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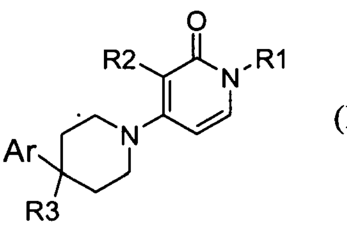
(54) Title: 1',3'-DISUBSTITUTED-4-PHENYL-3,4,5,6-TETRAHYDRO-2H, 1'H-[1, 4'] BIPYRIDINYL-2'-ONES



(I)

(57) Abstract: The present invention relates to novel compounds, in particular novel pyridinone derivatives according to Formula (I) wherein all radicals are as defined in the application and claims. The compounds according to the invention are positive allosteric modulators of metabotropic receptors - subtype 2 ("mGluR2") 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. In particular, such diseases are central nervous system disorders selected from the group of anxiety, schizophrenia, migraine, depression, and epilepsy. The invention is also directed to pharmaceutical compositions and processes to prepare such compounds and compositions, as well as to the use of such compounds for the prevention and treatment of such diseases in which mGluR2 is involved.

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1',3'-DISUBSTITUTED-4-PHENYL-3,4,5,6-TETRAHYDRO-*2H,1'H-[1,4']*BIPYRIDINYL-2'-ONES

Field of the Invention

The present invention relates to novel pyridinone-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 receptors channels (iGluRs), and the NMDA, AMPA and kainate receptors which are responsible for fast excitatory transmission.

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

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

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

Activating mGluR2 was shown in clinical trials to be efficacious to treat anxiety disorders. In addition, activating mGluR2 in various animal models was shown to be efficacious, thus representing a potential novel therapeutic approach for the treatment of schizophrenia, epilepsy, addiction/drug 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. WO2004/092135 (NPS & Astra Zeneca), WO2004/018386, WO2006/014918 and WO2006/015158 (Merck), WO2001/56990 (Eli Lilly) and WO2006/030032 (Addex & Janssen Pharmaceutica) describe respectively phenyl sulfonamide, acetophenone, indanone, pyridylmethyl sulfonamide and pyridinone derivatives as mGluR2 positive allosteric modulators. None of the specifically disclosed compounds therein are structurally related to the compounds of the present invention.

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.

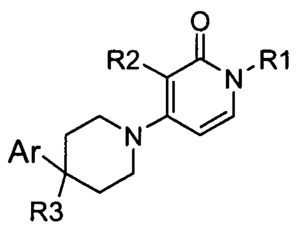
Animal data are suggesting that positive allosteric modulators of mGluR2 have effects in anxiety and psychosis models similar to those obtained with orthosteric agonists. Allosteric modulators of mGluR2 were shown to be active in fear-potentiated startle, and in stress-induced hyperthermia models of anxiety. Furthermore, such compounds were shown to be active in reversal of ketamine- or amphetamine-induced hyperlocomotion, and in reversal of amphetamine-induced disruption of prepulse inhibition of the acoustic startle effect models of schizophrenia. (J. Pharmacol. Exp. Ther. **2006**, *318*, 173-185; Psychopharmacology **2005**, *179*, 271-283).

Recent animal studies further reveal that the selective positive allosteric modulator of metabotropic glutamate receptor subtype 2 biphenyl-indanone (BINA) blocks a hallucinogenic drug model of psychosis, supporting the strategy of targeting mGluR2 receptors for treating glutamatergic dysfunction in schizophrenia. (Mol. Pharmacol. **2007**, *72*, 477-484).

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 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.

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

R^1 is C_{1-6}alkyl; or C_{1-3}alkyl substituted with C_{3-7}cycloalkyl, phenyl, or phenyl substituted with halo, trifluoromethyl or trifluoromethoxy;
R^2 is halo, trifluoromethyl, C_{1-3}alkyl or cyclopropyl;
R^3 is hydrogen, fluoro, hydroxyl, hydroxyC_{1-3}alkyl, hydroxyC_{1-3}alkyloxy, fluoroC_{1-3}alkyl, fluoroC_{1-3}alkyloxy or cyano; and
Ar is unsubstituted phenyl; or phenyl substituted with n radicals R^4, wherein n is 1, 2 or 3;
R^4 is selected from the group consisting of hydrogen, halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, polyhaloC_{1-3}alkyl , cyano, hydroxyl, amino, carboxyl,

C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, polyhaloC_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, mono- and di(C_{1-3}alkyl)amino, and morpholinyl; or

two vicinal R^4 radicals taken together form a bivalent radical of formula

–N=CH-NH- (a),

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

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

R^3 and a R^4 radical in ortho position taken together form a bivalent radical of formula

-CH_2-O- (d), or

-O-CH_2- (e);

and the pharmaceutically acceptable salts and solvates thereof.

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

R^1 is C_{1-6}alkyl; or C_{1-3}alkyl substituted with C_{3-7}cycloalkyl, phenyl, or phenyl substituted with halo, trifluoromethyl or trifluoromethoxy;

R^2 is halo, trifluoromethyl, C_{1-3}alkyl or cyclopropyl;

R^3 is hydrogen, fluoro, hydroxyl, hydroxyC_{1-3}alkyl, hydroxyC_{1-3}alkyloxy, fluoroC_{1-3}alkyl, fluoroC_{1-3}alkyloxy or cyano; and

Ar is unsubstituted phenyl, or phenyl substituted with n radicals R^4, wherein n is 1, 2 or 3;

R^4 is selected from the group consisting of hydrogen, halo ; C_{1-3}alkyl ; hydroxyC_{1-3}alkyl, polyhaloC_{1-3}alkyl ; cyano ; hydroxy ; amino ; carboxyl ; C_{1-3}alkyloxyC_{1-3}alkyl ; C_{1-3}alkyloxy ; polyhaloC_{1-3}alkyloxy; C_{1-3}alkylcarbonyl ; mono- and di(C_{1-3}alkyl)amino, and morpholinyl ; or

two vicinal R^4 radicals taken together form a bivalent radical of formula

–N=CH-NH- (a),

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

-O-CH_2-CH_2-NH- (c); and the pharmaceutically acceptable salts and solvates thereof.

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

R^1 is 1-butyl, 2-methyl-1-propyl, 3-methyl-1-butyl, (cyclopropyl)methyl or 2-(cyclopropyl)-1-ethyl;

R^2 is chloro, bromo, cyclopropyl or trifluoromethyl;

R^3 is hydrogen, fluoro or cyano; and

Ar is unsubstituted phenyl; or phenyl substituted with halo, trifluoromethyl, morpholinyl or hydroxyC_{1-3}alkyl;
or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, the invention relates to a compound according to Formula (I) or a stereochemically isomeric form thereof, wherein
R^1 is 1-butyl, 3-methyl-1-butyl, (cyclopropyl)methyl or 2-(cyclopropyl)-1-ethyl;
R^2 is chloro;
R^3 is hydrogen or fluoro; and
Ar is unsubstituted phenyl; or phenyl substituted with hydroxyC_{1-3} alkyl;
or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment the invention relates to the compound
3'-Chloro-1'-cyclopropylmethyl-4-phenyl-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (E1) or
1'-Butyl-3'-chloro-4-phenyl-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (E2).

The notation C_{1-3}alkyl as a group or part of a group defines a saturated, straight or branched, hydrocarbon radical having from 1 to 3 carbon atoms, such as methyl, ethyl, 1-propyl and 1-methylethyl; e.g. hydroxyC_{1-3}alkyl for example defines hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl and 1-hydroxy-1-methylethyl.

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

The notation C_{3-7}cycloalkyl defines a saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The notation halo or halogen as a group or part of a group is generic for fluoro, chloro, bromo, iodo.

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 salts are defined to comprise the therapeutically active non-toxic acid addition salt forms that the compounds according to Formula (I) are able to form. Said salts can be obtained by treating the base form of the compounds according to Formula (I) with appropriate acids, for example inorganic acids, for example hydrohalic acid, in particular hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid and phosphoric acid ; organic acids, for example acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclamic acid, salicylic acid, p-aminosalicylic acid and pamoic acid.

Conversely said salt forms can be converted into the free base form by treatment with an appropriate base .

The compounds according to Formula (I) containing acidic protons may also be converted into their therapeutically active non-toxic base salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkaline and earth alkaline metal salts, in particular lithium, sodium, potassium, magnesium and calcium salts, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hybramine salts, and salts with amino acids, for example arginine and lysine.

Conversely, said salt forms can be converted into the free acid forms by treatment with an appropriate acid.

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.

The term "stereochemically isomeric 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. The invention also embraces each of the individual isomeric forms of the compounds of Formula (I) and their salts and solvates, substantially free, *i.e.* associated with less than 10%, 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. Stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration.

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

In the framework of this application, an element, in particular when mentioned in relation to a compound according to Formula (I), comprises all isotopes and isotopic mixtures of this element, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. Radiolabelled compounds of Formula (I) may comprise a radioactive isotope selected from the group of ^{3}H, ^{11}C, ^{18}F, ^{122}I, ^{123}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br. Preferably, the radioactive isotope is selected from the group of ^{3}H, ^{11}C and ^{18}F.

Preparation

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

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

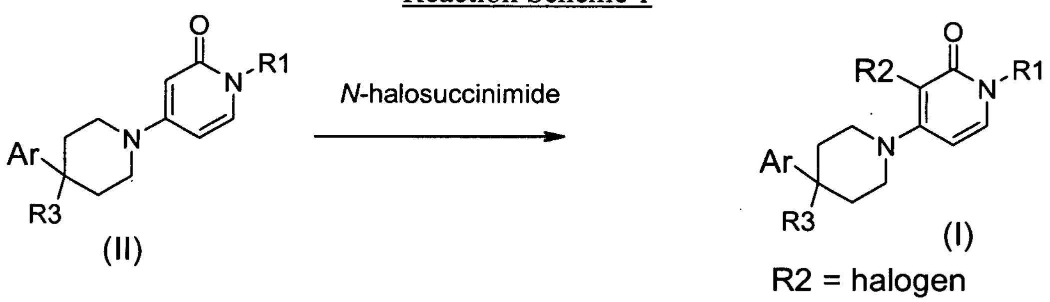
Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of Formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically.

A. Preparation of the final compounds

Experimental procedure 1

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

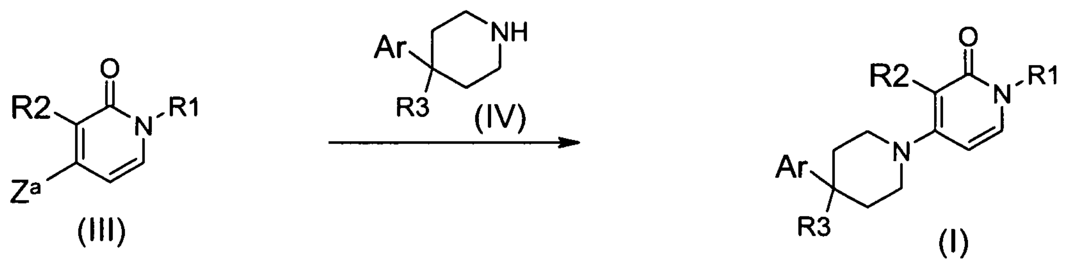
Reaction Scheme 1



Experimental procedure 2

Alternatively, compounds according to Formula (I) can be prepared by reacting an intermediate of Formula (III) with an intermediate of Formula (IV), which can be either commercially available or may be synthesized by procedures well known to anyone skilled in the art, according to reaction scheme (2). This reaction is performed in a suitable reaction-inert solvent such as, for example, toluene, in the presence of a suitable base such as, for example, sodium *tert*-butoxide, a metal-based catalyst, specifically a palladium catalyst, such as palladium(II) acetate, and a suitable ligand, such as for example [1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine] (BINAP), heating for a suitable period of time that allows the completion of the reaction, for example at 100 °C for 16 hours in a sealed tube. In reaction scheme (2), Z^a is a group suitable for Pd mediated coupling with amines, such as, for example, a halogen or triflate. All other variables are defined as in Formula (I).

Reaction Scheme 2



Such intermediates of Formula (II) and Formula (III) may be prepared according to reaction schemes (3) to (11) (see below). 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.

Additionally, compounds according to Formula (I) can be prepared by a skilled person using art known procedures by further modifications of compounds of Formula (I):

– Alkylation of compounds of Formula (I) that contain in their structure one or more hydroxy-substituents with a suitable alkylating agent such as for example 2-fluorethyl tosylate under thermal conditions using a suitable base such as for example sodium hydride, in a suitable reaction-inert solvent such as, for example 1,2-dimethoxyethane or dimethylformamide.

– Fluorination of compounds of Formula (I) that contain in their structure one or more hydroxy-substituents with a suitable fluorinating agent, such as for example (diethylamino)sulfur trifluoride. This reaction may be performed in a suitable reaction-inert solvent such as, for example, dichloromethane, under a moderately low temperature such as, for example, a temperature ranging from –78 °C to 30 °C during, for example, 0.5 to 12 hours.

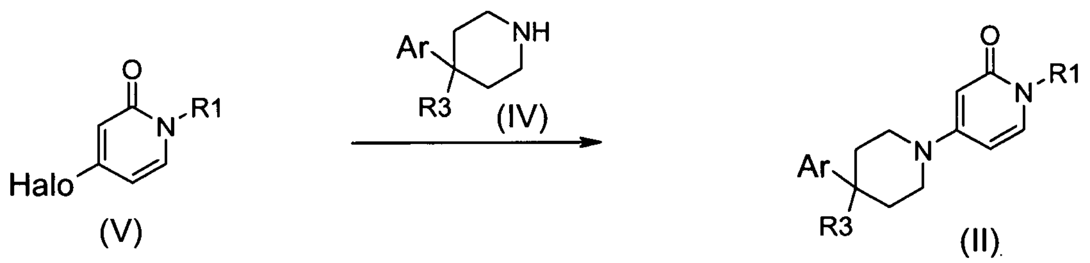
- Reaction of compounds of Formula (I) that contain in their structure one or more hydroxy-substituents with an alcohol derivative by using a suitable coupling system such as, for example, di-tert-butylazodicarboxylate/triphenylphosphine under thermal conditions.

B. Preparation of the intermediates

Experimental procedure 3

Intermediates of Formula (II) can be prepared by reacting an intermediate of Formula (V) with an intermediate of Formula (IV) according to reaction scheme (3). This reaction is performed in a suitable reaction-inert solvent such as, for example, toluene, in the presence of a suitable base such as, for example, sodium *tert*-butoxide, a metal-based catalyst, specifically a palladium catalyst, such as palladium(II) acetate, and a suitable ligand, such as for example [1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine] (BINAP), heating for a suitable period of time that allows the completion of the reaction, for example at 100°C for 16 hours in a sealed tube. In reaction scheme (3), all variables are defined as in Formula (I).

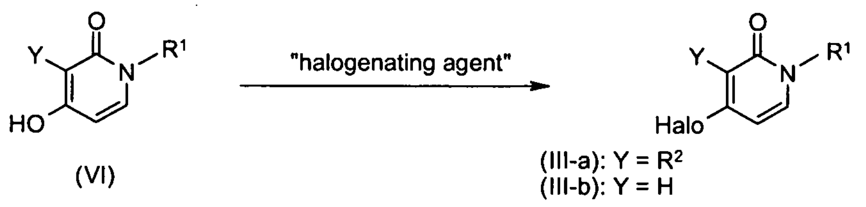
Reaction Scheme 3



Experimental procedure 4

Intermediates of Formula (III-a) and (III-b) can be prepared by reacting an intermediate of Formula (VI), wherein Y is H or R^2 (as defined as in Formula I), with a suitable halogenating agent such as, for example, phosphorus oxybromide. This reaction may be performed in a suitable reaction-inert solvent such as, for example, DMF, at a moderately elevated temperature such as, for example, 110 °C, for a suitable period of time that allows the completion of the reaction, for instance 1 hour. In reaction scheme (4), variable R^1 is defined as in Formula (I).

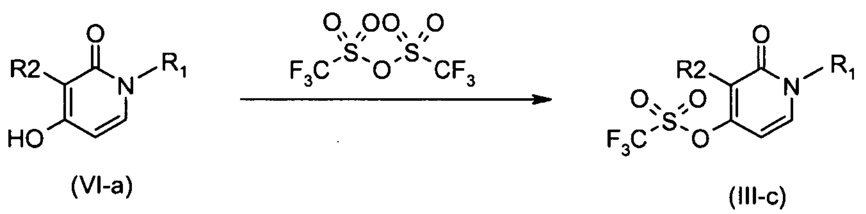
Reaction Scheme 4



Experimental procedure 5

Intermediates of Formula (III-c) can be prepared by reacting an intermediate of Formula (VI-a) with triflic anhydride (also called trifloromethanesulfonic anhydride). The reaction may be performed in a suitable reaction-inert solvent such as, for example, dichloromethane, in the presence of a base such as, for example, pyridine at a low temperature such as, for example, -78 °C. In reaction scheme (5), all variables are defined as in Formula (I).

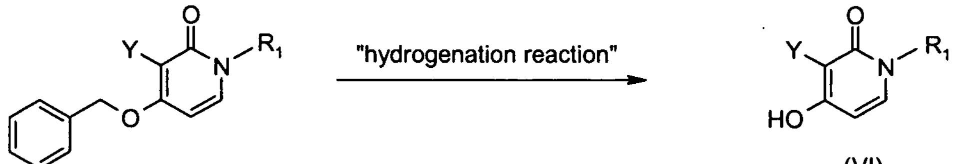
Reaction Scheme 5



Experimental procedure 6

Intermediates of Formula (VI) can be prepared by hydrogenolysis of intermediates of Formula (VII-a, VII-b or VII-c), in a suitable reaction-inert solvent such as, for example, ethanol, in the presence of a catalyst such as, for example, 10 % palladium on activated carbon, for a period of time that ensures the completion of the reaction, typically at room temperature and 1 atmosphere of hydrogen for 2 hours. In reaction scheme (6), variable R^1 is defined as in Formula (I).

Reaction Scheme 6



(VII) (VI)

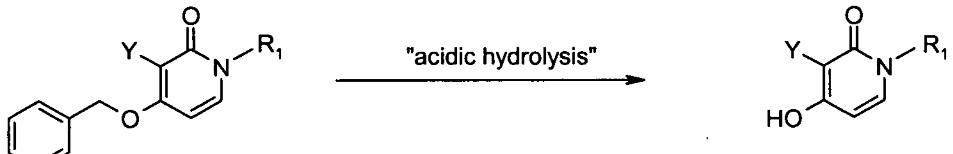
(VII-a): Y = H,
(VII-b): Y = CF_3,
(VII-c): Y = C_{1-3}alkyl or cyclopropyl

Y = H, CF_3, C_{1-3}alkyl or cyclopropyl

Experimental procedure 7

Alternatively, intermediates of Formula (VI), wherein Y = halogen, can be prepared by reacting an intermediate of Formula (VII-d) in a mixture of acetic acid and hydrobromic acid, and heating the mixture at a temperature and for the time required to allow completion of the reaction, typically at 130 °C for 30 minutes under microwave irradiation. In reaction scheme (7), variable R^1 is defined as in Formula (I).

Reaction Scheme 7



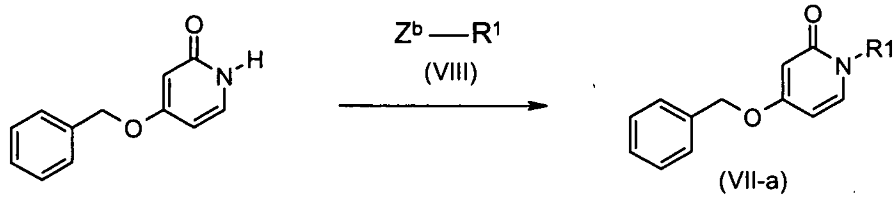
(VII-d): Y = Halogen

(VI)
Y = Halogen

Experimental procedure 8

Intermediates of Formula (VII-a) can be prepared by art known procedures by reacting commercially available 4-benzyloxy-*1H*-pyridin-2-one with a commercially available alkylating agent of Formula (VIII), in which Z^b is a suitable leaving group, using a base such as, for example, K_2CO_3, and, optionally an iodine salt such as, for example, KI, in an inert solvent such as, for example, acetonitrile or DMF, at a moderately high temperature such as, for example, 80-120 °C, for a suitable period of time that allows the completion of the reaction, for example 16 hours. In reaction scheme (8), variable R^1 is defined as in Formula (I) and Z^b is a suitable leaving group such as, for example, halogen.

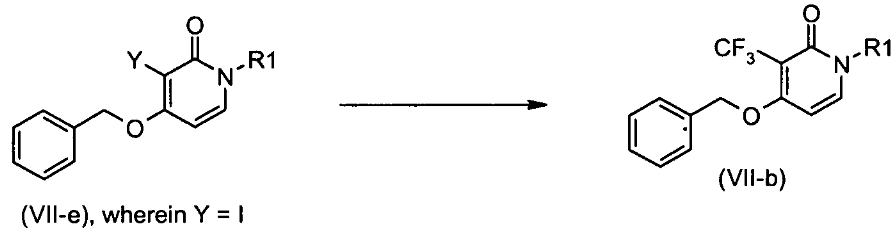
Reaction Scheme 8



Experimental procedure 9

Intermediates of Formula (VII-b) can be prepared by reacting an intermediate of Formula (VII-e), wherein Y is iodine, with commercially available methyl 2,2-difluoro-2-(fluorosulfonyl)acetate, in a suitable reaction-inert solvent such as, for example, DMF, in presence of a suitable copper salt such as copper(I) iodide, heating for a suitable period of time that allows the completion of the reaction, for example at 100°C for 5 hours. In reaction scheme (9), variable R^1 is defined as in Formula (I).

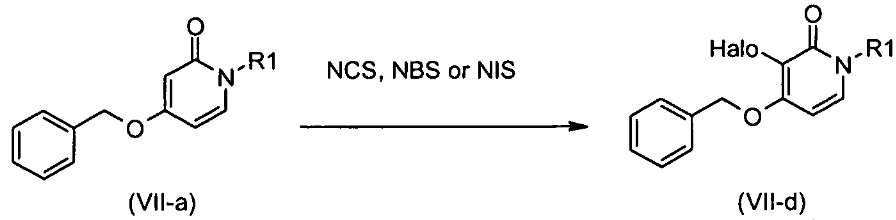
Reaction Scheme 9



Experimental procedure 10

Intermediates of Formula (VII-d) can be prepared by reacting an intermediate of Formula (VII-a) with a commercially available *N*-halosuccinimide, such as *N*-chloro- (NCS), *N*-bromo- (NBS) or *N*-iodosuccinimide (NIS), in a suitable reaction-inert solvent such as, for example, DMF, dichloromethane or acetic acid, typically at room temperature for 1 to 24 hours. In reaction scheme (10), variable R^1 is defined as in Formula (I).

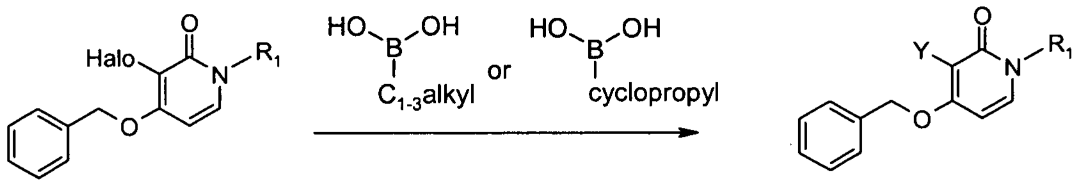
Reaction Scheme 10



Experimental procedure 11

Intermediates of Formula (VII-c) can be prepared by reacting an intermediate of Formula (VII-d) with a $C_{1\text{-}3}$alkyl- or cyclopropyl-boronic acid derivative, such as cyclopropyl- boronic acid or methyl- boronic acid, in a suitable reaction-inert solvent such as, for example, 1,4-dioxane, in the presence of a suitable palladium catalyst-complex such as, for example, [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) – DCM complex, and in the presence of a suitable base such as sodium hydrogencarbonate, heating for a suitable period of time that allows the completion of the reaction, for example at 175 °C for 20 minutes under microwave irradiation. In reaction scheme (11), variable R^1 is defined as in Formula (I).

Reaction Scheme 11

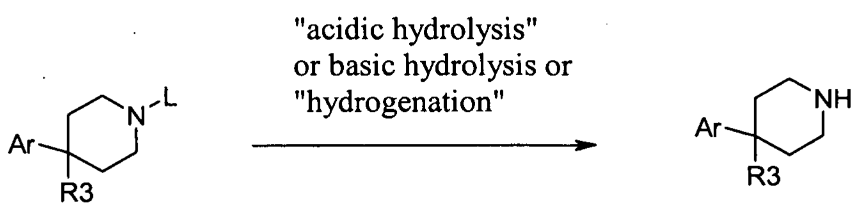


(VII-d) (VII-c): Y = $C_{1\text{-}3}$alkyl or cyclopropyl

Experimental procedure 12

Intermediates of formula (IV) can be prepared by deprotection of the piperidine nitrogen in an intermediate of formula (IX) wherein L is a suitable protecting group for the nitrogen atom of a piperidine derivative, such as for example tert-butoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, benzyl and methyl, applying art known procedures, according to reaction scheme (12). In reaction scheme (12), all variables are defined as in formula (I).

Reaction Scheme (12)

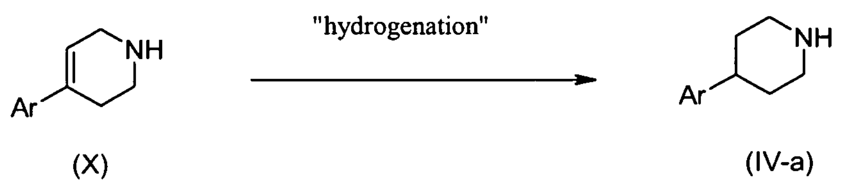


(IX) (IV)

Experimental procedure 13

Intermediates of formula (IV-a) can be prepared by hydrogenation of an intermediate of formula (X) applying art known procedures, according to reaction scheme (13). In reaction scheme (13), Ar is defined as in formula (I).

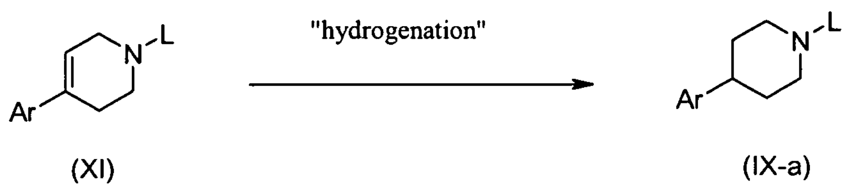
Reaction Scheme (13)



Experimental procedure 14

Intermediates of formula (IX-a) can be prepared by hydrogenation of an intermediate of formula (XI) wherein L is a suitable protecting group for the nitrogen atom of a tetrahydropyridine derivative, such as for example tert-butoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, benzyl and methyl, applying art known procedures, according to reaction scheme (14). In reaction scheme (14), Ar is defined as in Formula (I).

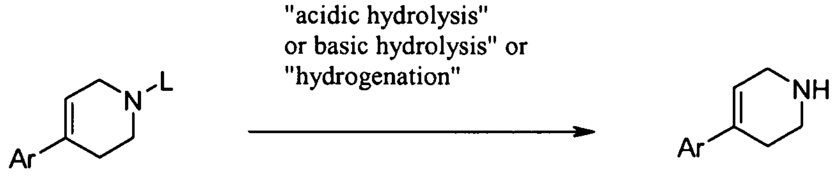
Reaction Scheme (14)



Experimental procedure 15

Intermediates of formula (X) can be prepared by deprotection of the tetrahydropyridine nitrogen in an intermediate of formula (XI) wherein L is a suitable protecting group for the nitrogen atom of a tetrahydropyridine derivative, such as for example tert-butoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, benzyl and methyl, applying art known procedures, according to reaction scheme (15). In reaction scheme (15), Ar is defined as in formula (I).

Reaction Scheme (15)

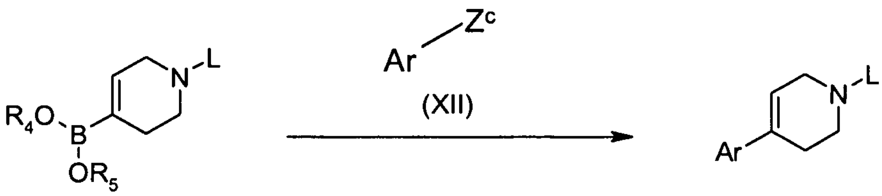


(XI) (X)

Experimental procedure 16

Intermediates of formula (XI) can be prepared by reacting an intermediate of formula (XII) with an intermediate of formula (XIII) according to reaction scheme (16). The reaction may be 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 suitable catalyst, such as for example 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, during, for example, 10 minutes. In reaction scheme (16), all variables are defined as in formula (I); Z^c is a group suitable for Pd mediated coupling with boronic acids or boronic esters, such as, for example, a halo or triflate; L is a suitable protecting group for the nitrogen atom of a tetrahydropyridine derivative, such as for example tert-butoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, benzyl and methyl and R_4 and R_5 are hydrogen or C_{1-4}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 (16)

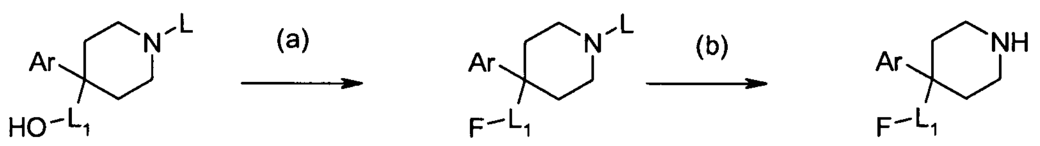


(XIII) (XI)

Experimental procedure 17

Intermediates of formula (IV) wherein R_3 represents fluoro or C_{1-3}alkyl substituted with fluoro, said R_3 being represented by $-L_1$-F wherein L_1 represents C_{1-3}alkyl or a covalent bond, and said intermediates being represented by formula (IV-b), can be prepared by art known procedures by reacting an intermediate of formula (IX-b) wherein L is a suitable protecting group for the nitrogen atom of the piperidine moiety, such as for example tert-butoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, benzyl and methyl, with a suitable fluorinating agent such as for example (diethylamino)sulfur trifluoride , resulting in an intermediate of formula (IX-c) according to reaction scheme (17) step (a). The reaction may be performed in a suitable reaction-inert solvent, such as, for example, dichloromethane. The reaction may be performed under a moderately low temperature such as, for example, a temperature ranging from –78 °C to 30 °C during for example 0.5 to 12 hours. The resulting intermediate of formula (IX-c) can then be transformed according to reaction scheme (17) step (b), in an intermediate of Formula (IV-b) by deprotection of the piperidine nitrogen applying art known procedures, such as for example those described in experimental procedure 15 herein above. In reaction scheme (17), Ar is defined as in formula (I).

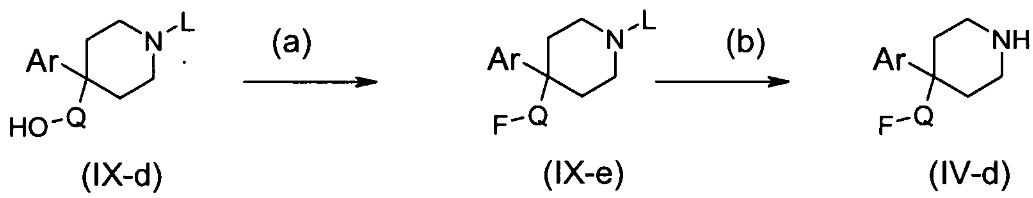
Reaction Scheme (17)



Experimental procedure 18

Intermediates of formula (IV) wherein R_3 represents C_{1-3}alkyloxy substituted with fluoro, said C_{1-3}alkyloxy being represented by Q, said R_3 being represented by –Q-F, and said intermediates being represented by formula (IV-d), can be prepared by art known procedures by reacting a hydroxyl-substituted intermediate of formula (IX-d) wherein L is a suitable protecting group for the nitrogen atom of the piperidine moiety, such as for example tert-butoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, benzyl and methyl, with a suitable fluorinating agent such as (diethylamino)sulfur trifluoride , resulting in an intermediate of formula (IX-e) according to reaction scheme (18) step (a). The reaction can be performed in a suitable reaction-inert solvent, such as, for example, dichloromethane, under a moderately low temperature such as, for example, a temperature ranging from –78 °C to 30 °C during for example 0.5 to 12 hours. The intermediate of Formula (IX-e) can then be transformed according to reaction scheme (18) step (b) in an intermediate of Formula (IV-d) by deprotection of the piperidine nitrogen applying art known procedures, such as for example those described in experimental procedure 17 hereinabove. In reaction scheme (18), Ar is defined as in formula (I).

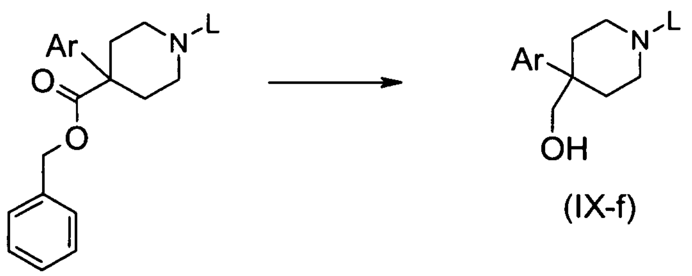
Reaction Scheme (18)



Experimental procedure 19

Intermediates of formula (IX-b) wherein L1 represents CH_2, said intermediates being represented by formula (IX-f), can be prepared by reacting an intermediate of formula (XIV) wherein L is a suitable protecting group for the nitrogen atom of the piperidine moiety, such as for example tert-butoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, benzyl and methyl, with a suitable reducing agent, such as for example, lithium aluminium hydride, according to reaction scheme (19). The reaction may be performed in a suitable solvent, such as for example tetrahydrofuran, at a moderately low temperature such as, for example from –20 °C. In reaction scheme (19) Ar is defined as in formula (I)

Reaction Scheme (19)



(XIV) (IX-f)

The starting materials according to Formulas (VIII), (IX-b), (IX-d), (XII), (XIII) and XIV are either commercially available or may be prepared according to conventional reaction procedures generally known by those skilled in the art.

Pharmacology

The compounds provided in this invention are positive allosteric modulators 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. Hence, the present invention relates to a compound according to the present invention for use as a medicine, as well as to the use of a compound according to the invention or a pharmaceutical composition according to the invention for the manufacture of a medicament for treating or preventing, in particular treating, 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 present invention or a pharmaceutical composition according to the invention for use in the manufacture of a medicament for treating or preventing, in particular treating, 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 present invention or a pharmaceutical composition according to the invention for treating or preventing, in particular treating, 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.

Also, the present invention relates to the use of a compound according to the invention 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.

Where the invention is said to relate to the use of a compound or composition according to the invention for the manufacture of a medicament for e.g. the treatment of a mammal, it is understood that such use is to be interpreted in certain jurisdictions as a method of e.g. treatment of a mammal, comprising administering to a mammal in need of such e.g. treatment, an effective amount of a compound or composition according to the invention.

In particular, the neurological and psychiatric disorders associated with glutamate dysfunction, include one or more of the following conditions or diseases: acute neurological and psychiatric disorders such as, for example, cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, dementia (including AIDS-induced dementia), Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, migraine (including migraine headache), urinary incontinence, substance tolerance, substance withdrawal (including substances such as, for example, opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), psychosis, schizophrenia, anxiety (including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder), mood disorders (including depression, mania, bipolar disorders), 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), 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-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 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, substance-induced persisting dementia and mild cognitive impairment.

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.

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.

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 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 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.

To prepare the pharmaceutical compositions of this invention, an 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 administration orally, rectally, percutaneously, 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, 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, and segregated multiples thereof.

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 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 as to the use of such a composition for the manufacture of a medicament. 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

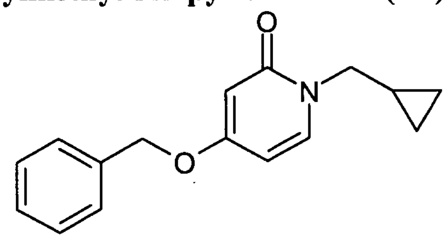
Several methods for preparing the compounds of this invention are illustrated in the following Examples. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification.

Hereinafter, "THF" means tetrahydrofuran; "DMF" means *N,N*-dimethylformamide; "EtOAc" means ethyl acetate; "DCM" means dichloromethane; "DME" means 1,2-dimethoxyethane; "DCE" means 1,2-dichloroethane; "DIPE" means diisopropylether; "DMSO" means dimethylsulfoxide; "BINAP" means[1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine]; "DBU" means 1,8-diaza-7-bicyclo[5.4.0]undecene; Xantphos means (9,9-dimethyl-*9H*-xanthene-4,5-diyl)bis[diphenylphosphine]; MeOH means methanol; "q.s." means quantum sufficit; "M.P." means melting point;

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.).

Description 1

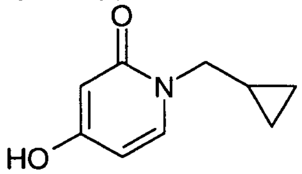
4-Benzyloxy-1-cyclopropylmethyl-*1H*-pyridin-2-one (D1)



Bromomethyl-cyclopropane (3.68 g, 27.33 mmol) and potassium carbonate (10.3 g, 74.52 mmol) were added to a solution of 4-benzyloxy-*1H*-pyridin-2-one (5.0 g, 24.84 mmol) in acetonitrile (200 ml) and the mixture was heated at reflux for 16 hours. The reaction mixture was filtered through diatomaceous earth and concentrated *in vacuo*. The crude residue was then triturated with diethylether to yield pure **D1** (6.32 g, 98 %) as a white solid.

Description 2

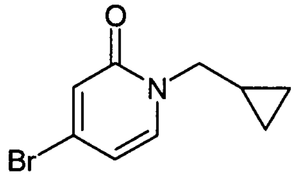
1-Cyclopropylmethyl-4-hydroxy-*1H*-pyridin-2-one (D2)



A mixture of intermediate **D1** (2.0 g, 7.83 mmol) and a catalytic amount of 10% palladium on activated carbon in ethanol (300 ml) was stirred under a hydrogen atmosphere for two hours. The mixture was filtered through diatomaceous earth and the solvent was evaporated *in vacuo* to yield intermediate **D2** (1.3 g, 100 %) that was used without further purification.

Description 3

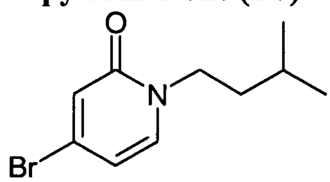
4-Bromo-1-cyclopropylmethyl-*1H*-pyridin-2-one (D3)



Phosphorus oxybromide (5.4 g, 18.9 mmol) was added to a solution of intermediate **D2** (1.42 g, 8.6 mmol) in DMF (140 ml) and the mixture was heated at 110 °C for 1 hour. After cooling in an ice bath the solution was partitioned between water and EtOAc. After three extractions with EtOAc, the combined organic fractions were dried (Na_2SO_4) and 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 evaporated *in vacuo* to yield intermediate **D3** (1.82 g, 93 %).

Description 7

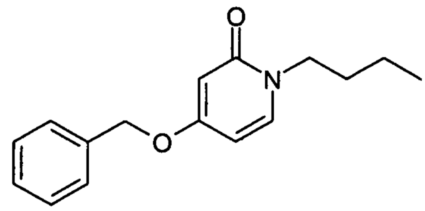
4-Bromo-1-(3-methylbutyl)-*1H*-pyridin-2-one (D7)



Intermediate **D7** was prepared following the same procedure implemented for the synthesis of **D3**, using 4-hydroxy-1-(3-methylbutyl)-*1H*-pyridin-2-one as starting material, which was prepared by the same method used for the synthesis of intermediate **D2**, by reaction of 4-benzyloxy-*1H*-pyridin-2-one with 1-bromo-3-methylbutane.

Description 4

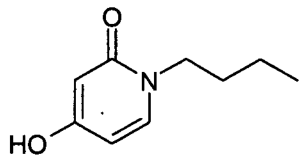
4-Benzyloxy-1-butyl-*1H*-pyridin-2-one (D4)



1-Bromobutane (3.75 g, 27.33 mmol) and potassium carbonate (10.3 g, 74.52 mmol) were added to a solution of 4-benzyloxy-*1H*-pyridin-2-one (5.0 g, 24.84 mmol) in acetonitrile (200 ml) and the mixture was heated at reflux for 16 hours. The reaction mixture was filtered through diatomaceous earth and concentrated *in vacuo*. The crude residue was then triturated with diethylether to yield pure **D4** (6.26 g, 98 %) as a white solid.

Description 5

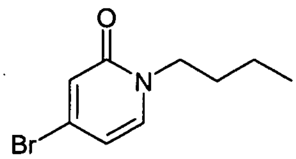
1-Butyl-4-hydroxy-*1H*-pyridin-2-one (D5)



A mixture of **intermediate D4** (2.01 g, 7.83 mmol) and a catalytic amount of 10% palladium on activated carbon in ethanol (300 ml) was stirred under a hydrogen atmosphere for two hours. The mixture was filtered through diatomaceous earth and the solvent was evaporated *in vacuo* to yield **intermediate D5** (1.3 g, 100 %) that was used without further purification.

Description 6

4-Bromo-1-butyl-*1H*-pyridin-2-one (D6)

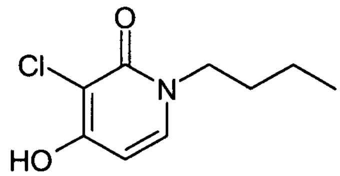


Phosphorus oxybromide (5.4 g, 18.9 mmol) was added to a solution of intermediate **D5** (1.44 g, 8.6 mmol) in DMF (140 ml) and the mixture was heated at 110 °C for 1 hour.

After cooling in an ice bath, the solution was partitioned between water and EtOAc. After three extractions with EtOAc, the combined organic fractions were dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate **D6** (1.82 g, 93 %).

Description 8

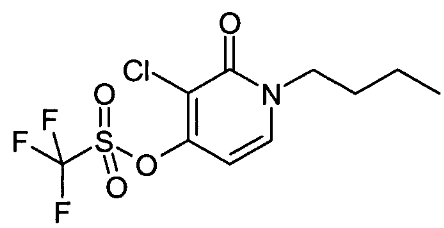
1-Butyl-3-chloro-4-hydroxy-*1H*-pyridin-2-one (D8)



N-Chlorosuccinimide (1.6 g, 11.96 mmol) was added to a solution of intermediate **D5** (2.0 g, 11.96 mmol) in DMF (30 ml). The reaction was stirred at room temperature overnight and then it was concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel; 0-5% methanol / DCM as eluent) to yield intermediate **D8** (2.0 g, 83 %).

Description 9

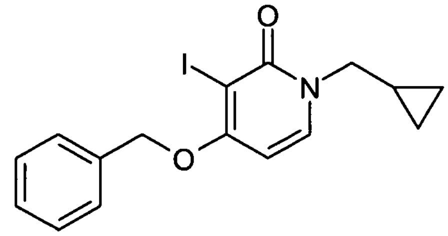
Trifluoro-methanesulfonic acid 1-butyl-3-chloro-2-oxo-1,2-dihydropyridin-4-yl ester (D9)



Pyridine (1.60 ml, 19.8 mmol) was added to a cooled (- 78 °C) solution of intermediate **D8** (2.0 g, 9.92 mmol) in DCM (80 ml). The resulting solution was stirred for 10 minutes after which trifloromethanesulfonic anhydride (1.90 ml, 10.9 mmol) was added, and the resulting solution was stirred at –78 °C for 3 hours. Then the mixture was warmed to room temperature and was quenched by the addition of aqueous saturated ammonium chloride. The mixture was diluted with water,extracted with DCM, dried (Na_2SO_4) and the solvent evaporated *in vacuo*, yielding intermediate **D9** (3.31 g, 100 %) as a crude that was used without further purification.

Description 10

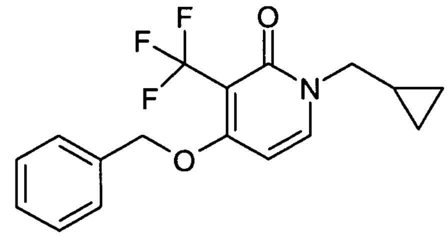
4-Benzyloxy-1-cyclopropylmethyl-3-iodo-*1H*-pyridin-2-one (D10)



N-Iodosuccinimide (2.64 g, 11.74 mmol) was added to a solution of intermediate **D1** (3.0 g, 11.74 mmol) in acetic acid (40 ml). The reaction mixture was stirred at room temperature for 1 hour, after which it was concentrated *in vacuo*, purified by flash chromatography (silica gel; 0-3% methanol / DCM as eluent) and finally recrystallized from diethyl ether to afford intermediate **D10** (4.12 g, 92 %) as a solid.

Description 11

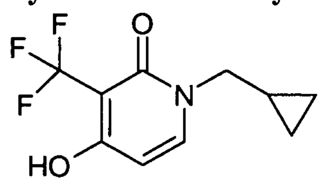
4-Benzyloxy-1-cyclopropylmethyl-3-trifluoromethyl-*1H*-pyridin-2-one (D11)



Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.67 ml, 5.24 mmol) and intermediate **D10** (1.0 g, 2.63 mmol) were added to a solution of copper(I) iodide (0.99 g, 5.24 mmol) in DMF (30 ml). The mixture was then heated at 100 °C for 5 hours, after which it was filtered through diatomaceous earth and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM as eluent) to yield intermediate **D11** (0.76 g, 89 %).

Description 12

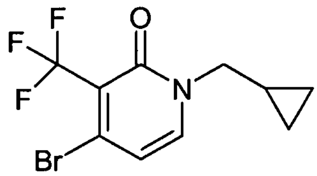
1-Cyclopropylmethyl-4-hydroxy-3-trifluoromethyl-*1H*-pyridin-2-one (D12)



A mixture of intermediate **D11** (2.0 g, 6.19 mmol), a catalytic amount of 10% palladium on activated carbon and ethanol (60 ml) was stirred under hydrogen atmosphere for 2 hours. The mixture was filtered through diatomaceous earth and the solvent was evaporated *in vacuo* to yield crude intermediate **D12** (1.45 g, 100 %) that was used without further purification.

Description 13

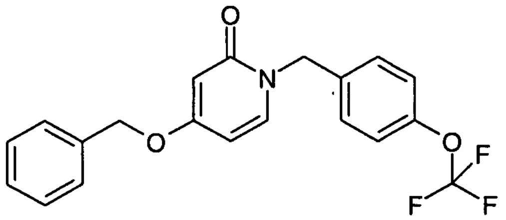
4-Bromo-1-cyclopropylmethyl-3-trifluoromethyl-*1H*-pyridin-2-one (D13)



Phosphorus oxybromide (7.03 g, 24.5 mmol) was added to a solution of intermediate **D12** (2.60 g, 11.1 mmol) in DMF (50 ml) and the mixture was heated at 110 °C for 1 hour. After cooling in an ice bath the solution was partitioned between water and EtOAc. After three extractions with EtOAc, the combined organic fractions were dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate **D13** (1.38 g, 42 %).

Description 14

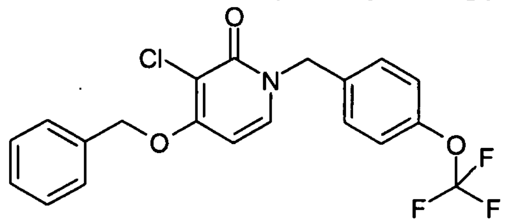
4-Benzyloxy-1-(4-trifluoromethoxy-benzyl)-*1H*-pyridin-2-one (D14)



1-Bromomethyl-4-trifluoromethoxybenzene (3.32 g, 13.04 mmol) and potassium carbonate (3.51 g, 25.46 mmol) were added to a mixture of 4-benzyloxy-*1H*-pyridin-2-one (2.5 g, 12.42 mmol) in acetonitrile (10 ml). The reaction mixture was heated at reflux temperature for 24 hours. After cooling to room temperature, it was filtered through diatomaceous earth, the solid residues were washed with methanol and the combined organic extracts were evaporated *in vacuo*. The crude residue thus obtained was precipitated with DIPE to yield intermediate **D14** (4.5 g, 96%) as a white solid.

Description 15

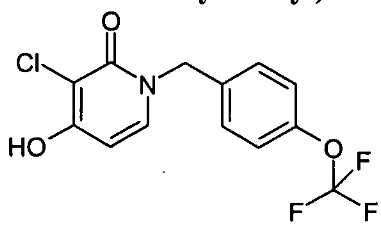
4-Benzyloxy-3-chloro-1-(4-trifluoromethoxy-benzyl)-*1H*-pyridin-2-one (D15)



N-Chlorosuccinimide (1.68 g, 12.61 mmol) was added to a solution of intermediate **D14** (4.31 g, 11.47 mmol) in DMF (30 ml) and the mixture was stirred at room temperature for 24 hours. The solvent was evaporated and the solid residue was washed with water (4 x 25 ml). The crude solid was washed with DIPE to yield intermediate **D15** (4.5 g, 95 %) as a white solid.

Description 16

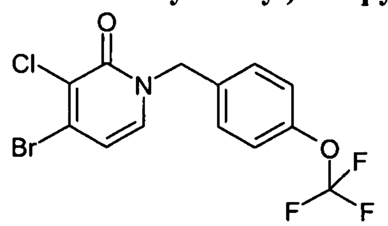
3-Chloro-4-hydroxy-1-(4-trifluoromethoxy-benzyl)-*1H*-pyridin-2-one (D16)



Hydrobromic acid (0.1 ml) was added to a mixture of intermediate **D15** (4.5 g, 10.98 mmol) in acetic acid (20 ml). The solution was heated at 130 °C for 30 minutes under microwave irradiation. After cooling to room temperature, the solvent was evaporated *in vacuo* and the residue was treated with an aqueous saturated solution of $NaHCO_3$ until the solution reached a pH of approximately 8. The white solid that precipitated was collected by filtration and washed with cold DIPE to yield intermediate **D16** (1.1 g, 31 %).

Description 17

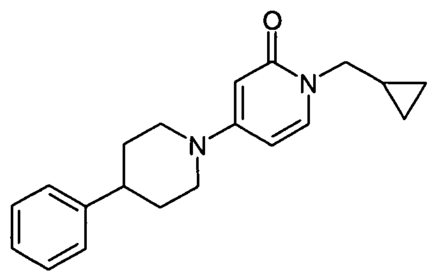
4-Bromo-3-chloro-1-(4-trifluoromethoxy-benzyl)-*1H*-pyridin-2-one (D17)



Phosphorus oxybromide (1.05 g, 3.75 mmol) was added to a solution of intermediate **D16** (1.0 g, 3.13 mmol) in DMF (5 ml) and the mixture was heated at 115 °C for 4 hours. The solvent was evaporated *in vacuo* and the crude residue was treated with an aqueous saturated solution of $NaHCO_3$. The mixture was extracted with DCM (3 x 5 ml), the organic fractions were dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; diethyl ether as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate **D17** (0.21 g, 18 %) as a yellow oil.

Description 18

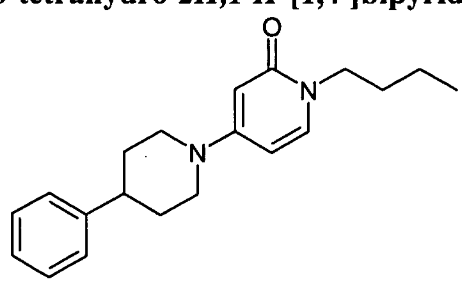
1'-Cyclopropylmethyl-4-phenyl-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (D18)



4-Phenylpiperidine (0.45 g, 2.78 mmol), palladium(II) acetate (0.016 g, 0.069 mmol), sodium *tert*-butoxide (0.34 g, 3.5 mmol) and BINAP (0.065 g, 0.104 mmol) were added to a solution of intermediate **D3** (0.32 g, 1.39 mmol) in toluene (5 ml). The reaction mixture was heated at 100 °C for 16 hours in a sealed tube, after which it was cooled to room temperature, diluted with water (5 ml) and then extracted with EtOAc (3 x 5 ml). The combined organic fractions were dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; 0-4% methanol/DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate **D18** (0.33 g, 78 %).

Description 19

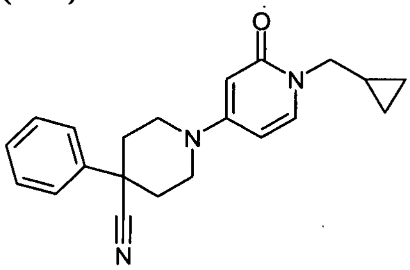
1'-Butyl-4-phenyl-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (D19)



4-Phenylpiperidine (0.45 g, 2.78 mmol), palladium(II) acetate (0.016 g, 0.069 mmol), sodium *tert*-butoxide (0.34 g, 3.5 mmol) and BINAP (0.065 g, 0.104 mmol) were added to a solution of intermediate **D6** (0.32 g, 1.39 mmol) in toluene (5 ml). The reaction mixture was heated at 100 °C for 16 hours in a sealed tube, after which it was cooled to room temperature and then diluted with water (5 ml) and extracted with EtOAc (3 x 5 ml). The combined organic fractions were dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; 0-4% methanol / DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate **D19** (0.38 g, 89 %).

Description 20

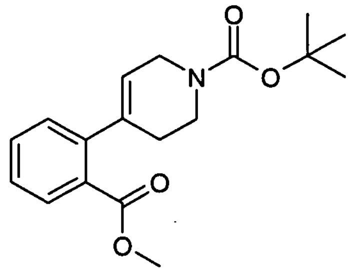
1'-Cyclopropylmethyl-2'-oxo-4-phenyl-3,4,5,6,1',2'-hexahydro-*2H*-[1,4'] bipyridinyl-4-carbonitrile (D20) JNJ-38818468



4-Cyano-4-phenylpiperidine hydrochloride (0.314 g, 1.41 mmol), palladium(II) acetate (0.013 g, 0.059 mmol) sodium *tert*-butoxide (0.347 g, 3.54 mmol) and BINAP (0.051 g, 0.08 mmol) were added to a stirred solution of intermediate **D3** (0.27 g, 1.18 mmol) in toluene (5 ml). The reaction mixture was heated at 100 °C for 16 hours in a sealed tube. After cooling to room temperature the mixture was diluted with water and extracted with EtOAc. The combined organic phase was dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; 10 % ammonia in methanol (7M) / DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **D20** (0.35 g, 87 %) as a pale yellow oil.

Description 21

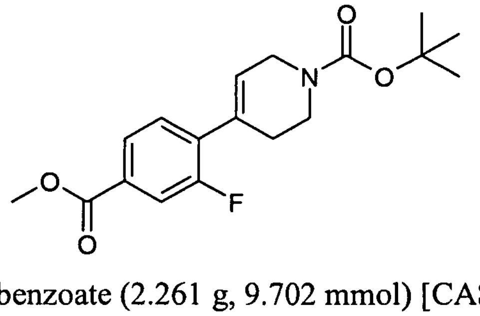
4-Hydroxy-4-phenylpiperidine-1-carboxilic acid tert-butyl ester (D21)



Methyl 2-bromobenzoate (1.816 ml, 12.936 mmol) [CAS 610-94-6] was added to a solution of 1,2,3,6-tetrahydro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyridine (4 g, 12.936 mmol) [CAS 375853-82-0] (synthesis described in WO 2004072025 A2 20040826) in 1,4-dioxane (28 ml) and an aqueous saturated solution of $NaHCO_3$ (24 ml). The resulting solution was degassed using a stream of nitrogen and $Pd(PPh_3)_4$ (0.747 g, 0.647 mmol) was added to this solution. The reaction was then microwaved in a sealed tube at 140 °C for 5 minutes. The resulting cooled reaction mixture was then diluted with EtOAc and filtered through a pad of diatomaceous earth. The filtrate was collected, dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was then purified by column chromatography (silica gel; DCM to DCM/EtOAc up to 6% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **D21** (4.04 g, 98 %).

Description 22

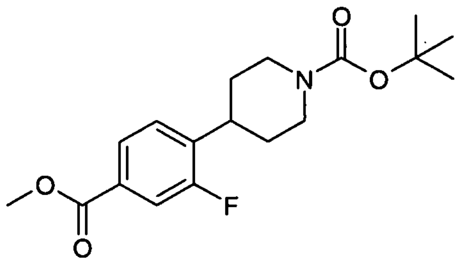
4-(2-Fluoro-4-methoxycarbonyl-phenyl)-3,6-dihydro-*2H*-pyridine-1-carboxylic acid tert-butyl ester (D22)



Methyl 4-bromo-3-fluorobenzoate (2.261 g, 9.702 mmol) [CAS 849758-12-9] was added to a solution of 1,2,3,6-tetrahydro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyridine (3 g, 9.702 mmol) [CAS 375853-82-0] (synthesis described in WO 2004072025 A2 20040826) in 1,4-dioxane (21 ml) and an aqueous saturated solution of $NaHCO_3$ (18 ml). The resulting solution was degassed using a stream of nitrogen and $Pd(PPh_3)_4$ (0.561 g, 0.485 mmol) was added to this solution. The reaction was then microwaved in a sealed tube at 150 °C for 5 minutes. The resulting cooled reaction mixture was then diluted with EtOAc and filtered through a pad of diatomaceous earth. The filtrate was collected, dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was then purified by column chromatography (silica gel; DCM to DCM/EtOAc up to 6% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **D22** (2.107 g, 65 %).

Description 23

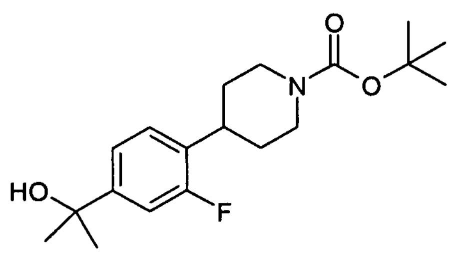
4-(2-Fluoro-4-methoxycarbonyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester (D23)



A solution of **intermediate D22** (2.81 g, 8.379 mmol) in methanol (120 ml) was hydrogenated at room temperature in the presence of palladium 10% on activated carbon (0.588 g) until the reaction was completed. The solids were filtered off and the filtrate was evaporated *in vacuo* to give **D23** (2.73 g, 97 %).

Description 24

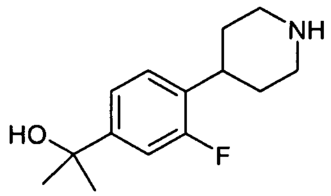
4-[2-Fluoro-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-piperidine-1-carboxylic acid tert-butyl ester (D24)



A 1.4 M solution of methylmagnesium bromide in toluene/THF (17.339 ml, 24.274 mmol) was added dropwise to a cooled (0 °C) solution of intermediate **D23** (2.73 g, 8.091 mmol) in diethylether (150 ml) under nitrogen atmosphere. The resulting reaction mixture was then stirred at 50 °C for 2 hours. After cooling in an ice bath the mixture was carefully quenched with a saturated aqueous solution of ammonium chloride, and then was extracted with EtOAc. The combined organic phase was dried (Na_2SO_4) and the solvent evaporated *in vacuo* to yield **D24** (3.16 g, 100 %).

Description 25

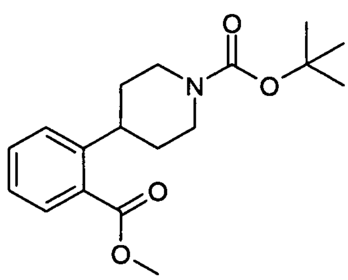
2-(3-Fluoro-4-piperidin-4-yl-phenyl)-propan-2-ol (D25)



A mixture of intermediate **D24** (3.067 g, 7.852 mmol) and KOH (2.54 g, 45.268 mmol) in isopropyl alcohol (13.5 ml) and water (27 ml) was microwaved in a sealed tube at 180 °C for 60 minutes. The resulting cooled reaction mixture was then diluted with water and brine and extracted with dichloromethane. The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The residue was treated with dichloromethane giving rise to a solid that was filtered off to yield 1.03 g intermediate **D25**. The filtrate was evaporated *in vacuo* and the residue thus obtained was then purified by column chromatography (silica gel; DCM/(NH_3 7N solution in MeOH) gradient up to 10 % as eluent). The desired fractions were collected and evaporated *in vacuo* to yield a second batch of 0.5 g of **D25** (total amount = 1.53 g, 82 %). M.P. 151°C.

Description 26

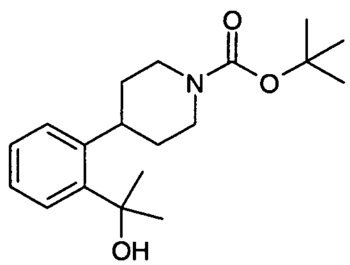
4-(2-Methoxycarbonyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester (D26)



A solution of **intermediate D21** (4.04 g, 12.729 mmol) in methanol (120 ml) was hydrogenated at room temperature in the presence of palladium 10% on activated carbon (0.846 g) until the reaction was completed. The solids were filtered off and the filtrate was evaporated *in vacuo* to give **D26** as white solid (3.67 g, 90 %).

Description 27

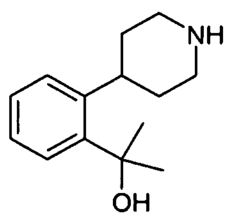
4-[2-(1-Hydroxy-1-methyl-ethyl)-phenyl]-piperidine-1-carboxylic acid tert-butyl ester (D27)



A 1.4 M solution of methylmagnesium bromide in toluene/THF (17.443 ml, 24.421 mmol) was added dropwise to a cooled (0 °C) solution of intermediate **D26** (2.6 g, 8.14 mmol) in diethylether (150 ml) under nitrogen atmosphere. The resulting reaction mixture was stirred at 45 °C for 2 hours. After cooling in an ice bath, the mixture was carefully quenched with a saturated aqueous solution of ammonium chloride, and then extracted with EtOAc. The combined organic phase was dried (Na_2SO_4) and the solvent evaporated *in vacuo* to yield **D27** (2.77 g, 69 %).

Description 28

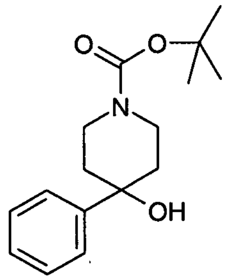
2-(2-Piperidin-4-yl-phenyl)-propan-2-ol (D28)



A mixture of intermediate **D27** (2.77 g, 5.636 mmol) and KOH (2.43 g, 43.357 mmol) in isopropyl alcohol (13.5 ml) and water (27 ml) was microwaved in a sealed tube at 180 °C for 60 minutes. The resulting cooled reaction mixture was then diluted with water and brine and extracted with dichloromethane. The residue was treated with dichloromethane giving rise to a solid that was filtered off. Yield: 0.737 g of intermediate **D28**. The filtrate was evaporated *in vacuo* and the residue was then purified by column chromatography (silica gel; DCM/(NH_3 7N solution in MeOH) gradient up to 10 % as eluent). The desired fractions were collected and evaporated *in vacuo* to yield a second batch of 0.306 g of intermediate **D28** (total amount = 1.04 g, 84 %). M.P. 219.5°C.

Description 29

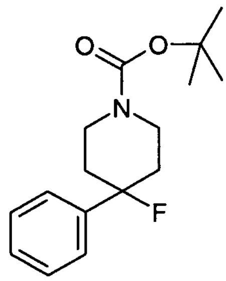
4-Hydroxy-4-phenylpiperidine-1-carboxilic acid tert-butyl ester (D29)



Di-tert-butyl dicarbonate (2.95 g, 13.53 mmol) was added to a solution of 4-hydroxy-4-phenylpiperidine (2 g, 11.28 mmol) in DCM (50 ml). The reaction was stirred at room temperature for 5 hours. The solvent was removed *in vacuo*, affording the desired intermediate **D29** (3.12 g, 100 %) as a crude that was used without further purification.

Description 30

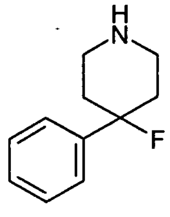
4-fluoro-4-phenylpiperidin-1-carboxilic acid tert-butyl ester (D30)



A solution of (diethylamino)sulfur trifluoride (0.74 ml, 5.67 mmol) in dry DCM (q.s.) was added to a cooled (-78 °C) solution of **D29** (1.5 g, 5.4 mmol) in dry DCM (30 ml) under N_2 atmosphere. After the addition was complete, the reaction mixture was stirred at –78°C for 1 hour and then allowed to reach room temperature and stirred for a further 30 minutes. An aqueous saturated $NaHCO_3$ solution (90 ml) was added and the mixture was stirred for 15 minutes, then the organic layer was separated. After this, 3-chloroperoxybenzoic acid (0.2 g, 1.18 mmol) was added and the reaction stirred at room temperature for 30 minutes. The reaction mixture was washed with aqueous saturated $NaHCO_3$, H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in* *vacuo* affording the desired intermediate **D30** (1.48 g, 98 %) as a crude that was used without further purification.

Description 31

4-fluoro-4-phenylpiperidine hydrochloride (D31)

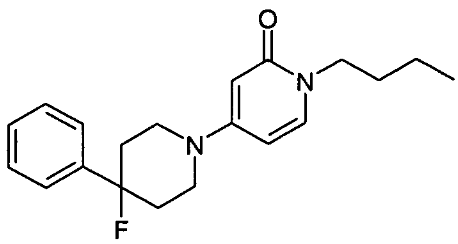


.HCl

D30 (1.48 g, 5.29 mmol) was dissolved in 4N HCl in dioxane. The reaction was stirred at room temperature for 2 hours. The solvent was removed. The crude was triturated with diethyl ether and dried *in vacuo* to afford the desired intermediate **D31** (1.10 g, 97 %) as a chlorohydrate that was used without further purification.

Description 32

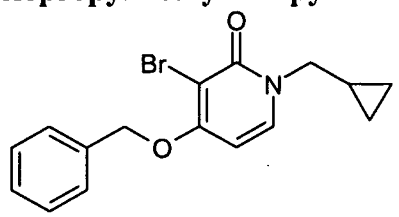
1'-Butyl-4-fluoro-4-phenyl-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2-one (D32)



D31 (0.2 g, 0.94 mmol), palladium(II) acetate (0.009 g, 0.04 mmol) sodium *tert*-butoxide (0.25 g, 2.58 mmol) and BINAP (0.037 g, 0.06 mmol) were added to a stirred solution of intermediate **D6** (0.20 g, 0.86 mmol) in toluene (5 ml). The reaction mixture was heated at 100 °C for 16 hours in a sealed tube. After cooling to room temperature the mixture was diluted with water and extracted with EtOAc. The combined organic phase was dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; 10 % ammonia in methanol (7N) / DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **D32** (0.21 g, 87 %) as a pale yellow oil.

Description 33

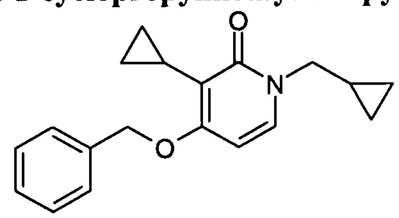
4-Benzyloxy-3-bromo-1-cyclopropylmethyl-*1H*-pyridin-2-one (D33)



A solution of intermediate **D1** (3.0 g, 11.7 mmol) and *N*-bromosuccinimide (2.09 g, 11.7 mmol) in DCM (100 ml) was stirred at room temperature for 1 hour. The solvent was evaporated *in vacuo* and the crude residue was purified by column chromatography (silica gel; DCM as eluent). The desired fractions were collected and evaporated *in vacuo* yielding **D33** (3.56 g, 91%).

Description 34

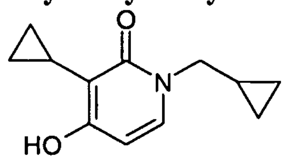
4-Benzyloxy-3-cyclopropyl-1-cyclopropylmethyl-*1H*-pyridin-2-one (D34)



$NaHCO_3$ (1.0 g, excess), cyclopropylboronic acid (0.74 g, 8.93 mmol), potassium carbonate (1.23 g, 8.93 mmol) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) – DCM complex (0.36 g, 0.45 mmol) were added to a solution of intermediate **D10** (1.0 g, 2.98 mmol) in 1,4-dioxane (10 ml). The resulting mixture was heated at 175 °C for 20 minutes under microwave irradiation, after which it was filtered through diatomaceous earth and the solvent was evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; 0-3 % methanol / DCM as eluent). The desired fractions were collected and evaporated *in vacuo* yielding **D34** (0.6 g, 69 %).

Description 35

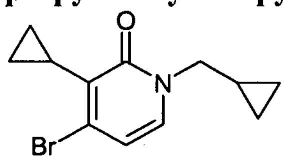
3-Cyclopropyl-1-cyclopropylmethyl-4-hydroxy-*1H*-pyridin-2-one (D35)



A mixture of intermediate **D34** (1.0 g, 3.38 mmol) and a catalytic amount of 10% palladium on activated carbon in ethanol (150 ml) was stirred under a hydrogen atmosphere for 2 hours. The mixture was filtered through diatomaceous earth and the solvent was evaporated *in vacuo* to yield intermediate **D35** (0.69 g, 100 %) that was used without further purification.

Description 36

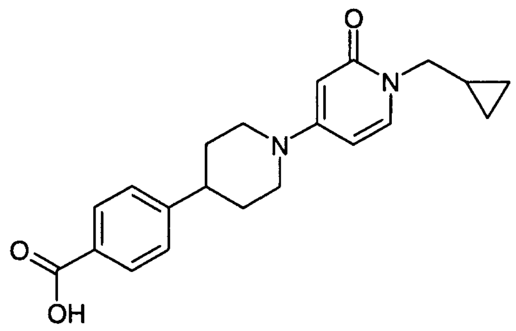
4-Bromo-3-cyclopropyl-1-cyclopropylmethyl-*1H*-pyridin-2-one (D36)



Phosphorus oxybromide (2.4 g, 8.28 mmol) was added to a solution of intermediate **D35** (0.85 g, 4.14 mmol) in DMF (60 ml), and the mixture was heated at 110 °C for 1 hour. After cooling in an ice bath, the solution was partitioned between water and EtOAc. The mixture was extracted with EtOAc (3 x 200 ml), the combined organic fractions were dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate **D36** (0.99 g, 89 %).

Description 37

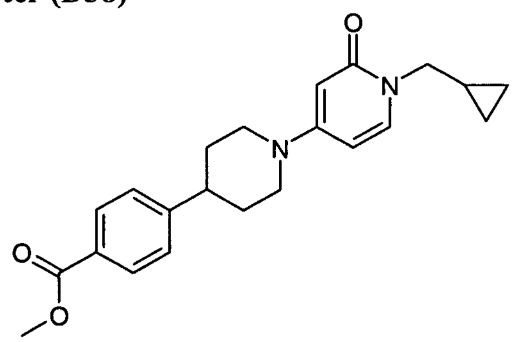
4-(1'-Cyclopropylmethyl-2'-oxo-3,4,5,6,1',2'-hexahydro-*2H*-[1,4']bipyridinyl-4-yl)-benzoic acid (D37)



4-Piperidin-4-ylbenzoic acid methyl ester (0.40 g, 1.81 mmol), palladium(II) acetate (0.015 g, 0.069 mmol) sodium *tert*-butoxide (0.34 g, 3.44 mmol) and BINAP (0.06 g, 0.096 mmol) were added to a stirred solution of intermediate **D3** (0.31 g, 1.37 mmol) in toluene (10 ml). The reaction mixture was heated at 100 °C for 16 hours in a sealed tube. After cooling to room temperature the mixture was diluted with EtOAc and then filtered through diatomaceous earth, after which the solvent was evaporated *in vacuo*. The crude residue was treated with a mixture of DCM / methanol and then filtered off. The filtrate was evaporated to dryness *in vacuo* to yield crude **D37** (0.48 g, 100 %) that was used without further purification.

Description 38

4-(1'-Cyclopropylmethyl-2'-oxo-3,4,5,6,1',2'-hexahydro-*2H*-[1,4']bipyridinyl-4-yl)-benzoic acid methyl ester (D38)

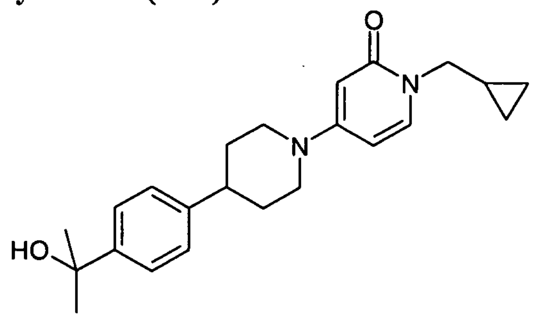


A mixture of intermediate **D37** (0.43 g, 1.23 mmol), DBU (0.18 g, 1.23 mmol), dimethyl carbonate (4.5 ml, excess, 93 mmol), and acetonitrile (5 ml) was heated at 160 °C for 20 minutes under microwave irradiation. The cooled crude mixture was diluted with water and EtOAc was added, after which the organic layer was washed with an aqueous 10% citric acid solution, dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; 0-3% methanol /

DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **D38** (0.19 g, 38 %).

Description 39

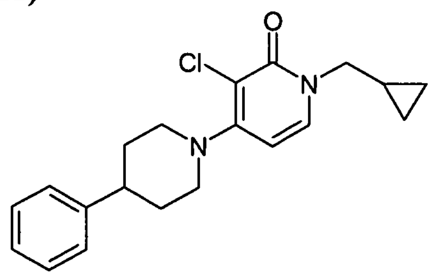
1'-Cyclopropylmethyl-4-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (D39)



A 1.4 M solution of methylmagnesium bromide in toluene/THF (1.12 ml, 1.57 mmol) was added dropwise to a cooled (0 °C) solution of intermediate **D38** (0.19 g, 0.52 mmol) in THF (20 ml) under nitrogen atmosphere. The resulting reaction mixture was stirred at 45 °C for 2 hours. After cooling in an ice bath the mixture was carefully quenched with a saturated aqueous solution of ammonium chloride, and then was extracted with EtOAc. The combined organic phase was dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; 0-5% methanol / DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **D39** (0.077 g, 40 %) as an oil.

Example 1

3'-Chloro-1'-cyclopropylmethyl-4-phenyl-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (E1)



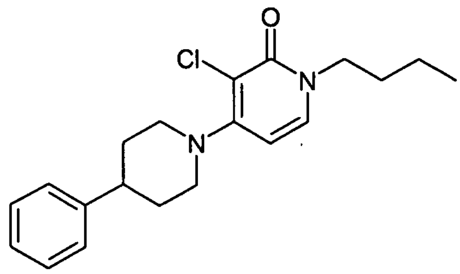
A solution of intermediate **D18** (0.2 g, 0.65 mmol) and *N*-chlorosuccinimide (0.09 g, 0.65 mmol) in DCM (10 ml) was stirred at room temperature for 1 hour. The solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (silica gel; 0-3 % methanol / DCM as eluent). The desired fractions

were collected and evaporated *in vacuo* and the resulting solid was recrystallized from diethyl ether to yield compound **E1** (0.10 g, 47 %) as a white solid.
Melting point: 170.8 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.35 - 0.42 (m, 2 H), 0.57 - 0.64 (m, 2 H), 1.19 - 1.33 (m, 1 H), 1.85 - 2.00 (m, 4 H), 2.64 - 2.76 (m, 1 H), 2.85 - 2.99 (m, 2 H), 3.76 - 3.87 (m, 4 H), 6.05 (d, *J*=7.6 Hz, 1 H), 7.19 - 7.29 (m, 4 H), 7.29 - 7.38 (m, 2 H).

Example 2

1'-Butyl-3'-chloro-4-phenyl-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (E2)

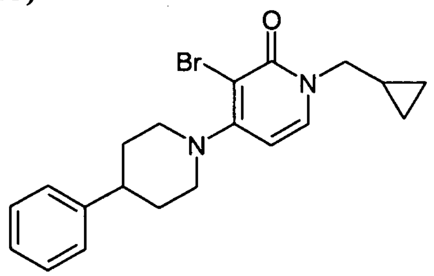


A solution of intermediate **D19** (0.43 g, 1.40 mmol) and *N*-chlorosuccinimide (0.19 g, 1.40 mmol) in DCM (10 ml) was stirred at room temperature for 1 hour. The solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (silica gel; 0-3 % methanol / DCM as eluent). The desired fractions were collected and evaporated *in vacuo* and the resulting solid was recrystallized from diethyl ether to yield compound **E2** (0.39 g, 82 %) as a white solid.
Melting point: 149.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.95 (t, *J*=7.3 Hz, 3 H), 1.31 - 1.42 (m, 2 H), 1.68 - 1.78 (m, 2 H), 1.85 - 1.98 (m, 4 H), 2.64 - 2.73 (m, 1 H), 2.87 - 2.96 (m, 2 H), 3.82 (br d, *J*=12.1 Hz, 2 H), 3.93 (t, *J*=7.3 Hz, 2 H), 6.03 (d, *J*=7.6 Hz, 1 H), 7.10 (d, *J*=7.6 Hz, 1 H), 7.19 - 7.28 (m, 3 H), 7.29 - 7.37 (m, 2 H).

Example 3

3'-Bromo-1'-cyclopropylmethyl-4-phenyl-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (E3)



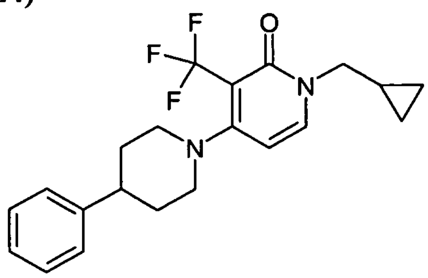
N-Bromosuccinimide (0.145 g, 0.82 mmol) was added to a solution of intermediate **D18** (0.25 g, 0.82 mmol) in DCM (10 ml). The reaction mixture was stirred at room temperature for 1 hour. Subsequently, the solvent was evaporated *in vacuo* and the crude residue was purified by column chromatography (silica gel; 0-3 % methanol / DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **E3** (0.20 g, 64 %) as a white solid.

Melting point: 150 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.34 - 0.40 (m, 2 H), 0.44 - 0.50 (m, 2 H), 1.16 - 1.26 (m, 1 H), 1.77 (qd, *J*=12.38, 3.61 Hz, 2 H), 1.88 (br d, *J*=12.1 Hz, 2 H), 2.68 - 2.78 (m, 1 H), 2.91 (br t, *J*=11.9 Hz, 2 H) 3.69 (br d, *J*=12.1 Hz, 2 H), 3.74 (d, *J*=7.2 Hz, 2 H), 6.21 (d, *J*=7.5 Hz, 1 H), 7.19 - 7.25 (m, 1 H), 7.27 - 7.36 (m, 4 H), 7.69 (d, *J*=7.5 Hz, 1 H).

Example 4

1'-Cyclopropylmethyl-4-phenyl-3'-trifluoromethyl-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (E4)



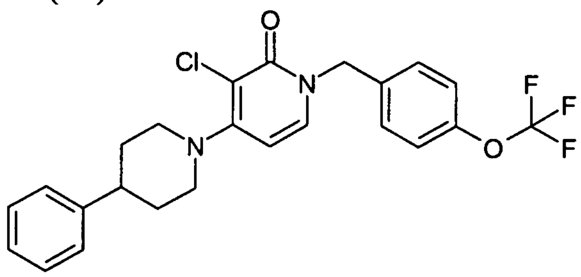
4-Phenylpiperidine (0.33 g, 2.02 mmol), palladium(II) acetate (0.012 g, 0.05 mmol), sodium *tert*-butoxide (0.24 g, 2.52 mmol) and BINAP (0.05 g, 0.08 mmol) were added to a solution of intermediate **D13** (0.3 g, 1.01 mmol) in toluene (7 ml). The reaction mixture was heated at 100 °C for 16 hours in a sealed tube, after which it was cooled to room temperature and then it was diluted with water (5 ml) and extracted with EtOAc

(3 x 5 ml). The combined organic fractions were dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; 0-4% methanol / DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **E4** (0.11 g, 31 %) as a white solid.
Melting point: 177.2 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.33 - 0.38 (m, 2 H), 0.45 - 0.50 (m, 2 H), 1.13 - 1.22 (m, 1 H), 1.64 - 1.75 (m, 2 H), 1.84 (br d, *J*=11.0 Hz, 2 H), 2.72 - 2.80 (m, 1 H), 3.14 (br t, *J*=12.1 Hz, 2 H), 3.59 (br d, *J*=13.0 Hz, 2 H), 3.65 (d, *J*=7.2 Hz, 2 H), 6.21 (d, *J*=7.8 Hz, 1 H), 7.19 - 7.23 m, 1 H), 7.24 - 7.29 (m, 2 H), 7.29 - 7.34 (m, 2 H), 7.73 (d, *J*=7.8 Hz, 1 H).

Example 5

3'-Chloro-4-phenyl-1'-(4-trifluoromethoxybenzyl)-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (E5)

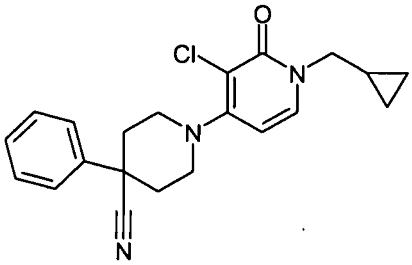


A mixture of intermediate **D17** (0.2 g, 0.52 mmol), 4-phenylpiperidine (0.1 g, 0.62 mmol), 2-(2'-Di-tert-butylphosphine)biphenylpalladium(II) acetate (0.01 g, 0.026 mmol) and potassium phosphate (0.23 g, 1.1 mmol) in 1,4-dioxane (3 ml) was stirred at 90 °C for 35 hours. The mixture was filtered through diatomaceous earth, and the filtrate was evaporated to dryness after washing with more 1,4-dioxane. The crude product was purified by column chromatography (silica gel; heptane / diethyl ether 1:1 as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **E5** (0.075 g, 31 %) as a white solid.
Melting point: 168.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.83 - 1.98 (m, 4 H), 2.65 - 2.75 (m, 1 H), 2.89 - 2.98 (m, 2 H), 3.84 (br d, *J*=12.2 Hz, 2 H), 5.12 (s, 2 H), 6.06 (d, *J*=7.6 Hz, 1 H), 7.14 (d, *J*=7.6 Hz, 2 H), 7.15 - 7.28 (m, 5 H), 7.29 - 7.40 (m, 4 H).

Example 6

3'-Chloro-1'-cyclopropylmethyl-2'-oxo-4-phenyl-3,4,5,6,1',2'-hexahydro-*2H*-[1,4']bipyridinyl-4-carbonitrile (E6)

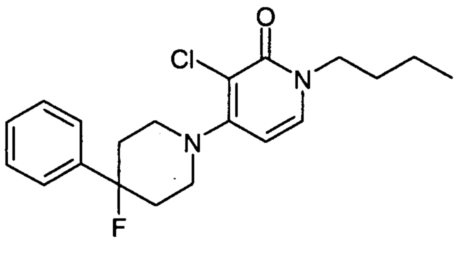


A solution of intermediate **D20** (0.35 g, 1.03 mmol) and *N*-chlorosuccinimide (0.14 g, 1.03 mmol) in DCM (25 ml) was stirred at room temperature for 1 hour. After addition of more DCM, the solution was washed with brine, dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; 10 % ammonia in methanol (7N) / DCM as eluent) and further purified by preparative HPLC. The desired fractions were collected and evaporated *in vacuo* to yield compound **E6** (0.17 g, 47 %) as a white solid.
Melting point: 173.7 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.17 - 0.23 (m, 2 H), 0.26 - 0.33 (m, 2 H), 0.97 - 1.09 (m, 1 H), 1.91 - 2.02 (m, 2 H), 2.11 (br d, *J*=12.9 Hz, 2 H) 2.98 (br t, *J*=12.4 Hz, 2 H), 3.54 - 3.63 (m, 4 H), 6.14 (d, *J*=7.4 Hz, 1 H), 7.20 - 7.26 (m, 1 H), 7.27 - 7.35 (m, 2 H), 7.40 - 7.44 (m, 2 H), 7.52 (d, *J*=7.4 Hz, 1 H).

Example 7

1'-Butyl-3-chloro-4-fluoro-4-phenyl-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2-one (E7)



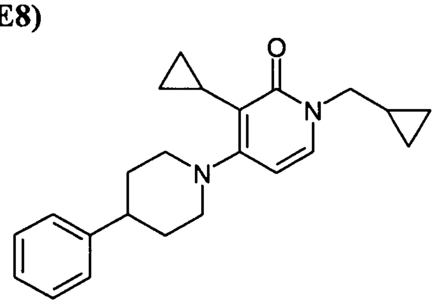
A solution of intermediate **D32** (0.21 g, 0.66 mmol) and *N*-chlorosuccinimide (0.08 g, 0.66 mmol) in DCM (30 ml) was stirred at room temperature for 10 minutes. After addition of more DCM the solution was washed with brine, dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; 10 % ammonia in methanol (7M) / DCM as eluent) and

further purified by preparative HPLC. The desired fractions were collected and evaporated *in vacuo* to yield compound **E7** (0.065 g, 27 %) as a white solid.
Melting point: 136.7 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.89 (t, *J*=7.4 Hz, 3 H), 1.21 - 1.32 (m, 2 H), 1.54 - 1.64 (m, 2 H), 2.03 (t, *J*=11.8 Hz, 2 H), 2.16 (td, *J*=13.9, 4.6 Hz, 1 H), 2.26 (td, *J*=13.6, 4.6 Hz, 1 H), 3.17 (dd, *J*=12.3, 11.1 Hz, 2 H), 3.54 - 3.64 (m, 2 H), 3.87 (t, *J*=7.2 Hz, 2 H), 6.26 (d, *J*=7.6 Hz, 1 H), 7.32 - 7.38 (m, 1 H), 7.42 (t, *J*=7.4 Hz, 2 H), 7.45 - 7.51 (m, 2 H), 7.62 (d, *J*=7.4 Hz, 1 H).

Example 8

3'-Cyclopropyl-1'-cyclopropylmethyl-4-phenyl-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (E8)

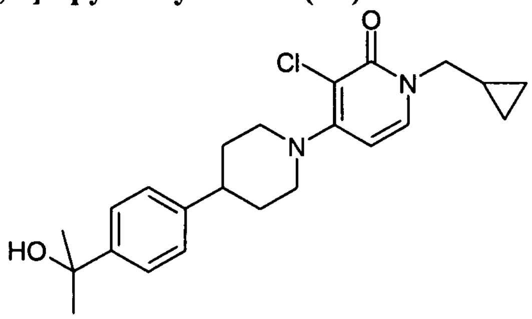


4-Phenylpiperidine (0.22 g, 1.34 mmol), palladium(II) acetate (0.008 g, 0.034 mmol), sodium *tert*-butoxide (0.16 g, 1.68 mmol) and BINAP (0.032 g, 0.05 mmol) were added to a solution of intermediate **D36** (0.18 g, 0.67 mmol) in toluene (5 ml). The reaction mixture was heated at 100 °C for 16 hours in a sealed tube, after which it was cooled to room temperature and then diluted with water (5 ml) and extracted with EtOAc (3 x 5 ml). The combined organic fractions were dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; 0-4% methanol / DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **E8** (0.18 g, 77 %) as a white solid.
Melting point: 201.9 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.30 - 0.35 (m, 2 H) 0.41 - 0.47 (m, 2 H) 0.74 - 0.80 (m, 2 H), 0.86 - 0.92 (m, 2 H), 1.11 - 1.21 (m, 1 H), 1.60 - 1.67 (m, 1 H), 1.73 - 1.89 (m, 4 H), 2.63 - 2.72 (m, 1 H), 2.87 (br t, *J*=11.1 Hz, 2 H), 3.57 - 3.65 (m, 4 H), 6.07 (d, *J*=7.5 Hz, 1 H), 7.19 – 7.24 (m, 1 H), 7.26 - 7.37 (m, 4 H), 7.46 (d, *J*=7.5 Hz, 1 H).

Example 9

3'-Chloro-1'-cyclopropylmethyl-4-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (E9)

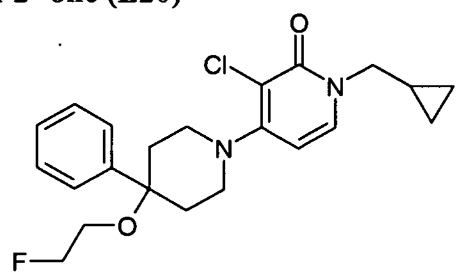


A solution of intermediate **D39** (0.077 g, 0.21 mmol) and *N*-chlorosuccinimide (0.03 g, 0.21 mmol) in DCM (8 ml) was stirred at room temperature for 5 minutes. The crude mixture was washed with a saturated $NaHCO_3$ solution, then it was extracted with DCM, the combined organic fractions were dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; 0-5 % methanol / DCM as eluent). A second chromatography was performed (silica gel; DCM / EtOAc 1:1, and finally 100% EtOAc as eluents). The desired fractions were collected and evaporated *in vacuo* and the resulting solid was crystallized from diethyl ether to yield compound **E9** (0.06 g, 71 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.35 - 0.41 (m, 2 H), 0.56 - 0.64 (m, 2 H), 1.19 - 1.30 (m, 1 H), 1.59 (s, 6 H), 1.73 (s, 1 H), 1.85 - 1.99 (m, 4 H), 2.65 - 2.76 (m, 1 H), 2.87 - 2.97 (m, 2 H), 3.78 - 3.87 (m, 4 H), 6.05 (d, *J*=7.6 Hz, 1 H), 7.21 - 7.26 (m, 3 H), 7.45 (d, *J*=8.3 Hz, 2 H).

Example 20

3'-Chloro-1'-cyclopropylmethyl-4-(2-fluoro-ethoxy)-4-phenyl-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (E20)

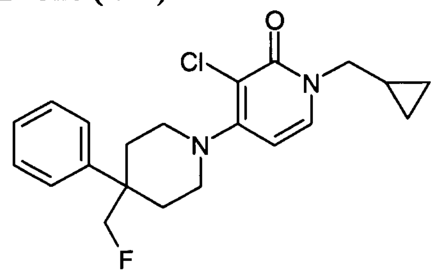


A solution of compound **E31** (0.164 g, 0.46 mmol) in 1,2-dimethoxyethane (3 ml) was added dropwise to a mixture of sodium hydride (0.023 g, 0.58 mmol) in 1,2-dimethoxyethane (0.5 ml) at 0 °C. The reaction mixture was stirred at room temperature for 15 minutes and subsequently a solution of 2-fluoroethyl tosylate [CAS: 383-50-6] (0.222 g, 1 mmol) in 1,2-dimethoxyethane (1 ml) was added. The reaction mixture was microwaved into a sealed tube at 180 °C for 20 minutes. The mixture was cooled to room temperature and an additional amount of sodium hydride (0.023 g, 0.58 mmol) was added. The mixture was the heated at 180 °C for 20 minutes under microwave irradiation. After cooling to room temperature, an aqueous saturated ammonium chloride solution was added and the mixture was extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified first by column chromatography (silica gel; eluent: DCM/EtOAc from 100/0 to 90/10). The desired fractions were collected and evaporated *in vacuo* to yield compound **E20** (0.041 g, 18 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.36 - 0.40 (m, 2 H), 0.58 - 0.62 (m, 2 H), 1.22 - 1.28 (m, 1 H), 2.12 - 2.21 (m, 4 H), 3.27 - 3.36 (m, 4 H), 3.57 (br d, *J*=12.1 Hz, 2 H), 3.80 (d, *J*=7.2 Hz, 2 H), 4.51 (dm, *J*=47.7 Hz, 2 H), 6.08 (d, *J*=7.5 Hz, 1 H), 7.23 (d, *J*=7.5 Hz, 1 H), 7.29 - 7.32 (m, 1 H), 7.37 - 7.41 (m, 2 H), 7.44 - 7.46 (m, 2 H).

Example 21

3'-Chloro-1'-cyclopropylmethyl-4-fluoromethyl-4-phenyl-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (E21)

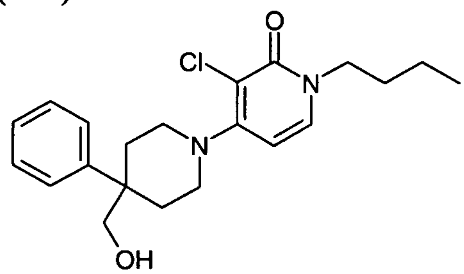


(Diethylamino)sulfur trifluoride (0.046 ml, 0.35 mmol) was added to a cooled (- 78 °C) solution of compound **E30** (0.119 g, 0.32 mmol) in DCM (1 ml). The reaction mixture was stirred at –78 °C for 3 hours and then additional for 2 hours at 0 °C. Subsequently, additional (diethylamino)sulfur trifluoride (0.046 ml, 0.35 mmol) was added and the mixture was further stirred for 1 hour at room temperature. Na_2CO_3 (aqueous saturated solution) was added and the mixture was diluted with DCM. The organic layer was separated, dried (Na_2SO_4) and evaporated till dryness. The crude product was purified by column chromatography (silica gel; eluent: DCM /EtOAc from 100/0 to 80/20). The desired fractions were collected, evaporated *in vacuo* and finally freeze dried to yield compound **E21** (0.019 g, 16 %) as a white foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.33 - 0.40 (m, 2 H), 0.52 - 0.65 (m, 2 H), 1.17 - 1.29 (m, 1 H), 1.74 - 1.96 (m, 4 H), 2.96 (d, *J*=22.7 Hz, 2 H), 3.06 (dt, *J*=11.6, 3.7 Hz, 2 H), 3.45 - 3.52 (m, 2 H), 3.79 (d, *J*=7.2 Hz, 2 H), 6.01 (d, *J*=7.6 Hz, 1 H), 7.20 - 7.36 (m, 6 H).

Example 22

1'-Butyl-3'-chloro-4-hydroxymethyl-4-phenyl-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (E22)

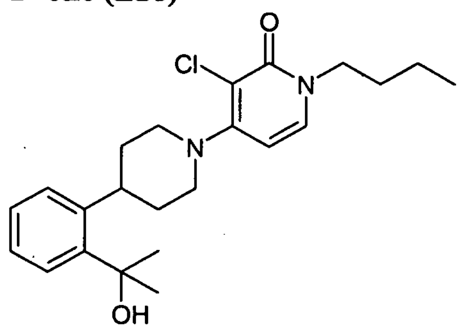


4-Hydroxymethyl-4-phenylpiperidine (0.172 g, 0.9 mmol), palladium(II) acetate (0.007 g, 0.03 mmol), cesium carbonate (0.391 g, 1.2 mmol) and Xantphos (0.035 g, 0.06 mmol) were added to a solution of intermediate **D9** (0.2 g, 0.6 mmol) in trifluoromethylbenzene (2 ml). The reaction mixture was heated at 100 °C for 24 hours in a sealed tube, after which it was cooled to room temperature. Subsequently, it was diluted with DCM, H_2O (5 ml) and extracted with EtOAc (3 x 5 ml). The mixture was filtered through diatomaceous earth, and the filtrate was evaporated to dryness. The crude product was purified first by column chromatography (silica gel; eluent: DCM/EtOAc from 90/10 to 0/100) and then by reversed phase HPLC. The desired fractions were collected, evaporated *in vacuo* and finally freeze dried to yield compound **E22** (0.041 g, 18 %) as a white foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.93 (t, *J*=7.3 Hz, 3 H), 1.13 (br t, *J*=6.7 Hz, 1 H), 1.28 - 1.40 (m, 2 H), 1.64 - 1.75 (m, 2 H), 1.98 - 2.08 (m, 2 H), 2.31 - 2.40 (m, 2 H), 2.98 - 3.10 (m, 2 H), 3.41 - 3.51 (m, 2 H), 3.63 (d, *J*=6.5 Hz, 2 H), 3.90 (t, *J*=7.3 Hz, 2 H), 5.92 (d, *J*=7.5 Hz, 1 H), 7.04 (d, *J*=7.5 Hz, 1 H), 7.27 - 7.33 (m, 1 H), 7.36 - 7.46 (m, 4 H).

Example 28

1'-Butyl-3'-chloro-4-[2-(1-hydroxy-1-methyl-ethyl)-phenyl]-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (E28)

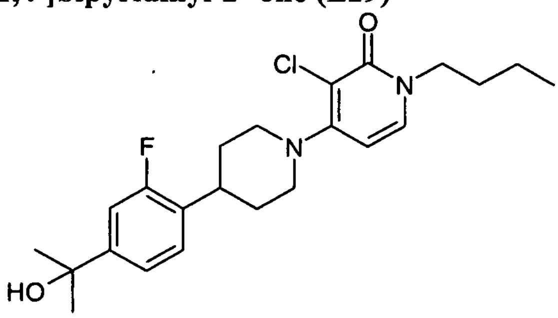


A mixture of intermediate **D9** (0.254 g, 0.76 mmol), intermediate **D28** (0.2 g, 0.912 mmol) and diisopropylethylamine (0.199 ml, 1.114 mmol) in acetonitrile (11 ml) was heated at 180 °C for 5 minutes under microwave irradiation. The cooled crude mixture was evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; DCM/EtOAc/MeOH as eluent). The desired fractions were collected and evaporated *in vacuo*. The solid residue obtained was treated with diisopropylether. The solid was filtered to yield compound **E28** (0.183 g, 61 %).
M.P. 182 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.95 (t, *J*=7.3 Hz, 3 H), 1.32 - 1.42 (m, 2 H), 1.70 (s, 6 H), 1.71 - 1.77 (m, 2 H), 1.79 (s, 1 H), 1.82 - 1.90 (m, 2 H), 1.91 - 2.05 (m, 2 H), 2.88 - 2.98 (m, 2 H), 3.76 - 3.87 (m, 3 H), 3.93 (t, *J*=7.3 Hz, 2 H), 6.03 (d, *J*=7.5 Hz, 1 H), 7.11 (d, *J*=7.5 Hz, 1 H), 7.16 (td, *J*=7.8, 1.4 Hz, 1 H), 7.28 (td, *J*=7.4, 1.4 Hz, 1 H), 7.41 (dd, *J*=7.7, 1.6 Hz, 1 H), 7.42 (dd, *J*=7.6, 1.7 Hz, 1 H).

Example 29

1'-Butyl-3'-chloro-4-[2-fluoro-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one (E29)

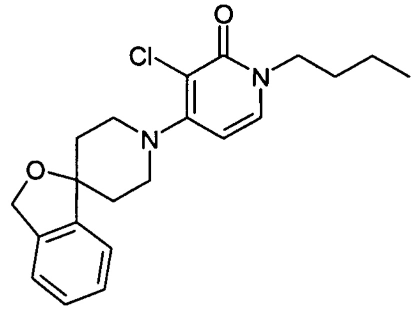


A mixture of intermediate **D9** (0.261 g, 0.781 mmol), intermediate **D25** (0.223 g, 0.938 mmol) and diisopropylethylamine (0.204 ml, 1.172 mmol) in acetonitrile (11 ml) was heated at 180 °C for 5 minutes under microwave irradiation. The cooled crude mixture was evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; DCM/EtOAc/MeOH/NH_3 as eluent). The desired fractions were collected and evaporated *in vacuo*. The solid residue obtained was treated with diisopropylether. The solid was filtered to yield compound **E29** (0.239 g, 73 %). M.P. 150.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.95 (t, *J*=7.3 Hz, 3 H), 1.31 - 1.43 (m, 2 H), 1.57 (s, 6 H), 1.68 - 1.76 (m, 2 H), 1.77 (s, 1 H), 1.87 - 1.96 (m, 4 H), 2.86 - 2.98 (m, 2 H), 2.98 - 3.09 (m, 1 H), 3.81 (br d, *J*=12.0 Hz, 2 H), 3.93 (t, *J*=7.3 Hz, 2 H), 6.03 (d, *J*=7.5 Hz, 1 H), 7.11 (d, *J*=7.5 Hz, 1 H), 7.16 - 7.25 (m, 3 H).

Example 32

1-butyl-3-chloro-4-(*1'H*,*3H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)pyridin-2(*1H*)-one (E32)

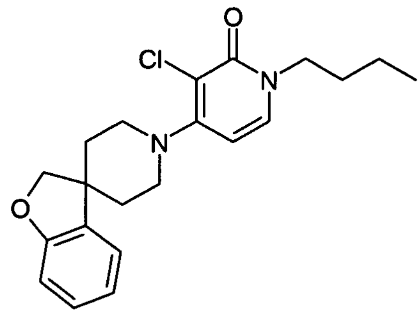


A mixture of intermediate **D9** (0.15 g, 0.45 mmol), *3H*-spiro[2-benzofuran-1,4'-piperidine] (0.102 g, 0.54 mmol) and diisopropylethylamine (0.097 ml, 0.056 mmol) in acetonitrile (4 ml) was heated at 180 °C for 5 minutes under microwave irradiation. The cooled crude mixture was evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; DCM/EtOAc/MeOH/NH_3 as eluent). The desired fractions were collected and evaporated *in vacuo*. The solid residue obtained was treated with diisopropylether. The solid was filtered to yield compound **E32** (0.14 g, 84 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.95 (t, *J*=7.3 Hz, 3 H), 1.30 - 1.43 (m, 2 H), 1.67 - 1.79 (m, 2 H), 1.85 (dd, *J*=13.8, 2.20 Hz, 2 H), 2.12 (dt, *J*=13.0, 4.7 Hz, 2 H), 3.25 (dt, *J*=12.4, 2.31 Hz, 2 H), 3.57 - 3.68 (m, 2 H), 3.94 (t, *J*=7.3 Hz, 2 H), 6.06 (d, *J*=7.4 Hz, 1 H), 7.12 (d, *J*=7.4 Hz, 1 H), 7.16 - 7.34 (m, 7 H).

Example 33

1-butyl-3-chloro-4-(*1'H*-spiro[1-benzofuran-3,4'-piperidin]-1'-yl)pyridin-2(*1H*)-one (E33)



A mixture of intermediate **D9** (0.15 g, 0.45 mmol), spiro[1-benzofuran-3,4'-piperidine] (0.102 g, 0.54 mmol) and diisopropylethylamine (0.097 ml, 0.056 mmol) in acetonitrile (4 ml) was heated at 180 °C for 5 minutes under microwave irradiation. The cooled crude mixture was evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; DCM/EtOAc/MeOH/NH_3 as eluent). The desired fractions were collected and evaporated *in vacuo*. The solid residue obtained was treated with diisopropylether. The solid was filtered to yield compound **E33** (0.116 g, 84 %).

^{1}H NMR (500 MHz, CDCl3) δ ppm 0.95 (t, *J*=7.4 Hz, 3 H), 1.30 - 1.43 (m, 2 H), 1.66 - 1.79 (m, 2 H), 1.86 (d, *J*=13.3 Hz, 2 H), 2.05 - 2.19 (m, 2 H), 2.84 - 2.97 (m, 2 H), 3.68 (d, *J*=12.7 Hz, 2 H), 3.94 (t, *J*=7.4 Hz, 2 H), 4.44 (s, 2 H), 6.01 (d, *J*=7.5 Hz, 1 H), 6.83 (d, *J*=7.8 Hz, 1 H), 6.92 (t, *J*=7.4 Hz, 1 H), 7.07 - 7.24 (m, 3 H).

Compounds E10, E11, E12, E13, E14, E15, E16, E17, E18, E19, E23, E24, E25 and E26 were prepared according to the reaction procedure described in Example 1.
Compound E27 was prepared according to the reaction procedure described in Example 9.
Compound E30 and compound E31 were prepared according to the reaction procedure described in Example 22.

Physico-Chemical Data

LCMS – general procedure

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 a MS spectrometer. The

MS detector was configured with an electrospray ionization source. Nitrogen was used as the nebulizer gas. The source temperature was maintained at 140 °C. Data acquisition was performed with MassLynx-Openlynx software.

LCMS Method: For all examples, except for Examples E5, E18, E25, E27, E28, E29, E30 and E31, the following method was used.

In addition to the general procedure: Reversed phase HPLC was carried out on an XDB-C18 cartridge (1.8 μm, 2.1 x 30 mm) from Agilent, with a flow rate of 1 ml/min, at 60°C. The gradient conditions used are: 90 % A (0.5 g/l ammonium acetate solution), 5 % B (acetonitrile), 5 % C (methanol) to 50 % B and 50 % C in 6.5 minutes, to 100 % B at 7 minutes and equilibrated to initial conditions at 7.5 minutes until 9.0 minutes. Injection volume 2 μl. High-resolution mass spectra (Time of Flight, TOF) were acquired only in positive ionization mode by scanning from 100 to 750 in 0.5 seconds using a dwell time of 0.1 seconds. The capillary needle voltage was 2.5 kV and the cone voltage was 20 V. Leucine-Enkephaline was the standard substance used for the lock mass calibration.

LCMS Method: This method was used for examples E5 and E18.

In addition to the general procedure: Reversed phase HPLC was carried out on an ACE-C18 column (3.0 μm, 4.6 x 30 mm) from Advanced Chromatography Technologies, with a flow rate of 1.5 ml/min, at 40 °C. The gradient conditions used are: 80 % A (0.5 g/l ammonium acetate solution), 10 % B (acetonitrile), 10 % C (methanol) to 50 % B and 50 % C in 6.5 minutes, to 100 % B at 7 minutes and equilibrated to initial conditions at 7.5 minutes until 9.0 minutes. Injection volume 5 μl. High-resolution mass spectra (Time of Flight, TOF) were acquired only in positive ionization mode by scanning from 100 to 750 in 0.5 seconds using a dwell time of 0.1 seconds. The capillary needle voltage was 2.5 kV for positive ionization mode and the cone voltage was 20 V. Leucine-Enkephaline was the standard substance used for the lock mass calibration.

LCMS Method : This method was used for example E25.

In addition to the general procedure: Reversed phase HPLC was carried out on a XDB-C18 cartridge (1.8 μm, 2.1 x 30 mm) from Agilent, with a flow rate of 0.8 ml/min, at 60°C. The gradient conditions used are: 90 % A (0.5 g/l ammonium acetate solution), 10 % B (mixture of Acetonitrile/ Methanol, 1/1), to 100 % B in 6.0 minutes, kept till 6.5 minutes and equilibrated to initial conditions at 7.0 minutes until 9.0 minutes. Injection volume 2 μl. Low-resolution mass spectra (SQD detector; quadrupole) were acquired only in positive ionization mode 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 and the cone voltage was 20 V.

LCMS Method : This method was used for example E27.

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 acetonitrile), 2.5 % B (acetonitrile), 2.5 % C (methanol) to 50 % B and 50 % C in 6.5 minutes, kept till 7 minutes and equilibrated to initial conditions at 7.3 minutes until 9.0 minutes. 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.

LCMS Method : This method was used for example E28, E29, E32 and E33.

In addition to the general procedure: Reversed phase HPLC 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 % acetonitrile), 5 % B (mixture of acetonitrile / methanol, 1/1), to 20 % A, 80 % B in 4.9 minutes, to 100 % B in 5.3 minutes, kept till 5.8 minutes and equilibrated to initial conditions at 6.0 minutes until 7.0 minutes. Injection volume 0.5 μl. Low-resolution mass spectra (SQD detector; quadrupole) 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.

LCMS Method : This method was used for examples E30 and E31.

In addition to the general procedure: Reversed phase HPLC was carried out on an XDB-C18 cartridge (1.8 μm, 2.1 x 30 mm) from Agilent, with a flow rate of 1 ml/min, at 60°C. The gradient conditions used are: 90 % A (0.5 g/l ammonium acetate solution), 5 % B (acetonitrile), 5 % C (methanol), kept 0.2 minutes, to 50 % B, 50 % C in 3.5 minutes, kept till 3.65 minutes and equilibrated to initial conditions at 3.8 minutes until 5.0 minutes. 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.

Melting points

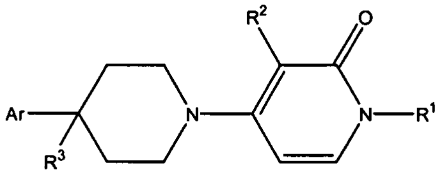
For a number of compounds, melting points were determined in open capillary tubes on a Mettler FP62 apparatus. Melting points were measured with a temperature gradient of 3 or 10 °C/minute. Maximum temperature was 300 °C. The melting point was read from a digital display and were obtained with experimental uncertainties that are commonly associated with this analytical method.

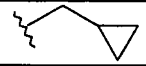
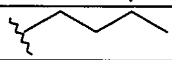
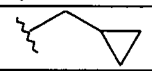
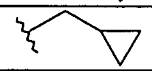
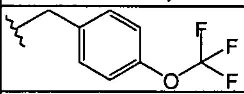
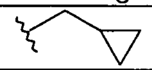
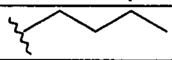
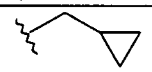
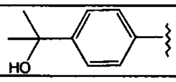
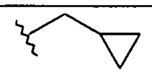
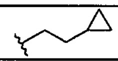
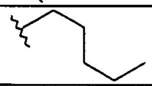
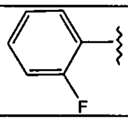
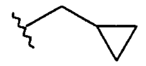
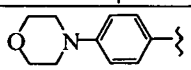
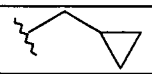
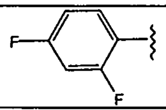
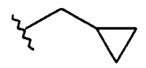
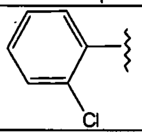
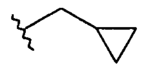
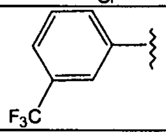
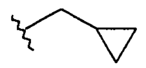
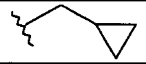
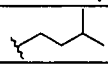
Nuclear Magnetic Resonance (NMR)

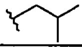
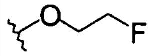
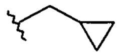
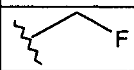
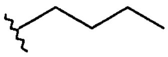
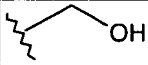
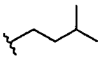
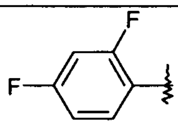
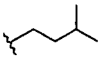
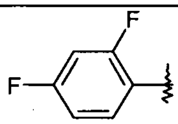
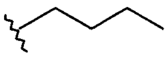
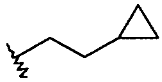
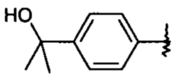
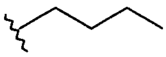
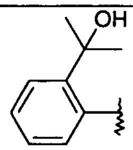
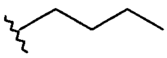
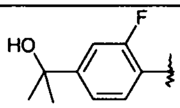
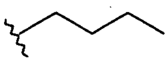
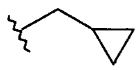
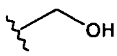
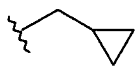
^{1}H NMR spectra were recorded either on Bruker DPX400 or Bruker AV-500 spectrometers operating at 400 and 500MHz respectively. All reported chemical shifts (δ) are expressed in ppm relative to tetramethylsilane.

Table 1 lists compounds of Formula (I) that were prepared according to one of the above Examples.

Table 1:

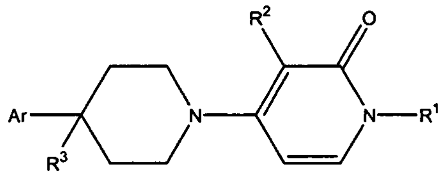


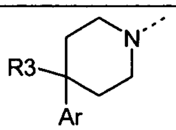
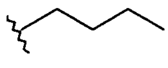
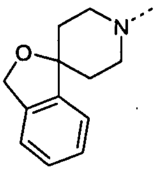
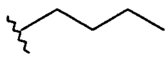
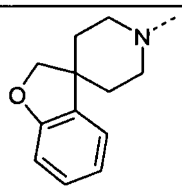
Ex.	Ar	R¹	R²	R³	M.P.(°C)	MH+	RT (min)
E1	Ph		Cl	H	170.8	343	4.67
E2	Ph		Cl	H	149.4	345	4.92
E3	Ph		Br	H	150.2	387	4.81
E4	Ph		CF_3	H	180.6	377	4.90
E5	Ph		Cl	H	168.6	463	5.71
E6	Ph		Cl	CN	173.7	368	4.01
E7	Ph		Cl	F	136.7	363	4.83
E8	Ph			H	201.9	349	5.17
E9			Cl	H	142.7	401	4.20
E10	Ph		Cl	H	244.6	357	4.97
E11	Ph		Cl	H	nd	359	5.29
E12			Cl	H	nd	361	4.76
E13			Cl	H	nd	428	4.47
E14			Cl	H	188.3	379	4.84
E15			Cl	H	145.9	377	5.06
E16			Cl	H	121.9	411	5.10
E17	Ph		Cl	F	195.3	361	4.55
E18	Ph		Cl	H	147.3	359	5.41

Ex.	Ar	R[1]	R[2]	R[3]	M.P.(°C)	MH+	RT (min)
E19	Ph		Cl	H	nd	345	4.87
E20	Ph		Cl		nd	405	4.51
E21	Ph		Cl		nd	375	4.68
E22	Ph		Cl		nd	375	3.88
E23	Ph		Cl	F	140.4	377	5.07
E24			Cl	H	nd	395	5.31
E25			Cl	H	nd	381	5.10
E26	Ph		Cl	F	nd	375	4.79
E27			Cl	H	144.4	403	4.56
E28			Cl	H	182.0	403	3.60
E29			Cl	H	150.5	421	3.65
E30	Ph		Cl		nd	373	2.82
E31	Ph		Cl	OH	nd	359	2.92

nd: not determined

Table 2:



Ex.	R^1	R^2		M.P.(°C)	MH+	RT (min)
E32		Cl		133.1	373	3.68
E33		Cl		156.5	373	3.67

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 Gαl-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 (Schaffhauser et al 2003, Pinkerton et al, 2004, Mutel et al (1998) Journal of Neurochemistry. 71:2558-64; Schaffhauser et al (1998) Molecular Pharmacology 53:228-33). 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 hours, 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 (15s) using an ultra-turrax homogenizer. The homogenate was centrifuged at 23 500 x g for 10 minutes and the supernatant discarded. The pellet was resuspended in 5 mM Tris-HCl, pH 7.4 and centrifuged again (30 000 x g, 20 min, 4°C). The final pellet was resuspended in 50 mM HEPES, 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 in membranes containing human mGluR2 was performed using frozen membranes that were thawed and briefly homogenized prior to pre-incubation in 96-well microplates (15 μg/assay well, 30 minutes, 30°C) in assay buffer (50 mM HEPES pH 7.4, 100 mM NaCl, 3 mM $MgCl_2$, 50 μM GDP, 10 μg/ml saponin,) with increasing concentrations of positive allosteric modulator (from 0.3 nM to 50 μM) and either a minimal pre-determined concentration of glutamate (PAM assay), or no added glutamate. For the PAM assay, membranes were pre-incubated with glutamate at EC_{25} concentration, i.e. a concentration that gives 25 % of the maximal response glutamate, and is in accordance to published data (Pin et al. (1999) Eur. J. Pharmacol. 375:277-294). After addition of [^{35}S]GTPγS (0.1 nM, f.c.) to achieve a total reaction volume of 200 µl, microplates were shaken briefly and further incubated to allow [^{35}S]GTPγS incorporation on activation (30 minutes, 30 °C). The reaction was stopped by rapid vacuum filtration over glass-fibre filter plates (Unifilter 96-well GF/B filter plates, Perkin-Elmer, Downers Grove, USA) microplate using a 96-well plate cell harvester (Filtermate, Perkin-Elmer, USA), and then by washing three times with 300 µl of ice-cold wash buffer ($Na_2PO_4.2H_20$ 10 mM, $NaH_2PO_4.H_20$ 10 mM, pH = 7.4). Filters were then air-dried, and 40 µl of liquid scintillation cocktail (Microscint-O) was added to each well, and membrane-bound [^{35}S]GTPγS was measured in a 96-well scintillation plate reader (Top-Count, Perkin-Elmer, USA). Non-specific [^{35}S]GTPγS binding is determined in the presence of cold 10 µM GTP. Each curve was performed at least once using duplicate sample per data point and at 11 concentrations.

Data analysis

The concentration-response curves of representative compounds of the present invention in the presence of added EC_{25} of mGluR2 agonist glutamate to determine positive allosteric modulation (PAM), were generated using the Prism GraphPad software (Graph Pad Inc, San Diego, USA). The curves were fitted to a four-parameter logistic equation (Y=Bottom + (Top-Bottom)/(1+10^((LogEC_{50}-X)*Hill Slope) allowing determination of EC_{50} values. The EC_{50} is the concentration of a compound that causes a half-maximal potentiation of the glutamate response. This is calculated by subtracting the maximal responses of glutamate in presence of a fully saturating concentration of a positive allosteric modulator from the response of glutamate in absence of a positive allosteric modulator. The concentration producing the half-maximal effect is then calculated as EC_{50}.

<u>Table 3</u>. Pharmacological data for compounds according to the invention.

All compounds were tested in presence of mGluR2 agonist, glutamate at a predetermined EC_{25} concentration, to determine positive allosteric modulation (GTPγS-PAM). Values shown are averages of duplicate values of 11-concentration response curves, from at least one experiment. All tested compounds showed a pEC_{50} (-logEC_{50}) value of more than 5.0, from 6.05 to 7.20. The error of determination of a pEC_{50} value for a single experiment is estimated to be about 0.3 log-units.

Comp. No.	GTPgS - hR2 PAM pEC_{50}
1	6.53
2	6.74
3	6.88
4	6.45
5	6.90
6	6.34
7	6.62
8	6.04
9	6.57
10	6.88
11	7.11
12	7.03
13	6.64
14	6.92
15	7.00
16	7.12
17	6.57

Comp. No.	GTPgS - hR2 PAM pEC_{50}
18	7.20
19	6.71
20	6.91
21	6.25
22	6.05
23	6.58
24	6.91
25	6.83
26	6.41
27	6.46
28	7.06
29	6.88
30	nd
31	nd
32	nd
33	nd

nd = not determined

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

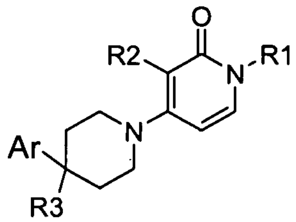
Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

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

R^1 is C_{1-6}alkyl; or C_{1-3}alkyl substituted with C_{3-7}cycloalkyl, phenyl, or phenyl substituted with halo, trifluoromethyl or trifluoromethoxy;

R^2 is halo, trifluoromethyl, C_{1-3}alkyl or cyclopropyl;

R^3 is hydrogen, fluoro, hydroxyl, hydroxyC_{1-3}alkyl, hydroxyC_{1-3}alkyloxy, fluoroC_{1-3}alkyl, fluoroC_{1-3}alkyloxy or cyano; and

Ar is unsubstituted phenyl; or phenyl substituted with n radicals R^4, wherein n is 1, 2 or 3;

R^4 is selected from the group consisting of hydrogen, halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, polyhaloC_{1-3}alkyl, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, polyhaloC_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, mono- and di(C_{1-3}alkyl)amino, and morpholinyl; or

two vicinal R^4 radicals taken together form a bivalent radical of formula

–N=CH-NH- (a),

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

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

R^3 and a R^4 radical in ortho position taken together form a bivalent radical of formula

-CH_2-O- (d), or

-O-CH_2- (e); or

a pharmaceutically acceptable salt or a solvate thereof.

2. The compound according to claim 1 wherein

R^1 is 1-butyl, 2-methyl-1-propyl, 3-methyl-1-butyl, (cyclopropyl)methyl or 2-(cyclopropyl)-1-ethyl;

R^3 is hydrogen, fluoro or cyano; and

Ar is unsubstituted phenyl; or phenyl substituted with halo, trifluoromethyl, morpholinyl or hydroxyC_{1-3}alkyl;

or a pharmaceutically acceptable salt or a solvate thereof

3. The compound according to claim 1 wherein

R^1 is 1-butyl, 3-methyl-1-butyl, (cyclopropyl)methyl or 2-(cyclopropyl)-1-ethyl;

R^2 is chloro;

R^3 is hydrogen or fluoro; and

Ar is unsubstituted phenyl; or phenyl substituted with hydroxyC_{1-3} alkyl;

or a pharmaceutically acceptable salt or a solvate thereof.

4. The compound according to claim 1 wherein said compound is selected from:

- 3'-chloro-1'-cyclopropylmethyl-4-phenyl-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one;

- 1'-butyl-3'-chloro-4-phenyl-3,4,5,6-tetrahydro-*2H,1'H*-[1,4']bipyridinyl-2'-one;

or a pharmaceutically acceptable salt or a solvate thereof.

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

6. A compound according to any one of claims 1 to 4 for use as a medicament.

7. Use of a compound according to any one of claims 1 to 4 or a pharmaceutical composition according to claim 5 for the manufacture of a medicament for treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR2 positive allosteric modulators.

8. Use of a compound according to any one of claims 1 to 4 or a pharmaceutical composition according to claim 5 for the manufacture of a medicament for 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.

9. Use according to claim 8, wherein the central nervous system disorder is an anxiety disorder, selected from the group of agoraphobia, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, posttraumatic stress disorder (PTSD), social phobia and other phobias.

10. Use according to claim 8, wherein 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.

11. Use according to claim 8, wherein the central nervous system disorder is a personality disorder selected from the group of obsessive-compulsive personality disorder and schizoid, schizotypal disorder.

12. Use according to claim 8, wherein the central nervous system disorder is a 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.

13. Use according to claim 8, wherein the central nervous system disorder is an eating disorder selected from the group of anorexia nervosa and bulimia nervosa.

14. Use according to claim 8, wherein 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 and substance-induced mood disorder.

15. Use according to claim 8, wherein the central nervous system disorder is migraine.

16. Use according to claim 8, wherein 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.

17. Use according to claim 8, wherein the childhood disorder is attention-deficit/hyperactivity disorder.

18. Use according to claim 8, wherein 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, substance-induced persisting dementia and mild cognitive impairment.

19. Use according to claim 8, wherein the central nervous system disorder is selected from the group of anxiety, schizophrenia, migraine, depression, and epilepsy.

20. Use of a compound according to any one of claims 1 to 4 in combination with an orthosteric agonist of mGluR2 for the manufacture of a medicament for treating or preventing a condition as cited in any one of claims 7 to 19.

21. A compound according to any one of claims 1 to 4 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.

22. A method of treating or preventing a central nervous system disorder selected from the group of anxiety disorders, psychotic disorders, personality disorders, substance-related disorders, eating disorders, mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, neurotoxicity and ischemia comprising administering to a subject a compound according to any one of claims 1 to 4.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/007551

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D493/10 A61K31/4545 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PINKERTON A B ET AL: "Phenyl-tetrazolyl Acetophenones: Discovery of Positive Allosteric Potentiators for the Metabotropic Glutamate 2 Receptor" J. MED. CHEM, vol. 47, 2004, pages 4595-4599, XP002503457 compound 3	1-22
A	WO 01/56990 A (LILLY CO ELI [US]; COLEMAN DARRELL STEPHEN [US]; JAGDMANN GUNNAR ERIK) 9 August 2001 (2001-08-09) cited in the application page 3, line 30 - page 5, line 14 page 8, line 17 - page 8, line 24	1-22

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 November 2008	21/11/2008

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/007551

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2008/107479 A (JANSSEN PHARMACEUTICA NV [BE]; ADDEX PHARMA S A [CH]; CID-NUNEZ JOSE M) 12 September 2008 (2008-09-12) page 3, line 22 - page 4, line 7 -----	1-22
P,A	WO 2007/104783 A (JANSSEN PHARMACEUTICA NV [BE]; ADDEX PHARMACEUTICALS S A [CH]; CID-NUN) 20 September 2007 (2007-09-20) page 4, line 14 - page 7, line 14 -----	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/007551

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			EP	1255735 A2	13-11-2002
WO 2008107479	A	12-09-2008	NONE		
WO 2007104783	A	20-09-2007	AR	059898 A1	07-05-2008
			AU	2007224431 A1	20-09-2007