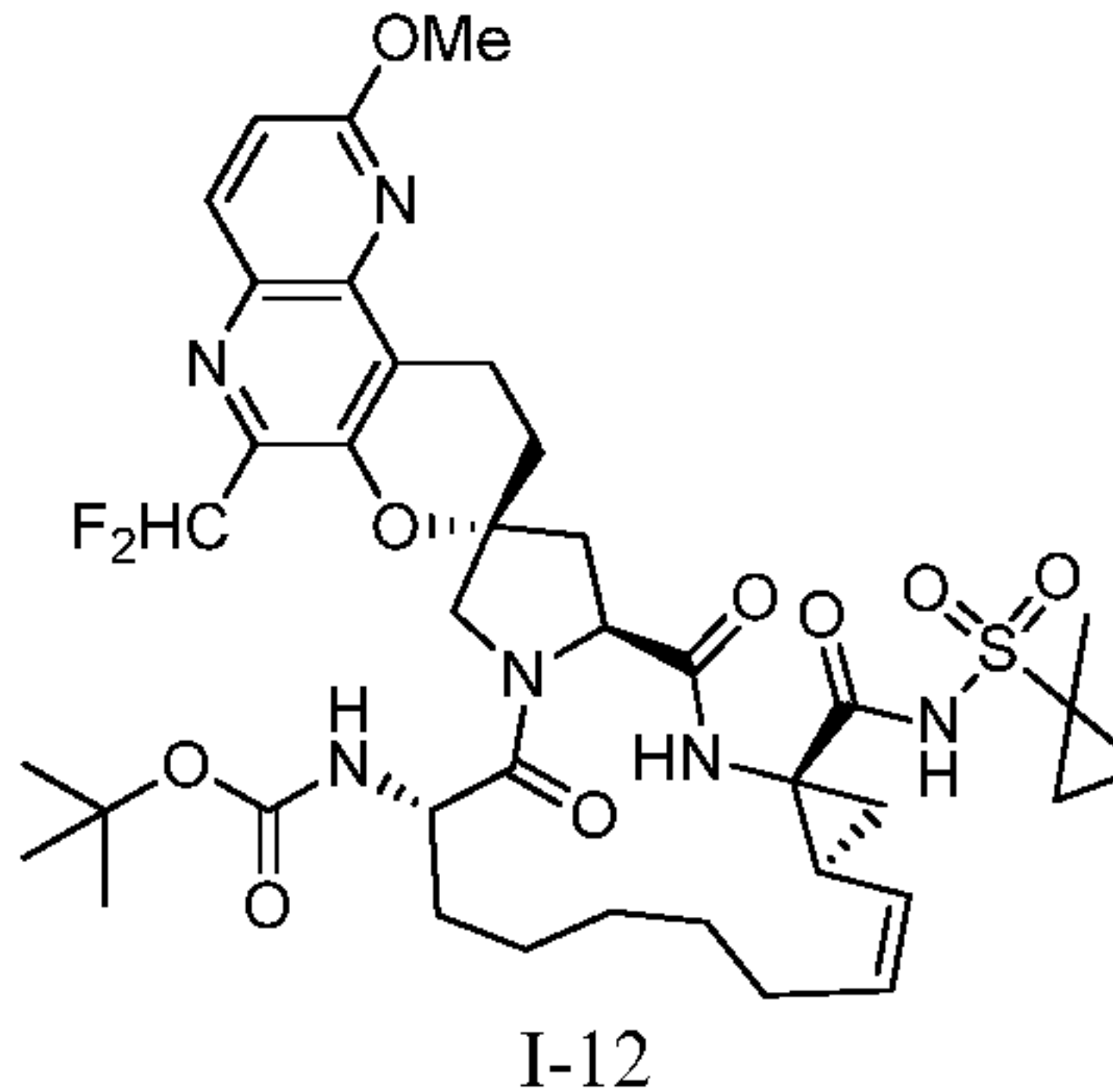
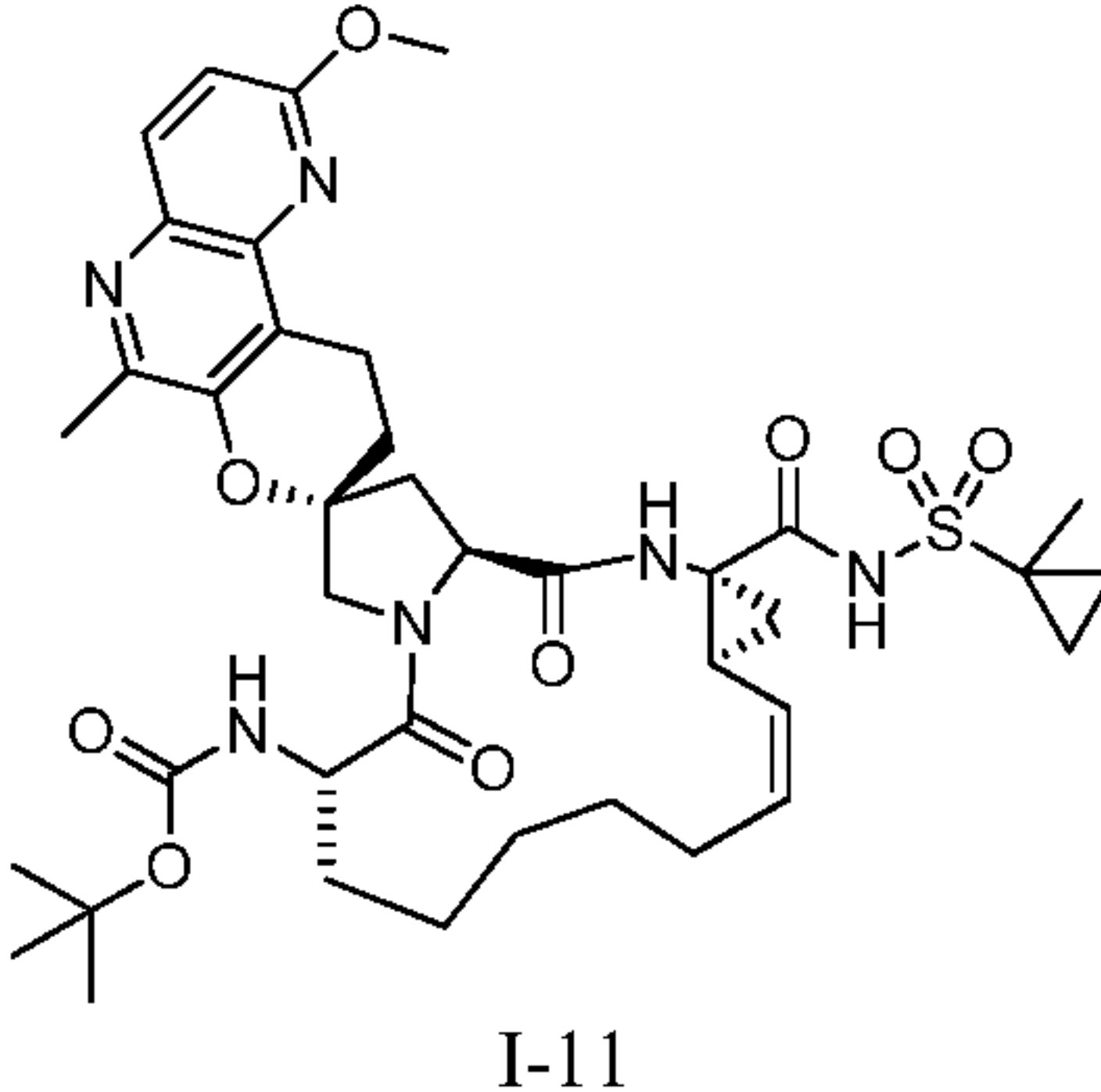
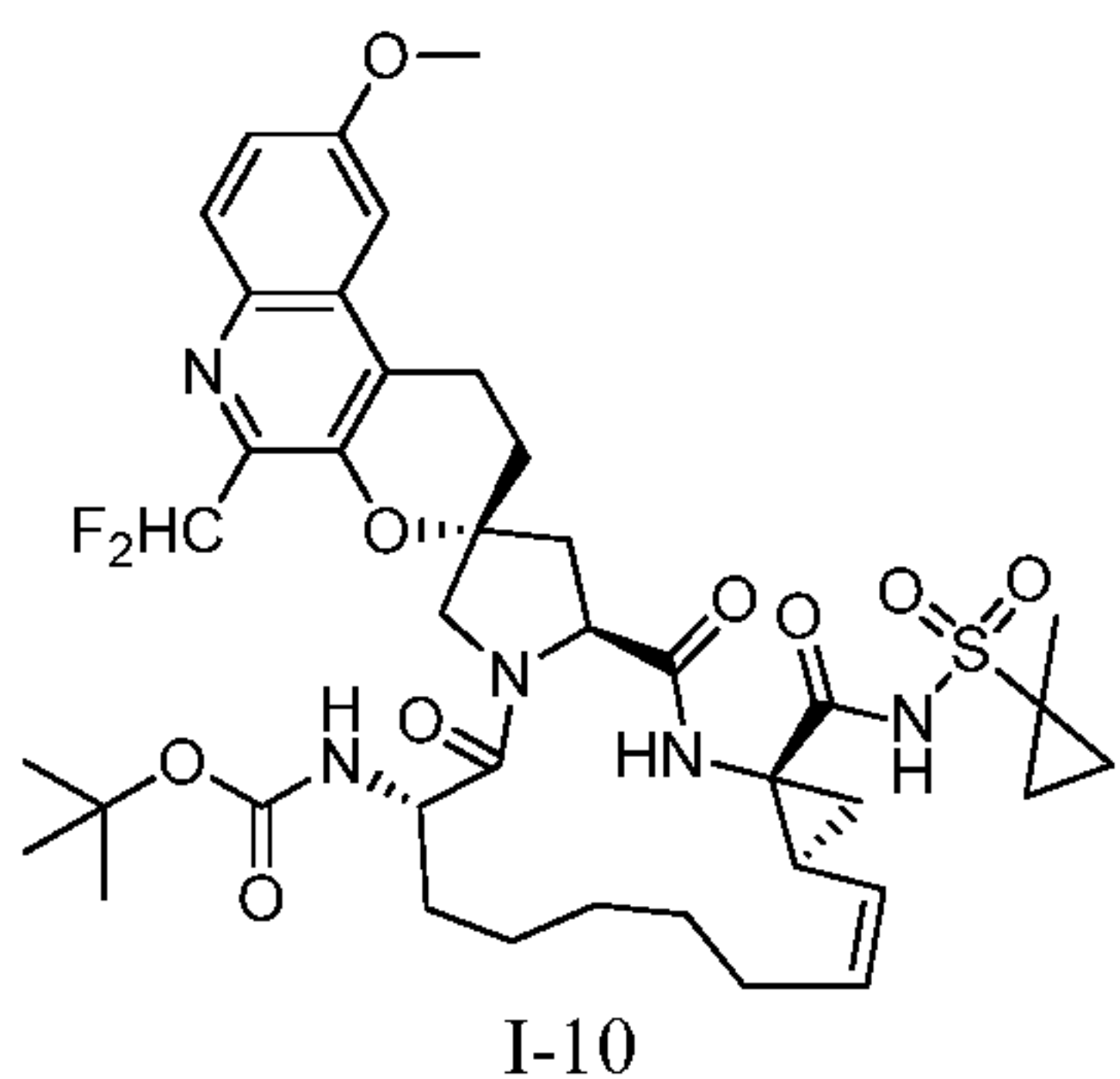
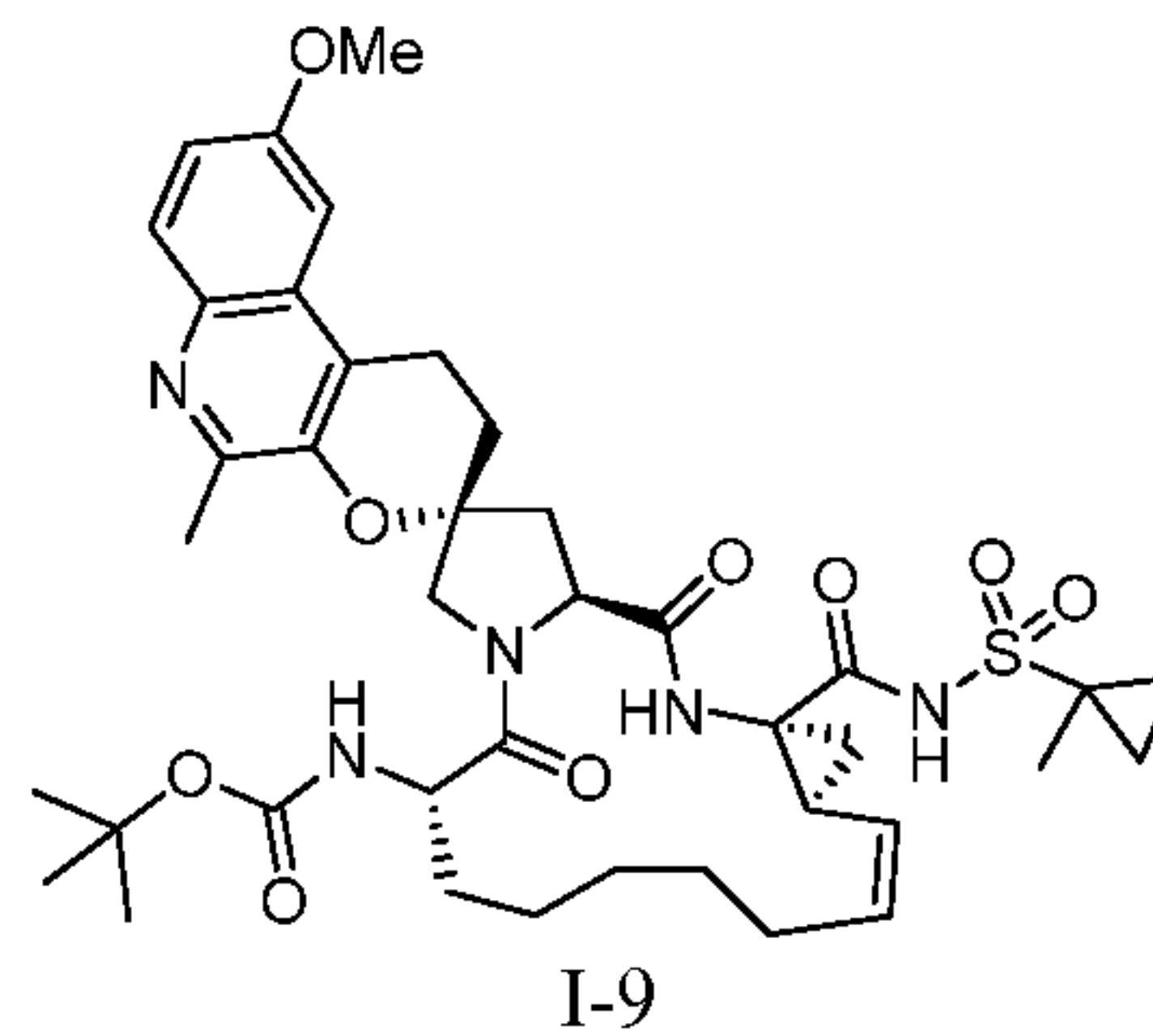
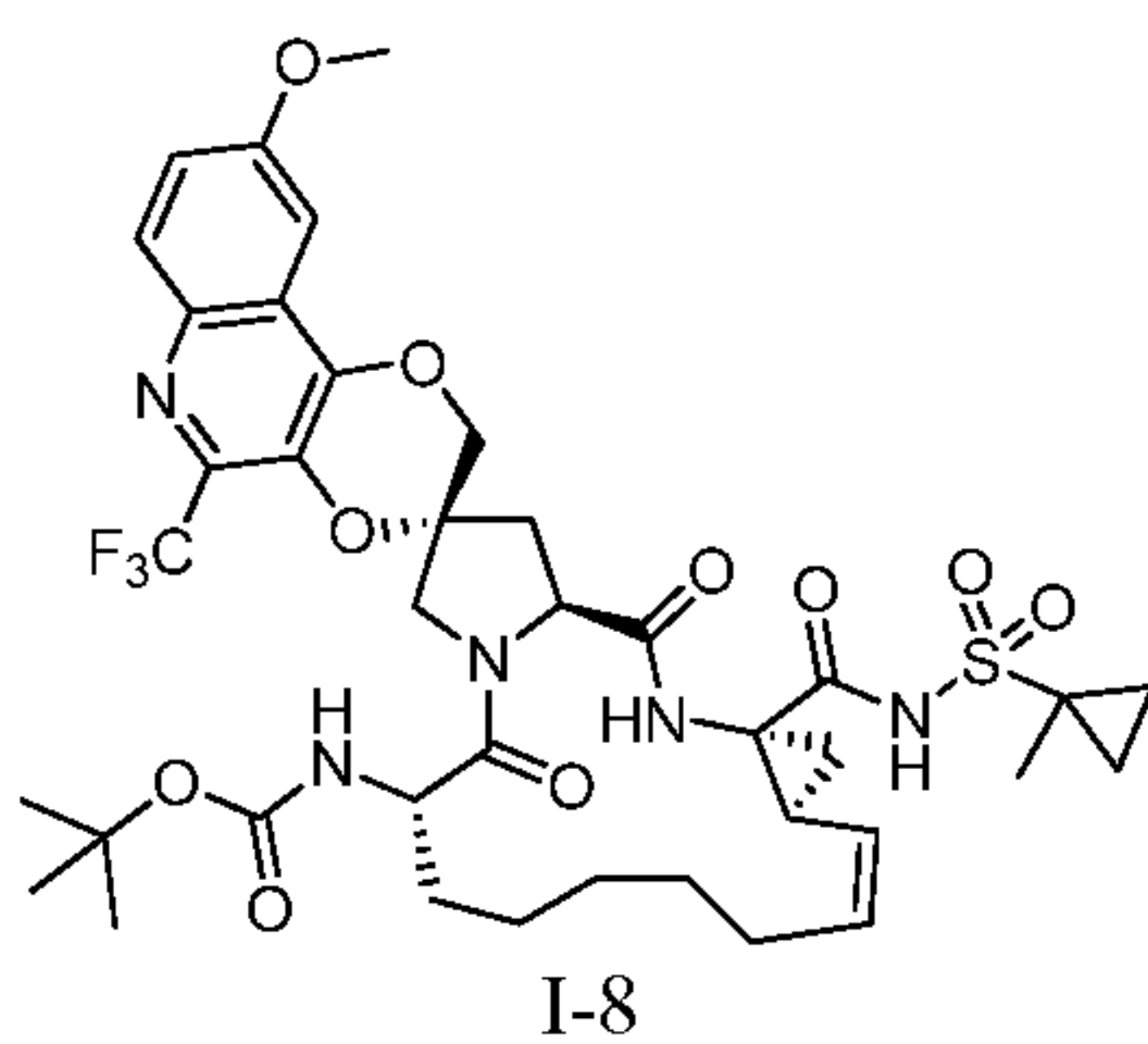
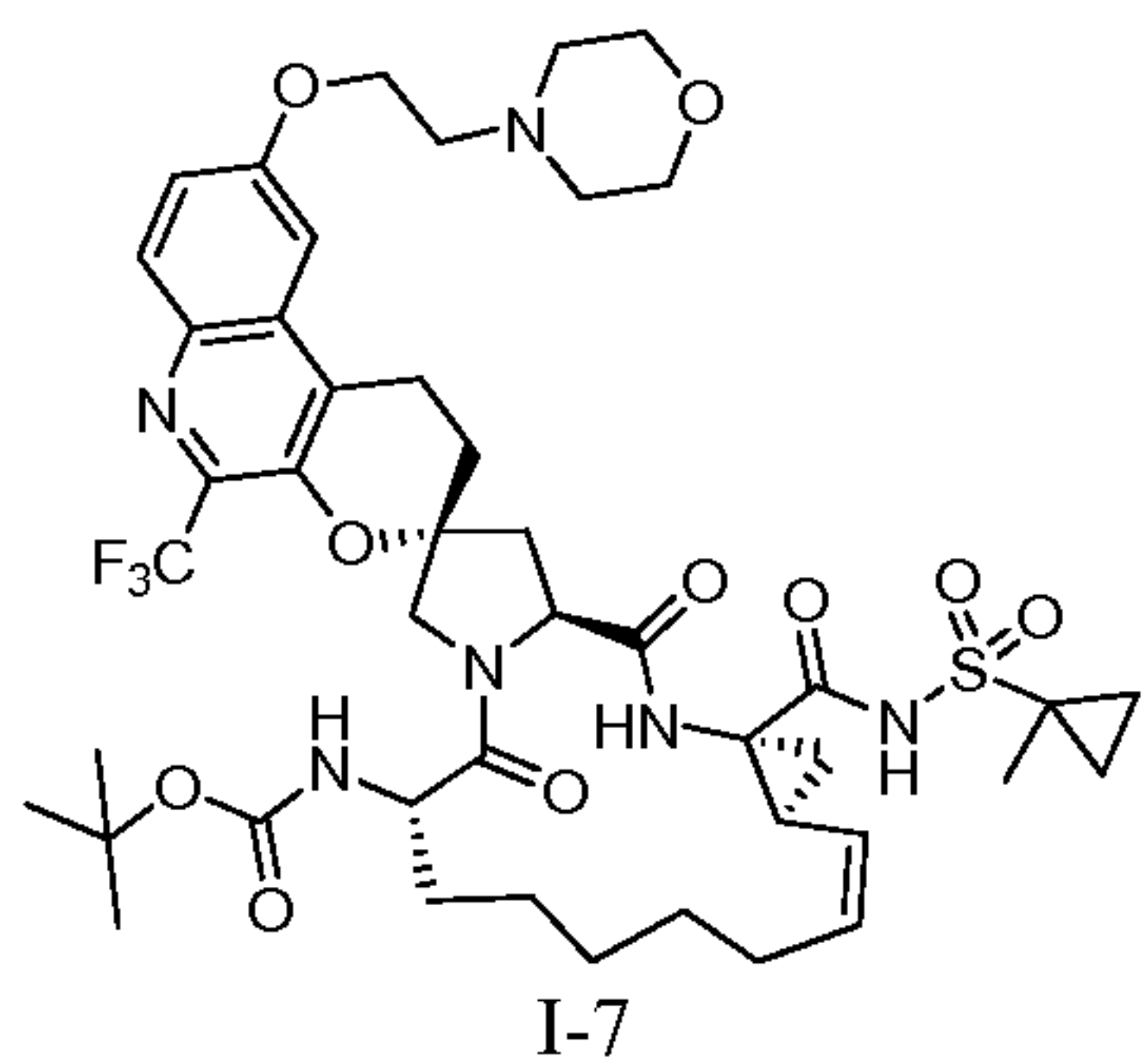


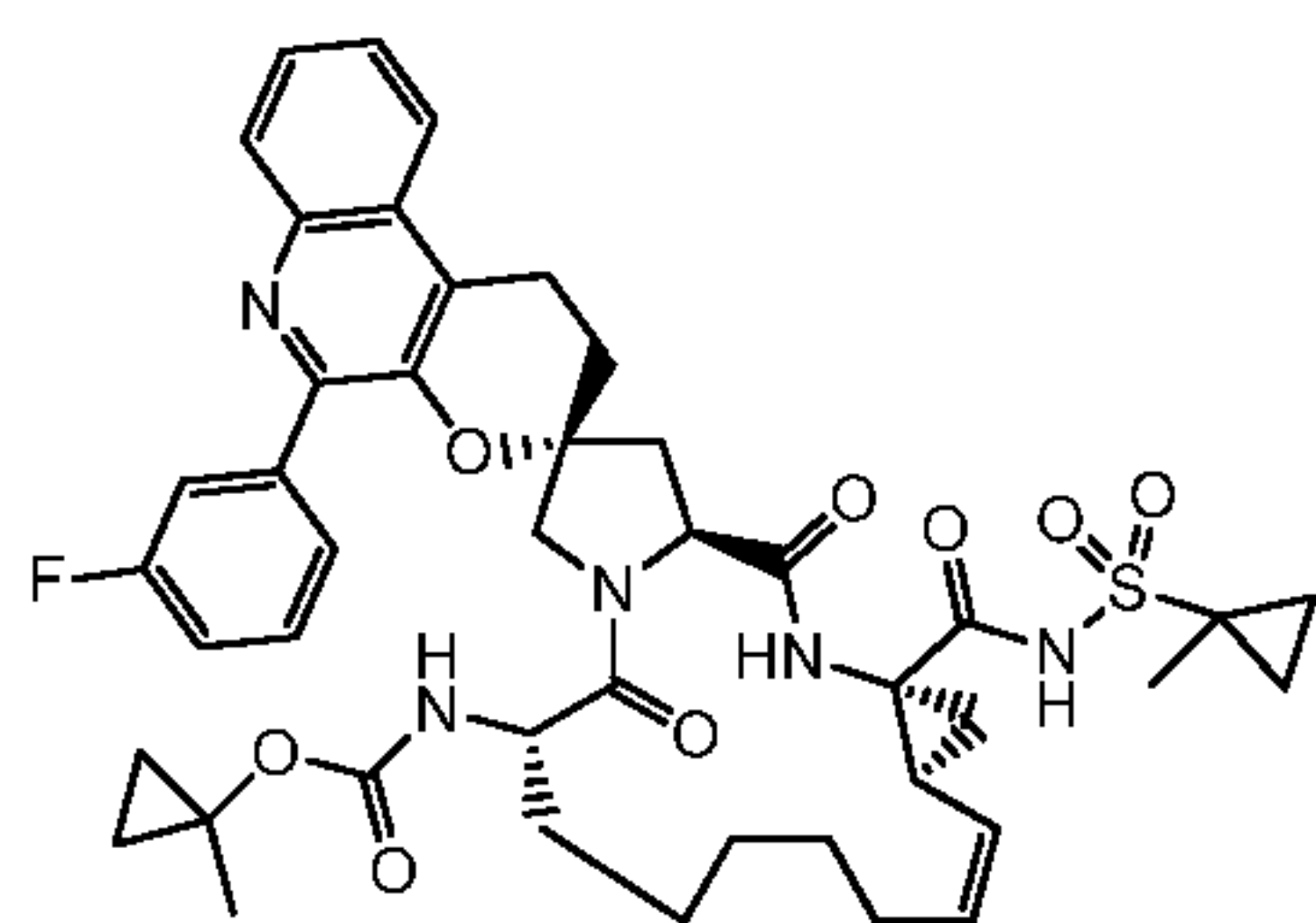
27. The compound according to any one of claim 1 to claim 26, wherein



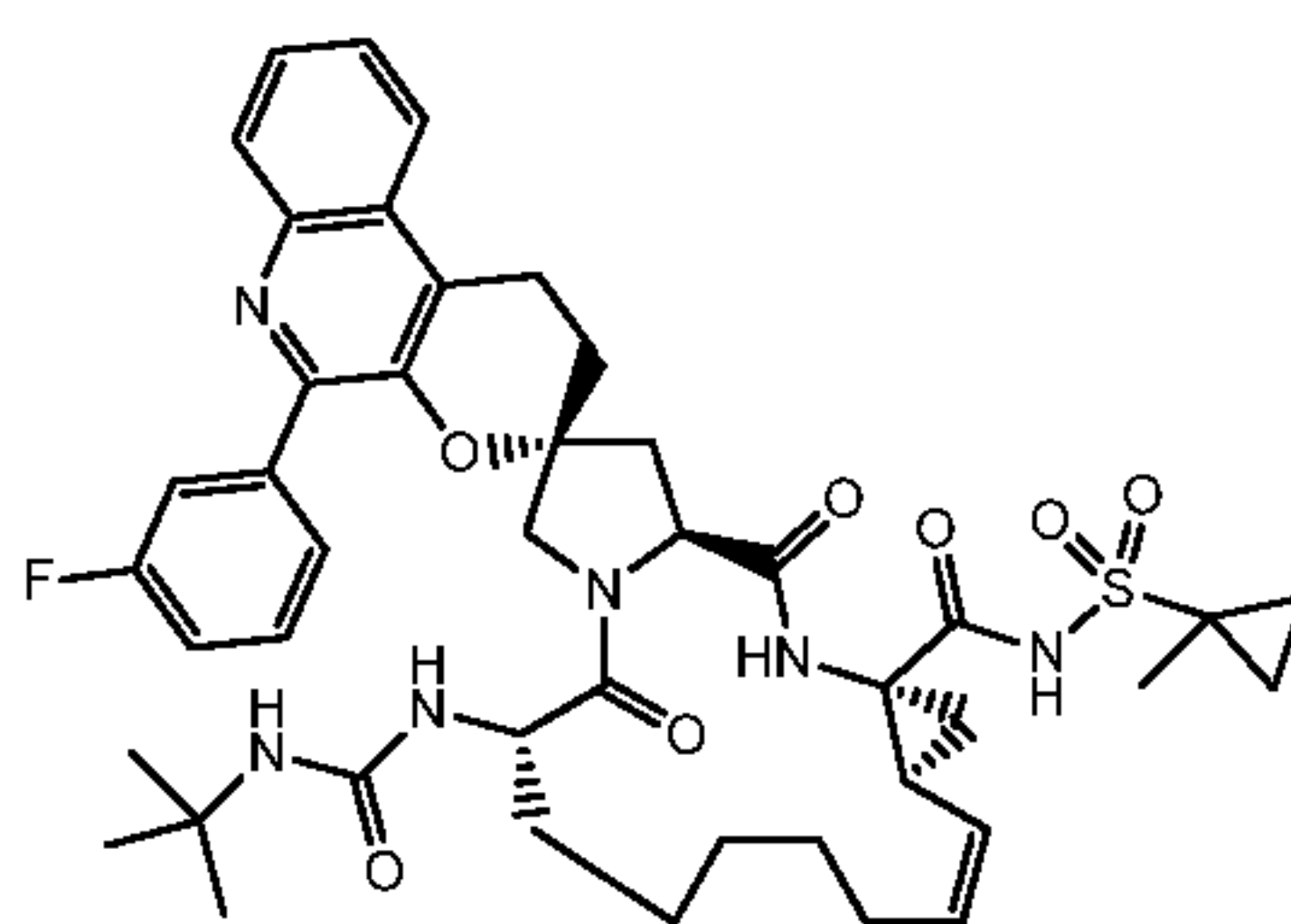
28. The compound according to claim 1, wherein the compound is selected from the group consisting of:



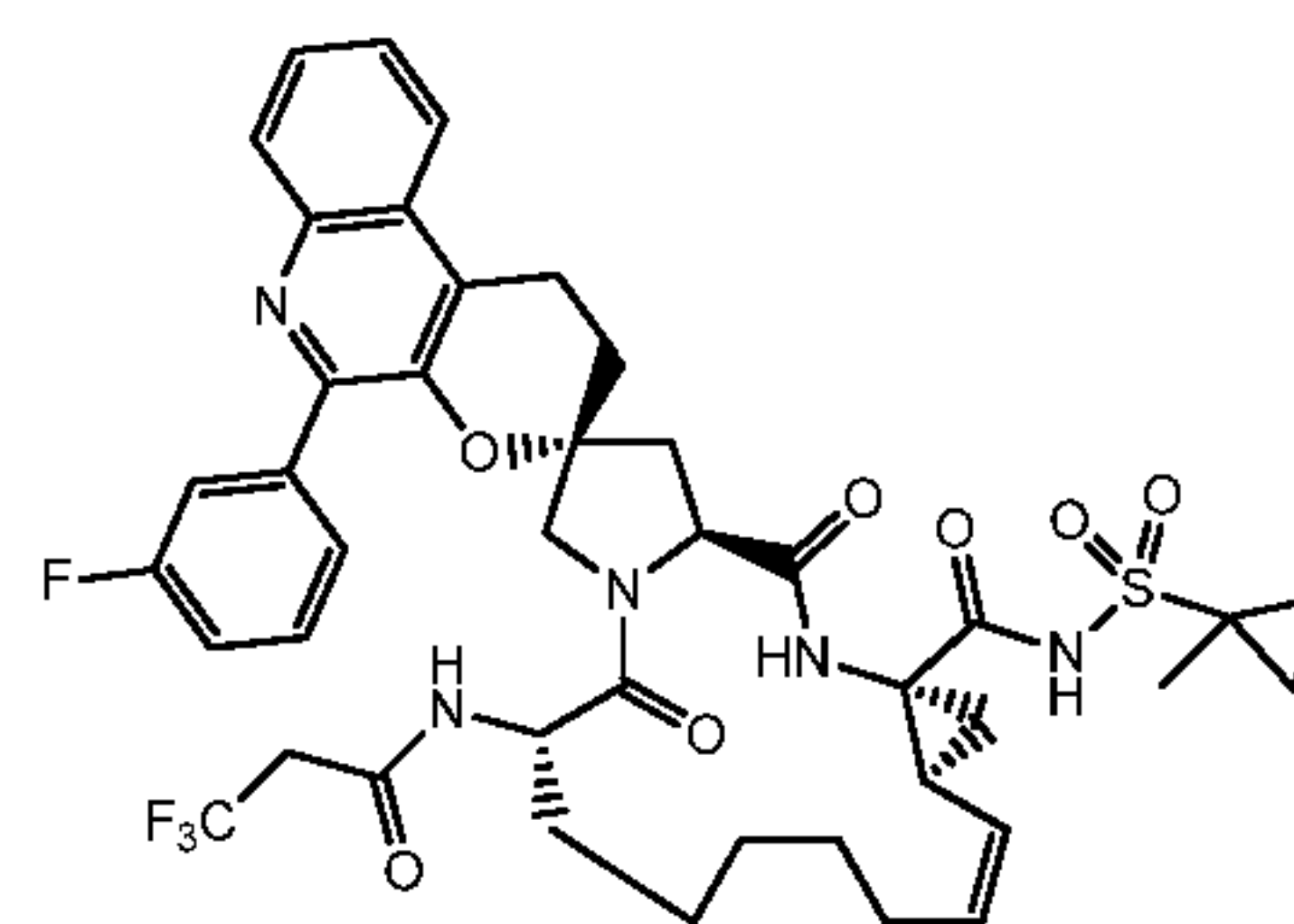




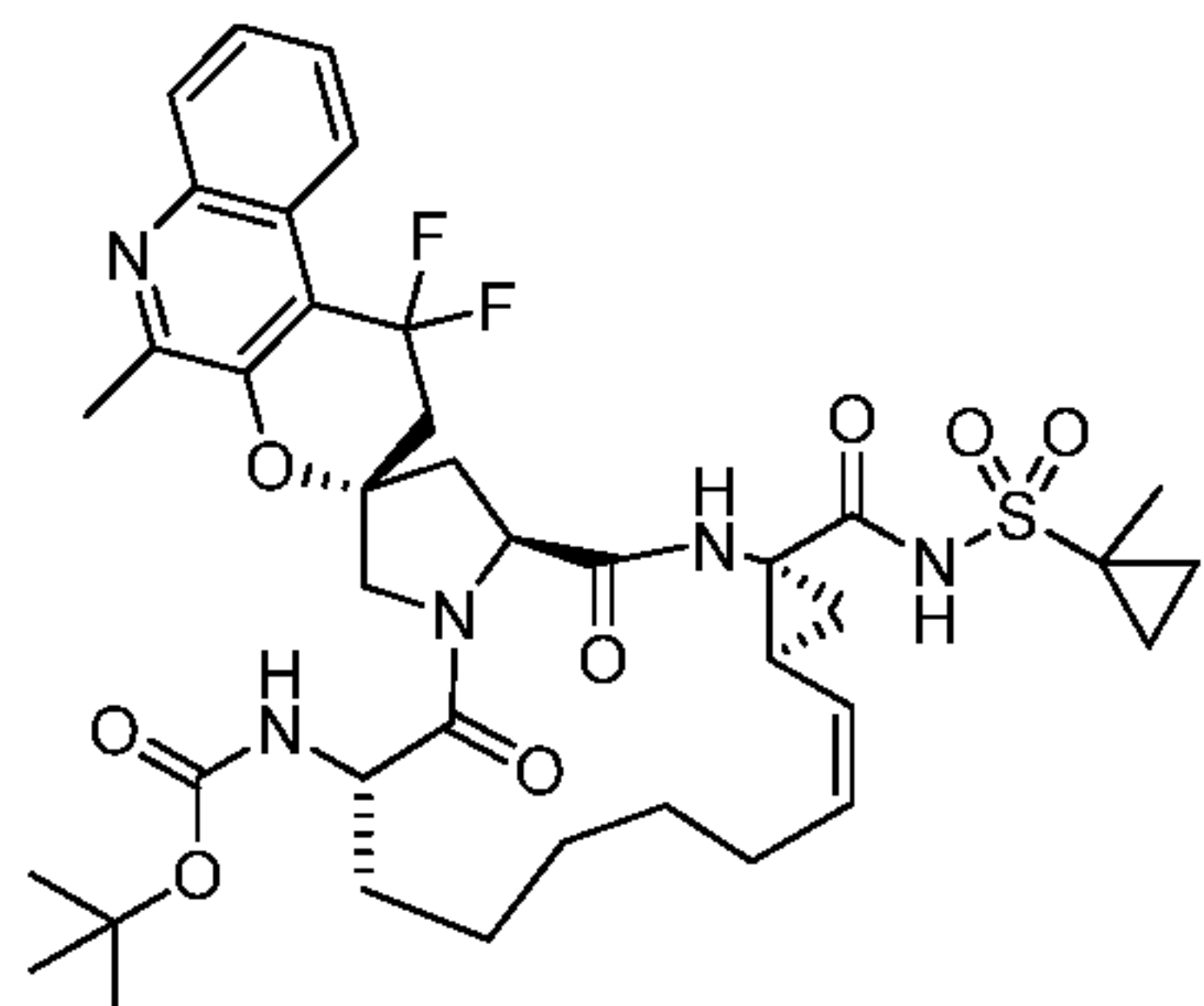
I-22



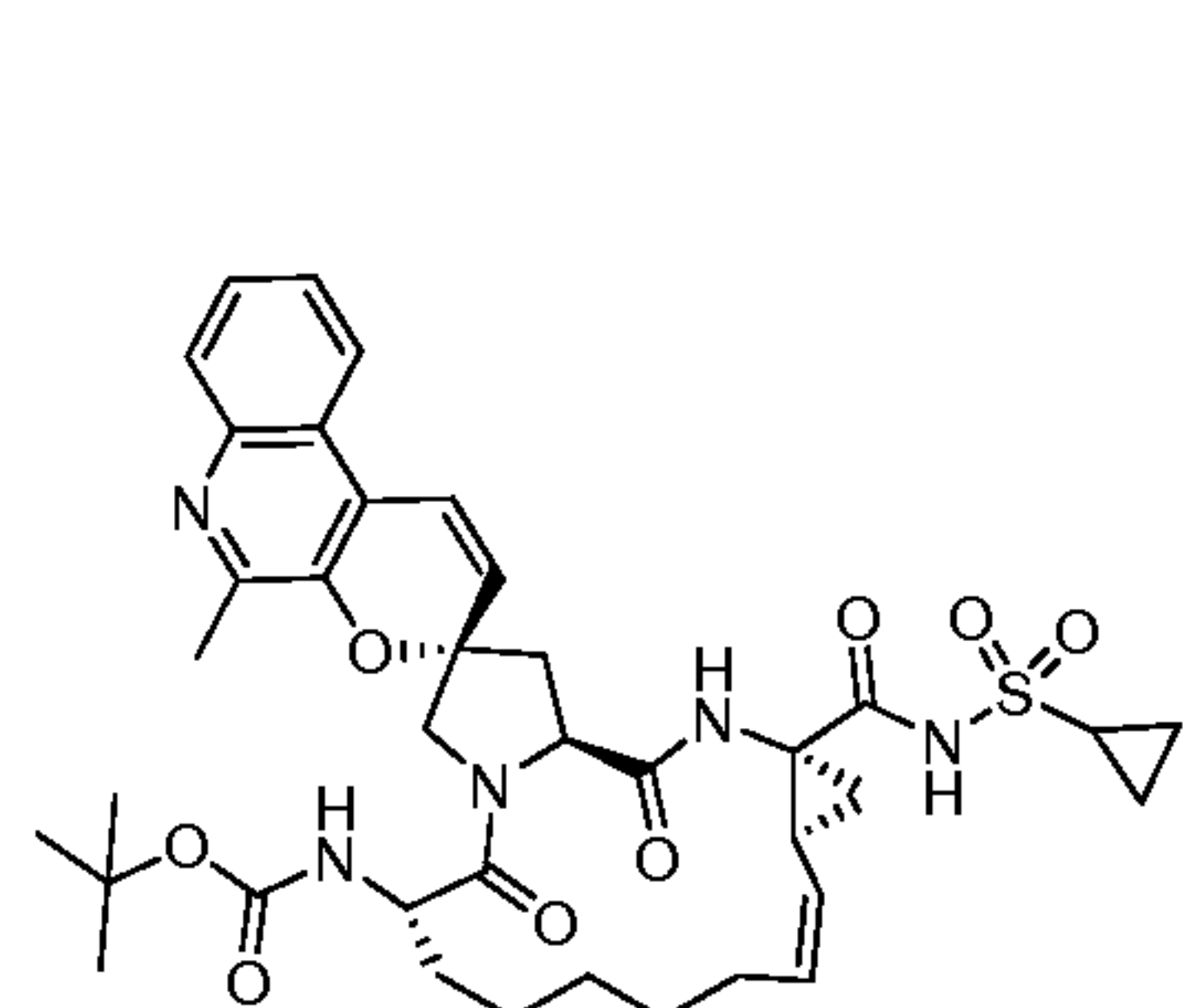
I-23



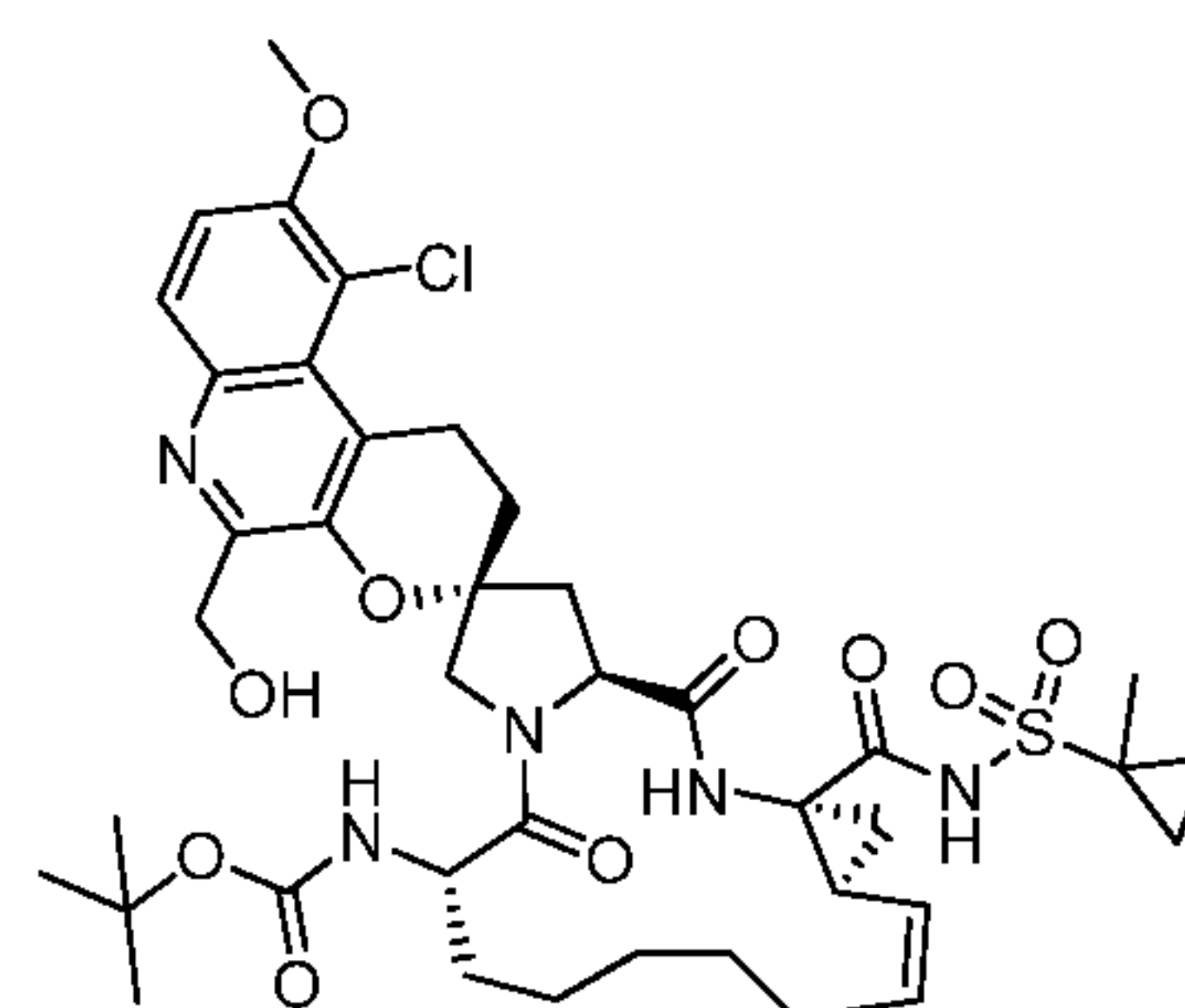
I-24



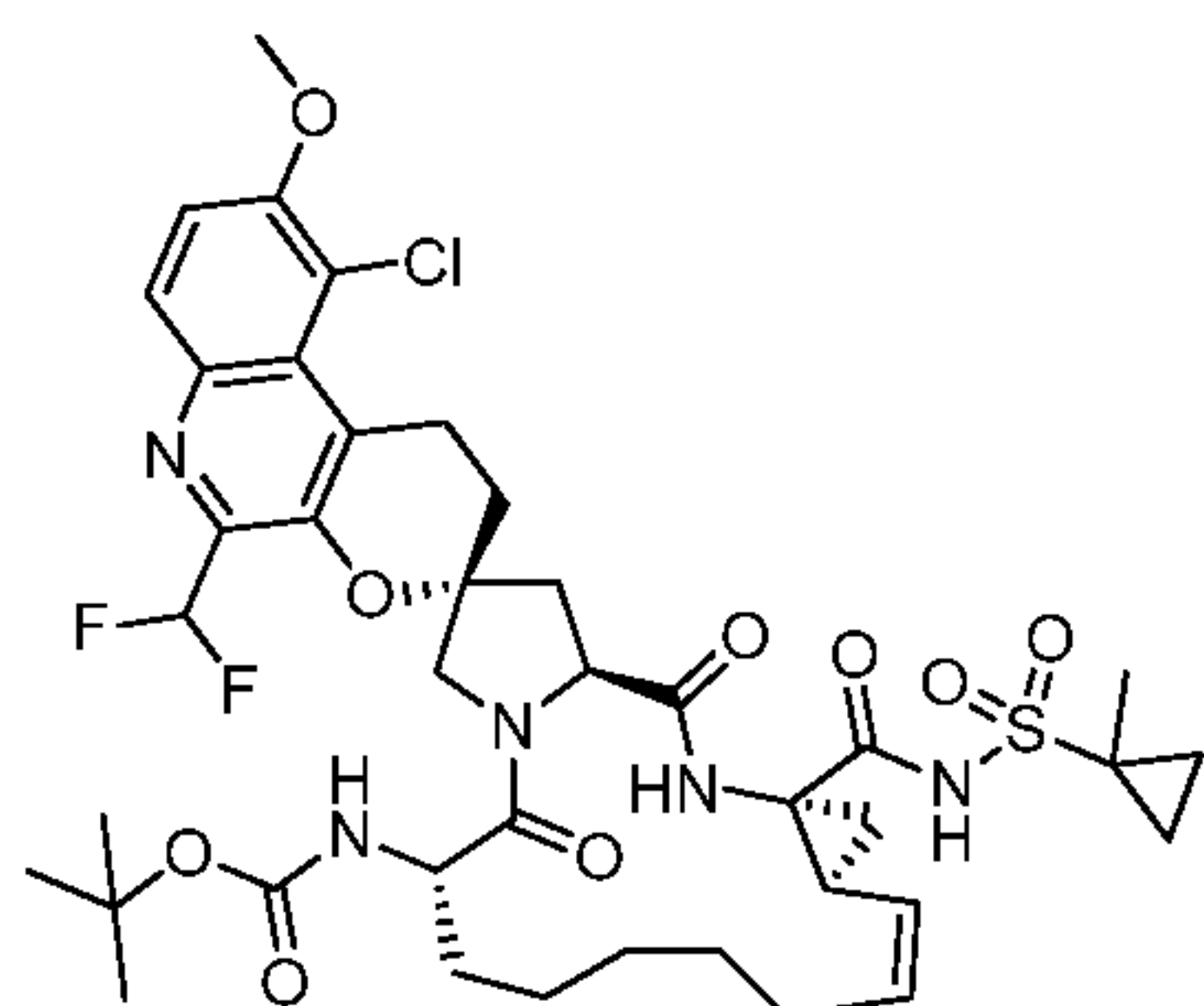
I-25



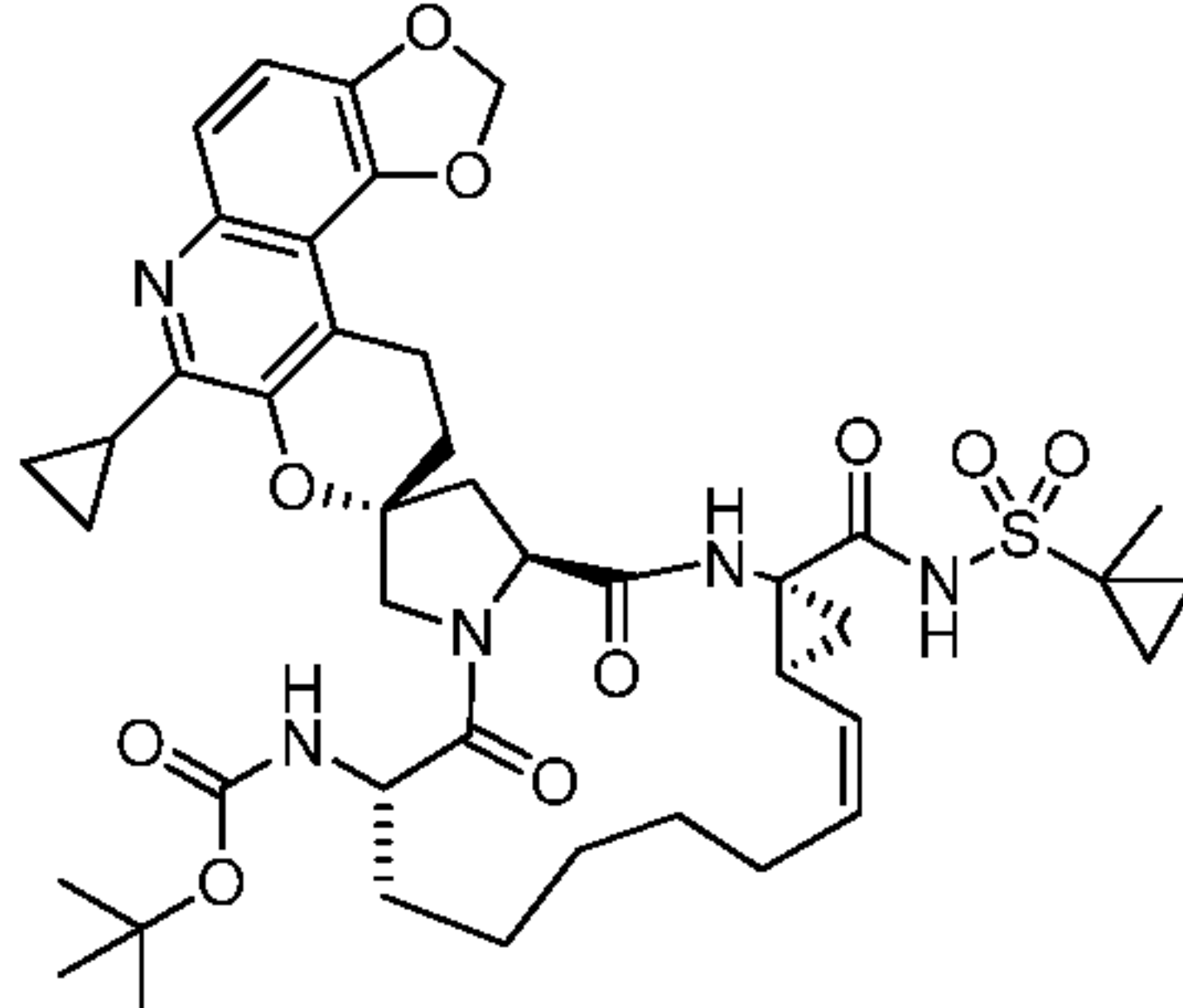
I-26



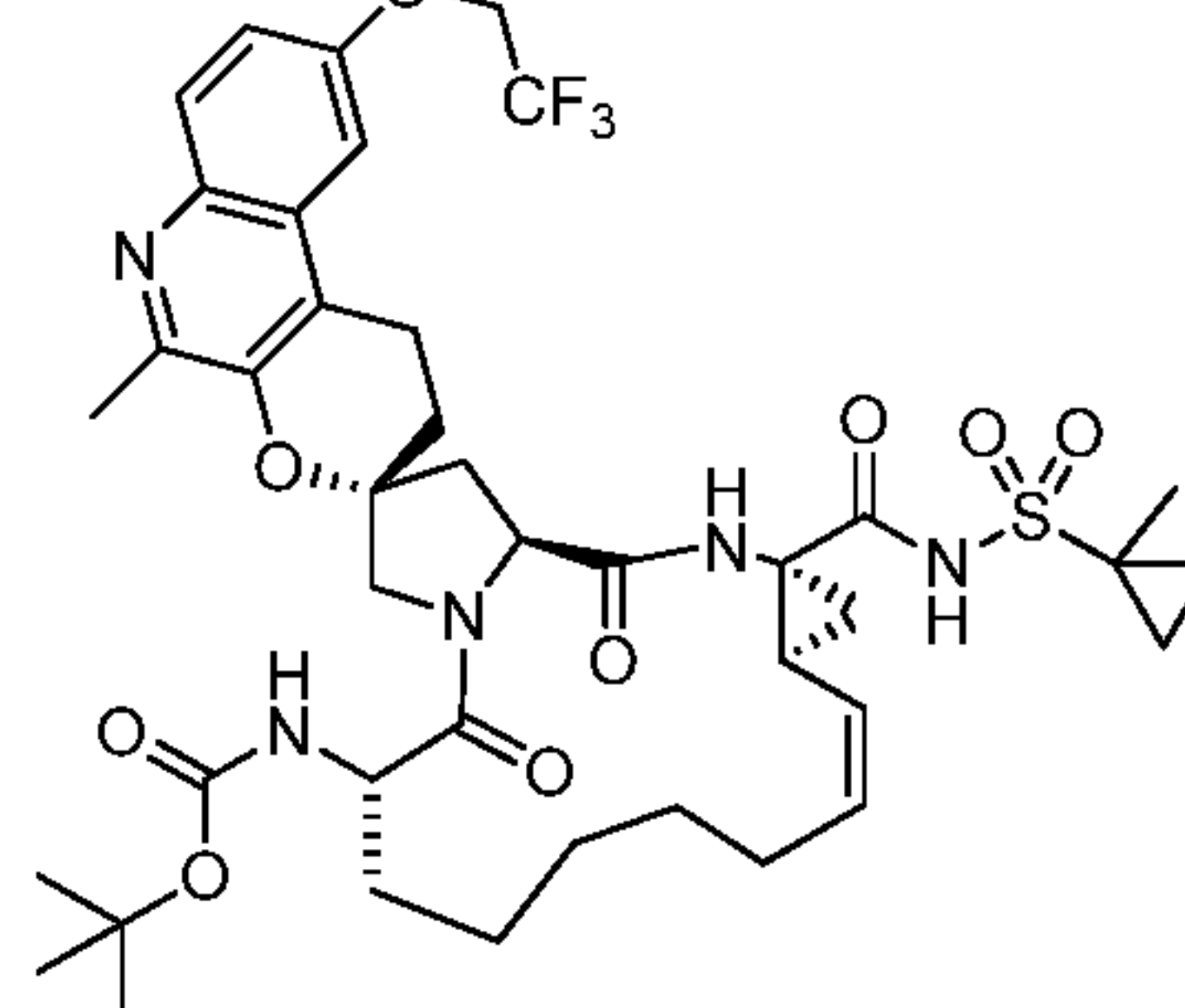
I-27



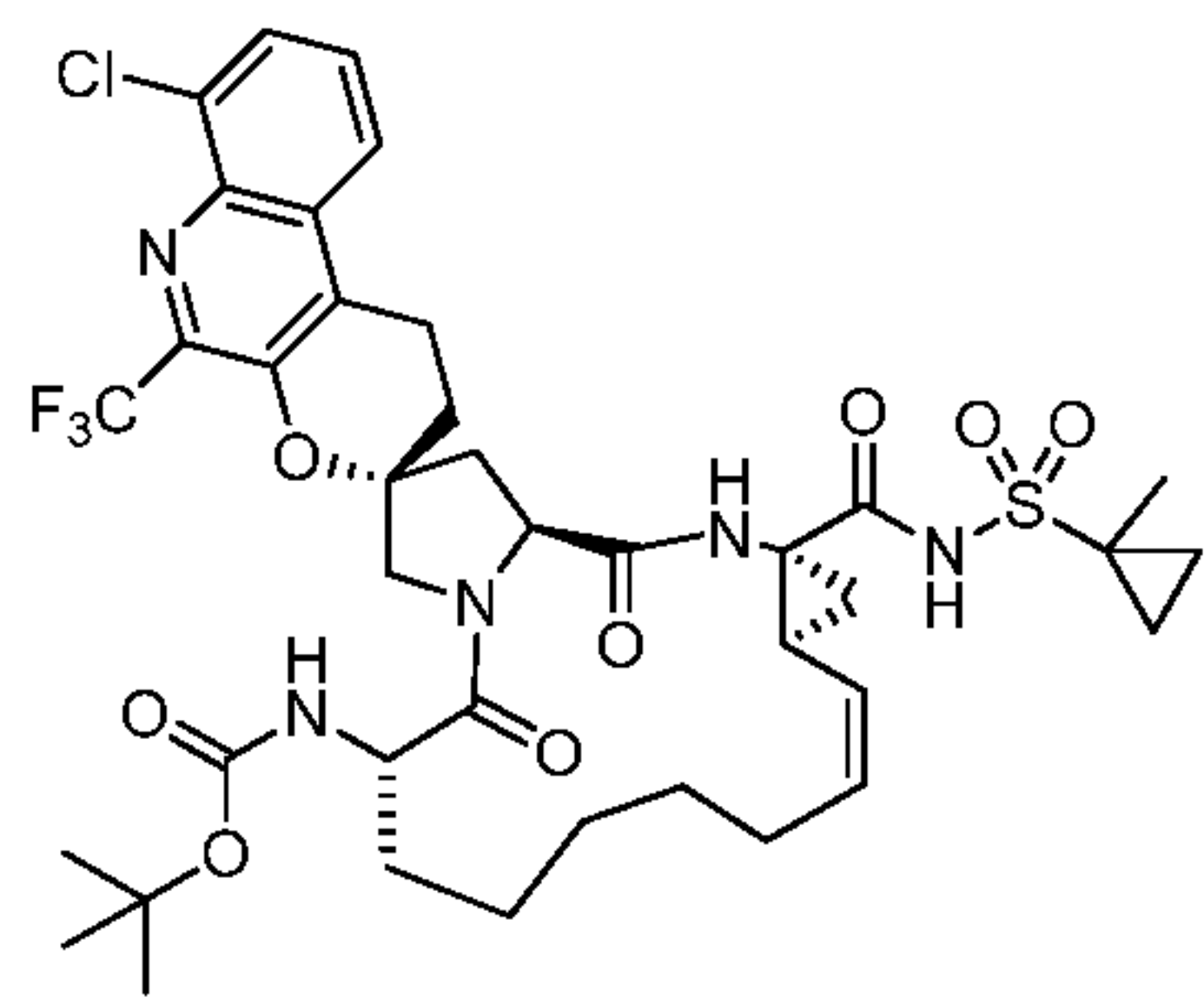
I-28



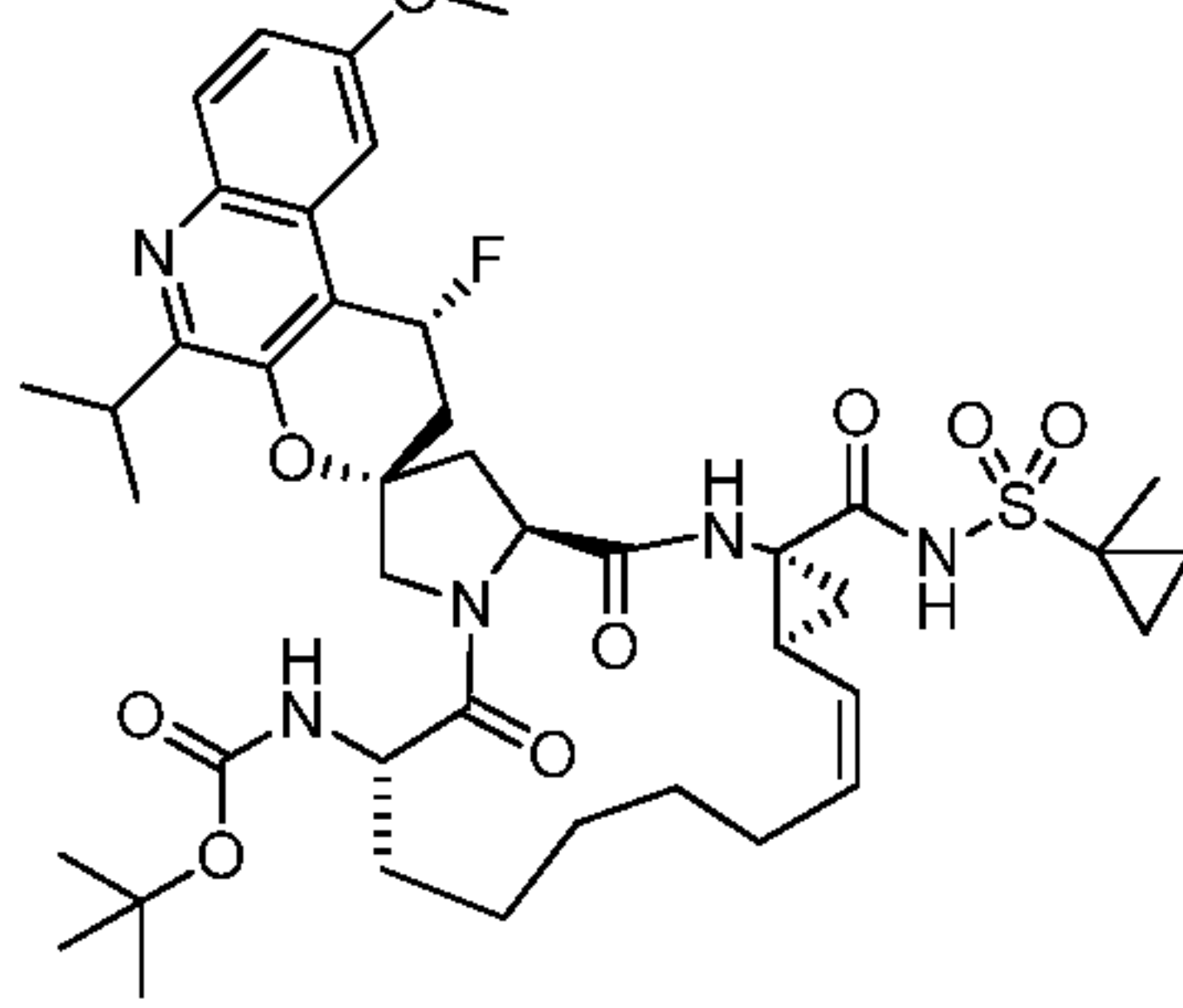
I-29



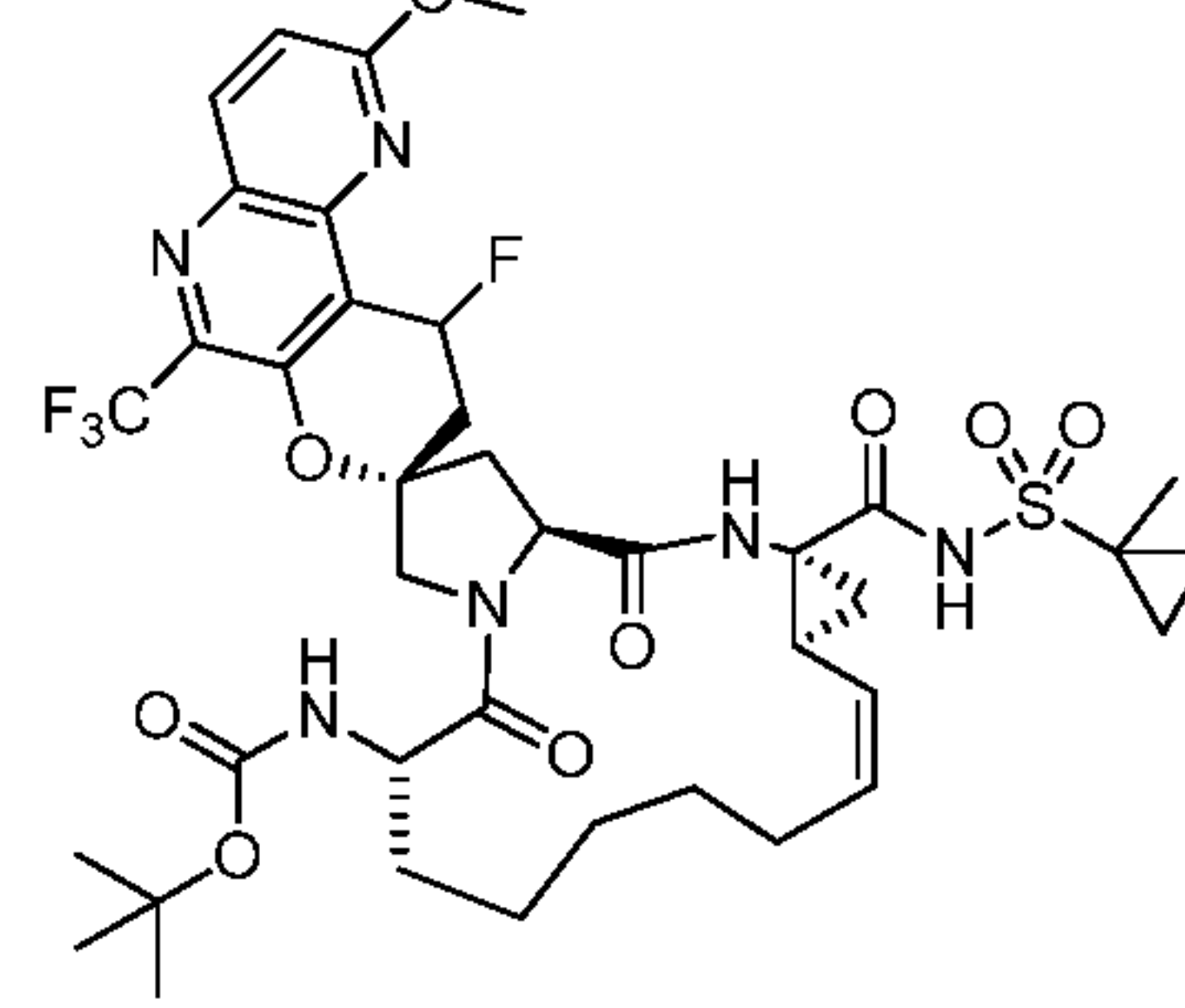
I-30



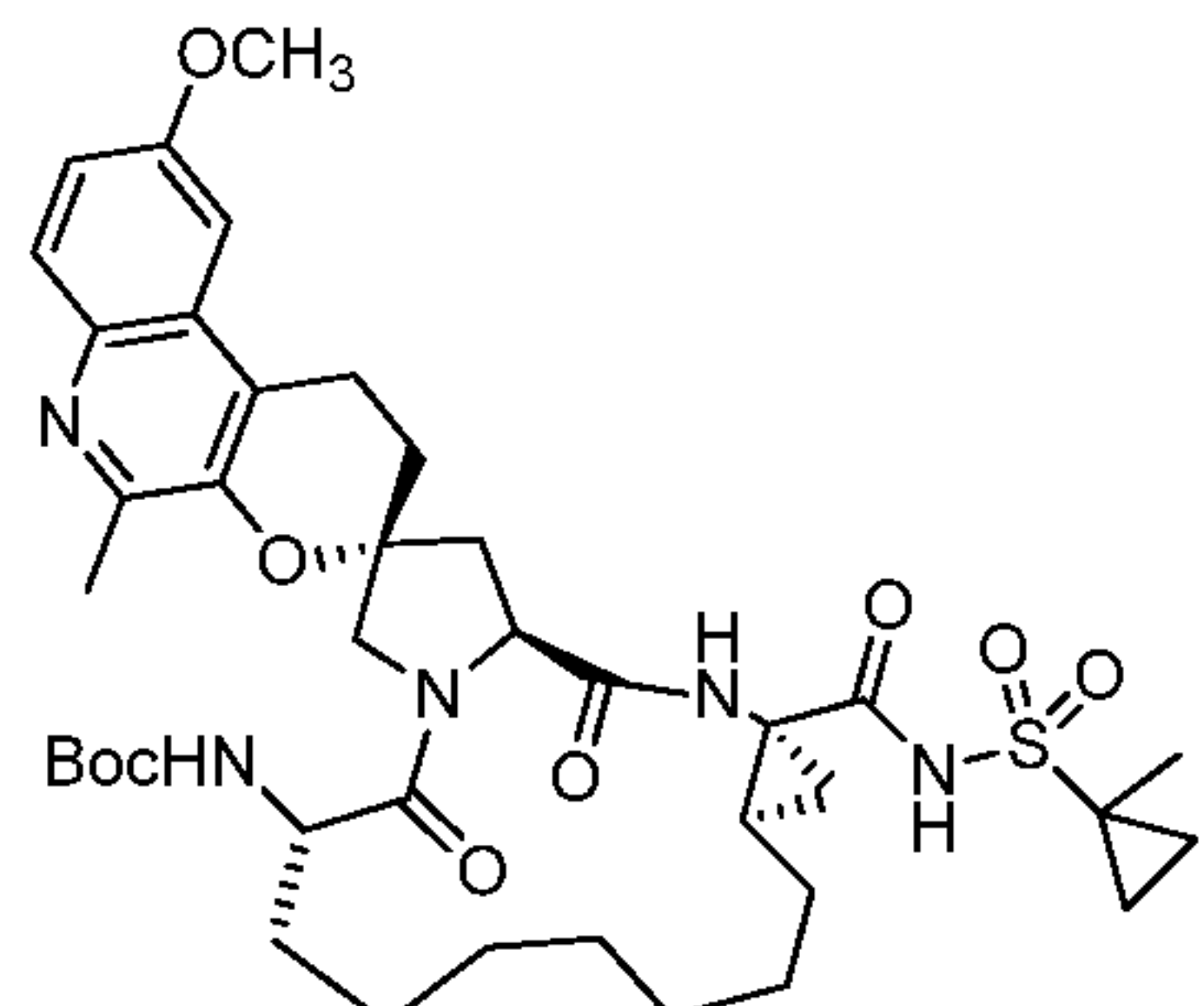
I-31



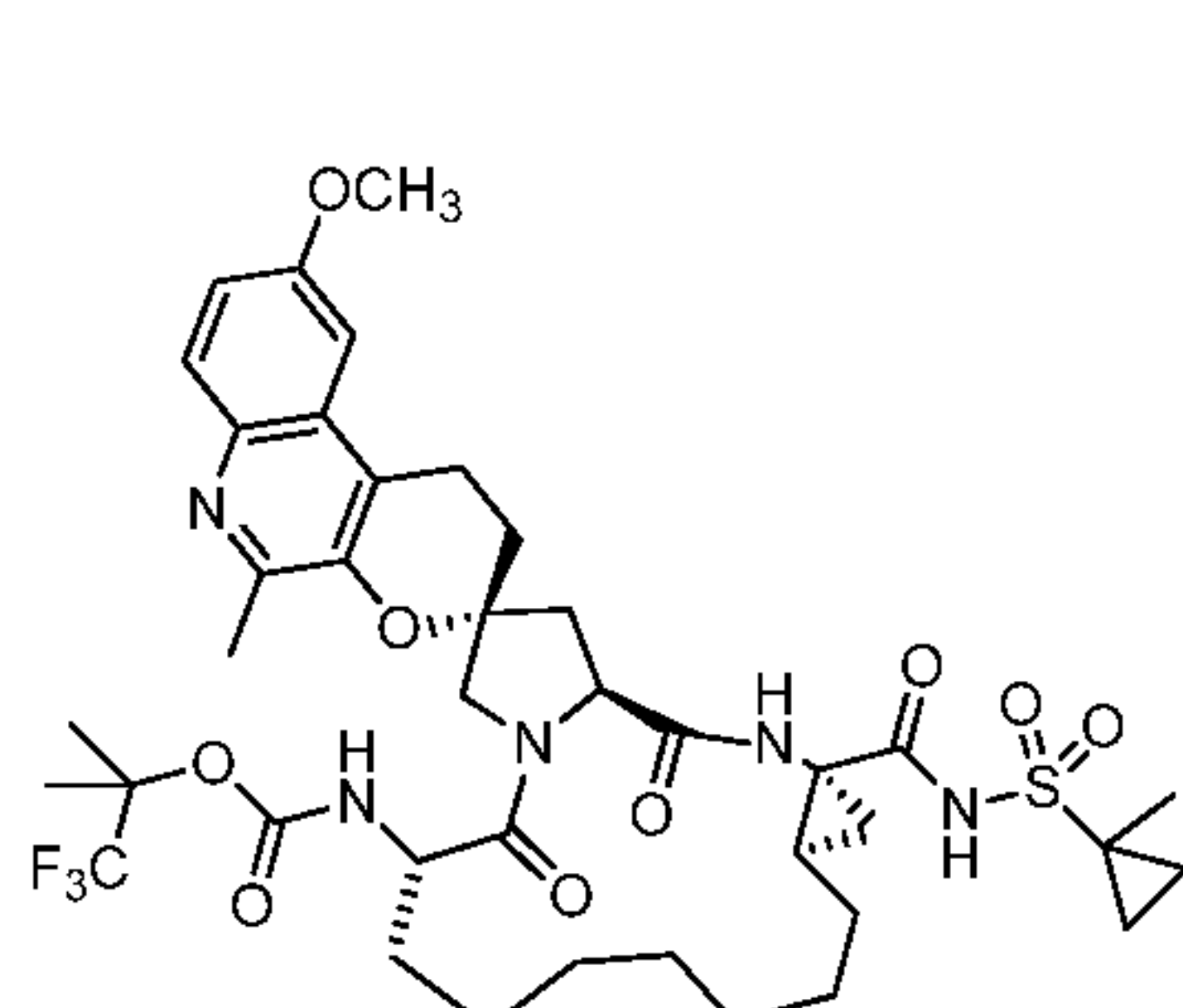
I-32



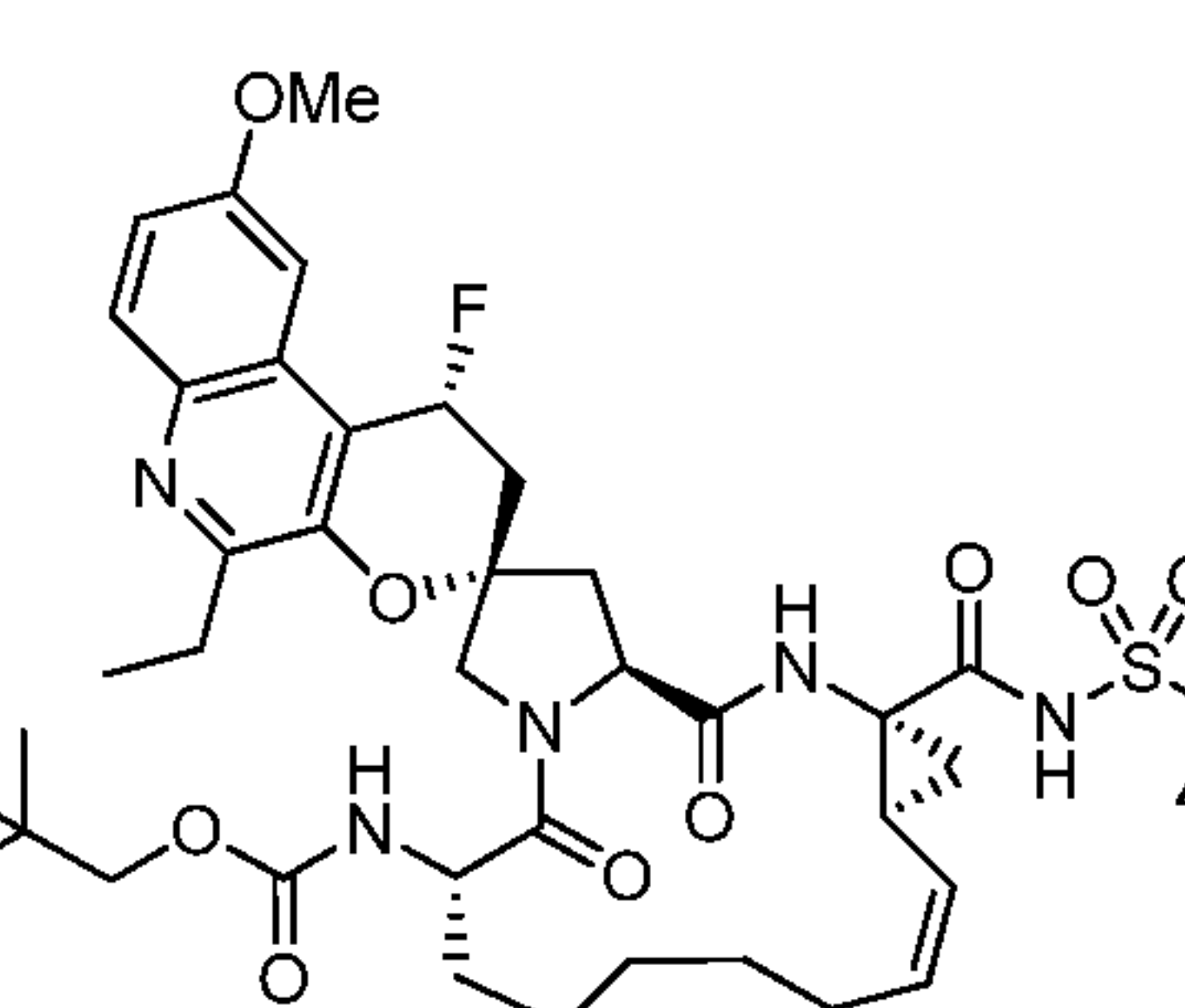
I-33



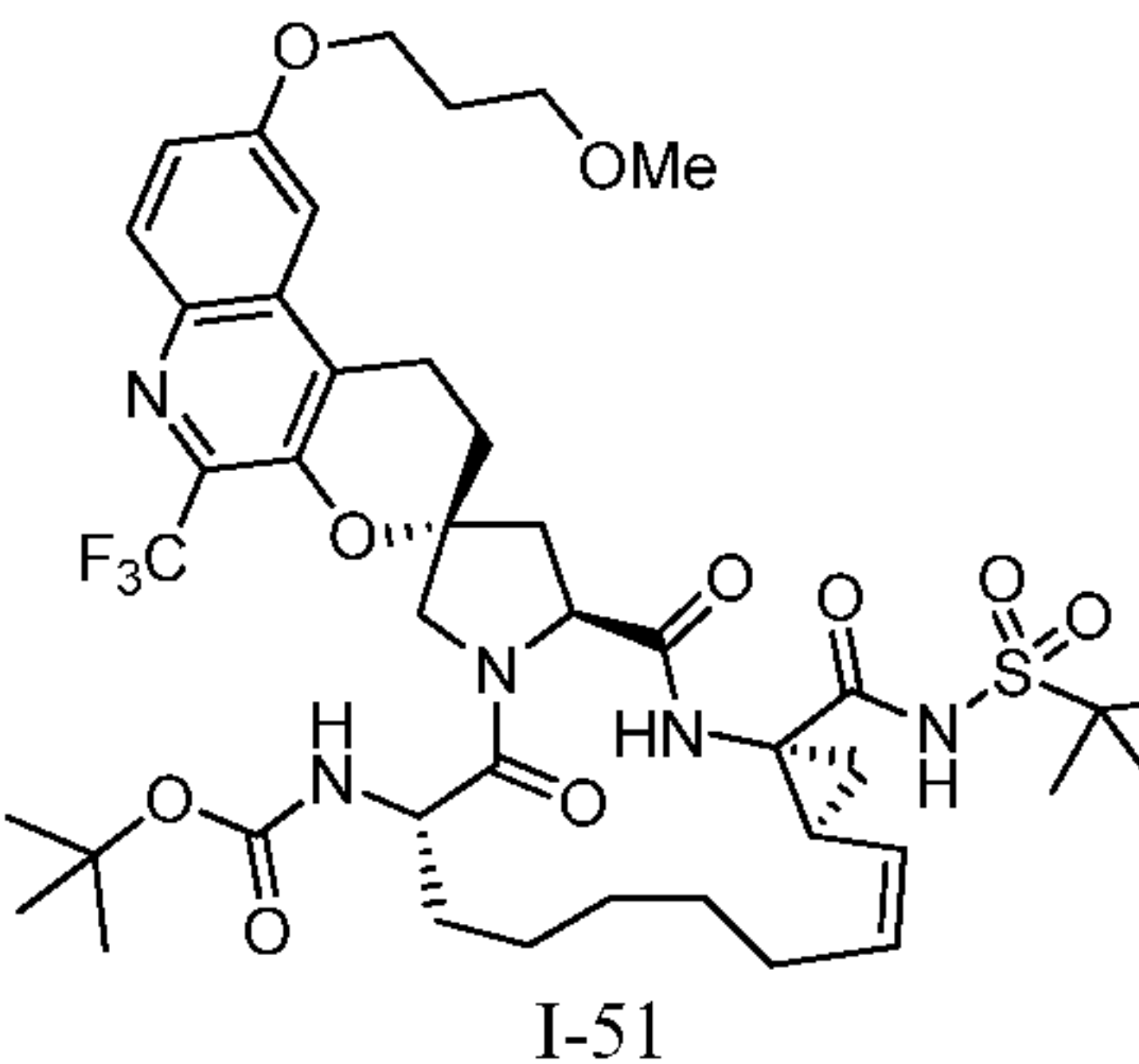
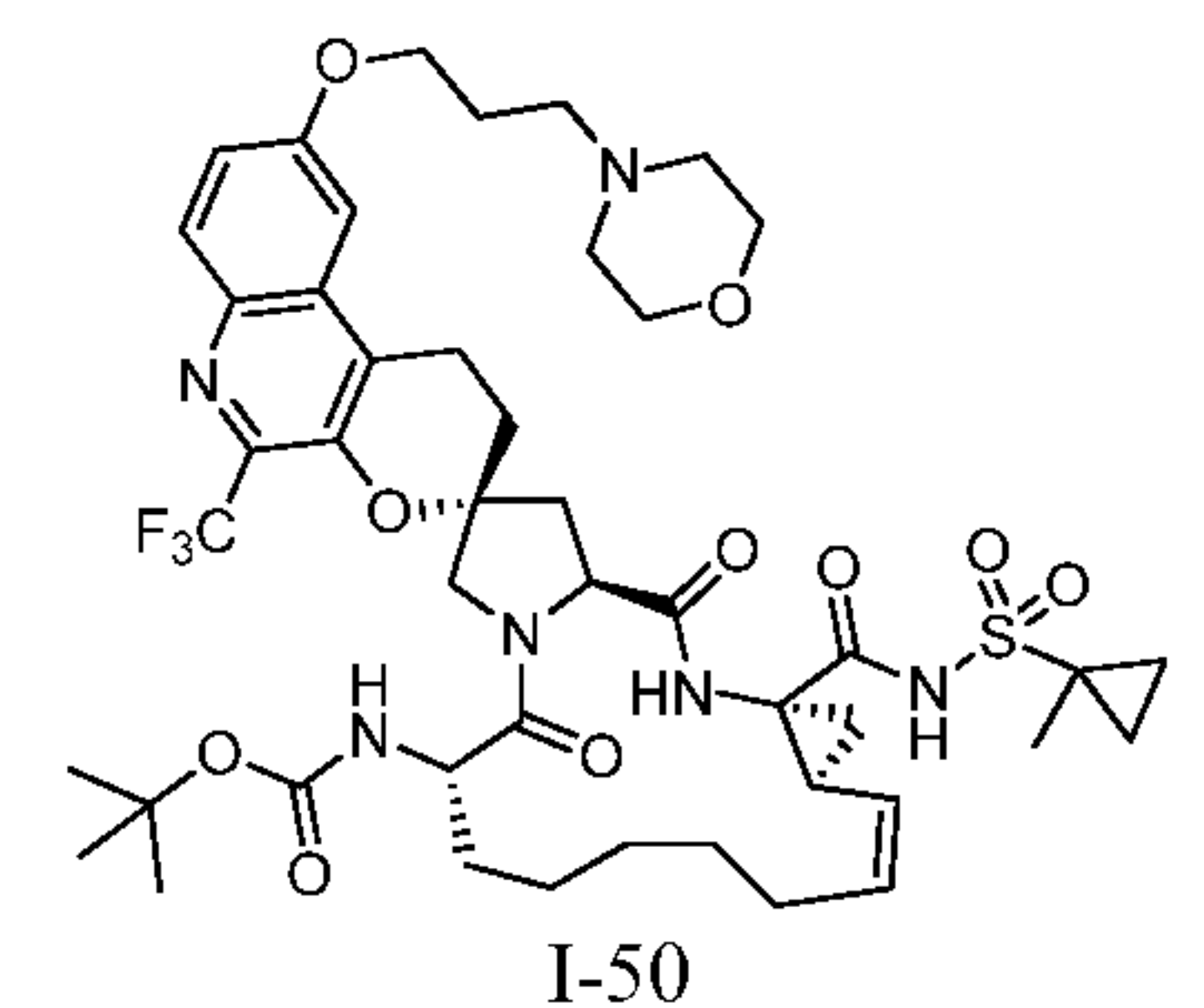
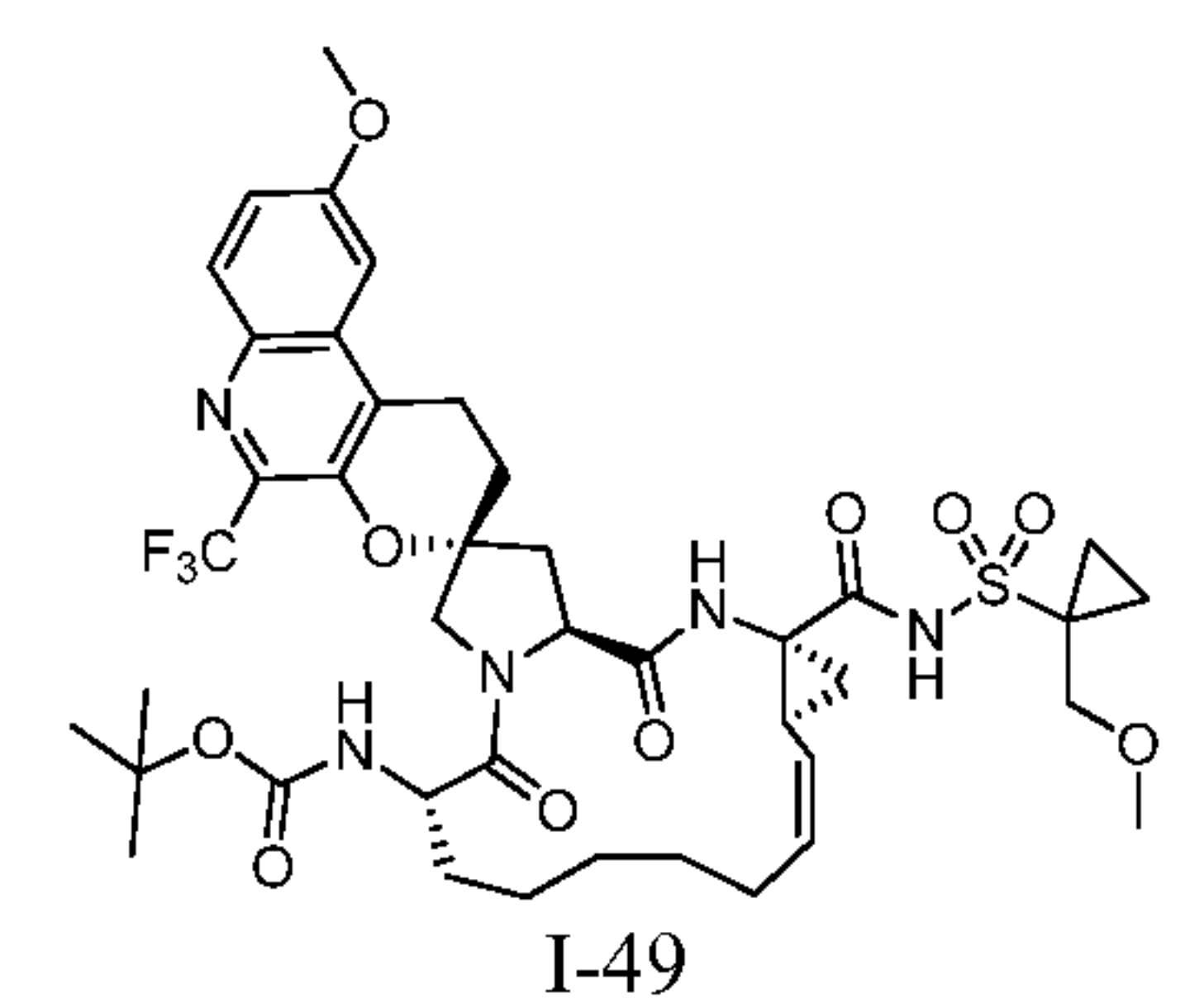
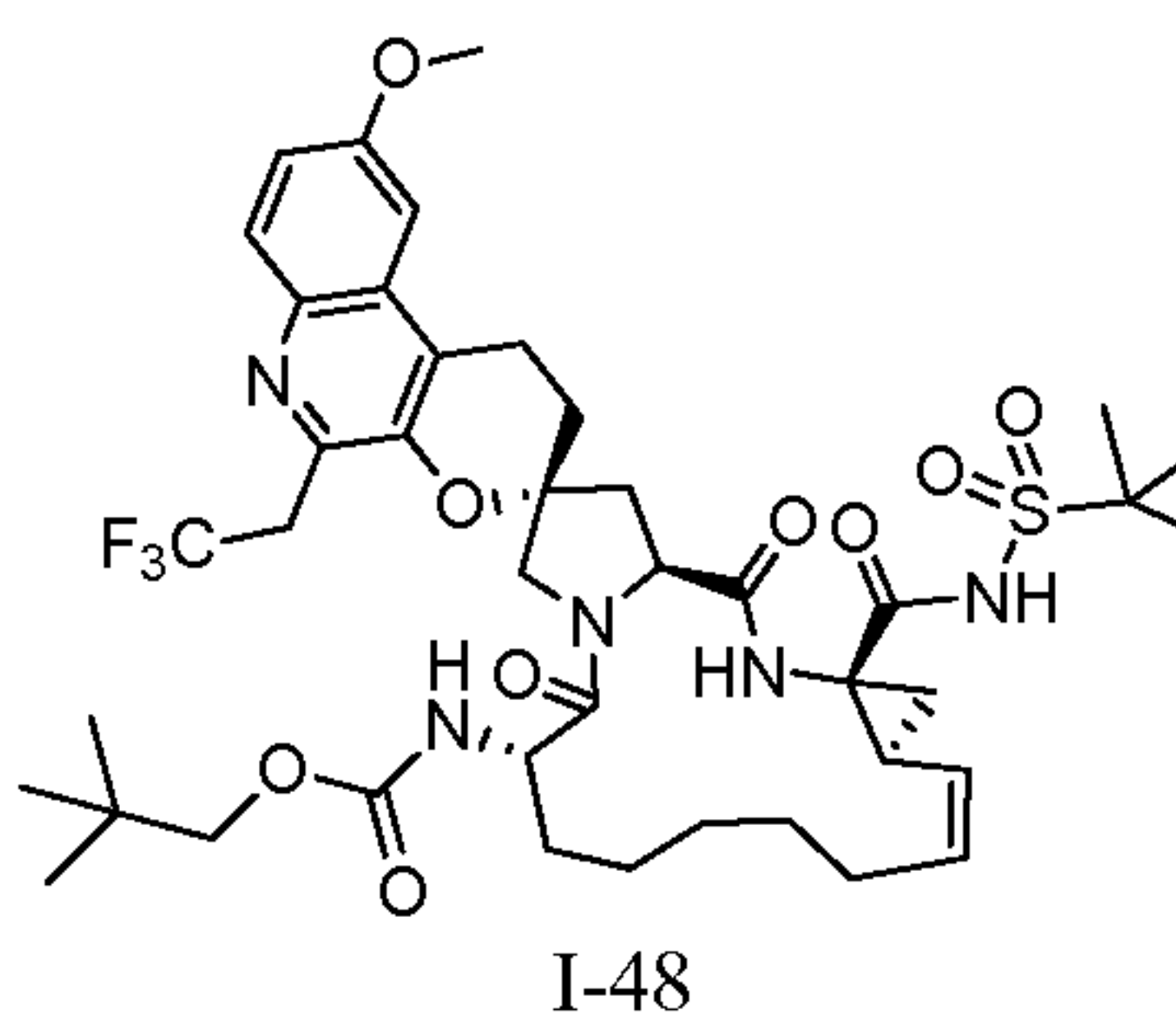
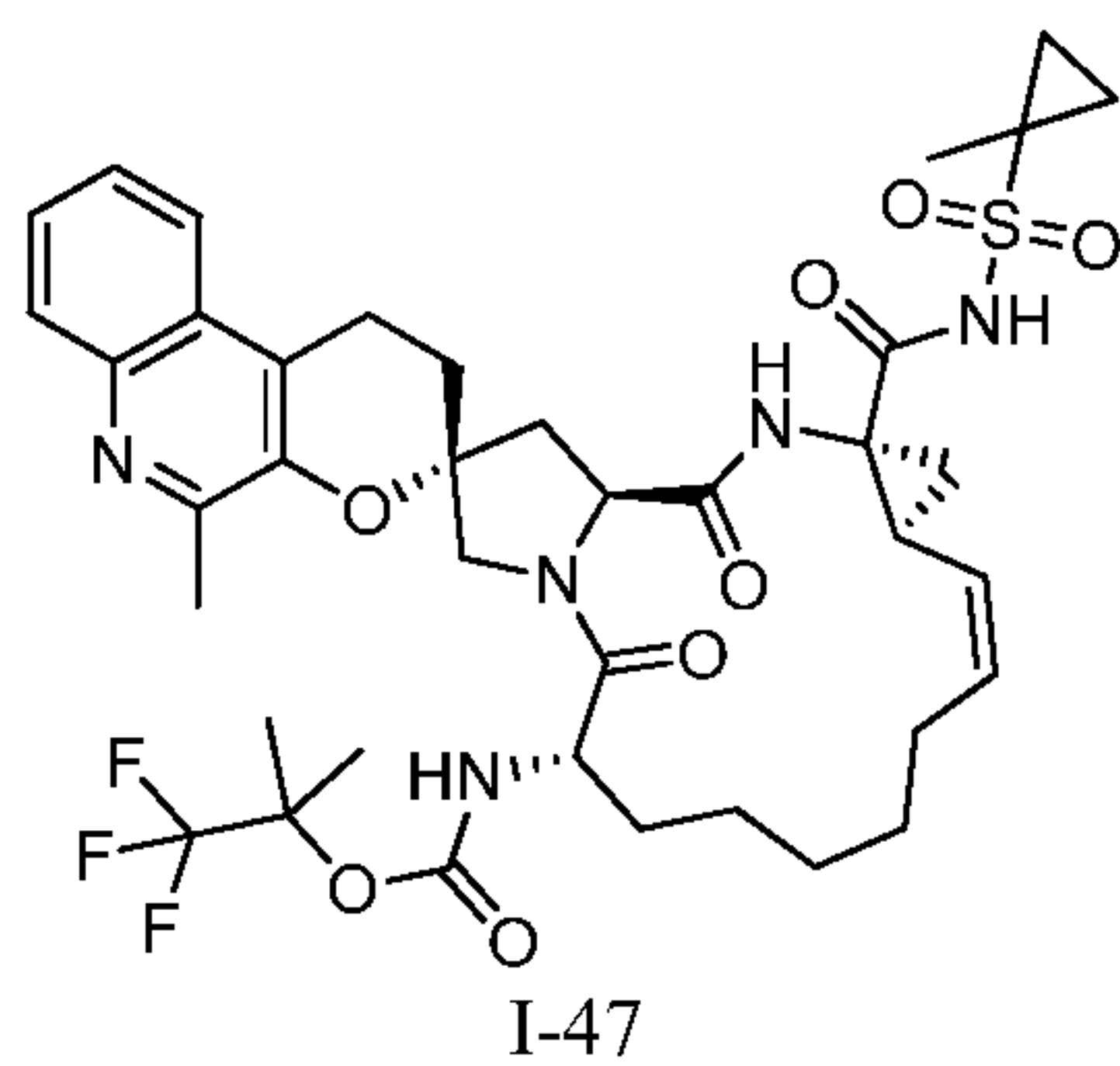
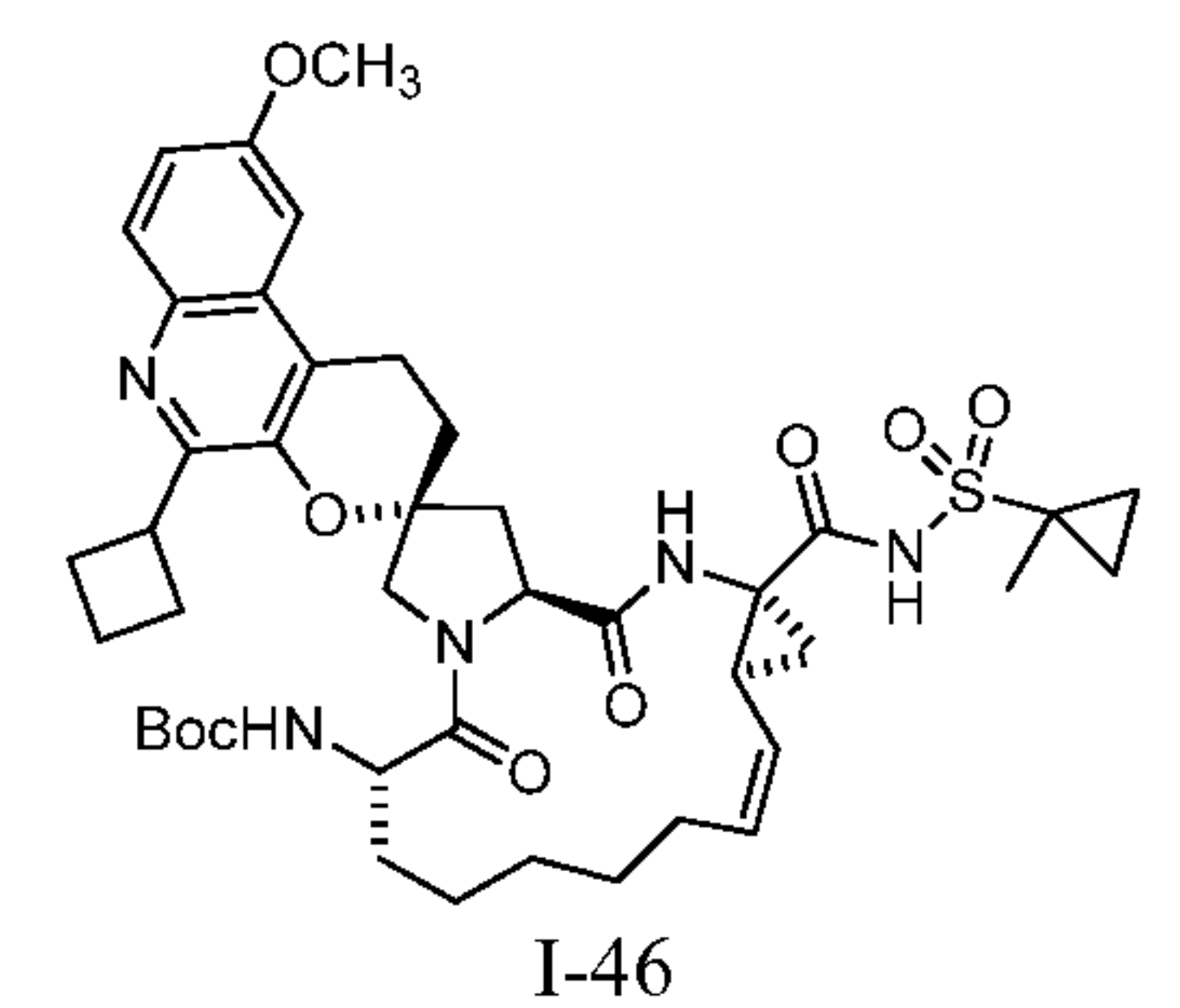
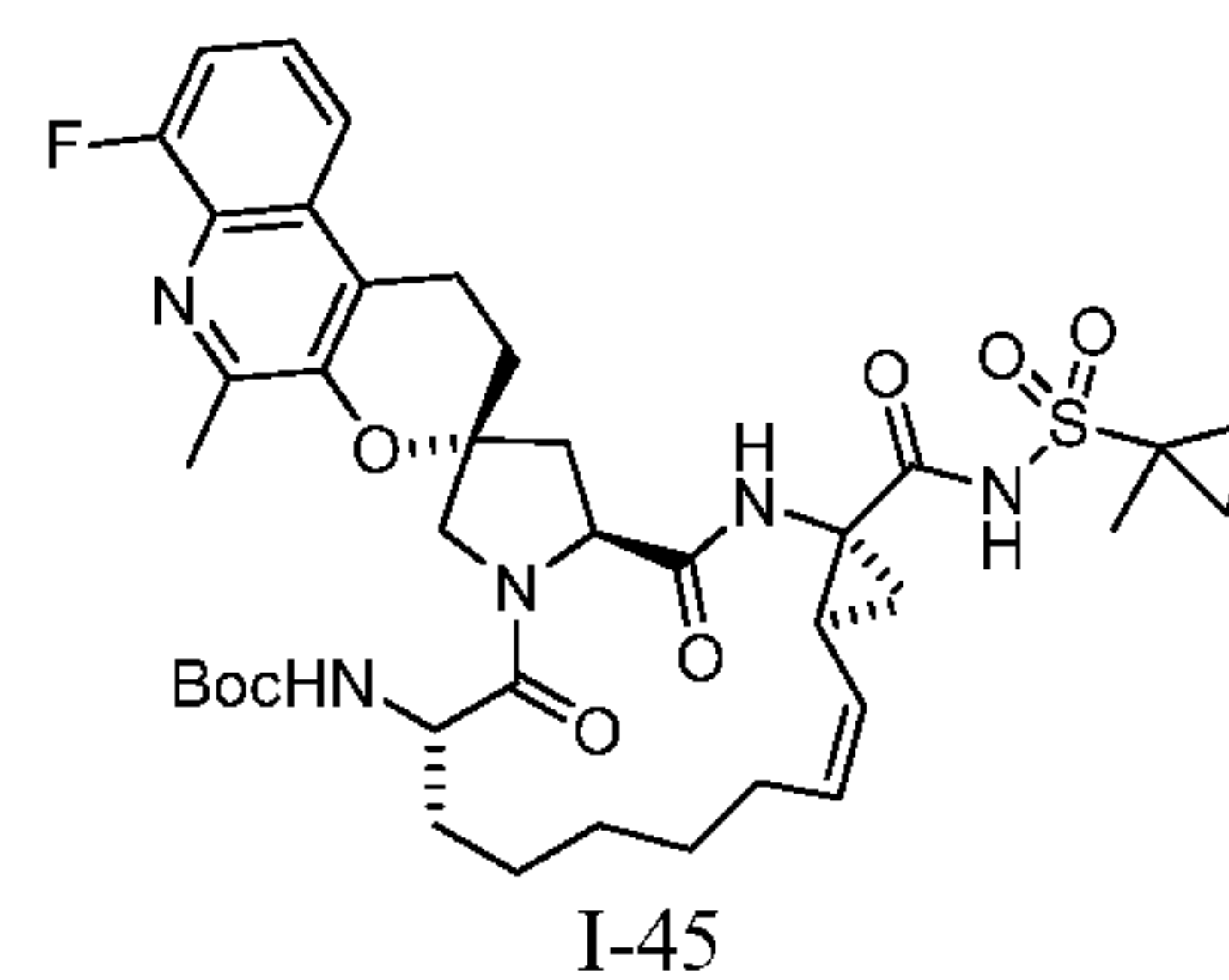
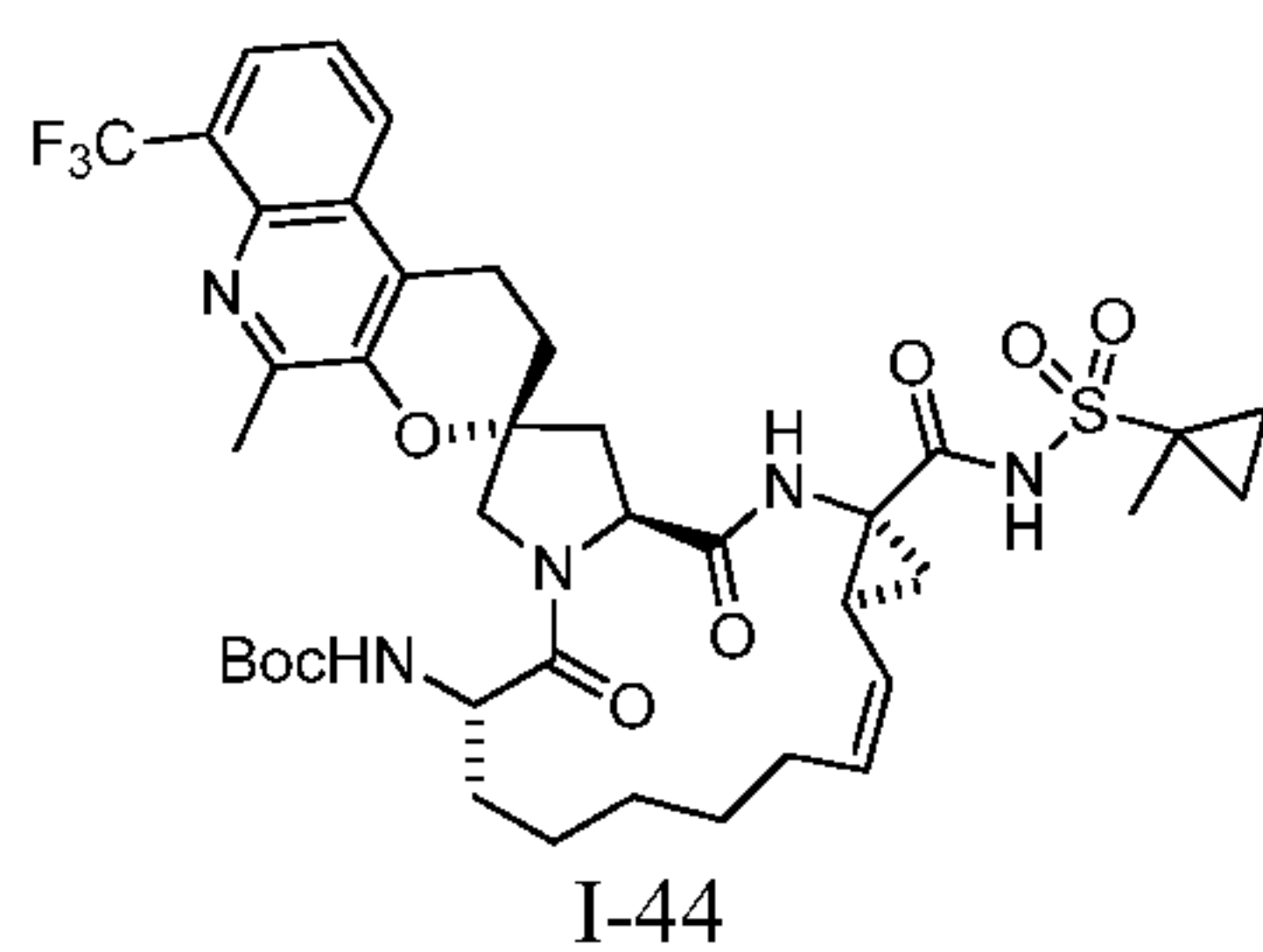
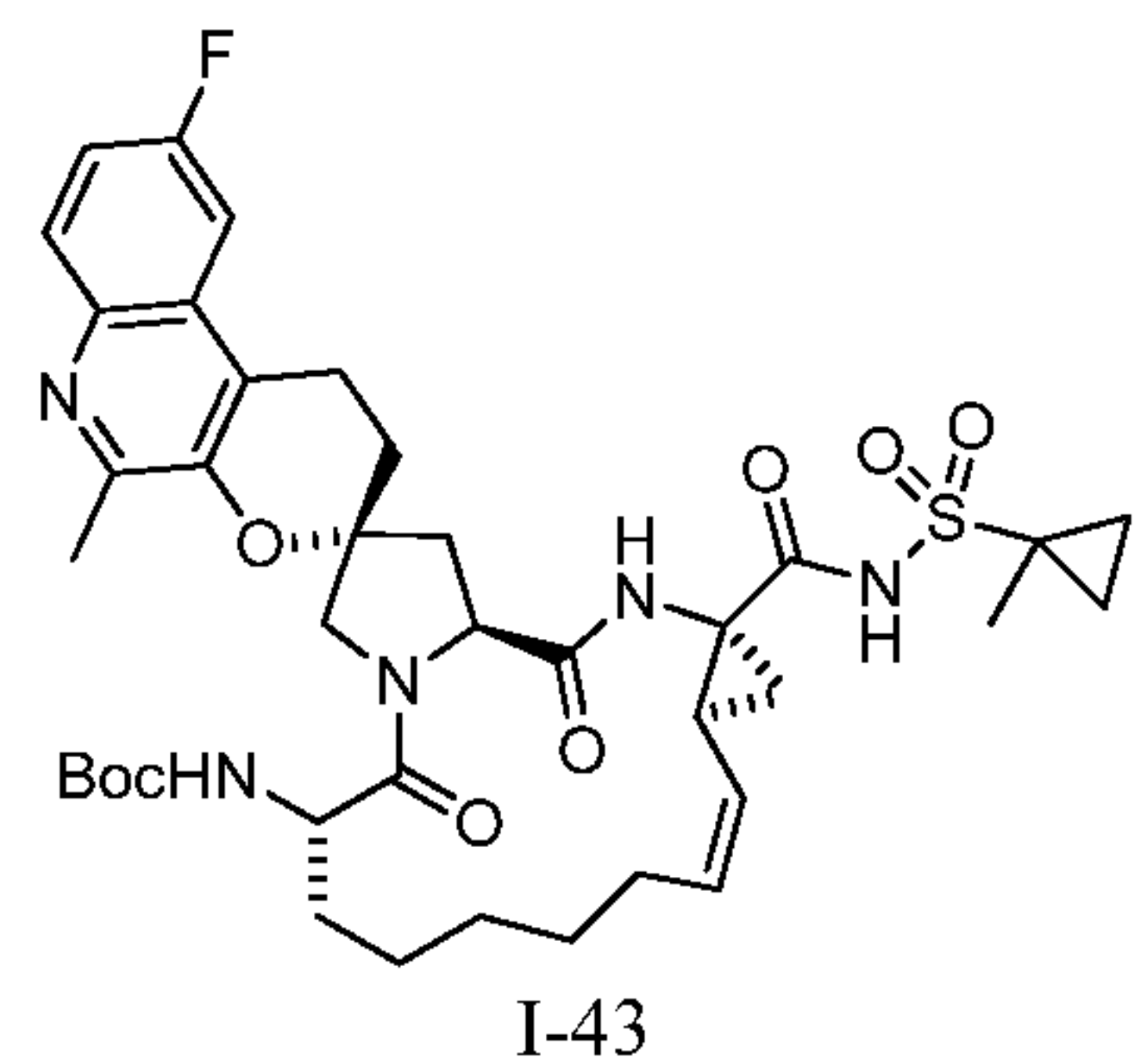
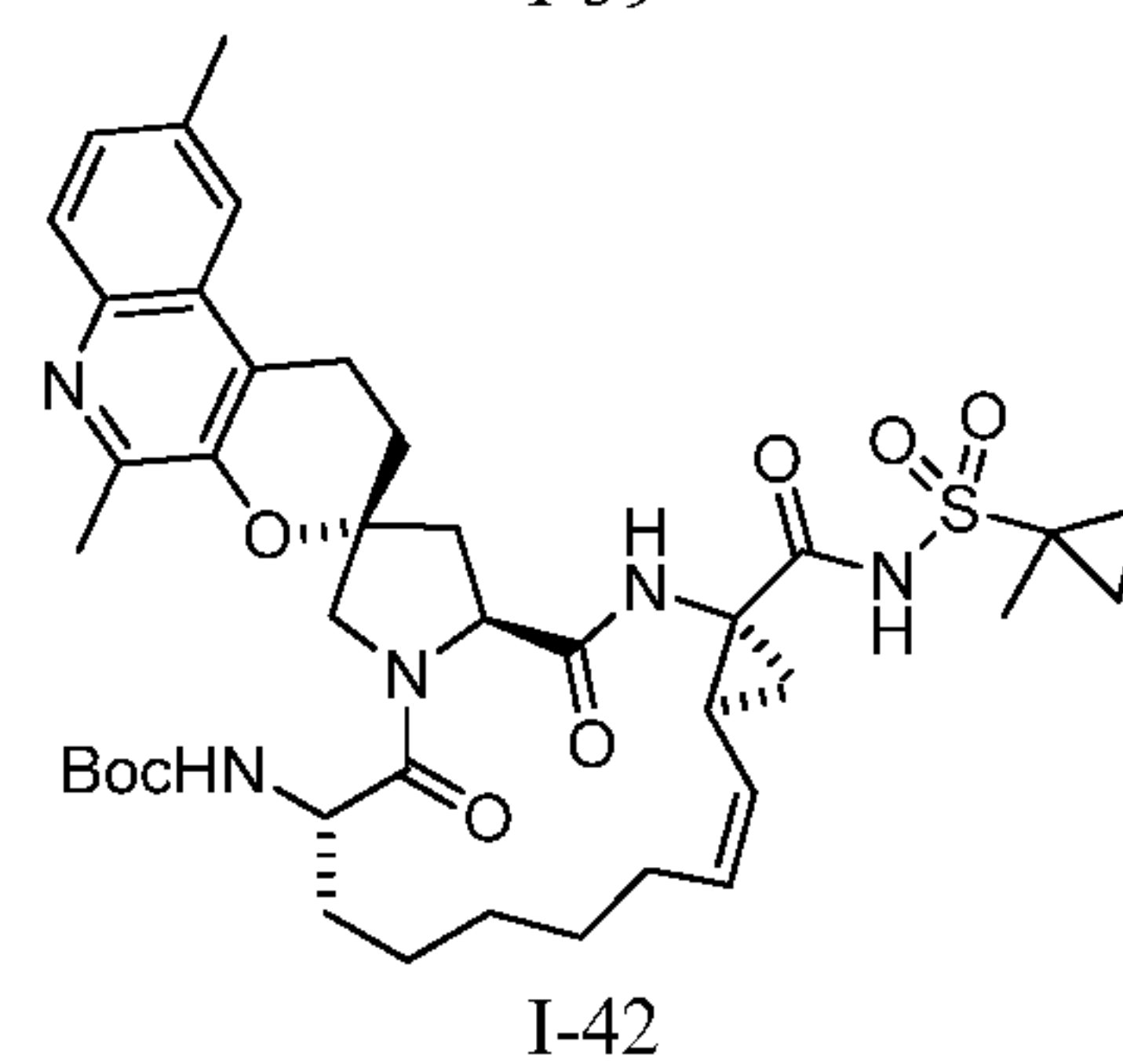
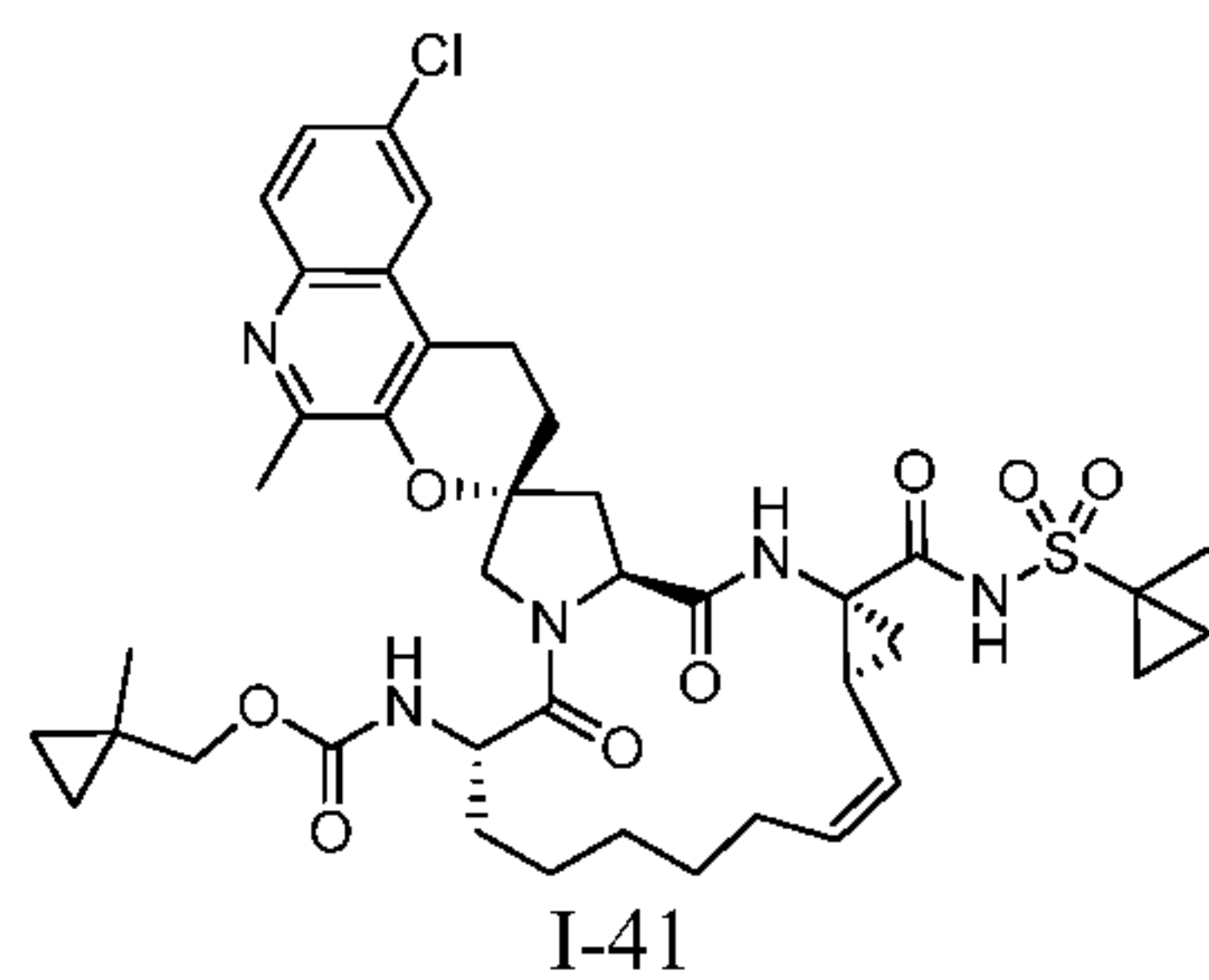
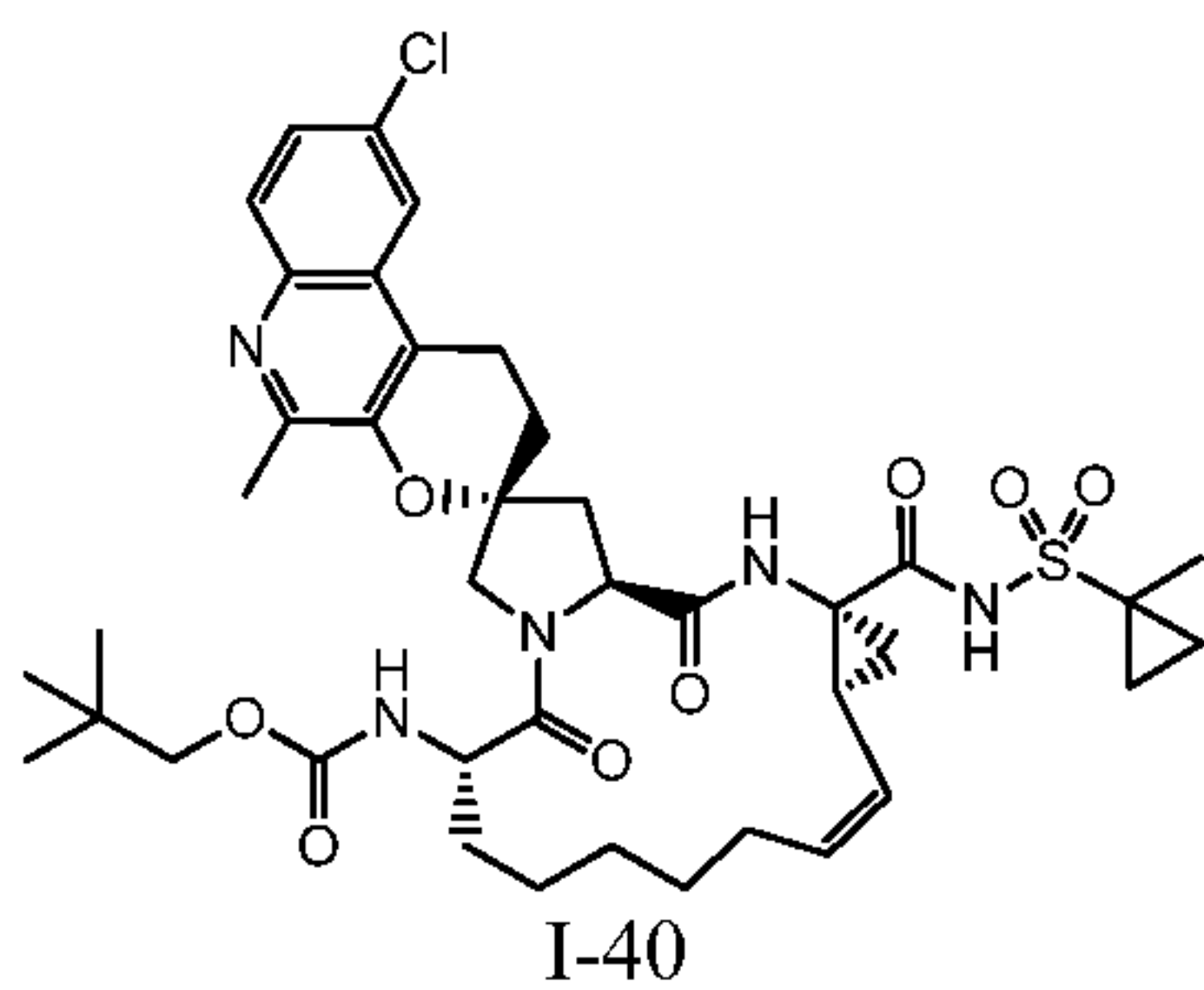
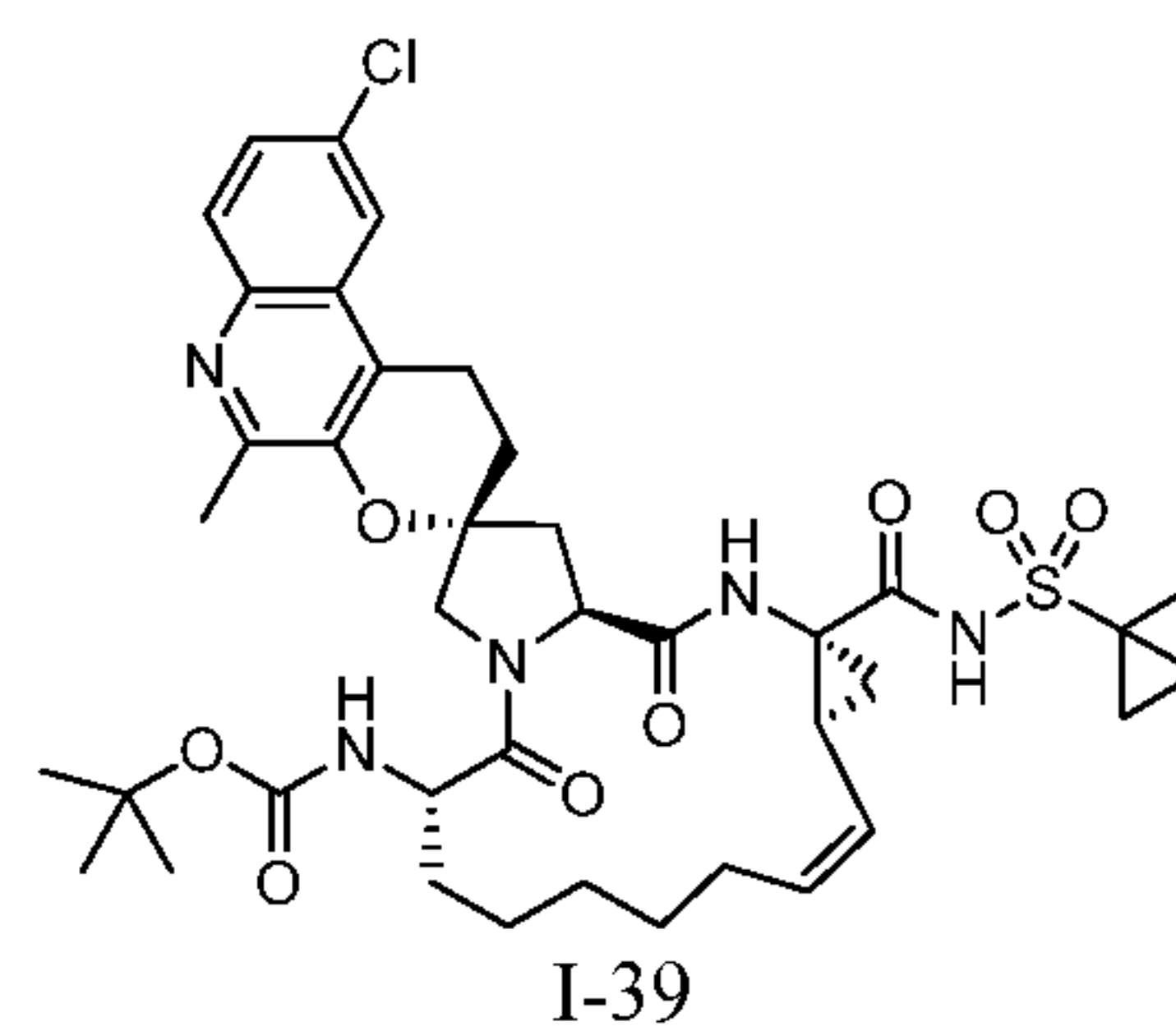
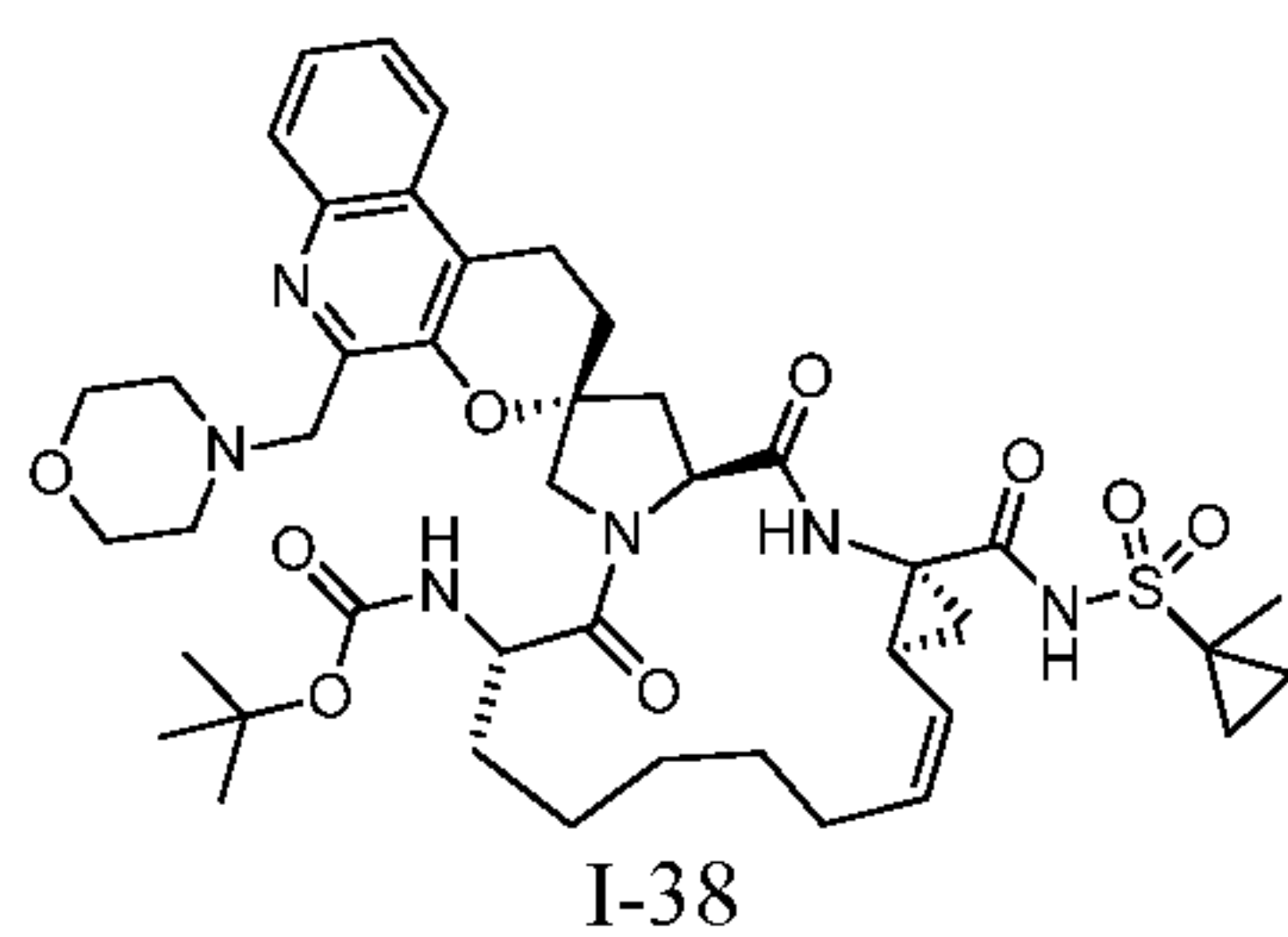
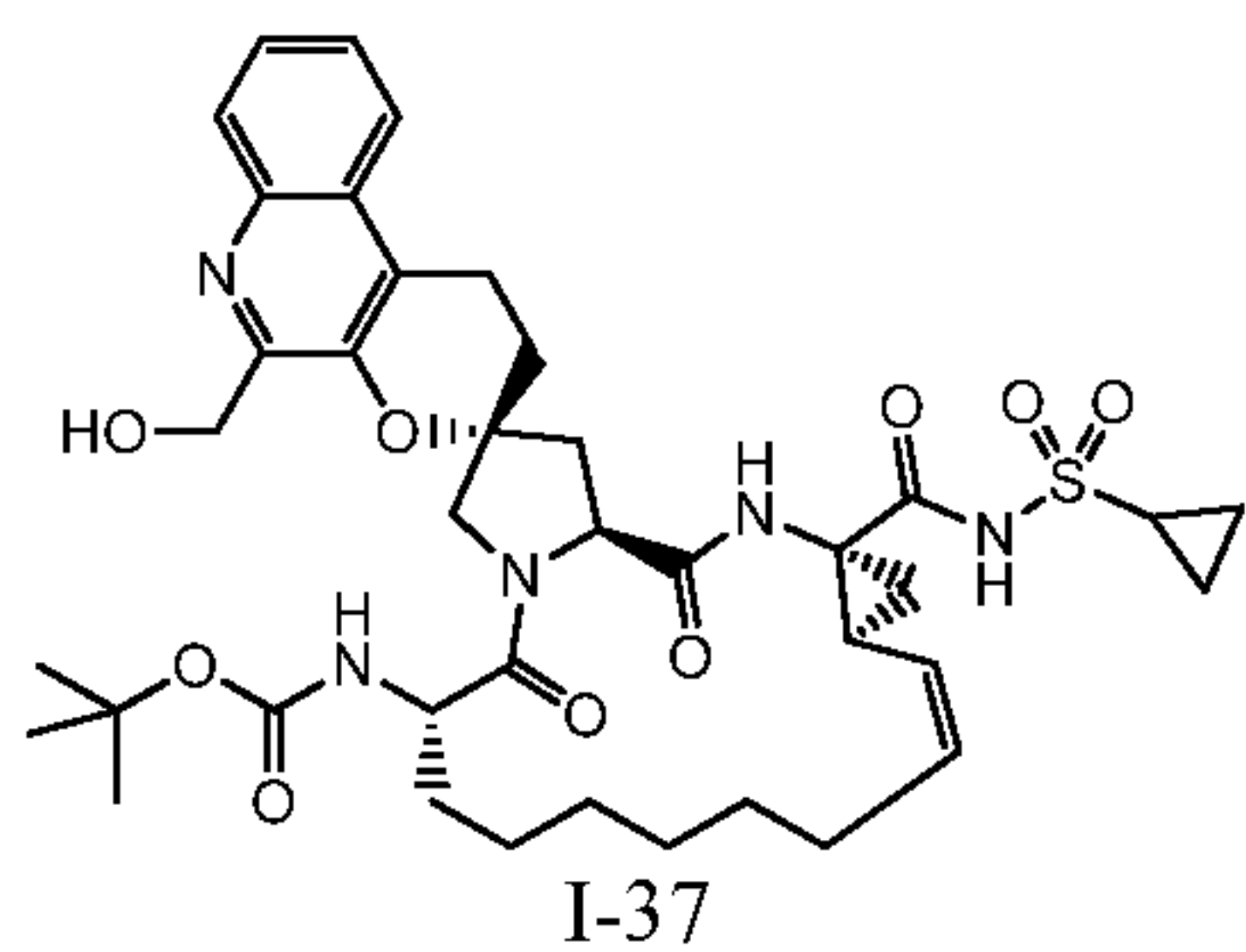
I-34

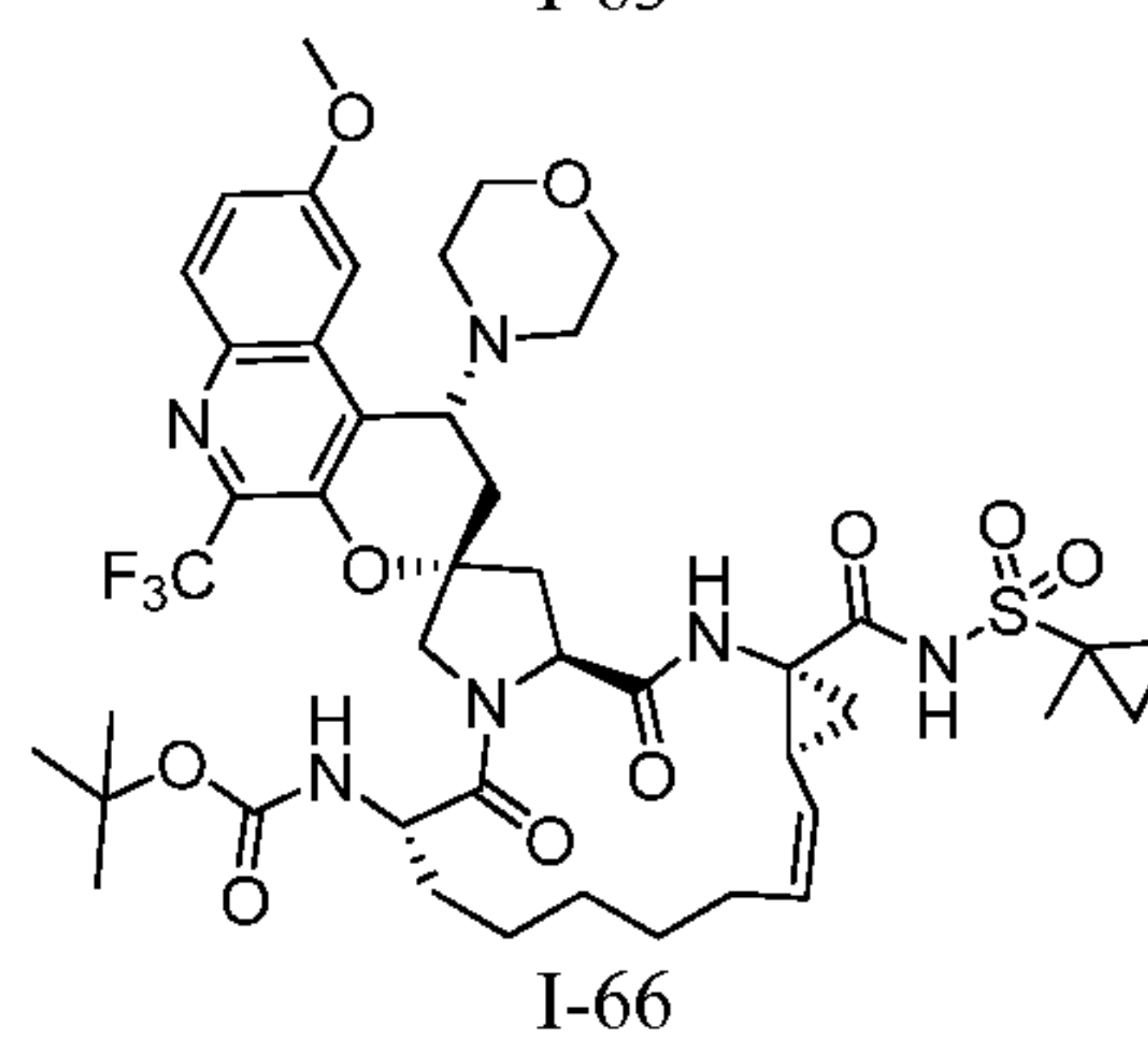
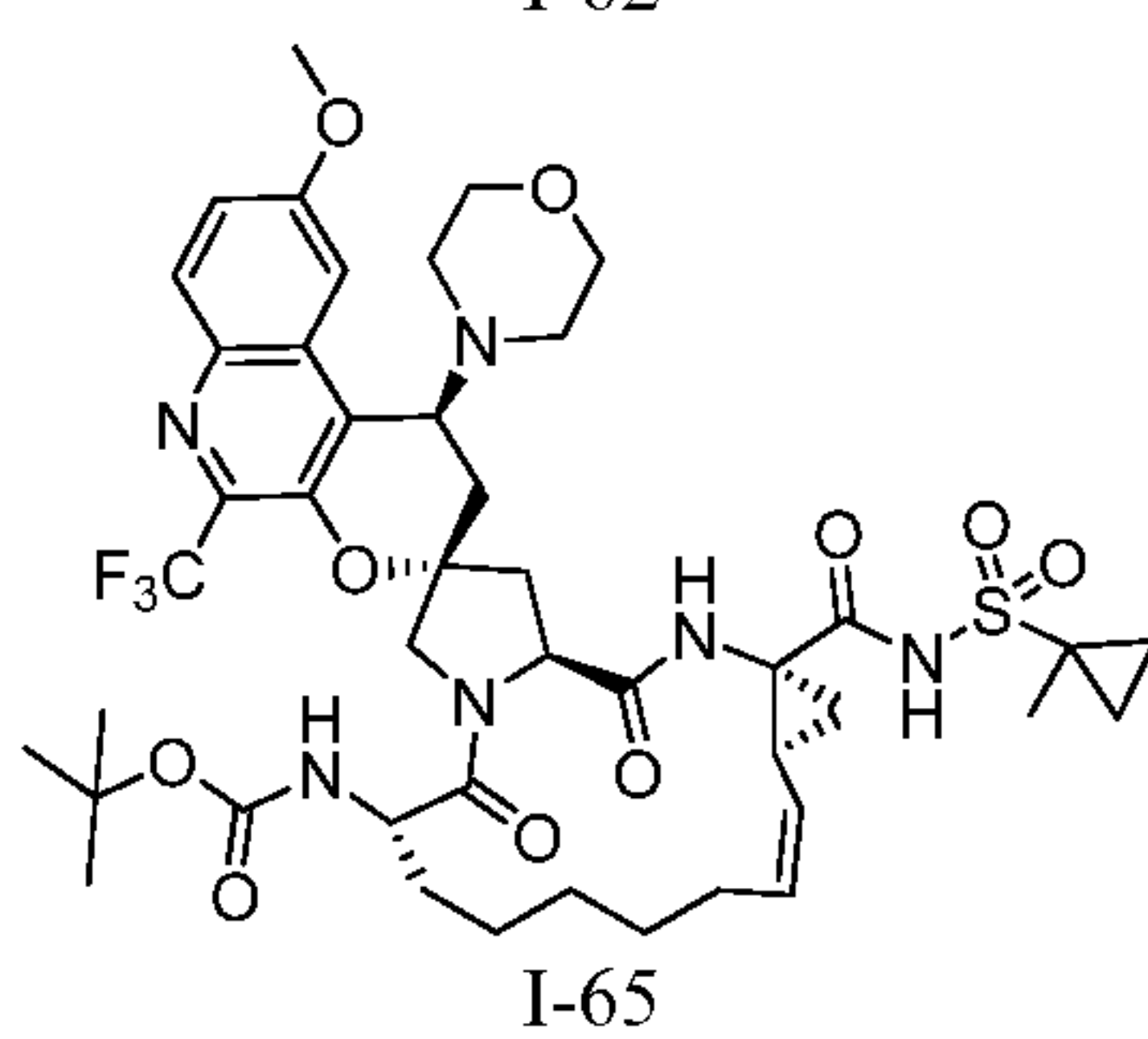
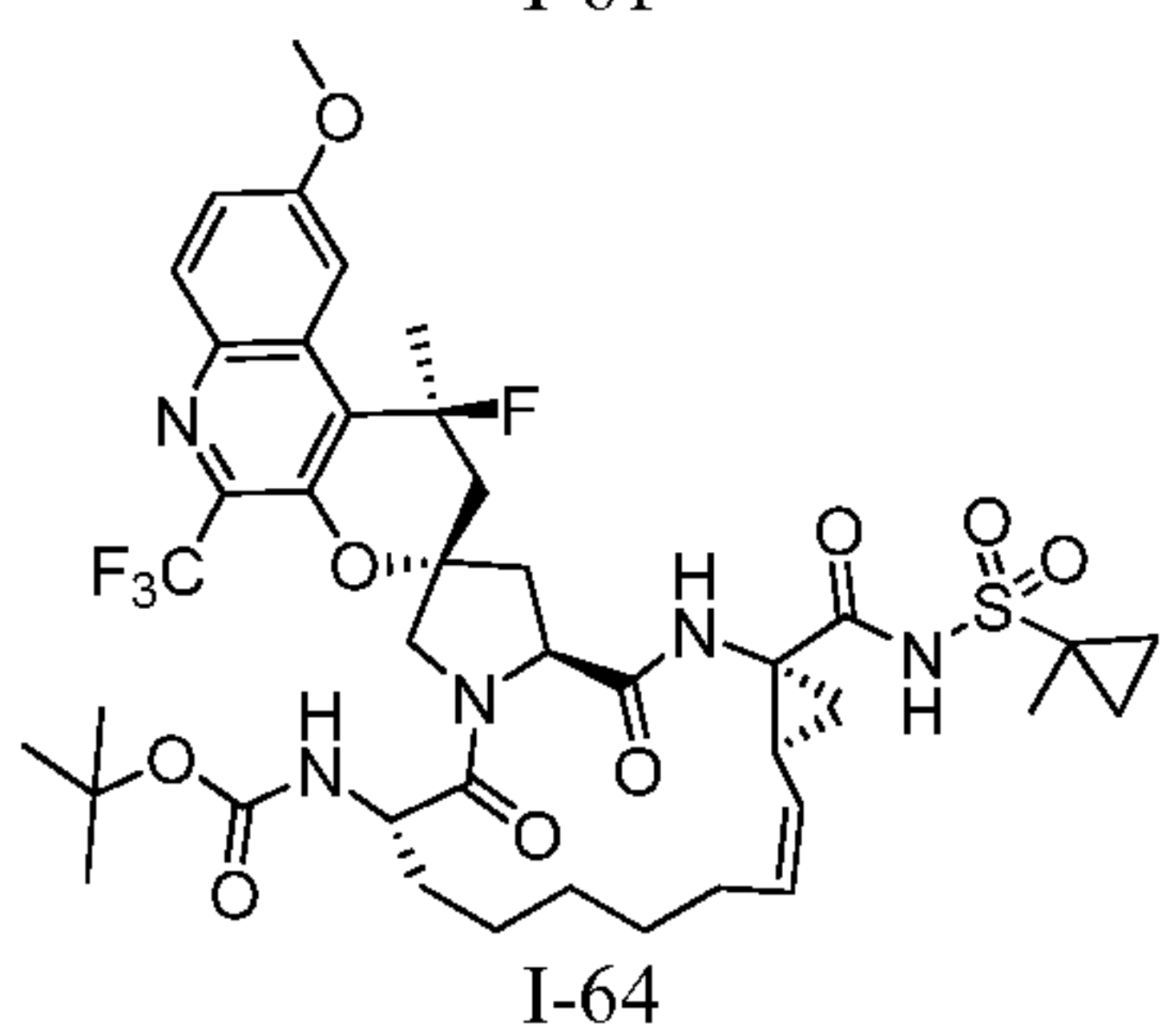
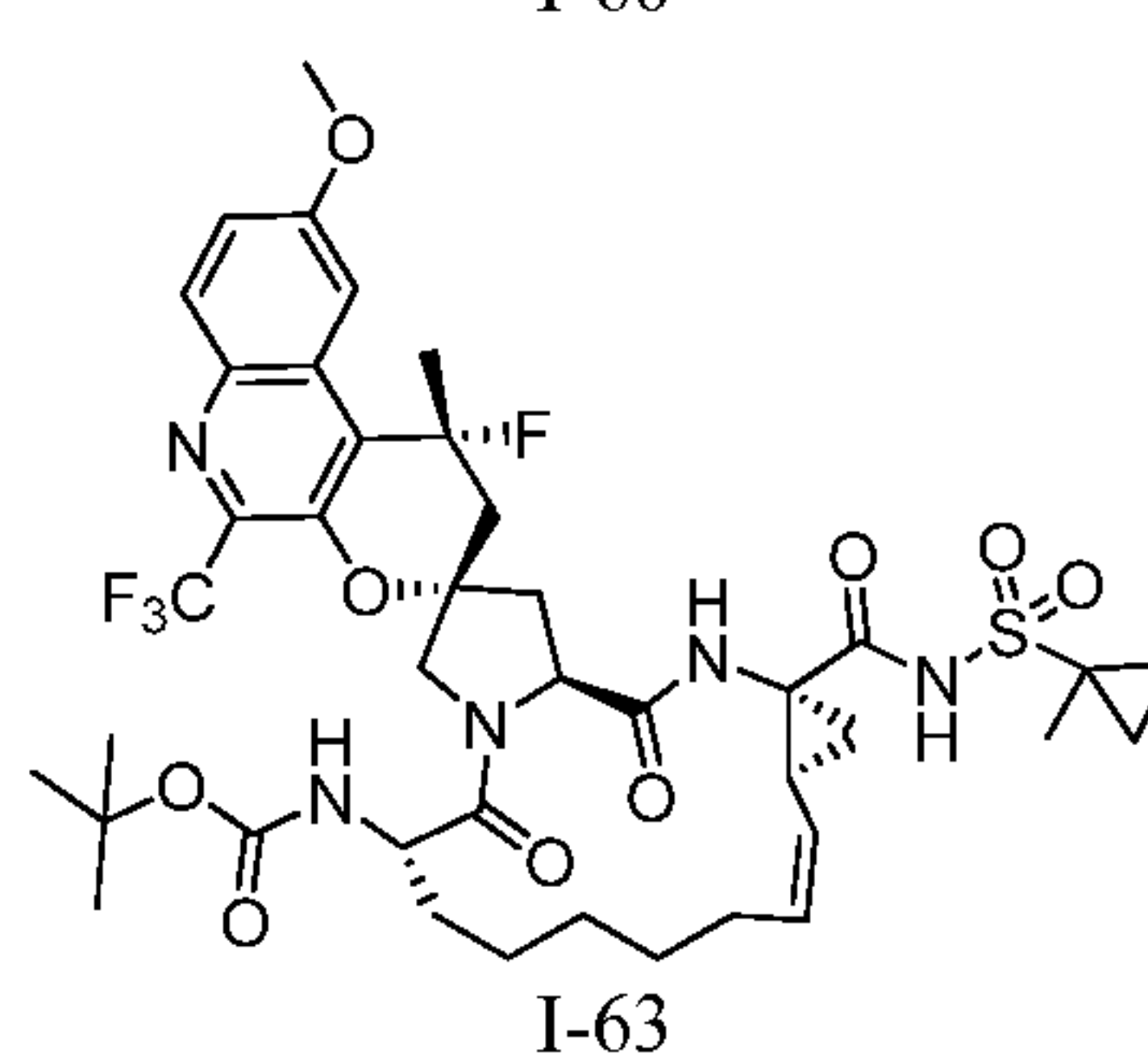
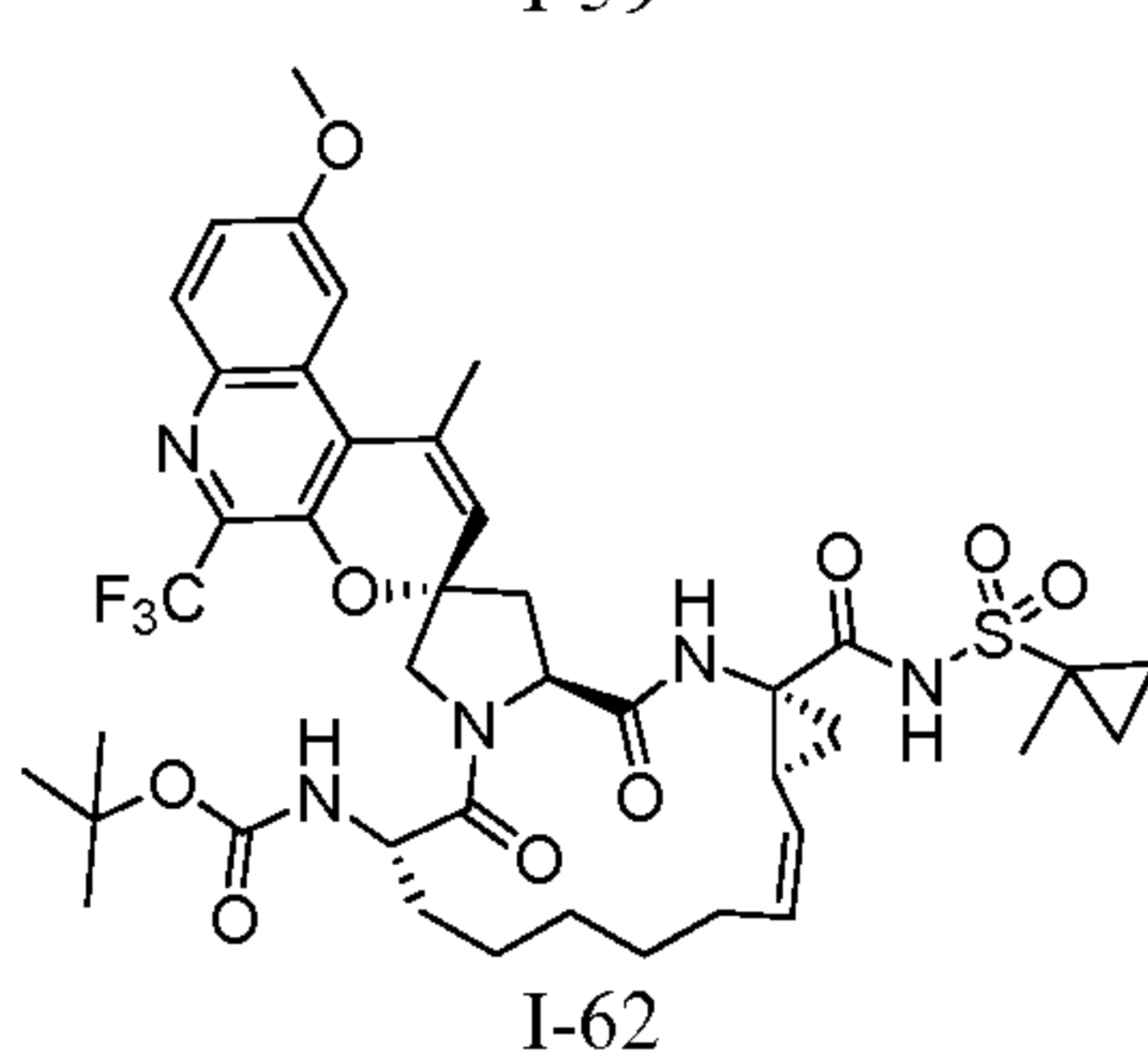
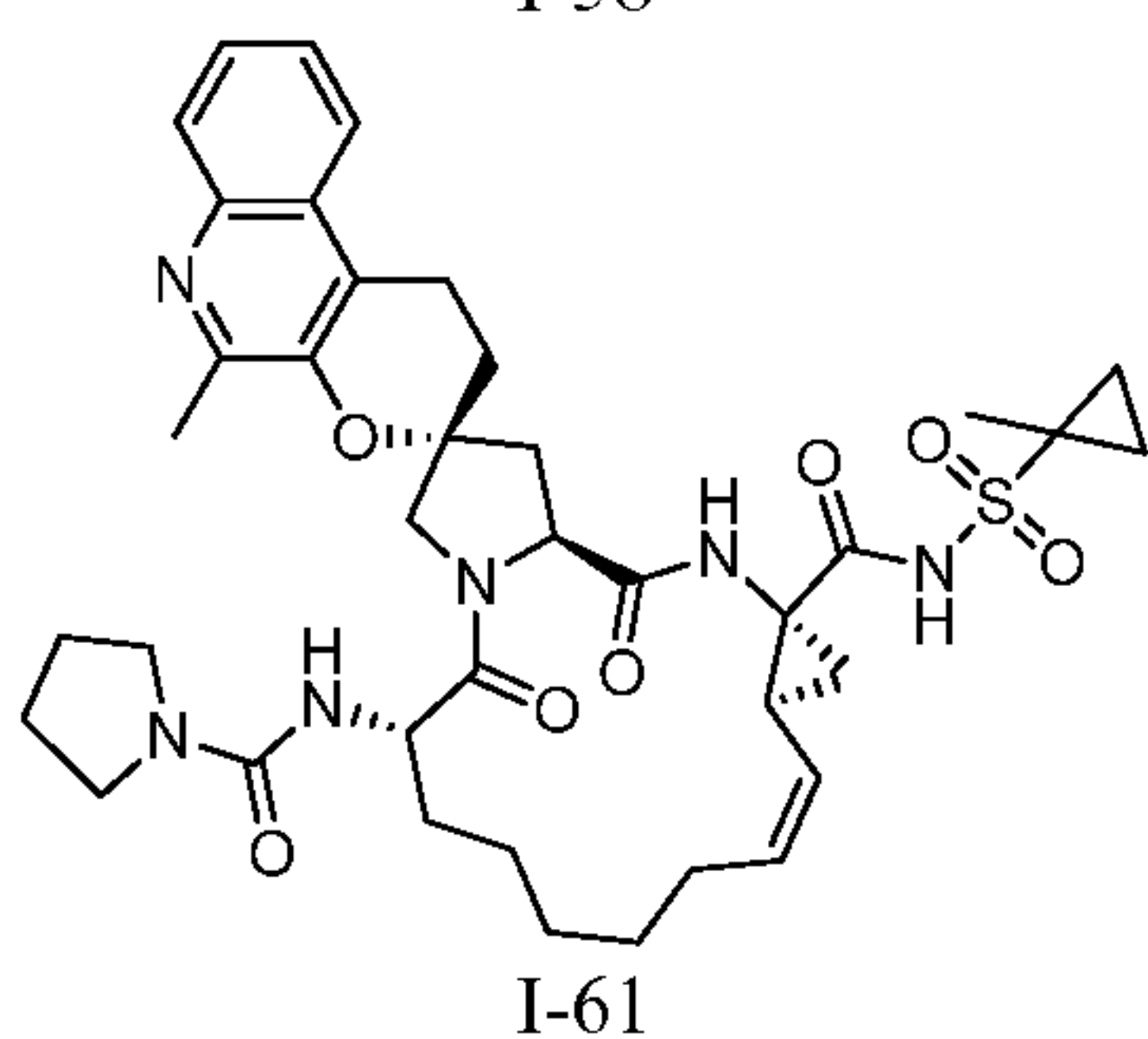
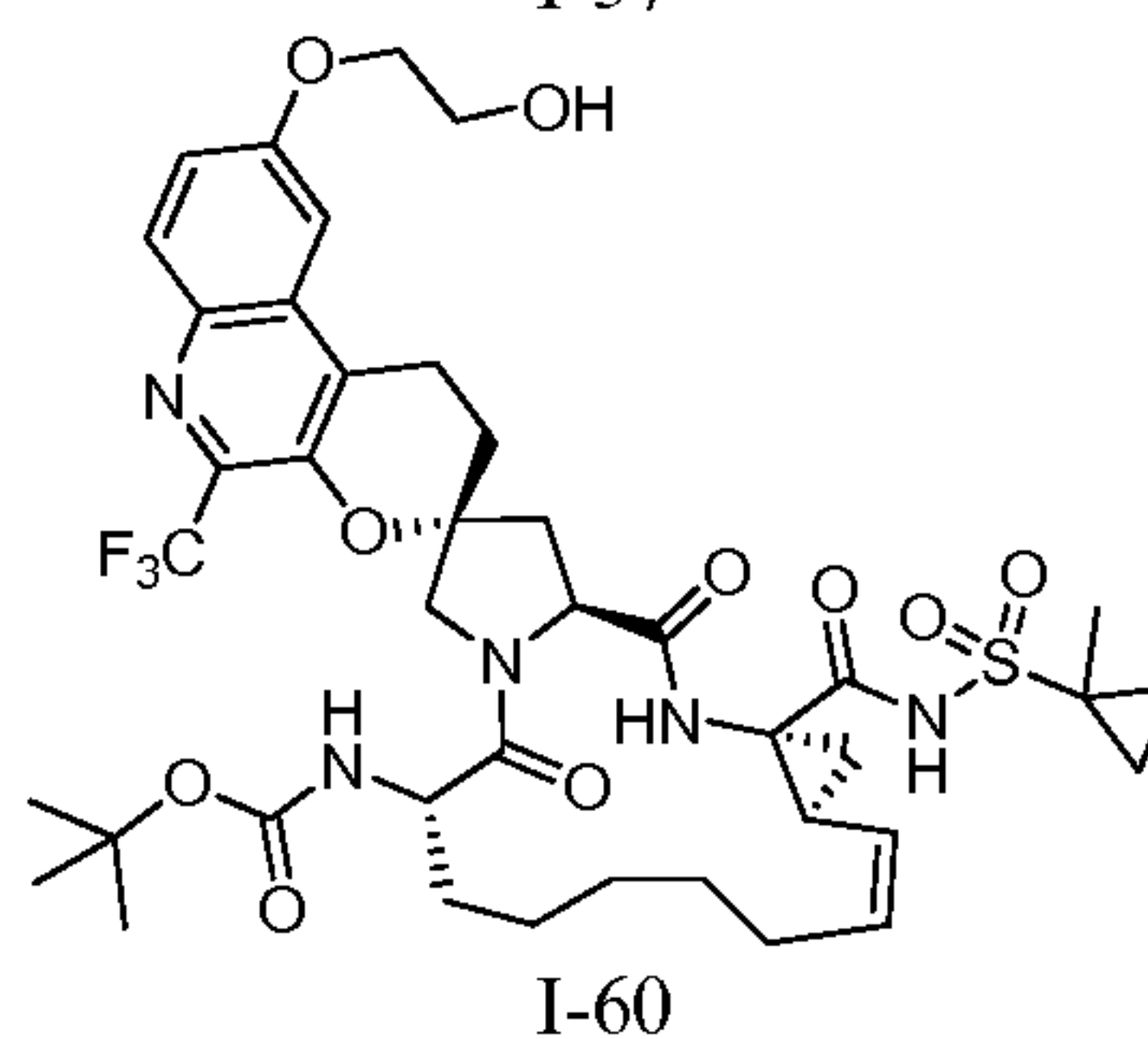
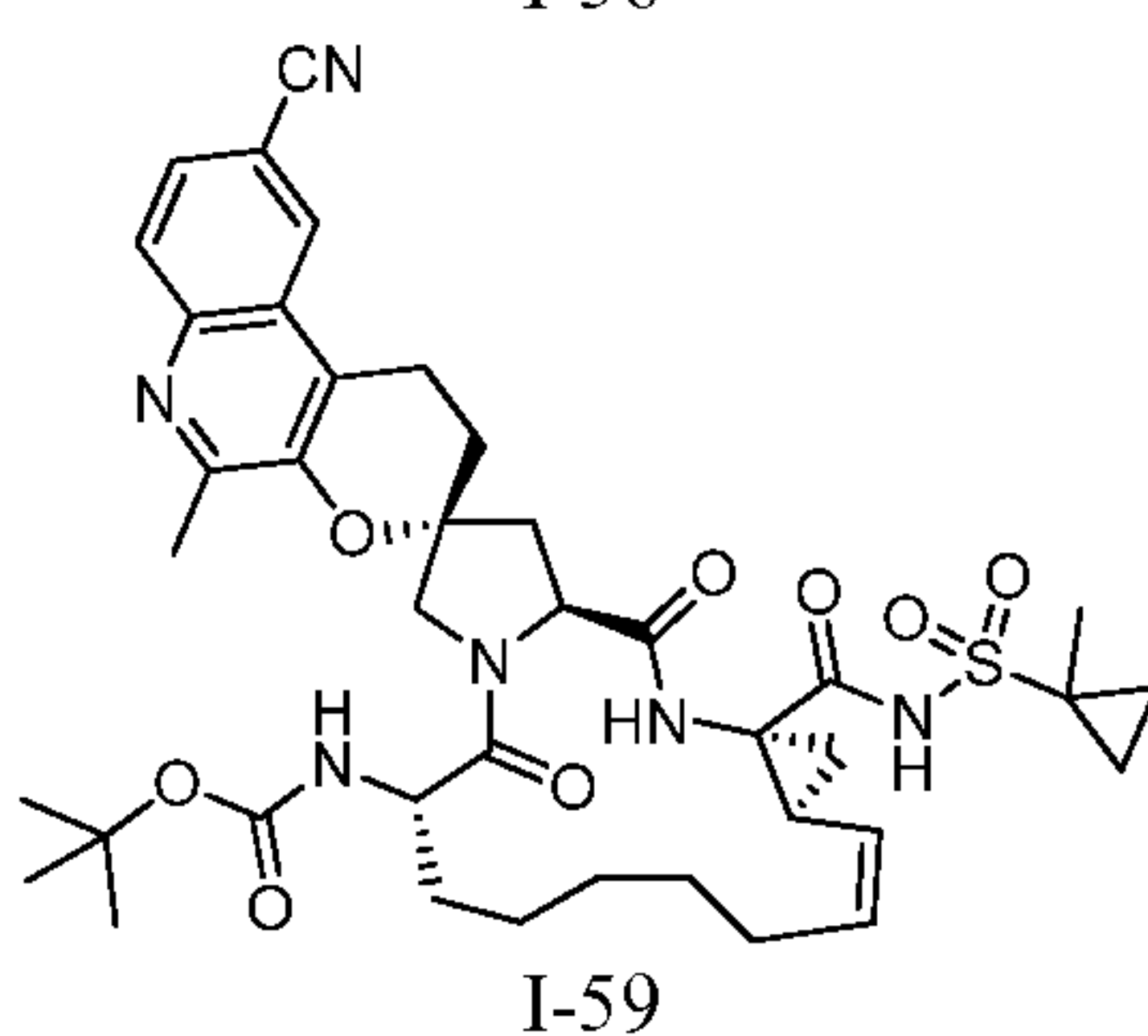
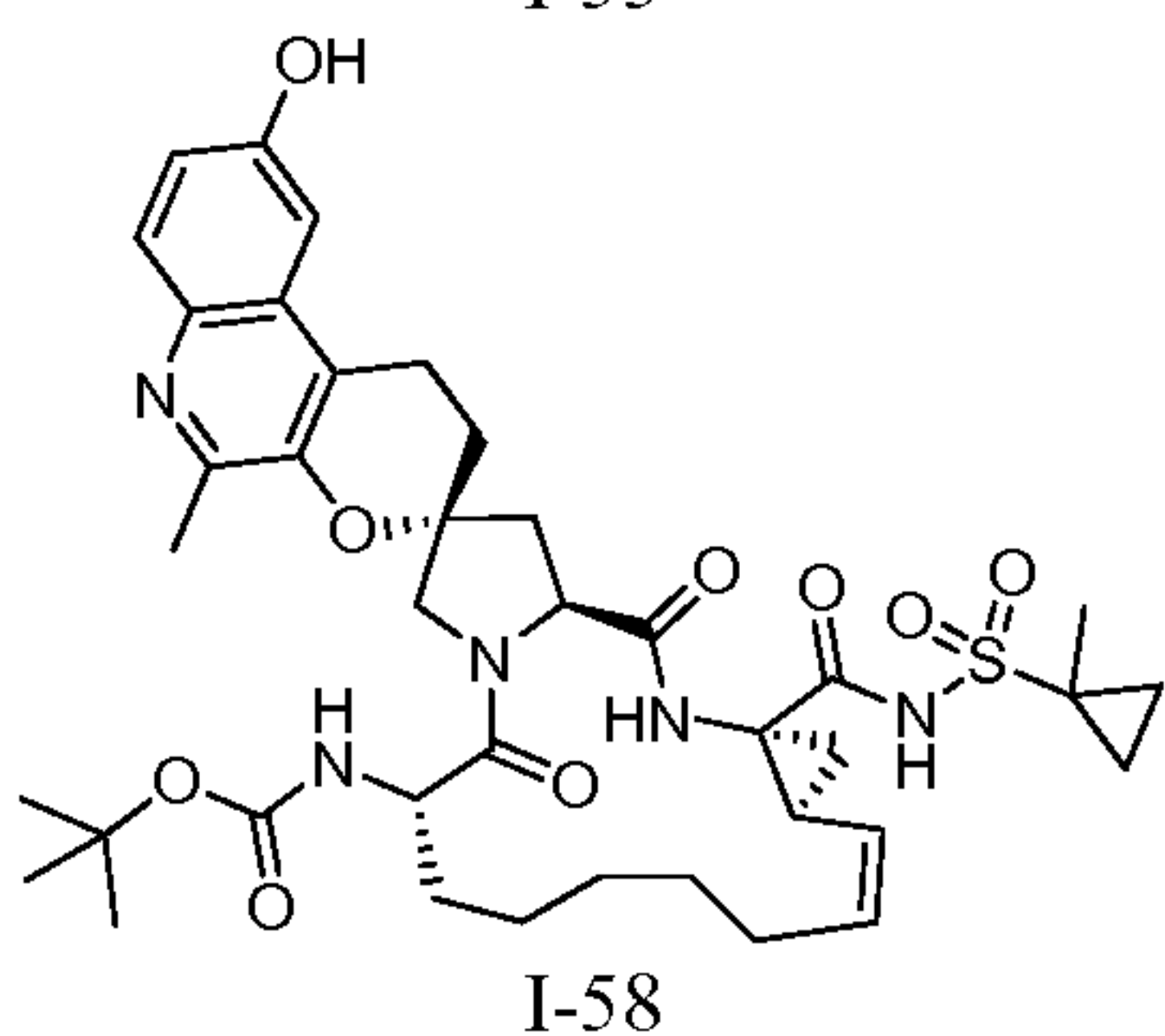
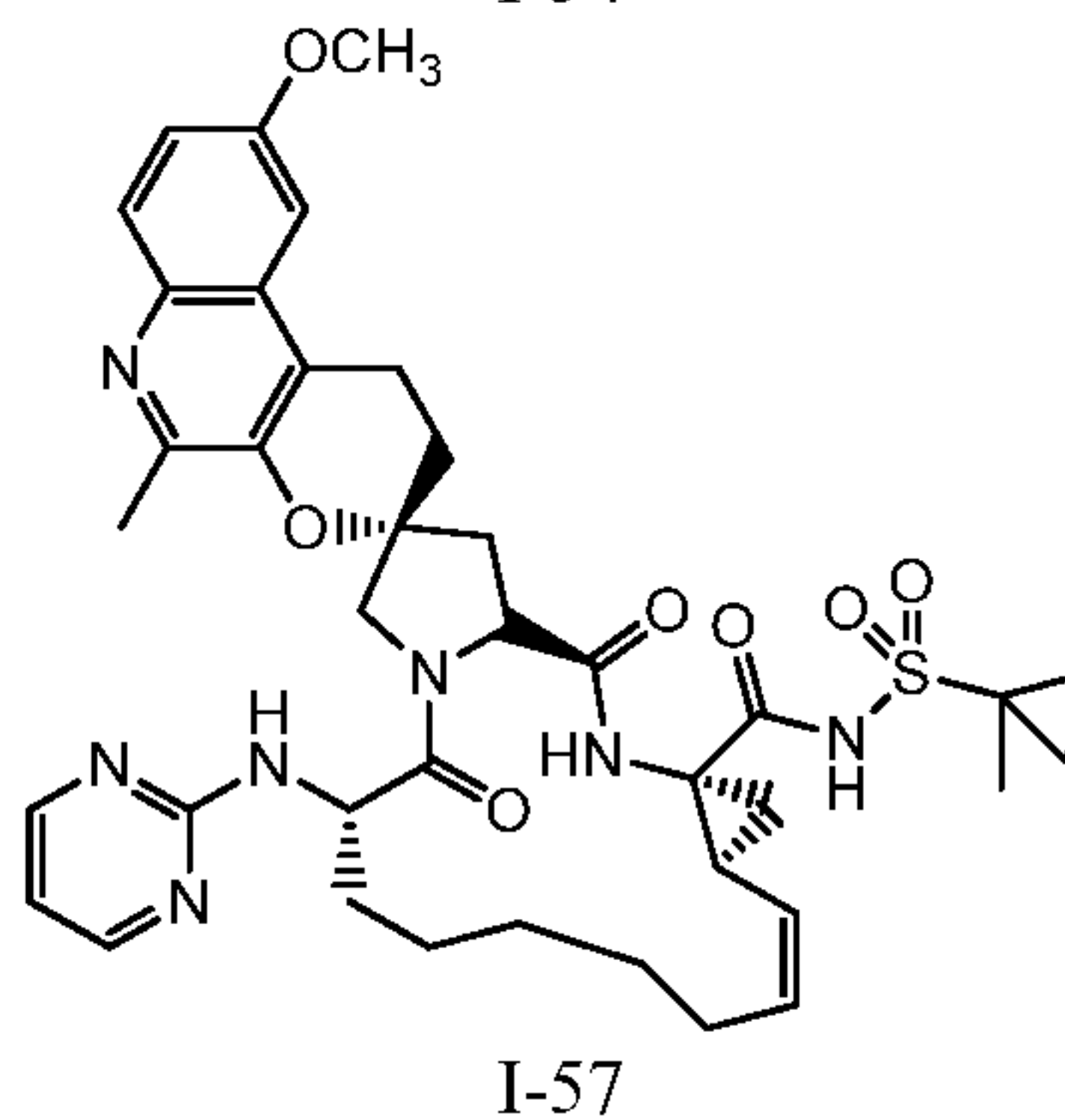
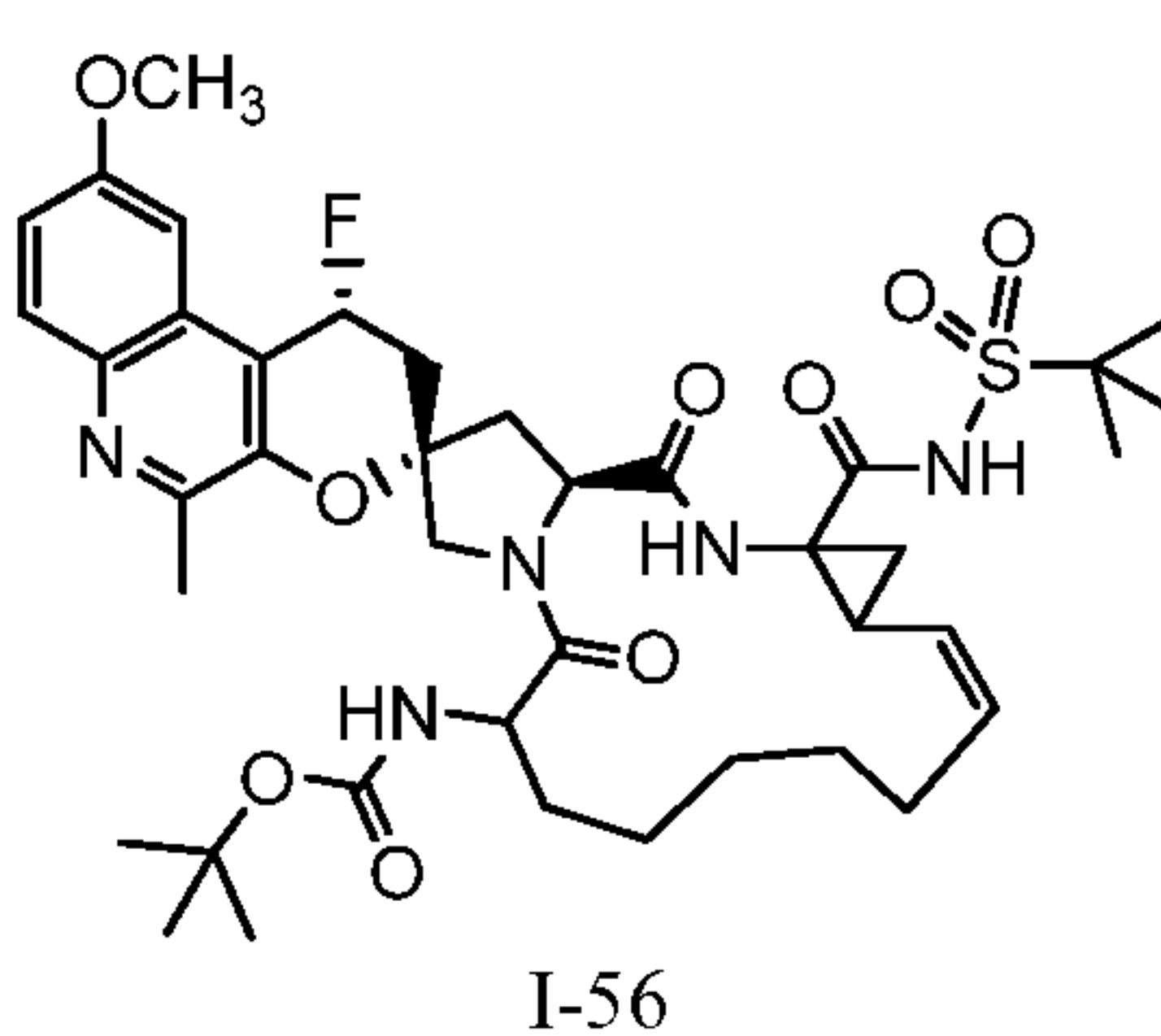
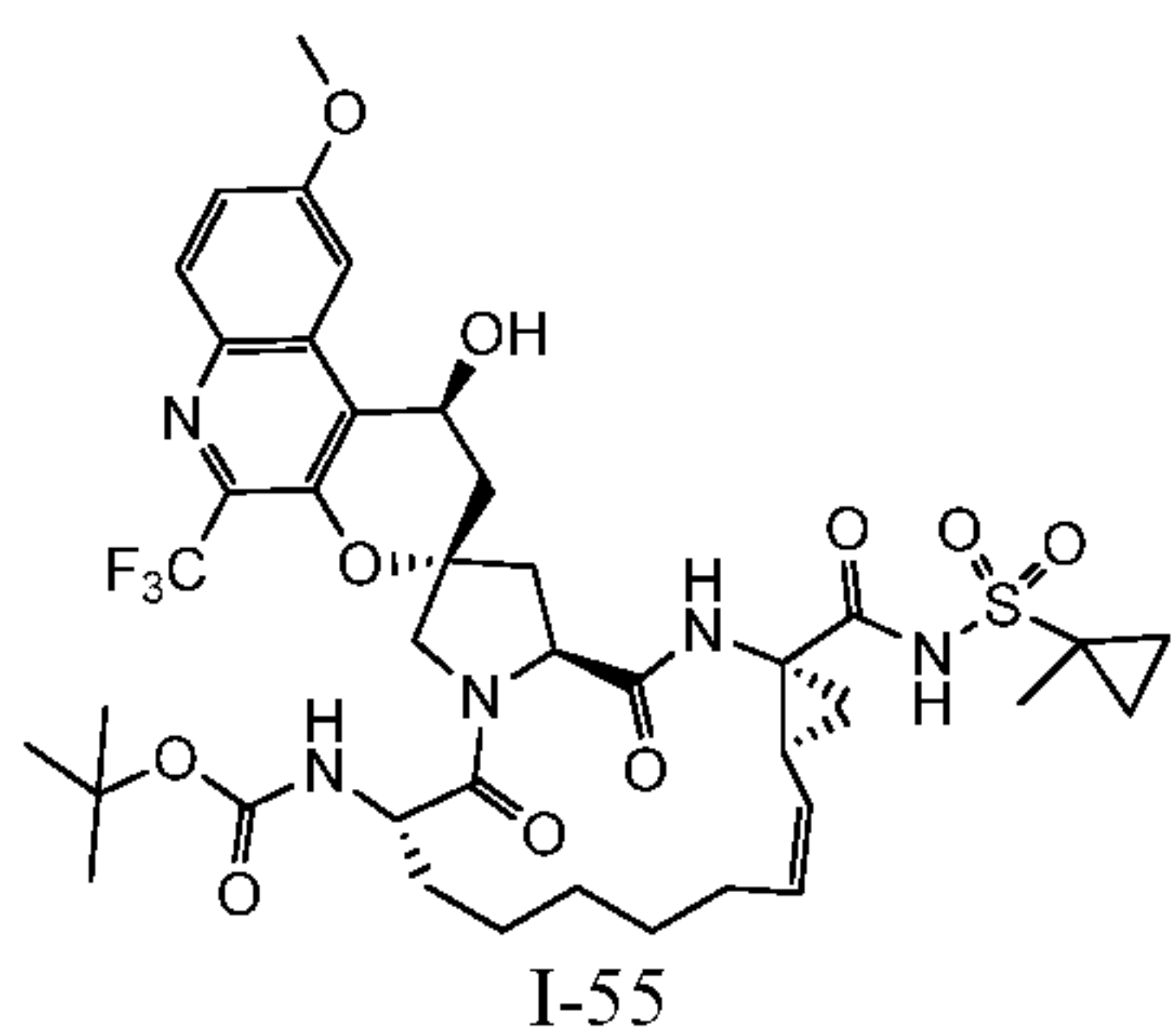
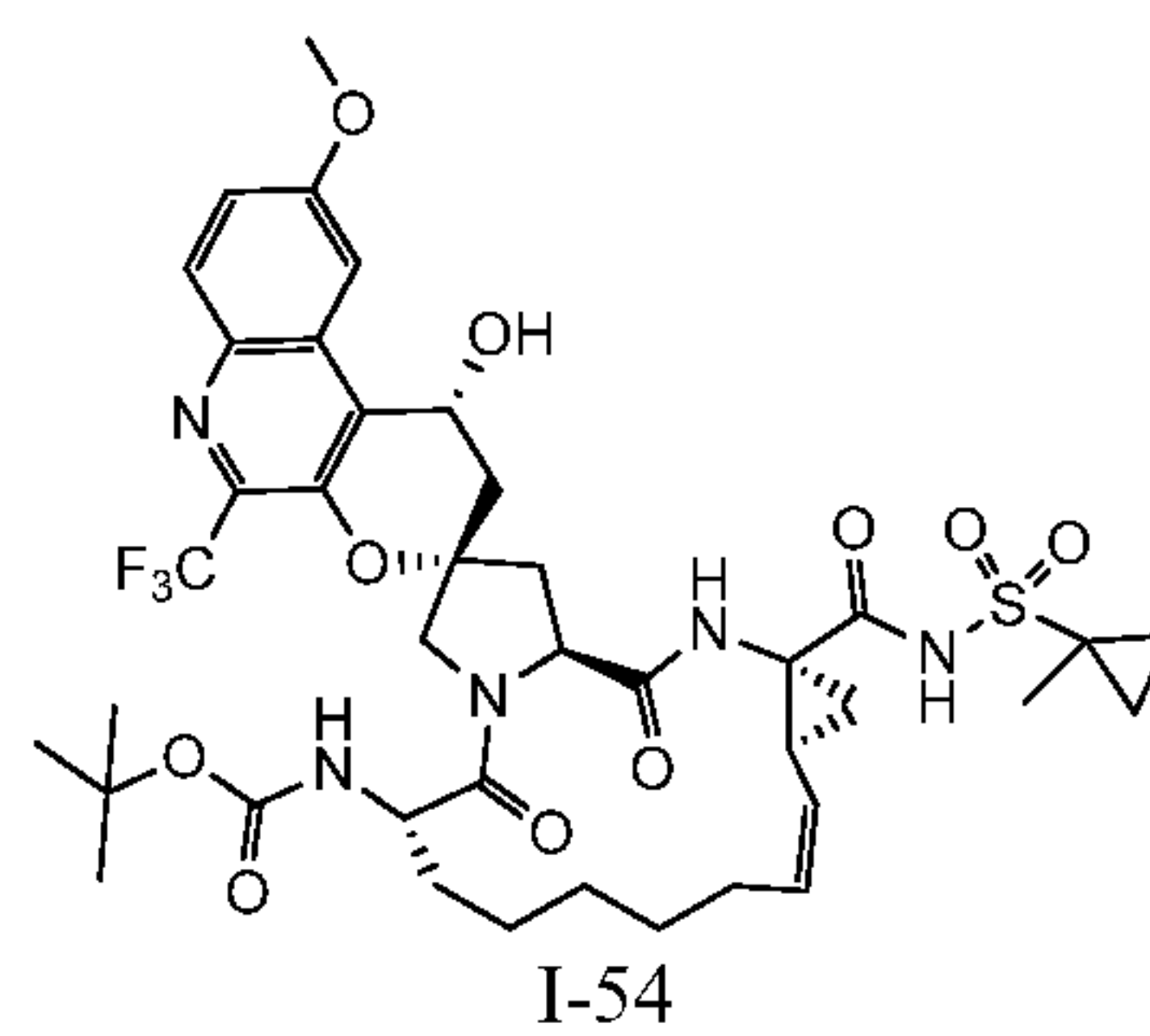
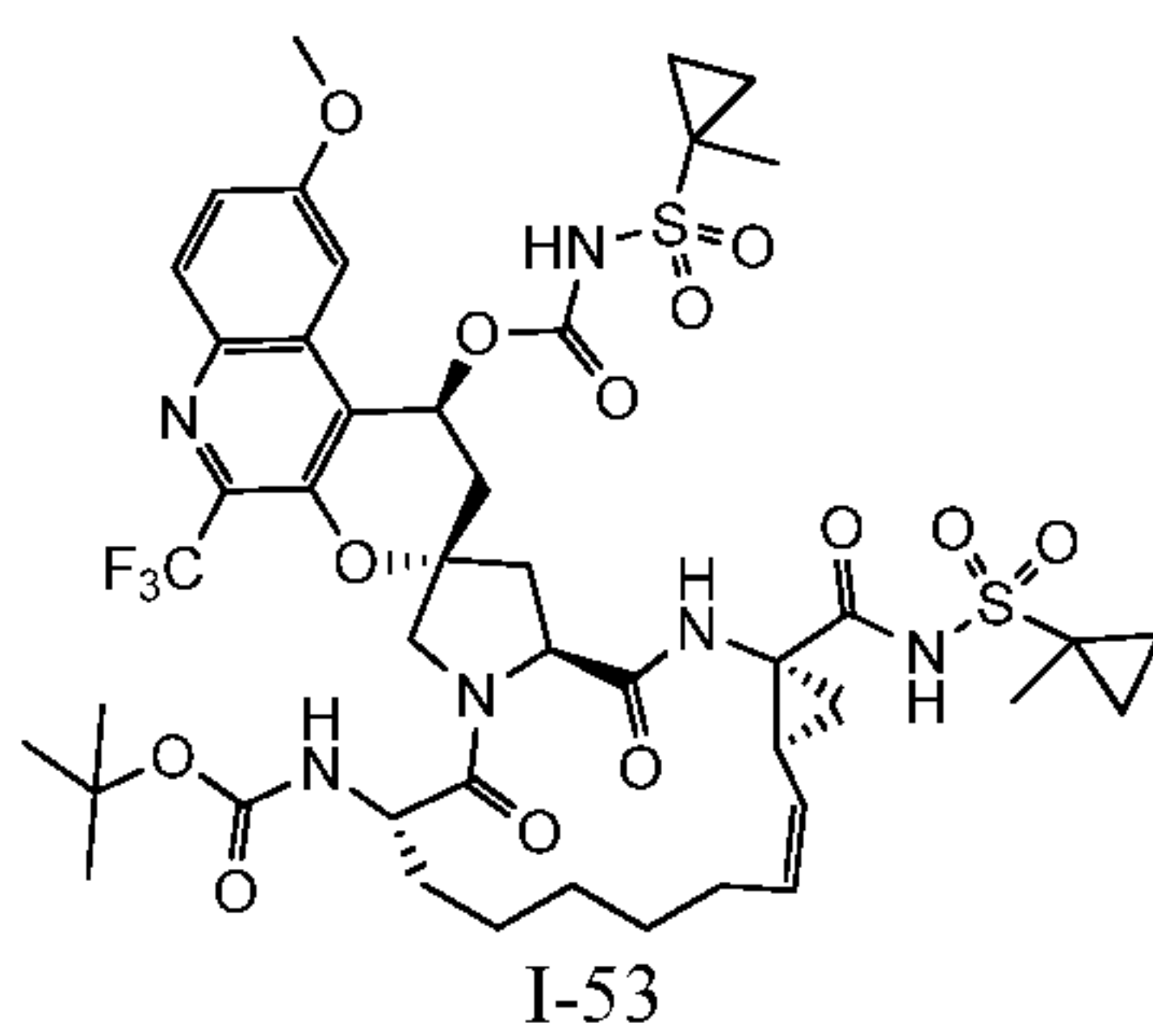
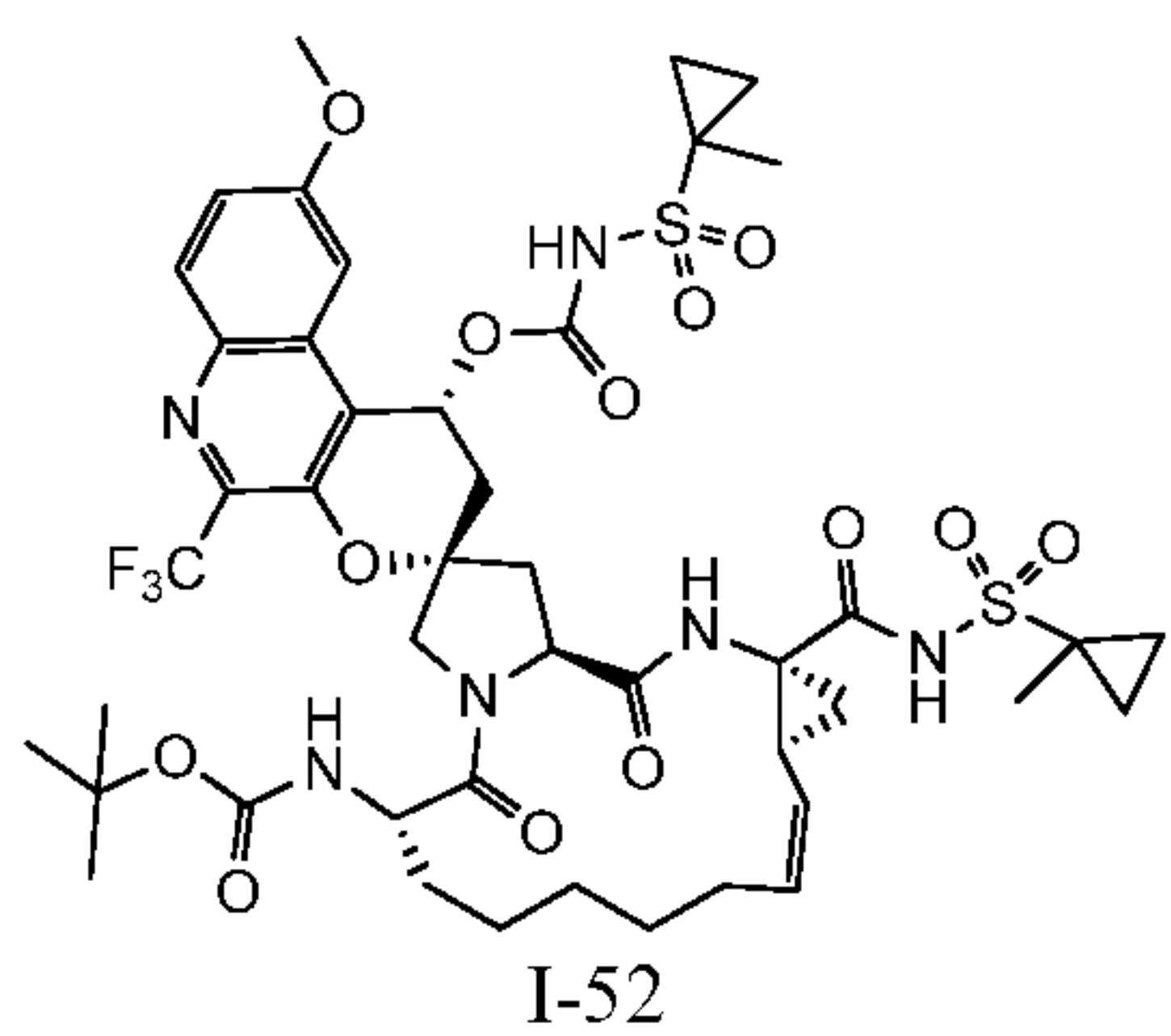


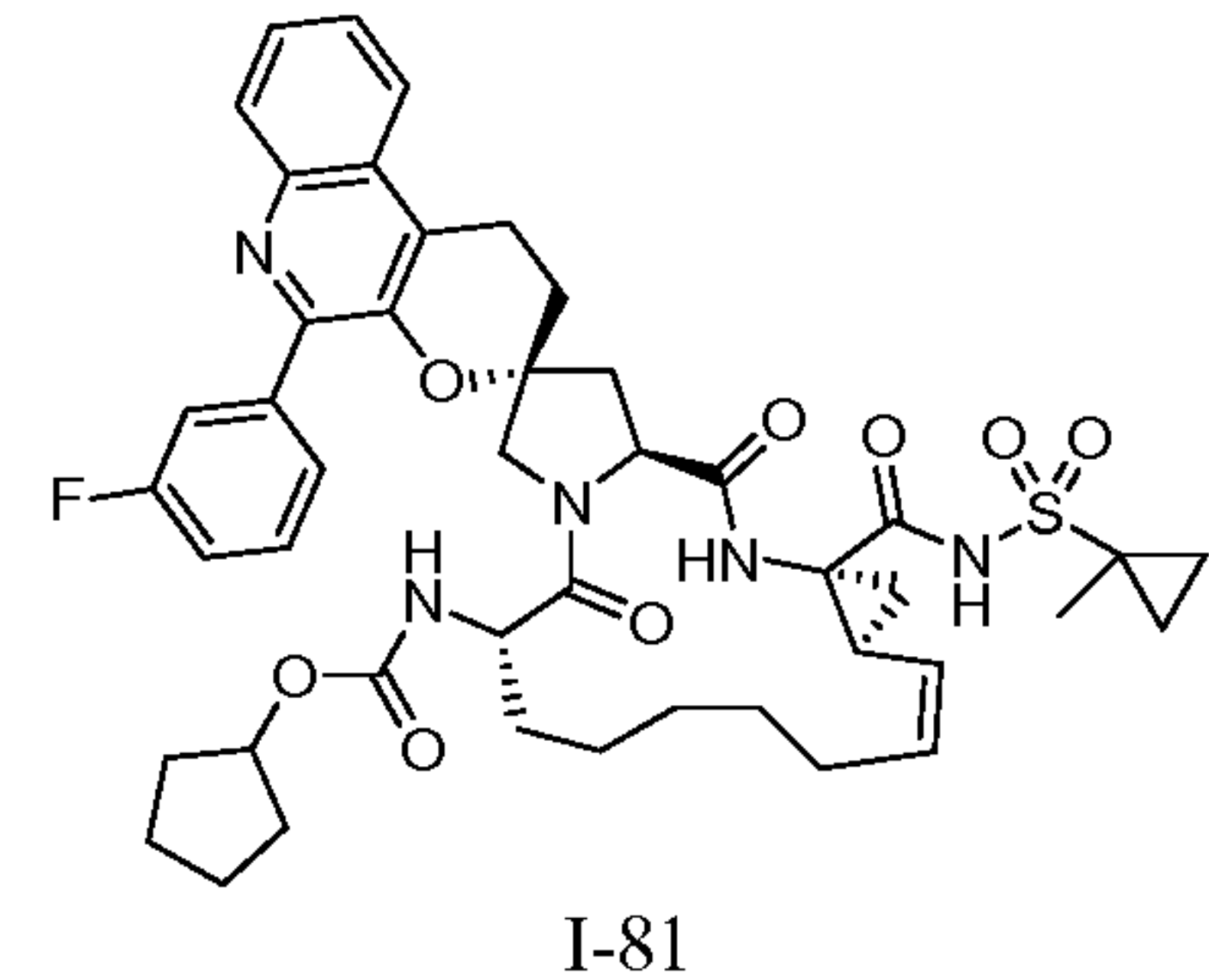
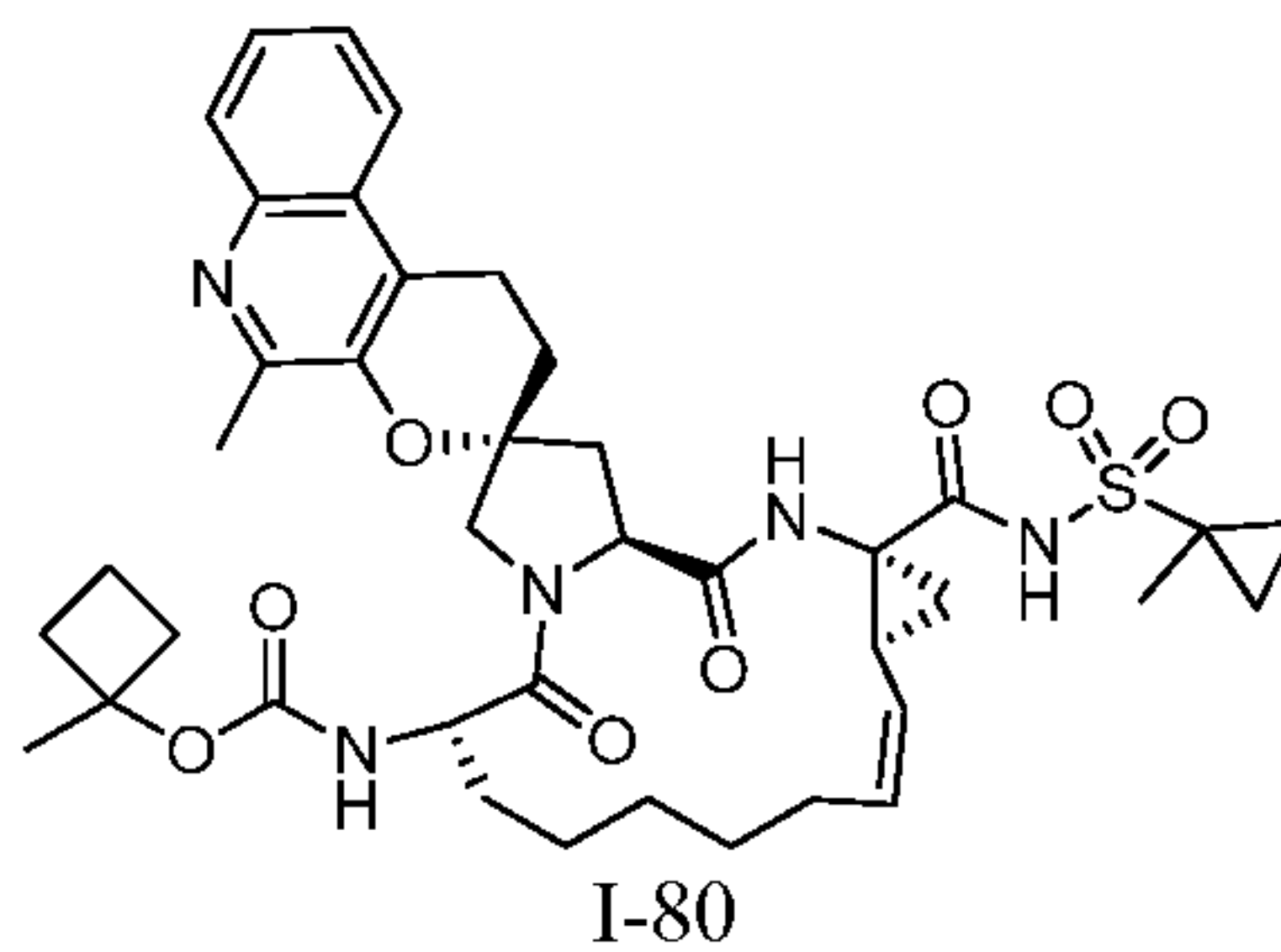
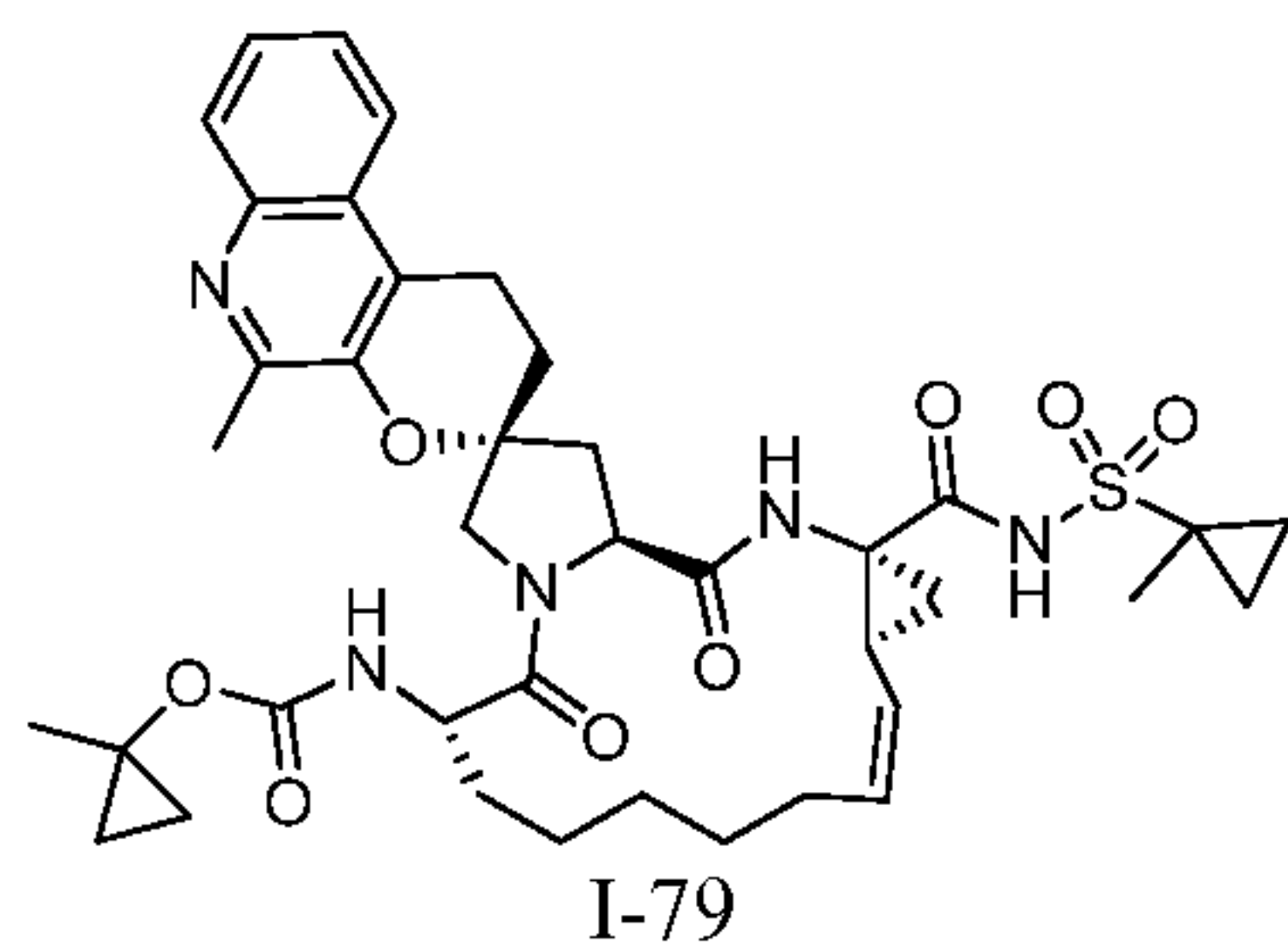
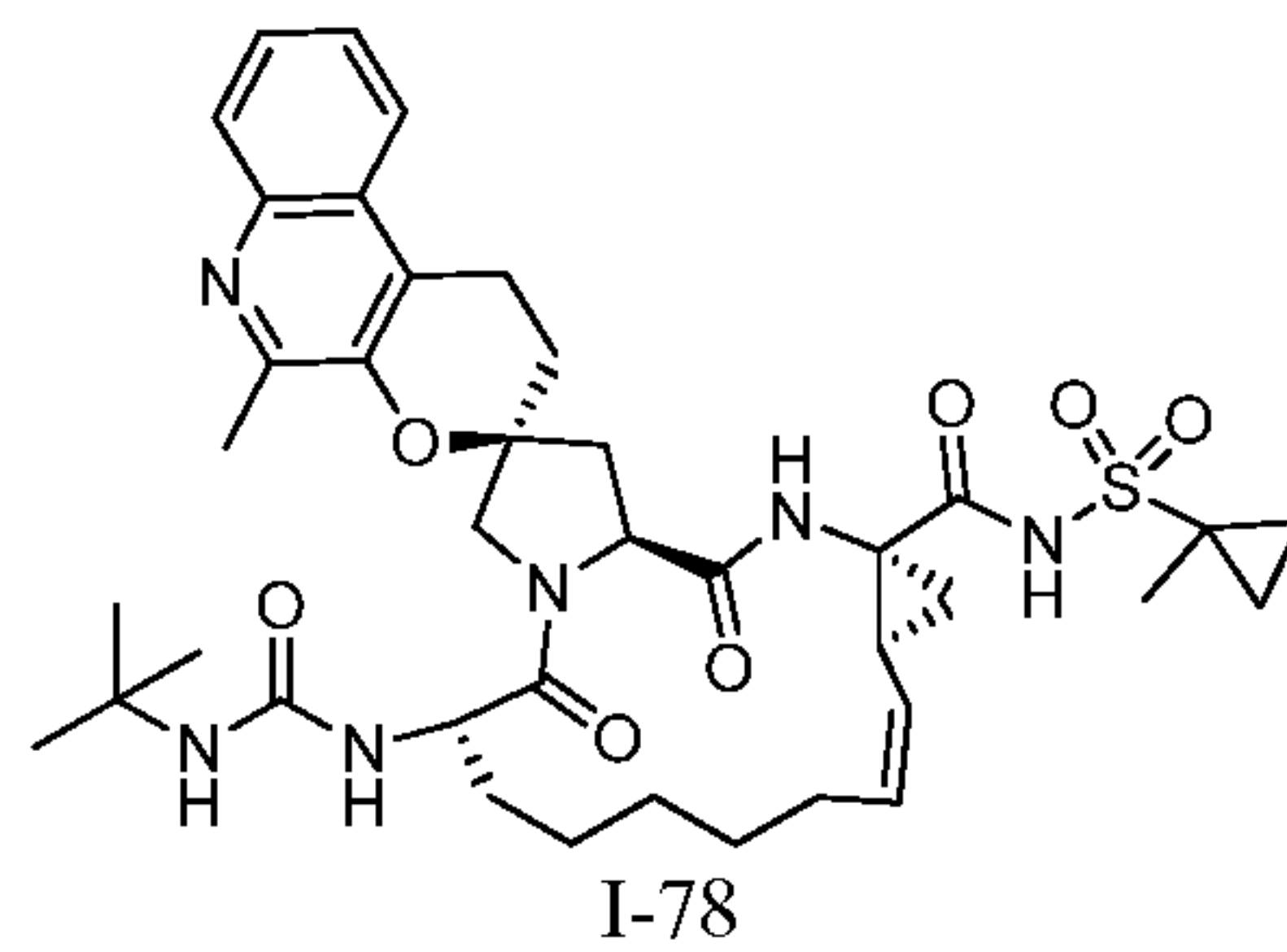
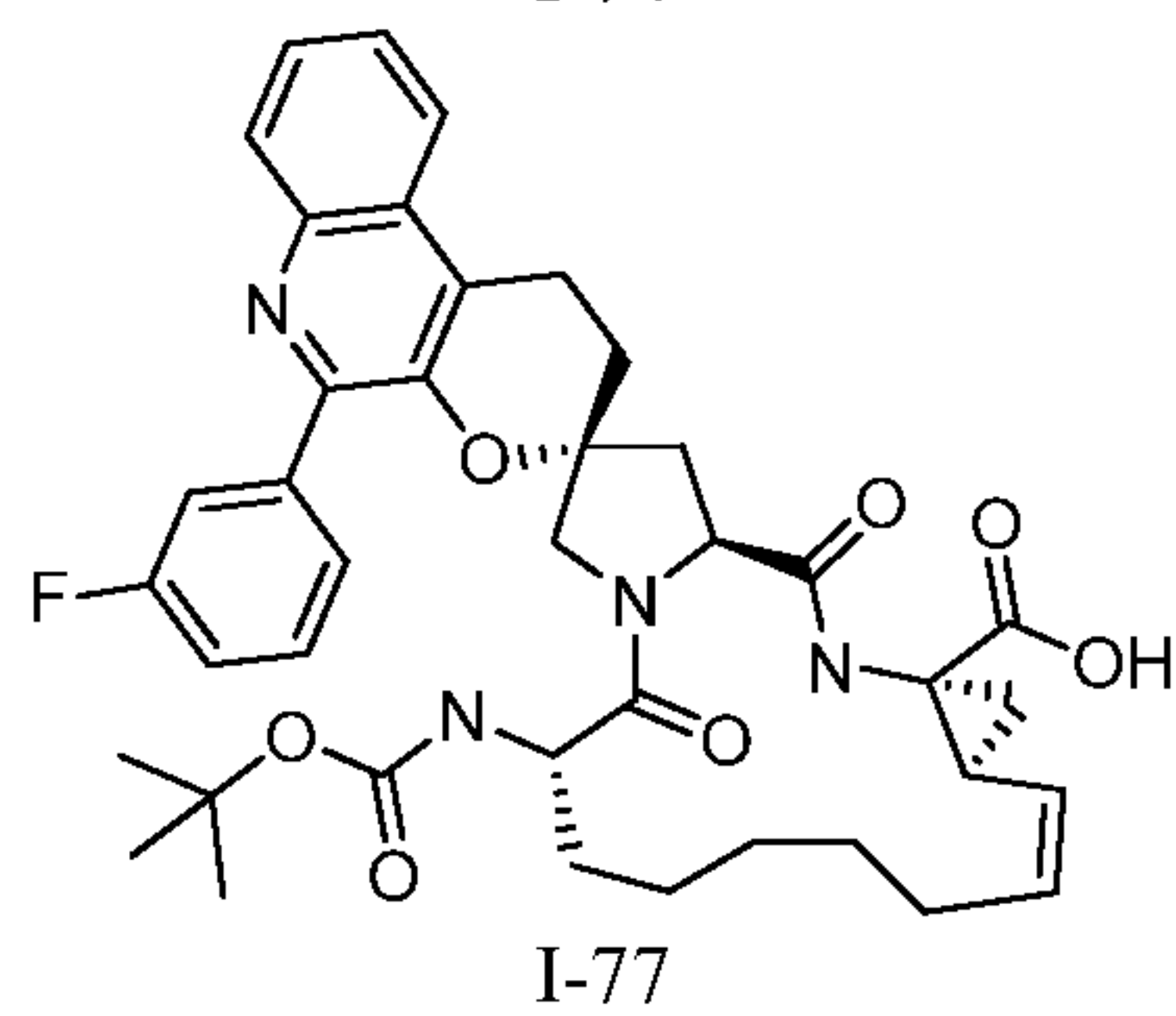
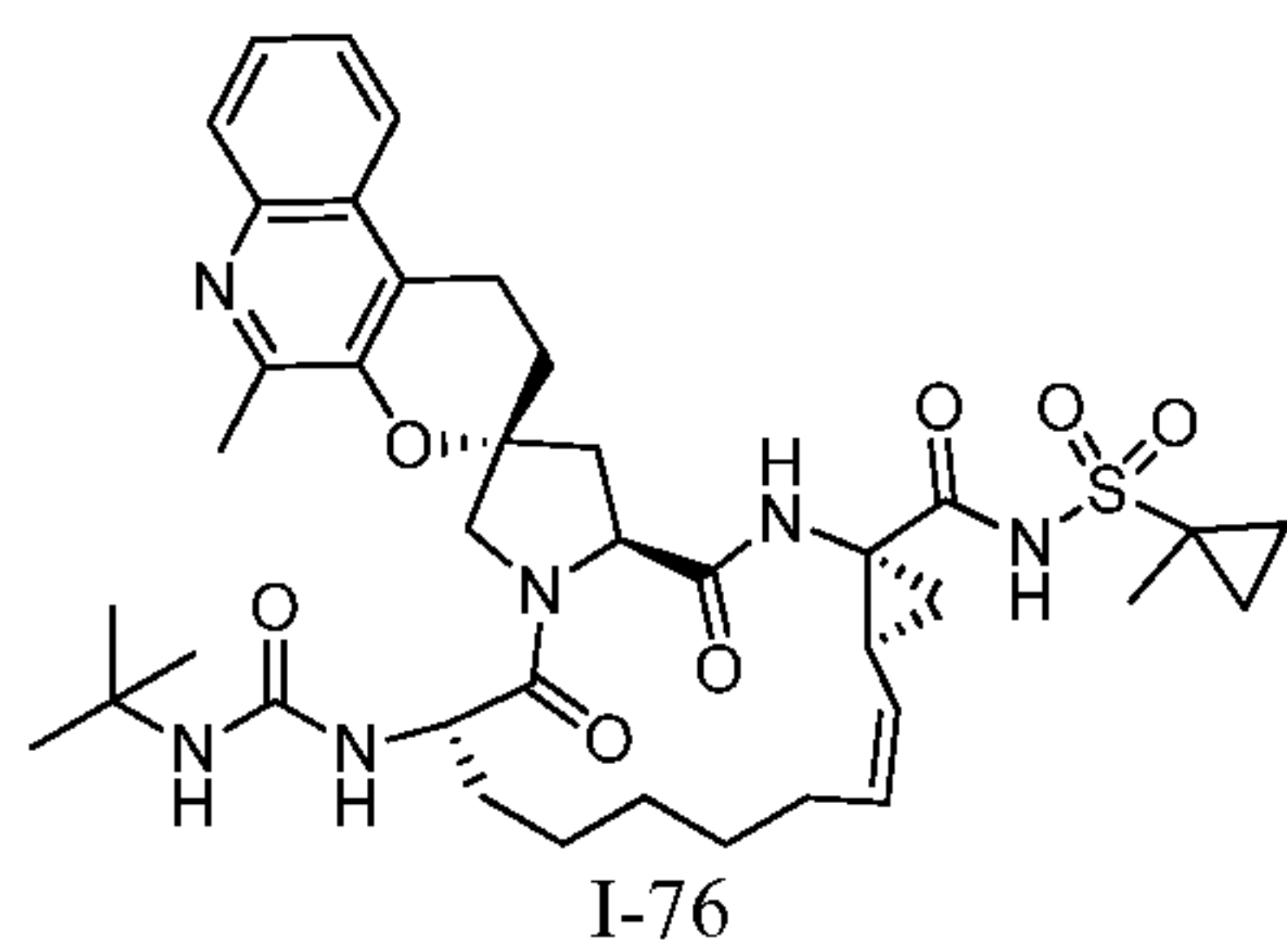
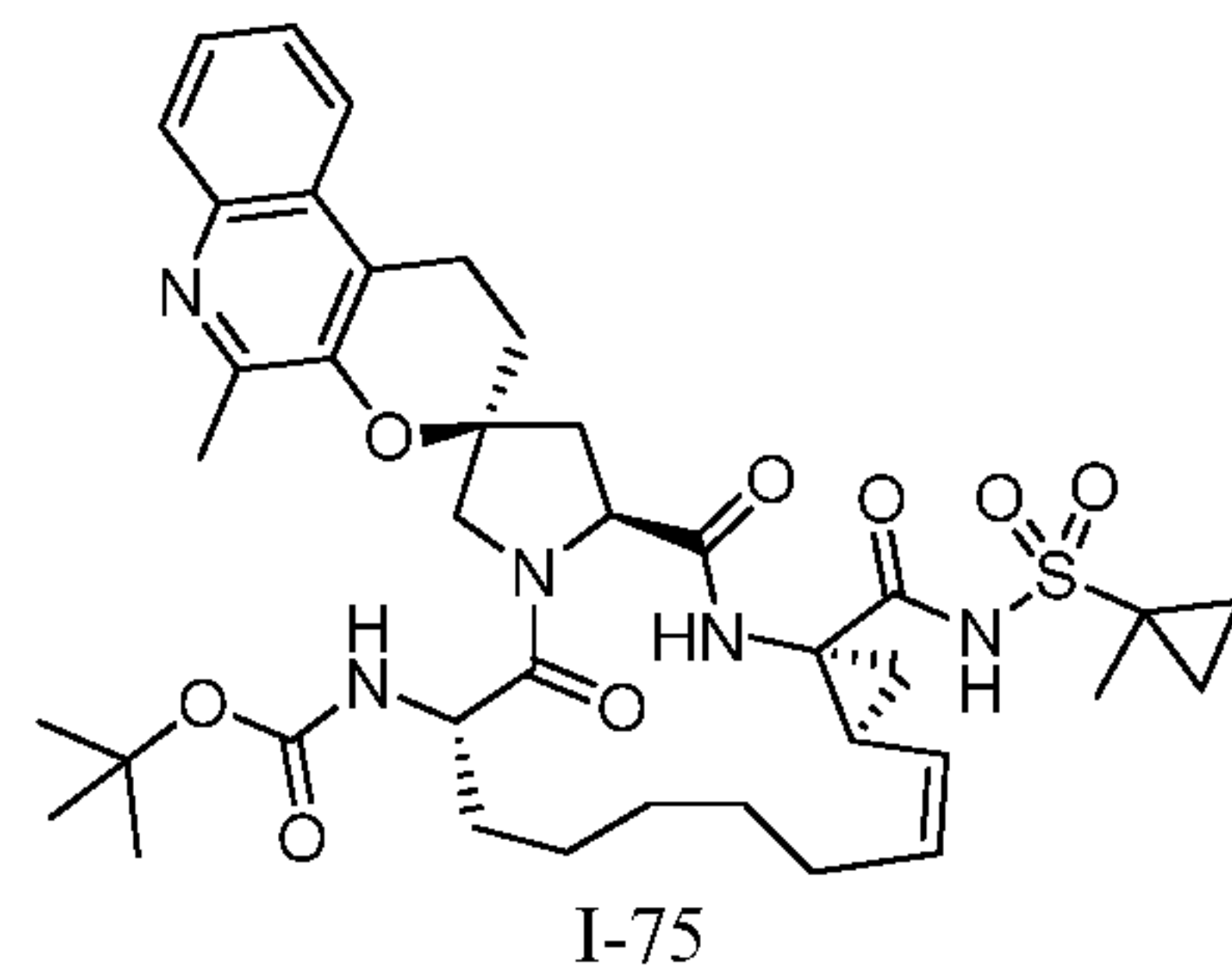
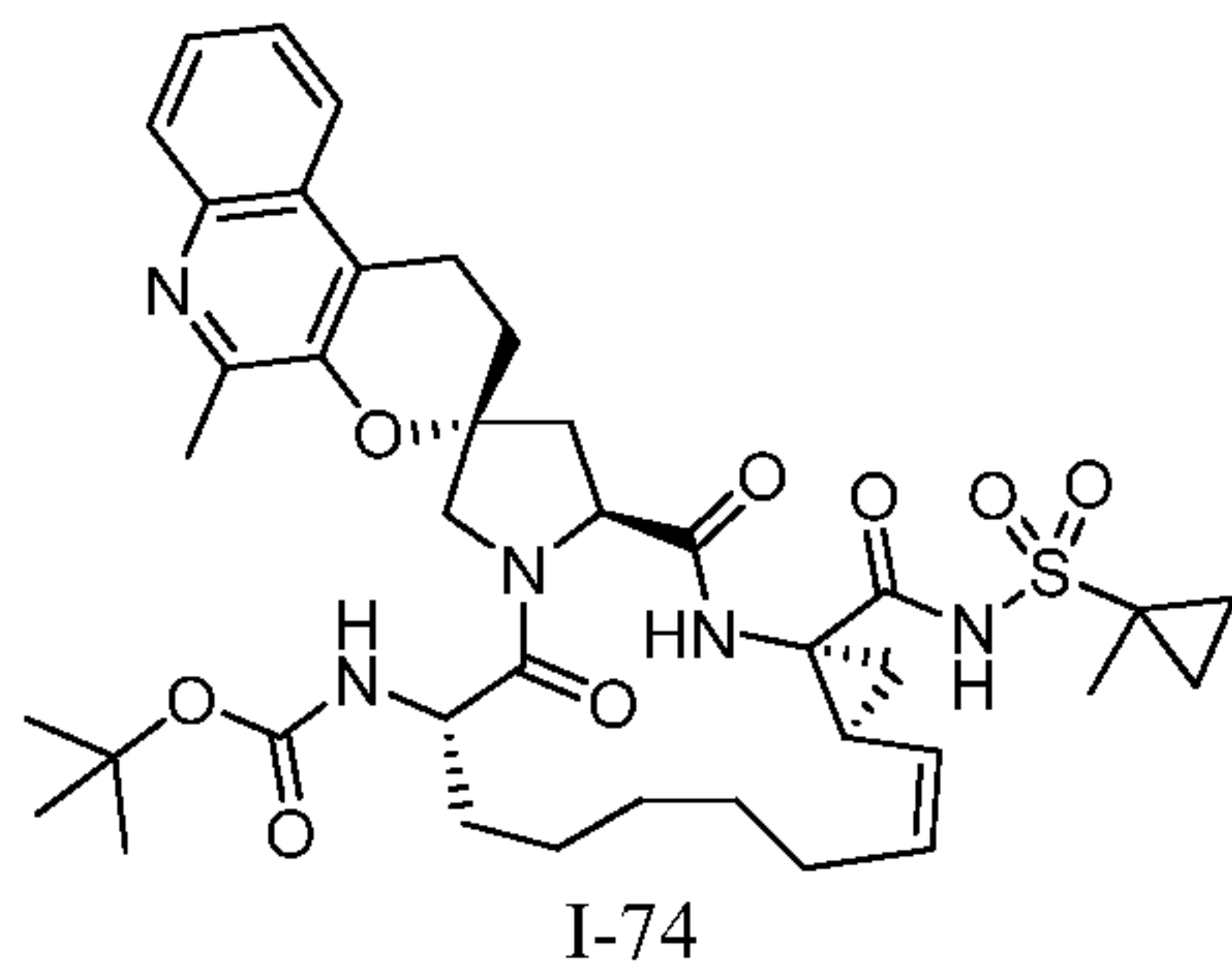
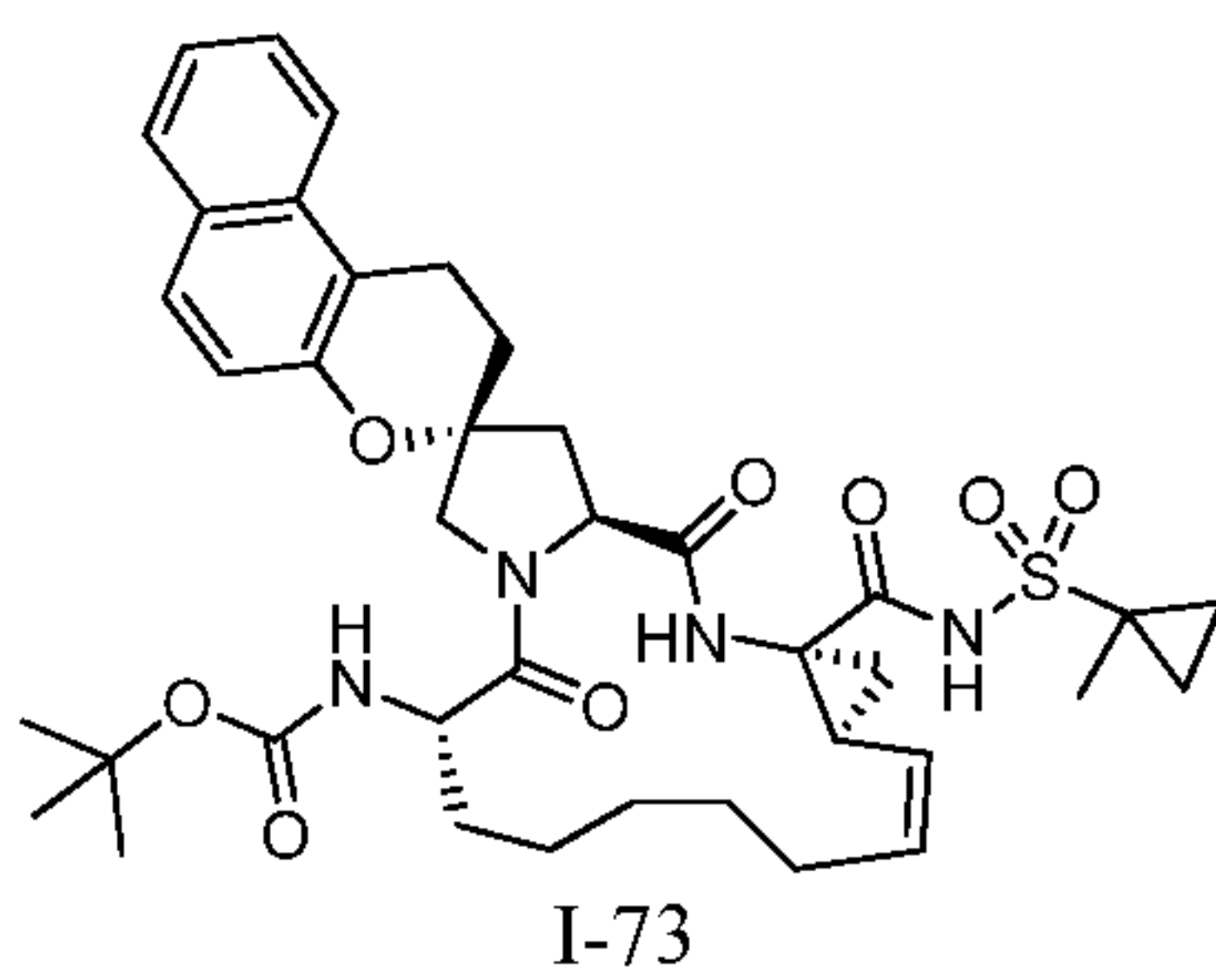
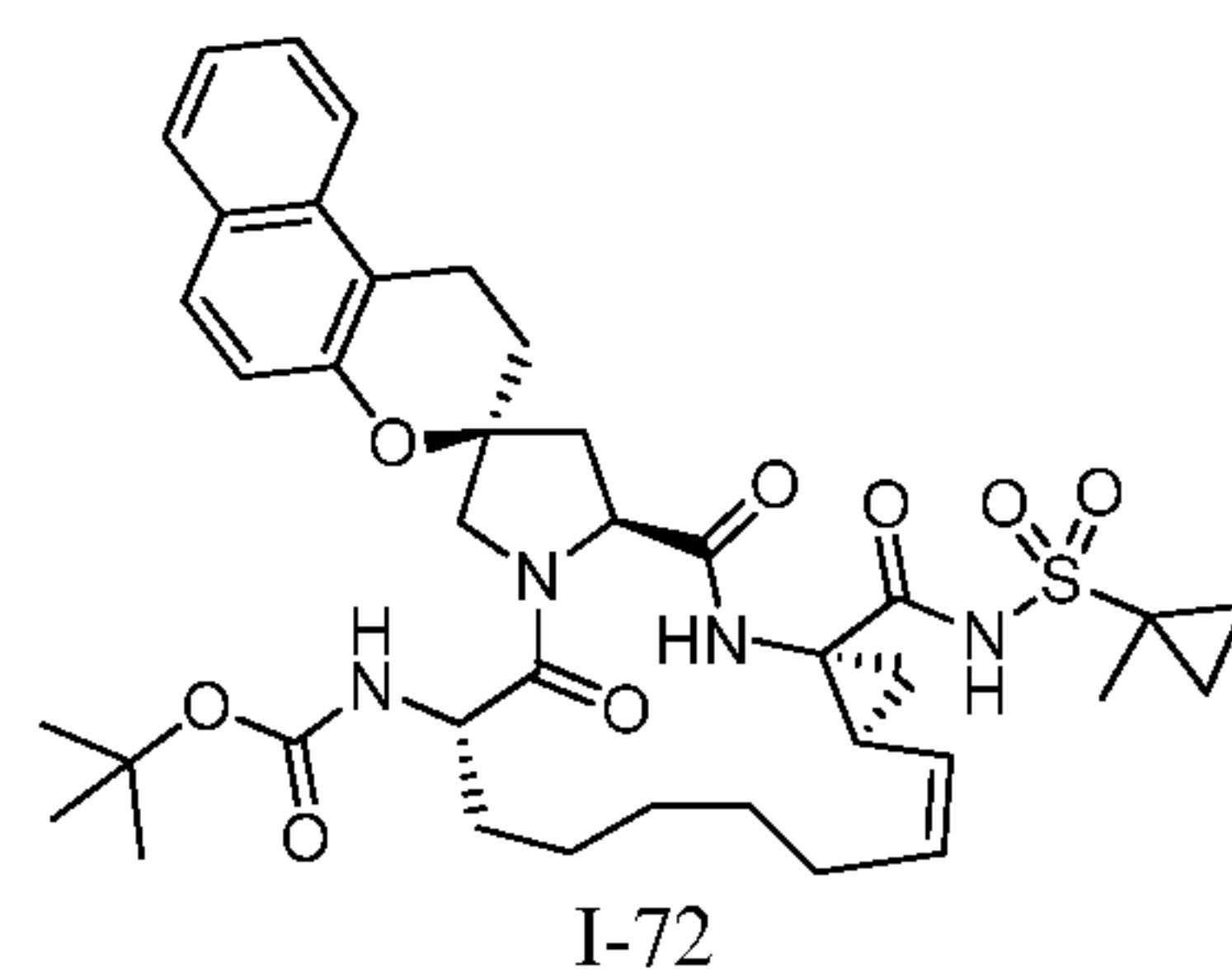
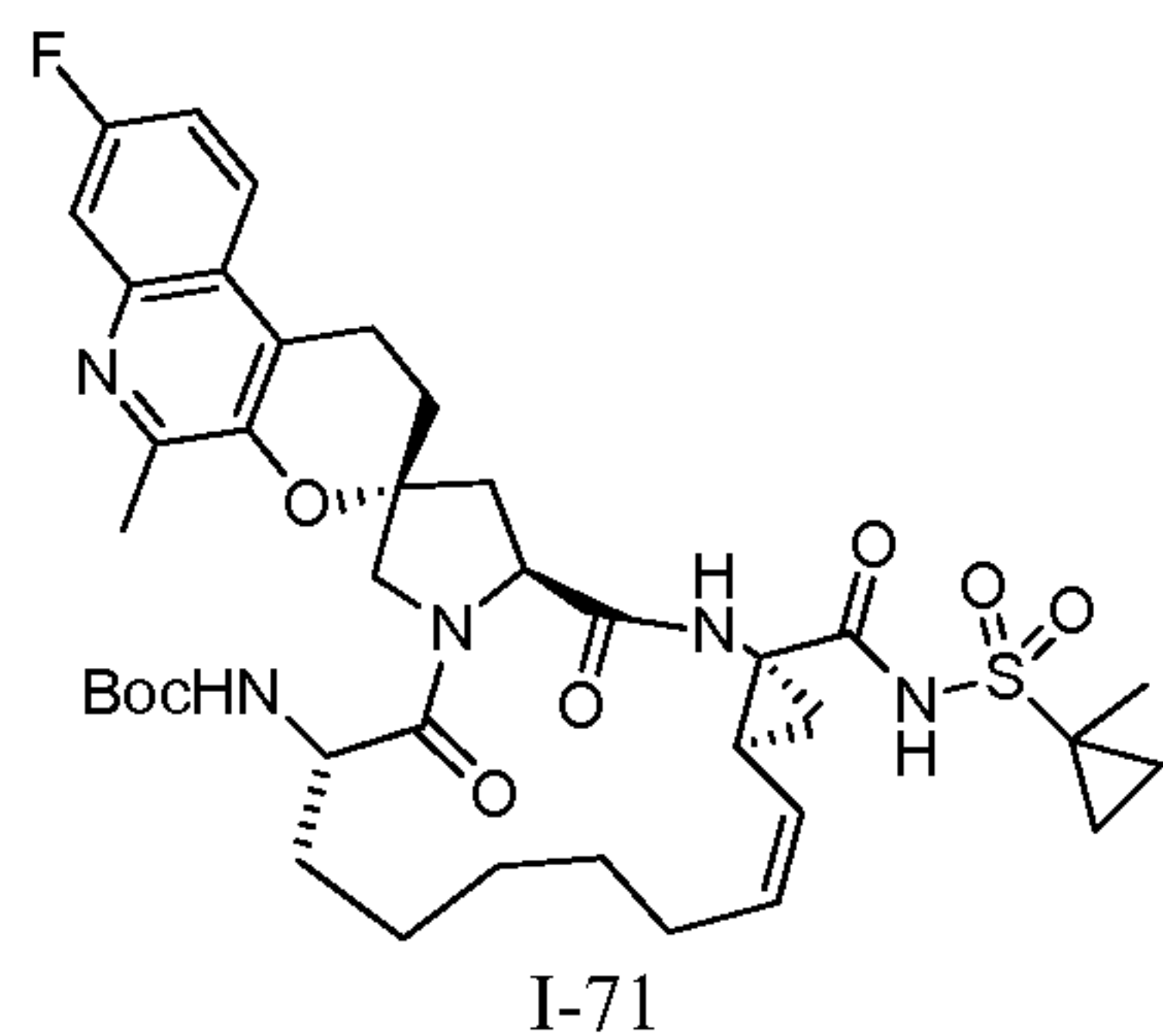
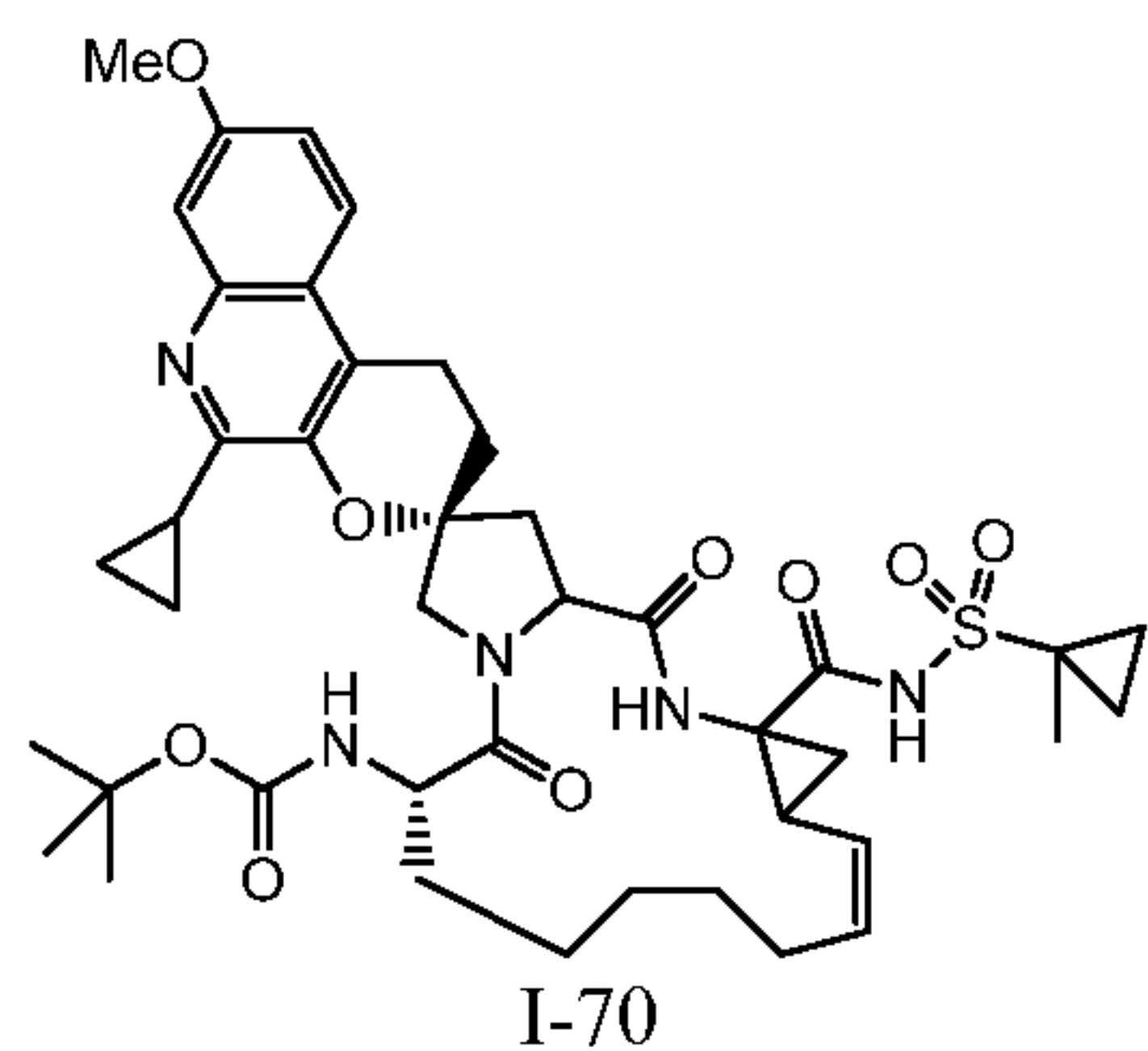
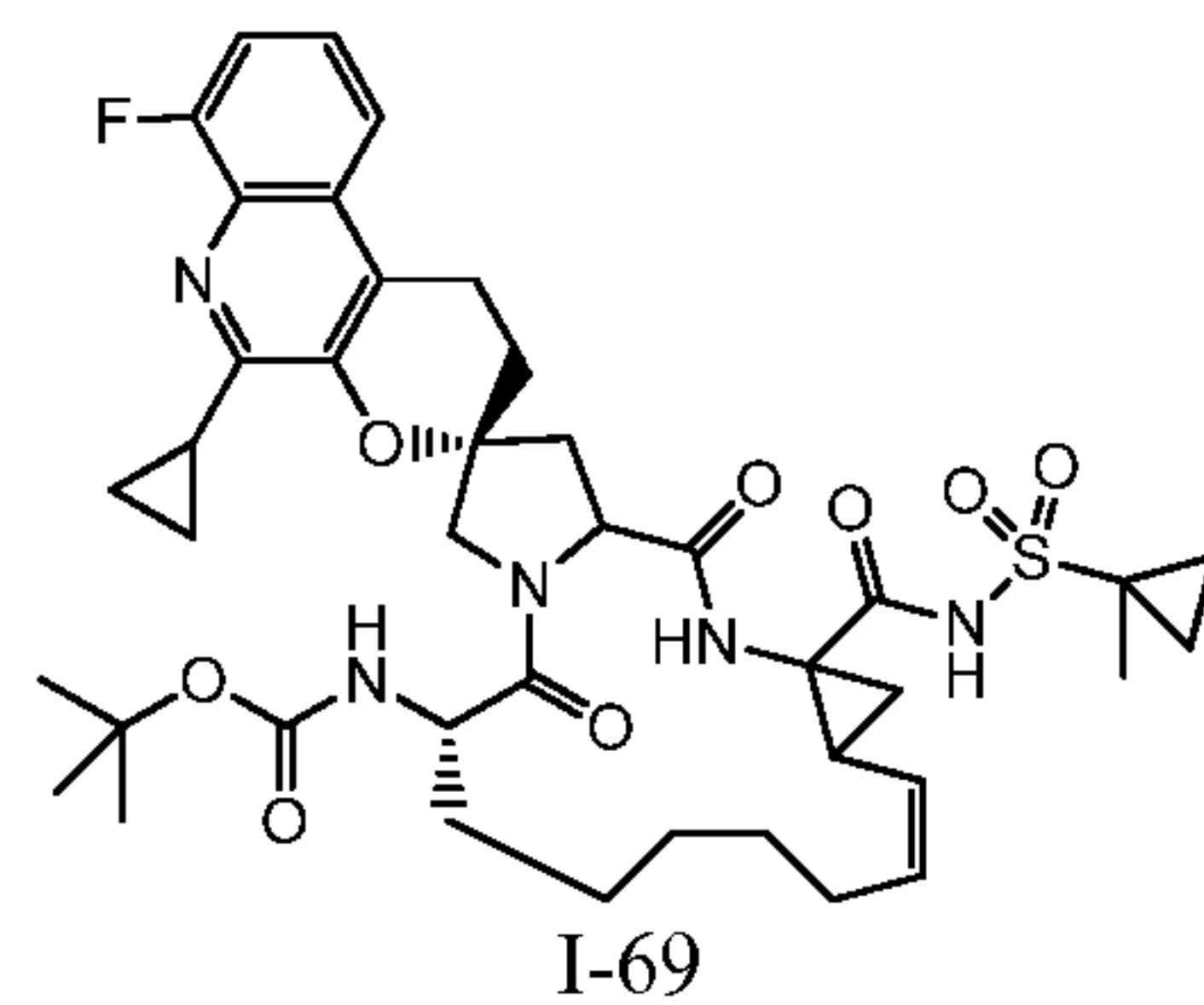
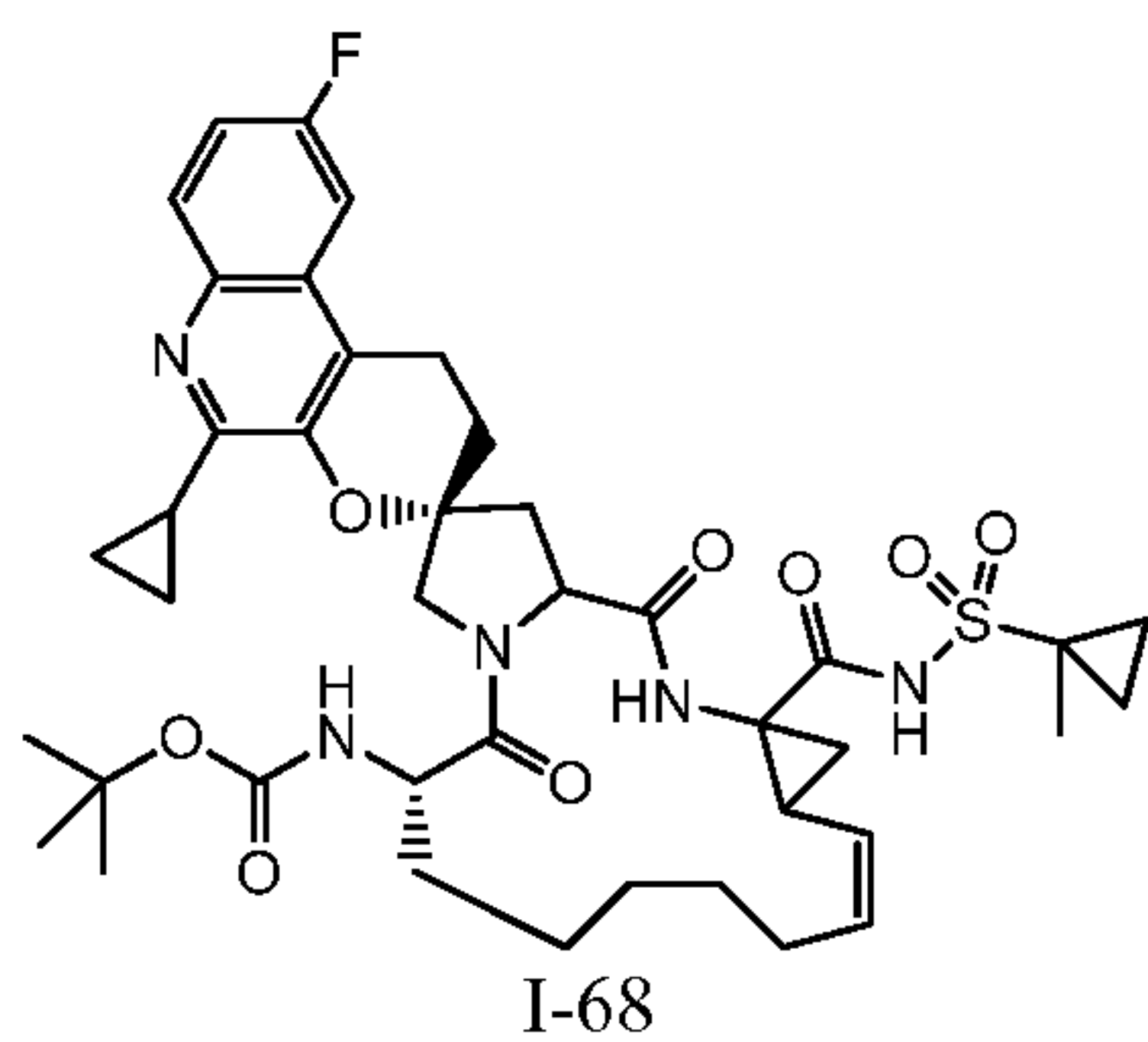
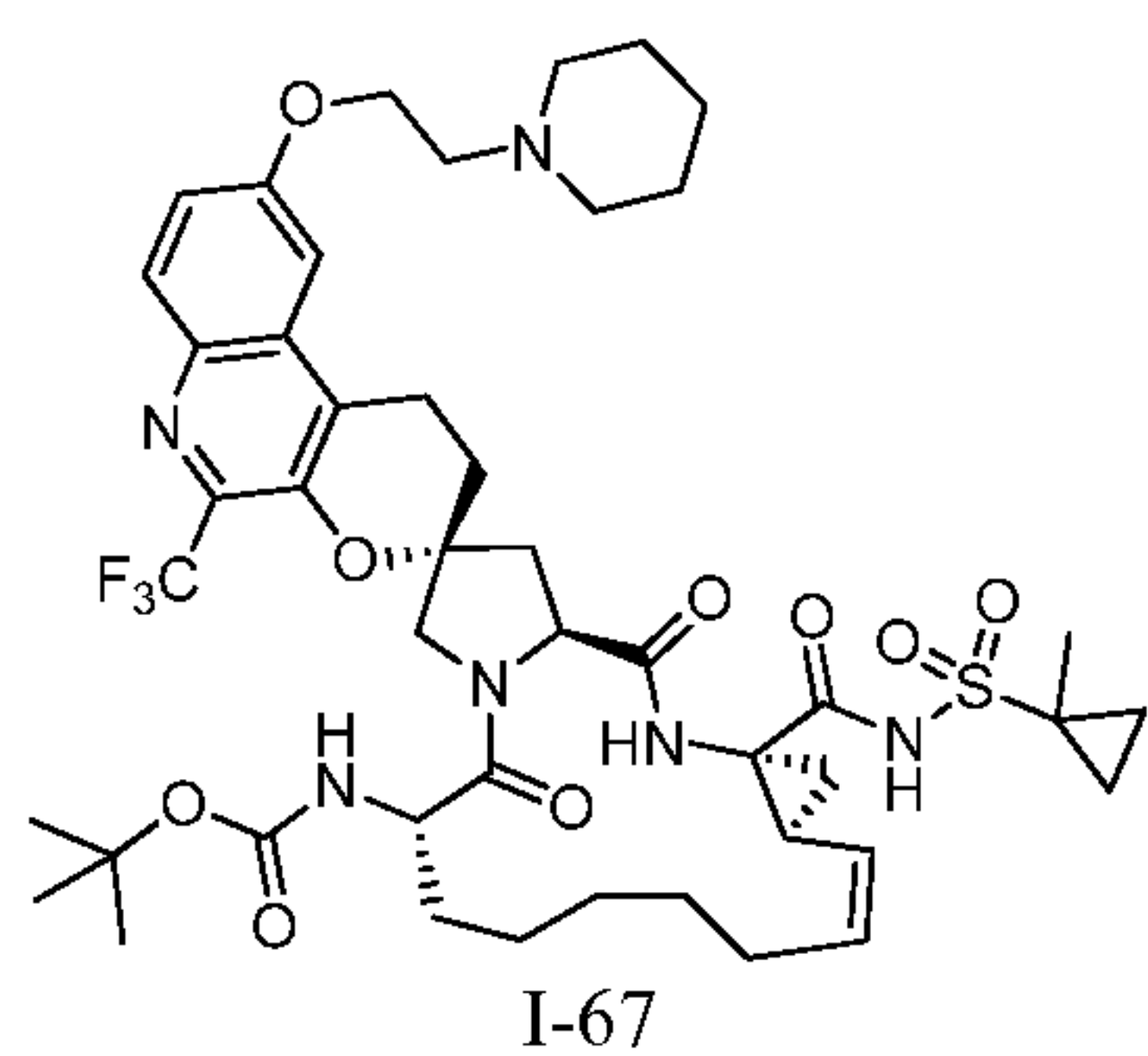
I-35

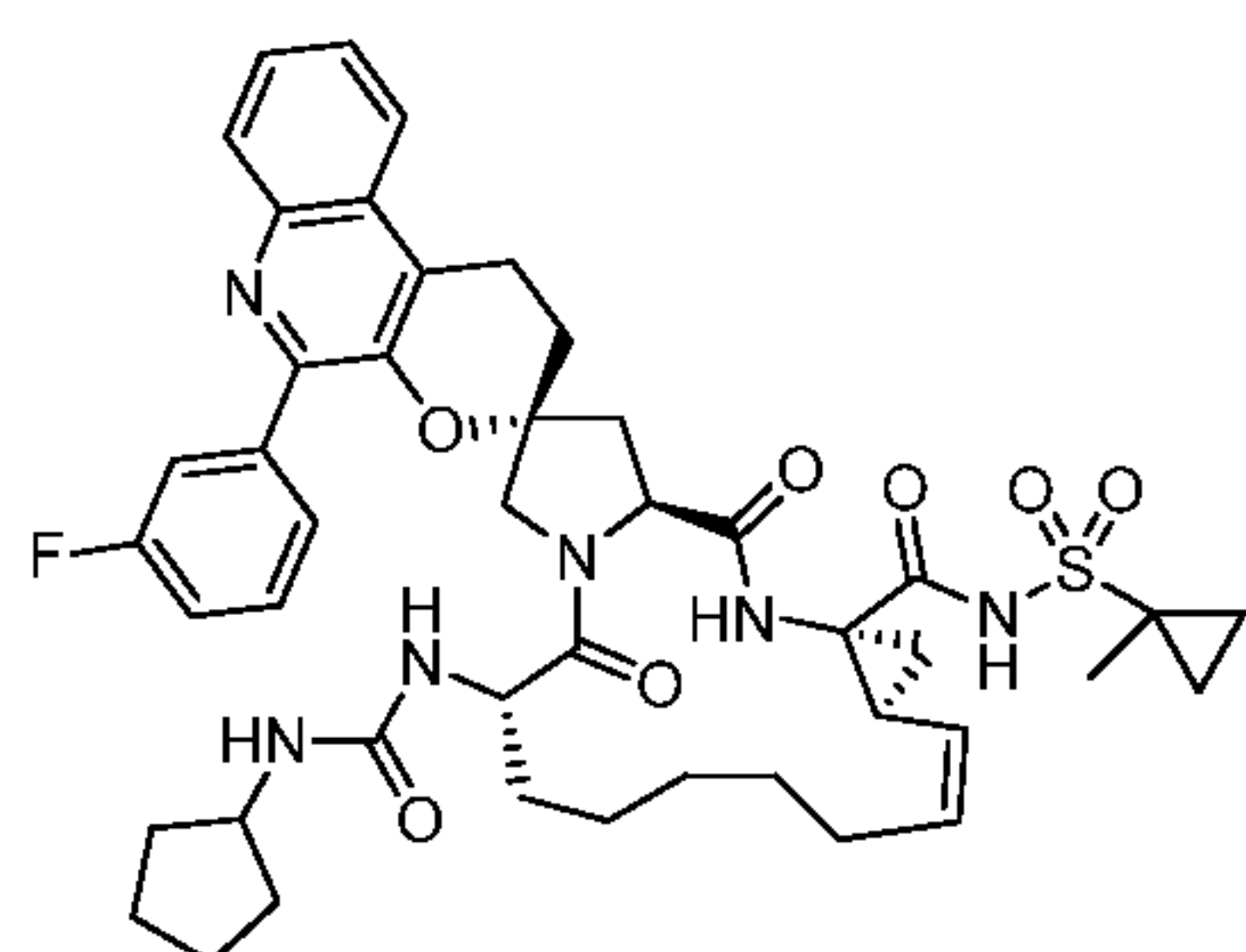


I-36

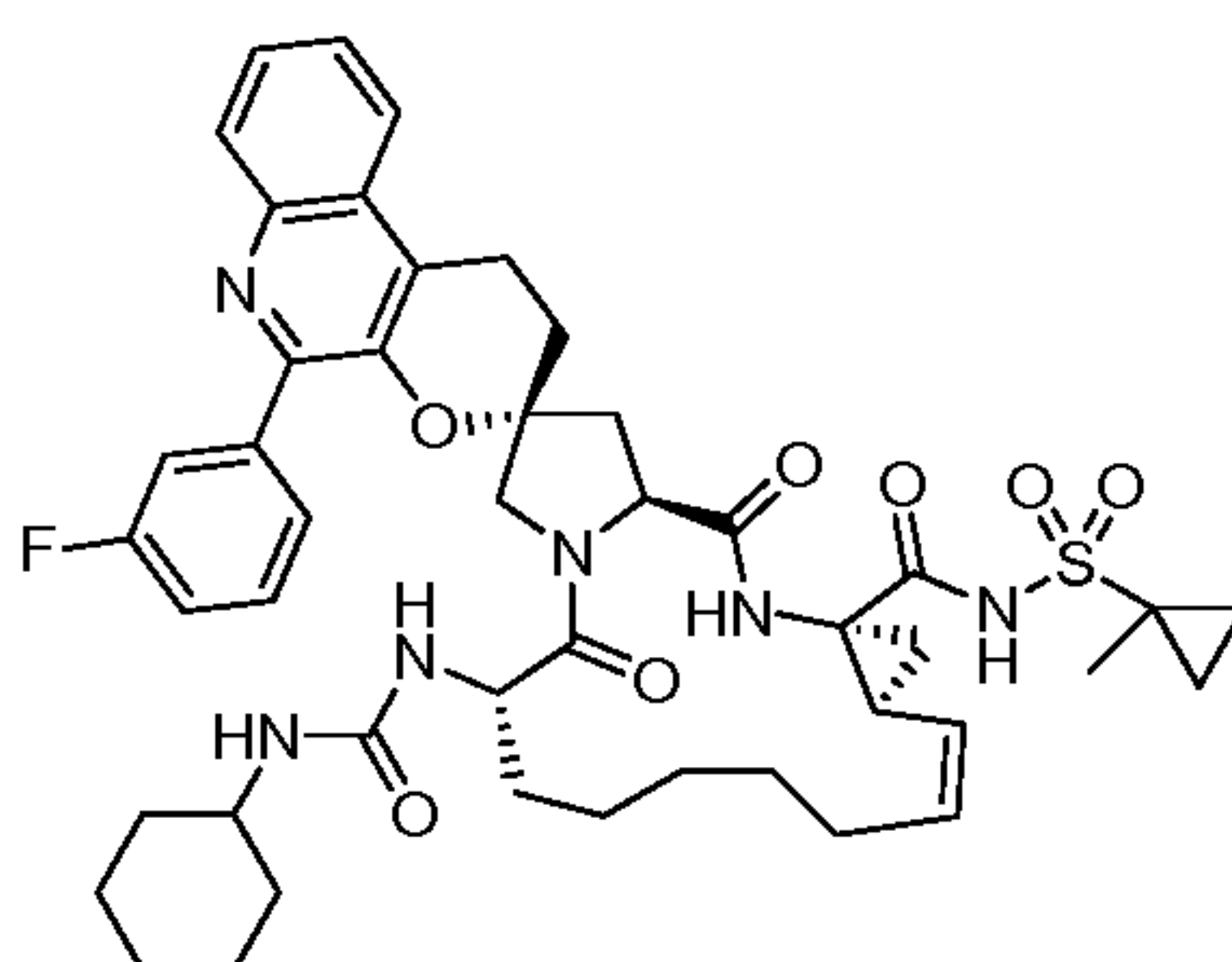




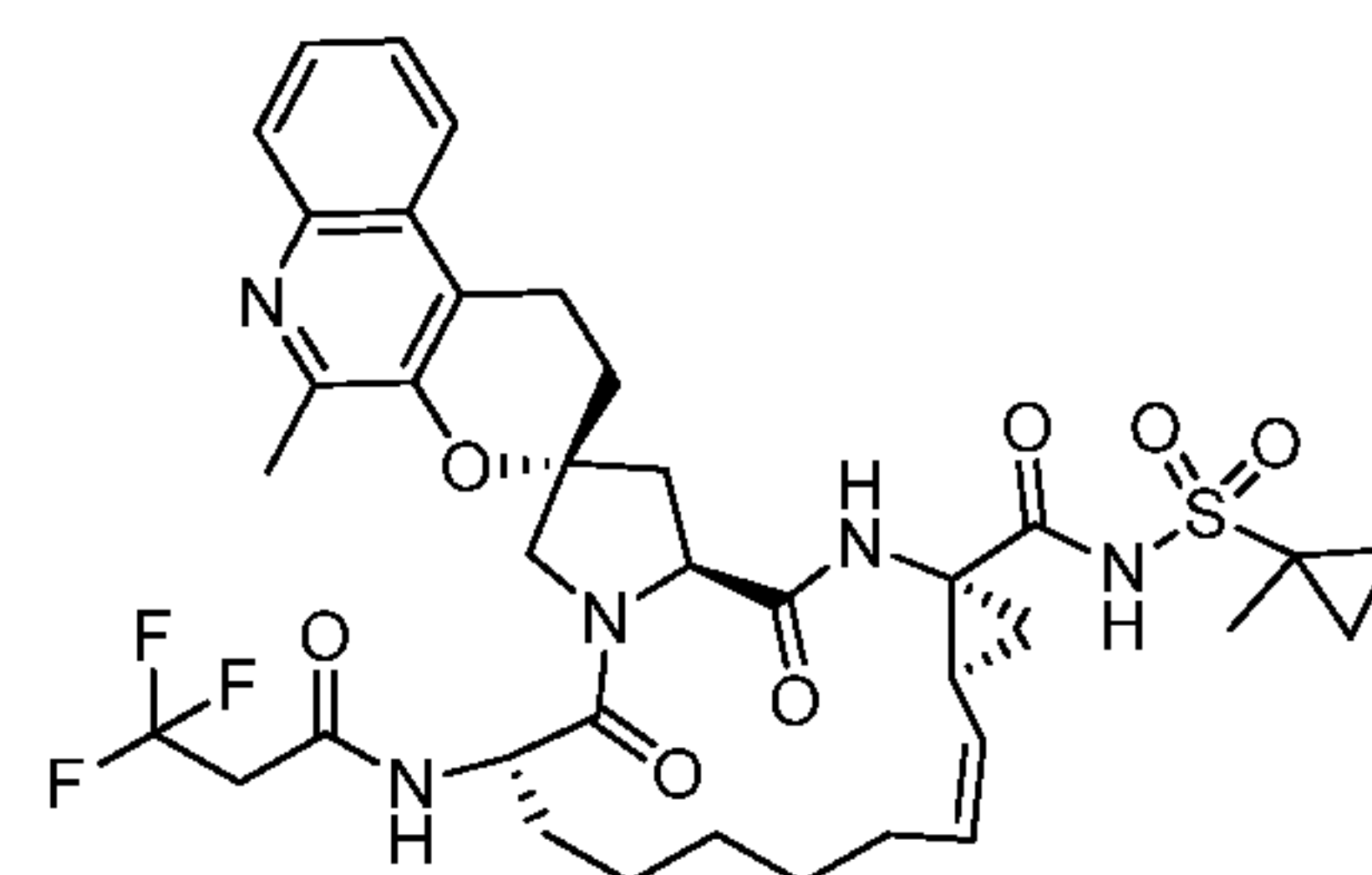




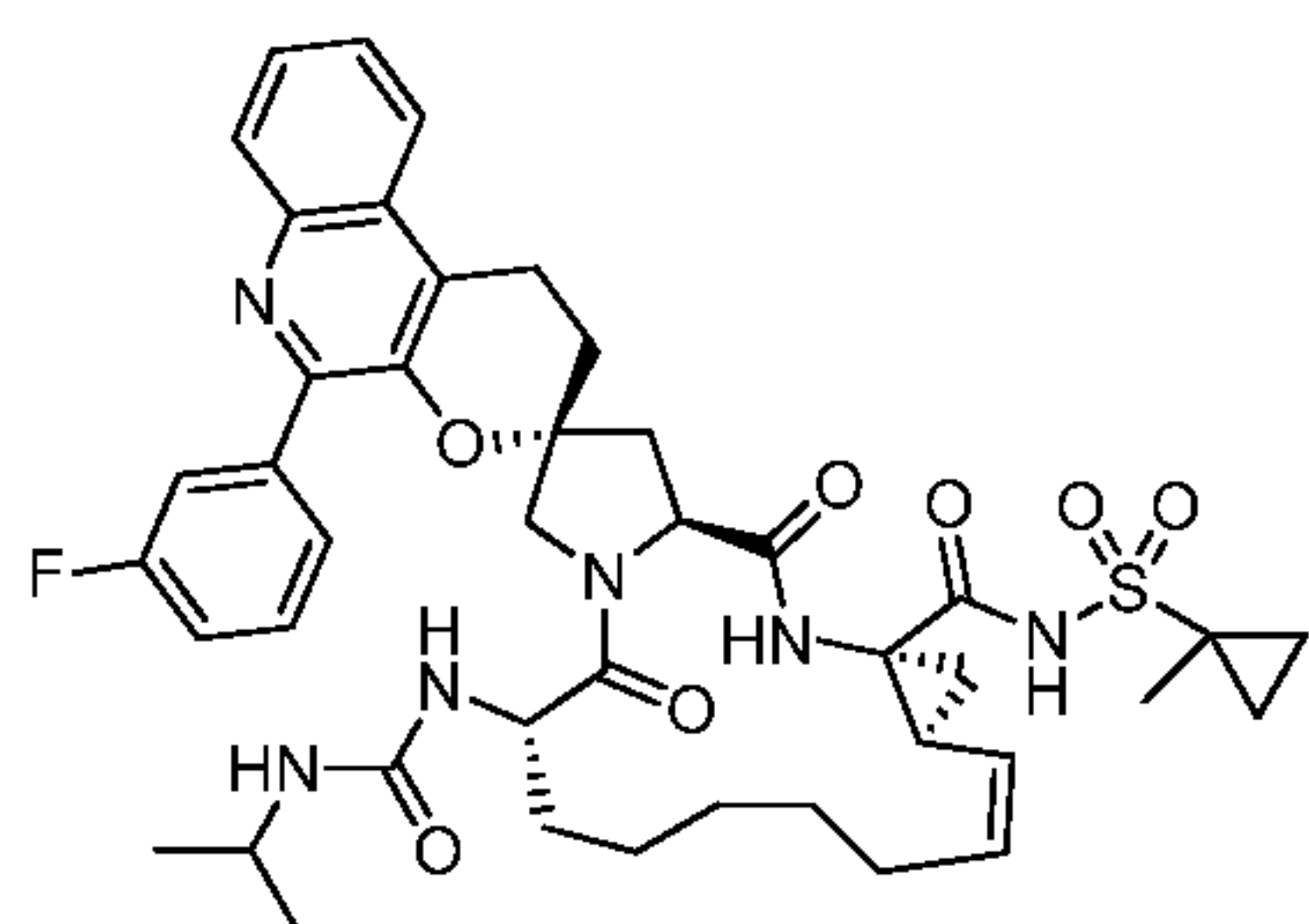
I-82



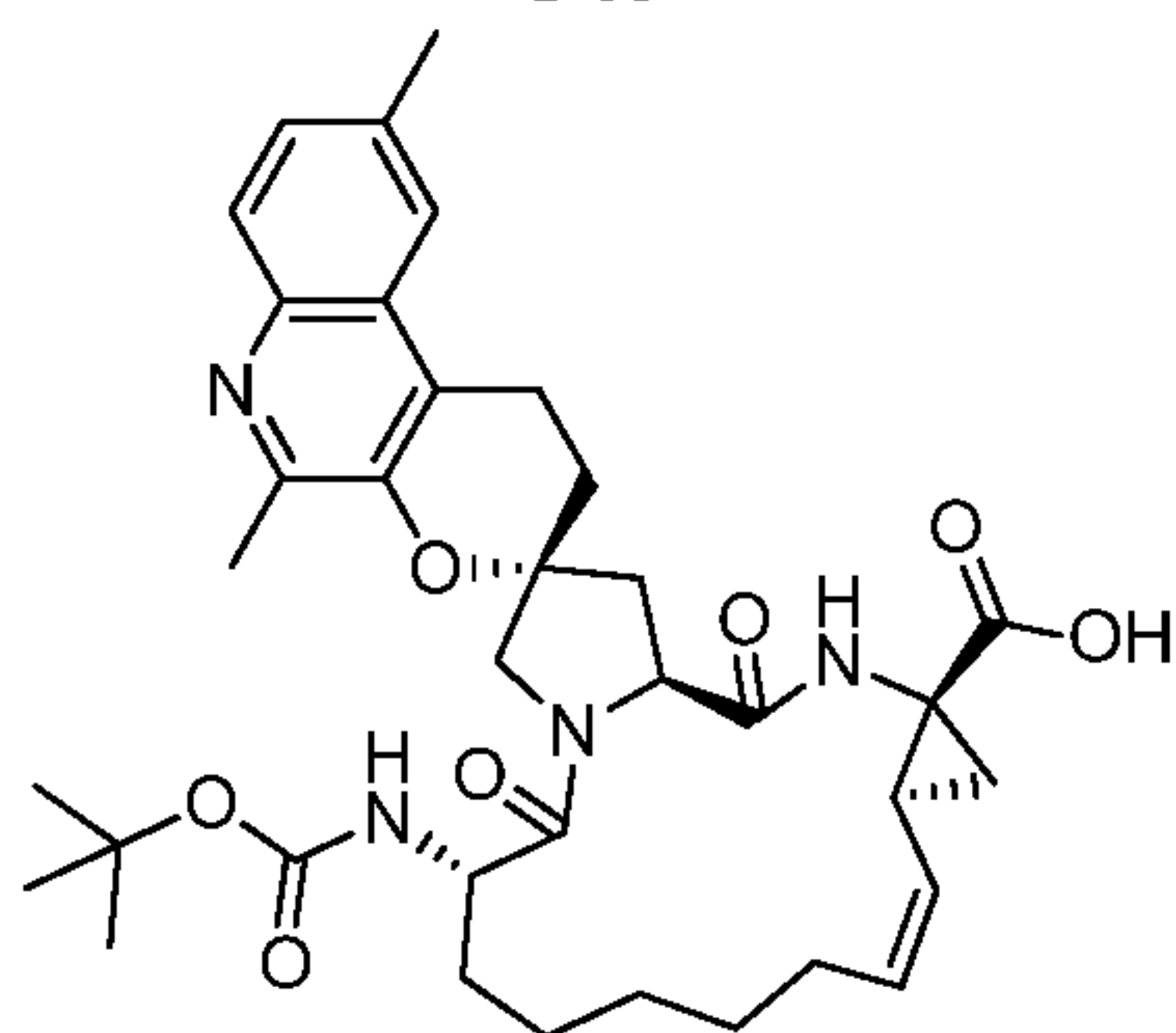
I-83



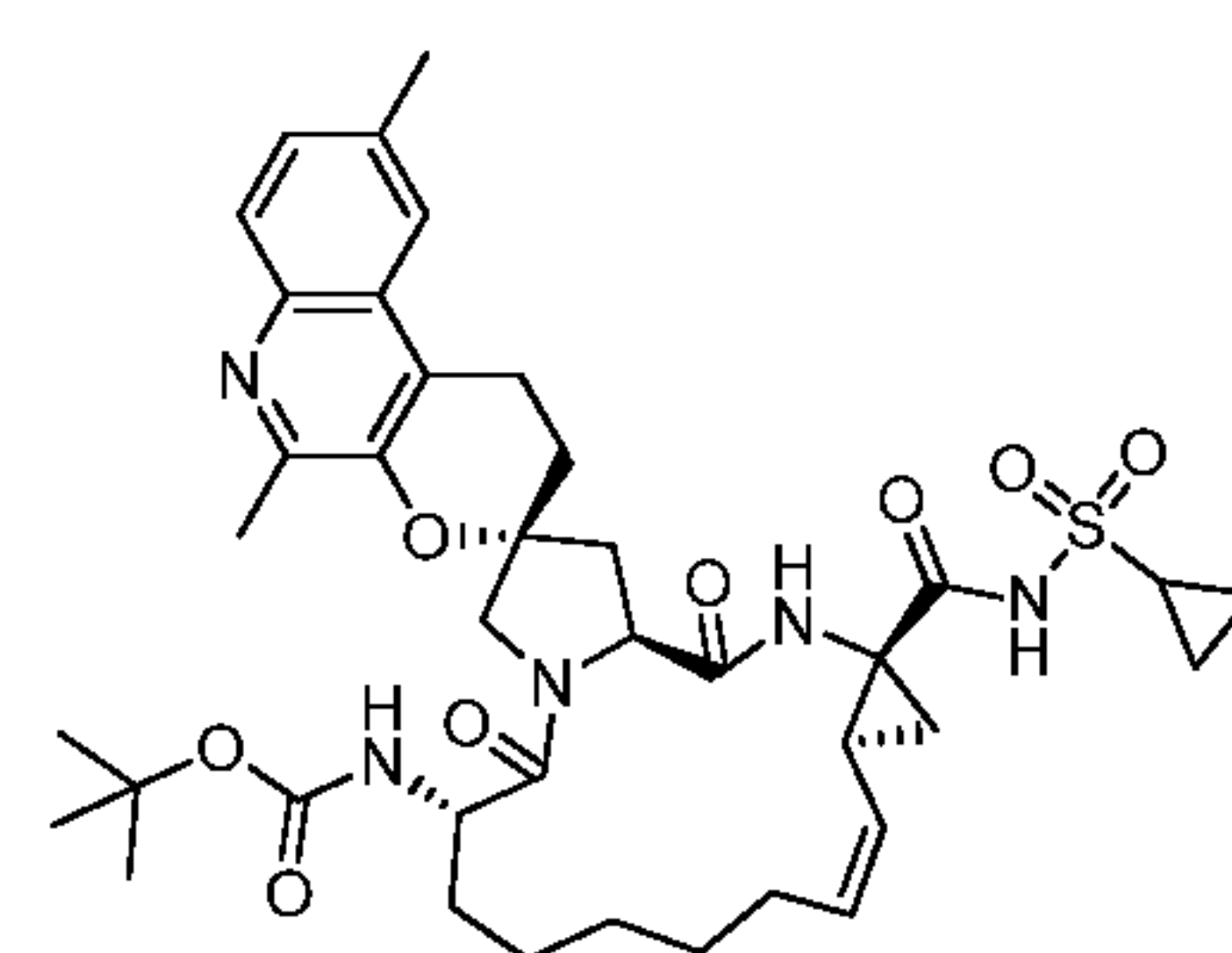
I-84



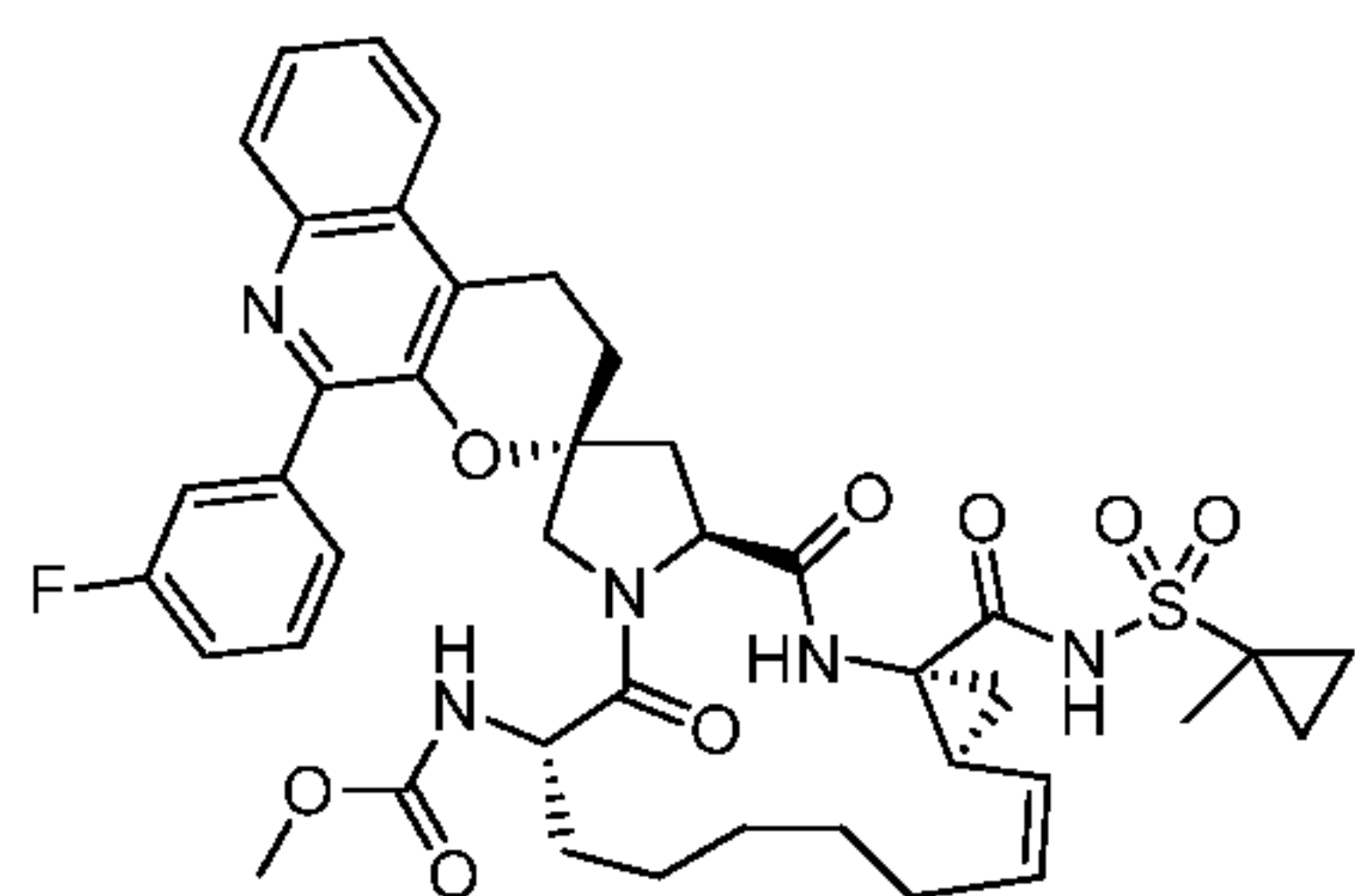
I-85



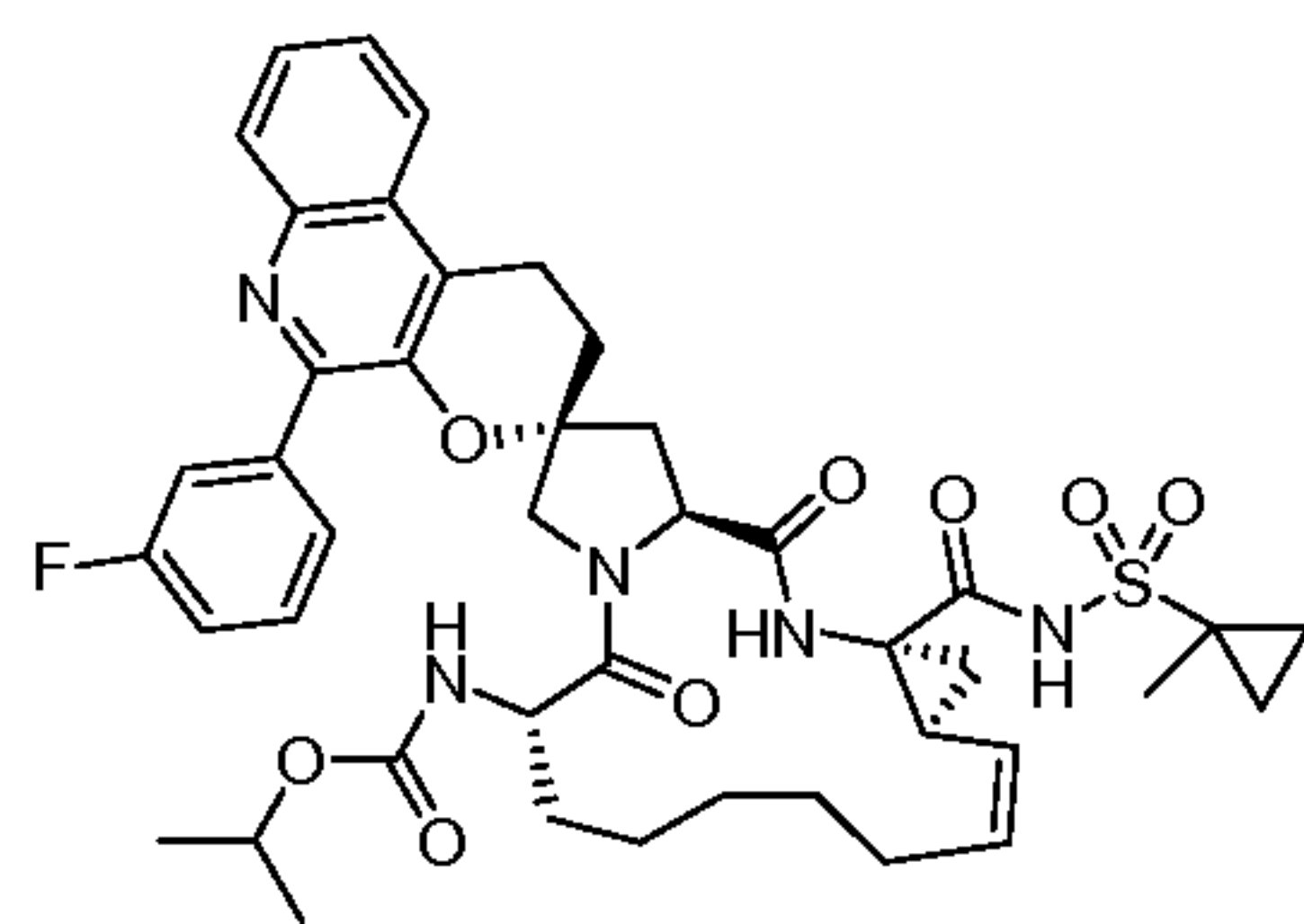
I-86



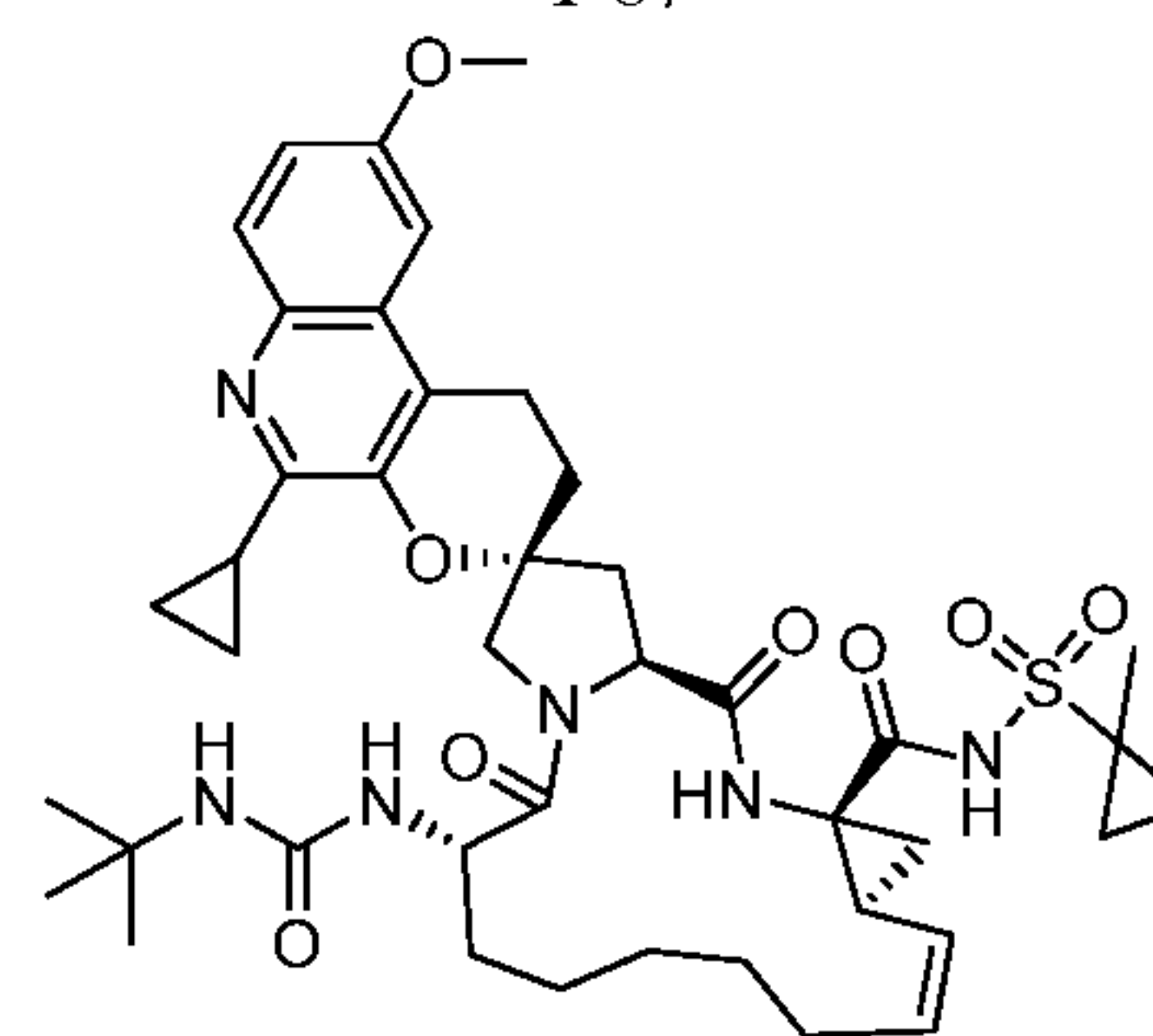
I-87



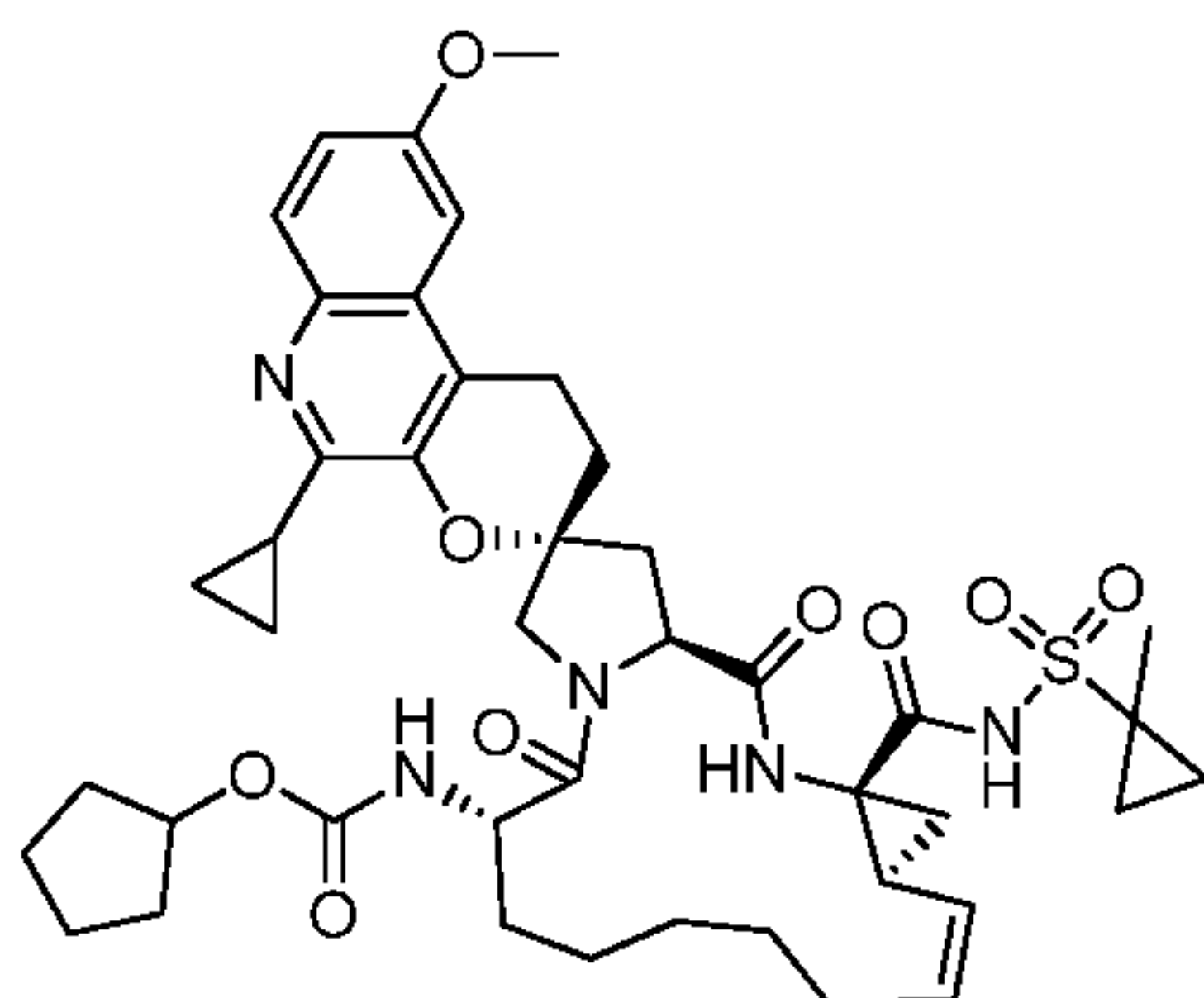
I-88



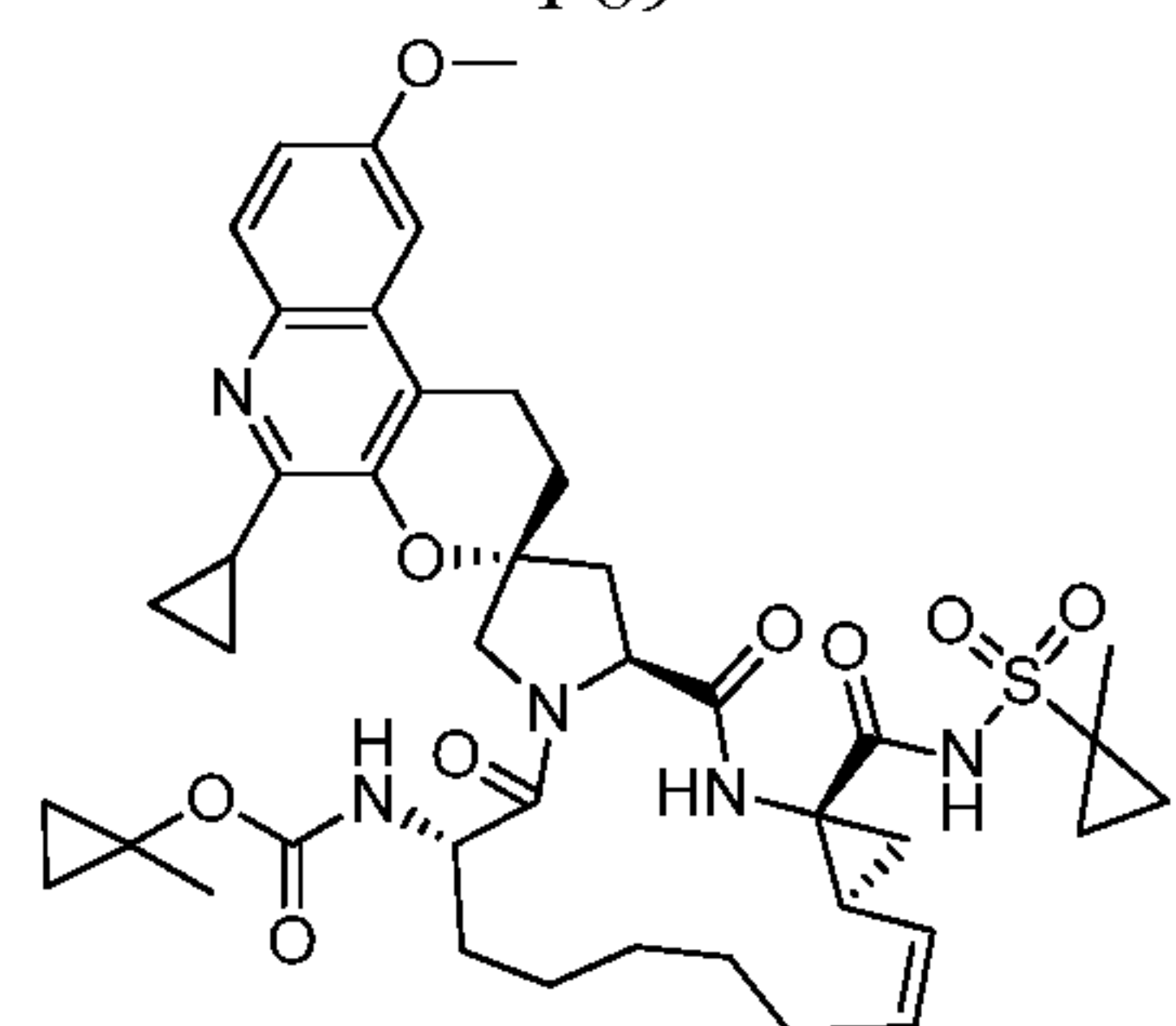
I-89



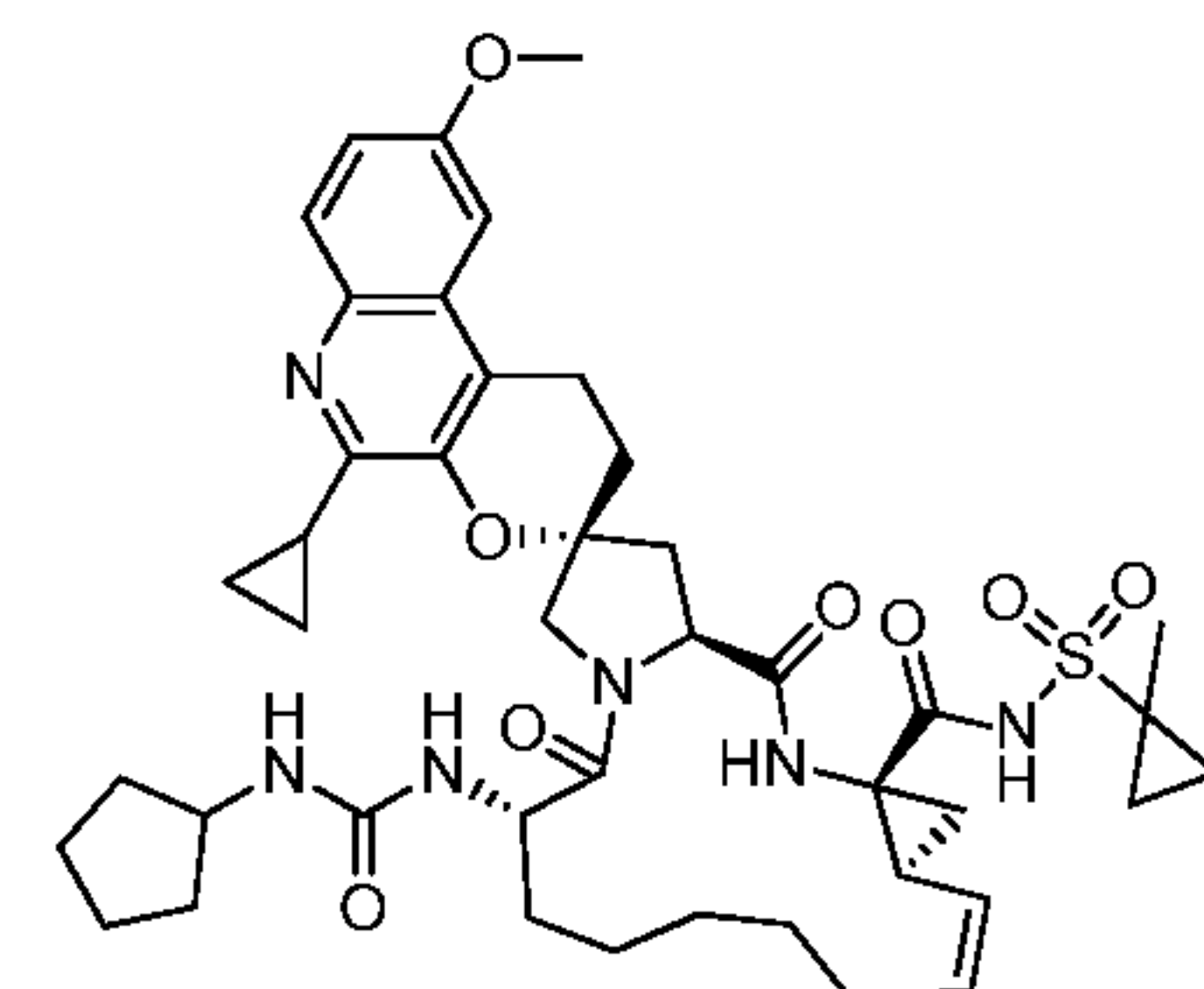
I-90



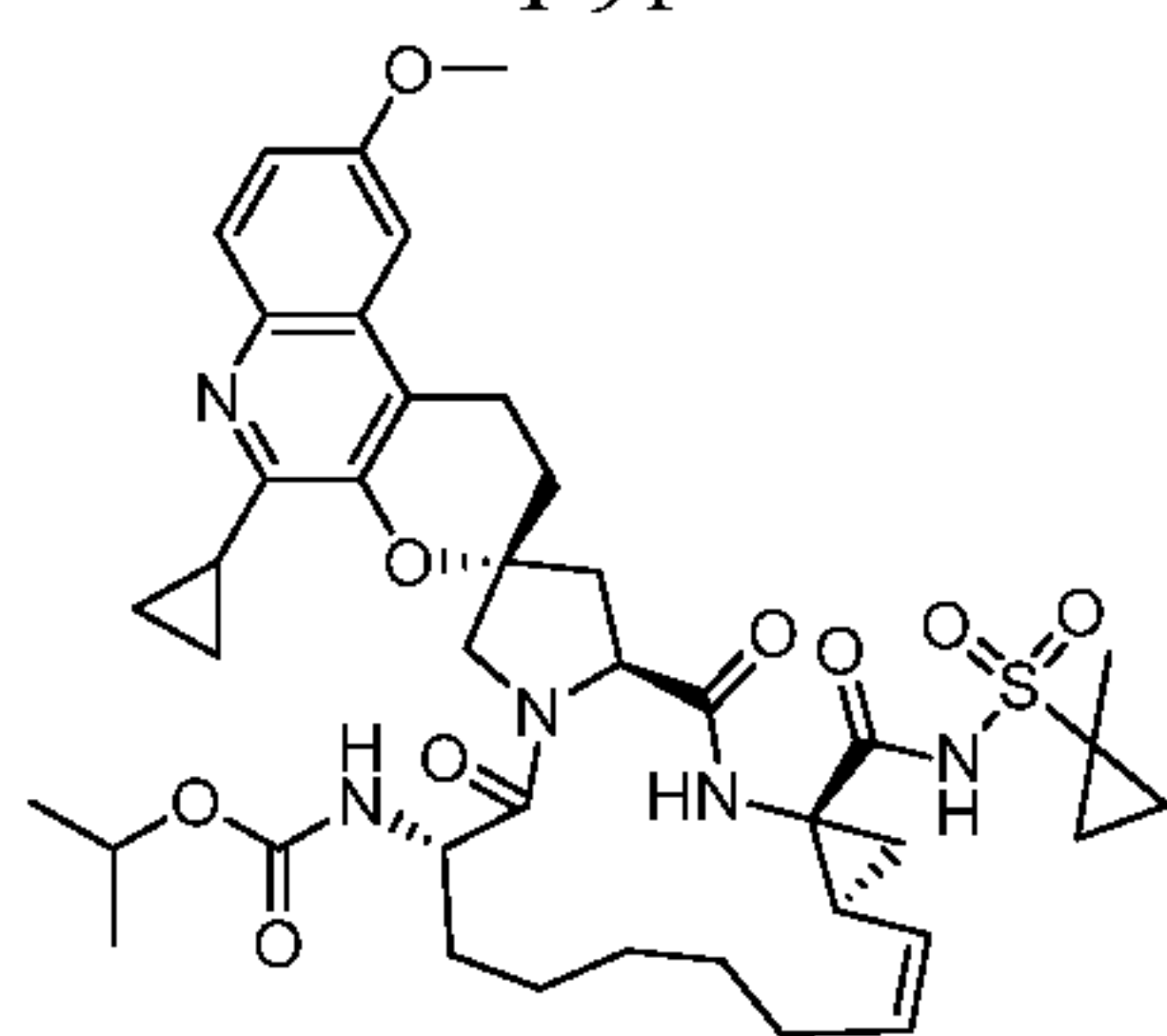
I-91



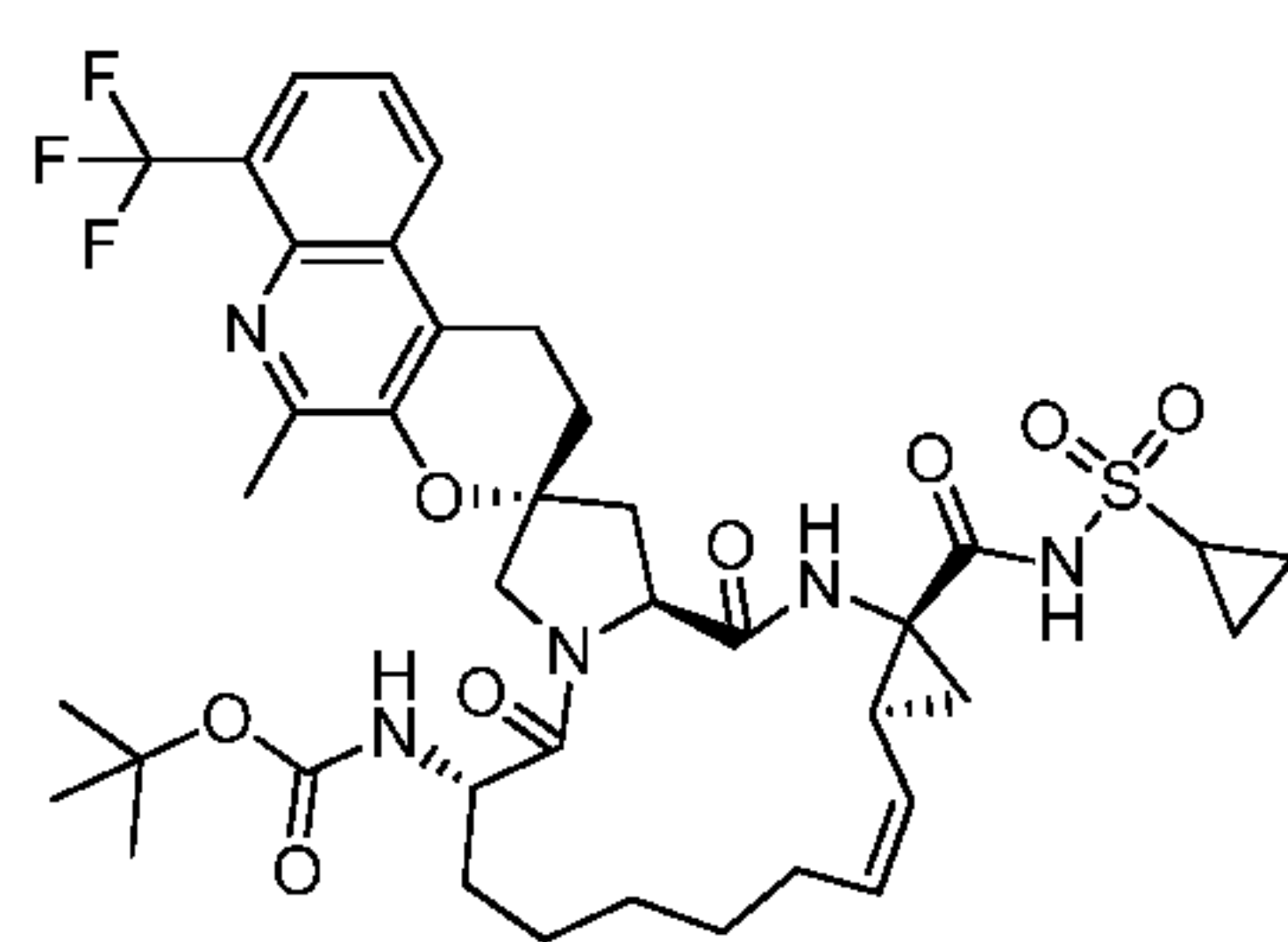
I-92



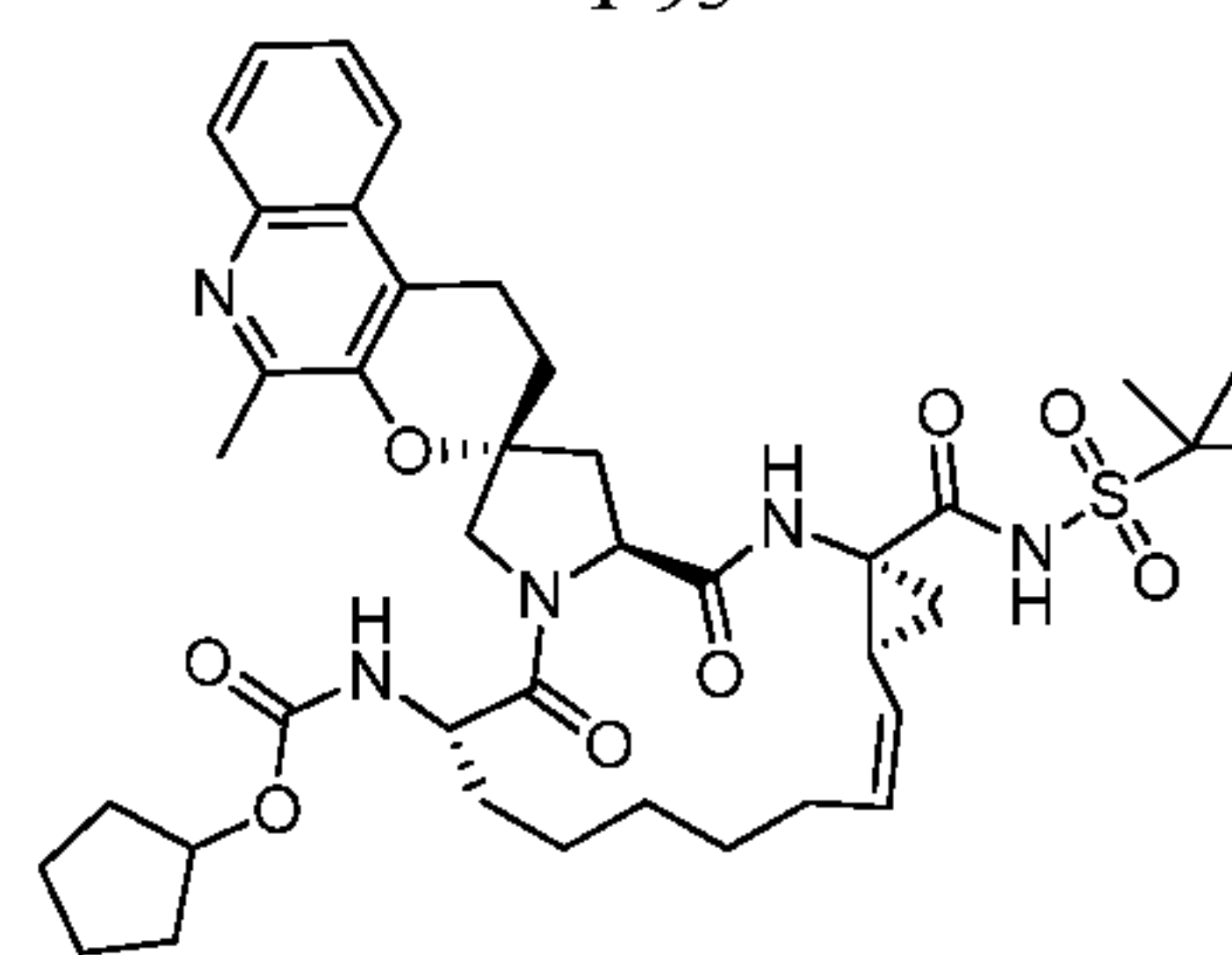
I-93



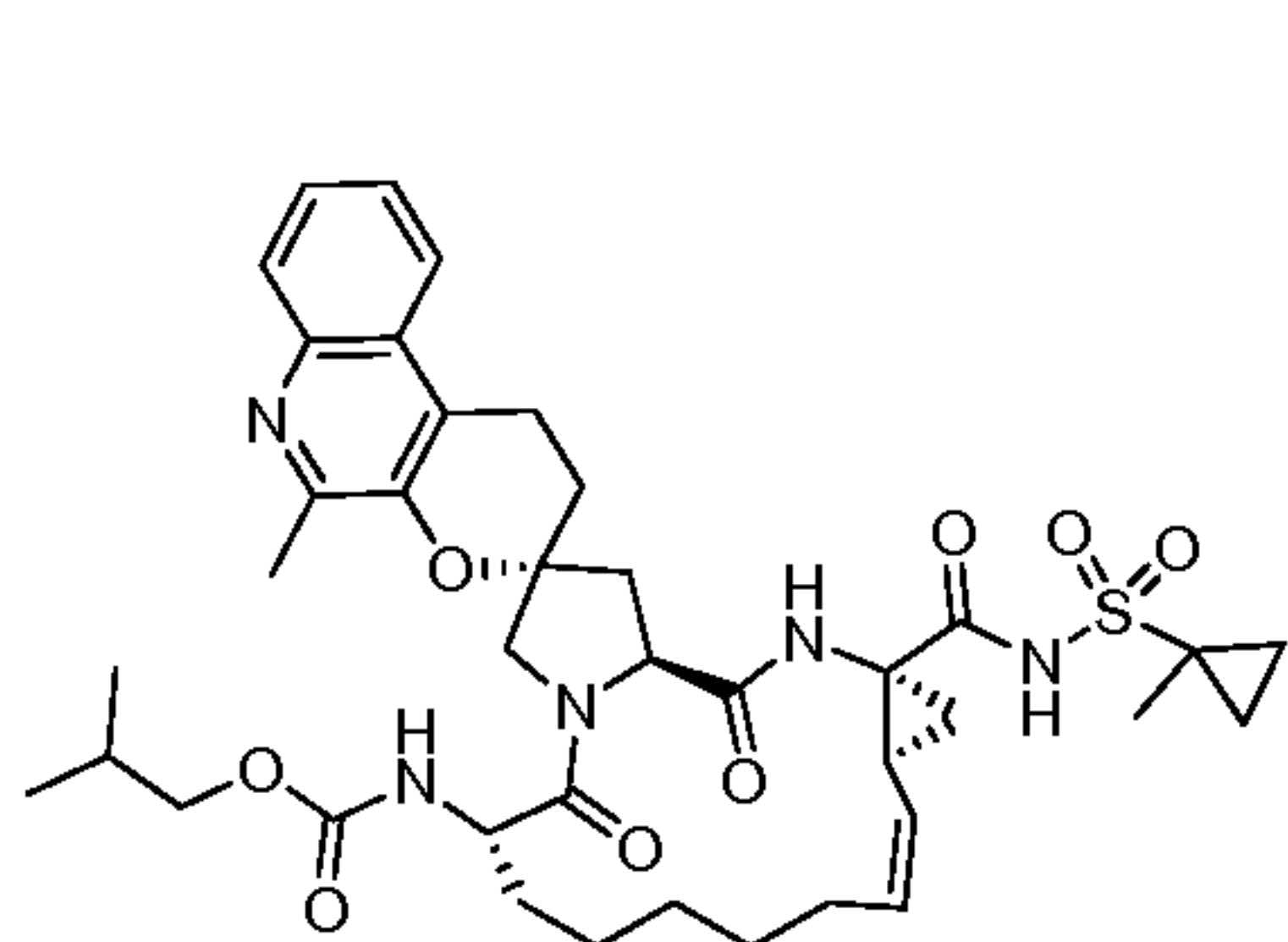
I-94



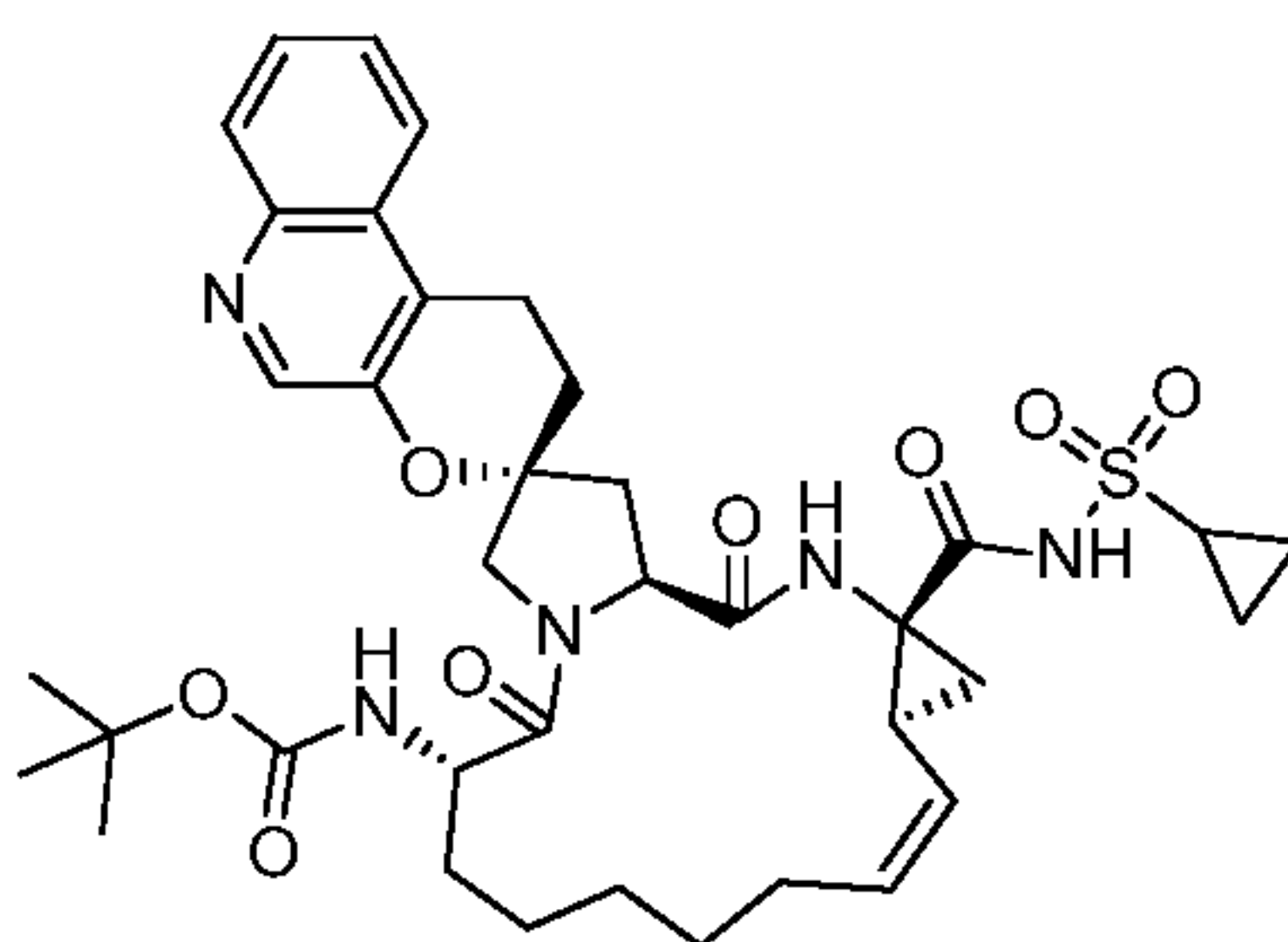
I-95



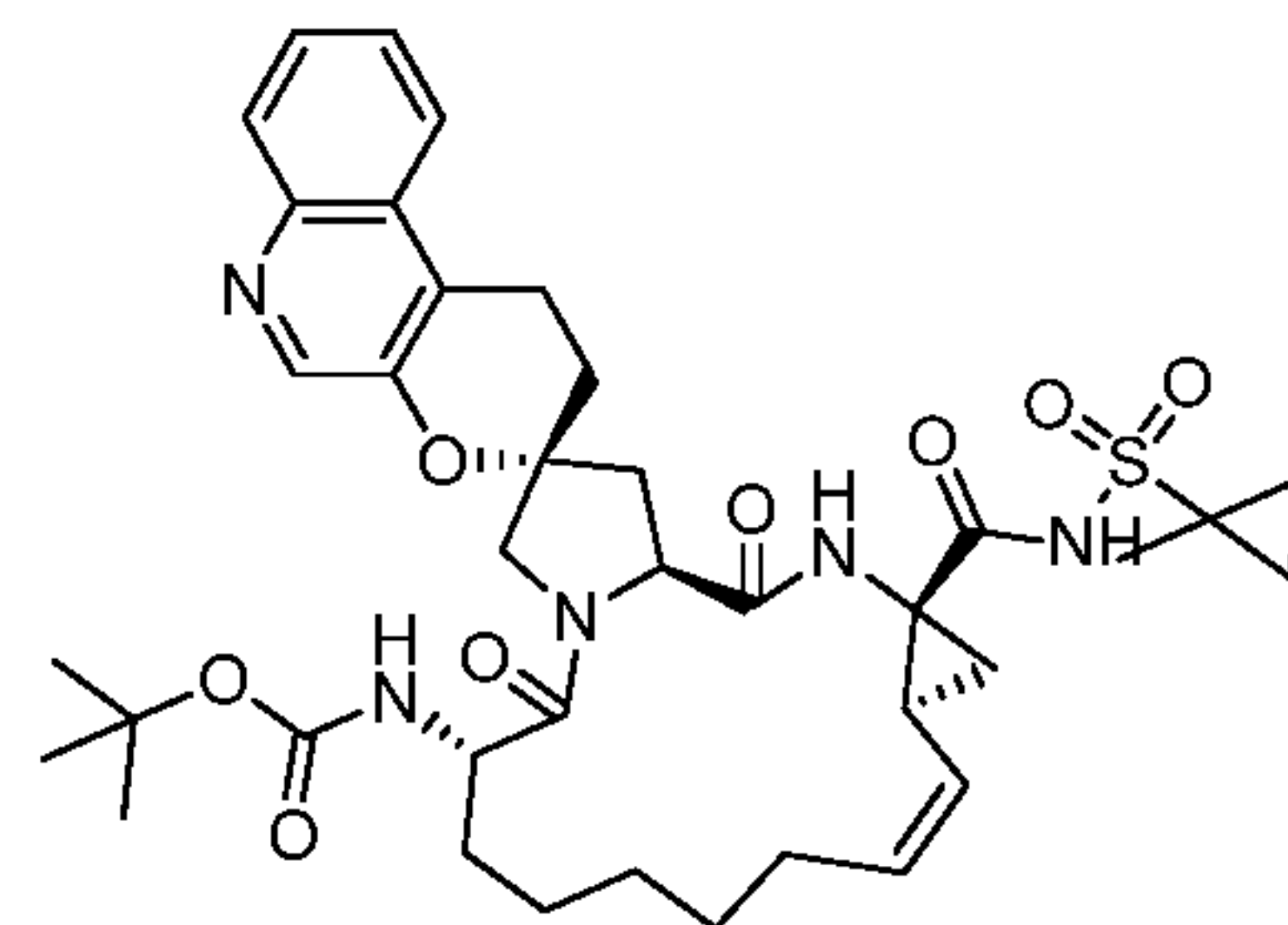
I-96



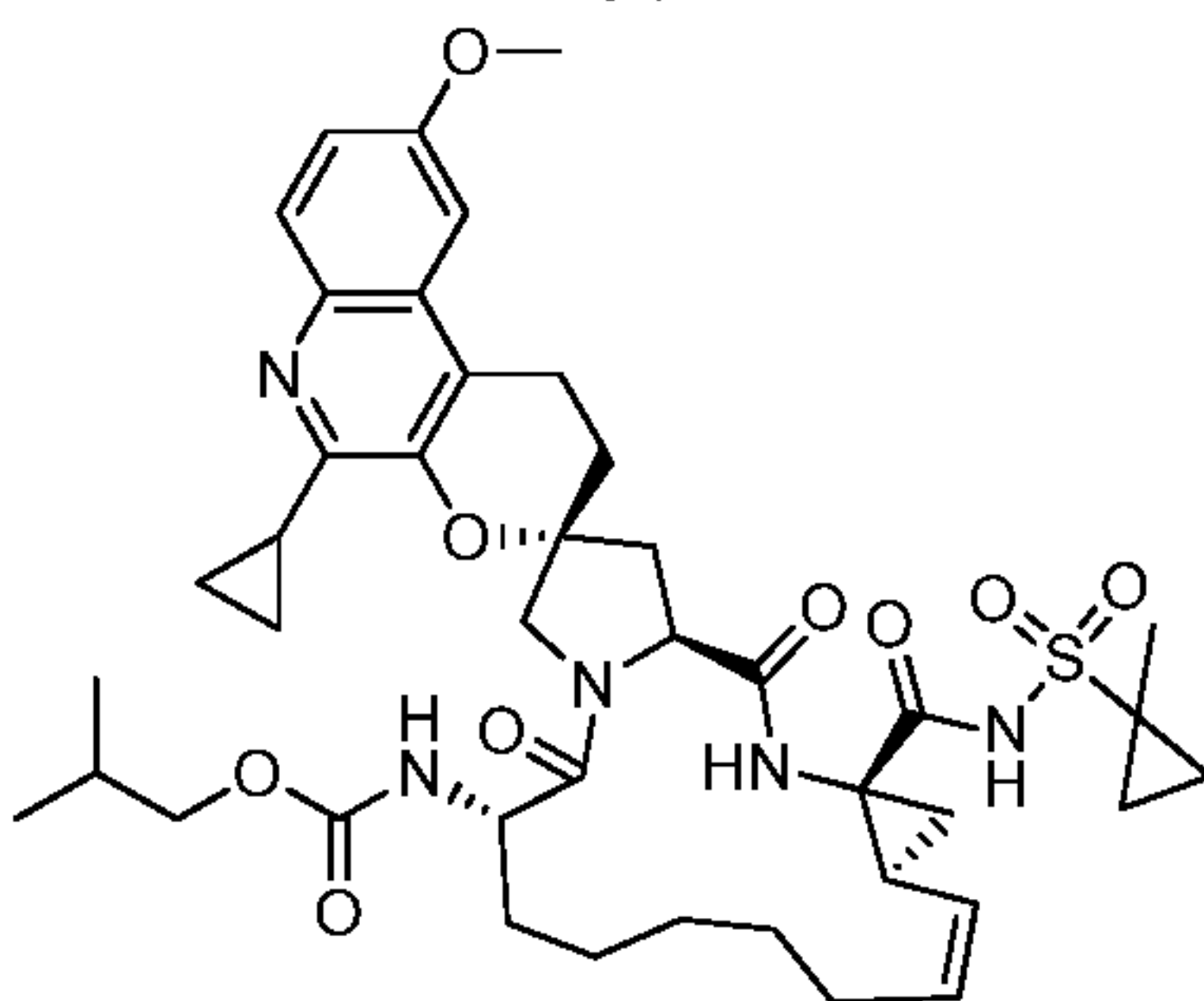
I-97



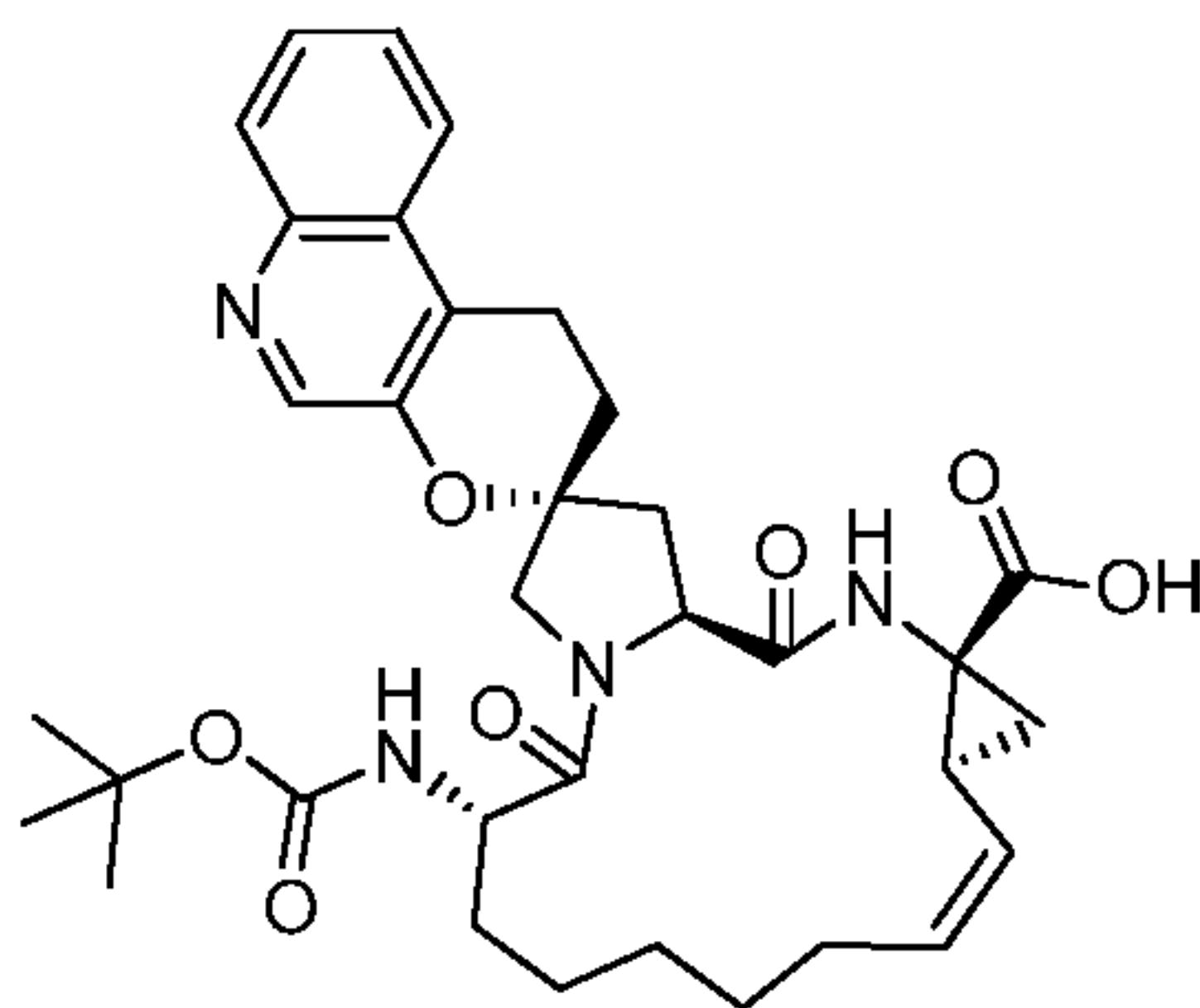
I-98



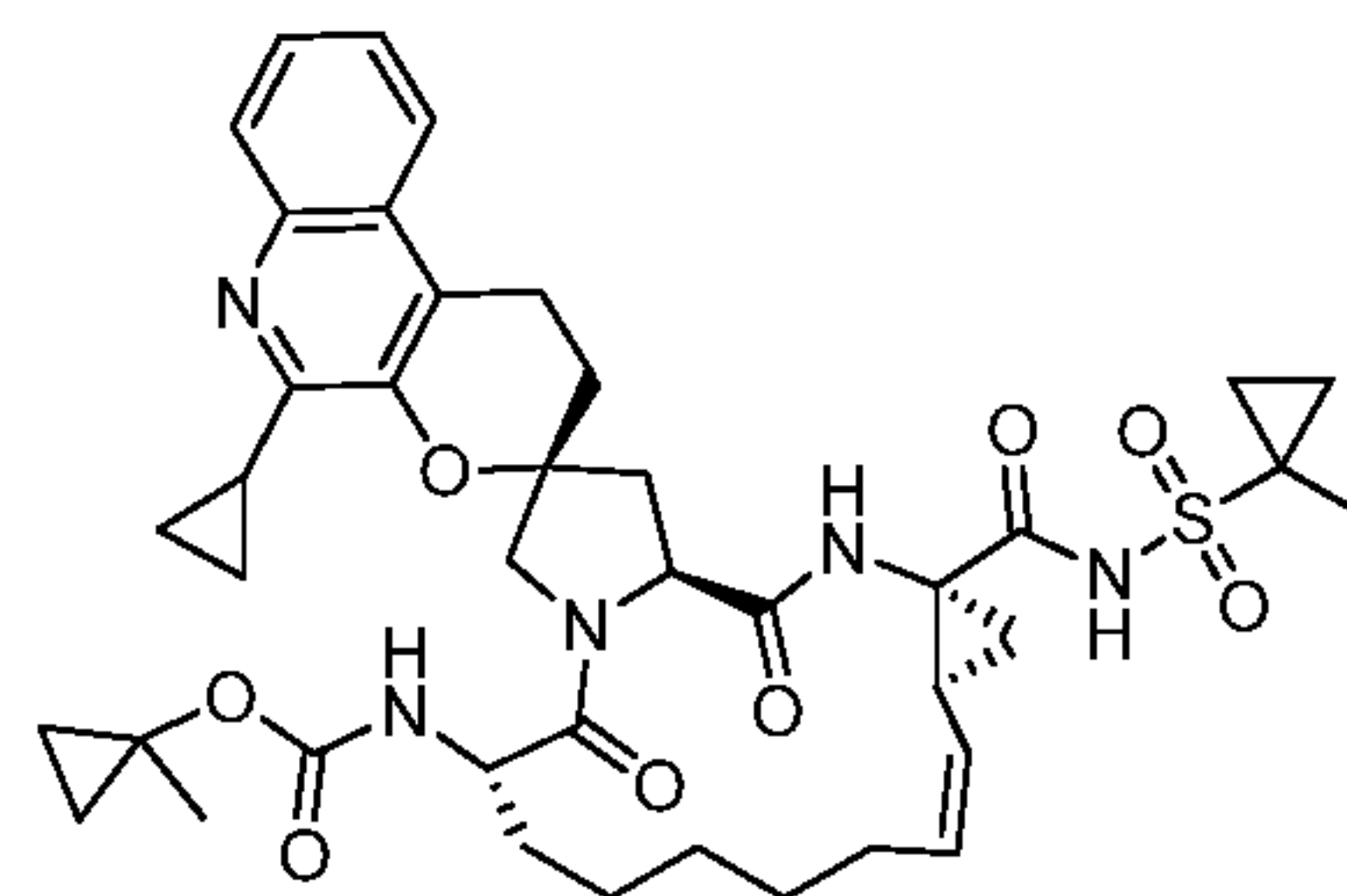
I-99



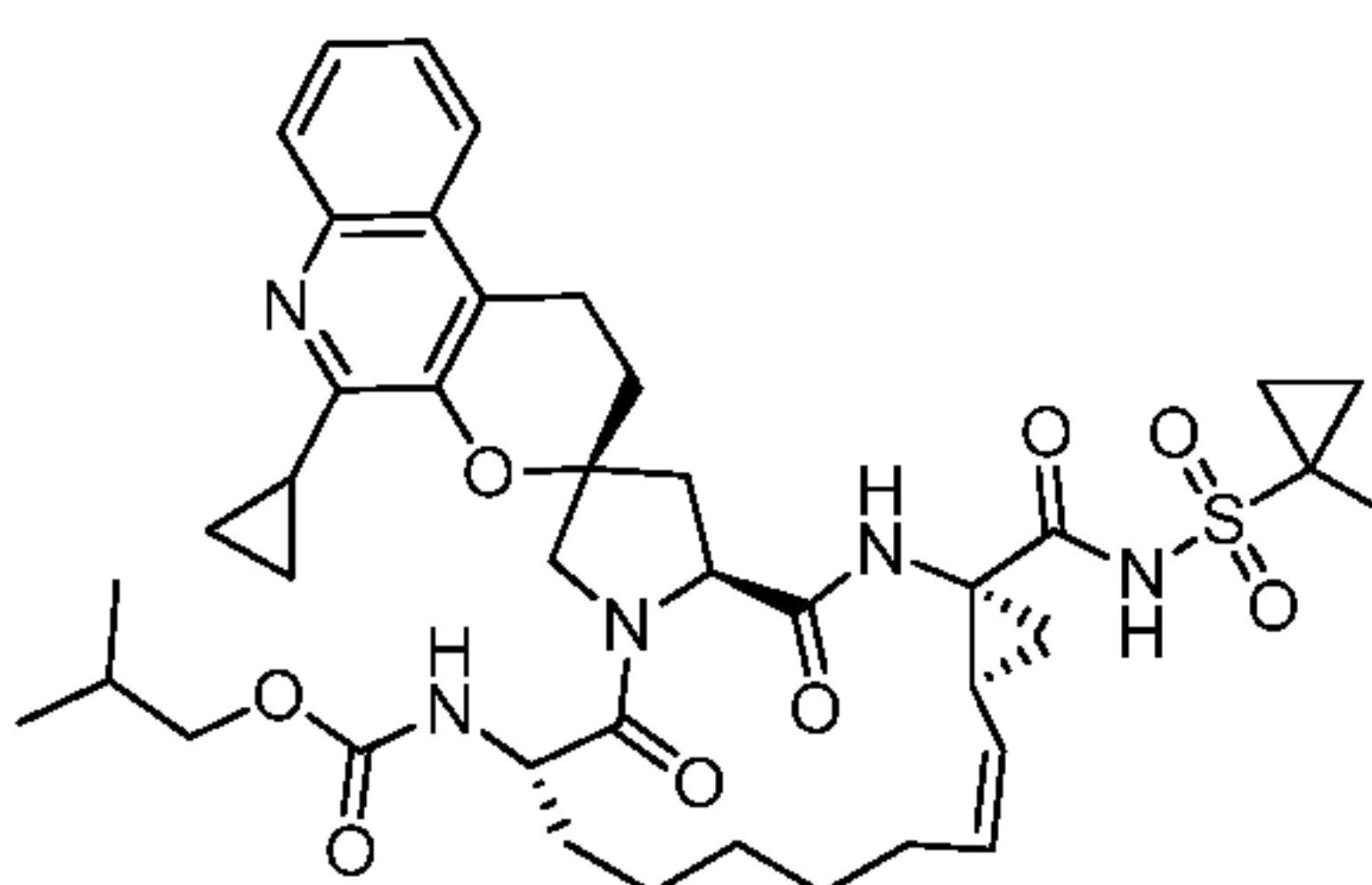
I-100



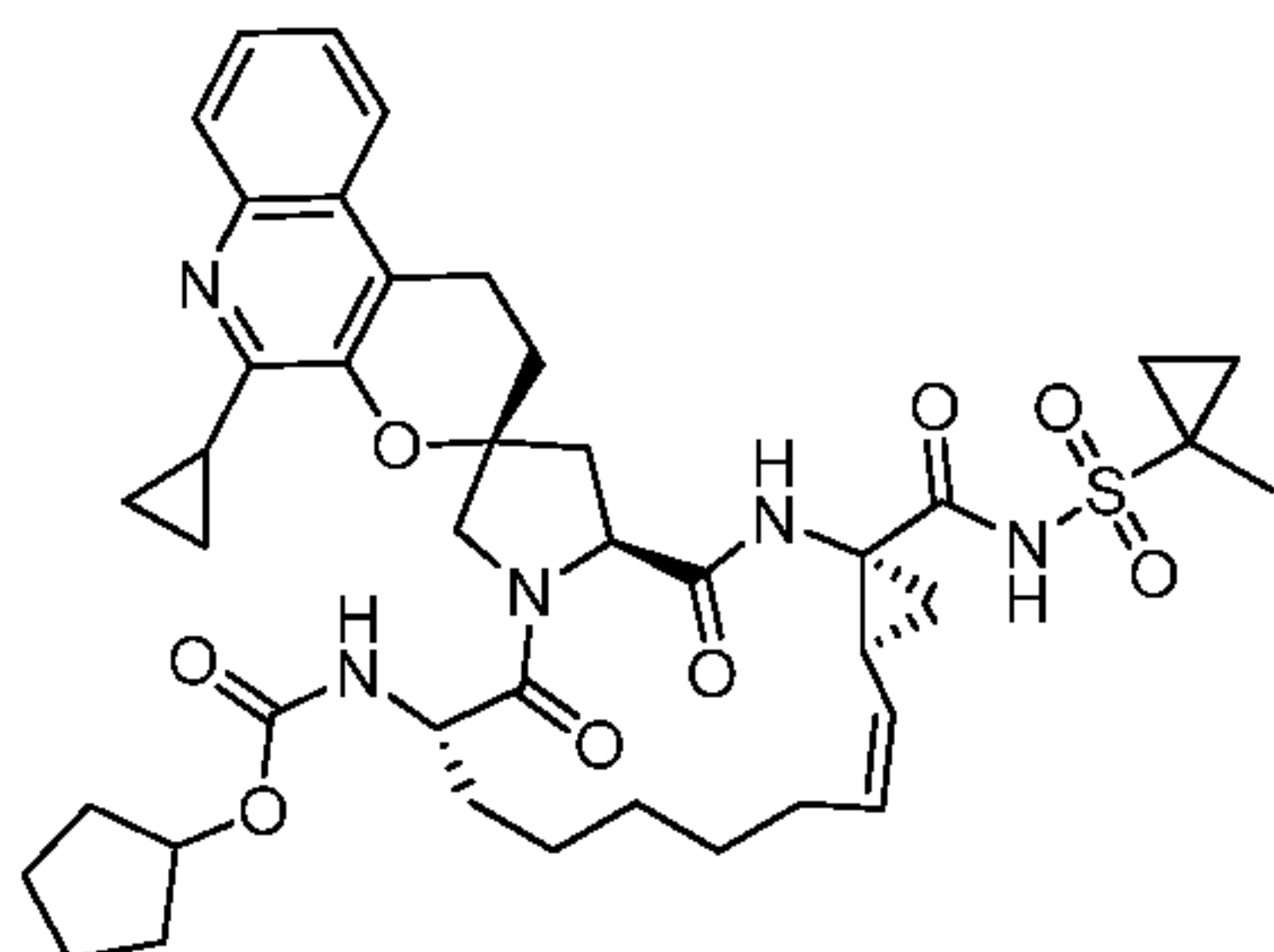
I-101



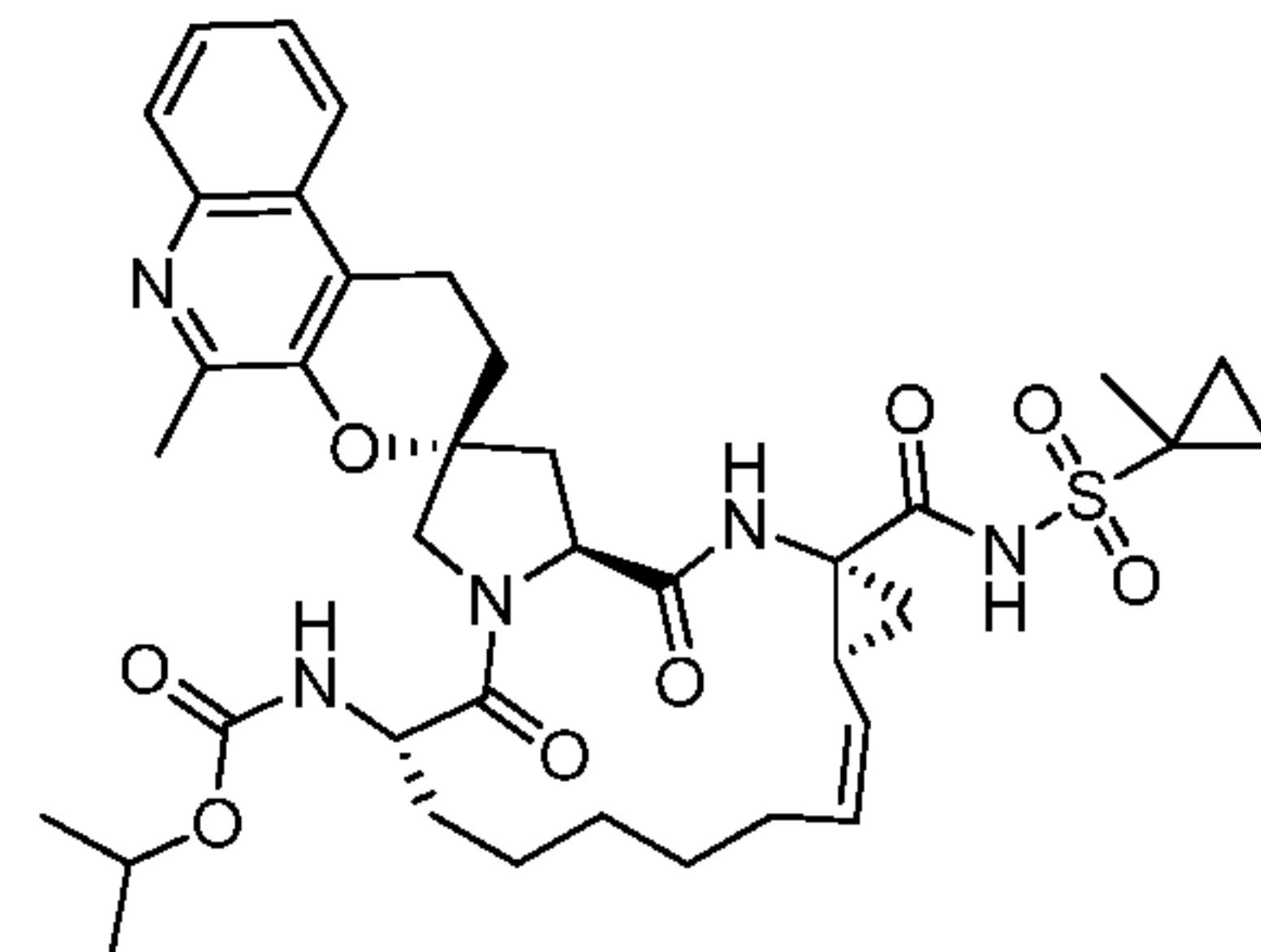
I-102



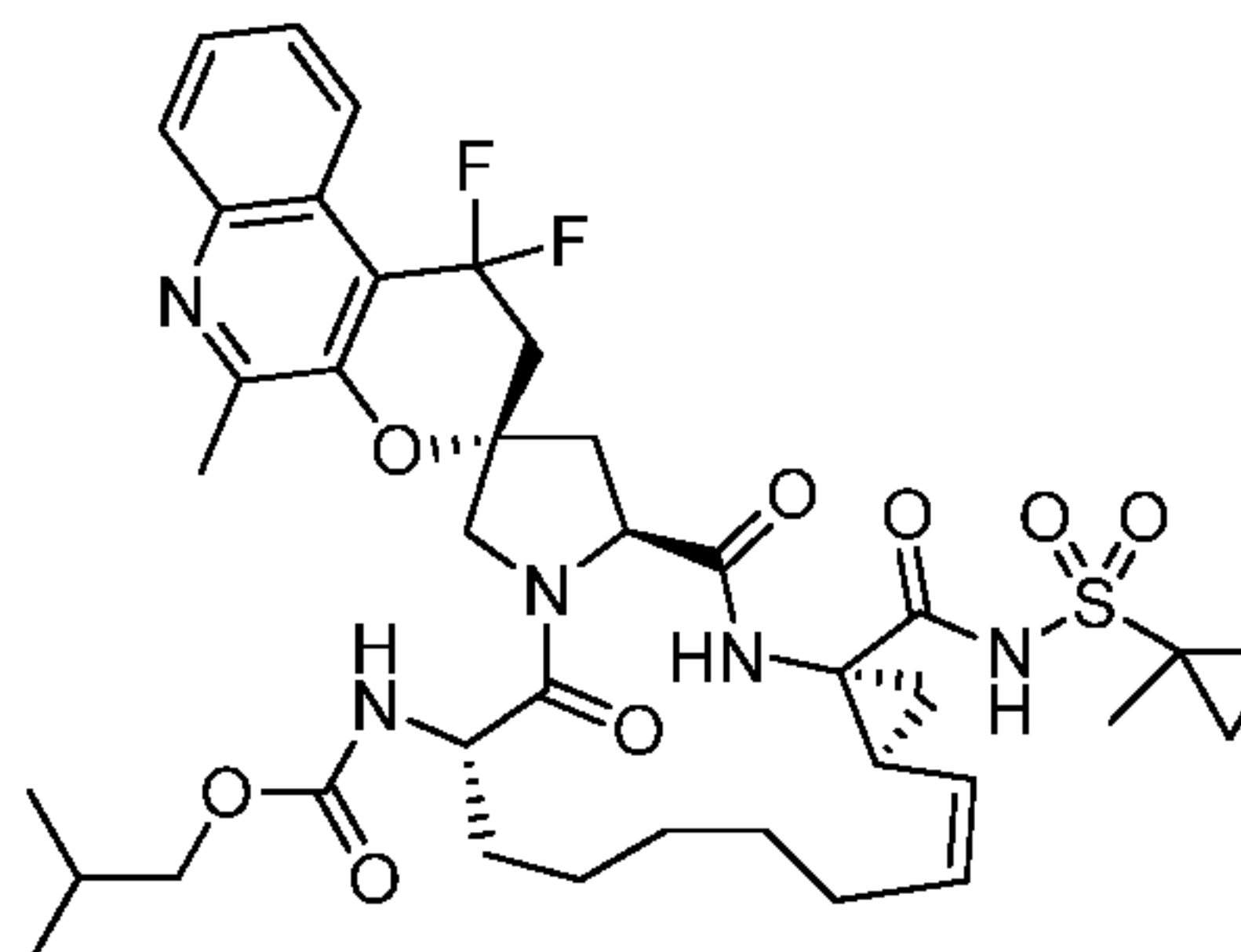
I-103



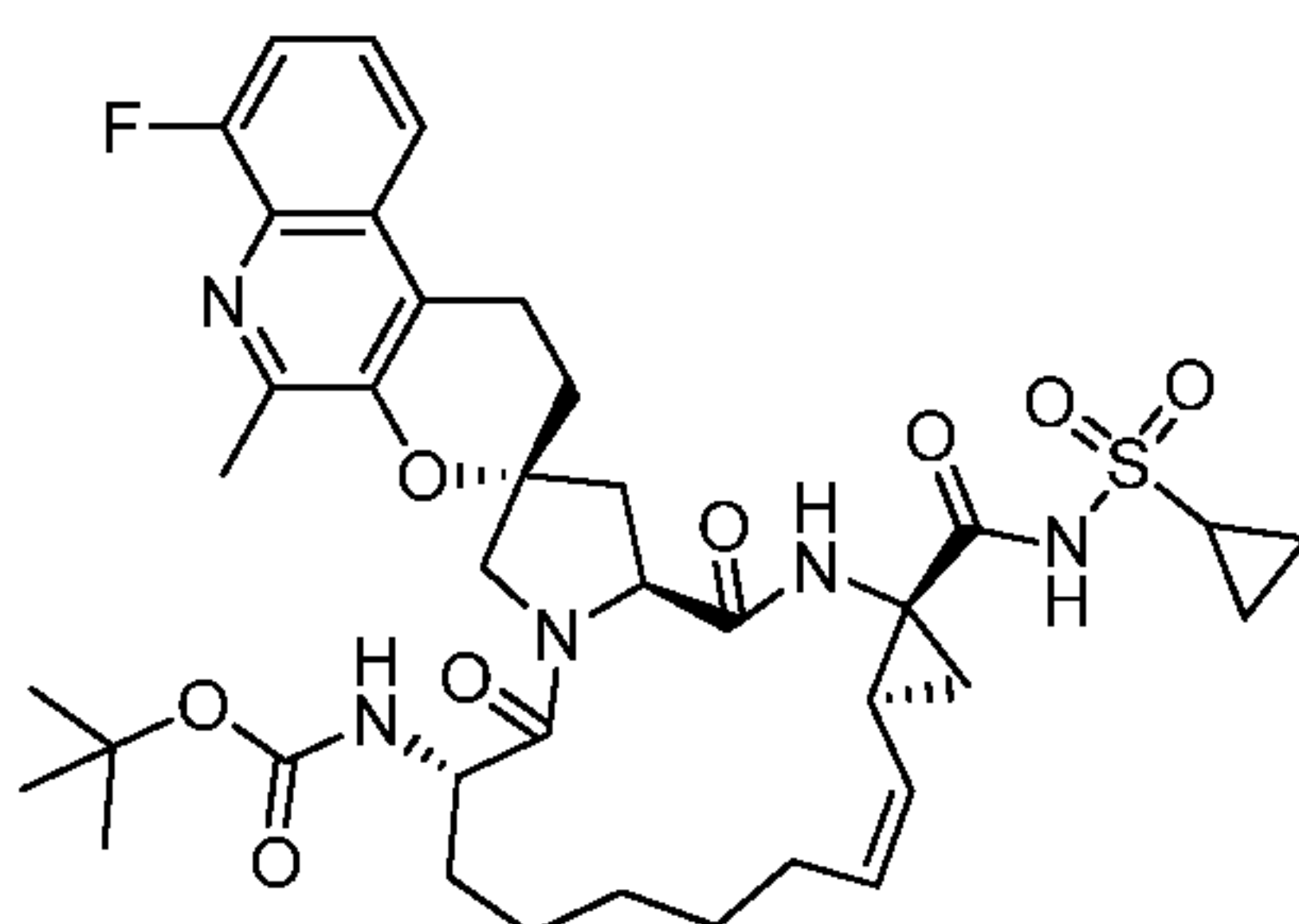
I-104



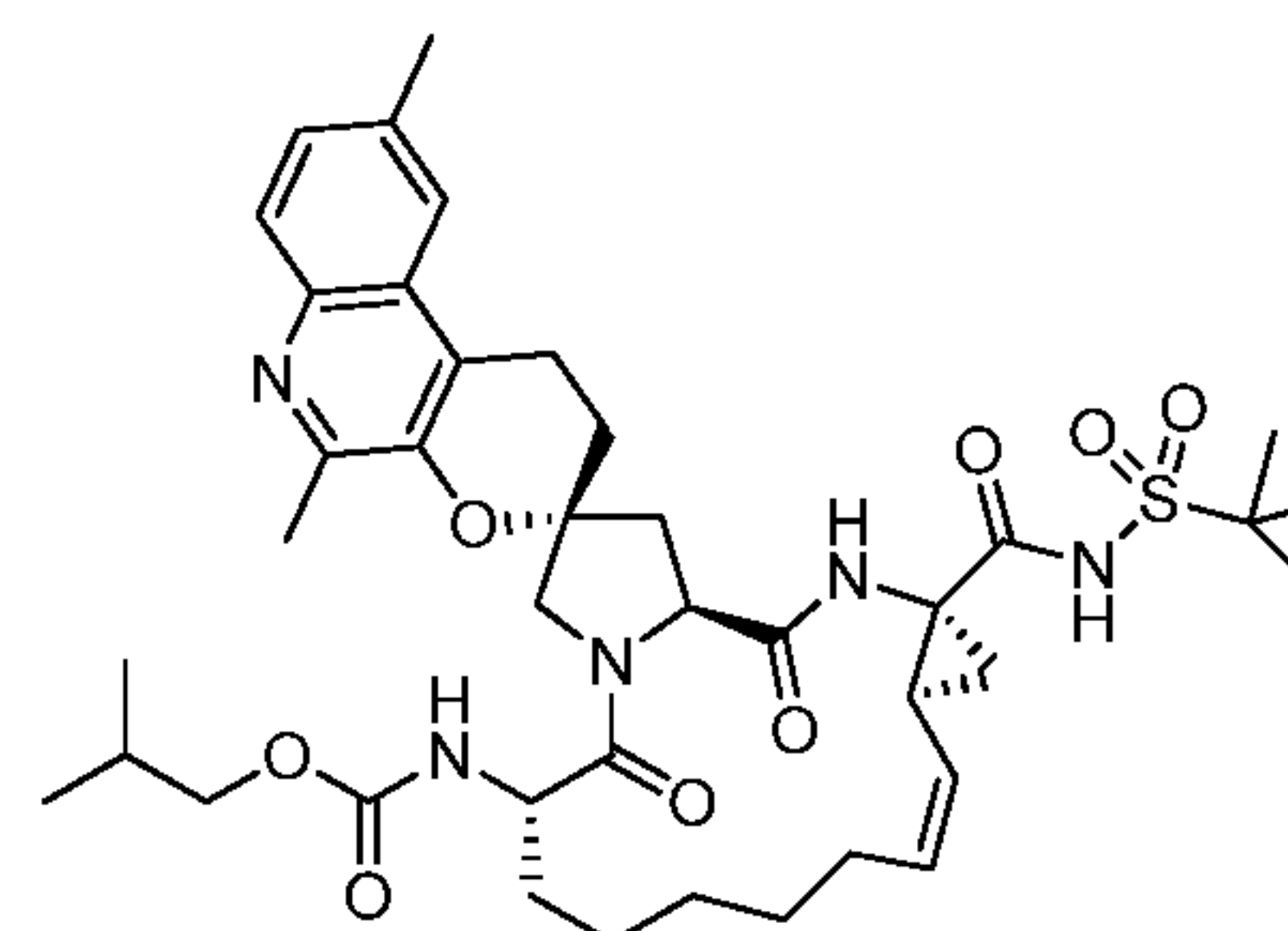
I-105



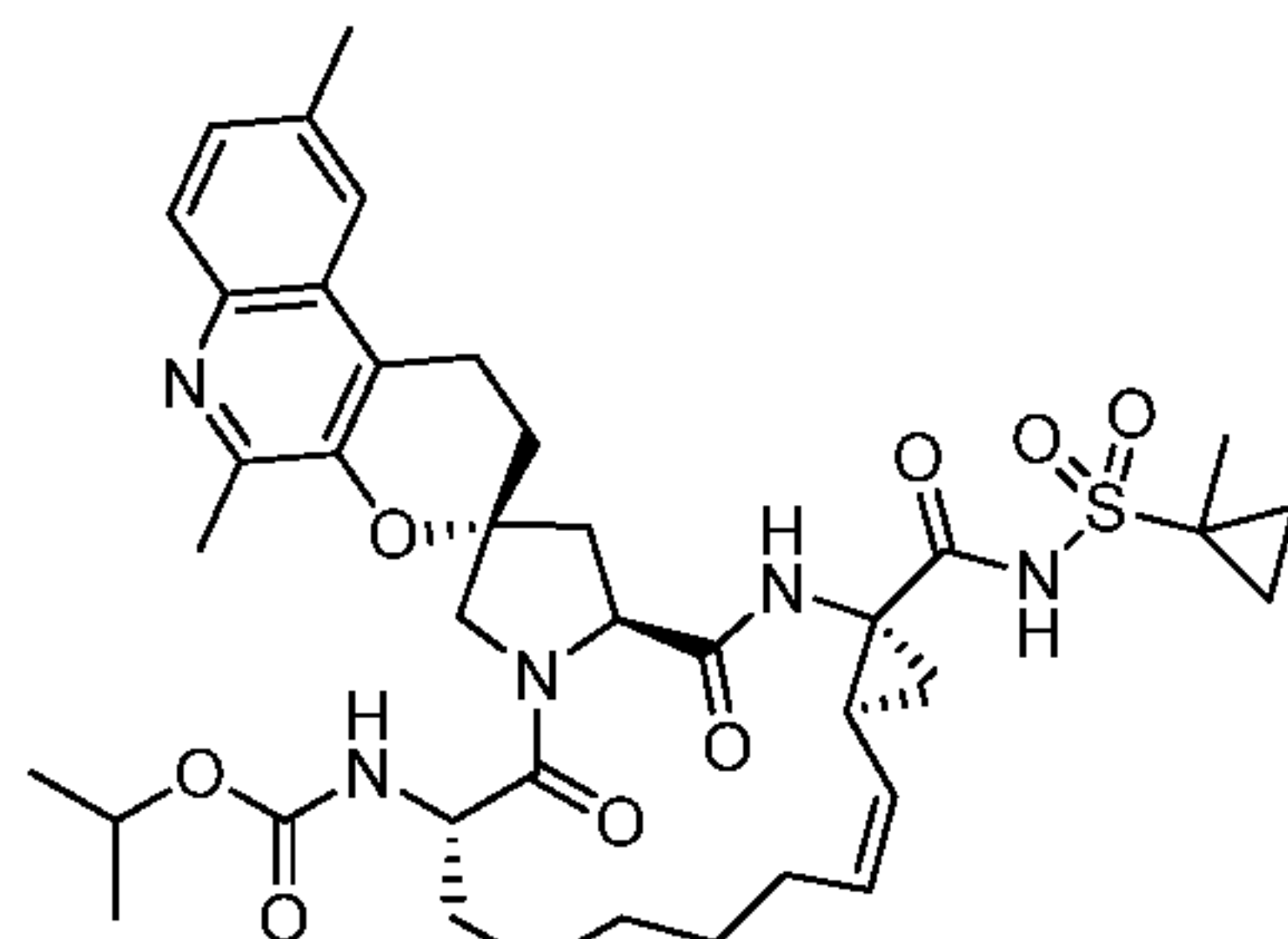
I-106



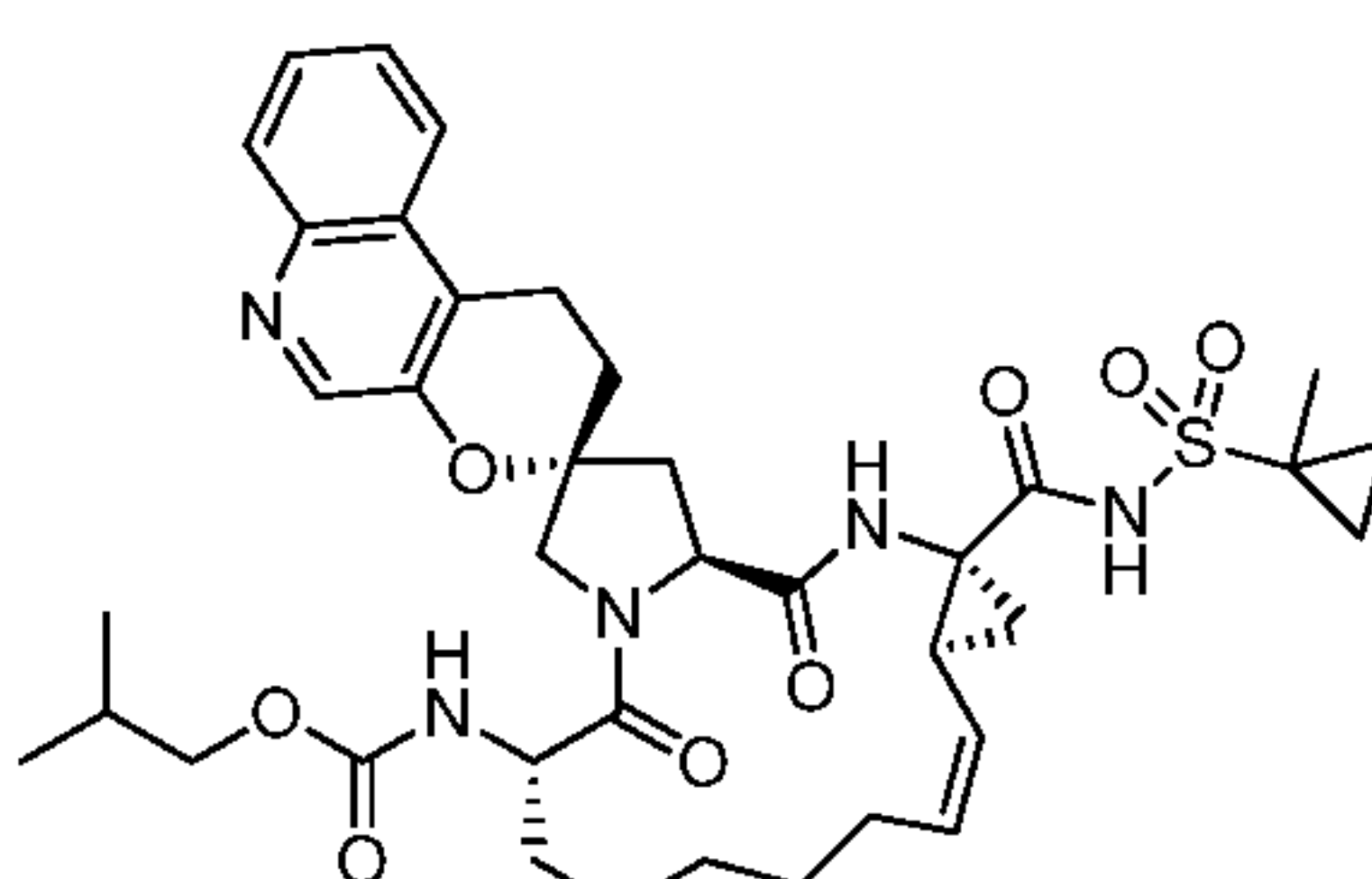
I-107



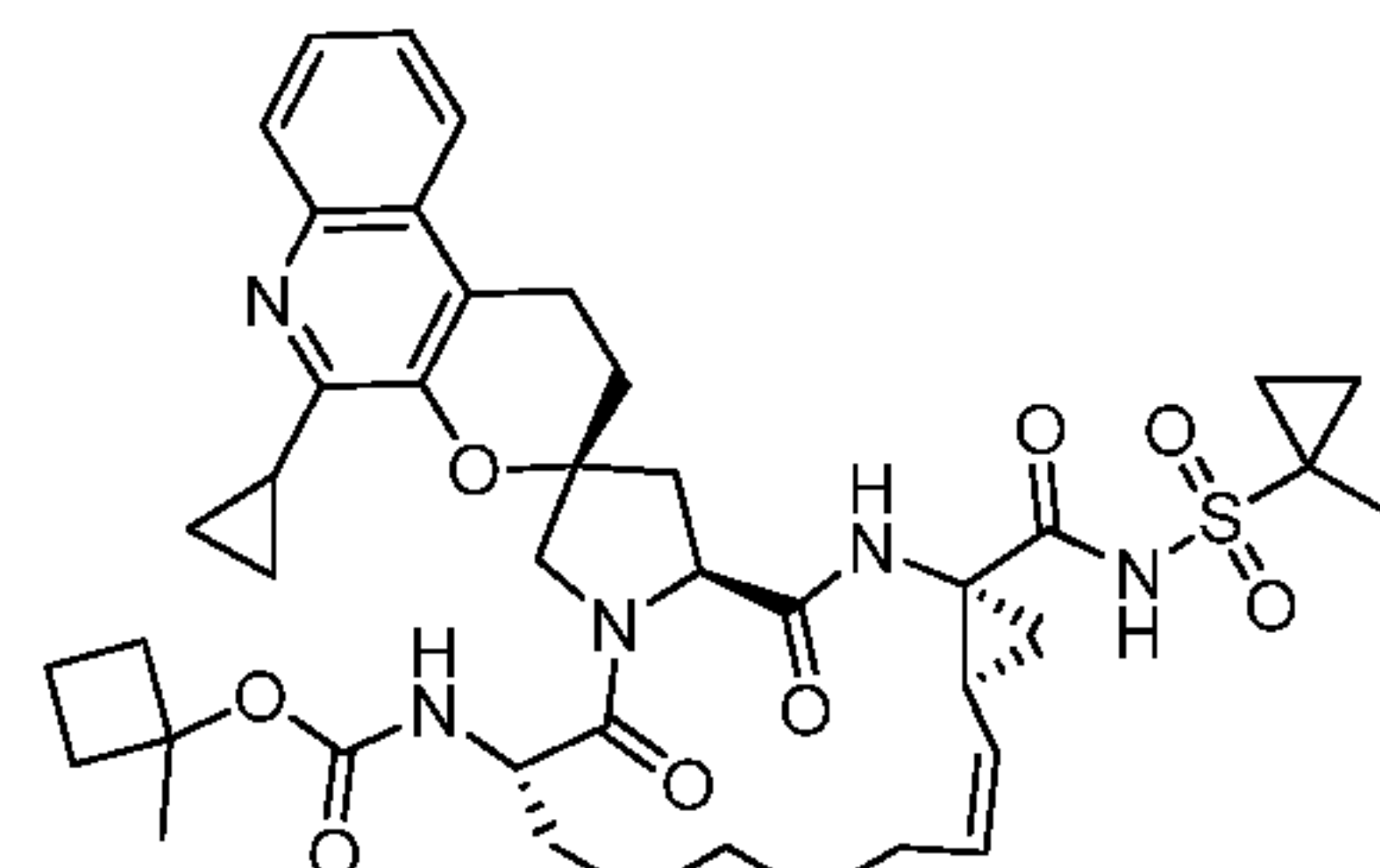
I-108



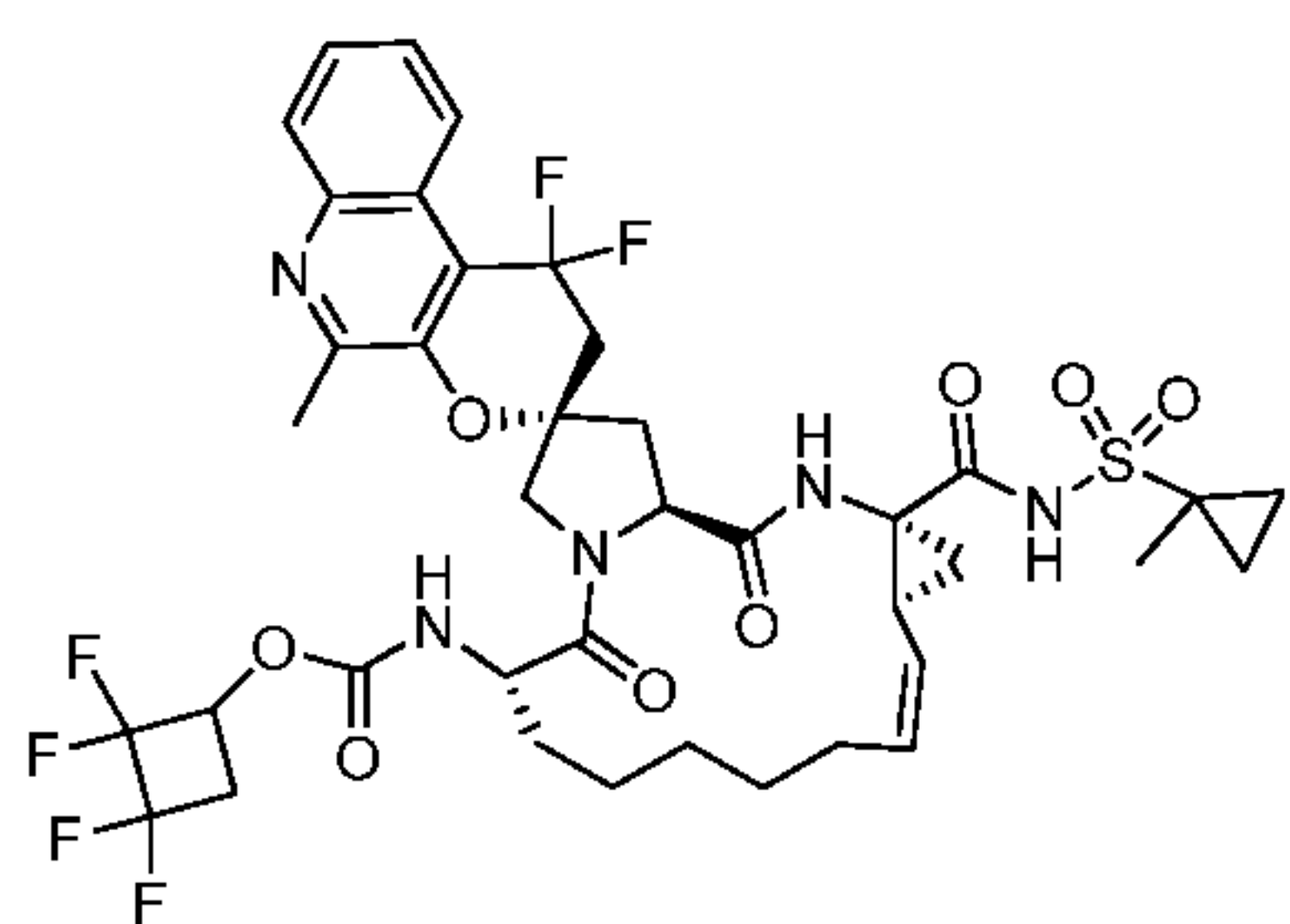
I-109



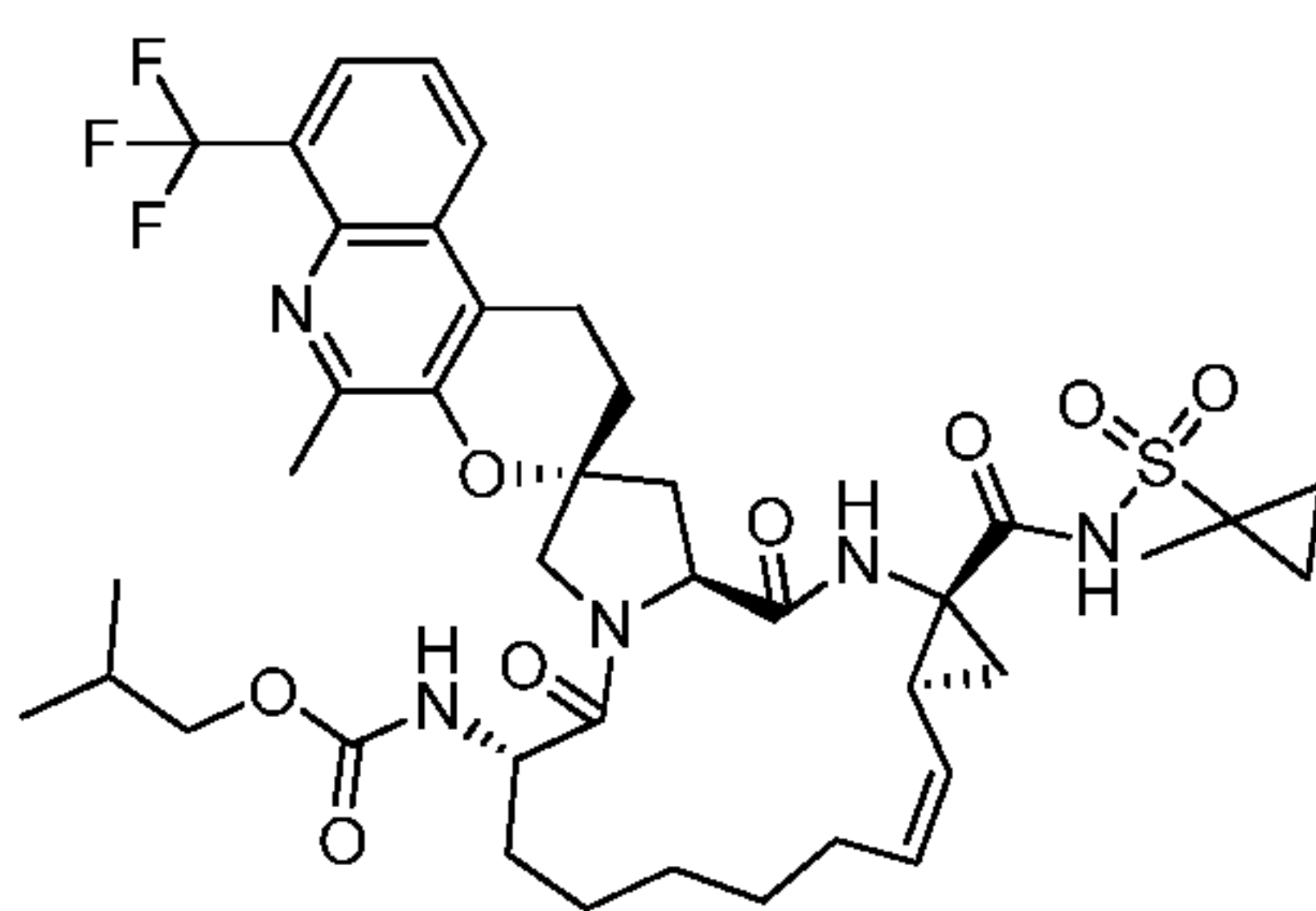
I-110



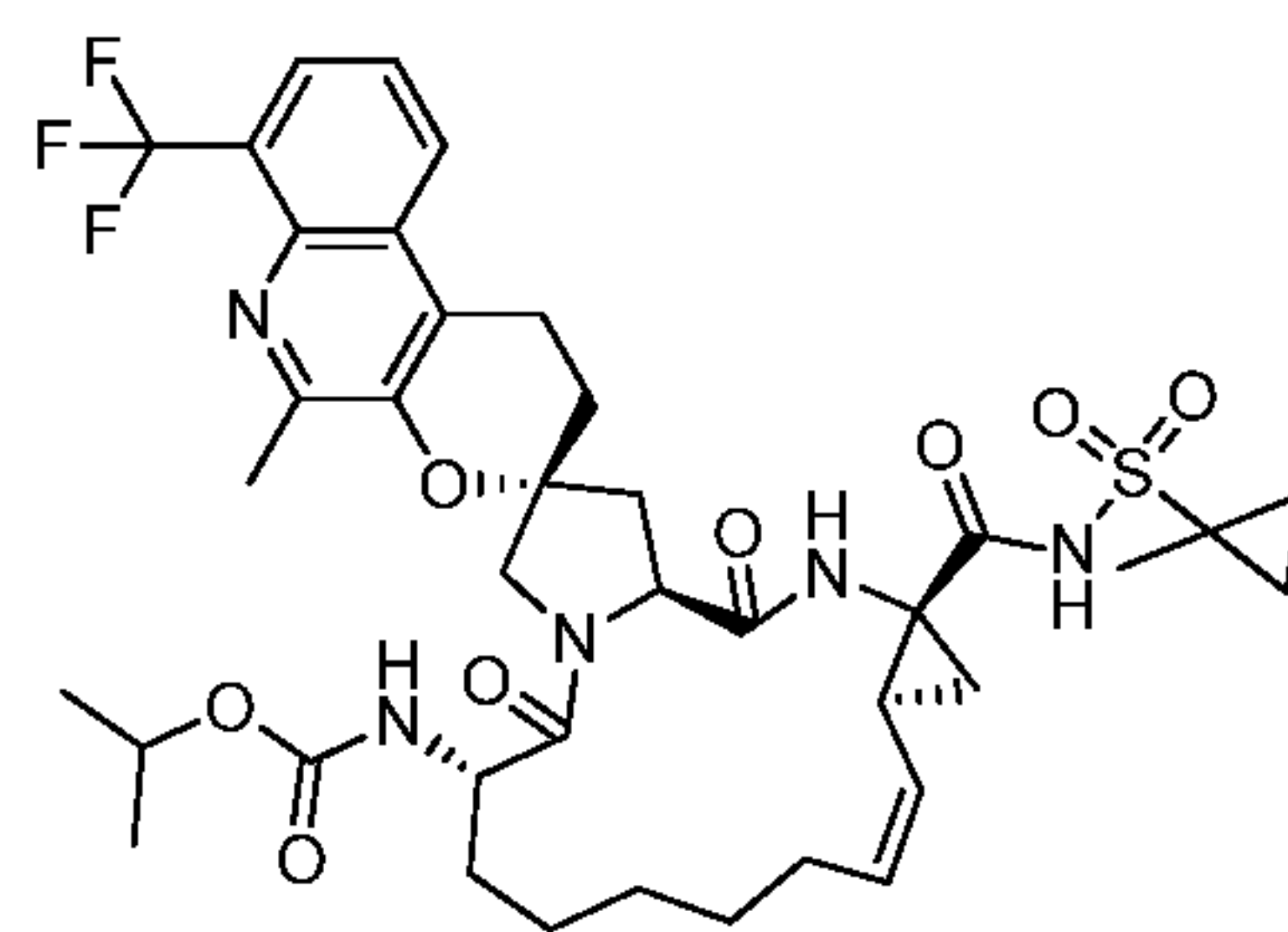
I-111



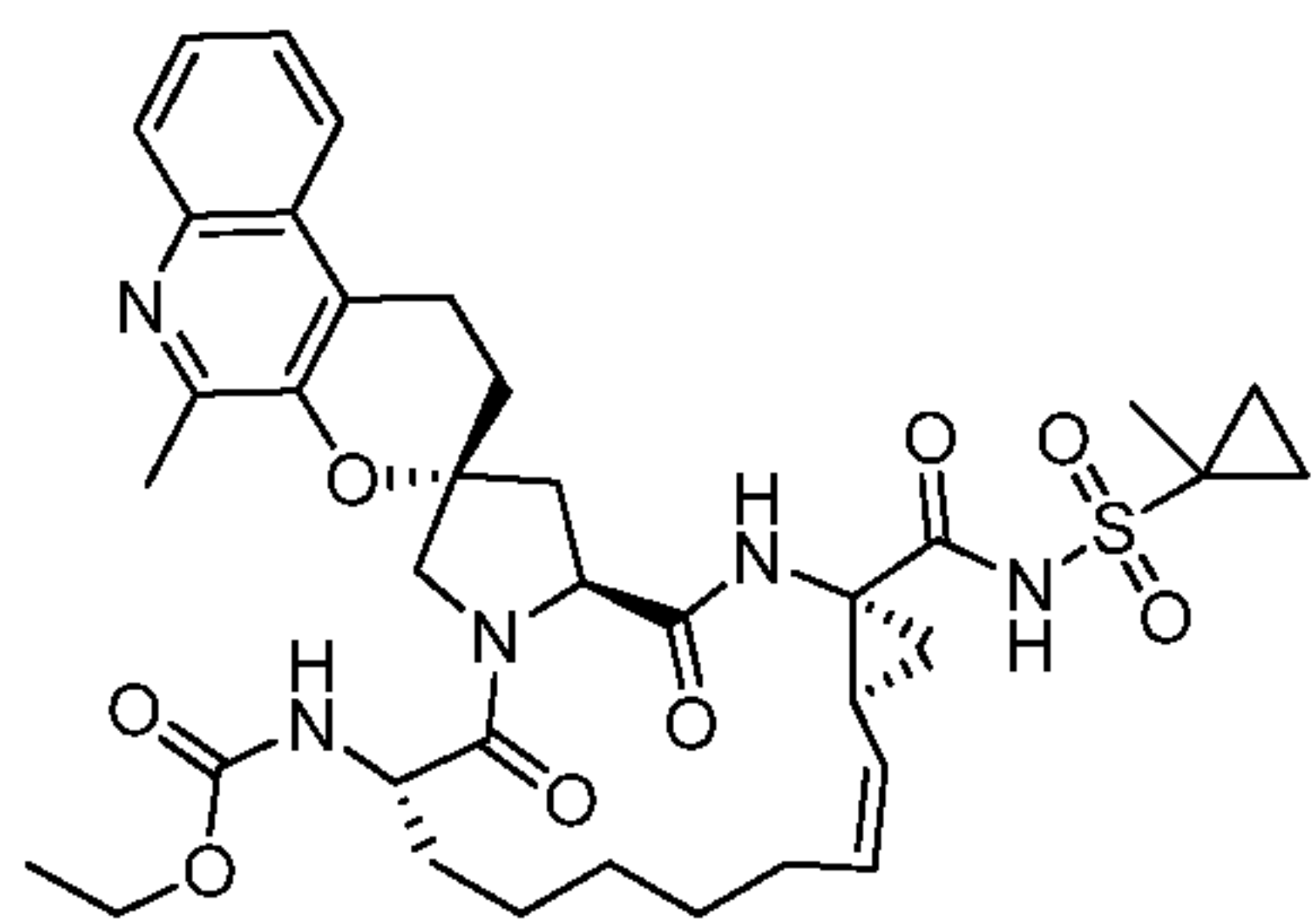
I-112



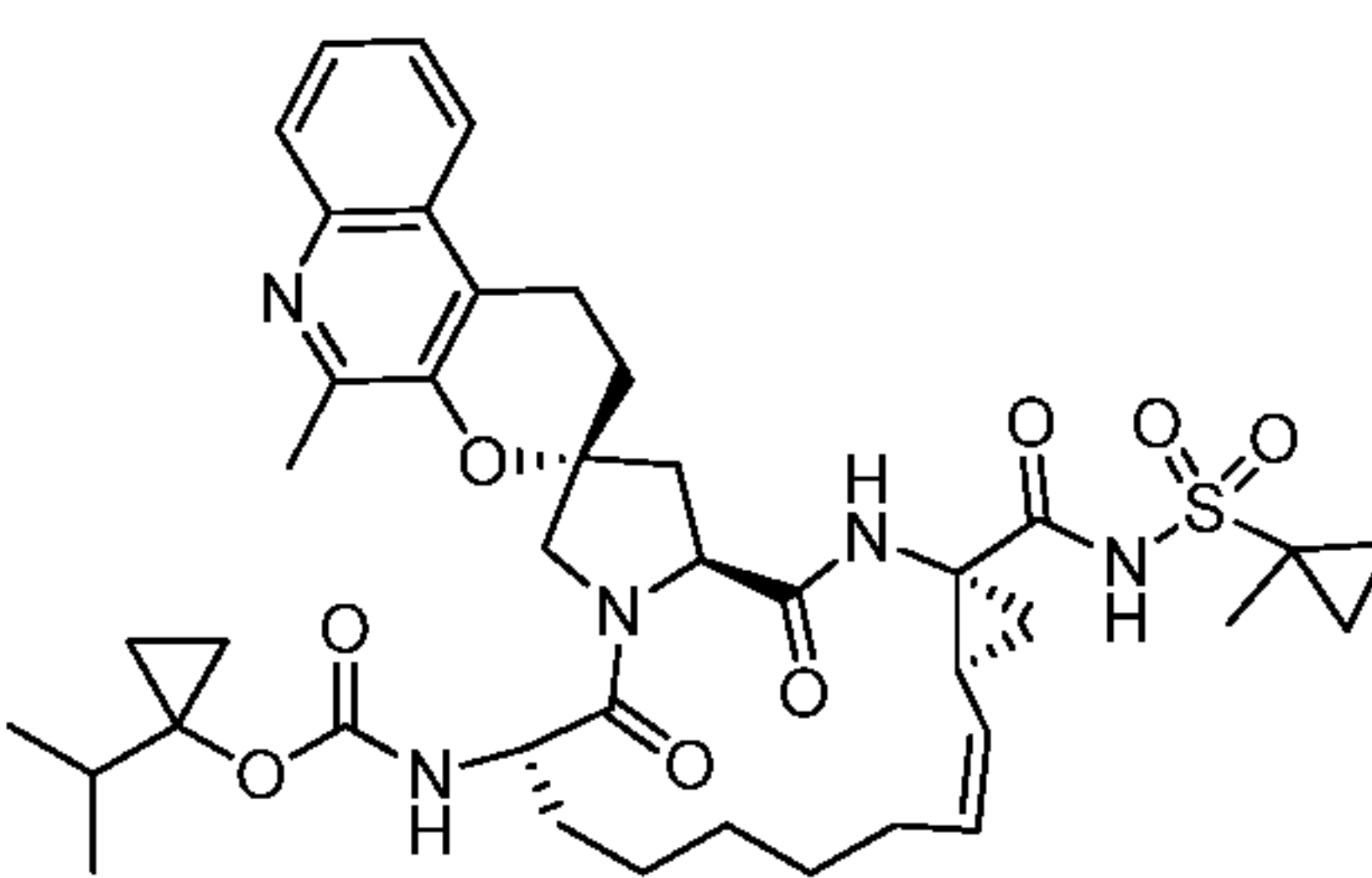
I-113



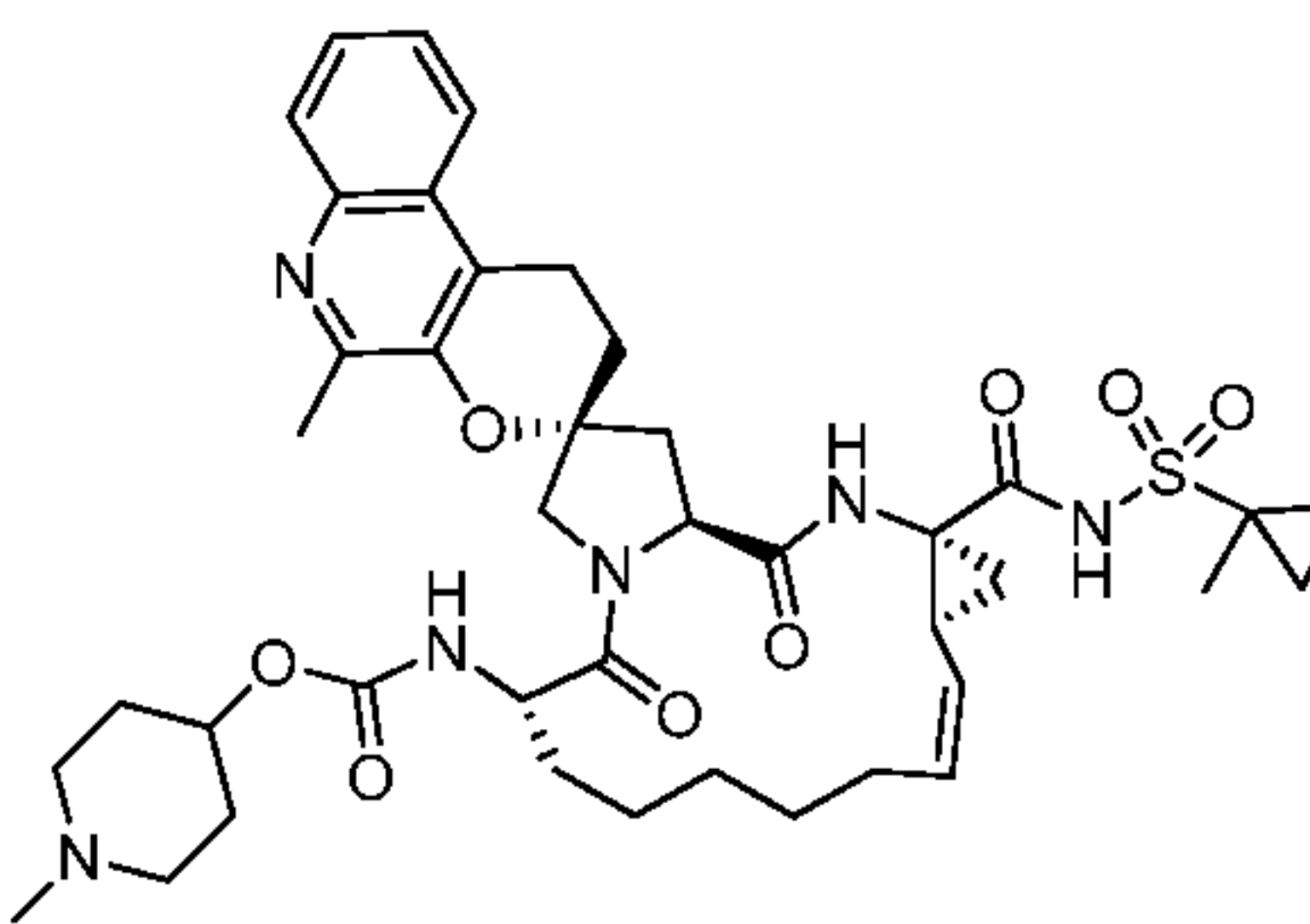
I-114



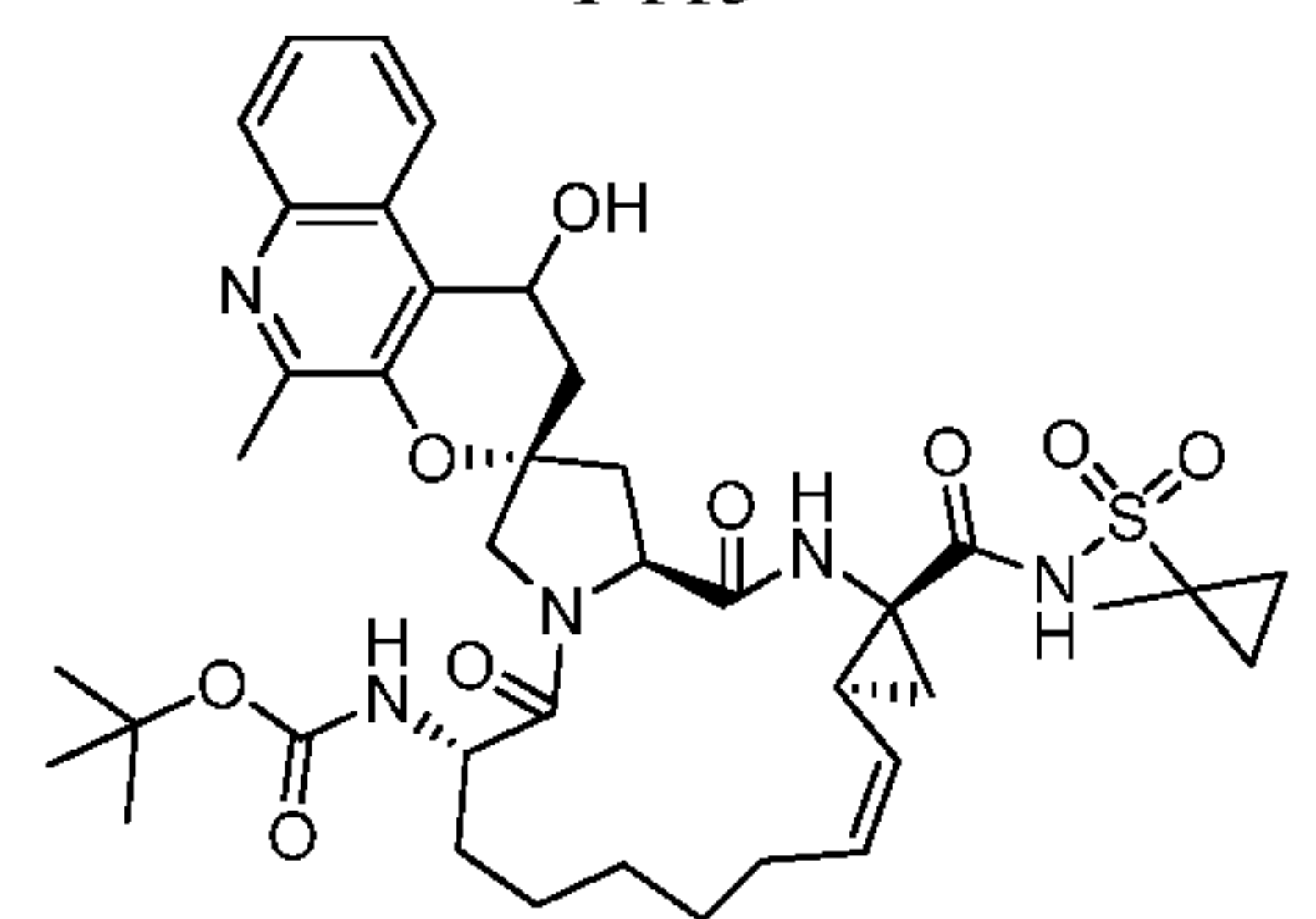
I-115



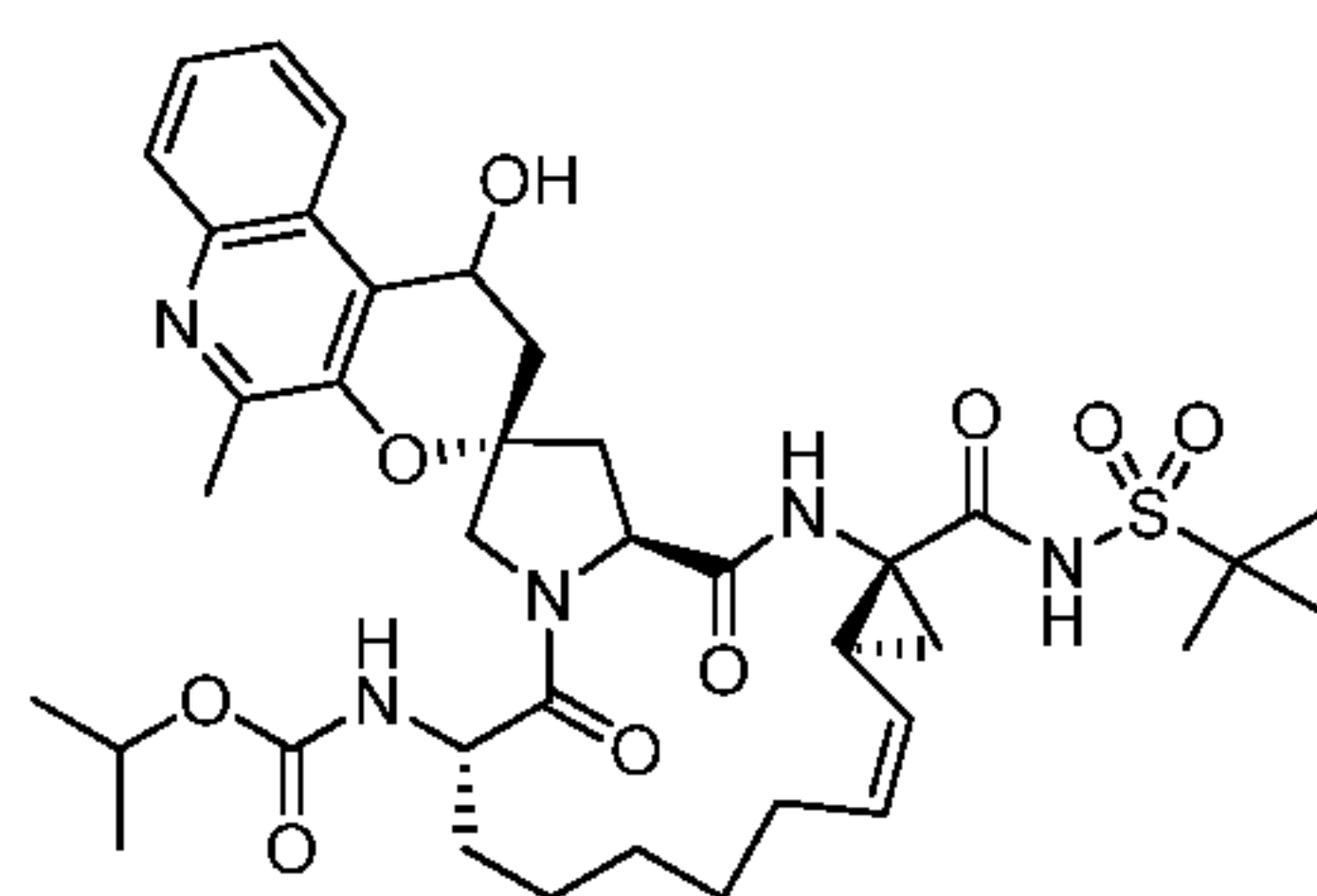
I-116



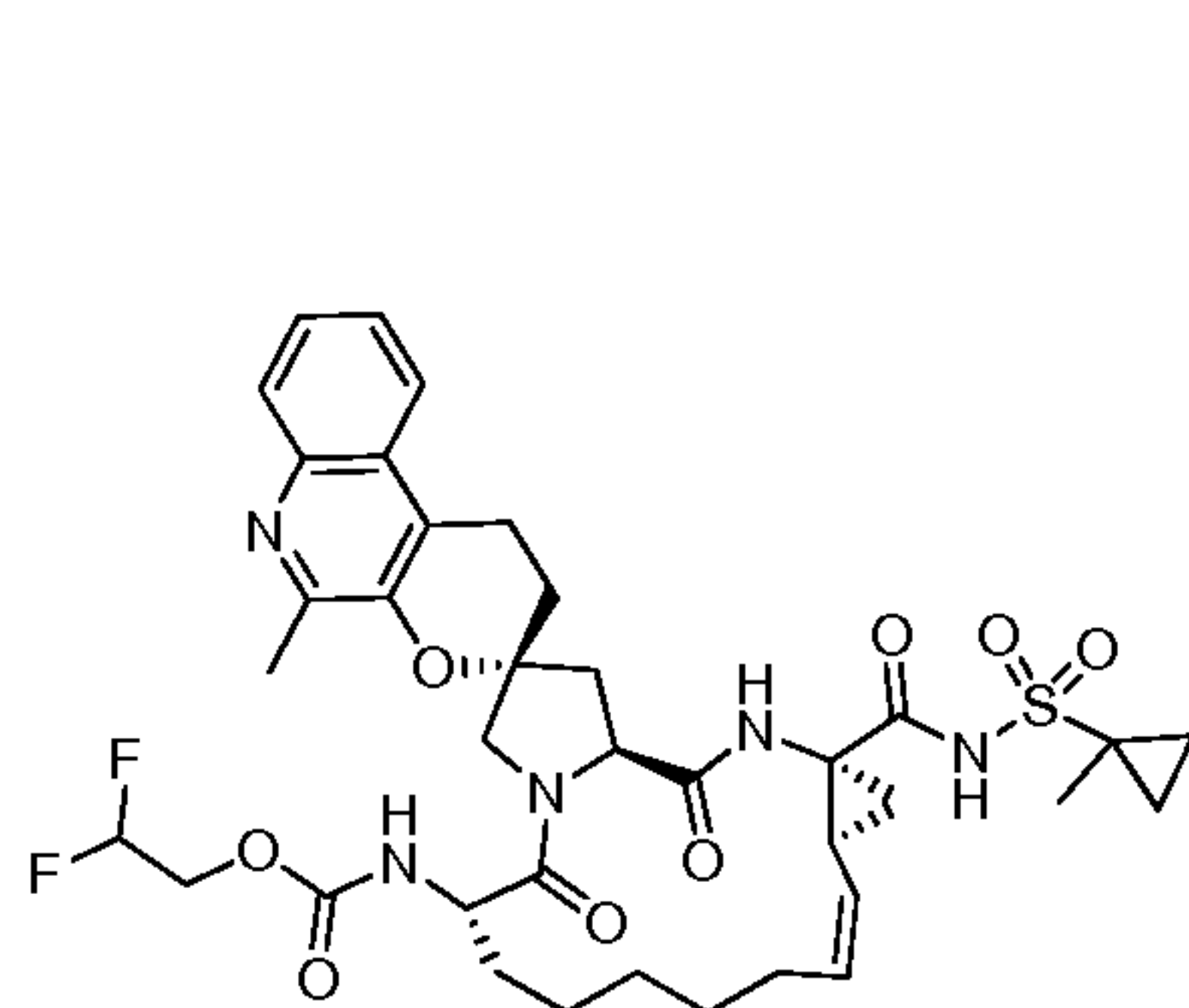
I-117



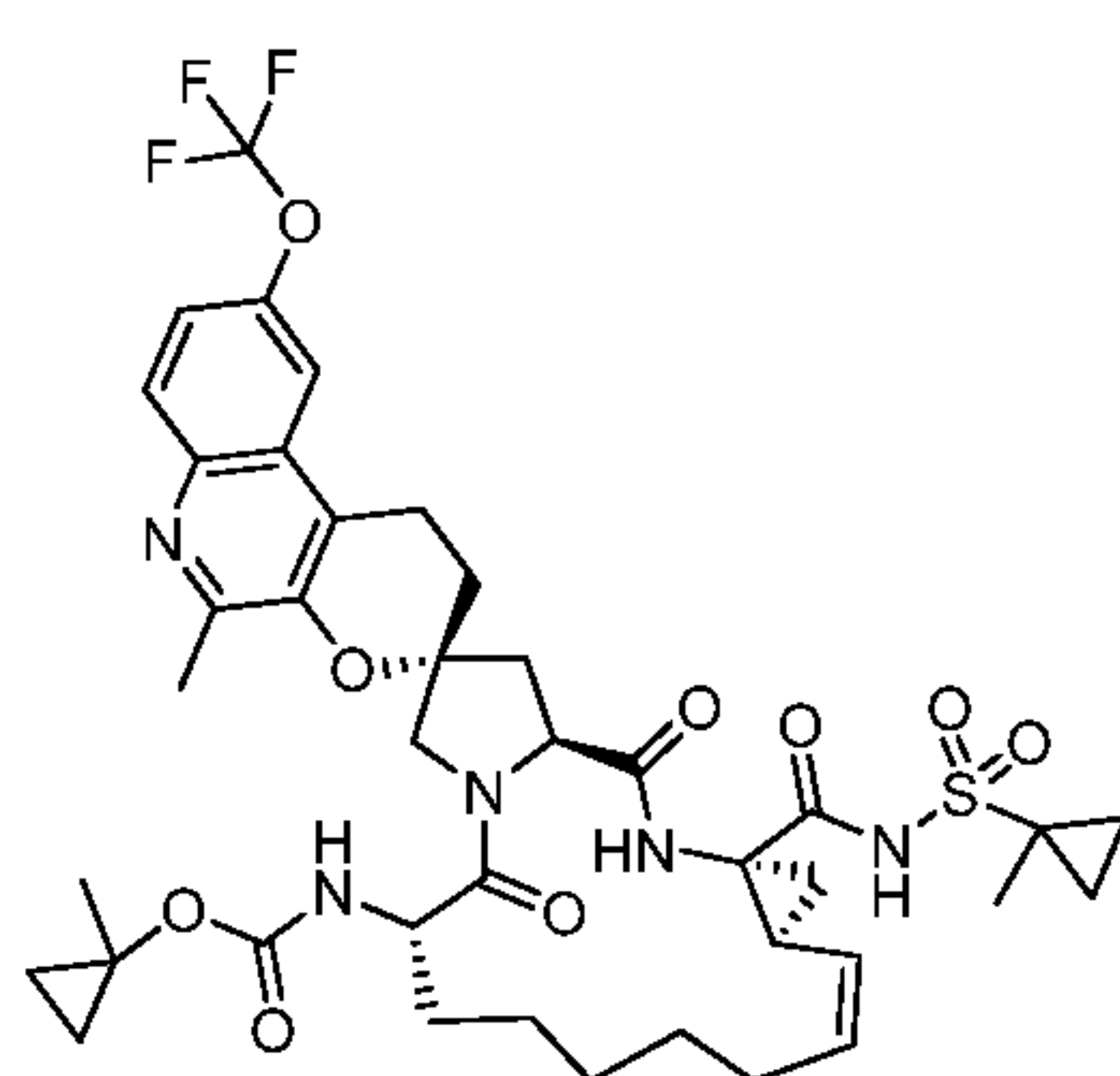
I-118/I-120



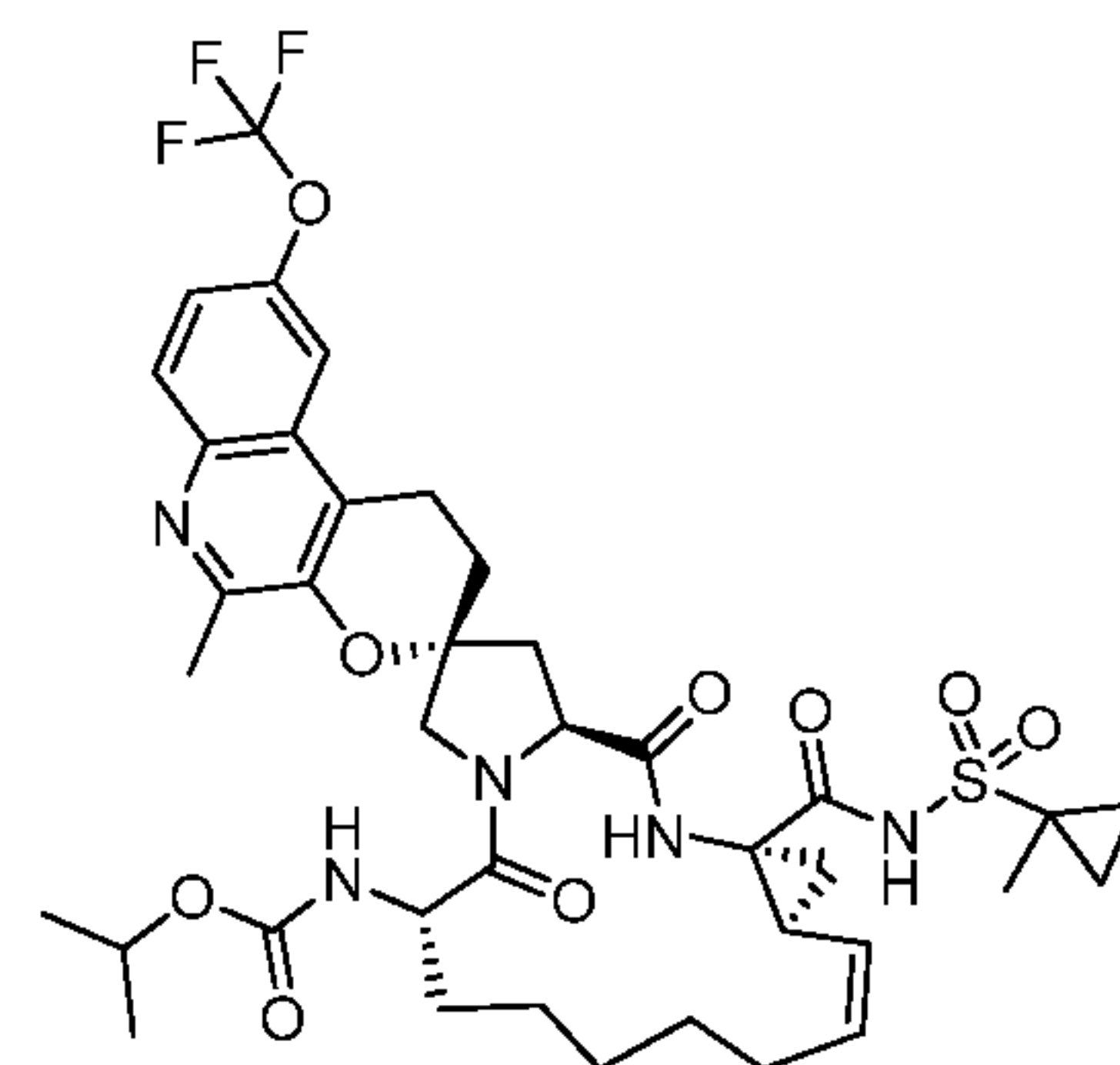
I-119



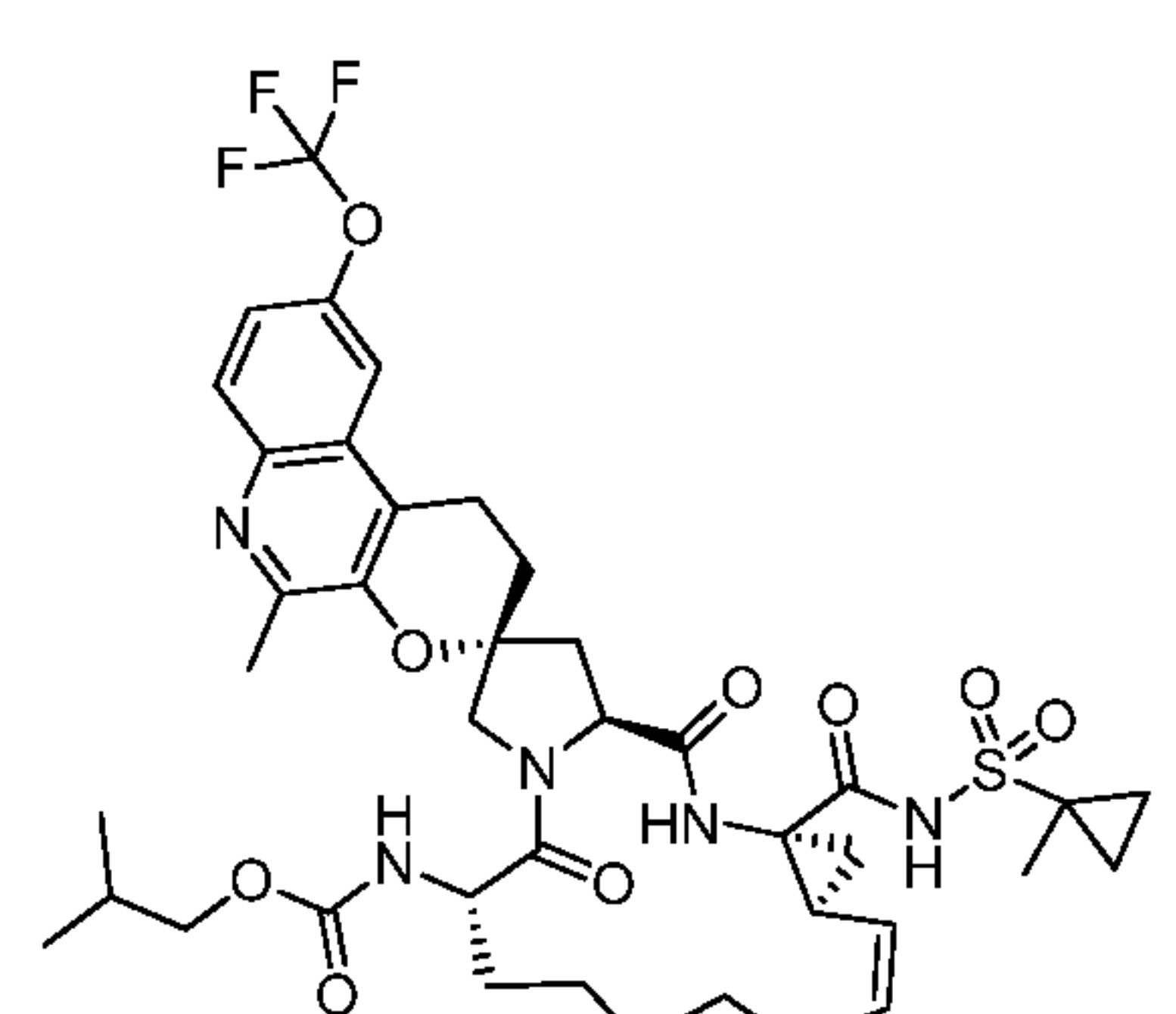
I-121



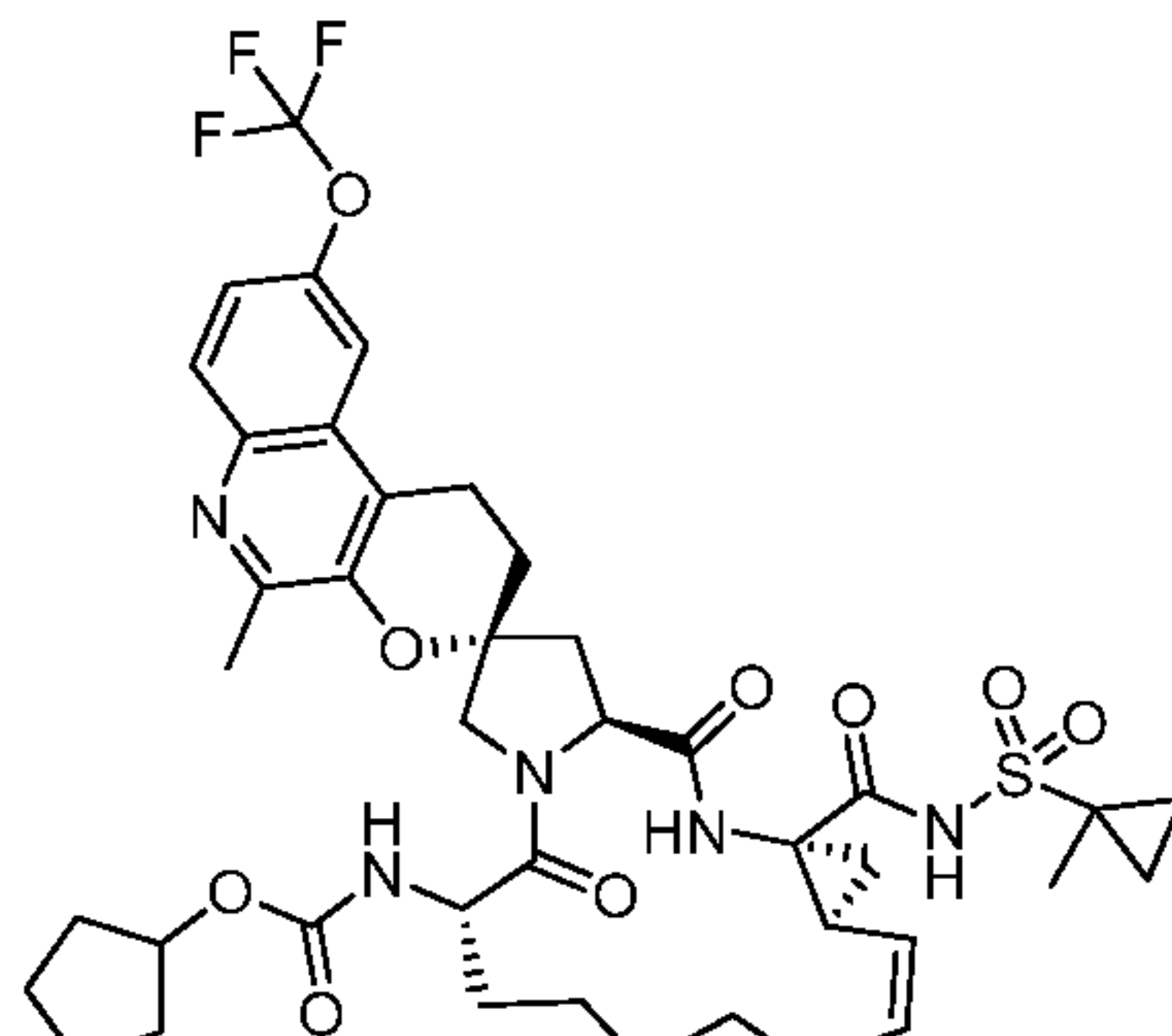
I-122



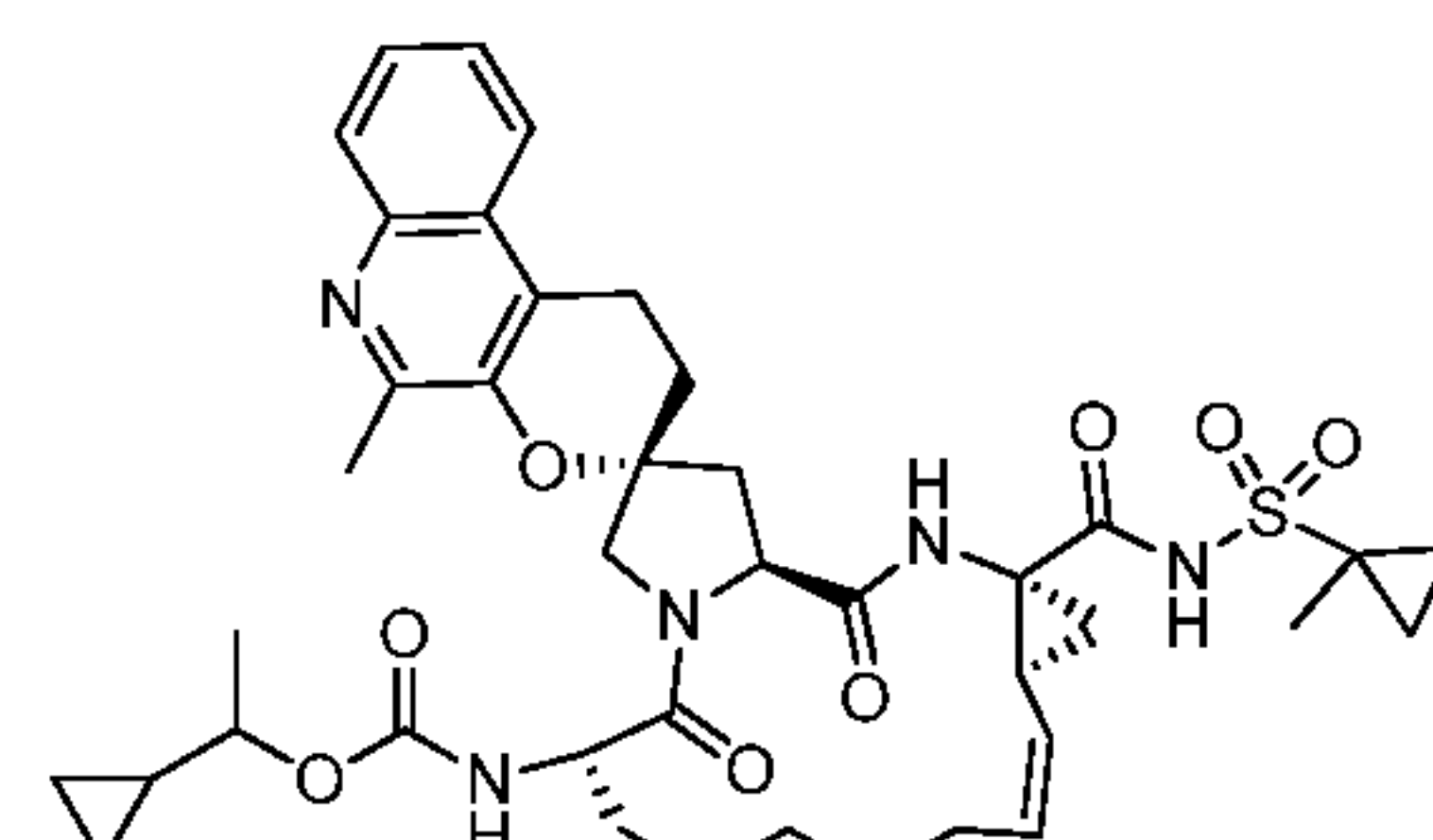
I-123



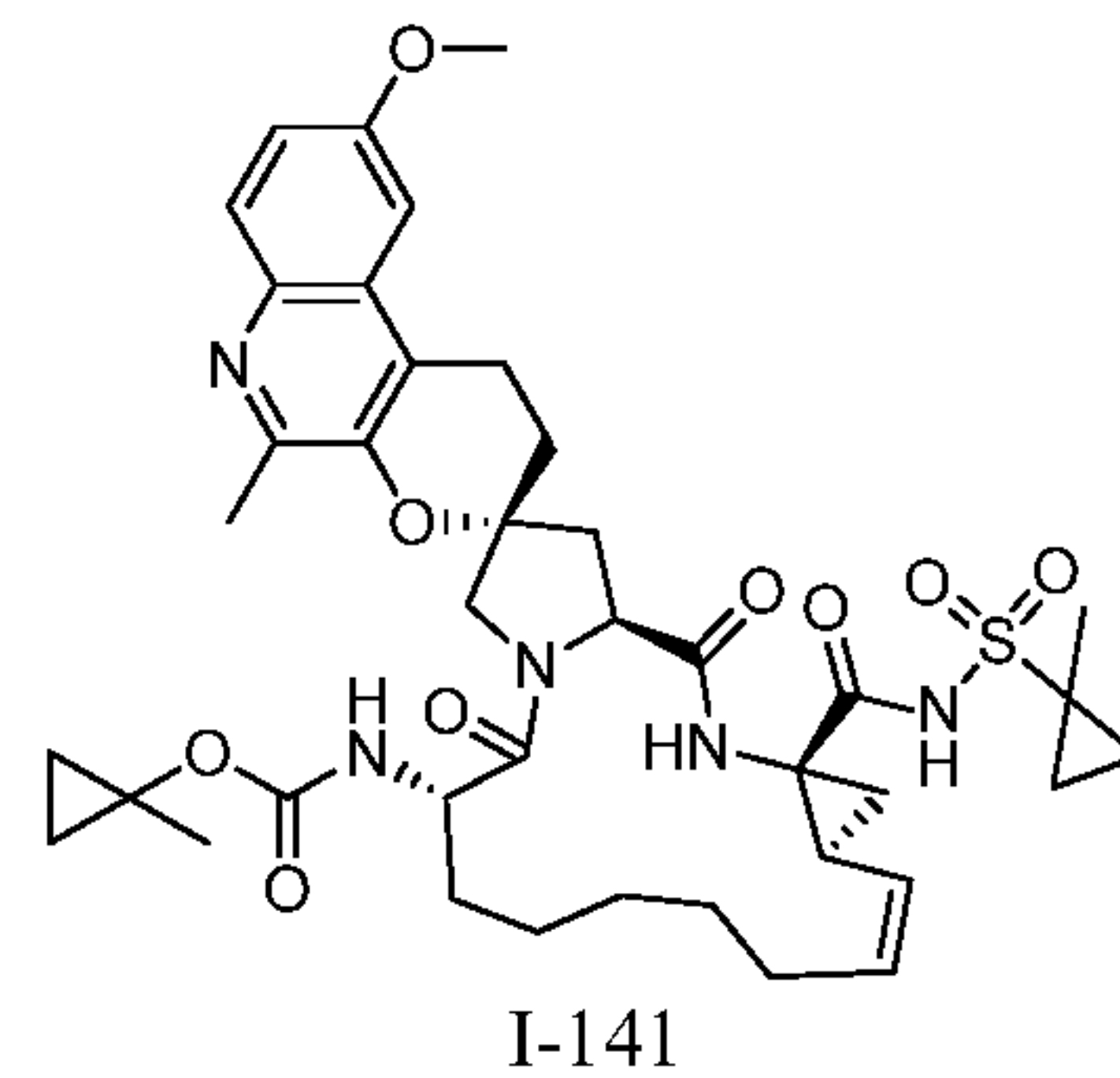
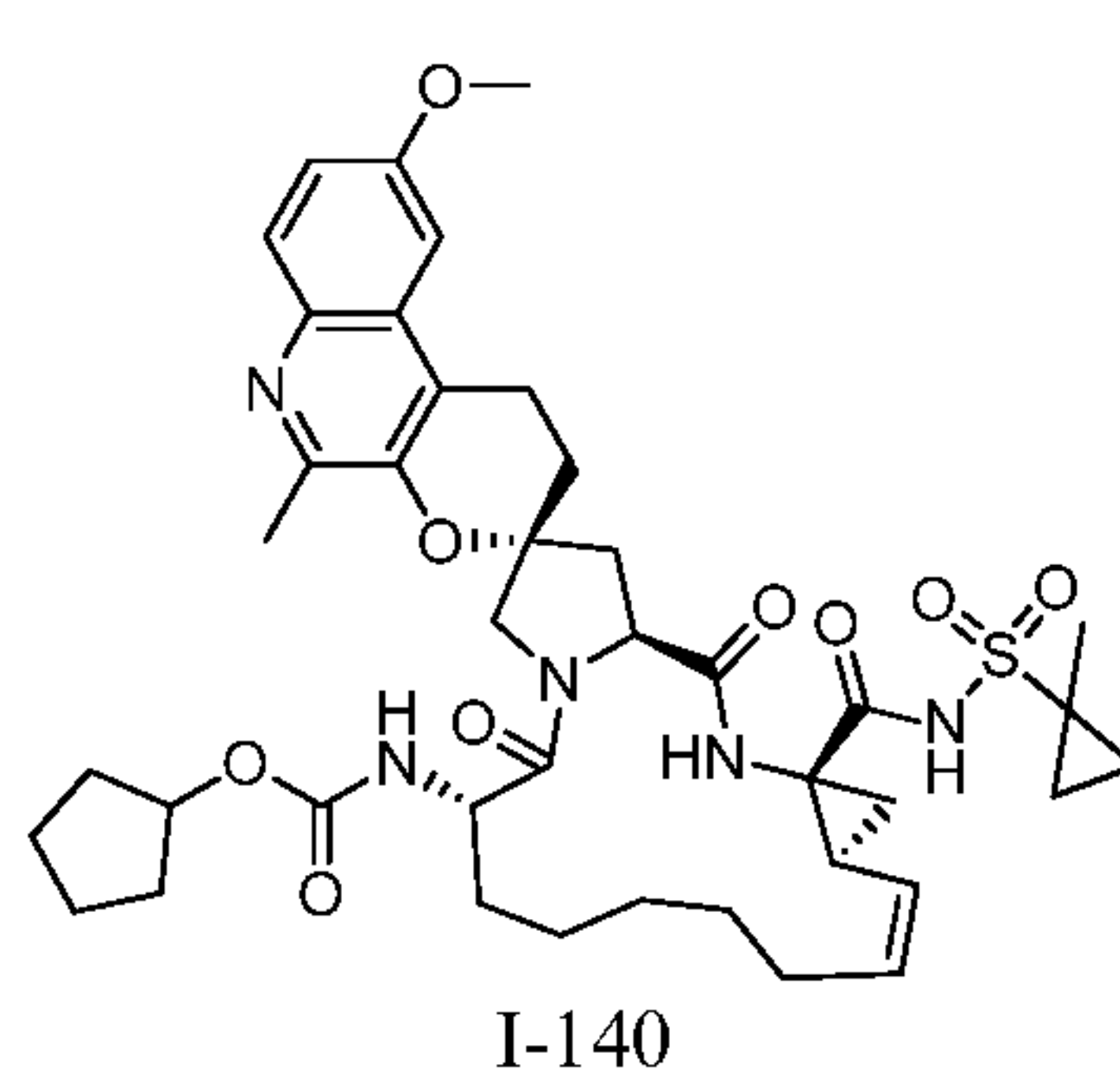
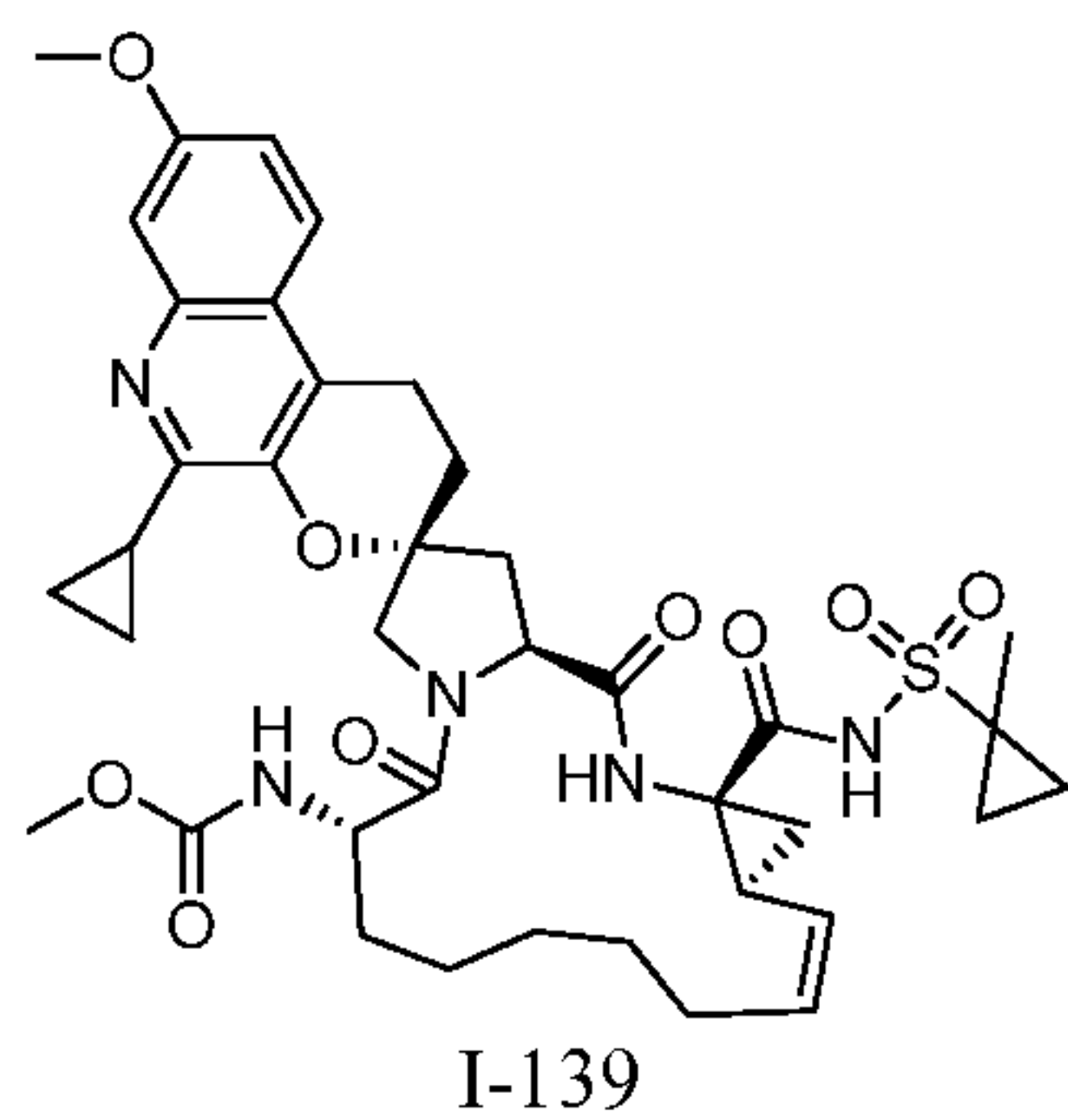
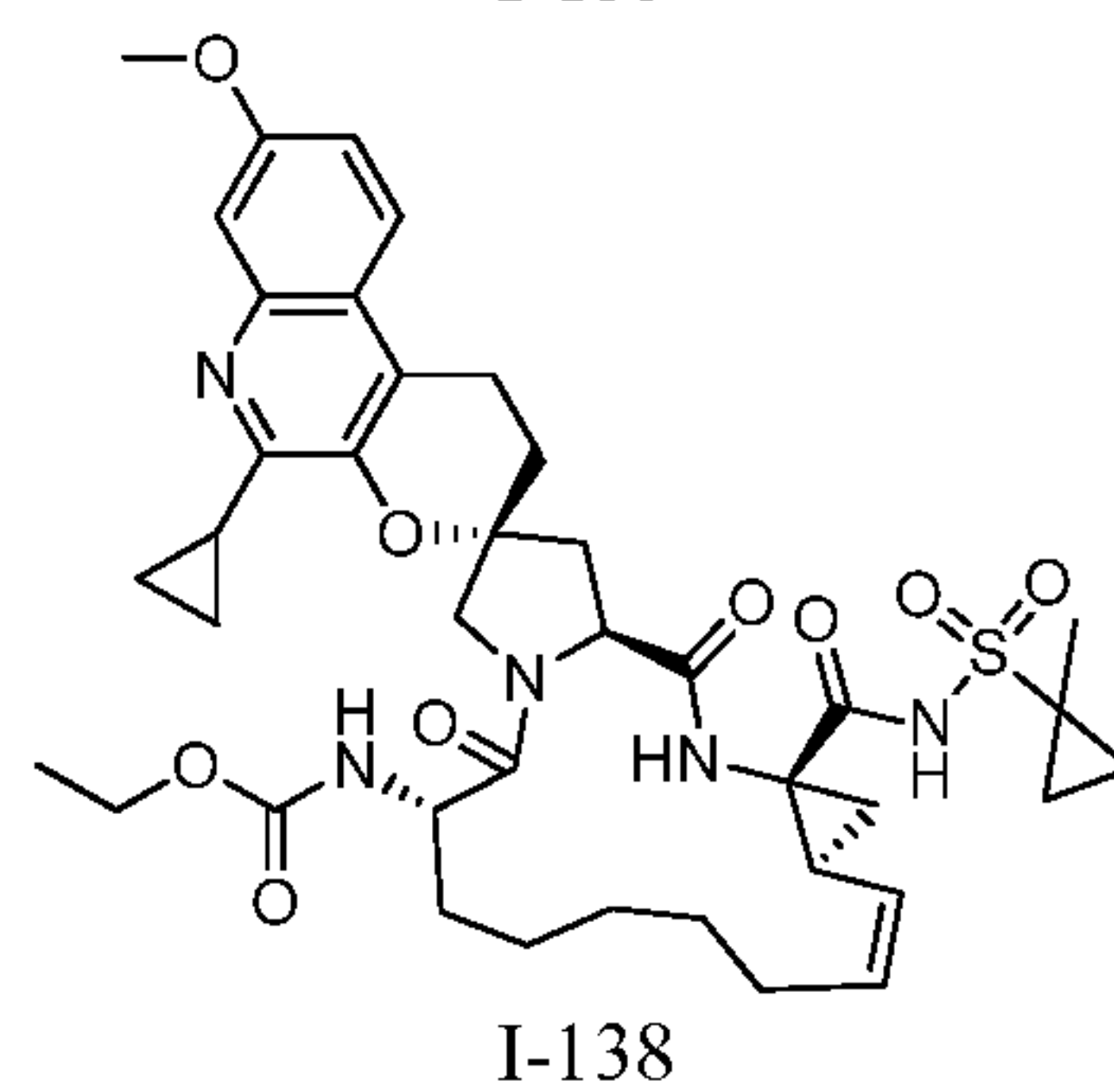
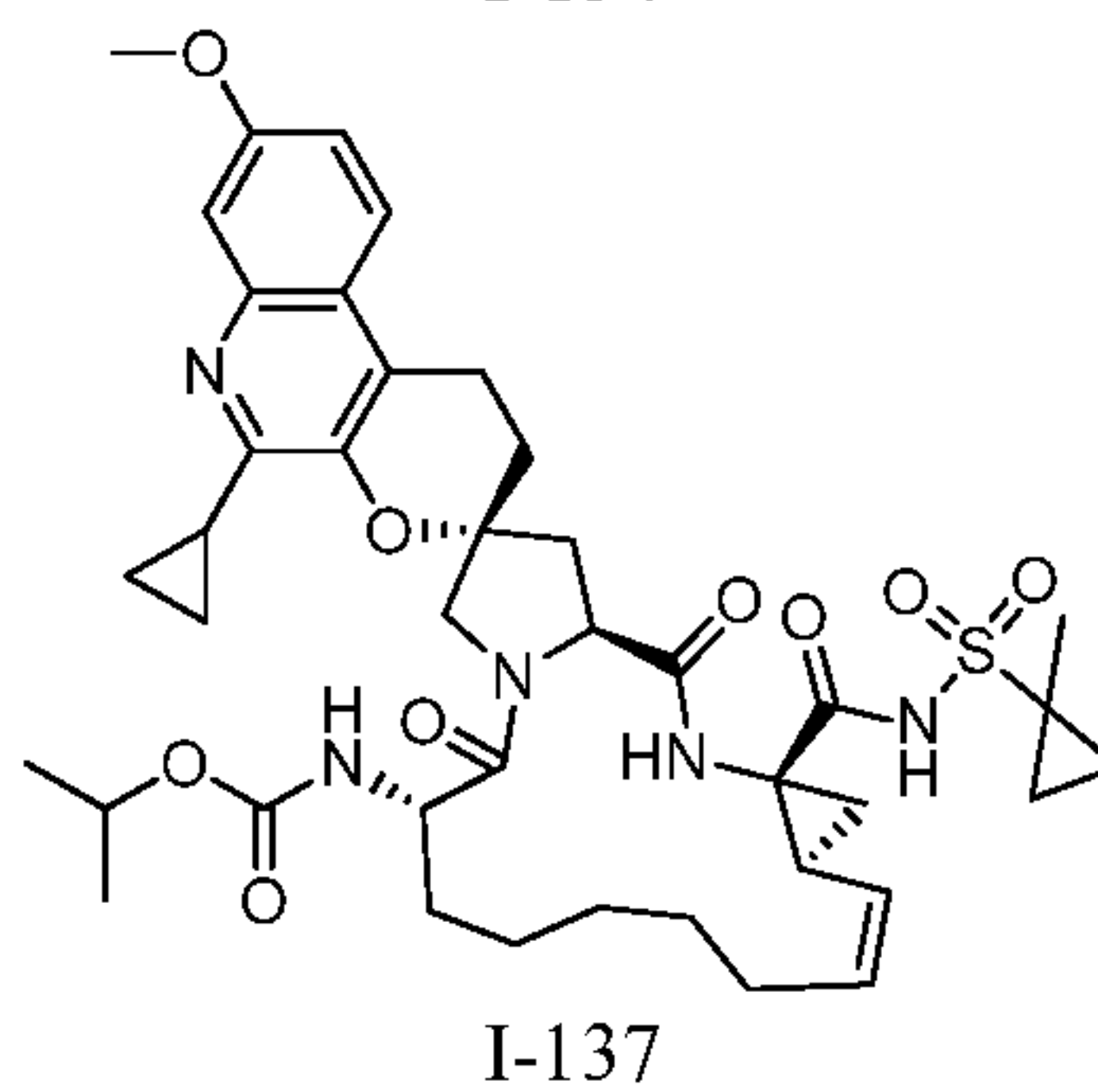
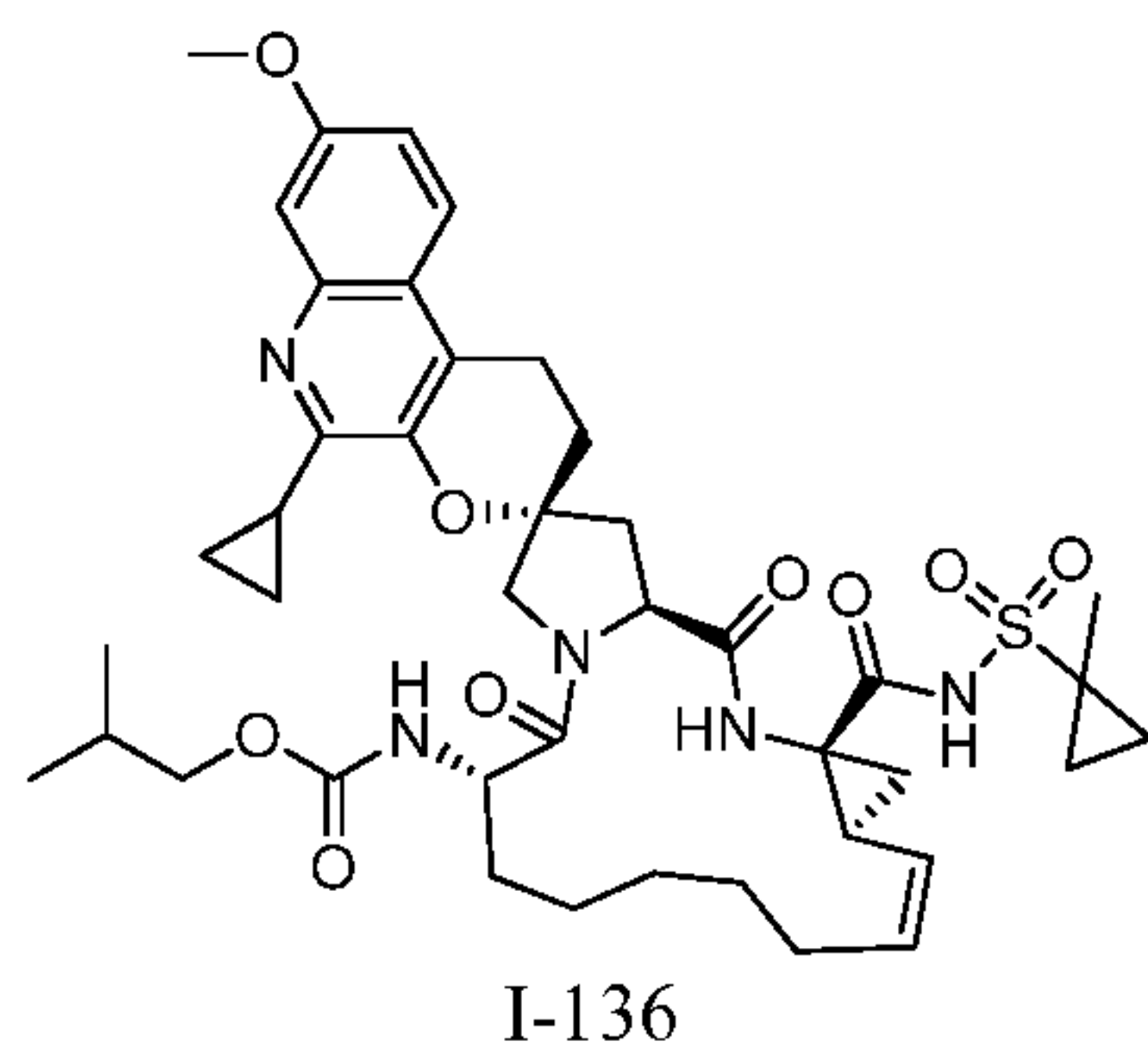
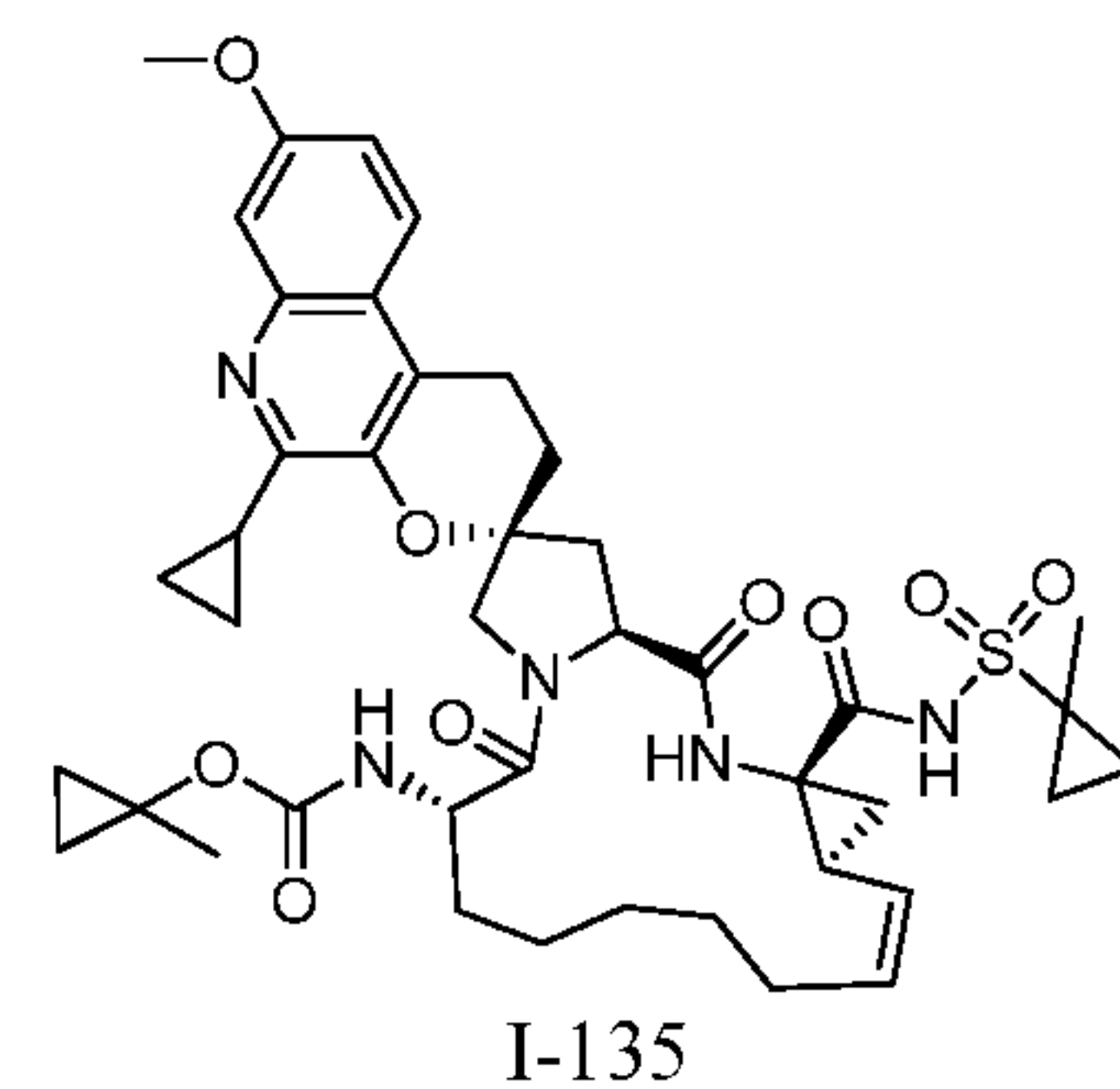
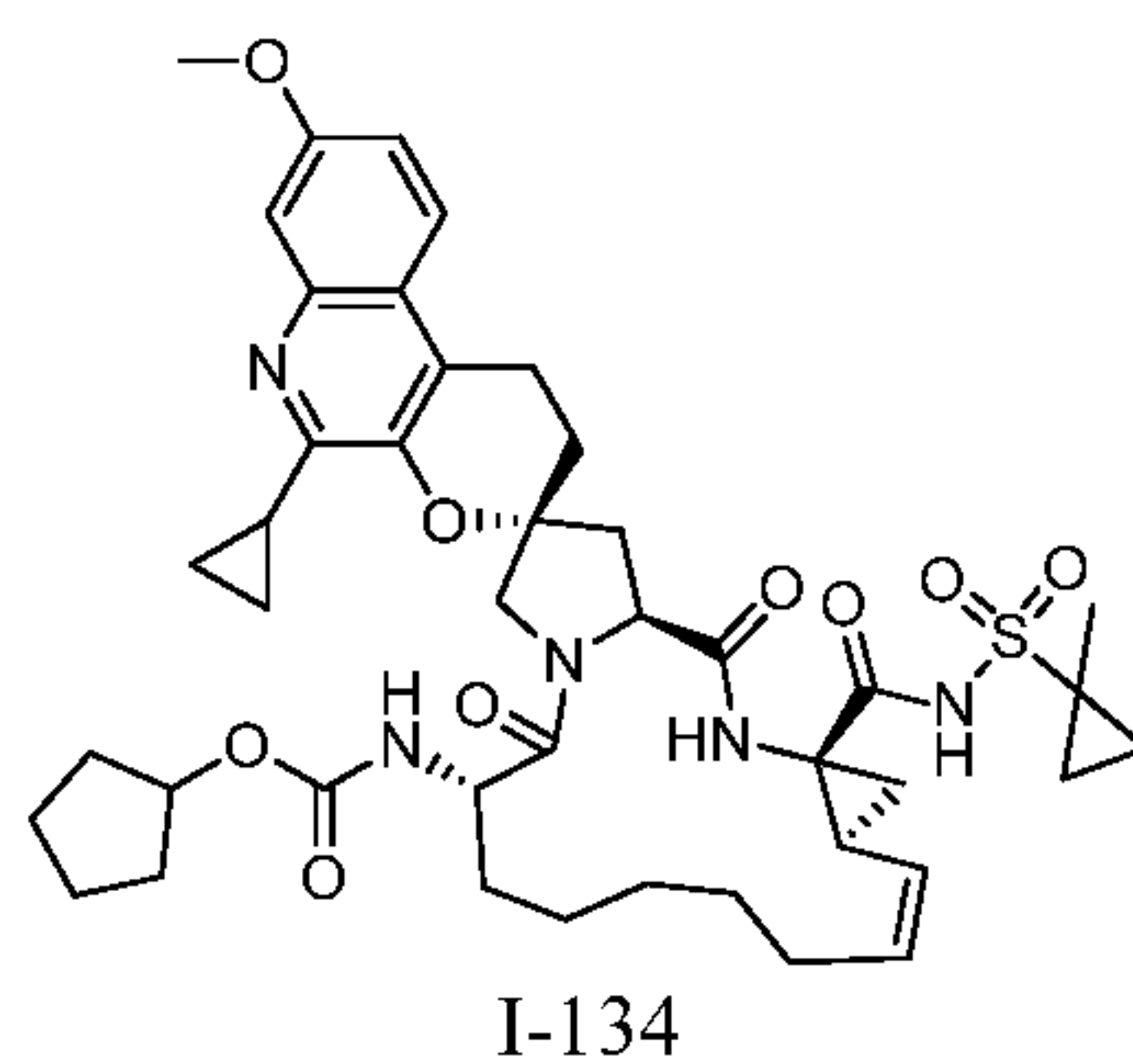
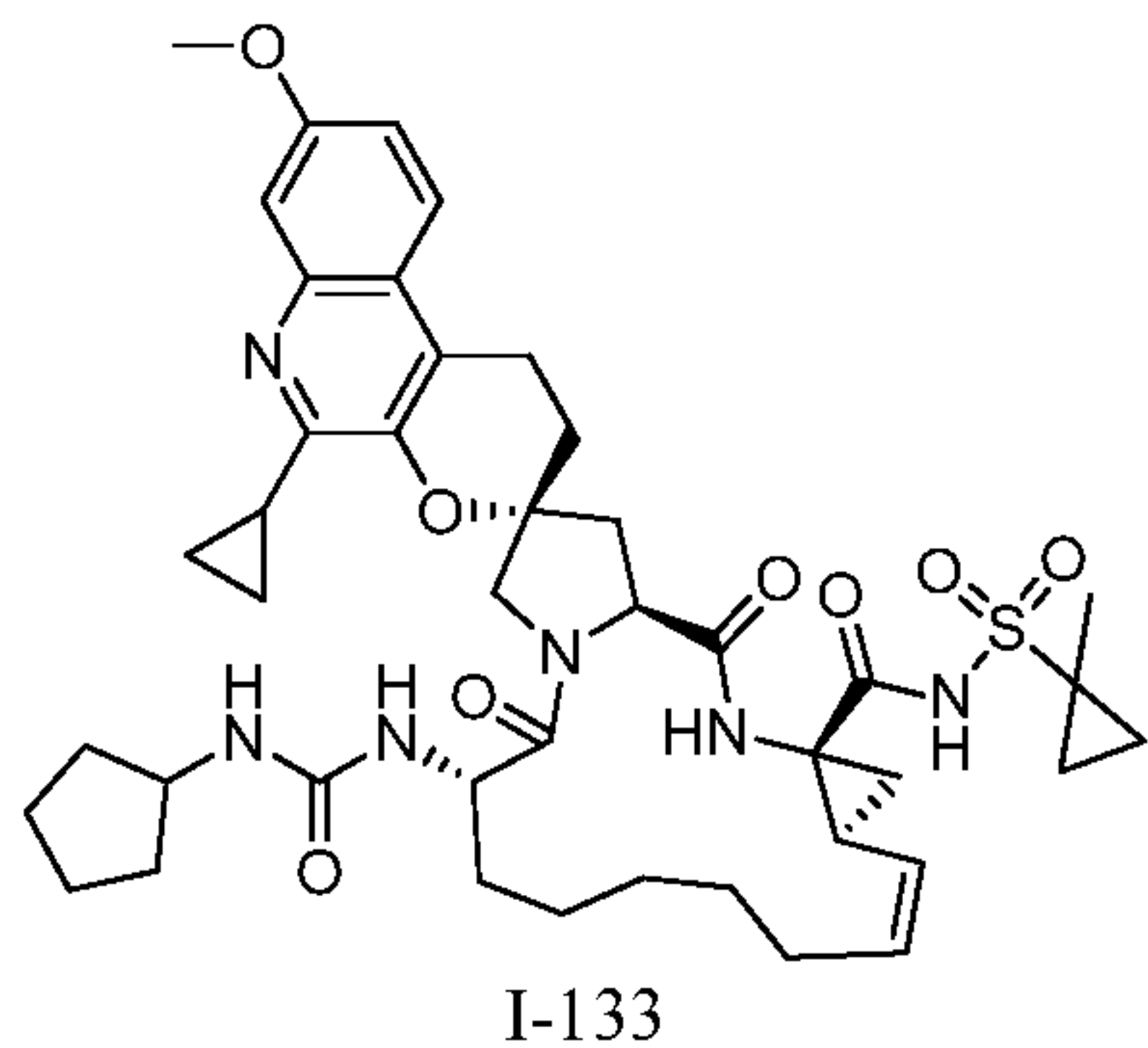
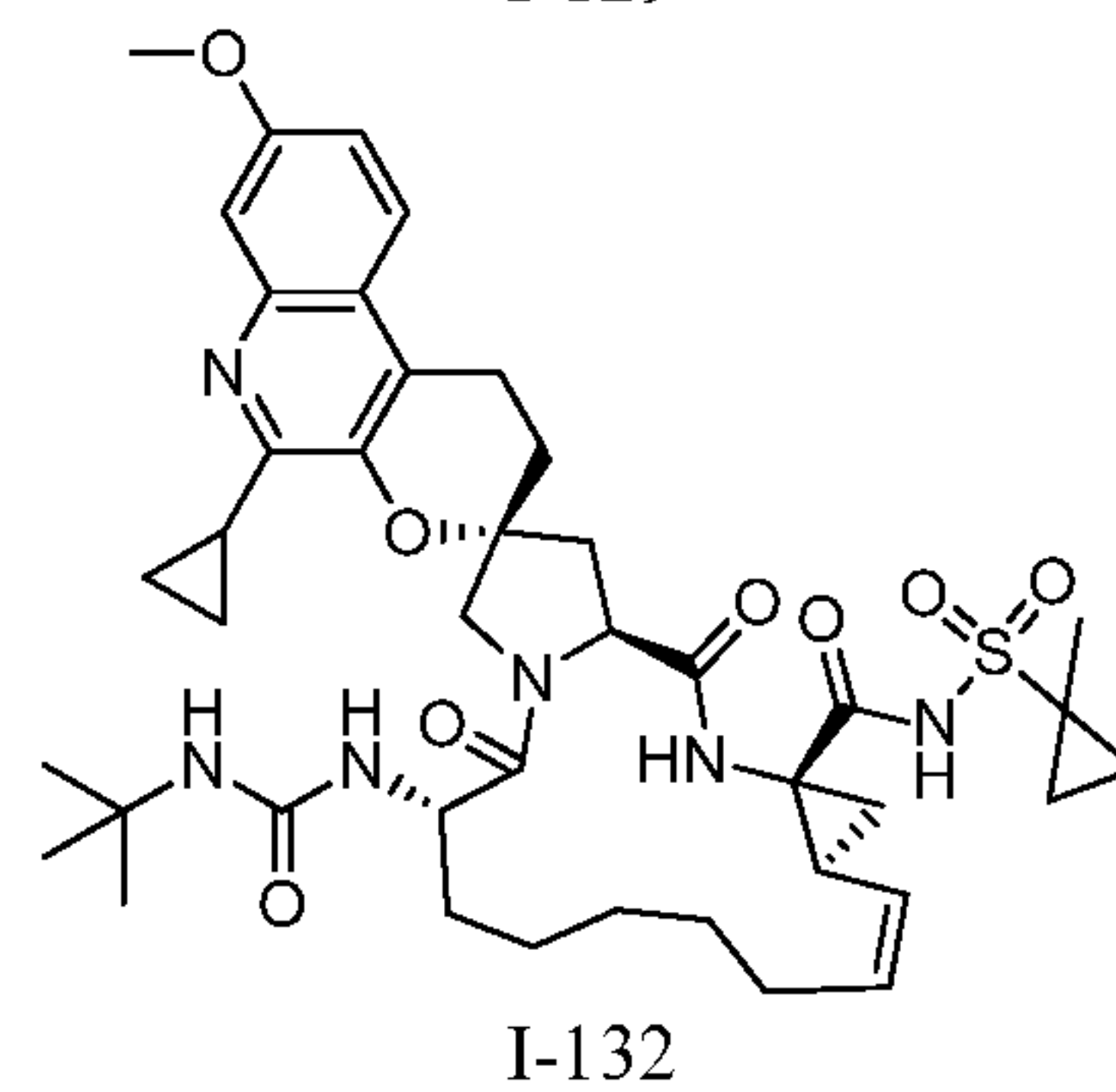
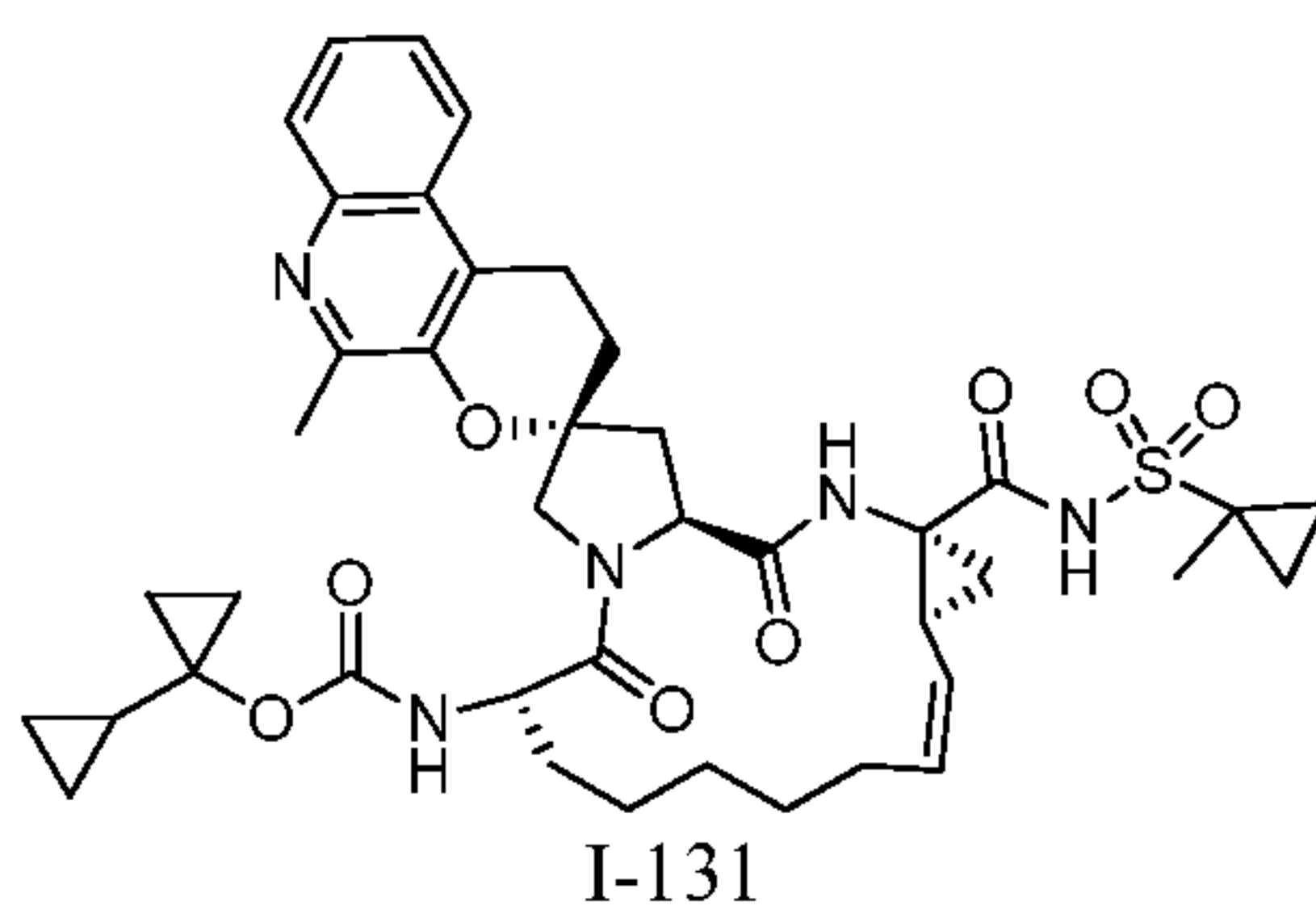
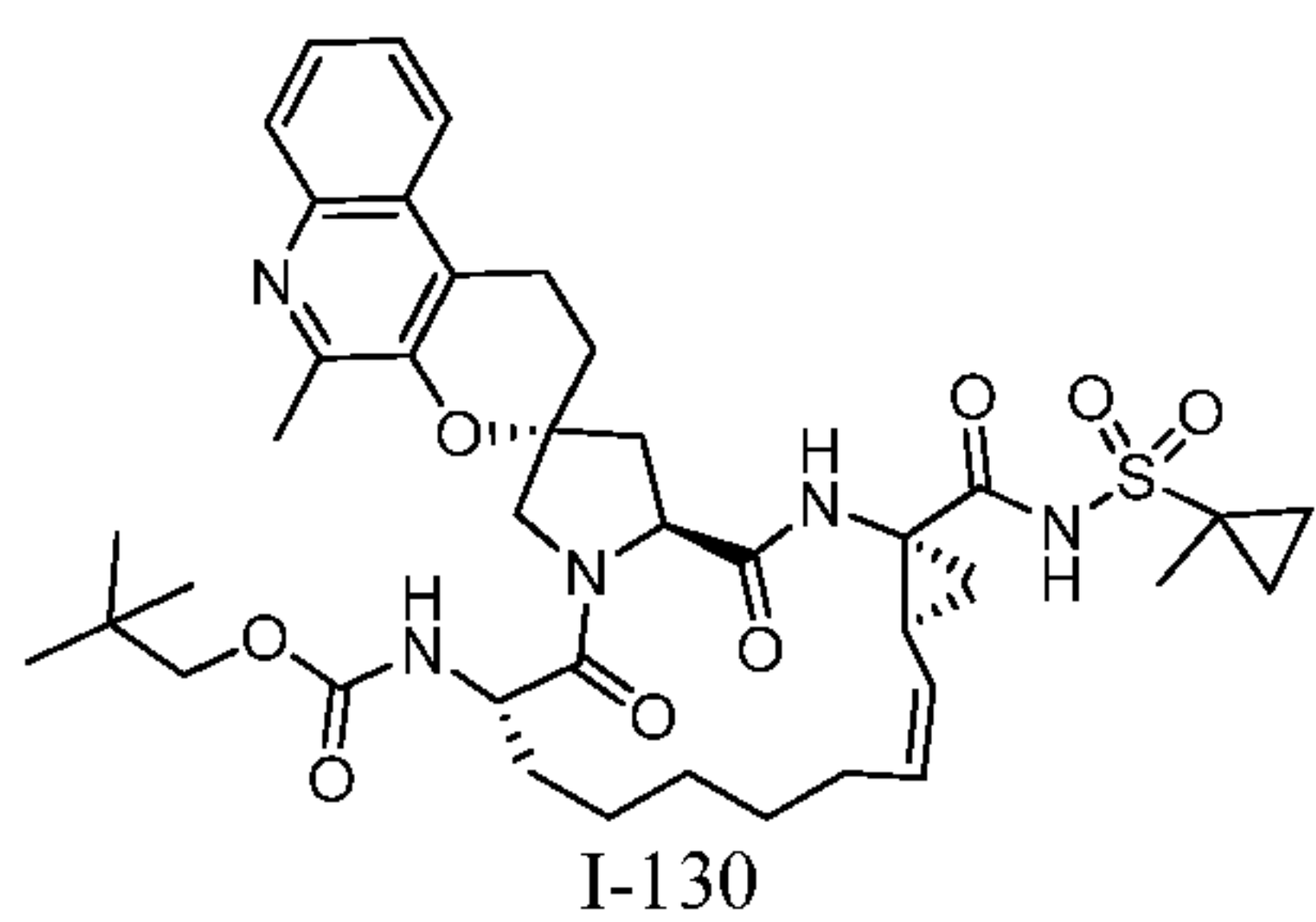
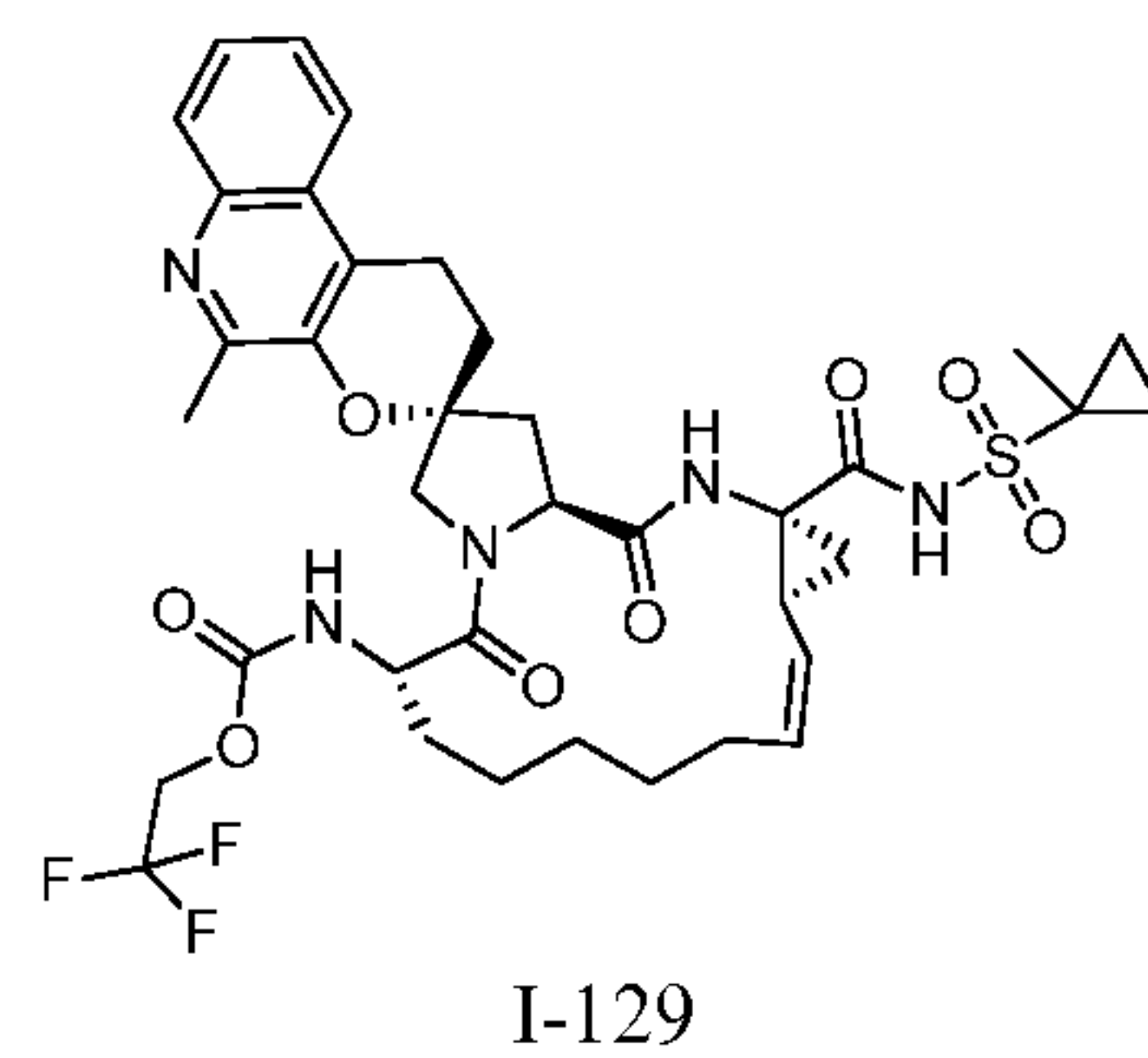
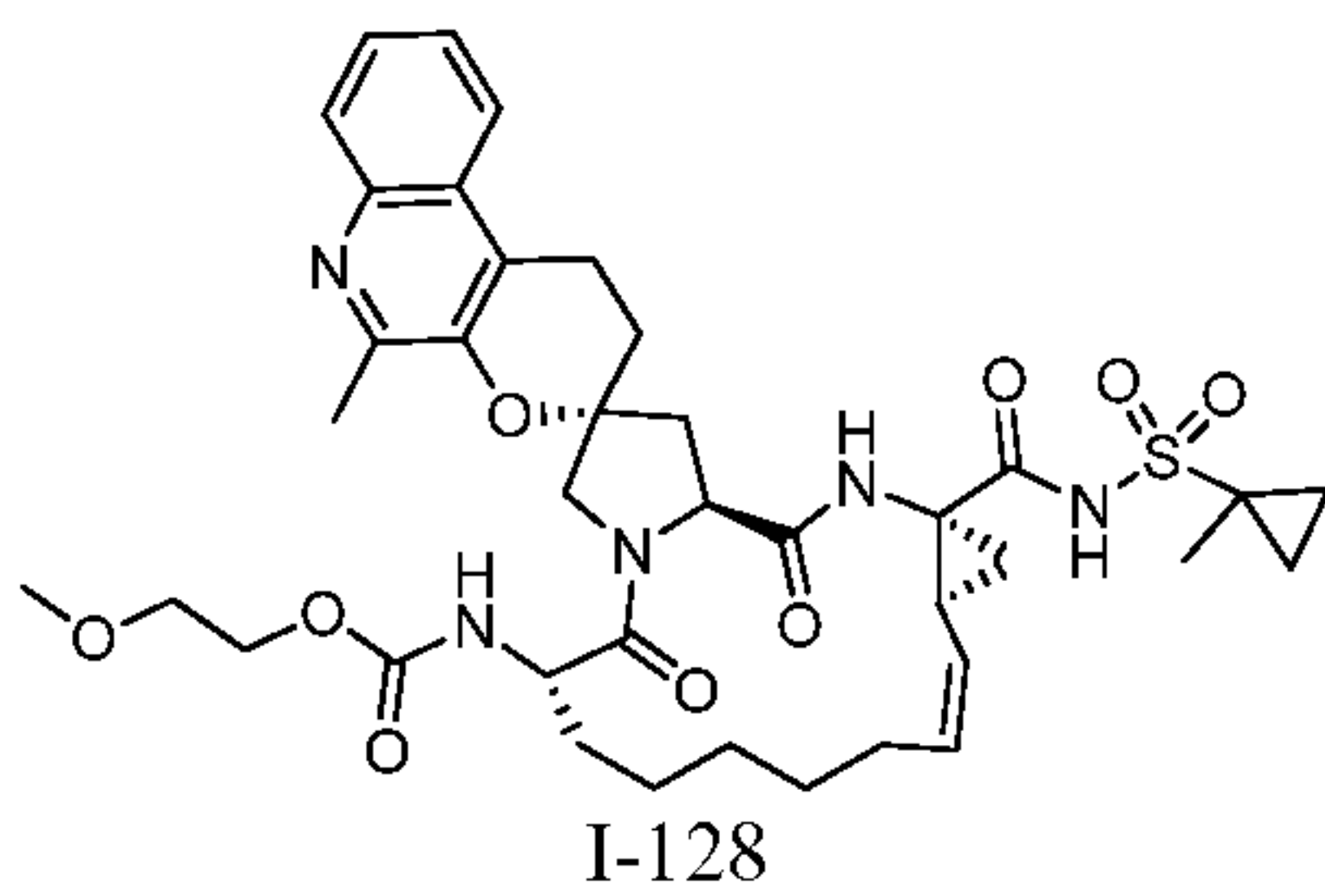
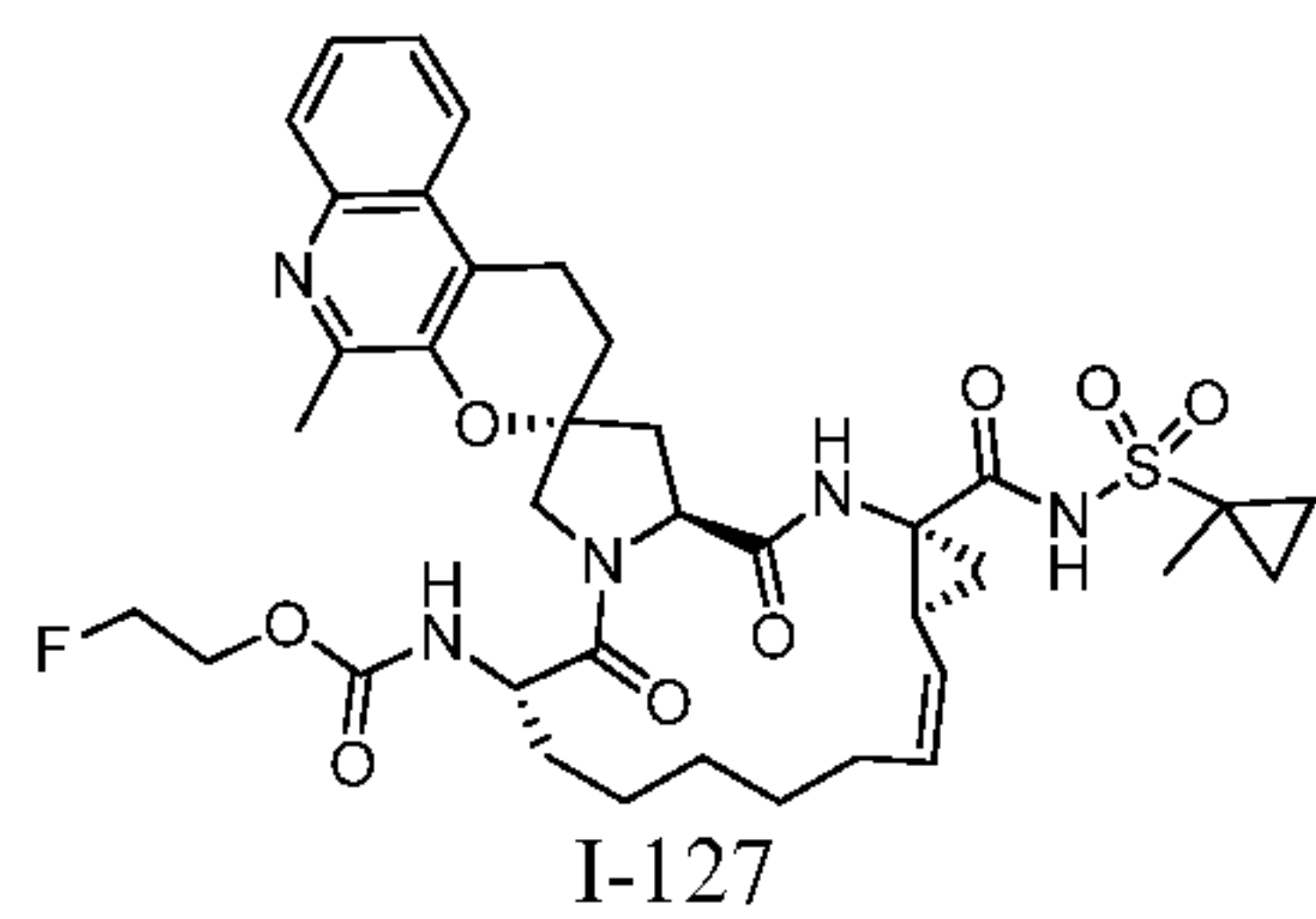
I-124

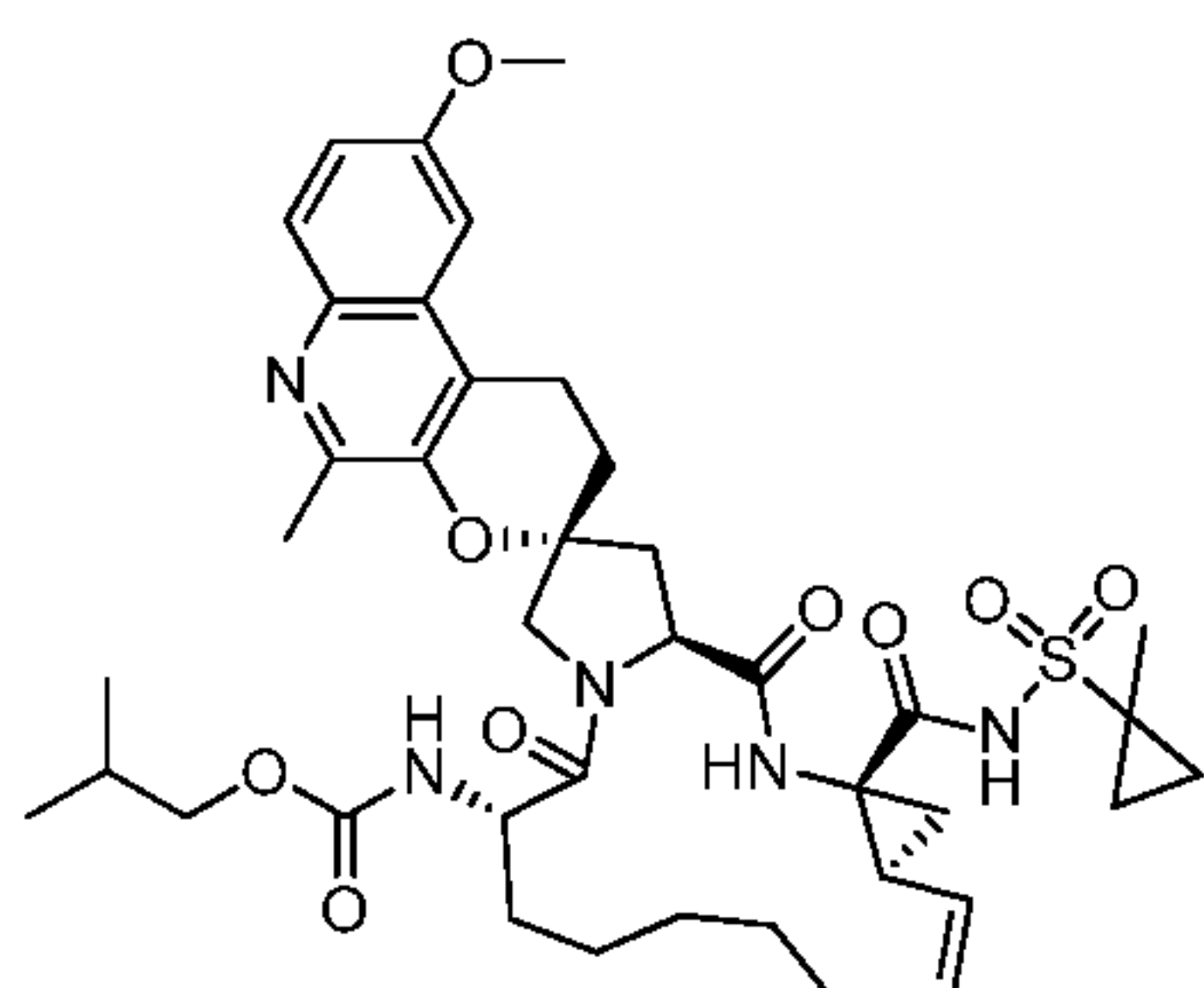


I-125

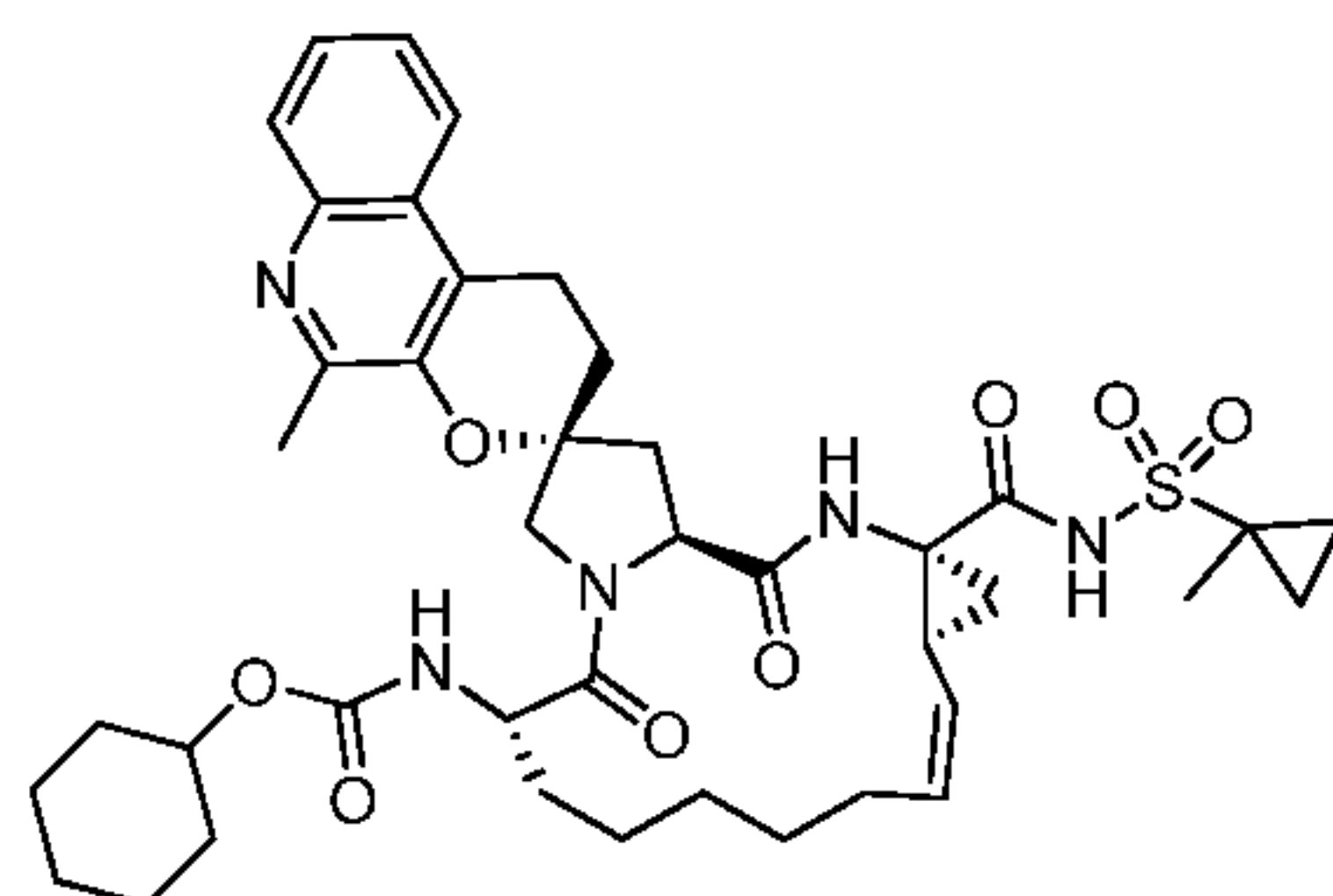


I-126

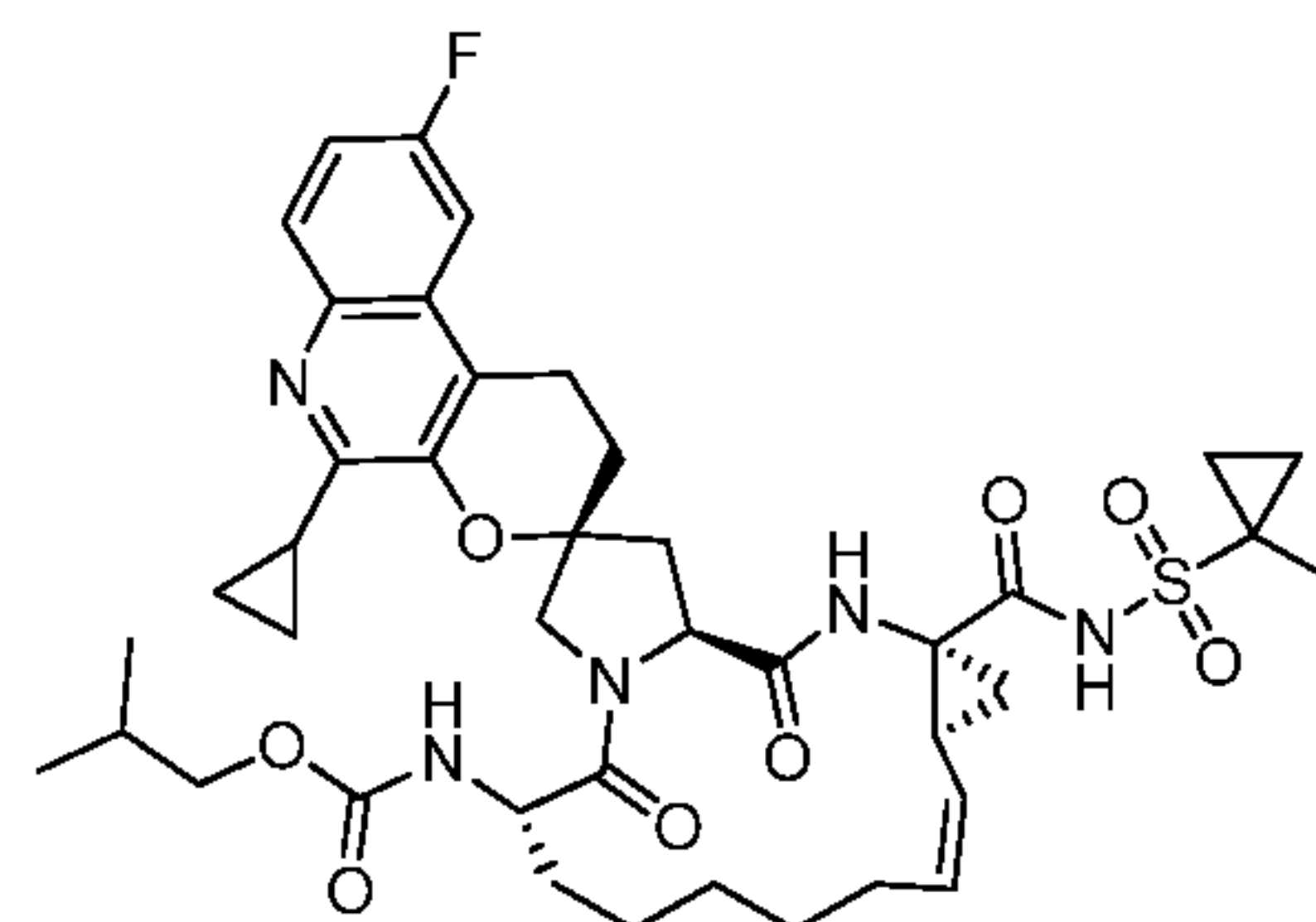




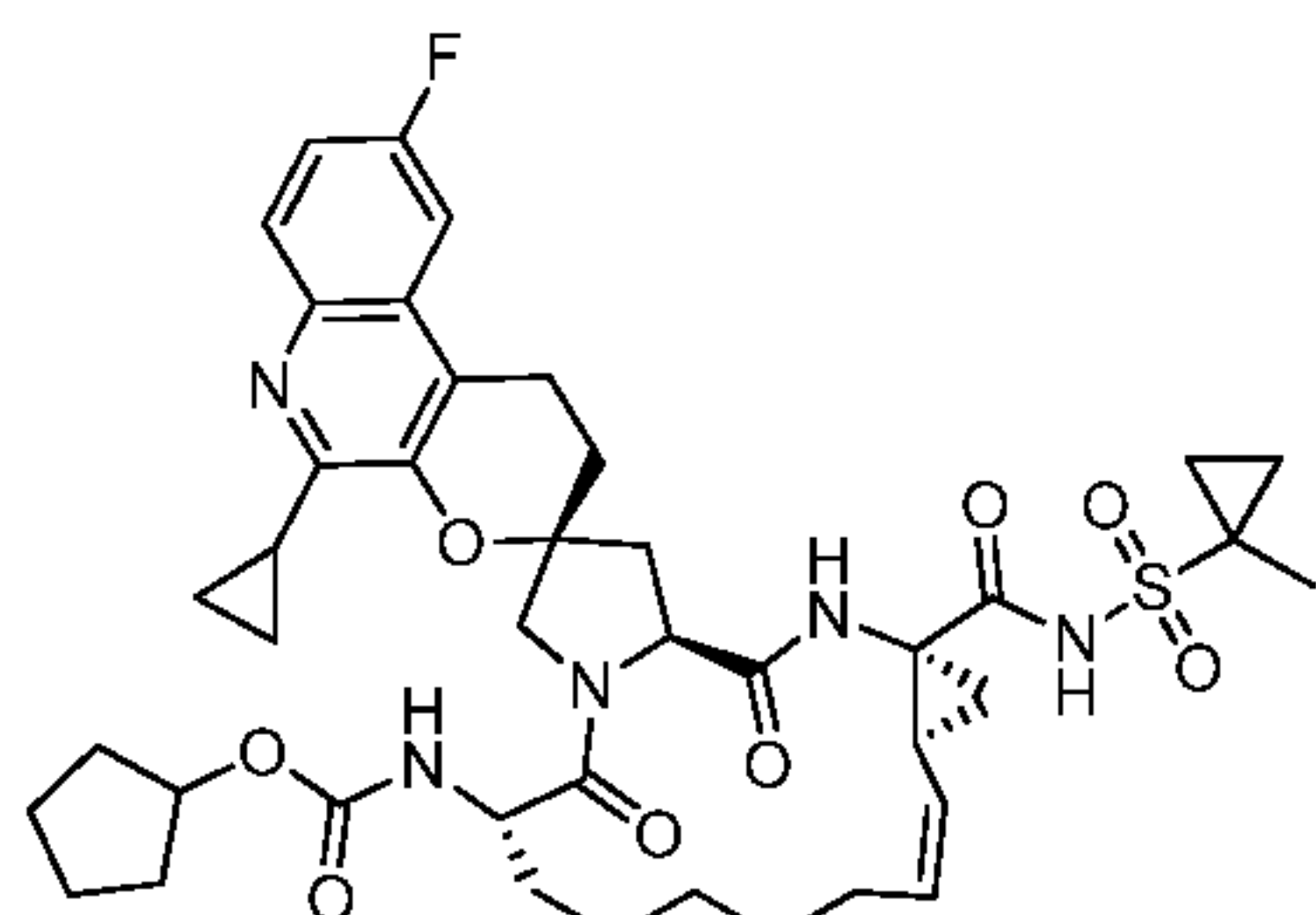
I-142



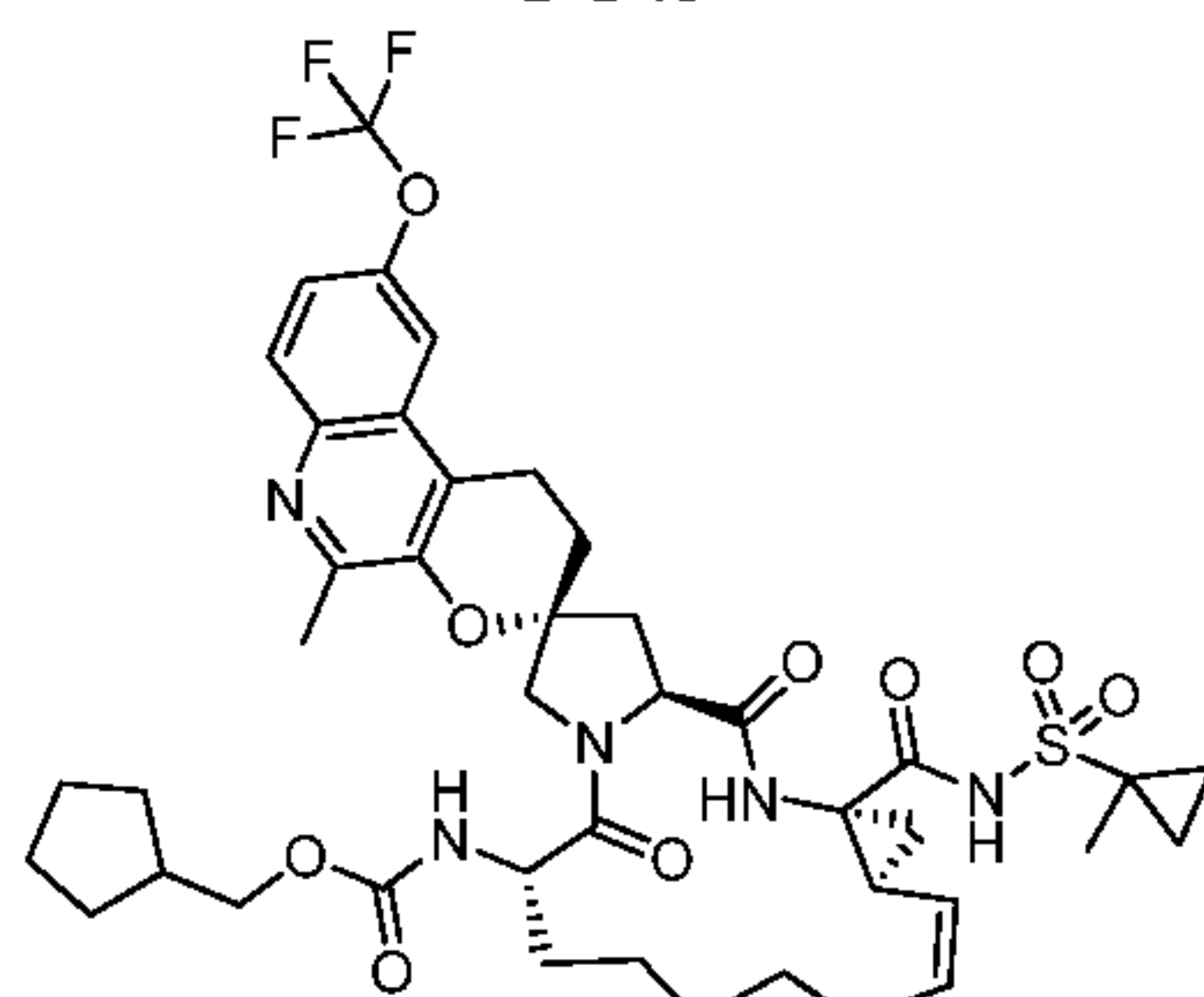
I-143



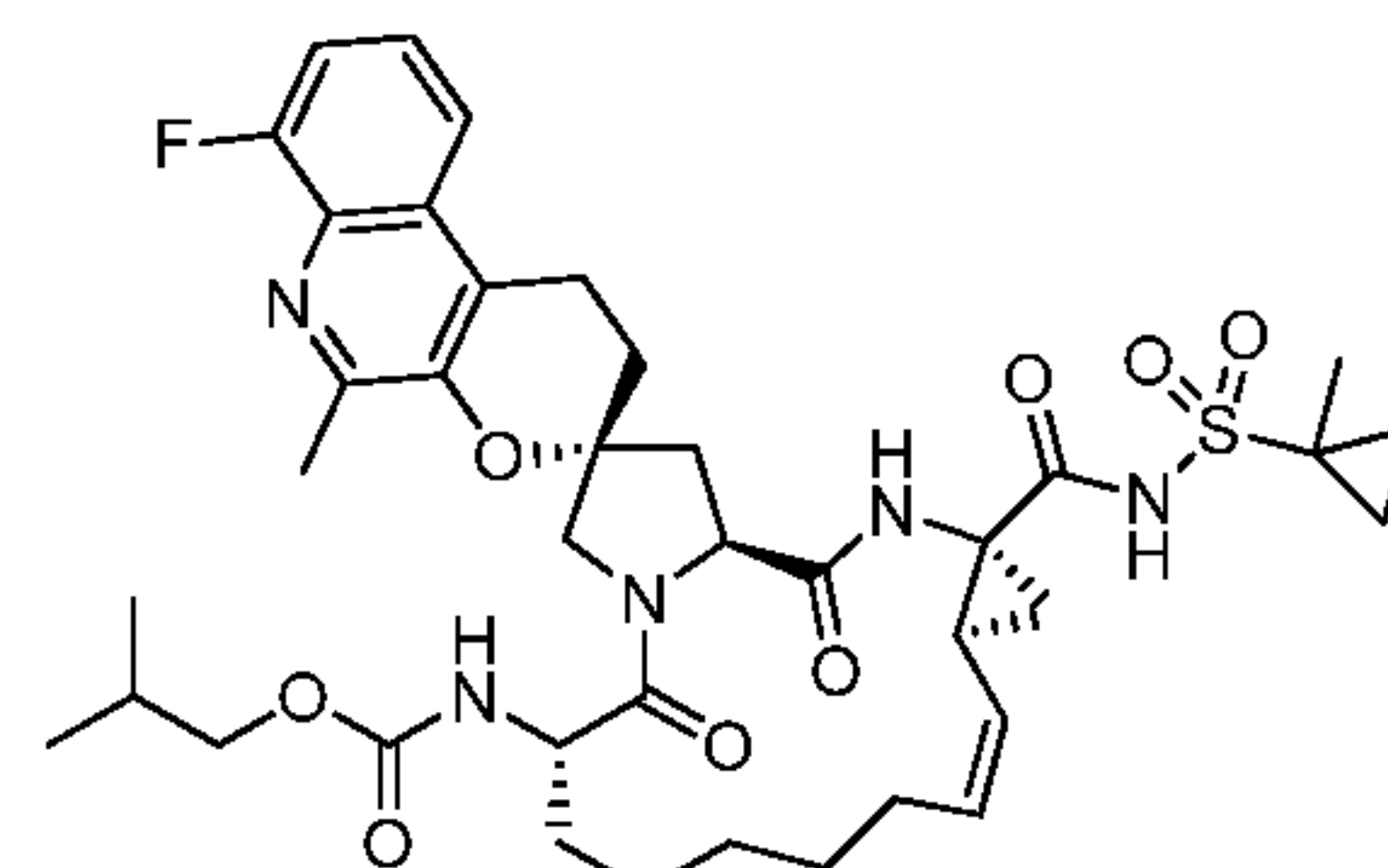
I-144



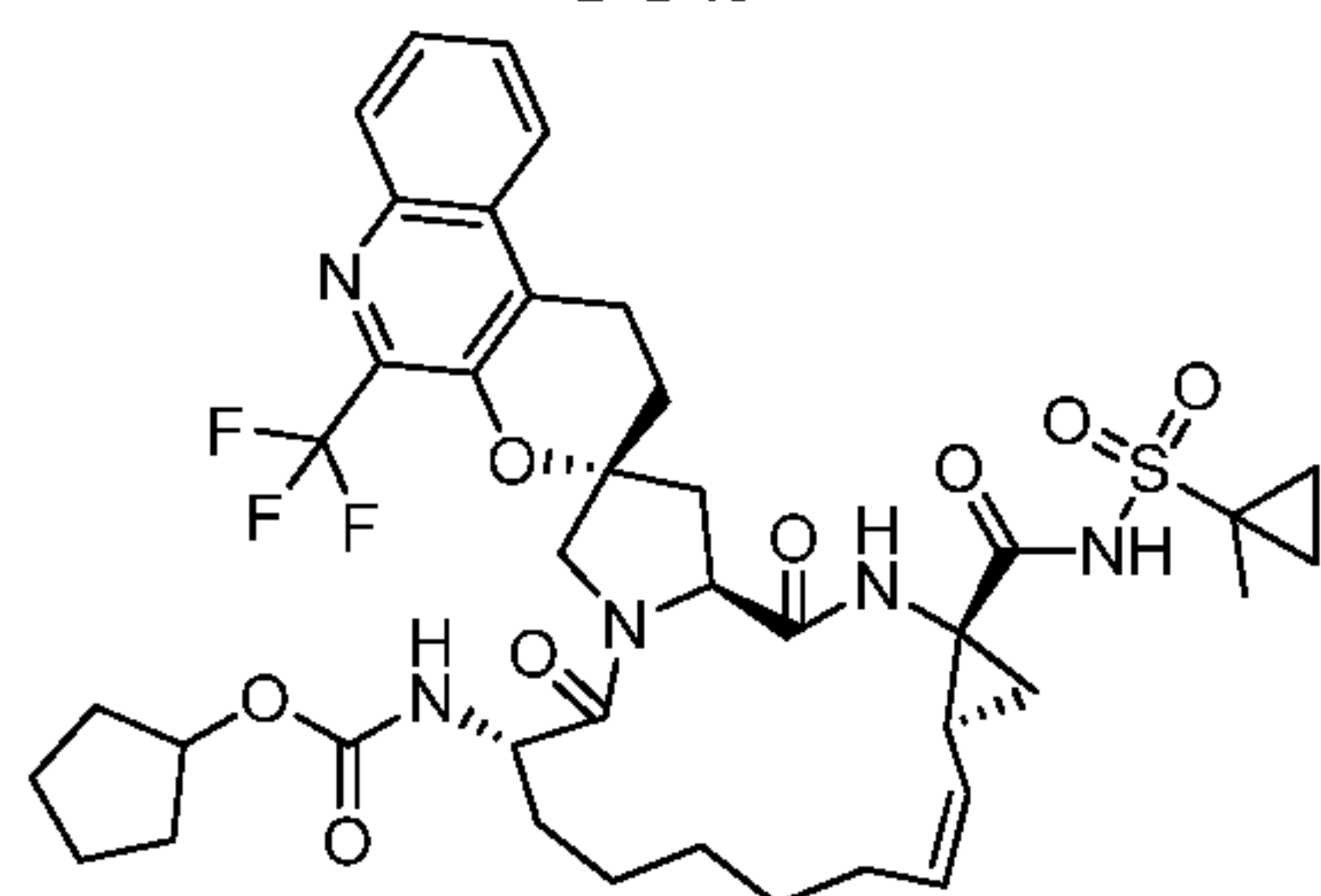
I-145



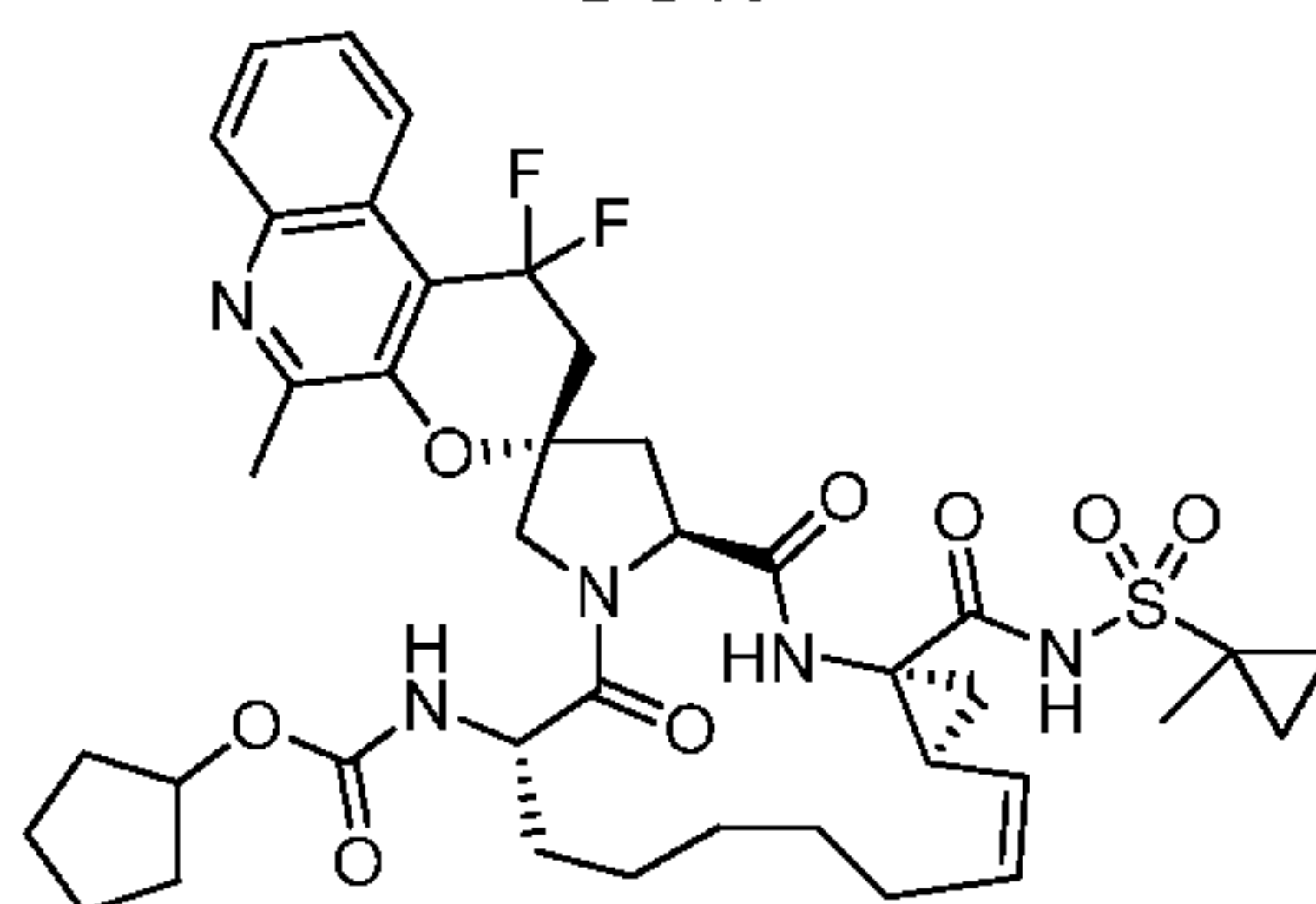
I-146



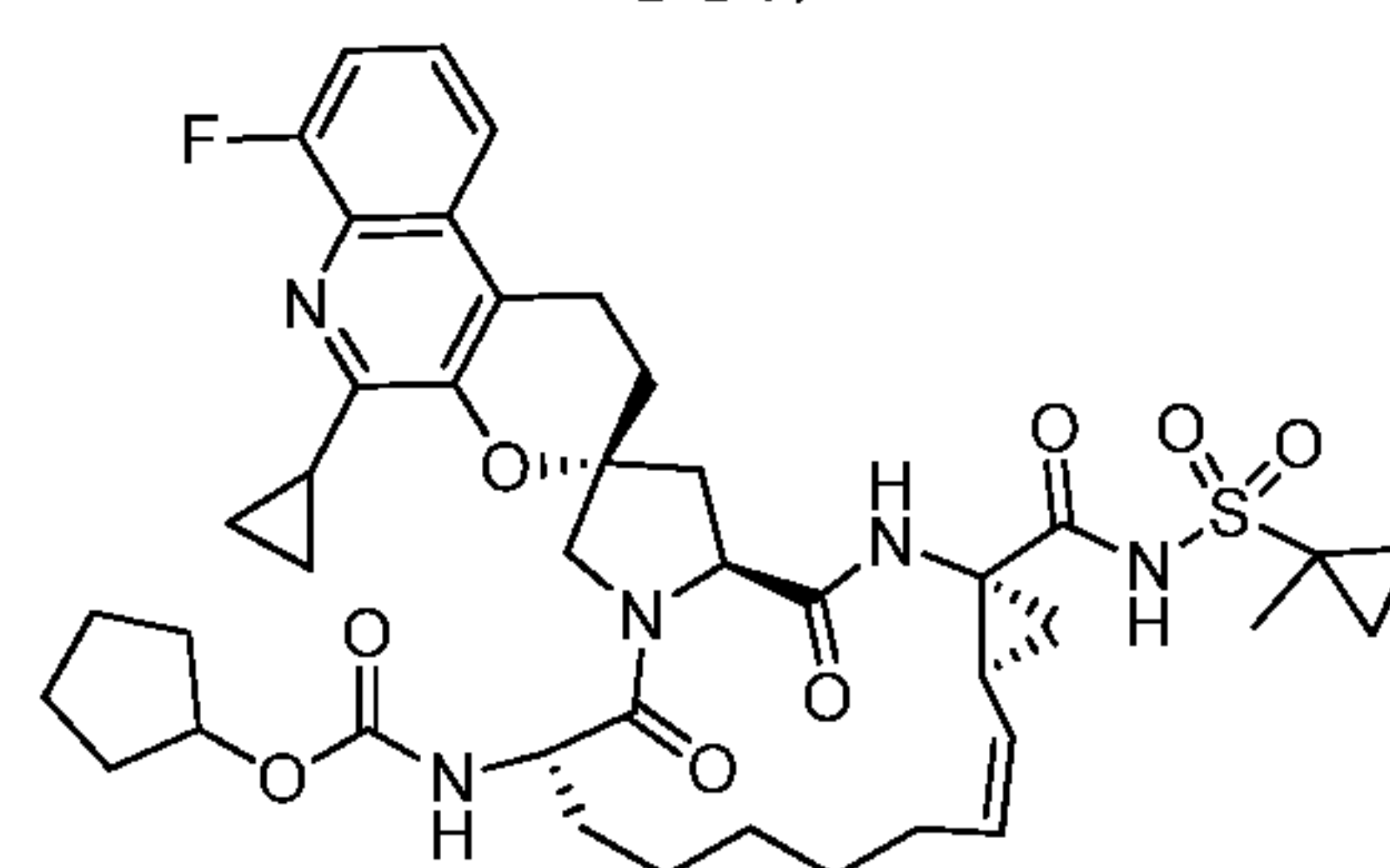
I-147



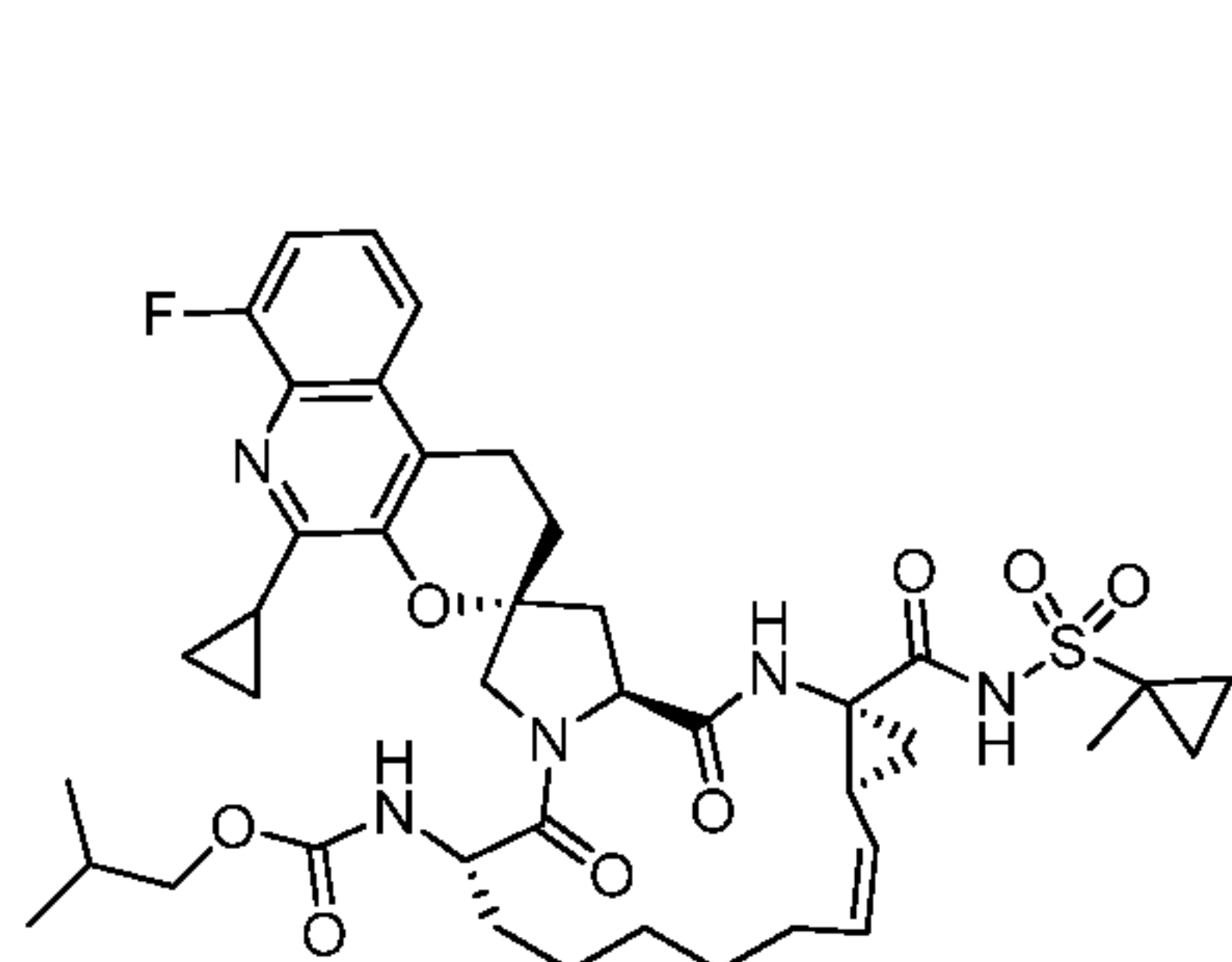
I-148



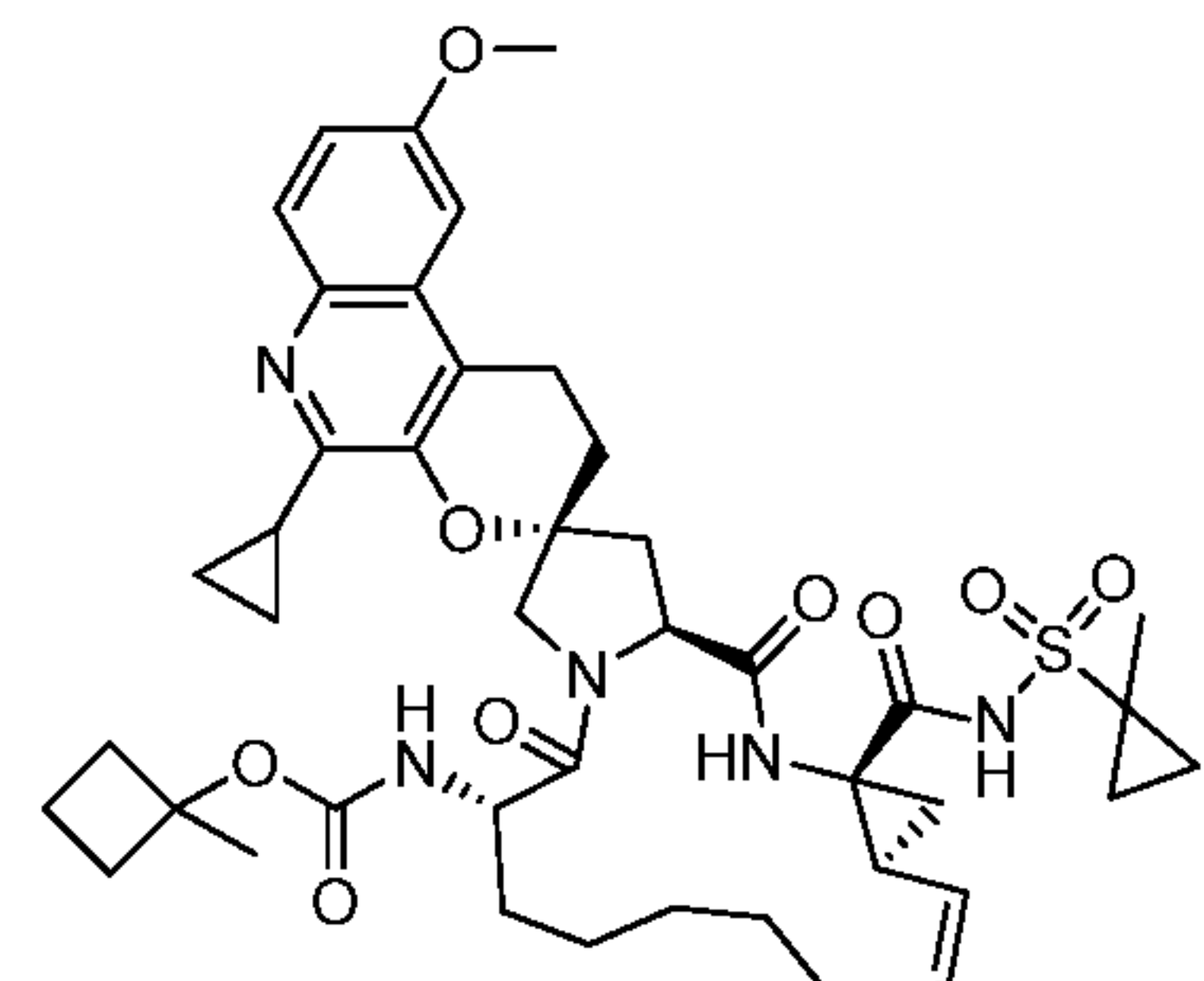
I-149



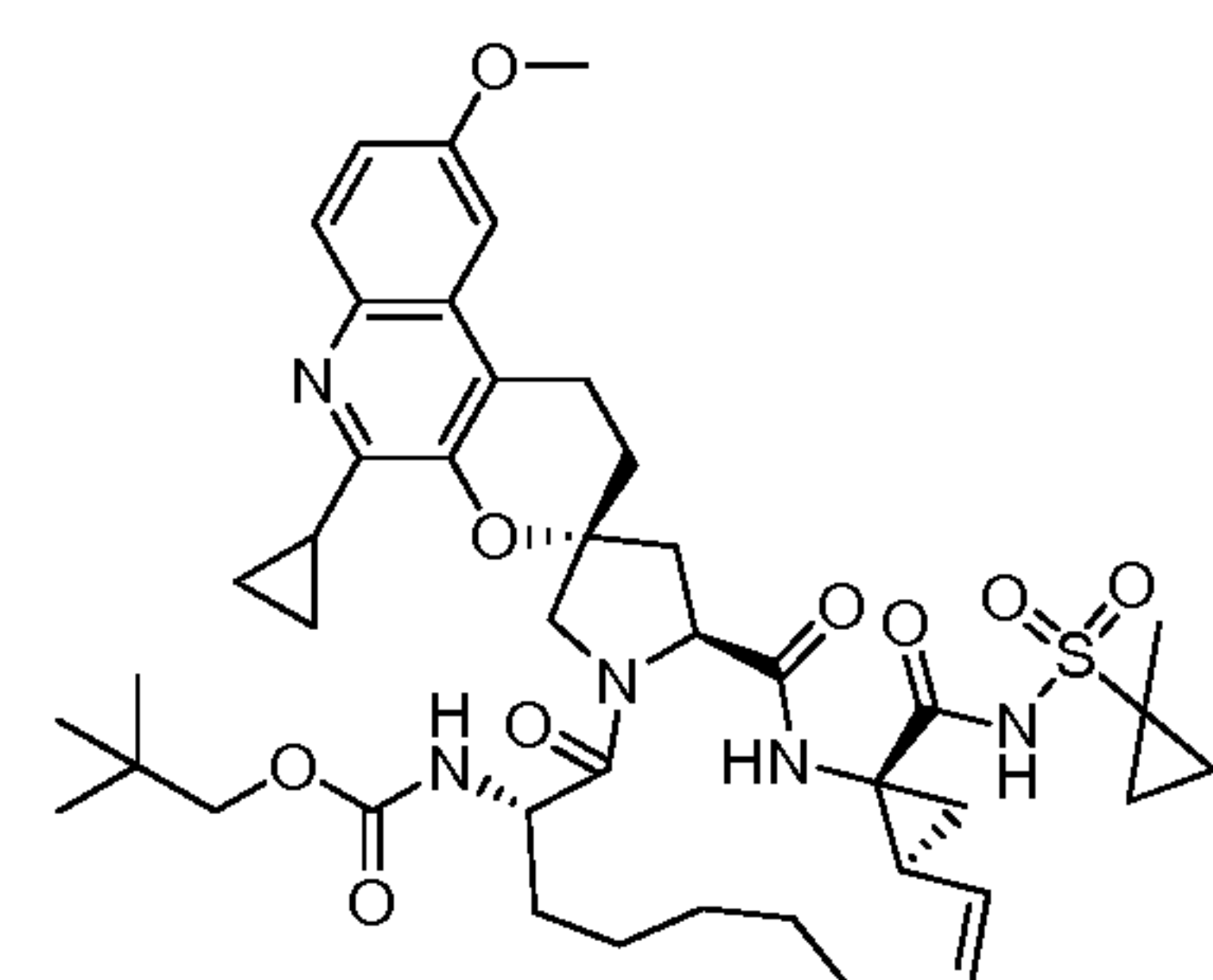
I-150



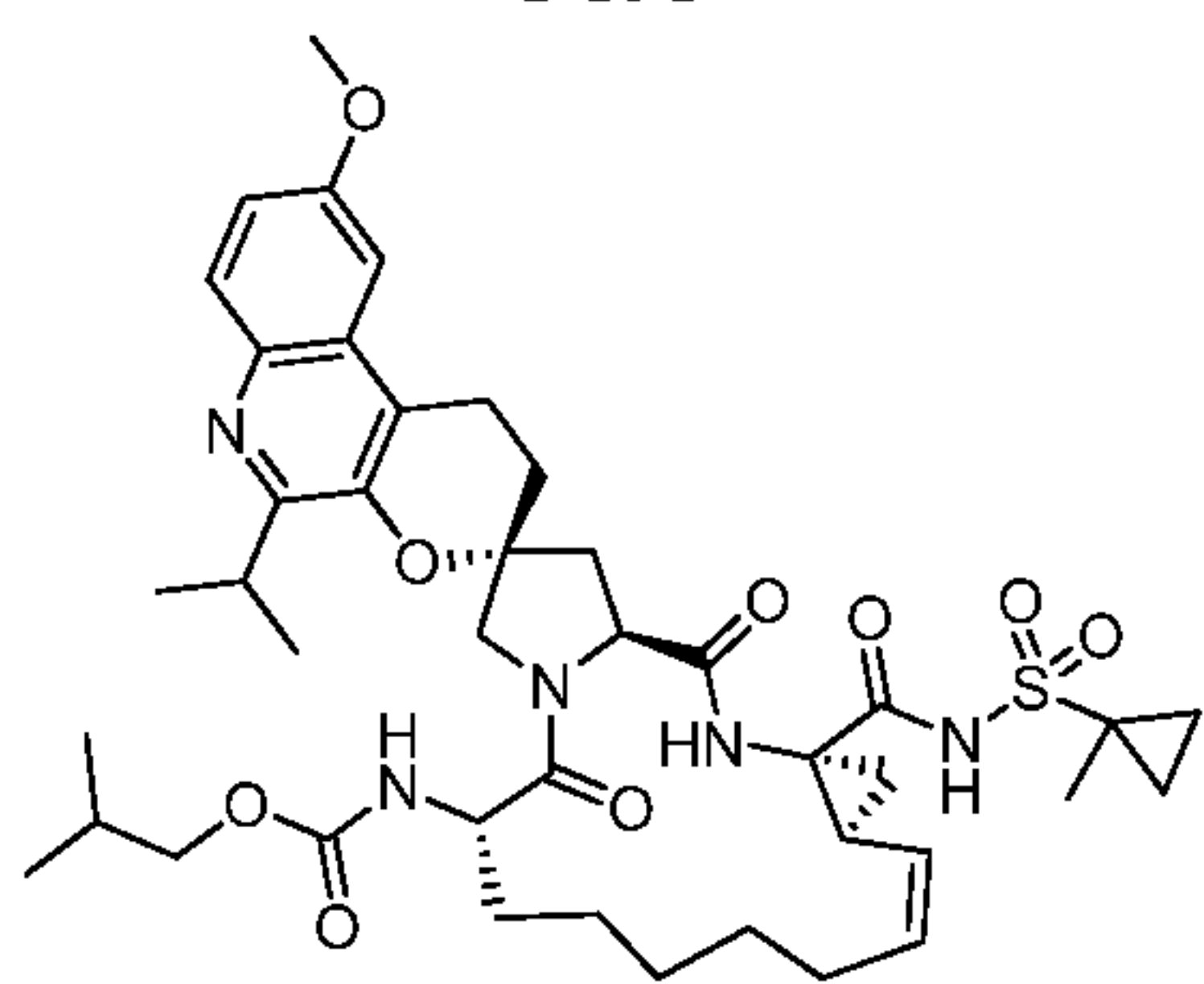
I-151



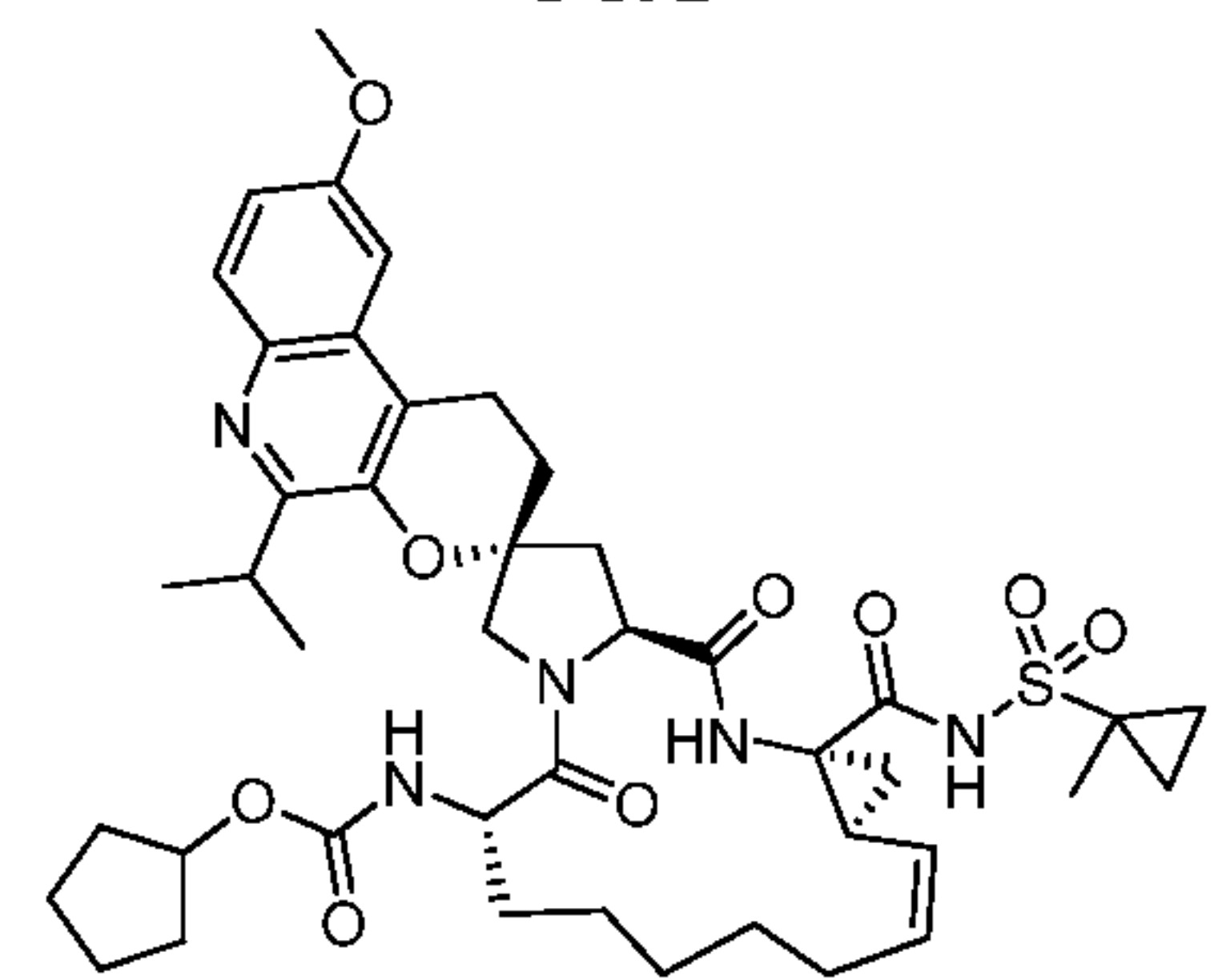
I-152



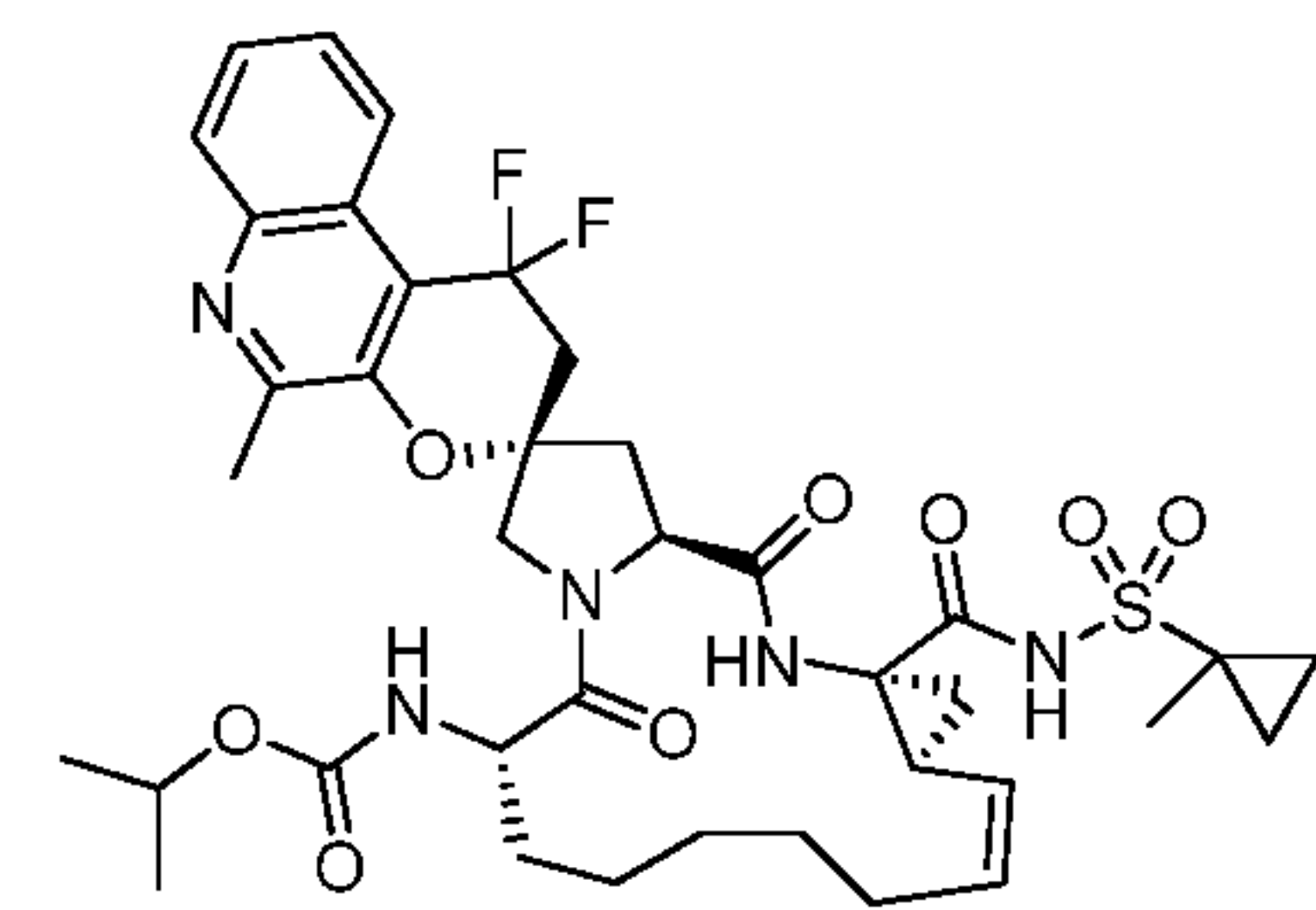
I-153



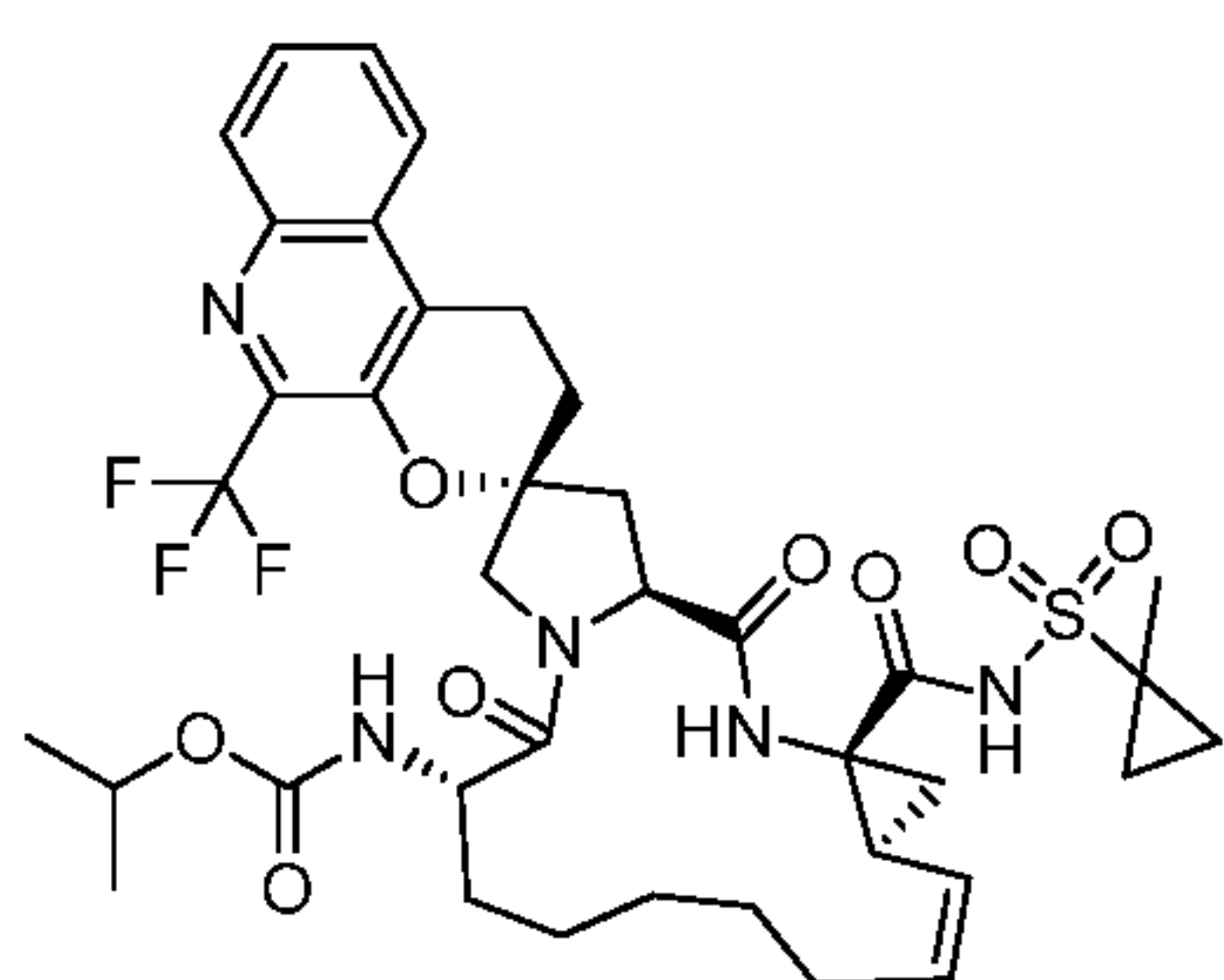
I-154



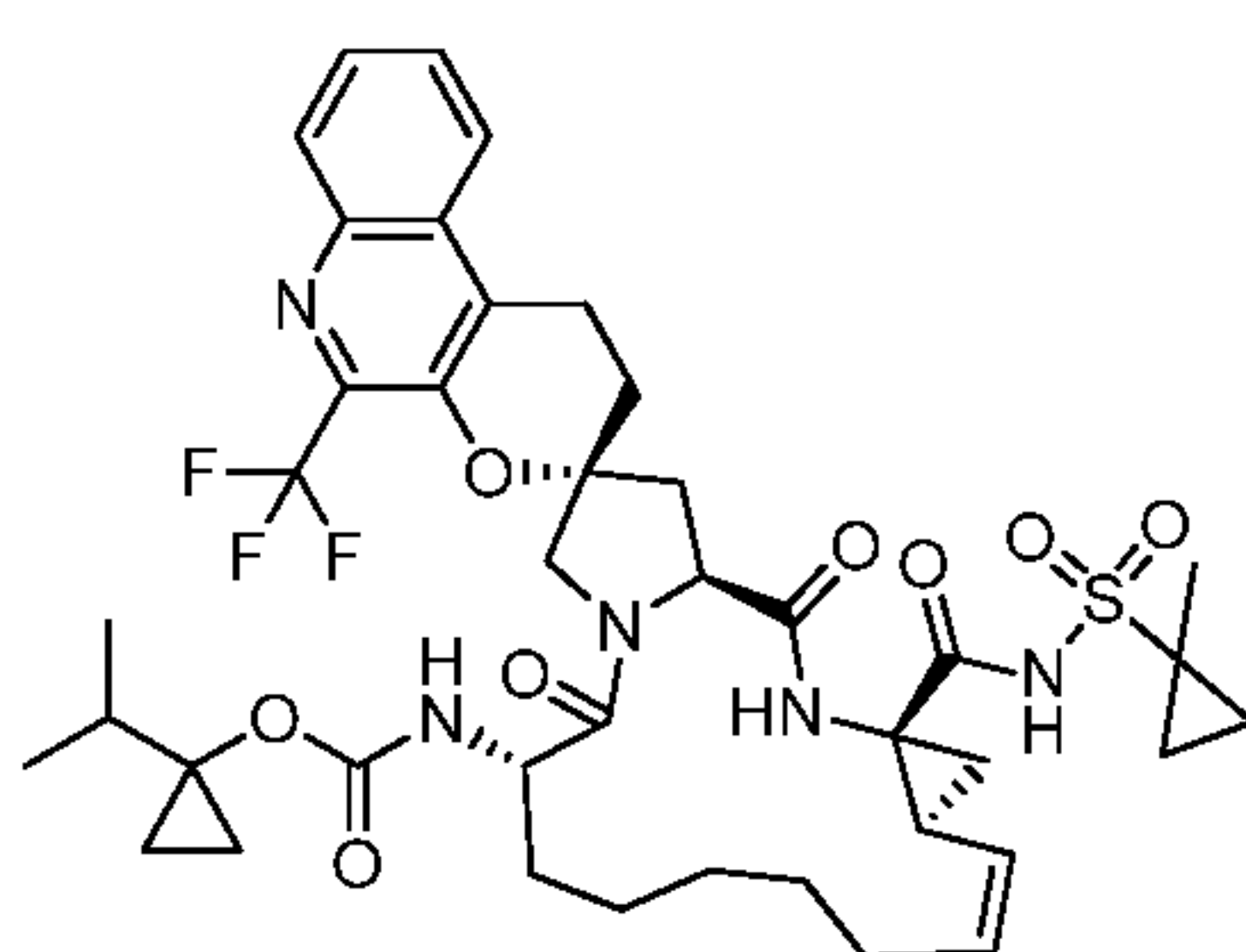
I-155



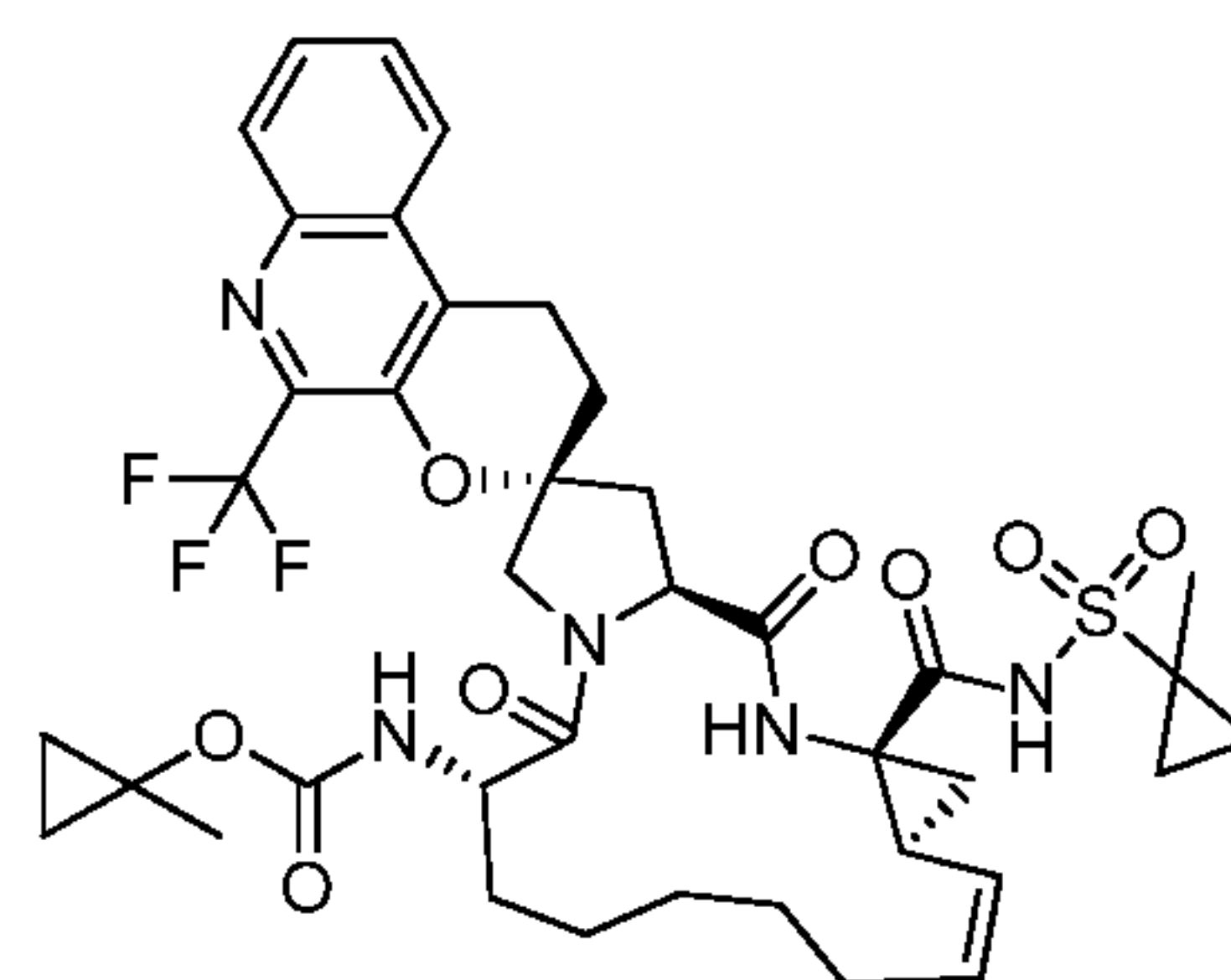
I-156



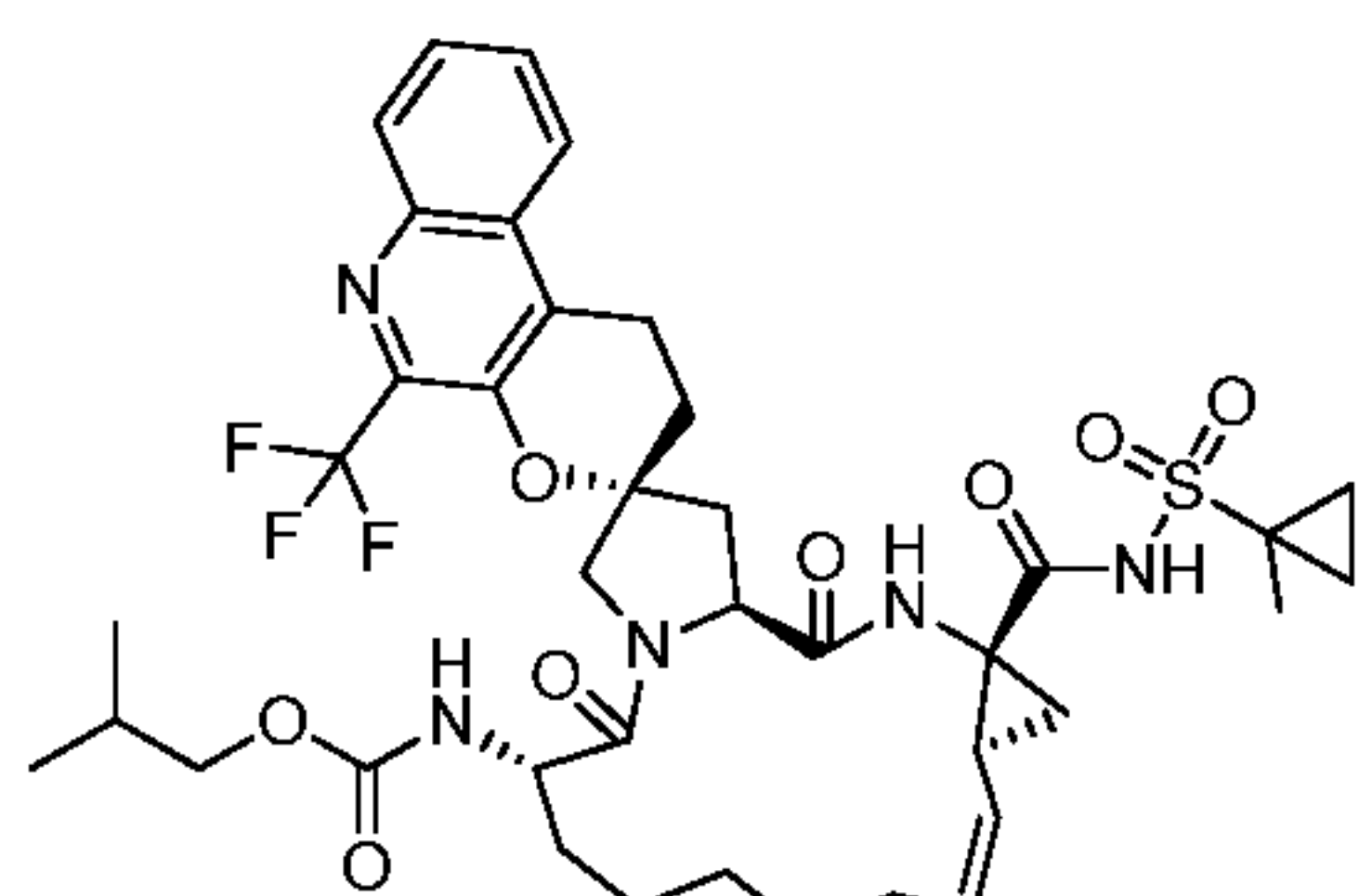
I-157



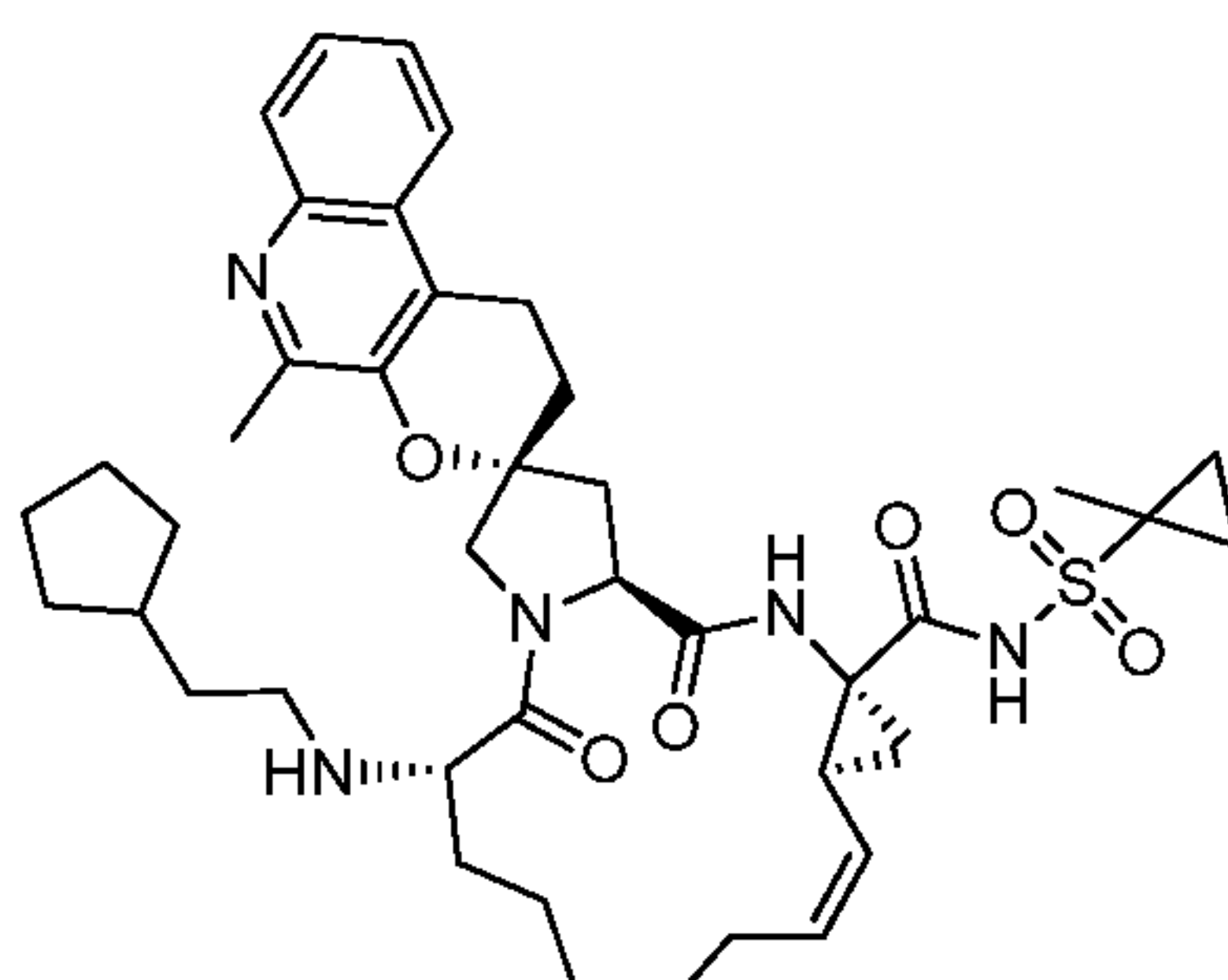
I-158



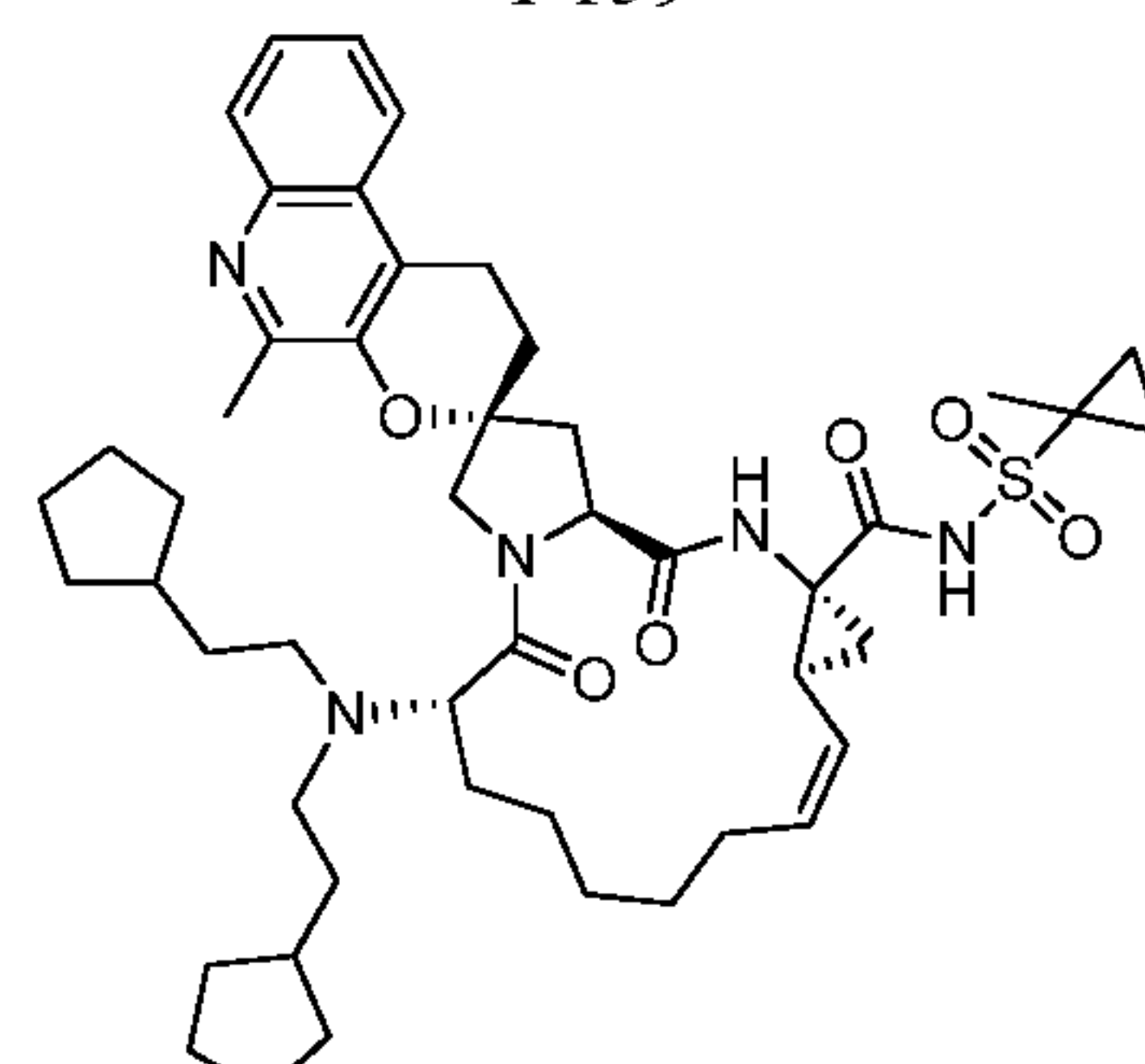
I-159



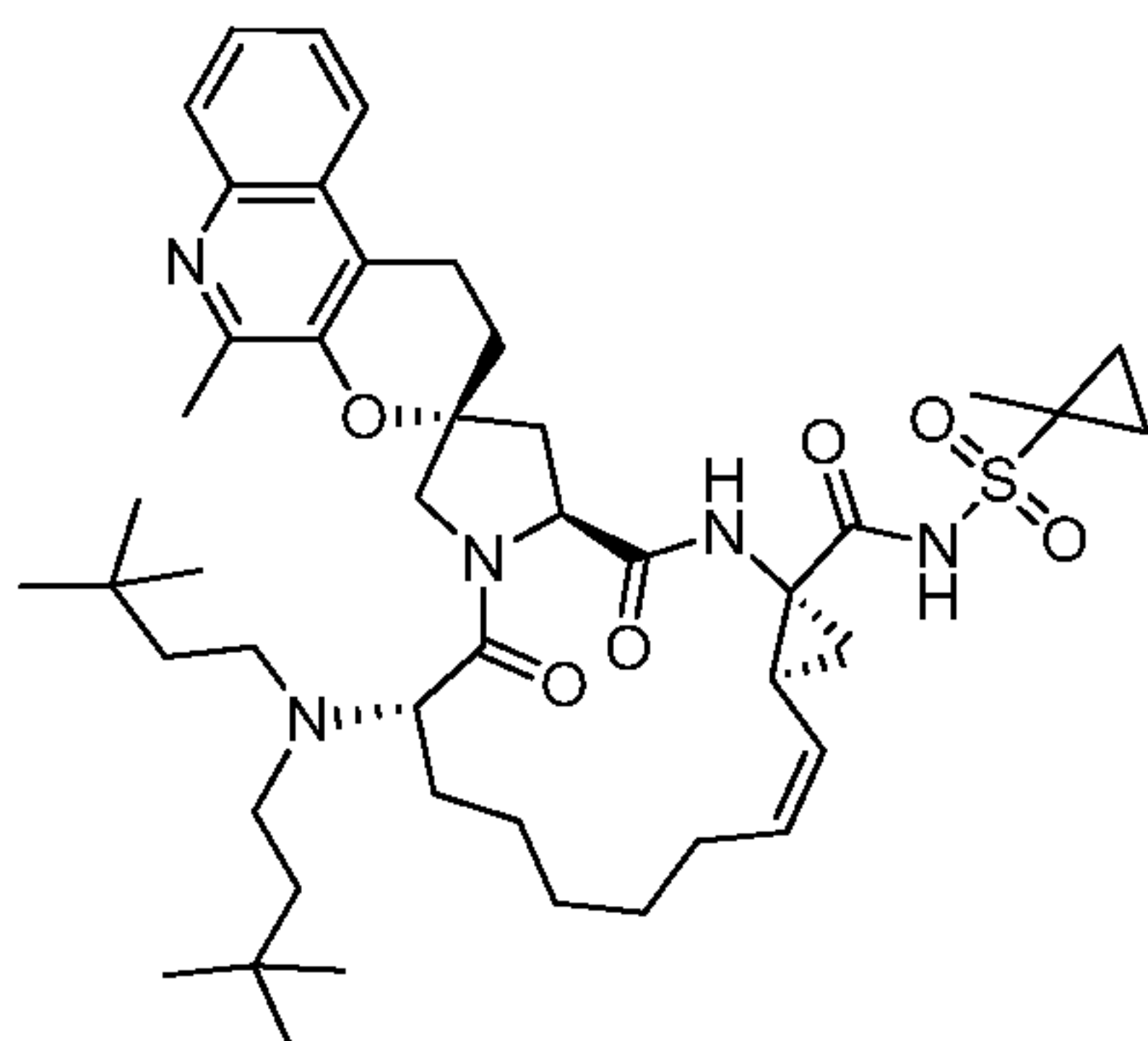
I-160



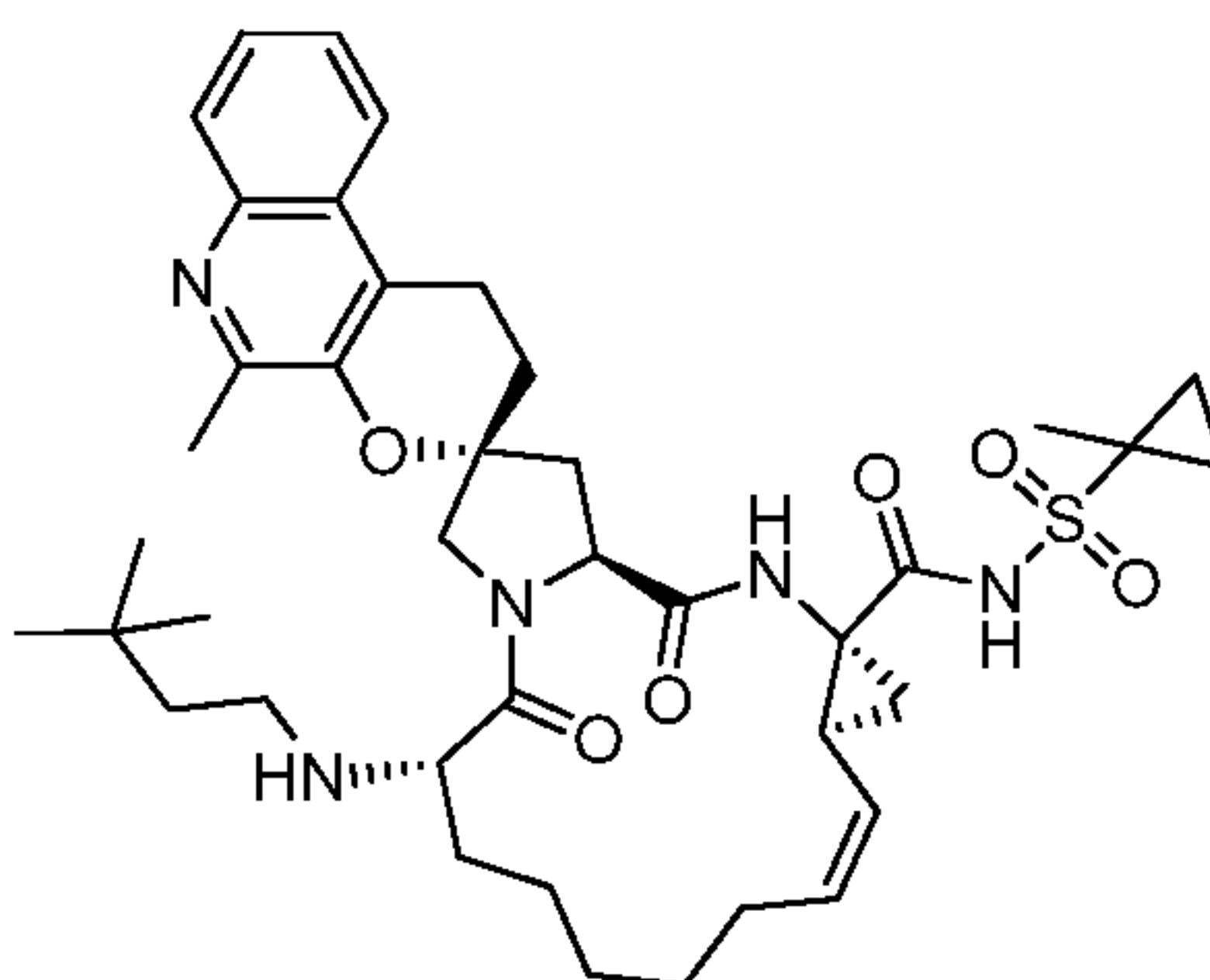
I-161



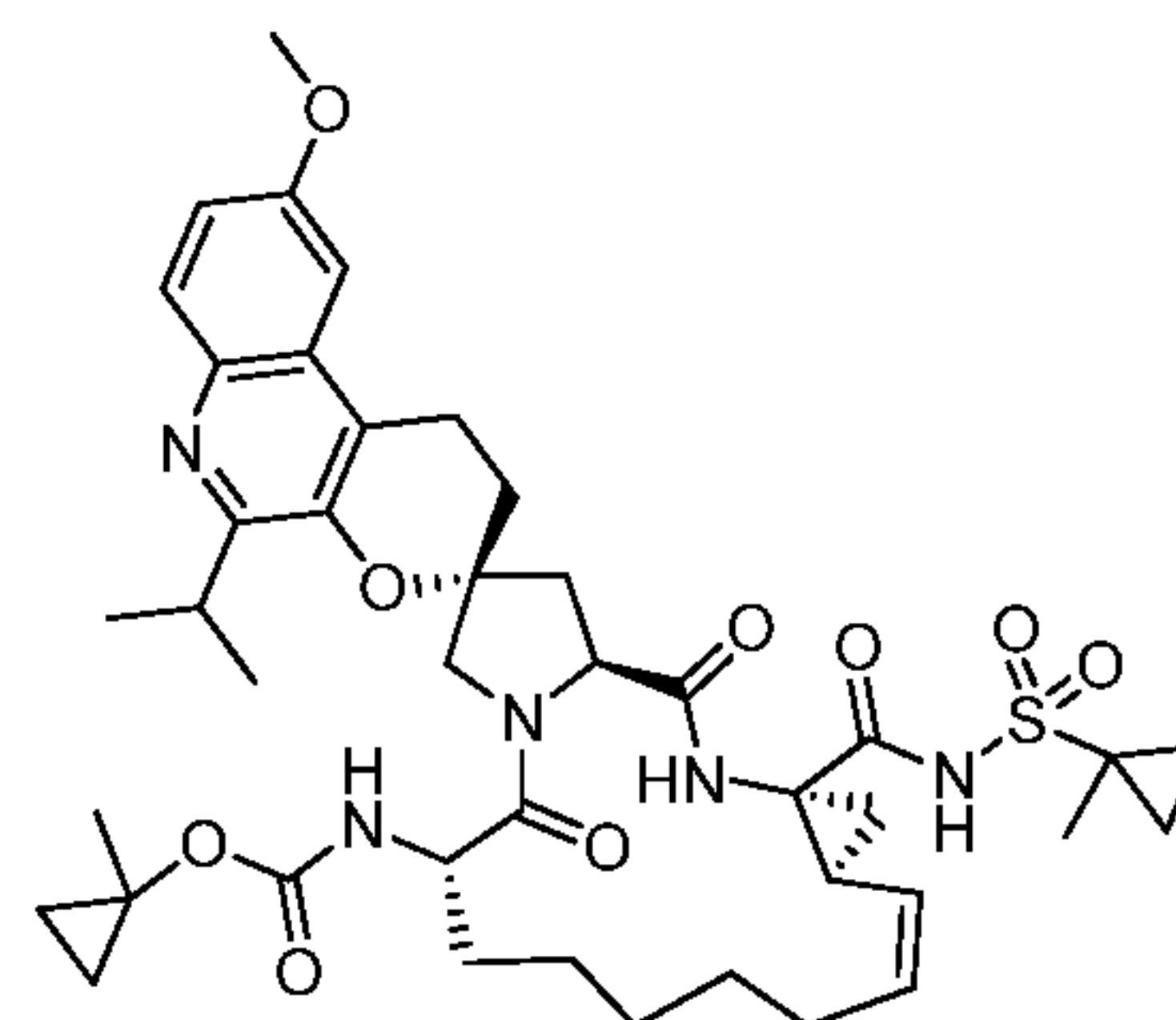
I-162



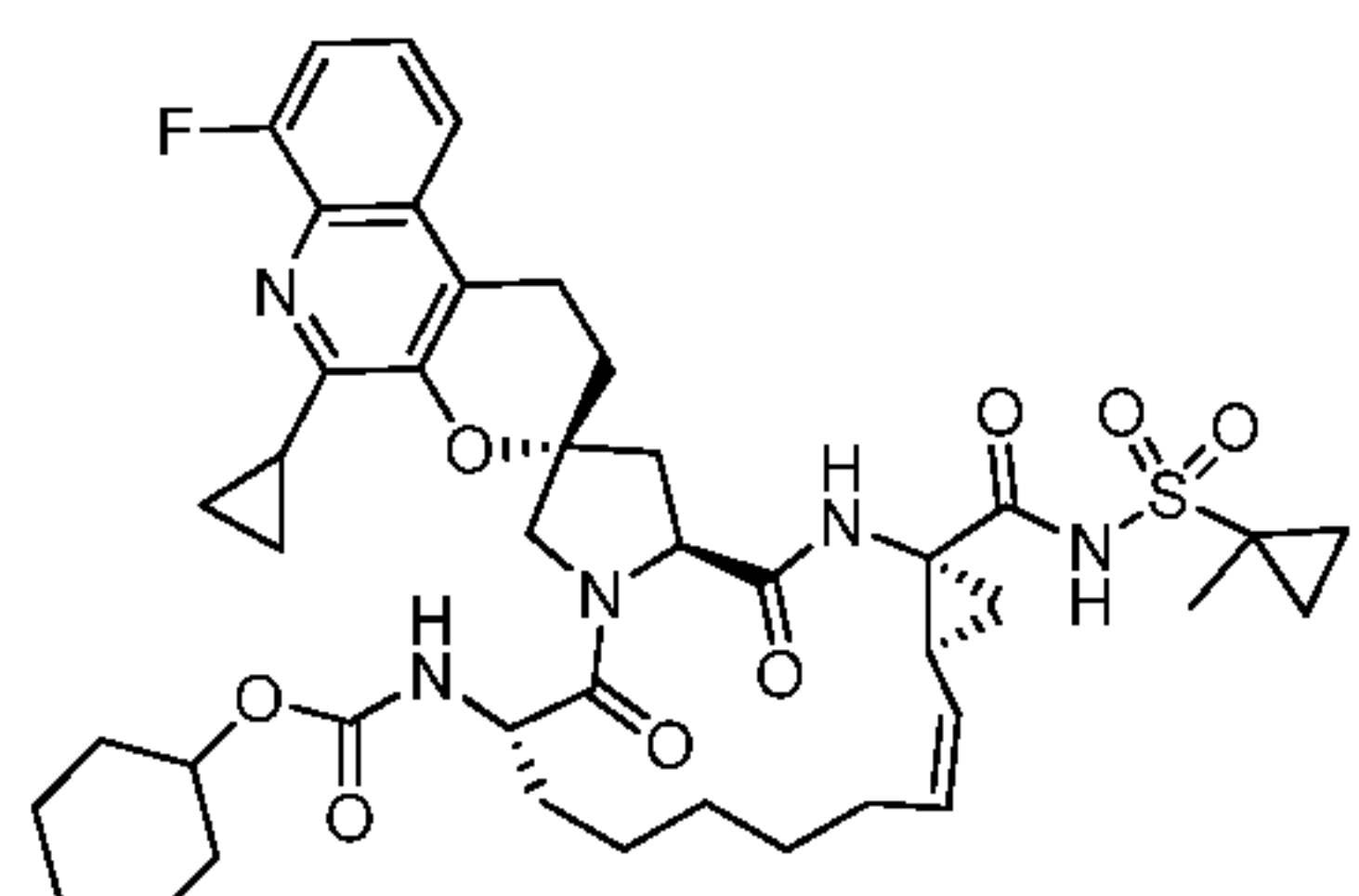
I-163



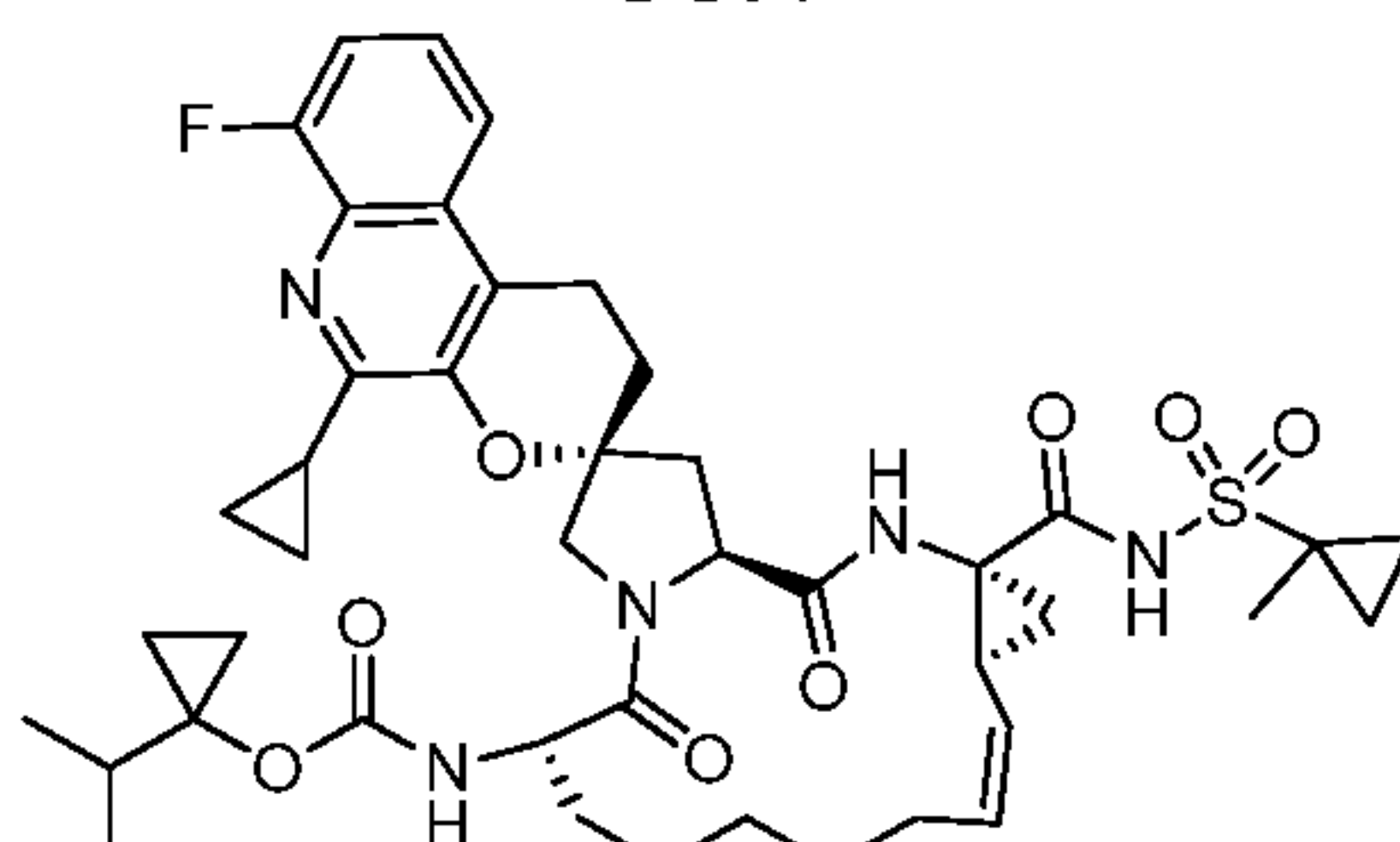
I-164



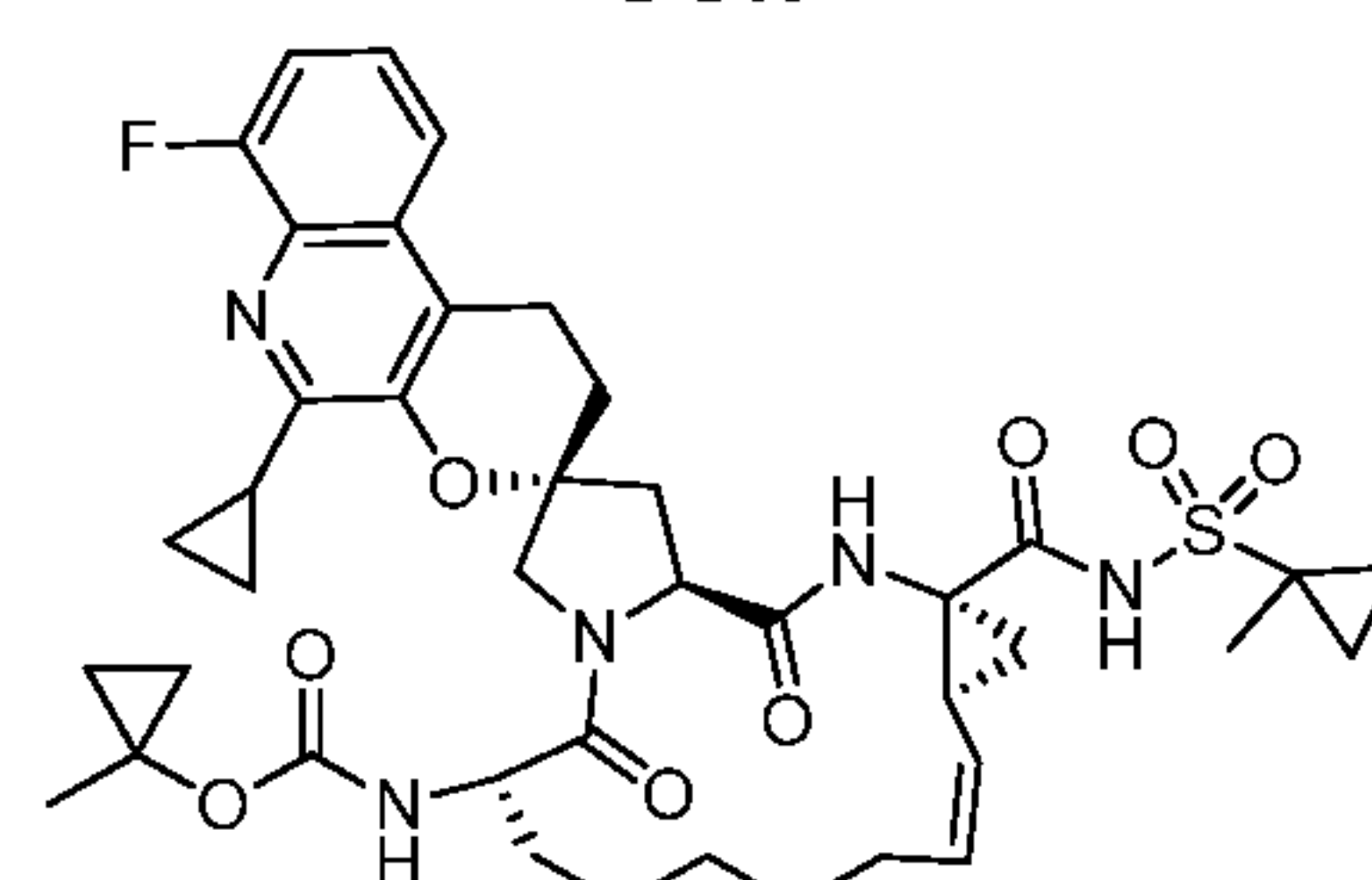
I-165



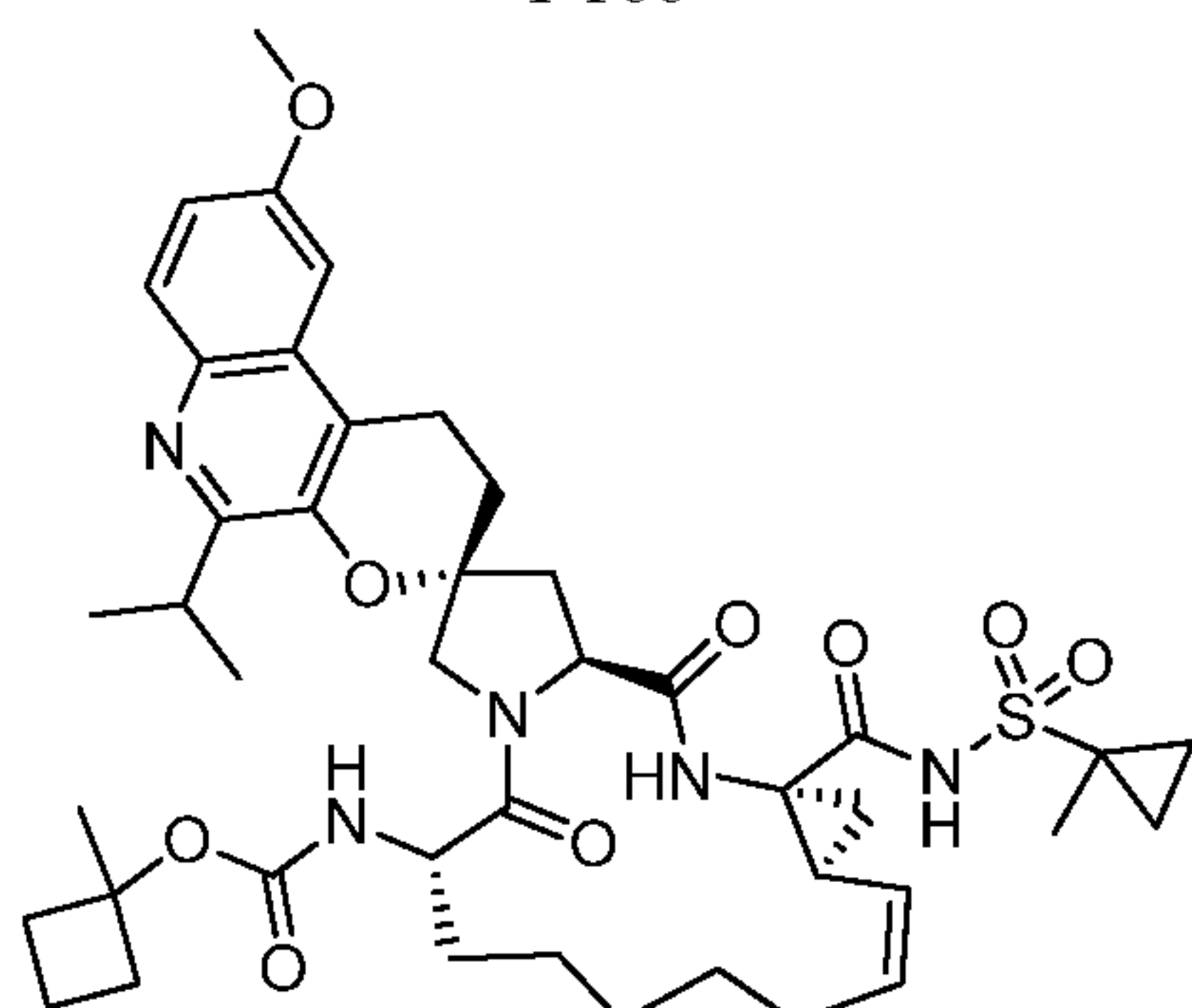
I-166



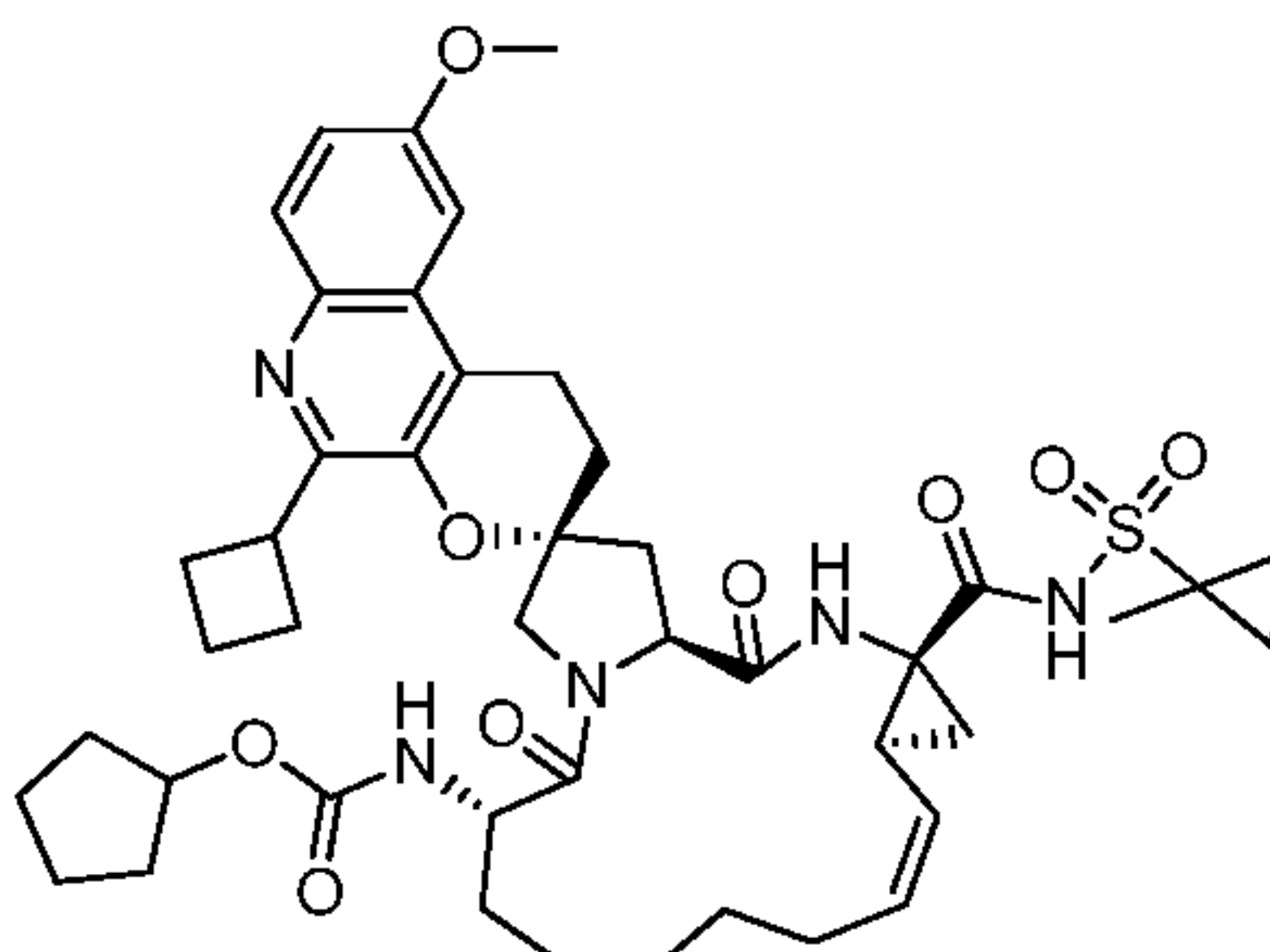
I-167



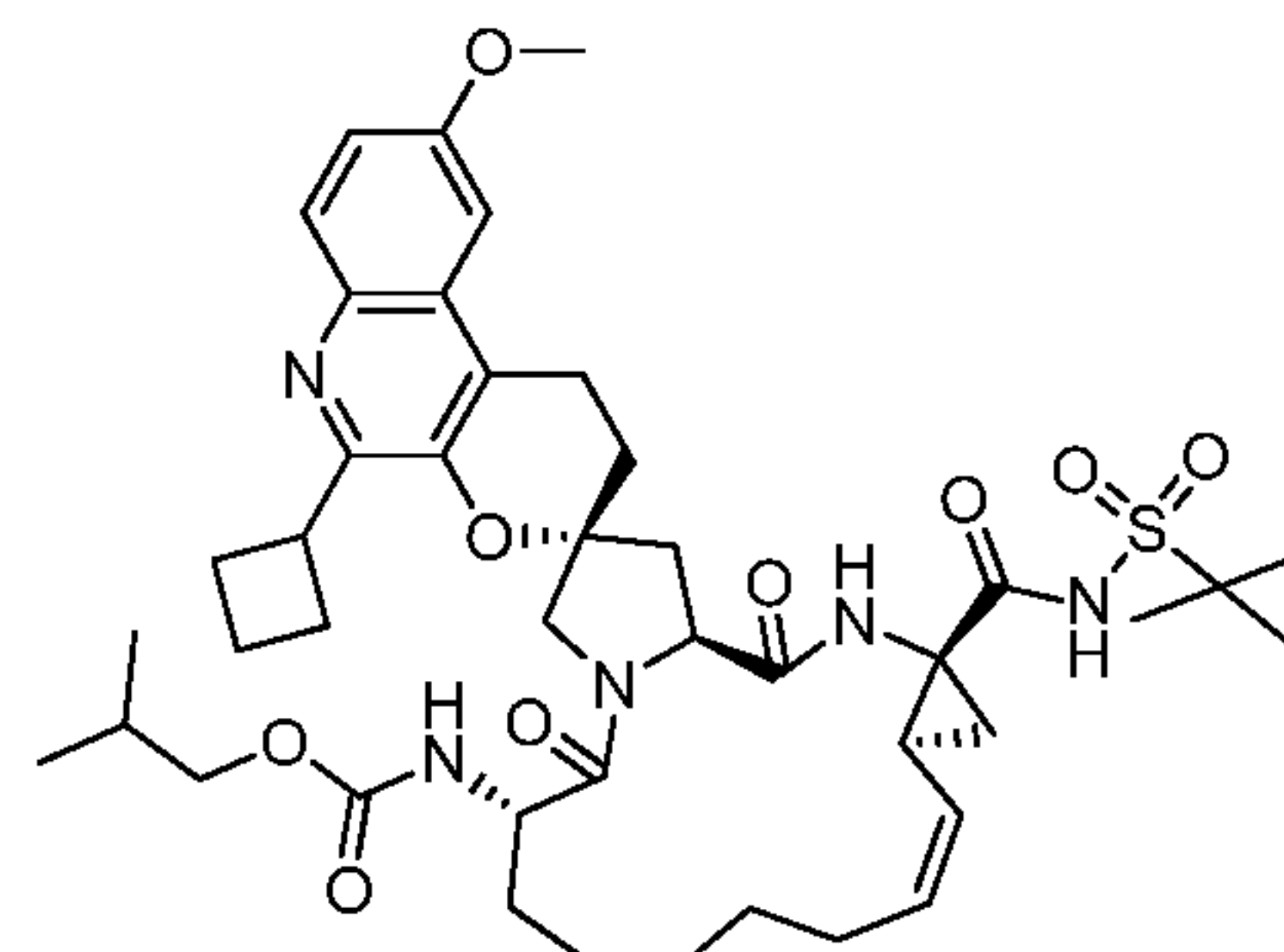
I-168



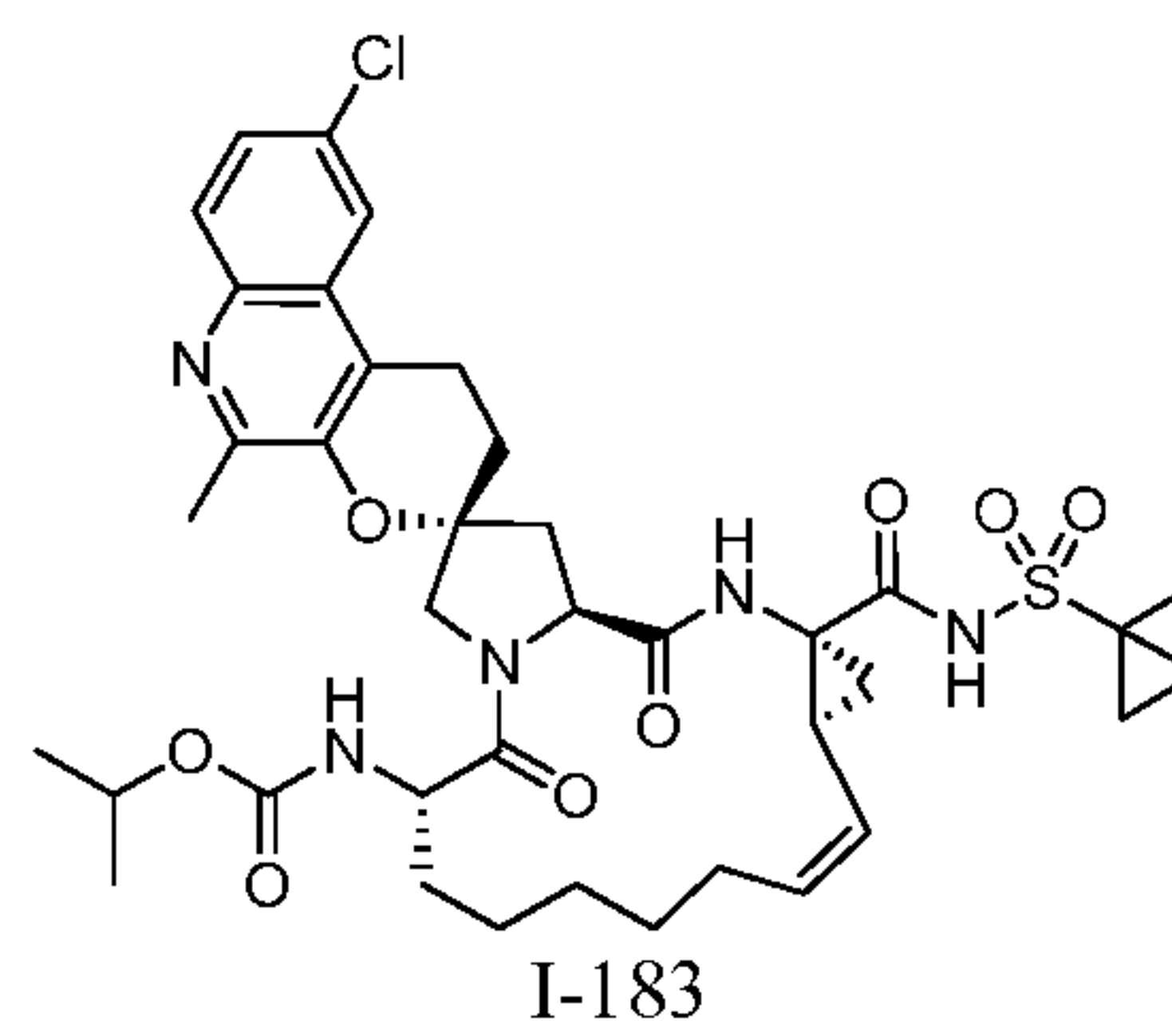
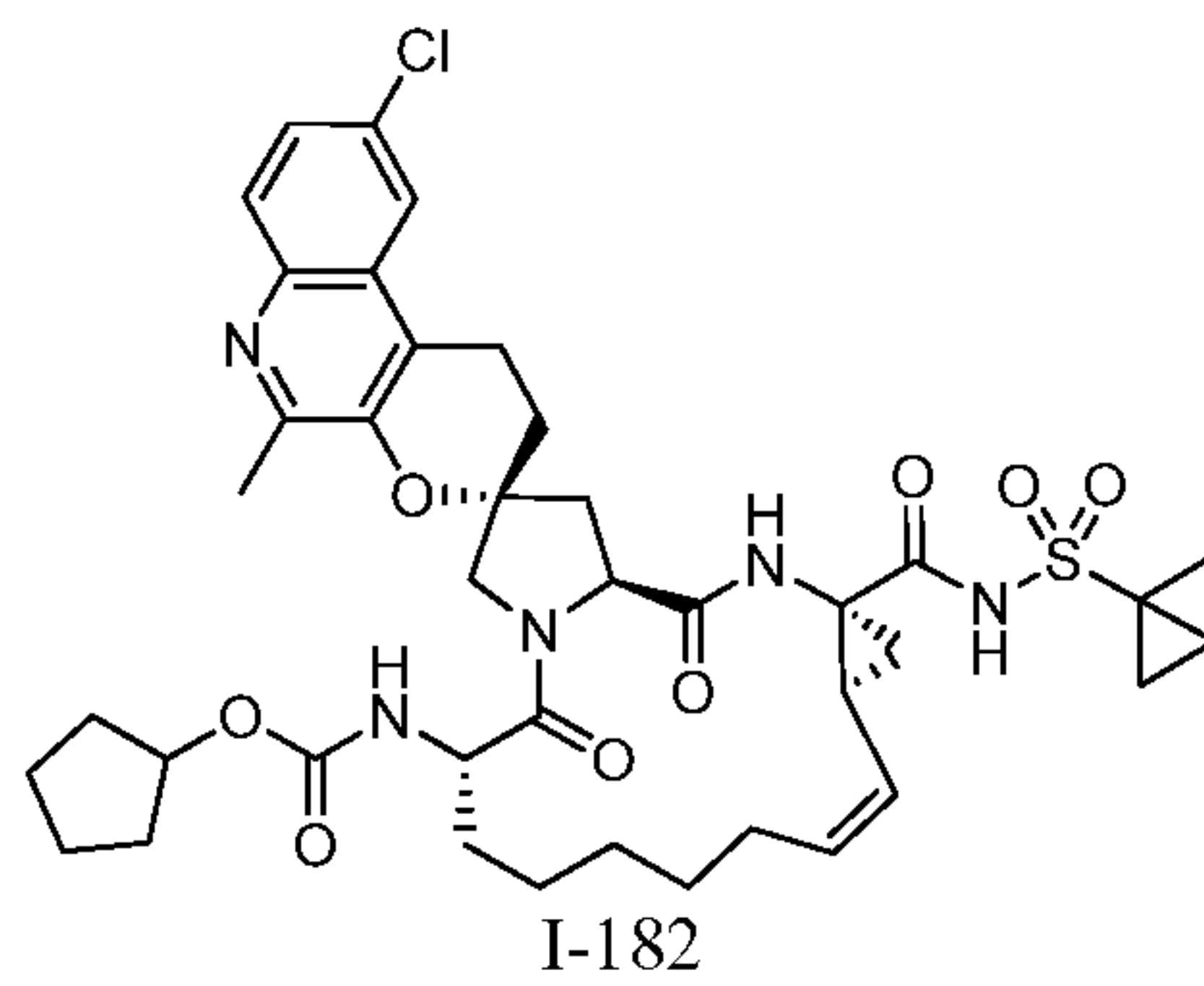
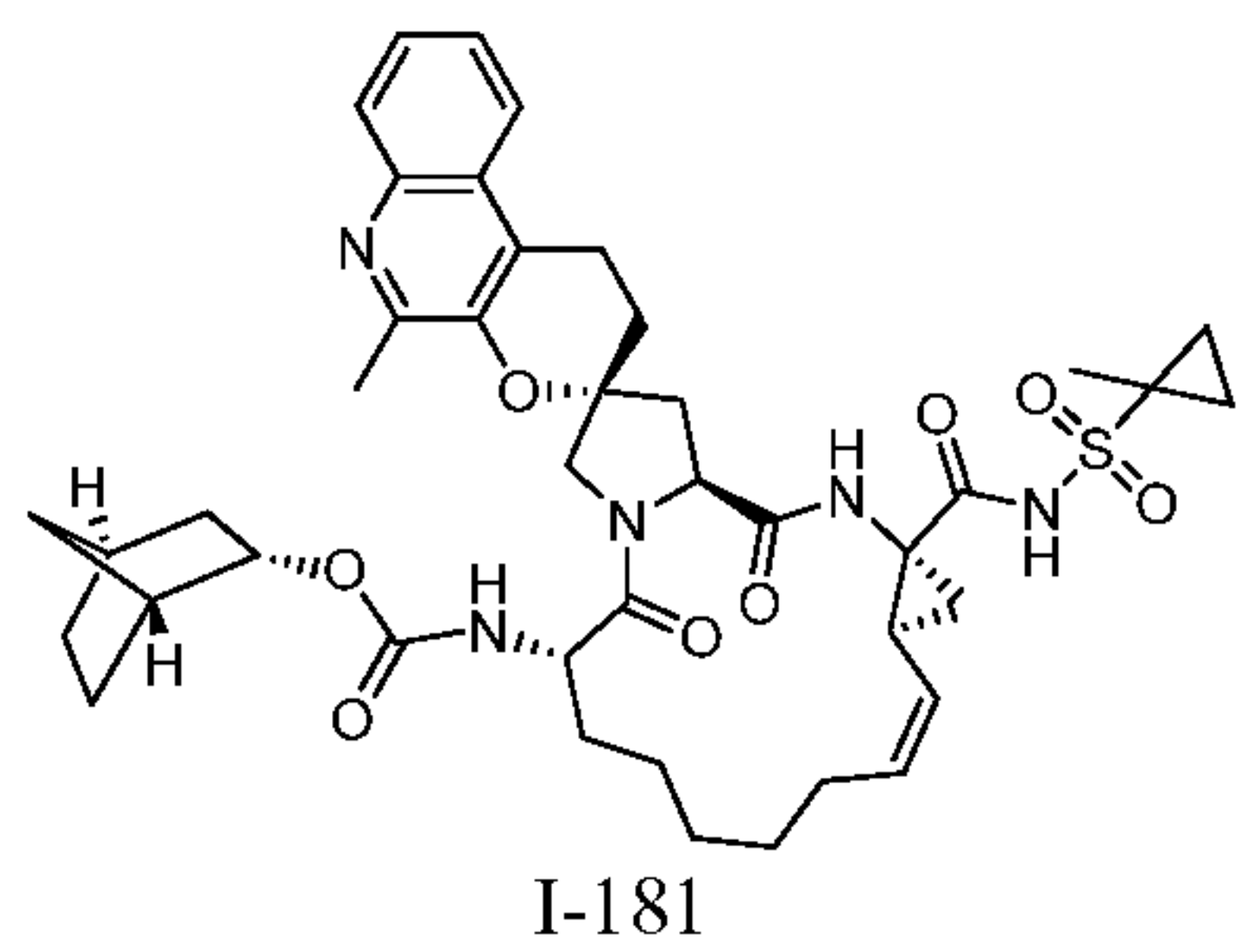
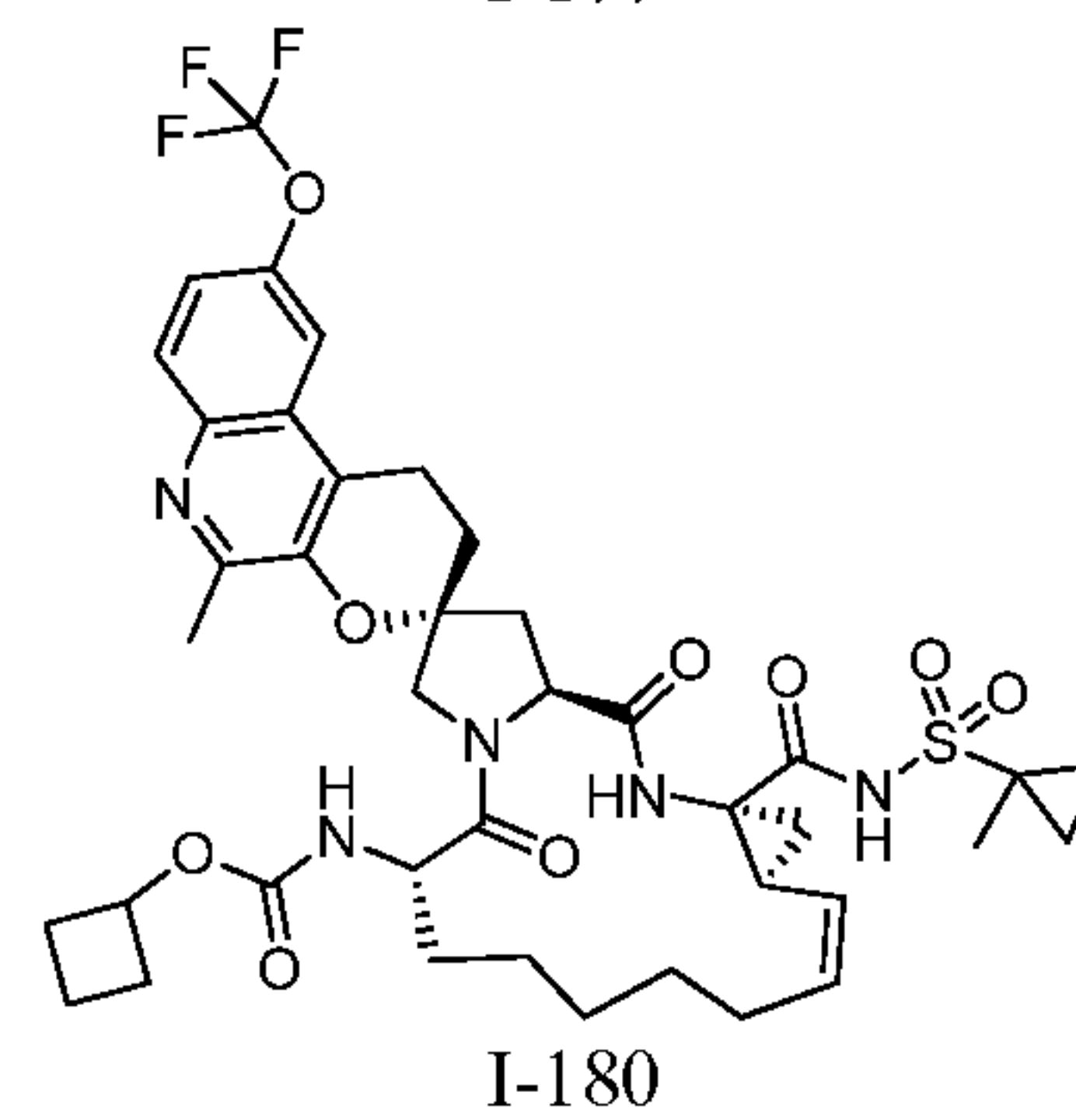
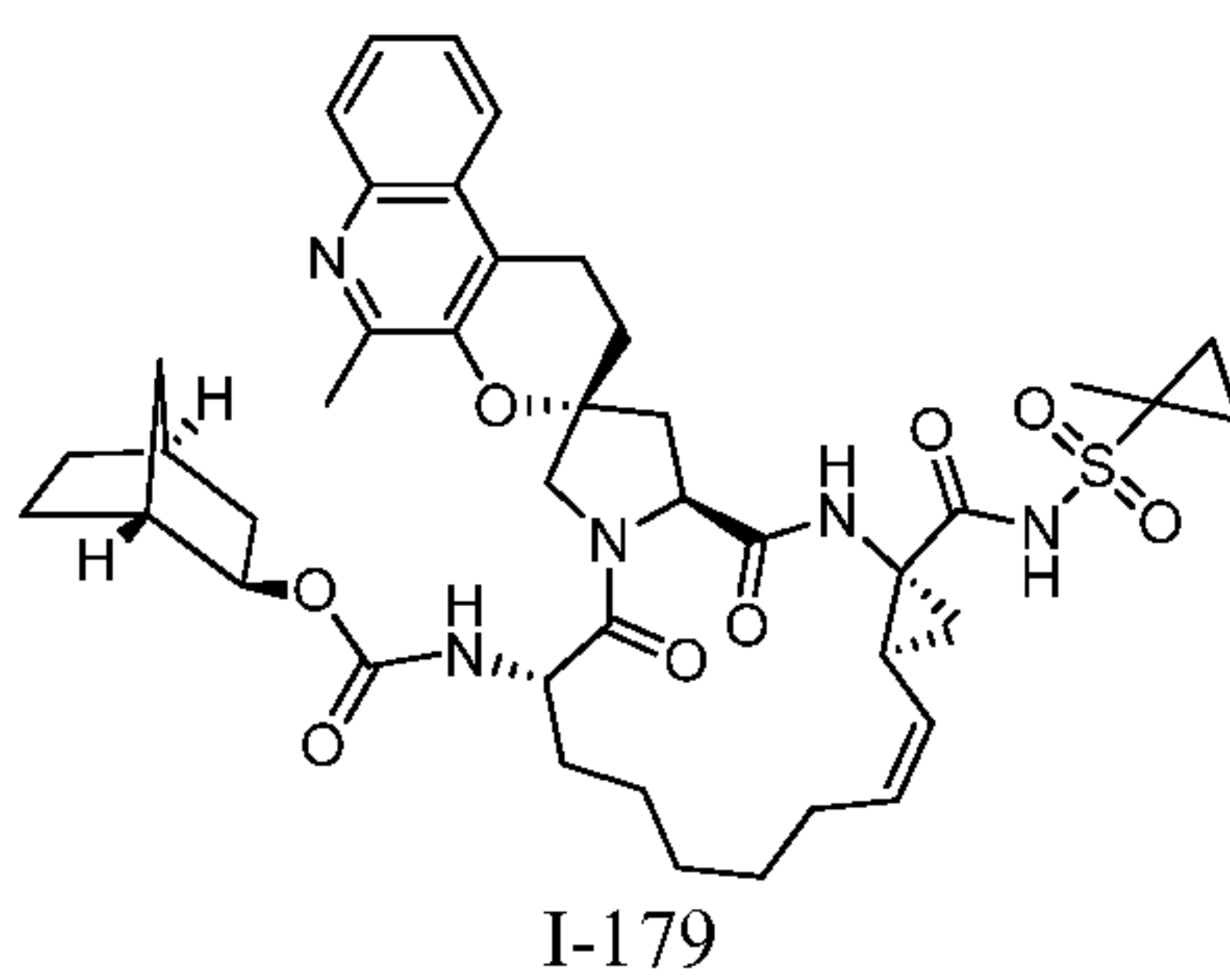
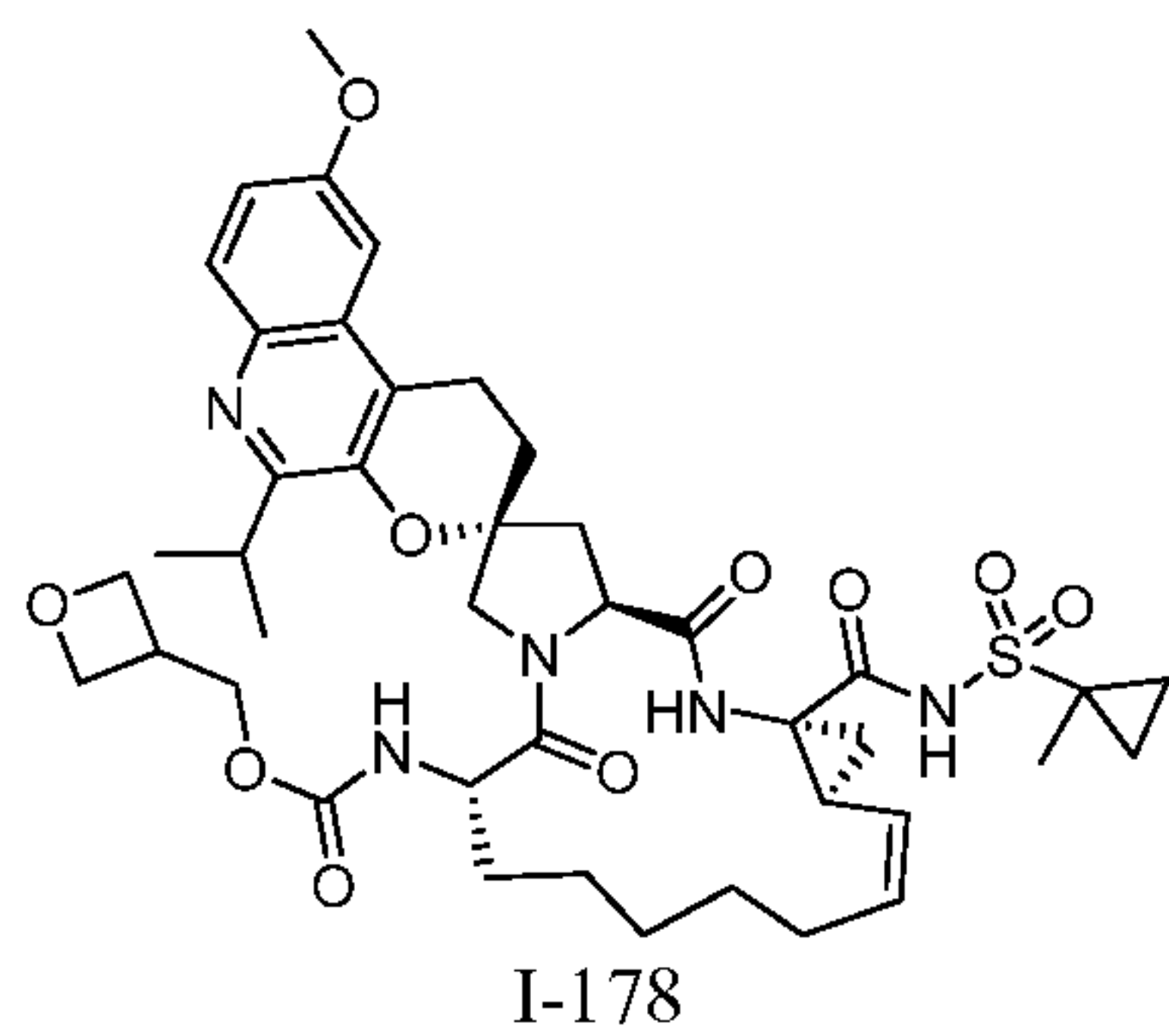
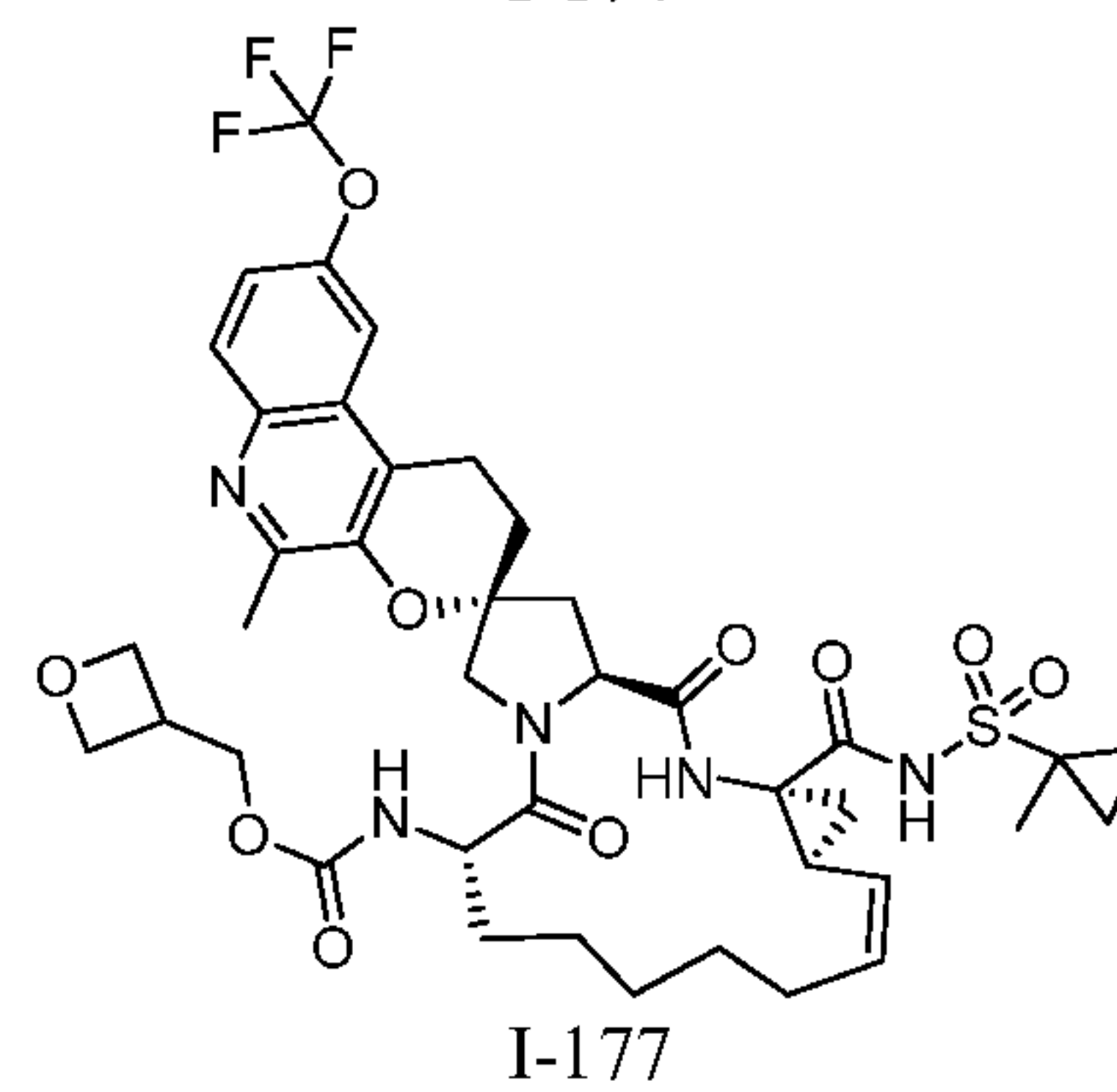
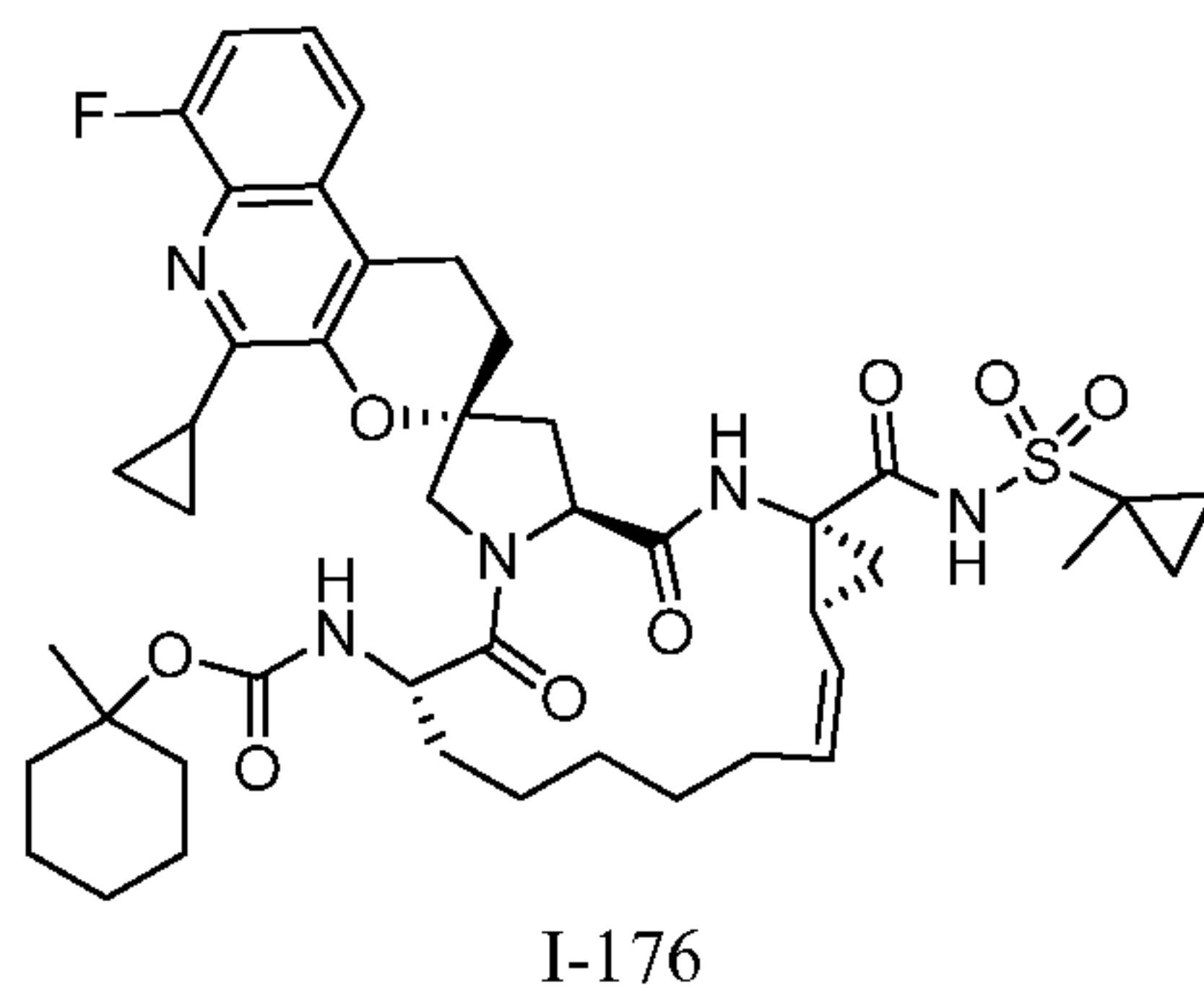
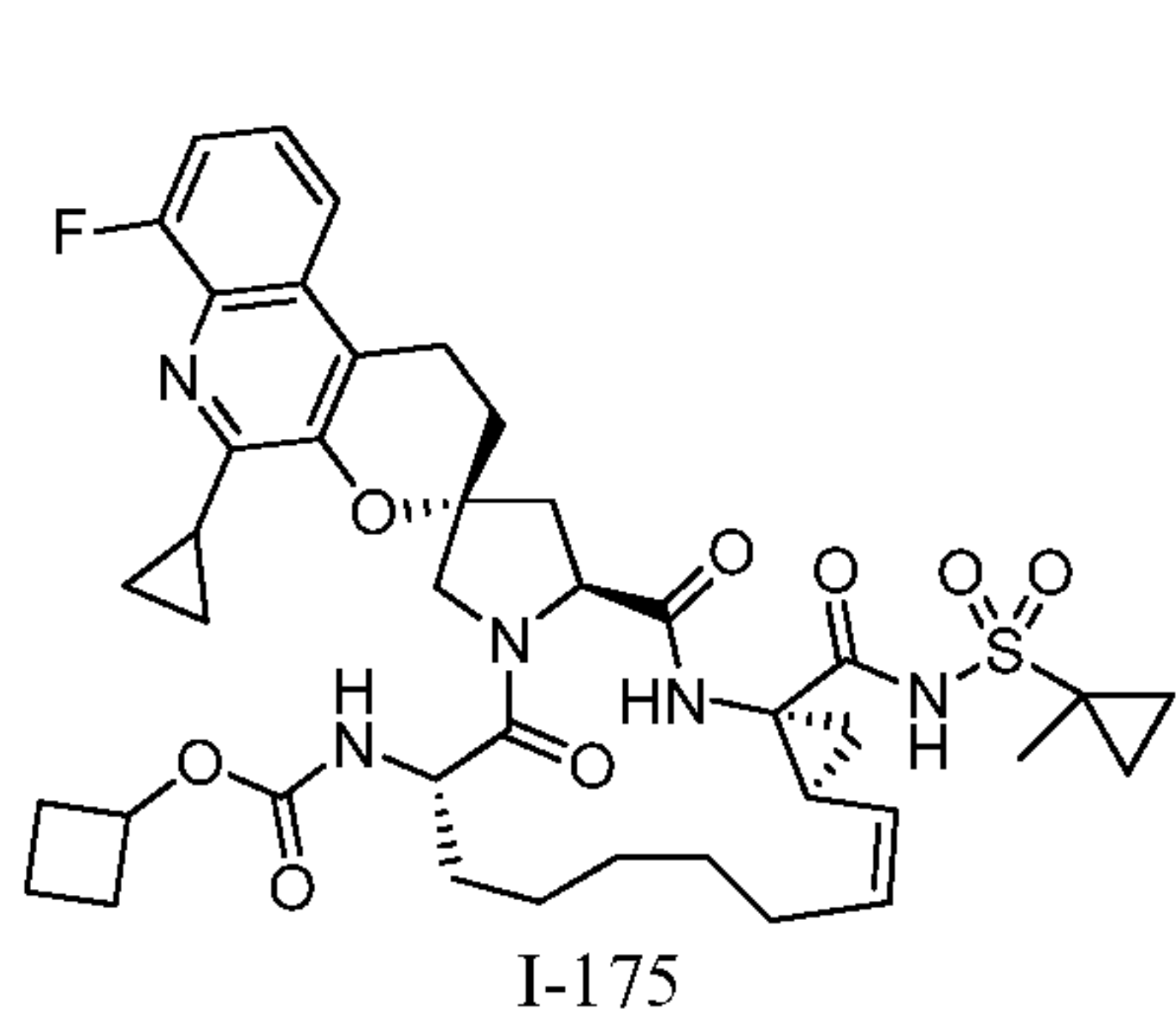
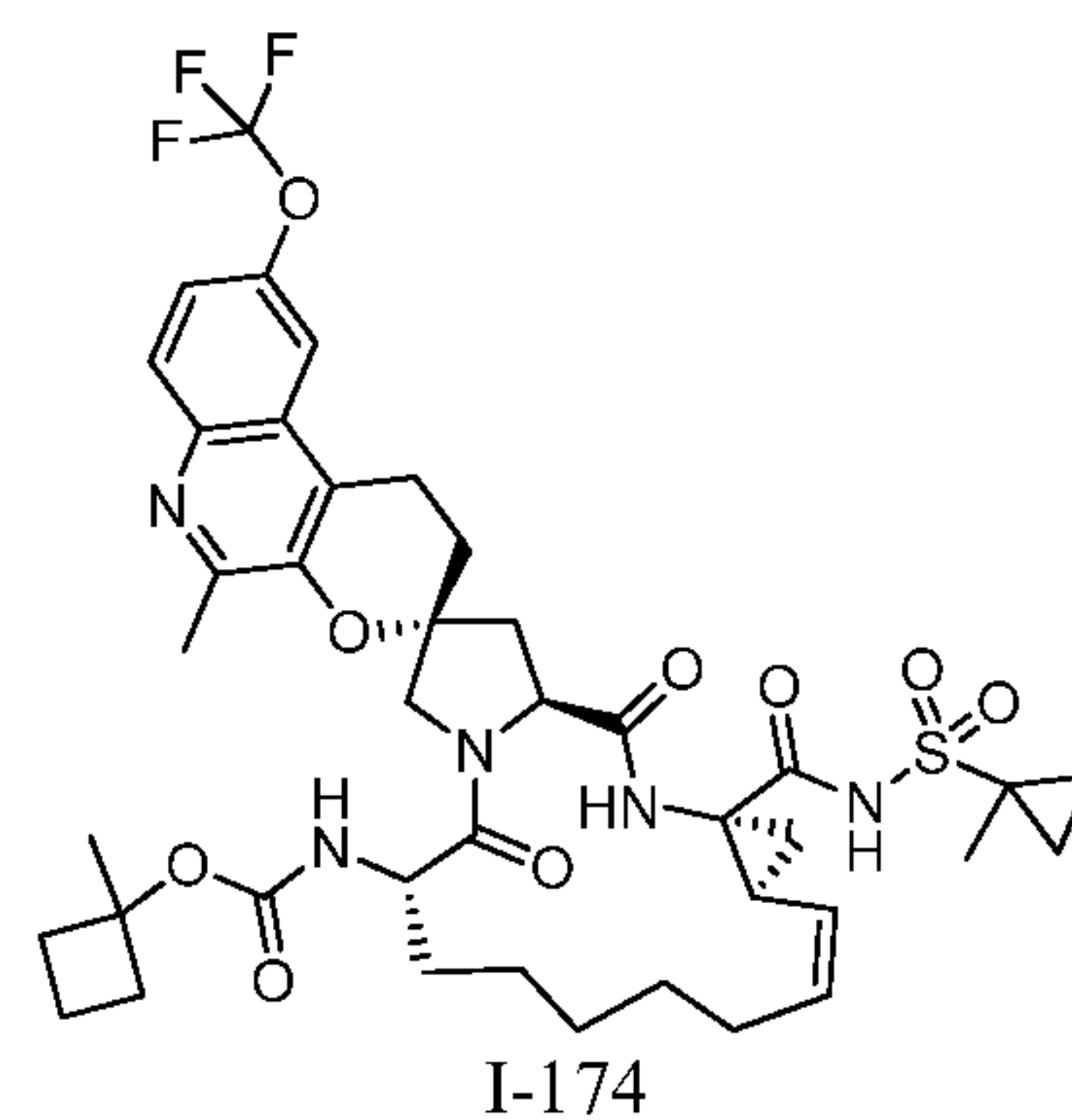
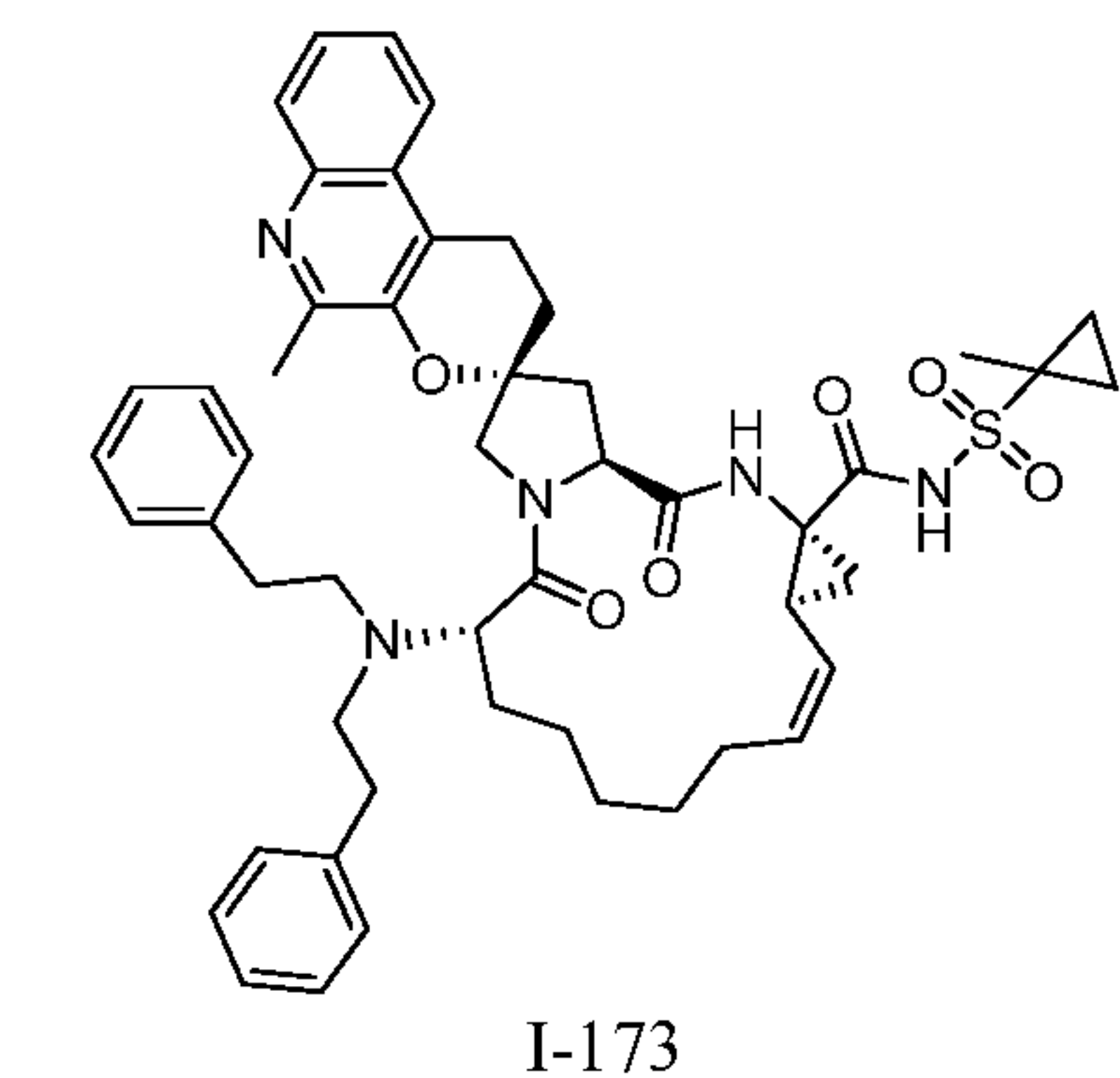
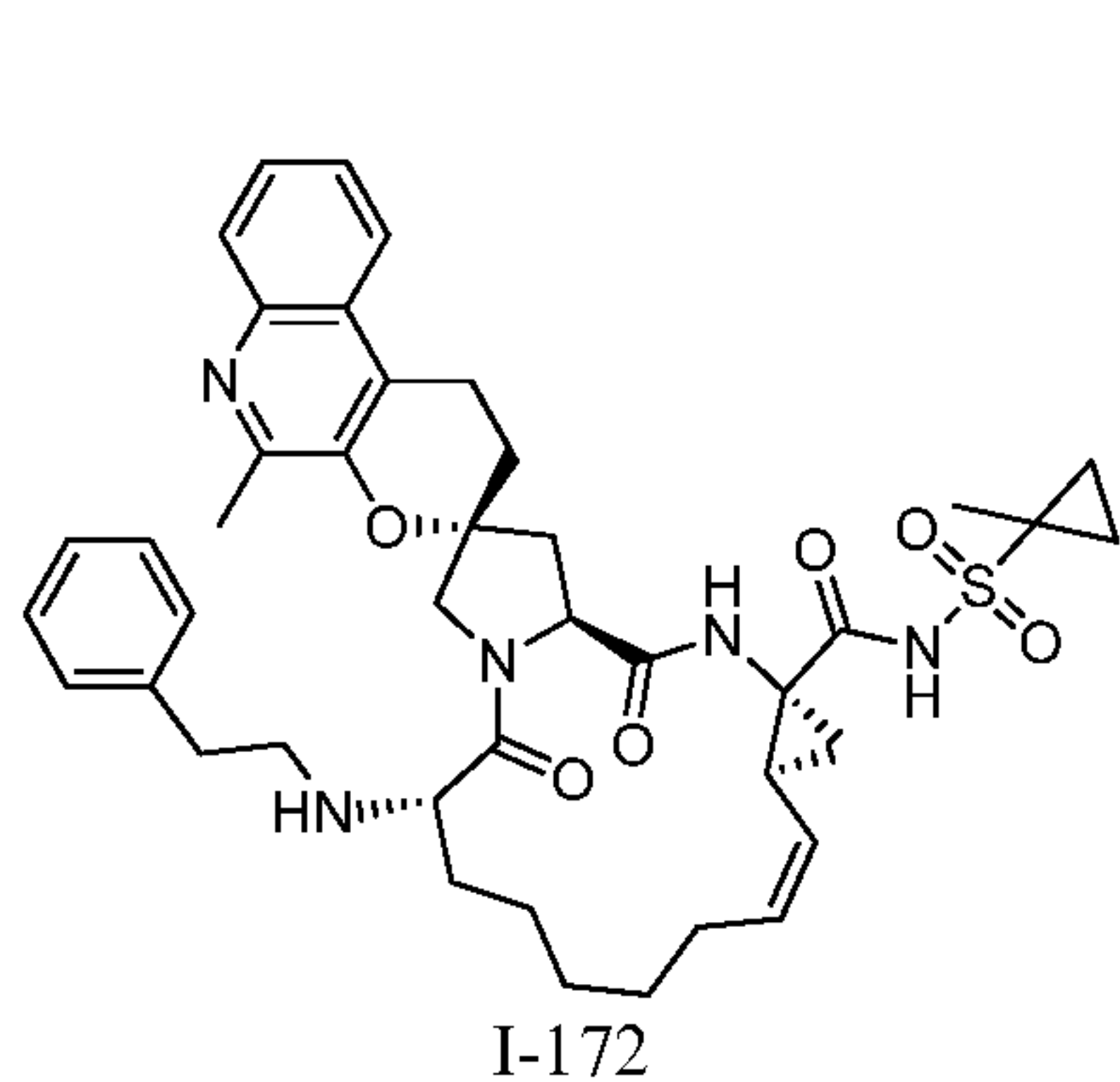
I-169

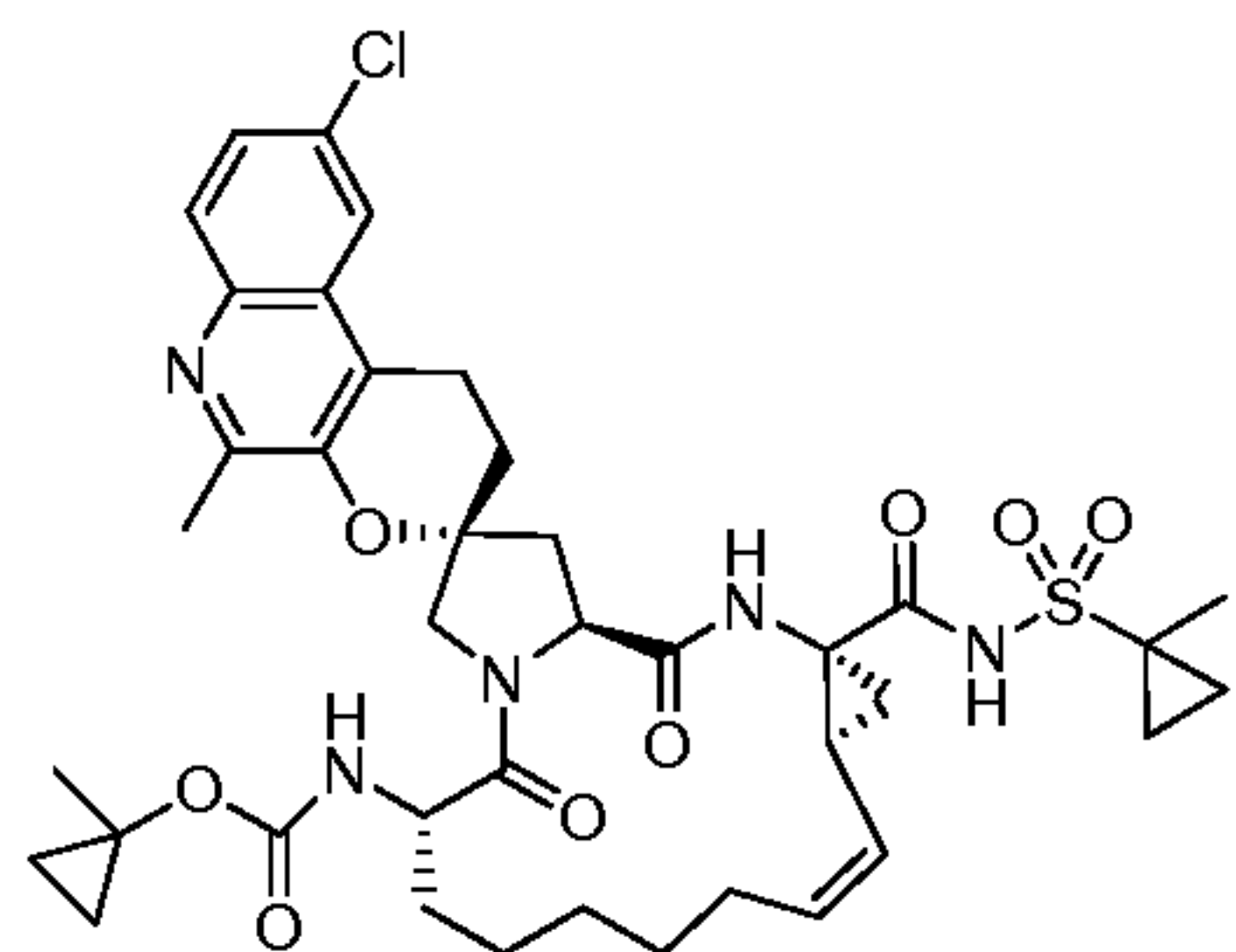


I-170

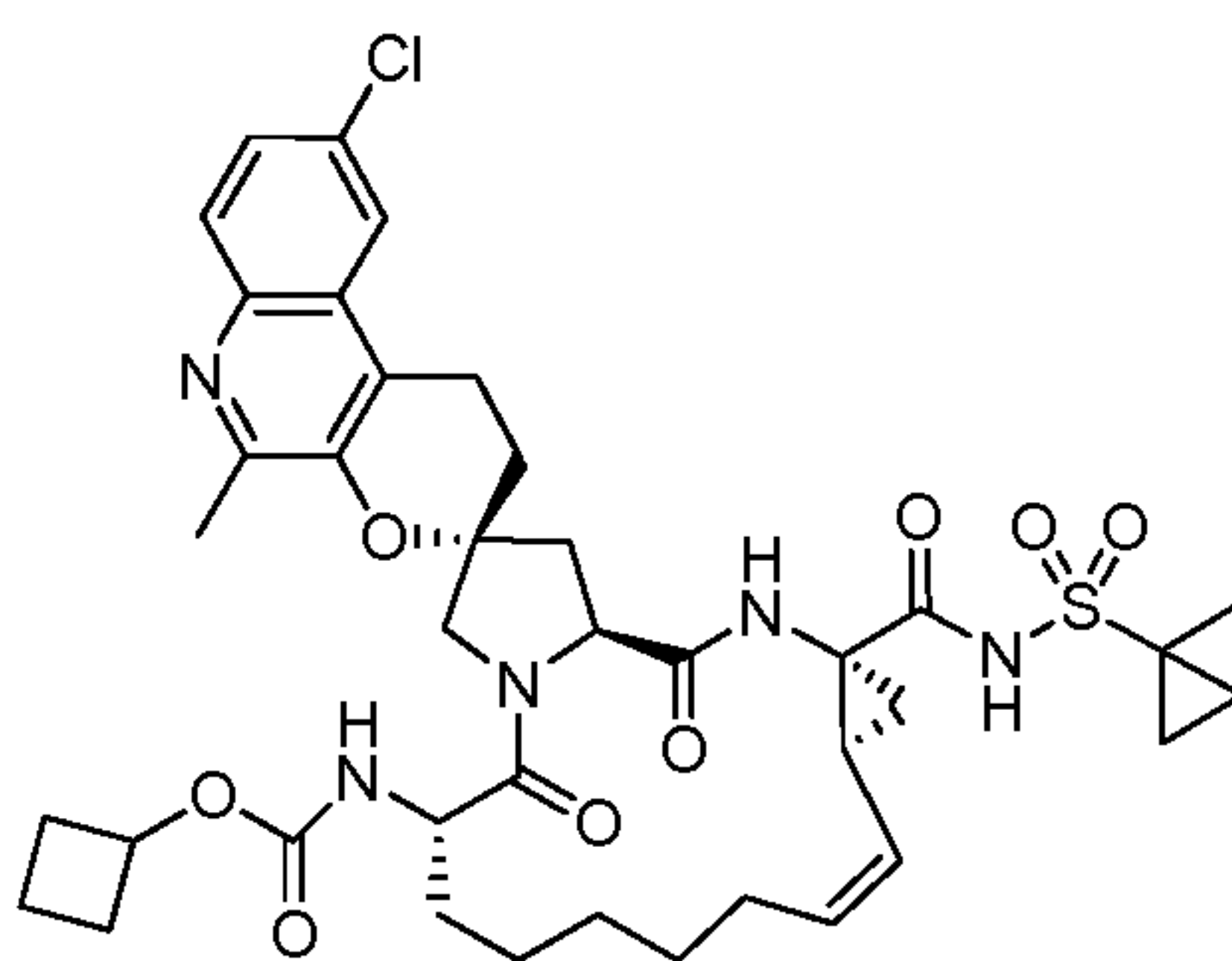


I-171

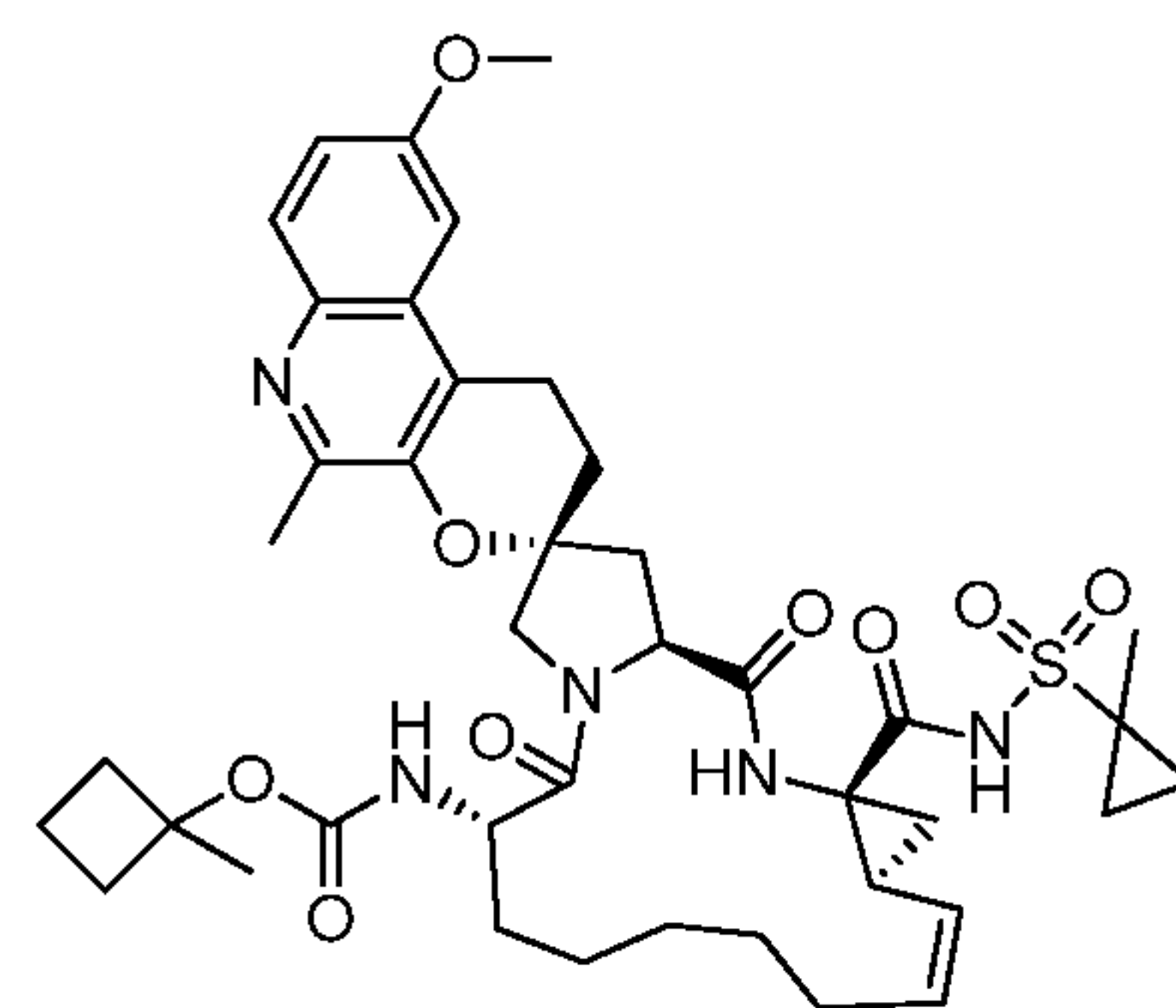




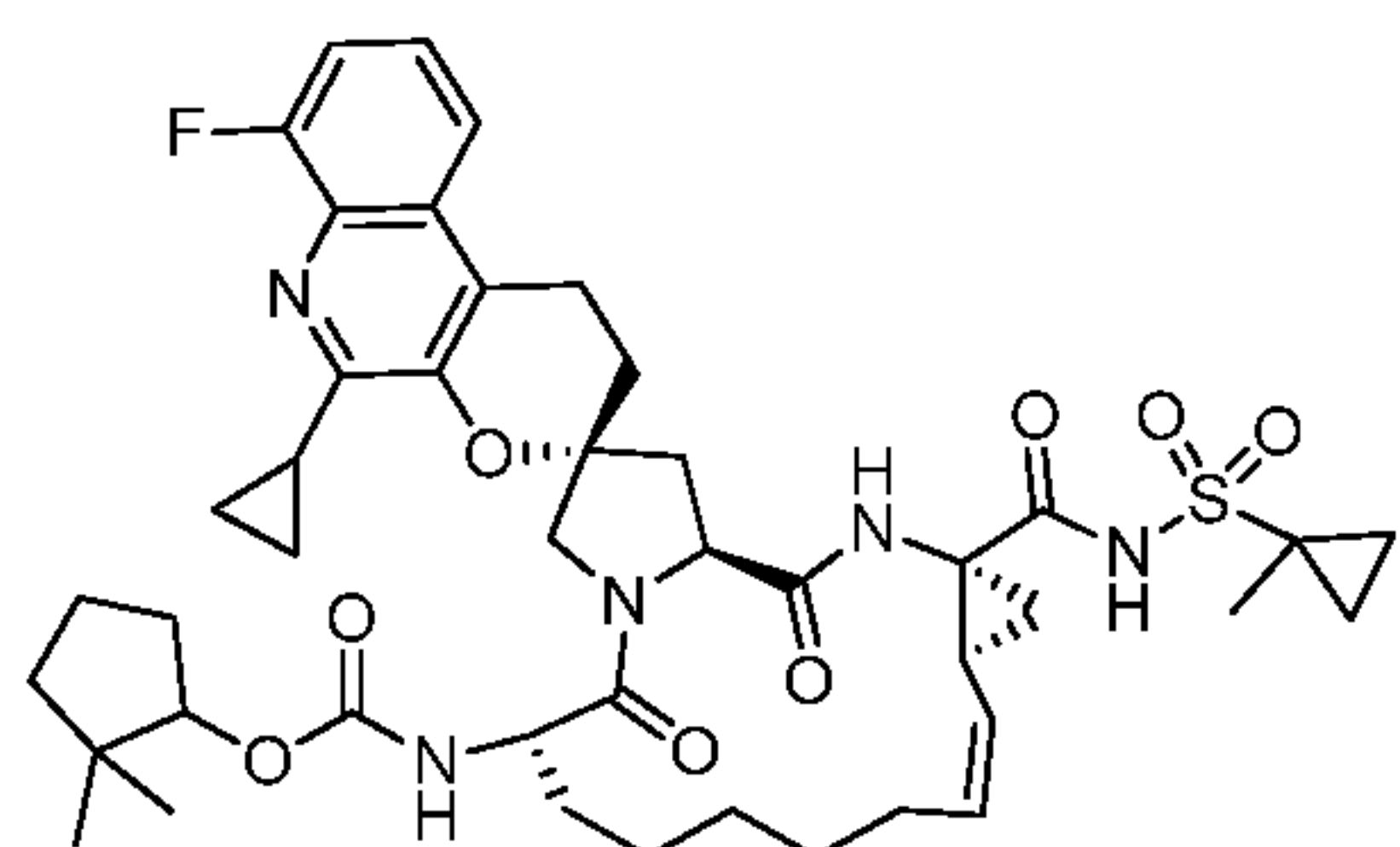
I-184



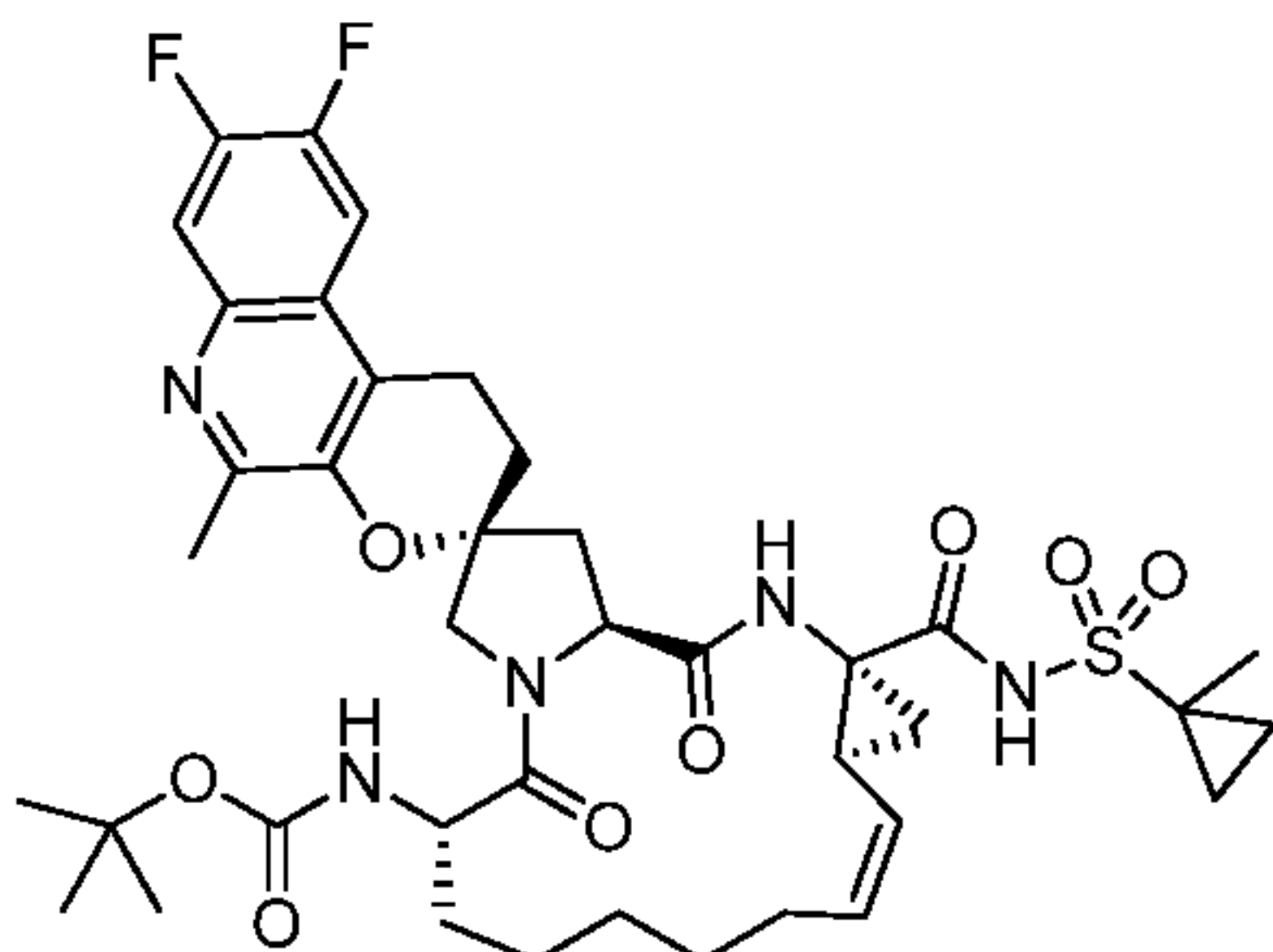
I-185



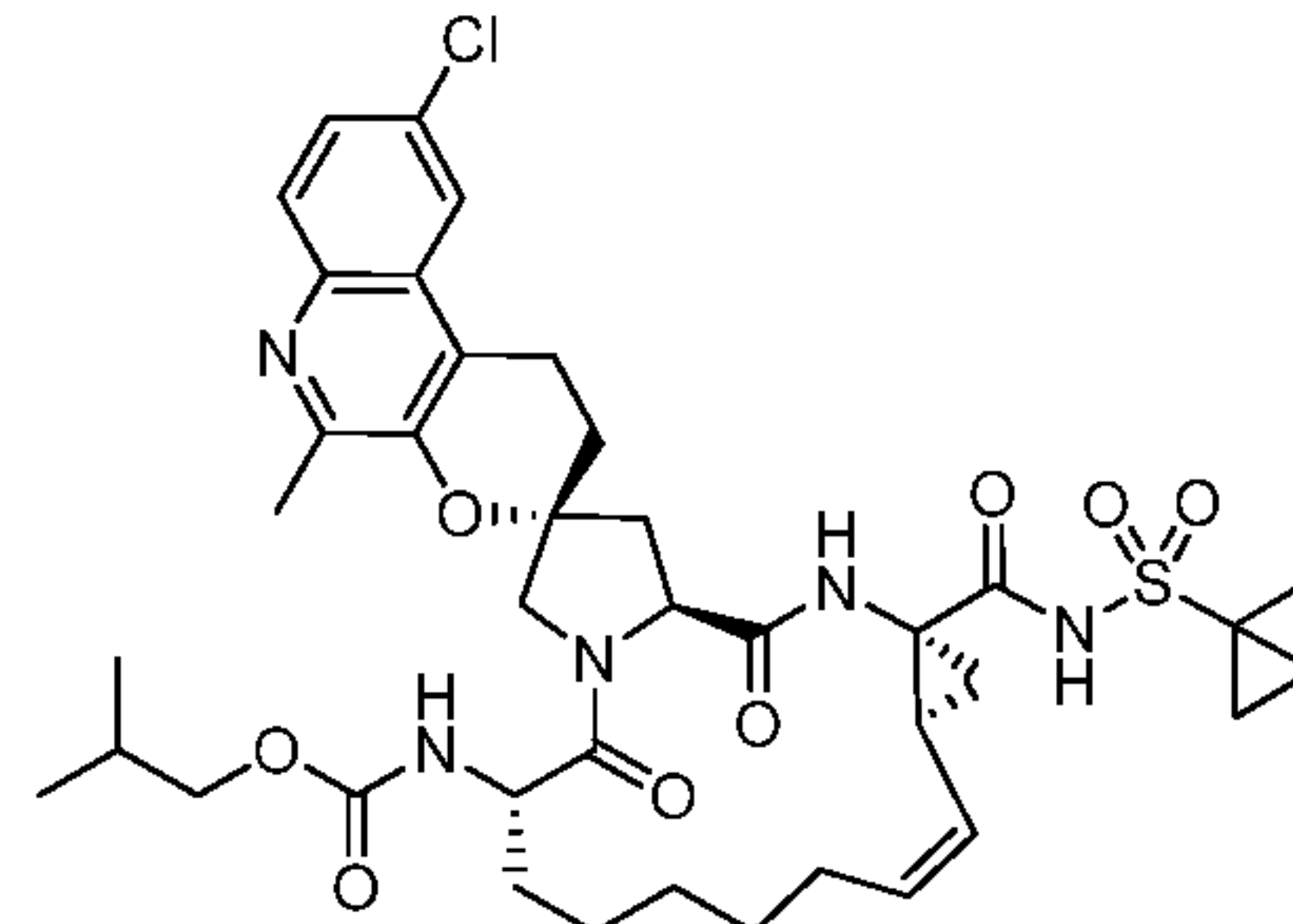
I-186



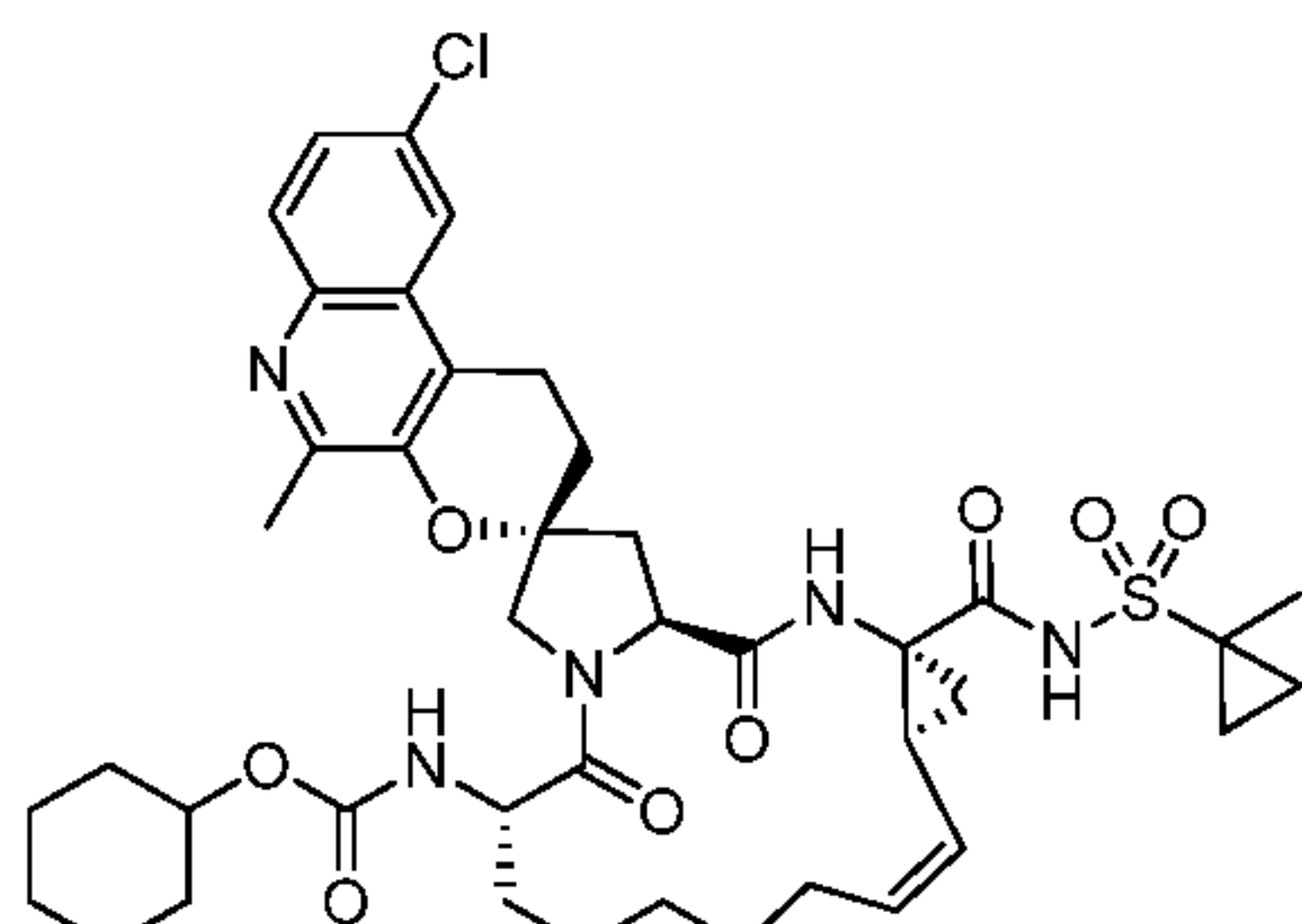
I-187



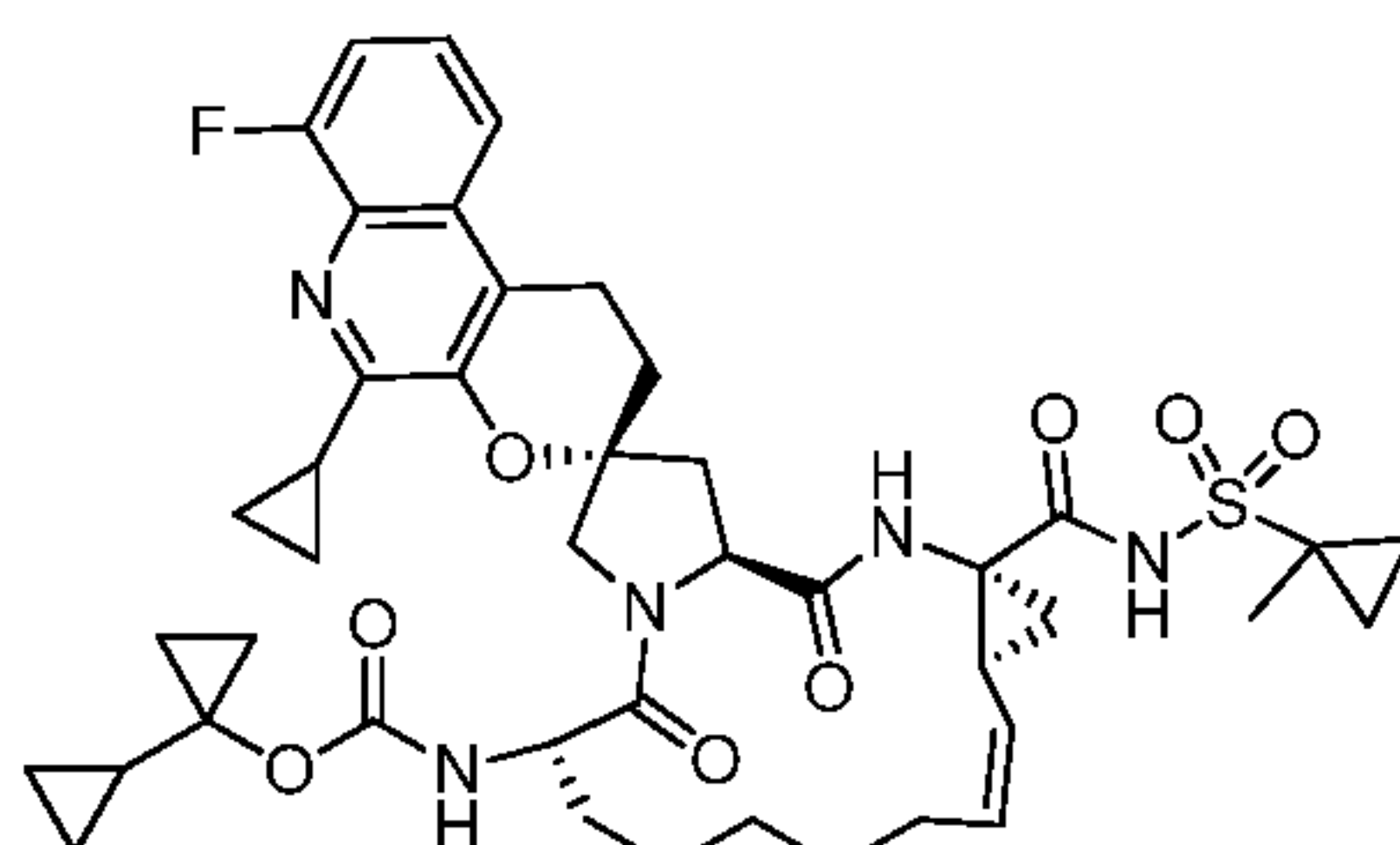
I-188



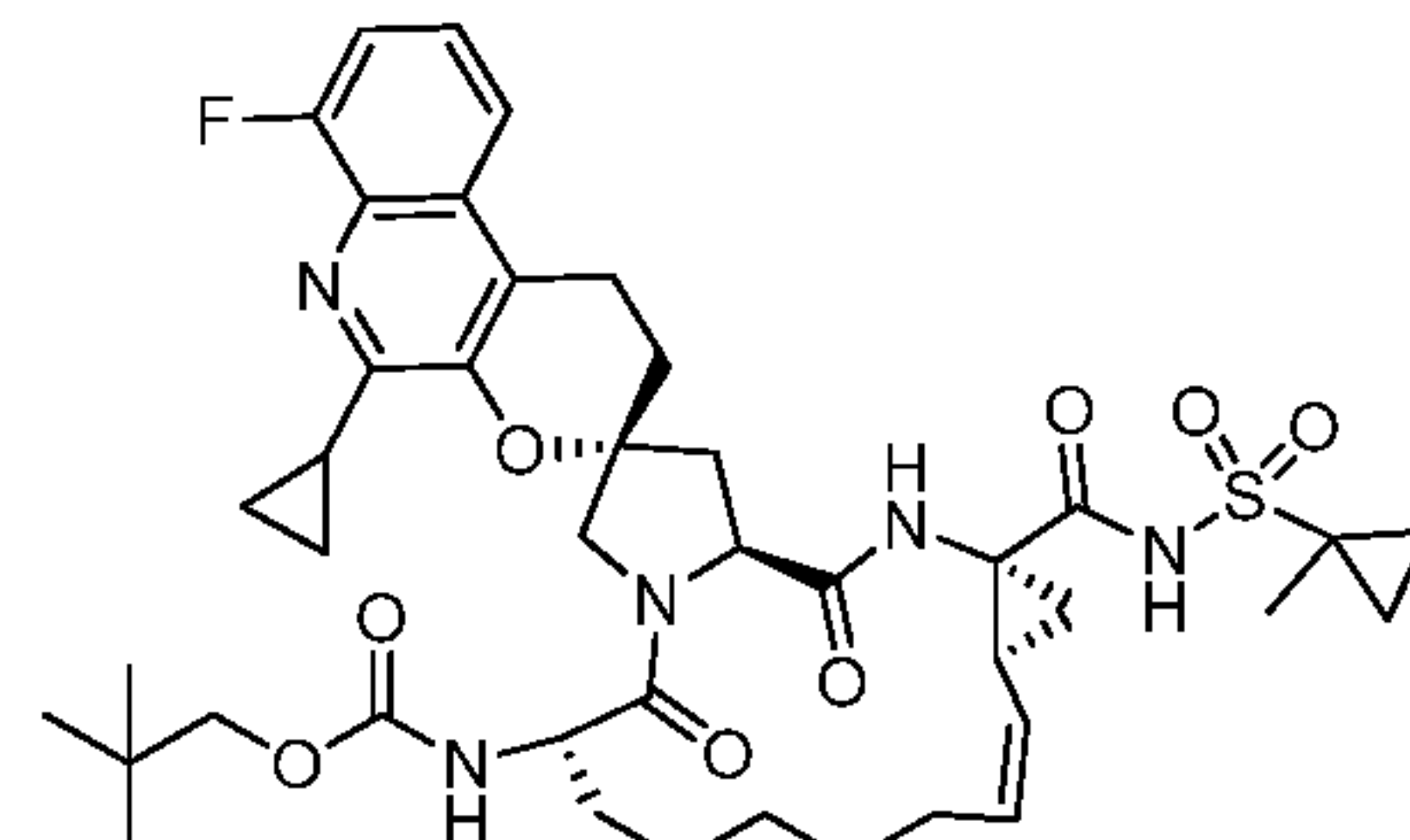
I-189



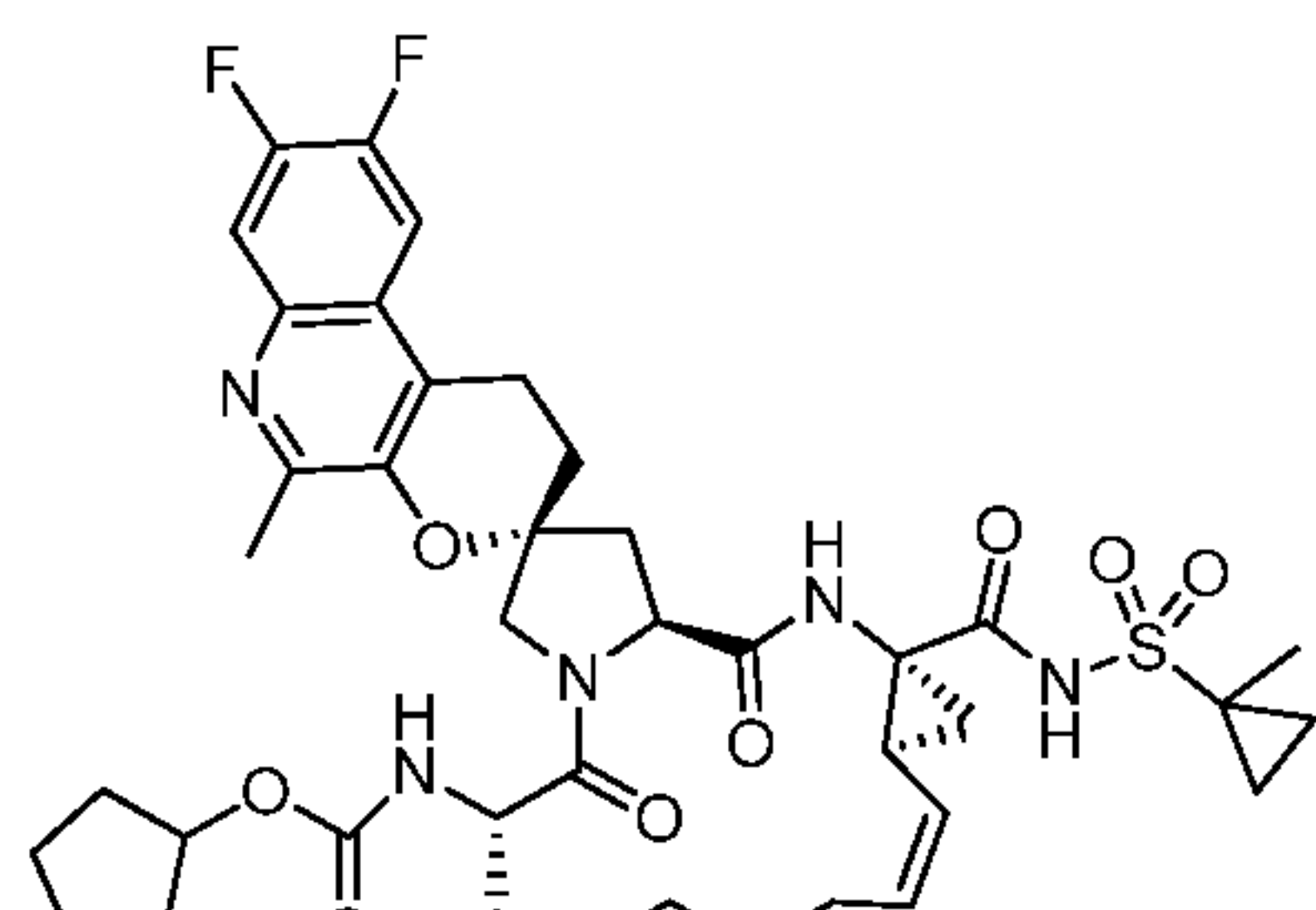
I-190



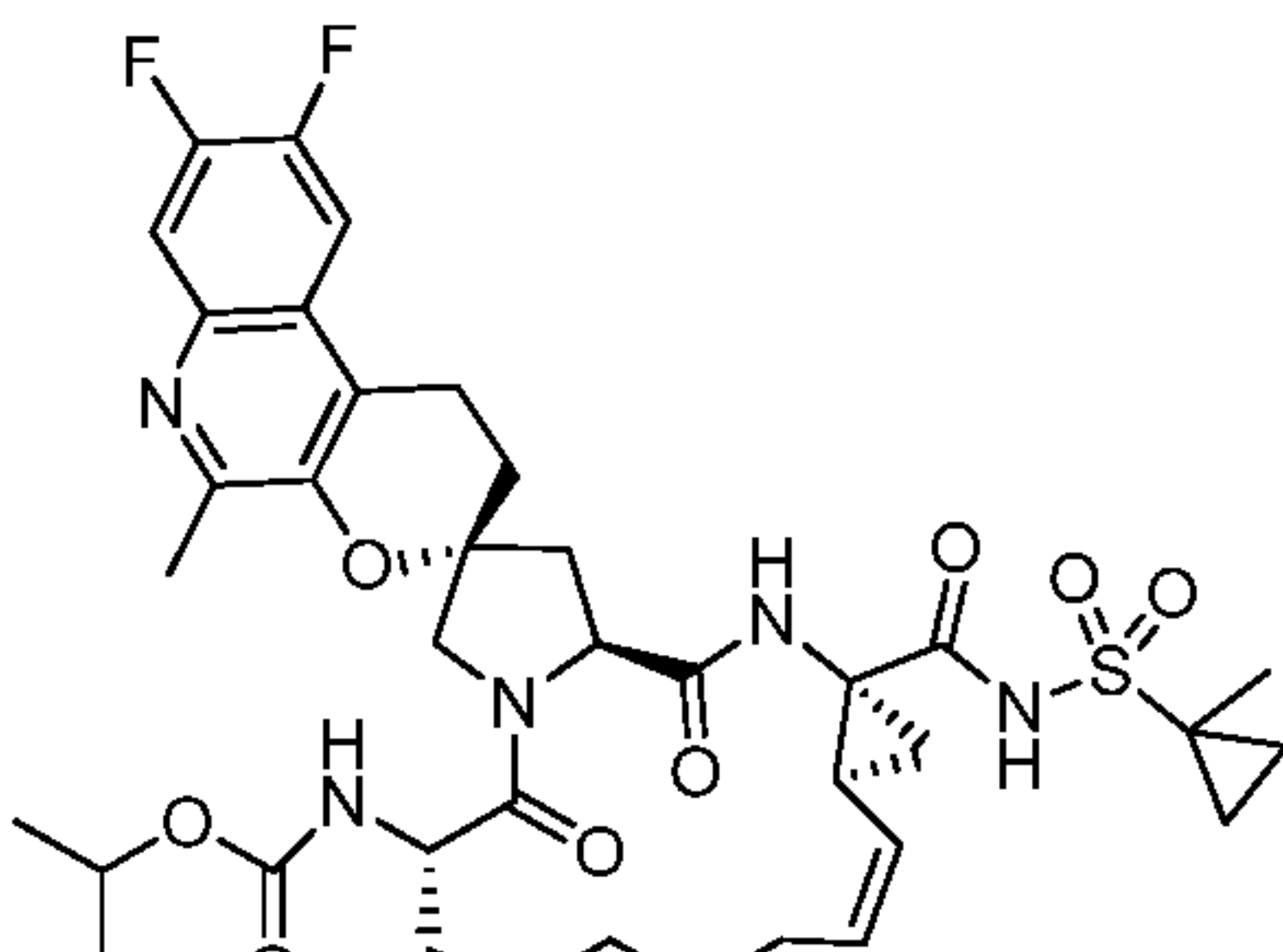
I-191



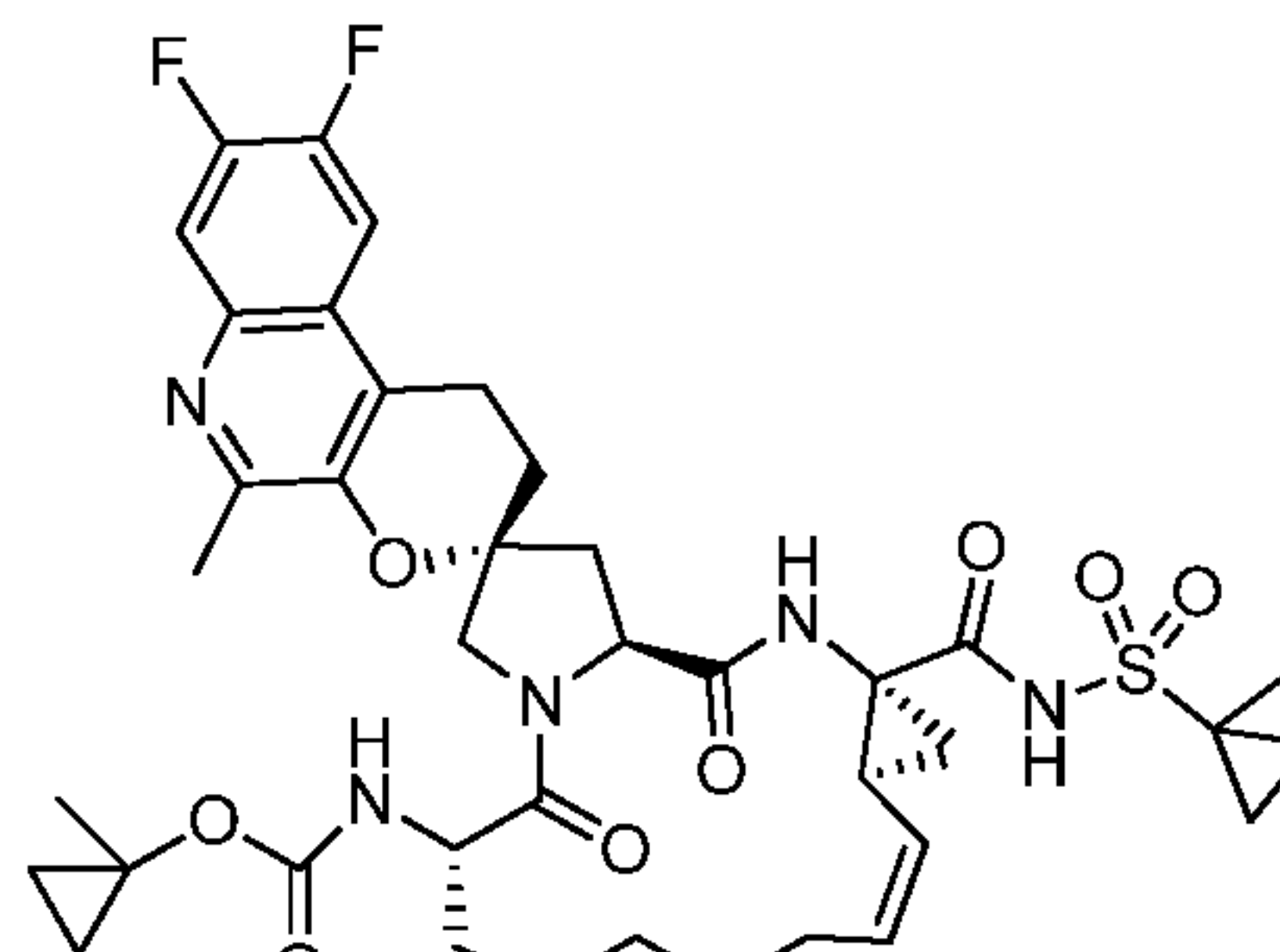
I-192



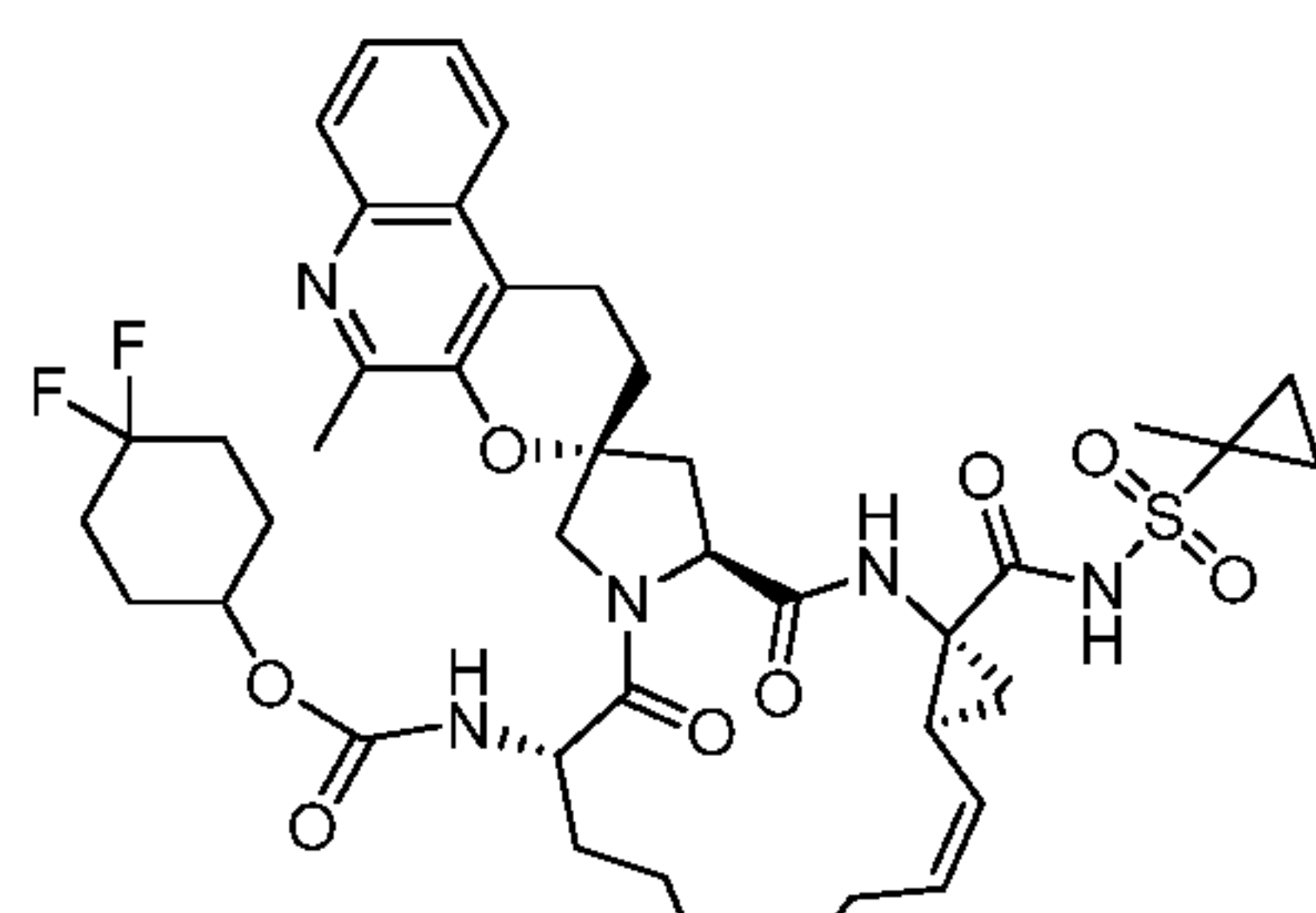
I-193



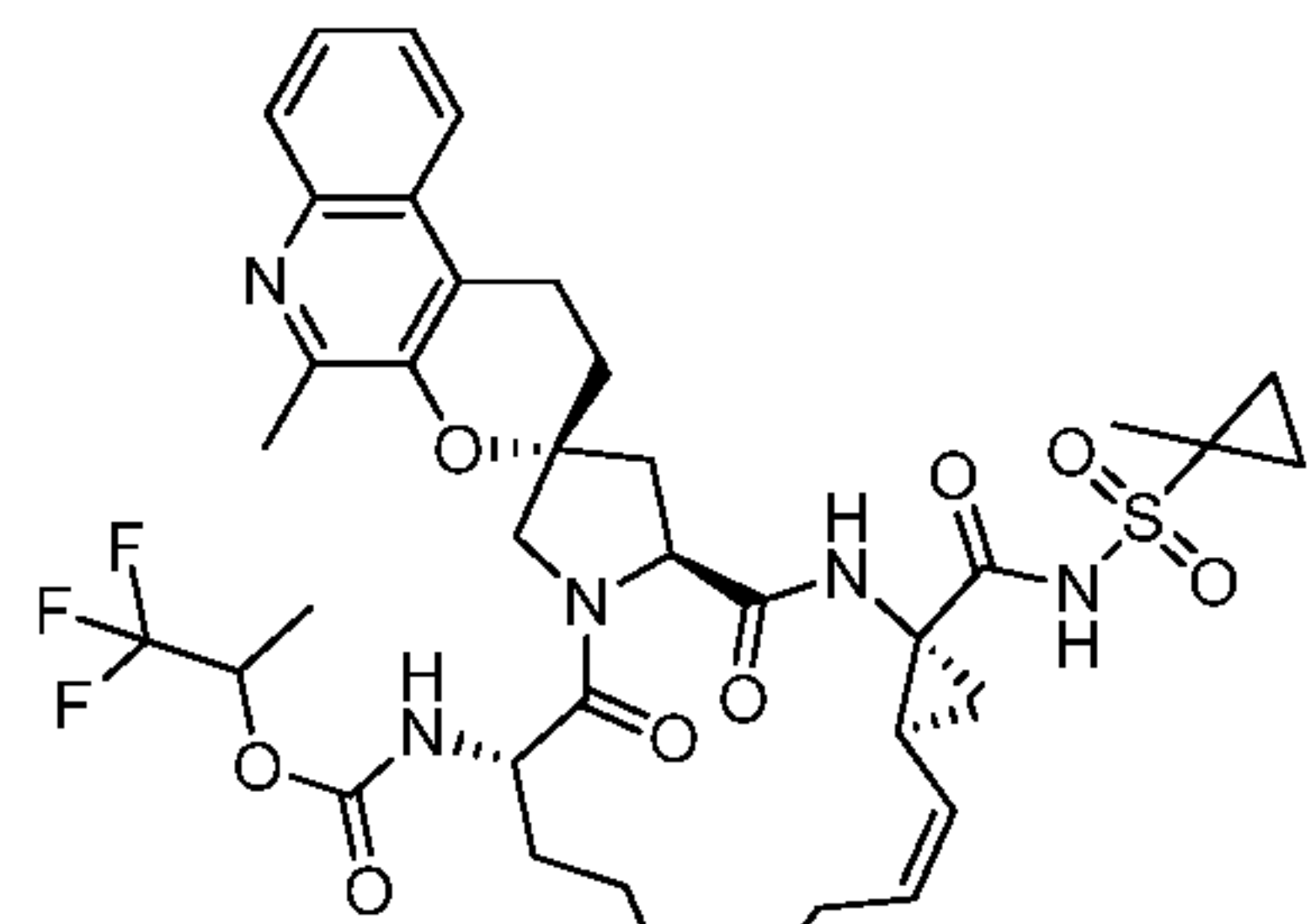
I-194



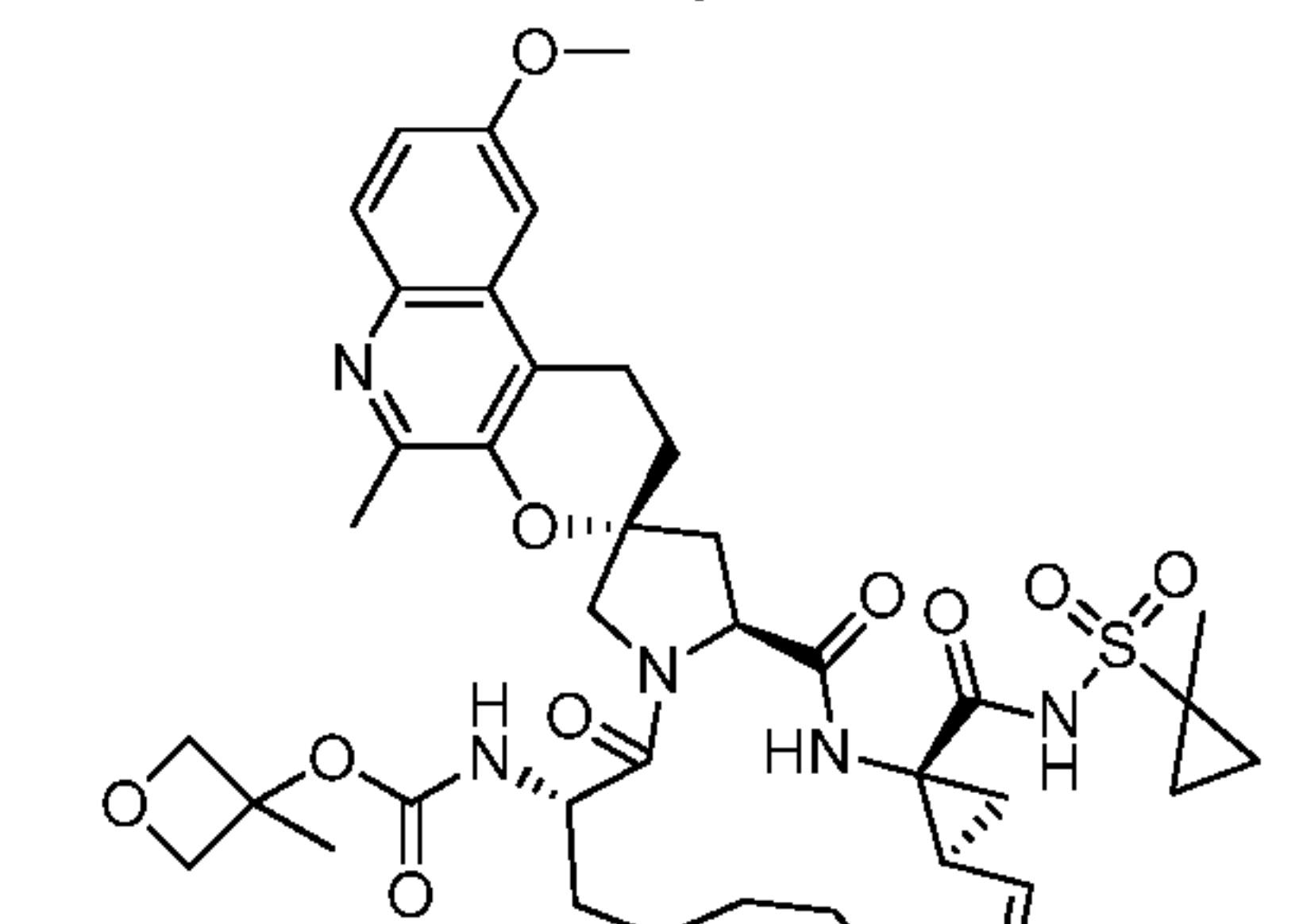
I-195



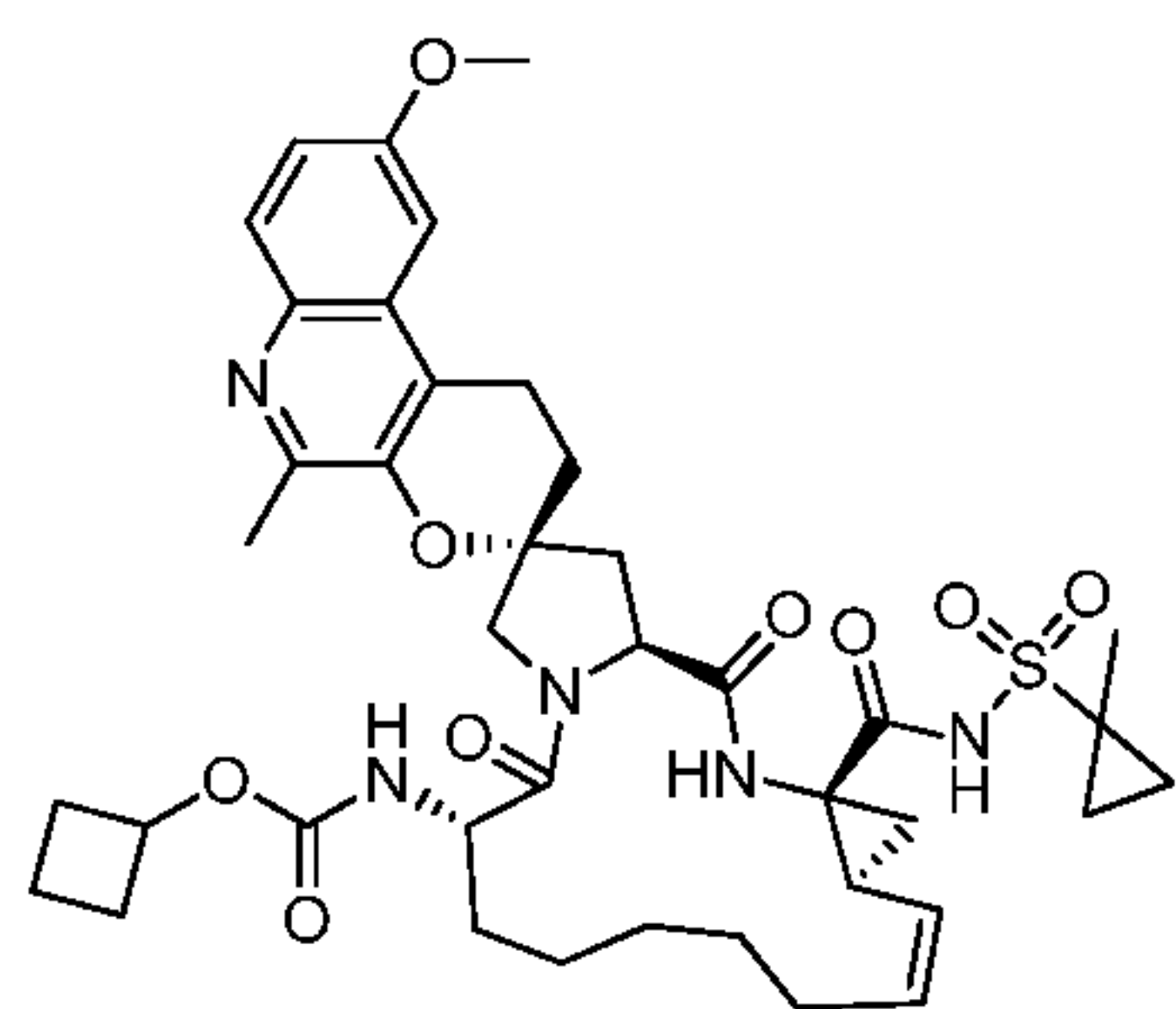
I-196



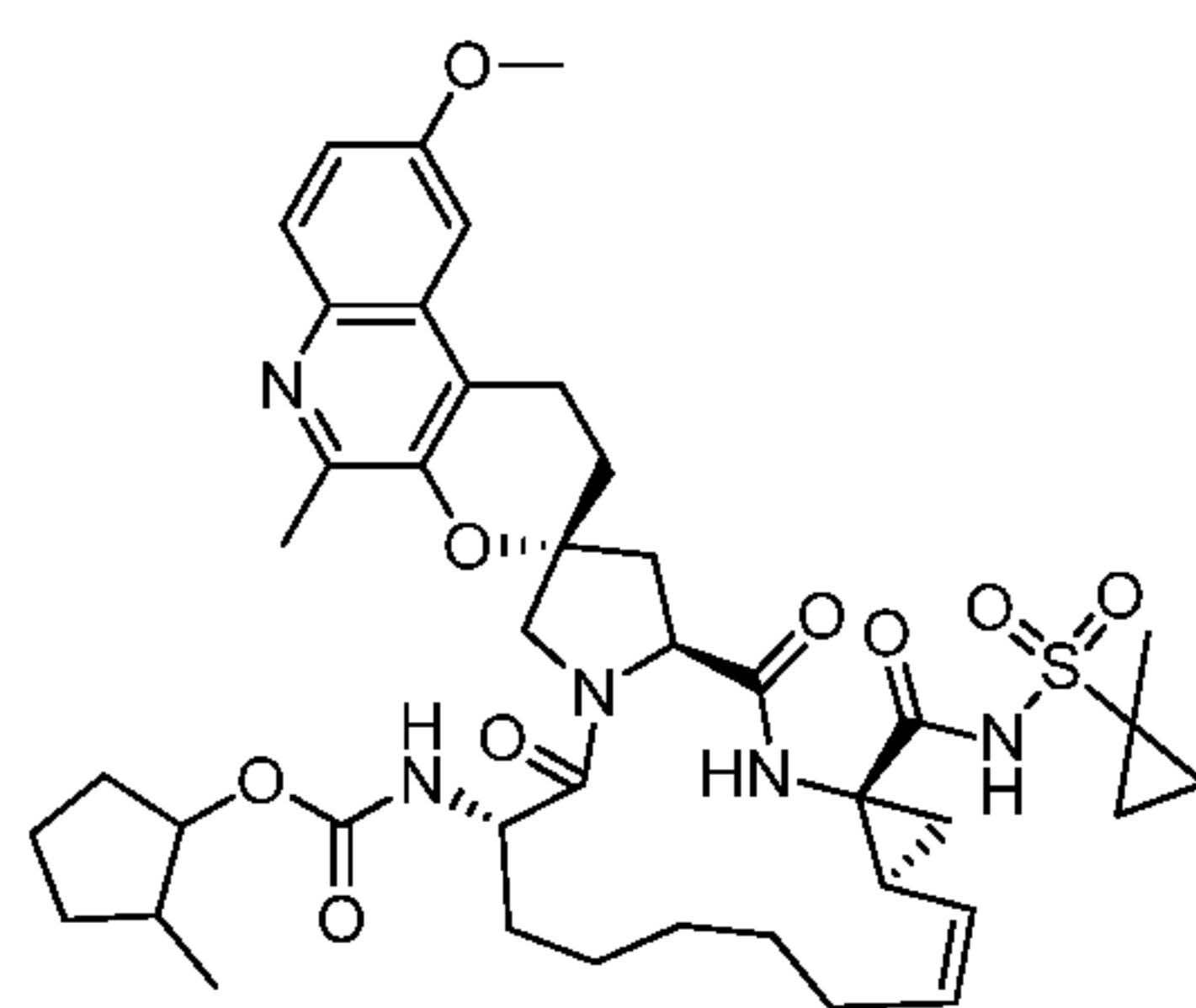
I-197



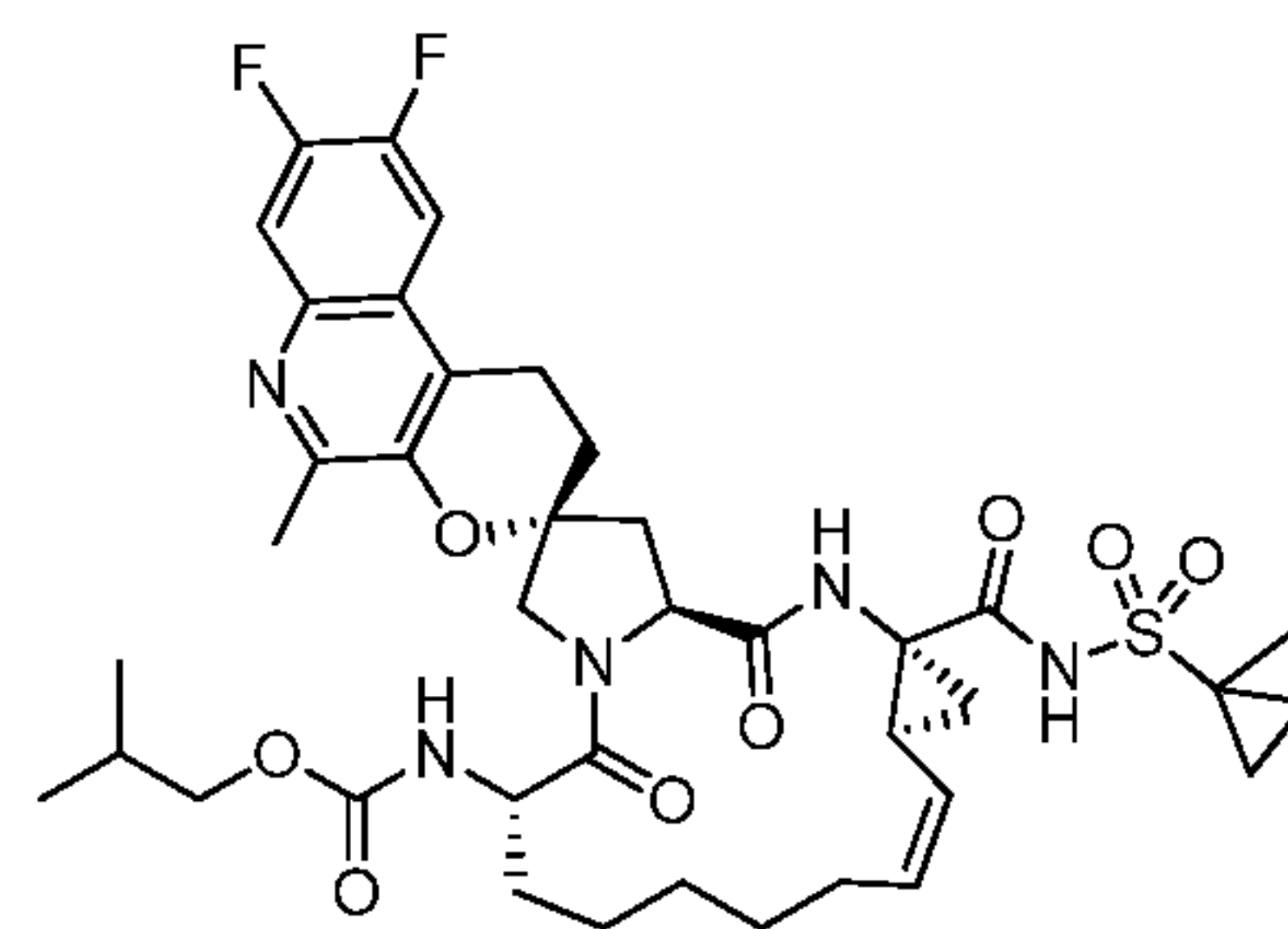
I-198



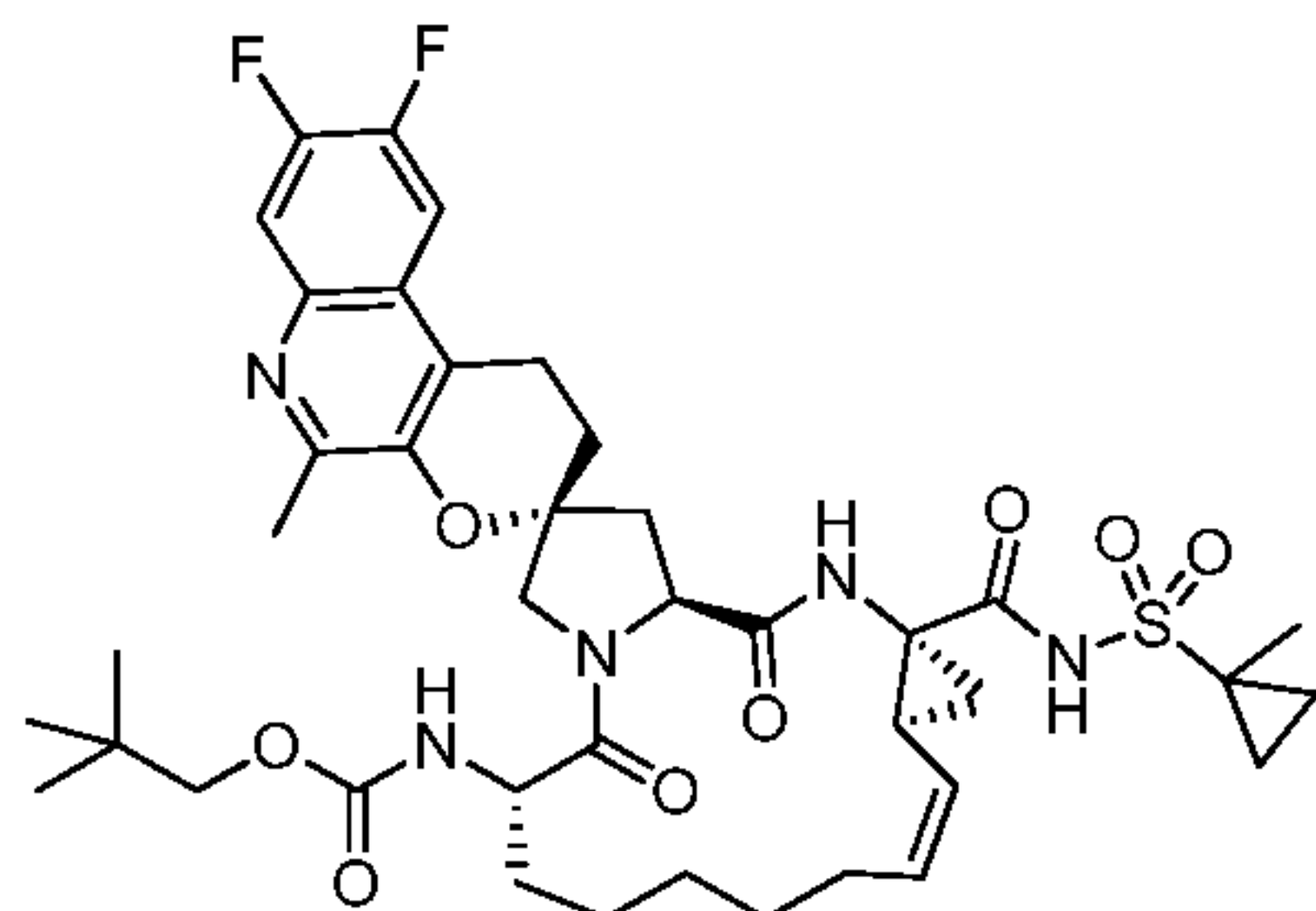
I-199



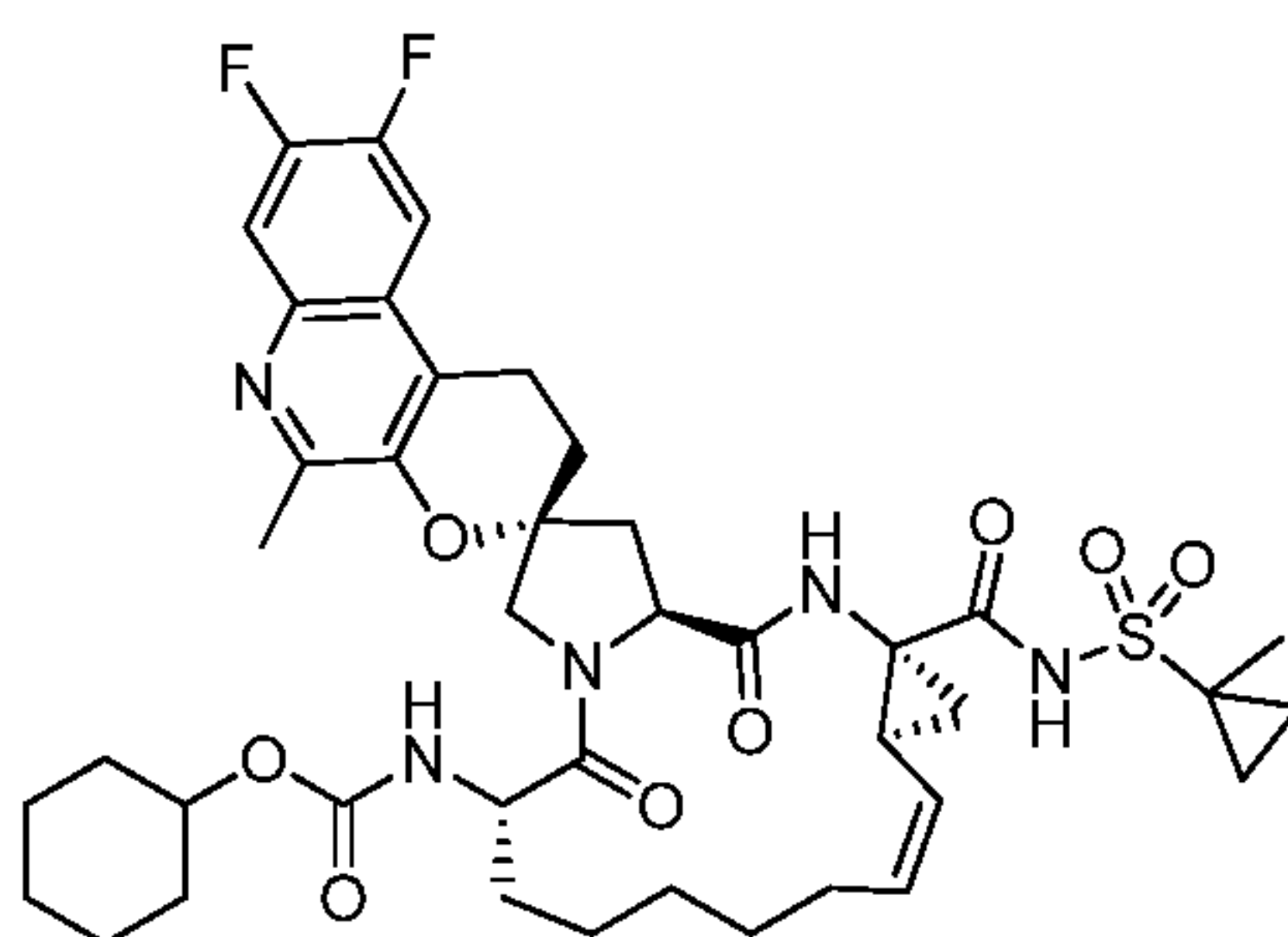
I-200



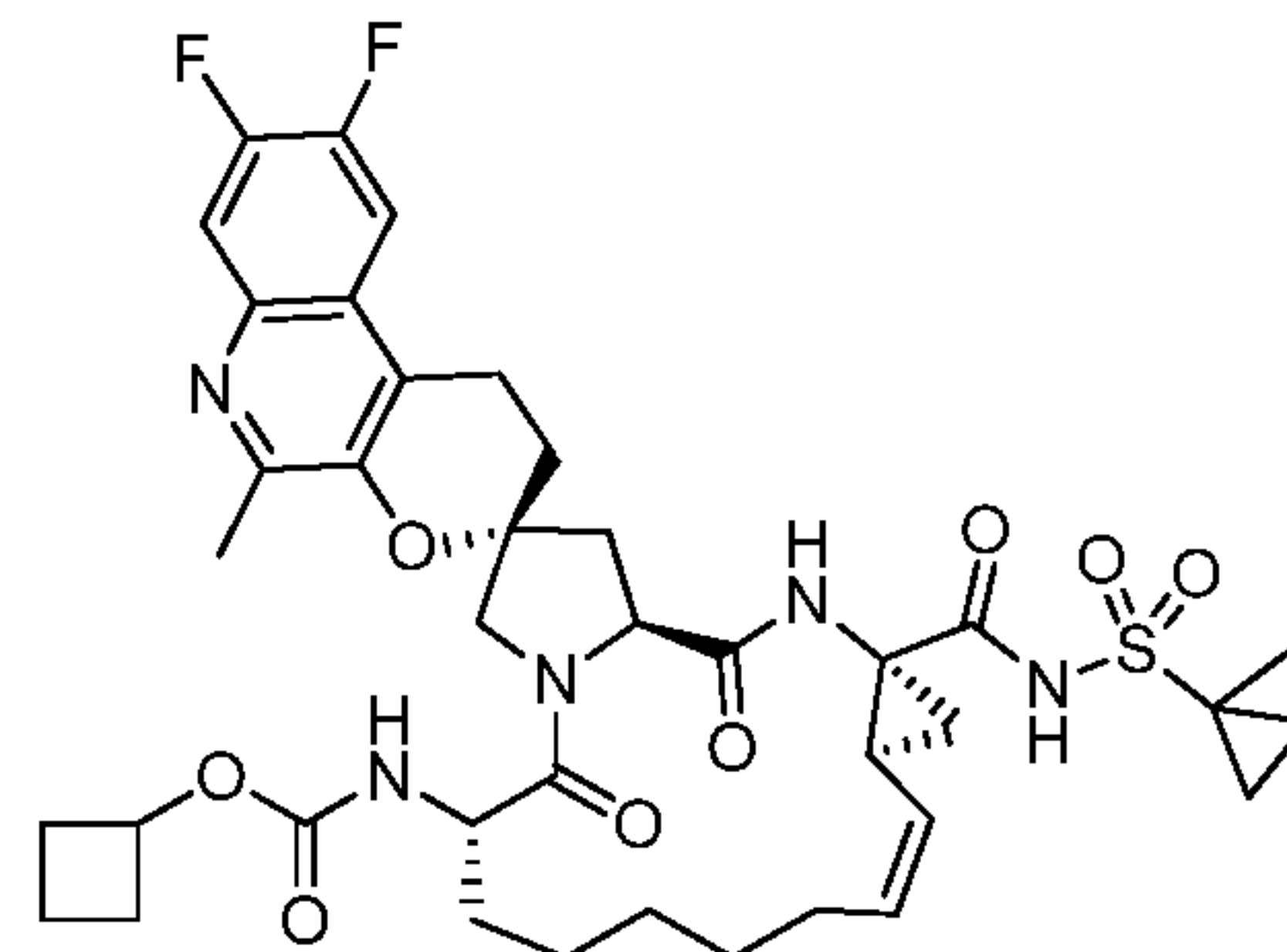
I-201



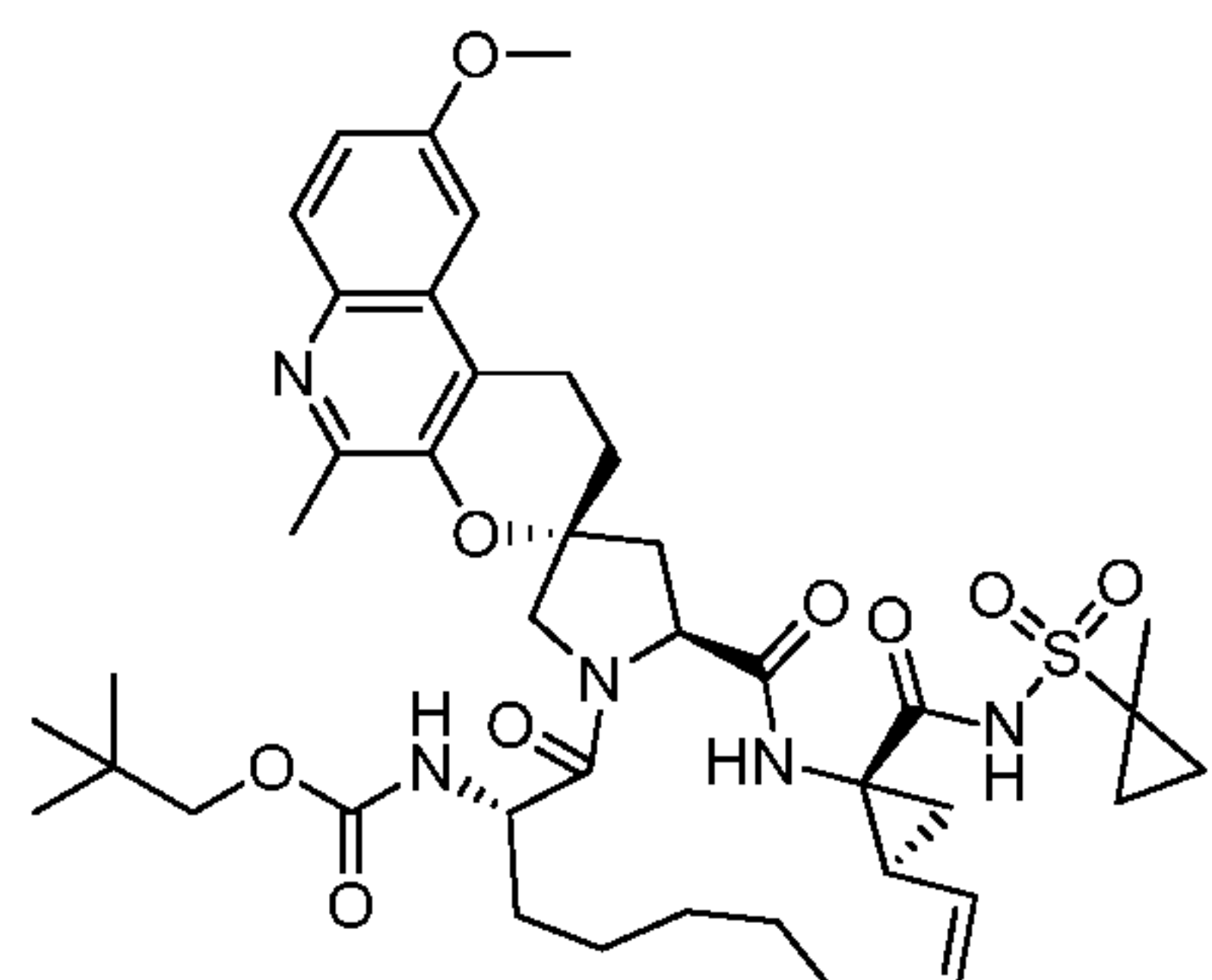
I-202



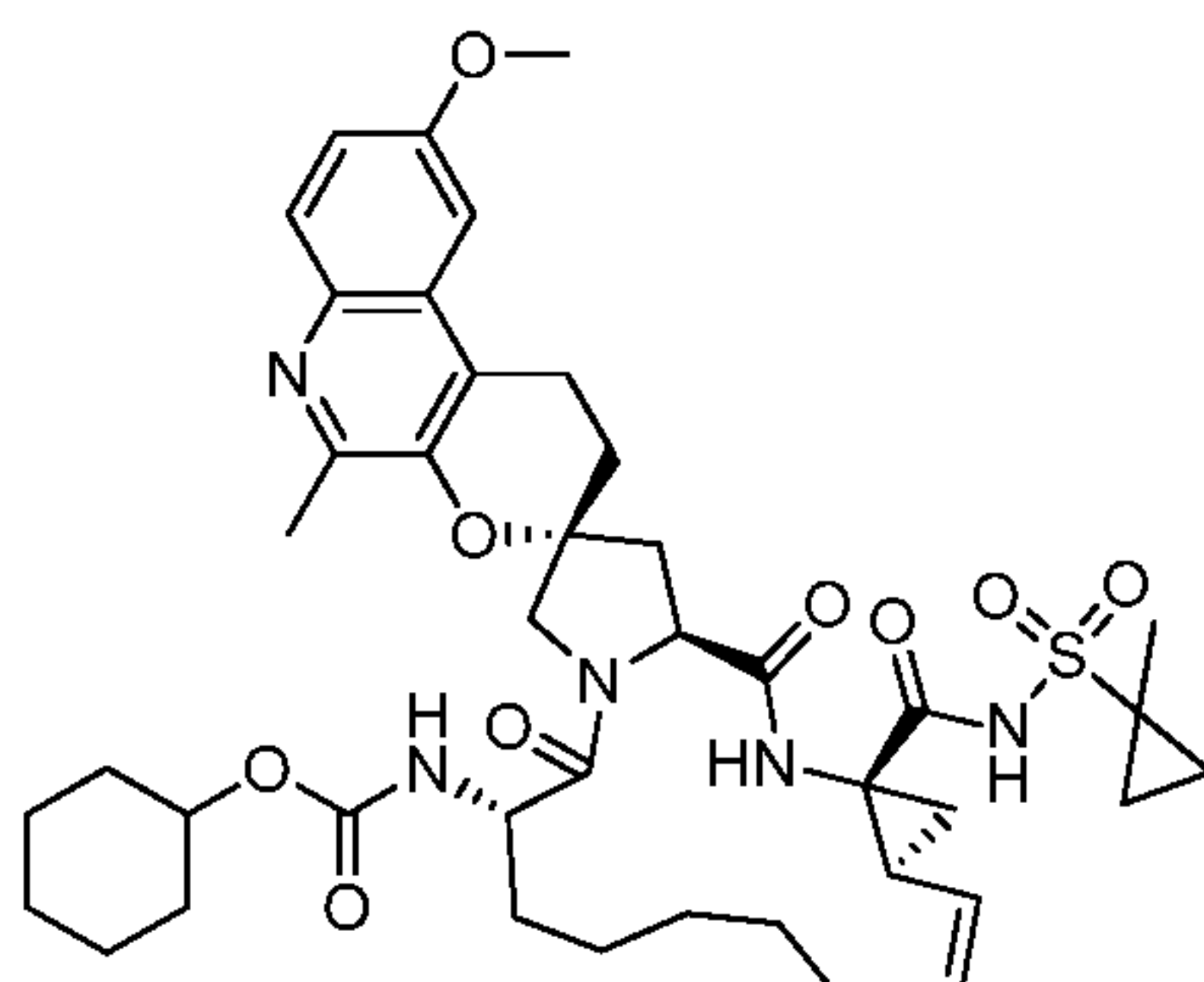
I-203



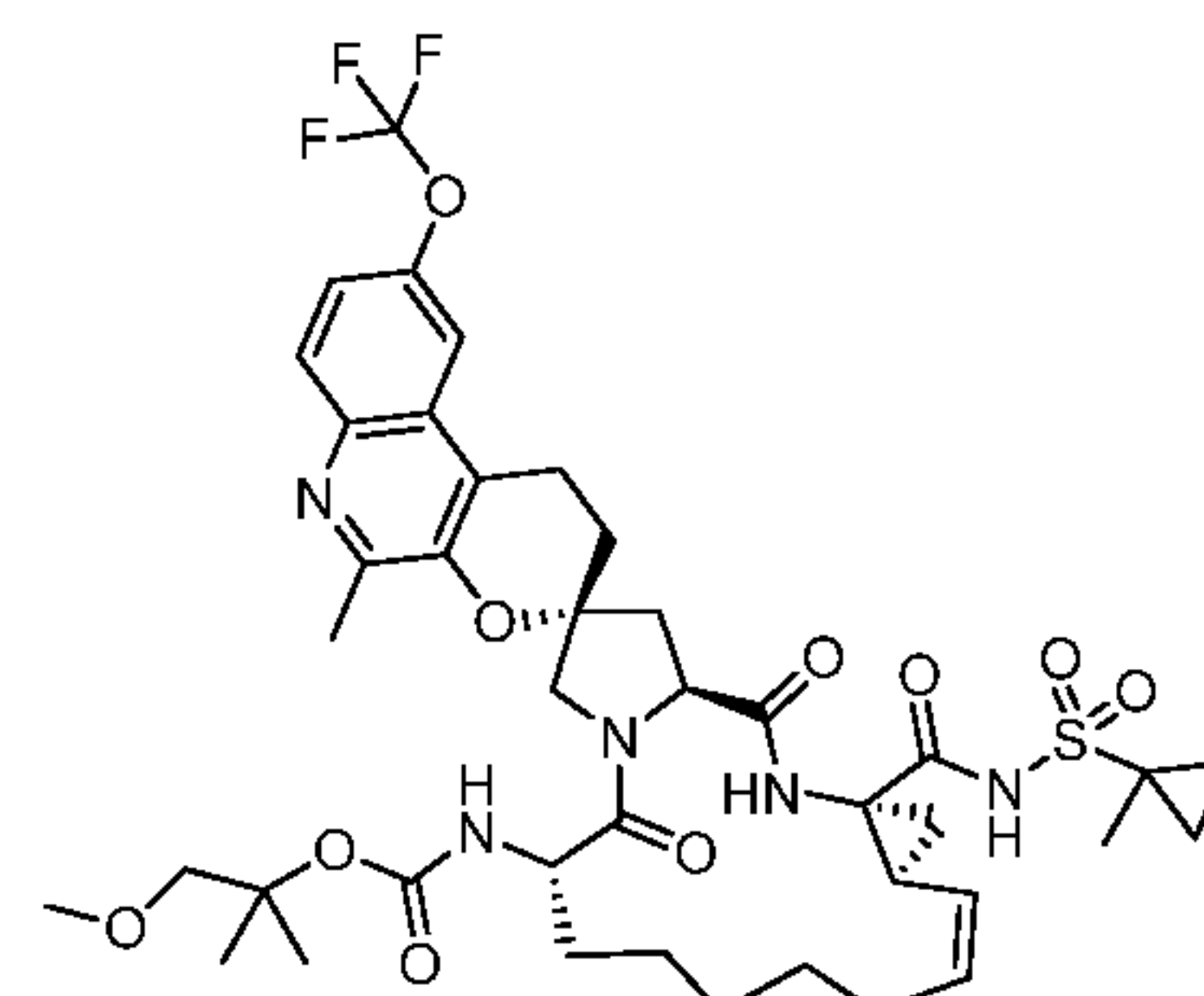
I-204



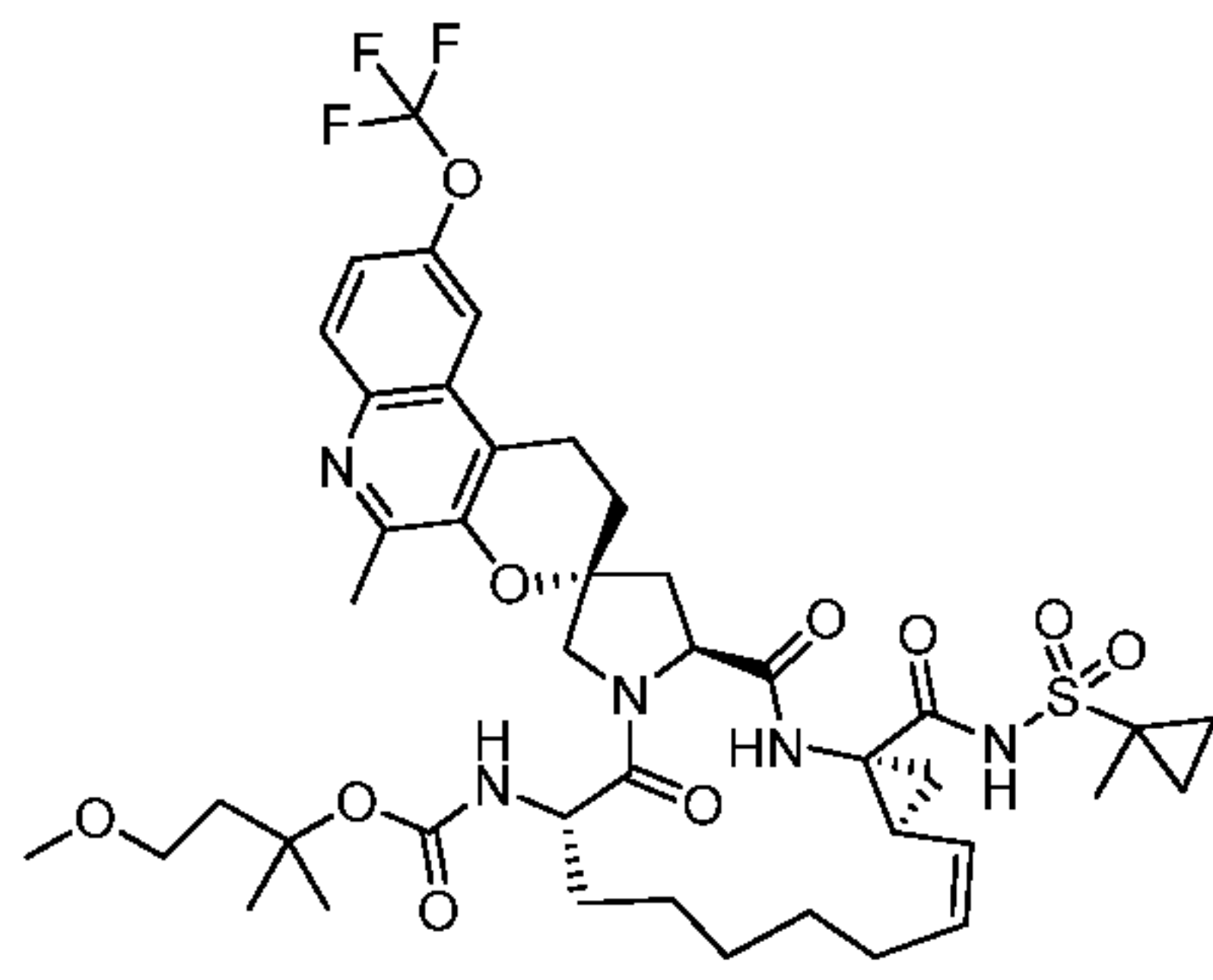
I-205



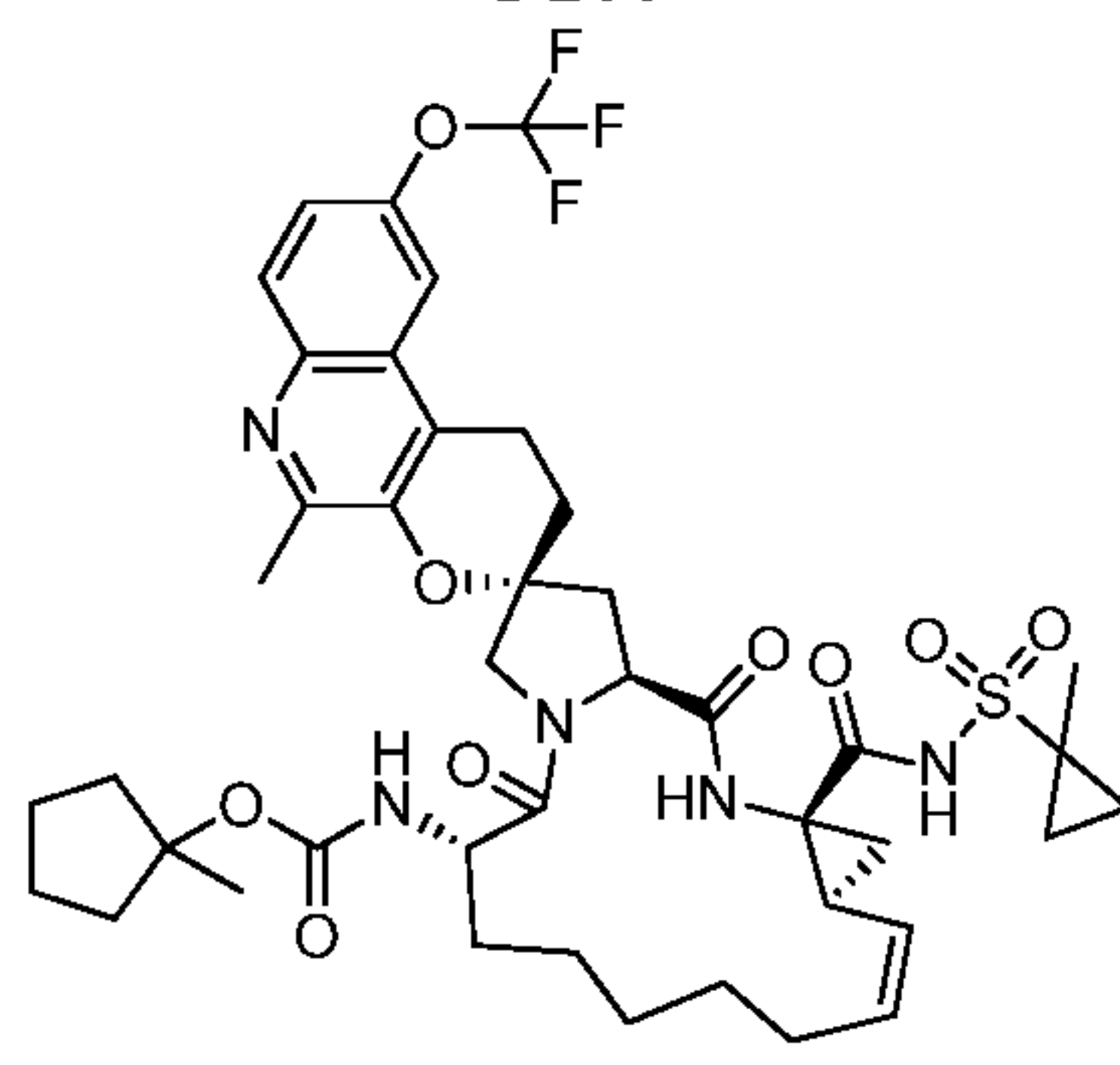
I-206



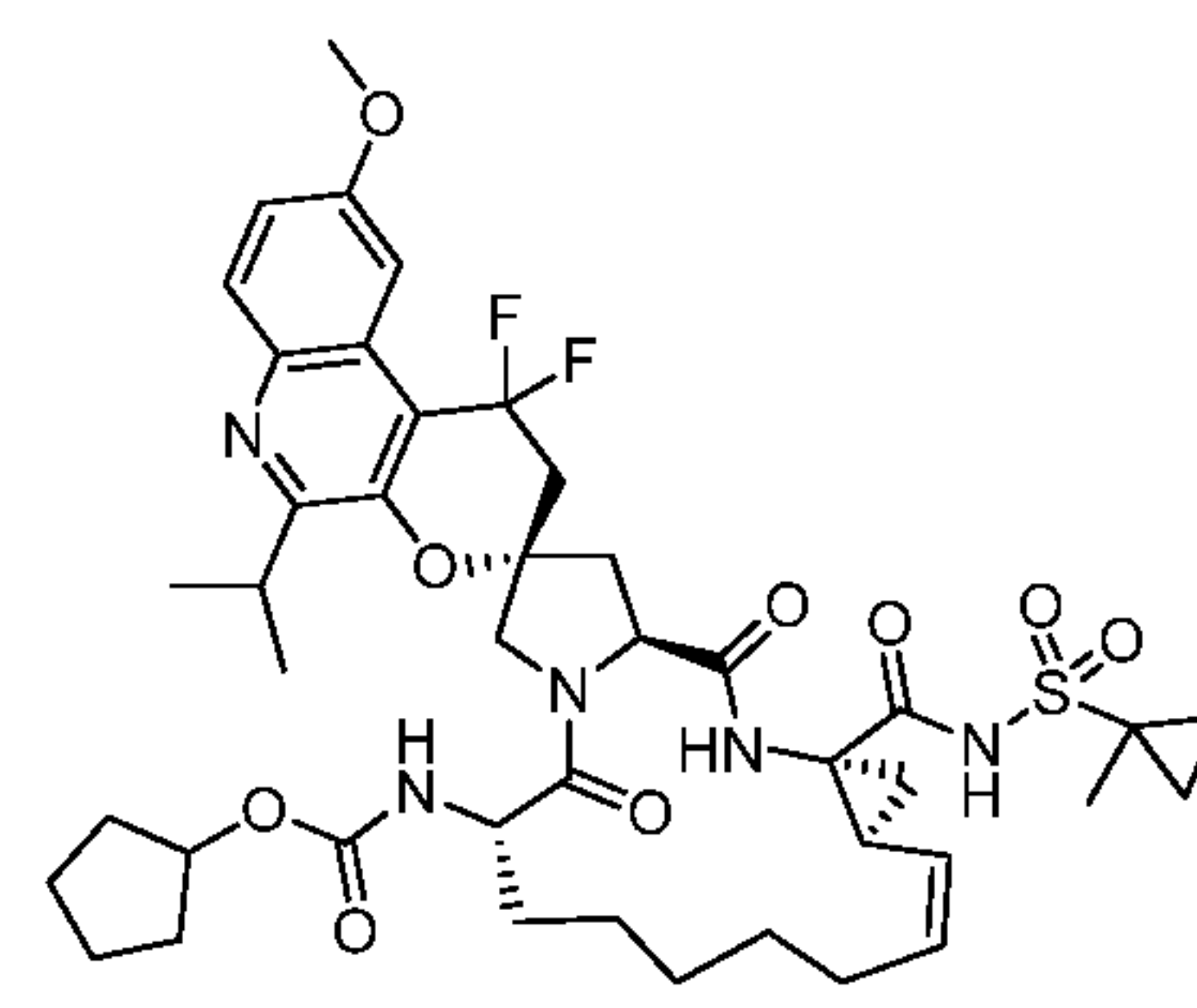
I-207



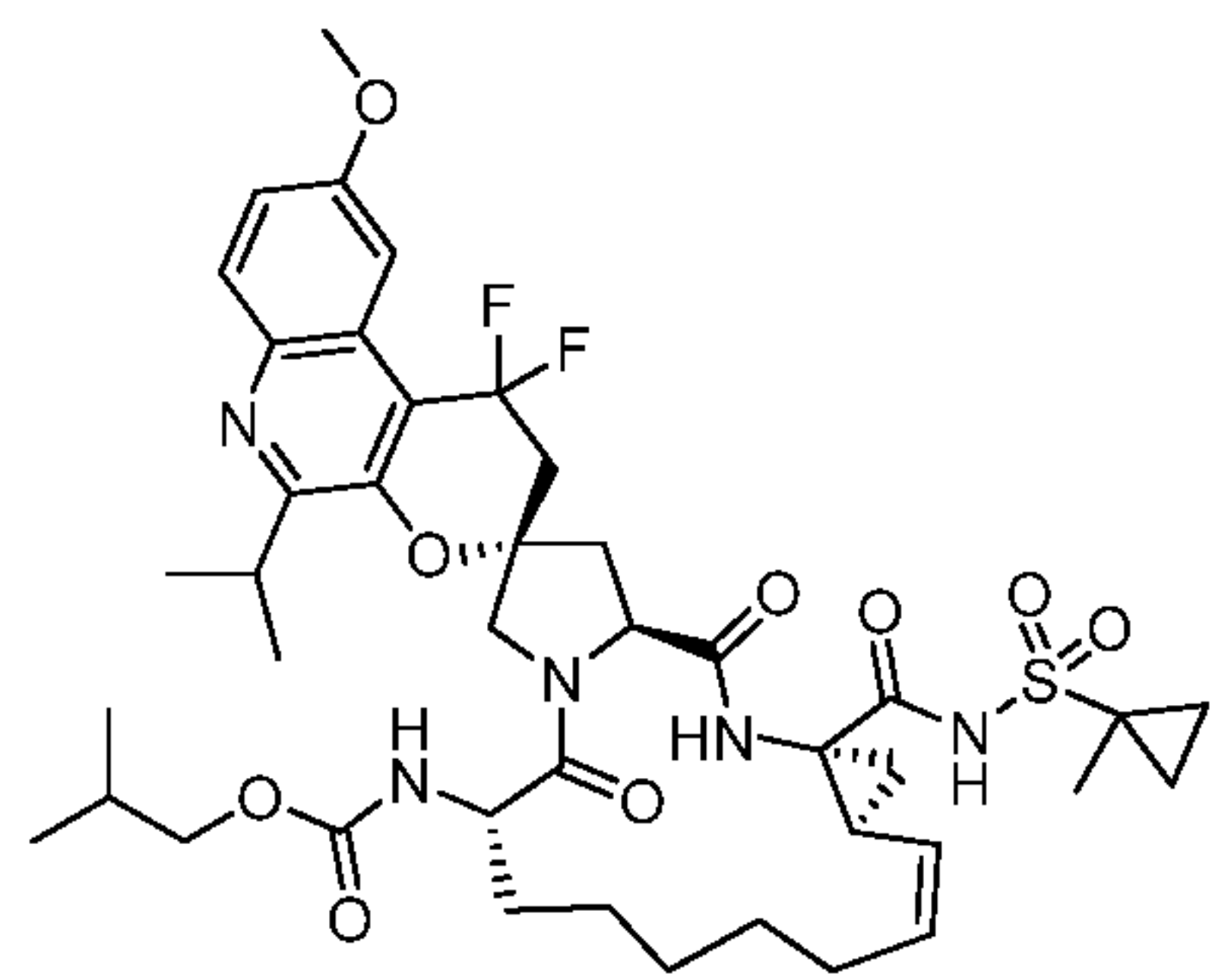
I-208



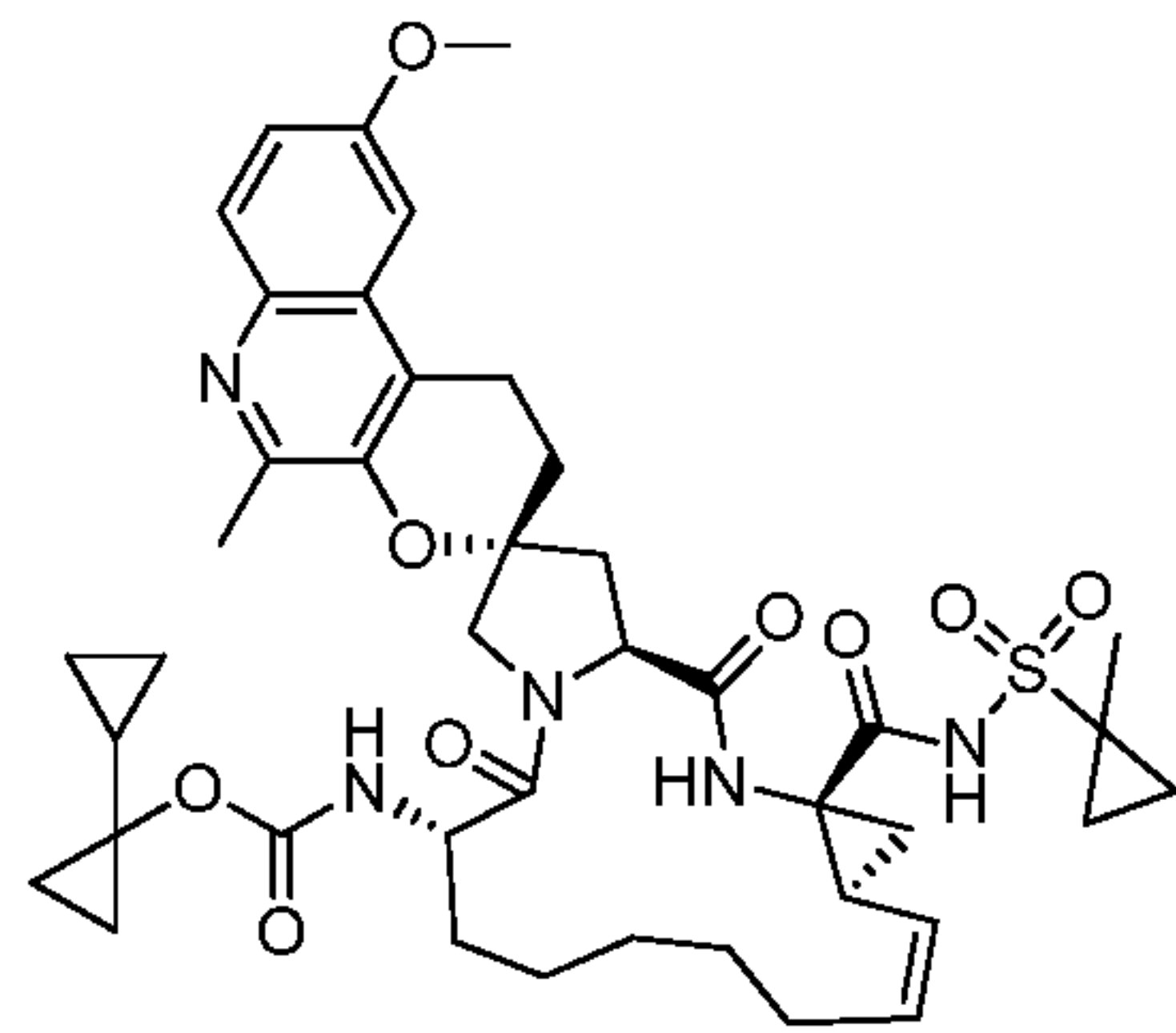
I-209



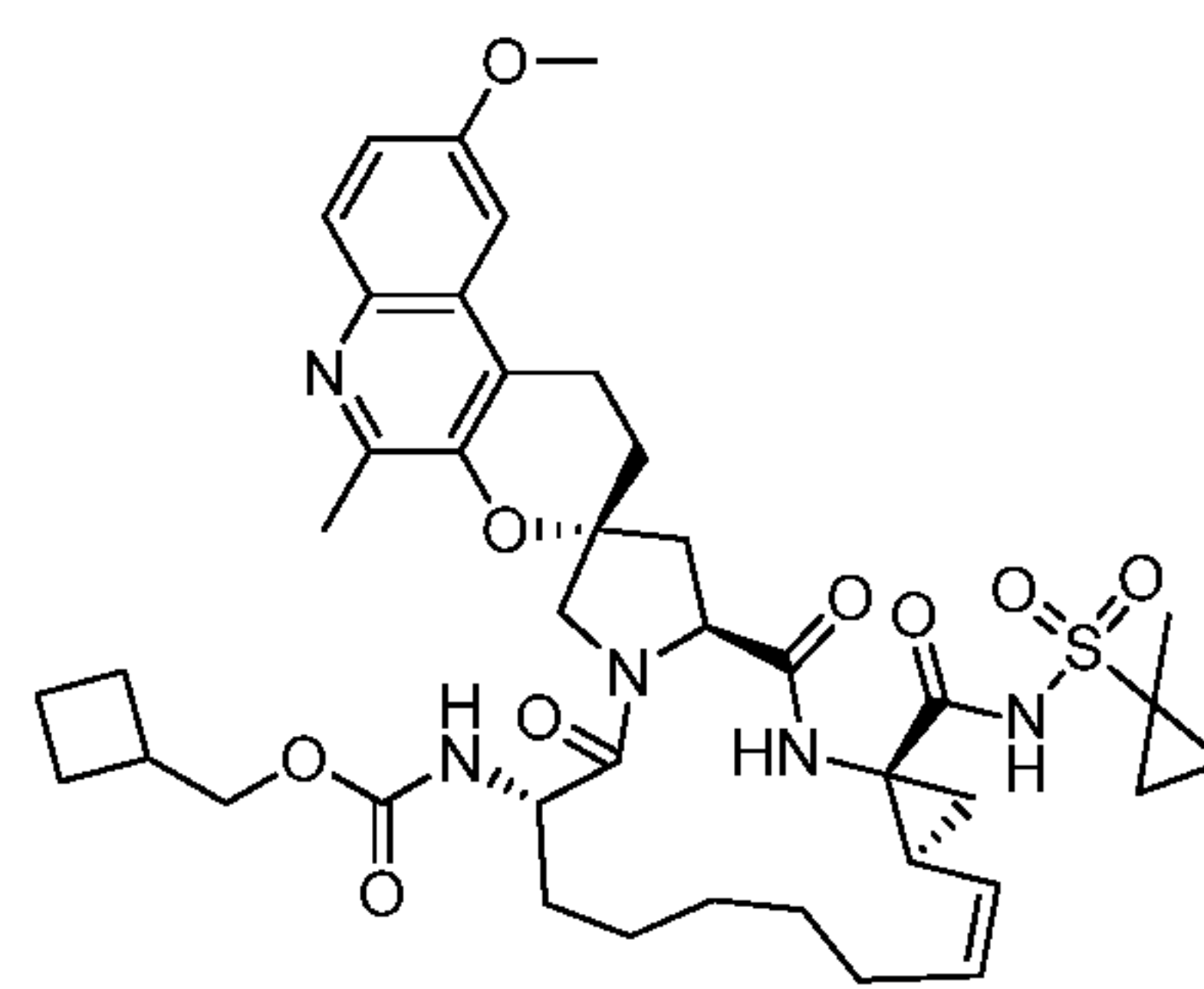
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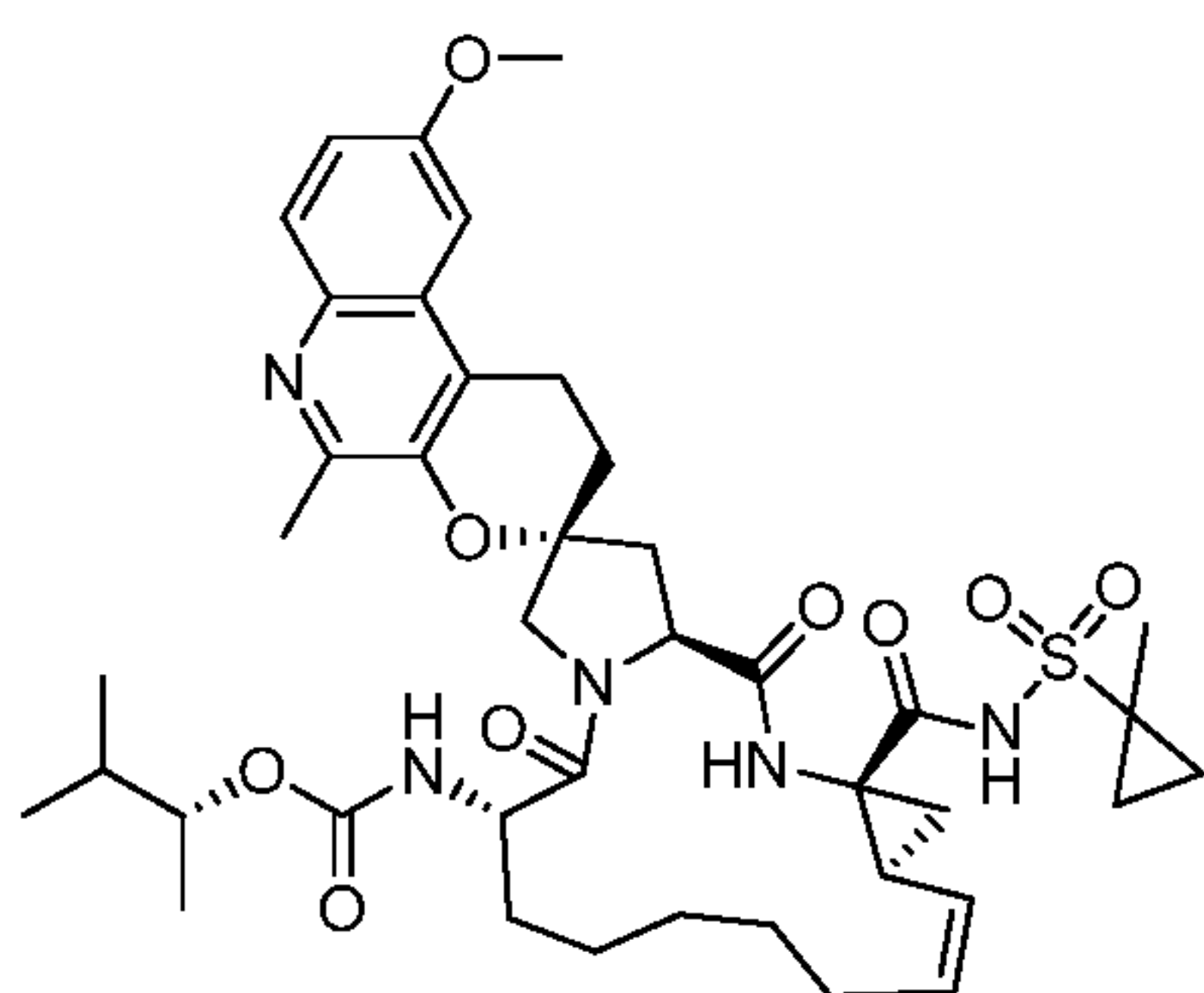
I-211



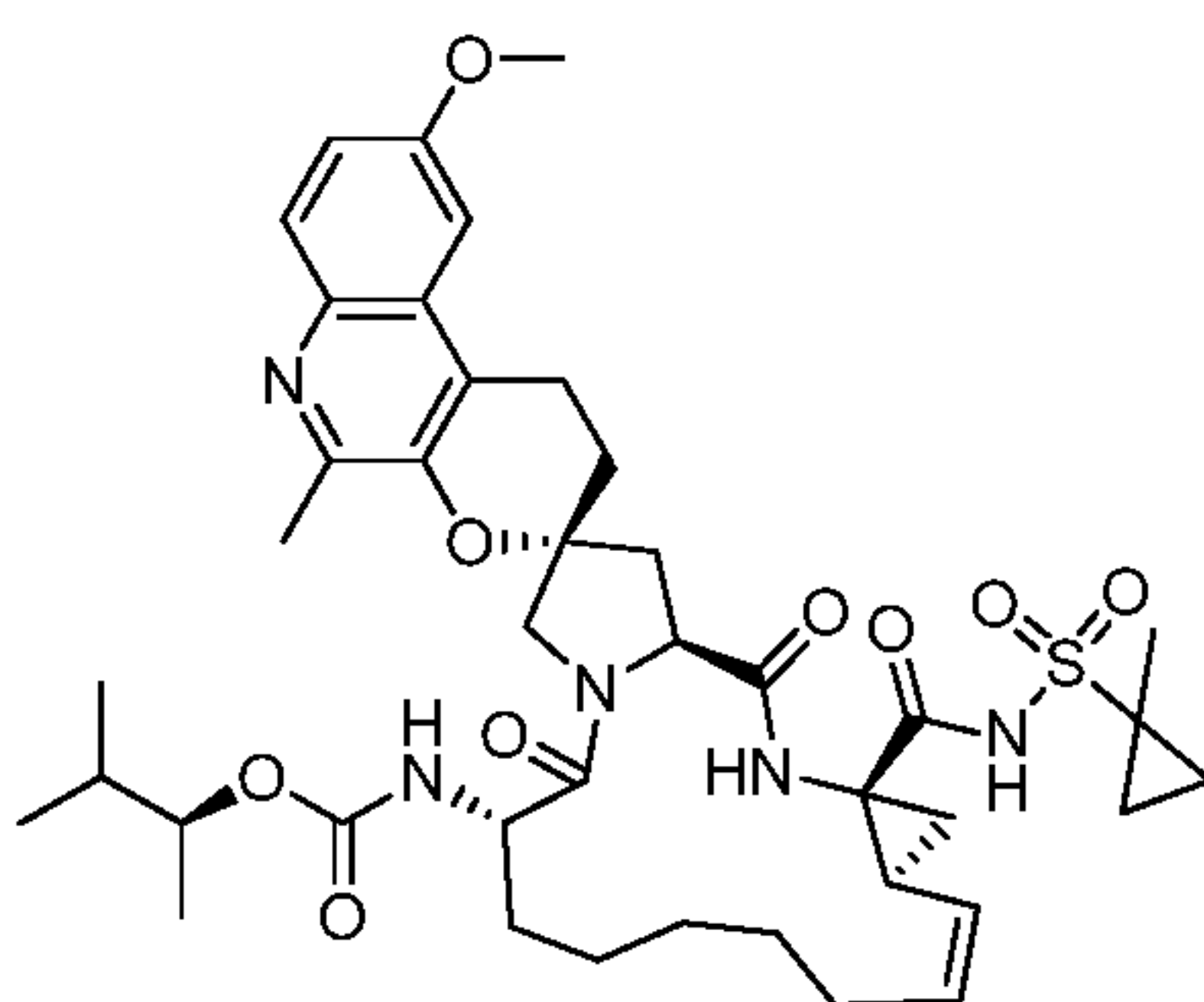
I-212



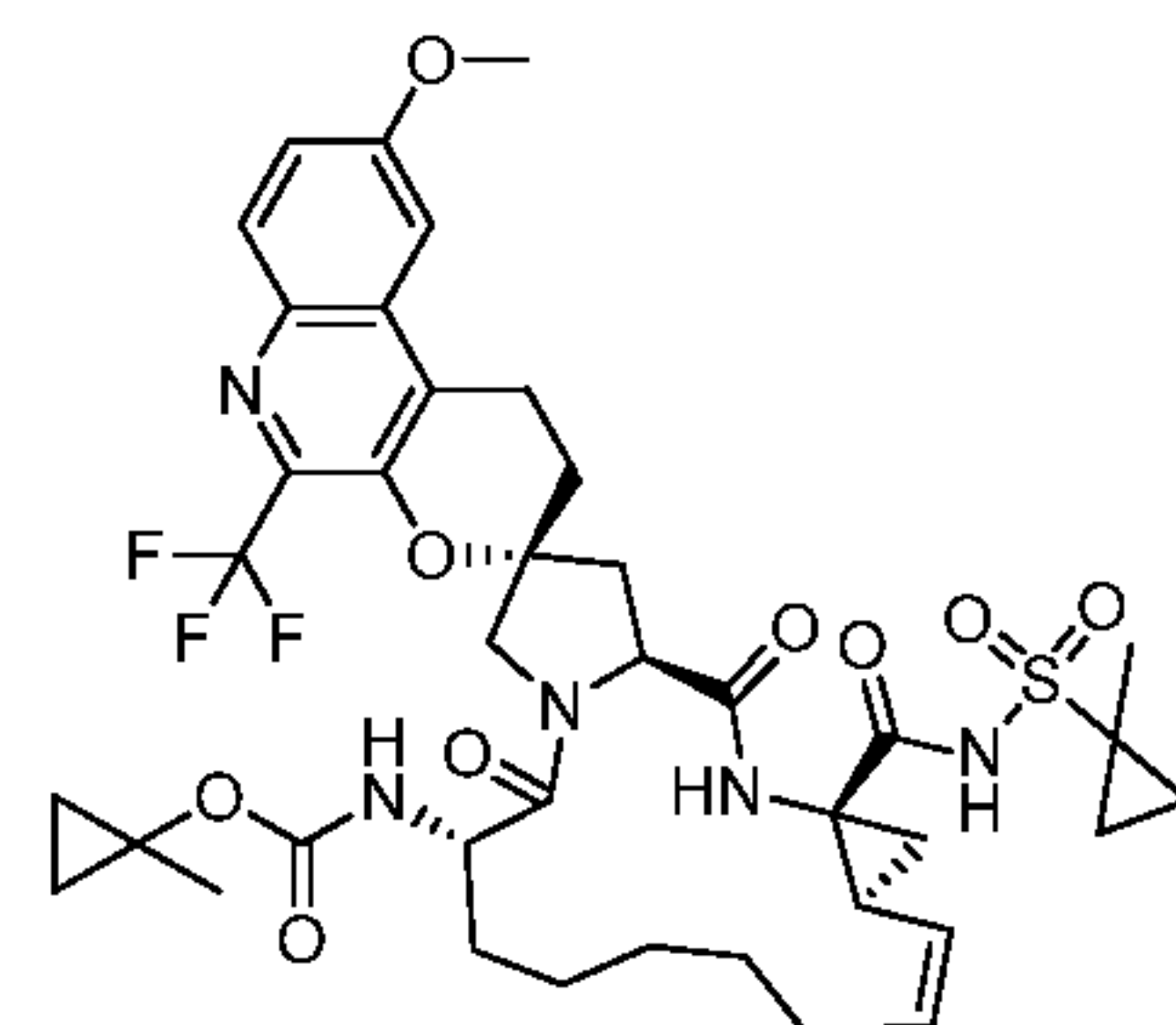
I-213



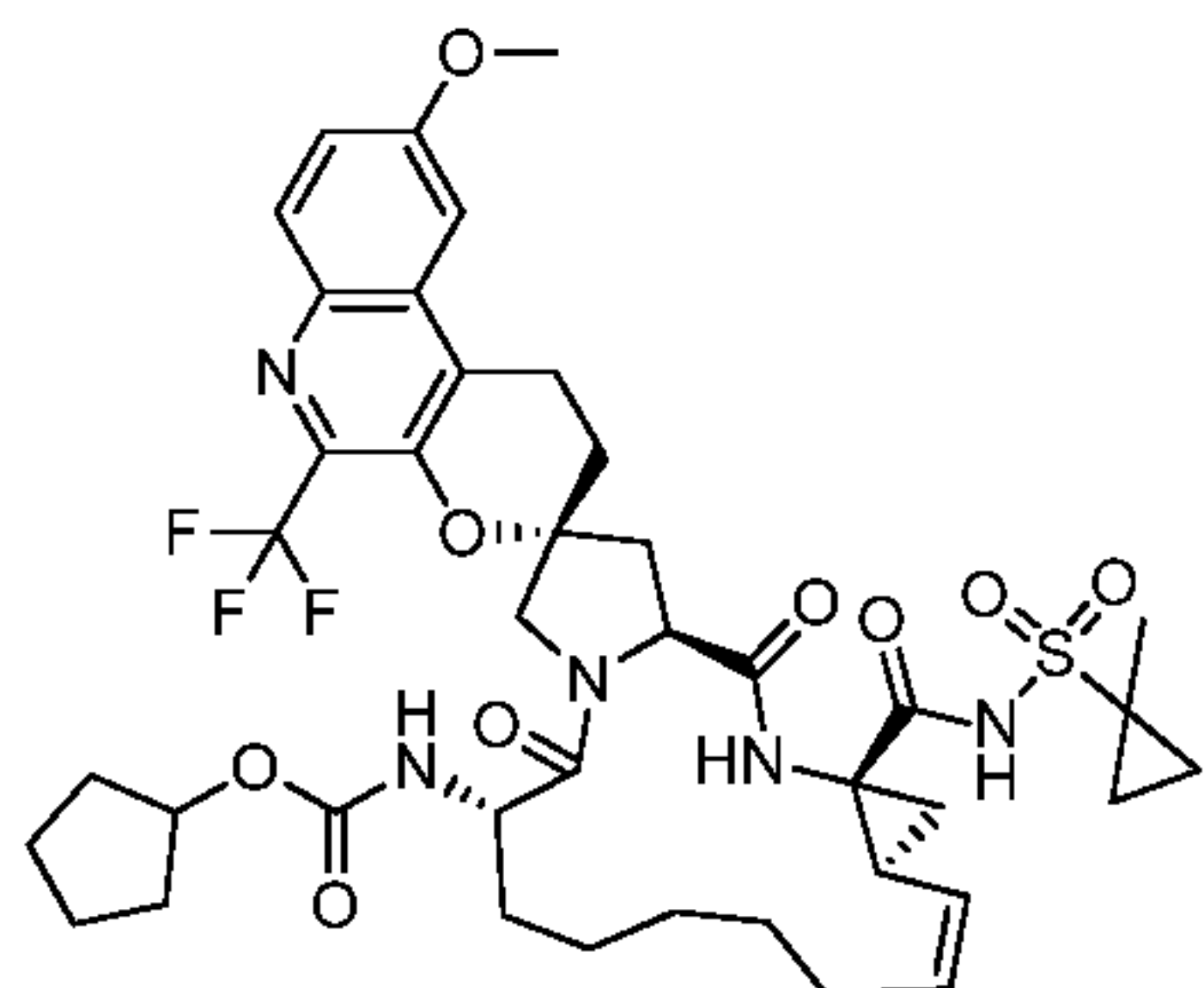
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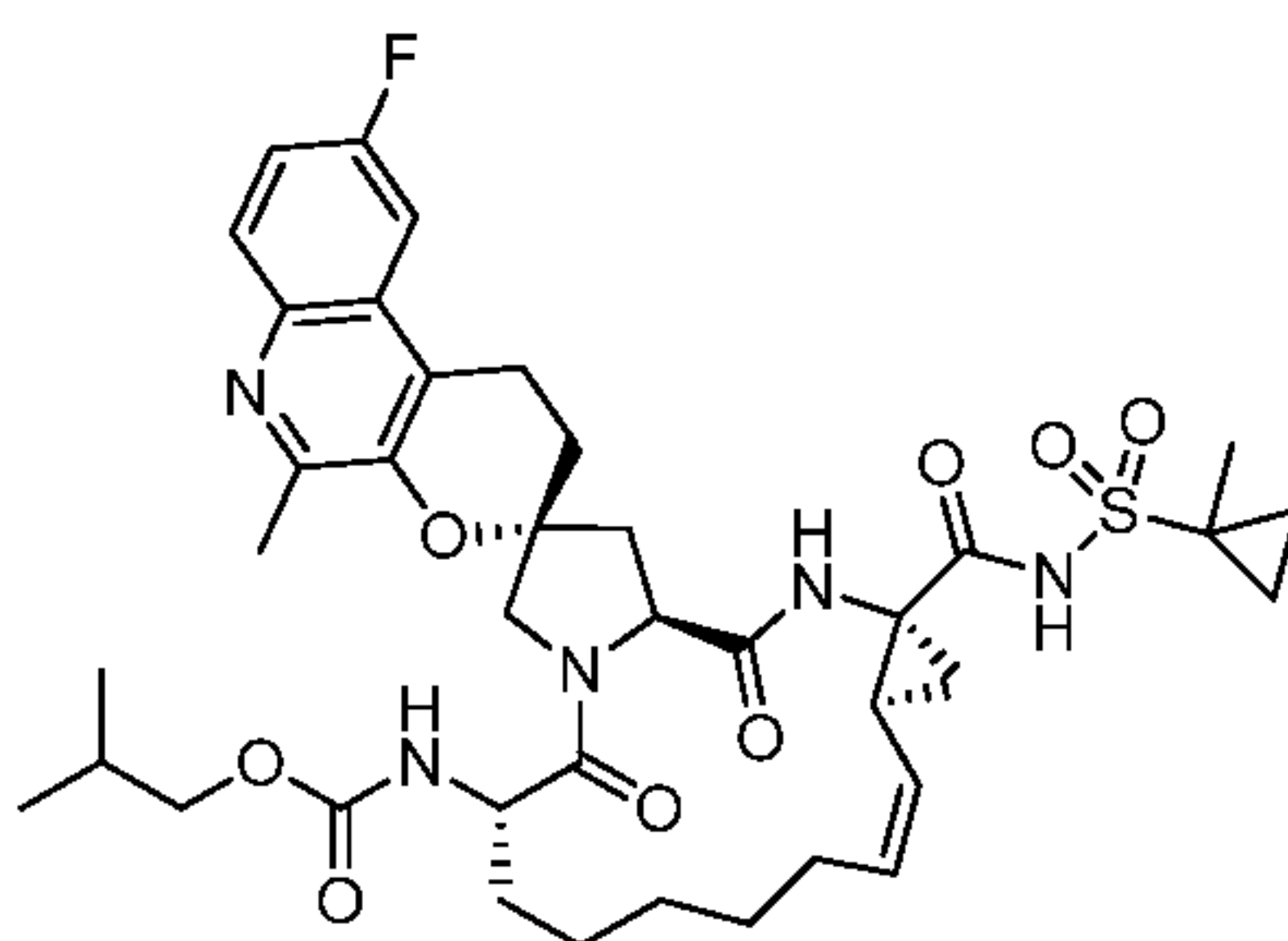
I-215



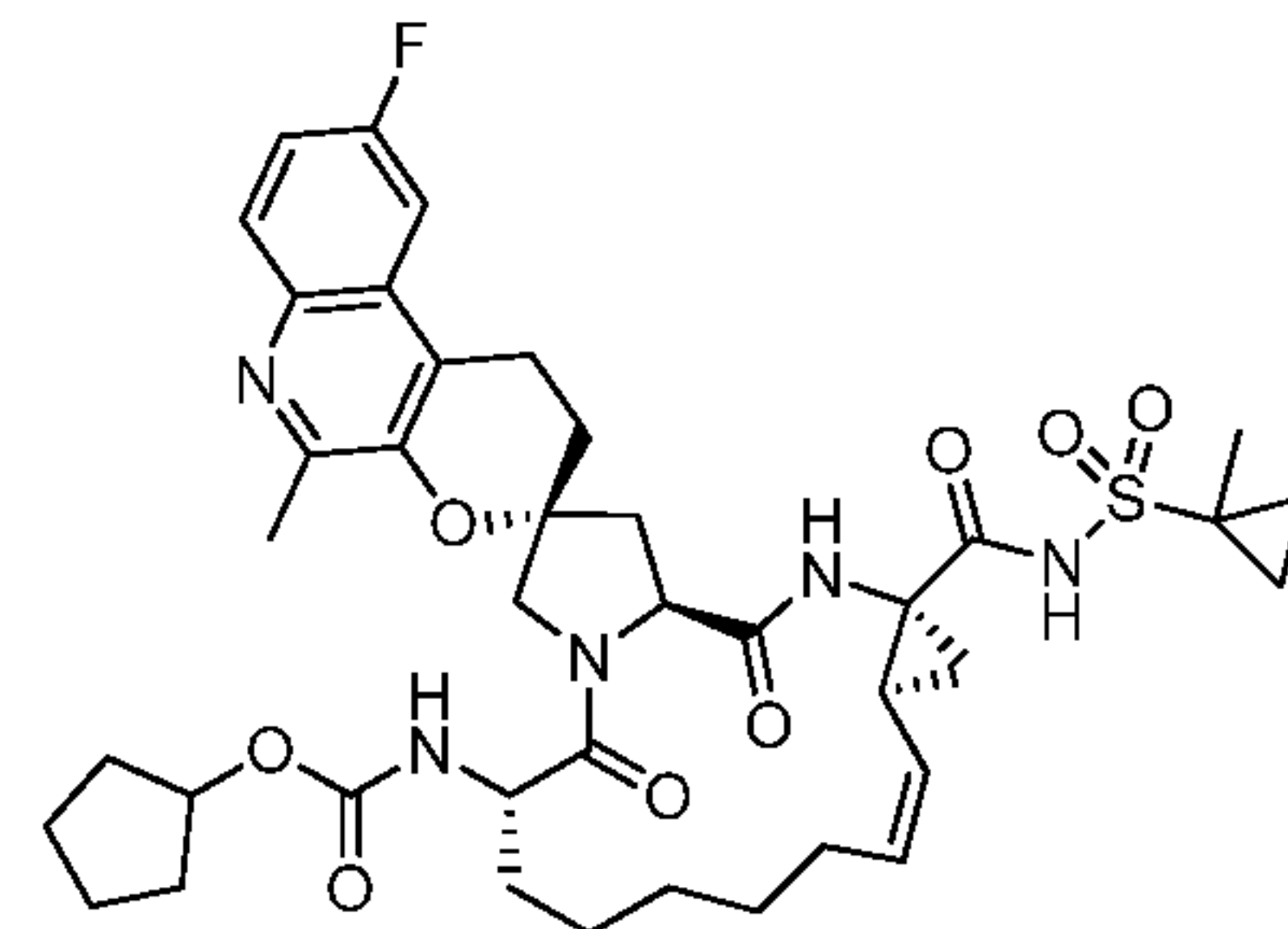
I-216



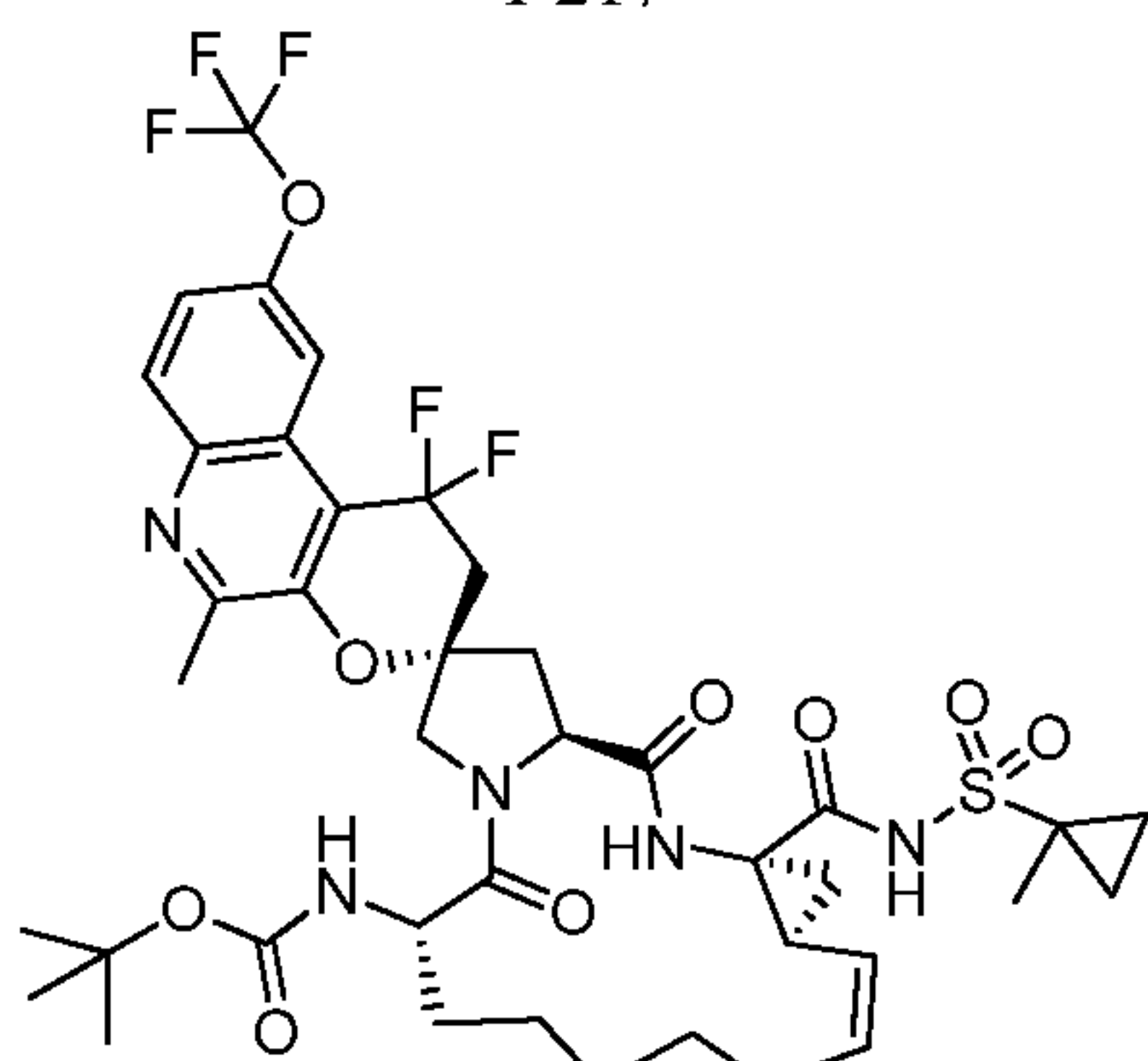
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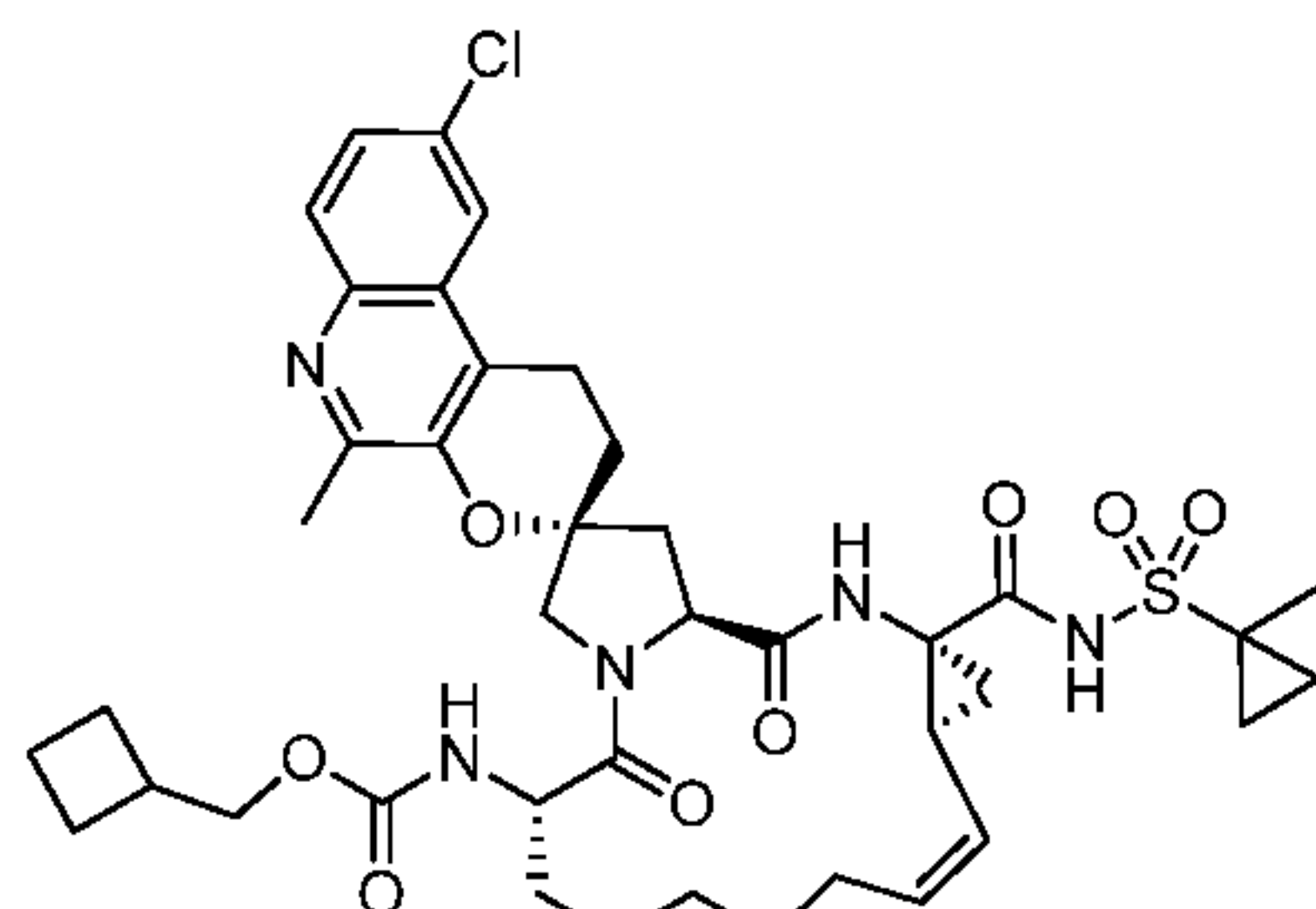
I-218



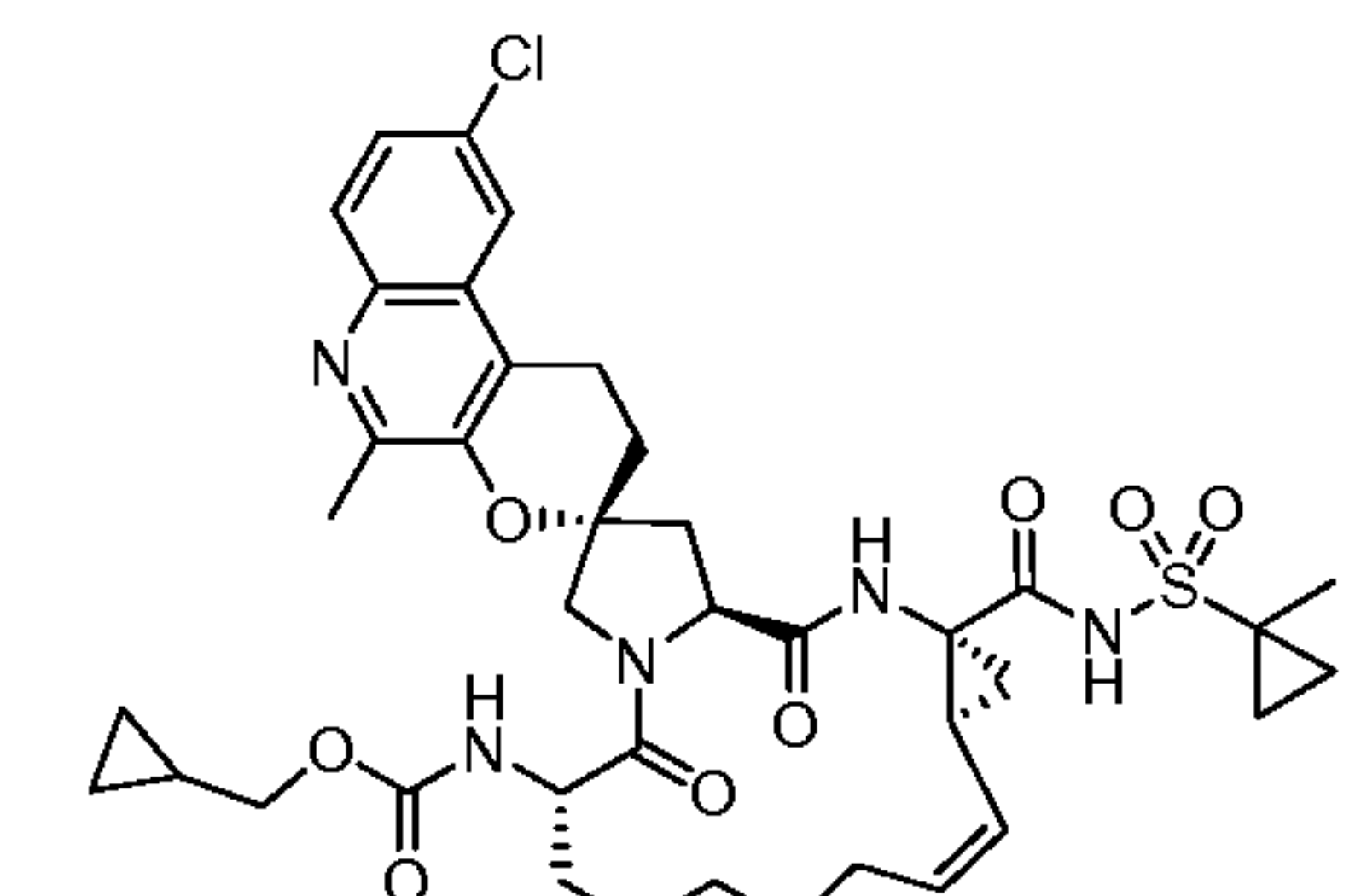
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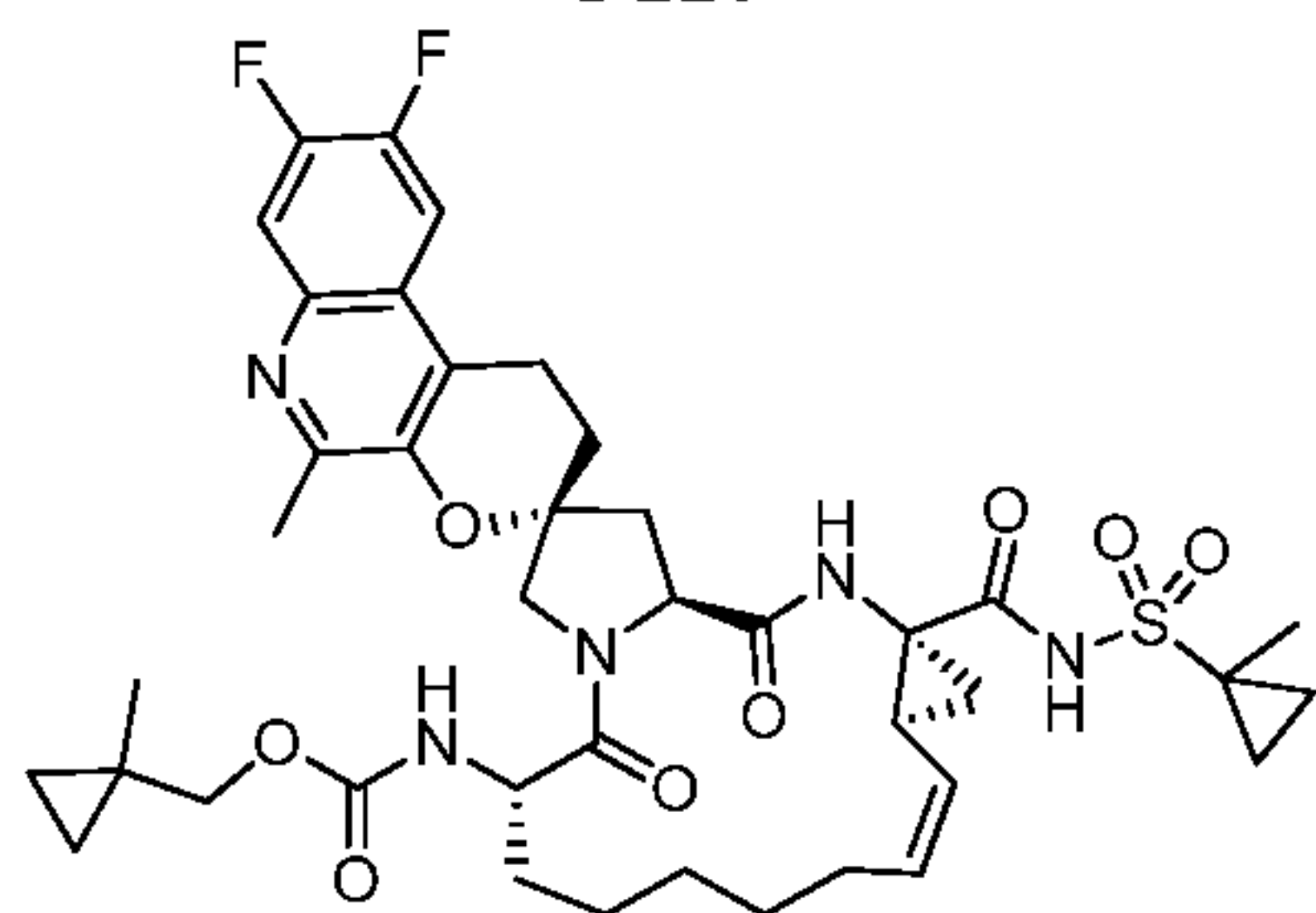
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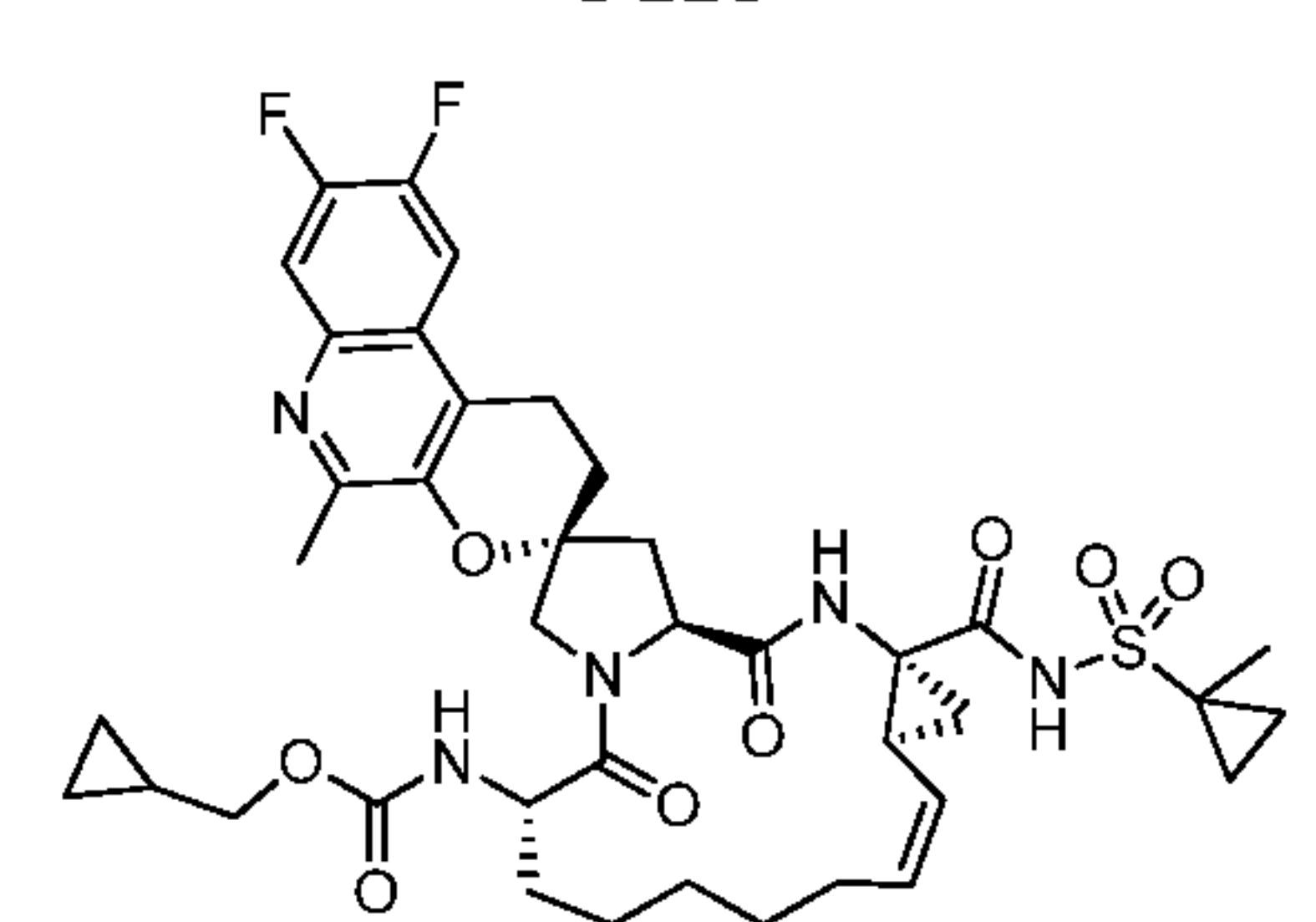
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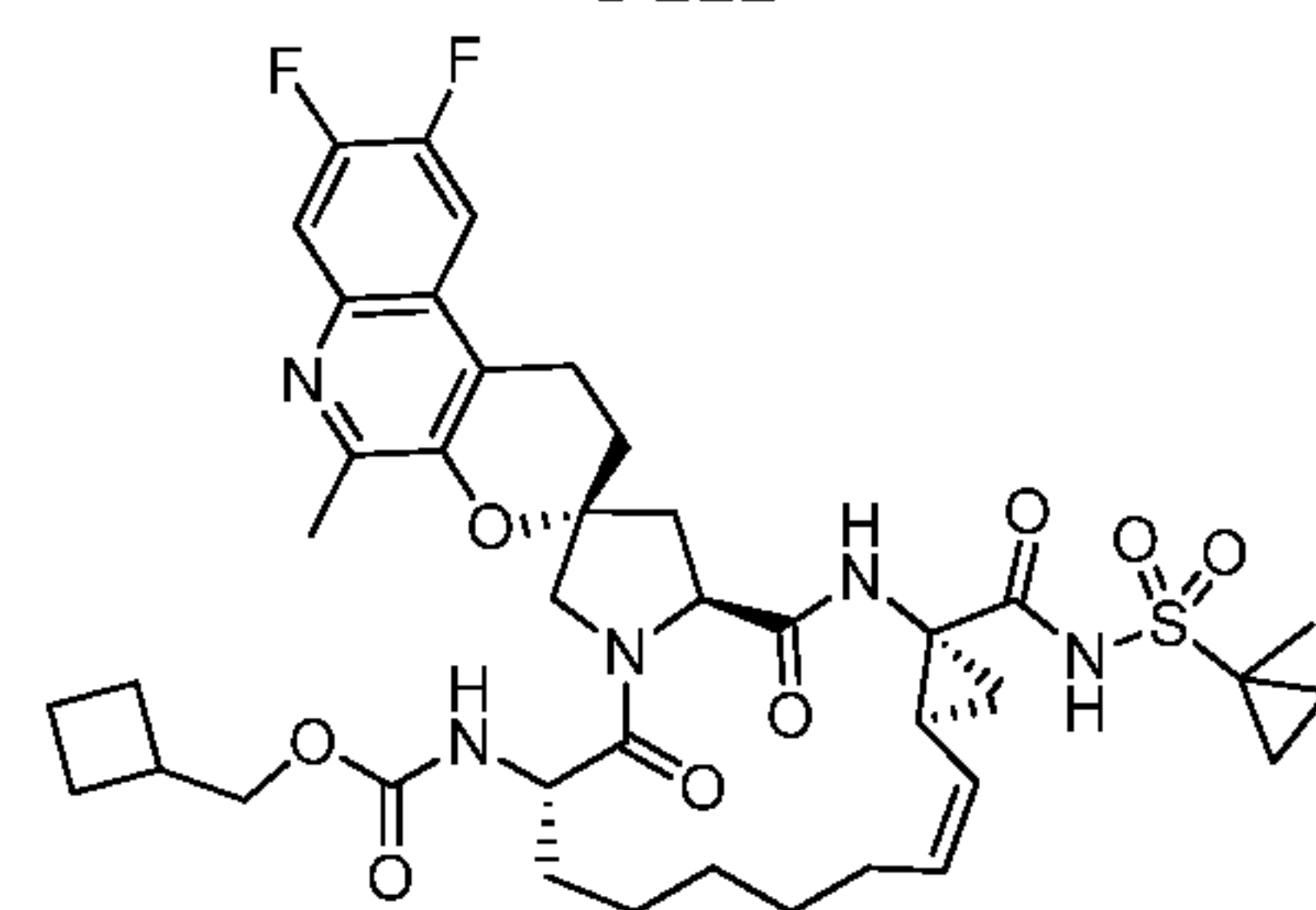
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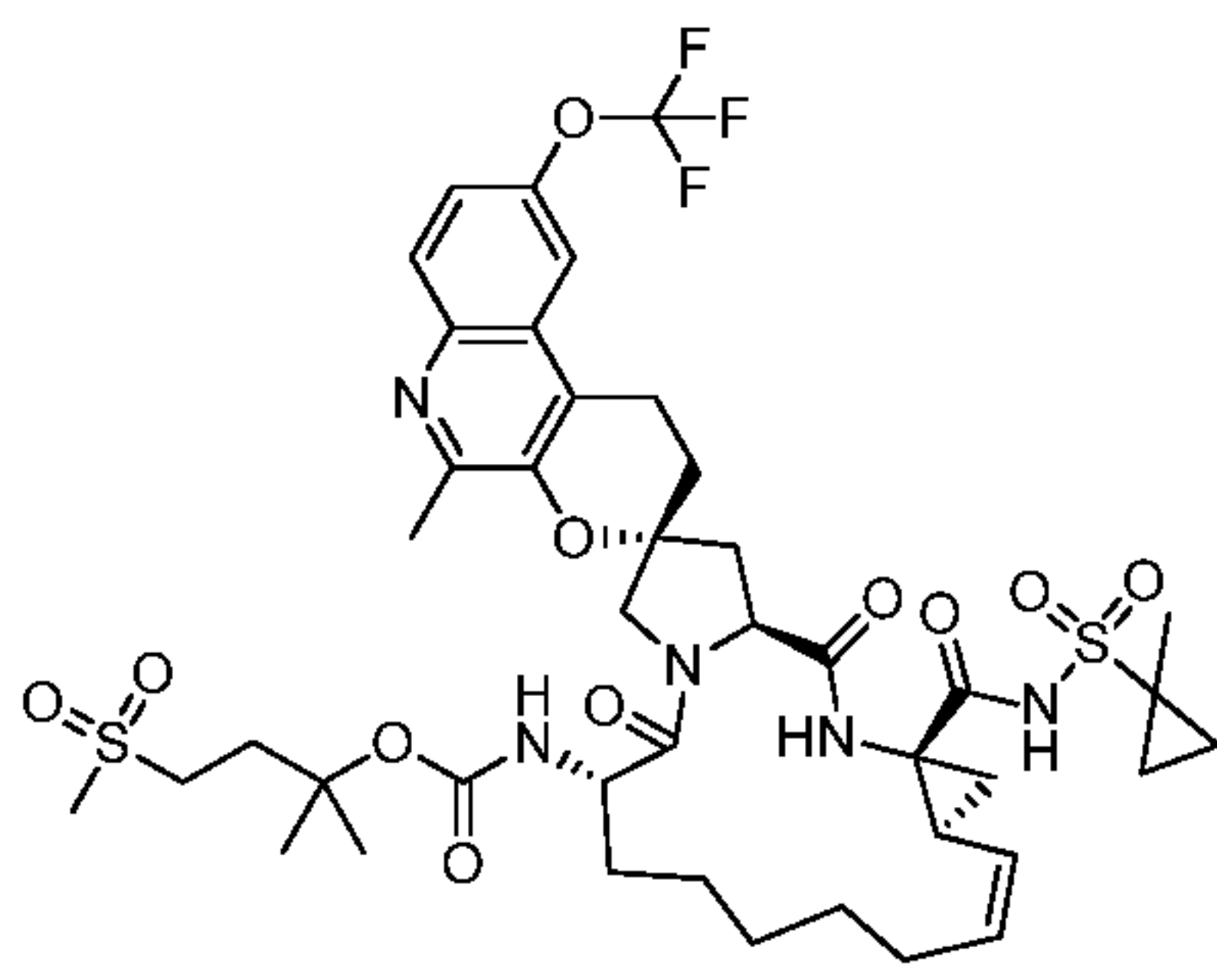
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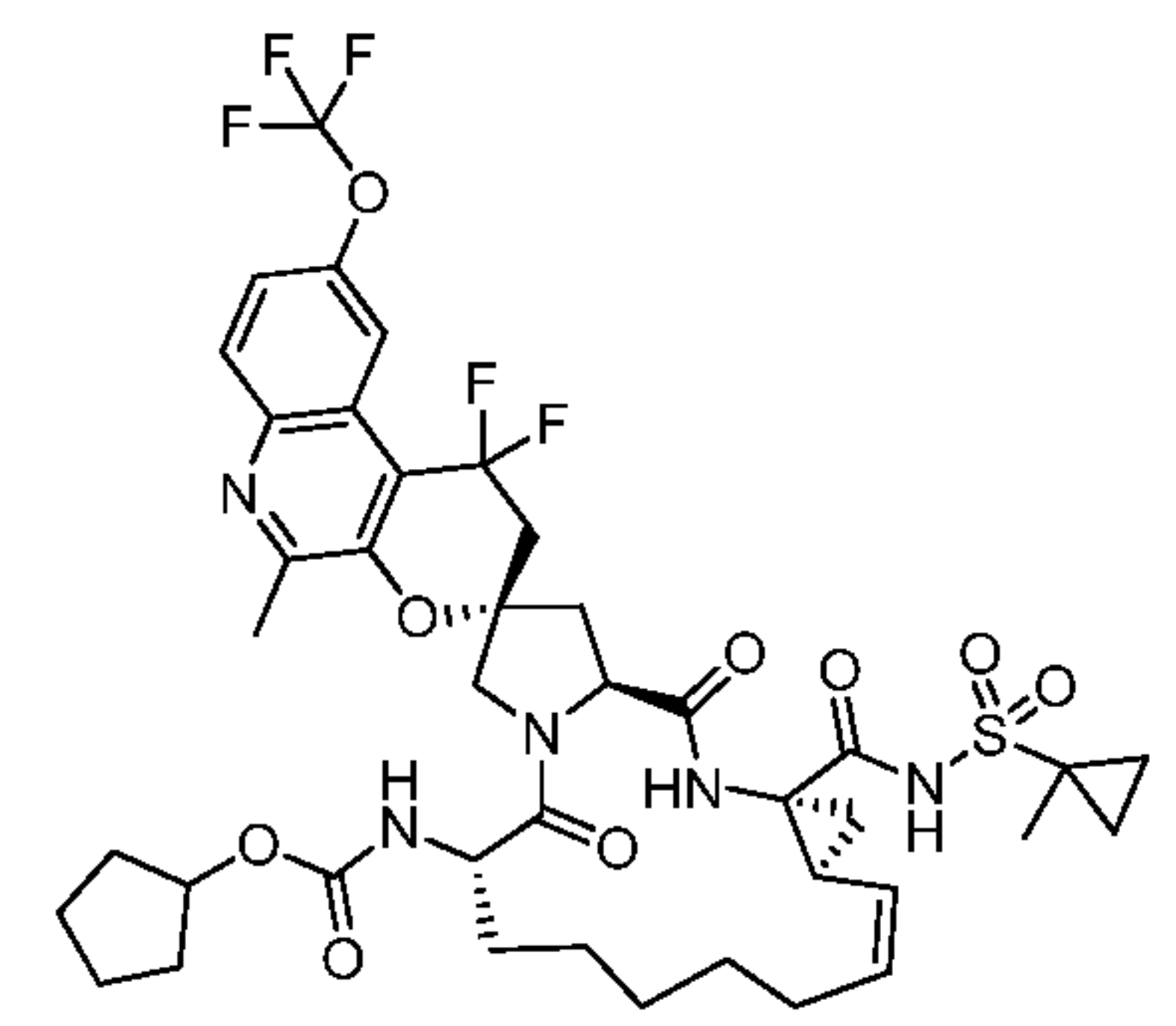
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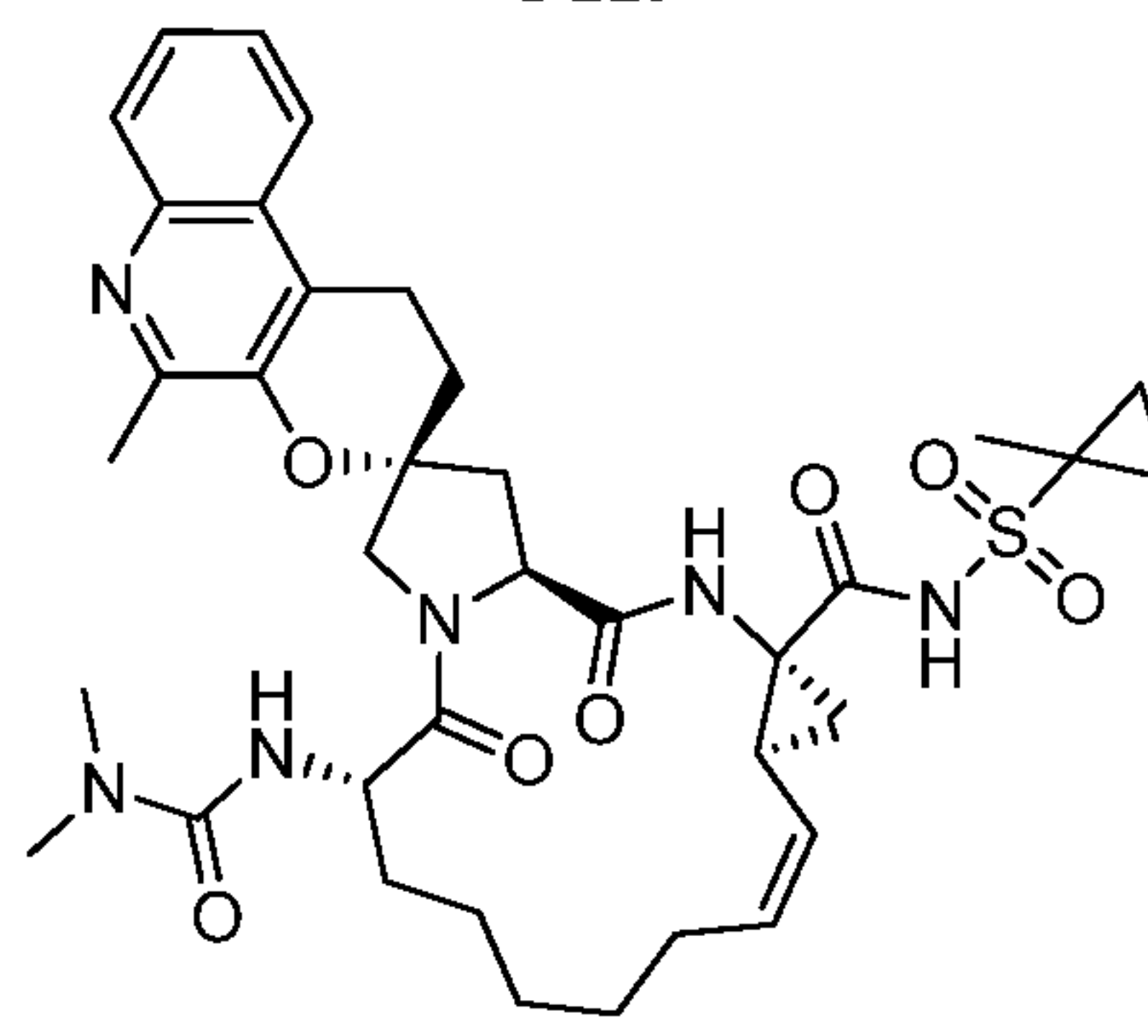
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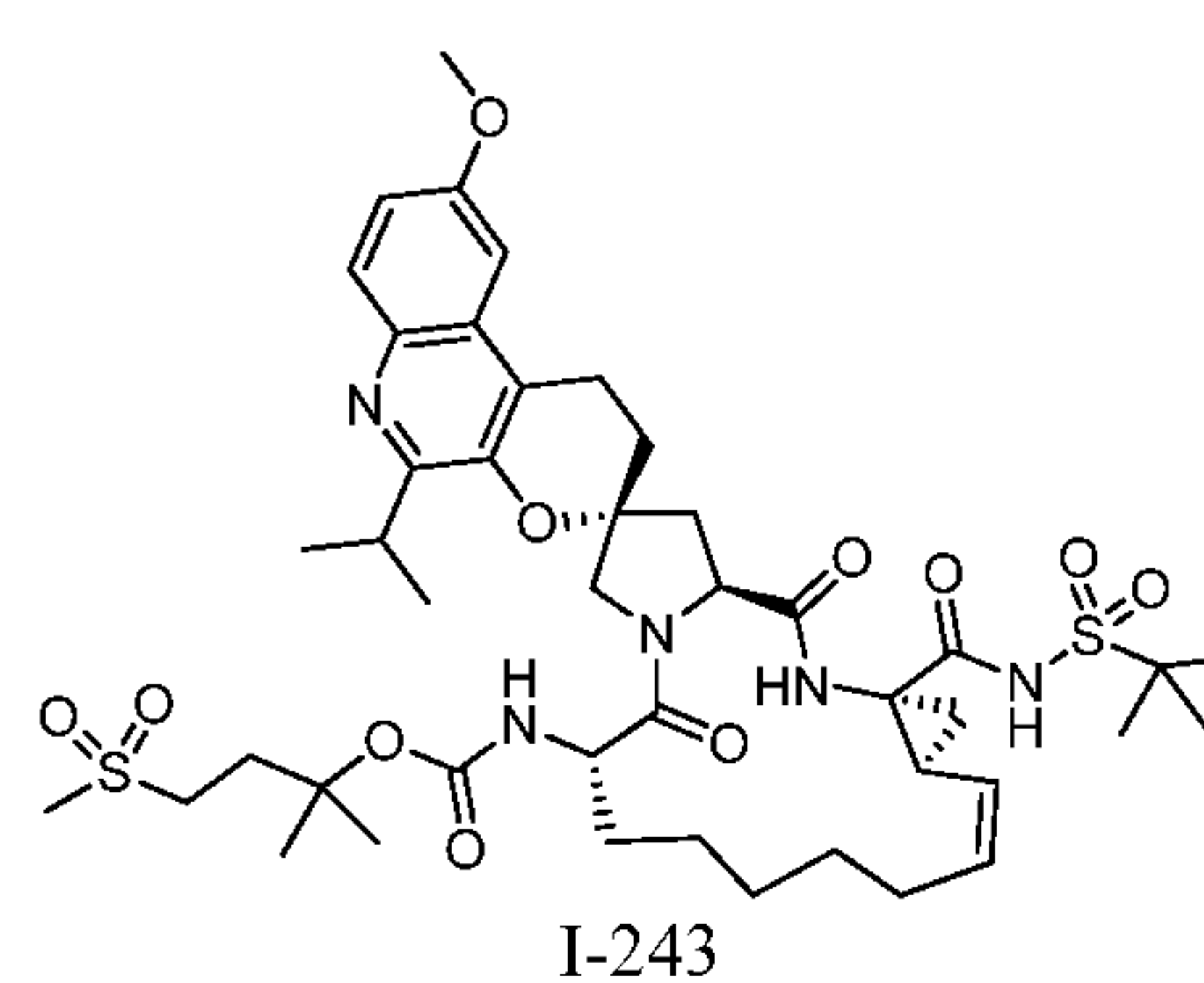
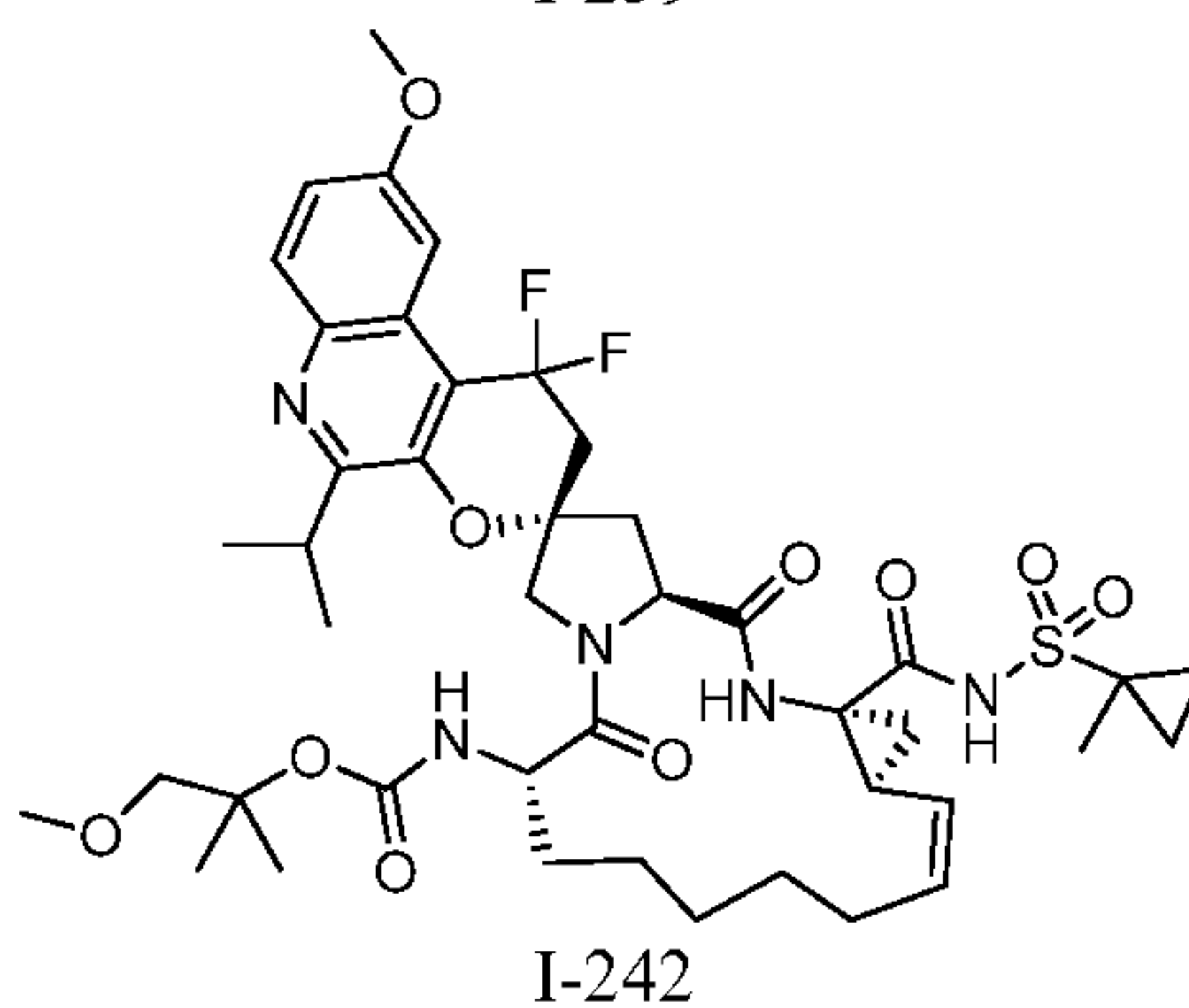
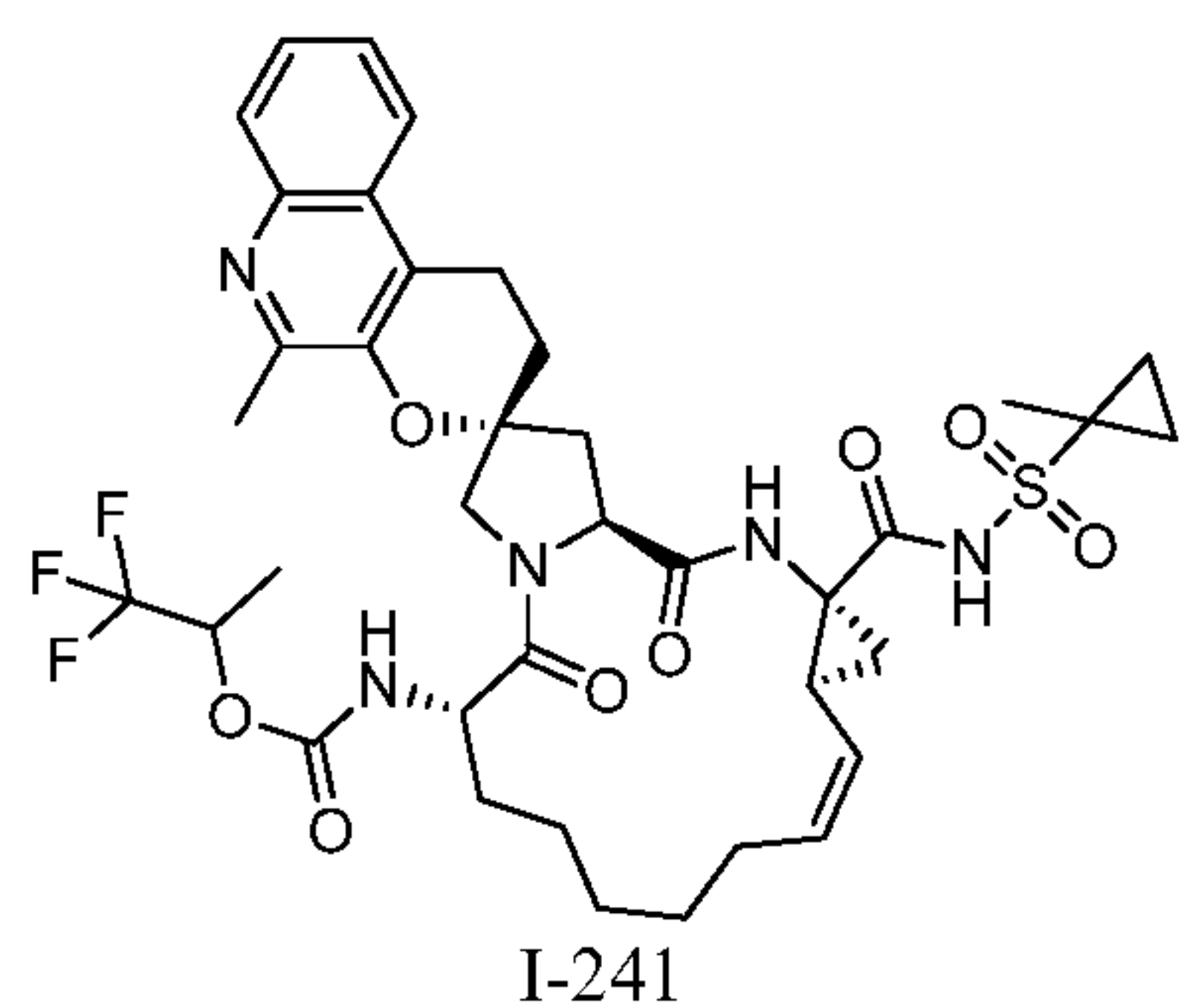
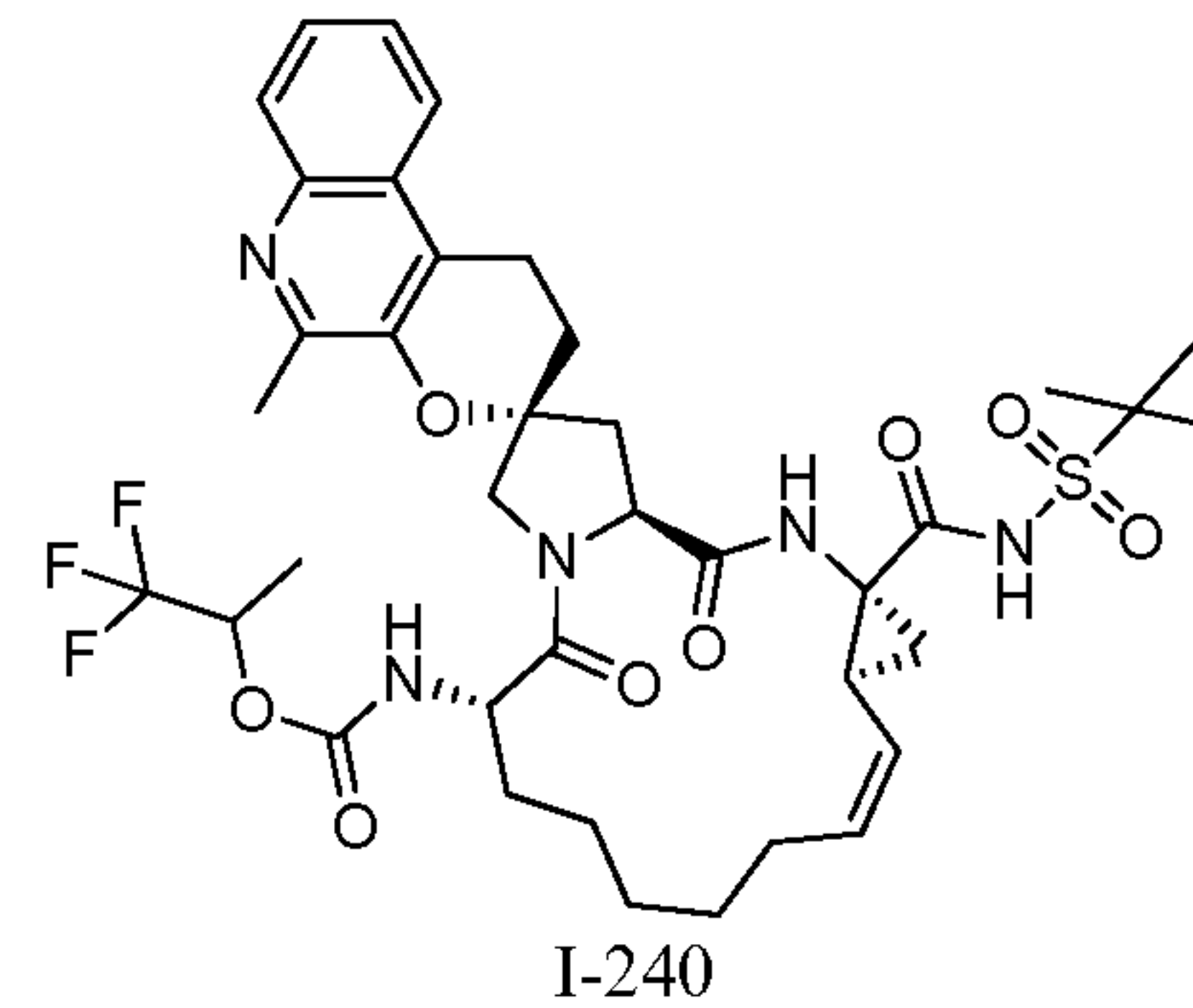
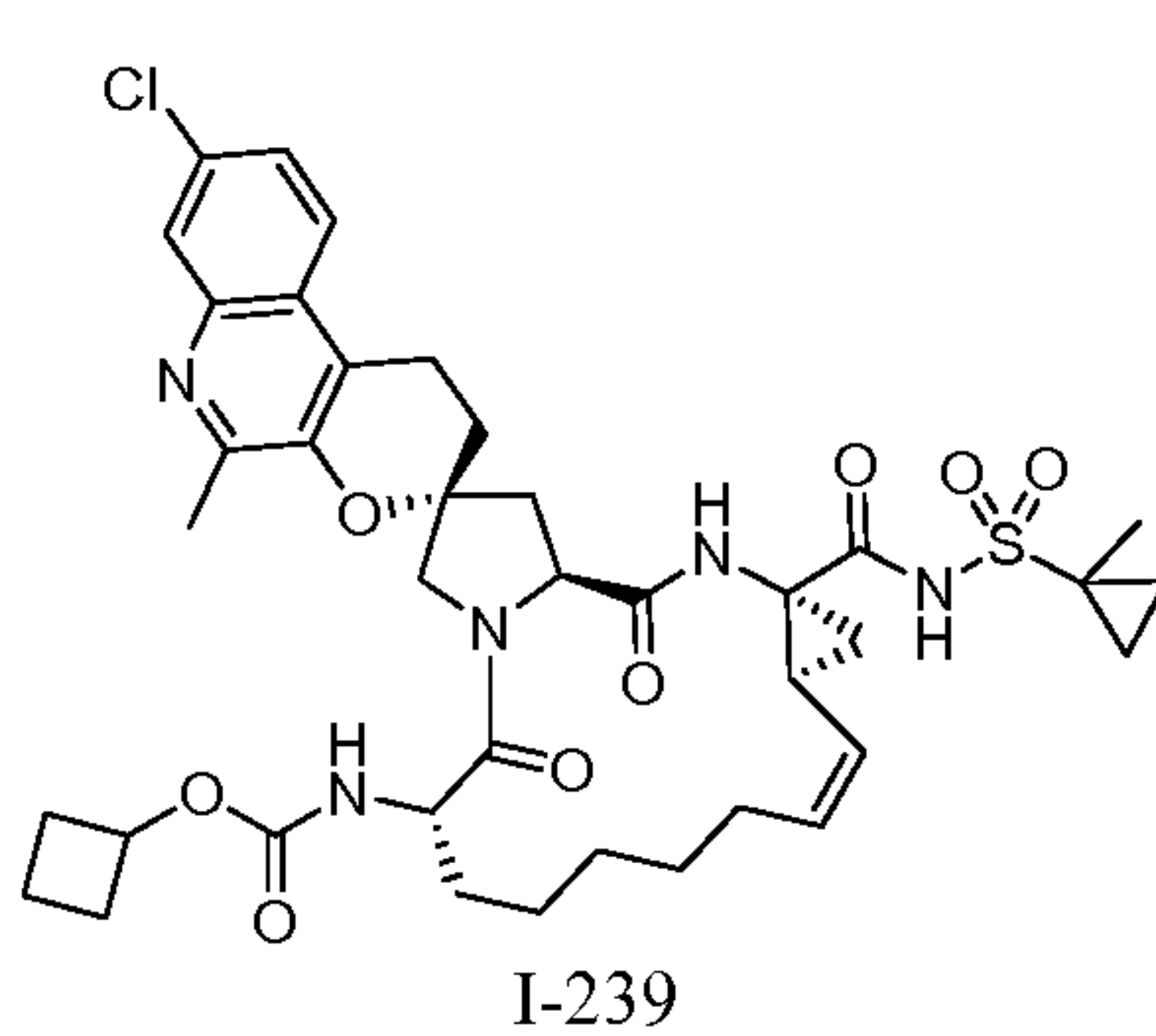
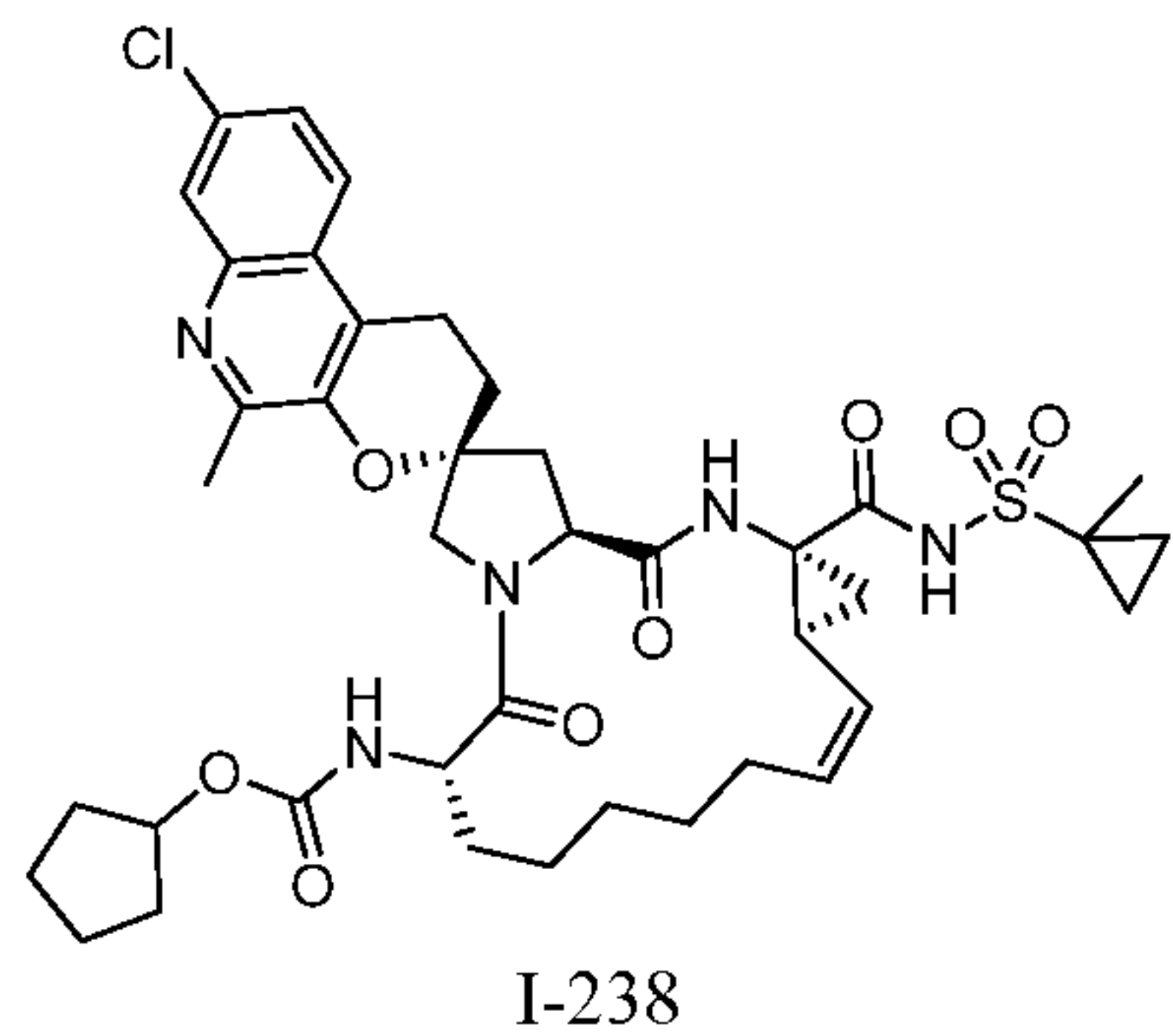
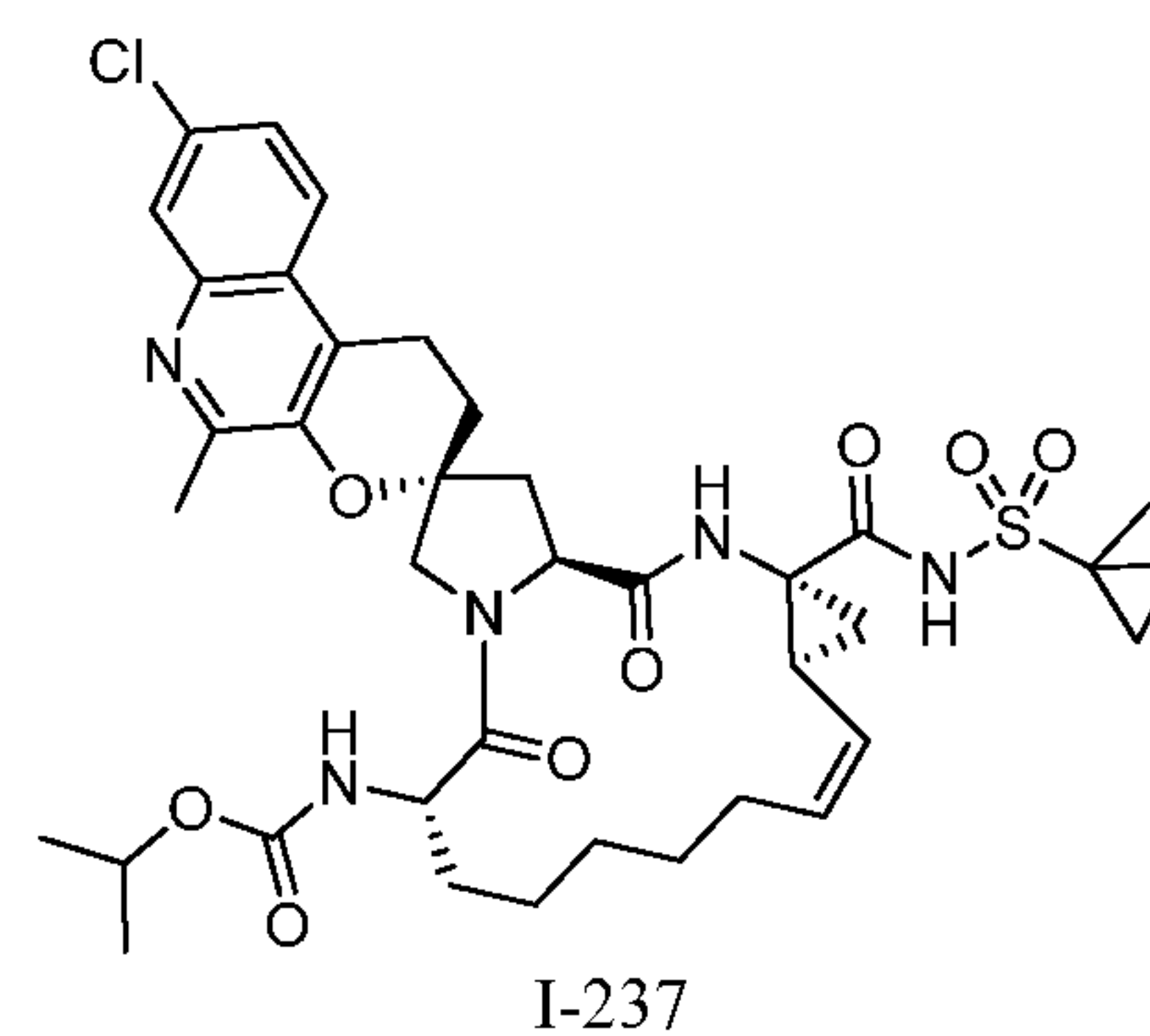
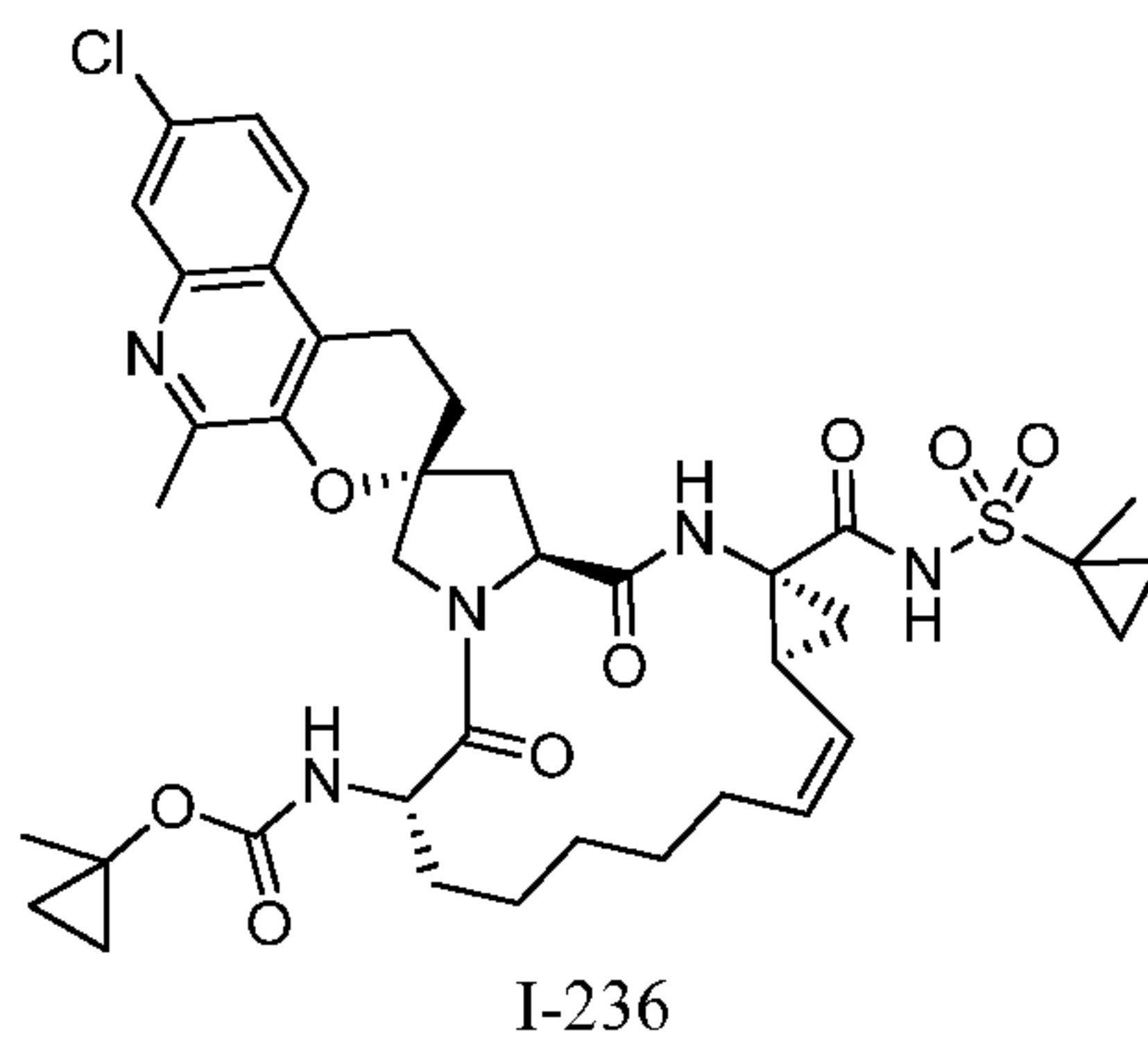
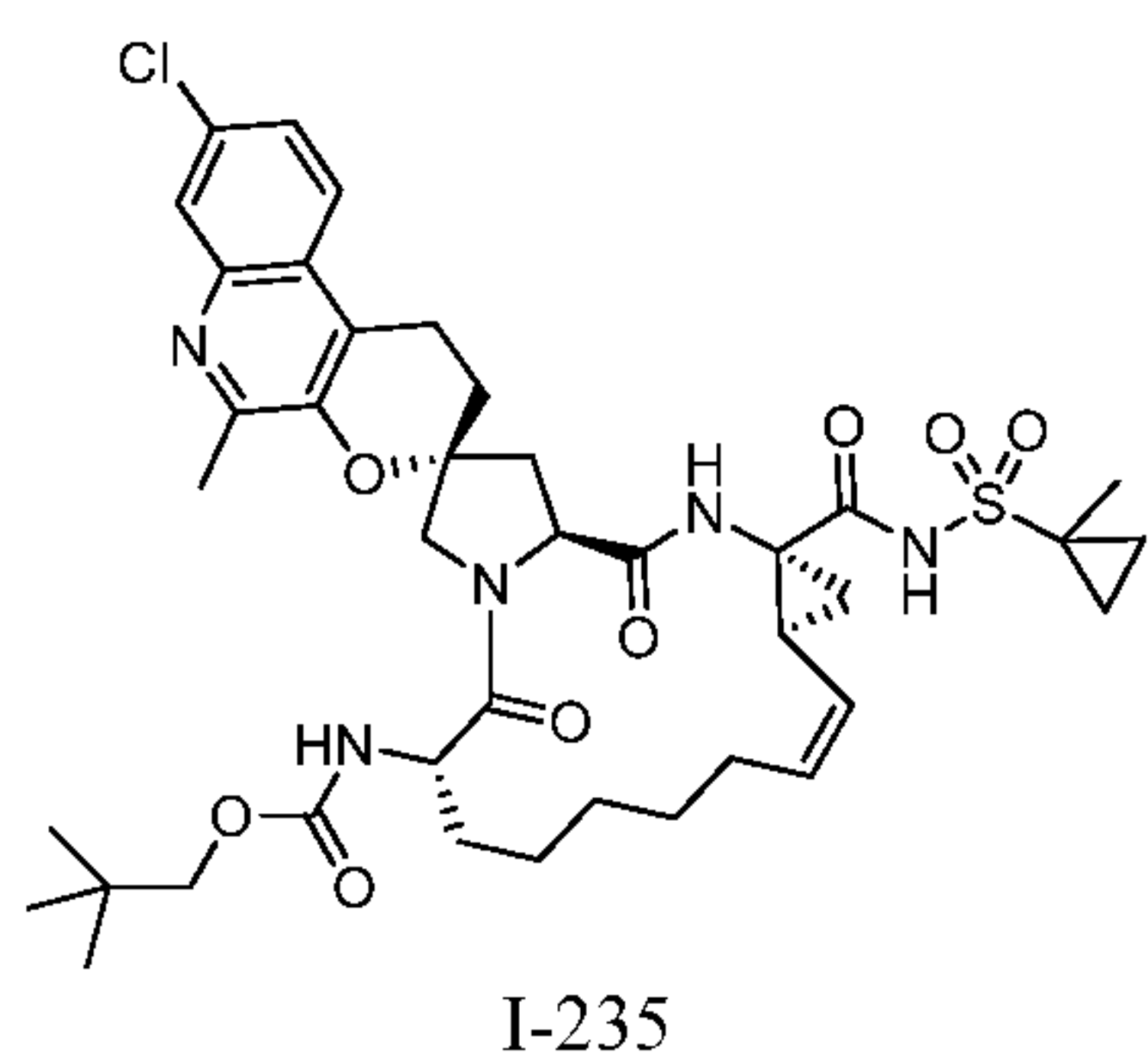
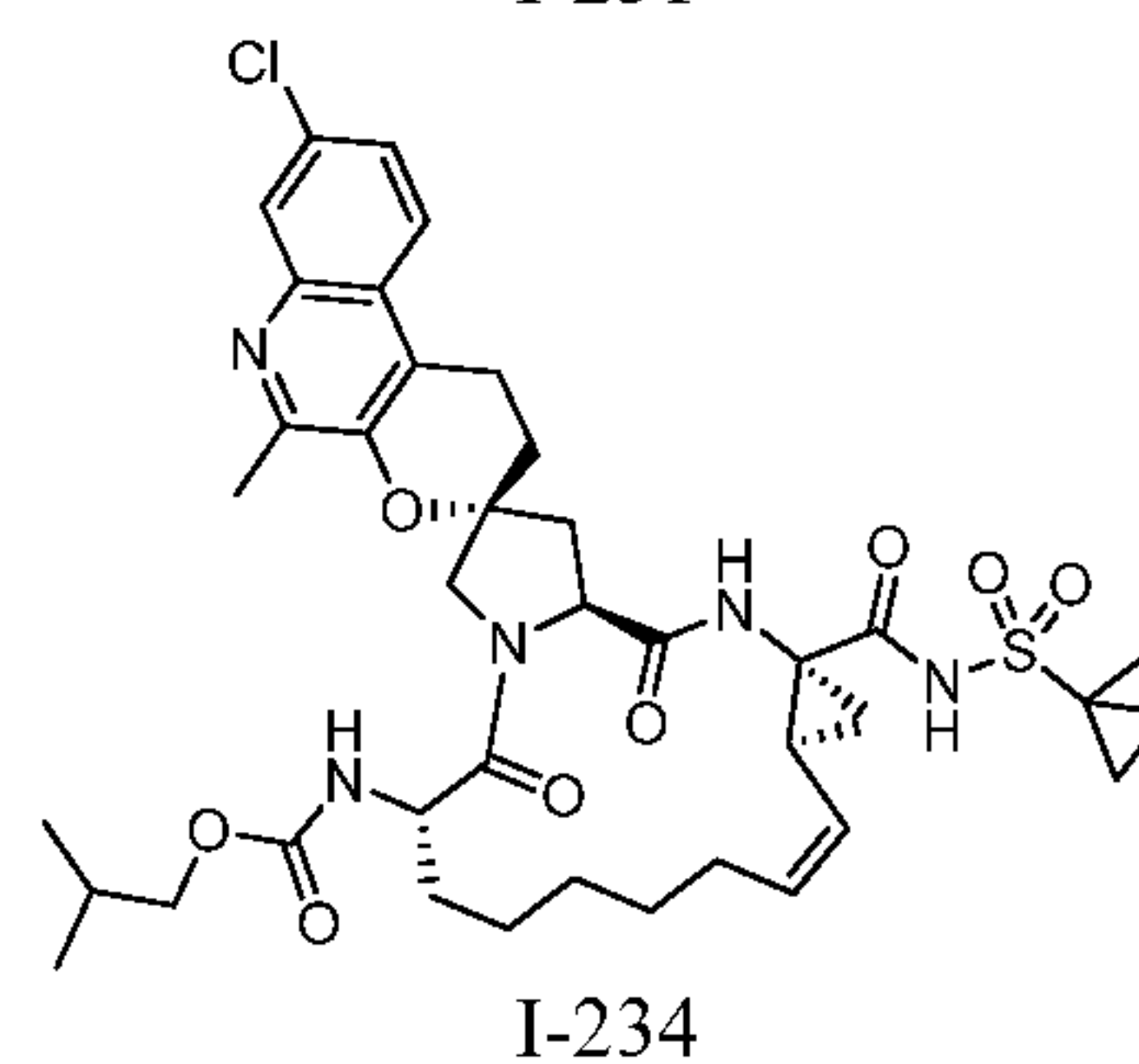
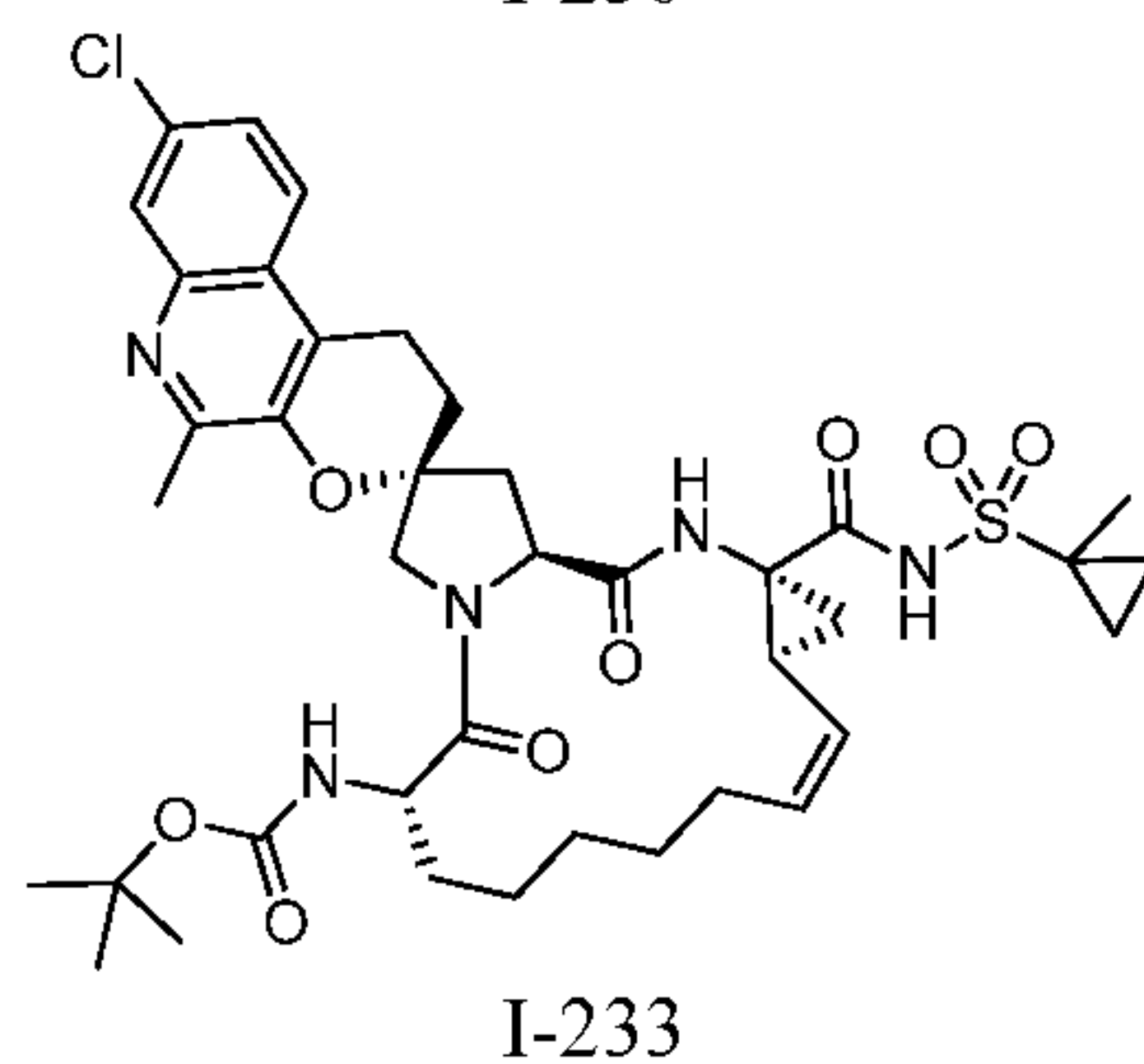
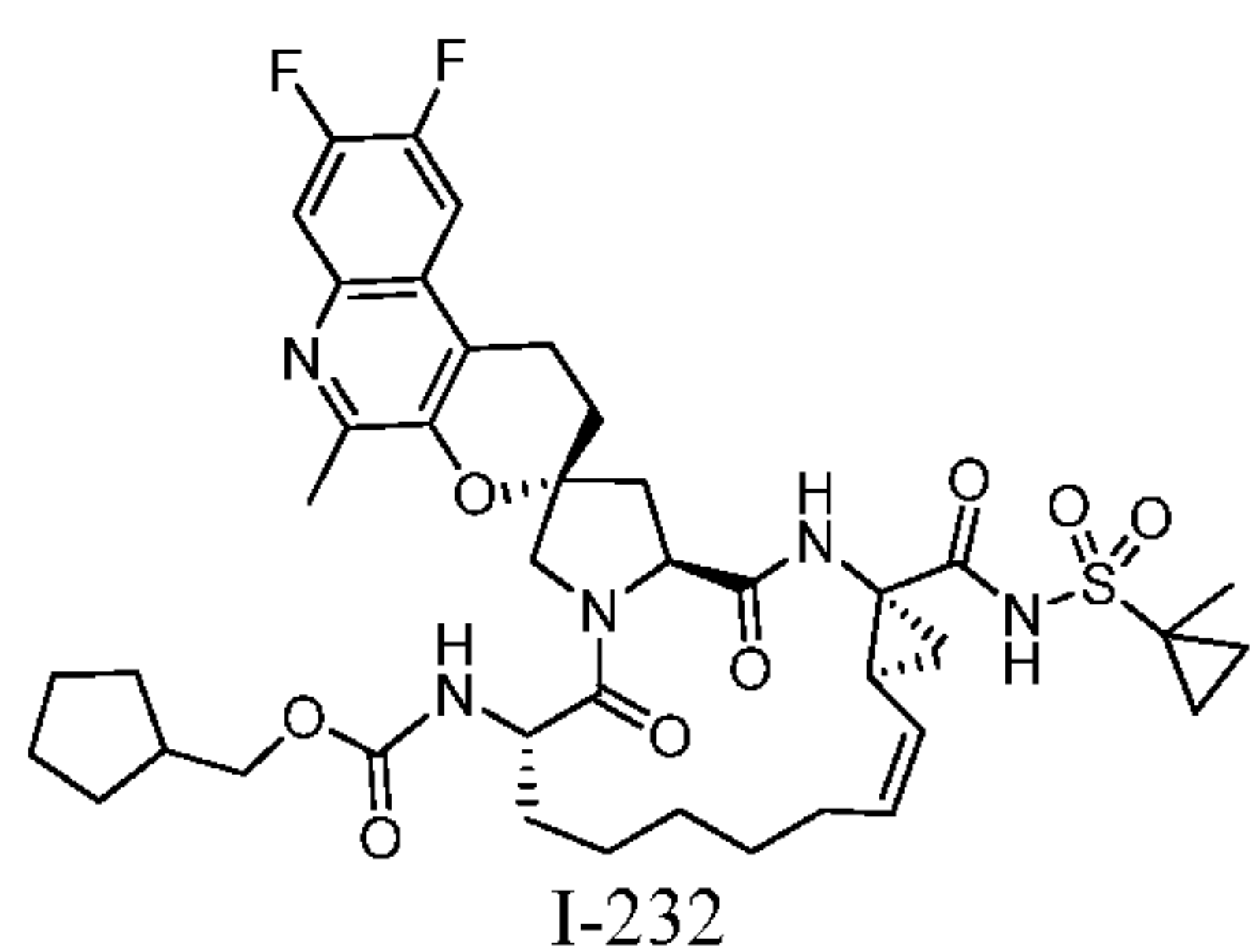
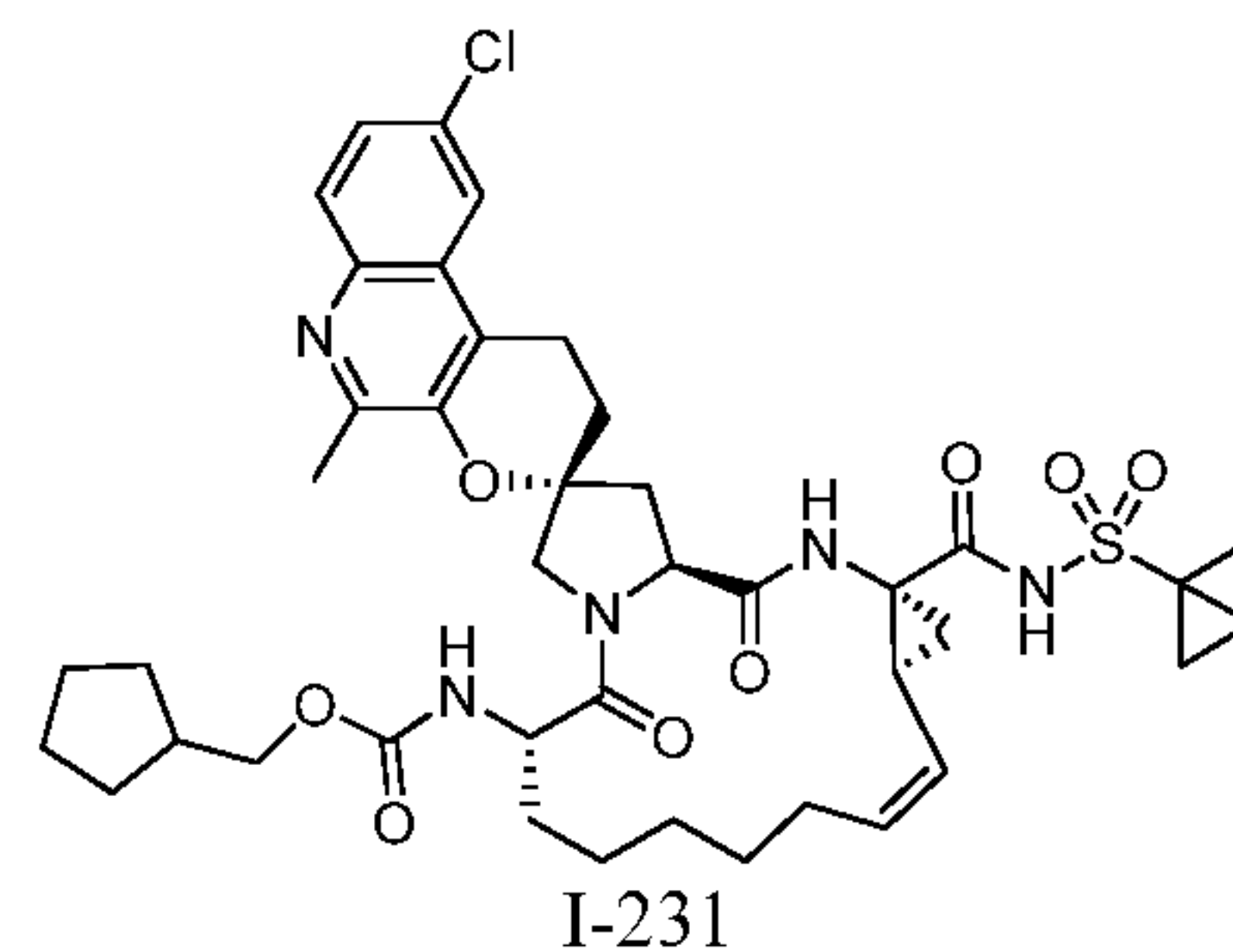
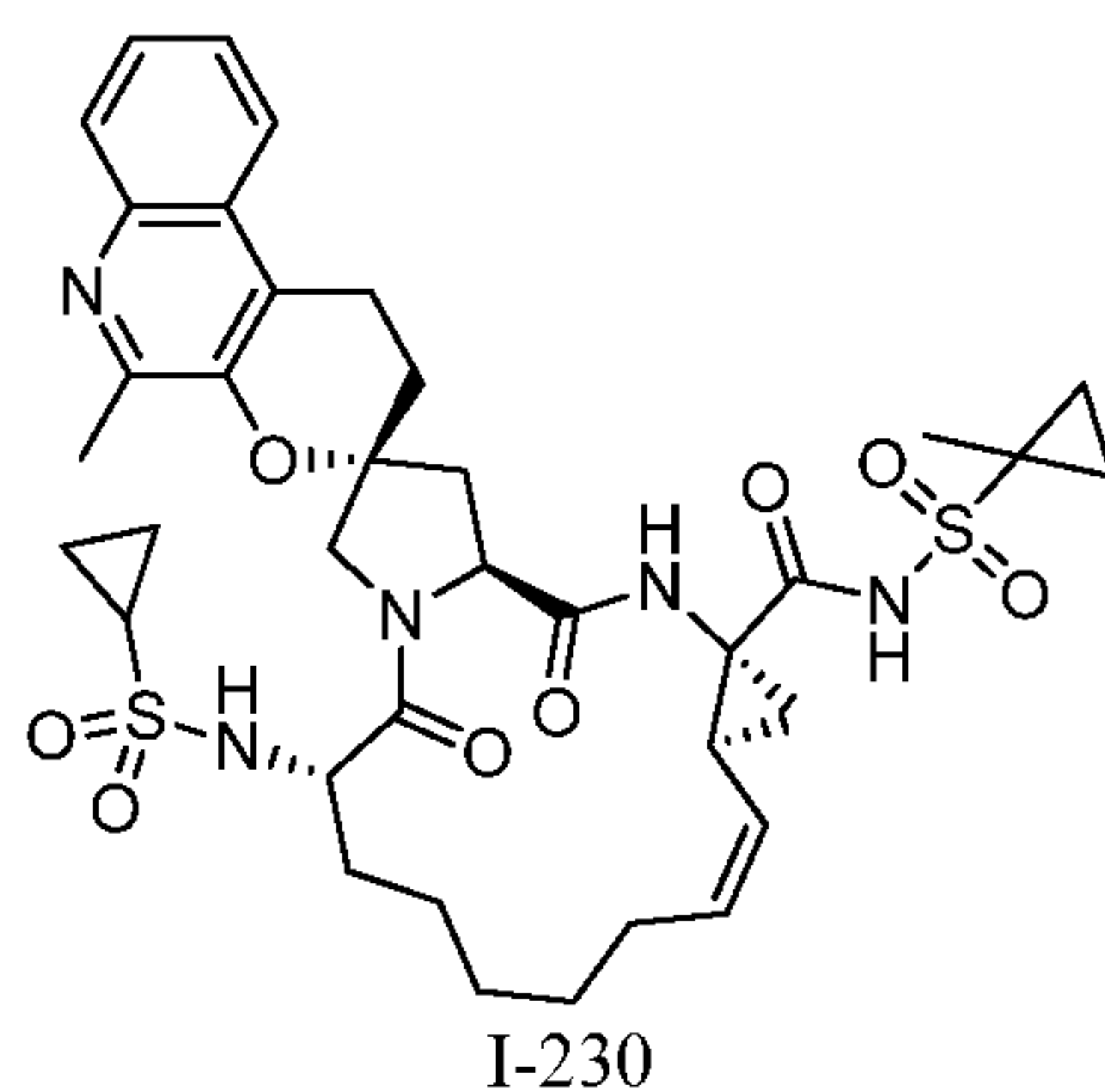
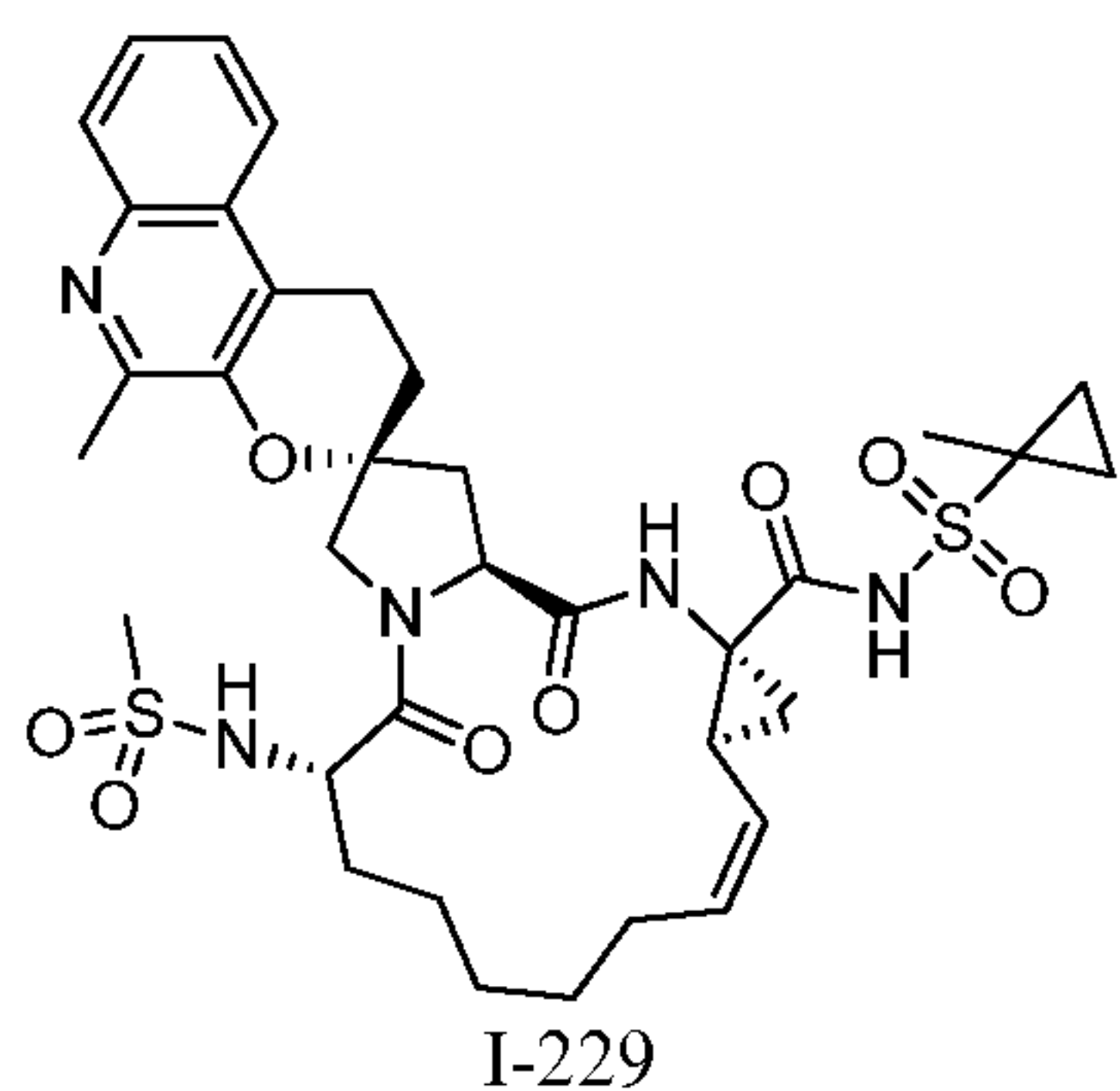
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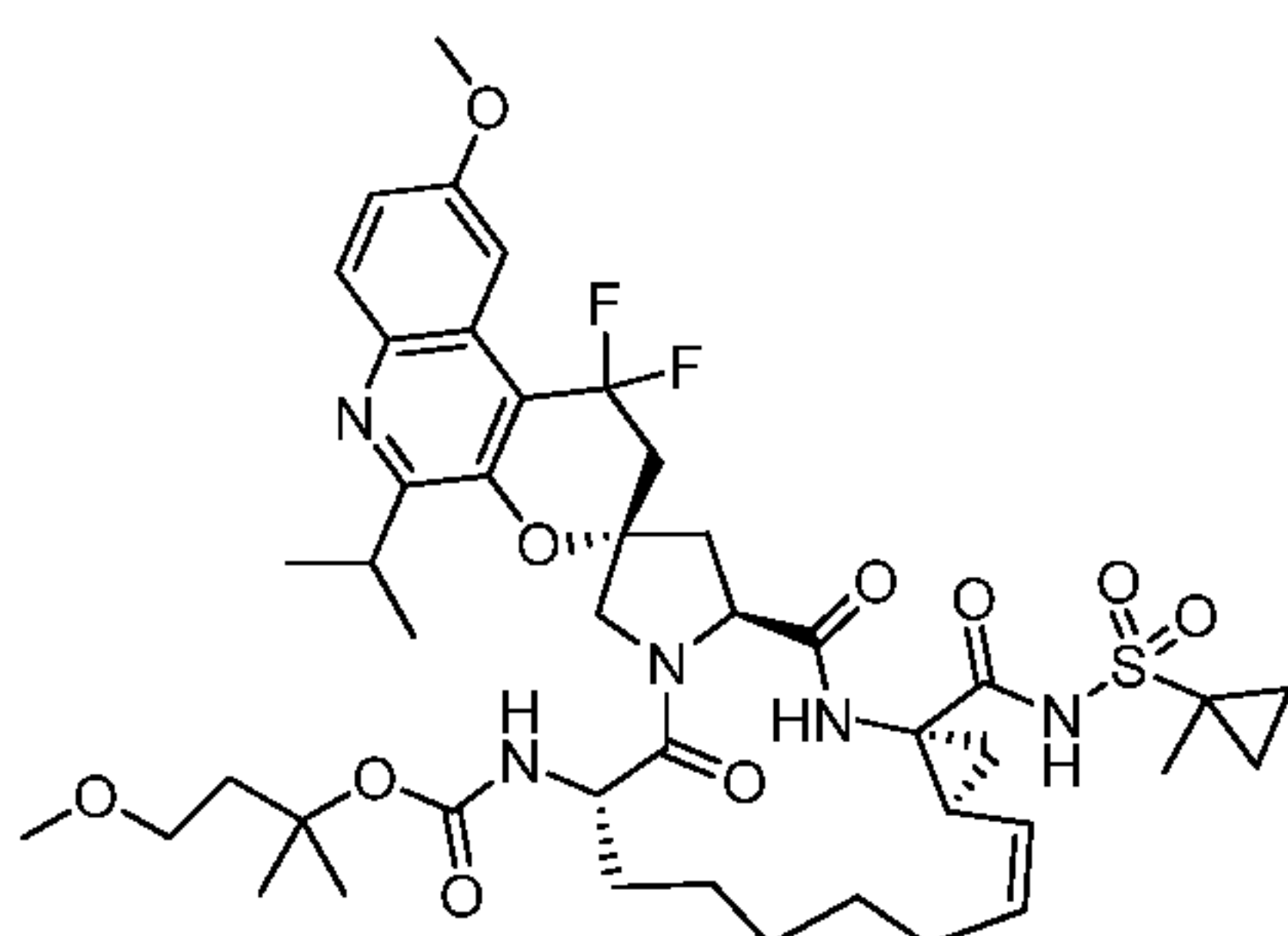


I-227

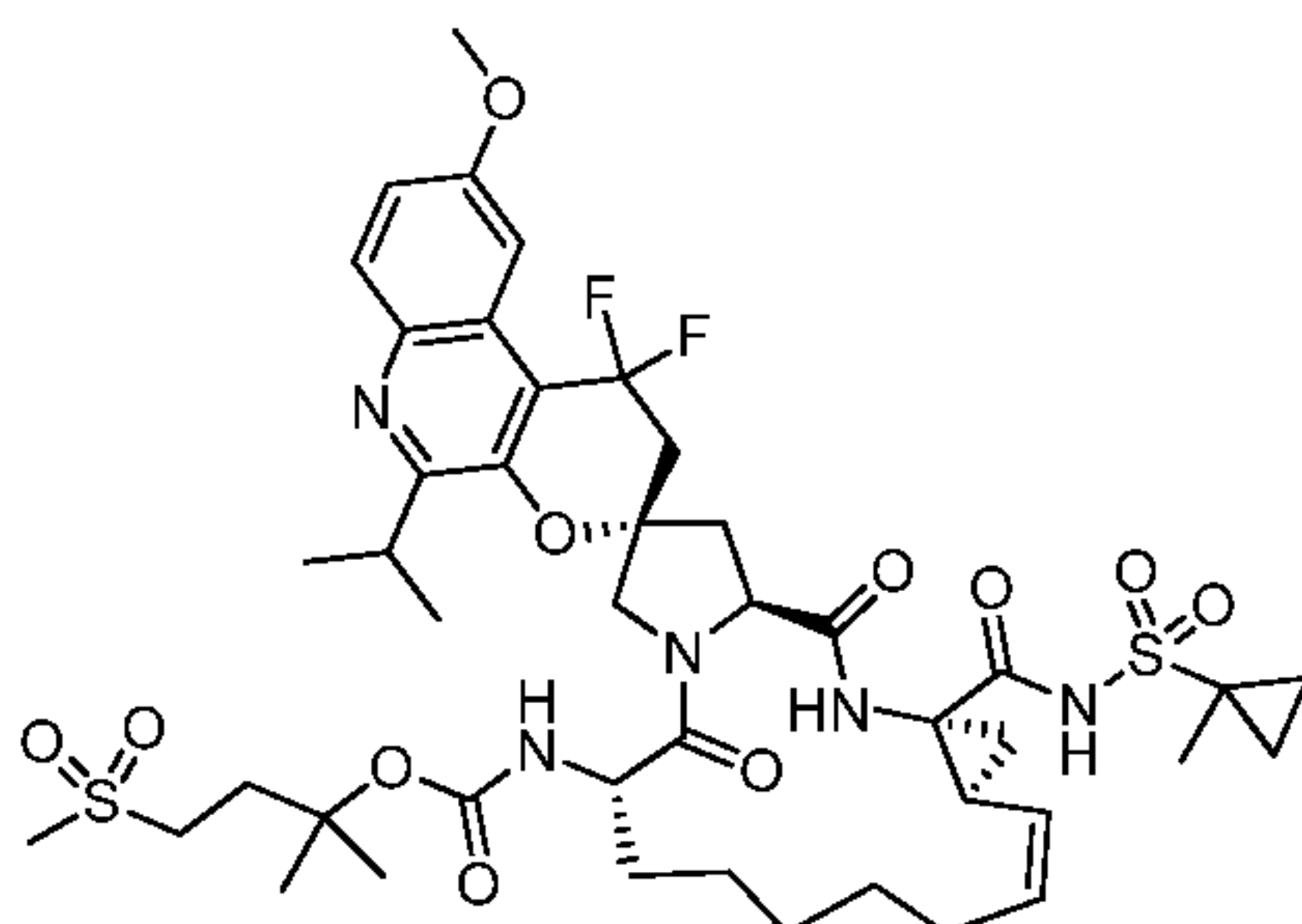


I-228

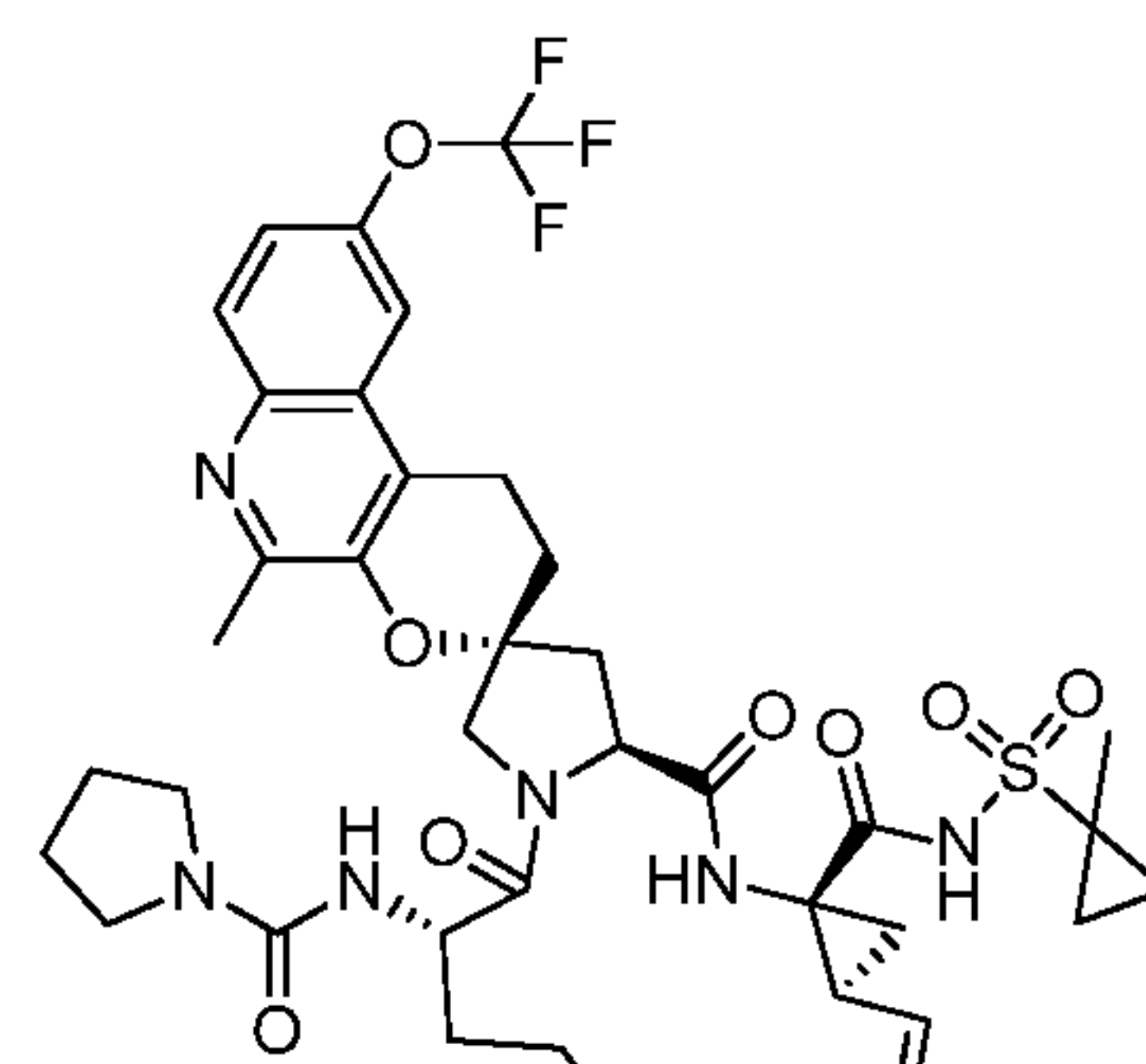




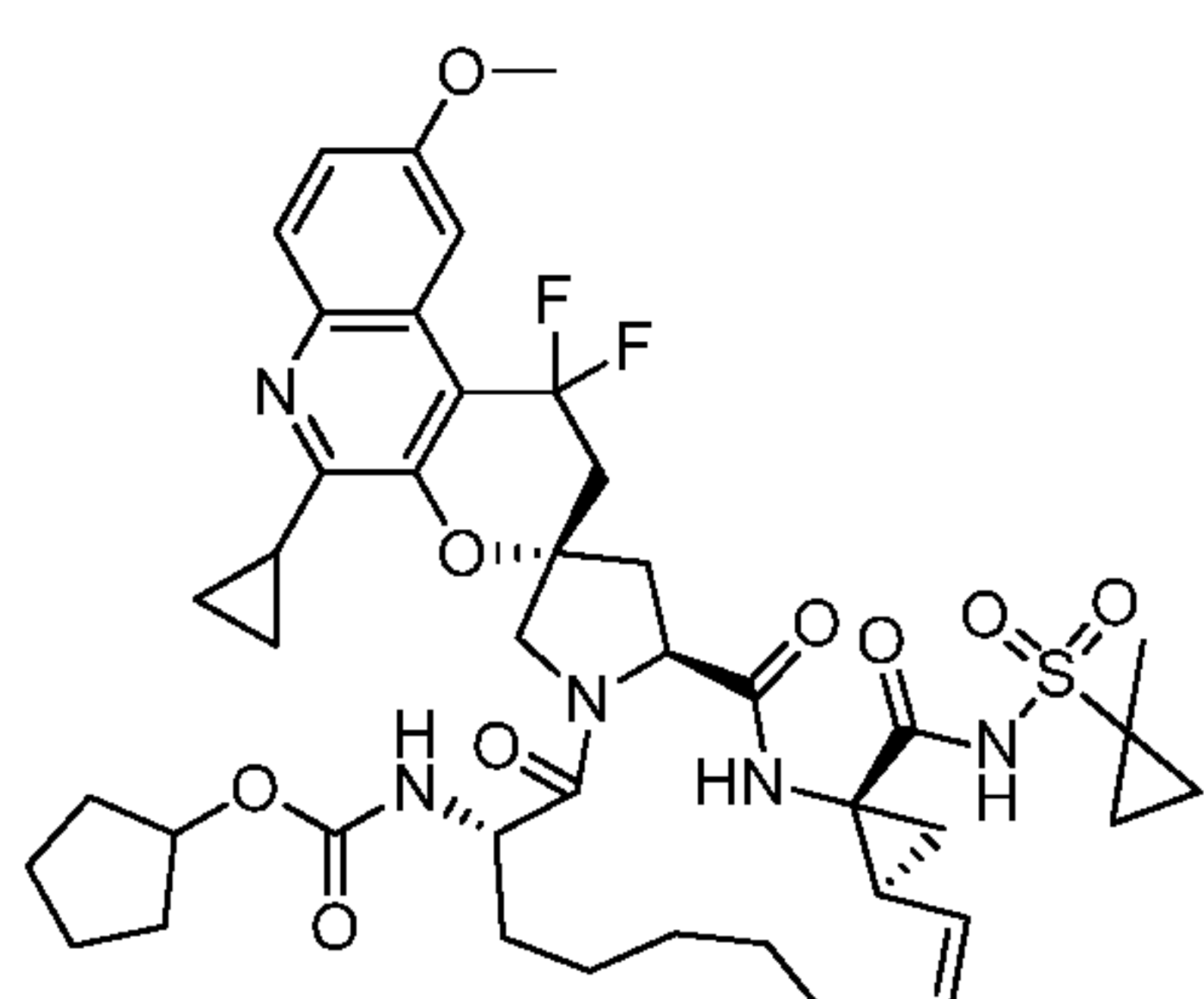
I-244



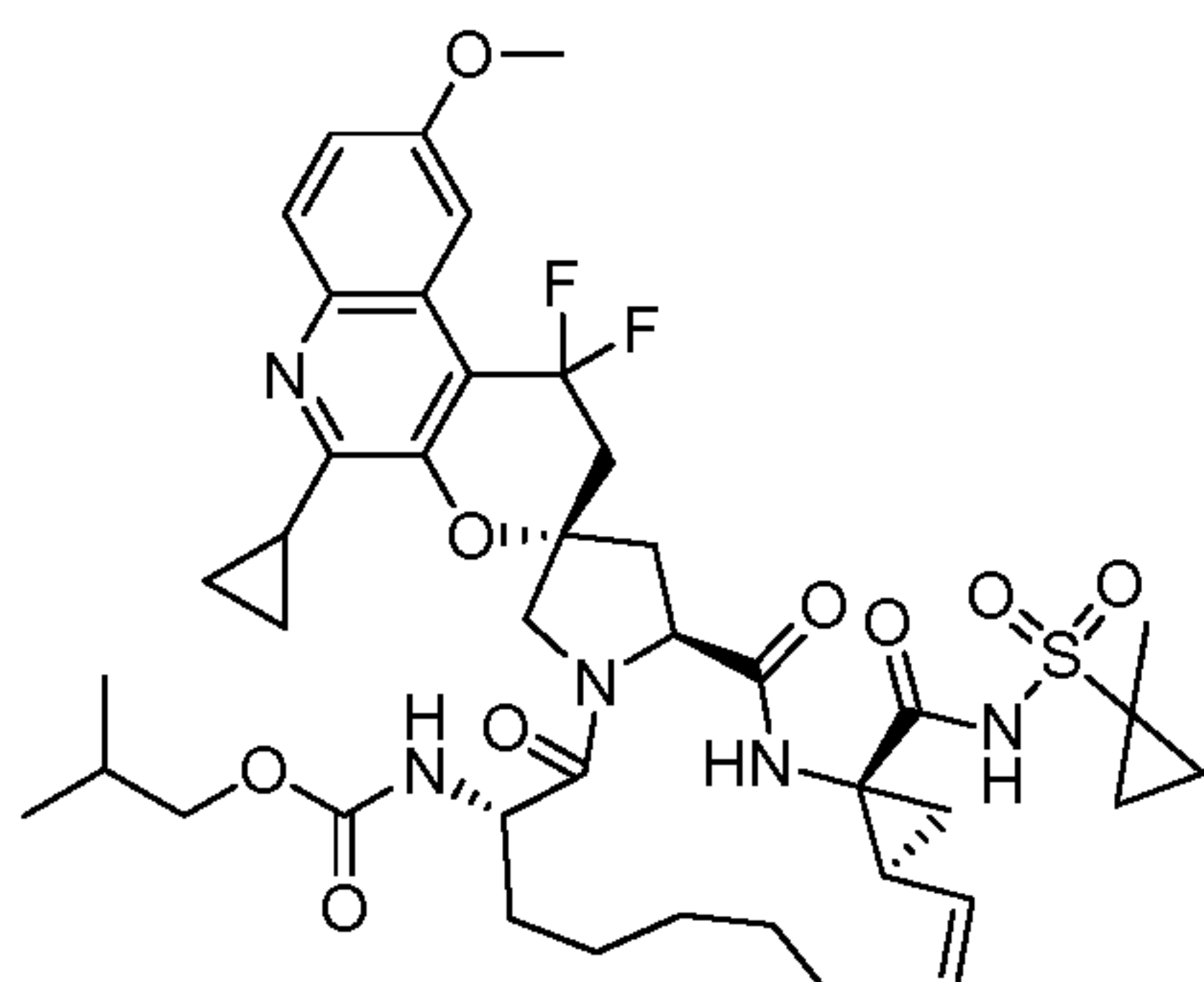
I-245



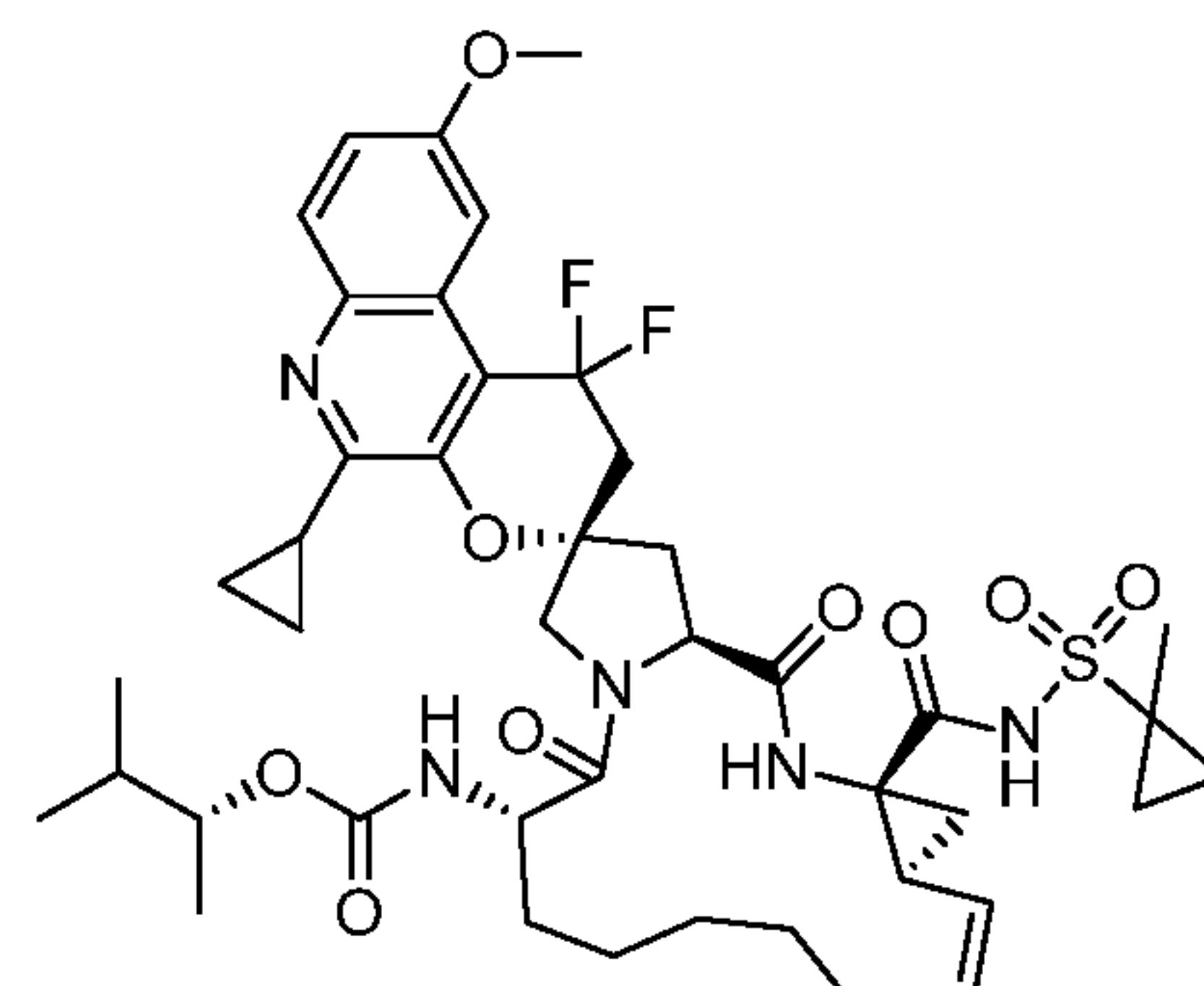
I-246



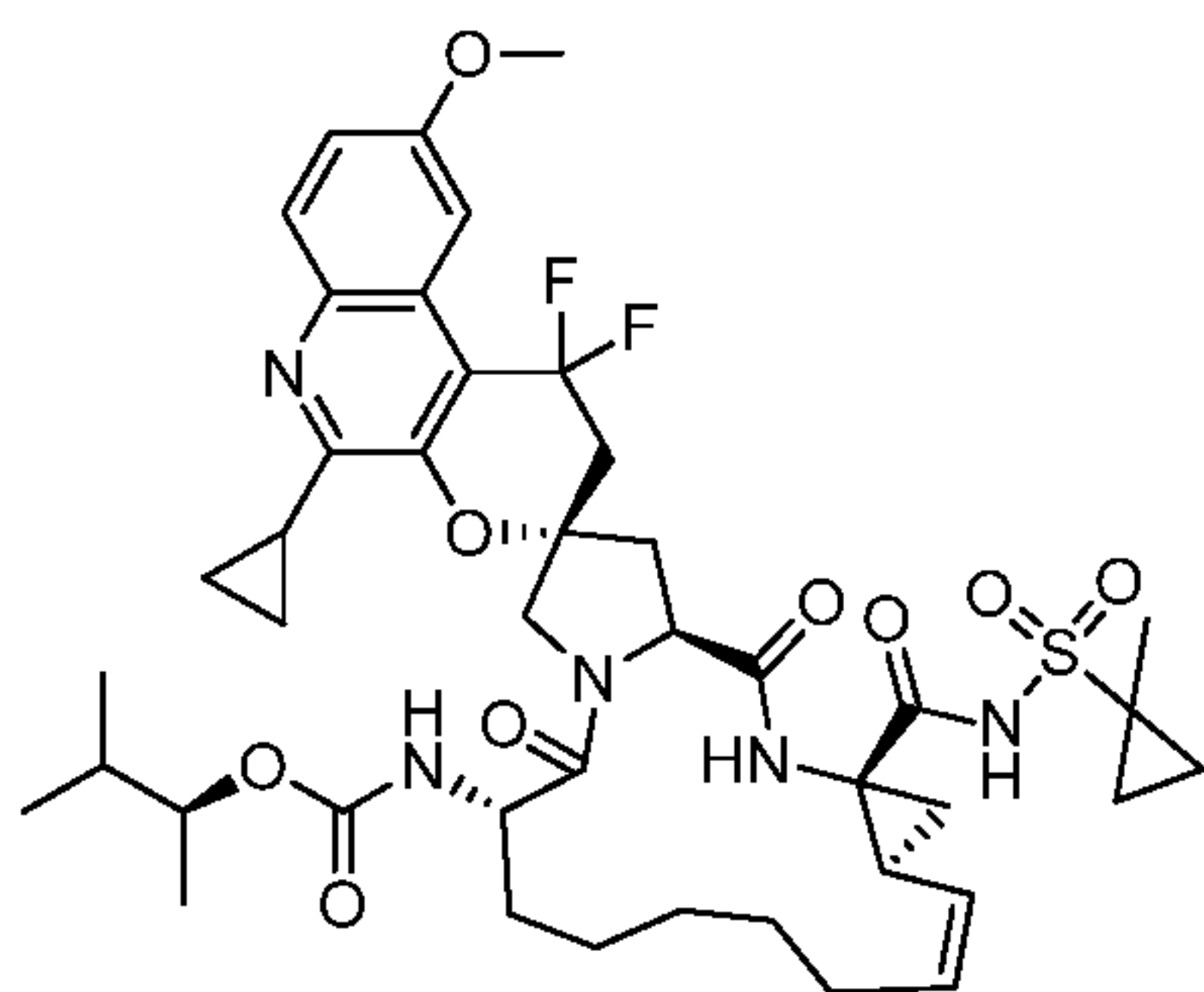
I-247



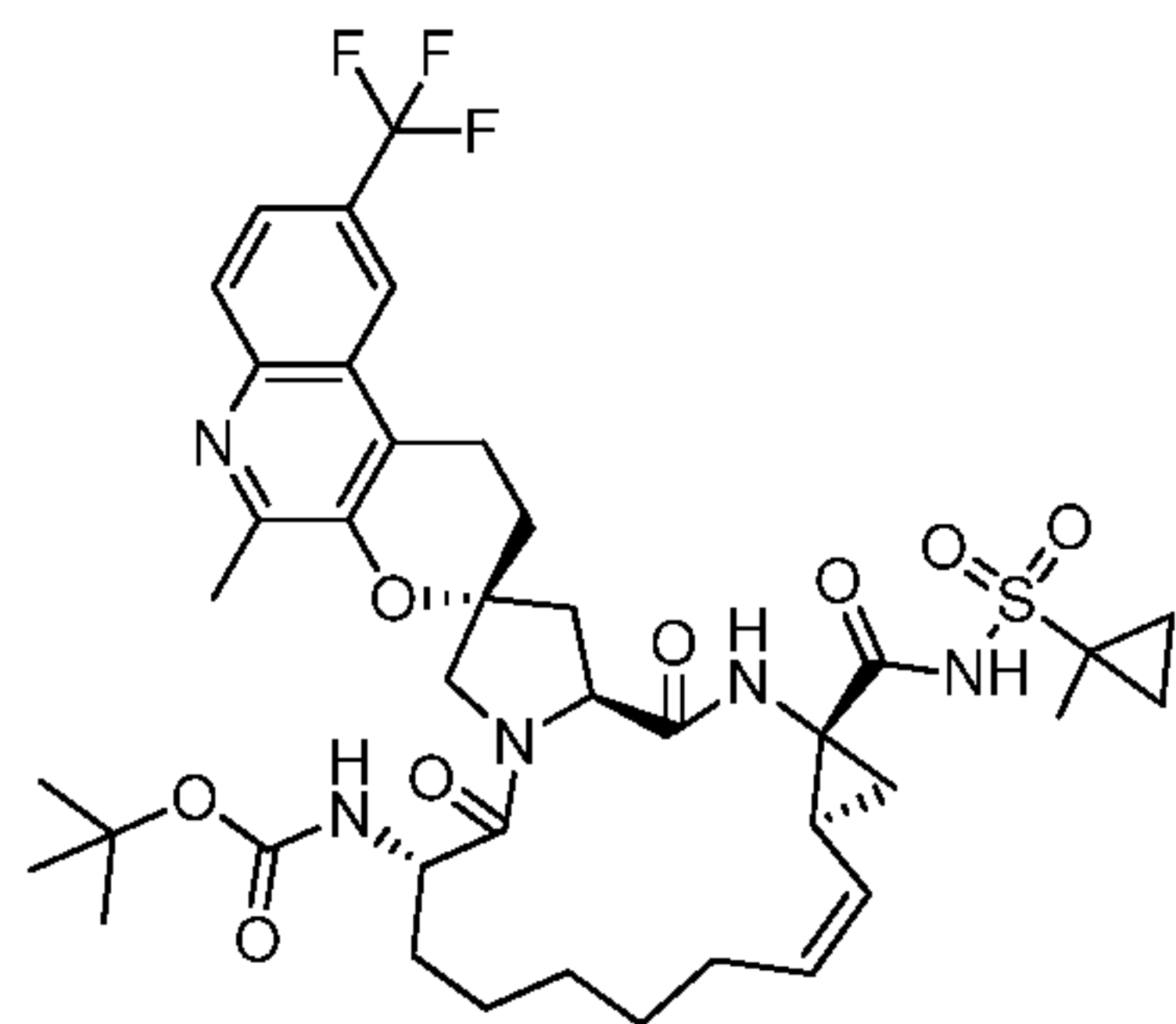
I-248



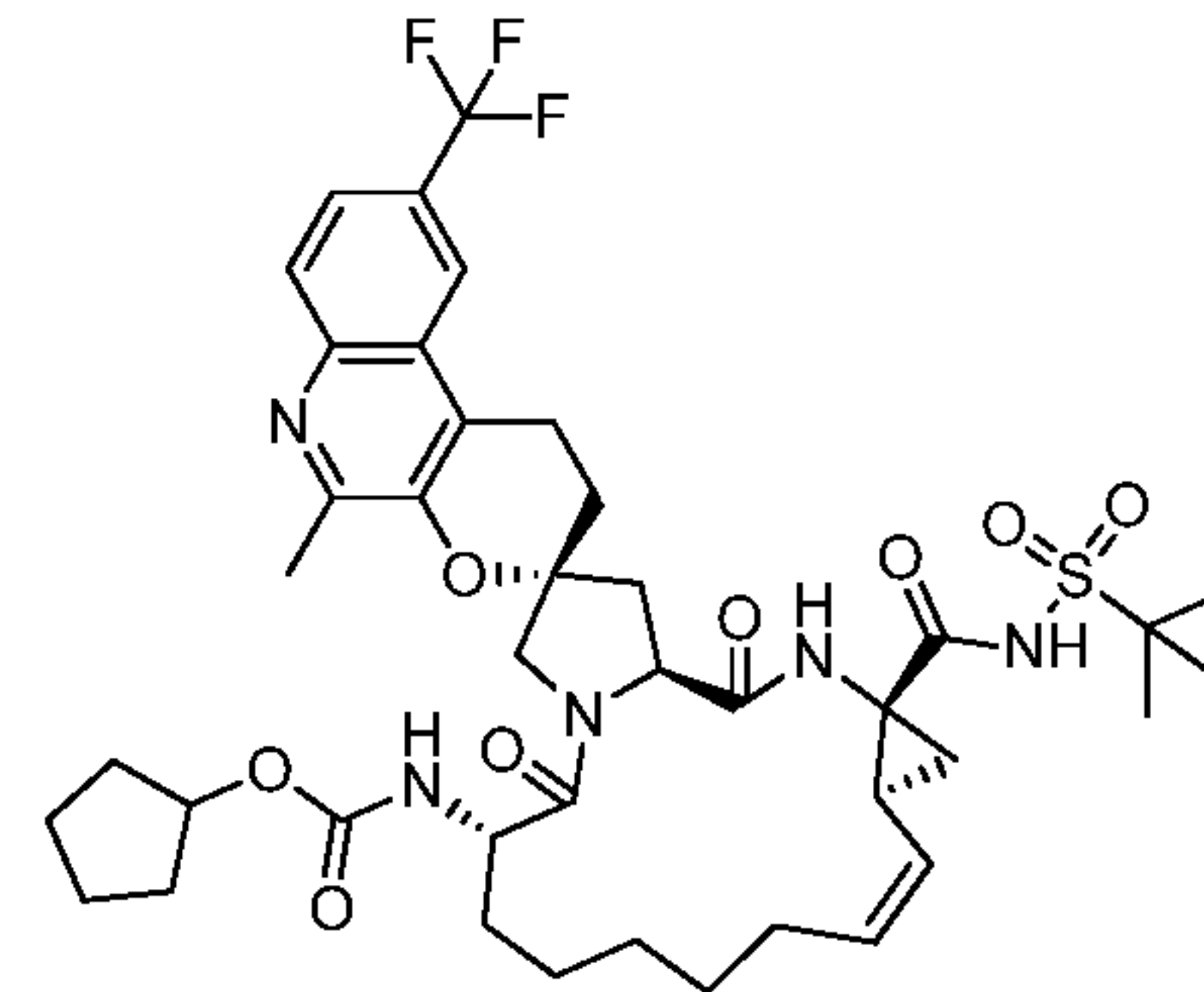
I-249



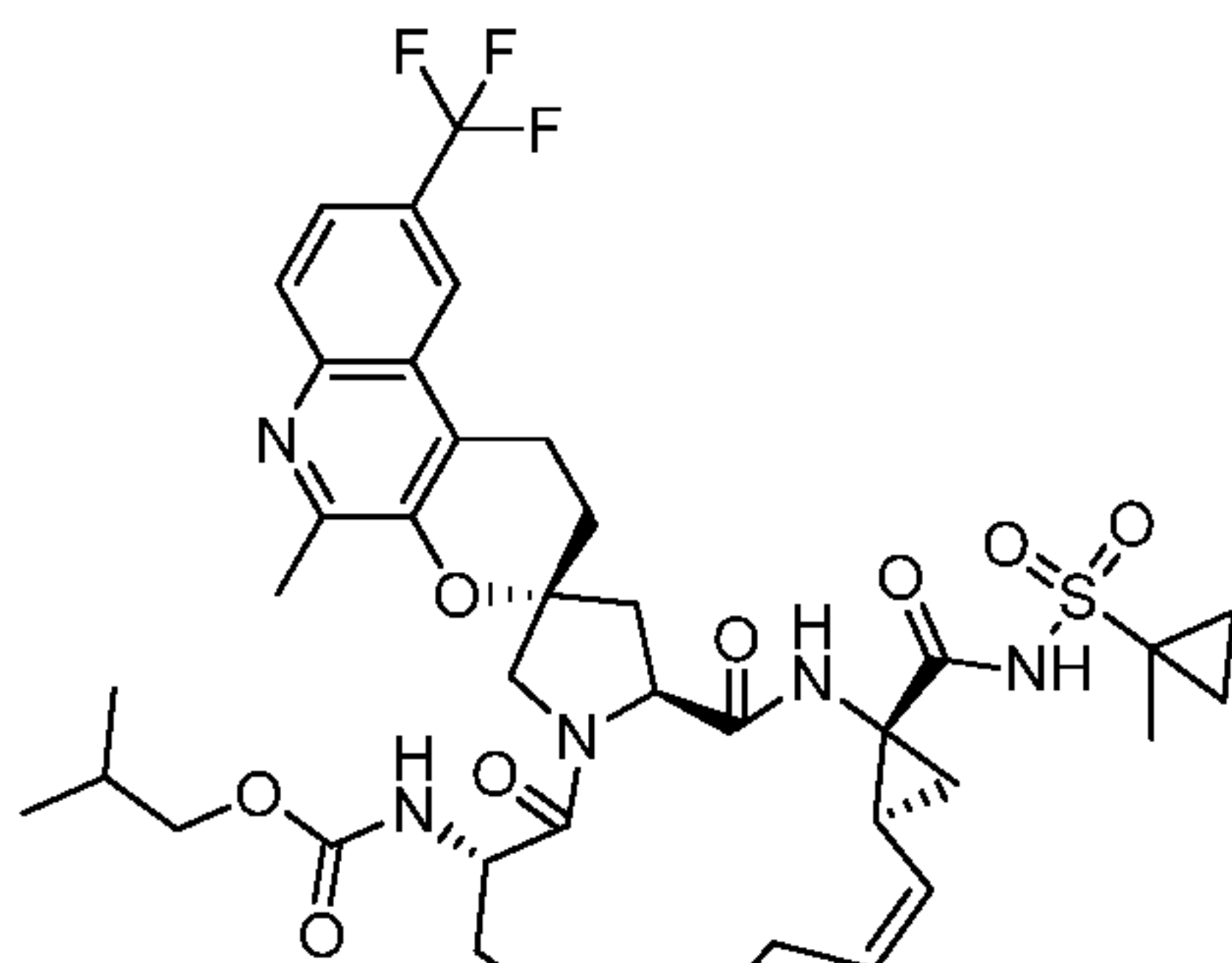
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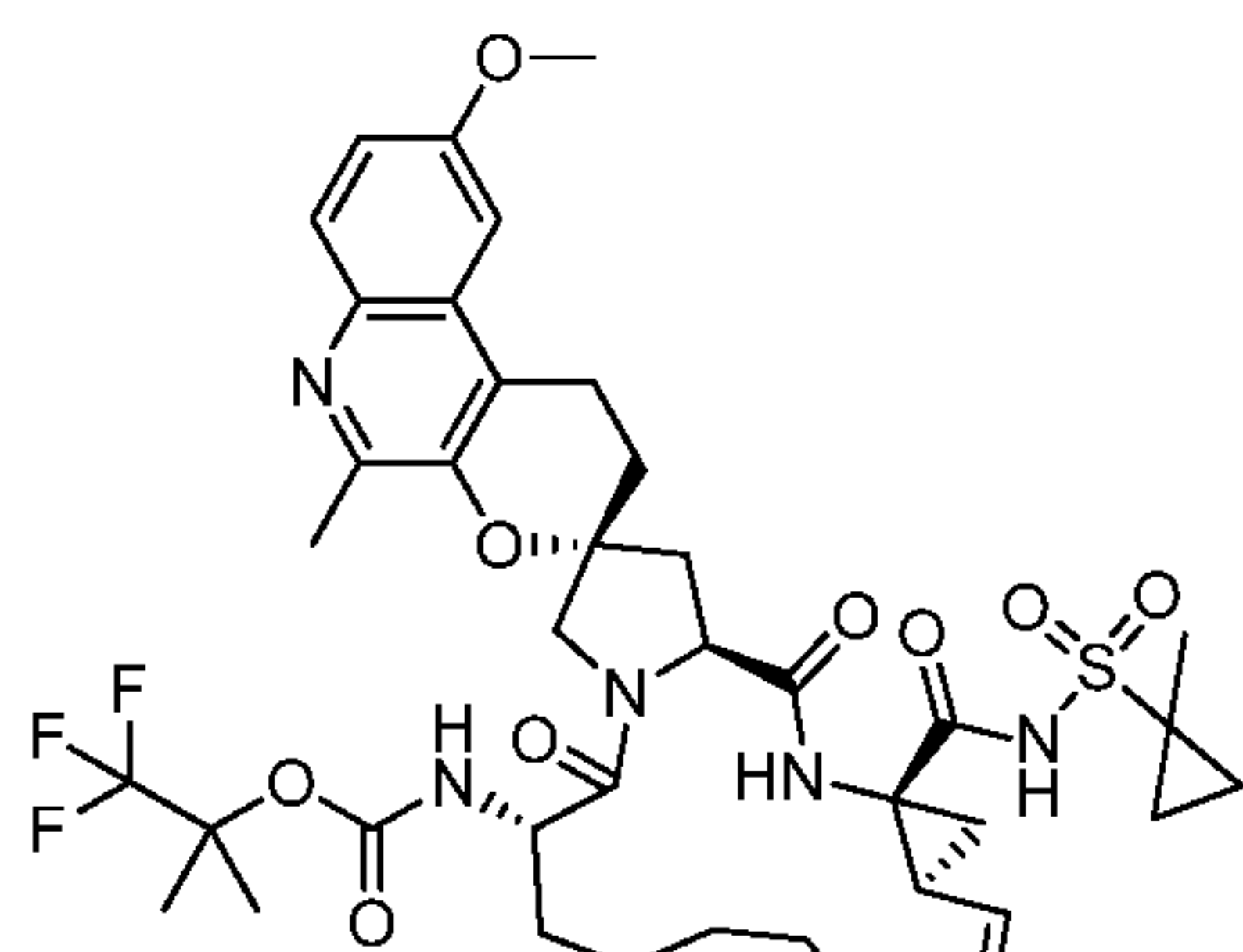
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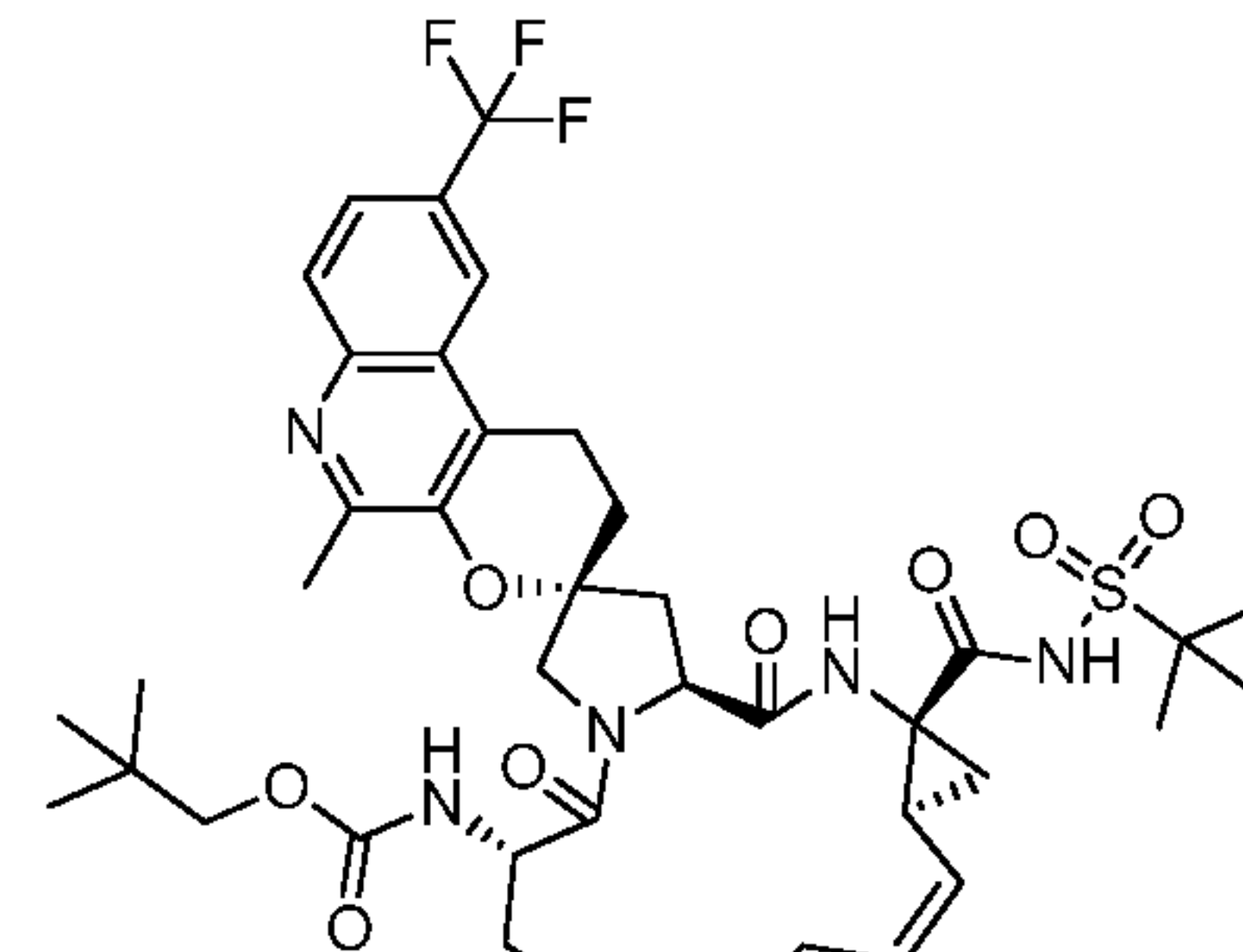
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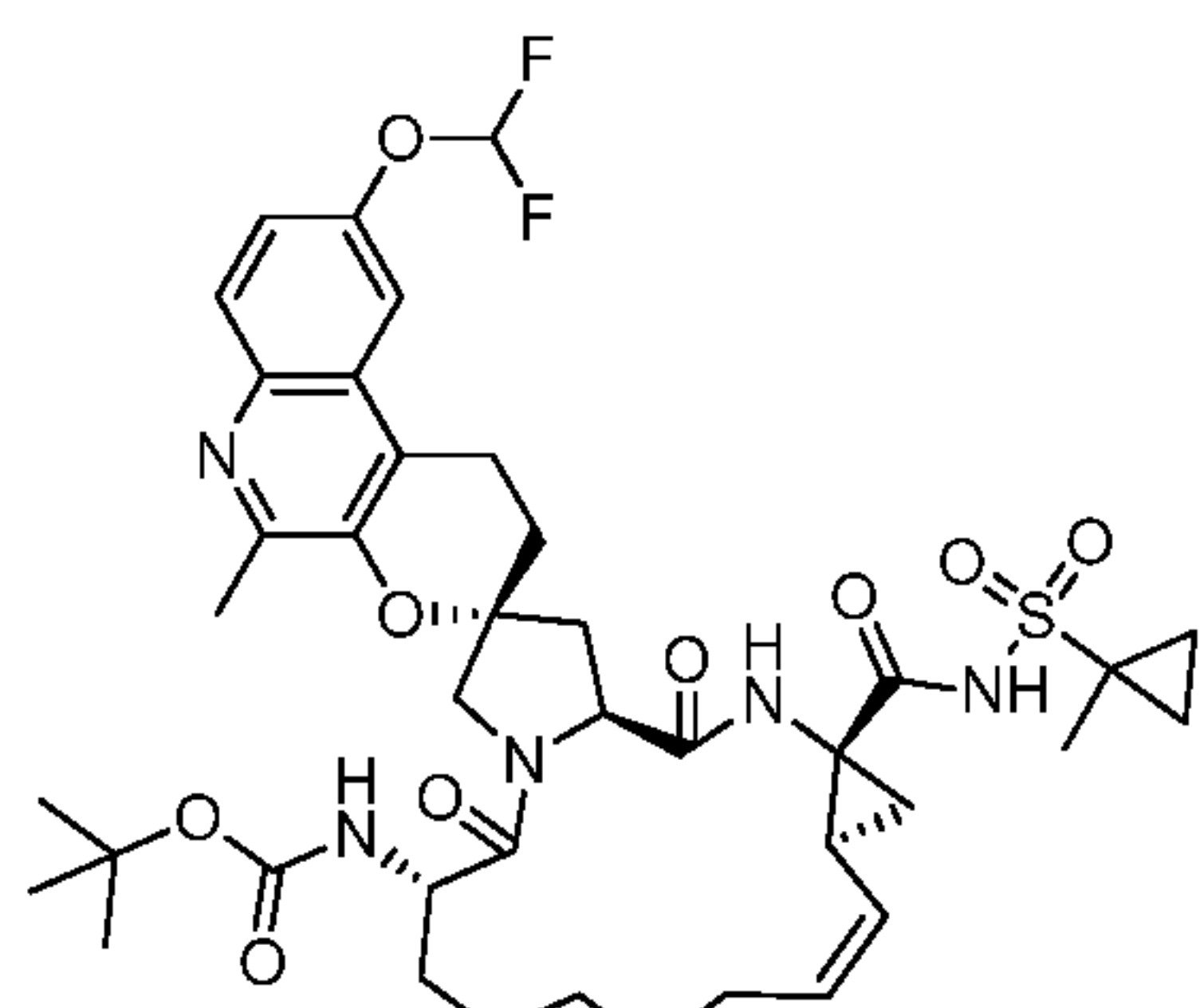
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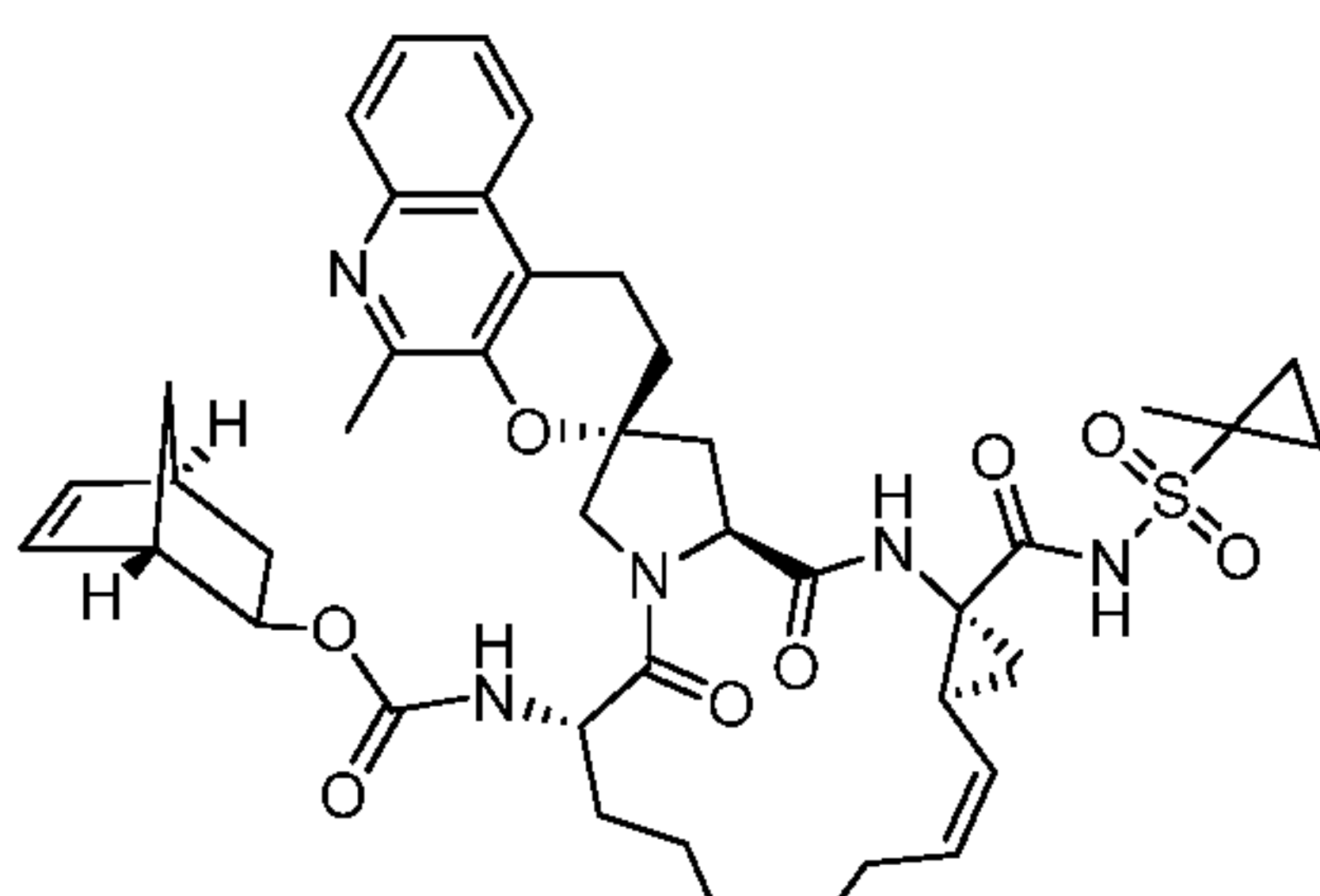
I-254



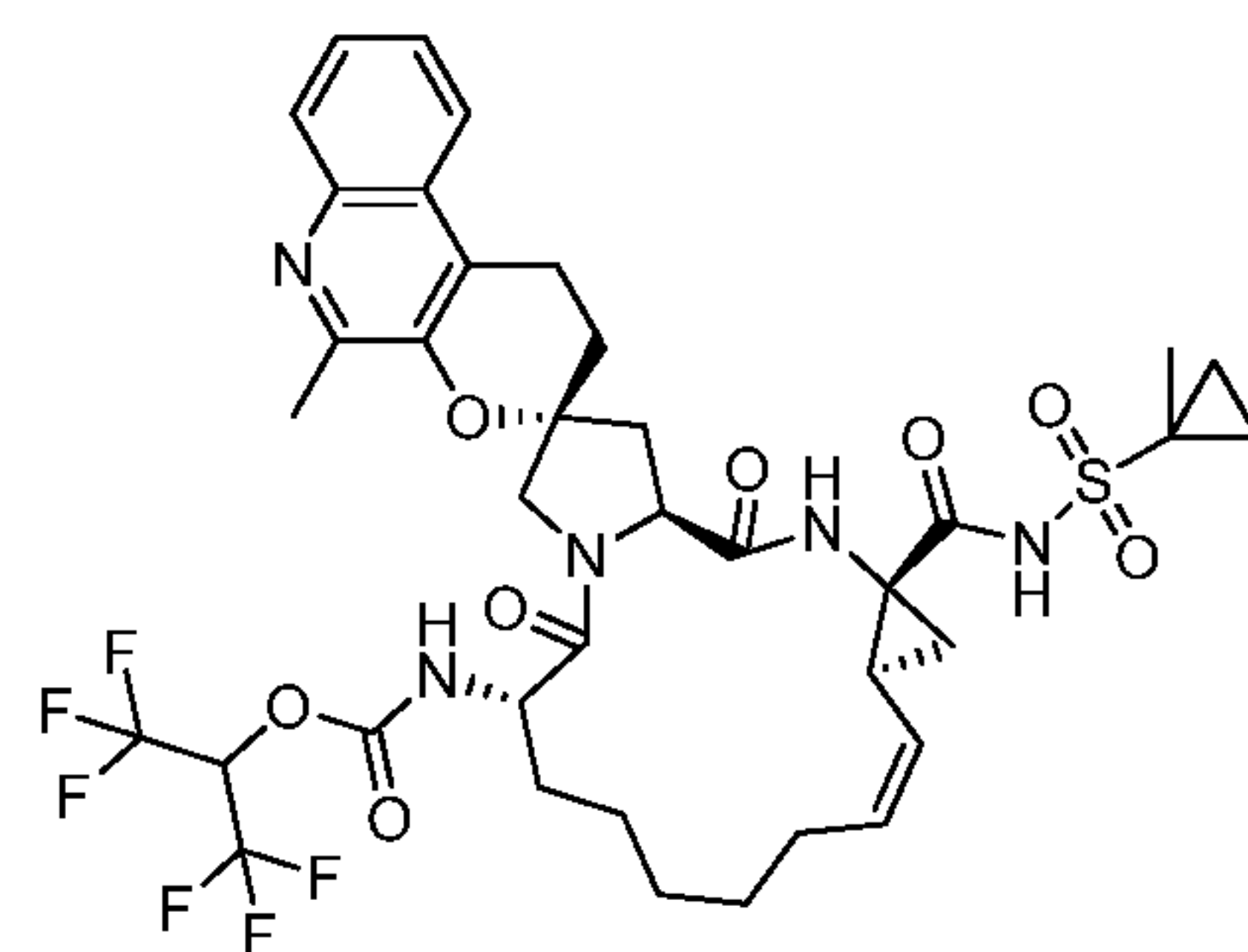
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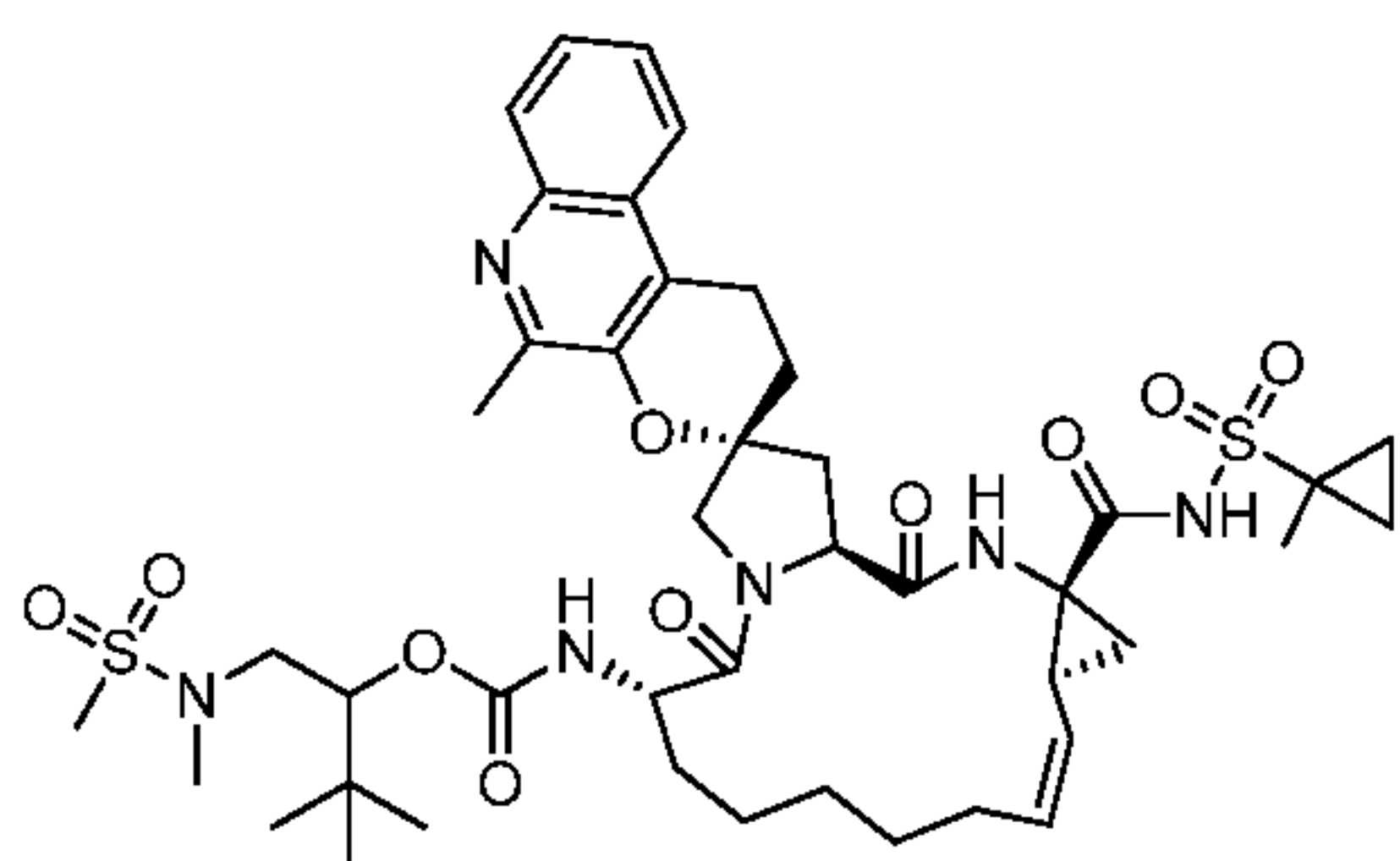
I-256



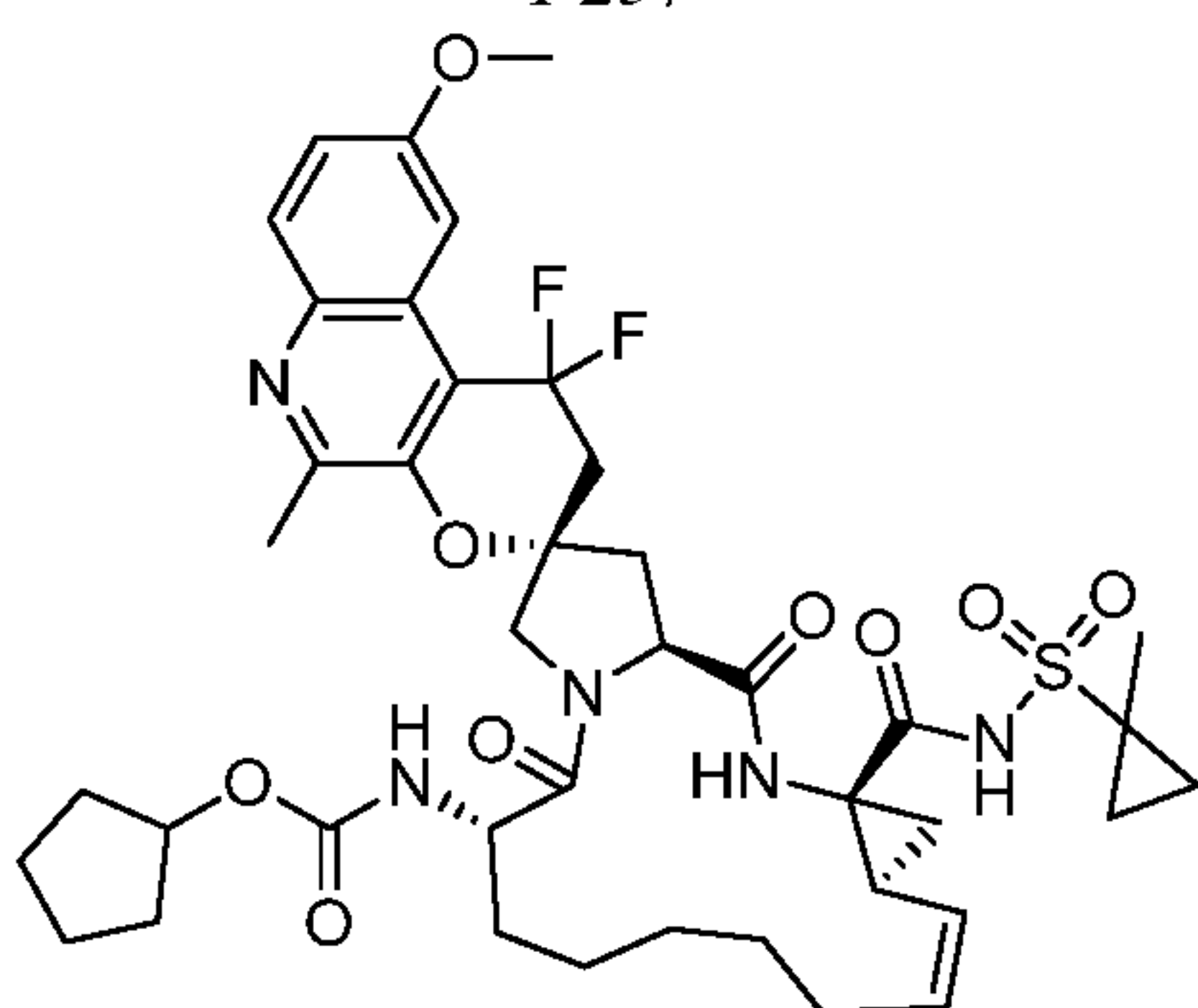
I-257



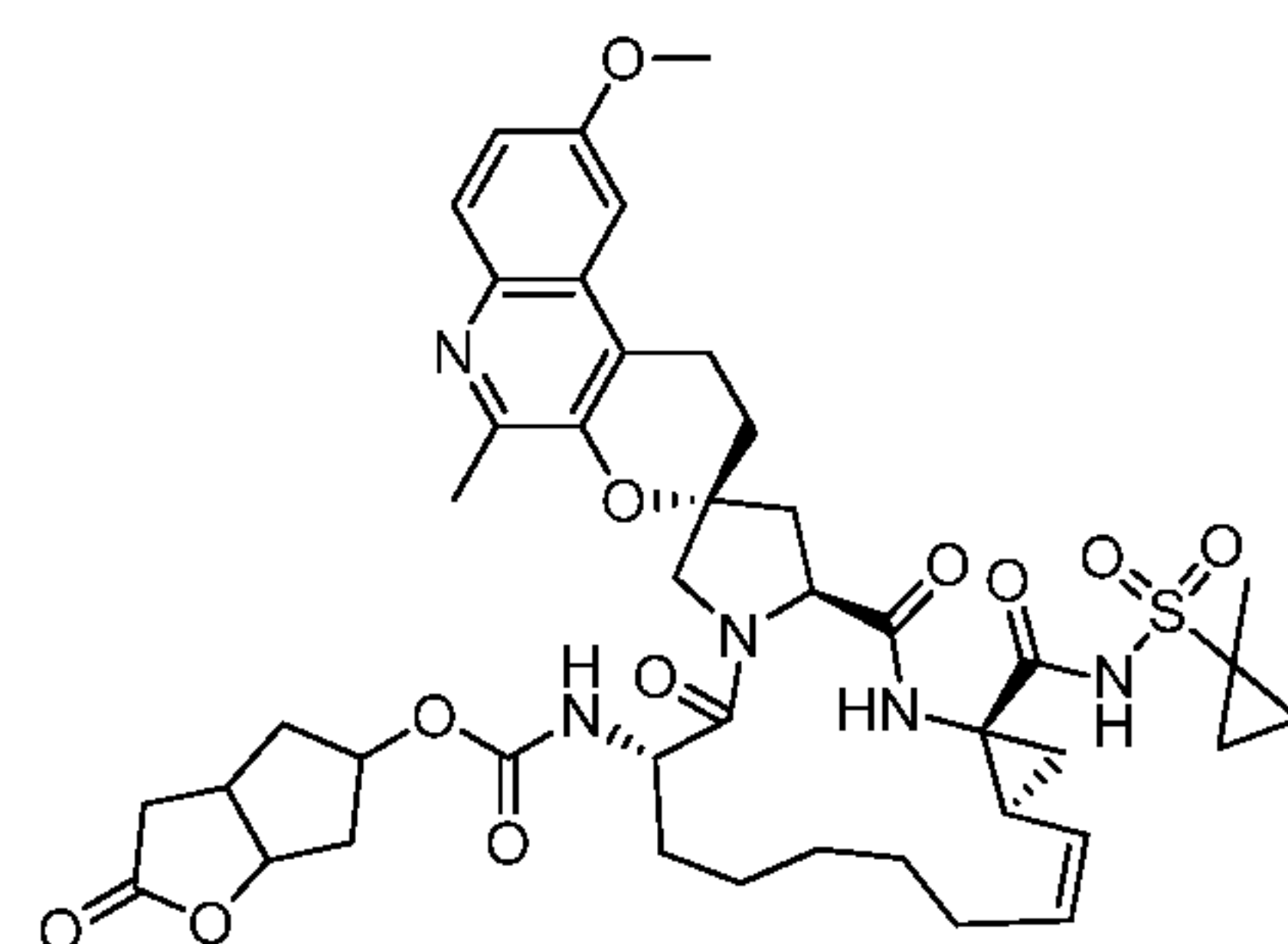
I-258



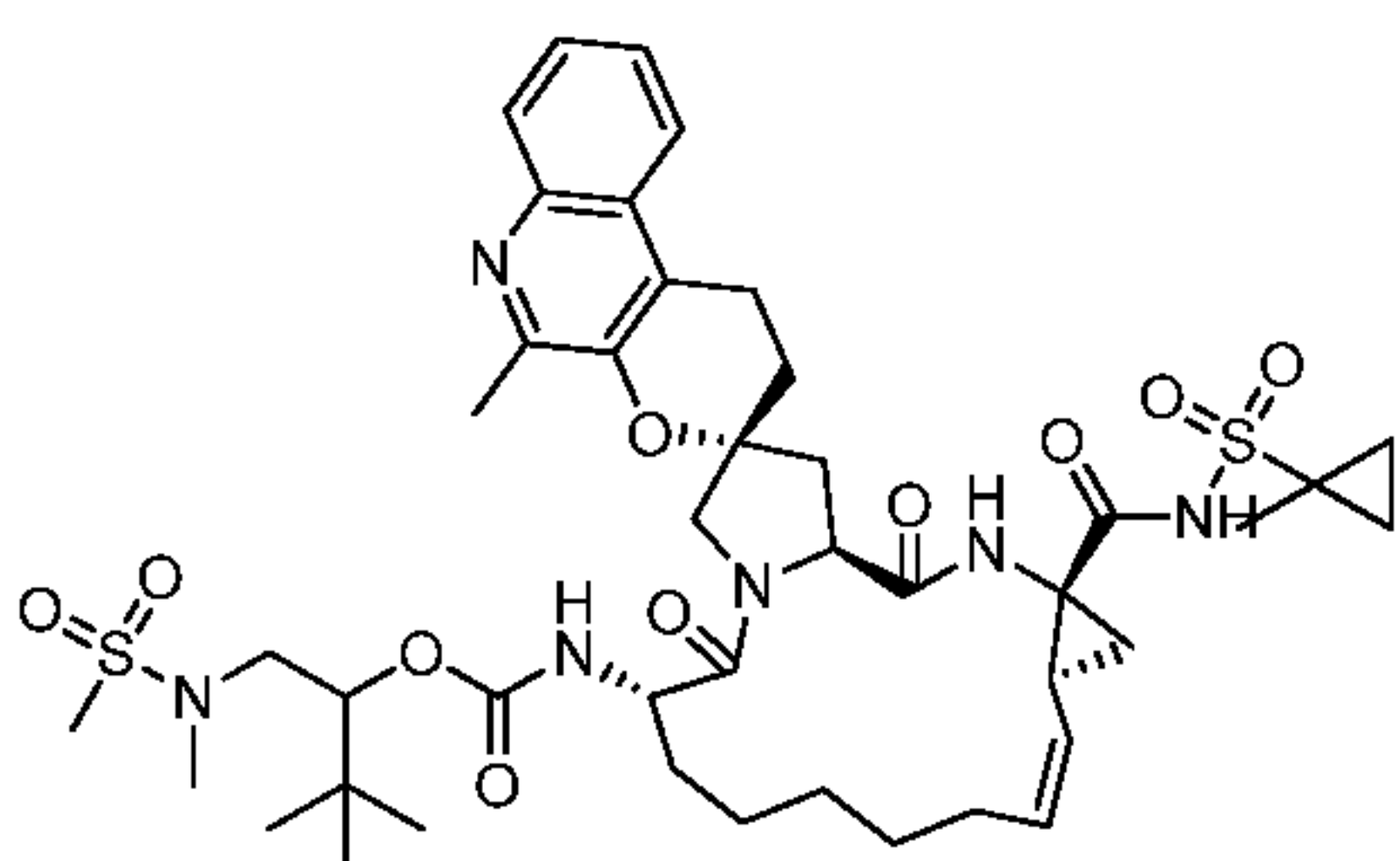
I-259



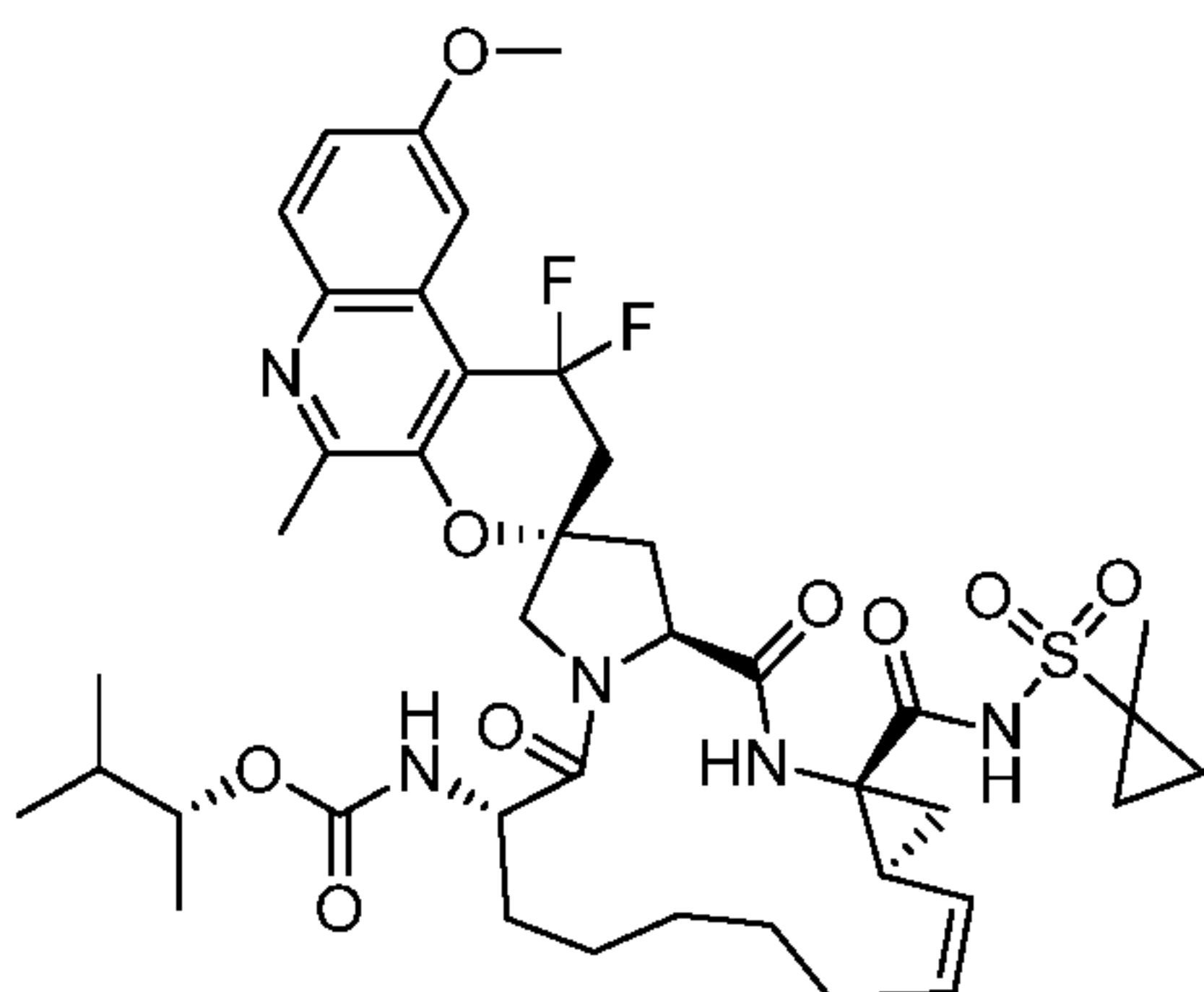
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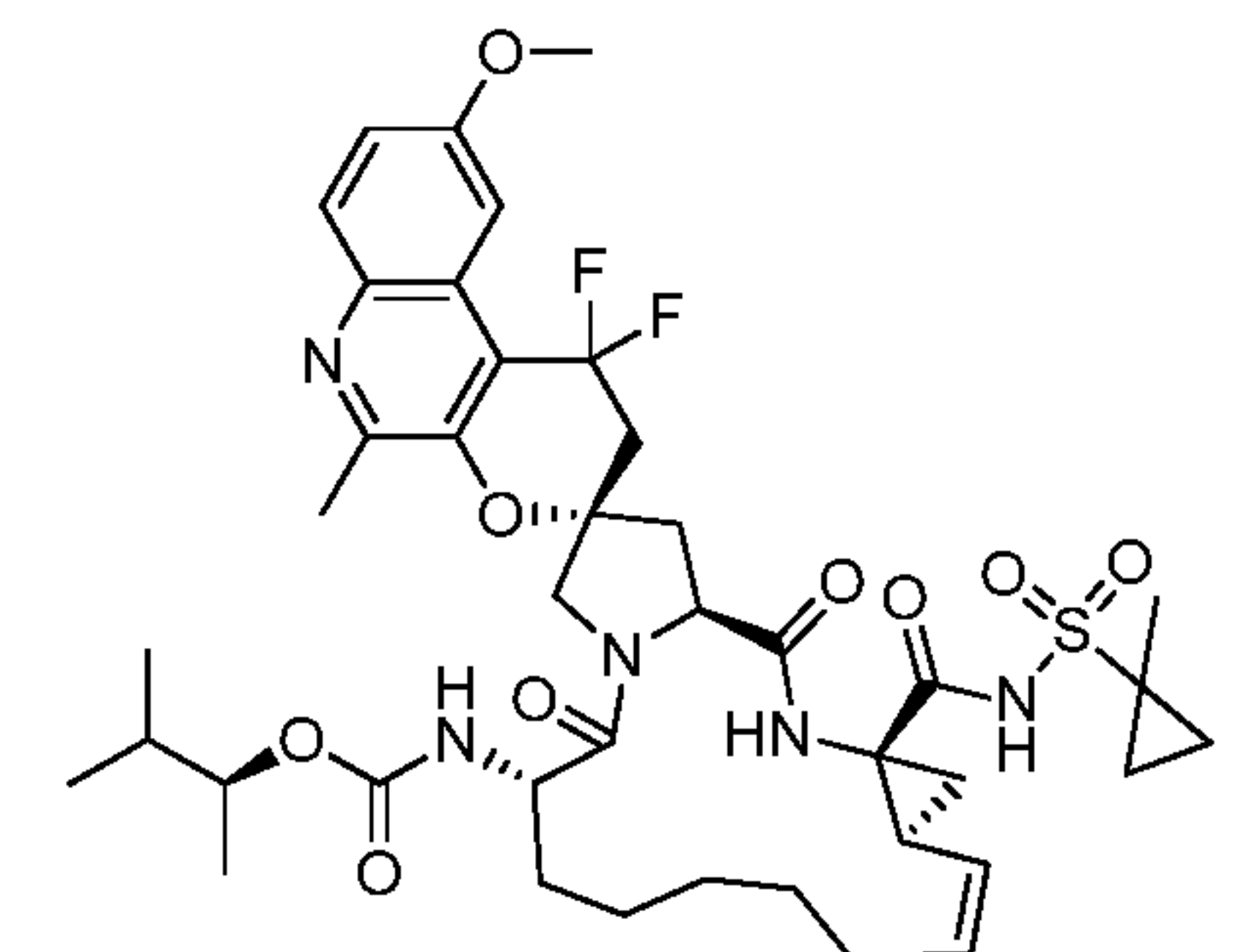
I-261



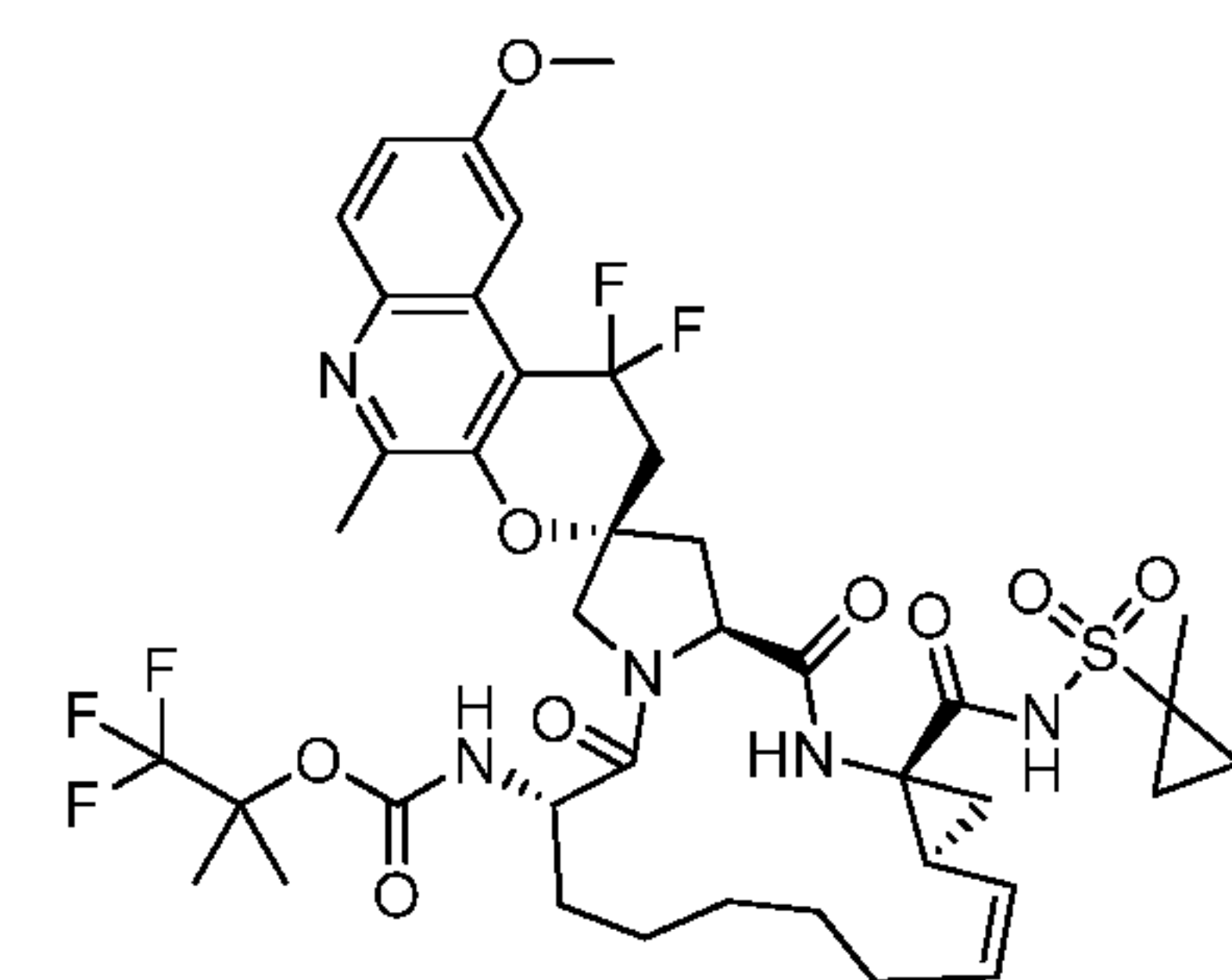
I-262



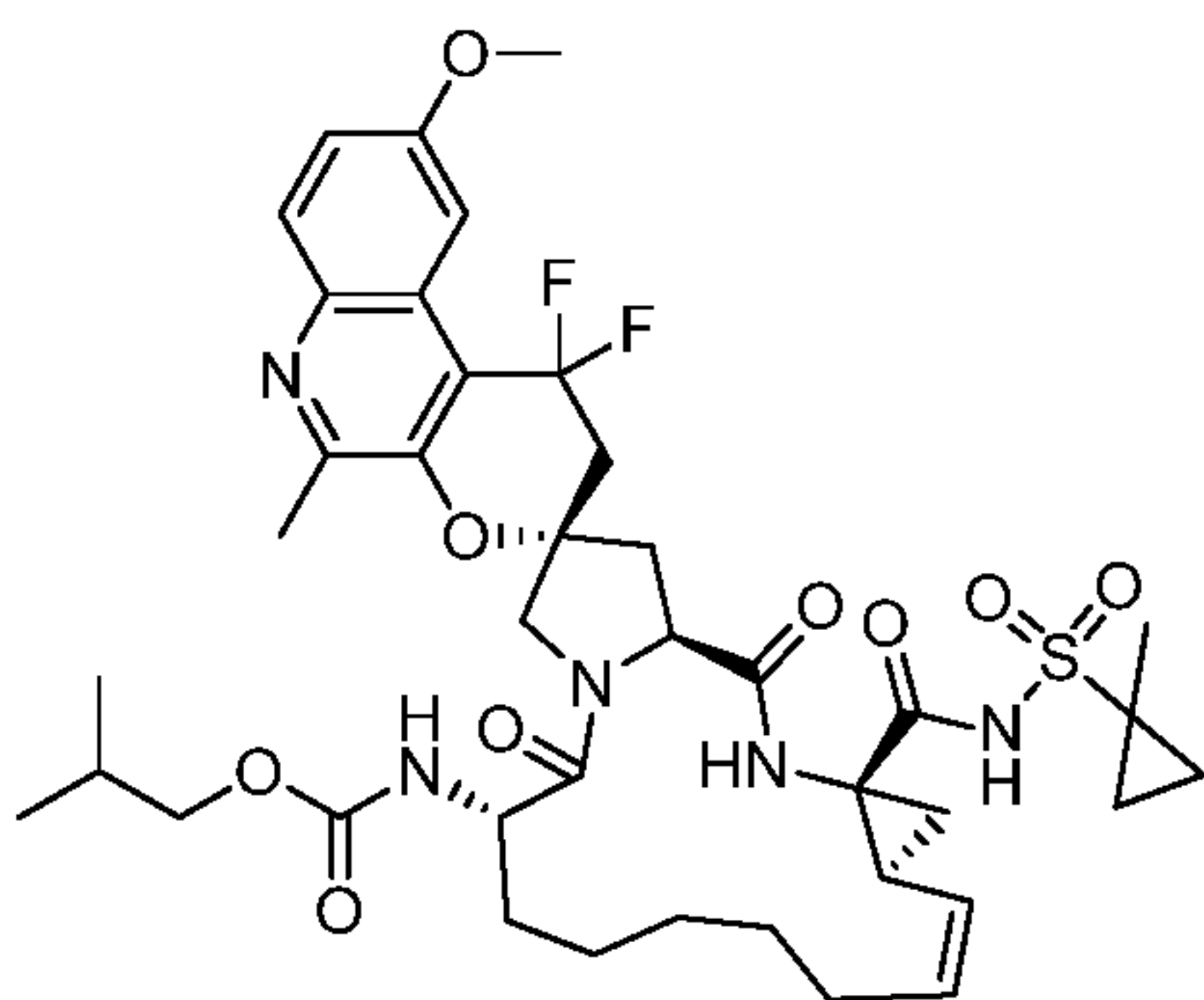
I-263



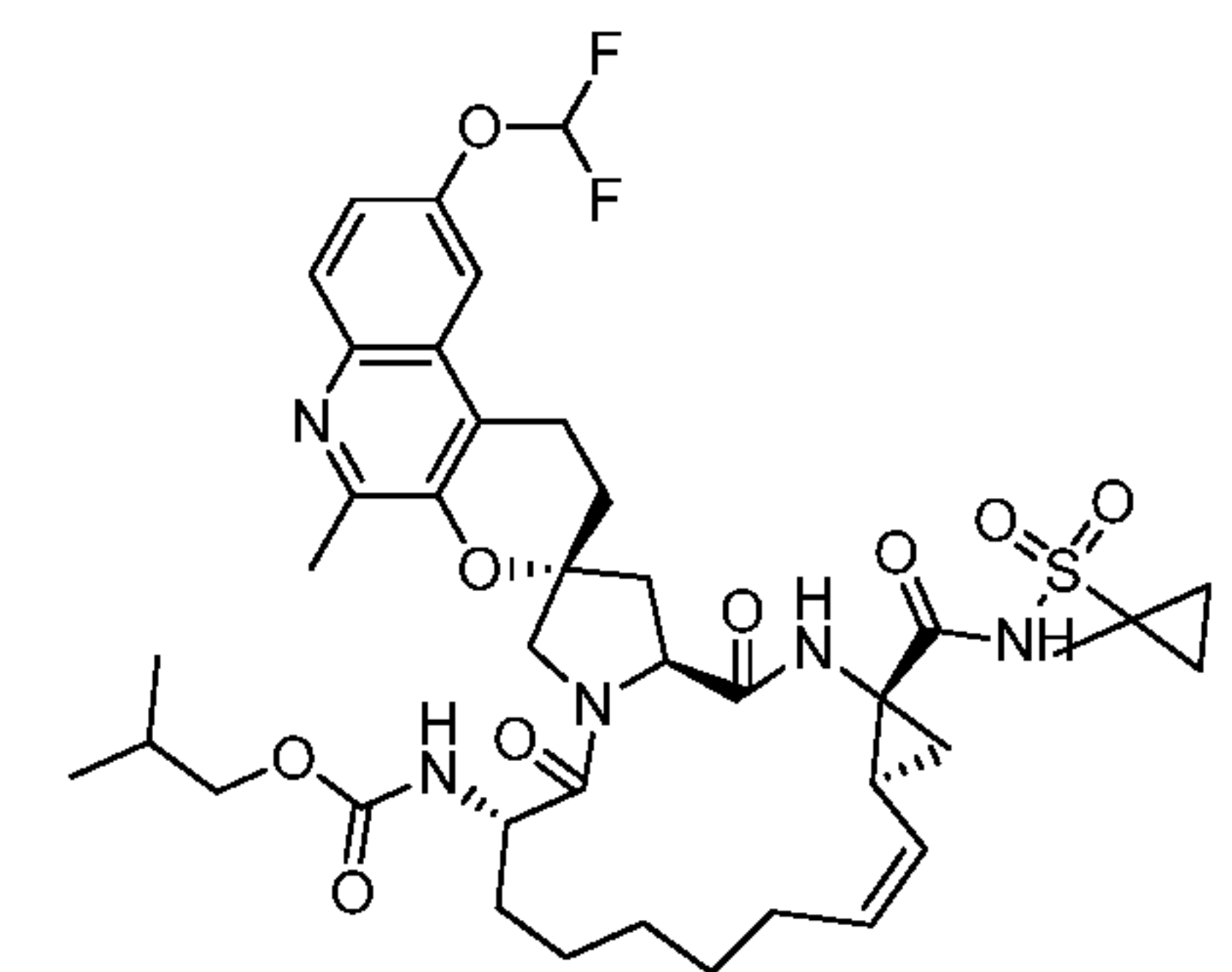
I-264



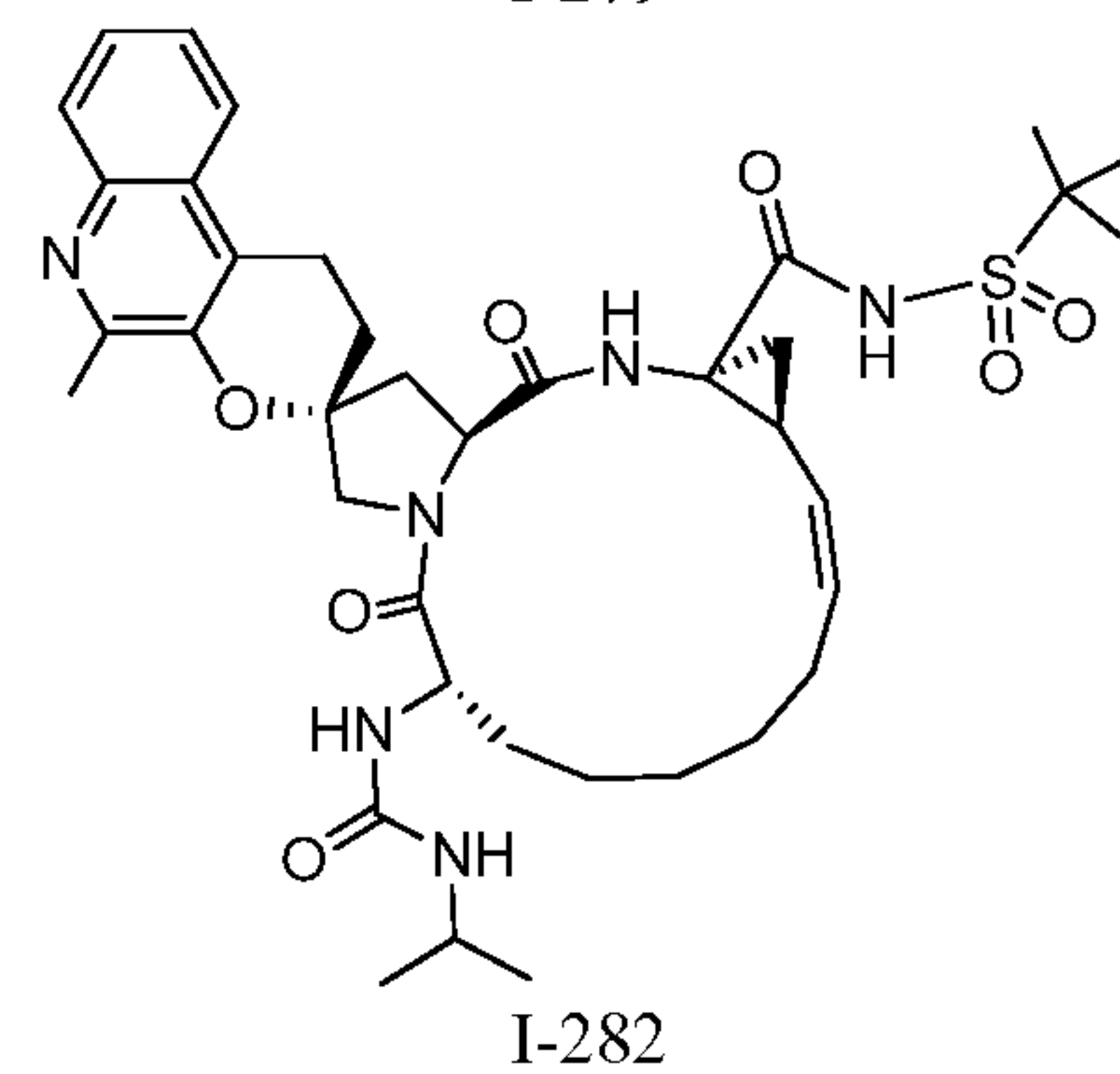
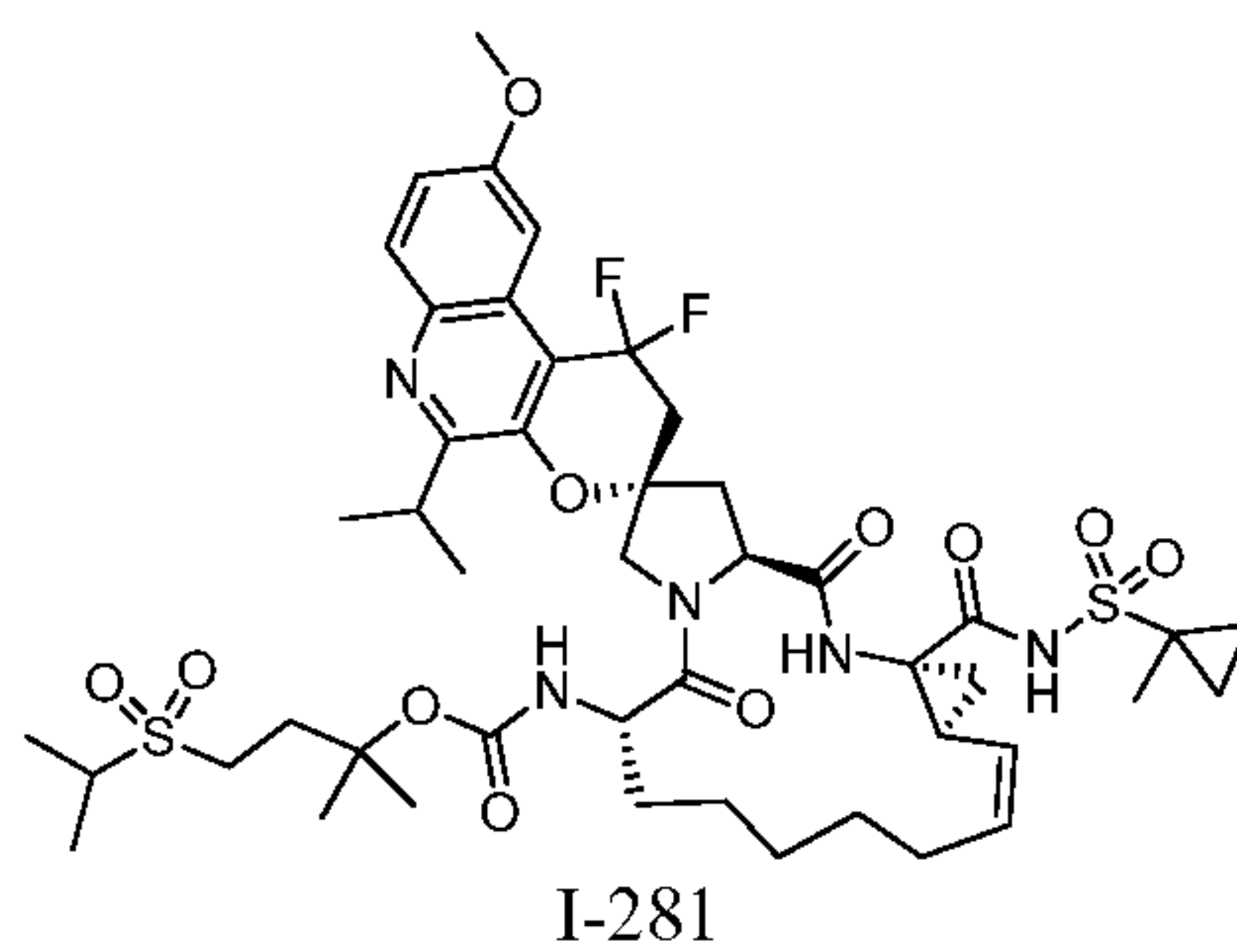
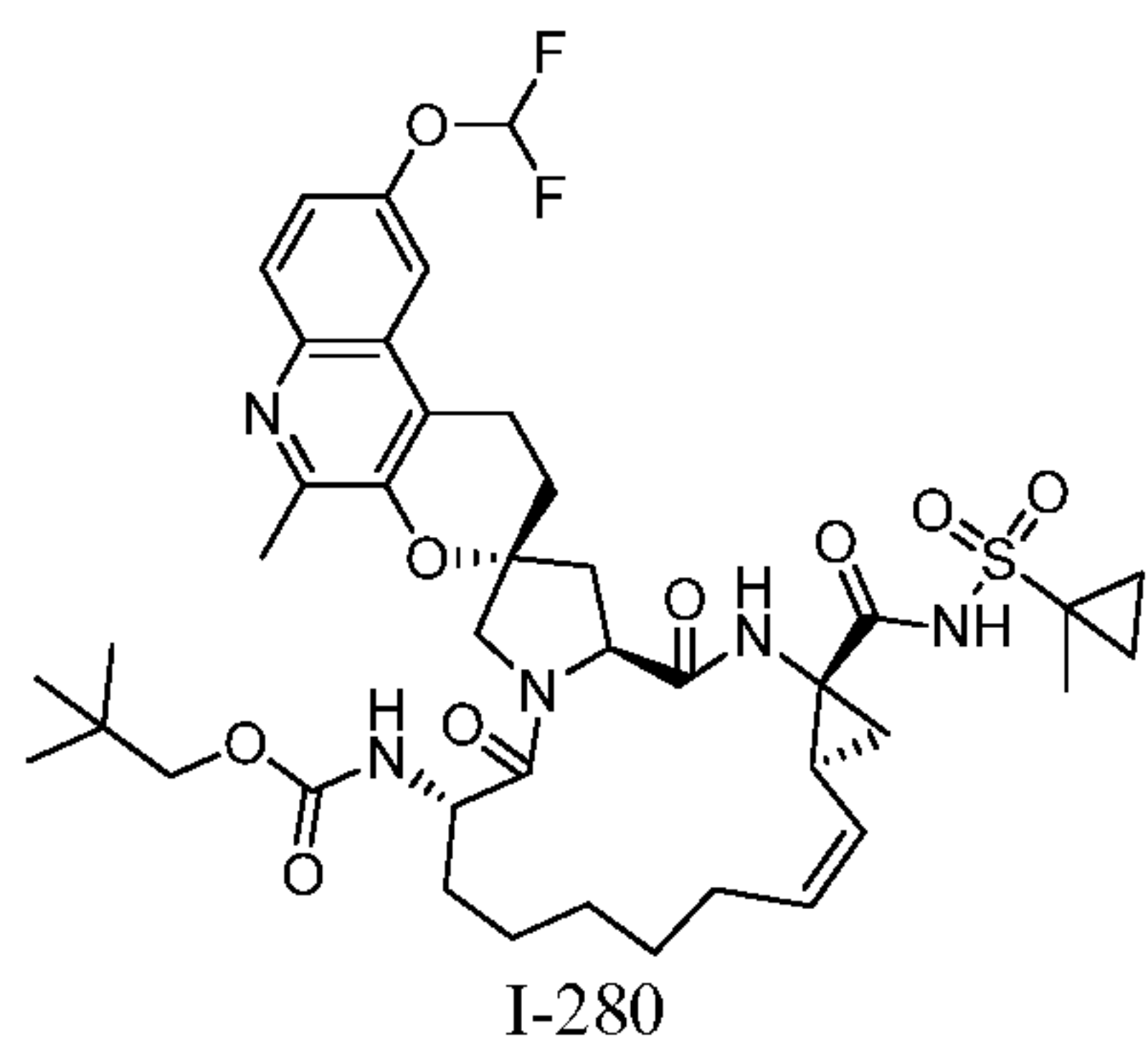
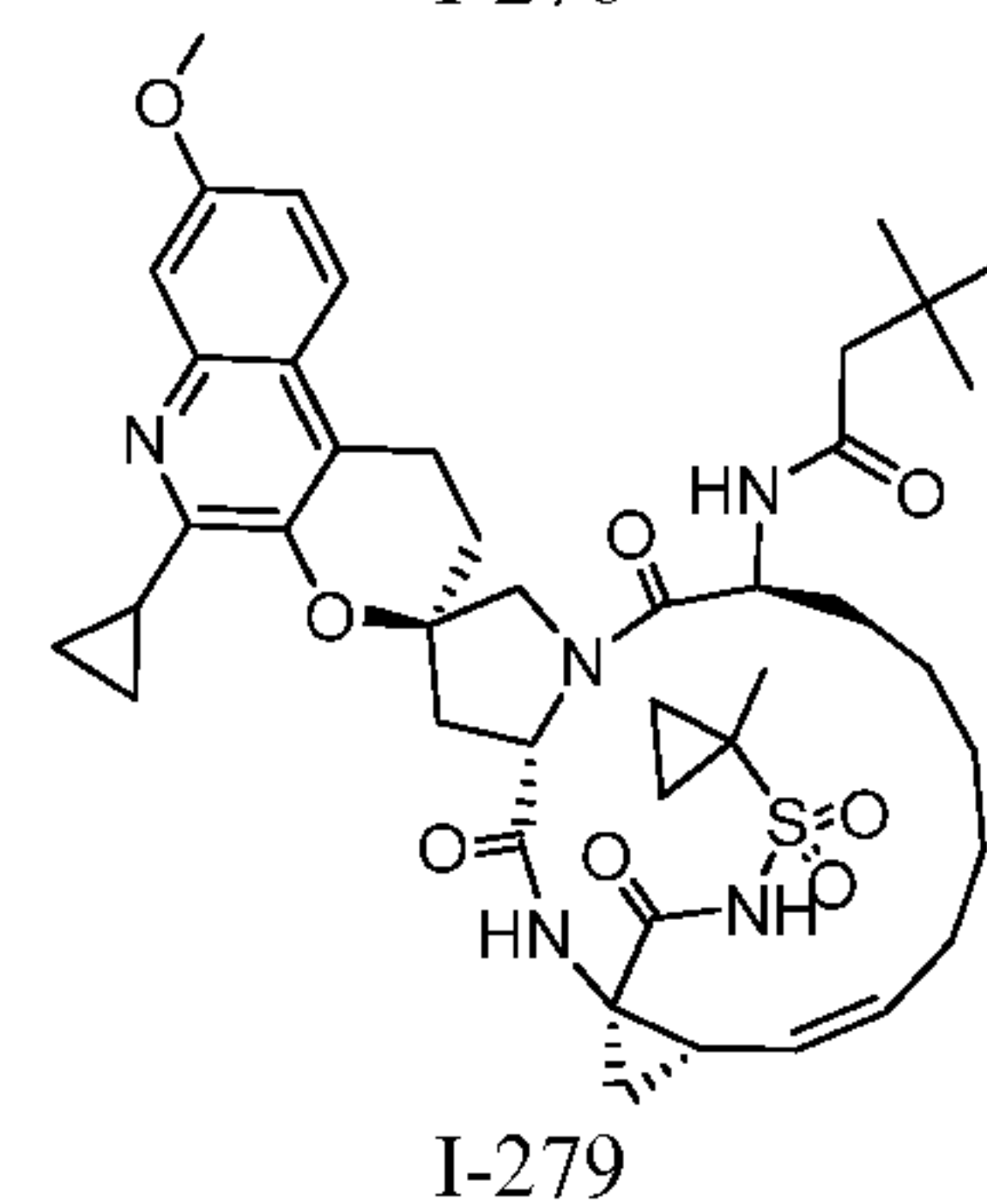
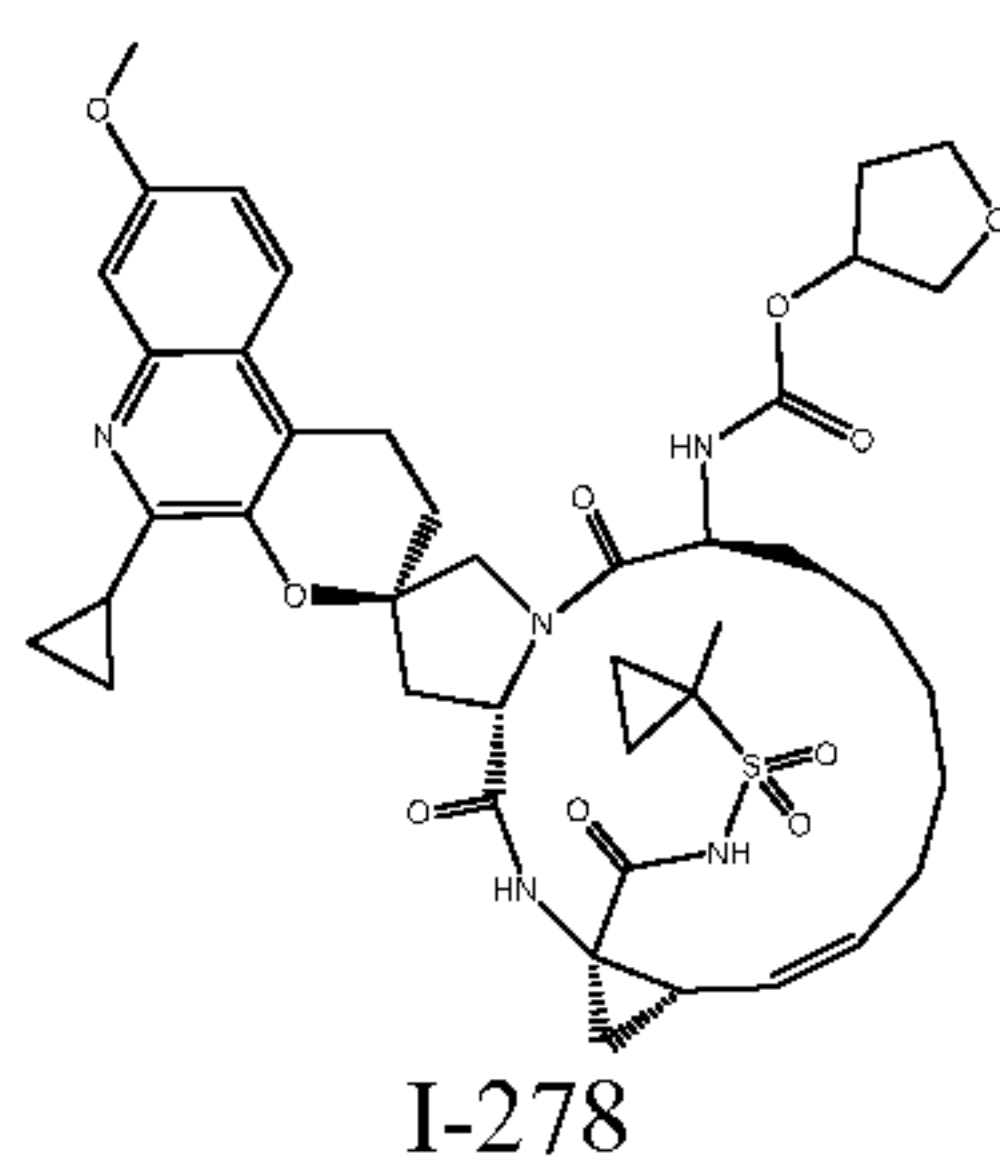
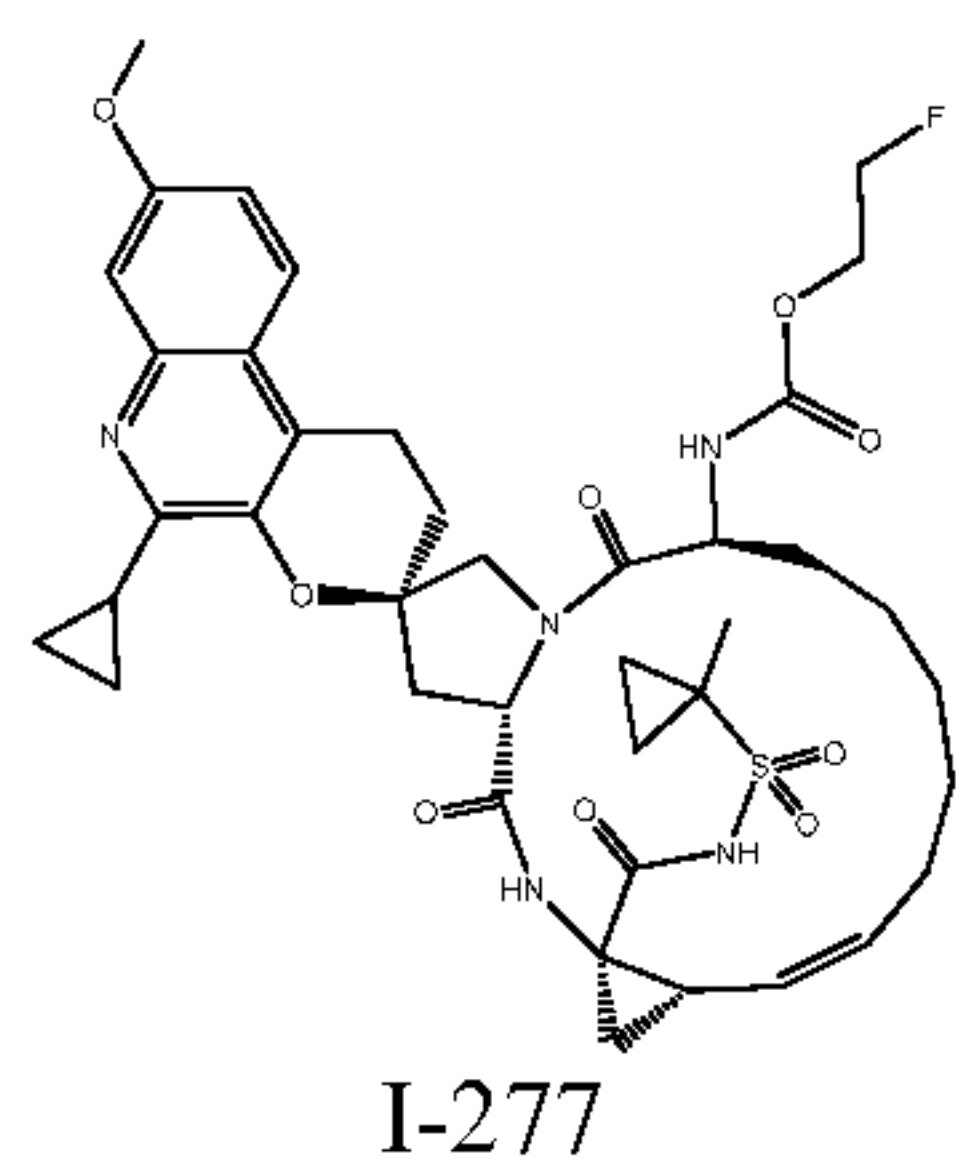
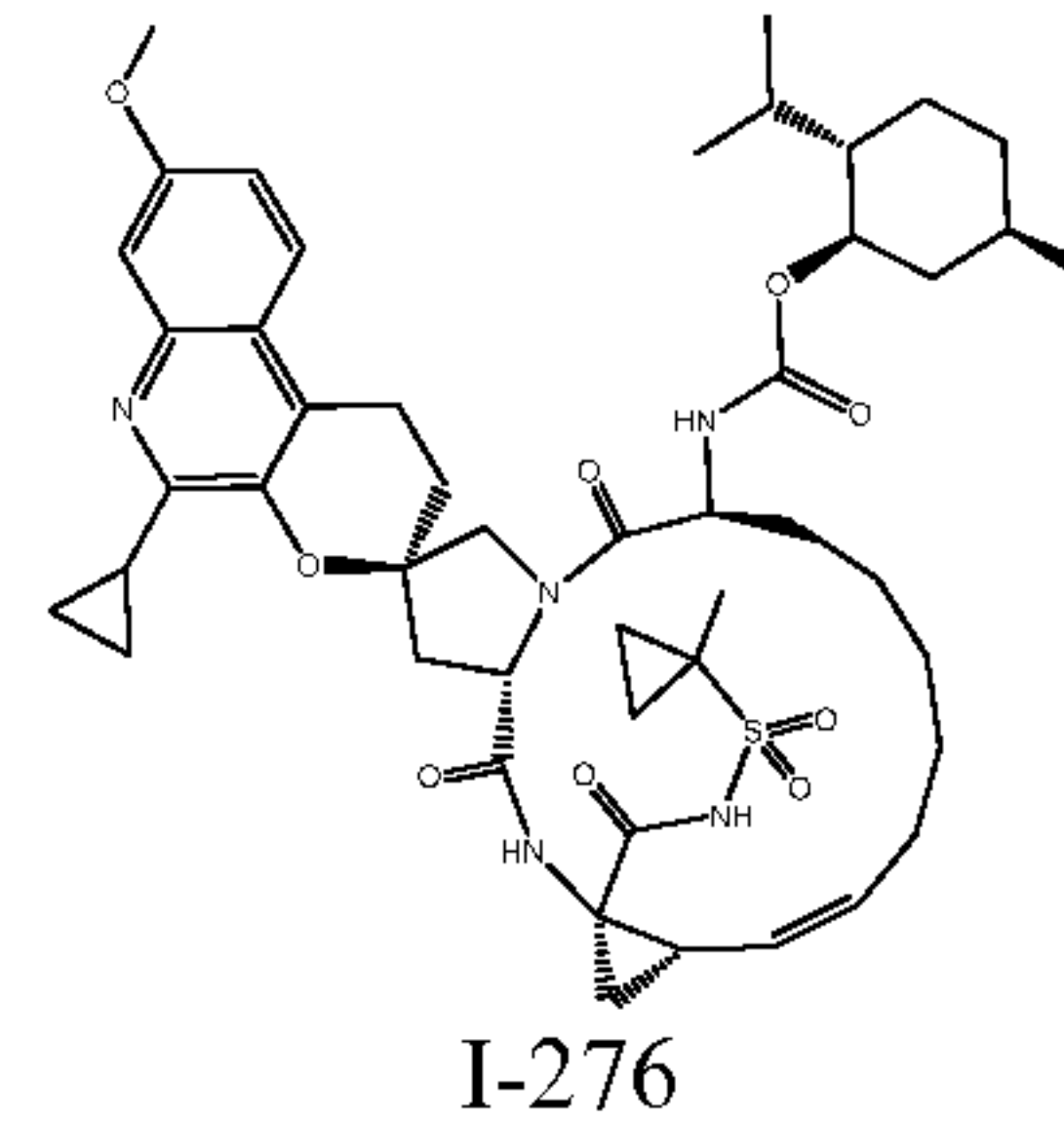
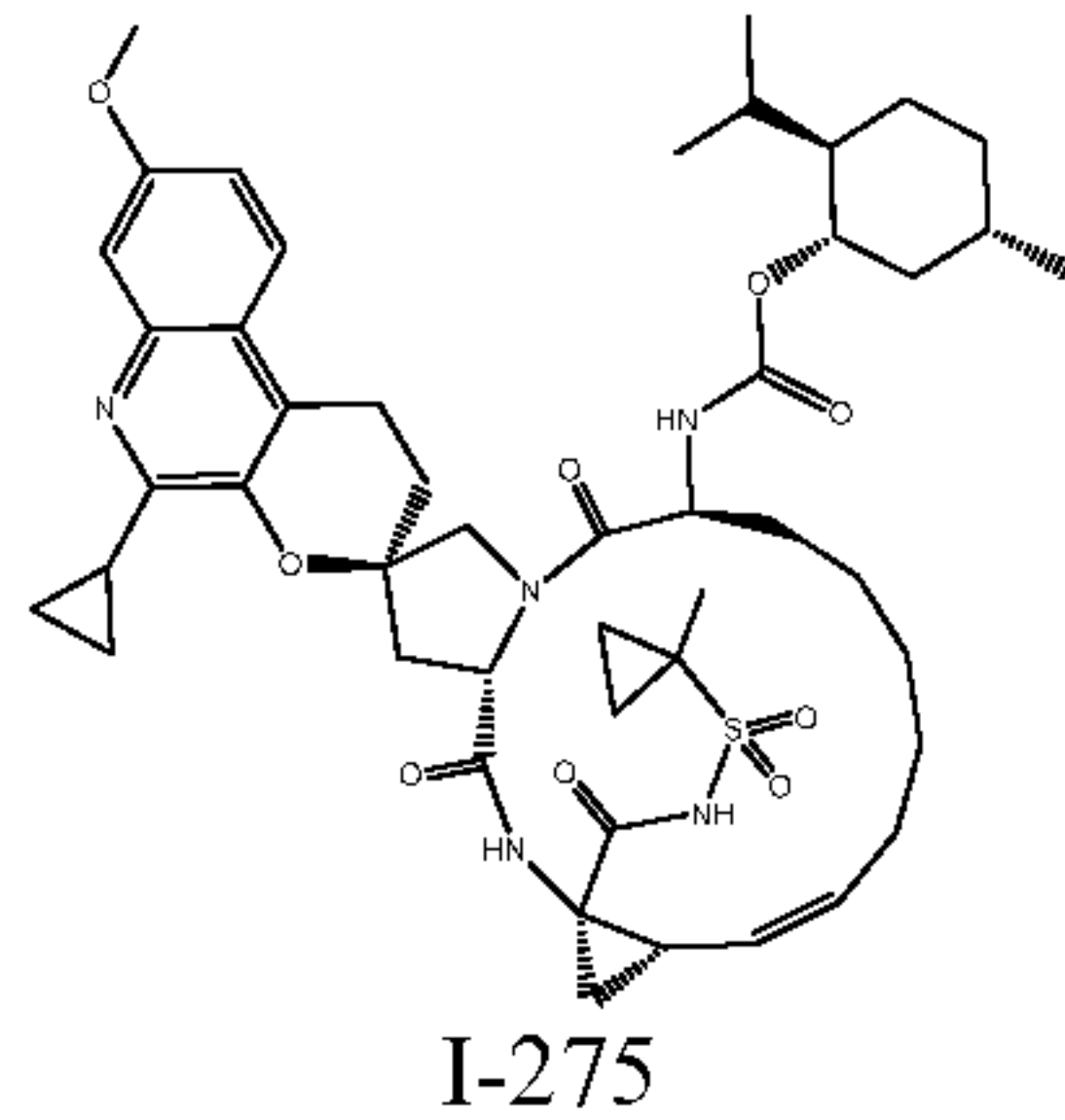
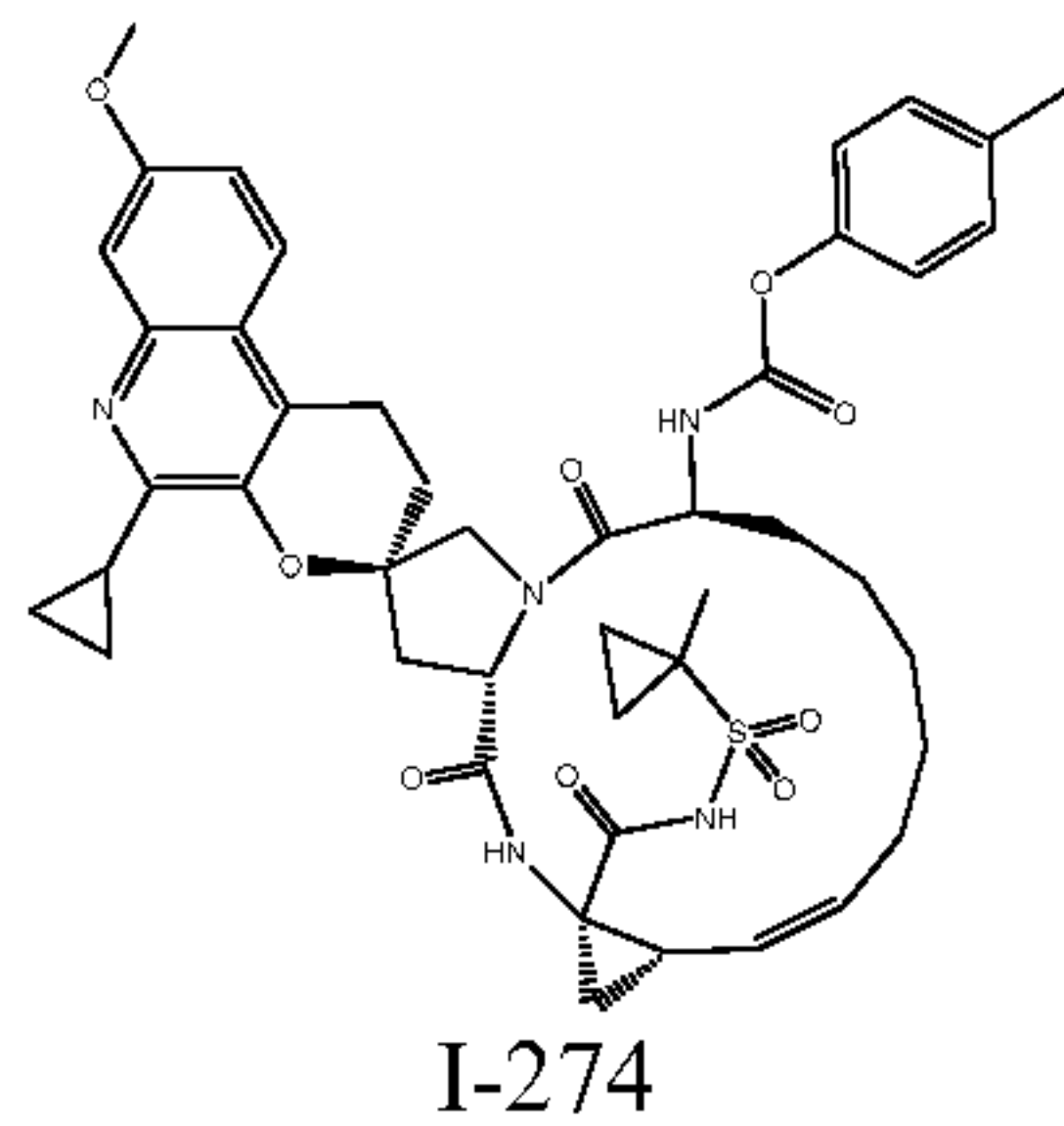
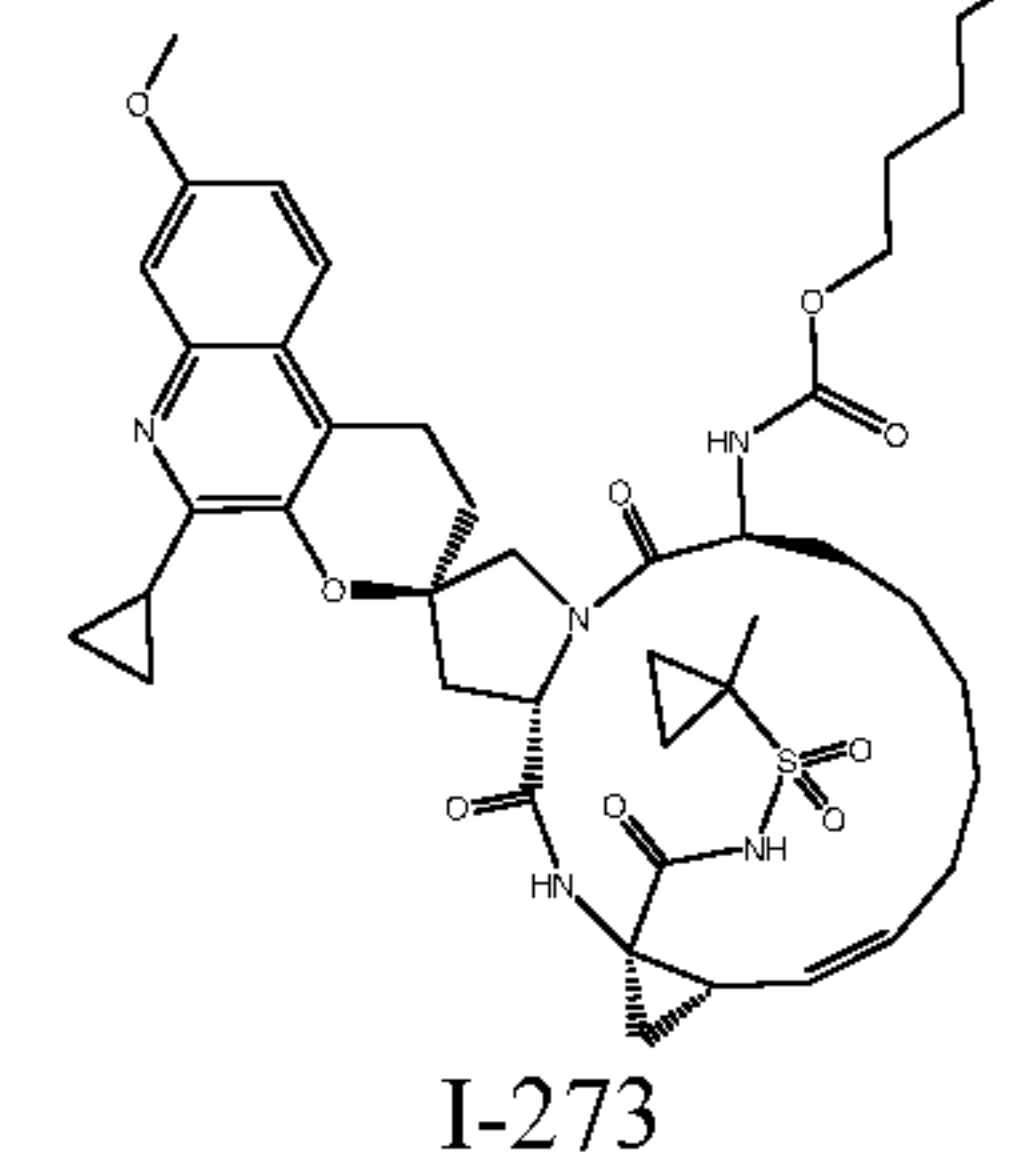
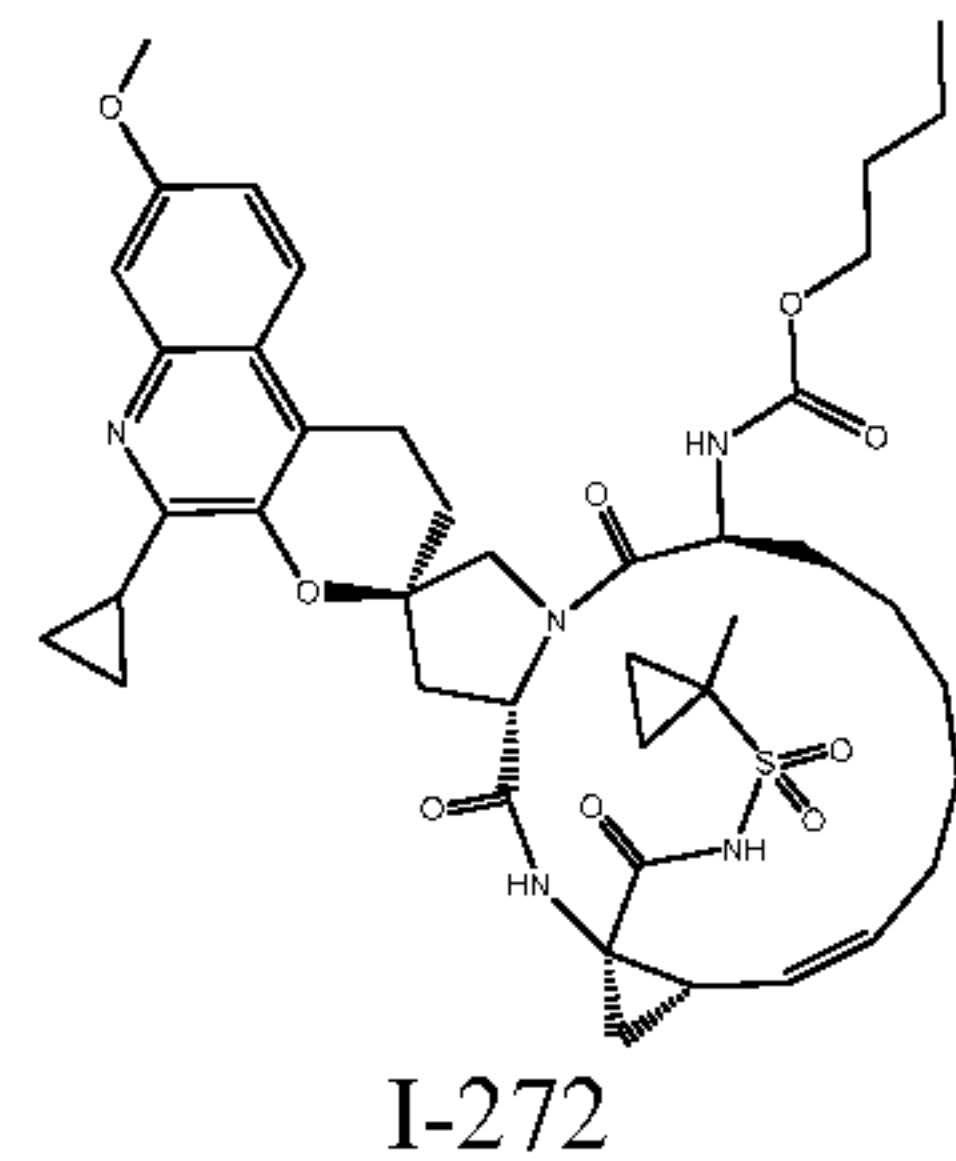
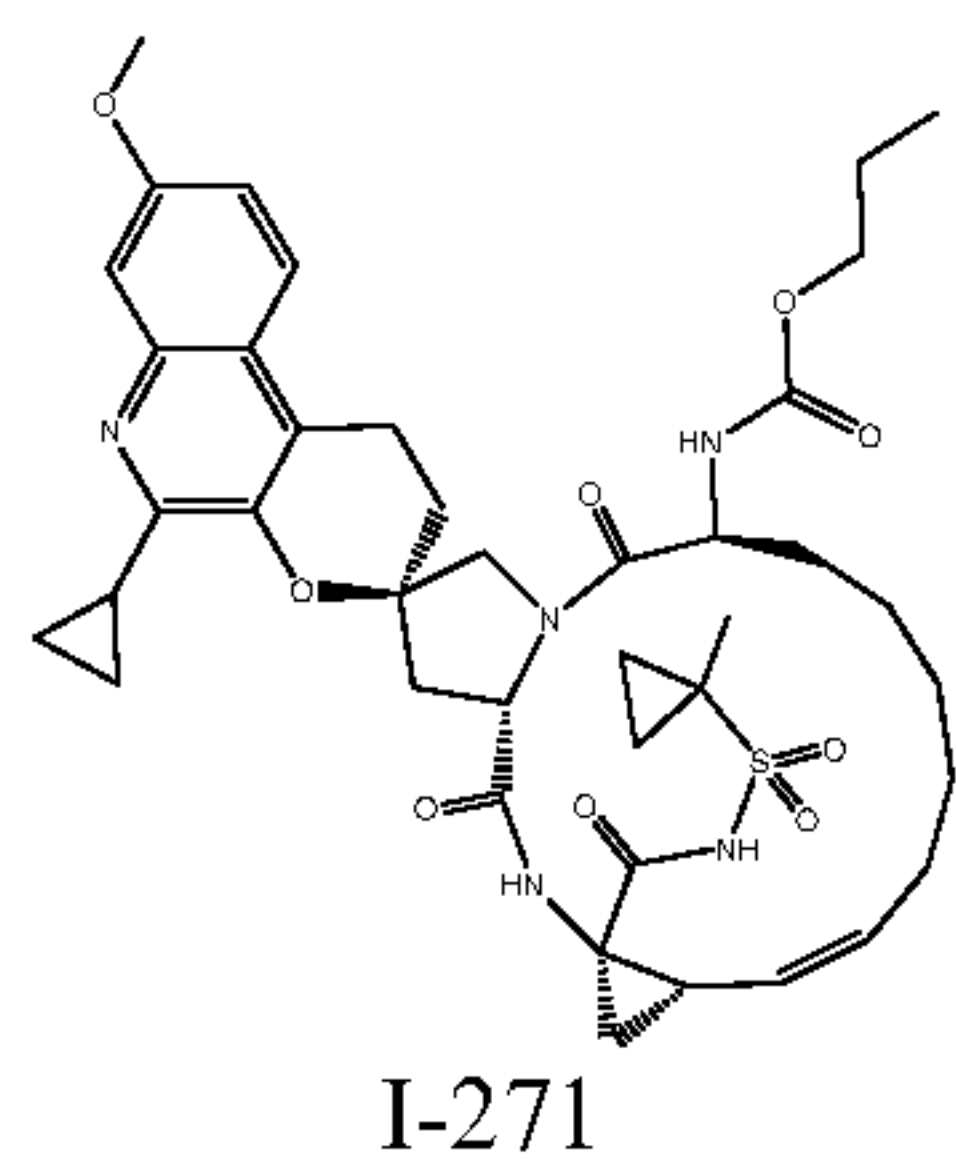
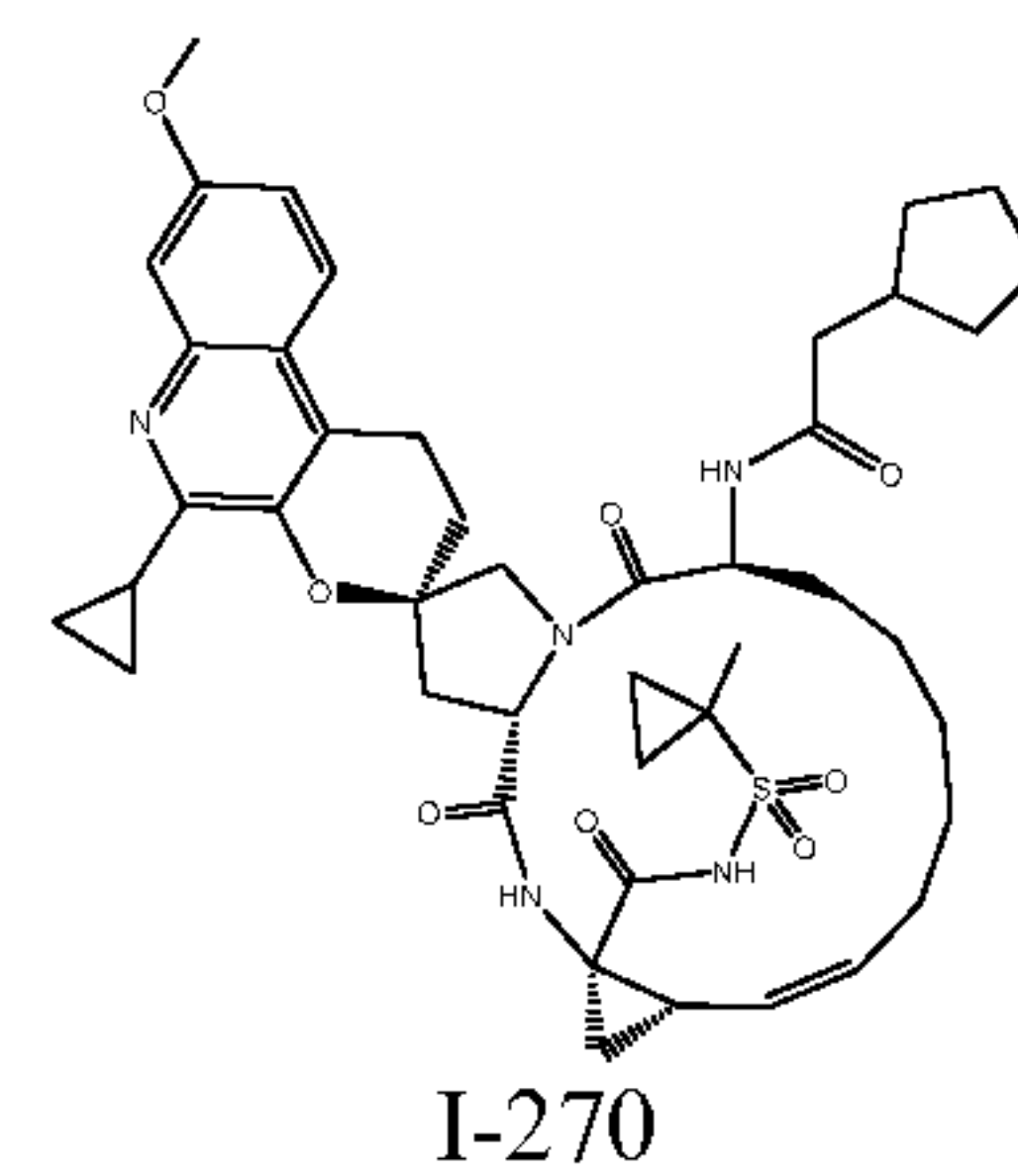
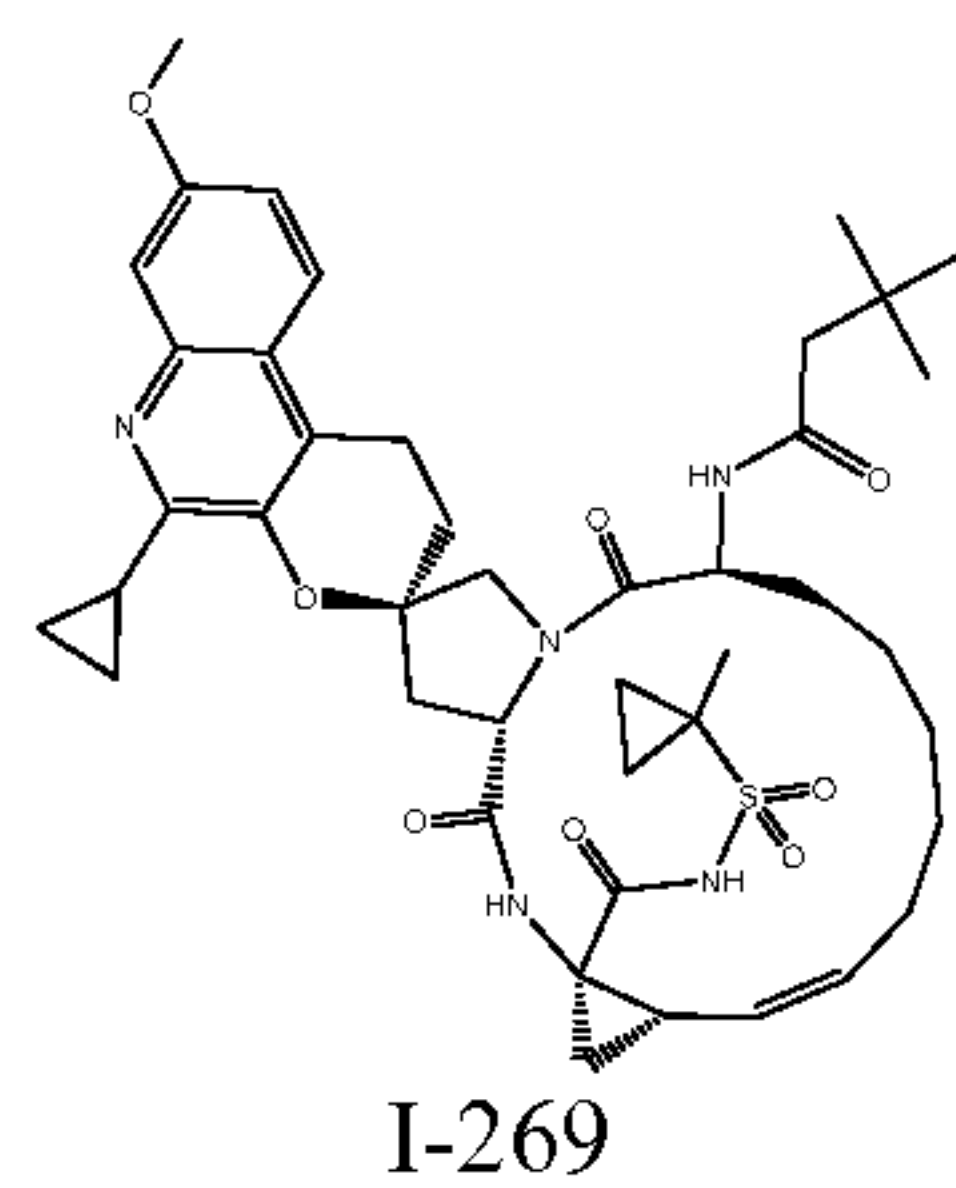
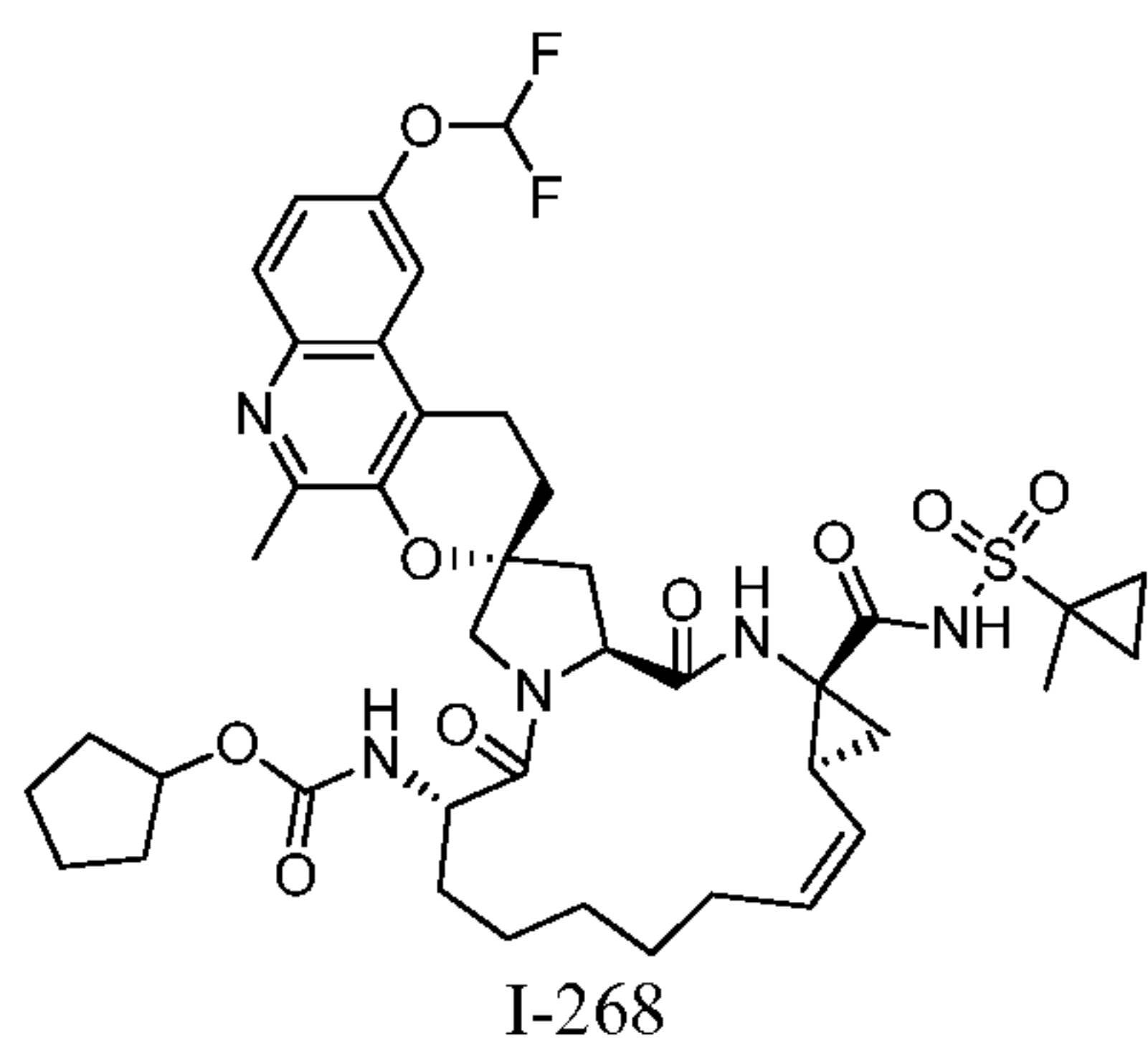
I-265

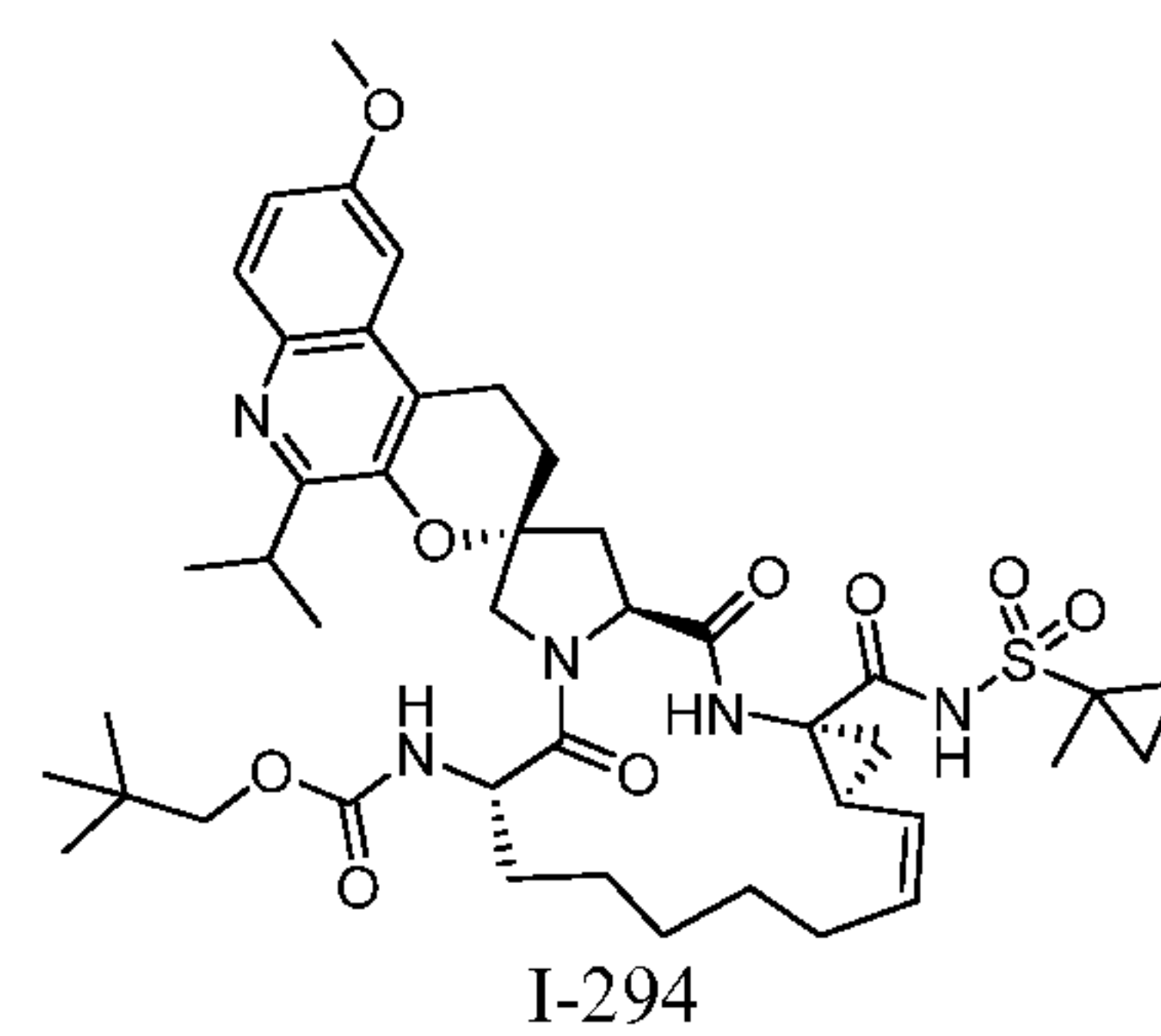
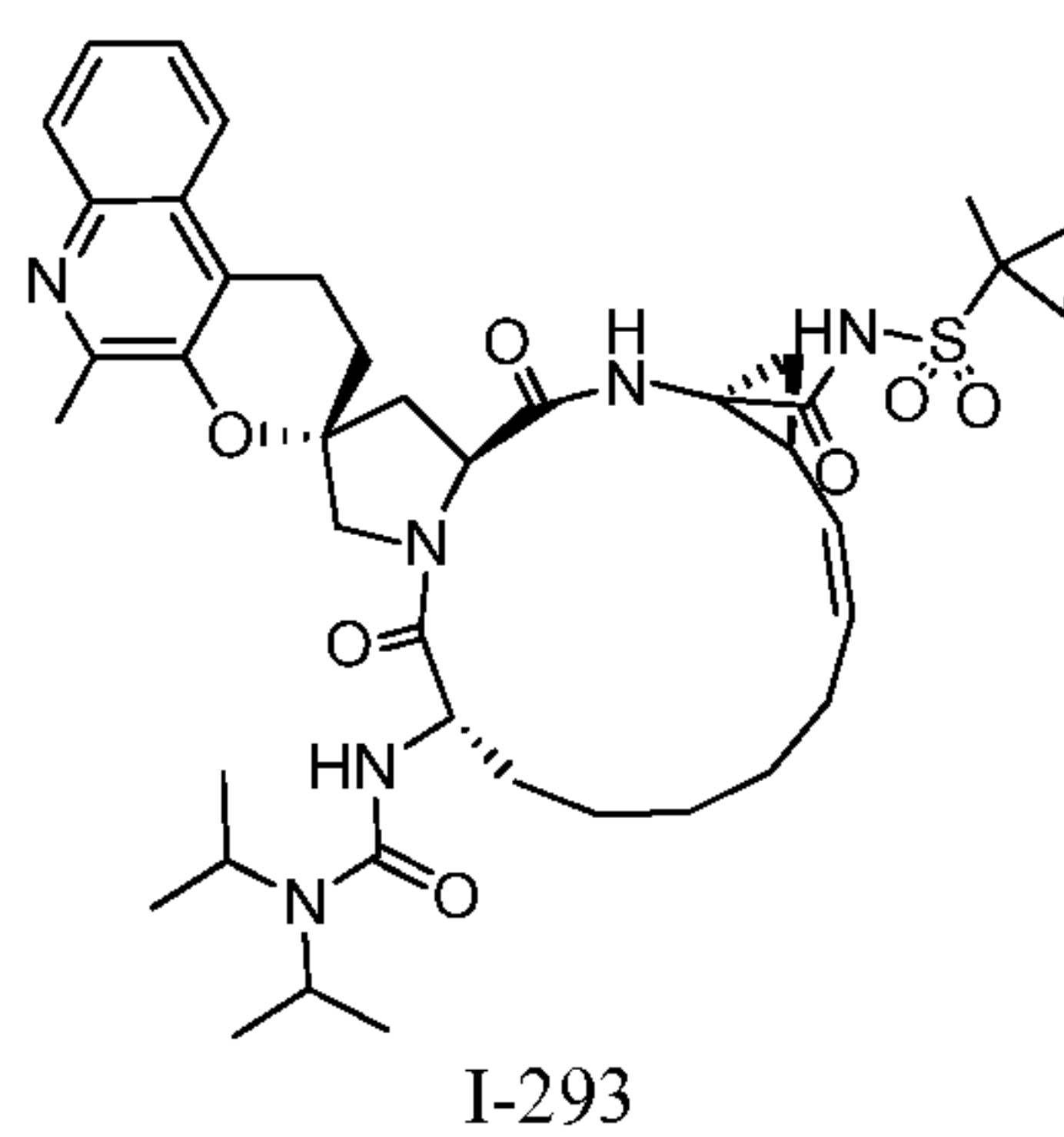
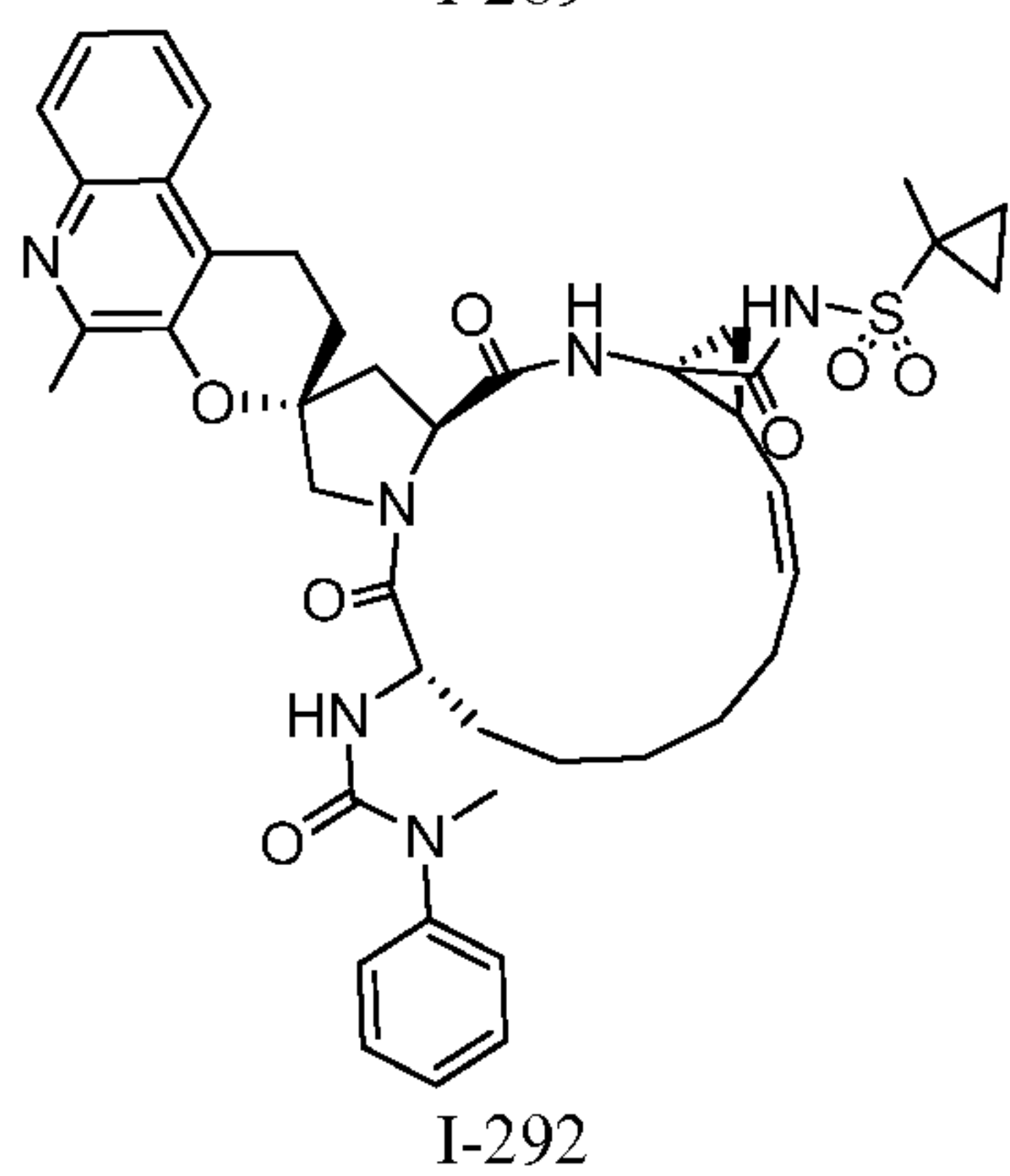
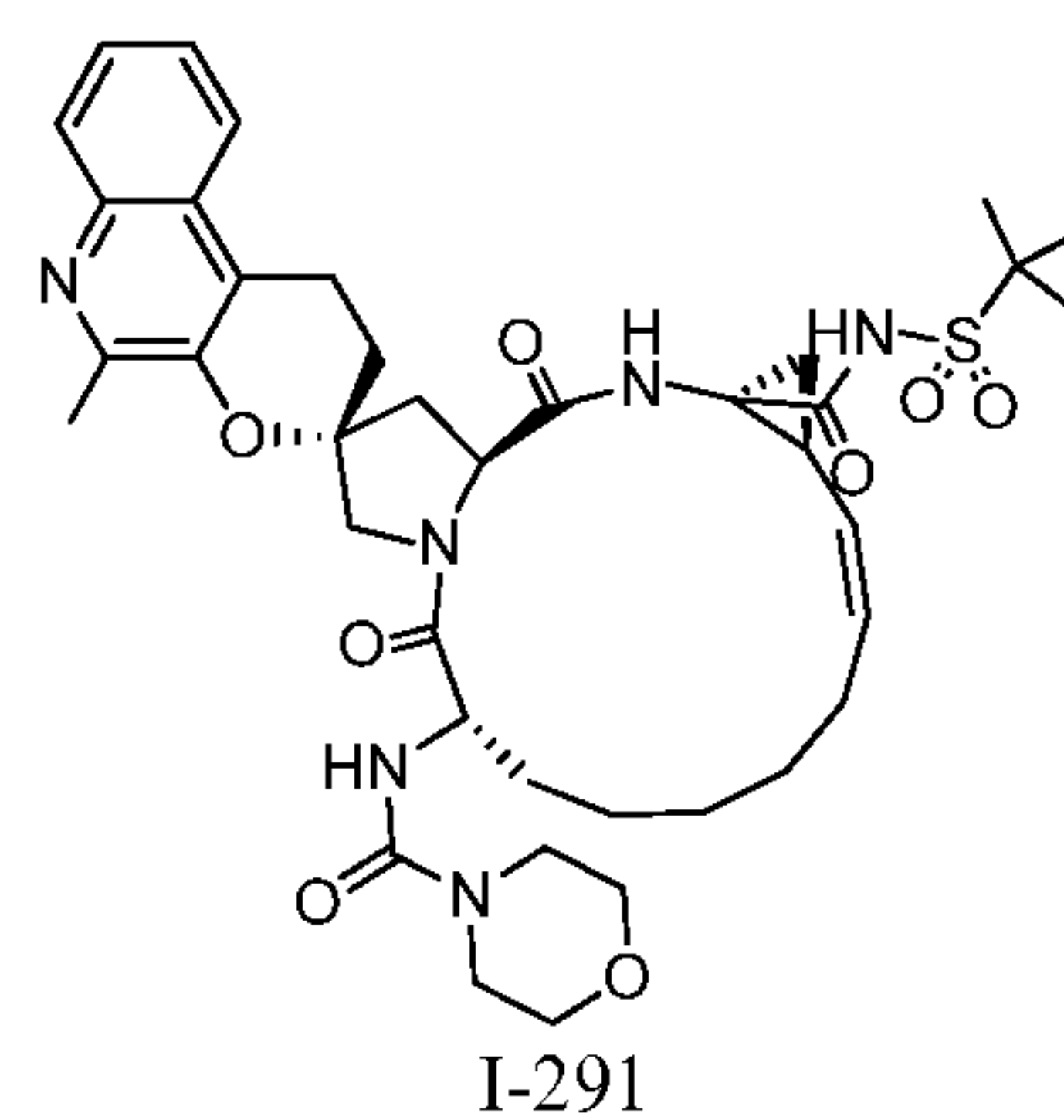
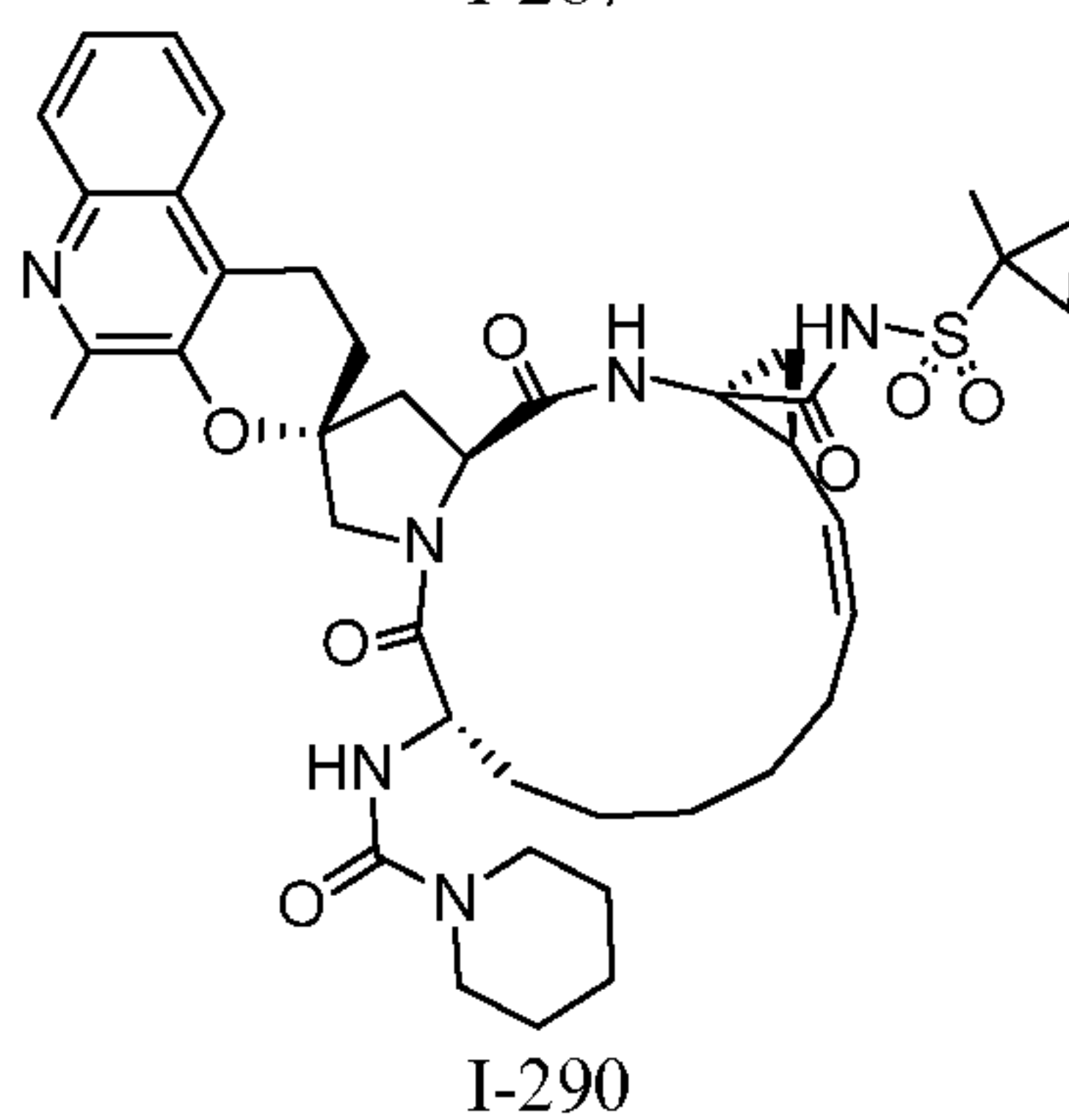
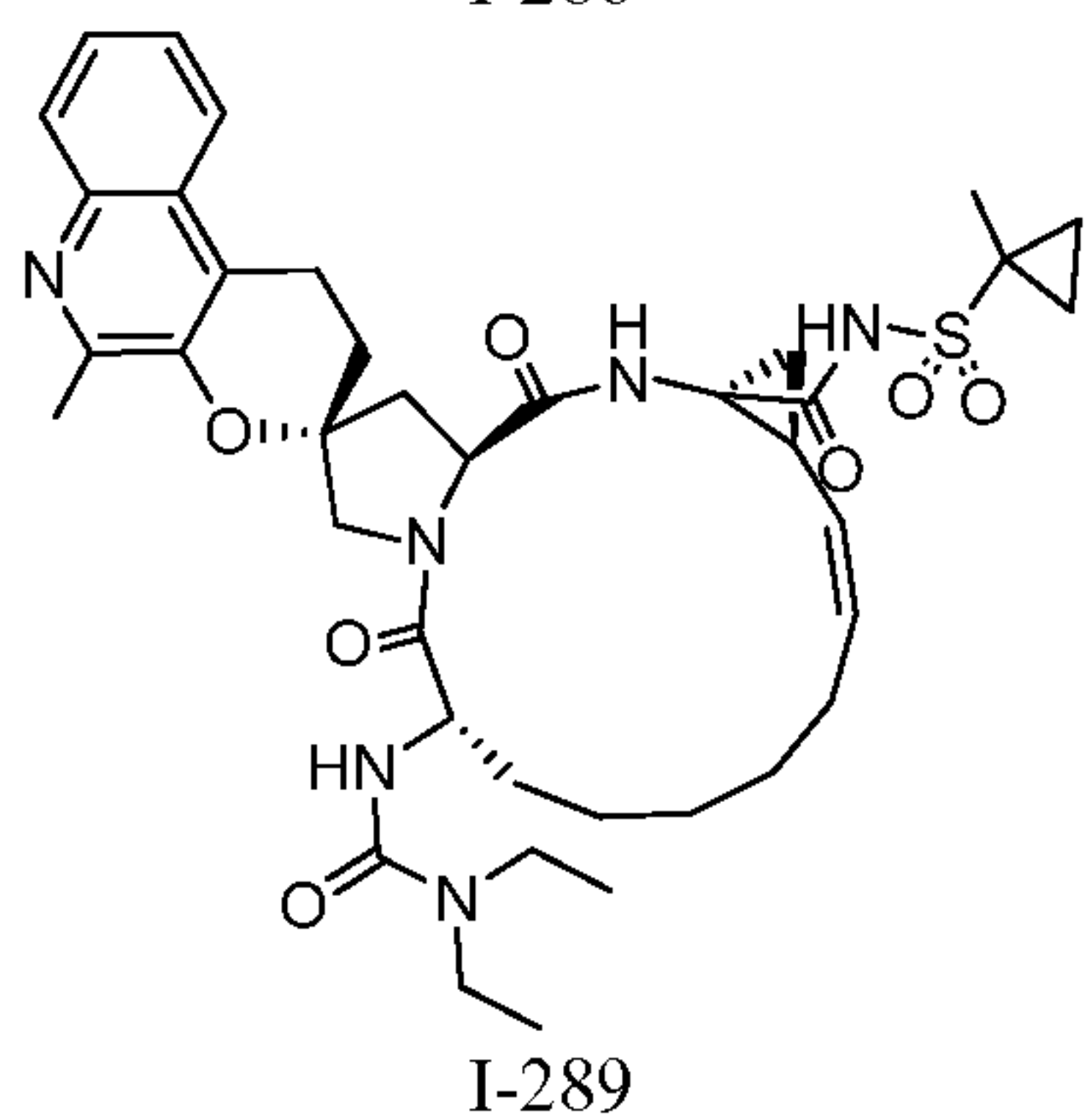
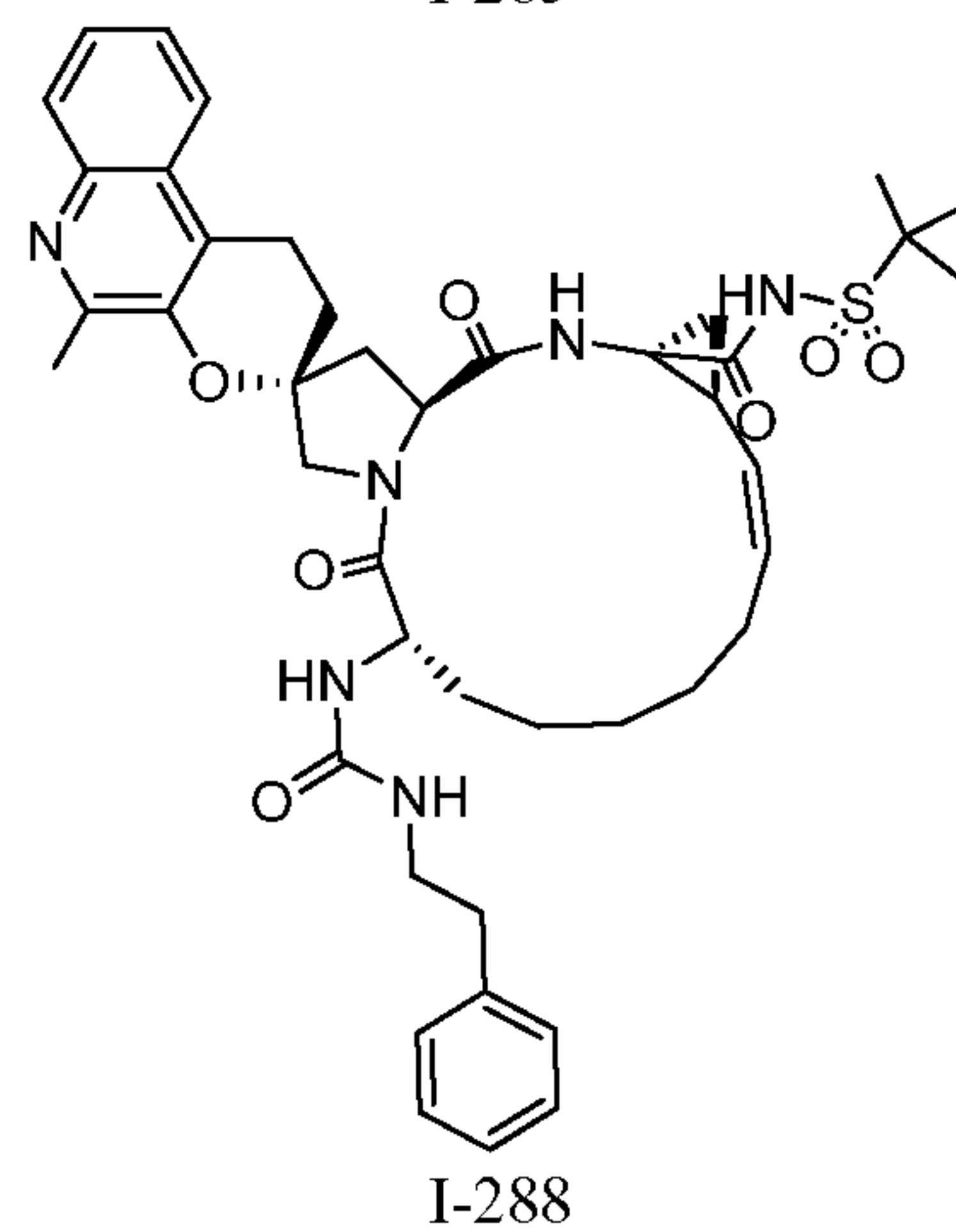
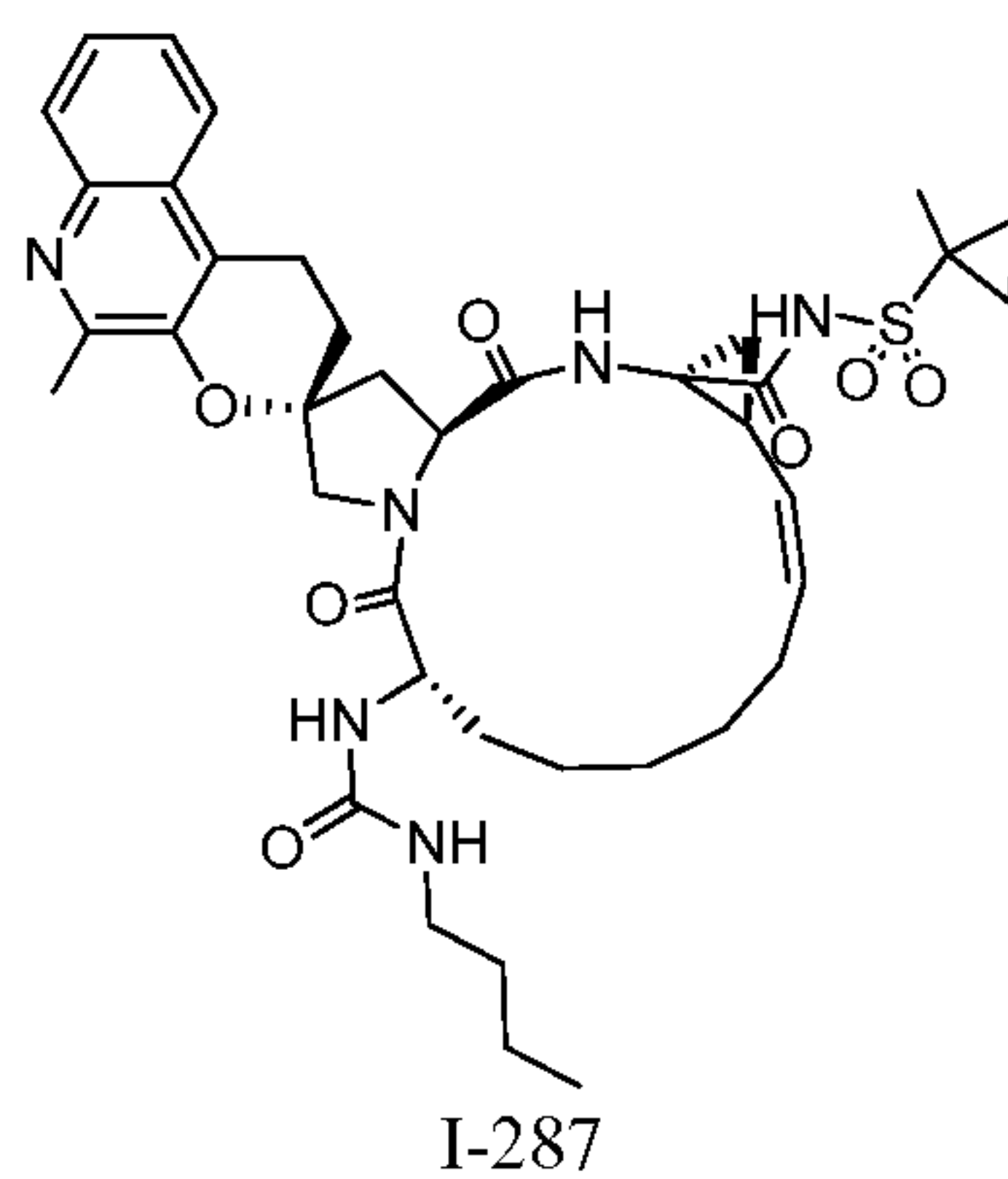
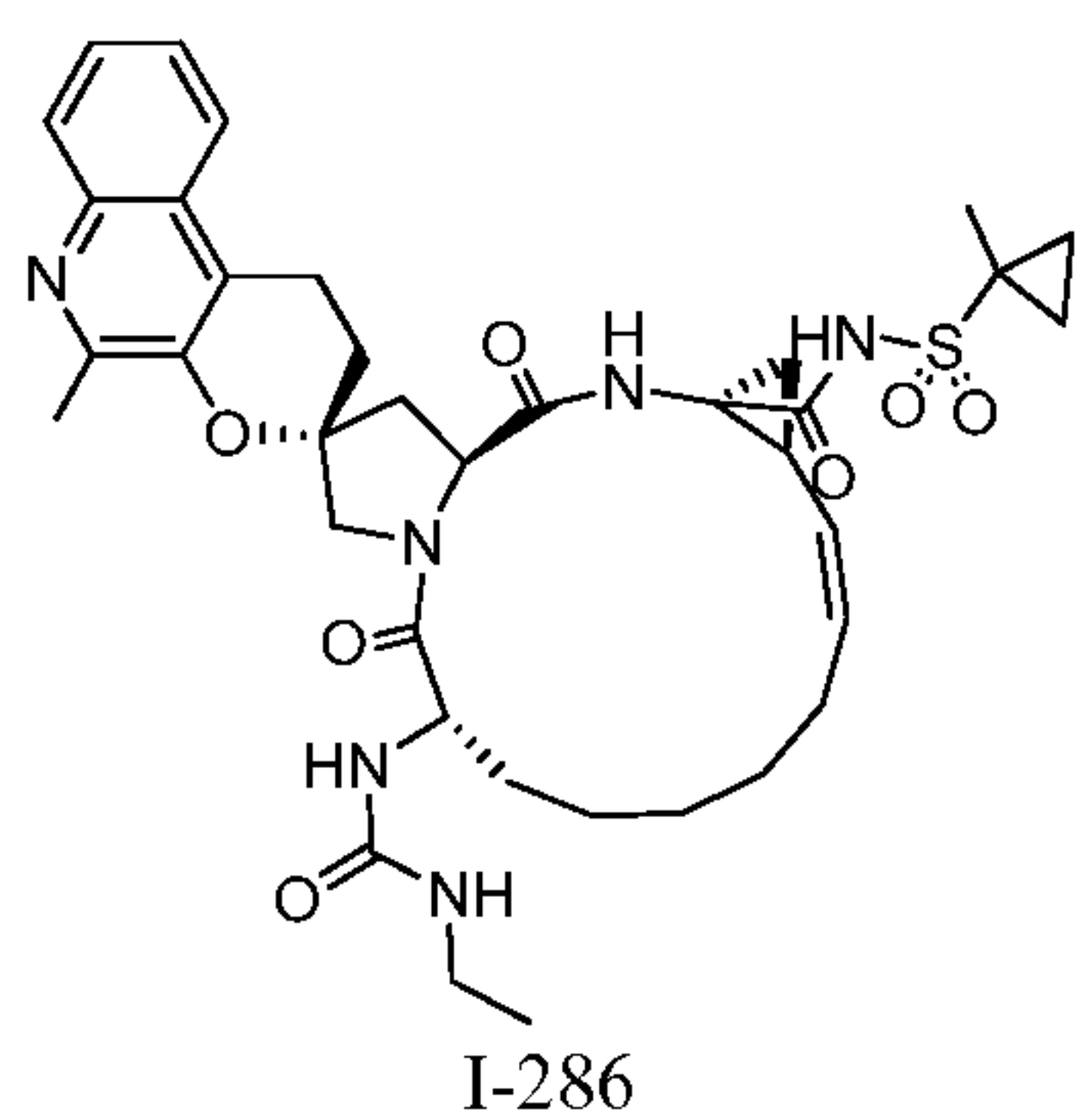
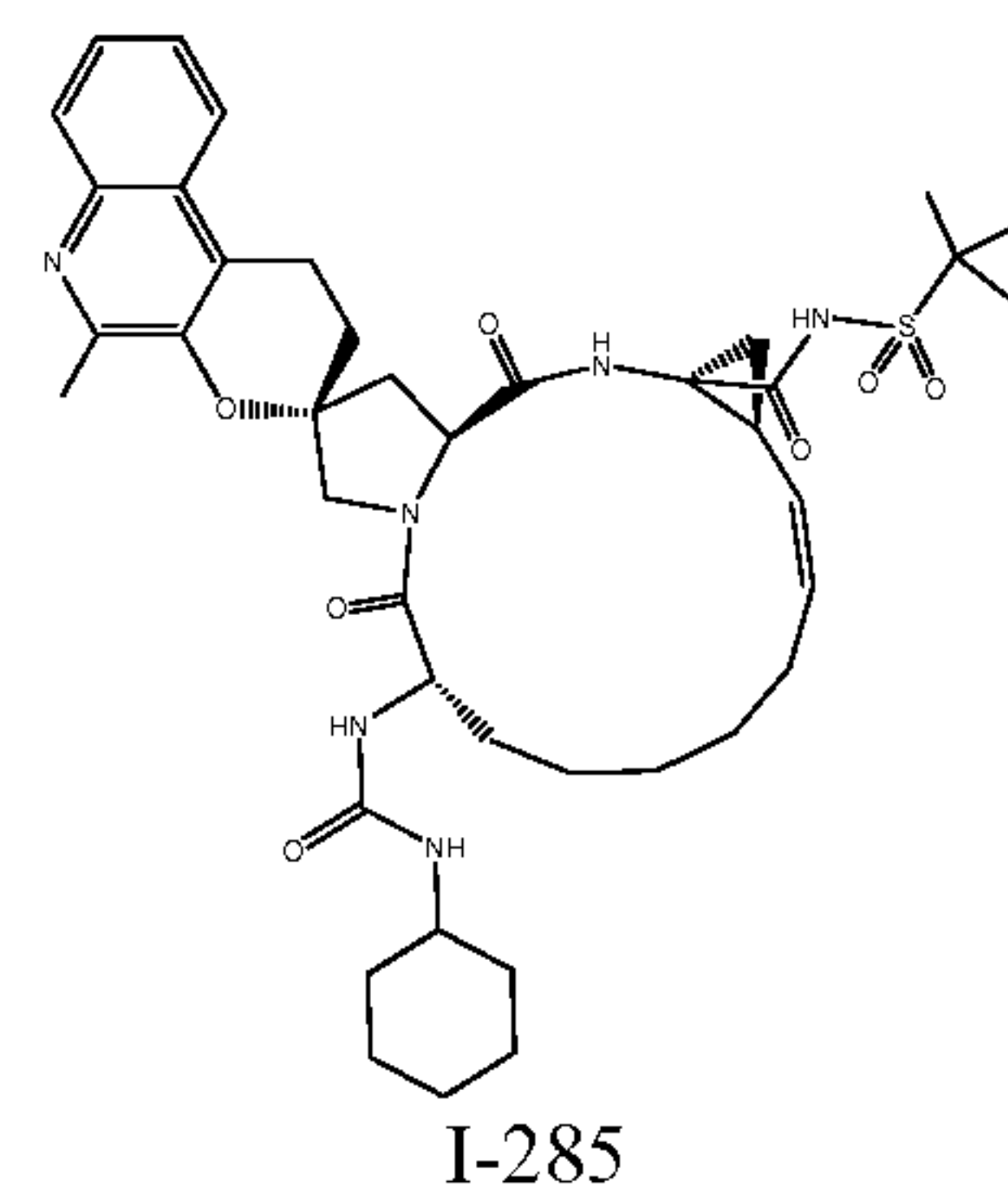
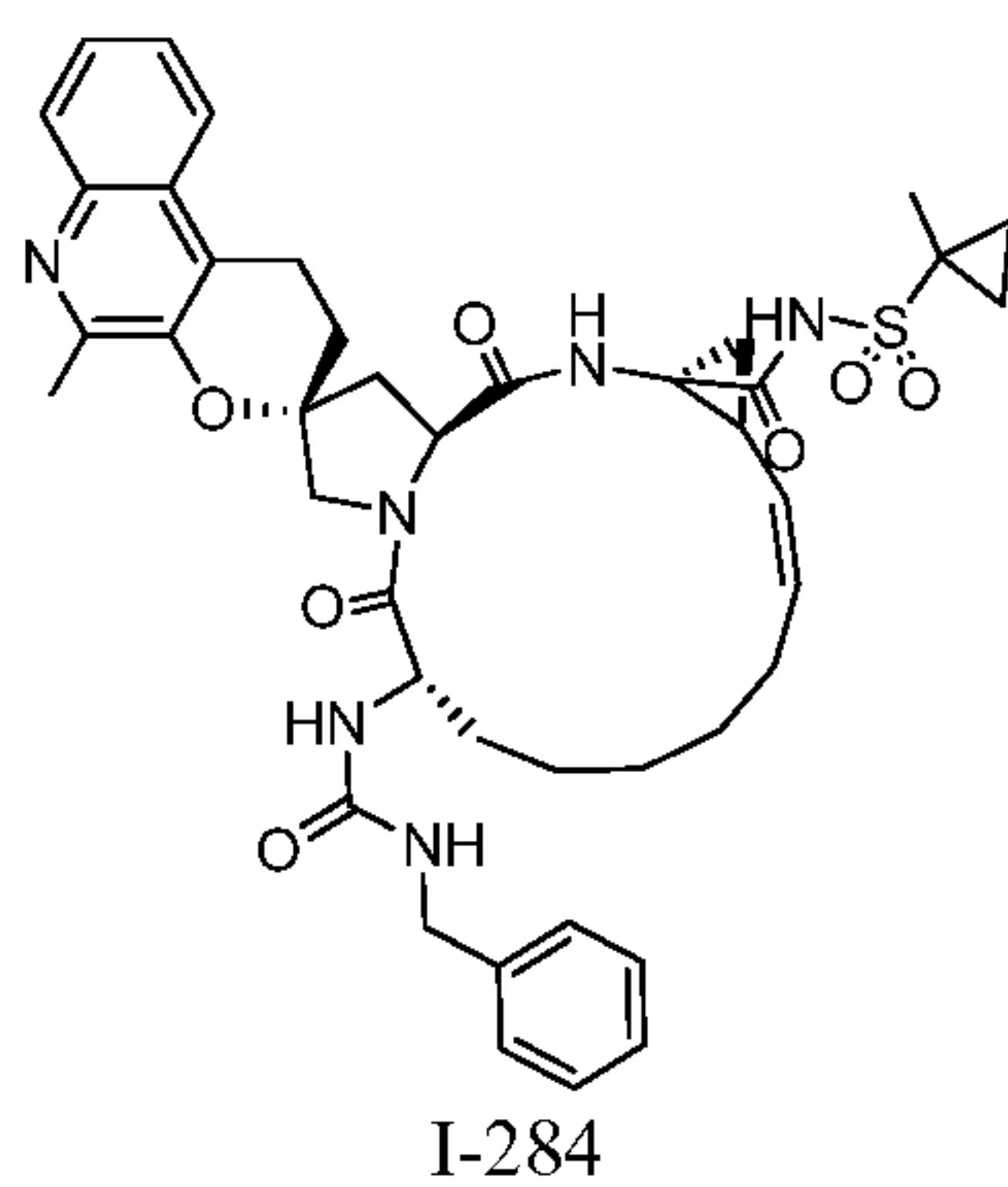
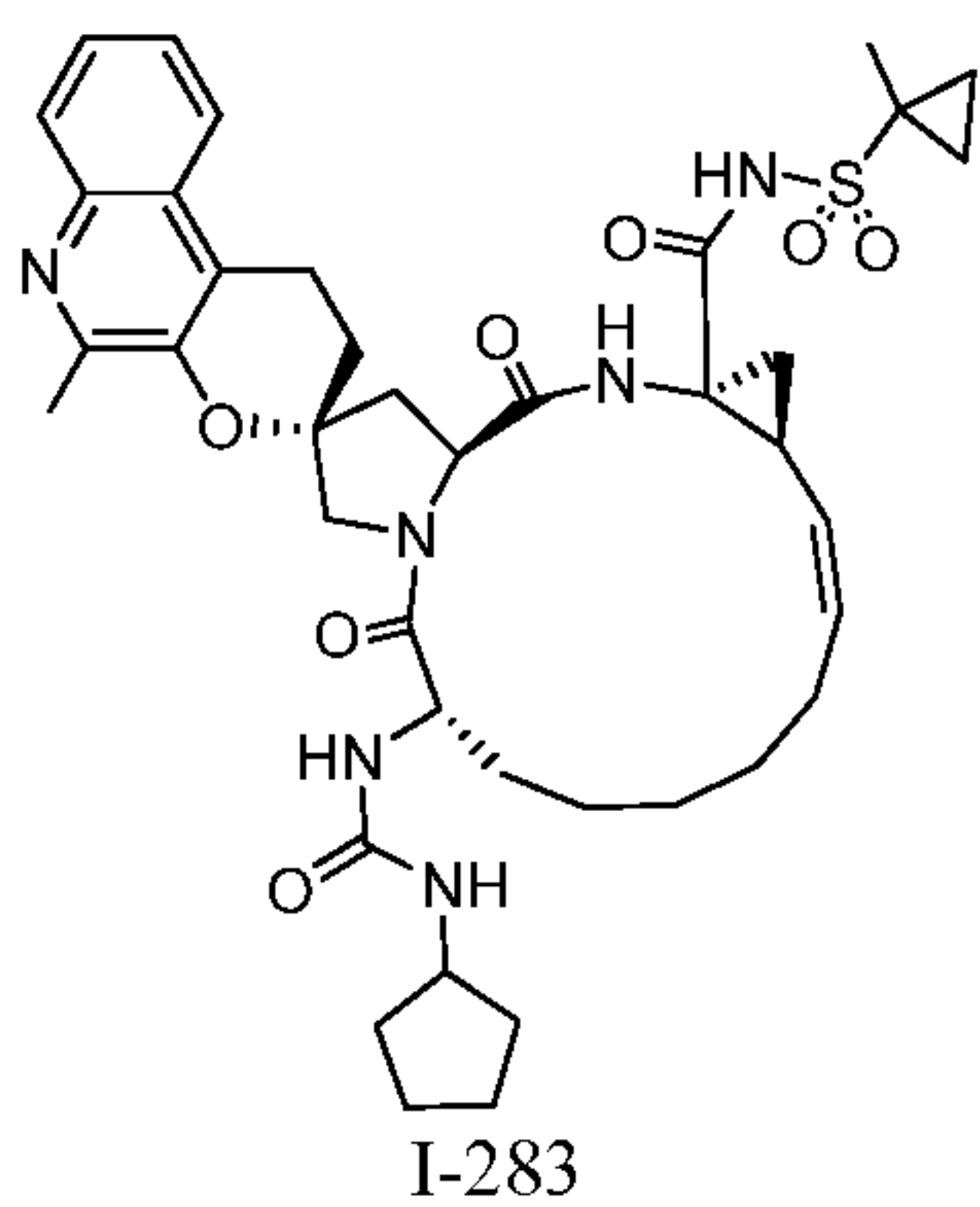


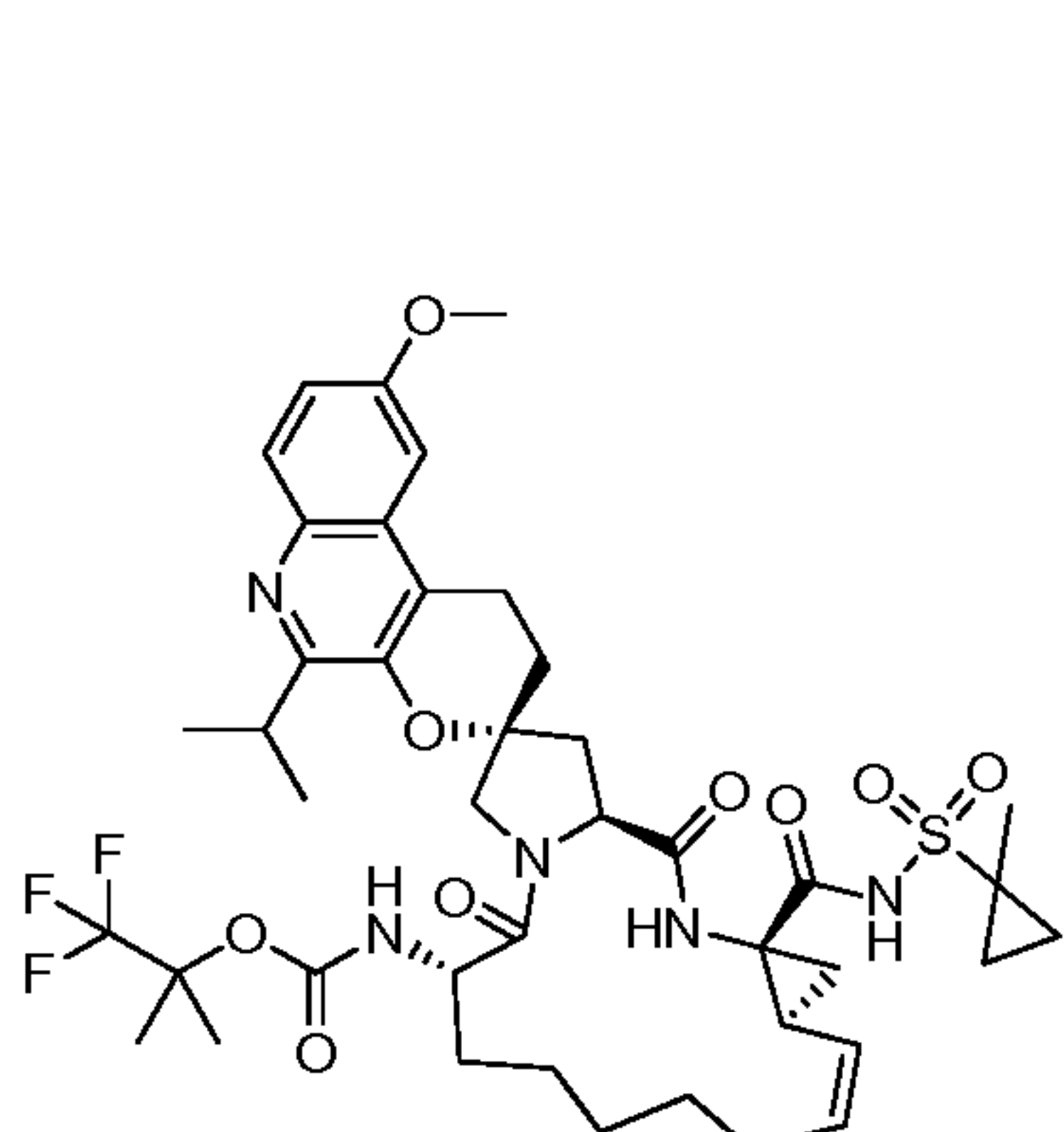
I-266



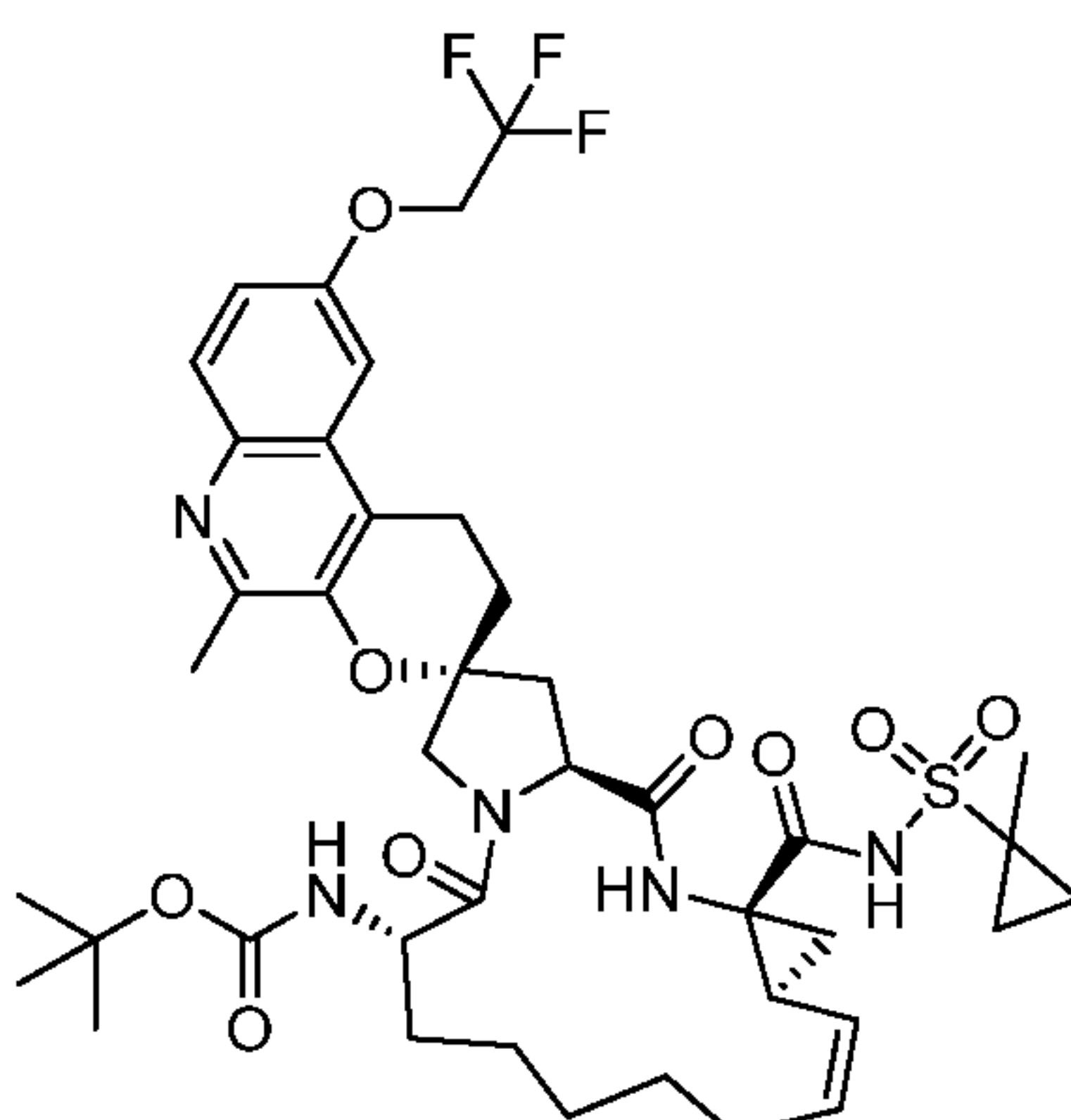
I-267



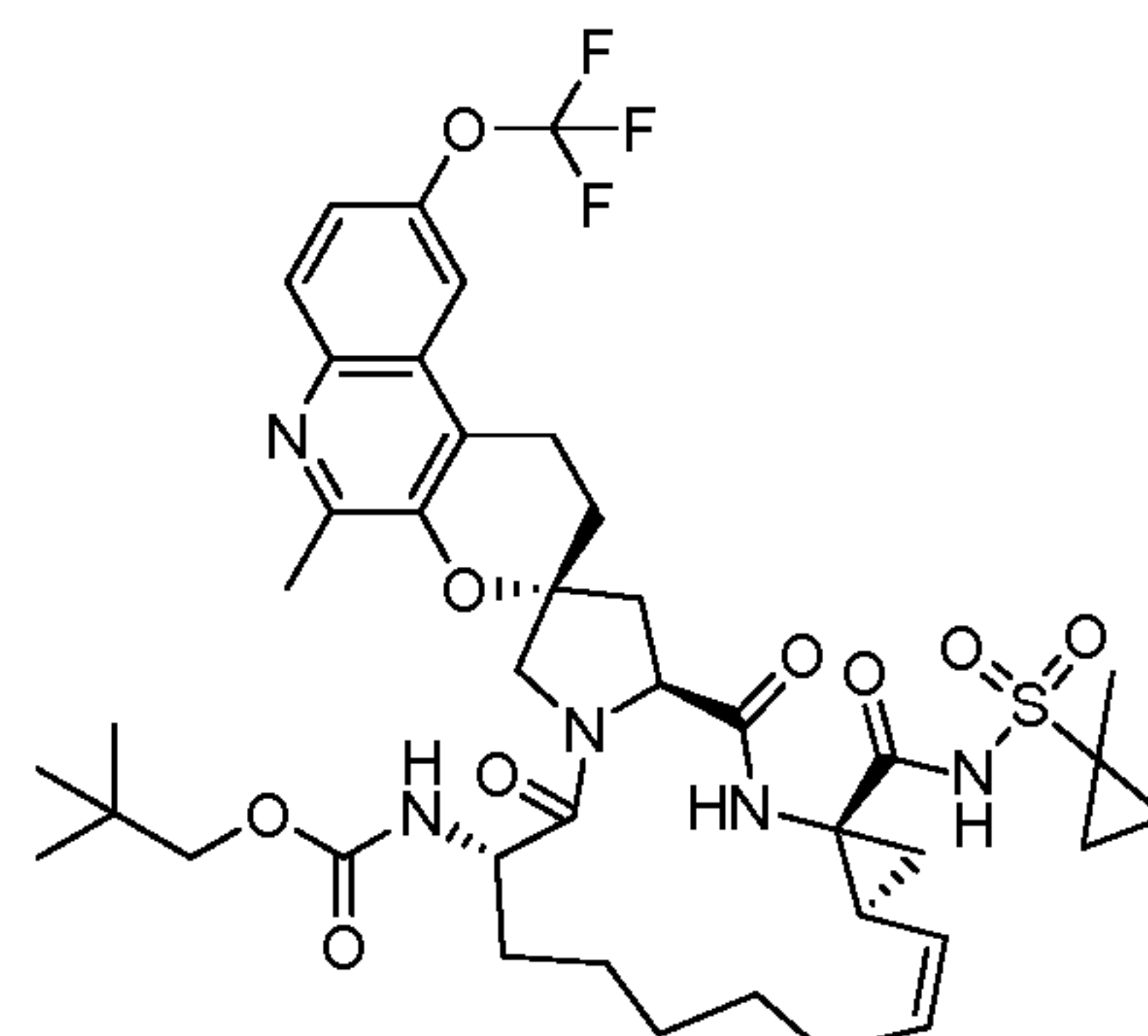




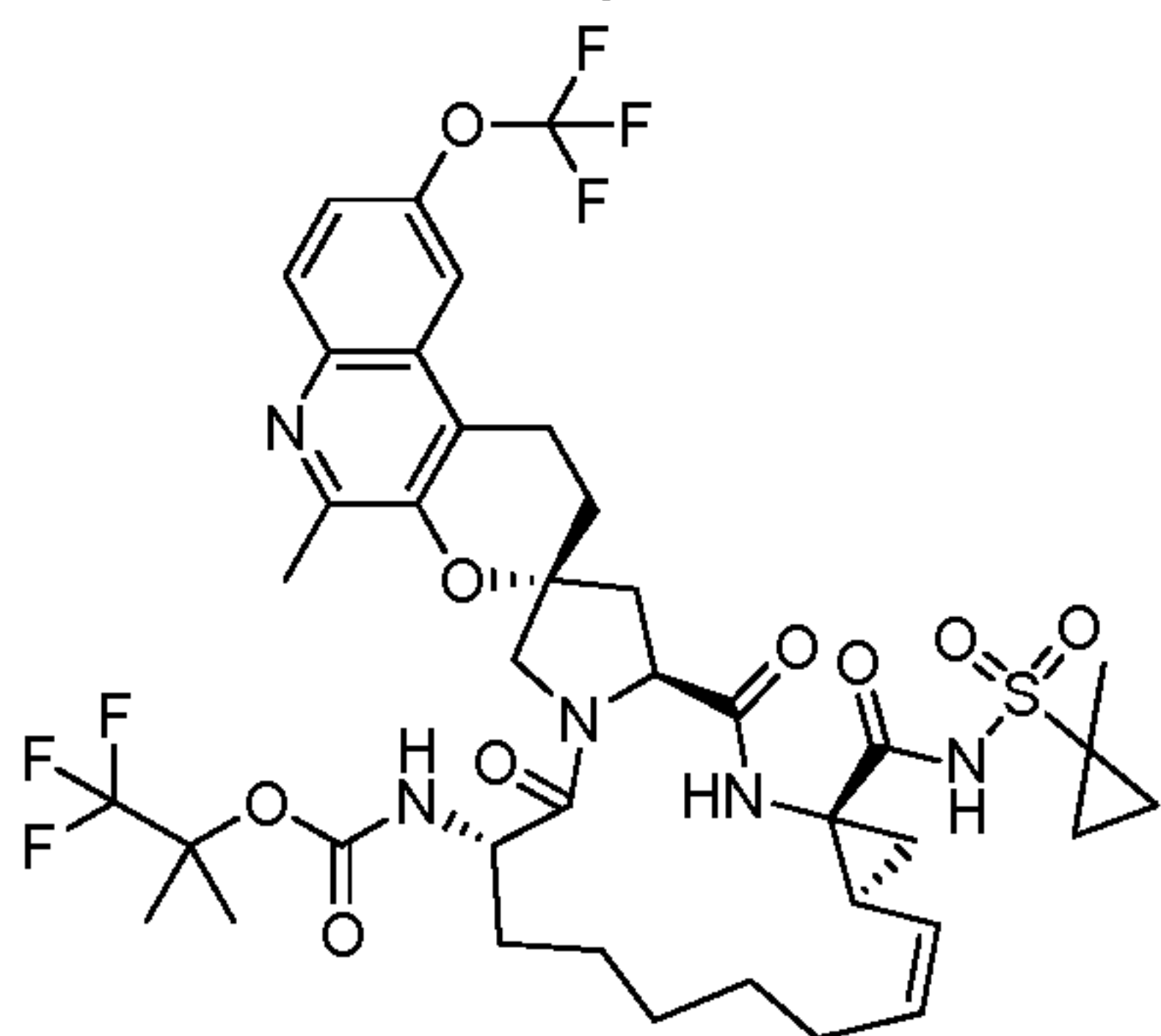
I-295



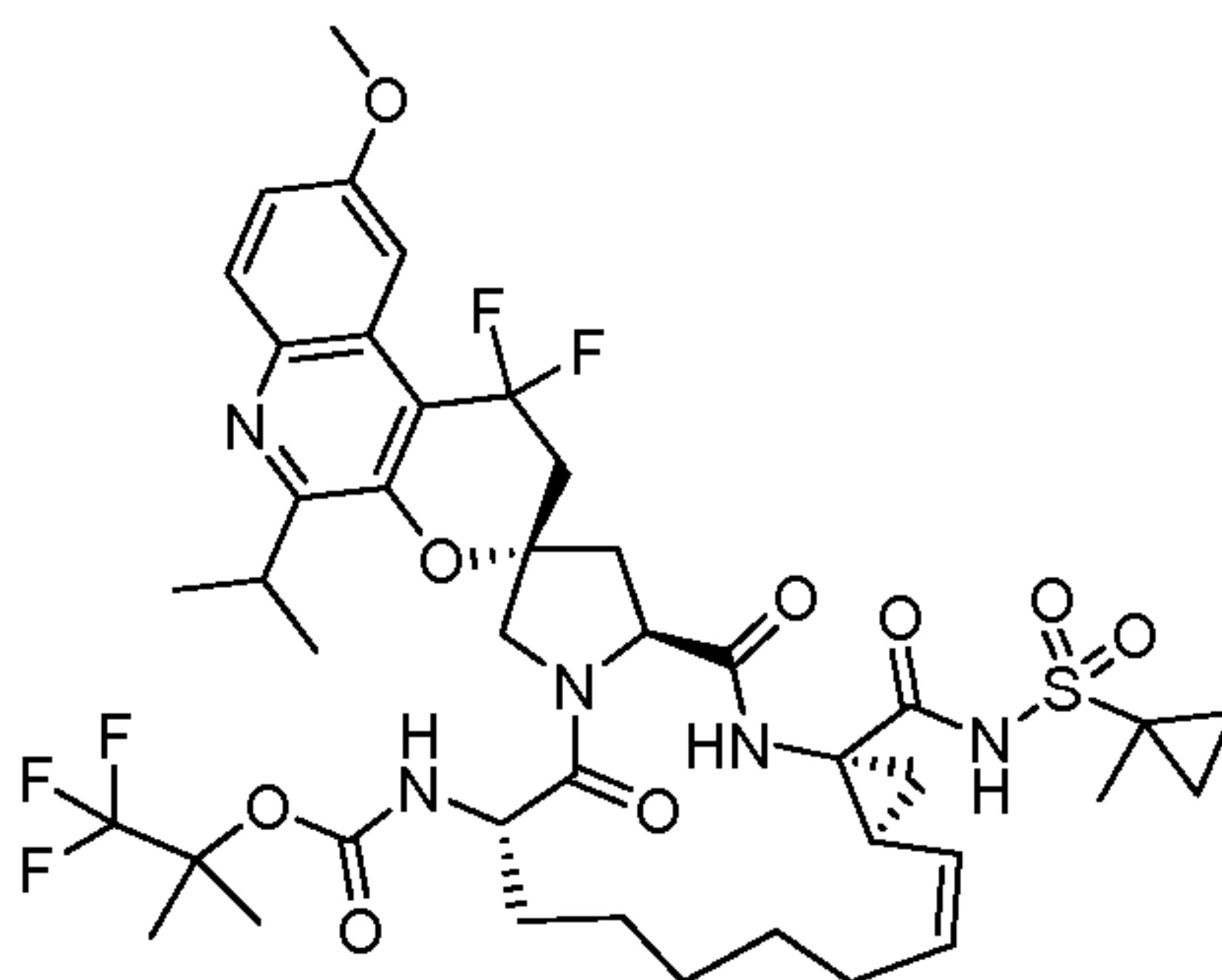
I-296



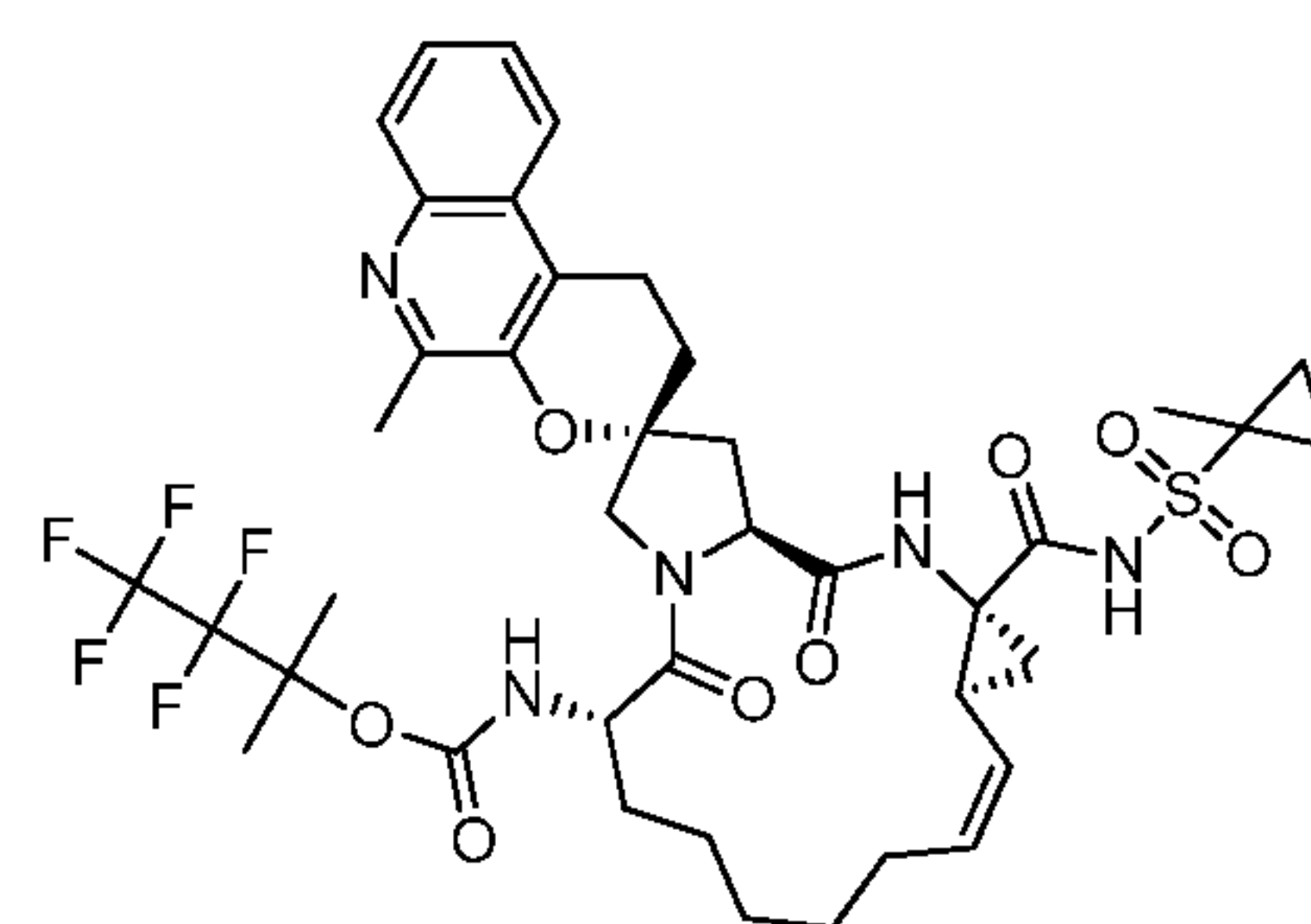
I-297



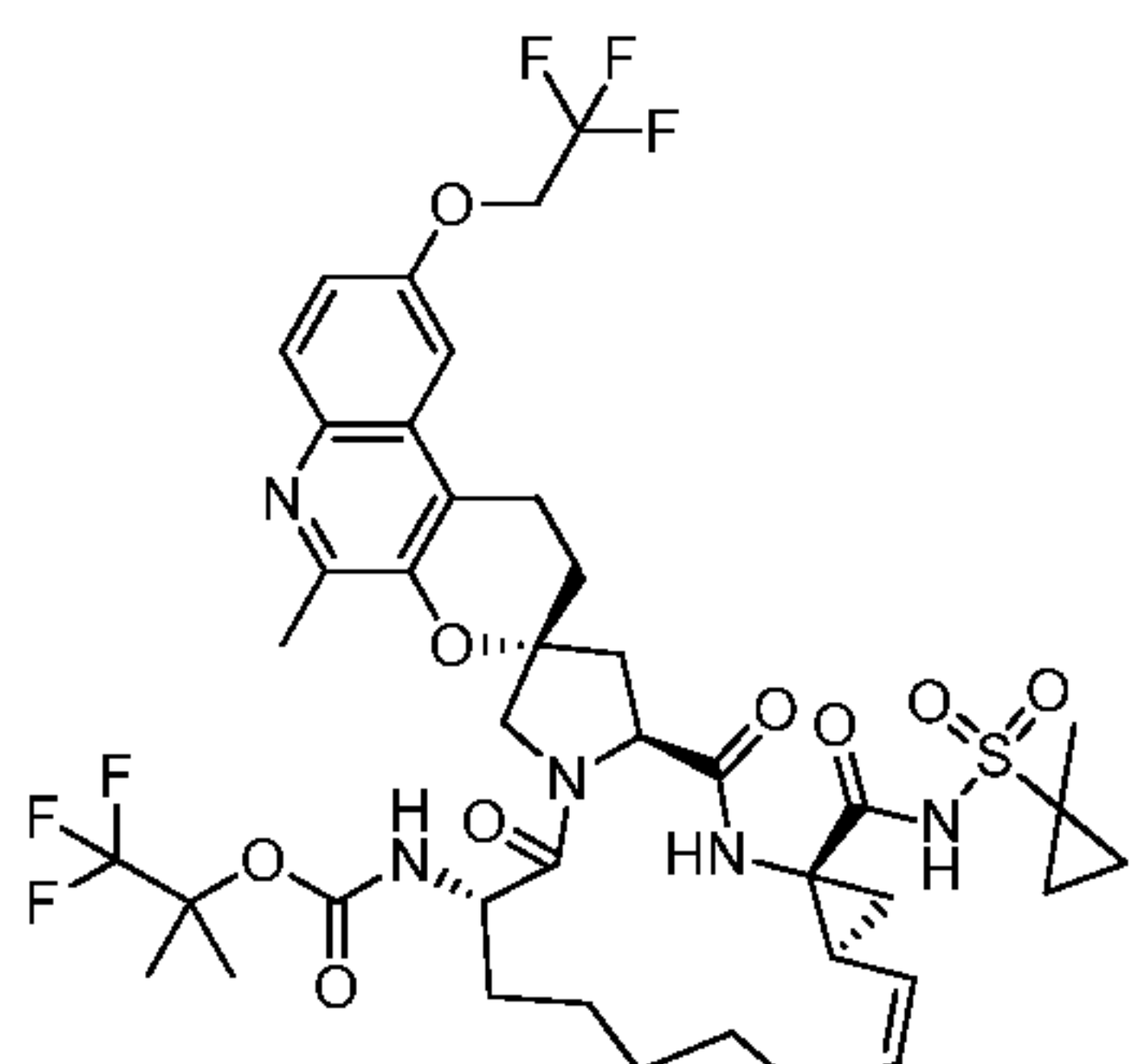
I-298



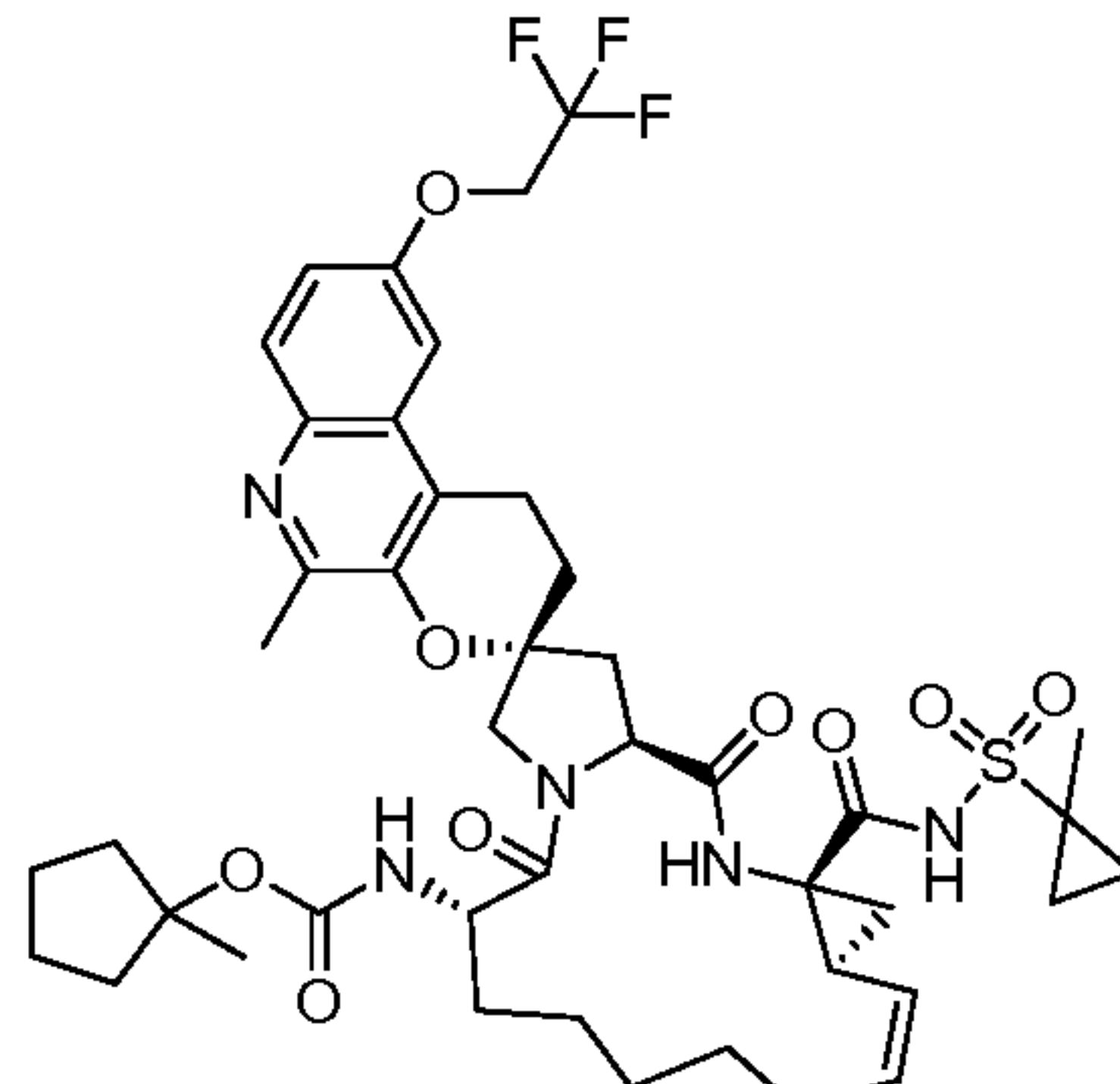
I-299



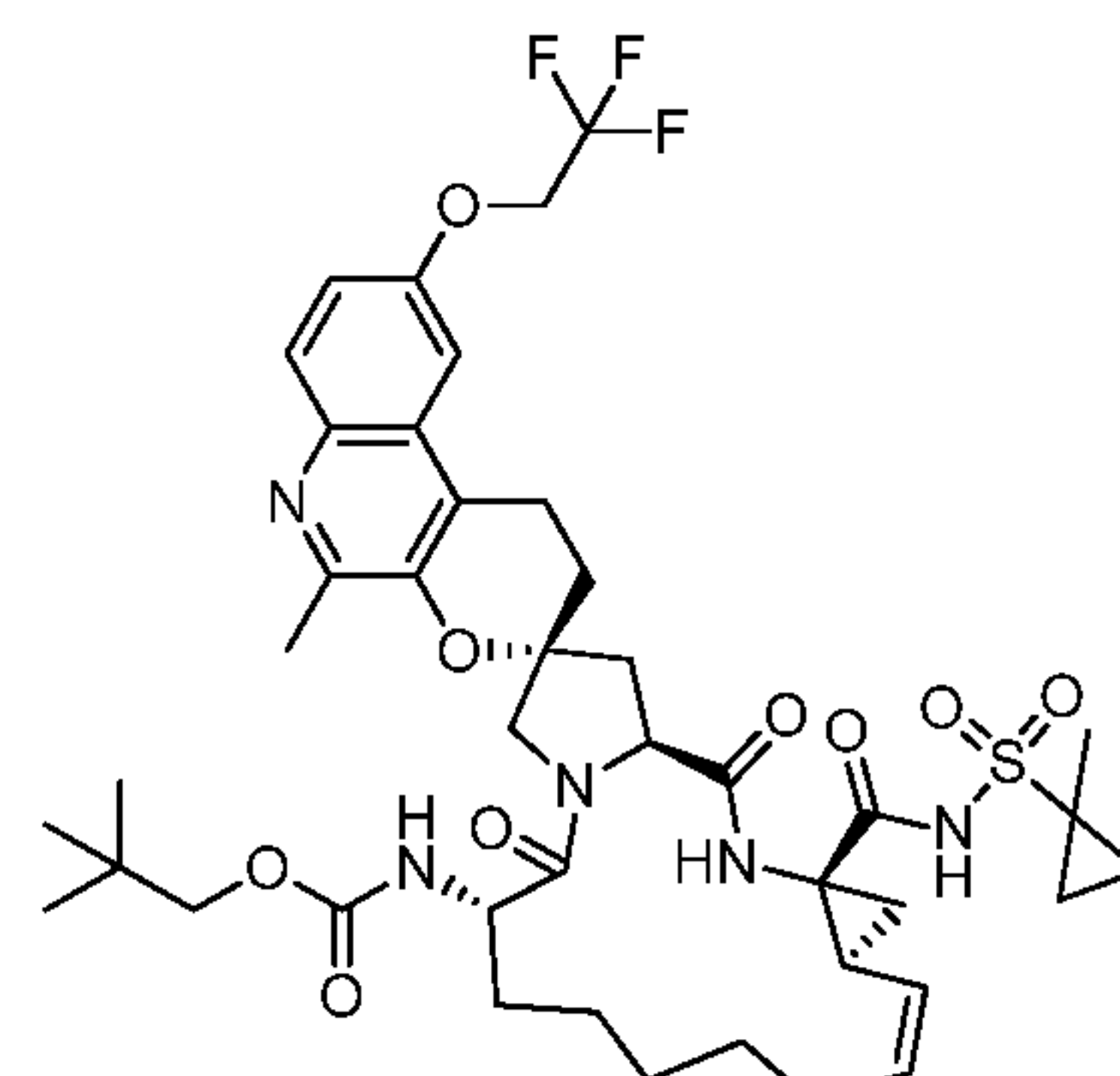
I-300



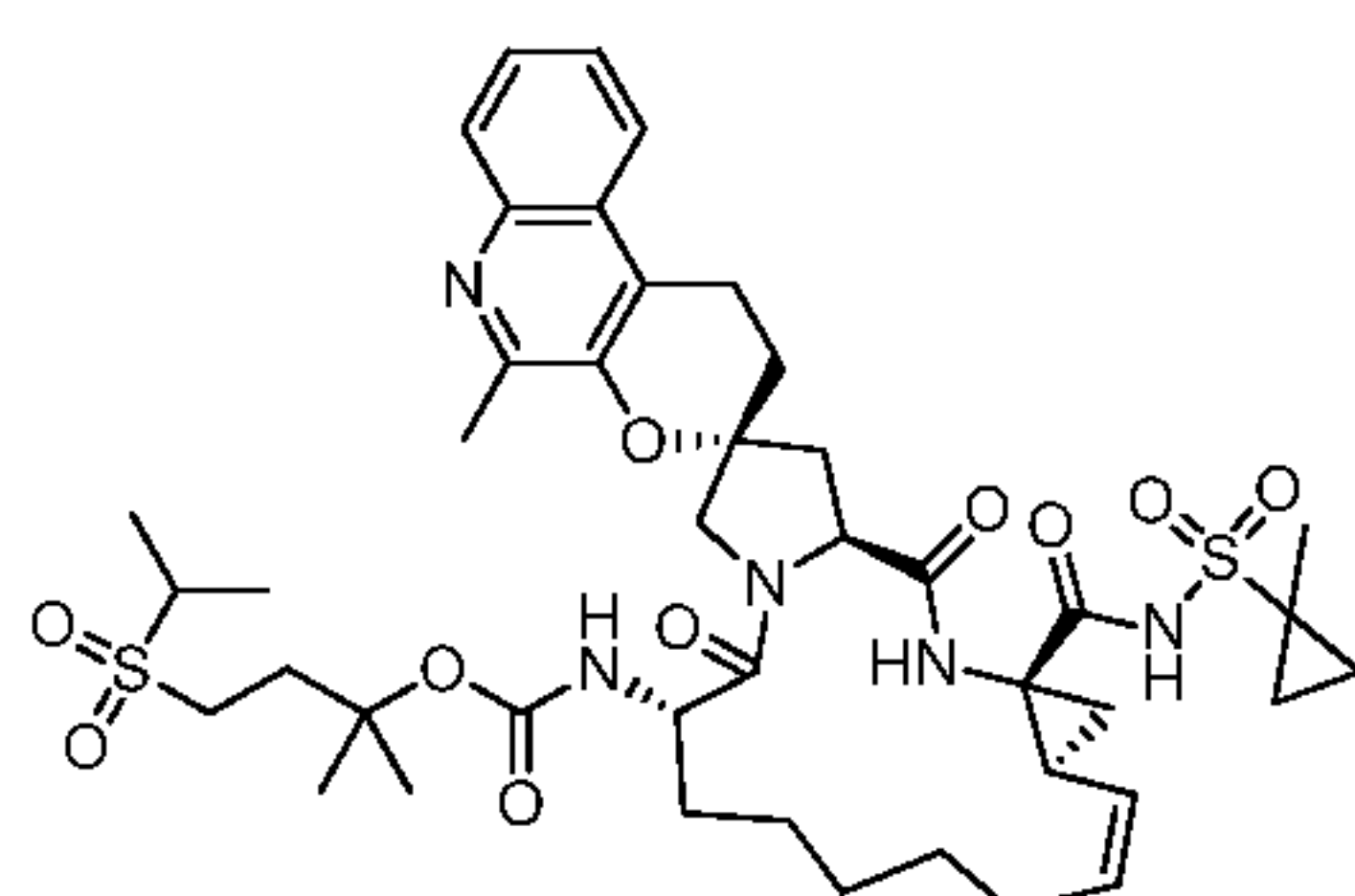
I-301



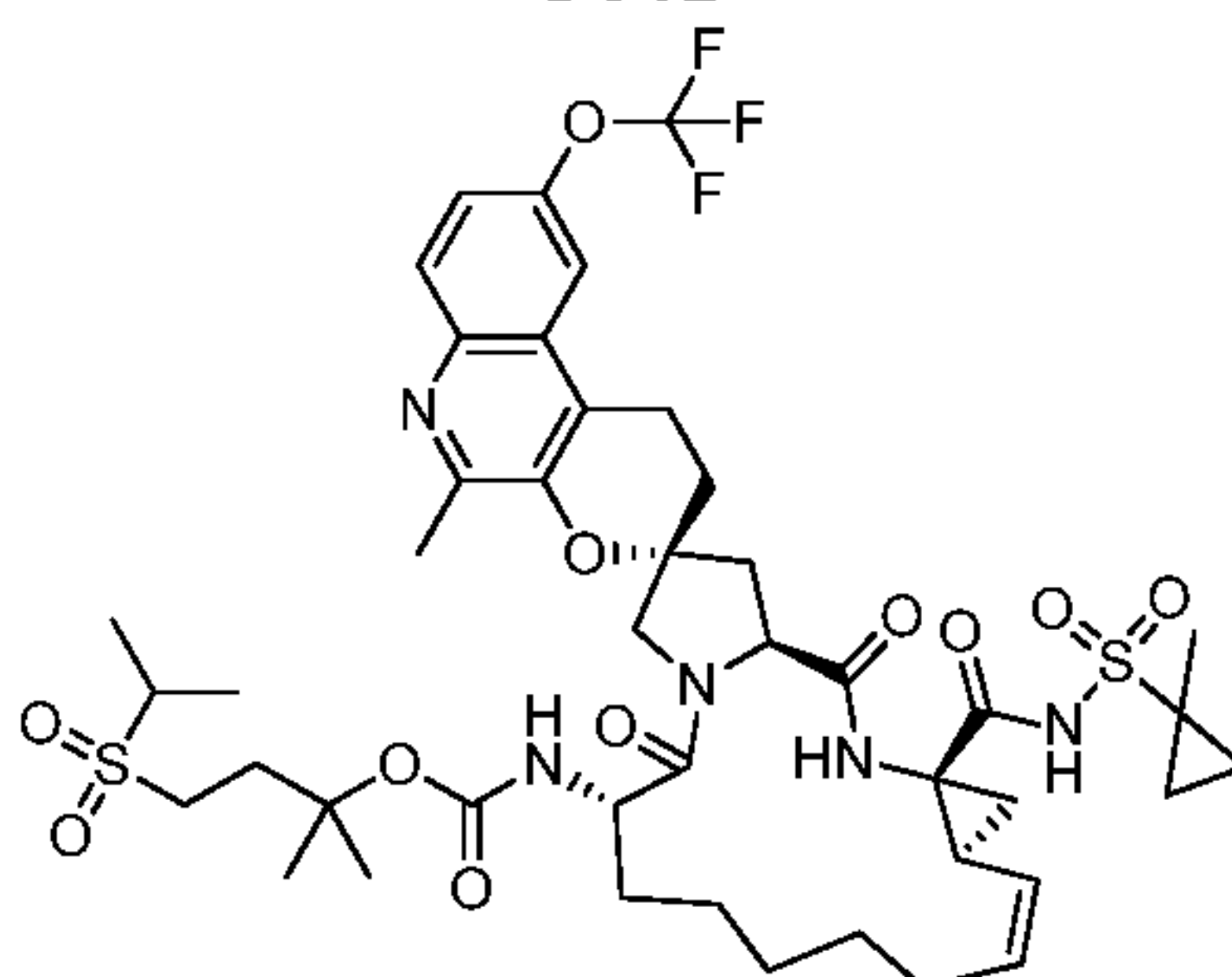
I-302



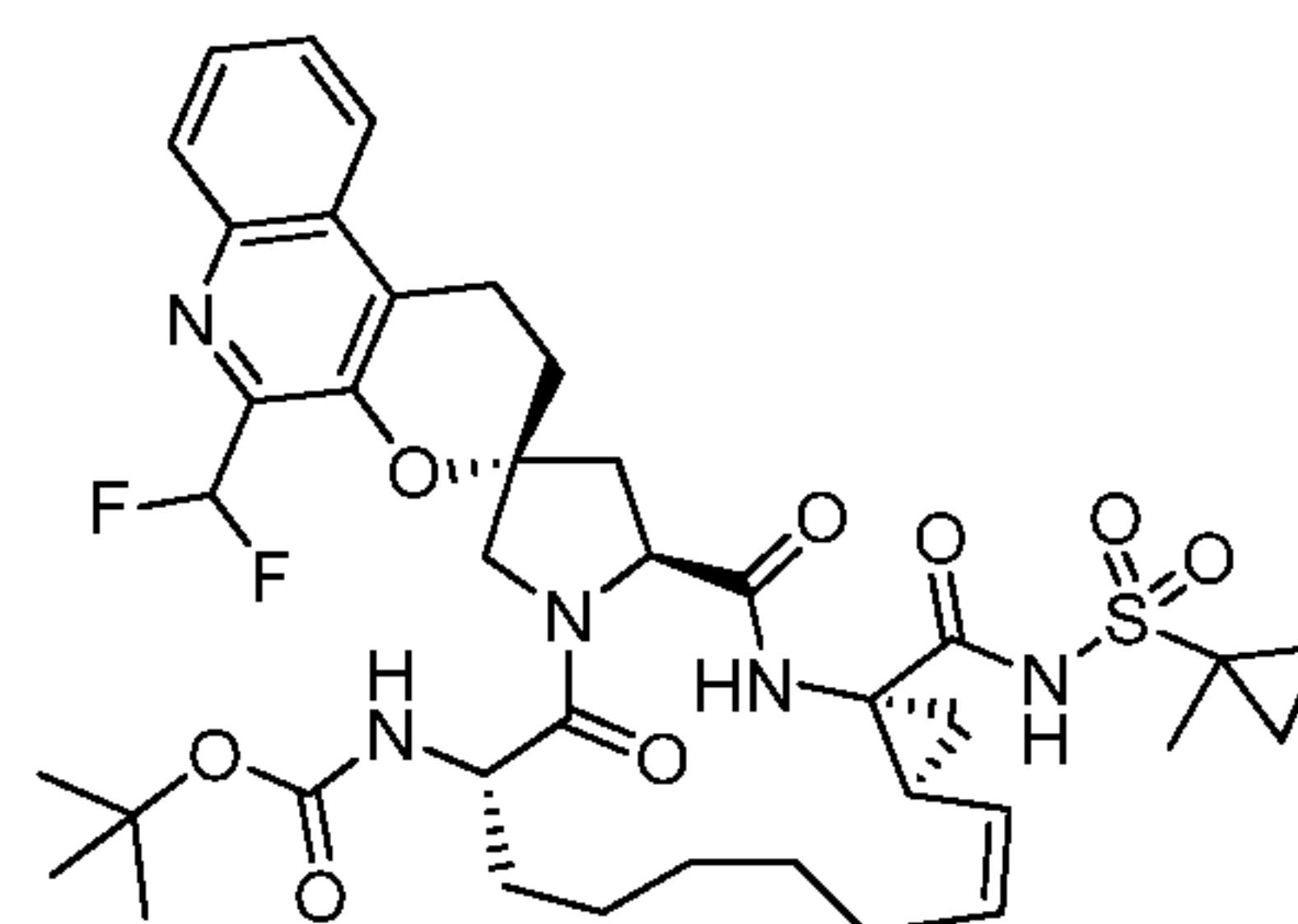
I-303



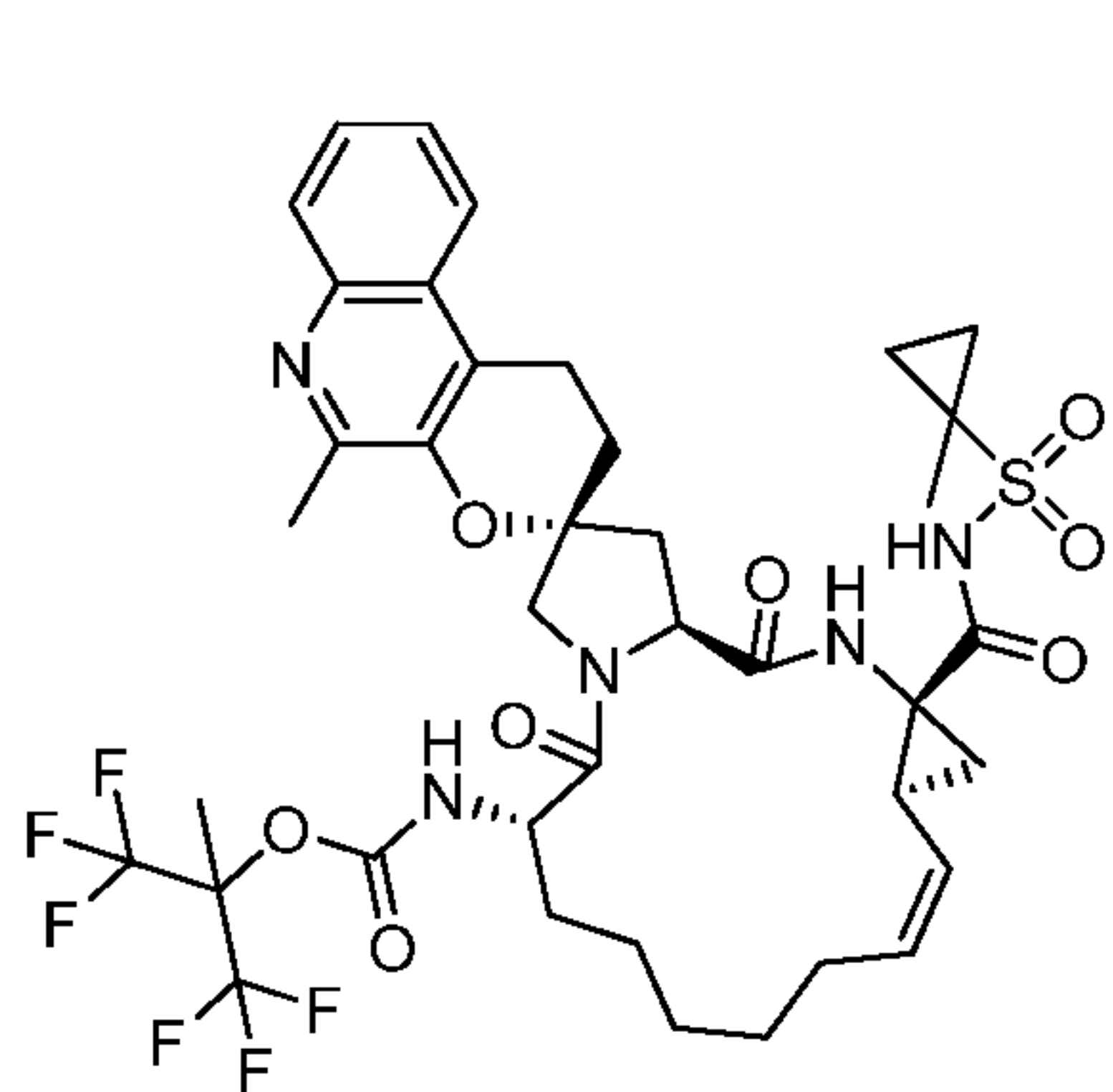
I-304



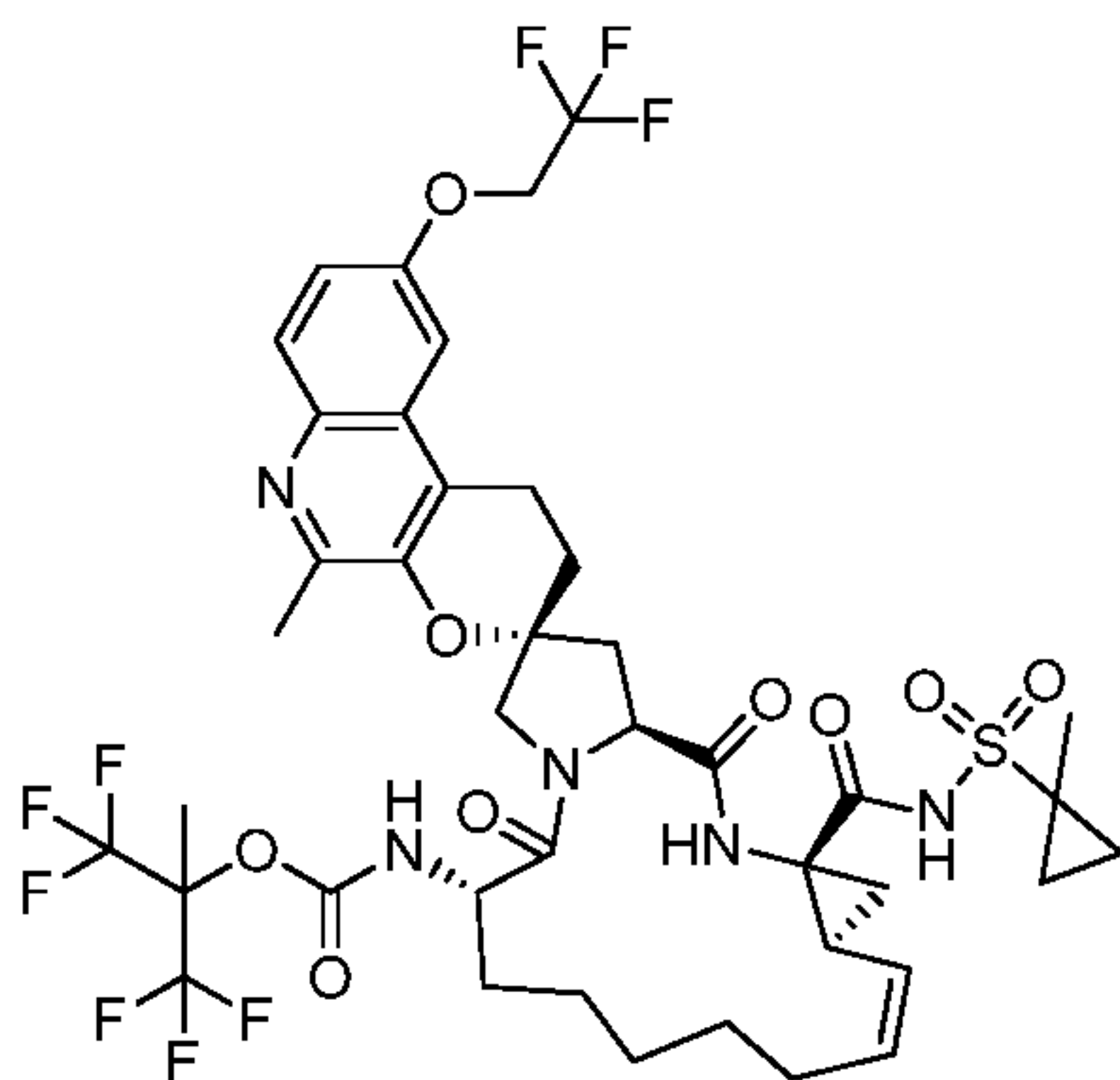
I-305



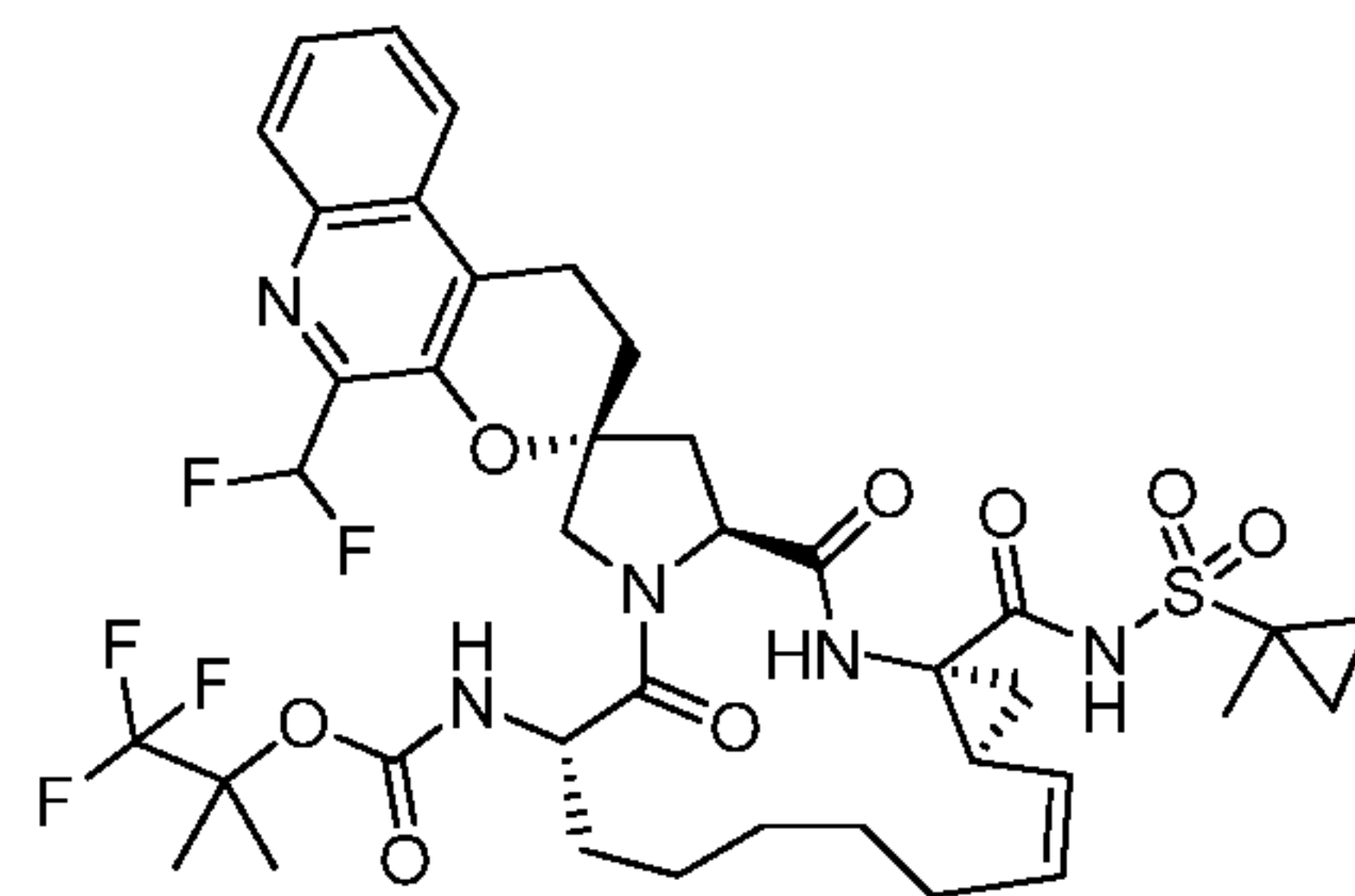
I-306



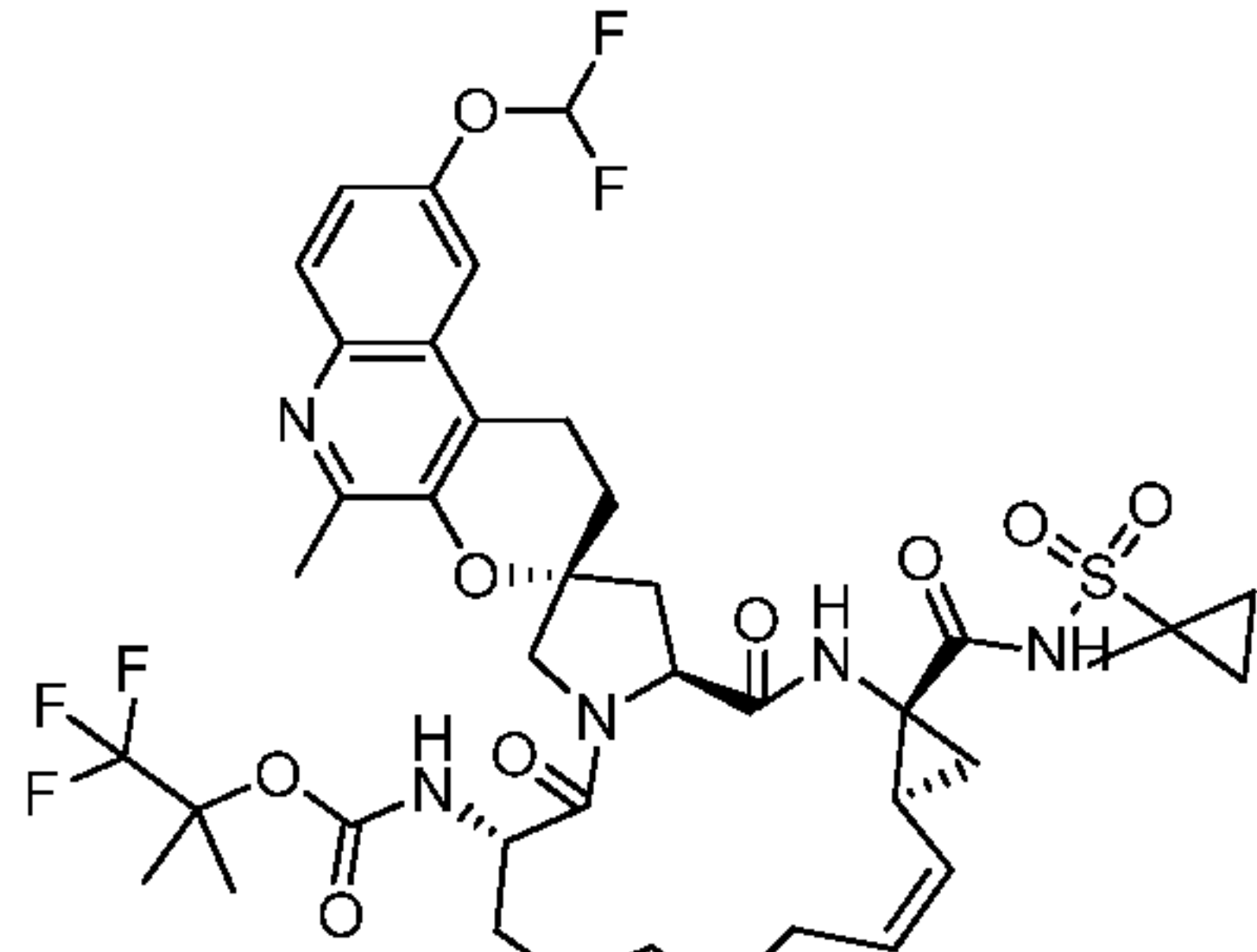
I-307



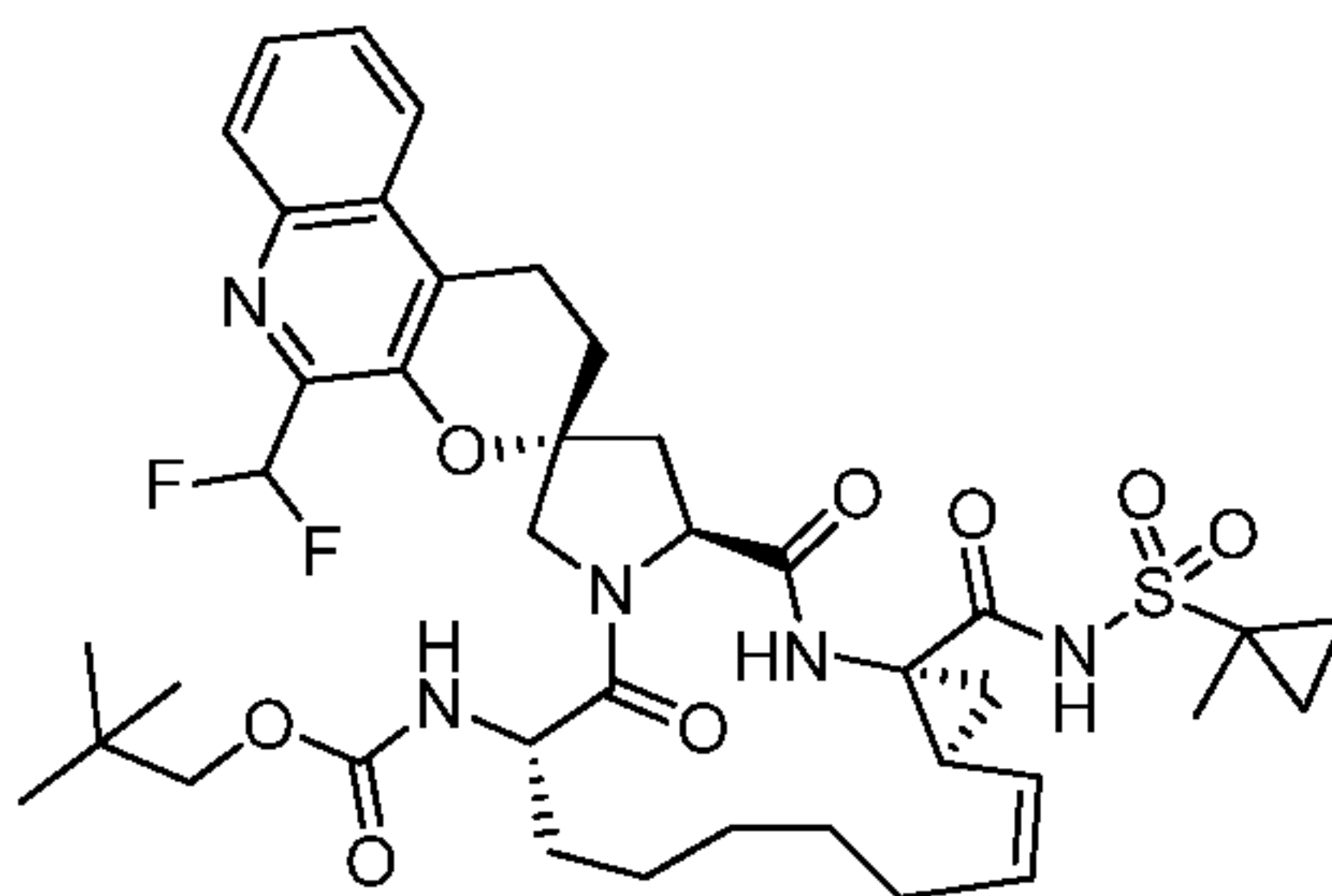
I-308



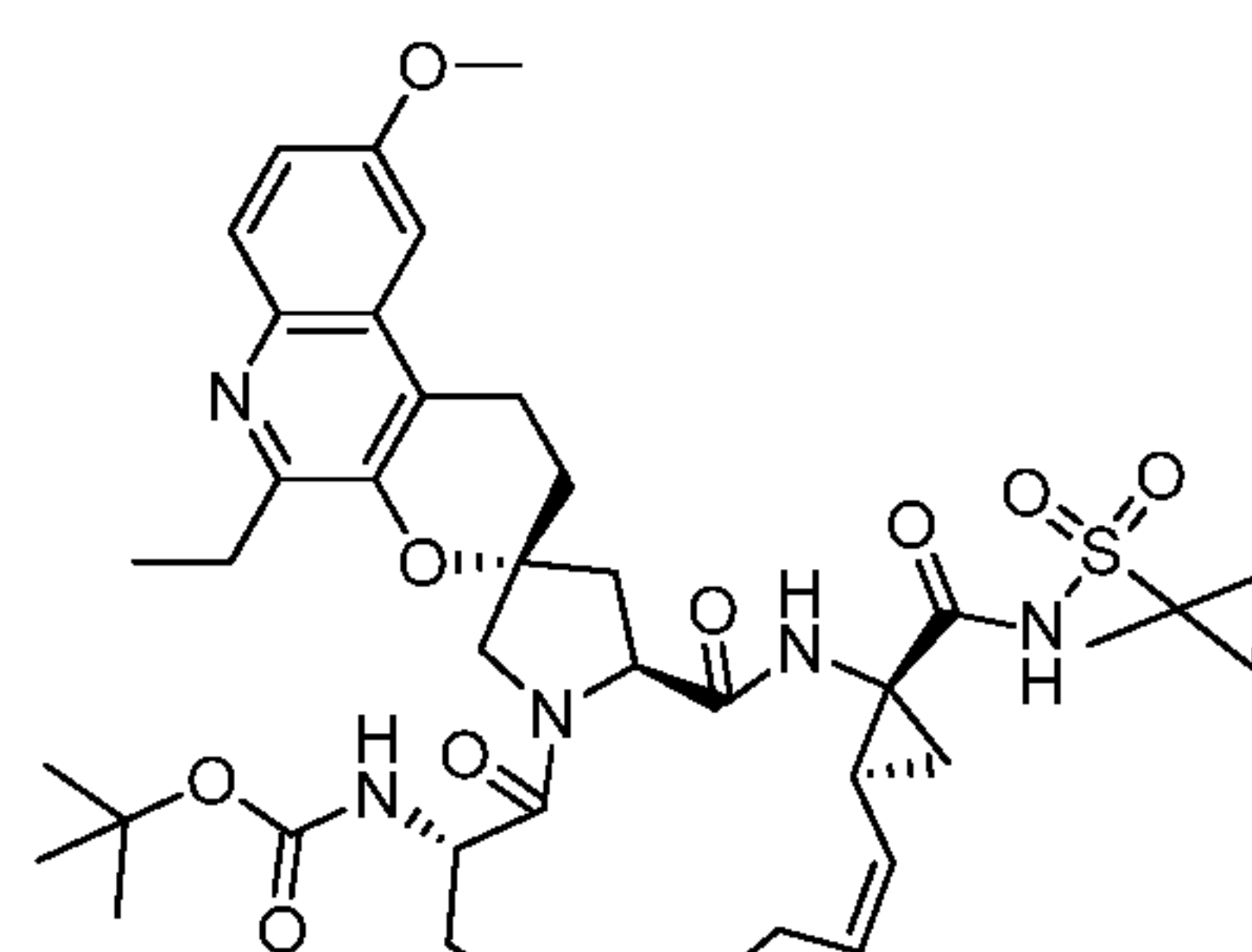
I-309



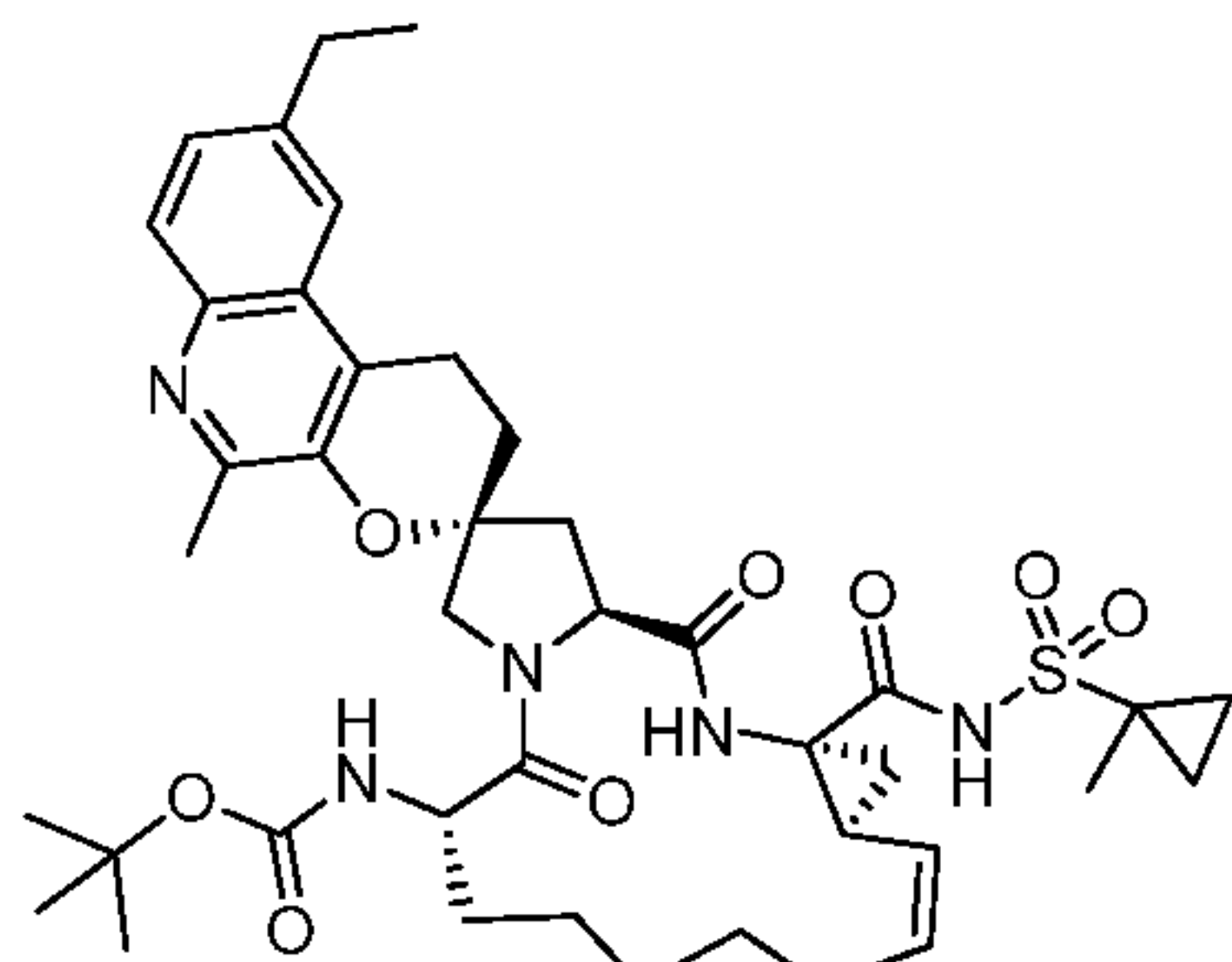
I-310



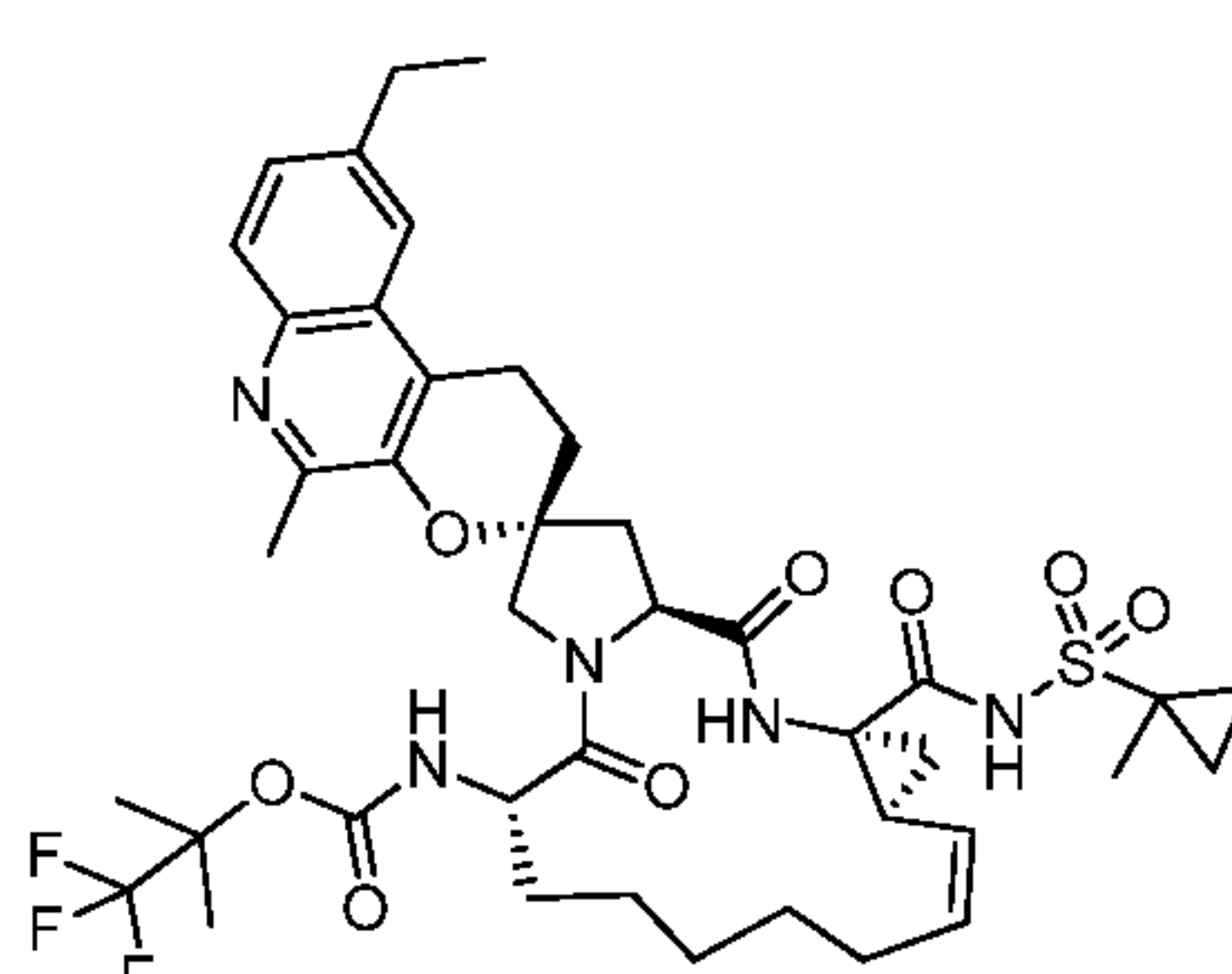
I-311



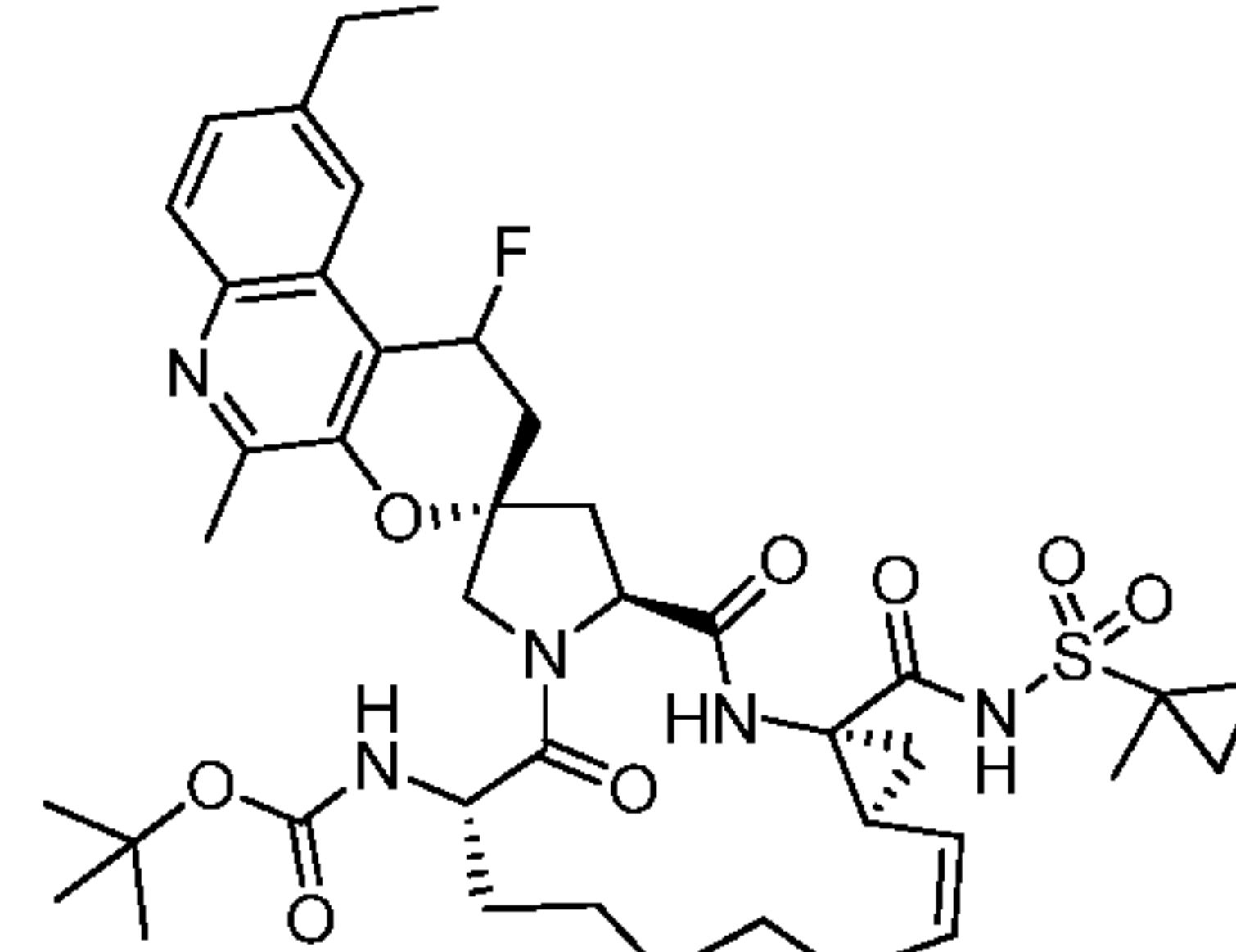
I-312



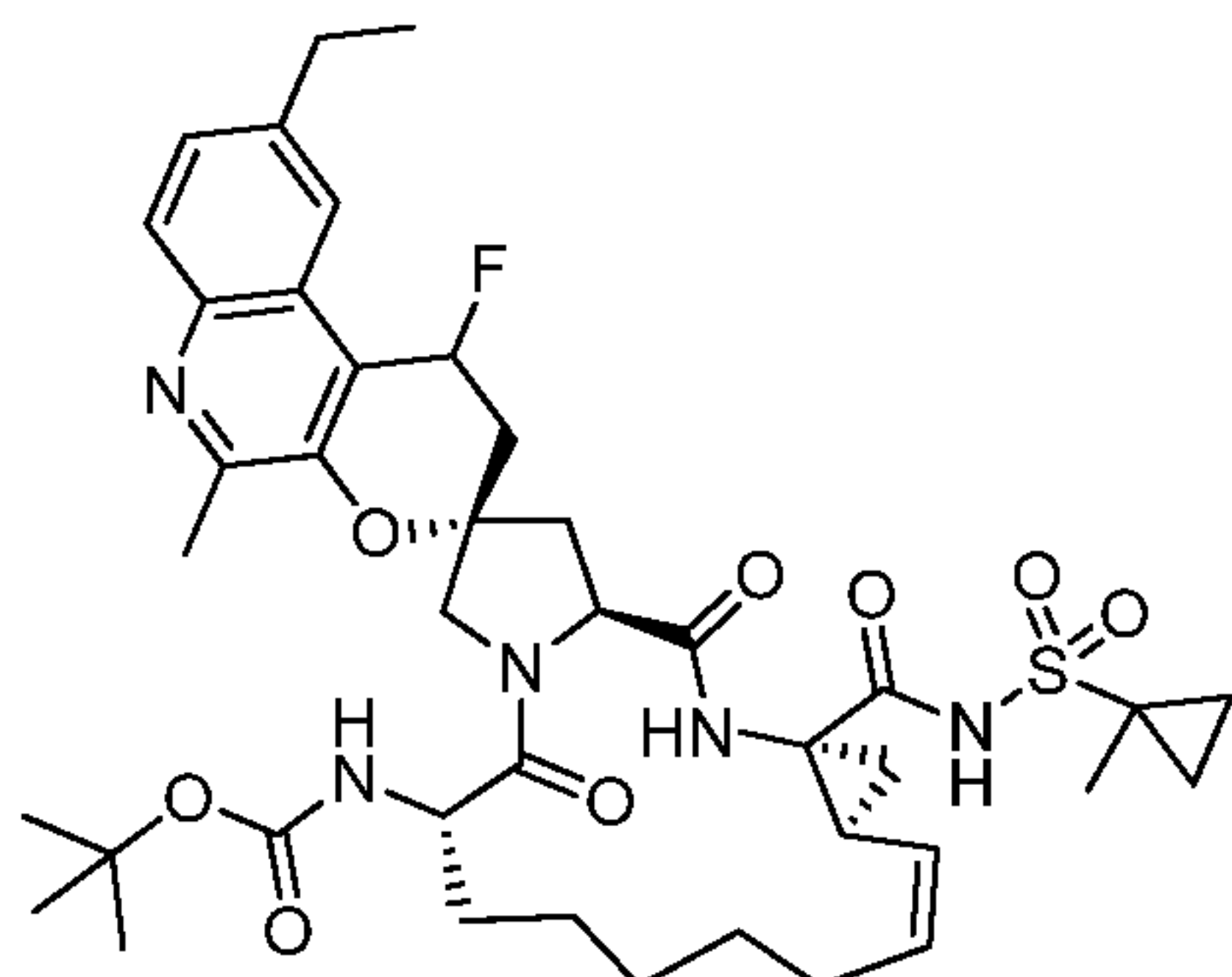
I-313



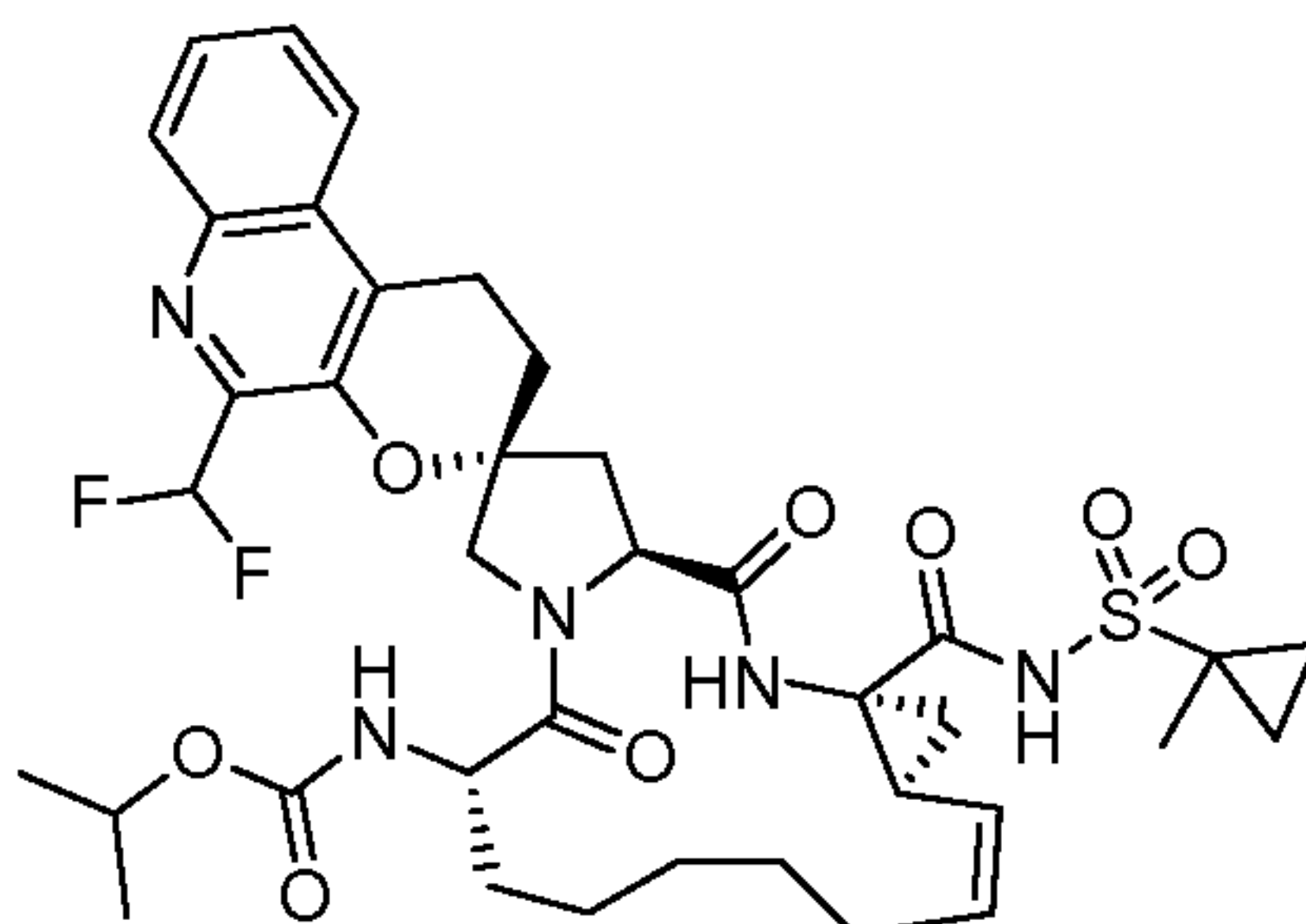
I-314



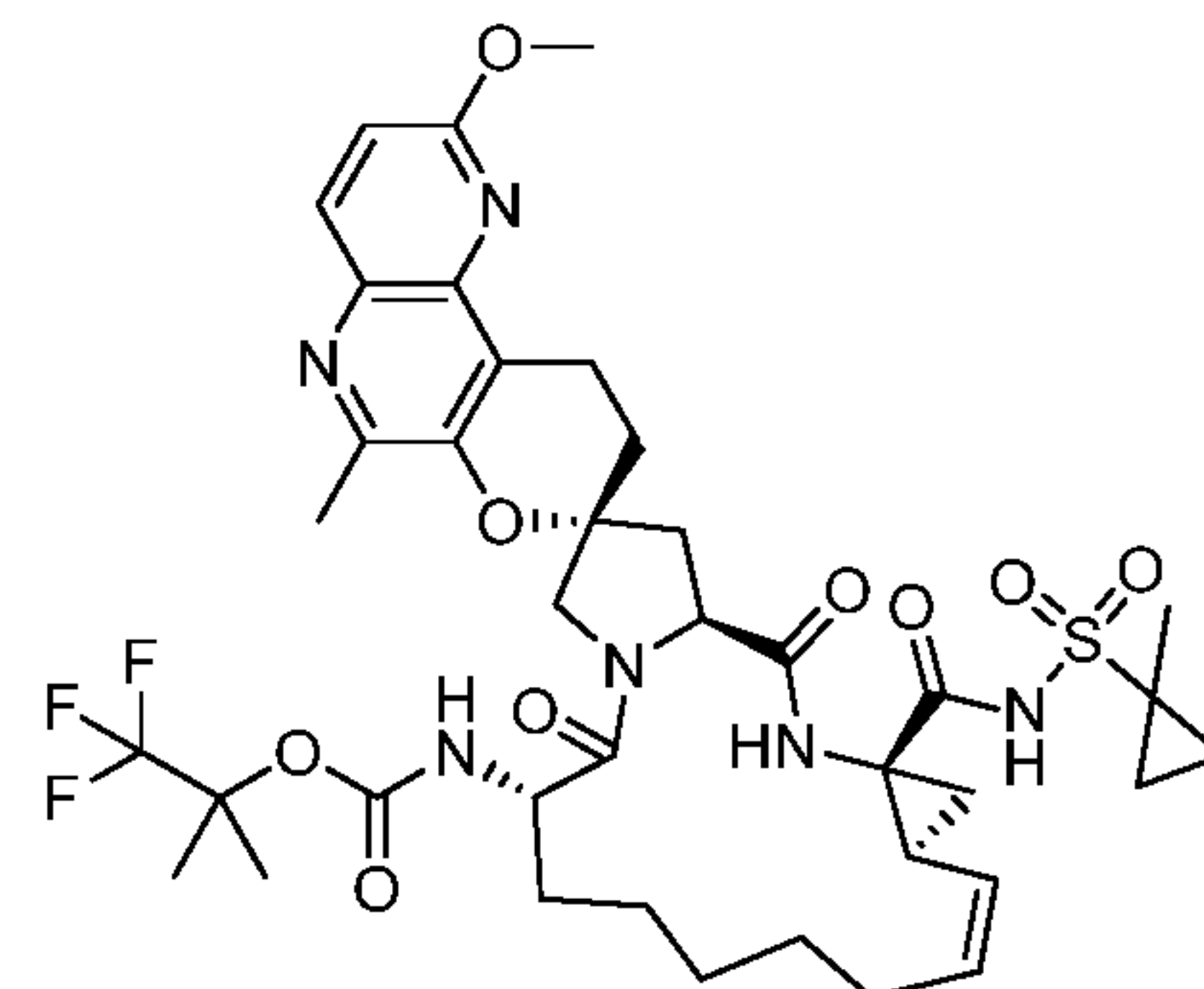
I-315



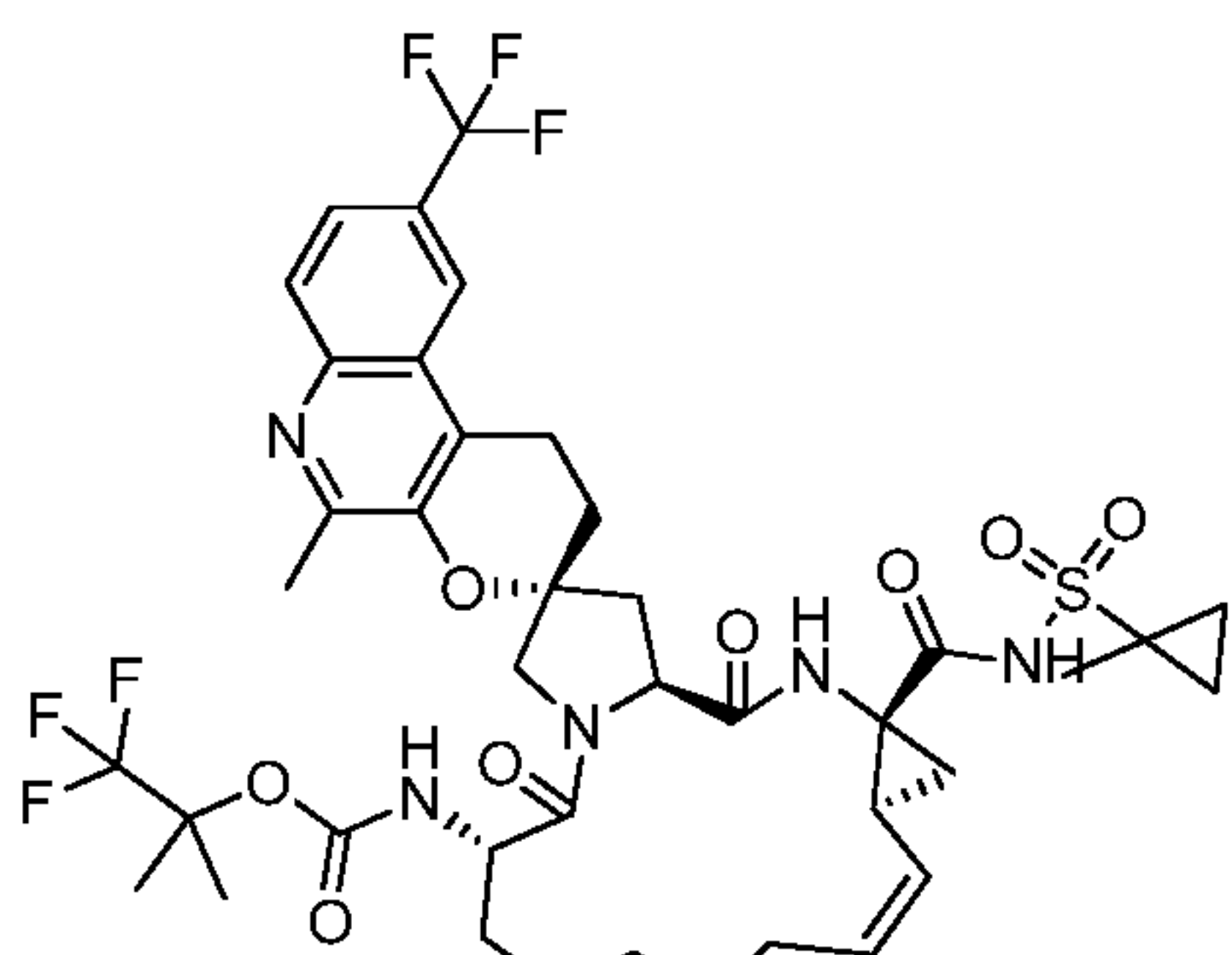
I-316



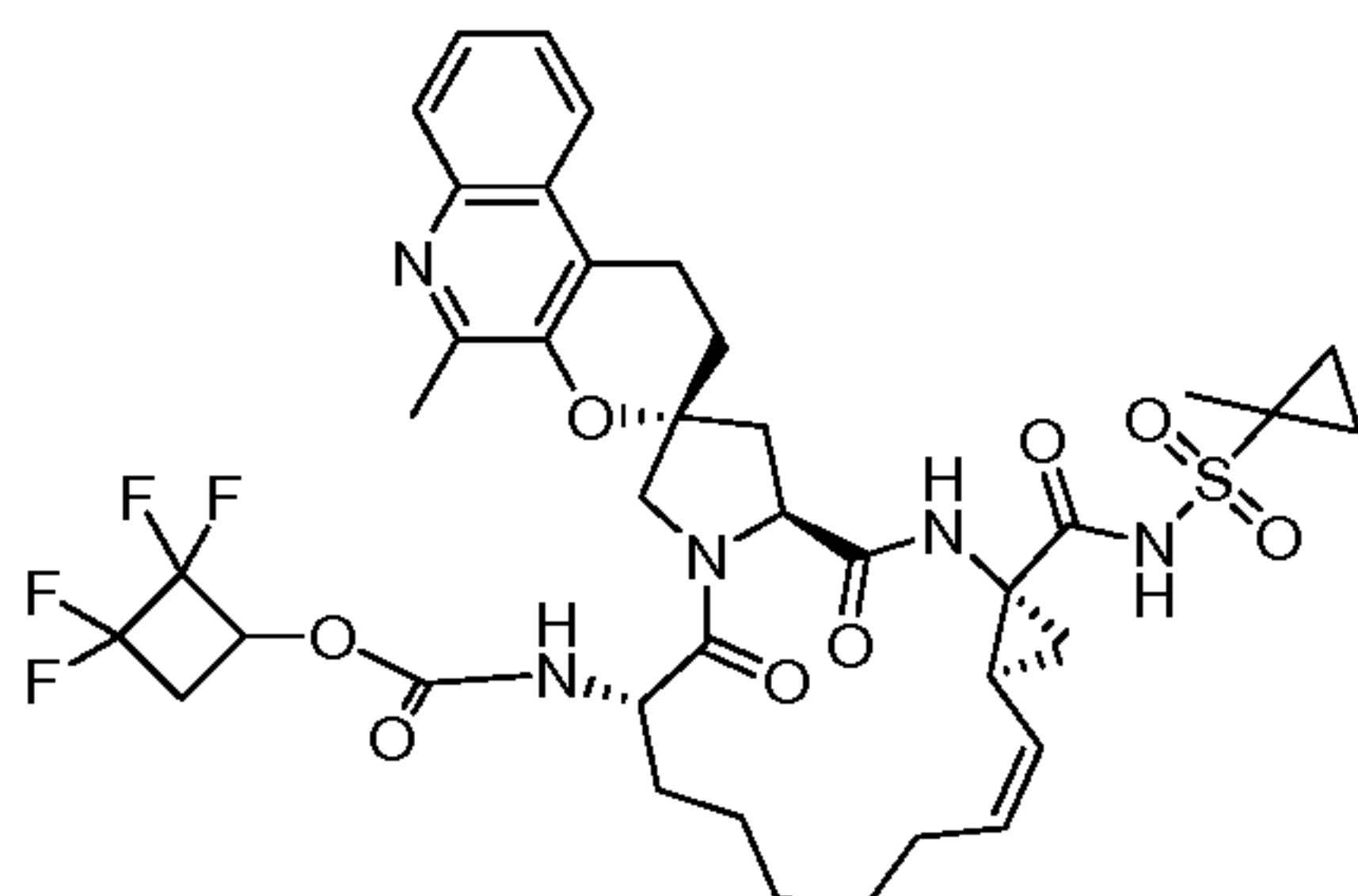
I-317



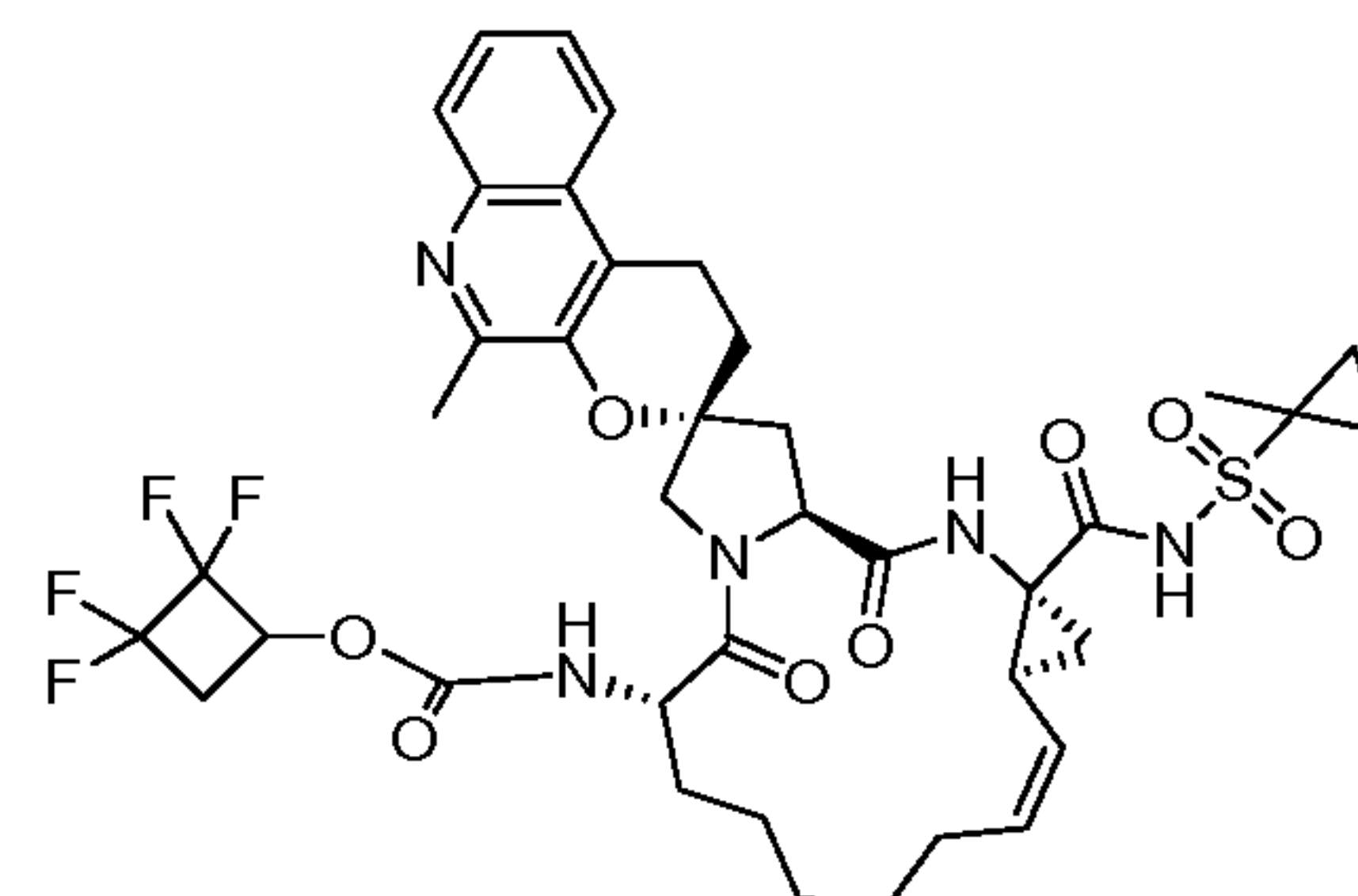
I-318



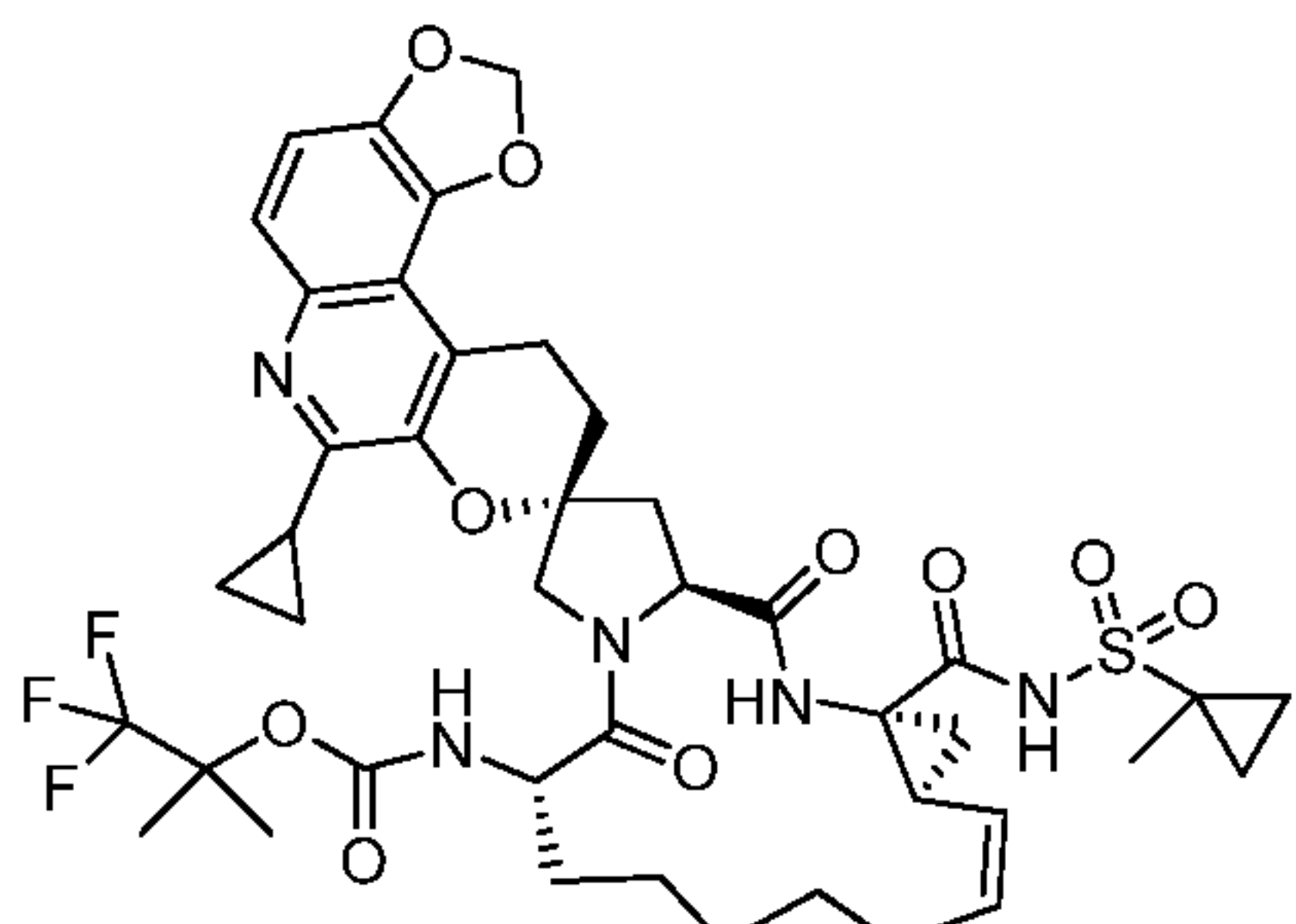
I-319



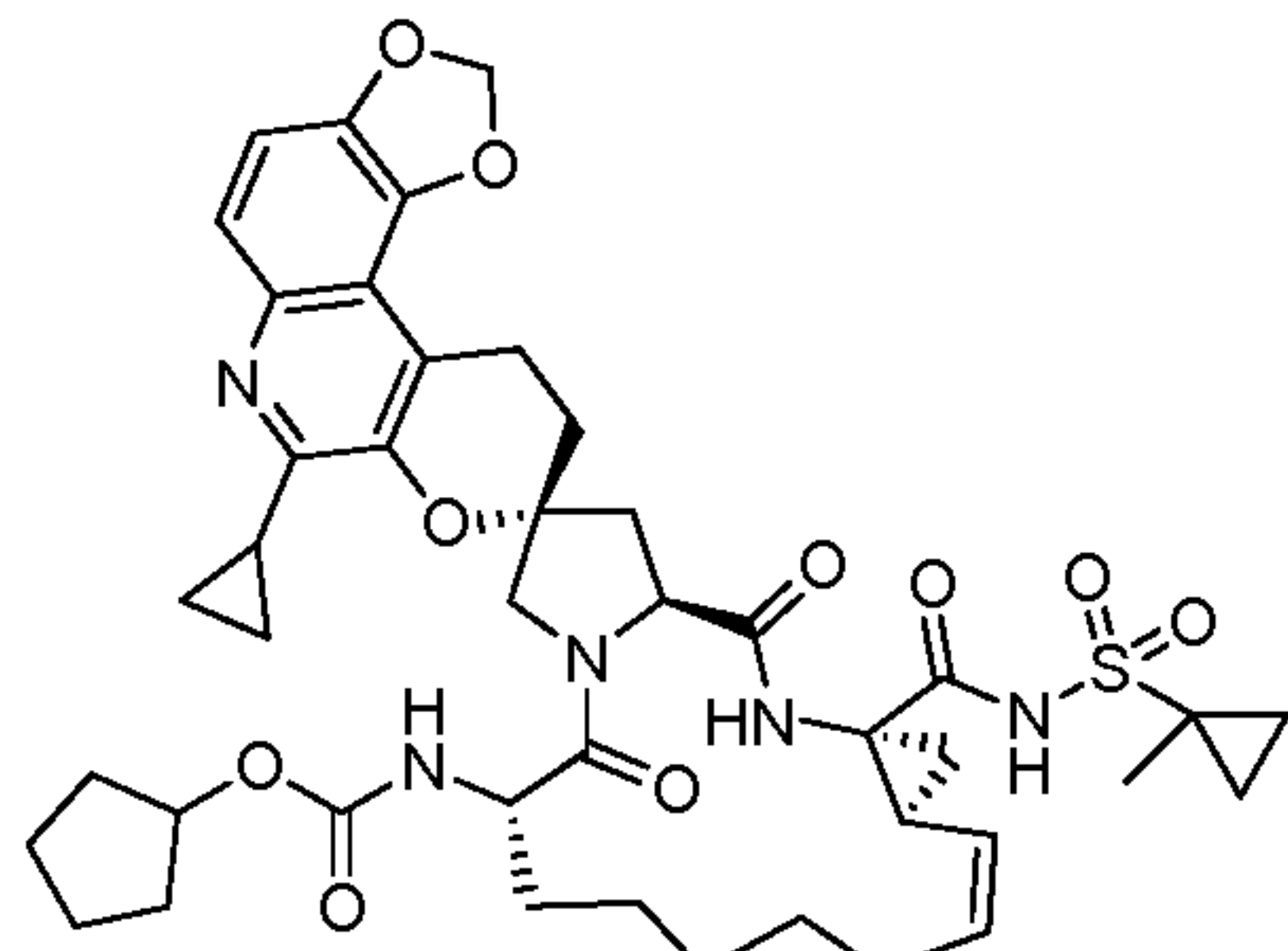
I-320



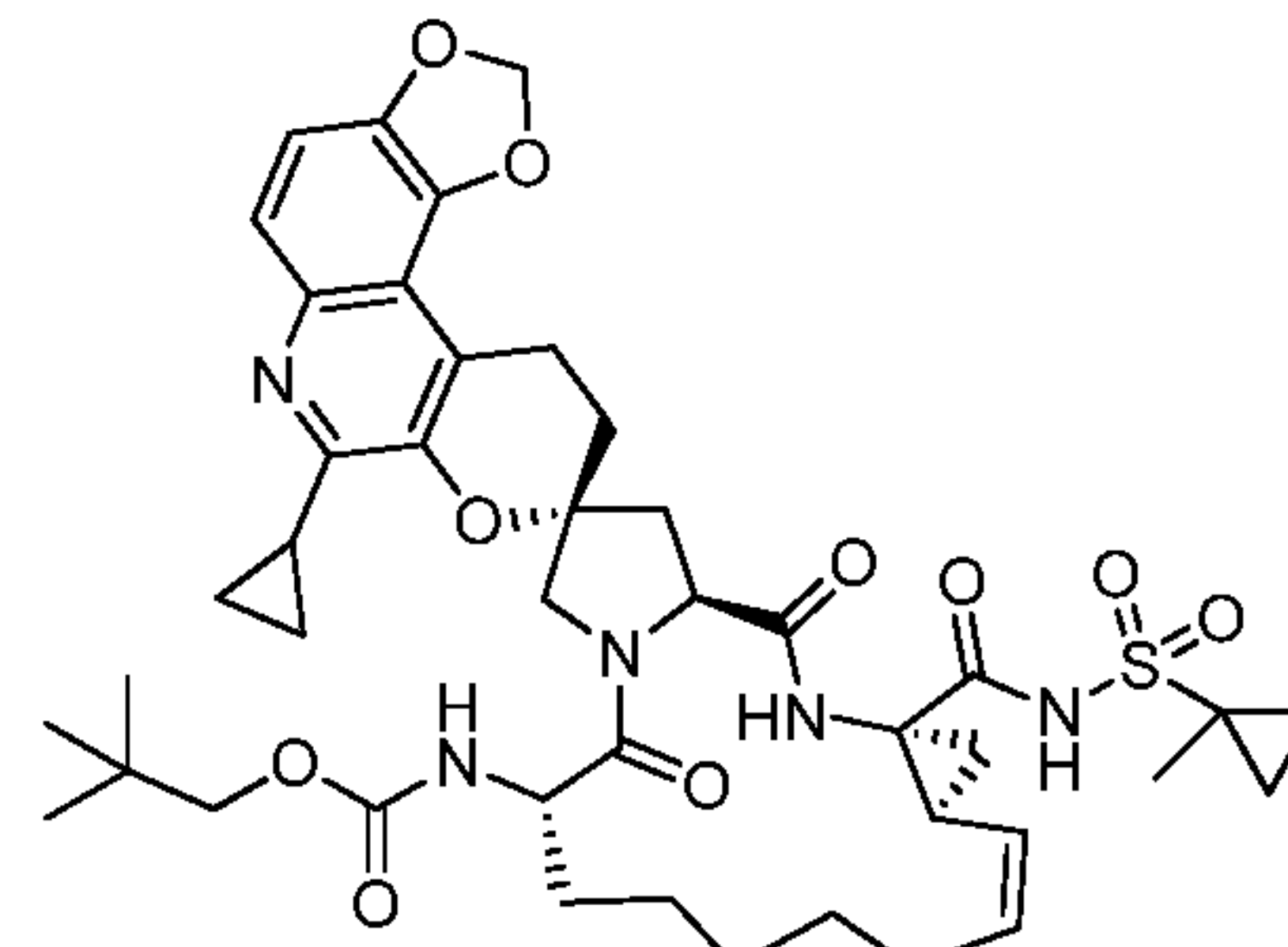
I-321



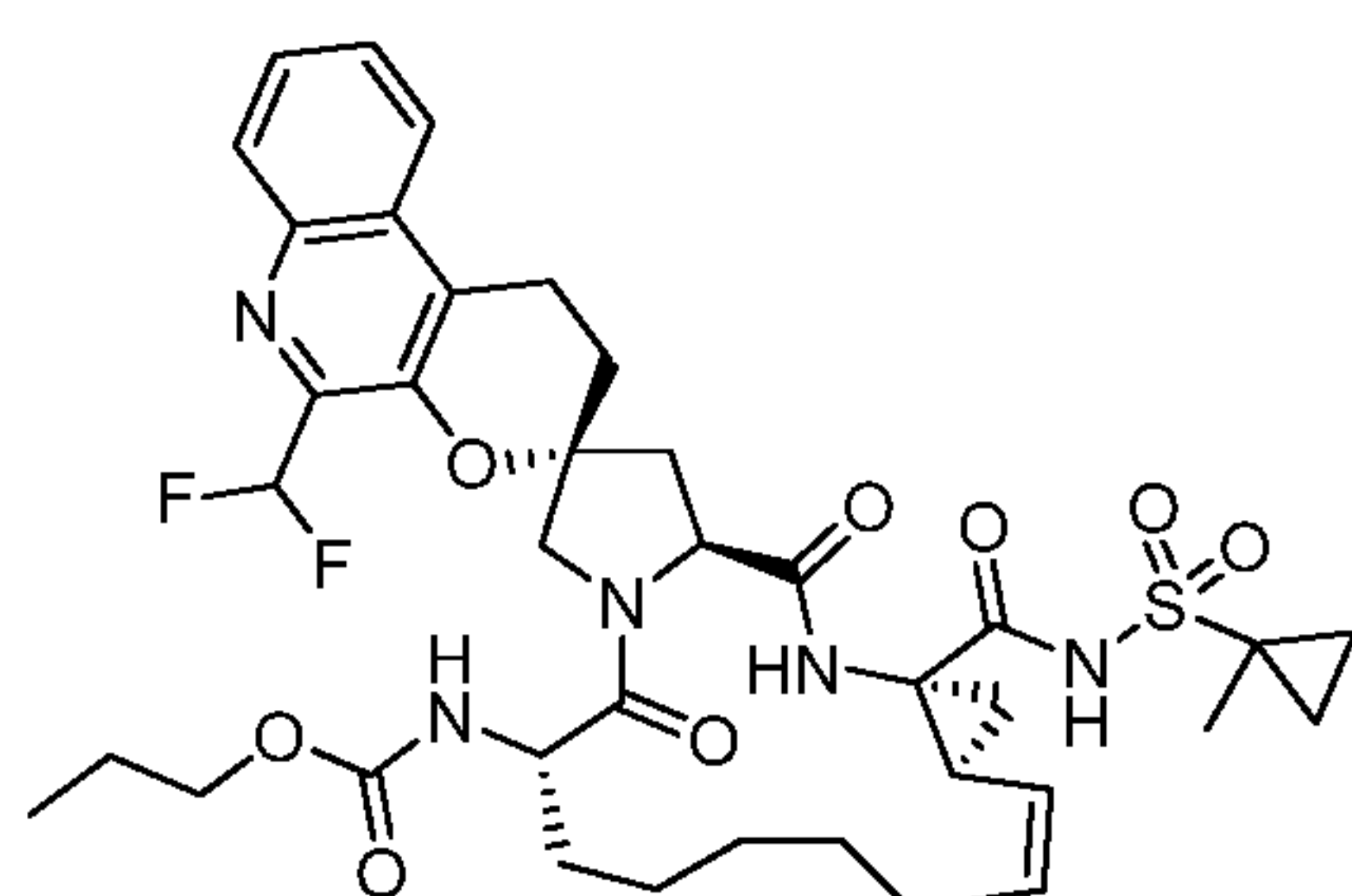
I-322



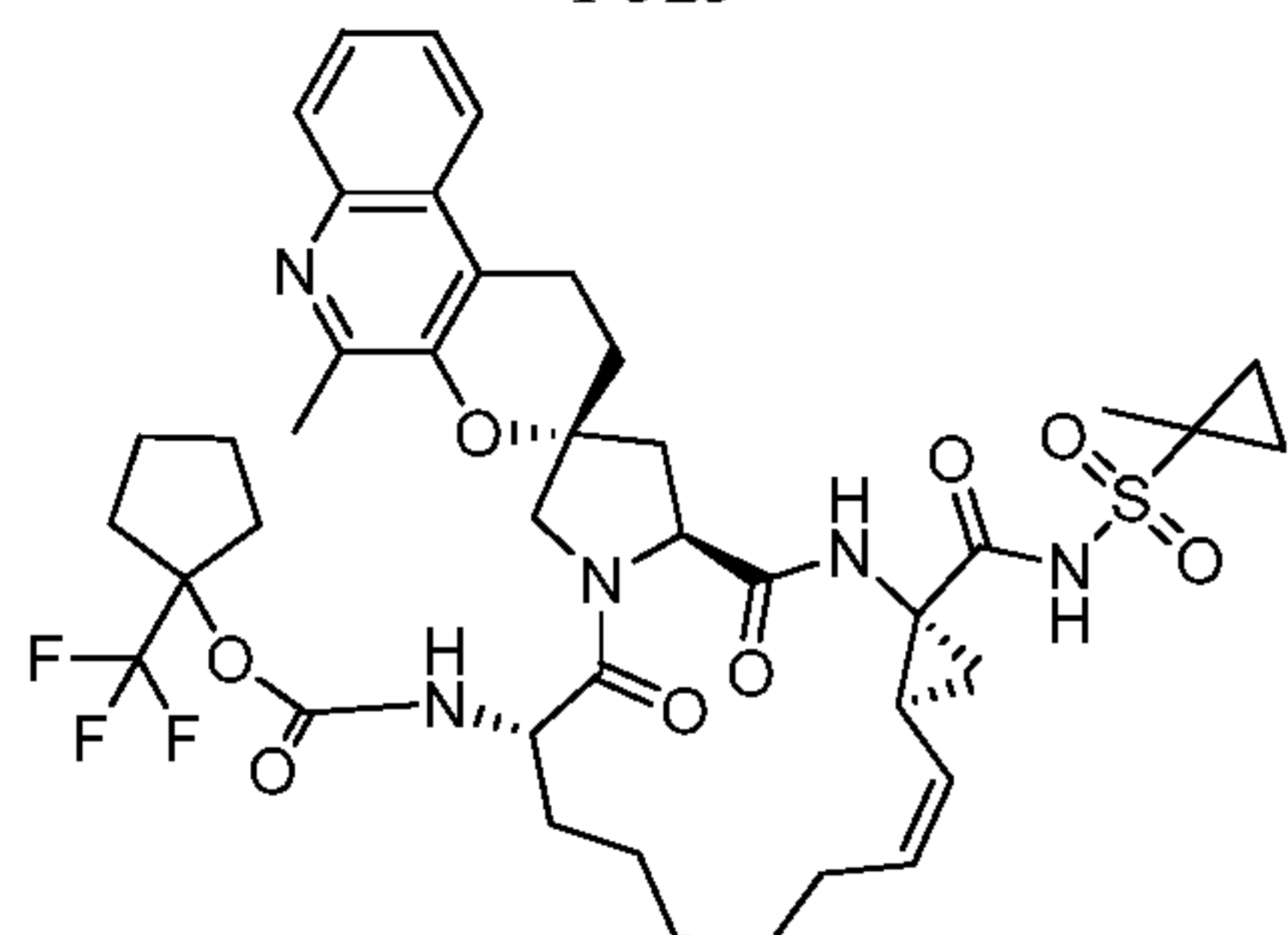
I-323



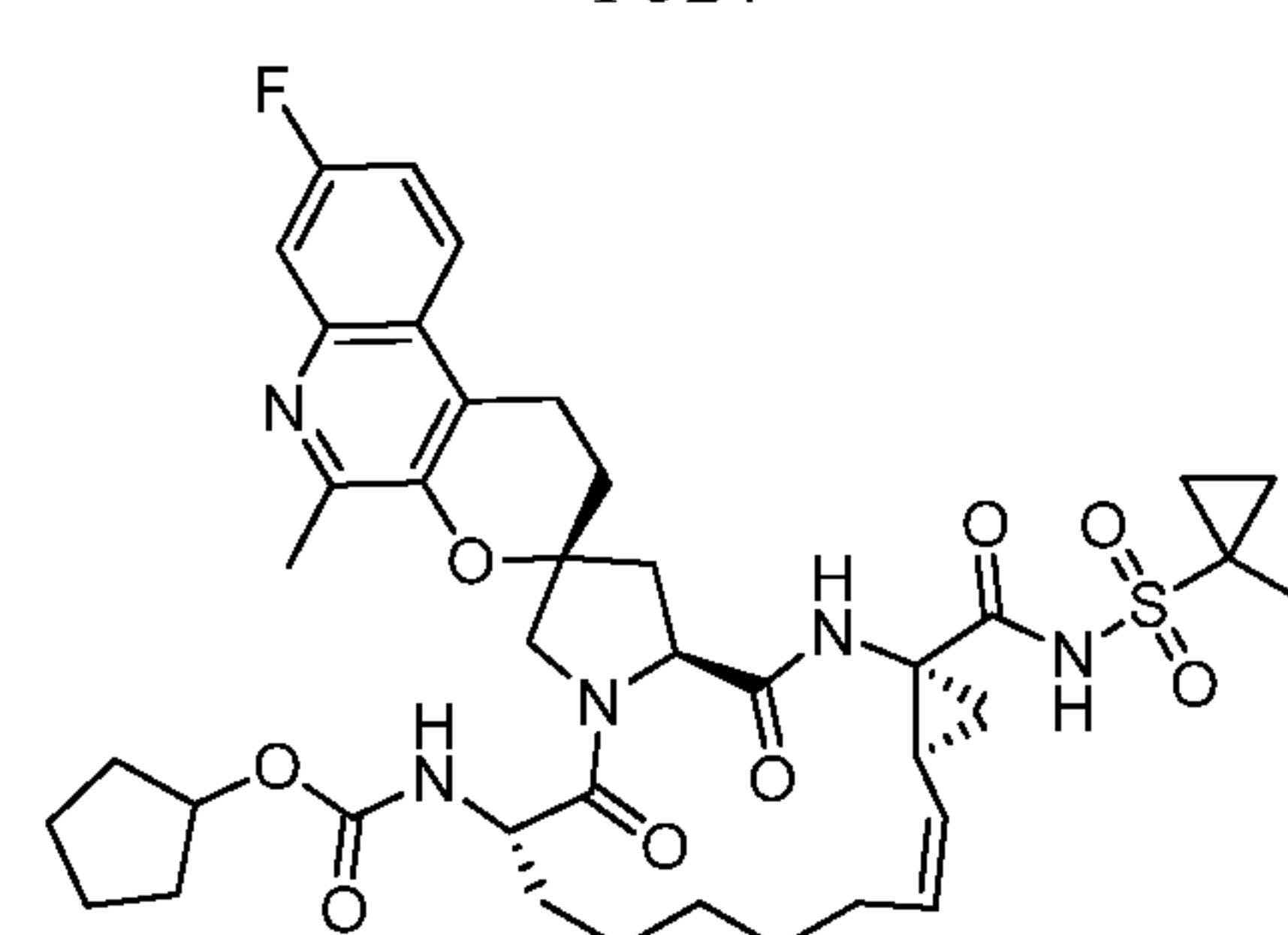
I-324



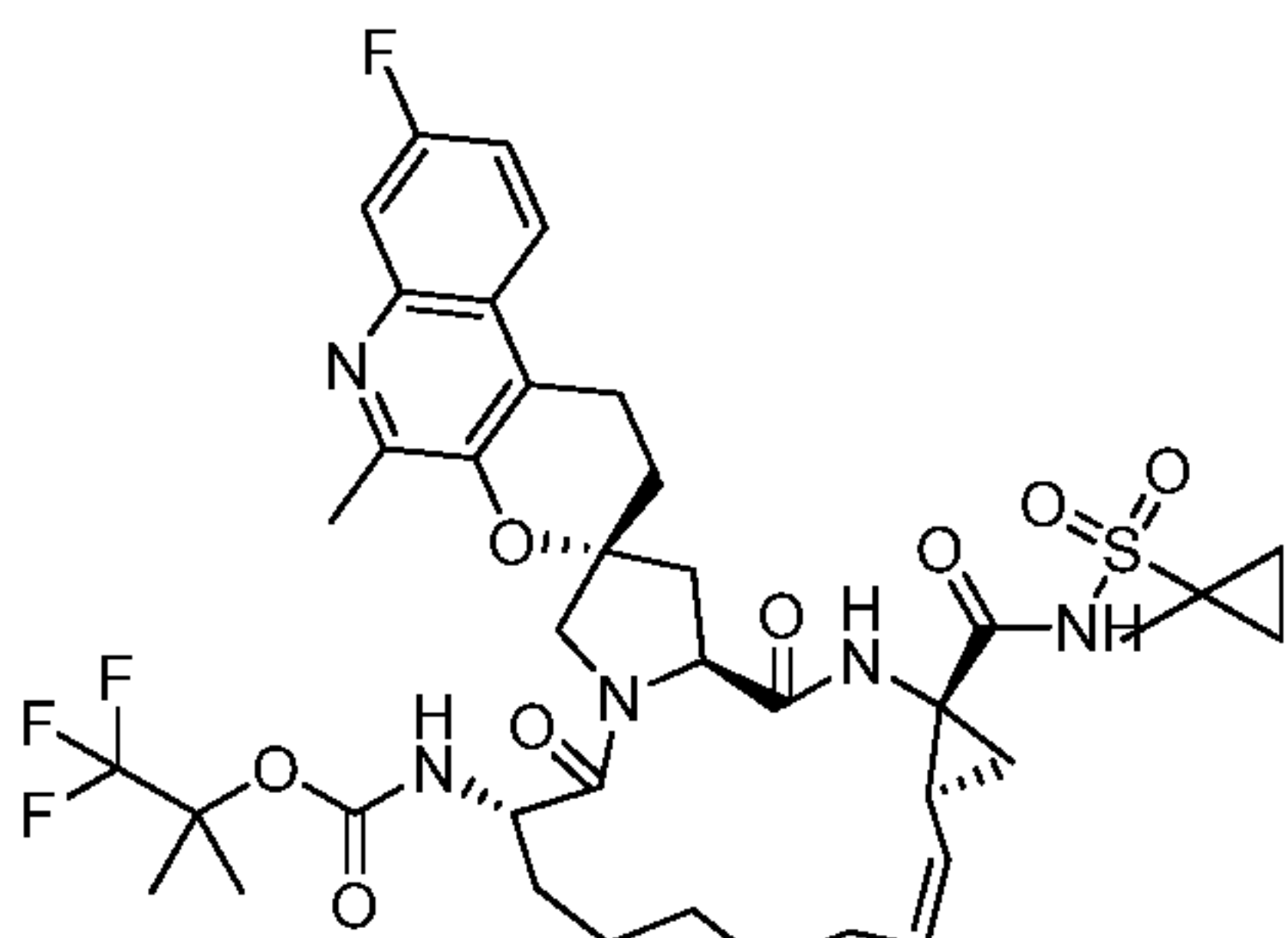
I-325



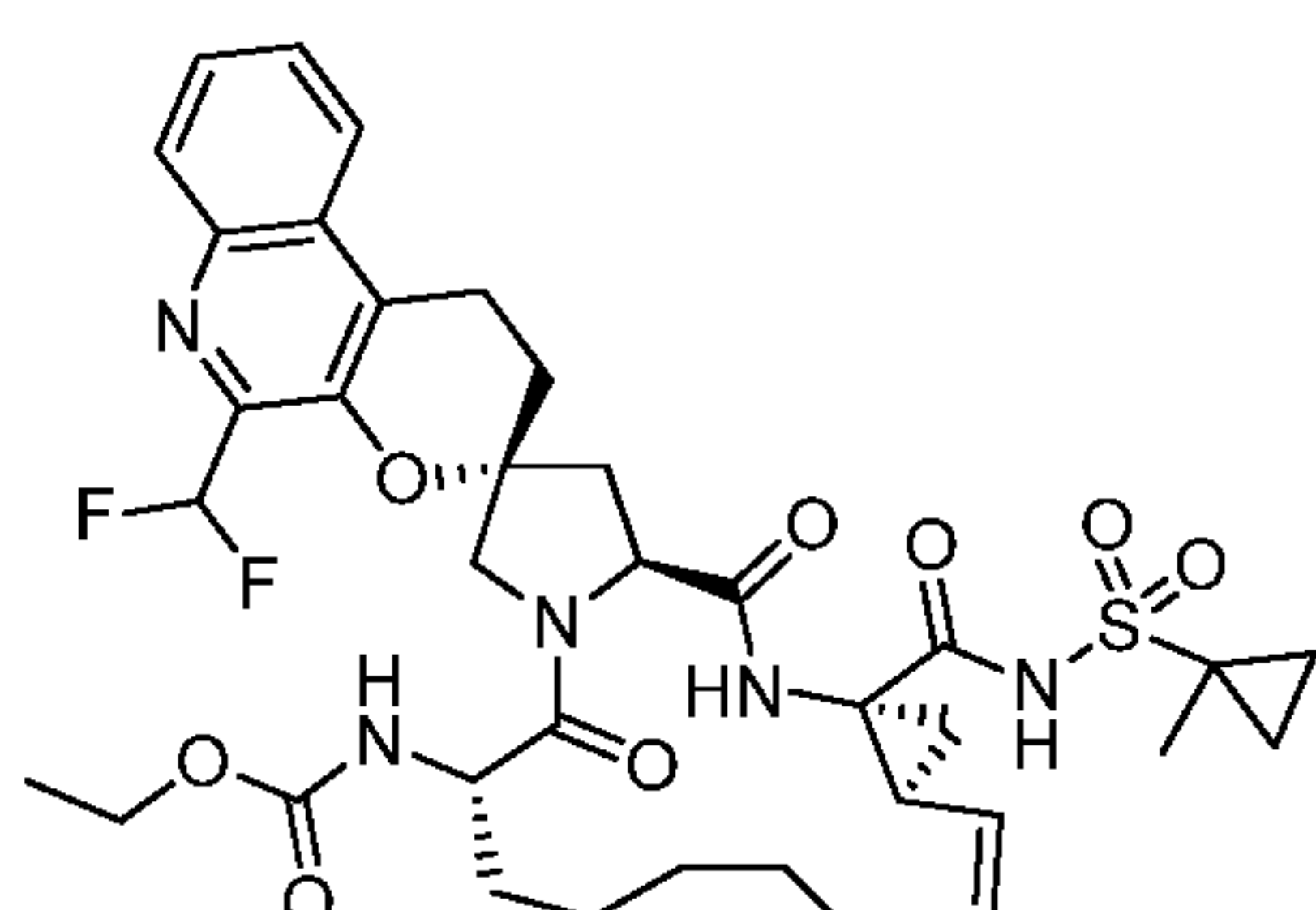
I-326



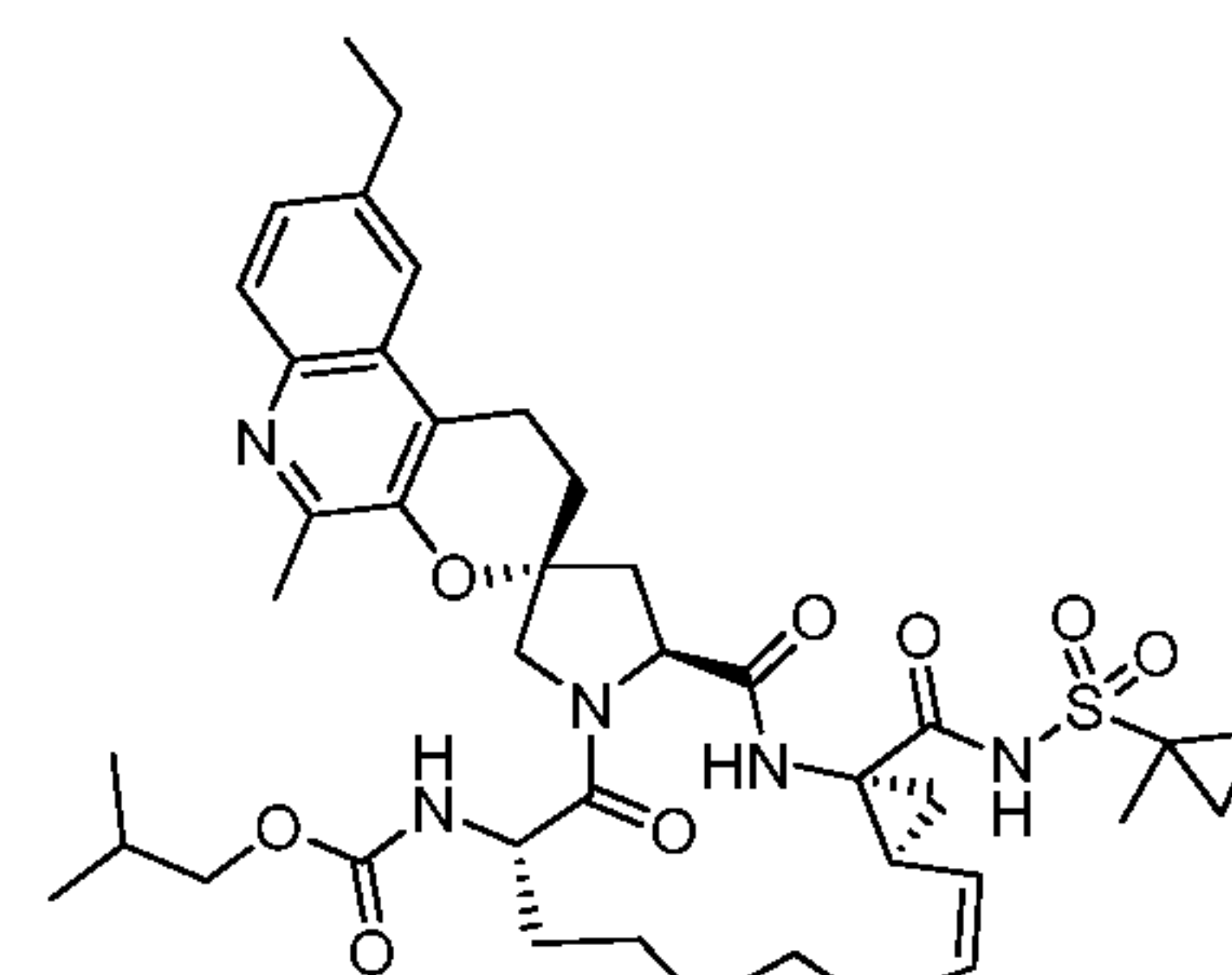
I-327



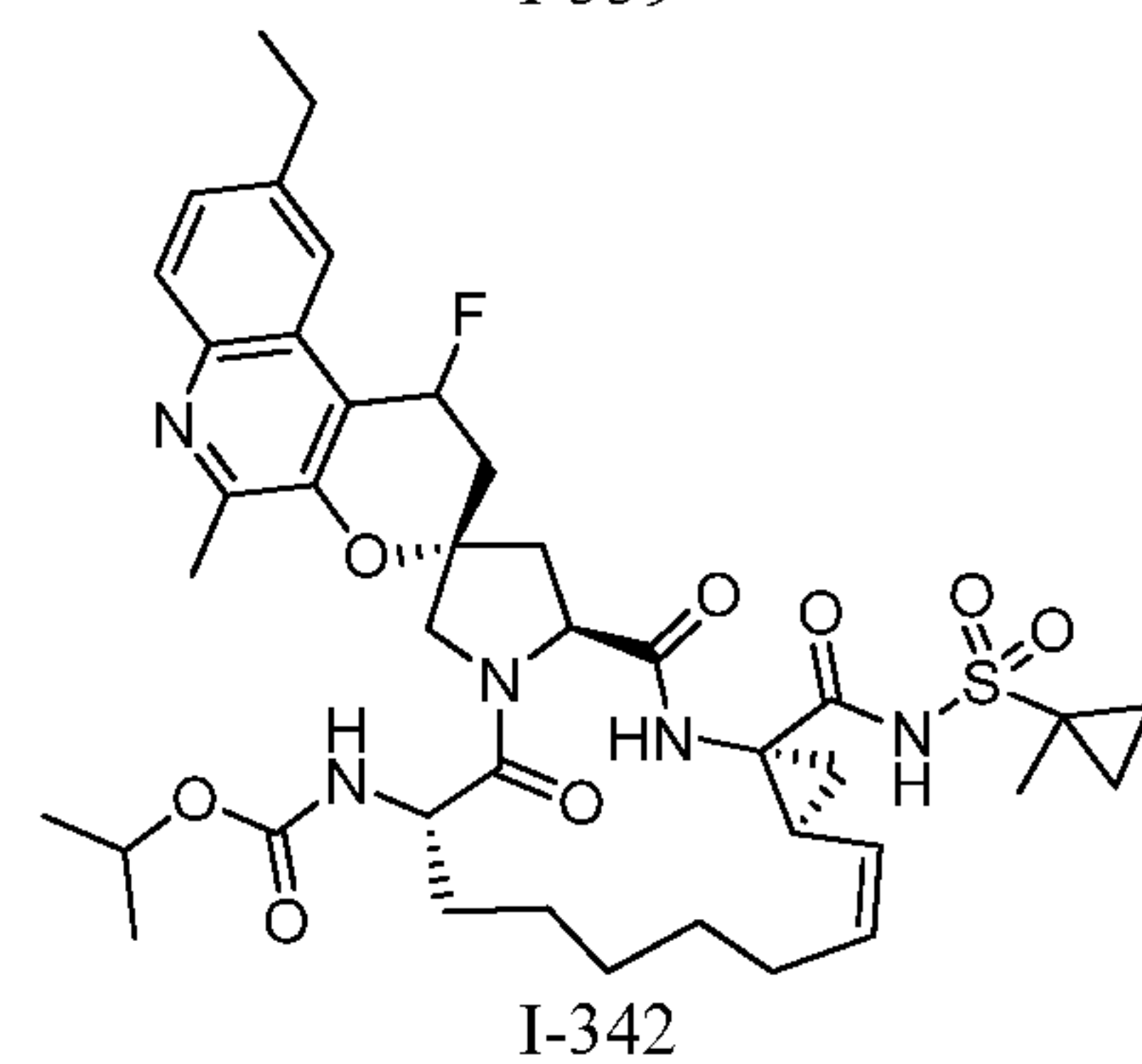
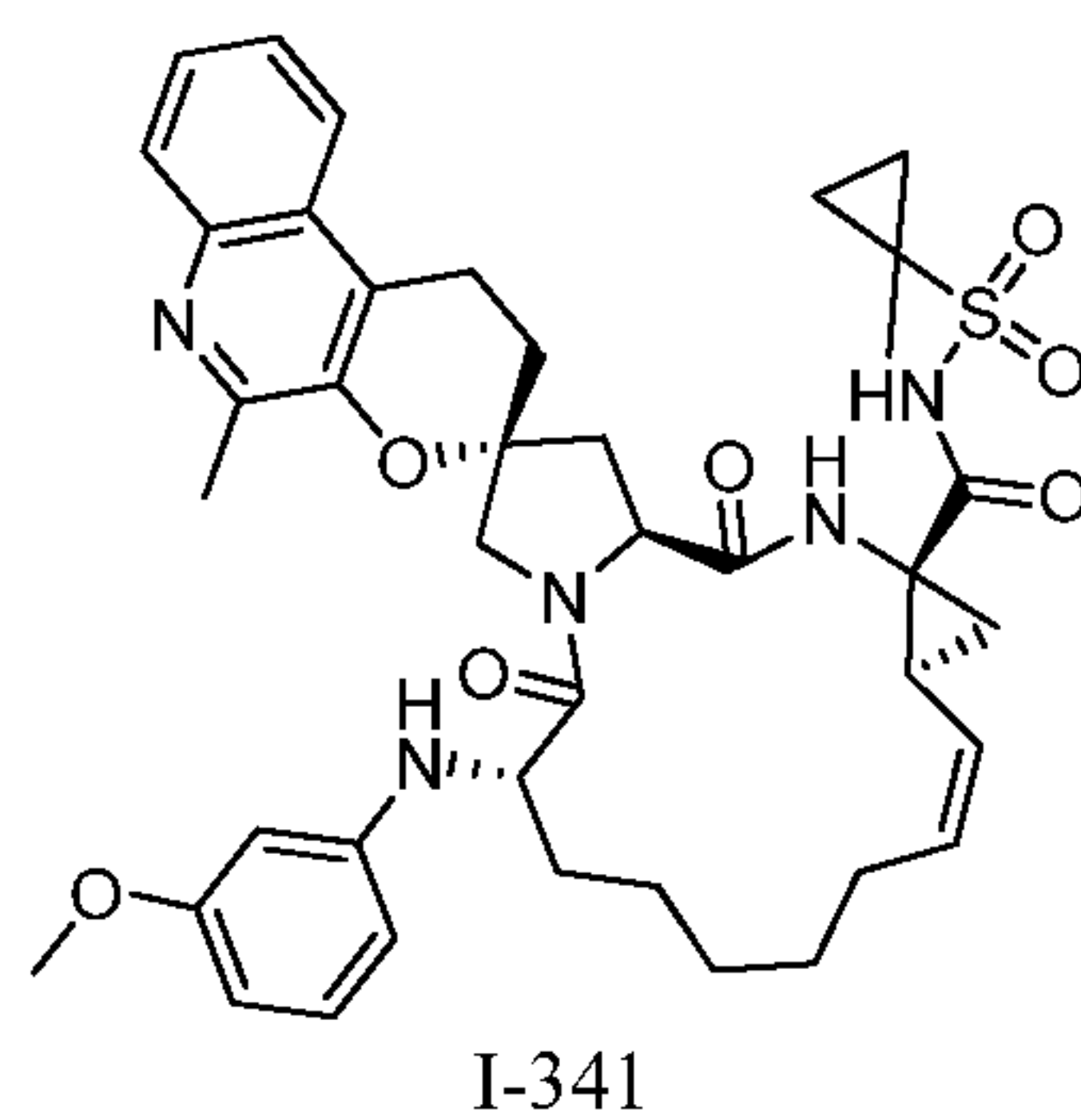
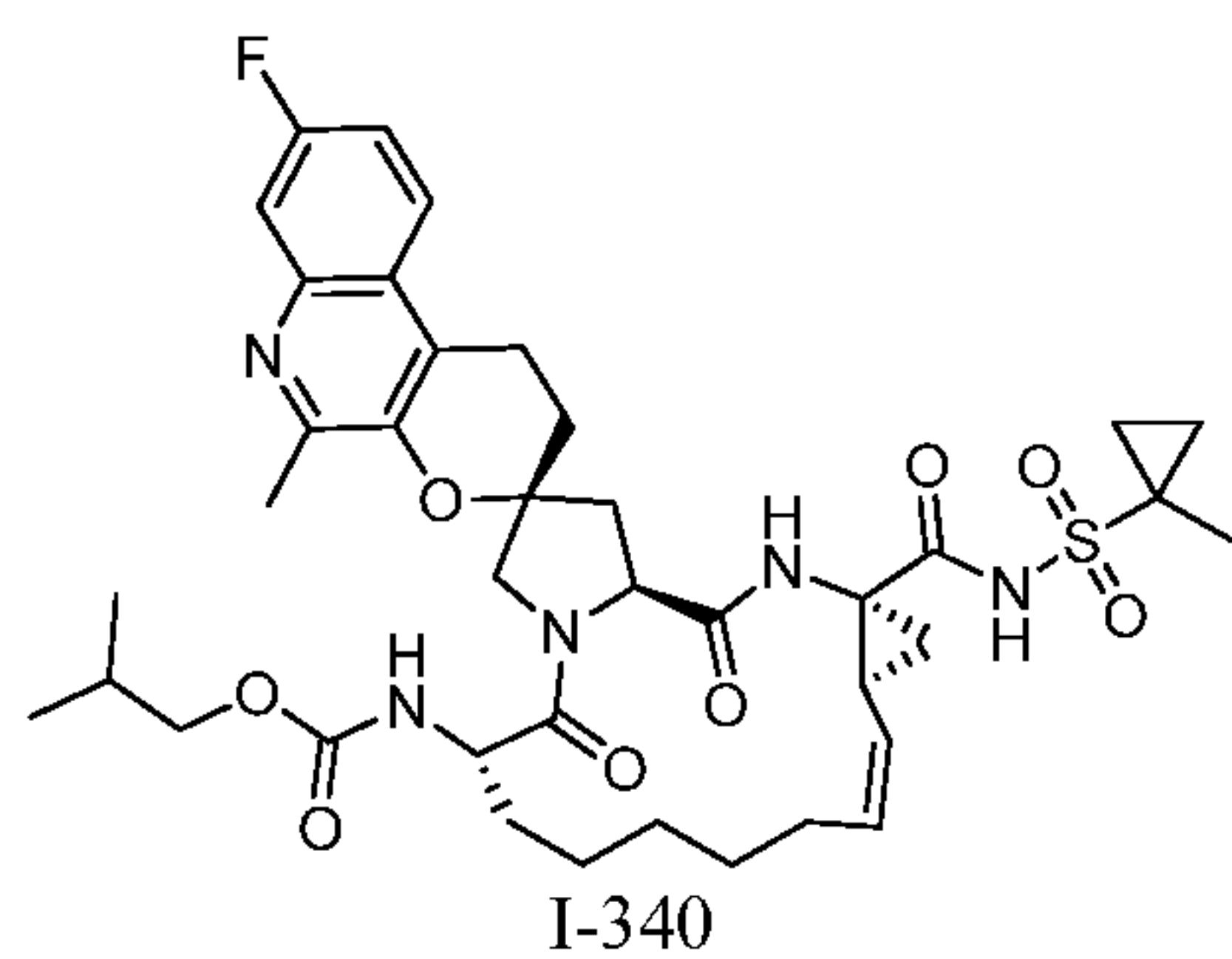
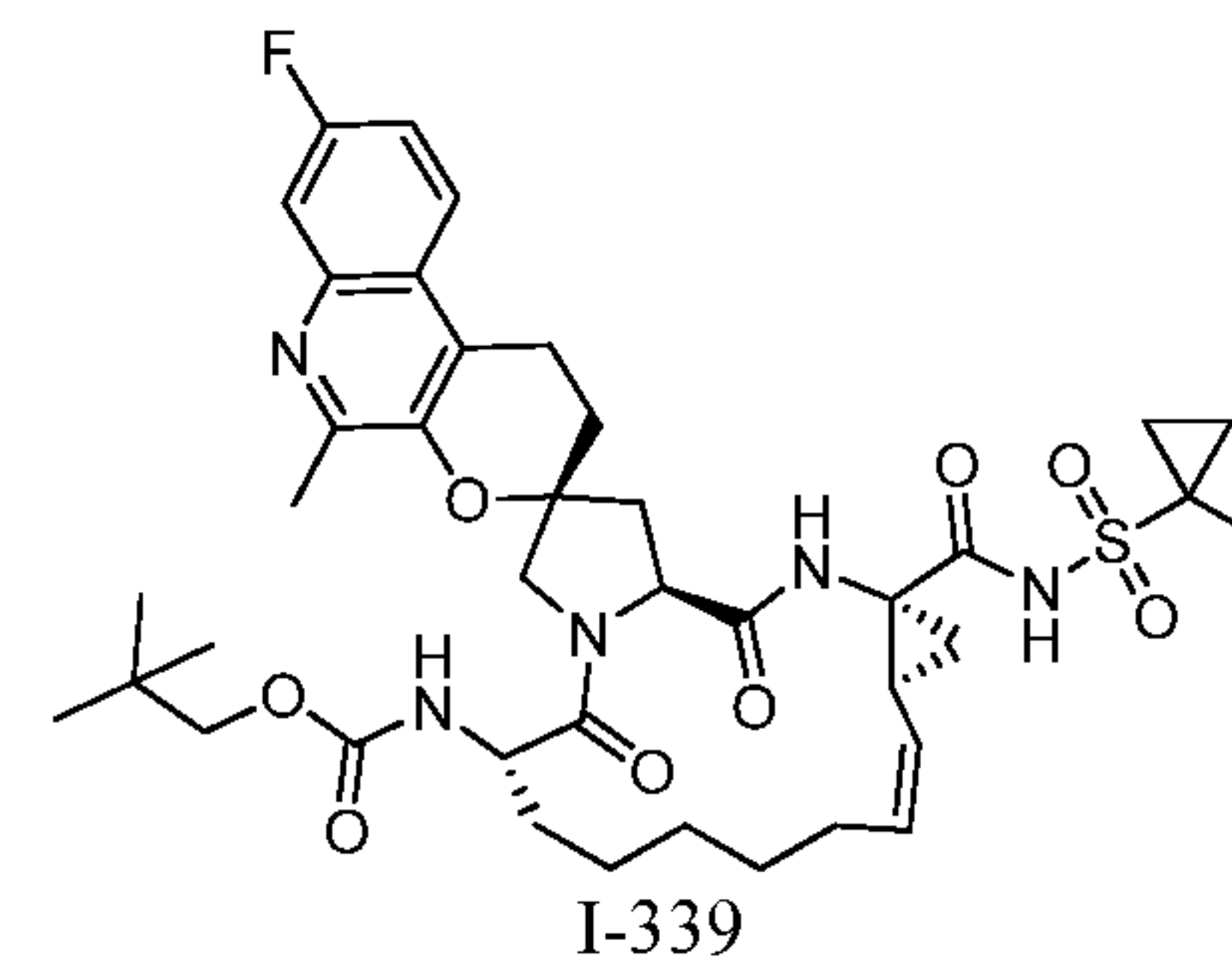
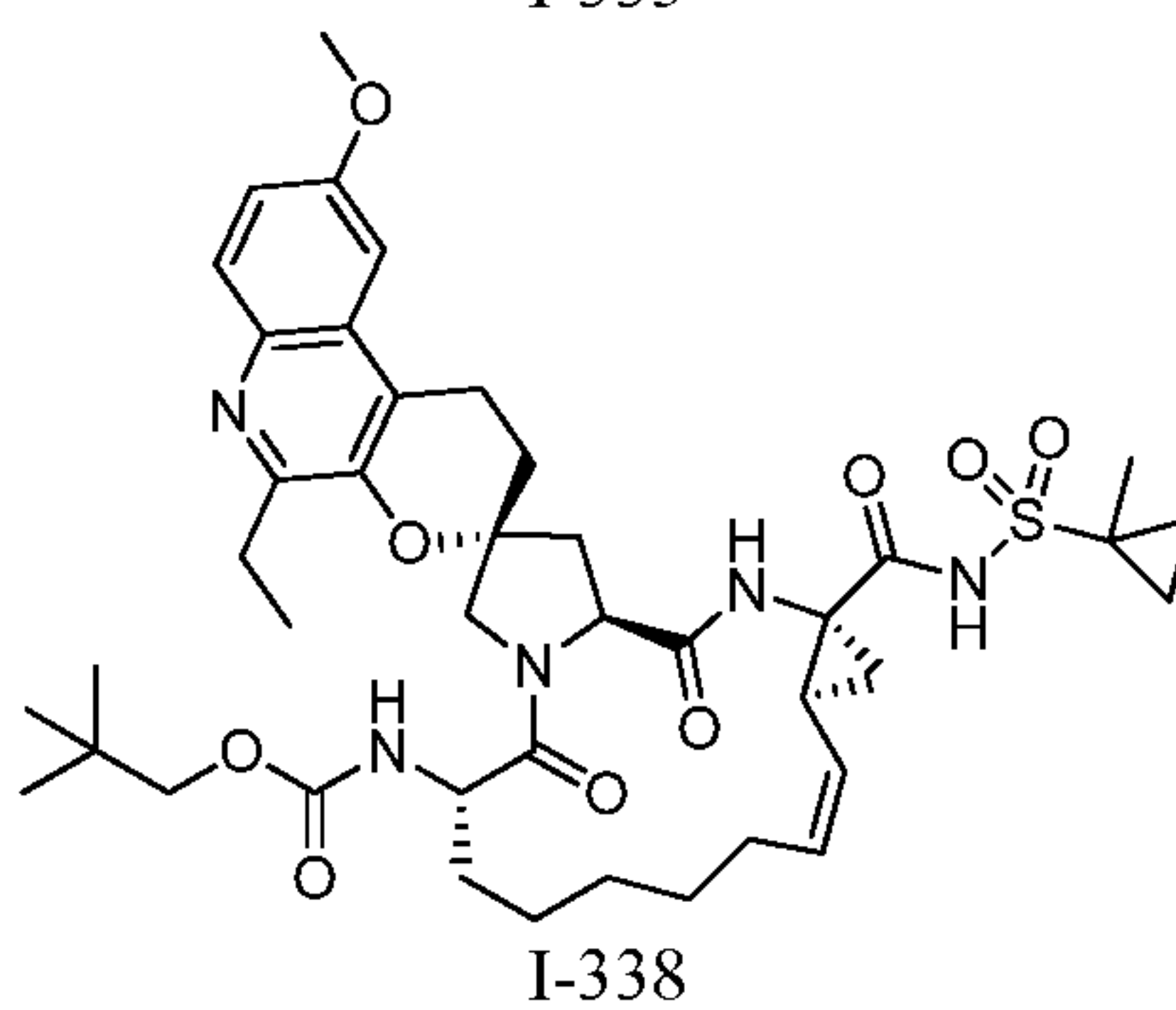
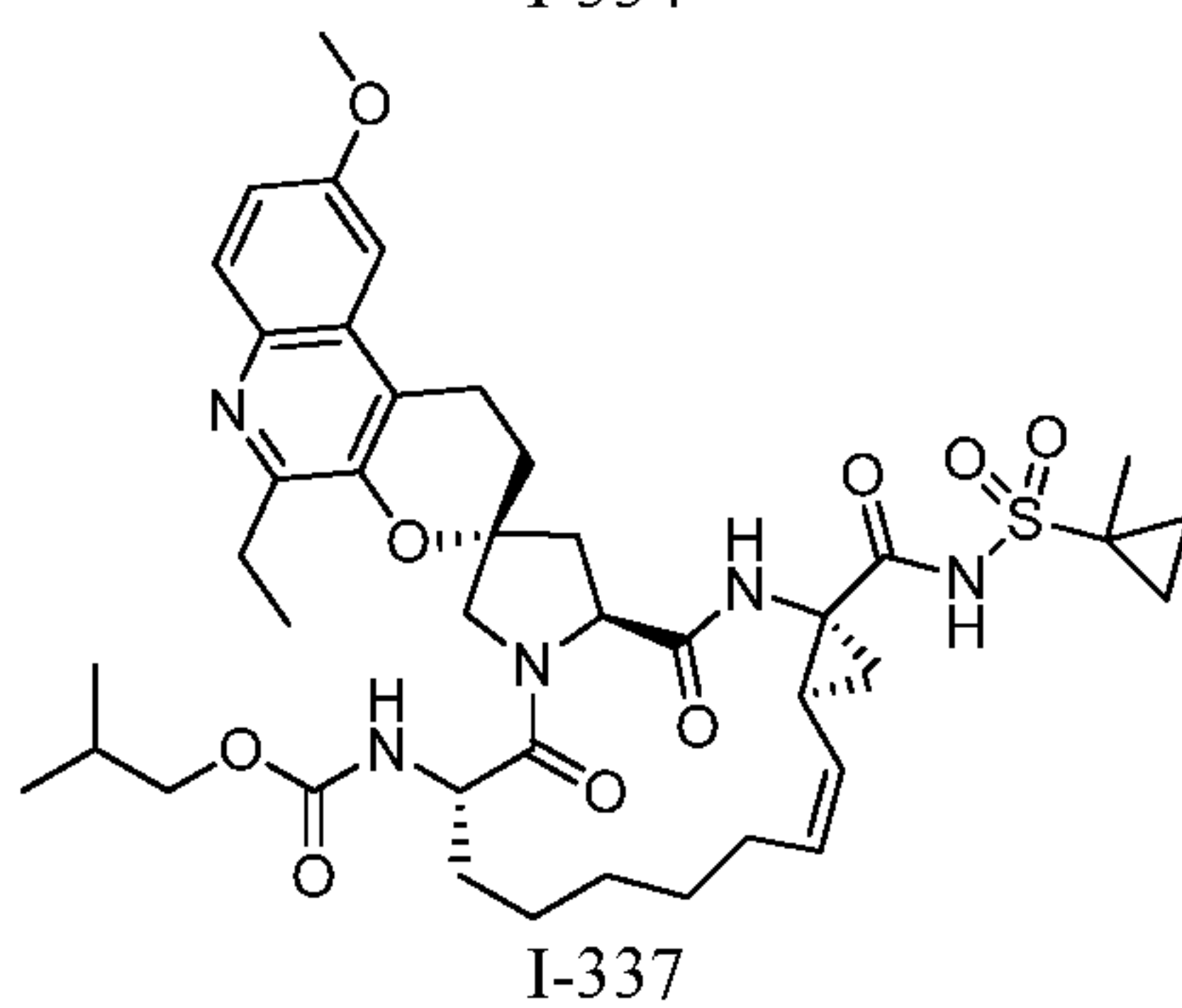
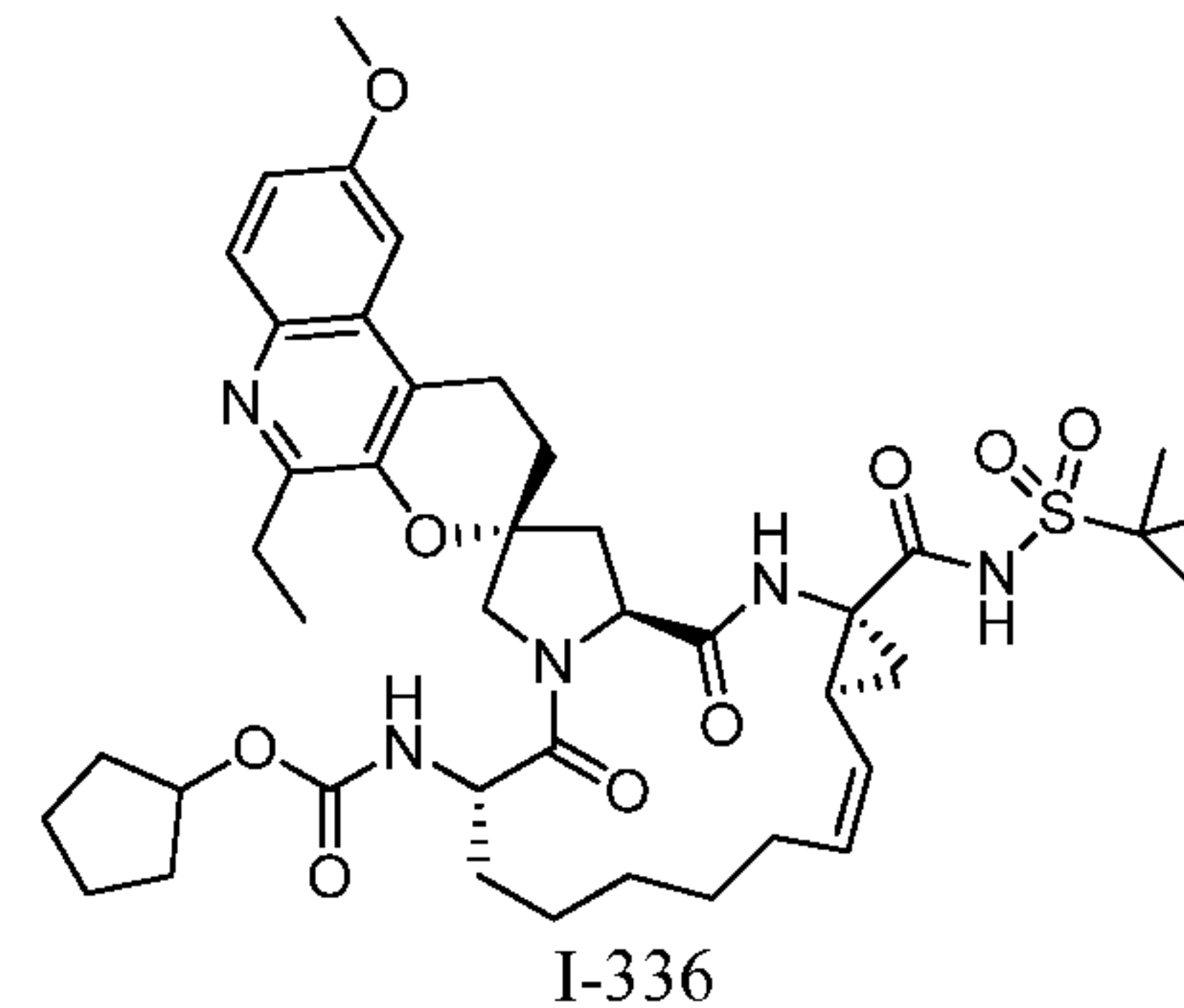
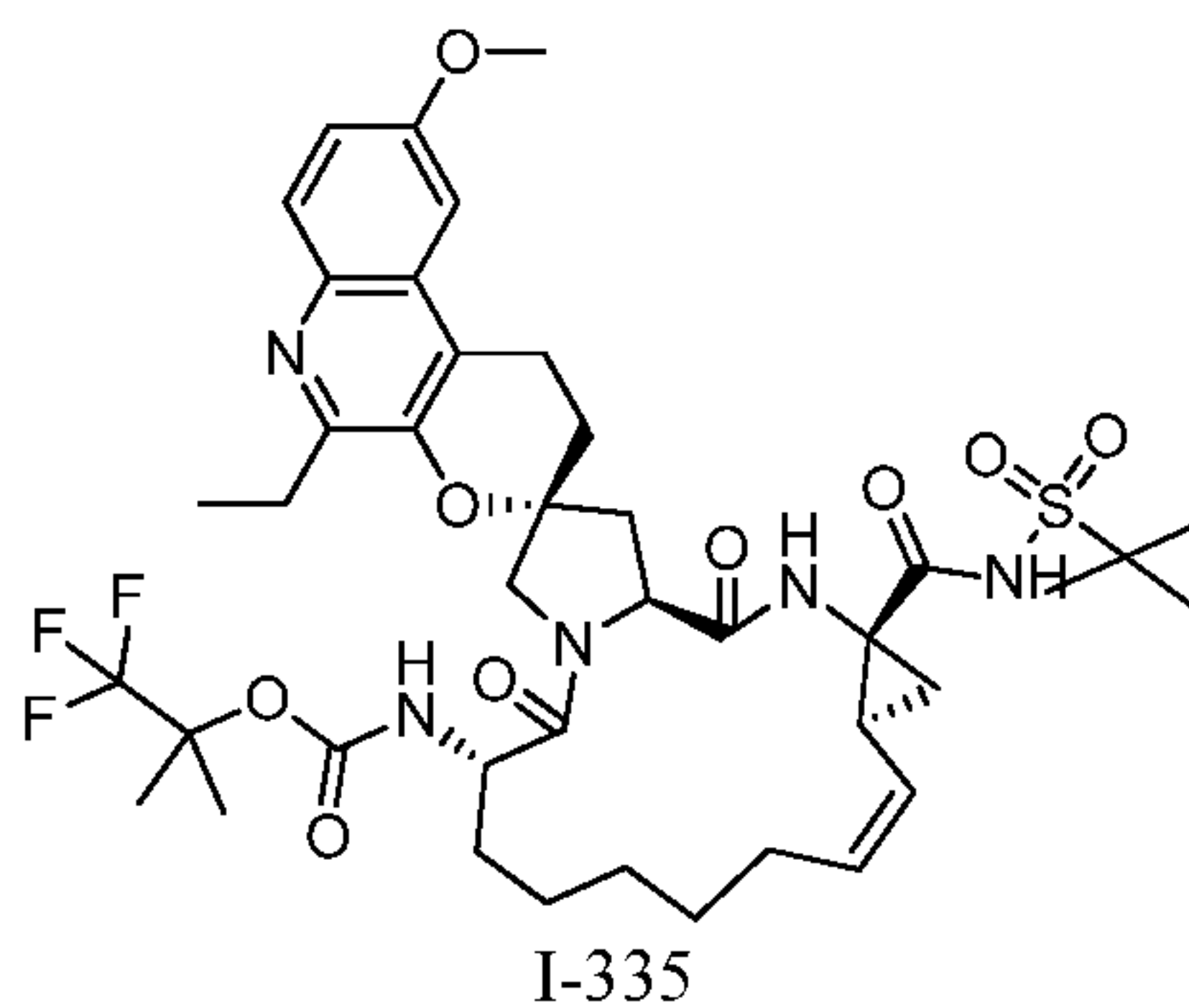
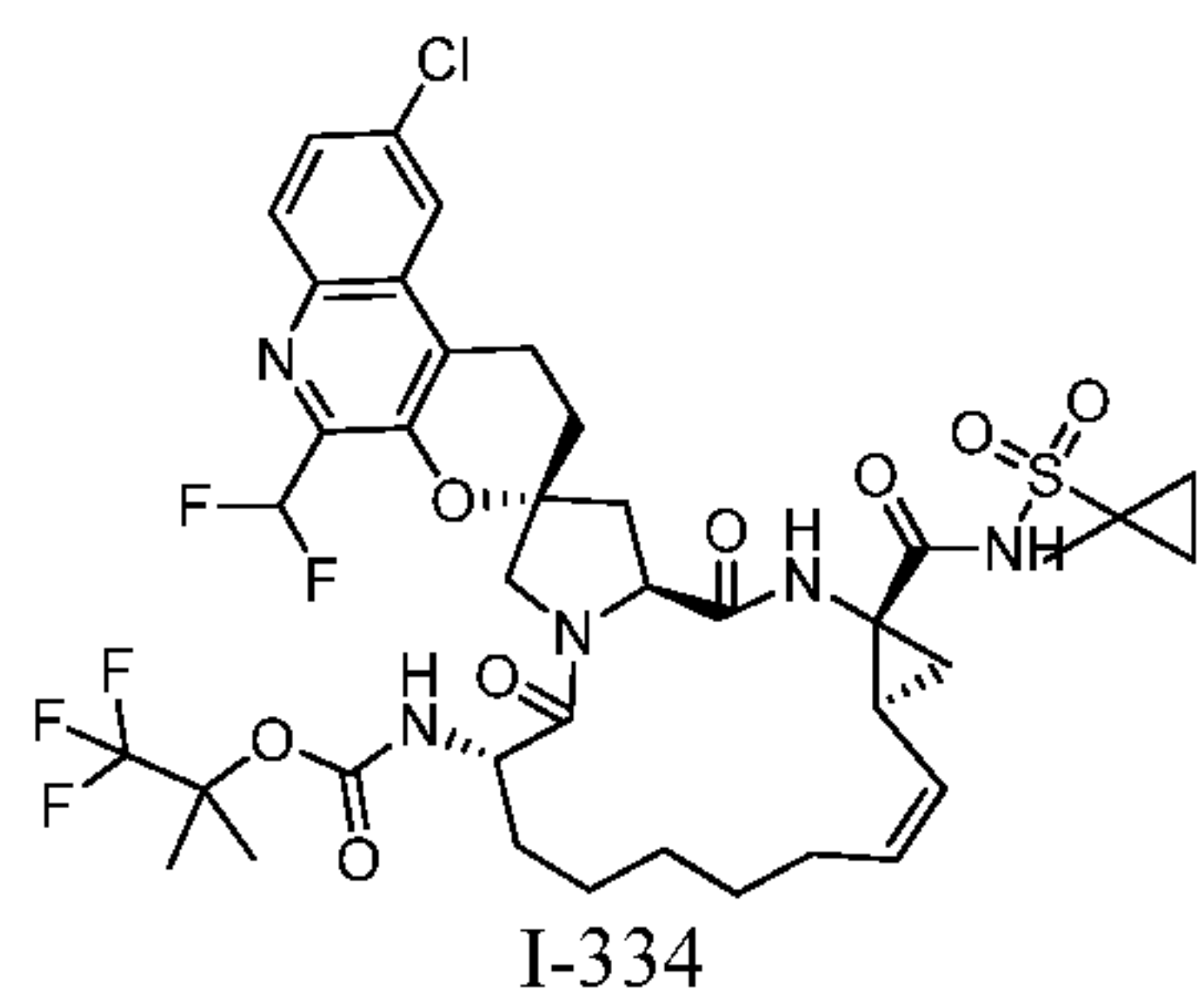
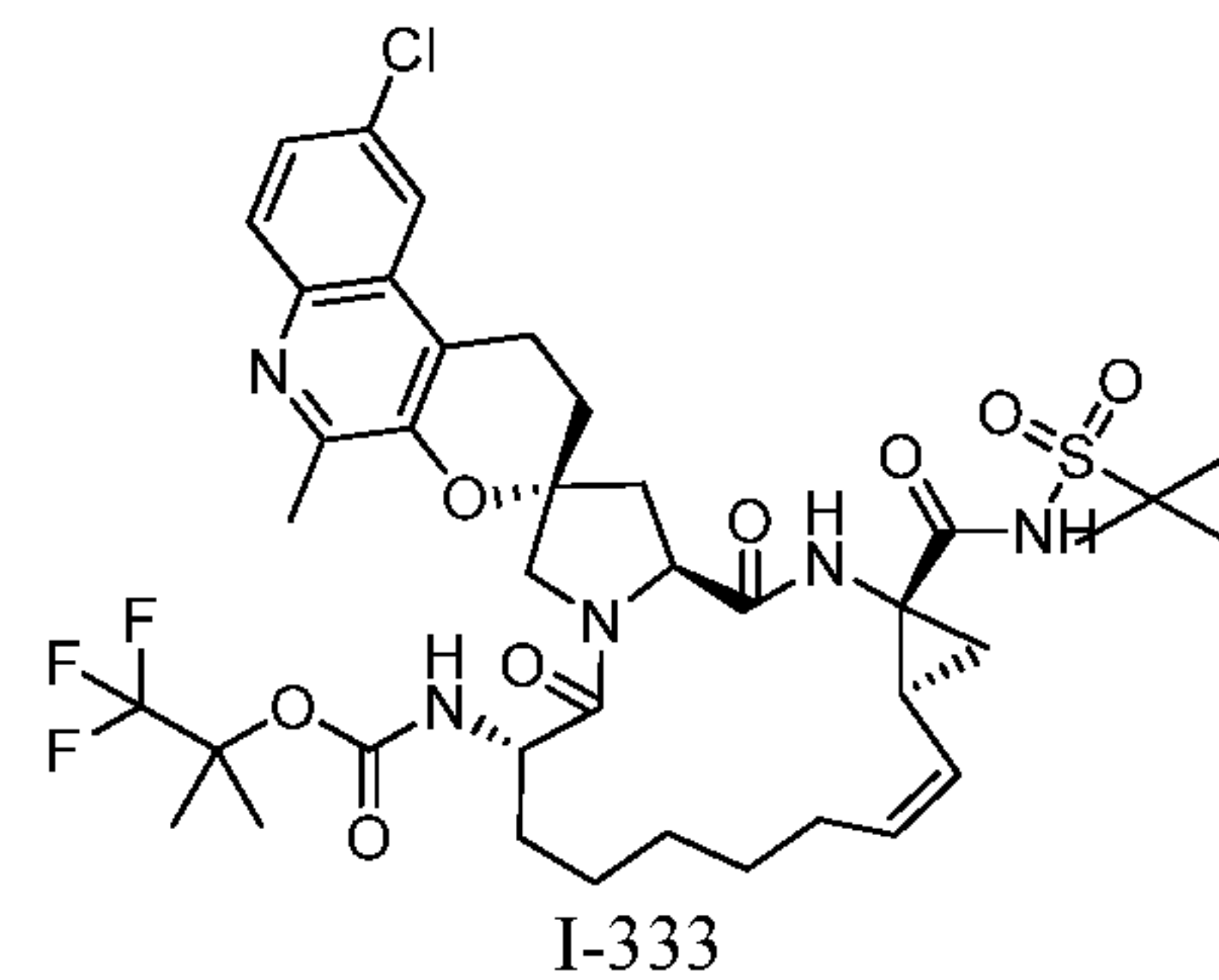
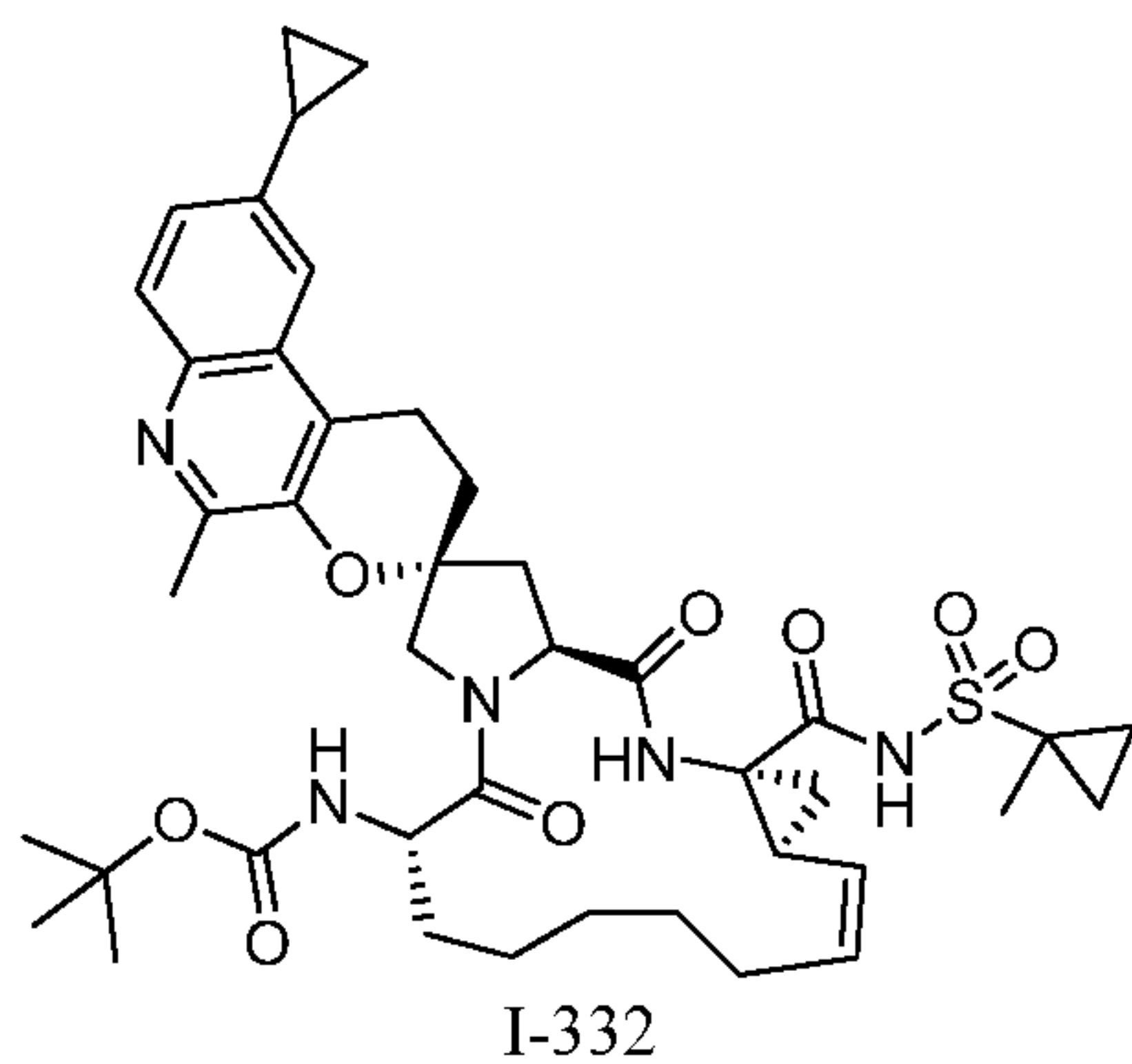
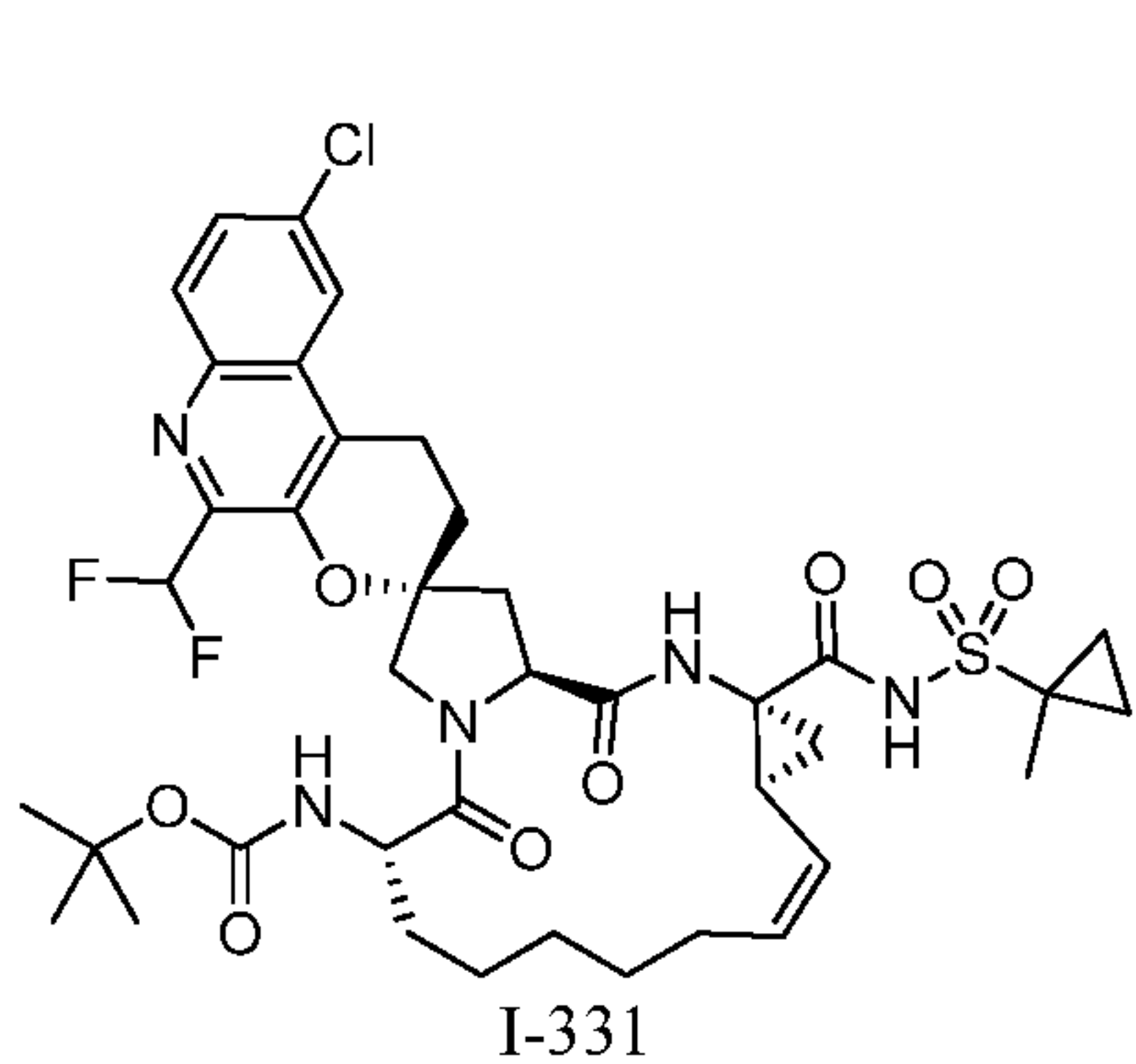
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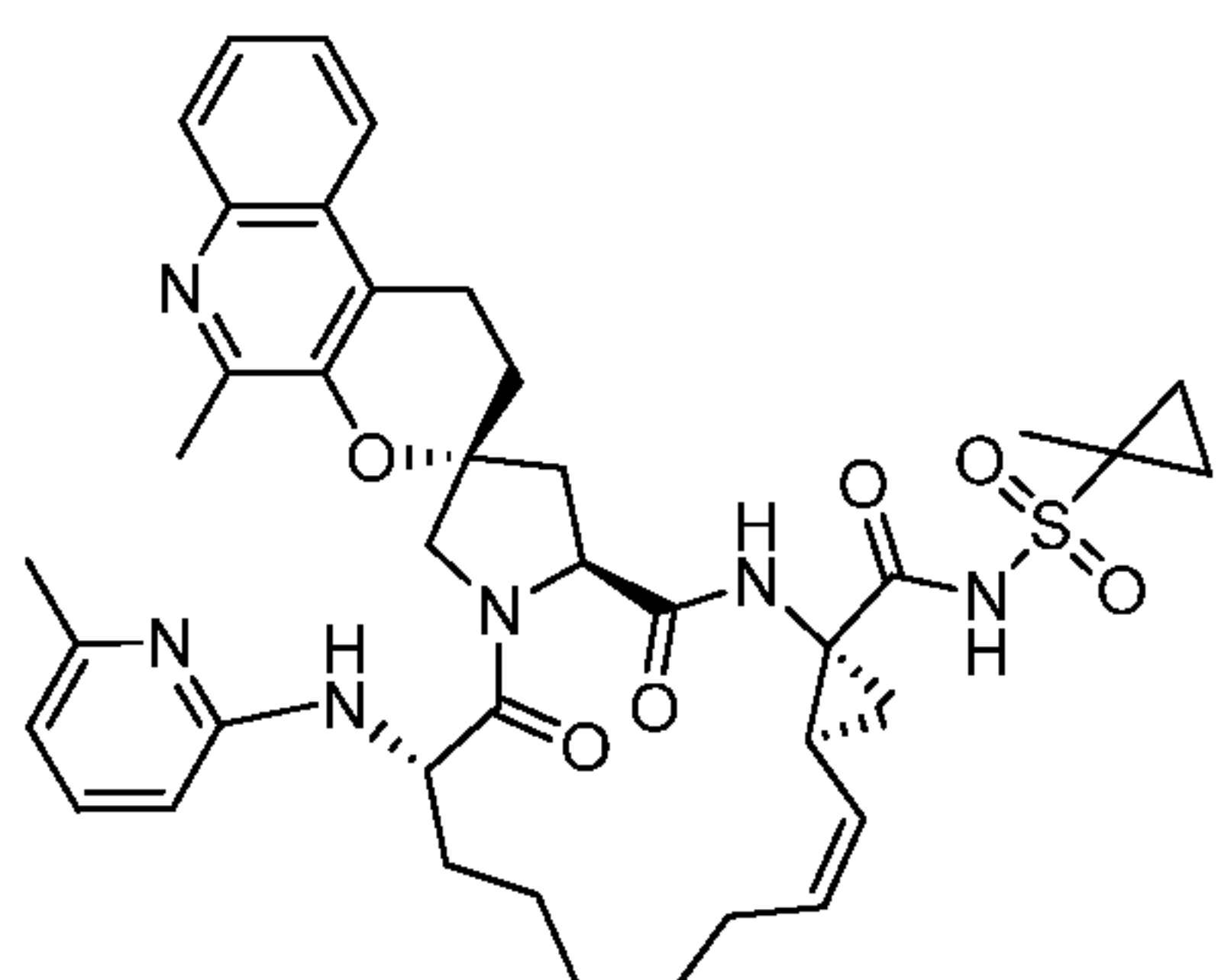


I-329

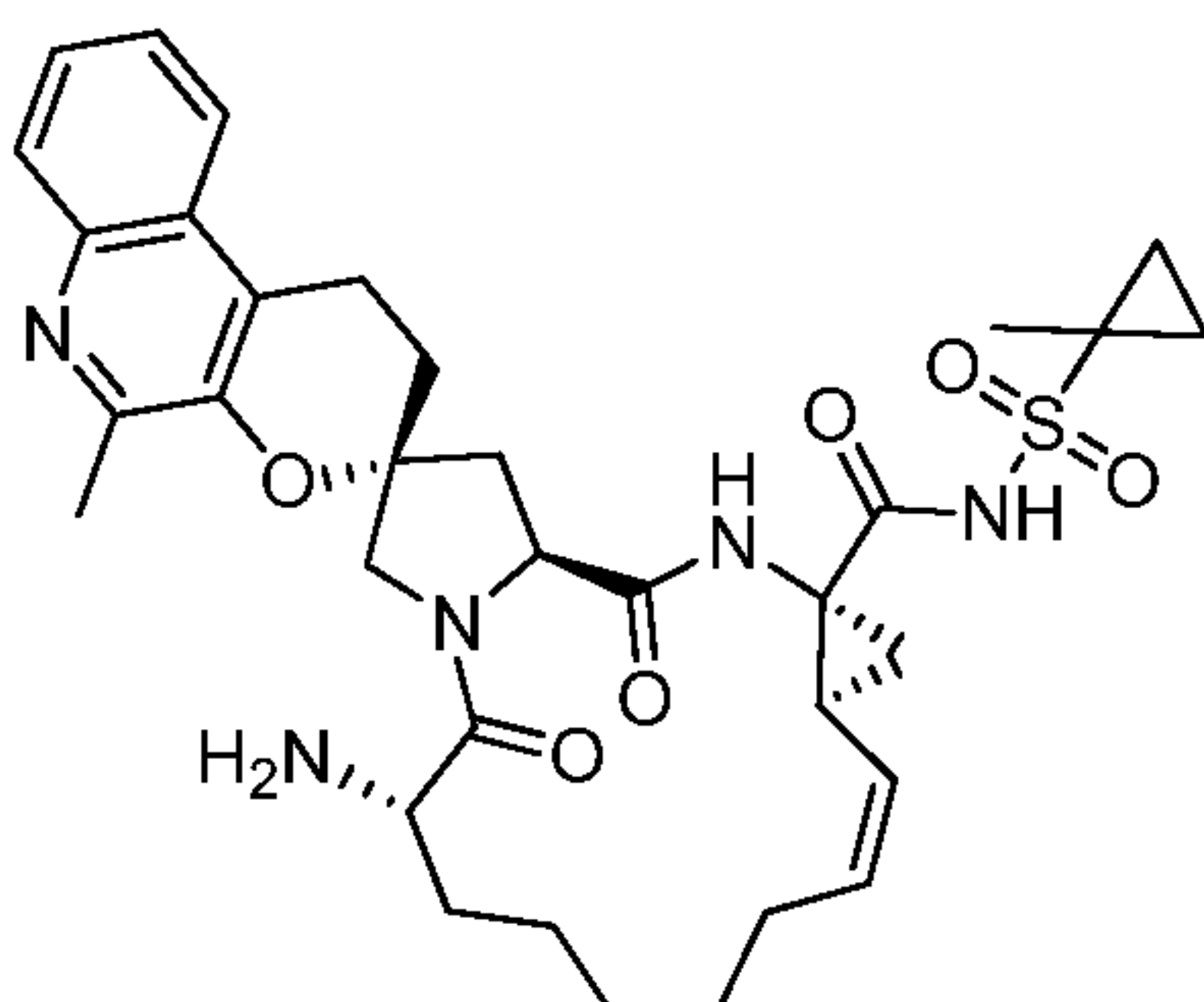


I-330

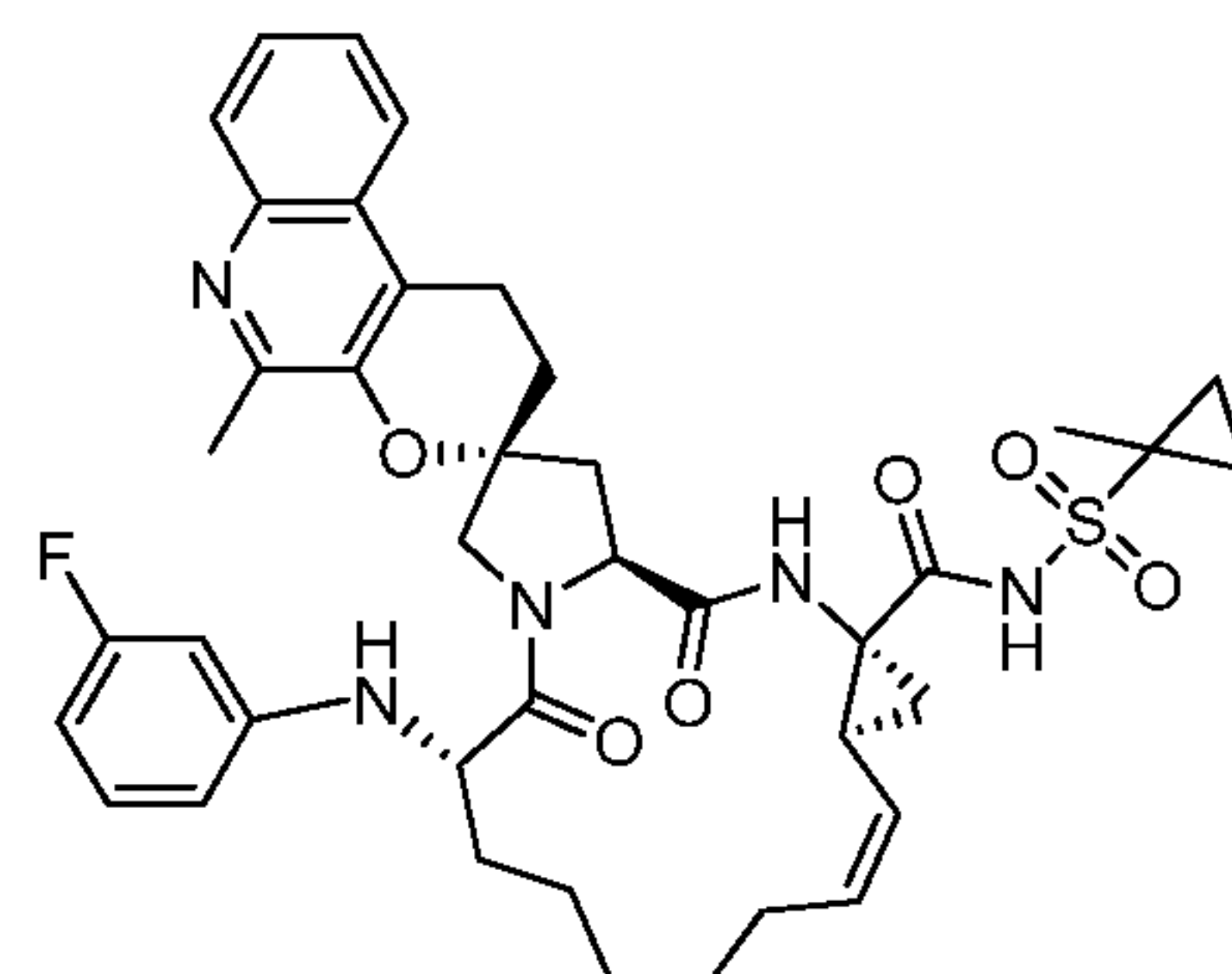




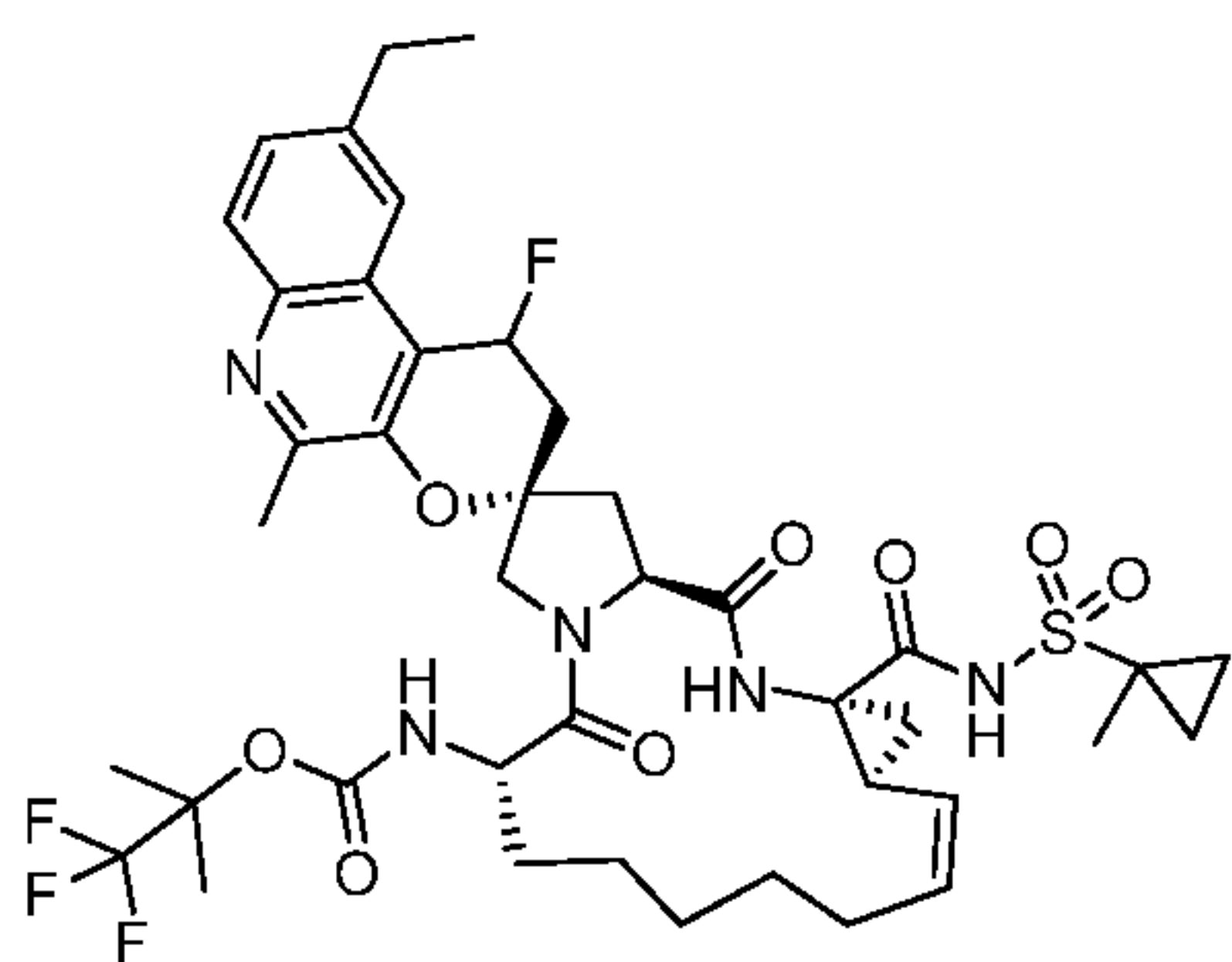
I-343



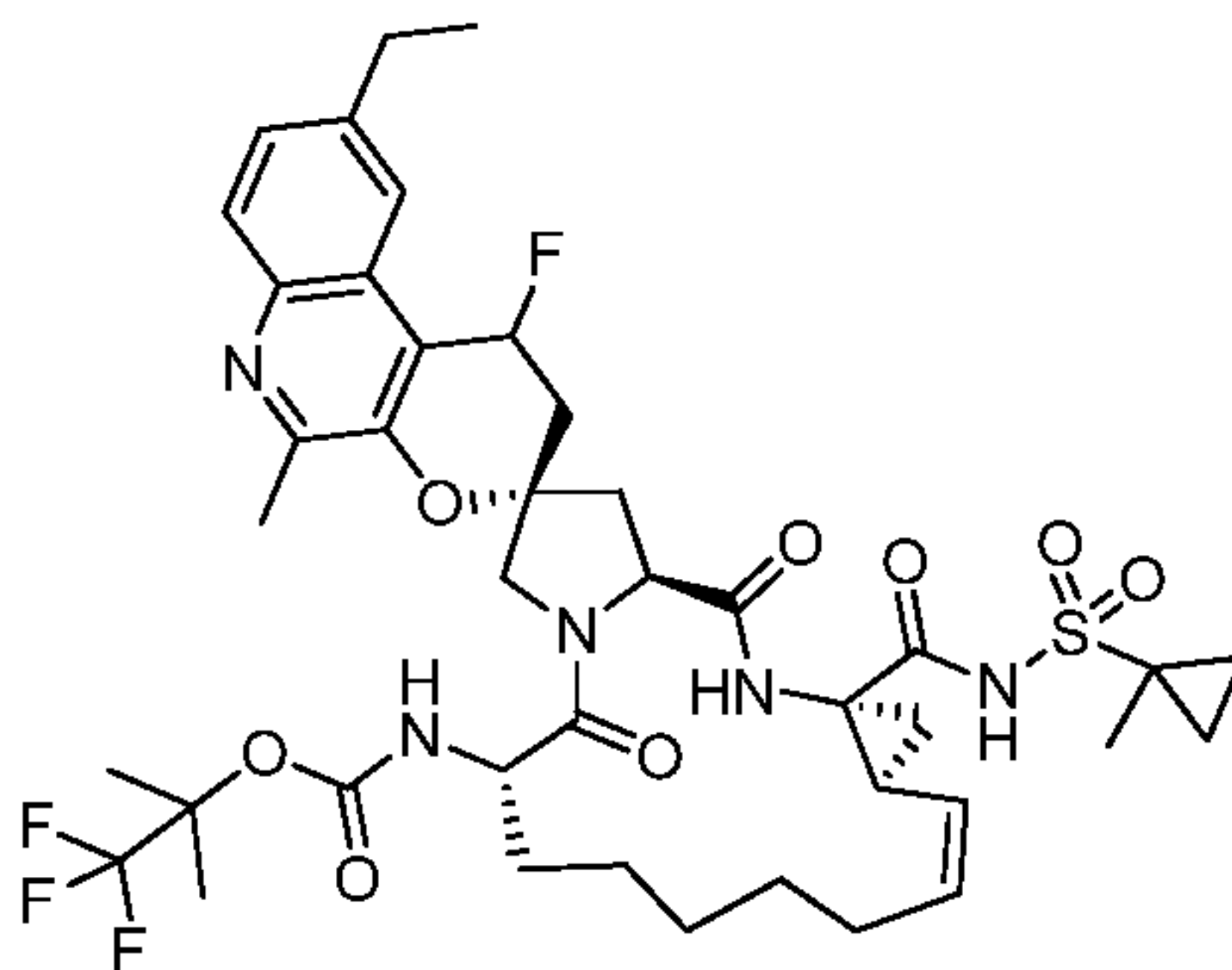
I-344



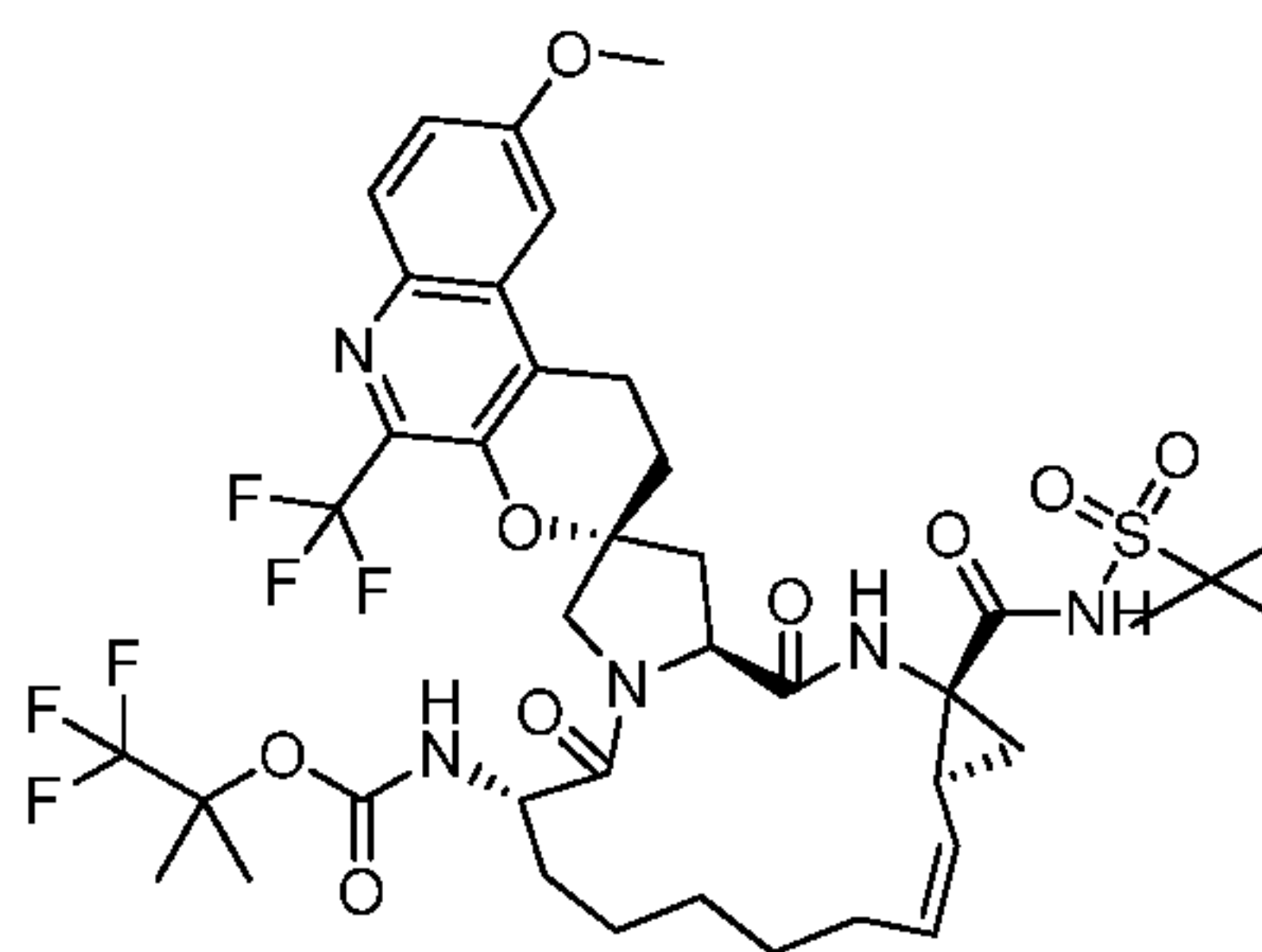
I-345



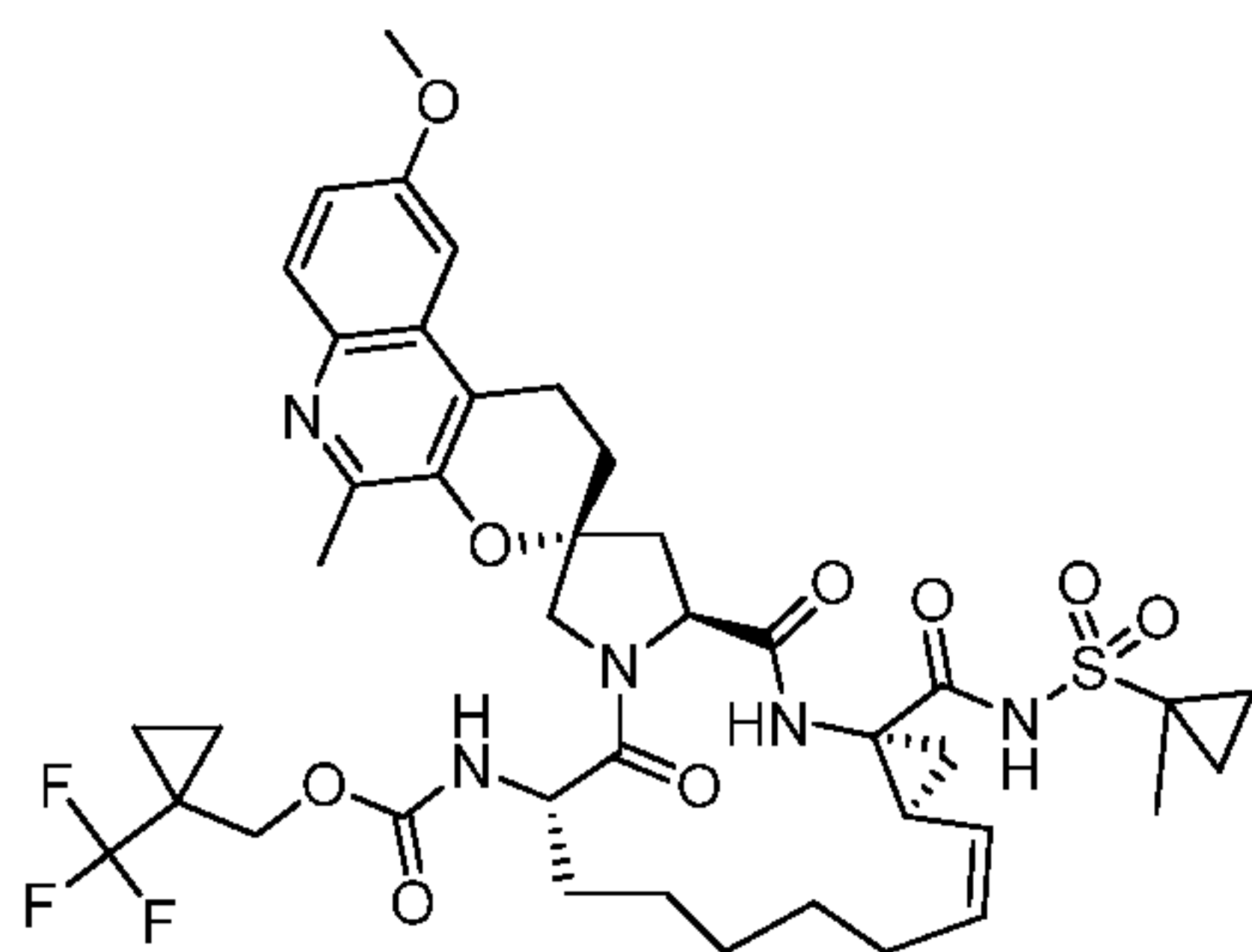
I-346



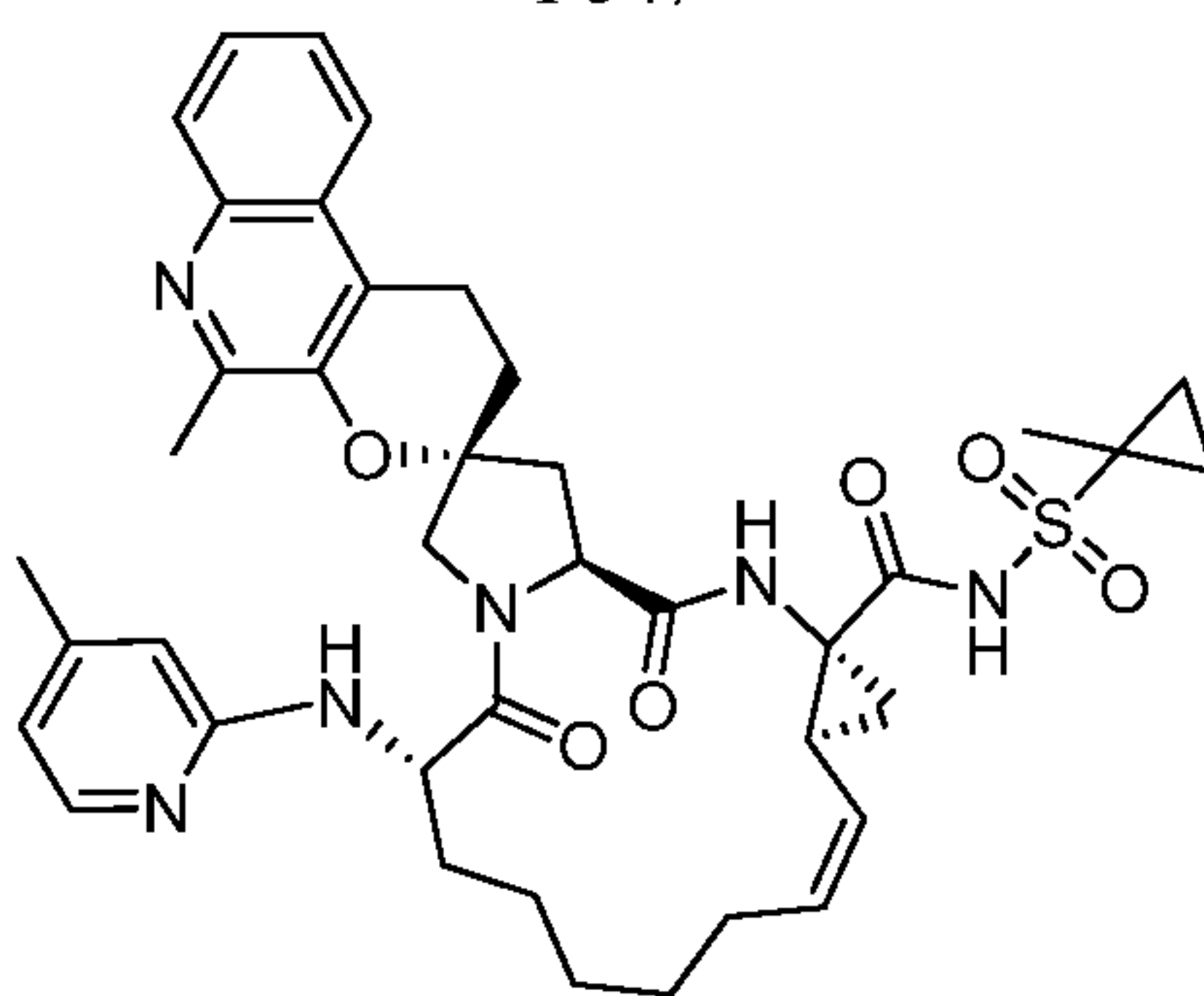
I-347



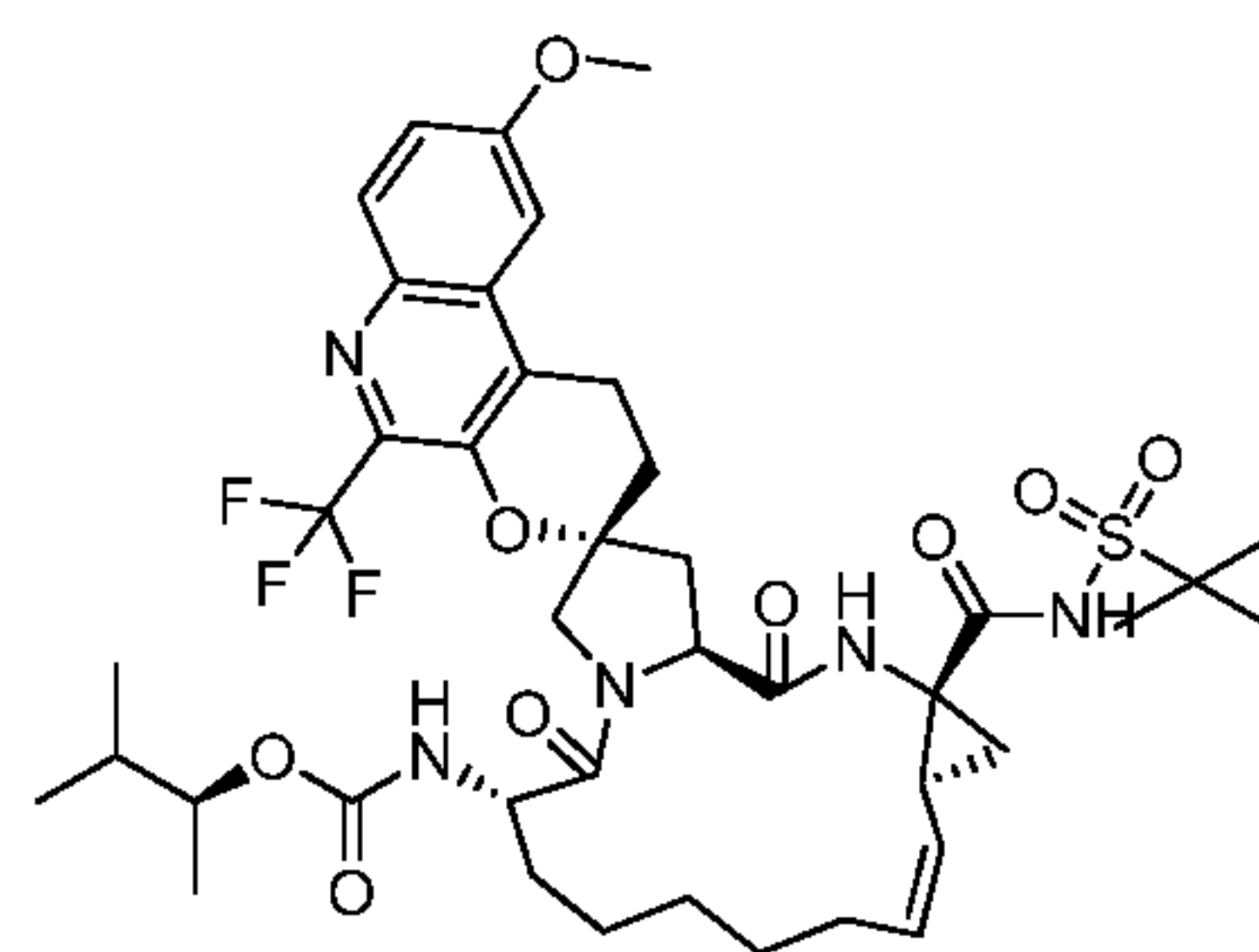
I-348



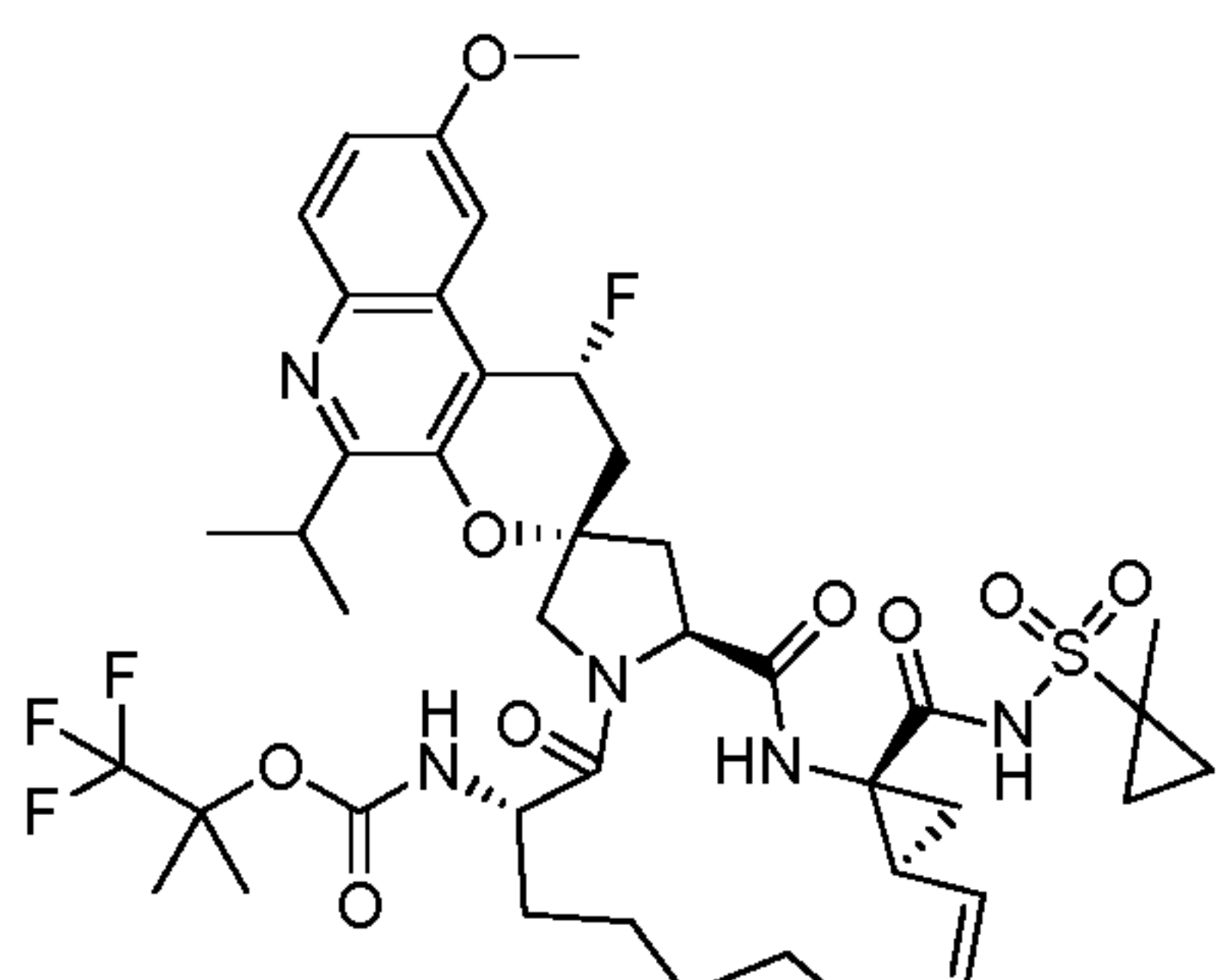
I-349



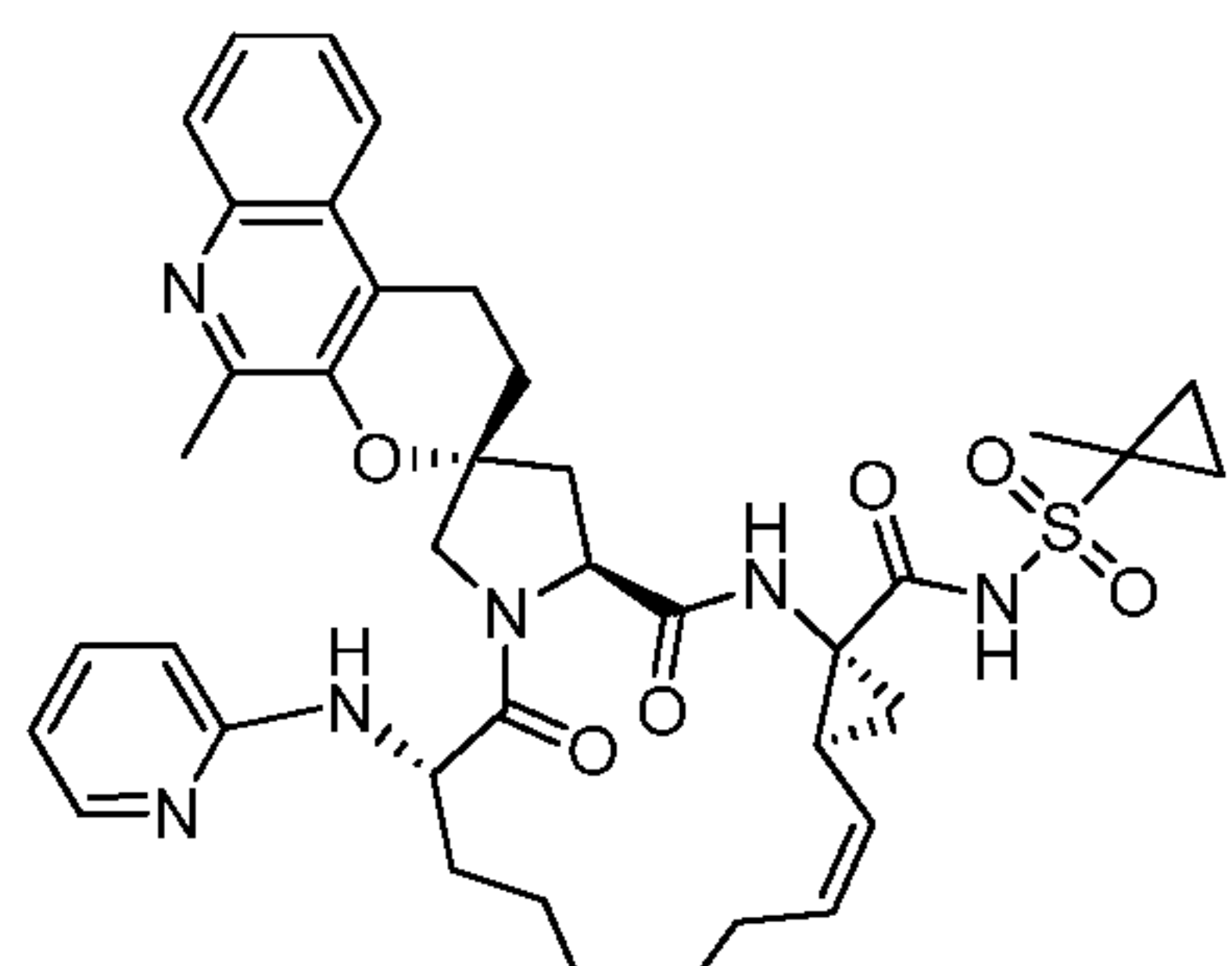
I-350



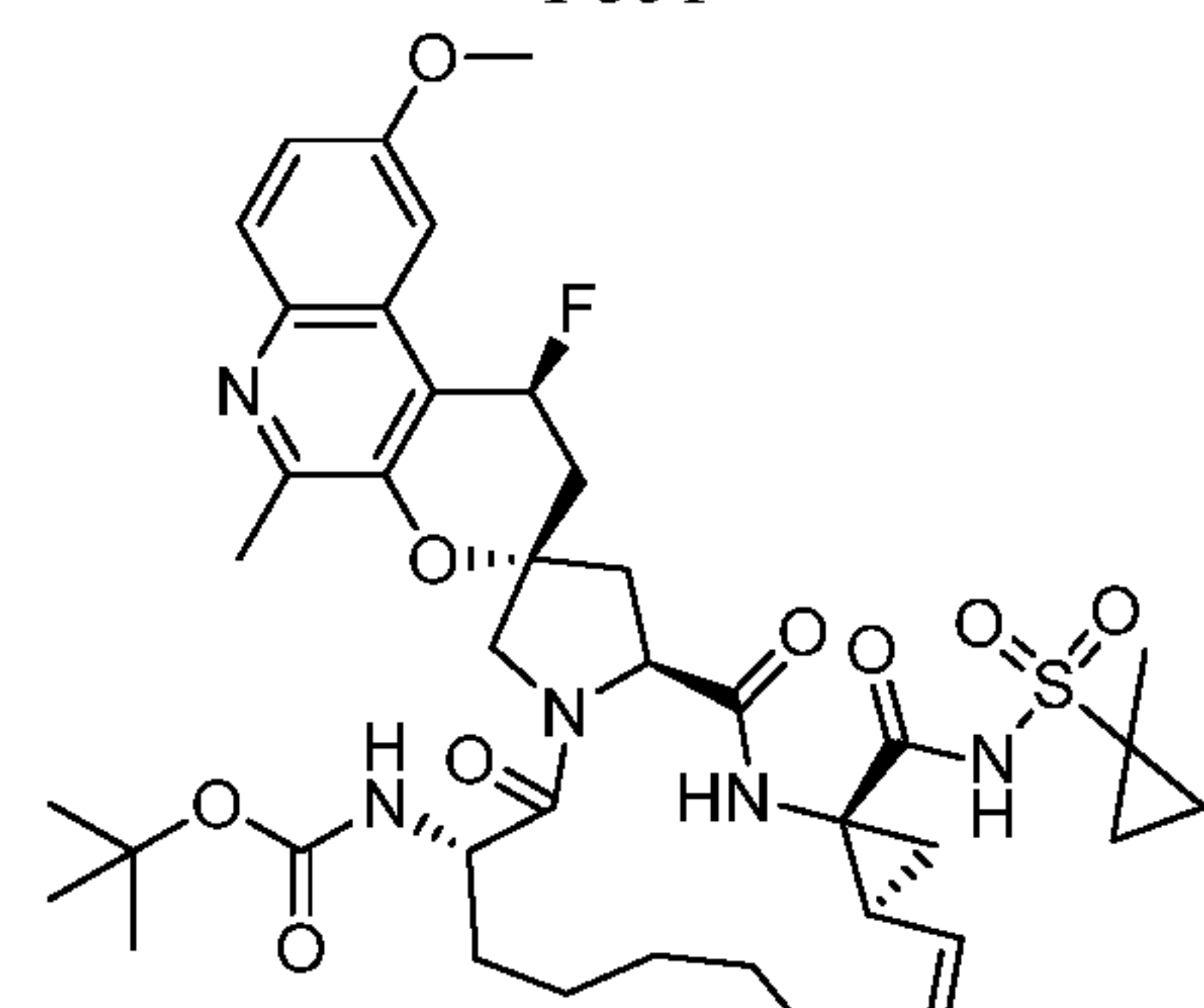
I-351



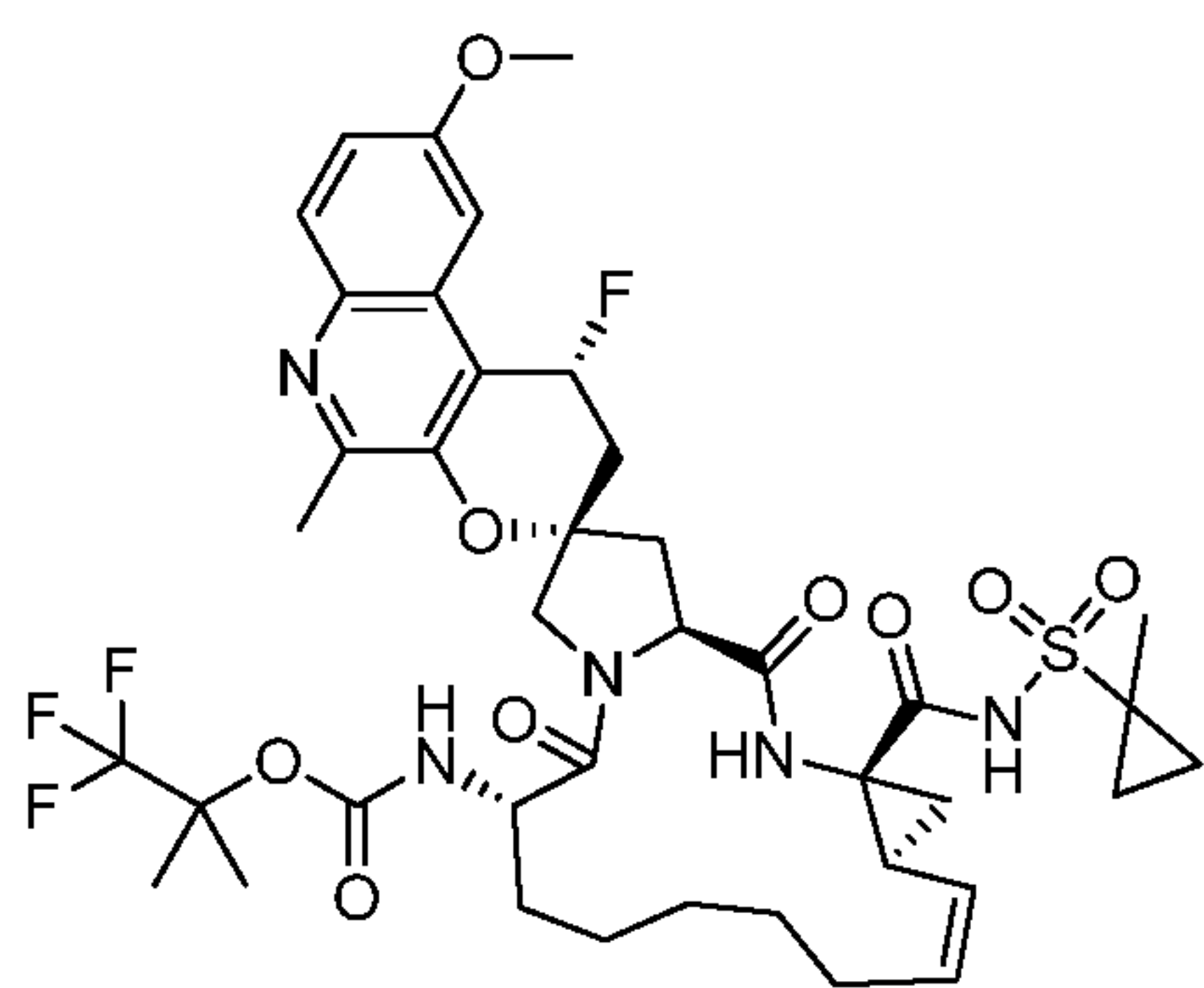
I-352



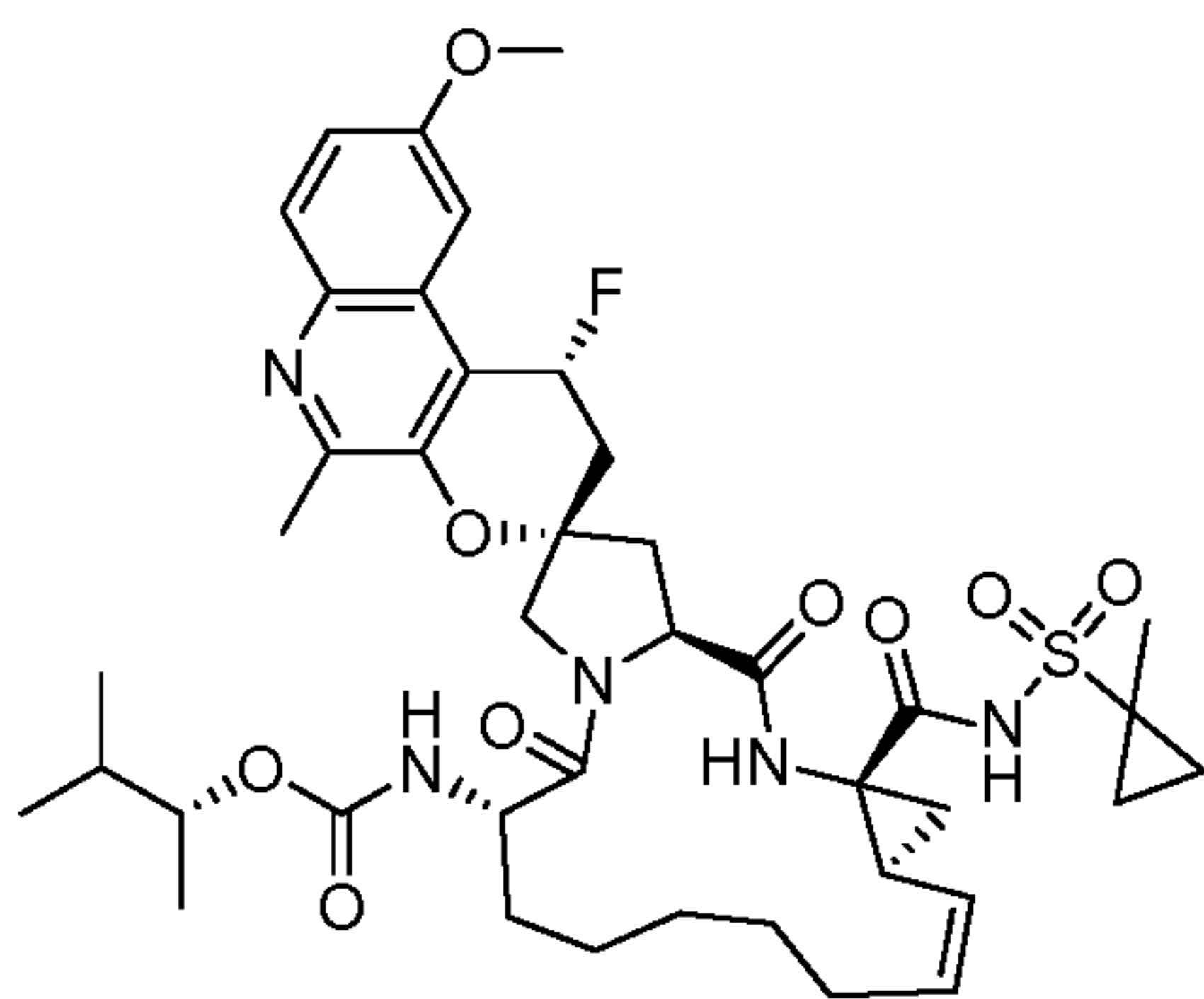
I-353



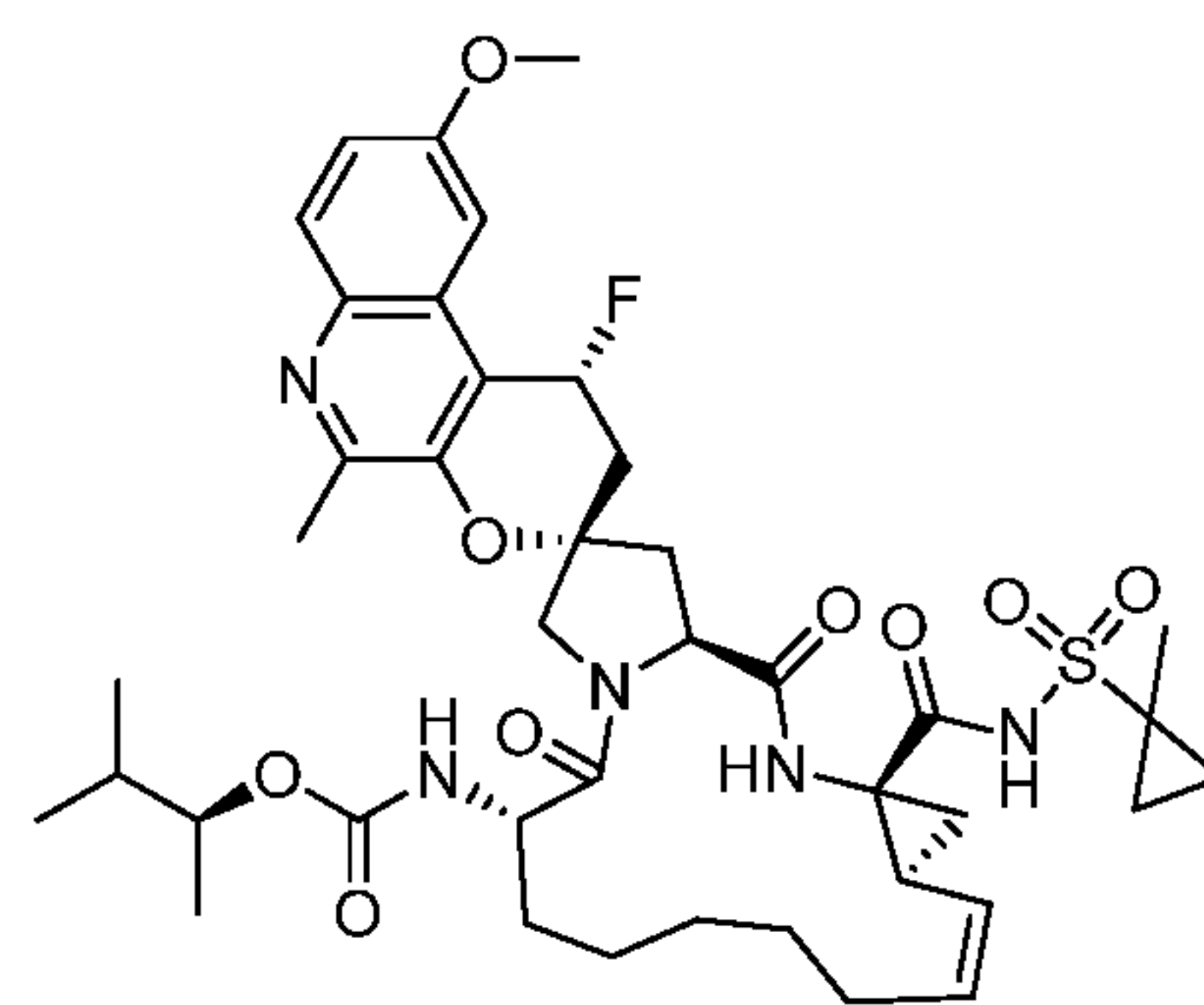
I-354



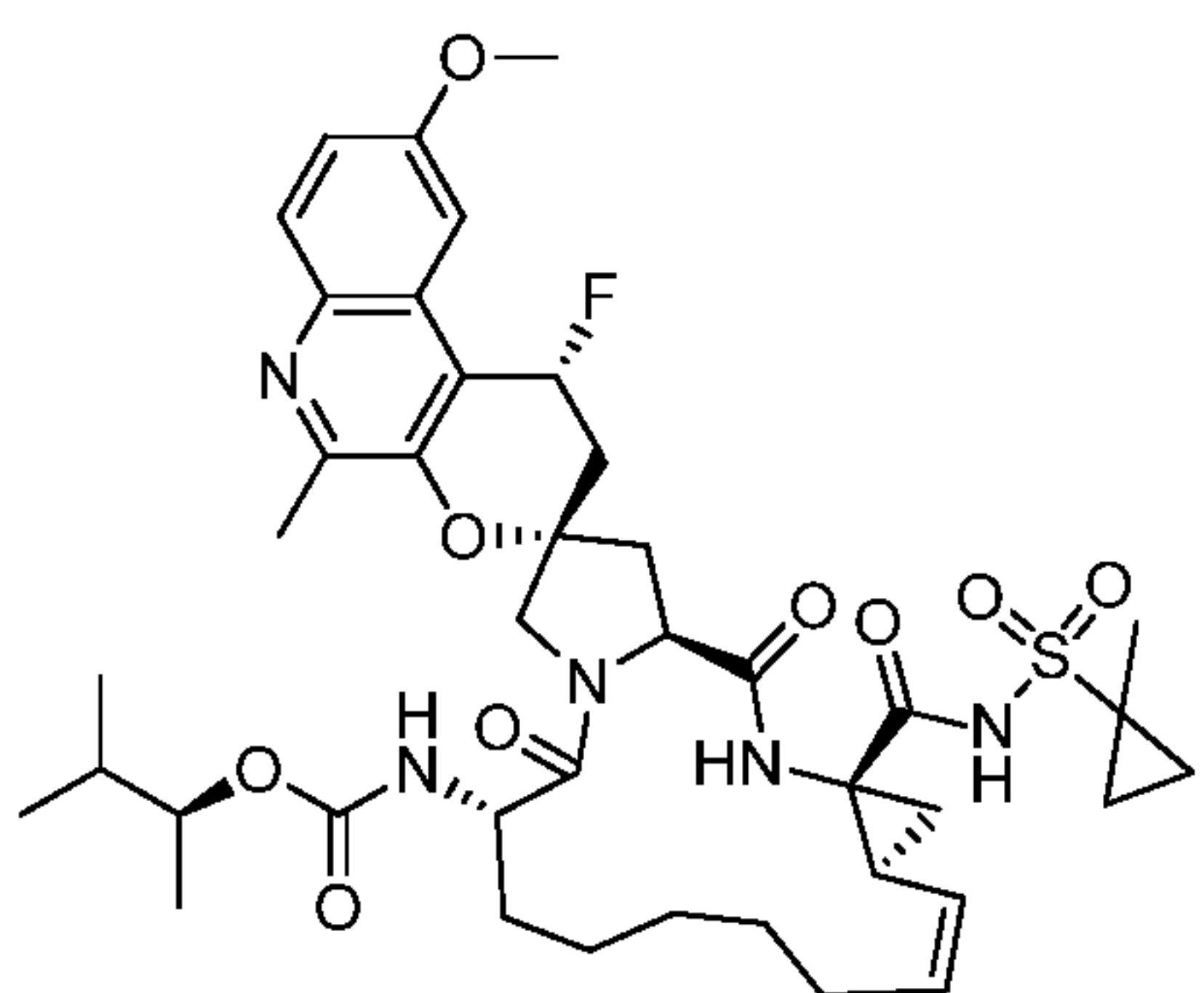
I-355



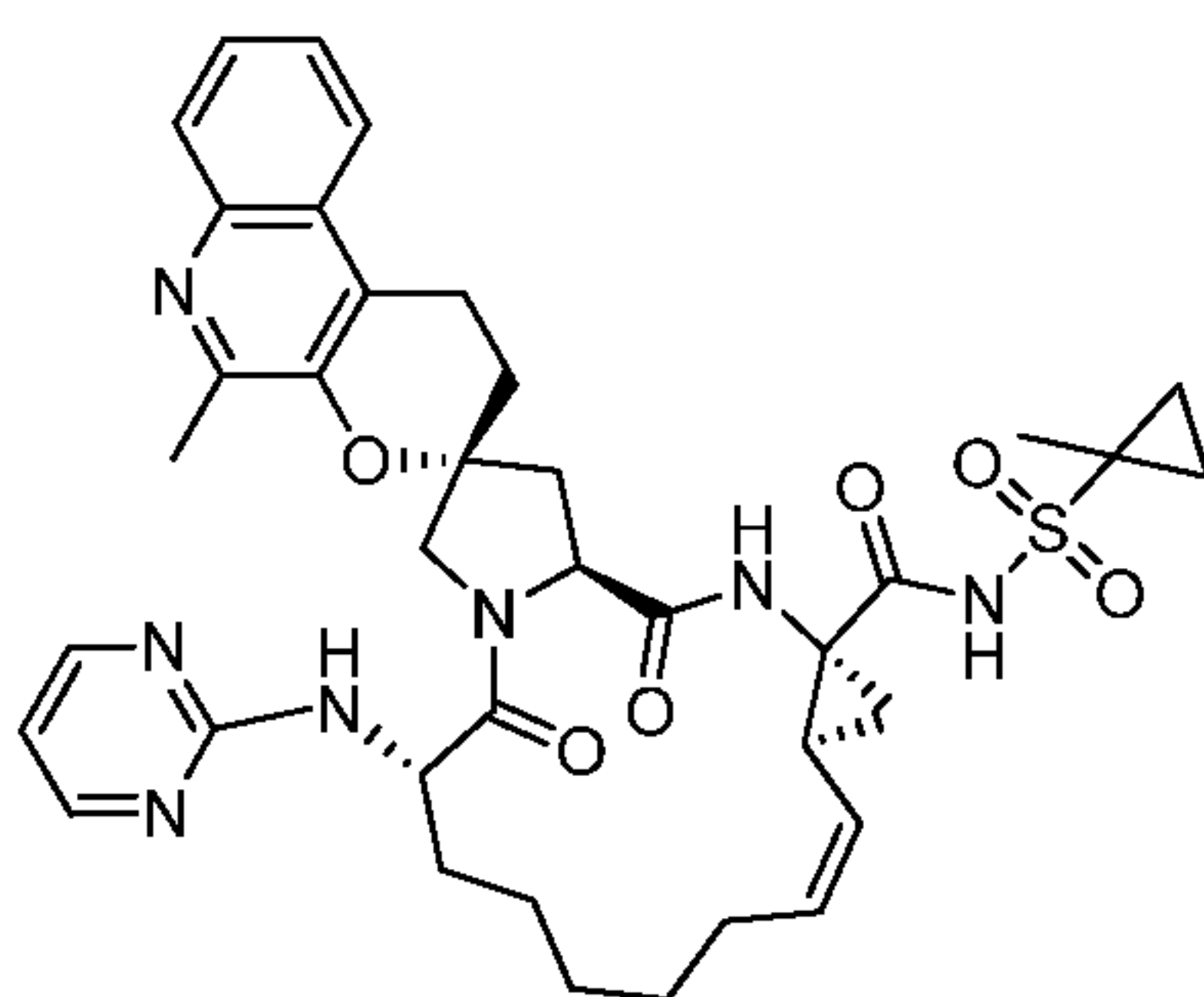
I-356



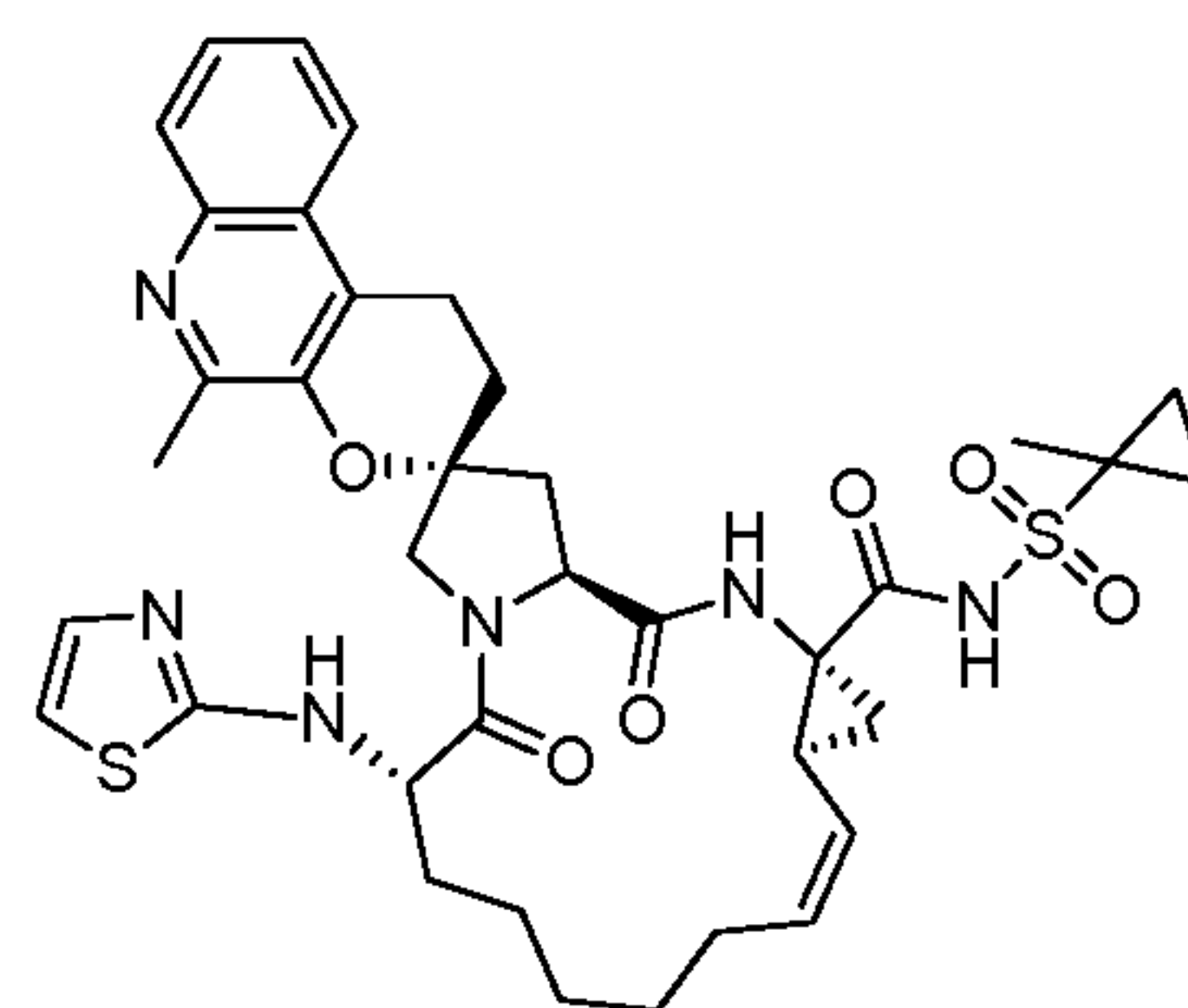
I-357



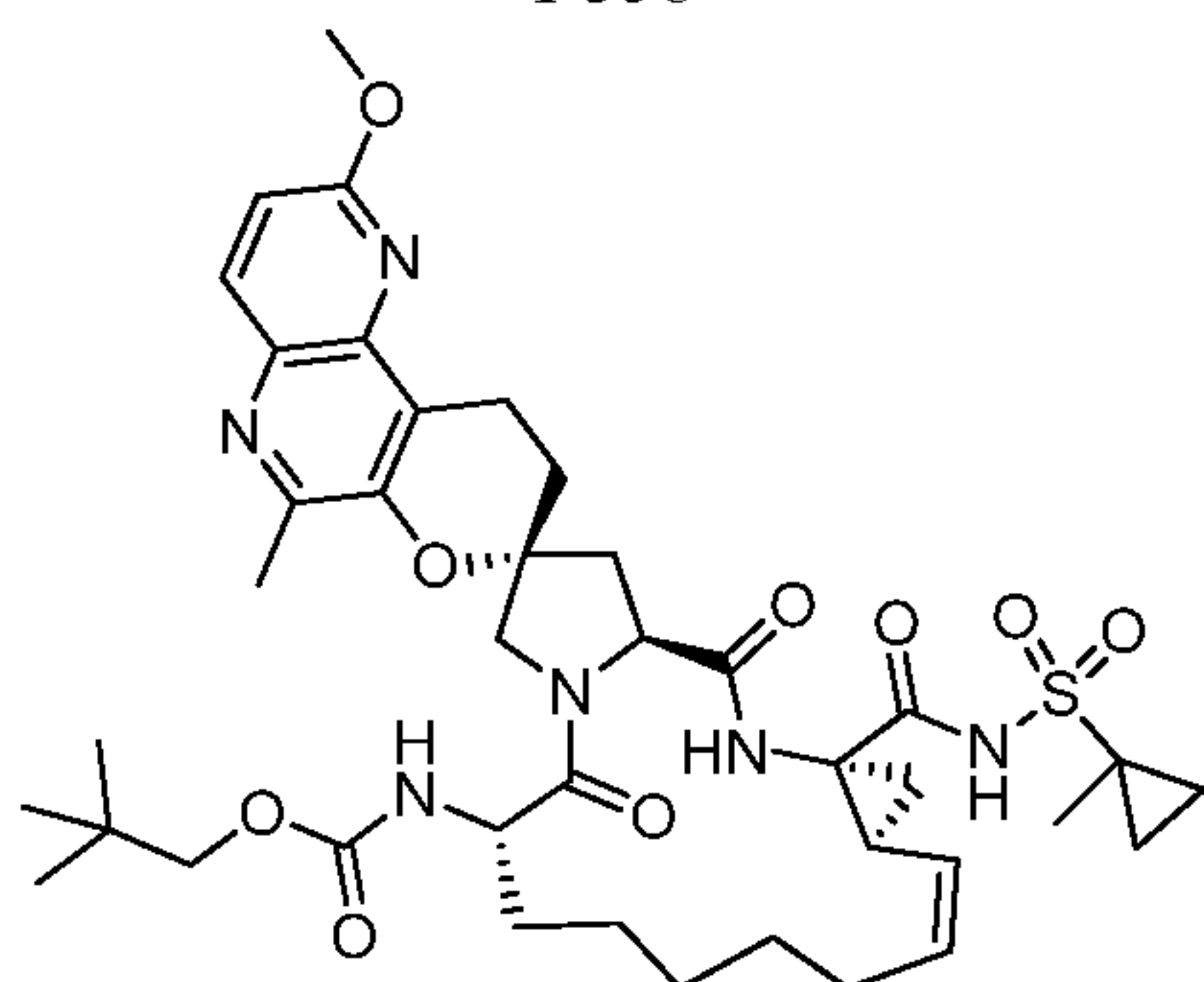
I-358



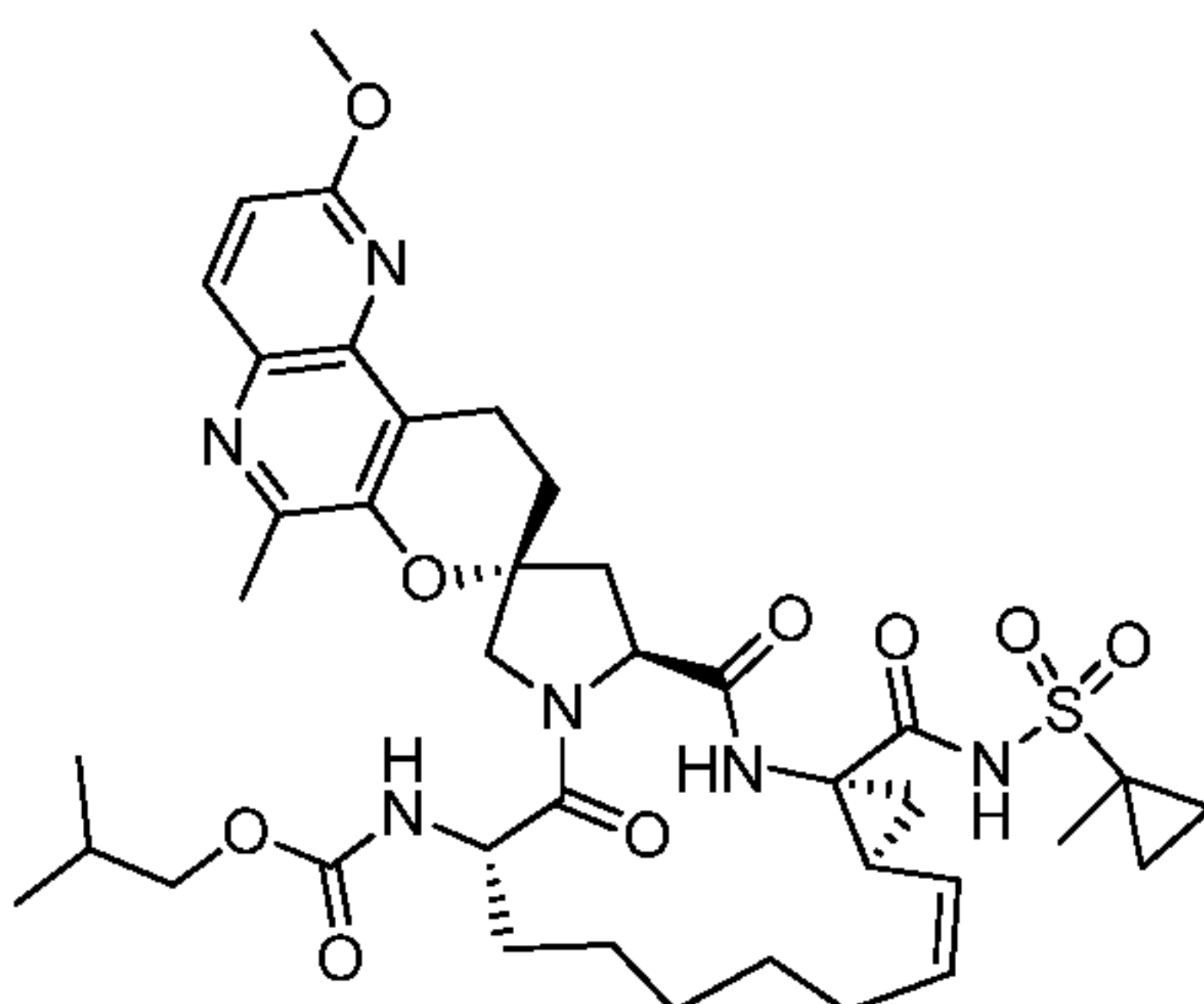
I-359



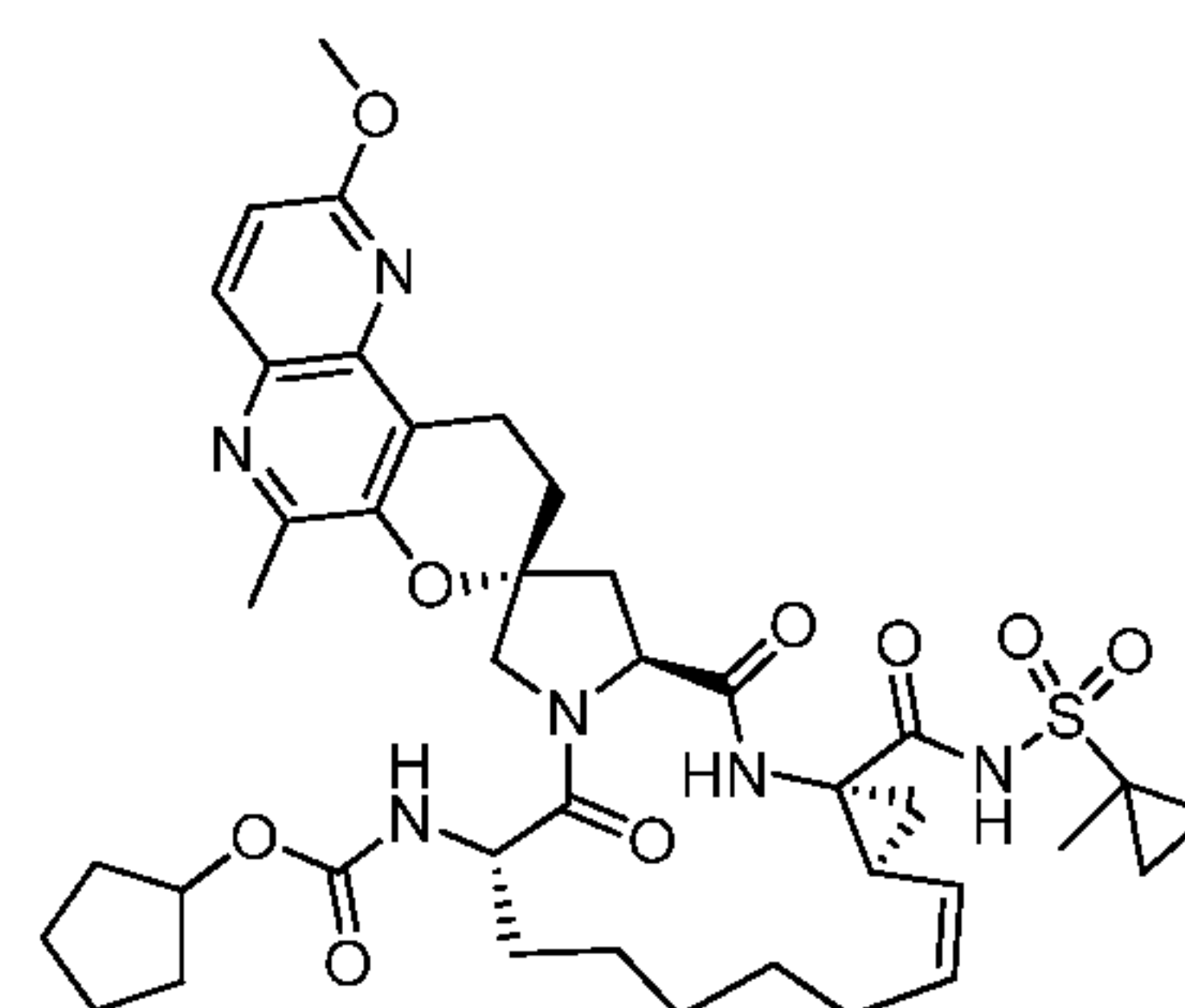
I-360



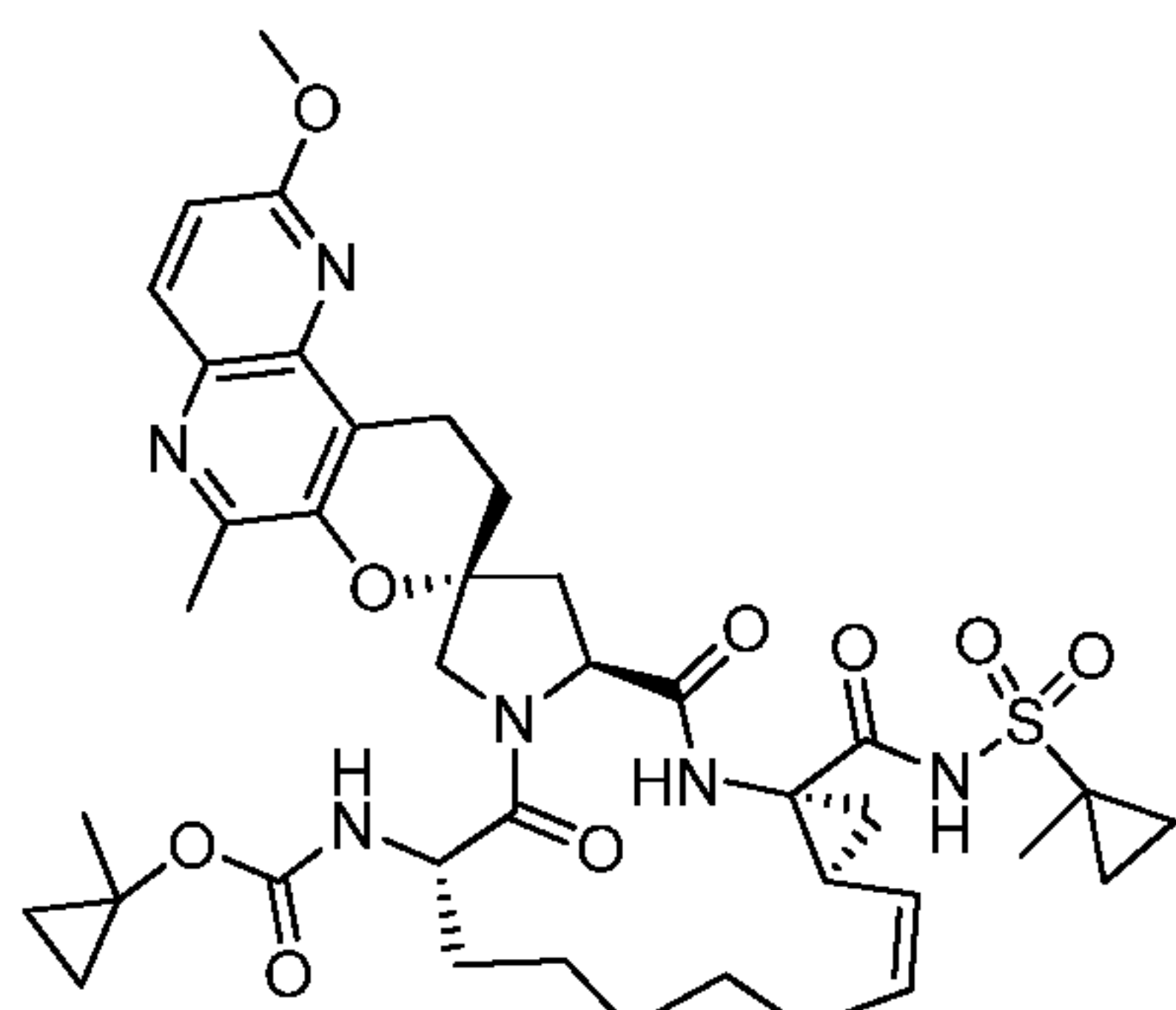
I-361



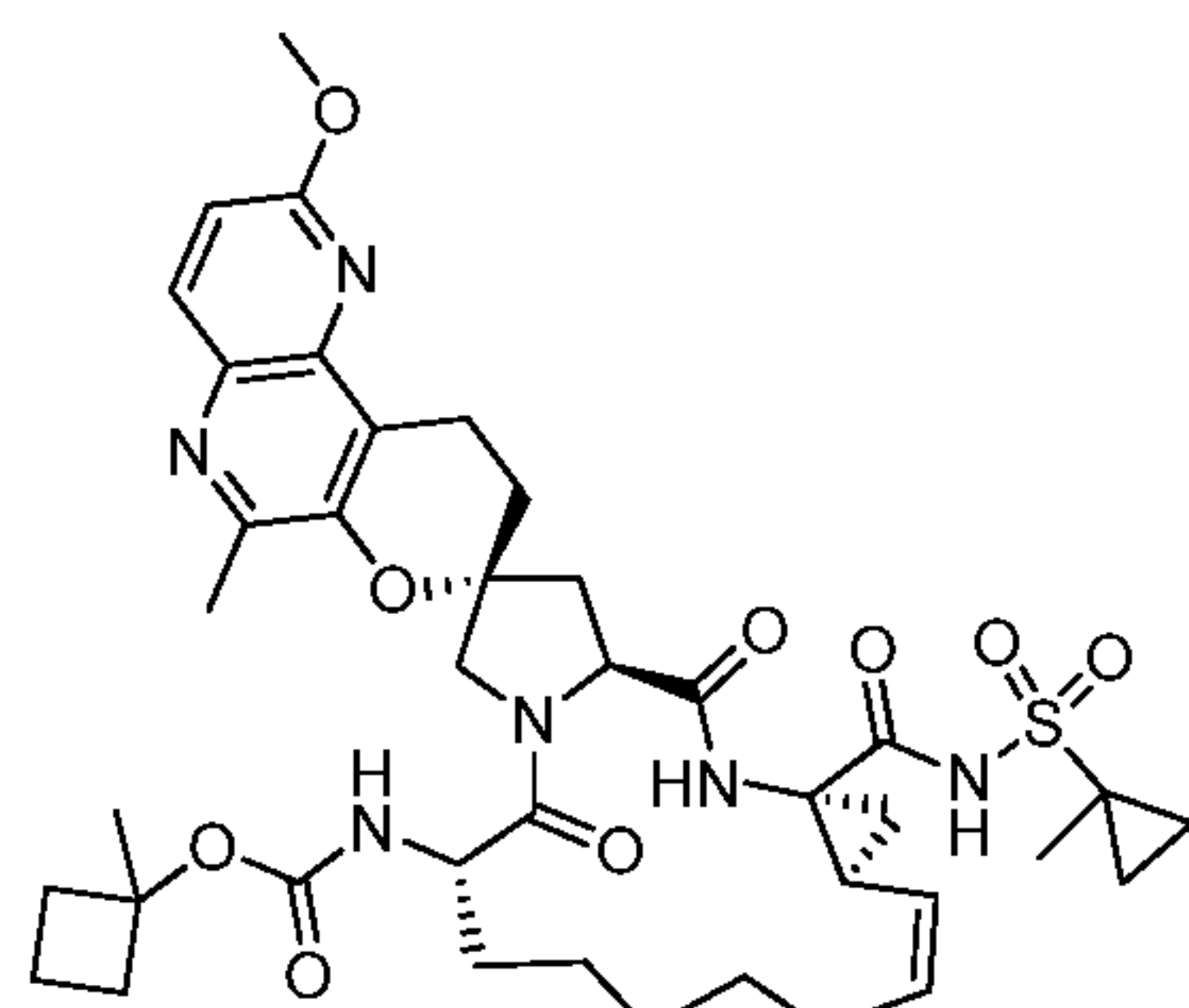
I-362



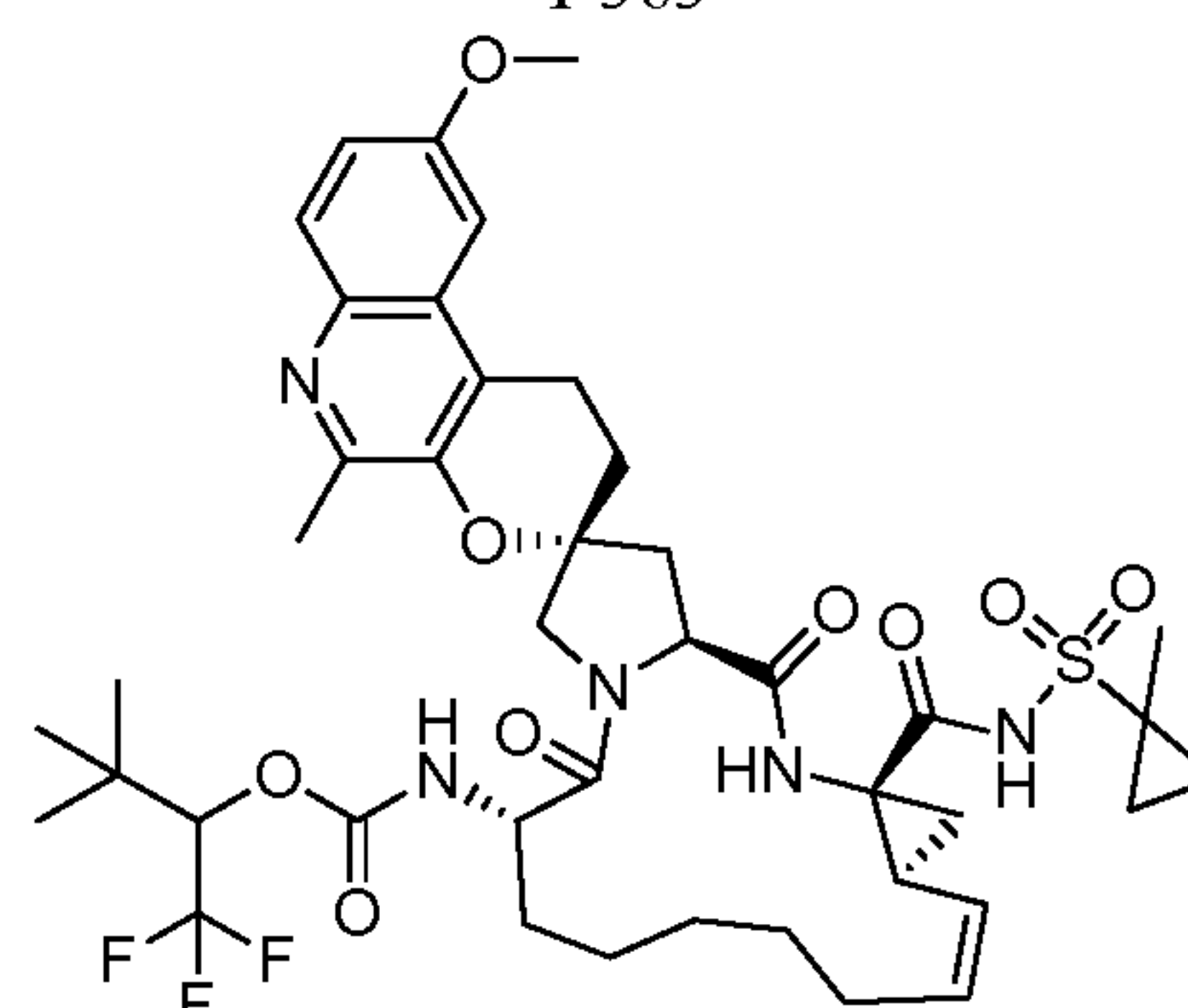
I-363



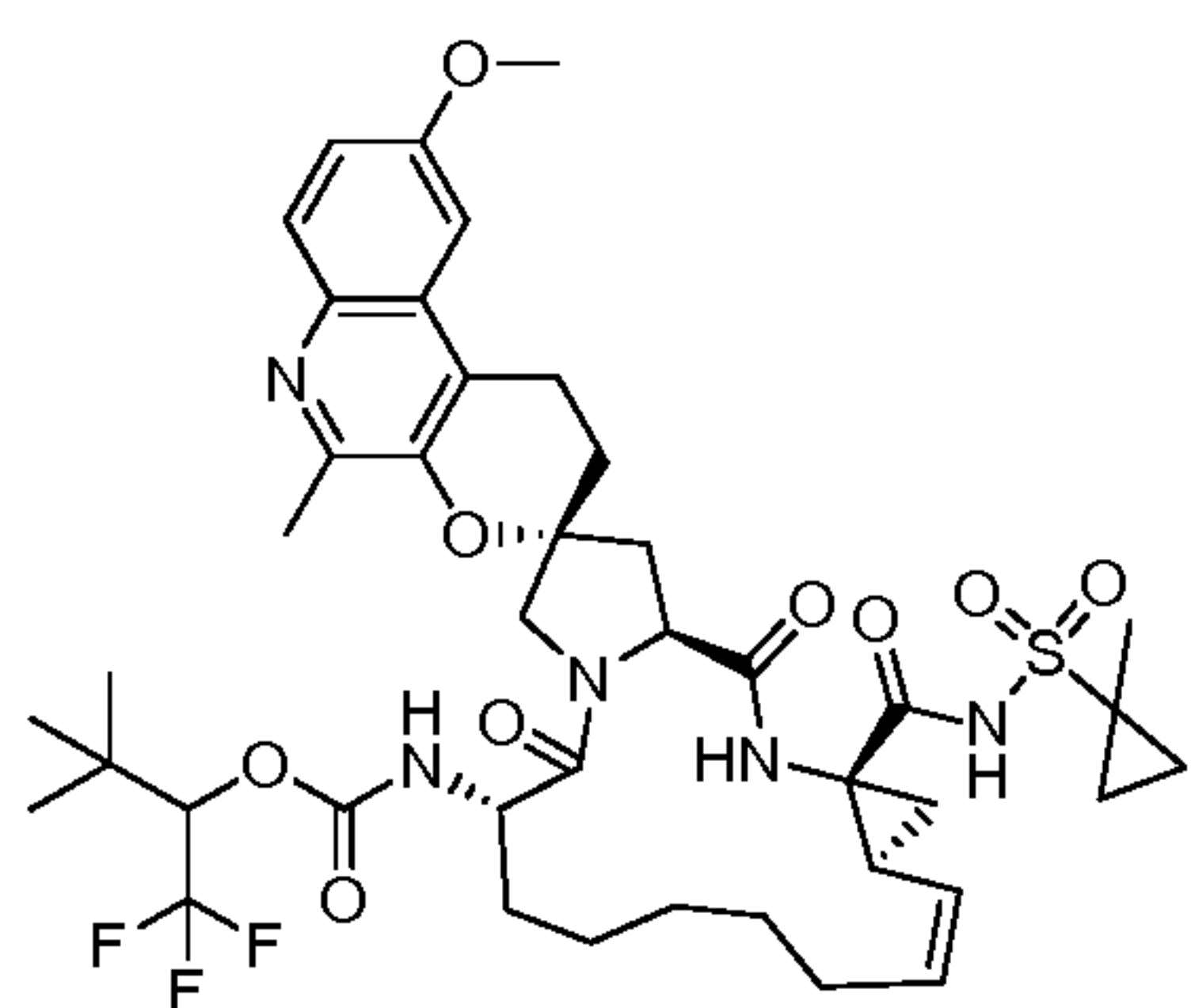
I-364



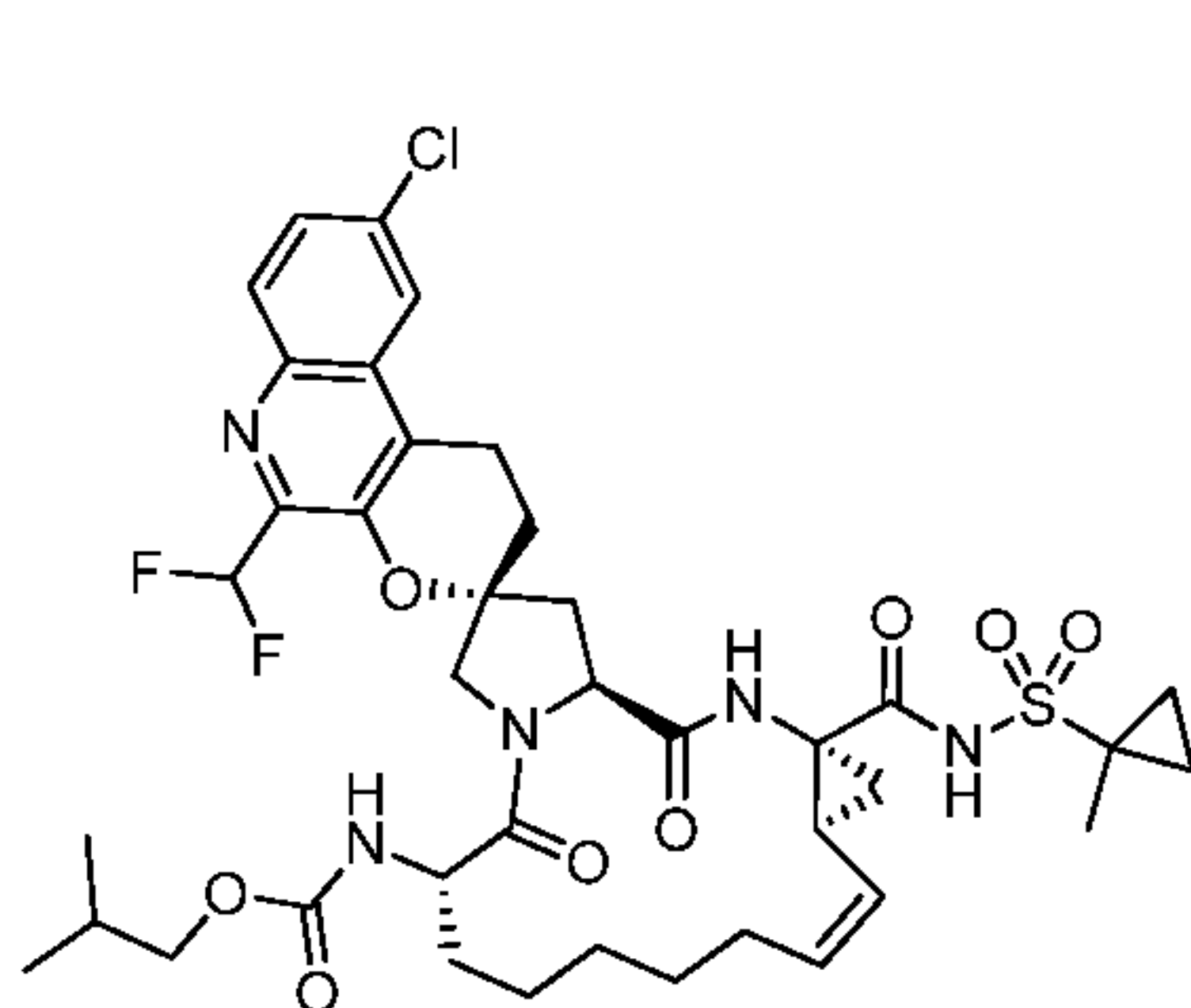
I-365



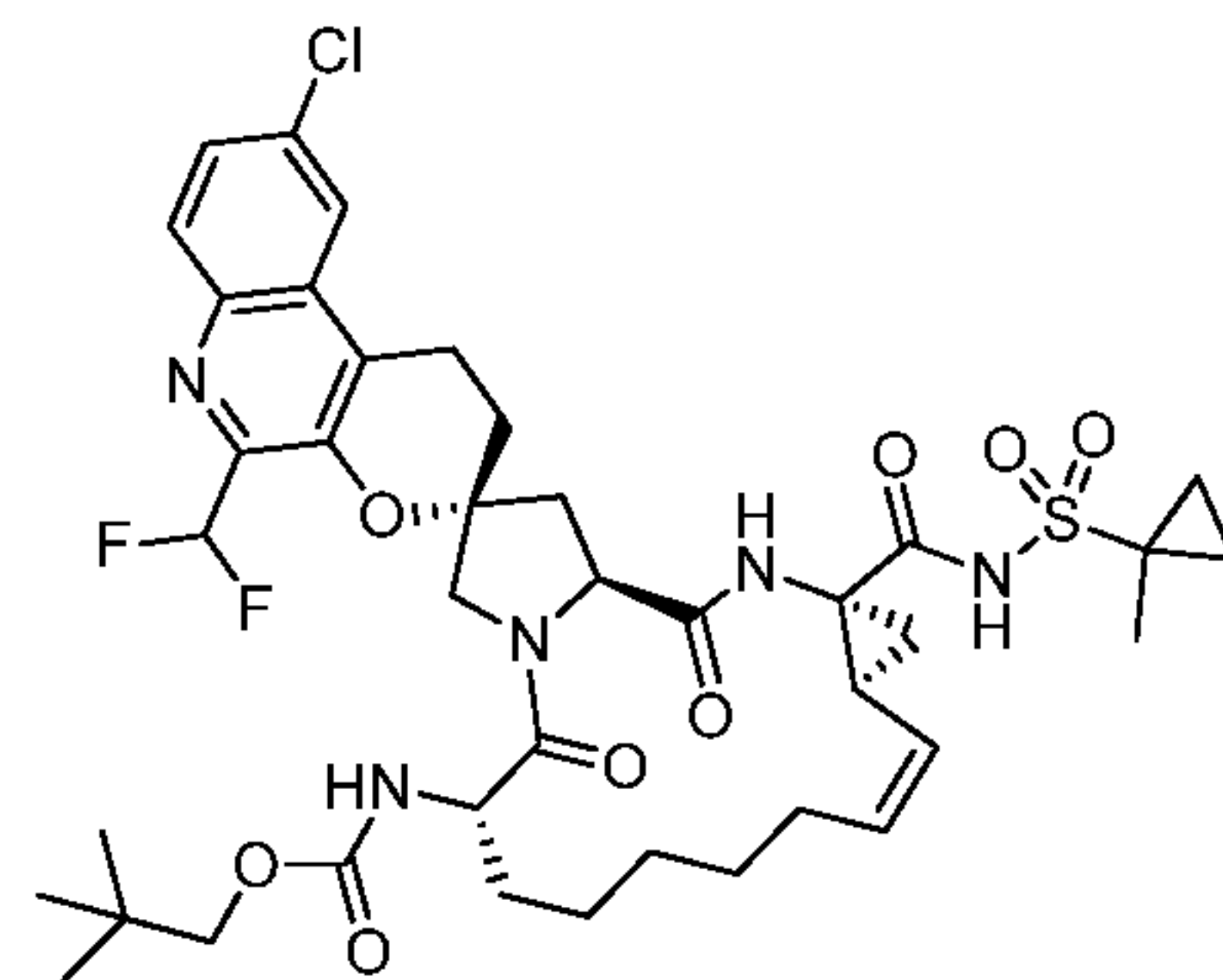
I-366



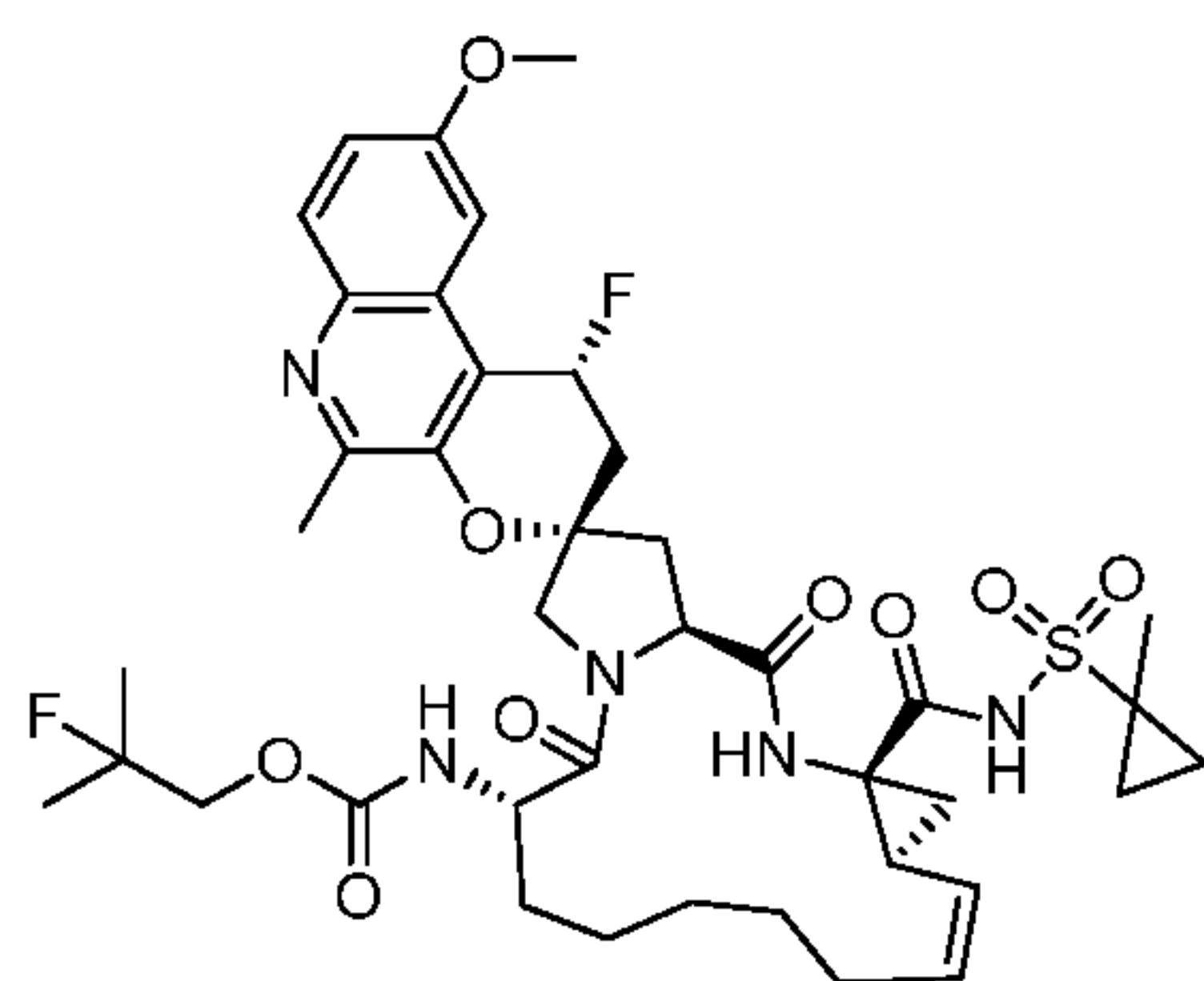
I-367



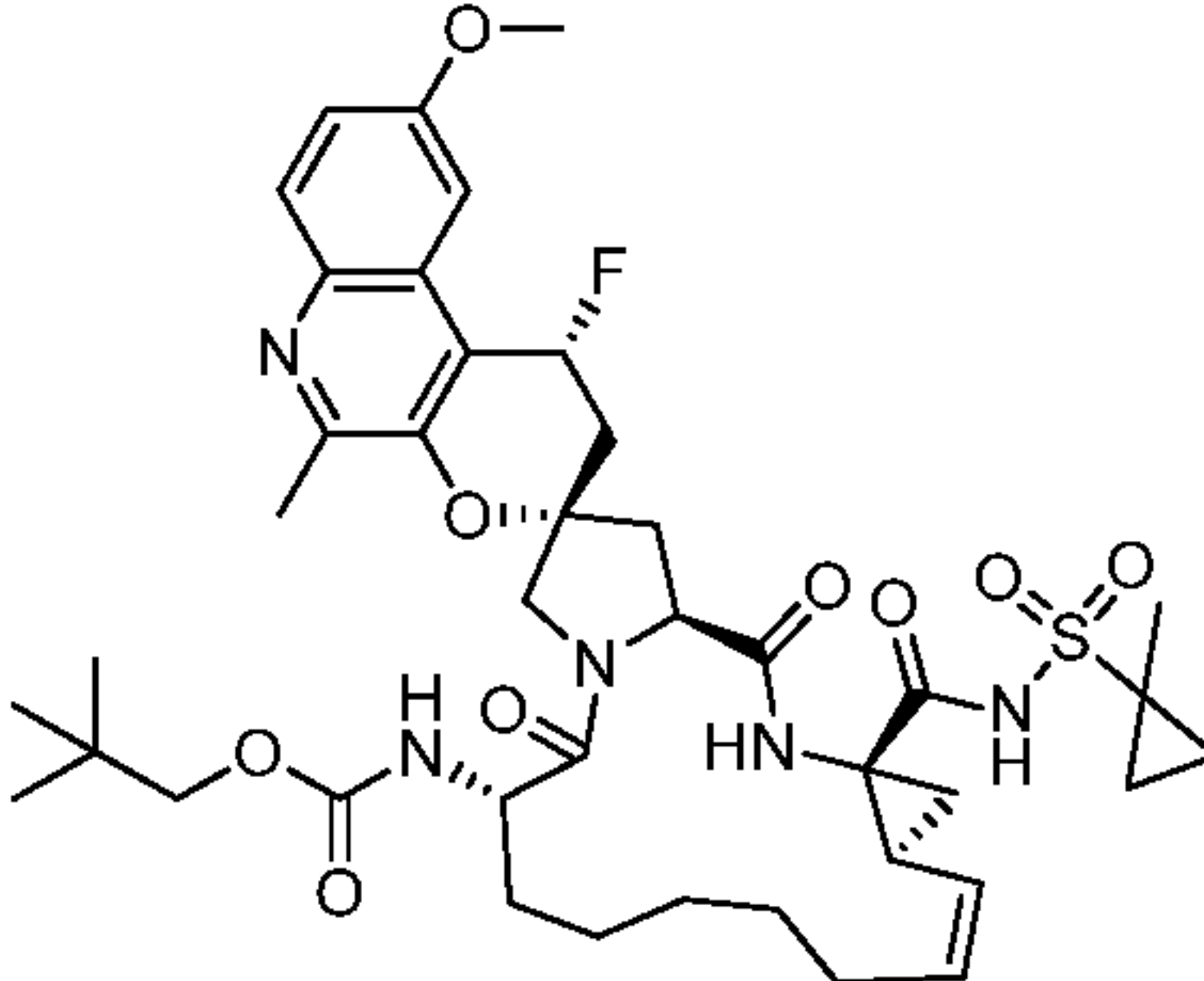
I-368



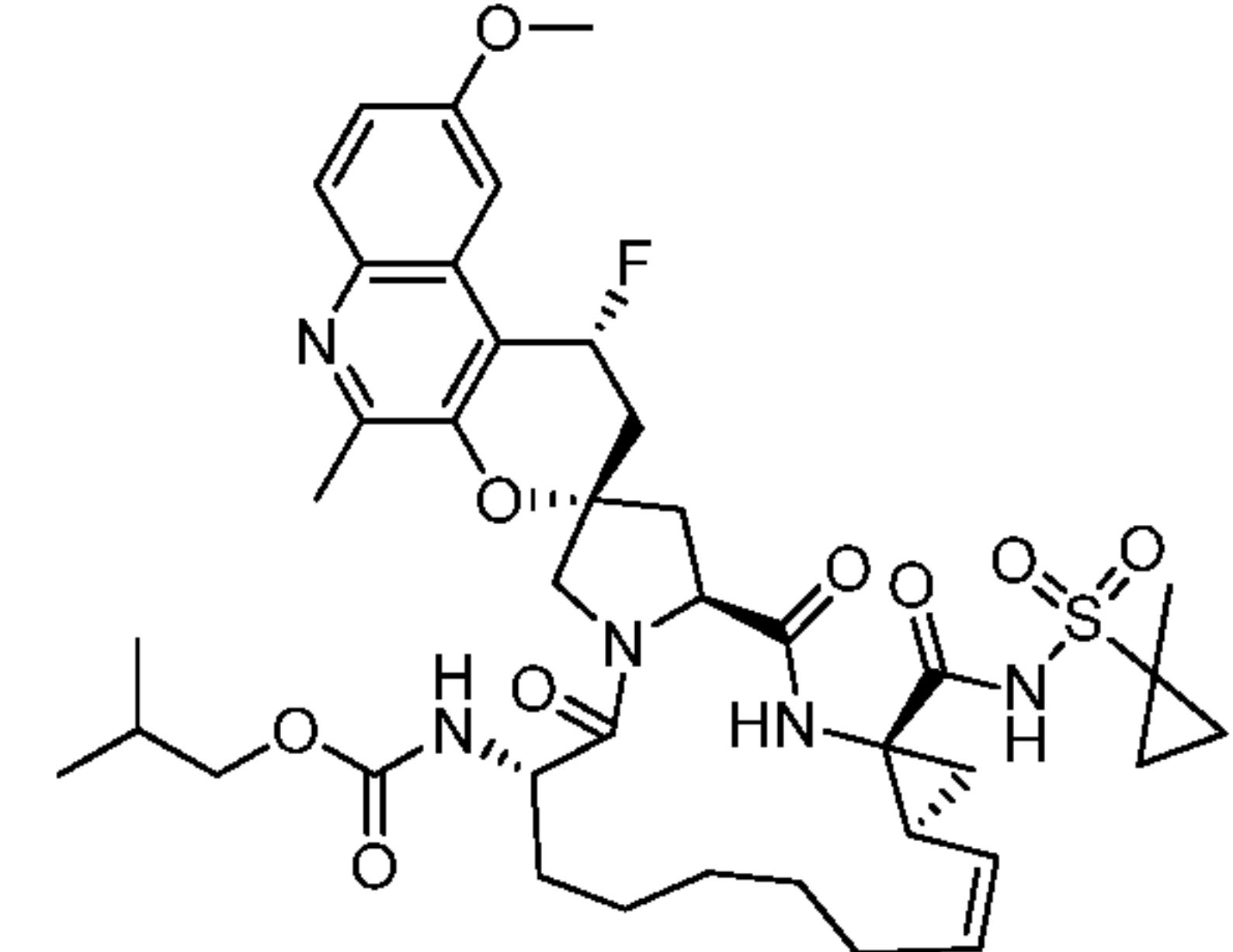
I-369



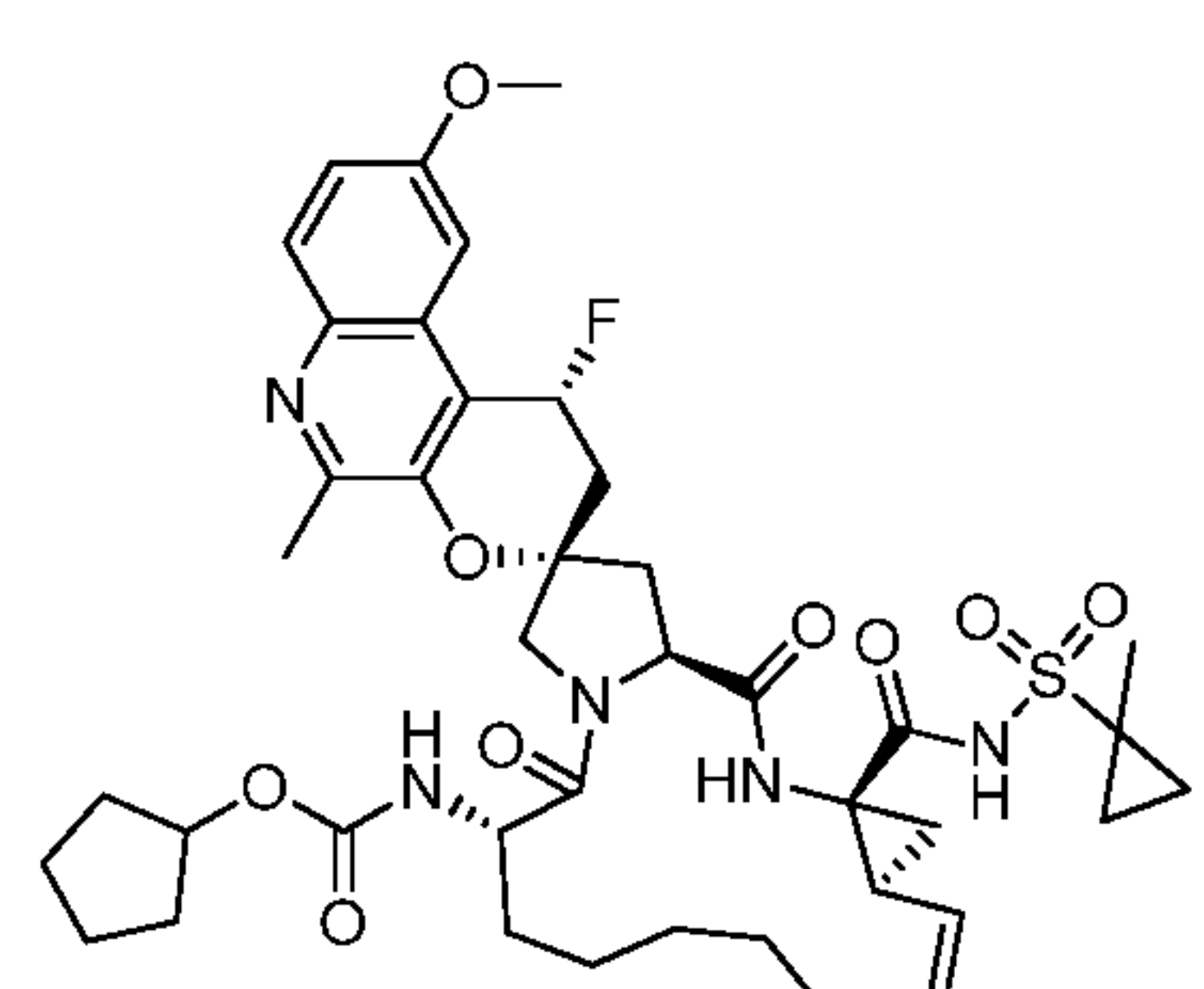
I-370



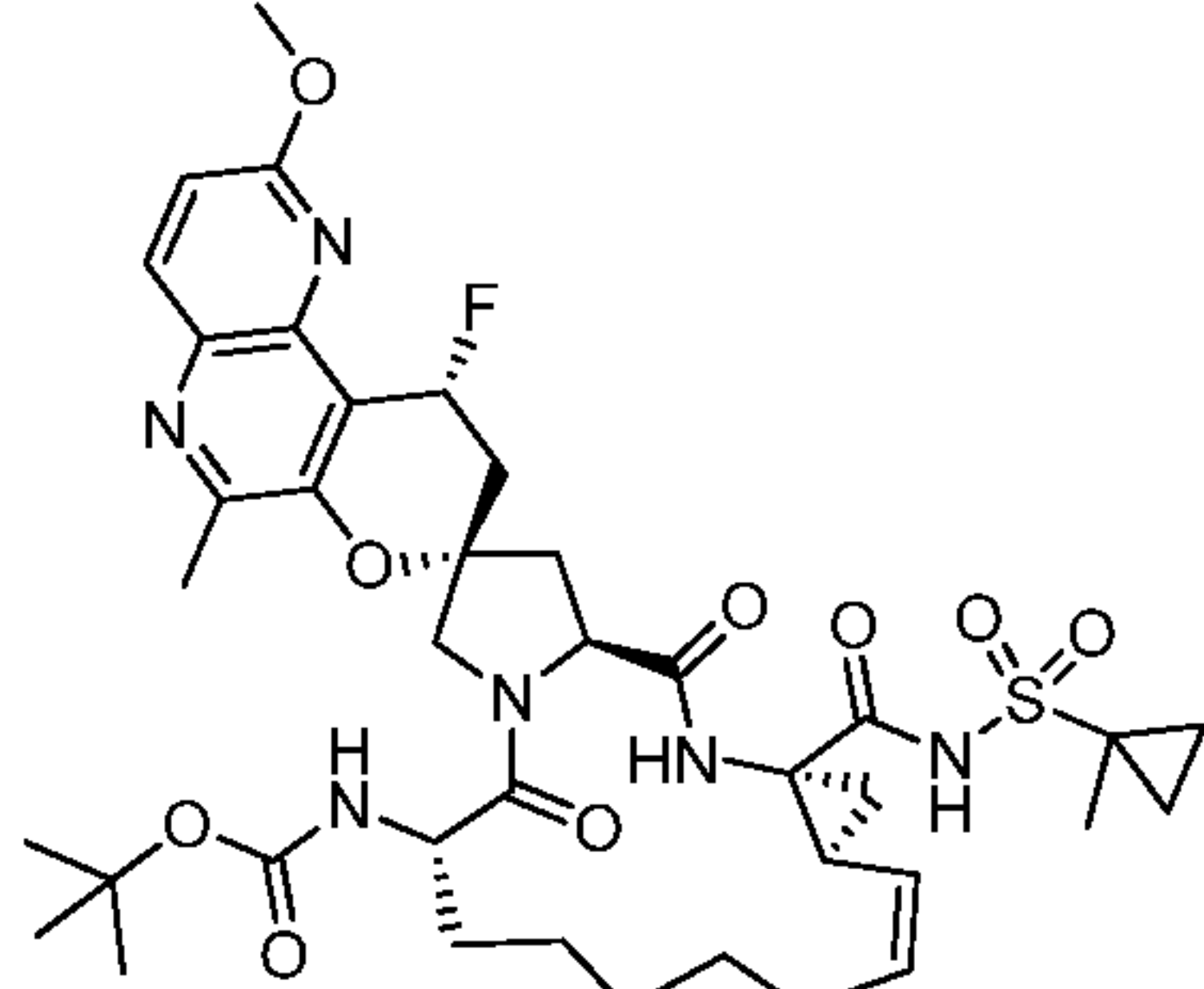
I-371



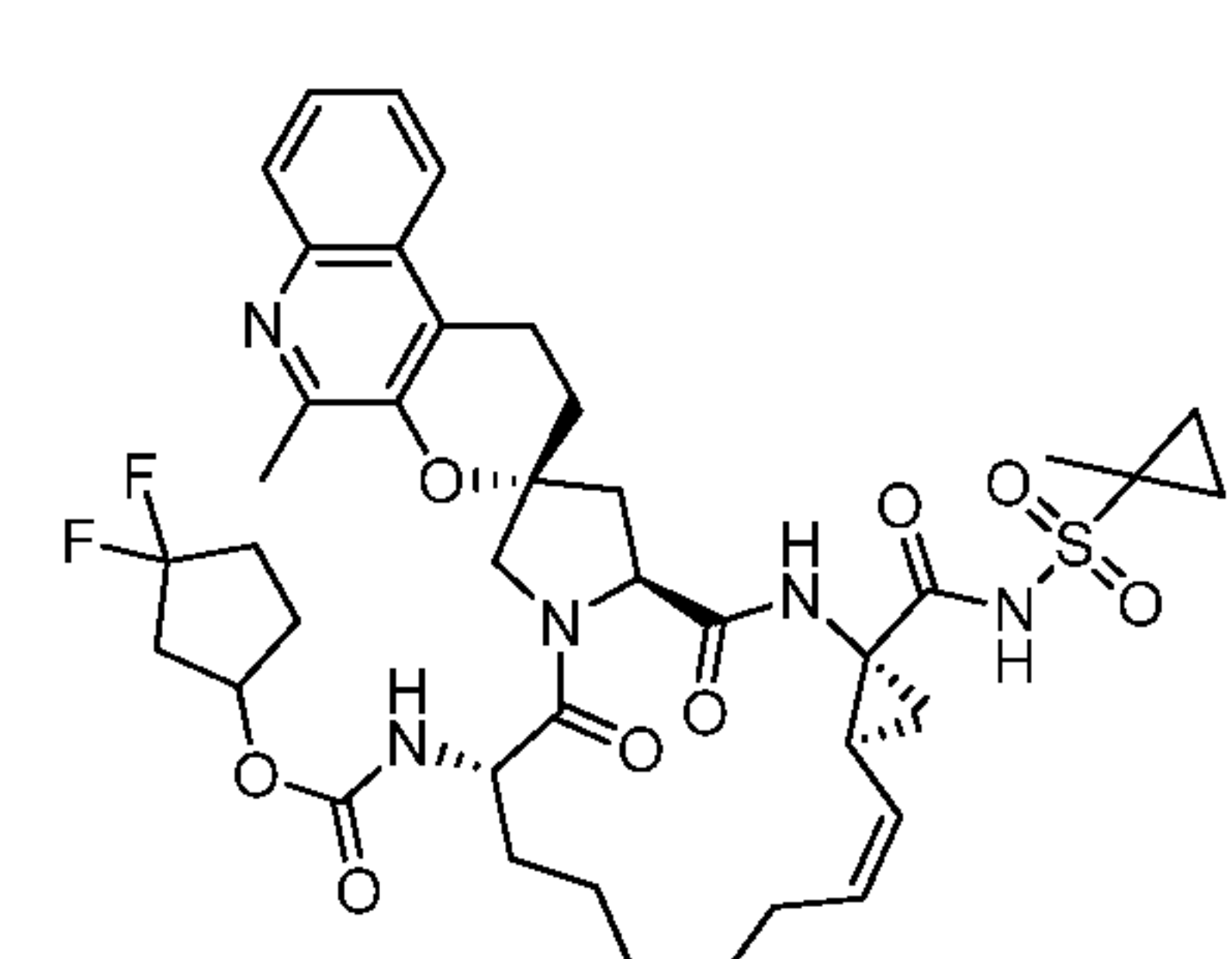
I-372



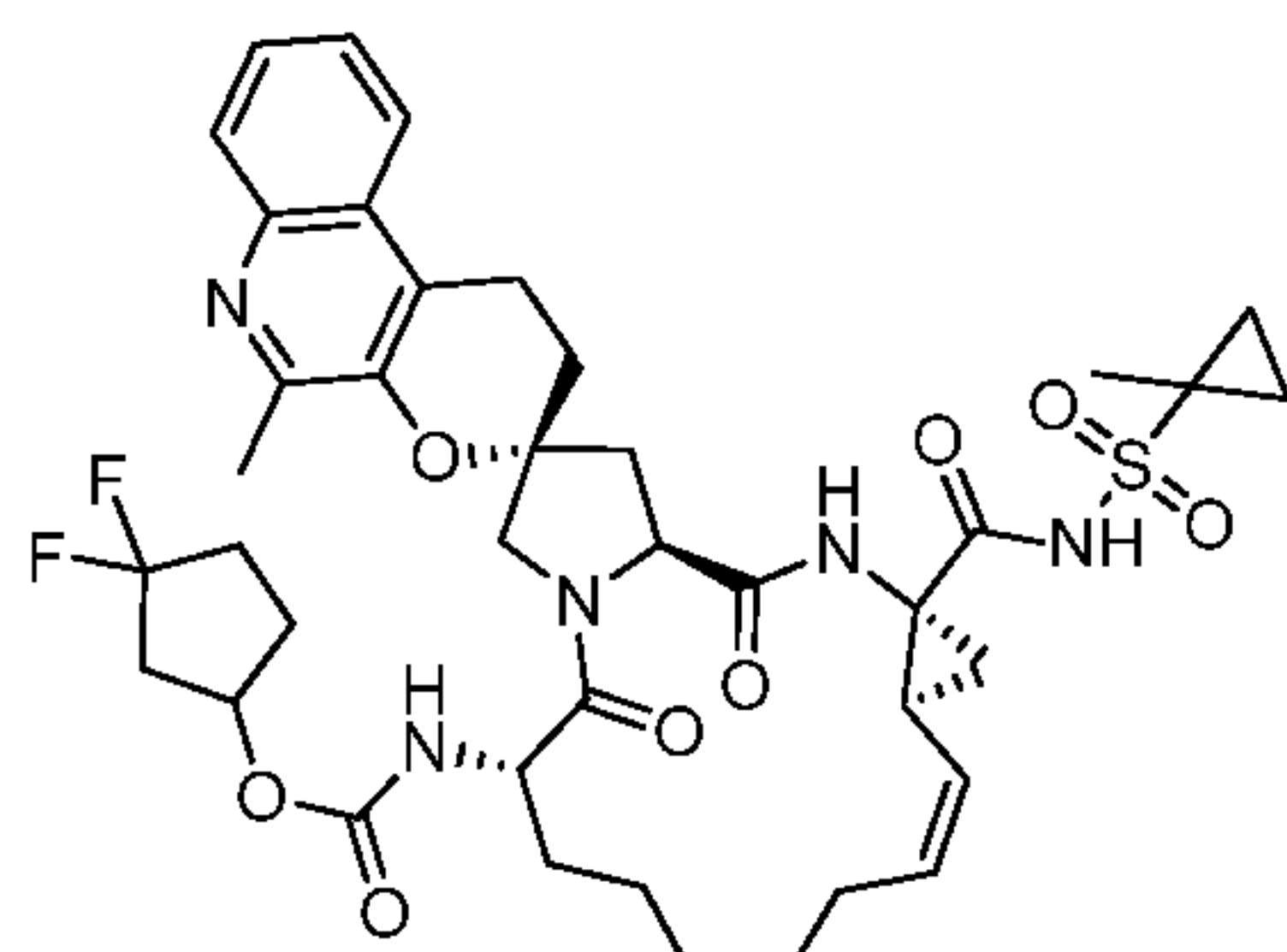
I-373



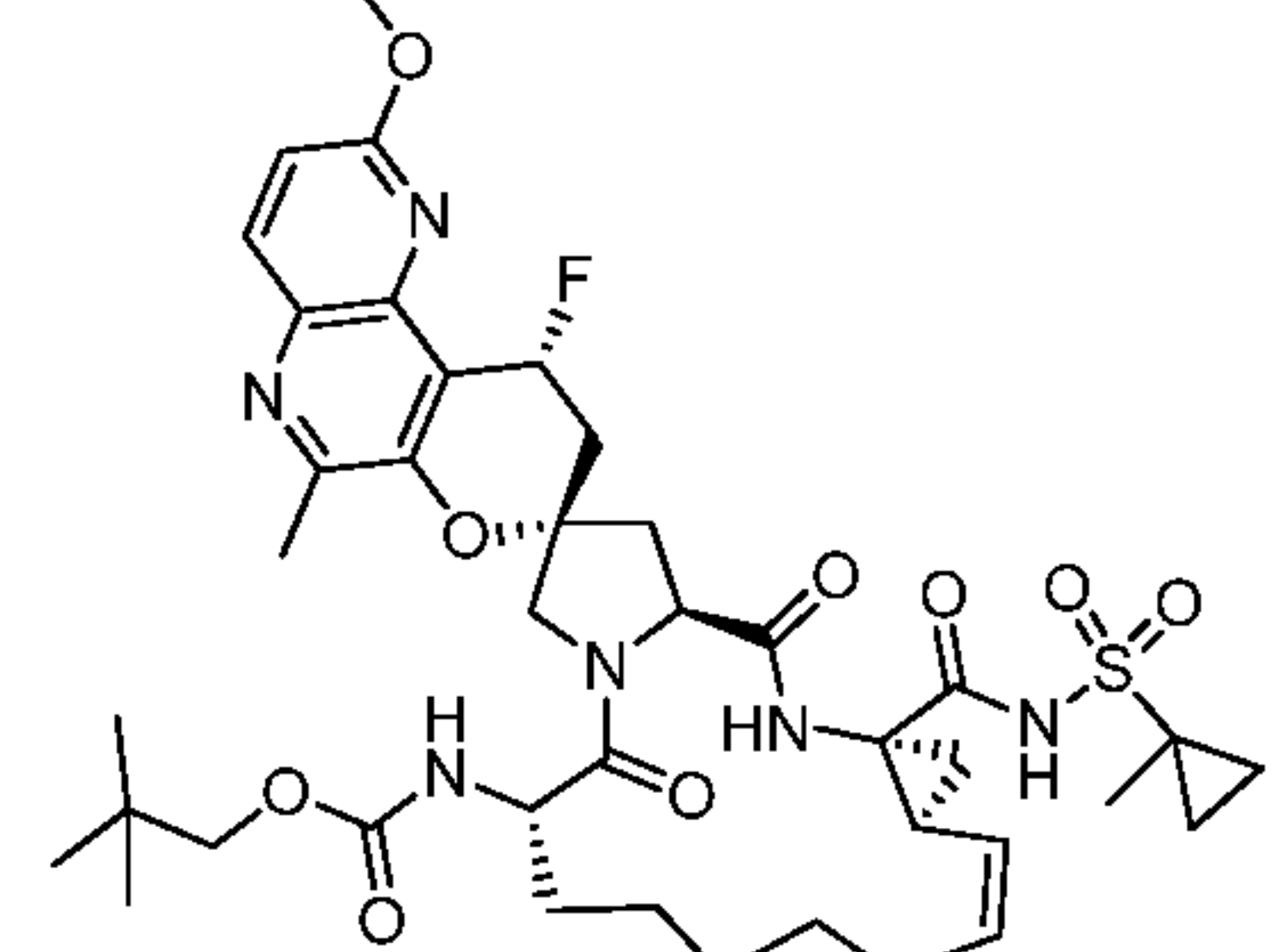
I-374



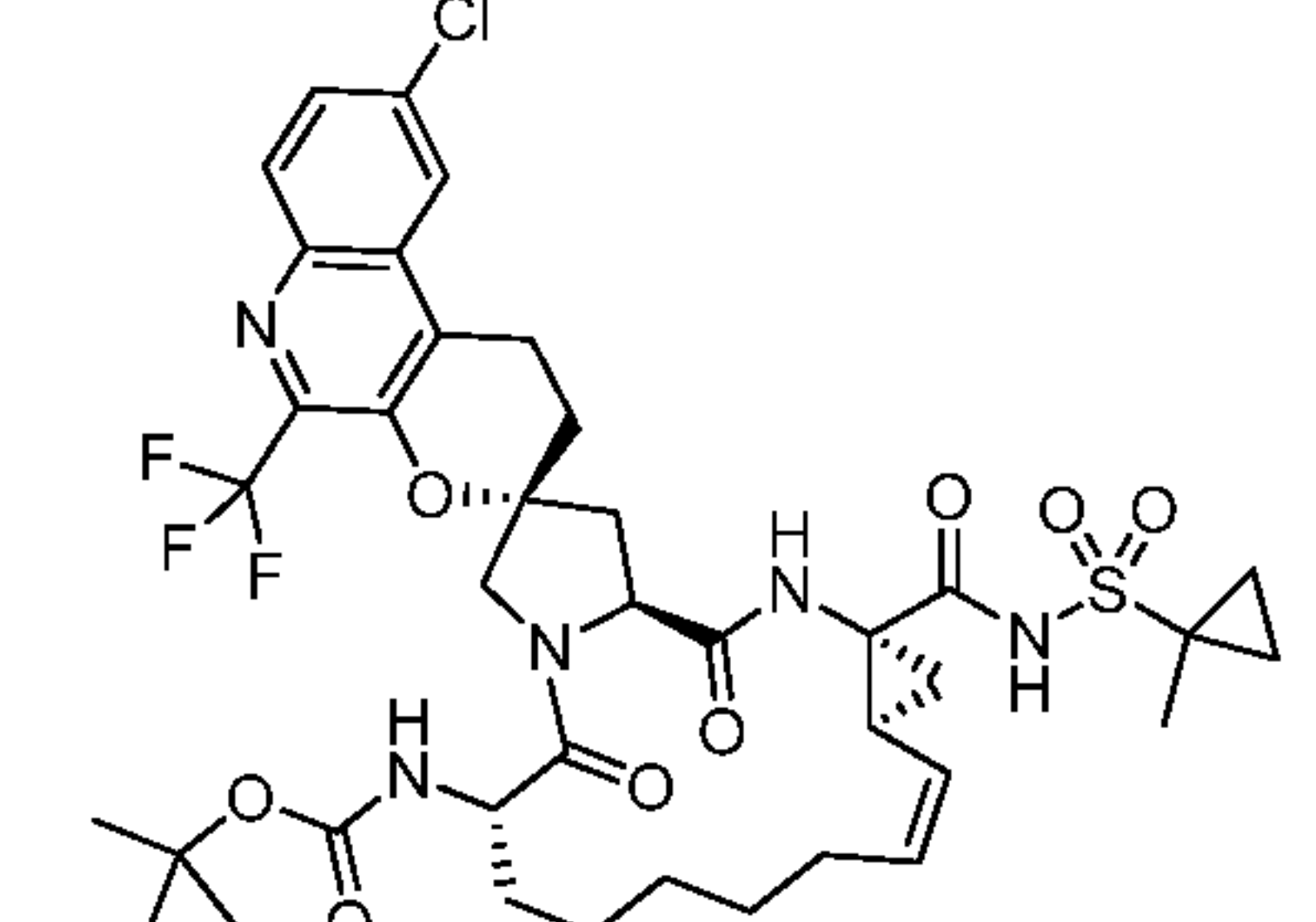
I-375



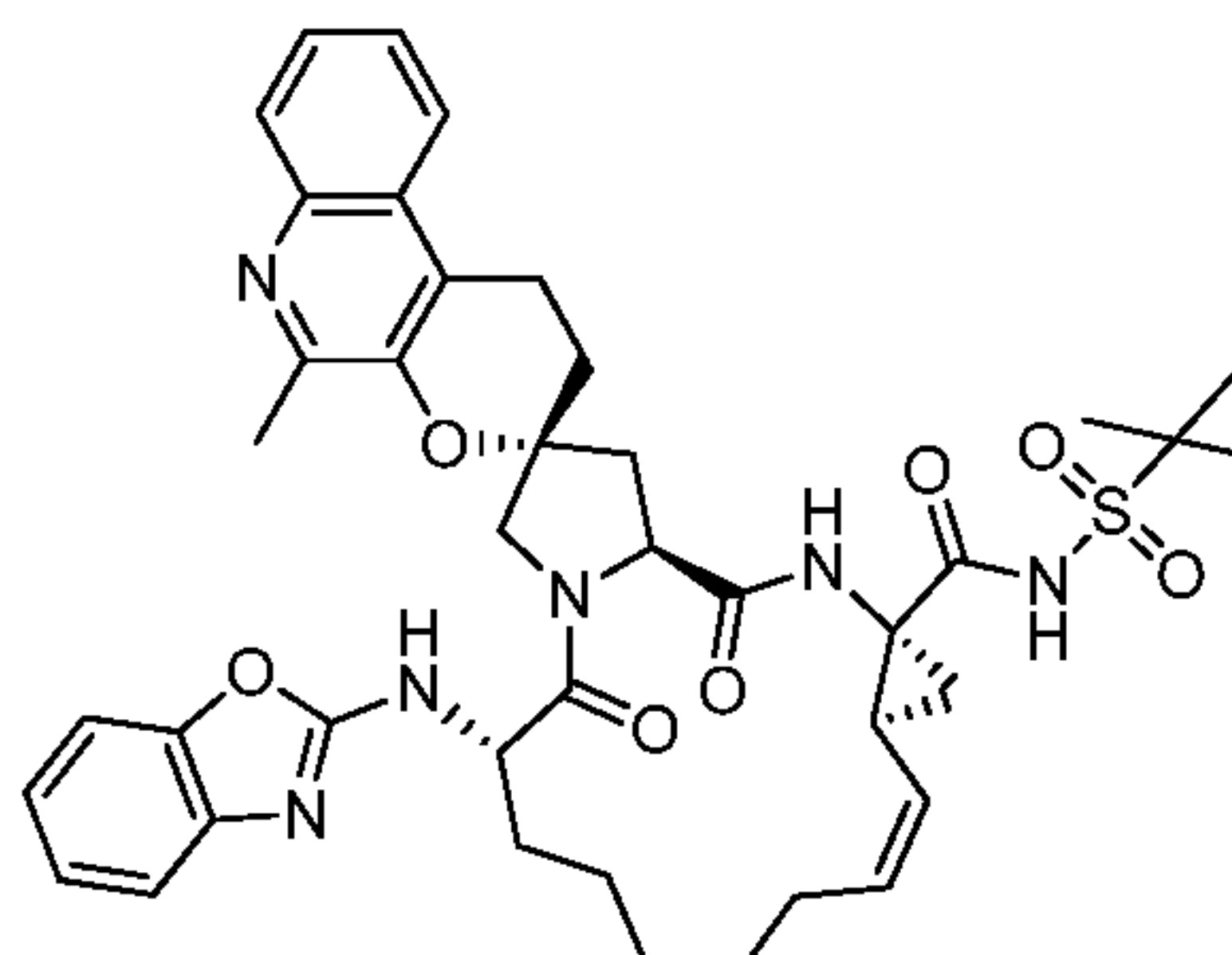
I-376



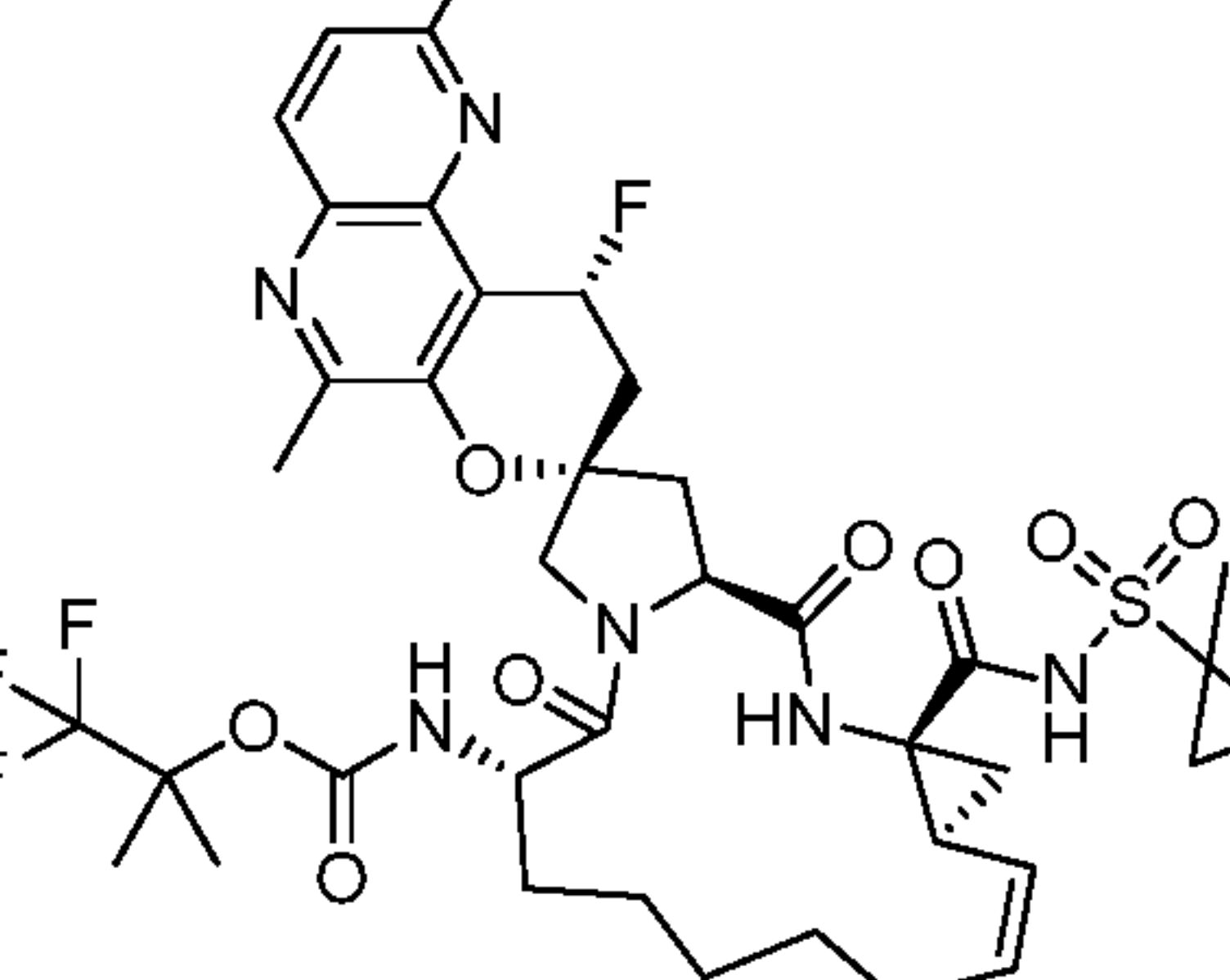
I-377



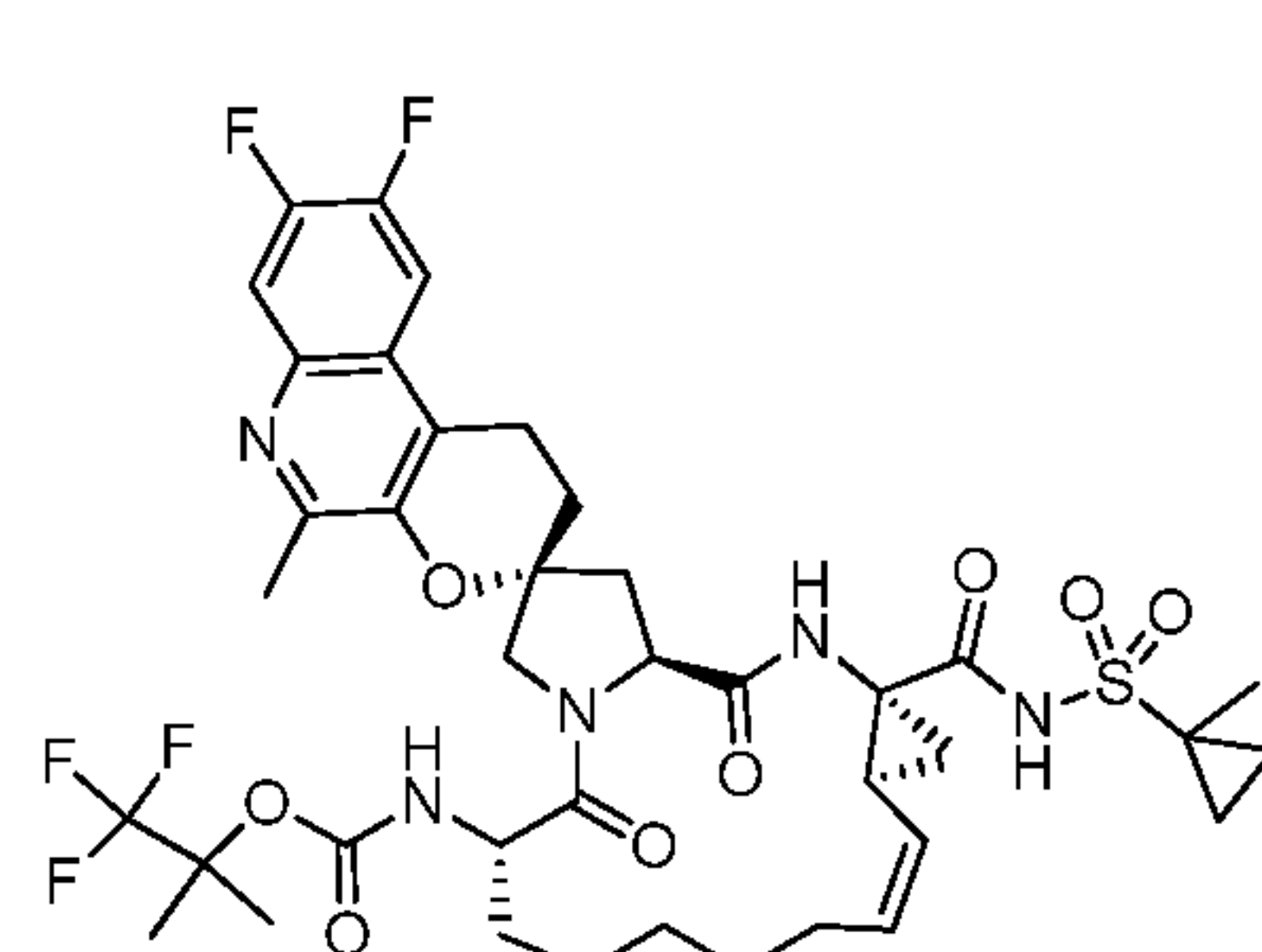
I-378



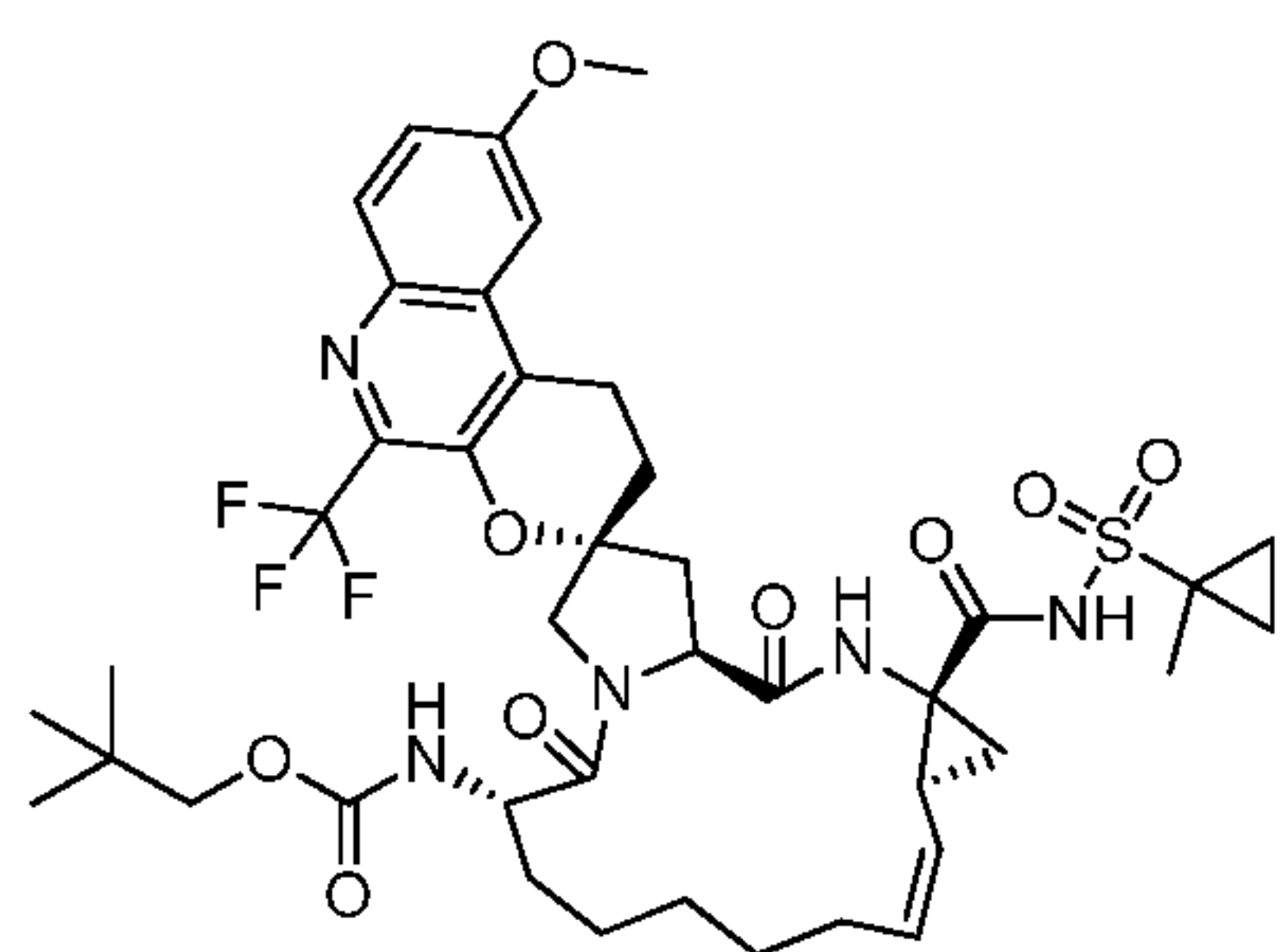
I-379



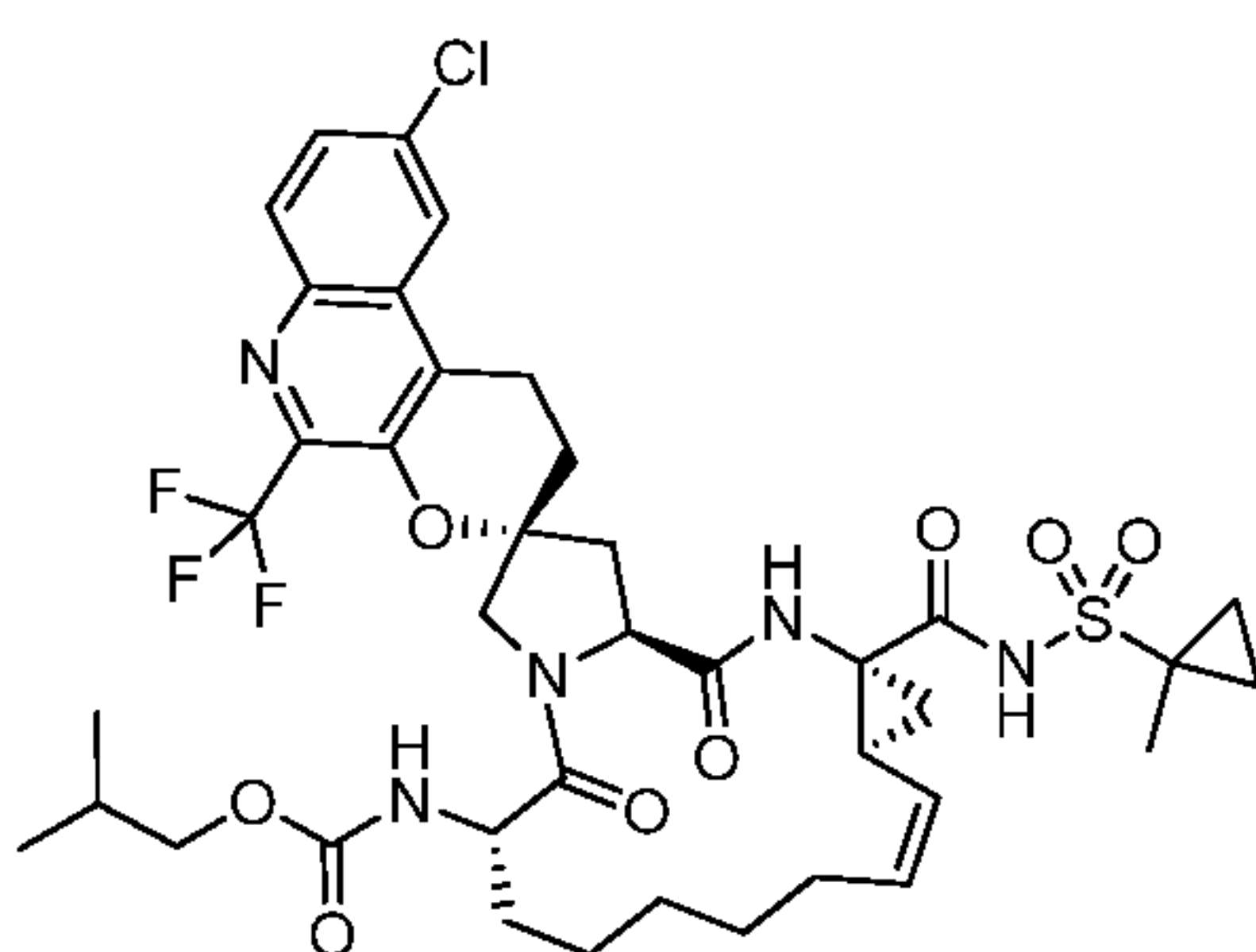
I-380



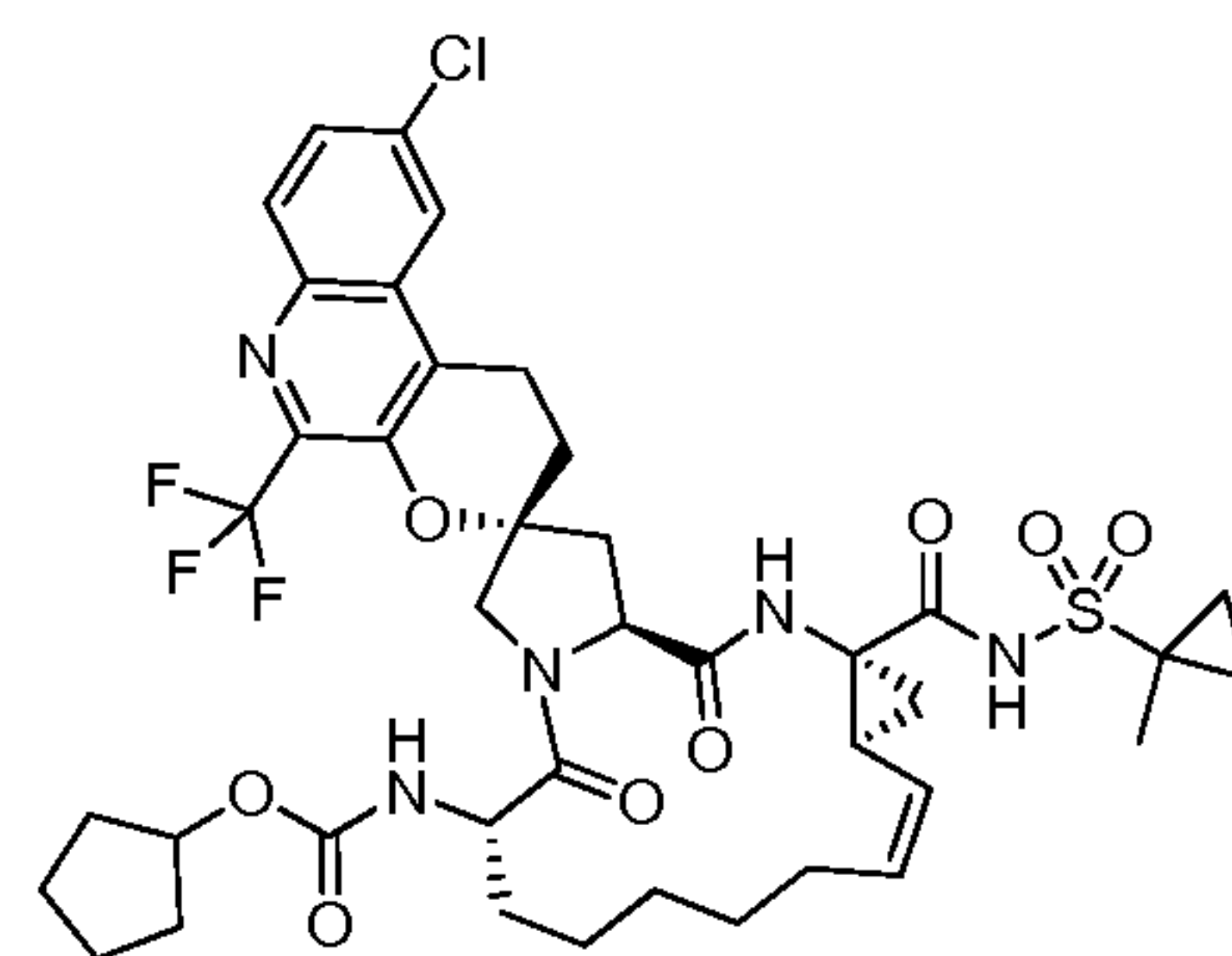
I-381



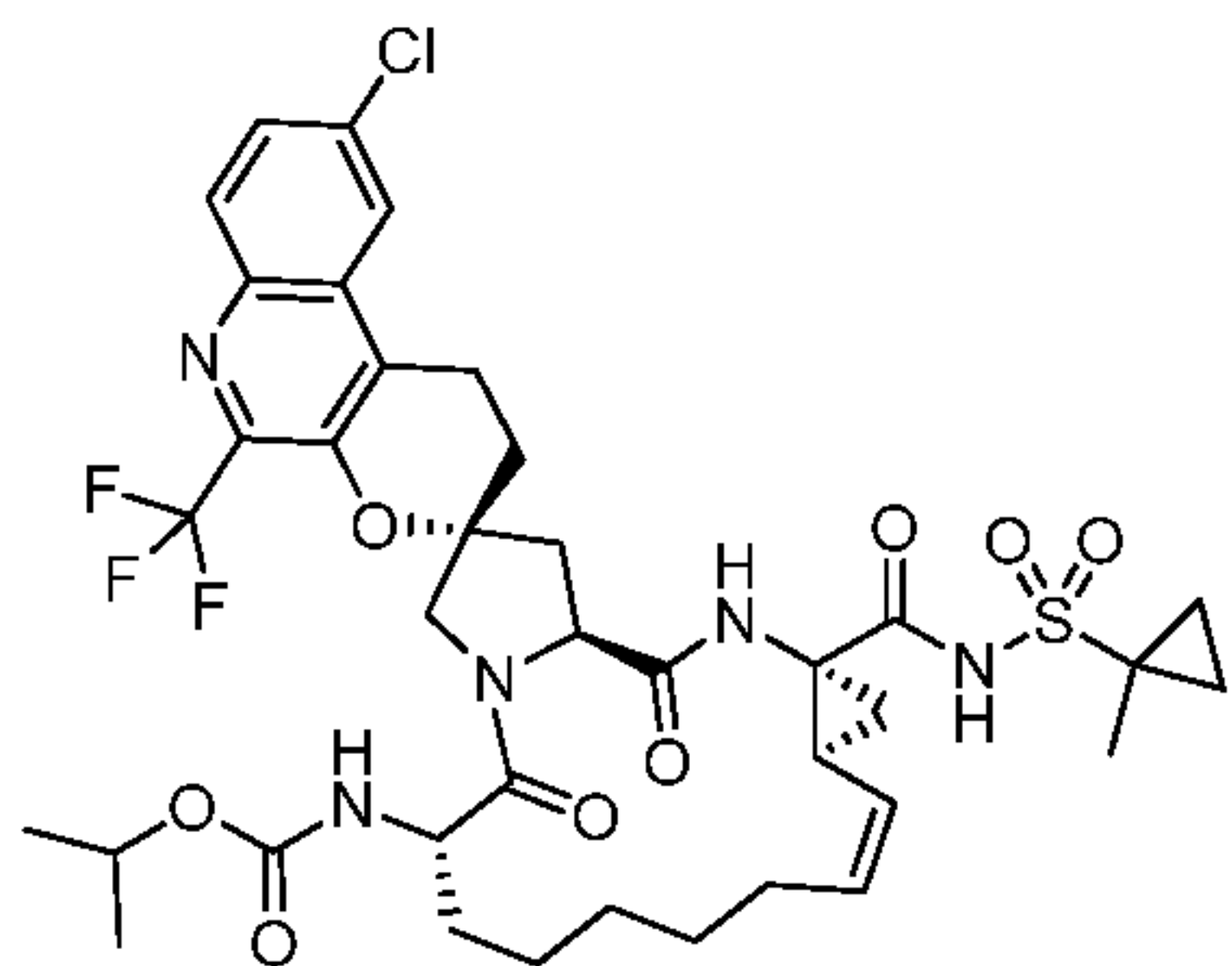
I-382



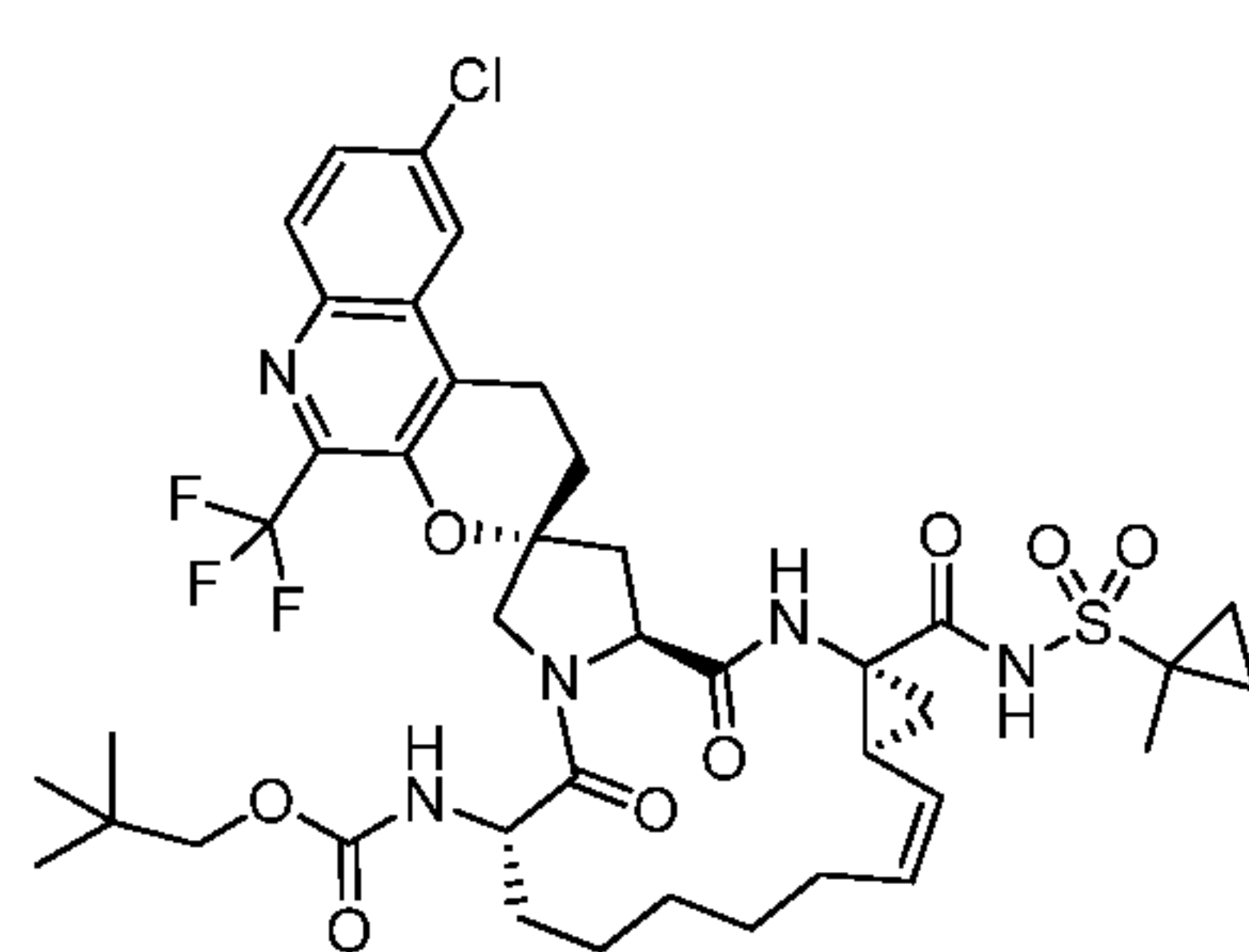
I-383



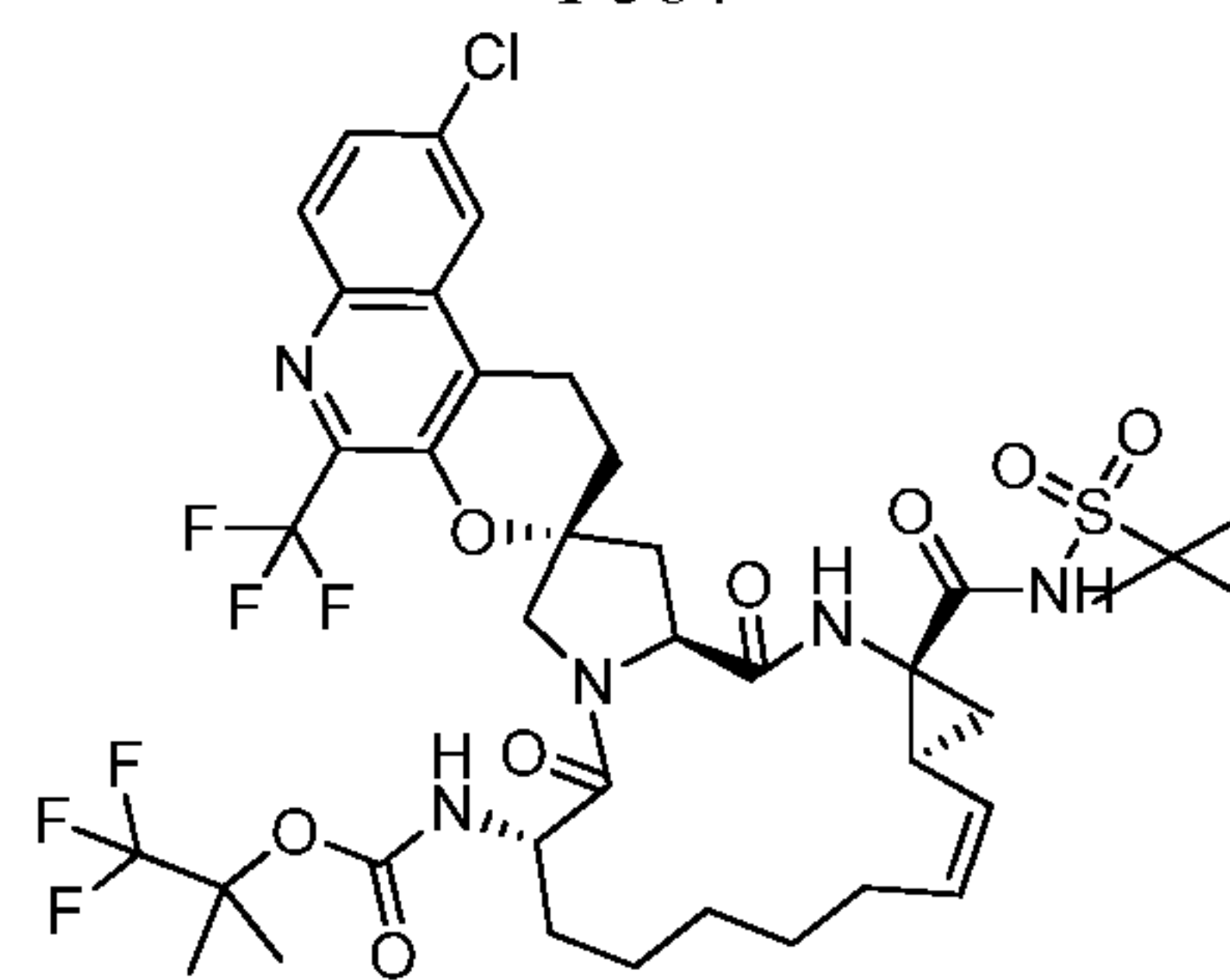
I-384



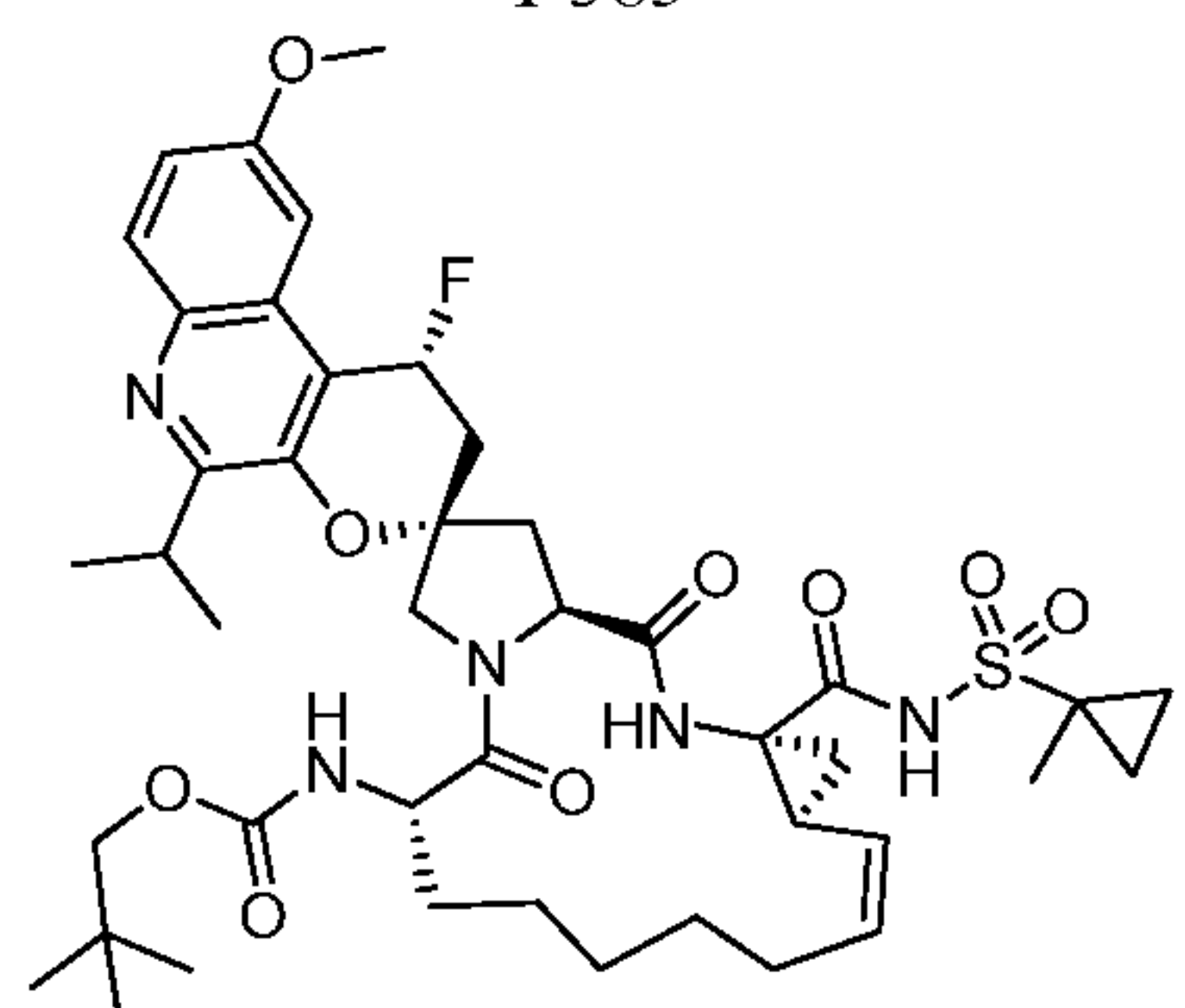
I-385



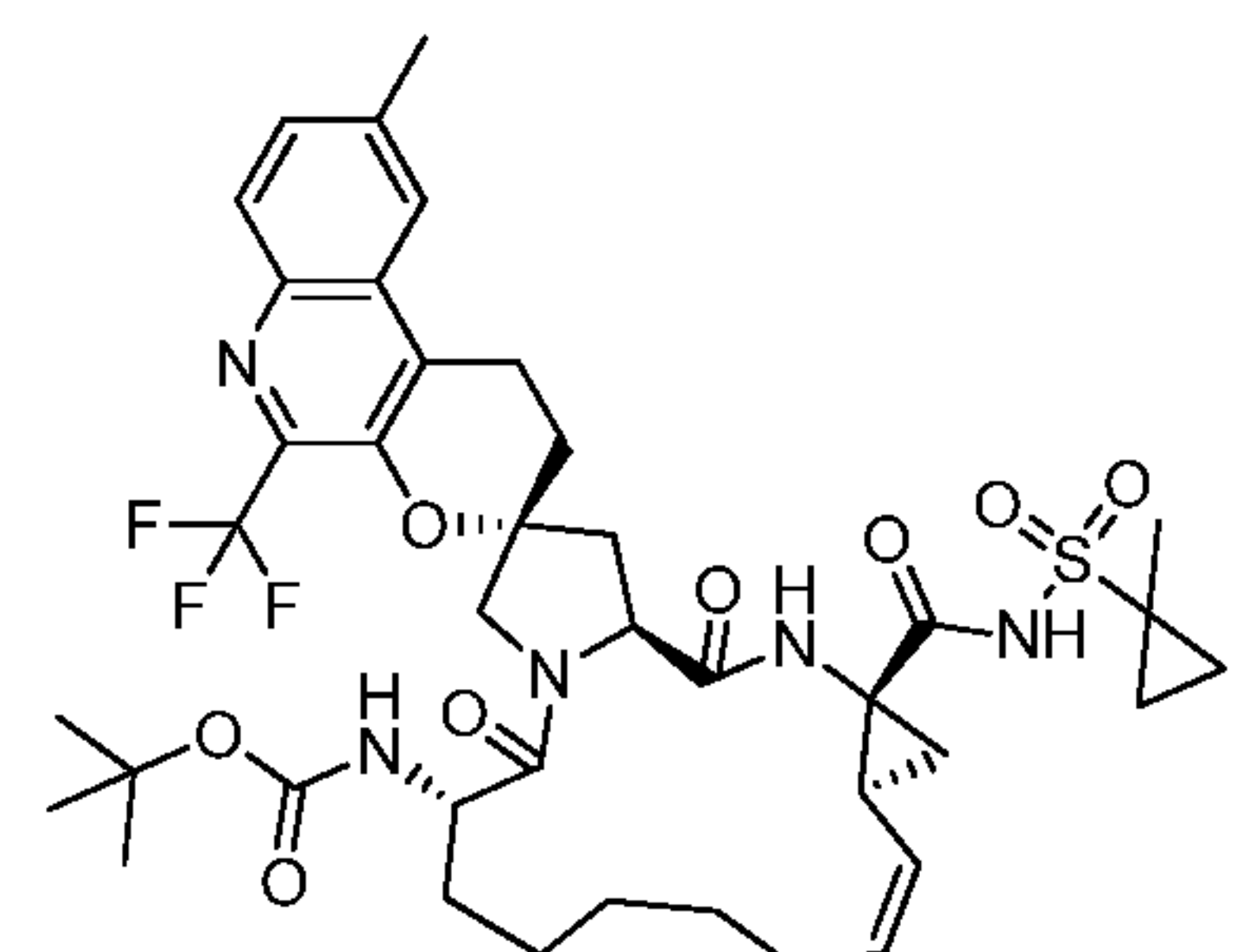
I-386



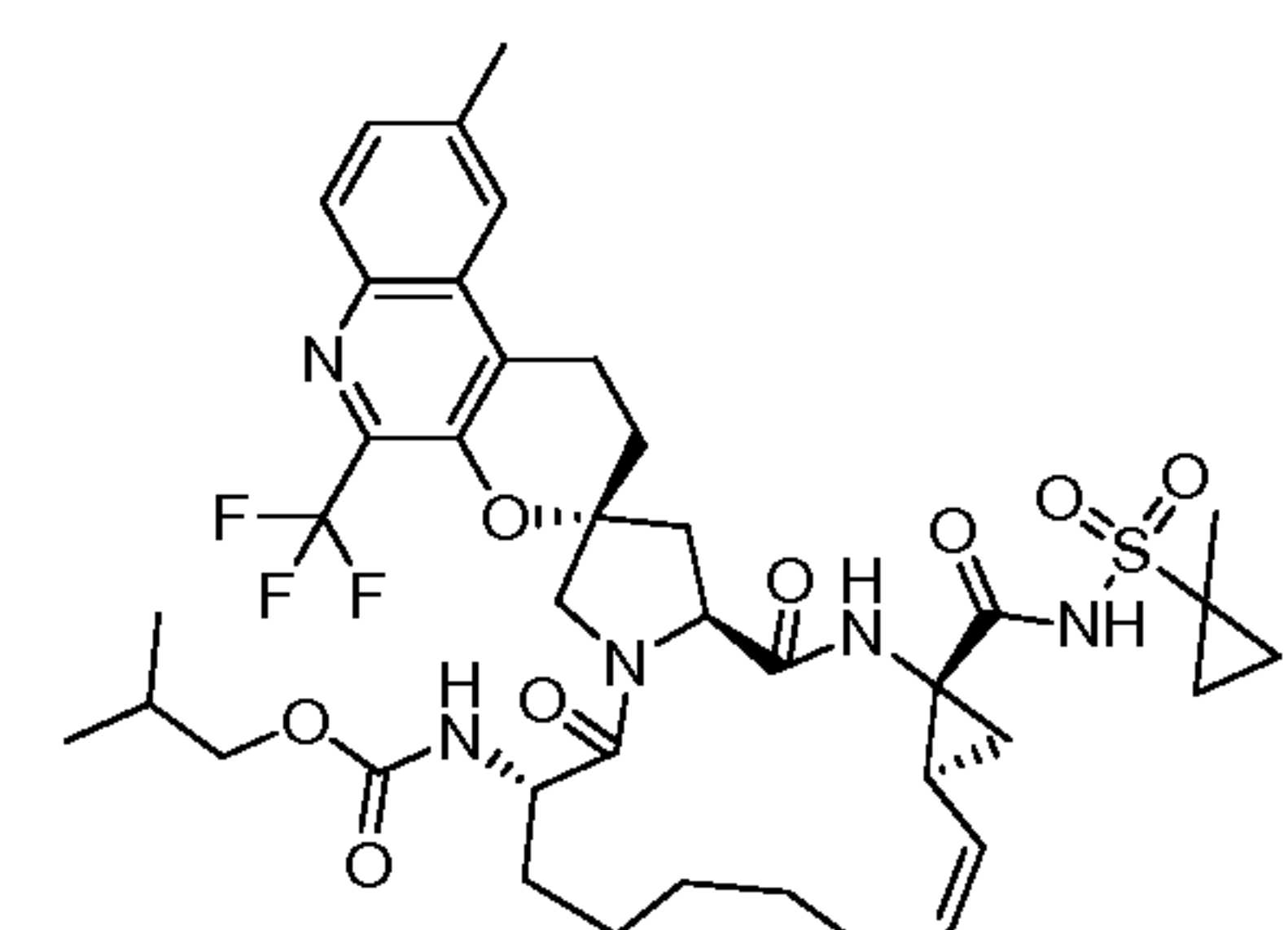
I-387



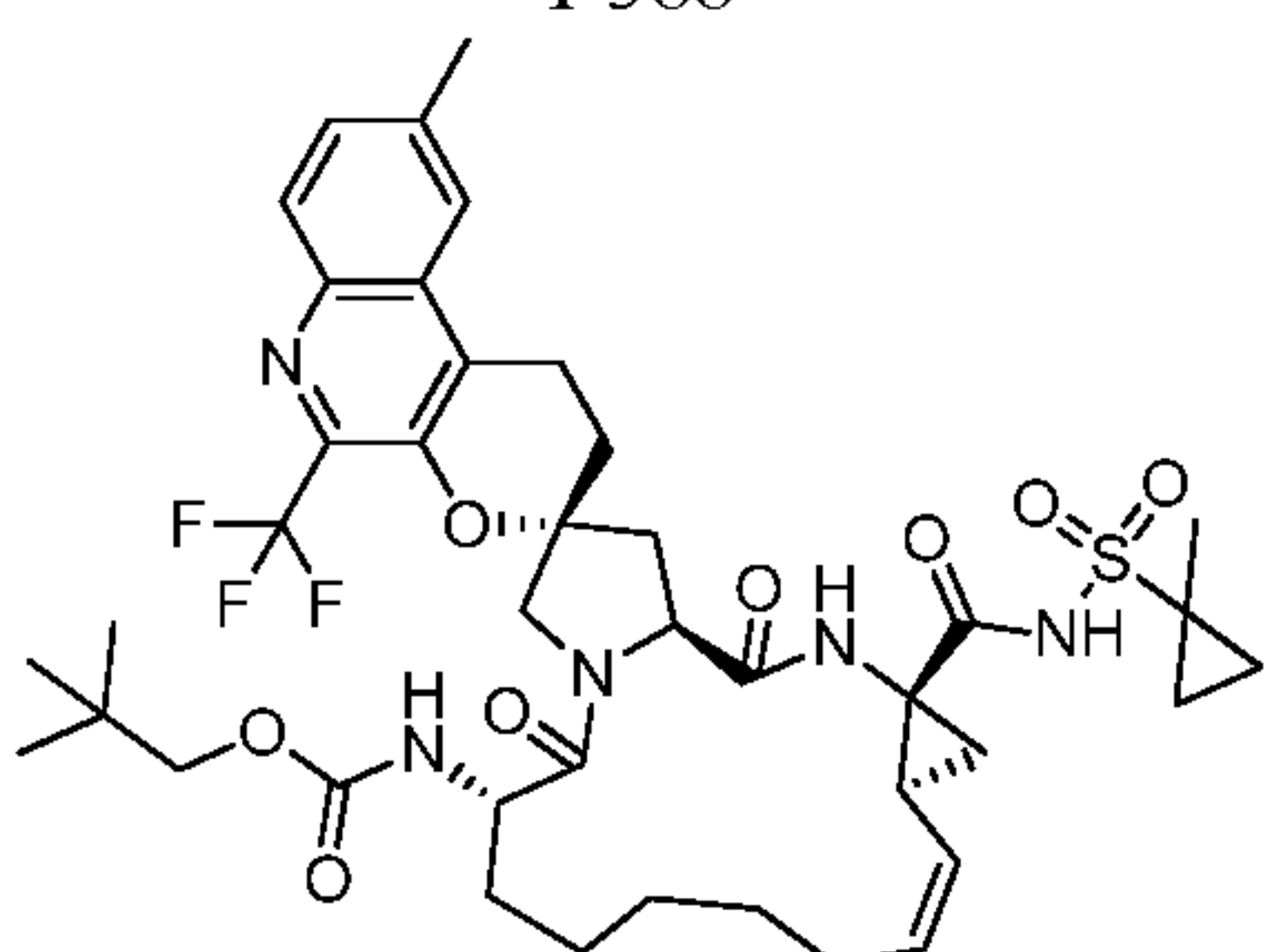
I-388



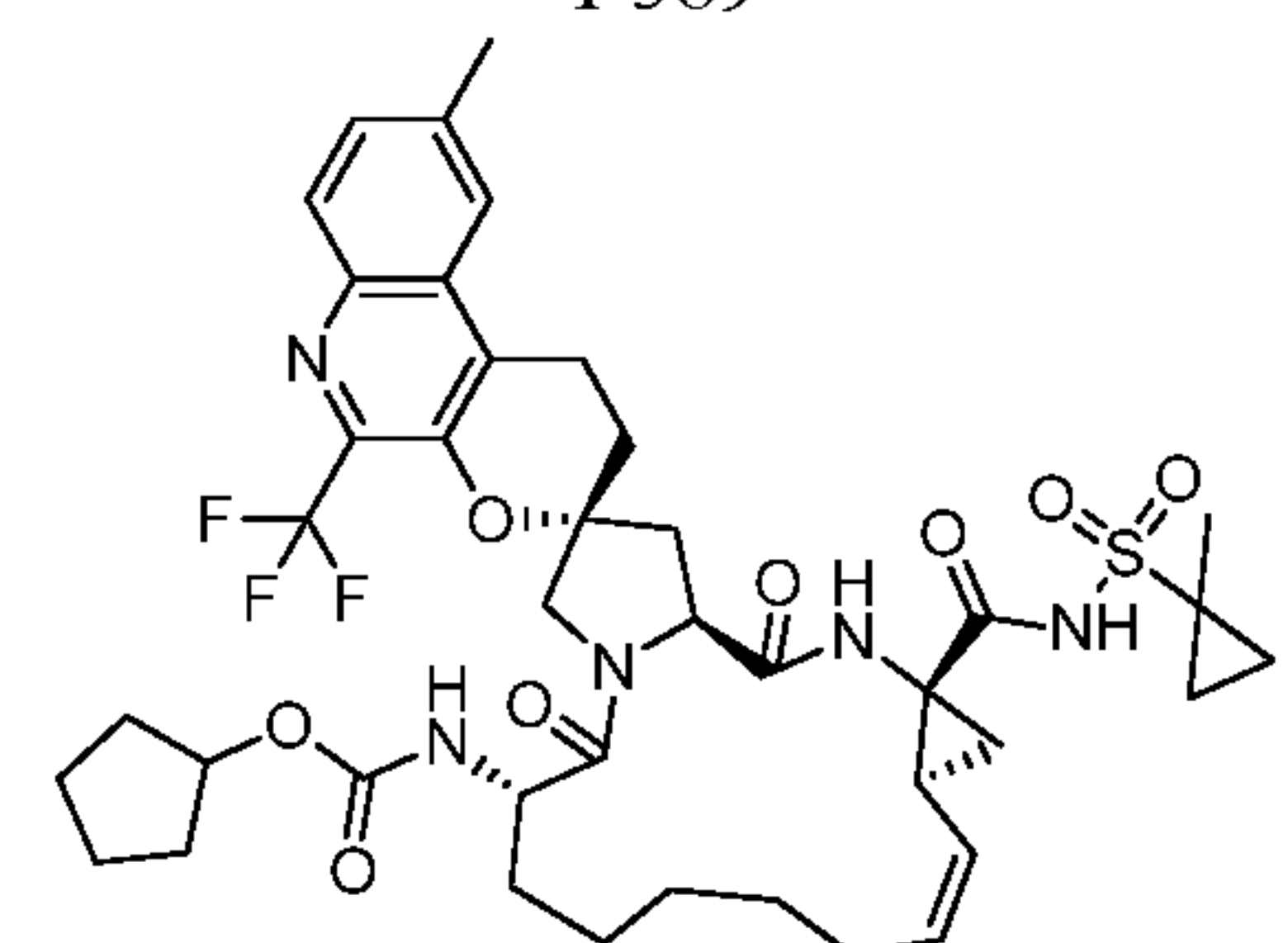
I-389



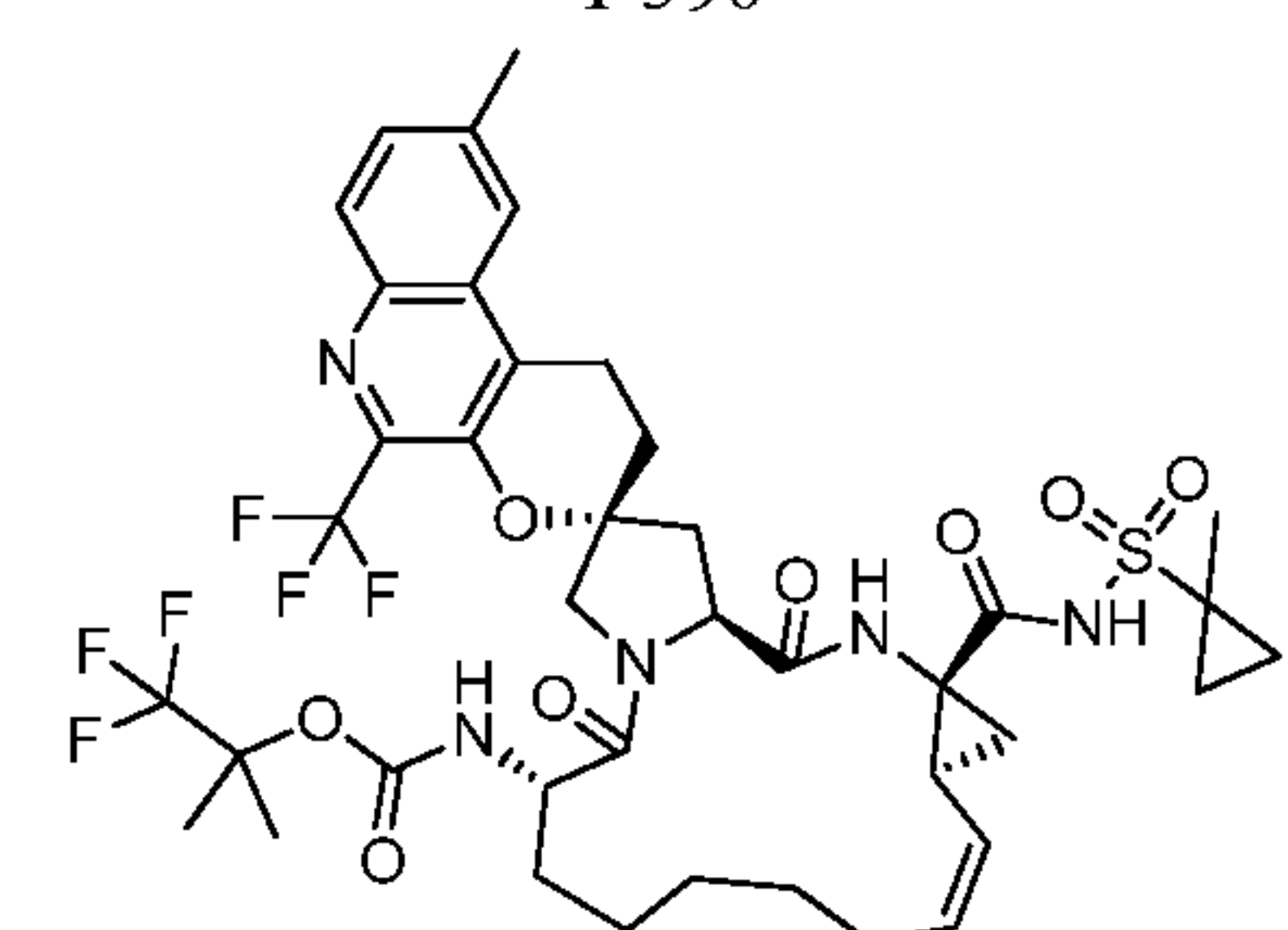
I-390



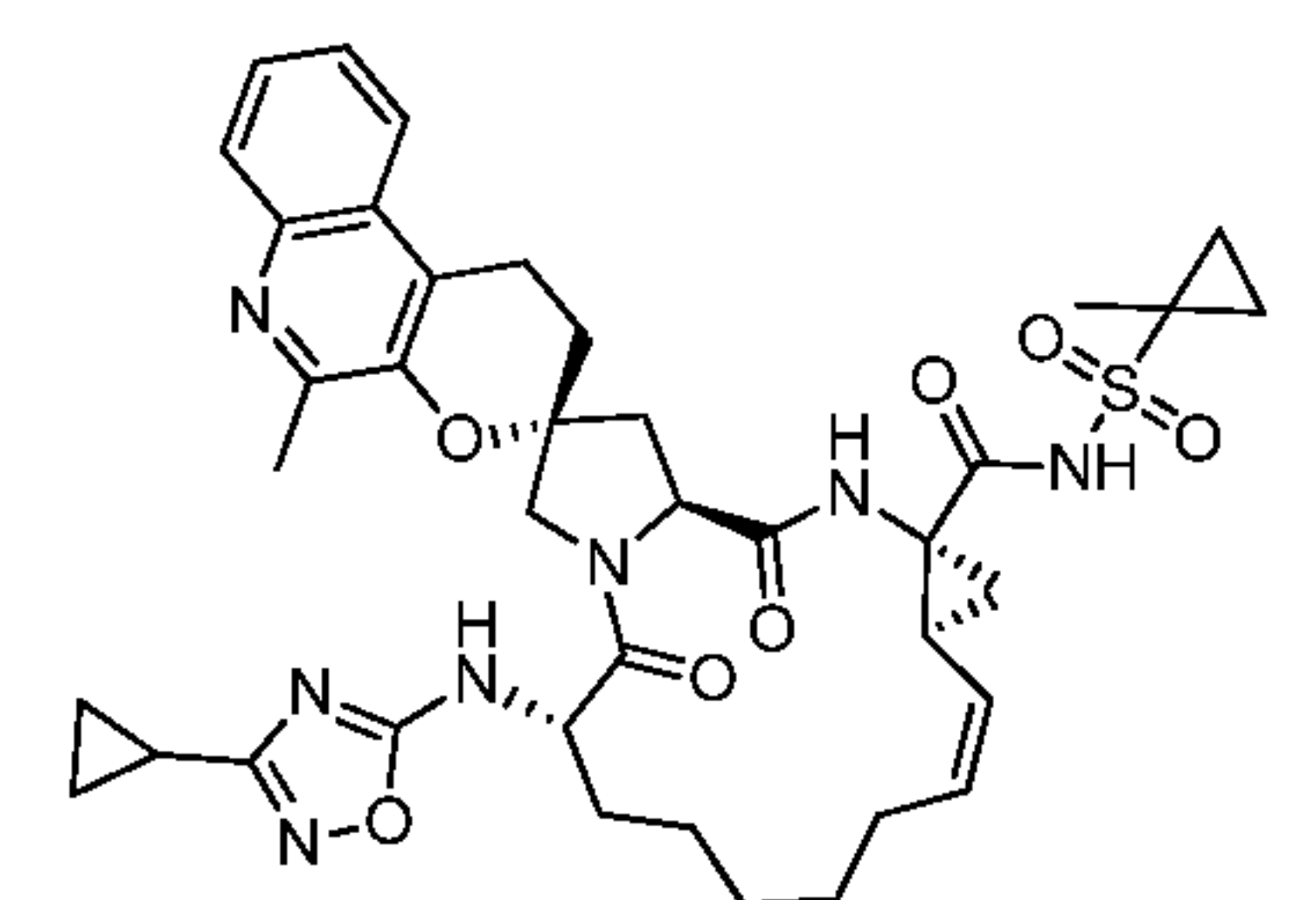
I-391



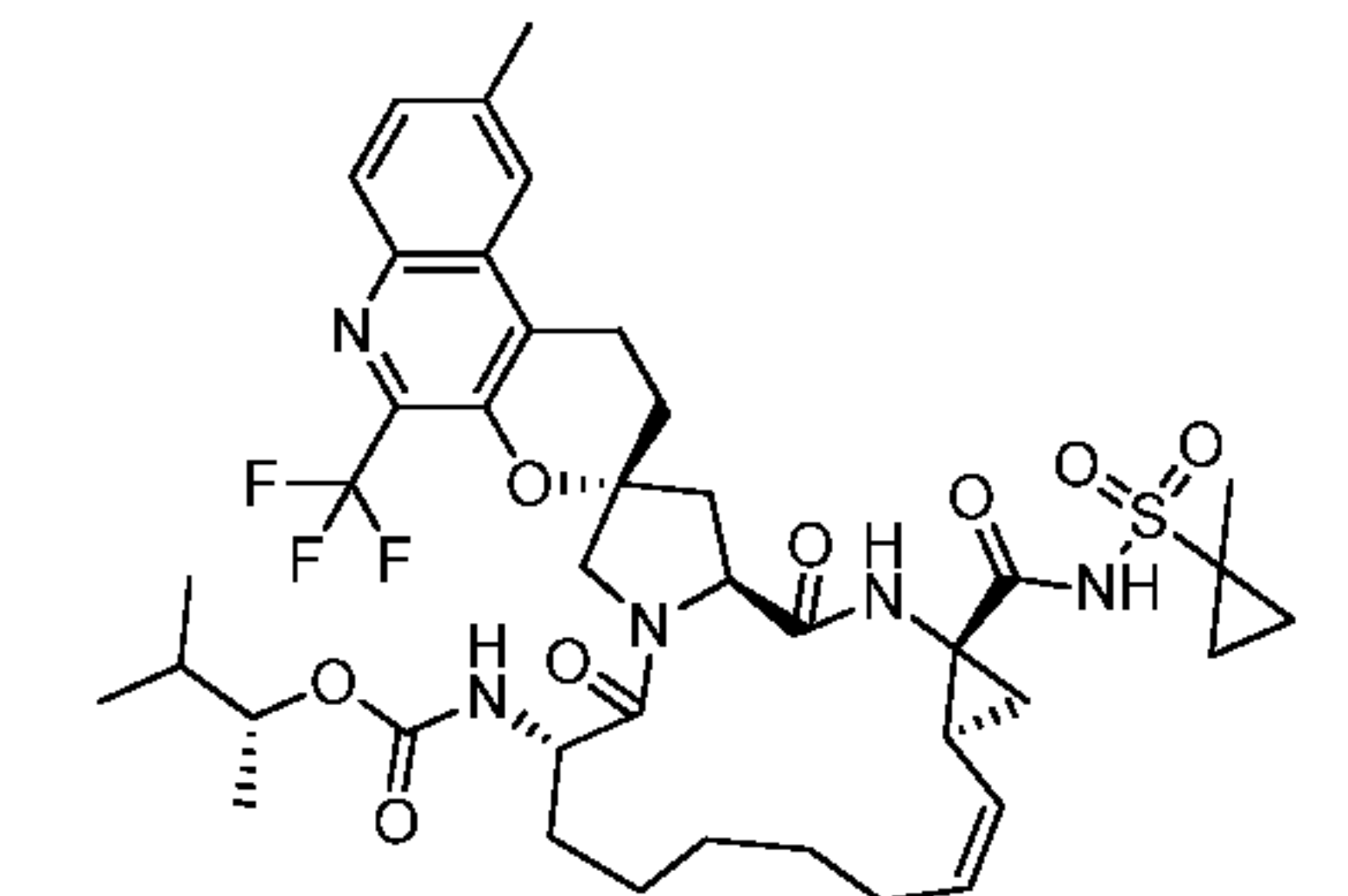
I-392



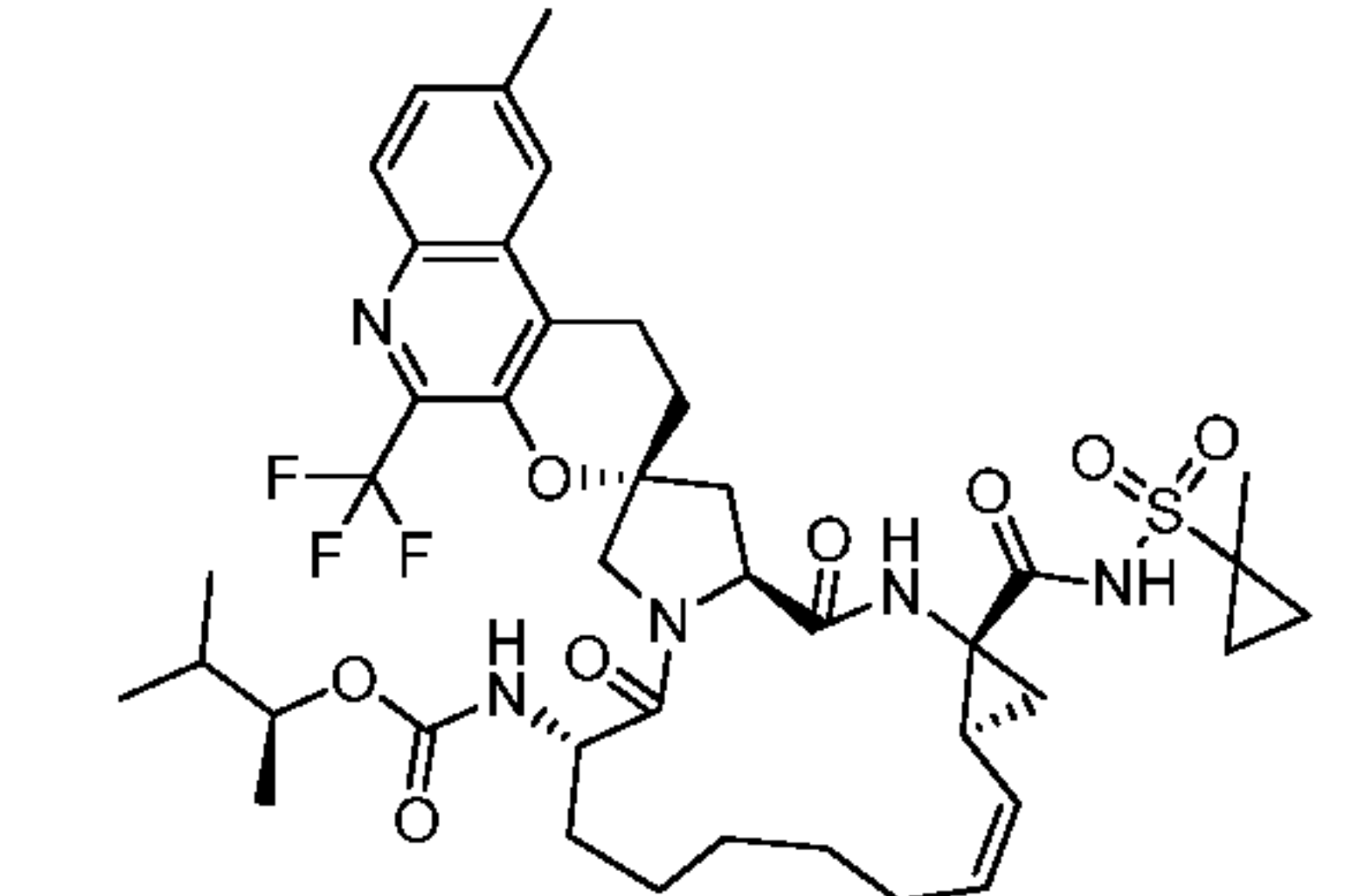
I-393



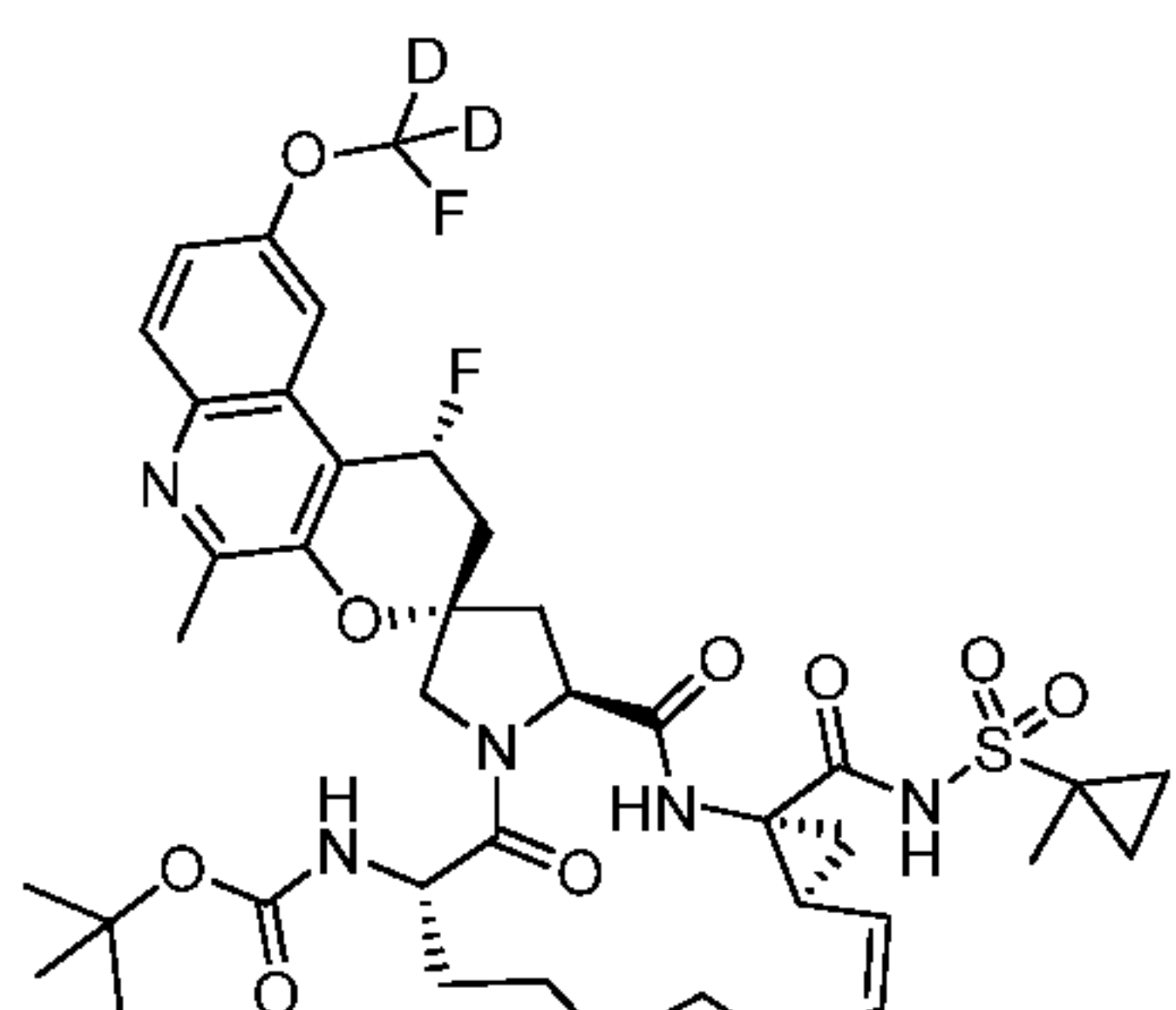
I-394



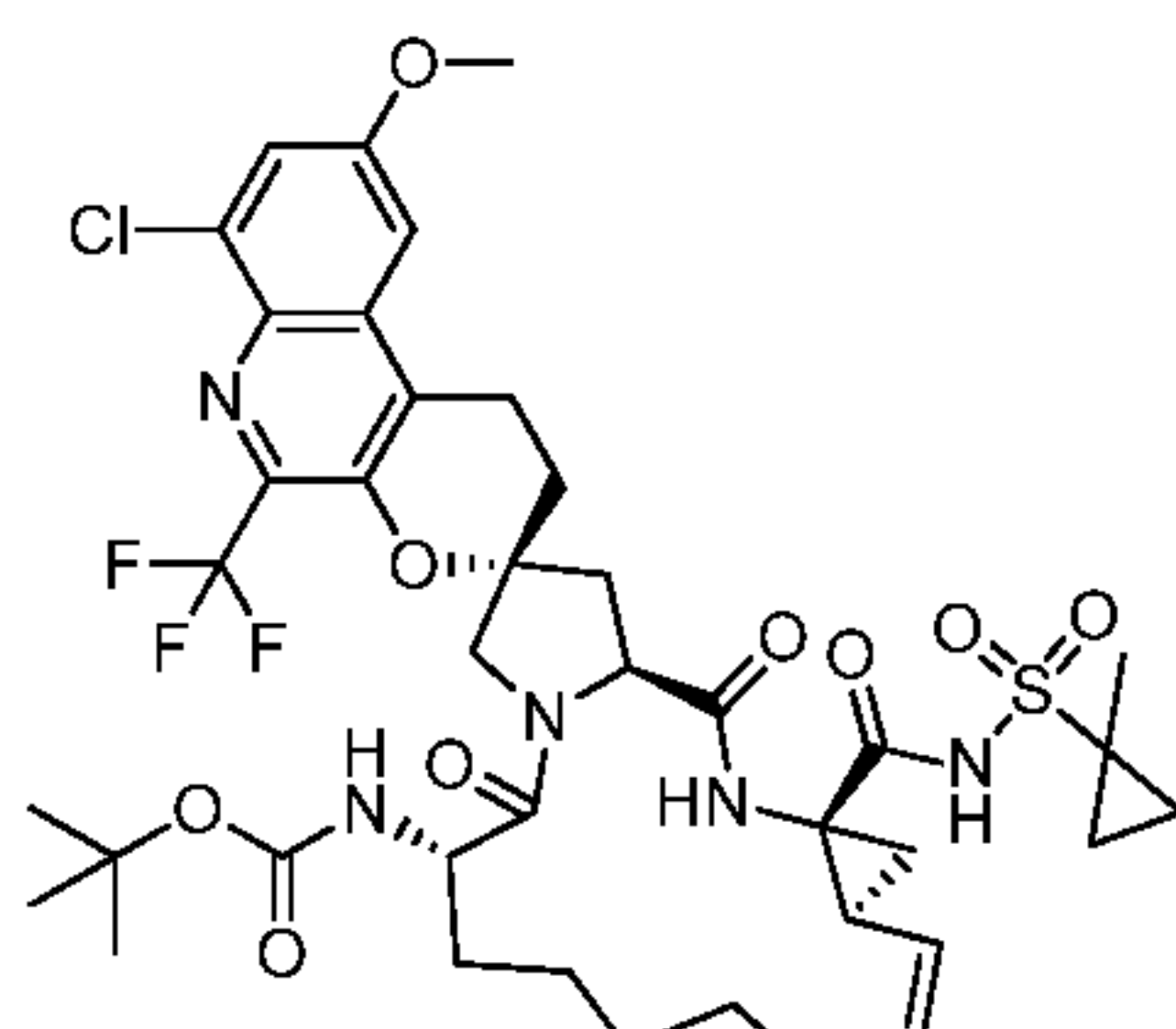
I-395



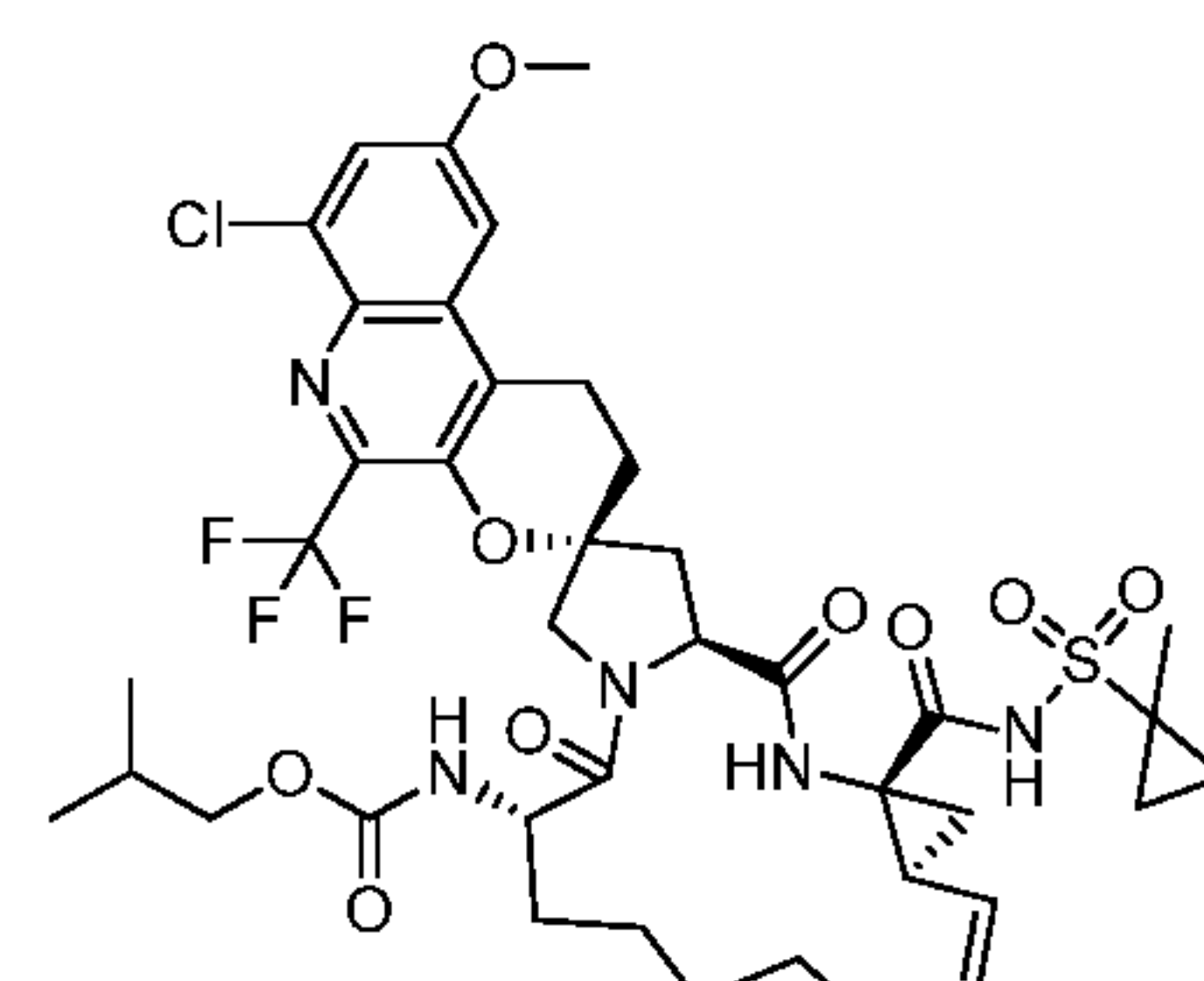
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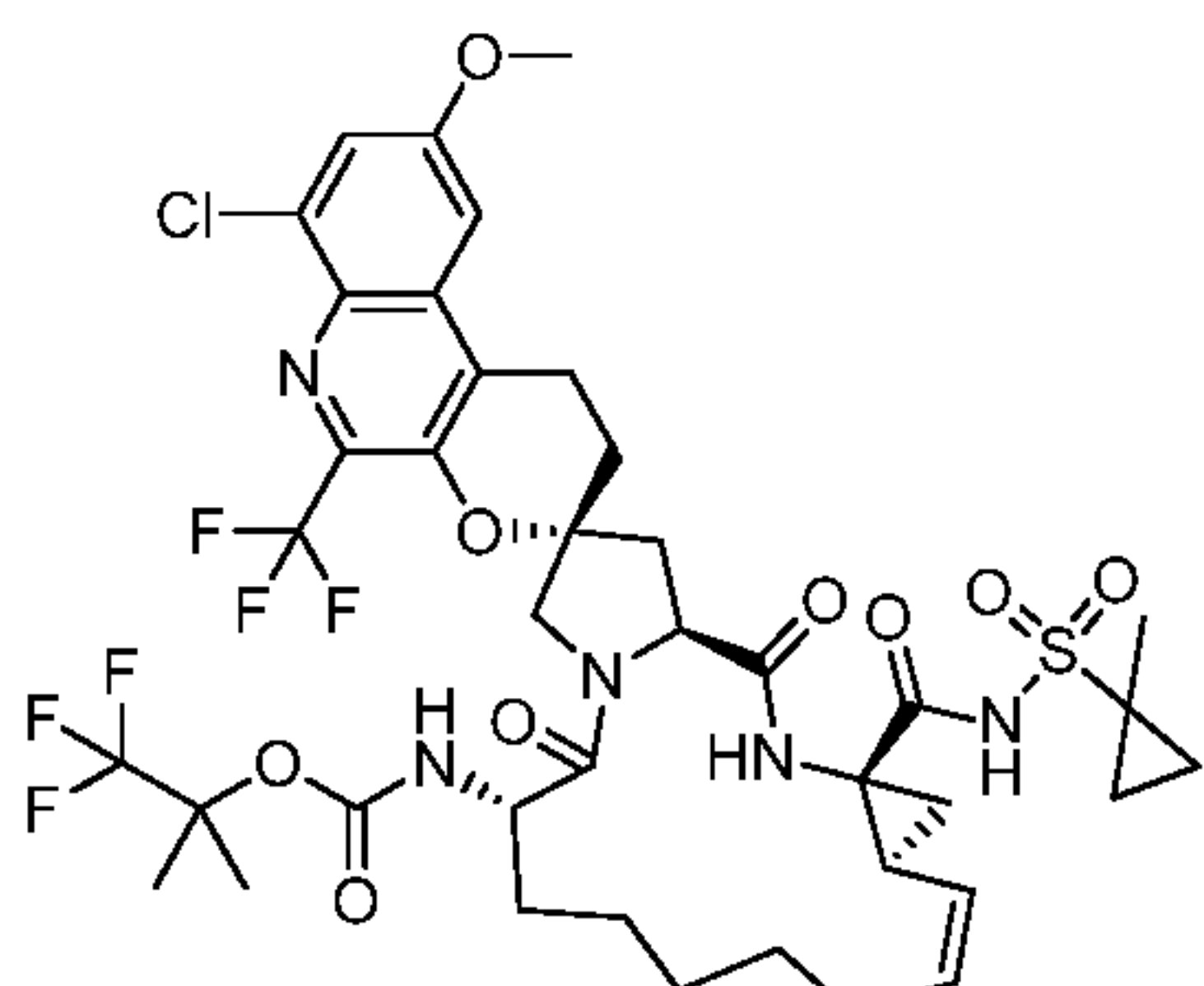
I-397



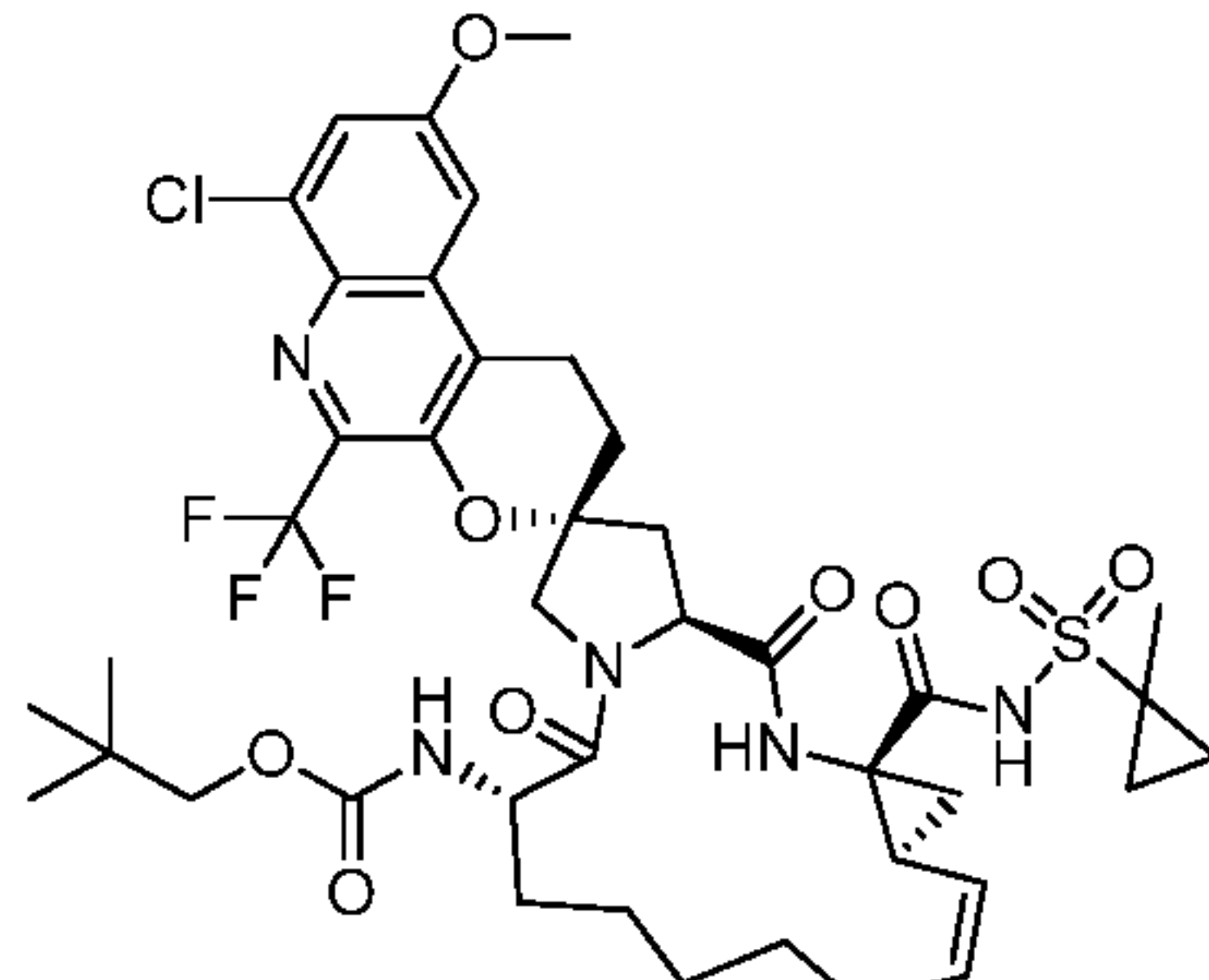
I-398



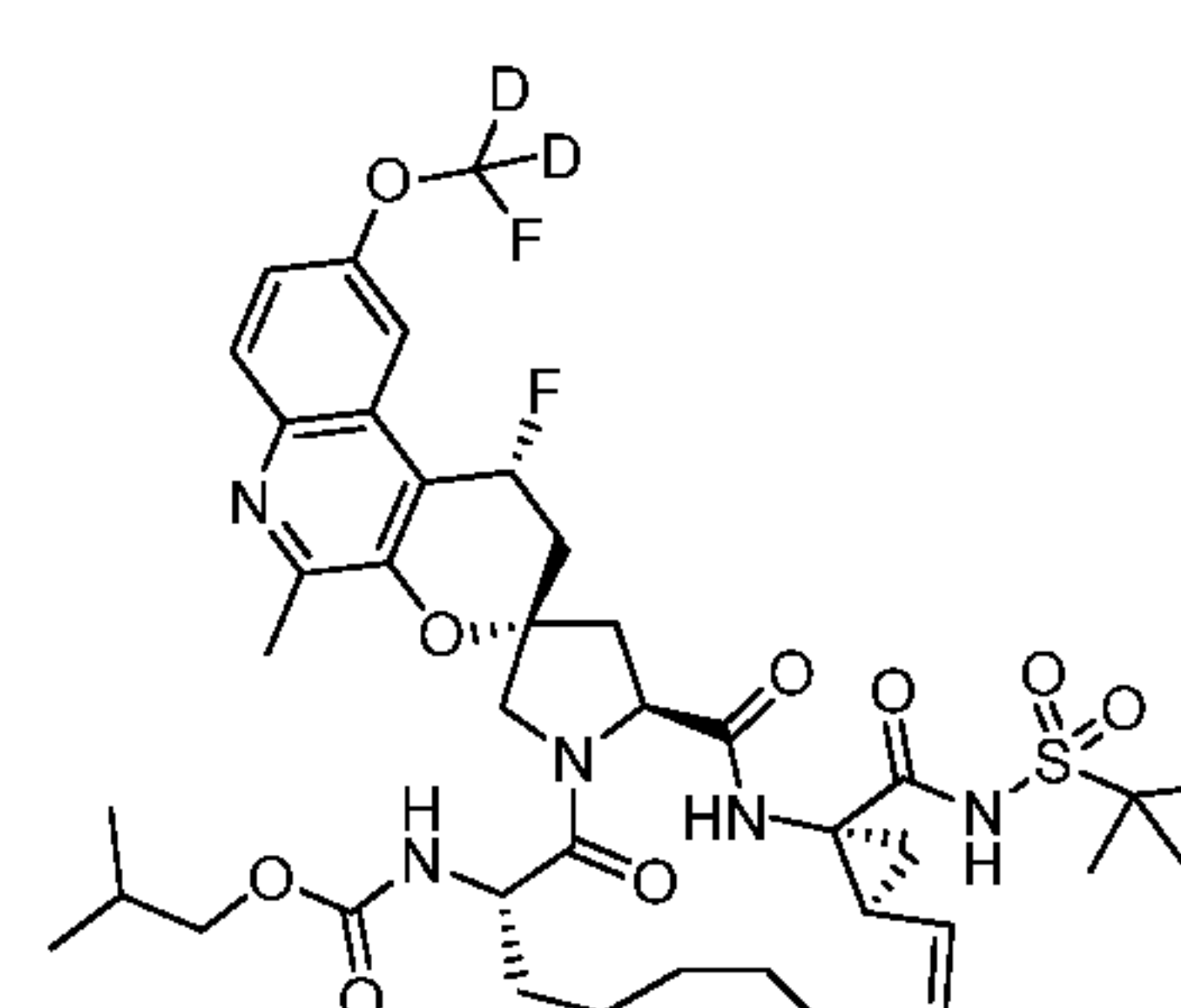
I-399



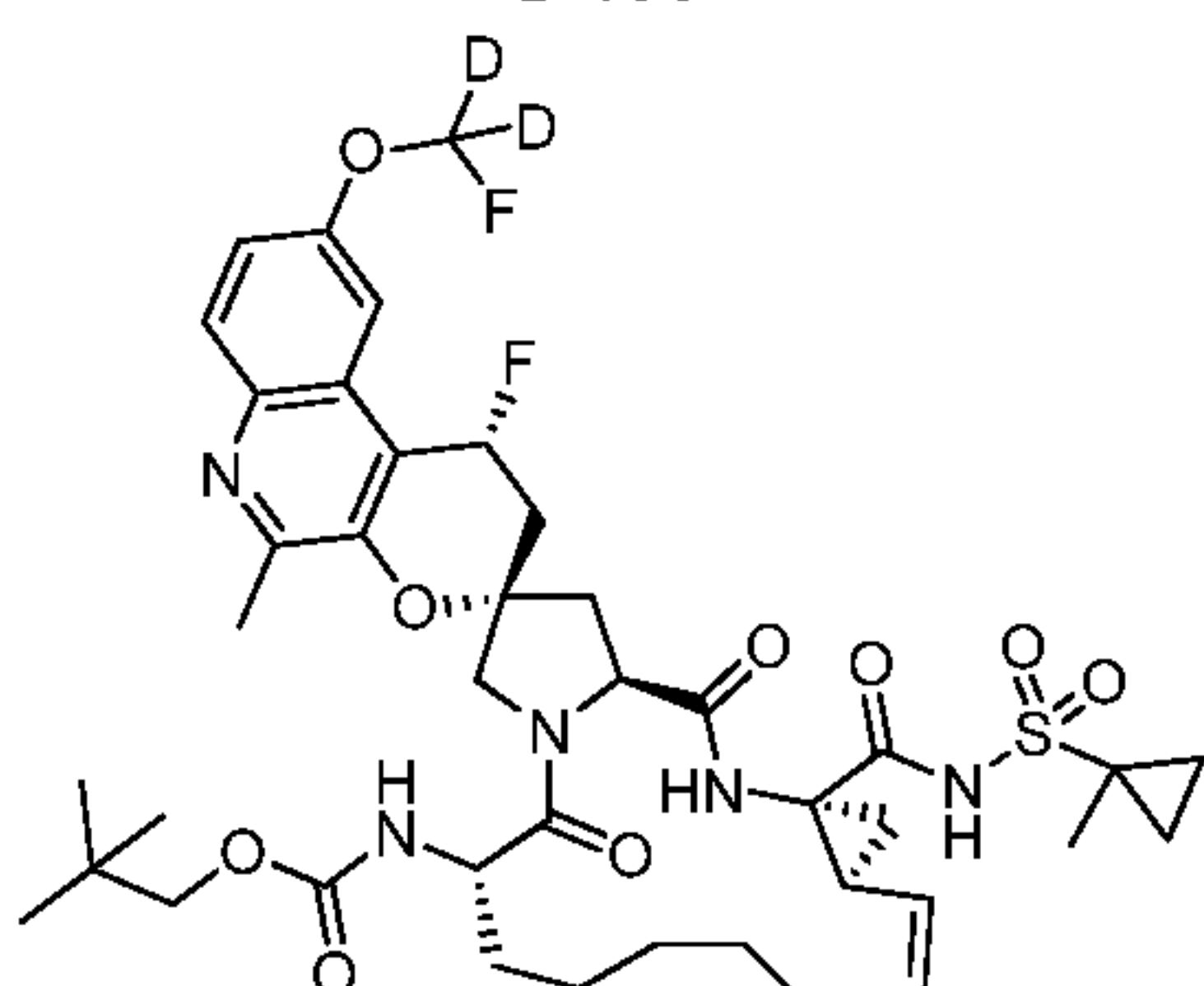
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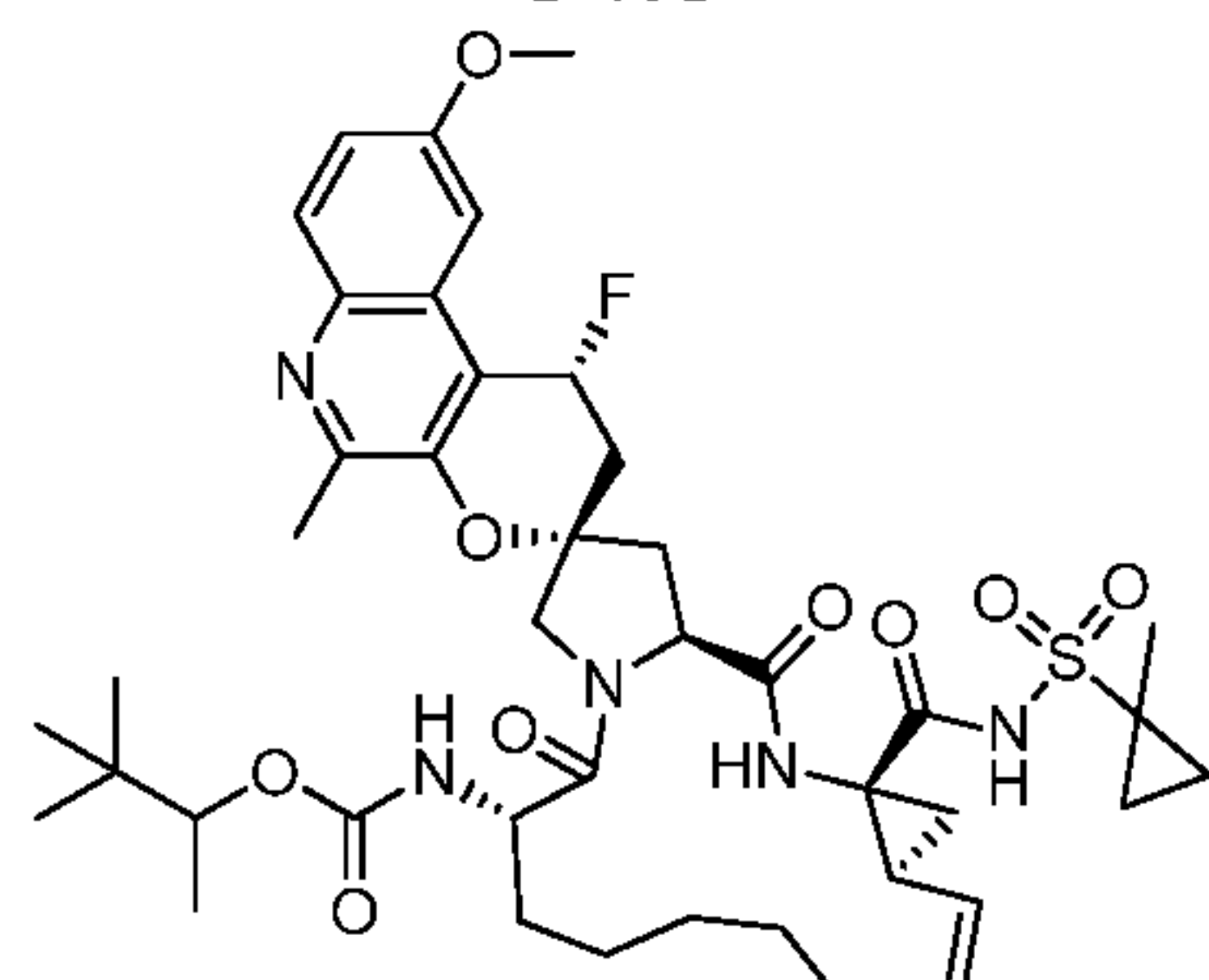
I-401



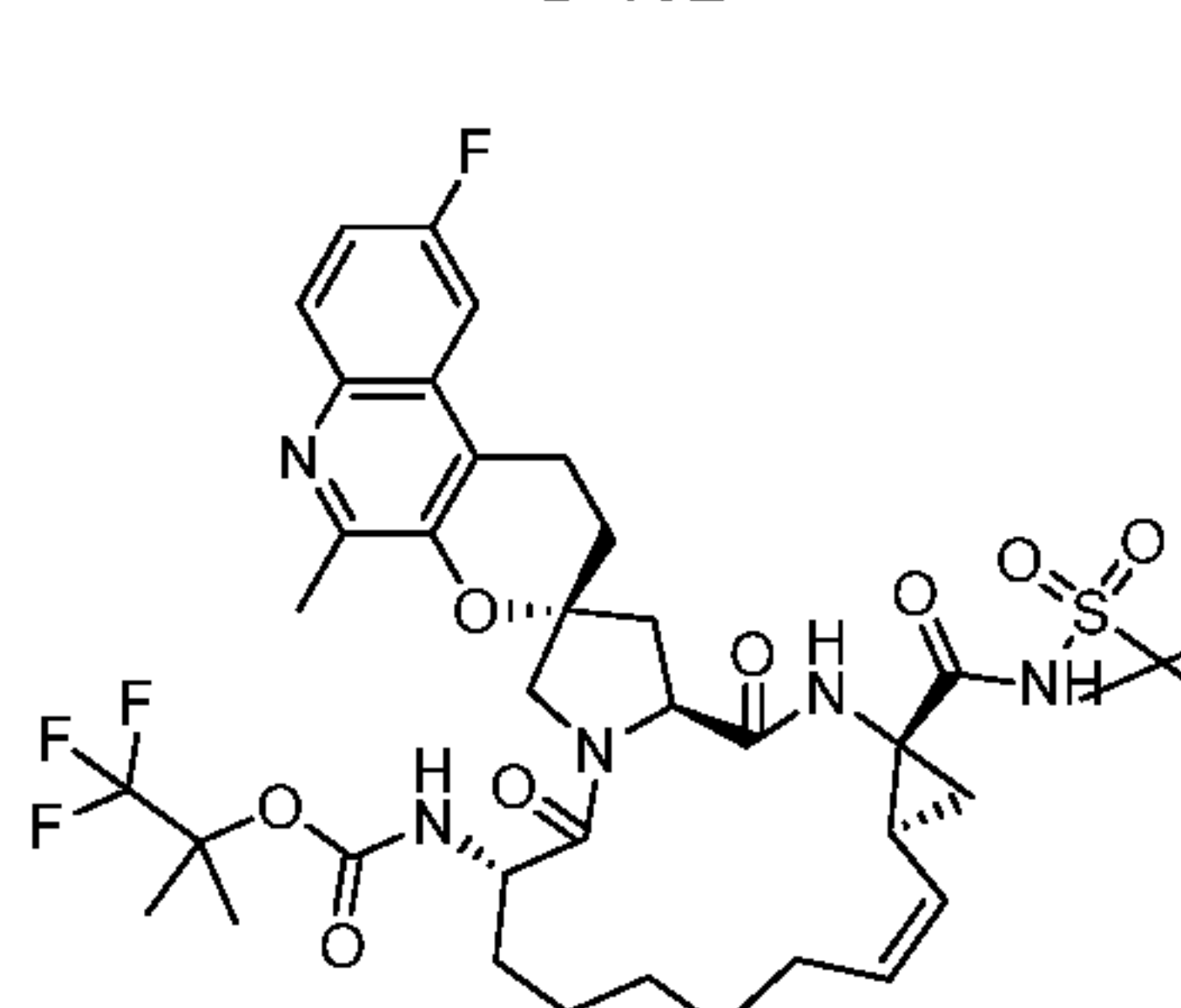
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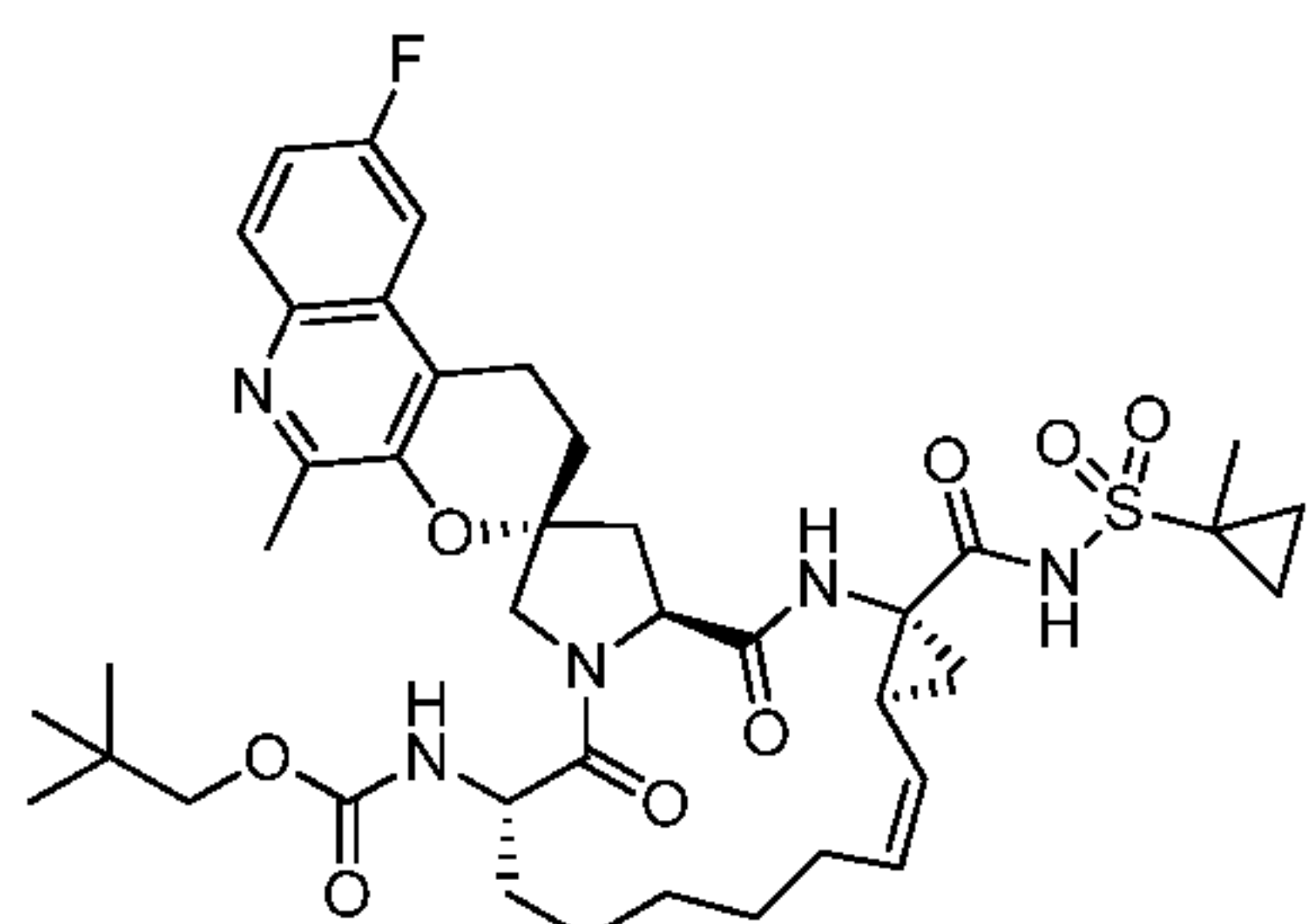
I-403



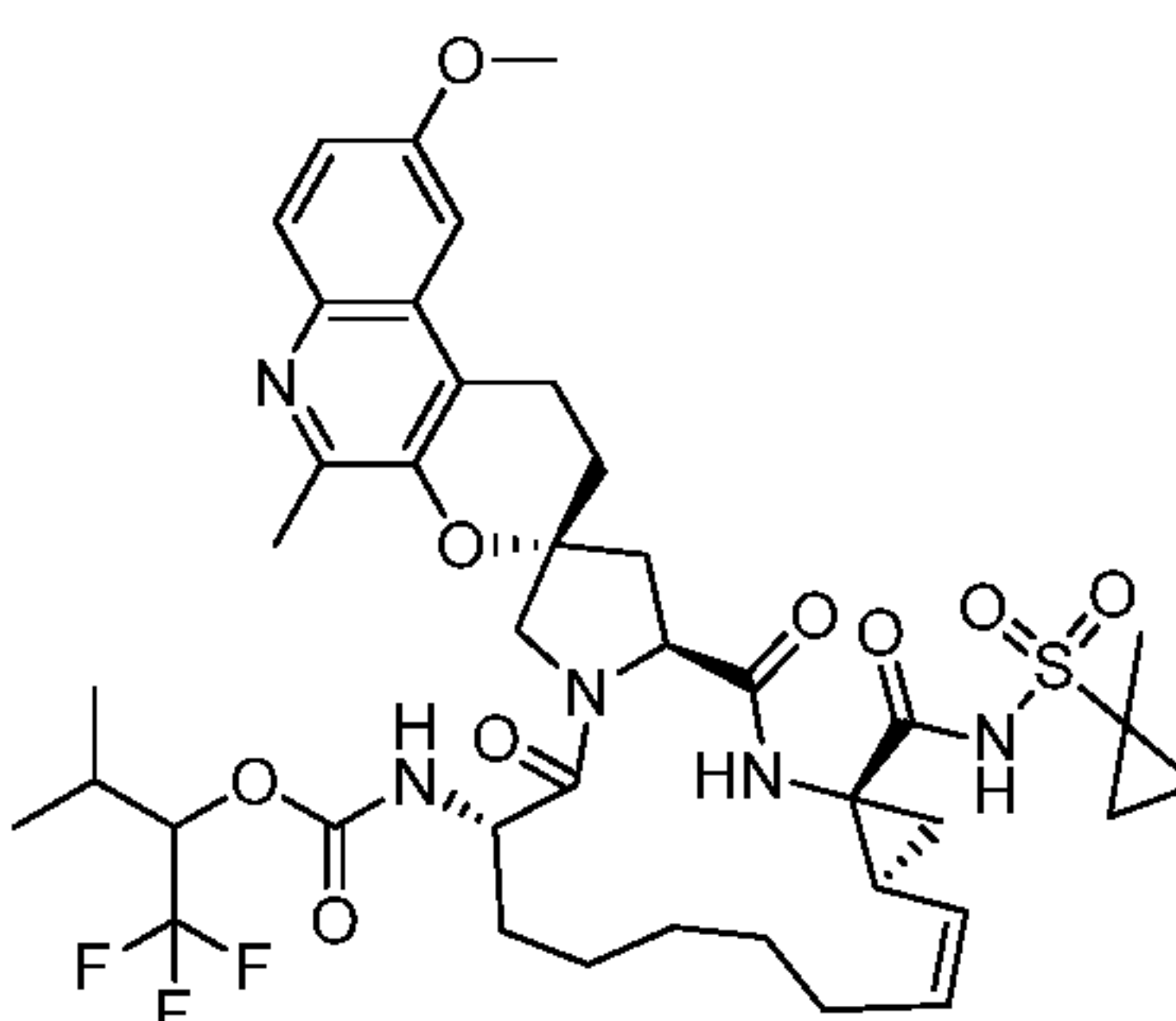
I-404



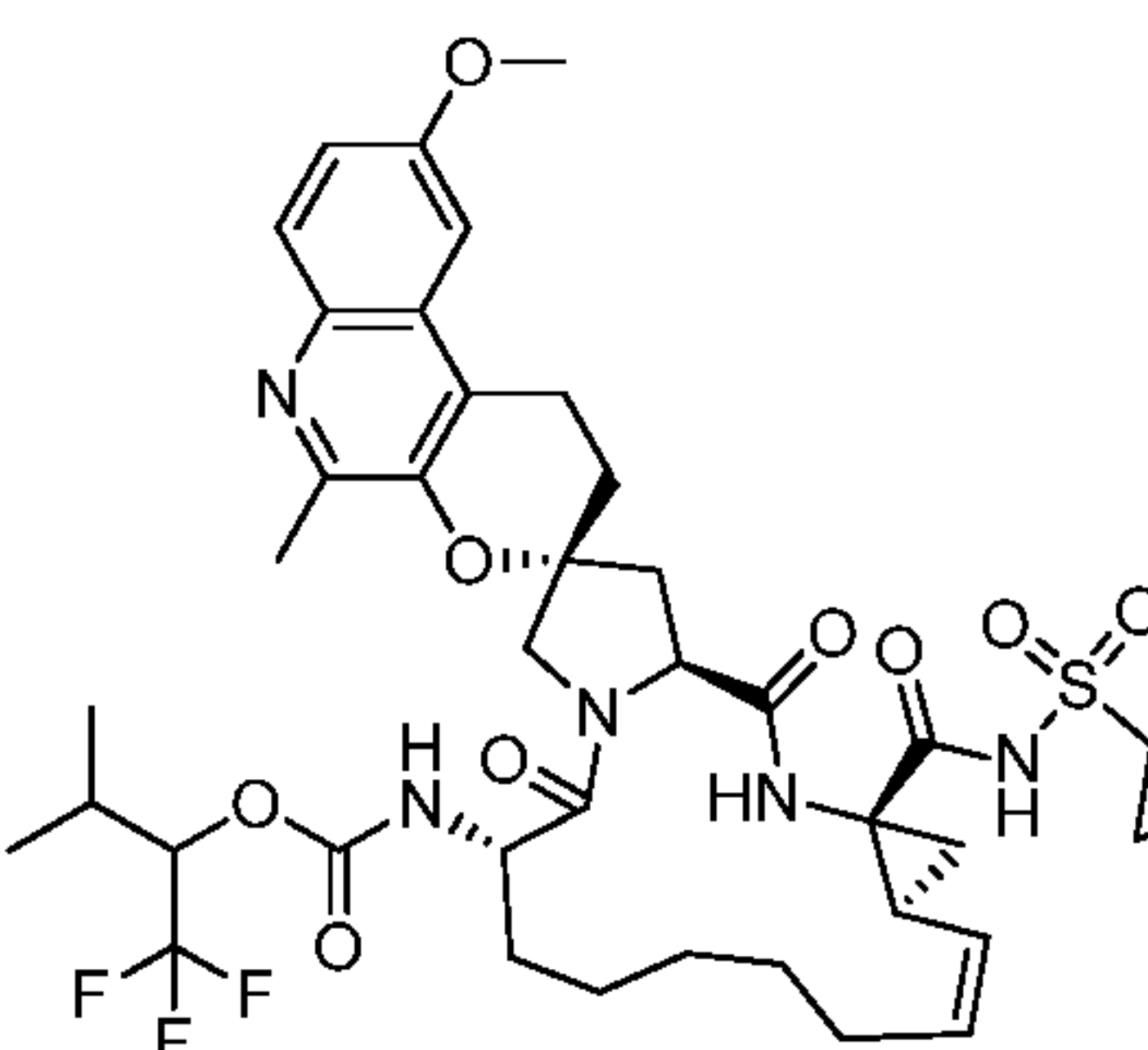
I-405



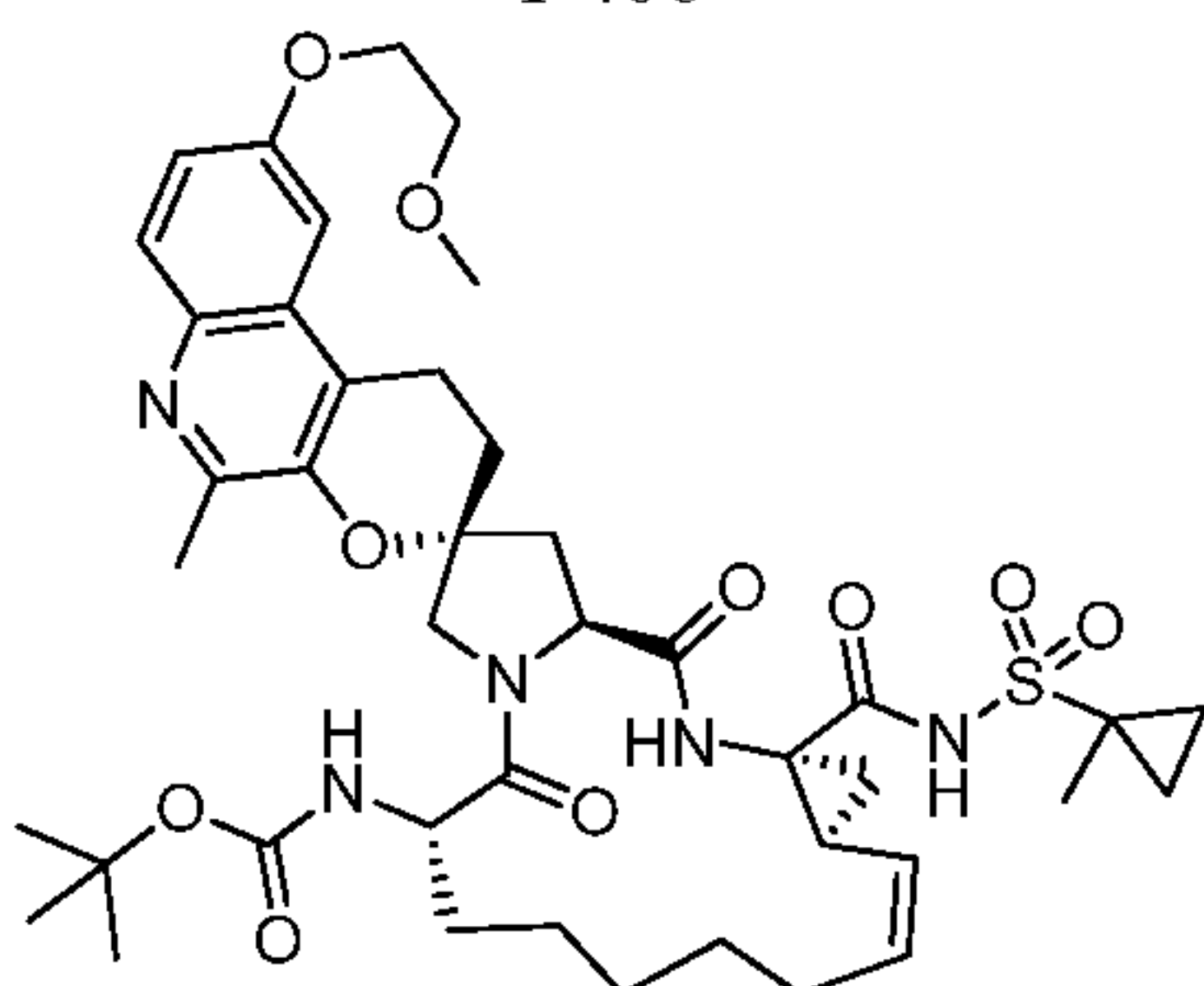
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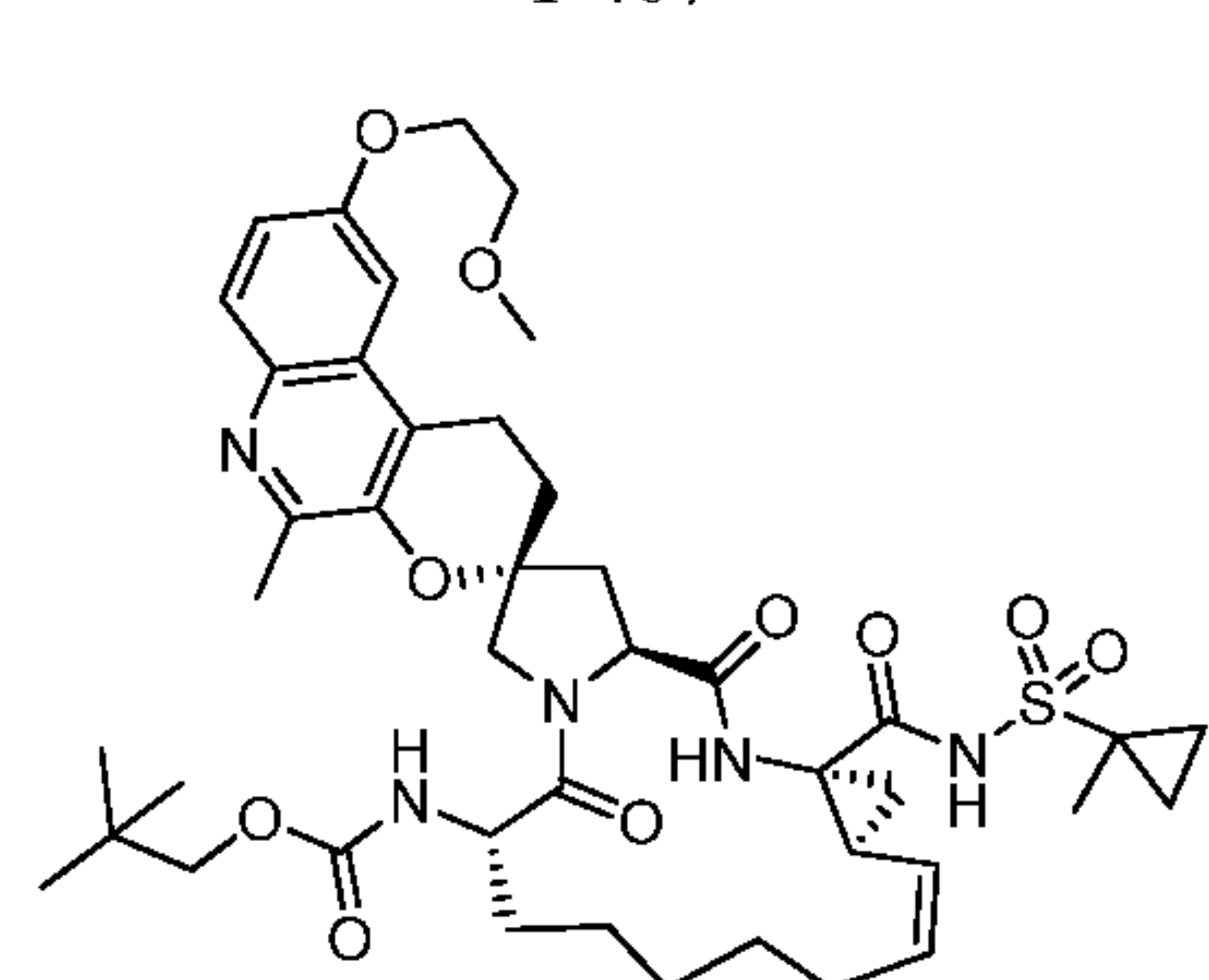
I-407



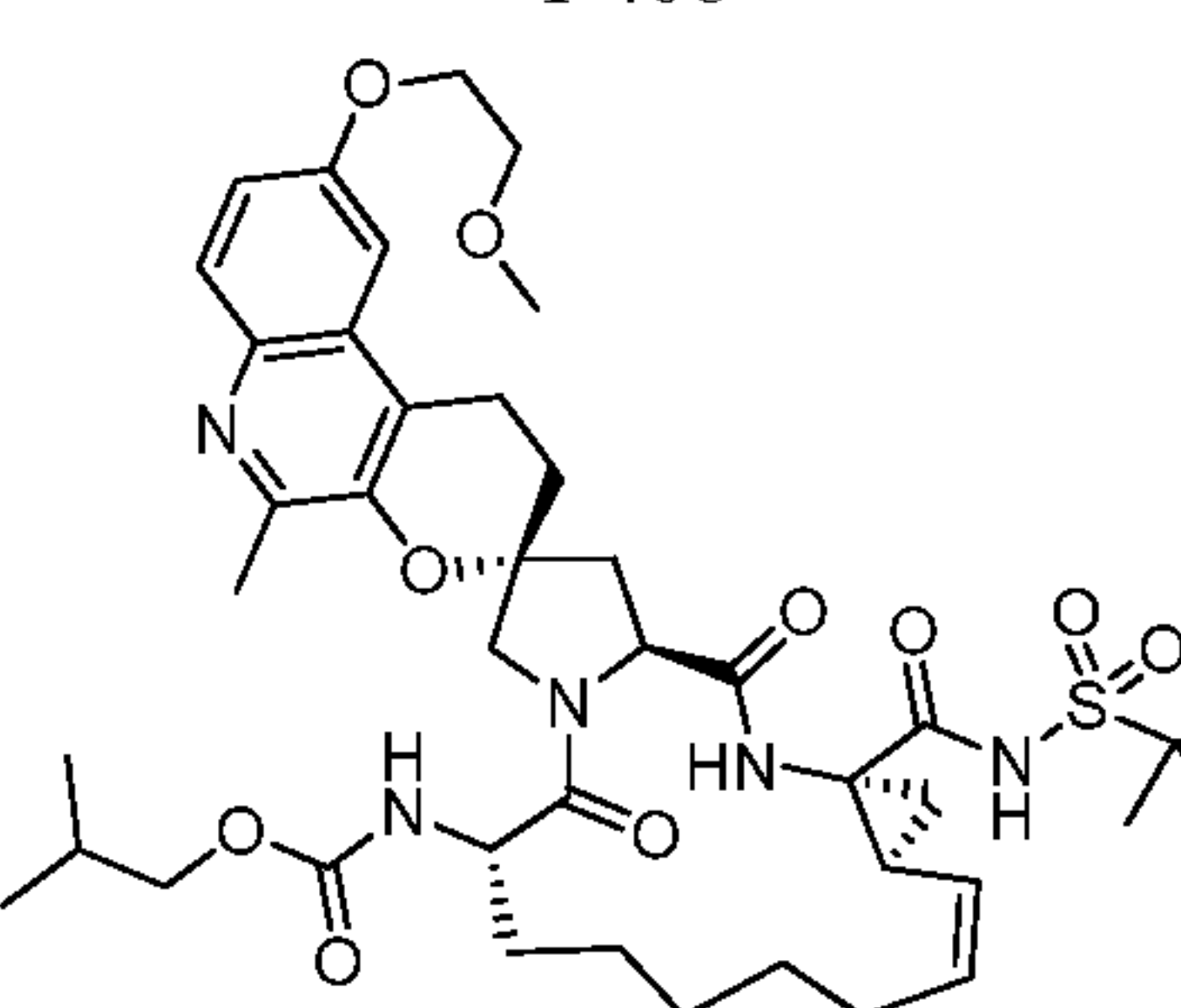
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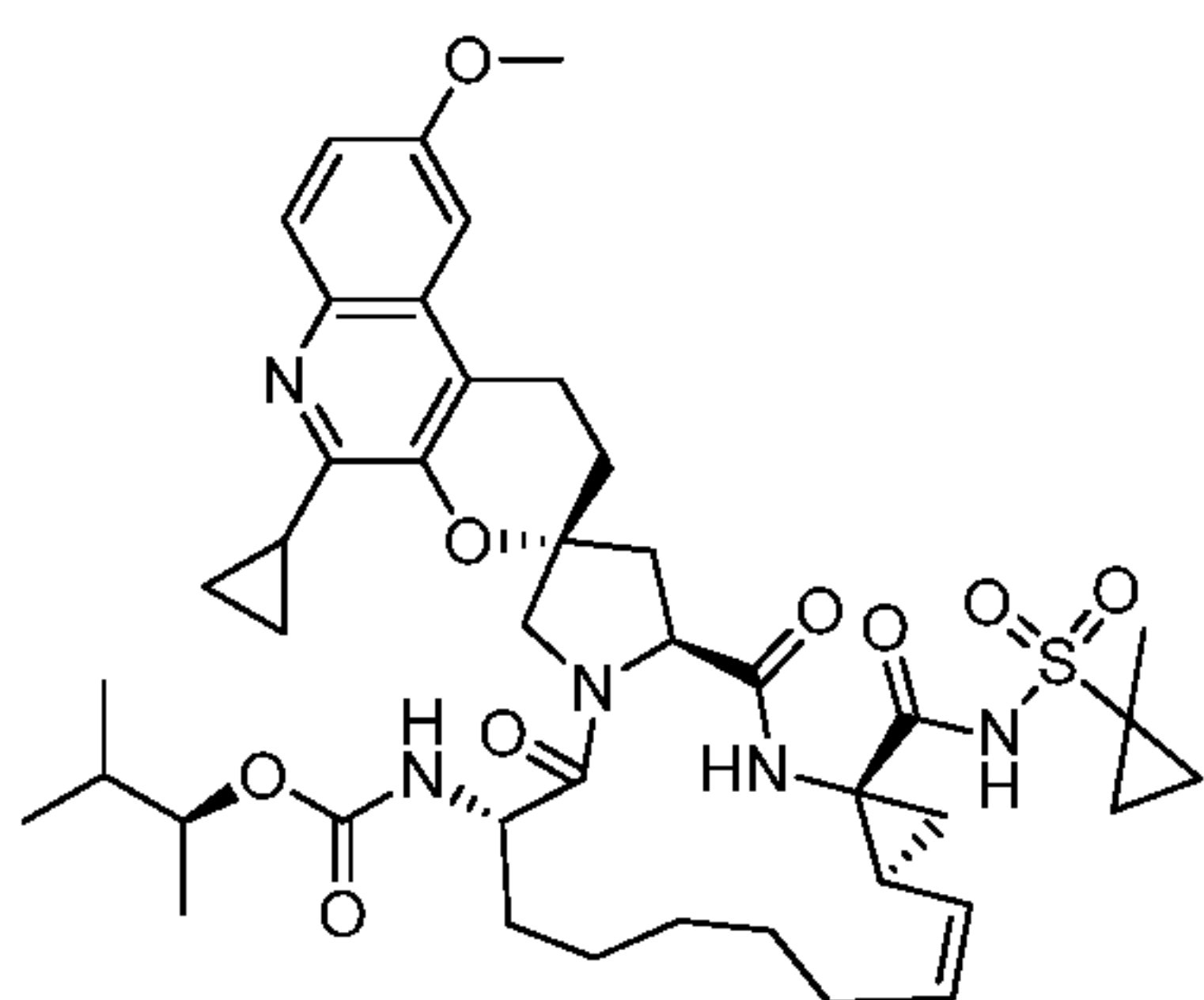
I-409



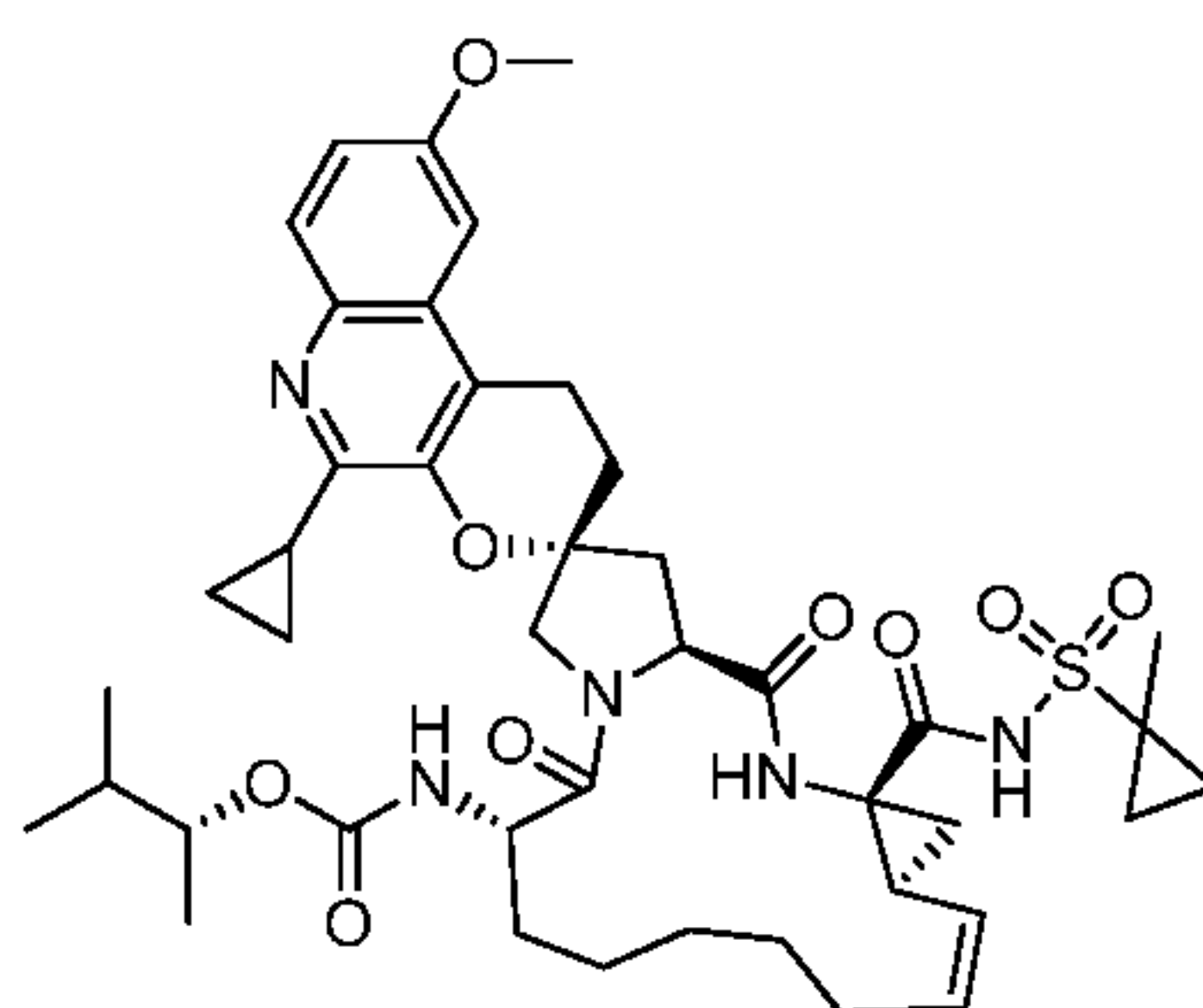
I-410



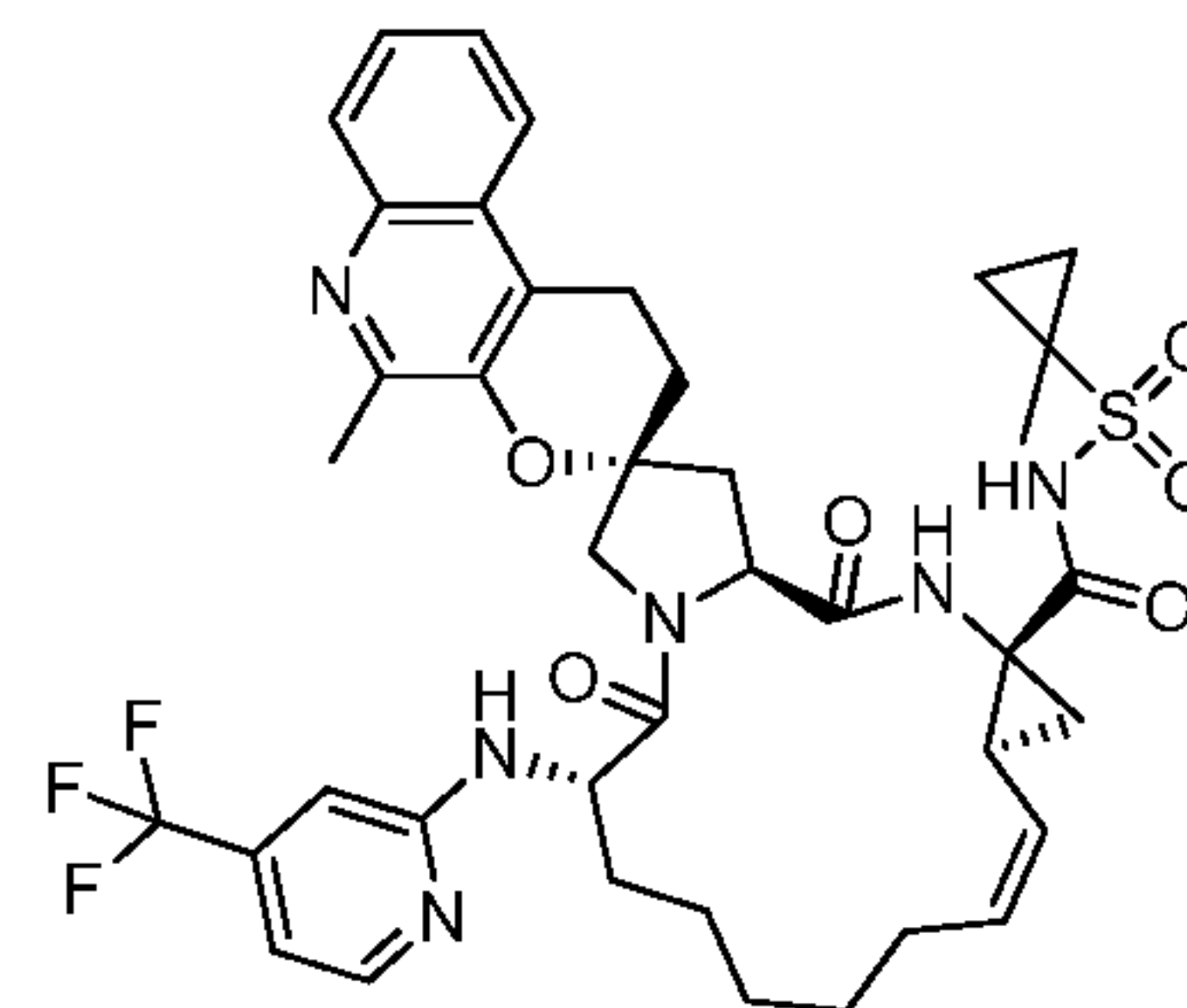
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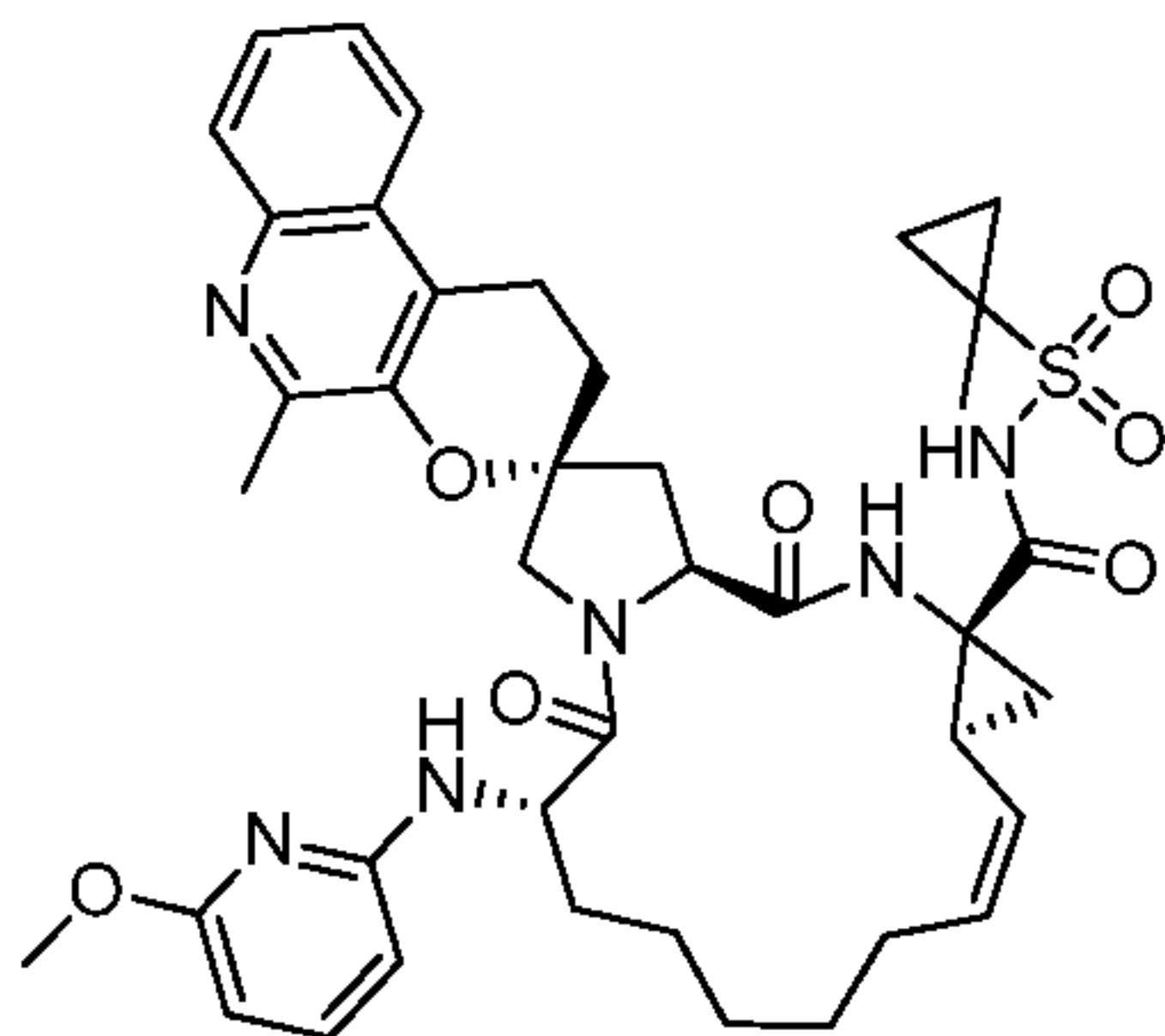
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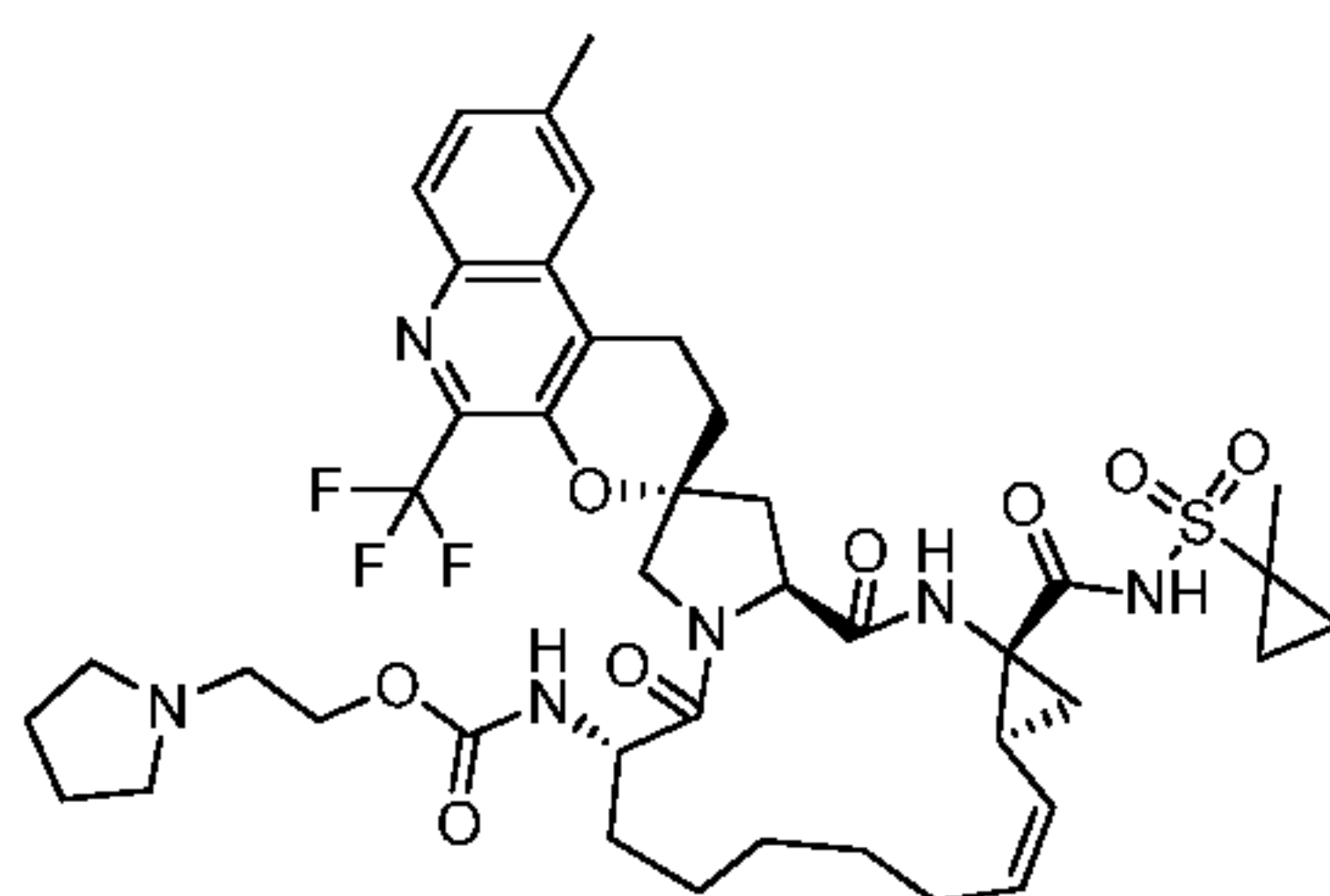
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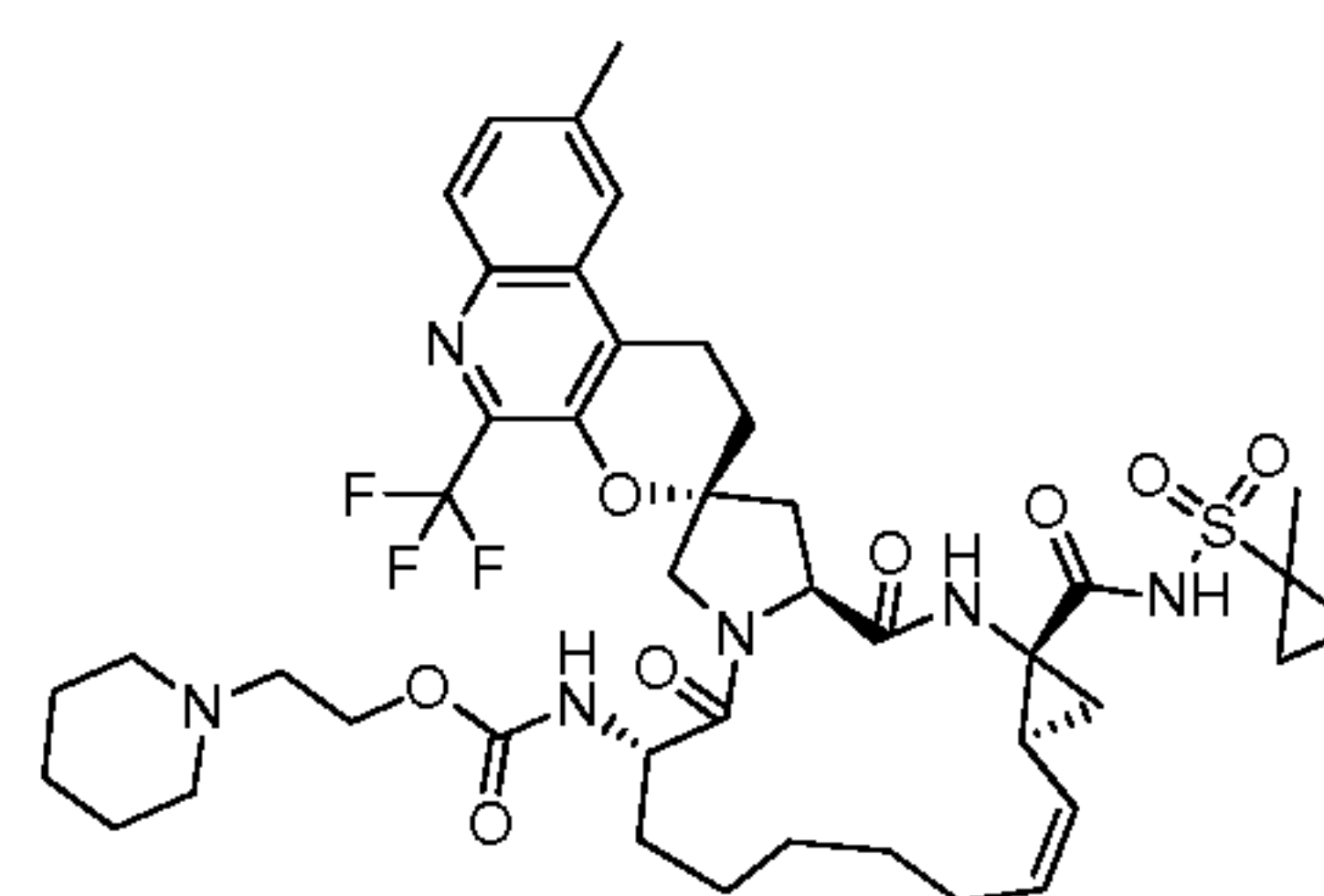
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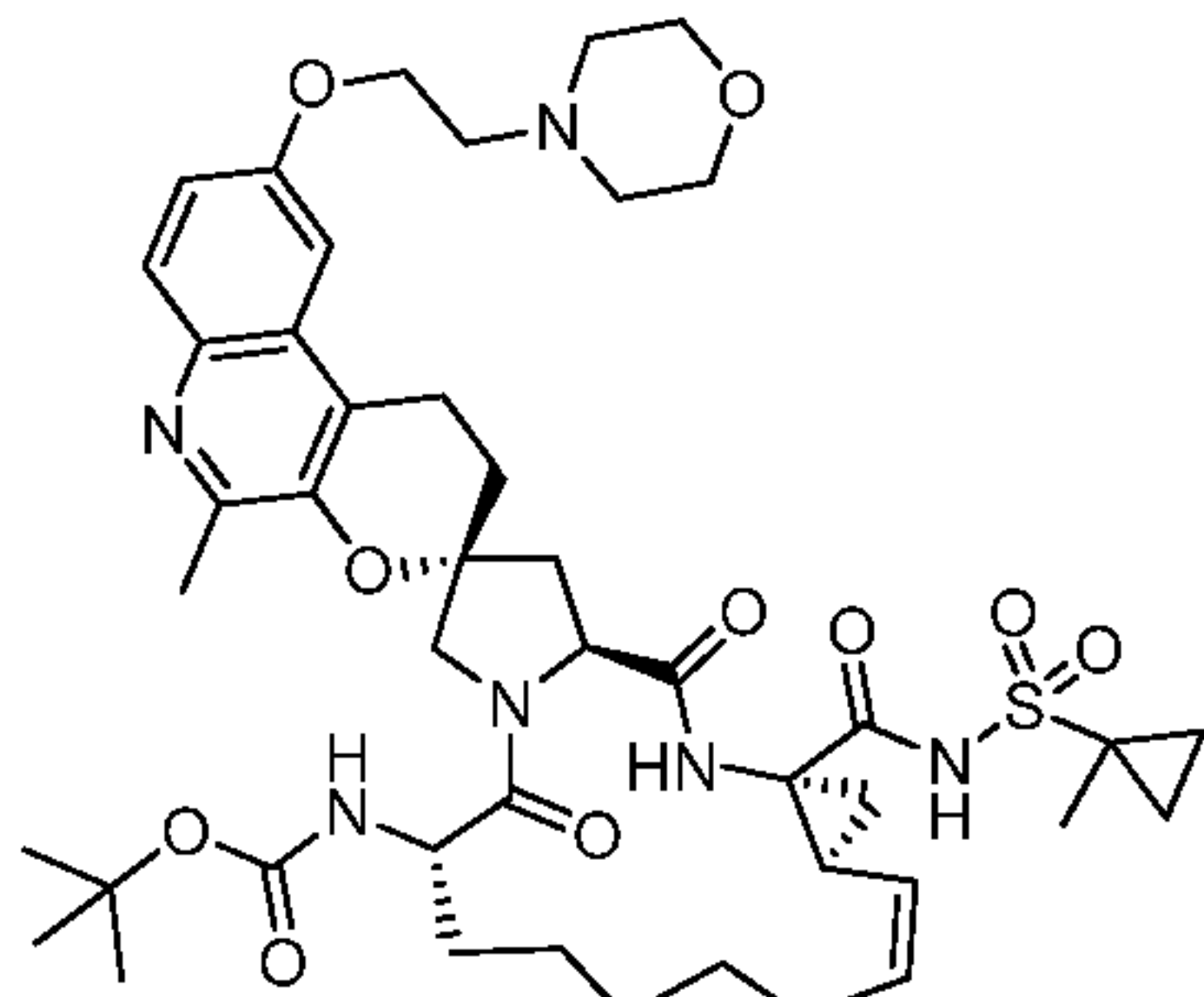
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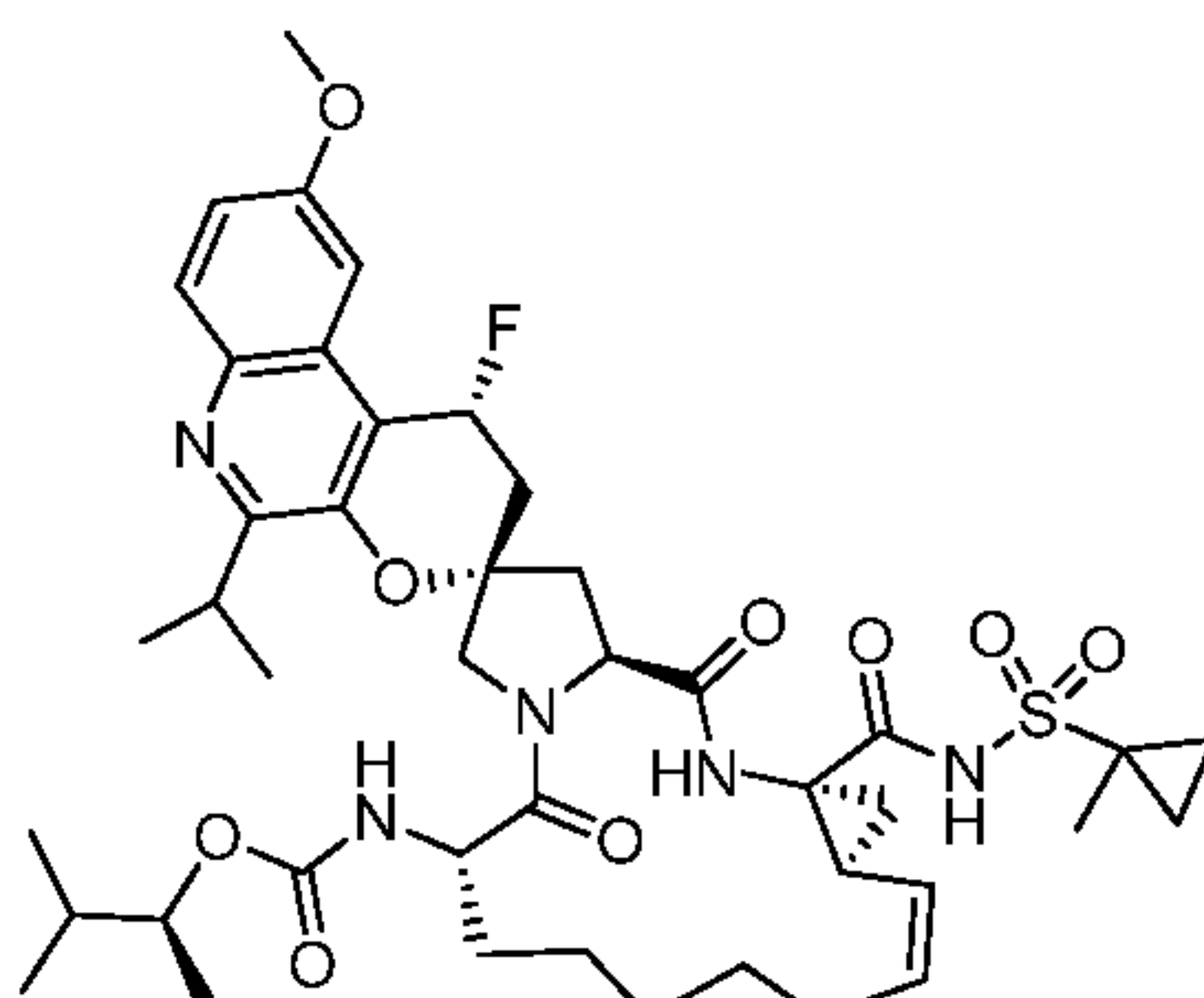
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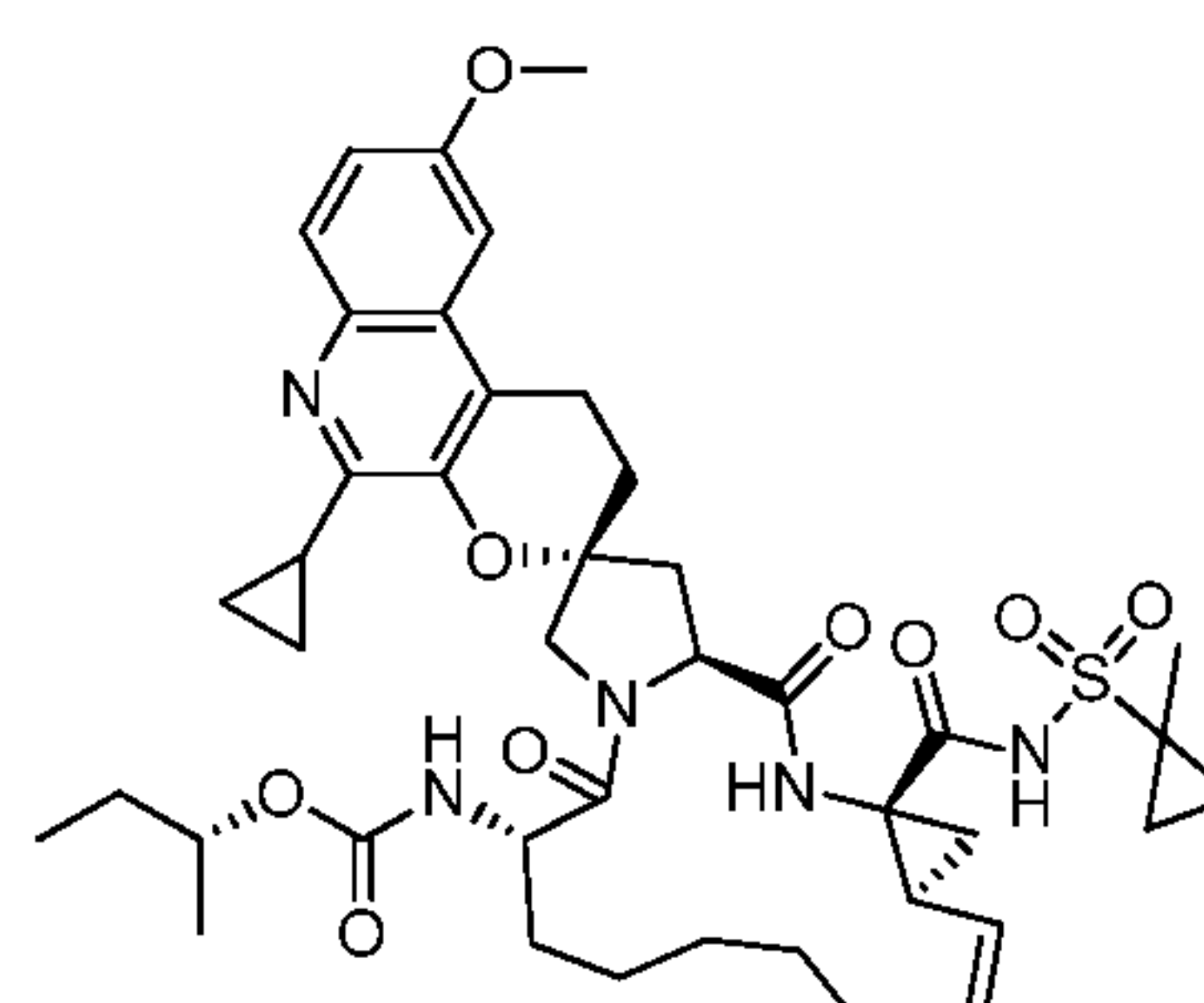
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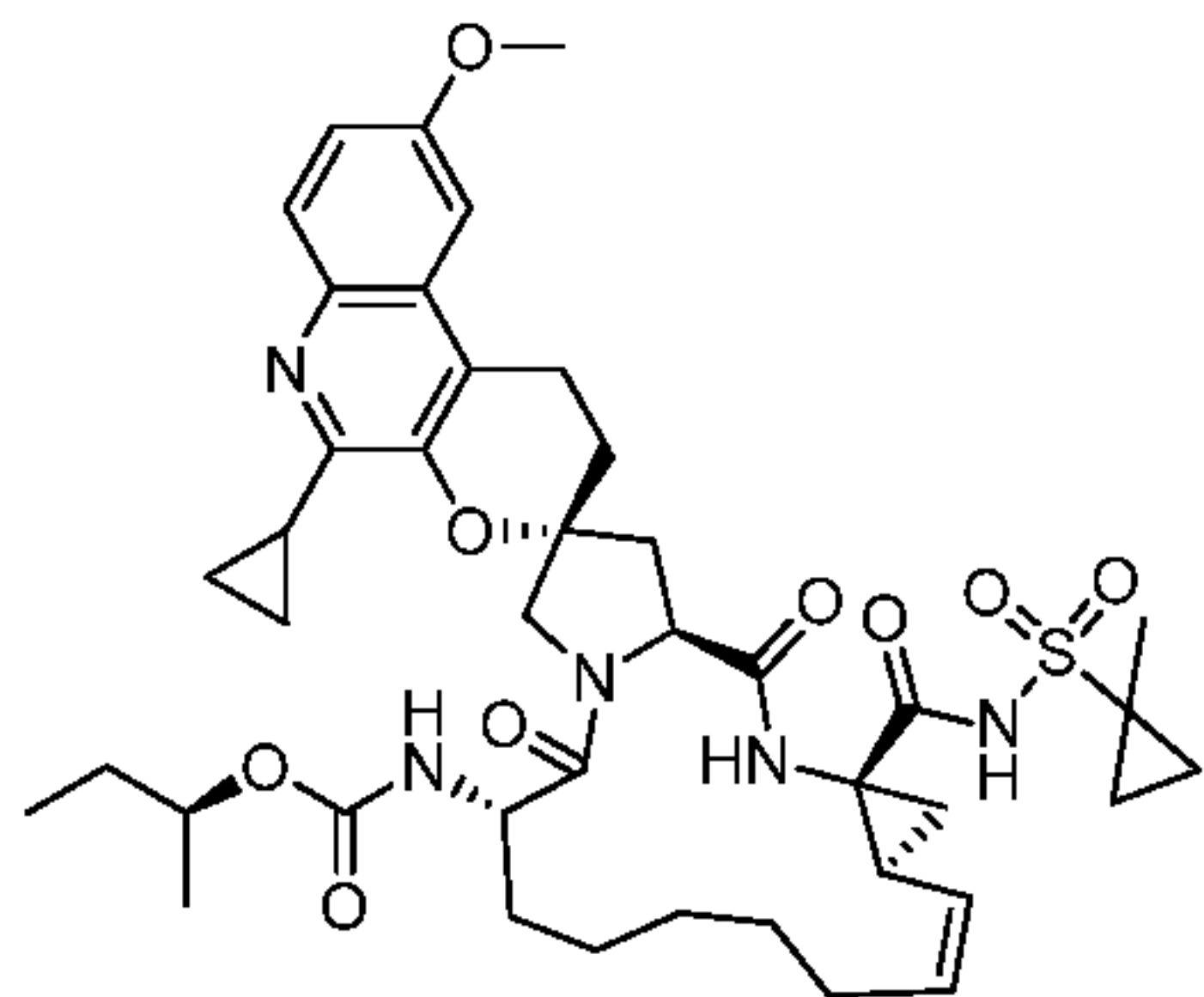
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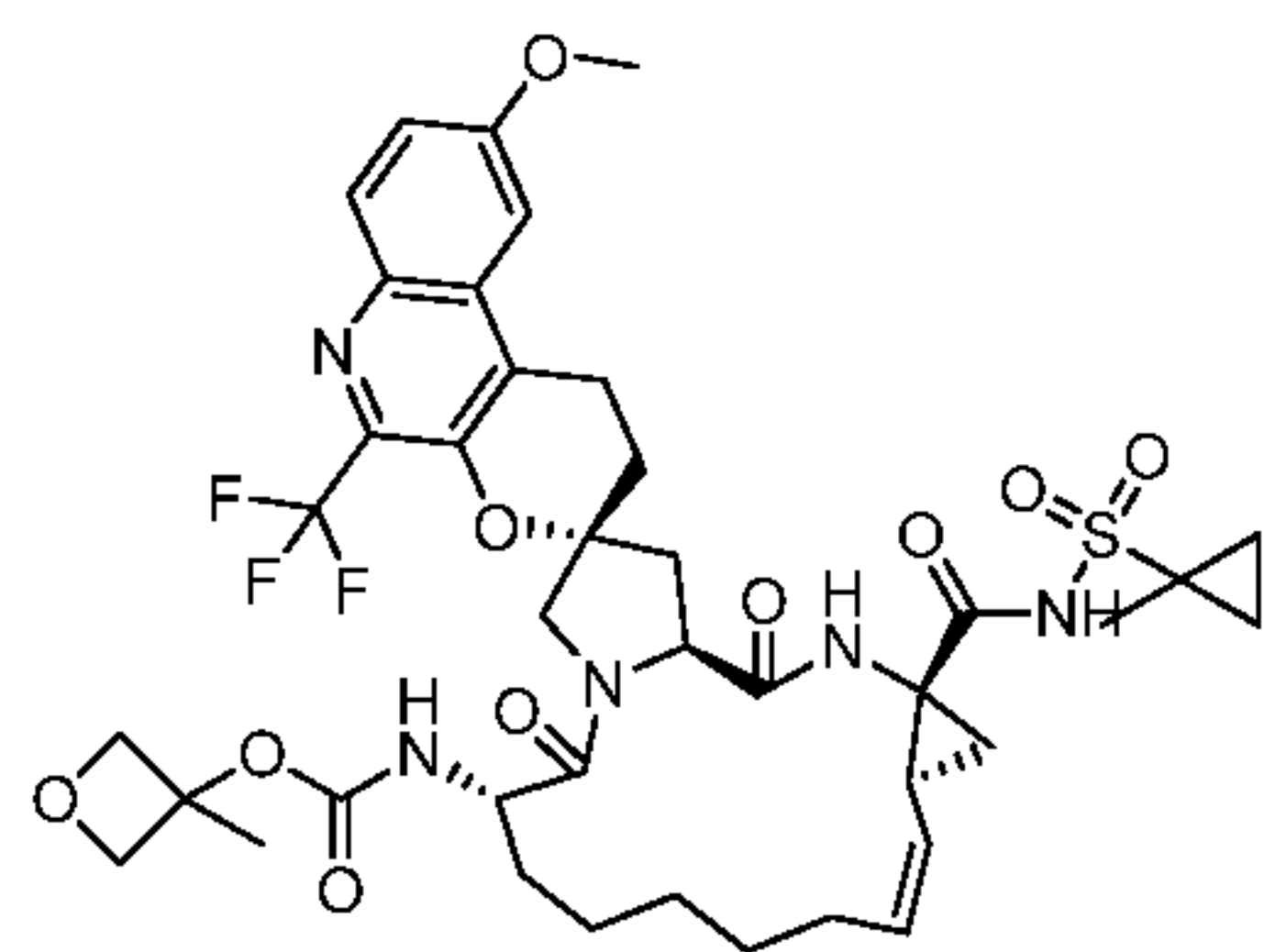
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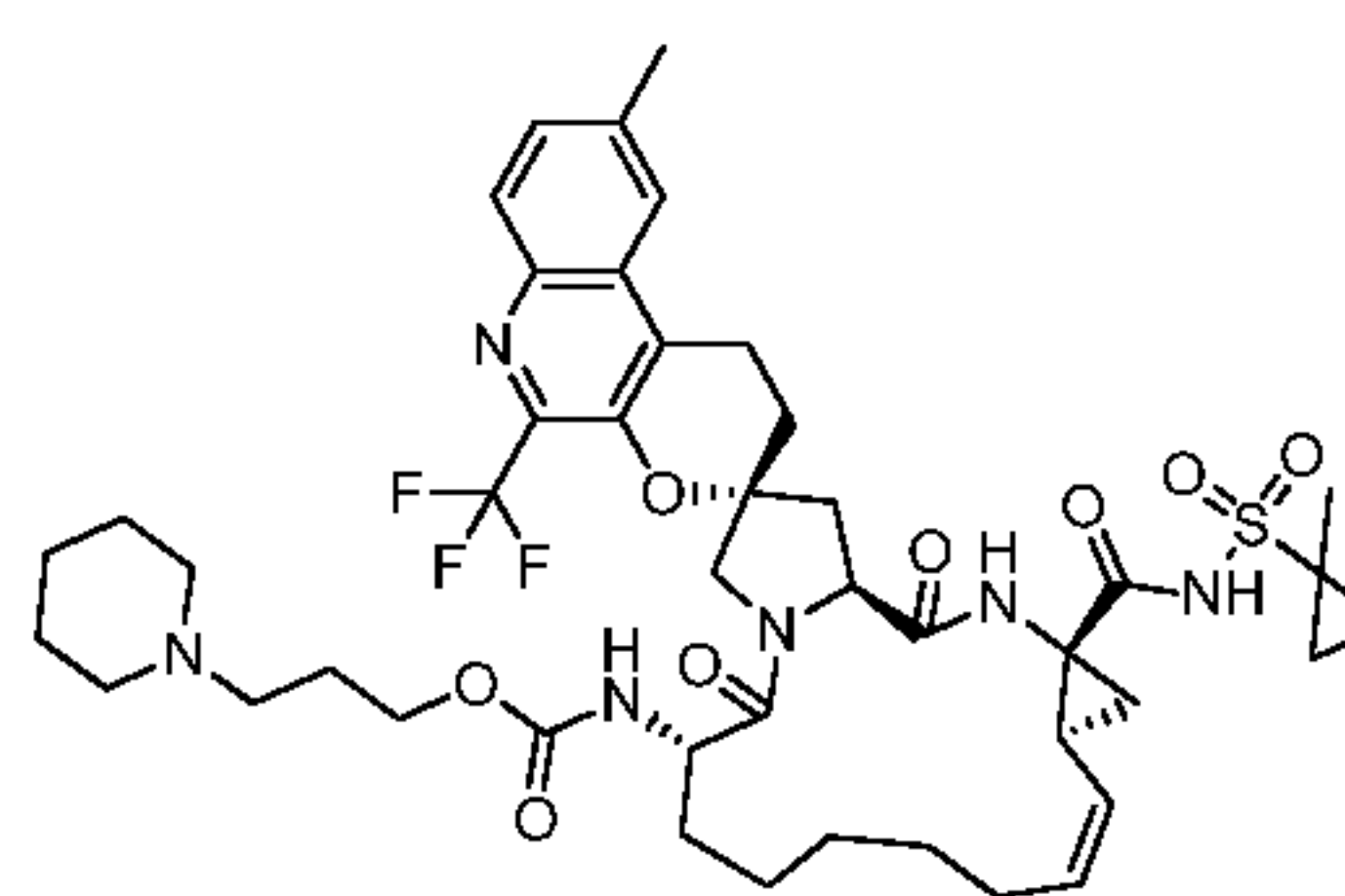
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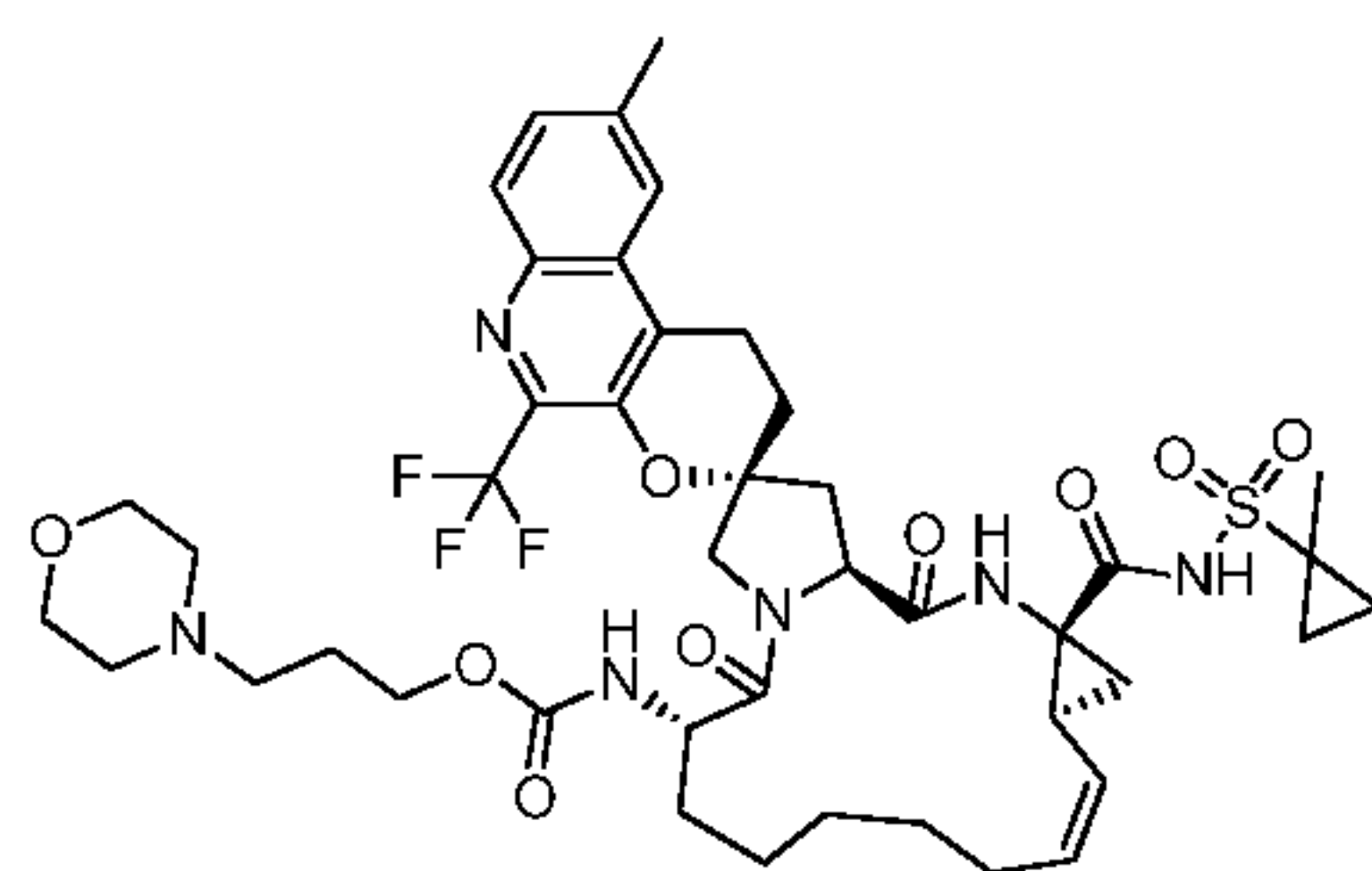
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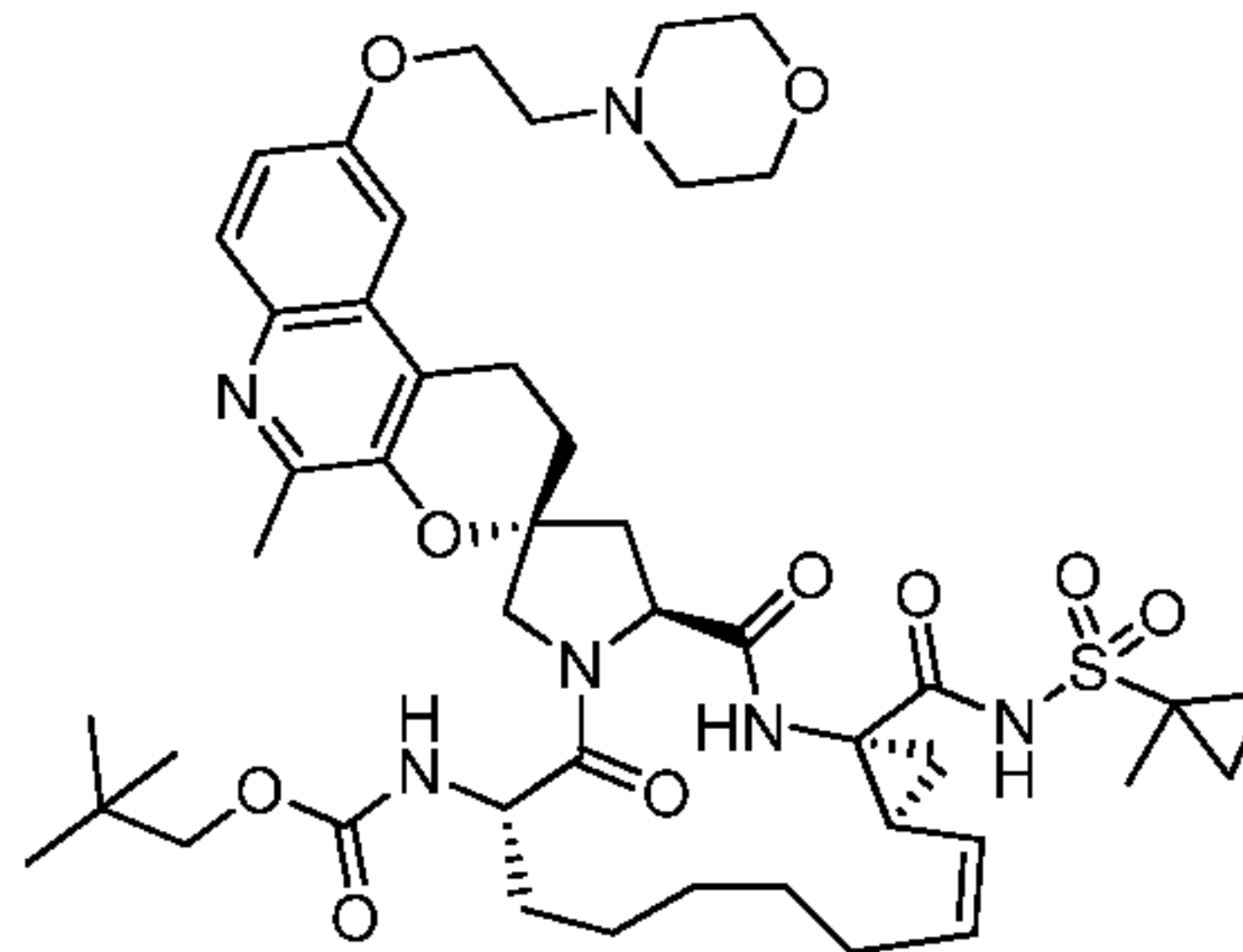
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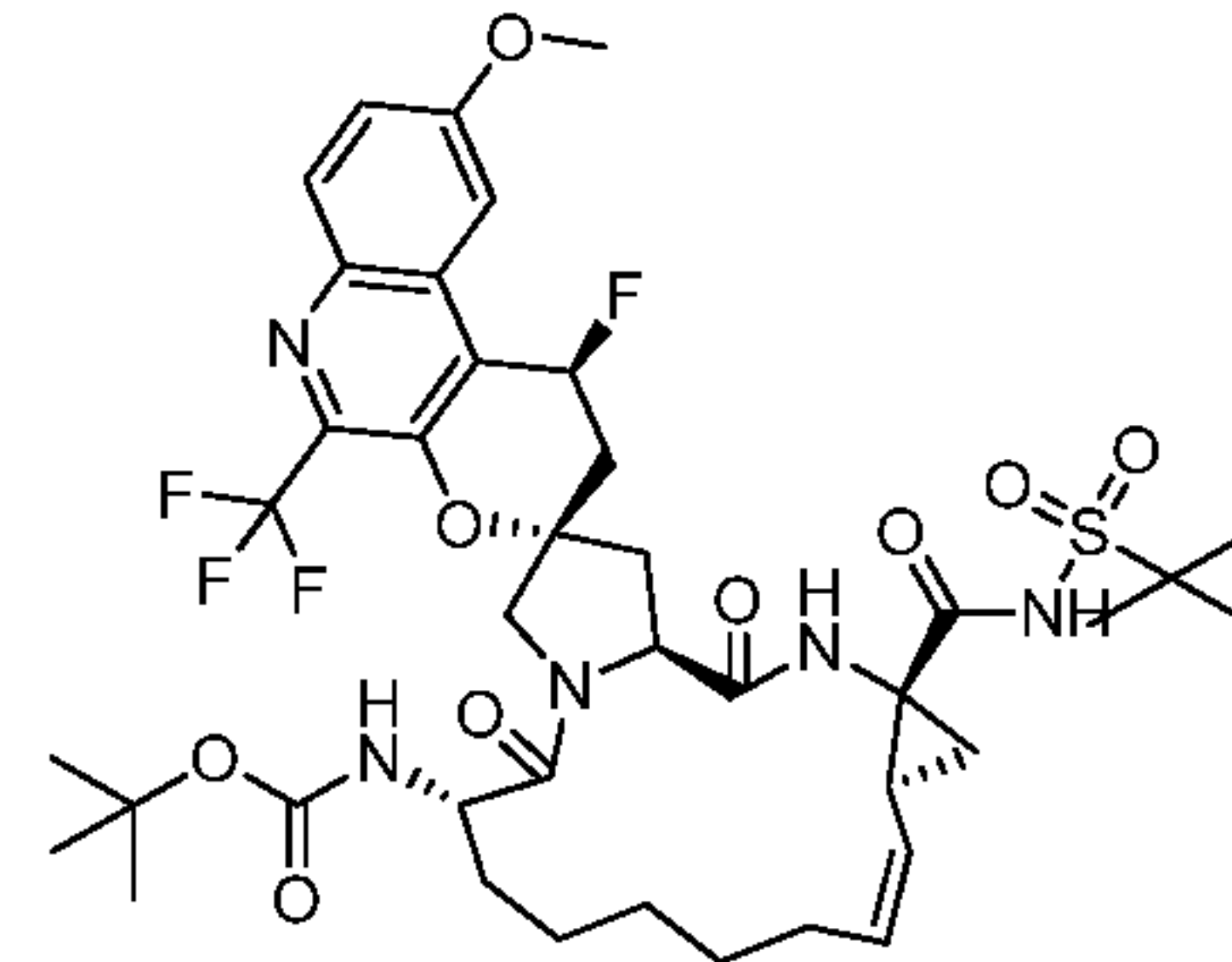
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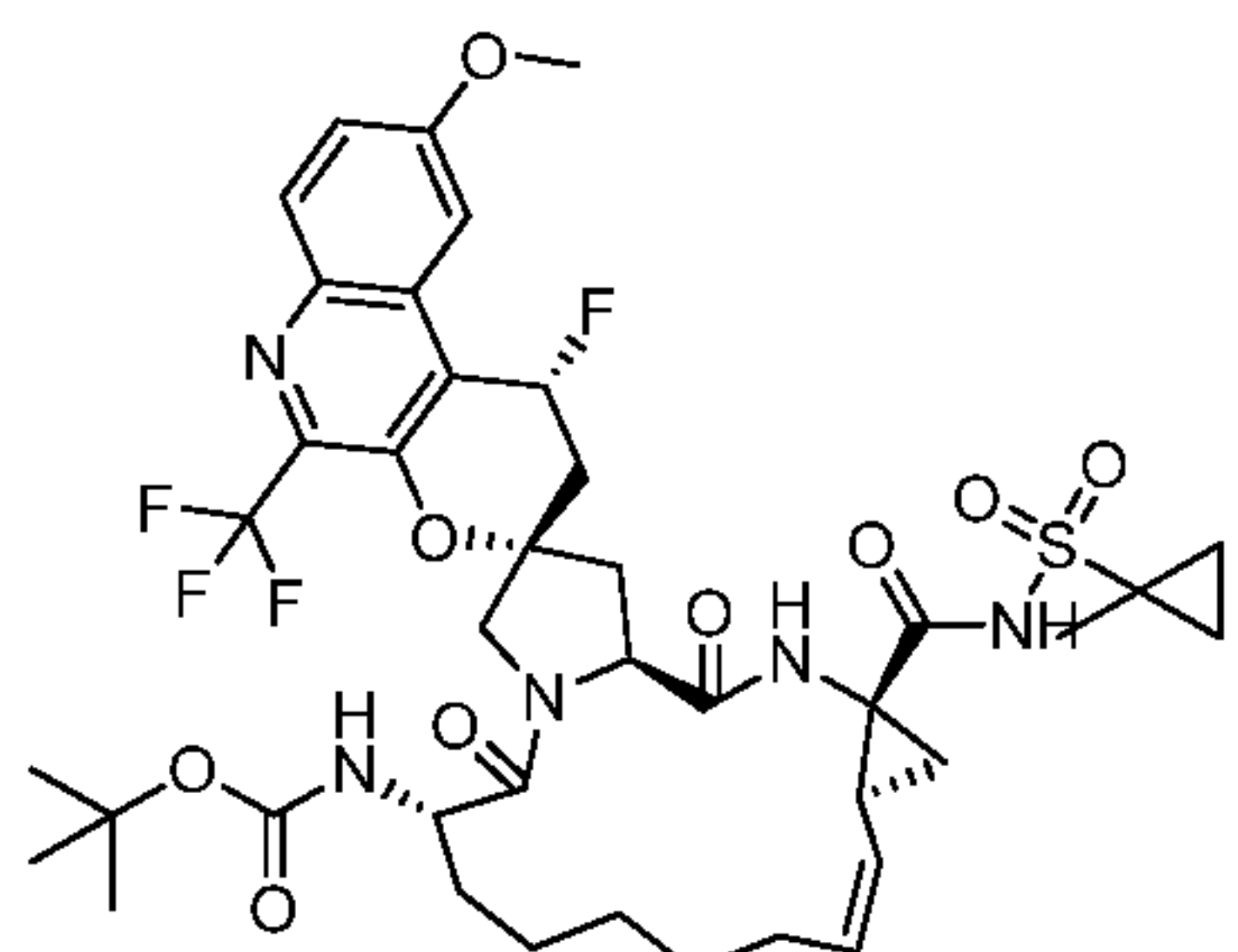
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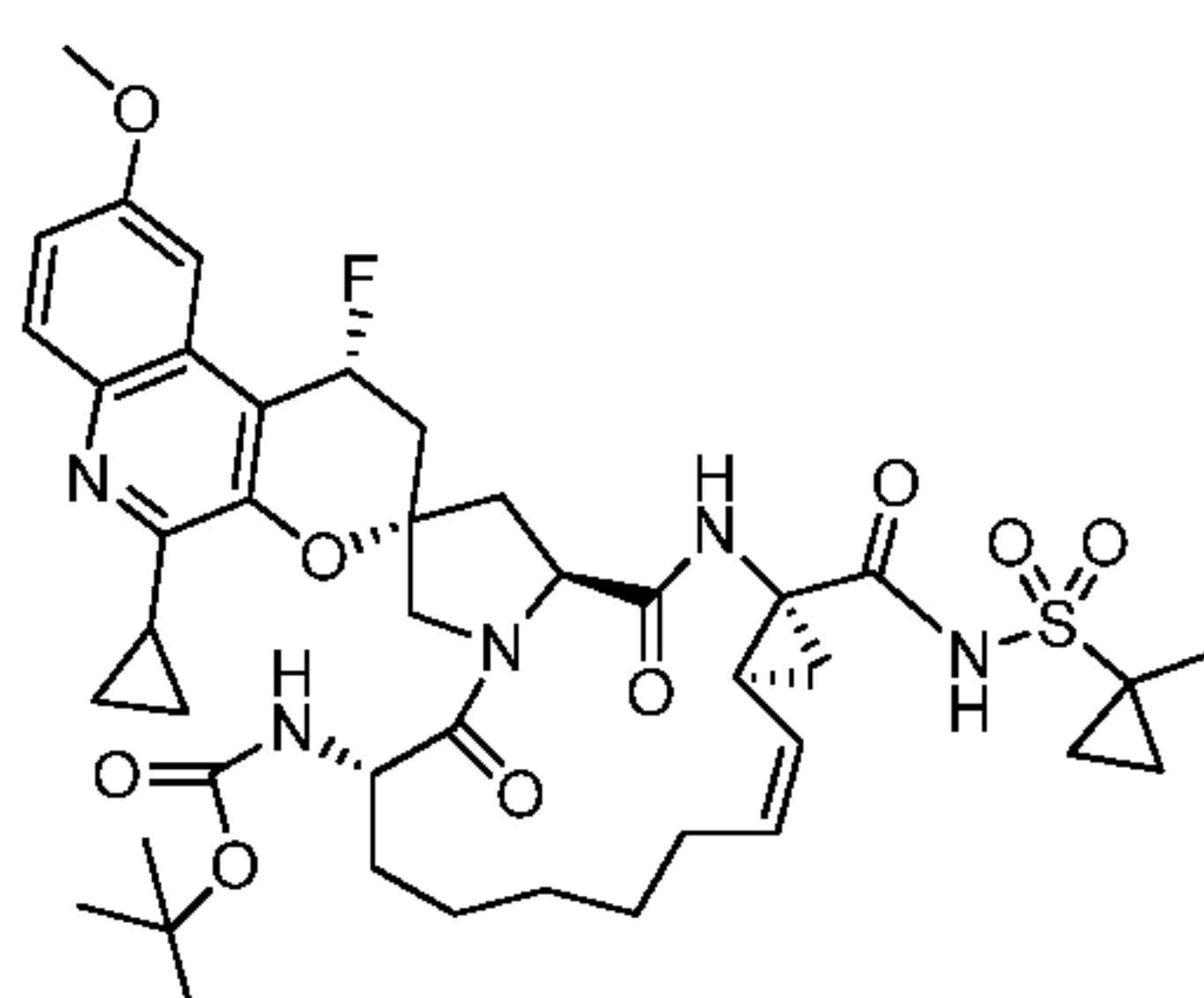
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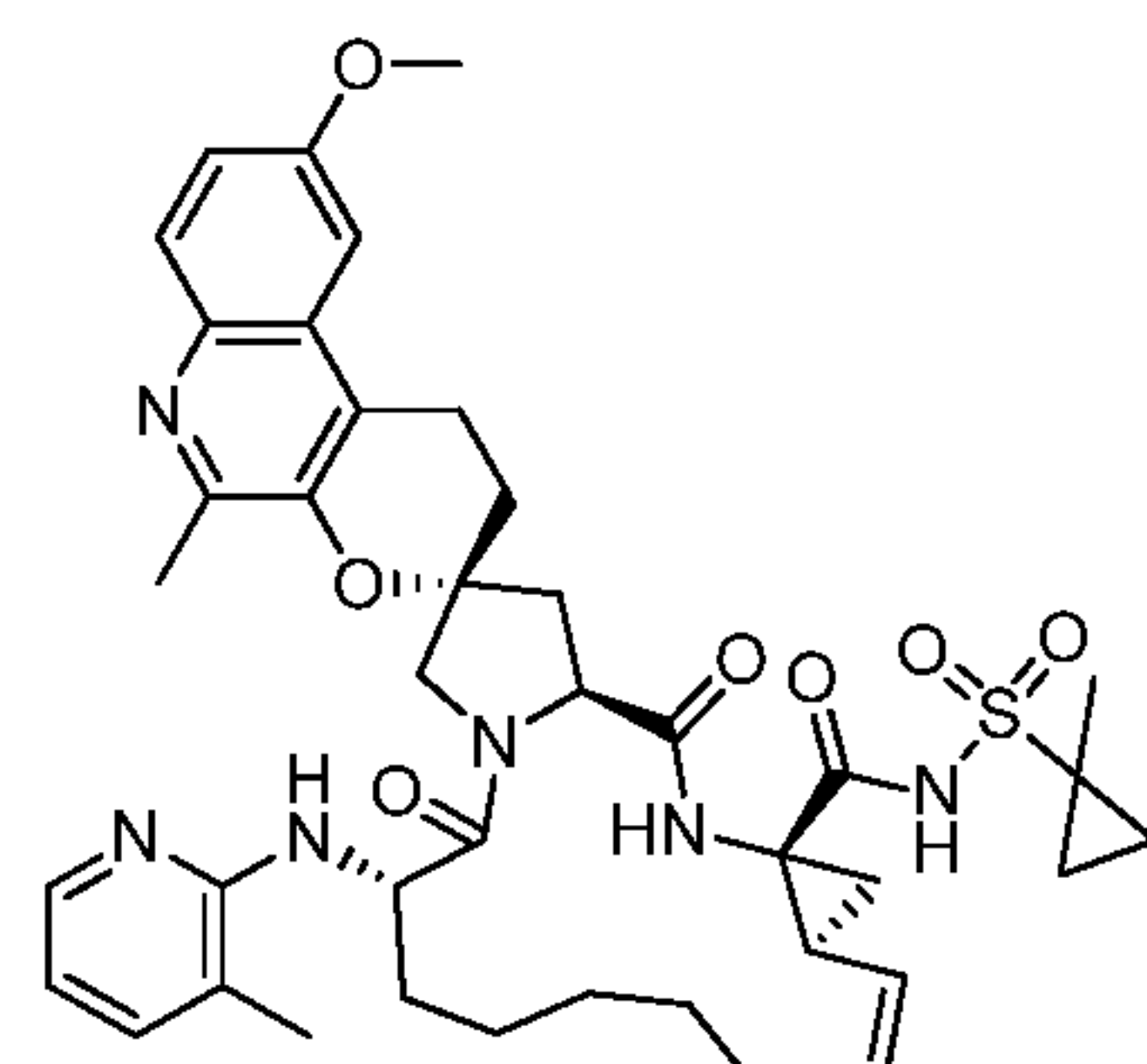
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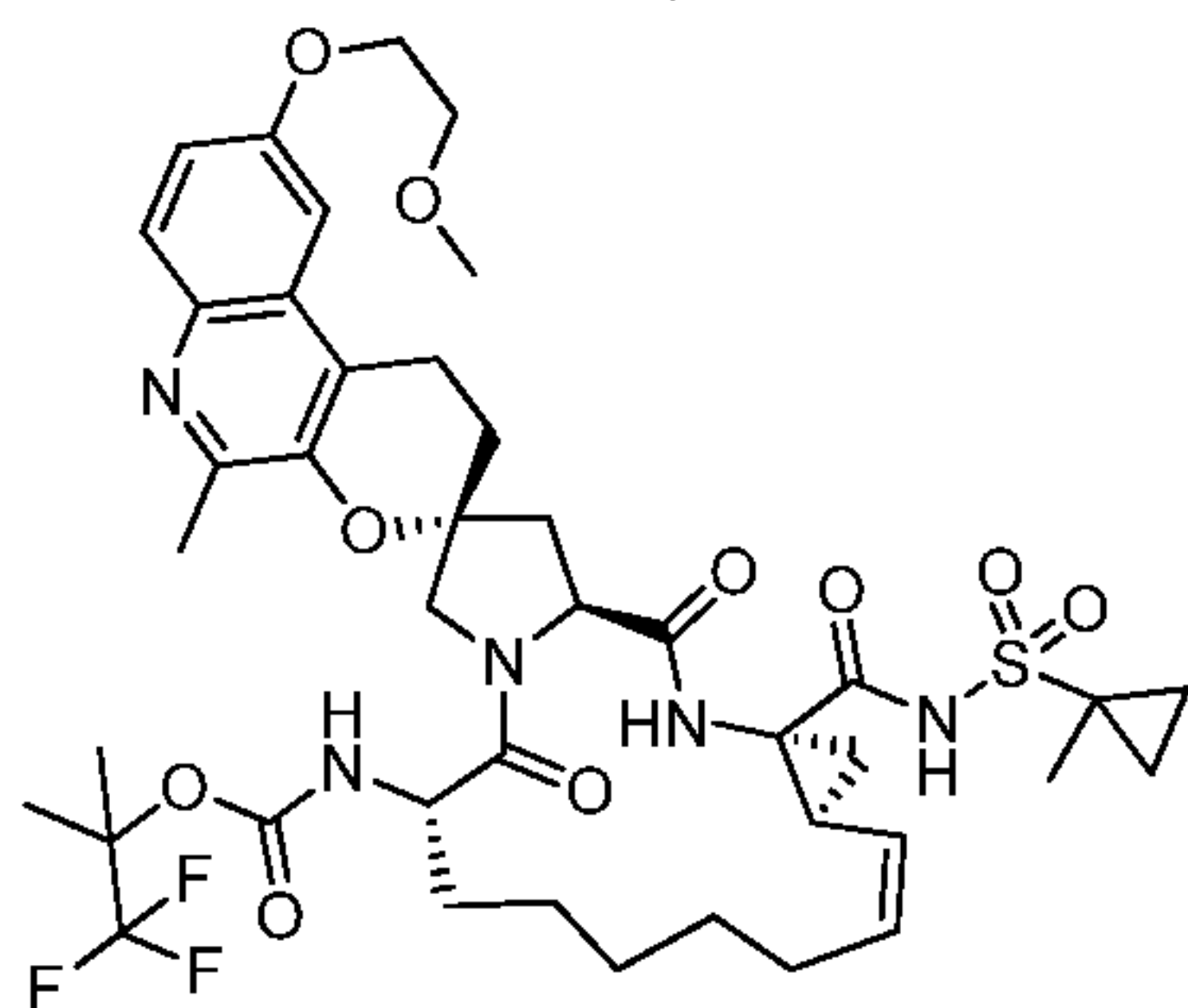
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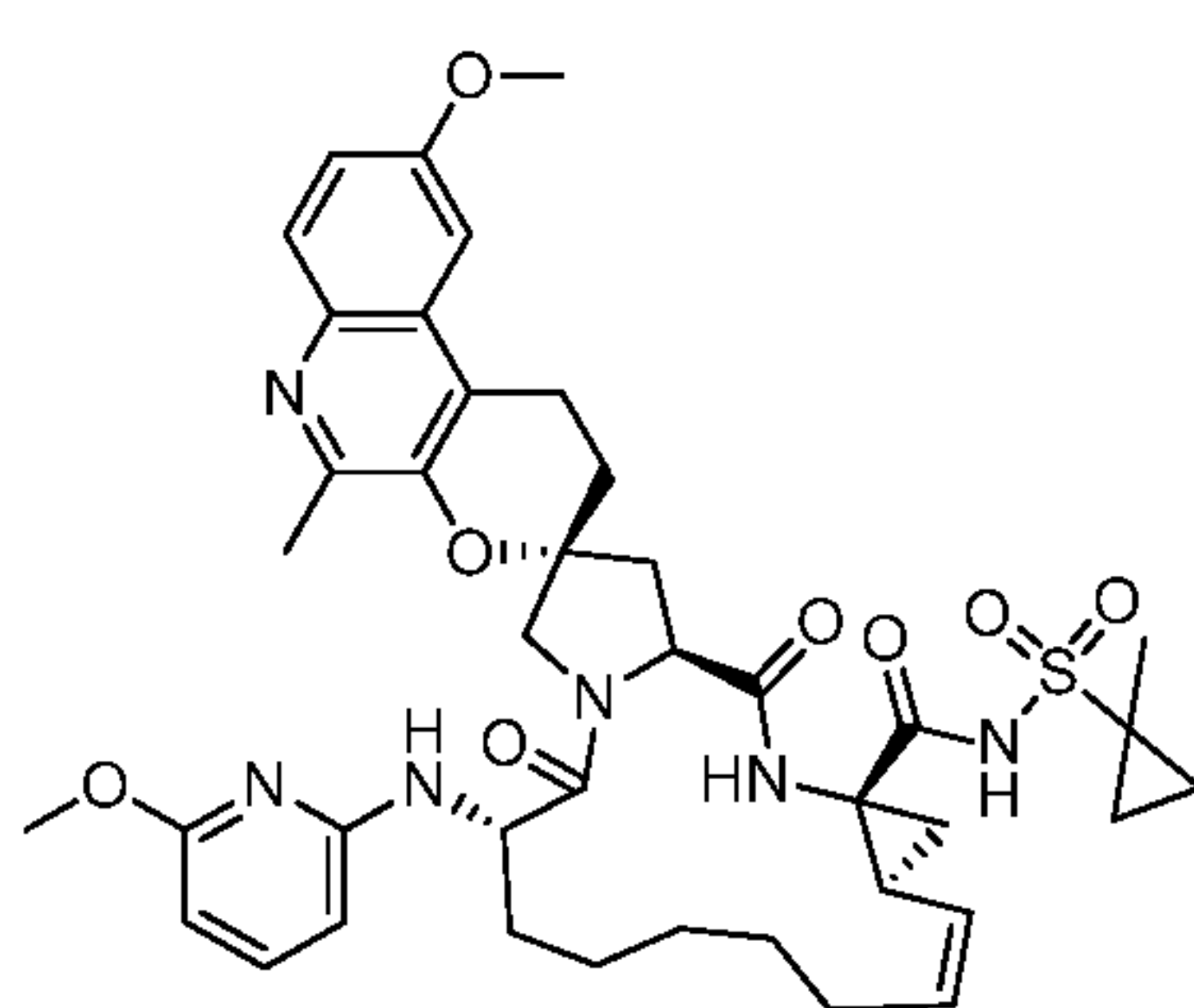
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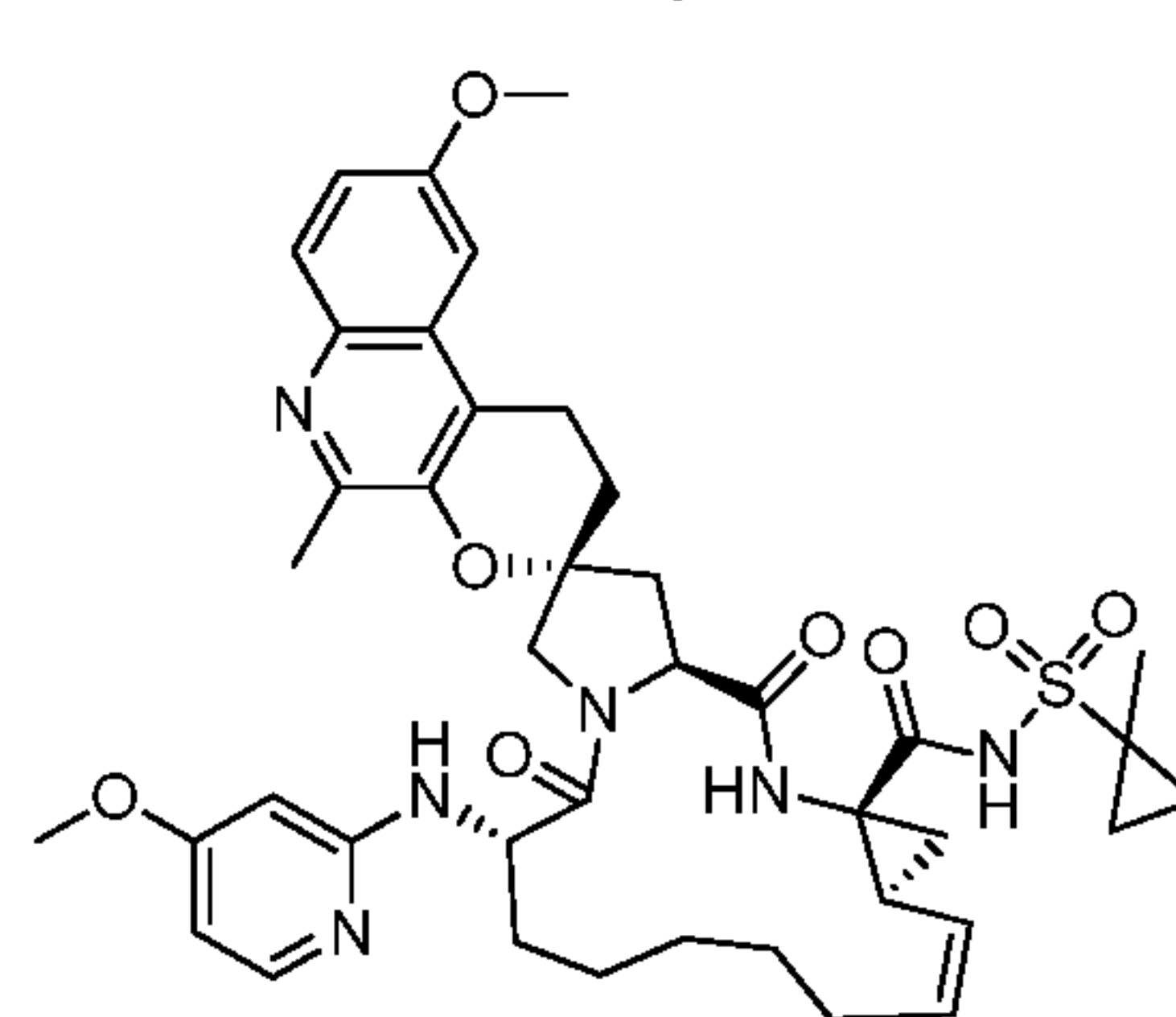
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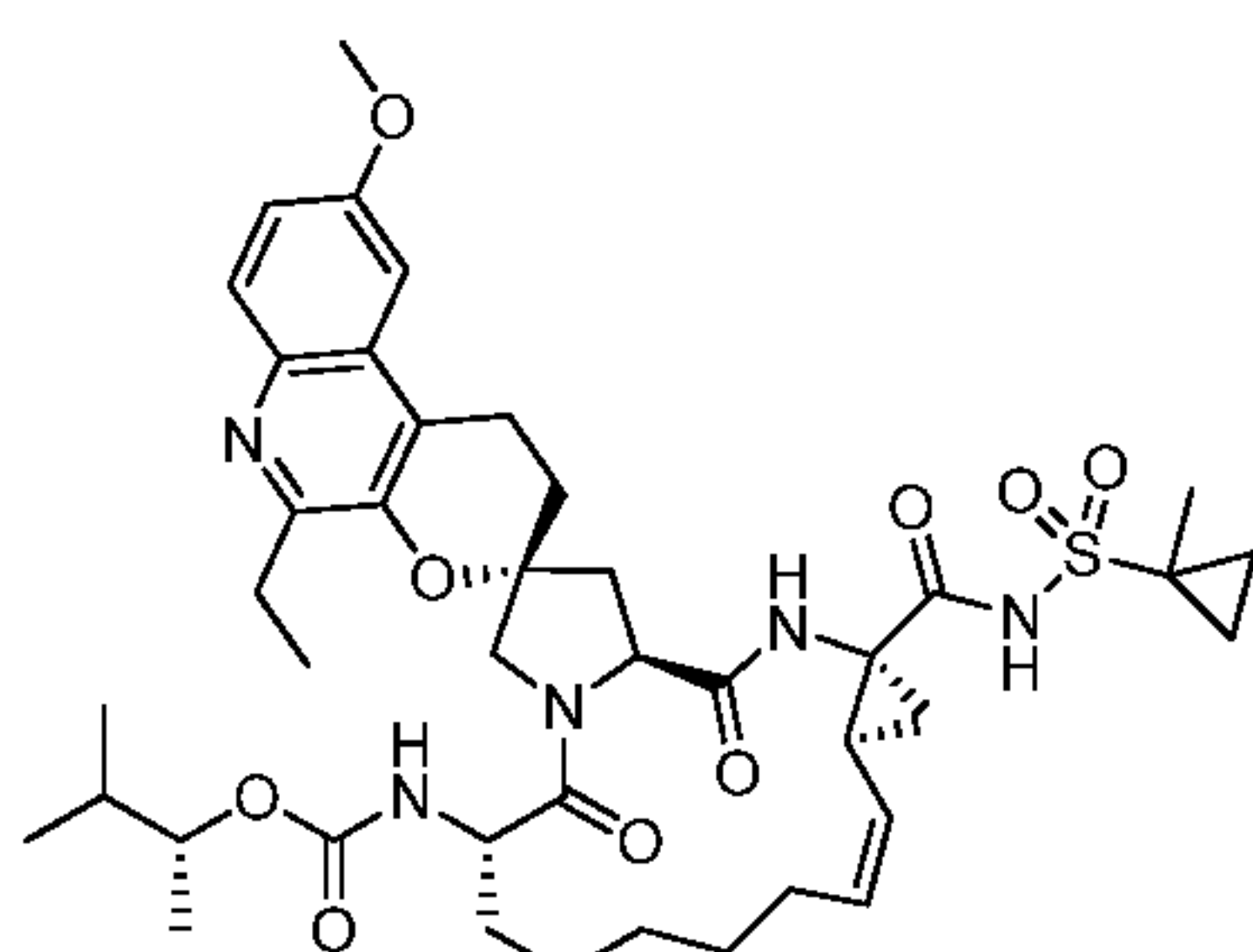
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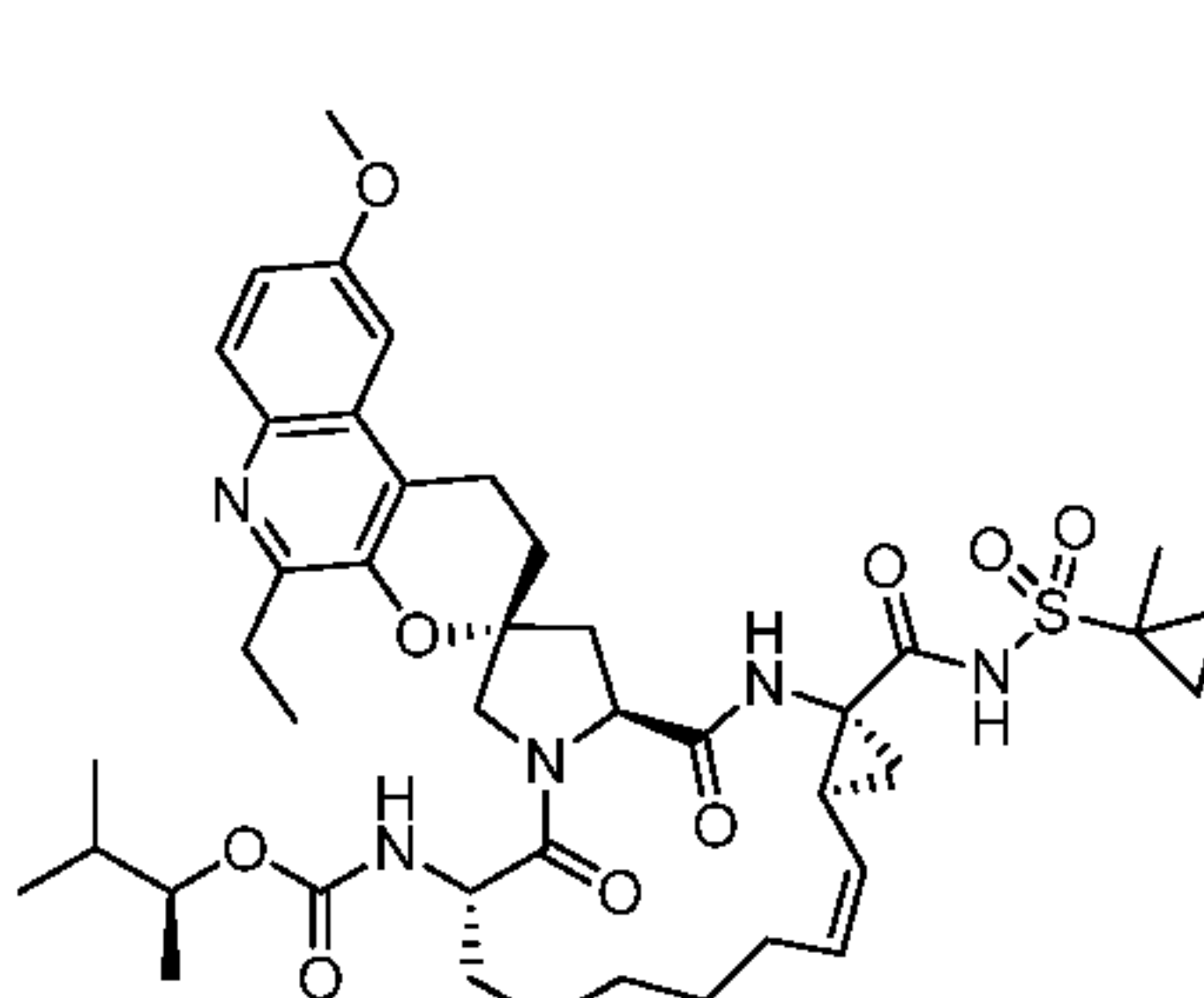
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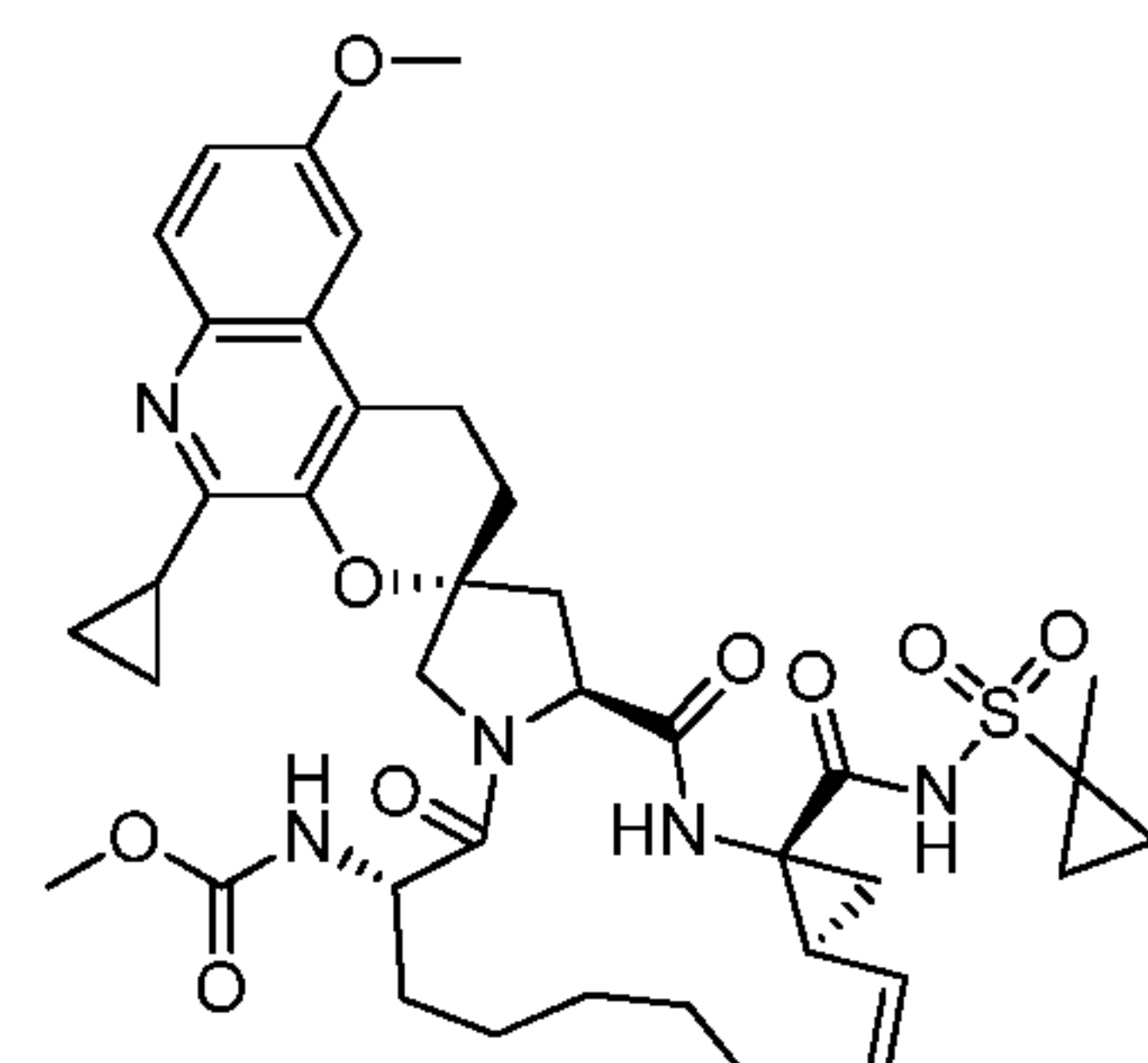
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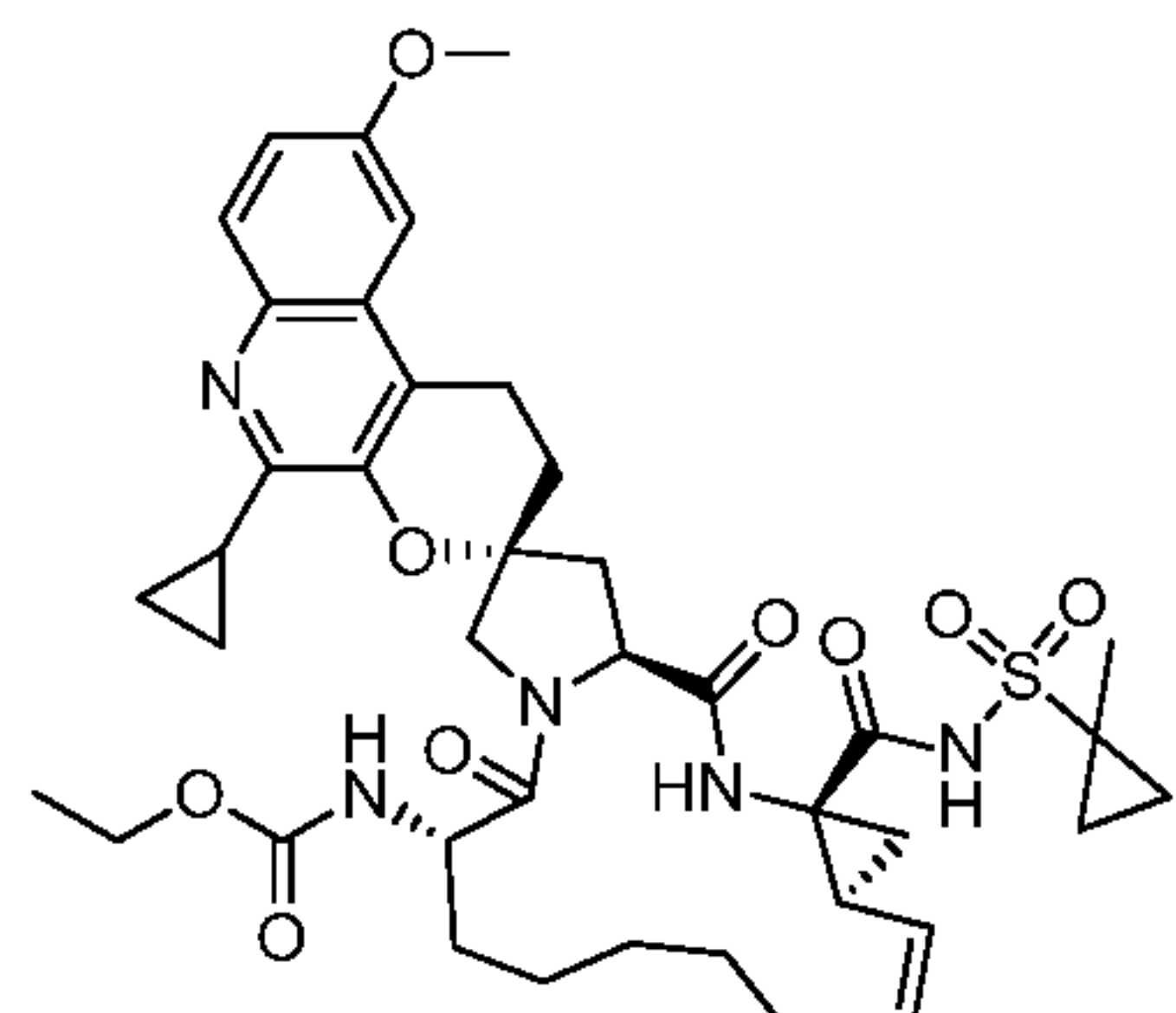
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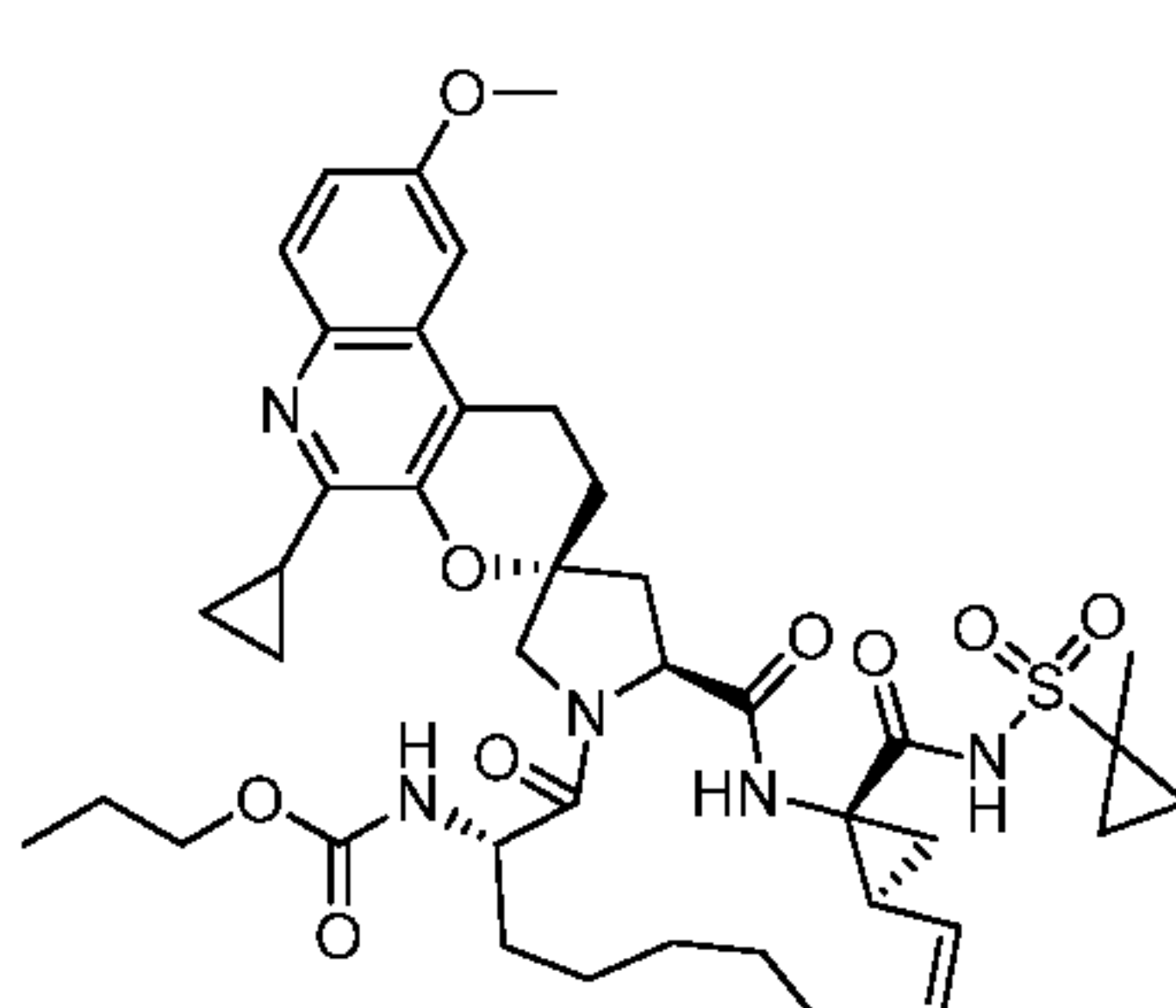
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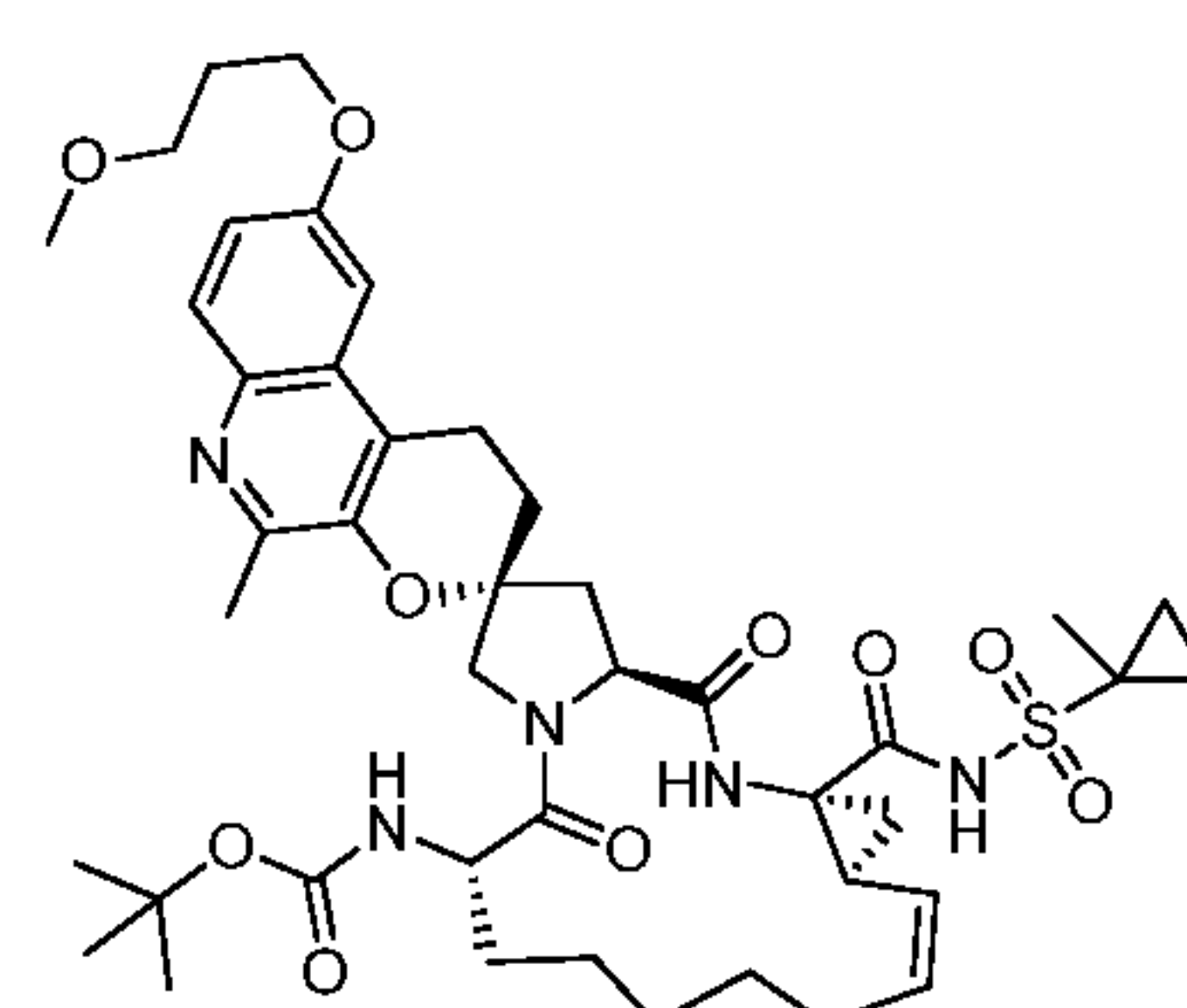
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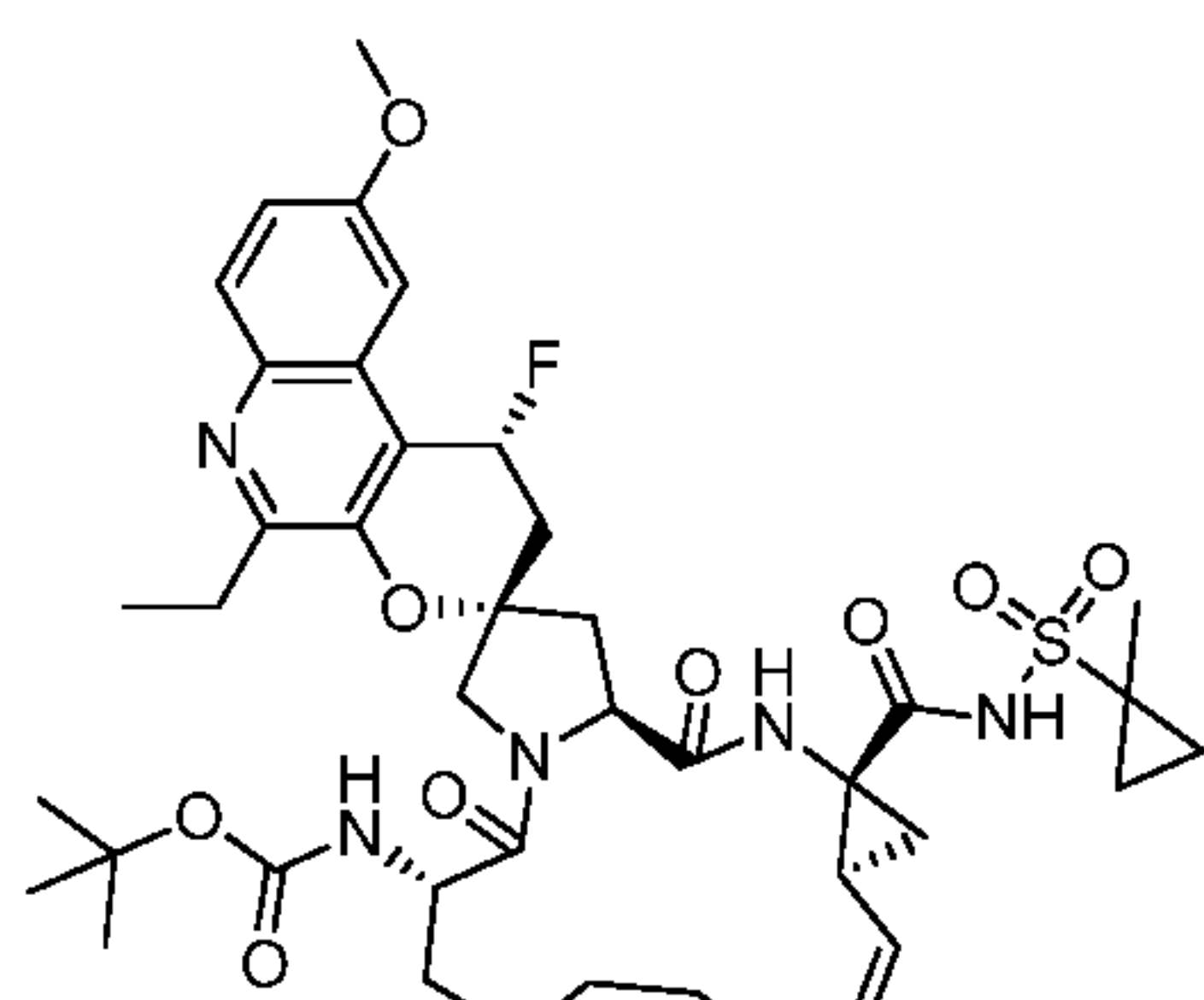
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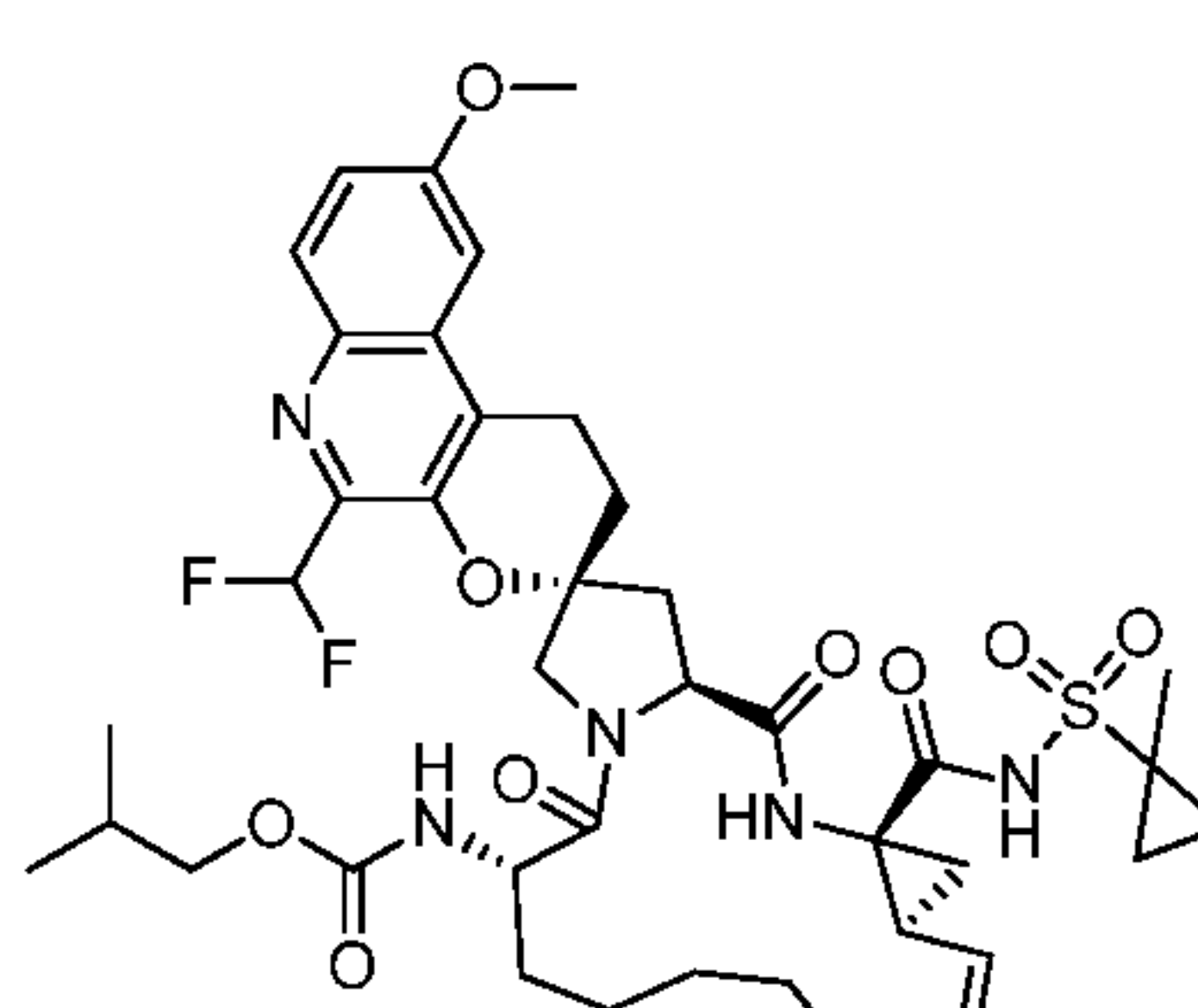
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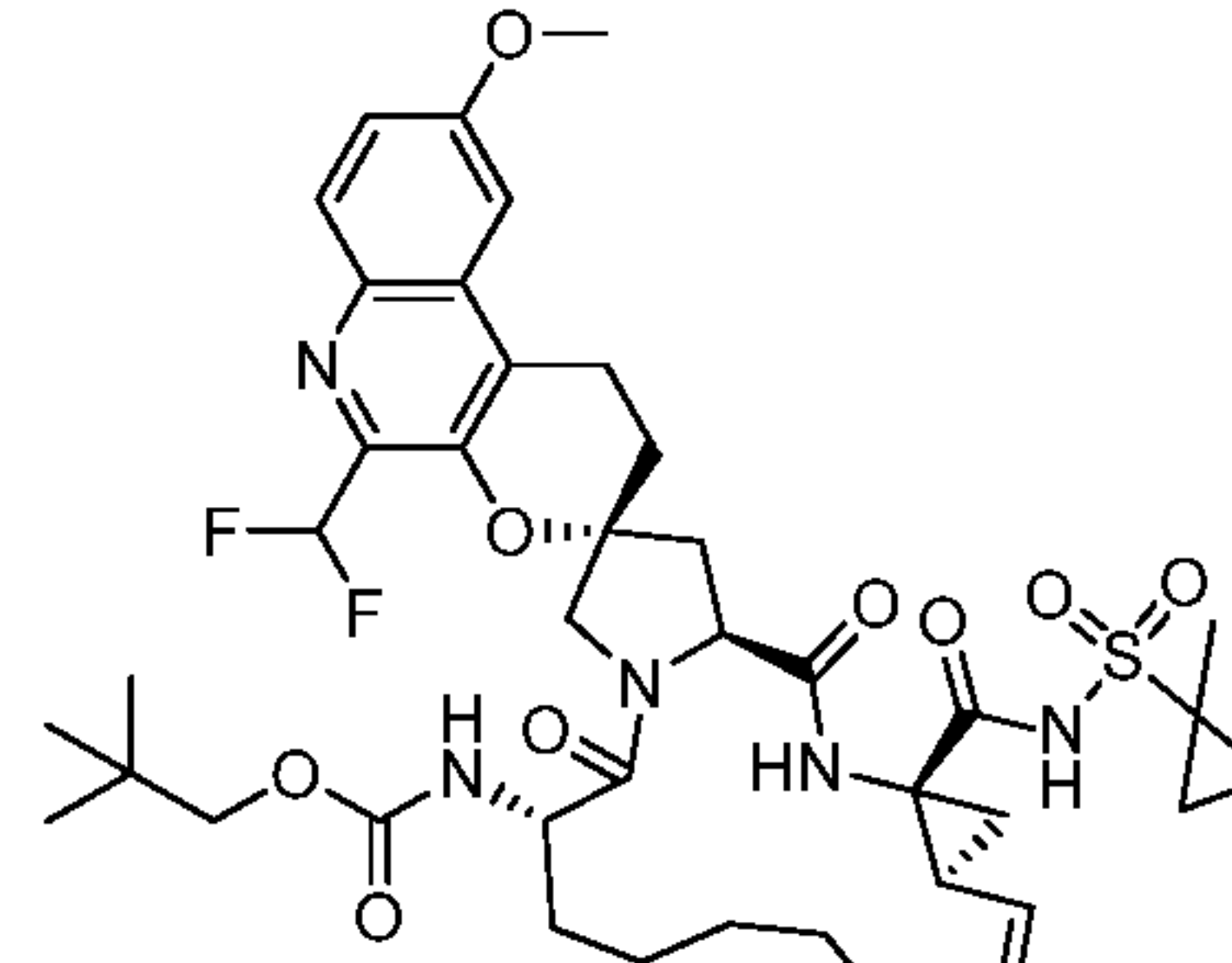
I-438



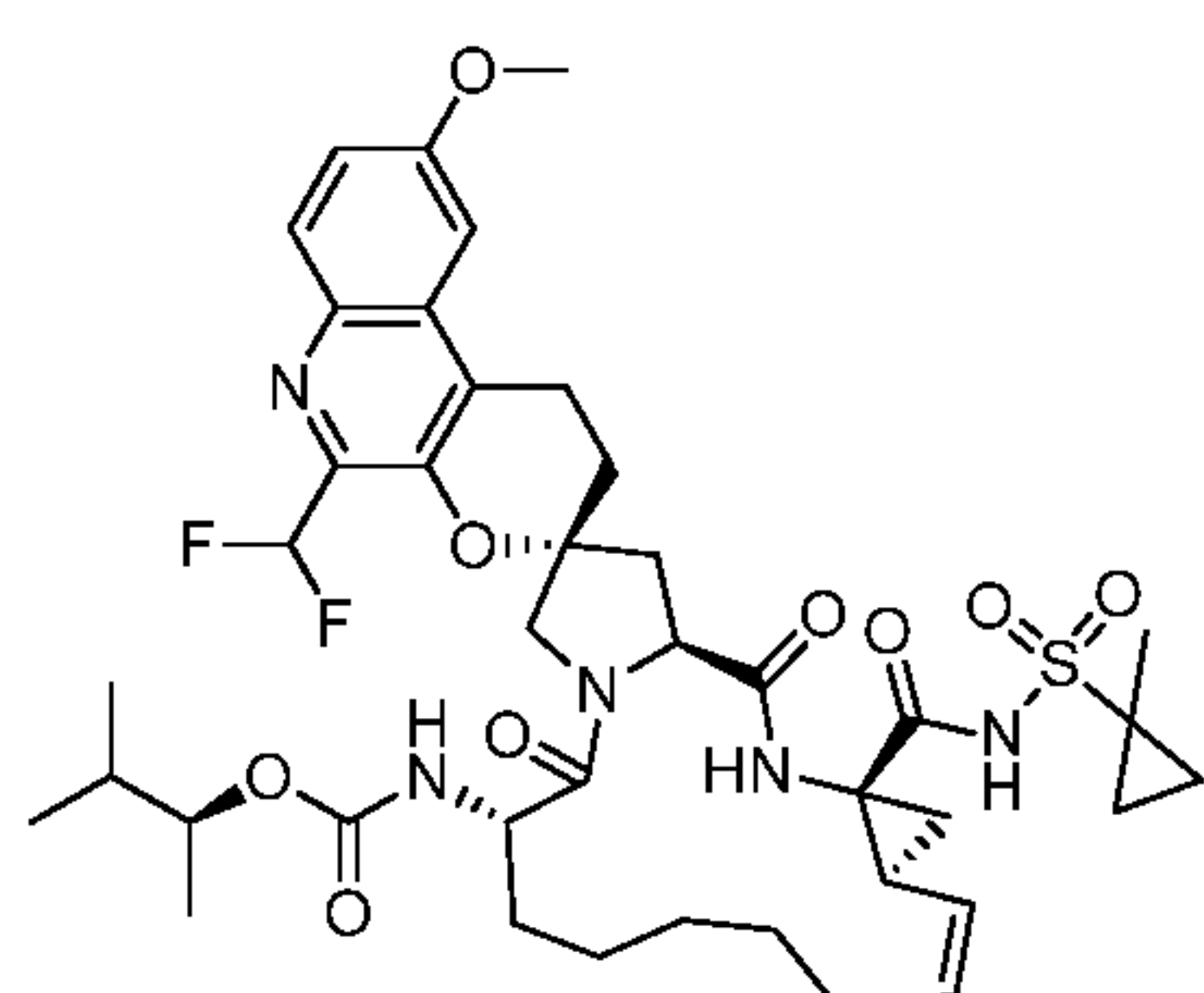
I-439



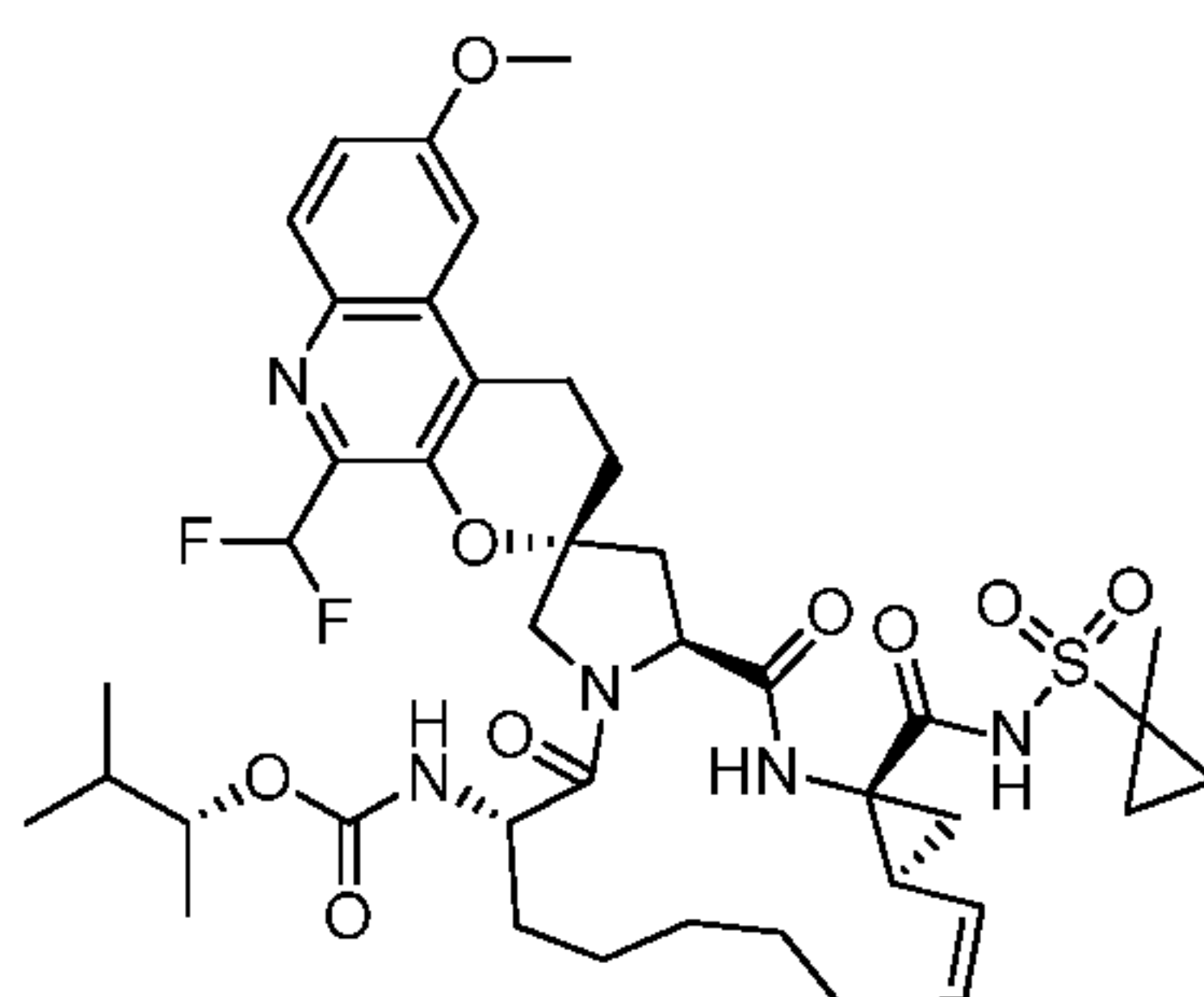
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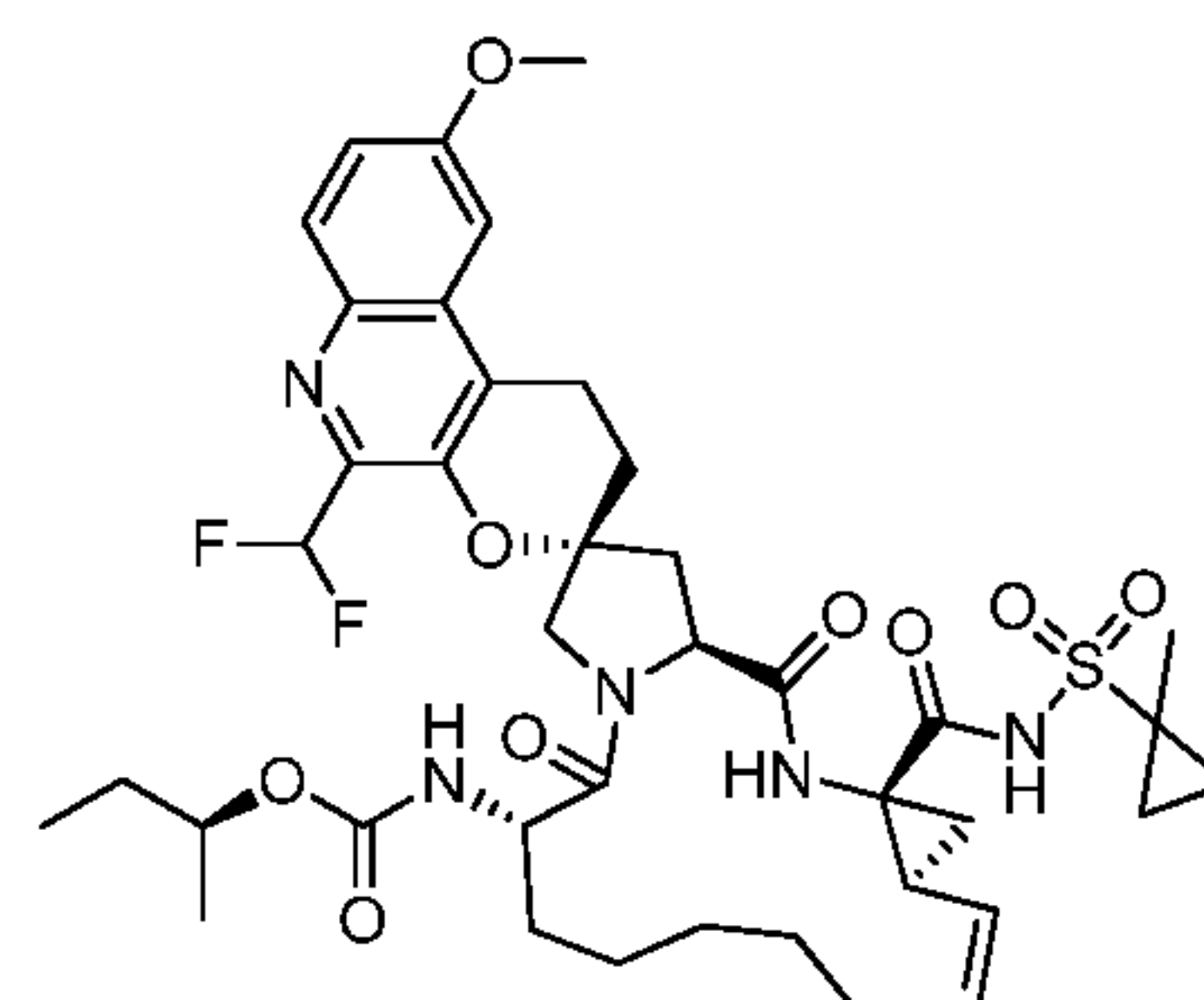
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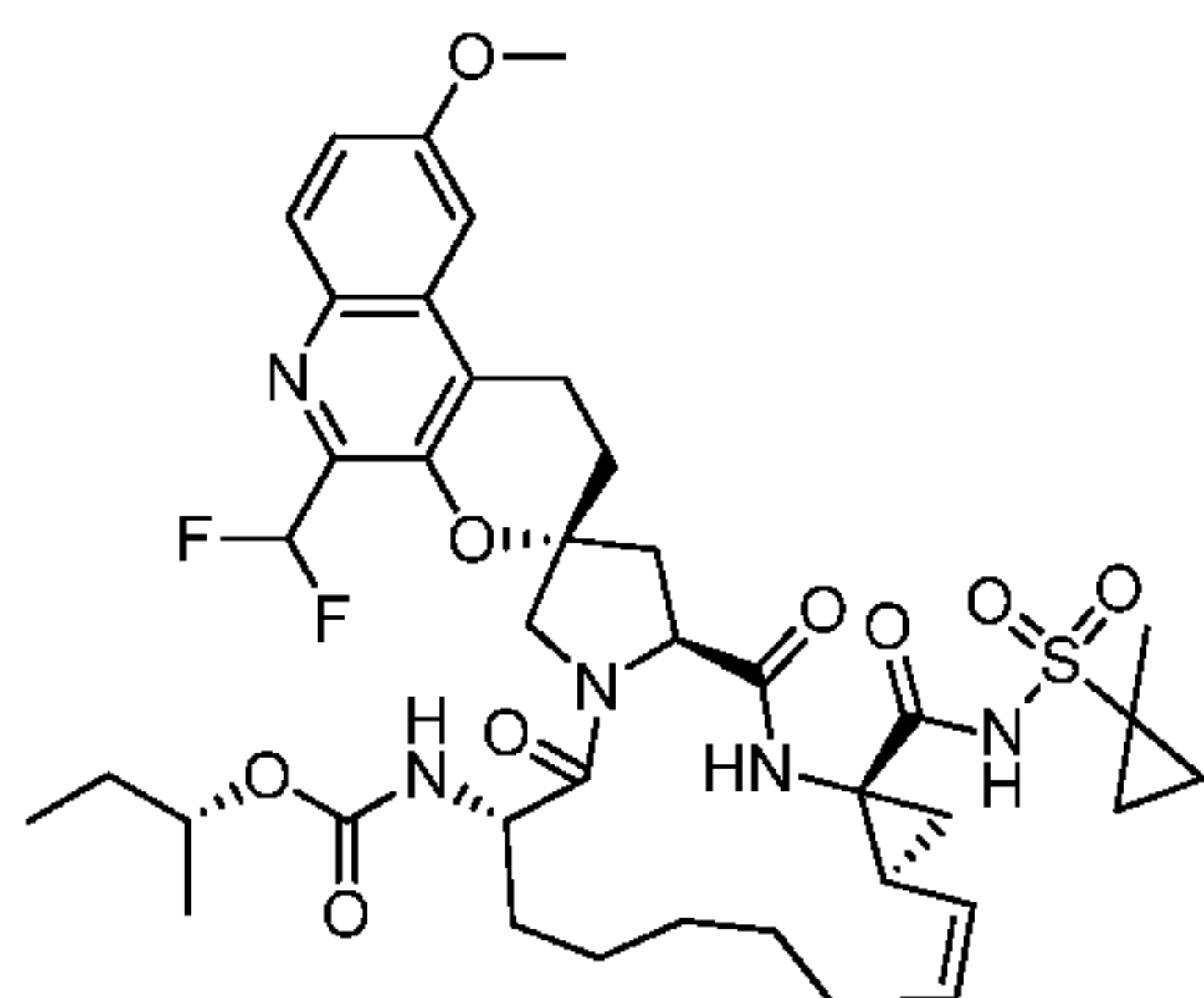
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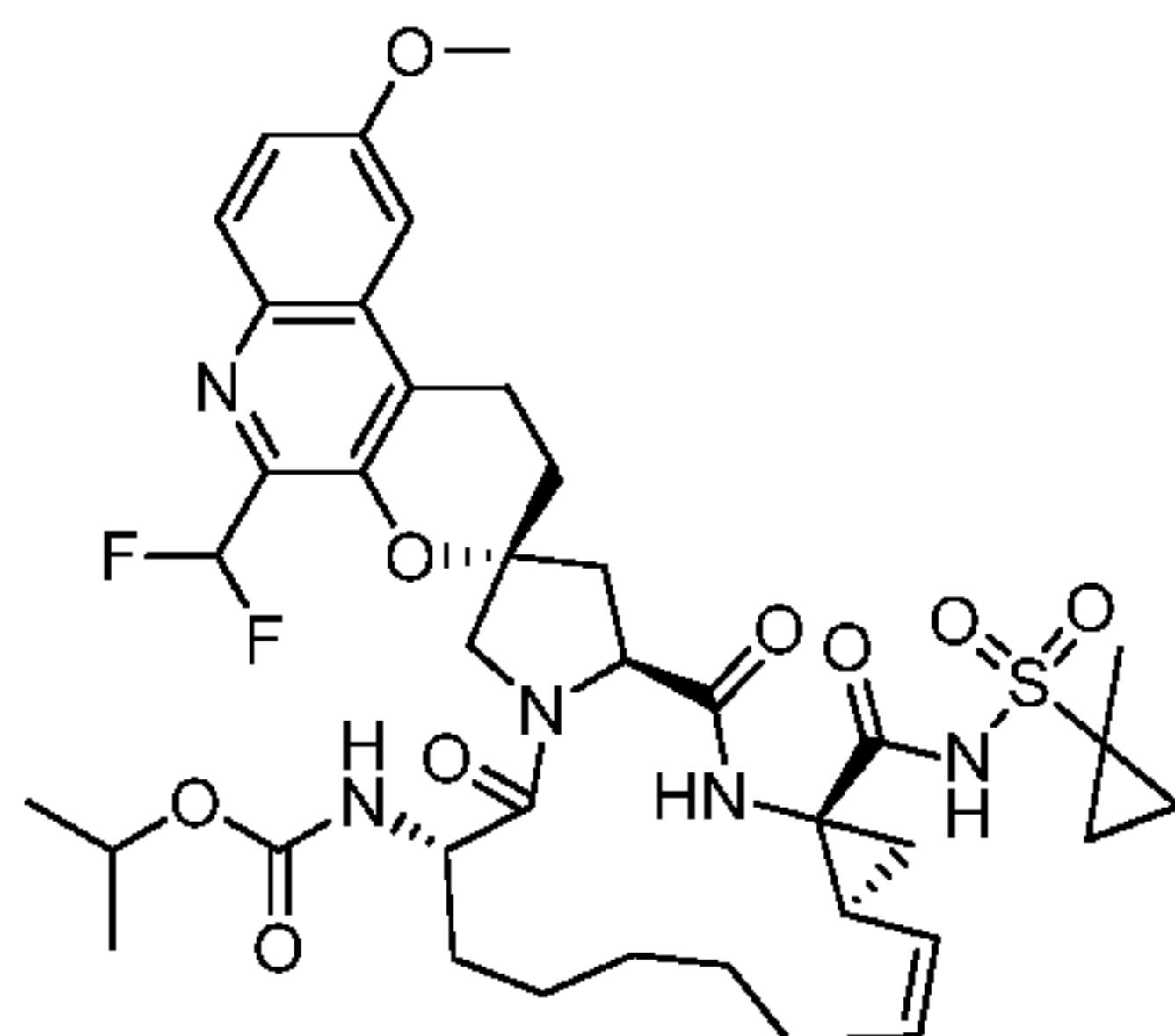
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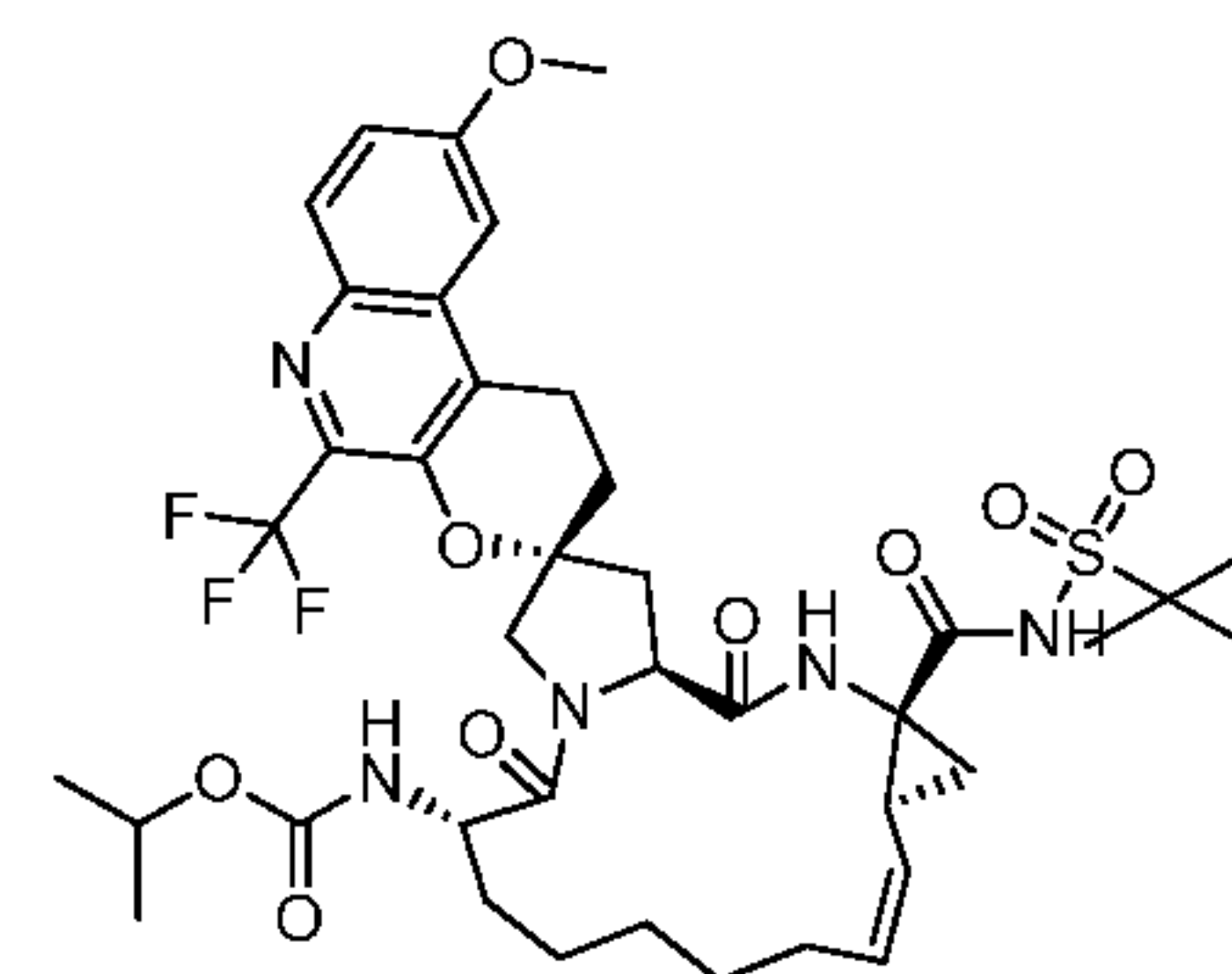
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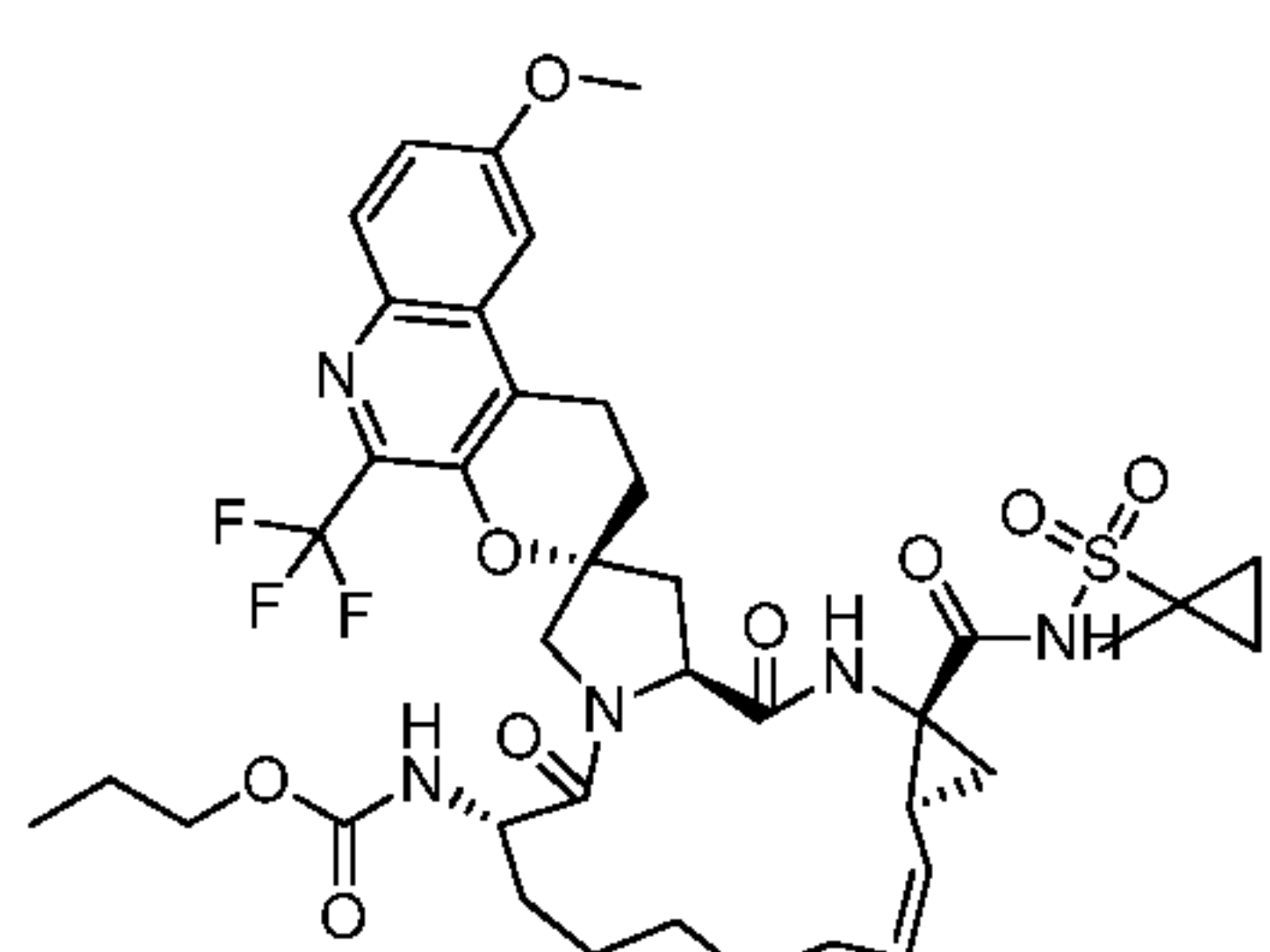
I-445



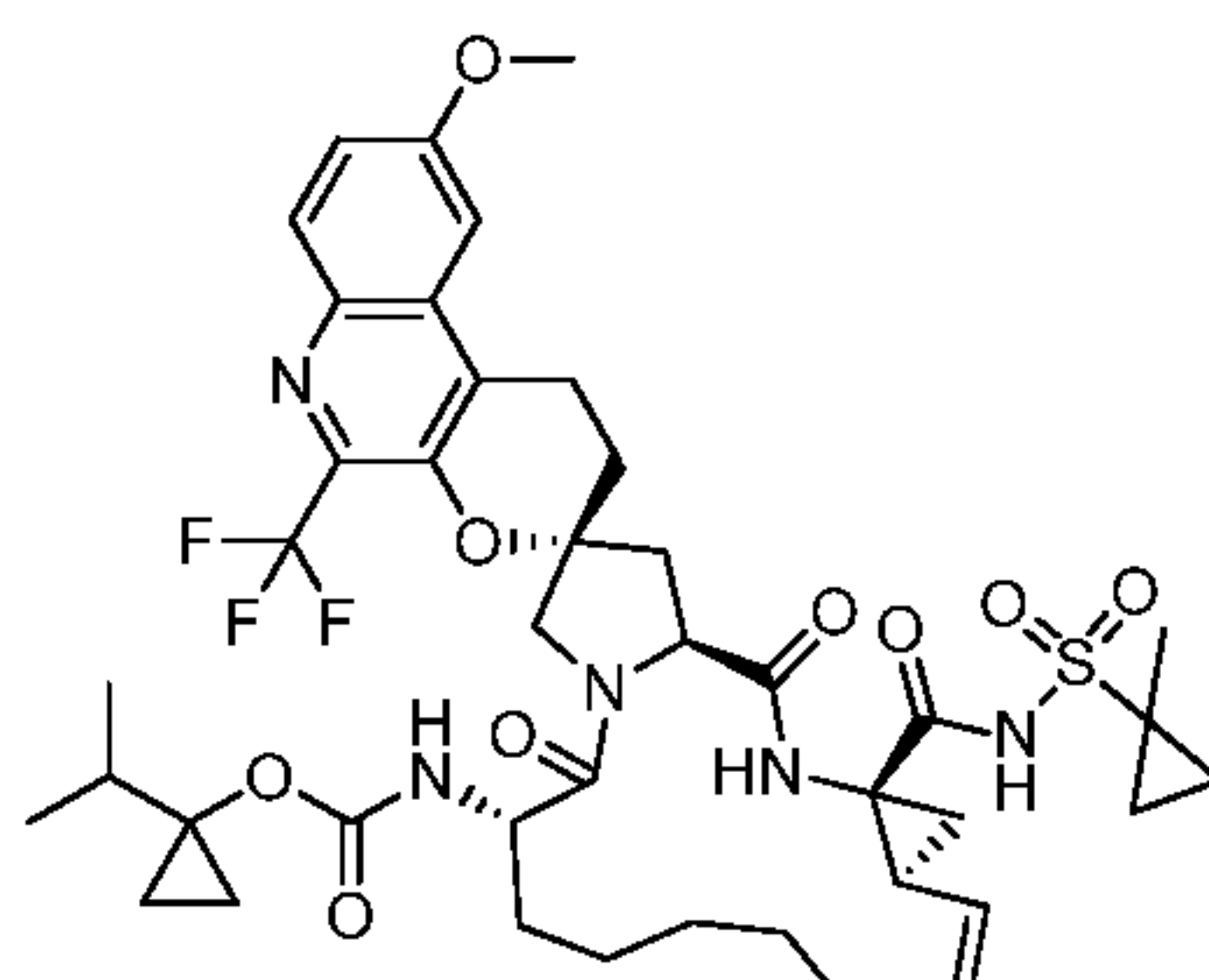
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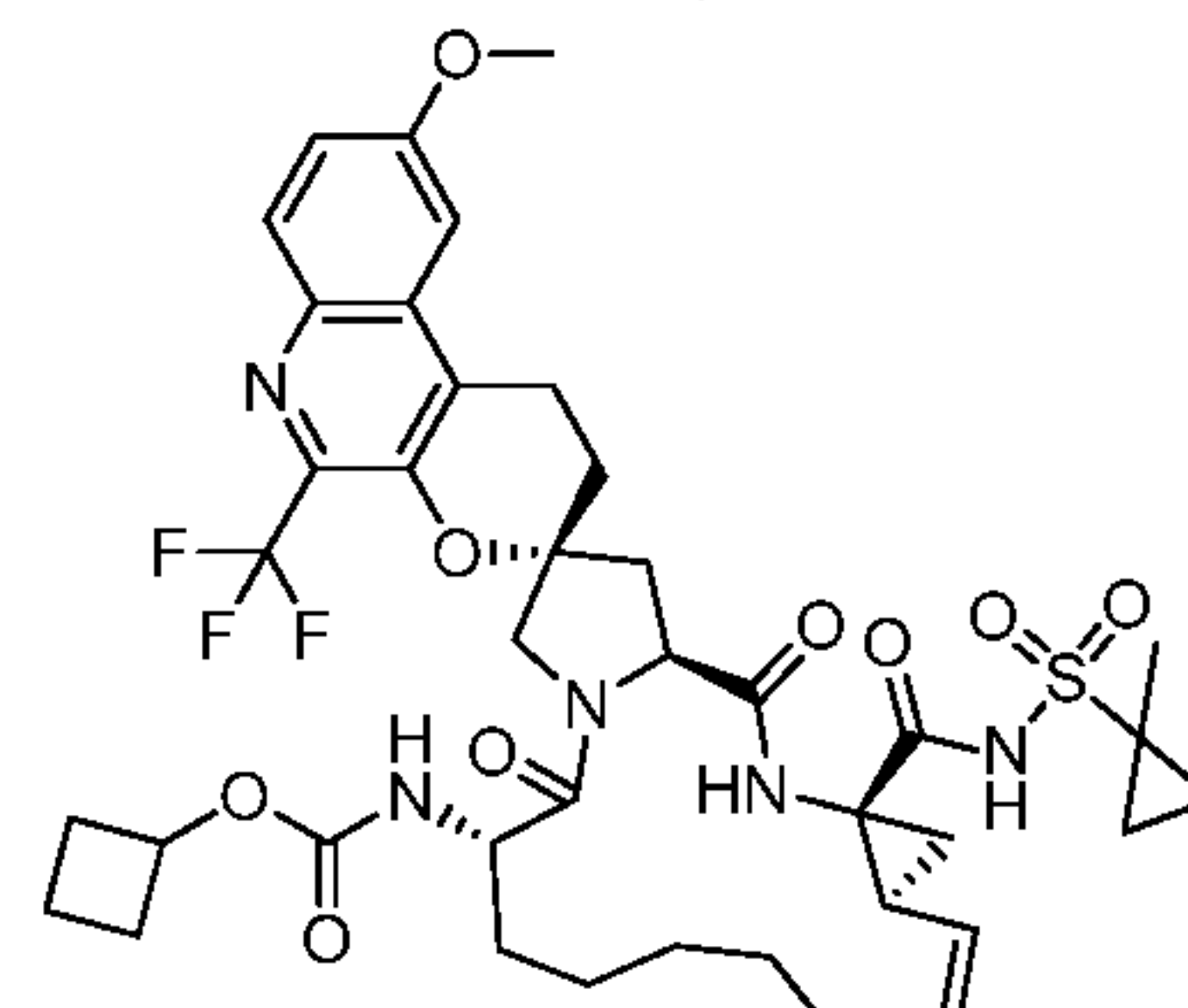
I-447



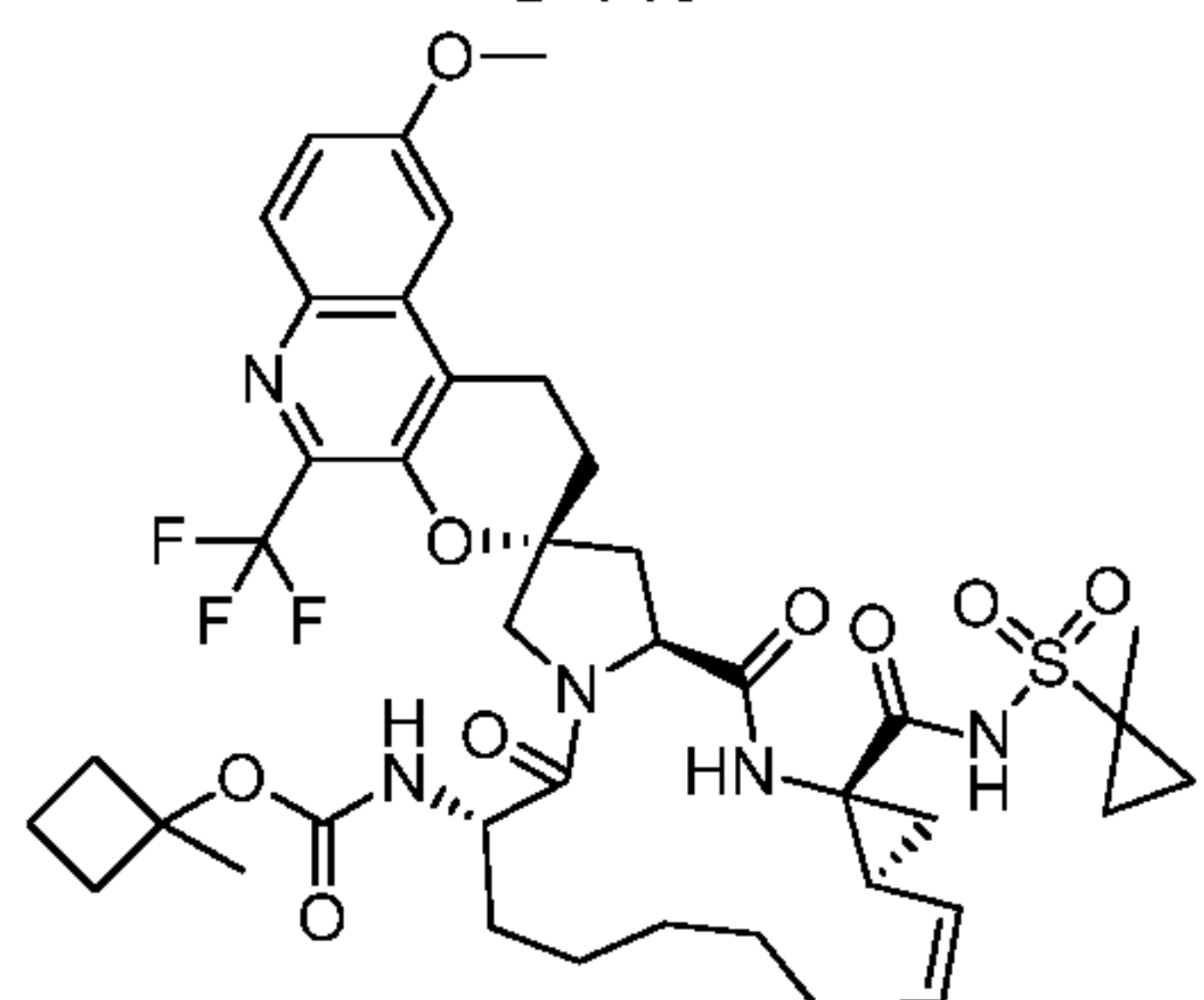
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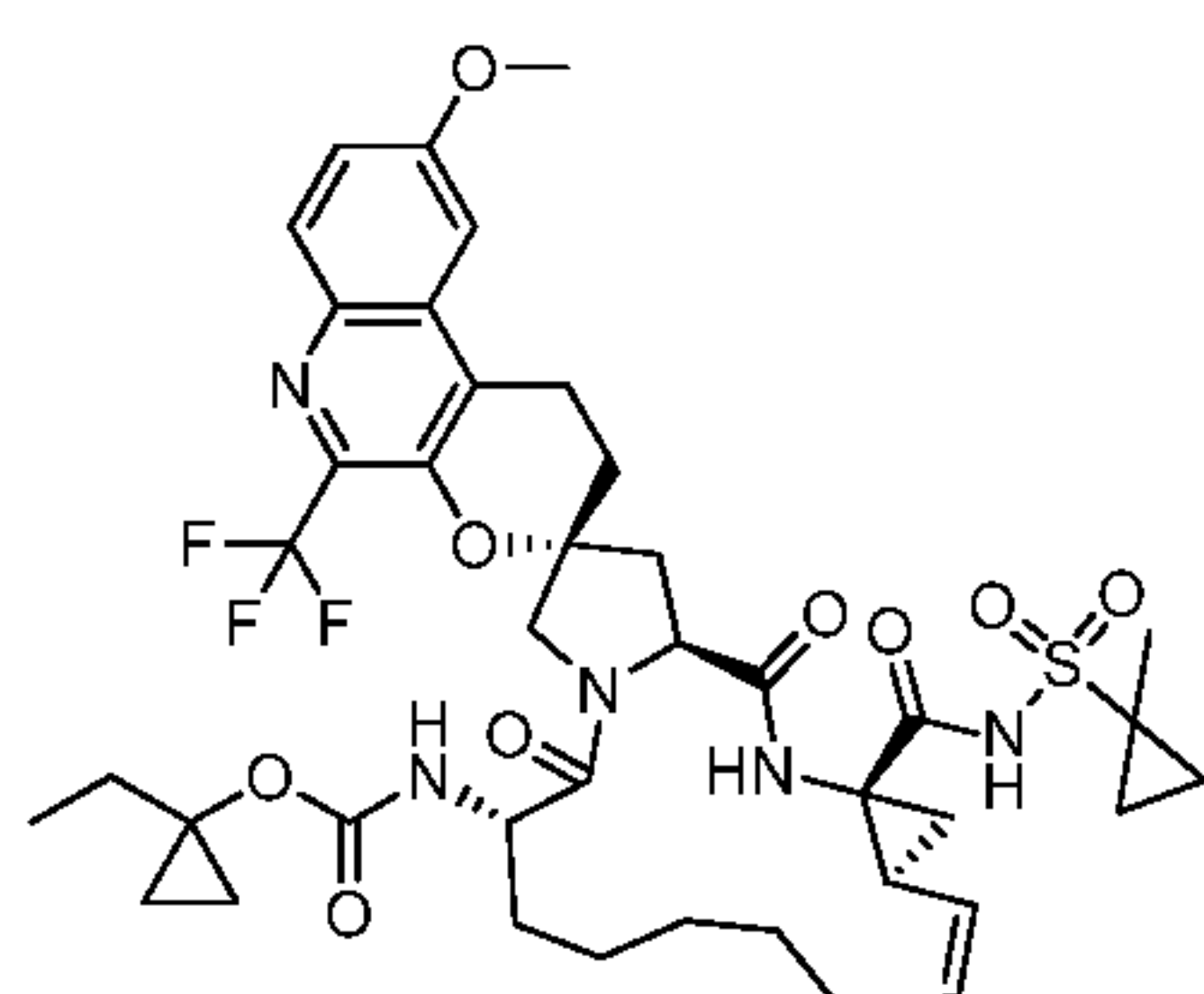
I-449



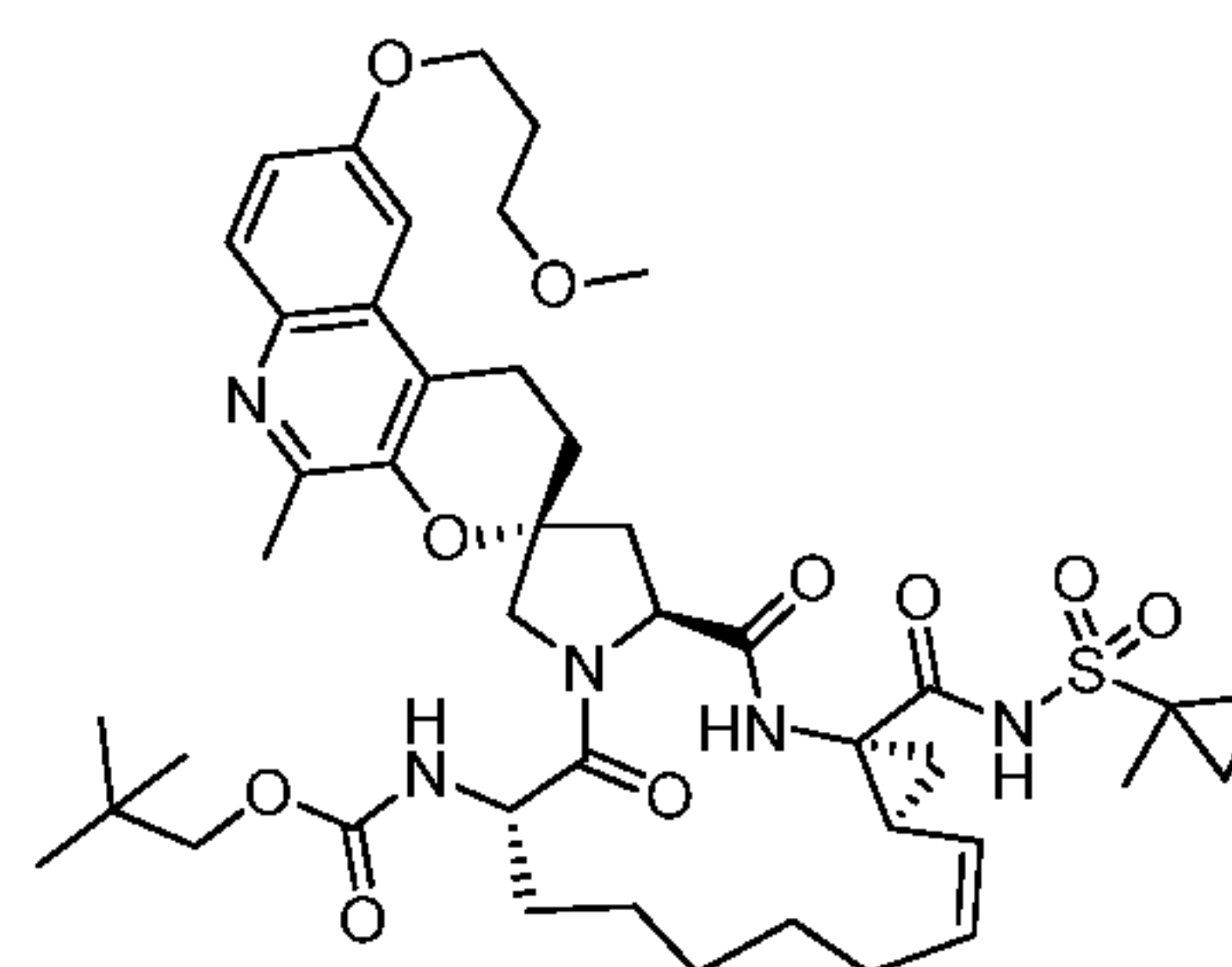
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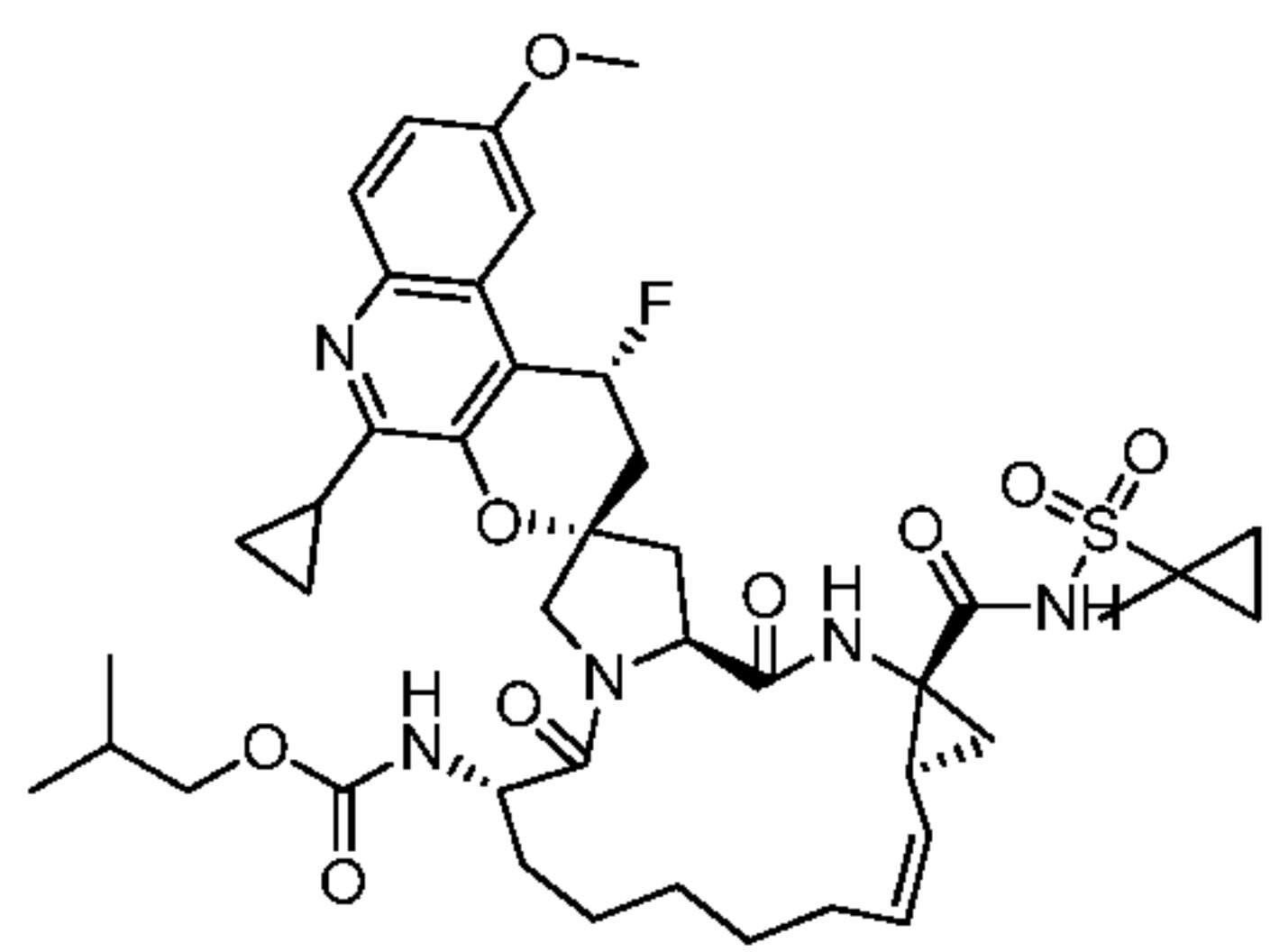
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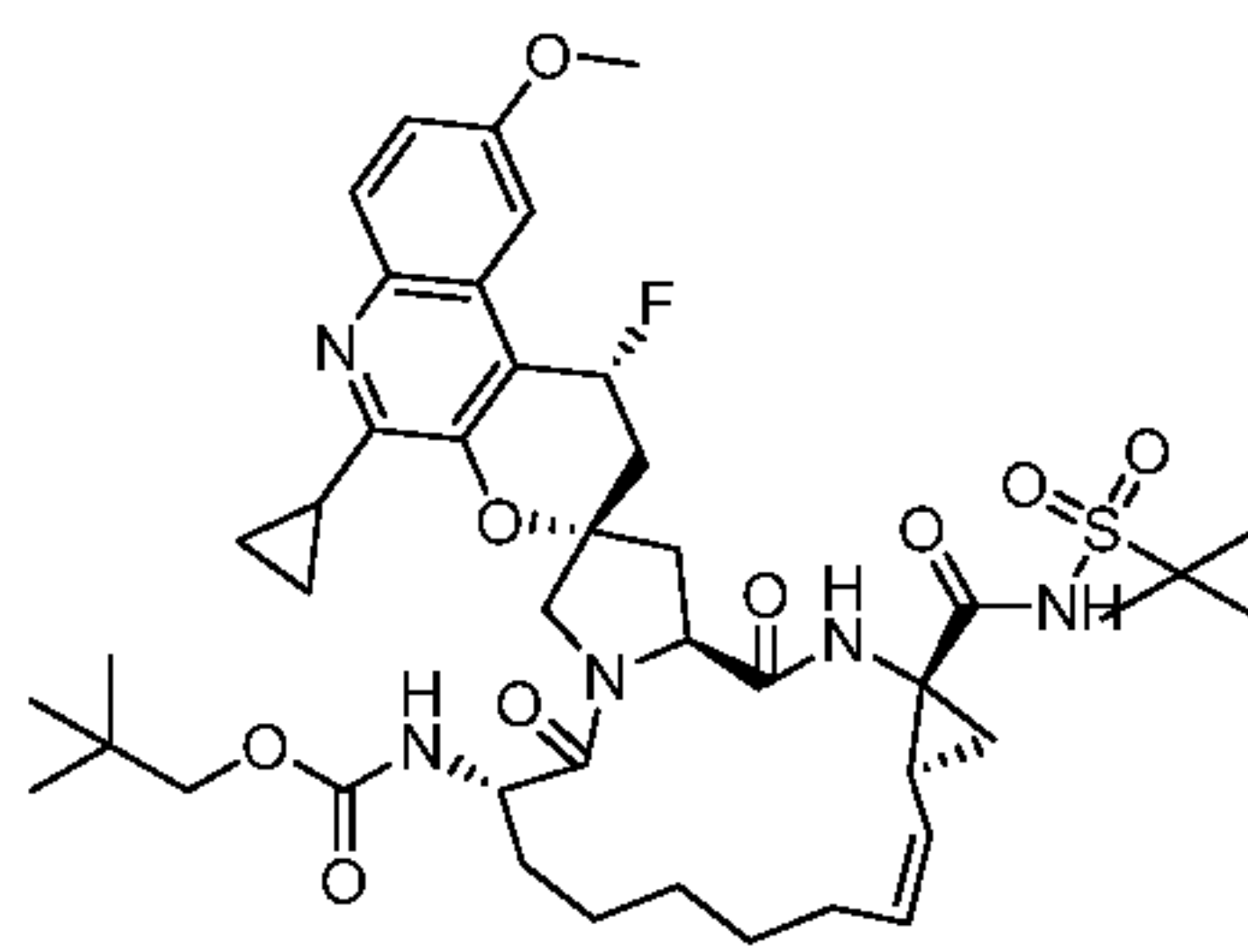
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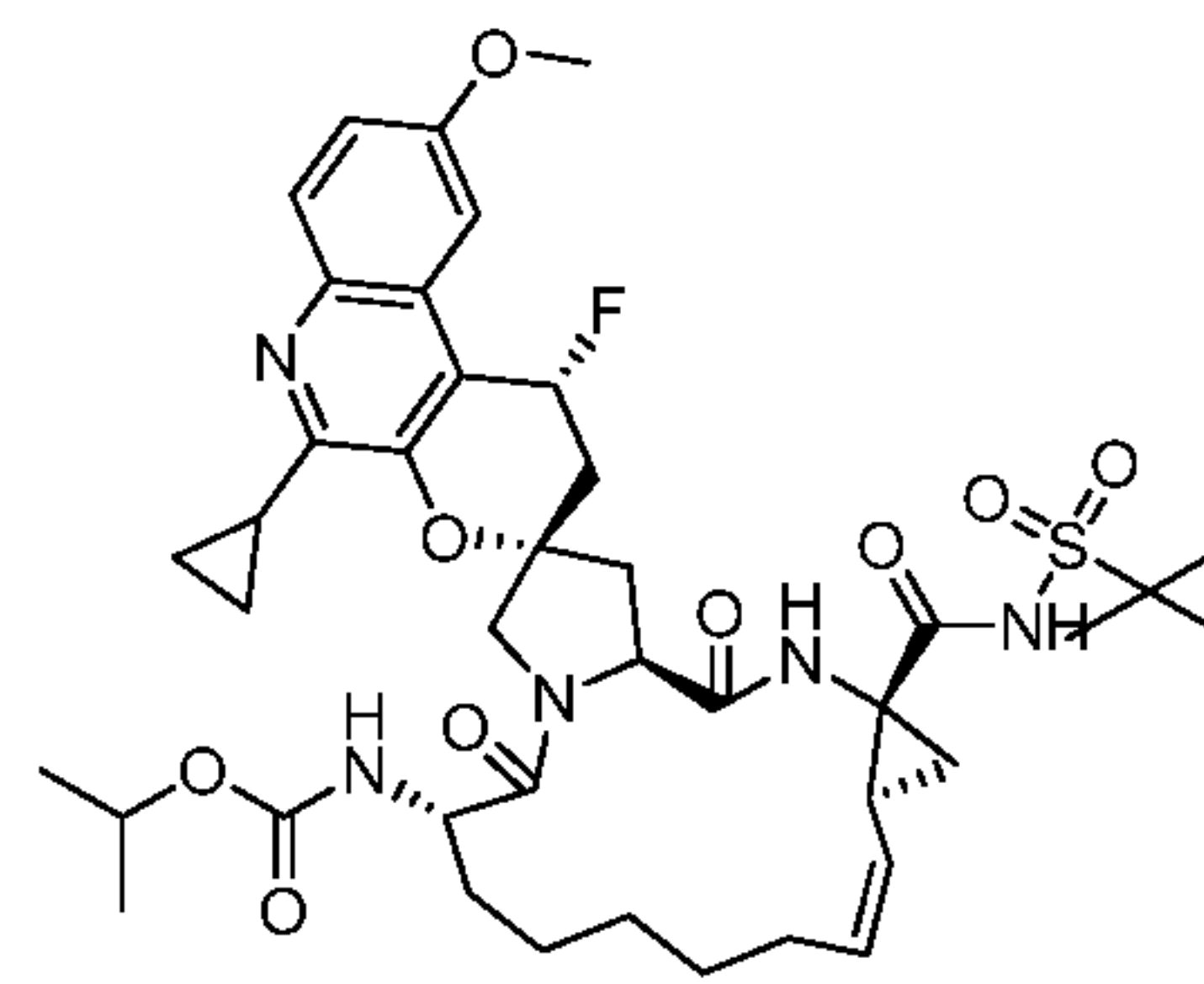
I-453



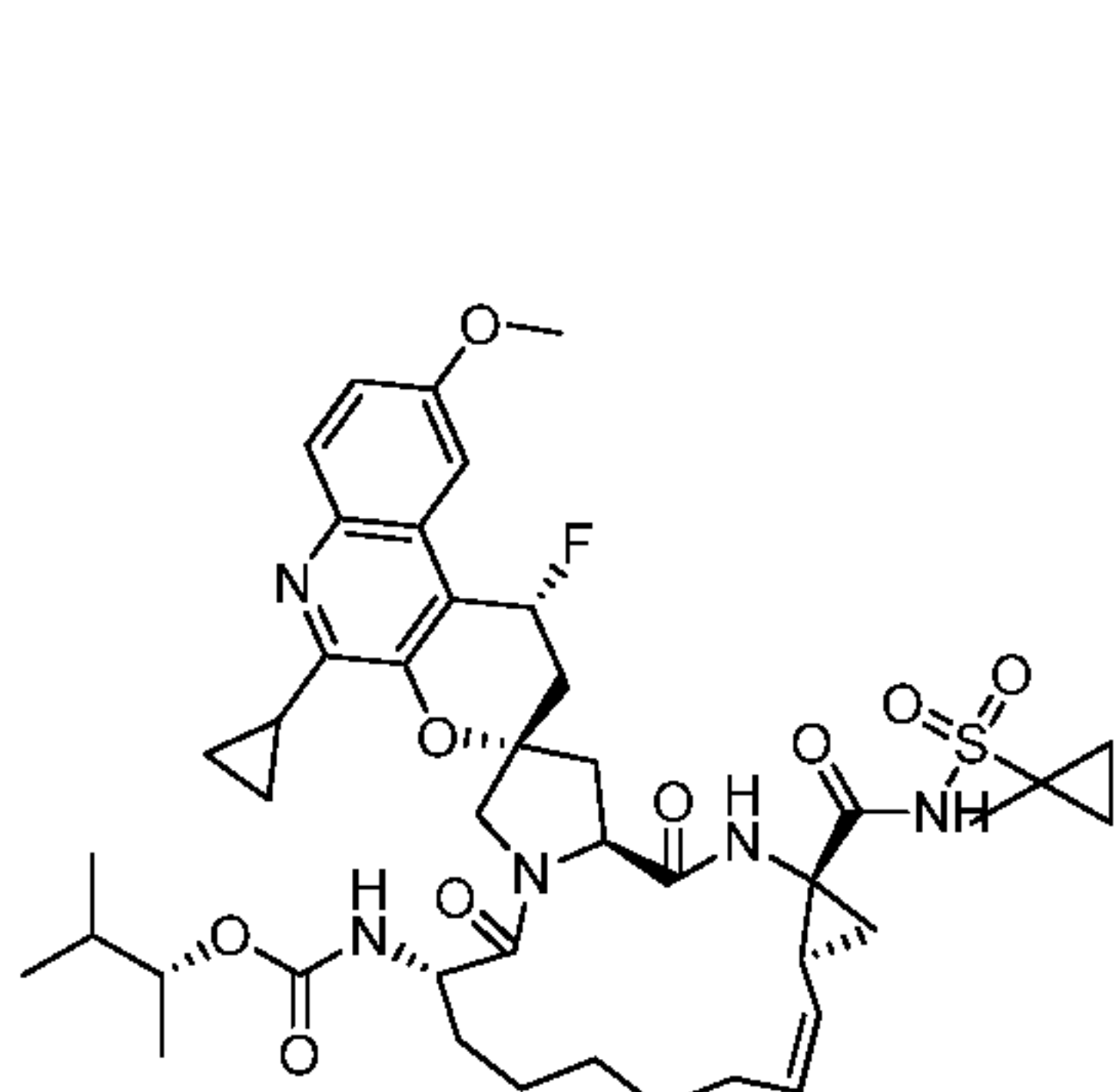
I-454



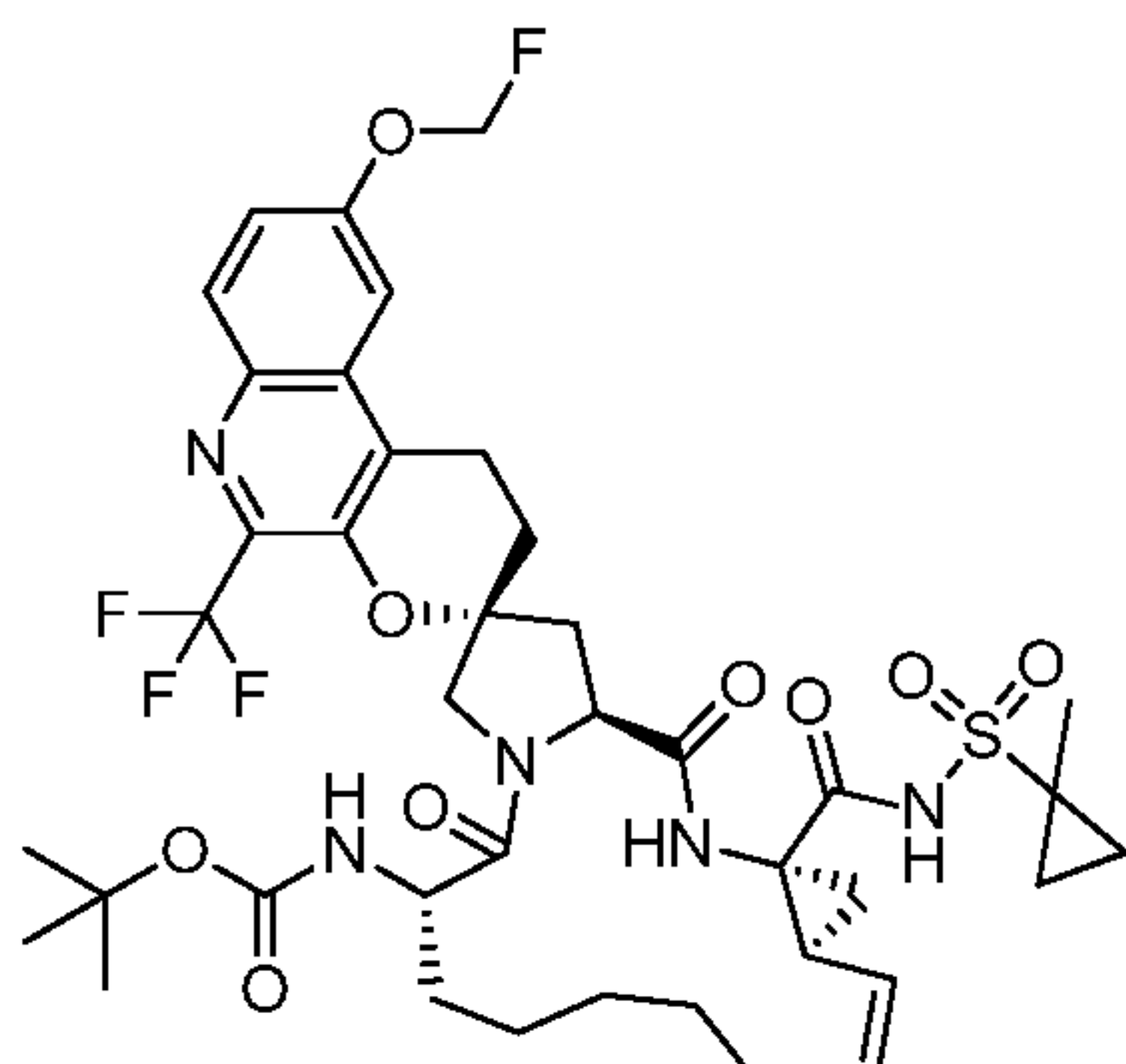
I-455



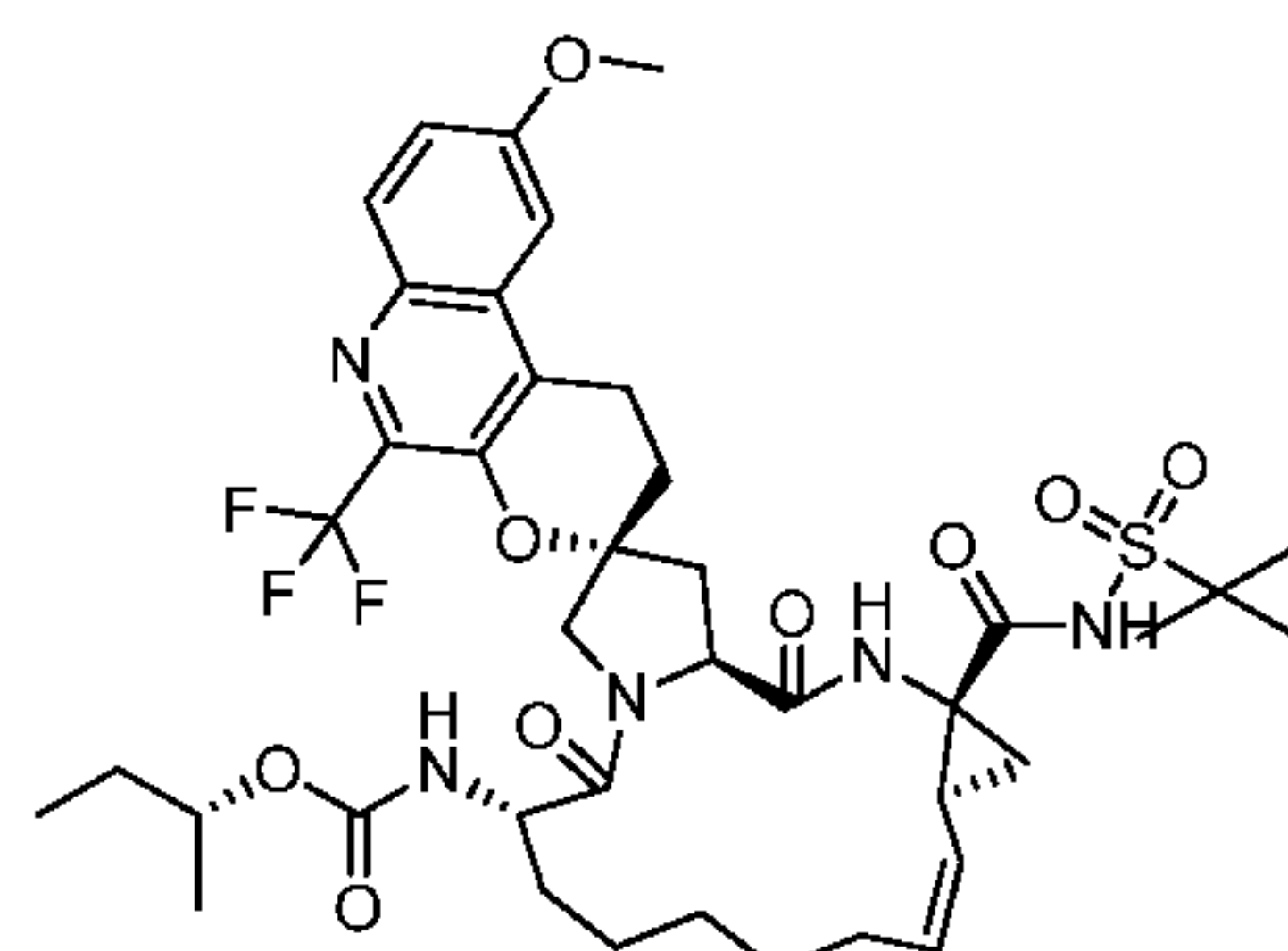
I-456



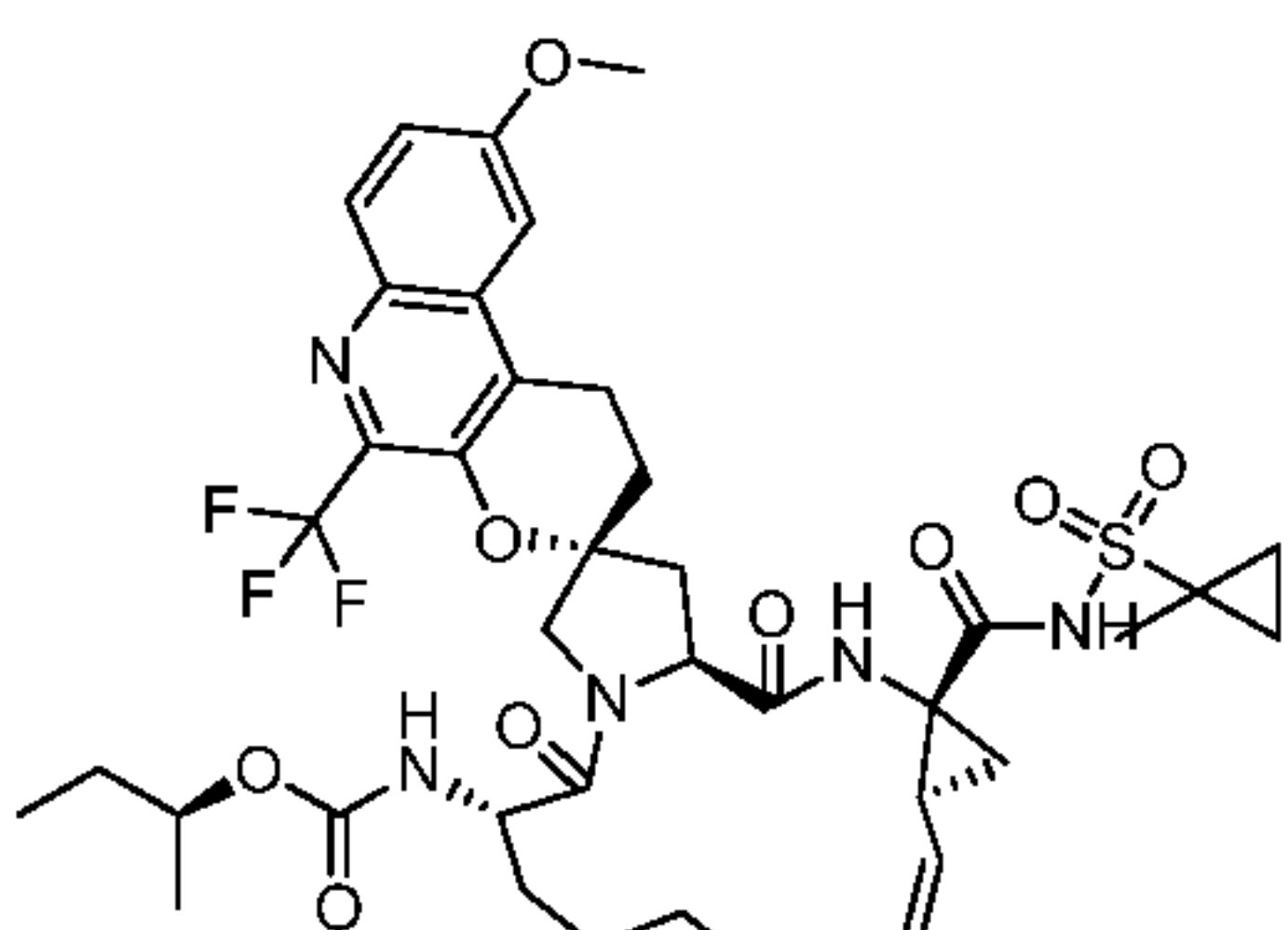
I-457



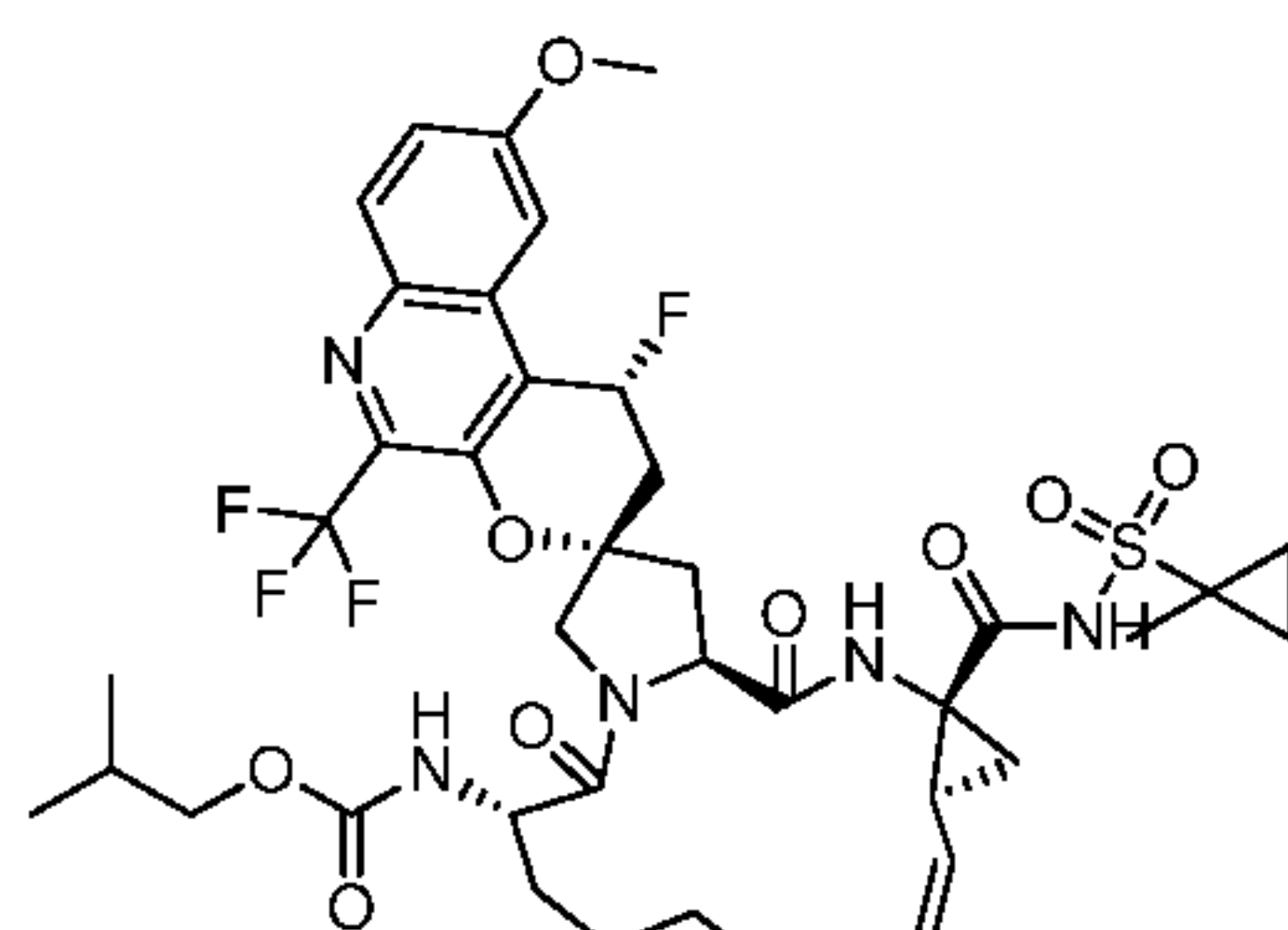
I-458



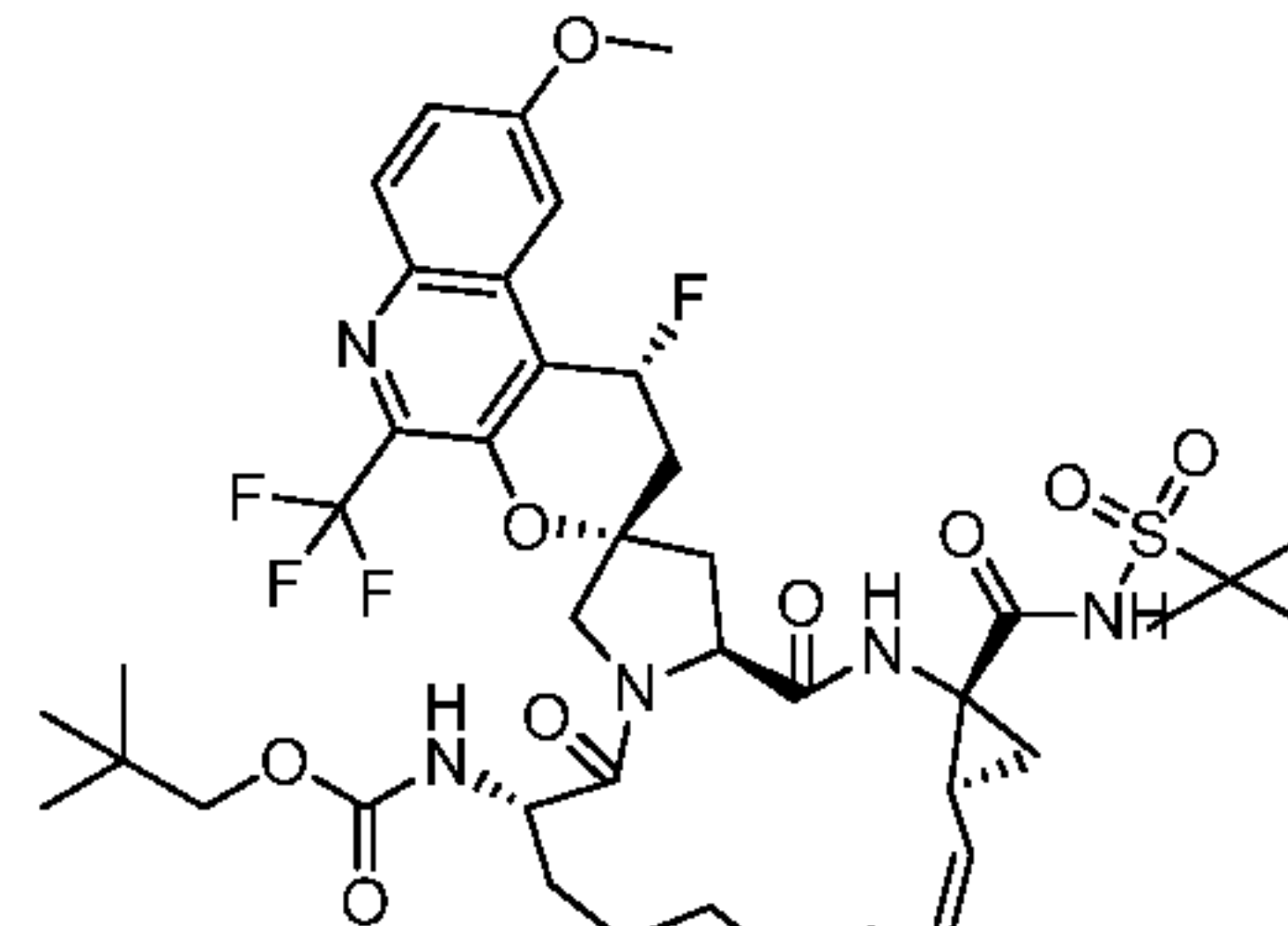
I-459



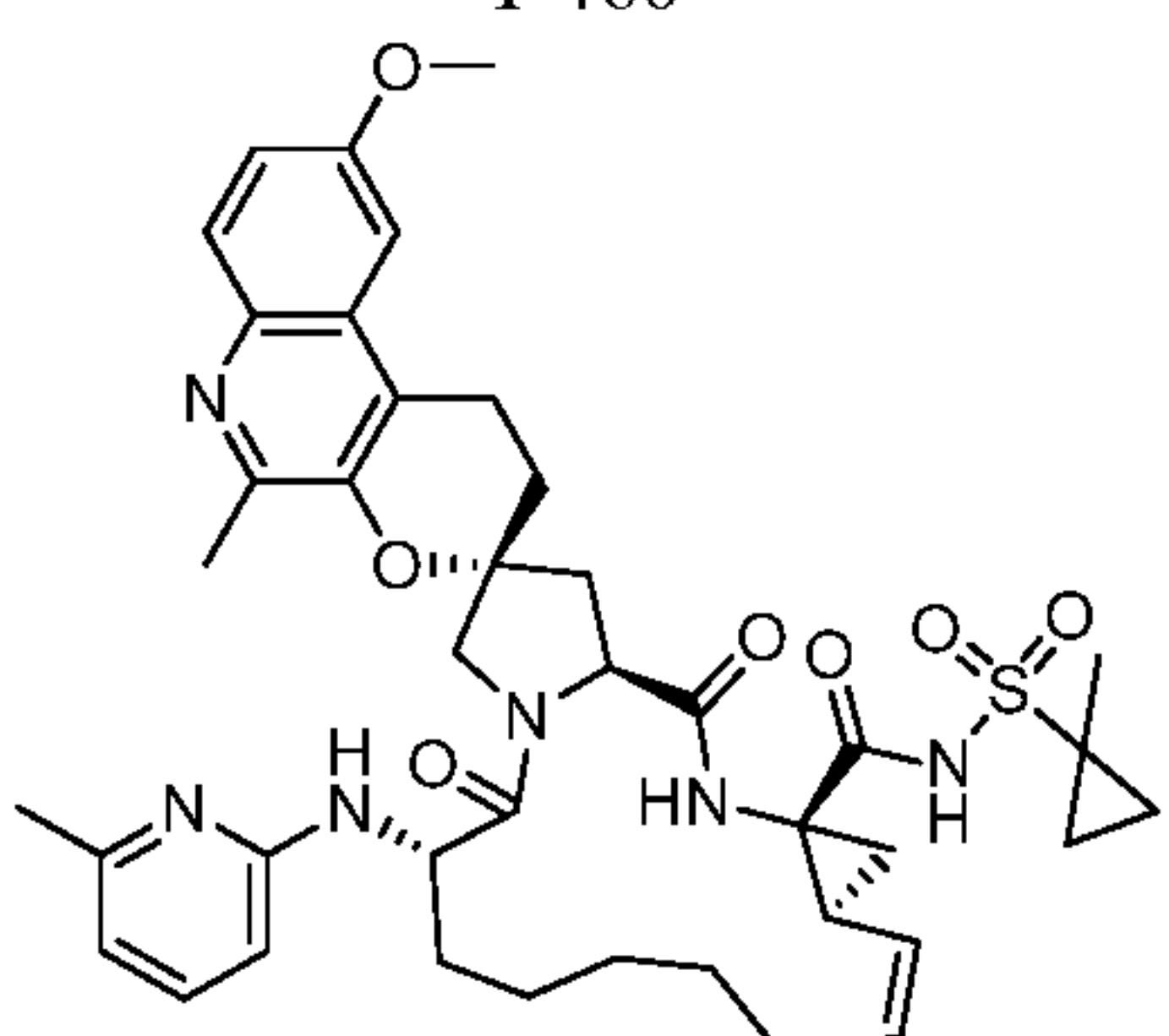
I-460



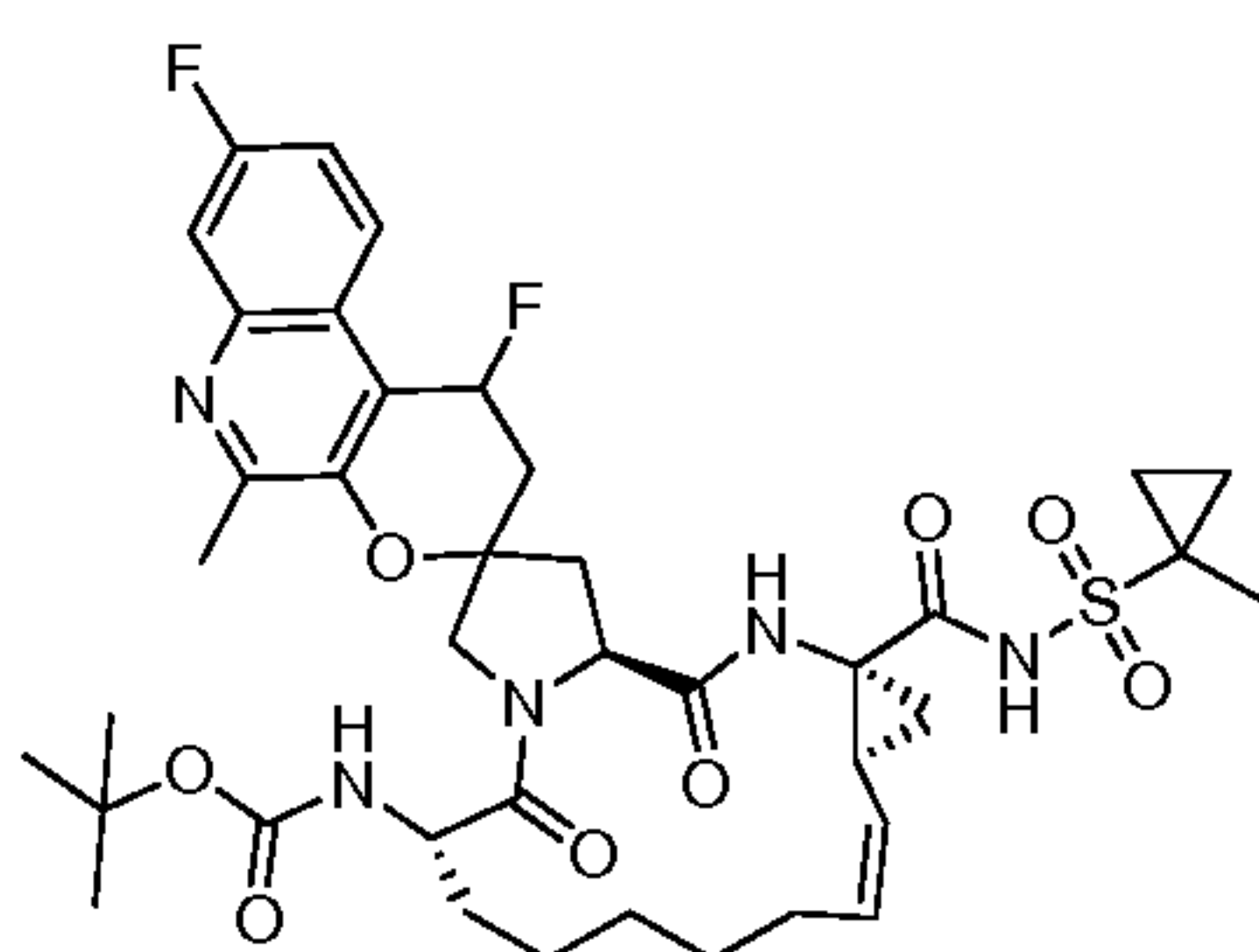
I-461



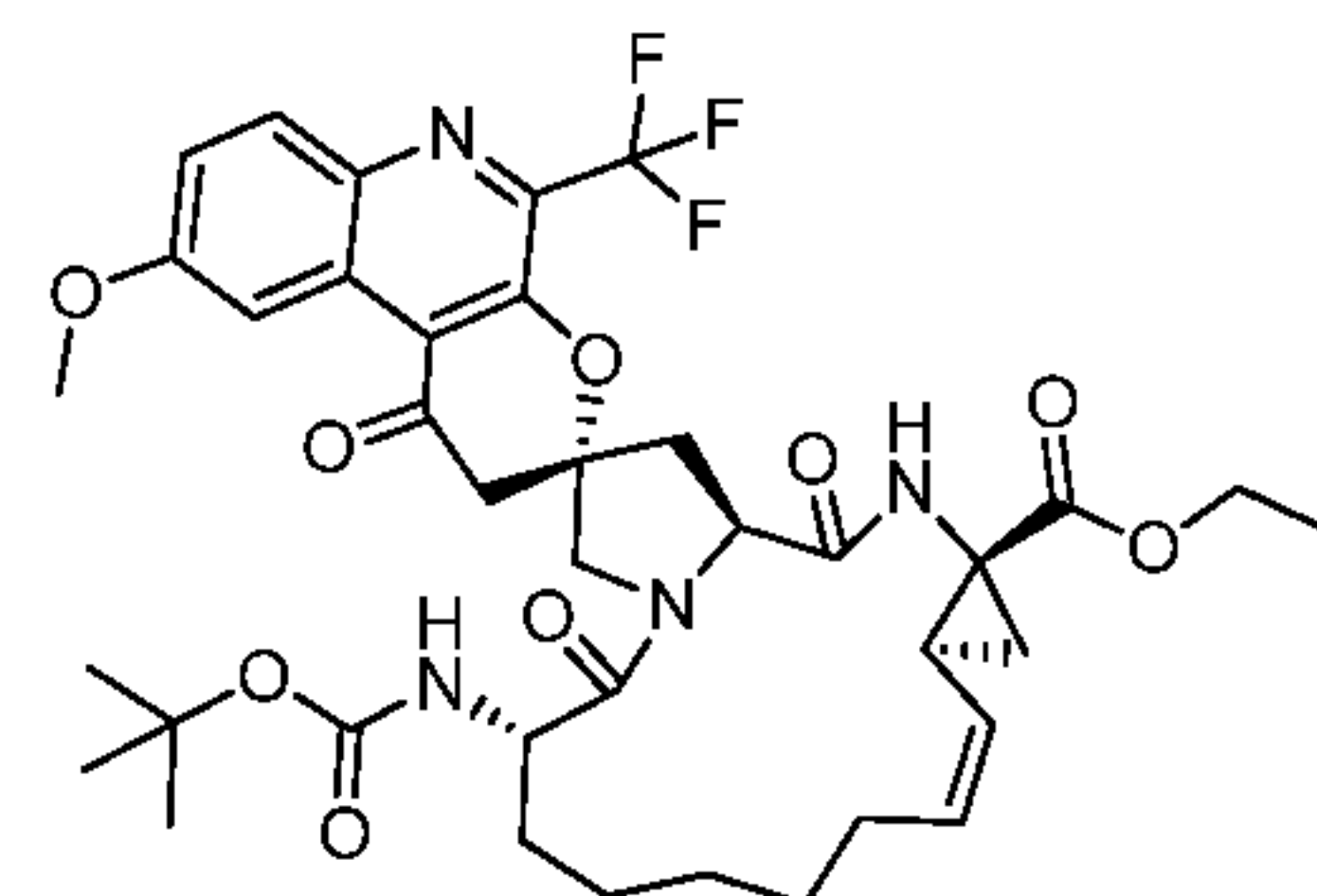
I-462



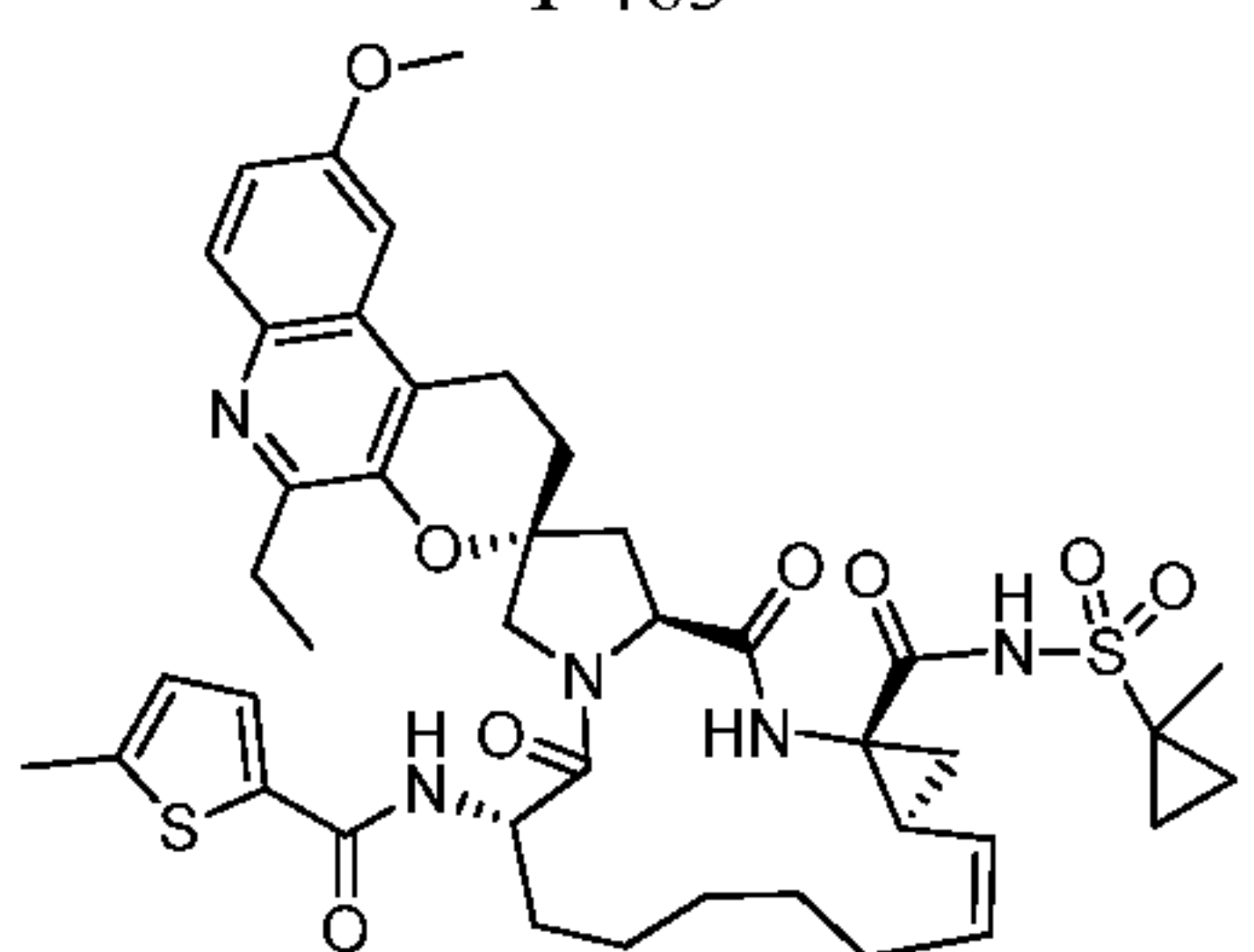
I-463



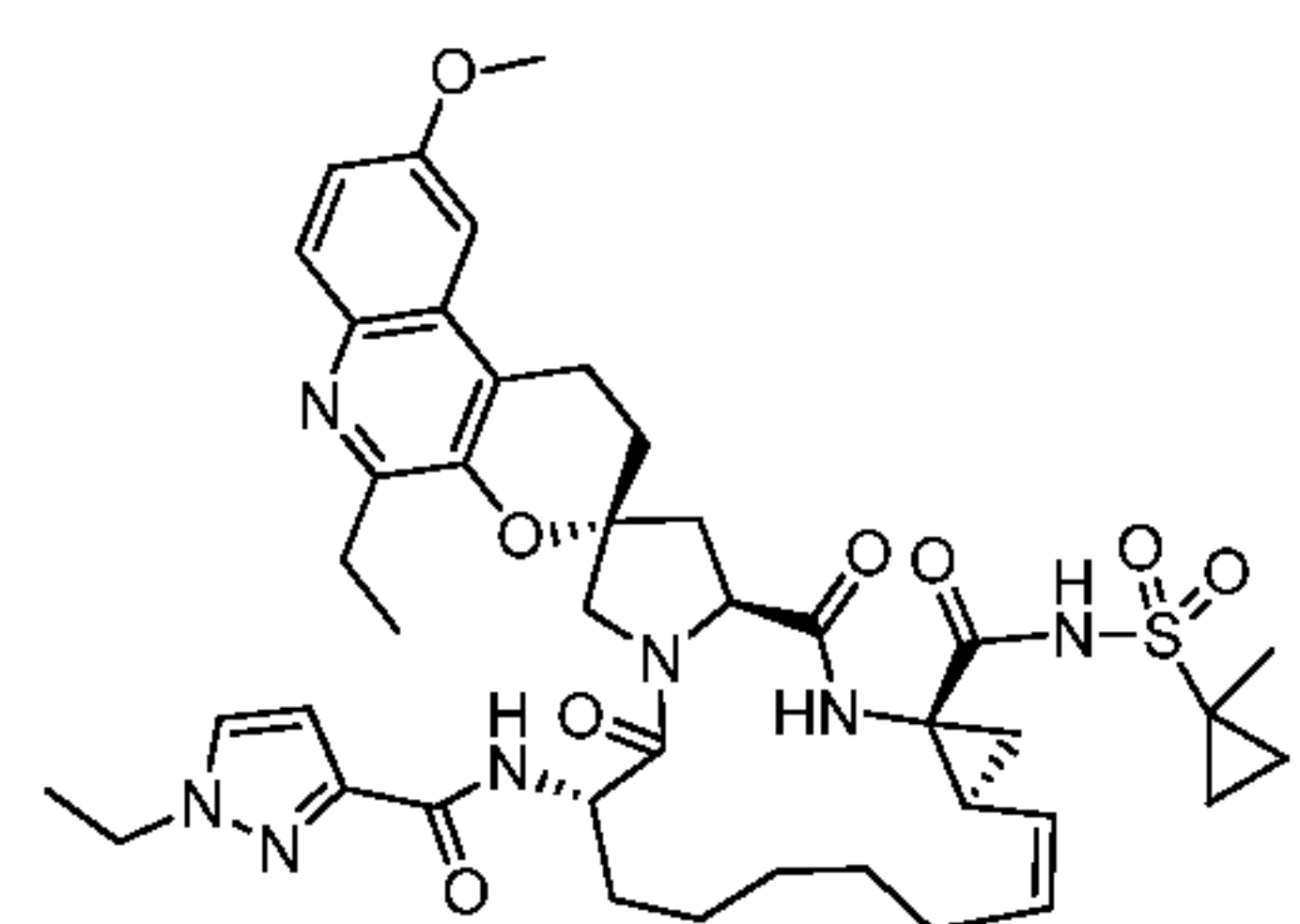
I-464



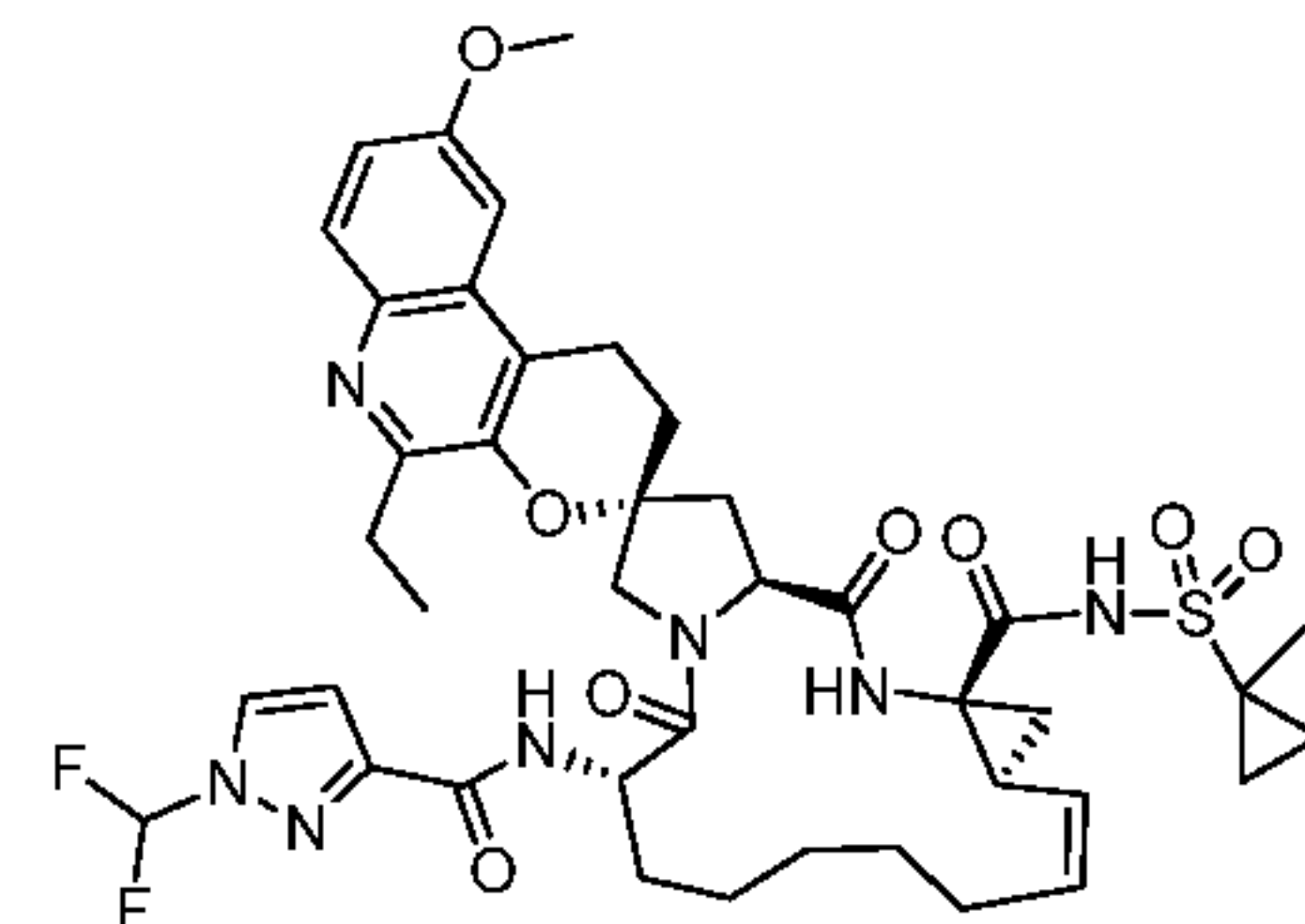
I-465



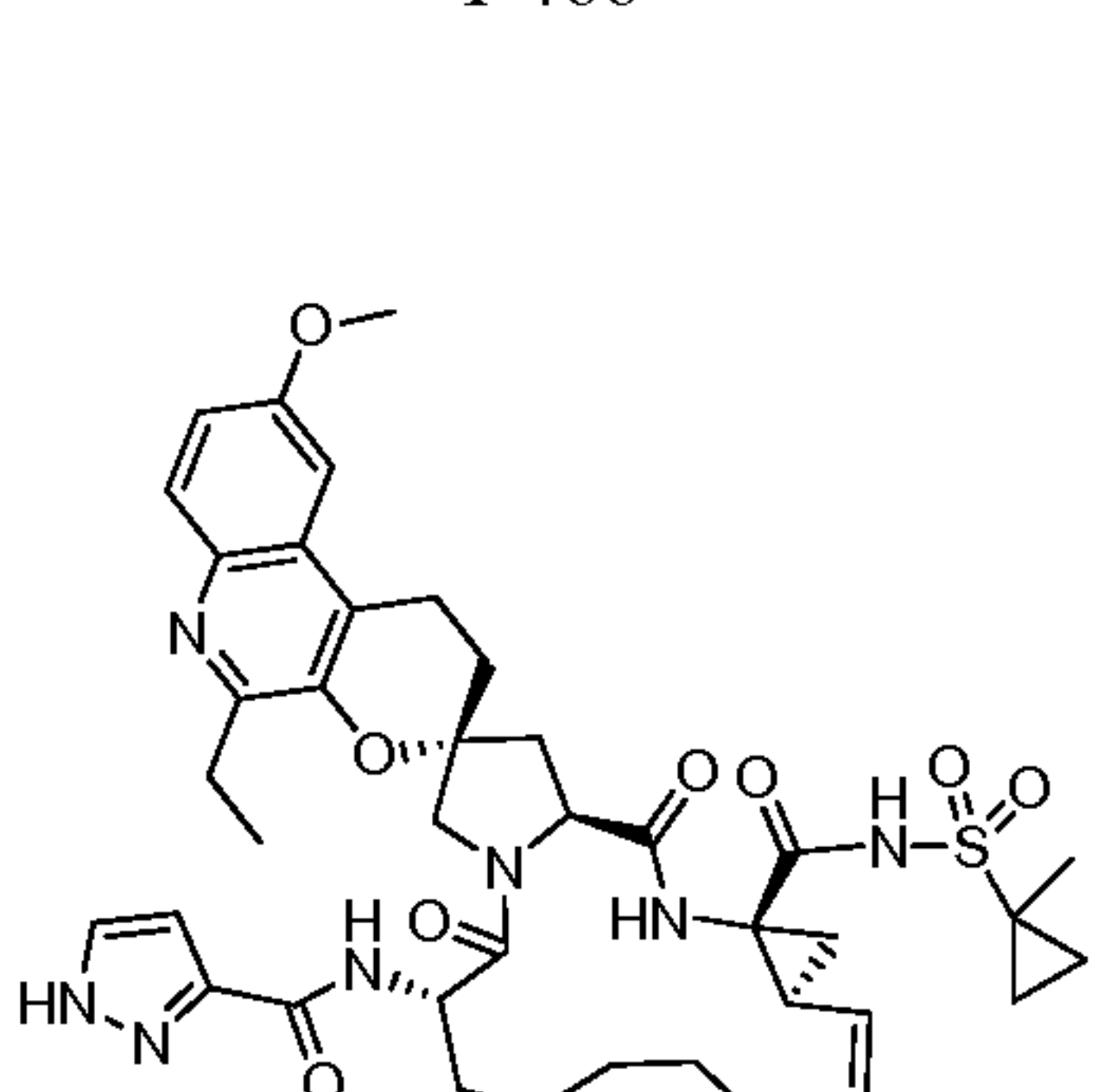
I-466



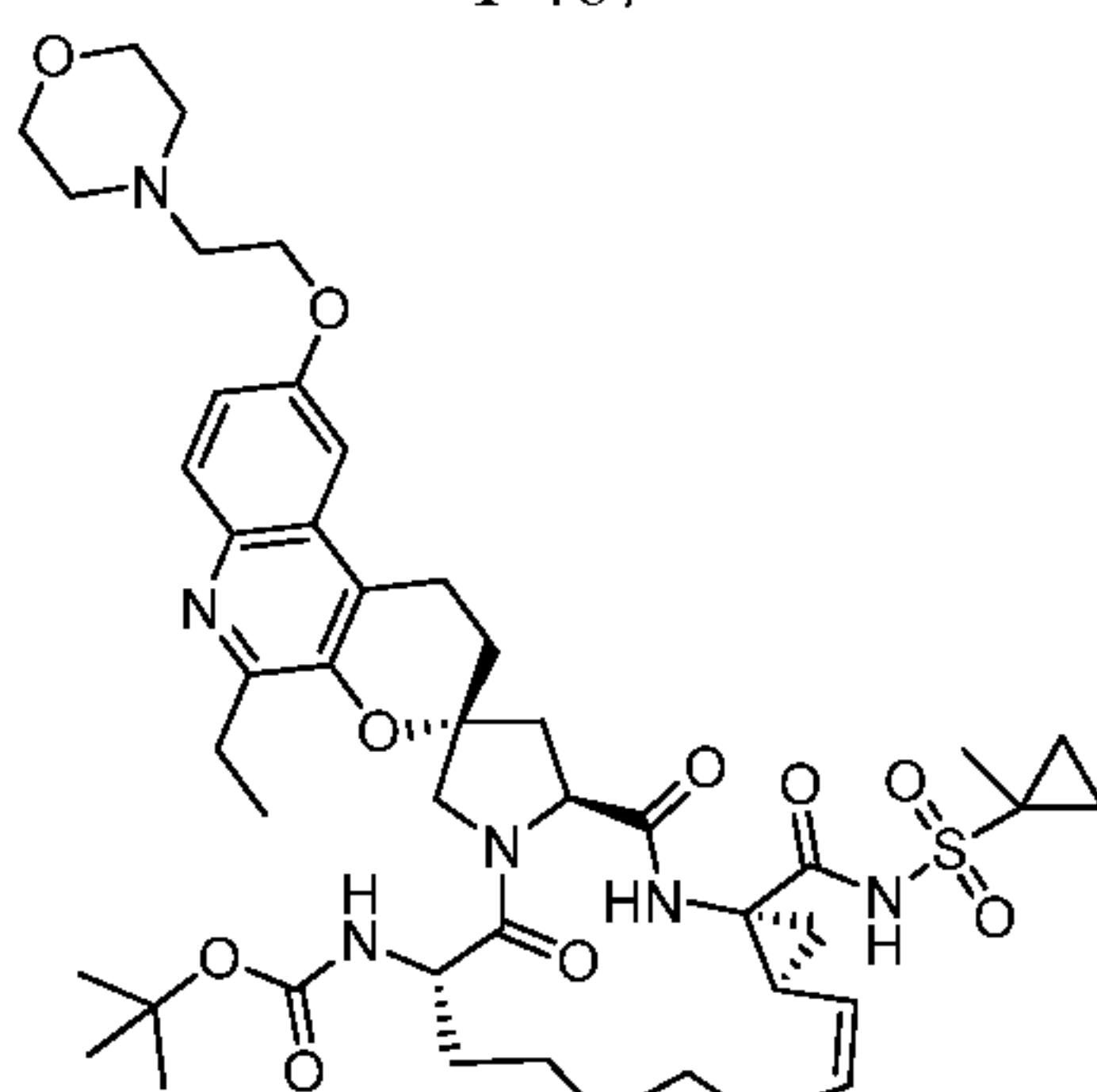
I-467



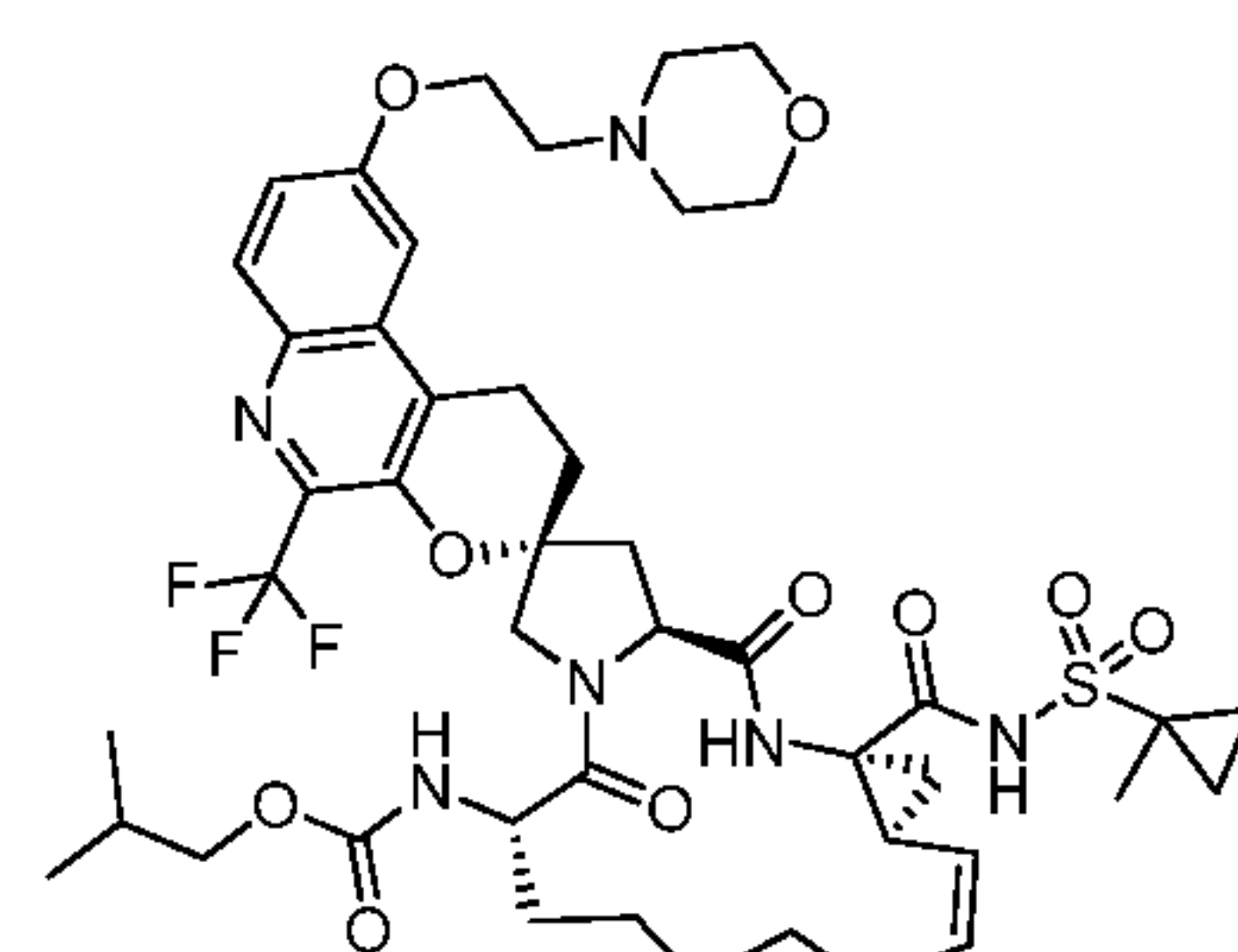
I-468



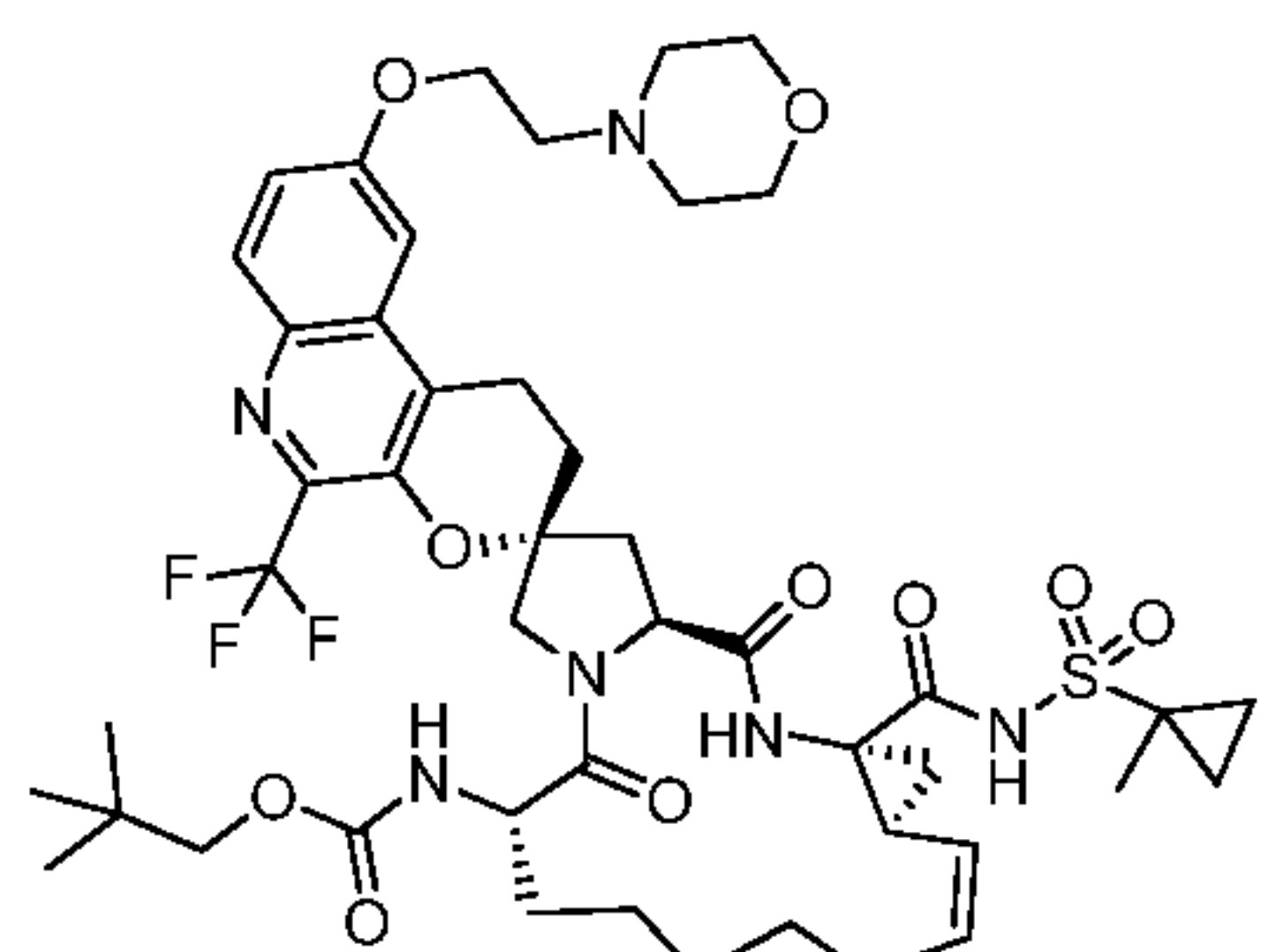
I-469



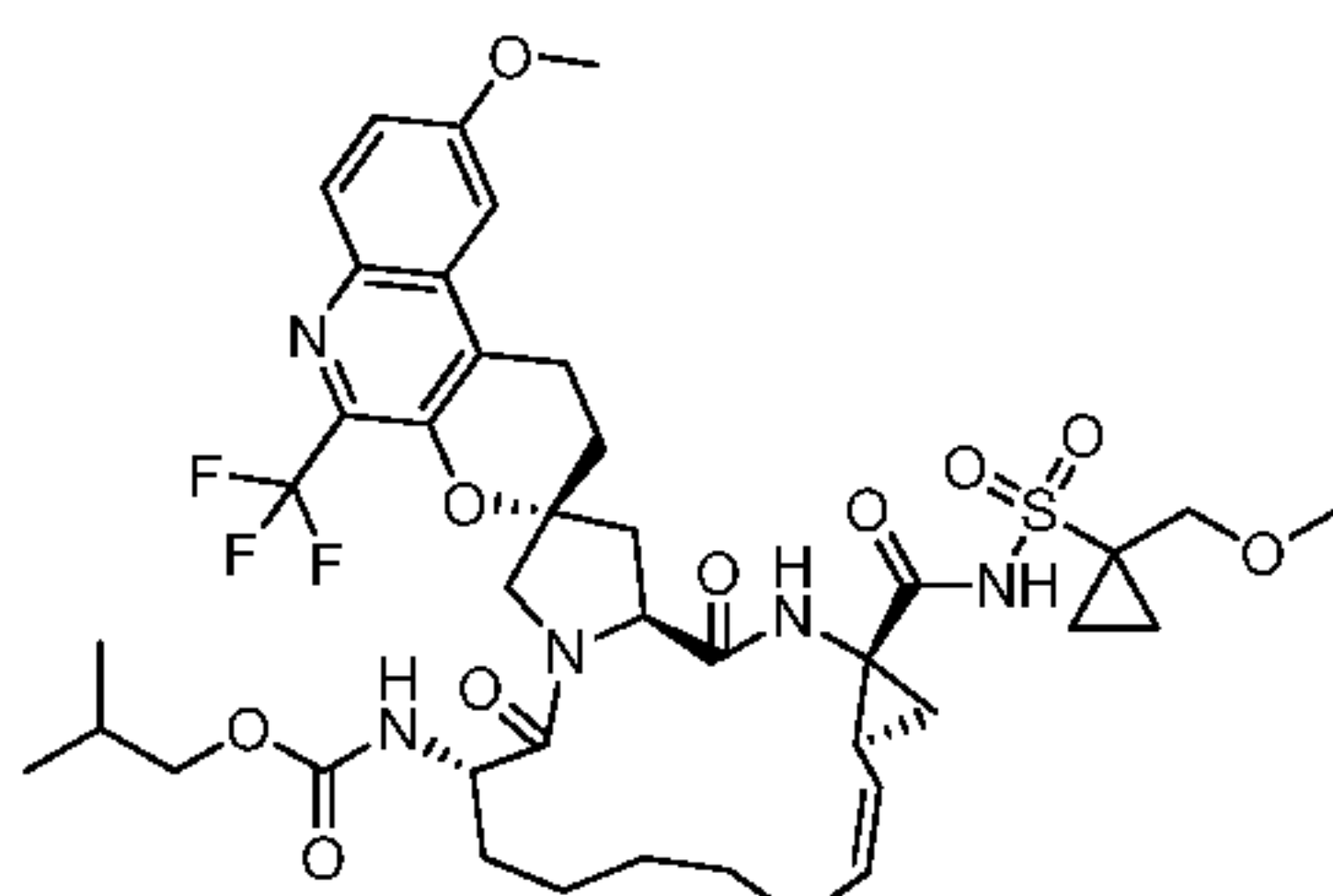
I-470



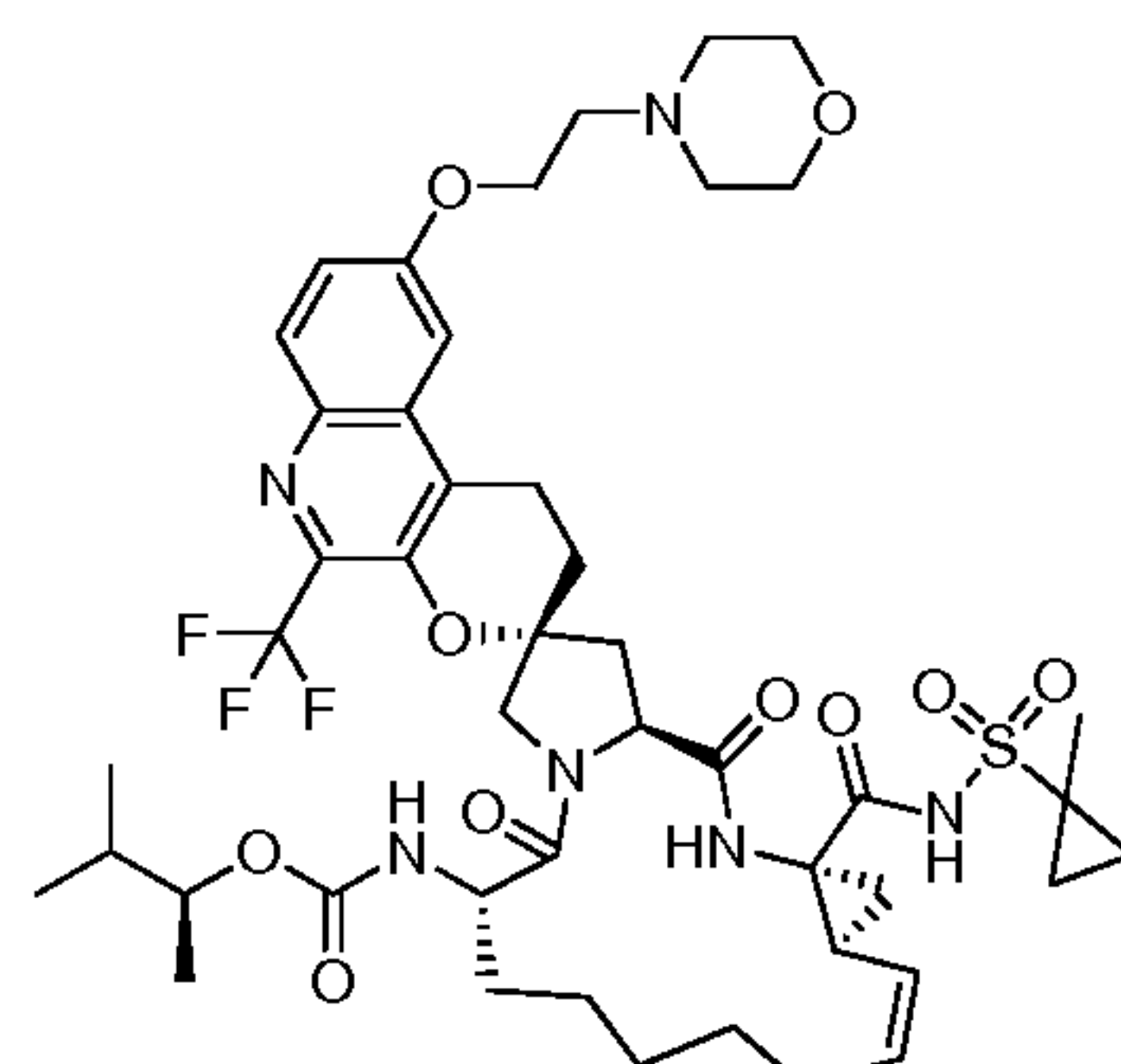
I-471



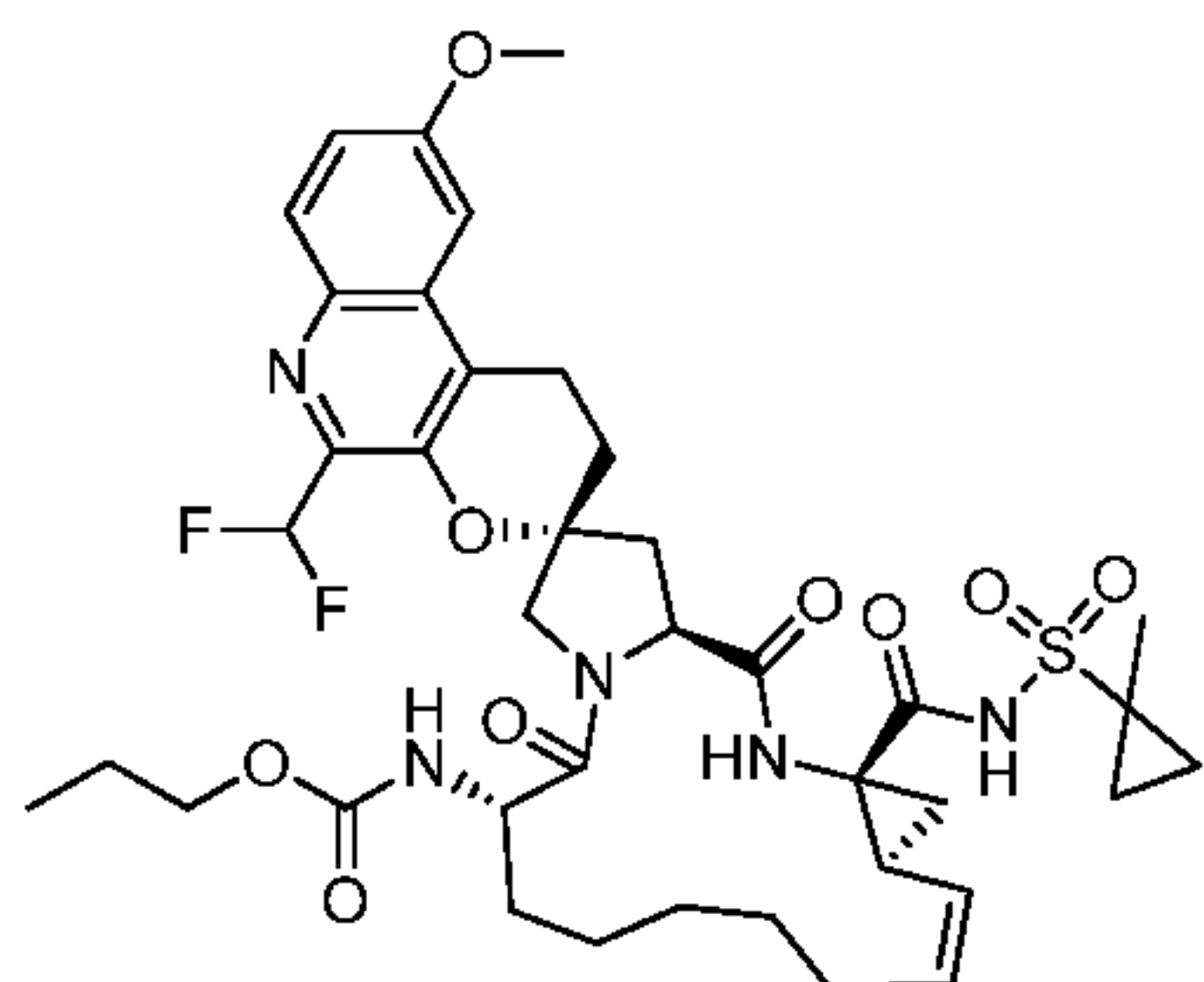
I-472



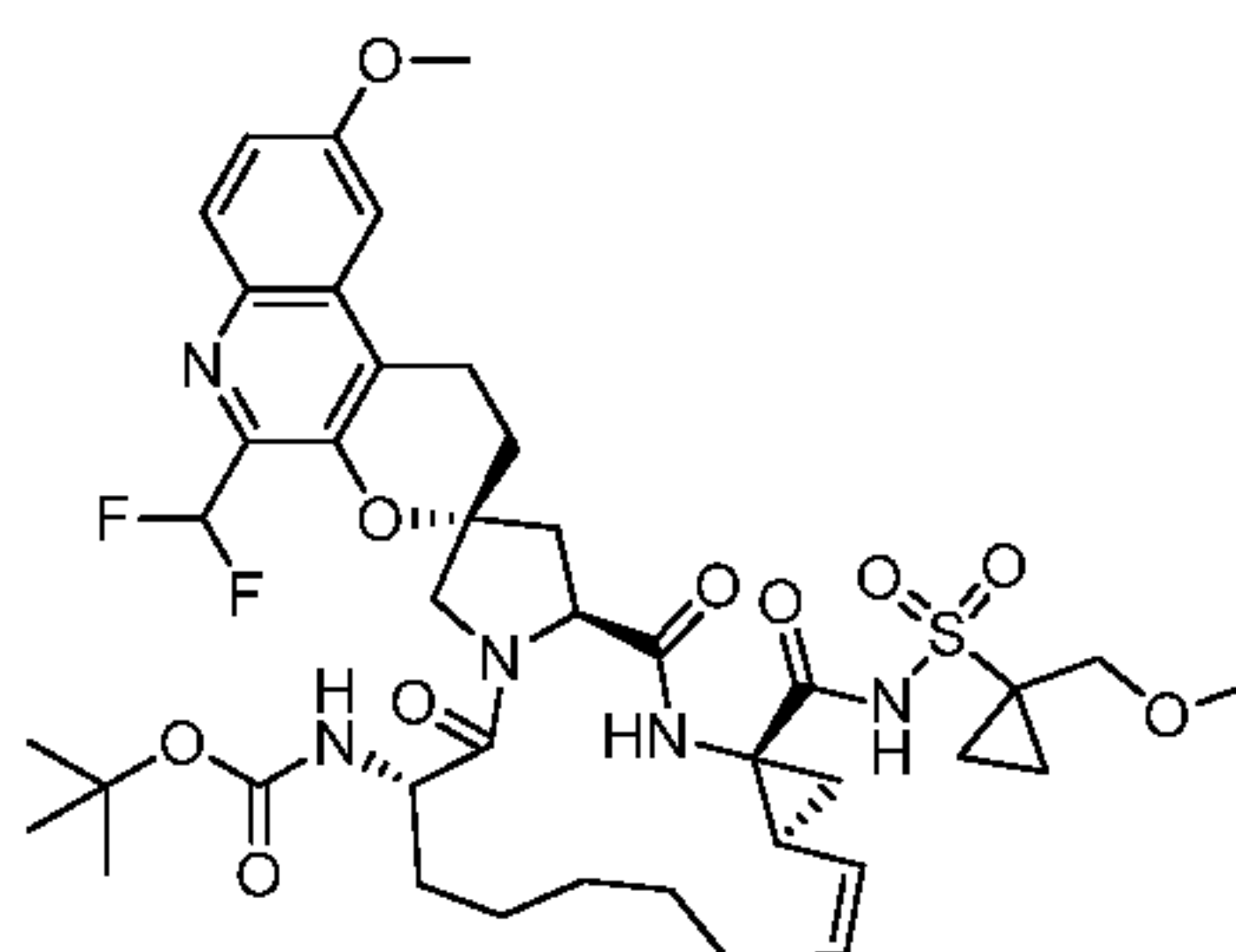
I-473



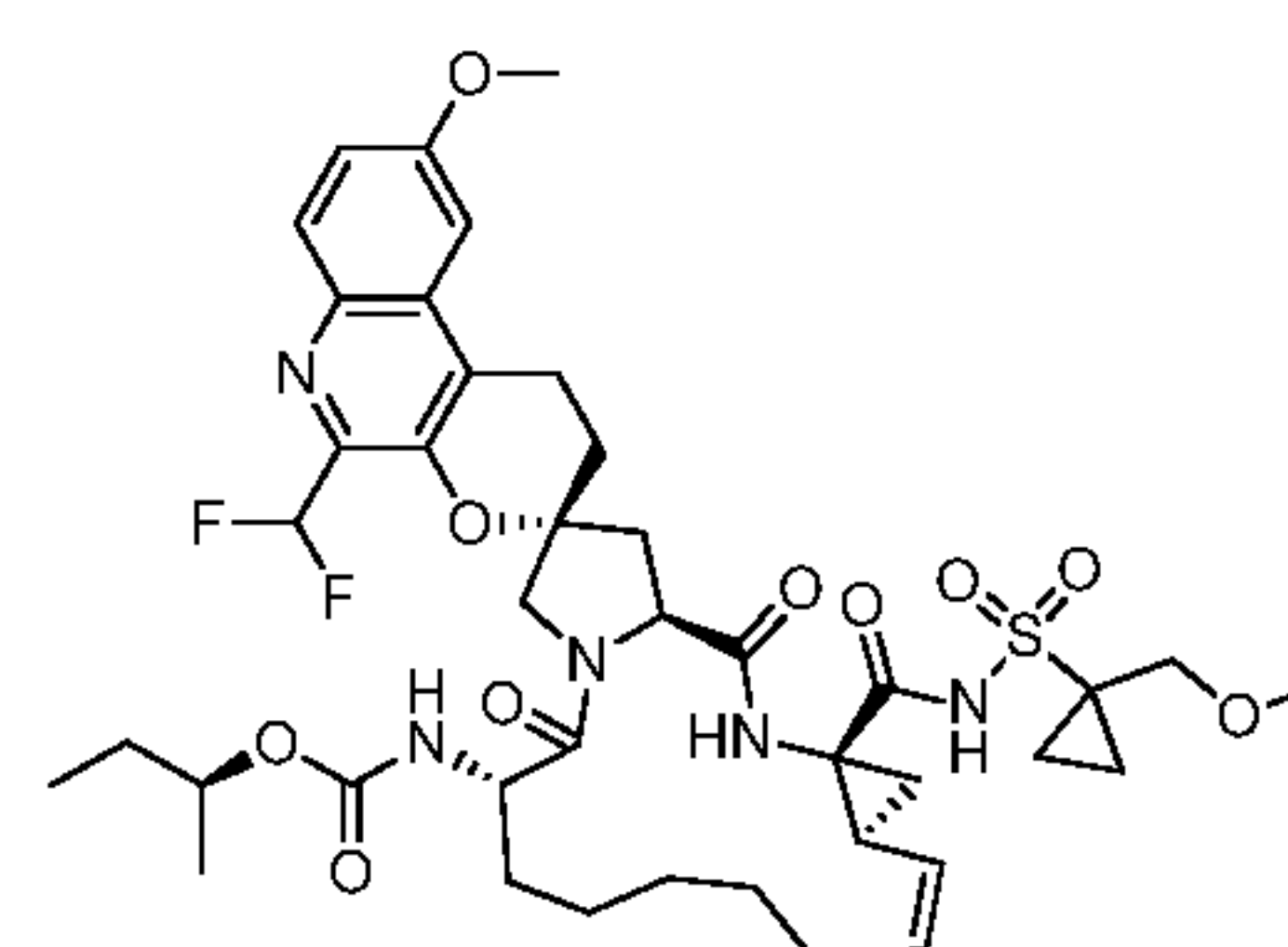
I-474



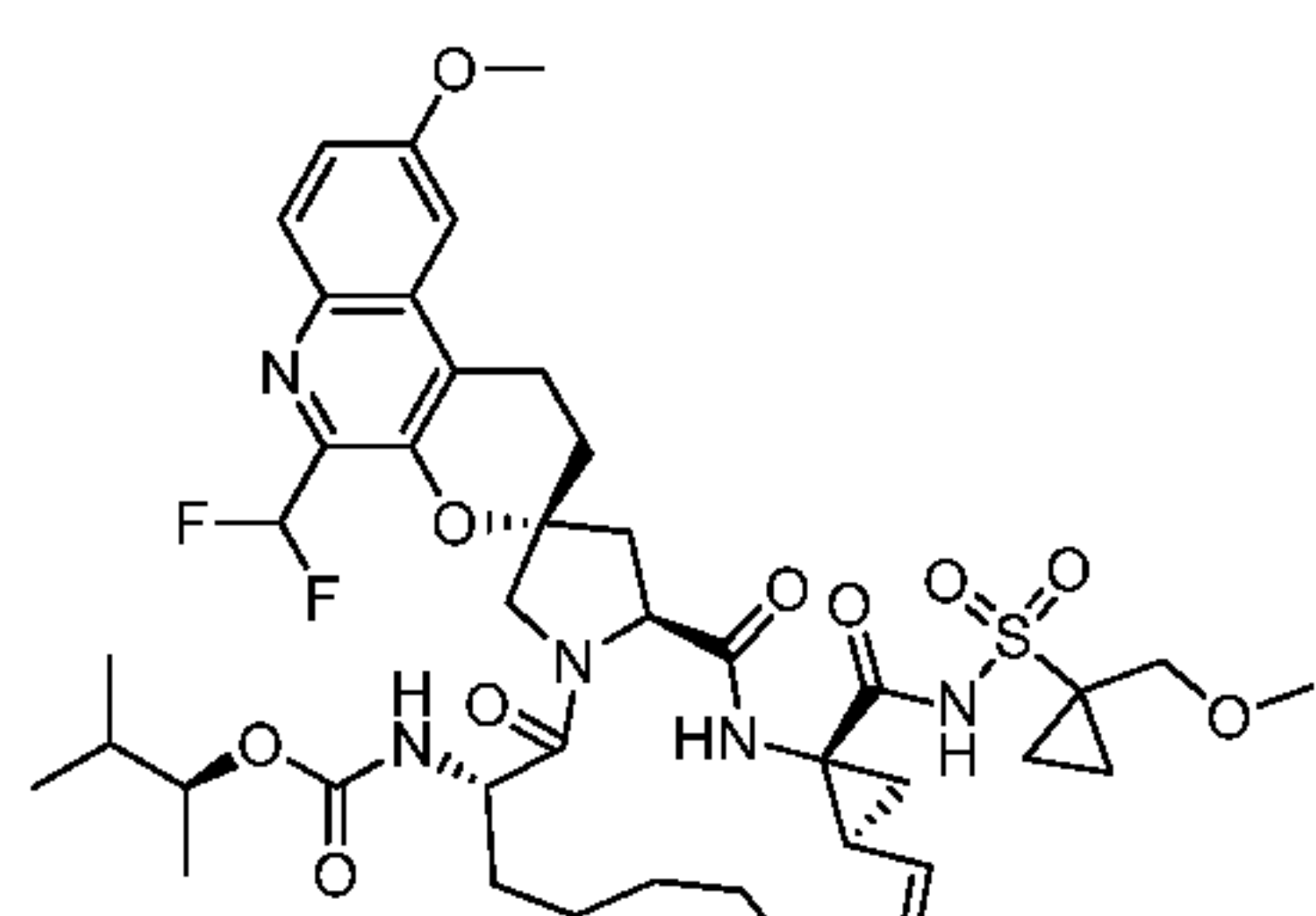
I-475



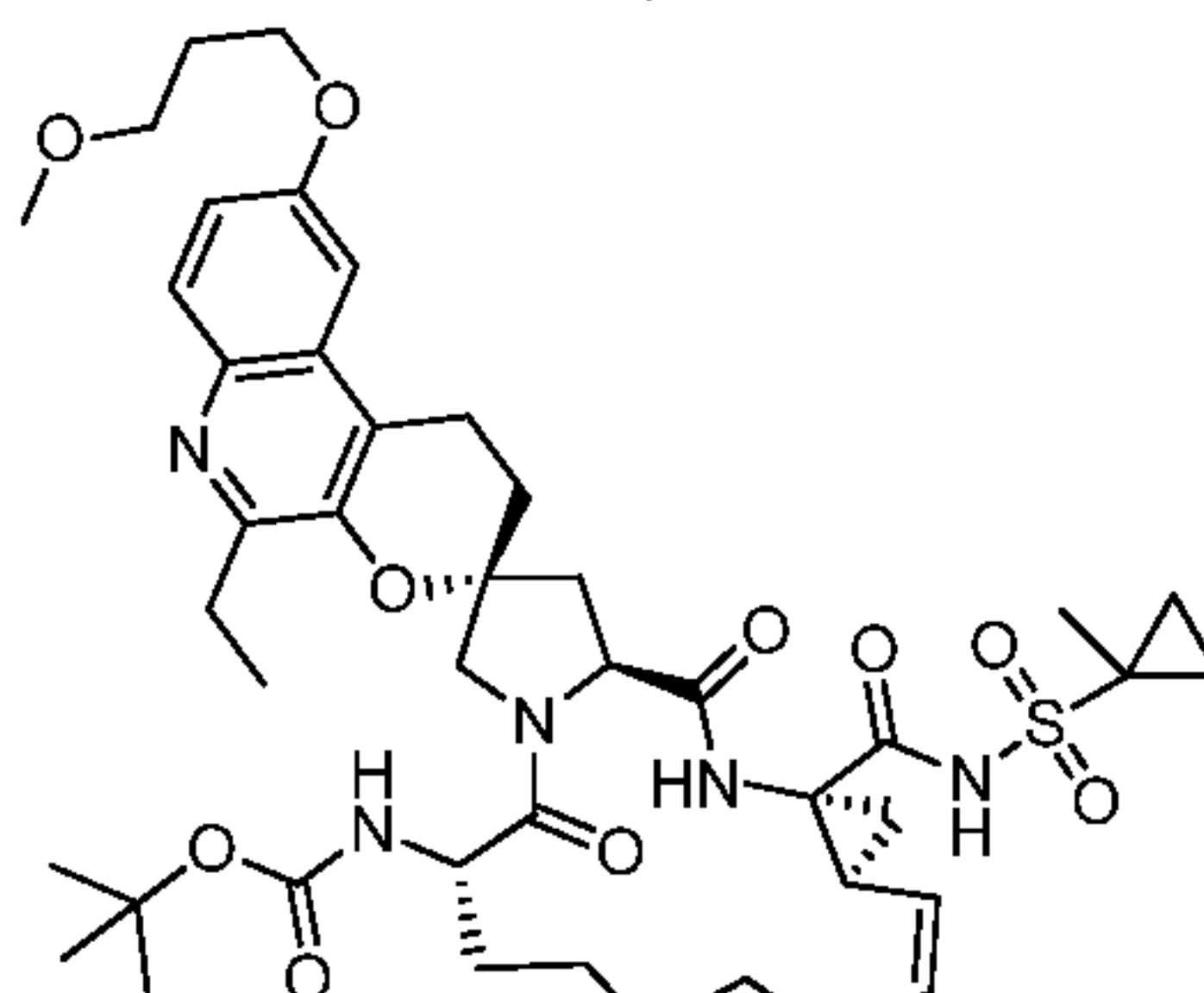
I-476



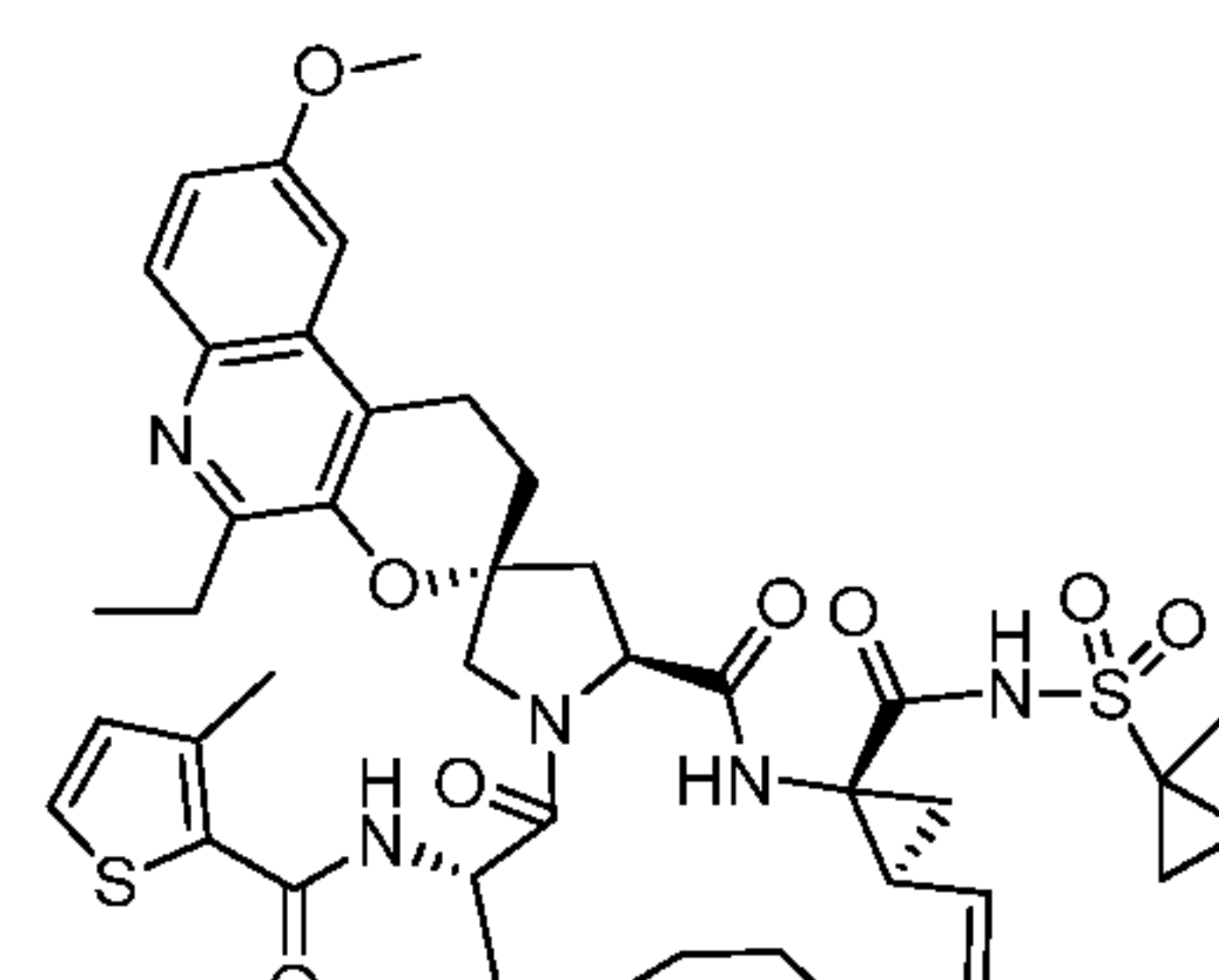
I-477



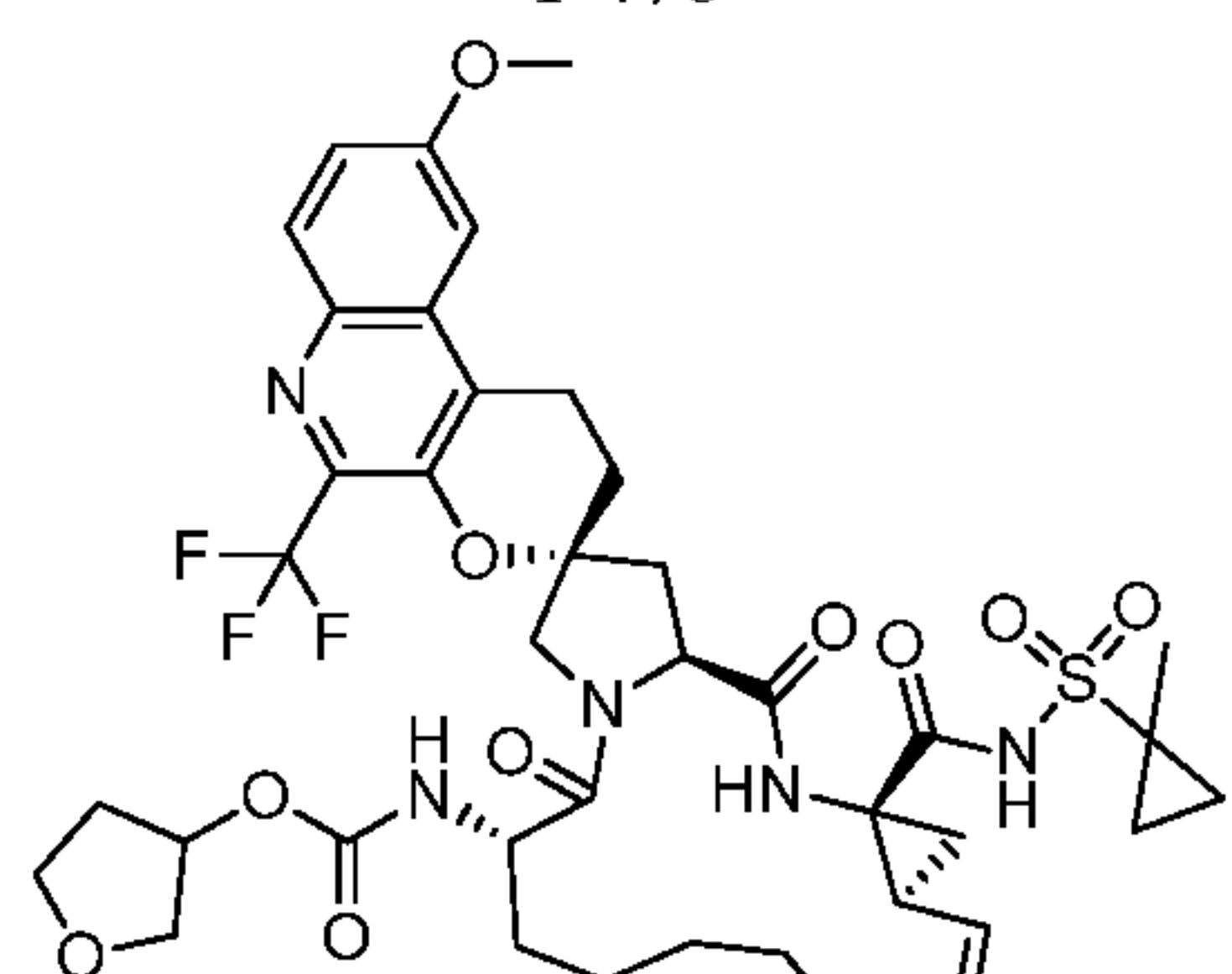
I-478



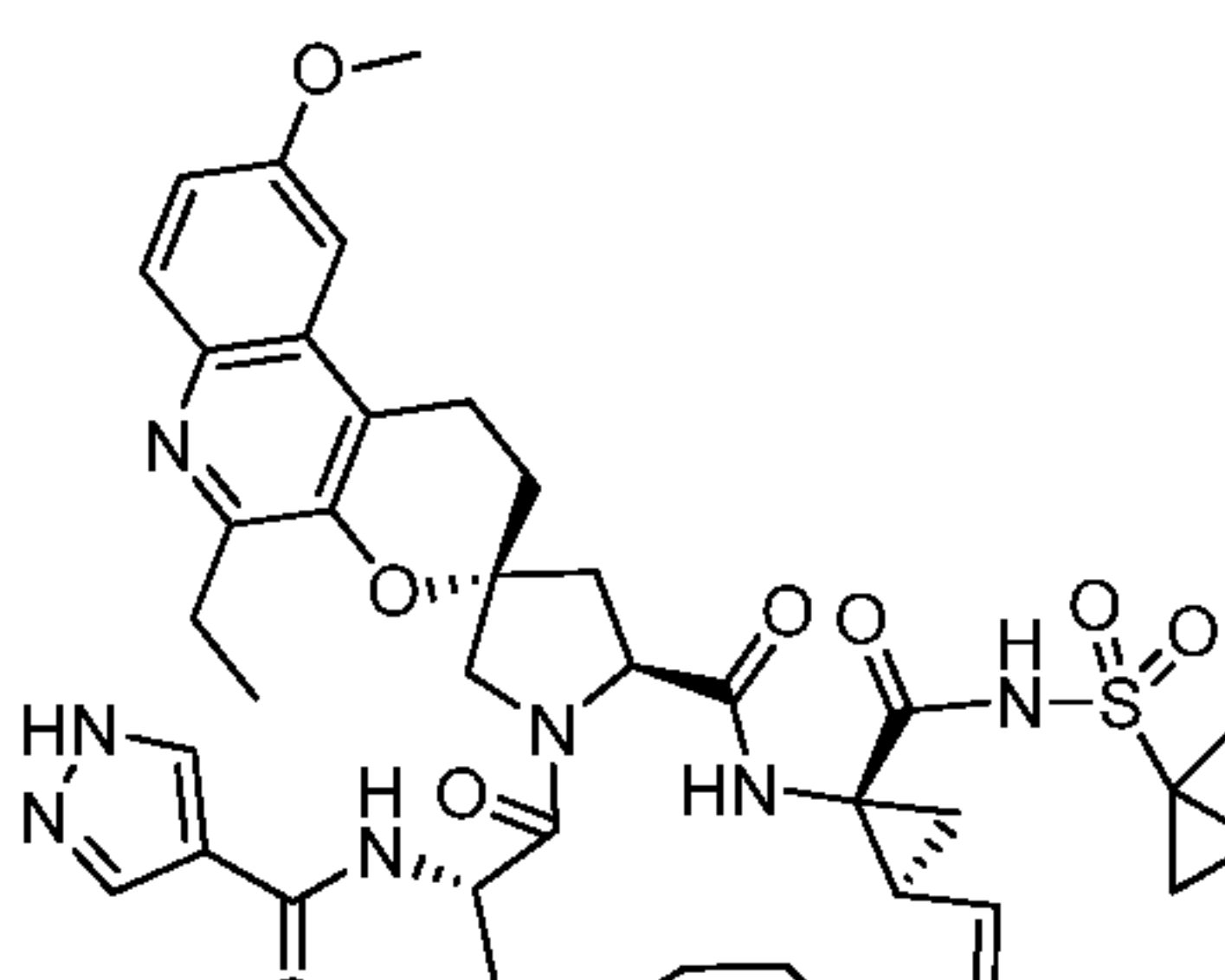
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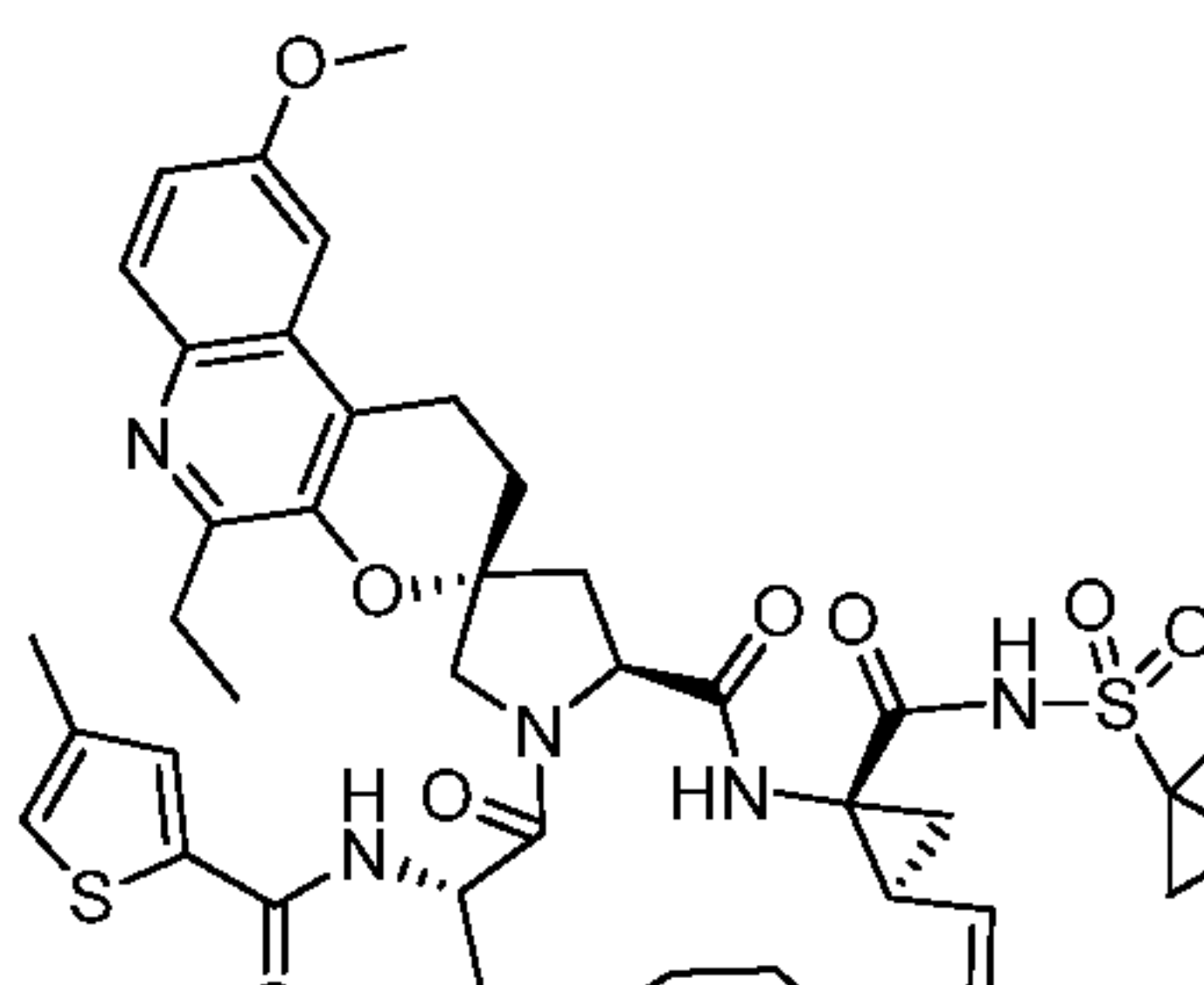
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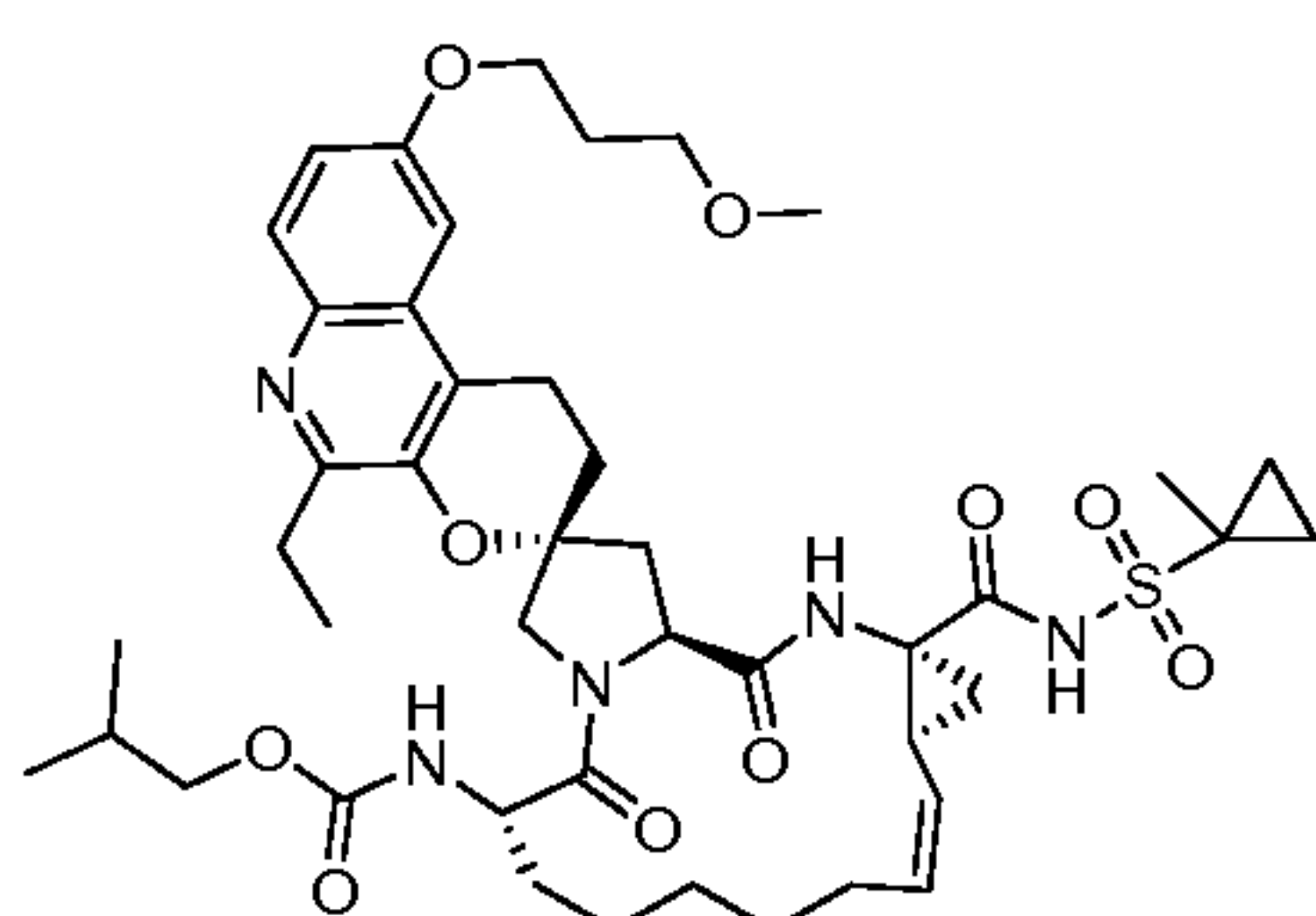
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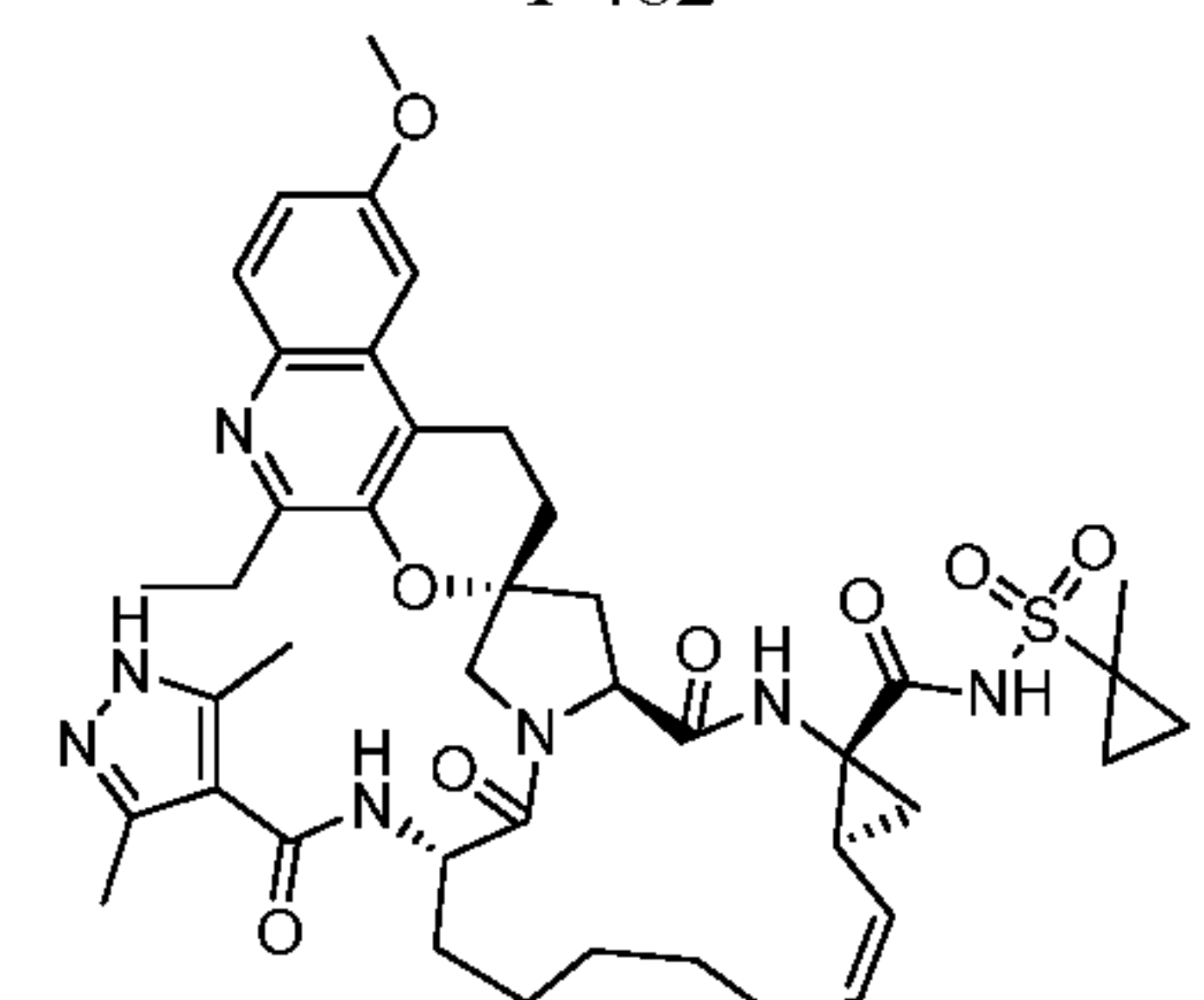
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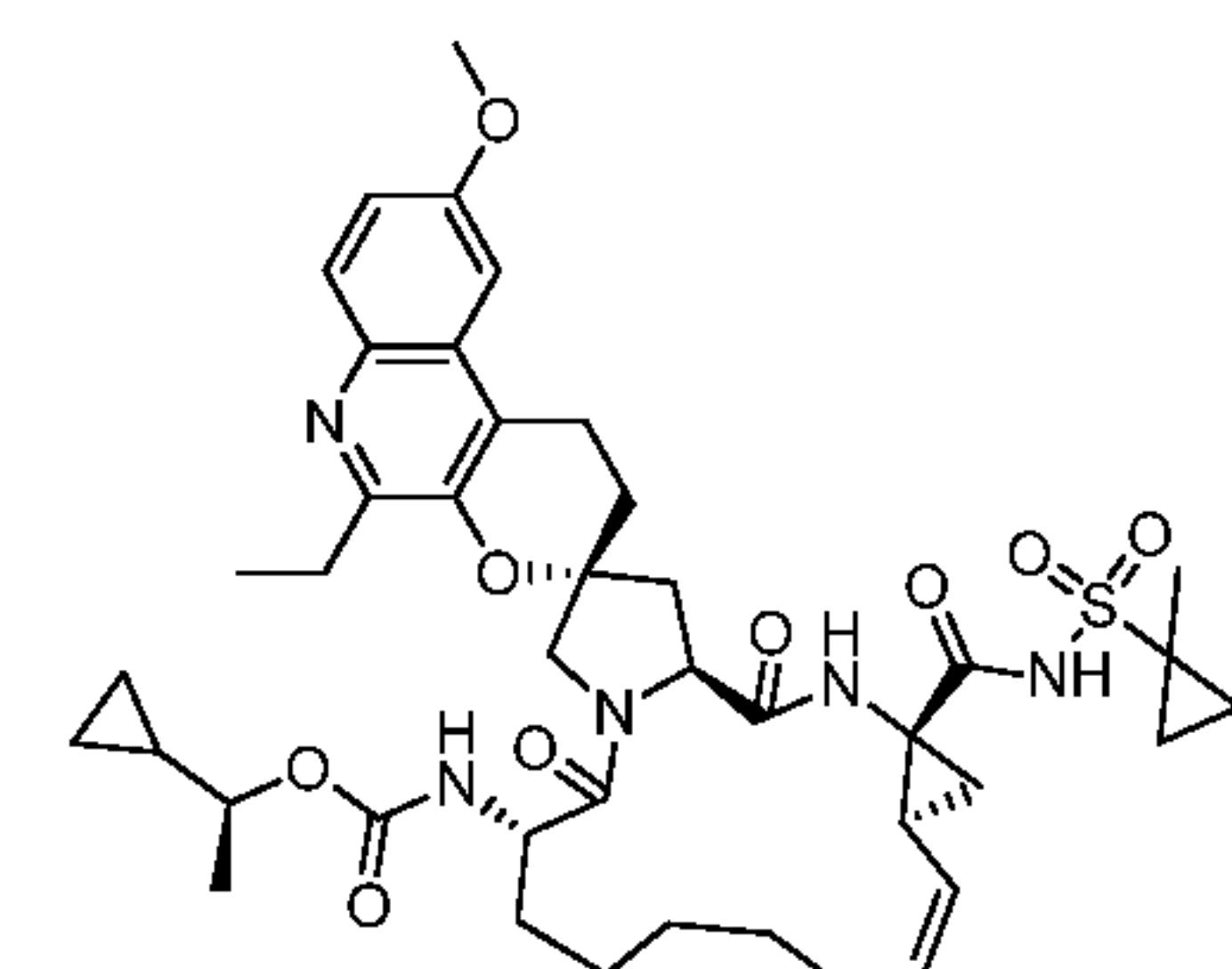
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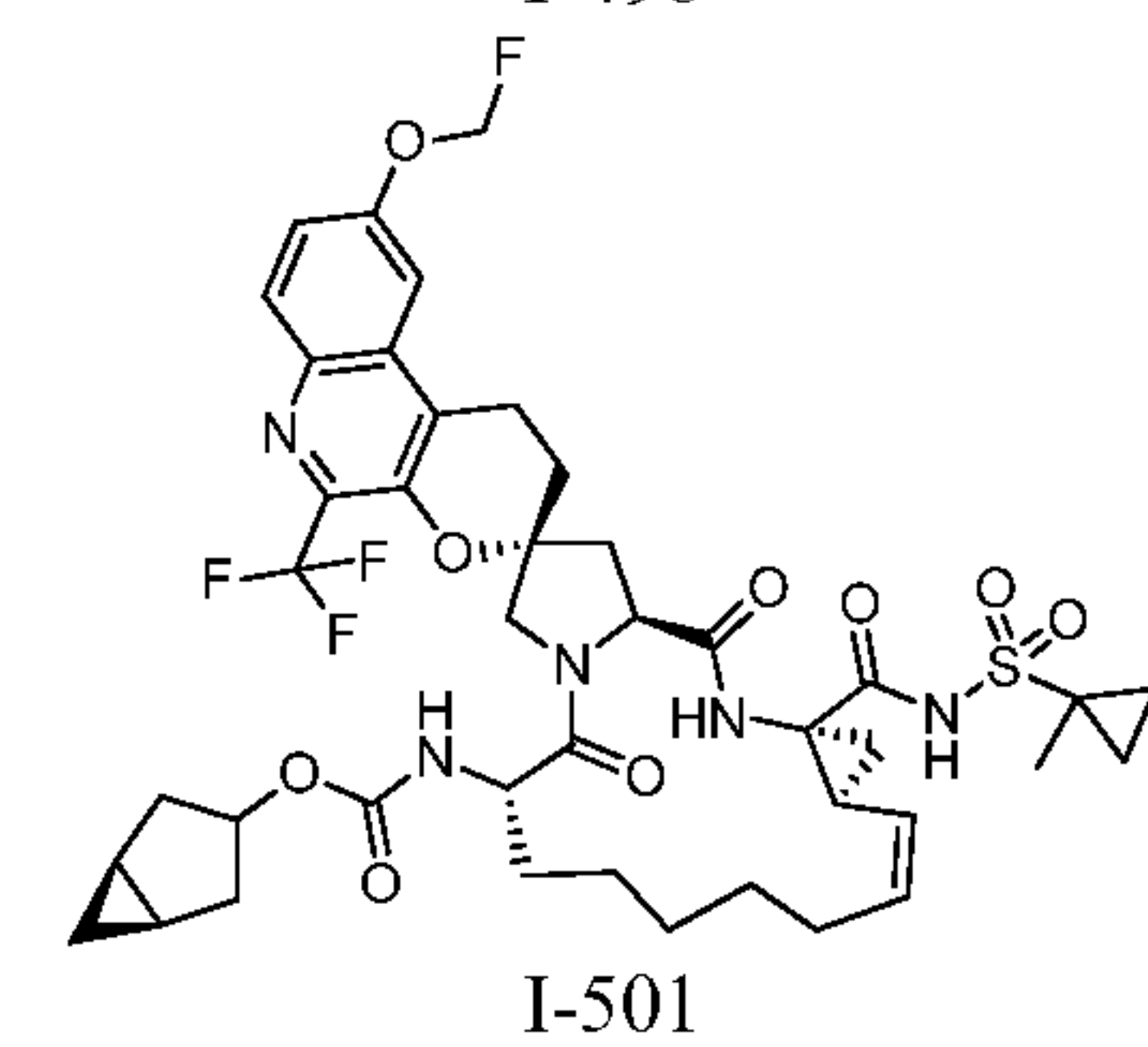
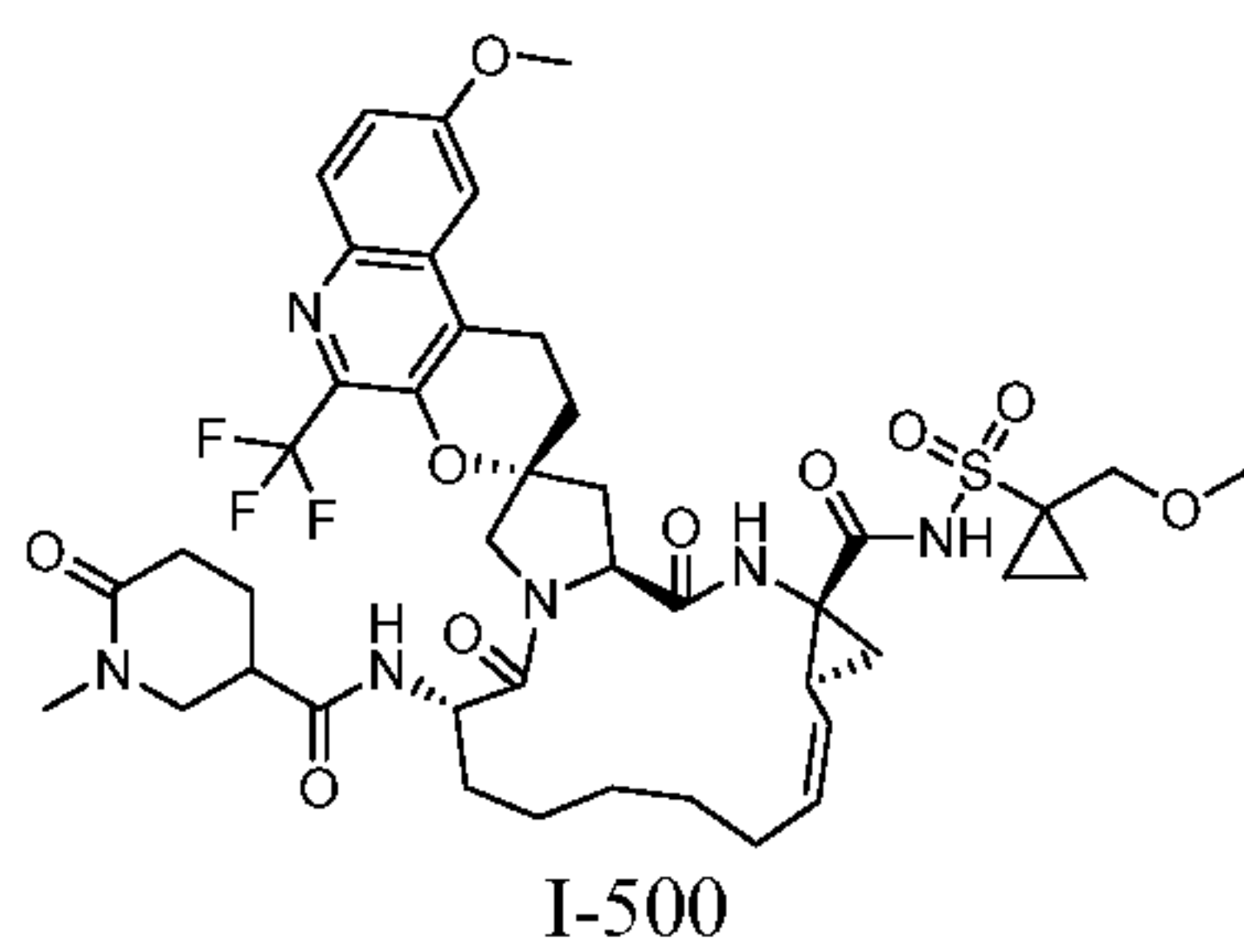
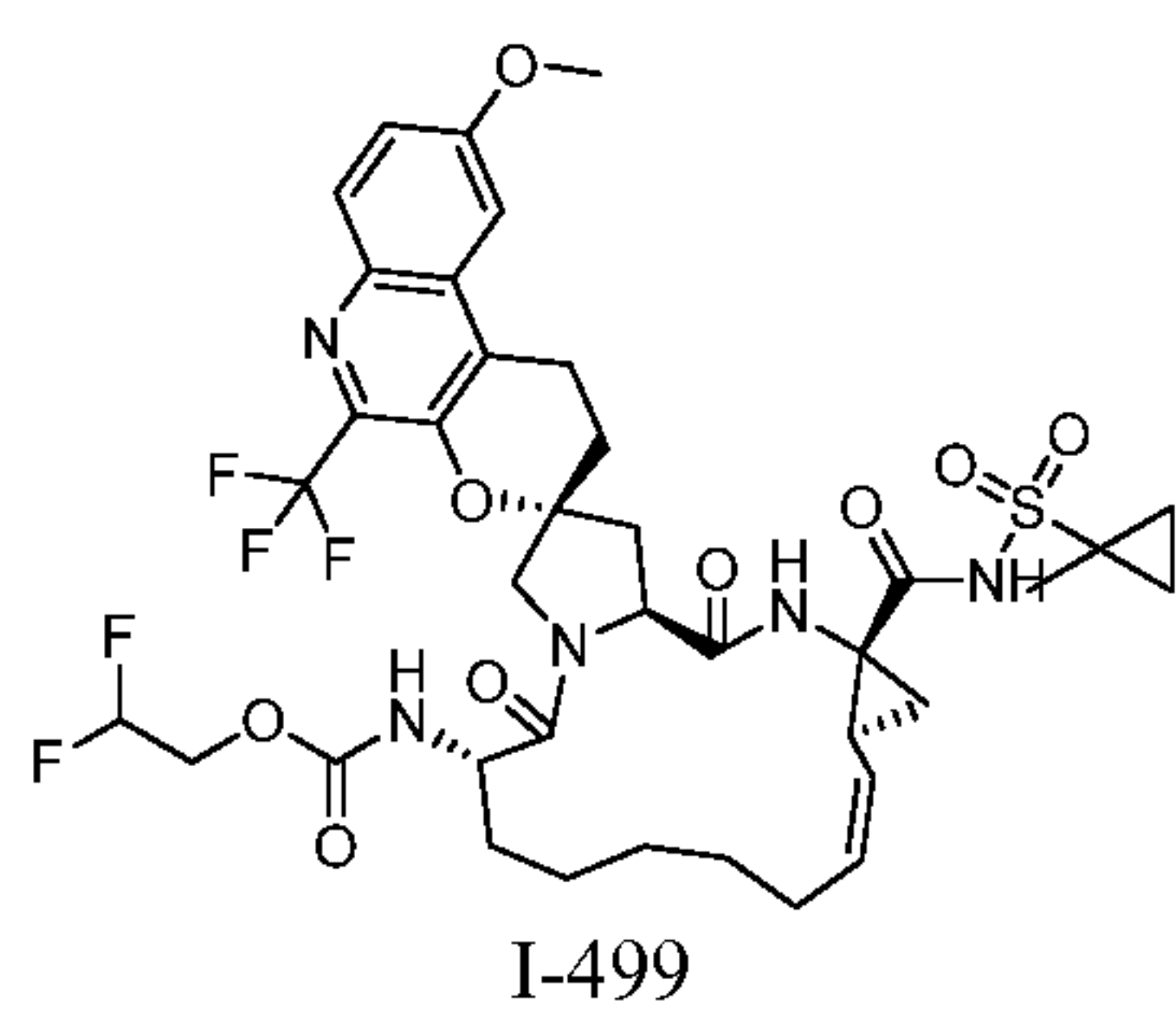
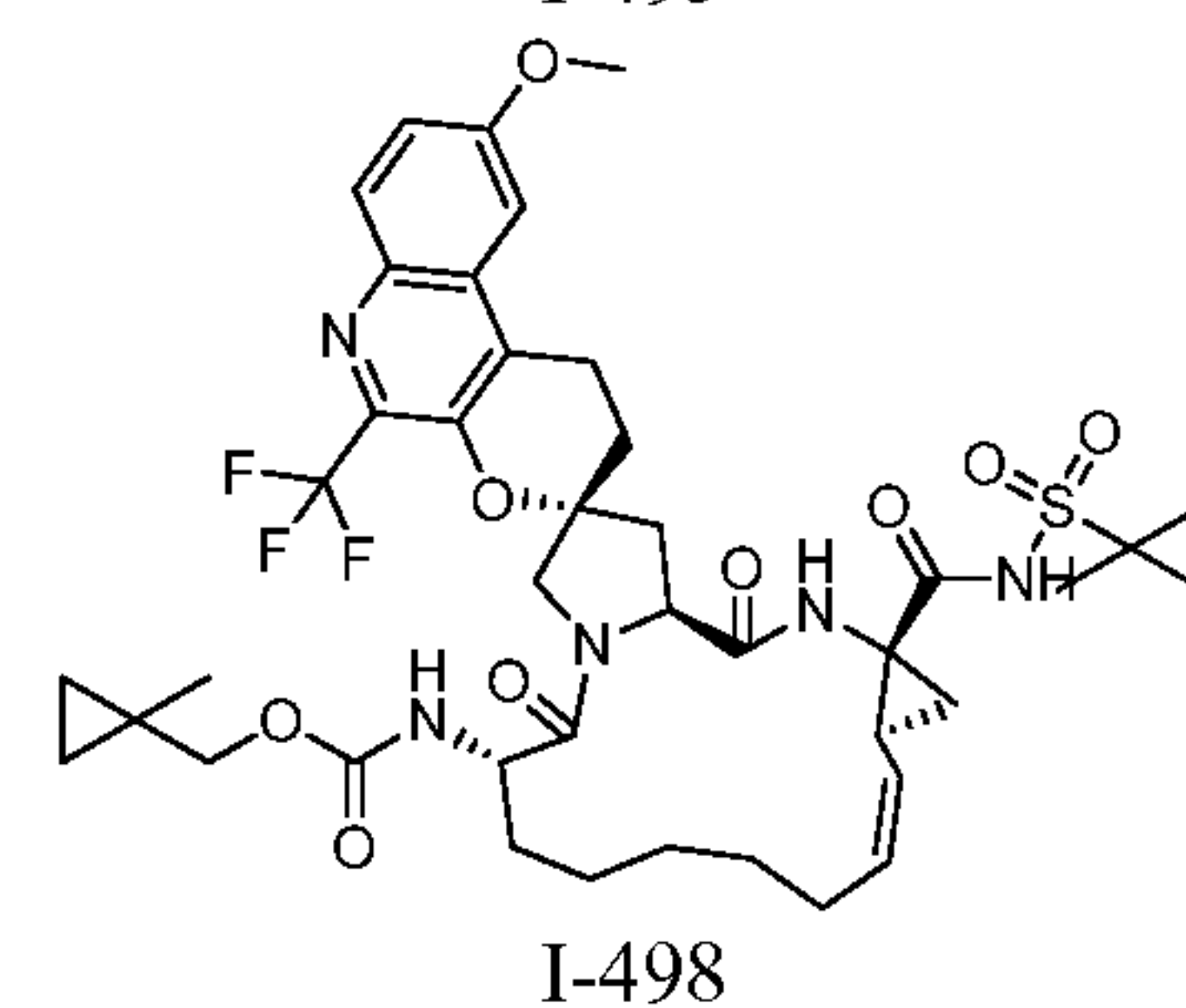
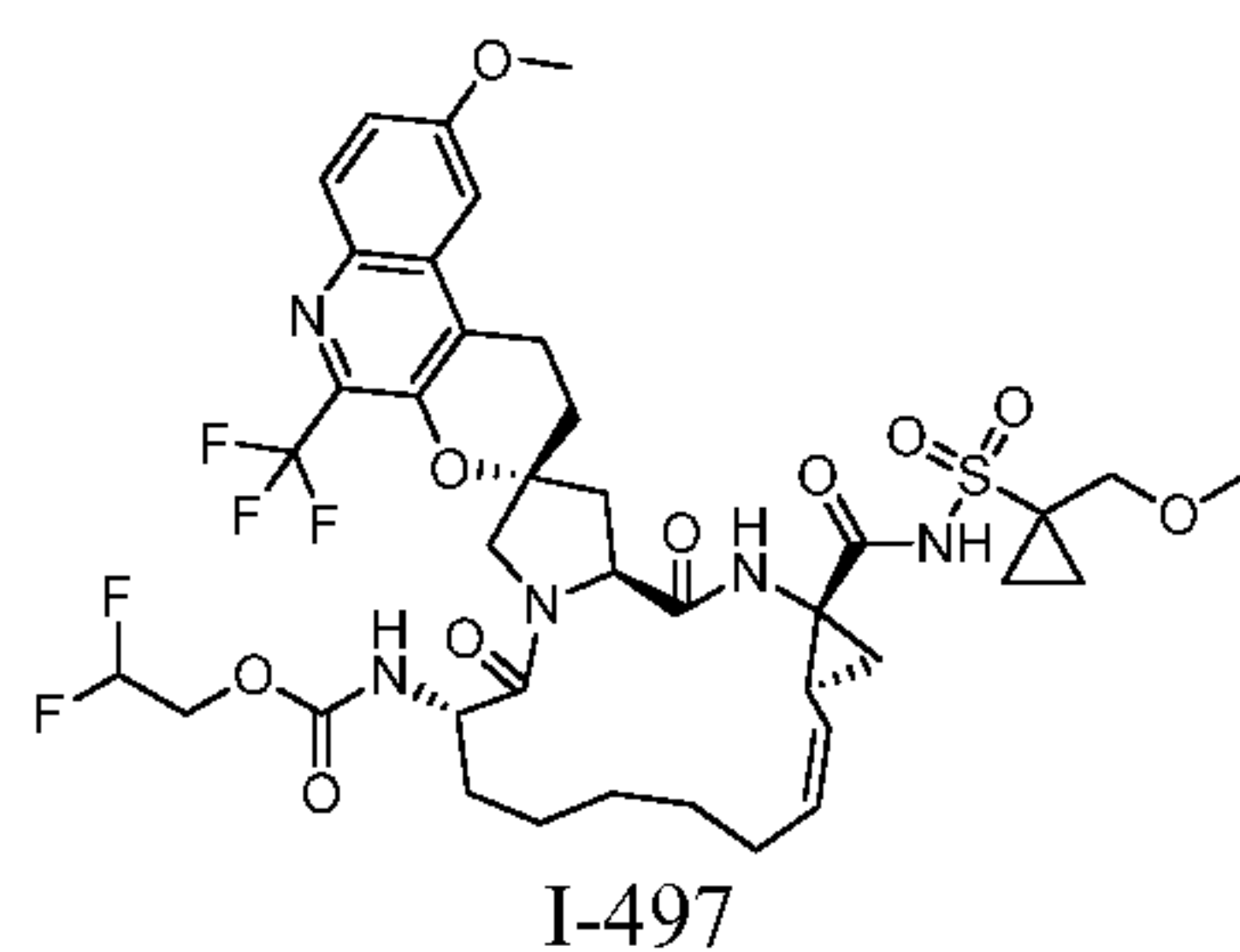
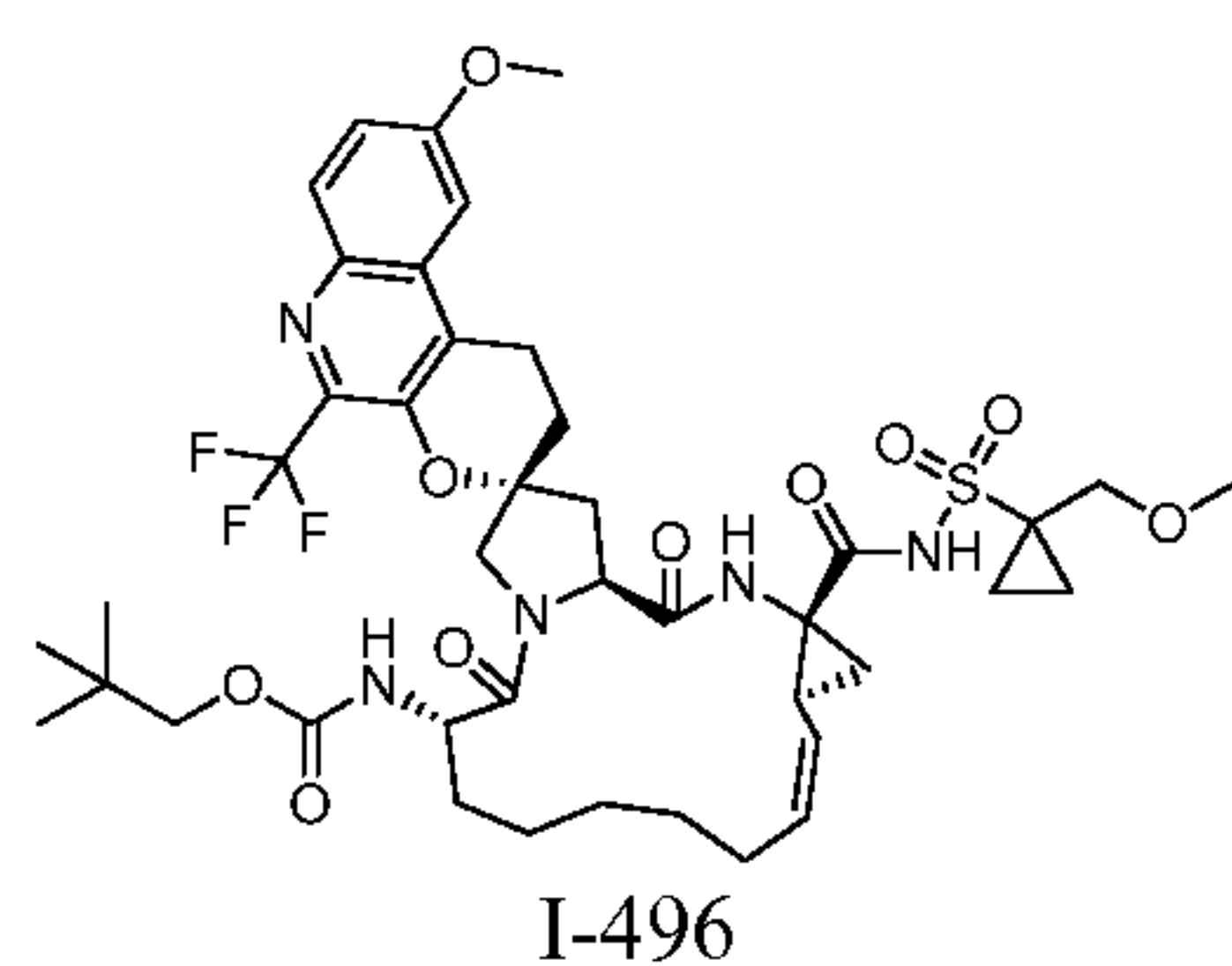
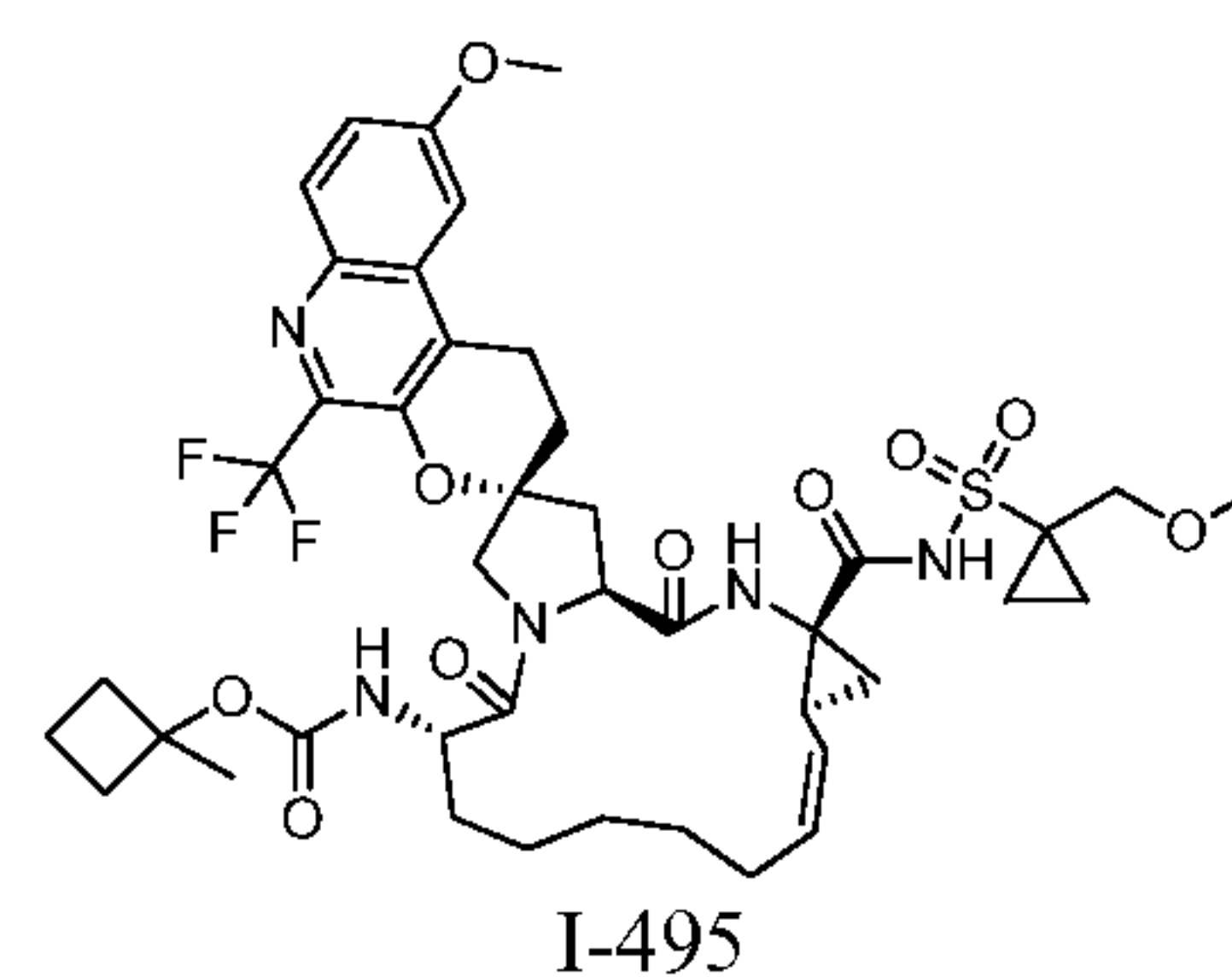
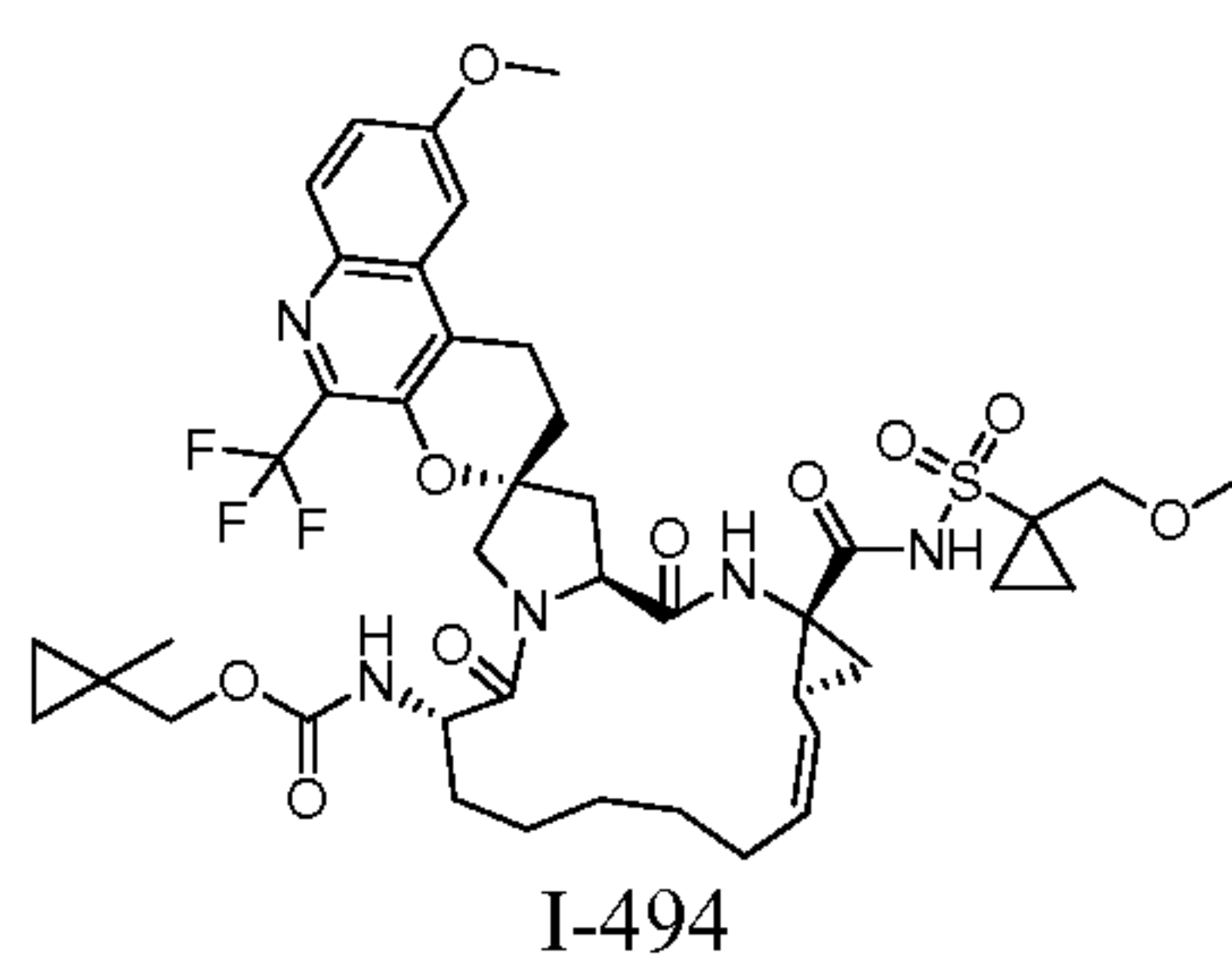
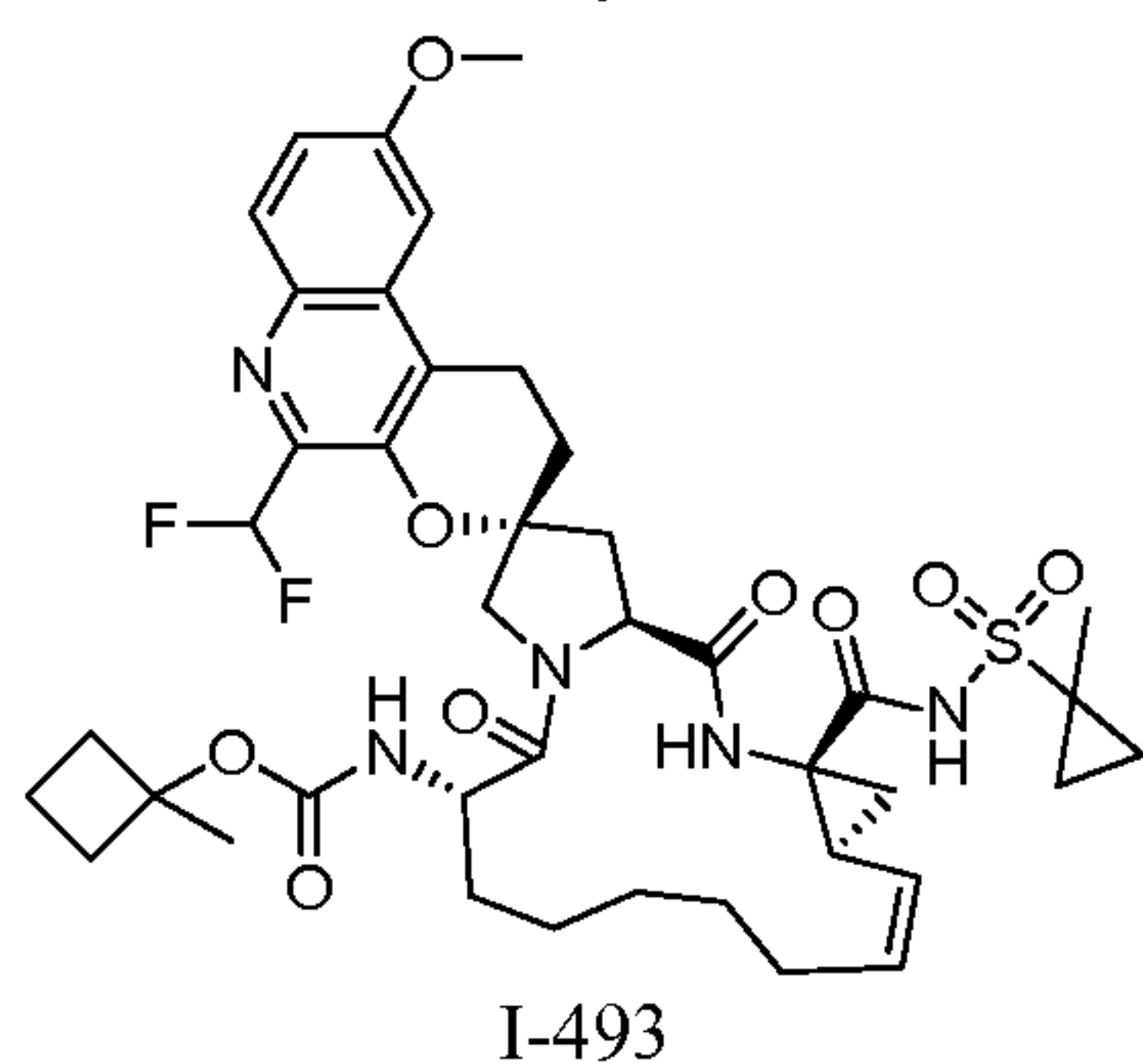
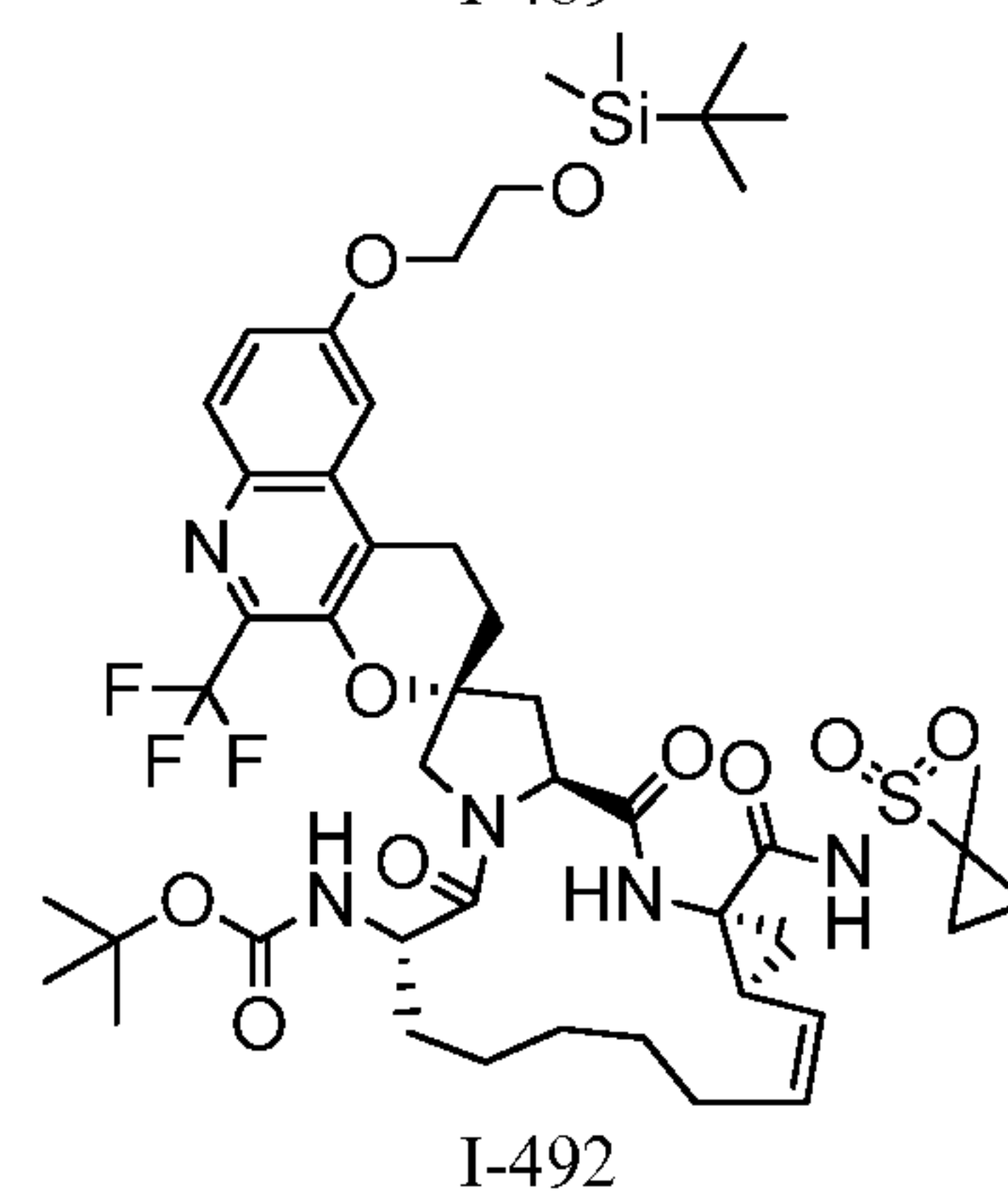
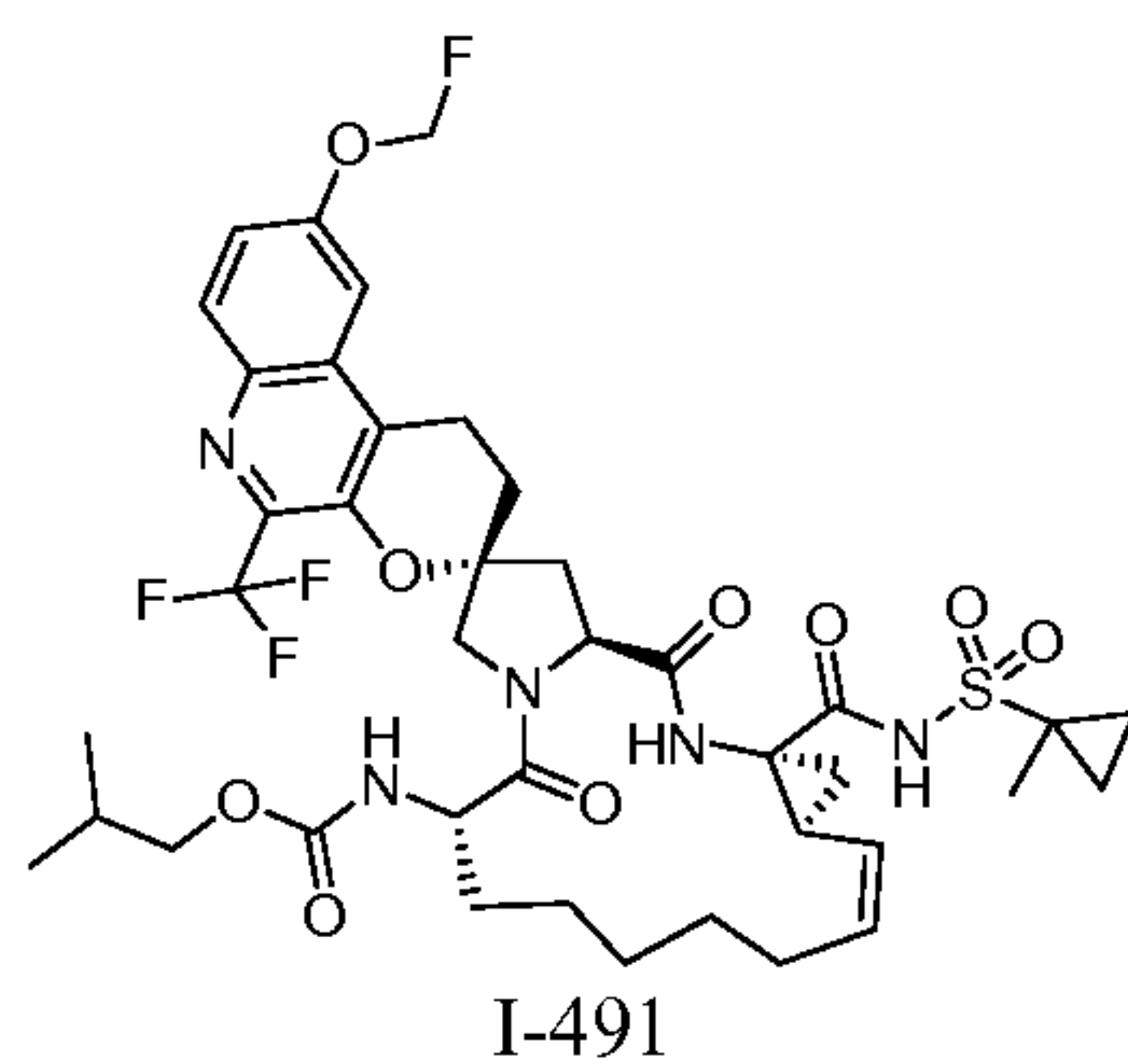
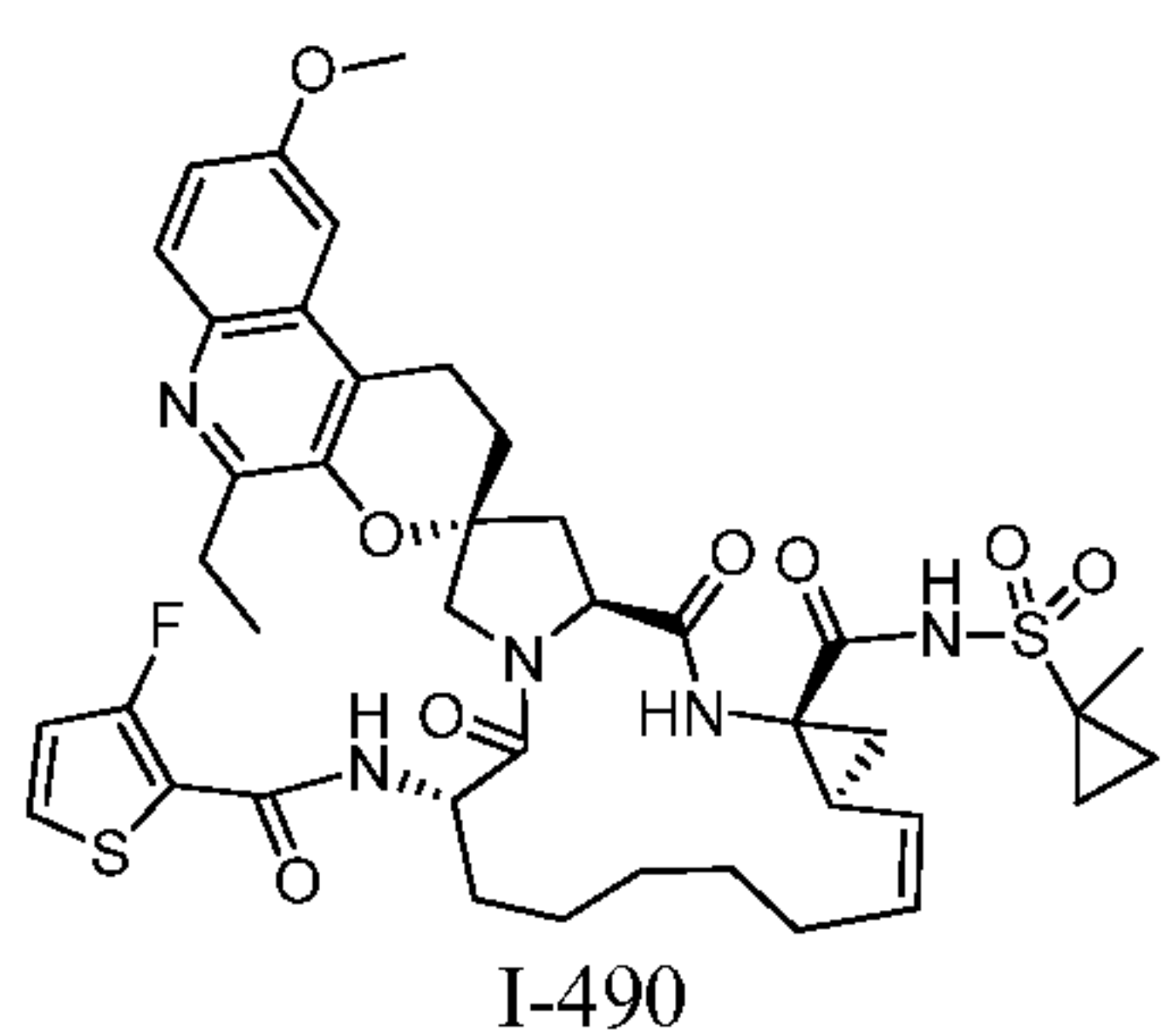
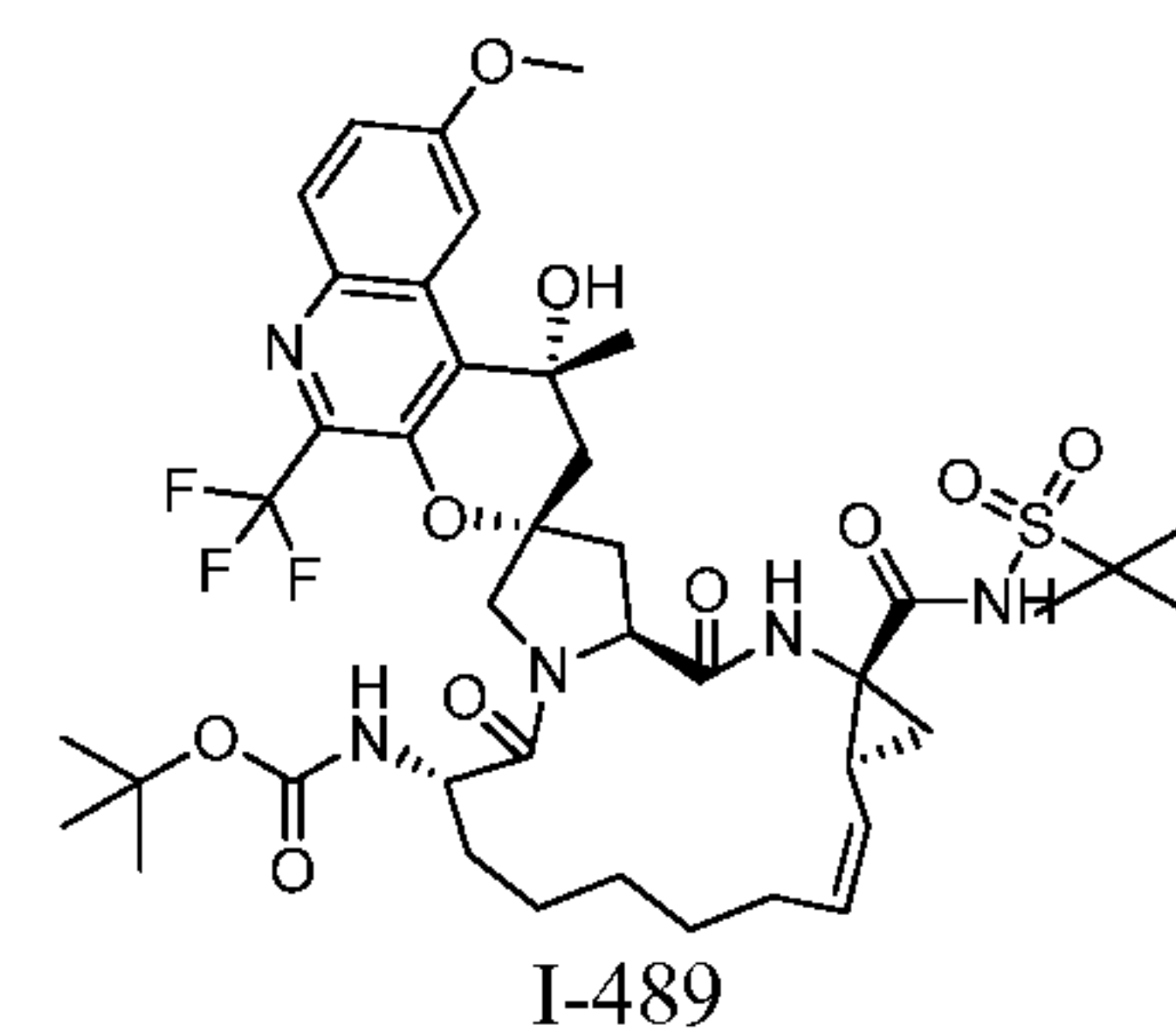
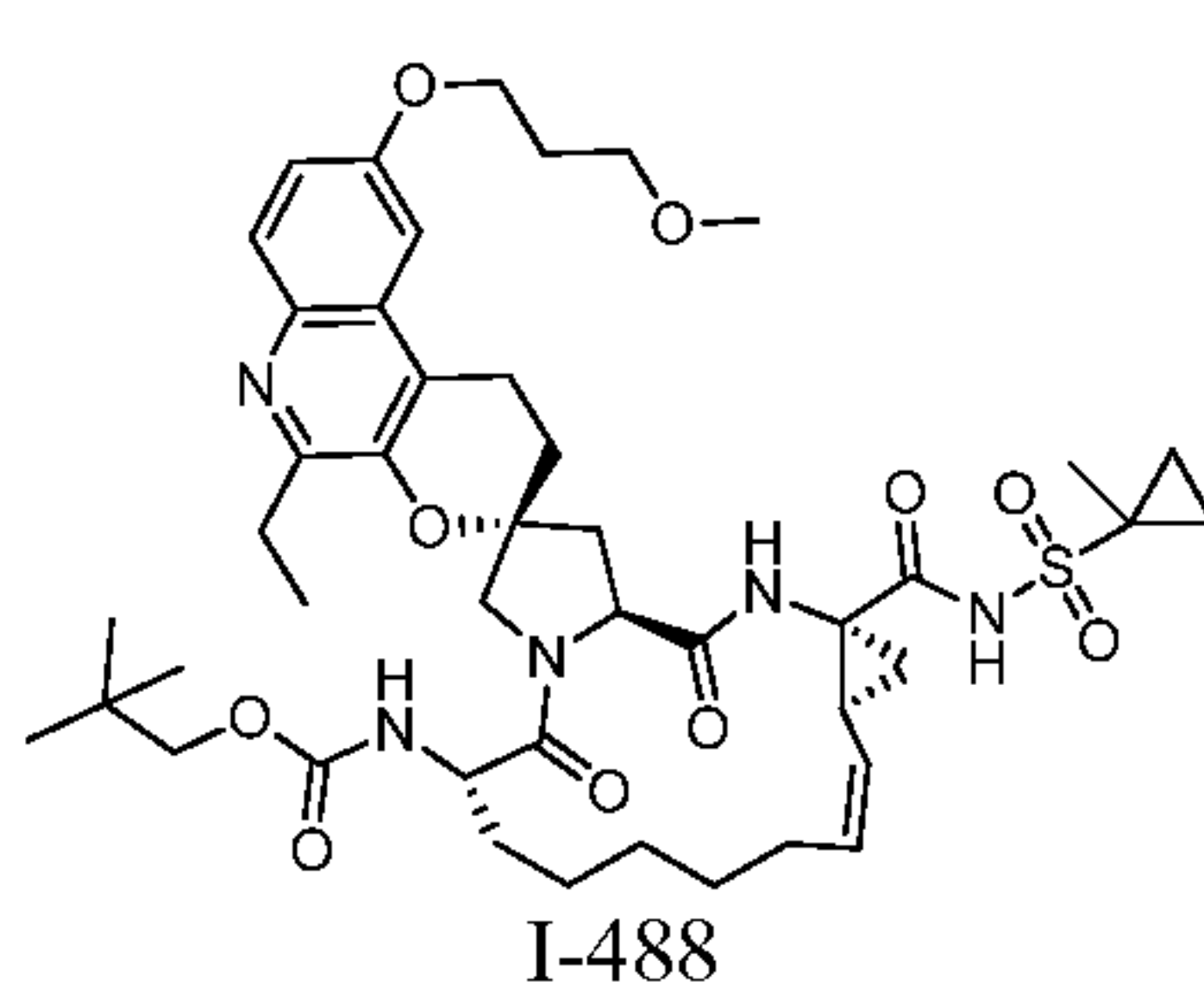
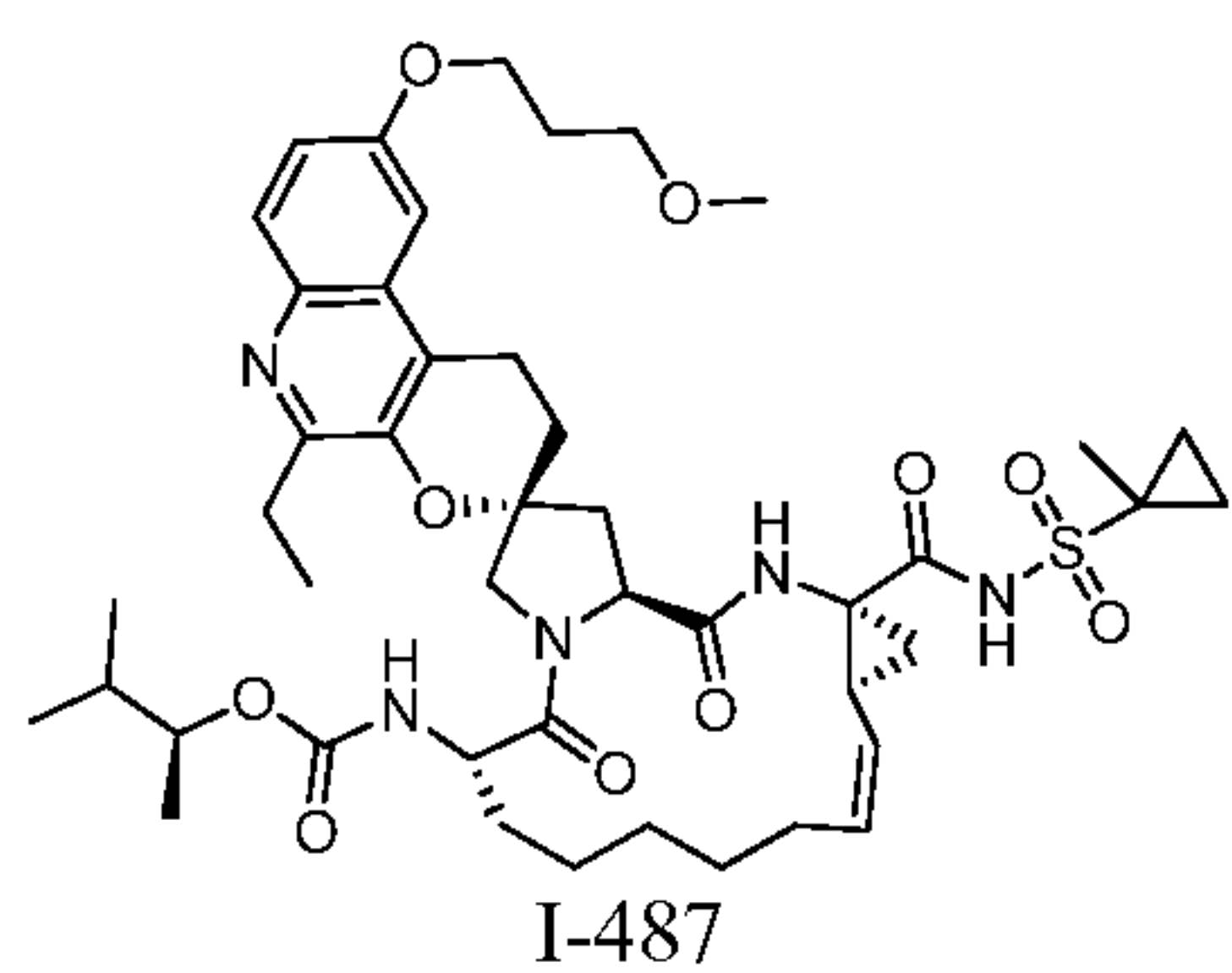
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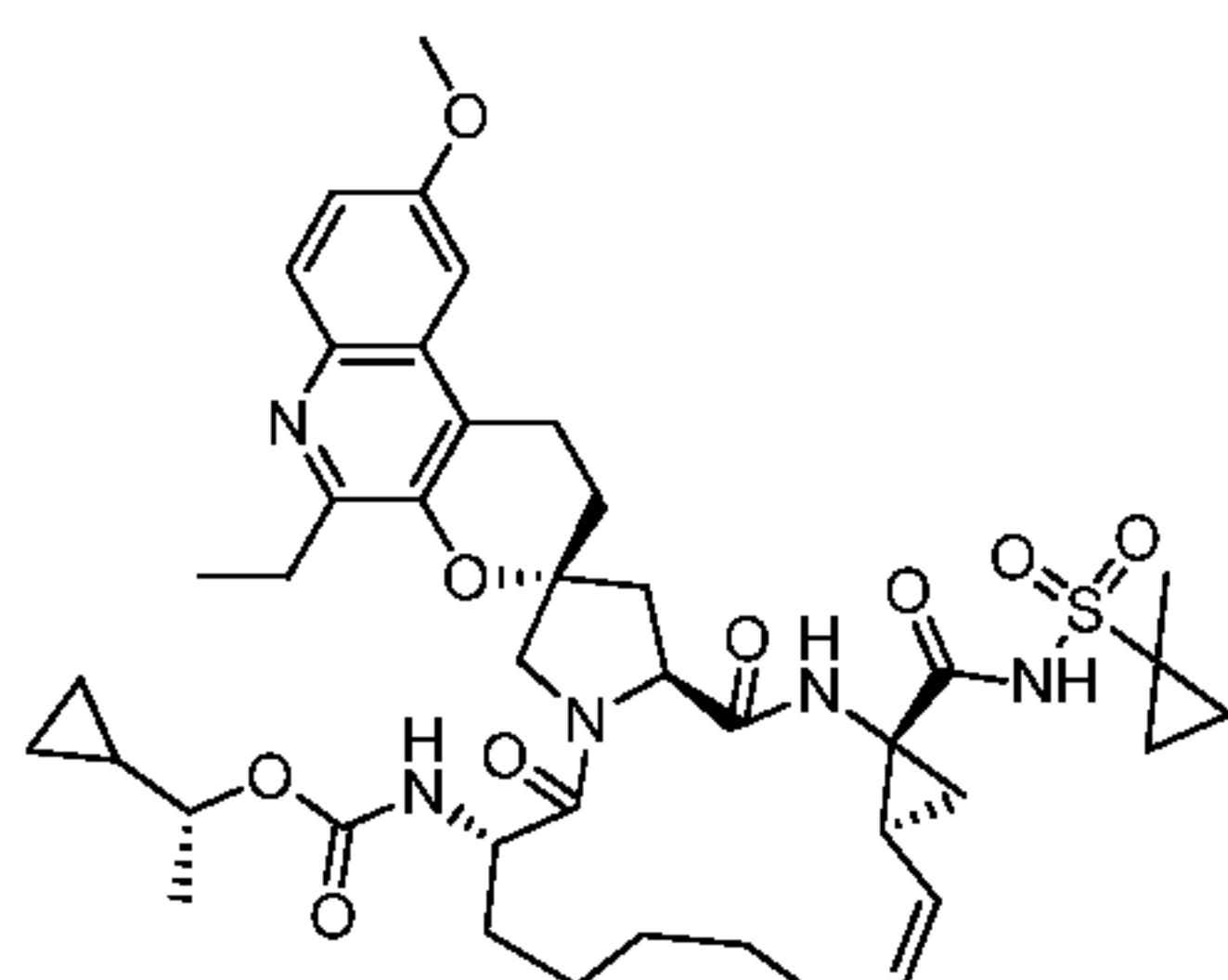


I-485

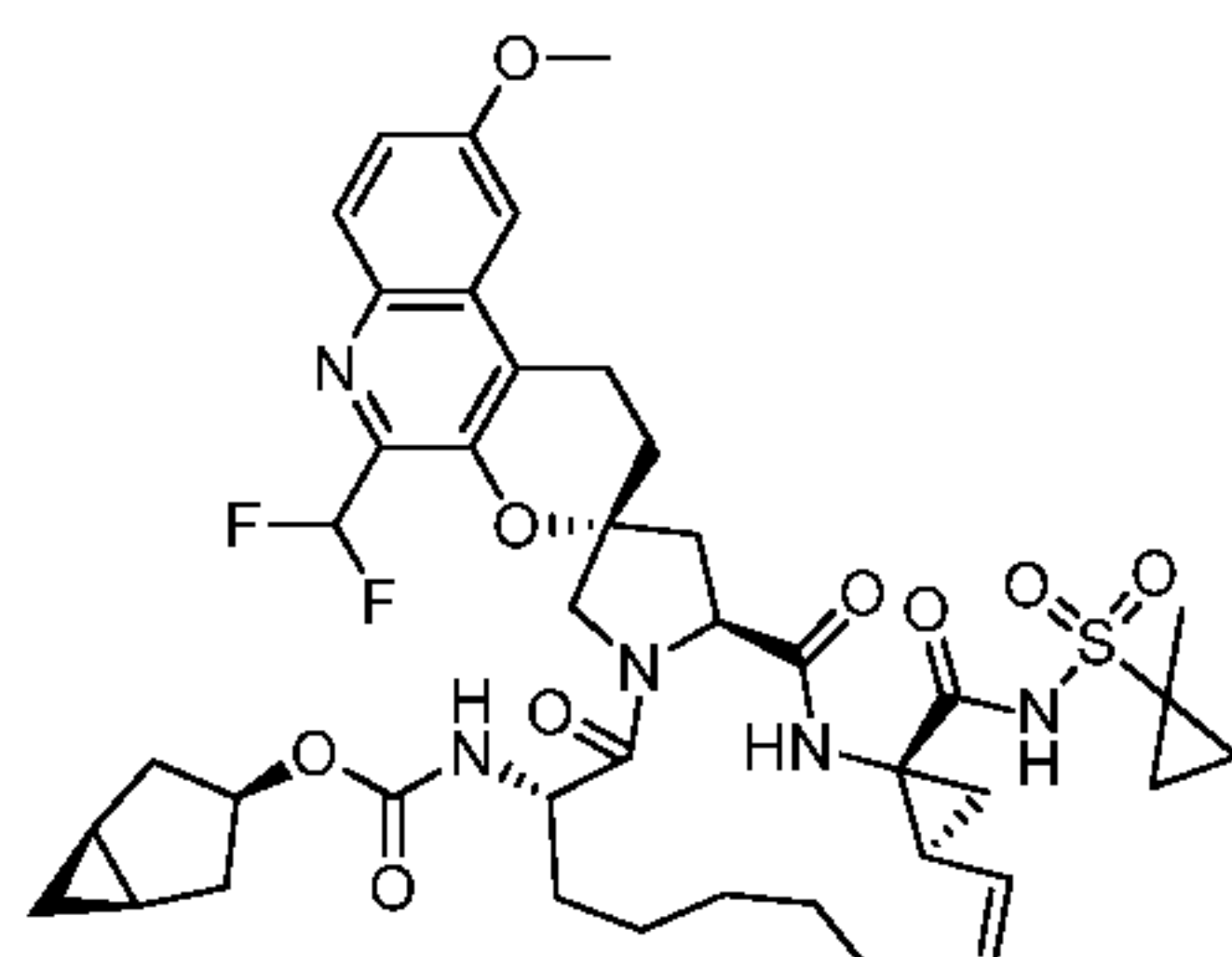


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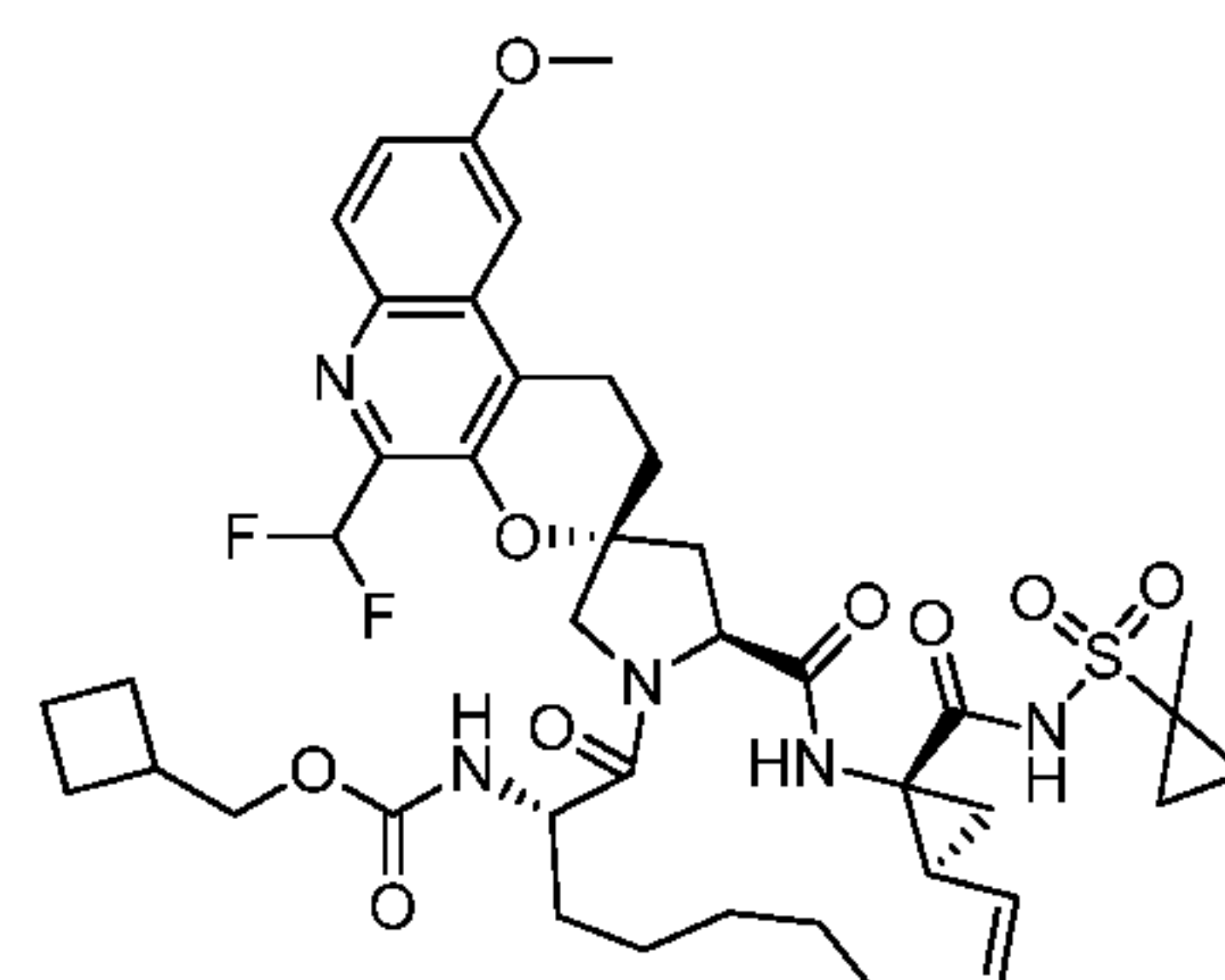




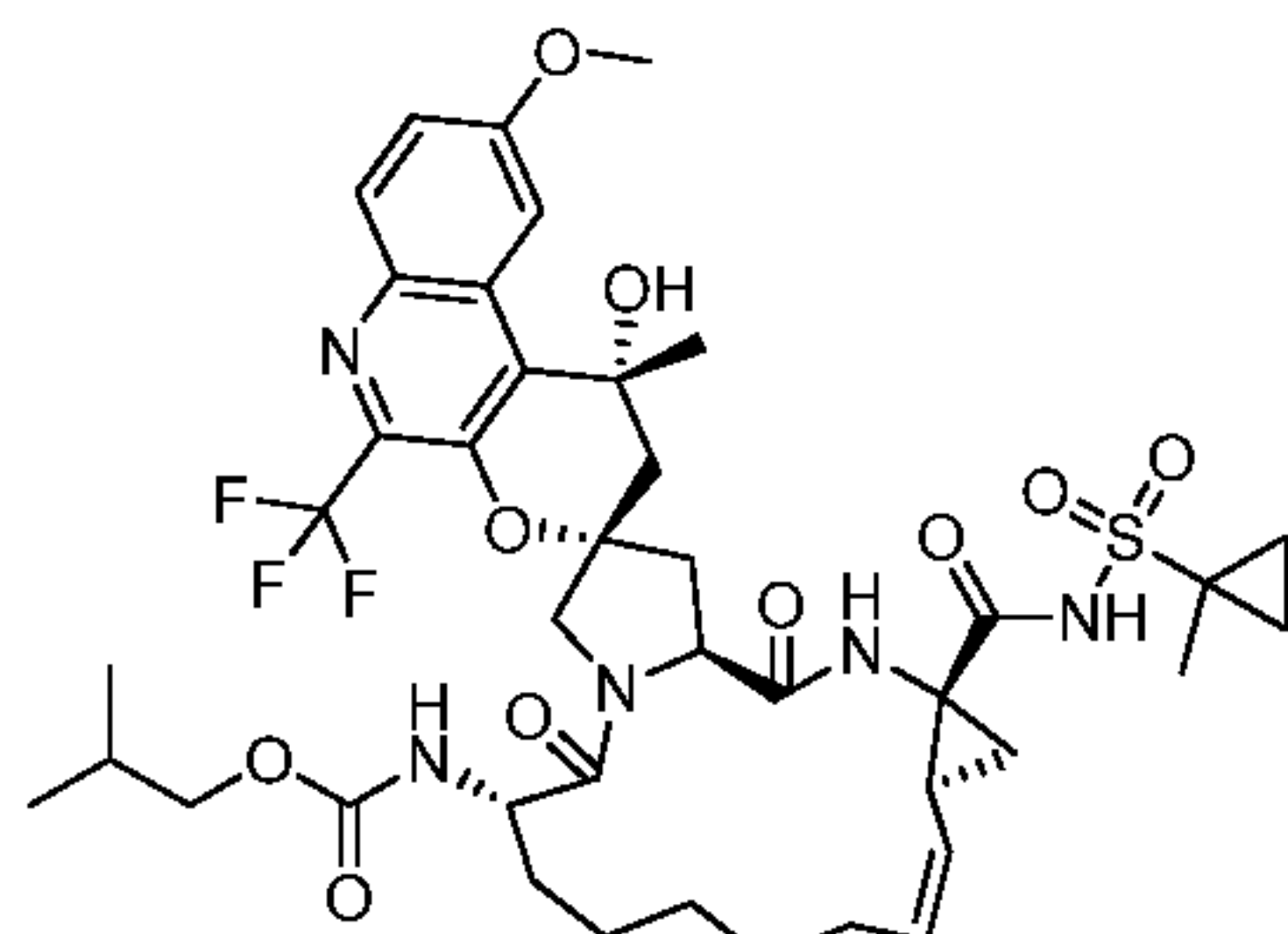
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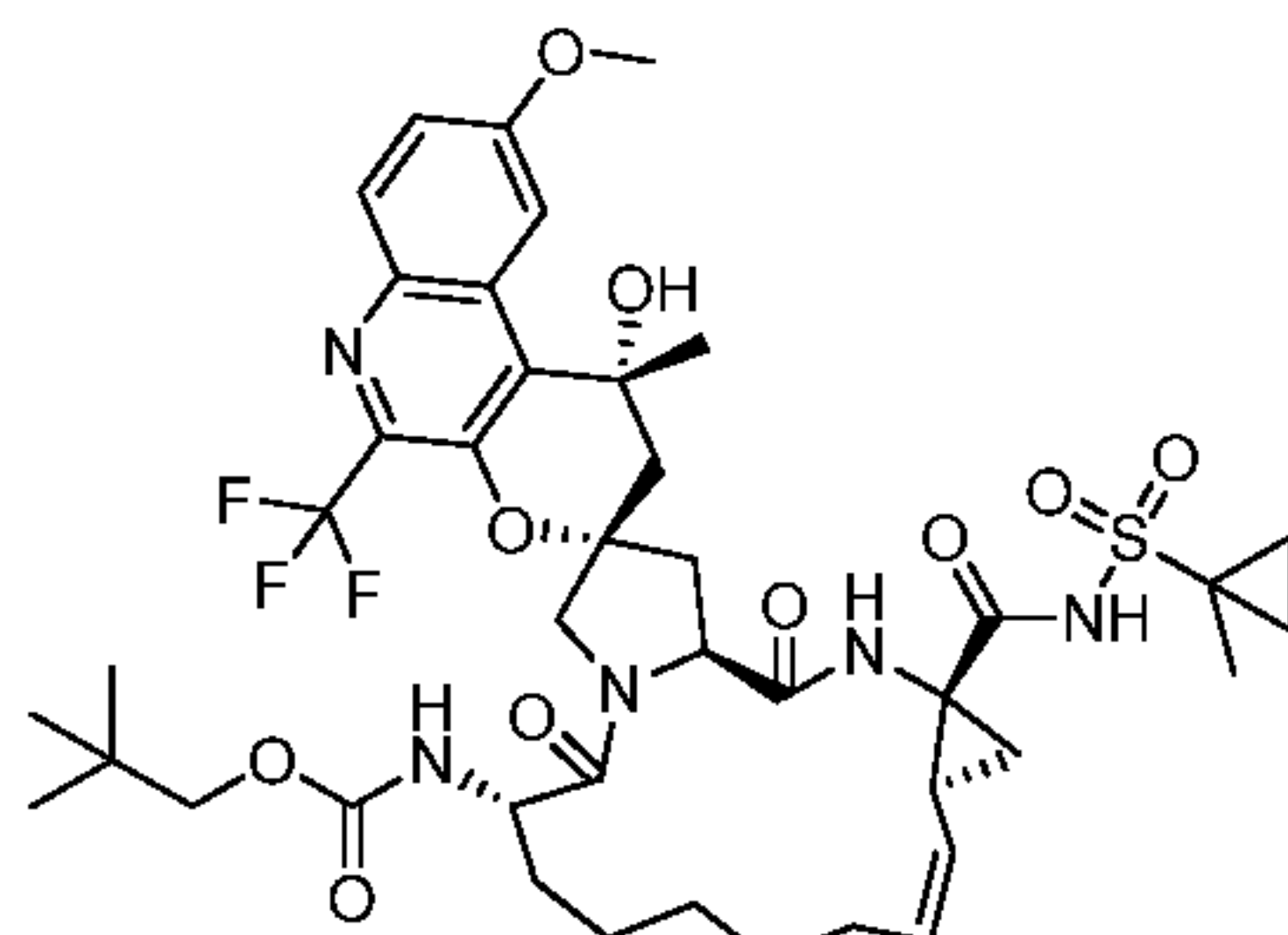
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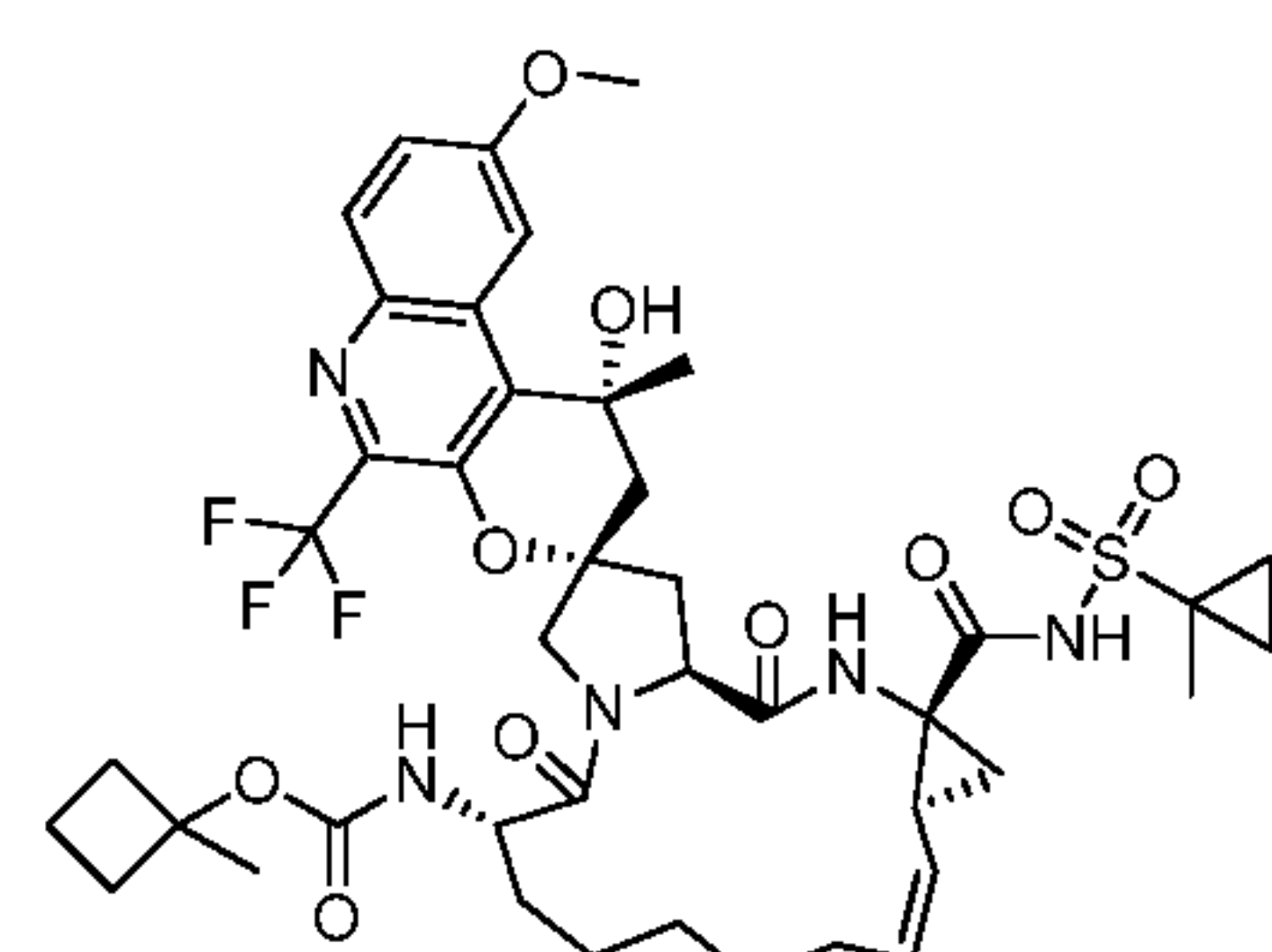
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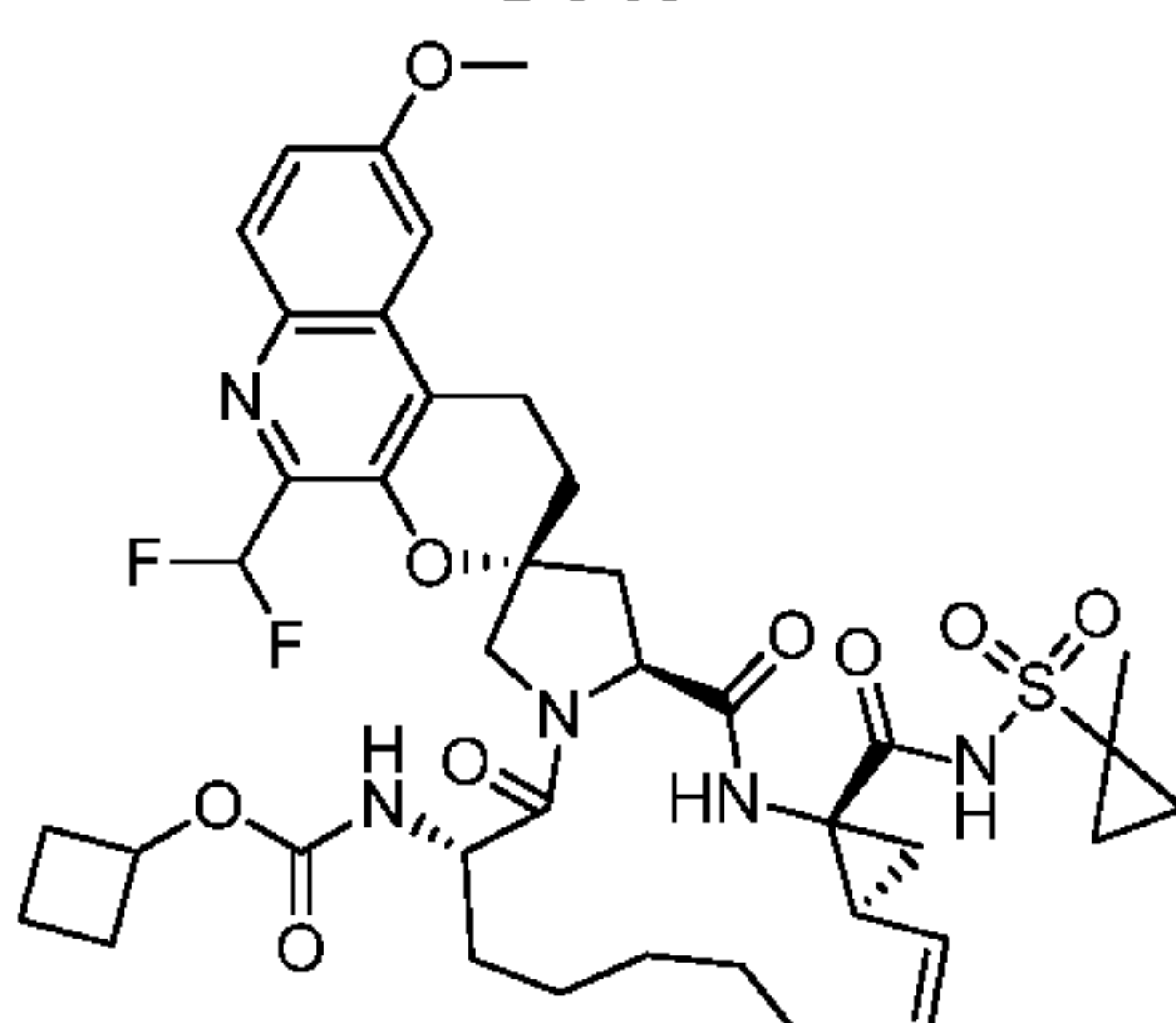
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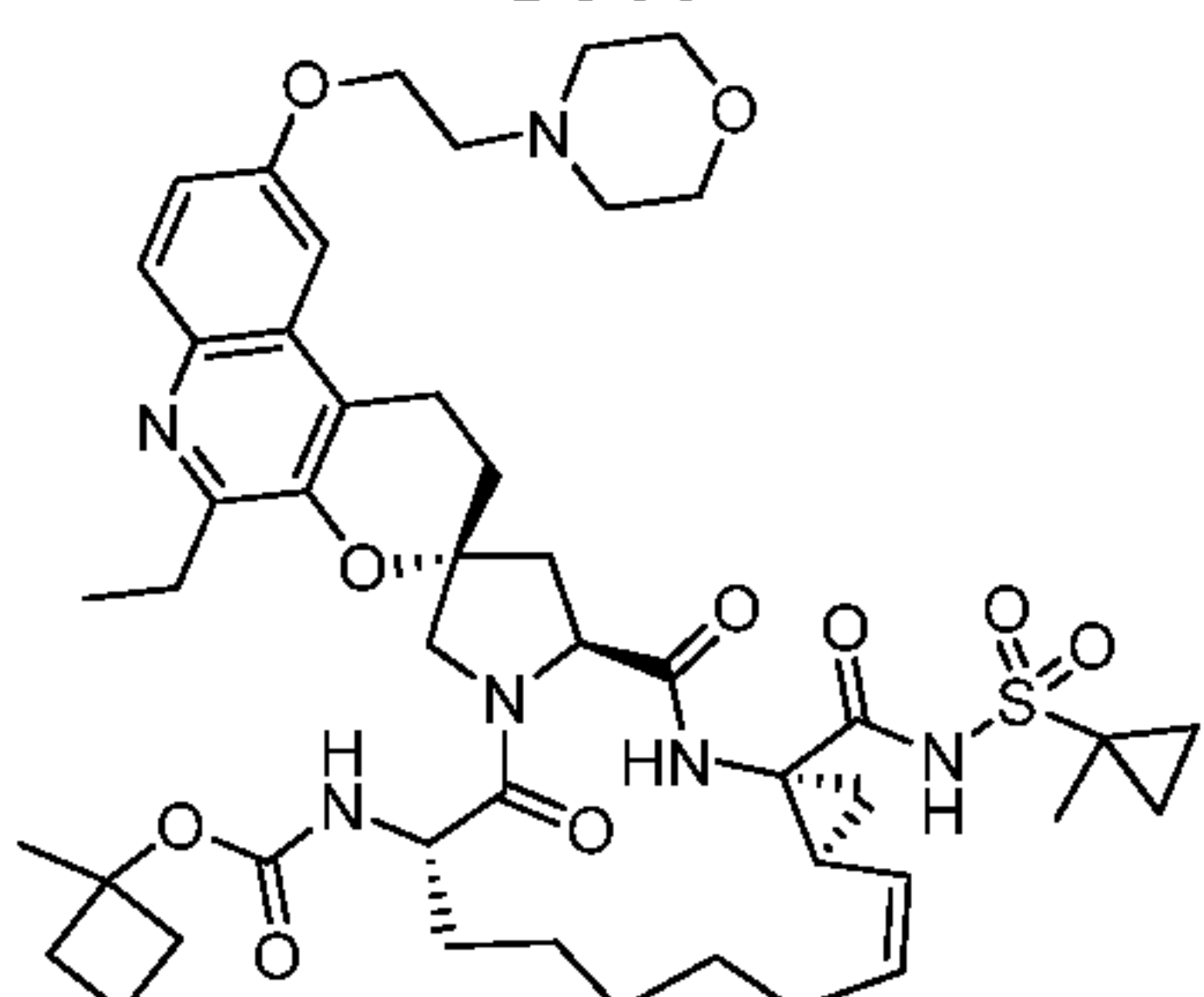
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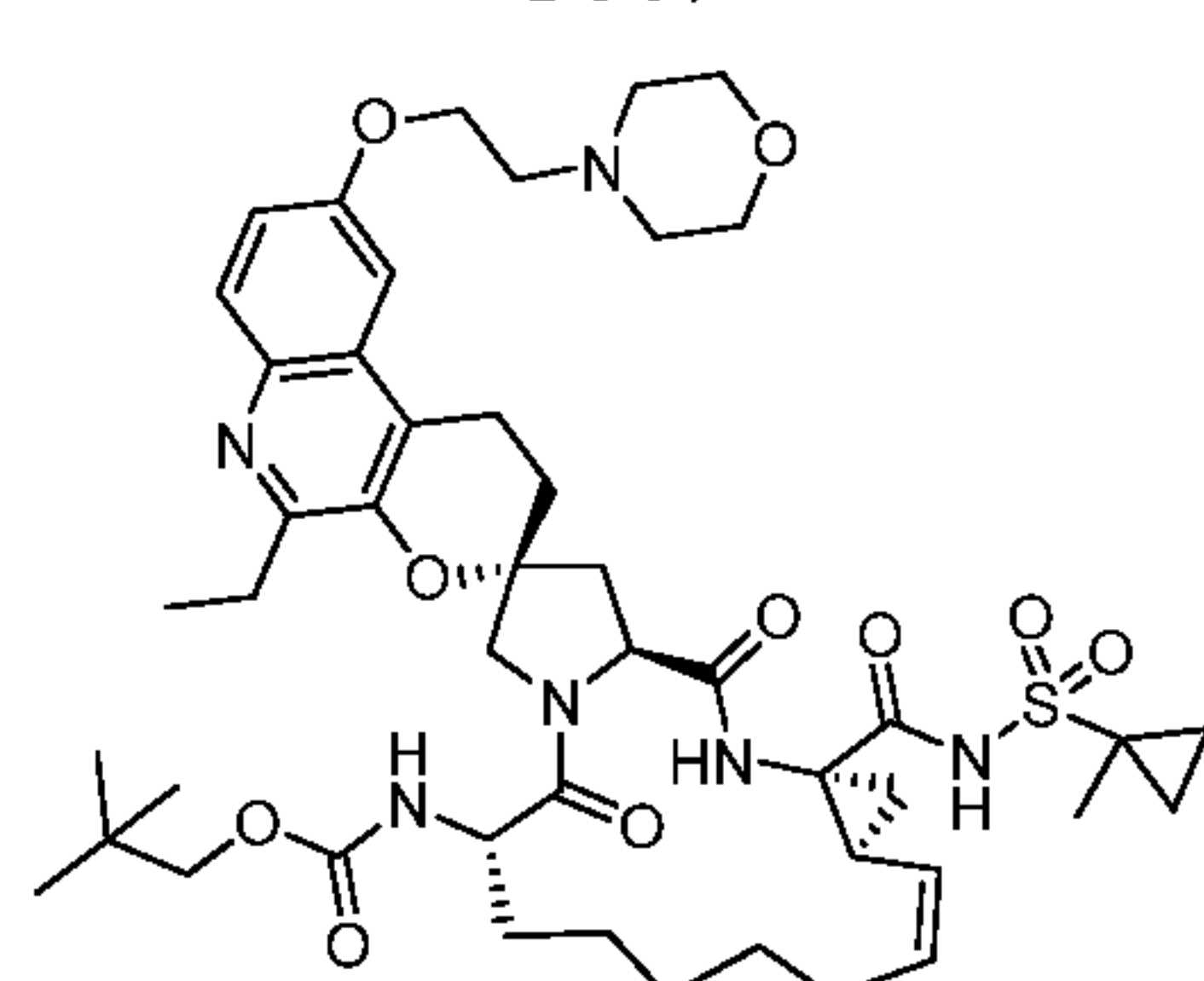
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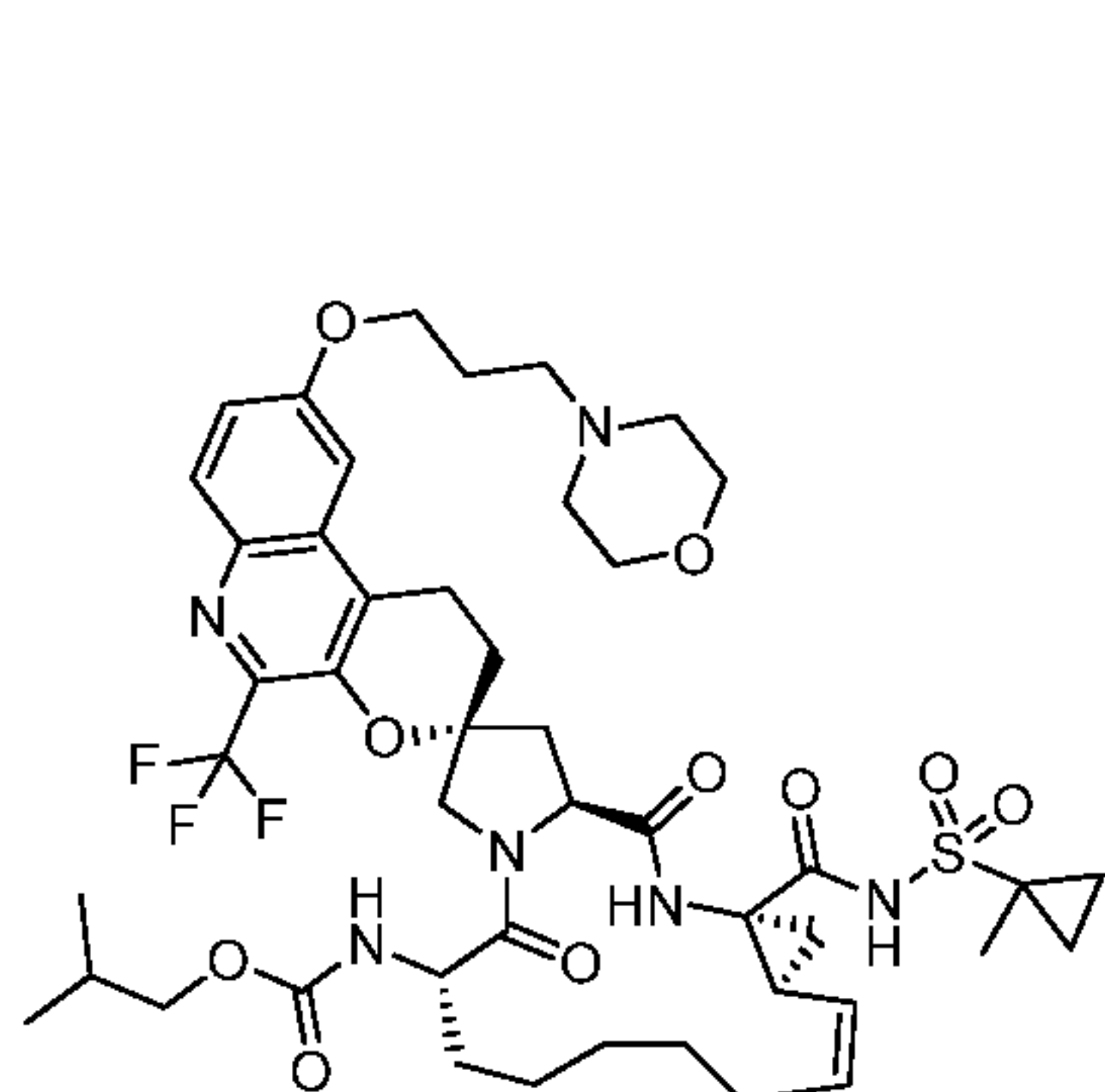
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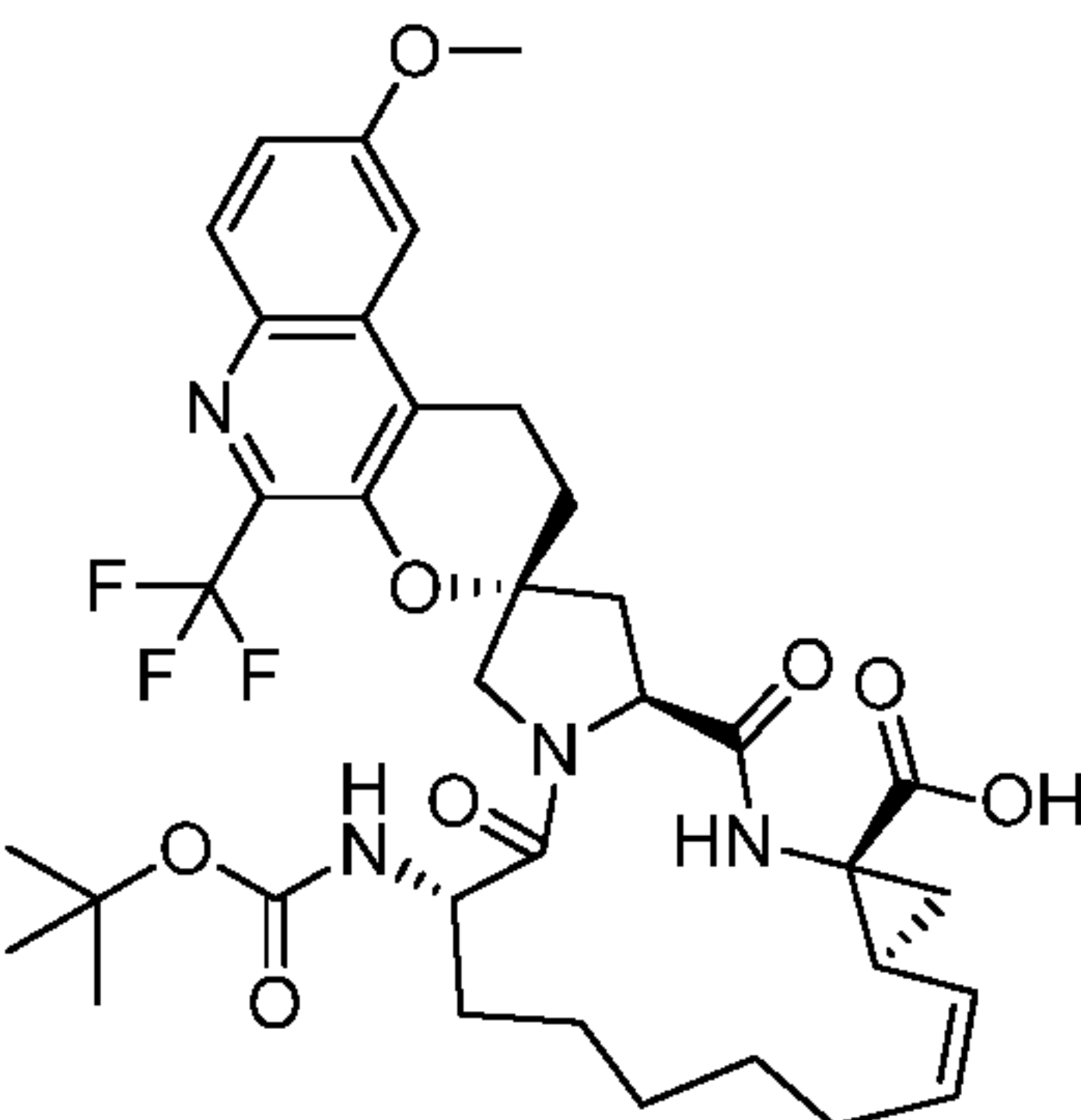
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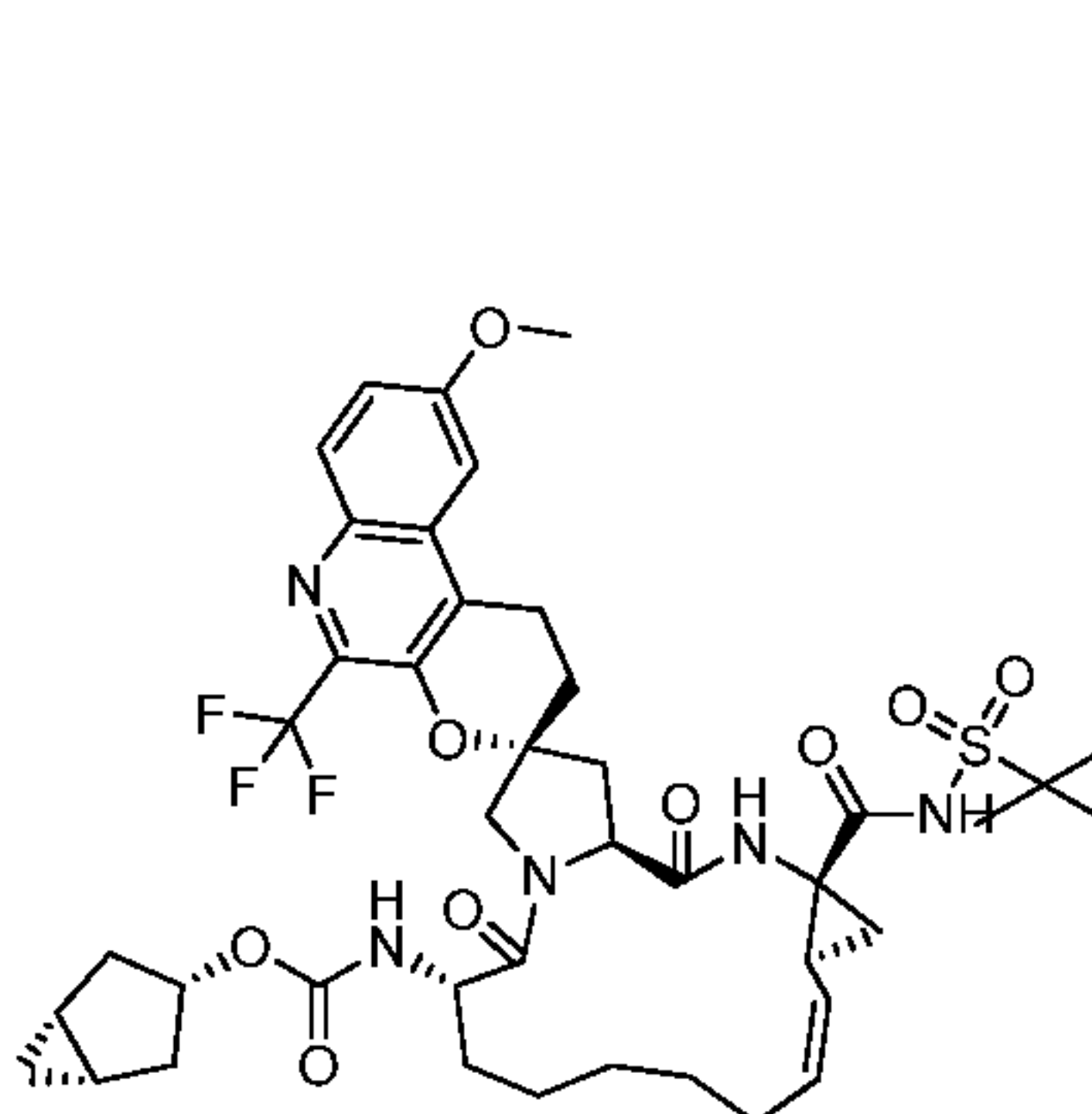
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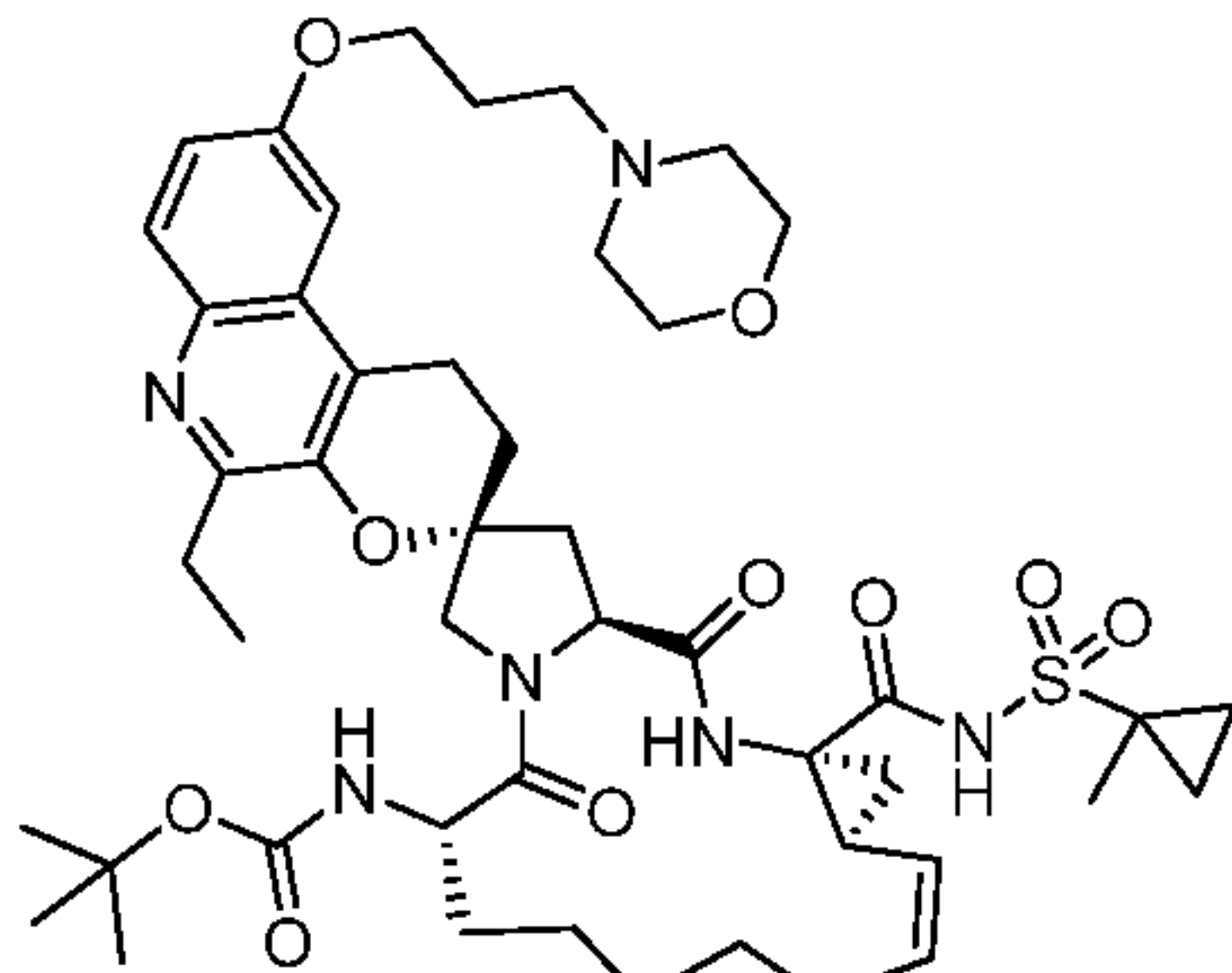
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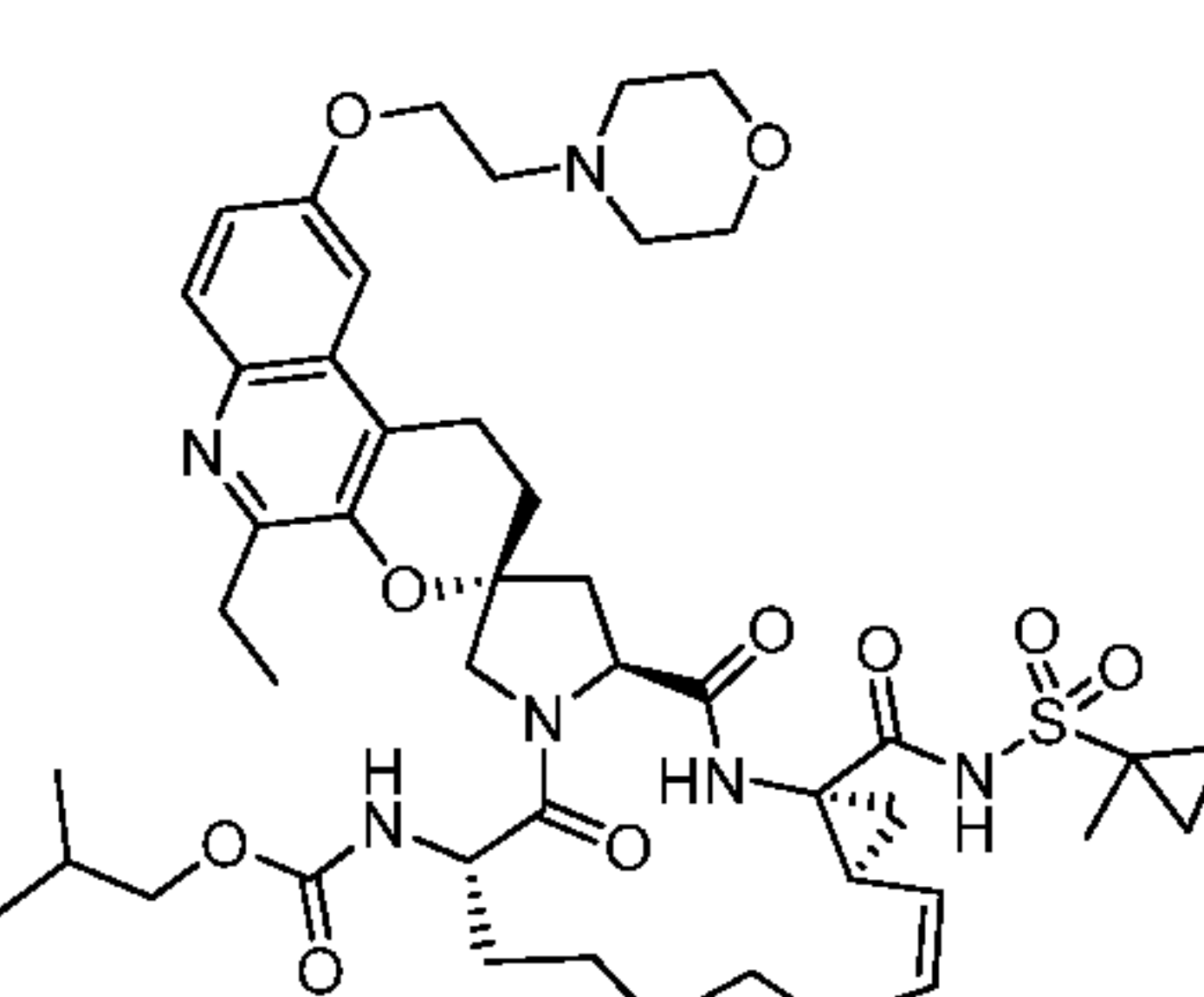
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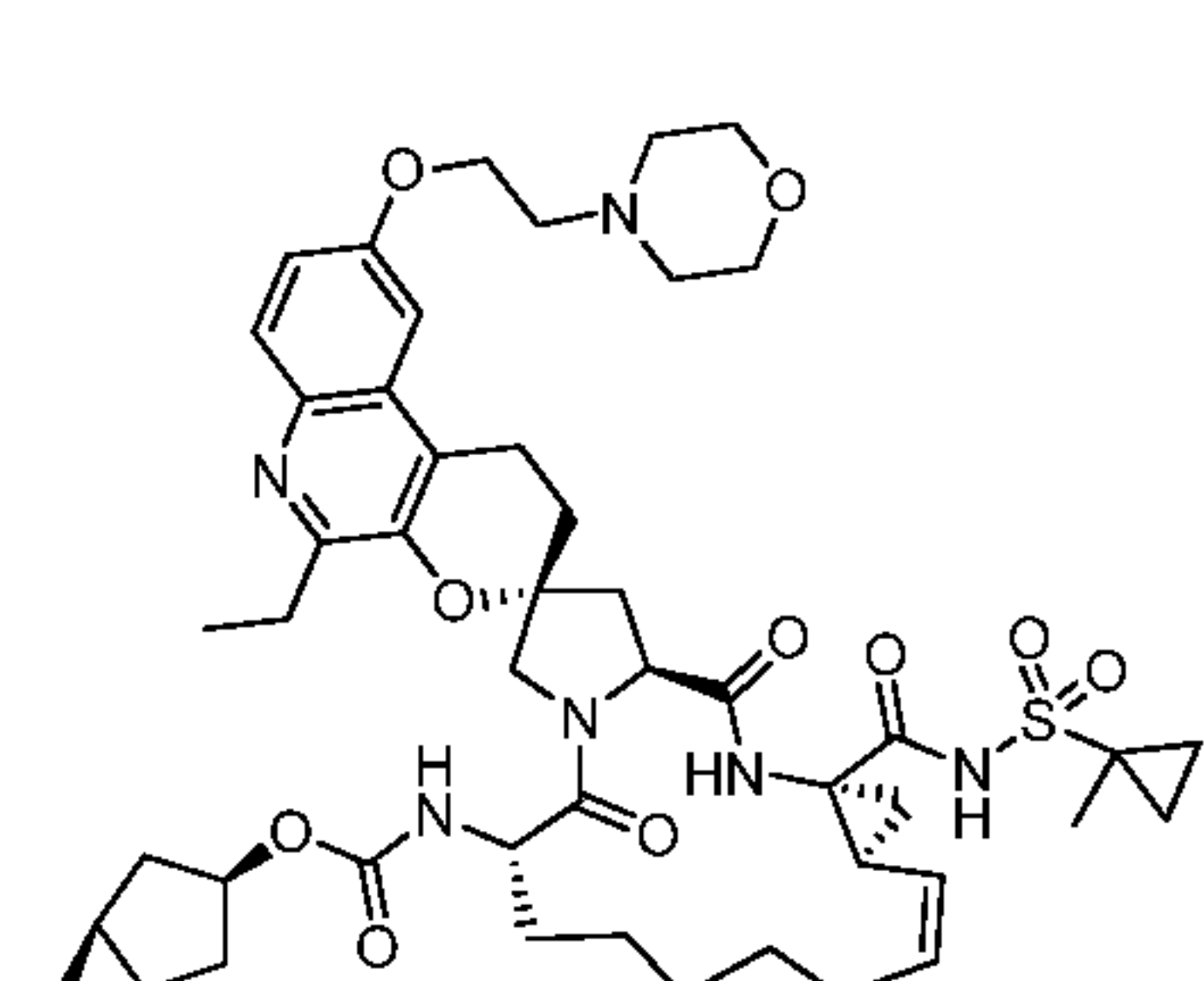
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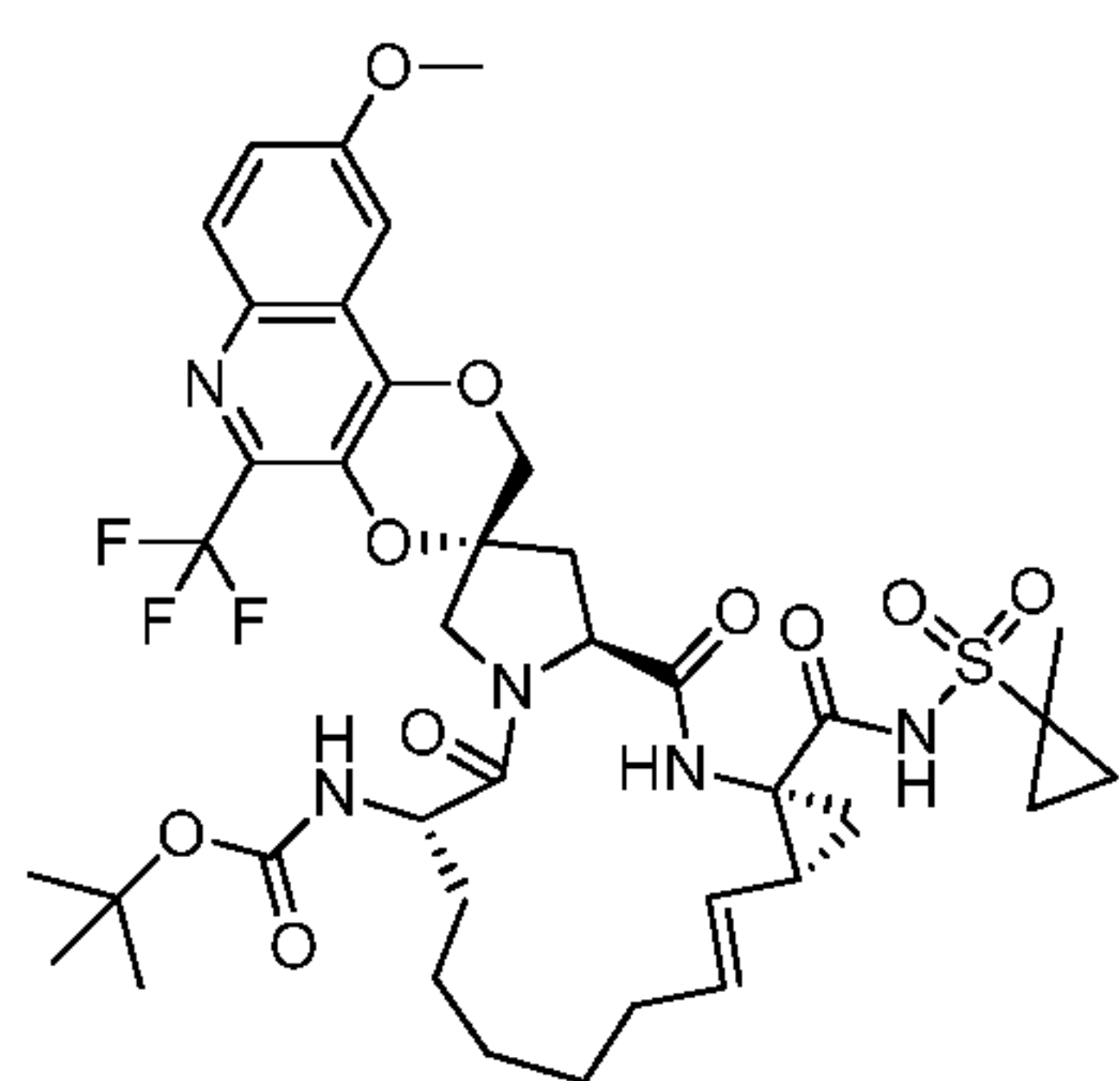
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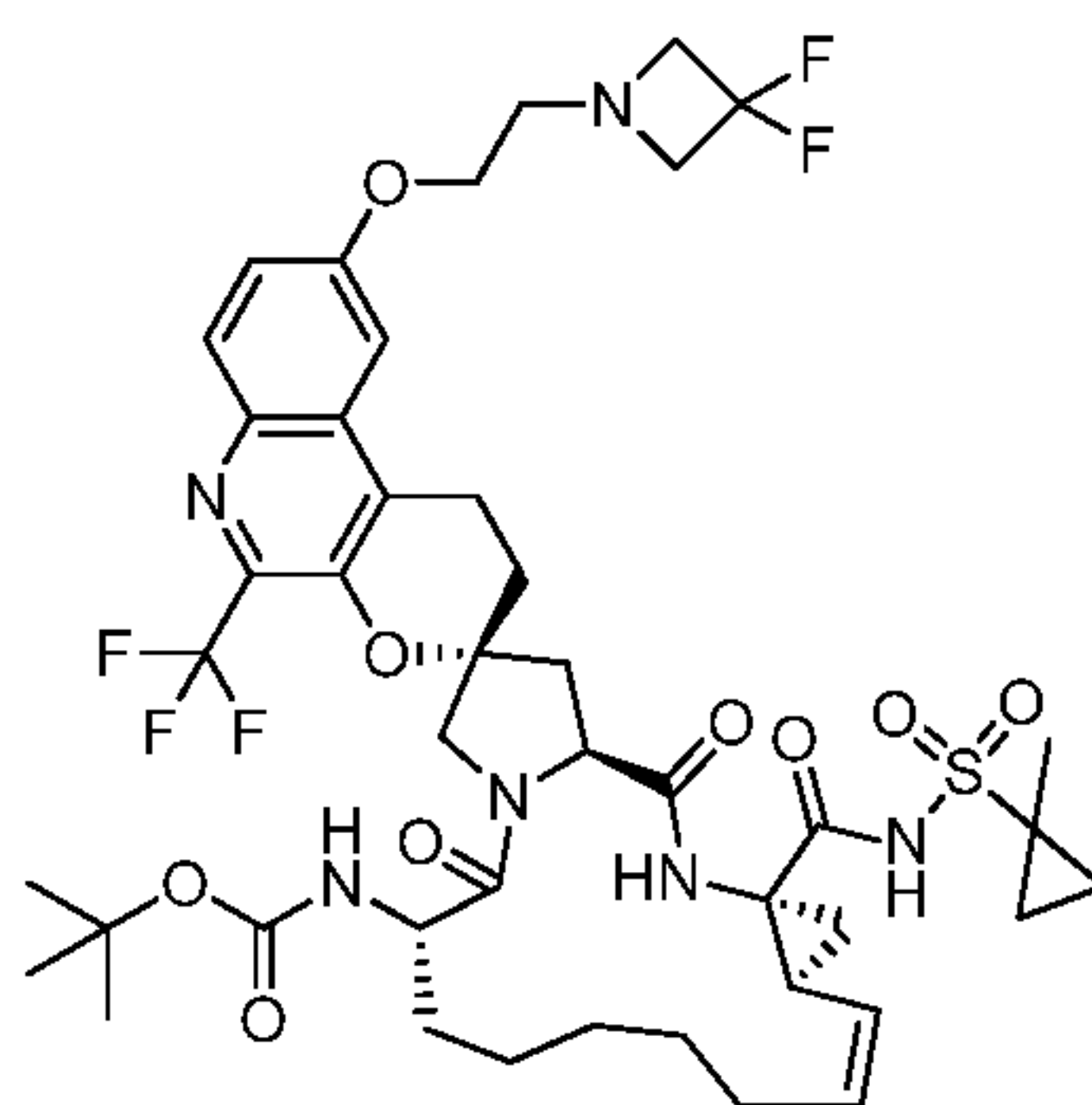
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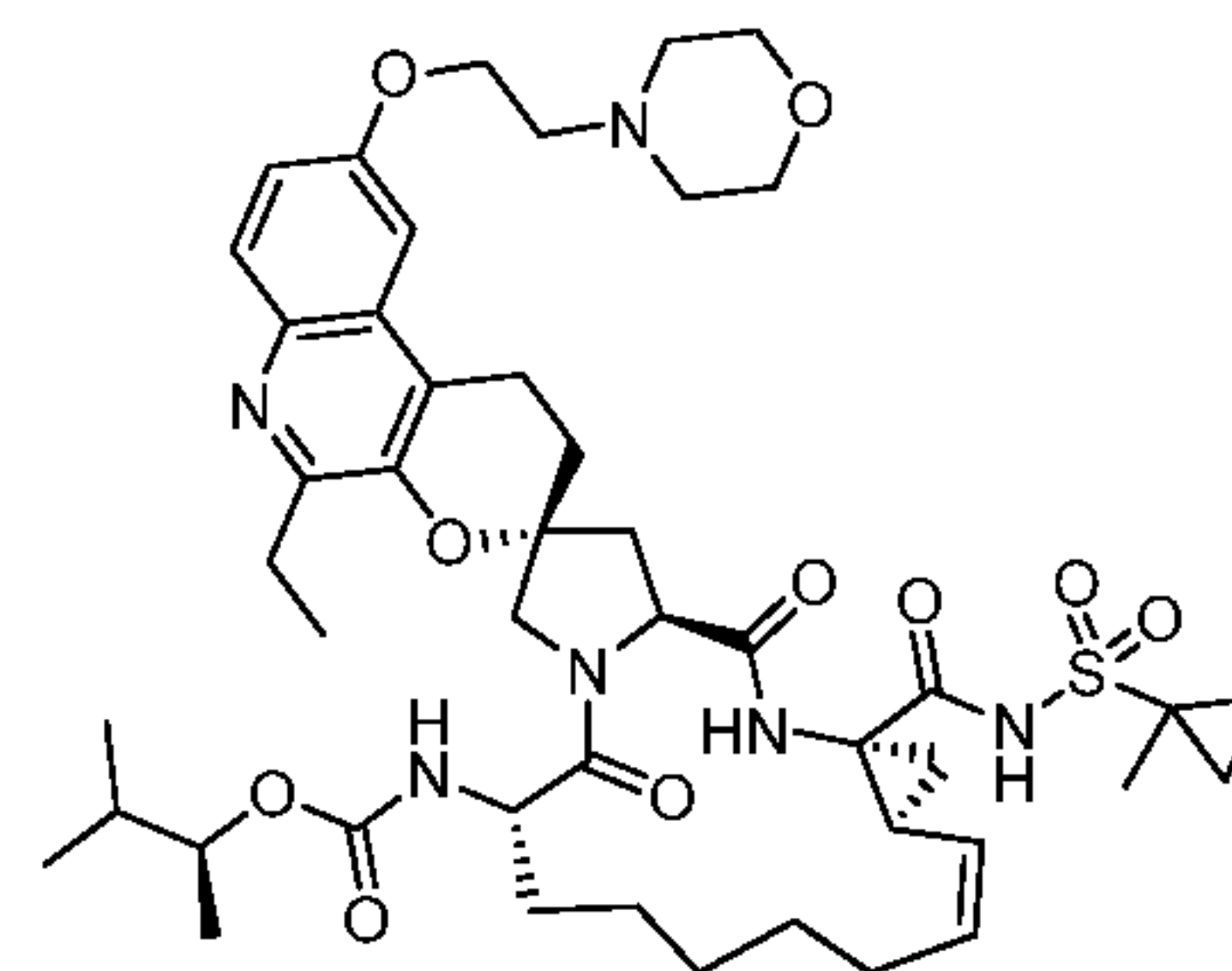
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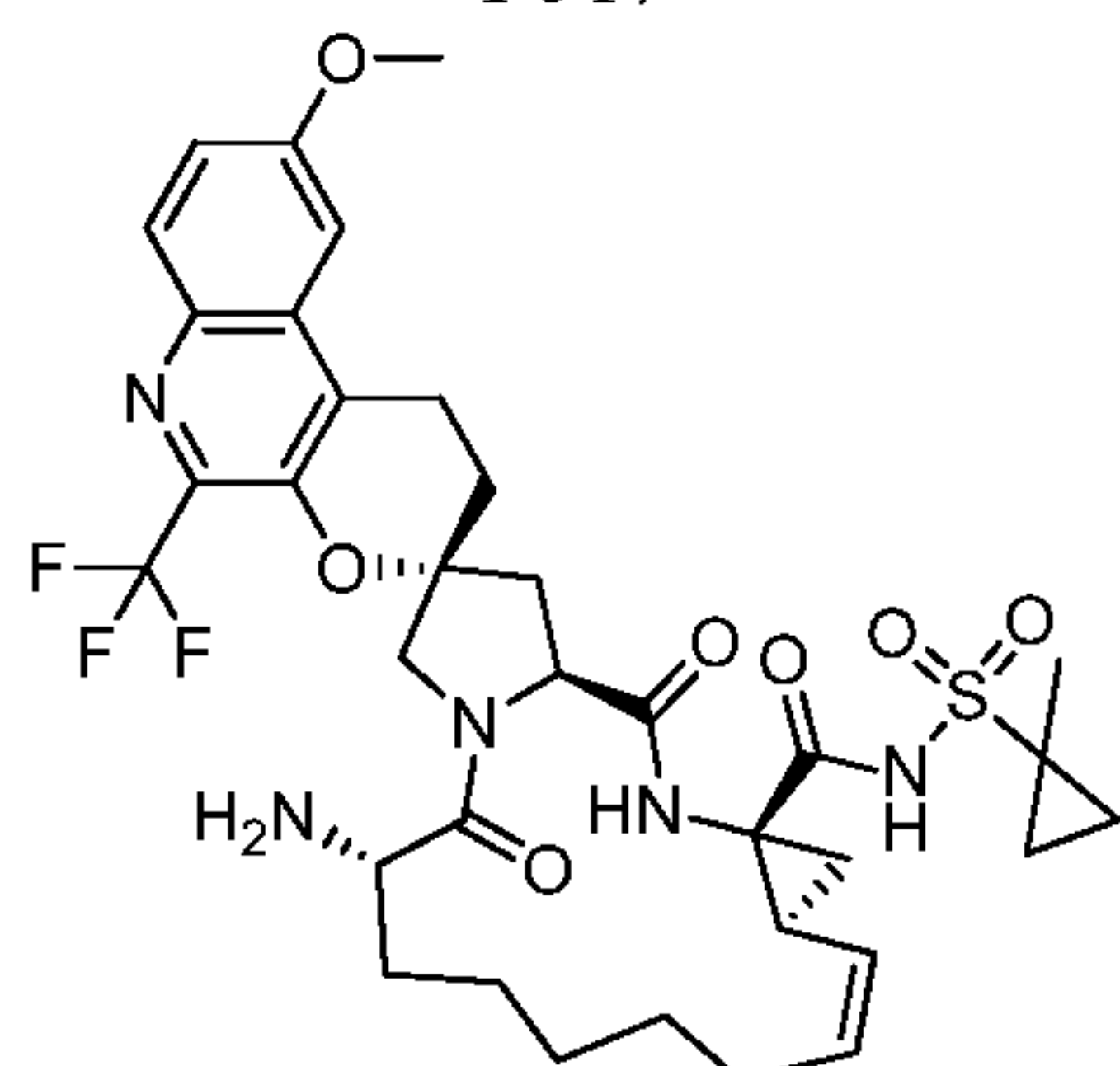
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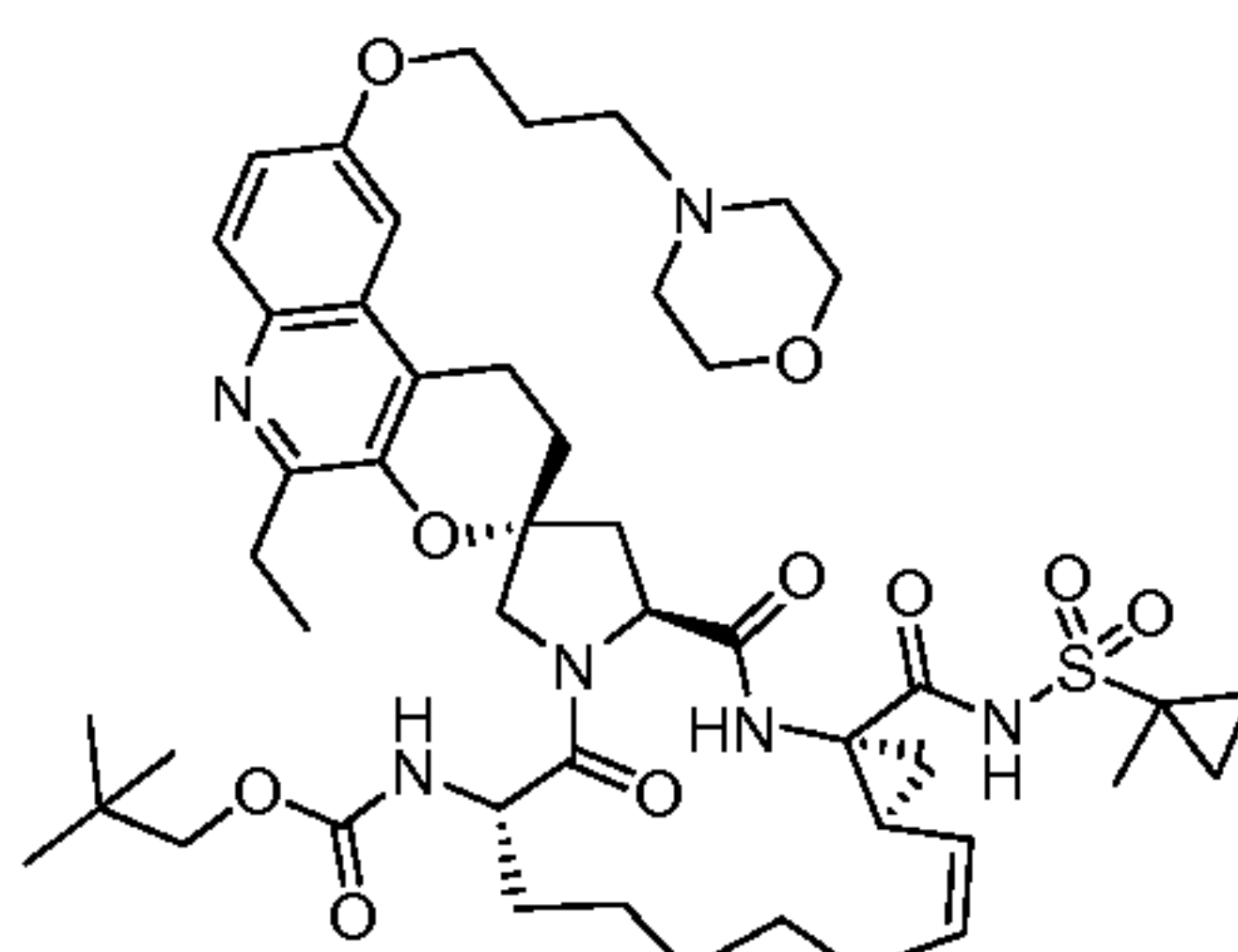
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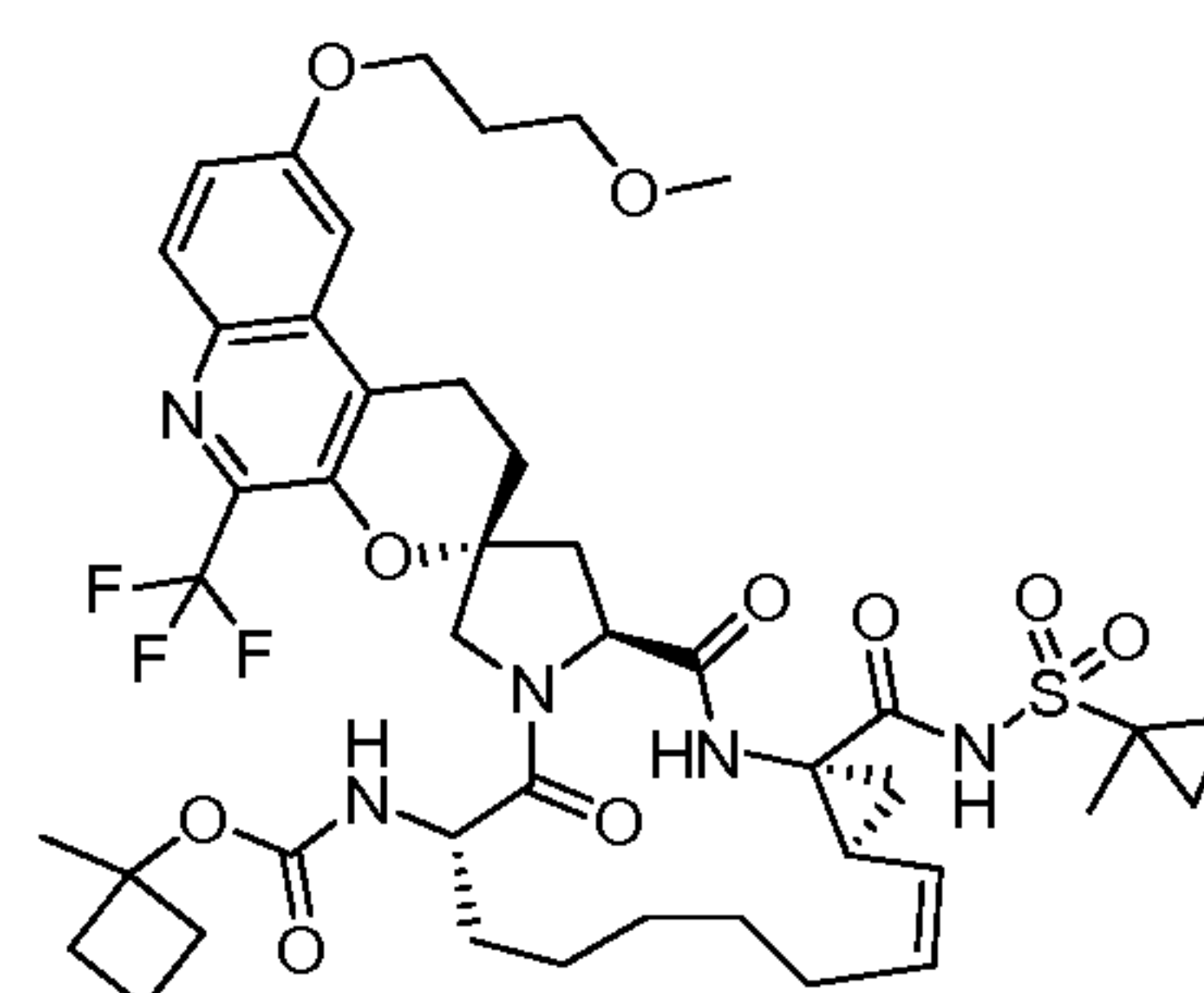
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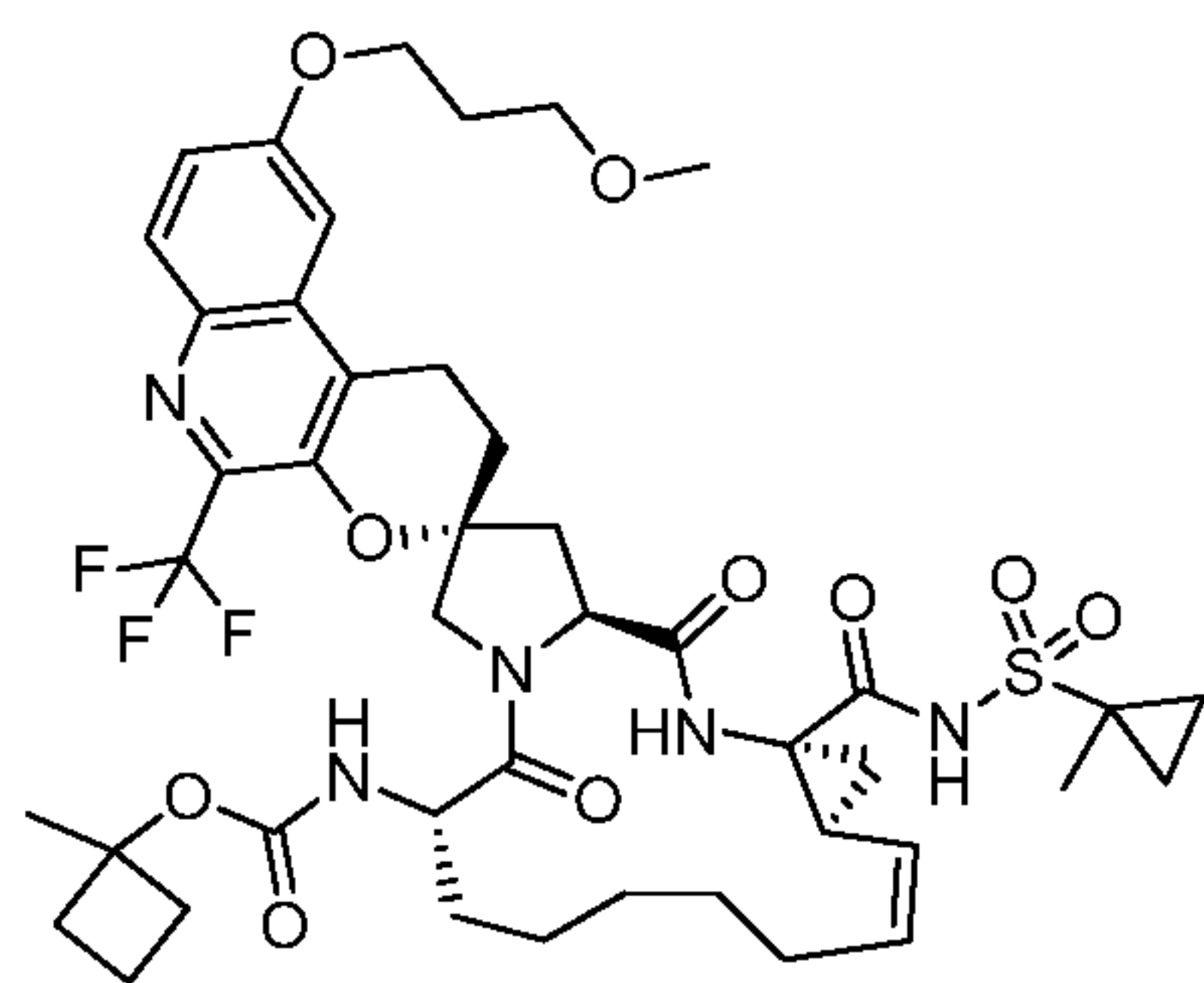
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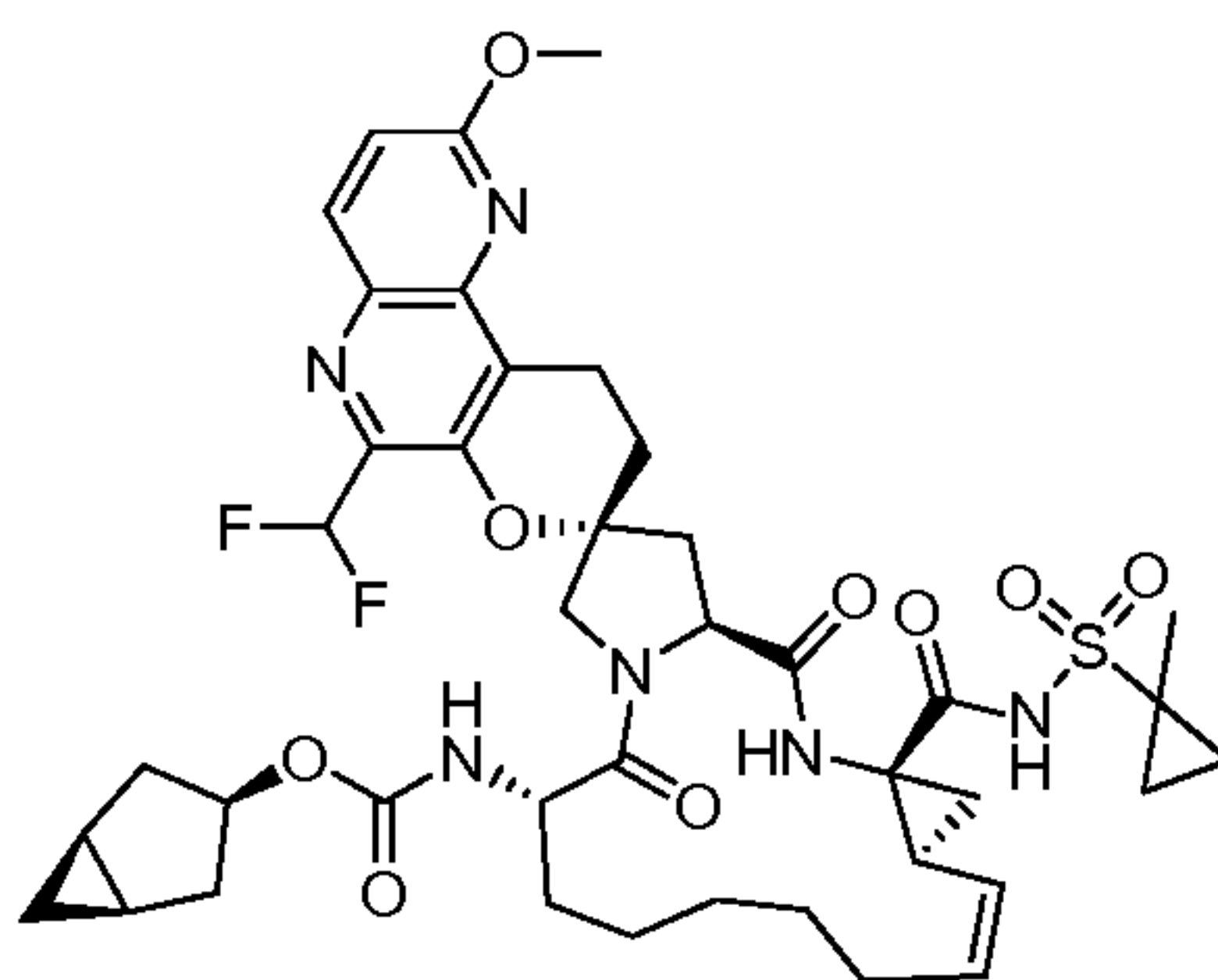
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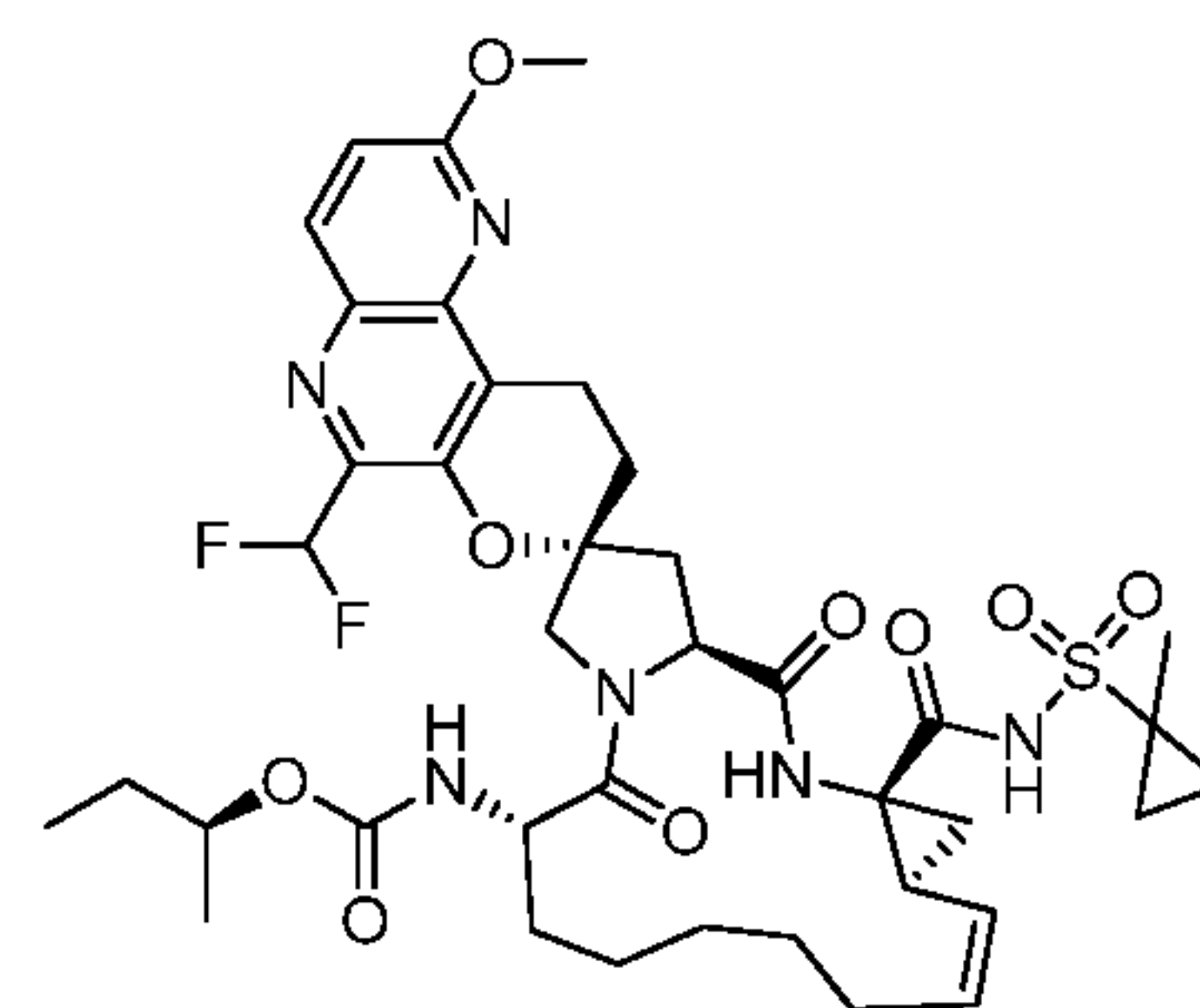
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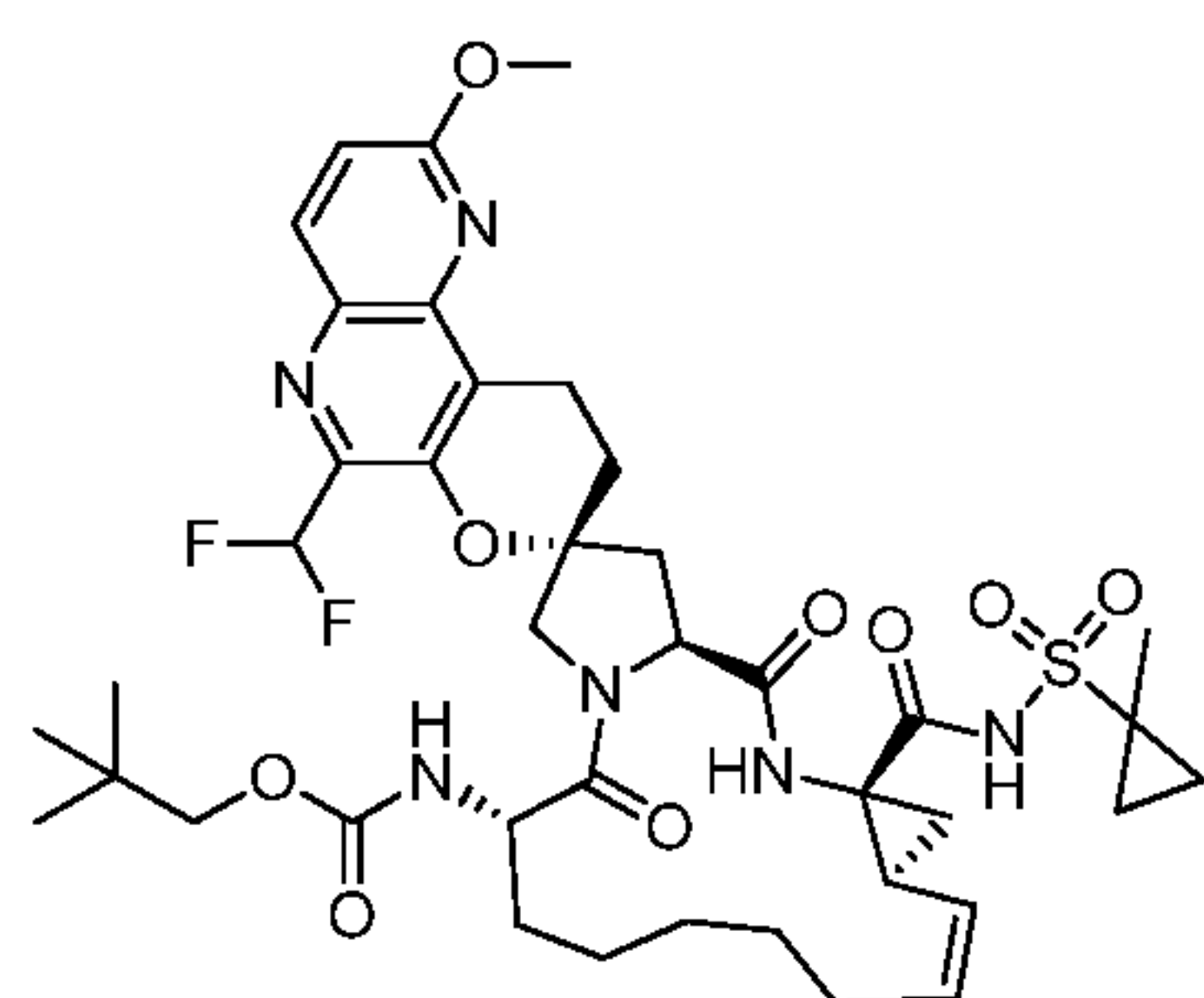
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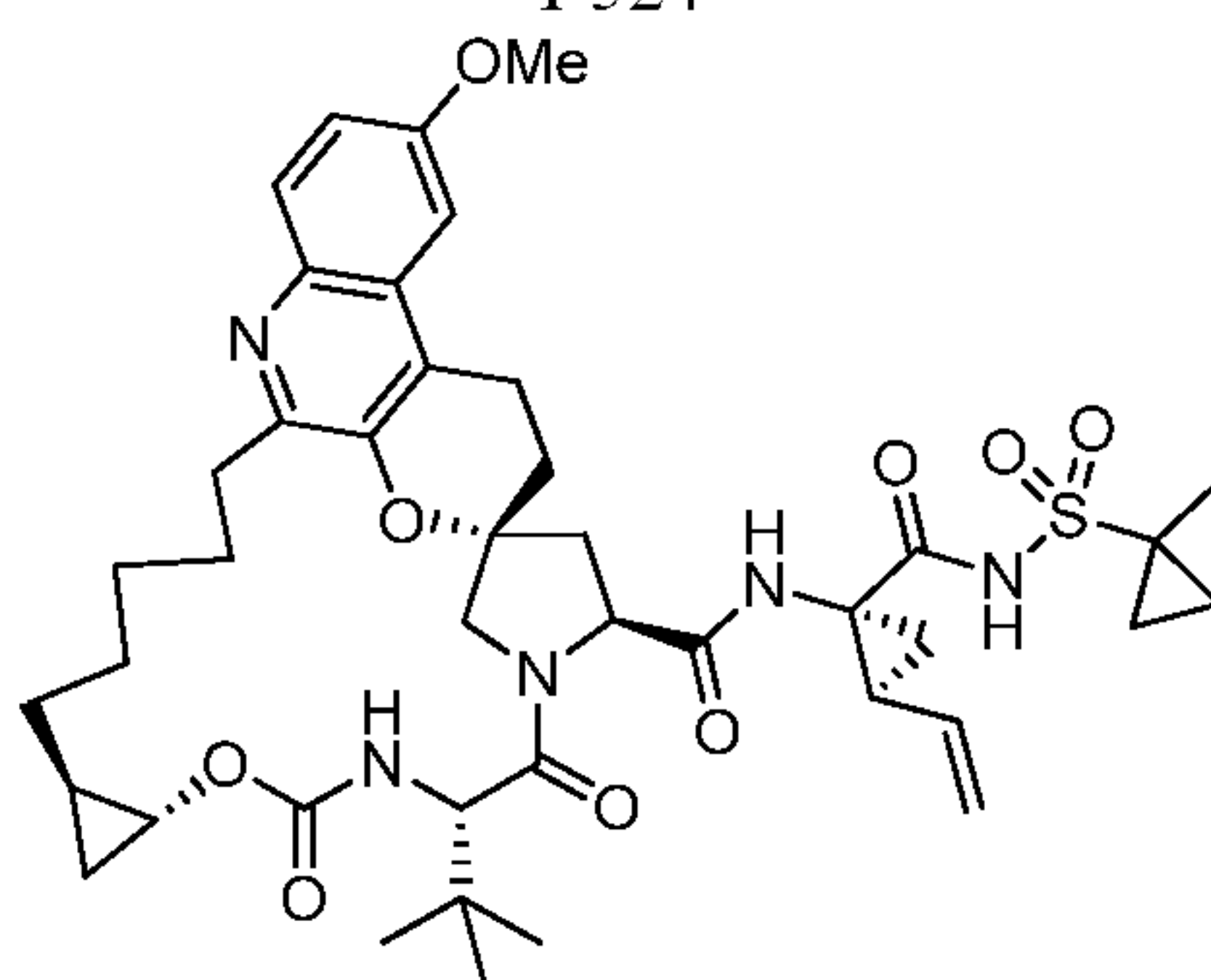
I-524



I-525



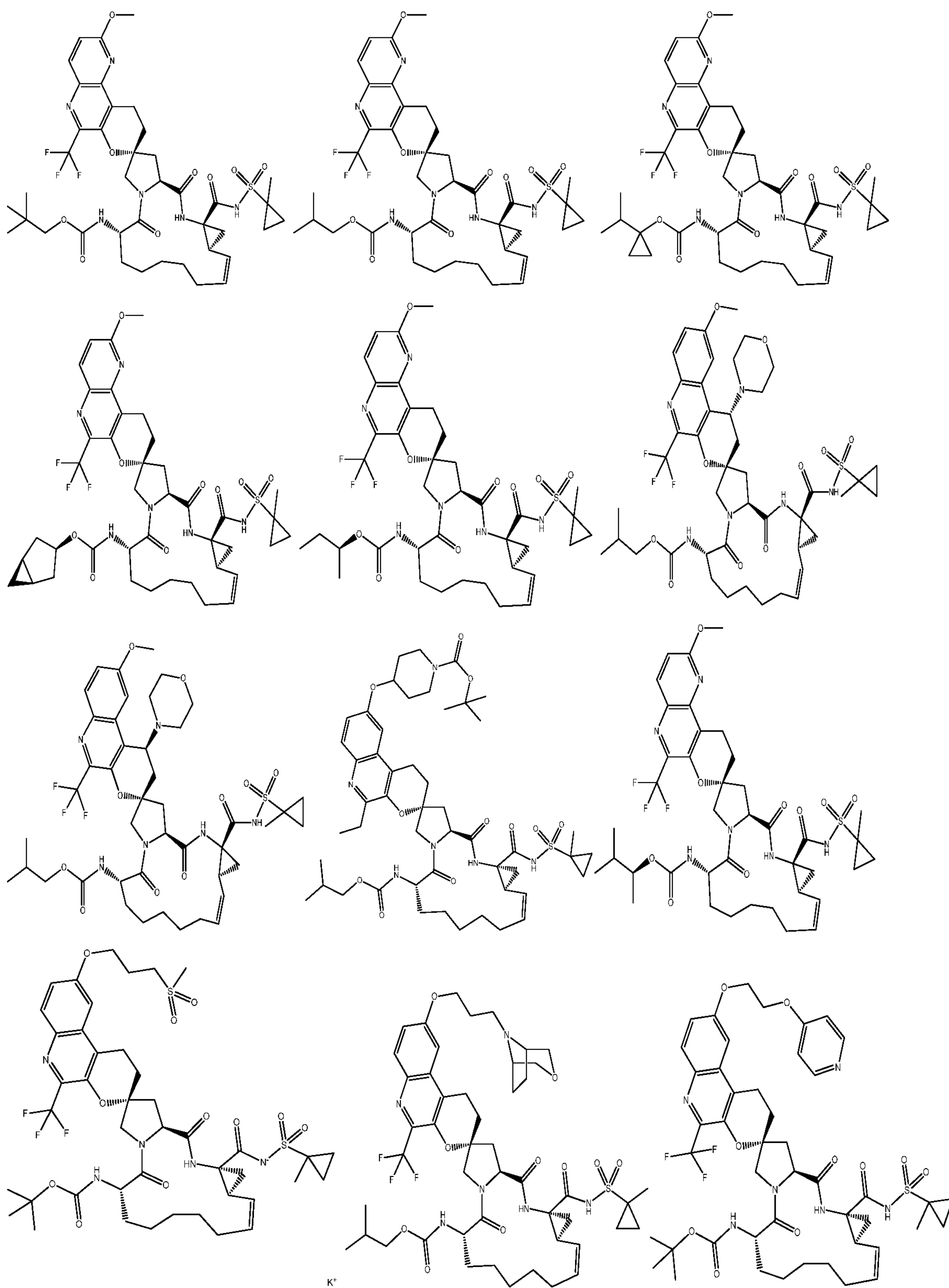
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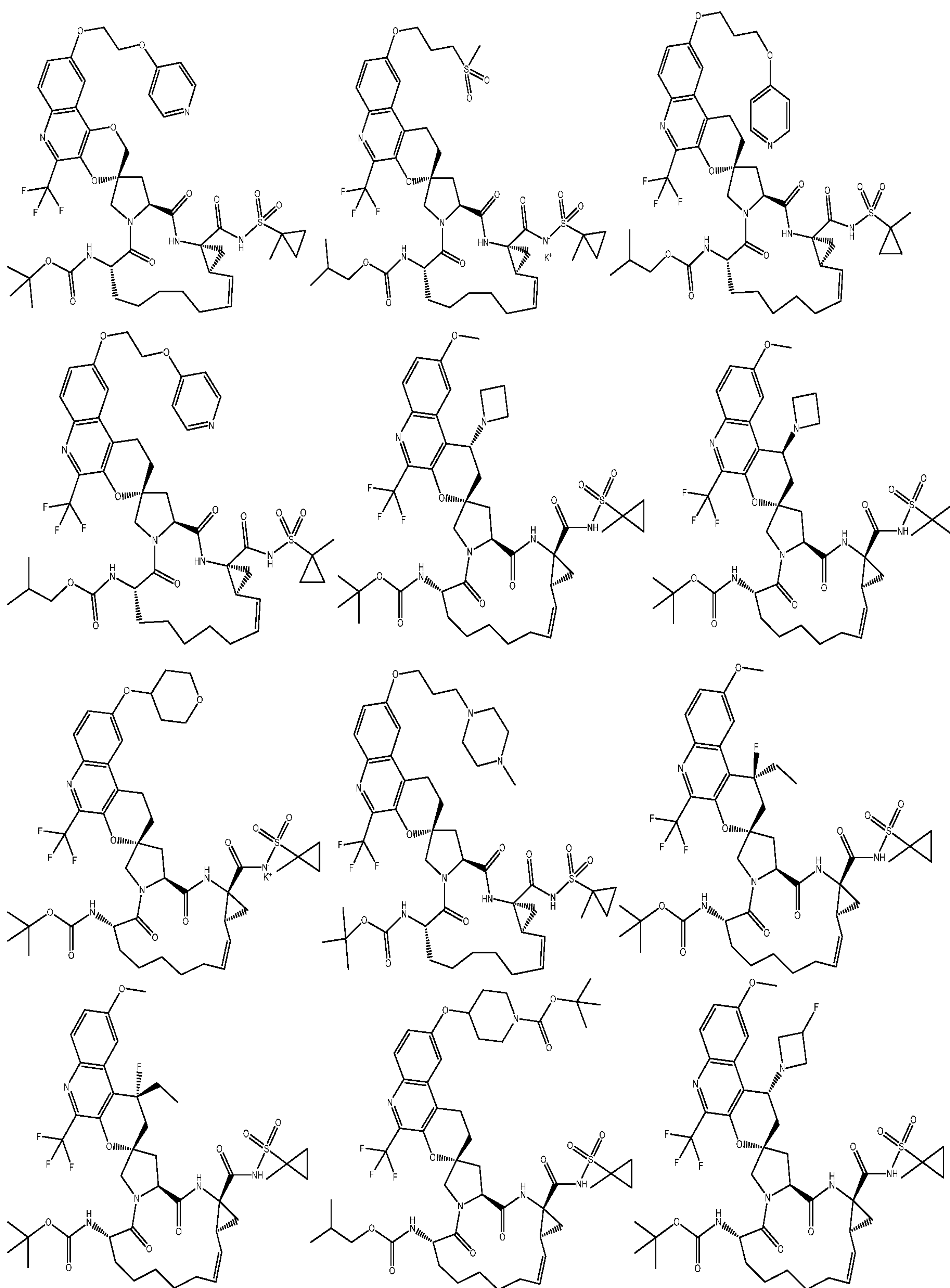


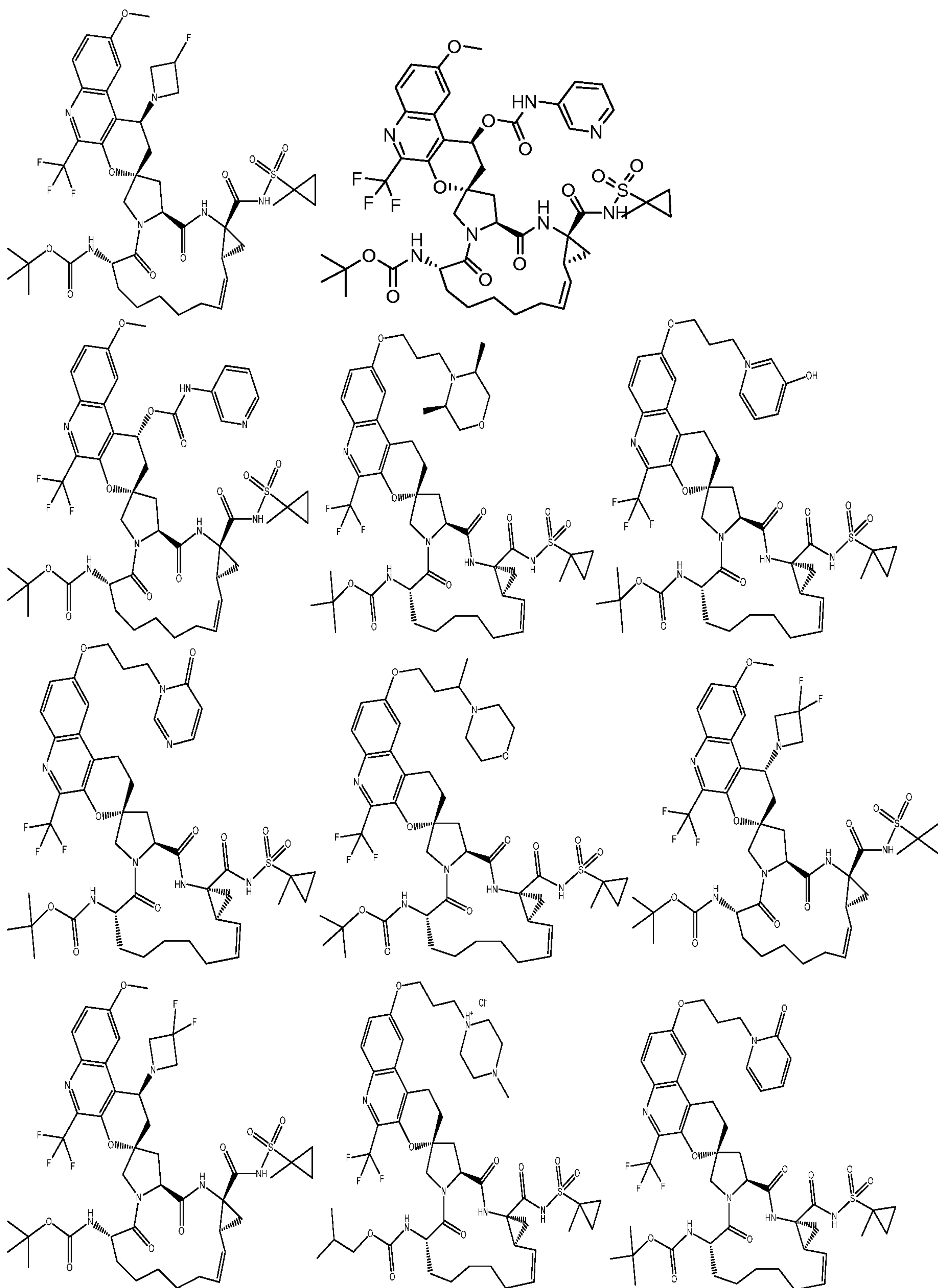
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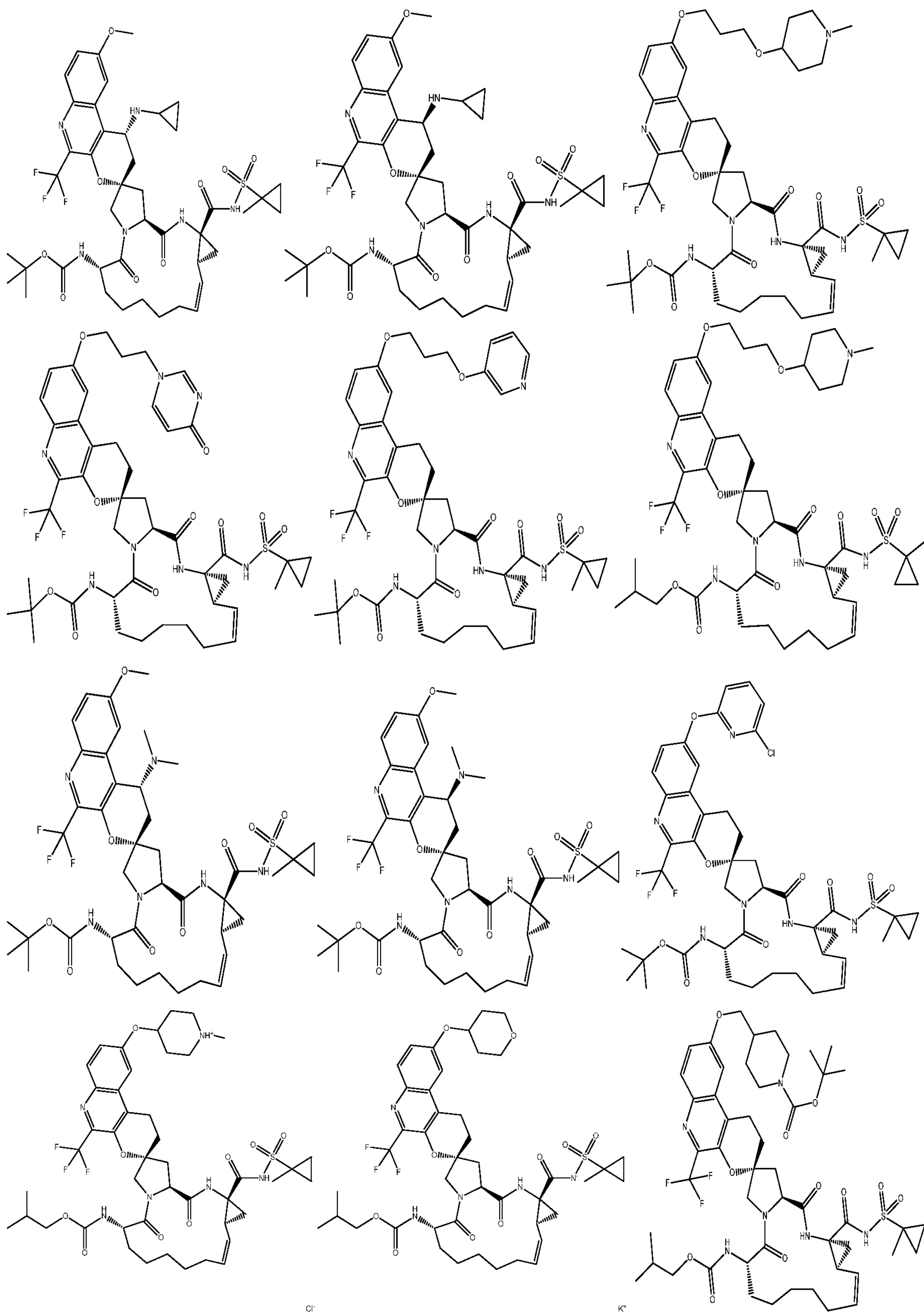
and pharmaceutically acceptable salts thereof.

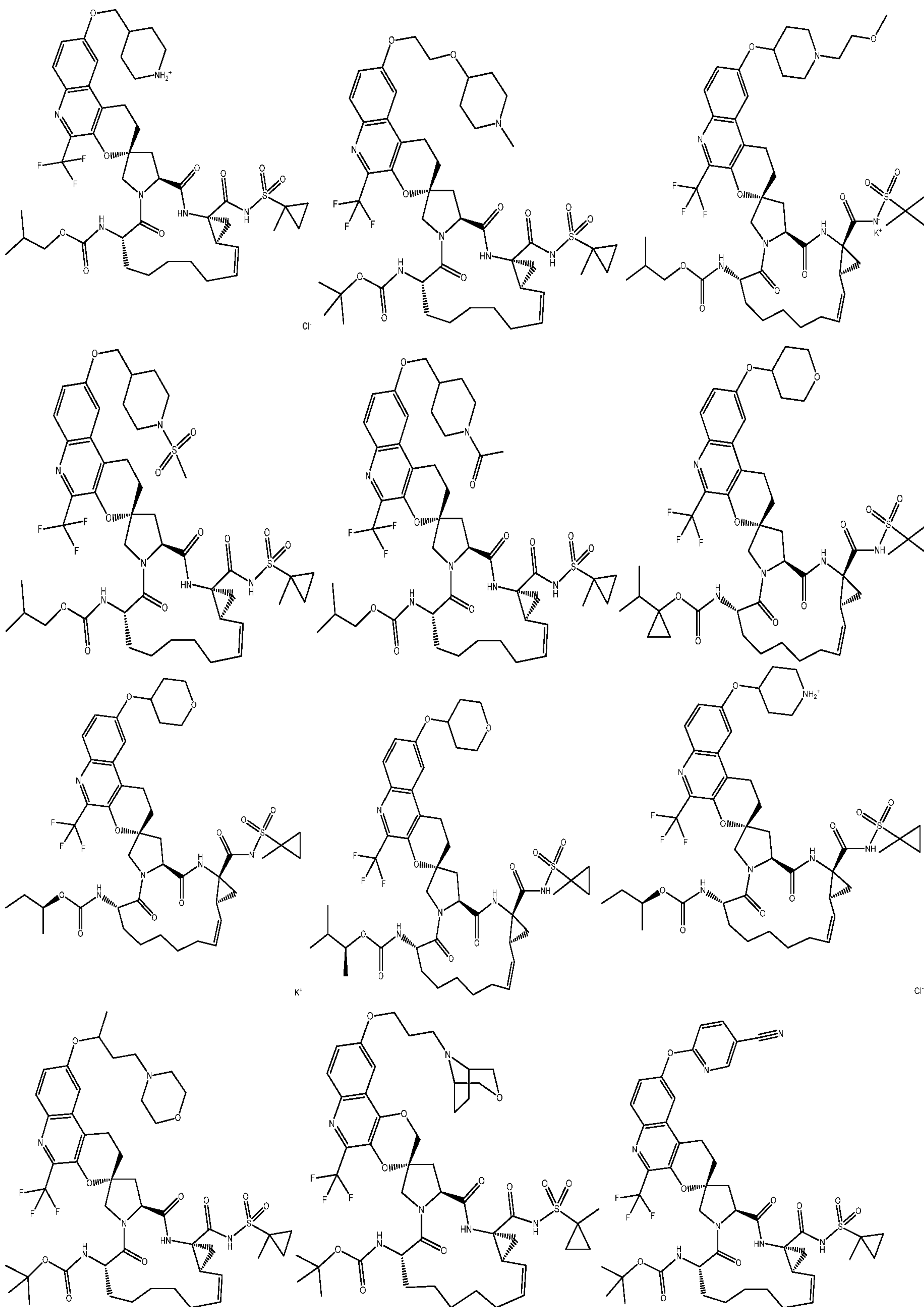
29. The compound according to claim 1, wherein the compound is selected from the group consisting of:

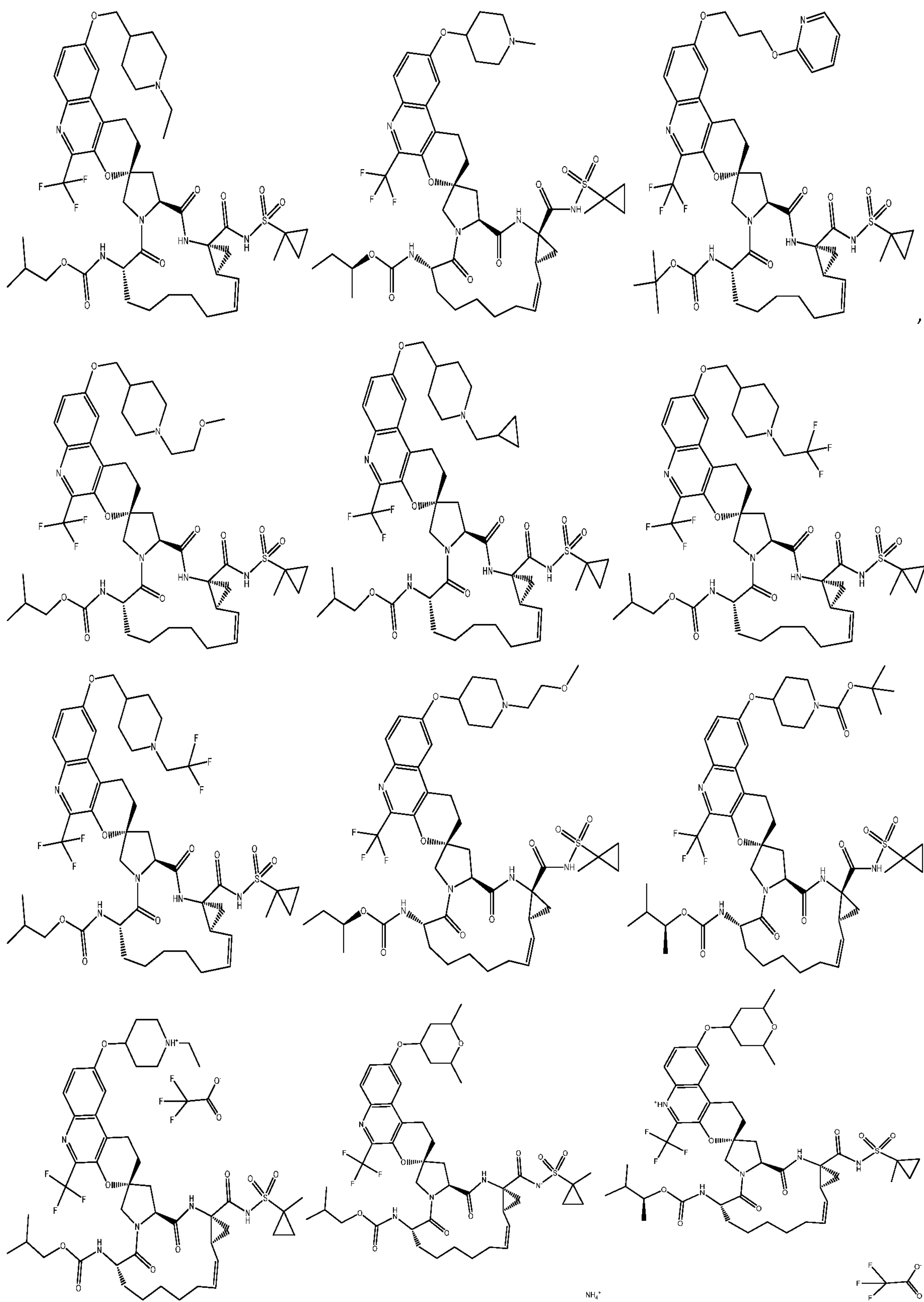


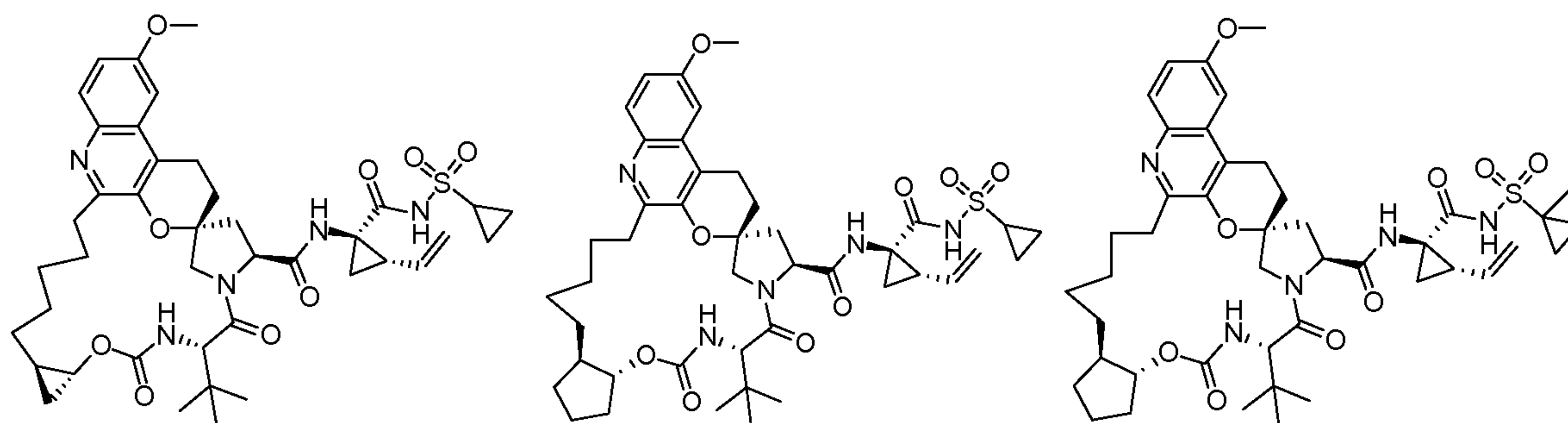
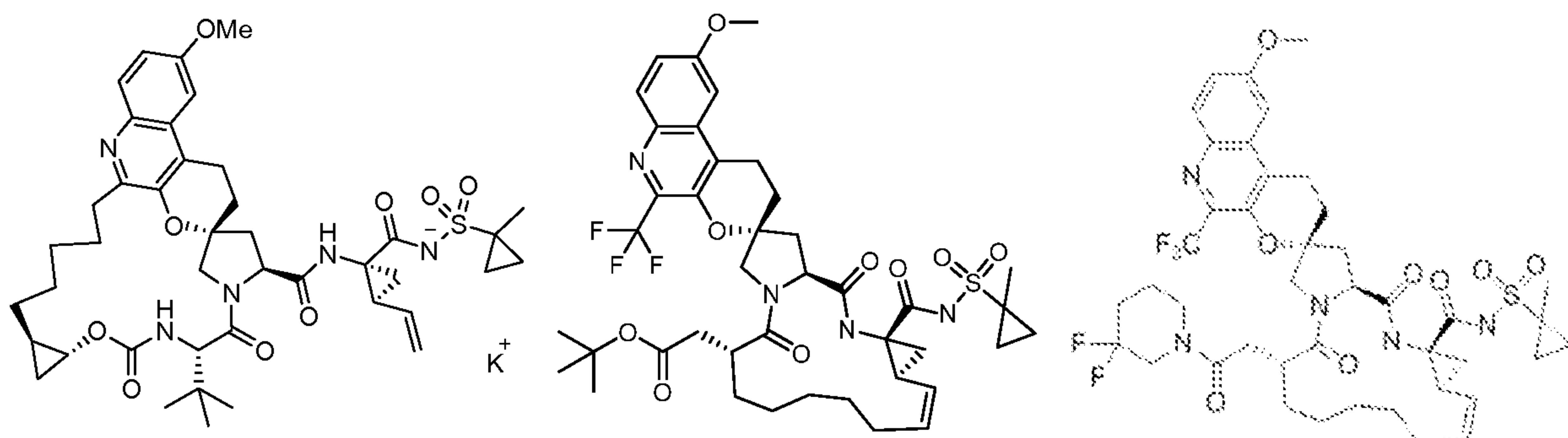
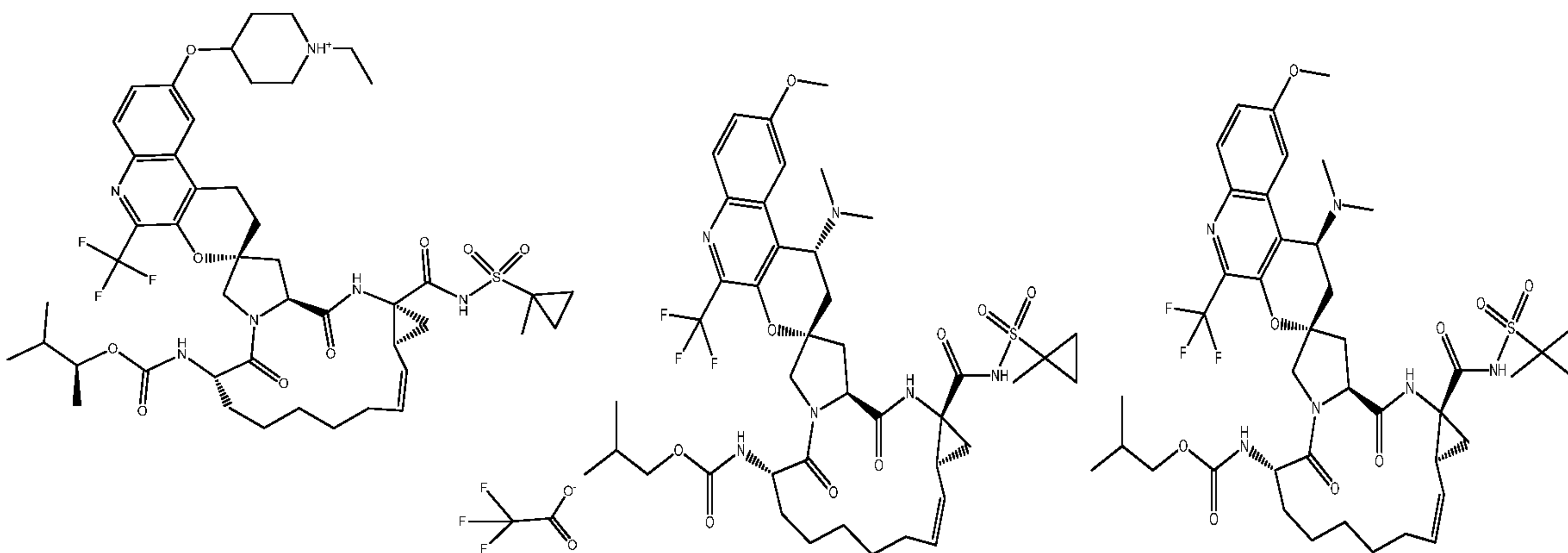
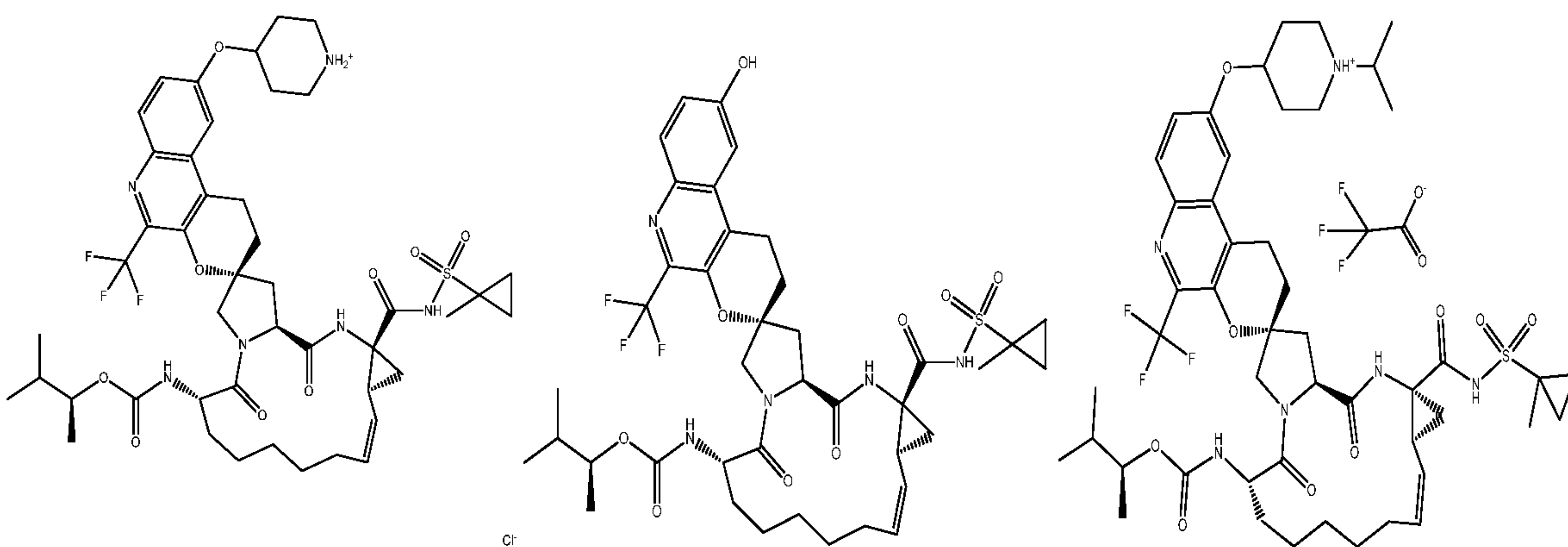




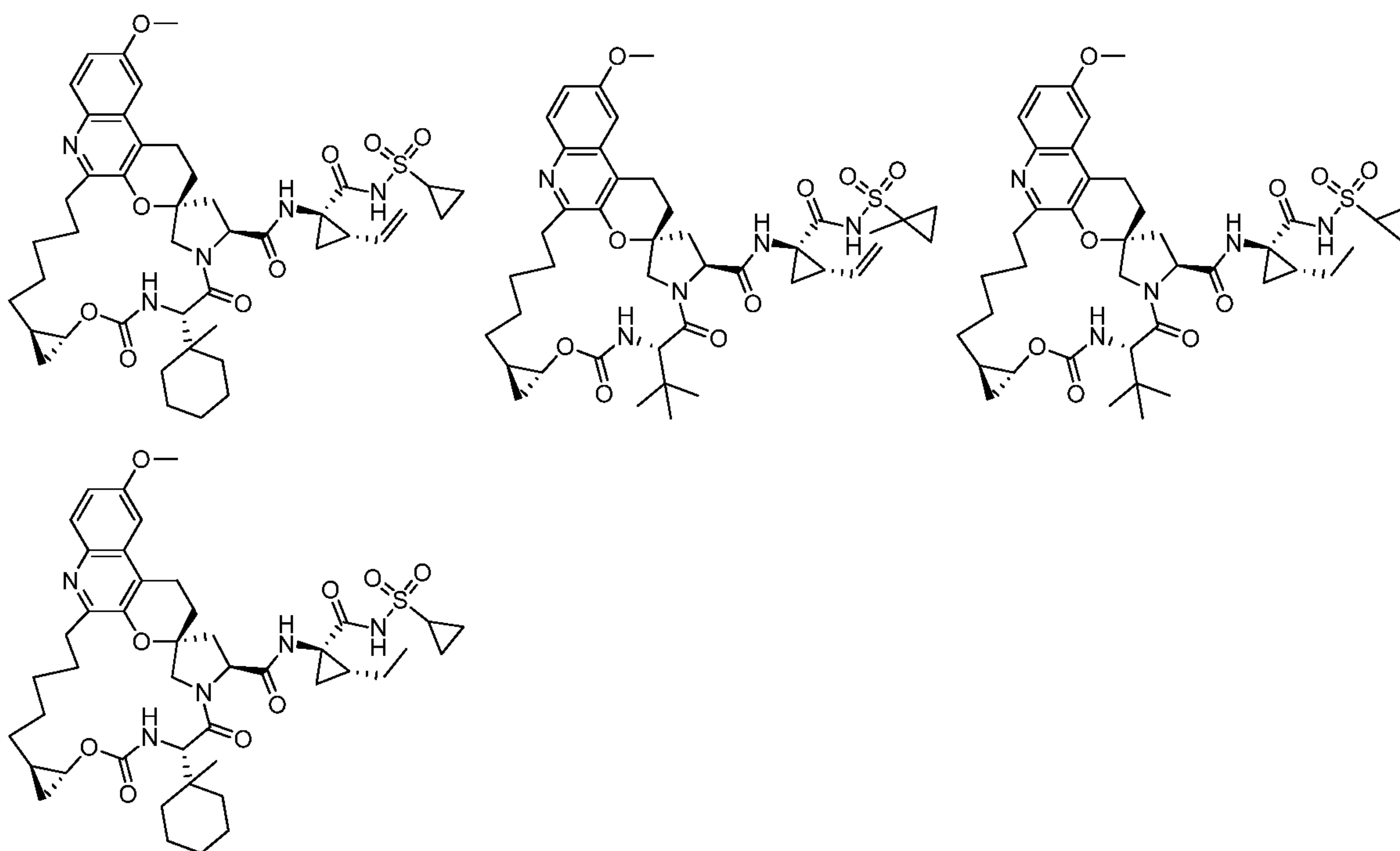






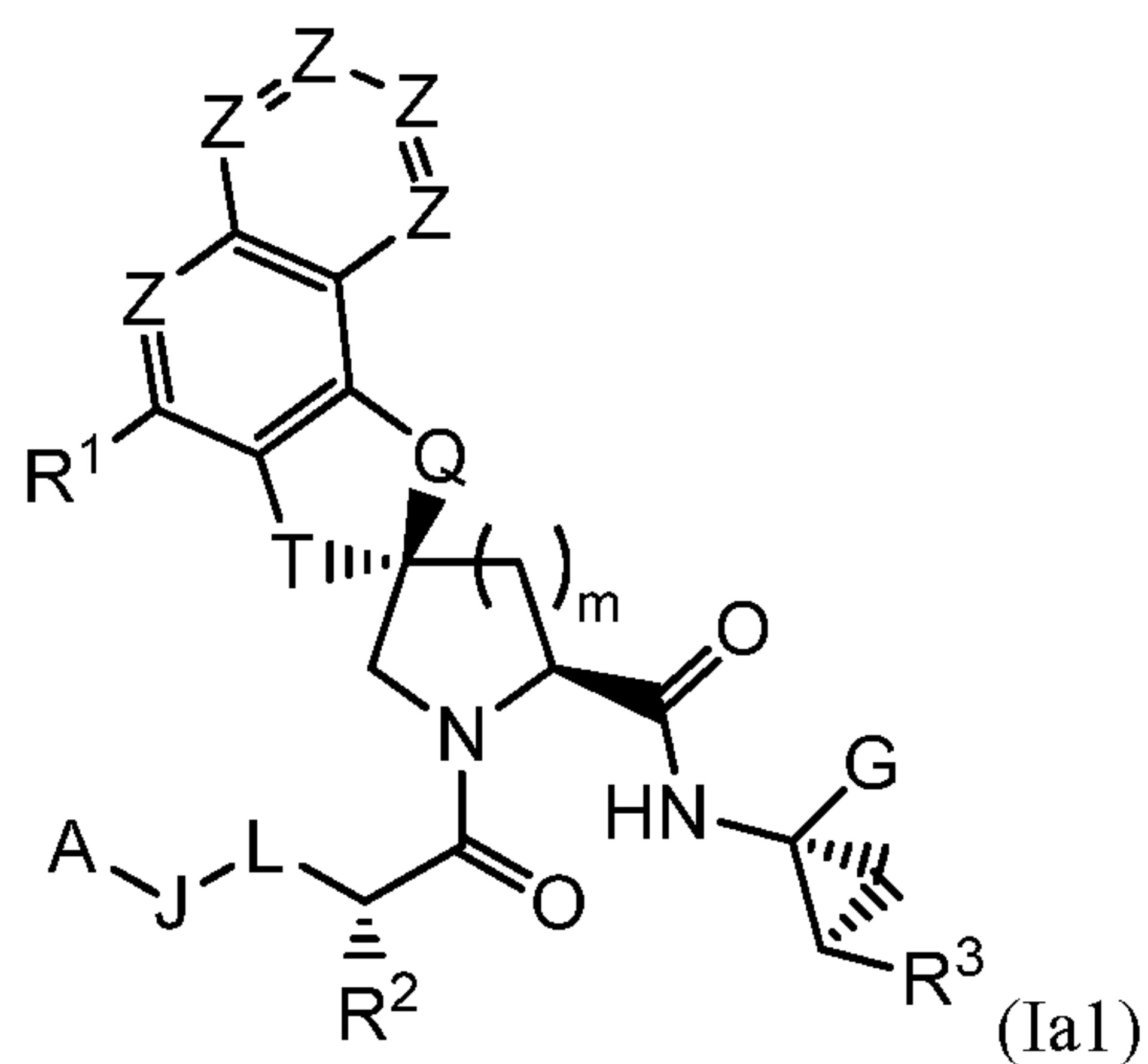


5



or a pharmaceutically acceptable salt thereof.

30. The compound according to any one of claim 1 to claim 11, wherein the
5 compound is a compound of formula Ia1:



or a pharmaceutically acceptable salt thereof, wherein:

A is selected from the group consisting of C₁-C₈ alkyl and aryl, wherein

said A aryl groups contain 0, 1 or 2 heteroatoms independently selected

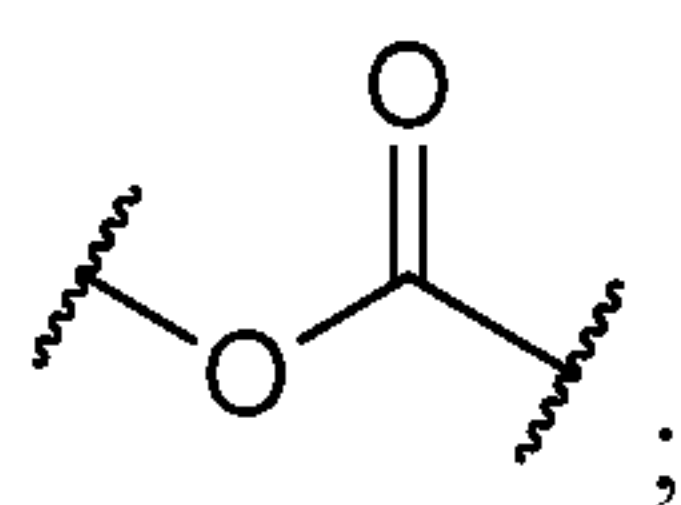
10 from the group consisting of O, S and N,

each A aryl is independently selected from the group consisting of 5- and

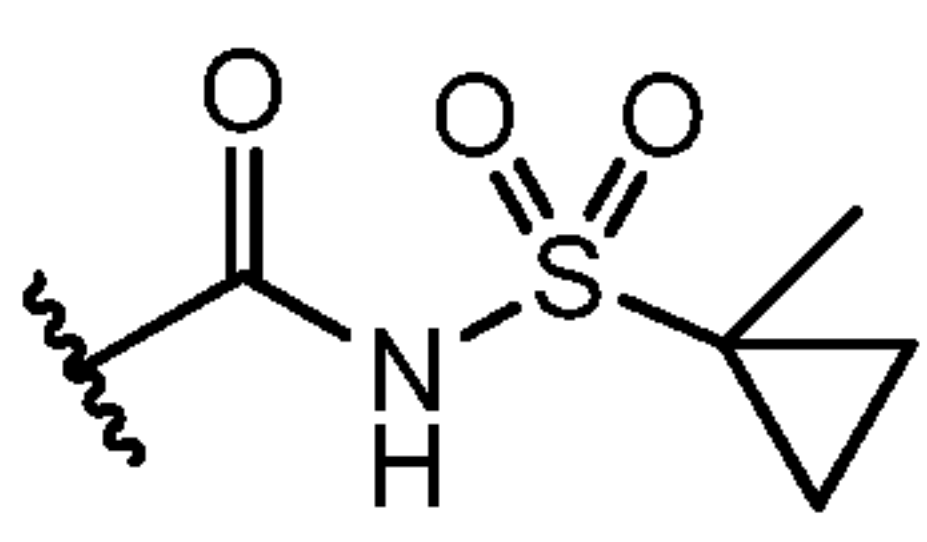
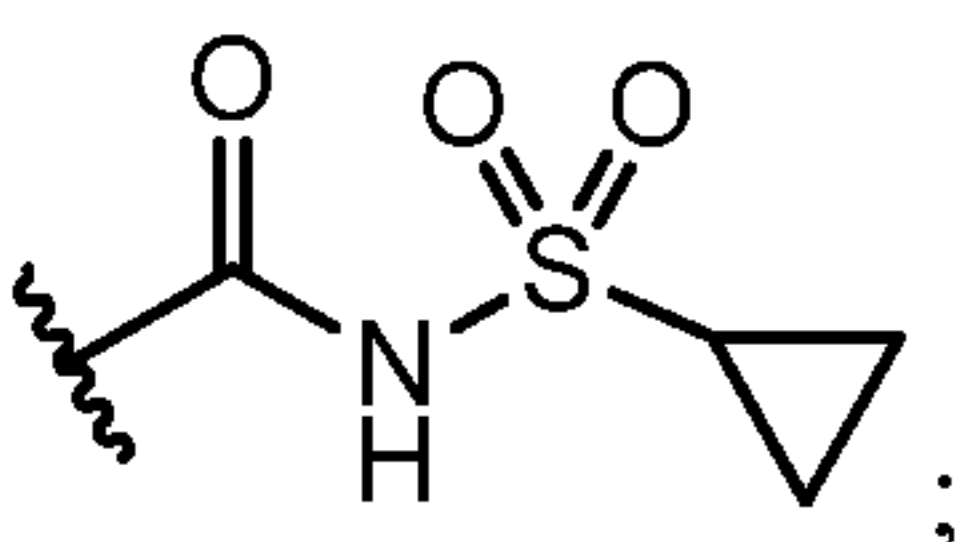
6-membered aromatic rings,

said A is substituted with 0, 1 or 2 substituents R^A;

each R^A is independently selected from the group consisting of H, F, C_1 - C_3 alkyl and C_3 - C_6 cycloalkyl;

J is a direct bond or  ;

L is NH;

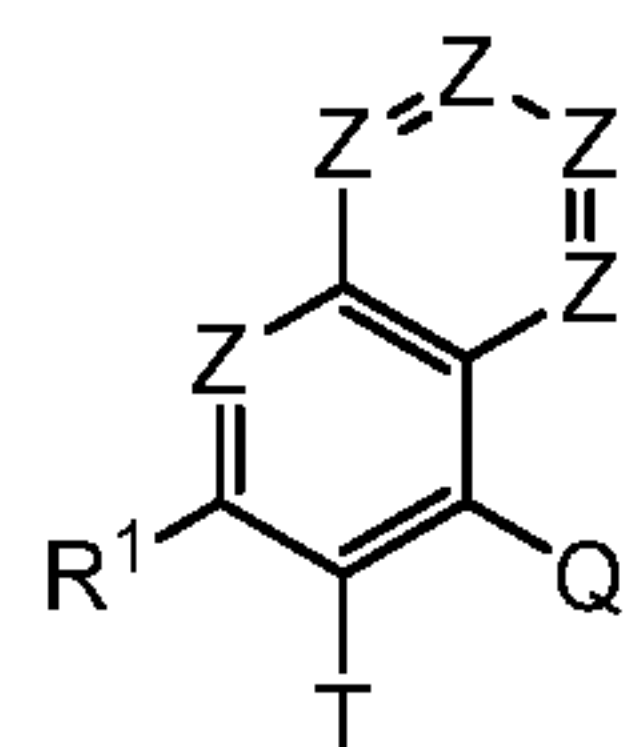
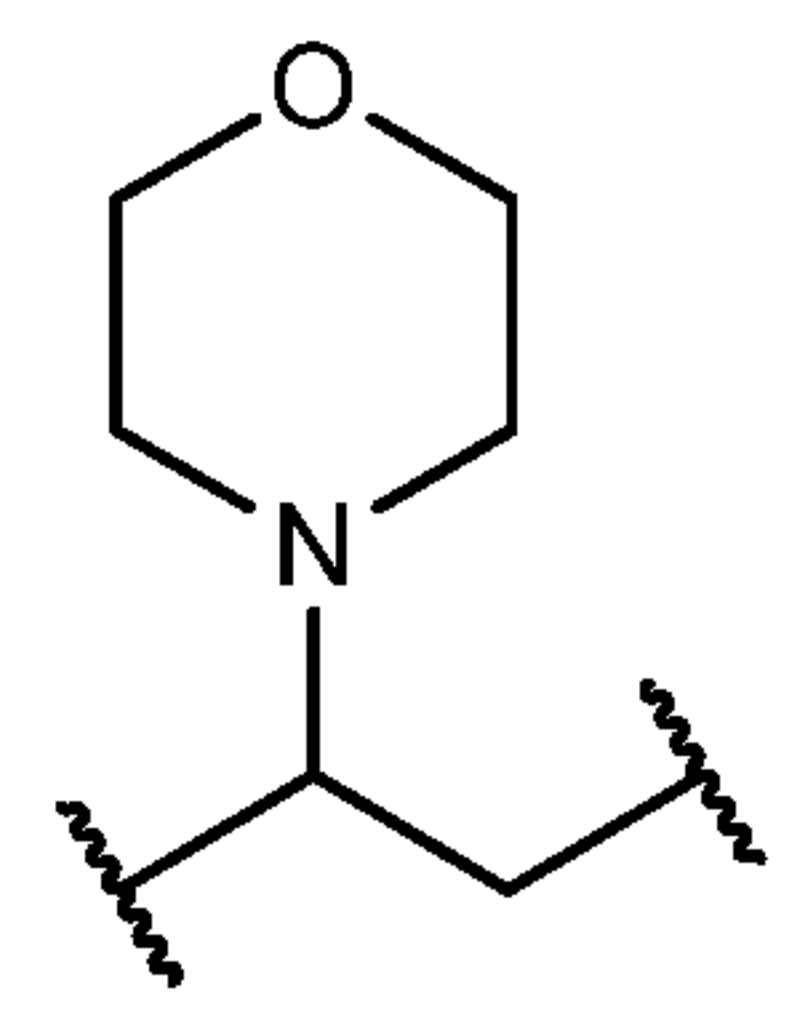
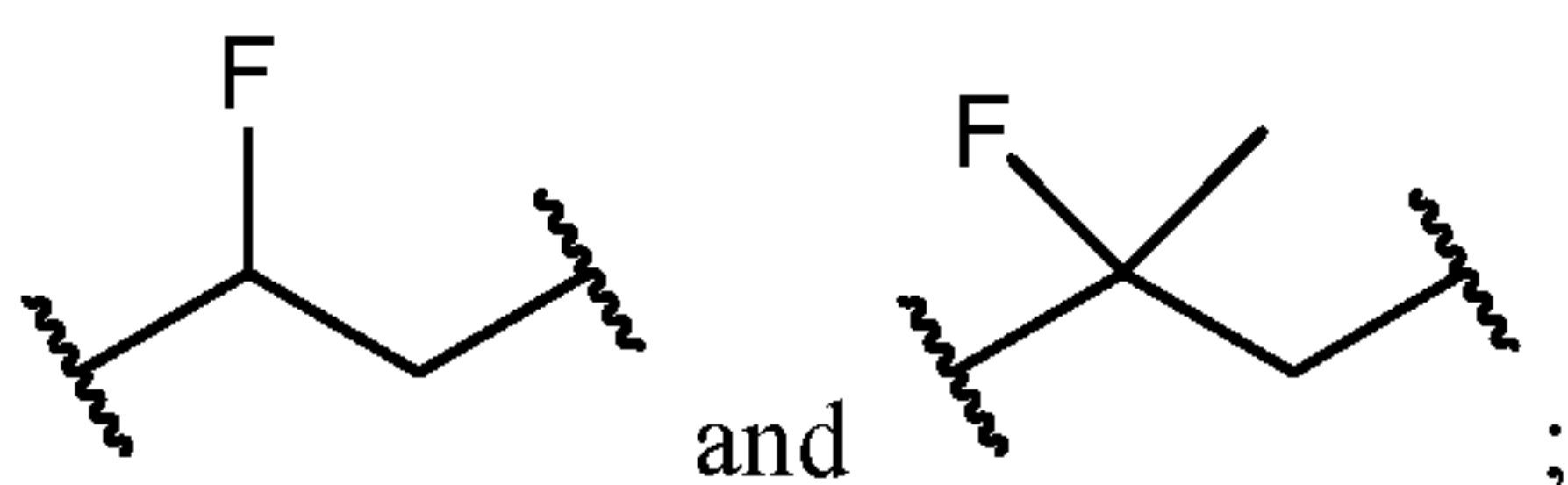
5 G is  or  ;

R^2 is C_5 alkyl;

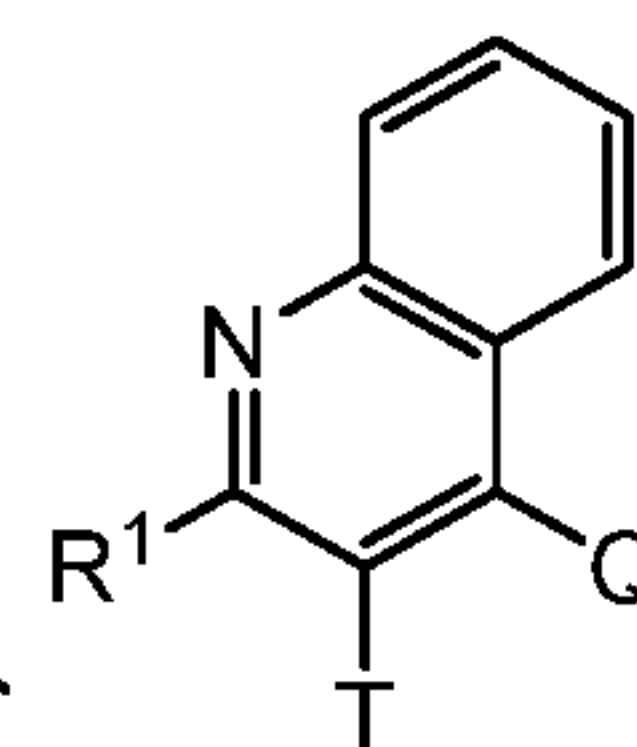
R^3 is $-\text{CH}=\text{CH}-$ (bond to R^2), wherein R^2 and R^3 form a macrocyclic linkage that contains 1 double bonds;

T is $-\text{O}-$;

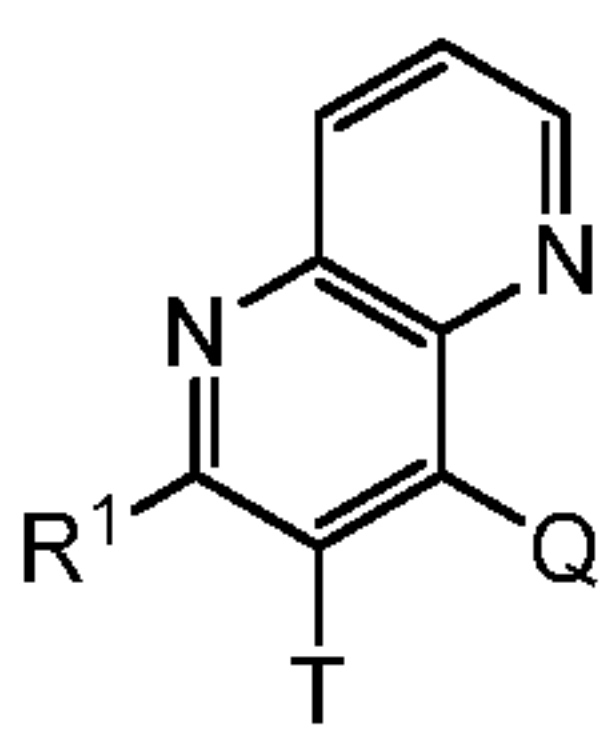
10 Q is selected from the group consisting of selected from $-(\text{CH}_2)_2-$,



is selected from the group consisting of



and



, substituted by 1 R^4 substituent;

R^1 is selected from the group consisting of H, C_1 - C_9 alkyl, and aryl groups;

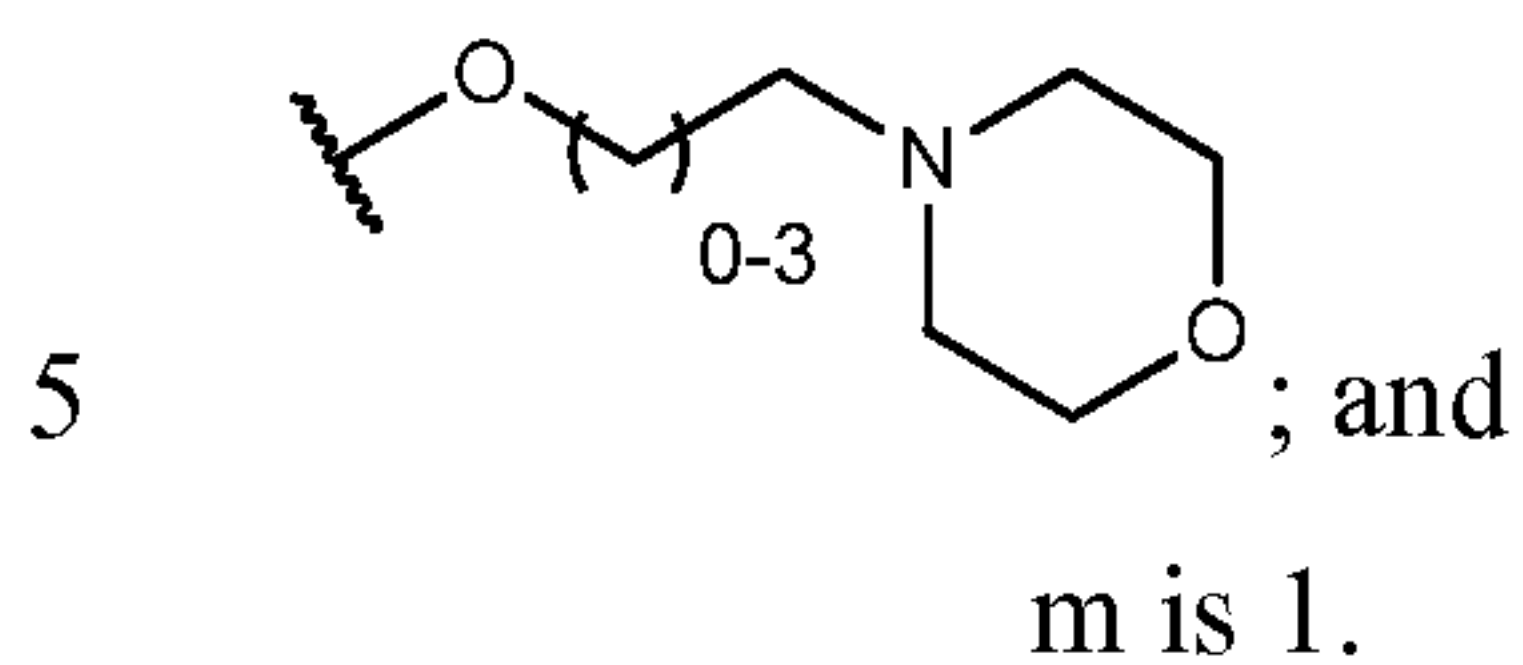
15 wherein:

said R^1 aryl groups contain 0 or 1 heteroatoms independently selected from the group consisting of O, S and N,

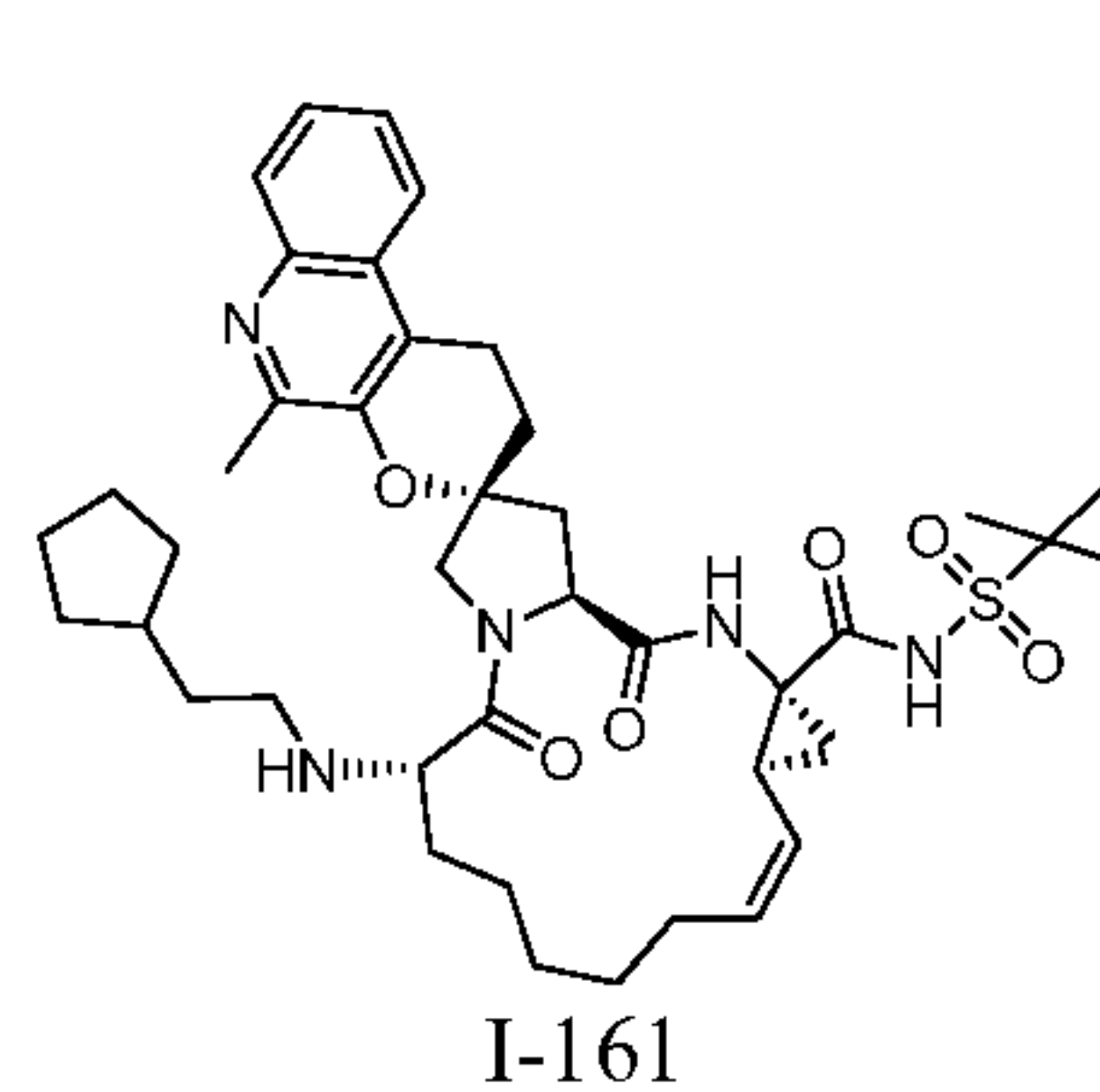
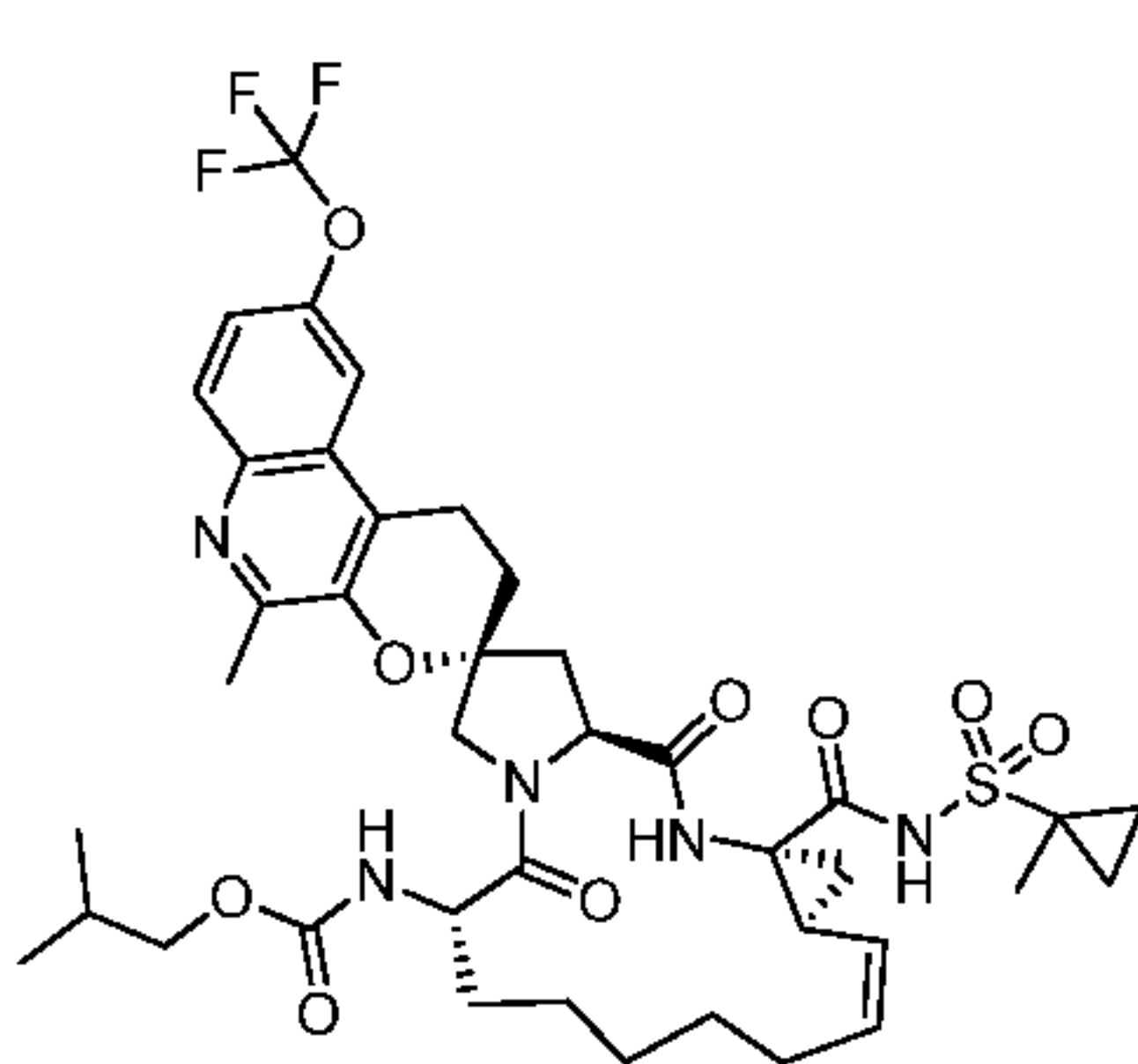
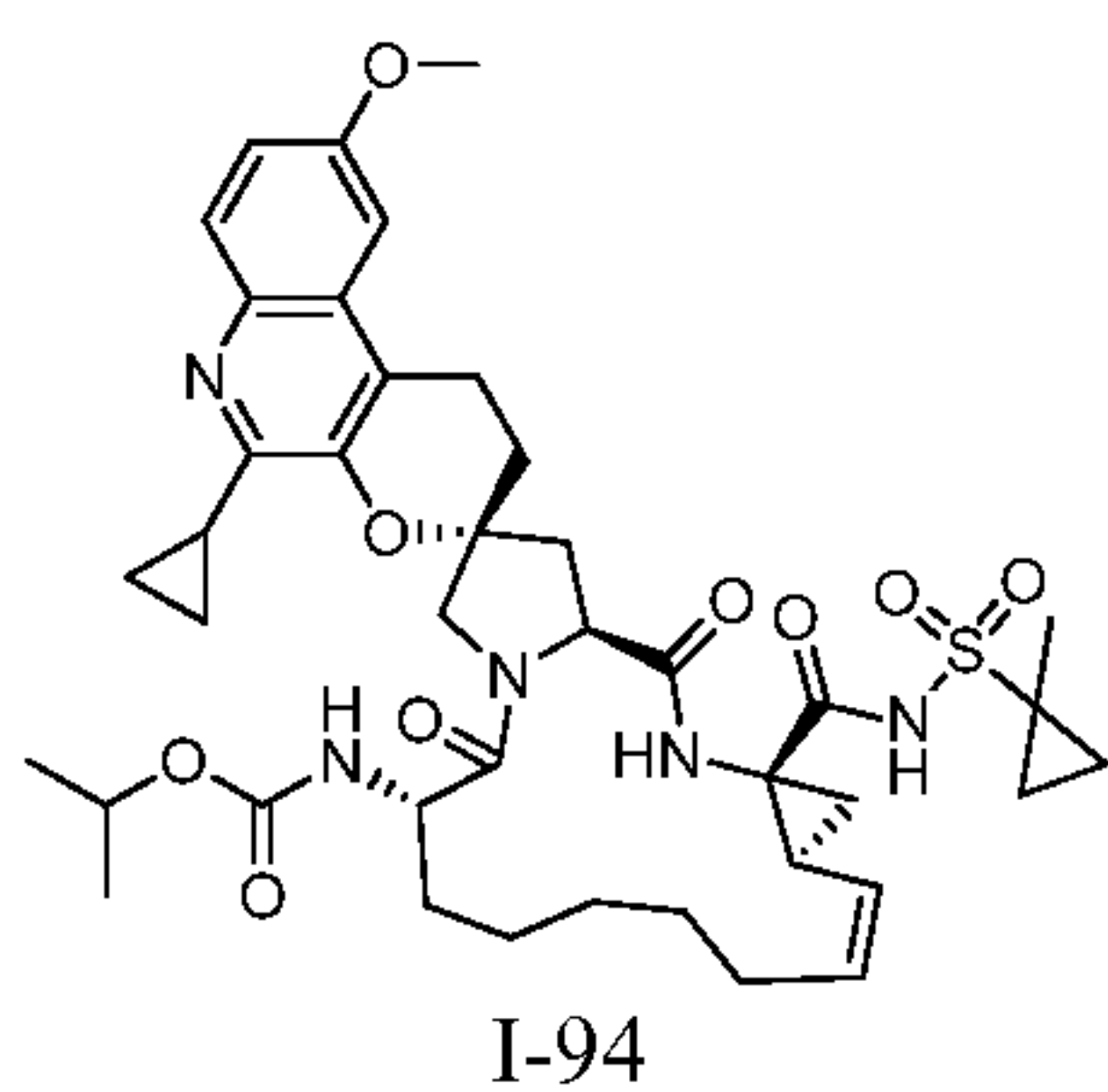
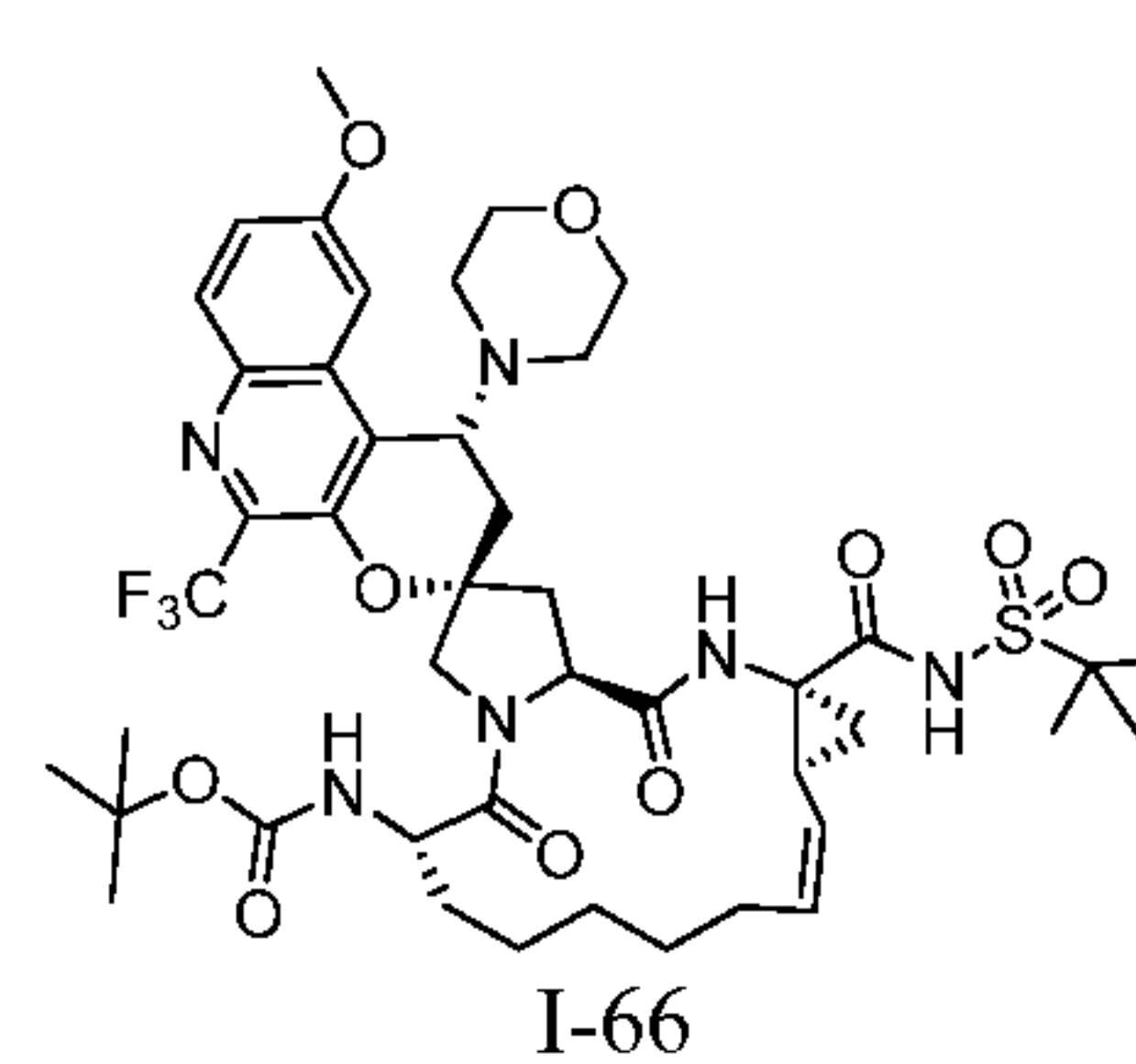
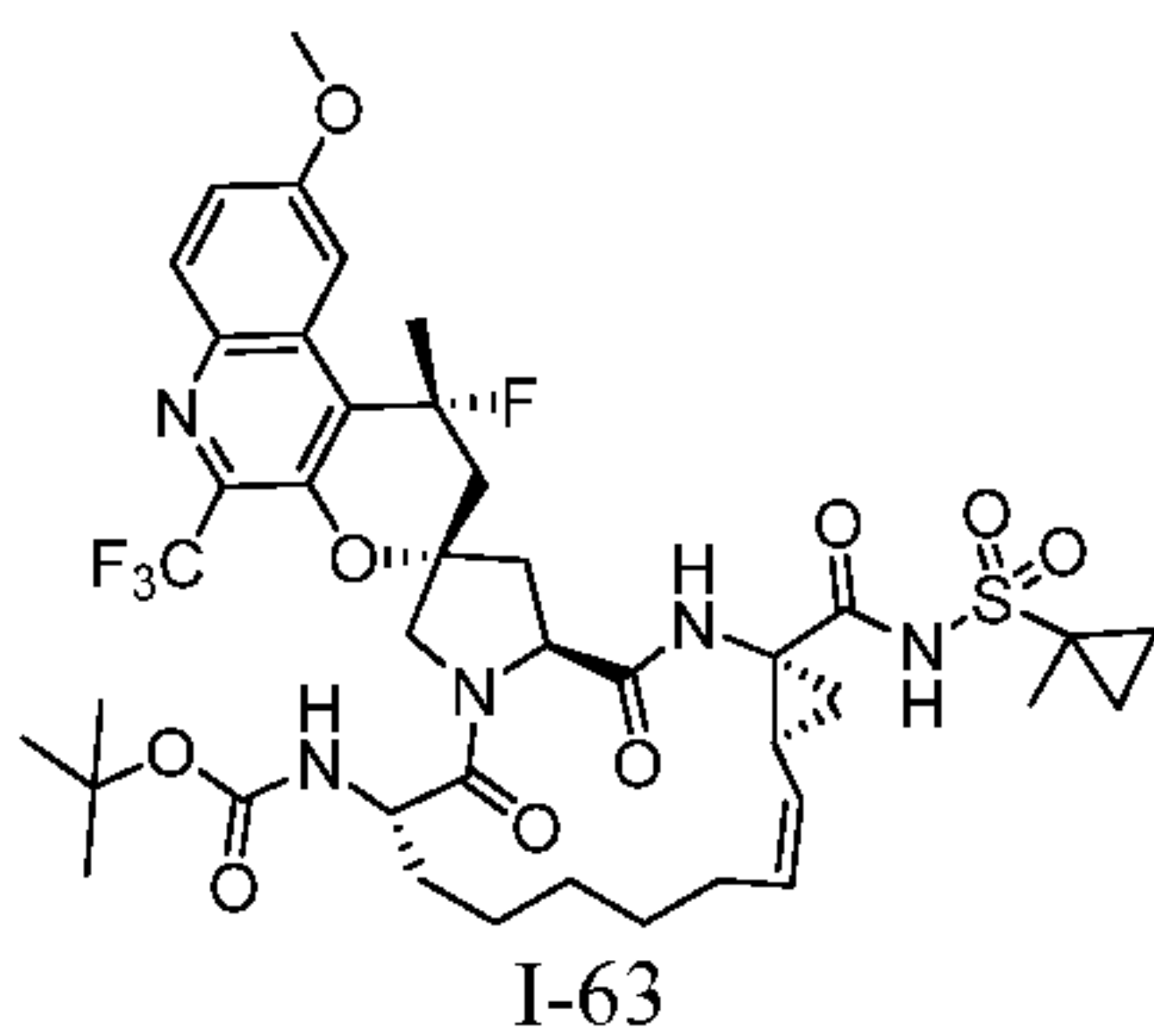
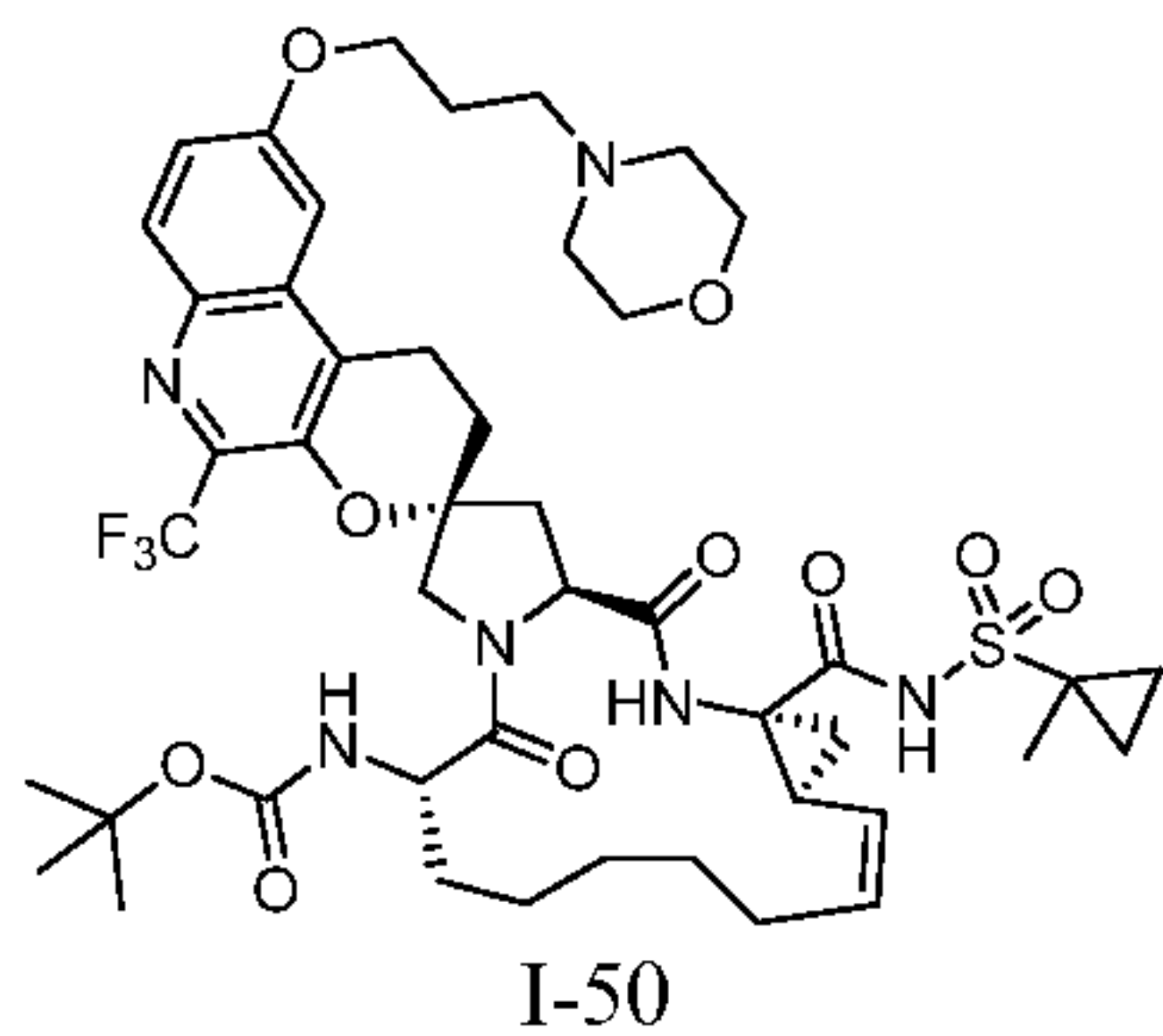
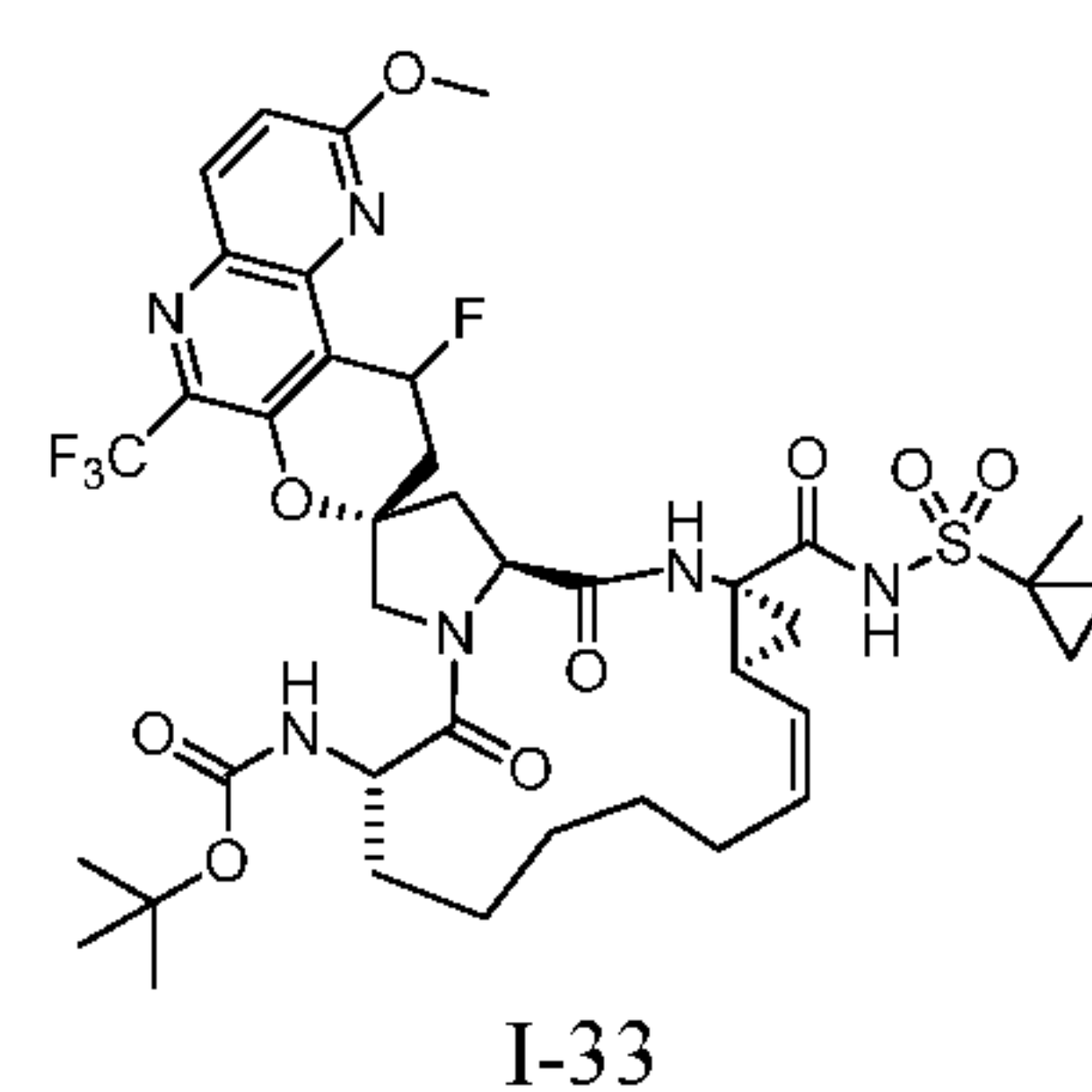
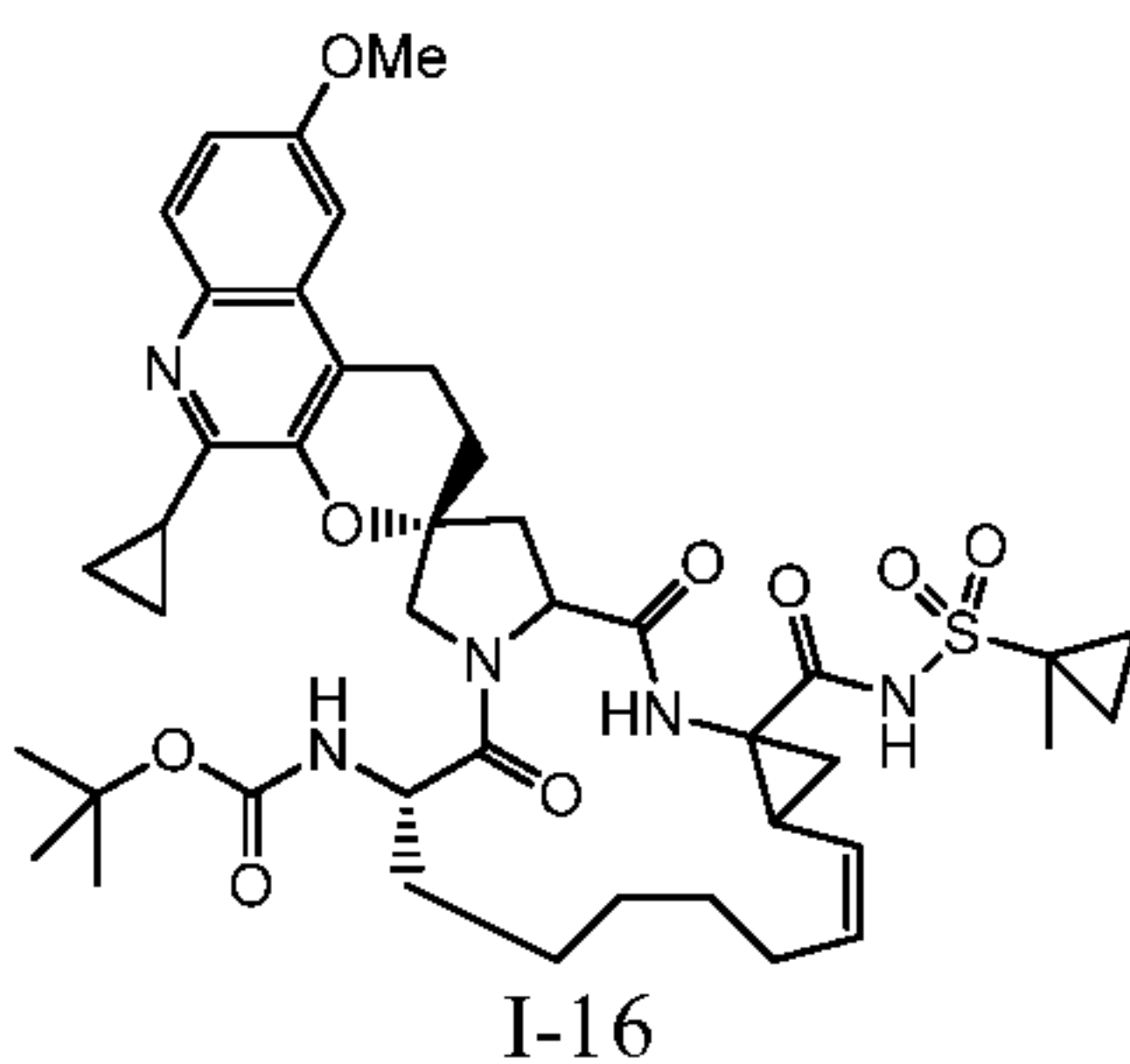
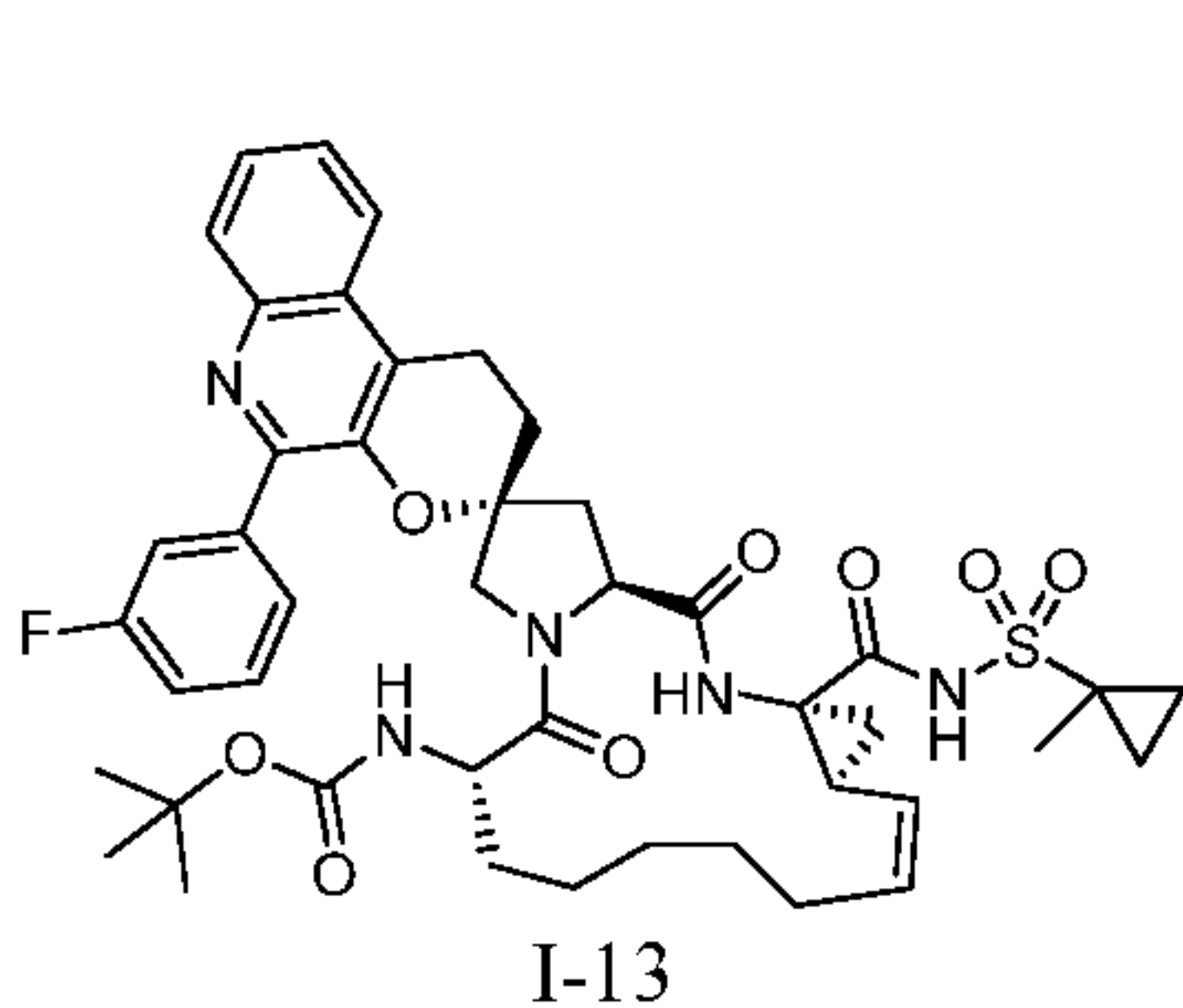
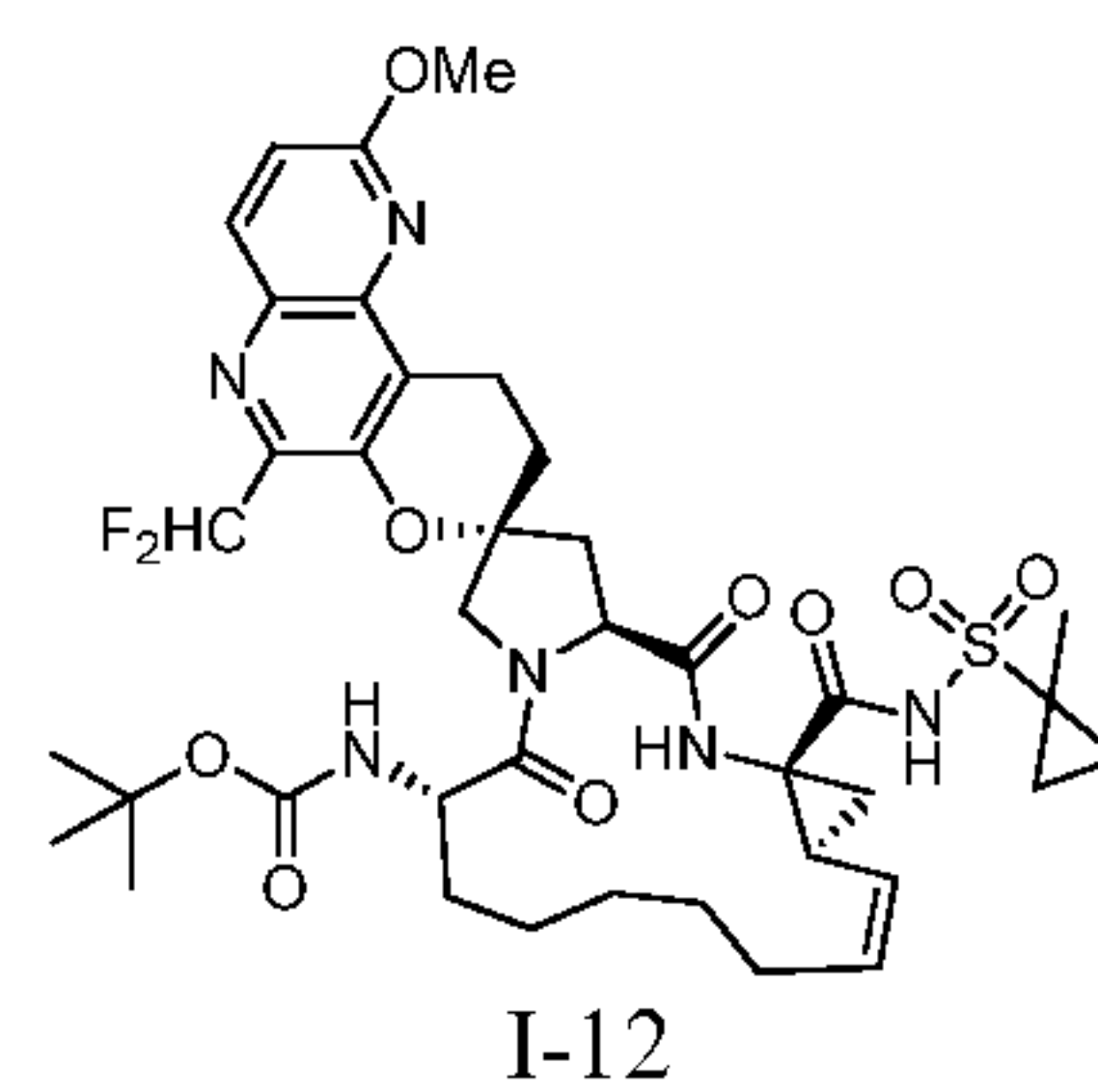
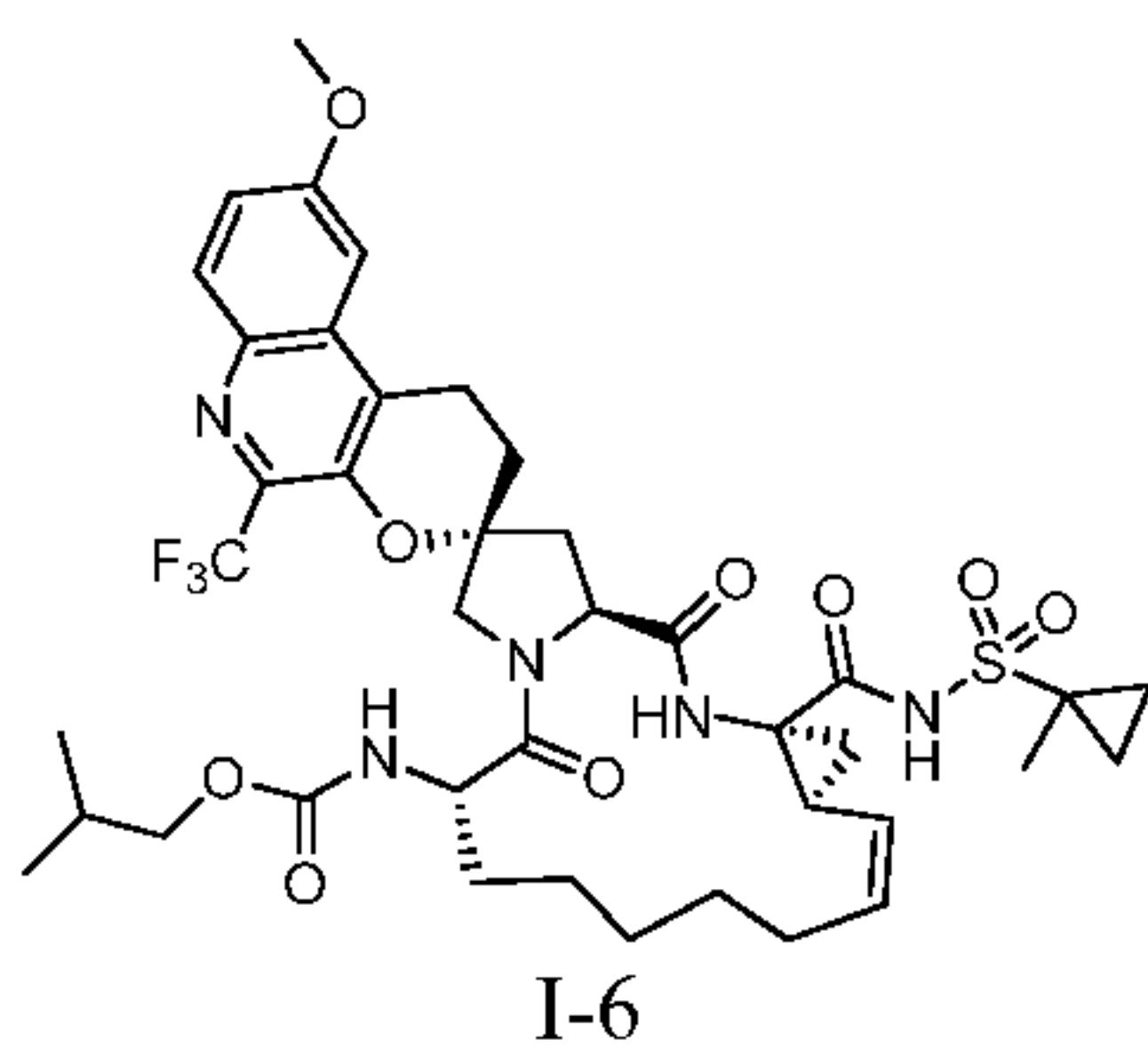
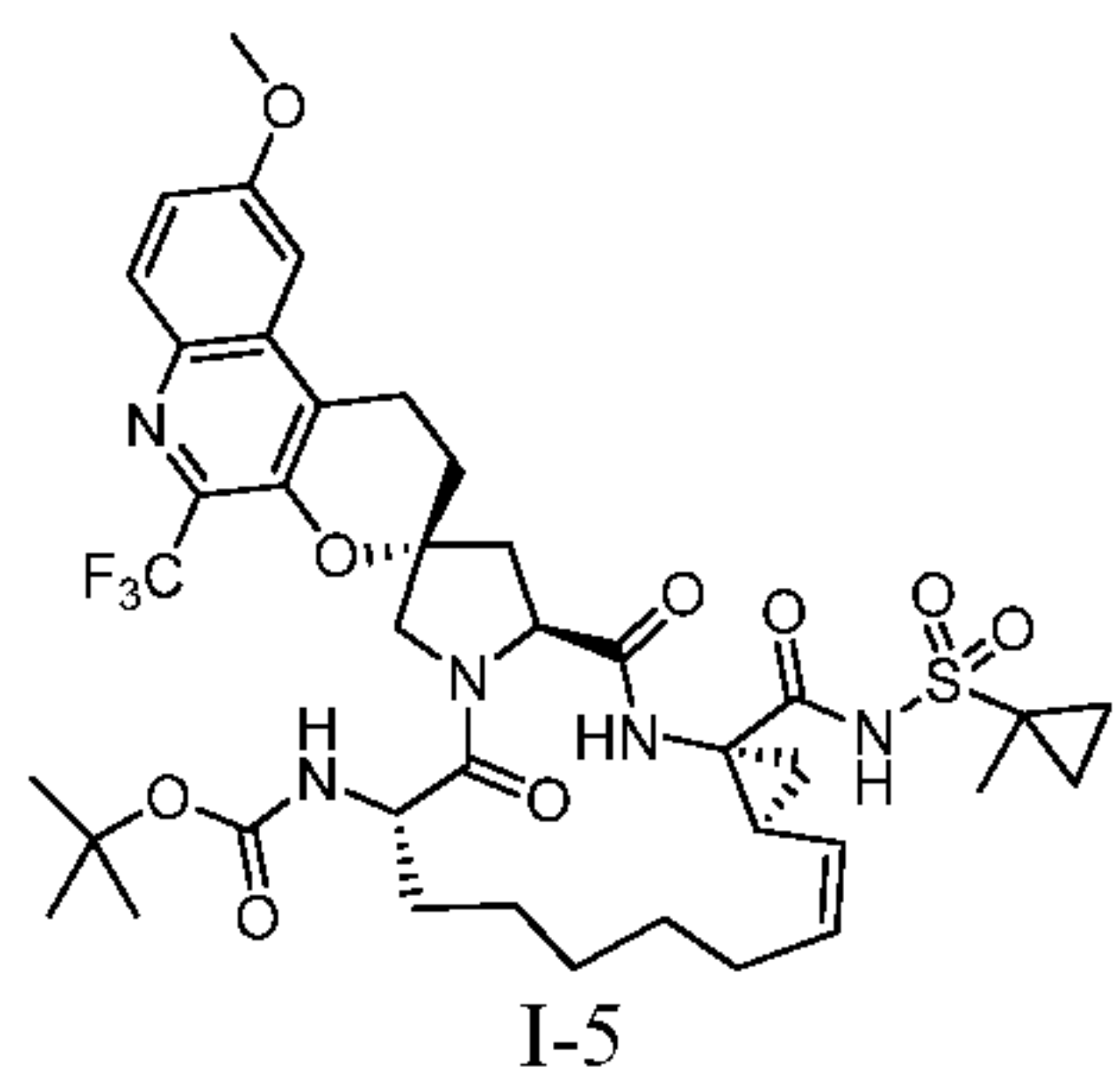
each R¹ aryl is independently selected from the group consisting of 5- and 6-membered aromatic rings,

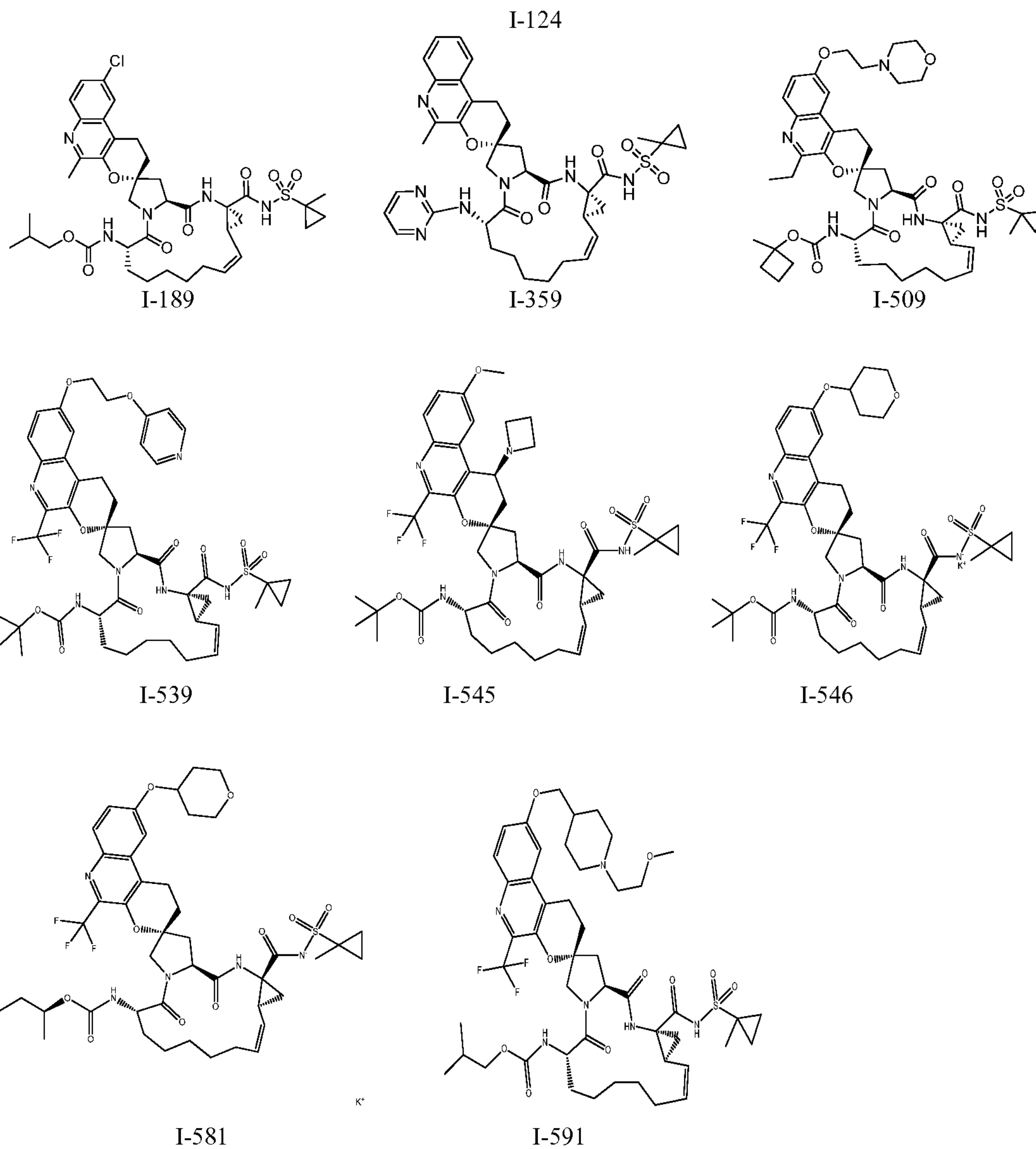
said R¹ groups are substituted with 0 to 4 substituents R^A;

each R^A is selected from the group consisting of H, Cl, OCH₃, OCF₃ and



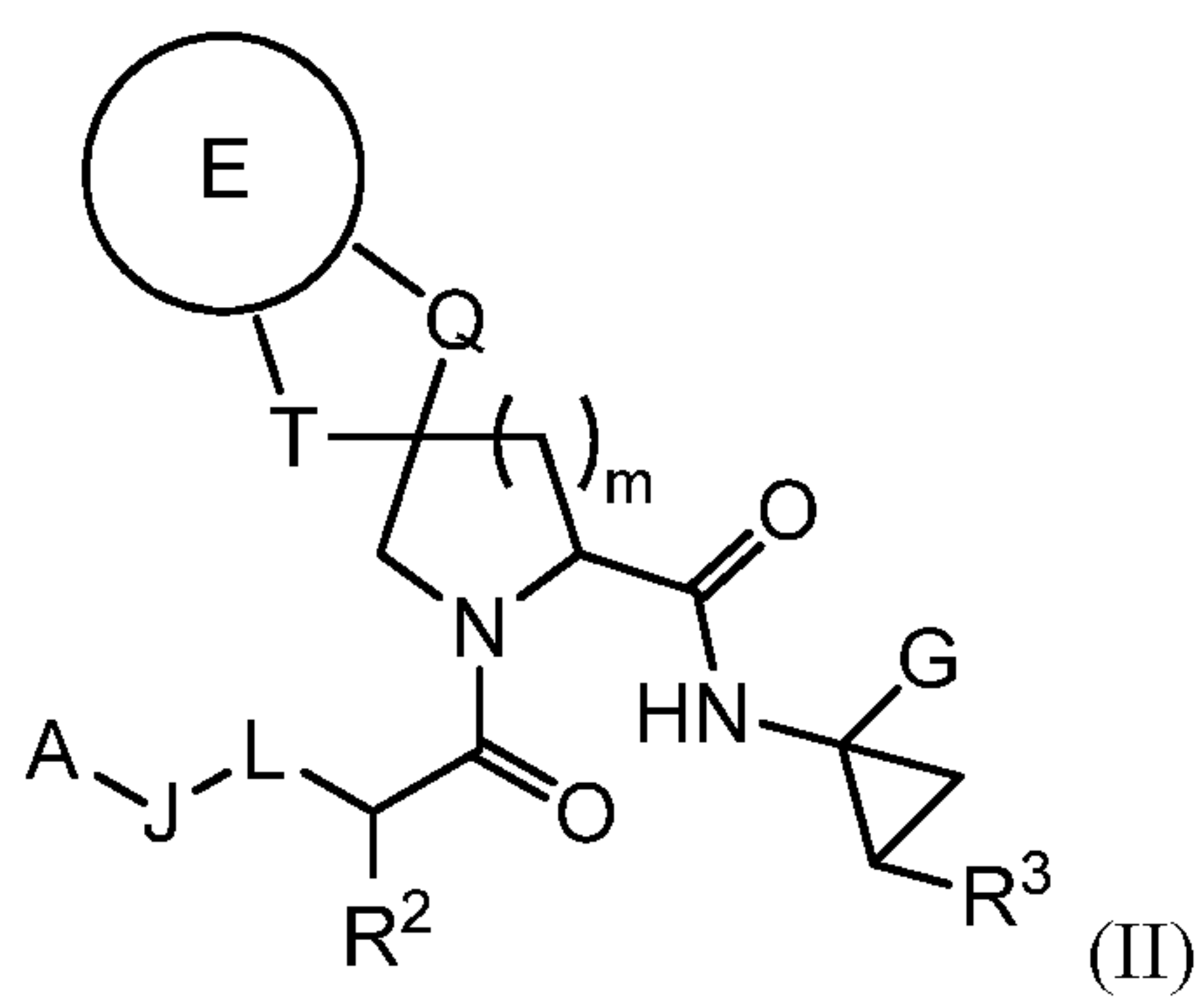
31. The compound according to claim 30, wherein the compound is selected from the group consisting of:

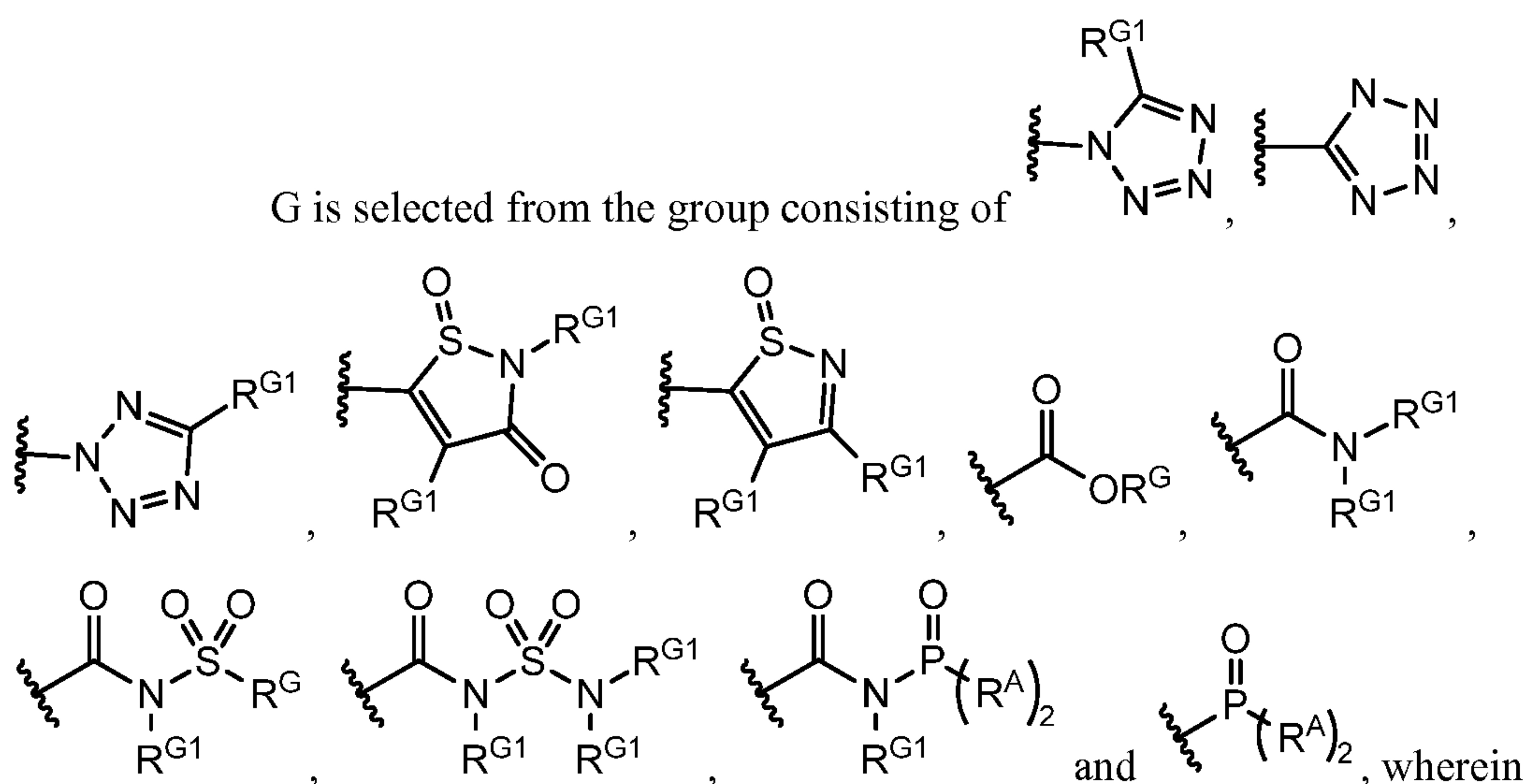




or a pharmaceutically acceptable salt thereof.

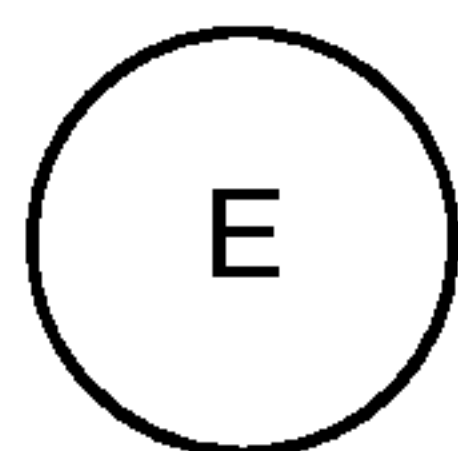
32. A compound of Formula II:





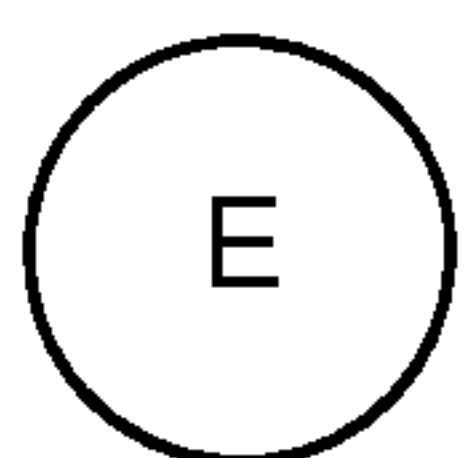
R^G is selected from the group consisting of H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkyl- C_1 - C_5 alkyl, C_1 - C_6 alkyl substituted with R^A , C_3 - C_6 cycloalkyl substituted with R^A , or C_3 - C_6 cycloalkyl- C_1 - C_5 alkyl substituted with R^A ;

each R^{G1} is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, and benzyl;



is selected from the group consisting of:

- 1) an aryl ring attached to Q and T at two independently selected carbon ring atoms, wherein the aryl ring is phenyl or naphthyl,
- 2) a C_3 - C_8 cycloalkyl attached to Q and T at two independently selected carbon ring atoms, and
- 3) a heterocyclic ring attached to Q and T at two independently selected ring atoms that are either two carbon ring atoms or one carbon ring atom and one nitrogen ring atom, wherein the heterocyclic ring is selected from the group consisting of:
 - a) a 5- or 6-membered saturated or unsaturated monocyclic ring with 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O and S,
 - b) a 8-, 9- or 10-membered saturated or unsaturated bicyclic ring with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S,
 - and
 - c) a 11- to 15-membered saturated or unsaturated tricyclic ring with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S,



wherein $\textcircled{\text{E}}$ further contains 1 R^1 substituent and 0, 1, 2, 3, 4 or 5 independently selected R^4 substituents;

each R^1 is selected from the group consisting of hydrogen, halogen, OH, $\text{C}_1\text{-C}_9$ alkyl, $\text{C}_1\text{-C}_6$ alkyl- R^{B} , $\text{C}_1\text{-C}_9$ hydroxylalkyl, $\text{C}_1\text{-C}_9$ alkoxy,

5 $\text{C}_1\text{-C}_9$ alkyl- $\text{C}_1\text{-C}_9$ alkoxy, CN, $\text{C}(\text{O})\text{OH}$, $\text{C}(\text{O})\text{CH}_3$, SR^5 , $\text{SO}_2(\text{C}_1\text{-C}_9 \text{ alkyl})$, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_3\text{-C}_8$ cycloalkyl- $\text{C}_1\text{-C}_9$ alkyl, $\text{C}_1\text{-C}_9$ alkyl- $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_9$ alkyl-O- $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_1\text{-C}_4$ haloalkyl, $\text{C}_1\text{-C}_5$ haloalkoxy, $-(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-O}\text{-}(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-}(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-S}\text{-}(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-}(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-S}(\text{O})_2\text{-}(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-}(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $\text{N}(\text{R}^5)_2$, $\text{C}_1\text{-C}_9$ alkyl- $\text{N}(\text{R}^5)_2$, Aryl, and Het;

10 R^2 is selected from the group consisting of $\text{C}_1\text{-C}_9$ alkyl, $\text{C}_2\text{-C}_9$ alkenyl, $\text{C}_2\text{-C}_9$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, Het, and Aryl;

R^3 is selected from the group consisting of $\text{C}_1\text{-C}_9$ alkyl, $\text{C}_2\text{-C}_9$ alkenyl, and $\text{C}_2\text{-C}_9$ alkynyl;

15 T is selected from the group consisting of O, $(\text{CH}_2)_{q_2}$, NH, SO_2 and S, wherein q_2 is 0, 1, 2, 3 or 4;

Q is selected from the group consisting of $-(\text{CR}^{\text{A}}_2)_p-$, $-(\text{CR}^{\text{A}}_2)_p\text{-CR}^{\text{A}}=\text{CR}^{\text{A}}-$, $(\text{CR}^{\text{A}}_2)_{p1}$, $-(\text{CR}^{\text{A}}_2)_p\text{-O}\text{-}(\text{CR}^{\text{A}}_2)_{p1}$, $-(\text{CR}^{\text{A}}_2)_p\text{-N}(\text{R}^{\text{A}})\text{-}(\text{CR}^{\text{A}}_2)_{p1}$, $-(\text{CR}^{\text{A}}_2)_p\text{-S}\text{-}(\text{CR}^{\text{A}}_2)_{p1}$, $-(\text{CR}^{\text{A}}_2)_p\text{-S}(\text{O})\text{-}(\text{CR}^{\text{A}}_2)_{p1}$, and $-(\text{CR}^{\text{A}}_2)_p\text{-S}(\text{O})_2\text{-}(\text{CR}^{\text{A}}_2)_{p1}$, where p and p1 are independently selected from 0, 1, 2, 3 or 4;

20 provided that $p + p_1 + q_2$ equals 0, 1, 2, 3, or 4;

each R^4 is independently selected from the group consisting of:

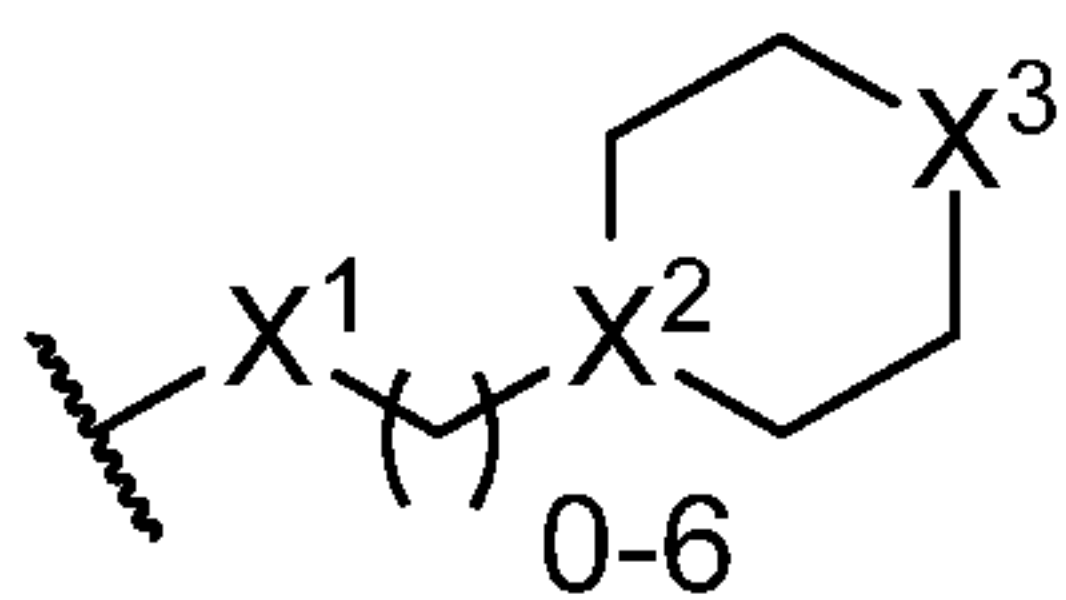
hydrogen, halogen, OH, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkoxy,

$\text{C}_1\text{-C}_6$ alkyl- R^{B} , $\text{C}_1\text{-C}_6$ haloalkyl- R^{B} , $\text{C}_1\text{-C}_6$ alkoxy- R^{B} , $\text{C}_1\text{-C}_6$ haloalkoxy- R^{B} , $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_3\text{-C}_8$ cycloalkyl- $\text{C}_1\text{-C}_9$ alkyl, $\text{C}_1\text{-C}_6$ hydroxyalkyl, O- $\text{C}_1\text{-C}_6$ hydroxyalkyl,

25 O- $\text{C}_1\text{-C}_6$ alkyl- R^{B} , CN, SR^5 , CO_2R^5 , $\text{C}(\text{O})\text{N}(\text{R}^5)_2$, $\text{OC}(\text{O})\text{N}(\text{R}^5)_2$, O-($\text{C}_1\text{-C}_6$)alkyl- OR^5 ,

O-($\text{C}_1\text{-C}_5$ alkyl)-O-($\text{C}_1\text{-C}_3$ alkyl), O-($\text{C}_1\text{-C}_5$ alkyl)-O-($\text{C}_1\text{-C}_3$ alkyl)- R^{B} , $-(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-O}\text{-}(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-}(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-S}\text{-}(\text{C}_0\text{-C}_3 \text{ alkyl})\text{-}(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$,

-(C₀-C₃ alkyl)-S(O)₂-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), SO(R⁵), SO₂(R⁵), Het, Aryl, and



, wherein X¹ is either CH₂, NH, O, or S; X² is either CH or N; and X³ is either NH, N-R⁵, CH₂, CH-R⁵, O, or S;

provided that two R⁴ groups can join together to form methylene dioxy;

5 each R⁵ is independently selected from the group consisting of:

hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkyl(NH₂), C₆-C₈ bridged cycloalkyl, C₃-C₈ cycloalkyl, and C₃-C₈ halocycloalkyl;

each Aryl is independently phenyl or naphthyl optionally substituted with 1, 2, 3 or 4 R^C substituents;

10 each Het is independently either (a) 4-, 5- or 6-membered saturated or unsaturated monocyclic ring with 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O and S; (b) 8-, 9- or 10-membered saturated or unsaturated bicyclic ring with 1, 2, 3, 4, or 5 heteroatom ring atoms independently selected from the group consisting of N, O and S, or (c) 11- to 15-membered saturated or unsaturated tricyclic ring with 1, 2, 3, 4, or 5
15 heteroatom ring atoms independently selected from the group consisting of N, O and S; provided that said Het is optionally substituted with 1, 2, 3 or 4 R^C substituents;

each R^A is independently selected from the group consisting of:

H, F, Cl, Br, I, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkyl(NH₂), C₆-C₈ bridged cycloalkyl, C₃-C₈ cycloalkyl, C₁-C₆ haloalkoxy, C₃-C₈ halocycloalkyl,
20 SH, S(C₁-C₆ alkyl), NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, C(O)(C₁-C₆ alkyl), C(O)(C₃-C₈ cycloalkyl), CONH₂, SO₂NH₂, NO₂, CN, CF₃, CHF₂, CH₂F, OCHF₂, OCF₃, OCH₂F, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), -(C₁-C₆ alkyl)S(O)(C₁-C₆ alkyl), SO₂(C₃-C₆ cycloalkyl), -(C₁-C₆ alkyl)S(O)₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl)N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), SO₂N(C₁-C₆ alkyl)₂, -(C₁-C₆ alkyl)SO₂N(C₁-C₆ alkyl)₂, NHCOO(C₁-C₆ alkyl),
25 NHCO(C₁-C₆ alkyl), NHCONH(C₁-C₆ alkyl), CO₂(C₁-C₆ alkyl), C(O)N(C₁-C₆ alkyl)₂, -(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-O-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-S-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl),
-(C₀-C₅ alkyl)-S(O)₂-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), Aryl, and Het; provided that two R^A groups present on adjacent carbon atoms can together with the adjacent carbon atoms form a C₃-
30 C₆ cycloalkyl;

each R^B is independently either Het or Aryl;

each R^C is independently either hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl or C_1 - C_6 haloalkyl;

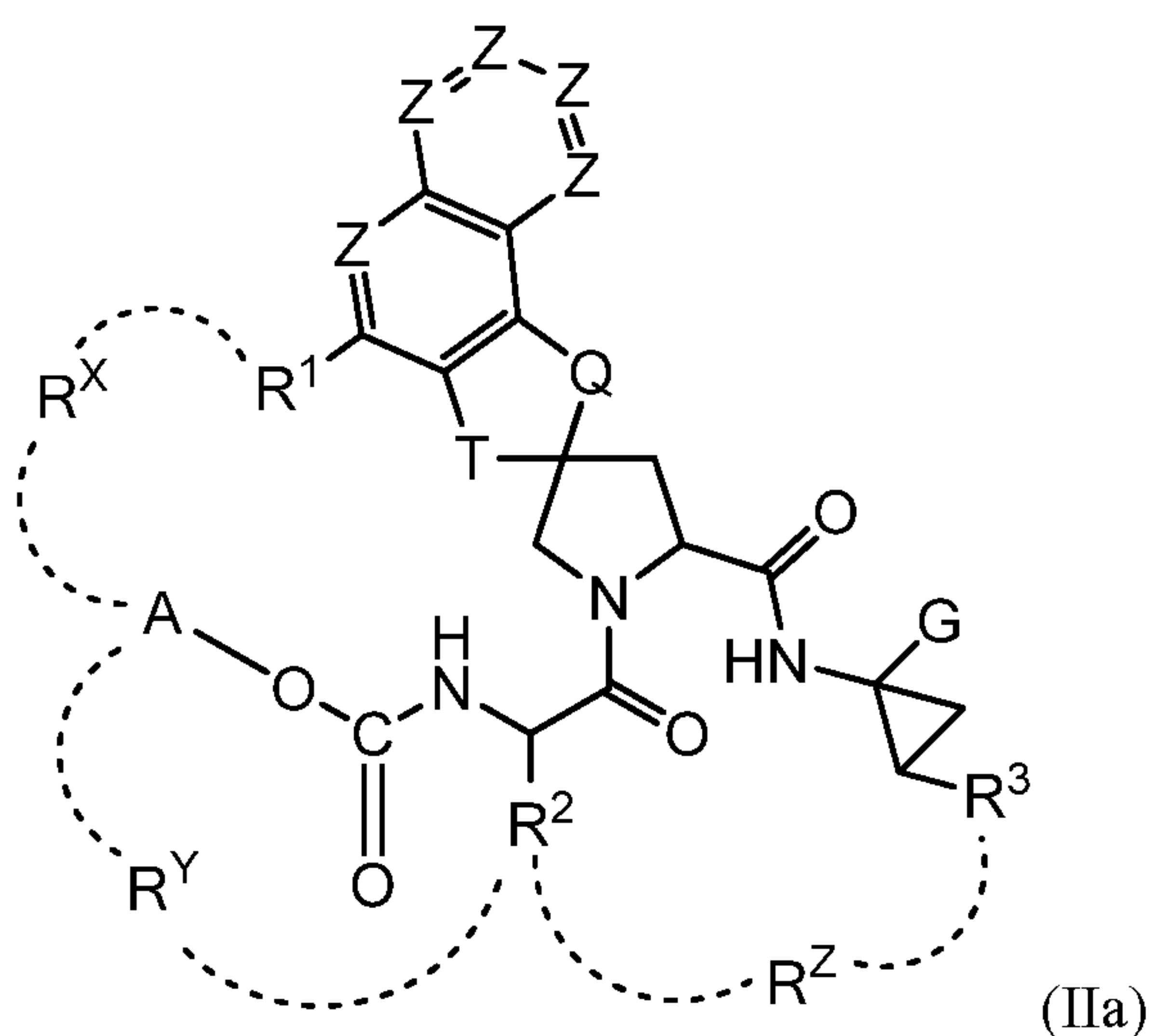
alternatively, with respect to A and R^1 , A is either C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, or C_3 - C_8 cycloalkyl, each of which is substituted with R^{A1} , and R^{A1} in combination with R^1 forms a C_3 - C_8 alkylene, a C_3 - C_8 alkenylene, or a C_3 - C_8 alkynylene, each of which may be substituted with 1 or 2 independently selected R^C ;

alternatively, with respect to A and R^2 , A is either C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, or C_3 - C_8 cycloalkyl, each of which is substituted with R^{A1} , and R^{A1} in combination with R^2 form a C_3 - C_8 alkylene, a C_3 - C_8 alkenylene, or a C_3 - C_8 alkynylene, each of which may be substituted 1 or 2 independently selected R^C ;

alternatively, with respect to R^2 and R^3 , R^2 and R^3 form a C_3 - C_8 alkylene, C_3 - C_8 alkenylene, or C_3 - C_8 alkynylene, each of which may be substituted with 1 or 2 independently selected R^C ; and

m is 0, 1, 2 or 3.

33. The compound of claim 32, wherein said compound of Formula II is a compound of Formula IIa:



20

or a pharmaceutically acceptable salt thereof,

wherein

each Z is independently either N or $C-R^4$;

A is selected from the group consisting of:

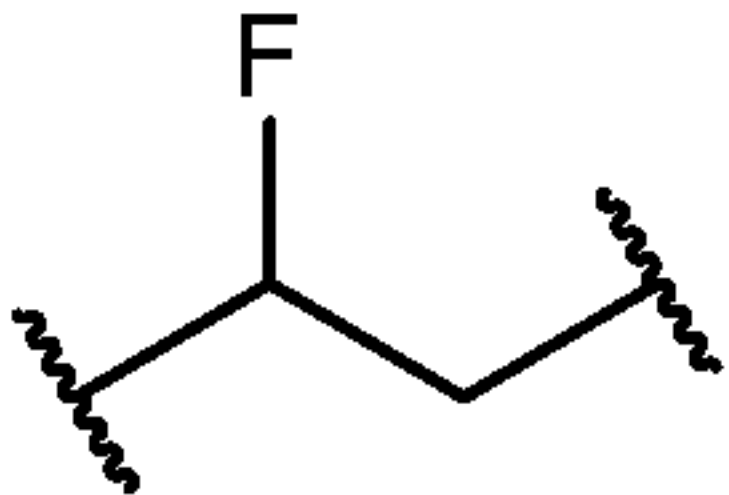
a) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₆-C₈ bridged cycloalkyl, or C₆-C₈ bridged cycloalkenyl,

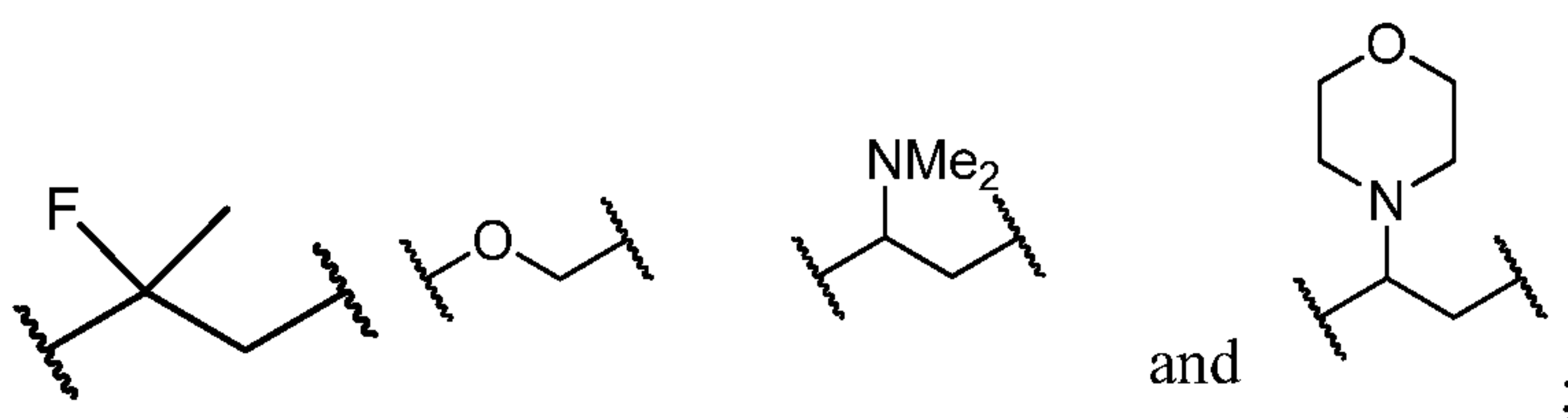
b) substituted C₁-C₈ alkyl, substituted C₂-C₈ alkenyl, substituted C₂-C₈ alkynyl, substituted C₃-C₈ cycloalkyl, substituted C₆-C₈ bridged cycloalkyl, or substituted C₆-C₈ bridged cycloalkenyl, each of which is substituted with 0, 1, 2, 3 or 4 R^A, and 0 or 1 R^B, provided that at least one R^A or R^B substituent is present,

c) C₁-C₈ haloalkyl, C₃-C₈ halocycloalkyl, or C₁-C₈ haloalkyl substituted with R^B,

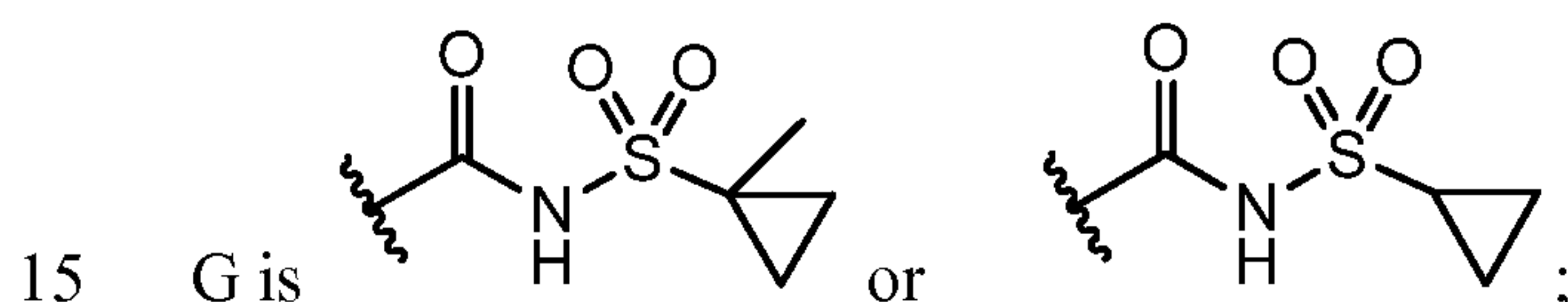
d) Aryl, and

10 e) Het;

Q is selected from the group consisting of -(CH₂)₂-,  and



T is selected from the group consisting of O, -(CH₂)_{q2}-, NH, SO₂ and S, wherein q₂ is 1 or 2;



R¹ is hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkyl-R^B, Aryl, or Het;

R² is selected from the group consisting of C₁-C₉ alkyl, C₂-C₉ alkenyl, C₂-C₉ alkynyl, C₃-C₈ cycloalkyl, Het, and Aryl;

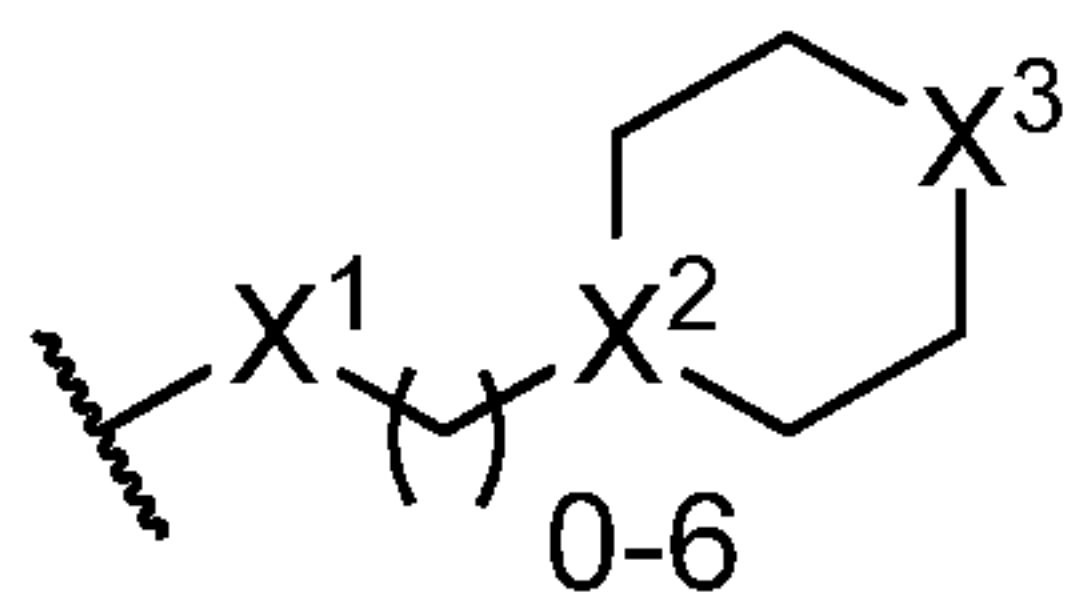
R³ is selected from the group consisting of C₁-C₉ alkyl, C₂-C₉ alkenyl, and C₂-C₉ alkynyl;

each R⁴ is independently selected from the group consisting of:

hydrogen, halogen, OH, C₁-C₆ alkyl, C₁-C₄ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ alkyl-R^B, C₁-C₆ haloalkyl-R^B, C₁-C₆ alkoxy-R^B, C₁-C₆ haloalkoxy-R^B, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkoxy, C₃-C₈ cycloalkyl-C₁-C₉ alkyl, C₁-C₆ hydroxyalkyl, O- C₁-C₆ hydroxyalkyl, O- C₁-C₆ alkyl-R^B, CN, O-(C₁-C₅ alkyl)-O-(C₁-C₃ alkyl), O-(C₁-C₅ alkyl)-O-(C₁-C₃ alkyl)-R^B, -(C₀-C₃ alkyl)-O-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl),

25

-(C₀-C₃ alkyl)-S-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₃ alkyl)-S(O)₂-(C₀-C₃ alkyl)-(C₃-C₈ cycloalkyl), Het, Aryl, and



, wherein X¹ is either CH₂, NH, O, or S; X² is either CH or N; and X³ is either NH, N-R⁵, CH₂, CH-R⁵, O, or S;

5 provided that two R⁴ groups can join together form methylene dioxy;

each R^A is independently selected from the group consisting of: F, Cl,

Br, I, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkyl(NH₂), C₆-C₈ bridged

cycloalkyl, C₃-C₈ cycloalkyl, C₁-C₆ haloalkoxy, C₃-C₈ halocycloalkyl, SH, S(C₁-C₆ alkyl), NH₂,

NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, C(O)(C₁-C₆ alkyl), C(O)(C₃-C₈ cycloalkyl), CONH₂, SO₂NH₂,

10 NO₂, CN, CF₃, CHF₂, CH₂F, OCHF₂, OCF₃, OCH₂F, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), -(C₁-

C₆ alkyl)S(O)(C₁-C₆ alkyl), SO₂(C₃-C₆ cycloalkyl), -(C₁-C₆ alkyl)S(O)₂(C₁-C₆ alkyl), -(C₁-C₆

alkyl)N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl), N(C₁-C₆ alkyl)SO₂(C₁-C₆ alkyl),

SO₂N(C₁-C₆ alkyl)₂, -(C₁-C₆ alkyl)SO₂N(C₁-C₆ alkyl)₂, NHCOO(C₁-C₆ alkyl),

NHCO(C₁-C₆ alkyl), NHCONH(C₁-C₆ alkyl), CO₂(C₁-C₆ alkyl), C(O)N(C₁-C₆ alkyl)₂,

15 -(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), -(C₀-C₅ alkyl)-O-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl),

-(C₀-C₅ alkyl)-S-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl),

-(C₀-C₅ alkyl)-S(O)₂-(C₀-C₅ alkyl)-(C₃-C₈ cycloalkyl), Aryl, and

Het; provided that two R^A groups present on adjacent carbon atoms can together with the adjacent carbon atoms form a C₃-C₆ cycloalkyl;

20 each R^B is independently either phenyl or a 5- or 6-membered saturated or unsaturated monocyclic ring with 1, or 2 heteroatom ring atoms independently selected from the group consisting of N, O and S, R^B may be substituted with 1 or 2 independently selected R^C;

each R^C is independently either halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl or, C₁-C₆ haloalkyl;

25 each Aryl is independently phenyl optionally substituted with 1 or 2 independently selected R^C;

each Het is independently a 4-, 5- or 6-membered saturated or unsaturated monocyclic rings with 1 or 2 heteroatom ring atoms independently selected from the group consisting of N, O and S; provided that said Het is optionally substituted with 1 or 2

30 independently selected R^C substituents;

R^X if present, is a C₃-C₈ alkylene, C₃-C₈ alkenylene, or C₃-C₈ alkynylene, formed between A and R¹,

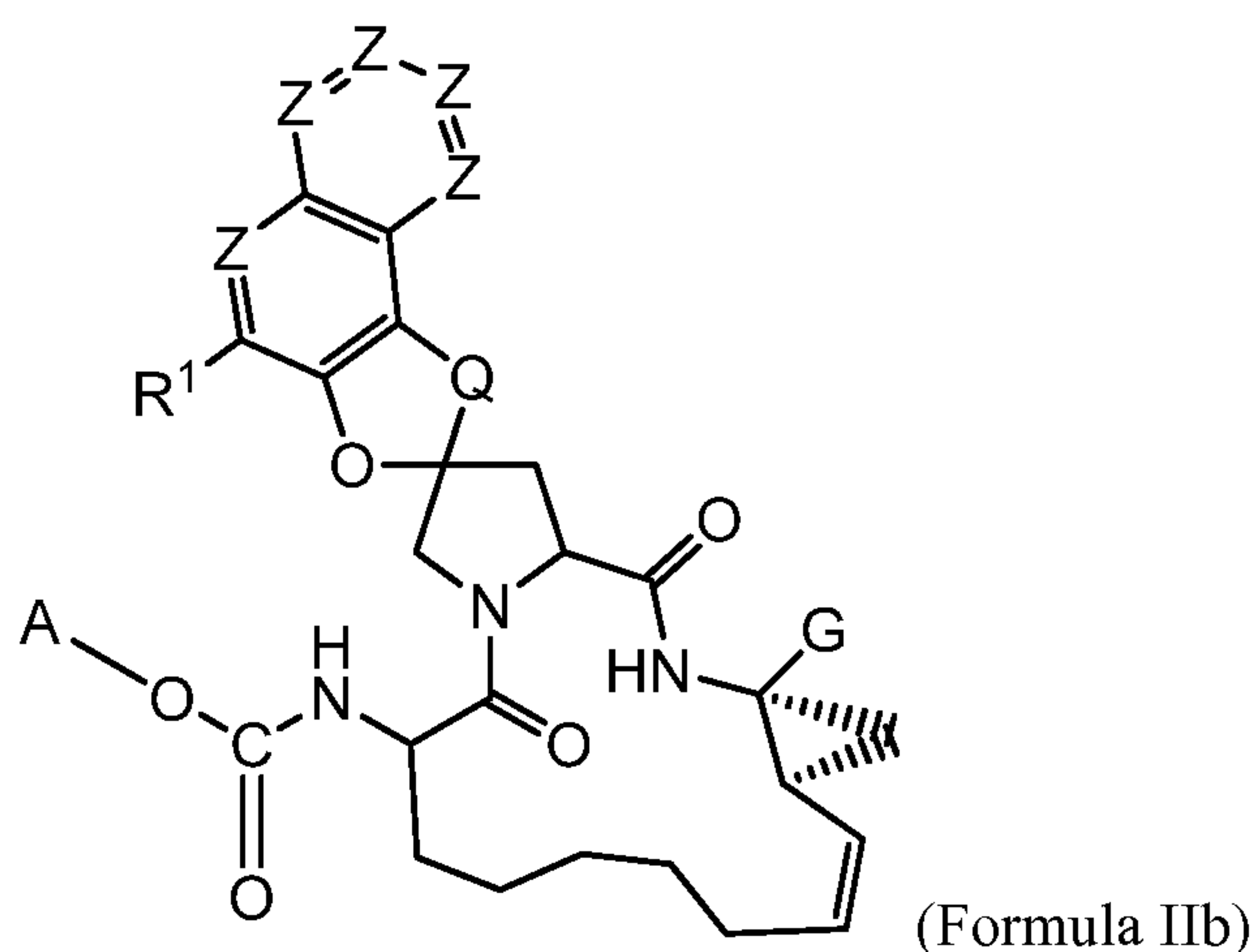
R^Y if present, is a C₃-C₈ alkylene, C₃-C₈ alkenylene, C₃-C₈ alkynylene, formed between A and R²,

5 R^Z if present, is a C₃-C₈ alkylene, C₃-C₈ alkenylene, or C₃-C₈ alkynylene, formed between R² and R³,

provided that either (a) R^X is present, R^Y is not present and R^Z is not present; (b) R^Y is present, R^X is not present and R^Z is not present; (c) R^Z is present, R^X is not present and R^Y is not present; or (d) R^X and R^Z are present, and R^Y is not present.

10 34. The compound of claim 33, wherein T is O.

35. The compound of claim 34, wherein said compound of Formula IIa is a compound of Formula IIb:



15 or a pharmaceutically acceptable salt thereof, wherein

each Z is independently either N or C-R⁴;

A is selected from the group consisting of

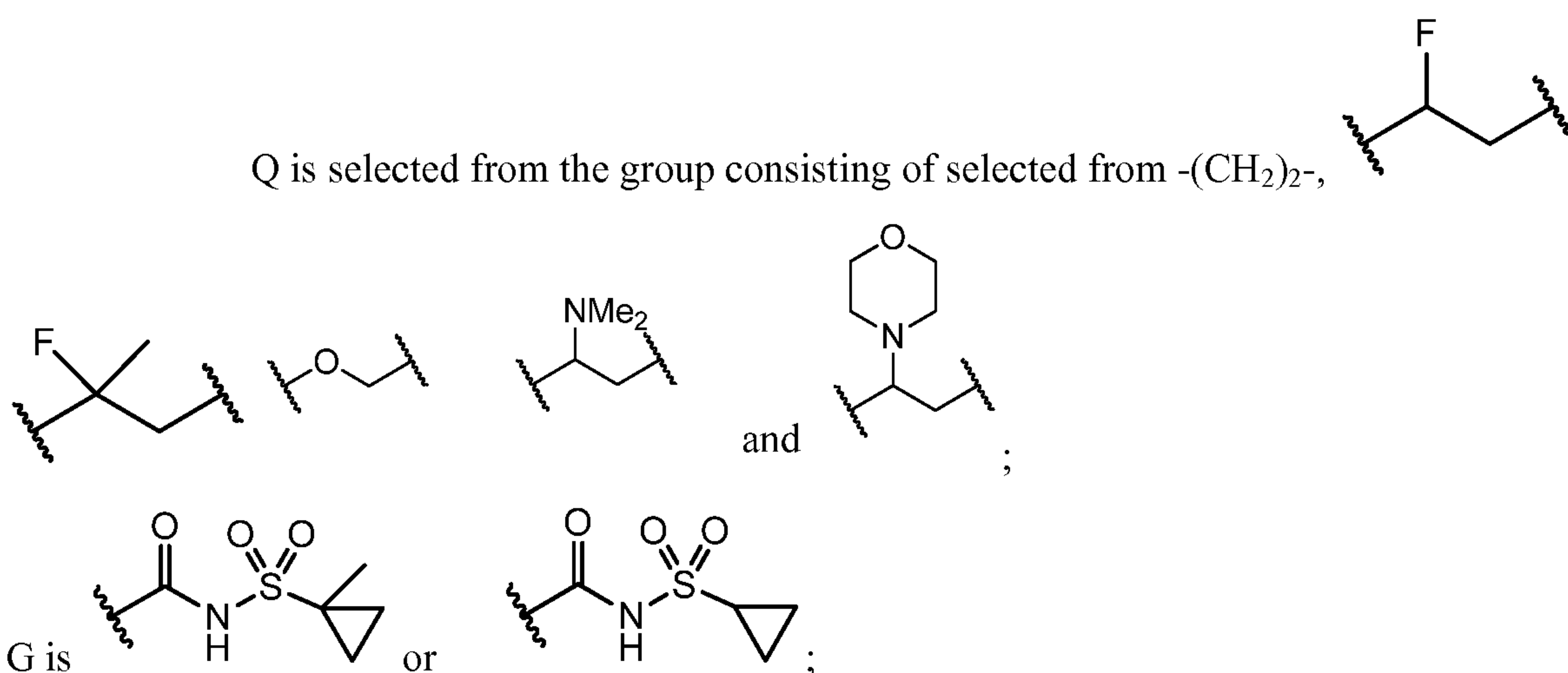
a) C₁-C₆ alkyl, C₃-C₈ cycloalkyl, or C₆-C₈ bridged cycloalkyl,

b) substituted C₁-C₆ alkyl, substituted C₃-C₈ cycloalkyl, or substituted C₆-

20 C₈ bridged cycloalkyl, each of which contains 0 or 1 R^A and 0 or 1 R^B, provided that at least one R^A or R^B substituent is present;

c) Aryl; and

d) Het;



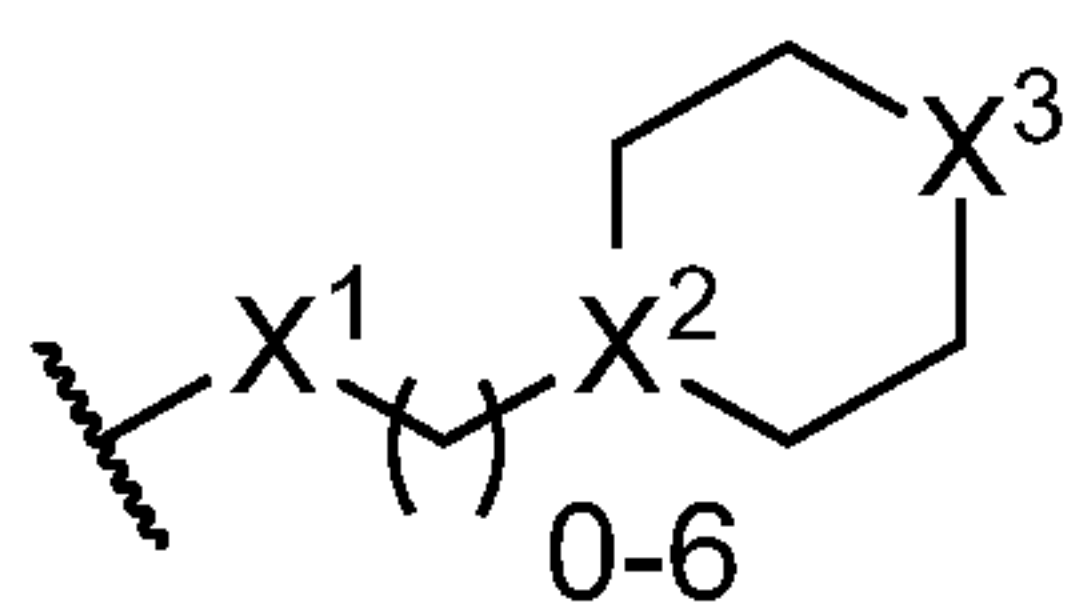
R^1 is either hydrogen, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_1 - C_4 haloalkyl, CF_3 ,

5 CH_2CF_3 , CF_2 , CH_3 , cyclopropyl, Aryl, or Het;

each R^4 is independently selected from the group consisting of:

hydrogen, F, Cl, OH, C_1 - C_6 alkyl, C_1 - C_2 haloalkyl, CF_3 , $\text{CH}_2\text{-CF}_3$, $\text{CF}_2\text{-CH}_3$,

CF_3 , C_1 - C_6 alkoxy, C_1 - C_4 haloalkoxy, C_1 - C_6 alkyl- R^B , C_3 - C_8 cycloalkyl, Het, Aryl and



, wherein X^1 is either CH_2 , NH, O, or S; X^2 is either CH or N; and X^3 is

10 either NH, N-R^5 , CH_2 , CH-R^5 , O, or S;

each Aryl is independently phenyl optionally substituted with 1 or 2

independently selected R^C ;

each Het is independently a 4-, 5- or 6-membered saturated or unsaturated

monocyclic ring with 1 or 2 heteroatom ring atoms independently selected from the group

15 consisting of N, O and S; provided that said Het is optionally substituted with 1 or 2

independently selected R^C ;

each R^A is independently selected from the group consisting of: F, Cl,

OH, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_3 - C_8 halocycloalkyl, and

C_1 - C_6 haloalkoxy;

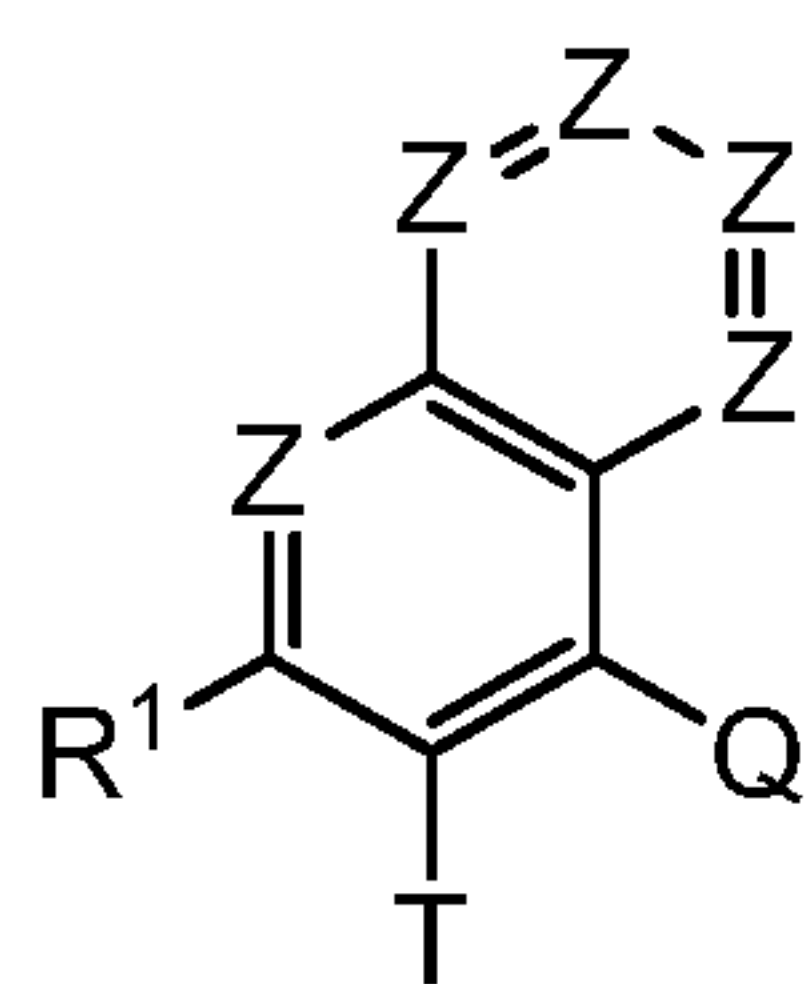
20 each R^B is independently either phenyl or 5- or 6-membered saturated or a

unsaturated monocyclic ring with 1, or 2 heteroatom ring atoms independently selected from the

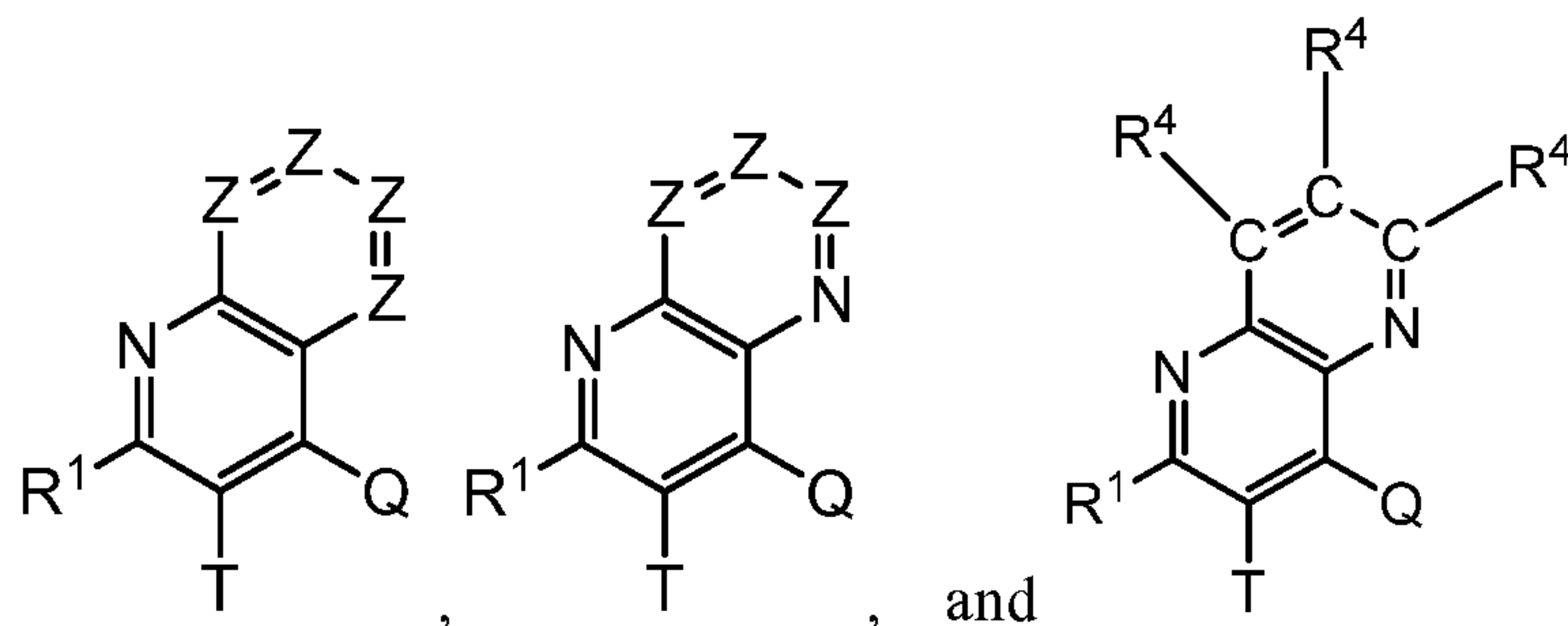
group consisting of N, O and S, R^B may be substituted with 1 or 2 independently selected R^C ; and

each R^C is independently either halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl or C₁-C₆ haloalkyl.

36. The compound of anyone of claims 33, 34, or 35 wherein



is selected from the group consisting of:

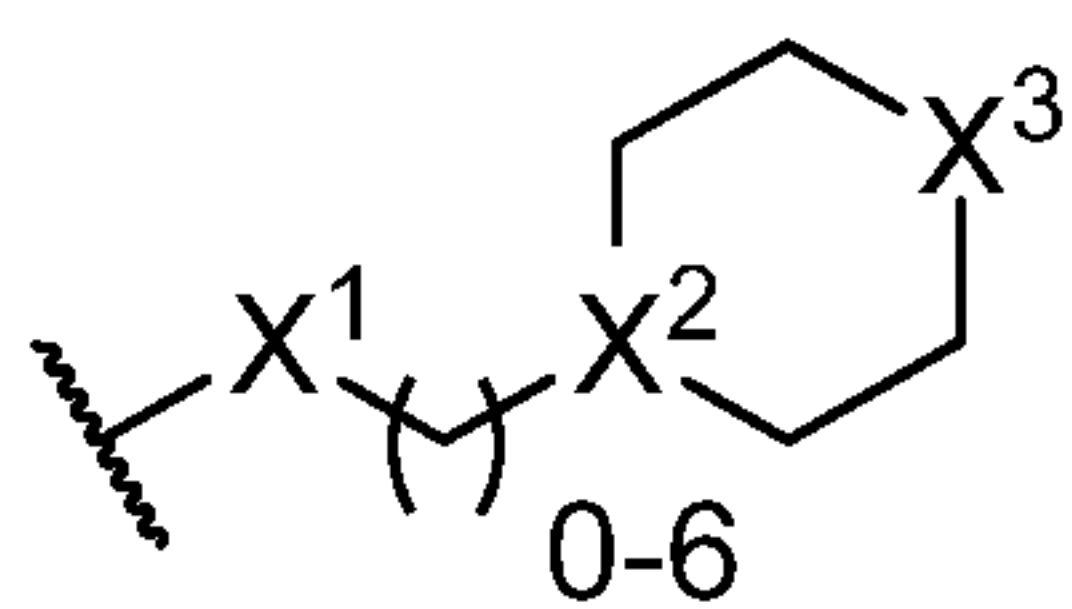


5

wherein each Z is independently either N or C-R⁴,

each R⁴ is independently selected from the group consisting of:

hydrogen, F, Cl, OH, C₁-C₆ alkyl, C₁-C₂ haloalkyl, CF₃, CH₂-CF₃, CF₂-CH₃, CF₃, C₁-C₆ alkoxy, C₁-C₄ haloalkoxy, C₁-C₆ alkyl-R^B, C₃-C₈ cycloalkyl Het, Aryl, and



10

, wherein X¹ is either CH₂, NH, O, or S; X² is either CH or N; and X³ is either NH, N-R⁵, CH₂, CH-R⁵, O, or S;

each Aryl is independently phenyl optionally substituted with 1 or 2 independently selected R^C;

each Het is independently a 4-, 5- or 6-membered saturated or unsaturated monocyclic ring with 1 or 2 heteroatom ring atoms independently selected from the group consisting of N, O and S; provided that said Het is optionally substituted with 1 or 2 independently selected R^C;

each R^A is independently selected from the group consisting of F, Cl, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₃-C₈ halocycloalkyl, and C₁-C₆ haloalkoxy;

20

each R^B is independently either phenyl or a 5- or 6-membered saturated or unsaturated monocyclic ring with 1, or 2 heteroatom ring atoms independently selected from the group consisting of N, O and S, wherein R^B may be substituted with 1 or 2 independently selected R^C; and

5 each R^C is independently either halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl or C₁-C₆ haloalkyl.

37. A pharmaceutical composition comprising an effective amount of the compound of anyone of claims 1-36 and a pharmaceutically acceptable carrier.

10 38. The pharmaceutical composition according to claim 37, further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

15 39. The pharmaceutical composition according to claim 38, further comprising a second therapeutic agent selected from the group consisting of HCV protease inhibitors, inhibitors of HCV NS4A, inhibitors of HCV NS4B, inhibitors of HCV NS5A and inhibitors of HCV NS5B.

40. Use of the compound according to any one of claims 1-36, in the preparation of a medicament for inhibiting HCV NS3 protease activity or treating HCV infection in a subject in need thereof.

20 41. Use the compound according to any one of claims 1-36 for inhibiting HCV NS3 protease activity or treating HCV infection in a subject in need thereof.

42. A method treating HCV in patient comprising the step of administering to said patient a therapeutically effective amount of the compound of any one of claims 1-36.