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, and to the use of such compounds for the prevention or treatment of neurological and psychiatric disorders and diseases in which mGluR2 is involved.

Background of the Invention

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

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

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

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

The mGluR2 subtype is negatively coupled to adenylate cyclase via activation of Gαi-protein, and its activation leads to inhibition of glutamate release in the synapse. In the central nervous system (CNS), mGluR2 receptors are abundant mainly throughout cortex, thalamic regions, accessory olfactory bulb, hippocampus, amygdala, caudate-putamen and nucleus accumbens.

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

Animal data suggest that positive allosteric modulators of mGluR2 have effects in anxiety and psychosis models similar to those obtained with orthosteric agonists. Allosteric modulators of mGluR2 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 have further revealed 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.

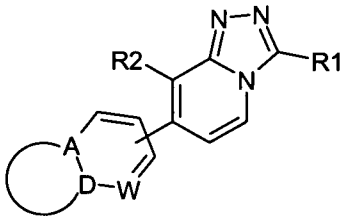
Positive allosteric modulators enable potentiation of the glutamate response, but they have also been shown to potentiate the response to orthosteric mGluR2 agonists such as LY379268 or DCG-IV. These data provide evidence for yet another novel therapeutic approach to treat the above mentioned neurological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

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

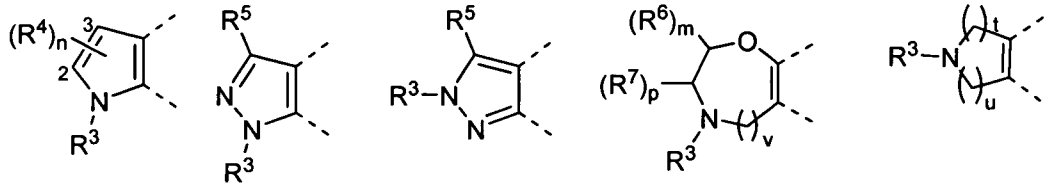
the bond drawn into the ring indicates that the bond may be attached to any carbon ring atom;

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}alkyl, (C_{1-3}alkyloxy)C_{1-3}alkyl, C_{1-3}alkyloxy, 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 one or more independently selected C_{1-3}alkyl substituted with one or more independently selected halo substituents; (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 substituted with one or more independently selected halo substituents; C_{1-3}alkyloxy substituted with one or more independently selected halo substituents; C_{1-3}alkyl; C_{3-7}cycloalkyl; and

(C_{3-7}cycloalkyl)C_{1-3}alkyl;


forms a radical selected from (a), (b), (c), (d) and (e):



(a) (b) (c) (d) (e)

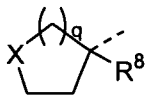
wherein

the bond drawn into (a) indicates that R^4 may be attached to any of carbon ring atoms 2 and 3;

each R^3 is independently selected from the group consisting of hydrogen; unsubstituted C_{1-6}alkyl; C_{1-6}alkyl substituted with one or more substituents independently selected from the group consisting of halo, hydroxy, C_{1-3}alkoxy and trifluoromethyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with one or more substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxy, C_{1-3}alkoxy and trifluoromethyl; C_{3-7}cycloalkylC_{1-3}alkyl; unsubstituted phenyl; phenyl substituted with one or more substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl; Het^3; and Het^3C_{1-3}alkyl;

or

each R^3 is independently selected from a cyclic radical of formula (f)

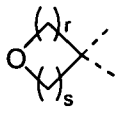

(f)

wherein R^8 is selected from hydrogen, C_{1-3}alkyl, C_{1-3}alkyloxy and hydroxyC_{1-3}alkyl;

q is 1 or 2 ;

X is selected from O, CH_2 and $CR^9(OH)$, wherein R^9 is selected from hydrogen, C_{1-3}alkyl and C_{3-7}cycloalkyl; or

X is a cyclic radical of formula (g)


(g)

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

each R^4, R^6 and R^7 are each independently selected from C_{1-3}alkyl and C_{1-3}alkyl substituted with one or more independently selected halo substituents;

each R^5 is independently selected from the group consisting of hydrogen, C_{1-3}alkyl, and C_{1-3}alkyl substituted with one or more independently selected halo substituents;

n, m and p are each independently selected from 0, 1 and 2;

v is 0 or 1; and

t and u are each independently selected from 1 and 2;

W is selected from N and CR^{10};

wherein R^{10} is selected from hydrogen, halo and trifluoromethyl;

wherein

each Het^1 is a saturated heterocyclic radical selected from pyrrolidinyl; piperidinyl; piperazinyl; and morpholinyl; each of which may be optionally substituted with one or more each 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 pyridyl or pyrimidinyl; and

each Het^3 is a heterocycle selected from the group consisting of tetrahydropyran, pyridyl; and pyrimidinyl; each of them being optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl;

halo is selected from fluoro, chloro, bromo and iodo;

and the pharmaceutically acceptable salts and the solvates thereof.

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

Build 15494, 1 Dec 2006). In case of tautomeric forms, the name of the depicted tautomeric form of the structure was generated. However it should be clear that the other non-depicted tautomeric form is also included within the scope of the present invention.

Definitions

The notation C_{1-3}alkyl or C_{1-6}alkyl as used herein alone or as part of a group defines a saturated, straight or branched, hydrocarbon radical having, unless otherwise stated, from 1 to 3 or 1 to 6 carbon atoms, such as methyl, ethyl, 1-propyl, 1-methylethyl, butyl, 2-methyl-1-propyl, 1,1-dimethylethyl, 3-methyl-1-butyl, 1-pentyl, 1-hexyl and the like.

The notation C_{3-7}cycloalkyl, as used herein alone or as part of a group, defines a saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms, such as 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 halogen or halo as used herein alone or as part of another group, refers to fluoro, chloro, bromo or iodo, with fluoro or chloro being preferred.

The notation mono-, di- or tri-haloC_{1-3}alkyl 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 or Het^3 substituent is pyridyl, it may be 2-pyridyl, 3-pyridyl or 4-pyridyl. Preferred Het^1 substituents are those linked to the rest of the molecule through the nitrogen atom.

It will be appreciated that some of the compounds of formula (I) and their pharmaceutically acceptable addition salts and solvates thereof may contain one or more centres of chirality and exist as stereoisomeric forms.

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

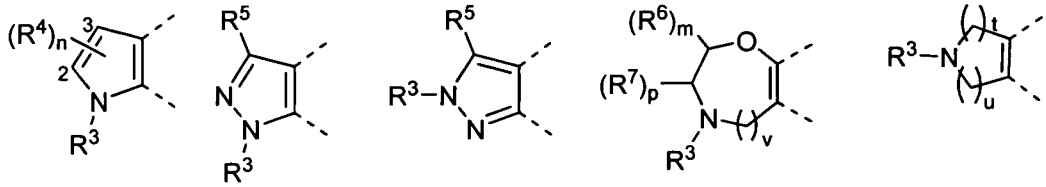
In an embodiment, the invention relates to compounds of Formula (I) and stereochemically isomeric forms thereof, wherein

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; and C_{1-3}alkyl substituted with one or more independently selected halo substituents;



is selected from (a), (b), (c) and (d):



(a) (b) (c) (d); (e)

each R^3 is independently selected from the group consisting of hydrogen; unsubstituted C_{1-6}alkyl; C_{1-6}alkyl substituted with one or more substituents independently selected from the group consisting of halo, hydroxyl, C_{1-3}alkoxy or trifluoromethy; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with one or more substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyl, C_{1-3}alkoxy or trifluoromethyl; (C_{3-7}cycloalkyl)C_{1-3}alkyl; unsubstituted phenyl; phenyl substituted with one or more independently selected halo substituents; Het^3; and Het^3C_{1-3}alkyl;

m, n and p are 0;

v is 0 or 1;

t and u are both 1;

each R^5 is hydrogen;

W is selected from N and CR^{10};

R^{10} is selected from hydrogen and halo;

Het^3 is a heterocycle selected from the group consisting of tetrahydropyran; pyridyl; and pyrimidinyl; each of theim being optionally substituted with one or more substituents each independently selected from halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl; and

halo is selected from fluoro and chloro

and the pharmaceutically acceptable salts and the solvates thereof.

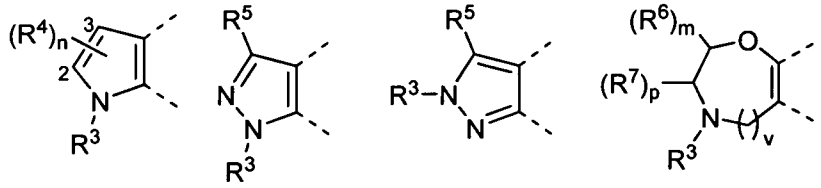
In an embodiment, the invention relates to compounds of Formula (I) and stereochemically isomeric forms thereof, wherein

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

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



is selected from (a), (b), (c) and (d):



(a) (b) (c) (d);

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

m, n and p are 0;

v is 0 or 1;

each R^5 is hydrogen;

W is selected from N and CR^{10};

R^{10} is selected from hydrogen and halo;

Het^3 is a heterocycle selected from the group consisting of tetrahydropyran; pyridyl; and pyrimidinyl; each of theim being optionally substituted with one or more substituents each independently selected from halo and C_{1-3}alkyl;

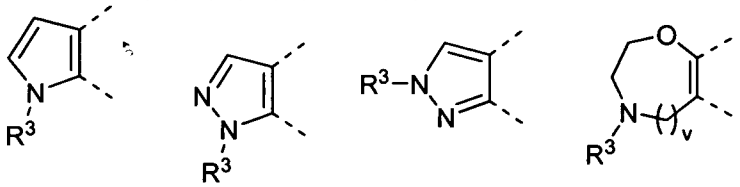
halo is selected from fluoro and chloro;

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



is selected from (a'), (b'), (c') and (d'):



(a') (b') (c') (d')

each R^3 is independently selected from the group consisting of hydrogen; hydroxyC_{1-6}alkyl; C_{3-7}cycloalkyl substituted with one hydroxy substituent; (C_{3-7}cycloalkyl)C_{1-3}alkyl; phenyl substituted with one halo substituent; Het^3; and Het^3C_{1-3}alkyl;

v is 0 or 1;

W is selected from the group consisting of N, CH, CCl and CF;

Het^3 is a heterocycle selected from the group consisting of tetrahydropyran; pyridyl optionally with one substituent selected from halo and C_{1-3}alkyl; and pyrimidinyl;

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



is selected from (a') and (d');

R^1 is C_{3-7}cycloalkylC_{1-3}alkyl;

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

R^3 is selected from hydrogen; C_{3-7}cycloalkyl substituted with one hydroxy substituent; (C_{3-7}cycloalkyl)C_{1-3}alkyl; pyridyl optionally with one substituent selected from halo and C_{1-3}alkyl; and pyrimidinyl;

W is selected from N, CH and CCl;

v is 0;

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; 2,2,2-trifluoroethyl; cyclopropylmethyl;

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



is selected from (a'), (b'), (c') and (d');

each R^3 is independently selected from the group consisting of hydrogen; 2-hydroxy-2-methyl-propyl; cyclopropylmethyl; cyclobutylmethyl; 4-hydroxy-cyclohexyl; 4-fluorophenyl; tetrahydropyran-4-yl; pyridin-2-yl; pyridin-3-yl; pyridin-4-yl; pyrimidin-2-yl; 2-methyl-pyridin-4-yl; 3-fluoro-pyridin-4-yl; 2-methyl-pyridin-5-yl; and pyridin-3-yl-methyl;

v is 0 or 1;

W is selected from the group consisting of N, CH, CF and CCl;

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



is selected from (a') and (d');

R^1 is cyclopropylmethyl;

R^2 is selected from chloro and trifluoromethyl;

R^3 is selected from hydrogen; cyclopropylmethyl; 4-hydroxy-cyclohexyl; pyridin-3-yl; and pyrimidin-2-yl;

W is selected from N, CH and CCl;

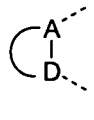
v is 0;

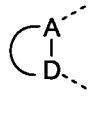
and the pharmaceutically acceptable salts and the solvates thereof.

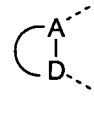
In an embodiment, the invention relates to compounds of Formula (I) and stereochemically isomeric forms thereof, as previously defined, wherein

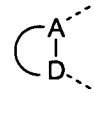


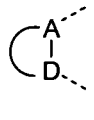
is selected from (a') and W is selected from N, CH, CF and CCl;

 is selected from (b') or (c') and W is CH;

 is selected from (d'); v is 0 or 1; and W is CH;

 is selected from (a') and W is selected from N, CH, CF and CCl;

 is selected from (a') and W is selected from N, CH, and CCl;

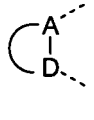
 is selected from (d'); v is 0; and W is CH;

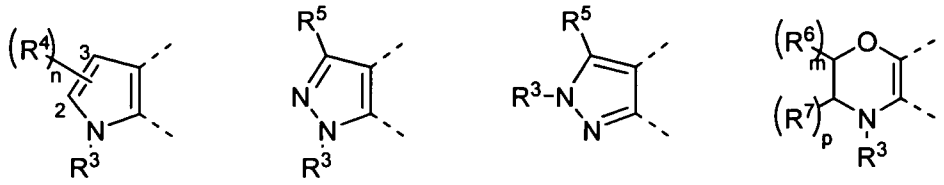
In an embodiment, the invention relates to compounds of Formula (I) and stereoisomeric forms thereof, wherein

the bond drawn into the ring indicates that the bond may be attached to any carbon ring atom;

R^1 is selected from hydrogen; C_{1-6}alkyl; (C_{1-3}alkyloxy)C_{1-3}alkyl; [(C_{1-3}alkyloxy)-C_{1-3}alkyloxy]C_{1-3}alkyl; mono-, di- or tri-haloC_{1-3}alkyl; unsubstituted benzyl; benzyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, (C_{1-3}alkyloxy)C_{1-3}alkyl, C_{1-3}alkyloxy, 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}alkyloxy; C_{1-3}alkyl; C_{3-7}cycloalkyl and (C_{3-7}cycloalkyl)C_{1-3}alkyl;

 forms a radical selected from (a), (b), (c) and (d):



(a) (b) (c) (d)

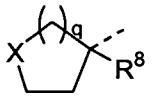
wherein

the bond drawn into (a) indicates that R^4 may be attached to any of carbon ring atoms 2 and 3;

R^3 is selected from hydrogen; unsubstituted C_{1-6}alkyl; C_{1-6}alkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, hydroxy, C_{1-3}alkoxy or trifluoromethyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxy, C_{1-3}alkoxy and trifluoromethyl; C_{3-7}cycloalkyl C_{1-3}alkyl; unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl; Het^3 and Het^3C_{1-3}alkyl;

or

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



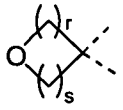
(f)

wherein R^8 is selected from hydrogen, C_{1-3}alkyl, C_{1-3}alkyloxy and hydroxyC_{1-3}alkyl;

q is 1 or 2 ;

X is selected from O, CH_2 or $CR^9(OH)$ wherein R^9 is selected from hydrogen, C_{1-3}alkyl and C_{3-7}cycloalkyl; or

X is a cyclic radical of formula (g)



(g)

wherein r and s are independently selected from 0, 1 or 2, provided that $r + s \geq 2$;

R^4, R^6 and R^7 are independently selected from C_{1-3}alkyl or mono-, di- and tri-halo-C_{1-3}alkyl;

R^5 is selected from hydrogen, C_{1-3}alkyl or mono-, di- and tri-haloC_{1-3}alkyl;
n, m and p are independently selected from 0, 1 and 2;

W is selected from N and CR^{10};
wherein R^{10} is selected from hydrogen, halo and trifluoromethyl;
wherein

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

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

each Het^3 is a heterocycle selected from the group consisting of tetrahydropyran, pyridyl or pyrimidinyl, each of them being optionally substituted with 1 or 2 substituents selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl;

and the pharmaceutically acceptable salts and the solvates thereof.

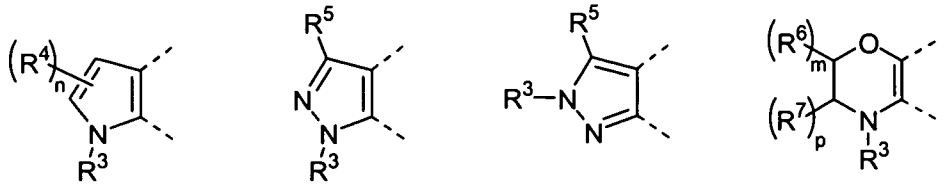
In an embodiment, the invention relates to compounds according to Formula (I) and the stereochemically isomeric forms thereof, wherein

R^1 is selected from C_{1-6}alkyl; mono-, di- or 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; Het^1C_{1-3}alkyl; and Het^2C_{1-3}alkyl;

R^2 is selected from halo or mono-, di- and tri-haloC_{1-3}alkyl;



forms a radical selected from (a), (b), (c) and (d):



(a) (b) (c) (d)

wherein

R^3 is selected from hydrogen; unsubstituted C_{1-6}alkyl; C_{1-6}alkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, hydroxy, C_{1-3}alkoxy and trifluoromethyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxy, C_{1-3}alkoxy or trifluoromethyl; (C_{3-7}cycloalkyl)C_{1-3}alkyl; Het^3 and Het^3C_{1-3}alkyl;

R^4, R^6 and R^7 are independently selected from C_{1-3}alkyl or mono-, di- and tri-halo-C_{1-3}alkyl;

R^5 is selected from hydrogen, C_{1-3}alkyl or mono-, di- and tri-haloC_{1-3}alkyl;
n, m and p are independently selected from 0, 1 and 2;

W is selected from N and CR^{10};

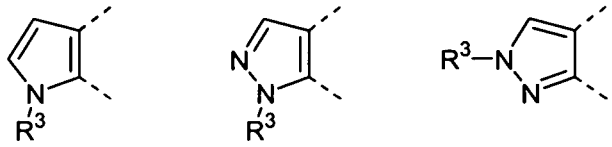
wherein R^{10} is selected from hydrogen and halo;
wherein Het^1, Het^2, Het^3 are as previously defined;
and the pharmaceutically acceptable salts and the solvates thereof.

In the previous embodiment, R^5 is preferably hydrogen and n, m and p are preferably, 0.

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

R^1 is selected from mono-, di- or tri-haloC_{1-3}alkyl; 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; Het^1; Het^1C_{1-3}alkyl; and Het^2C_{1-3}alkyl;


forms a radical selected from (a'), (b'), and (c'):



(a') (b') (c')

wherein

R^3 is selected from hydrogen; C_{1-6}alkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, hydroxy, C_{1-3}alkoxy or trifluoromethyl; C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxy, C_{1-3}alkoxy or trifluoromethyl; (C_{3-7}cycloalkyl)C_{1-3}alkyl; Het^3 and Het^3C_{1-3}alkyl;

W is selected from N and CR^{10};

wherein R^{10} is selected from hydrogen and halo;

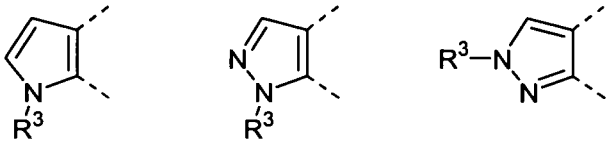
wherein R^2, Het^1, Het^2, Het^3 are as previously defined;

and the pharmaceutically acceptable salts and the solvates thereof.

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

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


forms a radical selected from (a'), (b'), and (c'):



(a') (b') (c')

wherein

R^3 is selected from hydrogen; C_{1-6}alkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, hydroxy, and trifluoromethyl; C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, hydroxy and trifluoromethyl; $(C_{3-7}cycloalkyl)C_{1-3}alkyl$; Het^3 and $Het^3C_{1-3}alkyl$;

wherein Het^3 is selected from tetrahydropyran, pyridyl and pyrimidinyl, each of them being optionally substituted with one or two substituents selected from the group consisting of halo and trifluoromethyl;

and R^2 and W are as previously defined;

and the pharmaceutically acceptable salts and the solvates thereof.

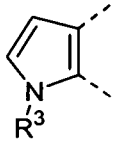
In an additional embodiment, the invention relates to compounds according to Formula (I) and the stereochemically isomeric forms thereof, wherein

R^1 is selected from CH_2CF_3 and cyclopropylmethyl;

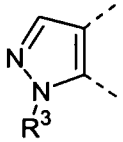
R^2 is selected from fluoro, chloro and trifluoromethyl;



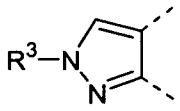
forms a radical selected from (a'), (b'), and (c'):



(a')



(b')



(c')

wherein

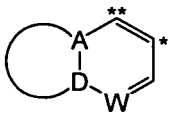
R^3 is selected from hydrogen; 2-hydroxy-2-methyl-propyl; 4-hydroxy-cyclohexyl; pyridyl; pyrimidinyl; tetrahydropyranyl; and pyridylmethyl;

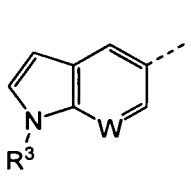
W is selected from N and CR^{10};

wherein R^{10} is selected from hydrogen and chloro;

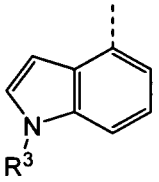
and the pharmaceutically acceptable salts and the solvates thereof.

In a further embodiment, the invention relates to compounds according to any of the other embodiments wherein R^2 is chloro or trifluoromethyl and R^3 is selected from the group consisting of hydrogen; 2-hydroxy-2-methyl-propyl; 4-hydroxy-cyclohexyl; 2-pyridyl; 2-pyrimidinyl; 4-tetrahydropyranyl; and 3-pyridylmethyl.

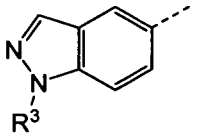
In the compounds of formula (I) the bicycle  is bound to the rest of the molecule through the * or the ** carbon atom and R^1, R^2, W, and  are as previously defined, or a pharmaceutically acceptable salt or a solvate thereof. In a particular embodiment, the bicycle may be selected from one of the following:



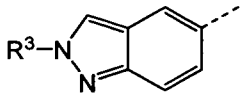
(a'-1)



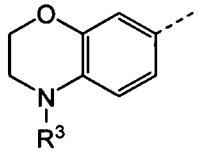
(a'-2)



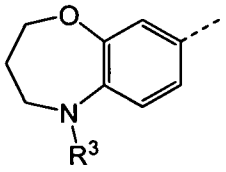
(b'-1)



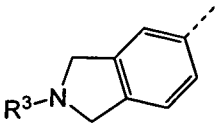
(b'-2)



(c'-1)



(c'-2)



(e'-1)

wherein R^3 is as previously defined.

In a more particular embodiment, the bicycle is selected from (a'-1), (c'-1) and (c'-2), wherein R^3 and W are as previously defined.

In a further embodiment, the invention relates to compounds according to any of the other embodiments, wherein the bicycle is selected from (a'-1) and R^3 is selected from hydrogen; cyclohexyl substituted with a hydroxyl radical; (C_{3-7}cycloalkyl)C_{1-3}alkyl and pyridinyl.

In a further embodiment, the invention relates to compounds according to any of the other embodiments, wherein the bicycle is selected from (c'-1) and R^3 is selected from pyrimidinyl.

Particular preferred compounds may be selected from the group of:

8-Chloro-7-[1-(2-pyridinyl)-*1H*-indol-5-yl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-[1-(tetrahydro-*2H*-pyran-4-yl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
3-(cyclopropylmethyl)-7-[1-(tetrahydro-*2H*-pyran-4-yl)-*1H*-indol-5-yl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
trans-4-[5-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]-pyridine-7-yl]-*1H*-indol-1-yl]-cyclohexanol;
8-chloro-3-(cyclopropylmethyl)-7-(*1H*-pyrrolo[2,3-b]pyridine-5-yl)-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-7-[1-(2-pyrimidinyl)-*1H*-indol-5-yl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine;
3-(cyclopropylmethyl)-7-[1-(2-pyrimidinyl)-*1H*-indol-5-yl-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-7-(7-chloro-*1H*-indol-5-yl)-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]-pyridine;
5-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridine-7-yl]-α,α-dimethyl-*1H*-indole-1-ethanol;
Trans-4-[5-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-*1H*-indol-1-yl]-cyclohexanol;
8-chloro-3-(cyclopropylmethyl)-7-[2-(3-pyridinylmethyl)-*2H*-indazol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-[1-(3-pyridinylmethyl)-*1H*-indazol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-(*1H*-indol-4-yl)-1,2,4-triazolo[4,3-a]pyridine;
7-(7-chloro-*1H*-indol-5-yl)-3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-[1-(2-pyrimidinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-[1-(2-pyridinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-[1-(3-pyridinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(ethoxymethyl)-7-[1-(2-pyridinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(ethoxymethyl)-7-[1-(2-pyrimidinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;

8-chloro-3-(cyclopropylmethyl)-7-(*1H*-indol-5-yl)-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-[1-(6-methyl-3-pyridinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-[1-(cyclopropylmethyl)-*1H*-pyrrolo[2,3-b]pyridin-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-7-(7-chloro-*1H*-indol-5-yl)-3-(ethoxymethyl)-1,2,4-triazolo[4,3-a]pyridine;
3-(cyclopropylmethyl)-7-(*1H*-pyrrolo[2,3-b]pyridin-5-yl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
3-(cyclopropylmethyl)-7-[1-(cyclopropylmethyl)-*1H*-pyrrolo[2,3-b]pyridin-5-yl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(ethoxymethyl)-7-[1-(3-pyridinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(ethoxymethyl)-7-[1-(6-methyl-3-pyridinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-(7-fluoro-*1H*-indol-5-yl)-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(ethoxymethyl)-7-(*1H*-indol-5-yl)-1,2,4-triazolo[4,3-a]pyridine;
3-(ethoxymethyl)-7-[1-(3-pyridinyl)-*1H*-indol-5-yl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-[7-fluoro-1-(6-methyl-3-pyridinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
3-(ethoxymethyl)-7-[1-(6-methyl-3-pyridinyl)-*1H*-indol-5-yl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
3-(ethoxymethyl)-7-(*1H*-indol-5-yl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
3-(cyclopropylmethyl)-7-[1-(3-pyridinyl)-*1H*-indol-5-yl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
3-(cyclopropylmethyl)-8-methyl-7-[1-(6-methyl-3-pyridinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
3-(cyclopropylmethyl)-7-[1-(6-methyl-3-pyridinyl)-*1H*-indol-5-yl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
8-cyclopropyl-3-(cyclopropylmethyl)-7-[1-(6-methyl-3-pyridinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
3-(cyclopropylmethyl)-7-[7-fluoro-1-(6-methyl-3-pyridinyl)-*1H*-indol-5-yl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-7-[1-(cyclobutylmethyl)-*1H*-pyrrolo[2,3-b]pyridin-5-yl]-3-

(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridine;
3-(cyclopropylmethyl)-7-[1-(cyclopropylmethyl)-*1H*-pyrrolo[2,3-b]pyridin-5-yl]-8-methyl-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-[1-(2-pyridinyl)-*1H*-pyrrolo[2,3-b]pyridin-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-[1-(3-fluoro-4-pyridinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
3-(cyclopropylmethyl)-7-[1-(4-pyridinyl)-*1H*-indol-5-yl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-[1-(4-pyridinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-[1-(4-fluorophenyl)-*1H*-pyrrolo[2,3-b]pyridin-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
3-(cyclopropylmethyl)-7-[1-(2-methyl-4-pyridinyl)-*1H*-indol-5-yl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-[1-(2-methyl-4-pyridinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-[7-fluoro-1-(3-pyridinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
3-(ethoxymethyl)-8-methyl-7-[1-(6-methyl-3-pyridinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
7-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,4-dihydro-4-(2-pyrimidinyl)-*2H*-1,4-benzoxazine;
7-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,4-dihydro-4-(2-pyrimidinyl)-*2H*-1,4-benzoxazine;
7-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,4-dihydro-4-(2-pyridinyl)- *2H*-1,4-benzoxazine;
7-[8-chloro-3-(ethoxymethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,4-dihydro-4-(2-pyridinyl)-*2H*-1,4-benzoxazine;
7-[8-chloro-3-(ethoxymethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,4-dihydro-4-(2-pyrimidinyl)-*2H*-1,4-benzoxazine;
7-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,4-dihydro-4-(3-pyridinyl)-*2H*-1,4-benzoxazine;
7-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,4-dihydro-4-(3-pyridinyl)-*2H*-1,4-benzoxazine;
7-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,4-dihydro-4-(6-methyl-3-pyridinyl)-*2H*-1,4-benzoxazine;

7-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,4-dihydro-4-(6-methyl-3-pyridinyl)-*2H*-1,4-benzoxazine;
7-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,4-dihydro-4-(4-pyridinyl)-*2H*-1,4-benzoxazine;
7-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,4-dihydro-4-(2-methyl-4-pyridinyl)-*2H*-1,4-benzoxazine;
8-(3-Cyclopropylmethyl-8-trifluoromethyl-[1,2,4]triazolo[4,3-a]pyridin-7-yl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine; and
3-(cyclopropylmethyl)-7-(2,3-dihydro-1*H*-isoindol-5-yl)-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:
trans-4-[5-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]-pyridine-7-yl]-*1H*-indol-1-yl]-cyclohexanol;
8-chloro-7-(7-chloro-*1H*-indol-5-yl)-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]-pyridine;
8-chloro-3-(cyclopropylmethyl)-7-[1-(3-pyridinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;
8-chloro-3-(cyclopropylmethyl)-7-[1-(cyclopropylmethyl)-*1H*-pyrrolo[2,3-b]pyridin-5-yl]-1,2,4-triazolo[4,3-a]pyridine; and
7-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,4-dihydro-4-(2-pyrimidinyl)-*2H*-1,4-benzoxazine;
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 be generally 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.

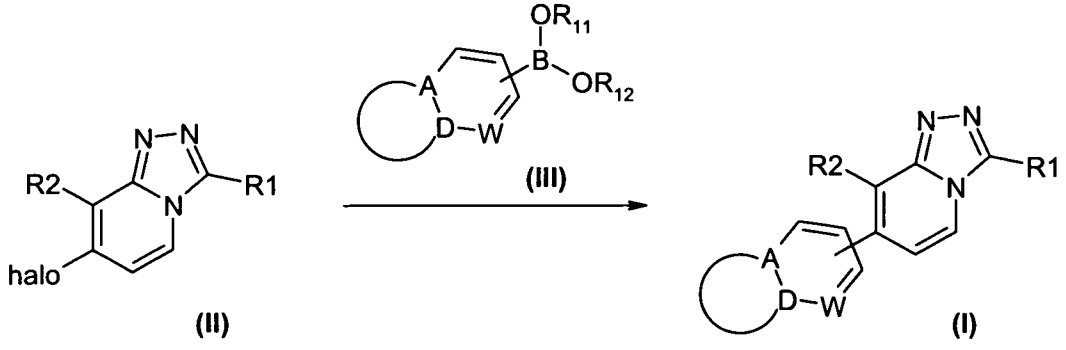
The compounds of Formula (I) may be synthesized in the form of racemic mixtures of enantiomers, which can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a 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 as defined in Formula (I) and halo is chloro, bromo or iodo. R^{11} and R^{12} 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

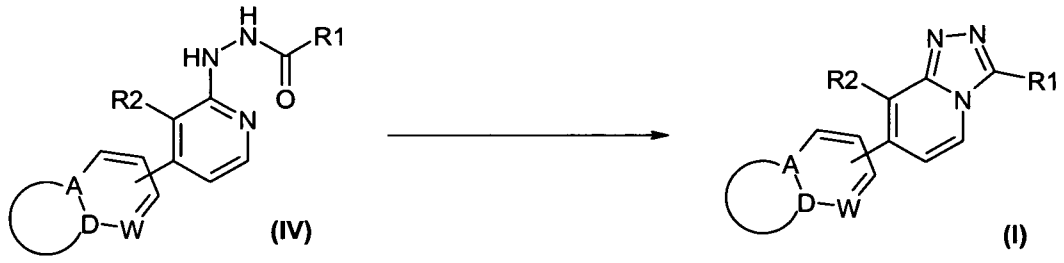


Experimental procedure 2

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 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



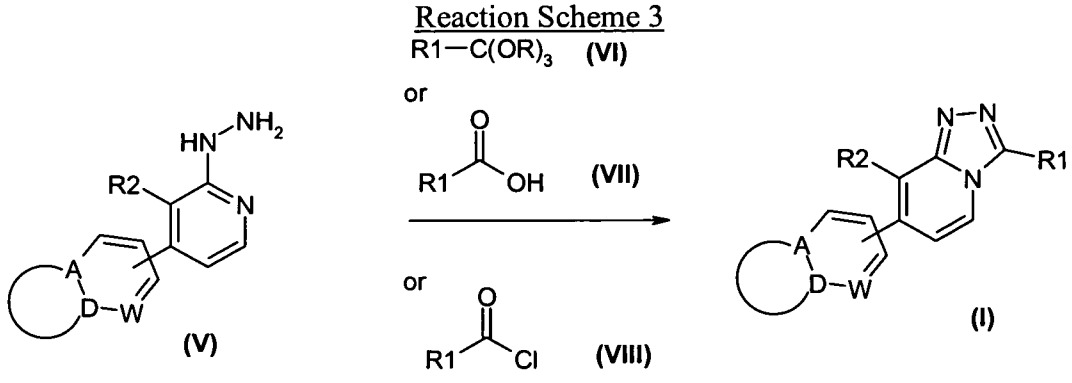
Experimental procedure 3

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 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 (I). The reaction can be carried out using a halogenating agent such as, for example, a trichloroacetonitrile-triphenylphosphine mixture in the presence

of suitable solvent such as for example dichloroethane, stirred at a temperature between 100-200 °C for 1 to 48 h or under microwave irradiation for 20 min. In reaction scheme (3), all variables are defined as in Formula (I).

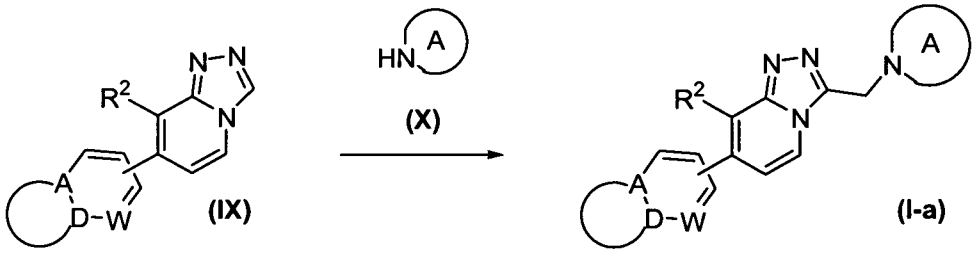
Reaction Scheme 3



Experimental procedure 4

Final compounds according to Formula (I), wherein R^1 is Het^1-C_1alkyl or a 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin)methyl substituent as previously defined wherein Het^1 is hereby represented as  and 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), wherein is as defined above. The reaction can be carried out in the presence of formaldehyde with a suitable solvent such as for example, AcOH 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

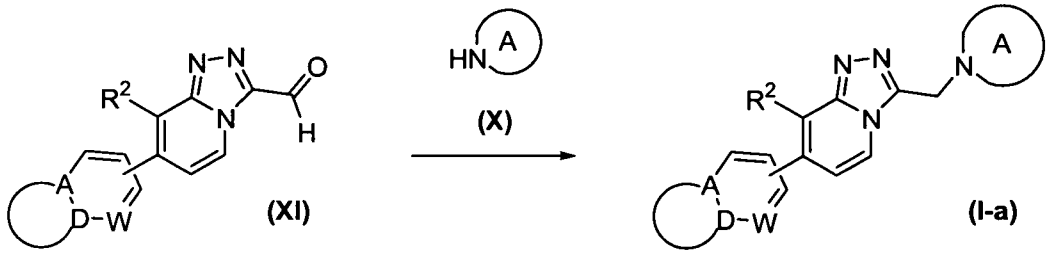


Experimental procedure 5

Alternatively final compounds according to Formula (I) wherein R^1 is Het^1-C_1alkyl or a 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin)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



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 by 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

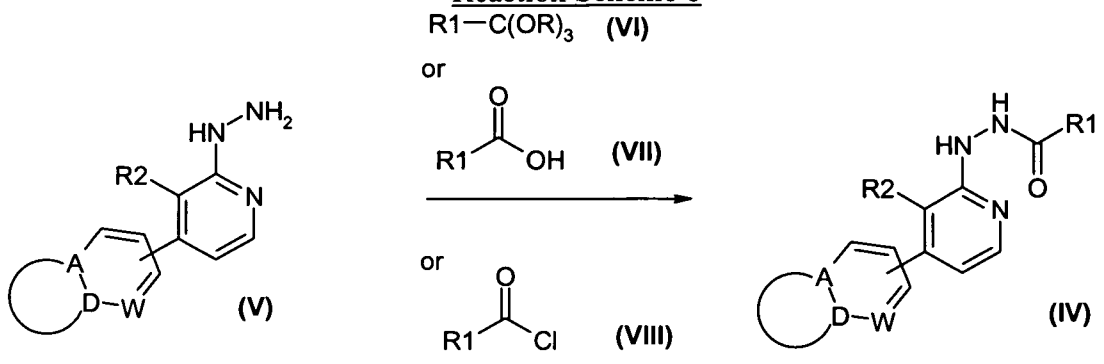
B. Preparation of the intermediate compounds

Experimental procedure 6

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 like for example methyl, according to reaction scheme (6). 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 (6), 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 equivalent 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 a suitable solvent such as for example, dichloroethane stirred at a temperature between 100-200 °C for 1 to 48 hours or under microwave irradiation for 20 min. In reaction scheme (6), all variables are defined as in Formula (I).

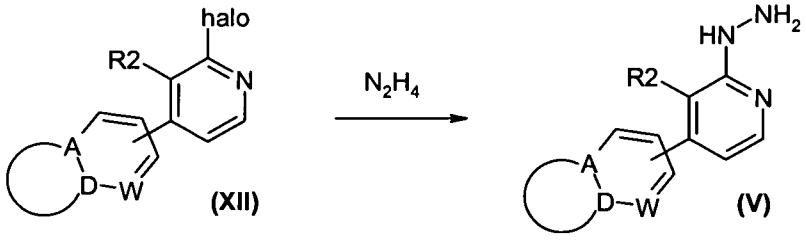
Reaction Scheme 6



Experimental procedure 7

Intermediate compounds according to Formula (V) can be prepared by reacting an intermediate compound of Formula (XII) with hydrazine according to reaction scheme (7), 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 (7), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo.

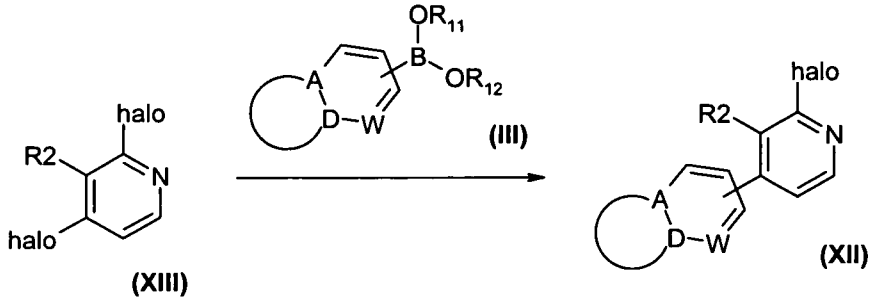
Reaction Scheme 7



Experimental procedure 8

Intermediate compounds of Formula (XII) can be prepared by reacting an intermediate compound of Formula (XIII) with a compound of Formula (III) according to reaction scheme (8). All variables are defined as in Formula (I) and (III) and halo is chloro, bromo or iodo.

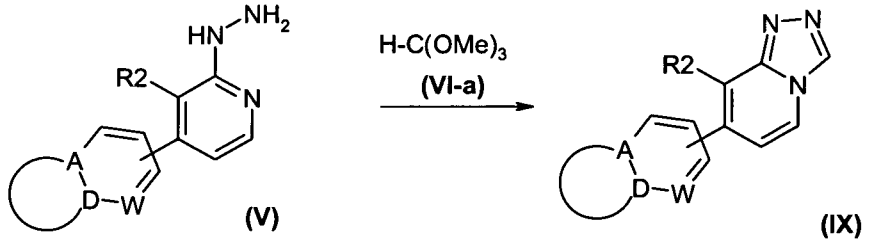
Reaction Scheme 8



Experimental procedure 9

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. Heterocycl. 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), such as for example methylorthoformate wherein R^1 is H and R is methyl, according to reaction scheme (9). 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 (9), all variables are defined as in Formula (I).

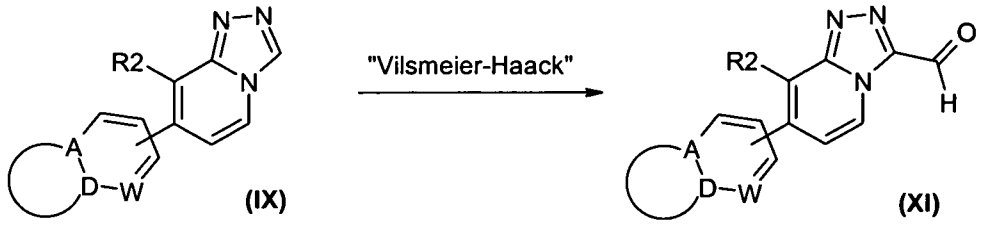
Reaction Scheme 9



Experimental procedure 10

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 (10), all variables are defined as in Formula (I).

Reaction Scheme 10

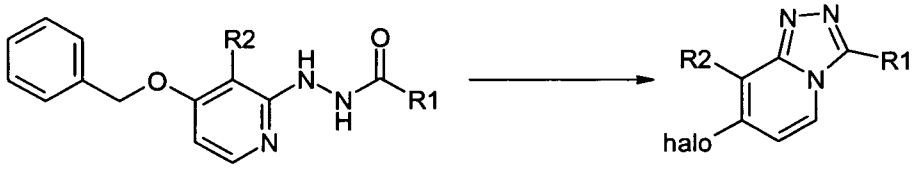


(IX) (XI)

Experimental procedure 11

Intermediate compounds of Formula (II) can be prepared following art known procedures by cyclization of intermediate compound of Formula (XIV) in the presence of a halogenating agent such as for example phosphorus (V) oxychloride ($POCl_3$) in a suitable solvent such as for example, dichloroethane, stirred under microwave irradiation, for a suitable period of time that allows the completion of the reaction, as for example, 5 min at a temperature between 140-200 °C. In reaction scheme (11), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo.

Reaction Scheme 11

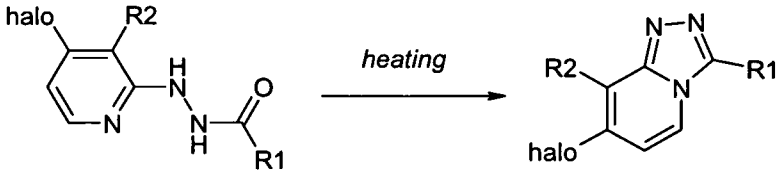


(XIV) (II)

Experimental procedure 12

Alternatively, intermediate compounds of Formula (II) can be prepared following art known procedures by cyclization of intermediate compound of Formula (XV) 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 (12), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo

Reaction Scheme 12



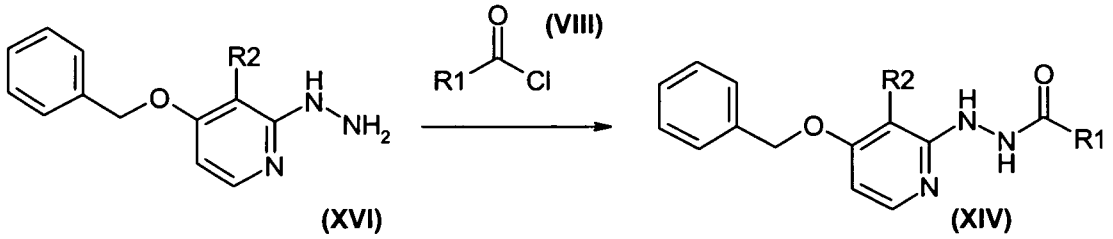
(XV) (II)

Experimental procedure 13

Intermediate compounds according to Formula (XIV) can be prepared by art known procedures by reaction of intermediate compound of Formula (XVI) with acid

halides of Formula (VIII). The reaction can be carried out using an inert-solvent such as for example, DCM in the presence of a base such as for example, 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 (13), all variables are defined as in Formula (I).

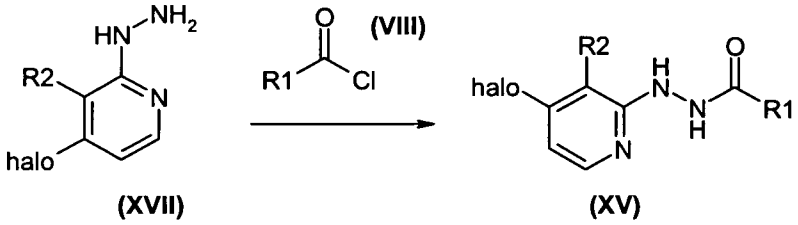
Reaction Scheme 13



Experimental procedure 14

Intermediate compounds according to Formula (XV) can be prepared by art known procedures by reaction of intermediate compounds of Formula (XVII) with acid halides of Formula (VIII). The reaction can be carried out using a inert-solvent such as for example DCM in the presence of a base such as for example, TEA, for example at room temperature for a suitable period of time that allows completion of the reaction, for example 20 min. In reaction scheme (14), all variables are defined as in Formula (I) and halo is chloro, bromo or iodo.

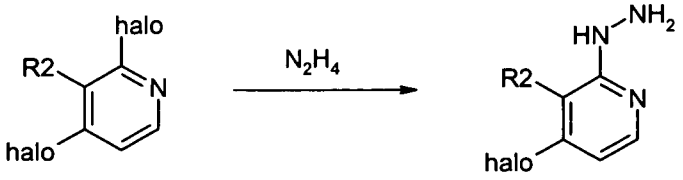
Reaction Scheme 14



Experimental procedure 15

Intermediate compounds according to Formula (XVII) can be prepared by reacting an intermediate compound of Formula (XIII) with hydrazine according to reaction scheme (15), 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 (15), R^2 is as defined in Formula (I) and halo is chloro, bromo or iodo.

Reaction Scheme 15

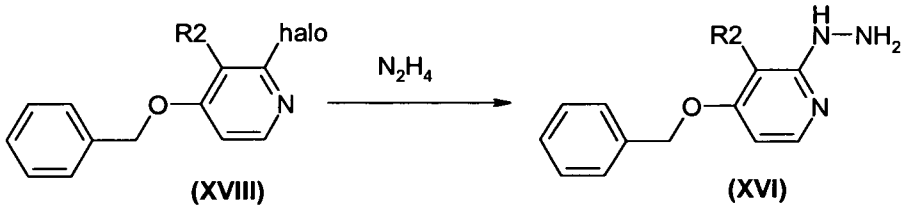


(XIII) (XVII)

Experimental procedure 16

Intermediate compounds according to Formula (XVI) can be prepared by reacting an intermediate compound of Formula (XVIII) with hydrazine according to reaction scheme (16), 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 (16), R^2 is as defined in Formula (I) and halo is chloro, bromo or iodo

Reaction Scheme 16

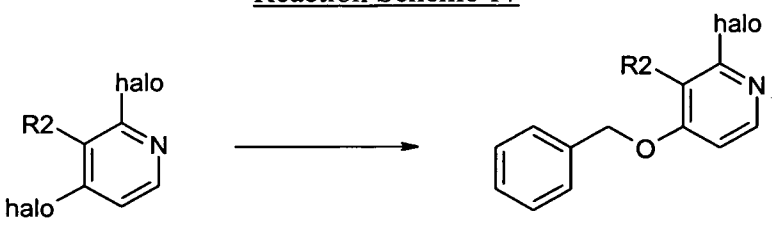


(XVIII) (XVI)

Experimental procedure 17

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

Reaction Scheme 17

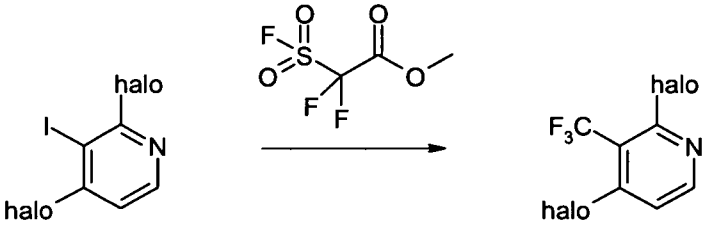


(XIII) (XVIII)

Experimental procedure 18

Intermediate compounds of Formula (XIII) wherein R^2 is trifluoromethyl, hereby named (XIII-a), can be prepared by reacting an intermediate of Formula (XIII) wherein R^2 is iodine, hereby named (XIII-b), with a suitable trifluoromethylating agent, such as for example, fluorosulfonyl(difluoro)acetic acid methyl ester, according to reaction scheme (18). 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 (18), halo is chloro, bromo or iodo.

Reaction Scheme 18

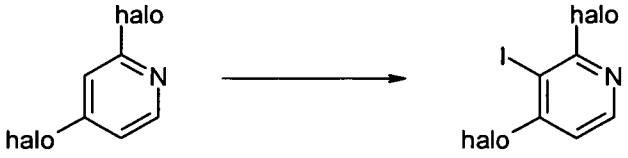


(XIII-b) (XIII-a)

Experimental procedure 19

Intermediate compounds of Formula (XIII) wherein R^2 is iodine, hereby named (XIII-b), can be prepared by reacting an intermediate compound of Formula (XIX) 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 a temperature of for example, –78 °C for a period of time that allows the completion of the reaction such as for example 2 h. In reaction scheme (19), halo may be chloro, bromo or iodo.

Reaction Scheme 19



(XIX) (XIII-b)

Experimental procedure 20

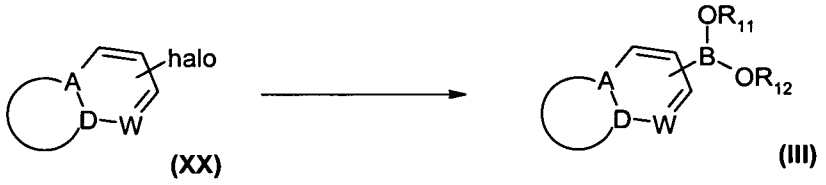
Intermediates of Formula (III) can be prepared by art known procedures by reacting an intermediate of Formula (XX) with a suitable boron source such as, for example, bis(pinacolato)diboron in the presence of a palladium catalyst such as, for example, 1,1'-bis(diphenylphosphino)ferrocenepalladium(II)dichloride in a reaction-

inert solvent such as, for example, DCM, as shown in reaction scheme (20). The reaction may be carried out in the presence of a suitable salt such as, for example, potassium acetate at a temperature of, for example, 110 °C during, for example, 16 h.

Additionally, intermediates of Formula (III) can be prepared by art known procedures of halogen-metal exchange and subsequent reaction with an appropriate boron source from intermediates of Formula (XX). This type of reaction can be carried out by using, for example, an intermediate of Formula (XX) and an organolithium compound such as, for example, *n*-butyllithium. The reaction can be performed at a temperature of, for example, -40 °C in an inert solvent such as, for example, THF. This reaction is followed by subsequent reaction with an appropriate boron source such as, for example, trimethoxyborane.

In reaction scheme (20), all variables are defined as in Formula (I), R^{11} and R^{12} 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 $-C(CH_3)_2C(CH_3)_2-$, and halo is a suitable halogen such as, for example, bromo.

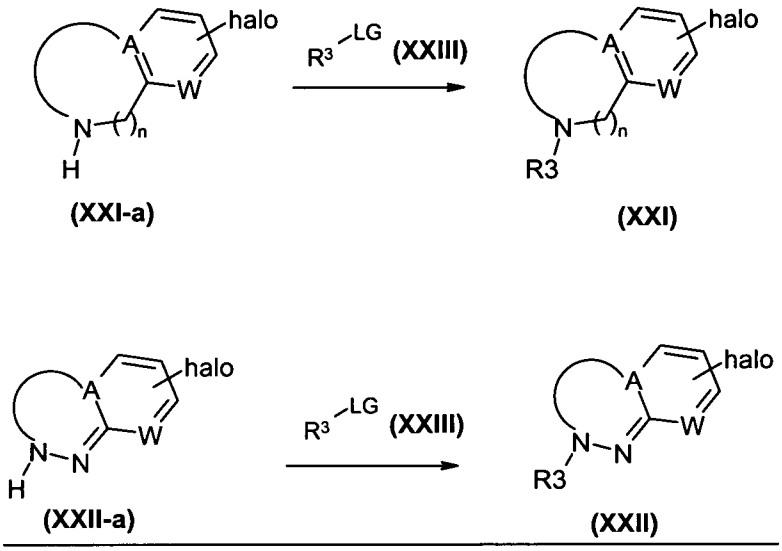
Reaction Scheme 20



Experimental procedure 21

Intermediates of Formula (XX) wherein  forms a radical selected from (a), (b), (c), (d) or (e) and wherein R^3 is as defined in Formula (I) but other than hydrogen, hereby named (XXI) or (XXII), can be prepared following art known procedures by reacting an intermediate of Formula (XXI-a) or (XXII-a) wherein R^3 is hydrogen, with an intermediate compound of Formula (XXIII) under alkylation conditions, for example, in the presence of a base such as, for example, K_2CO_3 or NaH in a suitable reaction-inert solvent such as, for example, DMF. The reaction may be carried out under microwave irradiation at a suitable temperature, typically 150 °C, for a suitable period of time that allows the completion of the reaction. In reaction scheme (21), all variables are defined as in Formula (I), LG is a suitable leaving group for alkylation reactions such as for example, halo, tosyl and mesyl, and halo may be chloro, bromo or iodo.

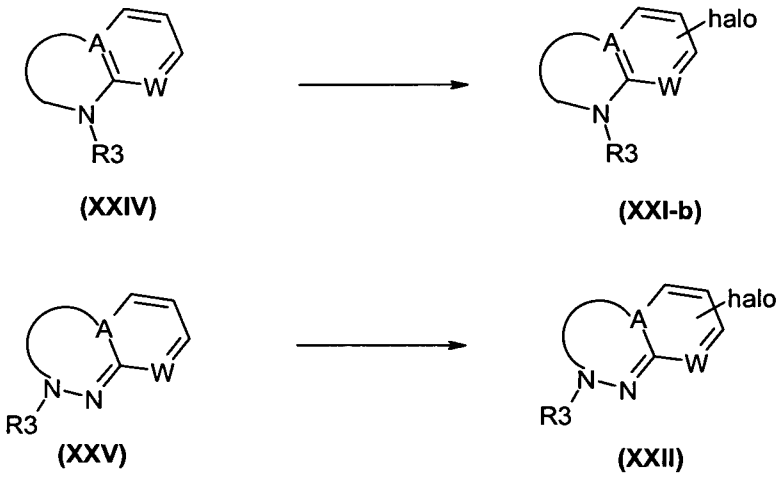
Reaction Scheme 21



Experimental procedure 22

Intermediates of Formula (XXI) wherein n is zero, hereby name (XXI-b) and (XXII) where halo is bromo or iodo can be prepared following art known procedures by reacting an intermediate of Formula (XXIV) or (XXV) with a suitable halogenating agent. This reaction is shown in reaction scheme (22). The reaction can be carried out with halogenating agents such as *N*-bromosuccinimide, *N*-iodosuccinimide, at temperatures ranging from room temperature to reflux temperature, in a reaction-inert solvent such as DMF, DCM, $CHCl_3$ or AcOH. Typically, the reaction mixture can be stirred for 15 minutes to 48 h at a temperature between 0-100 °C. In reaction scheme (22), all variables are defined as in Formula (I) and halo may be chloro, bromo or iodo.

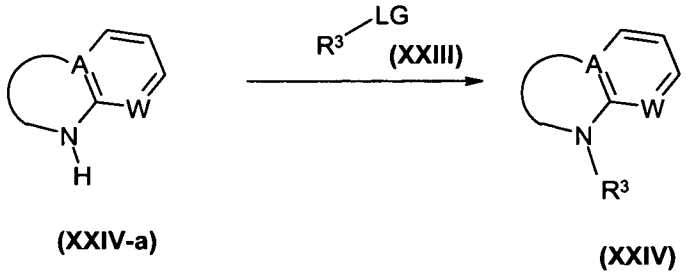
Reaction Scheme 22



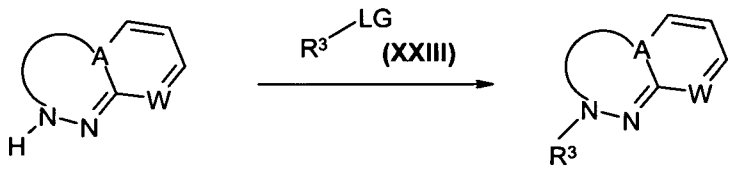
Experimental procedure 23

Intermediates of Formula (XXIV) or (XXV) wherein R^3 is as defined in Formula (I) but other than hydrogen, can be prepared by art known procedures by reacting an intermediate of Formula (XXIV) or (XXV) wherein R^3 is hydrogen, hereby named (XXIV-a) or (XXV-a), with an intermediate compound of Formula (XXIII) under alkylation conditions, as illustrated in reaction scheme (23). In reaction scheme (23), all variables are defined as in Formula (I), LG is a suitable leaving group for alkylation such as for example halo, tosyl, mesyl and halo may be chloro, bromo or iodo.

Reaction Scheme 23



(XXIV-a) (XXIV)

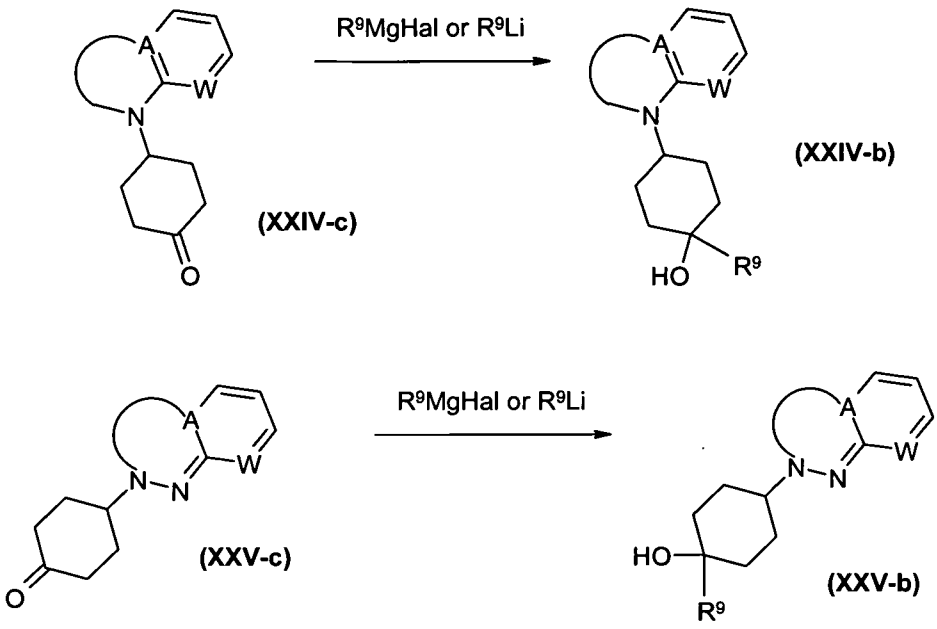


(XXV-a) (XXV)

Experimental procedure 24

Intermediates of Formula (XXIV) or (XXV) wherein R^3 is 4-hydroxy-4-alkylcyclohexan-1-yl, hereby named (XXIV-b) or (XXV-b), can be prepared by art known procedures by reacting an intermediate of Formula (XXIV-c) or (XXV-c) with a suitable organometallic alkyl source such as, for example, R^9MgHal or R^9Li, wherein Hal is a halide. This reaction is shown in reaction scheme (24). The reaction can be carried out in an inert solvent such as, for example, THF, diethyl ether or 1,4-dioxane. Typically, the mixture can be stirred from 1 to 48 h at a temperature between 0-100 °C. In reaction scheme (24), all variables are defined as in Formula (I), halo may be chloro or bromo and R^9 is C_{1-3}alkyl or C_{3-7}cycloalkyl.

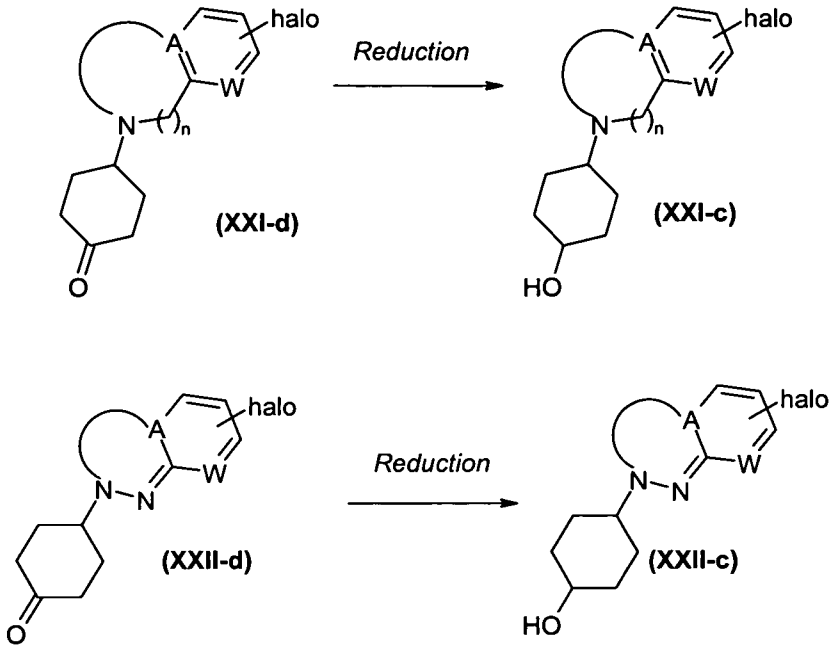
Reaction Scheme 24



Experimental procedure 25

Intermediates of Formula (XXI) and (XXII) wherein R^3 is 4-hydroxy-cyclohexan-1-yl, hereby named (XXI-c) and (XXII-c), can be prepared by reacting an intermediate of Formula (XXI-d) or (XXII-d) under reductive conditions that are known to those skilled in the art. The reaction is illustrated in reaction scheme (25). The reaction can be carried out in the presence of a reducing agent such as for example, sodium borohydride in a suitable solvent such as, for example, methanol. The reaction may be performed at a suitable temperature, typically room temperature, for a suitable period of time that allows the completion of the reaction. In reaction scheme (25), all variables are defined as in Formula (I) and halo may be chloro, bromo or iodo.

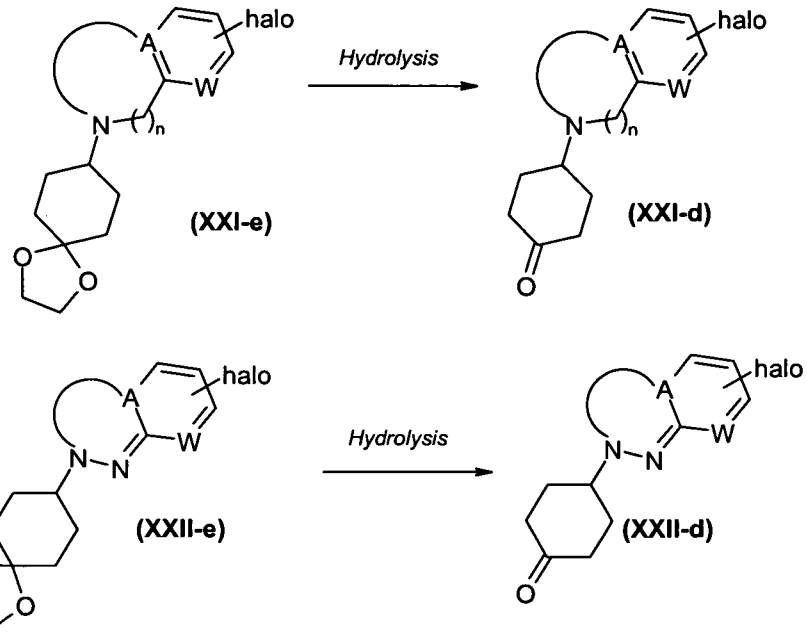
Reaction Scheme 25



Experimental procedure 26

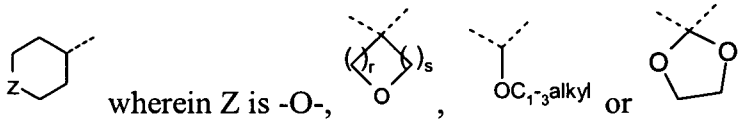
Intermediates of Formula (XXI) and (XXII) wherein R^3 is 4-oxo-cyclohexan-1-yl, hereby named (XXI-d) and (XXII-d), can be prepared by subjecting an acetal intermediate of Formula (XXI-e) or (XXII-e) to suitable deprotection conditions for the carbonyl function known to those skilled in the art. This reaction is illustrated in reaction scheme (26). The reaction can be performed in the presence of an acid such as, for example, *p*-toluenesulfonic acid, in a suitable reaction solvent such as, for example, acetone. The reaction may conveniently be carried out under microwave irradiation at a suitable temperature, typically at 100 °C, for a suitable period of time that allows the completion of the reaction. In reaction scheme (26), all variables are defined as in Formula (I) and halo may be chloro, bromo or iodo.

Reaction Scheme 26



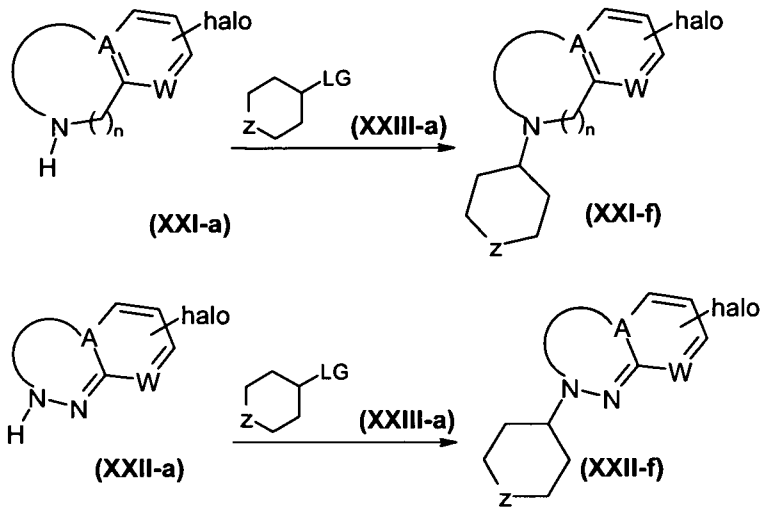
Experimental procedure 27

Intermediates of Formula (XXI) or (XXII) wherein  is a radical of formula (a), (b), (c) (d) or (e) and R^3 is

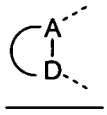
 wherein Z is -O-, , or

and each r and s is as defined in Formula (I), hereby named (XXI-c) or (XXI'-c) can be prepared by reacting an intermediate of Formula (XXI) wherein  is a radical of formula (a), (b), (c) (d) or (e) and R^3 is H, hereby named (XXI-f) or (XXI-f) with an intermediate of Formula R^3-LG (XXIII) wherein R^3 is as defined hereinbefore, hereby named (XXIII-a) according to reaction scheme (27). The reaction can be carried out under alkylation conditions that are known to those skilled in the art such as, for example, in the presence of base such as, for example, potassium hydroxide in a suitable reaction solvent such as, for example, dimethylsulphoxide. The reaction may be performed at a suitable temperature, typically at 60 °C, for a suitable period of time that allows the completion of the reaction. In reaction scheme (27), all variables are defined as in Formula (I), LG is a suitable leaving group for alkylation such as for example halo, tosyl, mesyl and halo may be chloro, bromo or iodo.

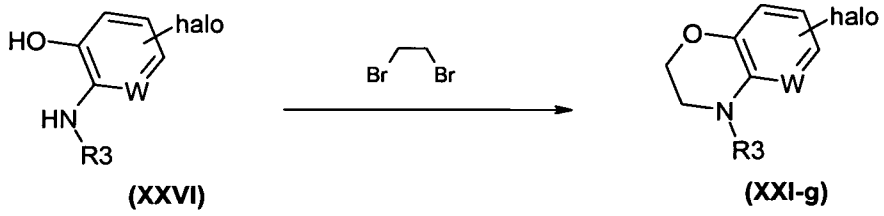
Reaction Scheme 27



Experimental procedure 28

Intermediates of Formula (XXI) wherein  is a radical of formula (d), hereby named (XXI-g), can be prepared by reacting an ortho-aminophenol derivative of Formula (XXVI) with commercially available 1,2-dibromoethane under alkylation conditions, such as for example, performing the reaction in the presence of a base such as for example K_2CO_3 in a suitable reaction-inert solvent such as, for example, DMF. The reaction may be carried out under microwave irradiation at a suitable temperature, typically 180 °C, for a suitable period of time that allows the completion of the reaction. In reaction scheme (28), all variables are defined as in Formula (I) and halo may be chloro, bromo or iodo.

Reaction Scheme 28

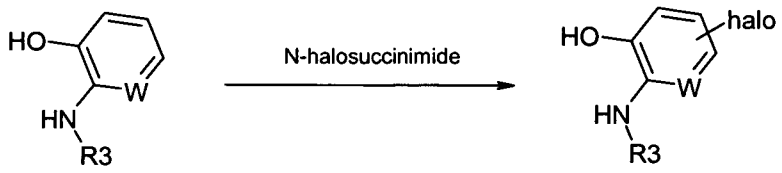


Experimental procedure 29

Intermediates of Formula (XXVI) can be prepared by reacting an intermediate of Formula (XXVII) with an *N*-halosuccinimide such as *N*-chloro- (NCS), *N*-bromo- (NBS) or *N*-iodosuccinimide (NIS) according to reaction scheme (29). This reaction can be performed in a suitable reaction-inert solvent such as, for example, DMF, DCM or AcOH. The reaction typically can be carried out at room temperature for 1 to 24 h.

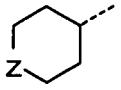
In reaction scheme (29), all variables are defined as in Formula (I) and halo may be chloro, bromo or iodo.

Reaction Scheme 29

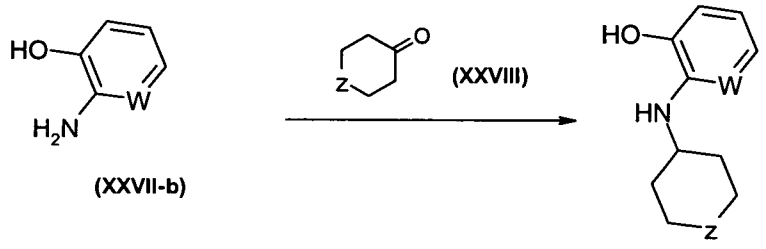


(XXVII) (XXVI)

Experimental procedure 30

Intermediates of Formula (XXVII) wherein R^3 is , hereby named (XXVII-a) can be prepared by reacting an intermediate of Formula (XVIII) wherein R^3 is H, hereby named (XXVII-b) with a cyclic ketone derivative of Formula (XXVIII) under reductive amination conditions that are known to those skilled in the art. This is illustrated in reaction scheme (30). The reaction may be performed, for example, in the presence of sodium triacetoxyborohydride in a suitable reaction-inert solvent such as, for example, DCE, at a suitable reaction temperature, typically at room temperature, for a suitable period of time that allows the completion of the reaction. In reaction scheme (30), all variables are defined as in Formula (I), and Z is as defined in experimental procedure (27).

Reaction Scheme 30



(XXVII-b) (XXVII-a)

Intermediates of Formula, (VI), (VII), (VIII), (XX), (XXII-a), (XXIII), (XXIII-a) (XXVII-b) and (XXVIII) are commercially available or can be prepared according to conventional reation procedures generally known to those skilled in the art.

Pharmacology

The compounds provided in this invention are positive allosteric modulators (PAMs) of metabotropic glutamate receptors, in particular they are positive allosteric

modulators of mGluR2. The compounds of the present invention do not appear to bind to the glutamate recognition site, the orthosteric ligand site, but instead to an allosteric site within the seven transmembrane region of the receptor. In the presence of glutamate or an agonist of mGluR2, the compounds of this invention increase the mGluR2 response. The compounds provided in this invention are expected to have their effect at mGluR2 by virtue of their ability to increase the response of such receptors to glutamate or mGluR2 agonists, enhancing the response of the receptor.

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

Hence, the present invention relates to a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, for use as a medicament.

The invention also relates to the use of a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, or a pharmaceutical composition according to the invention for the manufacture of a medicament.

The 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 altered or facilitated by the neuromodulatory effect of positive allosteric modulators of mGluR2.

Also, the present invention relates to the use of a compound according to the general Formula (I), the stereoisomeric forms thereof and the pharmaceutically acceptable acid or base addition salts and the solvates thereof, or a pharmaceutical composition according to the invention for the manufacture of a medicament for treating, preventing, ameliorating, controlling or reducing the risk of various neurological and psychiatric disorders associated with glutamate dysfunction in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of positive allosteric modulators of mGluR2.

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

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

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

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

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

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

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

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

Preferably, the central nervous system disorder is migraine.

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

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

Preferably, the central nervous system disorder is a cognitive disorder selected from the group of delirium, substance-induced persisting delirium, dementia, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, dementia of the Alzheimer's type, 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 compounds of Formula (I), there is provided a method of treating warm-blooded animals, including humans, suffering from any one

of the diseases mentioned hereinbefore and a method of preventing in warm-blooded animals, including humans, any one of the diseases mentioned hereinbefore.

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

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

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

Generally, a suitable dose is one that results in a concentration of the PAM at the treatment site in the range of 0.5 nM to 200 μM, and more usually 5 nM to 50 μM. To obtain these treatment concentrations, a patient in need of treatment likely will be administered an effective therapeutic daily amount of about 0.01 mg/kg to about 50 mg/kg body weight, preferably from about 0.01 mg/kg to about 25 mg/kg body weight, more preferably from about 0.01 mg/kg to about 10 mg/kg body weight, more preferably from about 0.01 mg/kg to about 2.5 mg/kg body weight, even more preferably from about 0.05 mg/kg to about 1 mg/kg body weight, more preferably from about 0.1 mg/kg 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 (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical preparations and their Manufacture). To prepare the pharmaceutical compositions of this invention, a therapeutically effective amount of the particular compound, optionally in salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier or diluent, which carrier or diluent may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for oral, topical, rectal or percutaneous administration, by parenteral injection or by inhalation. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as, for example, suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as, for example, starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of the ease in administration, oral administration is preferred, and tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example surfactants, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case

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

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

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;

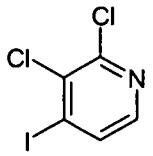
"EtOAc" means ethyl acetate; "DCM" means dichloromethane; "DCE" means dichloroethane; "BINAP" means 1,1'-[1,1'-binaphthalene]-2,2'-diylbis[1,1-diphenylphosphine]; "DBU" means 1,8-diaza-7-bicyclo[5.4.0]undecene; "l" or "L" means liter; "LRMS" means low-resolution mass spectrometry/spectra; "HRMS" means 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; "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); "Et_3N" or "TEA" mean triethylamine; "ES" means electrospray; "TOF" means time of flight; "NH_4Cl" means ammonium chloride; "K_2CO_3" means potassium carbonate; "$Pd(PPh_3)_4$" means tetrakis(triphenylphosphine)palladium(0); "*S*-Phos" means 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl

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

2,3-Dichloro-4-iodo-pyridine (D1)

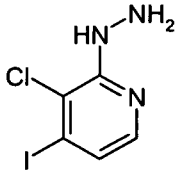


To a solution of *n*-butyllithium (27.6 ml, 69 mmol, 2.5 M in hexanes) in dry Et_2O (150 ml) cooled at –78 °C, under nitrogen atmosphere, was added 2,2,6,6-tetramethylpiperidine (11.64 ml, 69 mmol) dropwise. The resulting reaction mixture was stirred at –78 °C for 10 min, and then a solution of 2,3-dichloropyridine (10 g, 67.57 mmol) in dry THF (75 ml) was added dropwise. The mixture was stirred at –78 °C for 30 min and then a solution of iodine (25.38 g, 100 mmol) in dry THF (75 ml)

was added. The mixture was allowed to warm to room temperature 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 **D1** (8.21 g, 44%) as a pale cream solid.

Description 2

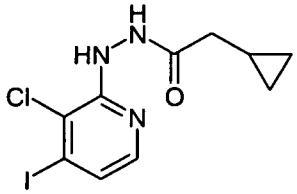
(3-Chloro-4-iodo-pyridin-2-yl)-hydrazine (D2)



To a solution of compound **D1** (8 g, 29.21 mmol) in 1,4-dioxane (450 ml), was added hydrazine monohydrate (14.169 ml, 175.255 mmol). The reaction mixture was heated in a sealed tube at 70 °C for 16 h. After cooling, NH_4OH (32% aqueous solution) was added and the resulting mixture was concentrated *in vacuo*. The white solid residue thus obtained was taken up in EtOH to obtain a suspension which was heated and filtered. The filtrate was cooled and the precipitate thus obtained was filtered off. The resulting filtrate was concentrated *in vacuo* to yield intermediate compound **D2** (2.67 g, 52%) as a white solid.

Description 3

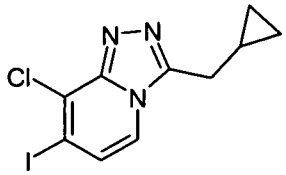
N'-(3-chloro-4-iodo-pyridin-2-yl)-2-cyclopropylacetohydrazide (D3)



To a solution of **D2** (0.73 g, 2.709 mmol) in dry DCM (8 ml), cooled at 0 °C, were added Et_3N (0.562 ml, 4.064 mmol) and cyclopropyl-acetyl chloride (0.385 g, 3.251 mmol). The resulting reaction mixture was stirred at room temperature 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 **D3** (0.94 g, 99%).

Description 4

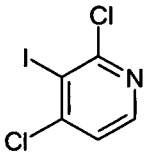
8-Chloro-3-cyclopropylmethyl-7-iodo-1,2,4-triazolo[4,3-a]pyridine (D4)



D3 (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 **D4** (0.74 g, 93%), which was used without further purification.

Description 5

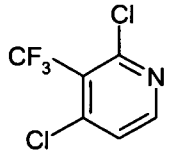
2,4-Dichloro-3-iodo-pyridine (D5)



To a solution of 2,4-dichloropyridine (5.2 g, 35.137 mmol) and DIPEA (3.911 g, 38.651 mmol) in dry THF (40 ml) cooled at –78 °C under a nitrogen atmosphere, was added *n*-butyllithium (24.157 ml, 38.651 mmol, 1.6 M in hexanes) dropwise. The resulting reaction mixture was stirred at –78 °C for 45 min. and then a solution of iodine (9.81 g, 38.651 mmol) in dry THF (20 ml) was added dropwise. The mixture was stirred at –78 °C for 1 h. The mixture was allowed to warm to room temperature, diluted with EtOAc and quenched with NH_4Cl (aqueous sat. solution) and $Na_2S_2O_3$ (aqueous sat. solution). The combined organic extracts were 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 **D5** (7.8 g, 81%).

Description 6

2,4-Dichloro-3-trifluoromethyl-pyridine (D6)

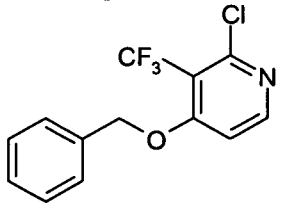


To a mixture of compound **D5** (2g, 7.302 mmol) in DMF (50 ml) were added fluorosulfonyl-difluoro-acetic acid methyl ester (1.858 ml, 14.605 mmol) [C.A.S. 680-15-9] and copper (I) iodide (2.796. g, 14.605 mmol). The reaction mixture was heated

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 **D6** (1.5 g, 95%).

Description 7

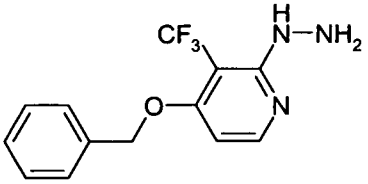
4-Benzyloxy-3-trifluoromethyl-2-chloro-pyridine (D7)



To a suspension of NaH (0.487 g, 12.732 mmol, 60% mineral oil) in DMF (50 ml) cooled at 0 °C, was added benzyl alcohol (1.262 ml, 12.2 mmol). The resulting mixture was stirred for 2 min. Then, intermediate compound **D6** (2.5 g, 11.575 mmol) was added. The resulting reaction mixture was gradually warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with water and extracted with Et_2O. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; Heptane/DCM gradient as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D7** (1.1 g, 33%).

Description 8

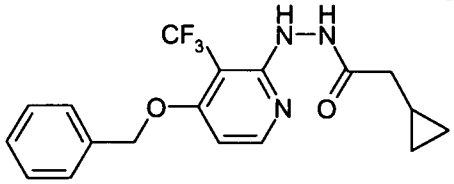
(4-Benzyloxy-3-trifluoromethyl-pyridin-2-yl)-hydrazine (D8)



To a suspension of compound **D7** (1.09 g g, 3.789 mmol) in 1,4-dioxane (9 ml), was added hydrazine monohydrate (3.676 ml, 75.78 mmol). The reaction mixture was heated at 160 °C under microwave irradiation for 30 min. After cooling the resulting solution was concentrated *in vacuo*. The residue thus obtained was dissolved in DCM and washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo* to yield intermediate compound **D8** (0.890 g, 83%) as a white solid.

Description 9

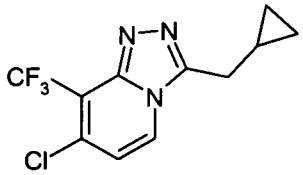
N'-(4-benzyloxy-3-trifluoromethyl-pyridin-2-yl)-2-cylclopropylacetohydrazide (D9)



To a solution of **D8** (0.890 g, 3.142 mmol) in dry DCM (3 ml) were added Et_3N (0.653 ml, 4.713 mmol) and cyclopropyl-acetyl chloride [C.A.S. 543222-65-5] (0.373 g, 3.142 mmol). The resulting reaction mixture was stirred at 0 °C for 20 min, then concentrated *in vacuo* to yield intermediate compound **D9** (1.1 g, 96%), which was used without further purification.

Description 10

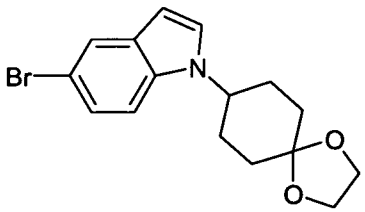
7-Chloro-8-trifluoromethyl-3-cyclopropylmethyl-1,2,4-triazolo[4,3-a]pyridine (D10)



D9 (1.14 g, 1.872 mmol) and phosphorous (V) oxychloride (0.349 g, 3.744 mmol) in CH_3CN (10 ml) was heated at 150 °C under microwave irradiation for 10 min. After cooling, the resulting reaction mixture was diluted with DCM and washed with $NaHCO_3$ (aqueous sat. solution), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/7M solution of NH_3 in MeOH up to 20% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D10** (0.261 g, 51%) as a white solid.

Description 11

5-Bromo-1-(1,4-dioxa-spiro[4.5]dec-8-yl)-*1H*-indole (D11)

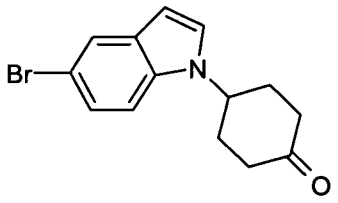


A mixture of 5-bromoindole (8.472 g, 43.216 mmol), [CAS: 10075-50-0]), toluene-4-sulfonic acid, 1,4-dioxa-spiro[4.5]dec-8-yl ester (13.5 g, 43.216 mmol) [C.A.S. 23551-05-9]; (prepared according to the procedure described in J. Chem. Soc., Perkin Trans. 1 **2002**, *20*, 2251-2255) and powdered potassium hydroxide (13.239 g, 235.958 mmol) in

DMSO (300 ml) was stirred at 80 °C for 6 h. Subsequently, the mixture was cooled to room temperature and poured into ice water. The resulting aqueous mixture was extracted with Et_2O, dried (Na_2SO_4), and the volatiles were evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; DCM/heptane 1:1 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D11** (2.897 g, 19.93 %) as a white solid.

Description 12

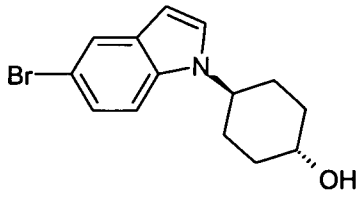
4-(5-Bromo-indol-1-yl)-cyclohexanone (D12)



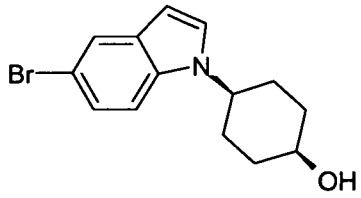
A mixture of intermediate **D11** (24 g, 71.38 mmol) and p-toluenesulfonic acid (0.679 mg, 3.569 mmol) in water (72 ml) and acetone (168 ml) was heated at 100 °C under microwave irradiation for 15 min. After cooling to room temperature, the reaction mixture was diluted with DCM and washed with $NaHCO_3$ (aqueous sat. solution), dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The residue was triturated with a mixture of Et_2O (100 ml)/acetone (30 ml). The solid was filtered off and the filtrate was concentrated *in vacuo* to yield intermediate compound **D12** (18.13 g, 73 %) as a yellow oil.

Description 13

4-(5-Bromo-indol-1-yl)-cyclohexanol (D13)



trans-**D13**



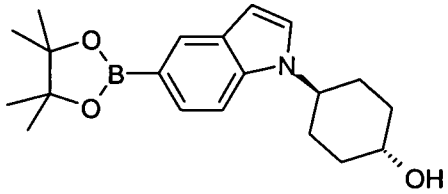
cis-**D13**

To a mixture of intermediate **D12** (2.074 g, 7.098 mmol) in MeOH (50 ml) stirred at 0 °C, was added sodium borohydride (62.198 mg, 1.644 mmol). The resulting reaction mixture was warmed to room temperature and further stirred for 1 h. Subsequently, the mixture was concentrated *in vacuo* and the residue was dissolved in DCM. This solution was washed with NH_4Cl (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; EtOAc/heptane gradient from 0:100 to

30:70 as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate compound *trans*-**D13** (1.809 g, 86.6 %) and intermediate compound *cis*-**D13** (0.110 g, 5.27 %).

Description *trans*-14

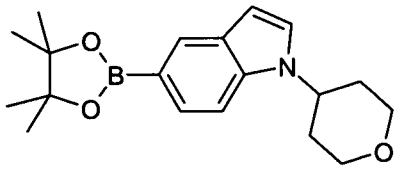
trans-4-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-indol-1-yl]-cyclohexanol (*trans*-**D14**)



To a solution of intermediate *trans*-**D13** (0.300 g, 1.02 mmol) in 1,4-dioxane (12 ml) and DMF (2 ml) were added bis(pinacolato)diboron (0.829 g, 3.263 mmol) and potassium acetate (0.300 g, 3.059 mmol). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (0.0374 g, 0.051 mmol) was added. The reaction mixture was heated at 160 °C under microwave irradiation for 1 h. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent: DCM/EtOAc gradient from 100:0 to 60:40). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate compound *trans*-**D14** (0.260 g, 74.6 %).

Description 15

1-(Tetrahydro-pyran-4-yl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-*1H*-indole (**D15**)

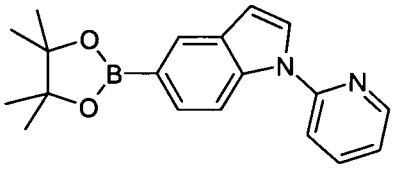


To a solution of 5-Bromo-1-(tetrahydro-pyran-4-yl)-*1H*-indole [C.A.S. 954387-14-5] (0.380 g, 1.356 mmol) in 1,4-dioxane (5 ml) were added, bis(pinacolato)diboron (0.482 g, 1.899 mmol) and potassium acetate (0.399 g, 4.069 mmol). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (0.0597 g, 0.0814 mmol) was added. The reaction mixture was heated at 95 °C overnight. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth and washed with EtOAc.

The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent: DCM). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate compound **D15** (0.312 g, 74.6 %) as a white solid.

Description 16

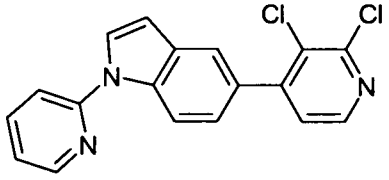
1-Pyridin-2-yl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-*1H*-indole **(D16)**



To a solution of 5-Bromo-1-pyridin-2-yl-*1H*-indole [CA.S. 504424-71-9] (1.73 g, 6.334 mmol) in DMSO (13 ml) were added bis(pinacolato)diboron (0.482 g, 1.899 mmol) and potassium acetate (1.865 g, 19.002 mmol). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (0.139 g, 0.19 mmol) was added. The reaction mixture was heated at 110 °C overnight. After cooling to room temperature, the reaction mixture was refilled with [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (0.280 g) and stirred at 110°C for 2 days. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth and washed with EtOAc. The filtrate was washed with water and NaCl (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent: Heptane/EtOAc 9:1 as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate compound **D16** (0.868 g, 42.8 %) as a white solid.

Description 17

5-(2,3-Dichloro-pyridin-4-yl)-1-pyridin-2-yl-*1H*-indole **(D17)**

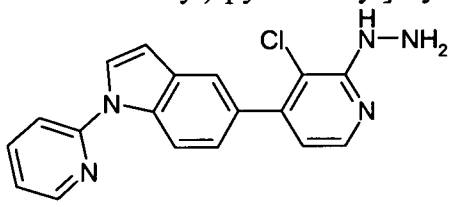


To a mixture of intermediate compound **D1** (0.5 g, 1.826 mmol) in 1,4-dioxane (11.25 ml) under a nitrogen atmosphere were added intermediate compound **D16** (0.684 g, 2.136 mmol), $Pd(PPh_3)_4$ (0.105 g, 0.0913 mmol) and $NaHCO_3$ (3.75 ml, aqueous sat.

solution). The reaction mixture was heated at 150 °C under microwave irradiation for 5 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with EtOAc. The filtrate was washed with water and NaCl (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent: Heptane/EtOAc up to 20% as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate compound **D17** (0.489 g, 79 %).

Description 18

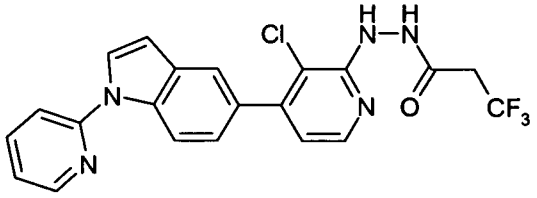
[3-Chloro-4-(1-pyridin-2-yl-*1H*-indol-5-yl)-pyridin-2-yl]-hydrazine (**D18**)



To a solution of intermediate compound **D17** (0.489 g, 1.438 mmol) in EtOH (4 ml), was added hydrazine monohydrate (2.537 ml, 28.765 mmol). The reaction mixture was heated at 90 °C for 16 hours. Then, after cooling to room temperature, the reaction mixture was refilled with hydrazine monohydrate (2.5 ml) and heated again at 100 °C for 16 hours. After cooling to room temperature, the precipitate that developed was collected and washed with water, EtOH and DIPE to yield intermediate compound **D18** (0.388 g, 80%) as a white solid. M.P. 173.3°C

Description 19

2-[3-chloro-4-[1-(2-pyridinyl)-*1H*-indol-5-yl]-2-pyridinyl]hydrazide 3,3,3-trifluoropropionic acid (**D19**)

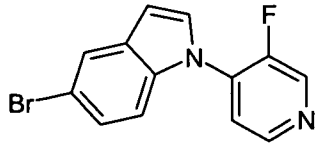


To a solution of intermediate compound **D18** (0.388 g, 1.155 mmol) in dry DCM (8 ml) at 0 °C were added trietylamine (0.126 ml, 0.902 mmol) and 3,3,3-trifluoro-propionyl chloride [C.A.S. 41463-83-6] (0.203 g, 1.387 mmol) was added. The resulting reaction mixture was gradually warmed to room temperature and stirred for 16 h. Additional trietylamine (0.22 ml) was added and the mixture was further stirred for 2 hours. The mixture was then washed with $NaHCO_3$ (aqueous sat. solution), the organic layer was

separated, dried (Na_2SO_4), and the solvent was evaporated *in vacuo* to yield intermediate compound **D19** (0.46 g, 66 %), which was used without further purification.

Description 20

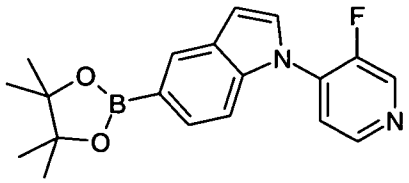
5-Bromo-1-(3-fluoro-pyridin-4-yl)-*1H*-indole **(D20)**



5-Bromo-*1H*-indole [CA.S. 10075-50-0] (2 g, 10.202 mmol) was dissolved in DMF (16 ml). A nitrogen stream was bubbled through the mixture and then were added 3-Fluoro-4-iodopyridine [CA.S. 22282-75-3] (2.502 g, 11.222 mmol), lithium chloride (0.432 g, 10.202 mmol), copper(I) iodide (0.0195 g, 0.102 mmol) and K_2CO_3 (4.23 g, 30.605 mmol). The reaction mixture was heated at 120 °C for 2 days. After cooling to room temperature, the reaction mixture was refilled with lithium chloride (0.100 g) and (copper(I) iodide (0.010) stirred at 120°C for 16 h. After cooling to room temperature, the reaction mixture was washed with NH_3 (aqueous sat. solution) and extracted with DCM. The organic layer was separated, washed with water, dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent: Heptane/EtOAc up to 15% as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate compound **D20** (1.37 g, 46 %).

Description 21

1-(3-Fluoro-pyridin-4-yl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-*1H*-indole **(D21)**

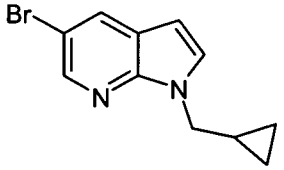


To a solution of intermediate compound **D20** (1.3 g, 4.465 mmol) in 1,4-dioxane (10 ml) were added bis(pinacolato)diboron (1.701 g, 6.698 mmol) and potassium acetate (1.315 g, 13.396 mmol). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (0.197 g, 0.268 mmol) was added. The reaction mixture was heated at 95 °C overnight. After cooling to room temperature, the reaction mixture was refilled with

bis(pinacolato)diboron (0.100 g) and [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (0.05 g) and stirred at 95°C for 2 day overnight. After cooling to room temperature, 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 4% as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate compound **D21** (1.18 g, 78 %).

Description 22

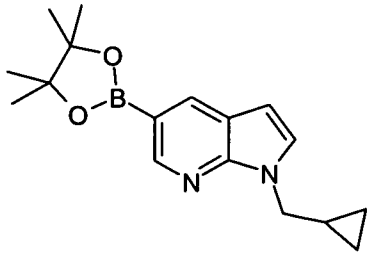
5-Bromo-1-cyclopropylmethyl-*1H*-pyrrolo[2,3-b]pyridine **(D22)**



To a solution of 5-Bromo-*1H*-pyrrolo[2,3-b]pyridine [CA.S. 183208-35-7] (0.95 g, 4.821 mmol) in DMF (8 ml) cooled at 0°C was added portionwise NaH (0.289 g, 7.232 mmol, 60% mineral oil). The resulting mixture was stirred for 15 min., then, cyclopropylmethyl bromide [CA.S. 7051-34-5] (0.716 g, 5.304 mmol) was added. The resulting reaction mixture was gradually warmed to room temperature and stirred for 1 h. The reaction mixture was refilled with cyclopropylmethyl bromide (0.430 mg) and stirred at room temperature for 1 hour.The reaction mixture was quenched with water and extracted with DCM. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo* to yield intermediate compound **D22** (1.2 g, 99%).

Description 23

1-Cyclopropylmethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-*1H*-pyrrolo[2,3-b]pyridine **(D23)**

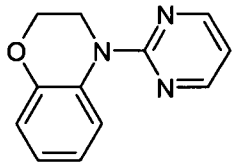


To a solution of intermediate compound **D22** (1.2 g, 4.778 mmol) in 1,4-dioxane (10 ml) were added bis(pinacolato)diboron (1.82 g, 7.168 mmol) and potassium acetate (1.407 g, 14.335 mmol). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM

(1:1) (0.21 g, 0.287 mmol) was added. The reaction mixture was heated at 95 °C overnight. After cooling to room temperature, 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 3% as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate compound **D23** (1.02 g, 71 %).

Description 24

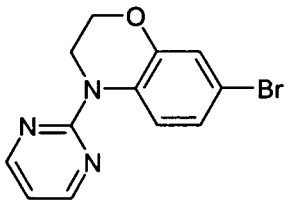
4-Pyrimidin-2-yl-3,4-dihydro-*2H*-benzo[1,4]oxazine **(D24)**



A nitrogen stream was bubbled through a mixture of 2-chloropyrimidine (1 g, 8.731 mmol), and potassium acetate (0.098 g, 0.437 mmol), racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.407 g, 0.655 mmol) and Cs_2CO_3 (5.689 g, 17.462 mmol). Then, 3,4-dihydro-*2H*-1,4-benzoxazino [CA.S. 5735-53-5] (1.77 g, 13.097 mmol) in THF (0.5 ml) was added. The reaction mixture was heated at 110 °C under microwave irradiation for 10 min. After cooling to room temperature, the reaction mixture was washed with EtOAc. The organic layer was separated, washed with water, dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent: DCM/Heptane up to 20% as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate compound **D24** (1.9 g, 81 %).

Description 25

7-Bromo-4-pyrimidin-2-yl-3,4-dihydro-*2H*-benzo[1,4]oxazine **(D25)**

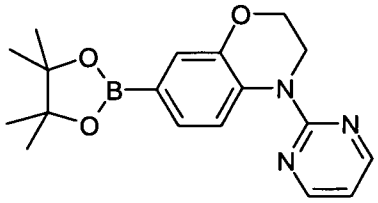


To a solution of intermediate compound **D24** (1.67 g, 7.832 mmol) in DMF (10 ml) was added *N*-bromosuccinimide (1.533 g, 8.615 mmol). The reaction mixture was heated at 180 °C under microwave irradiation for 20 min. After cooling to room

temperature, the reaction mixture was refilled with *N*-bromosuccinimide (1.53 g) and heated at 180 °C under microwave irradiation for 20 min. After cooling, the reaction mixture was washed with $NaHCO_3$ (aqueous sat. solution) and extracted with DCM. The organic layer was separated, dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; Heptane/DCM/EtOAc from 100/0 up to 40/60 as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate compound **D25** (1.2 g, 52 %) as an orange oil

Description 26

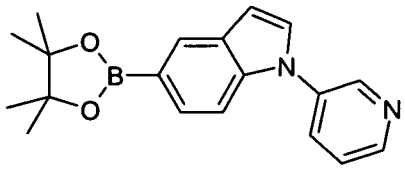
4-Pyrimidin-2-yl-7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-*2H*-benzo[1,4]oxazine **(D26)**



To a solution of intermediate compound **D25** (1.1 g, 3.765 mmol) in 1,4-dioxane (14 ml) were added bis(pinacolato)diboron (1.434 g, 5.648 mmol) and potassium acetate (1.109 g, 11.296 mmol). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (0.138 g, 0.188 mmol) was added. The reaction mixture was heated at 100 °C overnight. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth and washed with EtOAc. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent: DCM as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate compound **D26** (1.11 g, 86 %) as pale yellow oil which became a solid upon standing

Description 27

1-Pyridin-3-yl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-*1H*-indole **(D27)**

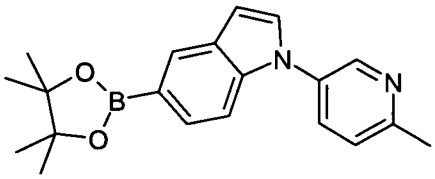


To a solution of 5-Bromo-1-pyridin-3-yl-*1H*-indole [CA.S. 95519-86-1] (1.1 g, 4.027 mmol) in 1,4-dioxane (8 ml) were added bis(pinacolato)diboron (0.125 g, 4.43 mmol)

and potassium acetate (1.186 g, 12.082 mmol). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (0.177 g, 0.242 mmol) was added. The reaction mixture was heated at 90 °C overnight. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth and washed with 1,4-dioxane and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent: Heptane/EtOAc from 100/0 to 85/15 as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate compound **D27** (0.96 g, 74 %) as a white solid.

Description 28

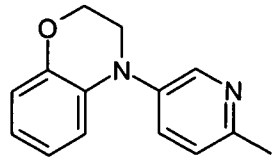
1-(2-Methylpyridin-5-yl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-*1H*-indole **(D28)**



To a stirred solution of 5-Bromo-1-(2-methyl-5-pyridin-3-yl-*1H*-indole [CA.S. 504424-81-1] (2 g, 6.965 mmol) in 1,4-dioxane (10 ml) were added bis(pinacolato)diboron (1.946 g, 7.661 mmol) and potassium acetate (2.051 g, 20.894 mmol). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (0.307 g, 0.418 mmol) was added. The reaction mixture was heated at 90 °C overnight. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth and washed with 1,4-dioxane and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent: Heptane/EtOAc from 100/0 to 85/15 as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate compound **D28** (1.025 g, 44 %).

Description 29

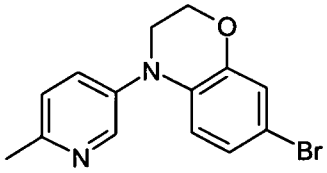
4-(6-Methyl-pyridin-3-yl)-3,4-dihydro-*2H*-benzo[1,4]oxazine **(D29)**



A nitrogen stream was bubbled through a mixture of 5-bromo-2-methylpyridine (3.818 g, 22.195 mmol) in toluene (28 ml), then, ^{t}BuONa (6.186 g, 64.365 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.615 g, 1.11 mmol), bis(dibenzylideneacetonato)palladium (0.383 g, 0.666 mmol) and 3,4-dihydro-*2H*-1,4-benzoxazino [CA.S. 5735-53-5] (1.77 g, 13.097 mmol) were added. The reaction mixture was heated at 80 °C overnight. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth and washed with EtOAc. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent: DCM/EtOAc from 100/0 to 80/10 as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate compound **D29** (3.812 g, 75 %) as a yellow oil.

Description 30

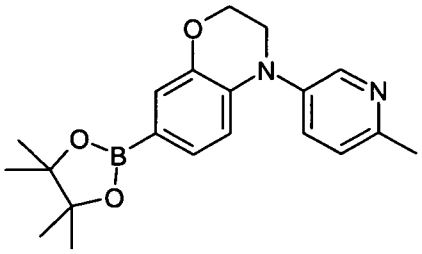
7-Bromo-4-(6-methyl-pyridin-3-yl)-3,4-dihydro-*2H*-benzo[1,4]oxazine **(D30)**



To a solution of intermediate compound **D29** (3.756 g, 16.559 mmol) in DMF (50 ml) was added *N*-bromosuccinimide (3.25 g, 18.259 mmol). The reaction mixture was washed with $NaHCO_3$ (aqueous sat. solution) and extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/AcOEt up to 3% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D30** (4.58 g, 90% as a yellow oil

Description 31

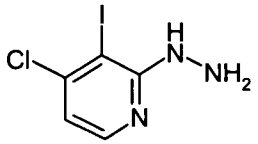
4-(6-Methyl-pyridin-3-yl)-7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-*2H*-benzo[1,4]oxazine **(D31)**



To a solution of intermediate compound **D30** (4.58 g, 15.008 mmol) in 1,4-dioxane (28 ml) were added bis(pinacolato)diboron (4.192 g, 16.509 mmol) and potassium acetate (2.209 g, 22.512 mmol). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (0.551 g, 0.75 mmol) was added. The reaction mixture was heated at 100 °C overnight. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth and washed with 1,4-dioxane. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent: DCM/EtOAc up to 50% as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate compound **D31** (5.23 g, 98 %)

Description 32

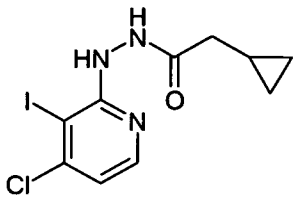
(4-Chloro-3-iodo-pyridin-2-yl)-hydrazine **(D32)**



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 Et_2O. The solid thus obtained was discarded. The mother liquours were concentrated *in vacuo* to yield intermediate compound **D32** (2.31 g, 49%)

Description 33

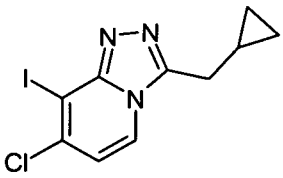
N'-(4-chloro-3-iodo-pyridin-2-yl)-2-cyclopropylcetohydrazide (**D33**)



To a solution of intermediate compound **D32** (3.46 g, 12.84 mmol) in dry DCM (40 ml), cooled at 0 °C, were added Et_3N (3.553 ml, 25.68 mmol) and 2-cyclopropyl-acetyl chloride (1.827 g, 15.408 mmol). The resulting reaction mixture was stirred at room temperature overnight. 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 **D33** (4.5 g, 99%).

Description 34

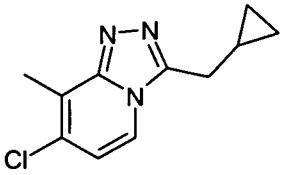
7-Chloro-3-cyclopropylmethyl-8-iodo-[1,2,4]triazolo[4,3-a]pyridine (**D34**)



Intermediate compound **D33** (13.5 g, 38.399 mmol) was heated at 160 °C for 2 h. After cooling, the brown gum was purified by column chromatography (silica gel; DCM/EtOAc from 100/0 up to 50/50 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D34** (7 g, 54%) as a yellow solid. M.P.: 246.7°C

Description 35

7-Chloro-3-cyclopropylmethyl-8-methyl-[1,2,4]triazolo[4,3-a]pyridine (**D35**)

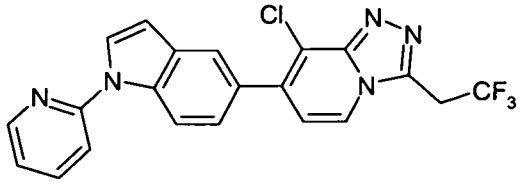


To a mixture of intermediate compound **D34** (0.600 g, 1.799 mmol) in toluene (15 ml) under a nitrogen atmosphere were added methylboronic acid (0.538 g, 8.994 mmol), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine; S-Phos (0.171 g, 0.36 mmol), Palladium(II) acetate (0.0410 g, 0.18 mmol) and K_2CO_3 (0.745 g, 5.396 mmol). The

reaction mixture was heated at 100 °C overnight. After cooling, the mixture was diluted with EtOAc and washed with water. The organic layer was separated and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/EtOAc from 100/0 to 20/80 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield intermediate compound **D35** (0.105 g, 24%) as a cream solid

Example 1

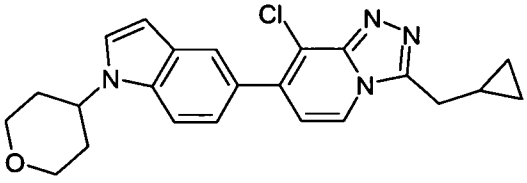
8-Chloro-7,8-dihydro-7-[1-(2-pyridinyl)-*1H*-indol-5-yl]-3-(2,2,2-trifluoroethyl)-1,2,4-triazolo[4,3-a]pyridine **(E1)**



A mixture of intermediate compound **D19** (0.46 g, 0.774 mmol) and phosphorus(V) oxychloride (0.144 ml, 1.548 mmol) in CH_3CN (9.5 ml) was heated at 150 °C under microwave irradiation for 5 min. After cooling, $NaHCO_3$ (aqueous sat. solution) was added. The resulting mixture was extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/AcOEt up to 100% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield final compound **E1** (0.137 g, 41% as a white solid.

Example 2

8-Chloro-3-(cyclopropylmethyl)-7,8-dihydro-7-[1-(tetrahydro-*2H*-pyran-4-yl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine **(E2)**

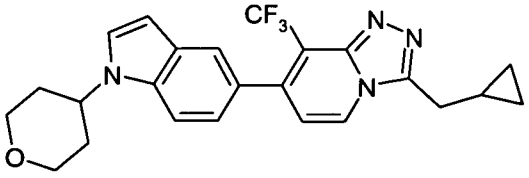


To a mixture of intermediate compound **D4** (0.2 g, 0.6 mmol) in 1,4-dioxane (3 ml) under a nitrogen atmosphere were added intermediate compound **D15** (0.255 g, 0.779 mmol), $Pd(PPh_3)_4$ (0.035 g, 0.03 mmol) and $NaHCO_3$ (0.75 ml, aqueous sat. solution). The reaction mixture was heated at 150 °C under microwave irradiation for 10 min. After cooling, the mixture was filtered through a pad of celite and washed with EtOAc. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; DCM/MeOH(NH_3) up to 9% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield a residue that was subjected

to a second purification by column chromatography (silica gel; DCM/AcOEt up to 80% as eluent) to yield final compound **E2** (0.110 g, 45%).

Example 3

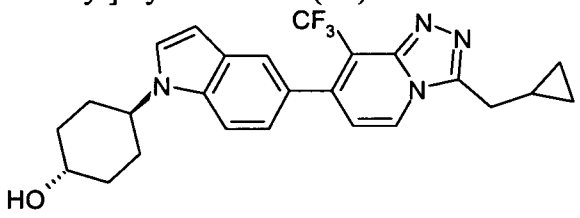
3-(Cyclopropylmethyl)-7,8-dihydro-7-[1-(tetrahydro-*2H*-pyran-4-yl)-*1H*-indol-5-yl]-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridine (**E3**)



To a mixture of intermediate compound **D10** (0.180 g, 0.653 mmol) in 1,4-dioxane (4 ml) under a nitrogen atmosphere were added intermediate compound **D15** (0.231 g, 0.66 mmol), $Pd(PPh_3)_4$ (0.075 g, 0.065 mmol) and $NaHCO_3$ (1 ml, aqueous sat. solution). The reaction mixture was heated at 150 °C under microwave irradiation for 7 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with AcOEt. 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 **E3** (0.09 g, 31%).

Example 4

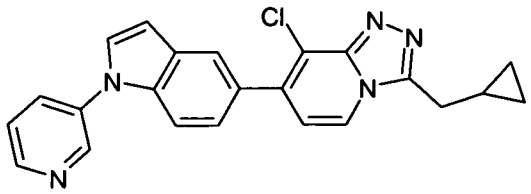
Trans-4-[5-(3-cyclopropylmethyl)-7,8-dihydro-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-*1H*-indol-1-yl]-cyclohexanol (E4)



To a mixture of compound **D10** (0.200 g, 0.726 mmol) in 1,4-dioxane (5 ml) under a nitrogen atmosphere were added compound *trans*-**D14** (0.309 g, 0.907 mmol), $Pd(PPh_3)_4$ (0.083 g, 0.0726 mmol) and $NaHCO_3$ (1.25 ml, aqueous sat. solution). The reaction mixture was heated at 150 °C under microwave irradiation 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 **E4** (0.113 g, 40%).

Example 17

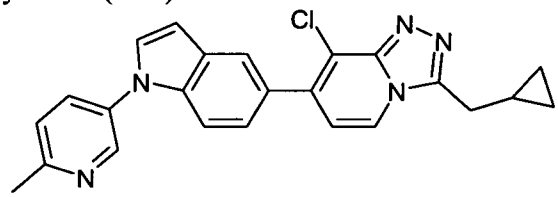
8-Chloro-3-cyclopropylmethyl-7-[1-(pyridin-3-yl)-*1H*-indol-5-yl]-[1,2,4]triazolo[4,3-a]pyridine (E17)



To a mixture of intermediate compound **D4** (0.6 g, 1.799 mmol) in 1,4-dioxane (5 ml) under a nitrogen atmosphere were added intermediate compound **D27** (0.634 g, 1.979 mmol), $Pd(PPh_3)_4$ (0.166 g, 0.144 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 room temperature, the reaction mixture was refilled with $Pd(PPh_3)_4$ (0.050 g) and irradiated 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/MeOH up to 4% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield a residue that was triturated with Et_2O/DIPE mixtures to give a solid that was purified by column chromatography (silica gel; DCM/EtOAc from 100/0 to 40/50 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield final compound **E17** (0.410 g, 57%)

Example 21

8-Chloro-3-cyclopropylmethyl-7-[1-(2-methylpyridin-5-yl)-*1H*-indol-5-yl]-[1,2,4]triazolo[4,3-a]pyridine (E21)

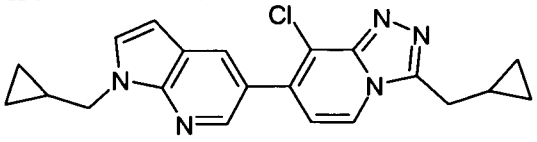


To a mixture of intermediate compound **D4** (0.335 g, 1.005 mmol) in 1,4-dioxane (6 ml) under a nitrogen atmosphere were added intermediate compound **D28** (0.37 g, 1.106 mmol), $Pd(PPh_3)_4$ (0.058 g, 0.050 mmol) and $NaHCO_3$ (2 ml, aqueous sat. solution). The reaction mixture was heated at 150 °C under microwave irradiation for 15 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with 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 10% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield a residue that was triturated with Et_2O to give a solid that was purified

by reversed phase chromatography on C18XBridge 30 X 100 5 μm) to yield final compound **E21** (0.046 g, 11%)

Example 22

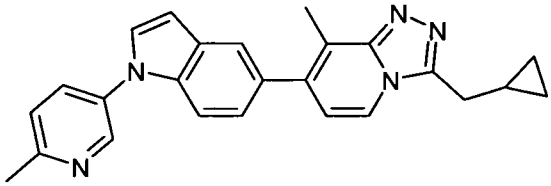
8-Chloro-3-cyclopropylmethyl-7-(1-cyclopropylmethyl-*1H*-pyrrolo[2,3-b]pyridin-5-yl)-[1,2,4]triazolo[4,3-a]pyridine **(E22)**



To a mixture of intermediate compound **D4** (0.3 g, 0.899 mmol) in 1,4-dioxane (4 ml) under a nitrogen atmosphere were added intermediate compound **D23** (0.295 g, 0.989 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 150 °C under microwave irradiation for 10 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with DCM. 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 a residue that was triturated with Et_2O to give final compound **E22** (0.180 g, 52%) as a white solid

Example 35

8-Methyl-3-cyclopropylmethyl-7-[1-(2-methylpyridin-5-yl)-*1H*-indol-5-yl]-[1,2,4]triazolo[4,3-a]pyridine **(E35)**

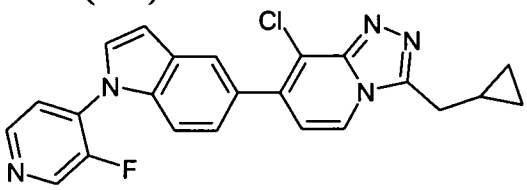


To a mixture of intermediate compound **D35** (0.070 g, 0.316 mmol) in 1,4-dioxane (2 ml) under a nitrogen atmosphere were added intermediate compound **D28** (0.137 g, 0.41 mmol), $Pd(PPh_3)_4$ (0.036 g, 0.031 mmol) and $NaHCO_3$ (1 ml, aqueous sat. solution). The reaction mixture was heated at 150 °C under microwave irradiation for 10 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with $NaHCO_3$ (1 ml, aqueous sat. solution). The solvent was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; DCM/AcOEt up to 100% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield a residue that was triturated with DIPE to give a solid

that was purified by reversed phase chromatography on C18XBridge 19 X 100 5 µm) to yield final compound **E35** (0.025 g, 25%)

Example 42

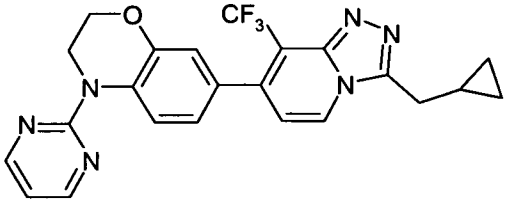
8-Chloro-3-cyclopropylmethyl-7-[1-(3-fluoro-pyridin-4-yl)-*1H*-indol-5-yl]-[1,2,4]triazolo[4,3-a]pyridine **(E42)**



To a mixture of intermediate compound **D4** (0.3 g, 0.899 mmol) in 1,4-dioxane (4 ml) under a nitrogen atmosphere were added intermediate compound **D21** (0.335 g, 0.989 mmol), $Pd(PPh_3)_4$ (0.083 g, 0.0726 mmol) and $NaHCO_3$ (1 ml, aqueous sat. solution). The reaction mixture was heated at 150 °C under microwave irradiation for 15 min. After cooling to room temperature, the reaction mixture was refilled with $Pd(PPh_3)_4$ (0.020 g) and irradiated at 150°C for 15 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with DCM. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; DCM/MeOH up to 4% as eluent). The desired fractions were collected and concentrated *in vacuo* to yield a residue that was triturated with Et_2O to give final compound **E42** (0.270 g, 71%) as a white solid

Example 50

8-Triluoromethyl-3-cyclopropylmethyl-7-[4-pyrimidin-2-yl-3,4-dihydro -*2H*-benzo[1,4]oxazin-6-yl]-[1,2,4]triazolo[4,3-a]pyridine (E50)

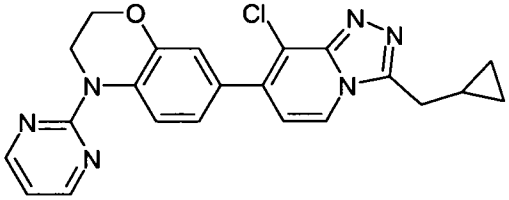


To a mixture of intermediate compound **D10** (0.812 g, 2.946 mmol) in 1,4-dioxane (10 ml) under a nitrogen atmosphere were added intermediate compound **D26** (0.335 g, 0.989 mmol), $Pd(PPh_3)_4$ (0.170 g, 0.147 mmol) and $NaHCO_3$ (2.5 ml, aqueous sat. solution). The reaction mixture was heated at 150 °C under microwave irradiation for 7 min. After cooling to room temperature, the reaction mixture was refilled with $Pd(PPh_3)_4$ (0.100 g) and irradiated at 150°C for 7 min. After cooling to room temperature, the reaction mixture was refilled again with $Pd(PPh_3)_4$ (0.050 g) and

irradiated at 150°C for 7 min After cooling, the mixture was washed with $NaHCO_3$. 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 from 100/0 up to 50/50 as eluent). The desired fractions were collected and concentrated *in vacuo* to yield final compound **E50** (0.680 g, 51% as a white solid.

Example 51

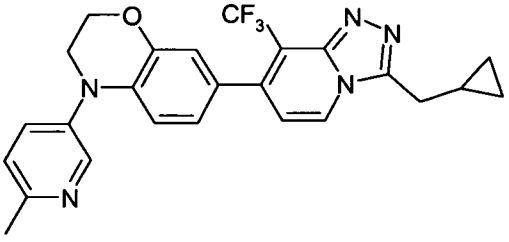
8-Chloro-3-cyclopropylmethyl-7-[4-pyrimidin-2-yl-3,4-dihydro -*2H*-benzo[1,4]oxazin-6-yl]-[1,2,4]triazolo[4,3-a]pyridine **(E51)**



To a mixture of intermediate compound **D4** (0.300 g, 0.899 mmol) in 1,4-dioxane (6 ml) under a nitrogen atmosphere were added intermediate compound **D26** (0.366 g, 1.079 mmol), $Pd(PPh_3)_4$ (0.051 g, 0.045 mmol) and $NaHCO_3$ (1.5 ml, aqueous sat. solution). The reaction mixture was heated at 150 °C under microwave irradiation for 10 min. After cooling, the mixture was washed with $NaHCO_3$. 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 from 100/0 up to 40/60 as eluent). The desired fractions were collected and concentrated *in vacuo* to give a residue that was crystallized from Et_2O to yield final compound **E51** (0.180 g, 47% as a white solid.

Example 57

8-Trifluoromethyl-3-cyclopropylmethyl-7-[4-(6-methyl-pyridin-3-yl)-3,4-dihydro-*2H*-benzo[1,4]oxazin-6-yl]-[1,2,4]triazolo[4,3-a]pyridine **(E57)**

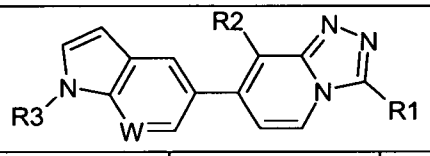


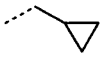
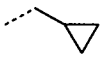
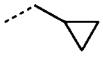
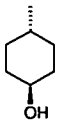
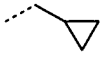
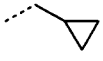
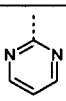
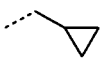
To a mixture of intermediate compound **D10** (0.180 g, 0.653 mmol) in 1,4-dioxane (6 ml) under a nitrogen atmosphere were added intermediate compound **D31** (0.189 g, 0.539 mmol), $Pd(PPh_3)_4$ (0.037 g, 0.032 mmol) and $NaHCO_3$ (1.5 ml, aqueous sat. solution). The reaction mixture was heated at 150 °C under microwave irradiation for 10 min. After cooling to room temperature, the reaction mixture was refilled with **D31**

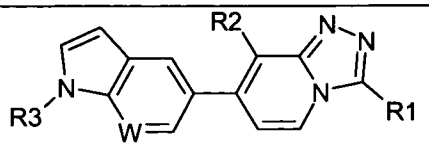
(0.22 equ.) and irradiated at 150°C for 10 min. After cooling to room temperature, the reaction mixture was refilled again with **D31** (0.11 equ.) and irradiated at 150°C for 10 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with $NaHCO_3$. The mixture was extracted with AcOEt. 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 give a residue that was triturated with DIPE to yield final compound **E57** (0.072 g, 23%) as a yellow solid.

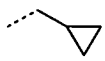
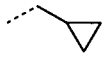
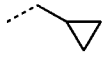
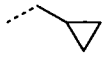
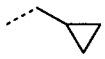
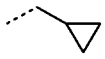
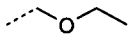
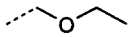
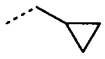
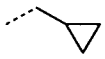
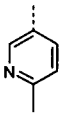
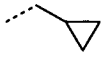
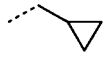
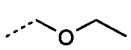
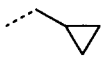
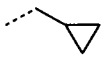
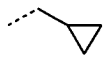
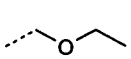
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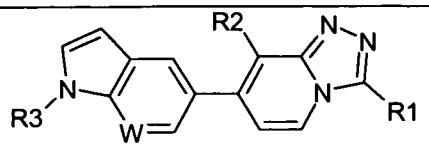
* means exemplified procedure according to which additional compounds were prepared.

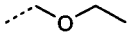
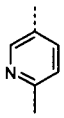
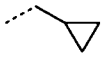
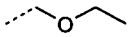
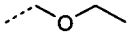
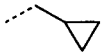
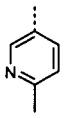
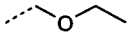
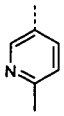
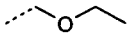
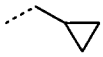
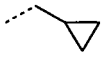
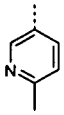
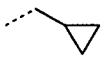
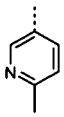
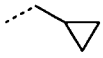
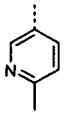
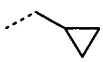
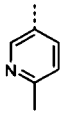
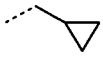
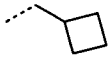


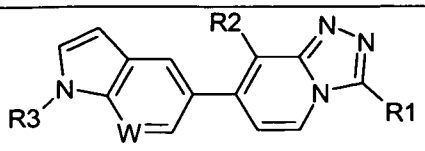
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3	E3*		--CF_3		CH
4	E4*		--CF_3		CH
5	E2		--Cl	H	N
6	E1	--CH_2CF_3	--Cl		CH
7	E2		--CF_3		CH
8	E2		--Cl	H	C-Cl



Co. Nr.	Exp nr.	R^1	R^2	R^3	W
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10	E2		--Cl		CH
14	E2		--CF_3	H	C-Cl
15	E2		--Cl		CH
16	E2		--Cl		CH
17	E17*		--Cl		CH
18	E1		--Cl		CH
19	E1		--Cl		CH
20	E2		--Cl	H	CH
21	E21*		--Cl		CH
22	E22*		--Cl		N
23	E1		--Cl	H	C-Cl
24	E2		--CF_3	H	N
25	E2		--CF_3		N
26	E1		--Cl		CH



Co. Nr.	Exp nr.	R^1	R^2	R^3	W
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30	E1		--CF_3		CH
31	E2		--Cl		C-F
32	E1		--CF_3		CH
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34	E2		--CF_3		CH
35	E35*		--CH_3		CH
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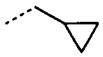
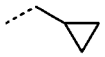
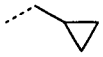
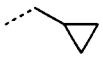
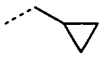
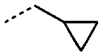
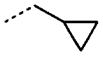
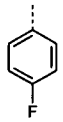
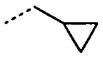
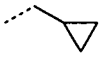
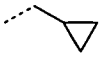
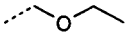
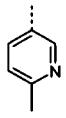
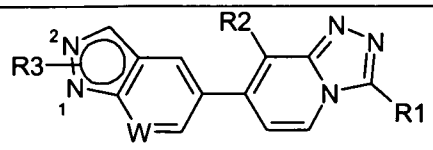
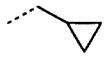
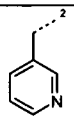
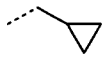
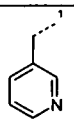
Co. Nr.	Exp nr.	R^1	R^2	R^3	W
40	E2		--CH_3		N
41	E2		--Cl		N
42	E42*		--Cl		CH
43	E2		--CF_3		CH
44	E2		--Cl		CH
45	E2		--Cl		N
46	E2		--CF_3		CH
47	E2		--Cl		CH
48	E2		--Cl		C-F
49	E2		--CH_3		CH

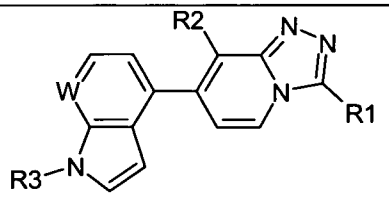
Table 1b : Compounds prepared according to Formula (I).



Co.nr.	Exp nr.	R^1	R^2	R^3	W
11	E2		--Cl		CH
12	E2		--Cl		CH

wherein in R^3, the "[1]" and "[2]" mean the binding position at the indazole ring.

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



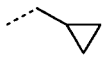
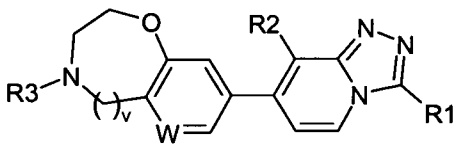
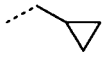
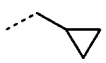
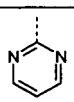
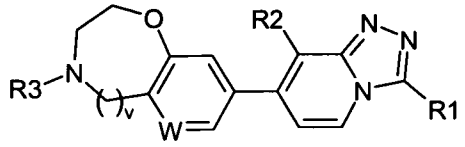
Co.nr.	Exp nr.	R^1	R^2	R^3	W
13	E2		--Cl	H	CH

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



Co.nr.	Exp nr.	R^1	R^2	R^3	W	v
50	E50*		$--CF_3$		CH	0
51	E51*		--Cl		CH	0



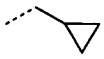
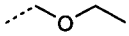
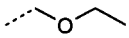
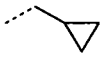
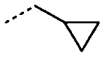
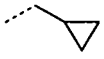
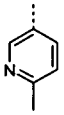
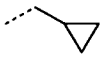
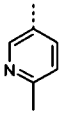
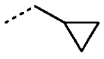
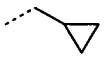
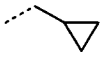
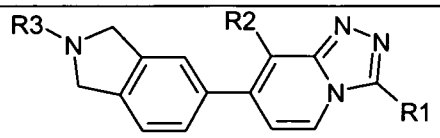
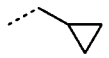
Co.nr.	Exp nr.	R^1	R^2	R^3	W	v
52	E2		--Cl		CH	0
53	E2		--Cl		CH	0
54	E2		--Cl		CH	0
55	E2		--Cl		CH	0
56	E2		--CF_3		CH	0
57	E2		--CF_3		CH	0
58	E2		--Cl		CH	0
59	E2		--CF_3		CH	0
60	E2		--CF_3		CH	0
61	E2		--CF_3	H	CH	1

Table 1e : Compound prepared according to Formula (I).



Co.nr.	Exp. nr.	R^1	R^2	R^3
62	E2		--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 (TOF, ZQ, SQD, Platform)

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 diode-array detector (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 electrospray ionization source or an ESCI dual ionization source (electrospray combined with atmospheric pressure chemical ionization). 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 (MSD)

The HPLC measurement was performed using a HP 1100 from Agilent Technologies comprising a binary pump with degasser, an autosampler, a column oven, a diode-array

detector (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 (electrospray combined with atmospheric pressure chemical ionization). 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 (Acquity-SQD)

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 diode-array detector (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 (electrospray combined with atmospheric pressure chemical ionization). 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 HP 1100-MS instruments (TOF, SQD or MSD)

The HPLC measurement was performed using an HP 1100 (Agilent Technologies) system comprising a pump (quaternary or binary) with degasser, an autosampler, a column oven, a diode-array detector (DAD) and a column as specified in the respective methods. The MS detector was configured with either an electrospray ionization source or an ESCI dual ionization source (electrospray combined with atmospheric pressure chemical ionization). Nitrogen was used as the nebulizer gas. The source temperature was maintained either at 140 °C or 100°C. Data acquisition was performed either with MassLynx-Openlynx software or Chemsation-Agilent Data Browser software.

MS Procedure for LC Method 3&5: Low-resolution mass spectra (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 1

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 ammonium acetate 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. Low-resolution mass spectra (quadrupole, SQD) were acquired by scanning from 100 to 1000 in 0.1 seconds using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 20 V for positive ionization mode and 30 V for negative ionization mode.

Method .2

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 ammonium acetate 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. High-resolution mass spectra (Time of Flight, TOF) were acquired by scanning from 100 to 750 in 0.5 seconds using a dwell time of 0.3 seconds. The capillary needle voltage was 2.5 kV for positive ionization mode and 2.9 kV for negative ionization mode. The cone voltage was 20 V for both positive and negative ionization modes. Leucine-Enkephaline was the standard substance used for the lock mass calibration.

Method 3

In addition to the general procedure: 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 ammonium acetate solution + 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.

Method 4

In addition to the general procedure: Reversed phase HPLC was carried out on an Eclipse Plus-C18 column (3.5 µm, 2.1 x 30 mm) from Agilent, with a flow rate of 1.0 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l ammonium acetate solution + 5 % CH_3CN), 5 % B (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. Low-resolution mass spectra (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 seconds using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 20 V for positive ionization mode and 30 V for negative ionization mode.

Method 5

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 50°C. The gradient conditions used are: 95 % A (formic acid solution, 0.1 %), 5 % B (MeOH), to 40 % A, 60 % B, then to 5 % A, 95 % B and equilibrated to initial conditions up to 7.0 min run; 0.5 injection volume.

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

Co. No.	mp (°C)	R_t	$[MH^+]$	LCMS Method
1	>300	3.32	428	1
2	>300	3.32	407	2
3	193.1	3.48	441	2
4	206.9	2.98	455	1
5	>300	2.03	324	1
6	n.d.	3.43	429	1
7	n.d.	3.3	435	3

Co. No.	mp (°C)	R_t	$[MH^+]$	LCMS Method
8	233.5	3.68	357	2
9	n.d.	2.82	395	1
10	>300	2.95	421	1
11	n.d.	2.2	415	1
12	n.d.	2.38	415	1
13	>300	2.39	323	1
14	>300	3.25	391	4
15	>300	3.11	401	3

Co. No.	mp (°C)	R_t	$[MH^+]$	LCMS Method
16	197.1	3.05	400	3
17	n.d.	1.81	400	3
18	235	2.96	404	3
19	n.d.	3.05	405	3
20	>300	2.18	323	3
21	137.2	2.80	414	3
22	184.7	2.84	378	3
23	n.d.	2.37	361	3
24	>300	1.85	358	3
25	>300	3.02	412	3
26	233.2	4.20	404	5
27	188.9	2.70	418	3
28	235.5	3.54	341	2
29	176.4	2.01	327	3
30	182.4	2.60	438	3
31	243.8	2.86	432	3
32	163.1	2.87	452	3
33	200.1	2.22	361	3
34	144.3	2.68	434	3
35	263.3	2.83	394	3
36	204	2.90	448	3
37	>300	3.21	420	3
38	>300	2.97	466	3
39	>300	2.29	392	3

Co. No.	mp (°C)	R_t	$[MH^+]$	LCMS Method
40	>300	2.04	358	3
41	>300	1.59	401	3
42	>300	1.93	418	3
43	>300	1.88	434	3
44	>300	1.76	400	3
45	>300	3.16	418	3
46	>300	2.01	448	3
47	>300	1.91	414	3
48	195.6	1.88	418	3
49	108.5	1.94	398	3
50	>300	2.86	453	3
51	194.9	2.62	419	3
52	194.9	2.82	418	3
53	138.4	2.70	422	3
54	278.5	2.59	423	3
55	251.2	3.75	418	2
56	247.1	2.52	452	3
57	>300	2.76	466	3
58	205.5	2.61	432	3
59	>300	2.24	452	3
60	248.9	2.31	466	3
61	154.9	1.21	389	3
62	>300	1.57	359	4

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 (500 MHz, $CDCl_3$) δ ppm 4.11 (q, *J*=9.8 Hz, 2 H), 6.81 (d, *J*=3.5 Hz, 1 H), 7.11 (d, *J*=6.9 Hz, 1 H), 7.23 (ddd, *J*=7.5, 4.9, 0.9 Hz, 1 H), 7.47 (dd, *J*=8.7, 1.7 Hz, 1 H), 7.53 (d, *J*=8.1 Hz, 1 H), 7.80 (d, *J*=3.5 Hz, 1 H), 7.85 (d, *J*=1.4 Hz, 1 H), 7.86 - 7.90 (m, 1 H), 8.00 (d, *J*=6.9 Hz, 1 H), 8.38 (d, *J*=8.7 Hz, 1 H), 8.59 - 8.63 (m, 1 H).

Co. No. 2: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.32 - 0.42 (m, 2 H), 0.59 - 0.70 (m, 2 H), 1.18 - 1.29 (m, 1 H), 2.06 - 2.11 (m, 2 H), 2.11 - 2.21 (m, 2 H), 3.13 (d, *J*=6.9 Hz, 2 H), 3.65 (td, *J*=11.8, 2.0 Hz, 2 H), 4.19 (dd, *J*=11.3, 4.0 Hz, 2 H), 4.53 (tt, *J*=11.6, 4.3 Hz, 1 H), 6.64 (d, *J*=3.2 Hz, 1 H), 6.99 (d, *J*=6.9 Hz, 1 H), 7.32 (d, *J*=3.2 Hz, 1 H), 7.41 (dd, *J*=8.4, 1.4 Hz, 1 H), 7.52 (d, *J*=8.4 Hz, 1 H), 7.82 (d, *J*=1.2 Hz, 1 H), 7.95 (d, *J*=7.2 Hz, 1 H).

Co. No. 3: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.32 - 0.44 (m, 2 H), 0.59 - 0.72 (m, 2 H), 1.17 - 1.29 (m, 1 H), 2.04 - 2.22 (m, 4 H), 3.15 (d, J=6.5 Hz, 2 H), 3.65 (td, J=11.8, 2.8 Hz, 2 H), 4.19 (dd, J=10.9, 3.7 Hz, 2 H), 4.46 - 4.57 (m, 1 H), 6.61 (d, J=3.2 Hz, 1 H), 6.89 (d, J=6.9 Hz, 1 H), 7.21 (dd, J=8.3, 1.2 Hz, 1 H), 7.32 (d, J=3.5 Hz, 1 H), 7.47 (d, J=8.6 Hz, 1 H), 7.64 (d, J=1.4 Hz, 1 H), 8.06 (d, J=7.2 Hz, 1 H).

Co. No. 4: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.33 - 0.42 (m, 2 H), 0.61 - 0.70 (m, 2 H), 1.18 - 1.29 (m, 1 H), 1.52 - 1.68 (m, 3 H), 1.81 - 1.96 (m, 2 H), 2.22 (br d, J=10.4 Hz, 4 H), 3.15 (d, J=6.7 Hz, 2 H), 3.75 - 3.88 (m, 1 H), 4.24 - 4.38 (m, 1 H), 6.58 (d, J=3.2 Hz, 1 H), 6.89 (d, J=7.2 Hz, 1 H), 7.20 (dd, J=8.4, 1.0 Hz, 1 H), 7.28 (d, J=3.2 Hz, 1 H), 7.44 (d, J=8.6 Hz, 1 H), 7.62 (d, J=1.2 Hz, 1 H), 8.05 (d, J=7.2 Hz, 1 H).

Co. No. 17: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.32 - 0.43 (m, 2 H), 0.59 - 0.71 (m, 2 H), 1.15 - 1.34 (m, 1 H), 3.14 (d, *J*=6.9 Hz, 2 H), 6.84 (d, *J*=3.2 Hz, 1 H), 7.00 (d, *J*=7.2 Hz, 1 H), 7.33 - 7.48 (m, 2 H), 7.52 (dd, *J*=8.1, 4.9 Hz, 1 H), 7.63 (d, *J*=8.7 Hz, 1 H), 7.83 - 7.93 (m, 2 H), 7.97 (d, *J*=7.2 Hz, 1 H), 8.67 (dd, *J*=4.8, 1.3 Hz, 1 H), 8.88 (d, *J*=2.6 Hz, 1 H).

Co. No. 21: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.32 - 0.44 (m, 2 H), 0.58 - 0.72 (m, 2 H), 1.17 - 1.31 (m, 1 H), 2.68 (s, 3 H), 3.14 (d, *J*=6.7 Hz, 2 H), 6.81 (dd, *J*=3.2, 0.7 Hz, 1 H), 6.99 (d, *J*=6.9 Hz, 1 H), 7.36 (d, *J*=8.3 Hz, 1 H), 7.39 (d, *J*=3.2 Hz, 1 H), 7.41 (dd, *J*=8.6, 1.6 Hz, 1 H), 7.58 (d, *J*=8.6 Hz, 1 H), 7.76 (dd, *J*=8.2, 2.7 Hz, 1 H), 7.88 (d, *J*=1.2 Hz, 1 H), 7.96 (d, *J*=6.9 Hz, 1 H), 8.73 (d, *J*=2.5 Hz, 1 H).

Co. No. 22: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.26 - 0.42 (m, 2 H), 0.42 - 0.55 (m, 2 H), 0.55 - 0.71 (m, 4 H), 1.19 - 1.29 (m, 1 H), 1.30 - 1.40 (m, 1 H), 3.14 (d, *J*=6.6 Hz, 2 H), 4.22 (d, *J*=6.9 Hz, 2 H), 6.57 (d, *J*=3.8 Hz, 1 H), 6.96 (d, *J*=7.2 Hz, 1 H), 7.46 (d, *J*=3.5 Hz, 1 H), 7.99 (d, *J*=6.9 Hz, 1 H), 8.12 (d, *J*=2.0 Hz, 1 H), 8.47 (d, *J*=2.0 Hz, 1 H).

Co. No. 35: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.29 - 0.43 (m, 2 H), 0.54 - 0.70 (m, 2 H), 1.19 - 1.31 (m, 1 H), 2.67 (s, 3 H), 2.68 (s, 3 H), 3.12 (d, *J*=6.7 Hz, 2 H), 6.79 (d, *J*=3.2 Hz, 1 H), 6.90 (d, *J*=7.2 Hz, 1 H), 7.25 (dd, *J*=8.6, 1.6 Hz, 1 H), 7.36 (d, *J*=8.3 Hz, 1 H), 7.38 (d, *J*=3.2 Hz, 1 H), 7.56 (d, *J*=8.6 Hz, 1 H), 7.69 (d, *J*=1.4 Hz, 1 H), 7.77 (dd, *J*=8.2, 2.7 Hz, 1 H), 7.88 (d, *J*=6.9 Hz, 1 H), 8.74 (d, *J*=2.5 Hz, 1 H).

Co. No. 45: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.31 - 0.44 (m, 2 H), 0.57 - 0.72 (m, 2 H), 1.16 - 1.32 (m, 1 H), 3.14 (d, *J*=6.9 Hz, 2 H), 6.87 (d, *J*=3.5 Hz, 1 H), 6.99 (d, *J*=6.9 Hz, 1 H), 7.41 - 7.50 (m, 2 H), 7.52 - 7.65 (m, 2 H), 7.88 (d, *J*=1.2 Hz, 1 H), 7.98 (d, *J*=6.9 Hz, 1 H), 8.59 (d, *J*=4.9 Hz, 1 H), 8.73 (d, *J*=2.6 Hz, 1 H).

Co. No. 50: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.27 - 0.43 (m, 2 H), 0.57 - 0.76 (m, 2 H), 1.11 - 1.31 (m, 1 H), 3.14 (d, *J*=6.6 Hz, 2 H), 4.24 - 4.49 (m, 4 H), 6.79 (t, *J*=4.8 Hz, 1 H), 6.84 (d, *J*=6.9 Hz, 1 H), 6.92 (dd, *J*=8.7, 2.0 Hz, 1 H), 6.95 (d, *J*=2.0 Hz, 1 H), 8.07 (d, *J*=7.2 Hz, 1 H), 8.21 (d, *J*=8.7 Hz, 1 H), 8.50 (d, *J*=4.6 Hz, 2 H).

Co. No. 51: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.26 - 0.44 (m, 2 H), 0.56 - 0.70 (m, 2 H), 1.12 - 1.31 (m, 1 H), 3.12 (d, *J*=6.6 Hz, 2 H), 4.28 - 4.46 (m, 4 H), 6.80 (t, *J*=4.8 Hz, 1 H), 6.92 (d, *J*=7.2 Hz, 1 H), 7.12 (dd, *J*=8.4, 2.0 Hz, 1 H), 7.17 (d, *J*=2.0 Hz, 1 H), 7.94 (d, *J*=7.2 Hz, 1 H), 8.21 (d, *J*=8.4 Hz, 1 H), 8.50 (d, *J*=4.6 Hz, 2 H).

Co. No. 57: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.29 - 0.46 (m, 2 H), 0.54 - 0.71 (m, 2 H), 1.15 - 1.24 (m, 1 H), 2.58 (s, 3 H), 3.12 (d, *J*=6.7 Hz, 2 H), 3.77 (t, *J*=4.4 Hz, 2 H), 4.39 (dd, *J*=4.6, 4.2 Hz, 2 H), 6.74 (dd, *J*=8.3, 1.8 Hz, 1 H), 6.81 (d, *J*=8.6 Hz, 2 H), 6.92 (d, *J*=1.8 Hz, 1 H), 7.20 (d, *J*=8.3 Hz, 1 H), 7.53 (dd, *J*=8.3, 2.5 Hz, 1 H), 8.04 (d, *J*=7.2 Hz, 1 H), 8.48 (d, *J*=2.5 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

The concentration-response curves of representative compounds of the present invention –obtained in the presence of EC_{20} of mGluR2 agonist glutamate to determine positive allosteric modulation (PAM)- were generated using the Lexis software interface (developed at J&J). Data were calculated as % of the control glutamate response, defined as the maximal response that is generated upon addition of glutamate alone. Sigmoid concentration-response curves plotting these percentages versus the log concentration of the test compound were analyzed using non-linear regression analysis. The concentration producing half-maximal effect is then calculated as EC_{50}. The pEC_{50} values below are calculated as the $-\log EC_{50}$ (wherein EC_{50} is expressed in mol/L). The results of this test are shown in table 3 below.

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.

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.

Sleep Wake Electroencephalography (SW-EEG) in rats

SW-EEG analyses are a highly sensitive read-out of a compound's central functional activity that may provide additional insight in the potential therapeutic application (i.e. via drug classification fingerprinting). Systemic administration of an mGlu2/3 receptor agonist and PAM has been shown to selectively suppress rapid eye movement (REM) sleep in rat. Internal efforts have confirmed that this effect is mGlu2 receptor-mediated, i.e. is absent in mGlu2 KO mice. Sleep abnormalities are often associated with CNS disorders; as such, the potential use of mGlu2 modulators could also have benefit in the treatment of CNS disorders in which (REM) sleep aberrations are manifested. More specifically, the combination of a persistent reduction in REM occurrence and an increase in REM latency is one of the key features of the typical SW architecture fingerprint of most clinically active antidepressants.

We investigated the effects of oral administration of compounds according to the invention on SW organization in rats. The mGlu2/3 receptor agonist LY404039 was also evaluated to allow comparison.

Compound 17 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 in the [^{35}S]GTPγS binding assay.

Co.No.	GTPγS-hR2 PAM pEC_{50}
1	7.36

Co.No.	GTPγS-hR2 PAM pEC_{50}
2	7.19

Co.No.	GTPγS-hR2 PAM pEC_{50}
3	7.55
4	7.95
5	n.c.
6	7.47
7	7.94
8	7.60
9	6.80
10	7.28
11	6.06
12	6.45
13	6.09
14	7.96
15	7.27
16	7.17
17	7.10
18	6.54
19	6.90
20	6.60
21	7.63
22	6.49
23	7.02
24	5.85
25	6.74
26	6.74
27	7.25
28	6.93
29	5.90

Co.No.	GTPγS-hR2 PAM pEC_{50}
30	7.47
31	7.64
32	7.76
33	6.76
34	7.52
35	7.15
36	8.03
37	7.40
38	7.77
39	6.90
40	6.39
41	6.22
42	7.54
43	7.78
44	7.18
45	6.82
46	8.09
47	7.40
48	7.33
49	6.76
50	6.89
51	6.60
52	6.86
53	6.48
54	6.13
55	7.18
56	7.85

Co.No.	GTPγS-hR2 PAM pEC_{50}
57	8.43
58	7.92
59	7.50
60	7.50
61	n.c.

n.c. means not calculated

EC_{50} values were not calculated in cases where the concentration-response curve did not reach a plateau level. By definition, the EC_{50} value of a compound is the concentration needed to reach 50% of the maximal response.

All compounds were tested in presence of mGluR2 agonist, glutamate at a predetermined EC_{20} concentration, to determine positive allosteric modulation (GTPγS-PAM). pEC_{50} values were calculated from a concentration-response experiment of at least 10 concentrations. If more experiments were performed, the average pEC_{50} value is reported and error deviation was <0.5.

Table 4. Pharmacological data for compounds according to the invention in the PCP-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.	CAR-Inh.
4	13.2	20
		≥40*
17	10.7	20*
31	7.1	n.t.

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

Compounds 4, 17 and 31 inhibited PCP-induced hyperlocomotion in mice and compounds 4 and 17 also inhibited the conditioned avoidance response in rats, attesting to their possible antipsychotic potential.

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

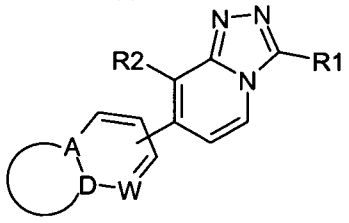
Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

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

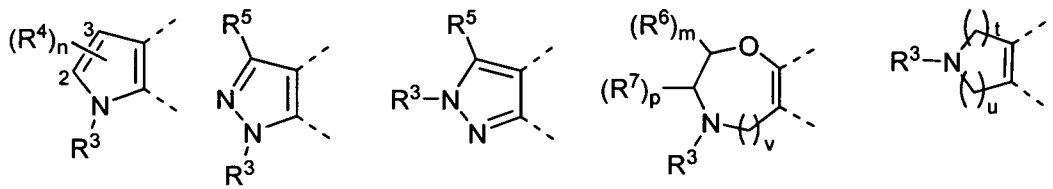
the bond drawn into the ring indicates that the bond may be attached to any carbon ring atom;

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}alkyl, (C_{1-3}alkyloxy)C_{1-3}alkyl, C_{1-3}alkyloxy, 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 one or more independently selected C_{1-3}alkyl substituted with one or more independently selected halo substituents; (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 substituted with one or more independently selected halo substituents; C_{1-3}alkyloxy substituted with one or more independently selected halo substituents; C_{1-3}alkyl; C_{3-7}cycloalkyl; and (C_{3-7}cycloalkyl)C_{1-3}alkyl;



forms a radical selected from (a), (b), (c), (d) and (e):



(a) (b) (c) (d) (e)

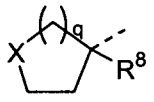
wherein

the bond drawn into (a) indicates that R^4 may be attached to any of carbon ring atoms 2 and 3;

each R^3 is independently selected from the group consisting of hydrogen; unsubstituted C_{1-6}alkyl; C_{1-6}alkyl substituted with one or more substituents independently selected from the group consisting of halo, hydroxy, C_{1-3}alkoxy and trifluoromethyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with one or more substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxy, C_{1-3}alkoxy and trifluoromethyl; C_{3-7}cycloalkylC_{1-3}alkyl; unsubstituted phenyl; phenyl substituted with one or more substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl; Het^3; and Het^3C_{1-3}alkyl;

or

each R^3 is independently selected from a cyclic radical of formula (f)

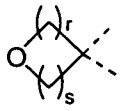

(f)

wherein R^8 is selected from hydrogen, C_{1-3}alkyl, C_{1-3}alkyloxy and hydroxyC_{1-3}alkyl;

q is 1 or 2 ;

X is selected from O, CH_2 and $CR^9(OH)$, wherein R^9 is selected from hydrogen, C_{1-3}alkyl and C_{3-7}cycloalkyl; or

X is a cyclic radical of formula (g)


(g)

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

each R^4, R^6 and R^7 are each independently selected from C_{1-3}alkyl and C_{1-3}alkyl substituted with one or more independently selected halo substituents;

each R^5 is independently selected from the group consisting of hydrogen, C_{1-3}alkyl, and C_{1-3}alkyl substituted with one or more independently selected halo substituents;

n, m and p are each independently selected from 0, 1 and 2;

v is 0 or 1;

t and u are each independently selected from 1 and 2;

W is selected from N and CR^{10};

wherein R^{10} is selected from hydrogen, halo and trifluoromethyl;

each Het^1 is a saturated heterocyclic radical selected from pyrrolidinyl; piperidinyl; piperazinyl; and morpholinyl; each of which may be optionally substituted with one or more each 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 pyridyl or pyrimidinyl; and

each Het^3 is a heterocycle selected from the group consisting of tetrahydropyran, pyridyl; and pyrimidinyl; each of them being optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl; and

halo is selected from fluoro, chloro, bromo and iodo;

or a pharmaceutically acceptable salt or a solvate thereof.

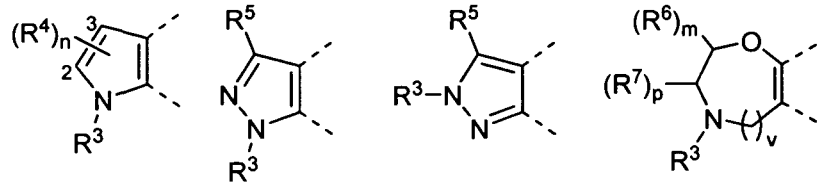
2. The compound of formula (I) according to claim 1, or a stereochemically isomeric form thereof, wherein

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 independently selected halo substituents; and (C_{3-7}cycloalkyl)C_{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 independently selected halo substituents;



is selected from (a), (b), (c) and (d):



(a) (b) (c) (d)

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

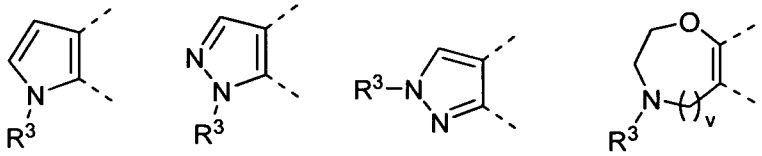
m, n and p are 0;

v is 0 or 1;

each R^5 is hydrogen;
W is selected from N and CR^{10};
R^{10} is selected from hydrogen and halo;
Het^3 is a heterocycle selected from the group consisting of tetrahydropyran; pyridyl; and pyrimidinyl; each of theim being optionally substituted with one or more substituents each independently selected from halo and C_{1-3}alkyl; 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 2, or a stereochemically isomeric form thereof, wherein

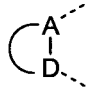

is selected from (a'), (b'), (c') and (d'):

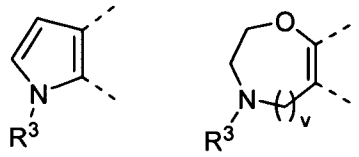


(a') (b') (c') (d')

each R^3 is independently selected from the group consisting of hydrogen; hydroxyC_{1-6}alkyl; C_{3-7}cycloalkyl substituted with one hydroxy substituent; (C_{3-7}cycloalkyl)C_{1-3}alkyl; phenyl substituted with one halo substituent; Het^3; and Het^3C_{1-3}alkyl;
v is 0 or 1;
W is selected from the group consisting of N, CH, CCl and CF;
Het^3 is a heterocycle selected from the group consisting of tetrahydropyran; pyridyl optionally with one substituent selected from halo and C_{1-3}alkyl; and pyrimidinyl;
halo is selected from fluoro and chloro;
and R^1 and R^2 are as defined in claim 1 or 2;
or a pharmaceutically acceptable salt or a solvate thereof.

4. The compound according to claim 1, wherein


is selected from (a') and (d'):



(a') (d')

R^1 is C_{3-7}cycloalkylC_{1-3}alkyl;

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

R^3 is selected from hydrogen; C_{3-7}cycloalkyl substituted with one hydroxy substituent; (C_{3-7}cycloalkyl)C_{1-3}alkyl; pyridyl optionally with one substituent selected from halo and C_{1-3}alkyl; and pyrimidinyl;

W is selected from N, CH and CCl;

v is 0; and

halo is selected from 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

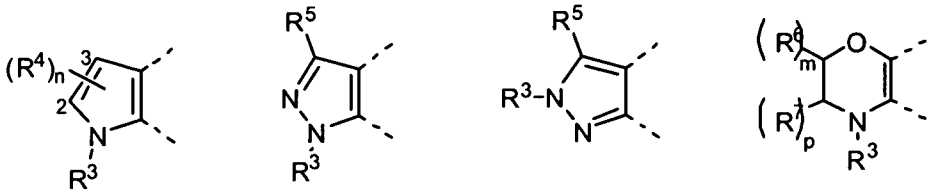
the bond drawn into the ring indicates that the bond may be attached to any carbon ring atom;

R^1 is selected from hydrogen; C_{1-6}alkyl; (C_{1-3}alkyloxy)C_{1-3}alkyl; [(C_{1-3}alkyloxy)-C_{1-3}alkyloxy]C_{1-3}alkyl; mono-, di- or tri-haloC_{1-3}alkyl; unsubstituted benzyl; benzyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, (C_{1-3}alkyloxy)C_{1-3}alkyl, C_{1-3}alkyloxy, 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}alkyloxy; C_{1-3}alkyl; C_{3-7}cycloalkyl and (C_{3-7}cycloalkyl)C_{1-3}alkyl;



forms a radical selected from (a), (b), (c) and (d):



(a) (b) (c) (d)

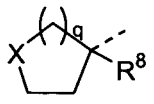
wherein

the bond drawn into (a) indicates that R^4 may be attached to any of carbon ring atoms 2 and 3;

R^3 is selected from hydrogen; unsubstituted C_{1-6}alkyl; C_{1-6}alkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, hydroxy, C_{1-3}alkoxy or trifluoromethyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxy, C_{1-3}alkoxy and trifluoromethyl; C_{3-7}cycloalkylC_{1-3}alkyl; unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl; Het^3 and Het^3C_{1-3}alkyl;

or

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



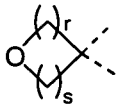
(f)

wherein R^8 is selected from hydrogen, C_{1-3}alkyl, C_{1-3}alkyloxy and hydroxyC_{1-3}alkyl;

q is 1 or 2 ;

X is selected from O, CH_2 and $CR^9(OH)$ wherein R^9 is selected from hydrogen, C_{1-3}alkyl and C_{3-7}cycloalkyl; or

X is a cyclic radical of formula (g)



(g)

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

R^4, R^6 and R^7 are independently selected from C_{1-3}alkyl and mono-, di- and tri-halo-C_{1-3}alkyl;

R^5 is selected from hydrogen, C_{1-3}alkyl and mono-, di- and tri-haloC_{1-3}alkyl;

n, m and p are independently selected from 0, 1 and 2;

W is selected from N and CR^{10};

wherein R^{10} is selected from hydrogen, halo and trifluoromethyl;

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

each Het^2 is pyridyl or pyrimidinyl; and

each Het^3 is selected from the group consisting of tetrahydropyran, pyridyl and pyrimidinyl, each of them being optionally substituted with 1 or 2 substituents selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl;

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:

trans-4-[5-[3-(cyclopropylmethyl)-8-(trifluoromethyl)-1,2,4-triazolo[4,3-a]-pyridine-7-yl]-*1H*-indol-1-yl]-cyclohexanol;

8-chloro-7-(7-chloro-*1H*-indol-5-yl)-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]-pyridine;

8-chloro-3-(cyclopropylmethyl)-7-[1-(3-pyridinyl)-*1H*-indol-5-yl]-1,2,4-triazolo[4,3-a]pyridine;

8-chloro-3-(cyclopropylmethyl)-7-[1-(cyclopropylmethyl)-*1H*-pyrrolo[2,3-b]pyridin-5-yl]-1,2,4-triazolo[4,3-a]pyridine; and

7-[8-chloro-3-(cyclopropylmethyl)-1,2,4-triazolo[4,3-a]pyridin-7-yl]-3,4-dihydro-4-(2-pyrimidinyl)-*2H*-1,4-benzoxazine;

and the pharmaceutically acceptable salts 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.

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 treating or preventing a central nervous system disorder selected from the group of anxiety disorders, psychotic disorders, personality disorders, substance-related disorders, eating disorders,

mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, neurotoxicity and ischemia.

10. A compound according to claim 9, for use in the treatment or prevention of a central nervous system disorder selected from the group of anxiety, schizophrenia, migraine, depression, epilepsy, behavioral and psychological symptoms of dementia, major depressive disorder, treatment resistant depression, bipolar depression, 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 treating or preventing 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.

14. A method of treating or preventing a central nervous system disorder selected from the group of anxiety disorders, psychotic disorders, personality disorders, substance-related disorders, eating disorders, mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, neurotoxicity and ischemia comprising admistering to a subject in need thereof a compound according to any one of claims 1 to 6 or a pharmaceutical composition according to claim 7.