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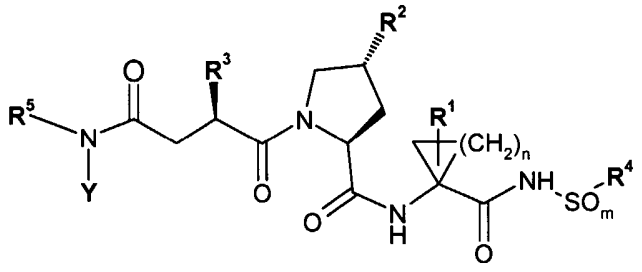
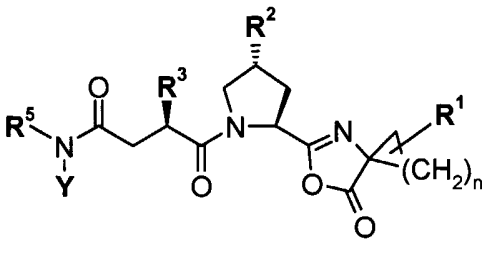
(54) Title: HEPATITIS C INHIBITOR PEPTIDE ANALOGS



(I)



(III)

(57) Abstract: The invention relates to compounds of formula (I) wherein R^1, R^2, R^3, R^4, R^5, Y, n and m are as defined herein. The compounds are useful for the treatment and prevention of hepatitis C viral infection in mammals by inhibiting HCV NS3 protease. The invention further relates to azalactone compounds of the formula (III) which can be reacted with an amide anion to produce the compounds of formula (I).

WO 2006/007708 A1

HEPATITIS C INHIBITOR PEPTIDE ANALOGS

FIELD OF THE INVENTION

The present invention relates to compounds, processes for their synthesis, compositions and methods for the treatment of hepatitis C virus (HCV) infection. In particular, the present invention provides novel peptide analogs, pharmaceutical compositions containing such analogs and methods for using these analogs in the treatment of HCV infection.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) is the major etiological agent of post-transfusion and community-acquired non-A non-B hepatitis worldwide. It is estimated that over 200 million people worldwide are infected by the virus. A high percentage of carriers become chronically infected and many progress to chronic liver disease, so-called chronic hepatitis C. This group is in turn at high risk for serious liver disease such as liver cirrhosis, hepatocellular carcinoma and terminal liver disease leading to death.

The mechanism by which HCV establishes viral persistence and causes a high rate of chronic liver disease has not been thoroughly elucidated. It is not known how HCV interacts with and evades the host immune system. In addition, the roles of cellular and humoral immune responses in protection against HCV infection and disease have yet to be established. Immunoglobulins have been reported for prophylaxis of transfusion-associated viral hepatitis, however, the Center for Disease Control does not presently recommend immunoglobulin treatment for this purpose. The lack of an effective protective immune response is hampering the development of a vaccine or adequate post-exposure prophylaxis measures, so in the near-term, hopes are firmly pinned on antiviral interventions.

Various clinical studies have been conducted with the goal of identifying pharmaceutical agents capable of effectively treating HCV infection in patients afflicted with chronic hepatitis C. These studies have involved the use of interferon-alpha, alone and in combination with other antiviral agents. Such studies have shown that a substantial number of the participants do not respond to these therapies, and of those that do respond favorably, a large proportion were found to

relapse after termination of treatment.

Interferon in combination with ribavirin has been approved for the treatment of patients with chronic hepatitis C. However, side effects caused by IFN (such as retinopathy, thyroiditis, acute pancreatitis, depression) are not alleviated with this combination therapy. Pegylated forms of interferons such as PEG-Intron® and Pegasys® can apparently partially address these deleterious side effects but antiviral drugs still remain the avenue of choice for oral treatment of HCV.

Therefore, a need exists for the development of effective antiviral agents for treatment of HCV infection that overcome the limitations of existing pharmaceutical therapies.

HCV is an enveloped positive strand RNA virus in the Flaviviridae family. The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non-structural (NS) proteins. In the case of HCV, the generation of mature nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) is effected by two viral proteases. The first (generally referred to as the NS2/3 protease) cleaves at the NS2-NS3 junction; the second (the NS3 protease) is a serine protease contained within the N-terminal region of NS3 and mediates all the subsequent cleavages downstream of NS3, both in *cis*, at the NS3-NS4A cleavage site, and in *trans*, for the remaining NS4A-NS4B, NS4B-NS5A and NS5A-NS5B sites. The NS4A protein appears to serve multiple functions, acting as a cofactor for the NS3 protease and possibly assisting in the membrane localization of NS3 and other viral replicase components. The complex formation of the NS3 protease with NS4A seems necessary to the processing events, enhancing the proteolytic efficiency at all of the sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B is a RNA-dependent RNA polymerase that is involved in the replication of HCV.

A general strategy for the development of antiviral agents is to inactivate virally encoded enzymes that are essential for the replication of the virus. In a two day clinical trial, it has been shown that the HCV NS3 protease inhibitor BILN 2061 is

effective in rapidly reducing viral loads in patients infected with the hepatitis C virus (*Gastroenterology* (2004) 127(5): 1347-1355), thus providing proof of principle of the clinical antiviral activity of HCV NS3 protease inhibitors.

The NS3 protease has been found to potentially have an additional impact by blocking the IFN-mediated cellular antiviral activity in the infected cell (Foy *et al.*, *Science*, 17 April 2003). This lends credence to a hypothesis that the NS3/NS4A protease may represent a dual therapeutic target, the inhibition of which may both block viral replication and restore interferon response of HCV infected cells.

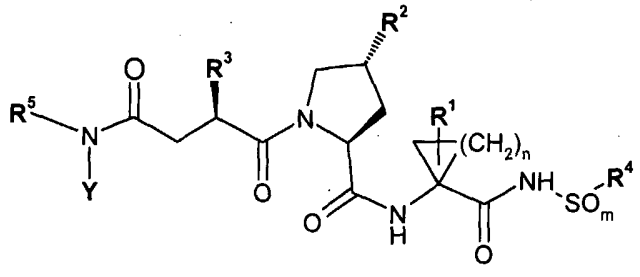
Inhibitors of the HCV NS3 protease have been described in WO 00/09543 (Boehringer Ingelheim), WO 03/064456 (Boehringer Ingelheim), WO 03/064416 (Boehringer Ingelheim), WO 02/060926 (Bristol-Myers Squibb), WO 03/053349 (Bristol-Myers Squibb), WO 03/099316 (Bristol-Myers Squibb), WO 03/099274 (Bristol-Myers Squibb), WO 2004/032827 (Bristol-Myers Squibb), and WO 2004/043339 (Bristol-Myers Squibb).

SUMMARY OF THE INVENTION

The present invention now provides novel compounds that are inhibitory to the NS3 protease. Furthermore, compounds being active in cell culture are provided.

An advantage of one aspect of the present invention resides in the fact that compounds according to this invention specifically inhibit the NS3 protease and do not show significant inhibitory activity against other serine proteases such as human leukocyte elastase (HLE), or cysteine proteases such as human liver cathepsin B (Cat B).

Included in the scope of the invention is a compound of formula (I):



(I)

wherein

n is 1 or 2;

m is 1 or 2;

R^1 is H, (C_{1-6})alkyl, (C_{2-6})alkenyl, or (C_{2-6})alkynyl; wherein each of said (C_{1-6})alkyl, (C_{2-6})alkenyl, and (C_{2-6})alkynyl are optionally substituted with from one to three halogen substituents;

R^2 is selected from -NH-R^{20}, -O-R^{20}, -S-R^{20}, -SO-R^{20}, -SO_2-R^{20}, -OCH_2-R^{20}, and -CH_2O-R^{20}, wherein

R^{20} is aryl or **Het**, wherein said aryl and **Het** are each optionally substituted with R^{200}, wherein

R^{200} is one to four substituents each independently selected from H, halogen, cyano, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl-(C_{1-6})alkyl-, aryl, **Het**, oxo, thioxo, -OR^{201}, -SR^{201}, -SOR^{201}, -SO_2R^{201}, -$N(R^{202})R^{201}$, and -$CON(R^{202})R^{201}$; wherein each of said alkyl, cycloalkyl, aryl and **Het** is optionally further substituted with R^{2000};

R^{201} in each case is independently selected from H, (C_{1-6})alkyl, aryl, (C_{2-4})alkenyl, (C_{2-4})alkynyl, -CO-(C_{1-6})alkyl and -CO-O-(C_{1-6})alkyl, wherein each of said alkyl and aryl is optionally further substituted with R^{2000};

R^{202} is H or (C_{1-6})alkyl;

R^{2000} is one to three substituents each independently selected from halogen, R^{2003}, aryl, **Het**, -OR^{2001}, -SR^{2001}, -SOR^{2001}, -SO_2R^{2001}, cyano and -$N(R^{2002})(R^{2001})$, wherein each of said aryl and **Het** are optionally substituted with one, two or three substituents each independently selected from (C_{1-6})alkyl and -O-(C_{1-6})alkyl;

R^{2001} in each case is independently selected from aryl, aryl-(C_{1-6})alkyl-, -C(O)-R^{2003}, –C(O)O-R^{2003}, -$CON(R^{2002})(R^{2004})$ and R^{2004};

R^{2002} in each case is independently selected from H and (C_{1-6})alkyl;

R^{2003} in each case is independently selected from (C_{1-8})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein each of said (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-(C_{1-4})alkyl- are optionally substituted with one to three (C_{1-3})alkyl substituents; and

R^{2004} in each case is independently selected from H or R^{2003};

R^3 is (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-3})alkyl-, wherein each said

cycloalkyl group is optionally substituted with one to three substituents each independently selected from halogen, -OH, (C_{1-4})alkyl, O-(C_{1-4})alkyl, S-(C_{1-4})alkyl, $-NH_2$, -NH(C_{1-4})alkyl, -N$((C_{1-4})alkyl)_2$, -COOH and $-CONH_2$;

R^4 is (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl, **Het**, aryl-(C_{1-4})alkyl-, or **Het**-(C_{1-4})alkyl-;

a) each of said (C_{1-6})alkyl, (C_{2-6})alkenyl, aryl, **Het**, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl-(C_{1-4})alkyl- and **Het**-(C_{1-4})alkyl- optionally being substituted with nitro and optionally being substituted with one to three substituents each independently selected from halogen, hydroxy, cyano, (C_{1-6})alkyl, O-(C_{1-6})alkyl, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$, $-NH_2$, -NH(C_{1-4})alkyl and -N$((C_{1-4})alkyl)_2$, wherein said (C_{1-6})alkyl and O-(C_{1-6})alkyl are optionally substituted with one to three halogen substituents; and

b) said (C_{3-7})cycloalkyl being optionally substituted with one or more substituents each independently selected from nitro, halogen, hydroxy, cyano, -O-(C_{1-6})alkyl, (C_{2-6})alkenyl, $-OCF_3$, $-NH_2$, -NH(C_{1-4})alkyl, -N$((C_{1-4})alkyl)_2$, tri(C_{1-6})alkylsilyl, R^{41}, -C(=O)-R^{41}, -C(=O)OR^{41}, -C(=O)N(R^{42})R^{41}, $-SO_2R^{41}$, and -OC(=O)-R^{41};

wherein R^{41} in each case is independently selected from:

i) H, (C_{3-7})cycloalkyl, (C_{4-7})cycloalkenyl, **Het**, or aryl-(C_{1-4})alkyl-O-;

ii) aryl or aryloxy, each of which being optionally substituted with (C_{1-6})alkyl; and

iii) (C_{1-8})alkyl optionally substituted with one or more substituents each independently selected from -O-(C_{1-6})alkyl, hydroxy, halogen, (C_{2-10})alkenyl, (C_{2-10})alkynyl, (C_{3-7})cycloalkyl, (C_{4-7})cycloalkenyl, aryl, **Het**, aryloxy, and aryl-(C_{1-4})alkyl-O-, wherein each of said aryl and aryloxy is optionally substituted with (C_{1-6})alkyl; and

R^{42} is selected from H and (C_{1-6})alkyl; or

R^4 is $-N(R^{N2})(R^{N1})$, wherein R^{N1} and R^{N2} are each independently selected from H, (C_{1-6})alkyl, -O-(C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl and aryl-(C_{1-6})alkyl-; wherein said (C_{1-6})alkyl, -O-(C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl and aryl-(C_{1-6})alkyl- are each optionally substituted with one or more substituents each

independently selected from halogen, (C_{1-6})alkyl, hydroxy, cyano, O-(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-4})alkyl, -N$((C_{1-4})alkyl)_2$, $-CO-NH_2$, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$, -COOH, and $-COO(C_{1-6})$alkyl; or

R^{N2} and R^{N1} are linked, together with the nitrogen to which they are bonded, to form a 3- to 7-membered monocyclic saturated or unsaturated heterocycle optionally fused to at least one other cycle to form a heteropolycycle, said heterocycle and heteropolycycle each optionally containing from one to three additional heteroatoms each independently selected from N, S and O, and being optionally substituted with one or more substituents each independently selected from halogen, (C_{1-6})alkyl, hydroxy, cyano, O-(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-4})alkyl, -N$((C_{1-4})alkyl)_2$, $-CO-NH_2$, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$, -COOH, and $-COO(C_{1-6})$alkyl;

R^5 is (C_{2-10})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, phenyl, phenyl-(C_{1-3})alkyl-, **Het** or **Het**-(C_{1-3})alkyl-; wherein each of said (C_{2-10})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, phenyl, phenyl-(C_{1-3})alkyl-, **Het** and **Het**-(C_{1-3})alkyl- is optionally substituted with one to three substituents each independently selected from halogen, -OH, (C_{1-4})alkyl, -O-(C_{1-4})alkyl, -S-(C_{1-4})alkyl, $-NH_2$, -NH(C_{1-4})alkyl, -N$((C_{1-4})alkyl)_2$, -NHC(=O)(C_{1-4})alkyl, -NHC(=O)O(C_{1-4})alkyl, -NH(C=O)NH(C_{1-4})alkyl, -NH(C=O)N$((C_{1-4})alkyl)_2$, $-CONH_2$, -CONH-(C_{1-4})alkyl, -CON$((C_{1-4})alkyl)_2$, -COOH, -COO(C_{1-6})alkyl, -CO-(C_{1-6})alkyl, $-SO_2(C_{1-4})$alkyl and $-SO_2NH(C_{1-4})$alkyl; and

Y is H or (C_{1-6})alkyl;

with the proviso that when

m is 2,

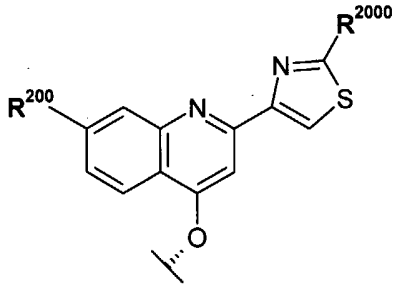
n is 1, and

R^4 is selected from (C_{1-6})alkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, phenyl, naphthyl, pyridinyl, phenyl-(C_{1-4})alkyl-, naphthyl-(C_{1-4})alkyl- and pyridinyl-(C_{1-4})alkyl-; each of which being optionally substituted with nitro and each of which being optionally substituted with one to three substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, $-CO-NH_2$, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$, $-NH_2$, -NH(C_{1-4})alkyl and -N$((C_{1-4})alkyl)_2$; wherein said (C_{1-4})alkyl and O-(C_{1-6})alkyl are each optionally

substituted with one to three halogen substituents;

or R^4 is (C_{3-7})cycloalkyl, said (C_{3-7})cycloalkyl being optionally substituted with nitro and optionally substituted with one or more substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, $-OCF_3$, $-CO-NH_2$, $-CO-NH(C_{1-4})$alkyl, $-CO-N((C_{1-4})alkyl)_2$, $-NH_2$, $-NH(C_{1-4})$alkyl and $-N((C_{1-4})alkyl)_2$, wherein said (C_{1-4})alkyl is optionally substituted with one or more halogen substituents;

then R^2 cannot be



;

wherein

R^{200} is -O-(C_{1-4})alkyl, -NH(C_{1-4})alkyl, or -N$((C_{1-4})alkyl)_2$; and

R^{2000} is R^{2003} or -N(R^{2002})(R^{2001}); wherein

R^{2001} is selected from -C(O)-R^{2003}, –C(O)O-R^{2003}, -CON(R^{2002})(R^{2004}) and R^{2004};

R^{2002} in each case is independently selected from H and methyl;

R^{2003} is (C_{1-8})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein said (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-(C_{1-4})alkyl- are optionally substituted with one to three (C_{1-3})alkyl substituents; and

R^{2004} is H or R^{2003};

wherein **Het** as used herein is defined as a 3- to 7-membered heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, which may be saturated, unsaturated or aromatic, and which is optionally fused to at least one other cycle to form a 4- to 14-membered heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S, said heteropolycycle being saturated, unsaturated or aromatic;

or a salt thereof.

One aspect of the invention provides a pharmaceutical composition comprising an anti-hepatitis C virally effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier

medium or auxiliary agent.

According to an embodiment of this aspect, the pharmaceutical composition according to this invention additionally comprises a therapeutically effective amount of at least one other antiviral agent.

Another important aspect of the invention involves a method of treating a hepatitis C viral infection in a mammal by administering to the mammal an anti-hepatitis C virally effective amount of a compound of formula (I), a pharmaceutically acceptable salt thereof, or a composition as described above, alone or in combination with at least one other antiviral agent, administered together or separately.

Also within the scope of this invention is the use of a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for the treatment of hepatitis C viral infection in a mammal.

Further encompassed within the scope of this invention is the use of a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of hepatitis C viral infection in a mammal.

A further aspect of the invention provides the use of a compound of formula (I), as described herein, or a pharmaceutically acceptable salt or ester thereof, in combination with at least one other antiviral agent, for the manufacture of a medicament for the treatment of hepatitis C viral infection.

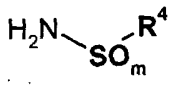
Still another aspect of this invention relates to a method of inhibiting the replication of hepatitis C virus by exposing the virus to a hepatitis C viral NS3 protease inhibiting amount of the compound of formula (I) according to this invention, or a pharmaceutically acceptable salt thereof.

Further included in the scope of the invention is the use of a compound of formula (I) according to this invention, or a pharmaceutically acceptable salt thereof, to inhibit the replication of hepatitis C virus.

An additional aspect of this invention refers to an article of manufacture comprising a composition effective to treat an HCV infection or to inhibit the NS3 protease of HCV; and packaging material comprising a label which indicates that the composition can be used to treat infection by the hepatitis C virus; wherein the composition comprises a compound of formula (I) according to this invention or a pharmaceutically acceptable salt thereof.

In a further aspect of this invention is provided a process for the preparation of a compound of formula (I) comprising the steps of:

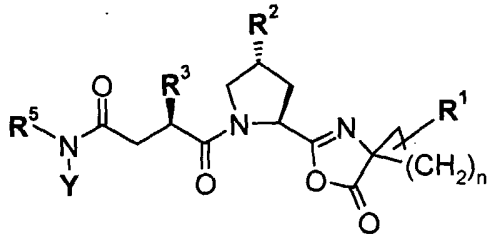
a) reacting a compound of formula (II):



(II)

wherein R^4 and **m** are as defined herein, with a strong base so as to form the corresponding amide anion and

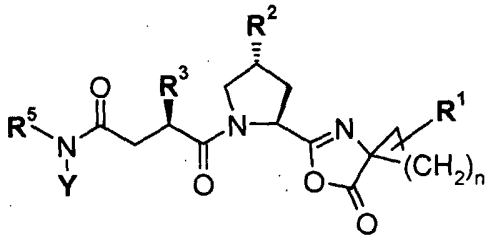
b) reacting an azalactone of formula (III):



(III)

wherein R^1, R^2, R^3, R^5, **Y**, and **n** are as defined herein, with the amide anion of step a).

In yet a further aspect of the present invention is provided an azalactone intermediate compound of formula (III):



(III)

wherein R^1, R^2, R^3, R^5, **Y**, and **n** are as defined herein.

A further aspect of this invention is the use of the intermediate azalactone of formula (III) as described hereinbefore in the preparation of an HCV NS3 protease inhibitor peptide analog.

Still another aspect of this invention is the use of the intermediate azalactone of formula (III) as described hereinbefore in the preparation of a compound of formula (I) as described herein.

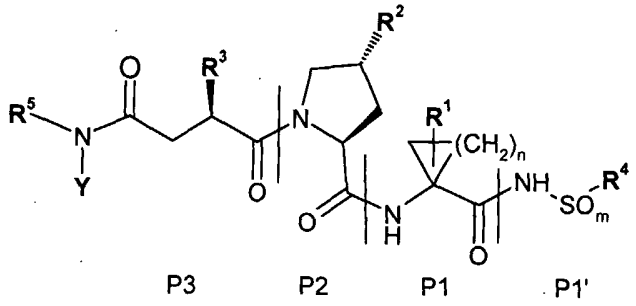
DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Definitions

As used herein, the following definitions apply unless otherwise noted:

With reference to the instances where *(R)* or *(S)* is used to designate the absolute configuration of a substituent or asymmetric center of a compound of formula I, the designation is done in the context of the whole compound and not in the context of the substituent or asymmetric center alone.

The designations "P3, P2, P1 and P1' " as used herein refer to the position of the amino acid residues starting from the N-terminus of the peptide analogs and extending towards and beyond the cleavage site, i.e. the bond in a substrate of the protease enzyme which is normally cleaved by the catalytic action of the protease enzyme. Thus, P3 refers to position 3 from the C-terminal side of the cleavage site, P2, position 2 from the C-terminal side of the cleavage site, etc.. The bond between the P1 and P1' residues corresponds to the cleavage site. Thus, the P1' position corresponds to the first position on the N-terminal side of the cleavage site (see Berger A. & Schechter I., Transactions of the Royal Society London series B257, 249-264 (1970)). In the context of the compounds of formula (I) herein described, these positions are as designated in the following formula:



The term "(C_{1-n})alkyl" as used herein, wherein n is an integer, either alone or in combination with another substituent, means acyclic, straight or branched chain alkyl substituents containing from 1 to n carbon atoms. "(C_{1-6})alkyl" includes, but is not limited to, methyl, ethyl, n-propyl, n-butyl, 1-methylethyl (*iso*-propyl), 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl (*tert*-butyl), pentyl and hexyl. The abbreviation Me denotes a methyl group and Et denotes an ethyl group.

The term "(C_{2-n})alkenyl", as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an unsaturated, acyclic straight or branched chain radical containing two to n carbon atoms, at least two of which are bonded to each other by a double bond. Examples of such radicals include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl, and 1-butenyl. Unless specified otherwise, the term "(C_{2-n})alkenyl" is understood to encompass individual stereoisomers where possible, including but not limited to (*E*) and (*Z*) isomers, and mixtures thereof. When a (C_{2-n}) alkenyl group is substituted, it is understood to be substituted on any carbon atom thereof which would otherwise bear a hydrogen atom, unless specified otherwise.

The term "(C_{2-n})alkynyl", as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an unsaturated, acyclic straight or branched chain radical containing two to n carbon atoms, at least two of which are bonded to each other by a triple bond. Examples of such radicals include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, and 1-butynyl. When a (C_{2-n})alkynyl group is substituted, it is understood to be substituted on any carbon atom thereof which would otherwise bear a hydrogen atom, unless specified otherwise.

The term "(C_{3-m})cycloalkyl" as used herein, wherein m is an integer, either alone or in

combination with another substituent, means a cycloalkyl substituent containing from 3 to m carbon atoms and includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "(C_{3-m})cycloalkyl-(C_{1-n})alkyl-" as used herein, wherein n and m are both integers, means an alkyl radical containing from 1 to n carbon atoms to which a cycloalkyl moiety containing from 3 to m carbon atoms is directly linked; including, but not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 1-cyclopentylethyl, 2-cyclopentylethyl, cyclohexylmethyl, 1-cyclohexylethyl and 2-cyclohexylethyl. Unless specified otherwise, a (C_{3-m})cycloalkyl-(C_{1-n})alkyl- group may be substituted on either the cycloalkyl or the alkyl portion thereof, or both.

The term "aryl" as used herein, either alone or in combination with another radical, means a carbocyclic aromatic monocyclic group containing 6 carbon atoms which may be further fused to a second 5- or 6-membered carbocyclic group which may be aromatic, saturated or unsaturated. Aryl includes, but is not limited to, phenyl, indanyl, 1-naphthyl and 2-naphthyl.

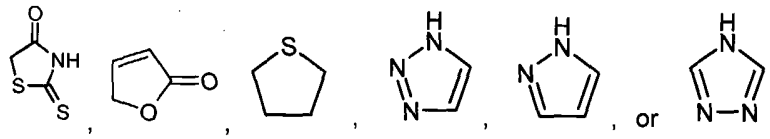
As used herein, the term "aryl-(C_{1-n})alkyl-" means an alkyl radical containing from 1 to n carbon atoms, wherein n is an integer, to which an aryl moiety is bonded. Examples of aryl-(C_{1-3})alkyl- include, but are not limited to, benzyl (phenylmethyl), 1-phenylethyl, 2-phenylethyl and phenylpropyl. Unless specified otherwise, an aryl-(C_{1-n})alkyl- group may be substituted on either the aryl or the alkyl portion thereof, or both.

As used herein, the term "**Het**" defines a 3- to 7-membered heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, which may be saturated, unsaturated or aromatic, and which is optionally fused to at least one other cycle to form a 4- to 14-membered heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S, said heteropolycycle being saturated, unsaturated or aromatic, unless specified otherwise.

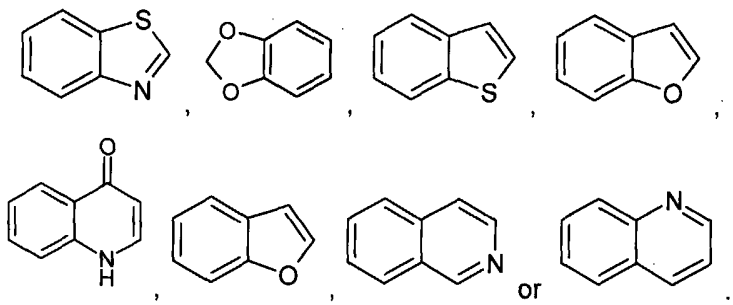
As used herein the term "heteroatom" means O, S or N.

As used herein, the term "heterocycle", either alone or in combination with another

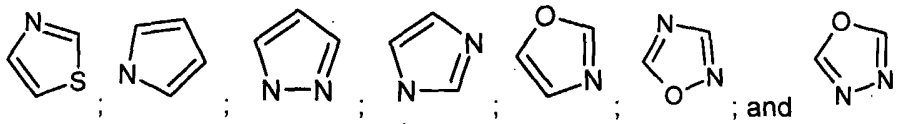
radical, means a monovalent radical derived by removal of a hydrogen from a three- to seven-membered saturated or unsaturated (including aromatic) heterocycle containing from one to four heteroatoms each independently selected from nitrogen, oxygen and sulfur. Examples of such heterocycles include, but are not limited to, azetidine, pyrrolidine, tetrahydrofuran, thiazolidine, pyrrole, thiophene, furan, hydantoin, diazepine, 1H-imidazole, isoxazole, thiazole, tetrazole, piperidine, piperazine, homopiperidine, homopiperazine, 1,4-dioxane, 4-morpholine, 4-thiomorpholine, pyridine, pyridine-N-oxide or pyrimidine, or the following heterocycles:



As used herein, the term "heteropolycycle" either alone or in combination with another radical, means a heterocycle as defined above fused to one or more other cycle, be it a heterocycle or any other cycle. Examples of such heteropolycycles include, but are not limited to, indole, benzimidazole, thiazolo[4,5-b]-pyridine, quinoline, isoquinoline, or coumarin, or the following:



Although generally covered under the term "**Het**", the term "heteroaryl" as used herein precisely defines an unsaturated heterocycle for which the double bonds form an aromatic system. Suitable examples of heteroaryl include but are not limited to, radicals derived by removal of a hydrogen atom from the following: pyridine, thiophene, furan,



As used herein, the term "**Het**-(C_{1-n})alkyl-" means an alkyl radical containing from 1 to n carbon atoms, wherein n is an integer, to which a **Het** moiety is bonded. Examples of **Het**-(C_{1-4})alkyl- include, but are not limited to, thienylmethyl, furylmethyl, piperidinylethyl, 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, quinolinylpropyl, and the like. Unless specified otherwise, a **Het**-(C_{1-n})alkyl- group may be substituted on either the **Het** or the alkyl portion thereof, or both.

As used herein, the term "heteroaryl-(C_{1-n})alkyl-" means an alkyl radical containing from 1 to n carbon atoms, wherein n is an integer, to which a heteroaryl moiety is bonded. Examples of heteroaryl-(C_{1-3})alkyl- include, but are not limited to, 2-thienylmethyl, 3-thienylmethyl, 2-pyridinylmethyl, 3-pyridinylmethyl and 4-pyridinylmethyl.

The term "O-(C_{1-n})alkyl" or "(C_{1-n})alkoxy" as used interchangeably herein, either alone or in combination with another radical, means an oxygen atom further bonded to an alkyl radical as defined above containing from 1 to n carbon atoms, and includes methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy and 1,1-dimethylethoxy. The latter radical is known commonly as *tert*-butoxy. When an O-(C_{1-n})alkyl radical is substituted, it is understood to be substituted on the (C_{1-n})alkyl portion thereof.

As used herein, the term "-S-(C_{1-n})alkyl" or "(C_{1-n})alkylthio", used interchangeably, refers to a sulfur atom further bonded to an alkyl radical as defined above containing from 1 to n carbon atoms. Examples of (C_{1-6})alkylthio include, but are not limited to, methylthio (CH_3S-), ethylthio (CH_3CH_2S-), propylthio ($CH_3CH_2CH_2S$-), 1-methylethylthio ($(CH_3)_2CHS$-), 1,1-dimethylethylthio ($(CH_3)_3CS$-), etc.. When an -S-(C_{1-n})alkyl radical is substituted, it is understood to be substituted on the (C_{1-n})alkyl portion thereof. Likewise, when an -SO-(C_{1-n})alkyl or an $-SO_2$-(C_{1-n})alkyl group is substituted, it is understood to be substituted on the (C_{1-n})alkyl portion thereof.

The term "halo" or "halogen" as used interchangeably herein means a halogen substituent selected from fluoro, chloro, bromo or iodo.

The term "oxo" as used herein means an oxygen atom attached as a substituent by a

double bond (=O).

The term "thioxo" as used herein means an sulfur atom attached as a substituent by a double bond (=S).

The term "salt thereof" means any acid and/or base addition salt of a compound according to the invention; preferably a pharmaceutically acceptable salt thereof.

The term "pharmaceutically acceptable salt" means a salt of a compound of formula (I) which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, generally water or oil-soluble or dispersible, and effective for their intended use. The term includes pharmaceutically-acceptable acid addition salts and pharmaceutically-acceptable base addition salts. Lists of suitable salts are found in, e.g., S.M. Birge et al., J. Pharm. Sci., 1977, 66, pp. 1-19.

The term "pharmaceutically-acceptable acid addition salt" means those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, phosphoric acid, and the like, and organic acids such as acetic acid, trifluoroacetic acid, adipic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, butyric acid, camphoric acid, camphorsulfonic acid, cinnamic acid, citric acid, digluconic acid, ethanesulfonic acid, glutamic acid, glycolic acid, glycerophosphoric acid, hemisulfic acid, hexanoic acid, formic acid, fumaric acid, 2-hydroxyethanesulfonic acid (isethionic acid), lactic acid, hydroxymaleic acid, malic acid, malonic acid, mandelic acid, mesitylenesulfonic acid, methanesulfonic acid, naphthalenesulfonic acid, nicotinic acid, 2-naphthalenesulfonic acid, oxalic acid, pamoic acid, pectinic acid, phenylacetic acid, 3-phenylpropionic acid, pivalic acid, propionic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, sulfanilic acid, tartaric acid, p-toluenesulfonic acid, undecanoic acid, and the like.

The term "pharmaceutically-acceptable base addition salt" means those salts which

retain the biological effectiveness and properties of the free acids and which are not biologically or otherwise undesirable, formed with inorganic bases such as ammonia or hydroxide, carbonate, or bicarbonate of ammonium or a metal cation such as sodium, potassium, lithium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Particularly preferred are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically-acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, quaternary amine compounds, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion-exchange resins, such as methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, isopropylamine, tripropylamine, tributylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, tetramethylammonium compounds, tetraethylammonium compounds, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, dibenzylamine, N,N-dibenzylphenethylamine, 1-ephenamine, N,N'-dibenzylethylenediamine, polyamine resins, and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

The term "mammal" as it is used herein is meant to encompass humans, as well as non-human mammals which are susceptible to infection by hepatitis C virus including domestic animals, such as cows, pigs, horses, dogs and cats, and non-domestic animals.

The term "antiviral agent" as used herein means an agent (compound or biological) that is effective to inhibit the formation and/or replication of a virus in a mammal. This includes agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a mammal. Such agents can be selected from: another anti-HCV agent, HIV inhibitor, HAV inhibitor and HBV inhibitor. Antiviral agents include, for example, ribavirin, amantadine, VX-497 (merimepodib, Vertex Pharmaceuticals), Levovirin, Viramidine, XTL-001 and XTL-002 (XTL Biopharmaceuticals).

The term "other anti-HCV agent" as used herein means those agents that are effective for diminishing or preventing the progression of hepatitis C related symptoms of disease. Such agents can be selected from: immunomodulatory agents, inhibitors of HCV NS3 protease, inhibitors of HCV polymerase or inhibitors of another target in the HCV life cycle.

The term "immunomodulatory agent" as used herein means those agents (compounds or biologicals) that are effective to enhance or potentiate the immune system response in a mammal. Immunomodulatory agents include, for example, class I interferons (such as α-, β-, δ-, ω- interferons, τ-interferons, consensus interferons and asialo-interferons), class II interferons (such as γ-interferons), pegylated interferons and conjugated interferons, including but not limited to interferons conjugated with other proteins including but not limited to human albumin.

The term "inhibitor of HCV NS3 protease" as used herein means an agent (compound or biological) that is effective to inhibit the function of HCV NS3 protease in a mammal. Inhibitors of HCV NS3 protease include, for example, those compounds described in WO 99/07733, WO 99/07734, WO 00/09558, WO 00/09543, WO 00/59929, WO 03/064416, WO 03/064455, WO 03/064456, WO 2004/037855, WO 2004/039833, WO 2004/101602, WO 2004/101605, WO 2004/103996, WO 2005/028501 and co-pending patent applications 11/039,698, 11/142,792, 11/142,794, 60/583,543, and 60/589,435; herein incorporated by reference in their entirety (all by Boehringer Ingelheim), WO 02/060926, WO 03/053349, WO 03/099274, WO 03/099316, WO 2004/032827, WO 2004/043339, WO 2004/094452, WO 2005/046712 (all by BMS), WO 2004/072243, WO 2004/093798, WO 2004/113365, WO 2005/010029 (all by Enanta), WO 2005/037214 (Intermune) and WO 2005/051980 (Schering), and the Vertex candidate identified as VX-950.

The term "inhibitor of HCV polymerase" as used herein means an agent (compound or biological) that is effective to inhibit the function of an HCV polymerase in a mammal. This includes, but is not limited to, non-nucleoside and nucleoside inhibitors of HCV NS5B polymerase.

Examples of inhibitors of HCV polymerase include but are not limited to those

compounds described in: WO 02/04425 (Boehringer Ingelheim) WO 03/007945 (Boehringer Ingelheim), WO 03/010140 (Boehringer Ingelheim), WO 03/010141 (Boehringer Ingelheim), WO 2004/064925 (Boehringer Ingelheim), WO 2004/065367 (Boehringer Ingelheim), WO 2005/012288 (Genelabs), WO 2004/087714 (IRBM), WO 03/101993 (Neogenesis), WO 03/026587 (BMS), WO 03/000254 (Japan Tobacco), and WO 01/47883 (Japan Tobacco), and the clinical candidates JTK-003 (Japan Tobacco), HCV 796 (ViroPharma/Wyeth), R-1626 (Roche) and NM 283 (Idenix/Novartis).

The term "inhibitor of another target in the HCV life cycle" as used herein means an agent (compound or biological) that is effective to inhibit the formation and/or replication of HCV in a mammal other than by inhibiting the function of the HCV NS3 protease. This includes agents that interfere with either host or HCV viral mechanisms necessary for the formation and/or replication of HCV in a mammal. Inhibitors of another target in the HCV life cycle include, for example, agents that inhibit a target selected from a helicase, a NS2/3 protease and an internal ribosome entry site (IRES) and agents that interfere with the function of other viral targets including but not limited to an NS5A protein.

The term "HIV inhibitor" as used herein means an agent (compound or biological) that is effective to inhibit the formation and/or replication of HIV in a mammal. This includes agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of HIV in a mammal. HIV inhibitors include, for example, nucleoside inhibitors, non-nucleoside inhibitors, protease inhibitors, fusion inhibitors and integrase inhibitors.

The term "HAV inhibitor" as used herein means an agent (compound or biological) that is effective to inhibit the formation and/or replication of HAV in a mammal. This includes agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of HAV in a mammal. HAV inhibitors include Hepatitis A vaccines, for example, Havrix® (GlaxoSmithKline), VAQTA® (Merck) and Avaxim® (Aventis Pasteur).

The term "HBV inhibitor" as used herein means an agent (compound or biological)

that is effective to inhibit the formation and/or replication of HBV in a mammal. This includes agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of HBV in a mammal. HBV inhibitors include, for example, agents that inhibit HBV viral DNA polymerase or HBV vaccines. Specific examples of HBV inhibitors include Lamivudine (Epivir-HBV®), Adefovir Dipivoxil, Entecavir, FTC (Coviracil®), DAPD (DXG), L-FMAU (Clevudine®), AM365 (Amrad), Ldt (Telbivudine), monoval-LdC (Valtorcitabine), ACH-126,443 (L-Fd4C) (Achillion), MCC478 (Eli Lilly), Racivir (RCV), Fluoro-L and D nucleosides, Robustaflavone, ICN 2001-3 (ICN), Bam 205 (Novelos), XTL-001 (XTL), Imino-Sugars (Nonyl-DNJ) (Synergy), HepBzyme; and immunomodulator products such as: interferon alpha 2b, HE2000 (Hollis-Eden), Theradigm (Epimmune), EHT899 (Enzo Biochem), Thymosin alpha-1 (Zadaxin®), HBV DNA vaccine (PowderJect), HBV DNA vaccine (Jefferon Center), HBV antigen (OraGen), BayHep B® (Bayer), Nabi-HB® (Nabi) and Anti-hepatitis B (Cangene); and HBV vaccine products such as the following: Engerix B, Recombivax HB, GenHevac B, Hepacare, Bio-Hep B, TwinRix, Comvax, Hexavac.

The term "class I interferon" as used herein means an interferon selected from a group of interferons that all bind to receptor type I. This includes both naturally and synthetically produced class I interferons. Examples of class I interferons include α-, β-, δ-, ω- interferons, τ-interferons, consensus interferons, asialo-interferons and pegylated forms thereof.

The term "class II interferon" as used herein means an interferon selected from a group of interferons that all bind to receptor type II. Examples of class II interferons include γ-interferons.

Specific preferred examples of some of these agents are listed below:

- antiviral agents: ribavirin and amantadine;
- immunomodulatory agents: class I interferons, class II interferons, pegylated interferons and conjugated interferons;
- HCV polymerase inhibitors: nucleoside analogs and non-nucleosides;
- inhibitor of another target in the HCV life cycle: agents that inhibit a target selected from a helicase, a NS2/3 protease and an internal ribosome entry site (IRES) and agents that interfere with the function of other viral targets including but not limited

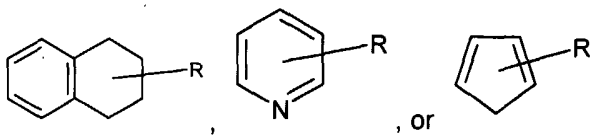
to an NS5A protein;

- HIV inhibitors: nucleoside inhibitors, non-nucleoside inhibitors, protease inhibitors, fusion inhibitors and integrase inhibitors; or
- HBV inhibitors: agents that inhibit viral DNA polymerase or is an HBV vaccine.

As discussed above, combination therapy is contemplated wherein a compound of formula (I), or a pharmaceutically acceptable salt thereof, is co-administered with at least one additional agent selected from: an antiviral agent, an immunomodulatory agent, another inhibitor of HCV NS3 protease, an inhibitor of HCV polymerase, an inhibitor of another target in the HCV life cycle, an HIV inhibitor, an HAV inhibitor and an HBV inhibitor. Examples of such agents are provided in the Definitions section above. These additional agents may be combined with the compounds of this invention to create a single pharmaceutical dosage form. Alternatively these additional agents may be separately administered to the patient as part of a multiple dosage form, for example, using a kit. Such additional agents may be administered to the patient prior to, concurrently with, or following the administration of wherein a compound of formula (I), or a pharmaceutically acceptable salt thereof.

As used herein, the term "treatment" means the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of the hepatitis C disease and/or to reduce viral load in a patient. The term "treatment" also encompasses the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectable levels in the blood.

As used herein, the designation whereby a bond to a substituent **R** is drawn as emanating from the center of a ring, such as, for example,



, , or ,

means that the substituent **R** may be attached to any free position on the ring that would otherwise be substituted with a hydrogen atom, unless specified otherwise.

The following sign ---- | is used in sub-formulas to indicate the bond which is connected to the rest of the molecule as defined.

PREFERRED EMBODIMENTS

In the following preferred embodiments, groups and substituents of the compounds of formula (I) according to this invention are described in detail. Groups, substituents and indices are defined as hereinbefore unless stated otherwise.

n:

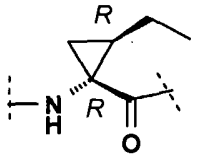
Preferably **n** is 1.

Any and each individual definition of **n** as set out herein may be combined with any and each individual definition of $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, **Y** and **m** as set out herein.

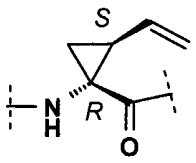
R^1:

Preferably $\mathbf{R^1}$ is selected from (C_{1-6})alkyl, (C_{2-6})alkenyl, and (C_{2-6})alkynyl, each of which being optionally substituted with one to three halogen substituents.
More preferably, $\mathbf{R^1}$ is (C_{2-6})alkenyl or (C_{2-6})alkyl.
Even more preferably, $\mathbf{R^1}$ is ethyl or ethenyl.
$\mathbf{R^1}$ is most preferably ethenyl.

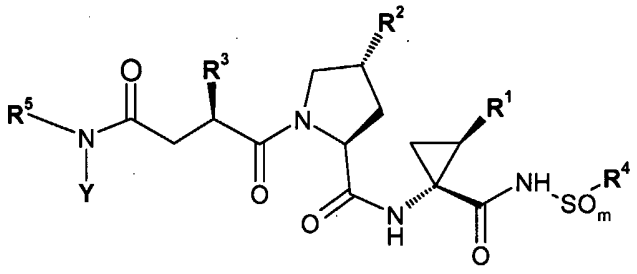
In the moiety **P1**, the substituent $\mathbf{R^1}$ and the carbonyl take a *syn* orientation.
Therefore, in the case $\mathbf{R^1}$ is ethyl and **n** is 1, the asymmetric carbon atoms in the cyclopropyl group take the *R,R* configuration according to the subformula:



In the case $\mathbf{R^1}$ is ethenyl and **n** is 1, the asymmetric carbon atoms in the cyclopropyl group take the *R,S* configuration according to the subformula:



Therefore, in a preferred embodiment, the compounds of the present invention have the formula (Ia):



(Ia)

Any and each individual definition of R^1 as set out herein may be combined with any and each individual definition of R^2, R^3, R^4, R^5, **Y**, **n**, and **m** as set out herein.

m:

Preferably, **m** is 2. Alternatively preferably, **m** is 1.

In yet another embodiment of the present invention, preferred compounds of formula (I) are those wherein **m** is 2, **n** is 1, and R^1 is ethyl or ethenyl.

Any and each individual definition of **m** as set out herein may be combined with any and each individual definition of R^1, R^2, R^3, R^4, R^5, **Y** and **n** as set out herein.

R^2:

Preferably, R^2 is selected from -O-R^{20} or -S-R^{20}, wherein R^{20} is as defined herein, and with the proviso that when

m of formula (I) is 2,

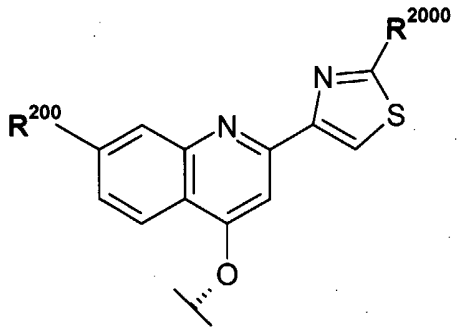
n of formula (I) is 1, and

R^4 is selected from (C_{1-6})alkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, phenyl, naphthyl, pyridinyl, phenyl-(C_{1-4})alkyl-, naphthyl-(C_{1-4})alkyl- and pyridinyl-(C_{1-4})alkyl-; each of which

being optionally substituted with nitro and each of which being optionally substituted with one to three substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$, -NH_2, -NH(C_{1-4})alkyl and -N$((C_{1-4})alkyl)_2$; wherein said (C_{1-4})alkyl and O-(C_{1-6})alkyl are each optionally substituted with one to three halogen substituents;

or R^4 is (C_{3-7})cycloalkyl, said (C_{3-7})cycloalkyl being optionally substituted with nitro and optionally substituted with one or more substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, -OCF_3, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$, -NH_2, -NH(C_{1-4})alkyl and -N$((C_{1-4})alkyl)_2$, wherein said (C_{1-4})alkyl is optionally substituted with one or more halogen substituents;

then R^2 cannot be



;

wherein

R^{200} is -O-(C_{1-4})alkyl, -NH(C_{1-4})alkyl, or -N$((C_{1-4})alkyl)_2$; and

R^{2000} is R^{2003} or -N(R^{2002})(R^{2001}); wherein

R^{2001} is selected from -C(O)-R^{2003}, –C(O)O-R^{2003}, -CON(R^{2002})(R^{2004}) and R^{2004};

R^{2003} is (C_{1-8})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein said (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-(C_{1-4})alkyl- are optionally substituted with one to three (C_{1-3})alkyl substituents; and

R^{2004} is H or R^{2003}.

More preferably, R^2 is -O-R^{20}, wherein R^{20} is as defined herein; and

with the proviso that when

m of formula (I) is 2,

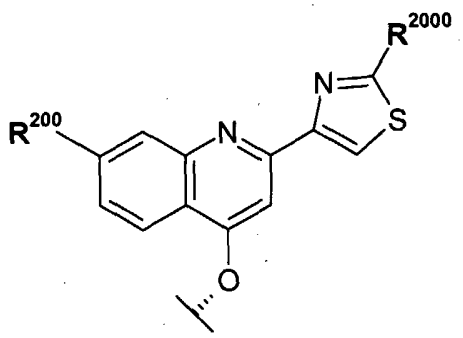
n of formula (I) is 1, and

R^4 is selected from (C_{1-6})alkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, phenyl, naphthyl, pyridinyl,

phenyl-(C_{1-4})alkyl-, naphthyl-(C_{1-4})alkyl- and pyridinyl-(C_{1-4})alkyl-; each of which being optionally substituted with nitro and each of which being optionally substituted with one to three substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, -NH_2, -NH(C_{1-4})alkyl and -N((C_{1-4})alkyl)$_2$; wherein said (C_{1-4})alkyl and O-(C_{1-6})alkyl are each optionally substituted with one to three halogen substituents;

or R^4 is (C_{3-7})cycloalkyl, said (C_{3-7})cycloalkyl being optionally substituted with nitro and optionally substituted with one or more substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, -OCF_3, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, -NH_2, -NH(C_{1-4})alkyl and -N((C_{1-4})alkyl)$_2$, wherein said (C_{1-4})alkyl is optionally substituted with one or more halogen substituents;

then R^2 cannot be



;

wherein

R^{200} is -O-(C_{1-4})alkyl, -NH(C_{1-4})alkyl, or -N((C_{1-4})alkyl)$_2$; and

R^{2000} is R^{2003} or -N(R^{2002})(R^{2001}); wherein

R^{2001} is selected from -C(O)-R^{2003}, –C(O)O-R^{2003}, -CON(R^{2002})(R^{2004}) and R^{2004};

R^{2002} in each case is independently selected from H and methyl;

R^{2003} is (C_{1-8})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein said (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-(C_{1-4})alkyl- are optionally substituted with one to three (C_{1-3})alkyl substituents; and

R^{2004} is H or R^{2003}.

Even more preferably, R^2 is -O-R^{20}, and R^{20} is **Het**, said **Het** being optionally substituted with R^{200}, wherein R^{200} is as defined herein; and

with the proviso that when

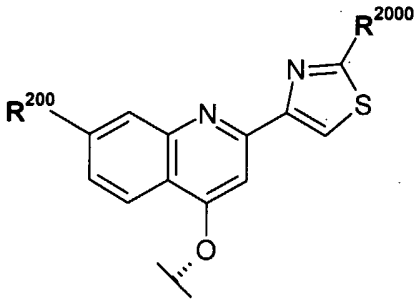
m of formula (I) is 2,

n of formula (I) is 1, and

R^4 is selected from (C_{1-6})alkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, phenyl, naphthyl, pyridinyl, phenyl-(C_{1-4})alkyl-, naphthyl-(C_{1-4})alkyl- and pyridinyl-(C_{1-4})alkyl-; each of which being optionally substituted with nitro and each of which being optionally substituted with one to three substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})$alkyl$)_2$, -NH_2, -NH(C_{1-4})alkyl and -N$((C_{1-4})$alkyl$)_2$; wherein said (C_{1-4})alkyl and O-(C_{1-6})alkyl are each optionally substituted with one to three halogen substituents;

or R^4 is (C_{3-7})cycloalkyl, said (C_{3-7})cycloalkyl being optionally substituted with nitro and optionally substituted with one or more substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, -OCF_3, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})$alkyl$)_2$, -NH_2, -NH(C_{1-4})alkyl and -N$((C_{1-4})$alkyl$)_2$, wherein said (C_{1-4})alkyl is optionally substituted with one or more halogen substituents;

then R^2 cannot be



;

wherein

R^{200} is -O-(C_{1-4})alkyl, -NH(C_{1-4})alkyl, or -N$((C_{1-4})$alkyl$)_2$; and

R^{2000} is R^{2003} or -N$(R^{2002})(R^{2001})$; wherein

R^{2001} is selected from -C(O)-R^{2003}, –C(O)O-R^{2003}, -CON$(R^{2002})(R^{2004})$ and R^{2004};

R^{2002} in each case is independently selected from H and methyl;

R^{2003} is (C_{1-8})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein said (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-(C_{1-4})alkyl- are optionally substituted with one to three (C_{1-3})alkyl substituents; and

R^{2004} is H or R^{2003}.

Yet more preferably, when R^2 is -O-R^{20}, and R^{20} is **Het**, **Het** comprises a heterocycle containing at least one nitrogen heteroatom, and is unsubstituted or substituted with R^{200}, wherein R^{200} is as defined herein; and

with the proviso that when

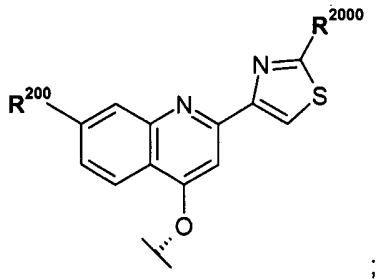
m of formula (I) is 2,

n of formula (I) is 1, and

R^4 is selected from (C_{1-6})alkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, phenyl, naphthyl, pyridinyl, phenyl-(C_{1-4})alkyl-, naphthyl-(C_{1-4})alkyl- and pyridinyl-(C_{1-4})alkyl-; each of which being optionally substituted with nitro and each of which being optionally substituted with one to three substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})$alkyl$)_2$, -NH_2, -NH(C_{1-4})alkyl and -N$((C_{1-4})$alkyl$)_2$; wherein said (C_{1-4})alkyl and O-(C_{1-6})alkyl are each optionally substituted with one to three halogen substituents;

or R^4 is (C_{3-7})cycloalkyl, said (C_{3-7})cycloalkyl being optionally substituted with nitro and optionally substituted with one or more substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, -OCF_3, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})$alkyl$)_2$, -NH_2, -NH(C_{1-4})alkyl and -N$((C_{1-4})$alkyl$)_2$, wherein said (C_{1-4})alkyl is optionally substituted with one or more halogen substituents;

then R^2 cannot be



;

wherein

R^{200} is -O-(C_{1-4})alkyl, -NH(C_{1-4})alkyl, or -N$((C_{1-4})$alkyl$)_2$; and

R^{2000} is R^{2003} or -N(R^{2002})(R^{2001}); wherein

R^{2001} is selected from -C(O)-R^{2003}, –C(O)O-R^{2003}, -CON(R^{2002})(R^{2004}) and R^{2004};

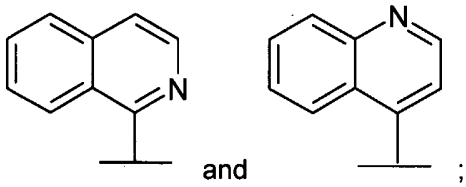
R^{2002} in each case is independently selected from H and methyl;

R^{2003} is (C_{1-8})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein said (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-(C_{1-4})alkyl- are optionally

substituted with one to three (C_{1-3})alkyl substituents; and

R^{2004} is H or R^{2003}.

Still more preferably, when R^2 is -O-R^{20}, and R^{20} is **Het**, **Het** is unsubstituted or substituted with R^{200}, wherein R^{200} is as defined herein, and **Het** is a group selected from:



and ;

with the proviso that when

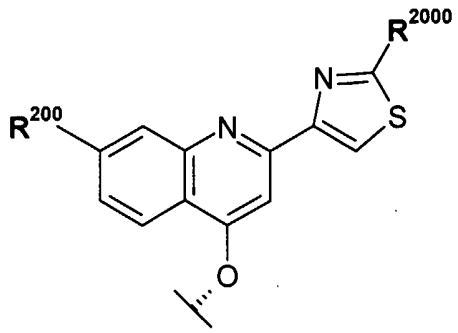
m of formula (I) is 2,

n of formula (I) is 1, and

R^4 is selected from (C_{1-6})alkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, phenyl, naphthyl, pyridinyl, phenyl-(C_{1-4})alkyl-, naphthyl-(C_{1-4})alkyl- and pyridinyl-(C_{1-4})alkyl-; each of which being optionally substituted with nitro and each of which being optionally substituted with one to three substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$, -NH_2, -NH(C_{1-4})alkyl and -N$((C_{1-4})alkyl)_2$; wherein said (C_{1-4})alkyl and O-(C_{1-6})alkyl are each optionally substituted with one to three halogen substituents;

or R^4 is (C_{3-7})cycloalkyl, said (C_{3-7})cycloalkyl being optionally substituted with nitro and optionally substituted with one or more substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, -OCF_3, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$, -NH_2, -NH(C_{1-4})alkyl and -N$((C_{1-4})alkyl)_2$, wherein said (C_{1-4})alkyl is optionally substituted with one or more halogen substituents;

then R^2 cannot be



;

wherein

R^{200} is -O-(C_{1-4})alkyl, -NH(C_{1-4})alkyl, or -N((C_{1-4})alkyl)$_2$; and

R^{2000} is R^{2003} or -N(R^{2002})(R^{2001}); wherein

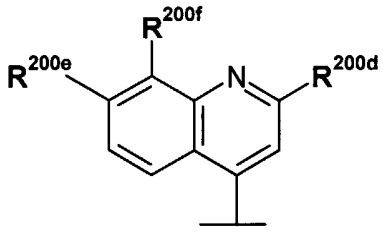
R^{2001} is selected from -C(O)-R^{2003}, –C(O)O-R^{2003}, -CON(R^{2002})(R^{2004}) and R^{2004};

R^{2002} in each case is independently selected from H and methyl;

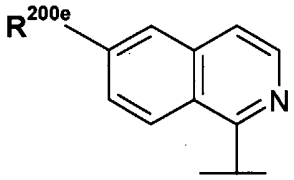
R^{2003} is (C_{1-8})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein said (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-(C_{1-4})alkyl- are optionally substituted with one to three (C_{1-3})alkyl substituents; and

R^{2004} is H or R^{2003}.

Even more preferably, R^2 is -O-R^{20}, wherein R^{20} is **Het**, wherein **Het** is a group selected from :



and



wherein

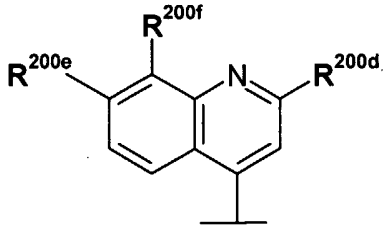
R^{200d} is H or -OR^{201}, wherein R^{201} is (C_{1-6})alkyl optionally further substituted with R^{2000}, wherein R^{2000} is one to three substituents each independently selected from halogen, (C_{3-7})cycloalkyl, -O-(C_{1-6})alkyl, **Het**, -O-(C_{3-7})cycloalkyl, -NH_2, -NH(C_{1-4})alkyl and -N((C_{1-4})alkyl)$_2$;

R^{200e} is H or -OR^{201}, wherein R^{201} is (C_{1-6})alkyl; and

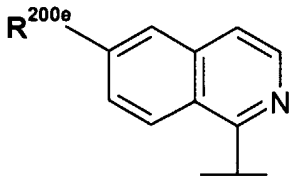
R^{200f} is H, (C_{1-6})alkyl, halogen, -SR^{201}, -SOR^{201}, -SO_2R^{201} or -OR^{201}; wherein R^{201} is (C_{1-6})alkyl.

Most preferably, R^2 is -O-R^{20}, wherein R^{20} is **Het**, wherein **Het** is a group selected

from:



and



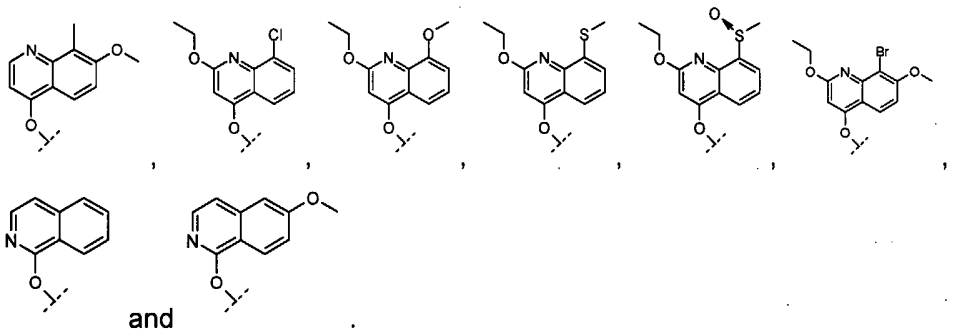
wherein

R^{200d} is H or $-OR^{201}$, wherein R^{201} is (C_{1-6})alkyl;

R^{200e} is H or $-OR^{201}$, wherein R^{201} is (C_{1-6})alkyl; and

R^{200f} is H, (C_{1-6})alkyl, halogen, $-OR^{201}$, $-SR^{201}$ or $-SOR^{201}$, wherein R^{201} is (C_{1-6})alkyl.

Therefore, preferably, R^2 is selected from:



and

Any and each individual definition of R^2 as set out herein may be combined with any and each individual definition of R^1, R^3, R^4, R^5, Y, n, and m as set out herein.

R^3:

R^3 is preferably (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-3})alkyl-, wherein each said cycloalkyl group is optionally substituted with one to three (C_{1-4})alkyl substituents.

More preferably, R^3 is selected from ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl; said ethyl, propyl and butyl optionally being substituted with one or two methyl substituents and said cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl optionally being substituted with one or two substituents each independently selected from methyl, ethyl and propyl.

Even more preferably R^3 is selected from 1-methylethyl, 1,1-dimethylethyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, cyclopentyl, cyclohexyl, 1-methylcyclopentyl, 1-methylcyclohexyl, cyclopentylmethyl, cyclohexylmethyl, (1-methylcyclopentyl)methyl and (1-methylcyclohexyl)methyl.

R^3 is yet more preferably selected from 1,1-dimethylethyl, cyclopentyl, cyclohexyl and 1-methylcyclohexyl.

R^3 is most preferably 1,1-dimethylethyl.

Any and each individual definition of R^3 as set out herein may be combined with any and each individual definition of R^1, R^2, R^4, R^5, **Y**, **n**, and **m** as set out herein.

R^4:

Preferably, R^4 is selected from methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, ethenyl, 1-propenyl, 2-propenyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, naphthyl, **Het**, phenylmethyl, naphthylmethyl and **Het**-methyl;

a) each of which optionally being substituted with one to three substituents each independently selected from fluoro and methyl; and

b) each of which optionally being substituted with one or two substituents each independently selected from hydroxy, trifluoromethyl, methoxy, phenoxy and trifluoromethoxy; and

c) each of which optionally being substituted with a substituent selected from chloro, bromo, cyano, nitro, $-CO-NH_2$, $-CO-NHCH_3$, $-CO-N(CH_3)_2$, $-NH_2$, $-NH(CH_3)$ and $-N(CH_3)_2$;

wherein **Het** is selected from thienyl, furyl, thiazolyl, benzothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, quinolinyl, isoquinolinyl, tetrahydrofuryl, tetrahydrothienyl, thiadiazolyl, isoxazolyl, benzothienyl, piperidinyl, piperazinyl, morpholinyl, triazolyl, and tetrazolyl.

In an alternative preferred embodiment, R^4 is selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

a) each of which optionally being substituted with one, two or three fluoro substituents; and

b) each of which optionally being substituted with one or two substituents each independently selected from hydroxy, trifluoromethyl, methoxy and trifluoromethoxy; and

c) each of which optionally being substituted with a substituent selected from chloro, bromo, cyano, nitro, -CO-NH_2, -CO-$NHCH_3$, -CO-$N(CH_3)_2$, -NH_2, -$NH(CH_3)$ and -$N(CH_3)_2$; and

d) each of which being optionally substituted with (C_{1-8})alkyl, wherein the (C_{1-8})alkyl is optionally substituted with one or more substituents each independently selected from -O-(C_{1-6})alkyl, hydroxy, halogen, (C_{2-10})alkenyl, (C_{2-10})alkynyl, (C_{3-7})cycloalkyl, (C_{4-7})cycloalkenyl, aryl, aryloxy, and aryl-(C_{1-4})alkyl-O-, wherein each of the aryl and aryloxy is optionally substituted with (C_{1-6})alkyl.

More preferably, the group R^4 is selected from methyl, ethyl, 1-methylethyl, propyl, ethenyl, cyclopropyl, cyclobutyl, cyclopentyl and phenyl wherein said cyclopropyl is optionally substituted at the 1-position with methyl, ethyl, propyl or butyl, each of said methyl, ethyl, propyl or butyl being optionally further substituted with phenyl, (C_{3-6})cycloalkyl, (C_{2-6})alkenyl or (C_{1-4})alkoxy .

Most preferably, R^4 is cyclopropyl or 1-methylcyclopropyl.

In another alternative preferred embodiment, R^4 is $-N(R^{N2})(R^{N1})$, wherein R^{N1} and R^{N2} are each independently selected from H, methyl, ethyl, propyl, 1-methylethyl, methoxy, ethoxy, propoxy, 1-methylethoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and phenylmethyl; wherein the methyl, ethyl, propyl, 1-methylethyl, methoxy, ethoxy, propoxy, 1-methylethoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and phenylmethyl are each optionally substituted with one or more substituents each independently selected from halogen, (C_{1-4})alkyl, hydroxy, cyano, O-(C_{1-4})alkyl, -NH_2, -$NH(C_{1-4})$alkyl, -$N((C_{1-4})alkyl)_2$, -CO-NH_2, -CO-$NH(C_{1-4})$alkyl, -CO-$N((C_{1-4})alkyl)_2$, –COOH, and –$COO(C_{1-4})$alkyl; or

R^{N2} and R^{N1} are linked, together with the nitrogen to which they are bonded, to form a 3-, 4-, 5- or 6-membered monocyclic saturated or unsaturated heterocycle, optionally containing from one to three additional heteroatoms each independently selected from N, S and O, and optionally substituted with one, two or three substituents each independently selected from halogen, (C_{1-4})alkyl, hydroxy, cyano, O-(C_{1-4})alkyl, -NH_2, -NH(C_{1-4})alkyl, -N$((C_{1-4})alkyl)_2$, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$, -COOH, and –COO(C_{1-4})alkyl.

In yet another alternative preferred embodiment, R^4 is –N(R^{N2})(R^{N1}), wherein R^{N1} and R^{N2} are each independently selected from methyl, ethyl, propyl, 1-methylethyl, methoxy, ethoxy, propoxy, 1-methylethoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and phenylmethyl; wherein said methyl, ethyl, propyl, 1-methylethyl, methoxy, ethoxy, propoxy, 1-methylethoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and phenylmethyl are optionally substituted with one or more substituents each independently selected from halogen, (C_{1-4})alkyl, hydroxy, cyano, O-(C_{1-4})alkyl, -NH_2, -NH(C_{1-4})alkyl, -N$((C_{1-4})alkyl)_2$, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$, –COOH, and –COO(C_{1-4})alkyl; or R^{N2} and R^{N1} are linked, together with the nitrogen to which they are bonded, to form a 3-, 4-, 5- or 6-membered monocyclic saturated or unsaturated heterocycle, optionally containing from one to three additional heteroatoms each independently selected from N, S and O, and optionally substituted with one, two or three substituents each independently selected from halogen, (C_{1-4})alkyl, hydroxy, cyano, O-(C_{1-4})alkyl, -NH_2, -NH(C_{1-4})alkyl, -N$((C_{1-4})alkyl)_2$, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$, -COOH, and –COO(C_{1-4})alkyl.

Most preferably, R^4 is -N$(CH_3)_2$.

Therefore preferably, R^4 is selected from methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, ethenyl, 1-propenyl, 2-propenyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, naphthyl, **Het**, phenylmethyl, naphthylmethyl and **Het**-methyl;

a) each of which optionally being substituted with one, two or three substituents each independently selected from fluoro and methyl; and

b) each of which optionally being substituted with one or two substituents each

independently selected from hydroxy, trifluoromethyl, methoxy, phenoxy and trifluoromethoxy; and

c) each of which optionally being substituted with a substituent selected from chloro, bromo, CF_3, cyano, nitro, -CO-NH_2, -CO-$NHCH_3$, -CO-$N(CH_3)_2$, -NH_2, -$NH(CH_3)$ and -$N(CH_3)_2$;

wherein **Het** is selected from thienyl, furyl, thiazolyl, benzothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, quinolinyl, isoquinolinyl, tetrahydrothienyl, tetrahydrofuryl, thiadiazolyl, isoxazolyl, benzothienyl, piperidinyl, piperazinyl, morpholinyl, triazolyl and tetrazolyl;

or $\mathbf{R^4}$ is selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

a) each of which optionally being substituted with one, two or three fluoro substituents; and

b) each of which optionally being substituted with one or two substituents each independently selected from hydroxy, trifluoromethyl, methoxy and trifluoromethoxy; and

c) each of which optionally being substituted with a substituent selected from chloro, bromo, cyano, nitro, -CO-NH_2, -CO-$NHCH_3$, -CO-$N(CH_3)_2$, -NH_2, -$NH(CH_3)$ and -$N(CH_3)_2$; and

d) each of which being optionally substituted with (C_{1-8})alkyl, wherein the (C_{1-8})alkyl is optionally substituted with one or more substituents each independently selected from -O-(C_{1-6})alkyl, hydroxy, halogen, (C_{2-10})alkenyl, (C_{2-10})alkynyl, (C_{3-7})cycloalkyl, (C_{4-7})cycloalkenyl, aryl, aryloxy, and aryl-(C_{1-4})alkyl-O-, wherein each of the aryl and aryloxy is optionally substituted with (C_{1-6})alkyl;

or $\mathbf{R^4}$ is $-N(\mathbf{R^{N2}})(\mathbf{R^{N1}})$, wherein $\mathbf{R^{N1}}$ and $\mathbf{R^{N2}}$ are each independently selected from H, methyl, ethyl, propyl, 1-methylethyl, methoxy, ethoxy, propoxy, 1-methylethoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and phenylmethyl; wherein the methyl, ethyl, propyl, 1-methylethyl, methoxy, ethoxy, propoxy, 1-methylethoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and phenylmethyl are each optionally substituted with one or more substituents each independently selected from halogen, (C_{1-4})alkyl, hydroxy, cyano, O-(C_{1-4})alkyl, -NH_2, -$NH(C_{1-4})$alkyl, -$N((C_{1-4})alkyl)_2$, -CO-NH_2, -CO-$NH(C_{1-4})$alkyl, -CO-$N((C_{1-4})alkyl)_2$, –COOH, and -$COO(C_{1-4})$alkyl; or

R^{N2} and R^{N1} are linked, together with the nitrogen to which they are bonded, to form a 3-, 4-, 5- or 6-membered monocyclic saturated or unsaturated heterocycle, optionally containing from one to three additional heteroatoms each independently selected from N, S and O, and optionally substituted with one, two or three substituents each independently selected from halogen, (C_{1-4})alkyl, hydroxy, cyano, O-(C_{1-4})alkyl, $-NH_2$, $-NH(C_{1-4})$alkyl, $-N((C_{1-4})alkyl)_2$, $-CO-NH_2$, $-CO-NH(C_{1-4})$alkyl, $-CO-N((C_{1-4})alkyl)_2$, -COOH, and $-COO(C_{1-4})$alkyl.

More preferably, R^4 is selected from methyl, ethyl, 1-methylethyl, propyl, ethenyl, cyclopropyl, cyclobutyl, cyclopentyl, phenyl and $-N(CH_3)_2$; wherein the cyclopropyl is optionally substituted at the 1-position with methyl, ethyl, propyl or butyl, each of the methyl, ethyl, propyl and butyl being optionally further substituted with phenyl, (C_{3-6})cycloalkyl, (C_{2-6})alkenyl or (C_{1-4})alkoxy.

Most preferably, R^4 is cyclopropyl, 1-methylcyclopropyl or $-N(CH_3)_2$.

Any and each individual definition of R^4 as set out herein may be combined with any and each individual definition of R^1, R^2, R^3, R^5, **Y**, **n**, and **m** as set out herein.

R^5:

Preferably, R^5 is (C_{2-10})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-3})alkyl-, phenyl or **Het**, wherein the **Het** is a 5- or 6-membered monocyclic aromatic heterocycle containing one to three heteroatoms each independently selected from N, O and S and wherein each of the (C_{2-10})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, phenyl and **Het** is optionally substituted with one to three substituents each independently selected from halogen, -OH, (C_{1-4})alkyl, -O-(C_{1-4})alkyl, -S-(C_{1-4})alkyl, $-NH_2$, $-NH(C_{1-4})$alkyl, $-N((C_{1-4})alkyl)_2$, $-NHC(=O)(C_{1-4})$alkyl, $-NHC(=O)O(C_{1-4})$alkyl, $-NH(C=O)NH(C_{1-4})$alkyl, $-NH(C=O)N((C_{1-4})alkyl)_2$, $-CONH_2$, $-CONH-(C_{1-4})$alkyl, $-CON((C_{1-4})alkyl)_2$, -COOH, $-COO(C_{1-6})$alkyl, $-CO-(C_{1-6})$alkyl, $-SO_2(C_{1-4})$alkyl and $-SO_2NH(C_{1-4})$alkyl.

More preferably R^5 is (C_{2-10})alkyl, (C_{3-7})cycloalkyl, or phenyl, each of which being optionally substituted with one to three substituents each independently selected from halogen, -OH, (C_{1-4})alkyl and -O-(C_{1-4})alkyl.

Even more preferably, R^5 is (C_{2-8})alkyl, (C_{3-6})cycloalkyl or phenyl, each of which being optionally substituted with one or two methyl substituents.

Yet more preferably, R^5 is selected from ethyl, propyl, butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and phenyl; each of which being optionally substituted with one or two methyl substituents.

Still more preferably R^5 is selected from 1,1-dimethylethyl, 1,1-dimethylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclopentyl, 1-methylcyclohexyl and phenyl.

Most preferably R^5 is selected from 1,1-dimethylethyl, cyclopentyl and phenyl.

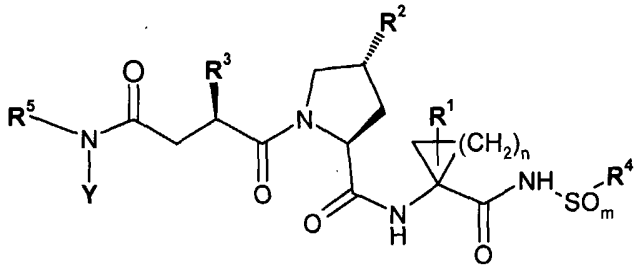
Any and each individual definition of R^5 as set out herein may be combined with any and each individual definition of R^1, R^2, R^3, R^4, **Y**, **n**, and **m** as set out herein.

Y:

Preferably, **Y** is H or methyl. More preferably, **Y** is H.

Any and each individual definition of **Y** as set out herein may be combined with any and each individual definition of R^1, R^2, R^3, R^4, R^5, **n**, and **m** as set out herein.

Therefore, one embodiment of the invention provides a compound of formula (I):



(I)

wherein

n is 1 or 2;

m is 1 or 2;

R^1 is H, (C_{1-6})alkyl, (C_{2-6})alkenyl, or (C_{2-6})alkynyl; wherein each of said (C_{1-6})alkyl,

(C_{2-6})alkenyl, and (C_{2-6})alkynyl are optionally substituted with from one to three halogen substituents;

R^2 is selected from -NH-R^{20}, -O-R^{20}, -S-R^{20}, -SO-R^{20}, -SO_2-R^{20}, -OCH_2-R^{20}, and -CH_2O-R^{20}, wherein

R^{20} is aryl or **Het**, wherein said aryl and **Het** are each optionally substituted with R^{200}, wherein

R^{200} is one to four substituents each independently selected from H, halogen, cyano, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl-(C_{1-6})alkyl-, aryl, **Het**, oxo, thioxo, -OR^{201}, -SR^{201}, -SOR^{201}, -SO_2R^{201}, -$N(R^{202})R^{201}$, and -$CON(R^{202})R^{201}$; wherein each of said alkyl, cycloalkyl, aryl and **Het** is optionally further substituted with R^{2000};

R^{201} in each case is independently selected from H, (C_{1-6})alkyl, aryl, (C_{2-4})alkenyl, (C_{2-4})alkynyl, -CO-(C_{1-6})alkyl and -CO-O-(C_{1-6})alkyl, wherein each of said alkyl and aryl is optionally further substituted with R^{2000};

R^{202} is H or (C_{1-6})alkyl;

R^{2000} is one to three substituents each independently selected from halogen, R^{2003}, aryl, **Het**, -OR^{2001}, -SR^{2001}, -SOR^{2001}, -SO_2R^{2001}, cyano and -$N(R^{2002})(R^{2001})$, wherein said each of aryl and **Het** are optionally substituted with one, two or three substituents each independently selected from (C_{1-6})alkyl and -O-(C_{1-6})alkyl;

R^{2001} in each case is independently selected from aryl, aryl-(C_{1-6})alkyl-, -C(O)-R^{2003}, –C(O)O-R^{2003}, -$CON(R^{2002})(R^{2004})$ and R^{2004};

R^{2002} in each case is independently selected from H and (C_{1-6})alkyl;

R^{2003} in each case is independently selected from (C_{1-8})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein each of said (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-(C_{1-4})alkyl- are optionally substituted with one to three (C_{1-3})alkyl substituents; and

R^{2004} in each case is independently selected from H or R^{2003};

R^3 is (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-3})alkyl-, wherein each said cycloalkyl group is optionally substituted with one to three substituents each independently selected from halogen, -OH, (C_{1-4})alkyl, O-(C_{1-4})alkyl, S-(C_{1-4})alkyl, -NH_2, -$NH(C_{1-4})$alkyl, -$N((C_{1-4})alkyl)_2$, -COOH and -$CONH_2$;

R^4 is (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl, **Het**,

aryl-(C_{1-4})alkyl-, or **Het**-(C_{1-4})alkyl-;

a) each of said (C_{1-6})alkyl, (C_{2-6})alkenyl, aryl, **Het**, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl-(C_{1-4})alkyl- and **Het**-(C_{1-4})alkyl- optionally being substituted with nitro and optionally being substituted with one to three substituents each independently selected from halogen, hydroxy, cyano, (C_{1-6})alkyl, O-(C_{1-6})alkyl, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, -NH_2, -NH(C_{1-4})alkyl and -N((C_{1-4})alkyl)$_2$, wherein said (C_{1-6})alkyl and O-(C_{1-6})alkyl are optionally substituted with one to three halogen substituents; and

b) said (C_{3-7})cycloalkyl being optionally substituted with one or more substituents each independently selected from nitro, halogen, hydroxy, cyano, -O-(C_{1-6})alkyl, (C_{2-6})alkenyl, -OCF_3, -NH_2, -NH(C_{1-4})alkyl, -N((C_{1-4})alkyl)$_2$, tri(C_{1-6})alkylsilyl, $\mathbf{R^{41}}$, -C(=O)-$\mathbf{R^{41}}$, -C(=O)O$\mathbf{R^{41}}$, -C(=O)N($\mathbf{R^{42}}$)$\mathbf{R^{41}}$, -$SO_2\mathbf{R^{41}}$, and -OC(=O)-$\mathbf{R^{41}}$;

wherein $\mathbf{R^{41}}$ in each case is independently selected from:

i) H, (C_{3-7})cycloalkyl, (C_{4-7})cycloalkenyl, **Het**, or aryl-(C_{1-4})alkyl-O-;

ii) aryl or aryloxy, each of which being optionally substituted with (C_{1-6})alkyl; and

iii) (C_{1-8})alkyl optionally substituted with one or more substituents each independently selected from -O-(C_{1-6})alkyl, hydroxy, halogen, (C_{2-10})alkenyl, (C_{2-10})alkynyl, (C_{3-7})cycloalkyl, (C_{4-7})cycloalkenyl, aryl, **Het**, aryloxy, and aryl-(C_{1-4})alkyl-O-, wherein each of said aryl and aryloxy is optionally substituted with (C_{1-6})alkyl; and

$\mathbf{R^{42}}$ is selected from H and (C_{1-6})alkyl; or

$\mathbf{R^4}$ is –N($\mathbf{R^{N2}}$)($\mathbf{R^{N1}}$), wherein $\mathbf{R^{N1}}$ and $\mathbf{R^{N2}}$ are each independently selected from H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl and aryl-(C_{1-6})alkyl-; wherein said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl and aryl-(C_{1-6})alkyl- are each optionally substituted with one or more substituents each independently selected from halogen, (C_{1-6})alkyl, hydroxy, cyano, O-(C_{1-6})alkyl, -NH_2, -NH(C_{1-4})alkyl, -N((C_{1-4})alkyl)$_2$, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, -COOH, and –COO(C_{1-6})alkyl; or

$\mathbf{R^{N2}}$ and $\mathbf{R^{N1}}$ are linked, together with the nitrogen to which they are bonded, to

form a 3- to 7-membered monocyclic saturated or unsaturated heterocycle optionally fused to at least one other cycle to form a heteropolycycle, said heterocycle and heteropolycycle each optionally containing from one to three additional heteroatoms each independently selected from N, S and O, and being optionally substituted with one or more substituents each independently selected from halogen, (C_{1-6})alkyl, hydroxy, cyano, O-(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-4})alkyl, -N$((C_{1-4})alkyl)_2$, $-CO-NH_2$, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$, -COOH, and –COO(C_{1-6})alkyl;

R^5 is (C_{2-10})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein

a) each said cycloalkyl and cycloalkyl-alkyl- is optionally substituted with one to three (C_{1-3})alkyl substituents; and

b) each said alkyl, cycloalkyl and cycloalkyl-alkyl- is optionally substituted with one or two substituents each independently selected from hydroxy and O-(C_{1-4})alkyl; and

c) each said alkyl group is optionally substituted with one to three halogen substituents; and

d) in each said cycloalkyl group being 5-, 6- or 7-membered, one or two $-CH_2-$ groups not being directly linked to each other are optionally replaced by -O- such that the O-atom is linked to the N atom to which R^5 is attached via at least two C-atoms;

or

R^5 is phenyl, phenyl-(C_{1-3})alkyl-, heteroaryl or heteroaryl-(C_{1-3})alkyl-, wherein the heteroaryl groups are 5- or 6-membered having from 1 to 3 heteroatoms each independently selected from N, O and S; wherein said phenyl and heteroaryl groups are each optionally substituted with one to three substituents each independently selected from halogen, -OH, (C_{1-4})alkyl, -O-(C_{1-4})alkyl, S-(C_{1-4})alkyl, $-NH_2$, –NH(C_{1-4})alkyl, -N$((C_{1-4})alkyl)_2$, $-CONH_2$, -CONH-(C_{1-4})alkyl, -COOH, -COO(C_{1-6})alkyl, and -CO-(C_{1-6})alkyl; and

Y is H or (C_{1-6})alkyl;

with the proviso that when

m is 2,

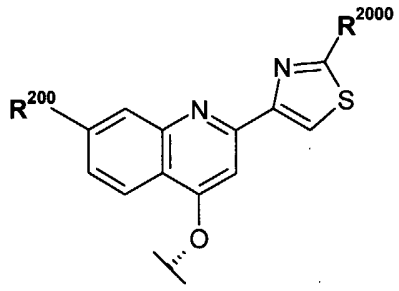
n is 1, and

R^4 is selected from (C_{1-6})alkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, phenyl, naphthyl, pyridinyl,

phenyl-(C_{1-4})alkyl-, naphthyl-(C_{1-4})alkyl- and pyridinyl-(C_{1-4})alkyl-; each of which being optionally substituted with nitro and each of which being optionally substituted with one to three substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, -NH_2, -NH(C_{1-4})alkyl and -N((C_{1-4})alkyl)$_2$; wherein said (C_{1-4})alkyl and O-(C_{1-6})alkyl are each optionally substituted with one to three halogen substituents;

or **R**^{4} is (C_{3-7})cycloalkyl, said (C_{3-7})cycloalkyl being optionally substituted with nitro and optionally substituted with one or more substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, -OCF_3, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, -NH_2, -NH(C_{1-4})alkyl and -N((C_{1-4})alkyl)$_2$, wherein said (C_{1-4})alkyl is optionally substituted with one or more halogen substituents;

then **R**^{2} cannot be



;

wherein

R^{200} is -O-(C_{1-4})alkyl, -NH(C_{1-4})alkyl, or -N((C_{1-4})alkyl)$_2$; and

R^{2000} is **R**^{2003} or -N(**R**^{2002})(**R**^{2001}); wherein

R^{2001} is selected from -C(O)-**R**^{2003}, –C(O)O-**R**^{2003}, -CON(**R**^{2002})(**R**^{2004}) and **R**^{2004};

R^{2002} in each case is independently selected from H and methyl;

R^{2003} is (C_{1-8})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein said (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-(C_{1-4})alkyl- are optionally substituted with one to three (C_{1-3})alkyl substituents; and

R^{2004} is H or **R**^{2003};

wherein **Het** as used herein is defined as a 3- to 7-membered heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, which may be saturated, unsaturated or aromatic, and which is optionally fused to at least one other cycle to form a 4- to 14-membered heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S, said heteropolycycle

being saturated, unsaturated or aromatic;
or a salt thereof.

According to a preferred embodiment, preferred are compounds of formula (I) wherein:

n is 1;

m is 2;

$\mathbf{R^1}$ is selected from (C_{1-6})alkyl, (C_{2-6})alkenyl, or (C_{2-6})alkynyl, each of which being optionally substituted with one to three halogen substituents;

$\mathbf{R^2}$ is selected from -O-$\mathbf{R^{20}}$ or -S-$\mathbf{R^{20}}$, wherein $\mathbf{R^{20}}$ is as defined herein,

$\mathbf{R^3}$ is (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-3})alkyl-, wherein each said cycloalkyl group is optionally substituted with one to three (C_{1-4})alkyl substituents;

$\mathbf{R^4}$ is (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl, **Het**, aryl-(C_{1-4})alkyl-, or **Het**-(C_{1-4})alkyl-;

a) each of said (C_{1-6})alkyl, (C_{2-6})alkenyl, aryl, **Het**, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl-(C_{1-4})alkyl- and **Het**-(C_{1-4})alkyl- optionally being substituted with nitro and optionally being substituted with one to three substituents each independently selected from halogen, hydroxy, cyano, (C_{1-6})alkyl, O-(C_{1-6})alkyl, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})$alkyl$)_2$, -NH_2, -NH(C_{1-4})alkyl and -N$((C_{1-4})$alkyl$)_2$, wherein said (C_{1-6})alkyl and O-(C_{1-6})alkyl are optionally substituted with one to three halogen substituents; and

b) said (C_{3-7})cycloalkyl being optionally substituted with one or more substituents each independently selected from nitro, halogen, hydroxy, cyano, -O-(C_{1-6})alkyl, (C_{2-4})alkenyl, -OCF_3, -NH_2, -NH(C_{1-4})alkyl, -N$((C_{1-4})$alkyl$)_2$, tri(C_{1-6})alkylsilyl, $\mathbf{R^{41}}$, -C(=O)-$\mathbf{R^{41}}$, -C(=O)O$\mathbf{R^{41}}$, -C(=O)N($\mathbf{R^{42}}$)$\mathbf{R^{41}}$, -$SO_2\mathbf{R^{41}}$, and -OC(=O)-$\mathbf{R^{41}}$;

wherein $\mathbf{R^{41}}$ in each case is independently selected from:

i) H, (C_{3-7})cycloalkyl, (C_{4-7})cycloalkenyl, **Het**, or aryl-(C_{1-4})alkyl-O-;

ii) aryl or aryloxy, each of which being optionally substituted with (C_{1-6})alkyl; and

iii) (C_{1-8})alkyl optionally substituted with one or more substituents each independently selected from -O-(C_{1-6})alkyl, hydroxy, halogen, (C_{2-10})alkenyl, (C_{2-10})alkynyl, (C_{3-7})cycloalkyl,

(C_{4-7})cycloalkenyl, aryl, **Het**, aryloxy, and aryl-(C_{1-4})alkyl-O-, wherein each of said aryl and aryloxy is optionally substituted with (C_{1-6})alkyl; and

R^{42} is selected from H and (C_{1-6})alkyl; or

R^4 is $-N(R^{N2})(R^{N1})$, wherein R^{N1} and R^{N2} are each independently selected from H, (C_{1-6})alkyl, -O-(C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl and aryl-(C_{1-6})alkyl-; wherein said (C_{1-6})alkyl, -O-(C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl and aryl-(C_{1-6})alkyl- are each optionally substituted with one or more substituents each independently selected from halogen, (C_{1-6})alkyl, hydroxy, cyano, O-(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-4})alkyl, -N((C_{1-4})alkyl)$_2$, $-CO-NH_2$, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, -COOH, and $-COO(C_{1-6})$alkyl; or

R^{N2} and R^{N1} are linked, together with the nitrogen to which they are bonded, to form a 3- to 7-membered monocyclic saturated or unsaturated heterocycle optionally fused to at least one other cycle to form a heteropolycycle, said heterocycle and heteropolycycle each optionally containing from one to three additional heteroatoms each independently selected from N, S and O, and being optionally substituted with one or more substituents each independently selected from halogen, (C_{1-6})alkyl, hydroxy, cyano, O-(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-4})alkyl, -N((C_{1-4})alkyl)$_2$, $-CO-NH_2$, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, -COOH, and $-COO(C_{1-6})$alkyl;

R^5 is (C_{2-10})alkyl, (C_{3-7})cycloalkyl, or phenyl, each of which being optionally substituted with one to three substituents each independently selected from halogen, -OH, (C_{1-4})alkyl and -O-(C_{1-4})alkyl; and

Y is H;

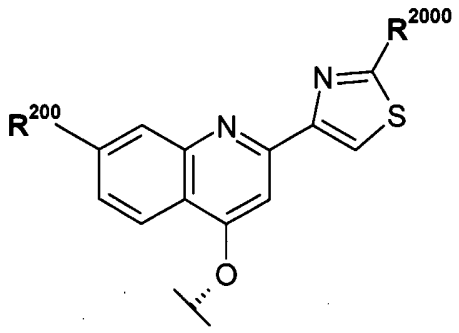
with the proviso that when

R^4 is selected from (C_{1-6})alkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, phenyl, naphthyl, pyridinyl, phenyl-(C_{1-4})alkyl-, naphthyl-(C_{1-4})alkyl- and pyridinyl-(C_{1-4})alkyl-; each of which being optionally substituted with nitro and each of which being optionally substituted with one to three substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, $-CO-NH_2$, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, $-NH_2$, -NH(C_{1-4})alkyl and

-N((C_{1-4})alkyl)$_2$; wherein said (C_{1-4})alkyl and O-(C_{1-6})alkyl are each optionally substituted with one to three halogen substituents;

or $\mathbf{R^4}$ is (C_{3-7})cycloalkyl, said (C_{3-7})cycloalkyl being optionally substituted with nitro and optionally substituted with one or more substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, $-OCF_3$, $-CO-NH_2$, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, $-NH_2$, -NH(C_{1-4})alkyl and -N((C_{1-4})alkyl)$_2$, wherein said (C_{1-4})alkyl is optionally substituted with one or more halogen substituents;

then $\mathbf{R^2}$ cannot be



;

wherein

$\mathbf{R^{200}}$ is -O-(C_{1-4})alkyl, -NH(C_{1-4})alkyl, or -N((C_{1-4})alkyl)$_2$; and

$\mathbf{R^{2000}}$ is $\mathbf{R^{2003}}$ or -N($\mathbf{R^{2002}}$)($\mathbf{R^{2001}}$); wherein

$\mathbf{R^{2001}}$ is selected from -C(O)-$\mathbf{R^{2003}}$, –C(O)O-$\mathbf{R^{2003}}$, -CON($\mathbf{R^{2002}}$)($\mathbf{R^{2004}}$) and $\mathbf{R^{2004}}$;

$\mathbf{R^{2002}}$ in each case is independently selected from H and methyl;

$\mathbf{R^{2003}}$ is (C_{1-8})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein said (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-(C_{1-4})alkyl- are optionally substituted with one to three (C_{1-3})alkyl substituents; and

$\mathbf{R^{2004}}$ is H or $\mathbf{R^{2003}}$;

wherein **Het** as used herein is defined as a 3- to 7-membered heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, which may be saturated, unsaturated or aromatic, and which is optionally fused to at least one other cycle to form a 4- to 14-membered heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S, said heteropolycycle being saturated, unsaturated or aromatic;

or a salt thereof.

More preferred are compounds of formula I wherein:

n is 1;

m is 2;

R^1 is ethyl or ethenyl;

R^2 is -O-R^{20}, wherein R^{20} is **Het**, said **Het** comprising a heterocycle containing at least one nitrogen heteroatom and being optionally substituted with R^{200}, wherein R^{200} is as defined herein;

R^3 is selected from 1-methylethyl, 1,1-dimethylethyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, cyclopentyl, cyclohexyl, 1-methylcyclopentyl, 1-methylcyclohexyl, cyclopentylmethyl, cyclohexylmethyl, (1-methylcyclopentyl)methyl and (1-methylcyclohexyl)methyl;

R^4 is selected from methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, ethenyl, 1-propenyl, 2-propenyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, naphthyl, **Het**, phenylmethyl, naphthylmethyl and **Het**-methyl;

a) each of which optionally being substituted with one, two or three substituents each independently selected from fluoro and methyl; and

b) each of which optionally being substituted with one or two substituents each independently selected from hydroxy, trifluoromethyl, methoxy, phenoxy and trifluoromethoxy; and

c) each of which optionally being substituted with a substituent selected from chloro, bromo, CF_3, cyano, nitro, -CO-NH_2, -CO-$NHCH_3$, -CO-$N(CH_3)_2$, -NH_2, -$NH(CH_3)$ and -$N(CH_3)_2$;

wherein **Het** is selected from thienyl, furyl, thiazolyl, benzothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, quinolinyl, isoquinolinyl, tetrahydrothienyl, tetrahydrofuryl, thiadiazolyl, isoxazolyl, benzothienyl, piperidinyl, piperazinyl, morpholinyl, triazolyl and tetrazolyl;

or R^4 is selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

a) each of which optionally being substituted with one, two or three fluoro substituents; and

b) each of which optionally being substituted with one or two substituents each independently selected from hydroxy, trifluoromethyl, methoxy and trifluoromethoxy; and

c) each of which optionally being substituted with a substituent selected from chloro, bromo, cyano, nitro, -CO-NH_2, -CO-$NHCH_3$, -CO-$N(CH_3)_2$, -NH_2, -$NH(CH_3)$ and -$N(CH_3)_2$; and

d) each of which being optionally substituted with (C_{1-8})alkyl, wherein the (C_{1-8})alkyl is optionally substituted with one or more substituents each independently selected from -O-(C_{1-6})alkyl, hydroxy, halogen, (C_{2-10})alkenyl, (C_{2-10})alkynyl, (C_{3-7})cycloalkyl, (C_{4-7})cycloalkenyl, aryl, aryloxy, and aryl-(C_{1-4})alkyl-O-, wherein each of the aryl and aryloxy is optionally substituted with (C_{1-6})alkyl;

or $\mathbf{R^4}$ is $-N(\mathbf{R^{N2}})(\mathbf{R^{N1}})$, wherein $\mathbf{R^{N1}}$ and $\mathbf{R^{N2}}$ are each independently selected from H, methyl, ethyl, propyl, 1-methylethyl, methoxy, ethoxy, propoxy, 1-methylethoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and phenylmethyl; wherein the methyl, ethyl, propyl, 1-methylethyl, methoxy, ethoxy, propoxy, 1-methylethoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and phenylmethyl are each optionally substituted with one or more substituents each independently selected from halogen, (C_{1-4})alkyl, hydroxy, cyano, O-(C_{1-4})alkyl, -NH_2, -$NH(C_{1-4})$alkyl, -$N((C_{1-4})alkyl)_2$, -CO-NH_2, -CO-$NH(C_{1-4})$alkyl, -CO-$N((C_{1-4})alkyl)_2$, –COOH, and -$COO(C_{1-4})$alkyl; or $\mathbf{R^{N2}}$ and $\mathbf{R^{N1}}$ are linked, together with the nitrogen to which they are bonded, to form a 3-, 4-, 5- or 6-membered monocyclic saturated or unsaturated heterocycle, optionally containing from one to three additional heteroatoms each independently selected from N, S and O, and optionally substituted with one, two or three substituents each independently selected from halogen, (C_{1-4})alkyl, hydroxy, cyano, O-(C_{1-4})alkyl, -NH_2, -$NH(C_{1-4})$alkyl, -$N((C_{1-4})alkyl)_2$, -CO-NH_2, -CO-$NH(C_{1-4})$alkyl, -CO-$N((C_{1-4})alkyl)_2$, –COOH, and -$COO(C_{1-4})$alkyl;

$\mathbf{R^5}$ is (C_{2-8})alkyl, (C_{3-6})cycloalkyl or phenyl, each of which being optionally substituted with one or two methyl substituents; and

Y is H;

with the proviso that when

$\mathbf{R^4}$ is selected from methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, naphthyl, pyridinyl, phenylmethyl, naphthylmethyl and pyridinylmethyl;

a) each of which optionally being substituted with one, two or three substituents each independently selected from fluoro and methyl; and

b) each of which optionally being substituted with one or two substituents each independently selected from hydroxy, trifluoromethyl, methoxy, and trifluoromethoxy; and

c) each of which optionally being substituted with a substituent selected from chloro, bromo, CF_3, cyano, nitro, -CO-NH_2, -CO-$NHCH_3$, -CO-$N(CH_3)_2$, -NH_2, -$NH(CH_3)$ and -$N(CH_3)_2$; or

R^4 is selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

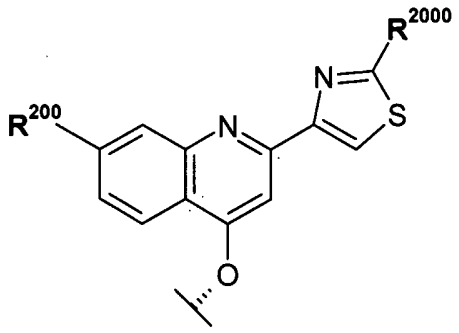
a) each of which optionally being substituted with one or more fluoro substituents; and

b) each of which optionally being substituted with one or more substituents each independently selected from hydroxy, trifluoromethyl, methoxy and trifluoromethoxy; and

c) each of which optionally being monosubstituted with a substituent selected from chloro, bromo, cyano, nitro, -CO-NH_2, -CO-$NHCH_3$, -CO-$N(CH_3)_2$, -NH_2, -$NH(CH_3)$ and -$N(CH_3)_2$; and

d) each of which being optionally substituted with (C_{1-4})alkyl, wherein said (C_{1-4})alkyl is optionally substituted with halogen;

then R^2 cannot be



;

wherein

R^{200} is -O-(C_{1-4})alkyl, -NH(C_{1-4})alkyl, or -N$((C_{1-4})alkyl)_2$; and

R^{2000} is R^{2003} or -N(R^{2002})(R^{2001}); wherein

R^{2001} is selected from -C(O)-R^{2003}, –C(O)O-R^{2003}, -CON(R^{2002})(R^{2004}) and R^{2004};

R^{2002} in each case is independently selected from H and methyl;

R^{2003} is (C_{1-8})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein said (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-(C_{1-4})alkyl- are optionally

substituted with one to three (C_{1-3})alkyl substituents; and

R^{2004} is H or R^{2003};

wherein **Het** as used herein is defined as a 3- to 7-membered heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, which may be saturated, unsaturated or aromatic, and which is optionally fused to at least one other cycle to form a 4- to 14-membered heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S, said heteropolycycle being saturated, unsaturated or aromatic;

or a salt thereof.

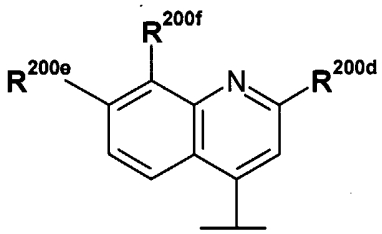
Most preferred are compounds of formula I wherein:

n is 1;

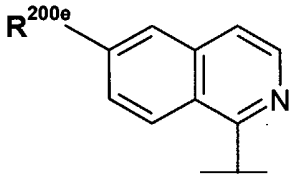
m is 2;

R^1 is ethenyl;

R^2 is -O-R^{20}, wherein R^{20} is **Het**, wherein **Het** is a group selected from:



and



wherein

R^{200d} is H or -OR^{201}, wherein R^{201} is (C_{1-6})alkyl;

R^{200e} is H or -OR^{201}, wherein R^{201} is (C_{1-6})alkyl; and

R^{200f} is H, (C_{1-6})alkyl, halogen, -OR^{201}, -SR^{201} or -SOR^{201}, wherein R^{201} is (C_{1-6})alkyl;

R^3 is 1,1-dimethylethyl;

R^4 is cyclopropyl, 1-methylcyclopropyl or $-N(CH_3)_2$;

R^5 is selected from 1,1-dimethylethyl, cyclopentyl and phenyl; and

Y is H;

or a salt thereof.

Examples of preferred compounds according to this invention are each single compound contained in Table 1.

As discussed above, included within the scope of this invention is a pharmaceutical composition comprising an anti-hepatitis C virally effective amount of a compound of formula I, or a pharmaceutically acceptable salt or ester thereof, and at least one pharmaceutically acceptable carrier medium or auxiliary agent.

According to a further aspect of this embodiment the pharmaceutical composition according to this invention further comprises a therapeutically effective amount of at least one other antiviral agent.

According to an alternate embodiment, the pharmaceutical composition of this invention may additionally comprise at least one other anti-HCV agent. Examples of anti-HCV agents include, but are not limited to, α- (alpha), β- (beta), δ- (delta), γ- (gamma), ω- (omega) and tau-interferon, pegylated α-interferon, ribavirin and amantadine.

According to another alternate embodiment, the pharmaceutical composition of this invention may additionally comprise at least one other inhibitor of HCV NS3 protease.

According to another alternate embodiment, the pharmaceutical composition of this invention may additionally comprise at least one inhibitor of HCV polymerase.

According to yet another alternate embodiment, the pharmaceutical composition of this invention may additionally comprise at least one inhibitor of other targets in the HCV life cycle, including but not limited to, an agent that inhibits a target selected from a helicase, an NS2/3 protease and an internal ribosome entry site (IRES) and an agent that interferes with the function of an NS5A protein.

The pharmaceutical composition of this invention may be administered orally, parenterally or via an implanted reservoir. Oral administration or administration by injection is preferred. The pharmaceutical composition of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein

includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, and intralesional injection or infusion techniques.

The pharmaceutical composition may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example Tween 80) and suspending agents.

The pharmaceutical composition of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

Other suitable vehicles or carriers for the above noted formulations and compositions can be found in standard pharmaceutical texts, e.g. in "Remington's Pharmaceutical Sciences", The Science and Practice of Pharmacy, 19th Ed. Mack Publishing Company, Easton, Penn., (1995).

Dosage levels of between about 0.001 and about 100 mg/kg body weight per day, preferably between about 0.01 and about 50 mg/kg body weight per day of the protease inhibitor compound described herein are useful in a monotherapy for the treatment of HCV mediated disease. Typically, the pharmaceutical composition of this invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. 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. A typical preparation will contain from about

5% to about 95% active compound (*w/w*). Preferably, such preparations contain from about 20% to about 80% active compound.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the peptide. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

When the composition of this invention comprises a combination of a compound of formula I, including a pharmaceutically acceptable salt thereof, and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

When these compounds or their pharmaceutically acceptable salts are formulated together with a pharmaceutically acceptable carrier, the resulting composition may be administered *in vivo* to mammals, such as man, to inhibit HCV NS3 protease or to treat HCV virus infection. Such treatment may also be achieved using a compound of this invention in combination with another antiviral agent. Preferred other antiviral agents are described within the Definitions section and the section of preferred pharmaceutical compositions according to this invention and include, but are not limited to: α-, β-, δ-, ω-, γ-and tau-interferon, ribavirin, amantadine; other inhibitors of HCV NS3 protease; inhibitors of HCV polymerase; inhibitors of other targets in the HCV life cycle, which include but are not limited to, agents that inhibit a target selected from a helicase, an NS2/3 protease and an internal ribosome entry site

(IRES) and agents that interfere with the function of an NS5A protein; or combinations thereof. The additional agents may be combined with compounds of this invention to create a single dosage form. Alternatively these additional agents may be separately administered to a mammal as part of a multiple dosage form.

Accordingly, another embodiment of this invention provides a method of inhibiting HCV NS3 protease activity in a mammal by administering a compound of the formula (I), including a pharmaceutically acceptable salt thereof.

In a preferred embodiment, this method is useful in decreasing the NS3 protease activity of the hepatitis C virus infecting a mammal.

As discussed above, combination therapy is contemplated wherein a compound of formula (I), or a pharmaceutically acceptable salt thereof, is co-administered with at least one additional antiviral agent. Preferred antiviral agents are described hereinbefore and examples of such agents are provided in the Definitions section. These additional agents may be combined with the compounds of this invention to create a single pharmaceutical dosage form. Alternatively these additional agents may be separately administered to the patient as part of a multiple dosage form, for example, using a kit. Such additional agents may be administered to the patient prior to, concurrently with, or following the administration of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

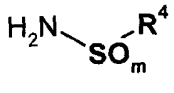
A compound of formula (I), or a pharmaceutically acceptable salt thereof, set forth herein may also be used as a laboratory reagent. Furthermore a compound of this invention, including a pharmaceutically acceptable salt thereof, may also be used to treat viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials (e.g. blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection apparatuses and materials).

A compound of formula (I), including a pharmaceutically acceptable salt thereof, set forth herein may also be used as a research reagent. A compound of formula (I), including a pharmaceutically acceptable salt thereof, may also be used as positive

control to validate surrogate cell-based assays or *in vitro* or *in vivo* viral replication assays.

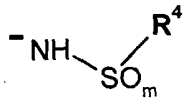
In a further aspect of this invention is provided a process for the preparation of compounds of formula (I) comprising the steps of:

a) reacting a compound of formula (II):



(II)

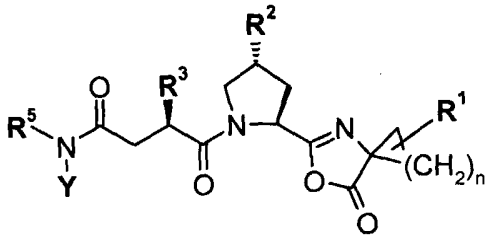
wherein R^4 and **m** are as defined herein, with a strong base so as to form the corresponding amide anion of formula (IIa)



(IIa)

and

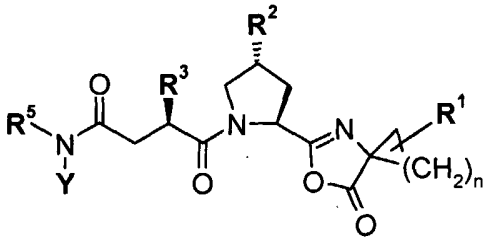
b) reacting an azalactone of formula (III):



(III)

wherein **Y**, R^1, R^2, R^3, R^5 and **n** are as defined herein, with the amide anion of formula IIa. The strong base referred to in step a) is well known to one skilled in the art and includes, but is not limited to, an alkyllithium reagent (including, but not limited to, butyllithium, *tert*-butyllithium and the like) and the alkali metal salt of a secondary amine or silyl analog thereof (including, but not limited to, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, lithium diisopropylamide, lithium N-isopropylcyclohexylamide, lithium tetramethylpiperidide, potassium diisopropylamide, and the like).

In yet a further aspect of this invention is provided an intermediate azalactone of formula (III):



(III)

wherein **Y**, R^1, R^2, R^3, R^5 and **n** are as defined herein.

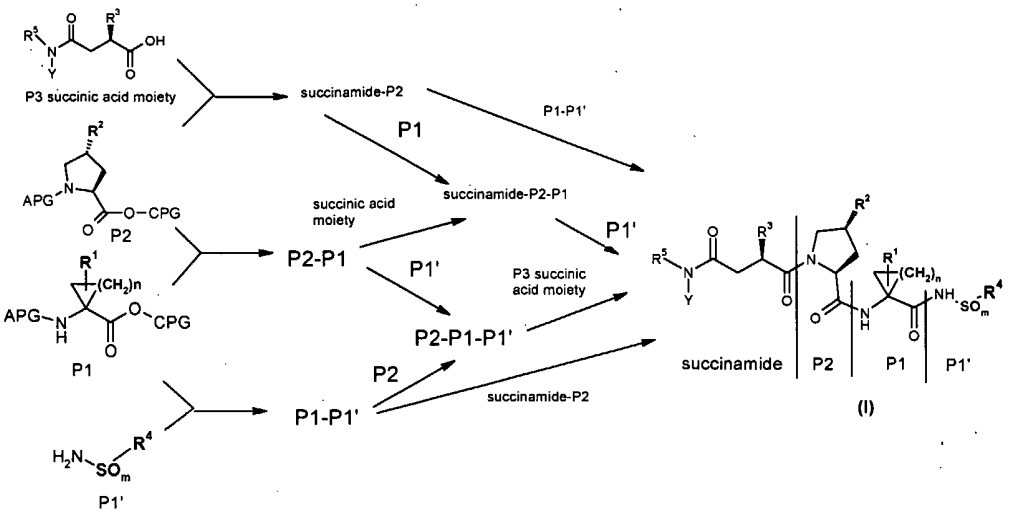
A further aspect of this invention is the use of the intermediate azalactone of formula III as described hereinbefore in the preparation of an HCV NS3 protease inhibitor peptide analog.

Still another aspect of this invention is the use of the intermediate azalactone of formula (III) as described hereinbefore in the preparation of a compound of formula (I) as described herein.

METHODOLOGY

The compounds of the present invention are synthesized according to a general process wherein the P3 succinic acid, P2, P1, and P1' fragments can be linked by well known peptide coupling techniques. The P3 succinic acid, P2, P1, and P1' fragments may be linked together in any order as long as the final compound corresponds to compounds of formula (I), wherein **Y**, R^1, R^2, R^3, R^5, **m**, **n** and R^4 are as defined herein. This process is illustrated in **Scheme I** (wherein **CPG** is a carboxyl protecting group and **APG** is an amino protecting group).

SCHEME I



The P2 fragment is generally formed by attaching the R^2 moiety to the proline fragment using methodology as described in the examples below. This attachment may take place at any stage in this synthetic scheme, i.e., when P2 is an isolated fragment or when it has already been coupled to P1 or P1-P1'. In cases where the R^2 moiety is to be added at an intermediate stage after coupling to the P1 and/or P1-P1' fragments, the P2 fragment shown above is replaced with a suitable precursor fragment for the purposes of this scheme.

Generally, peptides are elongated by deprotecting the α-amino group of the N-terminal residue and coupling the unprotected carboxyl group of the next suitably N-protected amino acid through a peptide linkage using well known methods. This deprotection and coupling procedure is repeated until the desired sequence is obtained. This coupling can be performed with the constituent amino acid fragments in stepwise fashion or by solid phase peptide synthesis according to the method originally described in Merrifield, J. Am. Chem. Soc., (1963), 85, 2149-2154.

Coupling between two amino acids, an amino acid and a peptide, or two peptide fragments can be carried out using standard coupling procedures such as the azide method, mixed carbonic-carboxylic acid anhydride (isobutyl chloroformate) method, carbodiimide (dicyclohexylcarbodiimide, diisopropylcarbodiimide, or water-soluble carbodiimide) method, active ester (p-nitrophenyl ester, N-hydroxysuccinic imido ester) method, Woodward reagent K-method, carbonyldiimidazole method,

phosphorus reagents or oxidation-reduction methods. Some of these methods (especially the carbodiimide method) can be enhanced by adding 1-hydroxybenzotriazole. These coupling reactions can be performed in either solution (liquid phase) or solid phase.

More explicitly, the coupling step involves the dehydrative coupling of a free carboxyl of one reactant with the free amino group of the other reactant in the presence of a coupling agent to form a linking amide bond. Descriptions of such coupling agents are found in general textbooks on peptide chemistry, for example, M. Bodanszky, "Peptide Chemistry", 2nd rev ed., Springer-Verlag, Berlin, Germany, (1993). Examples of suitable coupling agents are N,N'-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole in the presence of N,N'-dicyclohexylcarbodiimide or N-ethyl-N'-[(3-dimethylamino)propyl]carbodiimide. A practical and useful coupling agent is the commercially available (benzotriazol-1-yloxy)tris-(dimethylamino)-phosphonium hexafluorophosphate, either by itself or in the presence of 1-hydroxybenzotriazole. Another practical and useful coupling agent is commercially available 2-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate. Still another practical and useful coupling agent is commercially available O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate.

The coupling reaction is conducted in an inert solvent, e.g. dichloromethane, acetonitrile or dimethylformamide. An excess of a tertiary amine, e.g. diisopropylethylamine, N-methylmorpholine or N-methylpyrrolidine, is added to maintain the reaction mixture at a pH of about 8. The reaction temperature usually ranges between 0°C and 50°C and the reaction time usually ranges between 15 min and 24 h.

When a solid phase synthetic approach is employed, the C-terminal carboxylic acid is attached to an insoluble carrier (usually polystyrene). These insoluble carriers contain a group that will react with the carboxylic group to form a bond that is stable to the elongation conditions but readily cleaved later. Examples of which are: chloro- or bromomethyl resin, hydroxymethyl resin, trityl resin and 2-methoxy-4-alkoxy-benzylalcohol resin.

Many of these resins are commercially available with the desired C-terminal amino acid already incorporated. Alternatively, the amino acid can be incorporated on the solid support by known methods (Wang, S.-S., J. Am. Chem. Soc., (1973), 95, 1328; Atherton, E.; Shepard, R.C. "Solid-phase peptide synthesis; a practical approach" IRL Press: Oxford, (1989); 131-148). In addition to the foregoing, other methods of peptide synthesis are described in Stewart and Young, "Solid Phase Peptide Synthesis", 2nd ed., Pierce Chemical Co., Rockford, IL (1984); Gross, Meienhofer, Udenfriend, Eds., "The Peptides: Analysis, Synthesis, Biology", Vol. 1, 2, 3, 5, and 9, Academic Press, New-York, (1980-1987); Bodansky et al., "The Practice of Peptide Synthesis" Springer-Verlag, New-York (1984) in the literature.

EXAMPLES

The present invention is illustrated in further detail by the following non-limiting examples.

Temperatures are given in degrees Celsius. Solution percentages express a weight to volume relationship, and solution ratios express a volume to volume relationship, unless stated otherwise. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. Flash chromatography was carried out on silica gel (SiO_2) according to Still's flash chromatography technique (W.C. Still et al., J. Org. Chem., (1978), 43, 2923). Analytical HPLC was carried out under standard conditions using a Combiscreen ODS-AQ C18 reverse phase column, YMC, 50 x 4.6 mm i.d., 5 µM, 120 Å at 220 nM, elution with a linear gradient as described in the following table (Solvent A is 0.06% TFA in H_2O; solvent B is 0.06% TFA in CH_3CN):

Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0	3.0	95	5
0.5	3.0	95	5
6.0	3.0	50	50
10.5	3.5	0	100

Abbreviations used in the examples include

AcOH: acetic acid;

Bn: benzyl;

Boc: *tert*-butyloxycarbonyl {Me_3C-O-C(O)};

brosyl: *p*-bromobenzenesulfonyl;

CDI: N,N'-Carbonyldiimidazole;

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene;

DCC: 1,3-dicyclohexylcarbodiimide;

DCM: dichloromethane;

DIPEA: diisopropylethylamine;

DMAP: 4-dimethylaminopyridine;

DME: 1,2-dimethoxyethane;

DMF: dimethylformamide;

DMSO: dimethylsulfoxide;

EDTA: ethylenediaminetetraacetic acid;

Et: ethyl;

EtOH: ethanol;

EtOAc: ethyl acetate;

Et_2O: diethyl ether;

HATU: [O-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate];

HPLC: high performance liquid chromatography;

IBCF: *iso*-butyl chloroformate;

LAH: lithium aluminum hydride;

LHMDS: lithium hexamethyldisilazide;

Me: methyl;

MeOH: methanol;

MS: mass spectrometry;

NaHMDS: sodium hexamethyldisilazide;

NMO: N-methylmorpholine-N-oxide;

NMP: N-methylpyrrolidone (1-methyl-2-pyrrolidinone);

Pr: propyl;

t_R: retention time;

TBAF: tetra-*n*-butylammonium fluoride;

TBDMSCl: *tert*-butyldimethylsilyl chloride;

TBTU: 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate;

TEA: triethylamine;

TFA: trifluoroacetic acid;

THF: tetrahydrofuran;

TPAP: tetra-*n*-propylammonium perruthenate;

Tris/HCl: tris(hydroxymethyl)aminomethane hydrochloride;

Ts: tosyl (p-methylbenzenesulfonyl)

RT: room temperature.

Synthesis of P1 fragments

The preparation, separation and identification of the stereoisomers of the **P1** fragments of compounds of Formula (I) were prepared using the protocols outlined in WO 00/59929, published October 12, 2000, and WO 00/09543, published on February 24, 2000. In particular, reference is made to pages 33-35, Example 1 of WO00/59929 and pages 56-69 , Example 9 – 20 of WO00/09543 for the preparation of 1-aminocyclopropylcarboxylic acid **P1** moieties.

Synthesis of P2 fragments

Generally, **P2** moieties of compounds of Formula (I) can be prepared using the protocols outlined in WO 00/59929, WO 00/09543, WO 03/064456 and WO 03/064416.

R^2 moieties of compounds of formula 1 are either commercially available, have been described previously in the literature or are synthesized according to methods provided in the examples below. General methods for the synthesis of some of these fragments are described in WO 00/59929, WO 00/09543, WO 03/064456 and WO 03/064416 and more specific and pertinent examples are provided below.

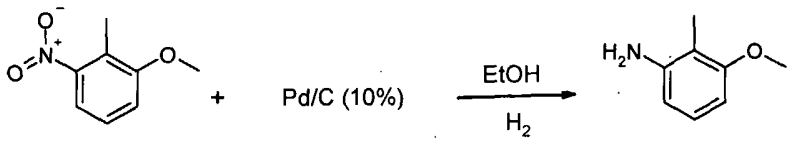
General methods for the introduction of the R^2 substituent on the proline to produce the required 4-substituted proline where R^{20} is attached to the proline ring via an oxygen (-O-) or a sulfur (-S-), can be carried out as described in WO 00/59929, WO 00/09543, WO 03/064456 and WO 03/064416. Other analogs can also be synthesized using this methodology.

Preparation of P2 aniline moieties

The corresponding anilines in P2 fragments are commercially available or may require some well known chemical transformation. For example it can be that the nitro is

commercially available and is then converted to the corresponding amine by using a reducing agent. Also when the carboxylic acid is commercially available, it can be transformed into the corresponding amine via a Curtius rearrangement.

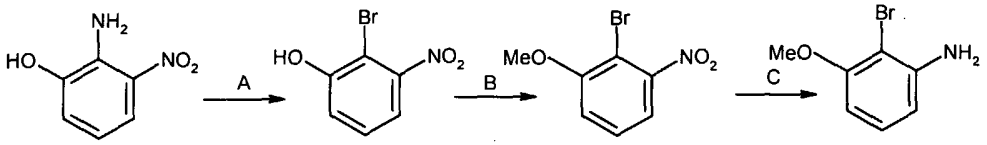
EXAMPLE 1A - SYNTHESIS OF P2 BULIDING BLOCK 2-METHYL-3-METHOXY ANILINE (1A2)



1a1 1a2

To a solution of 2-methyl-3-nitro anisole which is commercially available (**1a1**) (5.1 g; 30.33 mmol; requires ~30 min. to dissolve) in absolute ethanol (85 mL) was added 10% Pd/C catalyst (500 mg) . The solution was hydrogenated under a hydrogen filled balloon at atmospheric pressure and room temperature for 19 h. The reaction mixture was filtered through a Celite pad, rinsed and evaporated to dryness to obtain the compound **1a2** as a deep mauve oil (4.1 g; 29.81 mmol; 98% yield). MS 137 (MH)+. Reverse Phase HPLC Homogeneity @ 220nm (0.06 % TFA;CH_3CN;H_2O): 99%.

EXAMPLE 1B - SYNTHESIS OF P2 MOIETY 2-BROMO-3-METHOXY ANILINE (1B4)



1b1 1b2 1b3 1b4

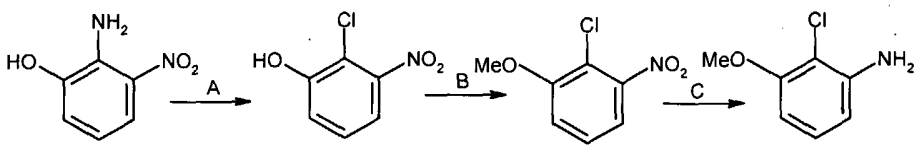
Step A: 2-Amino-3-nitrophenol **1b1** (5 g; 32.4 mmol) was dissolved in H_2O (29.5 mL) and 1,4-dioxane (14.7 mL). The mixture was heated to reflux and hydrobromic acid (48%; 16.7 mL; 147 mmol) was added dropwise over a period of 20 min. Upon completion of the addition, the reflux was maintained an additional 15 min. The reaction was cooled to 0°C (ice bath), and sodium nitrite (2.23 g; 32.3 mmol) in H_2O (20 mL) was added over a period of 30 min. The stirring was continued for 15 min. at 0°C, the mixture transferred to a jacketed dropping funnel (0°C) and added dropwise to a stirred mixture of Cu(I)Br (5.34 g; 37.2 mmol) in H_2O (29.5 mL) and HBr (48%; 16.7 mL; 147 mmol) at 0°C. The reaction was stirred for 15 min. at 0°C, warmed to 60°C, stirred for an additional 15 min., cooled to room temperature, and left to stir overnight. The reaction mixture was transferred to a separatory funnel and extracted with ether (3 X 150 mL). The organic layers were combined, washed with brine (1 X),

dried (Na_2SO_4), filtered and concentrated to afford the crude product (7.99 g) as a red-brown oil. The crude material was purified by flash column chromatography (1:25 ultra pure silica gel, 230-400 mesh, 40-60mm, 60 angstroms; CH_2Cl_2 as the solvent) to afford pure 2-bromo-3-nitrophenol **1b2** (45%; 3.16 g) as an orange-brown solid. MS 217.8 $(MH)^-$. Homogeneity by HPLC (TFA) @ 220 nm: 97%.

Step B: The nitrophenol starting material **1b2** (3.1 g; 14.2 mmol) was dissolved in DMF (20 mL) and to the solution was added ground cesium carbonate (5.58 g; 17.1 mmol) followed by MeI (2.6 mL; 42.5 mmol). The mixture was stirred at room temperature overnight. The DMF was evaporated, the residue taken up in ether (1 X 200 mL), washed with water (1 X 200 mL), brine (4 X 100 mL), dried ($MgSO_4$), filtered and evaporated to afford the crude 2-bromo-3-nitroanisole **1b3** (94%; 3.1 g) as an orange solid.MS 234 $(M+2H)^+$; Homogeneity by HPLC (TFA) @ 220nm: 98%

Step C: 2-Bromo-3-nitroanisole **1b3** (1.00 g; 4.31 mmol) was dissolved in glacial acetic acid (11.0 mL)/ethanol (11.0 mL) and to the solution was added iron powder (0.98 g; 17.5 mmol). The mixture was stirred at reflux for 3.5 hr and worked up. The reaction mixture was diluted with water (35 mL), neutralized with solid Na_2CO_3 and the product extracted with CH_2Cl_2(3X 50 mL). The extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product, 2-bromo-3 methoxyaniline **1b4** (91%; 0.79 g) as a pale yellow oil. MS 201.8 $(MH)^+$; Homogeneity by HPLC (TFA) @ 220nm: 95%

EXAMPLE 1C - SYNTHESIS OF P2 MOIETY 2-CHLORO-3-METHOXY ANILINE (1C3):



1b1 1c1 1c2 1c3

Step A: 2-Amino-3-nitrophenol **1b1** (5 g; 32.4 mmol) was dissolved in concentrated HCl (75 mL) and 1,4-dioxane (14.7 mL). The mixture was heated to 70°C until most of the solids were in solution. The reaction mixture was cooled to 0°C (ice bath), and sodium nitrite (2.23 g; 32.3 mmol) in H_2O (5.4 mL) was added over a period of 3 hours to the brown solution. The temperature was maintained below 10°C during the addition and the stirring was continued for an additional 15 min. at 0°C. This diazonium intermediate was poured into a solution of Cu(I)Cl (3.8 g; 38.9 mmol) in H_2O (18.5 mL) and conc. HCl (18.5 mL) at 0°C. The reaction was stirred for 15 min. at

0°C, warmed to 60°C, and stirred for an additional 15 min. The reaction mixture was then brought to room temperature, and left to stir overnight. The reaction mixture was transferred to a separatory funnel and extracted with ether (3 X 150 mL). The organic layers were combined, washed with brine (1 X), dried (Na_2SO_4), filtered and concentrated to afford the crude product (5.83 g) as a red-brown oil. The crude material was purified by flash column chromatography (1:25 ultra pure silica gel, 230-400 mesh, 40-60mm, 60 angstroms; 3:1 hexane/EtOAc as the solvent) to afford pure 2-chloro-3-nitrophenol **1c1** (48%; 2.7 g) as an orange solid. MS 171.8 $(MH)^-$: Homogeneity by HPLC (TFA) @ 220 nm: 96% .

Relevant literature for the Sandmeyer Reaction: *J. Med. Chem*, **1982**, 25(4), 446-451.

Step B: The nitrophenol starting material **1c1** (1.3 g; 7.49 mmol) was dissolved in DMF (10 mL) and to this solution was added ground cesium carbonate (2.92 g; 8.96 mmol), followed by MeI (1.4 mL; 22.5 mmol). The mixture was stirred at room temperature overnight. The DMF was evaporated in *vacuo* and the residue taken up in ether (150 mL), washed with water (150 mL), brine (4 X 100 mL), and then dried over ($MgSO_4$). The organic phase was filtered and evaporated to afford the crude 2-chloro-3-nitroanisole **1c2** (98%; 1.38 g) as an orange solid.
Homogeneity by HPLC (TFA) @ 220nm: 93%.

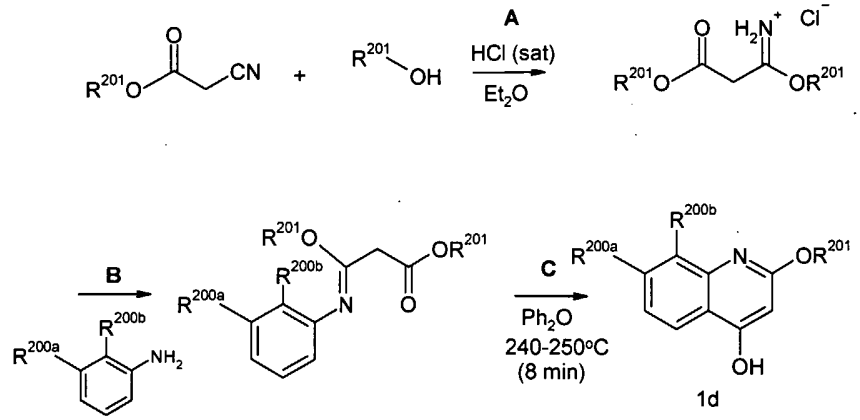
Step C: 2-Chloro-3-nitroanisole **1c2** (1.38 g; 7.36 mmol) was dissolved in a mixture of glacial acetic acid (19 mL)/ethanol (19 mL). To this solution was added iron powder (1.64 g; 29.4 mmol). The mixture was stirred at reflux for 3.5 hr and worked up. The reaction mixture was diluted with water (70 mL), neutralized with solid Na_2CO_3 and the product extracted with CH_2Cl_2 (3 X 150 mL). The extracts were combined and washed with sat. brine and then dried over (Na_2SO_4), filtered and concentrated in *vacuo* to afford the crude product, 2-chloro-3-methoxyaniline **1c3** (100%; 1.2 g) as a yellow oil. This material was used as such in the following steps. MS 157.9 $(MH)^+$; Homogeneity by HPLC (TFA) @ 220nm: 86%.

Preparation of P2 quinoline moieties

EXAMPLE 1D - GENERAL PROTOCOL FOR THE PREPARATION OF 2-ALKOXY SUBSTITUTED 4-HYDROXYQUINOLINES (1D):

The following P2 hydroxyquinoline moieties bearing an alkoxy group (OR^{201}) at the 2-position, wherein R^{200a} and R^{200b} are each independently selected from R^{200} wherein

R^{200} is as defined herein can be prepared according to the following scheme:

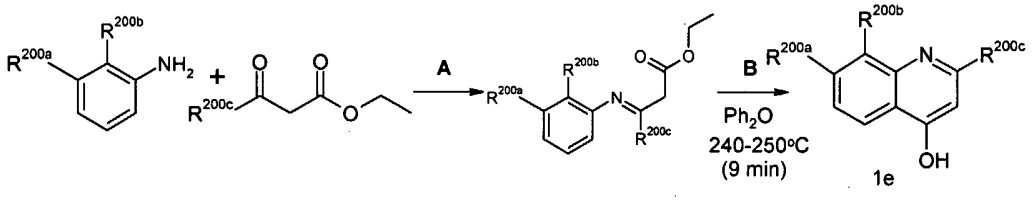


Briefly, following the known Pinner synthesis, a suitably functionalized cyanoester is condensed with the corresponding alcohol using a fully saturated HCl/Et_2O solution [Neilson, in Patai, "The Chemistry of Amidines and Imidates." pp. 385-489, Wiley, NY, 1975.]. The resulting imidate salt is then subsequently condensed with an appropriately substituted aniline to form the aniline derived imidate. Thermal cyclization affords the corresponding 2-alkoxy substituted 4-hydroxyquinolines **1d**.

For example, when R^{201} is Et in the above scheme, ethyl cyanoacetate and ethanol are used as reagents. When R^{201} is Me in the above scheme, methyl cyanoacetate and methanol are used as reagents.

EXAMPLE 1E - GENERAL PROTOCOL FOR THE PREPARATION OF 2-ALKYL SUBSTITUTED 4-HYDROXYQUINOLINES (1E):

The following P2 hydroxyquinoline moieties where R^{200c} of the β-ketoester moiety is an alkyl group and wherein R^{200a} and R^{200b} are each independently selected from R^{200} wherein R^{200} is as defined herein can be prepared according to the following scheme:

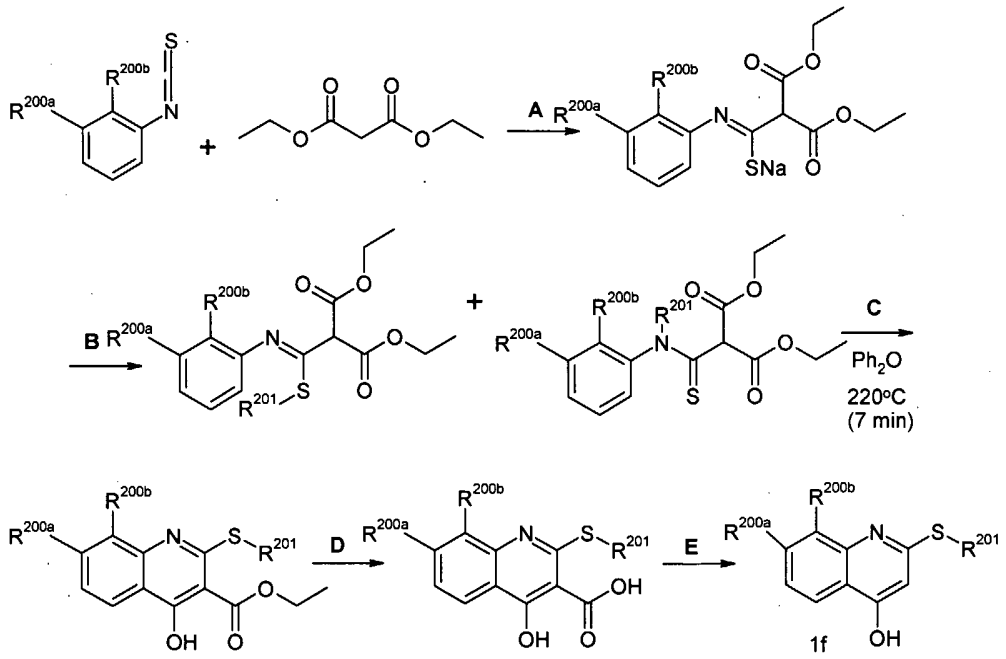


Briefly, appropriately substituted β-ketoesters are condensed with substituted anilines and subsequently thermally cyclized to afford the corresponding 2-alkyl substituted

hydroxyquinolines **1e**. For example, when the initial condensation reaction with the aniline (step A) is performed with the corresponding methyl ketone, a methyl group is incorporated in the 2-position of the resulting hydroxyquinoline.

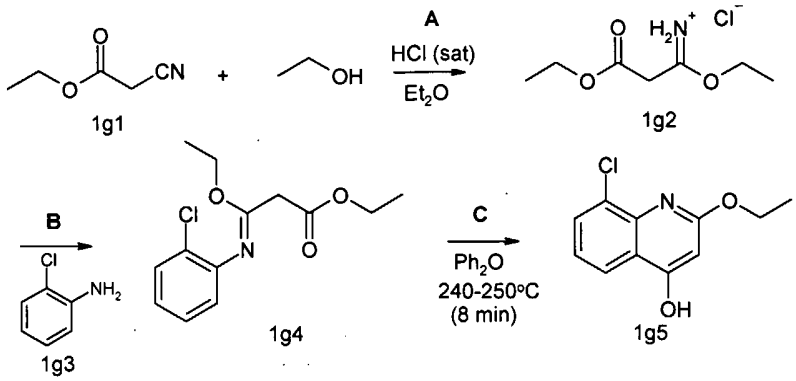
EXAMPLE 1F - GENERAL PROTOCOL FOR THE PREPARATION OF 2-ALKYLTHIO SUBSTITUTED 4-HYDROXYQUINOLINES (1F):

In general, various P2 hydroxyquinolines having a 2-alkylthio group (SR^{201} wherein R^{201} is (C_{1-6})alkyl at the 2-position wherein R^{200a} and R^{200b} are each independently selected from R^{200} wherein R^{200} is as defined herein were prepared as shown in the following scheme:



Briefly, condensation of diethyl malonate under basic conditions with a suitably functionalized isothiocyanate produces the malonate adduct as a salt. Treatment of the salt with an alkylating reagent (e.g. EtI) produces a mixture of S- and N-alkylated products. Thermal cyclization of this mixture gives the 3-ethyl carboxylate which is saponified and decarboxylated to produce the desired 2-alkylthio substituted hydroxyquinolines **1f**. For example, utilization of EtI in the alkylation step results in the formation of the 2-ethylthio analog.

EXAMPLE 1G - SYNTHESIS OF P2 MOIETY 2-ETHOXY-4-HYDROXY-8-CHLOROQUINOLINE (1G5)

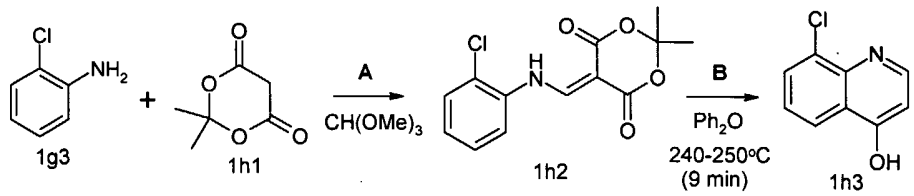


Step A: To ethyl cyanoacetate **1g1** (23 g, 0.203 mol) was added absolute ethanol (10 g, 12.7 mL, 0.22 mol) in diethyl ether (20 mL). The solution was cooled to 0°C in an ice bath before being treated with HCl gas (bubbled through solution for 12 minutes resulted in an increase in weight of 12 g (~0.33mol)). This solution was stirred at 0°C for 6 h and then allowed to warm to RT and was stirred for 16 h. The resultant solid was broken up and washed several times with ether and then placed in *vacuo* for several hours. The imidate salt **1g2** was obtained as a white solid (36.4 g, 92%) and was stored under a nitrogen atmosphere. The ^{1}H NMR was consistent with the desired product.

Step B: The imidate salt **1g2** (1.47 g, 7.5 mmol, 1 eq.) was combined with 2-chloroaniline **1g3** (0.96 g, 7.50 mmol, 1 eq.) in ethanol (15 mL) under an N_2 atmosphere. The reaction mixture was stirred at RT (16 h) and monitored by HPLC. The reaction mixture was concentrated and then purified directly over silica gel (eluent: 10% EtOAc/Hexanes) to afford the condensation product **1g4** as a clear oil (1.73 g, 86%). MS electrospray: $(MH)^+$; 270 and $(M - H)^-$; 268. TLC (UV) Rf = 0.50 (10% EtOAc/hexane).

Step C: The condensation product **1g4** (1.73 g, 6.41 mmol) was dissolved in diphenyl ether (10 mL) and placed in a sand bath (300°C). The internal temperature was monitored and allowed to stay between 240-250°C for 8 minutes. The mixture was cooled and then directly loaded on a silica gel column and eluted first with hexanes, then with 30% EtOAc/Hexanes and finally 50% EtOAc/hexanes. The product was concentrated and dried in *vacuo* to give the corresponding 4-hydroxyquinoline derivative **1g5** as a beige crystalline solid (0.76 g, 53%). MS electrospray: $(M + H)^+$; 224 and $(M - H)^-$; 222.

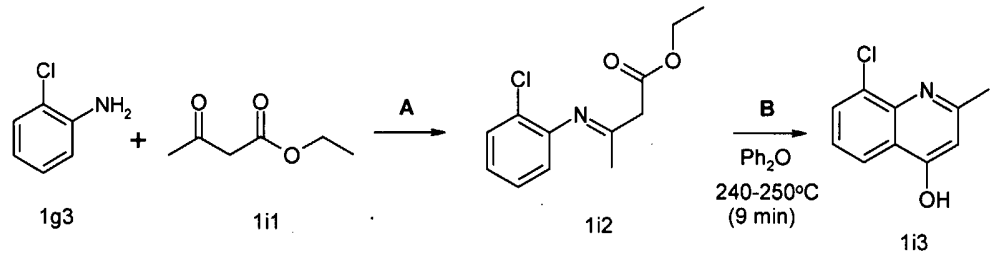
EXAMPLE 1H - SYNTHESIS OF P2 MOIETY 4-HYDROXY-8-CHLOROQUINOLINE 1H3



Step A: To 2-chloroaniline **1g3** (1.6 mL, 15.2 mmol, 1 eq) dissolved in anhydrous acetonitrile (50 mL) at RT was added Meldrum's acid **1h1** (2.41 g, 16.73 mmol, 1.1 eq), followed by trimethyl orthoformate (2.0 mL, 18.25 mmol, 1.2 eq). The resulting mixture was heated to reflux (95°C) for 2 h and monitoring by analytical HPLC until complete. The resulting solution was cooled to RT and evaporated to dryness to afford a beige solid that was recrystallized from boiling MeOH. After drying in *vacuo* adduct **1h2** was obtained as a bright yellow solid (2.29 g, 53%).

Step B: In a pre-heated sand bath (300-350°C), diphenyl ether (6 mL) was heated until the internal temperature reached 220°C. Adduct **1h2** (981 mg, 3.48 mmol) was added portionwise over ca. 4 min period (gas evolution) to the heated solvent. The temperature (220°C) was maintained for another 5 min. after which the solution was allowed to cool. Upon cooling, the product crashed out of solution and was filtered and washed with diethyl ether. After drying *in vacuo* (16h), product **1h3** was obtained as a beige solid (417 mg, 67%). MS: $(M + H)^+$; 180.

EXAMPLE 1I - SYNTHESIS OF P2 MOIETY 8-CHLORO-4-HYDROXY-2-METHYLQUINOLINE 2I3

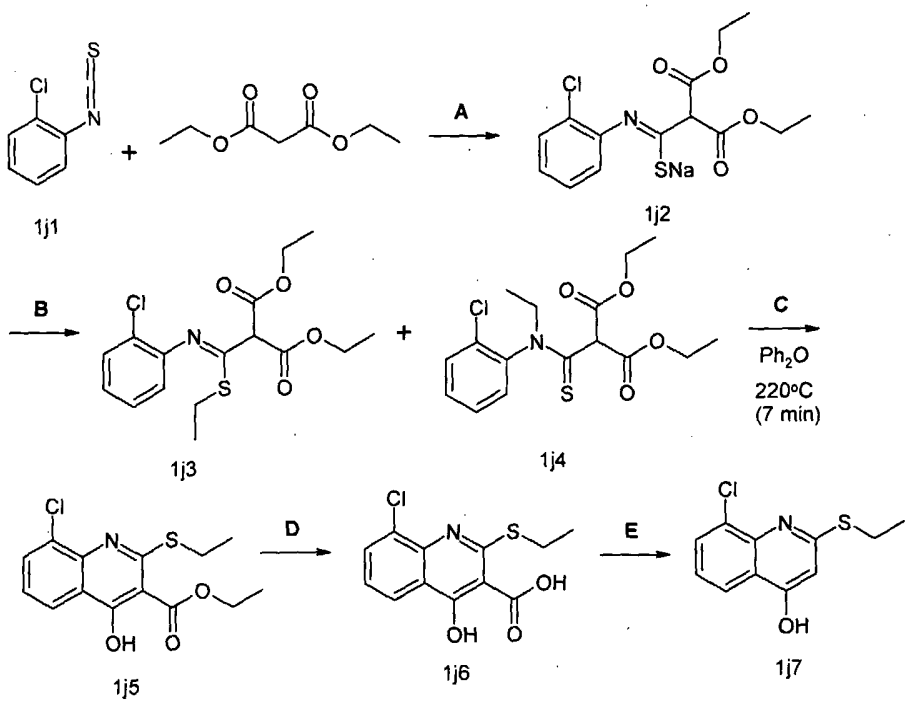


Step A: To a solution of ethyl acetoacetate **1i1** (1.21 mL, 9.51 mmol; 1 eq) in benzene (20 mL) was added 2-chloroaniline **1g3** (1.0 mL; 9.51 mmol; 1eq) followed by catalytic PTSA (13 mg). The reaction flask was equipped with a Dean-Stark apparatus and heated to reflux for 2 hours. The solvent was removed and the residue purified by column chromatography using silica gel (eluent: 10% EtOAc/Hexanes; R_f=0.48) to give compound **1i2** (1.46 g, 64%) as a clear oil. MS: $(M + H)^+$; 240, HPLC

homogeneity = 99.5%.

Step B: In a pre-heated sand bath (300-350°C), compound **1i2** (730 mg, 3.0 mmol) in diphenyl ether (8 mL) was heated until the internal temperature reached 220°C and that temperature was maintained for 7 minutes after which the solution was allowed to cool. Upon cooling, a beige solid crashed out and was filtered and washed with diethyl ether. After drying, the desired quinoline **1i3** was obtained as a beige solid (452 mg, 77%). MS: $(M + H)^+$; 194, HPLC homogeneity = 99%.

EXAMPLE 1J - SYNTHESIS OF P2 MOIETY 2-ETHYLTHIO-8-CHLORO-4-HYDROXYQUINOLINE (1J7):



Step A: To THF (30 mL) was added sodium hydride (60% in oil, 920 mg, 23 mmol, 1.2 eq) before being cooled to 0°C. Diethyl malonate (2.91 mL, 19.15 mmol, 1.0 eq) was then added dropwise (gas evolution) and this solution was allowed to warm to RT and was stirred for 1 hr. This mixture was cooled down to 0°C before the addition of 2-chlorophenyl isothiocyanate **1j1** (2.5 mL, 19.15 mmol, 1.0 eq). The resulting mixture was again allowed to warm to RT for 3 h until the starting material was consumed. The orange solution was concentrated down and dried in *vacuo* to afford the sodium salt adduct **1j2** (6.73 g, 100%) as an orange crystalline solid. This material was used as is for subsequent steps.

Step B: A solution of adduct **1j2** (6.0 g, 17.06 mmol, 1 eq) in DMF (50 mL) was

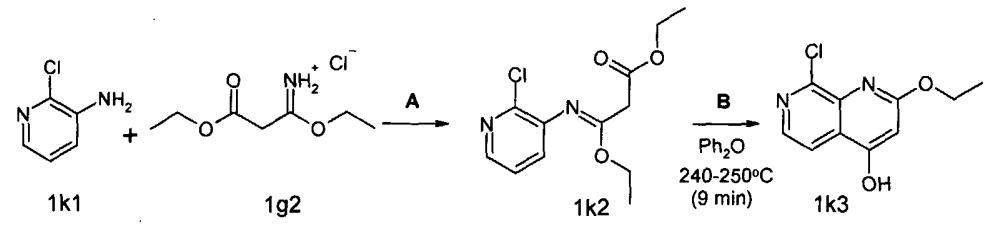
cooled down to -45°C. Ethyl iodide (1.64 mL, 20.5 mmol, 1.2 eq) was then slowly added and the solution was stirred at -45°C for 2 h and then at RT (16 h). Water was added and the mixture was extracted twice with a mixture of ether/hexanes (1:1, 3 X 150 mL). The combined organic fractions were washed with water (2x), dried over $MgSO_4$, filtered and concentrated to afford approximately a 1:1 mixture of **1j3** and **1j4** (S versus N alkylation)(6.1 g, 100%) as a yellow oil. This mixture can be used in the following step since only the S-alkylated analog will cyclize.

Step C: In a pre-heated sand bath (350°C) a solution of compounds **1j3** and **1j4** (6.1 g, 17.05 mmol, 1 eq.) in diphenyl ether (60 mL) was heated until the internal temperature reached 220°C, which was maintained for 7 minutes. The solution was cooled to RT and the mixture loaded directly on a silica gel column, being eluted first with hexanes (1L) to remove the diphenyl ether, and then 3% EtOAc/hexanes to afford the desired quinoline **1j5** (2.76 g, 52%) as a pale yellow solid.

Step D: To a solution of quinoline **1j5** (2.76 g crude; 8.85 mmol; 1 eq) in THF (10 mL) and methanol (10 mL) at RT was added 1N NaOH (45 mL; 45 mmol; 5.1 eq). The reaction was allowed to stir at reflux (85°C) for 24 h (monitored by HPLC). The mixture was acidified using 4N HCl and extracted using methylene chloride (3X). The organic fractions were dried over $MgSO_4$, filtered and concentrated to afford the quinoline acid **1j6** (2.43 g, 97%) as a pale yellow solid. MS: $(M + H)^+$; 284. This material was used as is for the following reaction.

Step E: Compound **1j6** (2.43 g, 8.56 mmol) was added to diphenyl ether (20 mL) and the heterogeneous mixture was heated to 250°C for 12 minutes before being cooled. The mixture was directly transferred to a silica gel column and eluted first with hexanes (to remove diphenyl ether), and then with 30% and 50% EtOAc/hexanes (R_f=0.48 in EtOAC/hexanes (1:1)). Evaporation of the solvent afforded the desired 2-ethylthio-8-chloro-4-hydroxyquinoline **1j7** (1.25 g, 61%) as a pale yellow solid. MS: $(M + H)^+$; 240, HPLC homogeneity = 99%.

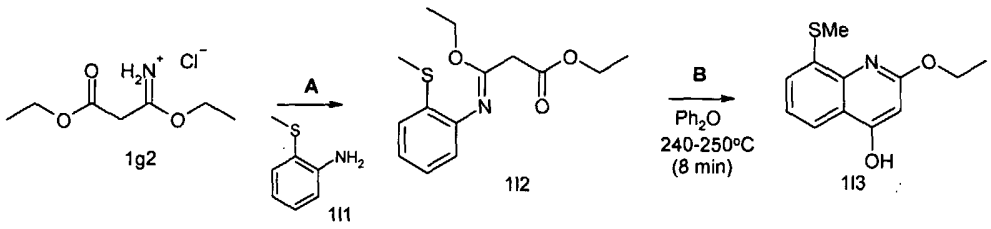
EXAMPLE 1K - SYNTHESIS OF P2 MOIETY 8-CHLORO-2-ETHOXY-4-HYDROXY-1,7-NAPHTHYRIDINE (1K3)



Step A: To 3-amino-2-chloro-pyridine **1k1** (964 mg, 7.5 mmol, 1 eq) was added imidate **1g2** (1.47 g, 7.5 mmol, 1 eq) in ethanol (15 mL) under a N_2 atmosphere. The mixture was stirred at RT for 24 h at which point the reaction was concentrated and purified directly on a silica gel column (eluent: EtOAc/Hexanes (1:9)) to afford adduct **1k2** (1.54 g, 76%) as a clear oil.

Step B: Adduct **1k2** (200 mg, 0.74 mmol) was dissolved in diphenyl ether (5 mL) and placed in a pre-heated sand bath (300°C). The internal temperature was monitored and allowed to stay between 210°C-225°C for 7 minutes. The mixture was directly loaded on a silica gel column and eluted with hexanes to remove diphenyl ether, followed by a gradient of 30% to 50% EtOAc/hexanes: (Rf =0.48 in 1:1 EtOAc/hexanes). Concentration and drying in *vacuo* afforded the desired napthyridine **1k3** (32mg, 19%) as a white solid. MS: 225 (M + H)+.

EXAMPLE 1L - SYNTHESIS OF P2 MOIETY 2-ETHOXY-8-METHYLTHIO-4-HYDROXYQUINOLINE (1L3)

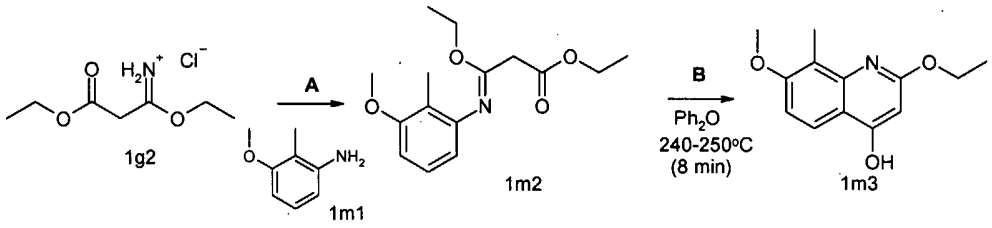


Step A: The imidate salt **1g2**(1.4 g, 7.2 mmol, 1 eq.) was combined with 2-(methylthio)aniline **1l1** (0.96 g, 7.50 mmol, 1 eq.) in ethanol (15 mL) under an N_2 atmosphere. The reaction mixture was stirred at RT (1 h) and monitored by HPLC. The reaction mixture was concentrated and then ether was added and the mixture filtered. The solids were washed with ether and the combined ether washes concentrated *in vacuo*. The resulting adduct **1l2** was obtained as a yellow oil (1.66 g, 82%) and used as is in the next step. MS electrospray: $(M + H)^+$; 282 and $(M - H)^-$;

280.

Step B: The condensation product **1l2** (1.66 g, 5.90 mmol) was dissolved in diphenyl ether (10 mL) and placed in a sand bath (300°C). The internal temperature was monitored and allowed to stay between 240-250°C for 10 minutes. The mixture was cooled and then directly loaded on a silica gel column and eluted first with hexanes, then with 30% EtOAc/Hexanes and finally 50% EtOAc/hexanes. The product was concentrated and dried in *vacuo* to give the corresponding 4-hydroxyquinoline derivative **1l3** as a yellow solid (0.735 g, 53%). MS electrospray: $(M + H)^+$; 236 and $(M - H)^-$; 234.

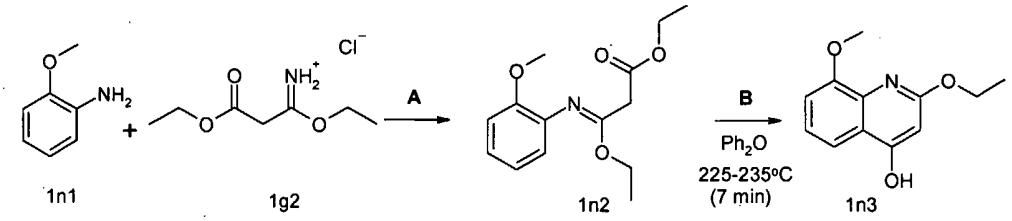
EXAMPLE 1M - SYNTHESIS OF P2 MOIETY 2-ETHOXY-7-METHOXY-8-METHYL-4-HYDROXYQUINOLINE (1M3)



Step A: The imidate salt **1g2** (1.5 g, 7.65 mmol) was combined with 2-methyl-3-aminoanisole **1m1** (1.05 g, 7.65 mmol, 1 eq.) in ethanol (15 mL) under an N_2 atmosphere. The reaction mixture was stirred at RT (24 h) and monitored by HPLC. The reaction mixture was concentrated and then ether was added and the mixture filtered. The solids were washed with ether and the combined ether washes concentrated *in vacuo*. The resulting adduct **1m2** was purified by chromatography (SiO_2, 15% EtOAc/hexanes) to obtain as a yellow oil (2.11 g, 99%). MS electrospray: $(M + H)^+$; 280 and (M – H)-; 278.

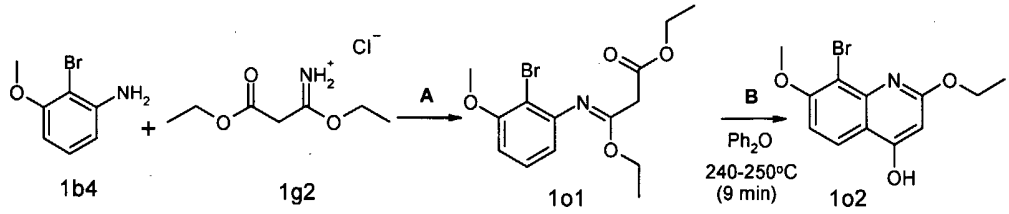
Step B: The condensation product **1m2** (2.1 g, 7.52 mmol) was dissolved in diphenyl ether (10 mL) and placed in a sand bath (300°C). The internal temperature was monitored and allowed to stay between 240-250°C for 10 minutes. The mixture was cooled and then directly loaded on a silica gel column and eluted first with hexanes, then with 30% EtOAc/Hexanes and finally 50% EtOAc/hexanes. The product was concentrated and dried in *vacuo* to give the corresponding 4-hydroxyquinoline derivative **1m3** as a yellow oil which solidified upon standing to a yellow solid (1.09g, 62%). MS electrospray: $(M + H)^+$; 233.4 and $(M - H)^-$; 231.9.

EXAMPLE 1N - SYNTHESIS OF P2 BUILDING BLOCK 2-ETHOXY-8-METHOXY-4-HYDROXYQUINOLINE (1N3)



Step A and B: Beginning with ortho-anisidine **1n1** and following the same protocol as outlined in previous examples, the desired 8-methoxyquinoline derivative **1n3** was obtained in 38% overall yield as a pale yellow solid. MS: 220 $(M+H)^+$.

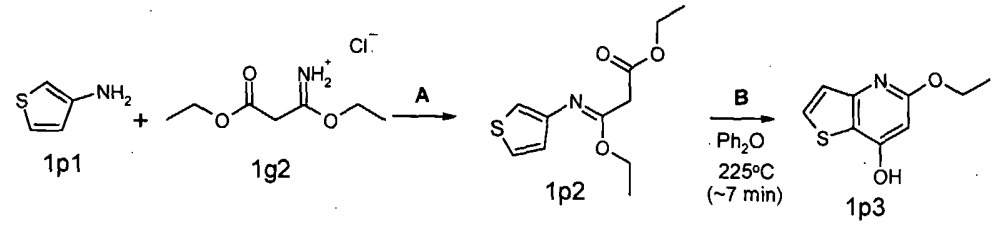
EXAMPLE 1O - SYNTHESIS OF P2 BUILDING BLOCK 8-BROMO-2-ETHOXY-4-HYDROXY 7-METHOXY-QUINOLINE (1O2)



Step A: To 2-bromo-3-aminoanisole **1b4** (750mg, 3.7mmol, 1eq) was added imidate **1g2** (0.73 g, 3.7 mmol, 1 eq) in ethanol (7 mL) under a N_2 atmosphere. The mixture was stirred at RT for 24 h at which point the reaction was concentrated and purified directly on a silica gel column (eluent: EtOAc/Hexanes (1:9)) to afford adduct **1o1** (1.12 g, 88%) as a pale yellow oil. MS: 344 $(M + H)^+$ and 346 $(MH + 2)^+$.

Step B: Adduct **1o1** (1.12 g, 3.25 mmol) was dissolved in diphenyl ether (10 mL) and placed in a pre-heated sand bath (300°C). The internal temperature was monitored and allowed to stay between 240°C-250°C for 8 minutes. The mixture was directly loaded on a silica gel column and eluted with hexanes to remove diphenyl ether, followed by a gradient of 30% to 50% EtOAc/hexanes: (R_f =0.25 in 1:1 EtOAc/hexanes). Concentration and drying in *vacuo* afforded the desired quinoline **1o2** (734mg, 76%) as a white solid. MS: 298 $(M + H)^+$ and 300 $(MH + 2)^+$.

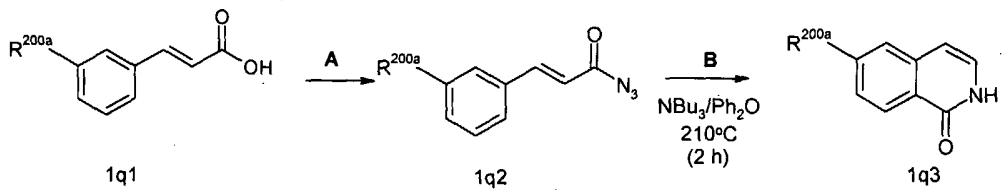
EXAMPLE 1P - SYNTHESIS OF P2 MOIETY 5-ETHOXY-THIENO[3.2-B]PYRIDIN-7-OL (1P3)



Step A: To available thiophen-3-ylamine **1p1** (0.50 g, 5.04 mmol) was added imidate **1g2** (1.08g, 5.5mmol) in ethanol (10 mL) under a N_2 atmosphere. The mixture was stirred at RT for 3 h at which point the reaction was concentrated. To the residue was added ether, and the suspension filtered and washed with ether to afford adduct **1p2**(1.0g, 82%). This material was sufficiently clean to be used in the subsequent step. MS: 242.1 (MH)+.

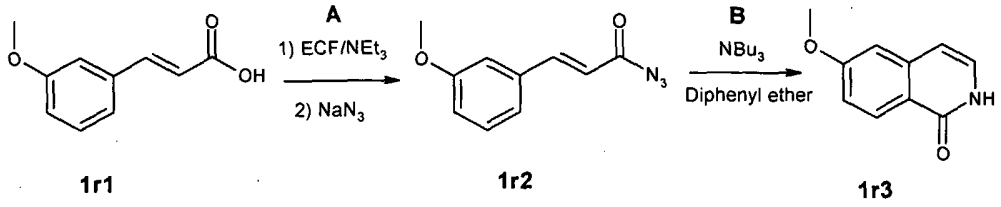
Step B: Adduct **1p2** (1.0g, 4.14mmol) was dissolved in diphenyl ether (5 mL) and placed in a pre-heated sand bath (300°C). The internal temperature was monitored and allowed to stay between 210°C-225°C for 7 minutes. The mixture was directly loaded on a silica gel column and eluted with hexanes to remove diphenyl ether, followed by a gradient of 30% EtOAc/hexane to neat EtOAc. Concentration and drying in *vacuo* afforded the desired thieno[3.2-b]pyridinol **1p3** (200mg, 25%) as a brown solid. MS: 196 (MH)+.

EXAMPLE 1Q - GENERAL SYNTHESIS OF P2 MOIETY 6-SUBSTITUTED-2H-ISOQUINOLINE-1-ONE (1Q3):



Briefly, 6-substituted isoquinolones, wherein R^{200a} is R^{200} as defined herein, can be made from 3-substituted cinnamic acid derivatives by first activation with a chloroformate in base followed by treatment with an azide source. The resulting acyl azide can undergo a Curtius rearrangement followed by thermal cyclization to afford the appropriately substituted isoquinolones. As described here, the cinnamic acid can be differentially substituted.

EXAMPLE 1R - PREPARATION OF 6-METHOXY-2H-ISOQUINOLINE-1-ONE (1R3):



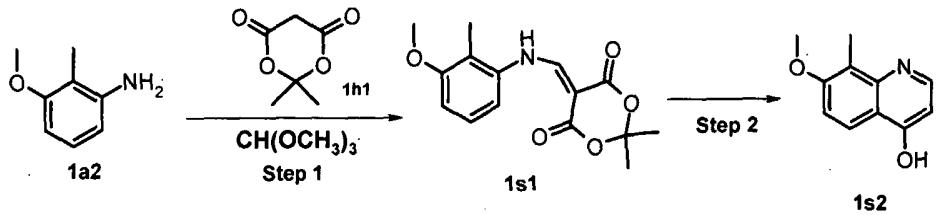
1r1 1r2 1r3

In general, the isoquinolines were prepared according to the following reference; Tetrahedron, **2002**, *58*, 5761-5766.

Step A: The 3-methoxycinnamic acid **1r1** (2.5 g, 14.03 mmol) was dissolved in acetone (40 mL) and treated with triethylamine (3.94 mL, 28.06 mmol). The solution was cooled to 0°C and then treated dropwise with ethyl chloroformate (2.0 mL, 21 mmol). A white precipitate immediately formed upon addition of each drop. The solution was stirred for 1h (with a suspension) before being treated with sodium azide (0.91 g; 14.03 mmol) in 10 mL of H_2O dropwise over 30 min. The mixture was allowed to stir at rt 16h before being diluted with water (20 mL) and the volatiles removed *in vacuo*. The aqueous phase was extracted with toluene (2 x 60 mL), dried over $MgSO_4$, and then filtered and concentrated to give a yellow oil (2.23 g) which solidified to a yellow solid **1r2** upon standing.

Step B: The diphenyl ether (10 mL) and tributylamine (7 mL) were heated in a sand bath to 190°C before the dropwise addition of the acyl azide **1r2** (behind an explosion shield) in toluene (5 mL) over several minutes. The toluene distilled off and the temperature was raised to 210°C for 2h. After cooling, the precipitated product was collected by filtration and washed with hexanes to give the desired isoquinoline **1r3** (0.47 g, 19%). MS (electrospray); $(M+H)^+$; 176 and $(M-H)^-$; 174. ^1H NMR (400MHz, DMSO-d_6) δ 11.05 (bs, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 7.16-7.09 (m, 2H), 7.04 (dd, *J* = 9, 2.4 Hz, 1H), 6.47 (d, *J* = 7.0 Hz, 1H), 3.86 (s, 3H).

EXAMPLE 1S - SYNTHESIS OF P2 MOIETY 4-HYDROXY-7-METHOXY-8-METHYL-QUINOLINE (1S2):



1a2 1s1 1s2

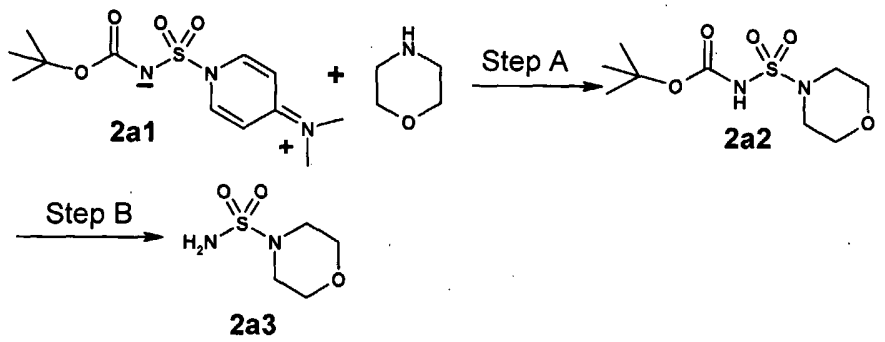
Step 1: To aniline **1a2** (Example 1A) (504 mg; 3.67 mmol) dissolved in anhydrous

acetonitrile (5.0 mL) was added Meldrum's acid **1h1** (582.4 mg; 4.04 mmol) followed by trimethyl orthoformate (482.3 μL; 4.41 mmol). The resulting brown solution was refluxed for 2 hours and the reaction judged complete by HPLC and TLC (Hexane:EtOAc; 6:4) Note : With the onset of heat a grey precipitate formed rendering stirring difficult . Therefore, an additional 5 mL of acetonitrile was added to eventually obtain a clear yellow solution within the first hour. The reaction mixture was cooled to RT and evaporated to dryness. The crude yellow solid was dissolved in a minimum amount of boiling MeOH and water slowly added till just cloudy to precipitate the product which was filtered, rinsed with water and dried to provide a light tan crystalline solid **1s1** (845.5 mg; 79 % yield). NMR ($CDCl_3$, 400 MHz) and MS 290.1 confirmed the product. Homogeneity by HPLC (TFA) @ 220 nm :99%.

Step 2 : A three- neck flask containing diphenyl ether (1.9 mL; 11.75 mmol) was placed into a preheated sand bath heated to ~300°C and the sand bath allowed to slowly heat further to ~330°C so as the internal temperature was between 245-250°C. The aniline derivative **1s1** was added portion-wise (immediately seeing gas evolution) at a rate as to maintain the internal temperature at 240-245°C (addition time 5-10min). Once addition was complete, the yellow solution was maintained at 245-250°C for 20 minutes. TLC (Hexane:EtOAc 6:4) indicated the consumption of starting material, however, the reaction mixture was left another 20 minutes to ensure complete intermediate decarboxylation. The mixture was worked-up by cooling the brownish solution to RT at which time a solid precipitated. The material was triturated with ether, filtered, rinsed and dried to provide the quinoline product **1s2** as a tan brown solid (216.7 mg; 83%). NMR (DMSO, 400 MHz) indicates the product to be mainly in the keto tautomer form. MS 187.9, 190.0 confirmed the product. Homogeneity by HPLC (TFA) @ 220 nm :97%.

Synthesis of P1' fragments

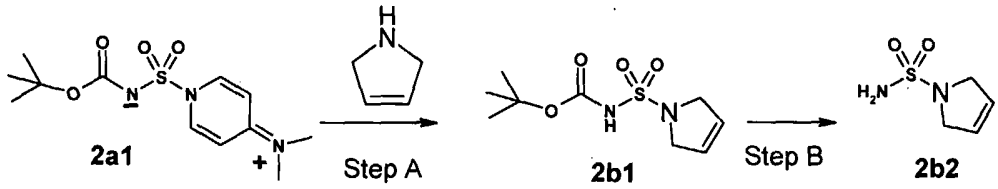
EXAMPLE 2A - SYNTHESIS OF P1' FRAGMENT SULFAMIDE 2A3:



Step 1 : Reagent **2a1** (0.3g, 0.99 mmol) [prepared according to Winum, J-Y; Toupet, L; Barragan, V; Dewynter, G; Montero, J-L., Org. Lett., 14(3), 2241-2243 (2001)] was suspended in CH_2Cl_2 before morpholine (0.086 mL, 0.99 mmol) was added and stirred for 5h. The reaction was followed by TLC. On completion the reaction mixture was directly adsorbed on the silica gel and eluted the product with 6% MeOH in $CHCl_3$ to afford 0.258g (98%) of compound **2a2** as a white solid.

Step 2: Compound **2a2** (0.150 g, 0.56 mmol) was dissolved in CH_2Cl_2 (5 mL) and treated with TFA (1 mL). The reaction was stirred for 4h and monitored by TLC. Upon completion, the solvent was evaporated and the residue directly adsorbed on the silica gel and eluted with 5% MeOH in $CHCl_3$ to afford 0.075g (80.2%) of compound **2a3** as a white solid.

EXAMPLE 2B - SYNTHESIS OF P1' FRAGMENT SULFAMIDE (2B2):

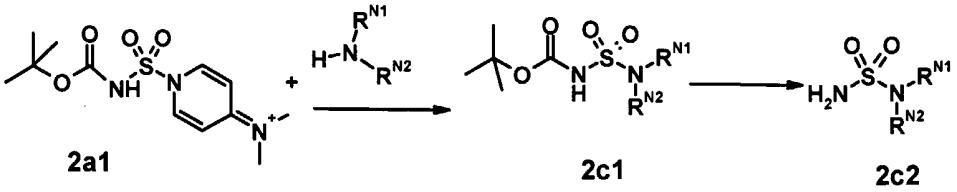


Step A : Reagent **2a1** (1.5g, 4.98 mmol) was suspended in 12 mL of CH_2Cl_2 before the pyrroline (0.40 mL, 5.22 mmol, 1.05 eq) was added and stirred overnight. On completion, the reaction mixture was directly adsorbed on the silica gel and eluted the product with 1% AcOEt in CH_2Cl_2 to afford 0.919g (74%) of compound **2b1** as a white solid.

Step B: Compound **2b1** (0.919 g, 3.70 mmol) was dissolved in 10 mL of CH_2Cl_2 and treated with TFA (2 mL). The reaction was stirred at room temperature for 4h. The solvent was then evaporated *in vacuo*, the residue was dried under vacuum to afford

0.565g (quantitative) of compound **2b2** as a beige solid.

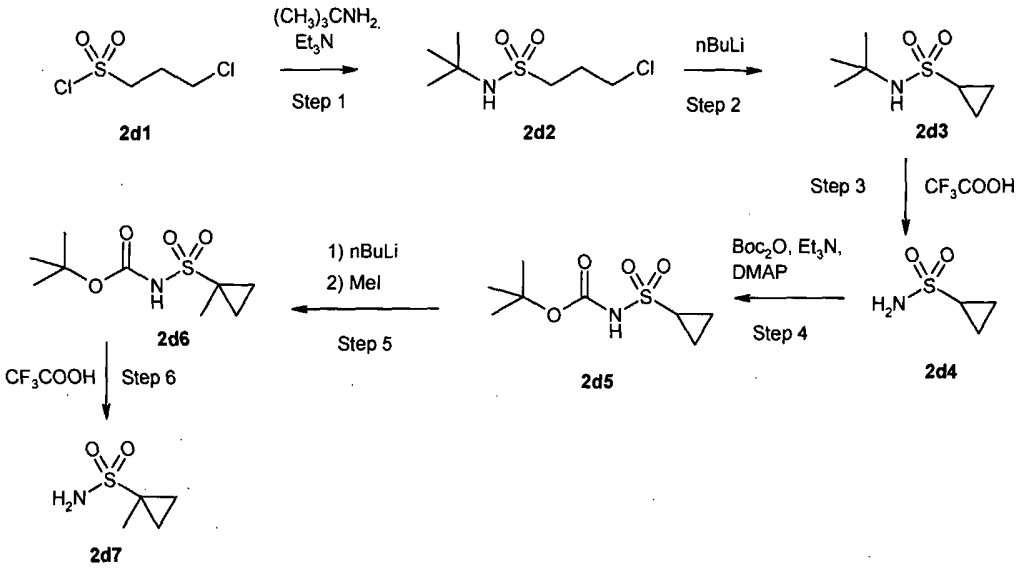
EXAMPLE 2C- SYNTHESIS OF P1' FRAGMENT SULFAMIDE (2C2):



Step A: Note: the reaction was performed on a solid phase synthesizer (Advanced Chemtech ACT 396), using the 96-wells block. The starting material **2a1** (45.2 mg, 0.15 mmol) was weighed in 96 Eppendorf vials and 96 different amines (0.18 mmol, 1.2 eq) were weighed and placed in separate Eppendorf vials. Each well of the reaction block were filled with 1.2 mL of 1,2-dichloroethane and the starting material **2a1** and the various amines were added. The reaction mixtures were shaken for 12 h in the case of aliphatic amines and for 36 h in the case of aniline derivatives. After the required stirring time, PS-trisamine resin was added to each well (Argonaut Technologies, 3.42 mmol/g loading, 0.63 mmol, 0.184 g, 4.2 eq). After shaking for 3 h, the solvent was drained and the resins were washed successively with CH_2Cl_2 (3 x 1 mL), MeOH (3 x 1 mL) and CH_2Cl_2 (3 x 1 mL). In each well was then added CH_2Cl_2 (1.2 mL) and AcOH (100 µl) and the shaking was maintained for 30 minutes. The solutions were drained in pre-tarred 2 drams vials to recover the filtrate and each resins were washed once with CH_2Cl_2 (1.2 mL) and MeOH (1.2 mL). The filtrates were recovered in the same 2-dram vials as before. The vials were finally placed on a vacuum centrifuge to remove the solvent and the desired products **2c1** were obtained in 41-54% yields (18-27 mg of product). Those compounds were used as is in the next step.

Step B: The products **2c1** in 2-dram vials were dissolved in 1,2-dichloroethane (0.5 mL) and TFA (0.5 mL) and the vials were shaken on an orbital shaker for 1.5 h. The volatiles were removed on a vacuum centrifuge to afford the desired products **2c2** in yields ranging from 71 % to quantitative (12-20 mg of product). Those compounds were used as is in the next step of synthesis of compounds of formula (I).

EXAMPLE 2D- SYNTHESIS OF P1' FRAGMENT 1-METHYLCYCLOPROPYLSULFONAMIDE (2D7):



Cyclopropanesulfonamide can be prepared by amination of cyclopropanesulfonyl chloride, according to the literature reference of J. King et al., *J. Org. Chem.*, **1993**, *58*, 1128-1135, or as set out below.

Step 1: A dry 3 L 3-neck flask equipped with a magnetic stir bar, addition funnel and argon inlet was flushed with argon, then charged with 3-chloropropanesulfonyl chloride **2d1** (100.48 g, 0.57 mol, 1.0 eq). Anhydrous dichloromethane (900 mL) was transferred into the flask via cannula, the mixture was cooled in an ice/water bath and tert-butylamine (72 mL, 0.68 mol, 1.2 eq) was added. The mixture was stirred 15 minutes then a solution of triethylamine (158 mL, 1.13 mol, 2.0 eq) in anhydrous dichloromethane (100 mL) was added dropwise over 45 minutes and stirring was continued for 1 h. The mixture was diluted with dichloromethane (500 mL) and washed with 1N HCl (3 x 400 mL) and brine. The organic layer was dried over sodium sulfate, filtered and evaporated to dryness to give compound **2d2** as an orange-beige solid (107.04 g, 88% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.46 (s, 1H), 3.71 (tr, 2H), 3.25 (tr, 2H), 2.31 (m, 2H), 1.41 (s, 9H).

Step 2: A dry 5 L 3-neck flask equipped with a magnetic stir bar, argon inlet and 2 addition funnels was flushed with argon and anhydrous THF (1.5 L) was transferred into the flask via cannula and cooled to -78°C. Compound **2d2** (96.73 g, 0.453 mol, 1.0 eq) was dissolved in anhydrous THF (390 mL) and the solution was transferred into one of the addition funnels. n-Butyllithium solution (2.5 M in hexanes, 390 mL,

0.975 mol, 2.15 eq) was transferred to the other addition funnel and the solutions in the addition funnels were added to the flask simultaneously over 4 hours. When addition was complete, the mixture was allowed to warm to room temperature. Once the internal temperature reached ~0°C, the reaction was quenched by dropwise addition of saturated NH_4Cl solution (200 mL). The THF was removed under vacuum and the residue was diluted with CH_2Cl_2 (2 L) and water (1 L). The layers were separated and the organic layer was washed with water (2 x 1 L) and brine (800 mL), dried over sodium sulfate, filtered and evaporated to dryness. Compound **2d3** was obtained as an orange-beige solid (77.32 g, 96% yield). ^1H NMR ($CDCl_3$, 400 MHz): δ 4.25 (s, 1H), 2.48 (m, 1H), 1.42 (s, 9H), 1.19 (m), 1.01 (m).

Step 3:A 2L flask equipped with a magnetic stir bar and condenser was charged with Compound **2d3** (82.53 g, 0.466 mol, 1.0 eq), dichloromethane (400 mL) and trifluoroacetic acid (460 mL, 5.97 mol, 13 eq). The mixture was heated to reflux for 2 h, allowed to cool, and evaporated and co-evaporated several times with CH_2Cl_2 to remove most of the TFA. The crude product was dissolved in 95:5 CH_2Cl_2:MeOH and NH_4OH and was purified by silica gel column chromatography (94:5:1 CH_2Cl_2:MeOH:NH_4OH). Compound **2d4** was obtained as a beige solid (46.38 g, 78% yield). ^1H NMR (DMSO-d_6, 400 MHz): δ 6.79 (s, 2H), 2.54 (1H, under DMSO peak), 0.92 (4H).

Step 4: To the solid cyclopropanesulfonamide **2d4** (1.51 g; 12.46 mmol) was added in sequence : di-t-butyl-dicarbonate (3.26 g; 14.95 mmol) dissolved in anhydrous dichloromethane (15 mL), triethylamine (2.6 mL; 18.65 mmol) and dimethylaminopyridine (76 mg; 0.622 mmol). The resulting solution was stirred at room temperature overnight and subsequently evaporated to near dryness. The residue was diluted with EtOAc, washed with 1N aq. HCl (3x) and brine (1x), dried ($MgSO_4$), filtered and evaporated to dryness to provide the Boc-cyclopropylsulfonamide product **2d5** as a white solid (2.6 g; 94%).

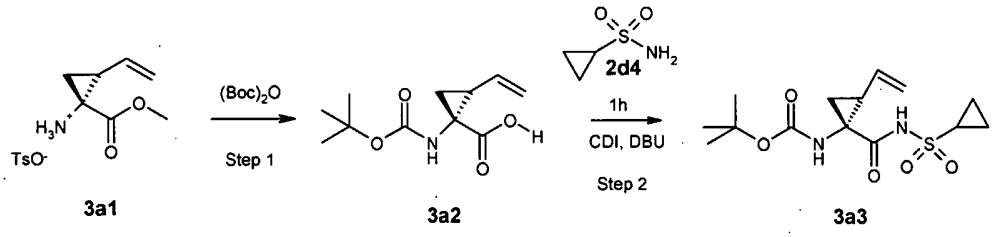
Step 5: To a cooled solution (-78°C) of the Boc-cyclopropanesulfonamide **2d5** (500 mg; 2.26 mmol) in anhydrous THF (15 mL) was added dropwise n-BuLi (2.1 mL; 5.20 mmol) and the mixture was allowed to stir 1 h at -78°C. Two portions of methyl iodide (each 280 µL; 4.52 mmol) were added with a one hour interval and the reaction mixture was allowed to warm slowly to RT and stir at RT overnight. The reaction mixture was adjusted to pH 3 with 1N aq. HCl and the product was extracted with EtOAc (3x). The combined EtOAc extracts were washed with brine (1x), dried

($MgSO_4$), filtered and evaporated to dryness to provide the crude alkylated product **2d6** as a light yellow oil . The crude material was purified by flash chromatography over silica gel with hexane : EtOAc (9 : 1) as eluent to provide pure product as a yellow oil (151.8 mg; 29%).

Step 6: To a solution of the Boc-1-methylcyclopropanesulfonamide **2d6** (151.8 mg: 0.65 mmol) in dichloromethane (6 mL) was added trifluroacetic acid (6 mL) and the mixture allowed to stir at RT for 3.5 h. Evaporation to dryness under high vacuum provided the deprotected material **2d7** as an off- white wax like solid (79.1 mg, 91%).^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.56 (s, 2H), 1.58 (s, 3H), 1.43-1.38 (m, 2H), 0.85-0.80 (2H).

Synthesis of P1-P1' fragments

EXAMPLE 3A – EXAMPLE OF P1-P1' FRAGMENT (3A3):



Step 1:

To a solution of compound **3a1** (12 g, 38.29 mmol) in a mixture of THF (50 mL) and 1 N aq. NaOH (85 mL, 85.00 mmol) was added Boc anhydride (10 g, 45.95 mmol). The reaction mixture was stirred at RT for 4 days. The pH was periodically adjusted to 9 by adding more NaOH. The THF was then removed *in vacuo* and the aqueous layer was washed with ether (3 X 150 mL) and then cooled to 0°C for the slow addition of 1 N aq. HCl until pH 3-4 was obtained. The aqueous layer was then extracted with EtOAc (3 X 150 mL) and the combined organic extracts were successively washed with water (3 X 100 mL) and brine. After drying over $MgSO_4$, filtration and concentration, 5.16 g of the desired Boc-protected intermediate **3a2** was isolated.

Step 2:

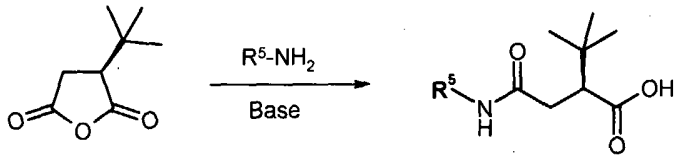
To a solution of acid **3a2** (567 mg, 2.49 mmol), in THF (20 mL), was added CDI (515 mg, 3.17 mmol). The resulting solution was stirred for 30 min, refluxed for 30 min and allowed to cool down to RT. Cyclopropylsulfonamide **2d4** (455 mg, 3.76 mmol) was added followed by the addition of DBU (0.75 mL, 5.02 mmol) and the reaction was stirred 12 h. The THF was removed *in vacuo* and the residue was diluted with EtOAc,

washed with 1 M HCl (2 X 100 mL) and brine, dried (MgSO4) and purified by flash chromatography (elution conditions: 70:30 hexane/EtOAc) to afford 682 mg (82%) of compound **3a3** as a white solid.

Synthesis of succinic acid moieties

Briefly, the succinate fragments can be made by a regioselective anhydride opening with the corresponding amine under basic conditions.

EXAMPLE 4A – GENERAL PROCEDURE FOR THE PREPARATION OF SUCCINIC ACID FRAGMENT 4A2:

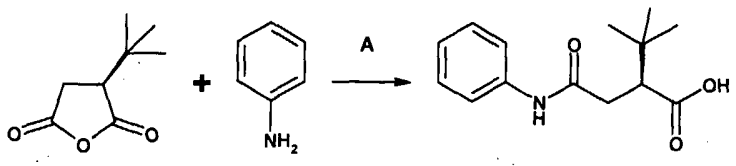


4a1 4a2

(S)-2-*tert*-Butylsuccinic anhydride **4a1** was prepared according to literature methods [P. Beaulieu *et.al.*, *J. Med. Chem.* **1997**, *40* (14), 2164-2176 and S. Widequist, *Ark. Kemi.* **1950**, 2, 321; *Chem.Abstr.* **1951**, *45*, 2870a and T. Polonski, *J. Chem. Soc. Perkin Trans.1,* **1988**, 629-637.]

The (*S*)-2-*tert*-butylsuccinic anhydride **4a1** (1 eq) was dissolved in pyridine and the solution cooled to -40°C (dry ice/acetone). The amine R^5-NH_2, wherein R^5 is defined as herein (1.2 eq) in pyridine was added dropwise and the mixture stirred for 10 min. The cooling bath was removed and the solution stirred overnight at room temperature. Pyridine and excess amine were evaporated under vacuum, and the oily residue was dissolved in EtOAc. The solution was washed successively with 20% aqueous citric acid (4×) and brine (2×) and then dried over $MgSO_4$. Removal of volatiles under reduced pressure and purification by crystallization or flash chromatography gave desired amides **4a2** usually as white solids.

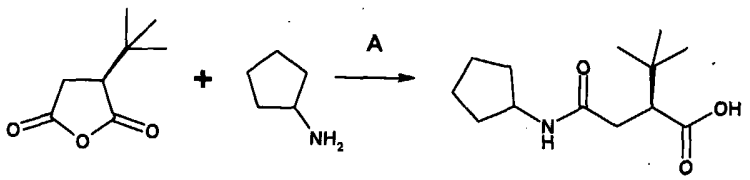
EXAMPLE 4B - PREPARATION OF (S)-2-*TERT*-BUTYLSUCCINIC N^4-ANILINE AMIDE 4B1:



4a1 4b1

Step A: The (S)-*tert*-butyl succinic anhydride **4a1** (0.5 g, 3.2 mmol) was dissolved in pyridine (12 mL) and cooled to -40°C before aniline (0.44 mL. 4.8 mmol) was added dropwise from a syringe over ca. 2 minutes. The solution was allowed to stir at -40°C for 10 minutes and then allowed to slowly warm to RT. The reaction was stirred 16 h before removing the pyridine *in vacuo*. The yellowish oil was taken up in EtOAc and washed sequentially with 10% citric acid and saturated brine, then dried over $MgSO_4$, filtered and concentrated to give the crude product **4b1** as an oil.This material was dissolved in EtOAc/Et_2O (5 mL each) and then hexane was added dropwise until cloudy. The solution was heated to form a homogeneous solution and then allowed to cool. The crystalline material was collected and washed with cold hexanes to give the desired succinic acid **4b1** (0.35 g, 44%). ^1H NMR (DMSO-d_6) δ 12.05 (s, 1H), 9.92 (s, 1H), 7.56 (d, J = 8 Hz, 2H), 7.27 (t, J = 8 Hz, 2H), 6.82 (t, J = 7 Hz, 1H), 2.75-2.5 (m, 3H), 0.96 (s, 9H). Homogeneity by analytical HPLC = 99.8%. MS: $(M+H)^+$; 250.1 and $(M+Na)^+$; 272.1.

EXAMPLE 4C - PREPARATION OF (S)-2-*TERT*-BUTYLSUCCINIC N^4-CYCLOPENTYLAMIDE 4C1:



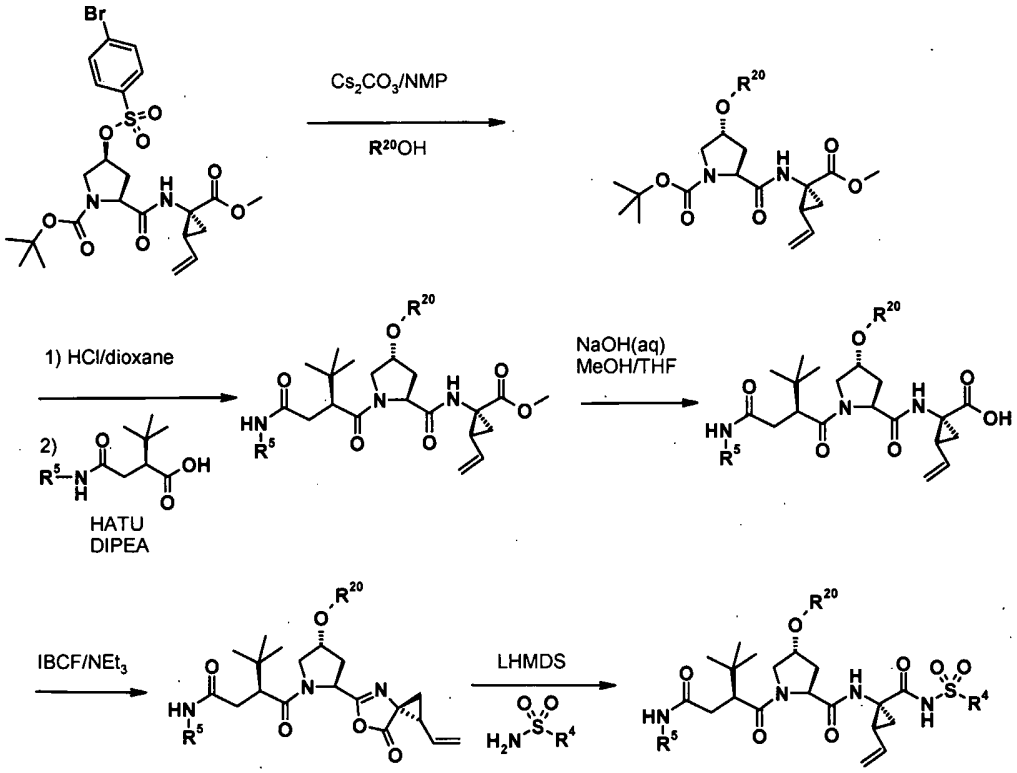
4a1 4c1

Step A: Using the same approach as described in Example 4B above but replacing aniline by cyclopentyl-amine, the corresponding succinic acid derivative **4c1** was prepared in 34% yield. ^1H NMR (DMSO-d_6) δ 11.01 (bs, 1H), 2.83-2.69 (m, 1H), 2.40-

2.30 (m, 1H), 2.20-2.08 (m, 1H),1.85-1.70 (m, 3H), 1.70-1.55 (m, 2H), 1.55-1.40 (m, 2H), 1.40-1.25 (m, 2H), 1.0 (s, 9H). MS: (M+H)+; 242.1, (M+Na)+; 264.1.

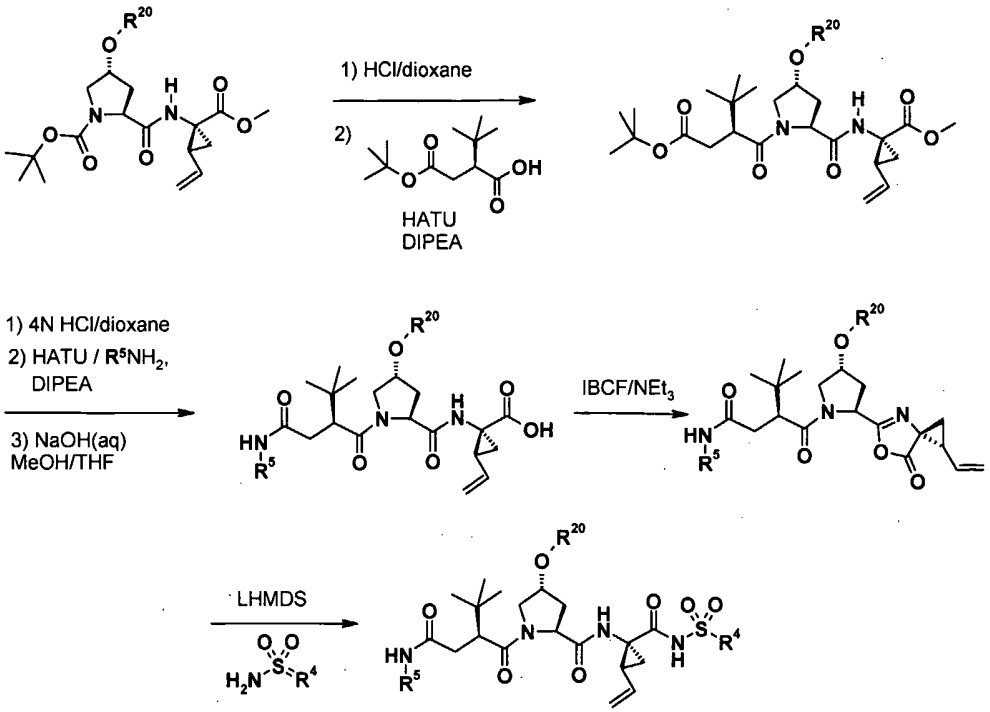
Synthesis of Inhibitors

EXAMPLE 5A – GENERAL METHOD FOR THE PREPARATION OF INHIBITORS:

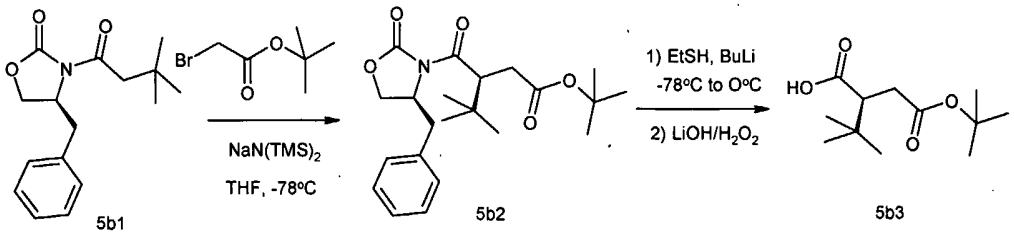


Briefly, the brosylate dipeptide can under go a displacement reaction with the cesium salts of quinolines, isoquinolines or other hydroxyl aromatic groups upon heating to incorporate with inversion of configuration the aryl group on the proline ring. Removal of the tert-butyl carbamate followed by coupling of the succinic acid moiety puts in place the succinamide moiety. The P1 ester can then be hydrolyzed before the formation of the azalactone. Opening of the azalactone with the lithium salt of a sulfonamides or sulfonyl diamides furnishes the final products.

EXAMPLE 5B – ALTERNATIVE GENERAL METHOD FOR THE PREPARATION OF INHIBITORS:



As an alternative approach for the preparation of a (*S*)-2-*tert*-butylsuccinic acid moiety, a general method for the synthesis of enantiomerically pure α-substituted succinic acid derivatives has been described by D. Evans et. al., J. Org. Chem. **1999**, 64(17), 6411-6417, the contents of which are incorporated herein by reference.

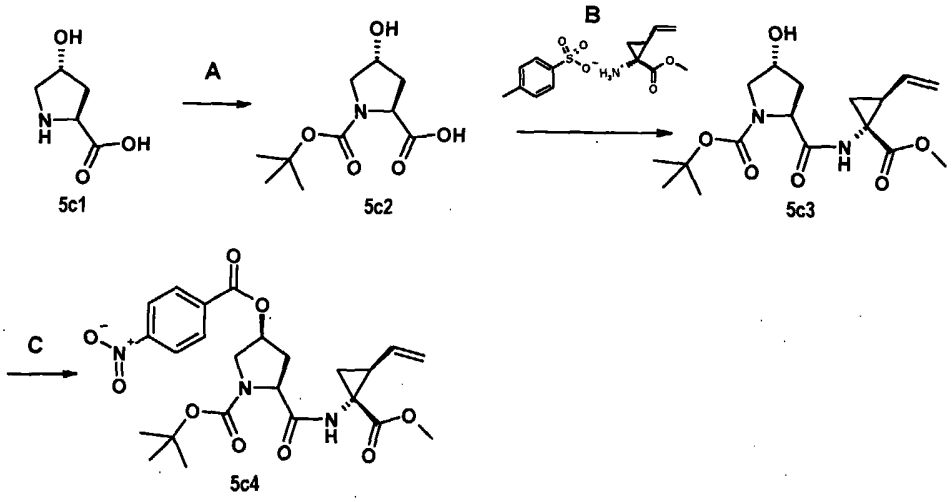


According to this approach, the oxazolidinone analog of tert-butylacetic acid is alkylated stereoselectively with *tert*-butyl bromoacetate at low temperature with a strong base to yield the enantiomerically pure succinate derivative. Removal of the chiral auxillary leads to the desired succinate analog. This succinate ester can be coupled to the dipeptide (with the R^{20} substitutent already introduced) using the coupling protocols as described hereinbefore and hereinafter to give the *tert*-butyl ester protected coupled succinate as shown in the reaction scheme below:

Briefly, the *tert*-butyl ester can be cleaved with HCl/dioxane to liberate the terminal

acid which can then be readily coupled with a variety of primary amines R^5-NH_2. Hydrolysis of the P1 methyl ester group and subsequent azalactone formation followed by azalactone opening with the lithium salt of sulfonamides or sulfonyl diamides yield the final products.

EXAMPLE 5C – PREPARATION OF DIPEPTIDE INTERMEDIATE:



Step A: To a 3-necked 5 L RB flask equipped with a mechanical stirrer was added 1N NaOH (aq) solution (1.68 L, 1.68 mol, 1.1 eq), followed by *trans*-L-4-hydroxyproline **5c1** (200 g, 1.525 mol, 1.0 eq) and *tert*-butanol (1000 mL). The Boc_2O (400 g, 1.83 mol, 1.2 eq) was added portionwise over ca. 60 minutes, keeping the internal temperature below 35°C. Upon completion of the addition, the reaction was allowed to stir 18 hours at RT. The mixture was extracted with pentane (2 x 300 mL) and the aqueous phase acidified to pH 1.0-1.5 with $KHSO_4$ (aq) [prepared by dissolving 315 g of $KHSO_4$ in 2L H_2O]. The turbid aqueous mixture was then extracted with EtOAc (4 x 500 mL), and washed with sat. brine (1x1L), dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was co-evaporated with methylene chloride/hexane to give white solid **5c2**, 333.3 g (95% yield). MS (electrospray): 132: $(MH - Boc)^+$, and 230 (M – H)-. ^1H NMR (DMSO-d_6), δ 12.47 (bs, 1H), 5.04 (s, 1H), 4.11 (t, 1H), 3.44-3.20 (m, 1H), 3.24 (d, J = 11.2 Hz, 1H), 2.16-2.04 (m, 1H), 1.94-1.83 (m, 1H), 1.39 and 1.34 rotamers (2 x s, 9H).

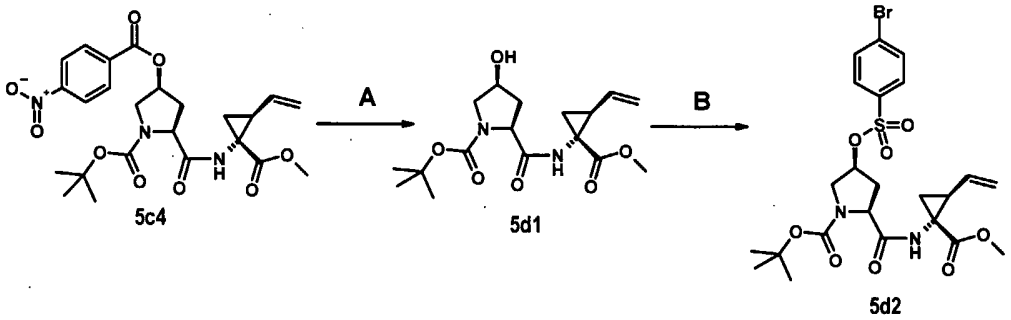
Step B: To a 3-necked RB flask fitted with a mechanical stirrer, a dropping funnel, and a thermometer, was added a mixture of 1-amino-2-ethenylcyclopropylcarboxylic

acid (100 g, 319 mmol, 1.1 eq) as the tosylate salt, Boc-hydroxyproline **5c2** (67 g, 290 mmol, 1 eq) and TBTU (2-1H-benzotriazol-1-yl-1,1,3,3-tetramethyluronium-hexafluoroborate) (102.4 g, 319 mmol, 1.1 eq). These reagents were completely dissolved in DMF (1 L) at 20°C and then cooled with an water/ice bath to about 15°C. Next, diisopropylethyl amine (DIPEA) (160 mL, 918 mmol, 3.17 eq) was added dropwise from the dropping funnel at a rate as to maintain the internal temperature at/or below 20°C (exothermic reaction). Upon completion of the base addition, the reaction mixture was stirred at RT for 4 hours (checked periodically by HPLC). The reaction mixture was concentrated on the rotary evaporator under high vacuum keeping the water bath temperature below 45°C to give an orange-red, oily residue. The residue was diluted with 1000 mL of EtOAc and the solution washed with sat. $NaHCO_3$ (aq) (4x300mL). All washes were combined and back-extracted with 4x300 mL EtOAc. All organic solutions were than combined, washed with brine (1x300 mL), dried with $NaCl+MgSO_4$, filtered and concentrated *in vacuo* to give a yellow foam, which was than dried in high vacuum to give yellow solid **5c3**. This solid was crushed with a mortar and pestle, then triturated with 1 L hexane and then filtered off and dried *in vacuo* to give 96.06 g of compound 4 (93.6% yield). This material can be used as is in the following Mitsunobu step.

Step C: In a 3-necked 5000 mL RB flask fitted with a mechanical stirrer, a 250 mL dropping funnel, and a thermometer, was placed dipeptide **5c3** (206.37 g, 542 mmol), 191 g (728 mmol, 1.3 eq) triphenylphosphine, and 121 g (724 mmol, 1.3 eq) p-nitrobenzoic acid in 2000 mL dry ("sure seal") THF. The mixture was stirred under an atmosphere of argon until all solids had dissolved. The reaction mixture was then cooled in an ice-bath to 0°C (internal temperature) and a mixture of 172 mL of DIAD (873 mmol, 1.6 eq) and 100 mL of dry THF were added dropwise from the dropping funnel over 1.5 hr at a rate as to maintain the temperature below 5°C. Upon completion of the addition, the reaction mixture was allowed to stir from 3°C to RT, slowly being allowed to warm overnight. After 16 hrs, the progress of the reaction was verified by analytical HPLC and TLC (neat EtOAc, visualized with molybdate stain) to show complete disappearance of the starting material. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in 2000 mL of EtOAc and then washed with 5x500 mL sat. $NaHCO_3$ (aq.) and 2x500 mL sat. brine. The organic phase was then checked by HPLC to show the absence of nitrobenzoic acid. The

organic phase was dried with NaCl + $MgSO_4$, filtered and concentrated *in vacuo* to give compound **5c4** (600 g) as a yellow-orange solid.

EXAMPLE 5D – PREPARATION OF KEY BROSYLATE DIPEPTIDE INTERMEDIATE:



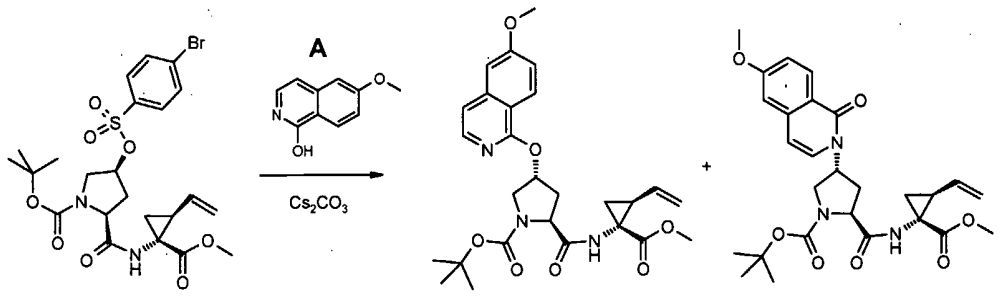
Step A: The purified compound **5c4** (2.15 g, 4.27 mmol) was dissolved in THF (57 mL) and water (9 mL) and cooled to 0°C (ice bath). Solid LiOH (monohydrate) (224 mg, 5.34 mmol, 1.3 eq) was dissolved in water (9 mL) and added to the cooled solution over ca. 10 minutes with rapid stirring. The reaction was stirred for 2 hours (0°C) until the starting material had been completely consumed by HPLC analysis. The excess base was neutralized with 0.5N HCl to give a final pH of ~6. The THF was evaporated off and the residue dissolved in EtOAc and washed 3x with sat. $NaHCO_3$ (aq), followed by sat. brine (1x). The organic phase was dried over MgSO4, filtered and concentrated to dryness to give a white foamy solid (1.35 g). Purification by flash chromatograghy (column diameter: 50 mm) with regular mesh silica gel (150 mL) to a height of about 13 cm. The initial eluent was Hexane/EtOAc (2:8), then neat EtOAc to obtain the desired product **5d1** as a white foamy solid (1.25 g, 83% yield). HPLC homogeneity was 97%,

MS: 353.1 $(M - H)^-$ and 377.1 $(M + Na)^+$.

Step B: The purified dipeptide **5d1** (1.25 g, 3.53 mmol) and 4-bromobenzene sulfonyl chloride (1.89 g, 7.41 mmol, 2.1 eq) were dissolved in methylene chloride (48 mL). To this solution was added triethylamine (1.74 mL, 12.5 mmol, 3.5 eq), and a catalytic amount of DMAP (43 mg, 0.35 mmol, 0.1 eq). The reaction was stirred at 40°C for 16 hours before being diluted with EtOAc, and then washed with sat. $NaHCO_3$ (aq) (2x), water(2x), and sat. brine (1x). The organic phase was dried over $MgSO_4$, filtered and concentrated to give a beige-orangy foam (2.3 g crude wt). This material was purified by flash chromatography and eluted with 1:1 hexane/EtOAc which provided 1.68 g of

an off-white foamy solid **5d2** (83%). HPLC analysis gave >99% homogeneity, MS: 571.1 and 573 (es- mode) and 573.1 and 575 (in es+ mode). ^{1}H NMR (400MHz, CDCl3) δ 7.77 (d, 2H), 7.70 (d, 2H), 5.83-5.71 (m, 1H), 5.28 (d, 1H), 5.15 (d, 1H), 5.07 (bs, 1H), 4.31 (bd, 1H), 3.77-3.63 (m, 2H), (3.69 (s, 3H), 2.49 (bs, 1H), 2.11-2.02 (m, 1H), 1.87-1.80 (m, 1H), 1.49 (d, 2H), 1.45 (s, 9H).

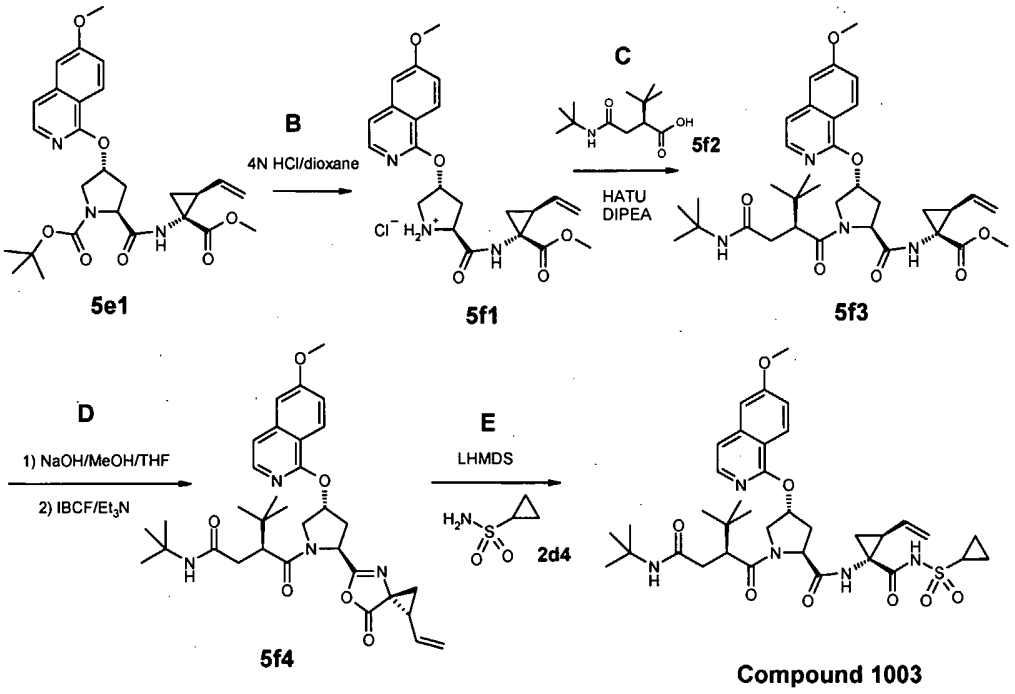
EXAMPLE 5E – PREPARATION OF INTERMEDIATE 5E2:



5d2 **5e1** **5e2**

Step A: The Boc-dipeptide **5d2** (300 mg, 0.52 mmol) was dissolved in NMP (5 mL) with the isoquinoline (76 mg, 0.52 mmol) and cesium carbonate (284 mg, 0.89 mmol) and stirred at 72°C for 3 hrs. The mixture was diluted with EtOAc (60 mL) and washed several times with sat. brine. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude material as two products **5e1** and **5e2**. Purification by flash chromatography (SiO_2, 80% EtOAc/hexanes) gave the desired O-alkylated product **5e1** (0.13 g, 48%). MS: $(M+H)_+$; 512.2.

EXAMPLE 5F – PREPARATION OF COMPOUND 1003 (TABLE 1):



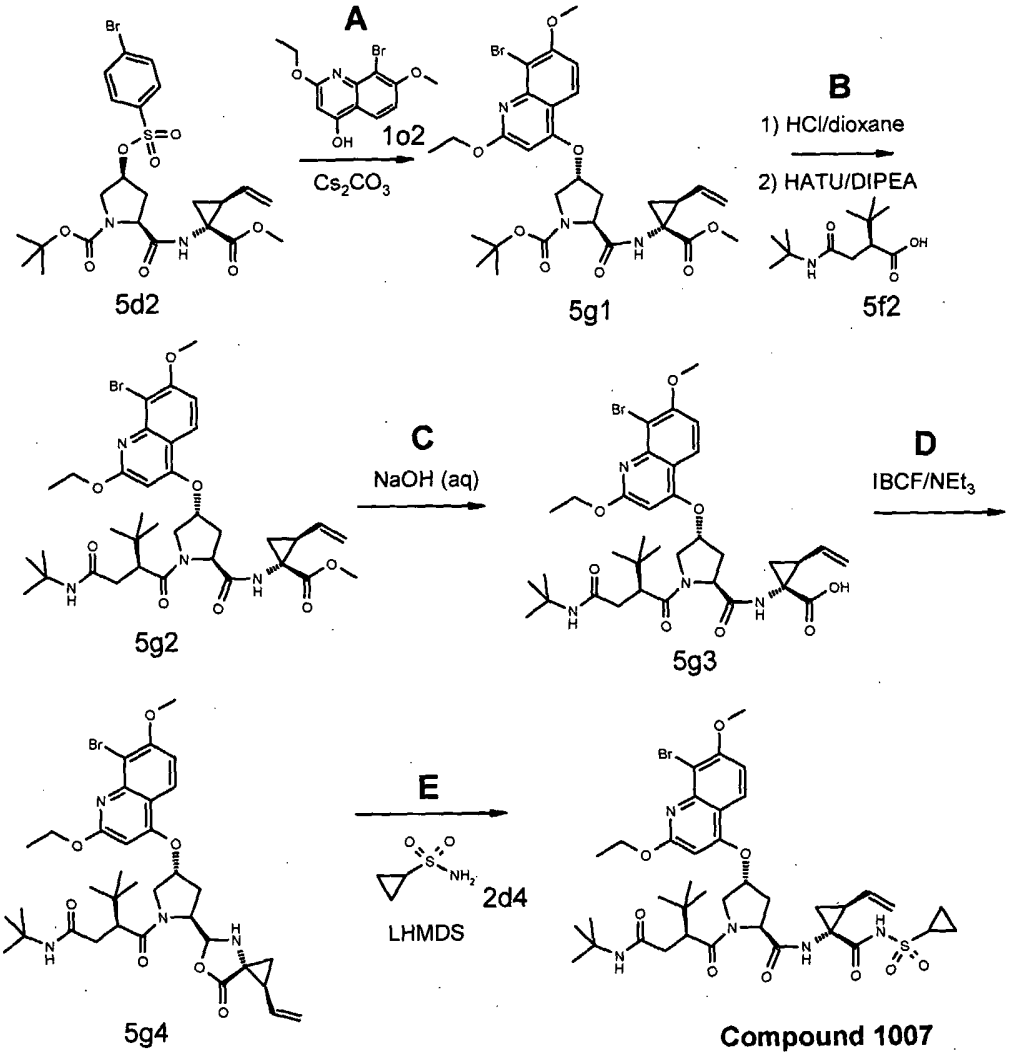
Steps B and C: The purified Boc-dipeptide **5e1** (139 mg, 0.27 mmol) was deprotected with 4N HCl/dioxane (4 mL) over 30 min at RT. The HCl salt was obtained in quantitative yield after concentration *in vacuo*. To the HCl salt **5f1** (80.6 mg, 0.18 mmol) was added the succinic acid derivative **5f2** (prepared using the method of Example 4A, wherein R^5 is 1,1-dimethylethyl) (45 mg, 0.20 mmol) and HATU (82 mg, 0.22 mmol) in DMF (2 mL). The solution was treated with DIPEA (110 µL, 0.63 mmol) and the reaction allowed to stir at RT (16 h). The mixture was concentrated *in vacuo* and then extracted into EtOAc and washed with sat. $NaHCO_3$ (aq), 10% HCl (aq) and finally sat. brine, and dried over ($MgSO_4$), filtered and concentrated to give the coupled product **5f3** (112 mg).

Step D: Compound **5f3** was dissolved in MeOH/THF (1 mL each) and treated with 1N NaOH (1.48 mL, 1.48 mmol). The mixture was stirred for 5 hours before being concentrated to dryness. The acid was partitioned between EtOAc and 5% HCl (aq) and then dried over $MgSO_4$, filtered and concentrated to give a white solid (105 mg, 93%). The dried acid (0.17 mmol) was dissolved in methylene chloride (4 mL) and cooled to 0°C before isobutyl chloroformate (27 µL, 0.21 mmol) and triethylamine (72 µL, 0.52 mmol) were added. The solution was allowed to warm to RT and stirred 4 hours. The mixture was concentrated to dryness and passed through a short plug of

SiO_2 (eluted with methylene chloride). Concentration gave the desired azalactone **5f4** (100 mg, 98%). MS: (M+H)+; 591.2.

Step E: The azalactone **5f4** was ring opened by first preparation of the lithium salt of the sulfonamide. To the sulfonamide **2d4** (17.8 mg, 0.15 mmol) in THF (3 mL) was added LHMDS (129 μl, 0.13 mmol, 1M in THF). This mixture was stirred 1h before being added to the azalactone **5f4** (51 mg, 0.086 mmol) in THF (2 mL) at 0°C. The cooling bath was removed after 30 min and the reaction allowed to stir 16h. The reaction was concentrated and dissolved in DMSO for purification by preparative HPLC to give after lyophilization, 15.4 mg (25%) of the final product, **compound 1003**. MS: (M+H)+; 712.3, (M-H)-; 710.3. Homogeneity by analytical HPLC (TFA) = 96.3%). ^{1}H NMR (DMSO-d_6) δ 10.45 (s, 1H), 9.03 (s, 1H), 8.29 (d, *J* = 9 Hz, 1H), 7.93 (d, *J* = 6 Hz, 1H), 7.295 (d, *J* = 6 Hz, 3H), 7.075 (dd, *J* = 8, 2 Hz, 1H), 5.76-5.71 (m, 1H), 5.70-5.57 (m, 1H), 5.21 (dd, *J* = 17, 1 Hz, 2H), 5.08 (dd, *J* = 10, 2 Hz, 1H), 4.375 (bd, *J* = 11 Hz, 1H), 4.34-4.27 (m, 1H), 3.93 (dd, *J* = 11, 4 Hz, 1H), 3.89 (s, 3H), 2.96-2.86 (m, 1H), 2.72-2.61 (m, 1H), 2.46-2.37 (m, 1H), 2.23-2.09 (m, 4H), 1.72-1.66 (m, 1H), 1.27-1.22 (m, 1H), 1.08 (s, 9H), 1.06-1.0 (m, 4H), 0.95 (s, 9H).

EXAMPLE 5G – PREPARATION OF COMPOUND 1007 (TABLE 1):



Step A: The brosylate **5d2** (0.227 g, 0.4 mmol) was combined with the quinoline **1o2** (0.118 g, 0.4 mmol) and cesium carbonate (0.28 g, 0.87 mmol) in NMP (5 mL) before being heated to 72°C for 3 hrs. The mixture was diluted with EtOAc and washed several times with sat. brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. This material was purified by chromatography (SiO_2, 50% EtOAc/hexane) to afford 0.215 g (86%) of the desired product **5g1**. MS: $(M+H)^+$; 634.2 and $(MH+2)^+$; 636. Homogeneity by analytical HPLC (98%, t_R = 7.2 min).

Step B: The dipeptide **5g1** (0.043 g, 0.068 mmol) was deprotected with 4N HCl/dioxane (1 mL) for 1 h before being concentrated to give the HCl salt. This was combined with the succinic acid residue **5f2** (Example 5F) (0.019 g, 0.082 mmol),

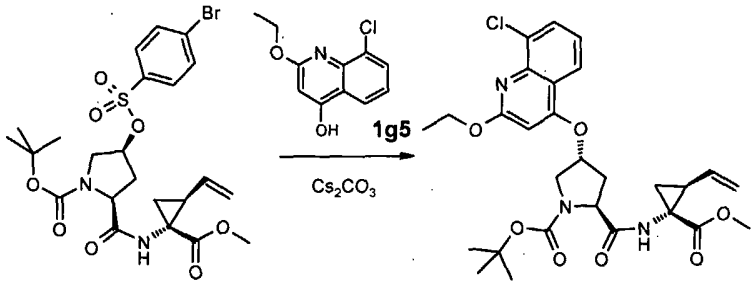
HATU (0.033g, 0.088 mmol), and finally DIPEA (0.059 mL, 0.34 mmol) in DMF (3.5 mL). The reaction was stirred 16h at rt before being concentrated to dryness. The residue was extracted into EtOAc, and washed with 5% HCl, sat.$NaHCO_3$ (aq) and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to give compound **5g2** as a white solid (0.051 g). MS: $(MH+2)^+$; 747.2. This material was used as is in the following step.

Step C: The tripeptide **5g2** (0.051 g, 0.068 mmol) was dissolved in MeOH/THF (2 mL and 1 mL) before being treated with 1N NaOH (aq) (0.54 mL, 0.54 mmol) at RT. The reaction was stirred 16 h before being concentrated to dryness. The residue was extracted into EtOAc and washed with 10% HCl and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated and placed on high vacuum for 16 h to furnish the acid **5g3** as a white solid (49 mg, 98%). Analytical HPLC, t_R = 6.87 min. This dried material was used in the azalactone formation step.

Step D: To the acid **5g3** (49 mg, 0.067 mmol) in methylene chloride (5 mL) was added IBCF (11.5 μL, 0.089 mmol), and triethylamine (41.4 μL, 0.295 mmol). The mixture was stirred at RT (monitoring by HPLC) for 4 hours,until complete by HPLC (t_R = 7.35 minutes, azalactone). The reaction mixture was concentrated to dryness and passed through a pad of silica gel (methylene chloride eluted) and the residue **5g4** was used in the next step without any further purification.

Step E: In a separate flask, the sulfonamide **2d4** (17.1 mg, 0.14 mmol) was dissolved in THF (3 mL) and treated at 0°C with LHMDS (1M in THF, 127 μL, 0.127 mmol). This mixture was stirred at RT for 30 minutes before being cooled to 0°C. The azalactone **5g4** from above (48 mg, 0.067 mmol) was added to the lithium salt in THF (2 mL) and stirred at 0°C (30 min) and then at RT (16h). The mixture was concentrated and dissolved in DMSO and purified by preparative HPLC to give the desired acyl sulphonamide, **compound 1007**, as a white solid 3.05 mg (6%). MS: $(M+H)^+$; 834.1 and (MH+2)+; 836.1. Homogeneity by analytical HPLC (TFA) = 100% (t_R = 7.55 min). ^1H NMR (400MHz, DMSO-d_6) δ 10.45 (s, 1H), 9.02 (s, 1H), 8.19 (d, *J* = 9 Hz, 1H), 7.28 (s, 1H), 7.12 (d, *J* = 9.2 Hz, 1H), 6.42 (s, 1H), 5.65 (dt, *J* = 18, 10 Hz, 1H), 5.41-5.35 (m, 1H), 5.22 (d, *J* = 18 Hz, 1H), 5.085 (d, *J* = 12 Hz, 1H), 4.50 (q, *J* = 7 Hz, 1H), 4.42 (bd, *J* = 12 Hz, 1H), 4.26 (dd, *J* = 11, 6.4 Hz, 1H), 3.94 (s, 3H), 3.90 (dd, *J* = 11. 4 Hz, 1H), 3.0-2.9 (m, 1H), 2.51 (d, *J* = 9 Hz, 1H), 2.23-2.07 (m, 4H), 1.39 (t, 3H), 1.38-1.33 (m, 1H), 1.12-1.05 (m, 4H), 1.03 (s, 9H), 0.94 (s, 9H).

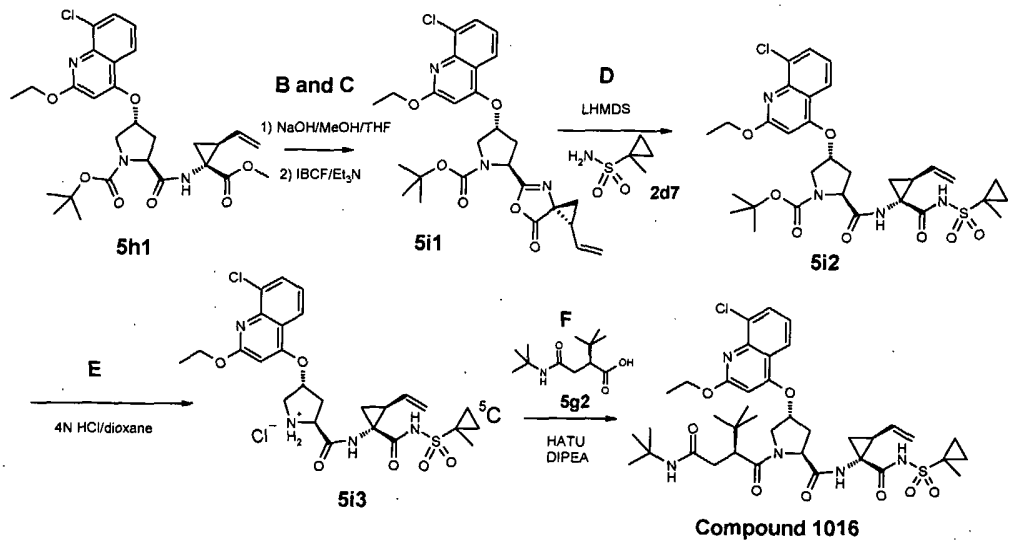
EXAMPLE 5H – PREPARATION OF DIPEPTIDE INTERMEDIATE 5H1:



5d2 **5h1**

Step A: The Boc-dipeptide **5d2** (1.0 g, 1.74 mmol) was dissolved in NMP (10 mL) with the 8-chloro-2-ethoxy-4-hydroxyquinoline **1g5** (0.41 g, 1.83 mmol) and cesium carbonate (0.85 g, 2.62 mmol) and stirred at 72°C for 4 hrs. The mixture was diluted with EtOAc (60 mL) and washed several times with sat. brine. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude material **5h1**. Purification by flash chromatography (SiO_2, 35% EtOAc/hexanes) gave the desired product **5h1** (0.91 g, 96%). MS: $(M+H)^+$; 560.2 and $(M-H)^-$; 558.2.

EXAMPLE 5I – PREPARATION OF COMPOUND 1016 (TABLE 1):



5h1 **5i1** **5i2**

5i3 **Compound 1016**

Steps B and C: The ester **5h1** was dissolved in MeOH and THF (6 mL each) and then treated with 1N NaOH (aq)(13.9 mL, 13.9 mmol). The clear reaction mixture was stirred at RT and was complete after 2 hr. The reaction was concentrated to dryness and partitioned between EtOAc and water. The aqueous phase was separated and

acidified to pH 5, then extracted into EtOAc. This phase was dried ($MgSO_4$), filtered and concentrated to give the corresponding acid. MS: (M-H)-; 544.2. This material was dried under high vacuum before being used in the next step.

The dried acid (0.912 g, 1.67 mmol) was dissolved in methylene chloride (15 mL) and cooled to 0°C before isobutyl chloroformate (0.32 mL, 2.5 mmol) and triethylamine (0.77 mL, 5.51 mmol) were added. After 1h, the solution was allowed to warm to RT and stirred 16 hrs. The mixture was concentrated to dryness and purified by column chromatography (SiO_2, 20% EtOAc/hexane). Concentration of the pure fractions gave the desired azalactone **5i1** (0.64 g, 73%).

Step D: The azalactone **5i1** was ring opened by first preparation of the lithium salt of the sulfonamide. To the sulfonamide **2d7** (16.8 mg, 0.124 mmol) in THF (4 mL) at 0°C was added LHMDS (114 µl, 0.114 mmol, 1M in THF). This mixture was stirred 20 min at 0°C before being stirred 20 min at RT. The mixture was re-cooled to 0°C before the addition of azalactone **5i1** (50 mg, 0.095 mmol) in THF (4 mL). The cooling bath was removed after 10 min and the reaction was complete after 45 min. The mixture was neutralized with 2 drops of AcOH before being concentrated. The crude reaction mixture extracted into EtOAc and washed several times with slightly basic saturated brine. The organic phase was dried ($MgSO_4$), filtered and concentrated to afford as a white solid of the acyl sulphonamide **5i2** (63 mg, 100%). MS: (M+H)+; 663.1 and (M-H)-; 661.1.

Step E: The acyl sulfonamide **5i2** (31.5 mg, 0.048 mmol) was Boc-deprotected using 4N HCl/dioxane (2 mL) over 35 minutes. The mixture was concentrated to dryness and dried overnight on the pump. To this amine salt **5i3** was added the succinamide moiety **5g2** (11 mg, 0.048 mmol) and HATU (22 mg, 0.058 mmol) in DMF before the addition of DIPEA (20 mg, 0.12 mmol). The reaction was stirred at RT and was complete after 1h. The mixture was concentrated to dryness and purified by preparative HPLC to give after lyophilization, **compound 1016** (18.5 mg, 50%) as a white solid. MS: $(M+H)^+$; 774.2 and $(M-H)^-$; 772.1. Homogeneity by analytical HPLC (TFA) = 99%). ^1H NMR (DMSO-d_6) δ 10.24 (s, 1H), 8.90 (s, 1H), 8.19 (d, *J* = 8 Hz, 1H), 7.80 (d, *J* = 9 Hz, 1H), 7.30 (s, 1H), 7.23 (dd, *J* = 8, 8 Hz, 1H), 6.60 (s, 1H), 5.63-5.5 (m, 1H), 5.40 (bs, 1H), 5.20 (dd, *J* = 17, 1 Hz,1H), 5.08 (dd, *J* = 10, 2 Hz, 1H), 4.50 (q, *J* = 7 Hz, 2H), 4.46 (d, *J* = 8 Hz, 1H), 4.26 (dd, *J* = 11, 6.5 Hz, 1H), 3.91 (dd, *J* = 11, 4 Hz, 1H), 2.70-2.60 (m, 1H), 2.30-2.10 (m, 3H), 1.67 (dd, *J* = 11, 7.8 Hz, 1H), 1.39 (t, *J* = 4 Hz, 3H), 1.35 (s, 3H), 1.37-1.29 (m, 2H), 1.03 (s, 9H), 0.95 (s, 9H), 0.94-

0.84 (m, 4H).

EXAMPLE 6 - NS3-NS4A PROTEASE ASSAY:

The enzymatic assay used to evaluate the present compounds is described in WO 00/09543 and WO 00/59929.

EXAMPLE 7 - CELL-BASED LUCIFERASE REPORTER HCV RNA REPLICATION ASSAY:

The assay used to evaluate the activity of the present compounds in cells expressing a stable subgenomic HCV replicon is described in WO 2005/028501.

Representative compounds according to this invention were found to be active when evaluated in the preceding enzymatic and cell based assays.

EXAMPLE 8 - SPECIFICITY ASSAYS:

The specificity assays used to evaluate the selectivity of compounds according to this invention were performed as described in WO 00/09543 except that the assay buffer for the Elastase assay was comprised of 50 mM Tris-HCl pH 8, 0.25 M NaCitrate, 0.01% n-dodecyl β-d-maltoside, and 5.25% DMSO.

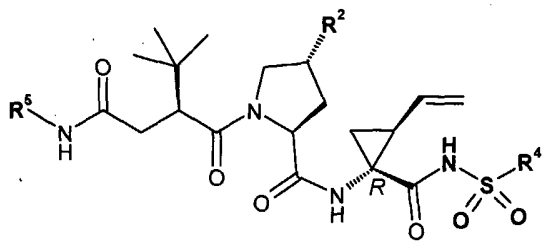
Representative compounds according to this invention were found to be selective in that they do not show significant inhibition (no measurable activity at concentrations up to 30 μM) in the Human Leukocyte Elastase assay or Human Liver Cathepsin B assays.

TABLES OF COMPOUNDS

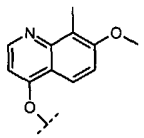
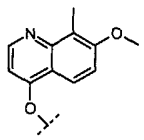
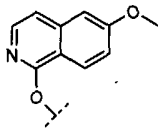
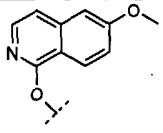
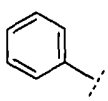
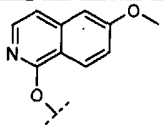
The following table lists compounds representative of the invention. Many of the compounds listed in the Table were found to have IC_{50} values below 0.1 μM in the NS3-NS4A protease assay of Example 6. In addition, many of the compounds listed in the Table have EC_{50} values below 1 μM in the cell-based luciferase reporter HCV RNA replication assay of Example 7. Retention times (t_R) for each compound were measured using the standard analytical HPLC conditions described in the Examples. As is well known to one skilled in the art, retention time values are sensitive to the specific measurement conditions. Therefore, even if identical conditions of solvent, flow rate, linear gradient, and the like are used, the retention time values may vary

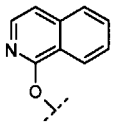
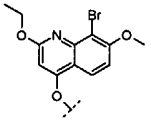
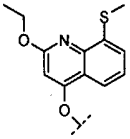
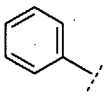
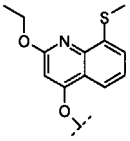
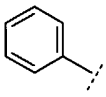
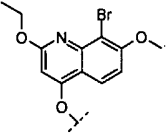
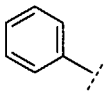
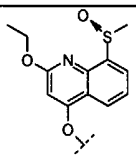
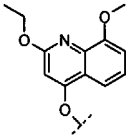
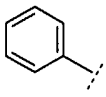
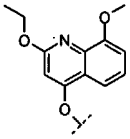
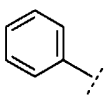
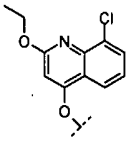
when measured, for example, on different HPLC instruments. Even when measured on the same instrument, the values may vary when measured, for example, using different individual HPLC columns, or, when measured on the same instrument and the same individual column, the values may vary, for example, between individual measurements taken on different occasions.

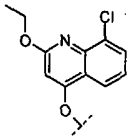
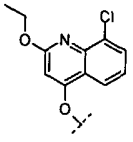
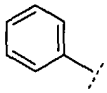
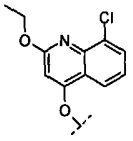
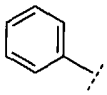
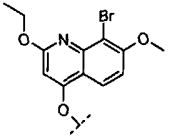
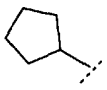
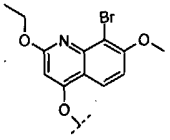
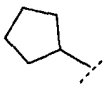
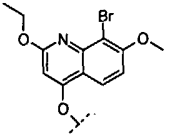
TABLE 1



wherein R^5, R^2 and R^4 are as defined below:

Cpd	R^5	R^2	R^4	$(MH)^+$	t_R (min)
1001				729.4	5.25
1002				726.3	5.25
1003				712.3	6.75
1004				715.4	6.75
1005				732.3	7.0

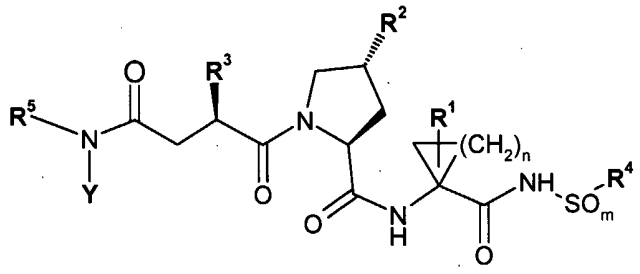
Cpd	R^5	R^2	R^4	$(MH)^+$	t_R (min)
1006				682.4	6.98
1007				834.1 836.1	7.45
1008				772.3	7.60
1009				792.3	7.73
1010				854.3 856.3	7.63
1011				8082.3	6.77
1012				756.4	5.38
1013				776.4	5.52
1014				780.3	7.83

Cpd	R^5	R^2	R^4	$(MH)^+$	t_R (min)
1015				760.3	7.69
1016				774.3	7.79
1017				794.3	7.88
1018					
1019					
1020					

CLAIMS

What is claimed is:

1. A compound of formula (I):



(I)

wherein

n is 1 or 2;

m is 1 or 2;

R^1 is H, (C_{1-6})alkyl, (C_{2-6})alkenyl, or (C_{2-6})alkynyl; wherein each of said (C_{1-6})alkyl, (C_{2-6})alkenyl, and (C_{2-6})alkynyl are optionally substituted with from one to three halogen substituents;

R^2 is selected from -NH-R^{20}, -O-R^{20}, -S-R^{20}, -SO-R^{20}, -SO_2-R^{20}, -OCH_2-R^{20}, and -CH_2O-R^{20}, wherein

R^{20} is aryl or **Het**, wherein said aryl and **Het** are each optionally substituted with R^{200}, wherein

R^{200} is one to four substituents each independently selected from H, halogen, cyano, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl-(C_{1-6})alkyl-, aryl, **Het**, oxo, thioxo, -OR^{201}, -SR^{201}, -SOR^{201}, -SO_2R^{201}, -$N(R^{202})R^{201}$, and -$CON(R^{202})R^{201}$; wherein each of said alkyl, cycloalkyl, aryl and **Het** is optionally further substituted with R^{2000};

R^{201} in each case is independently selected from H, (C_{1-6})alkyl, aryl, (C_{2-4})alkenyl, (C_{2-4})alkynyl, -CO-(C_{1-6})alkyl and -CO-O-(C_{1-6})alkyl, wherein each of said alkyl and aryl is optionally further substituted with R^{2000};

R^{202} is H or (C_{1-6})alkyl;

R^{2000} is one to three substituents each independently selected from halogen, R^{2003}, aryl, **Het**, -OR^{2001}, -SR^{2001}, -SOR^{2001}, -SO_2R^{2001}, cyano and -$N(R^{2002})(R^{2001})$, wherein each of said aryl and **Het** are optionally substituted with one, two or three substituents

each independently selected from (C_{1-6})alkyl and -O-(C_{1-6})alkyl;

R^{2001} in each case is independently selected from aryl, aryl-(C_{1-6})alkyl-, -C(O)-R^{2003}, –C(O)O-R^{2003}, -CON(R^{2002})(R^{2004}) and R^{2004};

R^{2002} in each case is independently selected from H and (C_{1-6})alkyl;

R^{2003} in each case is independently selected from (C_{1-8})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein each of said (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-(C_{1-4})alkyl- are optionally substituted with one to three (C_{1-3})alkyl substituents; and

R^{2004} in each case is independently selected from H or R^{2003};

R^3 is (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-3})alkyl-, wherein each said cycloalkyl group is optionally substituted with one to three substituents each independently selected from halogen, -OH, (C_{1-4})alkyl, O-(C_{1-4})alkyl, S-(C_{1-4})alkyl, -NH_2, -NH(C_{1-4})alkyl, -N((C_{1-4})alkyl)$_2$, -COOH and -$CONH_2$;

R^4 is (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl, **Het**, aryl-(C_{1-4})alkyl-, or **Het**-(C_{1-4})alkyl-;

a) each of said (C_{1-6})alkyl, (C_{2-6})alkenyl, aryl, **Het**, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl-(C_{1-4})alkyl- and **Het**-(C_{1-4})alkyl- optionally being substituted with nitro and optionally being substituted with one to three substituents each independently selected from halogen, hydroxy, cyano, (C_{1-6})alkyl, O-(C_{1-6})alkyl, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, -NH_2, -NH(C_{1-4})alkyl and -N((C_{1-4})alkyl)$_2$, wherein said (C_{1-6})alkyl and O-(C_{1-6})alkyl are optionally substituted with one to three halogen substituents; and

b) said (C_{3-7})cycloalkyl being optionally substituted with one or more substituents each independently selected from nitro, halogen, hydroxy, cyano, -O-(C_{1-6})alkyl, (C_{2-6})alkenyl, -OCF_3, -NH_2, -NH(C_{1-4})alkyl, -N((C_{1-4})alkyl)$_2$, tri(C_{1-6})alkylsilyl, R^{41}, -C(=O)-R^{41}, -C(=O)OR^{41}, -C(=O)N(R^{42})R^{41}, -SO_2R^{41}, and -OC(=O)-R^{41};

wherein R^{41} in each case is independently selected from:

i) H, (C_{3-7})cycloalkyl, (C_{4-7})cycloalkenyl, **Het**, or

aryl-(C_{1-4})alkyl-O-;

ii) aryl or aryloxy, each of which being optionally substituted with (C_{1-6})alkyl; and

iii) (C_{1-8})alkyl optionally substituted with one or more substituents each independently selected from -O-(C_{1-6})alkyl, hydroxy, halogen, (C_{2-10})alkenyl, (C_{2-10})alkynyl, (C_{3-7})cycloalkyl, (C_{4-7})cycloalkenyl, aryl, **Het**, aryloxy, and aryl-(C_{1-4})alkyl-O-, wherein each of said aryl and aryloxy is optionally substituted with (C_{1-6})alkyl; and

R^{42} is selected from H and (C_{1-6})alkyl; or

R^4 is $-N(R^{N2})(R^{N1})$, wherein R^{N1} and R^{N2} are each independently selected from H, (C_{1-6})alkyl, -O-(C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl and aryl-(C_{1-6})alkyl-; wherein said (C_{1-6})alkyl, -O-(C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl and aryl-(C_{1-6})alkyl- are each optionally substituted with one or more substituents each independently selected from halogen, (C_{1-6})alkyl, hydroxy, cyano, O-(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-4})alkyl, -N((C_{1-4})alkyl)$_2$, $-CO-NH_2$, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, -COOH, and -COO(C_{1-6})alkyl; or

R^{N2} and R^{N1} are linked, together with the nitrogen to which they are bonded, to form a 3- to 7-membered monocyclic saturated or unsaturated heterocycle optionally fused to at least one other cycle to form a heteropolycycle, said heterocycle and heteropolycycle each optionally containing from one to three additional heteroatoms each independently selected from N, S and O, and being optionally substituted with one or more substituents each independently selected from halogen, (C_{1-6})alkyl, hydroxy, cyano, O-(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-4})alkyl, -N((C_{1-4})alkyl)$_2$, $-CO-NH_2$, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, -COOH, and $-COO(C_{1-6})$alkyl;

R^5 is (C_{2-10})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, phenyl, phenyl-(C_{1-3})alkyl-, **Het** or **Het**-(C_{1-3})alkyl-; wherein each of said

(C_{2-10})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, phenyl, phenyl-(C_{1-3})alkyl-, **Het** and **Het**-(C_{1-3})alkyl- is optionally substituted with one to three substituents each independently selected from halogen, -OH, (C_{1-4})alkyl, -O-(C_{1-4})alkyl, -S-(C_{1-4})alkyl, $-NH_2$, -NH(C_{1-4})alkyl, -N$((C_{1-4})alkyl)_2$, -NHC(=O)(C_{1-4})alkyl, -NHC(=O)O(C_{1-4})alkyl, -NH(C=O)NH(C_{1-4})alkyl, -NH(C=O)N$((C_{1-4})alkyl)_2$, $-CONH_2$, -CONH-(C_{1-4})alkyl, -CON$((C_{1-4})alkyl)_2$, -COOH, -COO(C_{1-6})alkyl, -CO-(C_{1-6})alkyl, $-SO_2(C_{1-4})$alkyl and $-SO_2NH(C_{1-4})$alkyl; and

Y is H or (C_{1-6})alkyl;

with the proviso that when

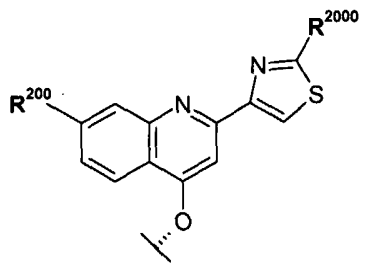
m is 2,

n is 1, and

R^4 is selected from (C_{1-6})alkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, phenyl, naphthyl, pyridinyl, phenyl-(C_{1-4})alkyl-, naphthyl-(C_{1-4})alkyl- and pyridinyl-(C_{1-4})alkyl-; each of which being optionally substituted with nitro and each of which being optionally substituted with one to three substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$, $-NH_2$, -NH(C_{1-4})alkyl and -N$((C_{1-4})alkyl)_2$; wherein said (C_{1-4})alkyl and O-(C_{1-6})alkyl are each optionally substituted with one to three halogen substituents;

or R^4 is (C_{3-7})cycloalkyl, said (C_{3-7})cycloalkyl being optionally substituted with nitro and optionally substituted with one or more substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, $-OCF_3$, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$, $-NH_2$, -NH(C_{1-4})alkyl and -N$((C_{1-4})alkyl)_2$, wherein said (C_{1-4})alkyl is optionally substituted with one or more halogen substituents;

then R^2 cannot be



;

wherein

R^{200} is -O-(C_{1-4})alkyl, -NH(C_{1-4})alkyl, or -N((C_{1-4})alkyl)$_2$; and

R^{2000} is R^{2003} or -N(R^{2002})(R^{2001}); wherein

R^{2001} is selected from -C(O)-R^{2003}, –C(O)O-R^{2003}, -CON(R^{2002})(R^{2004}) and R^{2004};

R^{2002} in each case is independently selected from H and methyl;

R^{2003} is (C_{1-8})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein said (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-(C_{1-4})alkyl- are optionally substituted with one to three (C_{1-3})alkyl substituents; and

R^{2004} is H or R^{2003};

wherein **Het** as used herein is defined as a 3- to 7-membered heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, which may be saturated, unsaturated or aromatic, and which is optionally fused to at least one other cycle to form a 4- to 14-membered heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S, said heteropolycycle being saturated, unsaturated or aromatic;

or a salt thereof.

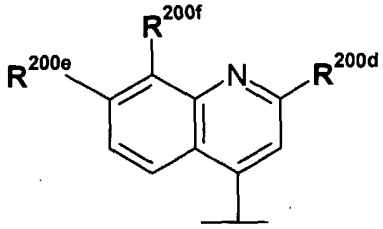
2. The compound according to claim 1 wherein **n** is 1.

3. The compound according to one or more of claims 1 or 2 wherein **m** is 2.

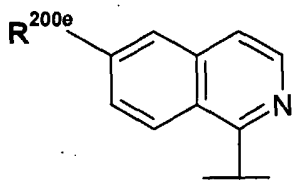
4. The compound according to one or more of the preceding claims wherein R^1 is (C_{2-6})alkenyl or (C_{2-6})alkyl.

5. The compound according to one or more of the preceding claims wherein R^2 is -O-R^{20}, wherein R^{20} is **Het**, said **Het** being optionally substituted with R^{200}, wherein R^{200} is defined as in claim 1; wherein **Het** is a heterocycle containing at least one nitrogen heteroatom.

6. The compound according to claim 5 wherein **Het** is a group selected from:



and



wherein

R^{200d} is H or $-OR^{201}$, wherein R^{201} is (C_{1-6})alkyl optionally further substituted with R^{2000}, wherein R^{2000} is one to three substituents each independently selected from halogen, (C_{3-7})cycloalkyl, $-O-(C_{1-6})$alkyl, **Het**, $-O-(C_{3-7})$cycloalkyl, $-NH_2$, $-NH(C_{1-4})$alkyl and $-N((C_{1-4})alkyl)_2$;

R^{200e} is H or $-OR^{201}$, wherein R^{201} is (C_{1-6})alkyl; and

R^{200f} is H, (C_{1-6})alkyl, halogen, $-SR^{201}$, $-SOR^{201}$, $-SO_2R^{201}$ or $-OR^{201}$; wherein R^{201} is (C_{1-6})alkyl.

7. The compound according to one or more of the preceding claims wherein R^3 is (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-3})alkyl-, wherein each said cycloalkyl group is optionally substituted with one to three (C_{1-4})alkyl substituents.

8. The compound according to one or more of the preceding claims wherein R^4 is selected from methyl, ethyl, 1-methylethyl, propyl, ethenyl, cyclopropyl, cyclobutyl, cyclopentyl, phenyl and $-N(CH_3)_2$; wherein the cyclopropyl is optionally substituted at the 1-position with methyl, ethyl, propyl or butyl, each of the methyl, ethyl, propyl and butyl being optionally further substituted with phenyl, (C_{3-6})cycloalkyl, (C_{2-6})alkenyl or (C_{1-4})alkoxy.

9. The compound according to one or more of the preceding claims wherein R^5 is (C_{2-10})alkyl, (C_{3-7})cycloalkyl, or phenyl, each of which being optionally substituted with one to three substituents each independently selected from halogen, -OH, (C_{1-4})alkyl and $-O-(C_{1-4})$alkyl.

10. The compound according to one or more of the preceding claims wherein **Y** is H or methyl.

11. The compound according to claim 1 wherein:

n is 1 or 2;

m is 1 or 2;

$\mathbf{R^1}$ is H, (C_{1-6})alkyl, (C_{2-6})alkenyl, or (C_{2-6})alkynyl; wherein each of said (C_{1-6})alkyl, (C_{2-6})alkenyl, and (C_{2-6})alkynyl are optionally substituted with from one to three halogen substituents;

$\mathbf{R^2}$ is selected from -NH-$\mathbf{R^{20}}$, -O-$\mathbf{R^{20}}$, -S-$\mathbf{R^{20}}$, -SO-$\mathbf{R^{20}}$, -SO_2-$\mathbf{R^{20}}$, -OCH_2-$\mathbf{R^{20}}$, and -CH_2O-$\mathbf{R^{20}}$, wherein

$\mathbf{R^{20}}$ is aryl or **Het**, wherein said aryl and **Het** are each optionally substituted with $\mathbf{R^{200}}$, wherein

$\mathbf{R^{200}}$ is one to four substituents each independently selected from H, halogen, cyano, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl-(C_{1-6})alkyl-, aryl, **Het**, oxo, thioxo, -$\mathbf{OR^{201}}$, -$\mathbf{SR^{201}}$, -$\mathbf{SOR^{201}}$, -$\mathbf{SO_2R^{201}}$, -N($\mathbf{R^{202}}$)$\mathbf{R^{201}}$, and -CON($\mathbf{R^{202}}$)$\mathbf{R^{201}}$; wherein each of said alkyl, cycloalkyl, aryl and **Het** is optionally further substituted with $\mathbf{R^{2000}}$;

$\mathbf{R^{201}}$ in each case is independently selected from H, (C_{1-6})alkyl, aryl, (C_{2-4})alkenyl, (C_{2-4})alkynyl, -CO-(C_{1-6})alkyl and -CO-O-(C_{1-6})alkyl, wherein each of said alkyl and aryl is optionally further substituted with $\mathbf{R^{2000}}$;

$\mathbf{R^{202}}$ is H or (C_{1-6})alkyl;

$\mathbf{R^{2000}}$ is one to three substituents each independently selected from halogen, $\mathbf{R^{2003}}$, aryl, **Het**, -$\mathbf{OR^{2001}}$, -$\mathbf{SR^{2001}}$, -$\mathbf{SOR^{2001}}$, -$\mathbf{SO_2R^{2001}}$, cyano and -N($\mathbf{R^{2002}}$)($\mathbf{R^{2001}}$), wherein each of said aryl and **Het** are optionally substituted with one, two or three substituents each independently selected from (C_{1-6})alkyl and -O-(C_{1-6})alkyl;

$\mathbf{R^{2001}}$ in each case is independently selected from aryl, aryl-(C_{1-6})alkyl-, -C(O)-$\mathbf{R^{2003}}$, –C(O)O-$\mathbf{R^{2003}}$, -CON($\mathbf{R^{2002}}$)($\mathbf{R^{2004}}$) and $\mathbf{R^{2004}}$;

$\mathbf{R^{2002}}$ in each case is independently selected from H and (C_{1-6})alkyl;

$\mathbf{R^{2003}}$ in each case is independently selected from (C_{1-8})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein each of

said (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-(C_{1-4})alkyl- are optionally substituted with one to three (C_{1-3})alkyl substituents; and

R^{2004} in each case is independently selected from H or R^{2003};

R^3 is (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-3})alkyl-, wherein each said cycloalkyl group is optionally substituted with one to three substituents each independently selected from halogen, -OH, (C_{1-4})alkyl, O-(C_{1-4})alkyl, S-(C_{1-4})alkyl, $-NH_2$, -NH(C_{1-4})alkyl, -N$((C_{1-4})alkyl)_2$, -COOH and $-CONH_2$;

R^4 is (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl, **Het**, aryl-(C_{1-4})alkyl-, or **Het**-(C_{1-4})alkyl-;

a) each of said (C_{1-6})alkyl, (C_{2-6})alkenyl, aryl, **Het**, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl-(C_{1-4})alkyl-, and **Het**-(C_{1-4})alkyl- optionally being substituted with nitro and optionally being substituted with one to three substituents each independently selected from halogen, hydroxy, cyano, (C_{1-6})alkyl, O-(C_{1-6})alkyl, $-CO-NH_2$, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$, $-NH_2$, -NH(C_{1-4})alkyl and -N$((C_{1-4})alkyl)_2$, wherein said (C_{1-6})alkyl and O-(C_{1-6})alkyl are optionally substituted with one to three halogen substituents; and

b) said (C_{3-7})cycloalkyl being optionally substituted with one or more substituents each independently selected from nitro, halogen, hydroxy, cyano, -O-(C_{1-6})alkyl, (C_{2-6})alkenyl, $-OCF_3$, $-NH_2$, -NH(C_{1-4})alkyl, -N$((C_{1-4})alkyl)_2$, tri(C_{1-6})alkylsilyl, R^{41}, $-C(=O)-R^{41}$, $-C(=O)OR^{41}$, $-C(=O)N(R^{42})R^{41}$, $-SO_2R^{41}$, and $-OC(=O)-R^{41}$;

wherein R^{41} in each case is independently selected from:

i) H, (C_{3-7})cycloalkyl, (C_{4-7})cycloalkenyl, **Het**, or aryl-(C_{1-4})alkyl-O-;

ii) aryl or aryloxy, each of which being optionally substituted with (C_{1-6})alkyl; and

iii) (C_{1-8})alkyl optionally substituted with one or more substituents each independently selected from -O-(C_{1-6})alkyl, hydroxy, halogen, (C_{2-10})alkenyl,

(C_{2-10})alkynyl, (C_{3-7})cycloalkyl, (C_{4-7})cycloalkenyl, aryl, **Het**, aryloxy, and aryl-(C_{1-4})alkyl-O-, wherein each of said aryl and aryloxy is optionally substituted with (C_{1-6})alkyl; and

$\mathbf{R^{42}}$ is selected from H and (C_{1-6})alkyl; or

$\mathbf{R^4}$ is $-N(\mathbf{R^{N2}})(\mathbf{R^{N1}})$, wherein $\mathbf{R^{N1}}$ and $\mathbf{R^{N2}}$ are each independently selected from H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl and aryl-(C_{1-6})alkyl-; wherein said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, aryl and aryl-(C_{1-6})alkyl- are each optionally substituted with one or more substituents each independently selected from halogen, (C_{1-6})alkyl, hydroxy, cyano, O-(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-4})alkyl, -N$((C_{1-4})\text{alkyl})_2$, $-CO-NH_2$, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})\text{alkyl})_2$, -COOH, and $-COO(C_{1-6})$alkyl; or

$\mathbf{R^{N2}}$ and $\mathbf{R^{N1}}$ are linked, together with the nitrogen to which they are bonded, to form a 3- to 7-membered monocyclic saturated or unsaturated heterocycle optionally fused to at least one other cycle to form a heteropolycycle, said heterocycle and heteropolycycle each optionally containing from one to three additional heteroatoms each independently selected from N, S and O, and being optionally substituted with one or more substituents each independently selected from halogen, (C_{1-6})alkyl, hydroxy, cyano, O-(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-4})alkyl, -N$((C_{1-4})\text{alkyl})_2$, $-CO-NH_2$, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})\text{alkyl})_2$, -COOH, and $-COO(C_{1-6})$alkyl;

$\mathbf{R^5}$ is (C_{2-10})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein

a) each said cycloalkyl and cycloalkyl-alkyl- is optionally substituted with one to three (C_{1-3})alkyl substituents; and

b) each said alkyl, cycloalkyl and cycloalkyl-alkyl- is optionally substituted with one or two substituents each independently selected from hydroxy and O-(C_{1-4})alkyl; and

c) each said alkyl group is optionally substituted with one to three halogen substituents; and

d) in each said cycloalkyl group being 5-, 6- or 7-membered, one or

two -CH_2-groups not being directly linked to each other are optionally replaced by -O- such that the O-atom is linked to the N atom to which R^5 is attached via at least two C-atoms;

or

R^5 is phenyl, phenyl-(C_{1-3})alkyl-, heteroaryl or heteroaryl-(C_{1-3})alkyl-, wherein the heteroaryl groups are 5- or 6-membered having from 1 to 3 heteroatoms each independently selected from N, O and S; wherein said phenyl and heteroaryl groups are each optionally substituted with one to three substituents each independently selected from halogen, -OH, (C_{1-4})alkyl, O-(C_{1-4})alkyl, S-(C_{1-4})alkyl, -NH_2, -NH(C_{1-4})alkyl, -N((C_{1-4})alkyl)$_2$, -$CONH_2$, -CONH-(C_{1-4})alkyl, -COOH, -COO(C_{1-6})alkyl, and -CO-(C_{1-6})alkyl; and

Y is H or (C_{1-6})alkyl;

with the proviso that when

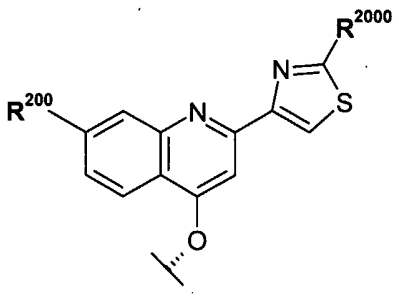
m is 2,

n is 1, and

R^4 is selected from (C_{1-6})alkyl, (C_{3-7})cycloalkyl-(C_{1-6})alkyl-, phenyl, naphthyl, pyridinyl, phenyl-(C_{1-4})alkyl-, naphthyl-(C_{1-4})alkyl- and pyridinyl-(C_{1-4})alkyl-; each of which being optionally substituted with nitro and each of which being optionally substituted with one to three substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, -NH_2, -NH(C_{1-4})alkyl and -N((C_{1-4})alkyl)$_2$; wherein said (C_{1-4})alkyl and O-(C_{1-6})alkyl are each optionally substituted with one to three halogen substituents;

or R^4 is (C_{3-7})cycloalkyl, said (C_{3-7})cycloalkyl being optionally substituted with nitro and optionally substituted with one or more substituents each independently selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, -OCF_3, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, -NH_2, -NH(C_{1-4})alkyl and -N((C_{1-4})alkyl)$_2$, wherein said (C_{1-4})alkyl is optionally substituted with one or more halogen substituents;

then R^2 cannot be



;

wherein

R^{200} is -O-(C_{1-4})alkyl, -NH(C_{1-4})alkyl, or -N((C_{1-4})alkyl)$_2$; and

R^{2000} is R^{2003} or -N(R^{2002})(R^{2001}); wherein

R^{2001} is selected from -C(O)-R^{2003}, –C(O)O-R^{2003}, -CON(R^{2002})(R^{2004}) and R^{2004};

R^{2002} in each case is independently selected from H and methyl;

R^{2003} is (C_{1-8})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl-(C_{1-4})alkyl-, wherein said (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-(C_{1-4})alkyl- are optionally substituted with one to three (C_{1-3})alkyl substituents; and

R^{2004} is H or R^{2003};

wherein **Het** as used herein is defined as a 3- to 7-membered heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, which may be saturated, unsaturated or aromatic, and which is optionally fused to at least one other cycle to form a 4- to 14-membered heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S, said heteropolycycle being saturated, unsaturated or aromatic;

or a salt thereof.

12. A pharmaceutical composition comprising an anti-hepatitis C virally effective amount of a compound according to one or more of claims 1 to 11, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier medium or auxiliary agent.

13. The pharmaceutical composition according to claim 12 additionally comprising a therapeutically effective amount of at least one other antiviral agent.

14. A method of treating a hepatitis C viral infection in a mammal by administering to the mammal an anti-hepatitis C virally effective amount of a compound according to one or more of claims 1 to 11, a pharmaceutically acceptable salt thereof, or a composition thereof.

15. Use of a compound according to one or more of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for the treatment of hepatitis C viral infection in a mammal.

16. Use of a compound according to one or more of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of hepatitis C viral infection in a mammal.

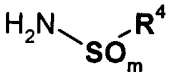
17. A method of inhibiting the replication of hepatitis C virus by exposing the virus to a hepatitis C viral NS3 protease inhibiting amount of the compound according to one or more of claims 1 to 11, or a pharmaceutically acceptable salt thereof.

18. Use of a compound according to one or more of claims 1 to 11, or a pharmaceutically acceptable salt thereof, to inhibit the replication of hepatitis C virus.

19. An article of manufacture comprising a composition effective to treat an HCV infection or to inhibit the NS3 protease of HCV; and packaging material comprising a label which indicates that the composition can be used to treat infection by the hepatitis C virus; wherein the composition comprises a compound according to one or more of claims 1 to 11 or a pharmaceutically acceptable salt thereof.

20. A process for the preparation of a compound according to one or more of claims 1 to 11, comprising:

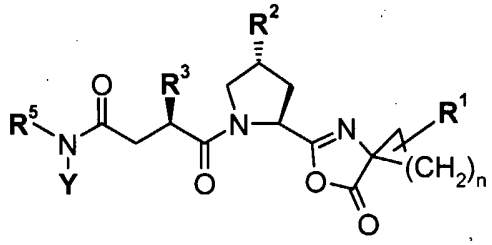
a) reacting a compound of formula (II):



(II)

wherein R^4 and **m** are defined as in claim 1, with a strong base so as to form the corresponding amide anion and

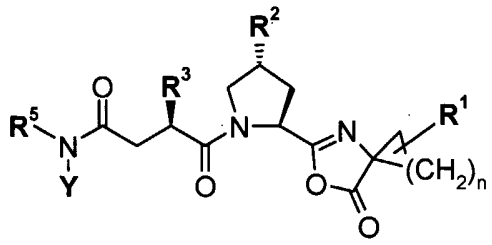
b) reacting an azalactone of formula (III):



(III)

wherein R^1, R^2, R^3, R^5, **Y** and **n** are defined as in claim 1, with the amide anion formed in step a).

21. An azalactone intermediate compound of formula (III):



(III)

wherein R^1, R^2, R^3, R^5, **Y** and **n** are defined as in claim 1.

22. Use of the azalactone intermediate compound according to claim 21 in the preparation of an HCV NS3 protease inhibitor peptide analog.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001126

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7): C07D 495/04, C07D 401/04, C07D 401/12, A61P 31/14, A61K 31/40, A61K 31/47, C07D 413/12, C07D 417/12, C07D 417/04, C07D 413/04

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(7): C07D 495/04, C07D 401/04, C07D 401/12, A61P 31/14, A61K 31/40, A61K 31/47, C07D 413/12, C07D 417/12, C07D 417/04, C07D 413/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Canadian Patent Database, STN, Delphion, Espacenet, search terms: "HCV", "hepatitis", "NS3", "azalactone", "RNA"

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/0077551 A1 (Campbell et al.) 22 April 2004 entire document (cited in the application)	1-19
A	US 2002/0111313 A1 (Campbell et al.) 15 August 2002 entire document (cited in the application)	1-19
A	US 2004/0072761 A1 (Campbell et al.) 15 April 2004 entire document (cited in the application)	1-19
P, A	US 2004/0224900 A1 (Bailey et al.) 11 November 2004 entire document (cited in the application)	1-19

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2005 (13-10-2005)	7 November 2005 (07-11-2005)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Authorized officer Cara Weir (819) 934-2322

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001126

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] Claim Nos. : 14 and 17

because they relate to subject matter not required to be searched by this Authority, namely :

Although claims 14 and 17 are directed to a method of medical treatment of the human or animal body, the search has been carried out based on the alleged effects of the compounds and pharmaceutically acceptable salts thereof.

2. [ ] Claim Nos. :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. [ ] Claim Nos. :

because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/CA2005/001126

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US20040077551	22-04-2004	US6878722	12-04-2005
		AU2003301959 A1	03-06-2004
		EP1505945 A2	16-02-2005
		WO2004043339 A2	27-05-2004
US20020111313	29-03-2005	CA2429359 A1	08-08-2002
		CN1531547 A	22-09-2004
		EP1337550 A2	27-08-2003
		HU0500456 A2	29-08-2005
		JP2004538251T T	24-12-2004
		MXPA03004299 A	12-02-2004
		WO02060926 A2	08-08-2002
US20040072761	22-03-2005	AU2003248535 A1	12-12-2003
		EP1506000 A1	16-02-2005
		WO03099316 A1	04-12-2003
US20040224900	21-06-2005	WO2004101602 A2	25-11-2004