7-ARYL-1,2,4-TRIAZOLO[4,3-a]PYRIDINE DERIVATIVES AND THEIR USE AS POSITIVE ALLOSTERIC MODULATORS OF MGLUR2 RECEPTORS

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, to the use of such compounds and pharmaceutical compositions as medicaments, and to the use of such compounds or pharmaceutical compositions 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 receptors 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 analogs 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.

Positive allosteric modulators of mGluRs have emerged recently as novel pharmacological entities offering this attractive alternative. Various compounds have been described as mGluR2 positive allosteric modulators. None of the specifically disclosed compounds herein are structurally related to the compounds disclosed in the art.

It has been 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 have been shown to be active in fear-potentiated startle, and in stress-induced hyperthermia models of anxiety. Furthermore, such compounds have been 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.

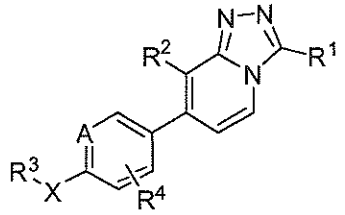
Positive allosteric modulators enable potentiation of the glutamate response, but they have also been shown to potentiate the response to orthosteric mGluR2 agonists

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.

The present triazolopyridine derivatives are centrally active, potent compounds providing alternative mGluR2 positive allosteric modulators with improved solubility and salt forming properties.

Summary of Invention

In a first aspect, the present invention refers to a compound having the formula (I)



(I)

or a stereochemically isomeric form thereof, wherein

A is CH or N;

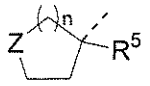
R^1 is selected from the group consisting of hydrogen; C_{1-6}alkyl; (C_{1-3}alkyloxy)C_{1-3}alkyl; [(C_{1-3}alkyloxy)-C_{1-3}alkyloxy]C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; unsubstituted benzyl; benzyl substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-3}alkoxy, C_{1-3}alkyl, 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 the group consisting of cyano; halo; C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more halo substituents; C_{1-3}alkoxy substituted with one or more halo substituents; C_{3-7}cycloalkyl; and (C_{3-7}cycloalkyl)C_{1-3}alkyl;

R^3 is selected from the group consisting of hydrogen; C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or more substituents each independently selected from the group consisting of hydroxyl, halo, C_{1-3}alkyl, tri-haloC_{1-3}alkyl and C_{3-7}cycloalkyl; unsubstituted phenyl; phenyl substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl, trifluoromethyl and trifluoromethoxy; Het^3; unsubstituted pyridyl; pyridyl substituted with

one or more substituents each independently selected from C_{1-3}alkyl, C_{1-3}alkyloxy, C_{3-7}cycloalkyl, and halo; trihaloC_{1-3}alkyl; and hydroxyC_{1-3}alkyl; or

R^3 is a cyclic radical of formula (a)



(a)

wherein

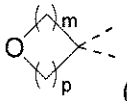
R^5 is selected from the group consisting of hydrogen; C_{1-3}alkyl; C_{1-3}alkyloxy; and hydroxyC_{1-3}alkyl;

n is 1 or 2 ;

Z is selected from CH_2 or $CR^6(OH)$ wherein R^6 is selected from the group consisting of hydrogen, C_{1-3}alkyl and trifluoromethyl;

or R^5 and R^6 together form a radical CH_2-CH_2; or

Z is a cyclic radical of formula (b)



(b)

wherein m and p are independently selected from 0, 1 and 2, provided that $m + p \geq 2$;

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

X is selected from the group consisting of a covalent bond, C_{1-3}alkanediyl, O, NH, S, SO, SO_2, $C(OH)(CH_3)$, CH_2-O, O-CH_2, CH_2-NH, NH-CH_2, CHF, and CF_2;

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

each Het^2 is unsubstituted pyridyl or pyrimidinyl; and

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

or a pharmaceutically acceptable salt or a solvate thereof.

In a second aspect, the present invention refers to a pharmaceutical composition comprising a therapeutically effective amount of a compound as defined above and a pharmaceutically acceptable carrier or excipient.

In a third aspect, the present invention refers to a compound as defined above for use as a medicament.

In a fourth aspect, the present invention refers to a compound as defined above or a pharmaceutical composition as defined above 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.

In a fifth aspect, the present invention refers to the compound as defined above, for use in the treatment or prevention of a central nervous system disorder selected from the group of anxiety, schizophrenia, migraine, depression, epilepsy, behavioural and psychological symptoms of dementia, major depressive disorder, treatment resistant depression, bipolar depression, generalized anxiety disorder, post-traumatic stress disorder, bipolar mania, substance abuse, and mixed anxiety and depression.

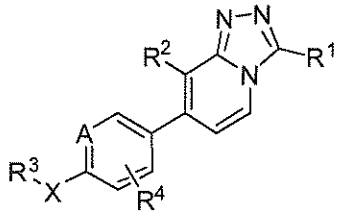
In a sixth aspect, the present invention refers to a compound as defined above in combination with an orthosteric agonist of mGluR2 for use in the treatment or prevention of a disorder as cited above.

In a seventh aspect, the present invention refers to a process for preparing a pharmaceutical composition as defined above, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as defined above.

In an eighth aspect, the present invention refers to a product comprising (a) a compound as defined above; 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 neuromodulatory effect of mGluR2 allosteric modulators, in particular positive mGluR2 allosteric modulators is beneficial.

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

A is CH or N;

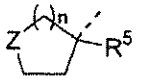
R^1 is selected from the group consisting of hydrogen; C_{1-6}alkyl; (C_{1-3}alkyloxy)C_{1-3}alkyl; [(C_{1-3}alkyloxy)-C_{1-3}alkyloxy]C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; unsubstituted benzyl; benzyl substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-3}alkoxy, C_{1-3}alkyl, 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 the group consisting of cyano; halo; C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more halo substituents; C_{1-3}alkoxy substituted with one or more halo substituents; C_{3-7}cycloalkyl; and (C_{3-7}cycloalkyl)C_{1-3}alkyl;

R^3 is selected from the group consisting of hydrogen; C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or more substituents each independently selected from the group consisting of hydroxyl, halo, C_{1-3}alkyl, tri-

haloC$_{1-3}$alkyl and C$_{3-7}$cycloalkyl; unsubstituted phenyl; phenyl substituted with one or more substituents each independently selected from the group consisting of halo, C$_{1-3}$alkyl, C$_{1-3}$alkoxy, hydroxyC$_{1-3}$alkyl, trifluoromethyl and trifluoromethoxy; Het^3; unsubstituted pyridyl; pyridyl substituted with one or more substituents each independently selected from C$_{1-3}$alkyl, C$_{1-3}$alkyloxy, C$_{3-7}$cycloalkyl, and halo; trihaloC$_{1-3}$alkyl; and hydroxyC$_{1-3}$alkyl; or

R^3 is a cyclic radical of formula (a)


(a)

wherein

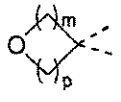
R^5 is selected from the group consisting of hydrogen; C$_{1-3}$alkyl; C$_{1-3}$alkyloxy; and hydroxyC$_{1-3}$alkyl;

n is 1 or 2 ;

Z is selected from CH_2 or $CR^6(OH)$ wherein R^6 is selected from the group consisting of hydrogen, C$_{1-3}$alkyl and trifluoromethyl;

or R^5 and R^6 together form a radical CH_2-CH_2; or

Z is a cyclic radical of formula (b)


(b)

wherein m and p are independently selected from 0, 1 and 2, provided that m + p ≥ 2;

R^4 is selected from the group consisting of hydrogen; halo; and C$_{1-3}$alkyl substituted with one or more halo substituents; and

X is selected from the group consisting of a covalent bond, C$_{1-3}$alkanediyl, O, NH, S, SO, SO_2, $C(OH)(CH_3)$, CH_2-O, O-CH_2, CH_2-NH, NH-CH_2, CHF, and CF_2;

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

each Het^2 is unsubstituted pyridyl or pyrimidinyl; and

each Het^3 is a saturated heterocyclic radical selected from the group consisting of pyrrolidinyl; piperidinyl; piperazinyl; tetrahydropyranyl; and morpholinyl; each of which may be optionally substituted with one or more substituents independently

selected from the group consisting of C_{1-6}alkyl, halo, hydroxyl, C_{1-3}alkyl substituted with one or more halo substituents, unsubstituted phenyl, and phenyl substituted with one or more substituents each independently selected from the group consisting of halo, trifluoromethyl, and trifluoromethoxy;

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 term "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 term "C_{1-3}alkyl" or "C_{1-6}alkyl" as employed herein alone or as part of another group, unless otherwise stated, refers to a saturated straight or branched hydrocarbon radical, having unless otherwise stated, from 1 to 3 or 1 to 6 carbon atoms, which is attached to the rest of the molecule by a single bond, such as methyl, ethyl, propyl, butyl, 1-pentyl, 1-methylethyl, 1,1-dimethylethyl, 2-methylpropyl, 3-methylbutyl and 1-hexyl.

The term "C_{1-3}alkanediyl" as employed herein alone or as part of another group unless otherwise stated refers to a bivalent straight chain saturated hydrocarbon radical having from 1 to 3 carbon atoms such as, for example, methylene; 1,2-ethanediyl; 1,3-propanediyl; and the branched isomers thereof.

The term "C_{3-7}cycloalkyl" as employed herein alone or as part of another group unless otherwise stated, is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "C_{3-7}cycloalkylC_{1-3}alkyl" as employed 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 "mono-, di- or tri-haloC_{1-3}alkyl" employed 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 and 1,1-difluoroethyl.

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.

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 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 available 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 pyridyl, it may be 2-pyridyl, 3-pyridyl or 4-pyridyl. Preferred Het^1 and Het^3 substituents are those linked to the rest of the molecule through the nitrogen atom.

When X is defined as CH_2-O, O-CH_2, CH_2-NH or HN-CH_2, the connectivity is to be understood read from R^3 to the phenyl or pyridinyl ring, thus, when X is defined as CH_2-NH, the methylene is to be understood as bound to R^3 and the NH bound to the phenyl or pyridinyl ring.

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. Stereisomeric 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**].

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

A is CH or N;

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 benzyl; (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^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; C_{3-7}cycloalkyl; and C_{1-3}alkyl substituted with one or more halo substituents;

R^3 is selected from the group consisting of hydrogen; C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with one or more substituents each independently selected from hydroxyl, halo, C_{1-3}alkyl, trihaloC_{1-3}alkyl, and C_{3-7}cycloalkyl; unsubstituted phenyl; phenyl substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl, trifluoromethyl and trifluoromethoxy; Het^3; unsubstituted pyridyl; and pyridyl substituted with one or more substituents each independently selected from the group consisting of C_{1-3}alkyl, C_{1-3}alkyloxy, C_{3-7}cycloalkyl, and halo; trihaloC_{1-3}alkyl; and hydroxyC_{1-3}alkyl;

R^4 is hydrogen or halo;

X is selected from the group consisting of a covalent bond; C_{1-3}alkanediyl; O; CH_2O; OCH_2; CH_2NH; $NHCH_2$ and NH;

each ^{1}Het is selected from the group consisting of pyrrolidinyl; piperidinyl; piperazinyl; and morpholinyl; each of which may be optionally substituted with one or more substituents each independently selected from the group consisting of unsubstituted phenyl and phenyl substituted with one or more substituents each independently selected from the group consisting of halo, trifluoromethyl, and trifluoromethoxy;

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

halo is selected from fluoro and chloro.

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

A is CH or N;

R^1 is selected from the group consisting of (C_{1-3}alkyloxy)C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more halo substituents; unsubstituted C_{3-7}cycloalkyl; (C_{3-7}cycloalkyl)-C_{1-3}alkyl; 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)methyl; and Het^1C_{1-3}alkyl;

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

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

Het^3; unsubstituted pyridyl; and pyridyl substituted with one or more substituents each independently selected from the group consisting of C_{1-3}alkyl, C_{1-3}alkyloxy, C_{3-7}cycloalkyl, and halo;

R^4 is hydrogen or halo;

X is selected from the group consisting of a covalent bond; C_{1-3}alkanediyl; O; CH_2O; CH_2NH; $NHCH_2$ and NH;

each ^1Het is piperidinyl, optionally substituted with 1 or more unsubstituted phenyl groups;

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

halo is selected from fluoro and 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

R^1 is selected from the group consisting of ethoxymethyl; CH_2CF_3; unsubstituted cyclobutyl; cyclopropylmethyl; cyclopropylethyl; 4-phenyl-piperidinylmethyl; and 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)methyl;

R^2 is selected from the group consisting of chloro, methyl, cyclopropyl, and CF_3;

R^3 is selected from the group consisting of hydrogen; propan-2-yl; cyclopropyl; cyclohexyl substituted with hydroxyl; cyclohexyl substituted with hydroxyl and cyclopropyl; unsubstituted phenyl; pyrrolidinyl substituted with 1 or 2 fluoro radicals; unsubstituted tetrahydropyranyl; unsubstituted morpholinyl; unsubstituted piperidinyl; piperidinyl substituted with 1 or 2 substituents selected from the group consisting of methyl, hydroxyl and CF_3; piperazinyl; piperazinyl substituted with 1 methyl radical; pyridyl substituted with 1 substituent selected from fluoro, ethyl, cyclopropyl and methoxy; and pyridyl substituted with 1 or 2 methyl radicals;

R^4 is selected from hydrogen, fluoro or chloro; and

X is selected from a covalent bond; CH_2; -O-; CH_2O; CH_2NH or NH;

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

A is CH;

A is N;

R^1 is selected from the group consisting of CH_2CF_3; ethoxymethyl; cyclobutyl; cyclopropylmethyl; cyclopropylethyl; 4-phenylpiperidinylmethyl; and 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)methyl;

R^2 is selected from the group consisting of chloro, methyl, cyclopropyl and CF_3;

R^3 is selected from the group consisting of hydrogen; propan-2-yl; cyclopropyl; 4-hydroxy-cyclohexyl; 4-hydroxy-4-cyclopropyl-cyclohexyl; phenyl; 3,3-difluoropyrrolidin-1-yl; piperidin-1-yl; 4-methyl-4-hydroxypiperidin-1-yl; piperazinyl; 4-methylpiperazinyl; tetrahydro-*2H*-pyran-4-yl; morpholin-4-yl; 4-trifluoromethyl-piperidin-1-yl; 2-methyl-pyridin-4-yl; 2-ethyl-pyridin-4-yl; 2-cyclopropyl-pyridin-4-yl; 2-methyl-pyridin-5-yl; 2-methoxy-pyridin-5-yl; 3-fluoro-pyridin-4-yl; 2,6-dimethyl-pyridin-4-yl; and 2,6-dimethyl-pyridin-3-yl;

and R^4 and X 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, whereinA is CH or N;

R^1 is selected from the group consisting of CH_2CF_3; ethoxymethyl; cyclopropylmethyl; and cyclopropylethyl;

R^2 is selected from the group consisting of chloro, methyl, cyclopropyl and CF_3;

R^3 is selected from the group consisting of propan-2-yl; cyclopropyl; 4-hydroxy-4-cyclopropyl-cyclohexyl; 3,3-difluoropyrrolidin-1-yl; piperidin-1-yl; 4-methyl-4-hydroxypiperidin-1-yl; piperazinyl; 4-methylpiperazinyl; tetrahydro-*2H*-pyran-4-yl; morpholin-4-yl; 2-methyl-pyridin-4-yl; 2-ethyl-pyridin-4-yl; 2-cyclopropyl-pyridin-4-yl; 2-methyl-pyridin-5-yl; 2-methoxy-pyridin-5-yl; 3-fluoro-pyridin-4-yl; 2,6-dimethyl-pyridin-4-yl; and 2,6-dimethyl-pyridin-3-yl;

and R^4 and X 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

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

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

R^3 is selected from the group consisting of unsubstituted $C_{3-7}cycloalkyl$; piperazin-1-yl; tetrahydro-2*H*-pyran-4-yl; and pyridyl substituted with one or more substituents

each independently selected from the group consisting of C_{1-3}alkyl, C_{1-3}alkyloxy, C_{3-7}cycloalkyl, and halo;

A is CH;

X is selected from a covalent bond; -O-; CH_2NH; and -NH-;

R^4 is selected from hydrogen; fluoro and 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

R^1 is selected from the group consisting of CH_2CF_3; ethoxymethyl; and cyclopropylmethyl;

R^2 is selected from the group consisting of chloro, methyl, and CF_3;

R^3 is selected from the group consisting of 2-methyl-pyridin-4-yl; 2,6-dimethyl-pyridin-3-yl; cyclopropyl; 2-ethyl-pyridin-4-yl; 2-methoxy-pyridin-5-yl; 2-cyclopropyl-pyridin-4-yl; 3-fluoropyridin-4-yl; tetrahydro-2*H*-pyran-4-yl; and piperazin-1-yl;

A is CH;

X is selected from a covalent bond; -O-; CH_2NH; and -NH-; and

R^4 is selected from hydrogen; fluoro and 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

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

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

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

A is CH;

X is selected from a covalent bond; -O-; and -NH-;

R^4 is selected from hydrogen; fluoro and 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

R^1 is selected from the group consisting of CH_2CF_3; ethoxymethyl; and cyclopropylmethyl;
R^2 is selected from the group consisting of chloro, methyl, and CF_3;
R^3 is selected from the group consisting of 2-methyl-pyridin-4-yl; 2,6-dimethyl-pyridin-3-yl; cyclopropyl; 2-cyclopropyl-pyridin-4-yl; 3-fluoropyridin-4-yl; and piperazin-1-yl;
A is CH;
X is selected from a covalent bond; -O-; and -NH-; and
R^4 is selected from hydrogen; fluoro and chloro;
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

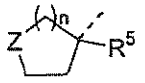
A is CH;

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}alkoxy, C_{1-3}alkyl, 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- or tri-haloC_{1-3}alkoxy; C_{1-3}alkyl; C_{3-7}cycloalkyl and (C_{3-7}cycloalkyl)C_{1-3}alkyl;

R^3 is selected from hydrogen; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or 2 substituents selected from hydroxyl, halo, C_{1-3}alkyl and tri-haloC_{1-3}alkyl; unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl, trifluoromethyl and trifluoromethoxy; Het^3; unsubstituted pyridyl; pyridyl substituted with 1 or 2 substituents independently selected from C_{1-3}alkyl, trihaloC_{1-3}alkyl and hydroxyC_{1-3}alkyl; or

R^3 is a cyclic radical of formula (a)



(a)

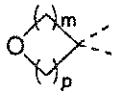
wherein

R^5 is selected from hydrogen; C_{1-3}alkyl; C_{1-3}alkyloxy and hydroxyC_{1-3}alkyl;

n is 1 or 2 ;

Z is selected from CH_2 and $CR^6(OH)$ wherein R^6 is hydrogen, C_{1-3}alkyl or trifluoromethyl;
or R^5 and R^6 together form a radical CH_2-CH_2; or

Z is a cyclic radical of formula (b)



(b)

wherein m and p are independently selected from 0, 1 and 2, provided that $m + p \geq 2$;

R^4 is selected from hydrogen; halo; and mono-, di- and tri-haloC_{1-3}alkyl; and

X is selected from the group consisting of a covalent bond, C_{1-3}alkanediyl, O, NH, S, SO, SO_2, $C(OH)(CH_3)$, CH_2-O, O-CH_2, CHF and CF_2;

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;

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

each Het^3 is a saturated heterocyclic radical selected from pyrrolidinyl; piperidinyl; piperazinyl; tetrahydropyranyl; 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 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

R^1 is selected from C_{1-6}alkyl; mono-, di- and tri-haloC_{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 selected from cyano, halo and trihaloC_{1-3}alkyl;

R^3 is selected from hydrogen; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or 2 substituents selected from hydroxyl, halo or C_{1-3}alkyl; unsubstituted phenyl; phenyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl, trifluoromethyl and trifluoromethoxy; Het^3; unsubstituted pyridyl; and pyridyl substituted with 1 or 2 substituents independently selected from C_{1-3}alkyl, trihaloC_{1-3}alkyl and hydroxyC_{1-3}alkyl;

R^4 is hydrogen or halo;

X is selected from the group consisting of a covalent bond, C_{1-3}alkanediyl, O and NH;

and A, Het^1 and Het^3 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

R^1 is selected from methyl; ethyl; propyl; *n*-butyl; 2-methylpropyl; *tert*-butyl; trifluoromethyl; CF_2CH_3; CH_2CF_3; unsubstituted cyclopropyl; cyclopropyl substituted with trifluoromethyl; unsubstituted cyclobutyl; cyclopropylmethyl; cyclobutylmethyl; 1-pyrrolidinylmethyl; 1-piperidinylmethyl; 4-phenyl-piperidinylmethyl; 4-trifluoromethyl-piperidinylmethyl; 4-morpholinylmethyl; and 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)methyl;

R^2 is selected from fluoro, chloro, and CF_3;

R^3 is selected from the group consisting of hydrogen; cyclopropyl; unsubstituted cyclohexyl; cyclohexyl substituted with hydroxyl; unsubstituted phenyl; unsubstituted tetrahydropyranyl; unsubstituted morpholinyl; unsubstituted piperidinyl; piperidinyl substituted with CF_3 and pyridyl substituted with 1 or 2 methyl radicals;

R^4 is selected from hydrogen, fluoro and chloro;

X is selected from a covalent bond, CH_2, -O- and NH;

and A is 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

R^1 is selected from CH_2CF_3; cyclobutyl; cyclopropylmethyl; 4-phenylpiperidinylmethyl; and 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)-methyl;

R^2 is chloro or CF_3; and

R^3 is selected from the group consisting of hydrogen; cyclopropyl; 4-hydroxy-cyclohexyl; phenyl; tetrahydropyran-4-yl; morpholin-4-yl; 4-trifluoromethyl-piperidin-1-yl; 2-methyl-pyridin-4-yl and 2,6-dimethyl-pyridin-3-yl;

and A, X and R^4 are as previously defined;

and the pharmaceutically acceptable salts and the solvates thereof.

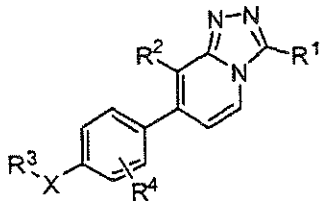
In a further embodiment, the invention relates to compounds according to any of the other embodiments, wherein R^3 is cyclopropyl.

In a further embodiment, the invention relates to compounds according to any of the other embodiments, wherein R^3 pyridyl substituted with 1 substituent selected from fluoro, ethyl, cyclopropyl and methoxy.

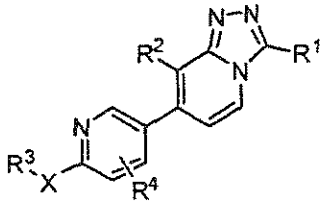
In a further embodiment, the invention relates to compounds according to any of the other embodiments, wherein R^3 pyridyl substituted with 1 or 2 methyl radicals.

In a further embodiment, the invention relates to compounds according to any of the other embodiments, wherein R^3 is piperazinyl.

In particular, the invention relates to a compound according to the general formula (Ia) or a compound according to the general formula (Ib), wherein A is CH or N, respectively, and the rest of the variables are as previously defined

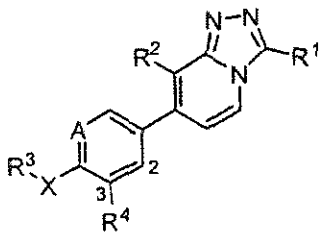


(Ia)

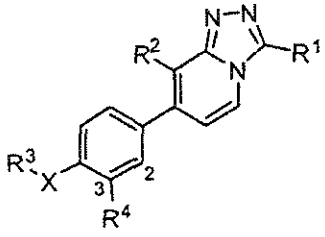


(Ib).

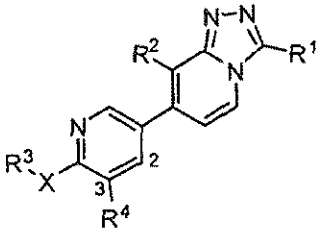
In particular, the invention relates to a compound according to the general formula (I), or a compound of general formula (Ia) or (Ib) as previously defined, wherein R^4 is bound at the 3-position of the phenyl or the pyridinyl ring, hereby designated as (I'), (Ia') or (Ib'), respectively



(I')



(Ia')



(Ib').

Particular preferred compounds may be selected from the group of:

- 8-chloro-7-(4-phenoxyphenyl)-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo-[4,3-a]pyridine;
- 8-chloro-3-(cyclopropylmethyl)-7-(4-phenoxyphenyl)-1,2,4-triazolo-[4,3-a]pyridine;
- 8-chloro-3-cyclobutyl-7-(4-phenoxyphenyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-3-(cyclopropylmethyl)-7-[4-(4-morpholinyl)phenyl]-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-3-(cyclopropylmethyl)-7-[4-[[4-(trifluoromethyl)-1-piperidinyl]-methyl]phenyl]-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-3-(cyclopropylmethyl)-7-[4-(4-morpholinylmethyl)phenyl]-1,2,4-triazolo[4,3-a]pyridine;
- *trans*-4-[[2-chloro-4-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo-[4,3-a]pyridin-7-yl]phenyl]amino]-cyclohexanol;
- *cis*-4-[[2-chloro-4-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]-pyridin-7-yl]phenyl]amino]-cyclohexanol;
- *N*-[2-chloro-4-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]phenyl]tetrahydro-2*H*-pyran-4-amine;

- 8-chloro-7-[3-fluoro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[4-[(2,6-dimethyl-3-pyridinyl)oxy]-3-fluorophenyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[3-chloro-4-[(tetrahydro-2*H*-pyran-4-yl)oxy]phenyl]-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[3-chloro-4-[(tetrahydro-2*H*-pyran-4-yl)oxy]phenyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 3-(cyclopropylmethyl)-7-[3-fluoro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 3-(cyclopropylmethyl)-7-[4-[(2,6-dimethyl-3-pyridinyl)oxy]-3-fluorophenyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- *N*-[2-chloro-4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo-[4,3-a]pyridin-7-yl]phenyl]tetrahydro-2*H*-pyran-4-amine;
- 7-[3-chloro-4-(4-morpholinyl)phenyl]-3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- *trans*-4-[[2-chloro-4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]phenyl]amino]-cyclohexanol;
- *cis*-4-[2-chloro-4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]phenoxy]-cyclohexanol;
- *trans*-4-[2-chloro-4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]phenoxy]-cyclohexanol;
- 7-[3-chloro-4-[(tetrahydro-2*H*-pyran-4-yl)oxy]phenyl]-3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 4-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-*N*-cyclopropyl-2-fluoro-benzenamine;
- 2-chloro-4-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-*N*-cyclopropyl-benzenamine;
- *cis*-4-[2-chloro-4-[8-chloro-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]-pyridin-7-yl]phenoxy]-cyclohexanol;
- *trans*-4-[2-chloro-4-[8-chloro-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]-pyridin-7-yl]phenoxy]-cyclohexanol;
- 8-chloro-7-phenyl-3-[(4-phenyl-1-piperidinyl)methyl]-1,2,4-triazolo[4,3-a]-pyridine;
- 4-[(8-chloro-7-phenyl-1,2,4-triazolo[4,3-a]pyridin-3-yl)methyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine;
- *trans*-4-[[2-chloro-4-[8-chloro-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]-

pyridin-7-yl]phenyl]amino]-cyclohexanol;

- *N*-[2-chloro-4-[8-chloro-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]phenyl]tetrahydro-2*H*-pyran-4-amine;
- 2-chloro-*N*-cyclopropyl-4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-benzenamine;
- 8-chloro-7-[4-(2,6-dimethyl-pyridin-3-yloxy)-3-fluoro-phenyl]-3-(cyclopropyl-methyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[4-(2-methyl-pyridin-4-yloxy)-3-fluoro-phenyl]-3-(cyclopropyl-methyl)-1,2,4-triazolo[4,3-a]pyridine;
- *N*-cyclopropyl-4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-2-fluoro-benzenamine;
- 8-chloro-7-[4-[(2,6-dimethyl-3-pyridinyl)oxy]-3-fluorophenyl]-3-(ethoxymethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[3-chloro-4-[(2,6-dimethyl-3-pyridinyl)oxy]phenyl]-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[3-chloro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-3-(ethoxymethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 3-(ethoxymethyl)-7-[3-fluoro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 7-[4-[(2,6-dimethyl-4-pyridinyl)oxy]-3-fluorophenyl]-3-(ethoxymethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 3-(cyclopropylmethyl)-7-[4-[(2,6-dimethyl-4-pyridinyl)oxy]-3-fluorophenyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[4-[(2,6-dimethyl-4-pyridinyl)oxy]-3-fluorophenyl]-3-(ethoxymethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[3-chloro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-3-(2-cyclopropylethyl)-7-[3-fluoro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-1,2,4-triazolo[4,3-a]pyridine;
- 7-[4-[(2,6-dimethyl-3-pyridinyl)oxy]-3-fluorophenyl]-3-(ethoxymethyl)-8-methyl-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-3-(cyclopropylmethyl)-7-[4-[(2-cyclopropyl-4-pyridinyl)oxy]-3-fluorophenyl]-1,2,4-triazolo[4,3-a]pyridine;
- 7-[4-[(2,6-dimethyl-3-pyridinyl)oxy]-3-fluorophenyl]-3-(ethoxymethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 7-[3-chloro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-3-(ethoxymethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;

- 3-(cyclopropylmethyl)-7-[4-[(2-cyclopropyl-4-pyridinyl)oxy]-3-fluorophenyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- *cis*-4-[[2-chloro-4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]phenyl]amino]-1-cyclopropyl-cyclohexanol;
- 8-chloro-3-(cyclopropylmethyl)-7-[4-[(2-ethyl-4-pyridinyl)oxy]-3-fluorophenyl]-1,2,4-triazolo[4,3-a]pyridine;
- 4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-2-fluoro-*N*-(1-methylethyl)-benzenamine;
- 4-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-2-fluoro-*N*-(1-methylethyl)-benzenamine;
- 2-chloro-4-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-*N*-(1-methylethyl)-benzenamine;
- 2-chloro-4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-*N*-(1-methylethyl)-benzenamine;
- 7-[3-chloro-4-[(2,6-dimethyl-3-pyridinyl)oxy]phenyl]-3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 7-[3-chloro-4-[(2-cyclopropyl-4-pyridinyl)oxy]phenyl]-3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[3-chloro-4-[(2,6-dimethyl-3-pyridinyl)oxy]phenyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 7-[3-chloro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 3-(cyclopropylmethyl)-7-[4-[(2-ethyl-4-pyridinyl)oxy]-3-fluorophenyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- *N*-[4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]phenyl]-6-methoxy-3-pyridinemethanamine;
- *N*-[4-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]phenyl]-6-methoxy-3-pyridinemethanamine;
- 3-(cyclopropylmethyl)-7-[4-[(2,6-dimethyl-3-pyridinyl)oxy]-3-fluorophenyl]-8-methyl-1,2,4-triazolo[4,3-a]pyridine;
- 7-[3-chloro-4-[(2,6-dimethyl-3-pyridinyl)oxy]phenyl]-3-(cyclopropylmethyl)-8-methyl-1,2,4-triazolo[4,3-a]pyridine;
- 8-cyclopropyl-3-(cyclopropylmethyl)-7-[4-[(2,6-dimethyl-3-pyridinyl)oxy]-3-fluorophenyl]-1,2,4-triazolo[4,3-a]pyridine;
- 3-(cyclopropylmethyl)-7-[4-[(3-fluoro-4-pyridinyl)oxy]phenyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 3-(cyclopropylmethyl)-7-[4-[(3,3-difluoro-1-pyrrolidinyl)methyl]phenyl]-8-

(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;

- 3-(cyclopropylmethyl)-7-[4-[(3,3-difluoro-1-pyrrolidinyl)methyl]phenyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine .HCl;
- 7-[3-chloro-4-[(2,6-dimethyl-3-pyridinyl)oxy]phenyl]-3-(ethoxymethyl)-8-methyl-1,2,4-triazolo[4,3-a]pyridine;
- 5-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-*N*-(1-methylethyl)-2-pyridinamine;
- 8-chloro-3-(cyclopropylmethyl)-7-[6-(4-morpholinyl)-3-pyridinyl]-1,2,4-triazolo[4,3-a]pyridine;
- 3-(cyclopropylmethyl)-7-[6-(4-morpholinyl)-3-pyridinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-3-(cyclopropylmethyl)-7-[6-(1-piperidinyl)-3-pyridinyl]-1,2,4-triazolo[4,3-a]pyridine;
- 3-(cyclopropylmethyl)-7-[6-(1-piperidinyl)-3-pyridinyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;

7-[3-chloro-4-(morpholin-4-ylmethyl)phenyl]-3-(cyclopropylmethyl)-8-(trifluoromethyl)[1,2,4]triazolo[4,3-*a*]pyridine;

- 1-{2-chloro-4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)[1,2,4]triazolo[4,3-*a*]pyridin-7-yl]benzyl}-4-methylpiperidin-4-ol;
- 7-(3-chloro-4-piperazin-1-ylphenyl)-3-(cyclopropylmethyl)-8-(trifluoromethyl)[1,2,4]triazolo[4,3-*a*]pyridine;
- *N*-{2-chloro-4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)[1,2,4]triazolo[4,3-*a*]pyridin-7-yl]benzyl}tetrahydro-2*H*-pyran-4-amine;
- 7-{3-chloro-4-[(3,3-difluoropyrrolidin-1-yl)methyl]phenyl}-3-(cyclopropylmethyl)-8-(trifluoromethyl)[1,2,4]triazolo[4,3-*a*]pyridine;
- 7-[3-chloro-4-(piperazin-1-ylmethyl)phenyl]-3-(cyclopropylmethyl)-8-(trifluoromethyl)[1,2,4]triazolo[4,3-*a*]pyridine;
- 2-fluoro-4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)[1,2,4]triazolo[4,3-*a*]pyridin-7-yl]-*N*-[(6-methoxypyridin-3-yl)methyl]aniline; and
- 2-fluoro-4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)[1,2,4]triazolo[4,3-*a*]pyridin-7-yl]-*N*-[(6-methylpyridin-3-yl)methyl]aniline;

3-Cyclopropylmethyl-7-[3-fluoro-4-(6-methoxy-pyridin-3-ylmethoxy)-phenyl]-8-trifluoromethyl-[1,2,4]triazolo[4,3-a]pyridine

3-Cyclopropylmethyl-7-[3-fluoro-4-(6-methoxy-pyridin-3-ylmethoxy)-phenyl]-8-trifluoromethyl-[1,2,4]triazolo[4,3-a]pyridine; and

7-(3-chloro-4-(4′-methyl)piperazin-1-ylphenyl)-3-(cyclopropylmethyl)-8-(trifluoromethyl)[1,2,4]triazolo[4,3-*a*]pyridine;

and the stereoisomeric forms, acid addition salts and solvates thereof.

In an embodiment the compound of Formula (I) is selected from the group of:
- 8-chloro-7-[3-fluoro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 3-(cyclopropylmethyl)-7-[3-fluoro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[4-[(2,6-dimethyl-3-pyridinyl)oxy]-3-fluorophenyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 3-(cyclopropylmethyl)-7-[4-[(2,6-dimethyl-3-pyridinyl)oxy]-3-fluorophenyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[3-chloro-4-[(tetrahydro-2*H*-pyran-4-yl)oxy]phenyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[4-(2,6-dimethyl-pyridin-3-yloxy)-3-fluoro-phenyl]-3-(cyclopropyl-methyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[4-(2-methyl-pyridin-4-yloxy)-3-fluoro-phenyl]-3-(cyclopropyl-methyl)-1,2,4-triazolo[4,3-a]pyridine;
- *N*-[2-chloro-4-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]phenyl]tetrahydro-2*H*-pyran-4-amine;
- 2-chloro-*N*-cyclopropyl-4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-benzenamine;
- 8-chloro-7-[3-chloro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-3-(ethoxymethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 7-[4-[(2,6-dimethyl-3-pyridinyl)oxy]-3-fluorophenyl]-3-(ethoxymethyl)-8-methyl-1,2,4-triazolo[4,3-a]pyridine;
- 3-(cyclopropylmethyl)-7-[4-[(2-cyclopropyl-4-pyridinyl)oxy]-3-fluorophenyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-3-(cyclopropylmethyl)-7-[4-[(2-ethyl-4-pyridinyl)oxy]-3-fluorophenyl]-1,2,4-triazolo[4,3-a]pyridine;
- 7-[3-chloro-4-[(2-cyclopropyl-4-pyridinyl)oxy]phenyl]-3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- *N*-[4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]phenyl]-6-methoxy-3-pyridinemethanamine;
- 3-(cyclopropylmethyl)-7-[4-[(3-fluoro-4-pyridinyl)oxy]phenyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine; and
- 7-(3-chloro-4-piperazin-1-ylphenyl)-3-(cyclopropylmethyl)-8-(trifluoromethyl)[1,2,4]triazolo[4,3-*a*]pyridine;

and the stereoisomeric forms, acid addition salts and solvates thereof.

In an embodiment the compound of Formula (I) is selected from the group of:
- 8-chloro-7-[3-fluoro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 3-(cyclopropylmethyl)-7-[3-fluoro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[4-[(2,6-dimethyl-3-pyridinyl)oxy]-3-fluorophenyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 2-chloro-*N*-cyclopropyl-4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-benzenamine;
- 8-chloro-7-[4-(2-methyl-pyridin-4-yloxy)-3-fluoro-phenyl]-3-(cyclopropyl-methyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[3-chloro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-3-(ethoxymethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 7-[4-[(2,6-dimethyl-3-pyridinyl)oxy]-3-fluorophenyl]-3-(ethoxymethyl)-8-methyl-1,2,4-triazolo[4,3-a]pyridine;
- 7-[3-chloro-4-[(2-cyclopropyl-4-pyridinyl)oxy]phenyl]-3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 3-(cyclopropylmethyl)-7-[4-[(3-fluoro-4-pyridinyl)oxy]phenyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine; and
- 7-(3-chloro-4-piperazin-1-ylphenyl)-3-(cyclopropylmethyl)-8-(trifluoromethyl)[1,2,4]triazolo[4,3-*a*]pyridine;

and the stereoisomeric forms, acid addition 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.

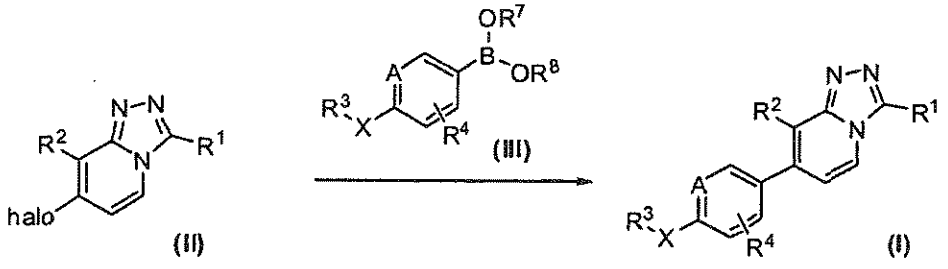
The compounds of Formula (I) may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable 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 by reacting an intermediate compound of Formula (II) with a compound of Formula (III) according to reaction scheme (1), 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 min. In reaction scheme (1), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo. R^7 and R^8 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 1

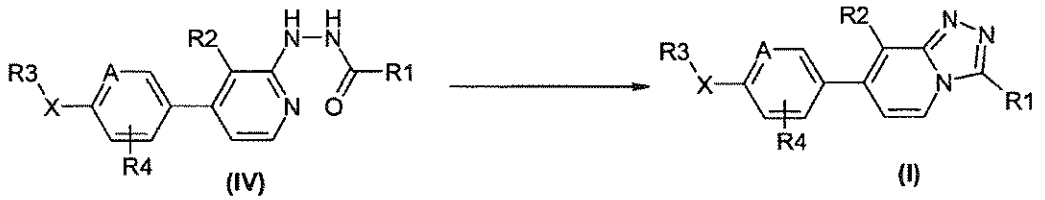


Experimental procedure 2

Final compounds according to Formula (I) can be prepared following art known procedures by cyclization of intermediate compound of Formula (IV) 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 1,2-dichloroethane or acetonitrile stirred under microwave irradiation, for a suitable period of time that allows the completion of the reaction, 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 (IV) 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 (2), all variables are defined as in Formula (I).

Reaction Scheme 2



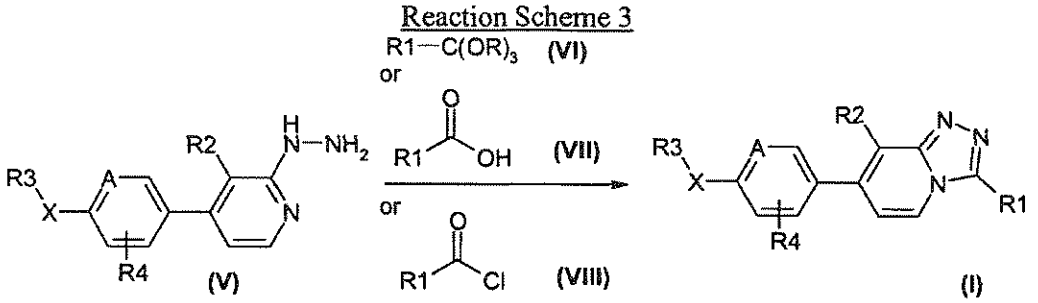
Experimental procedure 3

Final compounds according to Formula (I) can be prepared by art known procedures 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 (V) under suitable conditions in the presence of a suitable ortho-ester of Formula (VI), wherein R is a suitable substituent, like for example a methyl group, according to reaction scheme (3). 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 (3), 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 Letters*, **2007**, *48*, 2237 by reaction of intermediate compound of Formula (V) with carboxylic acids of Formula (VII) or acid equivalents such as acid halides of Formula (VIII) 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 1,2-dichloroethane, stirred at a temperature between 100-200 °C for 1 to 48 h or under microwave irradiation for 20 min. In reaction scheme (3), all variables are defined as in Formula (I).

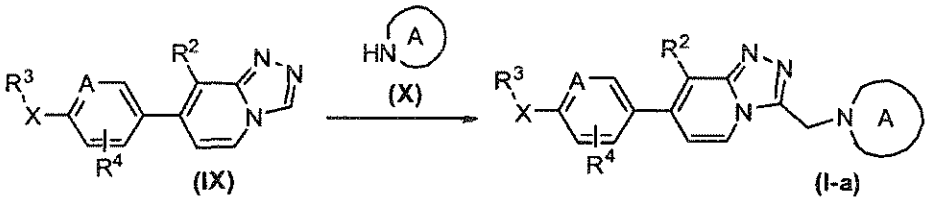
Reaction Scheme 3



Experimental procedure 4

Final compounds according to Formula (I) wherein R^1 is a Het^1-C_{1-3}alkyl 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 art known procedures by reaction of intermediate compound of Formula (IX) under standard Mannich conditions with intermediate compound of Formula (X). 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

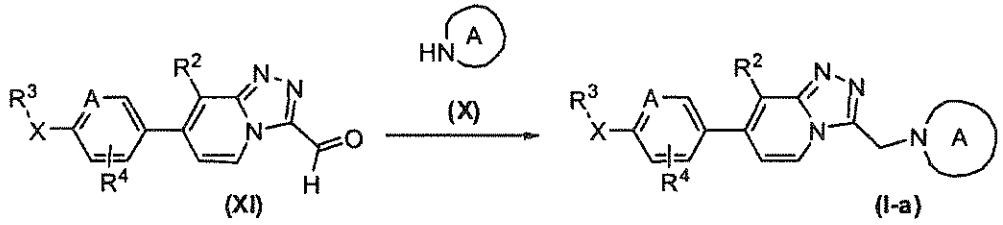


Experimental procedure 5

Alternatively, final compounds according to Formula (I) wherein R^1 is a Het^1-C_{1-3}alkyl 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 (X) with an intermediate of Formula (XI) 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 room temperature, for a suitable period of time that allows the completion of the reaction.

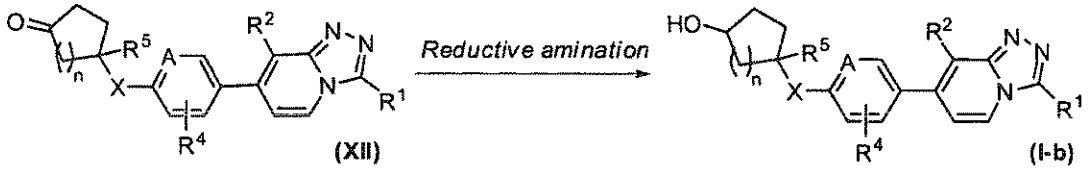
Reaction Scheme 5



Experimental procedure 6

Final compounds according to Formula (I) wherein R^3 is a cyclic radical of formula (a) and Z is CHOH, hereby named (I-b), can be prepared by reacting an intermediate of Formula (XII) under reductive conditions that are known to those skilled in the art. The reaction is illustrated in reaction scheme (6) wherein all substituents are defined as in Formula (I). The reaction can be carried out in the presence of, 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. R^5 and n are as defined in radical of formula (a) in the R^3 definition.

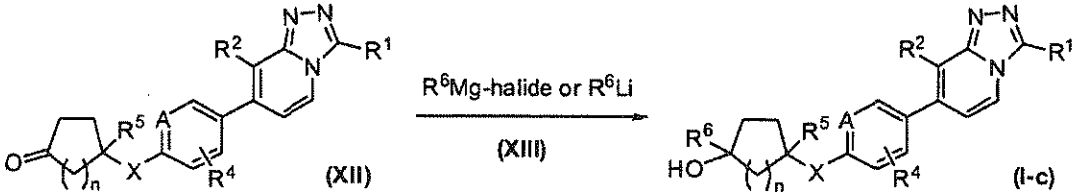
Reaction Scheme 6



Experimental procedure 7

Final compounds according to Formula (I), wherein R^3 is a cyclic radical of formula (a) and Z is CR^6OH, hereby named (I-c), can be prepared by art known procedures by reacting an intermediate of Formula (XII) with an intermediate compound of Formula (XIII) according to reaction scheme (7). The reaction can be carried out in an inert solvent such as, for example, THF, diethyl ether or dioxane. Typically, the mixture can be stirred for 1 to 48 h at a temperature between 0-100 °C. In reaction scheme (7), all variables are defined as in Formula (I). R^5 and n are as defined in radical of formula (a) in the R^3 definition.

Reaction Scheme 7



The transformations of different functional groups present in the final compounds, into other functional groups according to Formula (I), can be performed by synthesis methods well known to the person skilled in the art. For example, compounds of Formula (I) that contain carbamate function in their structure, could be hydrolysed following art known procedures for a person skilled in the art to give Final compounds of Formula (I) containing an amino.

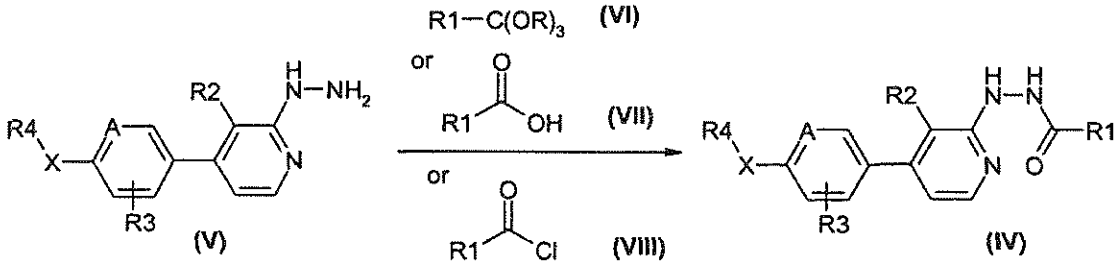
B. Preparation of the intermediate compounds

Experimental procedure 8

Intermediate compounds according to Formula (IV) 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 reaction of intermediate compounds of Formula (V) under suitable conditions in the presence of a suitable ortho-ester of Formula (VI) wherein R is a suitable group, for example methyl, according to reaction scheme (8). 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 (8), all variables are defined as in Formula (I).

Alternatively, final compounds according to Formula (IV) 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 (V) with carboxylic acids of Formula (VII) or acid equivalents such as acid halides of Formula (VIII) to afford final compounds of Formula (IV). The reaction can be carried out using a halogenating agent such as for example trichloroacetonitrile-triphenylphosphine mixture in the presence of suitable solvent such as for example 1,2-dichloroethane and stirred at a temperature between 100-200 °C for 1 to 48 hours or under microwave irradiation for 20 min. In reaction scheme (8), all variables are defined as in Formula (I).

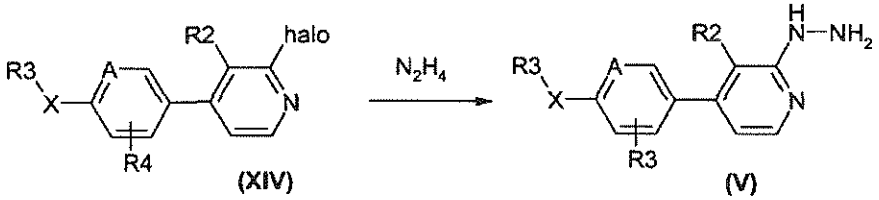
Reaction Scheme 8



Experimental procedure 9

Intermediate compounds according to Formula (V) can be prepared by reacting an intermediate compound of Formula (XIV) with hydrazine according to reaction scheme (9), 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 (9), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo.

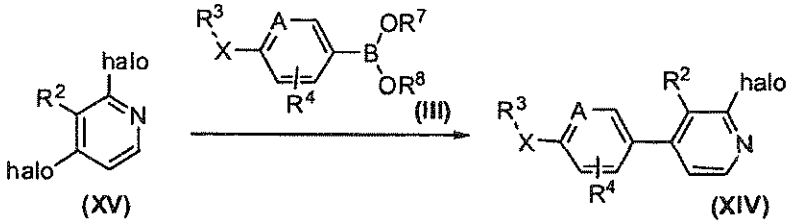
Reaction Scheme 9



Experimental procedure 10

Intermediate compounds of Formula (XIV) can be prepared by reacting an intermediate compound of Formula (XV) with a compound of Formula (III) according to reaction scheme (10). All variables are defined as in Formula (I); halo is chloro, bromo or iodo and R^7 and R^8 are as defined in Experimental procedure 1.

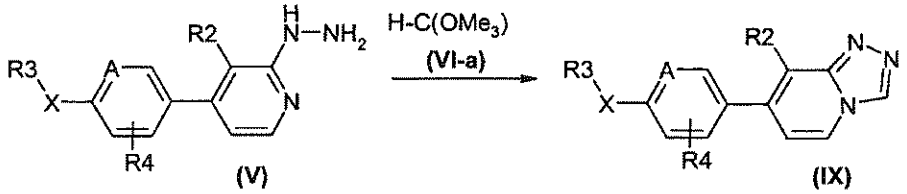
Reaction Scheme 10



Experimental procedure 11

Intermediate compounds according to Formula (IX) 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 compound of Formula (V) under suitable conditions in the presence of a suitable ortho-ester of Formula (VI) wherein R^1 is hydrogen and R is a suitable group, for example methyl, such as for example methylorthoformate (VI-a), according to reaction scheme (11). 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 (11), all variables are defined as in Formula (I).

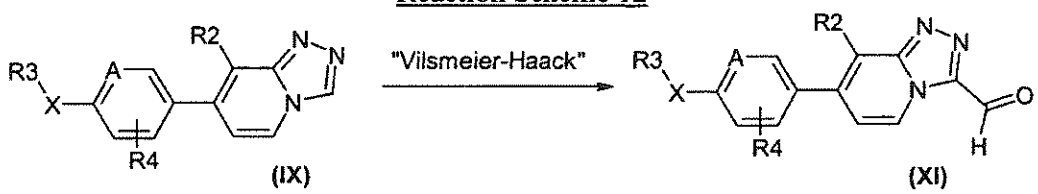
Reaction Scheme 11



Experimental procedure 12

Intermediate compounds of Formula (XI) can be prepared by reacting an intermediate compound of Formula (IX) under standard Vilsmeier-Haack reaction conditions such as, for example, DMF and phosphorus (V) oxychloride ($POCl_3$) from room temperature to 140 °C under classical thermal heating or under microwave irradiation, for a suitable period of time that allows the completion of the reaction, as for example 1 h. In reaction scheme (12), all variables are defined as in Formula (I).

Reaction Scheme 12

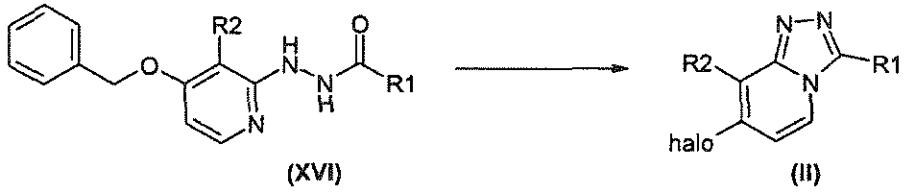


Experimental procedure 13

Intermediate compounds according to Formula (II) can be prepared following art known procedures by cyclization of intermediate compound of Formula (XVI) in the presence of a halogenating agent such as for example phosphorus (V) oxychloride ($POCl_3$) in a suitable solvent such as for example 1,2-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 (13), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo.

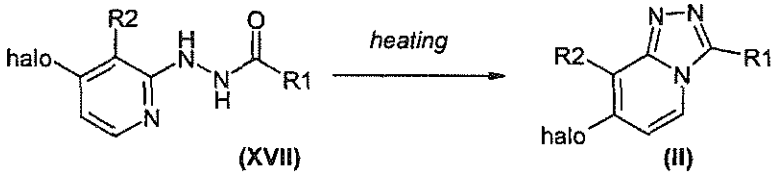
Reaction Scheme 13



Experimental procedure 14

Alternatively, intermediate compounds of Formula (II) can be prepared following art known procedures by cyclization of intermediate compound of Formula (XVII) 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 (14), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo.

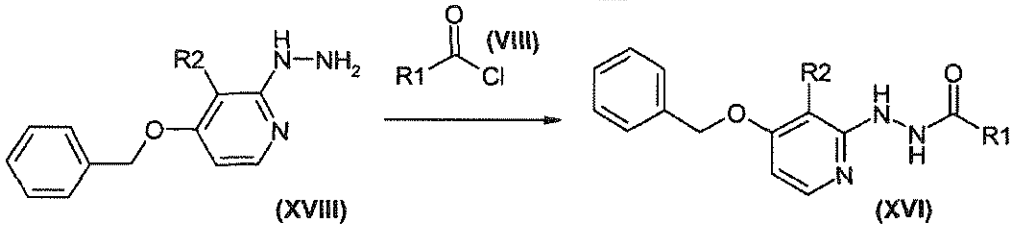
Reaction Scheme 14



Experimental procedure 15

Intermediate compounds according to Formula (XVI) can be prepared by art known procedures by reaction of intermediate compound of Formula (XVIII) with acid halides of Formula (VIII). The reaction can be carried out using an inert-solvent such as for example DCM in presence of a base such as for example TEA, for example at room temperature for a suitable period of time that allows completion of the reaction, for example 20 min. In reaction scheme (15), all variables are defined as in Formula (I).

Reaction Scheme 15

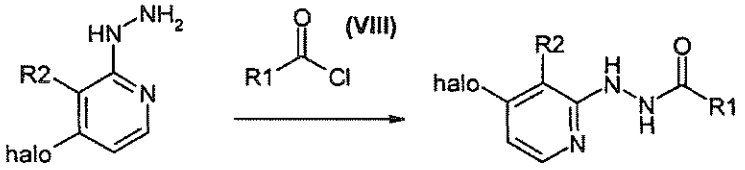


Experimental procedure 16

Intermediate compounds according to Formula (XVII) can be prepared by art known procedures by reaction of intermediate compounds of Formula (XIX) with acid halides

of Formula (VIII). The reaction can be carried out using an inert-solvent such as for example DCM in presence of a base such as for example TEA, for example a room temperature for a suitable period of time that allows completion of the reaction, for example 20 min. In reaction scheme (16), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo.

Reaction Scheme 16

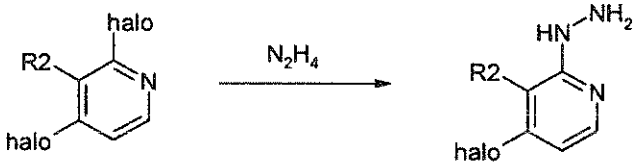


(XIX) (XVII)

Experimental procedure 17

Intermediate compounds according to Formula (XIX) can be prepared by reacting an intermediate compound of Formula (XV) with hydrazine according to reaction scheme (17), 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 (17), R^2 is defined as in Formula (I) and halo is chloro, bromo or iodo.

Reaction Scheme 17

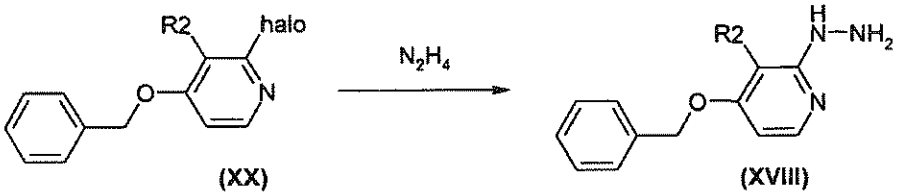


(XV) (XIX)

Experimental procedure 18

Intermediate compounds according to Formula (XVIII) can be prepared by reacting an intermediate compound of Formula (XX) with hydrazine according to reaction scheme (18), 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 minutes or classical thermal heating at 70 °C for 16 h. In reaction scheme (18), R^2 is defined as in Formula (I) and halo is chloro, bromo or iodo.

Reaction Scheme 18

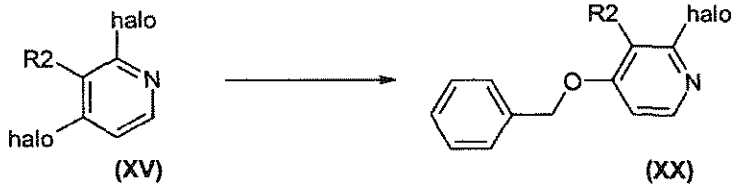


(XX) (XVIII)

Experimental procedure 19

Intermediate compounds according to Formula (XX) can be prepared by reacting an intermediate compound of Formula (XV) with benzyl alcohol according to reaction scheme (19), 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 room temperature for a suitable period of time that allows the completion of the reaction, such as for example 1 h. In reaction scheme (19), R^2 is defined as in Formula (I) and halo is chloro, bromo or iodo.

Reaction Scheme 19

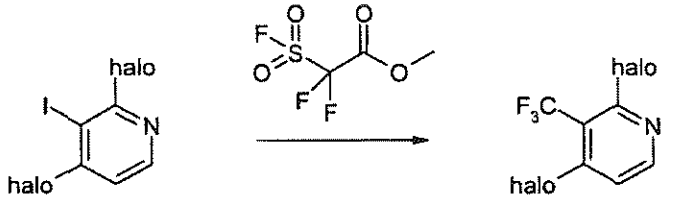


(XV) (XX)

Experimental procedure 20

Intermediate compounds of Formula (XV) wherein R^2 is trifluoromethyl, hereby named (XV-a), can be prepared by reacting an intermediate of Formula (XV) wherein R^2 is iodine, hereby named (XV-b), with a suitable trifluoromethylating agent, such as for example fluorosulfonyl(difluoro)acetic acid methyl ester, according to reaction scheme (20). 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 (20), halo is chloro, bromo or iodo.

Reaction Scheme 20

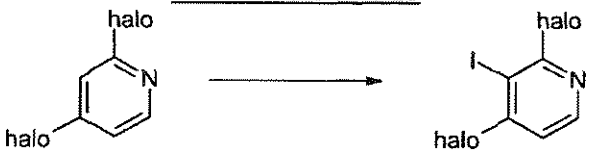


(XV-b) (XV-a)

Experimental procedure 21

Intermediate compounds of Formula (XV) wherein R^2 is iodine, hereby named (XV-b), can be prepared by reacting an intermediate compound of Formula (XXI) 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 as for example 2 h. In reaction scheme (21), halo may be chloro, bromo or iodo.

Reaction Scheme 21



(XXI) (XV-b)

Experimental procedure 22

Intermediate compounds of Formula (III) can be prepared by art known procedures by reacting an intermediate of Formula (XXII) with a suitable boron source such as, for example, bis(pinacolato)diboron in the presence of a palladium catalyst such as, for example, 1,1′-bis(diphenylphosphino)ferrocenepalladium(II)dichloride in a inert solvent such as, for example, DCM, in the presence of a suitable salt such as, for example, potassium acetate at moderately high temperature such as, for example, 110 °C for as, for example, 16 h.

Additionally, compounds of Formula (III) can be prepared by art known procedures of metal-halogen exchange and subsequent reaction with an appropriate boron source from compounds of Formula (XXII). Thus, for example, reaction of an intermediate compound of Formula (XXII) with an organolithium compound such as, for example, *n*-butyllithium at a moderately low temperature such as, for example, –40 °C in an inert solvent such as, for example, THF followed by subsequent reaction with an appropriate boron source such as, for example, trimethoxyborane. In reaction scheme (22), all variables are defined as in Formula (I) and R^7 and R^8 are as defined in Experimental procedure 1.

Reaction Scheme 22

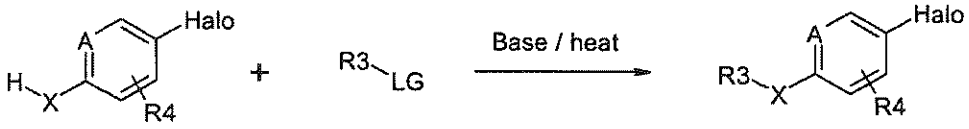


(XXII) (III)

Experimental procedure 23

Intermediate compounds of Formula (XXII) wherein X is O, N, S, SO, SO_2, $C(OH)(CH_3)$, CH_2-O, O-CH_2, CH_2-NH, HN-CH_2, CHF or CF_2, can be prepared by art known procedures by reacting an intermediate of Formula (XXIV) with a suitable intermediate of Formula (XXIII), in the presence of a suitable base such as, for example, sodium hydride in a inert solvent such as, for example, dimethylformamide, at moderately high temperature such as, for example, 180 °C, either under classical or microwave irradiation heating, for a suitable period of time to ensure completion of the reaction. In reaction scheme (23), all variables are defined as in Formula (I), halogen may be chloro, bromo or iodo and LG is a suitable leaving group such as halogen or nitro.

Reaction Scheme 23

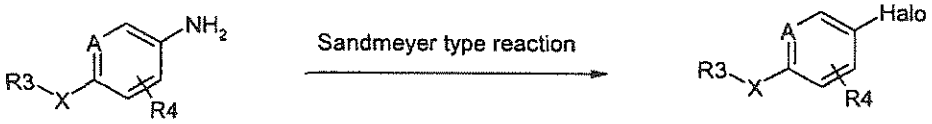


(XXIII) (XXIV) (XXII)

Experimental procedure 24

Additionally, compounds of Formula (XXII) can be prepared by art known procedures from intermediate compounds of Formula (XXV) via a Sandmeyer type reaction. In reaction scheme (24), all variables are defined as in Formula (I), halo may be chloro, bromo or iodo.

Reaction Scheme 24

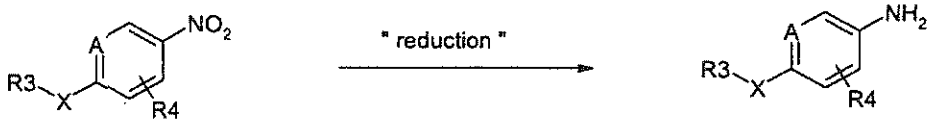


(XXV) (XXII)

Experimental procedure 25

Intermediate compounds of Formula (XXV) can be prepared by art known procedures from intermediate nitro compounds of Formula (XXVI) via reduction of the nitro group to the amino function by art known procedures, such as catalytic hydrogenation or the use of tin(II) chloride dihydrate as a reducing agent. In reaction scheme (25), X is O, NH, S, SO, SO_2, $C(OH)(CH_3)$, CH_2-O, O-CH_2, CH_2-NH, HN-CH_2, CHF and CF_2 and all other variables are defined as in Formula (I).

Reaction Scheme 25

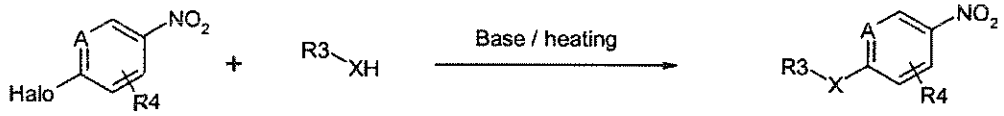


(XXVI) (XXV)

Experimental procedure 26

Intermediate compounds of Formula (XXVI) can be prepared by art known procedures by reacting an intermediate of Formula (XXVII) with a suitable intermediate of Formula (XXVIII), in the presence of a suitable base such as, for example, Cs_2CO_3 in an inert solvent such as, for example, tetrahydrofuran, heating at an appropriate temperature and for a suitable period of time that allows the completion of the reaction, either under traditional heating or under microwave irradiation. In reaction scheme (26), all variables are defined as in Formula (I); and X is O, NH, S, SO, SO_2, $C(OH)(CH_3)$, CH_2-O, O-CH_2, CH_2-NH, HN-CH_2, CHF or CF_2.

Reaction Scheme 26

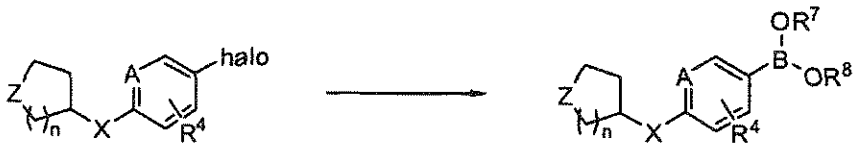


(XXVII) (XXVIII) (XXVI)

Experimental procedure 27

Intermediate compounds of Formula (III) wherein R^3 is a cyclic radical of formula (a), hereby named (III-a) can be prepared by art known procedures by reacting an intermediate of Formula (XXII) wherein R^3 is a cyclic radical of formula (a) wherein R^5 is hydrogen, hereby named (XXII-a) with a suitable boron source as defined in experimental procedure (22). In reaction scheme (27), all variables are defined as in Formula (I).

Reaction Scheme 27

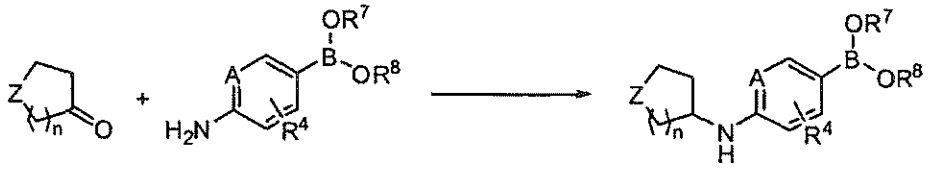


(XXII-a) (III-a)

Experimental procedure 28

Additionally, compounds of Formula (III) wherein R^3 is a cyclic radical of formula (a), and X is NH, hereby named (III-b) can be prepared by reacting the intermediate of Formula (XXIX) with a cyclic ketone derivative of Formula (XXX) under reductive amination conditions that are known to those skilled in the art, such as for example, in the presence of triacetoxy borohydride in a suitable reaction-inert solvent, such as for example 1,2-dichloroethane, at a suitable temperature, typically room temperature, for a suitable period of time that allows the completion of the reaction. In reaction scheme (28), all variables are defined as in Formula (III).

Reaction Scheme 28

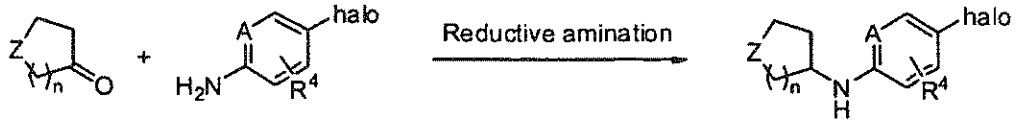


(XXX) (XXIX) (III-b)

Experimental procedure 29

Intermediate compounds of Formula (XXII) wherein R^3 is a cyclic radical of formula (a), and X is N, hereby named (XXII-b) can be prepared by art known procedures by reacting an intermediate of Formula (XXXI) with a cyclic ketone derivative of Formula (XXX), under reductive amination conditions that are known to those skilled in the art, such as for example, in the presence of triacetoxy borohydride in a suitable reaction-inert solvent, such as for example 1,2-dichloroethane, at a suitable temperature, typically room temperature, for a suitable period of time that allows the completion of the reaction. In reaction scheme (29), all variables are defined as in Formula (I) and halo- may be chloro, bromo or iodo.

Reaction Scheme 29

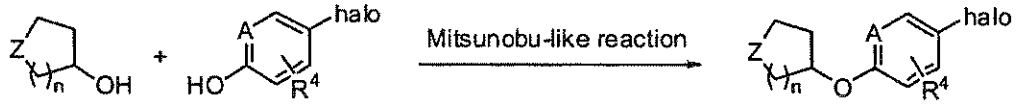


(XXX) (XXXI) (XXII-b)

Experimental procedure 30

Intermediate compounds of Formula (XXII) wherein R^3 is a cyclic radical of formula (a), and X is O, hereby named (XXII-c) can be prepared by art known procedures by reacting an intermediate of Formula (XXXII) with a cyclic alcohol of Formula (XXXIII), in the presence of a phosphine, such as for example triphenylphosphine and a suitable coupling agent for Mitsunobu-like couplings, such as for example di-*tert*-butyl azadicarboxylate in a inert solvent such as, for example, DCM, at moderately low temperature such as, for example, 25 °C for example 2 h. In reaction scheme (30), all variables are defined as in Formula (I) and halo may be chloro, bromo or iodo.

Reaction Scheme 30



(XXXIII) (XXXII) (XXII-c)

The starting materials according to Formulae (VI), (VII), (VIII), (X), (XIII), (XXII), (XXIV), (XXVIII), (XXIX), (XXX), (XXXI), (XXXII), and (XXXIII) 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 salt forms of the compounds, several procedures known to those skilled in the art can be used. In a typical procedure, for example, the free base can be dissolved in DIPE or Et_2O and subsequently, a 6 N 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 minutes after which the product can be filtered off. The HCl salt usually is 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 salts and the solvates thereof, or a pharmaceutical composition according to the invention for the manufacture of a medicament.

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 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 treatment, prevention, amelioration, control or reduction of the risk of various neurological and psychiatric disorders associated with glutamate dysfunction in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of 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 tolerance, 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, behavioural 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, behavioural and psychological symptoms of dementia, major depressive disorder, treatment resistant depression, bipolar depression, anxiety, depression, generalized anxiety disorder, post-traumatic stress disorder, bipolar mania, substance abuse and mixed anxiety and depression, are of 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 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 compound 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 disease 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 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, said 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 treatment, 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 as well. 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 a 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.

Examples

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.

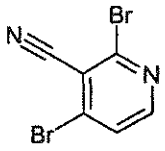
Hereinafter, "CI" means chemical ionisation; "DAD" means diode-array detector; "THF" means tetrahydrofuran; "DMF" means *N,N*-dimethylformamide; "EtOAc" means ethyl acetate; "DCM" means dichloromethane; "DCE" means 1,2-dichloroethane; "BINAP" means 1,1'-[1,1'-binaphthalene]-2,2'-diylbis[1,1-diphenyl-phosphine]; "DBU" means 1,8-diaza-7-bicyclo[5.4.0]undecene; "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; "DIPE" means diisopropylether; "$MgSO_4$" 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; "mp" means melting point; "min" means minutes; "h" means hours; "s" means second(s); "r.t." means room temperature; "Et_3N" or "TEA" mean triethylamine; "TOF" means time of flight; "NH_4Cl" means ammonium chloride; "Cs_2CO_3" means cessium carbonate; "K_2CO_3" means potassium carbonate; "$Pd(PPh_3)_4$" means tetrakis(triphenylphosphine)palladium(0).

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

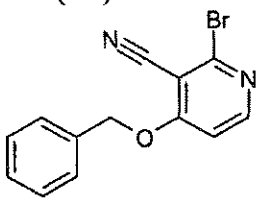
2,4-Dibromo-nicotinonitrile (**D1**)



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 portionwise phosphorus(V) oxybromide (250 g, 166 mmol). 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 evaporated *in vacuo*. The crude product thus obtained was triturated with DIPE to yield intermediate compound **D1** (34.5 g, 79%) as a white solid.

Description 2

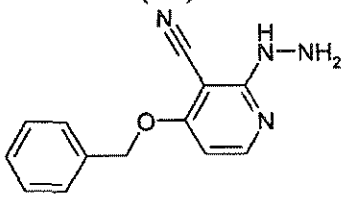
4-Benzyloxy-2-bromo-nicotinonitrile (**D2**)



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, intermediate compound **D1** (10 g, 38.18 mmol) was added. The resulting reaction mixture was gradually warmed to r.t. and stirred for 1 h, then quenched with NH_4Cl (aqueous sat. solution) and diluted with H_2O. 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

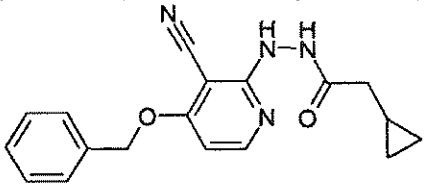
4-Benzyloxy-2-hydrazino-nicotinonitrile (**D3**)



To a solution of intermediate 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 subjected to microwave heating at 150 °C for 1 min. After cooling, additional hydrazine monohydrate (1 eq) was added to the resulting mixture, which was then subjected to microwave heating at 150 °C 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

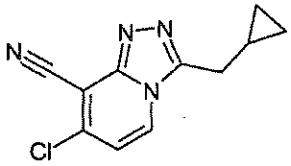
N'-(4-benzyloxy-3-cyano-pyridin-2-yl)-2-cyclopropylacetohydrazide (**D4**)



To a solution of intermediate compound **D3** (4.099 g, 17.06 mmol) in dry DCM (112 ml) were added triethylamine (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, then concentrated *in vacuo* to yield intermediate compound **D4** (5 g, 91%), which was used without further purification.

Description 5

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

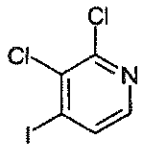


Intermediate compound **D4** (1.4 g, 4.343 mmol) and phosphorous (V) oxychloride (0.810 ml, 8.686 mmol) in DCE (15 ml) were subjected to microwave heating at 150 °C for 5 min. After cooling, the mixture was diluted with DCM and washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, 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

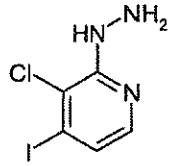
2,3-Dichloro-4-iodo-pyridine (**D6**)



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 and the resulting reaction mixture was stirred at –78 °C for 10 min. A solution of 2,3-dichloropyridine (10 g, 67.57 mmol) in dry THF (75 ml) was then 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 concentrated to yield intermediate compound **D6** (8.21 g, 44%) as a pale cream solid.

Description 7

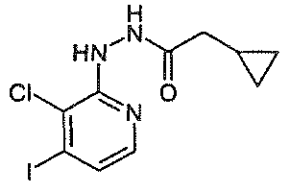
(3-Chloro-4-iodo-pyridin-2-yl)-hydrazine (**D7**)



To a solution of intermediate compound **D6** (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 80 °C for 16 h. After cooling, NH_4OH (32% aqueous solution) was added to the reaction mixture, which was then concentrated *in vacuo*. The white solid residue thus obtained was taken up in EtOH and heated. The suspension thus obtained was allowed to cool down and the precipitate obtained was filtered off, washed with EtOH and dried in the desiccator to yield intermediate compound **D7** (2.67 g, 52%) as a white solid

Description 8

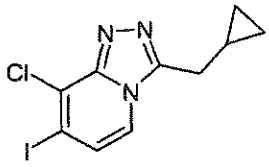
N'-(3-chloro-4-iodo-pyridin-2-yl)-2-cyclopropylacetohydrazide (**D8**)



To a solution of intermediate compound **D7** (0.73 g, 2.709 mmol) in dry DCM (8 ml), cooled at 0 °C, were added triethylamine (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. To this mixture was then added $NaHCO_3$ (aqueous sat. solution). The resulting solution was then extracted with DCM. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to yield intermediate compound **D8** (0.94 g, 99%).

Description 9

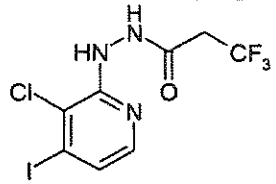
8-Chloro-3-cyclopropylmethyl-7-iodo-1,2,4-triazolo[4,3-a]pyridine (**D9**)



Intermediate compound **D8** (0.74 g, 2.389 mmol) was heated at 160 °C for 40 min. After cooling, the brown gum was triturated with DIPE yielding intermediate compound **D9** (0.74 g, 93%).

Description 10

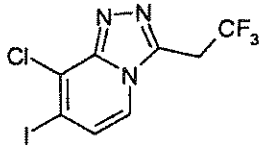
N'-(3-chloro-4-iodo-pyridin-2-yl)-3,3,3-trifluoropropanohydrazide (**D10**)



To a solution of intermediate compound **D7** (2.528 g, 9.38 mmol) in dry DCM (15 ml), cooled at 0 °C, were added triethylamine (3.244 ml, 23.45 mmol) and 3,3,3,-trifluoropropionyl chloride (1.924 g, 13.132 mmol). The resulting reaction mixture was stirred at r.t. for 3 h. After this period, $NaHCO_3$ (aqueous sat. solution) was added. The resulting solution was then extracted with DCM. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue thus obtained was triturated with DIPE to yield intermediate compound **D10** (4 g, 55%).

Description 11

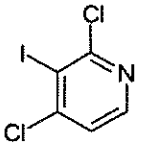
8-Chloro-3-(2,2,2-trifluoroethyl)-7-iodo-1,2,4-triazolo[4,3-a]pyridine (**D11**)



Intermediate compound **D10** (4 g, 5.27 mmol) was heated at 170 °C for 4 h. After cooling, the brown gum was triturated with DIPE. The solid thus obtained was then taken up in MeOH and the resulting suspension filtered off. The mother liqueurs were then 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 **D11** (0.85 g, 45%)

Description 12

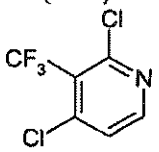
2,4-Dichloro-3-iodo-pyridine (**D12**)



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., then a solution of iodine (9.81 g, 38.651 mmol) in dry THF (20 ml) was added dropwise and the mixture was further stirred at –78 °C for 1 h. The mixture was 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 **D12** (7.8 g, 81%)

Description 13

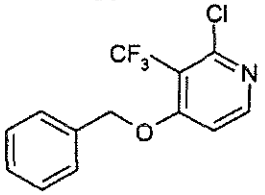
2,4-Dichloro-3-trifluoromethyl-pyridine (**D13**)



To a mixture of intermediate compound **D12** (2g, 7.302 mmol) in DMF (50 ml) were added fluorosulfonyl-difluoro-acetic acid methyl ester (1.858 ml, 14.605 mmol) [C.A.S. 680-15-9] and copper (I) iodide (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 **D13** (1.5 g, 95%).

Description 14

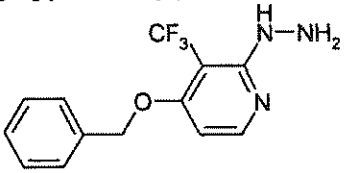
4-Benzyloxy-3-trifluoromethyl-2-chloro-pyridine (**D14**)



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. Intermediate compound **D13** (2.5 g, 11.575 mmol) was then added. The resulting reaction mixture was stirred for 1 h while gradually allowing it to warm to r.t., 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 **D14** (1.1 g, 33%).

Description 15

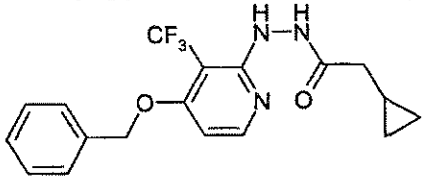
(4-Benzyloxy-3-trifluoromethyl-pyridin-2-yl)-hydrazine (**D15**)



To a suspension of intermediate compound **D14** (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 subjected to microwave heating at 160 °C 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 evaporated *in vacuo* to yield intermediate compound **D15** (0.890 g, 83%) as a white solid.

Description 16

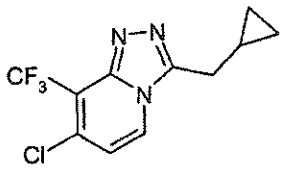
N'-(4-benzyloxy-3-trifluoromethyl-pyridin-2-yl)-2-cyclopropylacetohydrazide (**D16**)



To a solution of intermediate compound **D15** (0.890 g, 3.142 mmol) in dry DCM (3 ml) were added triethylamine (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, then concentrated *in vacuo* to yield intermediate compound **D16** (1.1 g, 96%).

Description 17

7-Chloro-8-trifluoromethyl-3-cyclopropylmethyl-1,2,4-triazolo[4,3-a]pyridine (**D17**)

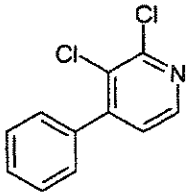


A solution of intermediate compound **D16** (1.14 g, 1.872 mmol) and phosphorous (V) oxychloride (0.349 g, 3.744 mmol) in CH_3CN (10 ml) was heated under microwave irradiation at 150 °C for 10 min. After cooling, the resulting reaction mixture was diluted with DCM, washed with $NaHCO_3$ (aqueous sat. 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 **D17** (0.261 g, 51%) as a white solid.

Description 18

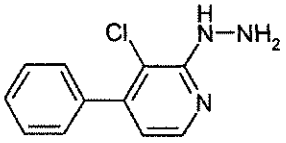
2,3-Dichloro-4-phenyl)-pyridine (**D18**)



To a mixture of intermediate compound **D6** (0.5 g, 1.826 mmol) in 1,4-dioxane (5 ml) under a nitrogen atmosphere were added phenyl boronic acid (0.267 g, 2.191 mmol), $Pd(PPh_3)_4$ (0.211 g, 0.183 mmol) and $NaHCO_3$ (5 ml, aqueous sat. solution). The reaction mixture was subjected to microwave heating at 150 °C for 10 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with EtOAc. The filtrate was evaporated *in vacuo* and the residue was purified by column chromatography (silica gel; DCM/MeOH up to 2% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate compound **D18** (0.4 g, 98%).

Description 19

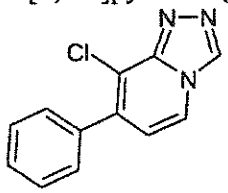
[3-Chloro-4-phenyl)-pyridin-2-yl]-hydrazine (**D19**)



To a solution of intermediate compound **D18** (0.4 g, 1.785 mmol) in EtOH (4 ml), was added hydrazine monohydrate (1.732 ml, 35.7 mmol). The reaction mixture was subjected to microwave heating at 160 °C for 20 min. After cooling, the solvent was evaporated *in vacuo*. The residue thus obtained was taken up in DCM, dried (Na_2SO_4) and evaporated *in vacuo* to yield intermediate compound **D19** (0.3 g, 77%) as a white solid.

Description 20

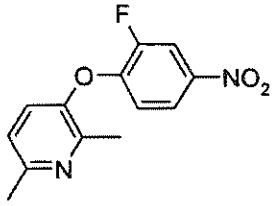
8-Chloro-7-(4-phenyl)-1,2,4-triazolo[4,3-a]pyridine (**D20**)



Intermediate compound **D19** (0.25 g, 1.138 mmol) and triethylorthoformate (2.839 ml, 17.071 mmol) in xylene (3 ml) was heated in a sealed tube at 180 °C for 1 h. After cooling, the resulting mixture was evaporated *in vacuo*. The residue thus obtained was triturated with Et_2O to yield intermediate compound **D20** (0.211 g, 80%).

Description 21

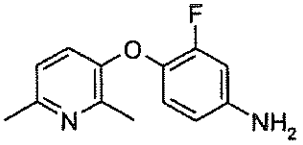
3-(2-Fluoro-4-nitro-phenoxy)-2,6-dimethyl-pyridine (**D21**)



To a solution of 2,6-dimethyl-3-pyridinol (3 g, 24.35 mmol) in THF (30 ml) at r.t., were added Cs_2CO_3 (15.87 g, 48.71 mmol) and 3,4-difluoro-1-nitro-benzene (3.87 g, 24.35 mmol). The reaction mixture was heated at reflux for 2 h. After cooling to r.t. the solids were filtered off and the filtrate was evaporated to dryness. 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 **D21** (5.88 g, 92 %).

Description 22

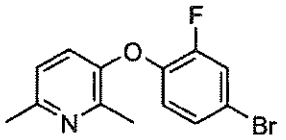
4-(2,6-Dimethyl-pyridin-3-yloxy)-3-fluoro-phenylamine (**D22**)



A solution of intermediate compound **D21** (5.88 g, 22.44 mmol) in EtOH (200 ml) was stirred under an atmosphere of hydrogen at r.t. in the presence of palladium 10% on activated carbon (0.58 g) for 3 h. The solids were filtered off and the filtrate was evaporated to dryness to yield intermediate compound **D22** (5.20 g, >99 %), which was used without further purification.

Description 23

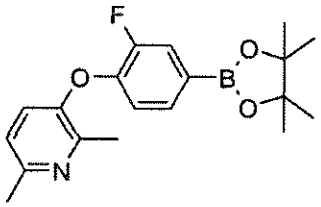
3-(4-Bromo-2-fluoro-phenoxy)-2,6-dimethyl-pyridine **(D23)**



To a solution of intermediate compound **D22** (7.7 g, 33.2 mmol) in HBr (75 ml, 48% aqueous), cooled to 0 °C, was added a solution of sodium nitrite (4.57 g, 66.3 mmol) in water (75 ml), dropwise over 45 min. The reaction mixture was warmed to r.t. and stirred for a further 15 min. The mixture was then cooled to 0 °C and copper (I) bromide (4.0 g, 28.4 mmol) was added portionwise. Stirring was continued for 15 min at 0 °C and then the mixture was warmed to r.t. and further stirred for 15 min. The reaction mixture was then heated at 140 °C for 1.5 h. The mixture was cooled to r.t. and carefully neutralized with an aqueous saturated solution of K_2CO_3. EtOAc was then added and the layers were separated. The organic phase was dried (Na_2SO_4) and concentrated to dryness. The crude product was purified by column chromatography (silica gel; heptane to heptane/EtOAc up to 10% as eluent). The desired fractions were then collected and concentrated *in vacuo* to yield intermediate compound **D23** (8.75 g, 89 %).

Description 24

3-[2-Fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-2,6-dimethyl-pyridine **(D24)**

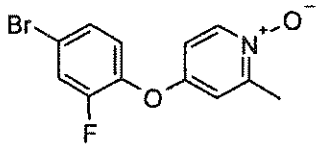


To a solution of intermediate compound **D23** (1 g, 3.377 mmol) in 1,4-dioxane (8 ml) and DMF (4 ml) were added bis(pinacolato)diborane (2.572 g, 10.13 mmol) and potassium acetate (0.964 g, 10.13 mmol). The mixture was degassed and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) complex with DCM (1:1) (0.083 g, 0.101 mmol; [CAS 95464-05-4]) was added. The reaction mixture was heated at 150 °C for 10 min. under microwave irradiation. After cooling to r.t., water was added and the mixture was extracted with EtOAc. The organic fraction was dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The residue thus obtained was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH gradient as

eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate compound **D24** (0.85 g, 73 %).

Description 25

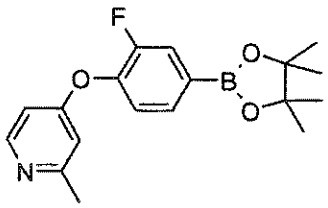
4-(4-Bromo-2-fluoro-phenoxy)-2-methyl-pyridine 1-oxide **(D25)**



To a solution of 4-bromo-2-fluorophenol (3.44 ml, 31.41 mmol) in *N*-methylpyrrolidone (20 ml) at r.t., was added sodium hydride (1.34 g, 56 mmol, 60% in mineral oil) portionwise. After stirring for 20 min, 4-nitro-2-picoline *N*-oxide (5.6 g, 36.12 mmol) was added. The reaction mixture was heated at 180 °C for 60 min. under microwave irradiation. After cooling to r.t. the mixture was diluted with EtOAc (250 ml), washed with water (250 ml) and then extracted with additional EtOAc (2 x 150 ml). The combined organic extracts were 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 2% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D25** (4.36 g, 47 %).

Description 26

4-[2-Fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-2-methyl-pyridine **(D26)**

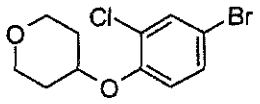


To a solution of intermediate compound **D25** (2 g, 6.709 mmol) in 1,4-dioxane (16 ml) and DMF (8 ml) were added bis(pinacolato)diborane (5.111 g, 20.127 mmol) and potassium acetate (1.975 g, 20.127 mmol). The mixture was degassed and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II); complex with DCM (1:1) (0.165 g, 0.201 mmol; [95464-05-4]) was added. The reaction mixture was heated at 150 °C for 10 min under microwave irradiation. After cooling to r.t. water was added and the mixture was extracted with EtOAc (20 ml). The organic fraction was dried

(Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product thus obtained was purified by column chromatography (silica gel; DCM to DCM/AcOEt up to 20%). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D26** (1.45 g, 65 %).

Description 27

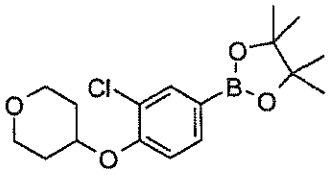
4-(4-Bromo-2-chloro-phenoxy)-tetrahydro-pyran **(D27)**



A mixture of 4-bromo-2-chloro-phenol (4 g, 19.28 mmol), tetrahydro-4-pyranol (2.20 ml, 23.13 mmol) and polymer supported triphenylphosphine (17.29 g, 39.29 mmol; purchased from Argonaut, loading 2.23 mmol/g) was suspended in DCM (250 ml) and then cooled to 0 °C. Di-*tert*-butyl azadicarboxylate (6.65 g, 28.92 mmol) was added portionwise and the reaction mixture was warmed to r.t. and shaken for 2 h. The resin was filtered off and washed with DCM. The combined filtrates were evaporated to dryness. The crude product thus obtained was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 2%). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D27** as colorless oil (5.38 g, 95 %).

Description 28

4-[2-Chloro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-tetrahydro-pyran **(D28)**

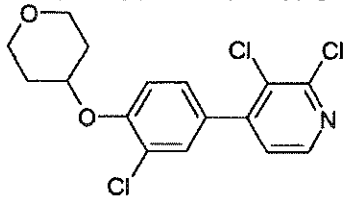


To a solution of intermediate compound **D27** (2 g, 6.85 mmol) in 1,4-dioxane (10.8 ml) and DMF (1.2 ml) were added bis(pinacolato)diboron (2.01 g, 8.23 mmol) and potassium acetate (2.01 g, 20.55 mmol). The mixture was degassed and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II); complex with DCM (1:1) (0.16 g, 0.2 mmol) was added. The reaction mixture was heated at 150 °C for 10 min under microwave irradiation. After cooling to r.t., the mixture was filtered through a pad of diatomaceous earth. The diatomaceous earth was washed with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and the solvent

evaporated *in vacuo* to afford intermediate compound **D28** (100%) as a crude that was used without further purification.

Description 29

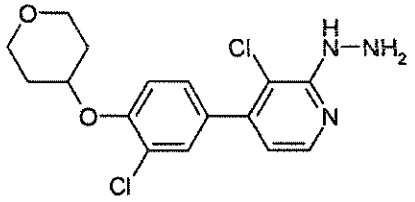
2,3-Dichloro-4-[3-chloro-4-(tetrahydro-pyran-4-yloxy)-phenyl]-pyridine (**D29**)



To a mixture of intermediate compound **D6** (0.390 g, 1.424 mmol) in 1,4-dioxane (8.25 ml) under a nitrogen atmosphere were added intermediate compound **D28** (0.530 g, 1.566 mmol), $Pd(PPh_3)_4$ (0.082 g, 0.0712 mmol) and $NaHCO_3$ (2.75 ml, aqueous sat. solution). The reaction mixture was subjected to microwave heating at 150 °C for 10 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with EtOAc. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; DCM as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D29** (0.387 g, 76%) as a colorless oil, which solidified on standing.

Description 30

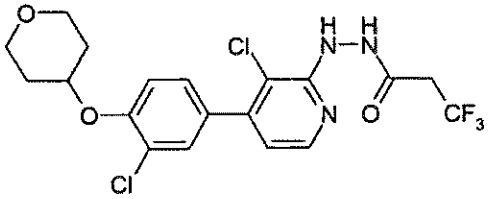
{3-Chloro-4-[3-chloro-4-(tetrahydro-pyran-4-yloxy)-phenyl]-pyridin-2-yl}-hydrazine (**D30**)



To a suspension of intermediate compound **D29** (0.387 g, 1.079 mmol) in EtOH (8 ml), was added hydrazine monohydrate (1.047 ml, 21.581 mmol). The reaction mixture was subjected to microwave heating at 160 °C for 20 min. Then, after cooling, additional hydrazine monohydrate (0.26 ml) was added to the reaction mixture, which was irradiated again at 160 °C for 20 min. After cooling, the solvent was evaporated *in vacuo*. The residue thus obtained was taken up in DCM and washed with K_2CO_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 **D30** (0.213 g, 56%) as a white solid. M.P. 173.3°C

Description 31

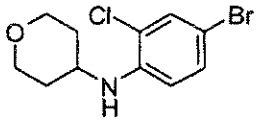
N'-{3-chloro-4-[3-chloro-4-(tetrahydro-*2H*-pyran-4-yloxy)-phenyl]-pyridin-2-yl}-3,3,3-trifluoropropanohydrazide **(D31)**



A solution of intermediate compound **D30** (0.213 g, 0.601 mmol) in dry DCM (7 ml) was cooled to 0 °C. Triethylamine (0.126 ml, 0.902 mmol) and 3,3,3-trifluoro-propionyl chloride [C.A.S. 41463-83-6] (0.087 ml, 0.691 mmol) was added. The resulting reaction mixture was gradually warmed to r.t. and stirred for 1 h. The mixture was concentrated *in vacuo*. The residue thus obtained was triturated with DIPE to yield intermediate compound **D31** (0.240 g; 86%). M.P. 190.8°C

Description 32

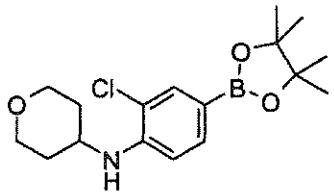
(4-Bromo-2-chloro-phenyl)-(tetrahydro-pyran-4-yl)-amine **(D32)**



A mixture of 4-bromo-2-chloro-phenylamine (4 g, 19.37 mmol), tetrahydro-4*H*-pyran-4-one (2.69 ml, 29.05 mmol), oven-dried molecular sieves 4 Å (2 g) and sodium triacetoxyborohydride (6.12 g, 29.05 mmol) in DCE (100 ml) was stirred at r.t. for 72 h. The mixture was filtered through a pad of diatomaceous earth. The diatomaceous earth pad was then washed with DCM. The combined filtrates were washed with $NaHCO_3$ (aqueous saturated solution), dried (Na_2SO_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 5%). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D32** as a brown oil (4.83 g, 86 %).

Description 33

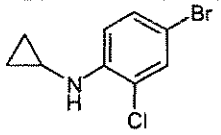
[2-Chloro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-(tetrahydro-pyran-4-yl)-amine **(D33)**



To a solution of intermediate compound **D32** (2 g, 6.88 mmol) in 1,4-dioxane (10.8 ml) and DMF (1.2 ml) were added bis(pinacolato)diboron (2.09 g, 8.25 mmol) and potassium acetate (2.02 g, 20.64 mmol). The mixture was degassed and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II); complex with DCM (1:1) (0.16 g, 0.2 mmol) was added. The reaction mixture was heated at 150 °C for 10 min. under microwave irradiation. After cooling to r.t., the mixture was filtered through a pad of diatomaceous earth and the diatomaceous earth washed with EtOAc. The combined organic extracts were washed with NaCl (aqueous sat. solution), dried (Na_2SO_4) and the solvent evaporated *in vacuo* to afford intermediate compound **D33** (100%) as a crude product that was used without further purification.

Description 34

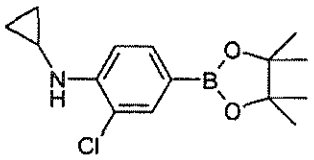
(4-Bromo-2-chloro-phenyl)-cyclopropyl-amine **(D34)**



To a solution of 4-bromo-2-chloroaniline (C.A.S. 38762-41-3), (1 g, 4.843 mmol) in AcOH (19 ml) and MeOH (10 mL) was added [(1-ethoxycyclopropyl) oxy]-trimethylsilane (1.199 ml, 5.57 mmol) dropwise at r.t. The reaction mixture was then refluxed at 67–69 °C for 3 h. under a N_2 atmosphere. The mixture was then concentrated *in vacuo* to obtain a crude oil. Into a 200 mL four-necked flask fitted with a reflux condenser, a mechanical stirrer and a thermometer were added $NaBH_4$ (0.366 g, 9.687 mmol) and anhydrous THF (10 mL). After cooling to 5 °C, $BF_3{\cdot}Et_2O$ complex (1.228 ml, 9.687 mmol) was added dropwise and the mixture stirred under a N_2 atmosphere at 5 °C for 1 h. The crude oil dissolved in THF (5 mL), was added dropwise at 5–10 °C over 20 min. After stirring at r.t. for 5 h, at reflux for 2 h. and then removing THF by distillation, the mixture was cooled to r.t. and poured into water. The resulting mixture was extracted with Et_2O. The Et_2O layer was washed with water and dried (Na_2SO_4) followed by the removal of Et_2O *in vacuo*. The crude product thus obtained was purified by column chromatography (silica gel; Heptane/AcOEt 99:1 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D34** (0.390 g, 32.6%).

Description 35

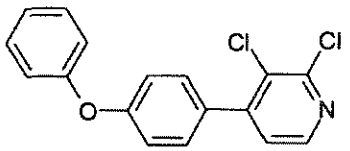
[2-Chloro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropyl-amine **(D35)**



Bis(pinacolato)diboron (0.643g, 2.531 mmol) and potassium acetate (0.466 g, 4.746 mmol) were added to a solution of intermediate compound **D34** (0.390 g, 1.582 mmol) in dioxane (2 ml) and DMF (0.5 ml). The mixture was degassed and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) - complex with DCM (1:1) (0.0348 g, 0.0475 mmol) was added. The reaction mixture was heated at 150 °C for 10 min. under microwave irradiation. After cooling to r.t., the reaction mixture was filtered through diatomaceous earth. The filtrate was evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; heptane as eluent). The desired fractions were collected and concentrated *in vacuo* to afford intermediate compound **D35** (0.269 g, 49%)

Description 36

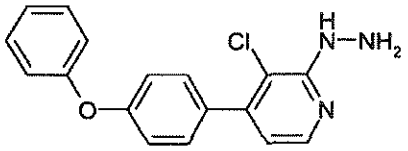
2,3-Dichloro-4-(4-phenoxy-phenyl)-pyridine **(D36)**



To a mixture of intermediate compound **D6** (0.5 g, 1.826 mmol) in 1,4-dioxane (11.25 ml) under a nitrogen atmosphere were added 4-phenoxyphenyl boronic acid [C.A.S. 51067-38-0] (0.469 g, 2.191 mmol), $Pd(PPh_3)_4$ (0.105 g, 0.0913 mmol) and $NaHCO_3$ (3.75 ml, aqueous sat. solution). The reaction mixture was subjected to microwave heating at 150 °C for 5 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with EtOAc. The filtrate was evaporated *in vacuo* and the residue was purified by column chromatography (silica gel; DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate compound **D36** (0.498 g, 86%).

Description 37

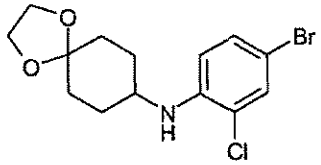
[3-Chloro-4-(4-phenoxy-phenyl)-pyridin-2-yl]-hydrazine (**D37**)



To a solution of intermediate compound **D36** (0.498 g, 1.575 mmol) in EtOH (12 ml), was added hydrazine monohydrate (7.64 ml, 15.75 mmol). The reaction mixture was subjected to microwave heating at 150 °C for 20 min. After cooling, additional hydrazine monohydrate (0.76 ml) was added to the reaction mixture, which was then irradiated again at 160 °C for 1 h. followed by thermal heating at 95 °C for 16 h. After cooling, the solvent was evaporated *in vacuo*. The residue 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** (0.42 g, 86%). M.P. 173.3°C

Description 38

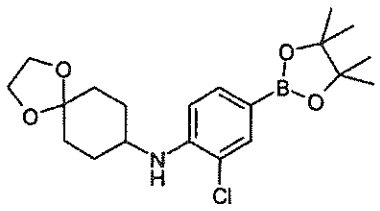
N-(4-Bromo-2-chlorophenyl)-1,4-dioxaspiro[4.5]decan-8-yl-amine (**D38**)



A mixture of 4-bromo-2-chloro-phenylamine (6 g, 29.06 mmol), [CAS 38762-41-3], 1,4-cyclohexanedione monoethyleneketal [CAS 4746-97-8], (6.908 g, 43.59 mmol), and sodium triacetoxy-borohydride (9.239 g, 43.59 mmol) in DCE (100 ml) and acetic acid (0.2 ml) was stirred at r.t. for 2 days. The mixture was then filtered through a pad of diatomaceous earth and washed with DCM. The filtrate was washed with $NaHCO_3$ (aqueous sat. solution), sodium chloride (aqueous sat. solution), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product thus obtained was purified by column chromatography (silica gel; DCM/AcOEt 4:1 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D38** (8.57 g, 85%).

Description 39

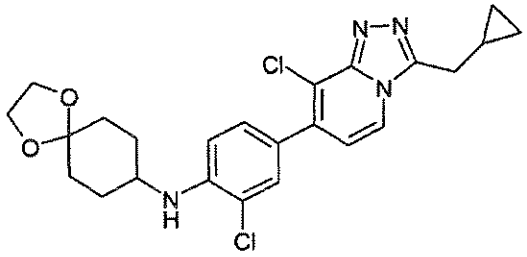
N-[2-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,4-dioxa-spiro[4.5]decan-8-yl-amine (**D39**)



Bis(pinacolato)diboron (1.099 g, 4.327 mmol) and potassium acetate (0.566 g, 5.769 mmol) were added to a solution of intermediate compound **D38** (1 g, 2.885 mmol) in dioxane (3 ml) and DMF (0.2 ml). The mixture was degassed and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) - complex with DCM (1:1) (0.063 g, 0.0865 mmol) was added. The reaction mixture was heated at 150 °C for 10 min. under microwave irradiation. After cooling to r.t., the reaction mixture was filtered through diatomaceous earth. The filtrate was concentrated *in vacuo*. The crude residue was purified by column chromatography (silica gel; heptane/AcOEt up to 25% as eluent). The desired fractions were collected and concentrated *in vacuo* to afford intermediate compound **D39** (1.18 g, 99%).

Description 40

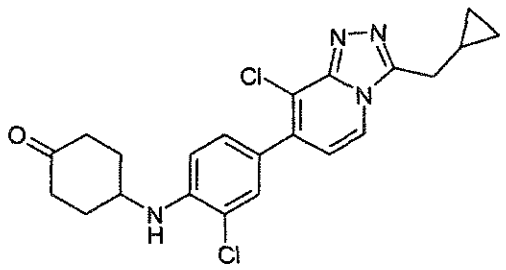
8-Chloro-7-[3-chloro-4-(1,4-dioxa-spiro[4.5]dec-8-yl)-amino)-phenyl]-3-cyclopropylmethyl-[1,2,4]triazolo[4,3-a]pyridine (**D40**)



To a mixture of intermediate compound **D9** (0.439 g, 1.316 mmol) in 1,4-dioxane (5 ml) under a nitrogen atmosphere were added intermediate compound **D39** (0.57 g, 1.448 mmol), $Pd(PPh_3)_4$ (0.076 g, 0.0658 mmol) and $NaHCO_3$ (2 ml, aqueous sat. solution). The reaction mixture was subjected to microwave heating at 150 °C for 10 min. After cooling, additional $Pd(PPh_3)_4$ (0.076 g, 0.0658 mmol) was added to the reaction mixture, which was then subjected to microwave heating at 150 °C for 7 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with EtOAc. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 2.5% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D40** (0.57 g, 91%).

Description 41

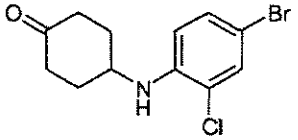
8-Chloro-7-[3-chloro-4-(4-oxo-cyclohexylamino)-phenyl]-3-cyclopropylmethyl-[1,2,4]triazolo[4,3-a]pyridine (**D41**)



A mixture of intermediate compound **D40** (0.57 g, 1.204 mmol), p-toluenesulfonic acid (23 mg, 0.12 mmol) in H_2O (11 ml) and acetone (6 ml) was heated at 110 °C for 20 min. under microwave irradiation. After cooling, solid precipitate was filtered and dried *in vacuo* to yield intermediate compound **D41** (0.389 g, 75 %)

Description 42

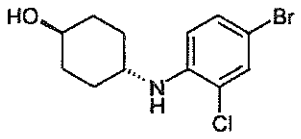
4-(4-Bromo-2-chloro-phenylamino)-cyclohexanone (**D42**)



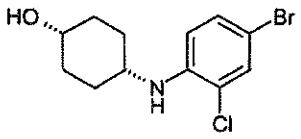
A mixture of intermediate compound **D38** (4 g, 11.539 mmol), p-toluenesulfonic acid (21.949 mg, 0.115 mmol) in H_2O (6 ml) and acetone (3 ml) was heated at 110 °C for 45 min. under microwave irradiation. After cooling to r.t., the reaction mixture was diluted with DCM and washed with a saturated aqueous NaCl solution, dried (Na_2SO_4) and concentrated *in vacuo*. The reaction mixture was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 0.1% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D42** (2.17 g, 62 %) as a white solid.

Description 43

4-(4-Bromo-2-chloro-phenylamino)-cyclohexanol (**D43**)



D43-a
(trans)



D43-b
(cis)

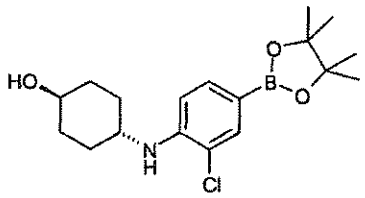
To a stirred solution of intermediate compound **D42** (2 g, 5.288 mmol) in MeOH (40 ml) at –78 °C was added sodium borohydride (220 mg, 5.816 mmol). The mixture was gradually warmed to r.t. and further stirred for 16 h. The resulting mixture was then quenched with an aqueous saturated ammonium chloride solution, washed with sodium chloride (aqueous sat. solution), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue thus obtained was purified by circular chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 5% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate compound **D43-a** *(trans)* (0.380 g, 23.6 %) and intermediate compound **D43-b** *(cis)* (0.710 g, 44 %).

D43-a *(trans)* M.P. > 300°C

D43-b *(cis)* M.P. > 300°C

Description 44

(trans)-4-[2-Chloro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamino] cyclohexanol (**D44**)

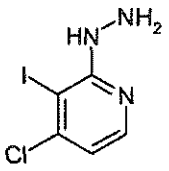


Bis(pinacolato)diboron (0.947 g, 3.729 mmol) and potassium acetate (0.686 g, 6.992 mmol) were added to a solution of intermediate compound **D43-a** (0.710 g, 2.331 mmol) in 1,4-dioxane (5 ml). The mixture was degassed and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) - complex with DCM (1:1) (0.051 g, 0.0699 mmol) was added. The reaction mixture was heated at 150 °C for 10 min. under microwave irradiation. After cooling to r.t., the reaction mixture was filtered through diatomaceous earth. The filtrate was concentrated *in vacuo*. The crude 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 afford a colourless oily residue that crystallized to yield intermediate compound *trans*-**D44** (0.950 g) as a white solid.

Description 45

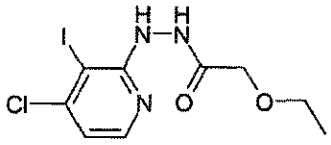
(4-Chloro-3-iodo-pyridin-2-yl)-hydrazine (**D45**)



To a solution of 2,4-dichloro-3-iodopyridine [CAS 343781-36-3] (4.7 g, 17.16 mmol) in 1,4-dioxane (240 ml), was added hydrazine monohydrate (5.096 ml, 102.962 mmol). The reaction mixture was heated in a sealed tube at 80 °C for 16 h. After cooling, the solvent was concentrated *in vacuo*. The white solid residue thus obtained was dissolved in DCM and washed with $NaHCO_3$ (aqueous saturated solution). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was washed with diethylether. The solid thus obtained was discarded. The mothe liquours were concentrated *in vacuo* to yield intermediate compound **D45** (2.31 g, 49%)

Description 46

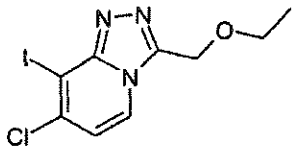
N'-(4-chloro-3-iodo-pyridin-2-yl)-2-ethoxyacetohydrazide (**D46**)



To a suspension of intermediate compound **D45** (1.54 g, 5.715 mmol) in dry DCM (39.6 ml), cooled at 0 °C, were added triethylamine (1.589 ml, 11.43 mmol) and ethoxy-acetyl chloride (0.77 g, 6.286 mmol). The resulting reaction mixture was stirred at r.t. for 1 h. To this mixture was then added $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo* to yield intermediate compound **D46** (2 g, 98%).

Description 47

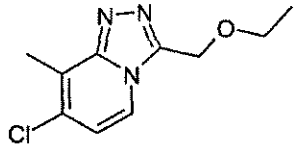
7-Chloro-3-ethoxymethyl-8-iodo-[1,2,4]triazolo[4,3-a]pyridine (**D47**)



Intermediate compound **D46** (2 g, 5.27 mmol) was heated at 160 °C for 2 h. After cooling, the brown gum was purified by column chromatography (silica gel; DCM/EtOAc gradient as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D47** (0.930 g, 49%) as a yellow solid. M.P.: 131.6°C

Description 48

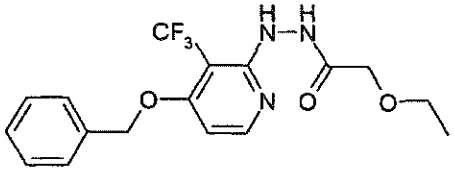
7-Chloro-3-ethoxymethyl-8-methyl-[1,2,4]triazolo[4,3-a]pyridine (**D48**)



To a mixture of intermediate compound **D47** (0.630 g, 1.866 mmol) in toluene (15 ml) under a nitrogen atmosphere were added methylboronic acid (0.558 g, 9.332 mmol), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine; S-Phos (0.153 g, 0.373 mmol), Palladium(II) acetate (0.041 g, 0.187 mmol) and K_2CO_3 (0.773 g, 5.599 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 10/90 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D48** (0.105 g, 24%). M.P.: 92.9°C

Description 49

N'-(4-benzyloxy-3-trifluoromethyl-pyridin-2-yl)-2-ethoxyacetohydrazide (**D49**)

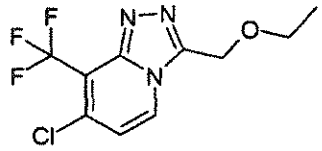


To a solution of intermediate compound **D15** (4 g, 14.122 mmol) in dry DCM (90 ml) at 0°C were added triethylamine (3.915 ml, 28.243 mmol) and ethoxy-acetyl chloride

(1.904 g, 15.534 mmol). The resulting reaction mixture gradually warmed to r.t. and stirred for 1 h. Then the mixture was washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4), then, concentrated *in vacuo* to yield intermediate intermediate compound **D49** (5.04 g, 96%).

Description 50

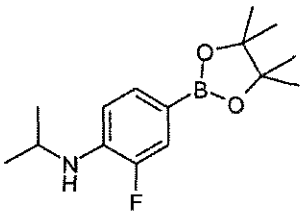
7-Chloro-3-ethoxymethyl-8-trifluoromethyl-[1,2,4]triazolo[4,3-a]pyridine **(D50)**



A solution of intermediate compound **D49** (1.24 g, 3.357 mmol) in DCE (12 mol) were added phosphorous (V) oxychloride (0.804 ml, 8.393 mmol. The mixture was heated under microwave irradiation at 150 °C for 30 min. After cooling, the resulting reaction mixture was carefully poured over a stirred saturated $NaHCO_3$ aqueous solution. The resulting aqueous solution was 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 60/40 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D50** (0.261 g, 51%) as a cream solid. M.P.: 104°C

Description 51

[2-Fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-isopropyl-amine **(D51)**

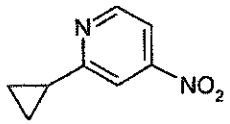


Bis(pinacolato)diboron (2.816 g, 11.09 mmol) and potassium acetate (2.512 g, 25.593 mmol) were added to a solution of *N*-(4-bromo-2-fluorophenyl)-*N*-isopropylamine [CAS 1019541-29-7] (1.98 g, 8.531 mmol) in 1,4-dioxane (28 ml). The mixture was degassed and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) - complex with DCM (1:1) (0.376 g, 0.512 mmol) was added. The reaction mixture was heated at 95 °C overnight. After cooling to r.t., the reaction mixture was filtered through diatomaceous earth. The filtrate was washed with EtOAc and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel;

Heptane/DCM from 100/0 to 0/100 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D51** (1.44 g, 56%)

Description 52

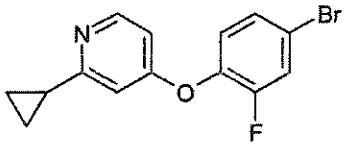
2-Cyclopropyl-4-nitropyridine **(D52)**



To a mixture of potassium cyclopropyltrifluoroborate (0.943 g, 6.37 mmol), palladium (II) acetate (0.0285 g, 0.126 mmol), di-1-adamantylbutylphosphine [CAS 321921-71-5] (0.0678 g, 0.189 mmol) and Cs2CO3 (6.165 g, 18.922 mmol) in toluene (20 ml) and water (4 ml) under a nitrogen atmosphere was added 2-chloro-4-nitropyridine (1 g, 6.307 mmo). The reaction mixture was heated at 98 °C for 2 days. After cooling, the mixture was washed with water. The organic phase was separated and dried (Na_2SO_4). The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; Heptane/DCM from 100/0 to 50/50 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D52** (0.800 g, 77%) as yellow oil which crystallized upon standing

Description 53

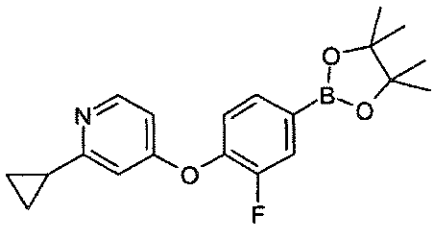
4-(4-Bromo-2-fluoro-phenoxy)-2-cyclopropyl-pyridine **(D53)**



To a solution of 2-fluoro-4-bromophenol (0.534 ml, 4.873 mmol) in DMSO (10 ml) was added K_2CO_3 (1.345 g, 9.746 mmol) and intermediate compound **D52** (0.800 g, 4.873 mmol). The reaction mixture was heated at 100°C for 1.5 days. After cooling to r.t. the reaction mixture was washed with $NaHCO_3$ (aqueous sat. solution), then extracted with DCM. The organic layer was separated, dried (Na_2SO_4) evaporated to dryness. The crude product was purified by column chromatography (silica gel; DCM to heptane/DCM from 100/0 to 30/70 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D53** (1.05 g, 69 %).

Description 54

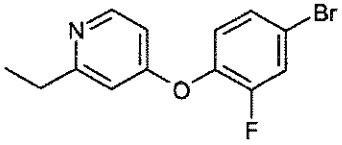
2-Cyclopropyl-4-[2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-pyridine **(D54)**



To a solution of intermediate compound **D53** (1.02 g, 3.31 mmol) in 1,4-dioxane (20 ml) were added bis(pinacolato)diboron (1.345 g, 5.296 mmol) and potassium acetate (0.975 g, 9.93 mmol). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (0.146 g, 0.199 mmol) was added. The reaction mixture was heated at 95 °C overnight. After cooling to r.t., the reaction mixture was filtered through diatomaceous earth and washed with DCM. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent: Heptane/EtOAc up to 5% as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate compound **D54** (0.930 g, 79 %)

Description 55

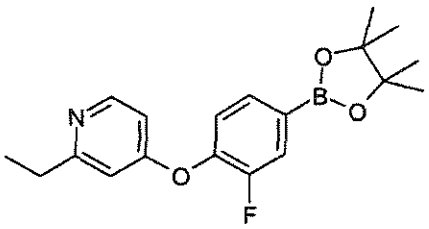
4-(4-Bromo-2-fluoro-phenoxy)-2-ethyl-pyridine **(D55)**



To a solution of 2-fluoro-4-bromophenol (0.576 ml, 5.258 mmol) in DMSO (8 ml) was added K_2CO_3 (1.451 g, 10.516 mmol) and 2-ethyl-4-nitropyridine [CAS. 101860-96-2] (0.800 g, 5.258 mmol). The reaction mixture was heated at 100°C for 2 days. Then the reaction mixture was refilled with 2-fluoro-4-bromophenol (0.115 ml) and heated at 100°C for 6 hours more. After cooling to r.t. the reaction mixture was washed with $NaHCO_3$ (aqueous sat. solution), then extracted with DCM. The organic layer was separated, dried (Na_2SO_4) evaporated to dryness. The crude product was purified by column chromatography (silica gel; DCM to heptane/DCM from 100/0 to 30/70 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D55** (0.985 g, 63 %).

Description 56

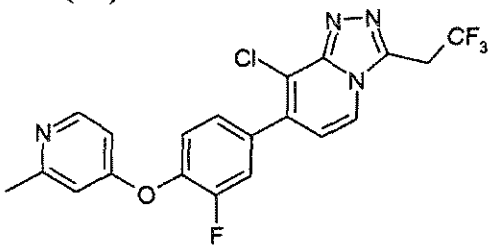
2-Ethyl-4-[2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-pyridine **(D56)**



To a solution of intermediate compound **D55** (0.985 g, 3.326 mmol) in 1,4-dioxane (20 ml) were added bis(pinacolato)diboron (1.267 g, 4.989 mmol) and potassium acetate (0.979 g, 9.97 mmol). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (0.146 g, 0.199 mmol) was added. The reaction mixture was heated at 95 °C overnight. After cooling to r.t., the reaction mixture was filtered through diatomaceous earth and washed with DCM. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent: Heptane/EtOAc up to 10% as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate compound **D56** (1 g, 87 %)

Example 1

7-[3-Fluoro-4-(2'-methyl-pyridin-4-yloxy)-phenyl]-8-chloro-3-(2,2,2-trifluoro-ethyl)-1,2,4-triazolo[4,3-a]pyridine **(E1)**

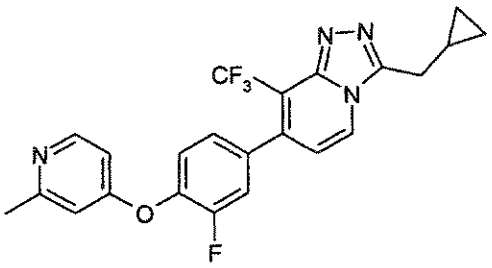


To a mixture of intermediate compound **D11** (0.2 g, 0.553 mmol) in 1,4-dioxane (3.5 ml) under a nitrogen atmosphere were added compound **D26** (0.267 g, 0.609 mmol), $Pd(PPh_3)_4$ (0.032 g, 0.0277 mmol) and $NaHCO_3$ (1.5 ml, aqueous sat. solution). The reaction mixture was subjected to microwave heating at 150 °C for 10 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with 1,4-dioxane. The filtrate was concentrated *in vacuo* and 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*. The residue thus obtained was triturated with Et_2O to yield final compound **E1** (0.029 g, 12%).

Example 2

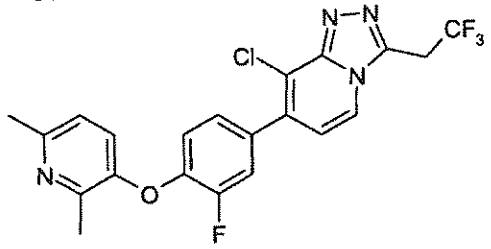
7-[3-Fluoro-4-(2'-methyl-pyridin-4-yloxy)-phenyl]-8-trifluoromethyl-3-cyclopropylmethyl-1,2,4-triazolo[4,3-a]pyridine (**E2**)



To a mixture of intermediate compound **D17** (0.025 g, 0.0903 mmol) in 1,4-dioxane (1 ml) under a nitrogen atmosphere were added compound **D26** (0.037 g, 0.113 mmol), $Pd(PPh_3)_4$ (0.010 g, 0.0091 mmol) and $NaHCO_3$ (0.25 ml, aqueous sat. solution). The reaction mixture was subjected to microwave heating at 150 °C for 7 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with 1,4-dioxane. The filtrate was concentrated *in vacuo* and 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* to yield final compound **E2** (0.015 g, 37%).

Example 3

7-[3-Fluoro-4-(2',6'-dimethyl-pyridin-3-yloxy)-phenyl]-8-chloro-3-(2,2,2-trifluoro-ethyl)-1,2,4-triazolo[4,3-a]pyridine (**E3**)

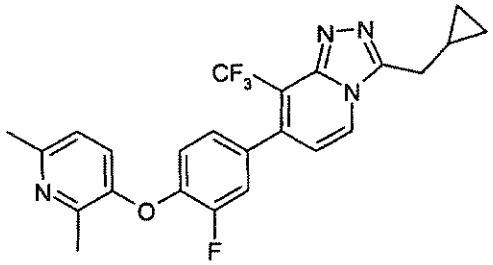


To a mixture of intermediate compound **D11** (0.2 g, 0.553 mmol) in 1,4-dioxane (3.5 ml) under a nitrogen atmosphere were added compound **D24** (0.228 g, 0.664 mmol), $Pd(PPh_3)_4$ (0.032 g, 0.0277 mmol) and $NaHCO_3$ (1.5 ml, aqueous sat. solution). The reaction mixture was subjected to microwave heating at 150 °C for 10 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with 1,4-dioxane. The filtrate was concentrated *in vacuo* and the residue was purified by

column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 2.5% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was triturated with DIPE to yield final compound **E3** (0.032 g, 12.8%).

Example 4

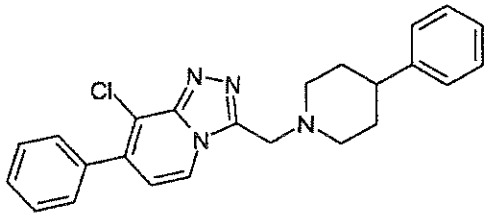
7-[3-Fluoro-4-(2',6'-dimethyl-pyridin-3-yloxy]-8-trifluoromethyl-3-cyclopropylmethyl-1,2,4-triazolo[4,3-a]pyridine **(E4)**



To a mixture of intermediate compound **D17** (0.050 g, 0.181 mmol) in 1,4-dioxane (2 ml) under a nitrogen atmosphere were added compound **D24** (0.78 g, 0.227 mmol), $Pd(PPh_3)_4$ (0.021 g, 0.0181 mmol) and $NaHCO_3$ (0.5 ml, aqueous sat. solution). The reaction mixture was subjected to microwave heating at 150 °C for 7 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with 1,4-dioxane. The filtrate was concentrated *in vacuo* and 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 thus obtained was triturated with *n*-heptane to yield final compound **E4** (0.070 g, 85%).

Example 5

3-(4-phenylpiperidinyl)methyl-8-chloro-7-phenyl)-1,2,4-triazolo[4,3-a]pyridine **(E5)**;

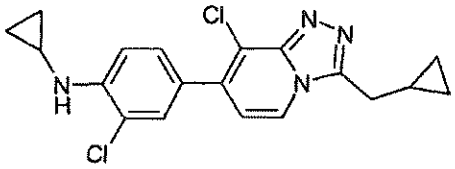


To a solution of intermediate compound **D20** (0.125 g, 0.544 mmol) in acetic acid (2 ml) was added 4-phenylpiperidine (0.158 g, 0.98 mmol) and formaldehyde (0.502 ml, 2.231 mmol; 37%). The resulting mixture was heated in a sealed tube at 80 °C for 3 days. The reaction mixture was diluted with DCM and 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 10% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield final compound **E5** (0.152 g, 69%).

Example 6

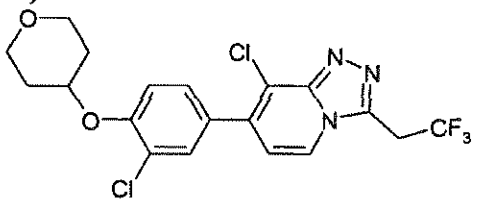
7-(3-Chloro-4-cyclopropylamino-phenyl)-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridine (**E6**)



To a mixture of intermediate compound **D9** (0.3 g, 0.899 mmol) in 1,4-dioxane (4 ml) under a nitrogen atmosphere were added compound **D35** (0.317 g, 1.079 mmol), $Pd(PPh_3)_4$ (0.052 g, 0.045 mmol) and $NaHCO_3$ (1 ml, aqueous sat. solution). The reaction mixture was heated at 90 °C for 16 h. After cooling, an additional amount of $Pd(PPh_3)_4$ (0.052 g, 0.045 mmol) was added to the reaction mixture, which was then heated at 90 °C for 16 h. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with dioxane. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 2% as eluent) followed by HPLC chromatography on (C18 Xbridge 30 x 100 5 µm; mobile phase, gradient from 80% 0.1% $NH_4CO_2CH_3$ solution in water, 20% MeOH to 0% 0.1 $NH_4CO_2CH_3$ solution in water, 100% MeOH). The desired fractions were collected and concentrated *in vacuo* to yield final compound **E6** (0.161 g, 48%)

Example 7

7-(3-Chloro-4-pyranyl-4-oxy-phenyl)-8-chloro-3-(2,2,2-trifluoro-ethyl)-1,2,4-triazolo[4,3-a]pyridine (**E7**)

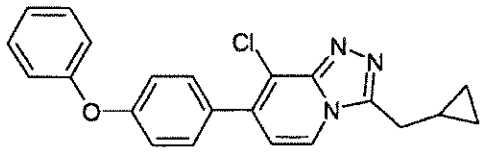


A solution of intermediate compound **D31** (0.2 g, 0.431 mmol) and phosphorous (V) oxychloride (0.080 ml, 0.862 mmol) in CH_3CN (2 ml) was heated under microwave irradiation at 150 °C for 5 min. After cooling, $NaHCO_3$ (aqueous sat. solution) was added. The resulting mixture was extrated with EtOAc. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/AcOEt up to 60% as eluent). The desired

fractions were collected and concentrated *in vacuo* to yield final compound **E7** (0.125 g, 65%) as a white solid.

Example 8

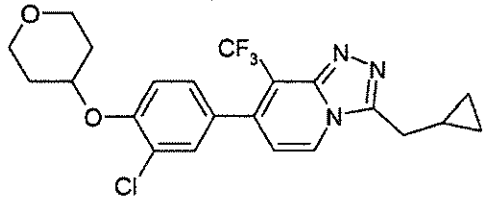
8-Chloro-3-cyclopropylmethyl-7-(4-phenoxy-phenyl)-1,2,4-triazolo[4,3-a]pyridine **(E8)**



Intermediate compound **D37** (0.1 g, 0.321 mmol), cyclopropyl-acetic acid (0.0321 g, 0.321 mmol), diisopropylethylamine (0.112 ml, 0.641 mmol), polymer-supported triphenylphosphine (0.448 g, 0.962 mmol, 2.15 mmol/g) and trichloroacetonitrile (0.0643 ml, 0.641 mmol) in DCM (3 ml) were heated under microwave irradiation at 150 °C for 18 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with DCM and MeOH. The filtrate was washed with water. 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/ EtOAc up to 20% as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was triturated with diethyl ether yielding final compound **E8** (0.054 g, 45%).

Example 9

8-Trifluoromethyl-7-[3-chloro-4-(tetrahydro-pyran-4-yloxy)-phenyl]-3-cyclopropylmethyl-[1,2,4]triazolo[4,3-a]pyridine **(E9)**

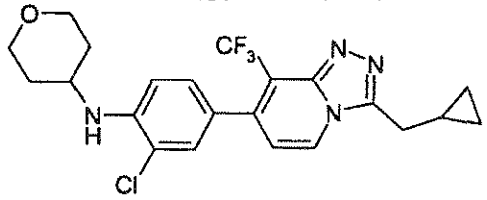


To a mixture of intermediate compound **D17** (0.09 g, 0.326 mmol) in 1,4-dioxane (3 ml) under a nitrogen atmosphere were added intermediate compound **D28** (0.138 g, 0.408 mmol), $Pd(PPh_3)_4$ (0.038 g, 0.033 mmol) and $NaHCO_3$ (0.75 ml, aqueous sat. solution). The reaction mixture was heated under microwave irradiation at 150 °C for 7 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with EtOAc. The filtrate was concentrated *in vacuo* and 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* to yield final compound **E9** (0.083 g, 56%).

Example 10

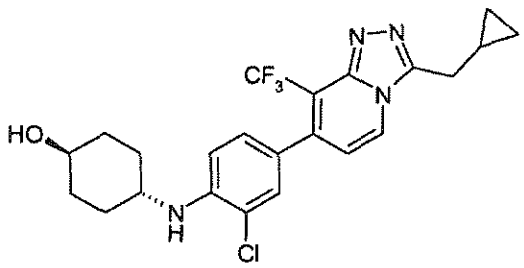
8-Trifluoromethyl-7-[3-chloro-4-(tetrahydro-pyran-4-ylamino)-phenyl]-3-cyclopropylmethyl-[1,2,4]triazolo[4,3-a]pyridine (**E10**)



To a mixture of intermediate compound **D17** (0.07 g, 0.254 mmol) in 1,4-dioxane (3 ml) under a nitrogen atmosphere were added intermediate compound **D33** (0.107 g, 0.317 mmol), $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol) and $NaHCO_3$ (0.75 ml, aqueous sat. solution). The reaction mixture was heated under microwave irradiation at 150 °C for 7 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with EtOAc. The filtrate was concentrated *in vacuo* and 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* to yield final compound **E10** (0.045 g, 39%).

Example 11

8-Trifluoromethyl-7-[3-chloro-4-(4-hydroxy-cyclohexylamino)-phenyl]-3-cyclopropylmethyl-[1,2,4]triazolo[4,3-a]pyridine (**E11**, *trans*)

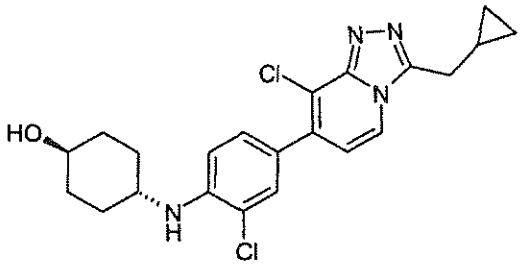


To a mixture of intermediate compound **D17** (0.07 g, 0.254 mmol) in 1,4-dioxane (3 ml) under a nitrogen atmosphere were added intermediate compound **D44** (0.086 g, 0.317 mmol), $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol) and $NaHCO_3$ (0.75 ml, aqueous sat. solution). The reaction mixture was heated under microwave irradiation at 150 °C for 7 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with EtOAc. The filtrate was concentrated *in vacuo* and the residue was

purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 3% as eluent) followed by HPLC chromatography on (C18 Xbridge 30 x 100 5 µm; mobile phase, gradient from 80% 0.1% NH_4CO_3H/NH_4OH pH 9 solution in water, 20% CH_3CN to 0% 0.1 NH_4CO_3H/NH_4OH pH 9 solution in water, 100% CH_3CN). The desired fractions were collected and concentrated *in vacuo* to yield final compound **E11** (0.058 g, 49%).

Example 12

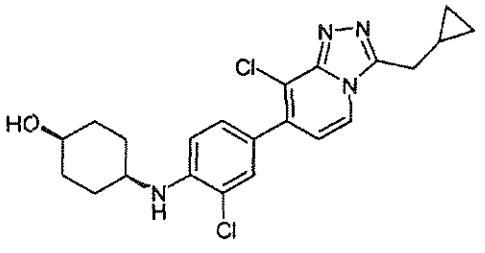
8-Cloro-7-[3-chloro-4-(4-hydroxy-cyclohexylamino)-phenyl]-3-cyclopropylmethyl-[1,2,4]triazolo[4,3-a]pyridine (**E12**, *trans*)



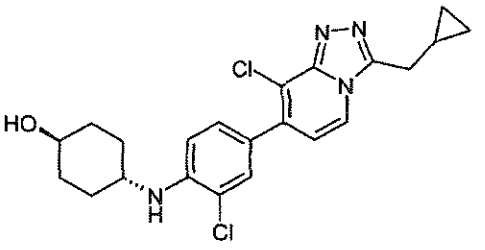
To a mixture of intermediate compound **D9** (0.129 g, 0.388 mmol) in 1,4-dioxane (3.5 ml) under a nitrogen atmosphere were added intermediate compound **D44** (0.15 g, 0.427 mmol), $Pd(PPh_3)_4$ (0.0224 g, 0.0194 mmol) and $NaHCO_3$ (1.5 ml, aqueous sat. solution). The reaction mixture was heated under microwave irradiation at 150 °C for 10 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with 1,4-dioxane. The filtrate was concentrated *in vacuo* and 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 final compound **E12** (0.06 g, 36%).

Examples 13-a (*cis*) and 13-b (*trans*)

7-[3-Chloro-4-(4-hydroxy-cyclohexylamino)-phenyl]-8-chloro-3-cyclopropylmethyl-[1,2,4]triazolo[4,3-a]pyridine. (**E13-a** (*cis*) and **E13-b** (*trans*))



E13-a
cis

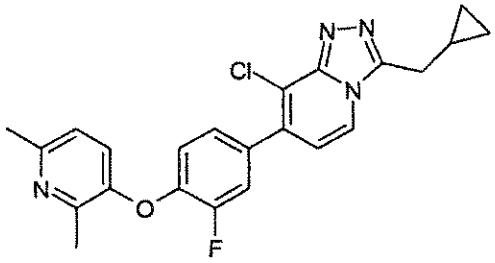


E13-b
trans

To a mixture of intermediate compound **D41** (0.389 g, 0.906 mmol) in MeOH (8 ml) stirred at r.t. was added sodium borohydride (0.0377 mg, 0.997 mmol) and the mixture was stirred for 16 h. $NaHCO_3$ (aqueous sat. solution) was then added and the resulting mixture was extracted with DCM. 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 0.03% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield final compound **E13-a** *(cis)* (0.04 g, 10 %) and final compound **E13-b** *(trans)* (0.07 g, 18%).

Example 14

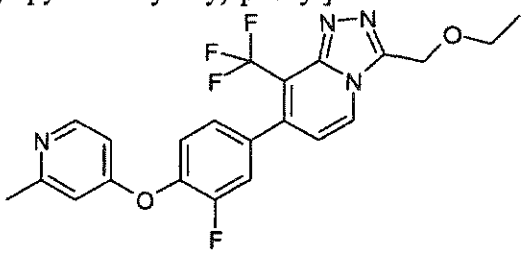
8-Chloro-3-cyclopropylmethyl-7-{4-[(2,6-dimethylpyridin-3-yl)oxy]-3-fluorophenyl}[1,2,4]triazolo[4,3-a]pyridine (**E14**)



To a mixture of intermediate compound **D9** (1.7 g, 5.097 mmol) in 1,4-dioxane (36 ml) under a nitrogen atmosphere were added intermediate compound **D24** (2.099 g, 6.116 mmol), $Pd(PPh_3)_4$ (0.589 g, 0.51 mmol) and $NaHCO_3$ (18 ml, aqueous sat. solution). The reaction mixture heated at 150 °C for 7 min under microwave irradiation. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with EtOAc. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; DCM/EtOAc/MeOH mixtures as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was triturated with DIPE to yield final compound **E14** (1.3 g, 60%).

Example 36

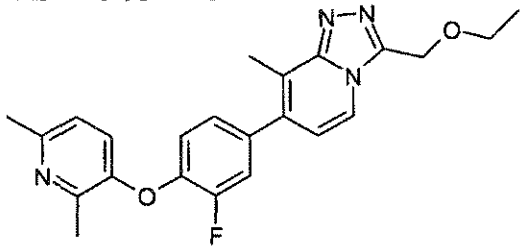
3-Ethoxymethyl-7-[3-fluoro-4-(2-methyl-pyridin-4-yloxy)-phenyl]-8-trifluoromethyl-[1,2,4]triazolo[4,3-a]pyridine (**E36**)



To a mixture of intermediate compound **D50** (0.190 g, 0.679 mmol) in 1,4-dioxane (6 ml) under a nitrogen atmosphere were added intermediate compound **D26** (0.268 g, 0.815 mmol), $Pd(PPh_3)_4$ (0.078 g, 0.0679 mmol) and $NaHCO_3$ (1.5 ml, aqueous sat. solution). The reaction mixture was heated at 150 °C for 10 min under microwave irradiation. After cooling, the mixture was washed with $NaHCO_3$ (aqueous sat solution). The organic layer was separated and dried (Na_2SO_4). The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; DCM/EtOAc/7M solution of NH_3 in MeOH) mixtures as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained washed with DIPE to yield final compound **E36** (0.23 g, 75%) as a white solid.

Example 42

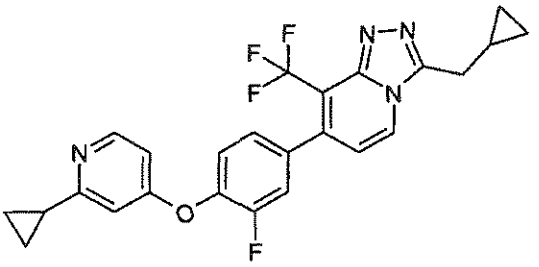
8-Methyl-3-ethoxymethyl-7-{3-fluoro-4-[(2,6-dimethylpyridin-3-yl)oxy]phenyl}[1,2,4]triazolo[4,3-a]pyridine **(E42)**



To a mixture of intermediate compound **D48** (0.100 g, 0.443 mmol) in 1,4-dioxane (2 ml) under a nitrogen atmosphere were added intermediate compound **D24** (0.197 g, 0.576 mmol), $Pd(PPh_3)_4$ (0.051 g, 0.044 mmol) and $NaHCO_3$ (1 ml, aqueous sat. solution). The reaction mixture was heated at 150 °C for 10 min under microwave irradiation. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with EtOAc. The filtrate was concentrated *in vacuo* and 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*. The residue thus obtained was triturated with DIPE to yield final compound **E42** (0.12 g, 66%) as a white solid.

Example 46

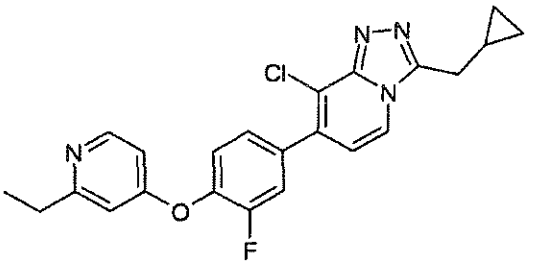
3-Cyclopropylmethyl-7-[4-(2-cyclopropyl-pyridin-4-yloxy)-3-fluoro-phenyl]-8-trifluoromethyl-[1,2,4]triazolo[4,3-a]pyridine **(E46)**



To a mixture of intermediate compound **D17** (0.380 g, 1.379 mmol) in 1,4-dioxane (5 ml) under a nitrogen atmosphere were added intermediate compound **D54** (0.538 g, 1.516 mmol), $Pd(PPh_3)_4$ (0.079 g, 0.068 mmol) and $NaHCO_3$ (2 ml, aqueous sat. solution). The reaction mixture was heated at 150 °C under microwave irradiation for 10 min. After cooling to r.t., the reaction mixture was refilled with $Pd(PPh_3)_4$ (0.040 g) and $NaHCO_3$ (1 ml, aqueous sat. solution) and irradiated at 150°C for 8 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with DCM and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH up to 4% 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 **E46** (0.390 g, 60% as a white solid.

Example 48

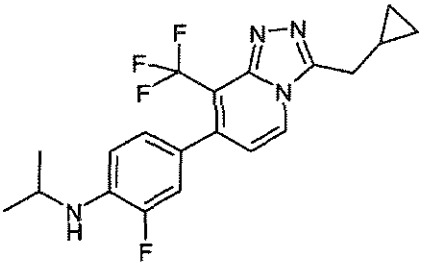
3-Cyclopropylmethyl-7-[4-(2-ethyl-pyridin-4-yloxy)-3-fluoro-phenyl]-8-chloro-[1,2,4]triazolo[4,3-a]pyridine (**E48**)



To a mixture of intermediate compound **D9** (0.26 g, 0.779 mmol) in 1,4-dioxane (5 ml) under a nitrogen atmosphere were added intermediate compound **D56** (0.294 g, 0.857 mmol), $Pd(PPh_3)_4$ (0.045 g, 0.039 mmol) and $NaHCO_3$ (2 ml, aqueous sat. solution). The reaction mixture 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 concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH up to 4% 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 **E48** (0.316 g, 95%) as a white solid.

Example 49

3-Cyclopropylmethyl-7-[3-fluoro-4-(isopropylamino)-phenyl]-8-trifluoromethyl-



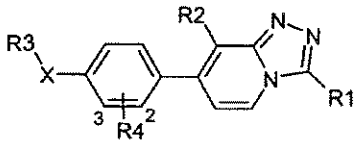
[1,2,4]triazolo[4,3-a]pyridine (**E49**)

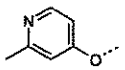
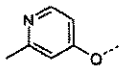
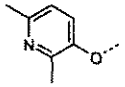
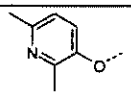
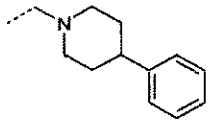
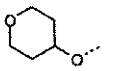
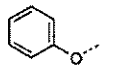
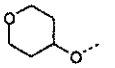
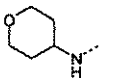
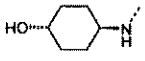
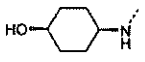
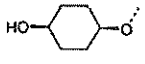
To a mixture of intermediate compound **D17** (0.350 g, 1.27 mmol) in 1,4-dioxane (2 ml) under a nitrogen atmosphere were added intermediate compound **D51** (0.460 g, 1.651 mmol), $Pd(PPh_3)_4$ (0.073 g, 0.0635 mmol) and $NaHCO_3$ (2 ml, aqueous sat. solution). The reaction mixture was heated at 150 °C for 30 min under microwave irradiation. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with EtOAc. The organic layer was washed with $NaHCO_3$ (aqueous sat. solution). 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 70/30 as eluent). The desired fractions were collected and concentrated *in vacuo*. The residue thus obtained was triturated with Et_2O to yield final compound **E49** (0.25 g, 50%) as a white solid.

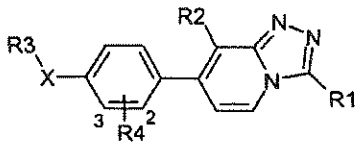
Tables 1a and 1b below list compounds of Formula (I), which were prepared according to the above examples.

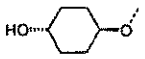
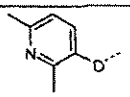
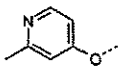
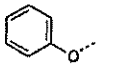
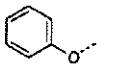
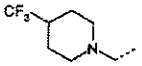
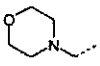
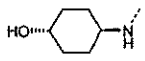
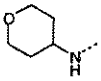
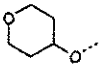
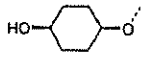
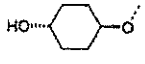
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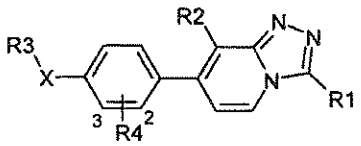
* means exemplified procedure according to which additional compounds were prepared

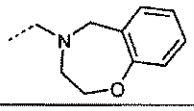
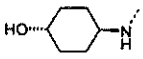
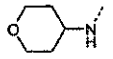
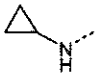
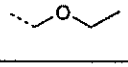
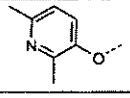
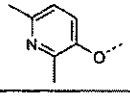
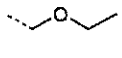
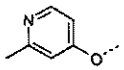
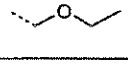
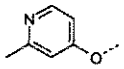
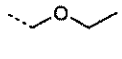
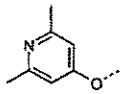
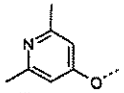
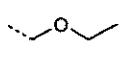
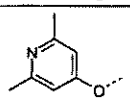
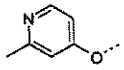
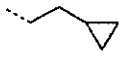
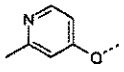
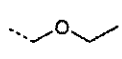
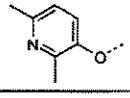


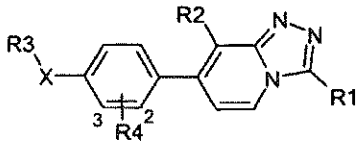
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4	E4*		--CF_3		3-F
5	E5*		--Cl	H	H
6	E6*		--Cl		3-Cl
7	E7*	--CH_2-CF_3	--Cl		3-Cl
8	E8*		--Cl		H
9	E9*		--CF_3		3-Cl
10	E10*		--CF_3		3-Cl
11	E11*		--CF_3		3-Cl
12	E12*		--Cl		3-Cl
13-a	E13*		--CF_3		3-Cl

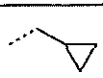
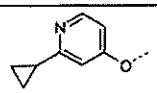
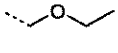
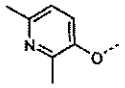
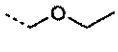
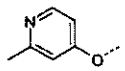
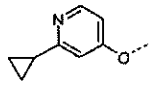
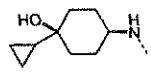
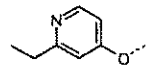
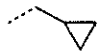
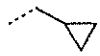
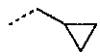
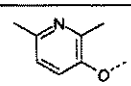
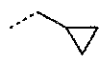
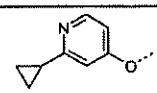
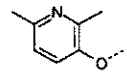
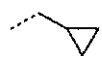
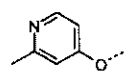
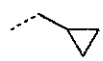
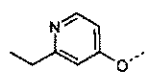


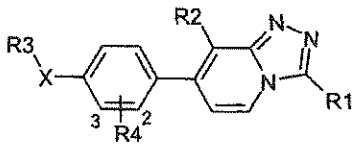
Co.nr.	Exp nr.	R^1	R^2	R^3-X	R^4
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14	E14		--Cl		3-F
15	E15		--Cl		3-F
16	E8	--CH_2-CF_3	--Cl		H
17	E8		--Cl		H
18	E1		--Cl		H
19	E1		--Cl		H
20	E1		--Cl		H
21	E13		--Cl		3-Cl
22	E1		--Cl		3-Cl
23	E1		--Cl		3-Cl
24	E1		--CF_3		3-Cl
25	E1		--Cl		3-F
26	E13	--CH_2-CF_3	--Cl		3-Cl
27	E13	--CH_2-CF_3	--Cl		3-Cl

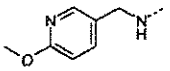
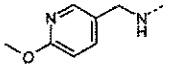
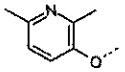
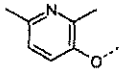
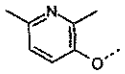
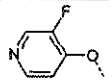
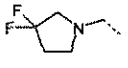
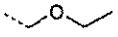
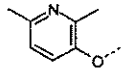
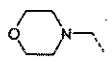
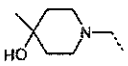
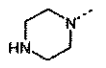
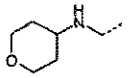
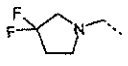
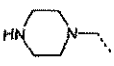
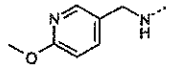


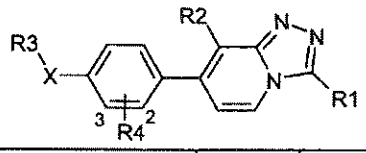
Co.nr.	Exp nr.	R^1	R^2	R^3-X	R^4
28	E5		--Cl	H	H
29	E13	--CH_2-CF_3	--Cl		3-Cl
30	E1	--CH_2-CF_3	--Cl		3-Cl
31	E1		--CF_3		3-Cl
32	E6		--CF_3		3-F
33	E1		--Cl		3-F
34	E4		--Cl		3-Cl
35	E1		--Cl		3-Cl
36	E2		--CF_3		3-F
37	E2		--CF_3		3-F
38	E4		--CF_3		3-F
39	E1		--Cl		3-F
40	E1	--CH_2-CF_3	--Cl		3-Cl
41	E8		--Cl		3-F
42	E2		--CH_3		3-F

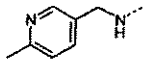
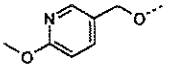
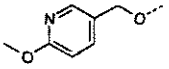
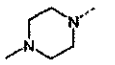


Co.nr.	Exp nr.	R^1	R^2	R^3-X	R^4
43	E8		--Cl		3-F
44	E2		--CF_3		3-F
45	E2		--CF_3		3-Cl
46	E4		--CF_3		3-F
47	E11		--CF_3		3-Cl
48	E8		--Cl		3-F
49	E10		--CF_3		3-F
50	E6		--Cl		3-F
51	E6		--Cl		3-Cl
52	E10		--CF_3		3-Cl
53	E4		--CF_3		3-Cl
54	E4		--CF_3		3-Cl
55	E1	--CH_2-CF_3	--Cl		3-Cl
56	E4		--CF_3		3-Cl
57	E4		--CF_3		3-F



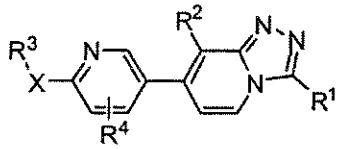
Co.nr.	Exp nr.	R^1	R^2	R^3-X	R^4
58	E10		--CF_3		H
59	E10		--Cl		H
60	E4		--CH_3		3-F
61	E4		--CH_3		3-Cl
62	E4				3-F
63	E4		--CF_3		H
64‡	E1		--CF_3		H
65	E1		--CH_3		3-Cl
71	E1		--CF_3		3-Cl
72	E1		--CF_3		3-Cl
73	E1		--CF_3		3-Cl
74	E1		--CF_3		3-Cl
75	E1		--CF_3		3-Cl
76	E1		--CF_3		3-Cl
77	E1		--CF_3		3-F



Co.nr.	Exp nr.	R^1	R^2	R^3-X	R^4
78	E1		--CF_3		3-F
79	E1		--CF_3		3-F
80	E1		--CF_3		H
81	E1		--CF_3		3-Cl

‡ means hydrochloride salt (.HCl).

Table 1b : Compounds prepared according to Formula (I).



Co. nr.	Exp. nr.	R^1	R^2	R^3-X	R^4
66	E10		--Cl		H
67	E1		--Cl		H
68	E1		--CF_3		H
69	E1		--Cl		H
70	E1		--CF_3		H

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.

LCMS

General procedure for Waters MS instruments

The HPLC measurement was performed using a HP 1100 from Agilent Technologies 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 for Agilent MS instrument

The HPLC measurement was performed using a HP 1100 from Agilent Technologies 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 pressureCI). 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 for Waters MS instruments

The UPLC measurement was performed using an Acquity system from Waters 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 is used without split to the MS detector. The MS detector is 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.

MS Procedure for LC Method 1

HRMS (TOF detector) were acquired only in positive ionization mode or in positive/negative modes by scanning from 100 to 750 umas. The capillary needle

voltage was 2.5 kV for positive mode 2.9Kv 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 1

In addition to the general procedure: 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) 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 2

In addition to the general procedure: 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 (quadrupole, SQD) 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 3

In addition to the general procedure: Reversed phase HPLC was carried out on a 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 (quadrupole, SQD) 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 4

In addition to the general procedure: 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) 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 5

In addition to the general procedure: 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 (quadrupole, SQD) 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: 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 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 7

In addition to the general procedure: Reversed phase UPLC was carried out on a HSS-T3 column (1.8 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 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.

MS Procedure for LC Method 8: LRMS(single quadrupole, SQD detector) were acquired only in positive ionization mode or in positive/negative modes by scanning from 100 to 1000 umas. The capillary needle voltage was 3 kV. For positive ionization mode the cone voltage was 20V, 25V or 20V/50V. For negative ionization mode the cone voltage was 30V.

Method 8

In addition to the general procedure: 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. The gradient conditions used are: 95 % A (0.5 g/l NH_4Acsolution + 5 % CH_3CN), 5 % B (CH_3CN), to 40 % A, 60 % B, then to 5 % A, 95 % B and equilibrated to initial conditions up to 7 and 5 min run; 0.5 or 2µl injection volume.

Table 2. Physico-chemical data for some compounds (nd = not determined).

Co. No.	mp (°C)	$[MH^+]$	R_t (min)	LCMS Method
1	130.1	437	3.99	5
2	n.d.	443	3.79	6
3	164.5	451	3.24	2
4	n.d.	457	3.38	2
5	n.d.	403	4.27	1
6	>300	373	3.8	1
7	186.7	446	3.46	3
8	156.7	376	4.66	4
9	176.9	452	3.33	2

Co. No.	mp (°C)	$[MH^+]$	R_t (min)	LCMS Method
10	198.4	451	3.29	2
11	n.d.	465	4.13	7
12	273.7	431	3.1	2
13a	n.d.	466	3	2
13b	n.d.	466	3.16	2
14	207.2	423	2.85	8
15	>300	409	2.57	8
16	>300	404	4.6	4
17	>300	376	4.7	4

Co. No.	mp (°C)	[MH+]	R_t (min)	LCMS Method
18	n.d.	369	2.7	2
19	n.d.	449	3.9	2
20	n.d.	383	2.6	2
21	270.9	431	3.1	2
22	221.3	417	4.1	1
23	n.d.	418	3.3	2
24	213.6	437	3.2	2
25	n.d.	357	3.3	2
26	196.7	460	3.1	1
27	>300	460	3.2	1
28	n.d.	391	3.6	1
29	>300	459	3.2	1
30	>300	445	3.4	1
31	n.d.	407	3.5	8
32	>300	391	3.18	8
33	180.3	427	2.77	8
34	182.7	439	3.09	8
35	160.6	429	2.7	8
36	171.2	447	2.68	8
37	172.5	462	2.87	8
38	232.5	457	2.94	8
39	167.4	427	2.65	8
40	>300	453	2.81	8
41	n.d.	423	2.83	8
42	144	407	2.78	8
43	>300	435	4.51	1
44	142.2	461	2.89	8

Co. No.	mp (°C)	[MH+]	R_t (min)	LCMS Method
45	171.6	463	2.84	8
46	211.1	469	3.31	8
47	n.d.	505	3.5	8
48	>300	423	2.86	8
49	196.9	393	3.33	8
50	196.5	359	3.11	8
51	n.d.	375	3.46	8
52	230	409	3.71	8
53	>300	473	3.22	8
54	n.d.	485	2.49	8
55	220.7	467	2.25	8
56	>300	459	2.10	8
57	>300	457	2.16	8
58	127.5	454	2.05	8
59	158.1	420	1.93	8
60	147.4	403	2.07	8
61	121	419	2.23	8
62	166.4	429	2.24	8
63	192.5	429	1.92	8
64	186.2	437	2.21	8
65	286.8	423	2.68	8
66	292.8	342	2.16	8
67	>300	370	1.39	8
68	>300	404	1.51	8
69	>300	368	2.10	8
70	>300	402	2.24	8
71	138.1	451	2.54	8

Co. No.	mp (°C)	[MH+]	Rt (min)	LCMS Method
72	150.5	479	2.03	8
73	206	436	1.37	8
74	n.d.	465	2.09	8
75	n.d.	471	3.19	8
76	n.d.	450	1.45	8
77	160.4	472	2.67	8

Co. No.	mp (°C)	[MH+]	Rt (min)	LCMS Method
78	107.3	456	2.32	8
79	148.5	473	2.79	8
80	159.1	455	3.73	3

n.d. means not determined

Nuclear Magnetic Resonance (NMR)

For a number of compounds, ^{1}H NMR spectra were recorded either 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 (400 MHz, $CDCl_3$) δ ppm 2.55 (s, 3 H), 4.13 (q, J=9.7 Hz, 2 H), 6.73 (dd, J=5.5, 2.3 Hz, 1 H), 6.78 (d, J=2.5 Hz, 1 H), 7.02 (d, J=7.2 Hz, 1 H), 7.32 (t, J=8.1 Hz, 1 H), 7.36 - 7.41 (m, 1 H), 7.45 (dd, J=10.9, 2.1 Hz, 1 H), 8.04 (d, J=6.9 Hz, 1 H), 8.42 (d, J=5.5 Hz, 1 H).

Co. No. 2: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.34 - 0.44 (m, 2 H), 0.61 - 0.73 (m, 2 H), 1.18 - 1.29 (m, 1 H), 2.55 (s, 3 H), 3.17 (d, J=6.6 Hz, 2 H), 6.70 (dd, J=5.8, 2.6 Hz, 1 H), 6.76 (d, J=2.3 Hz, 1 H), 6.83 (d, J=7.2 Hz, 1 H), 7.20 (br d, J=8.4 Hz, 1 H), 7.23 - 7.31 (m, 2 H), 8.14 (d, J=7.2 Hz, 1 H), 8.41 (d, J=5.8 Hz, 1 H).

Co. No. 3: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.53 (s, 3 H), 2.55 (s, 3 H), 4.11 (q, J=9.9 Hz, 2 H), 6.93 (t, J=8.3 Hz, 1 H), 6.98 (d, J=7.2 Hz, 1 H), 7.02 (d, J=8.3 Hz, 1 H), 7.16 (d, J=8.3 Hz, 1 H), 7.23 - 7.28 (m, 1 H), 7.42 (dd, J=11.1, 2.1 Hz, 1 H), 8.01 (d, J=7.2 Hz, 1 H).

Co. No. 4: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.31 - 0.43 (m, 2 H), 0.61 - 0.70 (m, 2 H), 1.16 - 1.30 (m, 1 H), 2.53 (s, 3 H), 2.55 (s, 3 H), 3.15 (d, J=6.7 Hz, 2 H), 6.79 (d, J=7.2 Hz, 1 H), 6.89 (t, J=8.3 Hz, 1 H), 7.01 (d, J=8.3 Hz, 1 H), 7.05 (br d, J=8.6 Hz, 1 H), 7.14 (d, J=8.3 Hz, 1 H), 7.22 (dd, J=10.9, 2.1 Hz, 1 H), 8.11 (d, J=7.2 Hz, 1 H).

Co. No. 5: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.73 (qd, J=12.3, 3.5 Hz, 2 H), 1.87 (br d, J=12.0 Hz, 2 H), 2.33 (td, J=11.8, 1.6 Hz, 2 H), 2.57 (tt, J=12.0, 3.7 Hz, 1 H),

2.95 (br d, J=11.6 Hz, 2 H), 4.17 (s, 2 H), 6.91 (d, J=7.2 Hz, 1 H), 7.16 - 7.24 (m, 3 H), 7.27 - 7.34 (m, 2 H), 7.43 - 7.61 (m, 5 H), 8.48 (d, J=6.9 Hz, 1 H).

Co. No. 6: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.29 - 0.42 (m, 2 H), 0.57 - 0.70 (m, 4 H), 0.78 - 0.92 (m, 2 H), 1.15 - 1.27 (m, 1 H), 2.49 - 2.56 (m, 1 H), 3.11 (d, J=6.7 Hz, 2 H), 4.94 (br.s, 1 H), 6.87 (d, J=6.9 Hz, 1 H), 7.18 (d, J=8.3 Hz, 1 H), 7.42 (dd, J=8.3, 2.1 Hz, 1 H), 7.47 (d, J=1.8 Hz, 1 H), 7.92 (d, J=7.2 Hz, 1 H)

Co. No. 7: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.87 - 1.97 (m, 2 H), 2.02 - 2.13 (m, 2 H), 3.61 - 3.70 (m, 2 H), 4.01 - 4.07 (m, 2 H), 4.11 (q, J=9.7 Hz, 2 H), 4.63 - 4.71 (m, 1 H), 6.98 (d, J=7.2 Hz, 1 H), 7.07 (d, J=8.6 Hz, 1 H), 7.43 (dd, J=8.6, 2.3 Hz, 1 H), 7.59 (d, J=2.3 Hz, 1 H), 8.00 (d, J=7.2 Hz, 1 H).

Co. No. 8: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.31 - 0.42 (m, 2 H), 0.58 - 0.70 (m, 2 H), 1.17 - 1.27 (m, 1 H), 3.12 (d, J=6.6 Hz, 2 H), 6.90 (d, J=7.2 Hz, 1 H), 7.08 - 7.14 (m, 4 H), 7.16 - 7.21 (m, 1 H), 7.37 - 7.43 (m, 2 H), 7.48 - 7.55 (m, 2 H), 7.96 (d, J=7.2 Hz, 1 H).

Co. No. 9: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.30 - 0.43 (m, 2 H), 0.58 - 0.73 (m, 2 H), 1.16 - 1.28 (m, 1 H), 1.86 - 1.97 (m, 2 H), 2.02 - 2.12 (m, 2 H), 3.14 (d, J=6.7 Hz, 2 H), 3.59 - 3.69 (m, 2 H), 4.00 - 4.09 (m, 2 H), 4.61 - 4.68 (m, 1 H), 6.78 (d, J=7.2 Hz, 1 H), 7.02 (d, J=8.6 Hz, 1 H), 7.20 (dd, J=8.6, 2.1 Hz, 1 H), 7.41 (d, J=2.1 Hz, 1 H), 8.09 (d, J=7.2 Hz, 1 H).

Co. No. 10: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.31 - 0.42 (m, 2 H), 0.58 - 0.71 (m, 2 H), 1.16 - 1.27 (m, 1 H), 1.55 - 1.68 (m, 2 H), 2.09 (br d, J=12.7 Hz, 2 H), 3.13 (d, J=6.7 Hz, 2 H), 3.56 (td, J=11.8, 2.3 Hz, 2 H), 3.56 - 3.67 (m, 1 H), 4.05 (dt, J=11.7, 3.7 Hz, 2 H), 4.47 (d, J=7.6 Hz, 1 H), 6.74 (d, J=8.6 Hz, 1 H), 6.78 (d, J=7.2 Hz, 1 H), 7.16 (dd, J=8.3, 1.8 Hz, 1 H), 7.32 (d, J=2.1 Hz, 1 H), 8.05 (d, J=7.2 Hz, 1 H).

Co. No. 11: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.30 - 0.43 (m, 2 H), 0.58 - 0.71 (m, 2 H), 1.16 - 1.25 (m, 1 H), 1.29 - 1.42 (m, 2 H), 1.42 - 1.53 (m, 3 H), 2.03 - 2.12 (m, 2 H), 2.20 (br d, J=12.0 Hz, 2 H), 3.13 (d, J=6.7 Hz, 2 H), 3.32 - 3.43 (m, 1 H), 3.70 - 3.80 (m, 1 H), 4.39 (d, J=7.6 Hz, 1 H), 6.72 (d, J=8.6 Hz, 1 H), 6.79 (d, J=7.2 Hz, 1 H), 7.16 (dd, J=8.6, 2.1 Hz, 1 H), 7.30 (d, J=2.1 Hz, 1 H), 8.04 (d, J=7.2 Hz, 1 H).

Co. No. 12: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.29 - 0.42 (m, 2 H), 0.56 - 0.71 (m, 2 H), 1.17 - 1.25 (m, 1 H), 1.47 (br. s., 1 H), 1.73 - 1.80 (m, 4 H), 1.80 - 1.91 (m, 4 H), 3.11 (d, J=6.7 Hz, 2 H), 3.46 - 3.57 (m, 1 H), 3.98 (br. s., 1 H), 4.60 (br d, J=7.6 Hz, 1 H), 6.76 (d, J=8.8 Hz, 1 H), 6.87 (d, J=7.2 Hz, 1 H), 7.39 (dd, J=8.3, 2.3 Hz, 1 H), 7.49 (d, J=2.1 Hz, 1 H), 7.91 (d, J=7.2 Hz, 1 H).

Co. No. 13-a *(cis)*: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.30 - 0.43 (m, 2 H), 0.59 - 0.72 (m, 2 H), 1.16 - 1.27 (m, 1 H), 1.45 (d, J=4.4 Hz, 1 H), 1.67 - 1.77 (m, 2 H), 1.77 - 1.92 (m, 4 H), 2.07 - 2.18 (m, 2 H), 3.14 (d, J=6.7 Hz, 2 H), 3.76 - 3.86 (m, 1 H), 4.51 -

4.57 (m, 1 H), 6.78 (d, J=7.2 Hz, 1 H), 7.01 (d, J=8.6 Hz, 1 H), 7.19 (dd, J=8.6, 2.3 Hz, 1 H), 7.40 (d, J=2.1 Hz, 1 H), 8.08 (d, J=7.2 Hz, 1 H).

Co. No. 13-b *(trans)*: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.30 - 0.43 (m, 2 H), 0.59 - 0.72 (m, 2 H), 1.15 - 1.29 (m, 1 H), 1.44 - 1.56 (m, 2 H), 1.61 (br. s., 1 H), 1.67 - 1.79 (m, 2 H), 2.05 - 2.22 (m, 4 H), 3.14 (d, J=6.7 Hz, 2 H), 3.86 - 3.95 (m, 1 H), 4.39 - 4.48 (m, 1 H), 6.78 (d, J=7.2 Hz, 1 H), 7.02 (d, J=8.8 Hz, 1 H), 7.20 (dd, J=8.6, 2.3 Hz, 1 H), 7.39 (d, J=2.3 Hz, 1 H), 8.09 (d, J=7.2 Hz, 1 H).

Co. No. 14: ^{1}H NMR (500 MHz, $CDCL_3$) δ ppm 0.32 - 0.42 (m, 2 H), 0.61 - 0.69 (m, 2 H), 1.17 - 1.28 (m, 1 H), 2.54 (s, 3 H), 2.55 (s, 3 H), 3.13 (d, *J*=6.9 Hz, 2 H), 6.87 (d, *J*=6.9 Hz, 1 H), 6.92 (t, *J*=8.4 Hz, 1 H), 7.02 (d, *J*=8.4 Hz, 1 H), 7.16 (d, *J*=8.4 Hz, 1 H), 7.25 (d, *J*=9.2 Hz, 1 H), 7.41 (dd, *J*=11.3, 1.7 Hz, 1 H), 7.98 (d, *J*=6.9 Hz, 1 H).

Co. No. 36: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.24 (t, *J*=6.9 Hz, 3 H), 2.55 (s, 3 H), 3.61 (q, *J*=6.9 Hz, 2 H), 5.14 (s, 2 H), 6.70 (dd, *J*=5.5, 2.3 Hz, 1 H), 6.76 (d, *J*=2.3 Hz, 1 H), 6.85 (d, *J*=7.2 Hz, 1 H), 7.08 - 7.23 (m, 1 H), 7.23 - 7.34 (m, 2 H), 8.41 (d, *J*=5.8 Hz, 1 H), 8.43 (d, *J*=6.9 Hz, 1 H).

Co. No. 42: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.22 (t, *J*=6.9 Hz, 3 H), 2.55 (s, 6 H), 2.65 (s, 3 H), 3.57 (q, *J*=6.9 Hz, 2 H), 5.08 (s, 2 H), 6.82 (d, *J*=7.2 Hz, 1 H), 6.93 (t, *J*=8.3 Hz, 1 H), 7.01 (d, *J*=8.1 Hz, 1 H), 7.08 (dt, *J*=8.4, 1.0 Hz, 1 H), 7.14 (d, *J*=8.3 Hz, 1 H), 7.23 (dd, *J*=11.2, 2.0 Hz, 1 H), 8.15 (d, *J*=7.2 Hz, 1 H).

Co. No. 46: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.32 - 0.45 (m, 2 H), 0.53 - 0.75 (m, 2 H), 0.96 - 1.03 (m, 2 H), 1.02 - 1.08 (m, 2 H), 1.16 - 1.30 (m, 1 H), 1.91 - 2.03 (m, 1 H), 3.16 (d, *J*=6.7 Hz, 2 H), 6.63 (dd, *J*=5.8, 2.3 Hz, 1 H), 6.75 (d, *J*=2.3 Hz, 1 H), 6.83 (d, *J*=7.2 Hz, 1 H), 7.15 - 7.22 (m, 1 H), 7.22 - 7.31 (m, 2 H), 8.15 (d, *J*=6.9 Hz, 1 H), 8.35 (d, *J*=5.5 Hz, 1 H).

Co. No. 48: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.31 - 0.43 (m, 2 H), 0.60 - 0.72 (m, 2 H), 1.15 - 1.29 (m, 1 H), 1.31 (t, *J*=7.7 Hz, 3 H), 2.82 (q, *J*=7.6 Hz, 2 H), 3.14 (d, *J*=6.6 Hz, 2 H), 6.72 (dd, *J*=5.8, 2.3 Hz, 1 H), 6.81 (d, *J*=2.3 Hz, 1 H), 6.91 (d, *J*=6.9 Hz, 1 H), 7.31 (t, *J*=8.2 Hz, 1 H), 7.35 - 7.42 (m, 1 H), 7.45 (dd, *J*=10.7, 2.0 Hz, 1 H), 8.01 (d, *J*=6.9 Hz, 1 H), 8.44 (d, *J*=5.8 Hz, 1 H).

Co. No. 49: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.28 - 0.42 (m, 2 H), 0.57 - 0.71 (m, 2 H), 1.12 - 1.26 (m, 1 H), 1.29 (d, *J*=6.4 Hz, 6 H), 3.12 (d, *J*=6.6 Hz, 2 H), 3.64 - 3.77 (m, 1 H), 3.96 (d, *J*=4.9 Hz, 1 H), 6.74 (t, *J*=8.4 Hz, 1 H), 6.80 (d, *J*=7.2 Hz, 1 H), 7.02 (d, *J*=10.1 Hz, 2 H), 8.04 (d, *J*=6.9 Hz, 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), are 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 mM Tris-HCl, pH 7.4 and stored

at –80 °C in appropriate aliquots before use. Protein concentration was determined by the Bradford method (Bio-Rad, USA) with bovine serum albumin as standard.

[^{35}S]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

–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 4 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). The results are shown in table 4 below.

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 4 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.

<u>Sleep Wake Electroencephalography (SW-EEG) in rats</u>

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 agonist LY404039 was also evaluated to allow comparison.

A selection of compounds was found to dose-dependently decrease REM sleep (lowest active dose was 10 mg/kg, p.o.); compound LY404039 was found to affect REM sleep (3 mg/kg, p.o.) qualitatively in a comparable way.

Table 3. Pharmacological data for compounds according to the invention.

Co. No.	GTPγS - hR2 PAM pEC_{50}
1	6.68
2	7.30
3	7.34
4	7.99
5	6.72
6	7.44
7	6.76
8	7.42
9	7.39
10	7.77
11	8.01
12	7.38
13-a	7.64
13-b	n.t.
14	7.37
15	6.65
16	7.34

Co. No.	GTPγS - hR2 PAM pEC_{50}
17	6.88
18	5.53
19	6.13
20	5.50
21	7.11
22	6.82
23	6.53
24	7.15
25	7.20
26	7.01
27	6.80
28	6.05
29	7.40
30	6.66
31	8.15
32	7.55
33	7.13

Co. No.	GTPγS - hR2 PAM pEC_{50}
34	7.91
35	6.55
36	6.66
37	6.63
38	7.16
39	6.11
40	6.78
41	6.54
42	6.77
43	7.06
44	7.51
45	7.35
46	7.75
47	8.79
48	6.84
49	7.22
50	6.65
51	7.13
52	7.77
53	8.79
54	8.38
55	8.00
56	7.83
57	7.44

Co. No.	GTPγS - hR2 PAM pEC_{50}
58	7.90
59	7.15
60	7.11
61	7.70
62	7.40
63	7.03
64	6.51
65	7.26
66	6.51
67	5.61
68	5.90
69	6.53
70	6.67
71	7.02
72	6.49
73	6.59
74	6.21
75	7.39
76	n.t.
77	8.3
78	7.98

n.t. means not tested

All compounds were tested in presence of mGluR2 agonist, glutamate at a predetermined EC_{20} concentration, to determine positive allosteric modulation (GTPγS-PAM). pEC50 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 4. Pharmacological data for compounds according to the invention in the PCP- and amphetamine-induced hyperlocomotion test in mice and CAR test in rats.

ED_{50} is the dose (mg/kg body weight) at which 50% of the tested animals show the effect.

	ED_{50} (mg/kg)		
	Mice		Rats
Co. No.	PCP-Inh.	Amp.-Inh.	CAR-Inh.
22	20	n.t.	n.t.
1	18.7	n.t.	21.4*
		n.t.	12.3
3	16.2	n.t.	24.6*
		n.t.	18.6
7	10	n.t.	n.t.
2	12.3	28.3*	21.4*
			18.7
4	15.2	n.t.	20*[a)]
		n.t.	7.9 [a)]
14	18	n.t.	24.6*
15	20	n.t.	≥40*
42	20 [a)]	n.t.	n.t.
46	20 [a)]	n.t.	n.t.
48	12.6 [a)]	n.t.	n.t.
35	n.t.	n.t.	20* [a)]
54	n.t.	n.t.	>40*
58	n.t.	n.t.	≥40*
63	1.58 [a)]	n.t.	n.t.
73	12.6 [a)]	n.t.	n.t.

Inh. means inhibition; Amp. means amphetamine; *means the compound was administered orally; n.t. means not tested.

[a)] Estimated ED_{50} values (n = 3 per dose; 4-fold separation between doses)

Compounds 22, 1, 3, 7, 2, 4, 14, 15, 42, 46, 48, 63 and 73 inhibited PCP-induced hyperlocomotion in mice, compound 2 was also active against d-amphetamine-induced hyperlocomotion in mice, and compounds 1, 3, 2, 4, 14 and 35 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.)
1	>10
2	10
4	≤10
15	≤10
42	5
46	≤10
48	≤10

≤ means that the compound was active at the indicated dose level and was not tested at lower doses.
>10 means the compound was found inactive at 10 mg/kg. This dose was taken as threshold (higher doses were not tested).

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

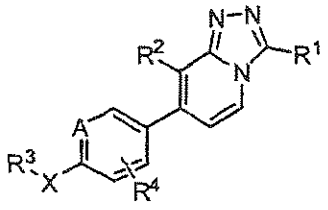
Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

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 having the formula (I)



(I)

or a stereochemically isomeric form thereof, wherein

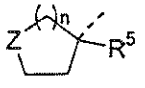
A is CH or N;

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 benzyl; benzyl substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-3}alkoxy, C_{1-3}alkyl, 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 the group consisting of cyano; halo; C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more halo substituents; C_{1-3}alkoxy substituted with one or more halo substituents; C_{3-7}cycloalkyl; and (C_{3-7}cycloalkyl)C_{1-3}alkyl;

R^3 is selected from the group consisting of hydrogen; C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or more substituents each independently selected from the group consisting of hydroxyl, halo, C_{1-3}alkyl, trihaloC_{1-3}alkyl and C_{3-7}cycloalkyl; unsubstituted phenyl; phenyl substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl, trifluoromethyl and trifluoromethoxy; Het^3; unsubstituted pyridyl; pyridyl substituted with one or more substituents each independently selected from C_{1-3}alkyl, C_{1-3}alkyloxy, C_{3-7}cycloalkyl, and halo; trihaloC_{1-3}alkyl; and hydroxyC_{1-3}alkyl; or

R^3 is a cyclic radical of formula (a)



(a)

wherein

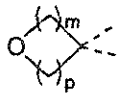
R^5 is selected from the group consisting of hydrogen; C_{1-3}alkyl; C_{1-3}alkyloxy; and hydroxyC_{1-3}alkyl;

n is 1 or 2 ;

Z is selected from CH_2 or $CR^6(OH)$ wherein R^6 is selected from the group consisting of hydrogen, C_{1-3}alkyl and trifluoromethyl;

or R^5 and R^6 together form a radical CH_2-CH_2; or

Z is a cyclic radical of formula (b)



(b)

wherein m and p are independently selected from 0, 1 and 2, provided that $m + p \geq 2$;

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

X is selected from the group consisting of a covalent bond, C_{1-3}alkanediyl, O, NH, S, SO, SO_2, $C(OH)(CH_3)$, CH_2-O, O-CH_2, CH_2-NH, NH-CH_2, CHF, and CF_2;

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

each Het^2 is unsubstituted pyridyl or pyrimidinyl; and

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

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

A is CH or N;

R^1 is selected from the group consisting of (C_{1-3}alkyloxy)C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more halo substituents; unsubstituted C_{3-7}cycloalkyl; (C_{3-7}cycloalkyl)-C_{1-3}alkyl; 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)methyl; and Het^1C_{1-3}alkyl;

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

R^3 is selected from the group consisting of hydrogen; C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with one or more substituents each independently selected from hydroxyl and C_{3-7}cycloalkyl; unsubstituted phenyl; Het^3; unsubstituted pyridyl; and pyridyl substituted with one or more substituents each independently selected from the group consisting of C_{1-3}alkyl, C_{1-3}alkyloxy, C_{3-7}cycloalkyl, and halo;

R^4 is hydrogen or halo;

X is selected from the group consisting of a covalent bond; C_{1-3}alkanediyl; O; CH_2O; CH_2NH; $NHCH_2$ and NH;

each ^{1}Het is piperidinyl, optionally substituted with 1 or more unsubstituted phenyl groups;

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

halo is selected from fluoro and chloro;

or a pharmaceutically acceptable salt or a solvate thereof.

3. The compound according to claim 1, or a stereochemically isomeric form thereof, wherein

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

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

R^3 is selected from the group consisting of unsubstituted C_{3-7}cycloalkyl; piperazin-1-yl; tetrahydro-*2H*-pyran-4-yl; and pyridyl substituted with one or more substituents each independently selected from the group consisting of C_{1-3}alkyl, C_{1-3}alkyloxy; C_{3-7}cycloalkyl, and halo;

A is CH;

X is selected from a covalent bond; -O-; CH_2NH; and -NH-; and

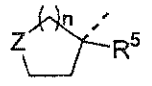
R^4 is selected from hydrogen; fluoro and chloro;
or a pharmaceutically acceptable salt or a solvate thereof.

4. The compound according to claim 1, or a stereochemically isomeric form thereof, wherein
R^1 is selected from the group consisting of CH_2CF_3; ethoxymethyl; and cyclopropylmethyl;
R^2 is selected from the group consisting of chloro, methyl, and CF_3;
R^3 is selected from the group consisting of 2-methyl-pyridin-4-yl; 2,6-dimethyl-pyridin-3-yl; cyclopropyl; 2-cyclopropyl-pyridin-4-yl; 3-fluoropyridin-4-yl; and piperazin-1-yl;
A is CH;
X is selected from a covalent bond; -O-; and -NH-; and
R^4 is selected from hydrogen; fluoro and chloro.
or a pharmaceutically acceptable salt or a solvate thereof.

5. The compound according to claim 1, or a stereochemically isomeric form thereof, wherein
A is CH;
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}alkoxy, C_{1-3}alkyl, 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- or tri-haloC_{1-3}alkoxy; C_{1-3}alkyl; C_{3-7}cycloalkyl and (C_{3-7}cycloalkyl)C_{1-3}alkyl;
R^3 is selected from hydrogen; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or 2 substituents selected from hydroxyl, halo, C_{1-3}alkyl and tri-haloC_{1-3}alkyl; unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl, trifluoromethyl and trifluoromethoxy; Het^3; unsubstituted

pyridyl; pyridyl substituted with 1 or 2 substituents independently selected from C_{1-3}alkyl, trihaloC_{1-3}alkyl and hydroxyC_{1-3}alkyl; or

R^3 is a cyclic radical of formula (a)


(a)

wherein

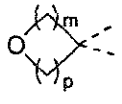
R^5 is selected from hydrogen; C_{1-3}alkyl; C_{1-3}alkyloxy and hydroxyC_{1-3}alkyl;

n is 1 or 2 ;

Z is selected from CH_2 and $CR^6(OH)$ wherein R^6 is hydrogen, C_{1-3}alkyl or trifluoromethyl;

or R^5 and R^6 together form a radical CH_2-CH_2; or

Z is a cyclic radical of formula (b)


(b)

wherein m and p are independently selected from 0, 1 and 2, provided that m + p ≥ 2;

R^4 is selected from hydrogen; halo; and mono-, di- and tri-haloC_{1-3}alkyl; and

X is selected from the group consisting of a covalent bond, C_{1-3}alkanediyl, O, NH, S, SO, SO_2, $C(OH)(CH_3)$, CH_2-O, O-CH_2, CHF and CF_2;

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;

each Het^2 is unsubstituted pyridyl or pyrimidinyl; and

each Het^3 is a saturated heterocyclic radical selected from pyrrolidinyl; piperidinyl; piperazinyl; tetrahydropyranyl; 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;

or a pharmaceutically acceptable salt or a solvate thereof.

6. 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-[3-fluoro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 3-(cyclopropylmethyl)-7-[3-fluoro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[4-[(2,6-dimethyl-3-pyridinyl)oxy]-3-fluorophenyl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 2-chloro-*N*-cyclopropyl-4-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-benzenamine;
- 8-chloro-7-[4-(2-methyl-pyridin-4-yloxy)-3-fluoro-phenyl]-3-(cyclopropyl-methyl)-1,2,4-triazolo[4,3-a]pyridine;
- 8-chloro-7-[3-chloro-4-[(2-methyl-4-pyridinyl)oxy]phenyl]-3-(ethoxymethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 7-[4-[(2,6-dimethyl-3-pyridinyl)oxy]-3-fluorophenyl]-3-(ethoxymethyl)-8-methyl-1,2,4-triazolo[4,3-a]pyridine;
- 7-[3-chloro-4-[(2-cyclopropyl-4-pyridinyl)oxy]phenyl]-3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
- 3-(cyclopropylmethyl)-7-[4-[(3-fluoro-4-pyridinyl)oxy]phenyl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine; and
- 7-(3-chloro-4-piperazin-1-ylphenyl)-3-(cyclopropylmethyl)-8-(trifluoromethyl)[1,2,4]triazolo[4,3-*a*]pyridine;

and the pharmaceutically acceptable salts thereof and the solvates 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, behavioural and psychological symptoms of dementia, major depressive disorder, treatment resistant depression, bipolar depression, generalized 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) a mGluR2 orthosteric agonist,

as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of a condition in neuromodulatory effect of mGluR2 allosteric modulators, in particular positive mGluR2 allosteric modulators is beneficial.