1,2,4-TRIAZOLO [4,3-A] PYRIDINE DERIVATIVES AND THEIR USE FOR THE TREATMENT OR PREVENTION OF NEUROLOGICAL AND PSYCHIATRIC DISORDERS

Field of the Invention

The present invention relates to novel triazolo[4,3-a]pyridine derivatives which are positive allosteric modulators of the metabotropic glutamate receptor subtype 2 ("mGluR2") and which are useful for the treatment or prevention of neurological and psychiatric disorders associated with glutamate dysfunction and diseases in which the mGluR2 subtype of metabotropic receptors is involved. The invention is also directed to pharmaceutical compositions comprising such compounds, to processes to prepare such compounds and compositions, and to the use of such compounds for the prevention or treatment of neurological and psychiatric disorders and diseases in which mGluR2 is involved.

Background of the Invention

Glutamate is the major amino acid neurotransmitter in the mammalian central nervous system. Glutamate plays a major role in numerous physiological functions, such as learning and memory but also sensory perception, development of synaptic plasticity, motor control, respiration, and regulation of cardiovascular function. Furthermore, glutamate is at the centre of several different neurological and psychiatric diseases, where there is an imbalance in glutamatergic neurotransmission.

Glutamate mediates synaptic neurotransmission through the activation of ionotropic glutamate receptor channels (iGluRs), and the NMDA, AMPA and kainate receptors which are responsible for fast excitatory transmission.

In addition, glutamate activates metabotropic glutamate receptors (mGluRs) which have a more modulatory role that contributes to the fine-tuning of synaptic efficacy.

Glutamate activates the mGluRs through binding to the large extracellular amino-terminal domain of the receptor, herein called the orthosteric binding site. This binding induces a conformational change in the receptor which results in the activation of the G-protein and intracellular signalling pathways.

The mGluR2 subtype is negatively coupled to adenylate cyclase via activation of Gαi-protein, and its activation leads to inhibition of glutamate release in the synapse. In the central nervous system (CNS), mGluR2 receptors are abundant mainly

throughout cortex, thalamic regions, accessory olfactory bulb, hippocampus, amygdala, caudate-putamen and nucleus accumbens.

Activating mGluR2 was shown in clinical trials to be efficacious to treat anxiety disorders. In addition, activating mGluR2 in various animal models was shown to be efficacious, thus representing a potential novel therapeutic approach for the treatment of schizophrenia, epilepsy, drug addiction/dependence, Parkinson's disease, pain, sleep disorders and Huntington's disease.

To date, most of the available pharmacological tools targeting mGluRs are orthosteric ligands which activate several members of the family as they are structural analogues of glutamate.

A new avenue for developing selective compounds acting at mGluRs is to identify compounds that act through allosteric mechanisms, modulating the receptor by binding to a site different from the highly conserved orthosteric binding site.

It was demonstrated that such compounds do not activate the receptor by themselves. Rather, they enable the receptor to produce a maximal response to a concentration of glutamate, which by itself induces a minimal response. Mutational analysis has demonstrated unequivocally that the binding of mGluR2 positive allosteric modulators does not occur at the orthosteric site, but instead at an allosteric site situated within the seven transmembrane region of the receptor.

Animal data suggest that positive allosteric modulators of mGluR2 have effects in anxiety and psychosis models similar to those obtained with orthosteric agonists. Allosteric modulators of mGluR2 were shown to be active in fear-potentiated startle, and in stress-induced hyperthermia models of anxiety. Furthermore, such compounds were shown to be active in reversal of ketamine- or amphetamine-induced hyperlocomotion, and in reversal of amphetamine-induced disruption of prepulse inhibition of the acoustic startle effect models of schizophrenia.

Recent animal studies further reveal that the selective positive allosteric modulator of metabotropic glutamate receptor subtype 2 biphenyl-indanone (BINA) blocks a hallucinogenic drug model of psychosis, supporting the strategy of targeting mGluR2 receptors for treating glutamatergic dysfunction in schizophrenia.

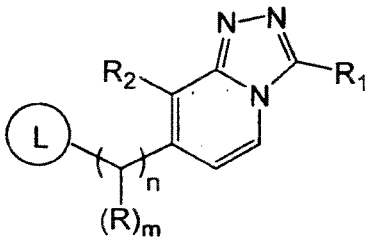
Positive allosteric modulators enable potentiation of the glutamate response, but they have also been shown to potentiate the response to orthosteric mGluR2 agonists such as LY379268 or DCG-IV. These data provide evidence for yet another novel therapeutic approach to treat the above mentioned neurological and psychiatric diseases

involving mGluR2, which would use a combination of a positive allosteric modulator of mGluR2 together with an orthosteric agonist of mGluR2.

WO 2007/104783, WO 2008/107479 and WO 2009/033704 (Addex & Janssen Pharmaceutica) describe pyridinone derivatives as mGluR2 positive allosteric modulators. WO 2009/062676 (Addex & Janssen) published on 22 May 2009 discloses imidazopyridine derivatives as mGluR2 positive allosteric modulators. The present triazolopyridine derivatives are centrally active, potent compounds providing alternative mGluR2 positive allosteric modulators with improved solubility and salt forming properties.

Detailed description of the Invention

The present invention relates to compounds having metabotropic glutamate receptor 2 modulator activity, said compounds having the Formula (I)



(I)

and the stereochemically isomeric forms thereof, wherein

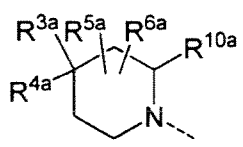
n is selected from the group consisting of 0, 1 and 2;
m is selected from the group consisting of 0, 1, and 2;
R is selected from methyl or trifluoromethyl;

R^1 is selected from the group consisting of hydrogen; C_{1-6}alkyl; (C_{1-3}alkyloxy)-C_{1-3}alkyl; [(C_{1-3}alkyloxy)C_{1-3}alkyloxy]C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; unsubstituted phenyl; unsubstituted benzyl; benzyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxyC_{1-3}alkyl, hydroxyC_{1-3}alkyl, cyano, hydroxyl, amino, C(=O)R', C(=O)OR', C(=O)NR'R'', mono- or di(C_{1-3}alkyl)amino, morpholinyl, (C_{3-7}cycloalkyl)C_{1-3}alkyloxy, trifluoromethyl and trifluoromethoxy, wherein R' and R'' are independently selected from hydrogen and C_{1-6}alkyl; (benzyloxy)C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with C_{1-3}alkyl substituted with one or more independently selected halo substituents; (C_{3-7}cycloalkyl)C_{1-3}alkyl; [(C_{3-7}cycloalkyl)C_{1-3}alkyloxy]C_{1-3}alkyl; (C_{3-7}cycloalkyl)C_{1-3}alkyloxy; 4-(2,3,4,5-

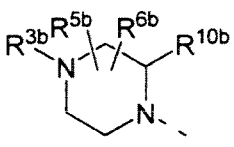
tetrahydro-benzo[f][1,4]oxazepine)methyl; Het^1; Het^1C_{1-3}alkyl; Het^2; and Het^2C_{1-3}alkyl;

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

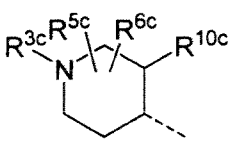
(L) is an *N*-containing heterocycle selected from the group consisting of (L-a), (L-b), (L-c), (L-d), (L-e), (L-f), (L-g) and (L-h) below



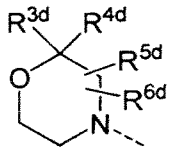
(L-a)



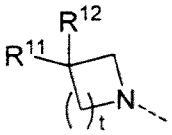
(L-b)



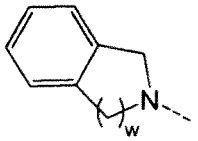
(L-c)



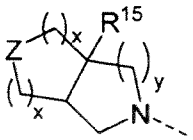
(L-d)



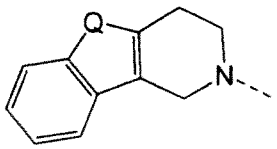
(L-e)



(L-f)



(L-g)



(L-h)

wherein

R^{3a} is selected from the group consisting of C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents or hydroxyl; unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxy-C_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxy substituted with one or more independently selected halo substituents, C_{1-3}alkylcarbonyl, mono- and di(C_{1-3}alkyl)amino, and morpholinyl; unsubstituted (phenyl)C_{1-3}alkyl; (phenyl)C_{1-3}alkyl wherein the phenyl and the C_{1-3}alkyl part of the substituent may each be independently substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more

independently selected halo substituents, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxy substituted with one or more independently selected halo substituents, C_{1-3}alkylcarbonyl, mono- or di(C_{1-3}alkyl)amino, morpholinyl and (C_{3-7}cycloalkyl)C_{1-3}alkyloxy; unsubstituted phenyloxy; phenyloxy substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, C_{1-3}alkyloxy, and C_{1-3}alkyloxy substituted with one or more independently selected halo substituents; unsubstituted phenyloxy(C_{1-3}alkyl)oxy; unsubstituted (phenylC_{1-3}alkyl)oxy; phenyl(C_{1-3}alkyl)oxy wherein the phenyl part of the substituent is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, C_{1-3}alkyloxy, and C_{1-3}alkyloxy substituted with one or more independently selected halo substituents; unsubstituted phenyloxyC_{1-3}alkyl; (phenyloxy)C_{1-3}alkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, C_{1-3}alkyloxy, and C_{1-3}alkyloxy substituted with one or more independently selected halo substituents; unsubstituted phenylamino; phenylamino substituted with 1 or 2 independently selected halo substituents; (phenylC_{1-3}alkyl)amino; (phenylamino)(C_{1-3}alkyl); (C_{3-7}cycloalkyl)C_{1-3}alkyl; [phenyl(C_{3-7}cycloalkyl)]C_{1-3}alkyl; Het^1; Het^2; Het^2oxy; Het^2methyloxy; Het^3; and phenyl with two vicinal substituents which taken together form a bivalent radical of formula

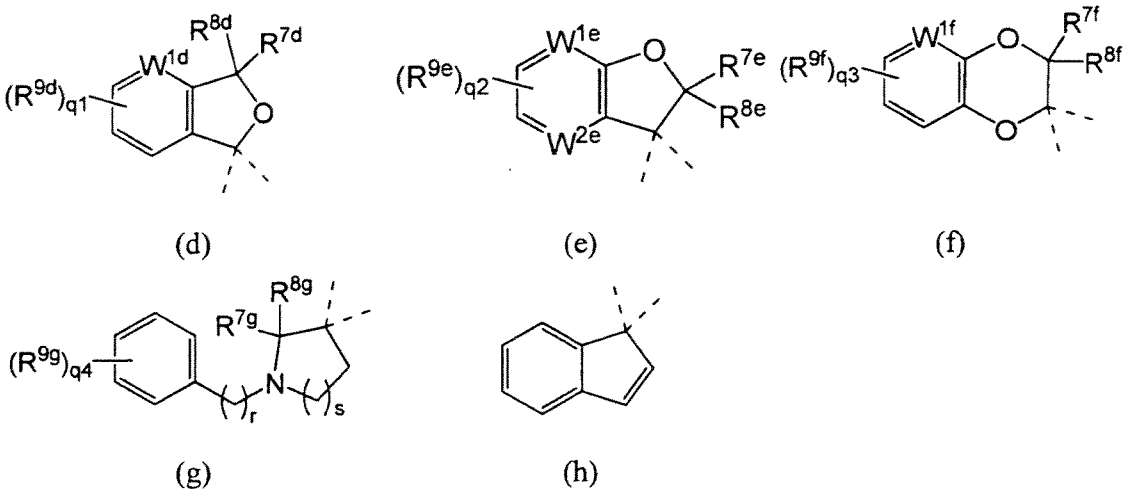
-N=CH-NH- (a),

-CH=CH-NH- (b), or

-O-CH_2-CH_2-NH- (c);

R^{4a} is selected from the group consisting of hydrogen; halogen; trifluoromethyl; trifluoromethoxy; hydroxyl; C_{1-3}alkyl; C_{1-3}alkyloxy; hydroxyC_{1-3}alkyl; hydroxyl-C_{1-3}alkyloxy; fluoroC_{1-3}alkyl; fluoroC_{1-3}alkyloxy; cyano; unsubstituted phenyl; and phenyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyloxy, hydroxyC_{1-3}alkyl, trifluoromethyl and trifluoromethoxy;

or $CR^{3a}R^{4a}$ forms a radical of formula (d), (e), (f), (g) or (h);



(d) (e) (f)

(g) (h)

wherein

each W^{1d}, W^{1e}, W^{2e} and W^{1f} is independently selected from CH and N;

each R^{7d}, R^{7e}, R^{7f}, R^{7g}, R^{8d}, R^{8e}, R^{8f}, R^{8g} is independently selected from hydrogen, methyl and fluoro; or each $CR^{7d}R^{8d}$, $CR^{7e}R^{8e}$, $CR^{7f}R^{8f}$, $CR^{7g}R^{8g}$ form a carbonyl group;

each R^{9d}, R^{9e}, R^{9f}, and R^{9g} is fluoro;

each q1, q2, q3 or q4 is independently selected from 0, 1 and 2;

r is 0 or 1;

s is 0 or 1;

each R^{3b} and R^{3c} is selected from the group consisting of C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxy substituted with one or more independently selected halo substituents, C_{1-3}alkylcarbonyl, mono- and di(C_{1-3}alkyl)amino, and morpholinyl; unsubstituted (phenyl)C_{1-3}alkyl; (phenyl)C_{1-3}alkyl wherein the phenyl and the C_{1-3}alkyl part of the substituent may each be independently substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxy substituted with one or more independently selected halo substituents, C_{1-3}alkylcarbonyl, mono- or di(C_{1-3}alkyl)amino, morpholinyl, C_{3-7}cycloalkyl, (C_{3-7}cycloalkyl)C_{1-3}alkyl, and (C_{3-7}cycloalkyl)-C_{1-3}alkyloxy; unsubstituted

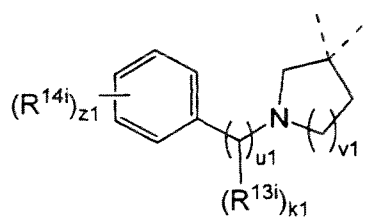
(phenyloxy)C_{1-3}alkyl; (phenyloxy)C_{1-3}alkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, C_{1-3}alkyloxy, and C_{1-3}alkyloxy substituted with one or more independently selected halo substituents; (phenylamino)(C_{1-3}alkyl); phenyl with two vicinal substituents which taken together form a bivalent radical of formula (a), (b) or (c) as previously defined; Het^1; Het^2; Het^3; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, or hydroxyl; (C_{3-7}cycloalkyl)C_{1-3}alkyl; and [phenyl(C_{3-7}cycloalkyl)]C_{1-3}alkyl;

R^{3d} and R^{4d} are each independently selected from the group consisting of hydrogen and C_{1-3}alkyl;

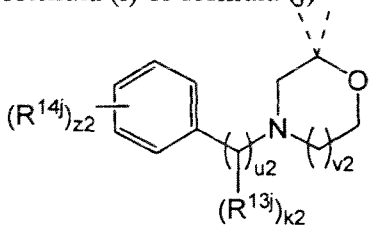
each R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{6a}, R^{6b}, R^{6c} and R^{6d} is independently selected from the group consisting of hydrogen and C_{1-3}alkyl; or each pair $R^{5a}R^{6a}$, $R^{5b}R^{6b}$, $R^{5c}R^{6c}$, $R^{5d}R^{6d}$ are substituents on the same carbon atom and each $CR^{5a}R^{6a}$, $CR^{5b}R^{6b}$, $CR^{5c}R^{6c}$, $CR^{5d}R^{6d}$ together form a (C=O) or a C_{3-7}cycloalkylidene radical;

each R^{10a}, R^{10b} and R^{10c} is selected from H, C_{1-3}alkyl and C_{1-3}alkyloxy;

wherein, in (L-e),
when t is 1 or 2, R^{11} is hydrogen and R^{12} is selected from a substituent selected from the group consisting of phenyl, phenyloxy and phenylamino, each of which may be optionally substituted with 1 or 2 halo substituents; or
when t is 1 or 3, then $CR^{11}R^{12}$ form a radical of formula (i) or formula (j)



(i)



(j)

wherein
each R^{13i} and R^{13j} is independently selected from methyl and trifluoromethyl;
each R^{14i} or R^{14j} is fluoro;
each u1 and u2 is independently 0, 1 or 2;
v1 is selected from the group of 0, 1 and 2;
v2 is selected from the group of 1 and 2;

each z1 and z2 is independently selected from the group of 0, 1 and 2;
each k1 and k2 is independently selected from the group of 0, 1 and 2;

wherein, in (L-f) w is 1 or 2;

wherein in (L-g)
Z is $CR^{16}R^{17}$ and R^{15} is hydrogen when each x is 0 and y is 1; or
Z is $CR^{16}R^{17}$ and R^{15} is selected from the group consisting of hydrogen, methyl and phenyl when each x is 0 and y is 2; or
Z is NR^{16} when each x is 1 and y is 1;
wherein R^{16} and R^{17} are each independently selected from the group consisting of hydrogen; unsubstituted phenyl; and phenyl substituted with 1, 2 or 3 halo substituents;

wherein in (L-h),
Q is O or N-R^{18}, wherein R^{18} is selected from hydrogen and C_{1-3}alkyl;

wherein

each Het^1 is a saturated heterocyclic radical selected from pyrrolidinyl; piperidinyl; piperazinyl; and morpholinyl; each of which may be optionally substituted with 1 or 2 substituents independently selected from the group consisting of C_{1-6}alkyl, halo, C_{1-3}alkyl substituted with one or more independently selected halo substituents, unsubstituted phenyl or phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, trifluoromethyl, and trifluoromethoxy; and

each Het^2 is an aromatic heterocyclic radical selected from pyridinyl and pyrimidinyl; each of which is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of halo; C_{1-3}alkyl; C_{1-3}alkyloxy; and C_{1-3}alkyl substituted with one or more independently selected halo substituents;

each Het^3 is a heterocyclic radical selected from 1,3-thiazolyl optionally substituted with C_{1-3}alkyl; unsubstituted benzofuranyl; unsubstituted 3,4-dihydro-*2H*-chromenyl; and unsubstituted *1H*-indolyl;

each halo is selected from the group consisting of fluoro, chloro, bromo and iodo;

and the pharmaceutically acceptable salts and the solvates thereof.

The names of the compounds of the present invention were generated according to the nomenclature rules agreed upon by the Chemical Abstracts Service (CAS) using Advanced Chemical Development, Inc., software (ACD/Name product version 10.01; Build 15494, 1 Dec 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.

Definitions

The notation "C_{1-3}alkyl" or "C_{1-6}alkyl" 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 3 or 1 to 6 carbon atoms, such as methyl, ethyl, 1-propyl, 1-methylethyl, butyl, 1-methyl-propyl, 2-methyl-1-propyl, 1,1-dimethylethyl, 3-methyl-1-butyl, 1-pentyl, 1-hexyl and the like.

The notation "C_{3-7}cycloalkyl" as used herein alone or as part of another group, defines a saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The notation "C_{3-7}cycloalkylC_{1-3}alkyl" as used herein alone or as part of another group, defines a saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms bound through a saturated, straight hydrocarbon radical having from 1 to 3 carbon atoms, such as cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl and the like.

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 "C_{1-3}alkyl substituted with one or more independently selected halo substituents" as used herein alone or as part of another group, defines an alkyl group as defined above, substituted with 1, 2, 3 or more halogen atoms, such as fluoromethyl; difluoromethyl; trifluoromethyl; 2,2,2-trifluoroethyl; 1,1-difluoroethyl; 3,3,3-trifluoropropyl. Preferred examples of these groups are trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl and 1,1-difluoroethyl.

The notation "mono-, di- or tri-haloC_{1-3}alkyl" as used herein alone or as part of another group, defines an alkyl group as defined above, substituted with 1, 2 or 3 halogen atoms, such as fluoromethyl; difluoromethyl; trifluoromethyl; 2,2,2-trifluoroethyl; 1,1-difluoroethyl; 3,3,3-trifluoropropyl. Preferred examples of these groups are trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl and 1,1-difluoroethyl.

The notation "C_{3-7}cycloalkylidene" as used herein, refers to a bivalent C_{3-7}cycloalkane group, by removal of 2 hydrogen atoms from the same carbon atom, such as for example, cyclopropylidene, cyclobutylidene, cyclopentylidene, cyclohexylidene and the like.

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, 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.

The substituents covered by the terms Het^1, Het^2 or Het^3 may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate, if not otherwise specified. Thus, for example, when the Het^1 substituent is morpholinyl, it may be 2-morpholinyl, 3-morpholinyl or 4-morpholinyl; when the Het^2 substituent is pyridinyl, it may be 2-pyridinyl, 3-pyridinyl or 4-pyridinyl. Preferred Het^1 substituents are those linked to the rest of the molecule through the nitrogen atom.

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 "stereoisomeric forms" as used hereinbefore defines all the possible isomeric forms that the compounds of Formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centres may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration. Compounds encompassing double bonds can have an E- or Z-stereochemistry at said double bond. Stereoisomeric forms of the compounds of Formula (I) are embraced within the scope of this invention.

When a specific stereoisomeric form is indicated, this means that said form 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.

Following CAS nomenclature conventions, when two stereogenic centres of known absolute configuration are present in a compound, an *R* or *S* descriptor is assigned (based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral centre, the reference centre. The configuration of the second stereogenic centre is indicated using relative descriptors [*R**,*R**] or [*R**,*S**], where *R** is always specified as the reference centre and [*R**,*R**] indicates centres with the same chirality and [*R**,*S**] indicates centres of unlike chirality. For example, if the lowest-numbered chiral centre in the compound has an *S*-configuration and the second centre is *R*, the stereo descriptor would be specified as *S*-[*R**,*S**]. If "α" and "β" are used: the position of the highest priority substituent on the asymmetric carbon atom in the ring system having the lowest ring number, is arbitrarily always in the "α" position of the mean plane determined by the ring system. The position of the highest priority substituent on the other asymmetric carbon atom in the ring system (hydrogen atom in compounds according to Formula (I)) relative to the position of the highest priority substituent on the reference atom is denominated "α" if it is on the same side of the mean plane determined by the ring system, or "β", if it is on the other side of the mean plane determined by the ring system.

Preferred features of the compounds of this invention are now set forth.

In an embodiment, the invention relates to compounds of Formula (I) and stereochemically isomeric forms thereof, wherein

n is selected from the group consisting of 0 and 1;

m is selected from the group consisting of 0 and 1;

R is selected from methyl or trifluoromethyl;

R^1 is selected from the group consisting of C_{1-6}alkyl; (C_{1-3}alkyloxy)C_{1-3}alkyl; [(C_{1-3}alkyloxy)C_{1-3}alkyloxy]C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; unsubstituted phenyl; unsubstituted benzyl; benzyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxyC_{1-3}alkyl, hydroxyC_{1-3}alkyl, cyano, hydroxyl, morpholinyl, trifluoromethyl and trifluoromethoxy; (benzyloxy)C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with C_{1-3}alkyl substituted with one or more independently selected halo substituents; (C_{3-7}cycloalkyl)C_{1-3}alkyl; [(C_{3-7}cycloalkyl)C_{1-3}alkyloxy]C_{1-3}alkyl; (C_{3-7}cycloalkyl)C_{1-3}alkyloxy; Het^1; Het^1C_{1-3}alkyl; Het^2; and Het^2C_{1-3}alkyl;

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

Ⓛ is selected from the group consisting of (L-a), (L-b), (L-c), (L-d), (L-e), (L-f), (L-g) and (L-h); wherein

R^{3a} is selected from the group consisting of C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents or hydroxyl; unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, cyano, hydroxyl, C_{1-3}alkyloxy-C_{1-3}alkyl, C_{1-3}alkyloxy, and morpholinyl; unsubstituted (phenyl)C_{1-3}alkyl; (phenyl)C_{1-3}alkyl wherein the phenyl and the C_{1-3}alkyl part of the substituent may each be independently substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, C_{1-3}alkyloxy, and (C_{3-7}cycloalkyl)-C_{1-3}alkyloxy; unsubstituted phenyloxy; phenyloxy substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, and C_{1-3}alkyloxy; unsubstituted (phenylC_{1-3}alkyl)oxy; phenyl(C_{1-3}alkyl)oxy wherein the phenyl part of the substituent is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, and C_{1-3}alkyloxy; (phenyloxy)C_{1-3}alkyl substituted with 1 or 2 halo substituents; unsubstituted phenylamino; phenylamino substituted with 1 or 2 halo substituents; (phenylC_{1-3}alkyl)amino; (phenylamino)(C_{1-3}alkyl); Het^1; Het^2; Het^2oxy; Het^2methyloxy; and Het^3;

R^{4a} is selected from the group consisting of hydrogen; halogen; trifluoromethyl; trifluoromethoxy; hydroxyl; C_{1-3}alkyl; C_{1-3}alkyloxy; and unsubstituted phenyl;

or $CR^{3a}R^{4a}$ forms a radical of formula (d), (e), (f), (g) or (h); wherein

each W^{1d}, W^{1e}, W^{2e} and W^{1f} is independently selected from CH and N;

each R^{7d}, R^{7e}, R^{7f}, R^{7g}, R^{8d}, R^{8e}, R^{8f}, R^{8g} is independently selected from hydrogen, methyl and fluoro; or each $CR^{7d}R^{8d}$, $CR^{7g}R^{8g}$ form a carbonyl group;

each R^{9d}, R^{9e}, R^{9f}, and R^{9g} is fluoro;

each q1, q2, q3 or q4 is independently selected from 0, 1 and 2;

r is 0 or 1;

s is 0 or 1;

each R^{3b} and R^{3c} is selected from the group consisting of C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, C_{1-3}alkyloxyC_{1-3}alkyl, and C_{1-3}alkyloxy; unsubstituted (phenyl)C_{1-3}alkyl; (phenyl)C_{1-3}alkyl wherein the phenyl and the C_{1-3}alkyl part of the substituent may each be independently substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, C_{3-7}cycloalkyl, (C_{3-7}cycloalkyl)-C_{1-3}alkyl, and (C_{3-7}cycloalkyl)-C_{1-3}alkyloxy; (phenyloxy)C_{1-3}alkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, and C_{1-3}alkyl substituted with one or more independently selected halo substituents; (phenylamino)(C_{1-3}alkyl); Het^1; Het^2; Het^3; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, and hydroxyl; and [phenyl(C_{3-7}cycloalkyl)]C_{1-3}alkyl;

R^{3d} and R^{4d} are each independently selected from the group consisting of hydrogen and C_{1-3}alkyl;

each R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{6a}, R^{6b}, R^{6c} and R^{6d} is independently selected from the group consisting of hydrogen and C_{1-3}alkyl; or each pair $R^{5a}R^{6a}$, $R^{5b}R^{6b}$, $R^{5c}R^{6c}$, $R^{5d}R^{6d}$ are substituents on the same carbon atom and each $CR^{5a}R^{6a}$, $CR^{5b}R^{6b}$, $CR^{5c}R^{6c}$, $CR^{5d}R^{6d}$ together form a (C=O) or a C_{3-7}cycloalkylidene radical;

each R^{10a}, R^{10b} and R^{10c} is selected from H, and C_{1-3}alkyl;

wherein, in (L-e),
when t is 1 or 2, R^{11} is hydrogen and R^{12} is selected from a substituent selected from the group consisting of phenyl, phenyloxy and phenylamino, each of which may be optionally substituted with 1 or 2 halo substituents; or
when t is 1 or 3, then $CR^{11}R^{12}$ form a radical of formula (i); wherein
R^{13i} is methyl;
R^{14i} is fluoro;
u1 is 0 or 1;
v1 is 0, 1 or 2;
z1 is selected from the group of 0, 1 and 2;
k1 is 0 or 1;

wherein, in (L-f) w is 1 or 2;

wherein in (L-g)
Z is $CR^{16}R^{17}$ and R^{15} is hydrogen when each x is 0 and y is 1; or
Z is $CR^{16}R^{17}$ and R^{15} is selected from the group consisting of hydrogen, methyl and phenyl when each x is 0 and y is 2; or
Z is NR^{16} when each x is 1 and y is 1;
wherein R^{16} and R^{17} are each independently selected from the group consisting of hydrogen; unsubstituted phenyl; and phenyl substituted with 1, 2 or 3 halo substituents;

wherein in (L-h),
Q is O or N-R^{18}, wherein R^{18} is selected from hydrogen and C_{1-3}alkyl;

wherein

each Het^1 is a saturated heterocyclic radical selected from pyrrolidinyl; piperidinyl; piperazinyl; and morpholinyl; each of which may be optionally substituted with 1 or 2 substituents independently selected from the group consisting of C_{1-6}alkyl, halo, C_{1-3}alkyl substituted with one or more independently selected halo substituents, unsubstituted phenyl or phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, trifluoromethyl, and trifluoromethoxy;

each Het^2 is an aromatic heterocyclic radical selected from pyridinyl and pyrimidinyl; each of which is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of halo; C_{1-3}alkyl; C_{1-3}alkyloxy; and C_{1-3}alkyl substituted with one or more independently selected halo substituents;

each Het^3 is a heterocyclic radical selected from 1,3-thiazolyl optionally substituted with C_{1-3}alkyl; unsubstituted benzofuranyl; unsubstituted 3,4-dihydro-*2H*-chromenyl; and unsubstituted *1H*-indolyl;

each halo is selected from the group consisting of fluoro, chloro, and bromo;

and the pharmaceutically acceptable salts and the solvates thereof.

In an embodiment, the invention relates to compounds of Formula (I) and stereochemically isomeric forms thereof, wherein

n is selected from 0 and 1;
m is selected from 0 and 1;
R is methyl;

R^1 is selected from the group consisting of C_{1-6}alkyl; (C_{1-3}alkyloxy)C_{1-3}alkyl; [(C_{1-3}alkyloxy)-C_{1-3}alkyloxy]C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more halo substituents; unsubstituted phenyl; (benzyloxy)C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with C_{1-3}alkyl substituted with one or more halo substituents; (C_{3-7}cycloalkyl)C_{1-3}alkyl; [(C_{3-7}cycloalkyl)C_{1-3}alkyloxy]-C_{1-3}alkyl; (C_{3-7}cycloalkyl)C_{1-3}alkyloxy; Het^1C_{1-3}alkyl; Het^2; and Het^2C_{1-3}alkyl;

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

Ⓛ is an *N*-containing heterocycle selected from the group consisting of (L-a), (L-b), (L-c), (L-d), (L-e), (L-f), (L-g) and (L-h); wherein

R^{3a} is selected from the group consisting of C_{1-3}alkyl substituted with one or more halo substituents; unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, hydroxyC_{1-3}alkyl,

C_{1-3}alkyl substituted with one or more halo substituents, hydroxyl, and C_{1-3}alkyloxy; phenyloxy substituted with 1 or 2 independently selected halo substituents; phenyl(C_{1-3}alkyl)oxy wherein the phenyl part of the substituent is substituted with 1, 2, or 3 independently selected halo substituents; (phenyloxy)C_{1-3}alkyl wherein the phenyl part of the substituent is substituted with 1 or 2 halo substituents; unsubstituted phenylamino; phenylamino substituted with 1 or 2 halo substituents; (phenylC_{1-3}alkyl)amino; Het^1; Het^2; Het^2oxy; Het^2methyloxy; and Het^3;

R^{4a} is selected from the group consisting of hydrogen; halogen; trifluoromethyl; C_{1-3}alkyl; C_{1-3}alkyloxy; and unsubstituted phenyl;

or $CR^{3a}R^{4a}$ forms a radical of formula (d), (e), (f), (g) or (h); wherein

each W^{1d}, W^{1e}, W^{2e} and W^{1f} is independently selected from CH and N;

each R^{7d}, R^{7e}, R^{7f}, R^{7g}, R^{8d}, R^{8e}, R^{8f}, R^{8g} is independently selected from hydrogen, methyl and fluoro; or each $CR^{7d}R^{8d}$, $CR^{7g}R^{8g}$ form a carbonyl group;

each R^{9d}, R^{9e}, R^{9f}, and R^{9g} is fluoro;

each q1, q2, q3 or q4 is independently selected from 0, 1 and 2;

r is 0 or 1;

s is 0 or 1;

each R^{3b} and R^{3c} is selected from the group consisting of C_{1-3}alkyl substituted with one or more halo substituents; unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyloxy and C_{1-3}alkyl substituted with one or more halo substituents; unsubstituted (phenyl)C_{1-3}alkyl; (phenyl)C_{1-3}alkyl wherein the phenyl and the C_{1-3}alkyl parts of the substituent may each be independently substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more halo substituents, and (C_{3-7}cycloalkyl)-C_{1-3}alkyloxy; Het^2; Het^3; C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from the group consisting of C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more halo substituents, and hydroxyl; and [phenyl(C_{3-7}cycloalkyl)]C_{1-3}alkyl;

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

each R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{6a}, R^{6b}, R^{6c} and R^{6d} is independently selected from the group consisting of hydrogen and C_{1-3}alkyl; or $CR^{5b}R^{6b}$ together form a (C=O) or a C_{3-7}cycloalkylidene radical;

each R^{10a}, R^{10b} and R^{10c} is H;

wherein, in (L-e),
when t is 1 or 2, R^{11} is hydrogen and R^{12} is selected from a substituent selected from the group consisting of phenyl, phenyloxy and phenylamino, each of which may be optionally substituted with 1 or 2 halo substituents; or
when t is 1, then $CR^{11}R^{12}$ form a radical of formula (i); wherein
R^{14i} is fluoro;
u1 is 0 or 1;
v1 is 2;
z1 is selected from the group of 1 and 2;
k1 is 0; or
when t is 3, then $CR^{11}R^{12}$ form a radical of formula (i); wherein
R^{14i} is fluoro;
u1 is 0 or 1;
v1 is 0;
z1 is selected from the group of 1 and 2;
k1 is 0;

wherein, in (L-f) w is 1 or 2;

wherein in (L-g)
Z is $CR^{16}R^{17}$ and R^{15} is hydrogen when each x is 0 and y is 1; or
Z is $CR^{16}R^{17}$ and R^{15} is phenyl when each x is 0 and y is 2; or
Z is NR^{16} when each x is 1 and y is 1;
wherein R^{16} and R^{17} are each independently selected from the group consisting of hydrogen; unsubstituted phenyl; and phenyl substituted with 1, 2 or 3 halo substituents;

wherein in (L-h), Q is O;

each Het^1 is a saturated heterocyclic radical selected from pyrrolidinyl; piperidinyl; piperazinyl; and morpholinyl; each of which is unsubstitued or substituted with 1

or 2 substituents independently selected from the group consisting of fluoro, C_{1-3}alkyl substituted with one or more halo substituents, and unsubstituted phenyl; and

each Het^2 is an aromatic heterocyclic radical selected from pyridinyl and pyrimidinyl; each of which is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of halo; C_{1-3}alkyl; and C_{1-3}alkyloxy;

each Het^3 is a heterocyclic radical selected from 1,3-thiazolyl optionally substituted with C_{1-3}alkyl; unsubstituted benzofuranyl; unsubstituted 3,4-dihydro-*2H*-chromenyl; and unsubstituted *1H*-indolyl;

each halo is selected from the group consisting of fluoro, chloro, and bromo;

and the pharmaceutically acceptable salts and the solvates thereof.

In an embodiment, the invention relates to compounds of Formula (I) and stereochemically isomeric forms thereof, wherein

n is selected from 0 and 1;
m is selected from 0 and 1;
R is methyl;

R^1 is selected from the group consisting of C_{1-6}alkyl; (C_{1-3}alkyloxy)C_{1-3}alkyl; [(C_{1-3}alkyloxy)-C_{1-3}alkyloxy]C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more halo substituents; unsubstituted phenyl; (benzyloxy)C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with trifluoromethyl; (C_{3-7}cycloalkyl)C_{1-3}alkyl; [(C_{3-7}cycloalkyl)C_{1-3}alkyloxy]-C_{1-3}alkyl; (C_{3-7}cycloalkyl)C_{1-3}alkyloxy; pyrrolidinylmethyl; morpholinylmethyl; piperidinylmethyl substituted with phenyl; piperidinylmethyl substituted with trifluoromethyl; pyridinyl; and pyridinylmethyl;
R^2 is selected from the group consisting of cyano; halo; C_{1-3}alkyl substituted with one or more halo substituents; C_{1-3}alkyl; and cyclopropyl;

Ⓛ is an *N*-containing heterocycle selected from the group consisting of (L-a), (L-b), (L-c), (L-e), (L-f), (L-g) and (L-h); wherein

R^{3a} is selected from the group consisting of trifluoromethyl; phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, 2-hydroxyprop-2-yl, trifluoromethyl, hydroxyl, methoxy, and ethoxy; phenyloxy substituted with 1 or 2 independently selected halo substituents; phenyl(C_{1-3}alkyl)oxy wherein the phenyl part of the substituent is substituted with 1, 2, or 3 independently selected halo substituents; (phenyloxy)C_{1-3}alkyl wherein the phenyl part is substituted with 1 or 2 halo substituents; phenylamino; phenylamino substituted with 1 or 2 halo substituents; benzylamino; morpholinyl; pyrrolidinyl substituted with 1 or 2 halo substituents; piperidinyl substituted with 1 or 2 halo substituents; pyridinyl; pyridinyl substituted with 1 or 2 substituents independently selected from halo, methyl and methoxy; pyrimidinyl; pyrimidinyl substituted with 1 or 2 substituents independently selected from halo and methoxy; pyridinylmethyloxy; and *1H*-indol-1-yl;

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

or $CR^{3a}R^{4a}$ forms a radical of formula (d), (e), (f), (g) or (h); wherein

each W^{1d}, W^{1e}, W^{2e} is independently selected from CH and N;

W^{1f} is CH;

R^{7d} and R^{8d} are selected from hydrogen, methyl and fluoro; or $CR^{7d}R^{8d}$ forms a carbonyl group;

R^{7e}, R^{7f}, R^{8e} and R^{8f} are hydrogen;

R^{7g} and R^{8g} are hydrogen; or $CR^{7g}R^{8g}$ forms a carbonyl group;

each R^{9d} and R^{9g} is fluoro;

q1 is selected from 0 or 1;

each q2 and q3 is 0;

q4 is selected from 1 and 2;

r is 0 or 1;

s is 0 or 1;

R^{3b} is selected from the group consisting of 3,3,3-trifluoropropyl; phenyl; phenyl substituted with 1, or 2 substituents independently selected from the group consisting of halo, methoxy, ethoxy and trifluoromethyl; benzyl; (phenyl)methyl wherein the phenyl part of the substituent may be substituted with 1 or 2 substituents independently selected from the group consisting of halo,

trifluoromethyl and cyclopropylmethyloxy, and the methyl part of the substituent may be optionally substituted with methyl or trifluoromethyl; phenylethyl; cyclohexyl substituted with 1 or 2 substituents independently selected from the group consisting of methyl, trifluoromethyl, and hydroxyl; (2-phenylcyclopropyl)methyl; pyridinyl; pyridinyl substituted with 1 or 2 substituents independently selected from the group consisting of halo; and methoxy; pyrimidinyl; pyrimidinyl substituted with 1 or 2 substituents independently selected from halo, methyl and methoxy; 1,3-thiazolyl substituted with methyl; unsubstituted benzofuranyl; and unsubstituted 3,4-dihydro-*2H*-chromenyl;

R^{3c} is phenyl substituted with 1 or 2 halo substituents;

R^{5a} and R^{6a} are independently selected from the group consisting of hydrogen and methyl;

R^{5b} and R^{6b} are independently selected from the group consisting of hydrogen and methyl; or $CR^{5b}R^{6b}$ together forms a carbonyl or a cyclopropylidene radical;

R^{5c} and R^{6c} are hydrogen;

each R^{10a}, R^{10b} and R^{10c} is H;

wherein, in (L-e),

when t is 1 or 2, R^{11} is hydrogen and R^{12} is selected from a substituent selected from the group consisting of phenyl; phenyloxy; and phenylamino substituted with 1 or 2 halo substituents; or

when t is 1, then $CR^{11}R^{12}$ form a radical of formula (i); wherein

R^{14i} is fluoro;

u1 is 0, 1 or 2;

v1 is 2;

z1 is selected from 1 and 2;

k1 is 0; or

when t is 3, then $CR^{11}R^{12}$ form a radical of formula (i); wherein

R^{14i} is fluoro;

u1 is 0 or 1;

v1 is 0;

z1 is selected from 1 and 2;

k1 is 0;

wherein, in (L-f) w is 1 or 2;

wherein in (L-g)
Z is $CR^{16}R^{17}$ and R^{15} is hydrogen when each x is 0 and y is 1; or
Z is $CR^{16}R^{17}$ and R^{15} is phenyl when each x is 0 and y is 2; or
Z is NR^{16} when each x is 1 and y is 1;
wherein R^{16} and R^{17} are each independently selected from the group consisting of hydrogen; unsubstituted phenyl; and phenyl substituted with 1 or 2 halo substituents;

wherein in (L-h), Q is O;
each halo is selected from the group consisting of fluoro, chloro and bromo;
and the pharmaceutically acceptable salts and the solvates thereof.

In an embodiment, the invention relates to compounds of Formula (I) and stereochemically isomeric forms thereof, wherein

n is selected from 0 and 1;
m is 0 or 1;
R is methyl;
R^1 is selected from the group consisting of C_{1-6}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; (C_{1-3}alkyloxy)C_{1-3}alkyl; and (C_{3-7}cycloalkyl)C_{1-3}alkyl;
R^2 is selected from halo; cyano; C_{1-3}alkyl; and C_{1-3}alkyl substituted with one or more independently selected halo substituents;
(L) is selected from (L-a); (L-b); and (L-g) wherein
R^{3a} is selected from the group consisting of unsubstituted phenyl; phenyl substituted with 1 or 2 independently selected halo substituents; pyridinyl; pyridinyl substituted with 1 or 2 halo substituents; pyrimidinyl; and pyrimidinyl substituted with 1 or 2 independently selected halo substituents;
R^{4a} is selected from hydrogen; halo; C_{1-3}alkyl; and trifluoromethyl;
or $CR^{3a}R^{4a}$ forms a radical of formula (d); wherein
W^{1d} is CH;
R^{7d} and R^{8d} are both methyl;
R^{9d} is fluoro;
q1 is 1;

R^{3b} is selected from unsubstituted phenyl; phenyl substituted with 1 or 2 halo substituents; unsubstituted pyridinyl; and pyridinyl substituted with 1 or 2 halo substituents;

R^{5a}, R^{5b}, R^{6a} and R^{6b} are hydrogen; and

R^{10a} and R^{10b} are hydrogen;

each x is 0 and y is 1;

R^{15} is hydrogen;

Z is $CR^{16}R^{17}$; wherein

R^{16} and R^{17} are each independently selected from hydrogen; unsubstituted phenyl; and phenyl substituted with 1 or 2 halo substituents;

halo is fluoro or chloro;

and the pharmaceutically acceptable salts and the solvates thereof.

In an embodiment, the invention relates to compounds of Formula (I) and stereochemically isomeric forms thereof, wherein

n is selected from 0 or 1;

m is 0 or 1;

R is methyl;

R^1 is selected from the group consisting of C_{1-6}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; and (C_{3-7}cycloalkyl)C_{1-3}alkyl;

R^2 is selected from halo, C_{1-3}alkyl, and C_{1-3}alkyl substituted with one or more independently selected halo substituents;

Ⓛ is selected from (L-a) and (L-b); wherein

R^{3a} is selected from the group consisting of unsubstituted phenyl; phenyl substituted with 1 or 2 independently selected halo substituents; pyridinyl; and pyrimidinyl;

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

or $CR^{3a}R^{4a}$ forms a radical of formula (d); wherein

W^{1d} is CH;

R^{7d} and R^{8d} are both methyl;

R^{9d} is fluoro;

q1 is 1;

R^{3b} is phenyl substituted with 1 or 2 halo substituents;

R^{5a}, R^{5b}, R^{6a} and R^{6b} are hydrogen; and

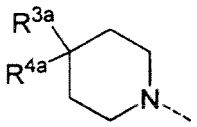
R^{10a} and R^{10b} are hydrogen;

halo is fluoro or chloro;

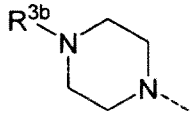
and the pharmaceutically acceptable salts and the solvates thereof.

In an embodiment, the invention relates to compounds of Formula (I) and stereochemically isomeric forms thereof, wherein

n is selected from 0 and 1;
m is 0 or 1;
R is methyl;
R^1 is selected from the group consisting of ethyl; propyl; butyl; CH_2CF_3; $CH_2CH_2CF_3$; and cyclopropylmethyl;
R^2 is selected from chloro, methyl, and CF_3;
(L) is selected from (L-a1) and (L-b1);

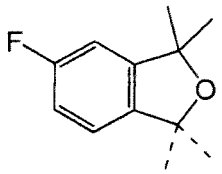


(L-a1)



(L-b1)

wherein
R^{3a} is selected from the group consisting of unsubstituted phenyl; 2-fluorophenyl; 4-fluorophenyl; 2-chlorophenyl; 2,6-difluorophenyl; 2-pyridinyl; 2-pyrimidinyl;
R^{4a} is selected from hydrogen; fluoro and methyl;
or $CR^{3a}R^{4a}$ forms a radical of formula (d4);



(d4)

R^{3b} is 2,4-difluorophenyl;
and the pharmaceutically acceptable salts and the solvates thereof.

In an embodiment, the invention relates to compounds of Formula (I) and stereochemically isomeric forms thereof, wherein

n is selected from 0 and 1;
m is 0;

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

R^2 is selected from halo and C_{1-3}alkyl substituted with one or more independently selected halo substituents;

Ⓛ is selected from (L-a) and (L-b); wherein

R^{3a} is selected from the group consisting of unsubstituted phenyl; and phenyl substituted with 1 or 2 independently selected halo substituents;

R^{4a} is hydrogen, fluoro or methyl;

or $CR^{3a}R^{4a}$ forms a radical of formula (d); wherein

W^{1d} is CH;

R^{7d} and R^{8d} are both methyl;

R^{9d} is fluoro;

q1 is 1;

R^{3b} is phenyl substituted with 1 or 2 halo substituents;

R^{5a}, R^{5b}, R^{6a} and R^{6b} are hydrogen; and

R^{10a} and R^{10b} are hydrogen;

halo is fluoro or chloro;

and the pharmaceutically acceptable salts and the solvates thereof.

In an embodiment, the invention relates to compounds of Formula (I) and stereochemically isomeric forms thereof, wherein

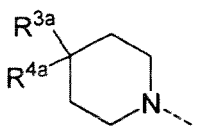
n is selected from 0 and 1;

m is 0;

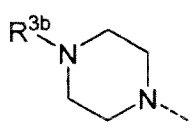
R^1 is selected from the group consisting of C_{1-3}alkyl substituted with one or more fluoro substituents; and (C_{3-7}cycloalkyl)C_{1-3}alkyl;

R^2 is selected from chloro and C_{1-3}alkyl substituted with one or more fluoro substituents;

Ⓛ is selected from (L-a1) and (L-b1);



(L-a1)



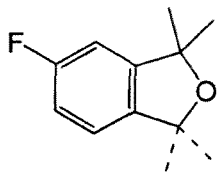
(L-b1)

wherein

R^{3a} is selected from the group consisting of unsubstituted phenyl; and phenyl substituted with fluoro;

R^{4a} is hydrogen, fluoro or methyl;

or $CR^{3a}R^{4a}$ forms a radical of formula (d4);



(d4)

R^{3b} is phenyl substituted with 2 fluoro substituents;

and the pharmaceutically acceptable salts and the solvates thereof.

In an embodiment, the invention relates to compounds of Formula (I) and stereochemically isomeric forms thereof, wherein

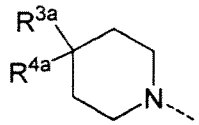
n is selected from 0 or 1;

m is 0;

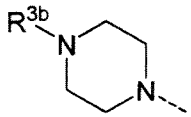
R^1 is selected from 2,2,2-trifluoroethyl and cyclopropylmethyl;

R^2 is selected from chloro and trifluoromethyl;

Ⓛ is selected from (L-a1) and (L-b1);



(L-a1)



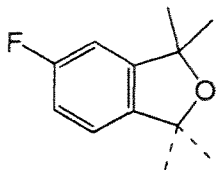
(L-b1)

wherein

R^{3a} is selected from the group consisting of unsubstituted phenyl; and 4-fluorophenyl;

R^{4a} is hydrogen, fluoro or methyl;

or $CR^{3a}R^{4a}$ forms a radical of formula (d4);

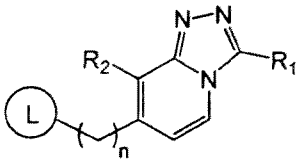


(d4)

R^{3b} is 2,4-difluorophenyl;

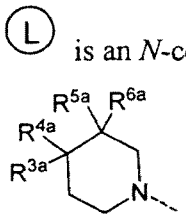
and the pharmaceutically acceptable salts and the solvates thereof.

In an embodiment, the invention relates to compounds of Formula (I')



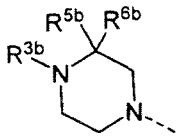
(I')

and the stereochemically isomeric forms thereof, wherein



is an *N*-containing heterocycle selected from the group consisting of

(L-a')



(L-b')

R^1 is selected from hydrogen; C_{1-6}alkyl; (C_{1-3}alkyloxy)C_{1-3}alkyl; [(C_{1-3}alkyloxy)-C_{1-3}alkyloxy]C_{1-3}alkyl; mono-, di- or tri-haloC_{1-3}alkyl; unsubstituted benzyl; benzyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxyC_{1-3}alkyl, hydroxyC_{1-3}alkyl, cyano, hydroxyl, amino, C(=O)R', C(=O)OR', C(=O)NR'R'', mono- or di(C_{1-3}alkyl)amino, morpholinyl, (C_{3-7}cycloalkyl)C_{1-3}alkyloxy, trifluoromethyl and trifluoromethoxy, wherein R' and R'' are independently selected from hydrogen and C_{1-6}alkyl; (benzyloxy)C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with trihaloC_{1-3}alkyl; (C_{3-7}cycloalkyl)C_{1-3}alkyl; 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)methyl; Het^1; Het^1C_{1-3}alkyl; Het^2 and Het^2C_{1-3}alkyl;

R^2 is selected from cyano; halo; mono-, di- or tri-haloC_{1-3}alkyl; mono-, di- and tri-haloC_{1-3}alkyloxy; C_{1-3}alkyl; C_{3-7}cycloalkyl; and (C_{3-7}cycloalkyl)C_{1-3}alkyl;

R^{3a} and R^{3b} are each selected from unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, mono-, di- and tri-haloC_{1-3}alkyl, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, mono-, di- or tri-haloC_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, mono- and di(C_{1-3}alkyl)amino, and morpholinyl; unsubstituted benzyl; benzyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, mono-, di- or tri-haloC_{1-3}alkyl,

cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, mono-, di- and tri-haloC_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, mono- or di(C_{1-3}alkyl)amino, morpholinyl and (C_{3-7}cycloalkyl)C_{1-3}alkyloxy; phenyl with two vicinal substituents which taken together form a bivalent radical of formula

-N=CH-NH- (a),

-CH=CH-NH- (b), or

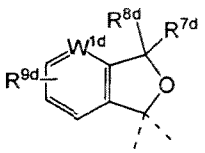
-O-CH_2-CH_2-NH- (c);

morpholinyl; pyridinyl; pyrimidinyl; pyridinyloxy substituted with 1 or 2 C_{1-3}alkyl groups; unsubstituted C_{3-7}cycloalkyl and C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from C_{1-3}alkyl, trihaloC_{1-3}alkyl and hydroxyl;

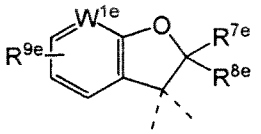
R^{4a} is selected from hydrogen; halogen; trifluoromethyl; trifluoromethoxy; hydroxyl; C_{1-3}alkyl; C_{1-3}alkyloxy; hydroxyC_{1-3}alkyl; hydroxylC_{1-3}alkyloxy; fluoroC_{1-3}alkyl; fluoroC_{1-3}alkyloxy; cyano; unsubstituted phenyl; and phenyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyloxy, hydroxyC_{1-3}alkyl, trifluoromethyl and trifluoromethoxy;

or

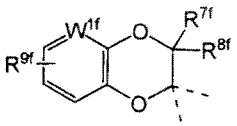
R^{3a}-C-R^{4a} together represent a radical of formula (d') or (e') or (f') or (g')



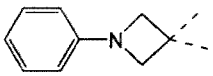
(d')



(e')



(f')



(g')

wherein

W^{1d}, W^{1e} and W^{1f} are each selected from CH or N;

R^{7d}, R^{7e}, R^{7f}, R^{8d}, R^{8e} and R^{8f} are each independently selected from hydrogen, methyl or fluoro;

R^{9d}, R^{9e} and R^{9f} are each selected from hydrogen and fluoro;

R^{5a}, R^{5b}, R^{6a} and R^{6b} are each independently selected from the group of hydrogen and C_{1-3}alkyl or $CR^{5a}R^{6a}$ and $CR^{5b}R^{6b}$ together form a C_{3-7}cycloalkyl radical;

n is 0 or 1;

wherein

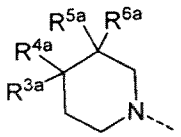
each Het^1 is a saturated heterocyclic radical selected from pyrrolidinyl; piperidinyl; piperazinyl; and morpholinyl; each of which may be optionally substituted with 1 or 2 substituents independently selected from the group consisting of C_{1-6}alkyl, mono-, di- and tri-haloC_{1-3}alkyl, unsubstituted phenyl, and phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, trifluoromethyl, and trifluoromethoxy; and

each Het^2 is an aromatic heterocyclic radical selected from unsubstituted pyridinyl and pyrimidinyl;

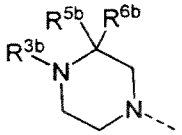
and the pharmaceutically acceptable salts and the solvates thereof.

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

Ⓛ is an *N*-containing heterocycle selected from the group consisting of



(L-a')



(L-b')

and the stereochemically isomeric forms thereof, wherein

R^1 is selected from hydrogen; C_{1-6}alkyl; (C_{1-3}alkyloxy)C_{1-3}alkyl; [(C_{1-3}alkyloxy)-C_{1-3}alkyloxy]C_{1-3}alkyl; mono-, di- or tri-haloC_{1-3}alkyl; unsubstituted benzyl; benzyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxyC_{1-3}alkyl, hydroxyC_{1-3}alkyl, cyano, hydroxyl, amino, C(=O)R', C(=O)OR', C(=O)NR'R'', mono- or di(C_{1-3}alkyl)amino, morpholinyl, (C_{3-7}cycloalkyl)C_{1-3}alkyloxy, trifluoromethyl and trifluoromethoxy, wherein R' and R'' are independently selected from hydrogen and C_{1-6}alkyl; (benzyloxy)C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with trihaloC_{1-3}alkyl; (C_{3-7}cycloalkyl)C_{1-3}alkyl; 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)methyl; Het^1; Het^1C_{1-3}alkyl; Het^2 and Het^2C_{1-3}alkyl;

R^2 is selected from cyano; halo; mono-, di- or tri-haloC_{1-3}alkyl; mono-, di- and tri-haloC_{1-3}alkyloxy; C_{1-3}alkyl; C_{3-7}cycloalkyl; and (C_{3-7}cycloalkyl)C_{1-3}alkyl;

R^{3a} is selected from unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, mono-, di- and tri-haloC_{1-3}alkyl, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, mono-, di- or tri-haloC_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, mono- and di(C_{1-3}alkyl)amino, and morpholinyl; unsubstituted benzyl; benzyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, mono-, di- or tri-haloC_{1-3}alkyl, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, mono-, di- and tri-haloC_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, mono- or di(C_{1-3}alkyl)amino, morpholinyl and (C_{3-7}cycloalkyl)C_{1-3}alkyloxy; phenyl with two vicinal substituents which taken together form a bivalent radical of formula

-N=CH-NH- (a),

-CH=CH-NH- (b), or

-O-CH_2-CH_2-NH- (c);

morpholinyl; pyridinyl; pyrimidinyl; pyridinyloxy substituted with 1 or 2 C_{1-3}alkyl groups; unsubstituted C_{3-7}cycloalkyl and C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from C_{1-3}alkyl, trihaloC_{1-3}alkyl and hydroxyl;

R^{3b} is selected from unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, mono-, di- and tri-haloC_{1-3}alkyl, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, mono-, di- or tri-haloC_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, mono- and di(C_{1-3}alkyl)amino, and morpholinyl; unsubstituted benzyl; benzyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, mono-, di- or tri-haloC_{1-3}alkyl, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, mono-, di- and tri-haloC_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, mono- or di(C_{1-3}alkyl)amino, morpholinyl and (C_{3-7}cycloalkyl)C_{1-3}alkyloxy; phenyl with two vicinal substituents which taken together form a bivalent radical of formula

-N=CH-NH- (a),

-CH=CH-NH- (b), or

-O-CH_2-CH_2-NH- (c);

pyridinyl; pyrimidinyl; unsubstituted C_{3-7}cycloalkyl and C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from C_{1-3}alkyl, trihaloC_{1-3}alkyl and hydroxyl;

R^{4a} is selected from hydrogen; halogen; trifluoromethyl; trifluoromethoxy; hydroxyl; C_{1-3}alkyl; C_{1-3}alkyloxy; hydroxyC_{1-3}alkyl; hydroxylC_{1-3}alkyloxy; fluoroC_{1-3}alkyl;

fluoroC_{1-3}alkyloxy; cyano; unsubstituted phenyl; and phenyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyloxy, hydroxyC_{1-3}alkyl, trifluoromethyl and trifluoromethoxy;

or

R^{3a}-C-R^{4a} together represent a radical of formula (d') or (e') or (f') or (g')

wherein

W^{1d}, W^{1e} and W^{1f} are each selected from CH or N;

R^{7d}, R^{7e}, R^{7f}, R^{8d}, R^{8e} and R^{8f} are each independently selected from hydrogen, methyl or fluoro;

R^{9d}, R^{9e} and R^{9f} are each selected from hydrogen and fluoro;

R^{5a}, R^{5b}, R^{6a} and R^{6b} are each independently selected from the group of hydrogen and C_{1-3}alkyl or $CR^{5a}R^{6a}$ and $CR^{5b}R^{6b}$ together form a C_{3-7}cycloalkyl radical;

n is 0 or 1;

wherein

each Het^1 is a saturated heterocyclic radical selected from pyrrolidinyl; piperidinyl; piperazinyl; and morpholinyl; each of which may be optionally substituted with 1 or 2 substituents independently selected from the group consisting of C_{1-6}alkyl, mono-, di- and tri-haloC_{1-3}alkyl, unsubstituted phenyl, and phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, trifluoromethyl, and trifluoromethoxy; and

each Het^2 is an aromatic heterocyclic radical selected from unsubstituted pyridinyl and pyrimidinyl;

and the pharmaceutically acceptable salts and the solvates thereof.

In one embodiment, the invention relates to a compound according to Formula (I') or a stereochemically isomeric form thereof, wherein

R^1 is selected from C_{1-6}alkyl; (C_{1-3}alkyloxy)C_{1-3}alkyl; [(C_{1-3}alkyloxy)C_{1-3}alkyloxy]-C_{1-3}alkyl; mono-, di- and tri-haloC_{1-3}alkyl; (benzyloxy)C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with trihaloC_{1-3}alkyl; (C_{3-7}cycloalkyl)-

C_{1-3}alkyl; 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)methyl; Het^1; and Het^1C_{1-3}alkyl;

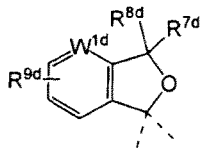
R^2 is cyano; halo or tri-haloC_{1-3}alkyl;

R^{3a} and R^{3b} are each selected from unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, hydroxyl-C_{1-3}alkyl, mono-, di- and tri-haloC_{1-3}alkyl, hydroxyl and C_{1-3}alkyloxy; unsubstituted benzyl; benzyl substituted with 1, 2 or 3 substituents independently selected from halo, mono-, di- or tri-haloC_{1-3}alkyl, and (C_{3-7}cycloalkyl)C_{1-3}alkyloxy; morpholinyl; pyridinyl; pyrimidinyl; pyridinyloxy substituted with 1 or 2 C_{1-3}alkyl groups; and C_{3-7}cycloalkyl substituted with 1 or 2 substituents selected from C_{1-3}alkyl, trihaloC_{1-3}alkyl and hydroxyl;

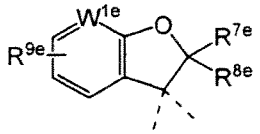
R^{4a} is selected from hydrogen; halogen; trifluoromethyl; unsubstituted phenyl; and phenyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyloxy, hydroxyC_{1-3}alkyl, trifluoromethyl and trifluoromethoxy;

or

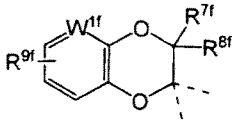
R^{3a}-C-R^{4a} together represent a radical of formula (d) or (e) or (f) or (g)



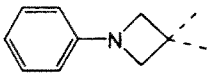
(d')



(e')



(f')



(g')

wherein

W^{1d}, W^{1e} and W^{1f} are each selected from CH and N;

R^{7d}, R^{7e}, R^{7f}, R^{8d}, R^{8e}, R^{8f}, R^{9d}, R^{9e} and R^{9f} are as previously defined;

R^{5a}, R^{5b}, R^{6a} and R^{6b} are each independently selected from the group of hydrogen and C_{1-3}alkyl;

n is 0 or 1;

Het^1 is as previously defined;

or a pharmaceutically acceptable salt or a solvate thereof.

In the previous embodiment, R^{7d}, R^{7e}, R^{7f}, R^{8d}, R^{8e}, R^{8f}, R^{9d}, R^{9e} and R^{9f} are preferably all hydrogen.

In the previous embodiment, R^{3a}-C-R^{4a} together preferably represent a radical of formula (d) or (e), wherein W^{1d}, W^{1e}, R^{7d}, R^{7e}, R^{8d}, R^{8e}, R^{9d} and $R^{9e}$are as previously defined.

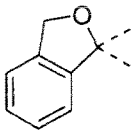
In an embodiment, the invention relates to a compound according to Formula (I) or a stereochemically isomeric form thereof, wherein

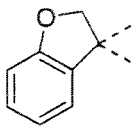
R^1 is selected from methyl; ethyl; propyl; *n*-butyl; 2-methylpropyl; *tert*-butyl; trifluoromethyl; 2,2,2-trifluoroethyl; 1,1-difluoroethyl; 3,3,3-trifluoropropyl; methoxymethyl; ethoxymethyl; 1-methyl-ethoxymethyl; methoxyethoxymethyl; unsubstituted cyclopropyl; cyclopropyl substituted with trifluoromethyl; unsubstituted cyclobutyl; cyclopropylmethyl; cyclobutylmethyl; phenylmethoxymethyl; pyrrolidinylmethyl; piperidinylmethyl; 4-phenyl-piperidinylmethyl; 4-trifluoromethyl-piperidinylmethyl; morpholinylmethyl; and 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)methyl;

R^2 is cyano; chloro or trifluoromethyl;

R^{3a} and R^{3b} are each selected from unsubstituted phenyl; phenyl substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, bromo, 2-hydroxy-2-propyl, methoxy, trifluoromethyl and hydroxyl; unsubstituted benzyl; benzyl substituted with 1 or 2 substituents independently selected from chloro, trifluoromethyl and cyclopropylmethyloxy; morpholinyl; pyridinyl; pyrimidinyl; pyridinyloxy substituted with 1 or 2 methyl groups; and cyclohexyl substituted with 1 or 2 substituents selected from methyl, trifluoromethyl and hydroxyl;

R^{4a} is selected from hydrogen, fluoro, trifluoromethyl and phenyl;
or
R^{3a}-C-R^{4a} together represent a radical of formula (d-1) or (e-1)


(d-1)


(e-1)

R^{5a}, R^{5b}, R^{6a} and R^{6b} are each independently selected from the group of hydrogen and methyl;

n is 0 or 1;

or a pharmaceutically acceptable salt or a solvate thereof.

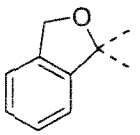
In the previous embodiment, R^{5a} and R^{6b}, and R^{5b} and R^{6b} are preferably both hydrogen or both methyl.

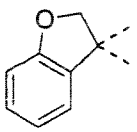
In an embodiment, the invention relates to a compound according to Formula (I) or a stereochemically isomeric form thereof, wherein

R^1 is selected from methyl; ethyl; propyl; *n*-butyl; 2-methylpropyl; *tert*-butyl; 2,2,2-trifluoroethyl; 1,1-difluoroethyl; 3,3,3-trifluoropropyl; methoxymethyl; ethoxymethyl; 1-methyl-ethoxymethyl; methoxyethoxymethyl; unsubstituted cyclopropyl; cyclopropyl substituted with trifluoromethyl; unsubstituted cyclobutyl; cyclopropylmethyl; cyclobutylmethyl; phenylmethoxymethyl; 1-pyrrolidinylmethyl; 1-piperidinylmethyl; 4-phenyl-piperidinylmethyl; 4-trifluoromethyl-piperidinylmethyl; and 4-morpholinylmethyl;

R^{3a} and R^{3b} are each selected from unsubstituted phenyl; (2-hydroxy-2-propyl)phenyl; 3-fluoro-6-methoxy-phenyl; 3-(trifluoromethyl)phenyl; 2,4-difluorophenyl; 4-(trifluoromethyl)cyclohexyl; 2-fluoro-6-methoxyphenyl; 2-pyridinyl; 3-methyl-2-pyridinyloxy; 4-hydroxy-4-methylcyclohexyl; 3-fluoro-2-methoxy-phenyl; 3-chloro-4-(cyclopropylmethoxy)phenylmethyl; 3-(trifluoromethyl)phenylmethyl; 4-morpholinyl; 2-pyrimidinyl; 3-fluoro-6-hydroxyphenyl and 3-bromo-5-fluoro-2-methoxyphenyl;

R^{4a} is selected from hydrogen, fluoro, trifluoromethyl and phenyl;
or
R^{3a}-C-R^{4a} together represent a radical of formula (d-1) or (e-1)


(d-1)


(e-1)

R^{5a} and R^{6a} and R^{5b} and R^{6b} are both hydrogen or both methyl;

and n and R^2 are as previously defined;
or a pharmaceutically acceptable salt or a solvate thereof.

In a further embodiment, the invention relates to compounds according to any of the other embodiments, wherein
R^1 is selected from C_{1-6}alkyl; (C_{1-3}alkyloxy)C_{1-3}alkyl; [(C_{1-3}alkyloxy)-C_{1-3}alkyloxy]C_{1-3}alkyl; mono-, di- or tri-haloC_{1-3}alkyl; unsubstituted benzyl; benzyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxyC_{1-3}alkyl, hydroxyC_{1-3}alkyl, cyano, hydroxyl, amino, C(=O)R', C(=O)OR', C(=O)NR'R'', mono- or di(C_{1-3}alkyl)amino, morpholinyl, (C_{3-7}cycloalkyl)C_{1-3}alkyloxy, trifluoromethyl and trifluoromethoxy, wherein R' and R'' are independently selected from hydrogen and C_{1-6}alkyl; (benzyloxy)C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with trihaloC_{1-3}alkyl; (C_{3-7}cycloalkyl)C_{1-3}alkyl; Het^2 and Het^2C_{1-3}alkyl;
and
R^2 is selected from halo; mono-, di- or tri-haloC_{1-3}alkyl; mono-, di- and tri-haloC_{1-3}alkyloxy; C_{1-3}alkyl; C_{3-7}cycloalkyl; and (C_{3-7}cycloalkyl)C_{1-3}alkyl;
and the rest of the variables are as previously defined;
and the pharmaceutically acceptable salts and the solvates thereof.

In an embodiment, the invention relates to compounds of Formula (I) and stereochemically isomeric forms thereof, wherein

n is selected from 0 or 1;
R^1 is selected from the group consisting of C_{1-6}alkyl; mono-, di- or tri-haloC_{1-3}alkyl; and (C_{3-7}cycloalkyl)C_{1-3}alkyl;
R^2 is selected from halo, C_{1-3}alkyl, and mono-, di- or tri-haloC_{1-3}alkyl;
Ⓛ is selected from (L-a') and (L-b'); wherein
R^{3a} is selected from the group consisting of unsubstituted phenyl; phenyl substituted with 1 or 2 halo substituents; pyridinyl; and pyrimidinyl;
R^{4a} is selected from hydrogen; halo and C_{1-3}alkyl;
or $CR^{3a}R^{4a}$ forms a radical of formula (d'); wherein
W^{1d} is CH;
R^{7d} and R^{8d} are both methyl;
R^{9d} is fluoro;
R^{3b} is phenyl substituted with 1 or 2 halo substituents;

R^{5a}, R^{5b}, R^{6a} and R^{6b} are hydrogen; and
halo is fluoro or chloro;
and the pharmaceutically acceptable salts and the solvates thereof.

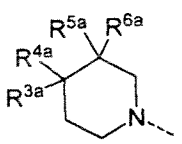
In an embodiment, the invention relates to compounds of Formula (I) and stereochemically isomeric forms thereof, wherein

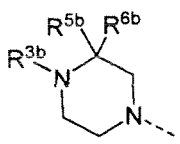
n is selected from 0 and 1;
R^1 is selected from the group consisting of mono-, di- or tri-haloC_{1-3}alkyl; and (C_{3-7}cycloalkyl)C_{1-3}alkyl;
R^2 is selected from halo and mono-, di- or tri-haloC_{1-3}alkyl;
Ⓛ is selected from (L-a') and (L-b'); wherein
R^{3a} is selected from the group consisting of unsubstituted phenyl; and phenyl substituted with 1 or 2 halo substituents;
R^{4a} is hydrogen, fluoro or methyl;
or $CR^{3a}R^{4a}$ forms a radical of formula (d'); wherein
W^{1d} is CH;
R^{7d} and R^{8d} are both methyl;
R^{9d} is fluoro;
R^{3b} is phenyl substituted with 1 or 2 halo substituents;
R^{5a}, R^{5b}, R^{6a} and R^{6b} are hydrogen; and
halo is fluoro or chloro;
and the pharmaceutically acceptable salts and the solvates thereof.

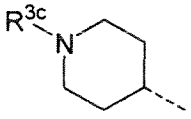
In a further embodiment, the invention relates to compounds according to any of the other embodiments wherein R^1 is 2,2,2-trifluoroethyl, propyl or cyclopropylmethyl.

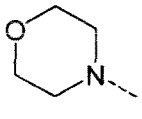
In a further embodiment, the invention relates to compounds according to any one of the other embodiments wherein R^2 is chloro, methyl or trifluoromethyl.

In a further embodiment, the L substituent may be selected from one or more of the following:

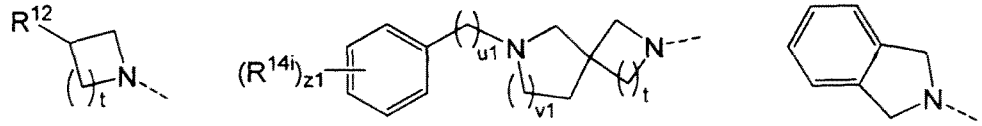




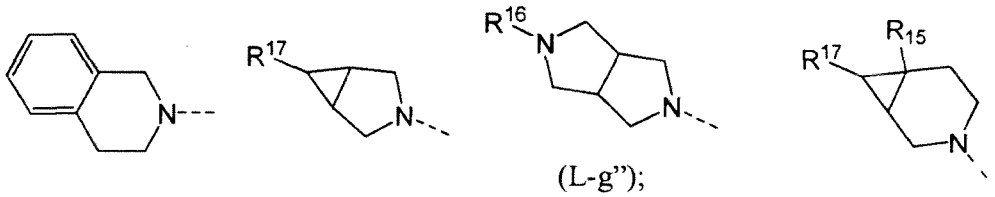




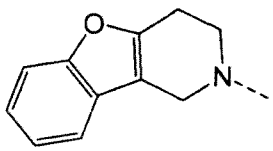
(L-a'); (L-b'); (L-c'); (L-d');



(L-e'); (L-e"); (L-f');



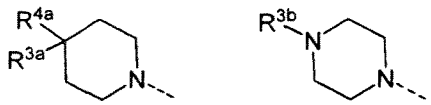
(L-f'); (L-g'); (L-g"); (L-g"'); or



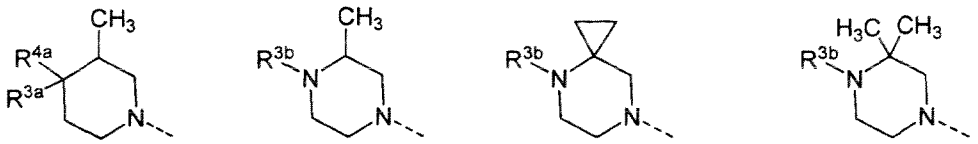
(L-h')

wherein all variables are as previously defined.

In a further particular embodiment, the L substituent may be selected from one or more of the following:



(L-a1); (L-b1);



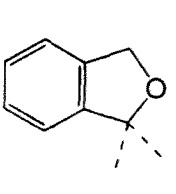
(L-a2); (L-b2); (L-b3); or (L-b4)

wherein all variables are as previously defined.

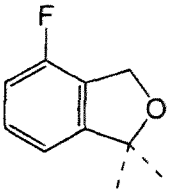
In a further particular embodiment, the L substituent may be selected from (L-a1) and (L-b1).

In a particular embodiment, R^{3a}-C-R^{4a} may be selected from one or more of the

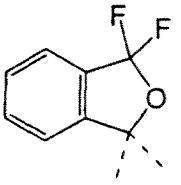
following:



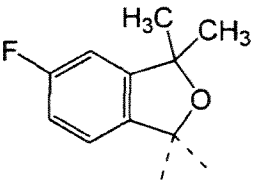
(d-1);



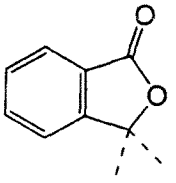
(d-2);



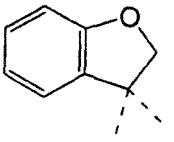
(d-3);



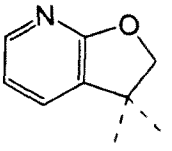
(d-4);



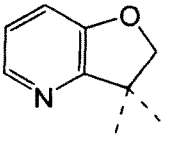
(d-5);



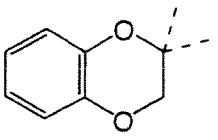
(e-1);



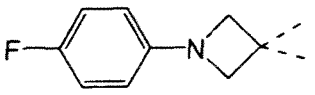
(e-2);



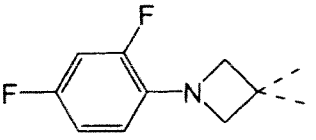
(e-3);



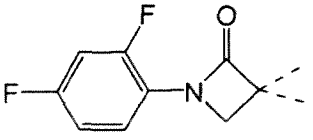
(f-1);



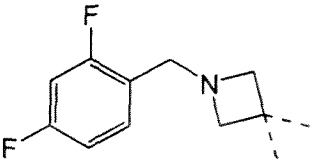
(g-1);



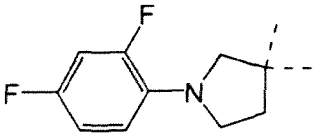
(g-2);



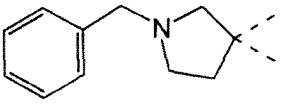
(g-3)



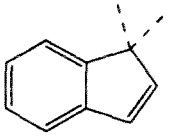
(g-4)



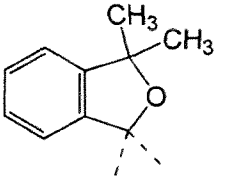
(g-5);



(g-6);



(h); or



(d-6).

In a particular embodiment, R^{3a}-C-R^{4a} is selected from any one of (d-1); (d-2); (d-3); (d-4); (d-5); (d-6); (e-1); (e-2); (e-3); (g-1); (g-2); (g-3); (g-4); (g-5) and (h).

Particular preferred compounds of formula (I) may be selected from the group of:

8-chloro-3-(cyclopropylmethyl)-7-[(4-phenyl-1-piperidinyl)methyl]-1,2,4-triazolo-[4,3-a]pyridine,

3-ethyl-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

3-methyl-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

7-(4-phenyl-1-piperidinyl)-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

3-cyclobutyl-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

3-(cyclopropylmethyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

3-ethyl-7-[4-(3-fluoro-2-methoxyphenyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

8-chloro-7-(4-phenyl-1-piperidinyl)-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine,

7-[4-(3-fluoro-2-methoxyphenyl)-1-piperidinyl]-3-propyl-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

3-(methoxymethyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

8-chloro-3-ethyl-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine,

7-[4-(3-fluoro-2-methoxyphenyl)-1-piperidinyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

7-(4-phenyl-1-piperidinyl)-3-propyl-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

3-cyclopropyl-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

8-chloro-7-[(4-phenyl-1-piperidinyl)methyl]-3-(2,2,2-trifluoroethyl)- 1,2,4-triazolo-[4,3-a]pyridine,

7-(4-phenyl-1-piperidinyl)-3-[1-(trifluoromethyl)cyclopropyl]-1,2,4-triazolo[4,3-a]-pyridine-8-carbonitrile,

3-[(phenylmethoxy)methyl]-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

3-(1,1-difluoroethyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

3-(4-morpholinylmethyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

3-(cyclobutylmethyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-

carbonitrile,

3-(1,1-dimethylethyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

7-(4-phenyl-1-piperidinyl)-3-(1-pyrrolidinylmethyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

7-(4-phenyl-1-piperidinyl)-3-[[4-(trifluoromethyl)-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

7-(4-phenyl-1-piperidinyl)-3-[(4-phenyl-1-piperidinyl)methyl]-1,2,4-triazolo[4,3-a]-pyridine-8-carbonitrile,

7-(4-phenyl-1-piperidinyl)-3-(2,2,2-trifluoroethyl)-8-(trifluoromethyl)-1,2,4-triazolo-[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[4-[3-(trifluoromethyl)phenyl]-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-(4-fluoro-4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

8-chloro-3-(cyclopropylmethyl)-7-[4-(2,4-difluorophenyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-(4-fluoro-4-phenyl-1-piperidinyl)-1,2,4-triazolo-[4,3-a]pyridine,

8-chloro-7-(4-fluoro-4-phenyl-1-piperidinyl)-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo-[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo-[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[4-[cis-4-(trifluoromethyl)cyclohexyl]-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

3-(cyclopropylmethyl)-7-[4-[trans-4-(trifluoromethyl)cyclohexyl]-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

8-chloro-3-(cyclopropylmethyl)-7-[4-(5-fluoro-2-methoxyphenyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[4-(2-pyridinyl)-1-piperidinyl]-1,2,4-triazolo-[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[4-[(3-methyl-2-pyridinyl)oxy]-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[4-(trans-4-hydroxy-4-methylcyclohexyl)-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

3-(cyclopropylmethyl)-7-[4-(cis-4-hydroxy-4-methylcyclohexyl)-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,

2-[1-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-4-piperidinyl]-alpha,alpha-dimethyl-benzenemethanol,
8-chloro-3-(ethoxymethyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine,
7-[4-(2-fluoro-6-methoxyphenyl)-1-piperidinyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,
7-[4-[[3-chloro-4-(cyclopropylmethoxy)phenyl]methyl]-1-piperazinyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,
8-chloro-3-[(2-methoxyethoxy)methyl]-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo-[4,3-a]pyridine,
7-(4-fluoro-4-phenyl-1-piperidinyl)-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,
8-chloro-3-(cyclopropylmethyl)-7-[4-(2-fluoro-6-methoxyphenyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-7-[4-(2-pyridinyl)-1-piperidinyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]-pyridine,
1'-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[isobenzofuran-1(3H),4'-piperidine],
3-(cyclopropylmethyl)-7-[4-(2-fluoro-6-methoxyphenyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,
3-(2,2,2-trifluoroethyl)-7-[4-[cis-4-(trifluoromethyl)cyclohexyl]-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,
8-chloro-7-[4-[(3-methyl-2-pyridinyl)oxy]-1-piperidinyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(2,2,2-trifluoroethyl)-7-[4-[[3-(trifluoromethyl)phenyl]methyl]-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,
8-chloro-7-[4-(5-fluoro-2-methoxyphenyl)-1-piperidinyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[4-(4-morpholinyl)-4-phenyl-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-7-[4-(2-pyrimidinyl)-1-piperazinyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo-[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[4-(2-pyrimidinyl)-1-piperazinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-7-[4-(2-fluoro-6-methoxyphenyl)-1-piperidinyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-ethyl-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

7-(4-phenyl-1-piperidinyl)-3-propyl-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-butyl-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[4-[(3-methyl-2-pyridinyl)oxy]-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
2-[1-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-4-piperidinyl]-4-fluoro-phenol,
7-[4-(3-bromo-5-fluoro-2-methoxyphenyl)-1-piperidinyl]-8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-7-(4-phenyl-1-piperidinyl)-3-(3,3,3-trifluoropropyl)-1,2,4-triazolo[4,3-a]-pyridine,
1'-[8-chloro-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[isobenzofuran-1(3H),4'-piperidine],
8-chloro-3-(2-methylpropyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine
3-(cyclopropylmethyl)-7-(4-fluoro-4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-(3,3-dimethyl-4-phenyl-1-piperazinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[4-phenyl-4-(trifluoromethyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,
7-(4-fluoro-4-phenyl-1-piperidinyl)-3-[(1-methylethoxy)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
1'-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[benzofuran-3(2H),4'-piperidine],
3-(cyclopropylmethyl)-7-(3,3-dimethyl-4-phenyl-1-piperazinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyridine,
3-(2,2,2-trifluoroethyl)-7-[4-[trans-4-(trifluoromethyl)cyclohexyl]-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,
3-(2-methylpropyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,
rac-(2aα,3α,3aα)-3-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-6-phenyl-3-azabicyclo[3.1.0]hexane,
3-(cyclopropylmethyl)-7-(4-phenyl-1-piperazinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
1'-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[isobenzofuran-1(3H),4'-piperidine],
3-(cyclopropylmethyl)-7-[4-(2-pyridinyl)-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-

triazolo[4,3-a]pyridine,

1'-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[1,4-benzodioxin-2(3H),4'-piperidine],

3-[(cyclopropylmethoxy)methyl]-7-(4-fluoro-4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

rac-(2aα,3α,3aα)-3-[8-chloro-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-6-phenyl-3-azabicyclo[3.1.0]hexane, ,

8-chloro-3-(ethoxymethyl)-7-[4-(2-methoxyphenyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(ethoxymethyl)-7-[4-(5-fluoro-2-methoxyphenyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-7-[4-(2,3-difluoro-6-methoxyphenyl)-1-piperidinyl]-3-(ethoxymethyl)-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-7-[4-(2,4-difluoro-6-methoxyphenyl)-1-piperidinyl]-3-(ethoxymethyl)-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-7-[4-(3,6-difluoro-2-methoxyphenyl)-1-piperidinyl]-3-(ethoxymethyl)-1,2,4-triazolo[4,3-a]pyridine,

1'-[3-propyl-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[benzofuran-3(2H),4'-piperidine],

1'-(8-chloro-3-propyl-1,2,4-triazolo[4,3-a]pyridin-7-yl)-spiro[benzofuran-3(2H),4'-piperidine],

1'-[3-ethyl-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[benzofuran-3(2H),4'-piperidine],

3-(cyclopropylmethyl)-7-[4-(5-methoxy-2-pyrimidinyl)-1-piperazinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[4-(3-methoxy-2-pyridinyl)-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[4-(3-methoxy-2-pyridinyl)-1-piperazinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

1'-(8-chloro-3-propyl-1,2,4-triazolo[4,3-a]pyridin-7-yl)-spiro[isobenzofuran-1(3H),4'-piperidine],

1'-[8-chloro-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[1,4-benzodioxin-2(3H),4'-piperidine],

8-chloro-7-[4-(2,4-difluorophenyl)-1-piperazinyl]-3-propyl-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[4-[[trans-2-phenylcyclopropyl]methyl]-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-7-[4-(2,4-difluorophenyl)-1-piperazinyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine,
1'-[8-chloro-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[benzofuran-3(2H),4'-piperidine],
8-chloro-3-(cyclopropylmethyl)-7-(4-phenyl-1-piperazinyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-7-(3,3-dimethyl-4-phenyl-1-piperazinyl)-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-7-(4-phenyl-1-piperazinyl)-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine,
1'-(8-chloro-3-ethyl-1,2,4-triazolo[4,3-a]pyridin-7-yl)-spiro[isobenzofuran-1(3H),4'-piperidine],
8-chloro-7-(3,3-dimethyl-4-phenyl-1-piperazinyl)-3-(ethoxymethyl)-1,2,4-triazolo[4,3-a]pyridine,
1'-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,3-dimethyl-spiro[isobenzofuran-1(3H),4'-piperidine],
8-chloro-3-(cyclopropylmethyl)-7-(3,3-dimethyl-4-phenyl-1-piperazinyl)-1,2,4-triazolo[4,3-a]pyridine,
1'-(8-chloro-3-propyl-1,2,4-triazolo[4,3-a]pyridin-7-yl)-4-fluoro-spiro[isobenzofuran-1(3H),4'-piperidine],
1'-(8-chloro-3-propyl-1,2,4-triazolo[4,3-a]pyridin-7-yl)-3,3-dimethyl-spiro[isobenzofuran-1(3H),4'-piperidine],
1'-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-4-fluoro-spiro[isobenzofuran-1(3H),4'-piperidine].1HCl.1.5 H_2O,
1'-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-4-fluoro-spiro[isobenzofuran-1(3H),4'-piperidine],
1'-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-4-fluoro-spiro[isobenzofuran-1(3H),4'-piperidine],
4-fluoro-1'-[3-propyl-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[isobenzofuran-1(3H),4'-piperidine],
3-(cyclopropylmethyl)-7-[4-(5-methoxy-2-pyrimidinyl)-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
1'-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,3-dimethyl-spiro[isobenzofuran-1(3H),4'-piperidine],
3,3-dimethyl-1'-[3-propyl-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[isobenzofuran-1(3H),4'-piperidine],
8-chloro-7-[4-(2-pyridinyloxy)-1-piperidinyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(ethoxymethyl)-7-[4-(4-fluorophenyl)-4-(trifluoromethyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[4-(4-fluorophenyl)-4-(trifluoromethyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[4-(3-fluorophenyl)-4-(trifluoromethyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,
2-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-1,2,3,4-tetrahydro-isoquinoline,
1'-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[furo[2,3-b]pyridine-3(2H),4'-piperidine],
3-(cyclopropylmethyl)-7-[4-phenyl-4-(trifluoromethyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,
7-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-4-phenyl-4,7-diazaspiro[2.5]octane,
3-[(1-methylethoxy)methyl]-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(2-cyclopropylethyl)-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[4-(2-pyridinyloxy)-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
1'-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[furo[2,3-b]pyridine-3(2H),4'-piperidine],
1'-[8-chloro-3-(ethoxymethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[furo[2,3-b]pyridine-3(2H),4'-piperidine],
8-chloro-7-(4-fluoro-4-phenyl-1-piperidinyl)-3-[(1-methylethoxy)methyl]-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[(3R)-3-methyl-4-phenyl-1-piperazinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(2-cyclopropylethyl)-7-[4-(2-pyridinyloxy)-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-(1,3-dihydro-*2H*-isoindol-2-yl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[(3S)-3-methyl-4-phenyl-1-piperazinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(ethoxymethyl)-7-[4-(2-pyridinyloxy)-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-(4-methyl-4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-

a]pyridine,

3-(ethoxymethyl)-7-[4-[(3-methyl-2-pyridinyl)oxy]-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-[(1-methylethoxy)methyl]-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine,

3-(ethoxymethyl)-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-(3-phenyl-1-azetidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

1'-[8-chloro-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[furo[2,3-b]pyridine-3(2H),4'-piperidine],

1'-[8-chloro-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,3-dimethyl-spiro[isobenzofuran-1(3H),4'-piperidine],

8-chloro-3-(2-cyclopropylethyl)-7-(4-fluoro-4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine,

3-(ethoxymethyl)-7-(4-fluoro-4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3,3-difluoro-1'-[3-propyl-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[isobenzofuran-1(3H),4'-piperidine],

1'-(8-chloro-3-propyl-1,2,4-triazolo[4,3-a]pyridin-7-yl)-3,3-difluoro-spiro[isobenzofuran-1(3H),4'-piperidine],

8-chloro-3-[(1-methylethoxy)methyl]-7-[4-phenyl-4-(trifluoromethyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-8-methyl-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(2-cyclopropylethyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine,

1'-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,3-difluoro-spiro[isobenzofuran-1(3H),4'-piperidine],

3-(cyclopropylmethyl)-7-[4-methyl-4-(2-pyridinyl)-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

1'-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[isobenzofuran-1(3H),4'-piperidin]-3-one,

3-[(1-methylethoxy)methyl]-7-[4-(2-pyridinyloxy)-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-(4-methyl-4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[(3S)-3-phenoxy-1-pyrrolidinyl]-8-(trifluoromethyl)-1,2,4-

triazolo[4,3-a]pyridine,
7-(4-phenyl-1-piperidinyl)-3-(2-pyridinylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
1'-[3-(cyclopropylmethyl)-8-methyl-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,3-dimethyl-spiro[isobenzofuran-1(3H),4'-piperidine],
3-[(1-methylethoxy)methyl]-7-(4-phenyl-1-piperazinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[4-(4-methyl-2-thiazolyl)-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine,
7-[4-(3-benzofuranyl)-1-piperazinyl]-8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[4-(3-pyridinylmethoxy)-4-(trifluoromethyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,
8-cyclopropyl-3-(cyclopropylmethyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine,
1'-[8-cyclopropyl-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,3-dimethyl-spiro[isobenzofuran-1(3H),4'-piperidine],
1'-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[furo[3,2-b]pyridine-3(2H),4'-piperidine],
3-[(1-methylethoxy)methyl]-7-[4-[(3-methyl-2-pyridinyl)oxy]-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[4-(2,2,2-trifluoro-1-phenylethyl)-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[4-(3,4-dihydro-*2H*-1-benzopyran-3-yl)-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[4-[(2-methyl-4-pyridinyl)oxy]-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
(rac)-cis-3-(cyclopropylmethyl)-7-[5-(2,4-difluorophenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[4-(3-pyridinyloxy)-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-(3-methyl-4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-(3-methyl-4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[4-(3-pyridinyloxy)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-8-ethyl-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[4-[(2-methyl-4-pyridinyl)oxy]-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-(3-phenyl-1-pyrrolidinyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-(3-phenyl-1-pyrrolidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
1-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-N-phenyl-4-piperidinamine,
1-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-N-(2-fluorophenyl)-4-piperidinamine,
3-(2,2-dimethylpropyl)-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
1-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-N-phenyl-4-piperidinamine,
8-chloro-3-(cyclopropylmethyl)-7-[4-[(3,5-difluorophenyl)methyl]-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[(3S)-4-(3,5-difluorophenyl)-3-methyl-1-piperazinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[(3S)-4-(3,5-difluorophenyl)-3-methyl-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[(3R)-4-(3,5-difluorophenyl)-3-methyl-1-piperazinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
1-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-N-(2-fluorophenyl)-4-piperidinamine,
8-chloro-3-(cyclopropylmethyl)-7-[(3R)-4-(3,5-difluorophenyl)-3-methyl-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclobutylmethyl)-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
(rac)-cis-8-chloro-3-(cyclopropylmethyl)-7-[5-(2,4-difluorophenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-8-methyl-7-[4-phenyl-4-(trifluoromethyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,
2-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-6-(2,4-difluorophenyl)-2,6-diazaspiro[3.5]nonane,
1-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-N-(2-fluorophenyl)-3-azetidinamine,

1-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-N-(2-fluorophenyl)-3-azetidinamine,
8-chloro-7-[(3S)-4-(3,5-difluorophenyl)-3-methyl-1-piperazinyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-7-[(3R)-4-(3,5-difluorophenyl)-3-methyl-1-piperazinyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[4-(2-fluorophenyl)-4-methyl-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[4-(4-fluorophenyl)-4-methyl-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[4-(2,4-difluorophenyl)-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[4-(2,4-difluorophenyl)-1-piperazinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[4-(3-fluorophenyl)-4-methyl-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[4-(3-pyridinyl)-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[4-(2-methyl-4-pyridinyl)-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
1'-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-5-fluoro-3,3-dimethyl-spiro[isobenzofuran-1(3H),4'-piperidine],
7-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-2-(2,4-difluorophenyl)-2,7-diazaspiro[3.5]nonane,
8-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-2-(2,4-difluorophenyl)-2,8-diazaspiro[4.5]decane,
1-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-N-(2,4-difluorophenyl)-4-piperidinamine,
3-(cyclopropylmethyl)-7-[1-(2,4-difluorophenyl)-4-piperidinyl]-8-methyl-1,2,4-triazolo[4,3-a]pyridine,
3-phenyl-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,
7-(4-phenyl-1-piperidinyl)-3-(4-pyridinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile,
8-bromo-3-(cyclopropylmethyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine,
cis-8-chloro-3-(cyclopropylmethyl)-7-[3-methyl-4-phenyl-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,
cis-3-(cyclopropylmethyl)-7-[3-methyl-4-phenyl-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-

triazolo[4,3-a]pyridine,

7-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-2-(2,4-difluorophenyl)-2,7-diazaspiro[3.5]nonane,

7-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-2-(2,4-difluorophenyl)-2,7-diazaspiro[3.5]nonan-1-one,

3-(cyclopropylmethyl)-7-[(4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine.1.8 HCl,

3-(cyclopropylmethyl)-7-[(4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[4-[(2,4-difluorophenyl)methyl]-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[4-(2-phenylethyl)-1-piperazinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[4-(2-phenylethyl)-1-piperazinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine.1 HCl,

8-chloro-3-(cyclopropylmethyl)-7-[4-[[3-(trifluoromethyl)phenyl]methyl]-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[[4-phenyl-4-(trifluoromethyl)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

1'-[[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-3,3-dimethyl-spiro[isobenzofuran-1(3H),4'-piperidine],

3-(cyclopropylmethyl)-7-[[4-(4-fluorophenyl)-4-methyl-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[4-(2-phenylethyl)-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[4-[cis-4-(trifluoromethyl)cyclohexyl]-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[[4-(2,4-difluorophenyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[[4-phenyl-4-(trifluoromethyl)-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[[4-(4-fluorophenyl)-4-methyl-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[4-[(2,4-difluorophenyl)methyl]-1-piperazinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[4-(3,3-difluoro-1-pyrrolidinyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[4-(3,3,3-trifluoropropyl)-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine,
1-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-N-(phenylmethyl)-4-piperidinamine,
6-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-2-[(2,4-difluorophenyl)methyl]-2,6-diazaspiro[3.5]nonane,
2-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-6-[(2,4-difluorophenyl)methyl]-2,6-diazaspiro[3.5]nonane,
3-(cyclopropylmethyl)-7-[4-(3,5-difluorophenyl)-3,3-dimethyl-1-piperazinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(2,4-difluorophenyl)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(2,4-difluorophenyl)-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[4-(3,5-difluoro-2-pyridinyl)-1-piperidinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
1'-[[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-3,3-dimethyl-spiro[isobenzofuran-1(3H),4'-piperidine],
3-(cyclopropylmethyl)-7-(4,4-difluoro[1,4'-bipiperidin]-1'-yl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
6-[[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-2-(4-fluorophenyl)-2,6-diazaspiro[3.5]nonane,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(2,4-difluorophenyl)-1-piperazinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(trifluoromethyl)-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-(4,4-difluoro[1,4'-bipiperidin]-1'-yl)-1,2,4-triazolo[4,3-a]pyridine,
6-[[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-2-(4-fluorophenyl)-2,6-diazaspiro[3.5]nonane,
3-(cyclopropylmethyl)-7-[1-(4-phenyl-1-piperidinyl)ethyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(2-methoxyphenyl)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
2-[[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-

6-(4-fluorophenyl)-2,6-diazaspiro[3.5]nonane,

3-(cyclopropylmethyl)-7-[[4-(2-fluorophenyl)-4-methyl-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[[4-(3-fluorophenyl)-4-methyl-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[(4-fluoro-4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[[4-(2-pyridinyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[[4-(2-pyrimidinyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

2-[[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-1,2,3,4-tetrahydro-benzofuro[3,2-c]pyridine,

3-(cyclopropylmethyl)-7-[[4-(2-pyridinyloxy)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[1-(4-phenyl-1-piperidinyl)ethyl]-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[[4-(2-pyrimidinyl)-1-piperazinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[[4-(3-fluorophenyl)-4-methyl-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,

2-[[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-1,2,3,4-tetrahydro-benzofuro[3,2-c]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[[4-(*1H*-indol-1-yl)-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,

1'-[[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-spiro[*1H*-indene-1,4'-piperidine],

8-chloro-3-(cyclopropylmethyl)-7-[[4-(2-fluorophenyl)-4-methyl-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[[4-(*1H*-indol-1-yl)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[[4-(4-fluoro-2-methoxyphenyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[[4-(2-ethoxy-3-fluorophenyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

rac-(2aα,3α,3aα)-3-[[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-6-phenyl-3-azabicyclo[3.1.0]hexane,
3-(cyclopropylmethyl)-7-[[4-(4,6-dimethyl-2-pyrimidinyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[(4-methoxy-4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(2,6-difluorophenyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(4,6-dimethyl-2-pyrimidinyl)-1-piperazinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
1'-[[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-spiro[*1H*-indene-1,4'-piperidine],
8-chloro-3-(cyclopropylmethyl)-7-[[4-(4-fluoro-2-methoxyphenyl)-1-piperazinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(2-ethoxy-3-fluorophenyl)-1-piperazinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(2-fluorophenyl)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(2-ethoxy-3-fluorophenyl)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(2-pyridinyl)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(4-fluoro-2-methoxyphenyl)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(2,6-difluorophenyl)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-[(2,4-difluorophenyl)methoxy]-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[4-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(2-fluorophenyl)-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(2,6-difluorophenyl)-1-piperazinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(2-ethoxy-3-fluorophenyl)-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-[(2,4-difluorophenyl)methoxy]-1-

piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[(4-methoxy-4-phenyl-1-piperidinyl)methyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(2-pyrimidinyl)-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
7-[[4-(2-chlorophenyl)-1-piperidinyl]methyl]-3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(2-pyridinyl)-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(4-fluoro-2-methoxyphenyl)-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
rac-(2aα,3α,3aα)-3-[[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-6-phenyl-3-azabicyclo[3.1.0]hexane,
8-chloro-7-[[4-(4-fluorophenyl)-4-methyl-1-piperidinyl]methyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(2-pyridinyloxy)-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethoxy)-7-[4-(2-methoxyphenyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(2-methoxyphenyl)-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-7-[[4-(5-chloro-2-pyridinyl)-1-piperazinyl]methyl]-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-*a*]pyridine,
3-(cyclopropylmethyl)-7-[[4-(4-fluoro-2-methoxyphenyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine. 1.1HCl,
3-(cyclopropylmethyl)-7-[(4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
2-[[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-6-(4-fluorophenyl)-2,6-diazaspiro[3.5]nonane,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(2,6-difluorophenyl)-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(2-fluoro-6-methoxyphenyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(2-fluoro-6-methoxyphenyl)-1-piperazinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-7-[[4-(2-chlorophenyl)-1-piperidinyl]methyl]-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridine,
7-[4-[[3,5-bis(trifluoromethyl)phenyl]methyl]-1-piperazinyl]-8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[4-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]-1-piperazinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
(1R,6S)-3-[[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-6-phenyl-3-azabicyclo[4.1.0]heptane,
8-chloro-3-(cyclopropylmethyl)-7-[(4-fluoro-4-phenyl-1-piperidinyl)methyl]-1,2,4-triazolo[4,3-a]pyridine,
4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-1-phenyl-2-piperazinone,
8-chloro-3-(ethoxymethyl)-7-[4-phenyl-4-(trifluoromethyl)-1-piperidinyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-7-[4-phenyl-4-(trifluoromethyl)-1-piperidinyl]-3-propyl-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-7-[[4-(2-fluorophenyl)-4-methyl-1-piperidinyl]methyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-7-[[4-(3-fluorophenyl)-4-methyl-1-piperidinyl]methyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(2,4-difluorophenoxy)-1-piperidinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(2-pyridinyl)-1-piperazinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(2,4-difluorophenoxy)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-8-methyl-7-[(4-phenyl-1-piperidinyl)methyl]-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(2,4-difluorophenyl)-1-piperazinyl]methyl]-8-methyl-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(2,4-difluorophenyl)-1-piperidinyl]methyl]-8-methyl-1,2,4-triazolo[4,3-a]pyridine
3-ethyl-7-[(4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
7-[[4-(2,4-difluorophenyl)-1-piperazinyl]methyl]-3-ethyl-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
7-[[4-(2,4-difluorophenyl)-1-piperazinyl]methyl]-3-ethyl-8-(trifluoromethyl)-1,2,4-

triazolo[4,3-a]pyridine

7-[(4-phenyl-1-piperidinyl)methyl]-3-propyl-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

7-[[4-(2,4-difluorophenyl)-1-piperazinyl]methyl]-3-propyl-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

7-[[4-(2,4-difluorophenyl)-1-piperidinyl]methyl]-3-propyl-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine

3-butyl-7-[(4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3-butyl-7-[[4-(2,4-difluorophenyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3-butyl-7-[[4-(2,4-difluorophenyl)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3-(2-methylpropyl)-7-[(4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

7-[[4-(2,4-difluorophenyl)-1-piperazinyl]methyl]-3-(2-methylpropyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

7-[[4-(2,4-difluorophenyl)-1-piperidinyl]methyl]-3-(2-methylpropyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[[4-(2-pyrimidinyl)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

3-(cyclopropylmethyl)-7-[[4-(2-fluoro-6-methoxyphenyl)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

8-chloro-3-(cyclopropylmethyl)-7-[4-[(1R)-1-(4-fluorophenyl)ethyl]-1-piperazinyl]-1,2,4-triazolo[4,3-a]pyridine,

rac-(2aα,3α,3aα)-3-[[3-ethyl-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-6-phenyl-3-azabicyclo[3.1.0]hexane,

rac-(2aα,3α,3aα)-3-[[3-(cyclopropylmethyl)-8-methyl-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-6-phenyl-3-azabicyclo[3.1.0]hexane,

3-ethyl-7-[(4-fluoro-4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,

rac-(2aα,3α,3aα)-6-phenyl-3-[[3-propyl-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-3-azabicyclo[3.1.0]hexane,

rac-(2aα,3α,3aα)-3-[[3-butyl-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-6-phenyl-3-azabicyclo[3.1.0]hexane,

7-[[4-(2,4-difluorophenyl)-1-piperidinyl]methyl]-3-(ethoxymethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine . HCl,

7-[[4-(2,4-difluorophenyl)-1-piperidinyl]methyl]-3-(ethoxymethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
7-[[4-(2,4-difluorophenyl)-1-piperazinyl]methyl]-3-(ethoxymethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine. HCl,
7-[[4-(2,4-difluorophenyl)-1-piperazinyl]methyl]-3-(ethoxymethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
7-[[4-(4-bromophenyl)-1-piperidinyl]methyl]-3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(2,5-difluorophenyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(ethoxymethyl)-7-[(4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine . HCl,
3-(ethoxymethyl)-7-[(4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
7-[(4-fluoro-4-phenyl-1-piperidinyl)methyl]-3-(2-methylpropyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyridine,
rac-(2aα,3α,3aα)-3-[[3-(2-methylpropyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyridin-7-yl]methyl]-6-phenyl-3-azabicyclo[3.1.0]hexane,
7-[(4-fluoro-4-phenyl-1-piperidinyl)methyl]-3-propyl-8-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyridine,
3-butyl-7-[(4-fluoro-4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyridine,
3-(cyclopropylmethyl)-7-[(4-fluoro-4-phenyl-1-piperidinyl)methyl]-8-methyl-1,2,4-triazolo[4,3-*a*]pyridine,
3-(ethoxymethyl)-7-[(4-fluoro-4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyridine,
rac-(2aα,3α,3aα)-3-[[3-(ethoxymethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]methyl]-6-phenyl-3-azabicyclo[3.1.0]hexane,
3-(cyclopropylmethyl)-7-[[4-(3,5-difluorophenyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(2,3-difluorophenyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(3,4-difluorophenyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyridine,
3-(cyclopropylmethyl)-7-[[4-(3,5-difluorophenyl)-3,3-dimethyl-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyridine,
7-[[4-(4-chloro-2-fluorophenyl)-1-piperazinyl]methyl]-3-(cyclopropylmethyl)-8-

(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyridine,
7-[[4-(2-chloro-4-fluorophenyl)-1-piperazinyl]methyl]-3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-[3-(trifluoromethyl)phenyl]-1-piperazinyl]methyl]-1,2,4-triazolo[4,3-*a*]pyridine,
8-bromo-3-(cyclopropylmethyl)-7-[(4-phenyl-1-piperidinyl)methyl]-1,2,4-triazolo[4,3-*a*]pyridine,
3-(cyclopropylmethyl)-7-[[4-(3,5-difluoro-2-pyridinyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyridine,
3-(cyclopropylmethyl)-7-[[4-(5-fluoro-2-pyridinyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyridine,
7-[[4-(5-chloro-2-pyridinyl)-1-piperazinyl]methyl]-3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-[(2,4-difluorophenoxy)methyl]-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(3,5-difluoro-2-pyridinyl)-1-piperazinyl]methyl]-1,2,4-triazolo[4,3-*a*]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(5-fluoro-2-pyridinyl)-1-piperazinyl]methyl]-1,2,4-triazolo[4,3-*a*]pyridine,
3-(2-cyclopropylethyl)-7-[[4-(2,4-difluorophenyl)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyridine,
3-(2,2-dimethylpropyl)-7-[[4-(2,4-difluorophenyl)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyridine,
3-(cyclobutylmethyl)-7-[[4-(2,4-difluorophenyl)-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyridine, and
8-chloro-7-[[4-(5-chloro-2-pyridinyl)-1-piperazinyl]methyl]-3-(cyclopropylmethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyridine,
and the pharmaceutically acceptable salts and the solvates thereof.

In an embodiment, the compound of Formula (I) is selected from the group of:
8-chloro-7-(4-fluoro-4-phenyl-1-piperidinyl)-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo-[4,3-a]pyridine;
3-(cyclopropylmethyl)-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo-[4,3-a]pyridine;
3-(cyclopropylmethyl)-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo-[4,3-a]pyridine .1.1HCl;

1'-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-5-fluoro-3,3-dimethyl-spiro[isobenzofuran-1(3H),4'-piperidine],
3-(cyclopropylmethyl)-7-[(4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine.1.8 HCl,
3-(cyclopropylmethyl)-7-[(4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(2,4-difluorophenyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(2,4-difluorophenyl)-1-piperazinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(4-fluorophenyl)-4-methyl-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine, and
3-(cyclopropylmethyl)-7-[(4-fluoro-4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
and the pharmaceutically acceptable salts and solvates thereof.

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. Radiolabelled compounds of Formula (I) may comprise a radioactive isotope selected from the group of ^{3}H, ^{11}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 ^{3}H, ^{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 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. 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.

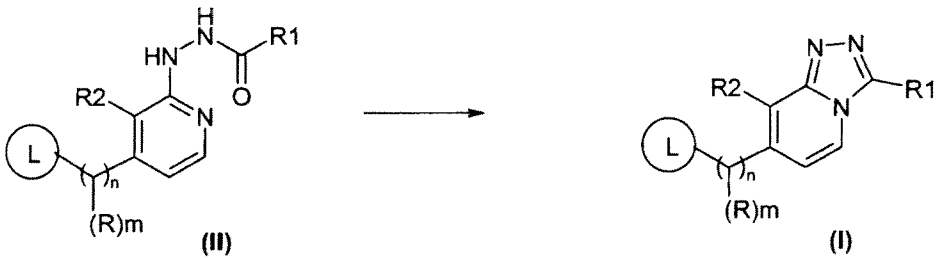
A. Preparation of the final compounds

Experimental procedure 1

Final compounds according to Formula (I) can be prepared following art known procedures by cyclization of intermediate compound of Formula (II) in the presence of a halogenating agent such as for example phosphorus (V) oxychloride ($POCl_3$) or trichloroacetonitrile-triphenylphosphine mixture in a suitable solvent such as for example DCE or CH_3CN stirred under microwave irradiation, for a suitable period of time that allows the completion of the reaction, such as for example 50 min at a temperature between 140-200°C.

Alternatively, final compounds of Formula (I) can be prepared by heating the intermediate compound of Formula (II) for a suitable period of time that allows the completion of the reaction, such as for example 1 h at a temperature between 140-200°C. In reaction scheme (1), all variables are defined as in Formula (I).

Reaction Scheme 1

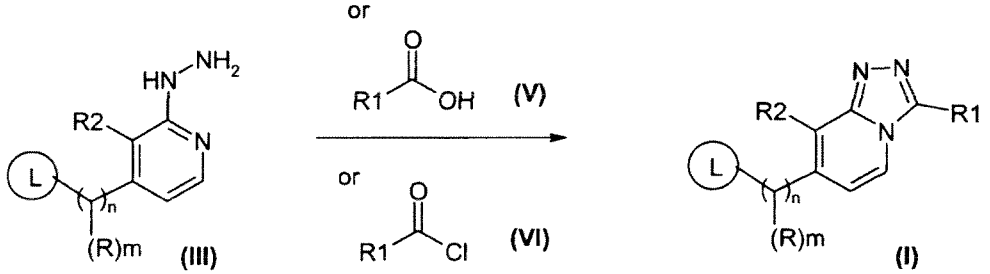


Experimental procedure 2

Final compounds according to Formula (I) can be prepared by art known procedures in analogy to the syntheses described in *J. Org. Chem.*, **1966**, *31*, 251, or *J. Heterocycl. Chem.*, **1970**, *7*, 1019, by cyclization of intermediate compounds of Formula (III) under suitable conditions in the presence of a suitable ortho-ester of Formula (IV), wherein R^1 is a suitable substituent like for example a methyl group, according to reaction scheme (2). The reaction can be carried out in a suitable solvent such as, for example, xylene. Typically, the mixture can be stirred for 1 to 48 h at a temperature between 100-200°C. In reaction scheme (2), all variables are defined as in Formula (I).

Alternatively, final compounds according to Formula (I) can be prepared by art known procedures in analogy to the synthesis described in *Tetrahedron Lett.*, **2007**, *48*, 2237-2240 by reaction of intermediate compound of Formula (III) with carboxylic acids of Formula (V) or acid equivalents such as acid halides of Formula (VI) to afford final compounds of Formula (I). The reaction can be carried out using a halogenating agent such as for example trichloroacetonitrile-triphenylphosphine mixture in the presence of a suitable solvent such as for example dichloroethane stirred at a temperature between 100-200°C for 1 to 48 h or under microwave irradiation for 20 min. In reaction scheme (2), all variables are defined as in Formula (I).

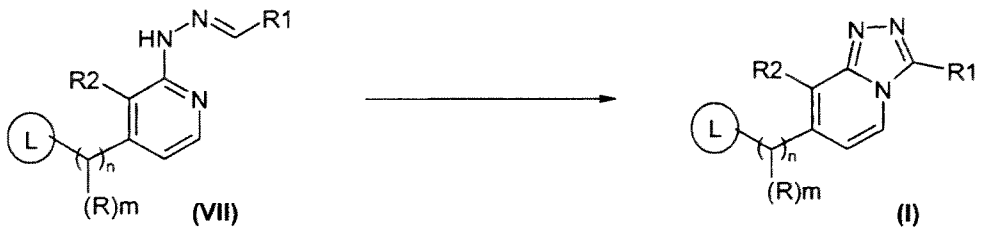
Reaction Scheme 2



Experimental procedure 3

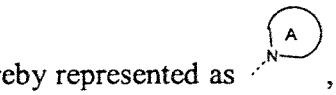
Final compounds according to Formula (I) can be prepared by art known procedures, by cyclization of intermediate compounds of Formula (VII) under suitable conditions in the presence of a suitable oxidising agent such as copper (II) chloride in a suitable solvent such as DMF, stirred for 1 to 48 h at a temperature between r.t. and 200°C. In reaction scheme (3), all variables are defined as in Formula (I).

Reaction Scheme 3

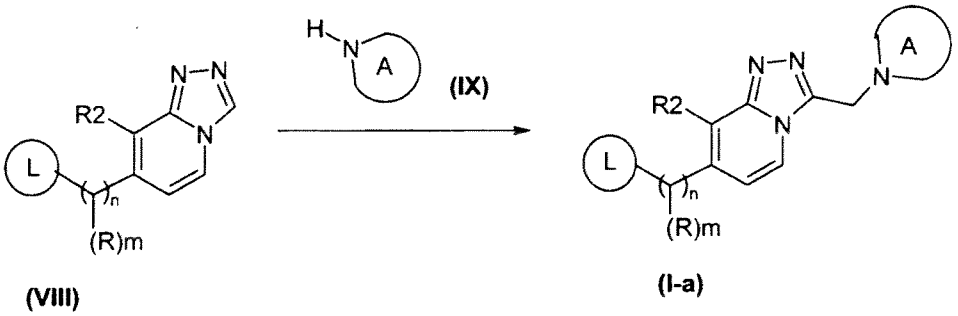


Experimental procedure 4

Final compounds according to Formula (I) wherein R^1 is a Het^1-C_1alkyl or a 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)methyl substituent as previously defined,

wherein Het^1 is bound through the Nitrogen atom hereby represented as , hereby named (I-a), can be prepared by art known procedures by reaction of intermediate compound of Formula (VIII) under standard Mannich conditions with intermediate compound of Formula (IX). The reaction can be carried out in the presence of formaldehyde with a suitable solvent such as for example acetic acid stirred at a suitable temperature, for example 80°C for a period of time that allows completion of the reaction, for example 16 h. In reaction scheme (4), all variables are defined as in Formula (I).

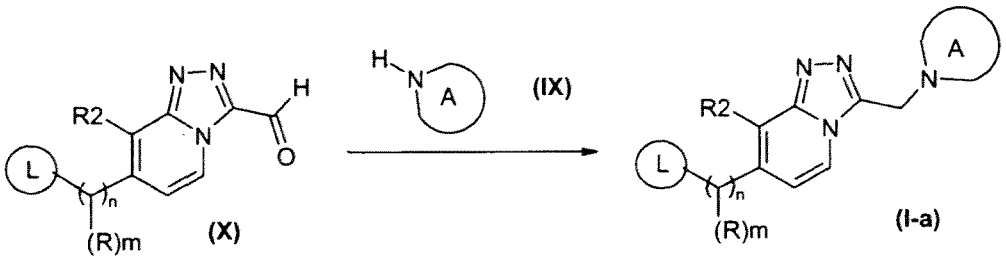
Reaction Scheme 4



Experimental procedure 5

Alternatively, final compounds according to Formula (I) wherein R^1 is a Het^1-C_1alkyl or a 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)methyl substituent as previously defined, wherein Het^1 is bound through the Nitrogen atom, hereby named (I-a) can be prepared by reacting an intermediate of Formula (IX) with an intermediate of Formula (X) under reductive amination conditions that are known to those skilled in the art. This is illustrated in reaction scheme (5) wherein all variables are defined as in Formula (I). The reaction may be performed, for example, in the presence of triacetoxy borohydride in a suitable reaction-inert solvent such as, for example, DCE, at a suitable temperature, typically at r.t., for a suitable period of time that allows the completion of the reaction.

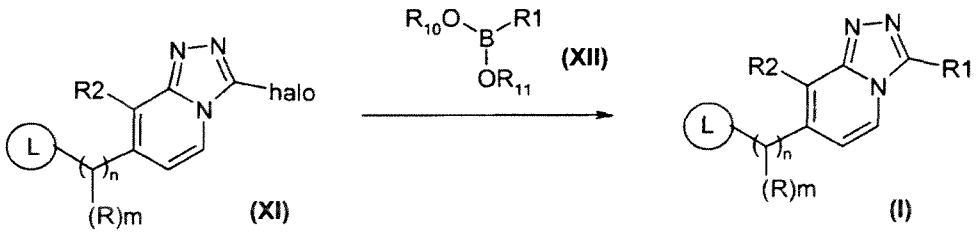
Reaction Scheme 5



Experimental procedure 6

The final compounds according to Formula (I), can be prepared by reacting an intermediate compound of Formula (XI) with a compound of Formula (XII) according to reaction scheme (6), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, 1,4-dioxane or mixtures of inert solvents such as, for example, 1,4-dioxane/DMF, in the presence of a suitable base, such as, for example, aqueous $NaHCO_3$ or Na_2CO_3, a Pd-complex catalyst such as, for example, $Pd(PPh_3)_4$ under thermal conditions such as, for example, heating the reaction mixture at 150 °C under microwave irradiation, for example for 10 minutes. In reaction scheme (6), all variables are defined as in Formula (I) and halo is a group suitable for Pd mediated coupling with boronic acids or boronic esters, such as, for example chloro, bromo or iodo. R^{10} and R^{11} may be hydrogen or alkyl, or may be taken together to form for example a bivalent radical of formula $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-C(CH_3)_2C(CH_3)_2-$.

Reaction Scheme 6



Experimental procedure 7

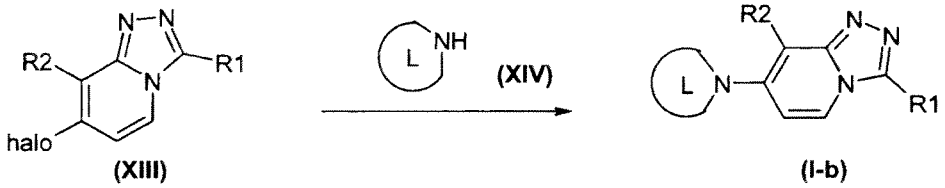
Final compounds according to Formula (I) wherein n is 0, and (L) is a radical of formula (L-a), (L-b), (L-d), (L-e), (L-f), (L-g) and (L-h) hereby represented by (L-N---), hereby named (I-b), can be prepared by reacting an intermediate compound of Formula (XIII) with a compound of Formula (XIV) according to reaction scheme (7), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, 1,4-dioxane, in the presence of a suitable base, such as, for example, K_3PO_4, a Pd-complex

catalyst such as, for example, 2-(2'-di-*tert*-butylphosphine)biphenylpalladium(II) acetate, under thermal conditions such as, for example, heating the reaction mixture for example at 80 °C for 12 h. In reaction scheme (7), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo, suitable for Pd-mediated coupling with amines.

Alternatively, compounds according to Formula (I-b) can be prepared by reacting an intermediate compound of Formula (XIII) with a compound of Formula (XIV) according to reaction scheme (7), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, 1,2-dimethoxyethane or acetonitrile, in the presence of a suitable base, such as, for example, Cs_2CO_3 or *N,N*-diisopropylethylamine, under thermal conditions such as, for example, heating the reaction mixture for example at 180 °C under microwave irradiation for 45 min.

Alternatively, compounds according to Formula (I-b) can be prepared by reacting an intermediate compound of Formula (XIII) with a compound of Formula (XIV) according to reaction scheme (5), a reaction that is performed in a suitable reaction-inert solvent such as, for example, toluene, in the presence of a suitable base such as, for example, sodium *tert*-butoxide, a metal-based catalyst, specifically a palladium catalyst, such as palladium(II) acetate, and a suitable ligand, such as for example 1,1'-[1,1'-binaphthalene]-2,2'-diylbis[1,1-diphenyl-phosphine] (BINAP), heating for a suitable period of time that allows the completion of the reaction, for example at 100 °C for 16 h in a sealed tube.

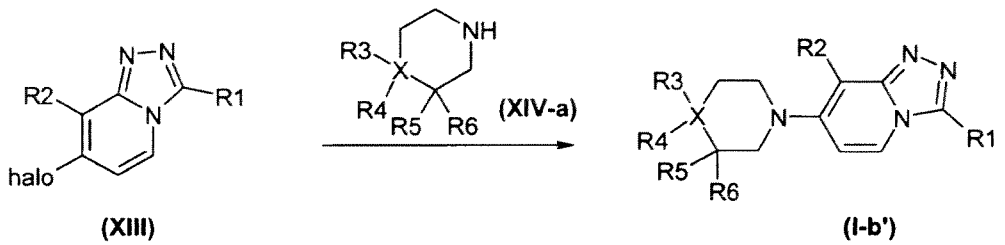
Reaction Scheme 7



(XIII) (I-b)

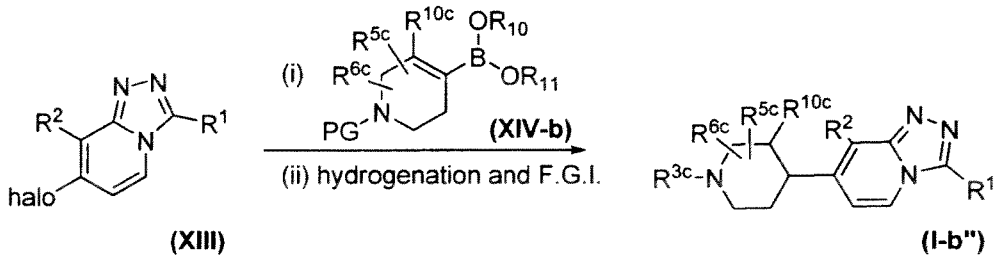
Reaction Scheme 7a represents an example for the preparation of a compound of formula (I-b') wherein (L) is (L-a) or (L-b), by reaction of intermediate (XIII) with a reagent formula (XIV-a) wherein R^{3a}-C-R^{4a}, R^{3b}-N, R^{5a}, R^{6a}, R^{5b} and R^{6b} are in general represented by R^3-X-R^4, R^5 and R^6, and all other variables are as previously defined.

Reaction Scheme 7a



Final compounds according to Formula (I) wherein n is 0, and (L) is (L-c), hereby named (I-b"), can be prepared by reacting an intermediate compound of Formula (XIII) with a reagent of formula (XIV-b) according to reaction scheme (7b), wherein R^{10} and R^{11} are as previously defined, and PG represents a suitable protecting group, such as tert-butyloxycarbonyl, a reaction that is performed in a suitable reaction-inert solvent, such as, for example, 1,4-dioxane, in the presence of a suitable base, such as, for example, $NaHCO_3$, a Pd-complex catalyst such as, for example, $Pd(PPh_3)_4$ under thermal conditions such as, for example, heating the reaction mixture at a suitable temperature, for example at 150 °C, under thermal conditions or microwave irradiation for a time sufficient to drive the reaction to completion. In reaction scheme (7b), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo, suitable for Pd-mediated coupling. Hydrogenation and further functional group interconversion (F.G.I.) performed under conditions known to a skilled person, afford compound (I-b").

Reaction Scheme 7b



Experimental procedure 8

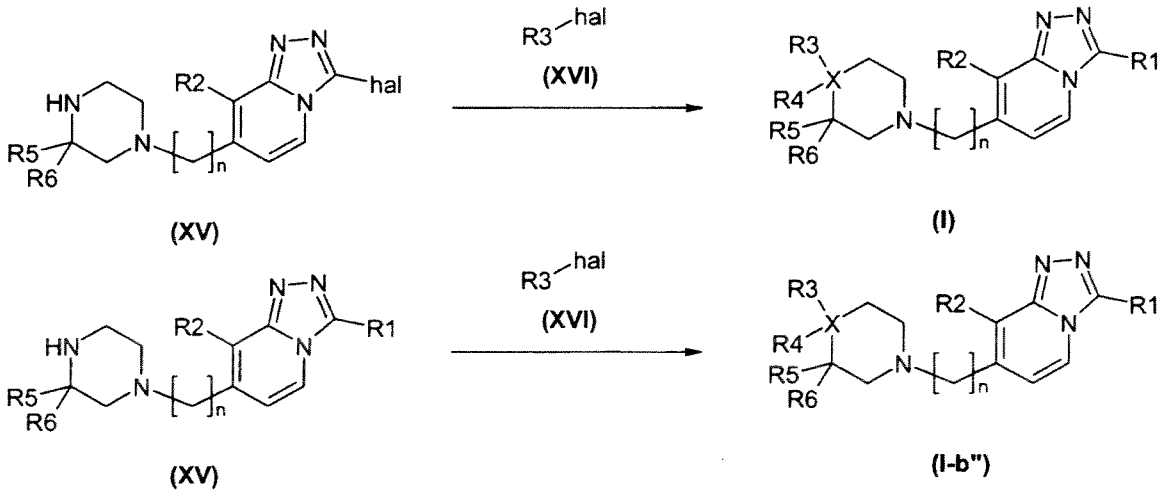
Final compounds according to Formula (I) wherein L is (L-b), hereby represented by (I-b"), can be prepared by reacting an intermediate compound of Formula (XV) with a compound of Formula (XVI) according to reaction scheme (8), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, 1,4-dioxane, in the presence of a suitable base, such as, for example, K_3PO_4, a Pd-complex

catalyst such as, for example, 2-(2'-di-*tert*-butylphosphine)biphenylpalladium(II) acetate, under thermal conditions such as, for example, heating the reaction mixture for example at 80 °C for 12 h. In reaction scheme (8), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo, suitable for Pd-mediated coupling with amines.

Alternatively, the reaction can be performed in a suitable reaction-inert solvent, such as, for example, 1,2-dimethoxyethane or acetonitrile, in the presence of a suitable base, such as, for example, Cs_2CO_3 or *N,N*-diisopropylethylamine, under thermal conditions such as, for example, heating the reaction mixture for example at 180 °C under microwave irradiation for 45 min.

Alternatively, the reaction can also be performed in a suitable reaction-inert solvent such as, for example, toluene, in the presence of a suitable base such as, for example, sodium *tert*-butoxide, a metal-based catalyst, specifically a palladium catalyst, such as palladium(II) acetate, and a suitable ligand, such as for example 1,1'-[1,1'-binaphthalene]-2,2'-diylbis[1,1-diphenyl-phosphine] (BINAP), heating for a suitable period of time that allows the completion of the reaction, for example at 100 °C for 16 h in a sealed tube.

Reaction Scheme 8

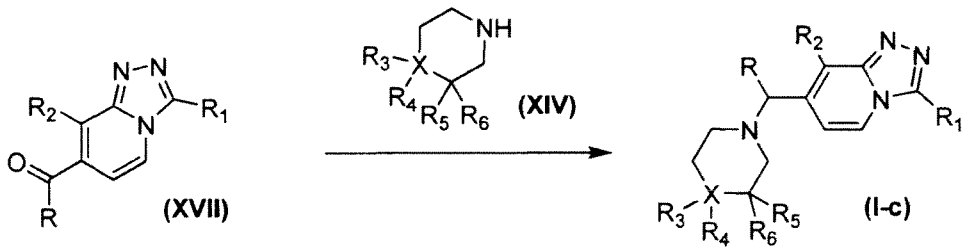


Experimental procedure 9

The final compounds according to Formula (I) wherein n=m=1 and L is (L-a), (L-b), (L-d), (L-e), (L-f), (L-g) or (L-h), hereby exemplified in general for (L-a) and (L-b), hereby represented as (I-c), can be prepared by reacting an intermediate of Formula (XVII) with an intermediate of Formula (XIV) under reductive amination conditions

that are known by those skilled in the art. This is illustrated in reaction scheme (9) wherein all variables are defined as in Formula (I). The reaction may be performed, for example, in the presence of sodium triacetoxy borohydride in a suitable reaction-inert solvent such as, for example, 1,2-dichloroethane, at a suitable temperature, for example at temperature between r.t. and 150°C, either classical heating or microwave irradiation, , for a suitable period of time that allows the completion of the reaction.

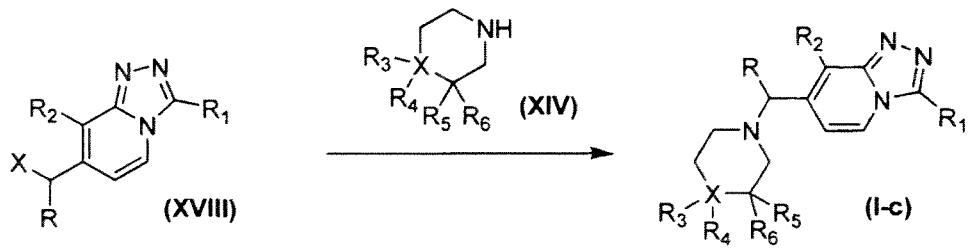
Reaction Scheme 9



Experimental procedure 10

Alternatively, final compounds according to Formula (I-c) can be prepared by reacting an intermediate of Formula (XVIII) with an intermediate of Formula (XIV) under alkylating conditions that are known by those skilled in the art. This is illustrated in reaction scheme (10) wherein all variables are defined as in mentioned hereabove and X is a group suitable for alkylation reactions such as for example halo, methylsulfonate or p-tolylsulfonate. The reaction may be performed, for example, in the presence of a base such as for example diisopropylethylamine in a suitable reaction solvent such as, for example, DMF for a suitable period of time that allows the completion of the reaction at suitable temperature such as for example 120°C.

Reaction Scheme 10

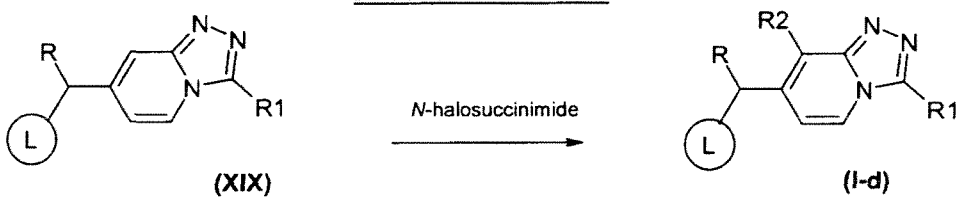


X = halo, $MeSO_3$, p-tolylSO_3

Experimental procedure 11

The final compounds according to Formula (I), wherein n=m=1 and R^2 is halogen hereby name (I-d), can be prepared by reacting an intermediate compound of Formula (XIX) with a *N*-halosuccinimide reagent, such as *N*-chlorosuccinimide, *N*-bromosuccinimide or *N*-iodosuccinimide, according to reaction scheme (11). This reaction is performed in a suitable reaction-inert and aprotic solvent, such as, for example, dichloromethane or 1,2-dichloroethane, stirring the reaction mixture at a suitable temperature, typically at room temperature, for the required time to achieve completion of the reaction, usually 1 hour. In reaction scheme (11), all other variables are defined as in Formula (I).

Reaction Scheme 11



(XIX) (I-d)

R2 = halogen

B. Preparation of the intermediates

Experimental procedure 12

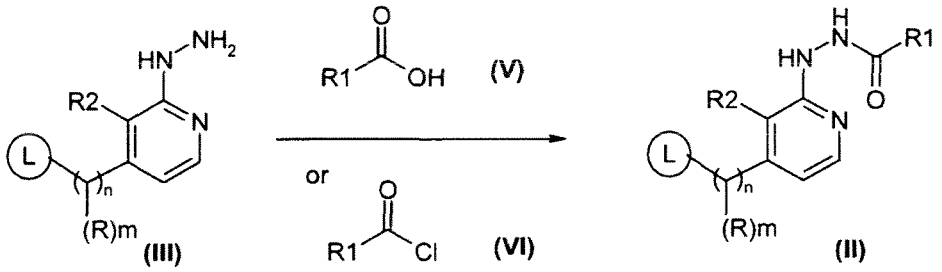
Intermediate compounds according to Formula (II) can be prepared following conditions that are known to those skilled in the art by reacting an intermediate of Formula (III) with a carboxylic acid of Formula (V) via an amide bond formation reaction in the presence of a suitable coupling reagent. This is illustrated in reaction scheme (6) wherein all variables are defined as in Formula (I).

Alternatively, intermediate compounds according to Formula (II) can be prepared by art known procedures by reacting an intermediate of Formula (III) with a carboxylic acid of formula (V). The reaction can be carried out using a halogenating agent such as for example a trichloroacetonitrile-triphenylphosphine mixture in the presence of a suitable solvent such as for example dichloroethane stirred at a temperature between 100-200°C for 1 to 48 h or under microwave irradiation for 20 min. In reaction scheme (12), all variables are defined as in Formula (I).

Alternatively, intermediate compounds according to Formula (II) can be prepared by art known procedures by reacting an intermediate of Formula (III) with an acid halide of formula (VI). The reaction can be carried out using a inert-solvent such

as for example DCM in the presence of a base such as for example TEA, for example at r.t. for a suitable period of time that allows completion of the reaction. In reaction scheme (12), all variables are defined as in Formula (I).

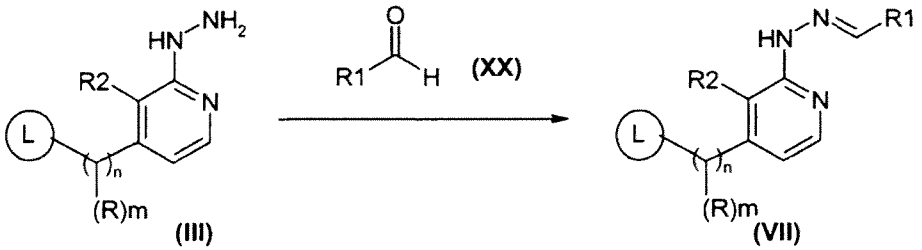
Reaction Scheme 12



Experimental procedure 13

Intermediate compounds according to Formula (VII) can be prepared following conditions that are known to those skilled in the art by reacting an intermediate of Formula (III) with an aldehyde of Formula (XX) via imine bond formation reaction. The reaction can be carried out using a protic solvent such as for example EtOH, for example at temperature between r.t. and 150°C for a suitable period of time that allows completion of the reaction. In reaction scheme (13), all variables are defined as in Formula (I).

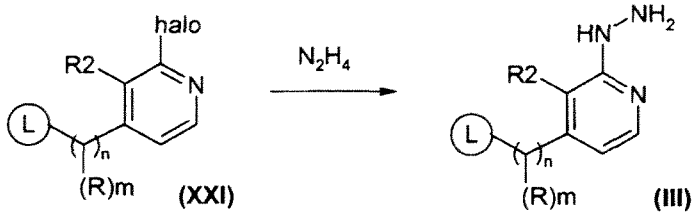
Reaction Scheme 13



Experimental procedure 14

Intermediate compounds according to Formula (III) can be prepared by reacting an intermediate compound of Formula (XXI) with hydrazine according to reaction scheme (14), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, ethanol or THF under thermal conditions such as, for example, heating the reaction mixture for example at 160 °C under microwave irradiation for 20 min or classical thermal heating at 90°C for 16 h. In reaction scheme (14), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo.

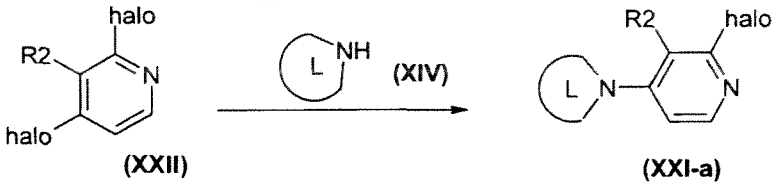
Reaction Scheme 14



Experimental procedure 15

Intermediate compounds according to Formula (XXI) wherein n is 0, and L is selected from (L-a), (L-b), (L-d), (L-e), (L-f), (L-g) and (L-h) hereby named (XXI-a) can be prepared by reacting an intermediate compound of Formula (XXII) with a compound of Formula (XIV) according to reaction scheme (15), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, acetonitrile, in the presence of a suitable base, such as, for example, *N,N*-diisopropylethylamine, under thermal conditions such as, for example, heating the reaction mixture for example at 110 °C for 4 h. In reaction scheme (15), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo.

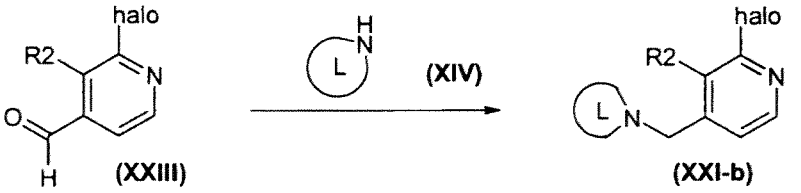
Reaction Scheme 15



Experimental procedure 16

Intermediate compounds according to Formula (XXI) wherein n is 1, hereby named (XXI-b) can be prepared by reacting an intermediate of Formula (XXIII) with an intermediate of Formula (XIV) under reductive amination conditions that are known to those skilled in the art. This is illustrated in reaction scheme (16) wherein all variables are defined as in Formula (I). The reaction may be performed, for example, in the presence of triacetoxy borohydride in a suitable reaction-inert solvent such as, for example, DCE, at a suitable temperature, typically at r.t., for a suitable period of time that allows the completion of the reaction.

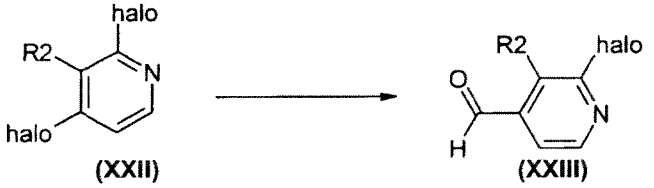
Reaction Scheme 16



Experimental procedure 17

Intermediate compounds according to Formula (XXIII) can be prepared by reacting an intermediate of Formula (XXII) under conditions that are known to those skilled in the art. This is illustrated in reaction scheme (17) wherein all variables are defined as mentioned hereabove. The reaction may be performed, for example, by first converting the aryl halide into an aryl metal derivative where the metal may be lithium, magnesium, boron or zinc followed by reaction with the appropriate carbonyl compound. Methods accomplishing these transformations are well known to those skilled in the art and include metal exchange with a Grignard reagent such as isopropylmagnesium chloride or strong base such as for example BuLi in a suitable reaction inert solvent such as THF, diethyl ether or toluene, preferably THF at a temperature between -78°C and 40°C, followed by reaction with the carbonyl compound such as for example DMF at a temperature between –78 °C and 100 °C.

Reaction Scheme 17

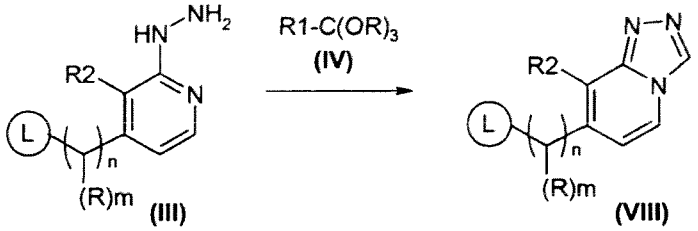


Experimental procedure 18

Intermediate compounds according to Formula (VIII) can be prepared by art known procedures in analogy to the syntheses described in *J. Org. Chem.*, **1966**, *31*, 251, or *J. Heterocyclic. Chem.*, **1970**, *7*, 1019, by cyclization of intermediate compounds of Formula (III) under suitable conditions in the presence of a suitable ortho-ester, for example, an orthoester of formula (IV) above, such as commercially available examples thereof wherein R^1 is H and R is methyl or ethyl, according to reaction scheme (18). The reaction can be carried out neat or in a suitable solvent such as, for example, xylene. Typically, the mixture can be stirred for 1 to 48 h at a

temperature between 100-200 °C. In reaction scheme (18), all variables are defined as in Formula (I).

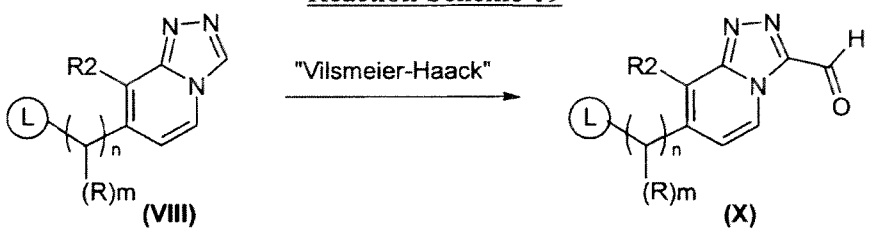
Reaction Scheme 18



Experimental procedure 19

Intermediate compounds of Formula (X) can be prepared by reacting an intermediate compound of Formula (VIII) under standard Vilsmeier-Haack reaction conditions such as, for example, DMF and phosphorus (V) oxychloride ($POCl_3$) at a temperature from r.t. to 140 °C under classical thermal heating or under microwave irradiation, for a suitable period of time that allows the completion of the reaction, for example 1 h. In reaction scheme (19), all variables are defined as in Formula (I).

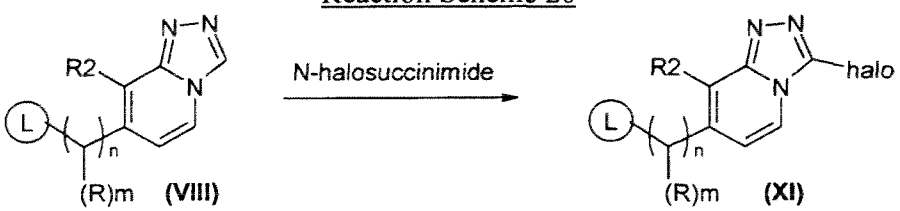
Reaction Scheme 19



Experimental procedure 20

Intermediate compounds of Formula (XI) can be prepared by reacting an intermediate compound of Formula (VIII) under standard halogenations standard conditions such as, for example, DMF and *N*-bromosuccinimide at a temperature from r.t. to 140 °C under classical thermal heating or under microwave irradiation, for a suitable period of time that allows the completion of the reaction, for example 1 h. In reaction scheme (20), all variables are defined as in Formula (I).

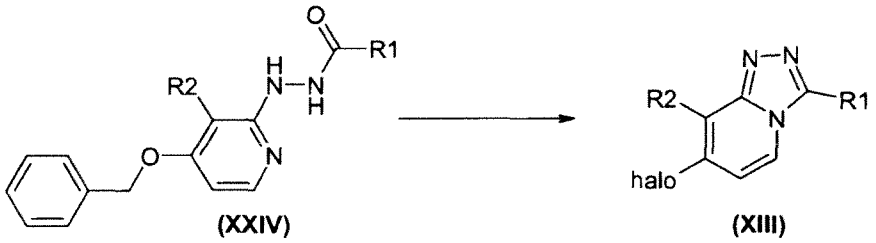
Reaction Scheme 20



Experimental procedure 21

Intermediate compounds according to Formula (XIII) can be prepared following art known procedures by cyclization of an intermediate compound of Formula (XXIV) in the presence of a halogenating agent such as for example phosphorus (V) oxychloride ($POCl_3$) in a suitable solvent such as, for example, dichloroethane, stirred under microwave irradiation, for a suitable period of time that allows the completion of the reaction, as for example 5 min at a temperature between 140-200 °C. In reaction scheme (21), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo.

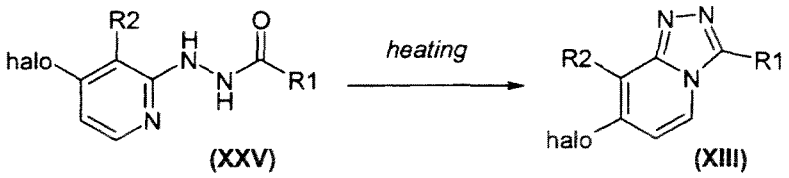
Reaction Scheme 21



Experimental procedure 22

Alternatively, intermediate compounds of Formula (XIII) can be prepared following art known procedures by cyclization of intermediate compound of Formula (XXV) under heating for a suitable period of time that allows the completion of the reaction, as for example 1 h at a temperature between 140-200 °C. In reaction scheme (22), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo.

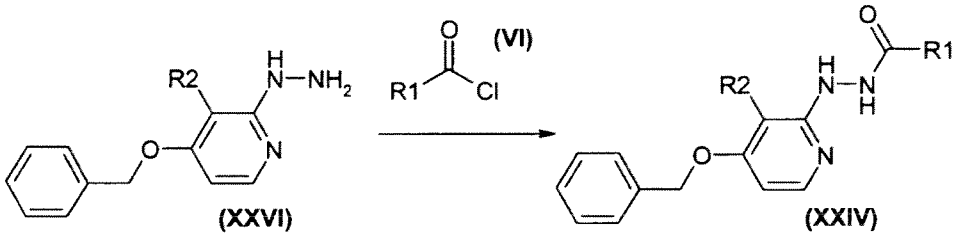
Reaction Scheme 22



Experimental procedure 23

Intermediate compounds according to Formula (XXIV) can be prepared by art known procedures by reaction of a hydrazine intermediate of Formula (XXVI) with acid halides of Formula (VI). The reaction can be carried out using an inert-solvent, such as for example DCM, in the presence of a base such as for example triethylamine, for example at r.t. for a suitable period of time that allows completion of the reaction, for example 20 min. In reaction scheme (23), all variables are defined as in Formula (I).

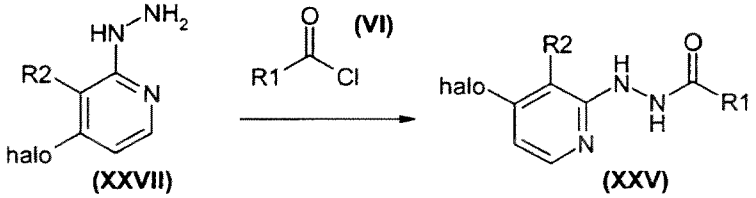
Reaction Scheme 23



Experimental procedure 24

Intermediate compounds according to Formula (XXV) can be prepared by art known procedures by reaction of intermediate compounds of Formula (XXVII) with acid halides of Formula (VI). The reaction can be carried out using an inert-solvent such as for example DCM in the presence of a base such as for example triethylamine, for example at r.t. for a suitable period of time that allows completion of the reaction, for example 20 min. In reaction scheme (24), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo.

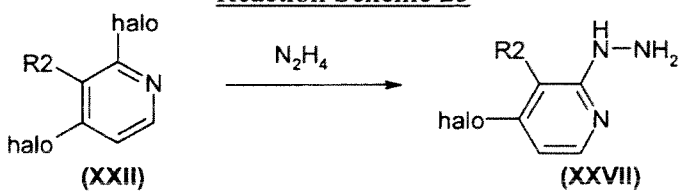
Reaction Scheme 24



Experimental procedure 25

Intermediate compounds according to Formula (XXVII) can be prepared by reacting an intermediate compound of Formula (XXII) with hydrazine according to reaction scheme (25), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, ethanol, THF or 1,4-dioxane under thermal conditions such as, for example, heating the reaction mixture for example at 160 °C under microwave irradiation for 30 min or classical thermal heating at 70 °C for 16 h. In reaction scheme (25), R^2 is defined as in Formula (I) and halo is chloro, bromo or iodo.

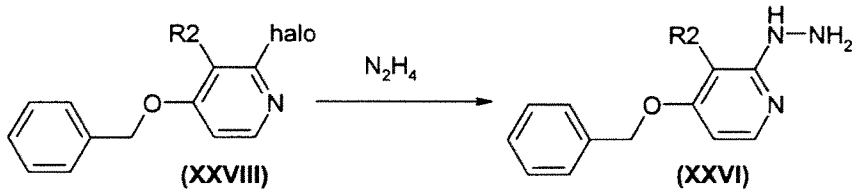
Reaction Scheme 25



Experimental procedure 26

Intermediate compounds according to Formula (XXVI) can be prepared by reacting an intermediate compound of Formula (XXVIII) with hydrazine according to reaction scheme (26), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, ethanol, THF or 1,4-dioxane under thermal conditions such as, for example, heating the reaction mixture for example at 160 °C under microwave irradiation for 30 min or classical thermal heating at 70°C for 16 h. In reaction scheme (26), R^2 is defined as in Formula (I) and halo is chloro, bromo or iodo.

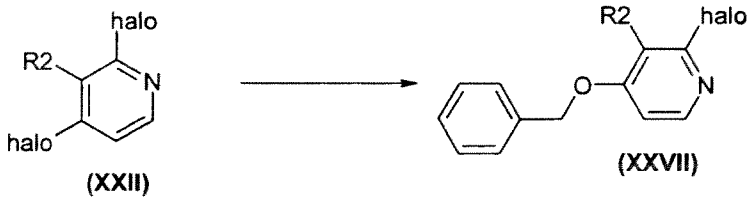
Reaction Scheme 26



Experimental procedure 27

Intermediate compounds according to Formula (XXVII) can be prepared by reacting an intermediate compound of Formula (XXII) with benzyl alcohol according to reaction scheme (27), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, *N,N*-dimethylformamide in the presence of a suitable base, such as for example sodium hydride at r.t. for a suitable period of time that allows the completion of the reaction, such as for example 1 h. In reaction scheme (27), R^2 is defined as in Formula (I) and halo is chloro, bromo or iodo.

Reaction Scheme 27

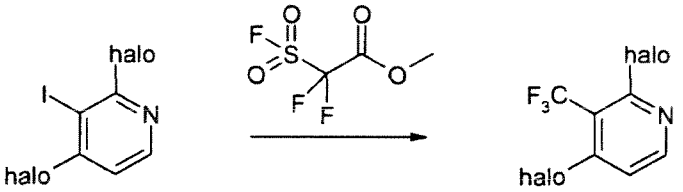


Experimental procedure 28

Intermediate compounds of Formula (XXII) wherein R^2 is trifluoromethyl, hereby named (XXII-a), can be prepared by reacting an intermediate of Formula (XXII) wherein R^2 is iodine, hereby named (XXII-b), with a suitable trifluoromethylating agent, such as for example fluorosulfonyl(difluoro)acetic acid methyl ester, according to reaction scheme (28). This reaction is performed in a suitable reaction-inert solvent such as, for example, *N,N*-dimethylformamide in the presence of a suitable coupling agent such as for example, copper iodide, under thermal conditions such as, for

example, heating the reaction mixture for example at 160 °C under microwave irradiation for 45 min. In reaction scheme (28), halo is chloro, bromo or iodo.

Reaction Scheme 28

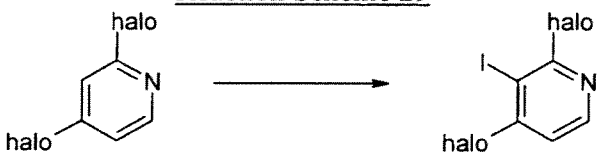


(XXII-b) (XXII-a)

Experimental procedure 29

Intermediate compounds of Formula (XXII) wherein R^2 is iodine, hereby named (XXII-b), can be prepared by reacting an intermediate compound of Formula (XXVIII') with a strong base such as, for example, *n*-butyllithium, and further treatment with an iodinating agent such as, for example, iodine. This reaction is performed in a suitable reaction-inert solvent such as, for example, THF at low temperature such as, for example –78 °C for a period of time that allows the completion of the reaction such as, for example 2 h. In reaction scheme (29), halo may be chloro, bromo or iodo

Reaction Scheme 29



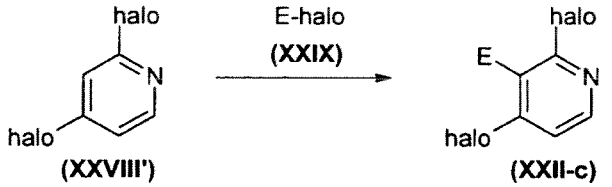
(XXVIII') (XXII-b)

Experimental procedure 30

Intermediate compounds of Formula (XXII) wherein R^2 is C_{1-3}alkyl, C_{3-7}cycloalkyl or (C_{3-7}cycloalkyl)C_{1-3}alkyl, hereby named (XXII-c), can be prepared by an ortho metallation strategy by reacting an intermediate of Formula (XXVIII') with a substituted or unsubstituted alkyl or an alkenyl halide (XXIX) in the presence of a suitable base, such as lithium diisopropylamide or butyllithium, according to reaction scheme (30) and following references: a) *Tetrahedron* **2001**, *57*(19), 4059-4090 or b) *Tetrahedron* **2001**, *57*(21), 4489-4505. This reaction is performed in a suitable reaction-inert solvent such as, for example, THF at low temperature such as, for example –78 °C for a period of time that allows the completion of the reaction such as, for example 2-5h. In reaction scheme (30), halo may be chloro, bromo or iodo and E represents an appropriate C_{1-3}alkyl, C_{3-7}cycloalkyl or (C_{3-7}cycloalkyl)C_{1-3}alkyl radical.

If required, intermediates (XXII-c) may be subjected to further simple functional group interconversion steps following art-known procedures to lead to the desirable final R^2 group.

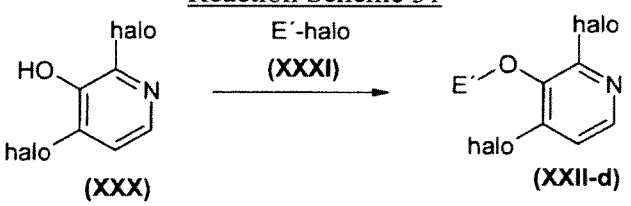
Reaction Scheme 30



Experimental procedure 31

Intermediate compounds of Formula (XXII) wherein R^2 is haloC_{1-3}alkoxy, hereby named (XXII-d), can be prepared for example by reacting an intermediate of formula (XXX) with a suitable alkyl or alkenyl halide (XXXI) in the presence of a suitable base such as potassium carbonate. This reaction is performed in a suitable reaction-inert solvent such as, for example, DMF under thermal conditions such as for example, heating the reaction mixture for example at 50-100 °C for a period of time that allows the completion of the reaction such as for example, 2 h. In reaction scheme (31), halo may be chloro, bromo or iodo and E' represents an appropriate C_{1-3}alkyl or C_{2-3}alkenyl radical, which may be further halogenated following procedures known to those skilled in the art.

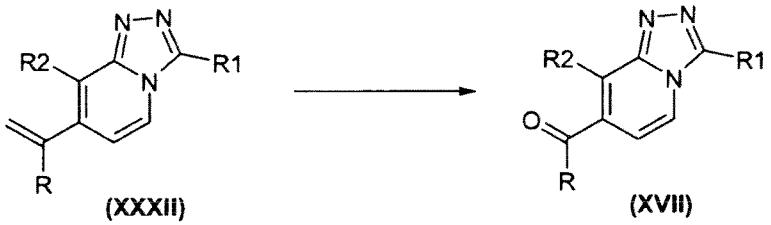
Reaction Scheme 31



Experimental procedure 32

Intermediate compounds according to Formula (XVII) can be prepared by reacting an intermediate of Formula (XXXII) under conditions that are known to those skilled in the art and can be realized for example with oxone, osmium tetroxide. The process may be carried out optionally in a solvent such as 1,4-dioxane, water and generally at temperatures between about -100°C and about 100°C. A summary of such methods is found in "Comprehensive Organic Transformations", VCH Publishers, (1989), R.C.Larock, pp.595-596. This is illustrated in reaction scheme (32) wherein all variables are defined as mentioned hereabove.

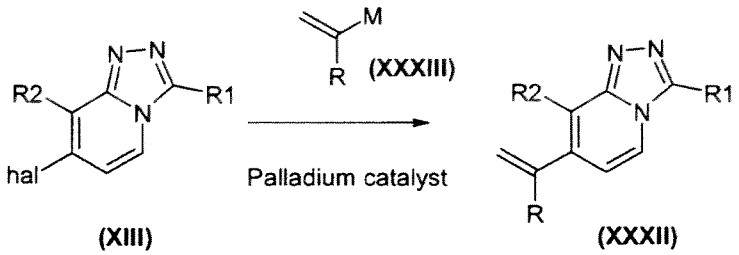
Reaction Scheme 32



Experimental procedure 33

Intermediate compounds according to Formula (XXXII) can be prepared by coupling reactions of an intermediate of Formula (XIII) with a compound of Formula (XXXIII) under conditions that are known to those skilled in the art. This is illustrated in reaction scheme (33) wherein all variables are defined as mentioned hereabove, wherein M is trialkyltin, boronic acid or boronate ester, and a palladium catalyst. The process may be carried out optionally in a solvent such as 1,4-dioxane, water and generally at temperatures between about r.t and about 200°C in the presence of a base.

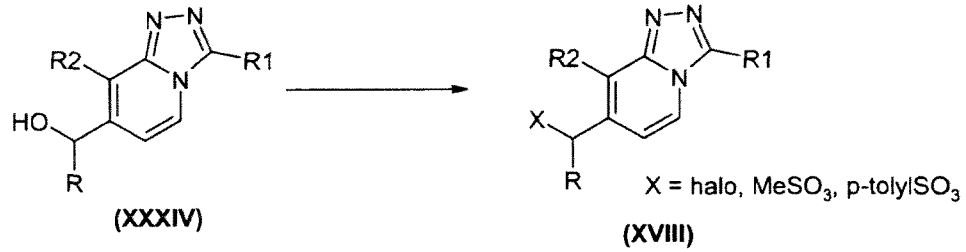
Reaction Scheme 33



Experimental procedure 34

Intermediate compounds according to Formula (XVIII) can be prepared from conversion of the hydroxyl group present in intermediate compound of Formula (XXXIV) into a suitable leaving group such as for example halogen or mesylate conditions that are known to those skilled in the art. The reaction may be performed, for example, by reacting an intermediate compound of Formula (XXXIV) with methyl sulfonic acid chloride in the presence of a base such as triethylamine, pyridine or halogenating reagens such as for example $P(O)Br_3$ in a suitable reaction-inert solvent such as, for example, DCM or DMF or mixtures of both, at a suitable temperature, typically at room temperature, for a suitable period of time that allows the completion of the reaction.

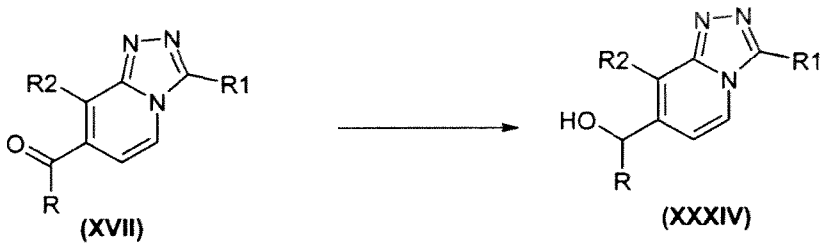
Reaction Scheme 34



Experimental procedure 35

Intermediate compounds according to Formula (XXXIV) can be prepared by reacting an intermediate of Formula (XVII) under conditions that are known to those skilled in the art. This is illustrated in reaction scheme (35) wherein all variables are defined as mentioned hereabove. The reaction may be performed, for example, by reacting intermediate of Formula (XVII) with a reductive reagent such as for example sodium borohydride in a suitable solvent such as for example methanol. The reaction may be performed at a suitable temperature, typically room temperature, for a suitable period of time that allows the completion of the reaction. This is illustrated in reaction scheme (35) wherein all variables are defined as mentioned hereabove

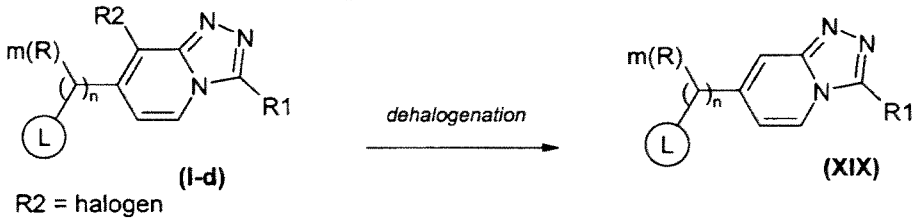
Reaction Scheme 35



Experimental procedure 36

Intermediate compounds of formula (XIX) as described in reaction scheme (11) can also be considered final compounds according to formula (I). The final compounds according to Formula (I-d), wherein n=m=1 and R^2 is halo, can be converted to compounds of formula (XIX) under hydrogenation conditions or hydrogen-metal exchange, according to reaction scheme (36). This reaction is performed in a suitable reaction-inert and aprotic solvent, such as, for example, dichloromethane or 1,2-dichloroethane, stirring the reaction mixture at a suitable temperature, typically at room temperature, for the required time to achieve completion of the reaction, usually 1 hour. In reaction scheme (36), all other variables are defined as in Formula (I).

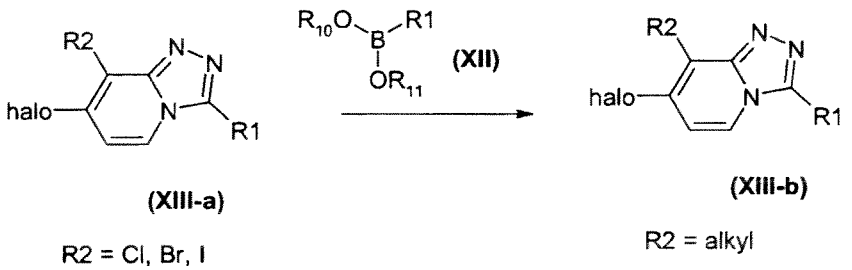
Reaction Scheme 36



Experimental procedure 37

The intermediate compounds according to Formula (XIII), wherein R2 is an alkyl, hereby named (XIII-b) can be prepared by reacting an intermediate compound of Formula (XIII) wherein R2 is an halo, hereby named (XIII-a) with a compound of Formula (XII) according to reaction scheme (37), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, 1,4-dioxane or mixtures of inert solvents such as, for example, 1,4-dioxane/DMF, in the presence of a suitable base, such as, for example, aqueous $NaHCO_3$ or Na_2CO_3, a Pd-complex catalyst such as, for example, $Pd(PPh_3)_4$ under thermal conditions such as, for example, heating the reaction mixture at 150 °C under microwave irradiation, for example for 10 minutes. In reaction scheme (6), all variables are defined as in Formula (I) and halo is a group suitable for Pd mediated coupling with boronic acids or boronic esters, such as, for example chloro, bromo or iodo. R^{10} and R^{11} may be hydrogen or alkyl, or may be taken together to form for example a bivalent radical of formula $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-C(CH_3)_2C(CH_3)_2-$.

Reaction Scheme 37

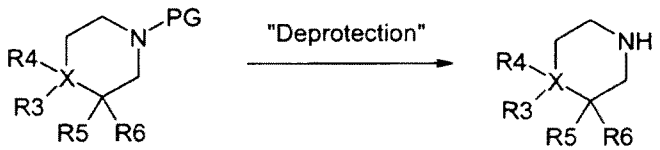


Experimental procedure 37

Intermediate compounds of Formula (XIV) can be prepared by deprotection of the nitrogen atom in an intermediate compound of formula (XXXV), wherein PG represents a suitable protecting group for the nitrogen atom, such as for example tert-butoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, benzyl and methyl, according to reaction scheme (37) applying art known procedures. For example, when PG represents

benzyl, then the deprotection reaction may be performed in a suitable reaction inert solvent, such as for example an alcohol, i.e. methanol, and 1,4-cyclohexadiene, in the presence of a suitable catalyst, such as for example palladium on charcoal, at a moderately high temperature such as, for example, 100 °C in a sealed vessel. Alternatively, when PG represents an alkyloxycarbonyl group, the deprotection reaction can be performed by reaction with a suitable acid, such as for example hydrochloric acid, in a suitable reaction-inert solvent, such as for example 1,4-dioxane at a moderately high temperature, such as for example reflux temperature. In reaction scheme (37), all variables are defined as in formula (I).

Reaction Scheme 37



(XXXV) **(XIV)**

Experimental procedure 38

Intermediate compounds of Formula (XIV) wherein R^4 is CF_3, X is C and R^5 and R^6 are H, hereby named (XIV-a), can be prepared by reacting an intermediate of Formula (XXXVI) according to reaction scheme (38), under conditions that are known to those skilled in the art [*Bioorganic & Medicinal Chemistry* **2006**, *14*, 2620–2626] by reduction of the phthalimide function with a reductive agent such as for example borane-THF in a suitable solvent such as, for example, THF, at a suitable temperature, typically at reflux, for a suitable period of time that allows the completion of the reaction. In reaction scheme (38), R^3 is as defined in Formula (I).

Reaction Scheme 38



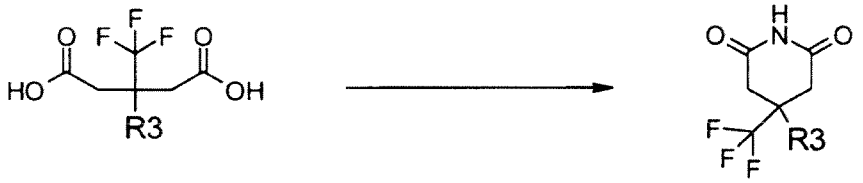
(XXXVI) **(XIV-a)**

Experimental procedure 39

Intermediate compounds of Formula (XXXVI) can be prepared by reacting an intermediate of Formula (XXXVII) according to reaction scheme (39), under conditions that are known to those skilled in the art [*Journal of Antibiotics* **1995**, *48*(10), 1179-81] by cyclization of the corresponding carboxylic acid (XXXVII) by reaction with acetic anhydride and urea at reflux for a suitable period of time that

allows the completion of the reaction. In reaction scheme (39), R^3 is as defined in Formula (I)

Reaction Scheme 39

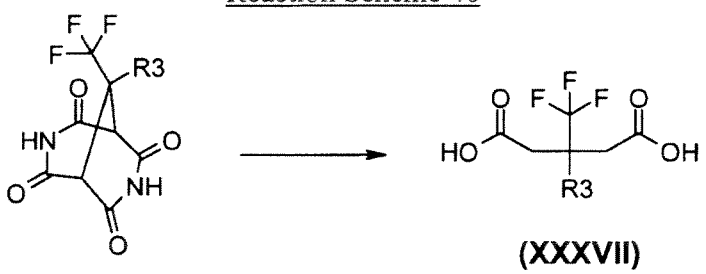


(XXXVIII) **(XXXVI)**

Experimental procedure 40

Intermediate compounds according to Formula (XXXVII) can be prepared by hydrolysis of an intermediate of formula (XXXVIII) according to reaction scheme (39), under conditions that are known to those skilled in the art [Journal of American Chem. Soc. **1958**, 80, 3915-3923]. The hydrolysis of intermediate of Formula (XXXVIII) may be performed in alkaline solution such as for example sodium hydroxide followed by a brief period of reflux in acid solution such as for example sulfuric acid. Both reactions are heated typically at reflux, for a suitable period of time that allows the completion of the reaction. In reaction scheme (40), R^3 is as defined in Formula (I).

Reaction Scheme 40

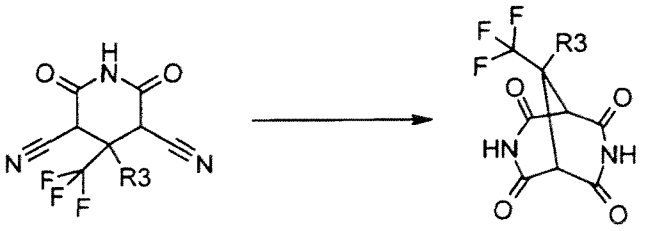


(XXXVIII) **(XXXVII)**

Experimental procedure 41

Intermediate compounds according to Formula (XXXVIII) can be prepared by reaction of an intermediate of formula (XXXIX) according to reaction scheme (41), under conditions that are known to those skilled in the art [*J. Am. Chem. Soc.* **1958**, *80*, 3915-3923], by hydrolysis of an intermediate of Formula (XXXVIII) in the presence of suitable acids such as a mixture of sulfuric acid, acetic acid and water at a suitable temperature, typically at reflux, for a suitable period of time that allows the completion of the reaction. In reaction scheme (41), R^3 is as defined in Formula (I).

Reaction Scheme 41

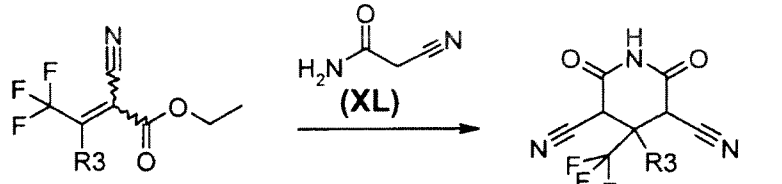


(XXXIX) (XXXVIII)

Experimental procedure 41a

Intermediate compounds according to Formula (XXXVIII) can be prepared from intermediate compound (XXXIX) according to reaction scheme (41a), by reacting intermediate of Formula (XXXIX) with cyanoacetamide (XL) under conditions that are known to those skilled in the art [*J. Am. Chem. Soc.* **1958**, *80*, 3915-3923]. The reaction may be performed, for example, in the presence of a suitable base such as for example sodium ethoxyde, in a suitable reaction-inert solvent such as, for example, EtOH, at a suitable temperature, typically r.t., for a suitable period of time that allows the completion of the reaction. In reaction scheme (41a), R^3 is as defined in Formula (I).

Reaction Scheme 41a

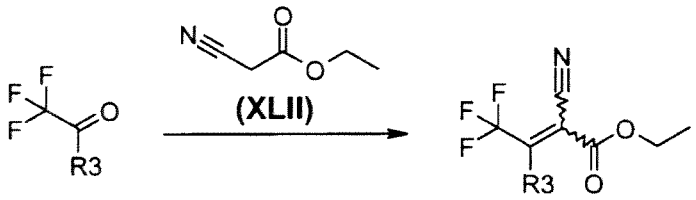


(XXXIX) (XL) (XXXVIII)

Experimental procedure 42

Intermediate compounds according to Formula (XXXIX) can be prepared by reacting an intermediate of Formula (XLI) with cyanoacetate (XLII) according to reaction scheme (42), under Knoevenagel condensation conditions that are known to those skilled in the art [*J. Am. Chem. Soc.* **1958**, *80*, 3915-3923]. The reaction may be performed, for example, in the presence of titanium tetrachloride, a suitable base such as for example pyridine and a suitable reaction-inert solvent such as, for example, DCM, at a suitable temperature, typically at r.t., for a suitable period of time that allows the completion of the reaction. In reaction scheme (42), R^3 is as defined in Formula (I).

Reaction Scheme 42



The starting materials according to Formulae (IV), (V), (VI), (IX), (XII), (XIV), (XVI), (XXII), (XXVIII), XXIX), (XXX), (XXXI), (XXXIII), (XL), (XLI), (XXXIII), XL, (XLI) or (XLII) are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known to those skilled in the art.

In order to obtain the HCl salts forms of the compounds, several procedures known to those skilled in the art can be used. In a typical procedure, for example, the free base can be dissolved in DIPE or Et_2O and subsequently, a 6N HCl solution in 2-propanol or a 1 N HCl solution in Et_2O can be added dropwise. The mixture typically is stirred for 10 min after which the product can be filtered off. The HCl salt is usually dried *in vacuo*.

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

The compounds provided in this invention are positive allosteric modulators (PAMs) of metabotropic glutamate receptors, in particular they are positive 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 glutamate or an agonist of mGluR2, the compounds of this invention increase the mGluR2 response. The compounds provided in this invention are expected to have their effect at mGluR2 by virtue of their ability to increase the response of such receptors to glutamate or mGluR2 agonists, enhancing the response of the receptor.

As used herein, the term "treatment" is intended to refer to all processes, wherein there may be a slowing, interrupting, arresting or stopping of the progression of a disease, 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), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, for use as a medicament.

The invention also relates to the use of a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates 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), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates 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, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of allosteric modulators of mGluR2, in particular positive allosteric modulators thereof.

The present invention also relates to the use of a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates 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 positive allosteric modulators thereof.

The present invention also relates to a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, or a pharmaceutical composition according to the invention for use in the treatmen, 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 positive allosteric modulators of mGluR2.

The present invention also relates to a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates 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 or which is altered or facilitated by the neuromodulatory effect of positive allosteric modulators of mGluR2.

Also, the present invention relates to the use of a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates 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 positive allosteric modulators of mGluR2.

In particular, the neurological and psychiatric disorders associated with glutamate dysfunction, include one or more of the following conditions or diseases: acute neurological and psychiatric disorders such as, for example, cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, dementia (including AIDS-induced dementia), Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, migraine (including migraine headache), urinary incontinence, substance dependence/abuse, substance withdrawal (including substances such as, for example, opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), psychosis, schizophrenia, anxiety (including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder), mood disorders (including depression, major depressive disorder, treatment resistant depression, mania, bipolar disorders, such as bipolar mania), posttraumatic stress disorder, trigeminal neuralgia, hearing loss, tinnitus, macular degeneration of the eye, emesis, brain edema, pain (including acute and chronic states, severe pain, intractable pain, neuropathic pain, and post-traumatic pain), tardive dyskinesia, sleep disorders (including narcolepsy), attention deficit/hyperactivity disorder, and conduct disorder.

In particular, the condition or disease is a central nervous system disorder selected from the group of anxiety disorders, psychotic disorders, personality disorders, substance-related disorders, eating disorders, mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, neurotoxicity and ischemia.

Preferably, the central nervous system disorder is an anxiety disorder, selected from the group of agoraphobia, generalized anxiety disorder (GAD), mixed anxiety and depression, obsessive-compulsive disorder (OCD), panic disorder, posttraumatic stress disorder (PTSD), social phobia and other phobias.

Preferably, the central nervous system disorder is a psychotic disorder selected from the group of schizophrenia, delusional disorder, schizoaffective disorder, schizophreniform disorder and substance-induced psychotic disorder.

Preferably, the central nervous system disorder is a personality disorder selected from the group of obsessive-compulsive personality disorder and schizoid, schizotypal disorder.

Preferably, the central nervous system disorder is a substance abuse or substance-related disorder selected from the group of alcohol abuse, alcohol dependence, alcohol withdrawal, alcohol withdrawal delirium, alcohol-induced psychotic disorder, amphetamine dependence, amphetamine withdrawal, cocaine dependence, cocaine withdrawal, nicotine dependence, nicotine withdrawal, opioid dependence and opioid withdrawal.

Preferably, the central nervous system disorder is an eating disorder selected from the group of anorexia nervosa and bulimia nervosa.

Preferably, the central nervous system disorder is a mood disorder selected from the group of bipolar disorders (I & II), cyclothymic disorder, depression, dysthymic disorder, major depressive disorder, treatment resistant depression, bipolar depression, and substance-induced mood disorder.

Preferably, the central nervous system disorder is migraine.

Preferably, the central nervous system disorder is epilepsy or a convulsive disorder selected from the group of generalized nonconvulsive epilepsy, generalized convulsive epilepsy, petit mal status epilepticus, grand mal status epilepticus, partial epilepsy with or without impairment of consciousness, infantile spasms, epilepsy partialis continua, and other forms of epilepsy.

Preferably, the central nervous system disorder is attention-deficit/hyperactivity disorder.

Preferably, the central nervous system disorder is a cognitive disorder selected from the group of delirium, substance-induced persisting delirium, dementia, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's

disease, dementia of the Alzheimer's type, behavioral and psychological symptoms of dementia, substance-induced persisting dementia and mild cognitive impairment.

Of the disorders mentioned above, the treatment of psychosis, such as schizophrenia, behavioral and psychological symptoms of dementia, major depressive disorder, treatment resistant depression, bipolar depression, anxiety, depression, generalised anxiety disorder, post-traumatic stress disorder, bipolar mania, substance abuse and mixed anxiety and depression, are or particular importance.

Of the disorders mentioned above, the treatment of anxiety, schizophrenia, migraine, depression, and epilepsy are of particular importance.

At present, 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 medical and scientific progresses.

Therefore, the invention also relates to a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates 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), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates 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), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates 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), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, for the manufacture of a medicament for the treatment or prevention of any one of the disease conditions mentioned hereinbefore.

The invention also relates to the use of a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid

or base addition salts and the solvates thereof, for the manufacture of a medicament for the treatment of any one of the disease conditions mentioned hereinbefore.

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

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

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 and a pharmaceutically acceptable addition salt or 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 compound according to the invention to a patient in need thereof.

One skilled in the art will recognize that a therapeutically effective amount of the PAMs 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 PAM 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 PAM at the treatment site in the range of 0.5 nM to 200 μM, and more usually 5 nM to 50 μM. 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.

Because such positive allosteric modulators of mGluR2, including compounds of Formula (I), enhance the response of mGluR2 to glutamate, it is an advantage that the present methods utilize endogenous glutamate.

Because positive allosteric modulators of mGluR2, including compounds of Formula (I), enhance the response of mGluR2 to agonists, it is understood that the present invention extends to the treatment of neurological and psychiatric disorders associated with glutamate dysfunction by administering an effective amount of a positive allosteric modulator of mGluR2, including compounds of Formula (I), in combination with an mGluR2 agonist. Examples of mGluR2 agonists include, for example, LY-379268; DCG-IV; LY-354740; LY-404039; LY-544344; LY-2140023; LY-181837; LY-389795; LY-446433; LY-450477; talaglumetad; MGS0028; MGS0039; (-)-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylate; (+)-4-amino-2-sulfonylbicyclo[3.1.0]hexane-4,6-dicarboxylic acid; (+)-2-amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; 1S,2R,5S,6S-2-amino-6-fluoro-4-oxobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; 1S,2R,4S,5S,6S-2-amino-6-fluoro-4-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid; 1S,2R,3R,5S,6S-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; 1S,2R,3S,5S,6S-2-amino-6-fluoro-3-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid; (+)-4-amino-2-sulfonylbicyclo[3.1.0]hexane-4,6-dicarboxylic acid; (+)-2-amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; 1S,2R,5S,6S-2-amino-6-fluoro-4-oxobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; 1S,2R,4S,5S,6S-2-amino-6-fluoro-4-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid; 1S,2R,3R,5S,6S-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; or 1S,2R,3S,5S,6S-2-amino-6-fluoro-3-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid. More preferable mGluR2 agonists include LY-379268; DCG-IV; LY-354740; LY-404039; LY-544344; or LY-2140023.

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.

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), 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 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 (18^{th} 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.

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

In order to enhance the solubility and/or the stability of the compounds of Formula (I) in pharmaceutical compositions, it can be advantageous to employ α-, β- or γ–cyclodextrins or their derivatives, in particular hydroxyalkyl substituted

cyclodextrins, e.g. 2-hydroxypropyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds according to the invention in pharmaceutical compositions.

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

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

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 mGluR2 orthosteric agonist. 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, a pharmaceutically acceptable salt thereof or a solvate thereof, and (b) a mGluR2 orthosteric agonist, 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 positive mGluR2 allosteric modulators. 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.

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.

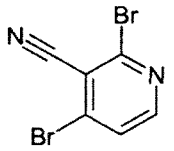
Hereinafter, "CI" means chemical ionisation; "DAD" means diode-array detector; "THF" means tetrahydrofuran; "DIPE" means diisopropylether; "DMF" means *N*,*N*-dimethylformamide; "EtOAc" means ethyl acetate; "DCM" means dichloromethane; "DCE" means dichloroethane; "BINAP" means 1,1'-[1,1'-binaphthalene]-2,2'-diylbis[1,1-diphenyl-phosphine]; "DBU" means 1,8-diaza-7-bicyclo[5.4.0]undecene; "DIPEA" means *N*,*N*-diisopropylethylamine; "l" or "L" means liter; "LRMS" means low-resolution mass spectrometry/spectra; "HRMS" means high-resolution mass spectra/spectrometry; "NH_4Ac" means ammonium acetate; "NH_4OH" means ammonium hydroxide; "$NaHCO_3$" means sodium hydrogencarbonate; "Et_2O" means diethyl ether; "$MgSO_4$" means magnesium sulphate; "EtOH" means ethanol; "ES" means electrospray; "Na_2SO_4" means sodium sulphate; "CH_3CN" means acetonitrile; "NaH" means sodium hydride; "MeOH" means methanol; "NH_3" means ammonia; "$Na_2S_2O_3$" means sodium thiosulphate; "AcOH" means acetic acid; "Et_3N" or "TEA" mean triethylamine; "NH_4Cl" means ammonium chloride; "K_2CO_3" means potassium carbonate; "$Pd(PPh_3)_4$" means tetrakis(triphenylphosphine)palladium(0); "eq" means equivalent; "S-Phos" means dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine; "X-Phos" means dicyclohexyl[2',4',6'-tris(1-methylethyl)[1,1'-biphenyl]-2-yl]phosphine; "r.t." means room temperature; "mp" means melting point; "min" means minutes; "h" means hours; "s" means second(s); "TEA" means triethylamine; "TOF" means time of flight; "SFC" means supercritical fluid chromatography. Sep-Pak® Silica is a cartridge with unbonded, highly-activated silica stationary phase; Amberlyst® 15 is a acidic cation exchange resin containing sulfonic acid groups; H-Cube® is a continuous flow microfluidic hydrogenation reactor.

Microwave assisted reactions were performed in a single-mode reactor: Initiator™ 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. Flash column chromatography was performed on silica gel, particle size 60 Å, mesh = 230-400 (Merck) using standard techniques. Automated flash column chromatography was performed using ready-to-connect cartridges from Merck, on irregular silica gel, particle size 15-40 μm (normal phase disposable flash columns) on a SPOT or FLASH system from Armen Instrument.

Description 1

2,4-Dibromo-nicotinonitrile (D1)

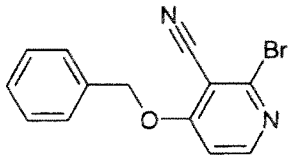


To a solution of commercially available 4-methoxy-2-oxo-1,2-dihydro-3-pyridinecarbonitrile (95.47 g, 333 mmol) [C.A.S. 21642-98-8] in CH_3CN (670 ml), was added phosphorus(V) oxybromide (250 g, 166 mmol) portionwise. The resulting suspension was heated at 60 °C for 16 h. After cooling to r.t., the reaction mixture was diluted with EtOAc and washed with water. The organic layer was separated and washed with $NaHCO_3$ (aqueous sat. solution), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product thus obtained was triturated with diisopropyl ether to yield intermediate compound **D1** (34.5 g, 79%) as a white solid.

GCMS (EI): MW (theor): 262; [M-2H$^+$]: 260; RT (min): 9.67.

Description 2

4-Benzyloxy-2-bromo-nicotinonitrile (D2)

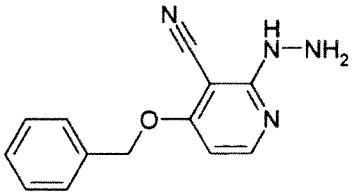


To a suspension of NaH (1.756 g, 45.818 mmol, mineral oil 60%) in DMF (200 ml) cooled at 0 °C, was added benzyl alcohol (4.542 g, 42 mmol). The resulting mixture was stirred for 5 min. Then compound **D1** (10 g, 38.18 mmol) was quickly added. The resulting reaction mixture was gradually warmed to r.t. and stirred for 1 h. The reaction mixture was quenched with NH_4Cl (aqueous sat. solution), diluted with H_2O and the resulting mixture was extracted with Et_2O. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column

chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 1% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D2** (9.2 g, 83%).

Description 3

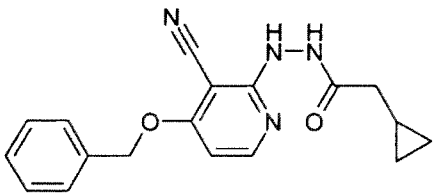
4-Benzyloxy-2-hydrazino-nicotinonitrile (D3)



To a solution of compound **D2** (1.2 g, 4.15 mmol) in THF (12 ml) was added hydrazine monohydrate (0.416 g, 8.301 mmol). The reaction mixture was heated at 150 °C under microwave irradiation for 1 min. After cooling, additional hydrazine monohydrate (1 eq) was added to the reaction mixture, which was then heated at 150 °C under microwave irradiation for 0.5 min. After cooling, the reaction mixture was concentrated *in vacuo*. The residue thus obtained was triturated with Et_2O to yield intermediate compound **D3** (0.95 g, 95%).

Description 4

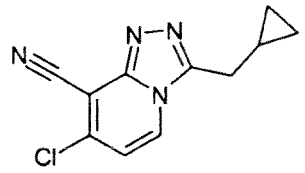
N'-[3-cyano-4-(benzyloxy)pyridin-2-yl]-2-cyclopropylacetohydrazide (D4)



To a solution of **D3** (4.099 g, 17.06 mmol) in dry DCM (112 ml) was added Et_3N (2.76 g, 27.294 mmol) and cyclopropyl-acetyl chloride (3.438 g, 29 mmol). The resulting reaction mixture was stirred at r.t. for 20 min. The mixture was concentrated *in vacuo* to yield compound **D4** (5 g, 91%).

Description 5

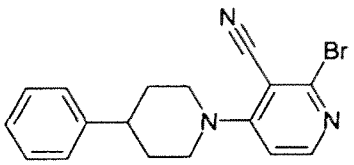
7-Chloro-3-(cyclopropylmethyl)[1,2,4]triazolo[4,3-a]pyridine-8-carbonitrile (D5)



A solution of **D4** (1.4 g, 4.343 mmol) and phosphorous (V) oxychloride (0.810 ml, 8.686 mmol) in DCE (15 ml) was heated at 150 °C under microwave irradiation for 5 min. After cooling, the mixture was diluted with DCM and washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 2% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D5** (0.650 g, 64%).

Description 6

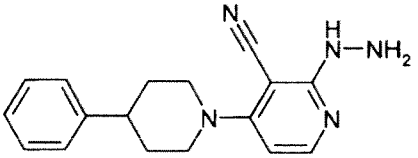
2-Bromo-3-cyano-4-(4-phenylpiperidinyl)pyridine (D6)



To a suspension of NaH (0.146 g, 3.818 mmol, 60%) in DMF (20 ml) cooled at 0 °C was added 4-phenylpiperidine (0.616 g, 3.818 mmol). The resulting mixture was stirred for 5 min., then compound **D1** (1 g, 3.016 mmol) was added. The resulting reaction mixture was stirred for 1 h. The reaction mixture was then quenched with NH_4Cl (aqueous sat. solution) and extracted with Et_2O. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH gradient as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D6** (0.985 g, 75%).

Description 7

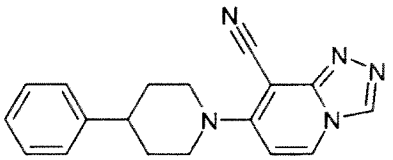
[3-Cyano-4-(4-phenylpiperidinyl)pyridin-2-yl]-hydrazine (D7)



To a solution of compound **D6** (0.5 mg, 1.461 mmol) in THF (4 ml), was added hydrazine monohydrate (0.366 g, 7.305 mmol). The reaction mixture was heated at 160 °C under microwave irradiation for 15 min. After cooling, the resulting mixture was concentrated *in vacuo*. The residue thus obtained was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 3% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D7** (0.380 g, 89%) as a white solid.

Description 8

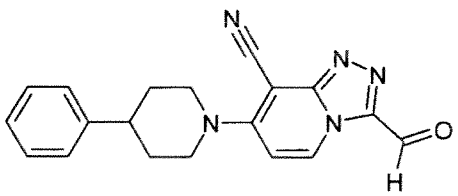
8-Cyano-7-(4-phenylpiperidinyl)[1,2,4]triazolo[4,3-a]pyridine (D8)



D7 (1 g, 3.409 mmol) and triethylorthoformate (7.577 g, 51.13 mmol) in xylene (25 ml) were heated in a sealed tube at 180 °C for 1 h. After cooling, the resulting mixture was concentrated *in vacuo*. The residue thus obtained was triturated with Et_2O to yield compound **D8** (0.932 g, 90%).

Description 9

8-Cyano-3-formyl-7-(4-phenylpiperidinyl)[1,2,4]triazolo[4,3-a]pyridine (D9)

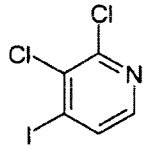


D8 (0.25 g, 0.824 mmol) and phosphorus (V) oxychloride (0.116 ml, 1.236 mmol) in DMF (5 ml) was heated in a sealed tube at 80 °C for 4 h. After cooling, the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 3% as eluent). The desired

fractions were collected and concentrated *in vacuo* to yield intermediate compound **D9** (0.070 g, 26%).

Description 10

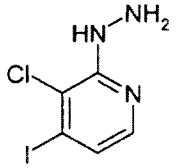
2,3-Dichloro-4-iodo-pyridine (D10)



To a solution of *n*-butyllithium (27.6 ml, 69 mmol, 2.5 M in hexanes) in dry Et_2O (150 ml) cooled at –78 °C, under a nitrogen atmosphere, was added 2,2,6,6-tetramethylpiperidine (11.64 ml, 69 mmol), dropwise. The resulting reaction mixture was stirred at –78 °C for 10 min., and then a solution of 2,3-dichloropyridine (10 g, 67.57 mmol) in dry THF (75 ml) was added dropwise. The mixture was stirred at –78 °C for 30 min. and then a solution of iodine (25.38 g, 100 mmol) in dry THF (75 ml) was added. The mixture was allowed to warm to r.t. overnight, quenched with $Na_2S_2O_3$ (aqueous sat. solution) and extracted twice with EtOAc. The combined organic extracts were washed with $NaHCO_3$ (aqueous sat. solution), dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was precipitated with heptane, filtered off and dried to yield intermediate compound **D10** (8.21 g, 44%) as a pale cream solid.

Description 11

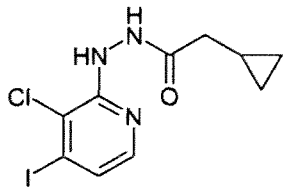
(3-Chloro-4-iodo-pyridin-2-yl)hydrazine (D11)



To a solution of compound **D10** (8 g, 29.21 mmol) in 1,4-dioxane (450 ml), was added hydrazine monohydrate (14.169 ml, 175.255 mmol). The reaction mixture was heated in a sealed tube at 70 °C for 16 h. After cooling, NH_4OH (32% aqueous solution) was added and the resulting mixture was concentrated *in vacuo*. The white solid residue thus obtained was taken up in EtOH. The suspension thus obtained was heated and then filtered off and the filtered solution cooled to r.t.. The precipitate formed was filtered off and then the filtrate concentrated *in vacuo* to yield intermediate compound **D11** (2.67 g, 52%) as a white solid.

Description 12

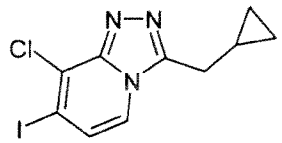
N'-(3-chloro-4-iodo-pyridin-2-yl)-2-cyclopropylacetohydrazide (D12)



To a solution of **D11** (0.73 g, 2.709 mmol) in dry DCM (8 ml), cooled at 0 °C, was added Et_3N (0.562 ml, 4.064 mmol) and cyclopropyl-acetyl chloride (0.385 g, 3.251 mmol). The resulting reaction mixture was stirred at r.t. for 16 h and then $NaHCO_3$ (aqueous sat. solution) was added. The resulting solution was extracted with DCM. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to yield intermediate compound **D12** (0.94 g, 99%).

Description 13

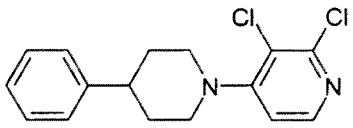
8-Chloro-3-cyclopropylmethyl-7-iodo[1,2,4]triazolo[4,3-a]pyridine (D13)



D12 (0.74 g, 2.389 mmol) was heated at 160 °C for 40 min. After cooling, the brown gum thus obtained was triturated with DIPE yielding intermediate compound **D13** (0.74 g, 93%).

Description 14

2,3-Dichloro-4-(4-phenyl-piperidin-1-yl)pyridine (D14)

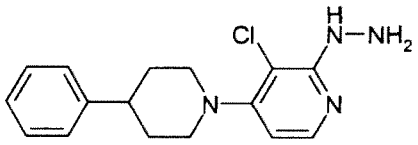


A mixture of **D10** (4 g, 14.605 mmol), 4-phenylpiperidine (3.532 g, 21.907 mmol) and DIPEA (5.088 ml, 29.209 mmol) in CH_3CN (150 ml) was heated in a sealed tube at 110 °C for 16 h. The mixture was then treated with $NaHCO_3$ (aqueous sat. solution). The resulting mixture was extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH/EtOAc gradient as

eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D14** (2.32 g, 52%) as a white solid.

Description 15

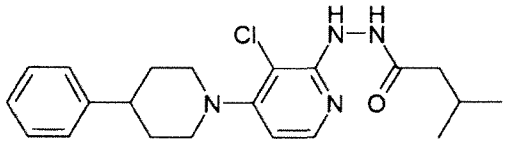
3-chloro-2-hydrazino-4-(4-phenylpiperidin-1-yl)pyridine (D15)



To a suspension of compound **D14** (0.25 g, 0.814 mmol) in 1,4-dioxane (3 ml) was added hydrazine monohydrate (0.789 ml, 16.275 mmol). The reaction mixture was heated at 160 °C under microwave irradiation for 30 min. Then, after cooling, the solvent was evaporated *in vacuo* and the residue obtained was taken up in DCM. The resulting solution was washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to yield intermediate compound **D15** (0.244 g, 99%).

Description 16

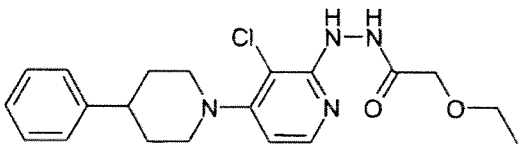
N'-[3-chloro-4-(4-phenylpiperidin-1-yl)pyridin-2-yl]-3-methylbutanohydrazide (D16)



To a solution of **D15** (0.6 g, 1.981 mmol) in dry DCE (10 ml) was added Et_3N (0.442 ml, 3.17 mmol) and isovaleryl chloride [C.A.S. 108-12-3] (0.311 ml, 2.576 mmol). The resulting reaction mixture was stirred at r.t. for 1 min. The mixture was concentrated *in vacuo* to yield compound **D16** (0.7 g, 91%).

Description 17

N'-[3-chloro-4-(4-phenylpiperidin-1-yl)pyridine-2-yl]-2-ethoxyacetohydrazide (D17)

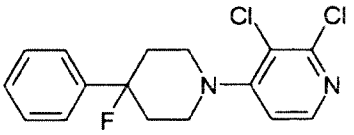


To a solution of **D15** (0.497 g, 1.643 mmol) in dry DCM (10 ml) were added Et_3N (0.366 ml, 2.629 mmol) and ethoxyacetyl chloride [C.A.S. 14077-58-8] (0.282 g, 2.3

mmol). The resulting reaction mixture was stirred at r.t. for 1 h. The mixture was then concentrated *in vacuo* to yield intermediate compound **D17** (0.580 g, 91%).

Description 18

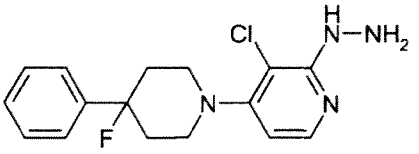
2,3-Dichloro-4-(4-fluoro-4-phenylpiperidin-1-yl)pyridine (D18)



A mixture of **D10** (2g, 7.302 mmol), 4-fluoro-4-phenylpiperidine hydrochloride (2.048 g, 9.493 mmol) [C.A.S. 1056382-25-2] and DIPEA (5.055 ml, 29.209 mmol) in CH_3CN (10 ml) was heated in a sealed tube at 110 °C for 16 h. The mixture was then treated with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; Heptane/DCM from 4:1 up to 1:4 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D18** (0.88 g, 37%) as a white solid.

Description 19

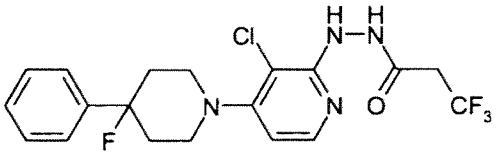
3-Chloro-4-(4-fluoro-4-phenylpiperidin-1-yl)-2-hydrazinopiridine (D19)



To a suspension of compound **D18** (0.966 g, 2.97 mmol) in EtOH (6 ml), was added hydrazine monohydrate (2.882 ml, 59.407 mmol). The reaction mixture was heated under microwave irradiation at 160 °C for 20 min. After cooling, the solvent was evaporated *in vacuo* and the residue thus obtained was taken up in DCM. The resulting solution was washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue thus obtained was triturated with Et_2O to yield intermediate compound **D19** (0.8 g, 84%) as a white solid.

Description 20

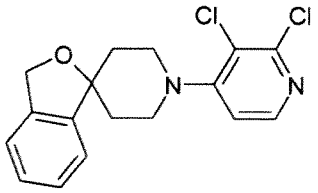
N'-[3-chloro-4-(4-fluoro-4-phenylpiperidin-1-yl)pyridin-2-yl]-3,3,3-trifluoropropanohydrazide (D20)



To a solution of **D19** (2.040 g, 6.359 mmol) in dry DCM (30 ml) cooled at 0 °C, were added Et_3N (1.418 ml, 10.175 mmol) and 3,3,3-trifluoropropionyl chloride [C.A.S. 41463-83-6] (1.035 ml, 8.267 mmol). The resulting reaction mixture was gradually warmed to r.t. and stirred for 1 h. $NaHCO_3$ (aqueous sat. solution) was added and the resulting solution was then extracted with DCM. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to yield intermediate compound **D20** (2.72 g, 99%).

Description 21

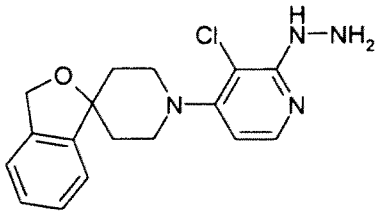
1'-(2,3-dichloropyridin-4-yl)-3*H*-spiro[2-benzofuran-1,4'-piperidine] (D21)



A mixture of **D10** (1 g, 3.655 mmol), spiro[isobenzofuran-1(3H),4'-piperidine], hydrochloride [CAS 37663-44-8] (0.83 g, 4.386 mmol) and DIPEA (1.273 ml, 7.309 mmol) in CH_3CN (9 ml) was heated in a sealed tube at 110 °C for 16 h. The mixture was then treated with $NaHCO_3$ (aqueous sat. solution) and extrated with EtOAc. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/EtOAc up to 2% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D21** (0.199 g, 16%) as a white solid. M.P. 160.8°C

Description 22

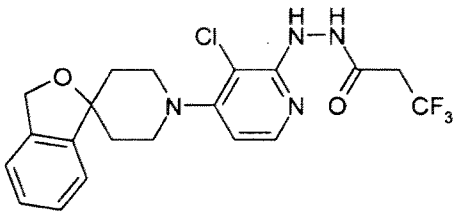
1'-(3-chloro-2-hydrazinopyridin-4-yl)-3*H*-spiro[2-benzofuran-1,4'-piperidine] (D22)



To a suspension of compound **D21** (0.199 g, 0.594 mmol) in EtOH (4 ml), was added hydrazine monohydrate (0.588 ml, 11.872 mmol). The reaction mixture was heated at 160 °C under microwave irradiation for 20 min. Then, additional hydrazine monohydrate (20 eq) was added to the reaction mixture, which was then subjected to microwave irradiation at 170 °C for 30 min. Upon cooling, a precipitate developed, which was filtered off and $NaHCO_3$ (aqueous sat. solution) was added to the filtrate. The resulting solution was extracted with DCM. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to yield intermediate compound **D22** (0.177 g, 90%).

Description 23

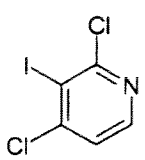
N'-[3-chloro-4-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)pyridin-2-yl]-2,2,2-trifluoroacetohydrazide (D23)



To a solution of **D22** (0.177 g, 0.535 mmol) in dry DCM (3 ml) cooled at 0 °C was added Et_3N (0.112 g, 0.803 mmol) and 3,3,3-trifluoropropionyl chloride [C.A.S. 41463-83-6] (0.087 ml, 0.696 mmol). The resulting reaction mixture was gradually warmed to r.t. and stirred for 2 h. The mixture was concentrated *in vacuo*. The residue thus obtained was triturated with Et_2O to yield intermediate compound **D23** (0.369 g) as a crude material, which was used without further purification.

Description 24

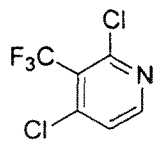
2,4-Dichloro-3-iodo-pyridine (D24)



To a solution of 2,4-dichloropyridine (5.2 g, 35.137 mmol) and diisopropylamine (3.911 g, 38.651 mmol) in dry THF (40 ml) cooled at –78 °C under a nitrogen atmosphere, was added *n*-butyllithium (24.157 ml, 38.651 mmol, 1.6 M in hexanes) dropwise. The resulting reaction mixture was stirred at –78 °C for 45 min. and then a solution of iodine (9.81 g, 38.651 mmol) in dry THF (20 ml) was added dropwise. The mixture was stirred at –78 °C for 1 h., allowed to warm to r.t., diluted with EtOAc and quenched with NH_4Cl (aqueous sat. solution) and $Na_2S_2O_3$ (aqueous sat. solution). The organic layer was separated, washed with $NaHCO_3$ (aqueous sat. solution), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; Heptane/DCM up to 20% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D24** (7.8 g, 81%).

Description 25

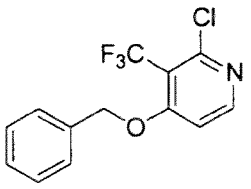
2,4-Dichloro-3-trifluoromethyl-pyridine (D25)



To a mixture of compound **D24** (2g, 7.302 mmol) in DMF (50 ml) were added fluorosulfonyl-difluoro-acetic acid methyl ester [C.A.S. 680-15-9] (1.858 ml, 14.605 mmol) and copper (I) iodine (2.796. g, 14.605 mmol). The reaction mixture was heated in a sealed tube at 100 °C for 5 h. After cooling, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D25** (1.5 g, 95%).

Description 26

4-Benzyloxy-2-chloro-3-trifluoromethyl-pyridine (D26)

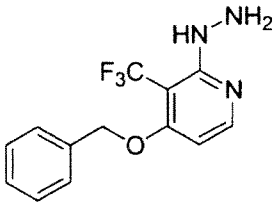


To a suspension of NaH (0.487 g, 12.732 mmol, 60% mineral oil) in DMF (50 ml) cooled at 0 °C, was added benzyl alcohol (1.262 ml, 12.2 mmol). The resulting mixture was stirred for 2 min., then, intermediate compound **D25** (2.5 g, 11.575 mmol) was added. The resulting reaction mixture was gradually warmed to r.t. and stirred for 1 h.

The reaction mixture was quenched with water and extracted with Et_2O. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; Heptane/DCM gradient as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D26** (1.1 g, 33%).

Description 27

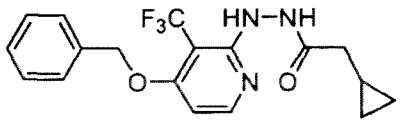
4-(benzyloxy)-2-hydrazino-3-(trifluoromethyl)pyridine (D27)



To a suspension of compound **D26** (1.09 g g, 3.789 mmol) in 1,4-dioxane (9 ml), was added hydrazine monohydrate (3.676 ml, 75.78 mmol). The reaction mixture was heated at 160 °C under microwave irradiation for 30 min. After cooling, the resulting solution was concentrated *in vacuo*. The residue thus obtained was dissolved in DCM and washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo* to yield intermediate compound **D27** (0.890 g, 83%) as a white solid.

Description 28

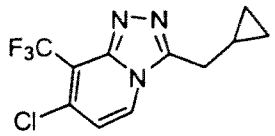
N'-[4-(benzyloxy)-3-(trifluoromethyl)pyridin-2-yl]-2-cyclopropylacetohydrazide (D28)



To a solution of **D27** (0.890 g, 3.142 mmol) in dry DCM (3 ml) was added Et_3N (0.653 ml, 4.713 mmol) and cyclopropyl-acetyl chloride [C.A.S. 543222-65-5] (0.373 g, 3.142 mmol). The resulting reaction mixture was stirred at 0 °C for 20 min. The resulting mixture was then concentrated *in vacuo* to yield intermediate compound **D28** (1.1 g, 96%).

Description 29

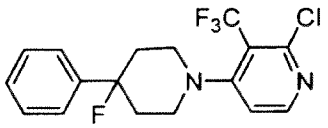
7-Chloro-3-cyclopropylmethyl-8-trifluoromethyl[1,2,4]triazolo[4,3-a]pyridine (D29)



D28 (1.14 g, 1.872 mmol) and phosphorous (V) oxychloride (0.349 g, 3.744 mmol) in CH_3CN (10 ml) were heated at 150 °C under microwave irradiation for 10 min. After cooling, the resulting reaction mixture was diluted with DCM and washed with $NaHCO_3$ (aqueous sat. solution), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 20% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D29** (0.261 g, 51%) as a white solid.

Description 30

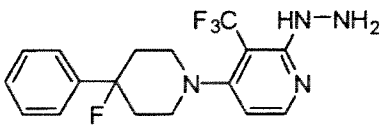
2-Chloro-3-trifluoromethyl-4-(4-Fluoro-4-phenylpiperidinyl)-pyridine (D30)



D25 (0.4 g, 1.852 mmol), 4-fluoro-4-phenylpiperidine hydrochloride [C.A.S. 1056382-25-2] (0.399 g, 1.852 mmol) and *N,N*-DIPEA (0.645 ml, 3.704 mmol) in CH_3CN (4 ml) were heated in a sealed tube at 110 °C for 4 h. The mixture was diluted with EtOAc and washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D30** (0.53 g, 62%).

Description 31

4-(4-fluoro-4-phenylpiperidin-1-yl)-2-hydrazino-3-(trifluoromethyl)pyridine (D31)

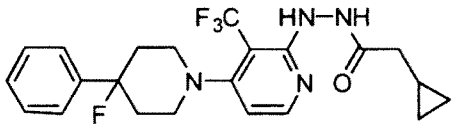


To a suspension of compound **D30** (0.530 g, 1.152 mmol) in THF (10 ml), was added hydrazine monohydrate (0.224 ml, 4.61 mmol). The reaction mixture was heated at 160

°C under microwave irradiation for 45 min. After cooling, the resulting solution was concentrated *in vacuo*. The residue thus obtained was triturated with Et_2O to yield intermediate compound **D31** (0.280 g, 69%) as a white solid.

Description 32

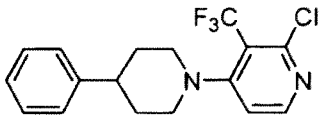
2-cyclopropyl-*N'*-[4-(4-fluoro-4-phenylpiperidin-1-yl)-3-(trifluoromethyl)pyridin-2-yl]acetohydrazide (D32)



To a solution of **D31** (0.29 g, 0.818 mmol) in dry DCM (10 ml) was added Et_3N (0.201 ml, 1.473 mmol) and cyclopropyl-acetyl chloride [C.A.S. 543222-65-5] (0.116 g, 0.982 mmol). The resulting reaction mixture was stirred at r.t. for 20 min. The mixture was then concentrated *in vacuo* to yield intermediate compound **D32** (0.354 g, 99%).

Description 33

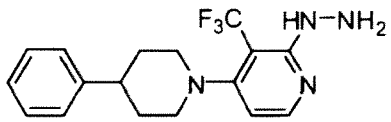
2-Chloro-3-trifluoromethyl-4-(4-phenylpiperidin-1-yl)-pyridine (D33)



To a solution of NaH (0.193 g, 4.834 mmol) in DMF (20 ml) cooled at 0 °C, was added 4-phenylpiperidine (0.844 g, 5.236 mmol) was added. The resulting reaction mixture was stirred at 0 °C for 10 min., before **D25** (0.87 g, 4.028 mmol) was added. The resulting mixture was warmed to r.t. and stirred for 1 h.. The mixture was then quenched with water and extracted with Et_2O. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 2% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D33** (0.73 g, 53%).

Description 34

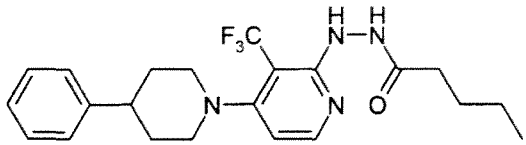
[2-Hydrazino-4-(4-phenylpiperidin-1-yl)-3-(trifluoromethyl)pyridine (D34)



To a suspension of compound **D33** (0.350 g, 1.027 mmol) in THF (6 ml), was added hydrazine monohydrate (0.199 ml, 4.108 mmol). The reaction mixture was heated at 160 °C under microwave irradiation for 45 min. Addition of hydrazine monohydrate (0.199 and 0.249 ml) to the reaction mixture followed by heating at 160 °C under microwave irradiation for 45 min was repeated twice. After cooling, the resulting solution was concentrated *in vacuo* and the residue thus obtained was triturated with Et_2O to yield intermediate compound **D34** (0.320 g, 93%) as a white solid.

Description 35

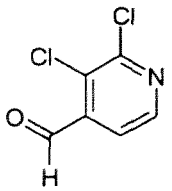
N'-[4-(4-phenylpiperidin-1-yl)-3-(trifluoromethyl)pyridin-2-yl]pentanehydrazide (D35)



To a solution of **D34** (0.350 g, 1.041 mmol) in dry DCM (10 ml) was added Et_3N (0.255 ml, 1.873 mmol) and pentanoyl chloride [C.A.S. 638-29-9] (0.126 ml, 1.041 mmol). The resulting reaction mixture was stirred at r.t. for 10 min. The mixture was then concentrated *in vacuo* to yield intermediate compound **D35** (0.435 g, 99%).

Description 36

2,3-Dichloro-pyridine-4-carbaldehyde (D36) [C.A.S. 884495-41-4]

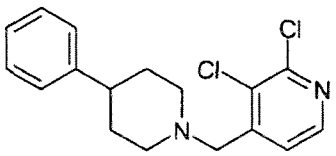


To a solution of 2,3-dichloropyridine [C.A.S. 2402-77-9] (10 g, 67.57 mmol) in dry THF (200 ml) cooled at −78 °C under a nitrogen atmosphere, was added dropwise *n*-butyllithium (37.165 ml, 74 mmol, 2 M in hexanes). The resulting reaction mixture was

stirred at –78 °C for 20 min. Then dry DMF (6.28 ml, 81.087 mmol) was added dropwise. After 15 min. stirring at –78 °C, the mixture was allowed to warm to r.t., quenched with water and extracted with DCM. The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was purified by short open column chromatography (DCM as eluent). The desired product fractions were collected and concentrated *in vacuo* to give a residue that was further purified by column chromatography (silica gel; DCM/heptane up to 50% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D36** (4.15 g, 34.9%) as a white solid.

Description 37

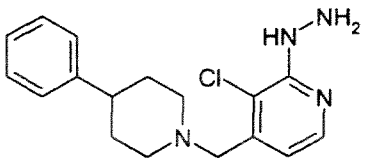
2,3-Dichloro-4-[(4-phenyl-piperidin-1-yl)methyl]pyridine (D37)



To a solution of 4-phenylpiperidine [CAS 771-99-3] (0.155 g, 0.818 mmol) in DCE (27 ml) was added **D36** (1 g, 5.68 mmol), sodium triacetoxy-borohydride (1.325 g, 6.25 mmol) and acetic acid (0.53 ml) and the resulting mixture was stirred at r.t. for 1 day. The reaction mixture was neutralized with $NaHCO_3$ (aqueous sat. solution) and extracted with DCM. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product thus obtained was purified by column chromatography (silica gel; DCM/MeOH up to 3% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D37** (0.582 g, 31.9%) as a white solid.

Description 38

3-Chloro-2-hydrazino-[4-(4-phenylpiperidin-1-yl)methyl]pyridine (D38)

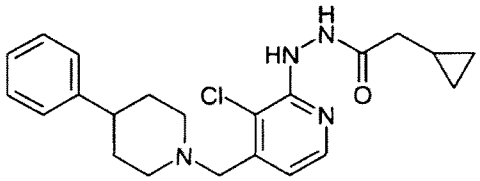


To a suspension of compound **D37** (0.521 g, 1.622 mmol) in EtOH (6 ml), was added hydrazine monohydrate (1.574 ml, 32.448 mmol). The reaction mixture was heated at 160 °C under microwave irradiation for 20 min. After cooling, a white solid

precipitated out. The solid was washed with Et_2O and dissolved in a DCM-7M solution of NH_3 in MeOH mixture. The resulting solution was washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to yield intermediate compound **D38** (0.452 g, 88%) as a white solid.

Description 39

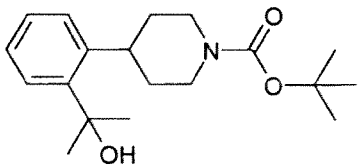
N'-{3-chloro-4-[(4-phenylpiperidin-1-yl)methyl]pyridin-2-yl}-2-cyclopropylacetohydrazide (D39)



To a solution of **D38** (0.179 g, 0.565 mmol) in dry DCM (3 ml) cooled at 0 °C were added Et_3N (0.118 ml, 0.847 mmol) and cyclopropyl-acetyl chloride [C.A.S. 543222-65-5] (0.080 g, 0.678 mmol). The resulting reaction mixture was gradually warmed to r.t. and stirred for 2 h. The mixture was concentrated *in vacuo* to yield intermediate compound **D39** (0.269 g) as a crude material, which was used without further purification.

Description 40

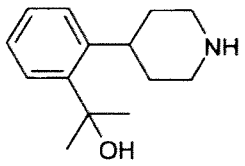
tert-butyl 4-[2-(1-hydroxy-1-methylethyl)phenyl]piperidine-1-carboxylate (D40)



To a solution of 4-[2-(methoxycarbonyl)phenyl]-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester [C.A.S. 732275-95-5] (2.6 g, 8.14 mmol) in THF (150 ml) cooled at 0 °C under a nitrogen atmosphere, was added methylmagnesium bromide – 1.4 M solution in toluene/THF (17.443 ml, 24.421 mmol), dropwise and the resulting reaction mixture was stirred at 45 °C for 2 h. After cooling in an ice bath the mixture was carefully quenched with NH_4Cl (saturated aqueous sat. solution) and then extracted with EtOAc. The combined organic phase was dried (Na_2SO_4) and the solvent evaporated *in vacuo* to yield **D40** (2.77 g, 69 %).

Description 41

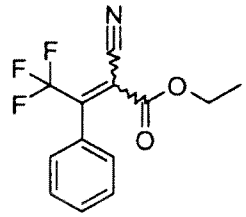
2-(2-Piperidin-4-ylphenyl)propan-2-ol (D41)



A solution of intermediate **D40** (27 g, 5.636 mmol) and KOH (2.433g, 43.357 mmol) in isopropyl alcohol (13.5 ml) and water (27 ml) was heated at 180 °C under microwave irradiation for 60 min. After cooling to r.t., the mixture was washed with water and NaCl (aqueous saturated solution). The organic phase was dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 10% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D41** as a yellow solid (1.041. g, 84 %). M.P. 219.5°C.

Description 42

2-Cyano-4,4,4-trifluoro-3-phenyl-but-2-enoic acid ethyl ester (D42)

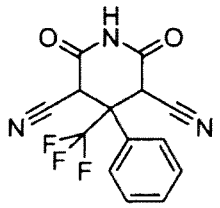


A mixture of trifluoromethylphenylketone [C.A.S. 434-45-7] (5g, 28.71 mmol) and ethyl cyanoacetate [C.A.S. 105-56-6] (3.61 mL, 31.58 mmol) in DCM (100 mL) was flushed with nitrogen, then cooled to 0 °C and maintained under a nitrogen atmosphere. Neat titanium(IV) chloride (6.79 mL, 60.30 mmol) was added dropwise, the reaction mixture was stirred for 10 min at 0 °C and then pyridine (1.5 mL) was added dropwise. When the addition was complete, the ice bath was removed, the reaction reaction was stirred for 30 min at r.t., additional pyridine was added (5 mL) and the reaction mixture was stirred for a further 20 h at r.t.. The mixture was then diluted in DCM (100 mL) and washed with HCl 2N (2 x 200 mL), water (300 mL) and brine (100 mL). The

organic phase was evaporated to yield intermediate compound **D42** (4.8 g, 61%) as a mixture of E/Z isomers, as a colourless oil which was used without further purification.

Description 43

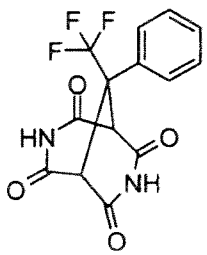
2,6-Dioxo-4-phenyl-4-trifluoromethyl-piperidine-3,5-dicarbonitrile (D43)



To a solution of intermediate **D42** (mixture of isomers) (4.71 g, 17.4 mmol) and 2-cyanoacetamide [C.A.S. 107-91-5] (2.51 g, 29.94 mmol), in dry EtOH (150 mL), was added a solution of sodium acetate (59.89 mmol) in EtOH, and the reaction mixture was stirred for 46 h at r.t.. The solvent was evaporated and the residue was treated with water (60 mL), the resulting aqueous solution was neutralized with HCl 1N to pH 3, extracted with EtOAc (3 x 100 mL) and the organic phase was dried over $MgSO_4$ and evaporated to give intermediate **D43** (4.71 g, 87%) as a brown oil which was used without further purification.

Description 44

9-Phenyl-9-trifluoromethyl-3,7-diaza-bicyclo[3.3.1]nonane-2,4,6,8-tetraone (D43)

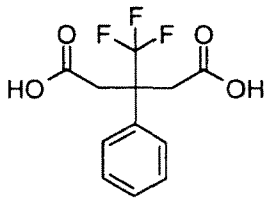


To a mixture of intermediate **D43** (4.71 g, 15.33 mmol) in AcOH (25 mL) and water (25 mL) was added concentrated sulfuric acid (25 g) and the reaction was heated at reflux for 20 h (bath temperature 170 °C). The reaction mixture was cooled to 0 °C and

30 mL of water were added. A solid precipitated that was filtered off and was washed with cold water to yield intermediate **D44** (3.6 g, 71%) as a cream solid that was used without further purification.

Description 45

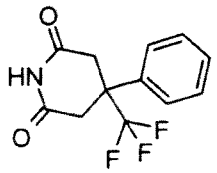
3-Phenyl-3-trifluoromethyl-pentanedioic acid (D45)



To 20 mL of an aqueous solution of KOH (20%) was added intermediate compound **D44** (2.6 g, 7.96 mmol) and the reaction mixture was heated at reflux for 3 h. The reaction mixture was then cooled to 0 °C and a solution of concentrated sulfuric acid (7 g) in water (20 mL) was added carefully. The resulting mixture was heated at reflux for 2 h, then cooled to r.t. and extracted with EtOAc (3x 50 mL). The organic phase was evaporated *in vacuo* to yield afford **D45** (1.81 g, 81%) as a yellowish oil.

Description 46

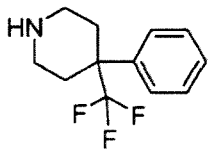
4-Phenyl-4-trifluoromethyl-piperidine-2,6-dione (46)



A mixture of intermediate **D45** (1.8 g, 6.51 mmol) in acetic anhydride (16.6 g) was heated at reflux (bath temperature 180 °C) for 2 h. The excess acetic anhydride was removed by evaporation, urea (0.42 g, 6.51 mmol) was added to the resulting residue and heated at 195 °C for 15 min. The resulting mixture was cooled and the crude was purified by column chromatography (DCM/MeOH 9.5/0.5) to afford intermediate **D46** (1.5g, 89%) as a white solid.

Description 47

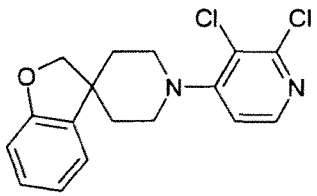
4-Phenyl-4-trifluoromethyl-piperidine (D47)



To a mixture of intermediate **D46** (1.6 g, 6.22 mmol) in dry THF (150 mL), was added BH_3-THF (21.77 mL, 1M) at r.t. and the reaction was heated at reflux for 20 h. The reaction mixture was cooled to r.t. and quenched by the careful addition of 6 N HCl (10 mL). After the gas evolution ceased, the mixture was concentrated under reduced pressure and the residue thus obtained was treated with additional 6 N HCl (70 mL). The mixture was heated at reflux for 1 hour, then cooled to r.t. and treated with a 2M solution of NaOH to pH 11. The crude was extracted with DCM (3 x 30 mL) to afford a transparent oil, which was purified by column chromatography (DCM/MeOH (1% NH_3) 9/1) to yield intermediate **D47** (0.91 g, 64 %) as a colorless oil which crystallized upon standing. M.P. = 87.6°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.01 - 2.12 (m, 2 H), 2.15 (br. s., 1 H), 2.47 (dd, *J*=14.1, 2.3 Hz, 2 H), 2.63 (br t, *J*=12.5 Hz, 2 H), 3.00 (br d, *J*=12.7 Hz, 2 H), 7.31 - 7.37 (m, 1 H), 7.38 - 7.49 (m, 4 H).

Description 48

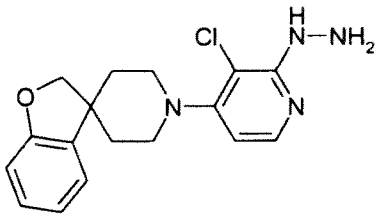
1'-(2,3-Dichloropyridin-4-yl)spiro[1-benzofuran-3,4'-piperidine] (D48)



A mixture of intermediate **D10** (3 g, 10.953 mmol), 4-spiro-[3-(2,3-dihydro-benzofuran)]piperidine [CAS 171-77-7] (2.28 g, 12.049 mmoland DIPEA (7.63 ml, 43.814 mmol) in CH_3CN (100 ml) was heated in a sealed tube at 110 °C for 3 days. The mixture was then treated with $NaHCO_3$ (aqueous sat. solution) and extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 4% as eluent), the desired fractions were collected and concentrated *in vacuo* to yield intermediate **D48** (2.9 g, 63%) as a white solid. M.P. 177.2°C

Description 49

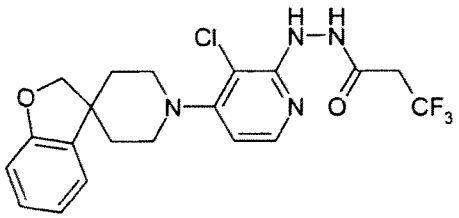
1'-(3-Chloro-2-hydrazinopyridin-4-yl)spiro-[1-benzofuran-3,4'-piperidine] (D49)



To a suspension of intermediate **D48** (1.13 g, 3.371 mmol) in EtOH (11.3 ml), was added hydrazine monohydrate (0.588 ml, 11.872 mmol). The reaction mixture was heated at 160 °C under microwave irradiation for 50 min. Additional hydrazine monohydrate (5 eq) was added to the reaction mixture, which was then heated at 160 °C for 35 min under microwave irradiation. The reaction mixture was diluted with DCM and washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo* to yield intermediate **D49** (1.05 g, 94%) which was used without further purification.

Description 50

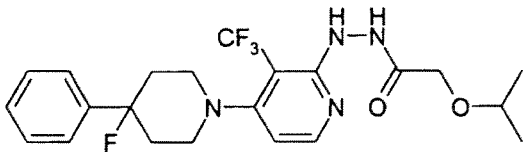
N'-[3-chloro-4-(1'H-spiro[1-benzofuran-3,4'-piperidin]-1'-yl)pyridin-2-yl]-3,3,3-trifluoropropanehydrazide (D49)



To a solution of intermediate **D49** (1.05 g, 3.174 mmol) in dry DCM (100 ml) cooled at 0 °C was added Et_3N (0.792 ml, 5.713 mmol) and 3,3,3-trifluoropropionyl chloride [C.A.S. 41463-83-6] (0.465 mg, 3.174 mmol). The resulting reaction mixture was gradually warmed to r.t. and stirred for 1 h. The mixture was concentrated *in vacuo* and the residue thus obtained was triturated with Et_2O to yield intermediate **D50** (1.39 g) as a crude material, which was used without further purification.

Description 51

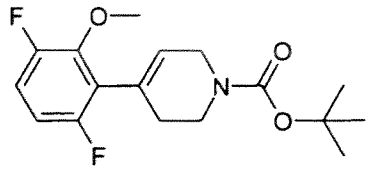
N'-[4-(4-fluoro-4-phenylpiperidin-1-yl)-3-(trifluoromethyl)pyridine-2-yl]-2-(1-methylethoxy)acetohydrazide (D51)



To a solution of intermediate **D31** (0.29 g, 0.818 mmol), 2-isopropoxyacetic acid [C.A.S. 33445-07-7] (0.116 g, 0.982 mmol) and 1-hydroxybenzotriazole (0.167 g, 1.233 mmol) in dry THF (3.5 ml) was added *N,N'*-dicyclohexylcarbodiimide (0.254 g, 1.233 mmol) in dry DCM (14 ml). The resulting reaction mixture was stirred at r.t. for 16 h. The resulting solution was washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/EtOAc gradient as eluent). The desired fractions were collected and concentrated *in vacuo*. The solid obtained was triturated with DCM. The soluble fraction was collected and concentrated *in vacuo* to yield intermediate **D51** (0.245 g, 52%).

Description 52

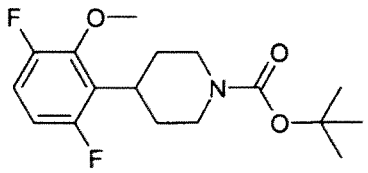
4-(3,6-Difluoro-2-methoxy-phenyl)-3,6-dihydro-*2H*-pyridine-1-carboxylic acid tert-butyl ester (D52)



2-Bromo-1,4-difluoro-3-methoxy-benzene (0.7 g, 3.139 mmol) [C.A.S. 1208076-11-2] was added to a stirred solution of 3,6-dihydro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1(2H)-pyridinecarboxylic acid, 1,1-dimethylethyl ester (1.262 g, 4.08 mmol) [C.A.S. 286961-14-6], $Pd(PPh_3)_4$ (0.072 g, 0.062 mmol) and K_2CO_3 (3.5 ml, aqueous sat. solution) in 1,4-dioxane (7 ml). The reaction mixture was heated at 150 °C under microwave irradiation for 10 min. After cooling, the mixture was diluted with water and extracted with Et_2O. The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; Heptane/EtOAc 90/10 to 80/2 as eluent). The desired fractions were collected and concentrated *in vacuo* to give a residue that was triturated with Et_2O to yield intermediate **D52** (0.233 g, 22%).

Description 53

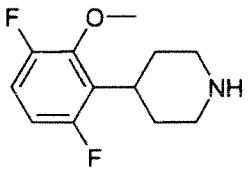
4-(3,6-Difluoro-2-methoxy-phenyl)-piperidine-1-carboxylic acid tert-butyl ester (D53)



A solution of intermediate **D52** (0.233 g, 0.716 mmol) in EtOH (15 ml) was hydrogenated in a H-Cube® reactor (1 ml/min, $Pd(OH)_2$ 20% cartridge, full H_2 mode, 80°C). The solvent was concentrated *in vacuo* to yield intermediate **D53** (0.197 g, 84%).

Description 54

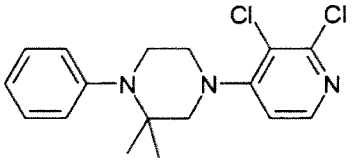
4-(3,6-Difluoro-2-methoxy-phenyl)-piperidine (D54)



Hydrochloric acid (7M in isopropanol) (2 ml) was added to a stirred solution of intermediate **D53** (0.197 g, 0.602 mmol) in MeOH (1 ml). The mixture was stirred at r.t. for 1.5 h. The mixture was diluted with Na_2CO_3 (aqueous saturated solution) and extracted with DCM. The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo* to yield intermediate **D54** (0.117 g, 85%).

Description 55

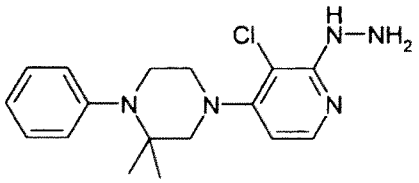
4-(2,3-Dichloro-pyridin-4-yl)-2,2-dimethyl-1-phenyl-piperazine (D55)



A mixture of **D10** (1.083 g, 3.955 mmol), 2,2-dimethyl-1-phenylpiperazine (0.903 g, 4.745 mmol) [C.A.S. 2946-75-0] and DIPEA (1.378 ml, 7.909 mmol) in CH_3CN (15 ml) was heated in a sealed tube at 100 °C for 5 days. After cooling, the solvent was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; Heptane/EtOAc 100/10 to 80/20 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D55** (0.56 g, 42%).

Description 56

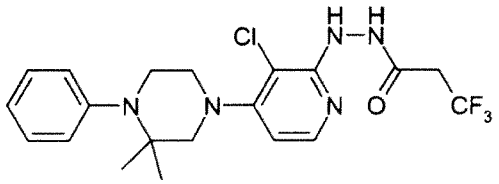
[3-Chloro-4-(3,3-dimethyl-4-phenyl-piperazin-1-yl)-pyridin-2-yl]-hydrazine (D56)



To a suspension of **D55** (0.56 g, 1.665 mmol) in DMSO (6 ml) was added hydrazine monohydrate (1.649 ml, 33.307 mmol). The reaction mixture was heated at 110 °C overnight. Then, after cooling, the mixture was diluted with $NaHCO_3$ (aqueous saturated solution) and extracted with EtOAc. The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was lyophilized to yield intermediate **D56** (0.371 g, 67%).

Description 57

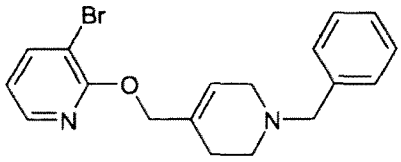
N'-[3-chloro-4-((3,3-dimethyl-4-phenyl-piperazin-1-yl)pyridin-2-yl]-3,3,3-trifluoropropanohydrazide (D57)



To a solution of **D56** (0.371 g, 1.12 mmol) and Et_3N (0.116 ml, 0.877 mmol) in dry DCM (17 ml) cooled at 0 °C, was added a solution of 3,3,3-trifluoropropionyl chloride [C.A.S. 41463-83-6] (0.82 ml, 0.56 mmol) in dry DCM (3 ml). The resulting reaction mixture was gradually warmed to r.t. and stirred for 1 h. The reaction mixture was cooled at 0°C and additional Et_3N (0.29 mmol) and 3,3,3-trifluoropropionyl chloride (0.25 mmol) were added. The resulting reaction mixture was gradually warmed to r.t. and stirred for an additional 1 h. $NaHCO_3$ (aqueous sat. solution) was added and the resulting solution was then extracted with DCM. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to yield intermediate **D57** (0.459 g, 92%).

Description 58

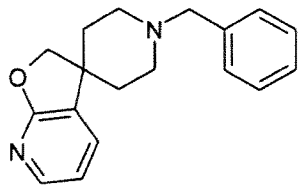
2-(1-Benzyl-1,2,3,6-tetrahydro-pyridin-4-ylmethoxy)-3-bromo-pyridine (D58)



To a solution of (1-benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-methanol (0.675 g, 3.019 mmol) [C.A.S. 158984-76-0] in dry THF (40 ml) cooled at 0 °C, was added NaH (0.138 g, 3.622 mmol; 60% mineral oil). The resulting reaction mixture was stirred at 0°C for 30 min. Then, a solution of 2-chloro-3-bromopyridine (0.58 g, 3.019 mmol) in dry THF (10 ml) was added and the mixture was heated in a sealed tube at 85°C for 2 h. After cooling, additional (1-benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-methanol (0.675 g, 3.019 mmol), NaH (0.138 g, 3.622 mmol; 60% mineral oil) were added to the reaction mixture, which was then heated at 85 °C overnight. Then, after cooling, the mixture was diluted with water and extracted with EtOAc. The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 2% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D58** (0.55 g, 50%).

Description 59

1-Benzyl-spiro[furo[2,3-b]pyridine-3(2H),4'-piperidine] (D59)

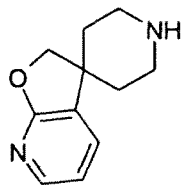


A solution of **D58** (1.12 g, 3.117 mmol), tributyltin hydride (0.963 ml, 3.585 mmol) and α,α'-azodiisobutyronitrile (0.512 mg, 3.117 mmol) in dry toluene (65 ml) was heated in a sealed tube at 135°C for 20 h. The mixture was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 3% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue was dissolved in MeOH and Amberlyst® 15 ion exchange resin (3.678 g) was added. The resulting mixture was shaken at r.t. for 16 h. The resin was filtered off, washed with MeOH and DCM, and dried *in vacuo*. The resin was suspended in NH_3 (7M in MeOH) and shaken at r.t. for 2 h. The resin was filtered off and the filtrate was concentrated *in vacuo*. The crude residue was dissolved in DCM (50 ml) and KF (50 ml of aqueous saturated solution) was added. The mixture was stirred at r.t. for 1 h. The organic phase was separated, washed with KF (aqueous sat.

solution), NaCl (aqueous sat. solution), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was triturated with heptane to give intermediate **D59** (0.45 g, 51%) as a pale yellow solid.

Description 60

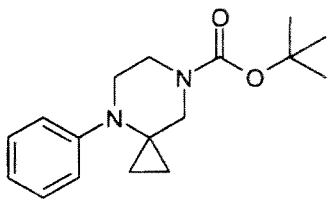
Spiro[furo[2,3-b]pyridine-3(2H),4'-piperidine] (D60)



To a stirred solution of **D59** (1.6 g, 5.707 mmol) and Et_3N (0.793 ml, 5.707 mmol) in DCM (32 ml) cooled at 0°C was added dropwise α-chloroethoxycarbonyl chloride (1.246 ml, 11.414 mmol). The mixture was stirred at 0°C for 1 min, then, the crude was concentrated *in vacuo*. The residue was dissolved in MeOH (32 ml), heated at reflux for 1 h and concentrated *in vacuo*. The residue was suspended in *n*-butanol and stirred at r.t. overnight. The solid was filtered off and washed with *n*-butanol and the filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH and Amberlyst® 15 ionexchange resin (2.78 g) was added. The resulting mixture was shaken at r.t. for 16 h. The resin was filtered off, washed with MeOH and DCM, and dried *in vacuo*. The resin was suspended in NH_3 (7M in MeOH) and shaken at r.t. for 2 h The resin was filtered off, washed with NH_3 (7M in MeOH) and the filtrate was concentrated *in vacuo* to give intermediate **D60** (0.688 g, 63%) as a brown oil.

Description 61

4-Phenyl-4,7-diaza-spiro[2.5]octane-7-carboxylic acid tert-butyl ester (D61)

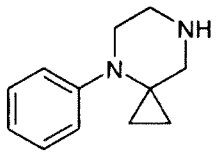


A stirred solution of 4,7-diaza-spiro[2.5]octane-7-carboxylic acid tert-butyl ester (0.1 g, 0.471 mmol) [C.A.S. 886766-28-5] , iodobenzene (0.026 ml, 0.236) and CsOH (0.079 g, 0.471 mmol) in DMSO (1 ml) was heated in a sealed tube at 120°C for 20 min. After cooling, additional 4,7-diaza-spiro[2.5]octane-7-carboxylic acid tert-butyl ester (2 eq.) was added, and the mixture was then heated at 120°C for 20 min. The mixture was cooled.The mixture was washed with NH_4Cl (aqueous sat. solution) was

added and extracted with Et_2O. The organic phase was separated, washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by manifold (Sep-Pak® silica cartridge; DCM as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D61** (0.021 g, 31%) as a white solid.

Description 62

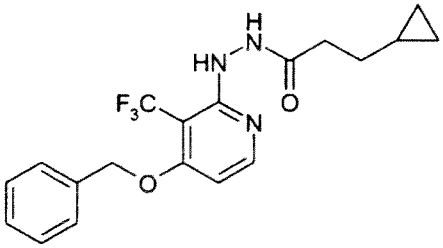
4-Phenyl-4,7-diaza-spiro[2.5]octane (D62)



To a stirred solution of **D61** (0.466 g, 1.616 mmol) in dry DCM (8.5 ml) was added, trifluoroacetic acid (1.4 ml). The mixture was stirred at r.t. overnight then concentrated *in vacuo*. The residue was treated with water and extracted with DCM. The aqueous phase was collected, basified with NaOH 50% (aqueous solution) and extracted with DCM. The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by manifold (Sep-Pak® silica cartridge; DCM/7M solution of NH_3 in MeOH up to 2% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D62** (0.101 g, 33%).

Description 63

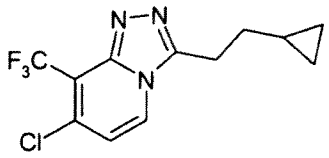
N'-[4-(benzyloxy)-3-(trifluoromethyl)pyridin-2-yl]-2-cyclopropylpropionic acid hydrazide (D63)



To a solution of **D27** (1.851 g, 6.536 mmol) in dry DCM (40 ml) was added Et_3N (3.617 ml, 26.146 mmol) and cyclopropyl-propionyl chloride [C.A.S. 56105-20-5] (1.04 g, 7.844 mmol). The resulting reaction mixture was stirred at r.t. for 1 h. The mixture was washed with $NaHCO_3$ (aqueous sat. solution). The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo* to yield intermediate **D63** (2.3 g, 93%).

Description 64

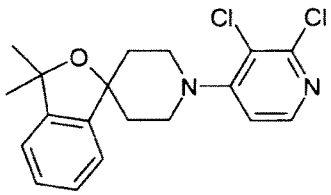
7-Chloro-3-cyclopropylethyl-8-trifluoromethyl[1,2,4]triazolo[4,3-a]pyridine (D64)



A mixture of **D63** (2.3 g, 6.062 mmol) and phosphorous (V) oxychloride (0.848 g, 9.094 mmol) and DIPEA (0.792 ml, 4.547 mmol) in CH_3CN (24 ml) were heated at 150 °C under microwave irradiation for 15 min. After cooling, the resulting reaction mixture was poured into ice-water, and washed with $NaHCO_3$ (aqueous sat. solution). The resulting mixture was extracted with DCM. The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/EtOAc 100/0 to 90/10 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D64** (0.9 g, 51%).

Description 65

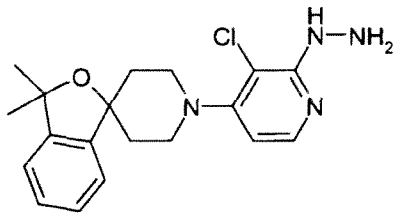
1'-(2,3-Dichloropyridin-4-yl) 3,3-dimethyl-*3H*-spiro[benzo[c]furan-1,4'-piperidine (D65)



A mixture of intermediate **D10** (0.35 g, 1.278 mmol), 3,3-dimethyl-*3H*-spiro[benzo[c]furan-1,4'-piperidine [C.A.S 180160-92-3] (0.333 g, 1.534 mmol)and DIPEA (0.534 ml, 3.068 mmol) in CH_3CN (5 ml) was heated in a sealed tube at 110 °C overnight. After cooling to r.t. the mixture was filtered through a pad of diatomaceous earth. The filtrate was concentrated *in vacuo*. The residue thus obtained was purified by column chromatography (silica gel; DCM/MeOH up to 5% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was purified again by HPLC to yield intermediate **D65** (0.030 g, 5 %).

Description 66

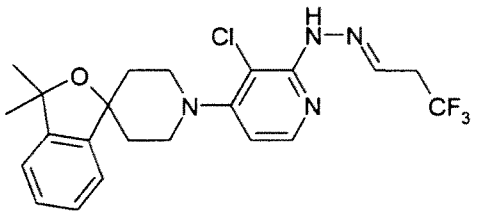
[3-Chloro-4-(3,3-dimethyl-*3H*-spiro[benzo[c]furan-1,4'-piperidyl)-pyridin-2-yl]-hydrazine (D66)



To a suspension of **D65** (0.4 g, 1.101 mmol) in 1,4-dioxane (11 ml) was added hydrazine monohydrate (0.327 ml, 6.606 mmol). The reaction mixture was heated at 160 °C under microwave irradiation for 30 min. After cooling, additional hydrazine monohydrate (20 eq.) was added. Then the mixture was heated at 160 °C under microwave irradiation for 20 min, cooled and concentrated *in vacuo*. The residue was suspended in Na_2CO_3 (aqueous sat. solution) and extracted with DCM. The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo* to yield intermediate **D66** (0.38 g, 96%).

Description 67

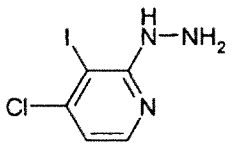
3,3,3-trifluoropropanal-*N'*-{3'-chloro-4'-(3,3-dimethyl-*3H*-spiro[benzo[c]furan-1,4'-piperidyl]pyridin-2-yl)-hydrazone (D67)



A solution of **D66** (0.38 g, 1.059 mmol) and 3,3,3-trifluoropropionaldehyde (0.125 g, 1.112 mmol) in EtOH (10.6 ml) was heated at 78°C for 2 h. The mixture was concentrated *in vacuo* to yield intermediate **D67** (0.5 g).

Description 68

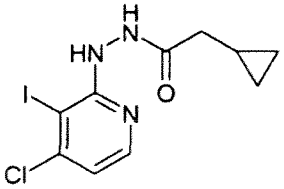
(4-Chloro-3-iodo-pyridin-2-yl)-hydrazine (D68)



To a suspension of **D24** (4.7 g, 17.16 mmol) in 1,4-dioxane (240 ml), was added hydrazine monohydrate (5.096 ml, 102.96 mmol). The reaction mixture was heated at 80 °C overnight. After cooling, the resulting solution was concentrated *in vacuo*. The residue thus obtained was dissolved in DCM and washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was treated with Et_2O. The solid obtained was filtered off. The filtrate was concentrated *in vacuo* to yield intermediate **D68** (2.26 g, 49%).

Description 69

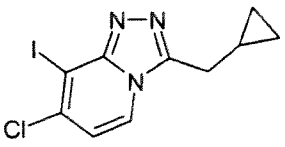
Cyclopropyl-acetic acid N'-(4-chloro-3-iodo-pyridin-2-yl)-hydrazide (D69)



To a solution of **D68** (3 g, 11.133 mmol) in dry DCM (40 ml) stirred at 0°C was added Et_3N (3.081 ml, 22.266 mmol) and cyclopropyl-acetyl chloride [C.A.S. 543222-65-5] (1.584 g, 13.359 mmol). The resulting reaction mixture was stirred at r.t. overnight. The mixture was washed with $NaHCO_3$ (aqueous sat. solution). The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo* to yield intermediate **D69** (4.04 g).

Description 70

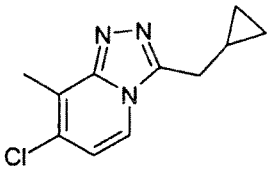
8-Iodo-3-cyclopropylmethyl-7-chloro[1,2,4]triazolo[4,3-a]pyridine (D70)



Intermediate **D69** (0.74 g, 2.389 mmol) was heated at 160 °C for 2 h. After cooling, the gum thus obtained was purified by short open column chromatography (silica gel; DCM/EtOAc 100/0 to 50/50 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D70** (7 g, 55 %) as a yellow solid. M.P. 246.7°C

Description 71

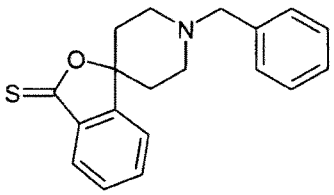
8-Methyl-3-cyclopropylmethyl-7-chloro[1,2,4]triazolo[4,3-a]pyridine (D71)



To a mixture of **D70** (0.6 g, 1.8 mmol) in toluene (15 ml) under a nitrogen atmosphere were added methylboronic acid (0.538 g, 9 mmol), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine; S-Phos (0.171 g, 0.36 mmol), palladium(II) acetate (0.04 g, 0.18 mmol) and K_2CO_3 (0.745 g, 5.396 mmol). The reaction mixture was heated at 100 °C overnight. After cooling, the mixture was diluted with EtOAc and washed with water. The organic layer was separated and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/EtOAc from 100/0 to 20/80 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D71** (0.312 g, 78%) as a cream solid.

Description 72

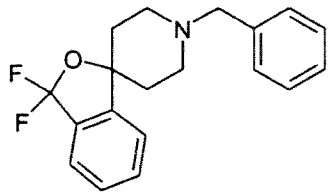
1'-(benzyl)-spiro[isobenzofuran-1(3H),4'-piperidin]-3-thione (D72)



To a mixture of 1'-(phenylmethyl)-spiro[isobenzofuran-1(3H),4'-piperidin]-3-one (25 g, 85.2 mmol) [C.A.S. 37663-42-6] in toluene (600 ml), was added 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent) (34.47 g, 85.2 mmol was added. The reaction mixture was heated at 140 °C for 2 h. After cooling, the mixture was poured into NH_4Cl (aqueous sat. solution) and extracted with DCM. The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/MeOH 3% as eluent). The desired fractions were collected and concentrated *in vacuo* to a residue that was purified by HPLC to yield intermediate **D72** (8 g, 30.3%).

Description 73

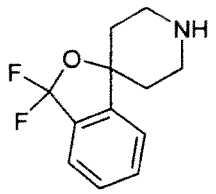
N-benzyl-3,3-difluoro-*3H*-spiro[benzo[c]furan-1,4'-piperidine (D73)



To a stirred solution of **D72** (8g, 25.85 mmol) and tetrabutylammonium dihydrogen trifluoride (48 g, 159 mmol) in DCM (1 L) was added *N*-bromosuccinimide (11.2 g). The reaction mixture was stirred at r.t. for 6 hour. Then a mixture of $NaHCO_3/NaHSO_3$ (10% aqueous solution) was added and stirred for 30 min. The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 2% as eluent). The desired fractions were collected and concentrated *in vacuo* to give a residue that was purified on SFC to yield intermediate D73 (1.3 g, 16%).

Description 74

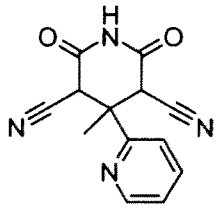
3,3-diFluoro-*3H*-spiro[benzo[c]furan-1,4'-piperidine (D74)



To a stirred solution of **D73** (1.3 g, 4.122 mmol) in DCM (450 ml), was added DIPEA (4 g). The resulting mixture was cooled to 0-5°C and a solution of α-chloroethoxycarbonyl chloride (2.947 g, 20.611 mmol) in DCM (50 ml) was added dropwise. The mixture was stirred at r.t. for 2 h then, concentrated *in vacuo*. The residue was dissolved in MeOH (400 ml), heated at reflux for 3 h and then concentrated *in vacuo*. The residue was dissolved in EtOAc and washed with Na_2CO_3 (aqueous sat. solution). The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 5% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D74** (0.6 g, 64.6%)

Description 75

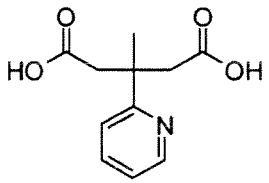
2,6-Dioxo-4-(2-pyridinyl)-4-methyl-piperidine-3,5-dicarbonitrile (D75)



To a solution of 2-acetylpyridine (5 g, 41.275 mmol) and ethyl cyanoacetate (9.805 g, 86.677 mmol) at 0°C, was added NH_3 (7M in MeOH, 200 ml), was added. The reaction mixture was stirred at r.t. for 48 h and then concentrated *in vacuo* to give intermediate **D75** (6 g, 57%)

Description 76

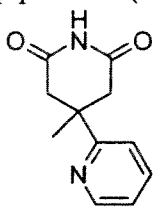
3-(2-Pyridinyl)-3-methyl-pentanedioic acid (D76)



To a mixture of **D75** (6 g, 23.6 mmol) in water (3 ml) stirred at r.t., sulfuric acid (3 ml) was carefully added. The resulting mixture was heated at 170°C for 24 h. After cooling, NaOH (50% aqueous solution) was added dropwise (to afford pH 5-6). Then, MeOH was added to the aqueous mixture. The precipitate thus obtained was filtered and dried *in vacuo* to yield intermediate **D76** (3.5 g, 66.4%) as a green dark oil

Description 77

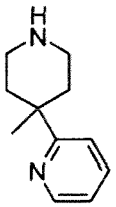
2,6-Dioxo-4-(2-pyridinyl)-4-methyl-piperidine (D77)



A solution of **D76** (1.7 g, 7.616 mmol) and urea (1.143 g, 19.039 mmol) in MeOH (10 ml) was concentrated *in vacuo*. The homogeneous solid mixture thus obtained was heated at 180°C for 3 h in a open flask. After cooling, the solid residue was suspended in water and extracted with EtOAc. The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; EtOAc as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D77** (0.6 g, 38.58%)

Description 78

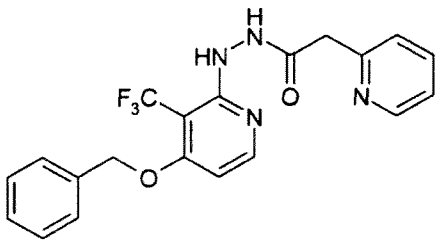
4-(2-Pyridinyl)-4-methyl-piperidine (D78)



To a mixture of intermediate **D77** (0.6 g, 2.938 mmol) in dry THF (25 mL), was added BH_3-THF (10.283 mL, 1M) at r.t. and the reaction was heated at reflux for 24 h. The reaction mixture was cooled to r.t. and quenched by the careful addition of 6 N HCl (50 mL). After the gas evolution ceased, the mixture was concentrated under reduced pressure and the residue thus obtained was treated with additional 6 N HCl (150 mL). The mixture was heated at reflux for 2 h, then cooled at r.t. and treated with a 2M solution of NaOH to pH 11. The resulting mixture was heated at reflux for 2 h. After cooling, the mixture was extracted with EtOAc to yield intermediate **D78** (0.4 g, 77 %) as an orange oil

Description 79

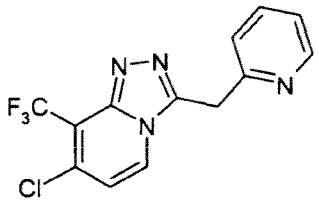
N'-[4-(benzyloxy)-3-(trifluoromethyl)pyridin-2-yl]-2-(2-pyridinyl)acetic acid hydrazide (D79)



To a stirred solution of **D27** (1.851 g, 6.536 mmol), 2-pyridine acetic acid, hydrochloride (1:1) (0.674 mg, 3.883 mmol), DIPEA (2.434 ml, 14.122 mmol) in DMF (20 ml) at r.t. was added 2-(7-aza-*1H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate [C.A.S.148893-10-1] (1.477 g, 3.883 mmol). The resulting reaction mixture was stirred at r.t. overnight. Water was added to the mixture and the precipitate obtained was filtered off, washed with water and dried *in vacuo* to yield intermediate **D79** (1.26 g, 88.7%).

Description 80

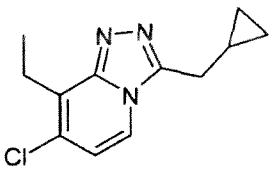
7-Chloro-3-(2-pyridinyl)methyl)-8-trifluoromethyl[1,2,4]triazolo[4,3-a]pyridine (D80)



D79 (1.1 g, 2.734 mmol), phosphorous (V) oxychloride (0.382 g, 4.101 mmol) and DIPEA (0.357 ml, 2.05 mmol) in CH_3CN (2 ml) were heated at 150 °C under microwave irradiation for 15 min. After cooling, the resulting reaction mixture was poured in ice/water, washed with $NaHCO_3$ (aqueous sat. solution) and extracted with DCM. The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/EtOAc from 100/0 to 20/80 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D80** (0.35 g, 41%).

Description 81

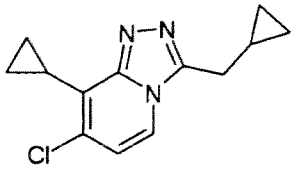
8-Ethyl-3-cyclopropylmethyl-7-chloro[1,2,4]triazolo[4,3-a]pyridine (D81)



To a mixture of intermediate **D70** (0.6 g, 1.8 mmol) in toluene (14 ml) under a nitrogen atmosphere were added ethylboronic acid (0.665 g, 9 mmol), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine; X-Phos (0.171 g, 0.36 mmol), palladium(II) acetate (0.04 g, 0.18 mmol) and K_2CO_3 (0.745 g, 5.396 mmol). The reaction mixture was heated at 100 °C overnight. After cooling, the mixture was diluted with EtOAc and washed with water. The organic layer was separated and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/EtOAc from 100/0 to 20/80 as eluent). The desired fractions were collected and concentrated *in vacuo* to give a residue that was purified by HPLC to yield intermediate **D81** (0.053 g, 12.6%).

Description 82

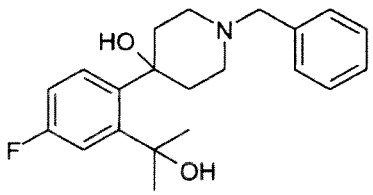
8-Cyclopropyl-3-cyclopropylmethyl-7-chloro[1,2,4]triazolo[4,3-a]pyridine (D82)



To a mixture of **D70** (0.6 g, 1.8 mmol) in toluene (14 ml) under a nitrogen atmosphere were added potassium cyclopropyltrifluoroborate (0.799 g, 5.4 mmol), bis(adamantan-1-yl)(butyl)phosphine (0.019 g, 0.054 mmol), palladium(II) acetate (8.15 mg, 0.036 mmol) and Cs_2CO_3 (1.758 g, 5.4 mmol). The reaction mixture was heated at 100 °C overnight. After cooling, additional potassium cyclopropyltrifluoroborate (0.7 g, 4.71 mmol), bis(adamantan-1-yl)(butyl)phosphine (0.019 g, 0.054 mmol) and palladium(II) acetate (8.15 mg, 0.036 mmol) were added to the reaction mixture, which was then heated at 100 °C for 48 h. After cooling, more potassium cyclopropyltrifluoroborate (0.35 g, 2.37 mmol) was added and heated at 100°C for 3 days. After cooling, the reaction mixture was diluted with EtOAc and washed with water. The organic layer was separated and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/EtOAc from 100/0 to 60/40 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D82** (0.217 g, 48.7%) as a yellow solid.

Description 83

1-Benzyl-4-[4-fluoro-2-(1-hydroxy-1-methyl-ethyl)-phenyl]-4-hydroxypiperidine (D83)

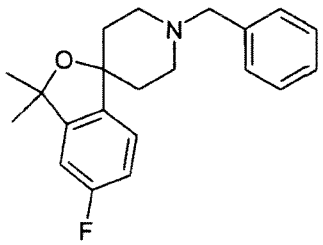


To an anhydrous THF (50 mL) cooled at -70°C stirred under nitrogen a 2.5 M solution of *n*-BuLi (4.22 mL, 10.54 mmol) was added. Then 2-bromo-5-fluoro-α,α-dimethyl-benzylalcohol (1.17 g, 5.02 mmol) [C.A.S.853271-16-6] was added dropwise. The resulting mixture was stirred at -70°C for 2 h. Then a solution of 1-benzylpiperidin-4-one (1.33 g, 7.028 mmol) in anhydrous THF (10 ml) was added dropwise. Then, the resulting solution was stirred at r.t. overnight. The reaction mixture was poured into NH_4Cl (aqueous sat. solution) at 5-10°C. The resulting aqueous solution was extracted with DCM. The organic layer was separated and concentrated *in vacuo*. The residue

was purified by column chromatography (silica gel; heptane/EtOAc from 100/0 to 60/40 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D83** (0.4 g, 23%).

Description 84

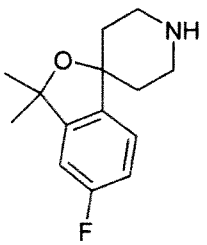
N-Benzyl-3,3-dimethyl-5-fluoro-*3H*-spiro[benzo[c]furan-1,4'-piperidine] (D84)



To a stirred solution of **D83** (0.4 g, 1.165 mmol) in toluene (8 ml) at r.t., borontrifluoride diethyletherate (1.463 ml, 11.647 mmol) was added dropwise. The resulting mixture was stirred at r.t. overnight. Then additional borontrifluoride diethyletherate (0.4 ml) was added and stirred overnight. Then, the reaction mixture was poured into NaOH (2N aqueous solution) and stirred for 10 min. The aqueous solution was extracted with DCM. The organic layer was separated, washed with Na_2CO_3 (aqueous sat. solution), dried (Na_2SO_4) and concentrated *in vacuo* to yield intermediate **D84** (0.271 g, 72%).

Description 85

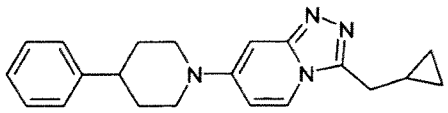
3,3-Dimethyl-5-fluoro-*3H*-spiro[benzo[c]furan-1,4'-piperidine] (D85)



A solution of intermediate **D84** (0.271 g, 0.833 mmol) in EtOH (17 ml) was hydrogenated in a H-Cube reactor® (1 ml/min, Pd/C 10% cartridge, full H_2 mode, 80°C). The solvent was concentrated *in vacuo* to yield intermediate **D85** (0.168 g, 86%) as off-white solid.

Description 86

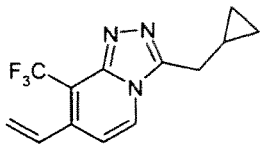
3-Cyclopropylmethyl-7-[4-phenyl-piperidin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine (D86)



A stirred suspension of final compound **E26** (0.225 g, 0.613 mmol), triethylsilane (0.195 ml, 1.227 mmol), $Pd(PPh_3)_4$ (0.071, 0.0613 mmol) and DIPEA (0.331 ml, 1.533 mmol) in propionitrile (3 ml) was heated at 200 °C under microwave irradiation for 30 min. After cooling, the reaction mixture was refilled with additional triethylsilane (0.195 ml) and $Pd(PPh_3)_4$ (0.050) and heated at 200 °C under microwave irradiation for 30 min. After cooling, the mixture was washed with $NaHCO_3$ (aqueous sat. solution) and extracted with DCM. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified again by column chromatography (silica gel; DCM/EtOAc from 100/0 to 10/90 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D86** (0.089 g, 43.7%).

Description 87

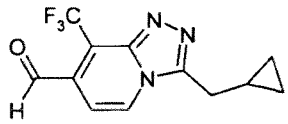
7-Vinyl-3-cyclopropylmethyl-8-trifluoromethyl[1,2,4]triazolo[4,3-a]pyridine (D87)



A suspension of **D29** (1.65 g, 5.986 mmol), vinylboronic acid pinacol ester (1.218 ml, 7.183 mmol), $Pd(PPh_3)_4$ (0.346, 0.3 mmol) and $NaHCO_3$ (aqueous sat. solution, 12.5 ml) in 1,4-dioxane (64.5 ml) was heated at 150 °C under microwave irradiation for 13 min. After cooling, the resulting reaction mixture was diluted with EtOAc/water and filtered through a pad of diatomaceous earth. The filtrate was washed with water and NaCl (aqueous sat. solution) and extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified again by column chromatography (silica gel; DCM/EtOAc from 100/0 to 60/40 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D87** (1.34 g, 83.7%).

Description 88

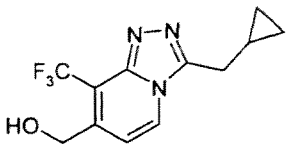
7-carboxaldehyde-3-cyclopropylmethyl-8-trifluoromethyl[1,2,4]triazolo[4,3-a]pyridine (D88)



A solution of **D87** (6.24 g, 21.014 mmol), sodium periodate (13.484 g, 63.041 mmol), osmium tetroxide (2.5% in tert-butanol, 10.873 ml, 0.841 mmol) in water (55 ml) and 1,4-dioxane (221 ml) was stirred at r.t. for 2 h. The resulting reaction mixture was diluted with EtOAc/water and filtered through a pad of diatomaceous earth. The filtrate was extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The solid residue was washed with Et_2O, filtered and dried *in vacuo* to yield intermediate **D88** (3.84 g, 67.9%).

Description 89

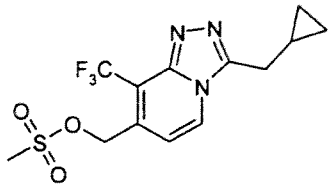
7-Hydroxymethyl-3-cyclopropylmethyl-8-trifluoromethyl[1,2,4]triazolo[4,3-a]pyridine (D89)



To a solution of **D88** (1.73 g, 6.426 mmol) in MeOH (58 ml) stirred at 0°C, was added portionwise sodium borohydride (0.243, 6.426 mmol). The resulting mixture was stirred at r.t. for 1 h. The resulting mixture was concentrated *in vacuo*. The residue was treated with water and NaCl (aqueous sat. solution) and extracted with EtOAc. The organic layer was separated and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 5% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D89** (1.015 g, 58%) as a brown syrup.

Description 90

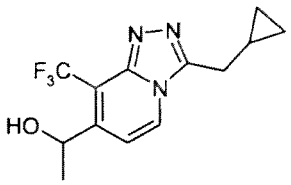
7-(methylsulfonyloxy)methyl-3-cyclopropylmethyl-8-trifluoromethyl[1,2,4]triazolo[4,3-a]pyridine (D90)



To a solution of **D89** (1.341 g, 9.678 mmol) and Et_3N (0.778 ml, 5.612 mmol) in DCM (42 ml) stirred at 0°C, was added dropwise methylsulfonyl chloride (0.749 ml, 9.678 mmol) and stirred at r.t. for 2 h. The resulting mixture was treated with $NaHCO_3$ (aqueous sat. solution) and extracted with DCM. The organic layer was separated and concentrated *in vacuo* to yield intermediate **D90** (2.6 g, 87%).

Description 91

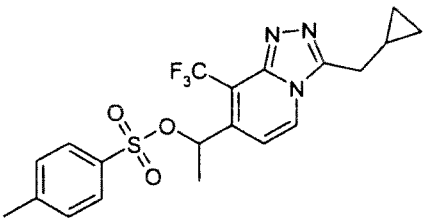
7-(1-hydroxyethyl)-3-cyclopropylmethyl-8-trifluoromethyl[1,2,4]triazolo[4,3-a]pyridine (D91)



To a solution of **D88** (0.3 g, 1.114 mmol) in THF (20 ml) cooled at -20°C stirred under nitrogen was added dropwise a 1.4 M solution of methylmagnesium bromide (0.876 mL, 1.226 mmol). The resulting mixture was stirred at -20°C for 30 min. The reaction mixture was treated with NH_4Cl (aqueous sat. solution) and extracted with EtOAc. The organic layer was separated and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 5% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D91** (0.287 g, 90%).

Description 92

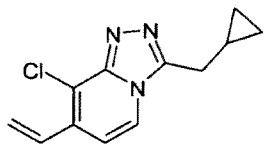
7-[1-(4-methylphenylsulfonyloxy)ethyl]-3-cyclopropylmethyl-8-trifluoromethyl[1,2,4]triazolo[4,3-a]pyridine (D92)



To an ice-cooled stirred solution of **D91** (0.154 g, 0.54 mmol) in DCM (1.5 ml) was added pyridine (0.130 ml) and 4-benzenesulfonyl chloride (0.205 g, 1.08 mmol) dropwise. The resulting mixture was stirred at r.t. for 5 days. The reaction was treated with 2N HCl (aqueous solution) and extracted with DCM. The organic layer was separated and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/EtOAc from 100/0 to 50/50 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D92** (0.142 g, 50%).

Description 93

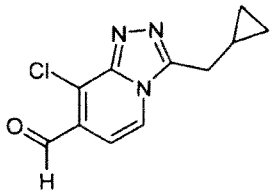
7-Vinyl-3-cyclopropylmethyl-8-chloro[1,2,4]triazolo[4,3-a]pyridine (D93)



To a solution of **D13** (12 g, 35.976 mmol), vinylboronic acid pinacol ester (6.713 ml, 39.573 mmol) in $NaHCO_3$ (aqueous sat. solution, 90 ml) in 1,4-dioxane (360 ml) under a nitrogen atmosphere was added $Pd(PPh_3)_4$ (2.079, 1.8 mmol). The resulting mixture was heated in a sealed tube at 100 °C for 16 h. After cooling, the resulting reaction mixture was diluted with $NaHCO_3$ (aqueous sat. solution) and extracted with DCM. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/EtOAc from 100/0 to 20/80 as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was triturated with DIPE to yield intermediate **D93** (6.09 g, 72%) as a yellow solid.

Description 94

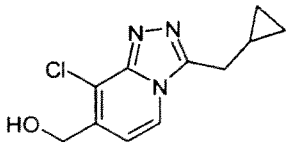
8-chloro-3-(cyclopropylmethyl)[1,2,4]triazolo[4,3-a]pyridine-7-carbaldehyde (D94)



To a solution of **D93** (6.09 g, 25.059 mmol) in 1,4-dioxane (320 ml) stirred at r.t. was added osmium tetroxide (2.5% in tert-butanol, 13.483 ml, 1.042 mmol). Then a solution of sodium periodate (16.721 g, 78.177 mmol) in water (80 ml) was added dropwise. The resulting mixture was stirred at r.t. for 2 h, then, diluted with water and extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The solid residue was triturated with Et_2O, filtered and dried *in vacuo* to yield intermediate **D94** (5.48 g, 89%) as a cream solid.

Description 95

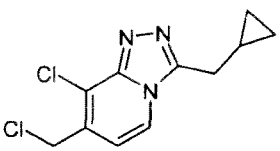
7-Hydroxymethyl-3-cyclopropylmethyl-8-chloro[1,2,4]triazolo[4,3-a]pyridine (D95)



To a stirred solution of **D94** (3 g, 12.73 mmol) in MeOH (100 ml) at 0°C, was added portionwise sodium borohydride (0.482, 12.73 mmol). The resulting mixture was stirred at r.t. for 2 h. The resulting mixture was concentrated *in vacuo*. The residue was treated with NaCl (aqueous sat. solution) and extracted with DCM. The organic layer was separated and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 6% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D95** (2.03 g, 67%) as a white solid.

Description 96

7-Chloromethyl-3-cyclopropylmethyl-8-chloro[1,2,4]triazolo[4,3-a]pyridine (D96)

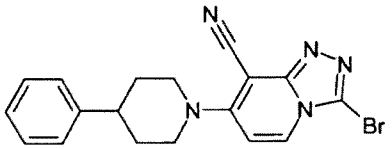


To a solution of **D95** (2 g, 8.414 mmol) and Et_3N (3.5 ml, 25.243 mmol) in DCM (80 ml) stirred at 0°C, was added dropwise methylsulfonyl chloride (1.954 ml, 25.243

mmol) and the mixture was stirred at r.t. for 16 h, then diluted with $NaHCO_3$ (aqueous sat. solution) and extracted with DCM. The organic layer was separated and concentrated *in vacuo* to yield intermediate **D96** (2.4 g, 100%) as a cream solid.

Description 97

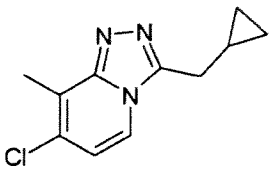
3-Bromo-8-cyano-7-(4-phenylpiperidinyl)[1,2,4]triazolo[4,3-a]pyridine (D97)



To a stirred solution of intermediate **D8** (0.49 g, 1.615 mmol) in DCM (20 ml) was added *N*-bromosuccinimide (0.316 g, 1.777 mmol). The resulting mixture was stirred at r.t. for 1.5 h. The mixture was carefully washed with $NaHCO_3$ (aqueous sat. solution) and extracted with DCM. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo* to yield intermediate **D97** (0.48 g, 78%).

Description 98

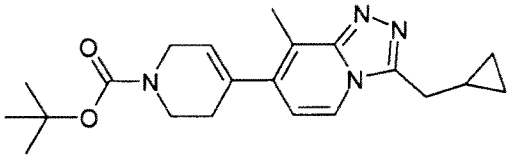
8-Methyl-3-cyclopropylmethyl-7-chloro[1,2,4]triazolo[4,3-a]pyridine (D98)



To a mixture of intermediate **D70** (1 g, 3 mmol) in toluene (25 ml) under a nitrogen atmosphere were added methylboronic acid (0.897 g, 15 mmol), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine; X-Phos (0.286 g, 0.6 mmol), palladium(II) acetate (0.067 g, 0.3 mmol) and K_2CO_3 (1.243 g, 9 mmol). The reaction mixture was heated at 100 °C for two days. After cooling, the mixture was diluted with EtOAc and washed with water. The organic layer was separated and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/EtOAc from 100/0 to 0/100 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D98** (0.365 g, 55%).

Description 99

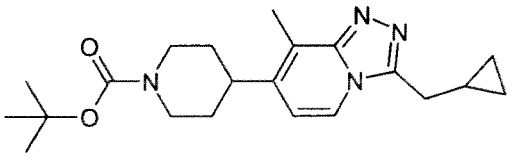
4-(3-Cyclopropylmethyl-8-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-3,6-dihydro-*2H*-pyridine-1-carboxylic acid tert-butyl ester (D99)



A mixture of **D98** (0.358 mg, 1.614 mmol), *N*-(tert-butoxycarbonyl)-3,6-dihydro-*2H*-pyridine-4-boronic acid pinacol ester (0.6 g, 1.937 mmol) and $Pd(PPh_3)_4$ (0.0933 g, 0.0801 mmol) in $NaHCO_3$, (3.5 ml, aqueous sat. solution) and 1,4-dioxane (9 ml) was heated at 150 °C under microwave irradiation for 5 min. After cooling, the mixture was refilled with additional *N*-(tert-butoxycarbonyl)-3,6-dihydro-*2H*-pyridine-4-boronic acid pinacol ester (0.5 g) and $Pd(PPh_3)_4$ (0.072 g) and $NaHCO_3$, (1 ml, aqueous sat. solution). The mixture was heated at 150 °C under microwave irradiation for 20 min. After cooling to r.t. the mixture was diluted with EtOAc/H_2O, filtered through a pad of diatomaceous earth and washed with EtOAc. The organic phase was collected, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; EtOAc/7M solution of NH_3 in MeOH up to 6% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D99** (0.458 g, 77%).

Description 100

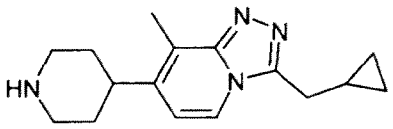
4-(3-Cyclopropylmethyl-8-methyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-piperidine-1-carboxylic acid tert-butyl ester (D100)



A solution of intermediate **D99** (0.606 g, 1.645 mmol) in EtOH (35 ml) was hydrogenated in a H-Cube® reactor (1 ml/min, Pd/C 10% cartridge, full H_2 mode, 80°C). The solvent was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; EtOAc/7M solution of NH_3 in MeOH up to 6% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate **D100** (0.214 g, 35%).

Description 101

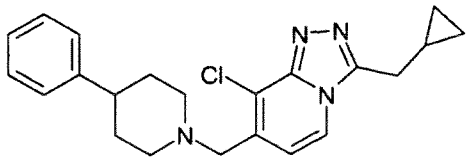
3-Cyclopropylmethyl-8-methyl-7-piperidin-4-yl-[1,2,4]triazolo[4,3-a]pyridine (D101)



To a stirred solution of **D100** (0.207 g, 0.560 mmol) in dry DCM (3.5 ml), was added trifluoroacetic acid (1.01 ml). The mixture was stirred at r.t. for 2 h and then concentrated *in vacuo*. The residue was basified with NaOH 50% (aqueous solution) and extracted with DCM. The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo* to yield intermediate **D101** (0.149 g, 99%).

Example 1

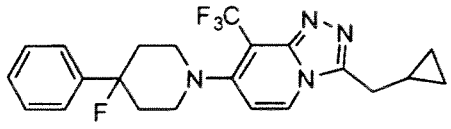
8-Chloro-3-cyclopropylmethyl-7-[(4-phenyl-1-piperidinyl)methyl]-1,2,4-triazolo[4,3-a]pyridine (E1)



D39 (0.268 g, 0.672 mmol) and phosphorous (V) oxychloride (0.125 ml, 1.344 mmol) in CH_3CN (3 ml) was heated at 150 °C under microwave irradiation for 5 min. After cooling, $NaHCO_3$ (aqueous sat. solution) was added and the resulting mixture was extracted with EtOAc (three times). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH up to 3% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield final compound **E1** (0.112 g, 43.8%) as a white solid.

Example 2

3-Cyclopropylmethyl-7-(4-fluoro-4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine (E2)

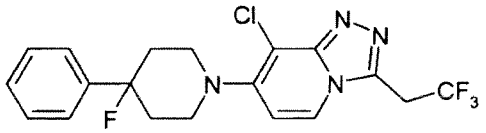


A suspension of **D32** (0.37 g, 0.848 mmol), DIPEA-polymer supported (0.652 g, 2.543 mmol, 3.9 mmol/g), triphenylphosphine-polymer supported (1.77 g, 2.119 mmol, 1.8 mmol/g) and trichloroacetonitrile (0.102 ml, 1.017 mmol) in DCE (10 ml) was heated

at 150 °C under microwave irradiation for 10 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with DCM and MeOH. The filtrate was concentrated *in vacuo* and the residue thus obtained was purified by column chromatography (silica gel; DCM/ EtOAc up to 40% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue was subjected to preparative Supercritical fluid purification (pyridine 20 mm; mobile phase, isocratic 85% CO_2, 15% MeOH) yielding compound **E2** (0.1 g, 28%).

Example 3

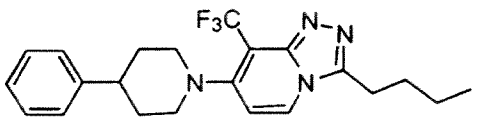
8-Chloro-7-(4-fluoro-4-phenyl-1-piperidinyl)-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine (E3)



A suspension of **D20** (7.768 g, 18.03 mmol), DIPEA-polymer supported (13.869 g, 54.09 mmol, 3.9 mmol/g), triphenylphosphine-polymer supported (25.042 g, 45.075 mmol, 1.8 mmol/g) and trichloroacetonitrile (2.169 ml, 21.636 mmol) in DCE (180 ml) was heated at 150 °C under microwave irradiation for 10 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with DCM and MeOH. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; DCM/ EtOAc up to 40% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue was subjected to preparative Supercritical fluid purification (pyridine 20 mm; mobile phase, isocratic 83% CO_2, 17% MeOH) yielding final compound **E3** (2.357 g, 31%).

Example 4

3-Butyl-7-(4-phenyl-1-piperidinyl)-8-trifluoromethyl-1,2,4-triazolo[4,3-a]pyridine (E4)

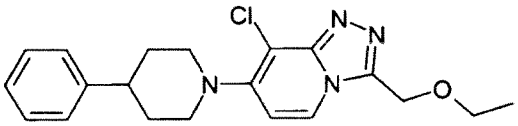


D35 (0.44 g, 1.046 mmol) and phosphorus (V) oxychloride (0.146 ml, 1.57 mmol) in DCE (5 ml) was heated at 150 °C under microwave irradiation for 5 min. After cooling, the mixture was diluted with DCM and washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/7M solution of NH_3

in MeOH up to 3% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield final compound **E4** (0.160 g, 38%).

Example 5

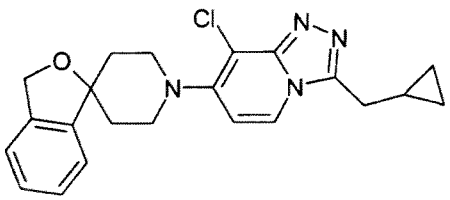
8-Chloro-3-(ethoxymethyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine (E5)



D17 (0.544 g, 1.4 mmol) and phosphorous (V) oxychloride (0.13 ml, 1.4 mmol) in DCE (5 ml) was heated at 150 °C under microwave irradiation for 5 min. After cooling, the mixture was diluted with DCM and washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 3% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield compound **E5** (0.175 g, 34%).

Example 6

1'-[8-Chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[isobenzofuran-1(3H),4'piperidine] (E6)

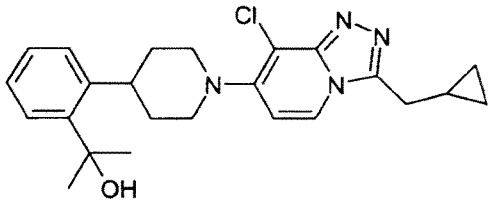


To a stirred solution of compound **D13** (0.2 g, 0.6 mmol) in toluene (3 ml) were added spiro[isobenzofuran-1(3H),4'-piperidine] hydrochloride [CAS 37663-44-8] (0.147 g, 0.779 mmol), palladium (II) acetate (0.007 g, 0.03 mmol), Cs_2CO_3 (0.488 g, 1.5 mmol) and BINAP (0.028 g, 0.045 mmol). The reaction mixture was heated at 95 °C for 16 h in a sealed tube. After cooling to r.t. the mixture was diluted with EtOAc and filtered through a pad of diatomaceous earth. The filtrate was washed with $NaHCO_3$ (aqueous sat. solution) and NaCl (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue thus obtained was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 1% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was purified again by column chromatography (silica gel; DCM/EtOAc up to

60% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was triturated with diisopropyl ether to yield final compound **E6** (0.074 g, 31 %) as a pale yellow solid.

Example 7

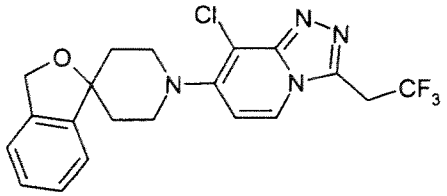
2-[1-[8-Chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-4-piperidinyl]-α,α-dimethyl-benzenemethanol (E7)



To a stirred solution of compound **D13** (003 g, 0.0899 mmol) in toluene (1 ml) were added **D41** (0.0256 g, 0.117 mmol), palladium (II) acetate (1.02 mg, 0.0045 mmol), Cs_2CO_3 (0.0733 g, 0.225 mmol) and BINAP (4.2 mg, 0.0067 mmol). The reaction mixture was heated at 95 °C for 16 h in a sealed tube. An additional amount of palladium (II) acetate (1.02 mg, 0.0045 mmol) and BINAP (4.2 mg, 0.0067 mmol) was added to the reaction mixture, which was then heated at 95 °C for 6 h under microwave irradiation. After cooling to r.t. the mixture was diluted with EtOAc and filtered through a pad of diatomaceous earth. The filtrate was washed with NaCl (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue thus obtained was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 3% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield **E7** (0.02 g, 52 %).

Example 8

1'-[8-Chloro-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-spiro[isobenzofuran-1(3H),4'-piperidine] (E8)

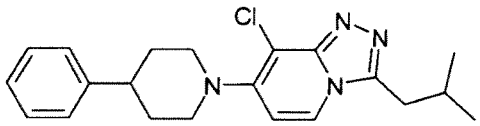


A solution of **D23** (0.369 g, 0.836 mmol) and phosphorus (V) oxychloride (0.156 ml, 1.673 mmol) in CH_3CN (5 ml) was heated at 150 °C under microwave irradiation for 5 min. Additional phosphorous (V) oxychloride (0.5 eq) was added to the reaction

mixture, which was then irradiated at 150 °C for 5 min. After cooling, $NaHCO_3$ (aqueous sat. solution) was added and the resulting mixture was extrated with EtOAc. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH up to 3% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was triturated with DIPE to yield final compound **E8** (0.015 g, 4%).

Example 9

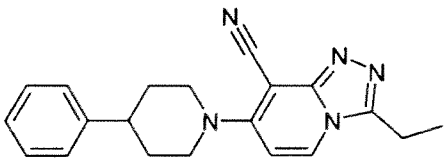
8-Chloro-3-(2-methylpropyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine (E9)



D16 (0.440 g, 1.137 mmol) and phosphorus (V) oxychloride (0.229 mg, 1.365 mmol) in DCE (4 ml) was heated at 150 °C under microwave irradiation for 5 min. After cooling, the resulting mixture was concentrated *in vacuo*. The residue was dissolved in DCM, washed with $NaHCO_3$ (aqueous sat. solution) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH up to 3% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was triturated with DIPE to yield final compound **E9** (0.320 g, 76%).

Example 10

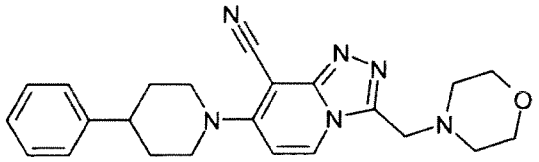
3-ethyl-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile (E10)



A solution of **D7** (0.05 g, 0.17 mmol) and triethylorthopropionate (0.462 ml, 2.556 mmol) in xylene (1 ml) was heated in a sealed tube at 180 °C for 2 h. After cooling, the resulting mixture was concentrated *in vacuo*. The residue thus obtained was triturated with Et_2O to yield final compound **E10** (0.042 g, 74%).

Example 11

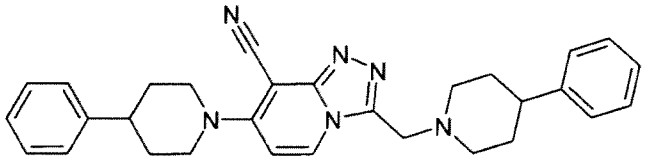
3-(4-Morpholinylmethyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile (E11)



To a solution of **D9** (0.065 g, 0.196 mmol) in DCM (2.5 ml) were added morpholine (0.026 g, 0.294 mmol) and sodium triacetoxy-borohydride (0.062 mg, 0.294 mmol). The resulting mixture was stirred at r.t. for 1 day. The reaction mixture was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product thus obtained was purified by column chromatography (silica gel; DCM/MeOH up to 3% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield final compound **E11** (0.04 g, 51%) as a white solid.

Example 12

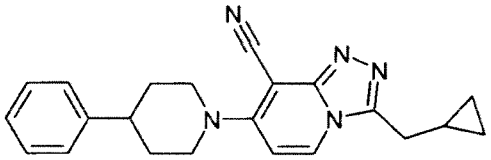
7-(4-phenyl-1-piperidinyl)-3-[(4-phenyl-1-piperidinyl)methyl]-1,2,4triazolo[4,3-a]pyridine-8-carbonitrile (E12)



To a solution of **D8** (0.301 g, 0.992 mmol) in acetic acid (4.5 ml) were added 4-phenylpiperidine (0.160 g, 0.992 mmol) and formaldehyde (0.223 ml, 0.992 mmol; 37%). The resulting mixture was heated in a sealed tube at 80 °C for 16 h. The reaction mixture was diluted with DCM and washed with 2M NaOH. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product thus obtained was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 2% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield a residue that was purified by HPLC (C18Xbridge 19 x 100; mobile phase AcONH4/CH_3CN gradient as eluent). The desired fractions were collected and concentrated *in vacuo* to yield final compound **E12** (0.085 g, 18%).

Example 13

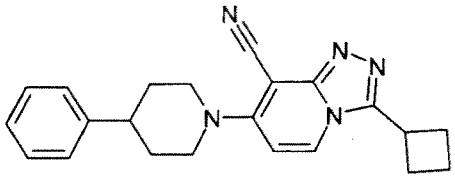
3-(cyclopropylmethyl)-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile (E13)



A mixture of compound **D5** (0.2 g, 0.86 mmol), 4-phenylpiperidine (0.166 g, 1.031 mmol), K_2CO_3 (0.148 g, 1.074 mmol) in CH_3CN (5 ml) was heated in a sealed tube at 150 °C under microwave irradiation for 5 min. The mixture was then cooled to r.t. and the solvents evaporated *in vacuo*. The residue thus obtained was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 3% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield compound **E13** as yellow solid (0.150 g, 49%).

Example 14

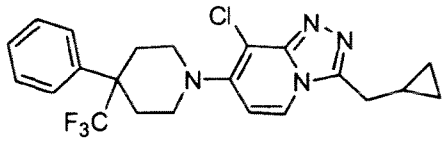
3-Cyclobutyl-7-(4-phenyl-1-piperidinyl)-1,2,4-triazolo[4,3-a]pyridine-8-carbonitrile (E14)



A solution of **D7** (0.190 g, 0.648 mmol), DIPEA (0.226 g, 1.295 mmol), triphenylphosphine (0.510 g, 1.943 mmol), trichloroacetonitrile (0.13 ml, 1.295 mmol) and cyclobutanecarboxylic acid [C.A.S. 3721-95-7] (0.065 g, 0.648 mmol) in DCE (1 0 ml) was heated at 150 °C under microwave irradiation for 18 min. After cooling, the mixture was filtered through a pad of diatomaceous earth. The filtrate was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/MeOH up to 5% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue was triturated with Et_2O yielding compound **E14** (0.06 g, 26%).

Example 15

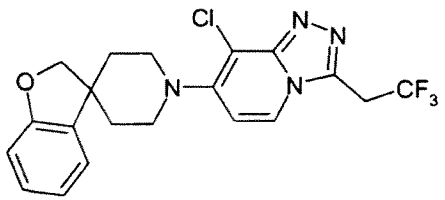
8-Chloro-3-(cyclopropylmethyl)-7-(4-trifluoromethyl-4-phenyl-piperidin-1-yl)-1,2,4-triazolo[4,3-a]pyridine (E15)



To a stirred solution of intermediate **D13** (1 g, 2.998 mmol) in toluene (10 ml) were added intermediate **D47** (0.962 g, 4.197 mmol), palladium(II) acetate (34 mg, 0.15 mmol), Cs_2CO_3 (1.465 g, 4.497 mmol) and BINAP (0.14 g, 0.225 mmol) and the reaction mixture was heated at 95 °C for 16 h in a sealed tube. After cooling to r.t. the mixture was concentrated *in vacuo* and the resulting residue was suspended in water and extracted with DCM. The organic layer was separated, dried (Na_2SO_4), concentrated *in vacuo* and purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 3% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was triturated with EtOAc, diisopropyl ether and EtOH to yield compound **E15** (0.503 g, 39 %).

Example 16

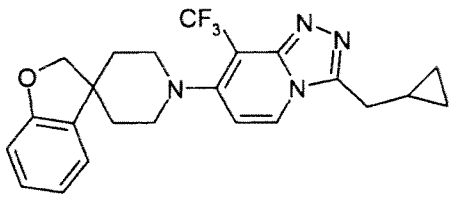
1'-[8-Chloro-3-(2,2,2-trifluoroethyl)[1,2,4]triazolo[4,3-a]pyridin-7-yl]-spiro[1-benzofuran-3,4'-piperidine] (E16)



A solution of intermediate **D50** (1.393 g, 3.16 mmol), phosphorus (V) oxychloride (0.333 ml, 3.476 mmol) and DIPEA (0.605 ml, 3.476 mol) in DCE (15 ml) was heated at 150 °C under microwave irradiation for 5 min. Additional phosphorous (V) oxychloride (0.6 eq) and diisopropyletheylamine (0.6 eq) were added to the reaction mixture, which was then irradiated at 150 °C for 5 min. After cooling, the reaction mixture was washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH up to 5% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was triturated with DIPE to yield final compound **E16** (0.307 g, 23%).

Example 17

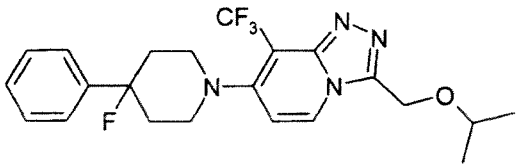
1'-[3-cyclopropylmethyl-8-(trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridin-7-yl]-spiro[1-benzofuran-3,4'-piperidine] (E17)



A mixture of intermediate **D29** (0.13 g, 0.472 mmol), 4-spiro-[3-(2,3-dihydro-benzofuran)]piperidine [CAS 171-77-7] (0.178 g, 0.943 mmol) and DIPEA (0.493 ml, 2.83 mmol) in CH_3CN (3 ml) was heated at 180 °C under microwave irradiation for 1 h. After cooling, $NaHCO_3$ (aqueous sat. solution) was added and the resulting mixture was extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/EtOAc up to 25% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was triturated with DIPE to yield final compound **E17** (0.115 g, 57%).

Example 18

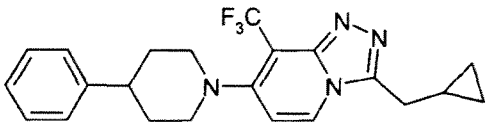
7-(4-Fluoro-4-phenylpiperidin-1-yl)-3-[(1-methylethoxy)methyl]-8-(trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridine (E18)



A suspension of intermediate **D51** (0.245 g, 0.539 mmol), DIPEA-polymer supported (0.616 g, 2.156 mmol, 3.5 mmol/g), triphenylphosphine-polymer supported (0.61 g, 1.348 mmol, 2.21 mmol/g) and trichloroacetonitrile (0.065 ml, 0.647 mmol) in DCE (12 ml) was heated at 150 °C under microwave irradiation for 15 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with DCM and MeOH. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; DCM/ EtOAc up to 80% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue was crystallized from Et_2O/DIPE yielding final compound **E18** (0.69 g, 29%).

Example 43

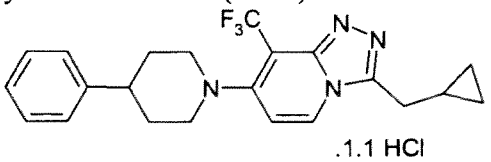
3-(Cyclopropylmethyl)-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine (E43)



A mixture of intermediate **D29** (22.1 g, 7.618 mmol), phenylpiperidine (1.734 g, 9.142 mmol)and DIPEA (2.654 ml, 15.236 mmol) in CH_3CN (8.5 ml) was heated at 180 °C under microwave irradiation for 20 min. After cooling, the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 6% as eluent followed by DCM/EtOAc from 50/50 to 0/100). The desired fractions were collected and concentrated *in vacuo*. The crude product was triturated with DIPE to yield final compound **E43** (0.93 g, 30.4%).

Example 297

3-(Cyclopropylmethyl)-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine hydrochloride salt (E297)

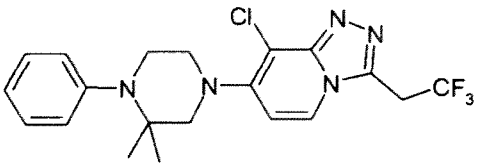


.1.1 HCl

To a stirred solution of final compound **E43** (0.498 g, 1.244 mmol) in 1,4-dioxane (30 ml) and MeOH (2 ml) was added dropwise HCl (4M in 1,4-dioxane, few drops). The resulting suspension was concentrated *in vacuo*. The solid residue was triturated with acetone, filtered and dried *in vacuo* to yield final compound **E297** (0.482 g, 88.7%) as a white solid.

Example 100

8-Chloro-3-(2,2,2-trifluoroethyl)-7-(3,3-dimethyl-4-phenyl-piperazin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine (E100)

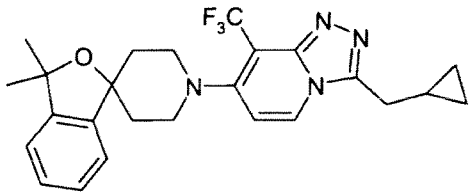


A solution of intermediate **D57** (0.463 g, 1.048 mmol) and phosphorus (V) oxychloride (0.146 ml, 1.572 mmol) in CH_3CN (11 ml) was heated at 150 °C under microwave irradiation for 10 min. After cooling, additional phosphorous (V) oxychloride (0.21 eq)

was added to the reaction mixture, which was then irradiated at 150 °C for 10 min. After cooling, the reaction mixture was poured over a stirred $NaHCO_3$ aqueous sat. solution at 0°C. The aqueous solution was extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 6% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was triturated with DIPE to yield final compound **E100** (0.242 g, 54%).

Example 112

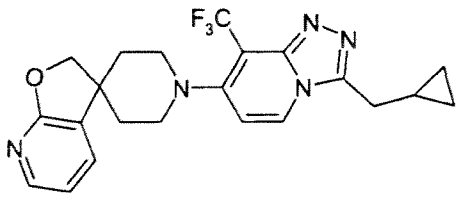
1'-[3-cyclopropylmethyl-8-(trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridin-7-yl]- 3,3-dimethyl-*3H*-spiro[benzo[c]furan-1,4'-piperidine] (E112)



A mixture of intermediate **D29** (0.25 g, 0.907 mmol), 3,3-dimethyl-*3H*-spiro[benzo[c]furan-1,4'-piperidine [C.A.S 180160-92-3] (0.25 g, 1.15 mmol)and DIPEA (0.826 ml, 4.602 mmol) in CH_3CN (5 ml) was heated at 180 °C under microwave irradiation for 20 min. After cooling, the solvent was concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/EtOAc 100/0 to 50/50, then DCM/7M solution of NH_3 in MeOH up to 5% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield final compound **E112** (0.2 g, 38%).

Example 119

1'-[3-cyclopropylmethyl-8-(trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridin-7-yl]-spiro[furo[2,3-b]pyridine-3(2H),4'-piperidine] (E119)

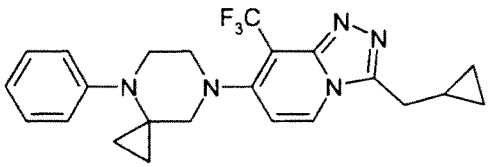


A mixture of intermediate **D29** (0.13 g, 0.472 mmol), **D60** (0.045 g, 0.239 mmol)and DIPEA (0.075 ml, 0.435 mmol) in CH_3CN (1 ml) was heated at 180 °C under microwave irradiation for 20 min. After cooling, additional DIPEA (0.075 ml, 0.435 mmol) was added to the reaction mixture, which was then irradiated at 180 °C for 10

min. After cooling, the mixture was filtered through a pad of diatomaceous earth and extracted with DCM. The solvent was concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH (NH_3) up to 3%, then, DCM/EtOAc 100/0 to 50/50 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield final compound **E119** (0.036 g, 38%) as a cream solid.

Example 121

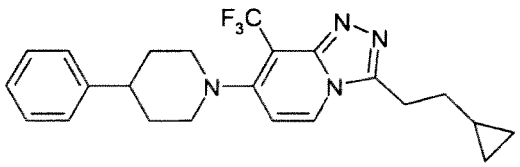
1'-[3-cyclopropylmethyl-8-(trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridin-7-yl]- 4-phenyl-4,7-diaza-spiro[2.5]octane (E121)



A mixture of intermediate **D29** (0.096 g, 0.347 mmol), **D62** (0.092 g, 0.416 mmol)and DIPEA (0.121 ml, 0.693 mmol) in CH_3CN (0.5 ml) was heated at 180 °C under microwave irradiation for 40 min. After cooling, the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/EtOAc 100/0 to 60/40 as eluent). The desired fractions were collected and concentrated *in vacuo*. The crude produdt was crystallized from DIPE to yield final compound **E121** (0.056 g, 38%).

Example 123

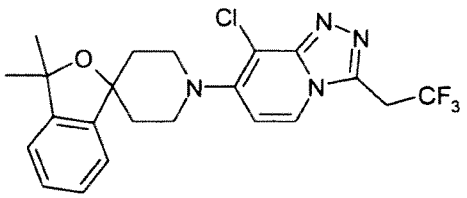
8-Trifluoromethyl-3-(2'-cyclopropyl)ethyl-7-(4-phenylpiperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine (E123)



A mixture of intermediate **D64** (0.15 g, 0.518 mmol), phenylpiperidine (0.109 g, 0.673 mmol)and DIPEA (0.316 ml, 1.812 mmol) in CH_3CN (4 ml) was heated in a sealed tube at 95 °C overnight. After cooling, additional phenylpiperidine (0.040 g) was added. The mixture was heated again at 95°C for 4 h and then at r.t. overnight. The precipitate was collected and washed with CH_3CN and DIPE to yield final compound **E123** (0.120 g, 56%) as a white solid.

Example 139

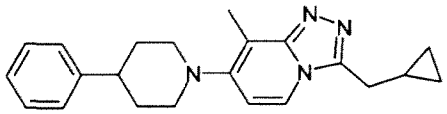
8-Chloro-3-(2,2,2-trifluoroethyl)-7-(3,3-dimethyl-*3H*-spiro[benzo[c]furan-1,4'-piperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine (E1139



A mixture of intermediate **D67** (0.527 g, 1.059 mmol) and copper (II) chloride (0.285 g, 2.118 mmol) in DMF (6.6 ml) was heated at 50°C for 1 h. After cooling at r.t., the mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc and washed with NH_4Cl/NH_4OH mixture and water. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 8% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield final compound **E139** (0.156 g, 32%).

Example 145

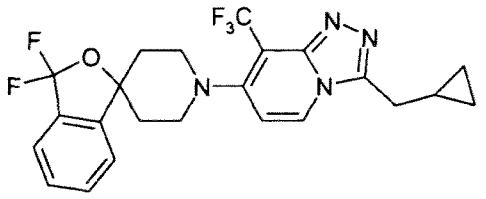
3-Cyclopropylmethyl-8-methyl-7-(4-phenyl-piperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine (E145)



To a stirred solution of intermediate **D71** (0.14 mg, 0.632 mmol) in toluene (6 ml) were added phenylpiperidine (0.132 g, 0.821 mmol), palladium(II) acetate (7.15 mg, 0.0316 mmol), tert-BuONa (0.091 g, 0.947 mmol) and BINAP (0.029 g, 0.047 mmol) and the reaction mixture was heated in a sealed tube at 100 °C for 24 h. After cooling, the reaction mixture was refilled with additional amount of phenylpiperidine (20 mg), palladium(II) acetate (7.15 mg), tert-BuONa (30 mg) and BINAP (30 mg) and heated at 100°C overnight. After cooling, the mixture was diluted with EtOAc and washed with water. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/EtOAc 100/0 to 100/0, then DCM/7M solution of NH_3 in MeOH up to 3% as eluent). The desired fractions were collected and concentrated *in vacuo* to a residue that was triturated with DIPE to yield final compound **E145** (0.15 g, 69%).

Example 147

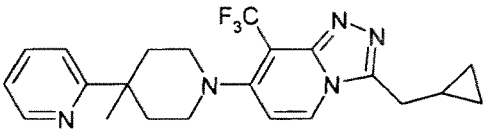
1'-[3-cyclopropylmethyl-8-(trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridin-7-yl]-3,3-difluoro-*3H*-spiro[benzo[c]furan-1,4'-piperidine] (E147)



A mixture of intermediate **D29** (0.159 g, 0.577 mmol), intermediate **D74** (0.13 g, 0.577 mmol)and DIPEA (0.298 g, 2.31 mmol) in CH_3CN (3 ml) was heated at 120 °C for 24 h. After cooling, the solvent was concentrated *in vacuo*. The residue was dissolved in DCM and washed with Na_2CO_3 (10% aqueous solution). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by HPLC to yield final compound **E147** (0.058 g, 21.6%).

Example 148

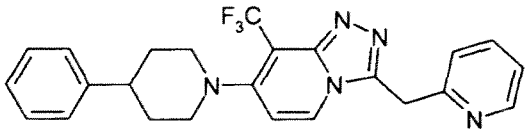
8-Trifluoromethyl-3-(cyclopropylmethyl)-7-(4-methyl-4-(2-pyridinyl)-piperidin-1-yl)-1,2,4-triazolo[4,3-a]pyridine (E148)



A mixture of intermediate **D29** (0.150 g, 0.544 mmol), **D78** (0.169 g, 0.816 mmol)and DIPEA (0.237 ml, 1.36 mmol) in CH_3CN (5 ml) was heated at 180 °C under microwave irradiation for 45 min. After cooling, the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH 95/5 as eluent). The desired fractions were collected and concentrated *in vacuo*. The crude product was treated with DIPE to yield final compound **E148** (0.085 g, 37.6%) as a cream solid.

Example 153

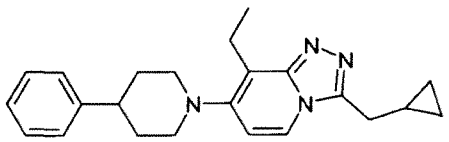
8-Trifluoromethyl-3-(2-pyridinylmethyl)-7-(4-phenylpiperidin-1-yl)-1,2,4-triazolo[4,3-a]pyridine (E153)



A mixture of intermediate **D80** (0.18 g, 0.576 mmol), phenylpiperidine (0.111 g, 0.691 mmol)and DIPEA (0.201 ml, 1.151 mmol) in CH_3CN (5 ml) was heated at 180 °C under microwave irradiation for 20 min. After cooling, the reaction mixture was refilled with additional phenylpiperidine (0.5 eq.) and DIPEA (0.1 ml) and heated at 180 °C under microwave irradiation for 20 min. After cooling, the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH as eluent). The desired fractions were collected and concentrated *in vacuo*. The crude product was triturated with Et_2O to yield final compound **E153** (0.11 g, 44%)

Example 171

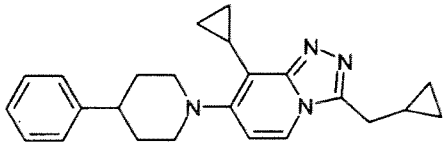
3-Cyclopropylmethyl-8-ethyl-7-(4-phenylpiperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine (E171)



To a stirred solution of intermediate **D81** (0.05 mg, 0.212 mmol) in toluene (3 ml) were added phenylpiperidine (0.044 g, 0.276 mmol), palladium(II) acetate (2.4 mg, 0.0106 mmol), tert-BuONa (0.031 g, 0.318 mmol) and BINAP (9.9 g, 0.016 mmol) and the reaction mixture was heated in a sealed tube at 100 °C for 24 h. After cooling, the mixture was diluted with EtOAc and washed with water. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH from 100/0 to 92/8 as eluent). The desired fractions were collected and concentrated *in vacuo* to a residue that was triturated with DIPE to yield final compound **E171** (0.042 g, 55%) as an off-white solid.

Example 159

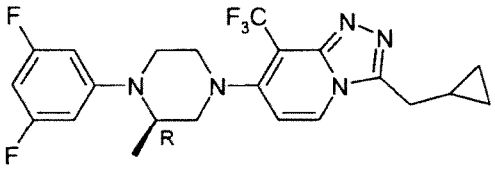
3-Cyclopropylmethyl-8-cyclopropyl-7-(4-phenylpiperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyridine (E159)



To a stirred solution of intermediate **D82** (0.07 mg, 0.283 mmol) in toluene (3 ml) were added phenylpiperidine (0.059 g, 0.367 mmol), palladium(II) acetate (3.2 mg, 0.014 mmol), tert-BuONa (0.041 g, 0.424 mmol) and BINAP (13.2 g, 0.0212 mmol) and the reaction mixture was heated in a sealed tube at 100 °C for 24 h. After cooling, the mixture was diluted with EtOAc and washed with water. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH from 100/0 to 95/5 as eluent). The desired fractions were collected and concentrated *in vacuo* to a residue that was triturated with DIPE to yield final compound **E159** (0.060 g, 57%) as a white solid.

Example 182

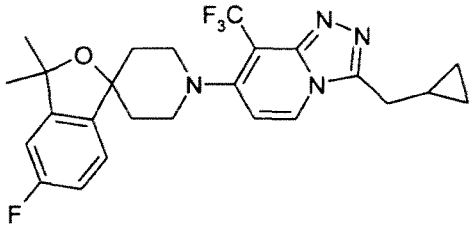
3-(Cyclopropylmethyl)-7-((3R)-4-3,5-difluorophenyl-3-methylpiperazin-1-yl)-(8-trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine (E182)



A mixture of intermediate **D29** (0.100 g, 0.363 mmol), (R)-1-(3,5-difluorophenyl)-2-methylpiperazine [C.A.S.845740-74-1] (0.137 g, 0.472 mmol)and DIPEA (0.126 ml, 0.726 mmol) in CH_3CN (1 ml) was heated at 180 °C under microwave irradiation for 40 min. After cooling, the reaction mixture was refilled with (R)-1-(3,5-difluorophenyl)-2-methylpiperazine (1 eq.) and then heated at 180 °C under microwave irradiation for 1 hour. After cooling, the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/EtOAc from 100/0 to 60/40 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield final compound **E182** (0.021 g, 13%). Optical rotation -131.7° (589 nm, c 0.63 w/v%, DMF, 20°C)

Example 200

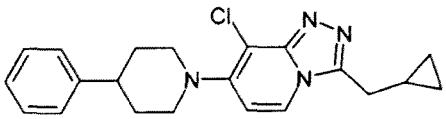
1'-[3-(Cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-5-fluoro-3,3-dimethyl-spiro[isobenzofuran-1(3H),4'-piperidine] (E200)



A mixture of intermediate **D29** (0.179 g, 0.649 mmol), intermediate **D85** (0.168 g, 0.714 mmol)and DIPEA (0.396 ml, 2.272 mmol) in CH_3CN (3 ml) was heated at 195°C overnight. After cooling, the precipitate was filtered off and washed with CH_3CN. The filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH from 100/0 to 97/3 as eluent). The desired fractions were collected and concentrated *in vacuo* to give a residue that was triturated with Et_2O to yield final compound **E200** (0.135 g, 61%).

Example 26

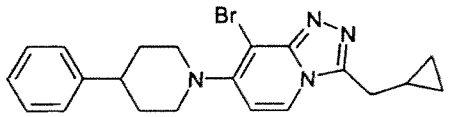
8-Chloro-3-cyclopropylmethyl-7-[4-phenyl-piperidin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine (E26)



To a stirred solution of intermediate **D13** (0.2 g, 0.6 mmol) in toluene (9.5 ml) were added phenylpiperidine (0.125 g, 0.78 mmol), palladium(II) acetate (6.8 mg, 0.03 mmol), Cs_2CO_3 (0.391 g, 1.2 mmol) and BINAP (0.028 g, 0.045 mmol) and the reaction mixture was heated at 120 °C for 16 h in a sealed tube. After cooling, the mixture was filtered through a pad of diatomaceous earth. The filtrate was concentrated *in vacuo*. The residue was purified again by column chromatography (silica gel; DCM/MeOH from 100/0 to 80/20 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield final compound **E26** (0.135 g, 61%).

Example 207

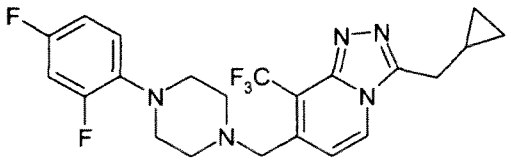
8-Bromo-3-cyclopropylmethyl-7-[4-phenylpiperidin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine (E207)



To a stirred solution of intermediate **D86** (0.08 g, 0.241 mmol) in DCM (4 ml) was added *N*-bromosuccinimide (0.051 g, 0.289 mmol). The resulting mixture was stirred at r.t. for 40 min. The mixture was carefully washed with $NaHCO_3$ (aqueous sat. solution) and extracted with DCM. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/EtOAc from 100/0 to 73/27 as eluent). The desired fractions were collected and concentrated *in vacuo* to a residue that was triturated with Et_2O to yield final compound **E207** (0.055 g, 56%).

Example 224

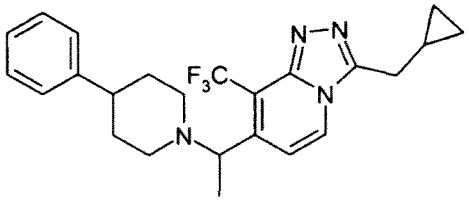
3-(Cyclopropylmethyl)-7-[[4-(2,4-difluorophenyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine (E224)



To a solution of 1-(2,4-difluorophenyl)piperazine [C.A.S. 115761-79-0] (0.088 g, 0.446 mmol) in DCE (2.14 ml) stirred at r.t. was added **D88** (0.1 g, 0.371 mmol) and the resulting mixture was stirred at r.t. overnight. Then, acetic acid (0.037 ml) was added and stirred at r.t. for 4 h more. Then, sodium triacetoxy-borohydride (0.87 g, 0.409 mmol) was added and stirred at r.t. overnight. The reaction mixture was neutralized with Na_2CO_3 (aqueous sat. solution) and extracted with DCM. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The crude product thus obtained was purified by column chromatography (silica gel; DCM/EtOAc from 100/0 to 50/50 as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue obtained was triturated with DIPE to yield final compound **E224** (0.107 g, 64%).

Example 244

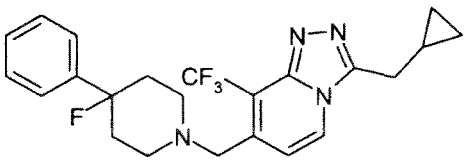
3-cyclopropylmethyl-7-[1-(4-phenyl-1-piperidinyl)ethyl]-8-trifluoromethyl-1,2,4-triazolo[4,3-a]pyridine (E244)



A mixture of **D92** (0.095 g, 0.216 mmol), phenylpiperidine (0.035 g, 0.216 mmol) and K_2CO_3 (0.06 g, 0.431 mmol) in CH_3CN (4.9 ml) was heated in a sealed tube at 85 °C for 5 days. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with EtOAc. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/EtOAc from 100/0 to 50/50 as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was triturated with DIPE to yield final compound **E244** (0.035 g, 32%).

Example 250

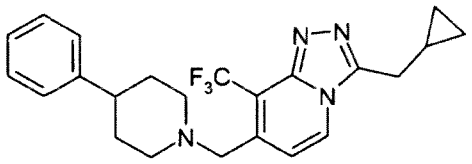
3-(Cyclopropylmethyl)-7-[(4-fluoro-4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine (E250)



To a solution of 4-fluoro-4-phenylpiperidine hydrochloride [C.A.S. 1056382-25-2] (0.096 g, 0.446 mmol) in DCE stirred at r.t. (2.14 ml) was added **D88** (0.1 g, 0.371 mmol) and the resulting mixture was stirred at r.t. overnight. Then, acetic acid (0.037 ml) was added and stirred at r.t. for 4 h. Then, sodium triacetoxy-borohydride (0.87 g, 0.409 mmol) was added and stirred at r.t. overnight. The reaction mixture was neutralized with Na_2CO_3 (aqueous sat. solution) and extracted with DCM. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The crude product thus obtained was purified by column chromatography (silica gel; DCM/EtOAc from 100/0 to 50/50 as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue obtained was triturated with Et_2O to yield final compound **E250** (0.029 g, 18%).

Example 298

3-(Cyclopropylmethyl)-7-[(4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine (E298)



Method A

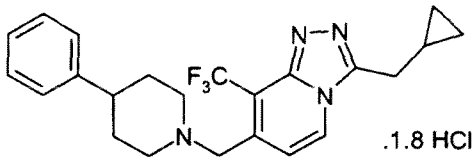
D90 (0.4 g, 0.9 mmol) was added to a stirred solution of phenylpiperidine (0.174 mg, 1.08 mmol) and DIPEA (0.233 ml, 1.35 mmol) in CH_3CN (10 ml). The resulting mixture was heated in a sealed tube at 100 °C for 4 h. The resulting mixture was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/EtOAc from 100/0 to 50/50 as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was triturated with DIPE to yield final compound **E298** (0.272 g, 77%) as a white solid.

Method B

To a mixture of compound **D29** (0.120 g, 0.435 mmol), potassium trifluoro[(4-phenyl-1-piperidinyl)methyl]-borate(1-) (1:1) [C.A.S. 1152617-06-5] (0.367 g, 1.306 mmol) in THF (4 ml) and water (0.4 ml) under a nitrogen atmosphere were added 2-(dicyclohexylphosphino)-2',4',6'-tri-i-propyl-1,1'-biphenyl X-Phos (12.45 mg, 0.026 mmol), palladium(II) acetate (2.93 mg, 0.013 mmol) and Cs_2CO_3 (0.426 g, 1.306 mmol). The reaction mixture was heated at 80 °C for 3 days and at r.t. for 2 days. The mixture was washed with water and extracted with EtOAc. The organic layer was separated and concentrated *in vacuo*. The residue was purified by manifold (Sep-Pak® silica cartridge; DCM/acetone from 100/0 to 90/10 as eluent) followed by column chromatography (silica gel; DCM/EtOAc from 100/0 to 80/20 as eluent). The desired fractions were collected and concentrated *in vacuo* to a residue that was triturated with DIPE to yield final compound **E298** (0.065 g, 25%).

Example 214

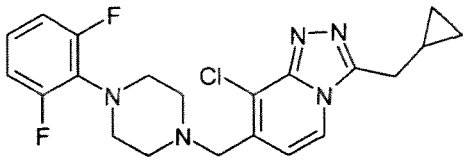
3-(Cyclopropylmethyl)-7-[(4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine hydrochloride salt (E214)



To a stirred solution of final compound **E298** (0.065 g, 0.156 mmol) in MeOH (0.25 ml) and 1,4-dioxane (3.76 ml) was added dropwise HCl (4M in 1,4-dioxane, few drops). The resulting suspension was concentrated *in vacuo*. The solid residue was triturated with acetone, filtered and dried *in vacuo* to yield final compound **E214** (0.061 g, 82%).

Example 282

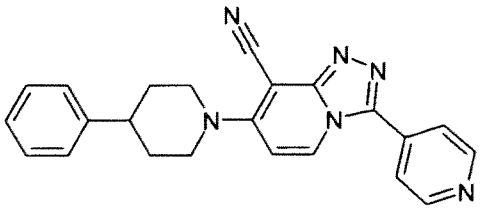
8-Chloro-3-cyclopropylmethyl-7-[(4-(2,6-difluorophenyl-1-piperazinyl)methyl]-1,2,4-triazolo[4,3-a]pyridine (E282)



D96 (0.1 g, 0.39 mmol) was added to a stirred solution of 1-(2,6-difluorophenyl)-piperazine (0.96 mg, 0.429 mmol) and DIPEA (0.094 ml, 0.547 mmol) in CH_3CN (2 ml). The resulting mixture was heated in a sealed tube at 100 °C for 4 h. The resulting mixture was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 4% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was triturated with DIPE to yield final compound **E282** (0.1 g, 61%) as an off white solid.

Example 206

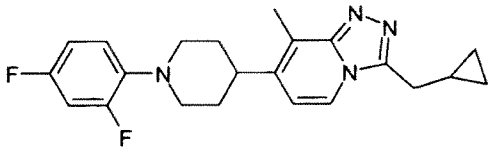
8-Cyano-3-(4-pyridinyl)-7-[4-phenylpiperidin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine (E206)



A suspension of **D97** (0.234 mg, 0.612 mmol), 4-pyridinyl boronic acid (0.113 g, 0.918 mmol) and $Pd(PPh_3)_4$ (0.035 g, 0.031 mmol) in $NaHCO_3$, (1.5 ml, aqueous sat. solution) and 1,4-dioxane (3 ml) was heated at 150 °C under microwave irradiation for 10 min. After cooling, the mixture was refilled with additional pyridinyl-4-boronic acid (0.050 g) and $Pd(PPh_3)_4$ (0.020 g). The mixture was heated at 150 °C under microwave irradiation for 10 min. After cooling to r.t. the mixture was filtered through a pad of diatomaceous earth and washed with DCM. The filtrate was collected, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/EtOAc 100/0 to 70/30 as eluent). The desired fractions were collected and concentrated *in vacuo* to give a residue that was triturated with Et_2O to yield final compound **E206** (0.055 g, 24%) as a yellow solid.

Example 204

3-Cyclopropylmethyl-7-[1-(2,4-difluoro-phenyl)-piperidin-4-yl]-8-methyl-[1,2,4]triazolo[4,3-a]pyridine (E204)



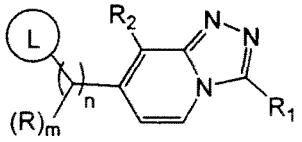
To a stirred solution of intermediate **D101** (0.148 mg, 0.546 mmol) in toluene (7 ml) were added 1-bromo-2,4-difluorobenzene (0.068 g, 0.6 mmol), palladium(II) acetate (6.2 mg, 0.0273 mmol), tert-BuONa (0.105 g, 1.092 mmol) and BINAP (0.034 g, 0.055 mmol) and the reaction mixture was heated in a sealed tube at 85 °C for two days. After cooling, the mixture was diluted with EtOAc and filtered through a pad of diatomaceous earth. The filtrate was washed with water and NaCl (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 5% as eluent). The desired fractions were collected and concentrated *in vacuo* to a residue that was crystallized from Et_2O to yield final compound **E204** (0.053 g, 25.4%).

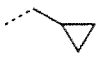
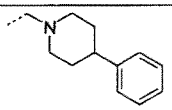
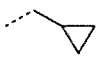
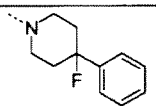
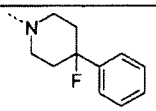
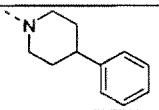
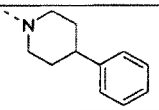
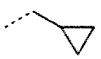
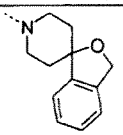
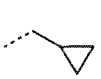
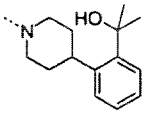
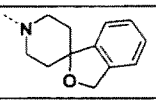
Table 1 below lists compounds of Formula (I), which were prepared according to the above examples.

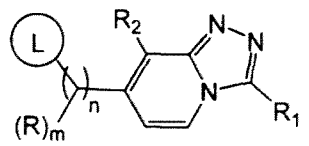
Table 1 : Compounds prepared according to Formula (I).

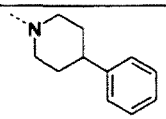
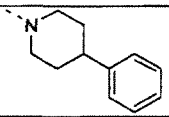
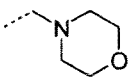
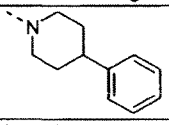
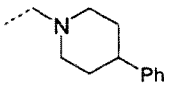
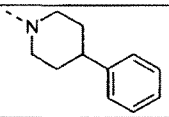
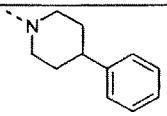
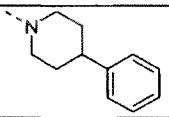
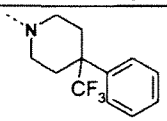
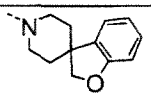
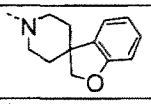
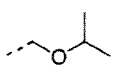
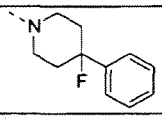
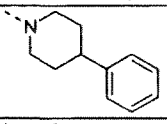
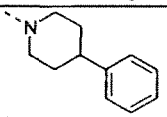
* means exemplified compounds in the experimental section.

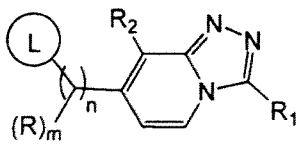
Whenever cis- or trans-stereochemistry is indicated, it denotes, that it is, where applicable, a mixture of all possible cis- or trans-stereoisomeric forms, in particular, a racemic mixture, unless otherwise indicated. When the mixture was separated, the different forms are denoted, for example, cis-a and cis-b.

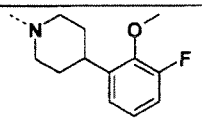
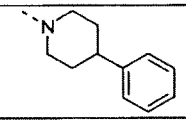
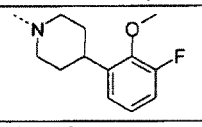
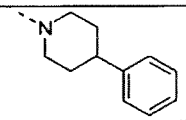
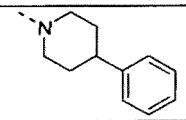
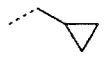
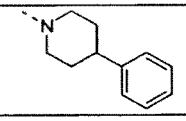
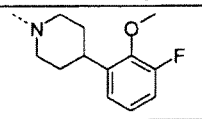
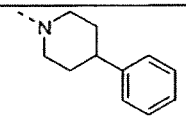
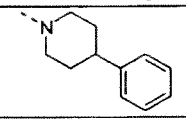
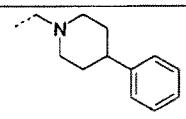
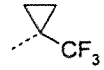
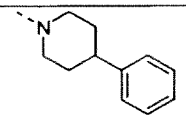
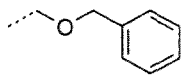
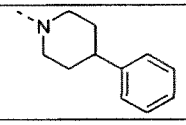


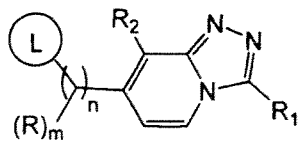
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2	E2*		$--CF_3$		
3	E3*	$--CH_2-CF_3$	--Cl		
4	E4*	$--(CH_2)_3-CH_3$	$--CF_3$		
5	E5*	$--CH_2-O-CH_2-CH_3$	--Cl		
6	E6*		--Cl		
7	E7*		--Cl		
8	E8*	$--CH_2-CF_3$	--Cl		

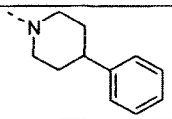
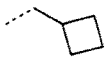
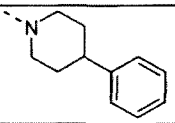
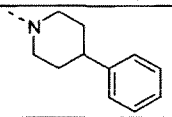
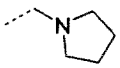
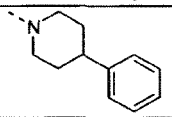
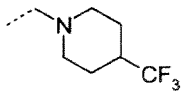
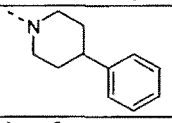
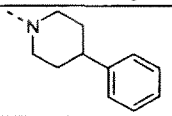
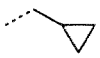
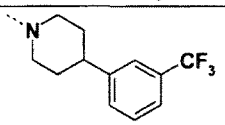
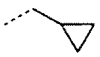
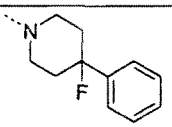
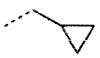
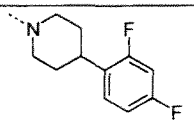
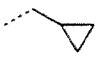
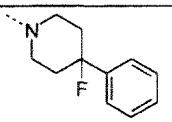
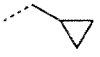
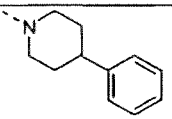


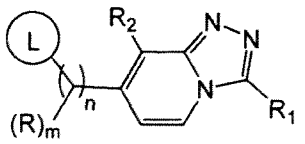
Co. no.	Exp. no.	R^1	R^2	$-[CH(R)_m]_n-L$	Stereochem./Salt Form/Optical Rotation (OR)
9	E9*		--Cl		
10	E10*	$--CH_2-CH_3$	--CN		
11	E11*		--CN		
12	E12*		--CN		
13	E13		--CN		
14	E14*		--CN		
15	E15		--Cl		
16	E16	$--CH_2-CF_3$	--Cl		
17	E17		$--CF_3$		
18	E18		$--CF_3$		
19	E10	$--CH_3$	--CN		
20	E2	$--CH_2-CF_3$	--CN		

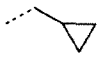
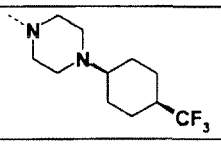
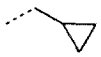
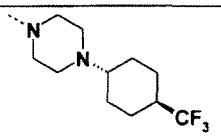
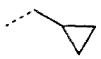
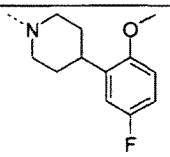
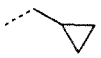
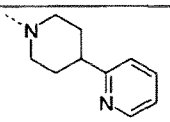
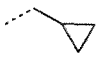
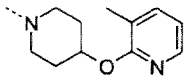
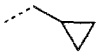
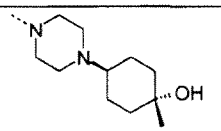
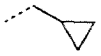
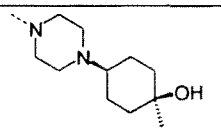
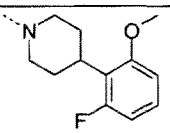
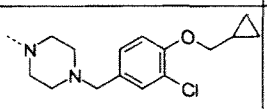
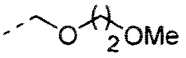
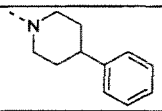
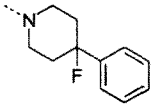


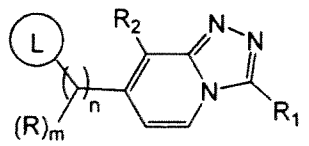
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
21	E10	--CH_2-CH_3	--CN		
22	E1	--CH_2-CF_3	--Cl		
23	E1	--CH_2-CH_2-CH_3	--CN		
24	E1	--CH_2-O-CH_3	--CN		
25	E10	--CH_2-CH_3	--Cl		
26	E26* ; E1		--Cl		
27	E1	--CH_2-CF_3	--CN		
28	E13	--$CH_2CH_2CH_3$	--CN		
29	E1		--CN		
30	E1	--CH_2-CF_3	--Cl		
31	E1		--CN		
32	E1		--CN		

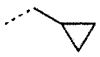
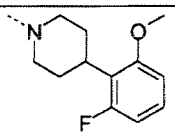
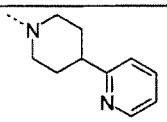
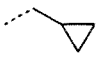
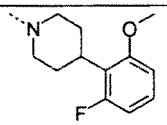
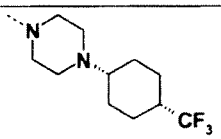
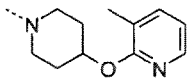
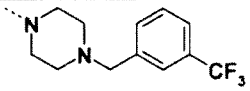
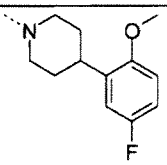
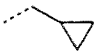
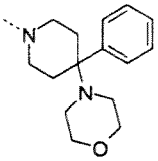
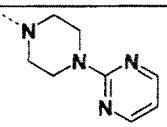
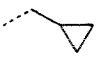
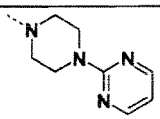


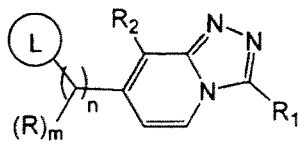
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
33	E1	--CF_2-CH_3	--CN		
34	E1		--CN		
35	E1	--$C(CH_3)_3$	--CN		
36	E12		--CN		
37	E12		--CN		
38	E1	--CH_2-CF_3	--CF_3		
39	E1		--Cl		
40	E13		--CN		
41	E2		--Cl		
42	E2		--Cl		
43	E1		--CF_3		

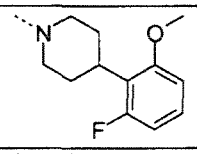
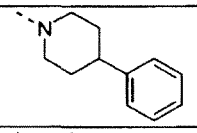
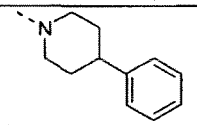
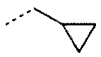
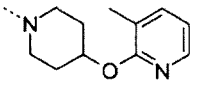
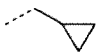
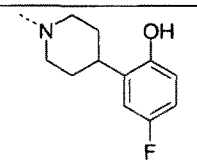
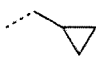
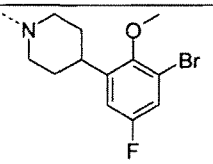
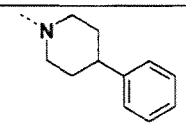
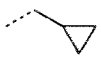
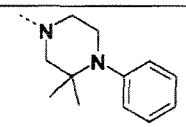
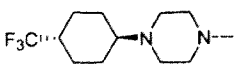
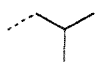
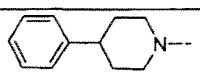
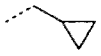
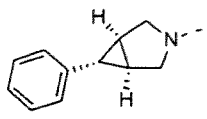


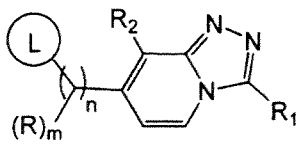
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
44	E13		--CN		cis
45	E13		--CN		trans
46	E1		--Cl		
47	E1		--Cl		
48	E1		--Cl		
49	E13		--CN		trans
50	E13		--CN		cis
51	E13	--CH_2-CF_3	--CN		
52	E13	--CH_2-CF_3	--CN		
53	E1		--Cl		
54	E13	--CH_2-CF_3	--CN		

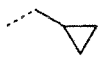
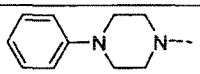
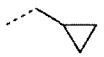
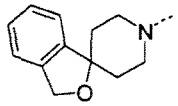
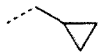
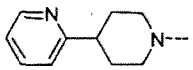
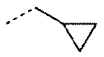
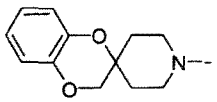
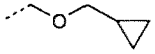
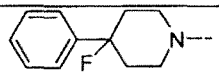
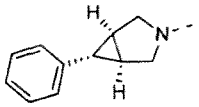
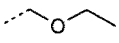
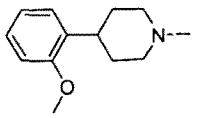
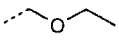
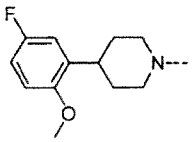
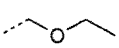
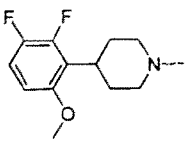
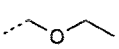
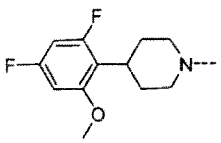


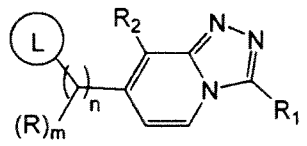
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
55	E13		--Cl		
56	E2	--CH_2-CF_3	--Cl		
57	E1		--CN		
58	E13	--CH_2-CF_3	--CN		cis
59	E2	--CH_2-CF_3	--Cl		
60	E13	--CH_2-CF_3	--CN		
61	E1	--CH_2-CF_3	--Cl		
62	E1		--CF_3		
63	E1	--CH_2-CF_3	--Cl		
64	E1		--CF_3		

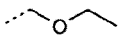
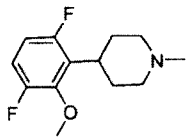
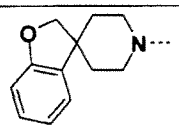
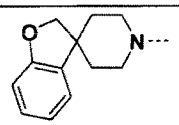
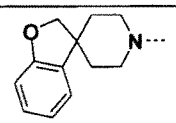
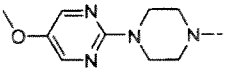
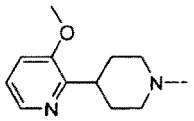
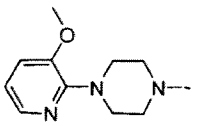
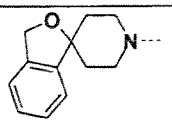
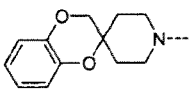
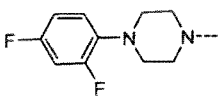


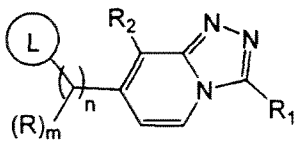
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
65	E1	--CH_2-CF_3	--Cl		
66	E1	--CH_2-CH_3	--CF_3		
67	E1	--CH_2-CH_2-CH_3	--CF_3		
68	E2		--CF_3		
69	E13		--Cl		
70	E6		--Cl		
71	E1	--CH_2-CH_2-CF_3	--Cl		
72	E2		--CF_3		
73	E13	--CH_2-CF_3	--CN		trans
74	E1		--CN		
75	E2		--CF_3		rac-(2aα,3α,3aα)

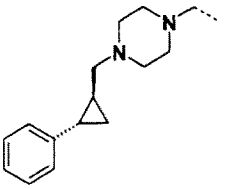
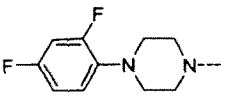
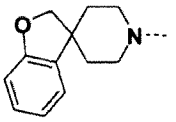
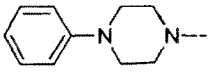
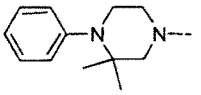
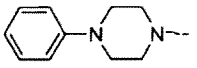
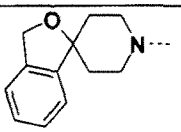
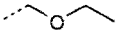
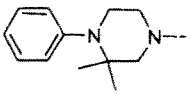
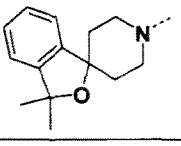
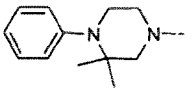


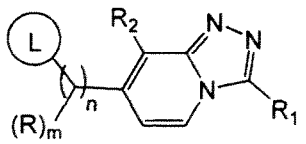
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
76	E13		--CF_3		
77	E13		--CF_3		
78	E13		--CF_3		
79	E13		--CF_3		
80	E2		--CF_3		
81	E1	--CH_2-CF_3	--Cl		rac-(2aα,3α,3aα)
82	E6		--Cl		
83	E6		--Cl		
84	E6		--Cl		
85	E6		--Cl		

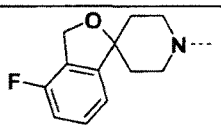
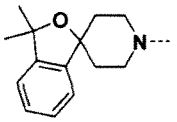
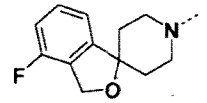
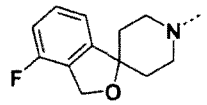
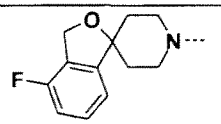
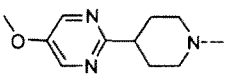
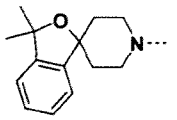
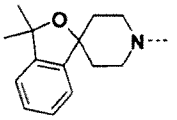
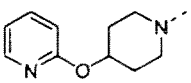
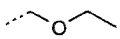
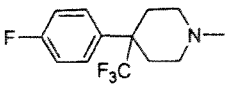
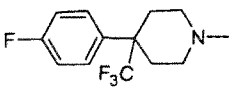


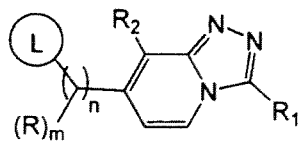
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
86	E6		--Cl		
87	E1		--CF_3		
88	E6		--Cl		
89	E13		--CF_3		
90	E13		--CF_3		
91	E13		--CF_3		
92	E13		--CF_3		
93	E6		--Cl		
94	E1	--CH_2-CF_3	--Cl		
95	E6		--Cl		

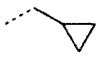
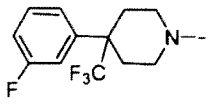
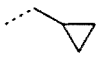
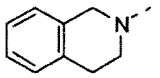
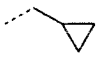
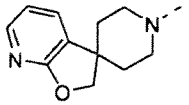
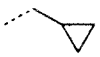
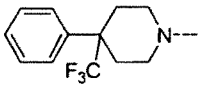
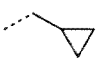
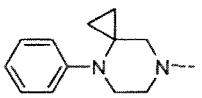
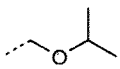
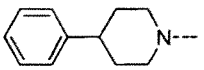
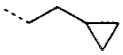
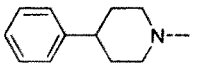
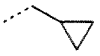
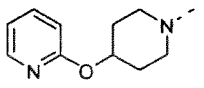
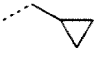
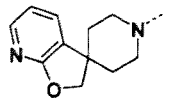
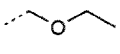
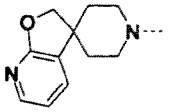
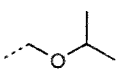
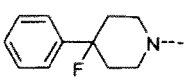


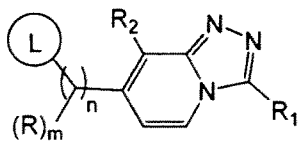
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
96	E6		--Cl		trans
97	E1	--CH_2-CF_3	--Cl		
98	E1	--CH_2-CF_3	--Cl		
99	E6		--Cl		
100	E100 *	--CH_2-CF_3	--Cl		
101	E1	--CH_2-CF_3	--Cl		
102	E6		--Cl		
103	E6		--Cl		
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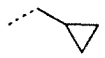
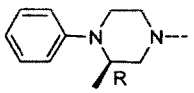
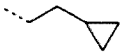
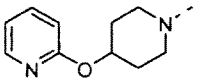
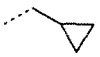
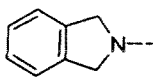
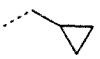
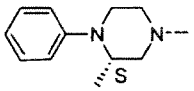
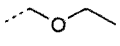
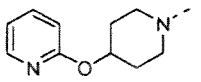
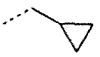
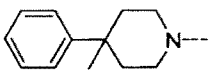
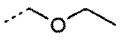
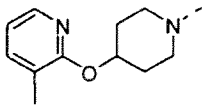
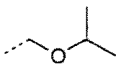
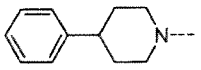
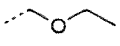
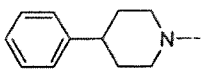
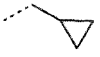
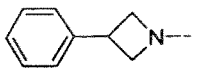
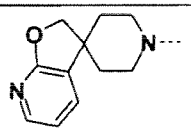


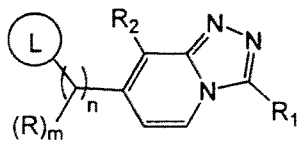
Co. no.	Exp. no.	R^1	R^2	$-[CH(R)_m]_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
106	E6		--Cl		
107	E6		--Cl		
108	E6		--Cl		.1HCl .1.5H_2O
109	E13		--CF_3		
110	E13		--CF_3		
111	E13		--CF_3		
112	E112 *		--CF_3		
113	E13		--CF_3		
114	E2	--CH_2-CF_3	--Cl		
115	E6		--Cl		
116	E6		--Cl		

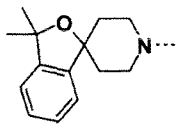
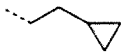
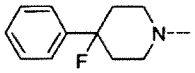
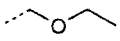
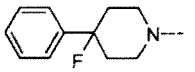
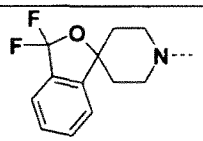
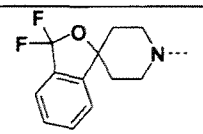
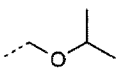
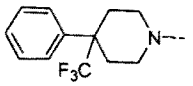
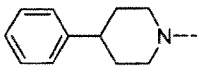
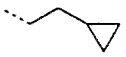
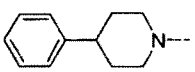
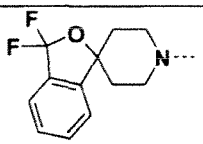
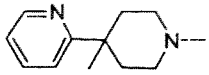
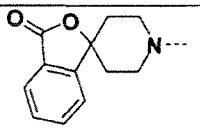


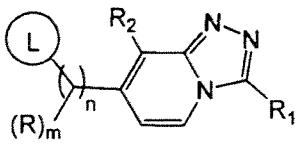
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
117	E6		--Cl		
118	E13		--CF_3		
119	E119 *		--CF_3		
120	E13		--CN		
121	E121 *; E13		--CF_3		
122	E13		--CF_3		
123	E123 *		--CF_3		
124	E13		--CF_3		
125	E6		--Cl		
126	E6		--Cl		
127	E6		--Cl		

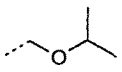
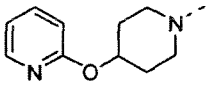
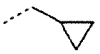
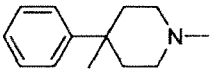
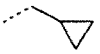
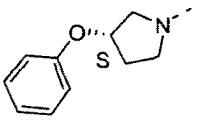
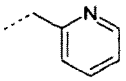
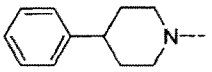
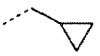
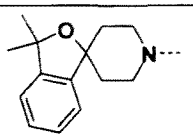
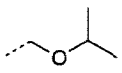
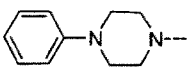
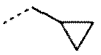
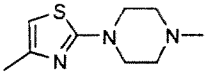
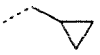
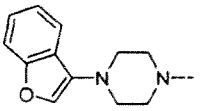
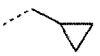
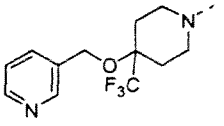
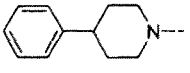


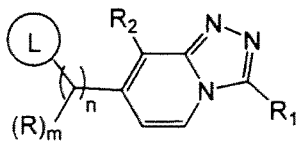
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
128	E13		--CF_3		OR: -131.1° (589 nm,c 0.52 w/v %, DMF, 20°C)
129	E13		--CF_3		
130	E13		--CF_3		
131	E13		--CF_3		OR: -132° (589 nm,c 0.52 w/v %, DMF, 20°C)
132	E13		--CF_3		
133	E6		--Cl		
134	E13		--CF_3		
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136	E13		--CF_3		
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138	E1	--CH_2-CF_3	--Cl		

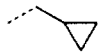
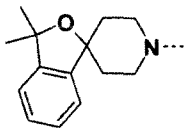
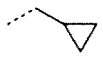
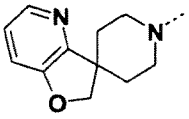
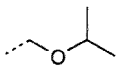
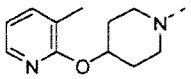
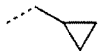
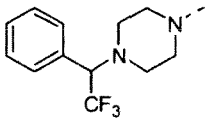
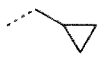
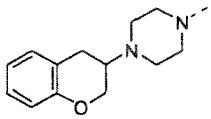
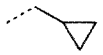
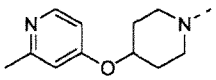
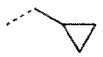
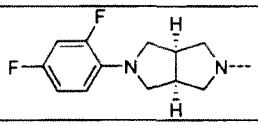
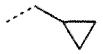
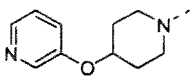
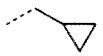
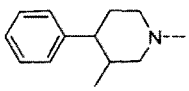
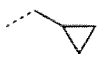
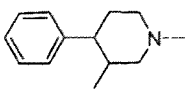
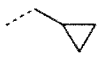
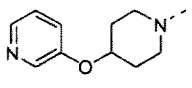


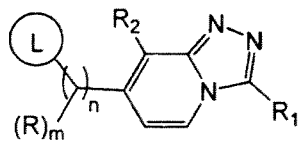
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
139	E139 *, E1	--CH_2-CF_3	--Cl		
140	E6		--Cl		
141	E13		--CF_3		
142	E13		--CF_3		
143	E6		--Cl		
144	E145		--Cl		
145	E145 *		--CH_3		
146	E6		--Cl		
147	E147 *		--CF_3		
148	E148 *		--CF_3		
149	E6		--Cl		

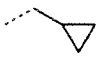
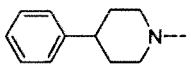
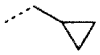
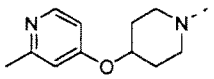
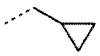
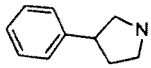
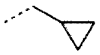
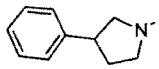
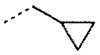
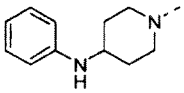
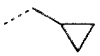
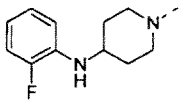
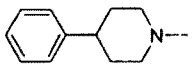
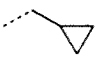
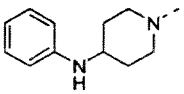
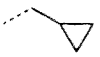
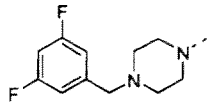
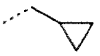
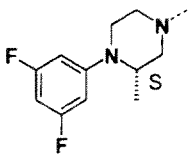
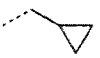
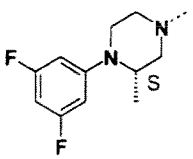


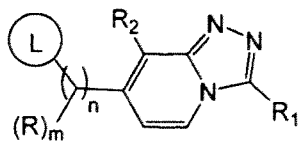
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
150	E13		--CF_3		
151	E13		--CF_3		
152	E13		--CF_3		S
153	E153 *, E13		--CF_3		
154	E6		--CH_3		
155	E13		--CF_3		
156	E6		--Cl		
157	E6		--Cl		
158	E6		--Cl		
159	E159 *				

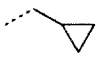
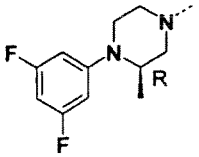
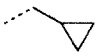
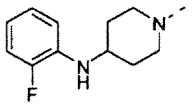
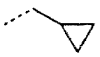
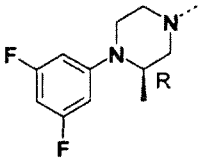
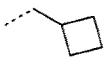
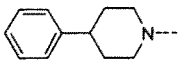
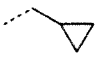
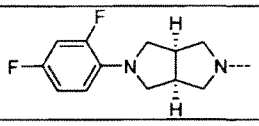
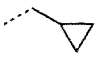
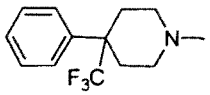
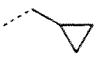
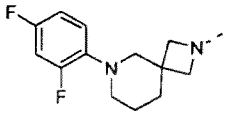
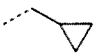
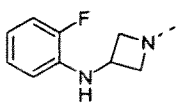
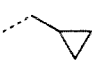
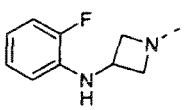


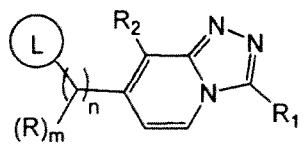
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
160	E6				
161	E6		--Cl		
162	E13		--CF_3		
163	E6		--Cl		
164	E6		--Cl		
165	E13		--CF_3		
166	E13		--CF_3		cis
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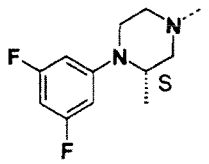
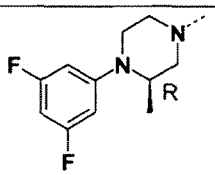
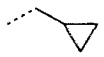
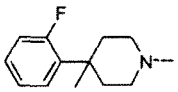
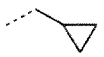
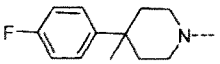
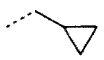
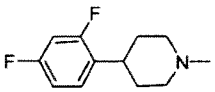
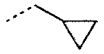
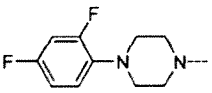
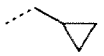
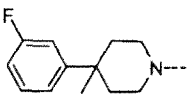
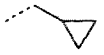
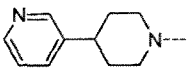
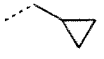
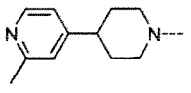
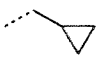
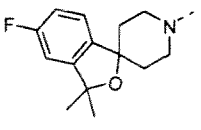


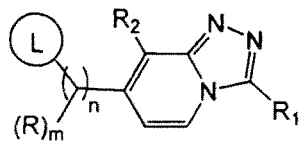
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
171	E171 *				
172	E6		--Cl		
173	E6		--Cl		
174	E13		--CF_3		
175	E13		--CF_3		
176	E6		--Cl		
177	E13		--CF_3		
178	E6		--Cl		
179	E6		--Cl		
180	E13		--CF_3		S-enantiomer OR: -138.4° (589 nm,c 0.51 w/v %, DMF, 20°C)
181	E6		--Cl		S-enantiomer OR: 26.2° (589 nm,c 0.52 w/v %, DMF, 20°C)

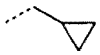
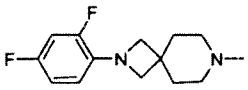
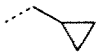
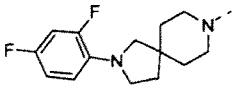
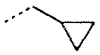
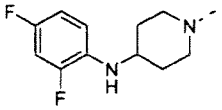
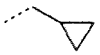
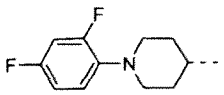
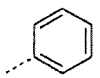
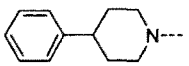
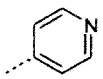
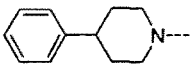
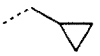
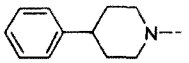
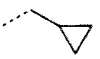
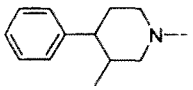
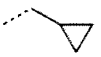
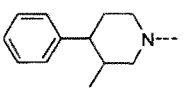
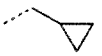
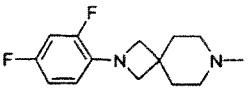


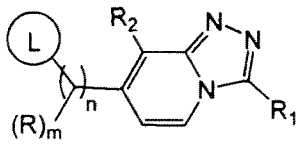
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
182	E182 *		--CF_3		R-enantiomer OR: -131.7° (589 nm,c 0.63 w/v %, DMF, 20°C)
183	E13		--CF_3		
184	E6		--Cl		R-enantiomer OR: -28.6° (589 nm,c 0.53 w/v %, DMF, 20°C)
185	E13		--CF_3		
186	E6		--Cl		cis
187	E6		--CH_3		
188	E212		--CF_3		
189	E13		--CF_3		
190	E6		--Cl		

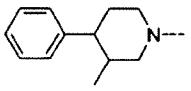
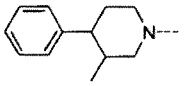
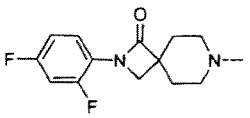
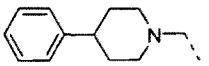
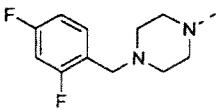
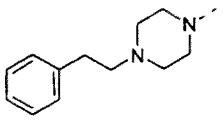
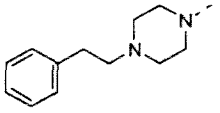


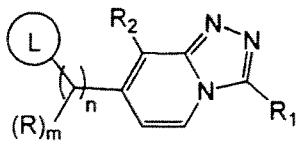
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
191	E1	--CH_2CF_3	--Cl		S-enantiomer OR: 63.4° (589 nm,c 0.54 w/v %, DMF, 20°C)
192	E1	--CH_2CF_3	--Cl		R-enantiomer
193	E13		--CF_3		
194	E13		--CF_3		
195	E13		--CF_3		
196	E13		--CF_3		
197	E13		--CF_3		
198	E13		--CF_3		
199	E13		--CF_3		
200	E200 *		--CF_3		

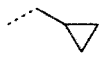
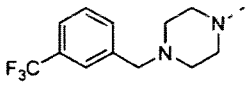
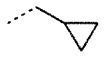
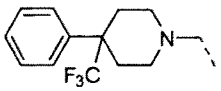
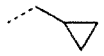
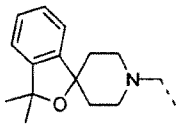
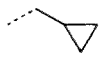
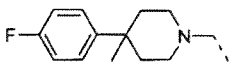
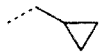
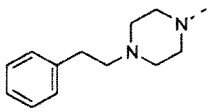
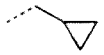
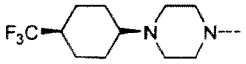
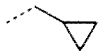
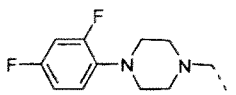
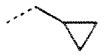
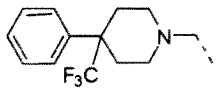
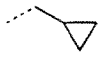
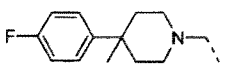


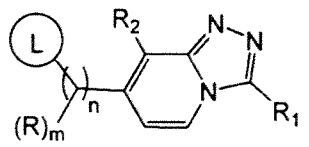
Co. no.	Exp. no.	R^1	R^2	$-[CH(R)_m]_n-L$	Stereochem./Salt Form/Optical Rotation (OR)
201	E13		--CF_3		
202	E13		--CF_3		
203	E13		--CF_3		
204	E204 *		--CH_3		
205	E206		--CN		
206	E206 *		--CN		
207	E207 *		--Br		
208	E6		--Cl		cis-a OR: -93.1° (589 nm,c 0.55 w/v %, MeOH, 20°C)
209	E13		--CF_3		cis-a OR: -226° (589 nM,c 0.59 w/v %, MeOH, 20°C)
210	E6		--Cl		

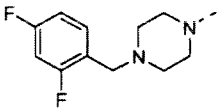
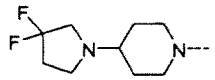
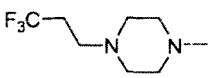
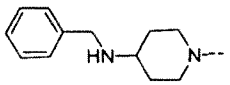
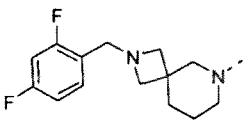
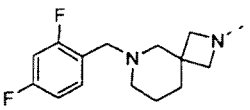
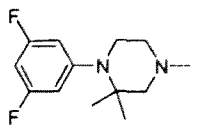
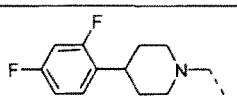
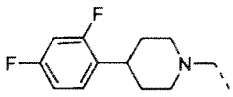
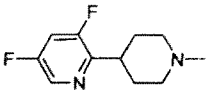


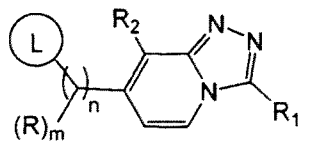
Co. no.	Exp. no.	R^1	R^2	$--[CH(R)_m]_n-L$	Stereochem./Salt Form/Optical Rotation (OR)
211	E6		--Cl		cis-b OR: 112.5° (589 nm,c 0.59 w/v %, MeOH, 20°C)
212	E13		$--CF_3$		cis-b OR: 229° (589 nm,c 0.58 w/v %, MeOH, 20°C)
213	E6		--Cl		
214	E214 *; E298 6-A		$--CF_3$		.1.8HCl
215	E6		--Cl		
216	E13		$--CF_3$		
217	E6		$--CF_3$		.1HCl

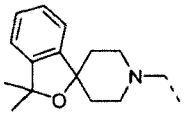
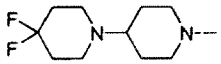
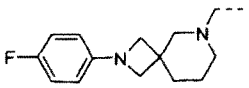
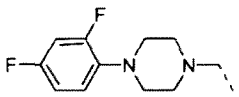
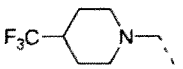
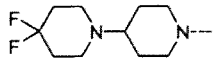
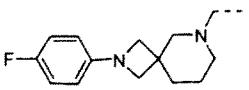
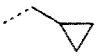
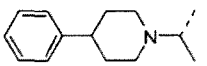
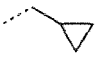
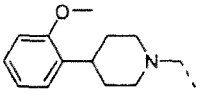
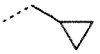
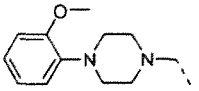
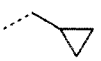
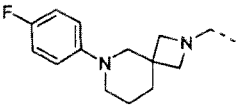


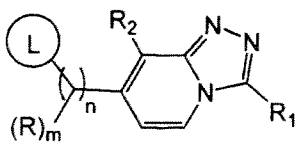
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
218	E6		--Cl		
219	E232		--CF_3		
220	E232		--CF_3		
221	E224		--CF_3		
222	E6		--Cl		
223	E6		--Cl		cis
224	E224 *		--CF_3		
225	E224		--Cl		
226	E224		--Cl		

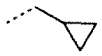
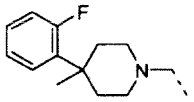
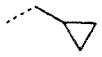
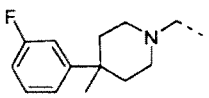
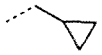
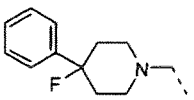
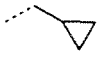
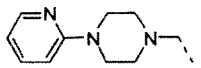
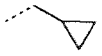
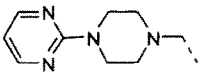
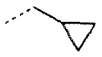
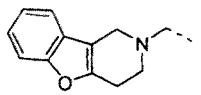
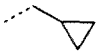
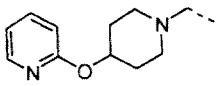
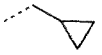
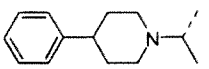
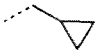
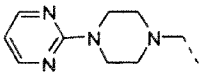
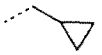
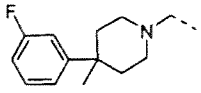
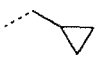
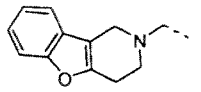
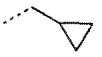
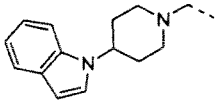


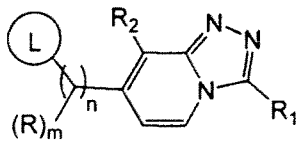
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
227	E13		--CF_3		
228	E6		--Cl		
229	E224		--Cl		
230	E224		--CF_3		
231	E13		--CF_3		
232	E224		--CF_3		
233	E13		--CF_3		
234	E224		--CF_3		
235	E224		--Cl		
236	E13		--CF_3		

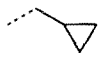
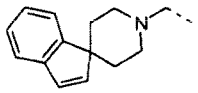
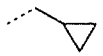
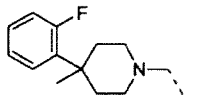
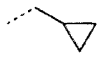
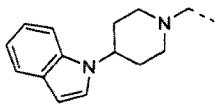
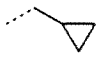
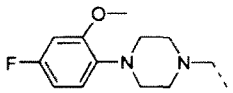
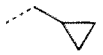
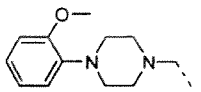
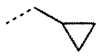
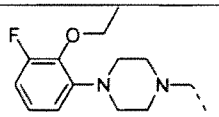
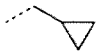
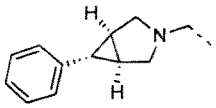
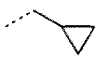
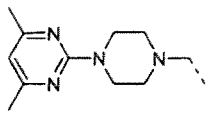
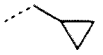
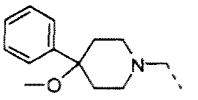
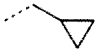
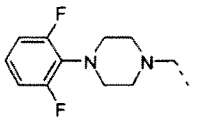
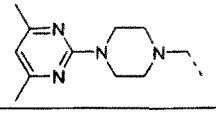


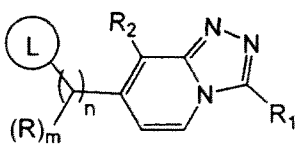
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
237	E224		--Cl		
238	E13		--CF_3		
239	E224		--Cl		
240	E224		--Cl		
241	E224		--Cl		
242	E6		--Cl		
243	E224		--CF_3		
244	E244 *		--CF_3		
245	E224		--CF_3		
246	E224		--CF_3		
247	E224		--CF_3		

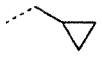
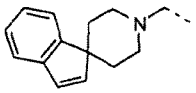
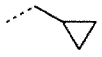
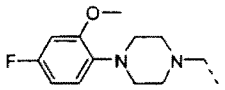
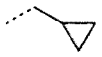
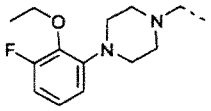
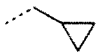
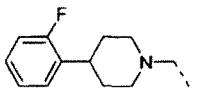
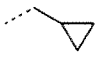
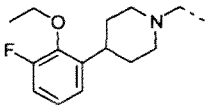
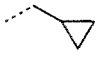
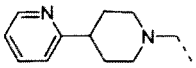
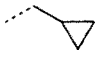
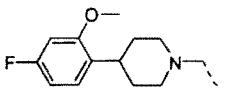
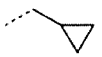
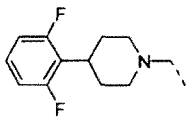
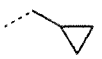
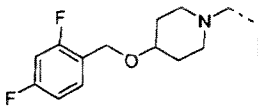
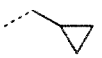
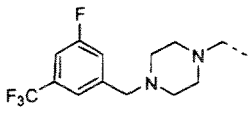


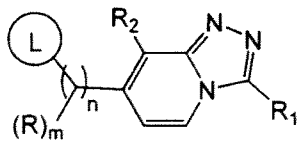
Co. no.	Exp. no.	R^1	R^2	--$[CH(R)_m]_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
248	E224		--CF_3		
249	E224		--CF_3		
250	E250 *		--CF_3		
251	E298 -A		--CF_3		
252	E224		--CF_3		
253	E224		--CF_3		
254	E224		--CF_3		
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256	E224		--Cl		
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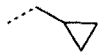
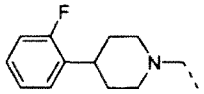
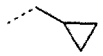
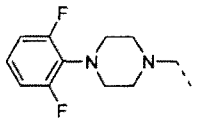
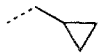
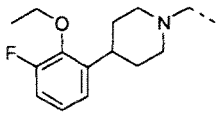
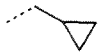
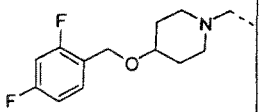
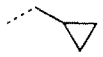
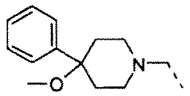
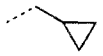
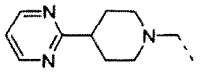
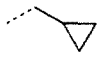
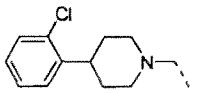
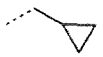
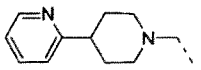
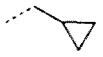
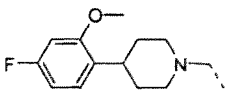
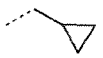
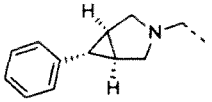
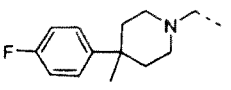


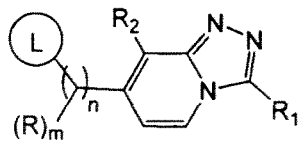
Co. no.	Exp. no.	R^1	R^2	--$[CH(R)_m]_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
260	E198 -A		--CF_3		
261	E224		--Cl		
262	E224		--CF_3		
263	E298 -A		--CF_3		
264	E224		--Cl		
265	E298 -A		--CF_3		
266	E298 -A		--CF_3		rac-(2aα,3α,3aα)
267	E298 -A		--CF_3		
268	E298 -A		--CF_3		
269	E298 -A		--CF_3		
270	E282		--Cl		

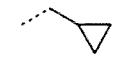
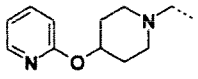
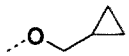
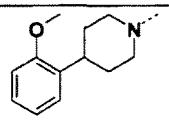
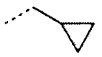
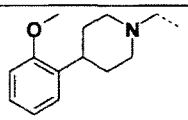
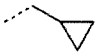
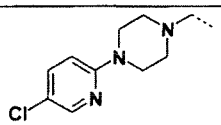
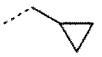
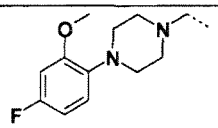
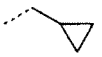
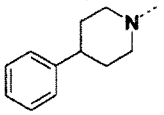
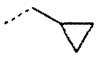
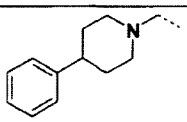
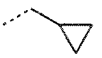
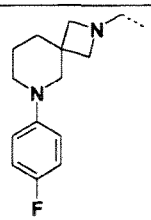
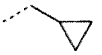
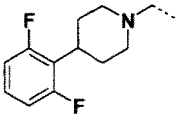
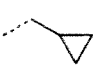
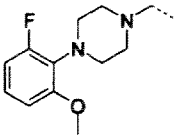


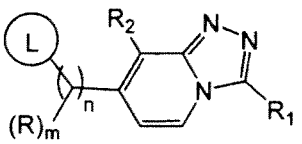
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
271	E281		--Cl		
272	E282		--Cl		
273	E282		--Cl		
274	E298 -A		--CF_3		
275	E298 -A		--CF_3		
276	E298 -A		--CF_3		
277	E298 -A		--CF_3		
278	E298 -A		--CF_3		
279	E298 -A		--CF_3		
280	E6		--Cl		

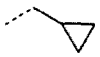
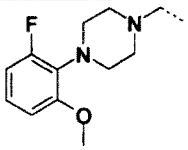
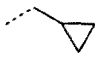
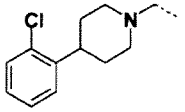
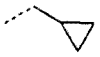
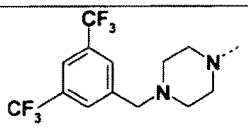
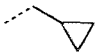
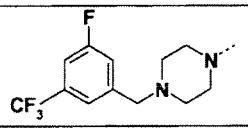
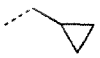
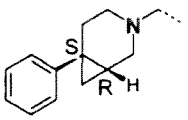
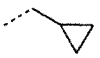
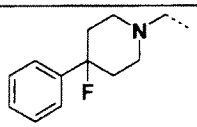
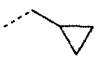
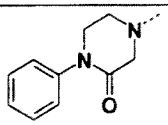
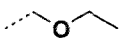
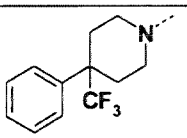
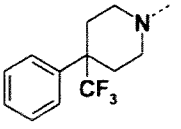
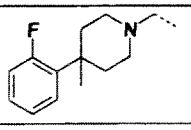


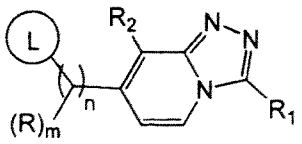
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
281	E282		--Cl		
282	E282 *		--Cl		
283	E282		--Cl		
284	E282		--Cl		
285	E282		--Cl		
286	E282		--Cl		
287	E298 -A		--CF_3		
288	E282		--Cl		
289	E282		--Cl		
290	E282		--Cl		rac-(2aα,3α,3aα)
291	E1	--CH_2CF_3	--Cl		

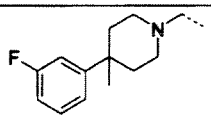
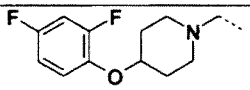
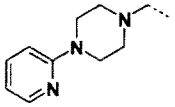
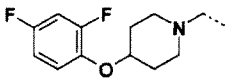
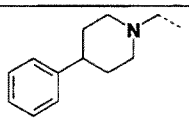
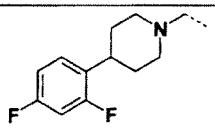
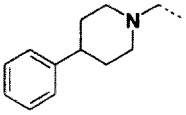
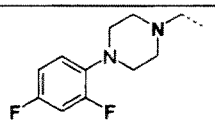
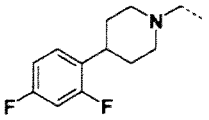
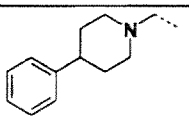


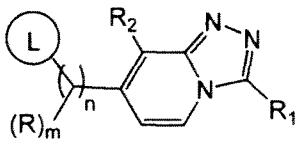
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
292	E224		-Cl		
293	E6		-Cl		
294	E224		-Cl		
295	E250		-Cl		
296	E298 -A		-CF_3		
297	E297 *		-CF_3		.1.1HCl
298	E298 *		-CF_3		
299	E282		-Cl		
300	E282		-Cl		
301	E298 -A		-CF_3		

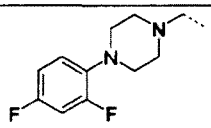
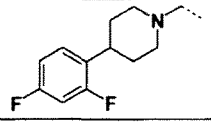
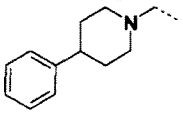
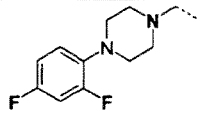
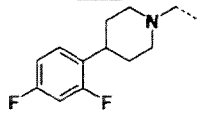
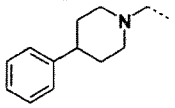
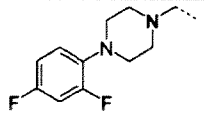
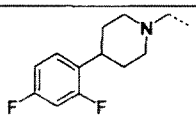
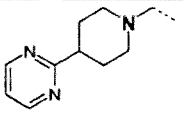
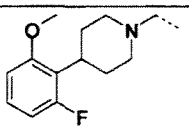
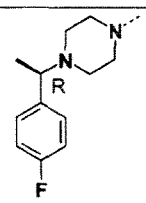


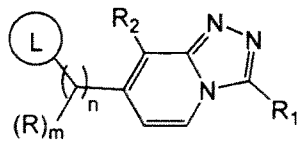
Co. no.	Exp. no.	R^1	R^2	$-[CH(R)_m]_n-L$	Stereochem./Salt Form/Optical Rotation (OR)
302	E282		-Cl		
303	E282		-Cl		
304	E6		-Cl		
305	E13		$-CF_3$		
306	E13		$-CF_3$		
307	E224		-Cl		
308	E13		$-CF_3$		
309	E6		-Cl		
310	E6		-Cl		
311	E1	$--CH_2-CF_3$	-Cl		

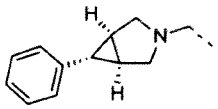
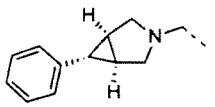
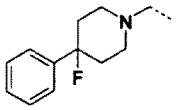
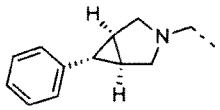
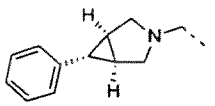
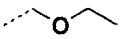
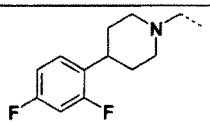
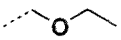
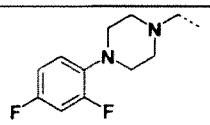
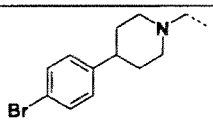
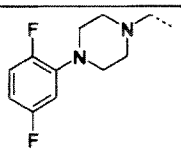
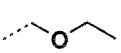
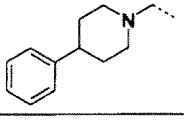
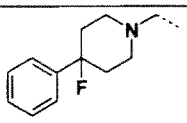


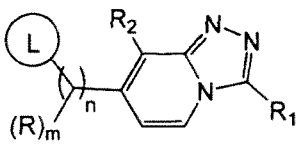
Co. no.	Exp. no.	R^1	R^2	$-[CH(R)_m]_n-L$	Stereochem./Salt Form/Optical Rotation (OR)
312	E1	$--CH_2-CF_3$	-Cl		
313	E282		-Cl		
314	E282		-Cl		
315	E298 -A		$-CF_3$		
316	E250		$--CH_3$		
317	E250		$--CH_3$		
318	E250		$--CH_3$		
319	E250		$-CF_3$		
320	E250		$-CF_3$		
321	E250		$-CF_3$		
322	E250		$-CF_3$		

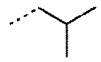
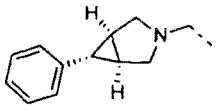
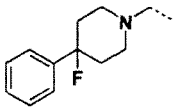
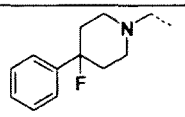
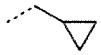
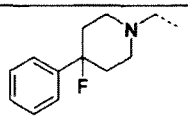
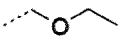
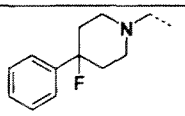
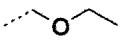
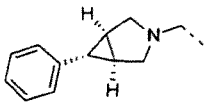
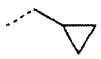
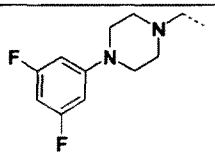
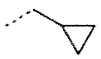
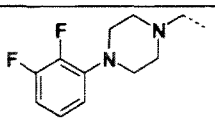
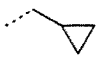
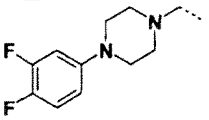
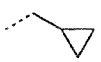
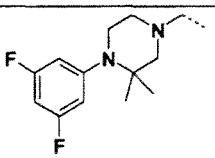
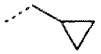
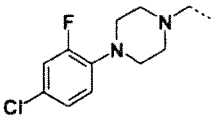


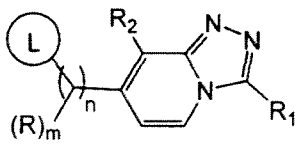
Co. no.	Exp. no.	R^1	R^2	--$[CH(R)_m]_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
323	E250		-CF_3		
324	E250		-CF_3		
325	E250		-CF_3		
326	E250		-CF_3		
327	E250		-CF_3		
328	E250		-CF_3		
329	E250		-CF_3		
330	E250		-CF_3		
331	E298 -A		--CF_3		
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333	E6		--Cl		

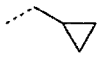
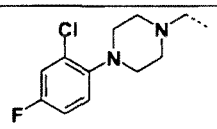
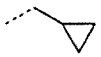
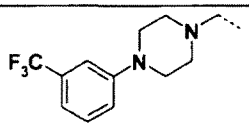
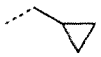
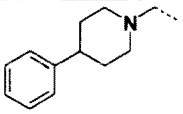
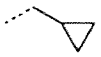
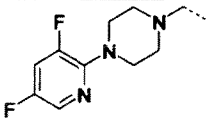
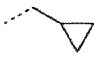
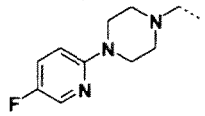
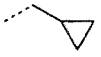
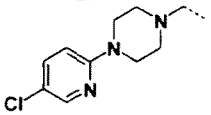
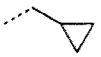
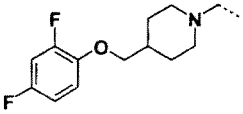
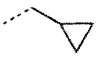
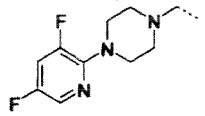
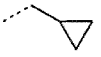
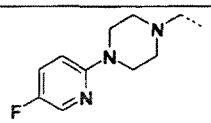
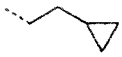
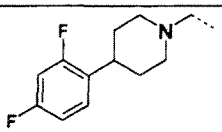
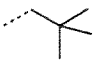
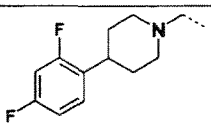


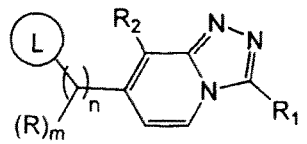
Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
334	E250		$-CF_3$		rac-(2aα,3α,3aα)
335	E250		$-CH_3$		rac-(2aα,3α,3aα)
336	E250		$-CF_3$		
337	E250		$-CF_3$		rac-(2aα,3α,3aα)
338	E250		$-CF_3$		rac-(2aα,3α,3aα)
339	E250		$-CF_3$		.HCl
340	E250		$-CF_3$		.HCl
341	E250		$-CF_3$		
342	E250		$-CF_3$		
343			$-CF_3$		.HCl
344	E250		$-CF_3$		

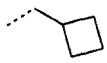
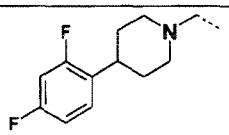
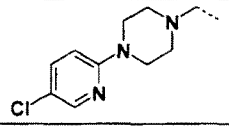


Co. no.	Exp. no.	R^1	R^2	$-[CH(R)_m]_n-L$	Stereochem./Salt Form/Optical Rotation (OR)
345	E250		$-CF_3$		rac-(2aα,3α,3aα)
346	E250		$-CF_3$		
347	E250		$-CF_3$		
348	E250		$-CH_3$		
349	E250		$-CF_3$		
350	E250		$-CF_3$		rac-(2aα,3α,3aα)
351	E250		$-CF_3$		
352	E250		$-CF_3$		
353	E250		$-CF_3$		
354	E250		$-CF_3$		
355	E250		$-CF_3$		



Co. no.	Exp. no.	R^1	R^2	$-[CH(R)_m]_n-L$	Stereochem./Salt Form/Optical Rotation (OR)
356	E250		$-CF_3$		
357	E250		-Cl		
358	E207		-Br		
359	E250		$-CF_3$		
360	E250		$-CF_3$		
361	E250		$-CF_3$		
362	E250		$-CF_3$		
363	E250		-Cl		
364	E250		-Cl		
365	E250		$-CF_3$		
366	E250		$-CF_3$		



Co. no.	Exp. no.	R^1	R^2	--[CH(R)$_m$]$_n$-L	Stereochem./Salt Form/Optical Rotation (OR)
367	E250		$-CF_3$		
368	E250		-Cl		

C. Analytical part

Melting points

Values are peak values, and are obtained with experimental uncertainties that are commonly associated with this analytical method. For a number of compounds, melting points were determined in open capillary tubes either on a Mettler FP62 or on a Mettler FP81HT-FP90 apparatus. Melting points were measured with a temperature gradient of 10 °C/min. Maximum temperature was 300 °C. The melting point was read from a digital display.

Optical rotation

Values were measured on a Perkin-Elmer 341 polarimeter with a sodium lamp and reported as follows: $[a]_l^{t°C}$ (c g/100ml, solvent).

LCMS

For LCMS characterization of the compounds of the present invention, the following methods were used.

General procedure A (for Waters MS instruments)

The HPLC measurement was performed using an HP 1100 (Agilent Technologies) system comprising a pump (quaternary or binary) with degasser, an autosampler, a column oven, a DAD and a column as specified in the respective methods below. Flow from the column was split to the MS spectrometer. The MS detector was configured with either an ES ionization source or an ESCI dual ionization source (ES combined with atmospheric pressure CI). Nitrogen was used as the nebulizer gas. The source temperature was maintained at 140 °C. Data acquisition was performed with MassLynx-Openlynx software.

General procedure B (for Agilent MS instrument (MSD))

The HPLC measurement was performed using an HP 1100 (Agilent Technologies) system comprising a binary pump with degasser, an autosampler, a column oven, a DAD and a column as specified in the respective methods below. Flow from the column was split to a MS spectrometer. The MS detector was configured with an ESCI dual ionization source (ES combined with atmospheric pressure CI). Nitrogen was used as the nebulizer gas. The source temperature was maintained at 100 °C. Data acquisition was performed with Chemsation-Agilent Data Browser software.

General procedure C (for Waters MS instruments (Acquity SQD))

The UPLC (Ultra Performance Liquid Chromatography) measurement was performed using an Acquity UPLC (Waters) system comprising a sampler organizer, a binary pump with degasser, a four column's oven, a DAD and a column as specified in the respective methods below. Column flow was used without split to the MS detector. The MS detector was configured with an ESCI dual ionization source (ES combined with atmospheric pressure CI). Nitrogen was used as the nebulizer gas. The source temperature was maintained at 140 °C. Data acquisition was performed with MassLynx-Openlynx software.

Method 1

In addition to the general procedure B: Reversed phase HPLC was carried out on an XDB-C18 cartridge (1.8 µm, 2.1 x 30 mm) from Agilent, at 60°C with a flow rate of

1 ml/min, at 60°C. The gradient conditions used are: 90 % A (0.5 g/l NH_4Ac solution), 5 % B (CH_3CN), 5 % C (MeOH) to 50 % B and 50 % C in 6.5 min, to 100 % B at 7 min and equilibrated to initial conditions at 7.5 min until 9.0 min. Injection volume 2 µl. HRMS (TOF detector) were acquired only in positive ionization mode by scanning from 100 to 750 in 0.5 s using a dwell time of 0.1 s. The capillary needle voltage was 2.5 kV and the cone voltage was 20 V. Leucine-Enkephaline was the standard substance used for the lock mass calibration.

Method 2

In addition to the general procedure A: Reversed phase HPLC was carried out on a Sunfire-C18 column (2.5 µm, 2.1 x 30 mm) from Waters, with a flow rate of 1.0 ml/min, at 60°C. The gradient conditions used are: 95 % A (0.5 g/l NH_4Ac solution + 5 % of CH_3CN), 2.5 % B (CH_3CN), 2.5 % C (MeOH) to 50 % B, 50 % C in 6.5 min, kept till 7.0 min and equilibrated to initial conditions at 7.3 min until 9.0 min. Injection volume 2 µl. HRMS (TOF detector) were acquired by scanning from 100 to 750 in 0.5 s using a dwell time of 0.3 s. The capillary needle voltage was 2.5 kV for positive ionization mode and 2.9 kV for negative ionization mode. The cone voltage was 20 V for both positive and negative ionization modes. Leucine-Enkephaline was the standard substance used for the lock mass calibration.

Method 3

In addition to the general procedure A: Reversed phase HPLC was carried out on a Sunfire-C18 column (2.5 µm, 2.1 x 30 mm) from Waters, with a flow rate of 1.0 ml/min, at 60°C. The gradient conditions used are: 95 % A (0.5 g/l NH_4Ac solution + 5 % of CH_3CN), 5 % B (CH_3CN) to 100 % B in 6.5 min, kept till 7.0 min and equilibrated to initial conditions at 7.3 min until 9.0 min. Injection volume 2 µl. HRMS (TOF detector) were acquired by scanning from 100 to 750 in 0.5 s using a dwell time of 0.3 s. The capillary needle voltage was 2.5 kV for positive ionization mode and 2.9 kV for negative ionization mode. The cone voltage was 20 V for both positive and negative ionization modes. Leucine-Enkephaline was the standard substance used for the lock mass calibration.

Method 4

In addition to the general procedure A: Reversed phase HPLC was carried out on a Sunfire-C18 column (2.5 µm, 2.1 x 30 mm) from Waters, with a flow rate of 1.0 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l NH_4Ac solution + 5 % CH_3CN), 5 % B (mixture of CH_3CN / MeOH, 1/1), to 100 % B in 5.0 min, kept till 5.15 min and equilibrated to initial conditions at 5.30 min until 7.0 min. Injection volume 2 µl. LRMS (single quadrupole, SQD detector) were acquired in positive ionization mode by scanning from 100 to 1000 in 0.1 s using an inter-channel delay of 0.08 s. The capillary needle voltage was 3 kV. The cone voltage was 20 V and 50 V for positive ionization mode and 30V for negative ionization mode.

Method 5

In addition to the general procedure A: Reversed phase HPLC was carried out on a Sunfire-C18 column (2.5 µm, 2.1 x 30 mm) from Waters, with a flow rate of 1.0 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l NH_4Ac solution + 5 % CH_3CN), 5 % B (mixture of CH_3CN / MeOH, 1/1), to 100 % B at 6.5 min, kept till 7.0 min and equilibrated to initial conditions at 7.3 min until 9.0 min. Injection volume 2 µl. LRMS (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 s using an inter-channel delay of 0.08 s. The capillary needle voltage was 3 kV. The cone voltage was 20 V for positive ionization mode and 30 V for negative ionization mode.

Method 6

In addition to the general procedure A: Reversed phase HPLC was carried out on a XBridge-C18 column (2.5 µm, 2.1 x 30 mm) from Waters, with a flow rate of 1.0 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l NH_4Ac solution + 5 % CH_3CN), 5 % B (mixture of CH_3CN / MeOH, 1/1), to 100 % B in 6.5 min, kept till 7.0 min and equilibrated to initial conditions at 7.3 min until 9.0 min. Injection volume 2 µl. LRMS (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 s using an inter-channel delay of

0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 20 V for positive ionization mode and 30 V for negative ionization mode.

Method 7

In addition to the general procedure B: Reversed phase HPLC was carried out on an Eclipse Plus-C18 column (3.5 µm, 2.1 x 30 mm) from Agilent, with a flow rate of 1.0 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l NH_4Ac solution + 5 % CH_3CN), 5 % B (mixture of CH_3CN / MeOH, 1/1), to 100 % B in 5.0 min, kept till 5.15 min and equilibrated to initial conditions at 5.30 min until 7.0 min. Injection volume 2 µl. LRMS (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 second using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 20 V for positive ionization mode and 30 V for negative ionization mode.

Method 8

In addition to the general procedure B: Reversed phase HPLC was carried out on an Eclipse Plus-C18 column (3.5 µm, 2.1 x 30 mm) from Agilent, with a flow rate of 1.0 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l NH_4Ac solution + 5 % CH_3CN), 5 % B (mixture of CH_3CN / MeOH, 1/1), to 100 % B at 6.5 min, kept till 7.0 min and equilibrated to initial conditions at 7.3 min until 9.0 min. Injection volume 2 µl. LRMS (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 s using an inter-channel delay of 0.08 s. The capillary needle voltage was 3 kV. The cone voltage was 20 V for positive ionization mode and 30 V for negative ionization mode.

Method 9

In addition to the general procedure B: Reversed phase HPLC was carried out on an Eclipse Plus-C18 column (3.5 µm, 2.1 x 30 mm) from Agilent, with a flow rate of 1.0 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l ammonium acetate solution + 5 % CH_3CN), 5 % B (CH_3CN), to 100 % B at 6.5 minutes, kept till 7.0 minutes and equilibrated to initial conditions at 7.3 minutes until 9.0 minutes. Injection volume 2 µl. Low-resolution mass spectra (single

quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 seconds using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 20 V for positive ionization mode and 30 V for negative ionization mode.

Method 10

In addition to the general procedure C: Reversed phase UPLC was carried out on a BEH-C18 column (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 0.8 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l NH_4Ac solution + 5 % CH_3CN), 5 % B (mixture of CH_3CN / MeOH, 1/1), to 20% A, 80 % B in 6.3 min, to 100 % B in 6.85 min, kept till 7.50 min and equilibrated to initial conditions at 7.75 min until 9.0 min. Injection volume 0.5 µl. LRMS (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 s using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 20 V for positive ionization mode and 30 V for negative ionization mode.

Method 11

In addition to the general procedure C: Reversed phase UPLC was carried out on a BEH-C18 column (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 0.8 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l NH_4Ac solution + 5 % CH_3CN), 5 % B (mixture of CH_3CN / MeOH, 1/1), to 20 % A, 80 % B in 4.9 min, to 100 % B in 5.3 min, kept till 5.8 min and equilibrated to initial conditions at 6.0 min until 7.0 min. Injection volume 0.5 µl. LRMS (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 s using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 20 V for positive ionization mode and 30 V for negative ionization mode.

Method 12

In addition to the general procedure C: Reversed phase UPLC was carried out on a BEH-C18 column (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 1.0 ml/min, at 50°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l ammonium acetate solution + 5 % CH_3CN), 5 % B (CH_3CN), to 40 % A, 60 % B in

4.4 minutes, to 5 % A, 95 % B in 5.6 minutes, kept till 5.8 minutes and equilibrated to initial conditions at 6.0 minutes until 7.0 minutes. Injection volume 0.5 µl. Low-resolution mass spectra (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 seconds using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 25 V for positive ionization mode and 30 V for negative ionization mode.

Method 13

In addition to the general procedure C: Reversed phase UPLC was carried out on a BEH-C18 column (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 1.0 ml/min, at 50°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l ammonium acetate solution + 5 % acetonitrile), 5 % B (acetonitrile), to 40 % A, 60 % B in 2.8 minutes, to 5 % A, 95 % B in 3.6 minutes, kept till 3.8 minutes and equilibrated to initial conditions at 4.0 minutes until 5.0 minutes. Injection volume 0.5 µl. Low-resolution mass spectra (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 seconds using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 25 V for positive ionization mode and 30 V for negative ionization mode.

Method 14

In addition to the general procedure C: Reversed phase UPLC was carried out on a BEH-C18 column (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 1.0 ml/min, at 50°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l ammonium acetate solution + 5 % acetonitrile), 5 % B (acetonitrile), to 40% A, 60 % B in 6.0 minutes, to 5 % A, 95 % B in 7.6 minutes, kept till 7.80 minutes and equilibrated to initial conditions at 8.0 minutes until 9.0 minutes. Injection volume 0.5 µl. Low-resolution mass spectra (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 seconds using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 25 V for positive ionization mode and 30 V for negative ionization mode.

Method 15

In addition to the general procedure C: Reversed phase UPLC was carried out on a BEH-C18 column (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 1.0 ml/min, at 50°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l ammonium acetate solution + 5 % acetonitrile), 5 % B (acetonitrile), to 40 % A, 60 % B in 3.8 minutes, to 5 % A, 95 % B in 4.6 minutes, kept till 5.0 minutes. Injection volume 2 µl. Low-resolution mass spectra (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 seconds using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 25 V for positive ionization mode and 30 V for negative ionization mode.

Method 16

In addition to the general procedure C: Reversed phase UPLC was carried out on a BEH-C18 column (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 1.0 ml/min, at 50°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l ammonium acetate solution + 5 % acetonitrile), 5 % B (acetonitrile), to 40% A, 60 % B in 7.0 minutes, to 5 % A, 95 % B in 8.6 minutes, kept till 9.0 minutes. Injection volume 2 µl. Low-resolution mass spectra (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 seconds using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 25 V for positive ionization mode and 30 V for negative ionization mode.

General procedure D

The HPLC measurement was performed using an Alliance HT 2790 (Waters) system comprising a quaternary pump with degasser, an autosampler, a column oven (set at 40 °C, unless otherwise indicated), a DAD and a column as specified in the respective methods below. Flow from the column was split to a MS spectrometer. The MS detector was configured with an ES ionization source. Mass spectra were acquired by scanning from 100 to 1000 in 1 second using a dwell time of 0.1 second. The capillary needle voltage was 3 kV and the source temperature was maintained at 140 °C. Nitrogen was used as the nebulizer gas. Data acquisition was performed with a Wafers-Micromass MassLynx-Openlynx data system.

Method 17

In addition to the general procedure D: Column heater was set at 45 °C. Reversed phase HPLC was carried out on an Atlantis C18 column (3.5 µm, 4.6 x 100 mm) with a flow rate of 1.6 ml/min. Two mobile phases (mobile phase A: 70 % MeOH + 30 % H_2O; mobile phase B: 0.1 % formic acid in H_2O/MeOH 95/5) were employed to run a gradient condition from 100 % B to 5 % B + 95 % A in 9 min and hold these conditions for 3 min. An injection volume of 10 µl was used. Cone voltage was 10 V for positive ionization mode and 20 V for negative ionization mode.

Method 18

In addition to the general procedure D: Reversed phase HPLC was carried out on an Xterra MS C18 column (3.5 µm, 4.6 x 100 mm) with a flow rate of 1.6 ml/min. Three mobile phases (mobile phase A: 95% 25 mM ammoniumacetate + 5 % acetonitrile; mobile phase B: acetonitrile; mobile phase C: methanol) were employed to run a gradient condition from 100 % A to 1 % A, 49 % B and 50 % C in 6.5 minutes, to 1 % A and 99 % B in 1 minute and hold these conditions for 1 minute and reequilibrate with 100 % A for 1.5 minutes. An injection volume of 10 µl was used. Cone voltage was 10 V for positive ionization mode and 20 V for negative ionization mode.

General procedure E

The LC measurement was performed using an Acquity UPLC (Waters) system comprising a binary pump, a sample organizer, a column heater (set at 55 °C), a DAD and a column as specified in the respective methods below. Flow from the column was split to a MS spectrometer. The MS detector was configured with an ES ionization source. MS were acquired by scanning from 100 to 1000 in 0.18 s using a dwell time of 0.02 s. The capillary needle voltage was 3.5 kV and the source temperature was maintained at 140 °C. Nitrogen was used as the nebulizer gas. Data acquisition was performed with a Waters-Micromass MassLynx-Openlynx data system.

Method 19

In addition to the general procedure E: Reversed phase UPLC was carried out on a bridged ethylsiloxane/silica hybrid (BEH) C18 column (1.7 µm, 2.1 x 50 mm; Waters Acquity) with a flow rate of 0.8 ml/min. Two mobile phases (mobile phase A: 0.1 % formic acid in H_2O/MeOH 95/5; mobile phase B: MeOH) were used to run a gradient condition from 95 % A and 5 % B to 5 % A and 95 % B in 1.3 min and hold for 0.2 min. An injection volume of 0.5 µl was used.
Cone voltage was 10 V for positive ionization mode and 20 V for negative ionization mode.

The results of the analytical measurements are shown in table 2.

Table 2 : Physico-chemical data for some compounds, retention time (R_t) in min, $[M+H]^+$ peak (protonated molecule), LCMS method and mp (melting point in °C). (nd = not determined).

Co. No.	mp (°C)	$[MH^+]$	R_t (min)	LCMS Method
1	181.8	381	4.43	6
2	n.d.	419	8.48	17
3	>300	413	8.27	17
4	n.d.	403	3.96	11
5	n.d.	371	4.27	2
6	194.5	395	4.27	5
7	n.d.	425	4.12	2
8	>300	423	3.53	3

Co. No.	mp (°C)	$[MH^+]$	R_t (min)	LCMS Method
9	n.d.	369	4.00	3
10	n.d.	332	3.46	2
11	300	403	3.71	5
12	n.d.	477	4.21	11
13	n.d.	358	3.88	1
14	n.d.	358	3.94	1
15	276.7	435	2.43	12
16	269.1	423	3.03	12

Co. No.	mp (°C)	[MH$^+$]	R_t (min)	LCMS Method
17	>300	429	3.17	12
18	153.7	437	3.92	9
19	n.d.	318	3.21	1
20	300	386	3.82	1
21	n.d.	380	3.85	2
22	228.6	395	4.64	2
23	n.d.	394	4.14	2
24	n.d.	348	3.62	2
25	227.7	341	4.34	2
26	194.1	367	3.69	11
27	n.d.	434	4.19	2
28	>300	346	3.03	11
29	>300	344	2.87	11
30	186.1	409	3.79	11
31	237.5	412	3.32	11
32	n.d.	424	4.27	6
33	n.d.	368	3.90	6
34	n.d.	372	4.40	2
35	>300	360	3.18	11
36	n.d.	387	4.09	5
37	n.d.	469	4.88	5
38	203.3	429	3.74	11
39	>300	435	4.05	11
40	n.d.	376	2.99	11
41	176.5	403	3.83	11
42	n.d.	385	8.08	17
43	n.d.	401	4.78	5

Co. No.	mp (°C)	[MH$^+$]	R_t (min)	LCMS Method
44	219	433	3.32	11
45	n.d.	433	3.13	11
46	>300	415	4.03	4
47	n.d.	368	2.66	11
48	n.d.	398	3.58	11
49	231.1	395	1.55	11
50	236.1	395	1.93	11
51	n.d.	434	3.98	2
52	249.3	505	3.96	4
53	n.d.	401	4.10	9
54	n.d.	404	2.96	11
55	n.d.	415	4.72	2
56	230.7	396	3.51	5
57	n.d.	406	3.48	7
58	>300	461	3.48	7
59	n.d.	426	3.60	7
60	n.d.	469	3.60	7
61	259	443	3.87	7
62	n.d.	486	3.63	7
63	232.2	398	3.15	8
64	n.d.	404	3.38	8
65	n.d.	443	3.70	11
66	n.d.	375	4.40	2
67	n.d.	389	4.65	2
68	n.d.	432	3.65	11
69	n.d.	401	3.04	11
70	n.d.	493	4.12	11

Co. No.	mp (°C)	[MH$^+$]	R_t (min)	LCMS Method
71	230.7	409	3.95	3
72	n.d.	430	3.80	11
73	n.d.	461	3.36	7
74	n.d.	360	3.5	3
75	>300	399	3.28	12
76	>300	402	3.03	12
77	n.d.	429	3.15	12
78	231.1	402	1.7	13
79	207.9	445	3.33	12
80	131	449	3.98	9
81	>300	393	3.61	9
82	n.d.	401	3.3	12
83	n.d.	419	3.34	12
84	n.d.	437	3.4	12
85	n.d.	437	3.51	12
86	n.d.	437	3.37	12
87	>300	417	3.13	12
88	255.7	383	2.89	12
89	231.7	403	2.85	12
90	n.d.	434	2.46	12
91	n.d.	432	2.69	12
92	n.d.	433	2.45	12
93	235.8	383	4.26	2
94	n.d.	439	3.16	12
95	247.2	392	2.96	12
96	144.4	422	2.83	12
97	>300	432	3.1	12

Co. No.	mp (°C)	[MH$^+$]	R_t (min)	LCMS Method
98	269.1	423	3.03	12
99	>300	368	2.79	12
100	260.2	424	3.36	12
101	249.5	396	2.84	12
102	252.4	369	2.6	12
103	>300	400	3.18	12
104	235.4	423	8.5	17
105	>300	396	3.29	12
106	209.43	401	1.41	19
107	229.43	411	6.13	18
108	n.d.	413	1.42	19
109	n.d.	447	1.43	19
110	239.9	435	1.43	19
111	n.d.	433	2.23	12
112	207.7	457	8.47	17
113	208.72	445	8.38	17
114	175.7	412	2.67	12
115	183.8	457	3.4	12
116	232.1	453	3.49	12
117	250.4	453	3.48	12
118	>300	373	4.2	2
119	n.d.	430	2.11	12
120	232.1	426	2.98	12
121	218.4	428	3.36	12
122	145.7	419	3.62	12
123	300	415	4.99	2
124	n.d.	418	4.19	2

Co. No.	mp (°C)	[MH$^+$]	R_t (min)	LCMS Method
125	n.d.	396	3.29	2
126	188.3	400	3.09	2
127	128.3	403	4.7	2
128	172.5	416	3.16	12
129	202.1	432	3.12	12
130	>300	359	2.66	12
131	234	416	3.22	12
132	144.3	422	4.09	2
133	>300	381	3.48	12
134	164.2	436	3.23	12
135	125.7	385	3.48	12
136	221.4	405	3.41	12
137	n.d.	373	2.92	12
138	n.d.	424	1.73	12
139	n.d.	451	2.54	13
140	n.d.	399	4.36	14
141	195.56	423	1.31	19
142	n.d.	453	6.05	18
143	223.95	419	8.39	17
144	100.7	453	3.55	12
145	>300	347	3.45	12
146	>300	381	3.56	12
147	n.d.	465	8.44	17
148	>300	416	2.72	12
149	229.27	409	7.24	17
150	n.d.	436	2.97	12
151	127.4	415	3.59	12

Co. No.	mp (°C)	[MH$^+$]	R_t (min)	LCMS Method
152	166.7	403	2.85	12
153	>300	438	3.22	12
154	>300	403	3.58	12
155	137.6	420	3.13	12
156	>300	389	2.27	12
157	162.6	408	2.99	12
158	178.9	466	2.62	12
159	>300	373	3.81	12
160	>300	429	4.01	12
161	>300	396	2.24	12
162	112.3	450	3.5	12
163	>300	450	3.41	12
164	n.d.	424	3.17	12
165	185.5	432	2.18	12
166	137.5	464	2.39	13
167	n.d.	418	2.15	12
168	166.2	381	4.52	14
169	182.3	415	3.64	12
170	160.8	384	1.46	13
171	>300	361	2.66	13
172	144	398	2	12
173	268.8	353	2.11	13
174	178.3	387	2.18	13
175	180.4	416	2.16	13
176	164.1	400	2.19	13
177	235.5	417	2.69	13
178	238.8	382	2.03	13

Co. No.	mp (°C)	[MH$^+$]	R_t (min)	LCMS Method
179	147.5	418	2.16	13
180	84.2	452	2.51	13
181	281.2	418	2.4	13
182	147.5	452	2.5	13
183	>300	434	2.3	13
184	269.7	418	2.41	13
185	>300	415	2.63	13
186	>300	430	2.31	13
187	193.3	415	2.46	13
188	n.d.	478	2.59	13
189	>300	406	2.03	13
190	>300	372	1.93	13
191	218.2	446	2.48	13
192	n.d.	446	2.48	13
193	160.2	433	2.64	13
194	148.4	433	2.59	13
195	>300	437	2.55	13
196	>300	438	2.32	13
197	137.4	433	2.58	13
198	201.9	402	1.58	13
199	199	416	1.68	13
200	>300	475	2.69	13
201	>300	478	2.64	13
202	>300	492	2.85	13
203	>300	452	2.37	13
204	283.5	383	2.4	13
205	n.d.	380	2.16	13

Co. No.	mp (°C)	[MH$^+$]	R_t (min)	LCMS Method
206	n.d.	381	2.24	13
207	281.5	411	2.4	13
208	187.5	381	9.18	17
209	182.5	415	9.01	17
210	184.5	444	3.59	12
211	186.7	381	1.35	19
212	181	415	9.02	17
213	>300	458	2.08	13
214	255.4	415	2.75	13
215	n.d.	418	2.01	13
216	n.d.	430	2.11	13
217	n.d.	430	2.11	13
218	n.d.	450	2.37	13
219	128	483	2.75	13
220	191.4	471	2.79	13
221	170.5	447	2.84	13
222	n.d.	396	1.91	13
223	188.4	442	2.26	13
224	141.5	452	3.16	15
225	188	449	3.14	15
226	124.3	413	3.13	15
227	n.d.	452	2.72	15
228	189	396	2.02	15
229	>300	388	2.02	15
230	n.d.	430	1.77	15
231	147.8	492	2.7	15
232	241.9	492	3.28	15

Co. No.	mp (°C)	[MH+]	R_t (min)	LCMS Method
233	n.d.	466	9.38	17
234	153.4	451	3.58	15
235	201.3	417	3.16	15
236	n.d.	438	1.11	19
237	258.7	437	3.07	15
238	>300	444	2.26	15
239	163.7	440	3.35	15
240	259.3	418	2.76	15
241	203.9	373	2.54	15
242	206.3	410	2.07	15
243	>300	474	3.66	15
244	142.3	429	3.61	15
245	259.7	445	3.47	15
246	186.2	446	2.86	15
247	n.d.	474	5.4	16
248	181.4	447	3.63	15
249	94.5	447	3.57	15
250	179.2	433	3.26	15
251	150..4	417	2.39	15
252	>300	418	2.23	15
253	167.2	427	3.23	15
254	209	432	2.8	15
255	182.1	395	3.17	15
256	288.1	384	1.81	15
257	120.4	413	3.15	15
258	251.8	393	2.86	15
259	216	420	3.06	15

Co. No.	mp (°C)	[MH+]	R_t (min)	LCMS Method
260	>300	439	3.56	15
261	129.4	413	3.2	15
262	199.2	454	3.43	15
263	174.4	464	2.93	15
264	157.6	412	2.45	15
265	175.5	478	3.55	15
266	>300	413	3.5	15
267	197.1	446	2.93	15
268	143.1	445	3.16	15
269	182.7	452	3.32	15
270	275.1	412	2.5	15
271	175.51	405	3.13	15
272	169.7	430	2.55	15
273	155.7	444	3.18	15
274	151	433	3.49	15
275	157.7	477	3.72	15
276	143.2	416	2.36	15
277	162	463	3.54	15
278	186.2	451	3.55	15
279	126	481	3.32	15
280	161	468	3.16	15
281	179.4	399	3.06	15
282	180.4	418	2.94	15
283	185.1	443	3.3	15
284	147.6	447	2.89	15
285	153.3	411	2.71	15
286	190.7	383	1.45	15

Co. No.	mp (°C)	[MH$^+$]	R_t (min)	LCMS Method
287	n.d.	449	3.76	15
288	175	382	1.88	15
289	295.7	429	3.1	15
290	174.6	379	3.2	15
291	144.6	441	3.18	15
292	176.6	398	2.31	15
293	n.d.	413	3.7	12
294	150.4	411	2.99	15
295	182.1	417	2.64	15
296	174.4	464	2.93	15
297	n.d.	401	3.48	12
298	144.6	415	3.46	15
299	132.1	440	2.95	15
300	199	417	3.14	15
301	n.d.	464	3.19	15
302	n.d.	430	2.8	15
303	189.2	415	3.32	15
304	165	518	3.51	15
305	n.d.	502	3.32	15
306	n.d.	427	3.65	15
307	154.5	399	0.87	19
308	229.2	416	1.83	12
309	177.2	439	3.36	12
310	255.1	423	3.38	12
311	119.9	441	3.24	15
312	122.8	441	3.18	15
313	150.9	433	2.89	15

Co. No.	mp (°C)	[MH$^+$]	R_t (min)	LCMS Method
314	261.3	383	1.98	15
315	n.d.	467	3.28	15
316	166.8	361	2.77	15
317	126.4	398	2.71	15
318	154.4	397	3.02	15
319	138.4	389	3.15	15
320	185.3	426	2.85	15
321	172.4	425	3.3	15
322	152.9	403	3.4	15
323	145.9	440	3.09	15
324	152.2	439	3.52	15
325	133.7	417	3.66	15
326	145.8	454	3.36	15
327	147.1	453	3.77	15
328	n.d.	417	4.38	7
329	142	454	4.15	7
330	131	453	4.46	7
331	n.d.	417	1.9	15
332	n.d.	463	3.53	15
333	256.4	414	2.6	15
334	>300	387	3.22	15
335	>300	359	3.14	15
336	155.6	407	3.15	15
337	209.5	401	3.45	15
338	146	415	3.7	15
339	n.d.	455	3.54	15
340	162.9	456	3.09	15

Co. No.	mp (°C)	[MH$^+$]	R_t (min)	LCMS Method
341	n.d.	491	3.88	15
342	161.9	452	3.17	15
343	>300	419	3.41	15
344	139.8	435	4.32	2
345	138.6	415	4.49	2
346	150.2	421	3.19	15
347	n.d.	435	4.36	2
348	n.d.	379	3.56	15
349	n.d.	437	4.14	2
350	123.8	417	3.43	15
351	>300	452	3.27	15
352	210.8	452	3.19	15
353	156.3	452	3.15	15
354	205.5	480	3.71	15

Co. No.	mp (°C)	[MH$^+$]	R_t (min)	LCMS Method
355	n.d.	468	4.39	1
356	n.d.	468	4.39	1
357	151.2	450	4.07	7
359	130	453	2.92	15
360	140.8	435	2.62	15
361	131.8	451	3.04	15
362	126	481	3.32	15
363	183.5	419	4.19	8
364	172.4	401	2.2	15
365	142.6	466	3.36	15
366	161.6	468	4.31	7
367	177.6	466	4.25	7
368	182.1	417	2.64	15

Nuclear Magnetic Resonance (NMR)

For a number of compounds, ^{1}H NMR spectra were recorded either on a Bruker 360, on a Bruker DPX-400 or on a Bruker AV-500 spectrometer with standard pulse sequences, operating at 360 MHz, 400 MHz and 500 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard.

Co. No. 1: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.30 - 0.40 (m, 2 H), 0.59 - 0.67 (m, 2 H), 1.15 - 1.25 (m, 1 H), 1.79 (qd, J=12.1, 3.5 Hz, 2 H), 1.86 (br d, J=10.7 Hz, 2 H), 2.29 (td, J=11.6, 2.3 Hz, 2 H), 2.55 (tt, J=11.8, 3.9 Hz, 1 H), 2.97 (br d, J=11.3 Hz, 2 H), 3.08 (d, J=6.6 Hz, 2 H), 3.73 (s, 2 H), 7.18 (d, J=6.9 Hz, 1 H), 7.19 - 7.22 (m, 1 H), 7.22 - 7.28 (m, 2 H), 7.28 - 7.34 (m, 2 H), 7.88 (d, J=7.2 Hz, 1 H).

Co. No. 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.27 - 0.41 (m, 2 H), 0.57 - 0.70 (m, 2 H), 1.11 - 1.22 (m, 1 H), 2.08 - 2.19 (m, 2 H), 2.20 - 2.31 (m, 1 H), 2.36 (td, J=13.2, 5.1 Hz, 1 H), 3.06 (d, J=6.5 Hz, 2 H), 3.33 - 3.43 (m, 2 H), 3.43 - 3.55 (m, 2 H),

6.83 (d, J=7.6 Hz, 1 H), 7.31 - 7.37 (m, 1 H), 7.38 - 7.48 (m, 4 H), 7.98 (d, J=7.6 Hz, 1 H).

Co. No. 3: ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 2.11 - 2.22 (m, 2 H), 2.30 (td, J=13.2, 4.8 Hz, 1 H), 2.41 (td, J=13.3, 4.9 Hz, 1 H), 3.39 (td, J=12.2, 2.0 Hz, 2 H), 3.53 - 3.64 (m, 2 H), 4.04 (q, J=9.9 Hz, 2 H), 6.90 (d, J=7.3 Hz, 1 H), 7.31 - 7.38 (m, 1 H), 7.38 - 7.50 (m, 4 H), 7.91 (d, J=7.7 Hz, 1 H).

Co. No. 4: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.97 (t, J=7.3 Hz, 3 H), 1.42 - 1.53 (m, 2 H), 1.78 - 1.87 (m, 2 H), 1.87 - 2.02 (m, 4 H), 2.65 - 2.78 (m, 1 H), 2.99 - 3.08 (m, 2 H), 3.12 - 3.24 (m, 2 H), 3.61 (br d, J=12.5 Hz, 2 H), 6.76 (d, J=7.6 Hz, 1 H), 7.20 - 7.30 (m, 3 H), 7.30 - 7.39 (m, 2 H), 7.81 (d, J=7.9 Hz, 1 H).

Co. No. 5: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.20 (t, J=7.1 Hz, 3 H), 1.93 - 2.07 (m, 4 H), 2.65 - 2.79 (m, 1 H), 2.96 - 3.10 (m, 2 H), 3.54 (q, J=6.9 Hz, 2 H), 3.75 (br d, J=12.5 Hz, 2 H), 5.02 (s, 2 H), 6.78 (d, J=7.6 Hz, 1 H), 7.21 - 7.31 (m, 3 H), 7.32 - 7.38 (m, 2 H), 8.10 (d, J=7.4 Hz, 1 H).

Co. No. 6: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.31 - 0.36 (m, 2 H), 0.58 - 0.66 (m, 2 H), 1.14 - 1.21 (m, 1 H), 1.90 (br d, J=12.1 Hz, 2 H), 2.20 (td, J=13.0, 4.6 Hz, 2 H), 3.06 (d, J=6.6 Hz, 2 H), 3.33 (td, J=12.1, 2.0 Hz, 2 H), 3.48 - 3.57 (m, 2 H), 5.13 (s, 2 H), 6.81 (d, J=7.5 Hz, 1 H), 7.20 - 7.28 (m, 2 H), 7.29 - 7.36 (m, 2 H), 7.86 (d, J=7.5 Hz, 1 H).

Co. No. 7: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.27 - 0.37 (m, 2 H), 0.56 - 0.66 (m, 2 H), 1.12 - 1.21 (m, 1 H), 1.72 (s, 6 H), 1.91 (br d, J=11.3 Hz, 2 H), 2.01 (s, 1 H), 2.00 - 2.10 (m, 2 H), 2.98 - 3.08 (m, 2 H), 3.04 (d, J=6.94 Hz, 2 H), 3.70 (br d, J=11.6 Hz, 2 H), 3.80 - 3.91 (m, 1 H), 6.78 (d, J=7.5 Hz, 1 H), 7.14 - 7.20 (m, 1 H), 7.26 - 7.32 (m, 1 H), 7.42 (dd, J=7.9, 1.0 Hz, 1 H), 7.46 (dd, J=7.8, 0.9 Hz, 1 H), 7.86 (d, J=7.5 Hz, 1 H).

Co. No. 8: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.91 (br d, J=12.3 Hz, 2 H), 2.20 (td, J=13.0, 4.7 Hz, 2 H), 3.38 (td, J=12.1, 1.8 Hz, 2 H), 3.51 - 3.65 (m, 2 H), 4.03 (q, J=9.7 Hz, 2 H), 5.14 (s, 2 H), 6.89 (d, J=7.4 Hz, 1 H), 7.18 - 7.27 (m, 2 H), 7.29 - 7.37 (m, 2 H), 7.88 (d, J=7.6 Hz, 1 H).

Co. No. 9: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.00 (d, J=6.5 Hz, 6 H), 1.73 - 1.88 (m, 2 H), 1.96 (br d, J=10.6 Hz, 2 H), 2.09 - 2.21 (m, 1 H), 2.87 (tt, J=12.1, 3.5 Hz, 1 H), 3.01 (d, J=7.2 Hz, 2 H), 3.22 - 3.32 (m, 2 H), 4.04 (br d, J=12.5 Hz, 2 H), 7.19 - 7.26 (m, 1 H), 7.27 - 7.39 (m, 5 H), 8.68 (d, J=7.6 Hz, 1 H).

Co. No. 10: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.31 (t, J=7.5 Hz, 3 H), 1.77 (qd, J=12.6, 3.8 Hz, 2 H), 1.95 (br d, J=11.3 Hz, 2 H), 2.86 - 2.95 (m, 1 H), 3.00 (q, J=7.5 Hz, 2 H), 3.34 - 3.42 (m, 2 H), 4.32 (br d, J=13.3 Hz, 2 H), 6.96 (d, J=7.8 Hz, 1 H), 7.19 - 7.25 (m, 1 H), 7.26 - 7.37 (m, 4 H), 8.34 (d, J=8.1 Hz, 1 H).

Co. No. 11: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.84 - 1.99 (m, 2 H), 2.08 (dd, J=12.4, 1.4 Hz, 2 H), 2.42 - 2.57 (m, 4 H), 2.86 (tt, J=12.1, 3.6 Hz, 2 H), 3.40 (td, J=12.8, 1.9 Hz, 2 H), 3.63 - 3.72 (m, 4 H), 4.01 (s, 2 H), 4.33 (br d, J=13.3 Hz, 2 H), 6.60 (d, J=8.1 Hz, 1 H), 7.22 - 7.27 (m, 3 H), 7.30 - 7.37 (m, 2 H), 8.28 (d, J=7.8 Hz, 1 H).

Co. No. 12: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.52 - 1.67 (m, 2 H), 1.69 - 1.86 (m, 4 H), 1.96 (br d, J=10.9 Hz, 2 H), 2.10 - 2.23 (m, 2 H), 2.85 - 2.98 (m, 3 H), 3.33 - 3.46 (m, 3 H), 3.99 (s, 2 H), 4.34 (br d, J=13.4 Hz, 2 H), 7.02 (d, J=7.9 Hz, 1 H), 7.15 - 7.20 (m, 2 H), 7.20 - 7.25 (m, 2 H), 7.25 - 7.37 (m, 6 H), 8.45 (d, J=7.9 Hz, 1 H).

Co. No. 13: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.27 - 0.37 (m, 2 H), 0.56 - 0.69 (m, 2 H), 1.08 - 1.18 (m, 1 H), 1.85 - 1.98 (m, 2 H), 2.07 (br d, J=11.6 Hz, 2 H), 2.85 (tt, J=12.1, 3.5 Hz, 1 H), 3.00 (d, J=6.6 Hz, 2 H), 3.39 (td, J=12.8, 1.9 Hz, 2 H), 4.31 (br d, J=13.3 Hz, 2 H), 6.61 (d, J=7.8 Hz, 1 H), 7.22 - 7.27 (m, 3 H), 7.30 - 7.38 (m, 2 H), 7.85 (d, J=7.8 Hz, 1 H).

Co. No. 14: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.84 - 1.96 (m, 2 H), 2.06 (dd, J=13.1, 1.3 Hz, 2 H), 2.08 - 2.14 (m, 1 H), 2.14 - 2.26 (m, 1 H), 2.46 - 2.56 (m, 2 H), 2.57 - 2.68 (m, 2 H), 2.84 (tt, J=12.1, 3.6 Hz, 1 H), 3.38 (td, J=12.8, 1.9 Hz, 2 H), 3.72 - 3.82 (m, 1 H), 4.30 (br d, J=13.3 Hz, 2 H), 6.58 (d, J=7.8 Hz, 1 H), 7.21 - 7.27 (m, 3 H), 7.30 - 7.37 (m, 2 H), 7.67 (d, J=7.8 Hz, 1 H).

Co. No. 15: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.24 - 0.34 (m, 2 H), 0.53 - 0.64 (m, 2 H), 1.07 - 1.19 (m, 1 H), 2.38 - 2.48 (m, 2 H), 2.64 (d, *J*=12.7 Hz, 2 H), 2.91 (t, *J*=11.8 Hz, 2 H), 3.02 (d, *J*=6.6 Hz, 2 H), 3.51 (br. d, *J*=12.1 Hz, 2 H), 6.57 (d, *J*=7.5 Hz, 1 H), 7.36 - 7.42 (m, 1 H), 7.46 (t, *J*=7.7 Hz, 2 H), 7.49 - 7.53 (m, 2 H), 7.76 (d, *J*=7.2 Hz, 1 H).

Co. No. 16: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.93 (br d, *J*=13.4 Hz, 2 H), 2.14 - 2.26 (m, 2 H), 3.02 (td, *J*=12.1, 2.3 Hz, 2 H), 3.61 - 3.70 (m, 2 H), 4.04 (q, *J*=9.9 Hz, 2 H), 4.48 (s, 2 H), 6.84 (d, *J*=8.1 Hz, 1 H), 6.85 (d, *J*=7.4 Hz, 1 H), 6.94 (td, *J*=7.4, 0.9 Hz, 1 H), 7.19 (td, *J*=7.7, 1.3 Hz, 1 H), 7.24 (dd, *J*=7.4, 0.9 Hz, 1 H), 7.91 (d, *J*=7.4 Hz, 1 H).

Co. No. 17: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.27 - 0.40 (m, 2 H), 0.56 - 0.69 (m, 2 H), 1.09 - 1.22 (m, 1 H), 1.89 (br d, *J*=13.6 Hz, 2 H), 2.14 (td, *J*=12.5, 3.7 Hz, 2 H), 3.06 (d, *J*=6.7 Hz, 2 H), 3.12 (br t, *J*=12.4 Hz, 2 H), 3.51 (br d, *J*=12.9 Hz, 2 H), 4.47 (s, 2 H), 6.77 (d, *J*=7.6 Hz, 1 H), 6.84 (d, *J*=7.9 Hz, 1 H), 6.93 (td, *J*=7.5, 0.8 Hz, 1 H), 7.15 - 7.23 (m, 1 H), 7.20 (d, *J*=7.4 Hz, 1 H), 7.96 (d, *J*=7.6 Hz, 1 H).

Co. No. 18: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.19 (d, *J*=6.0 Hz, 6 H), 2.08 - 2.19 (m, 2 H), 2.20 - 2.31 (m, 1 H), 2.36 (td, *J*=13.2, 5.1 Hz, 1 H), 3.39 - 3.46 (m, 2 H),

3.46 - 3.57 (m, 2 H), 3.70 (spt, *J*=6.1 Hz, 1 H), 5.03 (s, 2 H), 6.84 (d, *J*=7.6 Hz, 1 H), 7.32 - 7.37 (m, 1 H), 7.39 - 7.47 (m, 4 H), 8.26 (d, *J*=7.9 Hz, 1 H).

Co. No. 43: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.28 - 0.39 (m, 2 H), 0.57 - 0.72 (m, 2 H), 1.06 - 1.22 (m, 1 H), 1.78 - 2.11 (m, 4 H), 2.72 (tt, *J*=11.5, 4.4 Hz, 1 H), 3.04 (d, *J*=6.6 Hz, 2 H), 3.18 (td, *J*=12.1, 2.0 Hz, 2 H), 3.62 (br. d, *J*=12.4 Hz, 2 H), 6.76 (d, *J*=7.5 Hz, 1 H), 7.21 - 7.28 (m, 3 H), 7.34 (t, *J*=7.7 Hz, 2 H), 7.92 (d, *J*=7.8 Hz, 1 H).

Co. No. 297: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.25 - 0.45 (m, 2 H), 0.45 - 0.70 (m, 2 H), 1.11 - 1.31 (m, 1 H), 1.76 (qd, *J*=12.5, 3.2 Hz, 2 H), 1.93 (br. d, *J*=11.1 Hz, 2 H), 2.91 (tt, *J*=11.8, 3.2 Hz, 1 H), 3.06 (d, *J*=6.7 Hz, 2 H), 3.46 (br. t, *J*=12.4 Hz, 2 H), 3.57 (br. s., 1 H), 3.89 (br. d, *J*=12.7 Hz, 2 H), 7.18 - 7.24 (m, 1 H), 7.24 - 7.29 (m, 2 H), 7.29 - 7.36 (m, 2 H), 7.42 (d, *J*=7.9 Hz, 1 H), 8.66 (d, *J*=8.1 Hz, 1 H).

Co. No. 100: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.11 (s, 6 H), 3.18 (s, 2 H), 3.22 - 3.30 (m, 2 H), 3.30 - 3.40 (m, 2 H), 4.47 (q, *J*=10.8 Hz, 2 H), 7.06 - 7.24 (m, 4 H), 7.30 (d, *J*=7.4 Hz, 1 H), 7.31 (t, *J*=7.7 Hz, 1 H), 8.57 (d, *J*=7.4 Hz, 1 H).

Co. No. 112: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 0.14 - 0.40 (m, 2 H), 0.40 - 0.66 (m, 2 H), 1.08 - 1.30 (m, 1 H), 1.48 (s, 6 H), 1.67 (br. d, *J*=12.4 Hz, 2 H), 2.10 (td, *J*=12.3, 5.5 Hz, 2 H), 3.01 (d, *J*=6.6 Hz, 2 H), 3.39 - 3.54 (m, 4 H), 7.05 (d, *J*=8.1 Hz, 1 H), 7.18 - 7.44 (m, 4 H), 8.48 (d, *J*=7.7 Hz, 1 H).

Co. No. 119: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.26 - 0.40 (m, 2 H), 0.51 - 0.70 (m, 2 H), 1.10 - 1.20 (m, 1 H), 1.93 (br. d, *J*=13.4 Hz, 2 H), 2.05 - 2.23 (m, 2 H), 3.06 (d, *J*=6.7 Hz, 2 H), 3.11 (t, *J*=11.3 Hz, 2 H), 3.48 (br. d, *J*=12.9 Hz, 2 H), 4.50 (s, 2 H), 6.78 (d, *J*=7.6 Hz, 1 H), 6.88 (dd, *J*=7.2, 5.1 Hz, 1 H), 7.52 (dd, *J*=7.2, 1.4 Hz, 1 H), 7.99 (d, *J*=7.6 Hz, 1 H), 8.08 (dd, *J*=5.1, 1.4 Hz, 1 H).

Co. No. 121: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.24 - 0.38 (m, 2 H), 0.52 - 0.68 (m, 2 H), 0.95 (s, 4 H), 1.05 - 1.21 (m, 1 H), 3.03 (d, *J*=6.6 Hz, 2 H), 3.20 (t, *J*=4.6 Hz, 2 H), 3.23 (br. s., 2 H), 3.86 (t, *J*=4.6 Hz, 2 H), 6.69 (d, *J*=7.5 Hz, 1 H), 6.83 (t, *J*=7.2 Hz, 1 H), 7.05 (d, *J*=7.8 Hz, 2 H), 7.20 - 7.33 (m, 2 H), 7.91 (d, *J*=7.8 Hz, 1 H).

Co. No. 123: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.03 - 0.15 (m, 2 H), 0.42 - 0.52 (m, 2 H), 0.67 - 0.86 (m, 1 H), 1.77 (q, *J*=7.2 Hz, 2 H), 1.92 (qd, *J*=12.7, 3.8 Hz, 2 H), 1.94 - 2.01 (m, 2 H), 2.72 (tt, *J*=11.6, 4.0 Hz, 1 H), 3.14 (t, *J*=7.5 Hz, 2 H), 3.18 (ddd, *J*=12.1, 11.6, 2.0 Hz, 2 H), 3.61 (br. d, *J*=12.7 Hz, 2 H), 6.76 (d, *J*=7.8 Hz, 1 H), 7.21 - 7.27 (m, 3 H), 7.31 - 7.38 (m, 2 H), 7.86 (d, *J*=7.8 Hz, 1 H).

Co. No. 139: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.55 (s, 6 H), 1.72 - 1.95 (m, 2 H), 2.22 (td, *J*=12.9, 4.7 Hz, 2 H), 3.44 (td, *J*=12.4, 2.4 Hz, 2 H), 3.52 - 3.61 (m, 2 H),

4.02 (q, *J*=9.7 Hz, 2 H), 6.90 (d, *J*=7.4 Hz, 1 H), 7.10 - 7.22 (m, 2 H), 7.29 - 7.36 (m, 2 H), 7.87 (d, *J*=7.6 Hz, 1 H).

Co. No. 145: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.26 - 0.43 (m, 2 H), 0.49 - 0.66 (m, 2 H), 1.12 - 1.24 (m, 1 H), 1.86 - 2.09 (m, 4 H), 2.60 (s, 3 H), 2.61 - 2.73 (m, 1 H), 2.86 - 2.99 (m, 2 H), 3.05 (d, *J*=6.5 Hz, 2 H), 3.23 - 3.40 (m, 2 H), 6.79 (d, *J*=7.6 Hz, 1 H), 7.21 - 7.27 (m, 1 H), 7.27 - 7.32 (m, 2 H), 7.32 - 7.39 (m, 2 H), 7.81 (d, *J*=7.2 Hz, 1 H).

Co. No. 147: ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 0.14 - 0.40 (m, 2 H), 0.41 - 0.66 (m, 2 H), 1.01 - 1.31 (m, 1 H), 1.78 (br. d, *J*=13.2 Hz, 2 H), 2.34 (td, *J*=13.5, 5.1 Hz, 2 H), 3.03 (d, *J*=7.0 Hz, 2 H), 3.44 (br. t, *J*=12.4 Hz, 2 H), 3.48 - 3.58 (m, 2 H), 7.10 (d, *J*=7.7 Hz, 1 H), 7.55 - 7.64 (m, 1 H), 7.64 - 7.71 (m, 2 H), 7.71 - 7.78 (m, 1 H), 8.55 (d, *J*=7.7 Hz, 1 H).

Co. No. 148: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.23 - 0.37 (m, 2 H), 0.53 - 0.66 (m, 2 H), 1.05 - 1.18 (m, 1 H), 1.63 (s, 3 H), 1.91 (ddd, *J*=13.2, 9.3, 3.5 Hz, 2 H), 2.41 - 2.55 (m, 2 H), 3.01 (d, *J*=6.6 Hz, 2 H), 3.21 (ddd, *J*=12.1, 9.2, 2.9 Hz, 2 H), 3.33 - 3.45 (m, 2 H), 6.69 (d, *J*=7.8 Hz, 1 H), 7.15 (ddd, *J*=7.5, 4.9, 0.9 Hz, 1 H), 7.33 (d, *J*=8.1 Hz, 1 H), 7.68 (td, *J*=7.7, 1.9 Hz, 1 H), 7.84 (d, *J*=7.8 Hz, 1 H), 8.60 (dd, *J*=4.6, 0.9 Hz, 1 H).

Co. No. 153: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.89 (qd, *J*=12.7, 3.2 Hz, 2 H), 1.92 - 2.01 (m, 2 H), 2.70 (tt, *J*=11.6, 4.0 Hz, 1 H), 3.16 (br. t, *J*=11.1 Hz, 2 H), 3.60 (br. d, *J*=12.7 Hz, 2 H), 4.65 (s, 2 H), 6.69 (d, *J*=7.8 Hz, 1 H), 7.18 (dd, *J*=6.9, 5.2 Hz, 1 H), 7.21 - 7.27 (m, 3 H), 7.30 - 7.35 (m, 2 H), 7.36 (d, *J*=7.8 Hz, 1 H), 7.63 (td, *J*=7.7, 1.7 Hz, 1 H), 8.33 (d, *J*=7.8 Hz, 1 H), 8.51 (d, *J*=4.3 Hz, 1 H).

Co. No. 171: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.24 - 0.44 (m, 2 H), 0.50 - 0.68 (m, 2 H), 1.10 - 1.30 (m, 1 H), 1.43 (t, *J*=7.5 Hz, 3 H), 1.84 - 2.08 (m, 4 H), 2.57 - 2.73 (m, 1 H), 2.83 - 2.99 (m, 2 H), 3.04 (br. d, *J*=6.7 Hz, 2 H), 3.13 (q, *J*=7.5 Hz, 2 H), 3.21 (d, *J*=12.0 Hz, 2 H), 6.81 (d, *J*=7.4 Hz, 1 H), 7.20 - 7.28 (m, 1 H), 7.28 - 7.32 (m, 2 H), 7.32 - 7.40 (m, 2 H), 7.81 (d, *J*=7.4 Hz, 1 H).

Co. No. 159: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.22 - 0.38 (m, 2 H), 0.52 - 0.66 (m, 2 H), 1.03 - 1.10 (m, 2 H), 1.14 - 1.24 (m, 1 H), 1.66 - 1.80 (m, 2 H), 1.90 - 2.04 (m, 4 H), 2.34 (tt, *J*=8.7, 5.5 Hz, 1 H), 2.59 - 2.75 (m, 1 H), 2.90 - 2.97 (m, 2 H), 2.99 (d, *J*=6.6 Hz, 2 H), 3.52 (br. d, *J*=11.8 Hz, 2 H), 6.76 (d, *J*=7.5 Hz, 1 H), 7.24 (t, *J*=7.2 Hz, 1 H), 7.27 - 7.31 (m, 2 H), 7.31 - 7.38 (m, 2 H), 7.72 (d, *J*=7.2 Hz, 1 H).

Co. No. 182: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.26 - 0.45 (m, 2 H), 0.54 - 0.71 (m, 2 H), 1.07 - 1.20 (m, 1 H), 1.22 (d, *J*=6.5 Hz, 3 H), 3.06 (d, *J*=6.7 Hz, 2 H), 3.15 - 3.29 (m, 2 H), 3.30 - 3.41 (m, 2 H), 3.47 (dd, *J*=11.3, 3.0 Hz, 1 H), 3.49 - 3.58

(m, 1 H), 3.97 - 4.08 (m, 1 H), 6.29 (tt, *J*=8.8, 2.2 Hz, 1 H), 6.32 - 6.44 (m, 2 H), 6.78 (d, *J*=7.6 Hz, 1 H), 8.01 (d, *J*=7.6 Hz, 1 H).

Co. No. 200: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.27 - 0.39 (m, 2 H), 0.55 - 0.67 (m, 2 H), 1.09 - 1.19 (m, 1 H), 1.52 (s, 6 H), 1.77 (d, *J*=12.4 Hz, 2 H), 2.12 (td, *J*=12.9, 4.5 Hz, 2 H), 3.05 (d, *J*=6.9 Hz, 2 H), 3.39 (br. d, *J*=12.1 Hz, 2 H), 3.54 (t, *J*=12.0 Hz, 2 H), 6.81 (dd, *J*=8.4, 2.0 Hz, 1 H), 6.82 (d, *J*=7.2 Hz, 1 H), 7.00 (td, *J*=8.5, 2.3 Hz, 1 H), 7.09 (dd, *J*=8.2, 4.8 Hz, 1 H), 7.94 (d, *J*=7.8 Hz, 1 H).

Co. No. 204: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.25 - 0.40 (m, 2 H), 0.47 - 0.66 (m, 2 H), 1.15 - 1.25 (m, 1 H), 1.84 (br d, *J*=12.4 Hz, 2 H), 2.01 (qd, *J*=12.5, 3.8 Hz, 2 H), 2.68 (s, 3 H), 2.84 (br t, *J*=11.1 Hz, 2 H), 3.04 (tt, *J*=12.1, 3.8 Hz, 1 H), 3.06 (d, *J*=6.6 Hz, 2 H), 3.50 (br d, *J*=11.6 Hz, 2 H), 6.79 - 6.88 (m, 2 H), 6.85 (d, *J*=7.2 Hz, 1 H), 6.93 - 7.03 (m, 1 H), 7.84 (d, *J*=7.2 Hz, 1 H).

Co. No. 206: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.86 - 2.04 (m, 2 H), 2.05 - 2.15 (m, 2 H), 2.87 (tt, *J*=12.1, 3.8 Hz, 1 H), 3.40 (td, *J*=12.7, 2.3 Hz, 2 H), 4.26 - 4.41 (m, 2 H), 6.72 (d, *J*=7.9 Hz, 1 H), 7.22 - 7.28 (m, 3 H), 7.30 - 7.39 (m, 2 H), 8.10 - 8.17 (m, 2 H), 8.38 (d, *J*=7.6 Hz, 1 H), 8.72 - 8.79 (m, 2 H).

Co. No. 207: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.23 - 0.39 (m, 2 H), 0.47 - 0.67 (m, 2 H), 1.11 - 1.22 (m, 1 H), 1.92 - 2.11 (m, 4 H), 2.64 - 2.77 (m, 1 H), 2.99 (td, *J*=11.3, 3.5 Hz, 2 H), 3.06 (d, *J*=6.6 Hz, 2 H), 3.69 (br. d, *J*=11.8 Hz, 2 H), 6.75 (d, *J*=7.2 Hz, 1 H), 7.22 - 7.27 (m, 1 H), 7.28 - 7.32 (m, 2 H), 7.32 - 7.39 (m, 2 H), 7.89 (d, *J*=7.2 Hz, 1 H).

Co. No. 224: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.27 - 0.41 (m, 2 H), 0.56 - 0.70 (m, 2 H), 1.14 - 1.24 (m, 1 H), 2.69 (br. t, *J*=4.6 Hz, 4 H), 3.07 (br. t, *J*=4.0 Hz, 4 H), 3.10 (d, *J*=6.9 Hz, 2 H), 3.81 (d, *J*=1.2 Hz, 2 H), 6.72 - 6.85 (m, 2 H), 6.86 - 6.95 (m, 1 H), 7.40 (d, *J*=7.2 Hz, 1 H), 8.06 (d, *J*=7.2 Hz, 1 H).

Co. No. 244: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.25 - 0.41 (m, 2 H), 0.58 - 0.71 (m, 2 H), 1.15 - 1.24 (m, 1 H), 1.36 (d, *J*=6.4 Hz, 3 H), 1.54 - 1.67 (m, 1 H), 1.68 - 1.76 (m, 1 H), 1.77 - 1.89 (m, 1 H), 1.90 - 2.02 (m, 1 H), 2.07 (br t, *J*=11.1 Hz, 1 H), 2.18 (td, *J*=11.4, 2.3 Hz, 1 H), 2.54 (tt, *J*=12.1, 3.8 Hz, 1 H), 2.59 - 2.69 (m, 1 H), 2.98 - 3.20 (m, 2 H), 3.33 - 3.46 (m, 1 H), 3.83 - 3.96 (m, 1 H), 7.17 - 7.22 (m, 1 H), 7.22 (d, *J*=7.2 Hz, 2 H), 7.31 (t, *J*=7.7 Hz, 2 H), 7.49 (d, *J*=7.2 Hz, 1 H), 8.06 (d, *J*=7.5 Hz, 1 H).

Co. No. 250: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.31 - 0.41 (m, 2 H), 0.59 - 0.69 (m, 2 H), 1.14 - 1.24 (m, 1 H), 2.02 (br t, *J*=11.7 Hz, 2 H), 2.05 - 2.13 (m, 1 H), 2.17 (td, *J*=13.2, 4.8 Hz, 1 H), 2.65 (br t, *J*=11.0 Hz, 2 H), 2.71 - 2.81 (m, 2 H), 3.11 (d, *J*=6.9 Hz, 2 H), 3.82 (d, *J*=1.4 Hz, 2 H), 7.29 - 7.34 (m, 1 H), 7.36 - 7.46 (m, 4 H), 7.39 (d, *J*=7.2 Hz, 1 H), 8.06 (d, *J*=7.2 Hz, 1 H).

Co. No. 282: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.27 - 0.41 (m, 2 H), 0.56 - 0.69 (m, 2 H), 1.14 - 1.25 (m, 1 H), 2.59 - 2.72 (m, 4 H), 3.09 (d, *J*=6.6 Hz, 2 H), 3.24 (br. s., 4 H), 3.77 (s, 2 H), 6.75 - 6.89 (m, 2 H), 6.88 - 6.99 (m, 1 H), 7.18 (d, *J*=7.2 Hz, 1 H), 7.89 (d, *J*=7.2 Hz, 1 H).

Co. No. 298: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.27 - 0.40 (m, 1 H), 0.45 - 0.62 (m, 2 H), 1.14 - 1.34 (m, 1 H), 1.94 (br. d, *J*=13.3 Hz, 2 H), 2.15 - 2.34 (m, 2 H), 2.81 - 2.95 (m, 1 H), 3.12 (d, *J*=6.9 Hz, 2 H), 3.16 - 3.33 (m, 2 H), 3.54 (br. d, *J*=11.6 Hz, 2 H), 4.61 (br. s., 2 H), 7.17 - 7.29 (m, 3 H), 7.34 (t, *J*=7.5 Hz, 2 H), 7.88 (d, *J*=7.2 Hz, 1 H), 8.93 (d, *J*=7.2 Hz, 1 H), 11.22 (br. s., 1 H).

D. Pharmacological examples

The compounds provided in the present invention are positive allosteric modulators of mGluR2. These compounds appear to potentiate glutamate responses by binding to an allosteric site other than the glutamate binding site. The response of mGluR2 to a concentration of glutamate is increased 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 enhance the function of the receptor. The behaviour of positive allosteric modulators tested at mGluR2 using the [^{35}S]GTPγS binding assay method described below and which is suitable for the identification of such compounds, and more particularly the compounds according to Formula (I), is shown in Table 3.

[^{35}S]GTPγS binding assay

The [^{35}S]GTPγS 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]GTPγS (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]GTPγS, 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]GTPγS incorporation is a direct measure of the activity of the G-protein and hence the activity of the agonist can be determined. mGluR2 receptors are shown to be preferentially coupled to Gαi-protein, a preferential coupling for this method, and hence it is widely used to study receptor activation of mGluR2 receptors both in recombinant cell lines and in tissues. Here we describe the use of the [^{35}S]GTPγS binding assay using membranes from cells transfected with the human mGluR2 receptor and adapted from

Schaffhauser *et al.* ((2003) Molecular Pharmacology 4:798-810) for the detection of the positive allosteric modulation (PAM) 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, prior to washing in PBS, and then collected by scraping in homogenisation buffer (50 mM Tris-HCl buffer, pH 7.4, 4 °C). Cell lysates were homogenized briefly using an ultra-turrax homogenizer. The homogenate was centrifuged at 16,000 RPM (Sorvall RC-5C plus rotor SS-34) for 10 minutes and the supernatant discarded. The pellet was resuspended in 5 mM Tris-HCl, pH 7.4 and centrifuged again (18,000 RPM, 20 min, 4 °C). The final pellet was resuspended in 50 mMTris-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]GTPγS binding assay

Measurement of mGluR2 positive 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 $MgCl_2$ and 10 μM GDP. Human mGlu2 receptor-containing membranes were thawed on ice and diluted in assay buffer supplemented with 14 μg/ml saponin. Membranes were pre-incubated with compound alone or together with a predefined (~EC_{20}) concentration of glutamate (PAM assay) for 30 min at 30°C. After addition of [^{35}S]GTPγS (f.c. 0.1 nM) microplates were shaken briefly and further incubated to allow [^{35}S]GTPγS incorporation on activation (30 minutes, 30 °C). Final assay mixtures contained 7 μg of membrane protein in 10 mM HEPES acid, 10 mM HEPES salt, pH 7.4, 100 mM NaCl, 3 mM $MgCl_2$,10 μM GDP and 10 μg/ml saponin. Total reaction volume was 200 μl. Reactions were terminated by rapid filtration through Unifilter-96 GF/B filter plates (Packard, Meriden, CT) using a 96-well Packard filtermate harvester. Filters were washed 6 times with ice-cold 10 mM NaH_2PO_4/10 mM Na_2HPO_4, pH 7.4. Filters were then air-dried, and 40 μl of liquid scintillation cocktail (Microscint-O) was added to each well. Membrane-bound radioactivity was counted in a Microplate Scintillation and Luminescence Counter from Packard.

Data analysis

The concentration-response curves of representative compounds of the present invention -obtained in the presence of EC_{20} of mGluR2 agonist glutamate to determine positive allosteric modulation (PAM)- were generated using the Lexis software

interface (developed at J&J). Data were calculated as % of the control glutamate response, defined as the maximal response that is generated upon addition of glutamate alone. 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 effect is then calculated as EC_{50}. The pEC_{50} values below were calculated as the $-\log EC_{50}$, when the EC_{50} is expressed in M. Table 3 below shows the pharmacological data obtained for a selected set of compounds.

Motor Activity *(Video tracking)*

Apparatus and General Procedure

On the day of experiments, the mice were brought into the procedural room. They were housed individually and allowed to acclimate for at least a half hour prior to testing. Although the studies were conducted during the light cycle (from 8:00 to 16:00 h), the procedure room was only sparsely lit (3 to 30 LUX) to provide better contrast for the video tracking. Local lighting was used for the injection procedures. During each trial, an individual mouse was placed in an open field arena (grey PVC cylinder with a height of 40 cm and a diameter of 22.5 cm). Each arena was placed on an infrared LED (8 x 8 LEDs)-lit box (white PVC squared box; 40 x 40 cm^2; height 12.5 cm). Each mouse was placed in the center of the arena and allowed to explore freely for 30 min. After each trial, the arena was cleaned with a wet and subsequently with a dry cleaning cloth. An infrared sensitive tube camera and a white light source (in arena: 4-7 LUX) were mounted to the ceiling above the observation chamber to record and input activity to a computer. Animal behavior was recorded and analyzed using the Noldus Ethovision XT Video Tracking System (Version 3.1; Noldus, Wageningen, The Netherlands). The total distance traveled (cm) was calculated. Data were then exported to data management systems for further analysis and reporting.

Phencyclidine (PCP)-induced Hyperlocomotion in Mice

Test compound or solvent was administered at a pre-defined time before measurement (standard: 30 min) to male NMRI mice that were challenged with phencyclidine (PCP; 5 mg/kg, s.c.) 30 min before measurement. Activity was measured for a period of 30 min. Criterion for drug-induced inhibition of hyperlocomotion: total distance < 5500 counts (3.9% false positives in controls; n = 154). The results are shown in table 4a below.

d-Amphetamine-induced Hyperlocomotion in Mice

Test compound or solvent was administered at a pre-defined time before measurement (standard: 30 min) to male NMRI mice that were challenged with d-amphetamine (5 mg/kg, s.c.) 30 min before measurement. Activity was measured for a period of 30 min. Criterion for drug-induced inhibition of hyperlocomotion: total distance < 5500 counts (4.1% false positives in controls; n = 410). Compound 43 inhibited the amphetamine-induced hyperlocomotion (ED_{50}: 37 mg/kg s.c.).

Conditioned avoidance response (CAR) test

Apparatus

The apparatus consisted of an inner box surrounded by an outer box. The inner box was composed of four walls of transparent, synthetic material (length x width x height: 30 x 30 x 30 cm), an open top, and a grid floor made of 15 pairs of iron bars (2 mm diameter; 6 mm inter-bar distance). Odd and even bars were connected with a source of alternative current (1.0 mA; Coulbourn Instruments Solid State Shocker/Distributor), which could be interrupted by a switch. The outer box was composed of the same material (length x width x height: 40 x 40 x 36 cm), also with an open top, with a distance of 5 cm between the inner and outer box on all sides. To decrease the amount of environmental stimuli, three walls of the outer box were made non-transparent. The front wall was left transparent to allow the necessary inspection of the animal during the test. The upper edge of the outer and inner box served as a target for the rats on which to jump with fore- and hind-paws, respectively.

Avoidance Conditioning and Selection of Animals

From their arrival in the laboratory on the experimental day, male Wiga Wistar rats (230 ± 30 g) were housed in individual cages provided with bedding material. The rats received 5 training sessions at 15-min time intervals over a 1-h period during which, the rats were conditioned to avoid an electric shock: the rat was placed on the non-electrified grid floor and the grid was electrified 10 s later for not more than 30 s, if the rat did not jump out of the box. Only rats that showed correct avoidance responses in all the last 3 training sessions were included for further experiments, and received the test compound or solvent immediately after the last training session.

Experimental Sessions

The rats were tested 3 times, i.e. at 60, 90 and 120 min after the injection of test compound or solvent. Latency to avoidance was recorded. The median avoidance response obtained over the three experimental sessions for each rat were used for

further calculations. A median avoidance latency > 8 s was selected as an all-or-none criterion for drug-induced inhibition of avoidance (occurring in only 1.5% of solvent-pretreated control rats; n = 66). The results of this test are shown in table 4b below.

Reversal of memantine-induced brain activation in mice

NMDA receptor hypofunction is hypothesized to be involved in schizophrenia. Subanaesthetic doses of the NMDA antagonist ketamine have been shown to induce behavioural, perceptual and cognitive changes in healthy volunteers similar to positive, negative and cognitive symptoms of schizophrenia.

Autoradiographic assessment of radiolabeled [^{14}C]-2-deoxyglucose ([^{14}C]2DG) uptake is commonly used to investigate brain activation. In humans, cerebral blood flow is increased in specific brain regions after administration of a subanaesthetic dose of ketamine. Ketamine-induced alterations in 2DG uptake have therefore been suggested as a model to investigate the effects of antipsychotic drugs. When evaluating different NMDA antagonists, we found that memantine induced more robust brain activation with a greater dynamic window for testing drugs. Validating our choice to use memantine, we found that in accordance to the ketamine model, the atypical antipsychotic clozapine reversed memantine induced brain glucose metabolism, whereas the typical antipsychotic haloperidol was inactive in this test. In the same model, we have found that the mGlu2/3 agonist LY404039 inhibited memantine-induced increase in 2DG uptake in mouse brain.

Method

Male mice (C57BL/6, weight 24-28 g, fasted overnight; n=10 animals per group) were treated with vehicle or test compound (s.c.) in randomized order (t = 0 min). Memantine (20 mg/kg, s.c.) was injected 30 min later (t = 30 min). At t = 45 min, [^{14}C]2DG (0.16 µCi/g) was administered intraperitoneally (i.p.), followed by a 45 min uptake period. Animals were decapitated (t = 90 min), plasma glucose levels measured, the brain removed, rapidly frozen and stored at -20°C until sectioned. Brain sections were exposed together to a precalibrated [^{14}C]standard on film, which was developed after four days of exposure. Local tissue [^{14}C]concentration (nCi/mg tissue equivalent - TEQ-) in each region of interest was determined.

Data was analyzed statistically using a two-way ANOVA analysis followed by post-hoc tests (memantine response versus reversal by the compound). The results are shown in table 5 below, expressed as lowest active dose (L.A.D.) required to exert a statistically significant ($p<0.05$) reduction of 2DG uptake in the hippocampus compared to memantine response.

Sleep Wake Electroencephalography (SW-EEG) in rats

SW-EEG analyses are a highly sensitive read-out of a compound's central functional activity that may provide additional insight in the potential therapeutic application (i.e. via drug classification fingerprinting). Systemic administration of an mGlu2/3 receptor agonist and PAM has been shown to selectively suppress rapid eye movement (REM) sleep in rat. Internal efforts have confirmed that this effect is mGlu2 receptor-mediated, i.e. is absent in mGlu2 KO mice. Sleep abnormalities are often associated with CNS disorders; as such, the potential use of mGlu2 modulators could also have benefit in the treatment of CNS disorders in which (REM) sleep aberrations are manifested. More specifically, the combination of a persistent reduction in REM occurrence and an increase in REM latency is one of the key features of the typical SW architecture fingerprint of most clinically active antidepressants.

We investigated the effects of oral administration of compounds according to the invention on SW organization in rats. The mGlu2/3 receptor agonists LY404039 and LY354740 were also evaluated to allow comparison.

A selection of compounds was found to dose-dependently decrease REM sleep in rats (lowest active dose was 3 or 10 mg/kg, p.o.). Similarly, acute dosing of LY354740 showed a decrease in REM sleep (lowest active dose 3 mg/kg, s.c.); also compound LY404039 was found to affect REM sleep (3 mg/kg, p.o.) qualitatively in a comparable way.

Subchronic treatment (once daily dosing for 7 days) with LY354740 (1, 3, 10 mg/kg, s.c.) led to tolerance (from day 3 onward, the effect on REM sleep started to diminish, with loss of activity of the 3 and 10 mg/kg dose), whereas a similar treatment schedule (3, 10 and 30 mg/kg, p.o.) did not diminish the effects of compound 43.

Table 3. Pharmacological data for compounds according to the invention.

Co.No.	GTPγS - hR2 PAM pEC_{50}
1	6.68
2	7.41
3	6.94
4	7.62
5	6.88‡
6	6.89‡

Co.No.	GTPγS - hR2 PAM pEC_{50}
7	7.4
8	7.01‡
9	6.57
10	6.16
11	5.12‡
12	7.33
13	7.13
14	6.37
15	6.75
16	6.75
17	7.45
18	7.16
19	n.c.
20	7.25
21	6.61
22	7.26
23	6.98
24	6.33‡
25	6.42
26	6.99
27	7.51
28	6.53
29	n.c.
30	6.95
31	6.27

Co.No.	GTPγS - hR2 PAM pEC_{50}
32	7.03
33	5.15‡
34	7.35
35	5.91
36	5.95‡
37	6.51
38	7.74
39	7.52
40	6.67
41	7.21
42	6.83
43	7.79
44	6.02
45	6.07‡
46	8.03
47	n.c.
48	6.9‡
49	n.c.
50	n.c.
51	8.35‡
52	6.98‡
53	6.07
54	6.95
55	8.22
56	6.02‡

Co.No.	GTPγS - hR2 PAM pEC_{50}
57	8.16‡
58	6.23
59	7.17
60	6.33
61	7.98
62	6.41
63	6.08
64	6.65
65	8.41
66	6.94
67	7.36
68	7.55
69	n.t.
70	n.t.
71	6.65‡
72	7.06
73	6.13
74	6.85
75	7.05
76	6.93
77	7.68‡
78	6.83
79	7.28
80	7.27
81	6.85

Co.No.	GTPγS - hR2 PAM pEC_{50}
82	7.51
83	7.64
84	7.86
85	8.06
86	7.95
87	6.94
88	6.18
89	6.46‡
90	6.61
91	7.27
92	6.87
93	6.53
94	n.c.
95	5.93‡
96	5.88
97	6.3
98	6.75
99	6.03
100	6.51
101	6.24
102	6.5
103	5.63‡
104	7.7
105	6.17‡
106	6.45

Co.No.	GTPγS - hR2 PAM pEC_{50}
107	7.22
108	6.91‡
109	7.29
110	6.86
111	6.26
112	8.19
113	7.59
114	6.33
115	n.c.
116	n.c.
117	6.68
118	6.83
119	5.76
120	6.31
121	6.63
122	7.3
123	7.39
124	6.98
125	n.c.
126	n.c.
127	6.42
128	6.73
129	6.92
130	6.4
131	7.34

Co.No.	GTPγS - hR2 PAM pEC_{50}
132	6.68
133	7.05
134	7.17
135	6.77
136	7.69‡
137	6.87
138	n.c.
139	8.36
140	6.55
141	6.95
142	6.55‡
143	n.c.
144	6.25
145	6.38
146	7.02
147	6.61
148	6.44
149	6.5‡
150	6.97‡
151	7.48
152	6.78
153	6.71
154	7.13
155	6.83‡
156	n.c.

Co.No.	GTPγS - hR2 PAM pEC_{50}
157	6.18
158	6.14
159	6.69
160	6.73
161	5.68‡
162	6.93
163	6.97‡
164	6.46
165	6.41
166	7.22
167	6.47‡
168	7.22
169	7.77‡
170	5.84‡
171	6.6
172	n.c.
173	6.32‡
174	5.91‡
175	6.33
176	6.3
177	7.67
178	n.c.
179	5.79‡
180	7.23
181	n.c.

Co.No.	GTPγS - hR2 PAM pEC_{50}
182	7.03
183	7.08
184	6.81
185	8.26
186	7.27
187	6.19
188	8‡
189	6.4
190	6.5
191	6.76
192	6.63
193	8.26
194	7.69
195	7.98
196	7.06
197	7.82‡
198	6.29‡
199	6.8
200	8.45
201	6.9
202	7.86‡
203	6.73
204	5.87‡
205	6.61‡
206	n.c.

Co.No.	GTPγS - hR2 PAM pEC_{50}
207	7.45
208	7.06
209	7.52‡
210	6.5
211	7.44
212	8.08
213	6.03‡
214	7.68
215	5.6‡
216	6.68
217	n.t.
218	6.05‡
219	7.24‡
220	7.37
221	7.55
222	n.c.
223	6.03‡
224	7.06
225	6.8‡
226	6.4
227	6.31‡
228	n.c.
229	n.c.
230	5.61‡
231	n.c.

Co.No.	GTPγS - hR2 PAM pEC_{50}
232	7.64
233	7.23
234	7.83‡
235	n.c.
236	n.t.
237	n.c.
238	6.08‡
239	6.97
240	6.41‡
241	5.75‡
242	5.86
243	7.91
244	7.62‡
245	7.41
246	6.79
247	6.72
248	7.55
249	7.48‡
250	6.93
251	n.c.
252	n.c.
253	6.87
254	6.63
255	6.78‡
256	n.c.

Co.No.	GTPγS - hR2 PAM pEC_{50}
257	6.74
258	6.11‡
259	6.67‡
260	7.47
261	6.84‡
262	7.27‡
263	6.95
264	5.71‡
265	7.56
266	7.88‡
267	6.41
268	7.59‡
269	7.59
270	5.58‡
271	7.24‡
272	6.01
273	7.33
274	7.83‡
275	7.71
276	6.78‡
277	7.72
278	8.01
279	7.24‡
280	5.95‡
281	7.06

Co.No.	GTPγS - hR2 PAM pEC_{50}
282	6.69‡
283	7.26
284	6.5
285	6.77
286	n.c.
287	7.87‡
288	n.c.
289	6.87
290	7.13
291	6.83
292	5.84‡
293	6.31‡
294	6.59
295	6.32‡
296	6.95
297	7.61‡
298	7.77
299	5.97‡
300	7.24
301	7.45‡
302	6.55
303	7.3
304	6.12
305	n.t.
306	n.t.

Co.No.	GTPγS - hR2 PAM pEC_{50}
307	6.37
308	n.c.
309	n.c.
310	n.t.
311	7.05
312	6.82
313	6.44‡
314	6.31‡
315	7.24
316	5.83‡
317	n.c.
318	6.21
319	6.84
320	6.02
321	6.96
322	7.29
323	6.61‡
324	7.27
325	7.55
326	6.92
327	7.71‡
328	n.t.
329	n.t.
330	n.t.
331	n.c.

Co.No.	GTPγS - hR2 PAM pEC_{50}
332	n.t.
333	6.33‡
334	n.c.
335	6.42‡
336	6.08‡
337	7.23‡
338	7.42‡
339	7.15‡
340	6.57‡
341	7.9‡
342	7.35‡
343	n.c.
344	6.64‡
345	7.39‡
346	6.5‡
347	n.t.
348	n.t.
349	n.t.
350	7.11‡
351	7.46‡
352	7.71‡
353	7.24‡
354	8.25‡
355	n.t.
356	n.t.

Co.No.	GTPγS - hR2 PAM pEC_{50}
357	n.t.
359	7‡
360	6.44‡
361	7.25‡
362	7.24‡
363	5.96‡

Co.No.	GTPγS - hR2 PAM pEC_{50}
364	n.c.
365	6.77‡
366	6.98‡
367	7.23‡
368	6.32‡

n.t. means not tested

n.c. means that the EC_{50} could not be calculated

‡ means tested once

EC_{50} values were not calculated in cases where the concentration-response curve did not reach a plateau level. By definition, the EC_{50} value of a compound is the concentration needed to reach 50% of the maximal response.

All compounds were tested in presence of mGluR2 agonist, glutamate at a predetermined EC_{20} concentration, to determine positive allosteric modulation (GTPγS-PAM). pEC_{50} values were calculated from a concentration-response experiment of at least 10 concentrations. If more experiments were performed, the average pEC_{50} value is reported and error deviation was <0.5.

Table 4a. Pharmacological data for compounds according to the invention in the (PCP)-induced hyperlocomotion test in mice.

ED_{50} is the dose (mg/kg body weight) at which 50% of the tested animals show the effect; Inh. means inhibition.

	Mice
	ED_{50} (mg/kg)
Co. No.	**PCP-Inh.**
30	5 [a)]

	Mice
	ED_{50} (mg/kg)
Co. No.	**PCP-Inh.**
3	15.2

Co. No.	Mice ED_{50} (mg/kg) PCP-Inh.
43	5.4
44	>40
66	17.4
76	3.1
78	≥10
17	15.2
15	>10
97	6.3 [a)]
98	>40
112	2.0
151	12.6 [a)]
298	5.0 [a)]
221	12.6 [a)]
224	2.0 [a)]
226	7.9 [a)]
240	12.6 [a)]
244	5.0 [a)]

Co. No.	Mice ED_{50} (mg/kg) PCP-Inh.
250	> 10
307	1.25 [a)]
278	1.25 [a)]
281	3.2 [a)]
286	20 [a)]
288	12.6 [a)]
303	20 [a)]
300	12.6 [a)]
311	3.2 [a)]
319	20 [a)]
320	3.2 [a)]
323	1.25 [a)]
325	7.9 [a)]
322	7.9 [a)]
326	3.1 [a)]
316	12.6 [a)]
317	5.0 [a)]

[a)] Estimated ED_{50} values (n = 3 per dose; 4-fold separation between doses)

Table 4b. Pharmacological data for compounds according to the invention in the CAR test in rats.

ED_{50} is the dose (mg/kg body weight) at which 50% of the tested animals show the effect. Inh. means inhibition; * means the compound was administered orally.

Co. No.	Rats ED_{50} (mg/kg) CAR-Inh.
3	14.1*[a)]
	10.7
43	16.3*
	2.35
76	≥40*

	Rats
	ED_{50} (mg/kg)
Co. No.	**CAR-Inh.**
15	≥40*
97	32*[b)]
	16[b)]
298	5.0[b)]
224	5.0[b)]

[a)] Estimated ED_{50} value (irregular dose-response)

[b)] Estimated ED_{50} values (n = 3 per dose; 4-fold separation between doses)

Compounds 30, 3, 43, 66, 76, 17, 97, 112, 151, 298, 221, 224, 226, 240, 307, 278, 281, 286, 288, 298, 303, 300, 311, 319, 320, 323, 325, 326, 316 and 317 inhibited PCP-induced hyperlocomotion in mice, compound 43 was also active against d-amphetamine-induced hyperlocomotion in mice, and compounds 3, 43, 97, 224 and 298 also inhibited the conditioned avoidance response in rats, attesting to their possible antipsychotic potential.

Table 5. Pharmacological data for compounds according to the invention in the reversal of memantine-induced brain activation in mice.

Mice	
Co. No.	**L.A.D. (mg/kg, s.c.)**
3	≤2.5
43	≤2.5
97	≤10
98	≤10
112	≤2.5
151	10

≤ means that the compound was active at the indicated dose level and was not tested at lower doses.

The observed reversal in memantine-induced 2DG uptake indicates that mGlu2 PAMs may have antipsychotic-like properties.

E. 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 thereof.

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
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 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 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.

4. Ointment

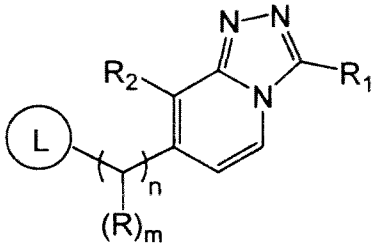
Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

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

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)



(I)

or a stereochemically isomeric form thereof

wherein

n is selected from the group consisting of 0, 1 and 2;

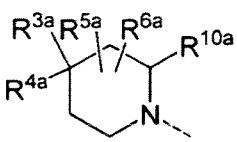
m is selected from the group consisting of 0, 1, and 2;

R is selected from methyl or trifluoromethyl;

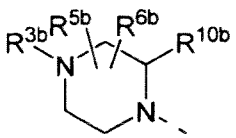
R^1 is selected from the group consisting of hydrogen; C_{1-6}alkyl; (C_{1-3}alkyloxy)-C_{1-3}alkyl; [(C_{1-3}alkyloxy)C_{1-3}alkyloxy]C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; unsubstituted phenyl; unsubstituted benzyl; benzyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxyC_{1-3}alkyl, hydroxyC_{1-3}alkyl, cyano, hydroxyl, amino, C(=O)R', C(=O)OR', C(=O)NR'R'', mono- or di(C_{1-3}alkyl)amino, morpholinyl, (C_{3-7}cycloalkyl)C_{1-3}alkyloxy, trifluoromethyl and trifluoromethoxy, wherein R' and R'' are independently selected from hydrogen and C_{1-6}alkyl; (benzyloxy)C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with C_{1-3}alkyl substituted with one or more independently selected halo substituents; (C_{3-7}cycloalkyl)C_{1-3}alkyl; [(C_{3-7}cycloalkyl)C_{1-3}alkyloxy]C_{1-3}alkyl; (C_{3-7}cycloalkyl)C_{1-3}alkyloxy; 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)methyl; Het^1; Het^1C_{1-3}alkyl; Het^2; and Het^2C_{1-3}alkyl;

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

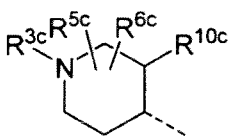
Ⓛ is an *N*-containing heterocycle selected from the group consisting of (L-a), (L-b), (L-c), (L-d), (L-e), (L-f), (L-g) and (L-h) below



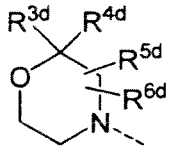
(L-a)



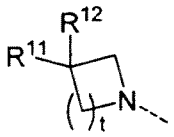
(L-b)



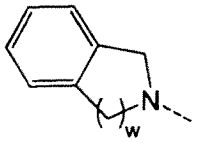
(L-c)



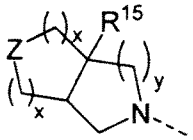
(L-d)



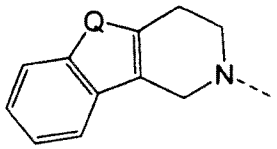
(L-e)



(L-f)



(L-g)



(L-h)

wherein

R^{3a} is selected from the group consisting of C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents or hydroxyl; unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxy-C_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxy substituted with one or more independently selected halo substituents, C_{1-3}alkylcarbonyl, mono- and di(C_{1-3}alkyl)amino, and morpholinyl; unsubstituted (phenyl)C_{1-3}alkyl; (phenyl)C_{1-3}alkyl wherein the phenyl and the C_{1-3}alkyl part of the substituent may each be independently substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxy substituted with one or more independently selected halo substituents, C_{1-3}alkylcarbonyl, mono- or di(C_{1-3}alkyl)amino, morpholinyl and (C_{3-7}cycloalkyl)C_{1-3}alkyloxy; unsubstituted phenyloxy; phenyloxy substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, C_{1-3}alkyloxy, and C_{1-3}alkyloxy substituted with one or more independently selected halo substituents; unsubstituted phenyloxy(C_{1-3}alkyl)oxy; unsubstituted (phenylC_{1-3}alkyl)oxy;

phenyl(C_{1-3}alkyl)oxy wherein the phenyl part of the substituent is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, C_{1-3}alkyloxy, and C_{1-3}alkyloxy substituted with one or more independently selected halo substituents; unsubstituted phenyloxyC_{1-3}alkyl; (phenyloxy)C_{1-3}alkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, C_{1-3}alkyloxy, and C_{1-3}alkyloxy substituted with one or more independently selected halo substituents; unsubstituted phenylamino; phenylamino substituted with 1 or 2 independently selected halo substituents; (phenylC_{1-3}alkyl)amino; (phenylamino)(C_{1-3}alkyl); (C_{3-7}cycloalkyl)C_{1-3}alkyl; [phenyl(C_{3-7}cycloalkyl)]C_{1-3}alkyl; Het^1; Het^2; Het^2oxy; Het^2methyloxy; Het^3; and phenyl with two vicinal substituents which taken together form a bivalent radical of formula

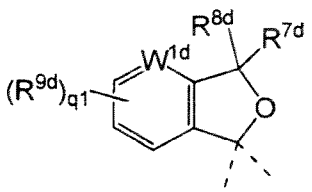
-N=CH-NH- (a),

-CH=CH-NH- (b), or

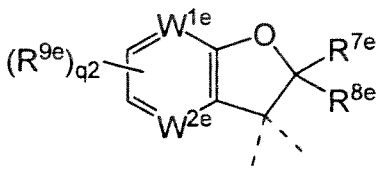
-O-CH_2-CH_2-NH- (c);

R^{4a} is selected from the group consisting of hydrogen; halogen; trifluoromethyl; trifluoromethoxy; hydroxyl; C_{1-3}alkyl; C_{1-3}alkyloxy; hydroxyC_{1-3}alkyl; hydroxyl-C_{1-3}alkyloxy; fluoroC_{1-3}alkyl; fluoroC_{1-3}alkyloxy; cyano; unsubstituted phenyl; and phenyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyloxy, hydroxyC_{1-3}alkyl, trifluoromethyl and trifluoromethoxy;

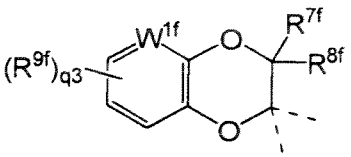
or $CR^{3a}R^{4a}$ forms a radical of formula (d), (e), (f), (g) or (h);



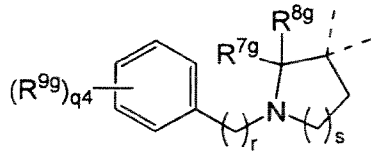
(d)



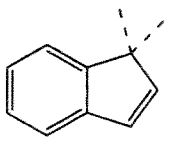
(e)



(f)



(g)



(h)

wherein

each W^{1d}, W^{1e}, W^{2e} and W^{1f} is independently selected from CH and N;

each R^{7d}, R^{7e}, R^{7f}, R^{7g}, R^{8d}, R^{8e}, R^{8f}, R^{8g} is independently selected from hydrogen, methyl and fluoro; or each $CR^{7d}R^{8d}$, $CR^{7e}R^{8e}$, $CR^{7f}R^{8f}$, $CR^{7g}R^{8g}$ form a carbonyl group;

each R^{9d}, R^{9e}, R^{9f}, and R^{9g} is fluoro;

each q1, q2, q3 or q4 is independently selected from 0, 1 and 2;

r is 0 or 1;

s is 0 or 1;

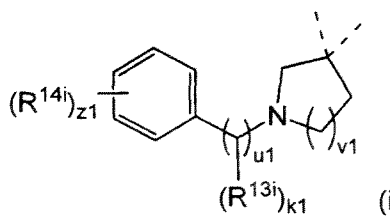
each R^{3b} and R^{3c} is selected from the group consisting of C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxy substituted with one or more independently selected halo substituents, C_{1-3}alkylcarbonyl, mono- and di(C_{1-3}alkyl)amino, and morpholinyl; unsubstituted (phenyl)C_{1-3}alkyl; (phenyl)-C_{1-3}alkyl wherein the phenyl and the C_{1-3}alkyl part of the substituent may each be independently substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxy substituted with one or more independently selected halo substituents, C_{1-3}alkylcarbonyl, mono- or di(C_{1-3}alkyl)amino, morpholinyl, C_{3-7}cycloalkyl, (C_{3-7}cycloalkyl)C_{1-3}alkyl, and (C_{3-7}cycloalkyl)-C_{1-3}alkyloxy; unsubstituted (phenyloxy)C_{1-3}alkyl; (phenyloxy)-C_{1-3}alkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, C_{1-3}alkyloxy, and C_{1-3}alkyloxy substituted with one or more independently selected halo substituents; (phenylamino)(C_{1-3}alkyl); phenyl with two vicinal substituents which taken together form a bivalent radical of formula (a), (b) or (c) as previously defined; Het^1; Het^2; Het^3; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, or hydroxyl; (C_{3-7}cycloalkyl)C_{1-3}alkyl; and [phenyl-(C_{3-7}cycloalkyl)]C_{1-3}alkyl;

R^{3d} and R^{4d} are each independently selected from the group consisting of hydrogen and C_{1-3}alkyl;

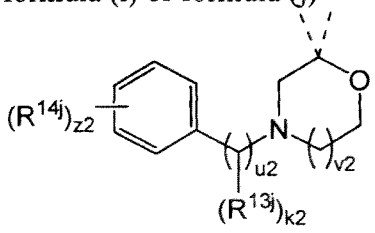
each R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{6a}, R^{6b}, R^{6c} and R^{6d} is independently selected from the group consisting of hydrogen and C_{1-3}alkyl; or each pair $R^{5a}R^{6a}$, $R^{5b}R^{6b}$, $R^{5c}R^{6c}$, $R^{5d}R^{6d}$ are substituents on the same carbon atom and each $CR^{5a}R^{6a}$, $CR^{5b}R^{6b}$, $CR^{5c}R^{6c}$, $CR^{5d}R^{6d}$ together form a (C=O) or a C_{3-7}cycloalkylidene radical;

each R^{10a}, R^{10b} and R^{10c} is selected from H, C_{1-3}alkyl and C_{1-3}alkyloxy;

wherein, in (L-e),
when t is 1 or 2, R^{11} is hydrogen and R^{12} is selected from a substituent selected from the group consisting of phenyl, phenyloxy and phenylamino, each of which may be optionally substituted with 1 or 2 halo substituents; or
when t is 1 or 3, then $CR^{11}R^{12}$ form a radical of formula (i) or formula (j)



(i)



(j)

wherein
each R^{13i} and R^{13j} is independently selected from methyl and trifluoromethyl;
each R^{14i} or R^{14j} is fluoro;
each u1 and u2 is independently 0, 1 or 2;
v1 is selected from the group of 0, 1 and 2;
v2 is selected from the group of 1 and 2;
each z1 and z2 is independently selected from the group of 0, 1 and 2;
each k1 and k2 is independently selected from the group of 0, 1 and 2;

wherein, in (L-f) w is 1 or 2;

wherein in (L-g)
Z is $CR^{16}R^{17}$ and R^{15} is hydrogen when each x is 0 and y is 1; or
Z is $CR^{16}R^{17}$ and R^{15} is selected from the group consisting of hydrogen, methyl and phenyl when each x is 0 and y is 2; or
Z is NR^{16} when each x is 1 and y is 1;

wherein R^{16} and R^{17} are each independently selected from the group consisting of hydrogen; unsubstituted phenyl; and phenyl substituted with 1, 2 or 3 halo substituents;

wherein in (L-h),
Q is O or N-R^{18}, wherein R^{18} is selected from hydrogen and C_{1-3}alkyl;

wherein
each Het^1 is a saturated heterocyclic radical selected from pyrrolidinyl; piperidinyl; piperazinyl; and morpholinyl; each of which may be optionally substituted with 1 or 2 substituents independently selected from the group consisting of C_{1-6}alkyl, halo, C_{1-3}alkyl substituted with one or more independently selected halo substituents, unsubstituted phenyl or phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, trifluoromethyl, and trifluoromethoxy; and

each Het^2 is an aromatic heterocyclic radical selected from pyridinyl and pyrimidinyl; each of which is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of halo; C_{1-3}alkyl; C_{1-3}alkyloxy; and C_{1-3}alkyl substituted with one or more independently selected halo substituents;

each Het^3 is a heterocyclic radical selected from 1,3-thiazolyl optionally substituted with C_{1-3}alkyl; unsubstituted benzofuranyl; unsubstituted 3,4-dihydro-*2H*-chromenyl; and unsubstituted *1H*-indolyl;

each halo is selected from the group consisting of fluoro, chloro, bromo and iodo;
or a pharmaceutically acceptable salt or a solvate thereof.

2. The compound of formula (I) according to claim 1, or a stereochemically isomeric form thereof, wherein
n is selected from 0 and 1;
m is selected from 0 and 1;
R is methyl;

R^1 is selected from the group consisting of C_{1-6}alkyl; (C_{1-3}alkyloxy)C_{1-3}alkyl; [(C_{1-3}alkyloxy)-C_{1-3}alkyloxy]C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more halo substituents; unsubstituted phenyl; (benzyloxy)C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with C_{1-3}alkyl substituted with one or

more halo substituents; (C_{3-7}cycloalkyl)C_{1-3}alkyl; [(C_{3-7}cycloalkyl)C_{1-3}alkyloxy]-C_{1-3}alkyl; (C_{3-7}cycloalkyl)C_{1-3}alkyloxy; Het^1C_{1-3}alkyl; Het^2; and Het^2C_{1-3}alkyl;

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

Ⓛ is an *N*-containing heterocycle selected from the group consisting of (L-a), (L-b), (L-c), (L-d), (L-e), (L-f), (L-g) and (L-h); wherein

R^{3a} is selected from the group consisting of C_{1-3}alkyl substituted with one or more halo substituents; unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more halo substituents, hydroxyl, and C_{1-3}alkyloxy; phenyloxy substituted with 1 or 2 independently selected halo substituents; phenyl(C_{1-3}alkyl)oxy wherein the phenyl part of the substituent is substituted with 1, 2, or 3 independently selected halo substituents; (phenyloxy)C_{1-3}alkyl wherein the phenyl part of the substituent is substituted with 1 or 2 halo substituents; unsubstituted phenylamino; phenylamino substituted with 1 or 2 halo substituents; (phenylC_{1-3}alkyl)amino; Het^1; Het^2; Het^2oxy; Het^2methyloxy; and Het^3;

R^{4a} is selected from the group consisting of hydrogen; halogen; trifluoromethyl; C_{1-3}alkyl; C_{1-3}alkyloxy; and unsubstituted phenyl;

or $CR^{3a}R^{4a}$ forms a radical of formula (d), (e), (f), (g) or (h); wherein

each W^{1d}, W^{1e}, W^{2e} and W^{1f} is independently selected from CH and N;

each R^{7d}, R^{7e}, R^{7f}, R^{7g}, R^{8d}, R^{8e}, R^{8f}, R^{8g} is independently selected from hydrogen, methyl and fluoro; or each $CR^{7d}R^{8d}$, $CR^{7g}R^{8g}$ form a carbonyl group;

each R^{9d}, R^{9e}, R^{9f}, and R^{9g} is fluoro;
each q1, q2, q3 or q4 is independently selected from 0, 1 and 2;
r is 0 or 1;
s is 0 or 1;

each R^{3b} and R^{3c} is selected from the group consisting of C_{1-3}alkyl substituted with one or more halo substituents; unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyloxy and C_{1-3}alkyl substituted with one or more halo substituents; unsubstituted (phenyl)C_{1-3}alkyl; (phenyl)C_{1-3}alkyl wherein the phenyl and the C_{1-3}alkyl parts of the substituent may each be independently substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more halo substituents, and (C_{3-7}cycloalkyl)-C_{1-3}alkyloxy; Het^2; Het^3; C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from the group consisting of C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more halo substituents, and hydroxyl; and [phenyl(C_{3-7}cycloalkyl)]C_{1-3}alkyl;

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

each R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{6a}, R^{6b}, R^{6c} and R^{6d} is independently selected from the group consisting of hydrogen and C_{1-3}alkyl; or $CR^{5b}R^{6b}$ together form a (C=O) or a C_{3-7}cycloalkylidene radical;

each R^{10a}, R^{10b} and R^{10c} is H;

wherein, in (L-e),
when t is 1 or 2, R^{11} is hydrogen and R^{12} is selected from a substituent selected from the group consisting of phenyl, phenyloxy and phenylamino, each of which may be optionally substituted with 1 or 2 halo substituents; or
when t is 1, then $CR^{11}R^{12}$ form a radical of formula (i); wherein
R^{14i} is fluoro;
u1 is 0 or 1;
v1 is 2;
z1 is selected from the group of 1 and 2;
k1 is 0; or
when t is 3, then $CR^{11}R^{12}$ form a radical of formula (i); wherein
R^{14i} is fluoro;
u1 is 0 or 1;
v1 is 0;
z1 is selected from the group of 1 and 2;
k1 is 0;

wherein, in (L-f) w is 1 or 2;

wherein in (L-g)
Z is $CR^{16}R^{17}$ and R^{15} is hydrogen when each x is 0 and y is 1; or
Z is $CR^{16}R^{17}$ and R^{15} is phenyl when each x is 0 and y is 2; or
Z is NR^{16} when each x is 1 and y is 1;
wherein R^{16} and R^{17} are each independently selected from the group consisting of hydrogen; unsubstituted phenyl; and phenyl substituted with 1, 2 or 3 halo substituents;

wherein in (L-h), Q is O;

each Het^1 is a saturated heterocyclic radical selected from pyrrolidinyl; piperidinyl; piperazinyl; and morpholinyl; each of which is unsubstitued or substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, C_{1-3}alkyl substituted with one or more halo substituents, and unsubstituted phenyl; and

each Het^2 is an aromatic heterocyclic radical selected from pyridinyl and pyrimidinyl; each of which is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of halo; C_{1-3}alkyl; and C_{1-3}alkyloxy;

each Het^3 is a heterocyclic radical selected from 1,3-thiazolyl optionally substituted with C_{1-3}alkyl; unsubstituted benzofuranyl; unsubstituted 3,4-dihydro-*2H*-chromenyl; and unsubstituted *1H*-indolyl;

each halo is selected from the group consisting of fluoro, chloro, and bromo;
or a pharmaceutically acceptable salt or a solvate thereof.

3. The compound according to claim 1, or a stereochemically isomeric form thereof, wherein
n is selected from 0 or 1;
m is 0 or 1;
R is methyl;
R^1 is selected from the group consisting of C_{1-6}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; and (C_{3-7}cycloalkyl)C_{1-3}alkyl;

R^2 is selected from halo, C_{1-3}alkyl, and C_{1-3}alkyl substituted with one or more independently selected halo substituents;

Ⓛ is selected from (L-a) and (L-b); wherein

R^{3a} is selected from the group consisting of unsubstituted phenyl; phenyl substituted with 1 or 2 independently selected halo substituents; pyridinyl; and pyrimidinyl;

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

or $CR^{3a}R^{4a}$ forms a radical of formula (d); wherein

W^{1d} is CH;

R^{7d} and R^{8d} are both methyl;

R^{9d} is fluoro;

q1 is 1;

R^{3b} is phenyl substituted with 1 or 2 halo substituents;

R^{5a}, R^{5b}, R^{6a} and R^{6b} are hydrogen; and

R^{10a} and R^{10b} are hydrogen;

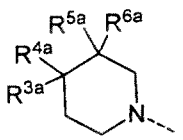
halo is fluoro or chloro;

or a pharmaceutically acceptable salt or a solvate thereof.

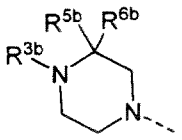
4. The compound according to claim 1 or a stereochemically isomeric form thereof wherein

m is 0;

Ⓛ is selected from the group consisting of (L-a') and (L-b')



(L-a')



(L-b')

R^1 is selected from hydrogen; C_{1-6}alkyl; (C_{1-3}alkyloxy)C_{1-3}alkyl; [(C_{1-3}alkyloxy)-C_{1-3}alkyloxy]C_{1-3}alkyl; mono-, di- or tri-haloC_{1-3}alkyl; unsubstituted benzyl; benzyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxyC_{1-3}alkyl, hydroxyC_{1-3}alkyl, cyano, hydroxyl, amino, C(=O)R', C(=O)OR', C(=O)NR'R'', mono- or di(C_{1-3}alkyl)amino, morpholinyl, (C_{3-7}cycloalkyl)C_{1-3}alkyloxy, trifluoromethyl and trifluoromethoxy, wherein R' and R'' are independently selected from hydrogen and C_{1-6}alkyl; (benzyloxy)C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with

trihaloC_{1-3}alkyl; (C_{3-7}cycloalkyl)C_{1-3}alkyl; 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)methyl; Het^1; Het^1C_{1-3}alkyl; Het^2 and Het^2C_{1-3}alkyl;

R^2 is selected from cyano; halo; mono-, di- or tri-haloC_{1-3}alkyl; mono-, di- and tri-haloC_{1-3}alkyloxy; C_{1-3}alkyl; C_{3-7}cycloalkyl; and (C_{3-7}cycloalkyl)C_{1-3}alkyl;

R^{3a} and R^{3b} are each selected from unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, mono-, di- and tri-haloC_{1-3}alkyl, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, mono-, di- or tri-haloC_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, mono- and di(C_{1-3}alkyl)amino, and morpholinyl; unsubstituted benzyl; benzyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, mono-, di- or tri-haloC_{1-3}alkyl, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, mono-, di- and tri-haloC_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, mono- or di(C_{1-3}alkyl)amino, morpholinyl and (C_{3-7}cycloalkyl)C_{1-3}alkyloxy; phenyl with two vicinal substituents which taken together form a bivalent radical of formula

-N=CH-NH- (a),

-CH=CH-NH- (b), or

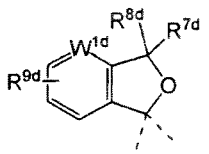
-O-CH_2-CH_2-NH- (c);

morpholinyl; pyridinyl; pyrimidinyl; pyridinyloxy substituted with 1 or 2 C_{1-3}alkyl groups; unsubstituted C_{3-7}cycloalkyl or C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from C_{1-3}alkyl, trihaloC_{1-3}alkyl or hydroxyl;

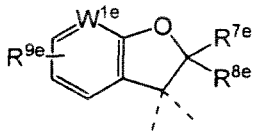
R^{4a} is selected from hydrogen; halogen; trifluoromethyl; trifluoromethoxy; hydroxyl; C_{1-3}alkyl; C_{1-3}alkyloxy; hydroxyC_{1-3}alkyl; hydroxyl-C_{1-3}alkyloxy; fluoroC_{1-3}alkyl; fluoroC_{1-3}alkyloxy; cyano; unsubstituted phenyl; or phenyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyloxy, hydroxyC_{1-3}alkyl, trifluoromethyl and trifluoromethoxy;

or

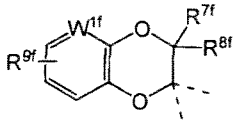
R^{3a}-C-R^{4a} together represent a radical of formula (d') or (e') or (f') or (g')



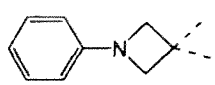
(d')



(e')



(f')



(g')

wherein

W^{1d}, W^{1e} and W^{1f} are each selected from CH or N;
R^{7d}, R^{7e}, R^{7f}, R^{8d}, R^{8e} and R^{8f} are each independently selected from hydrogen, methyl or fluoro;
R^{9d}, R^{9e} and R^{9f} are each selected from hydrogen or fluoro;
R^{5a}, R^{5b}, R^{6a} and R^{6b} are each independently selected from the group of hydrogen and C_{1-3}alkyl or $CR^{5a}R^{6a}$ and $CR^{5b}R^{6b}$ together form a C_{3-7}cycloalkyl radical;
n is 0 or 1;

wherein

each Het^1 is a saturated heterocyclic radical selected from pyrrolidinyl; piperidinyl; piperazinyl; and morpholinyl; each of which may be optionally substituted with 1 or 2 substituents independently selected from the group consisting of C_{1-6}alkyl, mono-, di- or tri-haloC_{1-3}alkyl, unsubstituted phenyl and phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, trifluoromethyl, and trifluoromethoxy; and

each Het^2 is an aromatic heterocyclic radical selected from unsubstituted pyridinyl and pyrimidinyl;

or a pharmaceutically acceptable salt or a solvate thereof.

5. The compound according to claim 1, including any stereochemically isomeric form thereof, wherein said compound is selected from the group consisting of:
8-chloro-7-(4-fluoro-4-phenyl-1-piperidinyl)-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo-[4,3-a]pyridine;
3-(cyclopropylmethyl)-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo-[4,3-a]pyridine;
3-(cyclopropylmethyl)-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo-[4,3-a]pyridine .1.1HCl;
1'-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-5-fluoro-3,3-dimethyl-spiro[isobenzofuran-1(3H),4'-piperidine],
3-(cyclopropylmethyl)-7-[(4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine.1.8 HCl,

3-(cyclopropylmethyl)-7-[(4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(2,4-difluorophenyl)-1-piperazinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
8-chloro-3-(cyclopropylmethyl)-7-[[4-(2,4-difluorophenyl)-1-piperazinyl]methyl]-1,2,4-triazolo[4,3-a]pyridine,
3-(cyclopropylmethyl)-7-[[4-(4-fluorophenyl)-4-methyl-1-piperidinyl]methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine, and
3-(cyclopropylmethyl)-7-[(4-fluoro-4-phenyl-1-piperidinyl)methyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine,
or a pharmaceutically acceptable salt thereof or a solvate thereof.

6. The compound according to claim 1, including any stereochemically isomeric form thereof, wherein said compound is selected from
3-(cyclopropylmethyl)-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo-[4,3-a]pyridine; and
3-(cyclopropylmethyl)-7-(4-phenyl-1-piperidinyl)-8-(trifluoromethyl)-1,2,4-triazolo-[4,3-a]pyridine .1.1HCl;
or a pharmaceutically acceptable salt thereof or a solvate thereof.

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 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 prevention of a central nervous system disorder selected from the group of anxiety disorders, psychotic disorders, personality disorders, substance-related disorders, eating disorders, mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, neurotoxicity and ischemia.

10. The compound according to claim 9, for use in the treatment or prevention of a central nervous system disorder selected from the group of anxiety, schizophrenia, migraine, depression, epilepsy, behavioral and psychological symptoms of dementia, major depressive disorder, treatment resistant depression, bipolar

depression, generalised anxiety disorder, post-traumatic stress disorder, bipolar mania, substance abuse and mixed anxiety and depression.

11. A compound according to any one of claims 1 to 6 in combination with an orthosteric agonist of mGluR2 for use in the treatment or prevention of a disorder as cited in claim 9 or 10.

12. A process for preparing a pharmaceutical composition as defined in claim 7, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as defined in any one of claims 1 to 6.

13. A product comprising

(a) a compound as defined in any one of claims 1 to 6; and

(b) an mGluR2 orthosteric agonist,

as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of a central nervous system disorder selected from the group of anxiety disorders, psychotic disorders, personality disorders, substance-related disorders, eating disorders, mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, neurotoxicity and ischemia.

14. A method of treating or preventing a central nervous system disorder selected from the group of anxiety disorders, psychotic disorders, personality disorders, substance-related disorders, eating disorders, mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, neurotoxicity and ischemia comprising administering to a subject in need thereof a compound according to any one of claims 1 to 6 or a pharmaceutical composition according to claim 7.