

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.

15 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, Alzheimer 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. 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).

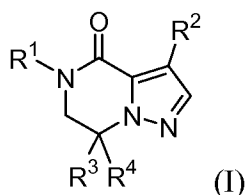
Clinical trials are, for example, underway with mGluR2/3 antagonist RO4995819 (F. Hoffmann-La Roche Ltd.) in adjunctive therapy in patients with Major Depressive Disorder having inadequate response to ongoing antidepressant treatment (ClinicalTrials.gov Identifier NCT01457677, retrieved 19 February 2014).

- 5 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
10 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
15 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
20 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 mediating synaptic plasticity, this mechanism is likely to contribute to both antidepressant and procognitive properties of these compounds. Inhibition of
25 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.

Description of the Invention

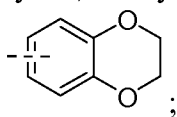
- 30 The present invention is directed to 6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one derivatives of Formula (I)



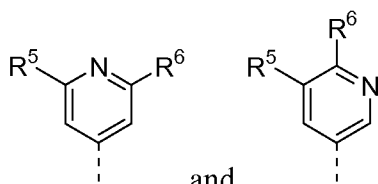
and stereoisomeric forms thereof,

wherein

R¹ is phenyl or 2-pyridinyl, each optionally substituted with one or more substituents each independently selected from the group of halo, C₁₋₄alkyl, mono- or poly-haloC₁₋₄alkyl, -O-C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl, mono- or poly-haloC₁₋₄alkyloxy, -C₁₋₄alkyl-OH, C₁₋₄alkylthio, mono- or poly-haloC₁₋₄alkylthio, cyano, C₃₋₇cycloalkyl optionally substituted with trifluoromethyl, and -SF₅; or is



R² is selected from



10

and

wherein R⁵ and R⁶ are each independently selected from the group of hydrogen, halo, cyano, C₁₋₄alkyl, -C₁₋₄alkyl-OH, C₃₋₇cycloalkyl, mono- or poly-haloC₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl, -O-C₁₋₄alkyl, mono- or poly-haloC₁₋₄alkyloxy, 1-acetylazetidin-3-yl, and NR'R'';

15 wherein R' is selected from hydrogen and C₁₋₄alkyl;

R'' is selected from hydrogen and C₁₋₄alkyl; or

R' and R'' together with the Nitrogen atom to which they are attached form a heterocyclic group selected from the group of 1-azetidiny, 1-pyrrolidinyl,

1-piperidinyl, 1-piperazinyl, and 4-morpholinyl; wherein each of the heterocyclic

20 groups may be optionally substituted with a substituent selected from halo, hydroxyl, C₁₋₄alkyl, mono- or poly-haloC₁₋₄alkyl, and -(CO)C₁₋₄alkyl;

R³ is selected from hydrogen and C₁₋₄alkyl;

R⁴ is selected from the group of hydrogen, C₁₋₄alkyl, mono- or poly-haloC₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl, and -C₁₋₄alkyl-OH;

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

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.

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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.

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 infancy, childhood or adolescence; substance-related disorders; schizophrenia and other psychotic disorders; somatoform disorders; and hypersomnic sleep disorder.

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).

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.

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, 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.

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Description of the figures

Figure 1 shows the frequency distributions for distance travelled obtained in historical series of solvent-pretreated control rats. In figure 1, — corresponds to scopolamine + JNJ 42153605; - - - corresponds to scopolamine alone; and — — — corresponds to no challenge.

Figure 2 shows the effect of Co. No. 1 (mg/kg p.o., 4 h prior to test) on exploration times of the new vs. the familiar arm by rats in the absence or presence of PCP (0 (= veh) or 0.75 mg/kg s.c., 0.5 h prior to test) in the V-maze. Data are reported as Mean $\pm$ SEM, n = 12/group; ANOVA with LSD-post hoc, p vs. familiar arm: *** p<0.001, *<0.05.

Figure 3 shows the interaction of Co. No. 1 with reserpine in rats. Shown are the effects on pupil diameter before reserpine challenge (Fig. 3a) and the reversal of the reserpine-induced ptosis (Fig. 3b), miosis (Fig. 3c) and sedation (Fig. 3d) measured 1 h after s.c. (left panel), 1 h after p.o. (middle panel) and 4 h after p.o. (right panel) administration of Co. No. 1.

Figure 4 illustrates the placement of the hippocampus brain slice in a well of a MEA biochip, with 60 $\times$ 3D-tip electrodes (black dots). Traces show the recorded potential at each electrode (Fig. 4a), and the captured fEPSP traces of paired pulses separated by 30 ms (Fig. 4b). The preparation was perfused with artificial cerebrospinal fluid (ACSF). (3D = three-dimensional; fEPSP = field excitatory postsynaptic potentials; MEA = micro-electrode array; ms = milliseconds).

Figure 5 shows how Co. No. 1 restores fEPSP depressed by 1 μ M LY-354740 in the dentate gyrus of rat hippocampal brain slices.

Figure 5a: fEPSP amplitude (% of baseline) is shown after the application of LY-354740 (1 μ M), followed by the application of Co. No. 1 (10 μ M), and then by the application of the mGlu2 antagonist LY-341495, and finally by a washout. At the end of experiments, the AMPA antagonist CNQX (6-cyano-7-nitroquinoxaline-2,3-dione, 50 μ M) and kynurenic acid (1 mM) were added as controls to block glutamate-mediated fEPSP.

Figure 5b: The same experiments as shown in Figure 5a, but presenting the PPR results. The error bars represent the SEM of 17 independent slices from 4 SD rats. (ACSF = artificial cerebrospinal fluid; fEPSP = field excitatory postsynaptic potential; PPR = paired-pulse ratio; SEM = standard error of the mean).

Figure 6 shows how Co. No. 1 facilitates long-term potentiation in the dentate gyrus of rat hippocampal brain slices.

Monitoring of the post-synaptic response for 80 min shows induction of LTP after weak theta stimulation (at 30 min).

Figure 6a: fEPSP in response to the weak theta stimulus under control conditions (vehicle: open circles) and following the application of 10 μ M Co. No. 1 (solid circles).

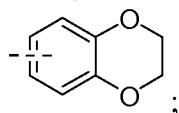
Figure 6b: PTP and LTP under control conditions and after application of 10 μ M Co. No. 1. The error bars represent the SEM of 22 independent slices from 4 SD rats.

LTP = long-term potentiation; NAM = negative allosteric modulator; PTP = post-theta potentiation; SEM = standard error of the mean.

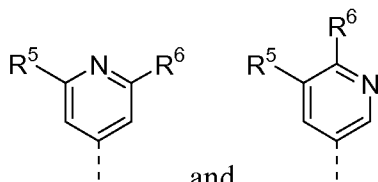
Detailed description of the invention

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

R^1 is phenyl or 2-pyridinyl, each optionally substituted with one or more substituents each independently selected from the group of halo, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, -O- C_{1-4} alkyl, - C_{1-4} alkyl-O- C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyloxy, - C_{1-4} alkyl-OH, mono- or poly-halo C_{1-4} alkylthio, cyano, and -SF₅; or is



R^2 is selected from



wherein R^5 and R^6 are each independently selected from the group of hydrogen, halo, cyano, C_{1-4} alkyl, - C_{1-4} alkyl-OH, C_{3-7} cycloalkyl, mono- or poly-halo C_{1-4} alkyl, - C_{1-4} alkyl-O- C_{1-4} alkyl, -O- C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyloxy, and $NR'R''$; wherein R' is selected from hydrogen and C_{1-4} alkyl;

R'' is selected from hydrogen and C_{1-4} alkyl; or

R' and R'' together with the Nitrogen atom to which they are attached form a heterocyclic group selected from the group of 1-azetidiny, 1-pyrrolidinyl, and

1-piperidinyl; wherein each of the heterocyclic groups may be optionally substituted with a halo substituent;

R^3 is selected from hydrogen and C_{1-4} alkyl;

R^4 is selected from the group of hydrogen, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl,

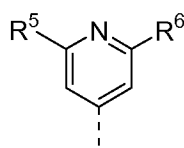
5 - C_{1-4} alkyl-O- C_{1-4} alkyl, and - C_{1-4} alkyl-OH;

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

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

10 R^1 is phenyl optionally substituted with one, two or three substituents each independently selected from the group of halo, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, -O- C_{1-4} alkyl, - C_{1-4} alkyl-O- C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyloxy, mono- or poly-halo C_{1-4} alkylthio, cyano, and -SF₅;

or 2-pyridinyl optionally substituted with one or two substituents each independently
15 selected from the group of halo, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, and -O- C_{1-4} alkyl;



R^2 is

wherein R^5 and R^6 are each independently selected from the group of hydrogen, halo, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl, mono- or poly-halo C_{1-4} alkyl, -O- C_{1-4} alkyl, mono- or
20 poly-halo C_{1-4} alkyloxy, and $NR'R''$;

wherein R' is selected from hydrogen and C_{1-4} alkyl;

R'' is selected from hydrogen and C_{1-4} alkyl; or

R' and R'' together with the Nitrogen atom to which they are attached form a
25 heterocyclic group selected from the group of 1-azetidiny, 1-pyrrolidinyl, and 1-piperidinyl; wherein each of the heterocyclic groups may be optionally substituted with a halo substituent;

R^3 is selected from hydrogen and C_{1-4} alkyl;

R^4 is selected from the group of C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, and

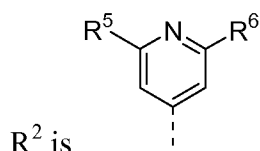
30 - C_{1-4} alkyl-O- C_{1-4} alkyl; in particular $>CR^3R^4$ is selected from the group of $>CH(CH_3)$, $>CH(CH_2CH_3)$, $>CH(CH_2F)$, and $>CH(CH_2OCH_3)$;

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

In an additional embodiment, the present invention relates to compounds of Formula (I)
35 as defined hereinabove, and stereoisomeric forms thereof, wherein

R^1 is phenyl optionally substituted with one, two or three substituents each independently selected from the group of halo, C_{1-4} alkyl, poly-halo C_{1-4} alkyl, -O- C_{1-4} alkyl, - C_{1-4} alkyl-O- C_{1-4} alkyl, poly-halo C_{1-4} alkyloxy, poly-halo C_{1-4} alkylthio, cyano, and $-SF_5$;

- 5 or 2-pyridinyl optionally substituted with one or two substituents each independently selected from the group of halo, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, and -O- C_{1-4} alkyl;



- 10 wherein R^5 and R^6 are each independently selected from the group of hydrogen, cyano, C_{1-4} alkyl, poly-halo C_{1-4} alkyl, -O- C_{1-4} alkyl, and $NR'R''$;
wherein R' is selected from hydrogen and C_{1-4} alkyl;

R'' is C_{1-4} alkyl; or

R' and R'' together with the Nitrogen atom to which they are attached form a

- 15 1-azetidiny;

R^3 is selected from hydrogen and C_{1-4} alkyl;

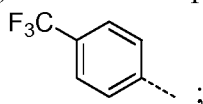
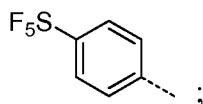
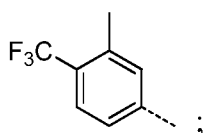
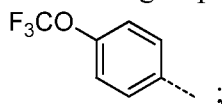
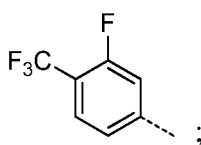
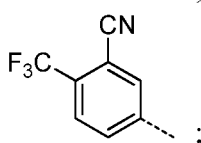
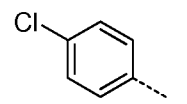
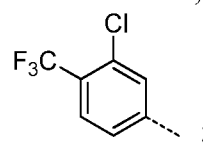
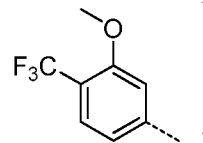
R^4 is selected from the group of C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, and - C_{1-4} alkyl-O- C_{1-4} alkyl; in particular $>CR^3R^4$ is selected from the group of $>CH(CH_3)$, $>CH(CH_2CH_3)$, $>CH(CH_2F)$, and $>CH(CH_2OCH_3)$;

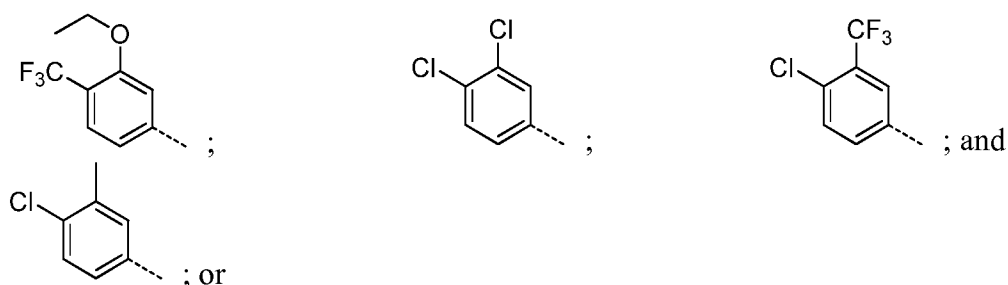
- 20 and the N-oxides, and the pharmaceutically acceptable salts and the solvates thereof.

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

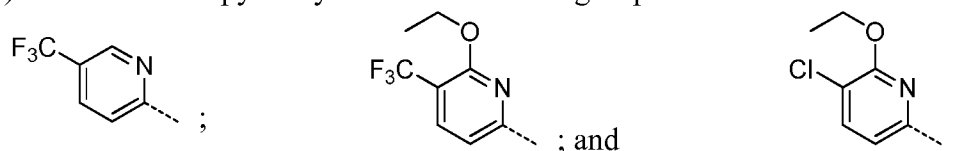
R^1 is selected from

- 25 (a) a substituted phenyl selected from the group of

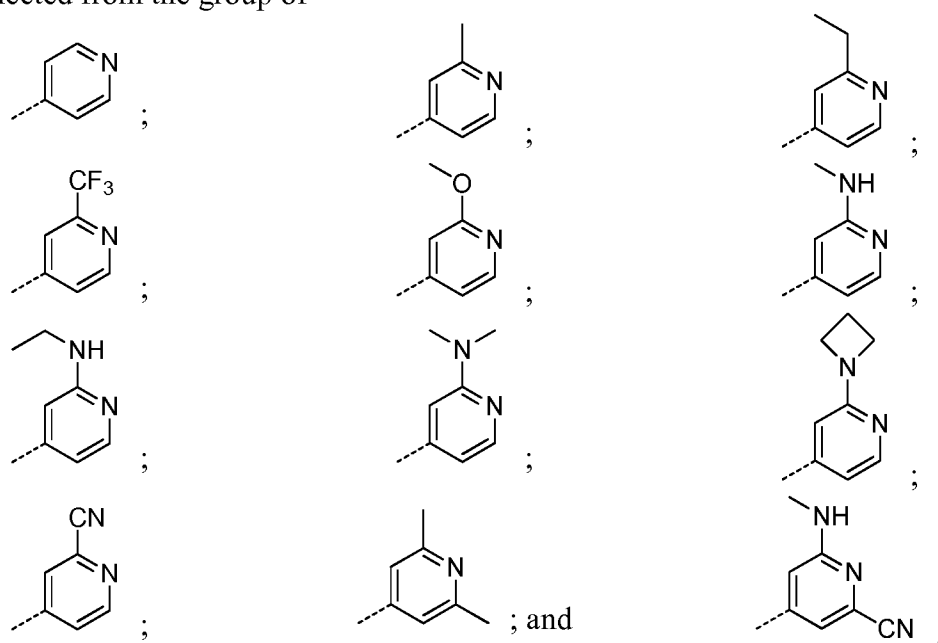




(b) a substituted 2-pyridinyl selected from the group of



R^2 is selected from the group of



R^3 is selected from hydrogen and C_{1-4} alkyl;

- 5 R^4 is selected from the group of C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, and $-C_{1-4}$ alkyl-O- C_{1-4} alkyl; in particular $>CR^3R^4$ is selected from the group of $>CH(CH_3)$, $>CH(CH_2CH_3)$, $>CH(CH_2F)$, and $>CH(CH_2OCH_3)$; and the N-oxides, and the pharmaceutically acceptable salts and the solvates thereof.

- 10 In an additional embodiment, the present invention relates to compounds selected from the group of
 (7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
 (7S)-5-[3-Ethoxy-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(4-Chlorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[3-Methoxy-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-pyridin-4-yl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3,4-Dichlorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[6-Ethoxy-5-(trifluoromethyl)pyridin-2-yl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[3-methyl-4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-(2,6-Dimethylpyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[3-Fluoro-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[4-Chloro-3-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

5-[(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl]-2-(trifluoromethyl)benzonitrile;

(7S)-3-(2-Methoxypyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-(2-Ethylpyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-3-(2,6-dimethylpyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3,4-Dichlorophenyl)-3-(2,6-dimethylpyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-[2-(Ethylamino)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethoxy)phenyl]-6,7-

dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-[2-(Dimethylamino)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(5-Chloro-6-ethoxypyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-[2-(methylamino)pyridin-4-yl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,4-Dichlorophenyl)-3-(2-methoxypyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-{4-[(trifluoromethyl)sulfanyl]phenyl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
4-{(7S)-7-Methyl-4-oxo-5-[4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl}pyridine-2-carbonitrile;
(7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-3-(2-methoxypyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-7-methyl-3-[2-(methylamino)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-(2-Azetidin-1-ylpyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-5-[4-(trifluoromethyl)phenyl]-3-[2-(trifluoromethyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
4-{(7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-7-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl}-6-(methylamino)pyridine-2-carbonitrile;
(7S)-3-(2-Methoxypyridin-4-yl)-5-[3-methoxy-4-(trifluoromethyl)phenyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3-Fluoro-4-(trifluoromethyl)phenyl]-7-methyl-3-[2-(methylamino)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one; and
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
and the N-oxides, and the pharmaceutically acceptable salts and the solvates thereof.

In an additional embodiment, the present invention relates to compounds selected from the group of

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one, or a hydrochloride salt, or a sulfate salt, or a methanesulfonate salt, or a maleate salt thereof;
(7S)-5-[3-Ethoxy-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-

dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Chlorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one or a hydrochloride salt thereof;
(7S)-5-[3-Methoxy-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one or a hydrochloride salt thereof;
(7S)-7-Methyl-3-pyridin-4-yl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,4-Dichlorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one or a hydrochloride salt thereof;
(7S)-5-[6-Ethoxy-5-(trifluoromethyl)pyridin-2-yl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[3-methyl-4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one or a hydrochloride salt thereof;
(7S)-3-(2,6-Dimethylpyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3-Fluoro-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[4-Chloro-3-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
5-[(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl]-2-(trifluoromethyl)benzonitrile;
(7S)-3-(2-Methoxypyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-(2-Ethylpyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-3-(2,6-dimethylpyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,4-Dichlorophenyl)-3-(2,6-dimethylpyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-[2-(Ethylamino)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

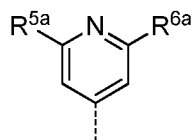
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethoxy)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
 (7S)-3-[2-(Dimethylamino)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
 (7S)-5-(5-Chloro-6-ethoxypyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
 (7S)-7-Methyl-3-[2-(methylamino)pyridin-4-yl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
 (7S)-5-(3,4-Dichlorophenyl)-3-(2-methoxypyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
 (7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-{4-[(trifluoromethyl)sulfanyl]phenyl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one or a hydrochloride salt thereof;
 4-{(7S)-7-Methyl-4-oxo-5-[4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl}pyridine-2-carbonitrile;
 (7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-3-(2-methoxypyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
 (7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-7-methyl-3-[2-(methylamino)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
 (7S)-3-(2-Azetidin-1-ylpyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
 (7S)-7-Methyl-5-[4-(trifluoromethyl)phenyl]-3-[2-(trifluoromethyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
 4-{(7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-7-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl}-6-(methylamino)pyridine-2-carbonitrile;
 (7S)-3-(2-Methoxypyridin-4-yl)-5-[3-methoxy-4-(trifluoromethyl)phenyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
 (7S)-5-[3-Fluoro-4-(trifluoromethyl)phenyl]-7-methyl-3-[2-(methylamino)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one; and
 (7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one.

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

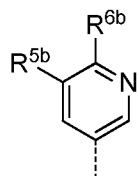
- R^1 is phenyl, optionally substituted with one, two or three substituents each
 5 independently selected from the group of halo, C_{1-4} alkyl, poly-halo C_{1-4} alkyl, -O- C_{1-4} alkyl, - C_{1-4} alkyl-OH and cyano; or

2-pyridinyl, substituted with one or two substituents each independently selected from the group of halo, poly-haloC₁₋₄alkyl, and -O-C₁₋₄alkyl;

R² is



- 5 wherein R^{5a} is selected from hydrogen and C₁₋₄alkyl, and R^{6a} is selected from the group of hydrogen, C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl, -OC₁₋₄alkyl, and -C₁₋₄alkyl-OH; or



wherein one of R^{5b} and R^{6b} is hydrogen, and the other R^{5b} or R^{6b} is C₁₋₄alkyl;

R³ is selected from hydrogen and C₁₋₄alkyl;

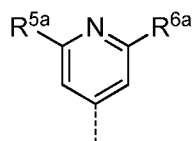
- 10 R⁴ is selected from the group of hydrogen, C₁₋₄alkyl, mono- or poly-haloC₁₋₄alkyl, and -C₁₋₄alkyl-O-C₁₋₄alkyl; in particular >CR³R⁴ is selected from the group of >CH₂, >CH(CH₃), >CH(CH₂CH₃), >CH(CH₂F), >CH(CH₂OCH₃) and >C(CH₃)₂; and the N-oxides, and the pharmaceutically acceptable salts and the solvates thereof.

- 15 In an additional embodiment, the present invention relates to compounds of Formula (I) as defined hereinabove, and stereoisomeric forms thereof, wherein

R¹ is phenyl, optionally substituted with one, two or three substituents each independently selected from the group of fluoro, chloro, methyl, CF₃, -O-CH₃, -O-CH₂CH₃, cyano, -CH(CH₃)(OH); or

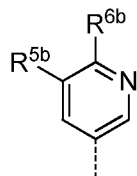
- 20 2-pyridinyl, substituted with one or two substituents each independently selected from the group of fluoro, chloro, CF₃, and -O-CH₂CH₃;

R² is

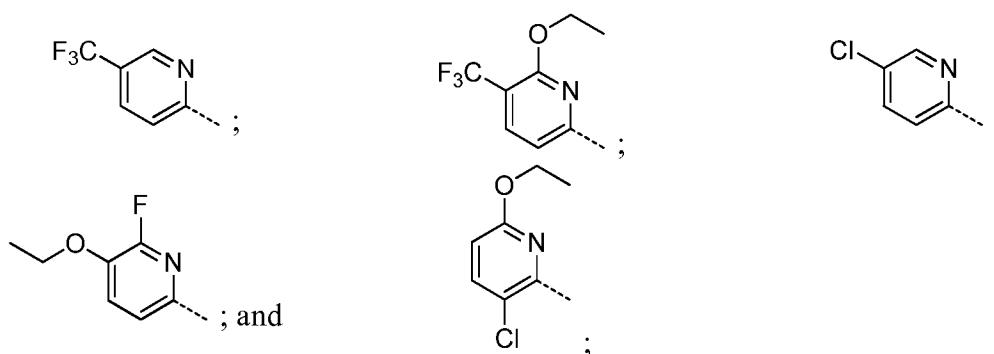
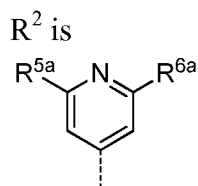


wherein R^{5a} is selected from hydrogen and methyl, and R^{6a} is selected from the group

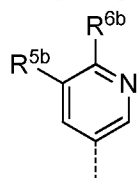
- 25 of hydrogen, methyl, -CH₂-O-CH₃, -O-CH₃, and -CH₂-OH; or



wherein one of R^{5b} and R^{6b} is hydrogen, and the other R^{5b} or R^{6b} is methyl;



- wherein R^{5a} is selected from hydrogen and methyl, and R^{6a} is selected from the group of hydrogen, methyl, $-\text{CH}_2\text{-O-CH}_3$, $-\text{O-CH}_3$, and $-\text{CH}_2\text{-OH}$; or



wherein one of R^{5b} and R^{6b} is hydrogen, and the other R^{5b} or R^{6b} is methyl;

- R^3 is selected from hydrogen and C_{1-4} alkyl;
- 10 R^4 is selected from the group of hydrogen, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, and $-\text{C}_{1-4}$ alkyl- O-C_{1-4} alkyl; in particular $>\text{CR}^3\text{R}^4$ is selected from the group of $>\text{CH}_2$, $>\text{CH}(\text{CH}_3)$, $>\text{CH}(\text{CH}_2\text{CH}_3)$, $>\text{CH}(\text{CH}_2\text{F})$, $>\text{CH}(\text{CH}_2\text{OCH}_3)$ and $>\text{C}(\text{CH}_3)_2$; and the N-oxides, and the pharmaceutically acceptable salts and the solvates thereof.
- 15 In an additional embodiment, the present invention relates to compounds selected from the group of
- (7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
- (7S)-7-Methyl-3-pyridin-4-yl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
- (7S)-3-[2-(Methoxymethyl)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
- (7S)-7-Methyl-3-(5-methylpyridin-3-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
- (7R)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-

dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7R)-5-[3-Ethoxy-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
5-[3-Ethoxy-4-(trifluoromethyl)phenyl]-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Methoxy-3,5-dimethylphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(6-methylpyridin-3-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
3-(2-Methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,4-Dimethoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-(2-Methoxypyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-5-(4-methylphenyl)-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-5-[3-(1-methylethoxy)phenyl]-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
4-[(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl]benzonitrile;
(7S)-5-(4-Ethoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,5-Difluorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3-Ethoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,4-Difluoro-5-methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3-Fluoro-5-methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-phenyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[4-(1-Hydroxyethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7R)-5-(3,4-Dichlorophenyl)-7-(fluoromethyl)-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7R)-5-(3,4-Dichlorophenyl)-7-(methoxymethyl)-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one; and
(7S)-5-(3,4-Dichlorophenyl)-3-[2-(hydroxymethyl)pyridin-4-yl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7R)-7-Ethyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-[2-(methylamino)pyridin-4-yl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3-(1-Hydroxyethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Chloro-2-methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(2,4-Dichlorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
7,7-Dimethyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Chloro-2-methylphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(5-Chloropyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-pyridin-4-yl-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(5-Ethoxy-6-fluoropyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-(2,6-Dimethylpyridin-4-yl)-7-methyl-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3-Chloro-6-ethoxypyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one; and
(7S)-5-[6-Ethoxy-5-(trifluoromethyl)pyridin-2-yl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
and the N-oxides, and the pharmaceutically acceptable salts and the solvates thereof.

In an additional embodiment, the present invention relates to compounds selected from the group of

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one, or a hydrochloride salt, or a sulfate salt, or a methanesulfonate salt, or a maleate salt thereof;

(7S)-7-Methyl-3-pyridin-4-yl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-[2-(Methoxymethyl)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one or a hydrochloride salt thereof;

(7S)-7-Methyl-3-(5-methylpyridin-3-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7R)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7R)-5-[3-Ethoxy-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

5-[3-Ethoxy-4-(trifluoromethyl)phenyl]-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(4-Methoxy-3,5-dimethylphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-(6-methylpyridin-3-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(4-Methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

3-(2-Methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3,4-Dimethoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-(2-Methoxypyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-5-(4-methylphenyl)-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-5-[3-(1-methylethoxy)phenyl]-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one or a hydrochloride salt thereof;

4-[(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl]benzonitrile;

(7S)-5-(4-Ethoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one or a hydrochloride salt thereof;

(7S)-5-(3,5-Difluorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3-Ethoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3,4-Difluoro-5-methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3-Fluoro-5-methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-phenyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[4-(1-Hydroxyethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7R)-5-(3,4-Dichlorophenyl)-7-(fluoromethyl)-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7R)-5-(3,4-Dichlorophenyl)-7-(methoxymethyl)-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one; and

(7S)-5-(3,4-Dichlorophenyl)-3-[2-(hydroxymethyl)pyridin-4-yl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7R)-7-Ethyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-[2-(methylamino)pyridin-4-yl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[3-(1-Hydroxyethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(4-Chloro-2-methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(2,4-Dichlorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

7,7-Dimethyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(4-Chloro-2-methylphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(5-Chloropyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-pyridin-4-yl-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-

dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(5-Ethoxy-6-fluoropyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-(2,6-Dimethylpyridin-4-yl)-7-methyl-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3-Chloro-6-ethoxypyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one; and
(7S)-5-[6-Ethoxy-5-(trifluoromethyl)pyridin-2-yl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
and the pharmaceutically acceptable salts and the solvates thereof.

In an additional embodiment, the present invention relates to compounds selected from the group of

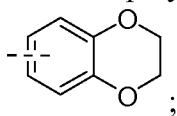
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one, or a hydrochloride salt, or a sulfate salt, or a methanesulfonate salt, or a maleate salt thereof;
(7S)-7-Methyl-3-pyridin-4-yl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-[2-(Methoxymethyl)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one or a hydrochloride salt thereof;
(7R)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7R)-5-[3-Ethoxy-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
5-[3-Ethoxy-4-(trifluoromethyl)phenyl]-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Methoxy-3,5-dimethylphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(6-methylpyridin-3-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
3-(2-Methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,4-Dimethoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-(2-Methoxypyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-

dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-5-[3-(1-methylethoxy)phenyl]-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one or a hydrochloride salt thereof;
4-[(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl]benzonitrile;
(7S)-5-(4-Ethoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one or a hydrochloride salt thereof;
(7S)-5-(3,5-Difluorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3-Ethoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,4-Difluoro-5-methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3-Fluoro-5-methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[4-(1-Hydroxyethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7R)-5-(3,4-Dichlorophenyl)-7-(methoxymethyl)-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one; and
(7S)-5-(3,4-Dichlorophenyl)-3-[2-(hydroxymethyl)pyridin-4-yl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-[2-(methylamino)pyridin-4-yl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3-(1-Hydroxyethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Chloro-2-methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(2,4-Dichlorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
7,7-Dimethyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Chloro-2-methylphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(5-Chloropyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

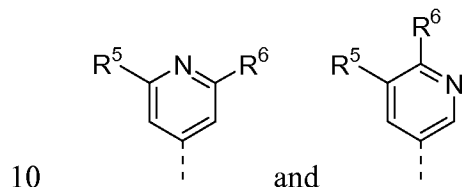
(7S)-7-Methyl-3-pyridin-4-yl-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
 (7S)-5-(5-Ethoxy-6-fluoropyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
 (7S)-3-(2,6-Dimethylpyridin-4-yl)-7-methyl-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
 (7S)-5-(3-Chloro-6-ethoxypyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one; and
 (7S)-5-[6-Ethoxy-5-(trifluoromethyl)pyridin-2-yl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one.

In an additional embodiment, the present 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 of halo, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, -O- C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyloxy, cyano and $-SF_5$; or is



R^2 is selected from



wherein R^5 and R^6 are each independently selected from the group of hydrogen, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, - C_{1-4} alkyl-O- C_{1-4} alkyl, -O- C_{1-4} alkyl, and $NR'R''$;

wherein R' is selected from hydrogen and C_{1-4} alkyl;

- 15 R'' is selected from hydrogen and C_{1-4} alkyl;

R^3 is selected from hydrogen and C_{1-4} alkyl;

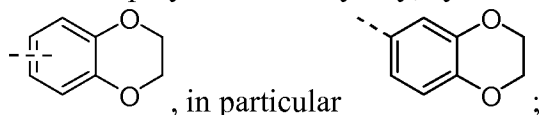
R^4 is selected from the group of hydrogen, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, - C_{1-4} alkyl-O- C_{1-4} alkyl, and - C_{1-4} alkyl-OH;

and the pharmaceutically acceptable salts and the solvates thereof.

20

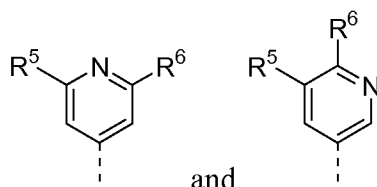
In an additional embodiment, the present invention relates to compounds of Formula (I) as defined hereinabove, and stereoisomeric forms thereof, wherein

R¹ is phenyl, optionally substituted with one or more substituents each independently selected from the group of halo, C₁₋₄alkyl, mono- or poly-haloC₁₋₄alkyl, -O-C₁₋₄alkyl, mono- or poly-haloC₁₋₄alkyloxy, cyano and -SF₅; or is



5

R² is selected from



wherein R⁵ and R⁶ are each independently selected from the group of hydrogen, C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl, -O-C₁₋₄alkyl, and NR'R'';

10

wherein R' is hydrogen;

R'' is hydrogen;

R³ is selected from hydrogen and C₁₋₄alkyl;

R⁴ is selected from the group of hydrogen and C₁₋₄alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

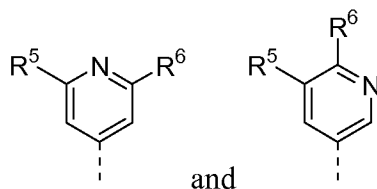
15

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

R¹ is phenyl, optionally substituted with one or more substituents each independently selected from the group of halo, C₁₋₄alkyl, poly-haloC₁₋₄alkyl and -SF₅;

20

R² is selected from



wherein R⁵ and R⁶ are each independently selected from the group of hydrogen, C₁₋₄alkyl and -O-C₁₋₄alkyl;

25

R³ is selected from hydrogen and C₁₋₄alkyl;

R⁴ is hydrogen;

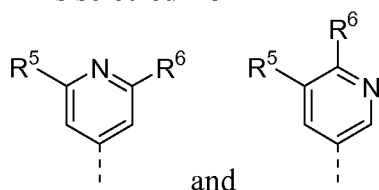
and the pharmaceutically acceptable salts and the solvates thereof.

In an additional embodiment, the present 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 of halo, C_{1-4} alkyl, poly-halo C_{1-4} alkyl and $-SF_5$;

5

R^2 is selected from



wherein R^5 and R^6 are each independently selected from the group of hydrogen, C_{1-4} alkyl and $-O-C_{1-4}$ alkyl;

10 R^3 is hydrogen;

R^4 is selected from hydrogen and C_{1-4} alkyl;

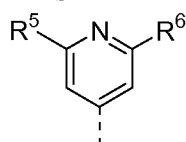
and the pharmaceutically acceptable salts and the solvates thereof.

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

15

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

R^2 is



20 wherein R^5 and R^6 are each independently selected from the group of hydrogen, C_{1-4} alkyl, $-O-C_{1-4}$ alkyl, and $NR'R''$;

wherein R' is hydrogen;

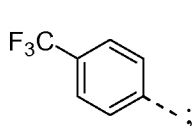
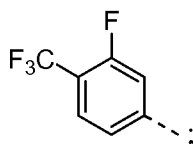
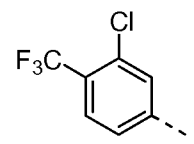
R'' is C_{1-4} alkyl;

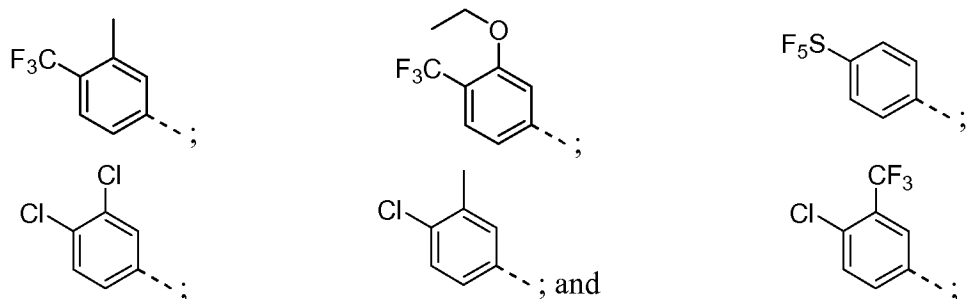
R^3 is hydrogen;

25 R^4 is hydrogen or C_{1-4} alkyl; in particular R^4 is C_{1-4} alkyl;

and the pharmaceutically acceptable salts and the solvates thereof.

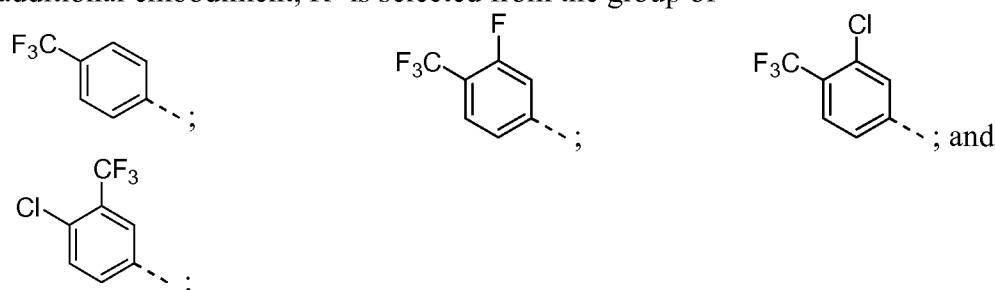
In an additional embodiment, R^1 is selected from the group of





and the rest of variables are as defined in Formula (I) herein.

In an additional embodiment, R^1 is selected from the group of

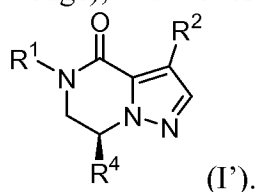


and the rest of variables are as defined in Formula (I) herein;

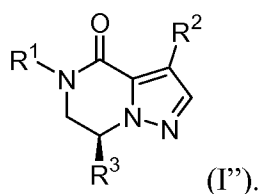
- 5 and the pharmaceutically acceptable salts and the solvates thereof.

In a further embodiment, the present invention relates to compounds of Formula (I) as defined herein wherein R^3 is hydrogen and R^4 is a substituent different from hydrogen having a configuration as depicted in the Formula (I') below, wherein the

- 10 6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one core, R^1 and R^2 are in the plane of the drawing and R^4 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



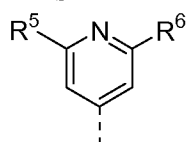
- 15 In a yet further embodiment, the present invention relates to compounds of Formula (I) as defined herein wherein R^4 is hydrogen and R^3 is a substituent different from hydrogen, for example a C_{1-4} alkyl substituent having a configuration as depicted in the Formula (I'') below, wherein the 6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one core, R^1 and R^2 are in the plane of the drawing and R^3 is projected above the plane of the
- 20 drawing (bond shown with a bold wedge), and the rest of variables are as defined in Formula (I) herein



In an additional embodiment, the present invention relates to compounds of Formula (I') as defined hereinabove, and stereoisomeric forms thereof, wherein

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

R² is



wherein R⁵ and R⁶ are each independently selected from the group of hydrogen,

- 10 C₁₋₄alkyl, -O-C₁₋₄alkyl, and NR'R'';

wherein R' is hydrogen;

R'' is C₁₋₄alkyl;

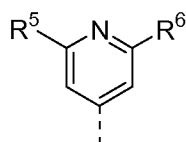
R⁴ is hydrogen or C₁₋₄alkyl; in particular R⁴ is C₁₋₄alkyl, more in particular methyl; and the pharmaceutically acceptable salts and the solvates thereof.

15

In an additional embodiment, the present 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 of halo, and poly-haloC₁₋₄alkyl;

- 20 R² is



wherein one of R⁵ and R⁶ is hydrogen or methyl, in particular hydrogen; and

the other one of R⁵ or R⁶ is selected from the group of C₁₋₄alkyl, -O-C₁₋₄alkyl, and NR'R'';

- 25 wherein R' is hydrogen;

R'' is C₁₋₄alkyl;

R⁴ is hydrogen or C₁₋₄alkyl; in particular R⁴ is C₁₋₄alkyl, more in particular methyl; and the pharmaceutically acceptable salts and the solvates thereof.

- 30 Specific compounds according to the invention include:

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-pyridin-4-yl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[3-methyl-4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3,4-Dichlorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(4-Chloro-3-methylphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[3-Ethoxy-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[4-Chloro-3-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[3-Fluoro-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[3-Methoxy-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

5-[(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl]-2-(trifluoromethyl)benzonitrile;

(7S)-3-(2,6-Dimethylpyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(4-Chlorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3-Chlorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3-Chloro-4-ethoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(4-Chloro-3-ethoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(4-Chloro-3-methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-

dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3-Chloro-4-methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Fluoro-3-methylphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-[2-(Methoxymethyl)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[3-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(5-methylpyridin-3-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,4-Difluorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7R)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[4-(Difluoromethoxy)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Fluorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-(5,6-Dimethylpyridin-3-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Chloro-2-fluorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7R)-5-[3-Ethoxy-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-pyridin-3-yl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
5-[3-Ethoxy-4-(trifluoromethyl)phenyl]-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Methoxy-3,5-dimethylphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3-Fluoro-4-methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(6-methylpyridin-3-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-(6-Aminopyridin-3-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(4-Methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

5-[3-Fluoro-4-(trifluoromethyl)phenyl]-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

3-(2-Methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3,4-Dimethoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(2,3-Dihydro-1,4-benzodioxin-6-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-3-(2,6-dimethyl-4-pyridyl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-3-[2-(ethylamino)-4-pyridyl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-3-(2-methoxy-4-pyridyl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-3-(2-ethyl-4-pyridyl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-5-(3,4-dichlorophenyl)-3-(2,6-dimethyl-4-pyridyl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-5-[3-(2-Fluoroethoxy)-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-(2,6-dimethyl-4-pyridyl)-5-[3-ethoxy-4-(trifluoromethyl)phenyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-7-methyl-3-(4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-3-(2,6-dimethyl-4-pyridyl)-5-[3-methoxy-4-(trifluoromethyl)phenyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

7-(fluoromethyl)-3-(2-methyl-4-pyridyl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-3-(2,6-dimethyl-4-pyridyl)-7-methyl-5-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-5-[4-chloro-3-(trifluoromethyl)phenyl]-3-(2,6-dimethyl-4-pyridyl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-5-[3-ethoxy-4-(trifluoromethyl)phenyl]-7-methyl-3-(4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-7-methyl-5-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]-3-(4-pyridyl)-6,7-

dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-(3,4-dichlorophenyl)-7-methyl-3-(4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-7-methyl-3-(2-methyl-4-pyridyl)-5-[3-(trifluoromethoxy)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
5-[(7S)-3-(2,6-dimethyl-4-pyridyl)-7-methyl-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-5-yl]-2-(trifluoromethyl)benzonitrile;
(7S)-5-[3-fluoro-4-(trifluoromethyl)phenyl]-7-methyl-3-(4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-(2,6-dimethyl-4-pyridyl)-5-[3-fluoro-4-(trifluoromethyl)phenyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-(4-Chloro-3-fluorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3-chloro-5-fluoro-phenyl)-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[3-methoxy-4-(trifluoromethyl)phenyl]-7-methyl-3-(4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-(4-isopropylphenyl)-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-7-methyl-3-(2-methyl-4-pyridyl)-5-(4-propylphenyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[4-Fluoro-3-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[4-chloro-3-(trifluoromethyl)phenyl]-7-methyl-3-(4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[3-(difluoromethoxy)-5-fluoro-phenyl]-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
7-ethyl-3-(2-methyl-4-pyridyl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-(2-Aminopyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-chlorophenyl)-3-(2,6-dimethyl-4-pyridyl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-(4-chlorophenyl)-7-methyl-3-(4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
5-[3-Ethoxy-4-(trifluoromethyl)phenyl]-7-(hydroxymethyl)-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

2-Fluoro-4-[(7S)-7-methyl-3-(2-methylpyridin-4-yl)-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl]benzonitrile;

(7S)-5-(3-Fluoro-4-methylphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[4-(2-fluoroethoxy)-3-(trifluoromethyl)phenyl]-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-7-Methyl-5-(4-methylphenyl)-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-5-[3-(1-methylethoxy)phenyl]-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

4-[(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl]benzonitrile;

(7S)-5-(4-Ethoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3,5-Difluorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3-Ethoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3,4-difluoro-5-methoxy-phenyl)-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-5-(3-fluoro-5-methoxy-phenyl)-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-phenyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

7-(Hydroxymethyl)-3-(2-methyl-4-pyridyl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

5-[(7S)-3-(2-Methoxypyridin-4-yl)-7-methyl-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl]-2-(trifluoromethyl)benzonitrile;

(7S)-5-(4-Chlorophenyl)-3-(2-methoxypyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

5-(3,4-Dichlorophenyl)-3-[2-(dimethylamino)pyridin-4-yl]-7-(fluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (7R or 7S);

5-(3,4-Dichlorophenyl)-3-[2-(dimethylamino)pyridin-4-yl]-7-(fluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (7S or 7R);

(7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-3-[2-(3-fluoroazetidin-1-yl)pyridin-4-yl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

5-(3,4-Dichlorophenyl)-7-(fluoromethyl)-3-[2-(methylamino)pyridin-4-yl]-6,7-

dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-[2-(3-Fluoroazetidin-1-yl)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
4-[(7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-7-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]-6-(methylamino)pyridine-2-carbonitrile;
(7S)-3-(2-Azetidin-1-ylpyridin-4-yl)-5-[3-chloro-4-(trifluoromethyl)phenyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-(2-Azetidin-1-ylpyridin-4-yl)-5-(3,4-dichlorophenyl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3-(Fluoromethyl)-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-5-[4-(trifluoromethyl)phenyl]-3-[2-(trifluoromethyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
4-[(7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-7-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]pyridine-2-carbonitrile;
(7S)-3-[2-(3-Hydroxyazetidin-1-yl)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-(2-Azetidin-1-ylpyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-7-methyl-3-[2-(methylamino)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-3-(2-methoxypyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(2-pyrrolidin-1-ylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-[2-(4-Acetylpiperazin-1-yl)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(2-piperidin-1-ylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(2-morpholin-4-ylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
4-[(7S)-5-(3,4-Dichlorophenyl)-7-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]pyridine-2-carbonitrile;
(7S)-5-(3,4-Dichlorophenyl)-7-methyl-3-[2-(methylamino)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,4-Dichlorophenyl)-3-[2-(1-hydroxyethyl)pyridin-4-yl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-[2-(Fluoromethyl)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(2,2,2-trifluoro-1-methylethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3,4-Dichlorophenyl)-3-[2-(difluoromethyl)pyridin-4-yl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

5-(3,4-Dichlorophenyl)-7-(fluoromethyl)-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (7S or 7R);

5-(3,4-Dichlorophenyl)-7-(fluoromethyl)-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (7R or 7S);

(7S)-5-(3,4-Dichlorophenyl)-3-[2-(fluoromethyl)pyridin-4-yl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

5-(3,4-Dichlorophenyl)-7-(methoxymethyl)-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (7S or 7R);

5-(3,4-Dichlorophenyl)-7-(methoxymethyl)-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (7R or 7S);

7-(Methoxymethyl)-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (7R or 7S);

7-(Methoxymethyl)-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (7S or 7R);

(7S)-3-(2-Cyclopropylpyridin-4-yl)-5-(3,4-dichlorophenyl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-(2-Ethoxypyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3,4-Dichlorophenyl)-7-methyl-3-[2-(1-methylethyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3,4-Dichlorophenyl)-3-[2-(hydroxymethyl)pyridin-4-yl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-[2-(1-methylethyl)pyridin-4-yl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

4-{(7S)-7-Methyl-4-oxo-5-[4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl}pyridine-2-carbonitrile;

(7S)-3-[2-(1-Hydroxyethyl)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7R)-7-Ethyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Ethyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-

dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-[2-(Difluoromethyl)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3,5-Difluoro-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,4-Dichlorophenyl)-3-(2-ethoxypyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,4-Dichlorophenyl)-3-(2-ethylpyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-[2-(Hydroxymethyl)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-{4-[1-(trifluoromethyl)cyclopropyl]phenyl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,4-Dichlorophenyl)-7-methyl-3-[2-(1-methylethoxy)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-[2-(1-methylethoxy)pyridin-4-yl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Bromophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(2-methyl-1-oxidopyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-tert-Butylphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,4-Dichlorophenyl)-3-(2-methoxypyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
5-(3,4-Dichlorophenyl)-7-(methoxymethyl)-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
7-(Methoxymethyl)-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-(2-Methoxy-6-methylpyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,4-Dichlorophenyl)-3-(2-methoxy-6-methylpyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-[2-(methylamino)pyridin-4-yl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3-(1-Hydroxyethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[4-(1-Hydroxyethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-(6-Methoxypyridin-3-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

5-[(7S)-7-Methyl-4-oxo-5-[4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl]pyridine-2-carbonitrile;

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethoxy)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-5-[3-methyl-4-(trifluoromethyl)phenyl]-3-pyridin-4-yl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-5-[3-(1-methylethoxy)-4-(trifluoromethyl)phenyl]-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

5-[(7S)-7-Methyl-4-oxo-3-pyridin-4-yl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl]-2-(trifluoromethyl)benzonitrile;

(7S)-5-(4-Cyclopropylphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-(2,6-Dimethylpyridin-4-yl)-7-methyl-5-[3-methyl-4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[3-(Methoxymethyl)-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3,5-Dichlorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(2,2,2-trifluoroethoxy)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(4-Chloro-2-methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[4-(Difluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[4-Chloro-3-(difluoromethoxy)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3,4-Dichlorophenyl)-3-(2-fluoropyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(2,2,2-trifluoro-1-methylethoxy)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-[2-(Dimethylamino)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(2,4-Dichlorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-

dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3-Chloro-4-(difluoromethoxy)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[4-Chloro-3-(trifluoromethoxy)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,4-Dichlorophenyl)-7-methyl-3-(2-methyl-1-oxidopyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
7,7-Dimethyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Chloro-2-methylphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-(2-Cyclopropylpyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3-Chloro-4-(difluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(2-piperazin-1-ylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-(6-piperazin-1-ylpyridin-3-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-3-[2-(2-fluoroethoxy)pyridin-4-yl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Chlorophenyl)-7-methyl-3-[2-(methylamino)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
5-[(7S)-7-Methyl-3-[2-(methylamino)pyridin-4-yl]-4-oxo-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl]-2-(trifluoromethyl)benzonitrile;
(7S)-3-(2-Methoxypyridin-4-yl)-5-[3-methoxy-4-(trifluoromethyl)phenyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
7-(Difluoromethyl)-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3-Fluoro-4-(trifluoromethyl)phenyl]-7-methyl-3-[2-(methylamino)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[3-Methoxy-4-(trifluoromethyl)phenyl]-7-methyl-3-[2-(methylamino)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
5-(3,4-Dichlorophenyl)-7-(fluoromethyl)-3-[2-(methylamino)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (7R or 7S);
5-(3,4-Dichlorophenyl)-7-(fluoromethyl)-3-[2-(methylamino)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (7S or 7R);

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(5-Chloropyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[6-Chloro-5-(trifluoromethyl)pyridin-2-yl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[4-Ethoxy-5-(trifluoromethyl)pyridin-2-yl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-pyridin-4-yl-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(5-Ethoxy-6-fluoropyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[6-methyl-5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-methyl-5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-(2,6-Dimethylpyridin-4-yl)-7-methyl-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(3-Chloro-6-ethoxypyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(5-Chloro-6-methylpyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-(2-Fluoropyridin-4-yl)-7-methyl-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(4-Chloro-5-methylpyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[6-Ethoxy-3-(trifluoromethyl)pyridin-2-yl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[6-Ethoxy-5-(trifluoromethyl)pyridin-2-yl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(5-Chloro-6-ethoxypyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(5,6-Dichloropyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(4,5-Dichloropyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[4-Chloro-5-(trifluoromethyl)pyridin-2-yl]-7-methyl-3-(2-methylpyridin-4-yl)-

6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-(2,6-Dimethylpyridin-4-yl)-5-[6-ethoxy-5-(trifluoromethyl)pyridin-2-yl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(5-Chloro-6-methoxypyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[6-Methoxy-5-(trifluoromethyl)pyridin-2-yl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[6-Ethoxy-5-(trifluoromethyl)pyridin-2-yl]-7-methyl-3-pyridin-4-yl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-(2-Azetidin-1-ylpyridin-4-yl)-5-[6-methoxy-5-(trifluoromethyl)pyridin-2-yl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-[2-(methylamino)pyridin-4-yl]-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
3-(2-Methylpyridin-4-yl)-5-[5-(trifluoromethyl)pyridin-2-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-[4-Iodo-5-(trifluoromethyl)pyridin-2-yl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4-Chloro-5-iodopyridin-2-yl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-7-Methyl-3-[2-(methylamino)-1-oxidopyridin-4-yl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-3-(2-Chloropyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
7-(1-Hydroxyethyl)-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (1R or 1S);
7-(1-Hydroxyethyl)-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (1S or 1R);
(7S)-3-(2-Chloropyridin-4-yl)-5-(3,4-dichlorophenyl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
5-(3,4-Dichlorophenyl)-7-(hydroxymethyl)-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(4,5-Dichloro-2-iodophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
(7S)-5-(3,4-Dichloro-2-iodophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;
5-(3,4-Dichlorophenyl)-7-(fluoromethyl)-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-(2-Bromopyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

5-(3,4-Dichlorophenyl)-3-(2-fluoropyridin-4-yl)-7-(hydroxymethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-(2-Iodopyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

5-(3,4-Dichlorophenyl)-3-(2-fluoropyridin-4-yl)-7-(hydroxymethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (7S or 7R);

5-(3,4-Dichlorophenyl)-3-(2-fluoropyridin-4-yl)-7-(hydroxymethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (7R or 7S);

(7S)-5-[3-Chloro-4-(trifluoromethyl)phenyl]-3-(2-fluoropyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[3-Bromo-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-(4-Iodophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

5-(3,4-Dichlorophenyl)-3-[2-(dimethylamino)pyridin-4-yl]-7-(hydroxymethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (7S or 7R);

5-(3,4-Dichlorophenyl)-3-[2-(dimethylamino)pyridin-4-yl]-7-(hydroxymethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (7R or 7S);

5-(3,4-Dichlorophenyl)-7-(hydroxymethyl)-3-[2-(methylamino)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-(2-Chloro-6-methoxypyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-3-[6-(1-Acetylazetidin-3-yl)pyridin-3-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-{4-[(trifluoromethyl)sulfanyl]phenyl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[6-Methoxy-5-(trifluoromethyl)pyridin-2-yl]-7-methyl-3-[2-(methylamino)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

3-(2-Methylpyridin-4-yl)-7-(trifluoromethyl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one;

(7S)-5-[3-(hydroxymethyl)-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-3-(2-methoxy-4-pyridyl)-5-[6-methoxy-5-(trifluoromethyl)-2-pyridyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-7-methyl-3-[2-methyl-6-(methylamino)-4-pyridyl]-5-[4-

(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-methoxy-6-(methylamino)-4-pyridyl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-fluoro-6-(methylamino)-4-pyridyl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
5-(2,4-dichlorophenyl)-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-(dimethylamino)-4-pyridyl]-5-[3-(hydroxymethyl)-4-(trifluoromethyl)phenyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-(dimethylamino)-4-pyridyl]-5-[3-(fluoromethyl)-4-(trifluoromethyl)phenyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-(2-fluoro-4-pyridyl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-(3,4-dichlorophenyl)-3-[2-(dimethylamino)-4-pyridyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-(dimethylamino)-4-pyridyl]-5-[3-(2-fluoroethoxy)-4-(trifluoromethyl)phenyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-(dimethylamino)-4-pyridyl]-5-[6-methoxy-5-(trifluoromethyl)-2-pyridyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-7-methyl-3-[2-(methylamino)-4-pyridyl]-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-methyl-1-oxido-pyridin-1-ium-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-[ethyl(methyl)amino]-4-pyridyl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-3-[2-[ethyl(methyl)amino]-4-pyridyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-3-[2-(ethylamino)-4-pyridyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-(ethylamino)-4-pyridyl]-7-methyl-5-[3-methyl-4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-(3,4-dichlorophenyl)-3-[2-(ethylamino)-4-pyridyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-7-methyl-5-[3-methyl-4-(trifluoromethyl)phenyl]-3-[2-(propylamino)-4-pyridyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-7-methyl-3-[2-(propylamino)-4-pyridyl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

(7S)-3-[2-(azetidin-1-yl)-4-pyridyl]-7-methyl-5-[3-methyl-4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-(isopropylamino)-4-pyridyl]-7-methyl-5-[3-methyl-4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-3-[2-(isopropylamino)-4-pyridyl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-3-[2-(fluoromethyl)-4-pyridyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-7-methyl-3-[2-(propylamino)-4-pyridyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-(3,4-dichlorophenyl)-7-methyl-3-[2-(propylamino)-4-pyridyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-[3-chloro-4-(trifluoromethyl)phenyl]-3-[2-(isopropylamino)-4-pyridyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;
(7S)-5-(3,4-dichlorophenyl)-3-[2-(isopropylamino)-4-pyridyl]-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one;

and the pharmaceutically acceptable salts and solvates of such compounds.

In another embodiment, specific compounds according to the invention include:

(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one sulfate salt;
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one methane sulfonate salt;
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one maleate salt;
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[3-methyl-4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;
(7S)-5-(3,4-Dichlorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;
(7S)-5-[3-Methoxy-4-(trifluoromethyl)phenyl]-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;
(7S)-5-(4-Chlorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;
(7S)-5-(3-Chloro-4-ethoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;

(7S)-5-(3-Chloro-4-methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;

(7S)-3-[2-(Methoxymethyl)pyridin-4-yl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;

(7S)-5-(3,4-Difluorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;

(7S)-5-(4-Fluorophenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;

(7S)-5-(3-Fluoro-4-methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;

(7S)-5-(4-Methoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;

(7S)-7-methyl-3-(2-methyl-4-pyridyl)-5-[3-(trifluoromethoxy)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one hydrochloride salt;

(7S)-5-(3-chloro-5-fluoro-phenyl)-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one hydrochloride salt;

(7S)-5-(4-isopropylphenyl)-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one hydrochloride salt;

(7S)-7-methyl-3-(2-methyl-4-pyridyl)-5-(4-propylphenyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one hydrochloride salt;

(7S)-5-[3-(difluoromethoxy)-5-fluoro-phenyl]-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one hydrochloride salt;

(7S)-7-Methyl-5-[3-(1-methylethoxy)phenyl]-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;

(7S)-5-(4-Ethoxyphenyl)-7-methyl-3-(2-methylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;

(7S)-7-Methyl-3-(2-piperidin-1-ylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;

(7S)-3-(2-Cyclopropylpyridin-4-yl)-5-(3,4-dichlorophenyl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;

(7S)-5-(3,4-Dichlorophenyl)-3-(2-ethoxypyridin-4-yl)-7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;

(7S)-5-(3,4-Dichlorophenyl)-7-methyl-3-[2-(1-methylethoxy)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;

(7S)-7-Methyl-3-[2-(1-methylethoxy)pyridin-4-yl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;

(7S)-3-(2-Cyclopropylpyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-

dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt;
(7S)-7-Methyl-3-(2-piperazin-1-ylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-
dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt, and
(7S)-7-Methyl-3-(2-methylpyridin-4-yl)-5-{4-[(trifluoromethyl)sulfanyl]phenyl}-6,7-
dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride salt.

The names of the compounds of the present invention were generated according to the nomenclature rules agreed upon by the Chemical Abstracts Service (C.A.S.) using Advanced Chemical Development, Inc., software (ACD/Name product version 10.01.0.14105, October 2006). In case of tautomeric forms, 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.

10 Definitions

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 “-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.

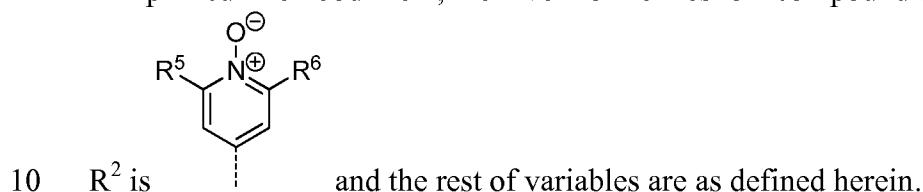
The notation “mono- and polyhaloC₁₋₄alkyl” as used herein alone or as part of another group, refers to C₁₋₄alkyl as defined before, substituted with 1, 2, 3 or where possible with more halo atoms as defined before.

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 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. 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), peroalkanoic acids,
 5 e.g. peroacetic acid, alkylhydroperoxides, e.g. tert-butyl hydroperoxide. Suitable
 solvents, e.g. 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.

In a particular embodiment, the invention relates to a compound of Formula (I) wherein



Whenever the term “substituted” is used in the present invention, it is meant,
 unless 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,
 15 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
 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.

20 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.

The term "therapeutically effective amount" as used herein, means that amount
 of active compound or pharmaceutical agent that elicits the biological or medicinal
 25 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.

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
 30 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
 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 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 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.

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 (+) 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

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.

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.

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 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, 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 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, 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 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 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 of ^3H , ^{11}C , ^{14}C , ^{18}F , ^{122}I , ^{123}I , ^{125}I , ^{131}I , ^{75}Br , ^{76}Br , ^{77}Br and ^{82}Br . Preferably, the radioactive isotope is selected from the group 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 be prepared according to the following synthesis methods.

The general preparation of some typical examples of the compounds of Formula (I) is described hereunder and in the specific examples, and are generally prepared from starting materials which are either commercially available or prepared by standard synthetic processes commonly used by those skilled in the art. The following schemes are only meant to represent examples of the invention and are in no way meant to be a limit of the invention.

Alternatively, compounds of the present invention may also be prepared by analogous reaction protocols as described in the general schemes below, combined with standard synthetic processes commonly used by those skilled in the art of organic chemistry.

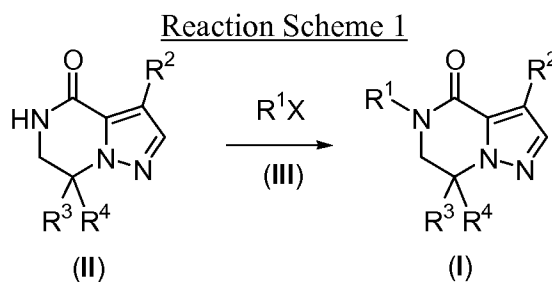
The compounds of Formula (I) may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said

diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of Formula (I) involves liquid chromatography using a chiral stationary phase or chiral supercritical fluid chromatography (SFC). 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. 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 or by chiral separation of mixtures, followed by vibrational circular dichroism (VCD) analysis of the particular enantiomer(s).

A. Preparation of the final compounds

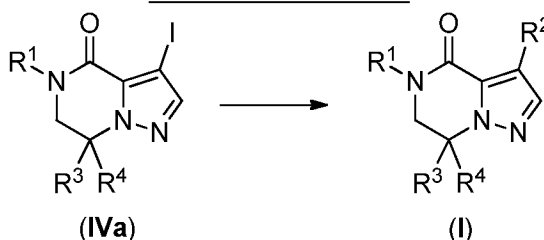
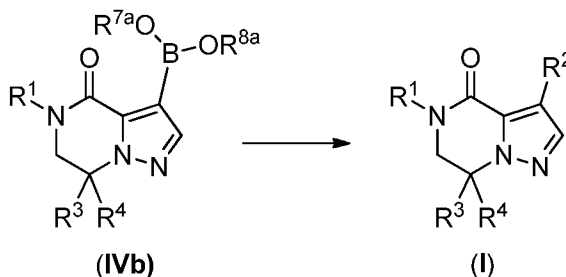
Experimental procedure 1

Final compounds according to Formula (I) can be prepared by a Goldberg coupling reaction of a compound of Formula (II) with an appropriate aryl halide of Formula (III) where X is halo, in particular bromo or iodo, according to conditions known to the skilled person. Such conditions include for example using 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 inorganic carbonates, for example sodium carbonate (Na_2CO_3) or potassium carbonate (K_2CO_3), in a suitable solvent, such as toluene or a mixture of toluene and *N,N*-dimethylformamide (DMF), under suitable reaction conditions, such as at a convenient temperature, typically ranging between 100 °C and 140 °C, in particular 110 °C, for a period of time to ensure the completion of the reaction. 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 Formula (I).

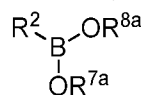


Experimental procedure 2

Alternatively, final compounds according to Formula (I) can be prepared by a Suzuki type coupling reaction of a compound of Formula (IVa) with a suitable boron species or a compound of Formula (IVb), wherein R^{7a} and R^{8a} may be each independently selected from H, C_{1-4} alkyl or R^{7a} and R^{8a} are 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 heteroaryl halide or aryl halide derivative 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 $\text{Pd}(\text{OAc})_2$ 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. In Reaction Schemes 2a and 2b, all variables are defined as in Formula (I).

Reaction Scheme 2aReaction Scheme 2b

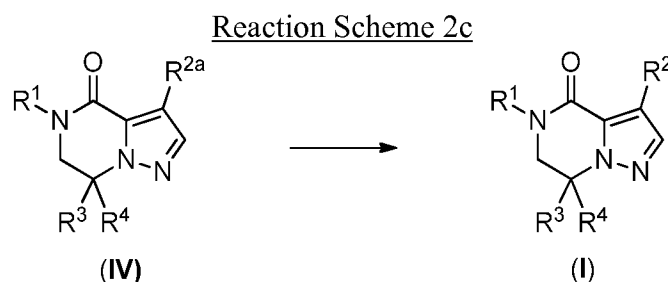
The suitable boron species may be selected for example from a boronic acid or a boronate ester, which may be conveniently represented as a compound of Formula



(IIIa) (IIIa), wherein R^2 is as defined in Formula (I) herein and R^{7a} and R^{8a} may

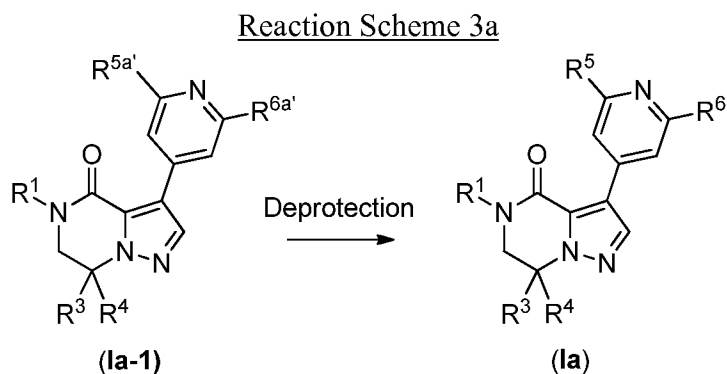
be each independently selected from H, C_{1-4} alkyl or R^{7a} and R^{8a} are taken together to form for example a bivalent radical of formula $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$ or

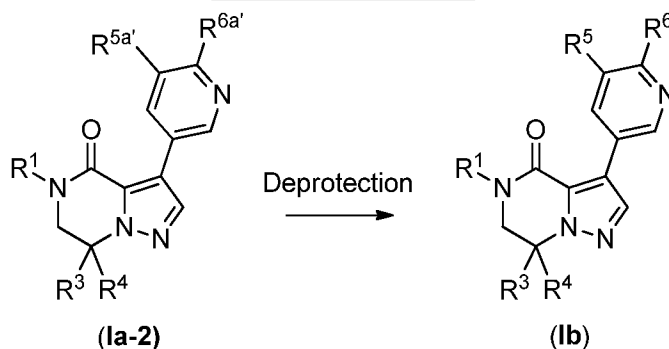
- C(CH₃)₂C(CH₃)₂–. A skilled person can envisage that the reaction under Reaction Scheme 2a can also be performed under similar conditions, when the compound of Formula (IVa) bears a bromo group in place of an iodo group. Such a reaction can be represented as in Reaction Scheme 2c, wherein the compound of Formula (IV),
 5 wherein R^{2a} is halo, in particular bromo or iodo and all other variables are as defined in Formula (I), undergoes a Suzuki type coupling as described hereinbefore.



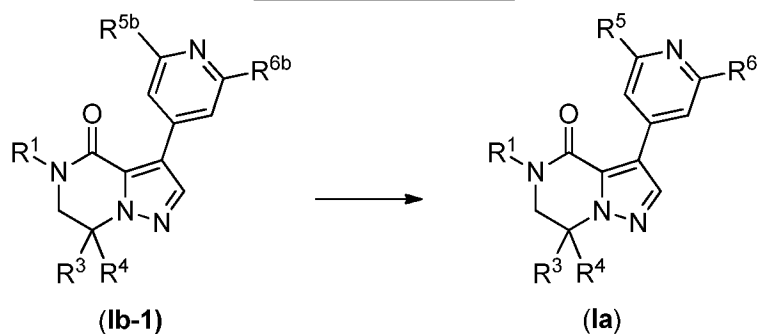
10 Experimental procedure 3

- Alternatively, final compounds according to Formula (I), wherein R² is an optionally substituted 4-pyridinyl or 3-pyridinyl, hereby referred to as compounds of Formula (Ia) or Formula (Ib), respectively, can be prepared by a reaction of deprotection of a compound of Formula (Ia-1) or a compound of Formula (Ia-2) following art known procedures. A compound of Formula (Ia) or a compound Formula (Ib) can be obtained by removal of the protecting group such as for example a Boc protecting group in the compound of Formula (Ia-1) or compound of Formula (Ia-2), in the presence of acidic media, such as trifluoroacetic acid, in an inert solvent such as dichloromethane (DCM), under suitable reaction conditions, such as at a convenient
 20 temperature, typically rt, for a period of time to ensure the completion of the reaction. In Reaction Schemes 3a and 3b, all variables are defined as in Formula (I) and R^{5a'} and R^{6a'} include the residues indicated in the scope as R⁵ and R⁶ as well as their protected forms.

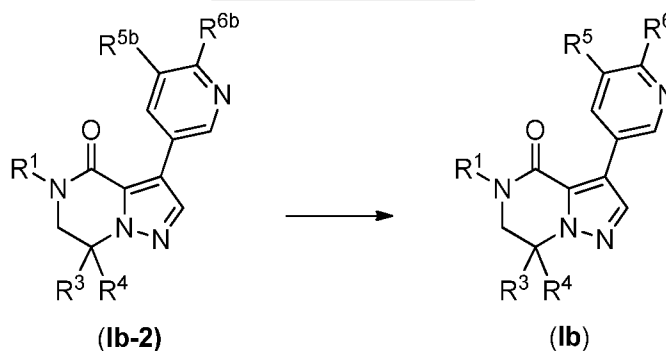


Reaction Scheme 3bExperimental procedure 4

- 5 Alternatively, final compounds according to Formula (Ia) and Formula (Ib) can be prepared by manipulation of a suitable precursor of Formula (Ib-1) and of Formula (Ib-2) respectively, bearing one or more functional groups which can be converted to the residues R⁵ and R⁶ by means of simple reactions known to the person skilled in the art, such as for example introduction of an alcohol or an amine in presence of a base
- 10 and a suitable solvent or acylation with an acyl chloride in the presence of a base and a suitable solvent or reduction for example by using a suitable reducing agent such as sodium borohydride, in a suitable solvent or by means of cross coupling reactions known to the person skilled in the art, such as for example the Suzuki reaction with a suitable boron species or the Stille reaction with a suitable tin species. In Reaction
- 15 Schemes 4a and 4b, all variables are defined as in Formula (I) and R^{5b} and R^{6b} include the residues indicated in the scope as R⁵ and R⁶ as well as their possible precursors. The person skilled in the art will recognize that suitable reaction conditions should be chosen for different R^{5b} and R^{6b} combinations, to avoid undesired side reactions.

Reaction Scheme 4a

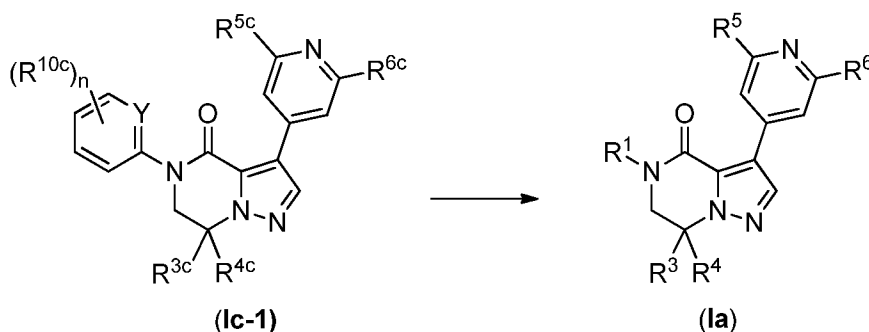
Reaction Scheme 4b

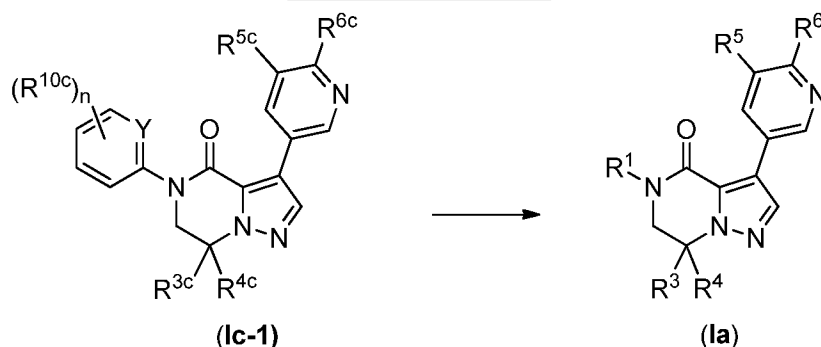


Experimental procedure 5

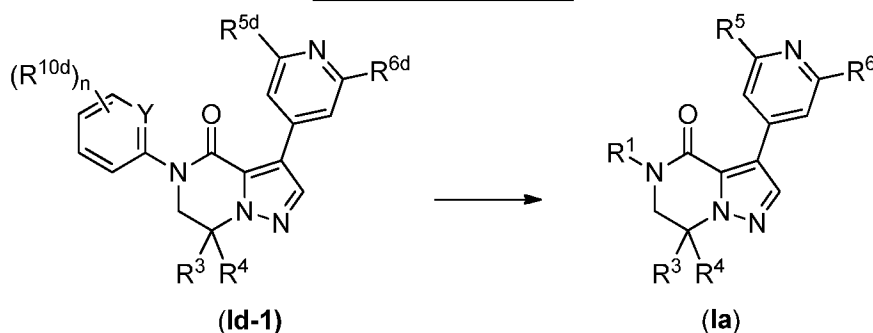
- Alternatively, final compounds according to Formula (Ia) and Formula (Ib) can be prepared respectively by a reaction of fluorination of a compound of Formula (Ic-1) and of Formula (Ic-2) wherein Y is N, CH or CR^{9c} and one of R^{5c}, R^{6c}, R^{3c}, R^{4c}, R^{9c} and R^{10c} may be each independently selected from C₁₋₄alkyl-OH or C₁₋₃alkyl-CHO and herein referred to as a compound of Formula (Ic-1) and compound of Formula (Ic-2) respectively. A compound of Formula (Ic-1) or compound of Formula (Ic-2) can be treated in the presence of a fluorinating agent such as for example ®Deoxofluor ([Bis(2-methoxyethyl)amino]sulfur trifluoride) or (diethylamino)sulfur trifluoride in a suitable solvent such as, for example DCM, and stirring the reaction mixture at rt. In Reaction Schemes 5a and 5b, all variables are defined as in Formula (I) and R^{5c}, R^{6c}, R^{3c}, and R^{4c} include the residues indicated in the scope of Formula (I) as R⁵, R⁶, R³, R⁴ as well as their possible precursors, and R^{9c} and R^{10c}, when present, include the residues indicated in the scope of Formula (I) as substituents in R¹ as well as their possible precursors, wherein one of R^{5c}, R^{6c}, R^{3c}, R^{4c}, and R^{9c} and R^{10c} when present, is C₁₋₄alkyl-OH or C₁₋₃alkyl-CHO and in (R^{10d})_n, n = 0-4.

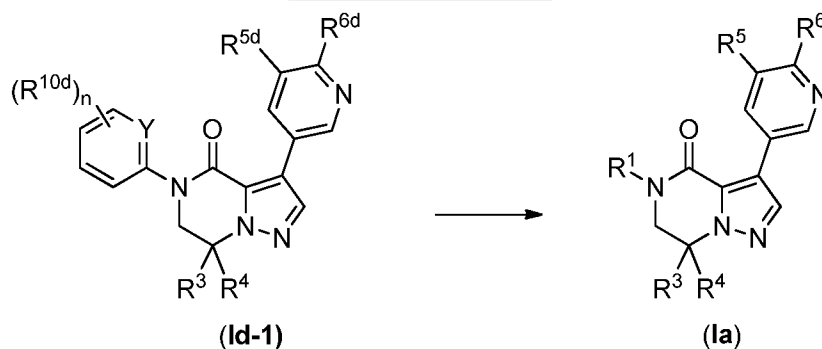
Reaction Scheme 5a



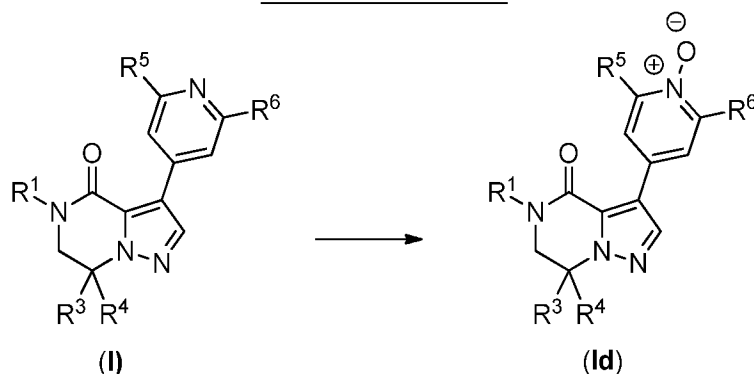
Reaction Scheme 5bExperimental procedure 6

- 5 Alternatively, final compounds according to Formula (Ia) and Formula (Ib) can be prepared by manipulation of a suitable precursor of Formula (Id-1) or of Formula (Id-2) respectively, wherein Y is N, CH or CR^{9d} , bearing one or more functional groups, R^{5d} , R^{6d} , R^{9d} and R^{10d} , which can be converted to the residues R^5 , R^6 and the substituents of R^1 as defined in Formula (I) by means of simple reactions known to the
- 10 person skilled in the art, such as for example by reduction of a double bond to the corresponding saturated form, for example by means of catalytic hydrogenation. In Reaction Schemes 6a and 6b, all variables are defined as in Formula (I) and R^{5d} and R^{6d} , include the residues indicated in the scope as R^5 , R^6 as well as their possible precursors, and R^{9d} and R^{10d} when present include the substituents of R^1 as well as
- 15 their possible precursors. The person skilled in the art will recognize that suitable reaction conditions should be chosen for different R^{5d} , R^{6d} , R^{9d} and R^{10d} combinations to avoid undesired side reactions and in $(R^{10d})_n$, $n = 0-4$.

Reaction Scheme 6a

Reaction Scheme 6bExperimental procedure 7

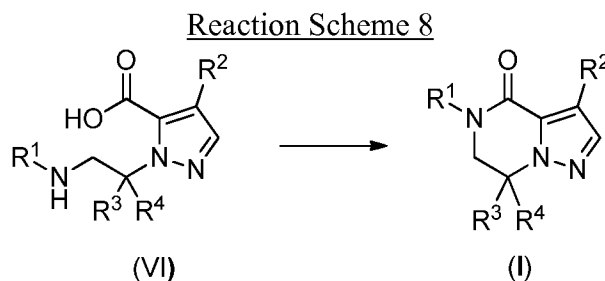
- 5 Alternatively, final compounds according to Formula (Id) can be prepared by means of an oxidation reaction of a compound of Formula (I) in the presence of an oxidant, such as for example 3-chloroperoxybenzoic acid and in a suitable solvent. In Reaction Scheme 7, all variables are defined as in Formula (I).

Reaction Scheme 7

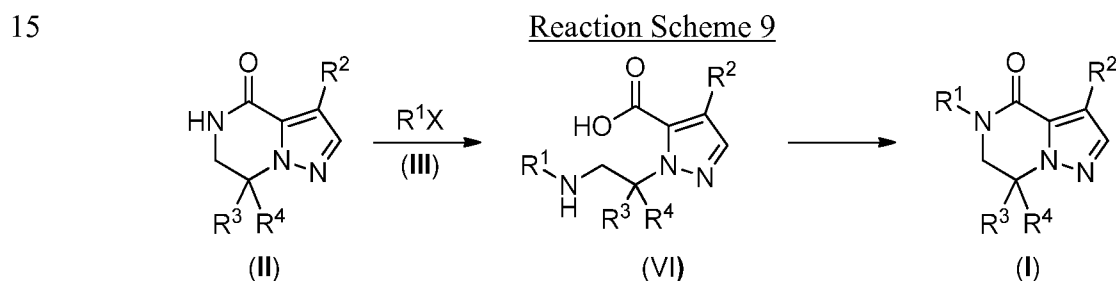
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Experimental procedure 8

- 15 Alternatively, final compounds according to Formula (I) can be prepared by intramolecular amidation starting from a compound of Formula (VI). Typically, amidation conditions can be applied, such as stirring the starting materials, dissolved in a suitable solvent, such as DMF, in the presence of a coupling agent, such as HATU (2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) and in the presence of a base, such as TEA (triethylamine). In Reaction Scheme 8, all variables are defined as in Formula (I).

Experimental procedure 9

- 5 Alternatively, final compounds according to Formula (I) can be prepared in one pot starting from a compound of Formula (II). First, a reaction of nucleophilic substitution of a compound of Formula (II) with an appropriate (hetero)aryl halide of Formula (III) where X is halo in the presence of a base such as for example sodium hydride in a suitable solvent such as for example DMF, followed by an intramolecular peptide type coupling of compound of Formula (VI) applying typical peptide type coupling conditions. Typically, peptide coupling conditions can be applied, such as stirring the starting materials, dissolved in a suitable solvent, such as DMF, in the presence of a peptide coupling agent, such as HATU and in the presence of a base, such as TEA. In Reaction Scheme 9, all variables are defined as in Formula (I).



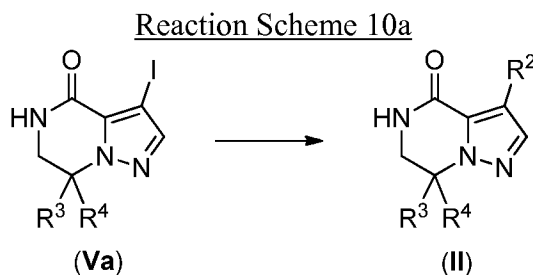
- 20 Alternatively, final compounds according to Formula (I) can be prepared in one pot starting from a compound of Formula (II). First by a coupling reaction of a compound of Formula (II) with an appropriate heteroaryl halide of Formula (III) where X is halo in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0), in the presence of a ligand, such as 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, in the presence of a base, such as Cs₂CO₃ and in a suitable solvent, such as 1,4-dioxane, 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, followed by an intramolecular peptide type coupling of compound of Formula (VI) applying typical peptide type coupling conditions. Typically, peptide coupling conditions can be applied, such as stirring the starting materials, dissolved in a suitable solvent, such as

DMF, in the presence of a peptide coupling agent, such as HATU and in the presence of a base, such as TEA. In Reaction Scheme 9, all variables are defined as in Formula (I).

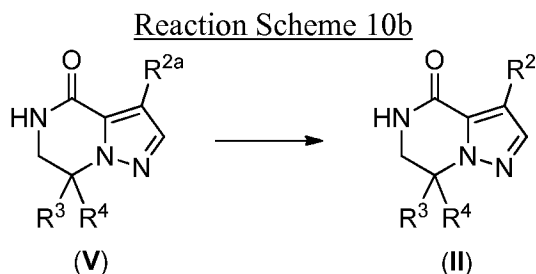
5 B. Preparation of the intermediate compounds

Experimental procedure 10

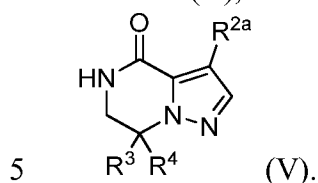
Intermediate compound according to Formula (II) (Reaction Scheme 10a) can be prepared following art known procedures, such as by subjecting an intermediate compound of Formula (Va) to a Suzuki type coupling reaction under conditions known to a skilled person. Such conditions include for example, reacting the intermediate compound of Formula (Va) with a suitable boron species, such as for example a boronic acid or a boronate ester, for example as described in Experimental procedure 2 hereinbefore, in the presence 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, NaHCO₃ and K₃PO₄, and in a suitable solvent, such as 1,4-dioxane, or a mixture of 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, in particular 80 °C, may enhance the reaction outcome. In Reaction Scheme 10a, all variables are defined as in Formula (I).



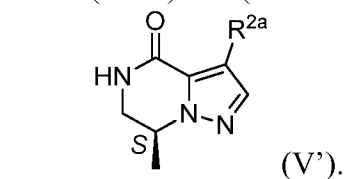
A skilled person can envisage that the reaction under Reaction Scheme 10a can also be performed under similar conditions, when the compound of Formula (Va) bears a bromo group in place of a iodo group. Such a reaction can be represented as in Reaction Scheme 10b, wherein the compound of Formula (V), wherein R^{2a} is halo, in particular bromo or iodo and all other variables are as defined in Formula (I), undergoes a Suzuki type coupling as described hereinbefore.



In particular aspect, the invention therefore relates to an intermediate compound of Formula (V), wherein R^{2a} is halo, in particular Br or I

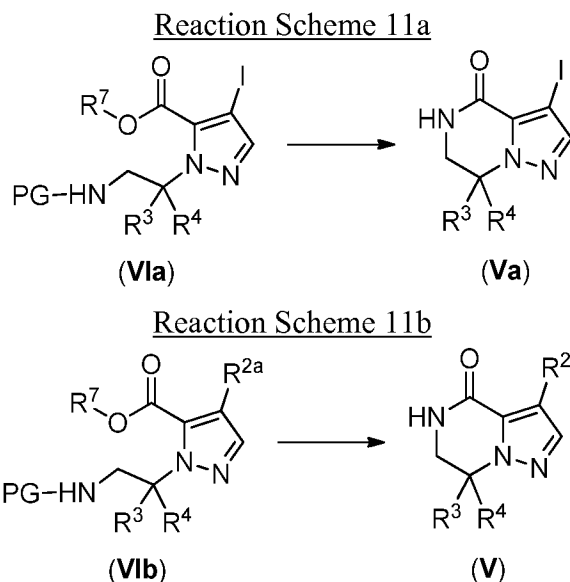


In a particular embodiment, the invention relates to an intermediate compound of Formula (V'), wherein R^{2a} is halo, in particular, Br (referred to herein as compound (I-13a) or I (referred to herein as compound (I-13))



Experimental procedure 11

Intermediate compound of Formula (Va) or of Formula (V) can be prepared by removal of the protecting group, for example a Boc group, in an intermediate of Formula (VIa) or of Formula (VIb), respectively, for example in the presence of acidic media, such as hydrochloric acid, in an inert solvent such as 1,4-dioxane or acetonitrile or ethyl acetate (EtOAc), under suitable reaction conditions, such as at a convenient temperature, such as from 15 to 80 °C, typically 80 °C or from 15-30 °C depending on the solvent system, for a period of time to ensure the completion of the reaction followed by treatment with a base such as Na_2CO_3 , K_2CO_3 or NaHCO_3 , under suitable reaction conditions, such as at a convenient temperature, typically ranging between 0 °C and 40 °C, in particular from 15 to 30 °C, for a period of time to ensure the completion of the reaction. In Reaction Schemes 11a and 11b, R^{2a} is halo, in particular bromo or iodo, R^7 is C_{1-4} alkyl, PG is a protecting group, for example Boc, and all other variables are defined as in Formula (I).



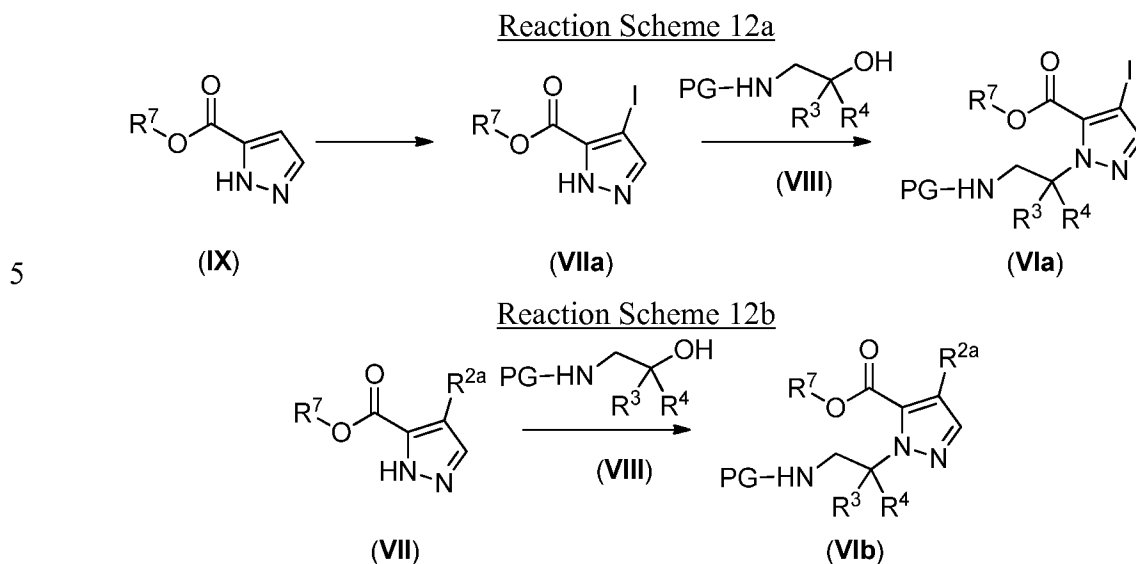
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Experimental procedure 12

Intermediate compound of Formula (VIa) or (VIb) wherein R^7 is C_{1-4} alkyl and PG is a protecting group, for example Boc, can be prepared by a Mitsunobu type reaction between an intermediate compound of Formula (VIIa) or (VII) respectively, and an appropriate alcohol of Formula (VIII), in the presence of a suitable triarylphosphine, such as triphenylphosphine typically 1.5 equivalents, or a suitable trialkylphosphine, and a suitable dialkyl azodicarboxylate reagent, such as di-*tert*-butyl azodicarboxylate or diethyl azodicarboxylate typically 1.5 equivalents, in a suitable inert solvent, such as tetrahydrofuran (THF), under suitable reaction conditions, such as at a convenient temperature, typically ranging 0 °C and rt, e.g. 20 °C, for a period of time to ensure the completion of the reaction. An intermediate compound of Formula (VIII) can be obtained commercially or synthesized according to literature procedures.

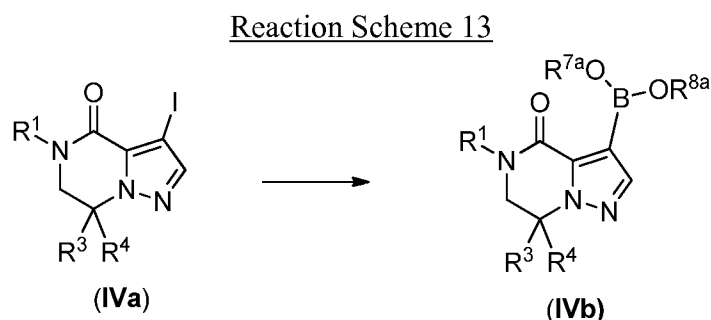
Intermediate compound of Formula (VIIa) wherein R^7 is C_{1-4} alkyl, can be prepared *via* a reaction of halogenation of intermediate of Formula (IX) with a halogenating reagent such as *N*-iodosuccinimide, in an inert solvent such as dichloromethane, under suitable reaction conditions, such as at a convenient temperature, typically rt, for a period of time to ensure the completion of the reaction. Intermediate compound of Formula (VII), wherein R^7 is methyl and R^{2a} is bromo, can be obtained commercially and is a particularly preferred material for use in the synthesis, including large scale, of a variety of final compounds of Formula (I) according to the general procedures described herein. An intermediate compound of Formula (IX) can be obtained commercially or synthesized according to literature procedures.

In Reaction Scheme 12a and 12b, R^{2a} is halo, in particular bromo or iodo, R^7 is C_{1-4} alkyl, PG is a protecting group, such as for example Boc, and all other variables are defined as in Formula (I).



Experimental procedure 13

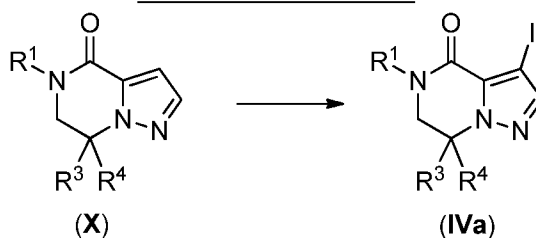
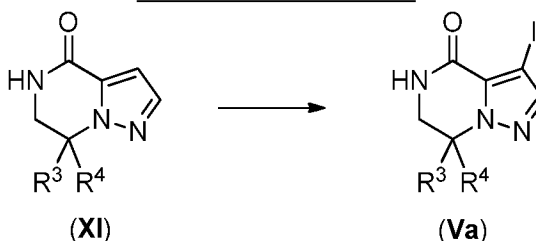
- Intermediate compound of Formula (IVb) can be prepared *via* a reaction of boronic ester or boronic acid formation starting from an intermediate of Formula (IVa) with a trans metallating agent such as for example BuLi or a Grignard reagent, a particular example of reagents includes isopropylmagnesium 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 or boronic acid are obtained. In Reaction Scheme 13, R^{7a} and R^{8a} are H or C_{1-4} alkyl or R^{7a} and R^{8a} are taken together to form for example a bivalent radical of formula – CH_2CH_2 –, $-\text{CH}_2\text{CH}_2\text{CH}_2-$ or $-\text{C}(\text{CH}_3)_2\text{C}(\text{CH}_3)_2-$, and all other variables are defined as in Formula (I).



Experimental procedure 14

Intermediate compound of Formula (IVa) can be prepared *via* a reaction of halogenation of an intermediate of Formula (X) 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 an analogous manner, intermediate compound of Formula (Va) can be prepared from intermediate of Formula (XI). In Reaction Schemes 14a and 14b, all variables are defined as in Formula (I).

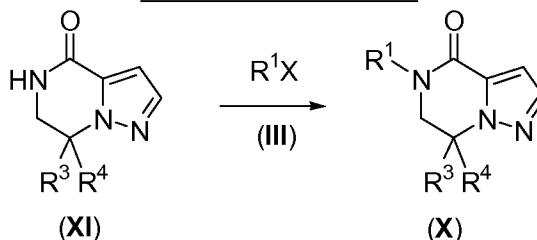
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Reaction Scheme 14aReaction Scheme 14b15 Experimental procedure 15

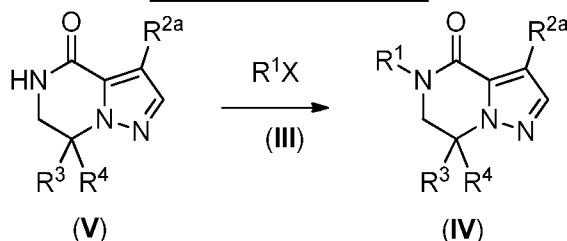
Intermediate compound of Formula (X) can be prepared by a coupling reaction of an intermediate compound of Formula (XI) with an appropriate aryl/heteroaryl halide of Formula (III) where X is halo with a suitable copper(I) catalyst such as copper(I) iodide, in the presence of a ligand, such as *N,N'*-dimethylethylenediamine, 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. In an analogous manner, intermediate compound of Formula (IV) can be prepared from intermediate of Formula (V). An intermediate compound of Formula (III) can be obtained commercially. In Reaction Schemes 15a and 15b, all variables are defined as in Formula (I) and R^{2a} is halo, in particular bromo or iodo.

25

Reaction Scheme 15a



Reaction Scheme 15b

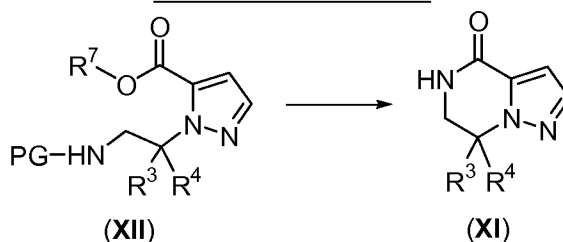


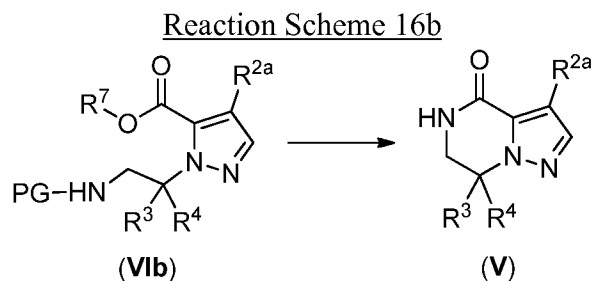
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Experimental procedure 16

Intermediate compound of Formula (XI) can be prepared by removal of the protecting group in an intermediate of Formula (XII), 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 an analogous manner, intermediate compound of Formula (V) can be prepared from intermediate of Formula (VIb). In Reaction Schemes 16a and 16b, R^{2a} is halo, in particular bromo or iodo, R⁷ is C₁₋₄alkyl, PG is a protecting group and all other variables are defined as in Formula (I).

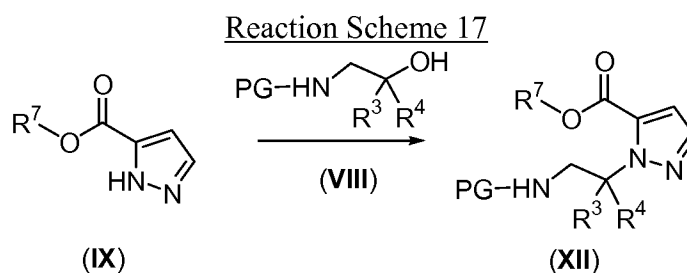
Reaction Scheme 16a





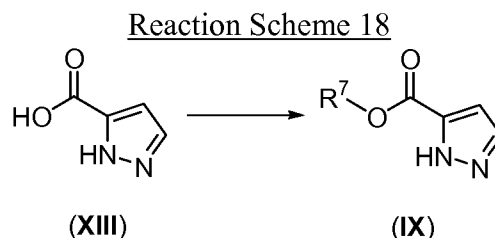
Experimental procedure 17

- 5 Intermediate compound of Formula (XII) wherein R^7 is C_{1-4} alkyl and PG is a protecting group, can be prepared by a Mitsunobu type reaction between a compound of Formula (IX) and an appropriate alcohol of Formula (VIII), 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,
- 10 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 (IX) and of Formula (VIII) can be obtained commercially or synthesized according to literature procedures. In Reaction Scheme 17, R^7 is C_{1-4} alkyl, PG is a protecting group and all other variables are defined
- 15 as in Formula (I).



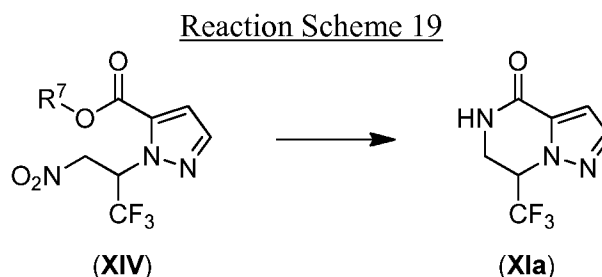
Experimental procedure 18

- 20 Intermediate compound of Formula (IX) wherein R^7 is C_{1-4} alkyl can be obtained by esterification of the commercially available intermediate compound of Formula (XIII), by methods known to the person skilled in the art, or may be commercially available. The reaction can be performed for example in the presence of an acidic agent, such as sulfuric acid, and an alcohol, such as EtOH, in a suitable solvent, such as
- 25 EtOH, under suitable reaction conditions, such as at a convenient temperature, typically between 80 °C and 100 °C, for a period of time to ensure the completion of the reaction. In Reaction Scheme 18, R^7 is C_{1-4} alkyl.



Experimental procedure 19

- 5 Intermediate compound of Formula (XI) wherein R^3 is H and R^4 is CF_3 herein referred to as compounds of Formula (XIa) can be prepared by hydrogenation of an intermediate of Formula (XIV) followed by one pot intramolecular cyclization, in the presence of a hydrogenation catalyst, such as Pd/C (palladium on carbon), under hydrogen atmosphere generated by using ammonium formate, in an inert solvent such as MeOH, 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 19, R^7 is C_{1-4} alkyl.

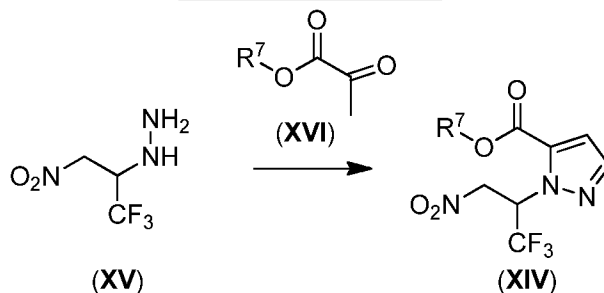


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Experimental procedure 20

- 20 Intermediate compound of Formula (XIV) wherein R^7 is C_{1-4} alkyl, can be prepared by an intermolecular reaction between an appropriate hydrazine of Formula (XV), in the presence of a suitable ketoester of Formula (XVI), such as ethyl pyruvate, in a suitable inert solvent, such as EtOH, 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 compound of Formula (XVI) can be obtained commercially or synthesized according to literature procedures. In Reaction Scheme 20, R^7 is C_{1-4} alkyl.

Reaction Scheme 20

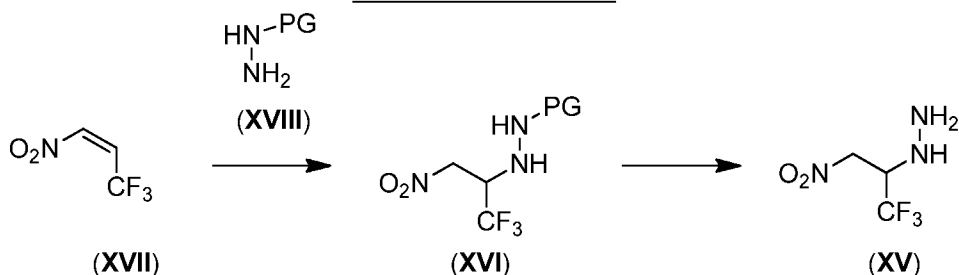


Experimental procedure 21

5 Intermediate compound of Formula (XV) can be prepared by a reaction of deprotection of a compound of Formula (XVI) following art known procedures. A compound of Formula (XV) can be obtained by removal of the protecting group such as for example a Boc protecting group in the compound of Formula (XVI), in the presence of acidic media, such as hydrochloric acid, in an inert solvent such as MeOH, 10 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 compound of Formula (XVI) can be obtained by addition of a protected hydrazine of Formula (XVIII) to 3,3,3-trifluoro-1-nitro-prop-1-ene (XVII) (prepared as described in *J. Fluorine Chem.* **2008**, 767-774). In Reaction Scheme 21, 15 PG is a protecting group, for example BOC.

Reaction Scheme 21



In order to obtain the HCl salt forms of the compounds, several procedures known 20 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, 4N HCl solution in dioxane, 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*.

25 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.

Pharmacology

5 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
10 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.

 As used herein, the term “treatment” is intended to refer to all processes,
15 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 (I), or a stereoisomeric form thereof, or an N-oxide thereof, or a
20 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 (I), or a stereoisomeric form thereof, or an N-oxide thereof, or a
25 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),
30 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 or prevention of, in particular treatment of, a condition in a mammal, including a human,
35 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 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 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), 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 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 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 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 diseases: 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.

In particular, the central nervous system disorder is a psychotic disorder selected from 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 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 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 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 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 amnestic disorder, such as substance-induced persisting amnestic 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 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.

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.

5 The fourth edition of the Diagnostic & Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association provides a diagnostic tool for the 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
10 medical and scientific progresses.

A skilled person will be familiar with alternative nomenclatures, nosologies, and 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”
15 (DSM-5TM) utilizes terms such as depressive disorders, in particular, major depressive disorder, persistent depressive disorder (dysthymia), substance-medication-induced 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
20 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 substance/medication-induced NCD; neurodevelopmental disorders, in particular, intellectual disability, specific learning disorder, neurodevelopmental motor disorder, communication disorder, and attention-deficit/hyperactivity disorder (ADHD);
25 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,
30 brief psychotic disorder, substance/medication-induced psychotic disorder; somatic 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
35 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
5 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
10 solvate thereof, 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
15 stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, for use in 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
20 stereoisomeric form thereof, or a pharmaceutically acceptable salt or a solvate thereof, for the 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
25 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.

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

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
35 animals, including humans, any one of the diseases mentioned hereinbefore.

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.

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.

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.

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.

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 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.

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 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 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 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 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 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 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.

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

10 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.

15 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
20 treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention.

25 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.

30 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
35 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.

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

20

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, "Boc" or "BOC" means *tert*-Butyloxycarbonyl; "CI" means chemical ionisation; "DAD" means diode-array detector; "THF" means tetrahydrofuran; "TEA" means triethylamine; "DIPE" means diisopropylether; "DMF" means *N,N*-dimethylformamide; "Et₂O" means diethylether; "EtOAc" means ethyl acetate; "DCM" means dichloromethane; "DMSO" means dimethylsulfoxide; "L" means liter; "LRMS" means low-resolution mass spectrometry/spectra; "HATU" means 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; "HPLC" means high performance liquid chromatography; "HRMS" means high-resolution mass spectrometry/spectra; "mL" or "ml" means milliliter; "NH₄Ac" means ammonium acetate; "EtOH" means ethanol; "ES" means electrospray; "iPrOH" means isopropanol; "iPrNH₂" means isopropylamine; "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; "SFC" means supercritical fluid chromatography; "sol." means solution.

- 5 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.).

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

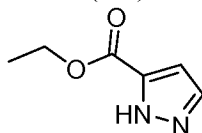
- Automated flash column chromatography was performed using ready-to-connect cartridges, on irregular silica gel, particle size 15-40 µm (normal phase disposable flash columns) on different flash systems: either a SPOT or LAFLASH systems from Armen Instrument, or PuriFlash® 430evo systems from Interchim, or 971-
15 FP systems from Agilent, or Isolera 1SV systems from Biotage.

- 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)
20 downfield from tetramethylsilane (TMS), which was used as internal standard.

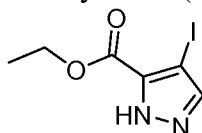
Synthesis of Intermediate Compounds

Intermediate 1 (I-1)

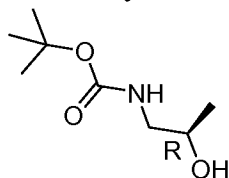
2H-Pyrazole-3-carboxylic acid ethyl ester (**I-1**)



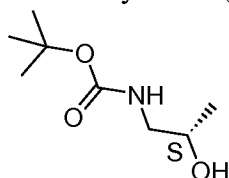
- 25 Sulfuric acid (10 mL, 187.6 mmol) was added to a solution of 1-H-pyrazole-3-carboxylic acid (1.93 g, 17.22 mmol) in EtOH (20 mL). The mixture was stirred at 90 °C for 15 h. Then it was allowed to cool to rt and the solvents were evaporated *in vacuo*. The residue was poured into water and the solution basified with K₂CO₃ and
30 extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent evaporated *in vacuo* to yield intermediate compound **I-1** as a white solid (2.28 g, 93 % purity, 94%) which was used in the following step without further purification.

Intermediate 2 (I-2)4-Iodo-2H-pyrazole-3-carboxylic acid ethyl ester (**I-2**)

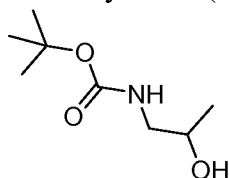
- Intermediate **I-1** (100 g, 0.68 mol), *N*-iodosuccinimide (213.5 g, 0.95 mol) were dissolved in DCM (2 L). The mixture was stirred at rt for 24 h. The mixture was treated with a sat. sol. of Na₂S₂O₃ and a sat. sol. of Na₂CO₃ and extracted with DCM. The organic layer was separated, dried (MgSO₄), filtered and the solvent evaporated *in vacuo* to yield intermediate compound **I-2** as a white solid (160 g, 85%).

Intermediate 3 (I-3)(2*R*-Hydroxy-propyl)-carbamic acid *tert*-butyl ester (**I-3**)

- Di-*tert*-butyl dicarbonate (58.1 g, 266.3 mmol) in DCM (50 mL) was added to a stirred solution of (*R*)-(-)-1-amino-2-propanol in DCM (50 mL) at 0 °C under nitrogen. The mixture was stirred at rt for 2 h. The mixture was diluted with cooled water and extracted with DCM. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated *in vacuo* to yield intermediate **I-3** as a colorless oil (47 g, quant.). The product was used in the next step without further purification.

Intermediate 4 (I-4)(2*S*-Hydroxy-propyl)-carbamic acid *tert*-butyl ester (**I-4**)

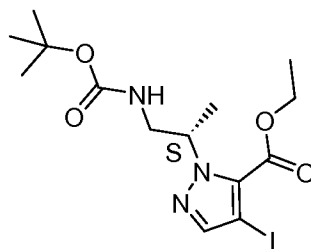
- Intermediate compound **I-4** was synthesized following a similar approach described for intermediate **I-3**. Starting from (*S*)-(-)-1-amino-2-propanol (3 mL, 38.1 mmol), intermediate compound **I-4** was obtained as a colorless oil (6.13 g, 89% purity, 82%), that solidified upon standing at rt.

Intermediate 5 (I-5)(2-Hydroxy-propyl)-carbamic acid *tert*-butyl ester (**I-5**)

Intermediate compound **I-5** was synthesized following a similar approach described for
 5 intermediate **I-3**. Starting from 1-amino-2-propanol (3 mL, 38.1 mmol), intermediate
 compound **I-5** was obtained as a colorless oil (6.69 g, 98%).

Intermediate 6 (I-6)

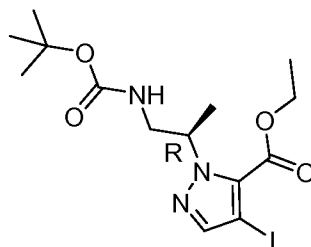
2-(2-*tert*-Butoxycarbonylamino-1*S*-methyl-ethyl)-4-iodo-2H-pyrazole-3-carboxylic
 10 acid ethyl ester (**I-6**)



Di-*tert*-butyl azodicarboxylate (4.67 g, 20.3 mmol) was added to a stirred solution of
 intermediate **I-2** (3 g, 11.28 mmol), intermediate **I-3** (4.44 g, 22.55 mmol) and
 triphenylphosphine (5.32 g, 20.3 mmol) in THF (56 mL) under nitrogen. The mixture
 15 was stirred at rt for 5 h. The solvent was evaporated *in vacuo* and the crude product was
 triturated with DIPE. The solid was filtered and the filtrate was evaporated *in vacuo*.
 The crude product was purified by flash column chromatography (silica; EtOAc in
 Heptane 0/100 to 30/70). The desired fractions were collected and the solvents
 evaporated *in vacuo* to give intermediate compound **I-6** as a colorless oil (4.9 g, 91%
 20 purity, 93%).

Intermediate 7 (I-7)

2-(2-*tert*-Butoxycarbonylamino-1*R*-methyl-ethyl)-4-iodo-2H-pyrazole-3-carboxylic
 acid ethyl ester (**I-7**)

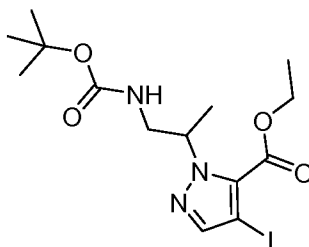


Intermediate compound **I-7** was synthesized following a similar approach described for intermediate **I-6**. Starting from intermediate **I-2** (1.18 g, 4.44 mmol) and intermediate **I-4** (1.75 g, 8.87 mmol), intermediate compound **I-7** was obtained as a white solid as two fractions (790 mg, 41%) and (900 mg, 86% purity, 41%).

5

Intermediate 8 (I-8)

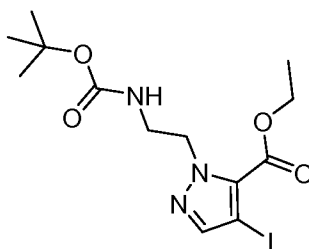
2-(2-*tert*-Butoxycarbonylamino-1-methyl-ethyl)-4-iodo-2H-pyrazole-3-carboxylic acid ethyl ester (**I-8**)



10 Intermediate compound **I-8** was synthesized following a similar approach described for intermediate **I-6**. Starting from intermediate **I-2** (2.87 g, 10.79 mmol) and intermediate **I-5** (3.78 g, 21.6 mmol), intermediate compound **I-8** was obtained as a colorless oil (3.46 g, 75%).

15 **Intermediate 9 (I-9)**

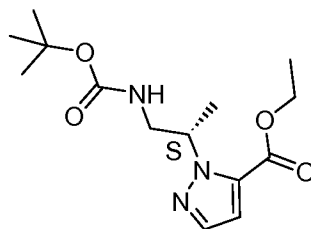
2-(2-*tert*-Butoxycarbonylamino-ethyl)-4-iodo-2H-pyrazole-3-carboxylic acid ethyl ester (**I-9**)



20 Intermediate compound **I-9** was synthesized following a similar approach described for intermediate **I-6**. Starting from intermediate **I-2** (3.18 g, 11.95 mmol) and *N*-(*tert*-butoxycarbonyl)ethanolamine (3.78 g, 23.9 mmol), intermediate compound **I-9** was obtained as a colorless oil (3.46 g, 75%).

Intermediate 10 (I-10)

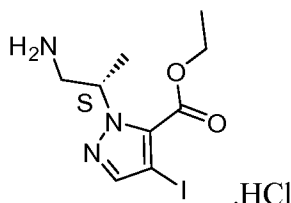
25 2-(2-*tert*-Butoxycarbonylamino-1*S*-methyl-ethyl)-2H-pyrazole-3-carboxylic acid ethyl ester (**I-10**)



Intermediate compound **I-10** was synthesized following a similar approach described for intermediate **I-6**. Starting from intermediate **I-1** (25.82 g, 184.25 mmol) and intermediate **I-3** (47.16 g, 239.5 mmol), intermediate compound **I-10** was obtained as a yellow oil (123 g, quant) which was used in the following step without further purification.

Intermediate 11 (I-11)

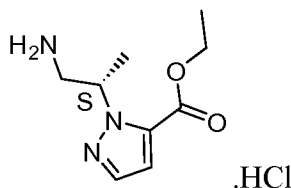
2-(2-Amino-1*S*-methyl-ethyl)-4-iodo-2*H*-pyrazole-3-carboxylic acid ethyl ester hydrochloride salt (**I-11**)



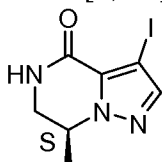
A 4M solution of HCl in 1,4-dioxane (10 mL, 40 mmol) was added to a solution of intermediate **I-6** (4.2 g, 9.63 mmol) in acetonitrile (20 mL). The mixture was stirred at 80 °C for 2 h. The solvent was evaporated *in vacuo* to yield intermediate compound **I-11** (3.5 g, 97%).

Intermediate 12 (I-12)

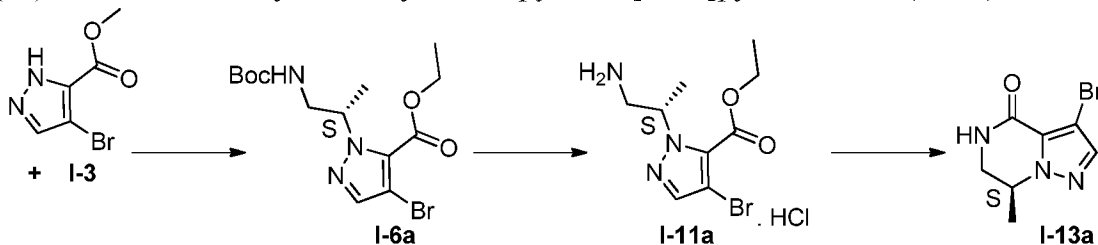
2-(2-Amino-1*S*-methyl-ethyl)-2*H*-pyrazole-3-carboxylic acid ethyl ester hydrochloride salt (**I-12**)



Intermediate compound **I-12** was synthesized following a similar approach described for intermediate **I-11**. Starting from intermediate **I-10** (54.79 g, 184.25 mmol) and a 4M solution of HCl in 1,4-dioxane (415 mL, 1.66 mol), intermediate compound **I-12** was obtained as a white solid (32.5 g, 82% purity, 75%) which was used in the following step without further purification.

Intermediate 13 (I-13)3-Iodo-7*S*-methyl-6,7-dihydro-5*H*-pyrazolo[1,5-*a*]pyrazin-4-one (**I-13**)

Intermediate **I-11** as HCl salt (180 g, 350.4 mmol) was dissolved in a sat. sol. of NaHCO₃ (2 L). The mixture was stirred at rt for 12 h. The mixture was diluted with water and extracted with DCM. The organic layers were separated, dried (Na₂SO₄), filtered and the solvents evaporated *in vacuo*. Then the residue was washed with *tert*-butyl methyl ether to yield intermediate compound **I-13** (92 g, 90%), mp 182.6-186.1°C. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.42 (d, *J*=6.65 Hz, 3 H) 3.26 - 3.35 (m, 1 H) 3.57 - 3.71 (m, 1 H) 4.44 - 4.60 (m, 1 H) 7.68 (s, 1 H) 8.26 (br. s., 1 H). LC-HRMS (ESI+) Calculated for C₇H₈IN₃O (M+H)⁺: 277.9790, Found: *m/z* 277.9796 (+0.6mDa), Rt = 0.76 min (Method 13, see table 2). [α] = +11.7° (589 nm, c 1.00 w/v %, CH₃OH, 25 °C).

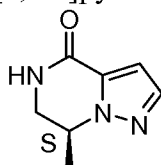
Intermediate 13a (I-13a)(7*S*)-3-Bromo-7-methyl-6,7-dihydro-5*H*-pyrazolo[1,5-*a*]pyrazin-4-one (**I-13a**)

Intermediate 13a was prepared in 71% yield according to the following general description of a synthesis performed at a large scale:
A mixture of methyl 4-bromo-1*H*-pyrazole-5-carboxylate (referred to as “pyrazole SM” herein) (1 eq.), triphenyl phosphine (1.2 eq.), **I-3** (1.2 eq.) and anhydrous THF (15 mL/g pyrazole SM) under nitrogen was cooled to 5-10 °C. Di-*tert*-butyl azodicarboxylate (1.2 eq.) was added in portions at 5-15 °C under nitrogen. The solution was heated to 20-30 °C and stirred at 20-30 °C for 2-3 h. The obtained solution was concentrated and co-evaporated with isopropyl acetate to remove THF to afford a solution of crude 4-bromo-1-[(1*S*)-1-[(1,1-dimethylethoxy)carbonyl]amino]ethyl]-1*H*-pyrazole-5-carboxylic acid methyl ester **I-6a** in isopropyl acetate (20 mL/g pyrazole SM). To the solution of **I-6a** was bubbled HCl gas at 15-30 °C until cleavage of the Boc protecting group was completed. The suspension was bubbled with nitrogen gas to

remove most of the HCl gas. The suspension was concentrated to a volume of about 5 mL/g pyrazole SM below 50 °C, and then isopropyl acetate (15 mL/g pyrazole SM) was added to the residue. Water (10 mL/g pyrazole SM) was added at 10-20 °C. The mixture was stirred at 10-20 °C for 20-30 min. The mixture was filtered and the aqueous layer was separated. The organic layer was extracted with water (2 mL/g pyrazole SM). The combined aqueous layers were washed with isopropyl acetate (2 x 10 mL/g pyrazole SM) to remove residual triphenylphosphine oxide. **I-11a** was obtained as an aqueous solution (6.25 mL/g pyrazole SM). To the aqueous solution of **I-11a** was added potassium carbonate (~1 g/g pyrazole SM) to adjust to pH=8-9 at 10-25 °C. The mixture was stirred at 10-25 °C for 5-6 h and solid **I-13a** precipitated. The suspension was cooled to 5-10 °C and stirred at 5-10 °C for 2-3 h, it was then filtered and washed with water (1 mL/g pyrazole SM) and heptanes (1 mL/g pyrazole SM), then dried in vacuo at 40-45 °C to afford **I-13a** as a white solid, mp. 196.12 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm 1.61 (d, *J*=6.36 Hz, 3 H) 3.48 (ddd, *J*=12.72, 7.22, 2.60 Hz, 1 H) 3.75 - 3.84 (m, 1 H) 4.49 - 4.59 (m, 1 H) 6.54 (br. s., 1 H) 7.56 (s, 1 H). LC-HRMS (ESI+) Calculated for C₇H₈BrN₃O (M+H)⁺: 229.9929, Found: *m/z* 229.9931 (+0.2mDa), Rt = 0.62 min (Method 13, see table 2). [α]_D²⁰ = +25.2 ° (589 nm, c 0.53 w/v %, DMF, 20 °C).

20 Intermediate 14 (I-14)

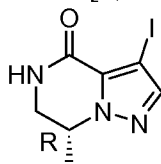
7*S*-Methyl-6,7-dihydro-5H-pyrazolo[1,5-*a*]pyrazin-4-one (**I-14**)



Intermediate compound **I-14** was synthesized following a similar approach described for intermediate **I-13**. Starting from intermediate **I-12** (32.5 g, 139.1 mmol), intermediate compound **I-14** was obtained as a solid (14.8 g, 70%).

Intermediate 15 (I-15)

3-Iodo-7*R*-methyl-6,7-dihydro-5H-pyrazolo[1,5-*a*]pyrazin-4-one (**I-15**)

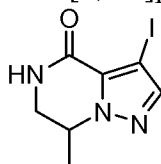


30 A 4M solution of HCl in 1,4-dioxane (2.3 mL, 9.2 mmol) was added to a solution of intermediate **I-7** (0.78 g, 1.84 mmol) in CH₃CN (8.3 mL). The mixture was stirred at 80 °C for 7 h. After Boc deprotection was complete, part of the solvent was evaporated *in*

vacuo and the solution was basified with a sat. sol. of NaHCO₃. The mixture was stirred for 16 h at rt. Then the mixture was diluted with water and extracted with DCM. The organic layers were separated, dried (MgSO₄), filtered and the solvents evaporated *in vacuo*. The solid was triturated with DIPE to yield intermediate compound **I-15** as a white solid (0.42 g, 82%).

Intermediate 16 (I-16)

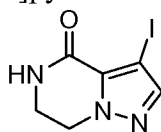
3-Iodo-7-methyl-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (**I-16**)



Intermediate compound **I-16** was synthesized following a similar approach described for intermediate **I-15**. Starting from intermediate **I-8** (3.46 g, 8.17 mmol), intermediate compound **I-16** was obtained as a white solid (1.87 g, 82%).

Intermediate 17 (I-17)

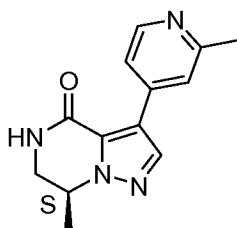
3-Iodo-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (**I-17**)



Intermediate compound **I-17** was synthesized following a similar approach described for intermediate **I-15**. Starting from intermediate **I-9** (4.89 g, 11.95 mmol), intermediate compound **I-17** was obtained as a white solid (1.87 g, 59%).

Intermediate 18 (I-18)

7*S*-Methyl-3-(2-methyl-pyridin-4-yl)-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (**I-18**)



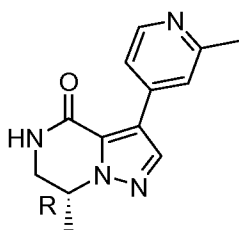
Pd(PPh₃)₄ (0.33 g, 0.29 mmol) was added to a stirred suspension of intermediate **I-13** (1.6 g, 5.77 mmol) and 2-picoline-4-boronic acid (0.95 g, 6.93 mmol) in 1,4-dioxane (8 mL) and a sat. sol. of NaHCO₃ (4 mL) in a sealed tube under nitrogen. The mixture was stirred at 100 °C for 16 h. Then the mixture 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 6/94). The desired fractions were collected and the solvents evaporated *in vacuo* to yield intermediate compound **I-18** as a white solid (1 g, 71%), mp 173.20 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm 1.67 (d, *J*=6.65 Hz, 3 H) 2.60 (s, 3 H) 3.52 (ddd, *J*=12.79, 7.15, 2.89 Hz, 1 H) 3.84 (dt, *J*=12.72, 4.00 Hz, 1 H) 4.57 - 4.66 (m, 1 H) 6.10 (br. s., 1 H) 7.51 (dd, *J*=5.20, 1.44 Hz, 1 H) 7.55 (s, 1 H) 7.78 (s, 1 H) 8.50 (d, *J*=5.20 Hz, 1 H). LC-HRMS (ESI+) Calculated for C₁₃H₁₄IN₄O (M+H)⁺: 243.1246, Found: *m/z* 243.1250 (+0.4mDa), Rt = 0.82 min (Method 13, see table 2). [α]_D = +32.8 ° (589 nm, c 0.52 w/v %, DMF, 20 °C).

Intermediate **I-18** was alternatively prepared in 70% yield according to the following general description of a synthesis performed at a large scale:
A mixture of **I-13a** (1 eq.), 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyridine (1.1 eq.), anhydrous potassium phosphate (2 eq.), DME (7.5 mL/g **I-13a**) and purified water (2.5 mL/g **I-13a**) was evacuated and backfilled with nitrogen 3 times. Triphenyl phosphine (0.261 eq.) and palladium (II) acetate (0.131 eq.) were added in one portion under nitrogen. The mixture was evacuated and backfilled with nitrogen 3 times again, it was heated to 75-80 °C and stirred at 75-80 °C for 12-15 h under nitrogen. The aqueous layer was separated at 60-70 °C and discarded, and then water (8 mL/g **I-13a**) was added to the organic layer. DME was removed by concentration below 40 °C. Isopropyl acetate (15 mL/g **I-13a**) was added, the pH of the mixture was adjusted to 1-2 with conc. HCl. The mixture was filtered and the filter cake was washed with water (1 mL/g **I-13a**), the aqueous layer was separated and the organic layer was extracted with water (2 mL/g **I-13a**). The combined aqueous layers were washed with Isopropyl acetate (2 x 15 mL/g **I-13a**). The aqueous layer was concentrated to remove residual DME and isopropyl acetate. MTBE (2 mL/g **I-13a**) was added and the mixture was cooled to 0-5 °C, stirred at 0-5 °C for 2-3 h. **I-18** was filtered, washed with cooled water (1 mL/g **I-13a**), and dried in vacuum at 45-50 °C to afford **I-18** as an off-white solid.

Intermediate 19 (I-19)

7*R*-Methyl-3-(2-methyl-pyridin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,5-*a*]pyrazin-4-one (**I-19**)

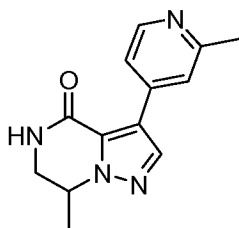


Intermediate compound **I-19** was synthesized following a similar approach described for intermediate **I-18**. Starting from intermediate **I-15** (0.62 g, 2.24 mmol), intermediate compound **I-19** was obtained as a white solid (0.38 g, 70%).

5

Intermediate 20 (I-20)

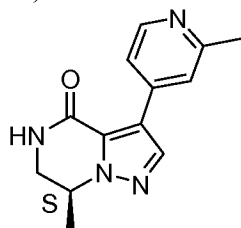
7-Methyl-3-(2-methyl-pyridin-4-yl)-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (**I-20**)



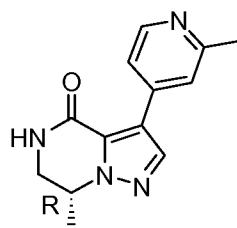
10 Intermediate compound **I-20** was synthesized following a similar approach described for intermediate **I-18**. Starting from intermediate **I-16** (846 mg, 3.05 mmol), intermediate compound **I-20** was obtained as a yellowish solid (585 mg, 79%).

Intermediate 18 (I-18) and intermediate 19 (I-19)

15 7*S*-Methyl-3-(2-methyl-pyridin-4-yl)-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (**I-18**) and 7*R*-Methyl-3-(2-methyl-pyridin-4-yl)-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (**I-19**).



(**I-18**)

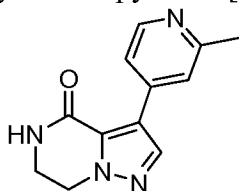


(**I-19**)

20 Intermediate **I-20** (975 mg, 4.02 mmol) was purified by RP HPLC (Stationary phase: irregular bare silica 40 g), Mobile phase: 0.5% NH₄OH, 95% DCM, 5% MeOH) then by chiral SFC ((Stationary phase: CHIRALCEL® OD-H 5μm 250x20mm), (Mobile phase: 75% CO₂, 25% iPrOH (0.3% iPrNH₂)) to yield intermediate compound **I-18** (390 mg) and intermediate compound **I-19** (395 mg).

Intermediate 21 (I-21)

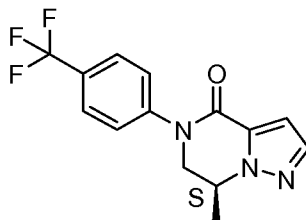
3-(2-Methyl-pyridin-4-yl)-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (**I-21**)



Intermediate compound **I-21** was synthesized following a similar approach described for intermediate **I-18**. Starting from intermediate **I-17** (908 mg, 3.45 mmol), intermediate compound **I-21** was obtained as a white solid (0.5 g, 63%).

Intermediate 22 (I-22)

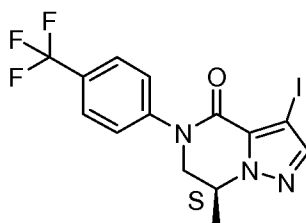
7*S*-Methyl-5-(4-trifluoromethyl-phenyl)-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (**I-22**)



A mixture of intermediate **I-14** (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 intermediate compound **I-22** as a pale yellow oil (9.6 g, 98%).

Intermediate 23 (I-23)

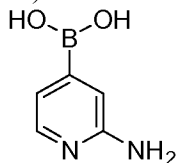
3-Iodo-7*S*-methyl-5-(4-trifluoromethyl-phenyl)-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (**I-23**)



- Iodine (11.55 g, 45.5 mmol) was added to a solution of intermediate **I-22** (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
- 5 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
- 10 yield intermediate compound **I-23** as a solid (24.8 g, 90%).

Intermediate 24 (I-24)

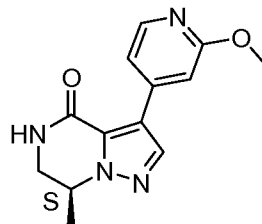
2-Amino-pyridine-4-boronic acid (**I-24**)



- 15 2-Amino-4-chloropyridine (3g, 23.34 mmol) was added to a mixture of bis(pinacolato)diboron (17.78 g, 70.01 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.38 g, 0.93 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.21 g, 0.23 mmol) and potassium acetate (3.89 g, 39.67 mmol) in 1,4-dioxane (78 mL) under nitrogen atmosphere. The resulting mixture was stirred at 100 °C for 3 h.
- 20 The hot reaction mixture was filtered through diatomaceous earth and washed with EtOAc. The organic layer was evaporated *in vacuo*. The residue was precipitated with DIPE to yield intermediate compound **I-24** as a white solid (5.84 g, quant.) that was used in the next reaction step without further purification.

Intermediate 25 (I-25)

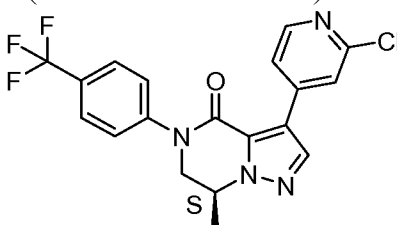
3-(2-Methoxy-pyridin-4-yl)-7*S*-methyl-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (I-25)



- 5 Pd(PPh₃)₄ (0.42 g, 0.36 mmol) was added to a stirred suspension of intermediate **I-13** (2 g, 7.22 mmol) and 2-methoxypyridine-4-boronic acid (1.77 g, 11.55 mmol) in 1,4-dioxane (16 mL) and a sat. sol. of NaHCO₃ (8 mL) in a sealed tube under nitrogen atmosphere. The mixture was stirred at 100 °C for 3 days. Then the mixture was diluted with H₂O and extracted with DCM. The organic layer was separated, dried (Na₂SO₄),
10 filtered and the solvent evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 6/94). The desired fractions were collected and the solvents evaporated *in vacuo* to yield intermediate compound **I-25** as a pale brown solid (1.6 g, 86%).

15 **Intermediate 26 and final compound 215 (I-26 and Co. No. 215)**

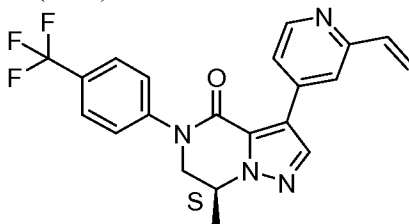
3-(2-Chloro-pyridin-4-yl)-7*S*-methyl-5-(4-trifluoromethyl-phenyl)-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (**I-26** and **Co. No. 215**)



- This reaction was divided in four batches to a combined total amount indicated herein
20 and combined for workup and purification. Pd(PPh₃)₄ (401 mg, 0.35 mmol) was added to a stirred suspension of intermediate **I-23** (2.92 g, 6.94 mmol) and 2-chloropyridine-4-boronic acid (1.42 g, 9.02 mmol) in 1,4-dioxane (39 mL) and a sat. sol. of NaHCO₃ (19.5 mL). The mixture was stirred at 150 °C for 10 min under microwave irradiation. Then the mixture was diluted with H₂O and extracted with DCM. The organic layer
25 was separated, dried (Na₂SO₄), filtered and the solvent evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; EtOAc in DCM 0/100 to 20/80). The desired fractions were collected and the solvents evaporated *in vacuo* to yield intermediate compound **I-26** as a yellow solid (1.84 g, 65%).

Intermediate 27 (I-27)

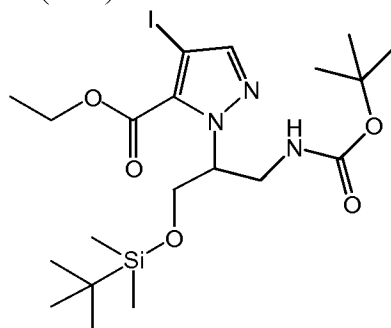
7*S*-Methyl-5-(4-trifluoromethyl-phenyl)-3-(2-vinyl-pyridin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,5-*a*]pyrazin-4-one (**I-27**)



- 5 Pd(PPh₃)₄ (51 mg, 0.044 mmol) was added to a stirred suspension of intermediate **I-26** (600 mg, 1.48 mmol) and vinylboronic acid pinacolester (0.325 mL, 1.92 mmol) in 1,4-dioxane (10 mL) and a sat. sol. of NaHCO₃ (5 mL). The mixture was stirred at 150 °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
- 10 solvent 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 intermediate compound **I-27** as a yellow oil (0.53 g, 90%).

Intermediate 28 (I-28)

Ethyl 2-[1-[(*tert*-butoxycarbonylamino)methyl]-2-[*tert*-butyl(dimethyl)silyl]oxy-ethyl]-4-iodo-pyrazole-3-carboxylate (**I-28**)

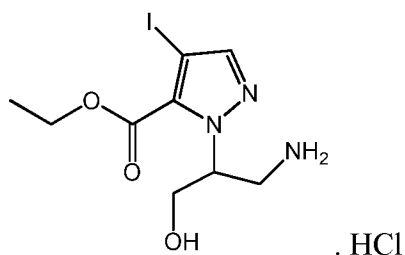


- Di-*tert*-butyl azodicarboxylate (1.97 g, 8.53 mmol) was added to a stirred solution of 4-iodo-1*H*-pyrazole-3-carboxylic acid ethyl ester (1.26 g, 4.74 mmol), [3-(*tert*-butyldimethylsilyloxy)-2-hydroxypropyl]carbamic acid *tert*-butyl ester (2.90 g, 9.48 mmol) and triphenylphosphine (2.24 g, 8.53 mmol) in THF (23.6 mL) under nitrogen atmosphere. The mixture was stirred at rt for 2.5 h. The solvent was evaporated and the residue was treated with DIPE. The solid (Ph₃PO) was filtered off and the filtrate was
- 20 evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; DCM in Heptane 50/50 to 100/0 then EtOAc in DCM 0/100 to 3/97). The
- 25

desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **I-28** (2.57 g, 98%) as a colorless oil.

Intermediate 29 (I-29)

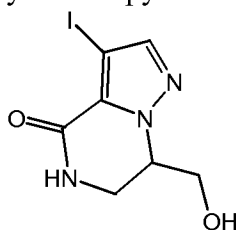
- 5 Ethyl 2-[1-(aminomethyl)-2-hydroxy-ethyl]-4-iodo-pyrazole-3-carboxylate hydrochloride salt (**I-29**)



- 10 Hydrochloric acid (4 M in 1,4-dioxane, 5.80 mL, 23.21 mmol) was added to a stirred solution of intermediate **I-28** (2.57 g, 4.64 mmol) in CH₃CN (21 mL). The mixture was stirred at rt for 1 h. The mixture was concentrated *in vacuo* to yield intermediate compound **I-29** (1.69 g) as a beige solid which was used in the next step without any further purification.

Intermediate 30 (I-30)

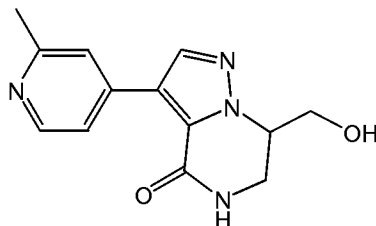
- 15 7-(Hydroxymethyl)-3-iodo-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (**I-30**)



- 20 TEA (1.38 mL, 9.93 mmol) was added to a stirred solution of intermediate **I-29** (1.68 g, 4.48 mmol) in DMF (16.8 mL). The mixture was stirred at rt for 3 h. The mixture was treated with a sat. sol. of NaHCO₃ and EtOAc and filtered. The filtrate was partitioned between water and EtOAc and extracted with EtOAc and EtOAc/THF. The organic layer was separated, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 20/80). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **I-30** (0.88 g, 67%) as a white solid.

Intermediate 31 (I-31)

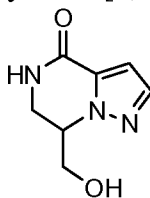
7-(Hydroxymethyl)-3-(2-methyl-4-pyridyl)-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (**I-31**)



- 5 Pd(PPh₃)₄ (134 mg, 0.12 mmol) was added to a stirred suspension of intermediate **I-30** (0.88 g, 3.00 mmol) and 2-picoline-4-boronic acid (658 mg, 3.00 mmol) in 1,4-dioxane (15.4 mL) and a sat. aq. NaHCO₃ (10 mL) under nitrogen atmosphere. The mixture was stirred at 90 °C for 16 h. Then additional 2-picoline-4-boronic acid (263 mg, 1.20 mmol) and Pd(PPh₃)₄ (35 mg, 0.03 mmol) were added at rt and under nitrogen. The mixture was stirred at 100 °C for 7 h. Then the mixture was diluted with water 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 10/90). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **I-31** (347 mg, 45%) as pale orange solid.

Intermediate 32 (I-32)

7-(Hydroxymethyl)-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (**I-32**)

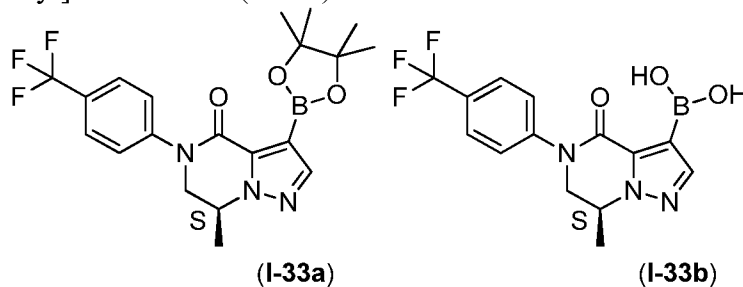


- 20 Palladium 10% on charcoal (907 mg, 0.0853 mmol) was added to a solution of intermediate **I-30** (2.5 g, 8.53 mmol) and TEA (4.74 mL, 34.12 mmol) in DMF (125 mL) under nitrogen atmosphere. The mixture was hydrogenated (at atmospheric pressure) at rt for 16 h. The mixture was filtered through a pad of diatomaceous earth and the residue was washed with MeOH and 7M solution of ammonia in MeOH. The filtrate was concentrated *in vacuo* and the residue was treated with a small amount of water and extracted with EtOAc/THF. The organic layer was separated, dried (Na₂SO₄), filtered and concentrated *in vacuo* to yield intermediate compound **I-32** (1.4 g, quant.) as a brown oil.

Intermediate 33a (I-33a) and intermediate 33b (I-33b)

(7*S*)-7-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**I-33a**)

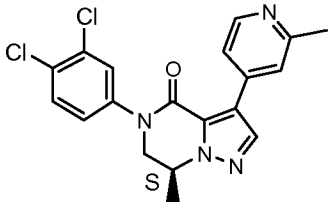
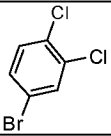
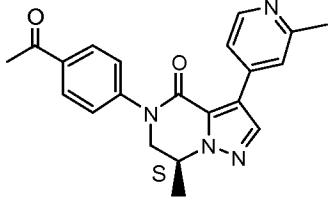
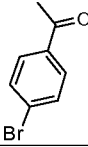
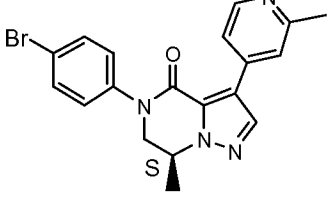
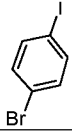
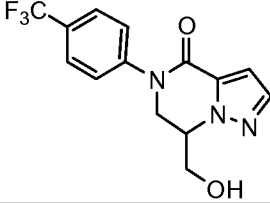
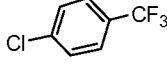
and [(7*S*)-7-methyl-4-oxo-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo-
5 [1,5-*a*]pyrazin-3-yl]boronic acid (**I-33b**)



Isopropylmagnesium chloride lithium chloride complex (1.3M solution, 32.9 mL, 42.7 mmol) was added dropwise to a stirred solution of intermediate **I-23** (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 intermediate compound **I-33a** (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 in DIPE/Heptane, filtered and dried to yield intermediate compound **I-33b** (1 g, 10%) as a white solid.

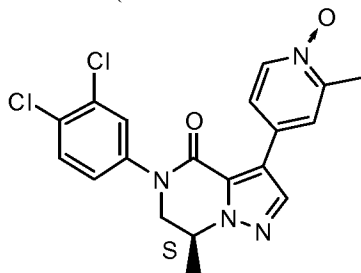
Intermediates I-34 to I-37

The following intermediates were synthesized by following an analogous synthetic procedure as reported for **intermediate 22**.

Structure	Intermediate number	Starting materials
	I-34	I-18
		
	I-35	I-18
		
	I-36	I-18
		
	I-37	I-32
		

Intermediate 38 and final compound 170

(7*S*)-5-(3,4-dichlorophenyl)-7-methyl-3-(2-methyl-1-oxido-pyridin-1-ium-4-yl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**I-38** and Co. No. 170)



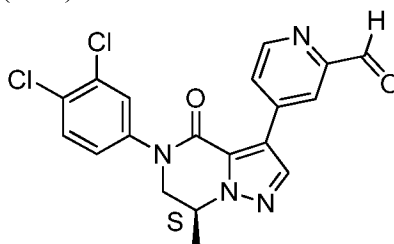
5

3-Chloroperoxybenzoic acid (2.03 g, 11.77 mmol) was added to a stirred solution of intermediate **I-34** (2.28 g, 5.88 mmol) in DCM (37 mL) at 0 °C. The mixture was allowed to reach rt and stirred at rt for 2 h. The mixture was treated with a sat sol. of Na₂CO₃ and diluted with DCM. The organic layer was separated, dried (Na₂SO₄),

10 filtered and the solvents evaporated *in vacuo* to yield intermediate compound **I-38** (1.84 g, 77%) that was used in the next step without any further purification.

Intermediate 39 (I-39)

4-[(7*S*)-5-(3,4-dichlorophenyl)-7-methyl-4-oxo-6,7-dihydropyrazolo[1,5-*a*]pyrazin-3-yl]pyridine-2-carbaldehyde (**I-39**)



5

Manganese dioxide (2.39 g, 27.57 mmol) was added to a solution of final compound 125 (**E-14**) (1.11 g, 2.75 mmol) in chloroform (11.7 mL). The mixture was stirred at rt for 16 h, at 60 °C for 5 h and then at rt for 16 h. Then, the mixture was filtered through a pad of diatomaceous earth and washed with DCM. The solvent was 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 intermediate compound **I-39** (537 mg, 48%) as a pale yellow solid.

10

Intermediate 40 (I-40)

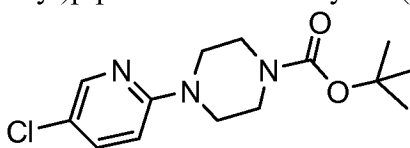
The following intermediate was synthesized by following an analogous synthetic procedure as reported for **intermediate 39**.

15

Structure	Intermediate number	Starting material
	I-40	I-37

Intermediate 41 (I-41)

tert-Butyl 4-(5-chloro-2-pyridyl)piperazine-1-carboxylate (**I-41**)



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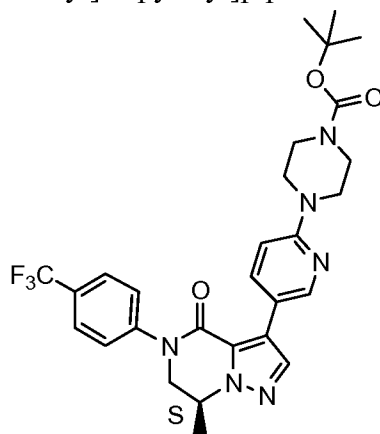
A mixture of 2-bromo-5-chloropyridine (1.5 g, 7.79 mmol), 1-BOC-piperazine (2.18 g, 11.69 mmol), sodium *tert*-butoxide (1.49 g, 15.59 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.451 g, 0.78 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.357 g, 0.390 mmol) in toluene (25 mL) was stirred at 120 °C for 16 h. The mixture was poured into water, and extracted with

25

EtOAc. The mixture was filtered through a short pad of diatomaceous earth. The organic layer was separated, washed with water and brine, dried (MgSO₄) and evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc in DCM 0/100 to 20/80). The desired fractions were collected and
5 evaporated *in vacuo* to yield intermediate compound **I-41** (0.888 g, 38%) as an orange solid.

Intermediate 42 (I-42)

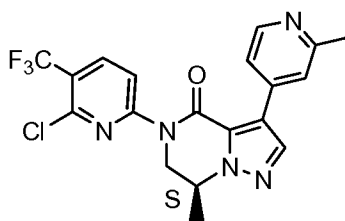
tert-Butyl 4-[5-[(7*S*)-7-methyl-4-oxo-5-[4-(trifluoromethyl)phenyl]-6,7-
10 dihydropyrazolo[1,5-*a*]pyrazin-3-yl]-2-pyridyl]piperazine-1-carboxylate (**I-42**)



A suspension of intermediate **I-41** (478 mg, 1.60 mmol), intermediate **I-33a** (653 mg, 1.55 mmol), palladium(II) acetate (7 mg, 0.032 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (26 mg, 0.064 mmol) and K₂CO₃ (554 mg, 4.013 mmol) in CH₃CN
15 (1.6 mL) and H₂O (2.5 mL) was flushed with nitrogen for a few minutes and the mixture was stirred at 80 °C for 24 h. Then the mixture was diluted with H₂O 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 DCM 0/100 to 50/50). The desired fractions were
20 collected and evaporated *in vacuo* to yield intermediate compound **I-42** (663 mg, 74%) as a yellow oil.

Intermediate 43 and final compound 188

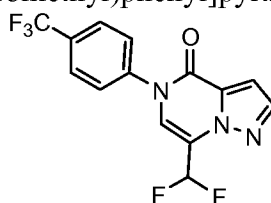
(7*S*)-5-[6-chloro-5-(trifluoromethyl)-2-pyridyl]-7-methyl-3-(2-methyl-4-pyridyl)-6,7-
25 dihydropyrazolo[1,5-*a*]pyrazin-4-one (**I-43** and **Co. No. 188**)



Pd(PPh₃)₄ (47 mg, 0.041 mmol) was added to a stirred suspension of intermediate **I-18** (100 mg, 0.413 mmol), 2,6-dichloro-3-(trifluoromethyl)pyridine (86 μ L, 0.620 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (47 mg, 0.082 mmol), Cs₂CO₃ (269 mg, 0.825 mmol) in 1,4-dioxane (3 mL) in a sealed tube and under nitrogen. The mixture was stirred at 120 °C for 4 h. The mixture was filtered through a pad of diatomaceous earth and washed with DCM. The filtrate was 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 concentrated *in vacuo*. Then the product was triturated with Et₂O and filtered to yield intermediate compound **I-43** (71 mg, 40%) as a white solid.

Intermediate 44 (I-44)

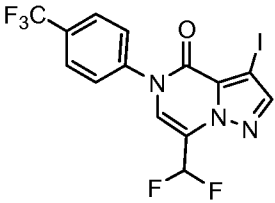
7-(Difluoromethyl)-5-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrazin-4-one (**I-44**)



Diethylaminosulfur trifluoride (0.373 mL, 3.866 mmol) was added to a stirred solution of intermediate **I-40** (297 mg, 0.966 mmol) in DCM (33 mL) at 0 °C. The mixture was allowed to warm to rt and stirred for 5 h. Then additional diethylaminosulfur trifluoride (0.355 mL, 2.9 mmol) was added at 0 °C and the mixture was stirred at rt for 20 h. The mixture was treated with water and extracted with DCM. The organic layer was separated, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica; DCM). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **I-44** (258 mg, 81%) as a colorless oil.

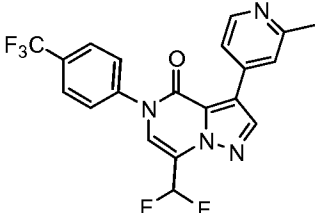
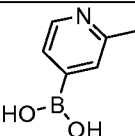
Intermediate 45 (I-45)

The following intermediate was synthesized by following an analogous synthetic procedure as reported for **intermediate 23**.

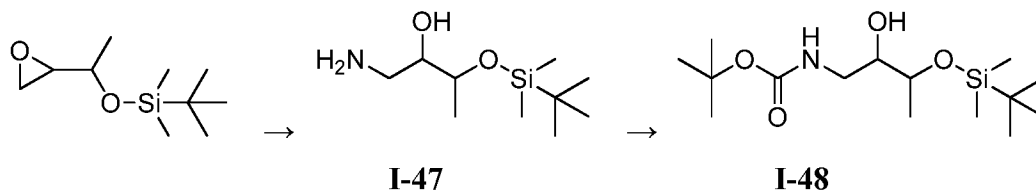
Structure	Intermediate number	Starting materials
	I-45	I-44

Intermediate 46 (I-46)

The following intermediate was synthesized by following an analogous synthetic procedure as reported for **intermediate 18**.

Structure	Intermediate number	Starting materials
	I-46	I-45 

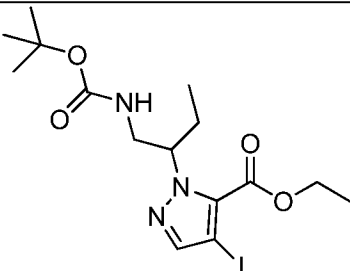
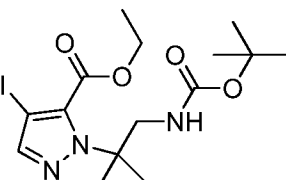
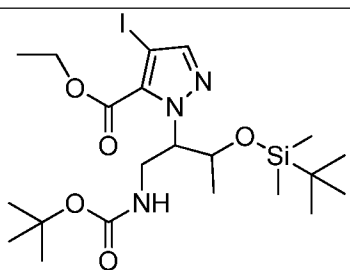
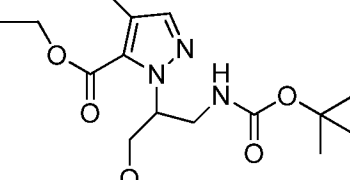
5

Intermediates 47 and 48 (I-47 and I-48)

- i) NH_3 (28% in water, 54 mL) was added over 2-[1-[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-oxirane (4.73 g, 23.373 mmol) and the mixture was stirred at 120 °C for 40 min under microwave irradiation. The solvent was then concentrated *in vacuo* to yield intermediate compound **I-47** as an orange oil (3.298 g, 64%).
- 10 ii) Intermediate **I-48** was synthesized following an analogous synthetic procedure as reported for **intermediate I-3**. Starting from intermediate **I-47** (3.269 g, 14.9 mmol), intermediate compound **I-48** was obtained as a colorless oil (4.642 g, 97.5%).
- 15

Intermediates 49-52 (I-49 to I-52)

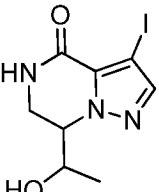
- The following intermediates were synthesized by following an analogous synthetic procedure as reported for **intermediate 6**.
- 20

Structure	Intermediate number	Starting materials
	I-49	I-2
		<i>N</i> -(2-hydroxybutyl)-carbamic acid 1,1-dimethylethyl ester
	I-50	I-2
		<i>N</i> -(2-hydroxy-2-methylpropyl)-carbamic acid 1,1-dimethylethyl ester
	I-51	I-2
		I-48
	I-52	I-2
		<i>tert</i> -butyl <i>N</i> -(2-hydroxy-3-methoxypropyl)carbamate

Intermediate 53 (I-53)

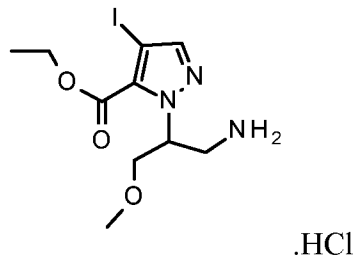
The following intermediate was synthesized following the procedure for the synthesis of intermediate **I-29**, followed by the procedure for the synthesis of intermediate **I-30**.

5

Structure	Intermediate number	Starting materials
	I-53	I-51

Intermediate 54 (I-54)

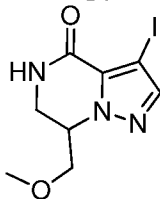
Ethyl 2-[1-(aminomethyl)-2-methoxy-ethyl]-4-iodo-pyrazole-3-carboxylate (**I-54**)



- 5 HCl (4 M in dioxane, 2.2 mL, 8.82 mmol) was added to a solution of intermediate **I-52** (0.8 g, 1.765 mmol) in CH₃CN (8 mL). The mixture was stirred at rt for 1 h and then the solvent was concentrated *in vacuo* to give intermediate compound **I-54** (700 mg, 87%) as a cream solid.

10 **Intermediate 55 (I-55)**

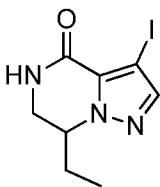
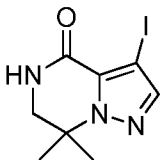
3-Iodo-7-(methoxymethyl)-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (**I-55**)



- Et₃N (0.55 mL, 3.98 mmol) was added to a solution of intermediate **I-54** (0.7 g, 1.80 mmol) in DMF (6.7 mL). The mixture was stirred at rt for 3 h then neutralized with a sat. sol. of NaHCO₃ and extracted with DCM. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated *in vacuo* to give intermediate compound **I-55** (440 mg, 80%) as a white solid.

Intermediates 56 and 57 (I-56 and I-57)

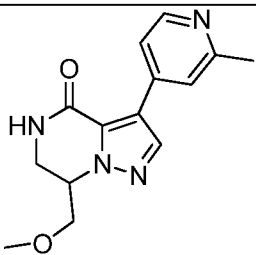
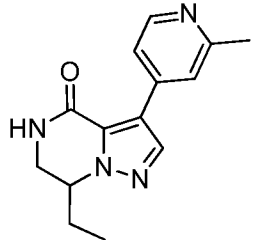
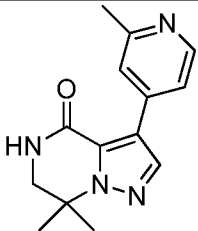
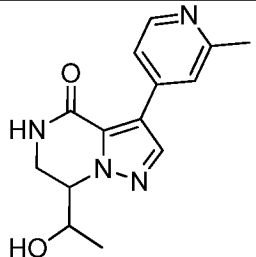
- 20 The following intermediates were synthesized by following an analogous synthetic procedure as that reported for **intermediate 15**.

Structure	Intermediate number	Starting material
	I-56	I-49
	I-57	I-50

Intermediates 58-61 (I-58 to I-61)

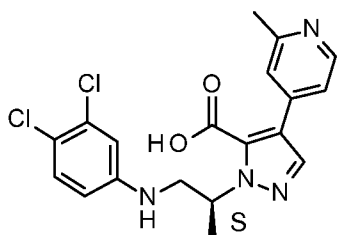
The following intermediates were synthesized by following an analogous synthetic procedure as reported for **intermediate 25**.

5

Structure	Intermediate number	Starting materials
	I-58	I-55
		2-picoline-4-boronic acid
	I-59	I-56
		2-picoline-4-boronic acid
	I-60	I-57
		2-picoline-4-boronic acid
	I-61	I-53
		2-picoline-4-boronic acid

Intermediate 62 (I-62)

2-[(1*S*)-2-(3,4-dichloroanilino)-1-methyl-ethyl]-4-(2-methyl-4-pyridyl)pyrazole-3-carboxylic acid (**I-62**)

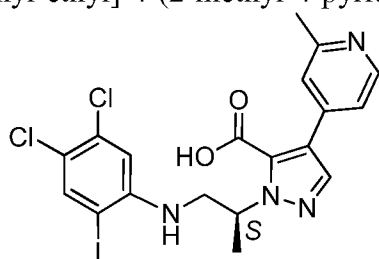
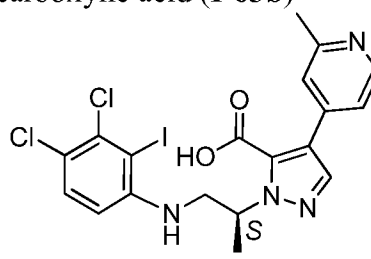


5

Sodium hydride (60% dispersion in mineral oil, 20 mg, 0.344 mmol) was added to a solution of compound **Co. No. 6a** (200 mg, 0.516 mmol) in DMF (4 mL) and the mixture was stirred at 60 °C for 24 h. Then more sodium hydride (60% dispersion in mineral oil, 11 mg, 0.172 mmol) was added and the mixture was stirred at 60 °C for 3 h. Then, the mixture was quenched with a NH₄Cl sat. sol. and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvents evaporated *in vacuo* to give intermediate compound **I-62** (230 mg, quantitative) as a solid which was used in the next step without further purification.

15 **Intermediate 63 (I-63)**

2-[(1*S*)-2-(4,5-dichloro-2-iodo-anilino)-1-methyl-ethyl]-4-(2-methyl-4-pyridyl)pyrazole-3-carboxylic acid (**I-63a**) and 2-[(1*S*)-2-(3,4-dichloro-2-iodo-anilino)-1-methyl-ethyl]-4-(2-methyl-4-pyridyl)pyrazole-3-carboxylic acid (**I-63b**)

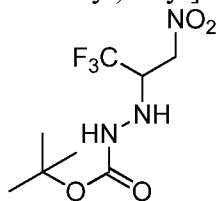
**(I-63a)****(I-63b)**

N-iodosuccinimide (124 mg, 0.552 mmol) was added to a solution of intermediate compound **I-62** (224 mg, 0.5523 mmol) in chloroform (5 mL) and the mixture was stirred at rt for 3 h. Then more *N*-iodosuccinimide (62 mg, 0.277 mmol) was added and the mixture was stirred at rt for 18 h. Then the reaction was quenched with a sat. sol. of Na₂SO₃ and extracted with DCM. The organic layer was separated, dried (MgSO₄), filtered and the solvent evaporated *in vacuo* to give a mixture of intermediates compounds **I-63a** and **I-63b** (240 mg, 41%) which was used in next step without further purification.

25

Intermediate 64 (I-64)

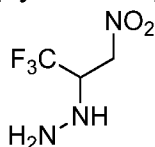
tert-Butyl *N*-[[2,2,2-trifluoro-1-(nitromethyl)ethyl]amino]carbamate (**I-64**)



- 5 *tert*-Butyl carbazate (281 mg, 2.13 mmol) was added to a stirred solution of 3,3,3-trifluoro-1-nitro-prop-1-ene (prepared as described in *J. Fluorine Chem.* **2008**, 767-774) (73 μ L, 0.709 mmol) in MeOH (3.1 mL) at rt. The mixture was stirred for 1 h and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc in Heptane 40/60 to 60/40) to yield intermediate
- 10 compound **I-64** (200 mg, quant.)

Intermediate 65 (I-65)

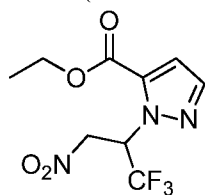
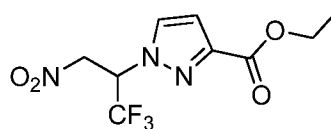
[2,2,2-Trifluoro-1-(nitromethyl)ethyl]hydrazine hydrochloride salt (**I-65**)



- 15 HCl (6M in 1,4-dioxane, 10.5 mL, 42 mmol) was added to a solution of intermediate **I-64** (1.15 g, 4.2 mmol) in MeOH (10 mL) at rt. The mixture was stirred for 2 h and the solvents were evaporated *in vacuo* to yield intermediate compound **I-65** (880 mg, quant.) that was used in the next step without further purification.

Intermediate 66 (I-66)

Ethyl 2-[2,2,2-trifluoro-1-(nitromethyl)ethyl]pyrazole-3-carboxylate (**I-66a**) and ethyl 1-[2,2,2-trifluoro-1-(nitromethyl)ethyl]pyrazole-3-carboxylate (**I-66b**)

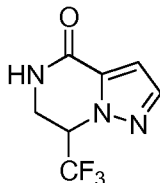
**I-66a****I-66b**

- 25 Ethyl pyruvate (77 μ L, 0.692 mmol) and *N,N*-dimethylformamide dimethyl acetal (92 μ L, 0.692 mmol) were stirred at rt for 16 h. The dark red/brown solution was added to a solution of intermediate **I-65** (145 mg, 0.692 mmol) in EtOH (2 mL). The mixture was stirred at 85 $^{\circ}$ C for 3 h. The solvent was concentrated *in vacuo*. The crude product was

purified by flash column chromatography (silica; EtOAc in Heptane 30/70 to 60/40) to yield intermediate compounds **I-66a** (78 mg, 40%) and **I-66b** (54 mg, 28%).

Intermediate 67 (I-67)

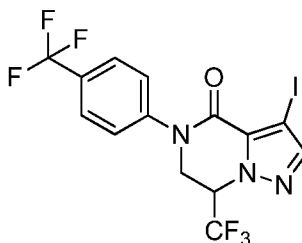
- 5 7-Methyl-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (**I-67**)



- Pd (10% on charcoal, 100 mg, 0.094 mmol) and ammonium formate (112 mg, 1.78 mmol) were added to a stirred solution of intermediate **I-66** (100 mg, 0.355 mmol) in MeOH (3.3 mL). The mixture was stirred in a sealed tube at 70 °C for 2 h. The solvent
10 was concentrated *in vacuo* to yield intermediate compound **I-67** (70 mg, 96%) that was used in the following step without further purification.

Intermediate 68 (I-68)

- 3-Iodo-7-(trifluoromethyl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-
15 a]pyrazin-4-one (**I-68**)

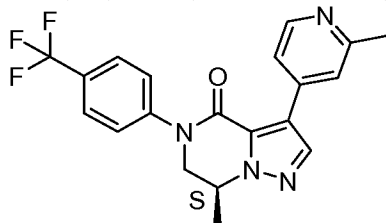


- Intermediate compound **I-68** was synthesized by following the sequence of an analogous synthetic procedure as reported for intermediate **I-22** starting from intermediate **I-67** and 4-bromobenzotrifluoride, followed by the procedure for
20 intermediate **I-23**.

Final Compounds

Example 1

- (7*S*)-7-Methyl-3-(2-methylpyridin-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-
25 dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (**E-1**, Co. No. 1)



Procedure A: Copper(I) iodide (872 mg, 4.58 mmol) was added to a stirred suspension of intermediate **I-18** (1.85 g, 7.64 mmol), 4-bromobenzotrifluoride (2.14 mL, 15.27 mmol), K₂CO₃ (2.11 g, 15.27 mmol) and *N,N'*-dimethylethylenediamine (0.492 mL, 4.58 mmol) in toluene (70 mL) in a sealed tube and under nitrogen. The mixture was stirred at 100 °C for 16 h. Then DMF (10 mL) was added and the mixture was stirred at 100 °C for additional 8 h. The mixture was filtered through diatomaceous earth and washed with EtOAc. The organic layer was washed with diluted NH₄OH sol, dried (Na₂SO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; EtOAc in Heptane 20/80 to 50/50). The desired fractions were collected and the solvents evaporated *in vacuo*. The product was precipitated with heptane, filtered and dried *in vacuo* to yield final product **compound 1** as a white solid (2.32 g, 78%). ¹H NMR (500 MHz, CDCl₃) δ ppm 1.75 (d, *J*=6.4 Hz, 3 H), 2.57 (s, 3 H), 4.02 (dd, *J*=12.7, 7.2 Hz, 1 H), 4.30 (dd, *J*=12.6, 4.2 Hz, 1 H), 4.75 - 4.84 (m, 1 H), 7.44 (d, *J*=5.2 Hz, 1 H), 7.49 (d, *J*=3.8 Hz, 2 H), 7.51 (s, 1 H), 7.71 (d, *J*=8.4 Hz, 2 H), 7.80 (s, 1 H), 8.48 (d, *J*=5.2 Hz, 1 H).

Procedure B: Copper(I) iodide (94 mg, 0.495 mmol) was added to a stirred suspension of intermediate **I-18** (200 mg, 0.825 mmol), 4-bromobenzotrifluoride (0.231 mL, 1.651 mmol), K₂CO₃ (228 mg, 1.65 mmol) and *N,N'*-dimethylethylenediamine (53 µL) in toluene (7.5 mL) in a sealed tube and under nitrogen. The mixture was stirred at 100 °C overnight. The mixture was filtered through a pad of diatomaceous earth and washed 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 Heptane 0/100 to 70/30). The desired fractions were collected and concentrated *in vacuo* to yield **compound 1** (283 mg, 89%) as a pinkish solid.

Procedure C: Pd(PPh₃)₄ (384 mg, 0.332 mmol) was added to a stirred suspension of intermediate **I-23** (2 g, 4.74 mmol) and 2-methylpyridine-4-boronic acid pinacol ester (1.66 g, 7.60 mmol) in 1,4-dioxane (10 mL) and a sat. sol. of Na₂CO₃ (5 mL) in a sealed tube under nitrogen. The mixture was stirred at 100 °C for 16 h. Then the mixture was diluted with H₂O and extracted with DCM and DCM with a small amount of EtOH. The organic layer was dried (Na₂SO₄), filtered and the solvent evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; 7M solution of ammonia in MeOH in DCM 0/100 to 3/97 then EtOAc in Heptane 0/100 to 100/0). The desired fractions were collected and evaporated *in vacuo* to yield **compound 1** as a white solid (480 mg, 26%). (1.31 g of starting material was recovered).

Procedure D; general description of a synthesis performed at a large scale by which Co. No. 1 was isolated in 90% yield before purification:

A mixture of **I-18** (1 eq.), potassium carbonate (2 eq.), copper(I) iodide (0.3 eq.), 4-bromobenzotrifluoride (1.3 eq.), N,N'-Dimethyl ethylenediamine (0.35 eq.), DMF (5 mL/g I-18) and toluene (8 mL/g I-18) was evacuated and backfilled with nitrogen 3 times. It was heated to 100-110 °C and stirred at 100-110 °C for 7-8 h under nitrogen. The reaction solution was concentrated to remove toluene below 50 °C. Isopropyl acetate (15 mL/g I-18) was added. The mixture was washed with 5% NH₄OH aqueous solution (3 x 7 mL/g I-18), and then 5% N-acetyl-L-cysteine and 5% K₂CO₃ aqueous solution (2 x 7 mL/g I-18) at 10-25 °C. Finally, it was washed with 5% NaCl aqueous solution (5 mL/g I-18). The obtained solution was concentrated and co-evaporated with MTBE to remove isopropyl acetate. The resulting solid was filtered and dried in vacuo at 45-50 °C. **Co. No. 1** was obtained as an off-white solid which was further purified as follows:

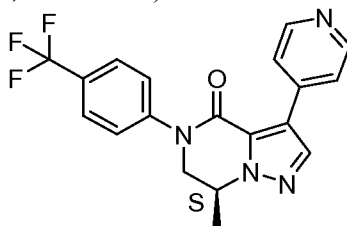
Co. No. 1 was dissolved in a solvent mixture of IPA (4 mL/g Co. No. 1) and water (1 mL/g Co. No. 1) at 48-55 °C. The solution was filtered and cooled to 0-5 °C. An IPA/water mixture (0.5 mL/g Co. No. 1, 4/1 v/v) was used to rinse. Water (650 µL/g Co. No. 1) was added drop-wise and seeding with **Co. No. 1** was performed. The mixture was stirred at 0-5 °C for 3-4 h. Water (14 mL/g Co. No. 1) was added drop-wise at 0-5 °C for 3-4 h, and then the suspension was stirred at 0-5 °C for 5-6 h. The wet product was filtered and rinsed with water (2 mL/g Co. No. 1), then dried in vacuo at 45-50 °C for 16 h to afford **Co. No. 1** as a white solid.

For compound 1 (DSC mp = 155.35 °C), the hydrochloride salt (.HCl) (DSC mp = decomposes above 200 °C); the sulfate salt (.H₂SO₄) (DSC mp = decomposes above 200 °C); the methane sulfonate salt (.CH₃SO₃H) (DSC mp = 252 °C); and the maleate salt (.HO₂CCH=CHCO₂H-*cis*) (DSC mp = 163 °C); wherein the mp were determined by DSC (Mettler Toledo Q2000 MDSC, heating from 25 to 350 °C at 10 °C /min) were obtained following the procedure described below:

Compound 1 (1.5 g) in 9 mL of IPA or acetone (hydrochloride and sulfate salts were generated in acetone; methanesulfonate and maleate salts were generated in IPA) were stirred at 50 °C until all the solid was dissolved. The acid (1.1 mol equivalents) was added to the solution and the reaction mixture was further stirred for 2 h at 50 °C, then cooled to 20 °C in 1 h and further stirred for 30 h at 20 °C. The suspension was filtered and the solids were dried at 50 °C in a vacuum oven overnight.

Example 2

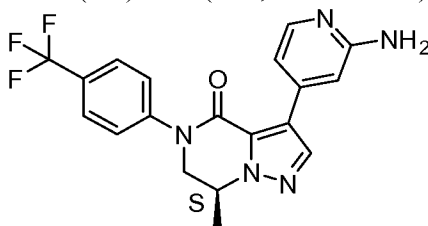
(7S)-7-Methyl-3-pyridin-4-yl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo
[1,5-a]pyrazin-4(5H)-one (**E-2**, Co. No. 2)



5 Pd(PPh₃)₄ (41 mg, 0.036 mmol) was added to a stirred suspension of intermediate **I-23** (300 mg, 0.71 mmol) and pyridine-4-boronic acid (114 mg, 0.93 mmol) in 1,4-dioxane (3.3 mL) and a sat. sol. of NaHCO₃ (1.5 mL). The mixture was stirred at 150 °C for 10 min under microwave irradiation. Then the mixture was diluted with H₂O and extracted
10 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 6/94). The desired fractions were collected and the solvents evaporated *in vacuo*. The residue was purified by ion exchange
15 chromatography using an ISOLUTE® SCX2 cartridge eluting first with MeOH and then with 7M solution of ammonia in MeOH. The desired fractions contained in the 7M solution of ammonia in MeOH were collected and the solvents evaporated *in vacuo*.
The residue was precipitated with DIPE to yield **compound 2** as a white solid (215 mg, 81%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.76 (d, *J*=6.5 Hz, 3 H), 4.03 (dd, *J*=12.7, 7.2 Hz, 1 H), 4.31 (dd, *J*=12.7, 4.2 Hz, 1 H), 4.81 (qdd, *J*=6.7, 6.7, 6.7, 6.5, 4.3 Hz, 1
20 H), 7.51 (d, *J*=8.1 Hz, 2 H), 7.65 (dd, *J*=4.4, 1.6 Hz, 2 H), 7.71 (d, *J*=8.3 Hz, 2 H), 7.83 (s, 1 H), 8.60 (dd, *J*=4.6, 1.8 Hz, 2 H).

Example 3

(7S)-3-(2-Aminopyridin-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-
25 dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (**E-3**, Co. No. 71)

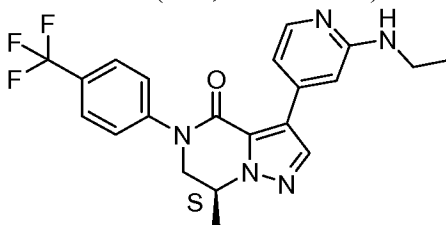


Pd(PPh₃)₄ (96 mg, 0.083 mmol) was added to a stirred suspension of intermediate **I-23** (700 mg, 1.66 mmol) and intermediate **I-24** (458 mg, 3.32 mmol) in 1,4-dioxane (10 mL) and a sat. sol. of NaHCO₃ (5 mL). The mixture was stirred at 150 °C for 10 min

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 DCM 0/100 to 10/90). The desired fractions were collected and the solvents evaporated *in vacuo* and the residue was purified by RP HPLC (RP C18 XBridgeTM 30 x 100 mm 5 um), mobile phase (gradient from 67% 0.1% NH₄CO₃H/NH₄OH pH 9 solution in Water, 33% CH₃CN to 50% 0.1% NH₄CO₃H/NH₄OH pH 9 solution in Water, 50% CH₃CN). The residue was purified by ion exchange chromatography using an ISOLUTE® SCX2 cartridge eluting first with MeOH and then with 7M solution of ammonia in MeOH. The desired fractions contained in the 7M solution of ammonia in MeOH were collected and the solvents evaporated *in vacuo* to yield final product **compound 71** as a white solid (163 mg, 25%). ¹H NMR (500 MHz, CDCl₃) δ ppm 1.74 (d, *J*=6.4 Hz, 3 H) 4.01 (dd, *J*=12.6, 7.1 Hz, 1 H) 4.29 (dd, *J*=12.6, 4.2 Hz, 1 H) 4.43 (br. s., 2 H) 4.78 (quind, *J*=6.6, 4.3 Hz, 1 H) 6.94 (dd, *J*=5.5, 1.4 Hz, 1 H) 6.98 (s, 1 H) 7.51 (br. d, *J*=8.4 Hz, 2 H) 7.71 (br. d, *J*=8.4 Hz, 2 H) 7.79 (s, 1 H) 8.06 (d, *J*=4.9 Hz, 1 H).

Example 4

(7*S*)-3-[2-(Ethylamino)-4-pyridyl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**E-4**, **Co. No. 44**)

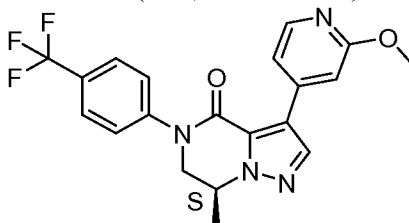


Sodium triacetoxyborohydride (246 mg, 1.16 mmol) was added to a stirred solution of **compound 71** (300 mg, 0.77 mmol) and acetaldehyde (0.048 mL, 0.85 mmol) in 1,2-dichloroethane (3 mL). The mixture was stirred at rt for 16 h. Then the mixture was diluted with a sat. sol. of NaHCO₃ and extracted with 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; EtOAc in heptane 0/100 to 40/60). The desired fractions were collected and the solvents evaporated *in vacuo*. The residue was purified by ion exchange chromatography using an ISOLUTE® SCX2 cartridge eluting first with MeOH and then with 7M solution of ammonia in MeOH. The desired fractions contained in the 7M solution of ammonia in MeOH were collected and the solvents evaporated *in vacuo* and the residue was purified by RP HPLC (RP C18 XBridgeTM 30 x 100 mm 5 um), 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). The residue was precipitated with DIPE to yield **compound 44** as a white solid (28 mg, 9%). ¹H NMR (500 MHz, CDCl₃) δ ppm 1.24 (t, *J*=7.2 Hz, 3 H) 1.74 (d, *J*=6.4 Hz, 3 H) 3.29 - 3.37 (m, 2 H) 4.00 (dd, *J*=12.6, 7.1 Hz, 1 H) 4.29 (dd, *J*=12.6, 4.2 Hz, 1 H) 4.42 (br. t, *J*=4.6 Hz, 1 H) 4.74 - 4.82 (m, 1 H) 6.83 (s, 1 H) 6.84 (dd, *J*=5.3, 1.3 Hz, 1 H) 7.51 (br. d, *J*=8.7 Hz, 2 H) 7.70 (br. d, *J*=8.7 Hz, 2 H) 7.79 (s, 1 H) 8.07 (d, *J*=5.5 Hz, 1 H).

Example 5

- 10 (7*S*)-3-(2-Methoxy-4-pyridyl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**E-5**, **Co. No. 45**)

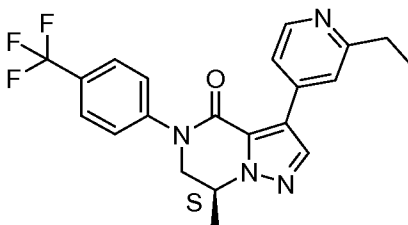


- Copper(I) iodide (66 mg, 0.348 mmol) was added to a stirred suspension of intermediate **I-25** (150 mg, 0.58 mmol), 4-bromobenzotrifluoride (209 mg, 0.93 mmol), K₂CO₃ (161 mg, 1.16 mmol) and *N,N'*-dimethylethylenediamine (0.037 mL, 0.348 mmol) in toluene (3.75 mL) in a sealed tube and under nitrogen. The mixture was stirred at 100 °C for 24 h. Then, more 4-bromobenzotrifluoride (131 mg, 0.58 mmol) was added and the mixture was stirred at 100 °C for additional 16 h. The mixture was filtered through diatomaceous earth and washed with DCM. The organic layer was evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; EtOAc in Heptane 0/100 to 20/80). The desired fractions were collected and the solvents evaporated *in vacuo*. The product was precipitated with Et₂O. The solid was purified by RP HPLC (RP 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 **compound 45** as a white solid (130 mg, 56%). ¹H NMR (500 MHz, CDCl₃) δ ppm 1.75 (d, *J*=6.6 Hz, 3 H) 3.94 (s, 3 H) 4.02 (dd, *J*=12.7, 7.2 Hz, 1 H) 4.30 (dd, *J*=12.6, 4.2 Hz, 1 H) 4.75 - 4.83 (m, 1 H) 7.09 (s, 1 H) 7.23 (dd, *J*=5.5, 1.2 Hz, 1 H) 7.50 (br. d, *J*=8.7 Hz, 2 H) 7.70 (br. d, *J*=8.7 Hz, 2 H) 7.79 (s, 1 H) 8.14 (d, *J*=5.5 Hz, 1 H).

30

Example 6

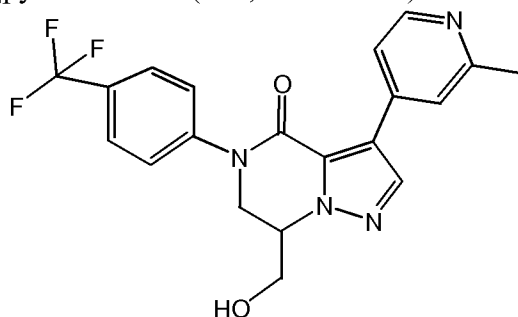
(7*S*)-3-(2-Ethyl-4-pyridyl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**E-6**, **Co. No. 46**)



A solution of intermediate **I-27** (114 mg, 0.29 mmol) in EtOH (5.7 mL) was hydrogenated in a H-Cube® reactor (1 mL/min, 30 mm Pd(OH)₂/C 20% cartridge, full H₂ mode, rt, 1 cycle). Then, the solvent was evaporated *in vacuo*. The crude product was purified by RP HPLC (RP 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 **compound 46** as a white solid (84 mg, 73%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.32 (t, *J*=7.6 Hz, 3 H) 1.75 (d, *J*=6.7 Hz, 3 H) 2.85 (q, *J*=7.6 Hz, 2 H) 4.02 (dd, *J*=12.7, 7.2 Hz, 1 H) 4.31 (dd, *J*=12.7, 4.2 Hz, 1 H) 4.80 (quind, *J*=6.7, 4.2 Hz, 1 H) 7.46 (dd, *J*=5.1, 1.6 Hz, 1 H) 7.48 (br. s, 1 H) 7.51 (br. d, *J*=8.3 Hz, 2 H) 7.71 (br. d, *J*=8.3 Hz, 2 H) 7.81 (s, 1 H) 8.51 (dd, *J*=5.3, 0.7 Hz, 1 H).

Example 7

7-(Hydroxymethyl)-3-(2-methyl-4-pyridyl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one (**E-7**, **Co. No. 87**)

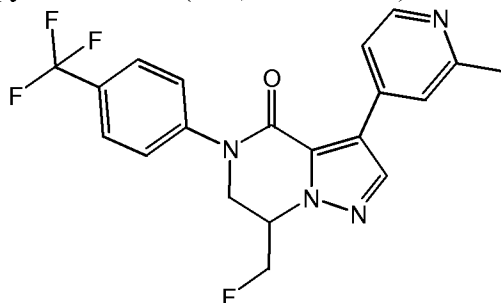


Copper(I) iodide (0.135 g, 0.709 mmol) was added to a stirred suspension of intermediate **I-31** (305 mg, 1.18 mmol), 4-bromobenzotrifluoride (298 µL, 2.12 mmol), K₂CO₃ (330 mg, 2.36 mmol) and *N,N'*-dimethylethylenediamine (76 µL, 0.71 mmol) in toluene (7.63 mL) in a sealed tube and under nitrogen. The mixture was stirred at 100 °C for 18 h. Then additional K₂CO₃ (160 mg, 1.18 mmol), copper(I) iodide (0.067 g, 0.354 mmol), *N,N'*-dimethylethylenediamine (38 µL, 0.35 mmol) and 4-bromobenzotrifluoride (132 µL, 0.95 mmol) were added under nitrogen and the mixture was stirred at 100 °C for 5 h. The mixture was filtered through a pad of diatomaceous earth and washed with DCM. The organic layer was separated, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by flash column

chromatography (silica; methanol in DCM 0/100 to 7/93). The desired fractions were collected and concentrated *in vacuo* to yield **compound 87** (321 mg, 68%) as yellow oil that precipitated upon standing at rt.

5 Example 8

7-(Fluoromethyl)-3-(2-methyl-4-pyridyl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one (**E-8**, Co. No. 52)

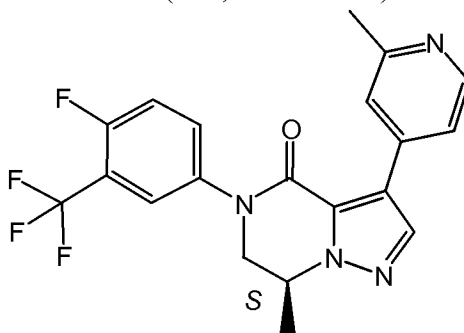


(Diethylamino)sulfur trifluoride (23 μ L, 0.185 mmol) was added to a stirred solution of **compound 87** (50 mg, 0.124 mmol) in DCM (2.4 mL) at -10 °C. The mixture was allowed to warm to rt and stirred for 18 h. The mixture was treated with water and extracted with DCM. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica; EtOAc in DCM 0/100 to 100/0 and MeOH in EtOAc 0/100 to 1/99). The desired fractions were collected and concentrated *in vacuo*. Then the compound was triturated with DIPE to yield **compound 52** (14.5 mg, 29%) as a white solid. ^1H NMR (500 MHz, CDCl_3) δ ppm 2.58 (s, 3 H) 4.31 (dd, $J=13.1$, 4.8 Hz, 1 H) 4.47 - 4.53 (m, 1 H) 4.86 - 5.07 (m, 3 H) 7.45 (br. d, $J=4.6$ Hz, 1 H) 7.51 (br. d, $J=8.7$ Hz, 2 H) 7.50 (s, 1 H) 7.72 (br. d, $J=8.7$ Hz, 2 H) 7.85 (s, 1 H) 8.49 (d, $J=5.2$ Hz, 1 H).

20

Example 9

(7S)-5-[4-Fluoro-3-(trifluoromethyl)phenyl]-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one (**E-9**, Co. No. 67)

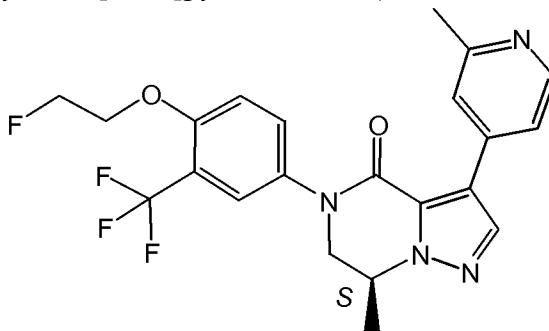


Compound 67 was obtained starting from intermediate **I-18** (160 mg, 0.66 mmol), 5-bromo-2-fluorobenzotrifluoride (149 μ L, 1.06 mmol), *N,N'*-dimethylethylenediamine (42 μ L, 0.396 mmol), copper(I) iodide (75 mg, 0.396 mmol), K_2CO_3 (182 mg, 1.32 mmol) in toluene (4.27 mL), following a procedure similar to that described in **E-1**, yielding **compound 67** (224 mg, 84%) as a pale yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.76 (d, $J=6.4$ Hz, 3 H) 2.58 (s, 3 H) 3.98 (dd, $J=12.7, 7.2$ Hz, 1 H) 4.25 (dd, $J=12.6, 4.2$ Hz, 1 H) 4.80 (quind, $J=6.6, 4.3$ Hz, 1 H) 7.29 (d, $J=9.5$ Hz, 1 H) 7.43 (dd, $J=5.2, 1.2$ Hz, 1 H) 7.48 (s, 1 H) 7.54 - 7.61 (m, 2 H) 7.80 (s, 1 H) 8.49 (d, $J=5.2$ Hz, 1 H).

10

Example 10

(7S)-5-[4-(2-Fluoroethoxy)-3-(trifluoromethyl)phenyl]-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one (**E-10**, **Co. No. 77**)



Sodium hydride (60% dispersion in mineral oil, 22 mg, 0.544 mmol) was added to a solution of 2-fluoroethanol (453 μ L, 0.495 mmol) in DMF (4.5 mL) at 0 $^{\circ}C$ and the mixture was stirred at rt for 10 minutes. Then **compound 67** (200 mg, 0.495 mmol) was added. The mixture was stirred at 110 $^{\circ}C$ for 23 h. The reaction mixture was cooled to rt and a solution of 2-fluoroethanol (227 μ L, 0.247 mmol) and Sodium hydride (60% dispersion in mineral oil, 12 mg, 0.297 mmol) in DMF (0.5 mL) was added. The resulting mixture was stirred at 110 $^{\circ}C$ for 16 h. The mixture was quenched with water and extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4) and the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; 7M solution of ammonia in MeOH in DCM/ DCM 0/100 to 2/98). The desired fractions were collected and the solvents evaporated *in vacuo* to afford 164 mg of **compound 77**, which was further purified by RP HPLC (Stationary phase: C18 XBridgeTM 30 x 100 mm 5 μ m), mobile phase: Gradient from 67% 0.1% NH_4CO_3H/NH_4OH pH 9 solution in Water, 33% CH_3CN to 50% 0.1% NH_4CO_3H/NH_4OH pH 9 solution in Water, 50% CH_3CN), yielding 125 mg of **compound 77**, which was further purified by RP HPLC (Stationary phase: C18 XBridgeTM 30 x 100 mm 5 μ m), mobile phase: Gradient from 67% 0.1%

NH₄CO₃H/NH₄OH pH 9 solution in Water, 33% CH₃CN to 50% 0.1%

NH₄CO₃H/NH₄OH pH 9 solution in Water, 50% CH₃CN), yielding 117 mg of

compound 77 which was further purified by RP HPLC (Stationary phase: C18 XBridgeTM 30 x 100 mm 5 μm), mobile phase: Gradient from 47% 0.1%

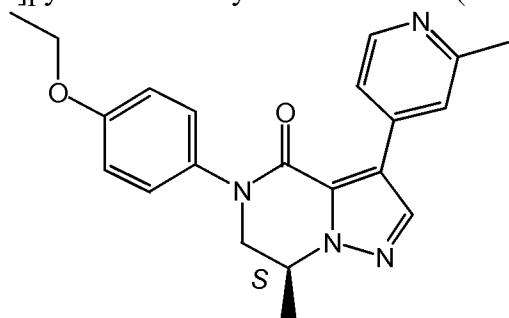
5 NH₄CO₃H/NH₄OH pH 9 solution in Water, 53% MeOH to 30% 0.1%

NH₄CO₃H/NH₄OH pH 9 solution in Water, 70% MeOH), yielding **compound 77** (39 mg, 18%), also recovering 38 mg of starting material, **compound 67**. For **compound**

77: ¹H NMR (400 MHz, CDCl₃) δ ppm 1.75 (d, *J*=6.5 Hz, 3 H) 2.57 (s, 3 H) 3.96 (dd, *J*=12.8, 7.3 Hz, 1 H) 4.24 (dd, *J*=12.7, 4.4 Hz, 1 H) 4.28 - 4.38 (m, 2 H) 4.70 - 4.87 (m, 2 H) 4.75 - 4.83 (m, 1 H) 7.08 (d, *J*=8.6 Hz, 1 H) 7.44 (dd, *J*=5.2, 1.3 Hz, 1 H) 7.48 - 7.57 (m, 3 H) 7.79 (s, 1 H) 8.47 (dd, *J*=5.3, 0.5 Hz, 1 H).

Example 11

(7S)-5-(4-Ethoxyphenyl)-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-
15 a]pyrazin-4-one hydrochloride salt (**E-11**, Co. No. 81)



. HCl

Copper(I) iodide (47 mg, 0.247 mmol) was added to a stirred suspension of intermediate **I-18** (0.1 g, 0.413 mmol), 4-iodophenetole (0.164 g, 0.661 mmol), K₂CO₃ (114 mg, 0.825 mmol) and *N,N'*-dimethylethylenediamine (26 μL, 0.211 mmol) in

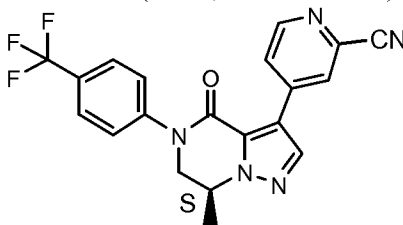
20 toluene (6 mL) in a sealed tube and under nitrogen. The mixture was stirred at 100 °C for 24 h. The mixture was filtered through a pad of diatomaceous earth and washed with DCM. The organic layer was evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; EtOAc in DCM 0/100 to 40/60). The desired fractions were collected and concentrated *in vacuo* to yield **compound 81** as an oil. The

25 residue was dissolved in EtOAc and HCl (4N) (103 μL, 0.413 mmol) was added. The residue was triturated from DIPE, filtered and dried *in vacuo* to yield **compound 81** (163 mg, 99%) as a white solid. Free base: ¹H NMR (300 MHz, CDCl₃) δ ppm 1.35 (t, *J*=6.9 Hz, 3 H) 1.65 (d, *J*=6.5 Hz, 3 H) 2.50 (s, 3 H) 3.84 (dd, *J*=12.9, 7.0 Hz, 1 H) 3.97 (q, *J*=7.0 Hz, 2 H) 4.16 (dd, *J*=12.9, 4.3 Hz, 1 H) 4.60 - 4.76 (m, 1 H) 6.87 (br. d, *J*=8.8 Hz, 2 H) 7.18 (br. d, *J*=8.7 Hz, 2 H) 7.43 (br. d, *J*=4.8 Hz, 1 H) 7.48 (br. s, 1 H) 7.72 (s, 30 1 H) 8.39 (br. d, *J*=4.3 Hz, 1 H); HCl salt: ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.34

(t, $J=6.9$ Hz, 3 H) 1.60 (d, $J=6.3$ Hz, 3 H) 2.68 (s, 3 H) 3.38 (br. s., 1 H) 3.90 - 4.14 (m, 3 H) 4.28 (dd, $J=13.0, 4.1$ Hz, 1 H) 4.78 - 4.94 (m, 1 H) 7.00 (br. d, $J=8.9$ Hz, 2 H) 7.35 (br. d, $J=8.8$ Hz, 2 H) 8.23 - 8.42 (m, 3 H) 8.69 (d, $J=6.3$ Hz, 1 H).

5 Example 12

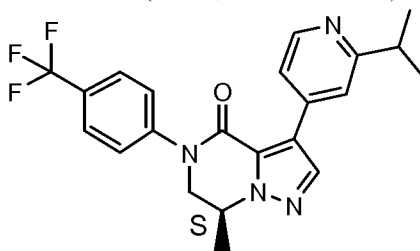
4-[(7*S*)-7-Methyl-4-oxo-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-3-yl]pyridine-2-carbonitrile (**E-12**, Co. No. 127)



Pd(PPh₃)₄ (42 mg, 0.036 mmol) was added to a stirred suspension of intermediate **I-33a** (250 mg, 0.593 mmol) and 4-bromopyridine-2-carbonitrile (162 mg, 0.884 mmol) in 1,4-dioxane (4 mL) and a sat. sol. of Na₂CO₃ (2 mL). The mixture was stirred at 150 °C for 10 min under microwave irradiation. Then the mixture was diluted with H₂O and extracted with DCM. The organic layer was dried (Na₂SO₄), filtered and the solvent 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*. The residue was precipitated with DIPE. The solid was filtered to yield **compound 127** as a white solid. ¹H NMR (500 MHz, CDCl₃) δ ppm 1.77 (d, $J=6.4$ Hz, 3 H) 4.05 (dd, $J=12.9, 7.4$ Hz, 1 H) 4.32 (dd, $J=12.7, 4.0$ Hz, 1 H) 4.79 - 4.88 (m, 1 H) 7.51 (br. d, $J=8.4$ Hz, 2 H) 7.74 (br. d, $J=8.4$ Hz, 2 H) 7.86 (s, 1 H) 7.92 (dd, $J=5.2, 1.7$ Hz, 1 H) 8.04 - 8.14 (m, 1 H) 8.67 (d, $J=5.2$ Hz, 1 H).

Example 13

(7*S*)-3-(2-Isopropyl-4-pyridyl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one (**E-13**, Co. No. 126)



25

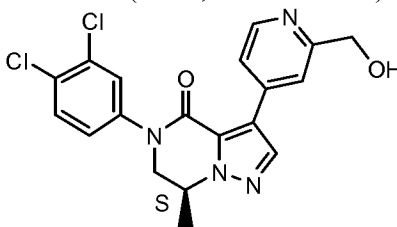
Pd(PPh₃)₄ (26 mg, 0.022 mmol) was added to a stirred suspension of intermediate **I-33b** (150 mg, 0.442 mmol) and 4-bromo-2-isopropyl-pyridine (prepared as described in WO2009/118292) (97 mg, 0.486 mmol) in a sat. aq. sol. NaHCO₃ (1 mL) and 1,4-

dioxane (1 mL). The mixture was stirred at 120 °C for 10 min under microwave irradiation. The mixture was filtered through diatomaceous earth and washed with DCM. The organic layer was washed with water, separated, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography ((silica; 7N solution of ammonia in MeOH in DCM 0/100 to 10/90) then (silica, EtOAc in DCM 0/100 to 30/70)) then by RP HPLC (Stationary phase: C18 XSelect™ 19 x 100 mm 5 µm, Mobile phase: Gradient from 80% 0.1% NH₄CO₃H/NH₄OH pH 9 solution in Water, 20% CH₃CN to 0% 0.1% NH₄CO₃H/NH₄OH pH 9 solution in Water, 100% CH₃CN)). The desired fractions were collected and evaporated *in vacuo* to yield **compound 126** as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.32 (d, *J*=6.9 Hz, 6 H) 1.75 (d, *J*=6.7 Hz, 3 H) 3.08 (spt, *J*=6.9 Hz, 1 H) 4.02 (dd, *J*=12.7, 7.2 Hz, 1 H) 4.31 (dd, *J*=12.6, 4.0 Hz, 1 H) 4.80 (quind, *J*=6.7, 4.3 Hz, 1 H) 7.45 - 7.48 (m, 2 H) 7.51 (br. d, *J*=8.3 Hz, 2 H) 7.71 (br. d, *J*=8.6 Hz, 2 H) 7.81 (s, 1 H) 8.50 - 8.55 (m, 1 H)

15

Example 14

(7*S*)-5-(3,4-Dichlorophenyl)-3-[2-(hydroxymethyl)-4-pyridyl]-7-methyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**E-14**, **Co. No. 125**)



A suspension of intermediate **I-34** (1.09 g, 4.56 mmol) in acetic anhydride (8 mL) was stirred at 100 °C for 2 h. The mixture was cooled to rt, and poured into water (15 mL) and EtOAc (30 mL). The organic layer was separated, washed with a sat. NaHCO₃ sol., dried (Na₂SO₄), filtered and concentrated *in vacuo*. The resultant oil was stirred with lithium hydroxide (259 mg, 10.81 mmol) in MeOH (5.45 mL) and H₂O (2.72 mL) at rt for 30 min. Then, EtOAc was added and the organic layer was washed with water, brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica; 7M solution of ammonia in MeOH in DCM 0/100 to 3/97). The desired fractions were collected and evaporated *in vacuo* to yield **compound 125** (670 mg, 61%).

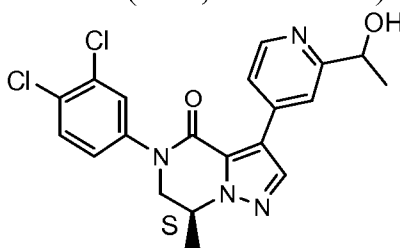
Crude **compound 125** (100 mg) was purified by RP HPLC (Stationary phase: C18 XBridge 30 x 100 mm 5 µm), Mobile phase: Gradient from 54% 0.1% NH₄CO₃H/NH₄OH pH 9 solution in Water, 46% CH₃CN to 64% 0.1% NH₄CO₃H/NH₄OH pH 9 solution in Water, 36% CH₃CN), yielding 72 mg **compound**

125. ^1H NMR (500 MHz, CDCl_3) δ ppm 1.74 (d, $J=6.4$ Hz, 3 H) 3.73 (br. s., 1 H) 3.96 (dd, $J=12.7, 7.2$ Hz, 1 H) 4.24 (dd, $J=12.7, 4.3$ Hz, 1 H) 4.72 - 4.83 (m, 3 H) 7.23 (dd, $J=8.7, 2.3$ Hz, 1 H) 7.49 (d, $J=2.3$ Hz, 1 H) 7.51 (d, $J=8.7$ Hz, 1 H) 7.55 (d, $J=4.9$ Hz, 1 H) 7.59 (s, 1 H) 7.82 (s, 1 H) 8.54 (d, $J=4.9$ Hz, 1 H).

5

Example 15

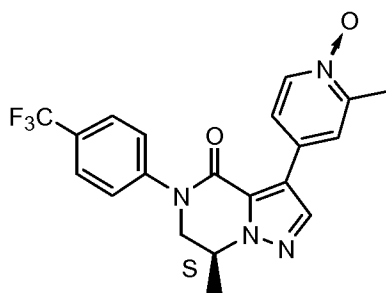
(7*S*)-5-(3,4-Dichlorophenyl)-3-[2-(1-hydroxyethyl)-4-pyridyl]-7-methyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**E-15**, Co. No. 111)



- 10 Methylmagnesium chloride 3M in THF (249 μL , 0.747 mmol) was added dropwise to a solution of intermediate **I-39** (150 mg, 0.374 mmol) in THF (1.24 mL) at -78°C and under nitrogen. The mixture was stirred at -78°C for 2 h. Then, more methylmagnesium chloride 3M in THF (125 μL , 0.374 mmol) was added and the mixture was stirred at -78°C for 1 h. Then, it was quenched at -78°C with a sat. NH_4Cl
- 15 sol. and allowed to reach rt. The mixture was extracted with EtOAc. 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 5/95). The desired fractions were collected and evaporated *in vacuo*. The residue was precipitated with Ether/Heptane to yield **compound 111** as a pale yellow solid. ^1H
- 20 NMR (400 MHz, CDCl_3) δ ppm 1.52 (dd, $J=6.6, 0.8$ Hz, 3 H) 1.74 (dd, $J=6.5, 2.3$ Hz, 3 H) 3.91 - 4.02 (m, 1 H) 4.13 - 4.31 (m, 2 H) 4.72 - 4.84 (m, 1 H) 4.92 (q, $J=6.5$ Hz, 1 H) 7.23 (dd, $J=8.6, 2.5$ Hz, 1 H) 7.49 (d, $J=2.3$ Hz, 1 H) 7.51 (d, $J=8.6$ Hz, 1 H) 7.56 (br. d, $J=5.3$ Hz, 1 H) 7.59 - 7.63 (m, 1 H) 7.82 (s, 1 H) 8.52 (dd, $J=5.1, 0.7$ Hz, 1 H)

25 Example 16

(7*S*)-7-Methyl-3-(2-methyl-1-oxido-pyridin-1-ium-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**E-16**, Co. No. 140)

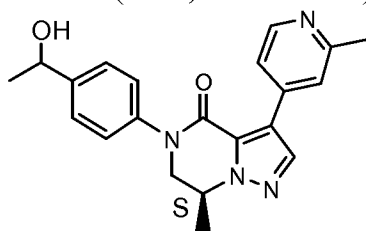


3-Chloroperoxybenzoic acid (2.96 g, 17.18 mmol) was added to a stirred solution of final compound **E-1** (3.32 g, 8.59 mmol) in DCM (133 mL) at 0 °C. The mixture was allowed to reach rt and stirred at rt for 3 h. The mixture was treated with Na₂CO₃ sat sol. and diluted with DCM. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated in vacuo to yield **compound 140** (3.4 g, 98%) as a pale yellow solid.

A small fraction (350 mg) was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 5/95). The desired fractions were collected and evaporated *in vacuo*. The residue was precipitated with Et₂O and filtered to yield pure **compound 140** (290 mg, 8%). ¹H NMR (500 MHz, CDCl₃) δ ppm 1.75 (d, *J*=6.4 Hz, 3 H) 2.53 (s, 3 H) 4.02 (dd, *J*=12.7, 7.2 Hz, 1 H) 4.30 (dd, *J*=12.7, 4.0 Hz, 1 H) 4.75 - 4.85 (m, 1 H) 7.50 (d, *J*=8.4 Hz, 2 H) 7.63 (dd, *J*=6.8, 2.5 Hz, 1 H) 7.67 - 7.77 (m, 3 H) 7.81 (s, 1 H) 8.21 (d, *J*=6.6 Hz, 1 H).

Example 17

(7*S*)-5-[4-(1-Hydroxyethyl)phenyl]-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**E-17**, Co. No. 149)

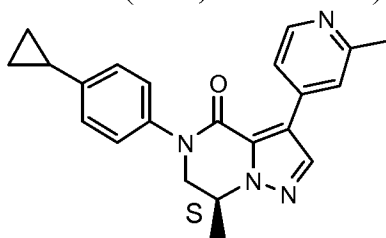


Sodium borohydride (6 mg, 0.166 mmol) was added to a stirred solution of intermediate **I-35** (60 mg, 0.166 mmol) in MeOH (5 mL) at 0 °C. The mixture was stirred at rt for 16 h. The solvent was concentrated *in vacuo*. The residue was dissolved with DCM and washed with a sat. Na₂CO₃ sol. The organic 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 100/0). The desired fractions were collected and concentrated *in vacuo* to yield **compound 149** (40 mg, 66%). ¹H NMR (300 MHz, CDCl₃) δ ppm 1.52 (d, *J*=6.5 Hz, 3 H) 1.73 (d, *J*=6.5 Hz, 3 H) 2.31 (br. s., 1 H) 2.57 (s, 3 H) 3.97 (dd, *J*=12.8, 6.9 Hz, 1 H) 4.16 - 4.39 (m, 1 H)

4.60 - 4.86 (m, 1 H) 4.95 (q, $J=6.4$ Hz, 1 H) 7.35 (br. d, $J=8.2$ Hz, 2 H) 7.42 - 7.59 (m, 4 H) 7.81 (s, 1 H) 8.37 - 8.49 (m, 1 H).

Example 18

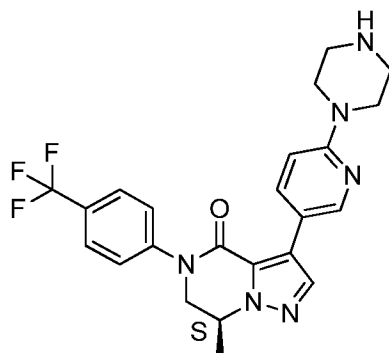
- 5 (7*S*)-5-(4-Cyclopropylphenyl)-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**E-18**, Co. No. 156)



- Pd(PPh₃)₄ (37 mg, 0.032 mmol) was added to a stirred suspension of intermediate **I-36** (255 mg, 0.642 mmol), cyclopropylboronic acid (165 mg, 1.92 mmol) and K₂CO₃ (177 mg, 1.28 mmol) in CH₃CN (5 mL) and H₂O (2 mL). The mixture was stirred at 150 °C for 10 min under microwave irradiation. Then more cyclopropylboronic acid (165 mg, 1.92 mmol) and Pd(PPh₃)₄ (37 mg, 0.032 mmol) were added. The mixture was stirred at 150 °C for another 10 min under microwave irradiation. Then the mixture was diluted with H₂O and extracted with DCM. The organic layer was dried (MgSO₄), filtered and the solvent evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; EtOAc in Heptane 0/100 to 75/25) and by RP HPLC (Stationary phase: C18 XBridgeTM 30 x 100 mm 5 um, Mobile phase: Gradient from 67% 0.1% NH₄CO₃H/NH₄OH pH 9 solution in Water, 33% CH₃CN to 50% 0.1% NH₄CO₃H/NH₄OH pH 9 solution in Water, 50% CH₃CN). The desired fractions were collected and concentrated *in vacuo* to yield **compound 156** (80 mg, 24%) as a solid.
- ¹H NMR (400 MHz, CDCl₃) δ ppm 0.62 - 0.77 (m, 2 H) 0.91 - 1.06 (m, 2 H) 1.72 (d, $J=6.7$ Hz, 3 H) 1.91 (tt, $J=8.5, 5.1$ Hz, 1 H) 2.56 (s, 3 H) 3.93 (dd, $J=12.9, 6.9$ Hz, 1 H) 4.25 (dd, $J=12.9, 4.2$ Hz, 1 H) 4.75 (quind, $J=6.6, 4.4$ Hz, 1 H) 7.09 - 7.18 (m, 2 H) 7.18 - 7.25 (m, 2 H) 7.48 (dd, $J=5.1, 1.2$ Hz, 1 H) 7.53 (s, 1 H) 7.79 (s, 1 H) 8.45 (d, $J=5.1$ Hz, 1 H)

Example 19

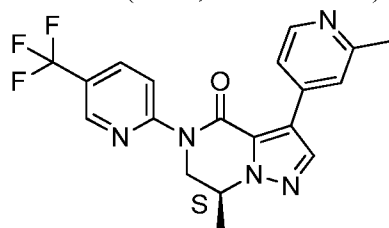
(7*S*)-7-Methyl-3-(6-piperazin-1-yl-3-pyridyl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**E-19**, Co. No. 176)



Trifluoroacetic acid (0.911 mL, 11.91 mmol) was added to a stirred solution of intermediate **I-42** (663 mg, 1.19 mmol) in DCM (1.9 mL). The mixture was stirred at rt for 1 h. The solvent was concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 20/80). The desired fractions were collected and evaporated *in vacuo*. The residue was precipitated with Et₂O and filtrated a solid that was purified by RP HPLC (Stationary phase: C18 XBridge™ 50 x 100 5 μm, Mobile phase: Gradient from 53% 0.1% NH₄CO₃H/NH₄OH pH 9 solution in Water, 43% CH₃CN to 40% 0.1% NH₄CO₃H/NH₄OH pH 9 solution in Water, 60% CH₃CN), to yield **compound 176** (151 mg, 28%) as a solid. ¹H NMR (500 MHz, CDCl₃) δ ppm 1.73 (d, *J*=6.6 Hz, 3 H) 1.76 (br. s., 1 H) 2.92 - 3.02 (m, 4 H) 3.50 - 3.57 (m, 4 H) 4.00 (dd, *J*=12.4, 7.2 Hz, 1 H) 4.27 (dd, *J*=12.4, 4.0 Hz, 1 H) 4.70 - 4.82 (m, 1 H) 6.63 (d, *J*=8.7 Hz, 1 H) 7.50 (br. d, *J*=8.7 Hz, 2 H) 7.68 (br. d, *J*=8.7 Hz, 2 H) 7.71 (s, 1 H) 7.96 (dd, *J*=9.0, 2.3 Hz, 1 H) 8.42 (d, *J*=2.3 Hz, 1 H)

Example 20

(7*S*)-7-Methyl-3-(2-methyl-4-pyridyl)-5-[6-(trifluoromethyl)-3-pyridyl]-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**E-20**, Co. No. 186)

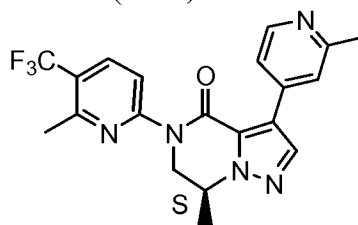


Pd(PPh₃)₄ (155 mg, 0.134 mmol) was added to a stirred suspension of intermediate **I-18** (325 mg, 1.341 mmol), 2-chloro-5-(trifluoromethyl)pyridine (365 mg, 2.012 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (155 mg, 0.268 mmol), Cs₂CO₃ (874 mg, 2.683 mmol) in 1,4-dioxane (10 mL) in a sealed tube and under nitrogen. The mixture was stirred at 120 °C for 7 h. The mixture was filtered through a pad of diatomaceous earth and washed with DCM. The filtrate was evaporated *in vacuo* and the crude product was purified by flash column chromatography (silica, EtOAc in DCM 0/100 to 30/70). The desired fractions were collected and concentrated *in vacuo*.

The residue was purified by ion exchange chromatography using an (ISOLUTE® SCX2 cartridge) eluting first with MeOH then with 7M solution of ammonia in MeOH. The desired fractions contained in the 7M solution of ammonia in MeOH were collected and the solvents evaporated *in vacuo*. The residue was triturated with Et₂O to yield **compound 186** (415 mg, 80%) as a white solid. ¹H NMR (500 MHz, , CDCl₃) δ ppm 1.73 (d, *J*=6.4 Hz, 3 H) 2.60 (s, 3 H) 4.35 - 4.44 (m, 1 H) 4.68 - 4.80 (m, 2 H) 7.41 (dd, *J*=5.2, 1.2 Hz, 1 H) 7.45 (s, 1 H) 7.78 (s, 1 H) 7.94 (dd, *J*=8.8, 2.2 Hz, 1 H) 8.24 (d, *J*=9.0 Hz, 1 H) 8.52 (d, *J*=5.2 Hz, 1 H) 8.69 - 8.73 (m, 1 H).

10 Example 21

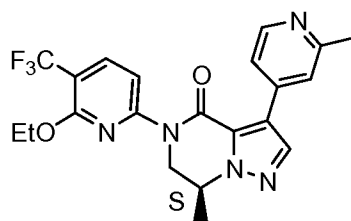
(7*S*)-7-Methyl-3-(2-methyl-4-pyridyl)-5-[6-methyl-5-(trifluoromethyl)-2-pyridyl]-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**E-21**, Co. No. 192)



Tetramethyltin (32 μL, 0.231 mmol) was added to a mixture of intermediate **I-43** (65 mg, 0.154 mmol), lithium chloride (13 mg, 0.308 mmol) and bis(triphenylphosphine)palladium(II) dichloride (6 mg, 0.007 mmol) in degassed DMF (2.4 mL), in a sealed tube under nitrogen. The mixture was stirred at 110 °C for 5 h. The mixture was diluted with a sat. sol. of NaHCO₃ 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; EtOAc in DCM 0/100 to 30/70). The desired fractions were collected and concentrated *in vacuo*. Then the product was triturated with Et₂O to yield **compound 192** (26 mg, 42%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.73 (d, *J*=6.5 Hz, 3 H) 2.60 (s, 3 H) 2.69 (br. d, *J*=1.6 Hz, 3 H) 4.34 - 4.46 (m, 1 H) 4.66 - 4.80 (m, 2 H) 7.41 (dd, *J*=5.1, 1.2 Hz, 1 H) 7.44 (s, 1 H) 7.78 (s, 1 H) 7.90 (d, *J*=8.8 Hz, 1 H) 8.02 (d, *J*=8.6 Hz, 1 H) 8.52 (d, *J*=4.9 Hz, 1 H).

Example 22a

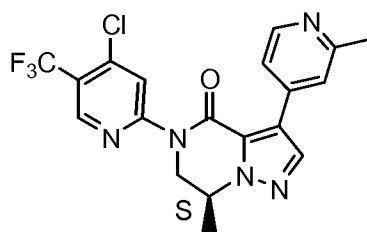
(7*S*)-5-[6-Ethoxy-5-(trifluoromethyl)-2-pyridyl]-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**E-22a**, Co. No. 189)



EtOH (114 μ L, 1.95 mmol) was added to a stirred suspension of sodium hydride (60% dispersion in mineral oil) (78 mg, 1.95 mmol) in DMF (5 mL) at 0 °C. The mixture was stirred at rt for 10 min. Then, a solution of 2-chloro-4-iodo-5-(trifluoromethyl)pyridine (0.5 g, 1.62 mmol) in DMF (5 mL) was added at 0 °C and the mixture was stirred at rt for 18 h. Then, more sodium hydride (60% dispersion in mineral oil) (26 mg, 0.65 mmol) and EtOH (38 μ L, 0.65 mmol) were added at 0 °C and the mixture was stirred at rt for 2 h. Intermediate **I-18** (157 mg, 0.65 mmol) was then added and the mixture was cooled to 0 °C. More sodium hydride (60% dispersion in mineral oil) (52 mg, 1.301 mmol) was added and the mixture was stirred at rt for 1 h and at 80 °C for 16 h. Then more sodium hydride (60% dispersion in mineral oil) (13 mg, 0.325 mmol) was added at rt and the mixture was stirred at 80 °C for 2 h more. The mixture was treated with a 10% NH₄Cl sol. and extracted with EtOAc/THF. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated *in vacuo*. The residue was dissolved in DMF (10 mL). TEA (0.226 mL, 1.626 mmol) and HATU (0.247 g, 0.605 mmol) were added. The mixture was stirred at rt for 1 h. The mixture was treated with a sat. NaHCO₃ sol./brine at 0 °C 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; EtOAc in DCM 0/100 to 100/0). The desired fractions were collected and concentrated *in vacuo*. Then the residue was repurified by RP HPLC (Stationary phase: C18 XBridgeTM 30 x 100 mm 5 μ m, Mobile phase: Gradient from 54% 0.1% NH₄CO₃H/NH₄OH pH 9 solution in Water, 46% CH₃CN to 64% 0.1% NH₄CO₃H/NH₄OH pH 9 solution in Water, 36% CH₃CN) to yield **compound 189** (27 mg, 4%) as a beige solid. ¹H NMR (500 MHz, CDCl₃) δ ppm 1.46 (t, *J*=6.9 Hz, 3 H) 1.71 (d, *J*=6.6 Hz, 3 H) 2.60 (s, 3 H) 4.15 - 4.27 (m, 2 H) 4.39 (dd, *J*=13.3, 7.2 Hz, 1 H) 4.65 - 4.80 (m, 2 H) 7.40 (dd, *J*=5.2, 1.2 Hz, 1 H) 7.43 (s, 1 H) 7.77 (s, 1 H) 7.82 (s, 1 H) 8.47 (s, 1 H) 8.52 (d, *J*=5.2 Hz, 1 H).

Example 22b

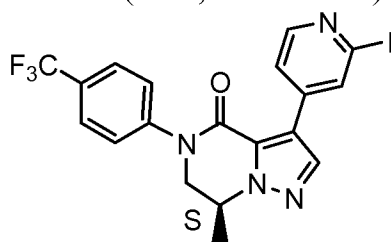
(7S)-5-[4-Chloro-5-(trifluoromethyl)-2-pyridyl]-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one (**E-22b**, Co. No. 204)



Pd(PPh₃)₄ (47 mg, 0.041 mmol) and 2,4-dichloro-5-(trifluoromethyl)pyridine (134 mg, 0.619 mmol) were added to a stirred suspension of intermediate **I-18** (100 mg, 0.413 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (48 mg, 0.082 mmol) and
 5 Cs₂CO₃ (269 mg, 0.082 mmol) in 1,4-dioxane (2.5 mL) in a sealed tube and under nitrogen. The mixture was stirred at 110 °C for 4 h and at 100 °C for 2 days. The mixture was filtered through a pad of diatomaceous earth and washed with DCM. The filtrate was evaporated *in vacuo*. The residue was dissolved in DMF (7 mL) and TEA (57 µL, 0.413 mmol) then HATU (157 mg, 0.413 mmol) were added. The mixture was
 10 stirred at rt for 2 h. The mixture was treated at 0 °C with a sat. sol. NaHCO₃/brine then EtOAc was added. The mixture was filtered through a pad of diatomaceous earth. 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 100/0). The desired fractions were collected and concentrated *in vacuo*. The residue was repurified by RP HPLC (Stationary phase: C18 XBridgeTM 30 x 100 mm 5 µm, Mobile phase: Gradient from 54% 0.1% NH₄CO₃H/NH₄OH pH 9 solution in Water, 46% CH₃CN to 64% 0.1% NH₄CO₃H/NH₄OH pH 9 solution in Water, 36% CH₃CN) to yield **compound 204** (27 mg, 15%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ ppm 1.72 (d, *J*=6.4 Hz, 3 H) 2.61 (s, 3 H) 4.36 - 4.45 (m, 1 H)
 20 4.68 - 4.79 (m, 2 H) 7.39 (dd, *J*=5.2, 1.7 Hz, 1 H) 7.43 (s, 1 H) 7.78 (s, 1 H) 8.42 (s, 1 H) 8.54 (d, *J*=5.2 Hz, 1 H) 8.68 (s, 1 H).

Example 23

(7*S*)-3-(2-Iodo-4-pyridyl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**E-23**, Co. No. 225)



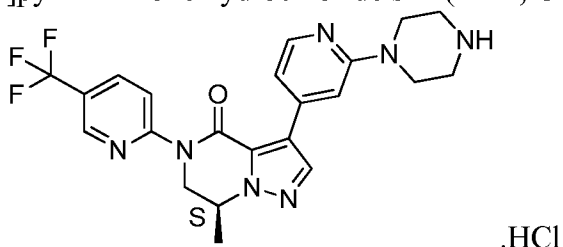
Acetyl chloride (84 µL, 1.18 mmol) was added to a stirred suspension of intermediate **I-26** (320 mg, 0.786 mmol) and NaI (1.18 g, 7.866 mmol) in CH₃CN (12.8 mL) at rt. The mixture was stirred at 120 °C for 30 min under MW irradiation. Then the mixture

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 crude product was purified by flash column chromatography (silica; EtOAc in Heptane 0/100 to 60/40). The desired fractions were collected and evaporated *in vacuo* to yield

5 **compound 225** (289 mg, 74%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.75 (d, *J*=6.5 Hz, 3 H) 4.02 (dd, *J*=12.8, 7.3 Hz, 1 H) 4.30 (dd, *J*=12.7, 4.2 Hz, 1 H) 4.80 (quind, *J*=6.7, 4.2 Hz, 1 H) 7.50 (br. d, *J*=8.3 Hz, 2 H) 7.67 (dd, *J*=5.1, 1.6 Hz, 1 H) 7.72 (br. d, *J*=8.3 Hz, 2 H) 7.80 (s, 1 H) 8.03 - 8.05 (m, 1 H) 8.32 (dd, *J*=5.2, 0.6 Hz, 1 H)

10 Example 24

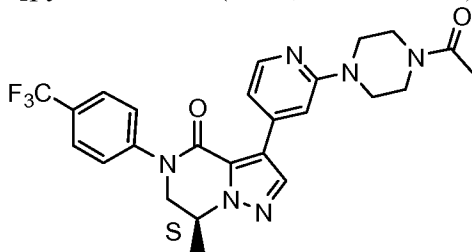
(7*S*)-7-Methyl-3-(2-piperazin-1-yl-4-pyridyl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one hydrochloride salt (**E-24**, Co. No. 175)



Compound 175 was obtained starting from intermediate **I-33a** (200 mg, 0.474 mmol), 1-(4-bromo-2-pyridyl)piperazine (CAS: 1201643-59-5, 157 mg, 0.649 mmol, 1.06 mmol), Pd(PPh₃)₄ (34 mg, 0.029 mmol) in 1,4-dioxane (4 mL) and a sat. sol. of Na₂CO₃ (2 mL), following a procedure similar to that described in **E-12**, then treatment with a solution of HCl 5N in *i*PrOH, yielded **compound 175** (224 mg, 84%) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.59 (d, *J*=6.5 Hz, 3 H) 3.22 (br. s., 4 H) 3.83 (br. s., 4 H) 4.10 (dd, *J*=12.9, 7.4 Hz, 1 H) 4.39 (dd, *J*=12.9, 4.2 Hz, 1 H) 4.81 - 4.92 (m, 1 H) 7.29 (br. d, *J*=4.4 Hz, 1 H) 7.56 (br. s., 1 H) 7.69 (br. d, *J*=8.6 Hz, 2 H) 7.84 (br. d, *J*=8.6 Hz, 2 H) 8.11 (d, *J*=5.8 Hz, 1 H) 8.19 (br. s., 1 H) 9.20 (br. s., 2 H).

Example 25

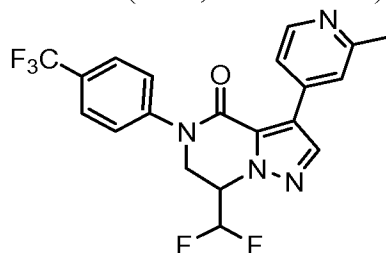
25 (7*S*)-3-[2-(4-Acetylpiperazin-1-yl)-4-pyridyl]-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**E-25**, Co. No. 106)



Acetyl chloride (4 μ L, 0.060 mmol) was added to a solution of **compound 175** (25 mg, 0.054 mmol) and TEA (16 μ L, 0.115 mmol) in DCM (1 mL) under nitrogen. The mixture was stirred at rt for 5 h. Then the mixture was diluted with HCl 0.1N and extracted with DCM. The organic layer was separated, dried (MgSO₄), filtered and the solvent
5 evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; MeOH in DCM 0/100 to 05/95). The desired fractions were collected and concentrated *in vacuo* to yield **compound 106** (17 mg, 62%) as a solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.75 (d, *J*=6.5 Hz, 3 H) 2.13 (s, 3 H) 3.49 - 3.55 (m, 2 H) 3.55 - 3.61 (m, 2 H) 3.61 - 3.67 (m, 2 H) 3.70 - 3.77 (m, 2 H) 4.01 (dd, *J*=12.7, 6.9 Hz, 1 H) 4.30 (dd,
10 *J*=12.7, 4.2 Hz, 1 H) 4.79 (quind, *J*=6.6, 4.4 Hz, 1 H) 6.94 (dd, *J*=5.2, 1.3 Hz, 1 H) 7.17 (br. s, 1 H) 7.46 - 7.55 (m, 2 H) 7.66 - 7.76 (m, 2 H) 7.80 (s, 1 H) 8.19 (dd, *J*=5.2, 0.6 Hz, 1 H).

Example 26

15 7-(Difluoromethyl)-3-(2-methyl-4-pyridyl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one (**E-26**, Co. No. **181**)

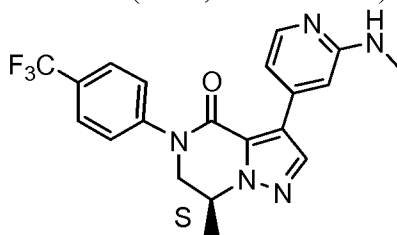


Compound 181 was obtained starting from intermediate **I-46** (71 mg, 0.169 mmol) using Pd/C 10% (36 mg, 0.033 mmol) in EtOH (3 mL) under H₂ atmospheric pressure,
20 following a procedure similar to that described in **E-6**, yielding **compound 181** (13 mg, 19%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 2.58 (s, 3 H) 4.36 (dd, *J*=13.6, 3.2 Hz, 1 H) 4.61 (ddd, *J*=13.6, 5.0, 1.3 Hz, 1 H) 4.88 - 4.99 (m, 1 H) 6.21 - 6.55 (m, 1 H) 7.45 (dd, *J*=5.2, 1.3 Hz, 1 H) 7.47 - 7.54 (m, 3 H) 7.73 (br. d, *J*=8.3 Hz, 2 H) 7.89 (s, 1 H) 8.50 (d, *J*=5.1 Hz, 1 H).

25

Example 27

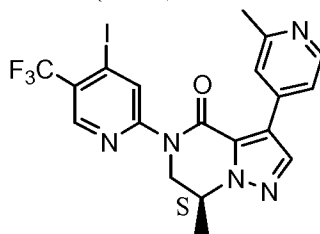
(7*S*)-7-Methyl-3-[2-(methylamino)-4-pyridyl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**E-27**, **Co. No. 147**)



- 5 **Compound 147** was obtained starting from intermediate **I-33a** (1.5 g, 3.561 mmol), 4-bromo-*N*-methyl-pyridin-2-amine (799 mg, 4.273 mmol, 1.06 mmol), Pd(PPh₃)₄ (206 mg, 0.178 mmol) in 1,4-dioxane (8.1 mL) and a sat. sol. of Na₂CO₃ (8.2 mL), following a procedure similar to that described in **E-12**, yielding **compound 147** (1.14 g, 80%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ ppm 1.74 (d, *J*=6.4 Hz, 3 H) 2.93 (d,
- 10 *J*=5.2 Hz, 3 H) 4.00 (dd, *J*=12.6, 7.1 Hz, 1 H) 4.29 (dd, *J*=12.7, 4.0 Hz, 1 H) 4.54 (br. d, *J*=3.2 Hz, 1 H) 4.73 - 4.82 (m, 1 H) 6.84 (s, 1 H) 6.86 (d, *J*=5.2 Hz, 1 H) 7.50 (br. d, *J*=8.4 Hz, 2 H) 7.70 (br. d, *J*=8.4 Hz, 2 H) 7.79 (s, 1 H) 8.09 (d, *J*=5.2 Hz, 1 H).

Example 28

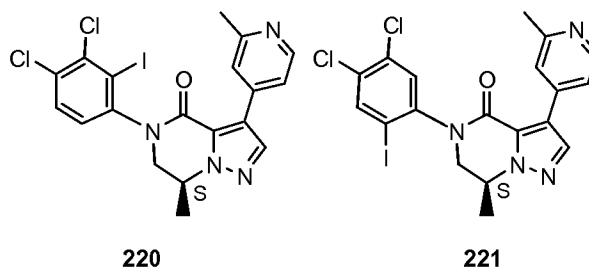
- 15 (7*S*)-5-[4-Iodo-5-(trifluoromethyl)-2-pyridyl]-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4-one (**E-28**, **Co. No. 212**)



- Intermediate **I-18** (320 mg, 1.32 mmol) was added portionwise to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 78 mg, 1.98 mmol) in DMF (5 mL)
- 20 at rt. The mixture was stirred at rt for 15 min and a solution of 2-chloro-4-iodo-5-(trifluoromethyl)pyridine (446 mg, 1.453 mmol) in DMF (5 mL) was added at rt. The mixture was stirred at 80 °C for 16 h. Then more sodium hydride (60% dispersion in mineral oil, 27 mg, 0.66 mmol) was added at rt and the mixture was stirred at 80 °C for 1 h. The mixture was treated with 10% NH₄Cl sol./brine and extracted with EtOAc.
- 25 The organic layer was separated, washed with brine, 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 100/0). The desired fractions were collected and the solvents concentrated *in vacuo* to yield **compound 212** (220 mg, 32%) as a white foam.

Example 29

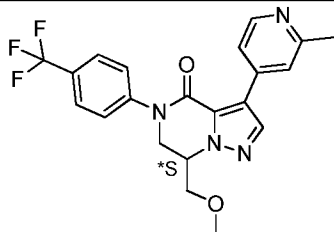
(7S)-5-(3,4-Dichloro-2-iodo-phenyl)-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one (**Co. No. 220**) and (7S)-5-(3,4-dichloro-6-iodo-1-methyl-cyclohexa-1,3,5-trien-1-yl)-7-methyl-3-(2-methyl-4-pyridyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one (**Co. No. 221**) (**E-29**, **Co. No. 220** and **Co. No. 221**)



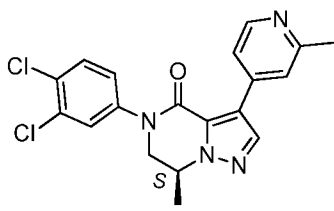
HATU (89 mg, 0.235 mmol) was added to a stirred solution of mixture intermediate compounds **I-63a** and **I-63b** (250 mg, 0.235 mmol) and TEA (65 μ L, 0.471 mmol) in DMF (3 mL). The mixture was stirred at rt for 2 h. The mixture was treated with a sat. sol. of NH_4Cl and a sat. sol. of NaHCO_3 and extracted with EtOAc. 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 Heptane 0/100 to 90/10). The desired fractions were collected and the solvents concentrated *in vacuo* to give two fractions that were triturated with DCM/Heptane to yield **compound 220** (55 mg, 45%) and **compound 221** (20 mg, 16%) as solids. Compound 220: ^1H NMR (500 MHz, CDCl_3) δ ppm 1.78 (d, $J=6.4$ Hz, 2 H) 1.85 (d, $J=6.6$ Hz, 1 H) 2.58 (s, 3 H) 3.82 (dd, $J=12.7, 9.2$ Hz, 0.65 H) 3.97 (dd, $J=12.7, 7.2$ Hz, 0.35 H) 4.00 - 4.07 (m, 1 H) 4.76 - 4.84 (m, 0.35 H) 4.92 - 5.00 (m, 0.65 H) 7.39 (s, 0.35 H) 7.40 (s, 0.65 H) 7.48 (br. d, $J=5.2$ Hz, 1 H) 7.52 - 7.56 (m, 1 H) 7.82 (s, 1 H) 8.03 (s, 0.35 H) 8.03 (s, 0.65 H) 8.48 (d, $J=5.2$ Hz, 1 H); compound 221: ^1H NMR (500 MHz, CDCl_3) δ ppm 1.78 (d, $J=6.6$ Hz, 2 H) 1.85 (d, $J=6.6$ Hz, 1 H) 2.57 (s, 3 H) 3.81 (dd, $J=12.7, 9.0$ Hz, 0.65 H) 3.98 (dd, $J=12.7, 4.6$ Hz, 0.35 H) 4.02 - 4.11 (m, 1 H) 4.76 - 4.84 (m, 0.35 H) 4.95 - 5.04 (m, 0.65 H) 7.16 (d, $J=8.7$ Hz, 0.35 H) 7.17 (d, $J=8.7$ Hz, 0.65 H) 7.49 (br. d, $J=5.2$ Hz, 1 H) 7.52 - 7.61 (m, 2 H) 7.83 (s, 0.65 H) 7.83 (s, 0.35 H) 8.47 (d, $J=5.2$ Hz, 1 H).

The following final compounds were synthesized by following an analogous synthetic procedure as reported for compound **1** (**E-1**) followed by the procedure for intermediates **I-18** and **I-19** when needed.

Structure	Compound number	Starting material
	Co. No. 70	I-59
	Co. No. 129	Co. No. 70
	Co. No. 130	
	Co. No. 171	I-60
	Co. No. 216	I-61
	Co. No. 217	
	Co. No. 120	I-58

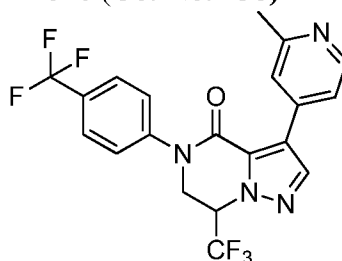
Structure	Compound number	Starting material
	Co. No. 121	

- The following compound was synthesized by following the sequence of an analogous synthetic procedure as reported for intermediate **I-22** starting from intermediate **I-14** and 1-bromo-3,4-dichlorobenzene, followed by the procedure for intermediates **I-23** then following an analogous synthetic procedure as reported for compound **2 (E-2)** using 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine.

Structure	Intermediate number	Starting material
	Co. No. 6a	I-14

Example 30

- 3-(2-Methyl-4-pyridyl)-7-(trifluoromethyl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4-one (**Co. No. 238**)

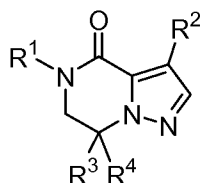


- Compound 238 (E-30)** was obtained starting from intermediate **I-68** (20 mg, 0.042 mmol), 2-picoline-4-boronic acid (8 mg, 0.059 mmol), Pd(PPh₃)₄ (2 mg, 0.002 mmol) in 1,4-dioxane (0.4 mL) and a sat. sol. of NaHCO₃ (0.4 mL) following a procedure similar to that described in **E-12** and purified by RP HPLC ((Stationary phase: C18 XBridge 30 x 100 5 um), (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)), yielding **compound 238** (14 mg, 75%). ¹H NMR (500 MHz, CDCl₃) δ ppm 2.53 (s, 3 H) 4.23 (dd, *J*=14.0, 1.3 Hz, 1 H) 4.67 - 4.74 (m, 1 H) 5.07 - 5.14 (m, 1 H) 7.38 - 7.43 (m, 3 H) 7.47 (s, 1 H) 7.67 (br. d, *J*=8.4 Hz, 2 H) 7.87 (s, 1 H) 8.44 (d, *J*=5.2 Hz, 1 H).

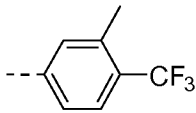
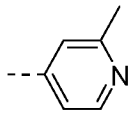
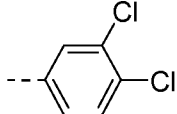
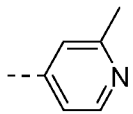
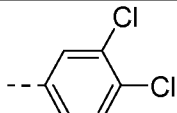
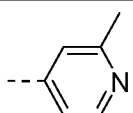
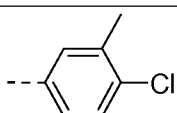
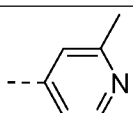
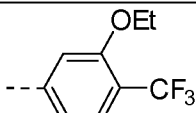
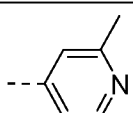
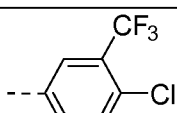
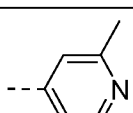
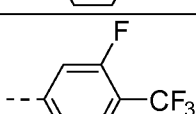
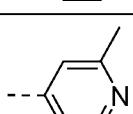
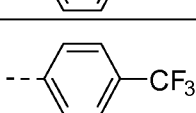
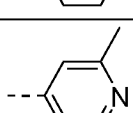
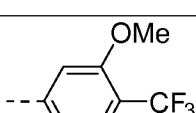
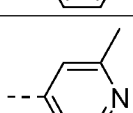
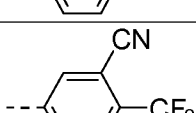
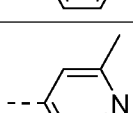
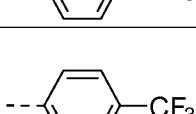
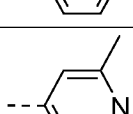
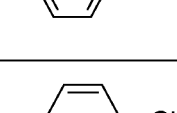
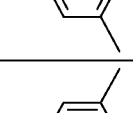
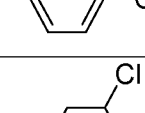
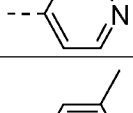
Tables 1a (compounds 1-87) and 1b (with an alternative representation for compounds 1-87) below list additional compounds of Formula (I).

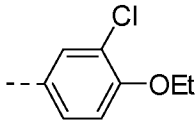
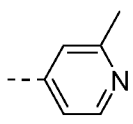
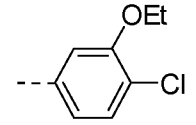
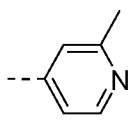
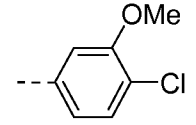
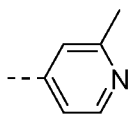
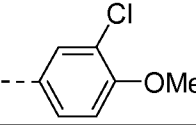
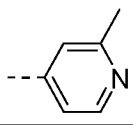
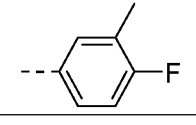
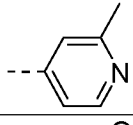
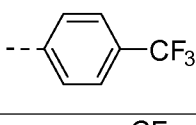
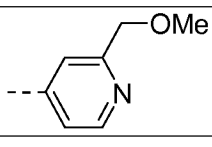
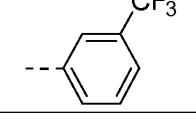
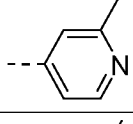
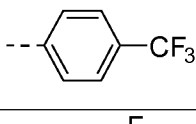
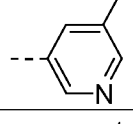
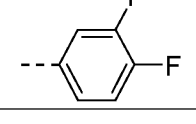
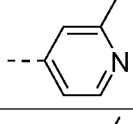
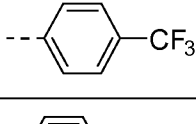
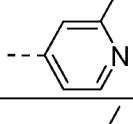
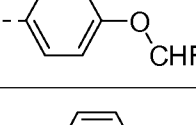
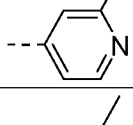
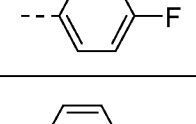
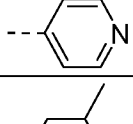
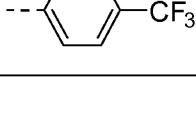
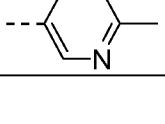
- 5 **Tables 1a and 1b.** The following compounds were prepared following the methods exemplified in the Experimental Part (Ex. No.). Compounds exemplified and described in the experimental part are marked with an asterisk *. The work-up for compounds synthesized by an analogous procedure to E1 can be performed either by filtration through a pad of diatomaceous earth or by extraction with an organic solvent, washing
- 10 with aqueous ammonia. The coupling agent used in the synthesis of compounds synthesized by an analogous procedure to E2 was either a boronic acid or a boronic ester. For some compounds the stereochemical configuration has been designated as *R or *S when the absolute stereochemistry is undetermined although the compound itself has been isolated as a single stereoisomer and is enantiomerically pure.

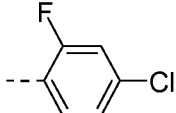
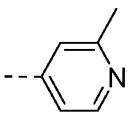
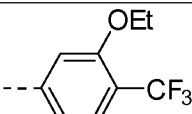
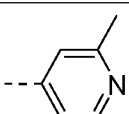
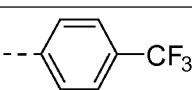
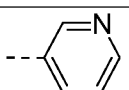
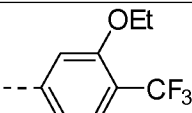
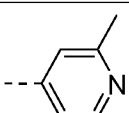
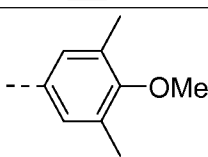
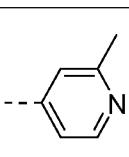
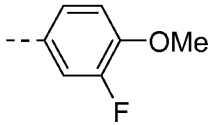
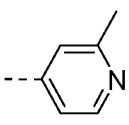
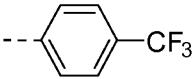
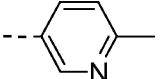
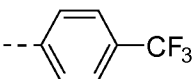
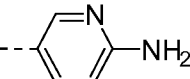
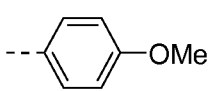
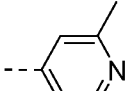
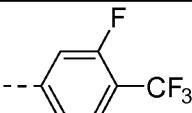
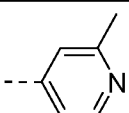
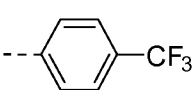
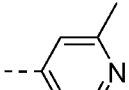
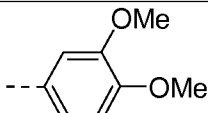
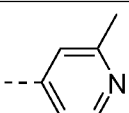
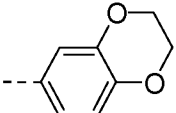
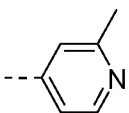
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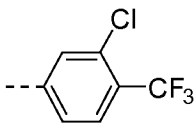
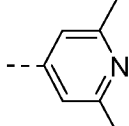
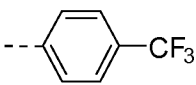
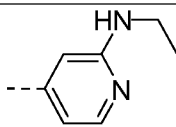
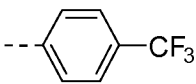
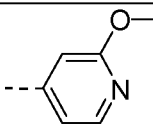
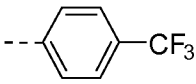
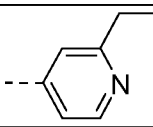
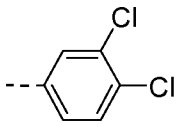
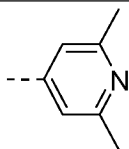
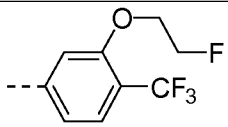
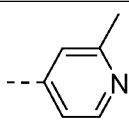
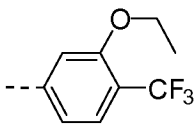
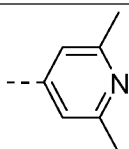
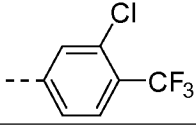
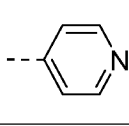
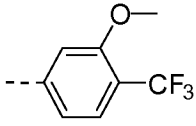
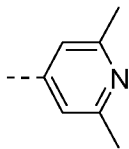
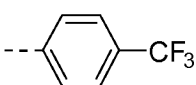
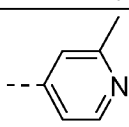
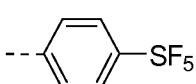
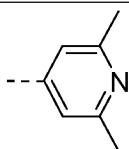
Table 1a

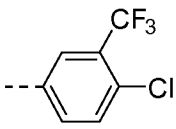
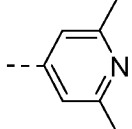
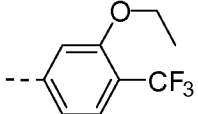
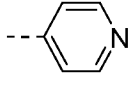
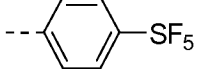
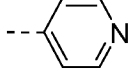
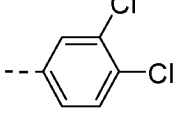
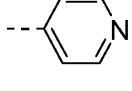
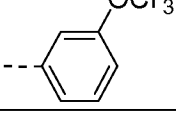
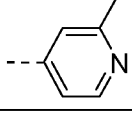
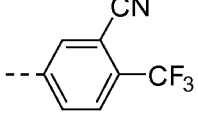
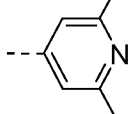
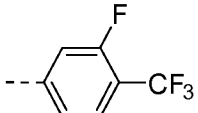
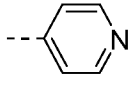
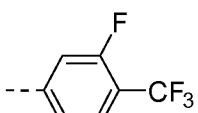
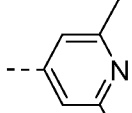
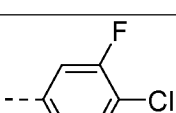
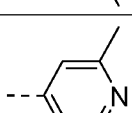
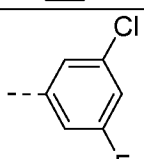
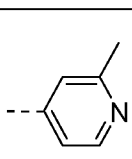
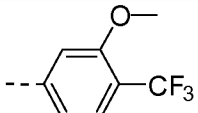
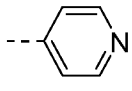
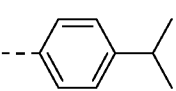
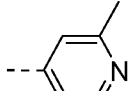
Co. No.	Ex. No.	R ¹	R ²	R ⁴	R ³	Salt form
1	E1*			-Me (S)	-H	
1a						.HCl
1b						.H ₂ SO ₄
1c						.CH ₃ SO ₃ H
1d						.HO ₂ CC H=CHC O ₂ H- <i>cis</i>
2	E2*			-Me (S)	-H	
3	E1			-Me (S)	-H	
4	E1			-Me (S)	-H	

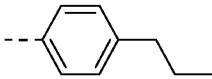
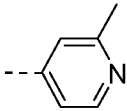
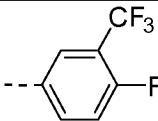
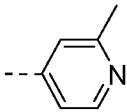
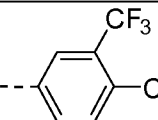
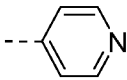
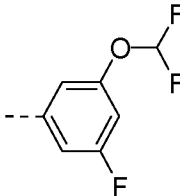
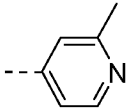
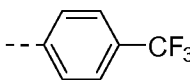
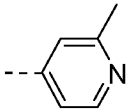
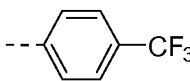
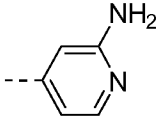
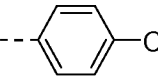
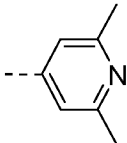
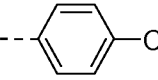
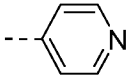
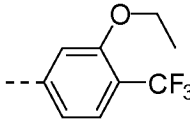
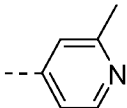
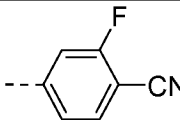
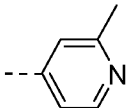
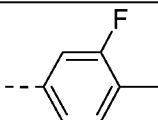
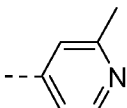
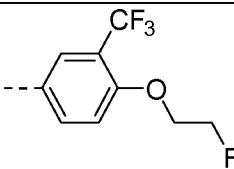
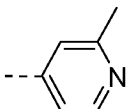
Co. No.	Ex. No.	R ¹	R ²	R ⁴	R ³	Salt form
5	E1			-Me (S)	-H	. HCl
6	E1			-Me (S)	-H	. HCl
6a	E1			-Me (S)	-H	
7	E1			-Me (S)	-H	
8	E1			-Me (S)	-H	
9	E1			-Me (S)	-H	
10	E1			-Me (S)	-H	
11	E1			-Me	-H	
12	E1			-Me (S)	-H	. HCl
13	E1			-Me (S)	-H	
14	E2			-Me (S)	-H	
15	E1			-Me (S)	-H	. HCl
16	E1			-Me (S)	-H	

Co. No.	Ex. No.	R ¹	R ²	R ⁴	R ³	Salt form
17	E1			-Me (S)	-H	. HCl
18	E1			-Me (S)	-H	
19	E1			-Me (S)	-H	
20	E1			-Me (S)	-H	. HCl
21	E1			-Me (S)	-H	
22	E2			-Me (S)	-H	. HCl
23	E1			-Me (S)	-H	
24	E2			-Me (S)	-H	
25	E1			-Me (S)	-H	. HCl
26	E1			-Me (R)	-H	
27	E1			-Me (S)	-H	
28	E1			-Me (S)	-H	. HCl
29	E2			-Me (S)	-H	

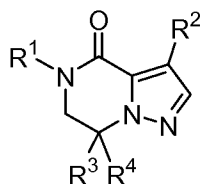
Co. No.	Ex. No.	R ¹	R ²	R ⁴	R ³	Salt form
30	E1			-Me (S)	-H	
31	E1			-Me (R)	-H	
32	E2			-Me (S)	-H	
33	E1			-H	-H	
34	E1			-Me (S)	-H	
35	E1			-Me (S)	-H	. HCl
36	E2			-Me (S)	-H	
37	E2			-Me (S)	-H	
38	E1			-Me (S)	-H	. HCl
39	E1			-H	-H	
40	E1			-H	-H	
41	E1			-Me (S)	-H	
42	E1			-Me (S)	-H	

Co. No.	Ex. No.	R ¹	R ²	R ⁴	R ³	Salt form
43	E1			-Me (S)	-H	
44	E4*			-Me (S)	-H	
45	E5*			-Me (S)	-H	
46	E6*			-Me (S)	-H	
47	E1			-Me (S)	-H	
48	E1			-Me (S)	-H	
49	E1			-Me (S)	-H	
50	E1			-Me (S)	-H	
51	E1			-Me (S)	-H	
52	E8*			-CH2F	-H	
53	E1			-Me (S)	-H	

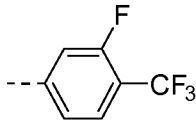
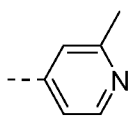
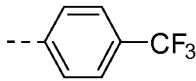
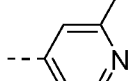
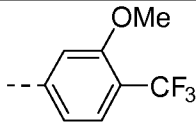
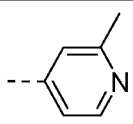
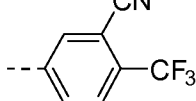
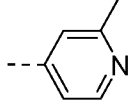
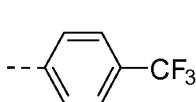
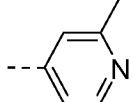
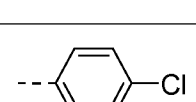
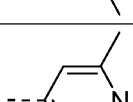
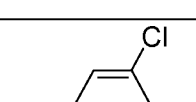
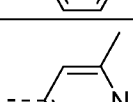
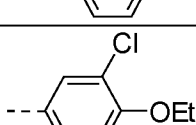
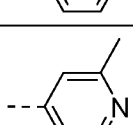
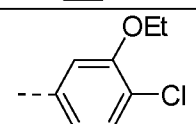
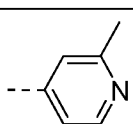
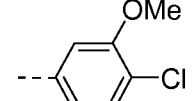
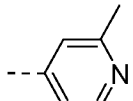
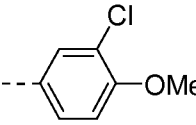
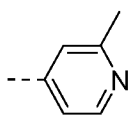
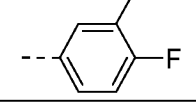
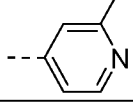
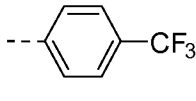
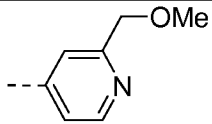
Co. No.	Ex. No.	R ¹	R ²	R ⁴	R ³	Salt form
54	E1			-Me (S)	-H	
55	E1			-Me (S)	-H	
56	E1			-Me (S)	-H	
57	E1			-Me (S)	-H	
58	E1			-Me (S)	-H	. HCl
59	E1			-Me (S)	-H	
60	E1			-Me (S)	-H	
61	E1			-Me (S)	-H	
62	E1			-Me (S)	-H	
63	E1			-Me (S)	-H	. HCl
64	E1			-Me (S)	-H	
65	E1			-Me (S)	-H	. HCl

Co. No.	Ex. No.	R ¹	R ²	R ⁴	R ³	Salt form
66	E1			-Me (S)	-H	. HCl
67	E9*			-Me (S)	-H	
68	E1			-Me (S)	-H	
69	E1			-Me (S)	-H	. HCl
70	E1			-CH ₂ CH ₃	-H	
71	E3*			-Me (S)	-H	
72	E1			-Me (S)	-H	
73	E1			-Me (S)	-H	
74	E1			-CH ₂ OH	-H	
75	E1			-Me (S)	-H	
76	E1			-Me (S)	-H	
77	E10*			-Me (S)	-H	

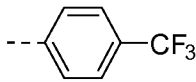
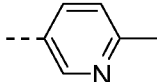
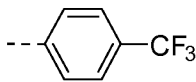
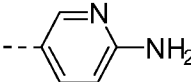
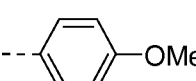
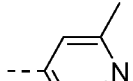
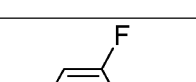
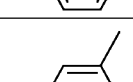
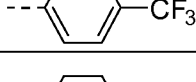
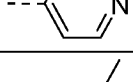
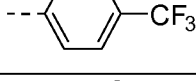
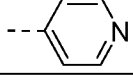
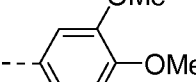
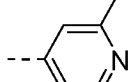
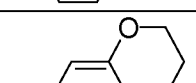
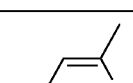
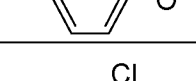
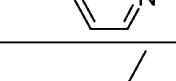
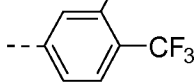
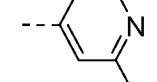
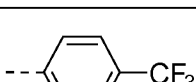
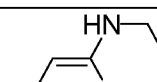
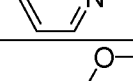
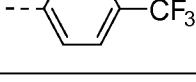
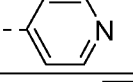
Co. No.	Ex. No.	R ¹	R ²	R ⁴	R ³	Salt form
78	E1			-Me (S)	-H	
79	E1			-Me (S)	-H	. HCl
80	E1			-Me (S)	-H	
81	E11*			-Me (S)	-H	. HCl
82	E1			-Me (S)	-H	
83	E1			-Me (S)	-H	
84	E1			-Me (S)	-H	
85	E1			-Me (S)	-H	
86	E1			-Me (S)	-H	
87	E7*			-CH ₂ OH	-H	

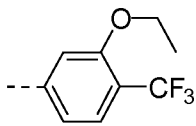
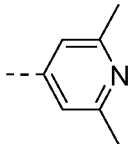
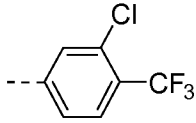
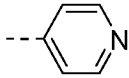
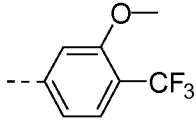
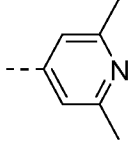
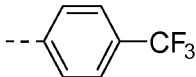
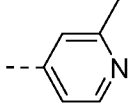
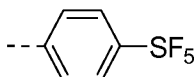
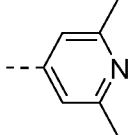
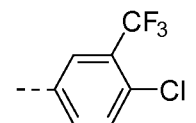
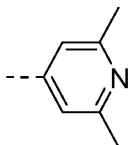
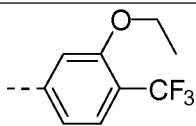
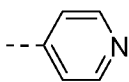
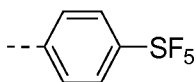
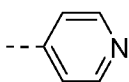
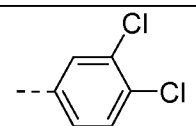
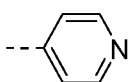
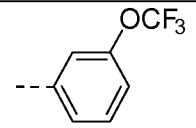
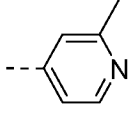
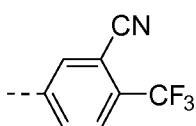
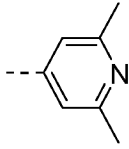
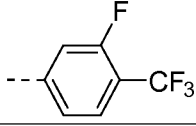
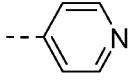
Table 1b

Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
1	E1*			CH(CH ₃) (S)	
1a					.HCl
1b					.H ₂ SO ₄
1c					.CH ₃ SO ₃ H
1d					.HO ₂ CCH=CHCO ₂ H- <i>cis</i>
2	E2*			CH(CH ₃) (S)	
3	E1			CH(CH ₃) (S)	
4	E1			CH(CH ₃) (S)	
5	E1			CH(CH ₃) (S)	. HCl
6	E1			CH(CH ₃) (S)	. HCl
6a	E1			CH(CH ₃) (S)	
7	E1			CH(CH ₃) (S)	
8	E1			CH(CH ₃) (S)	
9	E1			CH(CH ₃) (S)	

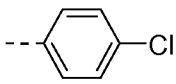
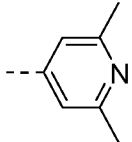
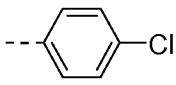
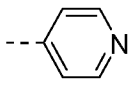
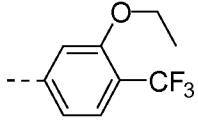
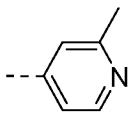
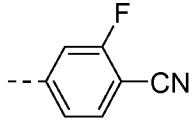
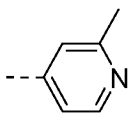
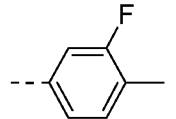
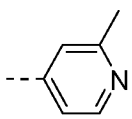
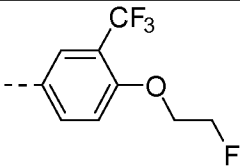
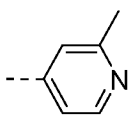
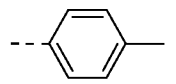
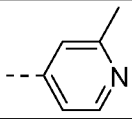
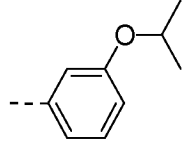
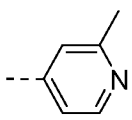
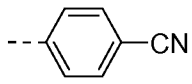
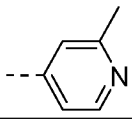
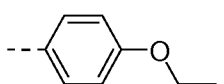
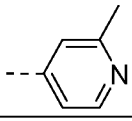
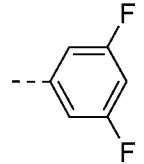
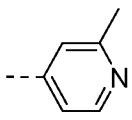
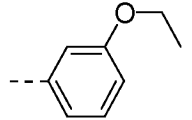
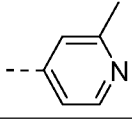
Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
10	E1			CH(CH ₃) (S)	
11	E1			CH(CH ₃)	
12	E1			CH(CH ₃) (S)	. HCl
13	E1			CH(CH ₃) (S)	
14	E2			CH(CH ₃) (S)	
15	E1			CH(CH ₃) (S)	. HCl
16	E1			CH(CH ₃) (S)	
17	E1			CH(CH ₃) (S)	. HCl
18	E1			CH(CH ₃) (S)	
19	E1			CH(CH ₃) (S)	
20	E1			CH(CH ₃) (S)	. HCl
21	E1			CH(CH ₃) (S)	
22	E2			CH(CH ₃) (S)	. HCl

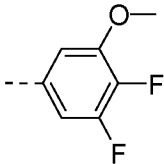
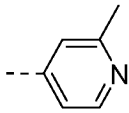
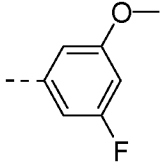
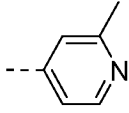
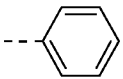
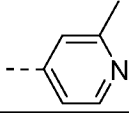
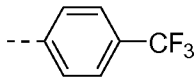
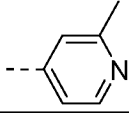
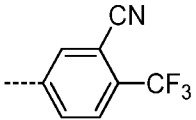
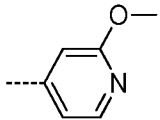
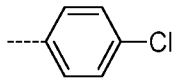
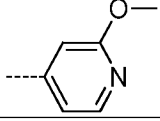
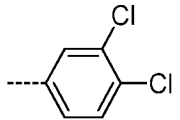
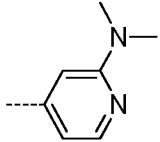
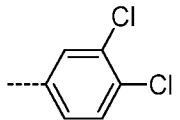
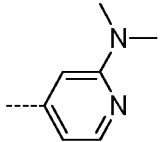
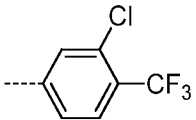
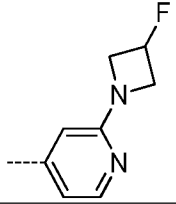
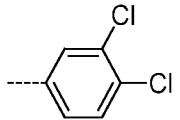
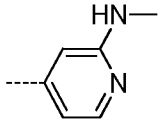
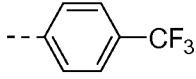
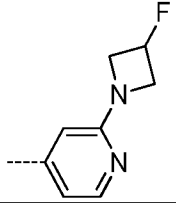
Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
23	E1			CH(CH ₃) (S)	
24	E2			CH(CH ₃) (S)	
25	E1			CH(CH ₃) (S)	. HCl
26	E1			CH(CH ₃) (R)	
27	E1			CH(CH ₃) (S)	
28	E1			CH(CH ₃) (S)	. HCl
29	E2			CH(CH ₃) (S)	
30	E1			CH(CH ₃) (S)	
31	E1			CH(CH ₃) (R)	
32	E2			CH(CH ₃) (S)	
33	E1			CH ₂	
34	E1			CH(CH ₃) (S)	
35	E1			CH(CH ₃) (S)	. HCl

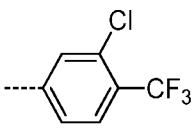
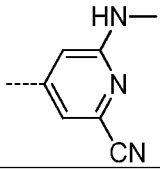
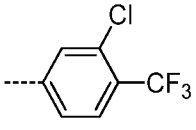
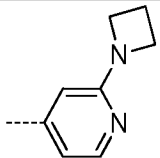
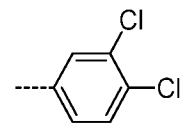
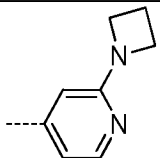
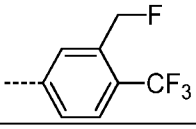
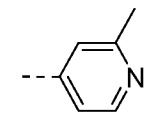
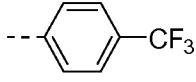
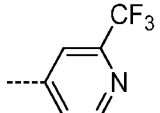
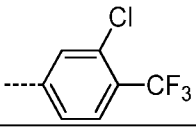
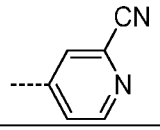
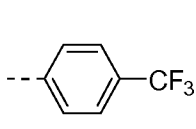
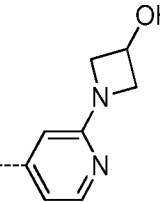
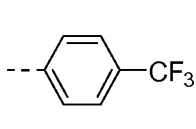
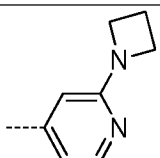
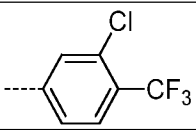
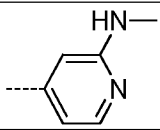
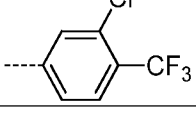
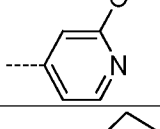
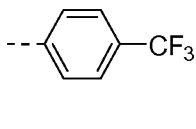
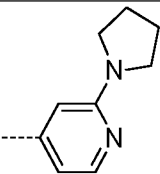
Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
36	E2			CH(CH ₃) (S)	
37	E2			CH(CH ₃) (S)	
38	E1			CH(CH ₃) (S)	. HCl
39	E1			CH ₂	
40	E1			CH ₂	
41	E1			CH(CH ₃) (S)	
42	E1			CH(CH ₃) (S)	
43	E1			CH(CH ₃) (S)	
44	E4*			CH(CH ₃) (S)	
45	E5*			CH(CH ₃) (S)	
46	E6*			CH(CH ₃) (S)	
47	E1			CH(CH ₃) (S)	
48	E1			CH(CH ₃) (S)	

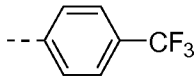
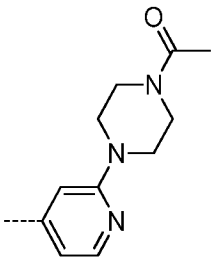
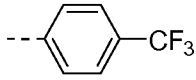
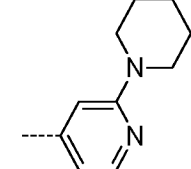
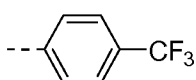
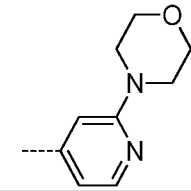
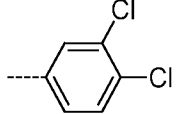
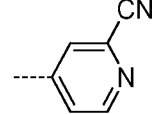
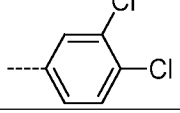
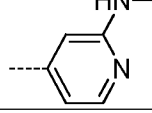
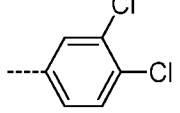
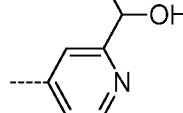
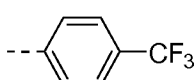
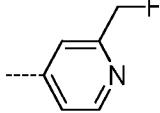
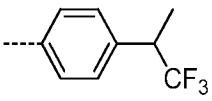
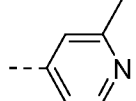
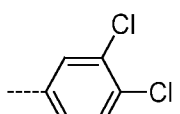
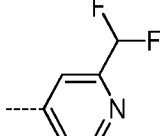
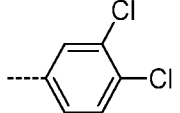
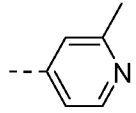
Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
49	E1			CH(CH ₃) (S)	
50	E1			CH(CH ₃) (S)	
51	E1			CH(CH ₃) (S)	
52	E8*			CH(CH ₂ F)	
53	E1			CH(CH ₃) (S)	
54	E1			CH(CH ₃) (S)	
55	E1			CH(CH ₃) (S)	
56	E1			CH(CH ₃) (S)	
57	E1			CH(CH ₃) (S)	
58	E1			CH(CH ₃) (S)	. HCl
59	E1			CH(CH ₃) (S)	
60	E1			CH(CH ₃) (S)	

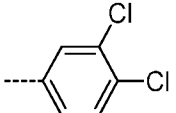
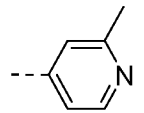
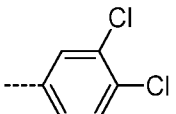
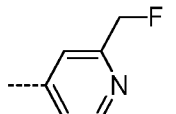
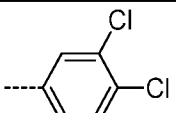
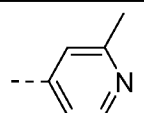
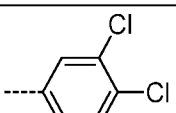
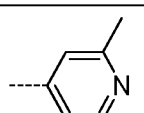
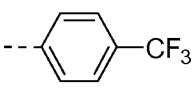
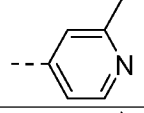
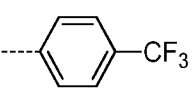
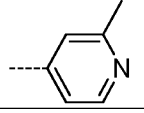
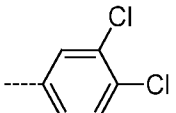
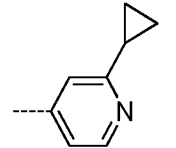
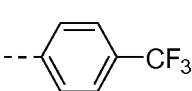
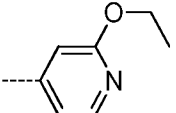
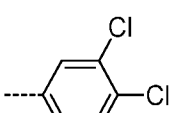
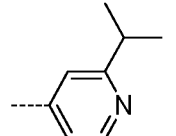
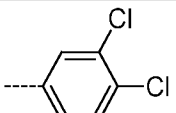
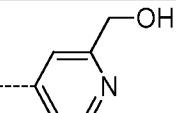
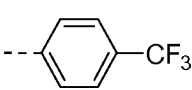
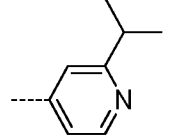
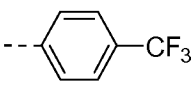
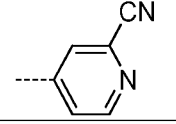
Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
61	E1			CH(CH ₃) (S)	
62	E1			CH(CH ₃) (S)	
63	E1			CH(CH ₃) (S)	. HCl
64	E1			CH(CH ₃) (S)	
65	E1			CH(CH ₃) (S)	. HCl
66	E1			CH(CH ₃) (S)	. HCl
67	E9*			CH(CH ₃) (S)	
68	E1			CH(CH ₃) (S)	
69	E1			CH(CH ₃) (S)	. HCl
70	E1			CH(CH ₂ CH ₃)	
71	E3*			CH(CH ₃) (S)	

Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
72	E1			CH(CH ₃) (S)	
73	E1			CH(CH ₃) (S)	
74	E1			CH(CH ₂ OH)	
75	E1			CH(CH ₃) (S)	
76	E1			CH(CH ₃) (S)	
77	E10*			CH(CH ₃) (S)	
78	E1			CH(CH ₃) (S)	
79	E1			CH(CH ₃) (S)	. HCl
80	E1			CH(CH ₃) (S)	
81	E11*			CH(CH ₃) (S)	. HCl
82	E1			CH(CH ₃) (S)	
83	E1			CH(CH ₃) (S)	

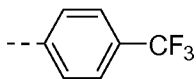
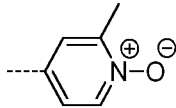
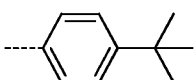
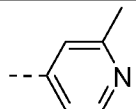
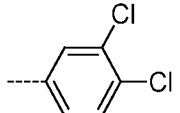
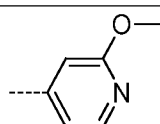
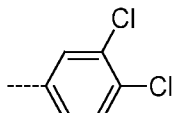
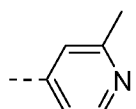
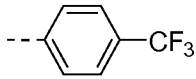
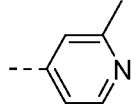
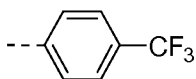
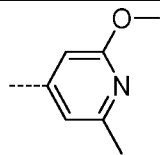
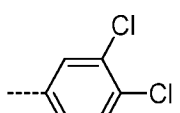
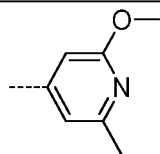
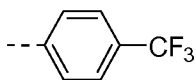
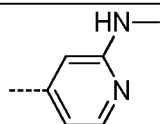
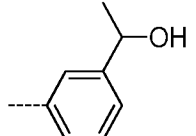
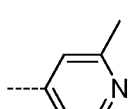
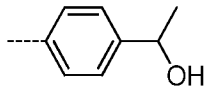
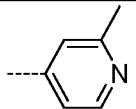
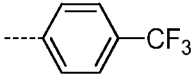
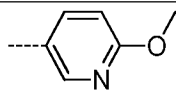
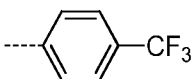
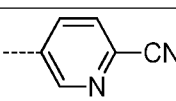
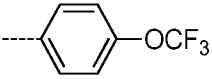
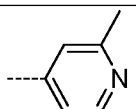
Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
84	E1			CH(CH ₃) (S)	
85	E1			CH(CH ₃) (S)	
86	E1			CH(CH ₃) (S)	
87	E7*			CH(CH ₂ OH)	
88	E3			CH(CH ₃) (S)	
89	E3			CH(CH ₃) (S)	
90	E8			CH(CH ₂ F) (*R)	
91	E8			CH(CH ₂ F) (*S)	
92	E13			CH(CH ₃) (S)	
93	E8			CH(CH ₂ F)	
94	E13			CH(CH ₃) (S)	

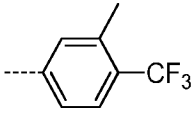
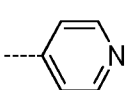
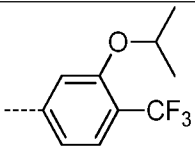
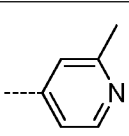
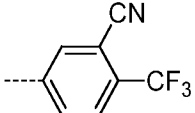
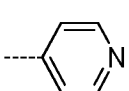
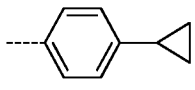
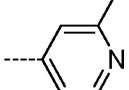
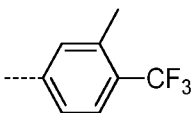
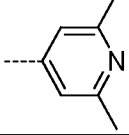
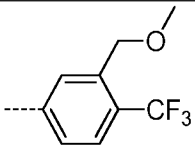
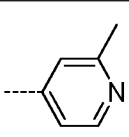
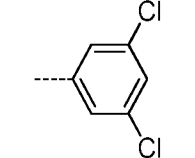
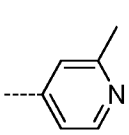
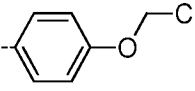
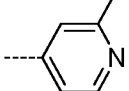
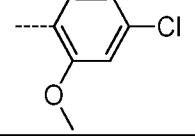
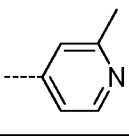
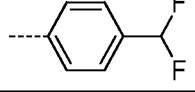
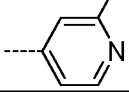
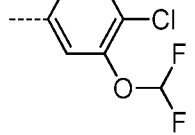
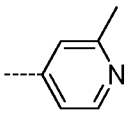
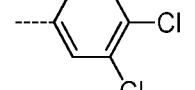
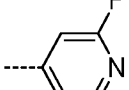
Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
95	E13			CH(CH ₃) (S)	
96	E1			CH(CH ₃) (S)	
97	E13			CH(CH ₃) (S)	
98	E8			CH(CH ₃) (S)	
99	E13			CH(CH ₃) (S)	
100	E13			CH(CH ₃) (S)	
101	E12			CH(CH ₃) (S)	
102	E12			CH(CH ₃) (S)	
103	E3			CH(CH ₃) (S)	
104	E3			CH(CH ₃) (S)	
105	E12			CH(CH ₃) (S)	

Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
106	E25*			CH(CH ₃) (S)	
107	E12			CH(CH ₃) (S)	. HCl
108	E12			CH(CH ₃) (S)	
109	E12			CH(CH ₃) (S)	
110	E13			CH(CH ₃) (S)	
111	E15*			CH(CH ₃) (S)	
112	E8			CH(CH ₃) (S)	
113	E6			CH(CH ₃) (S)	
114	E8			CH(CH ₃) (S)	
115	E8			CH(CH ₂ F) (*S)	

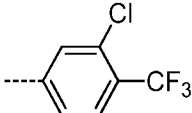
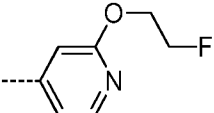
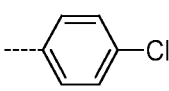
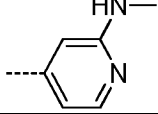
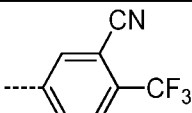
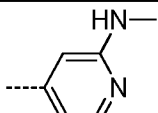
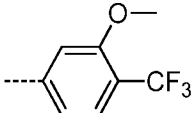
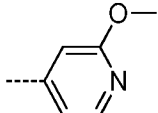
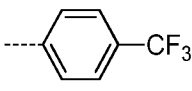
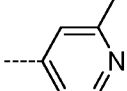
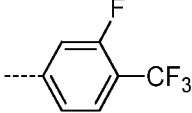
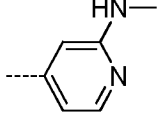
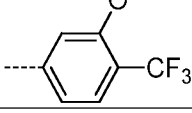
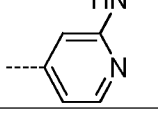
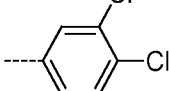
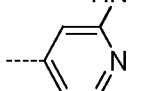
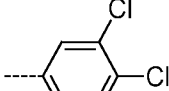
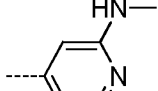
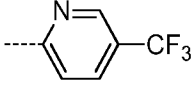
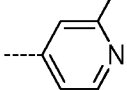
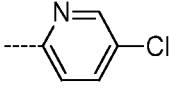
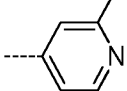
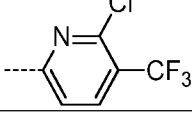
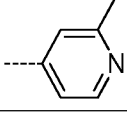
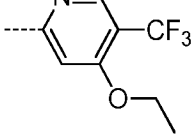
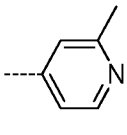
Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
116	E8			CH(CH ₂ F) (*R)	
117	E8			CH(CH ₃) (S)	
118	E1			CH(CH ₂ OMe) (*S)	
119	E1			CH(CH ₂ OMe) (*R)	
120	E1			CH(CH ₂ OMe) (*R)	
121	E1			CH(CH ₂ OMe) (*S)	
122	E13			CH(CH ₃) (S)	. 2 HCl
123	E2			CH(CH ₃) (S)	
124	E13			CH(CH ₃) (S)	
125	E14*			CH(CH ₃) (S)	
126	E13*			CH(CH ₃) (S)	
127	E12*			CH(CH ₃) (S)	

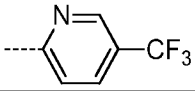
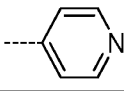
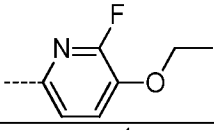
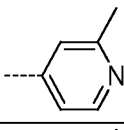
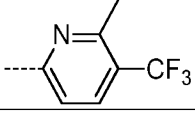
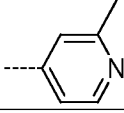
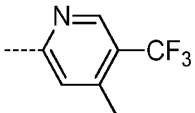
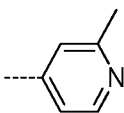
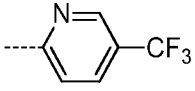
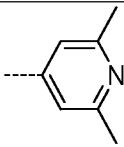
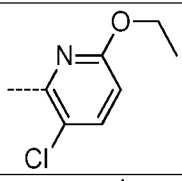
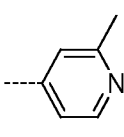
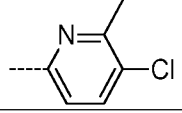
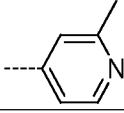
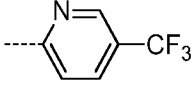
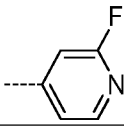
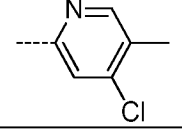
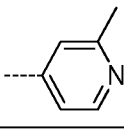
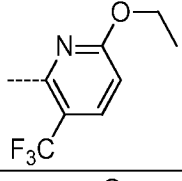
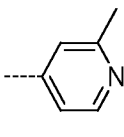
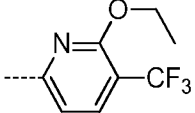
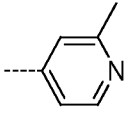
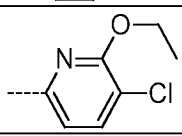
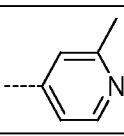
Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
128	E14			CH(CH ₃) (S)	
129	E1			CH(CH ₂ CH ₃) (R)	
130	E1			CH(CH ₂ CH ₃) (S)	
131	E8			CH(CH ₃) (S)	
132	E1			CH(CH ₃) (S)	
133	E2			CH(CH ₃) (S)	. HCl
134	E6			CH(CH ₃) (S)	
135	E17			CH(CH ₃) (S)	
136	E1			CH(CH ₃) (S)	
137	E2			CH(CH ₃) (S)	. HCl
138	E2			CH(CH ₃) (S)	. HCl
139	E1			CH(CH ₃) (S)	

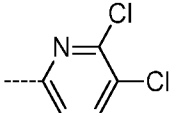
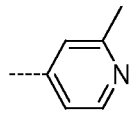
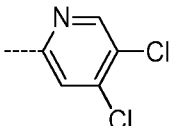
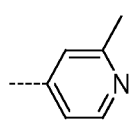
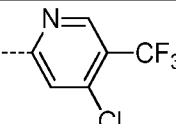
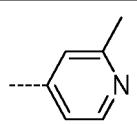
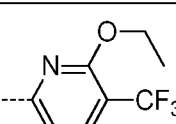
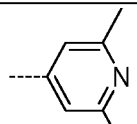
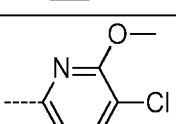
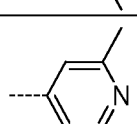
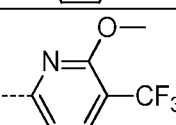
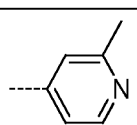
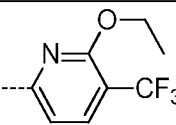
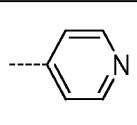
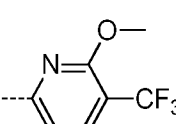
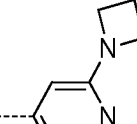
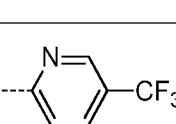
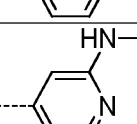
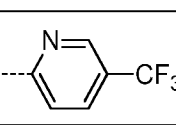
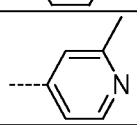
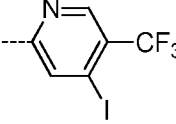
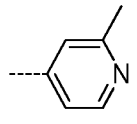
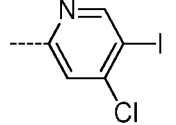
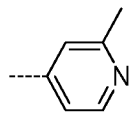
Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
140	E16*			CH(CH ₃) (S)	
141	E1			CH(CH ₃) (S)	
142	E3			CH(CH ₃) (S)	
143	E1			CH(CH ₂ OMe)	
144	E1			CH(CH ₂ OMe)	
145	E2			CH(CH ₃) (S)	
146	E2			CH(CH ₃) (S)	
147	E27*			CH(CH ₃) (S)	
148	E1			CH(CH ₃) (S)	
149	E17*			CH(CH ₃) (S)	
150	E3			CH(CH ₃) (S)	
151	E2			CH(CH ₃) (S)	
152	E1			CH(CH ₃) (S)	

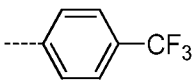
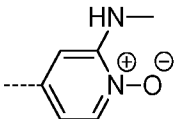
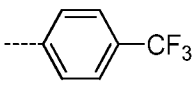
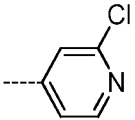
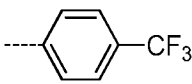
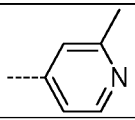
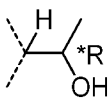
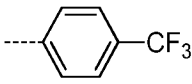
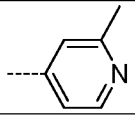
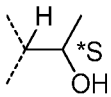
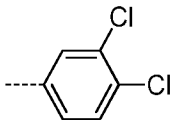
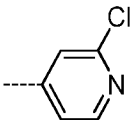
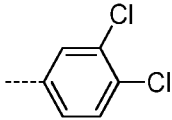
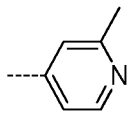
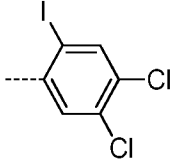
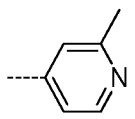
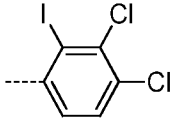
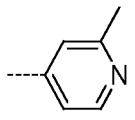
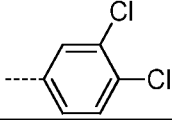
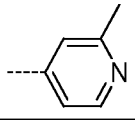
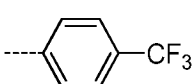
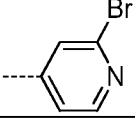
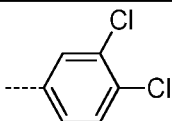
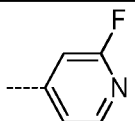
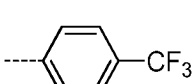
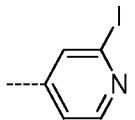
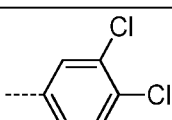
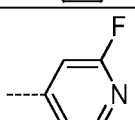
Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
153	E1			CH(CH ₃) (S)	
154	E1			CH(CH ₃) (S)	
155	E1			CH(CH ₃) (S)	
156	E18*			CH(CH ₃) (S)	
157	E1			CH(CH ₃) (S)	
158	E1			CH(CH ₃) (S)	
159	E1			CH(CH ₃) (S)	
160	E1			CH(CH ₃) (S)	
161	E1			CH(CH ₃) (S)	
162	E1			CH(CH ₃) (S)	
163	E1			CH(CH ₃) (S)	
164	E3			CH(CH ₃) (S)	

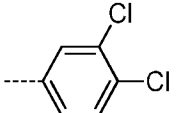
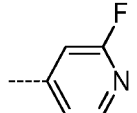
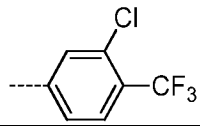
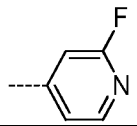
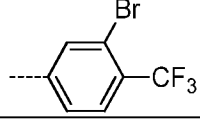
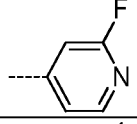
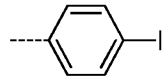
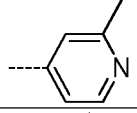
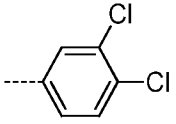
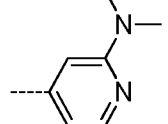
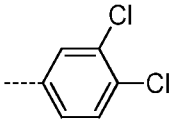
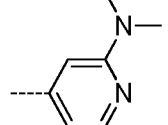
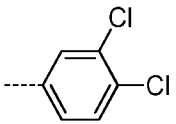
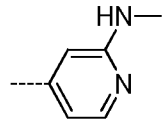
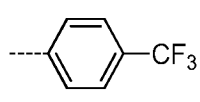
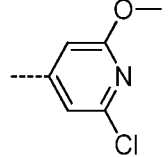
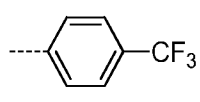
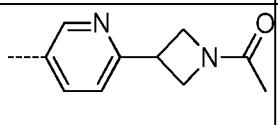
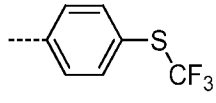
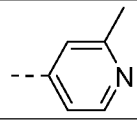
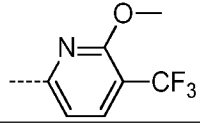
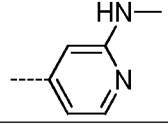
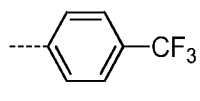
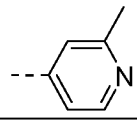
Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
165	E1			CH(CH ₃) (S)	
166	E13			CH(CH ₃) (S)	
167	E1			CH(CH ₃) (S)	
168	E1			CH(CH ₃) (S)	
169	E1			CH(CH ₃) (S)	
170	I-38* E16			CH(CH ₃) (S)	
171	E1			C(CH ₃) ₂	
172	E1			CH(CH ₃) (S)	
173	E13			CH(CH ₃) (S)	. HCl
174	E1			CH(CH ₃) (S)	
175	E24*			CH(CH ₃) (S)	. HCl
176	E19*			CH(CH ₃) (S)	

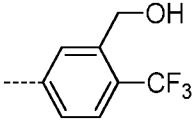
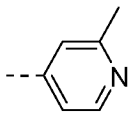
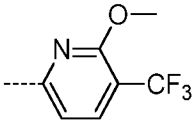
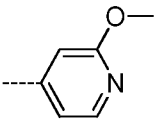
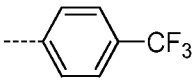
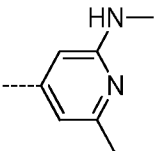
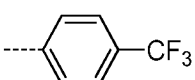
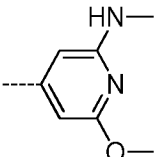
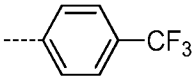
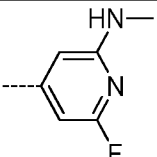
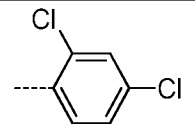
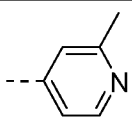
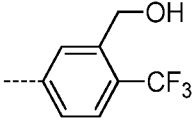
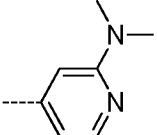
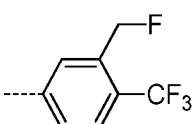
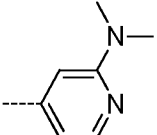
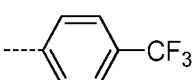
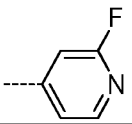
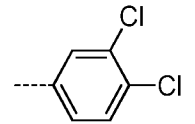
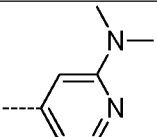
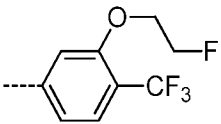
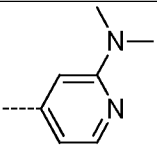
Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
177	E10			CH(CH ₃) (S)	
178	E3			CH(CH ₃) (S)	
179	E3			CH(CH ₃) (S)	
180	E3			CH(CH ₃) (S)	
181	E26*			CH(CHF ₂)	
182	E3			CH(CH ₃) (S)	
183	E3			CH(CH ₃) (S)	
184	E8			CH(CH ₂ F) (*R)	
185	E8			CH(CH ₂ F) (*S)	
186	E20*			CH(CH ₃) (S)	
187	E1			CH(CH ₃) (S)	
188	I-43* E20			CH(CH ₃) (S)	
189	E22a*			CH(CH ₃) (S)	

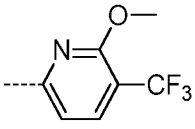
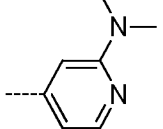
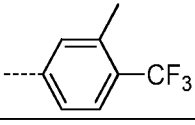
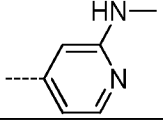
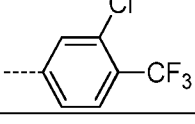
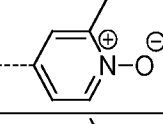
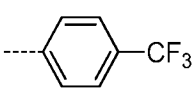
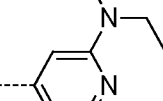
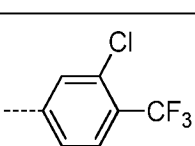
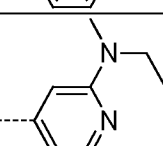
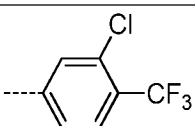
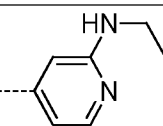
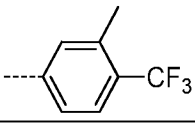
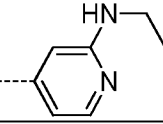
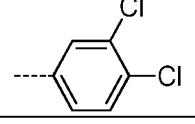
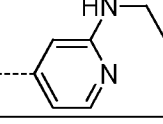
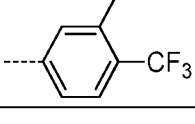
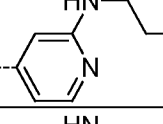
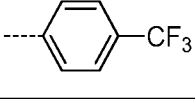
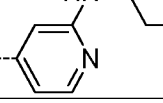
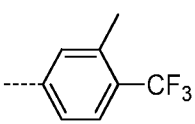
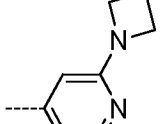
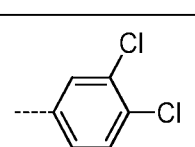
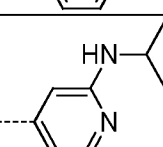
Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
190	E20			CH(CH ₃) (S)	
191	E1			CH(CH ₃) (S)	
192	E21*			CH(CH ₃) (S)	
193	E21			CH(CH ₃) (S)	
194	E20			CH(CH ₃) (S)	
195	E20			CH(CH ₃) (S)	
196	E20			CH(CH ₃) (S)	
197	E3			CH(CH ₃) (S)	
198	E18			CH(CH ₃) (S)	
199	E20			CH(CH ₃) (S)	
200	E20			CH(CH ₃) (S)	
201	E20			CH(CH ₃) (S)	

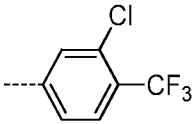
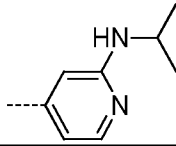
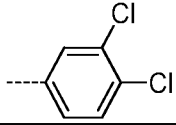
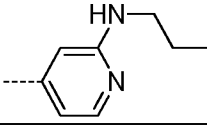
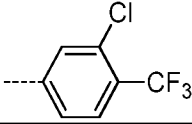
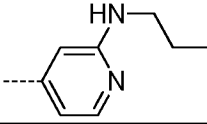
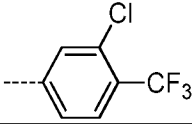
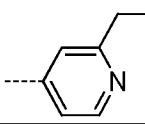
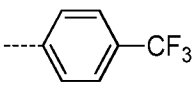
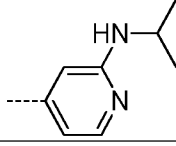
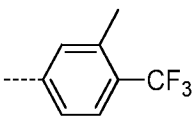
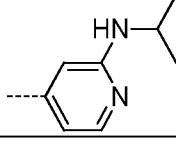
Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
202	E20			CH(CH ₃) (S)	
203	E20			CH(CH ₃) (S)	
204	E22b*			CH(CH ₃) (S)	
205	E20			CH(CH ₃) (S)	
206	E20			CH(CH ₃) (S)	
207	E20			CH(CH ₃) (S)	
208	E20			CH(CH ₃) (S)	
209	E1			CH(CH ₃) (S)	
210	E3			CH(CH ₃) (S)	
211	E1			CH ₂	
212	E28*			CH(CH ₃) (S)	
213	E28			CH(CH ₃) (S)	

Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
214	E13			CH(CH ₃) (S)	
215	I-26* E3			CH(CH ₃) (S)	
216	E1				
217	E1				
218	E3			CH(CH ₃) (S)	
219	E2			CH(CH ₂ OH)	
220	E29*			CH(CH ₃) (S)	
221	E29*			CH(CH ₃) (S)	
222	E8			CH(CH ₂ F)	
223	E2			CH(CH ₃) (S)	
224	E3			CH(CH ₂ OH)	
225	E23*			CH(CH ₃) (S)	
226	E3			CH(CH ₂ OH) (*S)	

Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
227	E3			CH(CH ₂ OH) (*R)	
228	E3			CH(CH ₃) (S)	
229	E1			CH(CH ₃) (S)	
230	E1			CH(CH ₃) (S)	
231	E10			CH(CH ₂ OH) (*S)	
232	E10			CH(CH ₂ OH) (*R)	
233	E10			CH(CH ₂ OH)	
234	E3			CH(CH ₃) (S)	
235	E13			CH(CH ₃) (S)	
236	E1			CH(CH ₃) (S)	. HCl
237	E3			CH(CH ₃) (S)	
238	E30*			CH(CF ₃)	

Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
239	E1			CH(CH ₃) (S)	
240	E3			CH(CH ₃) (S)	
241	E3			CH(CH ₃) (S)	
242	E2			CH(CH ₃) (S)	
243	E2			CH(CH ₃) (S)	
244	E1			CH ₂	
245	E1			CH(CH ₃) (S)	
246	E8			CH(CH ₃) (S)	
247	E13			CH(CH ₃) (S)	
248	E12			CH(CH ₃) (S)	
249	E1			CH(CH ₃) (S)	

Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
250	E20			CH(CH ₃) (S)	
251	E12			CH(CH ₃) (S)	
252	E16			CH(CH ₃) (S)	
253	E13			CH(CH ₃) (S)	
254	E4			CH(CH ₃) (S)	
255	E13			CH(CH ₃) (S)	
256	E12			CH(CH ₃) (S)	
257	E13			CH(CH ₃) (S)	
258	E12			CH(CH ₃) (S)	
259	E13			CH(CH ₃) (S)	
260	E12			CH(CH ₃) (S)	
261	E12			CH(CH ₃) (S)	

Co. No.	Ex. No.	R ¹	R ²	CR ³ R ⁴	Salt form
262	E12			CH(CH ₃) (S)	
263	E12			CH(CH ₃) (S)	
264	E12			CH(CH ₃) (S)	
265	E8			CH(CH ₃) (S)	
266	E13			CH(CH ₃) (S)	
267	E12			CH(CH ₃) (S)	

The values of salt stoichiometry or acid content in the compounds as provided herein, are those obtained experimentally and may vary when using different analytical methods. The content of hydrochloric acid reported herein was determined by ¹H NMR integration and/or elemental analysis. For compound 1 the salt stoichiometry was determined by ion chromatography (hydrochloride and sulfate salts) and by NMR (methanesulfonate and maleate salts).

Analytical part

Melting points

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

Mettler FP 62 (A): For a number of compounds, melting points were determined in

open capillary tubes on a Mettler FP62 apparatus. Melting points were measured with a temperature gradient of 3 or 10 °C/minute. Maximum temperature was 300 °C. The melting point was read from a digital display.

Mettler FP 62 (A1): Melting points (m.p.) were determined in open capillary tubes on a Mettler FP62 apparatus. Melting points were measured with a temperature ranging from 50°C to 300°C, using a gradient of 10 °C/minute. The melting point value was read from a digital display.

- 5 Mettler FP 81HT / FP90 (B): For a number of compounds, melting points were determined in open capillary tubes on a FP 81HT / FP90 apparatus (Mettler-Toledo). 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.

- 10 Mettler Toledo MP50 (C): For a number of compounds, melting points were determined in open capillary tubes on a Mettler Toledo MP50. Melting points were measured with a temperature gradient of 10 °C/minute. Maximum temperature was 300 °C. The melting point data was read from a digital display and checked from a video recording system.

- 15 DSC823e (D): For a number of compounds, melting points (m.p.) were determined with a DSC823e (Mettler-Toledo). Melting points were measured with a temperature gradient of 30 °C/minute. Maximum temperature was 400 °C. Peak values were recorded.

LCMS

- 20 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).

- 25 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). Data acquisition was performed with appropriate software.
- 30 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. $[M+NH_4]^+$, $[M+HCOO]^-$, $[M+CH_3COO]^-$ etc...). For molecules with multiple isotopic patterns (Br, Cl.), the reported value is the one obtained for the lowest isotope mass. All results
- 35 were obtained with experimental uncertainties that are commonly associated with the method used.

Hereinafter, “LCT” means LC-Time of Flight, “SQD” Single Quadrupole Detector, “MSD” Mass Selective Detector, “QTOF” Quadrupole-Time of Flight, “RT” room temperature, “BEH” bridged ethylsiloxane/silica hybrid, “DAD” Diode Array Detector.

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

Method	Instrument	Column	Mobile phase	Gradient	Flow ----- Col T	Run time
1	Waters: Acquity [®] UPLC [®] - DAD and SQD	Agilent: Eclipse Plus C18 RRHD (1.8µm, 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	Agilent: HP1100- DAD, Waters: SQD	Agilent: Eclipse Plus C18 (3.5µm, 2.1x30mm)	A: 95% CH ₃ COONH ₄ 6.5mM + 5% CH ₃ CN, B: 1/1 CH ₃ CN/ CH ₃ OH	95% A kept for 0.2 min, to 0% A in 2.8min, held for 0.15min, back to 95% A in 0.15min, held for 1.7min	1 ----- 60	5
3	Agilent 1100 - DAD-MSD G1956A	YMC-pack ODS-AQ C18 (50 x 4.6 mm, 3 µm)	A: 0.1% HCOOH in H ₂ O B: CH ₃ CN	From 95% A to 5% A in 4.8 min, held for 1.0 min, to 95% A in 0.2 min.	2.6 ----- 35	6.0
4	Waters: Acquity [®] UPLC [®] - DAD/SQD	Agilent: Eclipse Plus C18 RRHD (1.8µm, 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 1.8min, held for 0.2min	1 ----- 50	2
5	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

Method	Instrument	Column	Mobile phase	Gradient	Flow ----- Col T	Run time
6	Agilent: HP1100- DAD, MSD G1956B	Agilent: Eclipse Plus C18 (3.5µm, 2.1x30mm)	A: 95% CH ₃ COONH ₄ 6.5mM + 5% CH ₃ CN, B: CH ₃ CN	95% A for 0.2 min, to 0% A in 2.8min, held for 0.15min, back to 95% A in 0.15min, held for 1.7min	1 ----- - 60	5
7	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 40% A in 1.2min, to 5% A in 0.6min, held for 0.2min	1 ----- - 50	2
8	Waters: Acquity UPLC® - DAD / Quattro Micro™	Waters: BEH C18 (1.7µm, 2.1x100mm)	A: 95% CH ₃ COONH ₄ 7mM / 5% CH ₃ CN, B: CH ₃ CN	84.2% A for 0.49min, to 10.5% A in 2.18min, held for 1.94min, back to 84.2% A in 0.73min, held for 0.73min.	0.34 3 ----- - 40	6.2
9	Agilent: HP1100- DAD, Waters: LCT	Agilent: Eclipse Plus C18 (3.5µm, 2.1x30mm)	A: 95% CH ₃ COONH ₄ 6.5mM + 5% CH ₃ CN, B: CH ₃ CN/CH ₃ O H, 1/1	From 95% A to 0% A in 5.0min, held for 0.15min, back to 95% A in 0.15min, held for 1.7min	1 ----- - 60	7

Method	Instrument	Column	Mobile phase	Gradient	Flow ----- Col T	Run time
10	Agilent: HP1100- DAD, Waters: SQD	Agilent: Eclipse Plus C18 (3.5µm, 2.1x30mm)	A: 95% CH ₃ COONH ₄ 6.5mM + 5% CH ₃ CN, B: CH ₃ CN/CH ₃ O H, 1/1	From 95% A to 0% A in 5.0min, held for 0.15min, back to 95% A in 0.15min, held for 1.7min	1 ----- - 60	7
11	Waters: Acquity® UPLC® - DAD/SQD	Agilent: Eclipse Plus C18 RRHD (1.8µm, 2.1x50mm)	A: 95% CH ₃ COONH ₄ 6.5mM + 5% CH ₃ CN, B: CH ₃ CN	From 95% A to 40% A in 1.2min, to 5% A in 0.6min, held for 0.2min	1 ----- 50	2
12	Waters: Acquity® UPLC® - DAD / QTOF G2-S	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 40% A in 1.2min, to 5% A in 0.6min, held for 0.2min	1 ----- - 50	2
13	Waters: Acquity® UPLC® - DAD / QTOF G2-S	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

Table 3a. 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 $[M+CH_3COO]^-$. R_t means retention time (in min). For some compounds, exact mass was determined.

Co. No.	M.p. (°C)	$[M+H]^+$	$[M-H]^-$ or adduct	R_t	LCMS Method
1	152.6 (B)	387	445 (M+CH ₃ COO) ⁻	2.73	2
2	181.9 (A)	373	431 (M+CH ₃ COO) ⁻	2.07	1
3	103.3 (B)	421	479 (M+CH ₃ COO) ⁻	2.48	1
4	247.0 (A)	445	503 (M+CH ₃ COO) ⁻	2.4	1
5	>300 (A)	401	459 (M+CH ₃ COO) ⁻	2.42	1
6	>300 (A)	387	445 (M+CH ₃ COO) ⁻	2.29	1
7	126.7 (B)	367	425 (M+CH ₃ COO) ⁻	2.25	1
8	126.1 (B)	431	489 (M+CH ₃ COO) ⁻	2.5	1
9	143.6 (B)	421	479 (M+CH ₃ COO) ⁻	2.44	1
10	85.1 (B)	405	463 (M+CH ₃ COO) ⁻	2.32	1
11	159.3 (B)	387	445 (M+CH ₃ COO) ⁻	2.19	1
12	269.9 (A)	417	475 (M+CH ₃ COO) ⁻	2.22	1
13	128.9 (B)	412	470 (M+CH ₃ COO) ⁻	2.12	1
14	201.1 (B)	401	459 (M+CH ₃ COO) ⁻	2.33	1
15	>300 (A)	353	411 (M+CH ₃ COO) ⁻	1.96	1
17	>300 (B)	397	455 (M+CH ₃ COO) ⁻	2.25	1
18	98.5 (B)	397	455 (M+CH ₃ COO) ⁻	2.28	1
19	137 (B)	383	441 (M+CH ₃ COO) ⁻	2.01	1
20	293.6 (B)	383	441 (M+CH ₃ COO) ⁻	1.98	1
21	219.2 (A)	351	409 (M+CH ₃ COO) ⁻	1.99	1
22	282.3 (B)	417	475 (M+CH ₃ COO) ⁻	2.19	1
23	139.2 (A)	387	445 (M+CH ₃ COO) ⁻	2.18	1
24	119.6 (B)	387	445 (M+CH ₃ COO) ⁻	2.29	1
26	153.6 (B)	387	445 (M+CH ₃ COO) ⁻	2.73	2
27	137.1 (A)	385	443 (M+CH ₃ COO) ⁻	1.96	1
29	140.8 (B)	401	459 (M+CH ₃ COO) ⁻	2.41	1
30	78.6 (B)	371	429 (M+CH ₃ COO) ⁻	2.07	1
31	112.8 (B)	431	489 (M+CH ₃ COO) ⁻	2.49	1
32	n.d.	373	431 (M+CH ₃ COO) ⁻	2.05	1
33	162.8 (B)	417	475 (M+CH ₃ COO) ⁻	2.26	1

Co. No.	M.p. (°C)	[M+H] ⁺	[M-H] ⁻ or adduct	R _t	LCMS Method
34	>300 (B)	377	435 (M+CH ₃ COO) ⁻	2.1	1
36	128.2 (B)	387	445 (M+CH ₃ COO) ⁻	2.25	1
37	254.0 (B)	388	446 (M+CH ₃ COO) ⁻	1.89	1
38	294.0 (B)	349	407 (M+CH ₃ COO) ⁻	1.71	1
39	185.2 (B)	391	449 (M+CH ₃ COO) ⁻	2.08	1
40	137.0 (B)	373	431 (M+CH ₃ COO) ⁻	1.97	1
41	166.9 (B)	379	437 (M+CH ₃ COO) ⁻	1.56	1
43	203.9 (B)	435	493 (M+CH ₃ COO) ⁻	2.59	1
44	> 300 (B)	416	474 (M+CH ₃ COO) ⁻	2.21	5
45	143.9 (A1)	403	461 (M+CH ₃ COO) ⁻	2.51	1
46	124.6 (B)	401	459 (M+CH ₃ COO) ⁻	2.46	1
47	185.6 (B)	401	459 (M+CH ₃ COO) ⁻	2.3	5
49	183.9 (B)	445	503 (M+CH ₃ COO) ⁻	2.61	1
50	146.8 (B)	407	465 (M+CH ₃ COO) ⁻	2.23	5
51	93 (B)	431	489 (M+CH ₃ COO) ⁻	2.4	1
52	>300 (B)	405	463 (M+CH ₃ COO) ⁻	1.99	5
53	233.1 (B)	459	517 (M+CH ₃ COO) ⁻	2.37	5
54	205.1 (B)	435	493 (M+CH ₃ COO) ⁻	2.39	5
55	104.2 (B)	417	475 (M+CH ₃ COO) ⁻	2.29	5
56	199 (B)	431	489 (M+CH ₃ COO) ⁻	2.17	5
57	153.2 (B)	373	431 (M+CH ₃ COO) ⁻	2.04	5
59	214.1 (B)	426	484 (M+CH ₃ COO) ⁻	2.1	5
60	163.8 (B)	391	449 (M+CH ₃ COO) ⁻	2.07	5
61	73.3 (B)	419	477 (M+CH ₃ COO) ⁻	2.29	5
62	141.7 (B)	371	429 (M+CH ₃ COO) ⁻	2.09	1
64	273.9 (B)	403	461 (M+CH ₃ COO) ⁻	2.03	5
68	>300 (B)	407	465 (M+CH ₃ COO) ⁻	2.19	5
70	n.d.	401	459 (M+CH ₃ COO) ⁻	2.29	5
71	218.9 (B)	388	446 (M+CH ₃ COO) ⁻	1.88	1
72	88 (B)	367	425 (M+CH ₃ COO) ⁻	2.15	1
73	144.3 (B)	339	397 (M+CH ₃ COO) ⁻	1.77	5
74	99.1 (B)	447	505 (M+CH ₃ COO) ⁻	2.03	1

Co. No.	M.p. (°C)	[M+H] ⁺	[M-H] ⁻ or adduct	R _t	LCMS Method
77	60.8 (A, Temp. grad.: 3 °C/min)	449	507 (M+CH ₃ COO) ⁻	2.19	1
88	157.75 °C (D)	428	486 (M+CH ₃ COO) ⁻	2.29	5
92	n.d.	480	538 (M+CH ₃ COO) ⁻	2.48	5
93	n.d.	420	478 (M+CH ₃ COO) ⁻	2.00	5
94	n.d.	446	504 (M+CH ₃ COO) ⁻	2.28	5
95	210.61 °C (D)	461	519 (M+CH ₃ COO) ⁻	2.62	5
97	n.d.	428	486 (M+CH ₃ COO) ⁻	2.39	5
99	126.4 °C (B)	441	499 (M+CH ₃ COO) ⁻	2.63	5
100	144.9 °C (B)	432	490 (M+CH ₃ COO) ⁻	2.56	5
101	>300 °C (B)	444	502 (M+CH ₃ COO) ⁻	1.91	5
102	129.8 °C (B)	428	486 (M+CH ₃ COO) ⁻	2.33	5
103	164.7 °C (B)	436	494 (M+CH ₃ COO) ⁻	2.25	5
104	183 °C (B)	437	495 (M+CH ₃ COO) ⁻	2.66	5
105	124 °C (B)	442	500 (M+CH ₃ COO) ⁻	2.61	5
106	n.d.	499	557 (M+CH ₃ COO) ⁻	2.04	5
107	294 °C (B)	456	514 (M+CH ₃ COO) ⁻	2.92	5
108	128.1 °C (B)	458	516 (M+CH ₃ COO) ⁻	2.27	5
109	149.8 °C (B)	398	456 (M+CH ₃ COO) ⁻	2.38	5
110	257.9 °C (B)	402	460 (M+CH ₃ COO) ⁻	2.09	5
111	>300 °C (B)	417	475 (M+CH ₃ COO) ⁻	1.96	5
113	n.d.	415	473 (M+CH ₃ COO) ⁻	2.29	11
114	177.6 °C (B)	423	481 (M+CH ₃ COO) ⁻	2.94	2
115	n.d.	405	463 (M+CH ₃ COO) ⁻	2.79	8
116	n.d.	405	463 (M+CH ₃ COO) ⁻	2.79	8
118	n.d.	417	475 (M+CH ₃ COO) ⁻	2.87	8
119	n.d.	417	475 (M+CH ₃ COO) ⁻	2.87	8
120	n.d.	417	475 (M+CH ₃ COO) ⁻	2.78	8
121	n.d.	417	475 (M+CH ₃ COO) ⁻	2.78	8
122	n.d.	413	471 (M+CH ₃ COO) ⁻	2.55	5
123	189.5 °C (B)	417	475 (M+CH ₃ COO) ⁻	3.92	10

Co. No.	M.p. (°C)	[M+H] ⁺	[M-H] ⁻ or adduct	R _t	LCMS Method
124	62.4 °C (B)	415	473 (M+CH ₃ COO) ⁻	2.57	5
125	105.4 (A, temp. grad.: 3 °C/min)	403	461 (M+CH ₃ COO) ⁻	1.81	5
126	70.5 °C (B)	415	473 (M+CH ₃ COO) ⁻	2.49	5
127	155.1 °C (B)	398	456 (M+CH ₃ COO) ⁻	2.29	5
128	139.8 °C (B)	417	475 (M+CH ₃ COO) ⁻	1.87	5
129	135.1 °C (B)	401.3	459 (M+CH ₃ COO) ⁻	2.92	8
130	134.4 °C (B)	401.3	459 (M+CH ₃ COO) ⁻	2.92	8
131	134.7 °C (B)	423	481 (M+CH ₃ COO) ⁻	2.36	5
132	148 °C (B)	423	481 (M+CH ₃ COO) ⁻	2.33	5
133	191.5 °C (B)	417	475 (M+CH ₃ COO) ⁻	2.70	5
134	n.d.	401	459 (M+CH ₃ COO) ⁻	2.40	5
135	76.8 °C (B)	403	461 (M+CH ₃ COO) ⁻	1.76	5
136	126.2 °C (B)	427	485 (M+CH ₃ COO) ⁻	2.38	5
137	193.8 °C (B)	431	489 (M+CH ₃ COO) ⁻	2.90	5
138	173.9 °C (B)	431	489 (M+CH ₃ COO) ⁻	2.78	5
140	231.5 °C (B)	403	461 (M+CH ₃ COO) ⁻	1.62	5
143	>300 °C (B)	417	475 (M+CH ₃ COO) ⁻	2.17	5
144	133.2 °C (B)	417	475 (M+CH ₃ COO) ⁻	2.06	5
145	57.5 °C (B)	417	475 (M+CH ₃ COO) ⁻	2.59	5
146	166.8 °C (B)	417	475 (M+CH ₃ COO) ⁻	2.67	5
147	85.9 °C (B)	402	460 (M+CH ₃ COO) ⁻	2.01	5
150	>300 °C (B)	403	461 (M+CH ₃ COO) ⁻	2.39	5
151	157.6 °C (B)	398	456 (M+CH ₃ COO) ⁻	2.28	5
152	105.4 °C (B)	403	461 (M+CH ₃ COO) ⁻	2.13	5
153	162 °C (B)	387	445 (M+CH ₃ COO) ⁻	2.15	5
154	169.5 °C (B)	445	503 (M+CH ₃ COO) ⁻	2.52	5
155	101.8 °C (B)	398	456 (M+CH ₃ COO) ⁻	1.86	5
157	158.9 °C (B)	415	473 (M+CH ₃ COO) ⁻	2.37	5
158	48.2 °C (B)	431	489 (M+CH ₃ COO) ⁻	2.15	5
159	71.5 °C (B)	387	445 (M+CH ₃ COO) ⁻	2.27	5
160	129.5 °C (B)	417	475 (M+CH ₃ COO) ⁻	2.04	5
162	185.9 °C (B)	369	427 (M+CH ₃ COO) ⁻	1.78	5

Co. No.	M.p. (°C)	[M+H] ⁺	[M-H] ⁻ or adduct	R _t	LCMS Method
163	n.d.	419	477 (M+CH ₃ COO) ⁻	2.08	5
164	170.3 °C (A, temp. grad.: 3 °C/min)	391	389	3.75	9
165	n.d.	431	489 (M+CH ₃ COO) ⁻	2.22	5
166	99.8 °C (B)	416	474 (M+CH ₃ COO) ⁻	2.33	5
168	108.5 °C (B)	419	417	2.09	5
169	64.7 °C (B)	437	495 (M+CH ₃ COO) ⁻	2.39	5
171	158.8 °C (B)	401	459 (M+CH ₃ COO) ⁻	2.32	5
173	n.d.	413	471 (M+CH ₃ COO) ⁻	2.44	5
174	127.5 °C (B)	403	461 (M+CH ₃ COO) ⁻	2.12	5
175	220.8 °C (B)	457	515 (M+CH ₃ COO) ⁻	1.70	5
176	>300 °C (B)	457	515 (M+CH ₃ COO) ⁻	1.78	5
179	n.d.	427	485 (M+CH ₃ COO) ⁻	1.93	5
180	76.8 °C (A)	433	491 (M+CH ₃ COO) ⁻	2.41	5
181		423	481 (M+CH ₃ COO) ⁻	2.08	5
182	67.8 °C (B)	420	478 (M+CH ₃ COO) ⁻	2.11	5
183	125.6 °C (B)	432	490 (M+CH ₃ COO) ⁻	2.07	5
184	n.d.	420	478 (M+CH ₃ COO) ⁻	2.73	8
185	n.d.	420	478 (M+CH ₃ COO) ⁻	2.73	8
188	161.4 °C (B)	422	480 (M+CH ₃ COO) ⁻	2.50	5
189	142.4 °C (B)	432	490 (M+CH ₃ COO) ⁻	2.46	5
200	122.3 °C (A)	432	490 (M+CH ₃ COO) ⁻	2.81	1
201	119.7 °C (B)	398	456 (M+CH ₃ COO) ⁻	2.44	5
204	292.8 °C (B)	422	480 (M+CH ₃ COO) ⁻	2.51	5
205	179.2 °C (B)	446	504 (M+CH ₃ COO) ⁻	2.77	5
207	147.6 °C (B)	418	476 (M+CH ₃ COO) ⁻	2.44	5
208	141.3 °C (B)	418	476 (M+CH ₃ COO) ⁻	2.60	5
210	125.66 °C (D)	403	461 (M+CH ₃ COO) ⁻	2.09	5
214	n.d.	418	476 (M+CH ₃ COO) ⁻	1.67	5
216	n.d.	417	415	2.59	2
217	255.5 °C (B)	417	415	2.61	2
219	n.d.	403	401	1.72	5

Co. No.	M.p. (°C)	[M+H] ⁺	[M-H] ⁻ or adduct	R _t	LCMS Method
220	n.d.	513	572 (M+CH ₃ COO) ⁻	2.48	5
222	>300 °C (B)	405	463 (M+CH ₃ COO) ⁻	2.10	5
225	n.d.	499	557 (M+CH ₃ COO) ⁻	1.38	7
226	n.d.	407	405	1.10	7
227	n.d.	407	405	1.10	7
229	n.d.	465	523 (M+CH ₃ COO) ⁻	2.40	5
235	93 (B)	470	528 (M+CH ₃ COO) ⁻	1.84	5
236	>300 (B)	419	477 (M+CH ₃ COO) ⁻	2.37	5
237	125.82 (D)	433	431	2.34	5
238	n.d.		439.0995	2.32	13
240	107.87 (D)	434	492 (M+CH ₃ COO) ⁻	2.73	5
241	n.d.	416	474 (M+CH ₃ COO) ⁻	2.04	5
248	n.d.	416	474 (M+CH ₃ COO) ⁻	1.35	7
249	n.d.		478.1874	2.47	13

n.d. = not determined

Table 3b. Analytical data – melting point (M.p.) and LCMS: [M+H]⁺ means the protonated mass of the free base of the compound, R_t means retention time (in min), method refers to the method used for LCMS.

Co. No.	M.p. (°C)	[M+H] ⁺	R _t	LCMS Method
16	174.0 (A)	353	2.00	1
25	>300 (A)	355	1.87	1
28	>300 (A)	337	1.74	1
35	>300 (A)	367	1.79	1
42	250.1 (A)	377	1.71	1
48	75.2 (A)	449	2.27	1
58	281.9 (C)	403	2.51	3
63	>300 (C)	371	2.369	3
65	n.d.	361	2.626	3
66	281.8 (C)	361	2.68	3
67	138.0 (C)	405	1.16	4
69	n.d.	403	2.438	3
75	186.5 (C)	362	2.087	3

Co. No.	M.p. (°C)	[M+H]⁺	R_t	LCMS Method
76	124.5 (C)	351	2.327	3
78	91.1 (B)	333	2.149	3
79	266.7 (C)	377	2.314	3
80	n.d.	344	1.902	3
81	288.4 (C)	363	2.241	3
82	144.2 (B)	355	2.178	3
83	94.5 (A) (10°C/min)	363	2.178	3
84	101.2 (A) (10°C/min)	385	2.263	3
85	133.0 (A) (10°C/min)	367	2.278	3
86	137.9°C (A)	319.2	2	3
87	n.d.	403	0.99	1
89	136.75 (D)	369	2.17	5
90	93.7 (A, temp. grad.: 3 °C/min)	434	2.33	5
91	86 (A, temp. grad.: 3 °C/min)	434	2.34	5
96	262.88 (D)	462	2.85	6
98	n.d.	419	2.15	5
112	154.9 (A, temp. grad.: 3 °C/min)	405	2.16	5
117	n.d.	405	2.26	5
139	182.3 (B)	397	1.97	5
141	93.5 (B)	375	2.51	5
142	>300 (B)	403	2.45	5
148	149.7 (A1, 10°C/min)	363.2	1.79	3
149	197.7 (C)	363	0.36	3
156	123.7 (B)	359	2.06	5

Co. No.	M.p. (°C)	[M+H]⁺	R_t	LCMS Method
161	82.7 (B)	383	1.92	5
167	96.7 (B)	387	2.10	5
170	276.2 (B)	403	1.70	5
172	124.7 (B)	367	2.02	5
177	174.13 (D)	469	2.72	5
178	n.d.	368	1.81	5
186	>300 (A)	388	2.28	1
187	131.4 (B)	354	2.02	1
190	117.6 (B)	374	2.02	5
191	60.7 (A, temp. grad.: 3 °C/min)	382	1.97	5
192	155.9 (B)	402	2.43	5
193	58 (B)	402	2.31	5
194	>300 (B)	402	2.26	5
195	75.9 (B)	398	2.08	5
196	136.9 (B)	368	2.18	5
197	146.6 (A, temp. grad.: 3 °C/min)	392	2.37	5
198	112.8 (B)	368	2.09	5
199	112.8 (A)	432	2.37	1
202	255.8 (B)	388	2.35	5
203	131.8 (B)	388	2.31	5
206	n.d.	384	2.21	5
209	138.26 (D)	459	2.91	6
211	n.d.	374	1.99	1
212	n.d.	514	1.44	11
213	n.d.	480	1.32	7
215	n.d.	407	1.33	7
218	167.3 (A, temp. grad.: 3 °C/min)	407	2.50	5
221	n.d.	513	2.40	5

Co. No.	M.p. (°C)	[M+H] ⁺	R _t	LCMS Method
223	n.d.	451	2.97	2
224	n.d.	407	2.80	2
228	n.d.	425	1.40	7
230	n.d.	445	1.25	12
231	n.d.	432	1.12	7
232	n.d.	432	1.11	7
233	n.d.	418	0.96	7
234	n.d.	437	2.88	13
239	n.d.	417	0.99	7
242	n.d.	432	2.44	5
243	72.44 (D)	420. 1455	2.38	13
244	188.41 (D)	373.0626 (+0.3mDa)	1.11	12
245	n.d.	446.1820	2.0	13
246	n.d.	448.1765 (+0.5mDa)	2.43	13
247	155.12 (D)	391.1184 (+0.2mDa)	2.33	13
250	158.03 (D)	447.1756 (0.0mDa)	2.78	13
251	151.45 (D)	416.1698 (-0.0mDa)	2.29	13#
252	n.d.	437.0994 (+0.2mDa)	1.94	13
253	n.d.	430.1857 (+0.3mDa)	2.63	13
254	n.d.	464.1469 (+0.4mDa)	2.88	13
255	136.39 (D)	450.1310 (+0.2mDa)	2.52	13
256	153.60 (D)	430.1855 (+0.1mDa)	2.48	13
257	n.d.	416.1046 (+0.1mDa)	2.38	13
258	121.41 (D)	444.2012 (+0.1mDa)	2.7	13
259	115.50 (D)	430.1856 (+0.2mDa)	2.49	13
260	141.74 (D)	442.1852 (-0.2mDa)	2.56	13
261	n.d.	430.1202 (+0.1mDa)	2.54	13
262	116.12.	464.1463 (-0.2mDa)	2.71	13
263	n.d.	430.1199 (-0.2mDa)	2.55	13
264	n.d.	464.1465 (+0.0mDa)	2.72	13
265	n.d.	439.0951 (+0.2mDa)	2.50	13
266	173.08	430.1853 (-0.1mDa)	2.51	13

Co. No.	M.p. (°C)	[M+H] ⁺	R _t	LCMS Method
267	131.30	444.2012 (+0.1mDa)	2.69	13

n.d. = not determined

SFC-MS

General procedure

- 5 The SFC measurement was performed using Analytical system from Berger instrument comprising a FCM-1200 dual pump fluid control module for delivering carbon dioxide (CO₂) and modifier, a CTC Analytics automatic liquid sampler, a TCM-20000 thermal control module for column heating from room temperature to 80°C. An Agilent 1100 UV photodiode array detector equipped with a high-pressure flow cell standing up to
- 10 400 bars was used. Flow from the column was split to a MS spectrometer. The MS detector was configured with an atmospheric pressure ionization source. The following ionization parameters for the Waters ZQ mass spectrophotometer are: corona: 9µa, source temp: 140°C, cone: 30 V, probe temp 450°C, extractor 3 V, desolvation gas 400L/hr, cone gas 70 L/hr. Nitrogen was used as the nebulizer gas. Data acquisition
- 15 was performed with a Waters-Micromass MassLynx-Openlynx data system.

Table 4. Analytical SFC-MS Methods (Flow expressed in mL/min; column temperature (T) in °C; Pressure in Mpa).

Method	Column	Mobile Phase	Flow	T	Pressure
1	Chiralcel OD-H 250x4.6mm, 5µm Daicel	CO ₂ /EtOH (0.3% IPrNH ₂) 70/30	3	35	100
2	Chiralpak IC 250x4.6mm 5µm Daicel	CO ₂ /EtOH (0.3% IPrNH ₂) 70/30	3	35	100
3	Chiralpak IC 250x4.6mm 5µm Daicel	CO ₂ /EtOH (0.3% IPrNH ₂) 60/40	3	35	100

Method	Column	Mobile Phase	Flow	T	Pressure
4	Chiralpak IC 250x4.6mm, 5 μ m Daicel	CO ₂ /MeOH (0.3% IPrNH ₂)/iPrOH (0.3% IPrNH ₂) 80/10/10	3	35	100
5	Chiralpak AD-H 150x4.6mm, 5 μ m Daicel	CO ₂ /MeOH (0.3% IPrNH ₂)/iPrOH (0.3% IPrNH ₂) 60/20/20	3	35	100

Table 5. Analytical SFC data – R_t means retention time (in minutes), $[M+H]^+$ means the protonated mass of the compound, method refers to the method used for SFC/MS analysis of enantiomerically pure compounds. The measurement was compared against the mixture.

Co. No.	R_t	$[M+H]^+$	UV Area %	Isomer Elution Order	Method
130	2.65	401	100	A	1
129	3.84	401	100	B	1
120	3.28	417	100	A	2
121	4.40	417	100	B	2
119	4.86	417	100	A	3
118	6.86	417	100	B	3
116	3.74	405	100	A	4
115	5.24	405	100	B	4
184	3.62	420	100	A	5
185	5.22	420	100	B	5

Optical Rotations

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

- 10 $[\alpha]_\lambda^T = (100\alpha) / (l \times c)$: where l is the path length in dm and c is the concentration in g/100 ml for a sample at a temperature T (°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 (it is assumed to be g/100 ml).

5 **Table 6.** Optical Rotation data.

Co. No.	α_D (°)	Wavelength (nm)	Concentration w/v %	Solvent	Temp. (° C)
1	+21.2	589	0.59	DMF	20
3	+26.4	589	1.26	DMF	20
4	+16.8	589	0.48	DMF	20
7	+16.9	589	0.56	DMF	20
8	+21.5	589	0.54	DMF	20
9	+19.8	589	0.40	DMF	20
10	+21.6	589	0.82	DMF	20
12	+18.8	589	0.56	DMF	20
13	+22.4	589	0.52	DMF	20
14	+19.9	589	0.54	DMF	20
16	+25.8	589	0.49	DMF	20
18	+19.1	589	0.54	DMF	20
19	+22.5	589	0.49	DMF	20
21	+18.6	589	0.53	DMF	20
23	+23.5	589	0.63	DMF	20
24	+18.6	589	0.54	DMF	20
26	-22.5	589	0.59	DMF	20
27	+16.6	589	0.61	DMF	20
28	+20.7	589	0.68	DMF	20
29	+18.6	589	0.52	DMF	20
30	+14.9	589	0.54	DMF	20
31	-22.9	589	0.52	DMF	20
34	+18.1	589	0.64	DMF	20
36	+19.6	589	0.48	DMF	20
37	+17.7	589	0.49	DMF	20
42	+18.2	589	0.59	DMF	20

Co. No.	α_D (°)	Wavelength (nm)	Concentration w/v %	Solvent	Temp. (° C)
43	+25.1	589	0.54	DMF	20
44	+22.9	589	0.48	DMF	20
45	+20.5	589	0.68	DMF	20
46	+22.3	589	0.49	DMF	20
47	+26.0	589	0.50	DMF	20
48	+17.0	589	0.54	DMF	20
49	+21.1	589	0.50	DMF	20
50	+27.4	589	0.50	DMF	20
51	+19.9	589	0.52	DMF	20
53	+23.7	589	0.40	DMF	20
54	+26.7	589	0.50	DMF	20
55	+24.8	589	0.65	DMF	20
56	+16.1	589	0.50	DMF	20
57	+24.1	589	0.58	DMF	20
59	+27.9	589	0.42	DMF	20
60	+20.7	589	0.57	DMF	20
61	+23.1	589	0.52	DMF	20
62	+23.0	589	0.55	DMF	20
64	+20.4	589	0.58	DMF	20
68	+24.1	589	0.59	DMF	20
71	+24.9	589	0.50	DMF	20
72	+22.7	589	0.48	DMF	20
73	+22.9	589	0.58	DMF	20
77	+16.4	589	0.48	DMF	20
88	+20.3	589	1.0	DMF	20
90	-2.1	589	0.53	DMF	20
91	+3.0	589	0.51	DMF	20
92	+24.7	589	0.50	DMF	20
94	+22.3	589	0.60	DMF	20
95	+26.1	589	1.00	DMF	20
96	+45.1	589	0.60	DMF	25
97	+32.6	589	1.50	DMF	20
98	+22.5	589	0.45	DMF	20
99	+18.7	589	1.45	DMF	20

Co. No.	α_D (°)	Wavelength (nm)	Concentration w/v %	Solvent	Temp. (° C)
100	+26.4	589	0.49	DMF	20
101	+20.3	589	0.50	DMF	20
102	+21.2	589	0.51	DMF	20
103	+27.1	589	0.88	DMF	20
104	+25.2	589	0.50	DMF	20
105	+21.2	589	0.55	DMF	20
107	+18.8	589	0.55	DMF	20
108	+19.4	589	0.55	DMF	20
109	+26.1	589	0.51	DMF	20
110	+22.6	589	0.52	DMF	20
112	+20.7	589	0.49	DMF	20
113	+15.6	589	0.53	DMF	20
114	+20.0	589	0.49	DMF	20
115	+3.9	589	0.52	DMF	20
116	-2.5	589	0.56	DMF	20
117	+26.4	589	0.48	DMF	20
118	-33.8	589	0.61	DMF	20
119	+38.8	589	0.58	DMF	20
120	+44.2	589	0.63	DMF	20
121	-45.9	589	0.61	DMF	20
123	+18.8	589	0.62	DMF	20
124	+23.2	589	0.53	DMF	20
125	+23.6	589	0.52	DMF	20
126	+17.5	589	0.58	DMF	20
127	+25.7	589	0.58	DMF	20
129	+12.2	589	0.54	DMF	20
130	-12.6	589	0.52	DMF	20
131	+21.5	589	0.51	DMF	20
132	+21.1	589	0.6	DMF	20
133	+18.7	589	0.71	DMF	20
135	+19.5	589	0.55	DMF	25
136	+15.9	589	0.53	DMF	20
137	+17.6	589	0.50	DMF	20
138	+11.9	589	0.51	DMF	20

Co. No.	α_D (°)	Wavelength (nm)	Concentration w/v %	Solvent	Temp. (° C)
139	+21.6	589	0.57	DMF	20
140	+20.3	589	0.57	DMF	20
141	+17.2	589	0.45	DMF	20
142	+25.0	589	0.49	DMF	20
145	+18.6	589	0.54	DMF	20
146	+21.5	589	0.61	DMF	20
147	+21.1	589	0.51	DMF	20
150	+20.3	589	0.49	DMF	20
151	+19.8	589	0.59	DMF	20
152	+15.6	589	0.50	DMF	20
153	-30.9	589	0.58	DMF	20
154	+20.7	589	0.51	DMF	20
155	+19.9	589	0.51	DMF	20
156	+14.5	589	0.48	DMF	20
157	+22.6	589	0.52	DMF	20
158	+27.9	589	0.60	DMF	20
159	+14.0	589	0.51	DMF	20
160	+16.1	589	0.62	DMF	20
161	-16.8	589	0.46	DMF	20
162	-33.9	589	0.54	DMF	20
163	+20.4	589	0.50	DMF	20
164	+27.2	589	0.50	DMF	20
166	+21.8	589	0.50	DMF	20
167	+12.4	589	0.41	DMF	20
168	+22.2	589	0.61	DMF	20
169	+21.7	589	0.77	DMF	20
171	-0.7	589	0.74	DMF	20
172	+16.7	589	0.64	DMF	20
174	+25.8	589	0.52	DMF	20
175	+15.4	589	0.51	DMF	20
176	+13.3	589	0.50	DMF	20
177	+19.2	589	0.49	DMF	20
178	+11.5	589	0.49	DMF	20
179	+13.0	589	0.49	DMF	20

Co. No.	α_D (°)	Wavelength (nm)	Concentration w/v %	Solvent	Temp. (° C)
180	+15.5	589	0.45	DMF	20
182	+18.3	589	0.40	DMF	20
183	+19.7	589	0.40	DMF	20
184	+0.5	589	0.47	DMF	20
185	-4.9	589	0.51	DMF	20
186	+11.1	589	0.46	DMF	20
187	+30.5	589	0.49	DMF	20
188	-16.8	589	0.59	DMF	20
189	+42.8	589	0.53	DMF	20
190	+29.4	589	0.54	DMF	20
191	+28.3	589	0.53	DMF	20
195	-55.0	589	0.53	DMF	20
196	+26.8	589	0.62	DMF	20
197	+33.7	589	0.54	DMF	20
198	+35.2	589	0.52	DMF	20
199	-16.0	589	0.48	DMF	20
200	+0.8	589	0.46	DMF	20
201	-5.3	589	1.00	DMF	20
202	+24.2	589	0.54	DMF	20
203	+39.4	589	0.52	DMF	20
204	+46.3	589	0.84	DMF	20
205	+3.2	589	0.50	DMF	20
206	-2.2	589	0.49	DMF	20
207	+33.1	589	0.58	DMF	20
208	+1.3	589	0.54	DMF	25
209	+5.9	589	1.40	DMF	20
210	+28.5	589	0.51	DMF	20
218	+17.6	589	0.49	DMF	25
235	+18.6	589	0.60	DMF	25
237	+10.5	589	0.50	DMF	20
240	+2.2	589	0.55	DMF	20
241	+20.3	589	0.50	DMF	20
242	+21.5	589	0.50	DMF	20
243	+19.0	589	0.51	DMF	20

Co. No.	α_D (°)	Wavelength (nm)	Concentration w/v %	Solvent	Temp. (° C)
250	+2.3	589	0.48	DMF	20
253	+16.2	589	0.69	DMF	20
255	+25.0	589	0.54	DMF	20
257	+16.4	589	0.40	DMF	20
258	+23.7	589	0.80	DMF	20
259	+21.3	589	0.57	DMF	20
260	+19.4	589	0.49	DMF	20
261	+21.4	589	0.54	DMF	20
262	25.9	589	0.51	DMF	20
263	19.2	589	0.52	DMF	20
264	23.3	589	0.49	DMF	20
266	20.3	589	0.53	DMF	20
267	20.3	589	0.51	DMF	20

NMR

Co. No. 237: ^1H NMR (500 MHz, CDCl_3) δ ppm 1.72 (d, $J=6.6$ Hz, 3 H) 2.96 (d, $J=5.2$ Hz, 3 H) 4.05 (s, 3 H) 4.42 (dd, $J=13.7, 7.1$ Hz, 1 H) 4.53 - 4.59 (m, 1 H) 4.64 (dd, $J=13.6, 4.0$ Hz, 1 H) 4.70 - 4.78 (m, 1 H) 6.76 (s, 1 H) 6.84 (d, $J=5.2$ Hz, 1 H) 7.78 (d, $J=8.7$ Hz, 1 H) 7.77 (s, 1 H) 7.88 (d, $J=8.4$ Hz, 1 H) 8.13 (d, $J=5.2$ Hz, 1 H)

Pharmacological examples

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 virtue of their ability to reduce the function of the receptor. The effects of negative allosteric modulators tested at mGluR2 using the $[^{35}\text{S}]\text{GTP}\gamma\text{S}$ 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) $[^{35}\text{S}]\text{GTP}\gamma\text{S}$ binding assay

The $[^{35}\text{S}]\text{GTP}\gamma\text{S}$ 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, [^{35}S]GTP γ S (guanosine 5'-triphosphate, labelled with gamma-emitting ^{35}S), 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, [^{35}S]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 [^{35}S]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 [^{35}S]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.

[^{35}S]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 μM GDP. Human mGlu2 receptor-containing membranes were thawed on ice and diluted in assay buffer supplemented with 18 $\mu\text{g}/\text{ml}$ saponin. Membranes were pre-incubated with compound together with a predefined ($\sim\text{EC}_{80}$) 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

[³⁵S]GTP γ S incorporation on activation (30 minutes, 30 °C). Final assay mixtures contained 7 μ g of membrane protein in 10 mM HEPES acid, 10 mM HEPES salt, pH 7.4, 100 mM NaCl, 3 mM MgCl₂, 10 μ M GDP and 10 μ g/ml saponin. Total reaction volume was 200 μ l. 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 μ l 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 EC₈₀-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 IC₅₀.

The pIC₅₀ values were calculated as the -log IC₅₀, when the IC₅₀ is expressed in M.

E_{max} is defined as the relative maximal effect (i.e. maximal % inhibition relative to the control glutamate response).

Table 7. Pharmacological data for compounds according to the invention.

Co. No.	GTP γ S - hmGluR2 anGT pIC ₅₀	GTP γ S - hmGluR2 anGT E _{max}
1	8.05	106
2	7.65	104
3	8.75	106
4	8.48	104
5	8.29	105
6	8.3	106
6a	8.32	112
7	8.12	102
8	8.23	105

Co. No.	GTP γ S - hmGluR2 anGT pIC ₅₀	GTP γ S - hmGluR2 anGT E _{max}
9	7.98	103
10	7.93	104
11	7.72	103
12	7.71	104
13	7.53	103
14	7.62	104
15	7.58	103
16	7.29	102
17	7.32	104

Co. No.	GTPγS - hmGluR2 anGT pIC₅₀	GTPγS - hmGluR2 anGT E_{max}
18	7.28	102
19	7.16	105
20	7.06	104
21	7.21	107
22	7.16	104
23	6.96	104
24	6.92	104
25	6.84	103
26	6.76	105
27	6.86	104
28	6.62	105
29	6.64	102
30	6.59	104
31	6.36	107
32	6.25	101
33	6.24	99
34	6.25	100
35	6.22	100
36	6.08	100
37	6.01	99
38	6.02	103
39	5.79	100
40	5.83	105
41	5.45	95
42	5.51	102
43	8.54	107
44	8.21	105
45	8	104
46	8.2	105
47	8.19	105
48	8.11	100
49	8.06	103
50	8.02	103
51	7.96	104
52	7.98	107
53	8.01	102
54	7.98	105

Co. No.	GTPγS - hmGluR2 anGT pIC₅₀	GTPγS - hmGluR2 anGT E_{max}
55	7.79	104
56	7.79	102
57	7.89	104
58	7.66	107
59	7.45	98
60	7.5	101
61	7.55	106
62	7.48	105
63	7.47	105
64	7.58	103
65	7.35	106
66	7.39	107
67	7.2	104
68	7.15	100
69	7.27	103
70	7.1	106
71	7.01	103
72	6.97	103
73	6.89	102
74	6.67	100
75	6.56	100
76	6.55	100
77	6.41	101
78	6.32	103
79	6.29	104
80	6.29	107
81	6.27	103
82	6.2	101
83	6.1	104
84	6.09	104
85	6.02	101
86	6	102
87	n.t.	
88	7.39	102
89	7.38	104
90	8.51	103
91	7.25	103

Co. No.	GTPγS - hmGluR2 anGT pIC₅₀	GTPγS - hmGluR2 anGT E_{max}
92	8.53	107
93	7.74	105
94	7.26	108
95	8.75	110
96	8.91	108
97	8.78	104
98	8.19	111
99	7.84	108
100	8.16	109
101	6.39	109
102	8.08	107
103	8.55	107
104	8.43	108
105	7.56	108
106	6.22	109
107	7.75	114
108	6.91	108
109	7.73	107
110	8.29	108
111	6.53	108
112	7.45	103
113	7.04	103
114	8.15	104
115	8.15	108
116	6.25	105
117	8.12	109
118	7.71	105
119	5.6	100
120	7.19	106
121	4.79	75
122	8.43	108
123	8.18	107
124	8.52	108
125	6.75	105
126	8.24	108
127	7.56	103
128	6.23	104

Co. No.	GTPγS - hmGluR2 anGT pIC₅₀	GTPγS - hmGluR2 anGT E_{max}
129	6.16	100
130	7.77	102
131	7.61	105
132	7.62	103
133	8.08	104
134	8.49	104
135	6.19	103
136	7.36	102
137	7.74	107
138	7.17	105
139	7.44	106
140	6.29	104
141	7.21	102
142	8.18	105
143	7.61	104
144	7.02	103
145	7.73	105
146	7.78	105
147	8.24	106
148	5.25	100
149	<4.3	49
150	6.33	103
151	5.92	103
152	8	105
153	7.84	103
154	7.7	104
155	7.09	103
156	7.25	106
157	8.06	104
158	7.6	106
159	7.87	104
160	6.97	106
161	4.81	76
162	6.89	102
163	7.96	103
164	8.26	107
165	7.71	102

Co. No.	GTPγS - hmGluR2 anGT pIC₅₀	GTPγS - hmGluR2 anGT E_{max}
166	8.6	102
167	6.12	105
168	7.6	106
169	8.22	105
170	7.14	107
171	4.77	94
172	5.98	105
173	8.36	106
174	8	105
175	5.87	102
176	5.2	85
177	8.03	105
178	7.62	107
179	7.44	103
180	7.88	106
181	6.38	103
182	8.08	106
183	7.64	103
184	6.56	105
185	8.22	104
186	7.42	102
187	6.49	108
188	8.39	108
189	7.39	102
190	6.68	105
191	5.97	109
192	8.13	106
193	7.72	103
194	6.86	107
195	5.39	92
196	7.3	107
197	6.82	104
198	7.04	104
199	4.59	67
200	8.23	105
201	8.08	105
202	7.99	103

Co. No.	GTPγS - hmGluR2 anGT pIC₅₀	GTPγS - hmGluR2 anGT E_{max}
203	8.17	105
204	8.31	107
205	7.99	102
206	7.75	111
207	8.42	109
208	7.65	107
209	8.19	104
210	7.63	105
211	5.43	92
212	n.t.	
213	n.t.	
214	n.t.	
215	n.t.	
216	n.t.	
217	5.35	97
218	n.t.	
219	n.t.	
220	n.t.	
221	n.t.	
222	n.t.	
223	n.t.	
224	n.t.	
225	n.t.	
226	n.t.	
227	n.t.	
228	n.t.	
229	n.t.	
230	n.t.	
231	n.t.	
232	n.t.	
233	n.t.	
234	n.t.	
235	5.9	102
236	8.14	105
237	8.5	111
238	5.67	103
239	n.t.	

Co. No.	GTP γ S - hmGluR2 anGT pIC ₅₀	GTP γ S - hmGluR2 anGT E _{max}
240	8.17	109
241	7.74	109
242	7.89	110
243	7.65	116
244	5.06	80
245	n.t.	
246	8.38	116
247	7.52	109
248	n.t.	
249	8.08	109
250	8.4	120
251	8.2	116
252	n.t.	
253	8.21	111

Co. No.	GTP γ S - hmGluR2 anGT pIC ₅₀	GTP γ S - hmGluR2 anGT E _{max}
254	8.77	109
255	8.82	107
256	8.44	108
257	8.44	108
258	8.22	108
259	7.75	105
260	8.45	105
261	7.96	107
262	8.21	109
263	8.33	109
264	8.57	108
265	8.26	111
266	7.28	106
267	7.65	107

n.t. means not tested

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

5 Apparatus

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 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.

15

General Procedure

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.*

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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. 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 historical series of solvent-pretreated control rats are given in figure 1 and Table 8 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, two all-or-none criteria were adopted: (1) reversal: total distance > 1500 cm; (2) normalization: total distance > 4400 cm. The results on the reversal of the effect of JNJ-42153605 are shown in table 9 below.

Table 8. 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

Table 9. Reversal of the effect of JNJ 42153605 on scopolamine-induced hyperlocomotion. ED₅₀ means effective dose; PO means oral route; SC means subcutaneous route.

Co. No.	Route	ED ₅₀
26	SC	> 10
1	PO	0.45
	SC	3.54
8	PO	5

Co. No.	Route	ED ₅₀
	SC	≥ 10
16	SC	≥ 10
15	PO	1.26
12	PO	1.25

Co. No.	Route	ED ₅₀
2	PO	1.26
186	PO	3.15
6	PO	0.80
200	PO	3.15
4	PO	1.26
5	PO	≥ 2.5
14	PO	5
19	PO	≥ 10
3	PO	1.99
10	PO	0.79
9	PO	≥ 2.5
13	PO	7.94
18	PO	≥ 10
45	PO	1.26
46	PO	≥ 2.5
43	PO	1.26
47	PO	1.99
44	PO	≥ 2.5
152	PO	1.99
166	PO	0.50

Co. No.	Route	ED ₅₀
201	PO	> 2.5
147	PO	0.50
142	PO	1.99
236	PO	> 2.5
127	PO	1.99
104	PO	≥ 2.5
103	PO	0.96
102	PO	≥ 2.5
100	PO	> 10
99	PO	≥ 2.5
95	PO	> 2.5
180	PO	≥ 2.5
182	PO	1.99
237	PO	1.99
242	PO	> 2.5
251	PO	> 0.63
255	PO	0.79
256	PO	≥ 2.5
257	PO	≥ 2.5

3) V-maze test

The V-maze-test is a two-trial short term visual-spatial working memory task based on spontaneous exploration of a new and a familiar arm in a 2-arm maze (Embrechts et al. (2013) “Longitudinal characterization of the TauPS2APP mouse model of Alzheimer’s disease in a two trial discrimination task of visuo-spatial recognition memory”, 45th European Brain and Behaviour Society Meeting 6-9 September 2013, Munich, Abstract P202). Performance in this task can be disrupted by a low dose of PCP, such that the animals do not discriminate anymore between the new and a familiar arm.

Method

Male Long Evans rats (Janvier, France, body weight 280 to 295 g) were group housed in enriched individually ventilated cages and habituated to environmental conditions for 5 days. After acclimatization, animals were single housed for 4 days until testing.

During this period animals were handled for 2 min per day and received sham dosing

once a day for 3 days prior to the test. The V-maze consisted of two arms (LxWxH: 70×10×30 cm) at a 90° angle to each other to form a V-shaped maze connected by guillotine doors to a center zone. The walls of each arm were of a different context displaying horizontally black and white striped in one arm vs. uniform black walls in the other. Background infra-red illumination was provided via the bottom of the maze and a top view video camera above the platform was used for video recording of the experiments. The animal's exploration of each arm was automatically quantified using Ethovision XT 7.0 (Noldus, The Netherlands). Animals were treated with Co. No. 1 or its vehicle (20% HP-β-CD + 1 eq. HCl) administered p.o. 4 h before the start of the test. PCP (0.75 mg/kg s.c.) or its vehicle (0.9% NaCl solution) was administered 30 min prior to the test. The test consisted of 2 sessions of 5 min each: in the first session (exploration) the animal was placed in the center zone and given access to one of both arms (=familiar). After 5 min, the animal was taken out of the maze, the door of the other arm (new) was also opened, and the animal was put back in the center zone for a second session (choice). The time spent in the familiar and new arm respectively during the choice session was recorded for 5 min.

Results

Co. No. 1 was evaluated in rats in a series of dose-response studies evaluating doses from 0.16 to 10 mg/kg. While control animals (treated with vehicle of the test compound and the vehicle of PCP) displayed a strong preference for exploration of the new vs. the familiar arm in the second session, the PCP-treated rats did not discriminate anymore between both arms in each of these studies. PCP-challenged rats that were pretreated with Co. No. 1 at doses from 0.32 mg/kg onwards showed again a clear preference for the new arm (Figure 2). This reversal effect against PCP was observed up to the highest dose tested (10 mg/kg).

4) Reserpine interaction test in rats

Some exemplified compounds were observed to induce mydriasis in rats.

It was investigated to what extent the mydriatic action of test compounds was sufficient to counteract the miosis induced by the monoamines-depleting agent reserpine (10 mg/kg; SC) in Wiga rats. Test compounds induced mydriasis before the reserpine challenge (time = -1 h unless otherwise stated; Table 10).

For instance, Co. No. 1 induced mydriasis before the reserpine challenge (ED₅₀: 1.78 mg/kg s.c.; 1.55 mg/kg p.o., -1 h; 0.89 mg/kg, p.o., -4 h) and reversed the reserpine-induced ptosis (ED₅₀: 1.03 mg/kg s.c.; 0.78 mg/kg p.o., -1 h; 0.78 mg/kg, p.o., -4 h), miosis (ED₅₀: 4.1 mg/kg s.c.; 9.4 mg/kg p.o., -1 h; 9.4 mg/kg, p.o., -4 h) and sedation

(ED₅₀: 9.4 mg/kg s.c.; 7.1 mg/kg p.o., -1 h; 14 mg/kg, p.o., -4 h). The effects are illustrated in Figure 3. Co. No. 1 did not affect the tail-pinch response before reserpine nor the reserpine-induced blockade of the tail-pinch response and did not induce scratching or hyperemia after reserpine. The reference mGlu2 NAMs RO-4995819 (40 mg/kg, p.o.), RO-4491533 (40 mg/kg, p.o.; 10 mg/kg, s.c.) and [CAS 579473-69-1] (40 mg/kg, s.c.) were devoid of these interactions with reserpine.

Without wishing to be bound by theory, the observed effect may be mediated by a mechanism different from, and additional to, mGluR2 NAM activity.

10 **Table 10.** Reversal of reserpine-induced ptosis (reserpine; 10 mg/kg; SC; -1h) in Wistar rats.

Co. No.	Route	Time	ED ₅₀
40	PO	60	0.32
33	PO	60	0.5
26	PO	60	0.50
31	PO	60	0.79
1	PO	60	0.67
		240	0.89
	SC	60	1.01
2	PO	60	0.32
186	PO	60	3.15
200	PO	60	0.13
35	PO	60	> 10
41	PO	60	3.15
38	PO	60	5
36	PO	60	5
24	PO	60	≥ 10
34	PO	60	0.8
22	PO	60	0.13
79	PO	60	5
78	PO	60	≥ 10
82	PO	60	5
81	PO	60	5
80	PO	60	> 2.5
148	PO	60	1.99
83	PO	60	5

Co. No.	Route	Time	ED ₅₀
86	PO	60	≥ 10
187	PO	60	3.15
149	PO	60	1.99
84	PO	60	1.26
45	PO	60	1.26
150	PO	60	> 10
85	PO	60	1.99
190	PO	60	5
191	PO	60	3.15
44	PO	60	3.15
194	PO	60	5
195	PO	60	1.25
161	PO	60	3.15
167	PO	60	0.1
147	PO	60	7.94
171	PO	60	5
172	PO	60	1.26
129	PO	60	≥ 10
125	PO	60	5
119	PO	60	> 2.5
116	PO	60	≥ 10
244	PO	60	7.94

5) Ro-4-1284 interaction test in rats

The relative ability of Co. No. 1 to increase palpebral opening was also studied in rats challenged with another monoamines depleting agent, viz. Ro-4-1284 (1.25 mg/kg, s.c.). Effects on body temperature immediately before the injection of Ro-4-1284 were also measured. The cumulative palpebral opening score (every 5 min over a 1-h period) was used for evaluation. The median cumulative palpebral opening in solvent-pretreated control animals (n = 70) was 18; a scores > 25 occurred in only 1.4% of these control animals and was adopted as all-or-none criterion for drug-induced reversal of the Ro-4-1284-induced palpebral ptose. Co. No. 1 increased palpebral opening to scores > 25 (ED₅₀: 0.51 mg/kg, p.o.) without affecting body temperature (> 10 mg/kg, p.o.).

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

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. The local Ethical Committee approved all studies in compliance with the Declaration of Helsinki. Palpebral opening was scored every 5 min over the 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 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 ($n = 6335$)).

Table 11a 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 palpebral opening greater than 26.

Table 11a. 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

Table 11b. Reversal of LY-404039-induced decrease of palpebral opening in apomorphine challenged rats.

Co. No.	Route	ED ₅₀
33	PO	>2.5
31	PO	≥10
1	PO	0.45
	SC	0.3
8	PO	5
15	PO	11.22
2	PO	0.50
5	PO	>10
45	PO	0.79
46	PO	0.32
44	PO	0.50
167	PO	>40
147	PO	1.26
172	SC	>40
140	PO	1.99

7) Reversal of mGluR2-agonism in hippocampal brain slices

5 Introduction

Electrophysiology recordings of field excitatory postsynaptic potentials (fEPSPs) in acute hippocampal brain slices represent a model for testing synaptic transmission and plasticity. The effect of Co. No. 1 on synaptic transmission and plasticity in dentate gyrus synapses was investigated using this model. This region was chosen because of the high expression of mGluR 2 (Shigemoto et al., The Journal of Neuroscience, 10 October 1, 1997, 17(19), 7503-7522).

Methods

Recordings of fEPSPs were made from hippocampal brain slices using a multi-electrode array (MEA) biochip, and 3-dimensional- (3D) tip electrodes, according to a standard protocol. These recordings were used to monitor glutamate-mediated synaptic transmission (Figure 4).

Results

Superfusion of rat hippocampal brain slices with the mGlu2/3-specific agonist LY-354740 (1 μM) depressed fEPSP by 50% within 15 min of application (Figure 5) and was associated with an increase of the paired-pulse ratio (PPR), indicating a

presynaptic mechanism. Fifteen min after the application of 10 μ M Co. No. 1 the depression of fEPSP had recovered by 80%. This was associated with a decrease of the PPR, indicating an increase in neurotransmitter release (Figure 5, n = 17 slices from 4 rats).

- 5 Subsequently, the effects of Co. No. 1 on synaptic function using long-term potentiation (LTP) protocols in the dentate gyrus (Goeldner et. al., Neuropharmacology 2013, 64, 337-346) were evaluated.

- Small magnitude LTP (110%) was induced using isolated glutamatergic-mediated fEPSP: trains of theta-burst stimulation that are known to induce LTP at these particular synapses were applied (Dinklo et al., J. Pharmacol. Exp. Ther. 2011, 336(2), 560-574). In the presence of 10 μ M Co. No. 1, the magnitude of LTP was enhanced by 150% compared to baseline (p=0.005). Also noteworthy is the finding that the post-theta potentiation (PTP) in the presence of 10 μ M Co. No. 1 was significantly different from vehicle treatment: 160% vs. 120% respectively (p=0.01) (Figure 6, 10 22 slices from 4 SD rats). At the end of the experiments, addition of 1 mM kynurenic acid to block glutamatergic neurotransmission, confirmed that the post-synaptic response is mediated by glutamate neurotransmission.

Discussion

- LY-354740 stimulates presynaptic mGlu2/3 receptors to limit the release of glutamate. Furthermore, the effects of Group II mGluR agonists and antagonists in rodent models of cognition are totally absent in mGluR2 knock-out mice (Higgins et al. Neuropharmacology, 2004, 46, 907-917). Co. No. 1 reversed synaptic depression evoked by the mGlu2/3-agonist LY-354740. These data illustrate that Co. No. 1 is able to restore depressed synaptic transmission in rat hippocampal slices *in vitro*. The increase in network excitability, as a result of enhanced excitatory neurotransmission, affected the threshold of LTP induction. Thus, LTP was efficiently induced by weak theta stimulation, but only when Co. No. 1 was pre-applied. Thus, the compound might act as a cognitive enhancer via an ability to elevate the synaptic strength in glutamatergic synapses and by priming the system for enhanced LTP.

30

Prophetic composition examples

“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.

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

1. Tablets

Active ingredient	5 to 50 mg
Di-calcium phosphate	20 mg
Lactose	30 mg
5 Talcum	10 mg
Magnesium stearate	5 mg
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
10 of the exemplified compounds.

2. Suspension

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
15 cellulose, 1 mg of sodium benzoate, 500 mg of sorbitol and water ad 1 ml.

3. Injectable

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.
20

4. Ointment

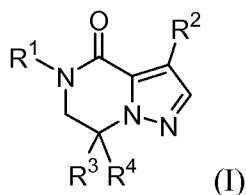
Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
25 White petroleum	15 g
Water	ad 100 g

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
30 of the exemplified compounds.

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)

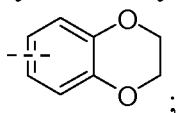


or a stereoisomeric form thereof,

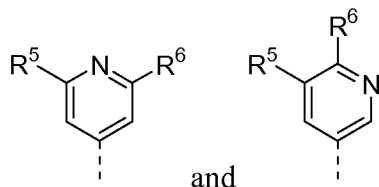
wherein

R^1 is phenyl or 2-pyridinyl, each optionally substituted with one or more substituents each independently selected from the group of halo, C_{1-4} alkyl, mono- or

- poly-halo C_{1-4} alkyl, -O- C_{1-4} alkyl, - C_{1-4} alkyl-O- C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyloxy, - C_{1-4} alkyl-OH, C_{1-4} alkylthio, mono- or poly-halo C_{1-4} alkylthio, cyano, C_{3-7} cycloalkyl optionally substituted with trifluoromethyl, and -SF₅; or is



- R^2 is selected from



wherein R^5 and R^6 are each independently selected from the group of hydrogen, halo, cyano, C_{1-4} alkyl, - C_{1-4} alkyl-OH, C_{3-7} cycloalkyl, mono- or poly-halo C_{1-4} alkyl, - C_{1-4} alkyl-O- C_{1-4} alkyl, -O- C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyloxy,

- 1-acetylazetidin-3-yl, and NR'R'';

wherein R' is selected from hydrogen and C_{1-4} alkyl;

R'' is selected from hydrogen and C_{1-4} alkyl; or

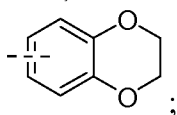
R' and R'' together with the Nitrogen atom to which they are attached form a heterocyclic group selected from the group of 1-azetidiny, 1-pyrrolidinyl,

- 1-piperidinyl, 1-piperazinyl, and 4-morpholinyl; wherein each of the heterocyclic groups may be optionally substituted with a substituent selected from halo, hydroxyl, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, and -(CO) C_{1-4} alkyl;

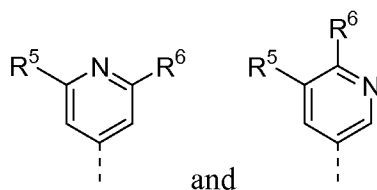
R^3 is selected from hydrogen and C_{1-4} alkyl;

R^4 is selected from the group of hydrogen, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, $-C_{1-4}$ alkyl-O- C_{1-4} alkyl, and $-C_{1-4}$ alkyl-OH; or a N-oxide, or a pharmaceutically acceptable salt or a solvate thereof.

- 5 **2.** A compound according to claim 1, or a stereoisomeric form thereof, wherein R^1 is phenyl or 2-pyridinyl, each optionally substituted with one or more substituents each independently selected from the group of halo, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, $-O-C_{1-4}$ alkyl, $-C_{1-4}$ alkyl-O- C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyloxy, $-C_{1-4}$ alkyl-OH, mono- or poly-halo C_{1-4} alkylthio, cyano, and $-SF_5$; or is

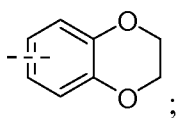


R^2 is selected from

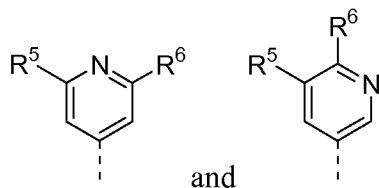


- 15 wherein R^5 and R^6 are each independently selected from the group of hydrogen, halo, cyano, C_{1-4} alkyl, $-C_{1-4}$ alkyl-OH, C_{3-7} cycloalkyl, mono- or poly-halo C_{1-4} alkyl, $-C_{1-4}$ alkyl-O- C_{1-4} alkyl, $-O-C_{1-4}$ alkyl, mono- or poly-halo C_{1-4} alkyloxy, and $NR'R''$; wherein R' is selected from hydrogen and C_{1-4} alkyl; R'' is selected from hydrogen and C_{1-4} alkyl; or
- 20 R' and R'' together with the Nitrogen atom to which they are attached form a heterocyclic group selected from the group of 1-azetidiny, 1-pyrrolidinyl, and 1-piperidinyl; wherein each of the heterocyclic groups may be optionally substituted with a halo substituent;
- R^3 is selected from hydrogen and C_{1-4} alkyl;
- 25 R^4 is selected from the group of hydrogen, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, $-C_{1-4}$ alkyl-O- C_{1-4} alkyl, and $-C_{1-4}$ alkyl-OH; or a N-oxide, or a pharmaceutically acceptable salt or a solvate thereof.

- 30 **3.** A compound according to claim 1 or 2, or a stereoisomeric form thereof, wherein R^1 is phenyl, optionally substituted with one or more substituents each independently selected from the group of halo, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, $-O-C_{1-4}$ alkyl, mono- or poly-halo C_{1-4} alkyloxy, cyano and $-SF_5$; or is

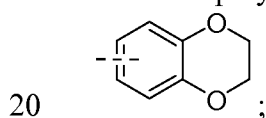


R^2 is selected from

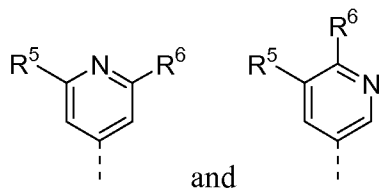


- 5 wherein R^5 and R^6 are each independently selected from the group of hydrogen, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, $-C_{1-4}$ alkyl-O- C_{1-4} alkyl, -O- C_{1-4} alkyl, and $NR'R''$;
 wherein R' is selected from hydrogen and C_{1-4} alkyl;
 R'' is selected from hydrogen and C_{1-4} alkyl;
 10 R^3 is selected from hydrogen and C_{1-4} alkyl;
 R^4 is selected from the group of hydrogen, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, $-C_{1-4}$ alkyl-O- C_{1-4} alkyl, and $-C_{1-4}$ alkyl-OH;
 or a pharmaceutically acceptable salt or a solvate thereof.

- 15 **4.** The compound according to any one of claims 1 to 3, or a stereoisomeric form thereof, wherein
 R^1 is phenyl, optionally substituted with one or more substituents each independently selected from the group of halo, C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyl, -O- C_{1-4} alkyl, mono- or poly-halo C_{1-4} alkyloxy, cyano and $-SF_5$; or is



R^2 is selected from

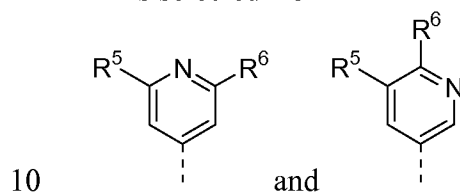


- 25 wherein R^5 and R^6 are each independently selected from the group of hydrogen, C_{1-4} alkyl, $-C_{1-4}$ alkyl-O- C_{1-4} alkyl, -O- C_{1-4} alkyl, and $NR'R''$;
 wherein R' is hydrogen;
 R'' is hydrogen;
 R^3 is selected from hydrogen and C_{1-4} alkyl;

R^4 is selected from the group of hydrogen and C_{1-4} alkyl;
or a pharmaceutically acceptable salt or a solvate thereof.

5. The compound according to any one of claims 1 to 4, or a stereoisomeric form thereof, wherein
 5 R^1 is phenyl, optionally substituted with one or more substituents each independently selected from the group of halo, C_{1-4} alkyl, poly-halo C_{1-4} alkyl and $-SF_5$;

R^2 is selected from



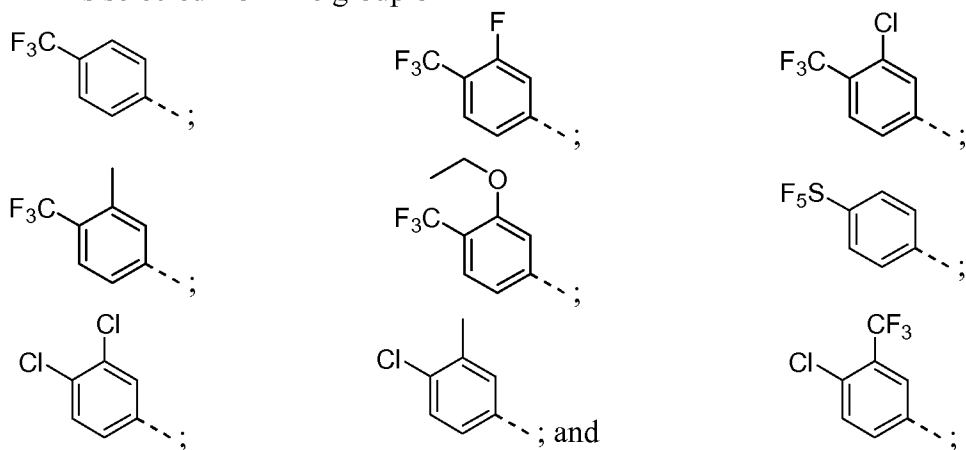
wherein R^5 and R^6 are each independently selected from the group of hydrogen, C_{1-4} alkyl and $-O-C_{1-4}$ alkyl;

R^3 is selected from hydrogen and C_{1-4} alkyl;

R^4 is hydrogen;

- 15 or a pharmaceutically acceptable salt or a solvate thereof.

6. A compound according to any one of claims 1 to 4, or a stereoisomeric form thereof, wherein R^1 is selected from the group of



and the rest of variables are as defined in any one of claims 1 to 4.

20

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 6 and a pharmaceutically acceptable carrier or excipient.

8. A compound according to any one of claims 1 to 6 or a pharmaceutical composition according to claim 7 for use as a medicament.
9. A compound according to any one of claims 1 to 6 or a pharmaceutical composition according to claim 7 for use in the treatment or in the prevention of central nervous system conditions or a 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.
10. A compound according to any one of claims 1 to 6 or a pharmaceutical composition according to claim 7 for use in the treatment or prevention of central nervous system disorders or conditions 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.
11. The compound or the pharmaceutical composition for use according to claim 9 or 10, wherein the central nervous system conditions or diseases are selected from dementia or neurocognitive disorder, major depressive disorder, depression, treatment resistant depression, attention-deficit/hyperactivity disorder and schizophrenia.
12. A process for preparing the pharmaceutical composition according to claim 7, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound according to any one of claims 1 to 6.
13. A method of treating or preventing a central nervous system disorder or condition 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 according to any one of claims 1 to 6 or a therapeutically effective amount of a pharmaceutical composition according to claim 7.
14. A method of treating or preventing a central nervous system disorder or condition selected from depressive disorders; neurocognitive disorders; neurodevelopmental

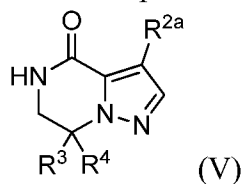
disorders; substance-related and addictive disorders; schizophrenia spectrum and other psychotic disorders; somatic symptom and related disorders; and hypersomnolence disorder; comprising administering to a subject in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 6 or a
5 therapeutically effective amount of a pharmaceutical composition according to claim 7.

15 **15.** The method according to claim 13 or 14 wherein the central nervous system conditions or diseases are selected from dementia or neurocognitive disorder, major depressive disorder, depression, treatment resistant depression, attention-
10 deficit/hyperactivity disorder and schizophrenia.

16. A product comprising a compound according to any one of claims 1 to 6 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
15 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.

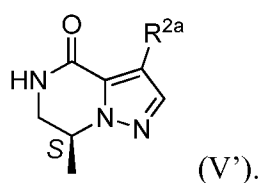
20 **17.** A product comprising a compound according to any one of claims 1 to 6 and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of central nervous system conditions or diseases selected from depressive disorders; neurocognitive disorders;
neurodevelopmental disorders; substance-related and addictive disorders; schizophrenia
25 spectrum and other psychotic disorders; somatic symptom and related disorders; and hypersomnolence disorder.

18. A compound of Formula (V)

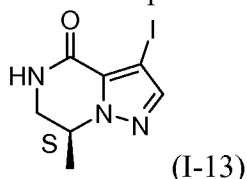
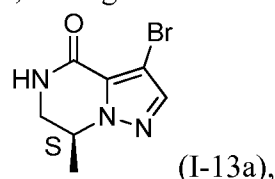


30 wherein R^{2a} is halo, and R^3 and R^4 are as defined in any one of claims 1 to 6.

19. A compound according to claim 18, having the Formula (V')

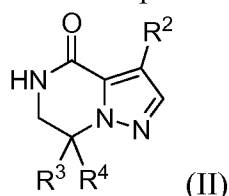


20. A compound according to claim 18 or 19, having the Formula (I-13) or (I-13a)



5 or a salt thereof.

21. A compound of Formula (II)



wherein R^2 , R^3 and R^4 are as defined in any one of claims 1 to 6.

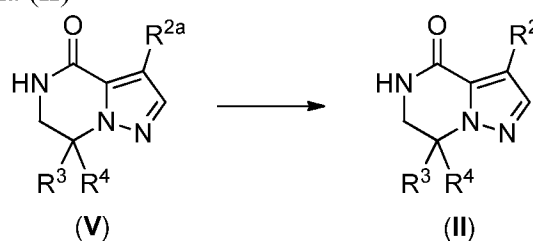
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22. A process for the preparation of a compound according to Formula (I) as defined in any one of claims 1 to 6, comprising steps a) and b)

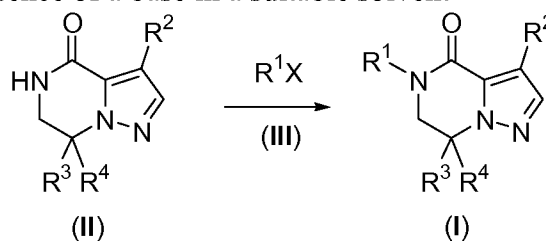
a) reacting a compound of Formula (V), wherein R^{2a} is halo, with a suitable boron species, in the presence of a palladium catalyst and a suitable base and solvent, to form

15

a compound of Formula (II)



b) reacting the compound of Formula (II) obtained in step a) with a compound of Formula (III) where X is halo, in the presence of a suitable coupling agent or a catalyst and ligand, in the presence of a base in a suitable solvent



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