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6,7-dihydropyrazolo(1,5-alpha)pyrazin-4(5H)-one compounds and their use as negative allosteric modulators of mGluR2 receptors

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(54) **Title:** 6,7-DIHYDROPYRAZOLO[1,5- α]PYRAZIN-4(5H)-ONE COMPOUNDS AND THEIR USE AS NEGATIVE ALLOSTERIC MODULATORS OF MGLUR2 RECEPTORS

(57) **Abstract:** The present invention relates to novel 6,7-dihydropyrazolo[1,5- α]pyrazin-4(5H)-one derivatives as negative allosteric modulators (NAMs) of the metabotropic glutamate receptor subtype 2 ("mGluR2"). The invention is also directed to pharmaceutical compositions comprising such compounds, to processes for preparing such compounds and compositions, and to the use of such compounds and compositions for the prevention or treatment of disorders in which the mGluR2 subtype of metabotropic receptors is involved.

**6,7-DIHYDROPYRAZOLO[1,5-*a*]PYRAZIN-4(5*H*)-ONE COMPOUNDS AND
THEIR USE AS NEGATIVE ALLOSTERIC MODULATORS OF MGLUR2
RECEPTORS**

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FIELD OF THE INVENTION

The present invention relates to novel 6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one derivatives as negative allosteric modulators (NAMs) of the metabotropic glutamate receptor subtype 2 (“mGluR2”). The invention is also directed to pharmaceutical compositions comprising such compounds, to processes for preparing such compounds and compositions, and to the use of such compounds and compositions for the prevention or treatment of disorders in which the mGluR2 subtype of metabotropic receptors is involved.

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BACKGROUND OF THE INVENTION

The glutamatergic system in the CNS is one of the neurotransmitter systems that play a key role in several brain functions. Metabotropic glutamate receptors (mGluR) belong to the G-protein-coupled family, and eight different subtypes have been identified to date, which are distributed to various brain regions (Ferraguti & Shigemoto, Cell & Tissue Research, 326:483-504, 2006). mGluRs participate in the modulation of synaptic transmission and neuronal excitability in the CNS by the binding of glutamate. This activates the receptor to engage intracellular signaling partners, leading to cellular events (Niswender & Conn, Annual Review of Pharmacology & Toxicology 50:295-322, 2010).

25 mGluRs are further divided into three subgroups based on their pharmacological and structural properties: group-I (mGluR1 and mGluR5), group-II (mGluR2 and mGluR3) and group-III (mGluR4, mGluR6, mGluR7 and mGluR8). Group-II ligands, both orthosteric and allosteric modulating, are considered to be potentially useful in the treatment of various neurological disorders, including psychosis, mood disorders, 30 Alzheimer’s disease and cognitive or memory deficiencies. This is consistent with their primary localisation in brain areas such as the cortex, hippocampus and the striatum (Ferraguti & Shigemoto, Cell & Tissue Research 326:483-504, 2006). Particularly antagonists and negative allosteric modulators are reported to hold potential for the treatment of mood disorders and cognitive or memory dysfunction. 35 This is based on findings with group-II receptor antagonists and negative allosteric modulators tested in laboratory animals subjected to a range of experimental conditions deemed relevant to these clinical syndromes (Goeldner et al, Neuropharmacology

64:337-346, 2013). Clinical trials are, for example, underway with mGluR2/3 antagonist declogurant RO4995819 (F. Hoffmann-La Roche Ltd.) in adjunctive therapy in patients with Major Depressive Disorder having inadequate response to ongoing antidepressant treatment (ClinicalTrials.gov Identifier NCT01457677, retrieved 19 February 2014).

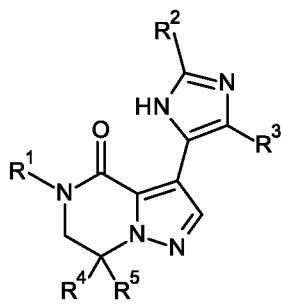
WO 2013066736 (Merck Sharp & Dohme Corp.) describes quinoline carboxamide and quinoline carbonitrile compounds as mGluR2 NAMs. WO2013174822 (Domain Therapeutics) describes 4H-pyrazolo[1,5-a]quinazolin-5-ones and 4H-pyrrolo-[1,2-a]quinazolin-5-ones and in vitro mGluR2 NAM activity thereof. WO 2014064028 (F. Hoffman-La Roche AG) discloses a selection of mGlu2/3 negative allosteric modulators and their potential use in the treatment of Autistic Spectrum Disorders (ASD).

The group-II receptors are mainly located on presynaptic nerve terminals where they exert a negative feedback loop to the release of glutamate into the synapse (Kelmendi et al, Primary Psychiatry 13:80-86, 2006). Functional inhibition of these receptors by antagonists or negative allosteric modulators therefore lifts the brake on glutamate release, resulting in enhanced glutamatergic signaling. This effect is believed to underlie the antidepressant-like and procognitive effects observed in preclinical species with inhibitors of the Group-II receptor. In addition, treatment of mice with group-II orthosteric antagonists has been shown to enhance signaling by growth factors such as brain derived neurotrophic factor (BDNF) (Koike et al, Behavioural Brain Research 238:48-52, 2013). Since BDNF and other growth factors have been shown to be critically involved in mediating synaptic plasticity, this mechanism is likely to contribute to both antidepressant and procognitive properties of these compounds. Inhibition of mGluRs of the group-II receptor family is therefore considered to represent a potential therapeutic mechanism for neurological disorders, including depression and cognitive or memory dysfunction.

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

DESCRIPTION OF THE INVENTION

According to a first aspect, the present invention provides a compound of Formula (I)



(I)

or a stereoisomeric form or a tautomer thereof, wherein

R¹ is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C₁₋₄alkyl, mono-haloC₁₋₄alkyl, poly-halo-C₁₋₄alkyl, -CN, and C₃₋₇cycloalkyl;

R² is selected from the group consisting of H; C₁₋₄alkyl; C₃₋₇cycloalkyl; -CN; -NR^aR^b; -C(O)NR^cR^d; -C(O)C₁₋₄alkyl; -C₁₋₄alkyl-OH; -C₁₋₄alkyl-O-C₁₋₄alkyl; Aryl; Het; and C₁₋₄alkyl substituted with one or more substituents each independently selected from the group consisting of halo and C₃₋₇cycloalkyl; wherein

R^a, R^b, R^c, and R^d are each independently selected from H and C₁₋₄alkyl;

Aryl is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C₁₋₄alkyl, mono-haloC₁₋₄alkyl, and poly-halo-C₁₋₄alkyl;

Het is (a) a 6-membered aromatic heterocyclyl substituent selected from the group consisting of pyridinyl, and pyrazinyl, each of which may be optionally substituted with one or more substituents each independently selected from the group consisting of halo, C₁₋₄alkyl, and -NR^eR^f;

or (b) a 5-membered aromatic heterocyclyl selected from the group consisting of thiazolyl, oxazolyl, *1H*-pyrazolyl, and *1H*-imidazolyl, each of which may be optionally substituted with one or more substituents each independently selected from the group consisting of halo, C₁₋₄alkyl, mono-haloC₁₋₄alkyl, and poly-halo-C₁₋₄alkyl;

R^e and R^f are each independently selected from hydrogen, and C₁₋₄alkyl;

R³ is selected from the group consisting of hydrogen, halo, C₁₋₄alkyl, C₃₋₇cycloalkyl, -CN, and -OC₁₋₄alkyl;

R⁴ is selected from hydrogen and C₁₋₄alkyl; and

R⁵ is selected from the group consisting of hydrogen, C₁₋₄alkyl, and -C₁₋₄alkyl-O-C₁₋₄alkyl;

or an N-oxide, or a pharmaceutically acceptable salt or a solvate thereof.

According to a second aspect, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound according to the invention and a pharmaceutically acceptable carrier or excipient.

According to a third aspect, the present invention provides a process for preparing the pharmaceutical composition according to the invention, wherein a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound according to the invention.

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5 According to a fourth aspect, the present invention provides a method of treating or preventing a central nervous system disorder or condition associated with glutamate dysfunction selected from mood disorders; delirium, dementia, amnesic and other cognitive disorders; disorders usually first diagnosed in infancy, childhood or adolescence; substance-related disorders; schizophrenia and other psychotic disorders; somatoform disorders; and hypersomnic sleep disorder comprising administering to a subject in need thereof, a therapeutically effective amount of a compound according to the invention or a therapeutically effective amount of a pharmaceutical composition according to the invention.

0 According to a fifth aspect, the present invention provides a method of treating or preventing a central nervous system disorder or condition associated with glutamate dysfunction selected from depressive disorders; neurocognitive disorders; neurodevelopmental disorders; substance-related and addictive disorders; schizophrenia spectrum and other psychotic disorders; somatic symptom and related disorders; and hypersomnolence disorder; comprising administering to a subject in need thereof, a therapeutically effective amount of a compound according to the invention or a therapeutically effective amount of a pharmaceutical composition according to the invention.

5 According to a sixth aspect, the present invention provides use of a compound according to the invention or a pharmaceutical composition according to the invention in the manufacture of a medicament for treating or preventing a central nervous system disorder or condition associated with glutamate dysfunction selected from mood disorders; delirium, dementia, amnesic and other cognitive disorders; disorders usually first diagnosed in infancy, childhood or adolescence; substance-related disorders; schizophrenia and other psychotic disorders; somatoform disorders; and hypersomnic sleep disorder.

10 According to a seventh aspect, the present invention provides use of a compound according to the invention or a pharmaceutical composition according to the invention in the manufacture of a medicament for treating or preventing a central nervous system disorder or condition associated with glutamate dysfunction selected from depressive disorders; neurocognitive disorders; neurodevelopmental disorders; substance-related and addictive disorders; schizophrenia spectrum and other psychotic disorders; somatic symptom and related disorders; and hypersomnolence disorder.

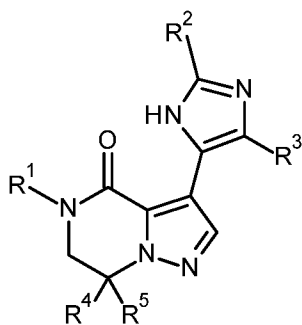
25 According to an eighth aspect, the present invention provides a method of treating or preventing a major depressive disorder, depression, or treatment resistant depression comprising administering to a subject in need thereof, a therapeutically effective amount of a compound according to the invention or a therapeutically effective amount of a

pharmaceutical composition according to the invention, wherein the major depressive disorder, depression, or treatment resistant depression is associated with glutamate dysfunction.

According to a ninth aspect, the present invention provides use of a compound according to the invention or a pharmaceutical composition according to the invention in the manufacture of a medicament for treating or preventing a major depressive disorder, depression, or treatment resistant depression, wherein the major depressive disorder, depression, or treatment resistant depression is associated with glutamate dysfunction.

Unless the context clearly requires otherwise, throughout the description and the claims, the words “comprise”, “comprising”, and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of “including, but not limited to”.

The present invention is directed to 6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one derivatives of Formula (I)



(I)

and stereoisomeric forms and tautomers thereof, wherein

5 R^1 is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4} alkyl, mono-halo C_{1-4} alkyl, poly-halo- C_{1-4} alkyl, -CN, and C_{3-7} cycloalkyl;

R^2 is selected from the group consisting of H; C_{1-4} alkyl; C_{3-7} cycloalkyl; -CN; -NR^aR^b; -C(O)NR^cR^d; -C(O) C_{1-4} alkyl; - C_{1-4} alkyl-OH; - C_{1-4} alkyl-O- C_{1-4} alkyl; Aryl; Het; and
10 C_{1-4} alkyl substituted with one or more substituents each independently selected from the group consisting of halo and C_{3-7} cycloalkyl; wherein

R^a , R^b , R^c , and R^d are each independently selected from H and C_{1-4} alkyl;

15 Aryl is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4} alkyl, mono-halo C_{1-4} alkyl, and poly-halo- C_{1-4} alkyl;

20 Het is (a) a 6-membered aromatic heterocyclyl substituent selected from the group consisting of pyridinyl, and pyrazinyl, each of which may be optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4} alkyl, and -NR^eR^f;

25 or (b) a 5-membered aromatic heterocyclyl selected from the group consisting of thiazolyl, oxazolyl, *1H*-pyrazolyl, and *1H*-imidazolyl, each of which may be optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4} alkyl, mono-halo C_{1-4} alkyl, and poly-halo- C_{1-4} alkyl;

30 R^e and R^f are each independently selected from hydrogen, and C_{1-4} alkyl; and

R^3 is selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, C_{3-7} cycloalkyl, -CN, and -OC C_{1-4} alkyl;

R⁴ is selected from hydrogen and C₁₋₄alkyl;

R⁵ is selected from the group consisting of hydrogen, C₁₋₄alkyl, and -C₁₋₄alkyl-O-C₁₋₄alkyl;

5

and the N-oxides thereof, and the pharmaceutically acceptable salts and the solvates thereof.

10 The present invention also relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or excipient.

15 Additionally, the invention relates to a compound of Formula (I) for use as a medicament, and to a compound of Formula (I) for use in the treatment or in the prevention of central nervous system conditions or diseases selected from mood disorders; delirium, dementia, amnestic and other cognitive disorders; disorders usually first diagnosed in infancy, childhood or adolescence; substance-related disorders; schizophrenia and other psychotic disorders; somatoform disorders; and hypersomnic sleep disorder.

20

The invention also relates to the use of a compound of Formula (I) in combination with an additional pharmaceutical agent for use in the treatment or prevention of central nervous system conditions or diseases selected from mood disorders; delirium, dementia, amnestic and other cognitive disorders; disorders usually first diagnosed in 25 infancy, childhood or adolescence; substance-related disorders; schizophrenia and other psychotic disorders; somatoform disorders; and hypersomnic sleep disorder.

30 Furthermore, the invention relates to a process for preparing a pharmaceutical composition according to the invention, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound of Formula (I).

35 The invention also relates to a method of treating or preventing a central nervous system disorder selected from mood disorders; delirium, dementia, amnestic and other cognitive disorders; disorders usually first diagnosed in infancy, childhood or adolescence; substance-related disorders; schizophrenia and other psychotic disorders; somatoform disorders; and hypersomnic sleep disorder comprising administering to a

subject in need thereof, a therapeutically effective amount of a compound of Formula (I) or a therapeutically effective amount of a pharmaceutical composition according to the invention.

- 5 The invention also relates to a product comprising a compound of Formula (I) and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of central nervous system conditions or diseases selected from mood disorders; delirium, dementia, amnesic and other cognitive disorders; disorders usually first diagnosed in infancy, childhood or
10 adolescence; substance-related disorders; schizophrenia and other psychotic disorders; somatoform disorders; and hypersomnic sleep disorder.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates in particular to compounds of Formula (I) as defined
15 hereinabove, and stereoisomeric forms and tautomers thereof, wherein

R^1 is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4} alkyl, mono-halo C_{1-4} alkyl, poly-halo- C_{1-4} alkyl, and -CN;

- 20 R^2 is selected from the group consisting of H; C_{1-4} alkyl; C_{3-7} cycloalkyl; -CN; $-NR^aR^b$; $-C(O)NR^cR^d$; $-C_{1-4}$ alkyl-O- C_{1-4} alkyl; Aryl; Het; and C_{1-4} alkyl substituted with one or more substituents each independently selected from halo; wherein

R^a , R^b , R^c , and R^d are each independently selected from H and C_{1-4} alkyl;

- 25 Aryl is phenyl;

Het is (a) pyridinyl optionally substituted with a $-NR^eR^f$ or a C_{1-4} alkyl substituent;

- 30 R^e and R^f are each hydrogen;

R^3 is selected from the group of hydrogen, halo, C_{1-4} alkyl and cyano;

R^4 is hydrogen; and

- 35 R^5 is C_{1-4} alkyl;

and the N-oxides thereof, and the pharmaceutically acceptable salts and the solvates thereof.

5 In a further embodiment, the invention relates to compounds of Formula (I) as defined hereinabove, and stereoisomeric forms thereof, wherein

R^1 is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4} alkyl, mono-halo C_{1-4} alkyl, poly-halo- C_{1-4} alkyl, and -CN;

10 R^2 is selected from the group consisting of H; C_{1-4} alkyl; C_{3-7} cycloalkyl; -CN; $-NR^aR^b$; $-C(O)NR^cR^d$; $-C_{1-4}$ alkyl-O- C_{1-4} alkyl; Aryl; Het; and C_{1-4} alkyl substituted with one or more substituents each independently selected from halo; wherein

R^a , R^b , R^c , and R^d are each independently selected from H and C_{1-4} alkyl;

15

Aryl is phenyl;

Het is (a) pyridinyl optionally substituted with a $-NR^eR^f$ or a C_{1-4} alkyl substituent;

20 R^e and R^f are each hydrogen;

R^3 is selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl;

R^4 is hydrogen; and

25

R^5 is C_{1-4} alkyl;

and the N-oxides thereof, and the pharmaceutically acceptable salts and the solvates thereof.

30 In a further embodiment, the invention relates to compounds of Formula (I) as defined hereinabove, and stereoisomeric forms thereof, wherein

R^1 is phenyl optionally substituted with one or two substituents each independently selected from the group consisting of halo, mono-halo C_{1-4} alkyl, and poly-halo- C_{1-4} alkyl;

35

R² is selected from the group consisting of C₁₋₄alkyl; C₃₋₇cycloalkyl; and C₁₋₄alkyl substituted with one or more substituents each independently selected from halo;

R³ is hydrogen;

5

R⁴ is hydrogen; and

R⁵ is C₁₋₄alkyl;

and the N-oxides thereof, and the pharmaceutically acceptable salts and the solvates thereof.

10

In a further embodiment, the invention relates to compounds of Formula (I) as defined hereinabove, and stereoisomeric forms thereof, wherein

R¹ is phenyl substituted with one or two substituents each independently selected from the group consisting of halo, mono-haloC₁₋₄alkyl, and poly-haloC₁₋₄alkyl;

15

R² is selected from the group consisting of C₁₋₄alkyl; C₃₋₇cycloalkyl; and C₁₋₄alkyl substituted with one or more substituents each independently selected from halo;

R³ is hydrogen;

20

R⁴ is hydrogen; and

R⁵ is C₁₋₄alkyl;

and the N-oxides thereof, and the pharmaceutically acceptable salts and the solvates thereof.

25

In a further embodiment, the invention relates to compounds of Formula (I) as defined hereinabove, and stereoisomeric forms thereof, wherein

R¹ is phenyl substituted with one or two substituents each independently selected from the group consisting of halo, mono-haloC₁₋₄alkyl, and poly-haloC₁₋₄alkyl;

30

R² is selected from the group consisting of C₁₋₄alkyl; and C₁₋₄alkyl substituted with one or more substituents each independently selected from halo;

35

R³ is hydrogen;

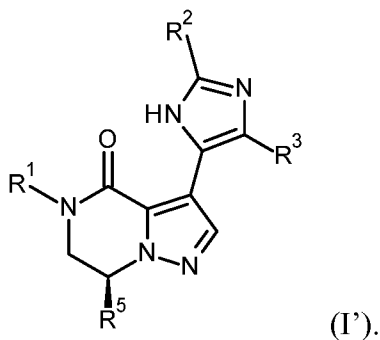
R⁴ is hydrogen; and

R⁵ is C₁₋₄alkyl;

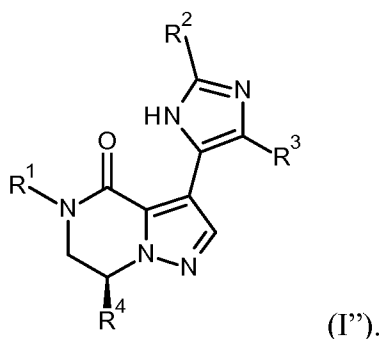
- 5 and the N-oxides thereof, and the pharmaceutically acceptable salts and the solvates thereof.

In a further embodiment, the invention relates to compounds of Formula (I) as defined herein, and stereoisomeric forms thereof, wherein R² is C₁₋₄alkyl and the rest of
10 variables are as defined herein.

In a further embodiment, the present invention relates to compounds of Formula (I) as defined herein wherein R⁴ is hydrogen and R⁵ is a substituent different from hydrogen having a configuration as depicted in the Formula (I') below, wherein the 6,7-
15 dihydropyrazolo[1,5-a]pyrazin-4(5H)-one core, R¹ and the imidazole substituent are in the plane of the drawing and R⁵ is projected above the plane of the drawing (bond shown with a bold wedge), and the rest of variables are as defined in Formula (I) herein



- 20 In a yet further embodiment, the present invention relates to compounds of Formula (I) as defined herein wherein R⁵ is hydrogen and R⁴ is a substituent different from hydrogen, for example a C₁₋₄alkyl substituent having a configuration as depicted in the
Formula (I'') below, wherein the 6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one core, R¹
25 and the imidazole substituent are in the plane of the drawing and R⁴ is projected above the plane of the drawing (bond shown with a bold wedge), and the rest of variables are as defined in Formula (I) herein



Specific compounds according to the invention include:

- (7S)-7-methyl-3-(2-methyl-1H-imidazol-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
- (7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methyl-1H-imidazol-5-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
- (7S)-3-(1H-imidazol-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
- (7S)-3-(5-bromo-1H-imidazol-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
- (7S)-3-(2-cyclopropyl-1H-imidazol-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
- (7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-3-(2-cyclopropyl-1H-imidazol-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
- (7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-3-(2-isopropyl-1H-imidazol-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
- (7S)-3-(2-isopropyl-1H-imidazol-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
- 4-[(7S)-7-methyl-4-oxo-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-3-yl]-1H-imidazole-2-carbonitrile;
- 4-[(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-7-methyl-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-3-yl]-1H-imidazole-2-carbonitrile;
- (7S)-7-methyl-3-[2-(methylamino)-1H-imidazol-5-yl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
- (7S)-3-[2-(methoxymethyl)-1H-imidazol-5-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
- 5-[(7S)-7-methyl-3-(2-methyl-1H-imidazol-4-yl)-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-5-yl]-2-(trifluoromethyl)benzotrile;
- (7S)-7-methyl-3-[2-(trifluoromethyl)-1H-imidazol-5-yl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

4-[(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-7-methyl-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-3-yl]-1H-imidazole-2-carboxamide;
4-[(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-7-methyl-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-3-yl]-N-methyl-1H-imidazole-2-carboxamide;
4-[(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-7-methyl-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-3-yl]-N,N-dimethyl-1H-imidazole-2-carboxamide;
(7S)-7-methyl-3-(2-phenyl-1H-imidazol-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-3-(2,4-dimethyl-1H-imidazol-5-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-3-(2-cyclopropyl-4-methyl-1H-imidazol-5-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-(6-amino-3-pyridyl)-5-bromo-1H-imidazol-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[3-(fluoromethyl)-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methyl-1H-imidazol-5-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-7-methyl-3-[5-methyl-2-(3-pyridyl)-1H-imidazol-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-(6-amino-3-pyridyl)-1H-imidazol-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-(2-cyclopropyl-4-methyl-1H-imidazol-5-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-(6-amino-3-pyridyl)-5-methyl-1H-imidazol-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-(6-amino-3-pyridyl)-5-methyl-1H-imidazol-4-yl]-5-[3-chloro-4-(trifluoromethyl)phenyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-(6-amino-3-pyridyl)-1H-imidazol-4-yl]-5-[3-chloro-4-(trifluoromethyl)phenyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-(6-amino-3-pyridyl)-5-chloro-1H-imidazol-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-7-methyl-3-[5-methyl-2-(3-pyridyl)-1H-imidazol-4-yl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-(6-amino-3-pyridyl)-1H-imidazol-4-yl]-7-methyl-5-[3-methyl-4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-7-methyl-3-[5-methyl-2-(2-pyridyl)-1H-imidazol-4-yl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-(6-amino-3-pyridyl)-1H-imidazol-4-yl]-5-(3,4-dichlorophenyl)-7-methyl-6,7-

dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-7-methyl-3-[2-(2-pyridyl)-1H-imidazol-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-7-methyl-5-[3-methyl-4-(trifluoromethyl)phenyl]-3-[2-(2-pyridyl)-1H-imidazol-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-7-methyl-3-[5-methyl-2-(2-pyridyl)-1H-imidazol-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-(2-cyclopropyl-4-methyl-1H-imidazol-5-yl)-7-methyl-5-[3-methyl-4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-7-methyl-3-[2-(3-pyridyl)-1H-imidazol-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-(3,4-dichlorophenyl)-7-methyl-3-[2-(2-pyridyl)-1H-imidazol-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-7-methyl-3-[2-(2-methyl-4-pyridyl)-1H-imidazol-5-yl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-(2-cyclobutyl-1H-imidazol-5-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
2-(6-amino-3-pyridyl)-4-[(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-7-methyl-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-3-yl]-1H-imidazole-5-carbonitrile;
(7S)-7-methyl-3-(2-pyrazin-2-yl-1H-imidazol-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-pyrazin-2-yl-1H-imidazol-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-3-(2-cyclobutyl-1H-imidazol-5-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
and the N-oxides thereof, and the pharmaceutically acceptable salts and solvates of such compounds.

In an additional embodiment, the compound is

(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-3-(2,4-dimethyl-1H-imidazol-5-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one or a hydrochloride salt thereof.

5

The names of the compounds of the present invention were generated according to the nomenclature rules agreed upon by the International Union of Pure and Applied Chemistry (IUPAC) generated by Accelrys Direct, Revision 8.0 SP1 (Microsoft Windows 64-bit Oracle11) (8.0.100.4), OpenEye:1.2.0.. In case of tautomeric forms,
10 the name of the depicted tautomeric form of the structure was generated. However it

should be clear that the other non-depicted tautomeric form is also included within the scope of the present invention.

Definitions

5 The notation "C₁₋₄alkyl" as used herein alone or as part of another group, defines a saturated, straight or branched, hydrocarbon radical having, unless otherwise stated, from 1 to 4 carbon atoms, such as methyl, ethyl, 1-propyl, 1-methylethyl, butyl, 1-methyl-propyl, 2-methyl-1-propyl, 1,1-dimethylethyl and the like. The notation
10 "-C₁₋₄alkyl-OH" as used herein alone or as part of another group, refers to C₁₋₄alkyl as defined before, substituted with one OH group at any available carbon atom. The notation "halogen" or "halo" as used herein alone or as part of another group, refers to fluoro, chloro, bromo or iodo, with fluoro or chloro being preferred. The notation
15 "mono-haloC₁₋₄alkyl, polyhaloC₁₋₄alkyl" as used herein alone or as part of another group, refers to C₁₋₄alkyl as defined before, substituted with 1, 2, 3 or where possible with more halo atoms as defined before. The notation "C₃₋₇cycloalkyl" as used herein refers to a saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A particular C₃₋₇cycloalkyl group is cyclopropyl.

The N-oxide forms of the compounds according to Formula (I) are meant to comprise
20 those compounds of Formula (I) wherein one or several nitrogen atoms are oxidized to the so called N-oxide, particularly those N-oxides wherein a nitrogen atom in a pyridinyl radical is oxidized. N-oxides can be formed following procedures known to the skilled person. The N-oxidation reaction may generally be carried out by reacting the starting material of Formula (I) with an appropriate organic or inorganic peroxide.
25 Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide/
appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chloroperoxybenzoic acid (or 3-chloroperbenzoic acid), peroxyalkanoic acids, e.g.
30 peroxyacetic acid, alkylhydroperoxides, e.g. tert-butyl hydroperoxide. Suitable solvents, are for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Whenever the term "substituted" is used in the present invention, it is meant, unless
35 otherwise is indicated or is clear from the context, to indicate that one or more

hydrogens, preferably from 1 to 3 hydrogens, more preferably from 1 to 2 hydrogens, more preferably 1 hydrogen, on the atom or radical indicated in the expression using “substituted” are replaced with a selection from the indicated group, provided that the normal valency is not exceeded, and that the substitution results in a chemically stable
5 compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who is or has been the object of treatment, observation or experiment.

10 The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

15 As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

It will be appreciated that some of the compounds of Formula (I) and their
20 pharmaceutically acceptable addition salts and solvates thereof may contain one or more centres of chirality and exist as stereoisomeric forms. The term “compounds of the invention” as used herein, is meant to include the compounds of Formula (I), and the salts and solvates thereof. As used herein, any chemical formula with bonds shown only as solid lines and not as solid wedged or hashed wedged bonds, or otherwise
25 indicated as having a particular configuration (e.g. R, S) around one or more atoms, contemplates each possible stereoisomer, or mixture of two or more stereoisomers. Hereinbefore and hereinafter, the term “compound of Formula (I)” is meant to include the stereoisomers thereof and the tautomeric forms thereof. The terms “stereoisomers”, “stereoisomeric forms” or “stereochemically isomeric forms” hereinbefore or
30 hereinafter are used interchangeably. The invention includes all stereoisomers of the compounds of the invention either as a pure stereoisomer or as a mixture of two or more stereoisomers. Enantiomers are stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a racemate or racemic mixture. Diastereomers (or diastereoisomers) are stereoisomers that are not

enantiomers, i.e. they are not related as mirror images. If a compound contains a double bond, the substituents may be in the E or the Z configuration. Substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration; for example if a compound contains a disubstituted cycloalkyl group, the substituents may be in the cis or trans configuration. Therefore, the invention includes enantiomers, diastereomers, racemates, E isomers, Z isomers, cis isomers, trans isomers and mixtures thereof, whenever chemically possible. The meaning of all those terms, i.e. enantiomers, diastereomers, racemates, E isomers, Z isomers, cis isomers, trans isomers and mixtures thereof are known to the skilled person.

- 5
- 10 The absolute configuration is specified according to the Cahn-Ingold-Prelog system. The configuration at an asymmetric atom is specified by either R or S. Resolved stereoisomers whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light. For instance, resolved enantiomers whose absolute configuration is not known can be designated by
- 15 (+) or (-) depending on the direction in which they rotate plane polarized light.

When a specific stereoisomer is identified, this means that said stereoisomer is substantially free, i.e. associated with less than 50%, preferably less than 20%, more preferably less than 10%, even more preferably less than 5%, in particular less than 2% and most preferably less than 1%, of the other isomers. Thus, when a compound of

20 Formula (I) is for instance specified as (R), this means that the compound is substantially free of the (S) isomer; when a compound of Formula (I) is for instance specified as E, this means that the compound is substantially free of the Z isomer; when a compound of Formula (I) is for instance specified as cis, this means that the compound is substantially free of the trans isomer.

- 25 Some of the compounds according to Formula (I) may also exist in their tautomeric form. Such forms in so far as they may exist, although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. It follows that a single compound may exist in both stereoisomeric and tautomeric forms.

For therapeutic use, salts of the compounds of Formula (I) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not, are included within the ambit of the present invention.

30

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove or hereinafter are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of Formula (I) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by

5 treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric,

10 methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids. Conversely said salt forms can be converted by treatment with an appropriate base into the free base form. The compounds of Formula (I) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and

15 inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. primary, secondary and tertiary aliphatic and aromatic amines such as methylamine, ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine,

20 diethylamine, diethanolamine, dipropylamine, diisopropylamine, di-*n*-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline; the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by

25 treatment with acid into the free acid form.

The term solvate comprises the solvent addition forms as well as the salts thereof, which the compounds of Formula (I) are able to form. Examples of such solvent addition forms are e.g. hydrates, alcoholates and the like.

In the framework of this application, an element, in particular when mentioned in

30 relation to a compound according to Formula (I), comprises all isotopes and isotopic mixtures of this element, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form, for example ^2H .

Radiolabelled compounds of Formula (I) may comprise a radioactive isotope selected from the group consisting of ^3H , ^{11}C , ^{14}C , ^{18}F , ^{122}I , ^{123}I , ^{125}I , ^{131}I , ^{75}Br , ^{76}Br , ^{77}Br and

35 ^{82}Br . Preferably, the radioactive isotope is selected from the group consisting of ^3H , ^{11}C

and ^{18}F .

PREPARATION

The compounds according to the invention can generally be prepared by a succession of steps, each of which is known to the skilled person. In particular, the compounds can
5 be prepared according to the following synthesis methods.

The compounds of Formula (I) may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said
10 diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically.

15 The absolute configuration of compounds of the invention reported herein was determined by analysis of the racemic mixture by supercritical fluid chromatography (SFC) followed by SFC comparison of the separate enantiomer(s) which were obtained by asymmetric synthesis, followed by vibrational circular dichroism (VCD) analysis of the particular enantiomer(s).

20

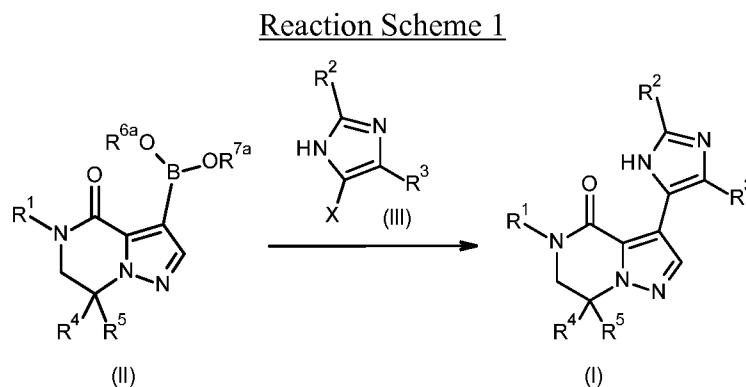
A. Preparation of the final compounds

Experimental procedure 1

Final compounds according to Formula (I) can be prepared by a Suzuki type coupling reaction of a compound of Formula (II) where R^{6a} and R^{7a} may be each independently
25 selected from H, C_{1-4} alkyl or R^{6a} and R^{7a} may be taken together to form for example a bivalent radical of formula $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$ or $-\text{C}(\text{CH}_3)_2\text{C}(\text{CH}_3)_2-$ with a suitable halo imidazole derivative compound of Formula (III) wherein X is a halogen, in particular bromo or iodo, in the presence of a palladium catalyst, according to reaction conditions known to the skilled person. Such reaction conditions include the
30 use of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0) or an alternative catalyst system prepared *in situ* from $\text{Pd}(\text{OAc})_2$ and PPh_3 , a suitable base, such as Na_2CO_3 , K_2CO_3 , NaOAc , NaHCO_3 or K_3PO_4 , and in a suitable solvent, such as 1,4-dioxane, or a mixture of dimethoxyethane (DME) and water. Degassing the reaction mixture with an inert gas, such as N_2 or argon, and heating the reaction

mixture to high temperatures, such as reflux temperature under classical heating or microwave irradiation, in particular 80 °C, may enhance the reaction outcome. A compound of Formula (III) can be obtained commercially or made according to procedures known in the art. In Reaction Scheme 1, all variables are defined as in

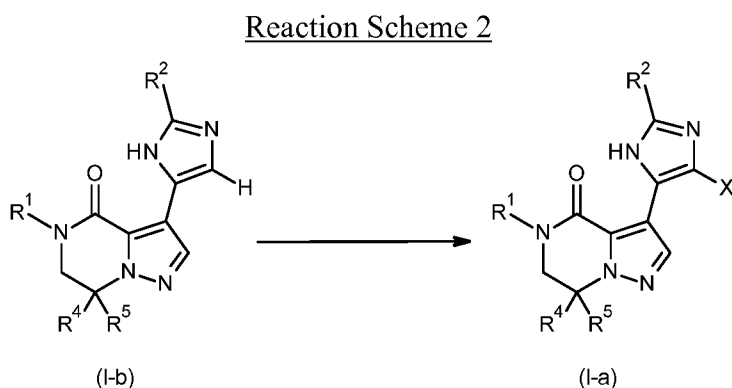
5 Formula (I).



Experimental procedure 2

Alternatively, final compounds according to Formula (I) wherein R^3 is halo ($R^3=X$) hereby referred to as compounds of Formula (I-a) can be prepared *via* a reaction of halogenation of a compound of Formula (I) wherein R^3 is hydrogen ($R^3=H$) hereby referred to as compounds of Formula (I-b) with a halogenating reagent such as *N*-bromosuccinimide, in an inert solvent such as acetonitrile, under suitable reaction conditions, such as at a convenient temperature, typically rt, for a period of time to

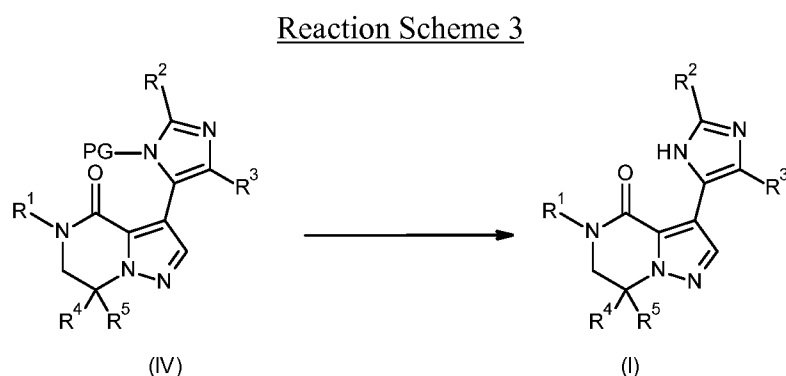
15 ensure the completion of the reaction. In Reaction Scheme 2, X is halo and all other variables are defined as in Formula (I).



Experimental procedure 3

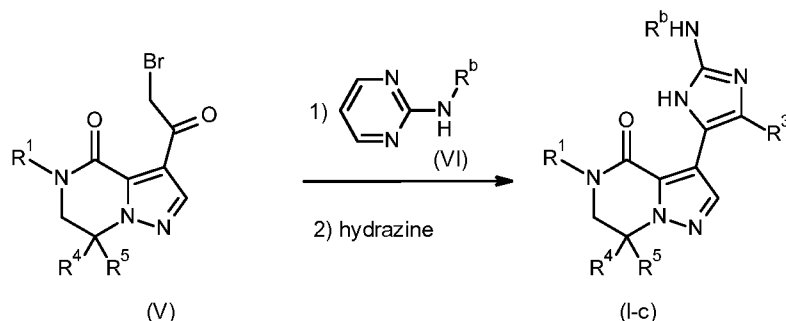
20 Alternatively, final compounds according to Formula (I) can be prepared by a reaction of deprotection of a compound of Formula (IV) according to conditions known to the skilled person. A compound of Formula (I) can be obtained by removal of the protecting group such as for example: a) A SEM (trimethylsilyl)ethoxymethyl)

protecting group in the compound of Formula (IV), in the presence of acidic media, such as hydrochloric acid in an inert solvent such as a 2-propanol, under suitable reaction conditions, such as at a convenient temperature, typically ranging between 50 °C and 70 °C, in particular 60 °C, for a period of time to ensure the completion of the reaction. Heating the reaction mixture under microwave irradiation, in particular 100 °C, may enhance the reaction outcome. b) A benzyloxymethyl group in the presence of a Lewis acid, such as boron tribromide, in an inert solvent such as toluene, under suitable reaction conditions, such as at a convenient temperature, in particular at 90 °C, for a period of time to ensure the completion of the reaction. c) A benzyl group by means of catalytic hydrogenation in the presence of an appropriate catalyst, such as palladium hydroxide, under hydrogen atmosphere, in an inert solvent such as a mixture of EtOH/acetic acid, at a convenient temperature, typically ranging between 90 to 110 °C, in particular 100 °C, for a period of time to ensure the completion of the reaction. In Reaction Scheme 3, PG is a protecting group and all other variables are defined as in Formula (I).

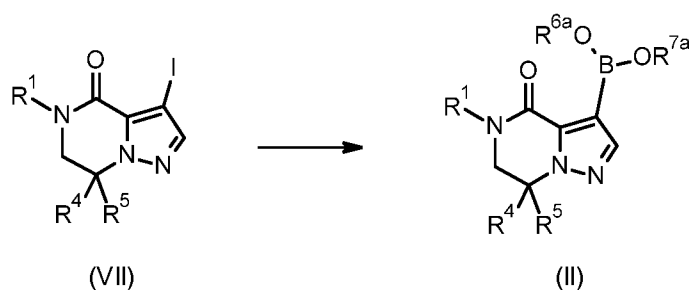


Experimental procedure 4

Alternatively, final compounds according to Formula (I) wherein R² is NHR^b herein referred to as a compound of Formula (I-c), can be prepared by one-pot two-step protocol from a compound of Formula (V) following conditions described by D.S. Ermolat'ev and al. in *Mol Divers.*, **2011**, 15(2), 491-6. This process involves the sequential formation of 2,3-dihydro-2-hydroxyimidazo[1,2-*a*]pyrimidinium salts from an α -bromoketone of Formula (V) and a compound of Formula (VI), followed by cleavage of the pyrimidine ring with hydrazine. A compound of Formula (VI) can be obtained commercially or made according to procedures known in the art. In Reaction Scheme 4, all variables are defined as in Formula (I).

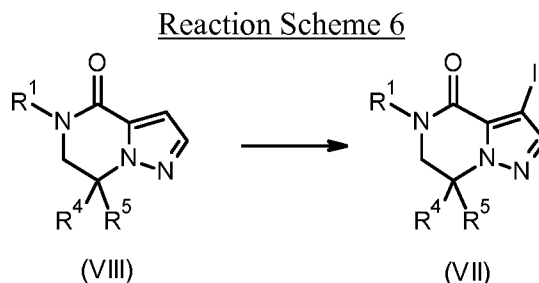
Reaction Scheme 4B. Preparation of the intermediate compounds5 Experimental procedure 5

Intermediate compound of Formula (II) can be prepared *via* a reaction of boronic ester or boronic acid formation starting from an intermediate of Formula (VII), with a trans metallating agent such as for example *n*BuLi or a Grignard reagent, a particular example of reagents includes isopropylmagnesium chloride lithium chloride complex solution and a boron species such as 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, in an inert solvent such as anhydrous THF, under suitable reaction conditions, such as at a convenient temperature, typically -25°C, for a period of time to ensure the completion of the reaction. Depending on reaction conditions, boronic ester and/or boronic acid are obtained. In Reaction Scheme 5, R^{6a} and R^{7a} are H or C₁₋₄ alkyl or R^{6a} and R^{7a} are taken together to form for example a bivalent radical of formula -CH₂CH₂-, -CH₂CH₂CH₂- or -C(CH₃)₂C(CH₃)₂-, and all other variables are defined as in Formula (I).

Reaction Scheme 520 Experimental procedure 6

Intermediate compound of Formula (VII) can be prepared *via* a reaction of halogenation of an intermediate of Formula (VIII) with a halogenating reagent such as iodine, in the presence of ammonium cerium(IV) nitrate and in an inert solvent such as acetonitrile, under suitable reaction conditions, such as at a convenient temperature,

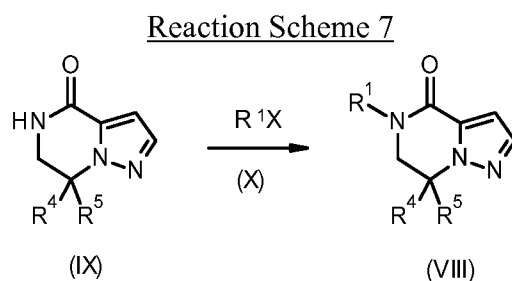
typically 70 °C, for a period of time to ensure the completion of the reaction. In Reaction Scheme 6, all variables are defined as in Formula (I).



5 Experimental procedure 7

Intermediate compound of Formula (VIII) can be prepared by a coupling reaction of an intermediate compound of Formula (IX) with an appropriate aryl/heteroaryl halide of Formula (X) where X is halo with a suitable copper(I) catalyst such as copper(I) iodide, in the presence of a ligand, such as *N,N*-dimethylethylenediamine, in the presence of a base, such as Na₂CO₃, in a suitable solvent, such as toluene, under suitable reaction conditions, such as at a convenient temperature, typically ranging between 100 °C and 140 °C, for a period of time to ensure the completion of the reaction. An intermediate compound of Formula (X) can be obtained commercially. In Reaction Scheme 7, all variables are defined as in Formula (I).

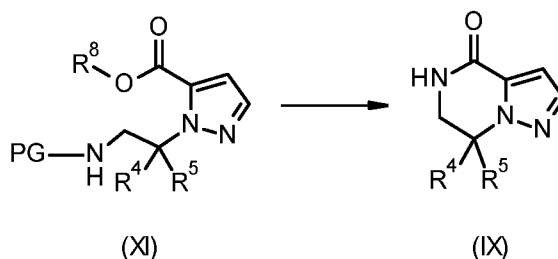
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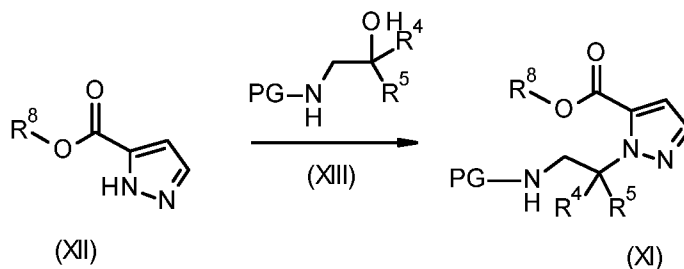
Experimental procedure 8

Intermediate compound of Formula (IX) can be prepared by removal of the protecting group in an intermediate of Formula (XI), for example in the presence of acidic media, such as hydrochloric acid, in an inert solvent such as 1,4-dioxane, under suitable reaction conditions, such as at a convenient temperature, typically 80 °C, for a period of time to ensure the completion of the reaction followed by treatment with a base, such as Na₂CO₃ or NaHCO₃, under suitable reaction conditions, such as at a convenient temperature, typically ranging between 0 °C and 40 °C, for a period of time to ensure the completion of the reaction. In Reaction Scheme 8, R⁸ is C₁₋₄alkyl, PG is a protecting group and all other variables are defined as in Formula (I).

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Reaction Scheme 8Experimental procedure 9

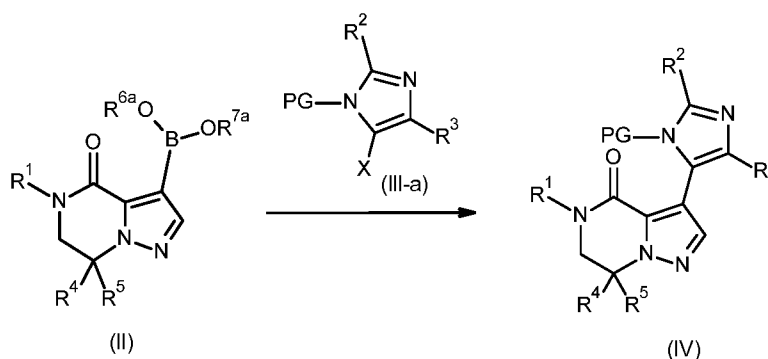
Intermediate compound of Formula (XI) wherein R^8 is C_{1-4} alkyl and PG is a protecting group, can be prepared by a Mitsunobu type reaction between a compound of Formula (XII) and an appropriate alcohol of Formula (XIII), in the presence of a suitable triarylphosphine, such as triphenylphosphine, or a suitable trialkylphosphine, and a suitable dialkyl azodicarboxylate reagent, such as di-*tert*-butyl azodicarboxylate, in a suitable inert solvent, such as THF, under suitable reaction conditions, such as at a convenient temperature, typically rt, for a period of time to ensure the completion of the reaction. Intermediate compounds of Formula (XII) or Formula (XIII) can be obtained commercially or synthesized according to literature procedures. In Reaction Scheme 9, R^8 is C_{1-4} alkyl, PG is a protecting group and all other variables are defined as in Formula (I).

Reaction Scheme 9Experimental procedure 10

Intermediate compound of Formula (IV) can be prepared by a Suzuki type coupling reaction of a compound of Formula (II) where R^{6a} and R^{7a} may be each independently selected from H, C_{1-4} alkyl or R^{6a} and R^{7a} may be taken together to form for example a bivalent radical of formula $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-C(CH_3)_2C(CH_3)_2-$ with a suitable *N*-protected halo imidazole derivative compound of Formula (III-a) and X is a halogen, in particular bromo or iodo, in the presence of a palladium catalyst, according to reaction conditions known to the skilled person. Such reaction conditions include the use of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0) or an alternative catalyst system prepared *in*

situ from Pd(OAc)₂ and PPh₃, a suitable base, such as Na₂CO₃, K₂CO₃, NaOAc, NaHCO₃ or K₃PO₄, and in a suitable solvent, such as 1,4-dioxane, or a mixture of dimethoxyethane (DME) and water. Degassing the reaction mixture with an inert gas, such as N₂ or argon, and heating the reaction mixture to high temperatures, such as reflux temperature under classical heating or microwave irradiation, in particular 80 °C, may enhance the reaction outcome. A compound of Formula (III-a) can be obtained commercially or made according to procedures known in the art. In Reaction Scheme 10a, PG is a protecting group and all other variables are defined as in Formula (I).

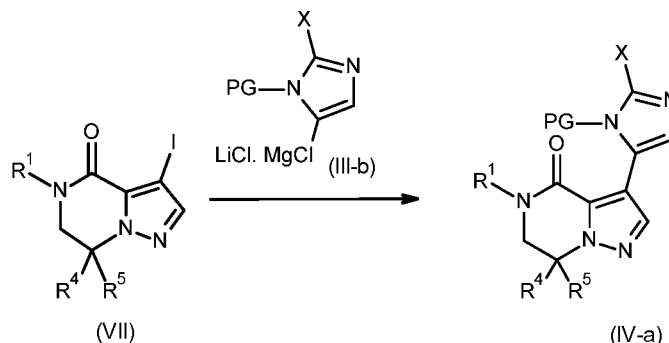
Reaction Scheme 10a



10

In particular, an intermediate compound of Formula (IV) wherein R²=X is halo, in particular chloro or bromo, and R³=H hereby referred to as compounds of Formula (IV-a) can be prepared by a Negishi type coupling reaction of a compound of Formula (VII) with a suitable *N*-protected halo imidazole compound such as a magnesium chloride derivative of Formula (III-b), in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0) and a zinc species, such as zinc chloride, in a suitable solvent, such as THF. In Reaction Scheme 10b, X is halo (bromo or chloro), PG is a protecting group and all other variables are defined as in Formula (I).

Reaction Scheme 10b



20

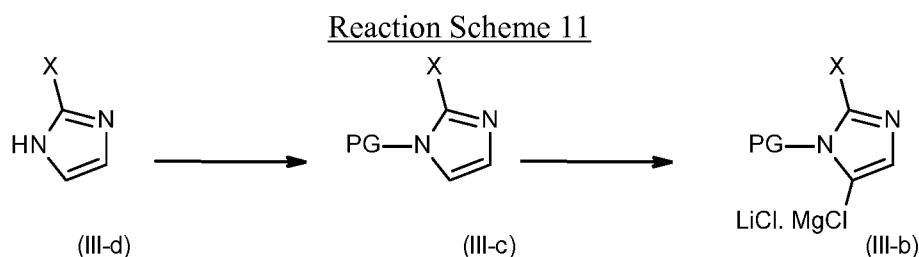
Experimental procedure 11

Intermediate compound of Formula (III-b) can be prepared by a metalation process from a compound of Formula (III-c) following conditions described by T. Petersen and

al. in *Angew. Chem. Int. Ed.* **2014**, *53*, 7933–7937. Performing the reaction under flow conditions may enhance the reaction outcome.

Intermediate compound of Formula (III-c) can be prepared by a reaction of protection of a compound of Formula (III-d) according to conditions known to the skilled person.

- 5 A compound of Formula (III-d) can be obtained commercially or made according to procedures known in the art. In Reaction Scheme 11, X is halo, in particular chloro or bromo, and PG is a protecting group.

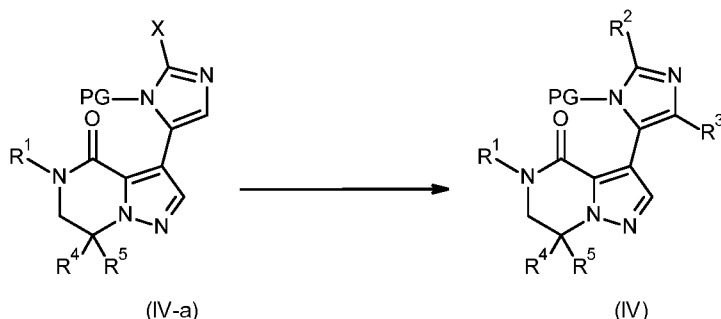


10 Experimental procedure 12

Intermediate compound of Formula (IV) can be prepared by a Suzuki type coupling reaction of a compound of Formula (IV-a) with a suitable boronate derivative or boronic acid, in the presence of a palladium catalyst, according to reaction conditions known to the skilled person. Such reaction conditions include the use of a palladium

- 15 catalyst, such as tetrakis(triphenylphosphine)palladium(0) or an alternative catalyst system prepared *in situ* from Pd(OAc)₂ and PPh₃, a suitable base, such as Na₂CO₃, K₂CO₃, NaOAc, NaHCO₃ or K₃PO₄, and in a suitable solvent, such as 1,4-dioxane, or a mixture of dimethoxyethane (DME) and water. Degassing the reaction mixture with an inert gas, such as N₂ or argon, and heating the reaction mixture to high temperatures, 20 such as reflux temperature under classical heating or microwave irradiation, in particular 90 °C, may enhance the reaction outcome.

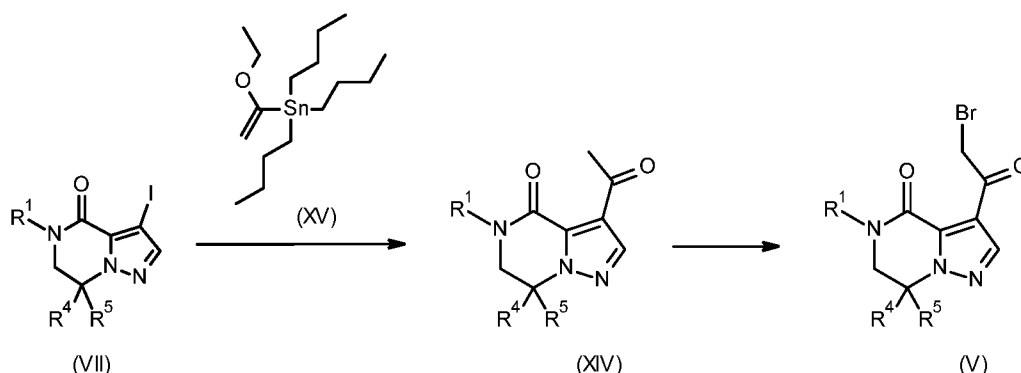
- Alternatively, intermediate compound of Formula (IV) can be prepared by a Negishi type coupling reaction of a compound of Formula (IV-a) with a suitable zincate species in the presence of a palladium catalyst, according to reaction conditions known to the skilled person. In Reaction Scheme 12, PG is a protecting group and all other variables 25 are defined as in Formula (I).

Reaction Scheme 12Experimental procedure 13

Intermediate compound of Formula (V) can be prepared *via* a reaction of halogenation
 5 of an intermediate of Formula (XIV) with a halogenating reagent such as for example
 pyridinium tribromide, in an inert solvent such as dichloromethane, under suitable
 reaction conditions, such as at a convenient temperature, ranging between 0 °C and 30
 °C, for a period of time to ensure the completion of the reaction.

Intermediate compound of Formula (XIV) can be prepared in a one pot reaction. First a
 10 Stille type coupling reaction of a compound of Formula (VII) with a suitable stannanyl
 compound of Formula (XV) such as for example tributyl-(1-ethoxyvinyl)tin, in the
 presence of a palladium catalyst such as bis(triphenylphosphine)palladium(II) chloride,
 a suitable base, such as K₂CO₃ and in a suitable solvent, such as a mixture of 1,4-
 dioxane and water under suitable reaction conditions, such as at a convenient
 15 temperature, typically 110 °C, for a period of time to ensure the completion of the
 reaction. Then hydrolysis in acid media such as for example with 2M aqueous solution
 of hydrochloric acid, under suitable reaction conditions, such as at a convenient
 temperature, typically 80 °C, for a period of time to ensure the completion of the
 reaction. In Reaction Scheme 13, all variables are defined as in Formula (I).

20

Reaction Scheme 13

In order to obtain the HCl salt forms of the compounds, several procedures known to
 those skilled in the art can be used. In a typical procedure, for example, the free base

can be dissolved in DIPE or Et₂O and subsequently, a 6N HCl solution in 2-propanol or a 1N HCl solution in Et₂O can be added dropwise. The mixture typically is stirred for 10 minutes after which the product can be filtered off. The HCl salt usually is dried *in vacuo*.

- 5 It will be appreciated by those skilled in the art that in the processes described above the functional groups of intermediate compounds may need to be blocked by protecting groups. In case the functional groups of intermediate compounds were blocked by protecting groups, they can be deprotected after a reaction step.

10 PHARMACOLOGY

The compounds provided in this invention are negative allosteric modulators (NAMs) of metabotropic glutamate receptors, in particular they are negative allosteric modulators of mGluR2. The compounds of the present invention do not appear to bind to the glutamate recognition site, the orthosteric ligand site, but instead to an allosteric site within the seven transmembrane region of the receptor. In the presence of
15 glutamate, the compounds of this invention decrease the mGluR2 response. The compounds provided in this invention are expected to have their effect at mGluR2 by virtue of their ability to decrease the response of such receptors to glutamate, attenuating the response of the receptor.

- 20 As used herein, the term “treatment” is intended to refer to all processes, wherein there may be a slowing, interrupting, arresting or stopping of the progression of a disease or an alleviation of symptoms, but does not necessarily indicate a total elimination of all symptoms.

Hence, the present invention relates to a compound according to the general Formula
25 (I), or a stereoisomeric form thereof, or an N-oxide thereof, or a pharmaceutically acceptable salt or a solvate thereof, in particular, a compound of Formula (I) or a stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof for use as a medicament.

The invention also relates to the use of a compound according to the general Formula
30 (I), or a stereoisomeric form thereof, or an N-oxide thereof, or a pharmaceutically acceptable salt or a solvate thereof, in particular, a compound of Formula (I) or a stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, or a pharmaceutical composition according to the invention for the manufacture of a medicament.

The invention also relates to a compound according to the general Formula (I), or a stereoisomeric form thereof, or an N-oxide thereof, or a pharmaceutically acceptable salt or a solvate thereof, in particular, a compound of Formula (I) or a stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, or a
5 pharmaceutical composition according to the invention for use in the treatment or prevention of, in particular treatment of, a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of allosteric modulators of mGluR2, in particular negative allosteric modulators thereof.

10 The present invention also relates to the use of a compound according to the general Formula (I), or a stereoisomeric form thereof, or an N-oxide thereof, or a pharmaceutically acceptable salt or a solvate thereof, in particular, a compound of Formula (I) or a stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, or a pharmaceutical composition according to the invention for the
15 manufacture of a medicament for the treatment or prevention of, in particular treatment of, a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of allosteric modulators of mGluR2, in particular negative allosteric modulators thereof.

The present invention also relates to a compound according to the general Formula (I),
20 or a stereoisomeric form thereof, or an N-oxide thereof, or a pharmaceutically acceptable salt or a solvate thereof, in particular, a compound of Formula (I) or a stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, or a pharmaceutical composition according to the invention for use in the treatment, prevention, amelioration, control or reduction of the risk of various neurological and
25 psychiatric disorders associated with glutamate dysfunction in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of negative allosteric modulators of mGluR2.

Also, the present invention relates to the use of a compound according to the general Formula (I), or a stereoisomeric form thereof, or an N-oxide thereof, or a
30 pharmaceutically acceptable salt or a solvate thereof, in particular, a compound of Formula (I) or a stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, or a pharmaceutical composition according to the invention for the manufacture of a medicament for treating, preventing, ameliorating, controlling or reducing the risk of various neurological and psychiatric disorders associated with
35 glutamate dysfunction in a mammal, including a human, the treatment or prevention of

which is affected or facilitated by the neuromodulatory effect of negative allosteric modulators of mGluR2.

In particular, the neurological and psychiatric disorders associated with glutamate dysfunction, include one or more of the following central nervous system conditions or
5 diseases: mood disorders; delirium, dementia, amnesic and other cognitive disorders; disorders usually first diagnosed in infancy, childhood or adolescence; substance-related disorders; schizophrenia and other psychotic disorders; somatoform disorders; and hypersomnic sleep disorder.

In particular, the central nervous system disorder is a psychotic disorder selected from
10 the group of schizophrenia (in particular in antipsychotic-stabilized patients), schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, and substance-induced psychotic disorder.

In particular, the central nervous system disorder is a substance-related disorder selected from the group of alcohol dependence, alcohol abuse, amphetamine
15 dependence, amphetamine abuse, caffeine dependence, caffeine abuse, cannabis dependence, cannabis abuse, cocaine dependence, cocaine abuse, hallucinogen dependence, hallucinogen abuse, nicotine dependence, nicotine abuse, opioid dependence, opioid abuse, phencyclidine dependence, and phencyclidine abuse.

In particular, the central nervous system disorder is a mood disorder selected from the
20 group of major depressive disorder, depression, treatment resistant depression, dysthymic disorder, cyclothymic disorder, and substance-induced mood disorder.

In particular, the central nervous system disorder is a disorder usually first diagnosed in
25 infancy, childhood, or adolescence selected from mental retardation, learning disorder, motor skills disorder, communication disorder, attention-deficit and disruptive behaviour disorders (such as Attention-Deficit/Hyperactivity Disorder (ADHD)). An additional disorder usually first diagnosed in infancy, childhood, or adolescence is autistic disorder.

In particular, the central nervous system disorder is a cognitive disorder selected from
30 the group of dementia, in particular, dementia of the Alzheimer's type, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson's disease, dementia due to Huntington's disease, dementia due to Pick's disease, dementia due to Creutzfeldt-Jakob disease, and substance-induced persisting dementia.

In particular, the central nervous system disorder is an amnesic disorder, such as substance-induced persisting amnesic disorder.

As already mentioned hereinabove, the term “treatment” does not necessarily indicate a total elimination of all symptoms, but may also refer to symptomatic treatment in any
5 of the disorders mentioned above. In particular, symptoms that may be treated include but are not limited to, memory impairment in particular in dementia or in major depressive disorder, age-related cognitive decline, mild cognitive impairment, and depressive symptoms.

10 Of the disorders mentioned above, the treatment of dementia, major depressive disorder, depression, treatment resistant depression, attention-deficit/hyperactivity disorder and schizophrenia, in particular in antipsychotic-stabilized patients, are of particular importance.

The fourth edition of the Diagnostic & Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association provides a diagnostic tool for the
15 identification of the disorders described herein. The person skilled in the art will recognize that alternative nomenclatures, nosologies, and classification systems for neurological and psychiatric disorders described herein exist, and that these evolve with medical and scientific progresses.

A skilled person will be familiar with alternative nomenclatures, nosologies, and
20 classification systems for the diseases or conditions referred to herein. For example, the “American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013” (DSM-5TM) utilizes terms such as depressive disorders, in particular, major depressive disorder, persistent depressive disorder (dysthymia), substance-medication-induced
25 depressive disorder; neurocognitive disorders (NCDs) (both major and mild), in particular, neurocognitive disorders due to Alzheimer’s disease, vascular NCD (such as vascular NCD present with multiple infarctions), NCD due to HIV infection, NCD due to traumatic brain injury (TBI), NCD due to Parkinson’s disease, NCD due to Huntington’s disease, frontotemporal NCD, NCD due to prion disease, and
30 substance/medication-induced NCD; neurodevelopmental disorders, in particular, intellectual disability, specific learning disorder, neurodevelopmental motor disorder, communication disorder, and attention-deficit/hyperactivity disorder (ADHD); substance-related disorders and addictive disorders, in particular, alcohol use disorder, amphetamine use disorder, cannabis use disorder, cocaine use disorder, other

hallucinogen use disorder, tobacco use disorder, opioid use disorder, and phencyclidine use disorder; schizophrenia spectrum and other psychotic disorders, in particular, schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance/medication-induced psychotic disorder; somatic
5 symptom disorders; hypersomnolence disorder; and cyclothymic disorder (which under DSM-5TM falls under the bipolar and related disorders category). Such terms may be used by the skilled person as an alternative nomenclature for some of the diseases or conditions referred to herein. An additional neurodevelopmental disorder includes
10 autism spectrum disorder (ASD), which encompasses according to the DSM-5TM, disorders previously known by the terms early infantile autism, childhood autism, Kanner's autism, high-functioning autism, atypical autism, pervasive developmental disorder not otherwise specified, childhood disintegrative disorder, and Asperger's disorder. In particular, the disorder is autism. Specifiers associated with ASD include those where the individual has a genetic disorder, such as in Rett syndrome or Fragile
15 X syndrome.

Therefore, the invention also relates to a compound according to the general Formula (I), or a stereoisomeric form thereof, or an N-oxide thereof, or a pharmaceutically acceptable salt or a solvate thereof, in particular, a compound of Formula (I) or a stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof,
20 for use in the treatment of any one of the diseases mentioned hereinbefore.

The invention also relates to a compound according to the general Formula (I), or a stereoisomeric form thereof, or an N-oxide thereof, or a pharmaceutically acceptable salt or a solvate thereof, in particular, a compound of Formula (I) or a stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, for use in
25 treating any one of the diseases mentioned hereinbefore.

The invention also relates to a compound according to the general Formula (I), or a stereoisomeric form thereof, or an N-oxide thereof, or a pharmaceutically acceptable salt or a solvate thereof, in particular, a compound of Formula (I) or a stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, for the
30 treatment or prevention, in particular treatment, of any one of the diseases mentioned hereinbefore.

The invention also relates to the use of a compound according to the general Formula (I), or a stereoisomeric form thereof, or an N-oxide thereof, or a pharmaceutically acceptable salt or a solvate thereof, in particular, a compound of Formula (I) or a

stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, for the manufacture of a medicament for the treatment or prevention of any one of the disease conditions mentioned hereinbefore.

5 The compounds of the present invention can be administered to mammals, preferably humans, for the treatment or prevention of any one of the diseases mentioned hereinbefore.

10 In view of the utility of the compounds of Formula (I), there is provided a method of treating warm-blooded animals, including humans, suffering from any one of the diseases mentioned hereinbefore, and a method of preventing in warm-blooded animals, including humans, any one of the diseases mentioned hereinbefore.

15 Said methods comprise the administration, i.e. the systemic or topical administration, preferably oral administration, of a therapeutically effective amount of a compound of Formula (I), a stereoisomeric form thereof, or an N-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, in particular, a compound of Formula (I) or a stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, to warm-blooded animals, including humans.

20 Therefore, the invention also relates to a method for the prevention and/or treatment of any one of the diseases mentioned hereinbefore comprising administering a therapeutically effective amount of a compound according to the invention to a subject in need thereof.

25 One skilled in the art will recognize that a therapeutically effective amount of the NAMs of the present invention is the amount sufficient to modulate the activity of the mGluR2 and that this amount varies *inter alia*, depending on the type of disease, the concentration of the compound in the therapeutic formulation, and the condition of the patient. Generally, an amount of NAM to be administered as a therapeutic agent for treating diseases in which modulation of the mGluR2 is beneficial, such as the disorders described herein, will be determined on a case by case by an attending physician.

30 Generally, a suitable dose is one that results in a concentration of the NAM at the treatment site in the range of 0.5 nM to 200 μ M, and more usually 5 nM to 50 μ M. To obtain these treatment concentrations, a patient in need of treatment likely will be administered an effective therapeutic daily amount of about 0.01 mg/kg to about 50 mg/kg body weight, preferably from about 0.01 mg/kg to about 25 mg/kg body weight,

more preferably from about 0.01 mg/kg to about 10 mg/kg body weight, more preferably from about 0.01 mg/kg to about 2.5 mg/kg body weight, even more preferably from about 0.05 mg/kg to about 1 mg/kg body weight, more preferably from about 0.1 to about 0.5 mg/kg body weight. The amount of a compound according to the present invention, also referred to here as the active ingredient, which is required to achieve a therapeutically effect will, of course vary on case-by-case basis, vary with the particular compound, the route of administration, the age and condition of the recipient, and the particular disorder or disease being treated. A method of treatment may also include administering the active ingredient on a regimen of between one and four intakes per day. In these methods of treatment the compounds according to the invention are preferably formulated prior to admission. As described herein below, suitable pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients.

The compounds of the present invention may be utilized in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of Formula (I) or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Examples of such combinations include the compounds of the invention in combination with antipsychotic(s), NMDA receptor antagonists (e.g. memantine), NR2B antagonists, acetylcholinesterase inhibitors (e.g. donepezil, galantamine, physostigmine and rivastigmine) and/or antidepressant neurotransmitter reuptake inhibitors. Particular combinations include the compounds of the invention in combination with antipsychotics, or the compounds of the invention in combination with memantine and/or NR2B antagonists.

25

PHARMACEUTICAL COMPOSITIONS

The present invention also provides compositions for preventing or treating diseases in which modulation of the mGluR2 receptor is beneficial, such as the disorders described herein. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition. Accordingly, the present invention also relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a therapeutically effective amount of a compound according to the invention, in particular a compound according to Formula (I), an N-oxide, a pharmaceutically acceptable salt thereof, a solvate thereof or a stereochemically isomeric form thereof, more in particular, a compound according

35

to Formula (I), a pharmaceutically acceptable salt thereof, a solvate thereof or a stereochemically isomeric form thereof. The carrier or diluent must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

- 5 The compounds according to the invention, in particular the compounds according to Formula (I), the N-oxides thereof, the pharmaceutically acceptable salts thereof, the solvates and the stereochemically isomeric forms thereof, more in particular the compounds according to Formula (I), the pharmaceutically acceptable salts thereof, the solvates and the stereochemically isomeric forms thereof, or any subgroup or
10 combination thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs.

The pharmaceutical compositions of this invention may be prepared by any methods well known in the art of pharmacy, for example, using methods such as those described
15 in Gennaro et al. Remington's Pharmaceutical Sciences (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical preparations and their Manufacture). To prepare the pharmaceutical compositions of this invention, a therapeutically effective amount of the particular compound, optionally in salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically
20 acceptable carrier or diluent, which carrier or diluent may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for oral, topical, rectal or percutaneous administration, by parenteral injection or by inhalation. For example, in preparing the compositions in oral dosage form, any of the usual
25 pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as, for example, suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as, for example, starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of the ease in
30 administration, oral administration is preferred, and tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, surfactants, to aid solubility, may be included. Injectable solutions, for example, may be prepared in
35 which the carrier comprises saline solution, glucose solution or a mixture of saline and

glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, teaspoonfuls, tablespoonfuls, and segregated multiples thereof.

Since the compounds according to the invention are orally administrable compounds, pharmaceutical compositions comprising said compounds for oral administration are especially advantageous.

In order to enhance the solubility and/or the stability of the compounds of Formula (I) in pharmaceutical compositions, it can be advantageous to employ α -, β - or γ -cyclodextrins or their derivatives, in particular hydroxyalkyl substituted cyclodextrins, e.g. 2-hydroxypropyl- β -cyclodextrin or sulfobutyl- β -cyclodextrin. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds according to the invention in pharmaceutical compositions.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated

subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention.

Depending on the mode of administration, the pharmaceutical composition will comprise from 0.05 to 99 % by weight, preferably from 0.1 to 70 % by weight, more preferably from 0.1 to 50 % by weight of the active ingredient, and, from 1 to 99.95 % by weight, preferably from 30 to 99.9 % by weight, more preferably from 50 to 99.9 % by weight of a pharmaceutically acceptable carrier, all percentages being based on the total weight of the composition.

The amount of a compound of Formula (I) that can be combined with a carrier material to produce a single dosage form will vary depending upon the disease treated, the mammalian species, and the particular mode of administration. However, as a general guide, suitable unit doses for the compounds of the present invention can, for example, preferably contain between 0.1 mg to about 1000 mg of the active compound. A preferred unit dose is between 1 mg to about 500 mg. A more preferred unit dose is between 1 mg to about 300 mg. Even more preferred unit dose is between 1 mg to about 100 mg. Such unit doses can be administered more than once a day, for example, 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day, so that the total dosage for a 70 kg adult is in the range of 0.001 to about 15 mg per kg weight of subject per administration. A preferred dosage is 0.01 to about 1.5 mg per kg weight of subject per administration, and such therapy can extend for a number of weeks or months, and in some cases, years. It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other drugs that have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those of skill in the area.

A typical dosage can be one 1 mg to about 100 mg tablet or 1 mg to about 300 mg taken once a day, or, multiple times per day, or one time-release capsule or tablet taken once a day and containing a proportionally higher content of active ingredient. The time-release effect can be obtained by capsule materials that dissolve at different pH values, by capsules that release slowly by osmotic pressure, or by any other known means of controlled release.

It can be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating

physician will know how and when to start, interrupt, adjust, or terminate therapy in conjunction with individual patient response.

As already mentioned, the invention also relates to a pharmaceutical composition comprising the compounds according to the invention and one or more other drugs for use as a medicament or for use in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of Formula (I) or the other drugs may have utility. The use of such a composition for the manufacture of a medicament as well as the use of such a composition for the manufacture of a medicament in the treatment, prevention, control, amelioration or reduction of risk of diseases or conditions for which compounds of Formula (I) or the other drugs may have utility are also contemplated. The present invention also relates to a combination of a compound according to the present invention and an additional drug selected from the group of antipsychotics; NMDA receptor antagonists (e.g. memantine); NR2B antagonists; acetylcholinesterase inhibitors (e.g. donepezil, galantamine, physostigmine and rivastigmine) and/or antidepressant neurotransmitter reuptake inhibitors. In particular, the present invention also relates to a combination of a compound according to the present invention and antipsychotic(s), or to a combination of a compound according to the present invention and memantine and/or an NR2B antagonist. The present invention also relates to such a combination for use as a medicine. The present invention also relates to a product comprising (a) a compound according to the present invention, an N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof, in particular, a pharmaceutically acceptable salt thereof or a solvate thereof, and (b) an additional component selected from antipsychotics, NMDA receptor antagonists (e.g. memantine), NR2B antagonists, acetylcholinesterase inhibitors and/or antidepressant neurotransmitter reuptake inhibitor(s), as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR2 allosteric modulators, in particular negative mGluR2 allosteric modulators. More in particular the additional component (b) is selected from antipsychotic(s) or memantine and/or an NR2B antagonist. The different drugs of such a combination or product may be combined in a single preparation together with pharmaceutically acceptable carriers or diluents, or they may each be present in a separate preparation together with pharmaceutically acceptable carriers or diluents.

35

The following examples are intended to illustrate but not to limit the scope of the

present invention.

CHEMISTRY

Several methods for preparing the compounds of this invention are illustrated in the following Examples. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification.

Hereinafter, "DAD" means diode-array detector; "THF" means tetrahydrofuran; "DIPE" means diisopropylether; "DMF" means *N,N*-dimethylformamide; "Et₂O" means diethylether; "EtOAc" means ethyl acetate; "DCM" means dichloromethane; "DMSO" means dimethylsulfoxide; "L" means liter; "HPLC" means high performance liquid chromatography; "mL" or "ml" means milliliter; "NH₄Ac" means ammonium acetate; "EtOH" means ethanol; "ES" means electrospray; "iPrOH" means isopropanol; "MeOH" means methanol; "eq" means equivalent(s); "RP" means Reverse Phase; "rt" means room temperature; "M.p." means melting point; "min" means minutes; "h" means hour(s); "s" means second(s); "TOF" means time of flight; "QTOF" means Quadrupole-Time of Flight; "sat." means saturated; "sol." means solution; "RT" means residence time; "S-Phos" means 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl.

Microwave assisted reactions were performed in a single-mode reactor: InitiatorTM Sixty EXP microwave reactor (Biotage AB), or in a multimode reactor: MicroSYNTH Labstation (Milestone, Inc.).

Flow chemistry reactions were performed in a 1 mL Sigma-Aldrich Starter Kit microreactor, pumping the reagents through it by a dual CHEMTRIX Labtrix Start syringe pump and using standard Dolomite PTFE tubing and ETFE connectors. For further information about this equipment visit the web: <http://www.chemtrix.com/products/Labtrix-Start-1> for the pumps, <http://www.sigmaaldrich.com/chemistry/chemical-synthesis/technology-spotlights/microreactor-explorer-kit.html> for the microreactors and <http://www.upchurch.com/> for tubing and connectors. Alternatively, LTF microreactors can be used. For further information visit the web: <http://www.ltf-gmbh.com/>.

Thin layer chromatography (TLC) was carried out on silica gel 60 F254 plates (Merck) using reagent grade solvents. Open column chromatography was performed on silica gel, particle size 60 Å, mesh = 230-400 (Merck) using standard techniques. Automated flash column chromatography was performed using ready-to-connect cartridges from

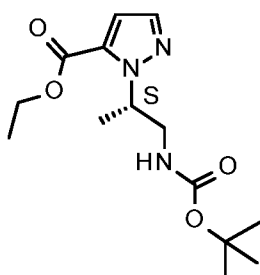
different vendors, on irregular silica gel, particle size 15-40 μm (normal phase disposable flash columns) on different flash systems: either a SPOT or LAFLASH systems from Armen Instrument, or PuriFlash® 430evo systems from Interchim, or 971-FP systems from Agilent, or Isolera 1SV systems from Biotage.

- 5 Nuclear Magnetic Resonance (NMR): For a number of compounds, ^1H NMR spectra were recorded either on a Bruker Avance III, on a Bruker DPX-400 or on a Bruker AV-500 spectrometer with standard pulse sequences, operating at 400 MHz and 500 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard.

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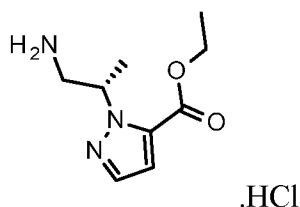
Synthesis of Intermediate Compounds

Intermediate 1 (I-1)

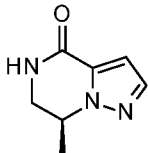


- 15 Di-*tert*-butyl azodicarboxylate (765 g, 3.32 mol) was added to a stirred solution of ethyl 1*H*-pyrazole-5-carboxylate (310 g, 2.21 mol), (2*R*-hydroxy-propyl)-carbamate *tert*-butyl ester (582 g, 3.32 mol) and triphenylphosphine (870 g, 3.31 mol) in THF (4 L) under nitrogen. The mixture was stirred at rt for 24 h. The solvent was evaporated *in vacuo* to yield **I-1** (2000 g, 91%), which was used in the following step without further purification.

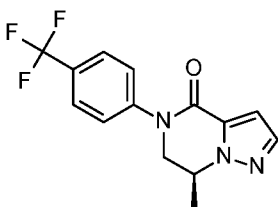
20 Intermediate 2 (I-2)



- 25 Intermediate **I-1** (2000 g, 2.02 mol) was dissolved in 4M solution of HCl in 1,4-dioxane (5 L). The mixture was stirred at 80 °C for 18 h. The solvent was evaporated *in vacuo* to yield **I-2** (1500 g, 23% purity, 87%), that was used in the following step without further purification.

Intermediate 3 (I-3)

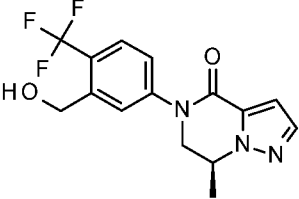
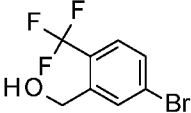
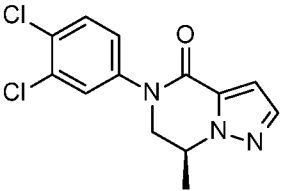
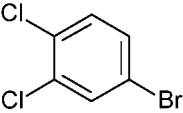
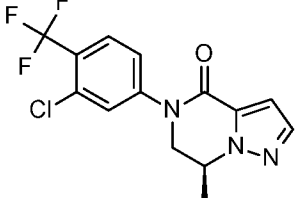
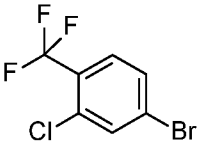
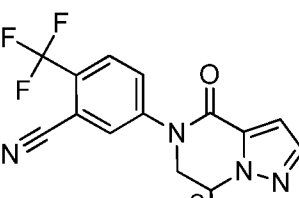
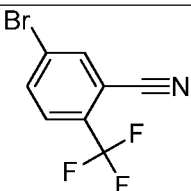
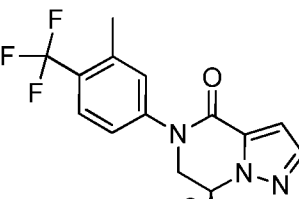
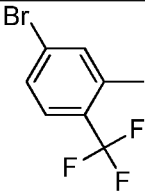
I-2 as HCl salt (1500 g, 1.48 mol) was dissolved in a sat. sol. of NaHCO₃ (4 L). The mixture was stirred at rt for 24 h. The mixture was filtered and the filtrate was extracted with DCM. The organic layers were separated, dried (Na₂SO₄), filtered and the solvents evaporated *in vacuo*. Then the residue was crystallized from DCM to yield **I-3** (92 g, 76% purity, 96%), which was used in the following step without further purification.

Intermediate 4 (I-4)

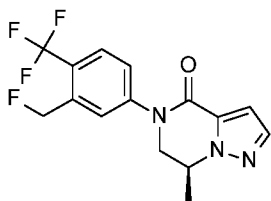
A mixture of **I-3** (5 g, 33.01 mmol), copper (I) iodide (3.78 g, 19.85 mmol) and K₂CO₃ (9.14 g, 66.15 mmol) in toluene (150 mL) was nitrogen flushed for a few min. Then 4-bromobenzotrifluoride (9.3 mL, 66.1 mmol) and *N,N*-dimethylethylenediamine (2.1 mL, 19.8 mmol) were added. The mixture was stirred under nitrogen at rt for 10 min and then stirred at 100 °C for 16 h. Then DMF (20 mL) was added and the mixture was stirred at 100 °C for 8 h. Then water, a conc. sol. of ammonia and DCM were added. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; EtOAc in DCM 0/100 to 50/50). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-4** (9.6 g, 98%) as a pale yellow oil.

Intermediates I-5 to I-9

The following intermediates were synthesized by following an analogous synthetic procedure as reported for **intermediate 4**.

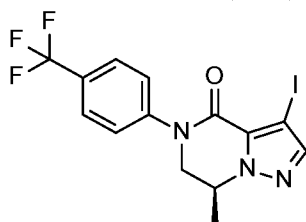
Intermediate	Starting materials
 <p style="text-align: right;">I-5</p>	<p style="text-align: center;">I-3</p> 
 <p style="text-align: right;">I-6</p>	<p style="text-align: center;">I-3</p> 
 <p style="text-align: right;">I-7</p>	<p style="text-align: center;">I-3</p> 
 <p style="text-align: right;">I-8</p>	<p style="text-align: center;">I-3</p> 
 <p style="text-align: right;">I-9</p>	<p style="text-align: center;">I-3</p> 

Intermediate 10 (I-10)



Bis(2-methoxyethyl)amino-sulfur trifluoride (1.83 mL, 9.92 mmol) was added to a stirred solution of **I-5** (646 mg, 1.98 mmol) in DCM (12.5 mL) at 0 °C and under nitrogen. The mixture was left to warm up to rt and stirred for 3 days. Then was treated with sat. NaHCO₃ at 0 °C and extracted with EtOAc. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica; EtOAc in DCM 0/100 to 80/20). The desired fractions were collected and the solvents concentrated *in vacuo* to yield **I-10** (345 mg, 53%) as colourless oil that solidified upon standing.

Intermediate 11 (I-11)



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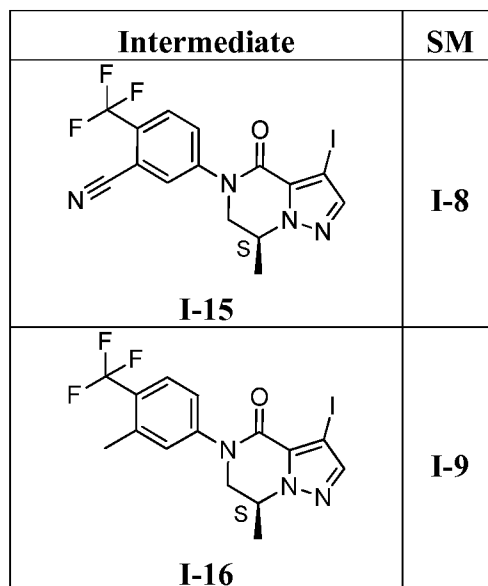
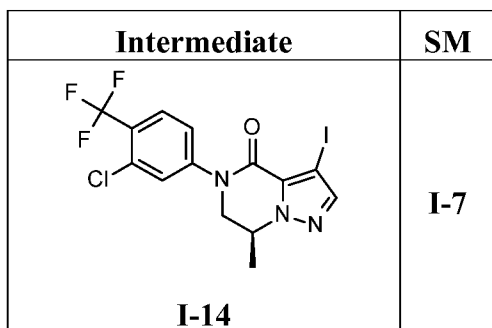
Iodine (11.55 g, 45.5 mmol) was added to a solution of **I-4** (19.2 g, 65.0 mmol) and ammonium cerium(IV) nitrate (24.95 g, 45.5 mmol) in acetonitrile (350 mL). The mixture was stirred at 70 °C for 1 h. Then the mixture was diluted with EtOAc and washed with a sat. sol. of Na₂S₂O₃ and brine. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated *in vacuo*. The residue was precipitated with DIPE and then was purified by short column chromatography (silica, DCM) then by flash column chromatography (silica; DCM in heptane 50/50 to 100/0). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-11** (24.8 g, 90%) as a solid.

20 Intermediates I-12 to I-16

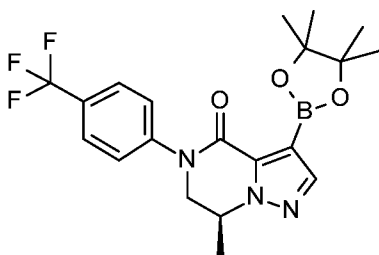
The following intermediates were synthesized by following an analogous synthetic procedure as reported for **I-16** (SM means starting material).

Intermediate	SM
<p style="text-align: center;">I-12</p>	I-5

Intermediate	SM
<p style="text-align: center;">I-13</p>	I-6

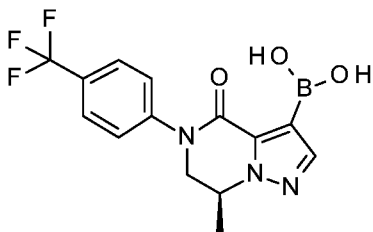


Intermediate 17a (I-17a)



(I-17a)

Isopropylmagnesium chloride lithium chloride complex (1.3M solution, 32.9 mL, 42.7 mmol) was added dropwise to a stirred solution of **I-11** (10 g, 23.7 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9.7 mL, 47.5 mmol) in anhydrous THF (100 mL) at -25 °C under nitrogen atmosphere. The mixture was stirred for 30 min at -25 °C. Then the reaction was quenched with a 10% NH₄Cl aq sol. and extracted with EtOAc. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 3/97). The desired fractions were collected and the solvents evaporated *in vacuo*. The crude product was triturated with DIPE, filtered and dried to yield **I-17a** (6.4 g, 64%) as a white solid. The solution and impure fractions from the column purification were combined and repurified by flash column chromatography (silica, EtOAc in Heptane 30/70 to 70/30). The desired fractions were collected and the solvents evaporated *in vacuo*. The product was triturated with DIPE/Heptane, filtered and dried to yield **I-17a** (1 g, 10%) as a white solid.

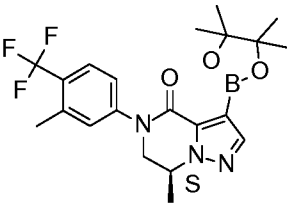
Intermediate 17b (I-17b)**(I-17b)**

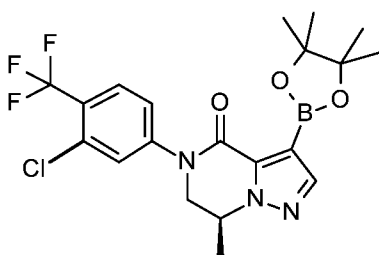
Isopropylmagnesium chloride lithium chloride complex (1.3M solution, 273 mL, 354.9 mmol) was added dropwise to a stirred solution of **I-11** (100 g, 237.4 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (20 mL, 95 mmol) in anhydrous THF (1 L) at -25 °C under nitrogen atmosphere. The mixture was stirred for 30 min at -10 °C. Then the reaction was quenched with sat. sol. NH₄Cl and extracted with EtOAc. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography to yield **I-17b** (43 g, 51%).

Intermediates I-18 to I-22

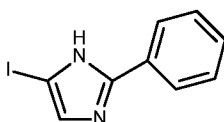
The following intermediates were synthesized by following an analogous synthetic procedure as reported for **intermediate I-17** (SM means starting material).

Intermediate	SM	Intermediate	SM
<p>I-18</p>	I-12	<p>I-20b</p>	I-14
<p>I-19</p>	I-13	<p>I-21</p>	I-15

Intermediate	SM
 <p style="text-align: center;">I-22</p>	I-16

Intermediate 20a (I-20a)**(I-20a)**

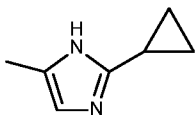
Two solutions of **I-11** (3 g, 6.58 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.69 mL, 13.16 mmol) in THF (64.5 mL) and isopropylmagnesium chloride lithium chloride complex (1.3M solution, 7.59 mL, 9.87 mmol) in THF (30 mL) were pumped through a LTF mixer (0.5 mL/min), at 0 °C, Rt= 1 min. The outlet solution was diluted with a sat. sol. NH₄Cl and extracted with EtOAc. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated *in vacuo*. The crude product was triturated with DIPE/heptane, filtered and dried to yield **I-17a** (1.772 g, 59%) as a white solid. The filtrate was evaporated *in vacuo* and the residue was purified by flash column chromatography (silica; EtOAc in DCM 0/100 to 100/0). The desired fractions were collected and the solvents concentrated *in vacuo*. The residue was triturated with DIPE, filtered and dried to yield other fraction of **I-17a** (0.406 g, 13%) as a white solid. The filtrate was evaporated *in vacuo* and the residue was triturated again with DIPE/Heptane, filtered and dried to yield another fraction of **I-17a** (0.238 g, 8%) as a white solid.

Intermediate 23 (I-23)

4,5-Diiodo-2-phenyl-1H-imidazole (0.59 g, 1.49 mmol) was added to a suspension of sodium sulfite (1.31 g, 10.43 mmol) in water (10 mL) and EtOH (2.85 mL). The

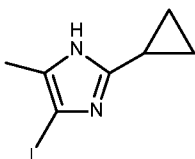
mixture was stirred at refluxed for 18 h. The solid was filtered and washed with H₂O. The solid was dried *in vacuo* to yield **I-23** (350 mg, 87%) as a beige solid.

Intermediate 24 (I-24)



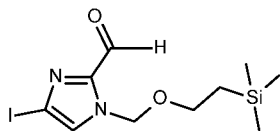
- 5 Cyclopropanecarboxaldehyde (0.6 mL, 8.03 mmol) in EtOH (4 mL) was treated with aqueous ammonia (28% in water, 4 mL) at 55 °C for 30 min. Pyruvic aldehyde (1.56 mL, 10.12 mmol) was added dropwise and the mixture was stirred at 60 °C for 16 h. The solvent was evaporated *in vacuo*. The mixture was treated with brine and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent
- 10 evaporated *in vacuo* to yield **I-24** (900 mg, 92%).

Intermediate 25 (I-25)



- N*-iodosuccinimide (1.62 g, 7.20 mmol) was added portionwise to a stirred solution of intermediate **I-24** (800 mg, 6.54 mmol) in acetonitrile (38 mL) and the mixture was
- 15 stirred at rt for 70 min. The mixture was treated with sat. sol. Na₂S₂O₄ and extracted with DCM. The organic layer was separated, dried (MgSO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc in DCM 0/100 to 30/70). The desired fractions were collected and the solvents concentrated *in vacuo* to yield **I-25** (1.345 g, 83%) as a solid.

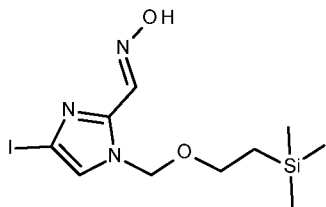
20 Intermediate 26 (I-26)



- Lithium diisopropylamide (2.38 mL, 4.77 mmol) was added dropwise to a solution of 2-[(4-iodoimidazol-1-yl)methoxy]ethyl-trimethyl-silane (1.29 g, 3.97 mmol) in dry THF (29.5 mL) under nitrogen at -78 °C. The mixture was stirred at
- 25 -78 °C for 10 min and then DMF (2.21 mL; 28.54 mmol) was added. The mixture was stirred at -78 °C for 30 min and then warmed to 0 °C for 2 h. Water was added carefully to the mixture and it was extracted with EtOAc. The organic layer was washed with brine. The organic layer was dried (MgSO₄), filtered and the solvents evaporated *in*

vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in Heptane 0/100 to 10/90). The desired fractions were collected and the solvents concentrated *in vacuo* to yield **I-26** (856 mg, 61%) as a white solid.

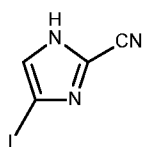
Intermediate 27 (I-27)



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Sodium carbonate (257 mg, 2.43 mmol) was added to a solution of **I-26** (856 mg, 2.43 mmol) and hydroxylamine hydrochloride (338 mg, 4.86 mmol) in water (4.86 mL). The mixture was stirred at 70 °C for 1 h. After cooling, a precipitate was formed, filtered, washed with water and dried *in vacuo* to yield **I-27** (884 mg, 99%) as a white solid.

10 Intermediate 28 (I-28)

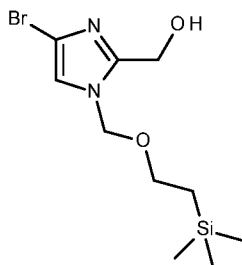


I-27 (884 mg, 2.41 mmol) was stirred at 140 °C in acetic anhydride (8.86 mL) for 6 h. The solvent was evaporated *in vacuo*. The residue was taken up in EtOAc and washed with sat. sol. Na₂CO₃. The organic layer was dried (MgSO₄), filtered and the solvents evaporated *in vacuo*. The residue was stirred in tetrabutylammonium fluoride (1M in THF, 2.65 mL) at 65 °C for 4 h. This mixture was cooled and poured into EtOAc and a K₂HPO₄-KH₂PO₄ buffer aq. sol. The organic layer was separated and the water layer was washed once more with EtOAc. The combined organic layers were dried (MgSO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 5/95). The desired fractions were collected and the solvents concentrated *in vacuo* to yield **I-28** (255 mg, 48%) as a yellowish solid.

15

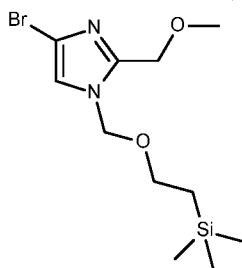
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Intermediate 29 (I-29)



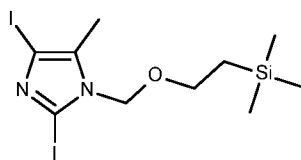
Sodium hydride (160 mg, 4.24 mmol) was added portionwise to a solution of ethyl 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-2-carboxylate (988 mg, 2.82 mmol) in EtOH (20 mL) at 0 °C. The reaction was stirred at rt for 16 h. Then, water was added and the mixture was extracted with DCM. The organic layer was separated, dried (Na₂SO₄), filtered and the solvent evaporated *in vacuo* to yield **I-29** (840 mg, 81% purity, 78%) as a colorless oil which was used in the next reaction step without further purification.

Intermediate 30 (I-30)



Sodium borohydride (102 mg, 2.562 mmol) was added portionwise to a stirred solution of **I-29** (820 mg, 2.135 mmol) in THF (10 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C. Then iodomethane (145 μL, 2.345 mmol) was added and the mixture was stirred at rt for 16 h. Then, more iodomethane (27 μL, 0.430 mmol) was added and the mixture was stirred at rt for 4 h. Then, water was added and the mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc in DCM 0/100 to 10/90). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-30** (570 mg, 83%) as a colorless oil.

Intermediate 31 (I-31)

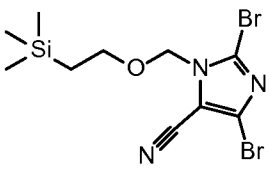


Sodium hydride (60% in mineral oils, 155 mg, 3.895 mmol) was added to 2,5-diiodo-4-methyl-1H-imidazole (867 mg, 2.596 mmol) in THF (8.7 mL) at 0 °C. The mixture was stirred at rt for 10 min. Then 2-(trimethylsilyl)ethoxymethyl chloride (689 μL, 3.895 mmol) was added at 0 °C and the mixture was stirred for 2 h. The reaction was diluted with NH₄Cl and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; EtOAc in Heptane 0/100 to 15/85). The

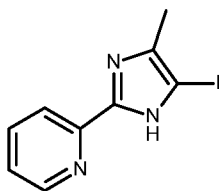
desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-31** (823 mg, 68%) as a solid.

Intermediate I-81

The following intermediate was synthesized by following an analogous synthetic procedure as reported for **I-31**.

Intermediate	Starting material
 <p>I-81</p>	CAS: 1067894-54-5

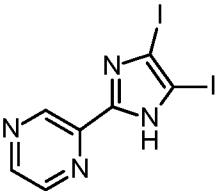
Intermediate 32 (I-32)

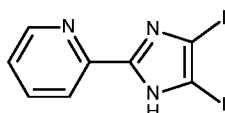


N-iodosuccinimide (2.48 g, 11.056 mmol) was added portionwise to a stirred solution of 2-(4-methyl-1H-imidazol-2-yl)pyridine (1.6 g, 11.056 mmol) in acetonitrile (58 mL) and the mixture was stirred at rt for 70 min. The mixture was treated with sat. sol. Na_2CO_3 and extracted with DCM. The organic layer was separated, dried (MgSO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc in DCM 0/100 to 30/70). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-32** (1.55 g, 54%) as a solid.

Intermediate I-82

The following intermediate was synthesized by following an analogous synthetic procedure as reported for **I-32**.

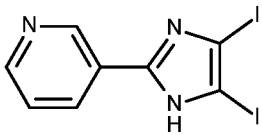
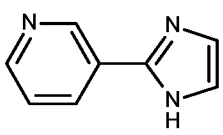
Intermediate	Starting material
 <p>I-82</p>	CAS: 119165-68-3

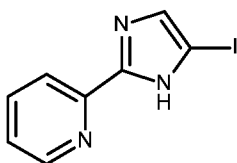
Intermediate 33 (I-33)

- A solution of iodine (6.99 g, 27.555 mmol) in DCM (29 mL) was added dropwise to a suspension of 2-(1H-imidazol-2-yl)pyridine (2g, 13.777 mmol) in NaOH (2M in water, 29 mL). The biphasic mixture was stirred vigorously at rt for 18 h. The aqueous layer was separated and neutralized with AcOH and then washed with sat. sol. Na₂S₂O₃ was added until the solution remained colorless. The suspension was stirred for 10 min and the precipitate was filtered and dried *in vacuo* to yield **I-33** (4.45 g, 81%) as a solid.

Intermediate I-34

- The following intermediate was synthesized by following an analogous synthetic procedure as reported for **I-33**.

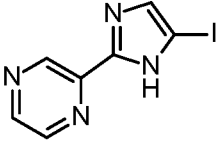
Intermediate	Starting material
 <p>I-34</p>	

Intermediate 35 (I-35)

- Sodium sulfite (4.89 g, 38.79 mmol) was added to a suspension of **I-33** (4.4 g, 11.08 mmol) in water (177 mL) and EtOH (90 mL). The mixture was stirred at reflux for 18 h. The solvents were partially evaporated in vacuo and the solid was filtered off and washed with water. The solid was dried *in vacuo* to yield **I-35** (2.5 g, 83%) as a beige solid.

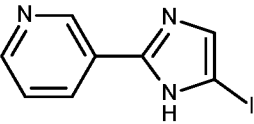
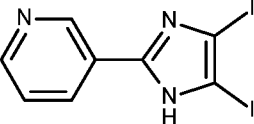
Intermediate I-83

The following intermediate was synthesized by following an analogous synthetic procedure as reported for **I-35**.

Intermediate	Starting material
 <p data-bbox="389 658 448 689">I-83</p>	<p data-bbox="692 568 746 600">I-82</p>

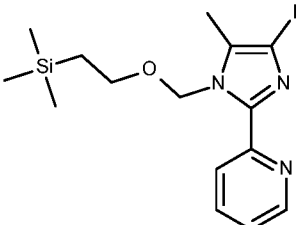
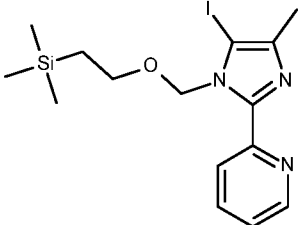
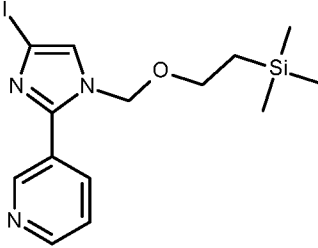
Intermediate I-36

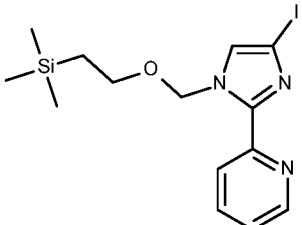
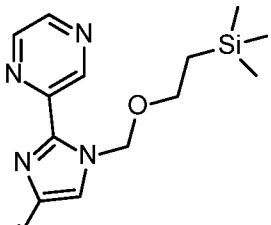
- 5 The following intermediate was synthesized by following an analogous synthetic procedure as reported for **I-35**.

Intermediate	Starting material
 <p data-bbox="389 1117 448 1149">I-36</p>	

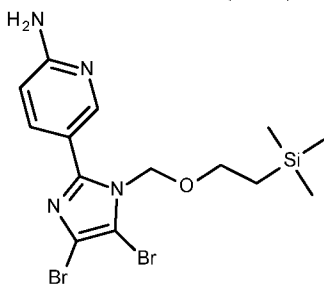
Intermediates I-37 to I-39 and I-84

The following intermediates were synthesized by following an analogous synthetic procedure as reported for **I-31** (SM means starting material).

Intermediate	SM
 <p>I-37a and</p>  <p>I-37b</p>	I-32
 <p>I-38</p>	I-36

Intermediate	SM
 <p>I-39</p>	I-35
 <p>I-84</p>	I-83

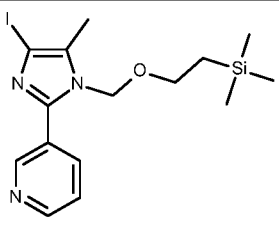
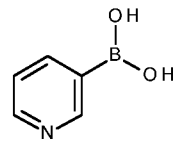
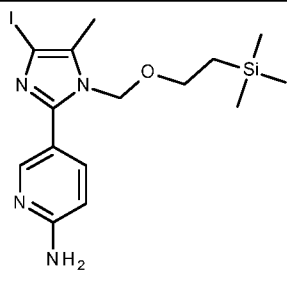
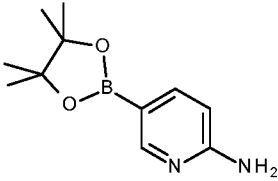
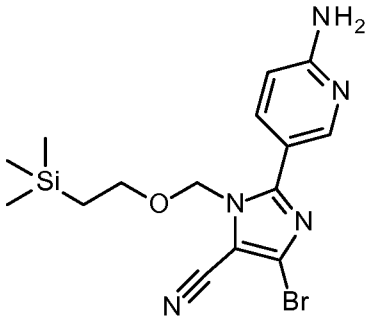
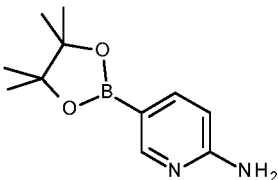
Intermediate 40 (I-40)

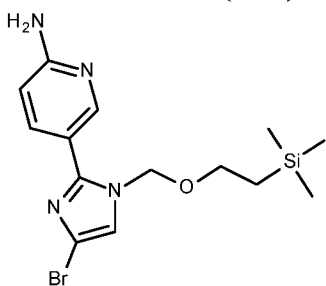


Pd(PPh₃)₄ (199 mg, 0.172 mmol) was added to a stirred suspension of 2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (759 mg, 3.45 mmol) and trimethyl-[2-[(2,4,5-tribromoimidazol-1-yl)methoxy]ethyl]silane (1.5 g, 3.45 mmol) in 1,4-dioxane (15 mL) and sat. sol. Na₂CO₃ (5 mL). The mixture was stirred at 80 °C for 16 h. Then the mixture was diluted with water and extracted with DCM. The organic layer was separated, dried (MgSO₄), filtered and the solvent evaporated *in vacuo*. The crude product was purified again by flash column chromatography (silica; EtOAc in DCM 0/100 to 85/15). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-40** (1.1 g, 71%) as an oil which solidified upon standing.

Intermediates I-41 to I-42

The following intermediates were synthesized by following an analogous synthetic procedure as reported for **I-40**.

Intermediate	Starting materials
 <p style="text-align: center;">I-41</p>	<p style="text-align: center;">I-31</p> 
 <p style="text-align: center;">I-42</p>	<p style="text-align: center;">I-31</p> 
	I-31
 <p style="text-align: center;">I-85</p>	

Intermediate 43 (I-43)

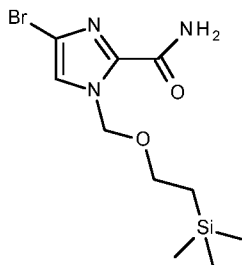
5

n-BuLi (1.6 M in hexanes, 2.1 mL, 3.346 mmol) was added to a solution of **I-40** (1 g, 2.231 mmol) in THF (15 mL) under nitrogen at -78 °C and the mixture was stirred at the same temperature for 30 min. Then water was added at -78 °C and the mixture was allowed to warm to rt and stirred for 1 h more. Then, the mixture was diluted with sat.

10 sol. NH₄Cl and extracted with DCM. The organic layer was separated, dried (MgSO₄),

filtered and the solvent evaporated *in vacuo*. The crude product was purified by flash chromatography (silica; MeOH in DCM 0/100 to 10/90). The desired fractions were collected and the solvents concentrated *in vacuo* to yield **I-43** (500 mg, 60%).

Intermediate 44 (I-44)

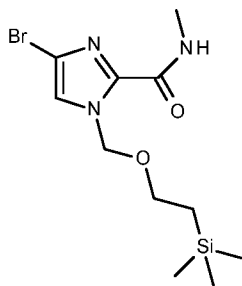


5

Ethyl 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-2-carboxylate (1.5 g, 4.29 mmol) was dissolved in 7M ammonia in MeOH (17.5 mL) and the mixture was stirred at 70°C for 16 h in a sealed tube. The solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 10/90). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-44** (705 mg, 51%).

10

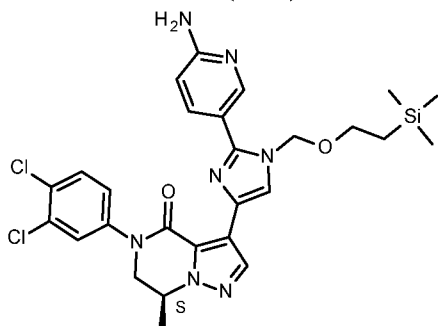
Intermediate 45 (I-45)



15

Lithium bis(trimethylsilyl)amide (4.23 mL, 4.23 mmol) was added to a stirred solution of ethyl 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-2-carboxylate (591 mg, 1.692 mmol) and methylamine (33% solution in EtOH, 318 μ L, 2.538 mmol) in THF (5.7 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was quenched with sat. sol. NH₄Cl at 0 °C and extracted with EtOAc. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica; 7M ammonia in MeOH in DCM 0/100 to 10/90). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-45** (380 mg, 64%).

20

Intermediate 46 (I-46)

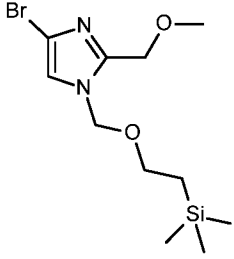
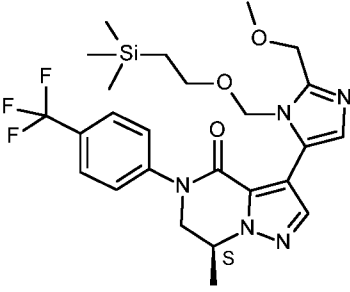
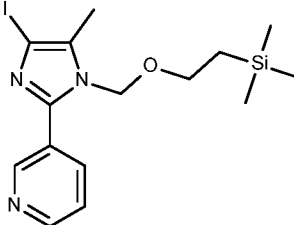
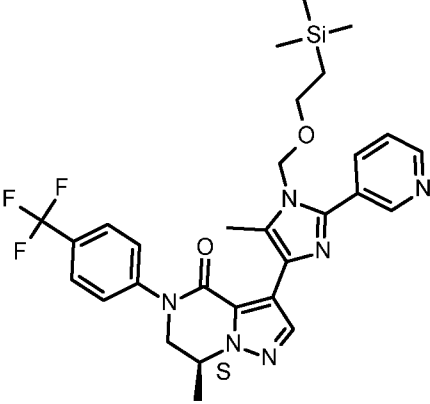
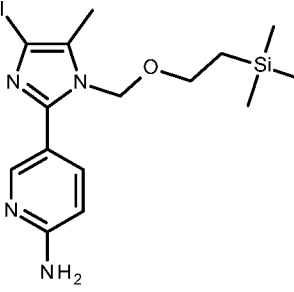
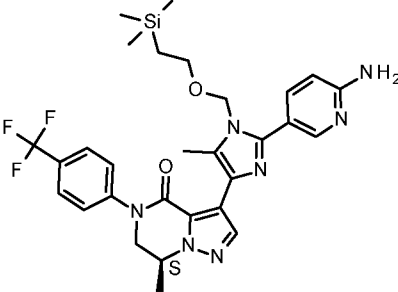
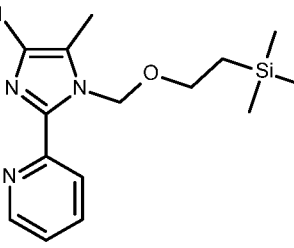
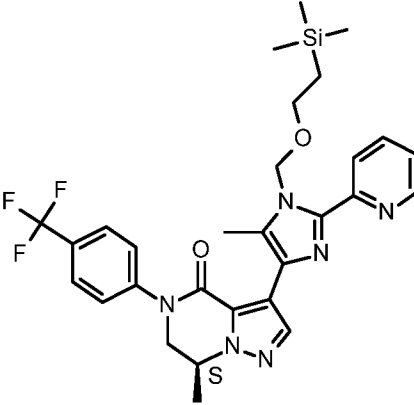
Pd(PPh₃)₄ (23 mg, 0.020 mmol) was added to a stirred suspension of **I-19** (189 mg, 0.446 mmol) and **I-43** (150 mg, 0.406 mmol) in 1,4-dioxane (3 mL) and sat. sol.

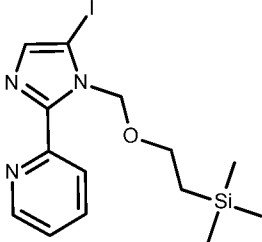
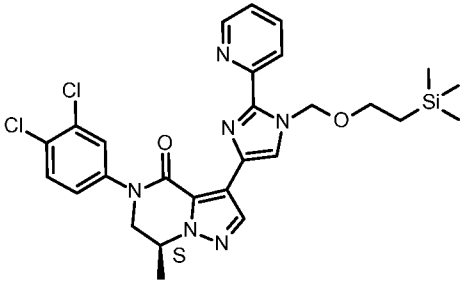
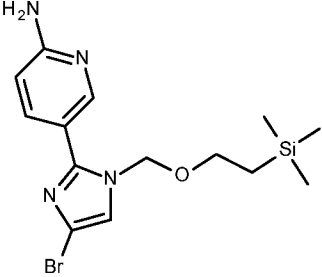
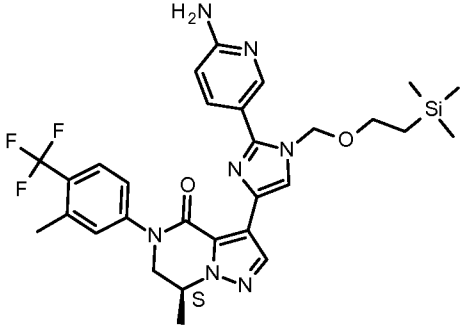
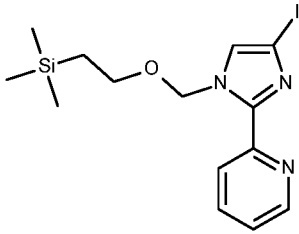
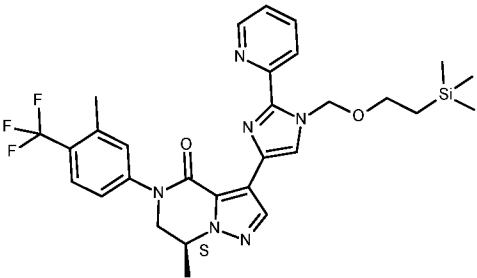
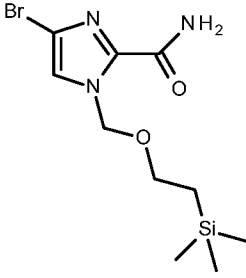
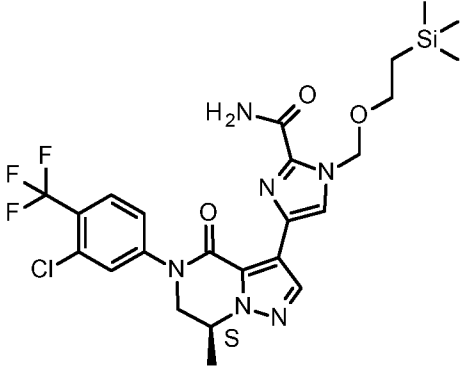
- 5 Na₂CO₃ (1 mL). The mixture was stirred at 90 °C for 16 h. Then the mixture was diluted with H₂O and extracted with DCM. The organic layer was separated, dried (Na₂SO₄), filtered and the solvent evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 10/90). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-46** (220 mg, 93%) as an oil.
- 10

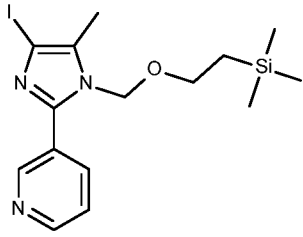
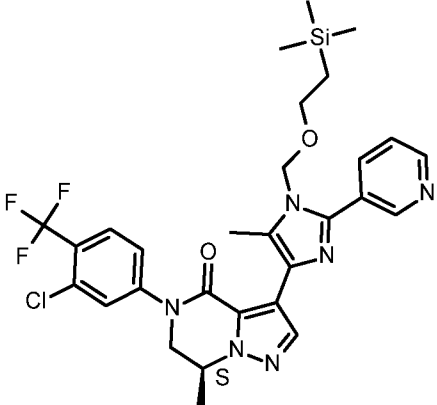
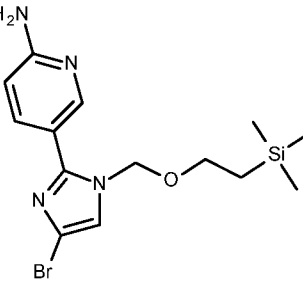
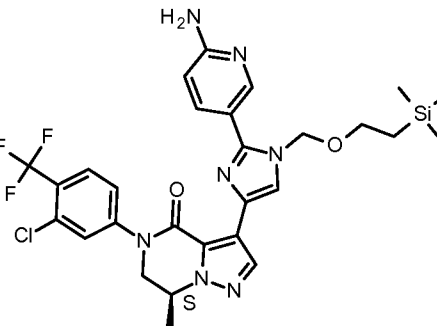
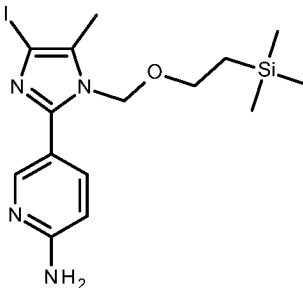
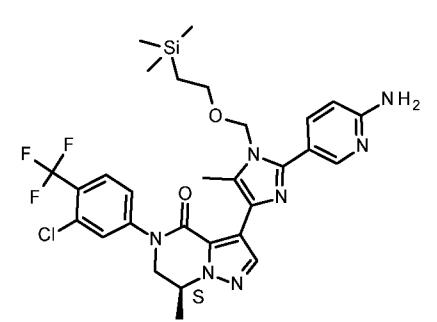
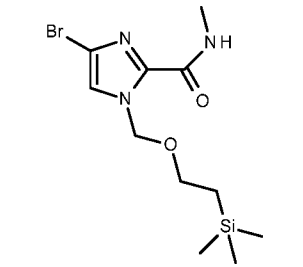
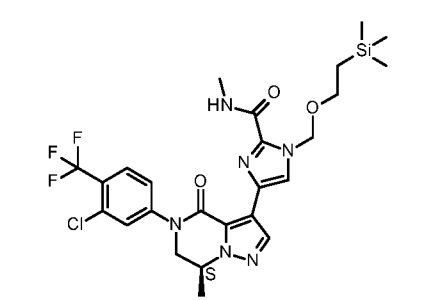
Intermediates I-47 to I-63

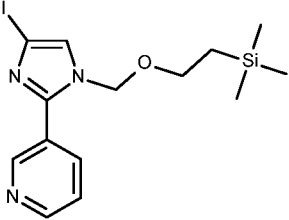
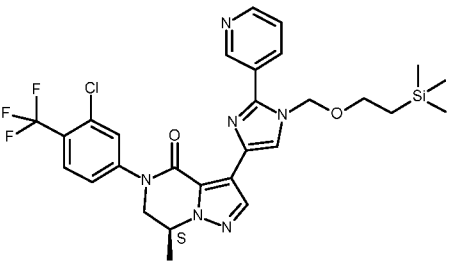
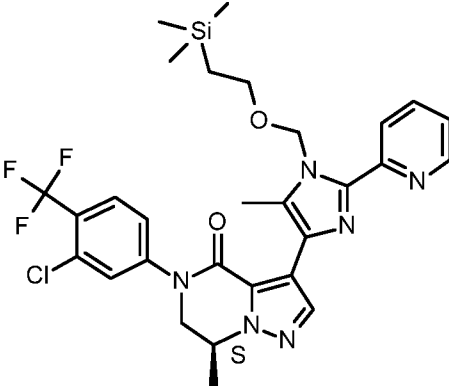
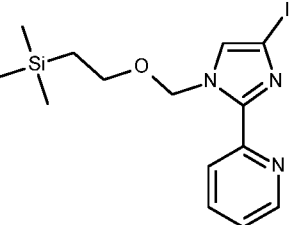
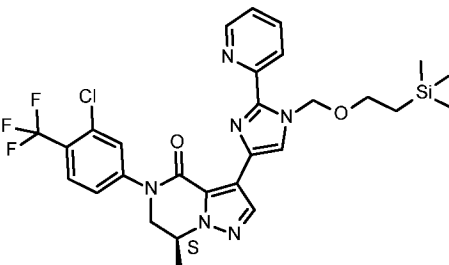
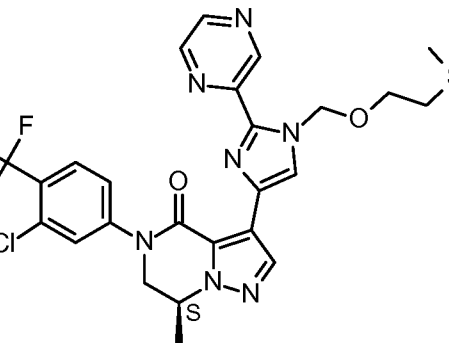
The following intermediates were synthesized by following an analogous synthetic procedure as reported for **intermediate I-46**.

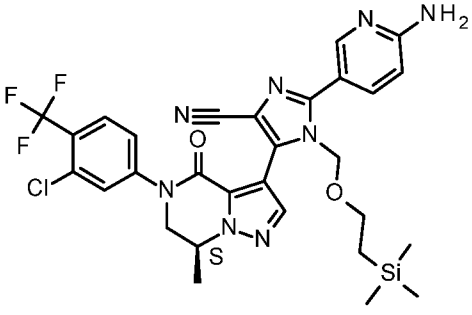
Reagents	Intermediate
<p>I-40</p>	<p>I-47</p>
I-17b	
<p>I-43</p>	<p>I-48</p>
I-17b	

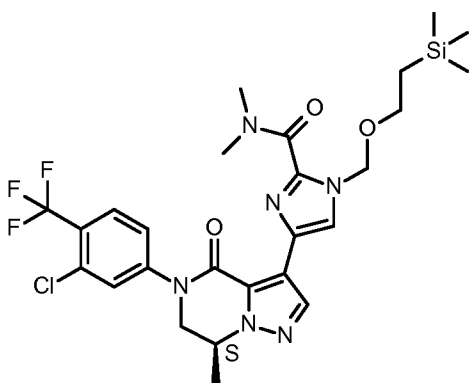
Reagents	Intermediate
 <p style="text-align: center;">I-30</p>	 <p style="text-align: center;">I-49</p>
I-17b	I-17b
 <p style="text-align: center;">I-41</p>	 <p style="text-align: center;">I-50</p>
I-17b	I-17b
 <p style="text-align: center;">I-42</p>	 <p style="text-align: center;">I-51</p>
I-17b	I-17b
 <p style="text-align: center;">I-37a</p>	 <p style="text-align: center;">I-52</p>
I-17b	I-17b

Reagents	Intermediate
 <p>I-39</p>	 <p>I-53</p>
I-19	
 <p>I-43</p>	 <p>I-54</p>
I-22	
 <p>I-39</p>	 <p>I-55</p>
I-22	
 <p>I-44</p>	 <p>I-56</p>
I-20b	

Reagents	Intermediate
 <p style="text-align: center;">I-41</p>	 <p style="text-align: center;">I-57</p>
<p style="text-align: center;">I-20a</p>	
 <p style="text-align: center;">I-43</p>	 <p style="text-align: center;">I-58</p>
<p style="text-align: center;">I-20a</p>	
 <p style="text-align: center;">I-42</p>	 <p style="text-align: center;">I-59</p>
<p style="text-align: center;">I-20a</p>	
 <p style="text-align: center;">I-45</p>	 <p style="text-align: center;">I-60</p>
<p style="text-align: center;">I-20b</p>	

Reagents	Intermediate
 <p>I-38</p>	 <p>I-61</p>
<p>I-20a</p>	 <p>I-62 (mixture of 2 regioisomers)</p>
<p>Mixture of I-37a and I-37b</p>	
<p>I-20a</p>	
 <p>I-39</p>	 <p>I-63</p>
<p>I-20a</p>	 <p>I-86</p>
<p>I-84</p>	
<p>I-20a</p>	

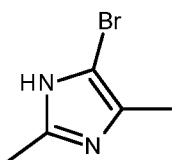
Reagents	Intermediate
I-85	 <p style="text-align: center;">I-87</p>
I-20a	

Intermediate 64 (I-64)

Sodium hydride (60% in mineral oils, 6 mg, 0.291 mmol) was added to **I-60** (100 mg, 0.171 mmol) in THF (0.3 mL) at 0 °C. The mixture was stirred at 0 °C for 40 min. Then

5 iodomethane (18 μ L, 0.291 mmol) was added at 0 °C and the mixture was stirred at 0 °C for 10 min and at rt for 2.5 h. The reaction was diluted with water and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 10/90). The desired fractions were collected and the

10 solvents evaporated *in vacuo* to yield **I-64** (50 mg, 48%).

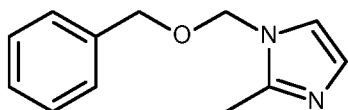
Intermediate 65 (I-65)

To a mixture of 2,4-dimethylimidazole (200 mg, 2.080 mmol) in acetonitrile (6 mL) at 0 °C was added *N*-bromosuccinimide (444 mg, 2.496 mmol) portionwise. Then the

15 mixture was left stirring at rt for 1 h. Then water, diluted sol. Na₂CO₃ and diluted sol. Na₂S₂O₃ were added and extracted with DCM. The organic layer was separated, dried

(Na₂SO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; 7N ammonia in MeOH in DCM 0/100 to 3/97). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-65** (210 mg, 58%) as a white solid.

5 **Intermediate 66 (I-66)**

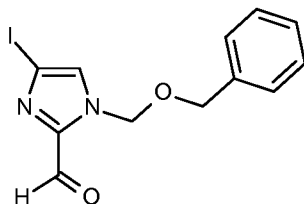


2-Methylimidazole (821 mg, 10 mmol) was added portionwise to a stirred suspension of sodium hydride (60% in mineral oils, 440 mg, 11 mmol) in THF (50 mL) at 0 °C. The mixture was stirred at rt for 30 min. Then benzyl chloromethyl ether (1.39 mL, 10 mmol) was added and the mixture was stirred at rt for 16 h. The mixture was treated with water and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica, 7 N solution of ammonia in MeOH in DCM 0/100 to 5/95). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-66** (1.68 g, 83%) as a colorless oil.

The following intermediates were synthesized by following an analogous synthetic procedure as reported for **intermediate I-66**.

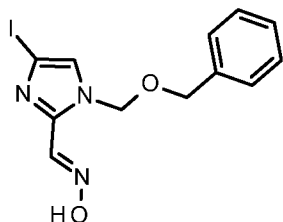
Intermediate	Starting material
<p>I-67</p>	

20 **Intermediate 68 (I-68)**

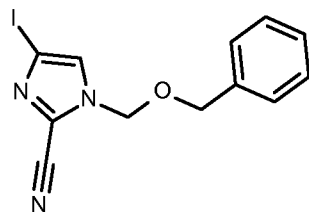


Lithium diisopropylamide (993 μL, 1.986 mmol) was added dropwise to a solution of **I-67** (520 mg, 1.655 mmol) in dry THF (10 mL) under nitrogen at -78 °C. The mixture

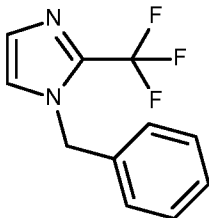
was stirred at -78 °C for 10 min then DMF (640 μ L, 8.277 mmol) was added. The mixture was stirred at -78 °C for 1 h and then left to rt for 18 h. Water was added carefully and it was extracted with EtOAc. The organic layer was dried (MgSO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 03/97). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-68** (267 mg, 47%) as a solid.

Intermediate 69 (I-69)

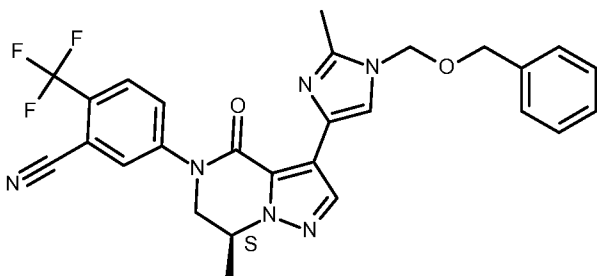
10 Sodium carbonate (165 mg, 1.56 mmol) was added to a solution of **I-68** (267 mg, 0.780 mmol) and hydroxylamine hydrochloride (108 mg, 1.56 mmol) in water (3.1 mL). The mixture was stirred at 70 °C for 90 min and a precipitate was formed. After cooling to rt, the suspension was filtered, washed with water and dried *in vacuo* to yield **I-69** (295 mg, quant.) as a white solid.

Intermediate 70 (I-70)

I-69 (278 mg, 0.778 mmol) in acetic anhydride (3 mL) was stirred at 140 °C for 20 h. The solvent was evaporated *in vacuo*. The residue was diluted with EtOAc and washed with sat. sol. Na₂CO₃. The organic layer was dried (MgSO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 02/98). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-70** (280 mg, quant.).

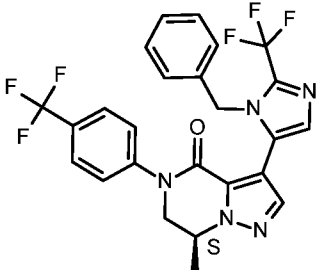
Intermediate 71 (I-71)

Diphenyl(trifluoromethyl)sulfonium trifluoromethanesulfonate (626 mg, 1.549 mmol) was added to a solution of 1-benzyl-2-iodoimidazole (220 mg, 0.774 mmol) and copper (147 mg, 2.323 mmol) in anhydrous DMF (3 mL). The mixture was stirred at 65 °C for 2.5 h. The mixture was diluted with water, quenched with aq. sol. NH₃ and extracted with DCM. The organic layer was dried (MgSO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; eluent DCM 100%). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-71** (65 mg, 37%) as an oil.

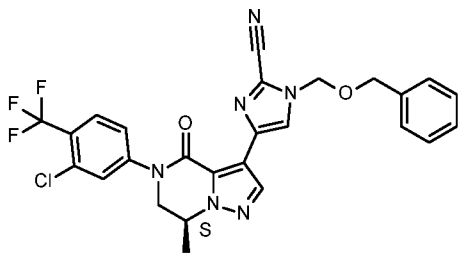
Intermediate 72 (I-72)

Palladium(II) acetate (5 mg, 0.022 mmol) and butyldi-1-adamantylphosphine (12 mg, 0.033 mmol) were added to a stirred mixture of **I-66** (200 mg, 0.448 mmol), **I-15** (109 mg, 0.538 mmol) and K₂CO₃ (124 mg, 0.896 mmol) in DMF (4 mL) (previously flushed with nitrogen for 5 min) in a sealed tube. The mixture was stirred at 120 °C for 30 h. The mixture was diluted with water and extracted with EtOAc. The organic layer was dried, filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 03/97). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-72** (110 mg, 47%).

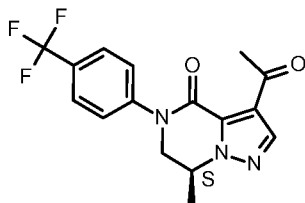
The following intermediate was synthesized by following an analogous synthetic procedure as reported for **intermediate I-72**.

Reagents	Intermediate
I-71	 <p style="text-align: center;">I-73</p>
I-11	

The following intermediate was synthesized by following an analogous synthetic procedure as reported for **intermediate I-46**.

Reagents	Intermediate
I-70	 <p style="text-align: center;">I-74</p>
I-20b	

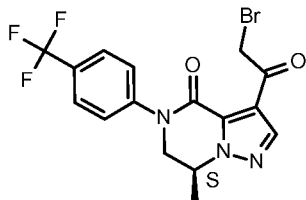
Intermediate 75 (I-75)



- 5 Bis(triphenylphosphine)palladium(II) chloride (0.25 g, 0.356 mmol) was added to a stirred suspension of **I-11** (3g, 7.12 mmol), tributyl-(1-ethoxyvinyl)tin (2.88 g, 8.548 mmol) and K_2CO_3 (1.969 g, 14.245 mmol) in a degassed mixture of 1,4-dioxane (30 mL) and water (6 mL) in a sealed tube and under nitrogen. The mixture was stirred at 110 °C for 20 h. Then the mixture was treated with sol. HCl (2M in H_2O , 17.8 mL, 35.6
- 10 mmol) and the mixture was stirred at 80 °C for 1 h. Then the mixture was basified with sol. NaOH (2M in H_2O) at 0 °C and extracted with EtOAc. The organic phase was separated, dried (Na_2SO_4), filtered and the solvent evaporated *in vacuo*. The crude compound was purified by flash column chromatography (silica, EtOAc in DCM 0/100

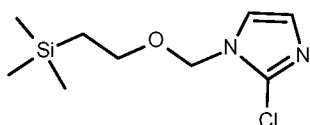
to 30/70). The desired fractions were collected and the solvent evaporated *in vacuo* to yield **I-75** (1.84 g, 76%) as a pale yellow solid.

Intermediate 76 (I-76)



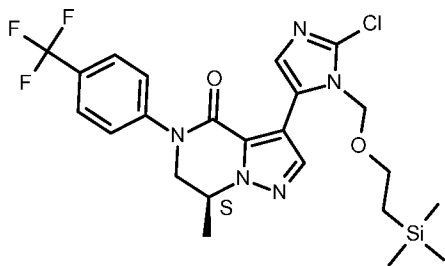
- 5 **I-75** (1.84 g, 5.455 mmol) was added to a stirred solution of pyridinium tribromide (1.22 g, 3.818 mmol) in DCM (38 mL) at 0 °C. The mixture was stirred at 0 °C for 20 min and then at rt for 30 min. The mixture was treated with sol. Na₂S₂O₃ and extracted with DCM. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography
- 10 (silica; EtOAc in DCM 0/100 to 10/90). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-76** (850 mg, 37%) as a colourless oil.

Intermediate 77 (I-77)



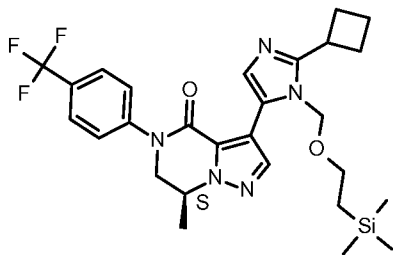
- Sodium hydride (60% in mineral oils, 468 mg, 11.7 mmol) was added to 2-chloro-1H-imidazole (800 mg, 7.8 mmol) in THF (24 mL) at 0 °C. The mixture was stirred at rt for
- 15 10 min. Then 2-(trimethylsilyl)ethoxymethyl chloride (2 mL, 11.7 mmol) was added at 0 °C and the mixture was stirred for 2 h. The mixture was diluted with sat. sol. NH₄Cl and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column
- 20 chromatography (silica; EtOAc in Heptane 0/100 to 50/50). The desired fractions were collected and the solvents concentrated *in vacuo* to yield **I-77** (1.52 g, 89%).

Intermediate 78 (I-78)



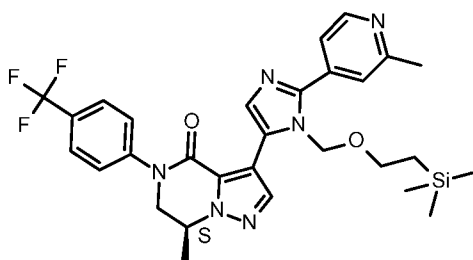
Two solutions of **I-77** (328 mg, 1.41 mmol) in THF (1.8 mL) and 2,2,6,6-tetramethylpiperidinylmagnesium chloride lithium chloride complex (0.9M in THF, 1.77 mL, 1.60 mmol) were pumped through a Sigma-Aldrich reactor (1 mL volume) at 0.5 ml/min each one (RT = 1 min) and at rt. The outlet solution was collected in a sealed vial under nitrogen atmosphere. To this solution zinc dichloride (0.5M in THF, 2 mL, 1.03 mmol) was added and the reaction mixture was stirred at rt for 15 min. Then, Pd(PPh₃)₄ (54 mg, 0.047 mmol) and **I-11** (400 mg, 0.940 mmol) in THF (1 mL) were added and the mixture was stirred at 50 °C for 16 h. Then the mixture was diluted with sat. sol. NH₄Cl and extracted with EtOAc. The organic layer was separated, dried (Na₂SO₄), filtered and the solvent evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; EtOAc in Heptane 0/100 to 40/60). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-78** (375 mg, 75%) as a white solid.

Intermediate 79 (I-79)



Cyclobutyl zinc bromide (0.5M in THF, 0.48 mL, 0.242 mmol) was added to a suspension of **I-78** (85 mg, 0.161 mmol), Pd₂(dba)₃ (7 mg, 0.008 mmol) and S-Phos (6 mg, 0.016 mmol) in THF (0.44 mL) under nitrogen atmosphere. The mixture was stirred at 60 °C for 3 h. Then, sat. sol. NH₄Cl was added and the mixture extracted with EtOAc. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc in DCM 0:100 to 50:50). The desired fractions were collected and evaporated *in vacuo* to yield **I-79** (68 mg, 77%) as a yellow oil.

Intermediate 80 (I-80)

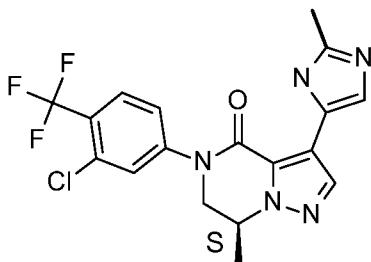


25

Pd(PPh₃)₄ (16 mg, 0.014 mmol) was added to a stirred suspension of **I-78** (150 mg, 0.285 mmol) and 2-methylpyridine-4-boronic acid pinacol ester (75 mg, 0.342 mmol) in 1,4-dioxane (2 mL) and sat. sol. Na₂CO₃ (1 mL). The mixture was stirred at 90 °C for 36 h. Additional Pd(PPh₃)₄ (16 mg, 0.014 mmol) was added and the mixture was stirred at 100 °C for 6 h. Then, the mixture was diluted with EtOAc and filtered through a pad of diatomaceous earth. The filtrate was evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc in DCM 0/100 to 100/0). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **I-80** (60 mg, 36%) as a yellow oil.

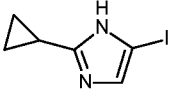
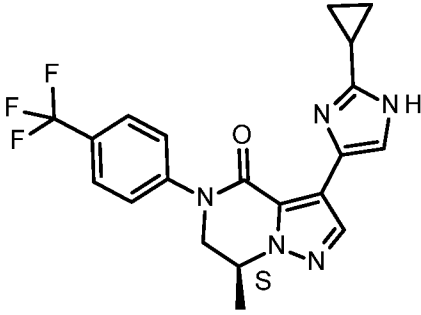
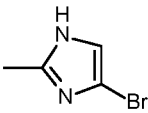
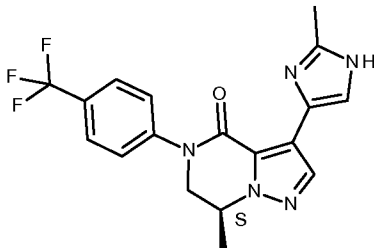
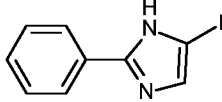
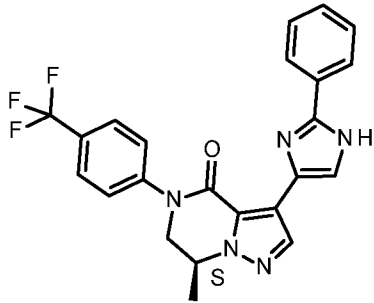
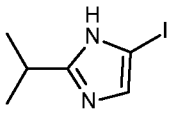
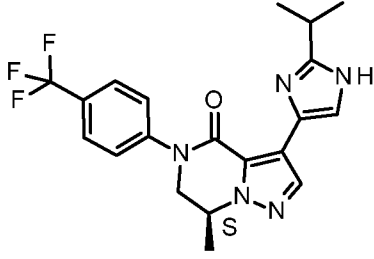
10 Preparation of final compounds

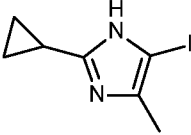
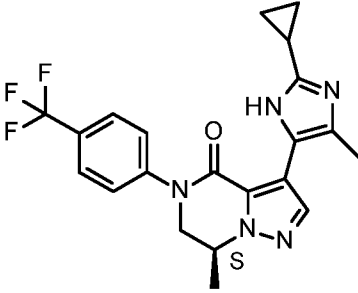
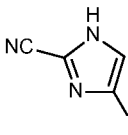
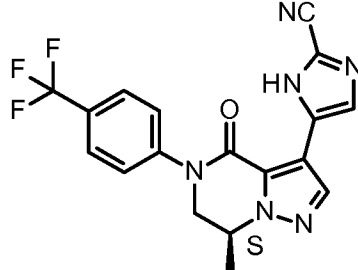
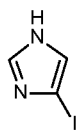
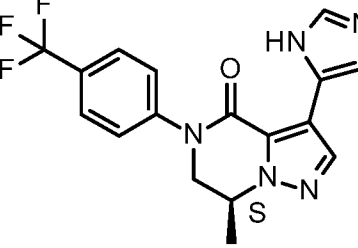
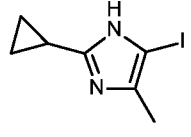
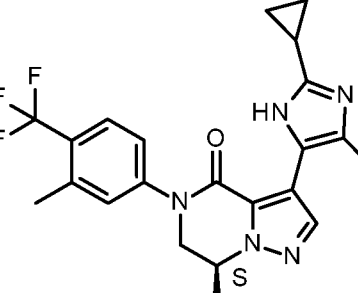
Example 1 (E-1, Co. No. 27)

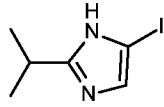
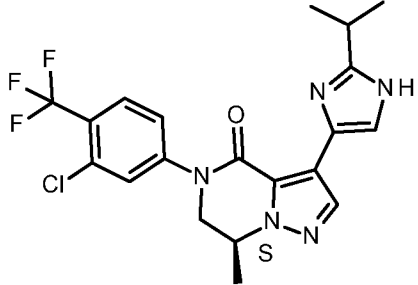
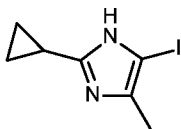
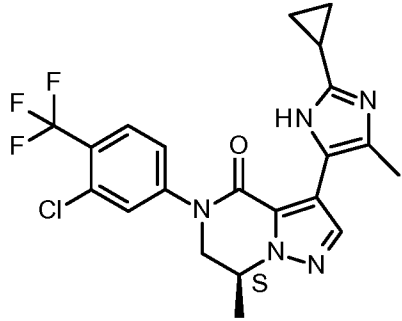
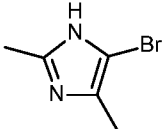
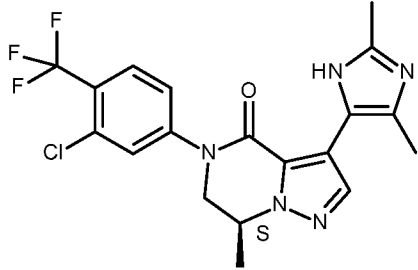
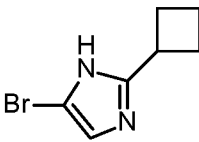
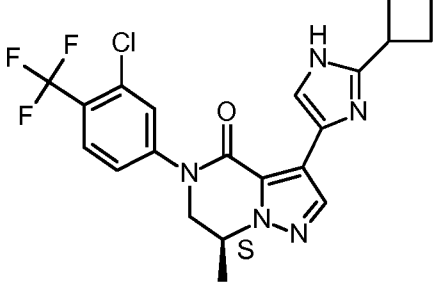


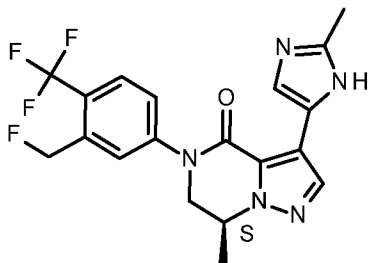
Pd(PPh₃)₄ (51 mg, 0.044 mmol) was added to a stirred suspension of **I-20a** (400 mg, 0.877 mmol) and 4-bromo-2-methyl-1H-imidazole (141 mg, 0.877 mmol) in 1,4-dioxane (8 mL) and sat. sol. Na₂CO₃ (4 mL). The mixture was nitrogen flushed and then stirred at 120 °C for 15 min under microwave irradiation. Then the mixture was diluted with H₂O and extracted with DCM. The organic layer was separated, dried (Na₂SO₄), filtered and the solvent evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; MeOH in EtOAc 0/100 to 2/98). The desired fractions were collected and the solvents evaporated *in vacuo*. The product was triturated with heptane, filtered and dried *in vacuo* to yield final compound **Co. No. 27** (200 mg, 56%) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.56 (d, *J*=6.6 Hz, 3 H) 2.29 (s, 2 H) 2.31 (s, 1 H) 3.99 - 4.13 (m, 1 H) 4.27 - 4.40 (m, 1 H) 4.68 - 4.81 (m, 1 H) 7.39 (d, *J*=1.2 Hz, 0.25 H) 7.61 - 7.68 (m, 1 H) 7.79 (d, *J*=2.0 Hz, 0.75 H) 7.88 (d, *J*=1.7 Hz, 0.75 H) 7.91 (d, *J*=1.2 Hz, 0.25 H) 7.94 (d, *J*=8.7 Hz, 0.75 H) 7.97 (d, *J*=9.0 Hz, 0.25 H) 7.98 (s, 0.75 H) 8.04 (s, 0.25 H) 11.73 (br. s., 0.75 H) 11.88 (br. s., 0.25 H).

Following a procedure analogous to that described for **E-1**, the following compounds were also synthesized:

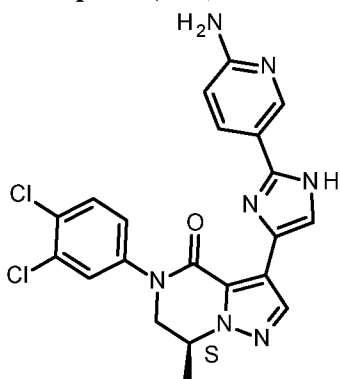
Intermediate	Reagent	Final Compound
I-17a		 Co. No. 2
I-17a		 Co. No. 4
I-17b	 I-23	 Co. No. 5
I-17a		 Co. No. 6

Intermediate	Reagent	Final Compound
<p data-bbox="395 533 472 562">I-17b</p>	 <p data-bbox="687 495 751 524">I-25 (made according to the procedure described in WO2014/008197)</p>	 <p data-bbox="1054 696 1182 725">Co. No. 7</p>
<p data-bbox="395 943 472 972">I-17a</p>	 <p data-bbox="767 976 815 1005">I-28</p>	 <p data-bbox="1054 1099 1182 1128">Co. No. 10</p>
<p data-bbox="395 1301 472 1330">I-17a</p>		 <p data-bbox="1054 1447 1182 1476">Co. No. 12</p>
<p data-bbox="403 1671 464 1700">I-22</p>	 <p data-bbox="687 1749 751 1778">I-25</p>	 <p data-bbox="1054 1850 1182 1879">Co. No. 21</p>

Intermediate	Reagent	Final Compound
I-20b		 Co. No. 26
I-20a	 I-25	 Co. No. 28
I-20a/I-20b	 I-65	 .HCl Co. No. 30
I-20a		 Co. No. 42

Example 2 (E-2, Co. No. 24)

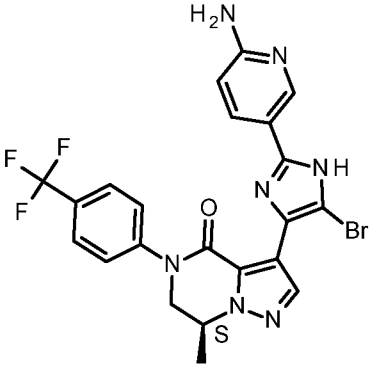
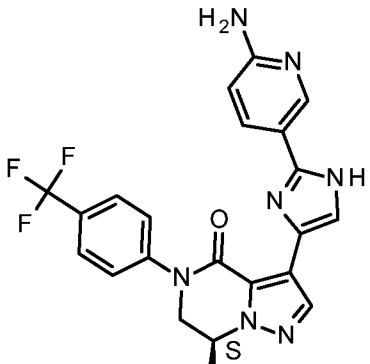
Pd(PPh₃)₄ (46 mg, 0.040 mmol) was added to a deoxygenated stirred mixture of **I-18** (261 mg, 0.576 mmol), 5-bromo-2-methyl-1H-imidazole (463 mg, 2.88 mmol) and
 5 K₂CO₃ (397 mg, 2.88 mmol) in 1,4-dioxane (7 mL) and water (1.9 mL) in a sealed tube under nitrogen. The mixture was stirred at 120 °C for 30 min under microwave irradiation. Then the mixture was diluted with water/brine and extracted with EtOAc. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated *in vacuo*. The crude product was triturated with DCM, filtered and dried *in vacuo*. The
 10 crude product was purified by flash column chromatography (silica; EtOAc in DCM 0/100 to 100/0 and MeOH in EtOAc 0/100 to 4/96). The desired fractions were collected and the solvents concentrated *in vacuo* to yield the product as a syrup which was triturated with DIPE, filtered and dried *in vacuo* to yield **Co. No. 24** (116 mg, 49%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.73 (d, *J*=6.5 Hz, 3 H) 2.42 (s, 3 H) 4.00 (dd, *J*=12.6, 7.5 Hz, 1 H) 4.26 (dd, *J*=12.7, 4.2 Hz, 1 H) 4.69 - 4.80 (m, 1 H) 5.68 (d, *J*=46.7 Hz, 2 H) 7.30 (d, *J*=1.4 Hz, 1 H) 7.50 (dd, *J*=8.4, 0.8 Hz, 1 H) 7.69 (s, 1 H) 7.81 (d, *J*=8.6 Hz, 1 H) 7.90 (s, 1 H) 11.85 (br. s., 1 H).

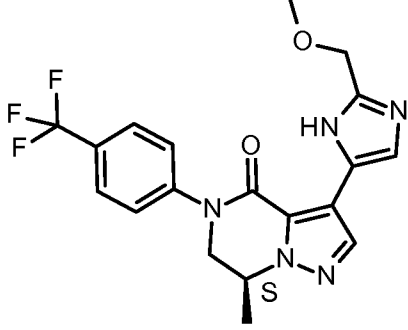
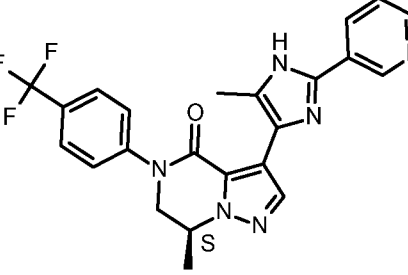
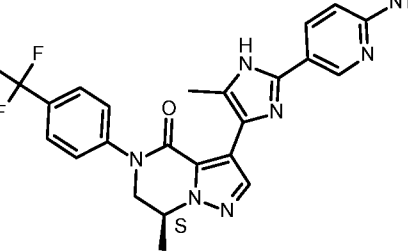
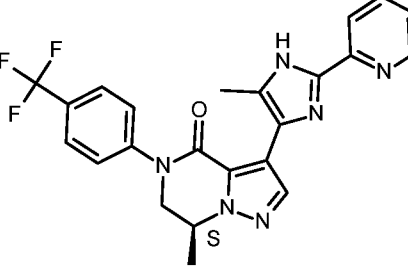
Example 3 (E-3, Co. No. 19)

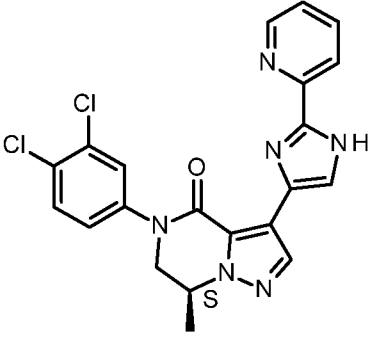
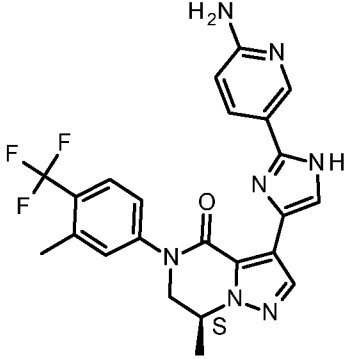
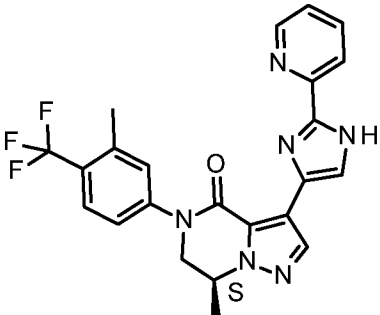
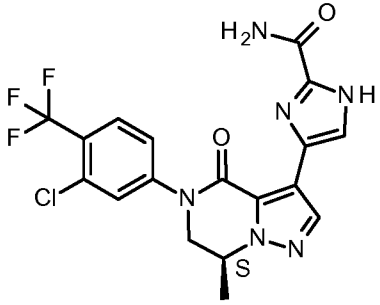
20 A solution of **I-46** (220 mg, 0.376 mmol) in HCl (6 M in iPrOH, 6.3 mL) was stirred at 60 °C for 16 h. Then the solvent was concentrated *in vacuo*. The mixture was diluted with sat. sol. Na₂CO₃ and extracted with DCM. The organic layer was separated, dried (MgSO₄), filtered and the solvents concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 10/90). The

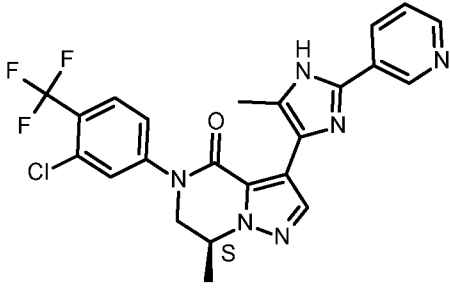
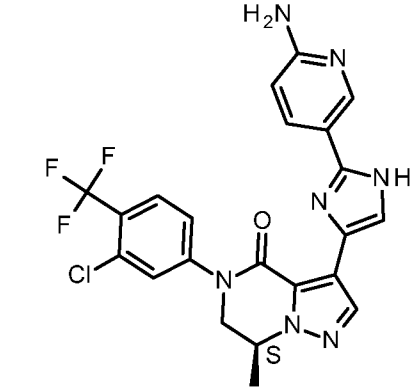
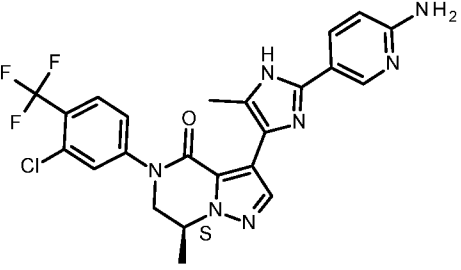
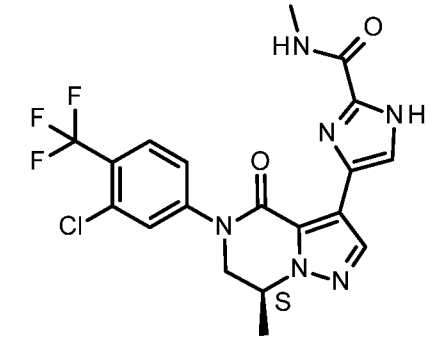
desired fractions were collected and the solvents evaporated *in vacuo*. The product was triturated with Et₂O, filtered and dried *in vacuo* to give a solid that was triturated with DCM, filtered and dried *in vacuo* to yield **Co. No. 19** (125 mg, 73%) as a solid as a solid (mixture of tautomers 90:10). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.72 (d, *J*=6.7 Hz, 3 H) 3.94 (dd, *J*=12.7, 7.4 Hz, 1 H) 4.21 (dd, *J*=12.7, 4.2 Hz, 1 H) 4.57 (s, 2 H) 4.68 - 4.81 (m, 1 H) 6.54 (d, *J*=8.6 Hz, 1 H) 7.28 (dd, *J*=8.6, 2.5 Hz, 1 H) 7.47 (d, *J*=1.2 Hz, 1 H) 7.52 (d, *J*=2.5 Hz, 1 H) 7.58 (d, *J*=8.6 Hz, 1 H) 7.93 (dd, *J*=8.6, 2.5 Hz, 1 H) 7.94 (s, 1 H) 8.64 (d, *J*=1.8 Hz, 1 H) 12.70 (br. s., 0.9 H) 12.79 (br. s., 0.1 H).

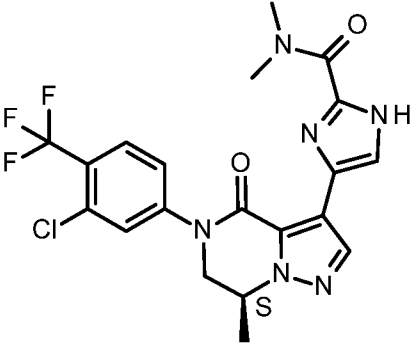
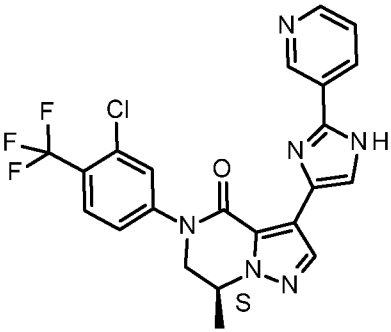
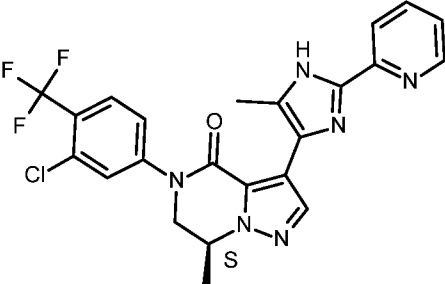
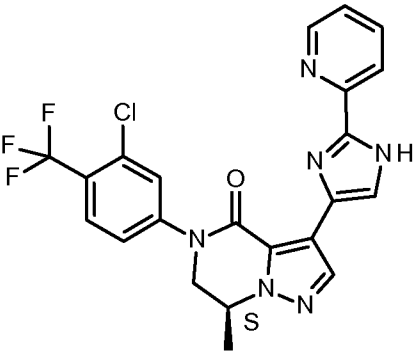
Following a procedure analogous to that described for **E-3**, the following compounds were also synthesized (in the table below, I means intermediate):

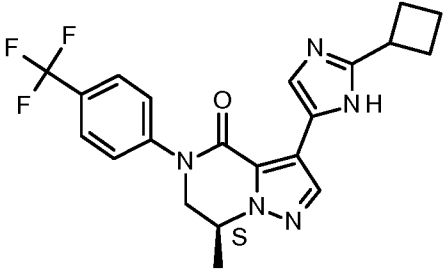
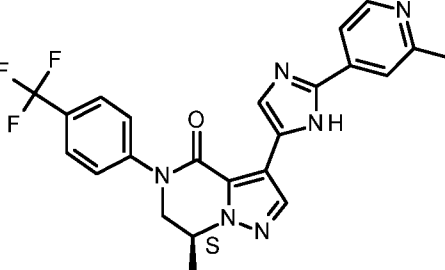
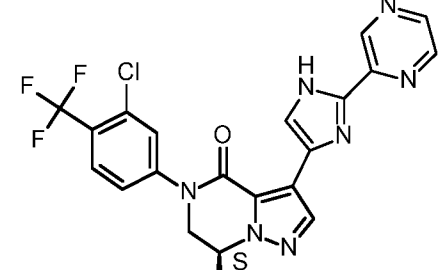
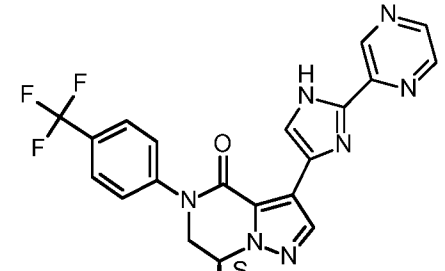
I	Final Compound
I-47	 <p style="text-align: center;">Co. No. 9</p>
I-48	 <p style="text-align: center;">Co. No. 11</p>

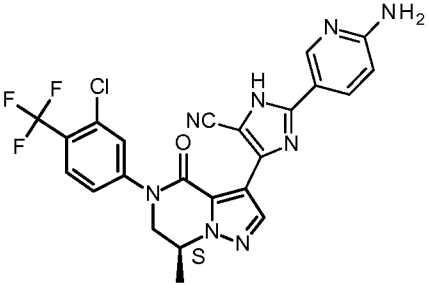
I	Final Compound
I-49	 <p>Chemical structure of Co. No. 13: A 6-membered ring containing a sulfur atom and a nitrogen atom, fused to a 5-membered ring containing two nitrogen atoms. The 6-membered ring has a carbonyl group and a trifluoromethyl group. The 5-membered ring has a methyl group and a 1H-imidazole ring attached to it. The imidazole ring has a methoxy group attached to it.</p> <p>Co. No. 13</p>
I-50	 <p>Chemical structure of Co. No. 14: A 6-membered ring containing a sulfur atom and a nitrogen atom, fused to a 5-membered ring containing two nitrogen atoms. The 6-membered ring has a carbonyl group and a trifluoromethyl group. The 5-membered ring has a methyl group and a 1H-imidazole ring attached to it. The imidazole ring has a pyridine ring attached to it.</p> <p>Co. No. 14</p>
I-51	 <p>Chemical structure of Co. No. 16: A 6-membered ring containing a sulfur atom and a nitrogen atom, fused to a 5-membered ring containing two nitrogen atoms. The 6-membered ring has a carbonyl group and a trifluoromethyl group. The 5-membered ring has a methyl group and a 1H-imidazole ring attached to it. The imidazole ring has a 4-aminopyridine ring attached to it.</p> <p>Co. No. 16</p>
I-52	 <p>Chemical structure of Co. No. 17: A 6-membered ring containing a sulfur atom and a nitrogen atom, fused to a 5-membered ring containing two nitrogen atoms. The 6-membered ring has a carbonyl group and a trifluoromethyl group. The 5-membered ring has a methyl group and a 1H-imidazole ring attached to it. The imidazole ring has a pyridine ring attached to it.</p> <p>Co. No. 17</p>

I	Final Compound
I-53	 <p>Chemical structure of Co. No. 18: A 6-membered ring containing a sulfur atom and a nitrogen atom, fused to a 5-membered ring containing two nitrogen atoms. The sulfur atom has a methyl group attached. The nitrogen atom in the 6-membered ring is substituted with a 3,4-dichlorophenyl group. The 5-membered ring is substituted with a 2-pyridylmethylamino group.</p> <p>Co. No. 18</p>
I-54	 <p>Chemical structure of Co. No. 20: A 6-membered ring containing a sulfur atom and a nitrogen atom, fused to a 5-membered ring containing two nitrogen atoms. The sulfur atom has a methyl group attached. The nitrogen atom in the 6-membered ring is substituted with a 2-(trifluoromethyl)-4-methylphenyl group. The 5-membered ring is substituted with a 4-amino-2-pyridylmethylamino group.</p> <p>Co. No. 20</p>
I-55	 <p>Chemical structure of Co. No. 22: A 6-membered ring containing a sulfur atom and a nitrogen atom, fused to a 5-membered ring containing two nitrogen atoms. The sulfur atom has a methyl group attached. The nitrogen atom in the 6-membered ring is substituted with a 2-(trifluoromethyl)-4-methylphenyl group. The 5-membered ring is substituted with a 2-pyridylmethylamino group.</p> <p>Co. No. 22</p>
I-56	 <p>Chemical structure of Co. No. 31: A 6-membered ring containing a sulfur atom and a nitrogen atom, fused to a 5-membered ring containing two nitrogen atoms. The sulfur atom has a methyl group attached. The nitrogen atom in the 6-membered ring is substituted with a 2-(trifluoromethyl)-4-chlorophenyl group. The 5-membered ring is substituted with a 2-pyridylmethylamino group.</p> <p>Co. No. 31</p>

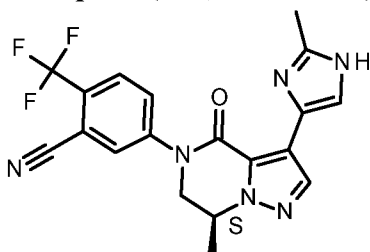
I	Final Compound
I-57	 <p data-bbox="582 633 715 667">Co. No. 32</p>
I-58	 <p data-bbox="582 1088 715 1122">Co. No. 33</p>
I-59	 <p data-bbox="582 1417 715 1451">Co. No. 34</p>
I-60	 <p data-bbox="582 1821 715 1854">Co. No. 35</p>

I	Final Compound
I-64	 <p>Chemical structure of Co. No. 36: A 6-membered ring containing a sulfur atom and a nitrogen atom, fused to a 5-membered ring containing two nitrogen atoms. The sulfur atom is substituted with a methyl group. The nitrogen atom in the 6-membered ring is substituted with a 4-(trifluoromethyl)phenyl group and a chlorine atom. The 5-membered ring is substituted with a 1,2,4-triazole ring, which is further substituted with a methylamino group and a hydrogen atom.</p> <p>Co. No. 36</p>
I-61	 <p>Chemical structure of Co. No. 37: A 6-membered ring containing a sulfur atom and a nitrogen atom, fused to a 5-membered ring containing two nitrogen atoms. The sulfur atom is substituted with a methyl group. The nitrogen atom in the 6-membered ring is substituted with a 3-(trifluoromethyl)phenyl group and a chlorine atom. The 5-membered ring is substituted with a 1,2,4-triazole ring, which is further substituted with a hydrogen atom and a 2-pyridyl group.</p> <p>Co. No. 37</p>
I-62	 <p>Chemical structure of Co. No. 38: A 6-membered ring containing a sulfur atom and a nitrogen atom, fused to a 5-membered ring containing two nitrogen atoms. The sulfur atom is substituted with a methyl group. The nitrogen atom in the 6-membered ring is substituted with a 3-(trifluoromethyl)phenyl group and a chlorine atom. The 5-membered ring is substituted with a 1,2,4-triazole ring, which is further substituted with a methyl group and a 2-pyridyl group.</p> <p>Co. No. 38</p>
I-63	 <p>Chemical structure of Co. No. 39: A 6-membered ring containing a sulfur atom and a nitrogen atom, fused to a 5-membered ring containing two nitrogen atoms. The sulfur atom is substituted with a methyl group. The nitrogen atom in the 6-membered ring is substituted with a 3-(trifluoromethyl)phenyl group and a chlorine atom. The 5-membered ring is substituted with a 1,2,4-triazole ring, which is further substituted with a hydrogen atom and a 2-pyridyl group.</p> <p>Co. No. 39</p>

I	Final Compound
I-79	 <p>Chemical structure of Co. No. 40: A 6-membered ring containing a nitrogen atom and a sulfur atom (with a methyl group on the sulfur) is fused to a 5-membered ring containing two nitrogen atoms. The nitrogen atom of the 6-membered ring is substituted with a 4-(trifluoromethyl)phenyl group. The 5-membered ring is substituted with a 1H-imidazole ring, which is further substituted with a cyclobutyl group.</p> <p>Co. No. 40</p>
I-80	 <p>Chemical structure of Co. No. 41: A 6-membered ring containing a nitrogen atom and a sulfur atom (with a methyl group on the sulfur) is fused to a 5-membered ring containing two nitrogen atoms. The nitrogen atom of the 6-membered ring is substituted with a 4-(trifluoromethyl)phenyl group. The 5-membered ring is substituted with a 1H-imidazole ring, which is further substituted with a 4-methylpyridin-2-yl group.</p> <p>Co. No. 41</p>
I-86	 <p>Chemical structure of Co. No. 43: A 6-membered ring containing a nitrogen atom and a sulfur atom (with a methyl group on the sulfur) is fused to a 5-membered ring containing two nitrogen atoms. The nitrogen atom of the 6-membered ring is substituted with a 3-(chloro(trifluoromethyl))phenyl group. The 5-membered ring is substituted with a 1H-imidazole ring, which is further substituted with a pyrimidin-2-yl group.</p> <p>Co. No. 43</p>
I-86	 <p>Chemical structure of Co. No. 44: A 6-membered ring containing a nitrogen atom and a sulfur atom (with a methyl group on the sulfur) is fused to a 5-membered ring containing two nitrogen atoms. The nitrogen atom of the 6-membered ring is substituted with a 4-(trifluoromethyl)phenyl group. The 5-membered ring is substituted with a 1H-imidazole ring, which is further substituted with a pyrimidin-2-yl group.</p> <p>Co. No. 44</p>

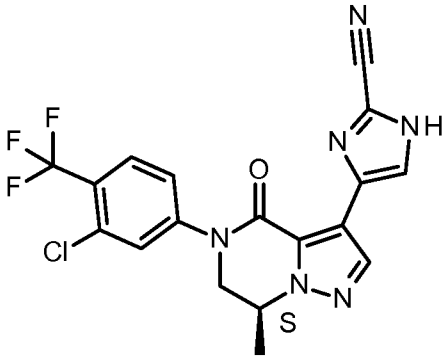
I	Final Compound
I-87	 <p data-bbox="574 627 726 660">Co. No. 45</p>

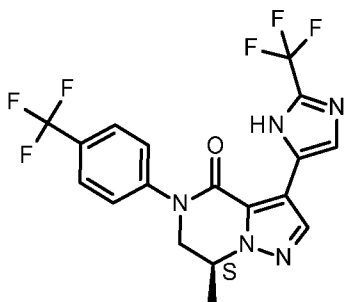
Example 4 (E-4, Co. No. 23)



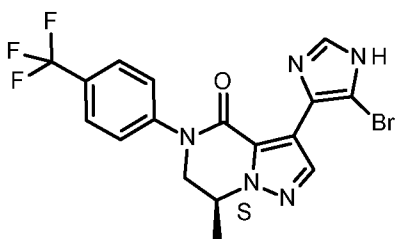
Boron tribromide (1M in DCM, 605 μ L, 0.605 mmol) was added to a suspension of **I-72** (105 mg, 0.202 mmol) in toluene (2 mL) under nitrogen. The mixture was stirred at 90 $^{\circ}$ C for 3 h. Then the mixture was quenched with 10% aq. sol. K_2CO_3 and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 07/93). The desired fractions were collected and the solvents evaporated *in vacuo*. The product was triturated with DIPE, filtered and dried *in vacuo* to yield **Co. No. 23** (42 mg, 52%) as a solid. 1H NMR (400 MHz, $CDCl_3$) δ ppm 1.74 (d, $J=6.5$ Hz, 3 H) 2.45 (s, 3 H) 4.03 (dd, $J=12.5, 7.6$ Hz, 1 H) 4.27 (dd, $J=12.5, 4.2$ Hz, 1 H) 4.72 - 4.82 (m, 1 H) 7.33 (br. s., 1 H) 7.77 (dd, $J=8.7, 1.5$ Hz, 1 H) 7.87 - 7.94 (m, 2 H) 7.95 (d, $J=2.1$ Hz, 1 H) 11.72 (br. s., 1 H).

Following a procedure analogous to that described for **E-4**, the following compounds were also synthesized:

Intermediate	Final Compound
I-74	 <p>Co. No. 29</p>

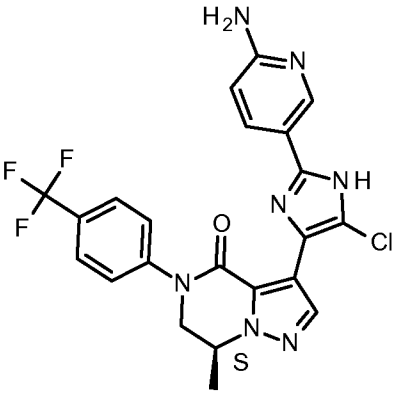
Example 5 (E-5, Co. No. 8)

A solution of **I-73** (62 mg, 0.119 mmol) and acetic acid (0.05 mL) in EtOH (2 mL) was hydrogenated in a H-cube reactor (1 mL/min, 30mm Pd(OH)₂ 20% cartridge, full H₂ mode, 100 °C, 3 cycles). The solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; EtOAc in Heptane 0/100 to 60/40). The desired fractions were collected and the solvent evaporated *in vacuo*. The product was purified *via* RP HPLC (Stationary phase: C18 Sunfire 30 x 100 mm 5µm, Mobile phase: Gradient from 80% 10mM NH₄CO₃H pH 9 solution in Water, 20% CH₃CN to 0% 10 mM NH₄CO₃H pH 9 solution in Water, 100% CH₃CN) to yield **Co. No. 8** (5 mg, 10%) as a solid. ¹H NMR (500 MHz, CDCl₃) δ ppm 1.75 (d, *J*=6.4 Hz, 3 H) 4.02 (dd, *J*=12.7, 7.5 Hz, 1 H) 4.29 (dd, *J*=12.7, 4.0 Hz, 1 H) 4.75 - 4.83 (m, 1 H) 7.48 (s, 1 H) 7.54 (d, *J*=8.4 Hz, 2 H) 7.78 (d, *J*=8.7 Hz, 2 H) 7.98 (s, 1 H) 13.15 (br. s., 1 H).

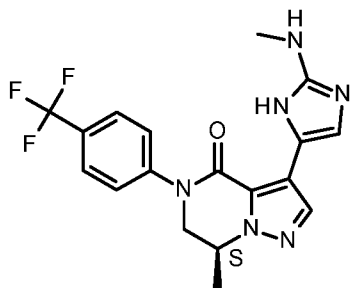
Example 6 (E-6, Co. No. 1)

N-bromosuccinimide (386 mg, 2.167 mmol) was added to a stirred solution of **Co. No. 12** (712 mg, 1.9705 mmol) in acetonitrile (3.6 mL) at 0 °C. The mixture was stirred at rt for 1 h. The mixture was treated with sat. sol. NaHCO₃ and extracted with EtOAc. The organic layer was dried (Na₂SO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; EtOAc in DCM 0/100 to 50/50). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **Co. No. 1** (580 mg, 67%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ ppm 1.75 (d, *J*=6.4 Hz, 3 H) 4.01 (dd, *J*=12.7, 7.5 Hz, 1 H) 4.29 (dd, *J*=12.9, 4.2 Hz, 1 H) 4.76 - 4.84 (m, 1 H) 7.47 (d, *J*=1.2 Hz, 1 H) 7.52 (d, *J*=8.4 Hz, 2 H) 7.78 (d, *J*=8.4 Hz, 2 H) 8.63 (s, 1 H) 12.98 (br. s., 1 H).

Following a procedure analogous to that described for **E-6**, the following compounds were also synthesized:

Intermediate	Final Compound
<p style="text-align: center;">Co. No. 11 and <i>N</i>-chlorosuccinimide</p>	 <p style="text-align: center;">Co. No. 3</p>

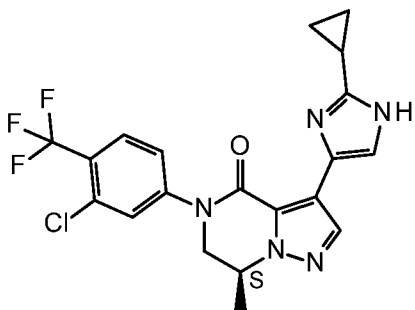
Example 7 (E-7, Co. No. 15)



15 A mixture of **I-76** (220 mg, 0.528 mmol), 2-methylaminopyrimidine (58 mg, 0.528 mmol) and 4-(dimethylamino)pyridine (0.6 mg, 0.005 mmol) in acetonitrile (2 mL) was stirred at 85 °C for 16 h. Then, hydrazine hydrate (179 μL, 3.7 mmol) was added and the mixture was stirred at 100 °C for 10 min under microwave irradiation. Then, the solvent was evaporated *in vacuo* and the crude product was purified by flash column

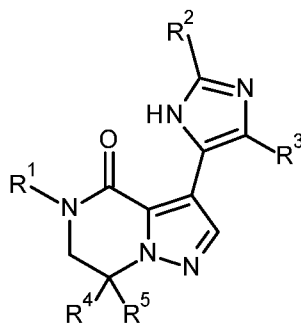
chromatography (silica; MeOH in DCM 0/100 to 10/90). The desired fractions were collected and the solvents evaporated *in vacuo* to yield **Co. No. 15** (135 mg, 65%) as a yellow solid. ¹H NMR (500 MHz, CDCl₃) δ ppm 1.70 (d, *J*=6.4 Hz, 3 H) 2.94 (s, 3 H) 3.96 (dd, *J*=12.6, 7.4 Hz, 1 H) 4.23 (dd, *J*=12.6, 4.2 Hz, 1 H) 4.26 (br. s., 1 H) 4.66 - 4.75 (m, 1 H) 7.07 (s, 1 H) 7.51 (d, *J*=8.4 Hz, 2 H) 7.75 (d, *J*=8.4 Hz, 2 H) 7.83 (s, 1 H) 11.10 (br. s., 1 H).

Example 8 (E-8, Co. No. 25)

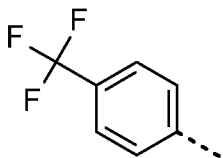
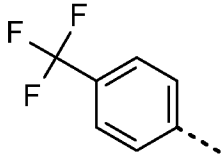
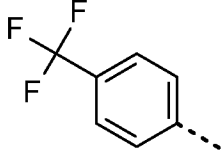
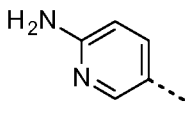
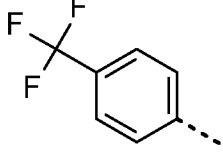
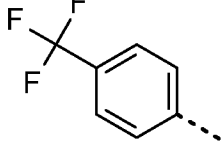
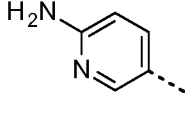
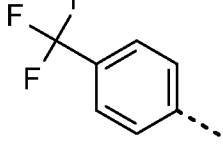
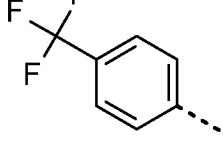
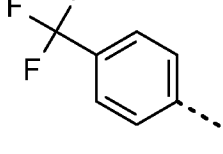
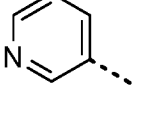


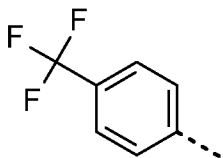
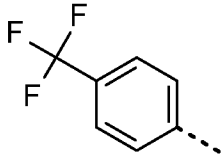
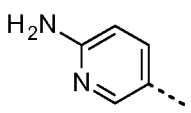
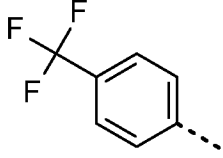
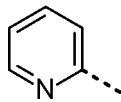
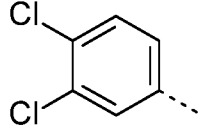
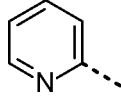
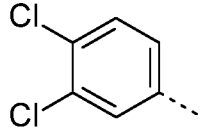
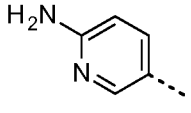
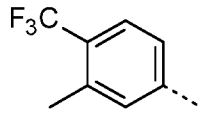
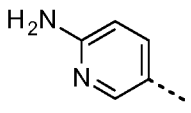
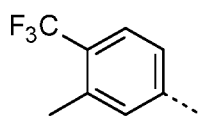
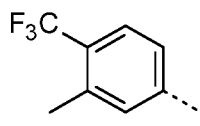
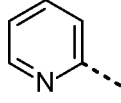
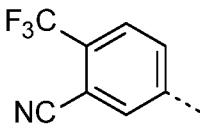
Pd(PPh₃)₄ (23.2 mg, 20.1 mmol) was added to a stirred suspension of **I-20b** (150 mg, 0.40 mmol) and 2-cyclopropyl-5-iodo-1H-imidazole (112.8 mg, 0.48 mmol) in a sat. sol. of NaHCO₃ (2 mL) and 1,4-dioxane (1 mL). The mixture was stirred at 120 °C for 10 min under microwave irradiation. The mixture was concentrated in vacuo. The crude product was purified by flash column chromatography (silica; MeOH/ DCM 0/100 to 6/94). The desired fractions were collected and evaporated in vacuo. The product was purified by RP HPLC (Stationary phase: C18 XBridge 30 x 100 mm 5 μm; mobile phase: gradient from 60% 0.1% NH₄CO₃H/NH₄OH pH 9 solution in water, 40% CH₃CN to 43% 0.1% NH₄CO₃H/NH₄OH pH 9 solution in water, 57% CH₃CN), to yield **Co. No. 25** (90 mg, 51%) as a light yellow fluffy solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.91 - 1.02 (m, 4 H) 1.72 (d, *J*=6.7 Hz, 3 H) 1.90 - 2.00 (m, 1 H) 3.98 (dd, *J*=12.5, 7.4 Hz, 1 H) 4.24 (dd, *J*=12.7, 4.2 Hz, 1 H) 4.68 - 4.79 (m, 1 H) 7.28 (s, 1 H) 7.42 (dd, *J*=8.3, 1.4 Hz, 1 H) 7.60 (d, *J*=2.1 Hz, 1 H) 7.82 (d, *J*=8.6 Hz, 1 H) 7.88 (s, 1 H) 11.88 (br s, 1 H).

Table 1. The following compounds were prepared following the methods exemplified in the Experimental Part (Ex. No.). Compounds exemplified and described in the experimental part are marked with an asterisk *. cPr means cyclopropyl, iPr means isopropyl and cBu means cyclobutyl.

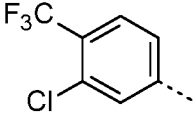
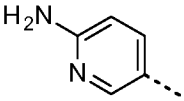
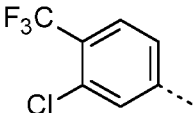
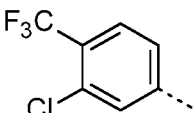
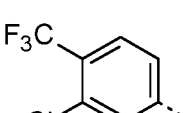
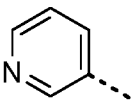
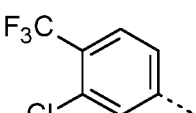
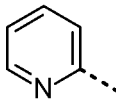
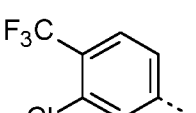
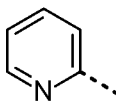
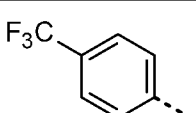
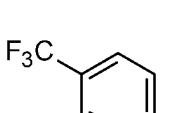
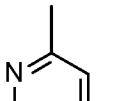
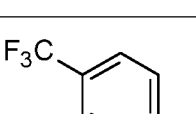

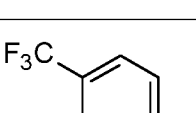
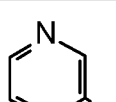


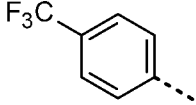
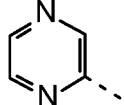
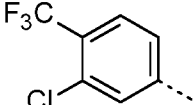
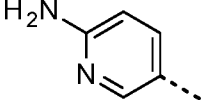
Co. No.	Ex. No.	R ¹	R ²	R ³	>CR ⁴ R ⁵	Salt Form
1	E-6*		--H	--Br	>CH(CH ₃) (S)	
2	E-1		--cPr	--H	>CH(CH ₃) (S)	
3	E-6			--Cl	>CH(CH ₃) (S)	
4	E-1		--CH ₃	--H	>CH(CH ₃) (S)	
5	E-1			--H	>CH(CH ₃) (S)	
6	E-1		--iPr	-H	>CH(CH ₃) (S)	

Co. No.	Ex. No.	R ¹	R ²	R ³	>CR ⁴ R ⁵	Salt Form
7	E-1		--cPr	--CH ₃	>CH(CH ₃) (S)	
8	E-5*		--CF ₃	-H	>CH(CH ₃) (S)	
9	E-3			-Br	>CH(CH ₃) (S)	
10	E-1		--CN	--H	>CH(CH ₃) (S)	
11	E-3			--H	>CH(CH ₃) (S)	
12	E-1		--H	--H	>CH(CH ₃) (S)	
13	E-3		--CH ₂ OCH ₃	--H	>CH(CH ₃) (S)	
14	E-3			--CH ₃	>CH(CH ₃) (S)	

Co. No.	Ex. No.	R ¹	R ²	R ³	>CR ⁴ R ⁵	Salt Form
15	E-7*		--NHCH ₃	--H	>CH(CH ₃) (S)	
16	E-3			--CH ₃	>CH(CH ₃) (S)	
17	E-3			--CH ₃	>CH(CH ₃) (S)	
18	E-3			--H	>CH(CH ₃) (S)	
19	E-3*			--H	>CH(CH ₃) (S)	
20	E-3			--H	>CH(CH ₃) (S)	
21	E-1		--cPr	--CH ₃	>CH(CH ₃) (S)	
22	E-3			--H	>CH(CH ₃) (S)	
23	E-4*		--CH ₃	--H	>CH(CH ₃) (S)	

Co. No.	Ex. No.	R ¹	R ²	R ³	>CR ⁴ R ⁵	Salt Form
24	E-2*		--CH ₃	--H	>CH(CH ₃) (S)	
25	E-1		--cPr	--H	>CH(CH ₃) (S)	
26	E-1		--iPr	--H	>CH(CH ₃) (S)	
27	E-1*		--CH ₃	--H	>CH(CH ₃) (S)	
28	E-1		--cPr	--CH ₃	>CH(CH ₃) (S)	
29	E-4		--CN	--H	>CH(CH ₃) (S)	
30	E-1		--CH ₃	--CH ₃	>CH(CH ₃) (S)	. HCl
31	E-3		--CONH ₂	--H	>CH(CH ₃) (S)	
32	E-3			--CH ₃	>CH(CH ₃) (S)	
33	E-3			--H	>CH(CH ₃) (S)	

Co. No.	Ex. No.	R ¹	R ²	R ³	>CR ⁴ R ⁵	Salt Form
34	E-3			--CH ₃	>CH(CH ₃) (S)	
35	E-3		--CONHCH ₃	--H	>CH(CH ₃) (S)	
36	E-3		--CON(CH ₃) ₂	--H	>CH(CH ₃) (S)	
37	E-3			--H	>CH(CH ₃) (S)	
38	E-3			--CH ₃	>CH(CH ₃) (S)	
39	E-3			--H	>CH(CH ₃) (S)	
40	E-3		--cBu	--H	>CH(CH ₃) (S)	
41	E-3			--H	>CH(CH ₃) (S)	
42	E-1			--H	>CH(CH ₃) (S)	
43	E-3			--H	>CH(CH ₃) (S)	

Co. No.	Ex. No.	R ¹	R ²	R ³	>CR ⁴ R ⁵	Salt Form
44	E-3			--H	>CH(CH ₃) (S)	
45	E-3			--CN	>CH(CH ₃) (S)	

ANALYTICAL PART

Melting points:

5 Values are peak values, and are obtained with experimental uncertainties that are commonly associated with this analytical method.

DSC823e (A)

For a number of compounds, melting points were determined with a DSC823e (Mettler-Toledo) apparatus. Melting points were measured with a temperature gradient of 10 °C/minute. Maximum temperature was 300 °C. Values are peak values.

10 Mettler Toledo Mettler FP 81HT / FP90 apparatus (B)

For a number of compounds, melting points were determined in open capillary tubes on a Mettler FP 81HT / FP90 apparatus. Melting points were measured with a temperature gradient of 1, 3, 5 or 10 °C/minute. Maximum temperature was 300 °C. The melting point was read from a digital display.

15 LCMS

General procedure

The High Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array (DAD) or a UV detector and a column as specified in the respective methods. If necessary, additional detectors were included (see table of methods below).

20 Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time...) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW) and/or exact mass monoisotopic molecular weight. Data acquisition was performed with appropriate software.

25 Compounds are described by their experimental retention times (R_t) and ions. If not specified differently in the table of data, the reported molecular ion corresponds to the

[M+H]⁺ (protonated molecule) and/or [M-H]⁻ (deprotonated molecule). In case the compound was not directly ionizable the type of adduct is specified (i.e. [M+NH₄]⁺, [M+HCOO]⁻, [M+CH₃COO]⁻ etc...). For molecules with multiple isotopic patterns (Br, Cl.), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used.

Hereinafter, “SQD” Single Quadrupole Detector, “MSD” Mass Selective Detector, “QTOF” Quadrupole-Time of Flight, “rt” room temperature, “BEH” bridged ethylsiloxane/silica hybrid, “CSH” charged surface hybrid, “UPLC” Ultra Performance Liquid Chromatography, “DAD” Diode Array Detector.

Table 2. LC-MS Methods (Flow expressed in mL/min; column temperature (T) in °C; Run time in min).

Method	Instrument	Column	Mobile phase	Gradient	Flow ----- Col T	Run time
1	Waters: Acquity® UPLC® - DAD/SQD	Waters: CSH™ C18 (1.7µm, 2.1x50mm)	A: 95% CH ₃ COONH ₄ 6.5mM + 5% CH ₃ CN, B: CH ₃ CN	From 95% A to 5% A in 4.6min, held for 0.4min	1 ----- 50	5
2	Waters: Acquity® Iclass UPLC® - DAD/ Xevo G2-S QTOF	Waters: CSH™ C18 (1.7µm, 2.1x50mm)	A: 95% CH ₃ COONH ₄ 6.5mM + 5% CH ₃ CN, B: CH ₃ CN	From 95% A to 5% A in 4.6min, held for 0.4min	1 ----- 50	5
3	Agilent: HP1100- DAD, MSD G1956B	Waters: Xbridge™ C18 (5.0µm, 4.6x100mm)	A: HCO ₃ NH ₄ 10mM + NH ₄ OH (pH=9.0) B: CH ₃ CN	From 90% A to 0% A in 6.0min, held for 0.5min, back to 90% A in 0.5min, held for 2.0min	1.2 ----- RT	9

Method	Instrument	Column	Mobile phase	Gradient	Flow ----- Col T	Run time
4	Waters: Acquity [®] IClass UPLC [®] - DAD/SQD	Waters: CSH [™] C18 (1.7 μ m, 2.1x50mm)	A: 95% CH ₃ COONH ₄ 6.5mM + 5% CH ₃ CN, B: CH ₃ CN	From 95% A to 5% A in 4.6min, held for 0.4min	1 ----- 50	5

(*) Different MS tuning parameters due to low sensitivity

Table 3. Analytical data – melting point (M.p.) and LCMS: [M+H]⁺ means the protonated mass of the free base of the compound, [M-H]⁻ means the deprotonated mass of the free base of the compound or the type of adduct specified [M+CH₃COO]). R_t means retention time (in min). For some compounds, exact mass was determined.

Co. No.	M.p. (°C)	[M+H] ⁺	R _t	LCMS Method
1	228.68 (A)	440	2.26	1
2	n.d.	402	2.31	1
3	n.d.	488.1208 (-0.5mDa)	2.29	2
4	167.9 (B)	376	1.82	1
5	119.88 (A)	438.1540 (-0.1mDa)	2.63	2
6	156.03 (A)	404	2.23	1
7	n.d.	416.1696 (-0.2mDa)	2.3	2
8	n.d.	430	2.42	1
9	n.d.	532.0705 (-0.3mDa)	2.35	2
10	219.19 (A)	386	2.08	1
11	276.61 (A)	454.1606 (+0.3mDa)	1.94	2
12	176.92 (A)	362	1.78	1
13	n.d.	406	1.91	1
14	244.74 (A)	453.1653 (+0.3mDa)	2.24	2
15	205.00 (A)	391	5.02	3
16	215.62 (A)	468.1758 (-0.1mDa)	2.04	2
17	198.73 (A)	453.1653 (+0.3mDa)	2.53	2
18	278.31 (A)	439.084 (-0.1mDa)	2.55	2
19	n.d.	454.0957 (+0.7mDa)	2.01	2

Co. No.	M.p. (°C)	[M+H] ⁺	R _t	LCMS Method
20	246.15 and 275.27(A)	468.1764 (+0.5mDa)	2.11	2
21	146.20 (A)	430.1856 (+0.2mDa)	2.5	2
22	140.50 (A)	453.1651 (+0.1mDa)	2.63	2
23	226.81 (A)	401	1.74	1
24	174.28 (A)	408.1447 (0.0 mDa)	1.97	2
25	n.d.	436	2.53	1
26	160.38 (A)	438	2.48	1
27	188.27 (A)	410.0993 (-0.2 mDa)	2.16	2
28	158.23 (A)	450.1309 (+0.1mDa)	2.55	2
29	212.06 (A)	421	2.32	1
30	270.45 (A)	424.1151 (-0.1mDa)	2.24	2
31	269.95 (A)	439	1.98	4
32	269.39 (A)	487.1274 (+1.3mDa)	2.44	2
33	267.48 and 286.55 (A)	488.1216 (+0.3mDa)	2.12	2
34	280.85 (A)	502	2.3	1
35	174.70 (A)	453.1063 (+1.0 mDa)	2.15	2
36	n.d.	467.1213 (+0.3mDa)	2.31	2
37	131.60 and 188.06 (A)	473.111 (+0.6mDa)	2.33	2
38	232.11 (A)	487.1267 (+0.6mDa)	2.74	2
39	n.d.	473.1128 (+2.4mDa)	2.67	2
40	n.d.	416.1698 (0.0 mDa)	2.36	2
41	n.d.	453.1661 (+1.1mDa)	2.21	2
42	173.18 (A)	450.1308 (0.0mDa)	2.63	2
43	227.75 (A)	474.1057 (0.0mDa)	2.45	2
44	n.d.	440.1446 (0.0mDa)	2.26	2
45	n.d.	513.1174 (+0.8mDa)	2.40	2

n.d. means not determined.

Optical Rotations

Optical rotations were measured on a Perkin-Elmer 341 polarimeter with a sodium lamp and reported as follows: $[\alpha]^\circ (\lambda, c \text{ g/100ml, solvent, } T \text{ }^\circ\text{C})$.

- 5 $[\alpha]_\lambda^T = (100\alpha) / (l \times c)$: where l is the path length in dm and c is the concentration in g/100 ml for a sample at a temperature T ($^\circ\text{C}$) and a wavelength λ (in nm). If the wavelength of light used is 589 nm (the sodium D line), then the symbol D might be used instead. The sign of the rotation (+ or -) should always be given. When using this equation the concentration and solvent are always provided in parentheses after the rotation. The rotation is reported using degrees and no units of concentration are given
- 10 (it is assumed to be g/100 mL).

Table 4. Optical Rotation data.

Co. No.	α_D ($^\circ$)	Wavelength (nm)	Concentration w/v %	Solvent	Temp. ($^\circ\text{C}$)
1	+28.0	589	0.53	DMF	25
2	+25.7	589	0.59	DMF	20
4	+26.7	589	0.52	DMF	20
5	+19.5	589	0.73	DMF	20
6	+20.6	589	0.56	DMF	20
7	+18.9	589	0.51	DMF	20
10	+24.7	589	0.5	DMF	20
11	+20.7	589	0.54	DMF	20
12	+24.3	589	0.55	DMF	20
13	+21.8	589	0.57	DMF	20
14	+10.8	589	0.51	DMF	20
15	+21.9	589	0.5	DMF	20
16	-0.1	589	0.5	DMF	20
17	+0.4	589	0.5	DMF	20
18	+19.6	589	0.76	DMF	20
20	+16.1	589	0.51	DMF	20
21	+18.4	589	0.51	DMF	20
22	+9.6	589	0.5	DMF	20
23	+24.6	589	0.5	DMF	20
24	+24.3	589	0.53	DMF	20

Co. No.	α_D (°)	Wavelength (nm)	Concentration w/v %	Solvent	Temp. (° C)
25	+25.7	589	0.59	DMF	20
26	+26.1	589	0.57	DMF	20
27	+28.7	589	0.51	DMF	20
29	+29.9	589	0.46	DMF	20
30	+25.4	589	0.52	DMF	20
31	+27.3	589	0.55	DMF	20
32	+8.3	589	0.49	DMF	20
33	+26.6	589	0.48	DMF	20
34	+5.0	589	0.51	DMF	20
37	+19.6	589	0.76	DMF	20
38	+3.4	589	0.51	DMF	20
39	+14.7	589	0.5	DMF	20
40	+19.2	589	0.51	DMF	20
42	+25.0	589	0.53	DMF	20
43	+9.1	589	0.92	DMF	20
44	+1.0	589	0.30	DMF	20
45	n.d.*				

n.d.*: not available data due to bad solubility

PHARMACOLOGICAL EXAMPLES

A) In vitro pharmacology

- 5 The compounds provided in the present invention are negative allosteric modulators of mGluR2. These compounds appear to inhibit glutamate responses by binding to an allosteric site other than the glutamate binding site. The response of mGluR2 to a concentration of glutamate is decreased when compounds of Formula (I) are present. Compounds of Formula (I) are expected to have their effect substantially at mGluR2 by
- 10 virtue of their ability to reduce the function of the receptor. The effects of negative allosteric modulators tested at mGluR2 using the [³⁵S]GTP γ S binding assay method described below and which is suitable for the identification of such compounds, and more particularly the compounds according to Formula (I), are shown in Table 7.

1) [³⁵S]GTP γ S binding assay

The [³⁵S]GTP γ S binding assay is a functional membrane-based assay used to study G-protein coupled receptor (GPCR) function whereby incorporation of a non-hydrolysable form of GTP, [³⁵S]GTP γ S (guanosine 5'-triphosphate, labelled with gamma-emitting ³⁵S), is measured. The G-protein α subunit catalyzes the exchange of guanosine 5'-diphosphate (GDP) by guanosine triphosphate (GTP) and on activation of the GPCR by an agonist, [³⁵S]GTP γ S, becomes incorporated and cannot be cleaved to continue the exchange cycle (Harper (1998) Current Protocols in Pharmacology 2.6.1-10, John Wiley & Sons, Inc.). The amount of radioactive [³⁵S]GTP γ S incorporation is a direct measure of the activity of the G-protein and hence the activity of the antagonist can be determined. mGlu2 receptors are shown to be preferentially coupled to G α i-protein, a preferential coupling for this method, and hence it is widely used to study receptor activation of mGlu2 receptors both in recombinant cell lines and in tissues. Here we describe the use of the [³⁵S]GTP γ S binding assay using membranes from cells transfected with the human mGlu2 receptor and adapted from Schaffhauser *et al.* (Molecular Pharmacology, **2003**, 4:798-810) for the detection of the negative allosteric modulation (NAM) properties of the compounds of this invention.

Membrane preparation

CHO-cells were cultured to pre-confluence and stimulated with 5 mM butyrate for 24 h. Cells were then collected by scraping in PBS and cell suspension was centrifuged (10 min at 4000 RPM in benchtop centrifuge). Supernatant was discarded and pellet gently resuspended in 50 mM Tris-HCl, pH 7.4 by mixing with an Ultra Turrax homogenizer. The suspension was centrifuged at 12,400 RPM (Sorvall F14S-6x250Y) for 10 minutes and the supernatant discarded. The pellet was homogenized in 5 mM Tris-HCl, pH 7.4 using an Ultra Turrax homogenizer and centrifuged again (13,000 RPM, 20 min, 4 °C). The final pellet was resuspended in 50 mM Tris-HCl, pH 7.4 and stored at -80 °C in appropriate aliquots before use. Protein concentration was determined by the Bradford method (Bio-Rad, USA) with bovine serum albumin as standard.

30 [³⁵S]GTP γ S binding assay

Measurement of mGluR2 negative allosteric modulatory activity of test compounds was performed as follows. Test compounds and glutamate were diluted in assay buffer containing 10 mM HEPES acid, 10 mM HEPES salt, pH 7.4, 100 mM NaCl, 3 mM MgCl₂ and 10 μ M GDP. Human mGlu2 receptor-containing membranes were thawed on ice and diluted in assay buffer supplemented with 18 μ g/ml saponin. Membranes

were pre-incubated with compound together with a predefined ($\sim EC_{80}$) concentration of glutamate (60 μM) for 30 min at 30 °C. After addition of [^{35}S]GTP γ S (f.c. 0.1 nM), assay mixtures were shaken briefly and further incubated to allow [^{35}S]GTP γ S incorporation on activation (30 minutes, 30 °C). Final assay mixtures contained 7 μg of membrane protein in 10 mM HEPES acid, 10 mM HEPES salt, pH 7.4, 100 mM NaCl, 3 mM MgCl₂, 10 μM GDP and 10 $\mu g/ml$ saponin. Total reaction volume was 200 μl . Reactions were terminated by rapid filtration through Unifilter-96 GF/B plates (Perkin Elmer, Massachusetts, USA) using a 96-well filtermate universal harvester. Filters were washed 6 times with ice-cold 10 mM NaH₂PO₄/10 mM Na₂HPO₄, pH 7.4. Filters were then air-dried, and 30 μl of liquid scintillation cocktail (Microscint-O) was added to each well. Membrane-bound radioactivity was counted in a Topcount.

Data analysis

The concentration-response curves of representative compounds of the present invention were generated using the Lexis software interface (developed at J&J). Data were calculated as % of the control glutamate response, defined as the response that is generated upon addition of an EC_{80} -equivalent concentration of glutamate. Sigmoid concentration-response curves plotting these percentages versus the log concentration of the test compound were analyzed using non-linear regression analysis. The concentration producing half-maximal inhibition was calculated as the IC_{50} . The pIC_{50} values were calculated as the $-\log IC_{50}$, when the IC_{50} is expressed in M. E_{max} is defined as the relative maximal effect (i.e. maximal % inhibition relative to the control glutamate response).

Table 5. Pharmacological data for compounds according to the invention.

Co. No.	GTP γ S - hmGluR2 anGT pIC_{50}	GTP γ S - hmGluR2 anGT E _{max}	8	7.48	107.65
1	7.94	99.26	9	7.46	108.155
2	7.7	103.485	10	7.44	106.915
3	7.6	107.81	11	7.26	108.945
4	7.59	103.88	12	7.15	100.61
5	7.56	104.81	13	7.08	103.715
6	7.51	103.905	14	6.96	102.565
7	7.5	105.645	15	6.77	102.105
			16	6.73	108.14
			17	6.84	106.335
			18	8.04	110.345
			19	7.3	107.82

20	7.27	107.245
21	8.24	107.93
22	7.79	109.72
23	7.19	103.86
24	7.8	106.205
25	8.7	105.86
26	8.57	111.21
27	8.46	106.485
28	8.43	111.495
29	8.41	111.36
30	8.2	108.795
31	7.99	107.24
32	7.81	108.8

33	7.79	106.065
34	7.51	108.665
35	7.42	110.71
36	6.96	106.185
37	7.89	109.01
38	7.67	105.425
39	8.08	103.79
40	8.16	107.01
41	6.78	105.555
42	8.73	109.175
43	8.31	105.635
44	7.41	103.425
45	7.46	105.79

B) *In vivo* pharmacology

1) Reversal of LY-404039-induced decrease of palpebral opening in apomorphine-challenged rats.

- 5 Male Wiga Wistar rats (Crl:WI; Charles River Germany; 220 ± 40 g) were housed under standard laboratory conditions (21 ± 2 °C; 50-65% relative humidity; light-dark cycle set at 12 h; lights on at 6.00 h) and fasted overnight prior to the start of the experiments (tap water remained available ad libitum). During the test period, they were housed in individual cages. Palpebral opening was scored every 5 min over the
- 10 first hour after injection of apomorphine (1.0 mg/kg, i.v.) in animals either pretreated or not pretreated with LY-404039 (2.5 mg/kg, s.c.) at 1 h prior to the apomorphine injection. The animals were also pretreated with test compound or solvent at a predefined interval before apomorphine challenge. The score system was: (5) exophthalmos, (4) wide open, (3) open for three-quarters, (2) half open, (1) open for
- 15 one-quarter, (0) closed. The scores for palpebral opening were cumulated over the 60-min observation period. A cumulative palpebral opening score > 26 was selected for drug-induced reversal of the LY-404039-induced decrease of palpebral opening (occurrence in 3.2% of control animals pretreated with LY-404039 ($n = 154$) versus in 99.5% of control rats not pretreated with LY-404039 ($n = 6335$)).
- 20 Table 6 shows the palpebral opening score in control animals receiving apomorphine alone and in animals receiving apomorphine and LY-404039. In animals receiving apomorphine alone the median palpebral opening is 43 whereas in animals receiving

apomorphine and LY-404039, the median palpebral opening is 17. In animals treated with apomorphine alone, the palpebral opening score is almost always (in 95.5% of the rats) greater than 34, whereas in animals treated with the combination (apomorphine + LY-404039) only 3.2% of the animals show a palpebral opening greater than 26.

5 **Table 6.** Palpebral opening score in control animals.

Measurement	Apomorphine alone (n = 6335)	Apomorphine + LY-404039 (n = 154)
<u>Palpebral opening score</u>		
Median score:	43	17
Occurrence score > 26 (%):	99.5	3.2
Occurrence score > 34 (%):	95.9	0.0

2) Reversal of the effect of the mGluR2 PAM JNJ-42153605-induced inhibition of scopolamine-induced hyperlocomotion

Apparatus

10 Motor activity was measured in microprocessor-based motor activity arenas (closed gray PVC cylinders with a height of 39 cm and a diameter of 31 cm). Each arena was placed on an infrared LED (8 x 8 LEDs) lit box (white PVC squared box; 40 x 40 cm²; height 12.5 cm. An infrared-sensitive tube camera and a white light source were mounted to the ceiling above the observation chamber to track the animal. The total distance traveled (cm) was recorded and analyzed using the Noldus Ethovision XT

15 Video Tracking System (Version 7.0.418; Noldus, Wageningen, The Netherlands). The intensity of the light within the activity cages (measured in the centre at the level of the floor) ranged between 4 and 8 LUX.

General Procedure

20 The rats were pretreated with test compound or vehicle at 60 min before the start of the activity recordings and placed into individual cages. The rats were challenged with JNJ-42153605 (3-(cyclopropylmethyl)-7-(4-phenylpiperidin-1-yl)-8-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine; WO2010/130424; Cid *et al. J. Med. Chem.* **2012**, 55, 8770-8789) (20 mg/kg, i.v.) 30 min before the start of the activity recording combined with scopolamine (0.16 mg/kg, i.v.) just before the start of the activity measurements.

25 Immediately after the injection of scopolamine, the rats were placed into the activity monitors and total distance travelled over the first 30 min was measured.

Solvent-pretreated control rats.

Frequency distributions obtained in a historical series of solvent-pretreated control rats are given in Table 7 below. Animals receiving the combination of JNJ-42153605 and scopolamine (n = 433) almost always travelled a distance of less than 1500 cm (< 1500 cm) (only 2.5% of the control rats travelled a distance of more than 1500 cm (> 1500 cm)). On the other hand, animals challenged with scopolamine alone (n = 215) always travelled a total distance of more than 1500 cm (> 1500 cm) and almost always (in 95.8% of the rats) a distance of more than 4400 cm (> 4400 cm). Rats that did not receive any challenge travelled almost always a distance of more than 1500 cm (> 1500 cm) (in 93.3% of the rats) and less than 4400 cm (< 4400 cm) (in 98.9% of the rats). For reversal of the inhibitory effect of JNJ-42153605 on the scopolamine-induced hyperlocomotion, the following all-or-none criteria were adopted: (1) reversal: total distance > 1500 cm.

Table 7. Frequency distributions obtained in historical series of solvent-pretreated control rats. N_{tested} means number of animals tested.

	Median (cm)	> 1500 cm (%)	> 4400 cm (%)	N_{tested}
Combination	480	2.5	0.0	433
No challenge	2618	93.3	1.1	638
Scopolamine	7246	100	95.8	215

3) Induction of mydriasis

The pupil diameter of Wiga rats was measured with a microscopic micrometer (1 unit = 1/24 mm). Criteria for drug-induced effects: pupil diameter > 25 units for mydriasis (in controls: 1.9%) 1 h post-administration of the test compound (test 1) or 1, 2 or 3 h post-administration of the test compound (test 2, wherein the maximum pupil diameter over the full 3 h period is reported).

Table 8 below provides the data obtained in the tests 1)-3) described above:

Table 8. Summary of data in tests 1)-3). In the table: SCOP JNJ-42153605 means Reversal of the effect of JNJ 42153605 on scopolamine-induced hyperlocomotion, APO LY-404039 means Reversal of LY-404039-induced decrease of palpebral opening in apomorphine challenged rats, MYD means Induction of mydriasis, ED₅₀ means median effective dose; PO means oral route.

Co. No.	Route	ED ₅₀ (mg/kg)			
		SCOP JNJ-42153605	APO LY-404039	MYD	
				Test 1	Test 2
4	PO	> 2.5			
27	PO	> 2.5 (*)	0.2	>10	> 40
25	PO	0.726	0.79		
26	PO	1.99			
29	PO	> 2.5			
31	PO	> 0.63			
30	PO	1.99			
28	PO	> 0.63			
32	PO	> 0.63			
11	PO	> 0.63			
7	PO	> 0.63			
16	PO	> 0.63			
34	PO	> 0.63			
33	PO	> 0.63			
22	PO	> 0.63			
21	PO	> 0.63			
18	PO	> 0.63			

(*)ED₅₀ = 1.25 mg/kg when applying a more sensitive criterion for drug-induced reversal of total distance > 1300 cm (occurring in only 4.8% of solvent-pretreated rats)

PROPHETIC COMPOSITION EXAMPLES

5 “Active ingredient” as used throughout these examples relates to a final compound of Formula (I), the pharmaceutically acceptable salts thereof, the solvates and the stereochemically isomeric forms and the tautomers thereof.

Typical examples of recipes for the formulation of the invention are as follows:

1. Tablets

10	Active ingredient	5 to 50 mg
	Di-calcium phosphate	20 mg
	Lactose	30 mg
	Talcum	10 mg
	Magnesium stearate	5 mg
15	Potato starch	ad 200 mg

In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

2. Suspension

- 5 An aqueous suspension is prepared for oral administration so that each 1 milliliter contains 1 to 5 mg of one of the active compounds, 50 mg of sodium carboxymethyl cellulose, 1 mg of sodium benzoate, 500 mg of sorbitol and water ad 1 ml.

3. Injectable

- 10 A parenteral composition is prepared by stirring 1.5 % by weight of active ingredient of the invention in 10% by volume propylene glycol in water.

4. Ointment

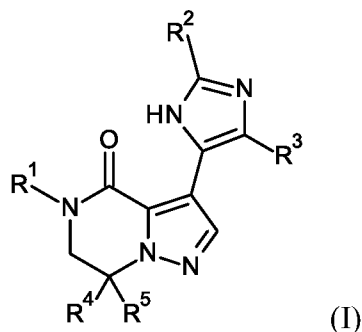
- | | |
|--------------------|--------------|
| Active ingredient | 5 to 1000 mg |
| Stearyl alcohol | 3 g |
| Lanoline | 5 g |
| 15 White petroleum | 15 g |
| Water | ad 100 g |

In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

- 20 Reasonable variations are not to be regarded as a departure from the scope of the invention. It will be obvious that the thus described invention may be varied in many ways by those skilled in the art.

CLAIMS

1. A compound of Formula (I)



or a stereoisomeric form or a tautomer thereof, wherein

R¹ is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C₁₋₄alkyl, mono-haloC₁₋₄alkyl, poly-halo-C₁₋₄alkyl, -CN, and C₃₋₇cycloalkyl;

R² is selected from the group consisting of H; C₁₋₄alkyl; C₃₋₇cycloalkyl; -CN; -NR^aR^b; -C(O)NR^cR^d; -C(O)C₁₋₄alkyl; -C₁₋₄alkyl-OH; -C₁₋₄alkyl-O-C₁₋₄alkyl; Aryl; Het; and C₁₋₄alkyl substituted with one or more substituents each independently selected from the group consisting of halo and C₃₋₇cycloalkyl; wherein

R^a, R^b, R^c, and R^d are each independently selected from H and C₁₋₄alkyl;

Aryl is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C₁₋₄alkyl, mono-haloC₁₋₄alkyl, and poly-halo-C₁₋₄alkyl;

Het is (a) a 6-membered aromatic heterocyclyl substituent selected from the group consisting of pyridinyl, and pyrazinyl, each of which may be optionally substituted with one or more substituents each independently selected from the group consisting of halo, C₁₋₄alkyl, and -NR^eR^f;

or (b) a 5-membered aromatic heterocyclyl selected from the group consisting of thiazolyl, oxazolyl, *1H*-pyrazolyl, and *1H*-imidazolyl, each of which may be optionally substituted with one or more substituents each independently selected from the group consisting of halo, C₁₋₄alkyl, mono-haloC₁₋₄alkyl, and poly-halo-C₁₋₄alkyl;

R^e and R^f are each independently selected from hydrogen, and C₁₋₄alkyl;

R³ is selected from the group consisting of hydrogen, halo, C₁₋₄alkyl, C₃₋₇cycloalkyl, -CN, and -OC₁₋₄alkyl;

R⁴ is selected from hydrogen and C₁₋₄alkyl; and

R⁵ is selected from the group consisting of hydrogen, C₁₋₄alkyl, and -C₁₋₄alkyl-O-C₁₋₄alkyl;

or an N-oxide, or a pharmaceutically acceptable salt or a solvate thereof.

2. The compound according to claim 1, or a stereoisomeric form or a tautomer thereof, wherein R^1 is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-4} alkyl, mono-halo C_{1-4} alkyl, poly-halo- C_{1-4} alkyl, and -CN;

R^2 is selected from the group consisting of H; C_{1-4} alkyl; C_{3-7} cycloalkyl; -CN; $-NR^aR^b$; $-C(O)NR^cR^d$; $-C_{1-4}$ alkyl-O- C_{1-4} alkyl; Aryl; Het; and C_{1-4} alkyl substituted with one or more substituents each independently selected from halo; wherein

R^a , R^b , R^c , and R^d are each independently selected from H and C_{1-4} alkyl;

Aryl is phenyl;

Het is (a) pyridinyl optionally substituted with a $-NR^eR^f$ or a C_{1-4} alkyl substituent;

R^e and R^f are each hydrogen;

R^3 is selected from the group of hydrogen, halo, C_{1-4} alkyl and cyano;

R^4 is hydrogen; and

R^5 is C_{1-4} alkyl;

or an N-oxide, or a pharmaceutically acceptable salt or a solvate thereof.

3. The compound according to claim 1 or claim 2, or a stereoisomeric form or a tautomer thereof, wherein

R^1 is phenyl optionally substituted with one or two substituents each independently selected from the group consisting of halo, mono-halo C_{1-4} alkyl, and poly-halo C_{1-4} alkyl;

R^2 is selected from the group consisting of C_{1-4} alkyl; C_{3-7} cycloalkyl; and C_{1-4} alkyl substituted with one or more substituents each independently selected from halo;

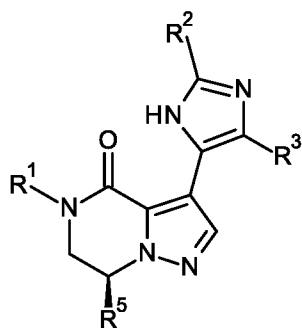
R^3 is hydrogen;

R^4 is hydrogen; and

R^5 is C_{1-4} alkyl;

or an N-oxide, or a pharmaceutically acceptable salt or a solvate thereof.

4. The compound according to any one of claims 1 to 3, having the formula (I')



(I')

wherein the 6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one core, R¹ and the imidazole substituent are in the plane of the drawing, R⁴ is hydrogen and R⁵ is projected above the plane of the drawing, and wherein R¹, R² and R³ are as defined in any one of claims 1 to 3.

5. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 4 and a pharmaceutically acceptable carrier or excipient.

6. A compound according to any one of claims 1 to 4 or a pharmaceutical composition according to claim 5 for use as a medicament.

7. A process for preparing the pharmaceutical composition according to claim 5, wherein a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound according to any one of claims 1 to 4.

8. A method of treating or preventing a central nervous system disorder or condition associated with glutamate dysfunction selected from mood disorders; delirium, dementia, amnesic and other cognitive disorders; disorders usually first diagnosed in infancy, childhood or adolescence; substance-related disorders; schizophrenia and other psychotic disorders; somatoform disorders; and hypersomnic sleep disorder comprising administering to a subject in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 4 or a therapeutically effective amount of a pharmaceutical composition according to claim 5.

9. A method of treating or preventing a central nervous system disorder or condition associated with glutamate dysfunction selected from depressive disorders; neurocognitive disorders; neurodevelopmental disorders; substance-related and addictive disorders; schizophrenia spectrum and other psychotic disorders; somatic symptom and related disorders; and hypersomnolence disorder; comprising administering to a subject in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 4 or a therapeutically effective amount of a pharmaceutical composition according to claim 5.

10. The method according to claim 8 or claim 9 wherein the central nervous system conditions or diseases associated with glutamate dysfunction are selected from dementia or neurocognitive disorder, major depressive disorder, depression, treatment resistant depression, attention-deficit/hyperactivity disorder and schizophrenia.

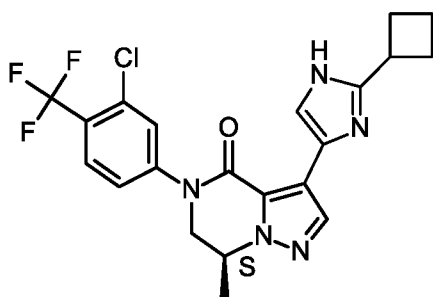
11. A product comprising a compound according to any one of claims 1 to 4 and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of central nervous system conditions or diseases selected from mood disorders; delirium, dementia, amnesic and other cognitive disorders; disorders usually first diagnosed in infancy, childhood or adolescence; substance-related disorders; schizophrenia and other psychotic disorders; somatoform disorders; and hypersomnic sleep disorder.

12. A product comprising a compound according to any one of claims 1 to 4 and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of central nervous system conditions or diseases selected from depressive disorders; neurocognitive disorders; neurodevelopmental disorders; substance-related and addictive disorders; schizophrenia spectrum and other psychotic disorders; somatic symptom and related disorders; and hypersomnolence disorder.

13. Use of a compound according to any one of claims 1 to 4 or a pharmaceutical composition according to claim 5 in the manufacture of a medicament for treating or preventing a central nervous system disorder or condition associated with glutamate dysfunction selected from mood disorders; delirium, dementia, amnesic and other cognitive disorders; disorders usually first diagnosed in infancy, childhood or adolescence; substance-related disorders; schizophrenia and other psychotic disorders; somatoform disorders; and hypersomnic sleep disorder.

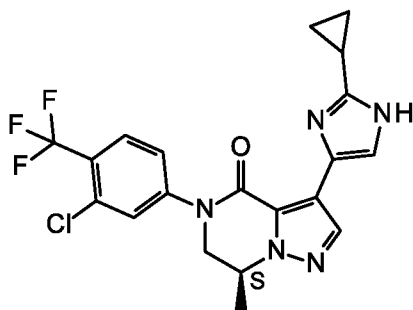
14. Use of a compound according to any one of claims 1 to 4 or a pharmaceutical composition according to claim 5 in the manufacture of a medicament for treating or preventing a central nervous system disorder or condition associated with glutamate dysfunction selected from depressive disorders; neurocognitive disorders; neurodevelopmental disorders; substance-related and addictive disorders; schizophrenia spectrum and other psychotic disorders; somatic symptom and related disorders; and hypersomnolence disorder.

15. The compound according to any one of claims 1 to 4, wherein the compound is



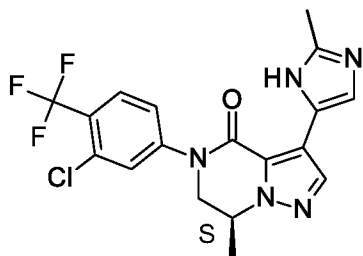
or a pharmaceutically acceptable salt or a solvate thereof.

16. The compound according to any one of claims 1 to 4, wherein the compound is



or a pharmaceutically acceptable salt or a solvate thereof.

17. The compound according to any one of claims 1 to 4, wherein the compound is



or a pharmaceutically acceptable salt or a solvate thereof.

18. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 15 to 17 and a pharmaceutically acceptable carrier or excipient.

19. A method of treating or preventing a major depressive disorder, depression, or treatment resistant depression comprising administering to a subject in need thereof, a therapeutically effective amount of a compound according to any one of claims 15 to 17 or a therapeutically effective amount of a pharmaceutical composition according to claim 18, wherein the major depressive disorder, depression, or treatment resistant depression is associated with glutamate dysfunction.

20. Use of a compound according to any one of claims 15 to 17 or a pharmaceutical composition according to claim 18 in the manufacture of a medicament for treating or preventing a major depressive disorder, depression, or treatment resistant depression, wherein the major depressive disorder, depression, or treatment resistant depression is associated with glutamate dysfunction.