Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2744138 C 2015/08/11

(11)(21) **2 744 138**

(12) **BREVET CANADIEN**
CANADIAN PATENT

(13) **C**

(86) Date de dépôt PCT/PCT Filing Date: 2009/11/24
(87) Date publication PCT/PCT Publication Date: 2010/06/03
(45) Date de délivrance/Issue Date: 2015/08/11
(85) Entrée phase nationale/National Entry: 2011/05/18
(86) N° demande PCT/PCT Application No.: EP 2009/008346
(87) N° publication PCT/PCT Publication No.: 2010/060589
(30) Priorité/Priority: 2008/11/28 (EP08170236.7)

(51) Cl.Int./Int.Cl. *C07D 471/04* (2006.01), *A61K 31/437* (2006.01), *A61K 31/538* (2006.01), *A61P 25/00* (2006.01)

(72) Inventeurs/Inventors:
CID-NUNEZ, JOSE MARIA, ES;
TRABANCO-SUAREZ, ANDRES AVELINO, ES;
MACDONALD, GREGOR JAMES, BE

(73) Propriétaires/Owners:
ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC., US;
ADDEX PHARMA S.A., CH

(74) Agent: SMART & BIGGAR

(54) Titre : DERIVES D'INDOLE ET DE BENZOXAZINE COMME MODULATEURS DES RECEPTEURS METABOTROPIQUES AU GLUTAMATE

(54) Title: INDOLE AND BENZOXAZINE DERIVATIVES AS MODULATORS OF METABOTROPIC GLUTAMATE RECEPTORS

(57) Abrégé/Abstract:
The present invention relates to novel indole and benzoxazine 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.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 June 2010 (03.06.2010)

PCT

(10) International Publication Number
WO 2010/060589 A1

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61P 25/00* (2006.01)
A61K 31/437 (2006.01)

(21) International Application Number:
PCT/EP2009/008346

(22) International Filing Date:
24 November 2009 (24.11.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
08170236.7 28 November 2008 (28.11.2008) EP

(71) Applicants *(for all designated States except US)*: **ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC.** [US/US]; 1125 Trenton-Harbourton Road, Titusville, NJ 08560 (US). **ADDEX PHARMA S.A.** [CH/CH]; 12 Chemin des Aulx, CH-1228 Plan-lès-Outes (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CID-NUNEZ, José, Maria** [ES/ES]; Janssen-Cilag, S.A., CaIle Jarama 75, Poligono Industrial, E-45007 Toledo (ES). **TRABANCO-SUAREZ, Andrès, Avelino** [ES/ES]; Janssen-Cilag, S.A., CaIle Jarama 75, Poligono Industrial, E-45007 Toledo (ES). **MACDONALD, Gregor, James** [GB/BE]; Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse (BE).

(74) Agent: **CAMPBELL, Neil**; Dehns, St. Bride's House, 10 Salisbury Square, London EC4Y 8JD (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2010/060589 A1

(54) **Title**: INDOLE AND BENZOXAZINE DERIVATIVES AS MODULATORS OF METABOTROPIC GLUTAMATE RECEPTORS

(57) **Abstract**: The present invention relates to novel indole and benzoxazine 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.

INDOLE AND BENZOXAZINE DERIVATIVES AS MODULATORS OF METABOTROPIC GLUTAMATE RECEPTORS

Field of the Invention

The present invention relates to novel indole and benzoxazine 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 and WO2007/104783 (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

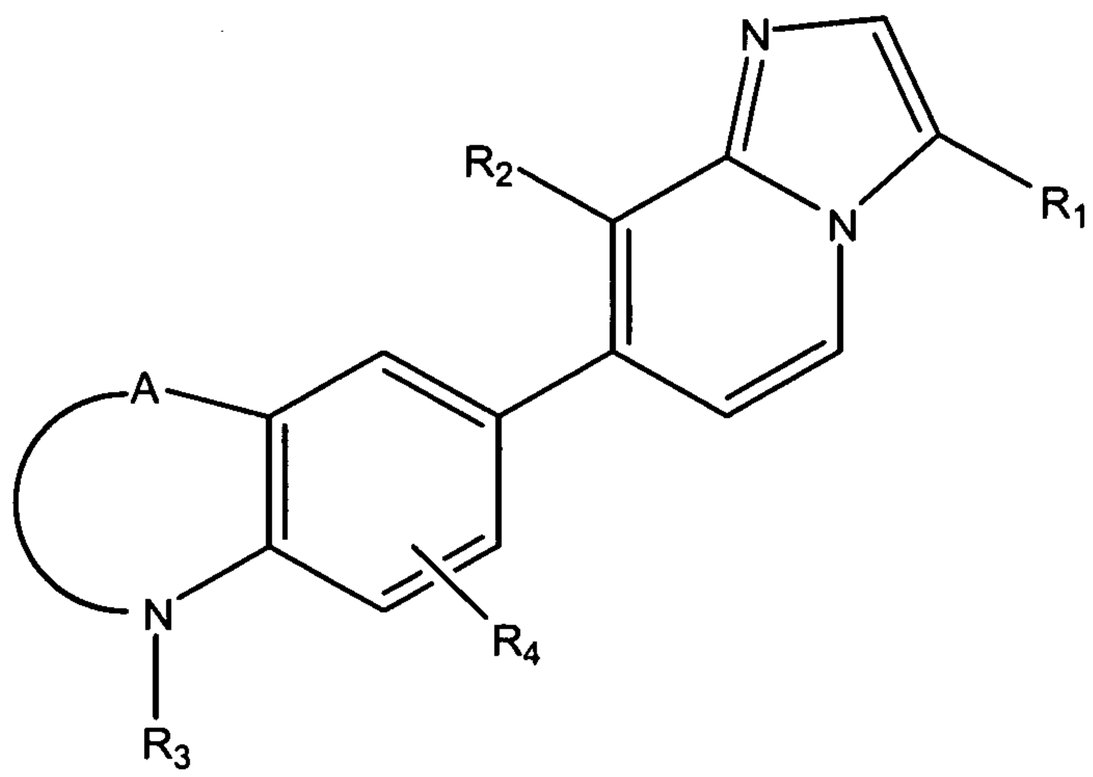
compounds were shown to be active in reversal of ketamine- or amphetamine-induced hyperlocomotion, and in reversal of amphetamine-induced disruption of prepulse inhibition of the acoustic startle effect models of schizophrenia (J. Pharmacol. Exp. Ther. **2006**, *318*, 173-185; Psychopharmacology **2005**, *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)

or a stereochemically isomeric form thereof, wherein

R^1 is C_{1-6}alkyl; C_{3-7}cycloalkyl; trifluoromethyl; C_{1-3}alkyl substituted with trifluoromethyl, 2,2,2-trifluoroethoxy, C_{3-7}cycloalkyl, phenyl, or phenyl substituted with halo, trifluoromethyl, or trifluoromethoxy; phenyl; phenyl substituted with 1 or 2

substituents selected from the group consisting of halo, trifluoromethyl, and trifluoromethoxy; or 4-tetrahydropyranyl;

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

R^3 is hydrogen; C_{1-3}alkyl; C_{1-3}alkyl substituted with C_{3-7}cycloalkyl, phenyl, phenyl substituted with 1 or 2 substituents selected from the group consisting of halo, cyano, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl; pyridinyl or pyridinyl substituted with 1 or 2 C_{1-3}alkyl groups; hydroxyC_{2-4}alkyl; C_{1-3}alkyloxyC_{2-4}alkyl; 4-tetrahydropyranyl; 1-oxa-spiro[3,5]non-7-yl; 2-oxa-spiro[3,5]non-7-yl; 1-oxa-spiro[4,5]dec-8-yl; 2-oxa-spiro[4,5]dec-8-yl; 4-(hydroxy)-cyclohexanyl; 4-(hydroxy)-4-(C_{1-3}alkyl)cyclohexanyl; 4-(hydroxy)-4-(C_{3-7}cycloalkyl)-cyclohexanyl; 4-(C_{1-3}alkyloxy)cyclohexanyl; phenyl; pyridinyl; pyridinylmethyl; or phenyl, pyridinyl or pyridinylmethyl substituted with one or two substituents selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl;

R^4 is hydrogen or halo;

A is a radical of formula

-CH=CH- (a), or

-CH_2-CH_2-O- (b);

wherein one or two hydrogen atoms may be replaced by C_{1-3}alkyl or polyhaloC_{1-3}alkyl;

or a pharmaceutically acceptable salt or a solvate thereof.

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

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

R^2 is cyano or halo;

R^3 is hydrogen; C_{1-3}alkyl; C_{1-3}alkyl substituted with C_{3-7}cycloalkyl; hydroxyC_{2-4}alkyl; C_{1-3}alkyloxyC_{2-4}alkyl; 4-tetrahydropyranyl; 4-(hydroxy)-cyclohexanyl; or 4-(hydroxy)-4-(C_{1-3}alkyl)cyclohexanyl;

R^4 is hydrogen, chloro or fluoro;

A is a radical of formula

-CH=CH- (a), or

-CH_2-CH_2-O- (b);

or a pharmaceutically acceptable salt or a solvate thereof.

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

R^1 is C_{1-3}alkyl substituted with trifluoromethyl;
R^2 is cyano or chloro;
R^3 is hydrogen; methyl; methylyl substituted with cyclopropyl; 2-hydroxy-2,2-dimethylethyl; 1-methylethyloxyethyl; 4-tetrahydropyranyl; 4-(hydroxy)-cyclohexanyl; or 4-(hydroxy)-4-(methyl)cyclohexanyl;
R^4 is hydrogen or chloro;
A is a radical of formula

-CH=CH- (a), or
-CH_2-CH_2-O- (b);

or a pharmaceutically acceptable salt or a solvate thereof.

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

R^1 is 2,2,2-trifluoroethyl;
R^2 is cyano or chloro;
A is a radical of formula -CH=CH- (a);
or a pharmaceutically acceptable salt or a solvate thereof.

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

R^1 is 2,2,2-trifluoroethyl;
R^2 is cyano or chloro;
A is a radical of formula -CH_2-CH_2-O- (b);
or a pharmaceutically acceptable salt or a solvate thereof.

Exemplary compounds according to the present invention are:
8-chloro-7-(7-chloro-*1H*-indol-5-yl)-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridine;
trans-4-[5-[8-chloro-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridin-7-yl]-*1H*-indol-1-yl]cyclohexanol;

trans-7-[1-(4-hydroxy-4-methylcyclohexyl)-*1H*-indol-5-yl]-3-(2,2,2-trifluoroethyl)-imidazo[1,2-a]pyridine-8-carbonitrile;
4-[7-[8-chloro-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridin-7-yl]-2,3-dihydro-*4H*-1,4-benzoxazin-4-yl]cyclohexanol;
trans-4-[5-[8-chloro-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridin-7-yl]-*1H*-indol-1-yl]-1-methylcyclohexanol.

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.

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 cycloC_{3-7}alkyl as a group or part of a group defines a saturated, cyclic hydrocarbon radical having from 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Halo may be fluoro, chloro, bromo or iodo, preferably fluoro or chloro.

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, hydrabamine 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

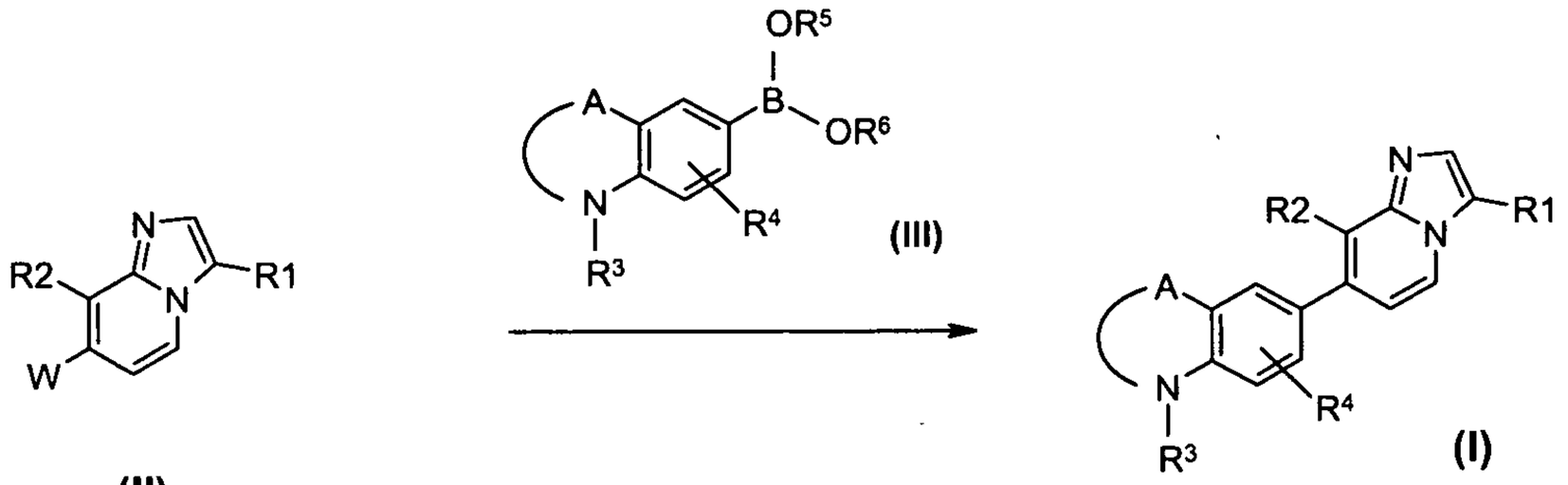
The compounds according to the invention can generally be prepared by a succession of steps, each of which is known to the skilled person. In particular, the compounds can be prepared according to the following synthesis methods.

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 final compounds according to Formula (I), can be prepared by reacting an intermediate compound of Formula (II) with a compound of Formula (III) according to reaction scheme (1), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, 1,4-dioxane or mixtures of reaction-inert solvents such as, for example, 1,4-dioxane/DMF, in the presence of a suitable base, such as, for example, aqueous $NaHCO_3$ or Na_2CO_3, a Pd-complex catalyst such as, for example, $Pd(PPh_3)_4$ under thermal conditions such as, for example, heating the reaction mixture at 150 °C under microwave irradiation, for example for 10 minutes. In reaction scheme (1), all variables are defined as in Formula (I) and W is a group suitable for Pd mediated coupling with boronic acids or boronic esters, such as, for example, halo or triflate. R^5 and R^6 may be hydrogen or alkyl, or may be taken together to form for example a bivalent radical of formula $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-C(CH_3)_2C(CH_3)_2-$.

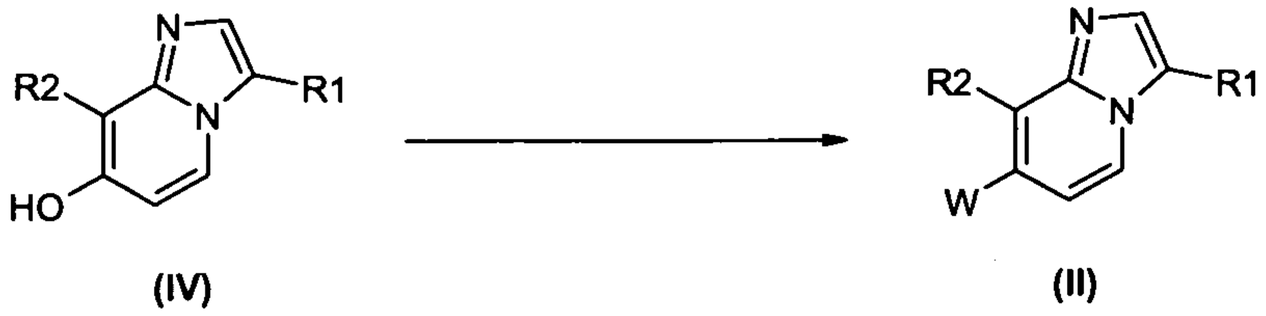


Reaction Scheme 1

B. Preparation of the intermediates

Experimental procedure 2

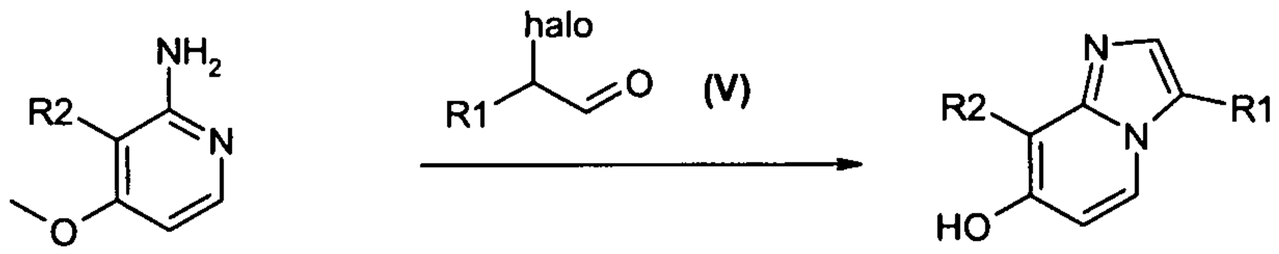
Intermediate compounds of Formula (II), where W is halo, can be prepared by reacting an intermediate compound of Formula (IV) with a suitable halogenating agent such as, for example, phosphorus (V) oxychloride, a reaction that is performed in a suitable reaction-inert solvent such as, for example, DMF, at a moderately elevated temperature such as, for example, 110 °C, for a suitable period of time that allows the completion of the reaction, as for example 1 h. In reaction scheme (2), all variables are defined as in Formula (I) and W is halo.



Reaction Scheme 2

Experimental procedure 3

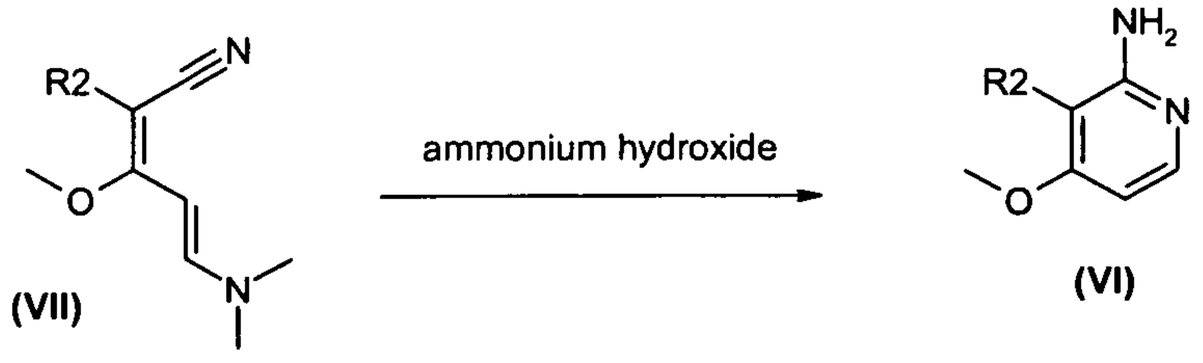
Intermediate compounds of Formula (IV) can be prepared by reacting an intermediate of Formula (V) with an intermediate compound of Formula (VI) according to reaction scheme (3). This reaction is performed in a suitable reaction-inert solvent such as, for example, ethanol under thermal conditions such as, for example, heating the reaction mixture for example at 160 °C under microwave irradiation for 45 minutes. In reaction scheme (3), R^1 and R^2 are defined as in Formula (I) and halo is for example chloro or bromo.



Reaction Scheme 3

Experimental procedure 4

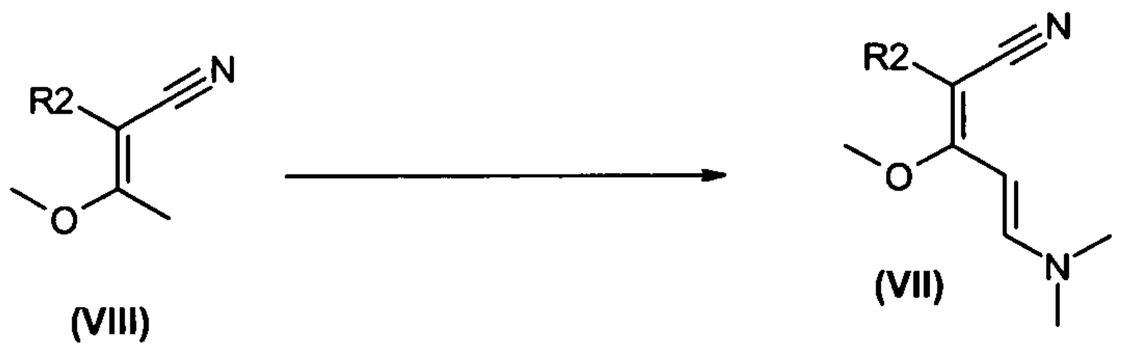
Intermediate compounds of Formula (VI) can be prepared by reacting an intermediate compound of Formula (VII) with an ammonia source such as for example ammonium hydroxide under thermal conditions such as, for example, heating the reaction mixture for example at reflux for 3 h. In reaction scheme (4), R^2 is defined as in Formula (I).



Reaction Scheme 4

Experimental procedure 5

Intermediate compounds of Formula (VII) can be prepared by reacting an intermediate of Formula (VIII) with *N*,*N*-dimethylformamide dimethyl acetal according to reaction scheme (5). This reaction is performed in a suitable reaction-inert solvent such as, for example, methanol under thermal conditions such as, for example, heating the reaction mixture for example at reflux for 2 h. In reaction scheme (5), R^2 is defined as in Formula (I).

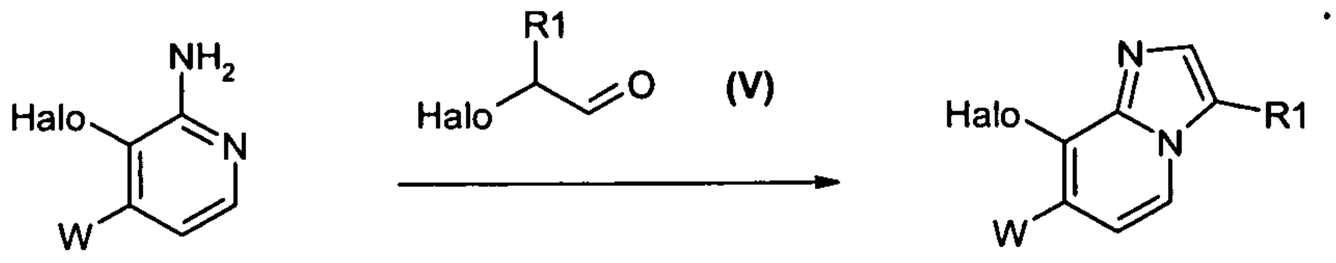


Reaction Scheme 5

Intermediate compounds of Formula (VIII) are either commercially available (R^2 = CN; C.A.S. 5515-16-2) or can be prepared following reaction procedures known by the person skilled in the art. Intermediate compounds of Formula (VIII) where R^2 is halo, for example, can be prepared according to the procedure described in Chemische Berichte (1976), 109(8), 2908-13.

Experimental procedure 6

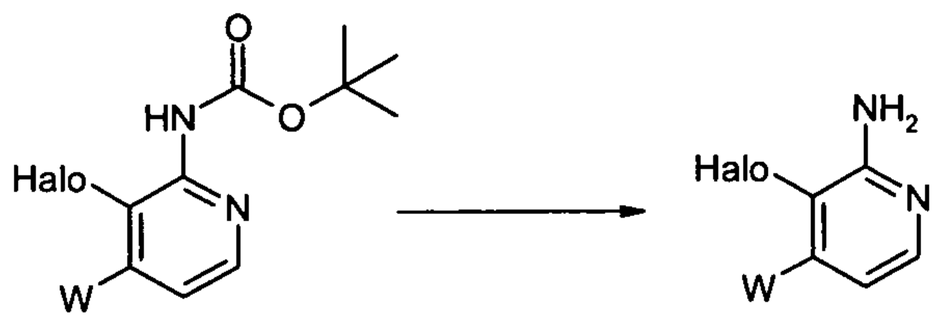
Intermediate compounds of Formula (II) wherein R^2 is halo, hereby named (II-a) can be prepared by reacting an intermediate of Formula (IX) with an intermediate compound of Formula (V) according to reaction scheme (6). This reaction is performed in a suitable reaction-inert solvent such as, for example, ethanol under thermal conditions such as, for example, heating the reaction mixture for example at 150 °C under microwave irradiation for 50 minutes. In reaction scheme (6), R^1 is defined as in Formula (I), halo may be chloro, bromo or iodo and W is defined as in Formula (II).



Reaction Scheme 6

Experimental procedure 7

Intermediate compounds of Formula (IX) can be prepared by treating an intermediate of Formula (X) with an acid such as for example trifluoroacetic acid according to reaction scheme (7). This reaction is performed in a suitable reaction-inert solvent such as, for example, DCM at room temperature for a period of time that allows the completion of the reaction as for example 2 h. In reaction scheme (7), halo may be chloro, bromo or iodo and W is defined as in Formula (II).

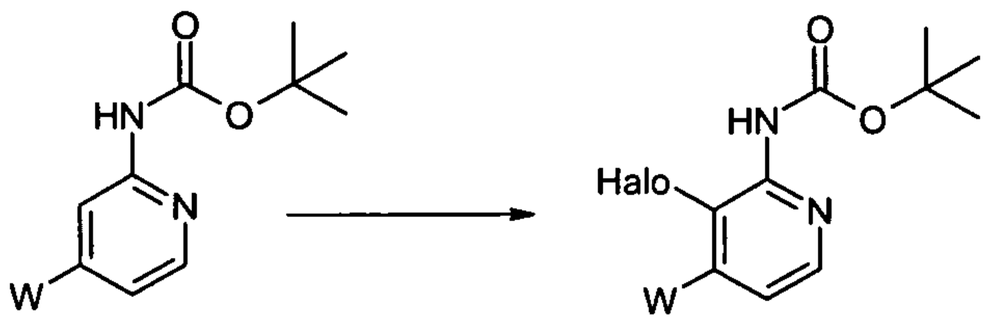


(X) (IX)

Reaction Scheme 7

Experimental procedure 8

Intermediate compounds of Formula (X) can be prepared according to reaction scheme (8) by reacting an intermediate compound of Formula (XI) with a strong base such as, for example, n-butyllithium, and further treatment with a halogenating agent such as, for example, N-chlorosuccinimide. This reaction is performed in a suitable reaction-inert solvent such as, for example, THF at low temperature such as for example –78 °C for a period of time that allows the completion of the reaction as for example 2 h. In reaction scheme (8), halo may be chloro, bromo or iodo and W is defined as in Formula (II).



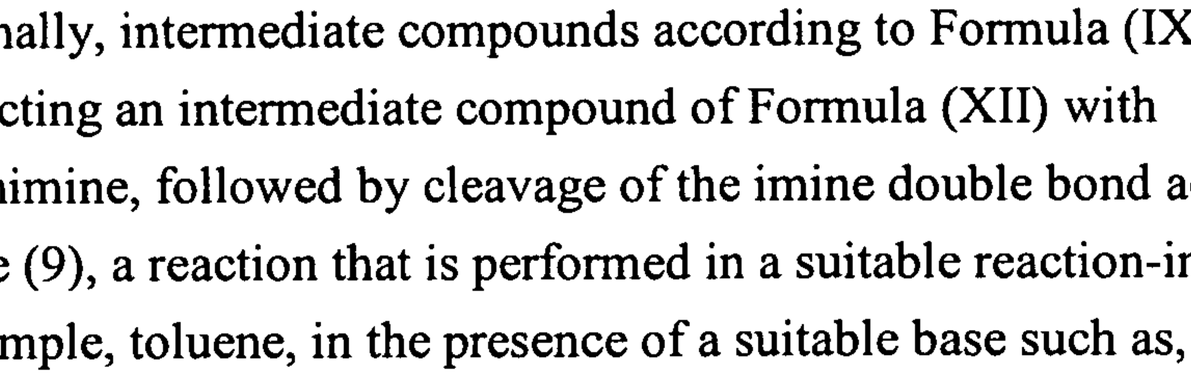
(XI) (X)

Reaction scheme (8)

Experimental procedure 9

Intermediate compounds of Formula (IX) wherein W is iodine, hereby named (IX-a), can be prepared by reacting an intermediate of Formula (XII) with ammonium hydroxide according to reaction scheme (9). This reaction is performed under thermal conditions such as, for example, heating the reaction mixture for example at 130 °C for 12 h.

Additionally, intermediate compounds according to Formula (IX-a) can be prepared by reacting an intermediate compound of Formula (XII) with diphenylmethanimine, followed by cleavage of the imine double bond according to reaction scheme (9), a reaction that is performed in a suitable reaction-inert solvent such as, for example, toluene, in the presence of a suitable base such as, for example, sodium *tert*-butoxide, a metal-based catalyst, specifically a palladium catalyst, such as palladium(II) acetate, and a suitable ligand, such as for example 1,1'-[1,1'-binaphthalene]-2,2'-diylbis[1,1-diphenyl-phosphine] (BINAP), heating for a suitable period of time that allows the completion of the reaction, for example at 100 °C for 16 h in a sealed tube, followed by the cleavage of the intermediate imine double bond with a suitable acid such as for example aqueous hydrochloric acid. In reaction scheme (9), halo may be chloro, bromo or iodo.



(XII) (IX-a)

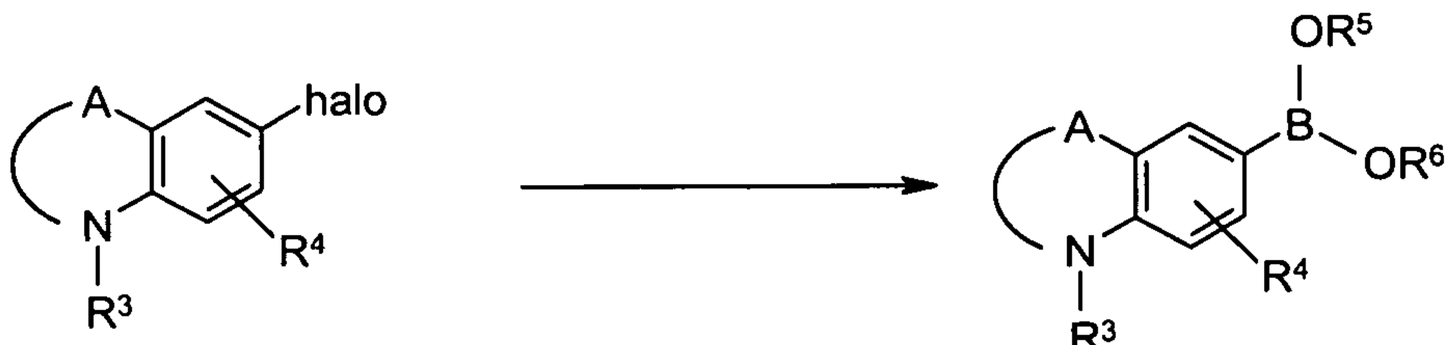
Reaction Scheme 9

Experimental procedure 10

Intermediates of Formula (III) can be prepared by art known procedures by reacting an intermediate of Formula (XIII) with a suitable boron source such as, for example, bis(pinacolato)diboron in the presence of a palladium catalyst such as, for example, 1,1´-bis(diphenylphosphino)ferrocenepalladium(II)dichloride in a reaction-inert solvent such as, for example, DCM, as shown in reaction scheme (10). The reaction may be carried out in the presence of a suitable salt such as, for example, potassium acetate at a moderately high temperature such as, for example, 110 °C during, for example, 16 h.

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

In reaction scheme (10), all variables are defined as in Formula (I), R^5 and R^6 may be hydrogen or alkyl, or may be taken together to form for example a bivalent radical of formula $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-C(CH_3)_2C(CH_3)_2-$, halo is a suitable halogen such as, for example, bromo and all other variables are defined as in Formula (I).

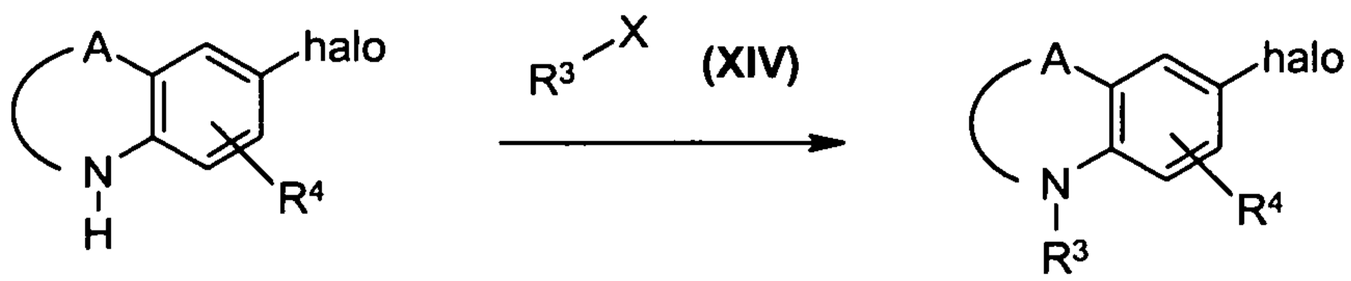


(XIII) (III)

Reaction Scheme 10

Experimental procedure 11

Intermediates of Formula (XIII) wherein R^3 is as defined in Formula (I) but other than hydrogen, hereby named (XIII-a), can be prepared following art known procedures by reacting an intermediate of Formula (XIII) wherein R^3 is hydrogen, hereby named (XIII-b) with an intermediate compound of Formula (XIV) under alkylation conditions, for example, in the presence of a base such as, for example, K_2CO_3 or NaH in a suitable reaction-inert solvent such as, for example, DMF. The reaction may be carried out under microwave irradiation at a suitable temperature, typically 150 °C, for a suitable period of time that allows the completion of the reaction. In reaction scheme (11), all variables are defined as in Formula (I), X is a suitable leaving group for alkylation reactions such as for example halo, tosyl, mesyl and halo may be chloro, bromo or iodo.

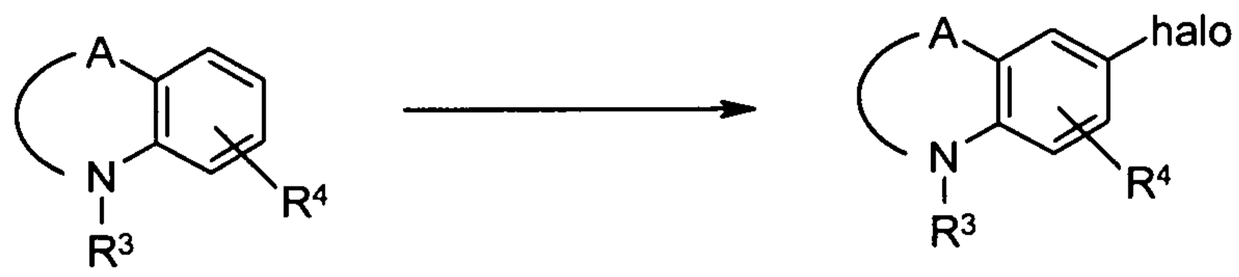


(XIII-b) (XIII-a)

Reaction Scheme 11

Experimental procedure 12

Intermediates of Formula (XIII) where halo is bromo or iodo can be prepared following art known procedures by reacting an intermediate of Formula (XV) with a suitable halogenating agent. This reaction is shown in reaction scheme (12). The reaction can be carried out with halogenating agents such as *N*-bromosuccinimide, *N*-iodosuccinimide at temperatures ranging from room temperature to reflux temperature, in a reaction-inert solvent such as DMF, DCM, $CHCl_3$ or acetic acid. Typically, the reaction mixture can be stirred for 15 minutes to 48 h at a temperature between 0-100 °C. In reaction scheme (12), all variables are defined as in Formula (I) and halo may be chloro, bromo or iodo.



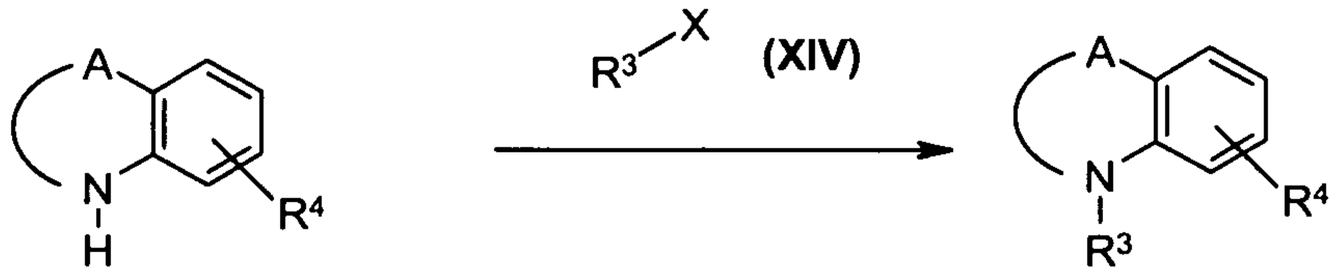
(XV) (XIII)

Reaction Scheme 12

Experimental procedure 13

Intermediates of Formula (XV) wherein R^3 is as defined in Formula (I) but other than hydrogen, hereby named (XV-a), can be prepared by art known procedures by reacting an intermediate of Formula (XV) wherein R^3 is hydrogen, hereby named (XV-b) with an intermediate compound of Formula (XIV) under alkylation conditions as is illustrated in reaction scheme (13). In reaction scheme (13), all variables are defined as

in Formula (I), X is a suitable leaving group for alkylation such as for example halo, tosyl, mesyl and halo may be chloro, bromo or iodo.

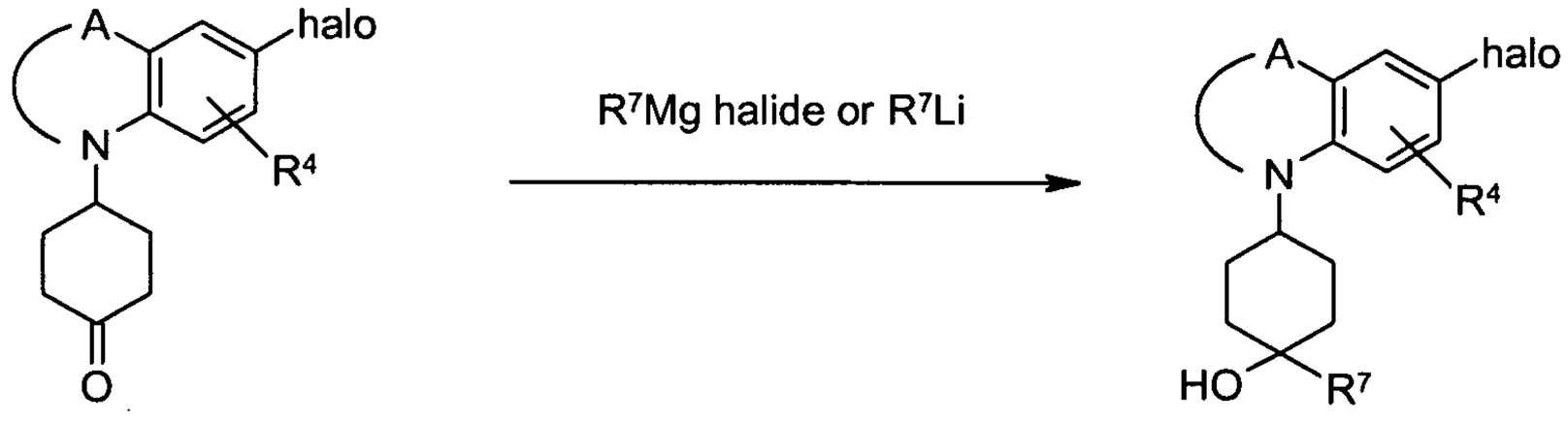


(XV-b) (XV-a)

Reaction Scheme 13

Experimental procedure 14

Intermediates of Formula (XIII) wherein R^3 is 4-hydroxy-4-methylcyclohexan-1-yl, hereby named (XIII-c), can be prepared by art known procedures by reacting intermediate of Formula (XVI) with a suitable organometallic alkyl source such as, for example, R^7-M, wherein M is magnesium halide or lithium. This reaction is shown in reaction scheme (14). The reaction can be carried out in an inert solvent such as, for example, THF, diethyl ether or 1,4-dioxane. Typically, the mixture can be stirred from 1 to 48 h at a temperature between 0-100 °C. In reaction scheme (14), all variables are defined as in Formula (I), halo may be chloro or bromo and R^7 is C_{1-3}alkyl or C_{3-7}cycloalkyl.

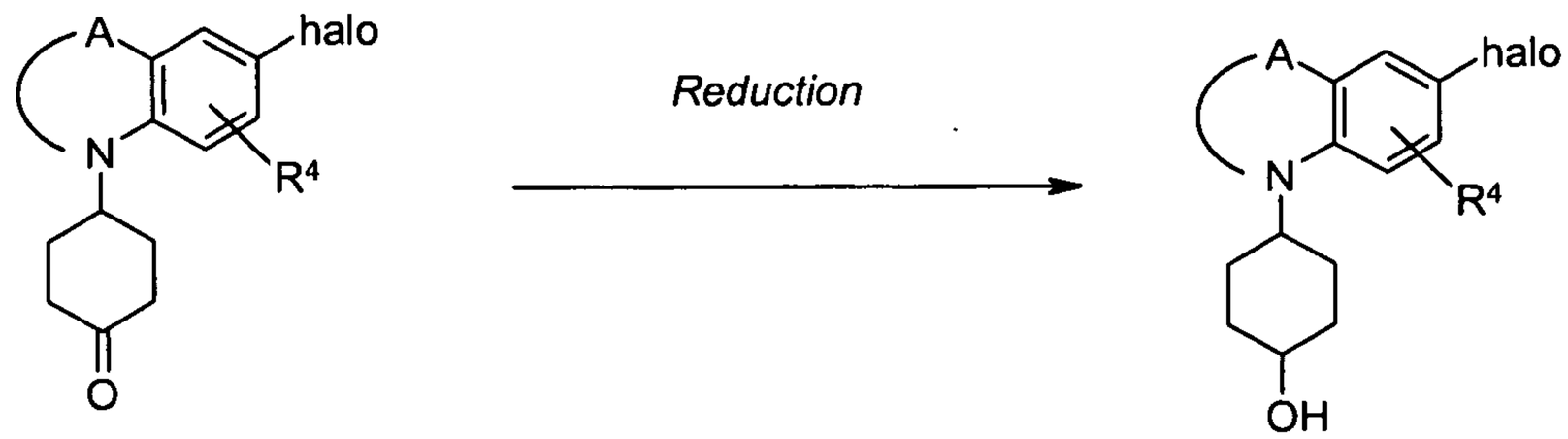


(XVI) (XIII-c)

Reaction Scheme 14

Experimental procedure 15

Intermediates of Formula (XIII) wherein R^3 is 4-hydroxy-cyclohexan-1-yl, hereby named (XIII-d), can be prepared by reacting an intermediate of Formula (XVI) under reductive conditions that are known by those skilled in the art. The reaction is illustrated in reaction scheme (15). The reaction can be carried out in the presence of a reducting agent as for example, sodium borohydride in a suitable solvent such as, for example, methanol. The reaction may be performed at a suitable temperature, typically room temperature, for a suitable period of time that allows the completion of the reaction. In reaction scheme (15), all variables are defined as in Formula (I) and halo may be chloro, bromo or iodo.

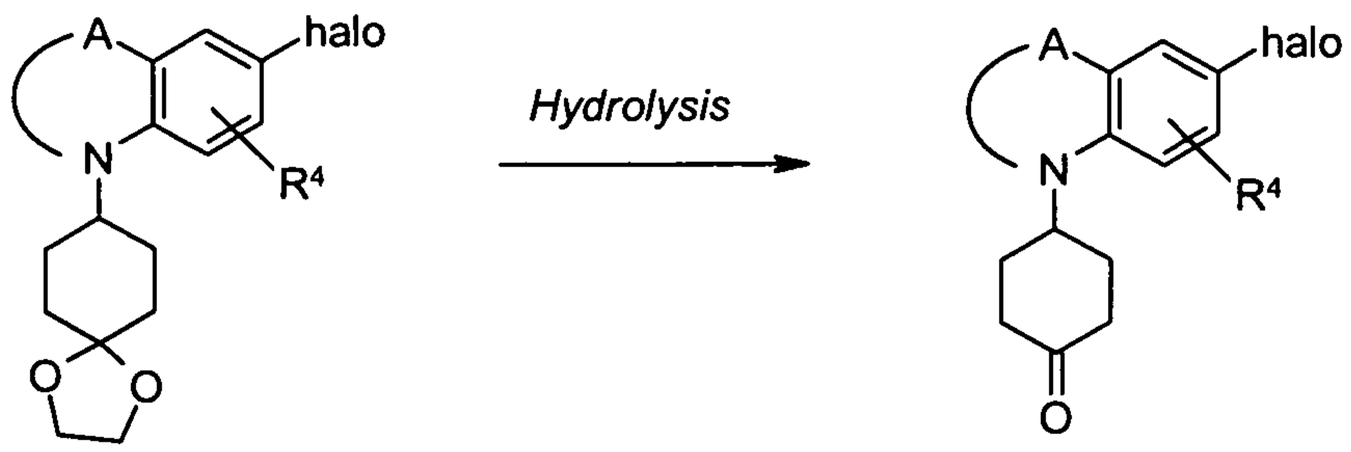


(XVI) (XIII-d)

Reaction Scheme 15

Experimental procedure 16

Intermediates of Formula (XVI) can be prepared by subjecting an acetal intermediate of Formula (XVII) to suitable deprotection conditions for the carbonyl function that are known by those skilled in the art. This reaction is illustrated in reaction scheme (16). The reaction can be performed in the presence of an acid such as, for example, *p*-toluenesulfonic acid, in a suitable reaction solvent such as, for example, acetone. The reaction may conveniently be carried out under microwave irradiation at a suitable temperature, typically at 100 °C, for a suitable period of time that allows the completion of the reaction. In reaction scheme (16), all variables are defined as in Formula (I) and halo may be chloro, bromo or iodo.

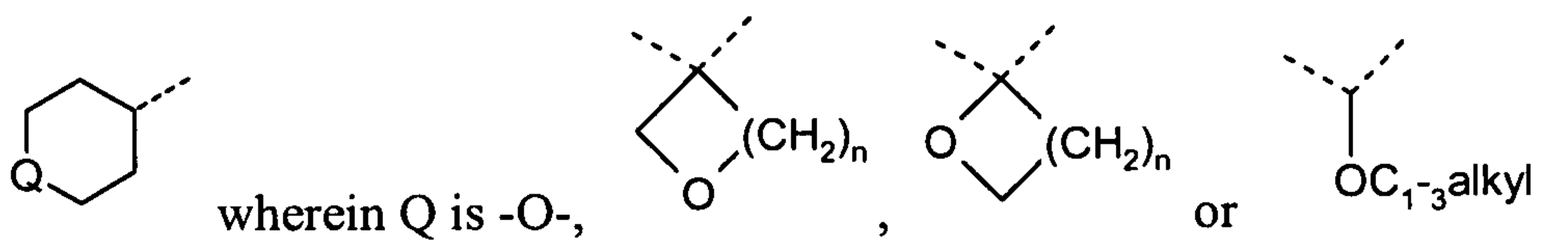


(XVII) (XVI)

Reaction Scheme 16

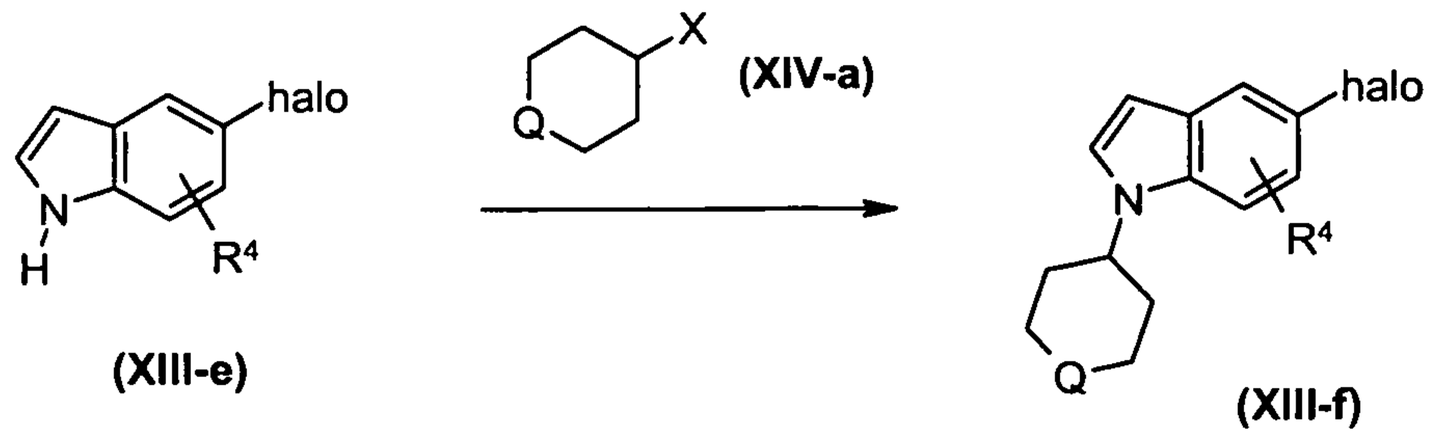
Experimental procedure 17

Intermediates of formula (XVII) and intermediates of Formula (XIII) wherein A is a radical of formula -CH=CH- and R^3 is



wherein Q is -O-, , or

and each n is 1 or 2, hereby named (XIII-f) can be prepared by reacting intermediate of Formula (XIII) wherein A is a radical of formula-CH=CH- and R^3 is H, hereby named (XIII-e) with an intermediate of Formula R^3-X (Formula XIV) wherein R^3 is as defined hereinbefore, hereby named (XIV-a) according to reaction scheme (17). The reaction can be carried out under alkylation conditions that are known by those skilled in the art such as, for example, in the presence of base such as, for example, potassium hydroxide in a suitable reaction solvent such as, for example, dimethylsulphoxide. The reaction may be performed at a suitable temperature, typically at 60 °C, for a suitable period of time that allows the completion of the reaction. In reaction scheme (17), all variables are defined as in Formula (I), X is a suitable leaving group for alkylation such as for example halo, tosyl, mesyl and halo may be chloro, bromo or iodo.

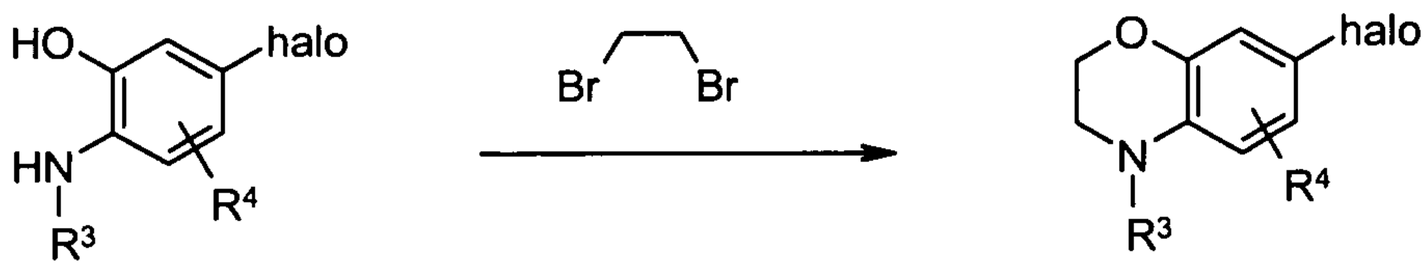


(XIII-e) (XIII-f)

Reaction Scheme 17

Experimental procedure 18

Intermediates of Formula (XIII) wherein A is a radical of formula $-CH_2-CH_2-O-$, hereby named (XIII-g), can be prepared by reacting an ortho-aminophenol derivative of Formula (XVIII) with commercially available 1,2-dibromoethane under alkylation conditions, such as for example, performing the reaction in the presence of a base such as for example K_2CO_3 in a suitable reaction-inert solvent such as, for example, DMF. The reaction may be carried out under microwave irradiation at a suitable temperature, typically 180 °C, for a suitable period of time that allows the completion of the reaction. In reaction scheme (18), all variables are defined as in Formula (I) and halo may be chloro, bromo or iodo.



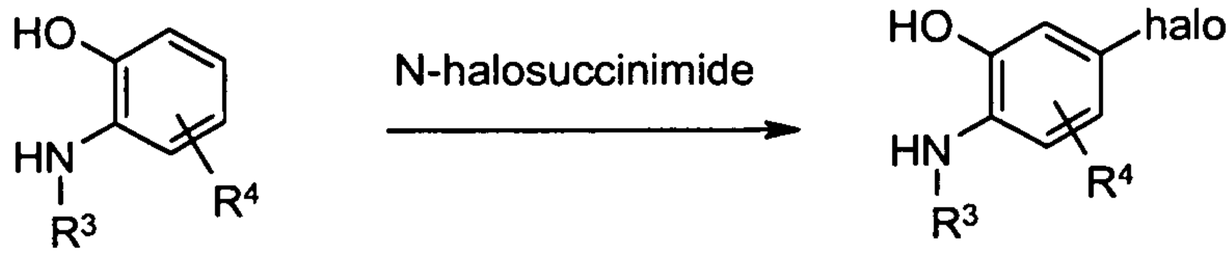
(XVIII) (XIII-g)

Reaction Scheme 19

Experimental procedure 20

Intermediates of Formula (XVIII) can be prepared by reacting an intermediate of Formula (XIX) with an *N*-halosuccinimide such as *N*-chloro- (NCS), *N*-bromo- (NBS) or *N*-iodosuccinimide (NIS) according to reaction scheme (20). This reaction can be performed in a suitable reaction-inert solvent such as, for example, DMF, DCM or acetic acid. The reaction typically can be carried out at room temperature for 1 to 24

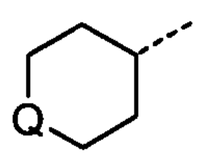
h. In reaction scheme (20), all variables are defined as in Formula (I) and halo may be chloro, bromo or iodo.



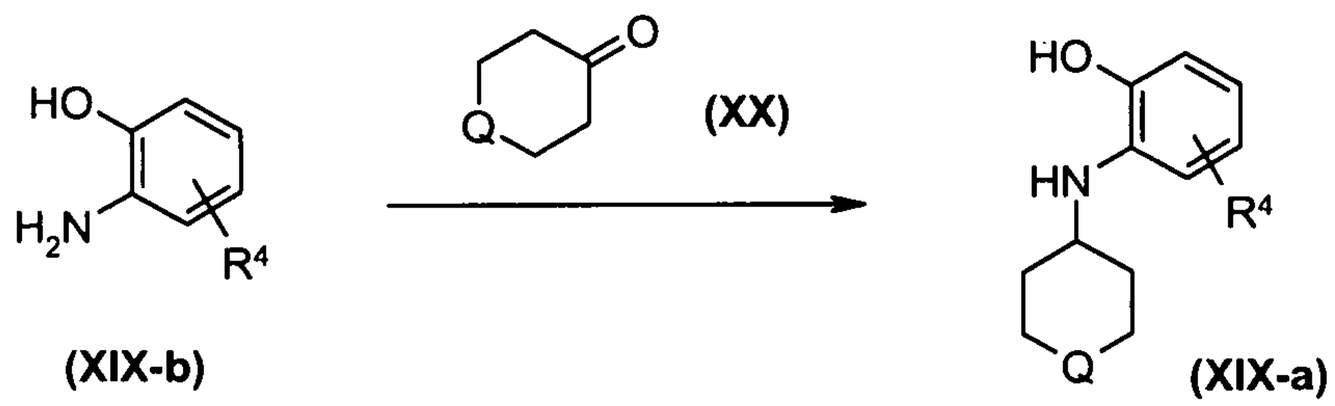
(XIX) (XVIII)

Reaction Scheme 20

Experimental procedure 21

Intermediates of Formula (XIX) wherein R^3 is 

, hereby named (XIX-a) can be prepared by reacting an intermediate of Formula (XIX) wherein R^3 is H, hereby named (XIX-b) with a cyclic ketone derivative of Formula (XX) under reductive amination conditions that are known by those skilled in the art. This is illustrated in reaction scheme (21). The reaction may be performed, for example, in the presence of sodium triacetoxyborohydride in a suitable reaction-inert solvent such as, for example, DCE, at a suitable reaction temperature, typically at room temperature, for a suitable period of time that allows the completion of the reaction. In reaction scheme (21), all variables are defined as in Formula (I), and Q is as defined

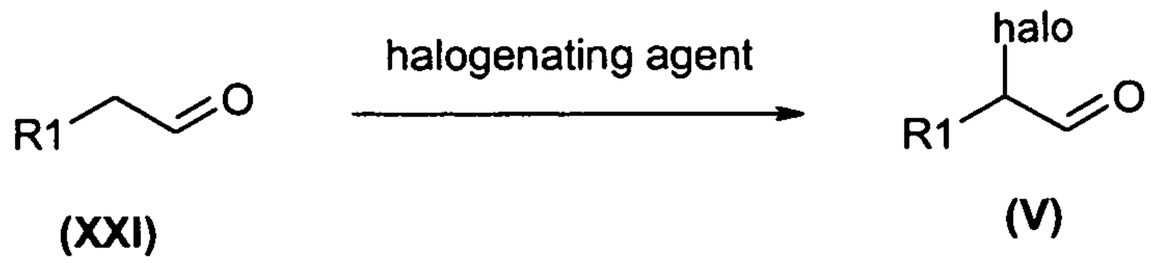


Reaction Scheme 21

Experimental procedure 22

Intermediate compounds of Formula (V) can be prepared by reacting an intermediate compound of Formula (XXI) with an halogenating agent such as, for example, bromine at a moderately low temperature such as, for example, 0 °C in an

inert solvent such as, for example, 1,4-dioxane. In reaction scheme (22), all variables are defined as in Formula (I).

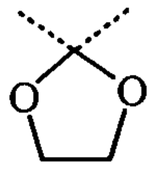


(XXI) (V)

Reaction Scheme 22

Intermediates of Formula, (VIII), (XI), (XII), (XIII-e), (XIV), (XIX-b), (XX) and (XXI) are commercially available or can be prepared by those skilled in the art.

The intermediate of Formula (XIV-a) wherein Q = -O- (CAS [97986-34-0])can be prepared according to synthetic procedures described in WO 2007148648 A1;

intermediates wherein Q is  , (CAS [23511-05-9]) can be prepared according to the synthetic procedure described in *J. Chem. Soc., Perkin Trans. 1*, 2002, 2251–2255.

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 medicament. The present invention also relates to a compound according to the invention or a pharmaceutical composition according to the invention for use in the treatment or prevention, in particular treatment, of a disease or a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of allosteric modulators of mGluR2, in particular positive allosteric modulators thereof. The present invention also relates to the use of a compound according to the 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.

An effective daily amount may range from about 0.01 mg/kg to about 10 mg/kg body weight, preferably from about 0.05 mg/kg to about 1 mg/kg body weight.

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 medicament. 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 present invention also relates to a compound according to the invention in combination with an orthosteric agonist of mGluR2 for use in the treatment or prevention of the above mentioned diseases or conditions. 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.

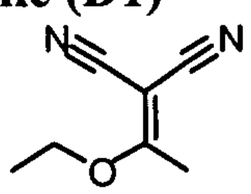
Hereinafter, "THF" means tetrahydrofuran; "DMF" means *N,N*-dimethylformamide; "EtOAc" means ethyl acetate; "DCM" means dichloromethane; "DME" means 1,2-dimethoxyethane; "DCE" means 1,2-dichloroethane; "DIPE" means diisopropylether; "DMSO" means dimethylsulfoxide; "DBU" means 1,8-diaza-7-bicyclo[5.4.0]undecene, "MeOH" means methanol, "h." means hour(s), "s." means second(s), "min." means minute(s), "r.t." means room temperature, "M.P." means melting point, DAPCy means *trans*-$(Cy_2NH)_2Pd(OAc)_2$.

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.).

^{1}H NMR spectra were recorded on a Bruker DPX-400 and on a Bruker AV-500 spectrometer with standard pulse sequences, operating at 400 MHz and 500 MHz respectively, using $CDCL_3$ and C_6D_6 as solvents. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard.

Description 1

2-(1-Ethoxy-ethylidene)-malononitrile (D1)

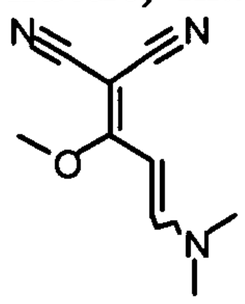


A mixture of malononitrile (17 g, 257.57 mmol) and triethylorthoacetate (45.95 g, 283.25 mmol) was heated at 95 °C for 1.5 h. The mixture was then evaporated *in vacuo* to yield compound **D1** (34 g, 99%) as a yellow solid. This compound was used in the next reaction step without further purification.

Compound **D1** is also commercially available CAS: 5417-82-3.

Description 2

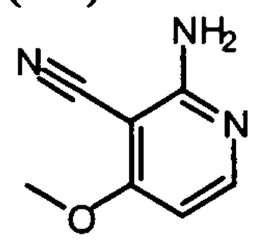
2-(3-Dimethylamino-1-methoxy-allylidene)-malononitrile (D2)



To a mixture of **D1** (34 g, 250 mmol) in MeOH (300 ml) was added *N,N*-dimethylformamide dimethyl acetal (44.68 g, 375 mmol). The reaction mixture was heated at reflux for 2 h. The mixture was then cooled to room temperature and a dark red solid precipitated upon cooling. The solid was filtered off, washed with cold methanol and dried *in vacuo* to yield compound **D2** (16.2 g, 38%) as a red solid.
LCMS: MW (theor): 177; [MH^+]: 178; RT (min): 2.25.
Compound **D2** is also commercially available CAS: 95689-38-6.

Description 3

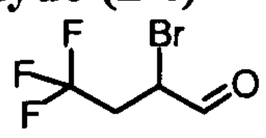
2-Amino-4-methoxy-nicotinonitrile (D3)



A mixture of **D2** (16 g, 90.39 mmol) in NH_4OH (100 ml, 30% in water) was heated at reflux for 3 h. After cooling in an ice bath a yellow solid precipitated. The solid was filtered off, washed with cold isopropanol and dried *in vacuo* to yield compound **D3** (10 g, 76%) as a white solid.
LCMS: MW (theor): 149; [MH^+]: 150; RT (min): 0.41.
Compound **D3** is also commercially available CAS: 98651-70-8.

Description 4

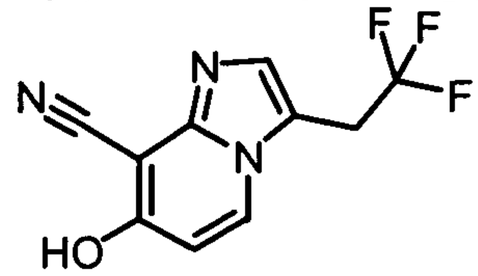
2-Bromo-4,4,4-trifluoro-butyraldehyde (D4)



To a mixture of 4,4,4-trifluorobutyraldehyde (5 g, 39.68 mmol) in 1,4-dioxane (5 ml) cooled to 0 °C, bromine (2.24 ml, 43.65 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h. The resulting reaction mixture was filtered through a pad of diatomaceous earth and the filtrate was washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried ($MgSO_4$) and evaporated *in vacuo* to yield compound **D4** (6.2 g, 76%) that was used in the next reaction step without further purification.
^{1}H-NMR ($CDCl_3$): 9.46 (s, 1H); 4.48 (t, J = 6.5 Hz, 1H); 3.26-3.13 (m, 1H); 2.74-2.60 (m, 1H).

Description 5

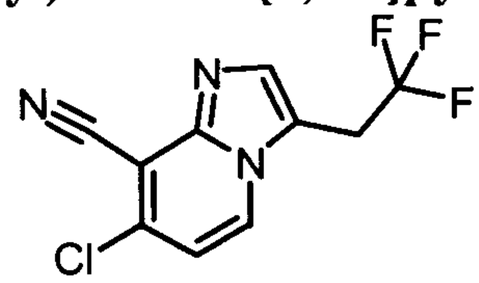
7-Hydroxy-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (D5)



A mixture of compound **D3** (3.31 g, 22.19 mmol) and **D4** (6.2 g, 21.86 mmol) in EtOH (10 ml) was subjected to microwave heating at 150 °C for 40 min. After cooling to room temperature, the solvent was evaporated *in vacuo*. The residue thus obtained was treated with Et_2O and a solid precipitated. The solid was filtered off, washed with EtOAc and dried *in vacuo* to yield compound **D5** (1 g, 18%).
LCMS: MW (theor): 241; $[MH^+]$: 242; RT (min): 1.06.

Description 6

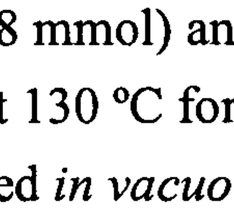
7-Chloro-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (D6)



A mixture of compound **D5** (1 g, 4.148 mmol) and phosphorus (V) oxychloride (2 ml) was subjected to microwave heating at 130 °C for 15 min. After cooling to room temperature, the solvent was evaporated *in vacuo*. The residue was then treated with $NaHCO_3$ (aqueous sat. solution) and extracted with DCM. The organic layer was separated, dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; Et_2O as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **D6** (0.6 g, 56%) as a yellow solid.
LCMS: MW (theor): 259; $[MH^+]$: 260; RT (min): 2.66. (Method 11)

Description 7

2,4-Dibromo-nicotinonitrile (D7)



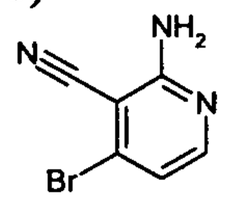
To a solution of commercially available 4-methoxy-2-oxo-1,2-dihydro-3-pyridinecarbonitrile (95.47 g, 333 mmol) [C.A.S. 21642-98-8] in acetonitrile (670 ml), phosphorus (V) oxybromide (250 g, 166 mmol) was added portionwise. The resulting suspension was heated at 60 °C for 16 h. After cooling to room temperature, the

reaction mixture was diluted with EtOAc and washed with water. The organic layer was separated and washed with $NaHCO_3$ (aqueous sat. solution), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was triturated with DIPE to yield compound **D7** (34.5 g, 79%) as white solid.

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

Description 8

2-Amino-4-bromo-nicotinonitrile (D8)

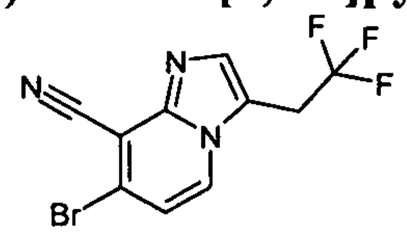


A mixture of compound **D7** (32 g, 122.2 mmol) in NH_4OH (200 ml, 30% in water) and THF (200 ml) was heated at 100 °C for 12 h. in a PARR pressure vessel. After cooling, EtOAc was added. The organic layer was separated, washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The solid residue thus obtained was triturated with DCM and then filtered off. The filtrate was evaporated *in vacuo* to yield compound **D8** (6.5 g, 26.8%) as a white solid.

LCMS: MW (theor): 197; [MH$^+$]: 198; RT (min): 1.14 (Method 2)

Description 9

7-Bromo-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (D9)

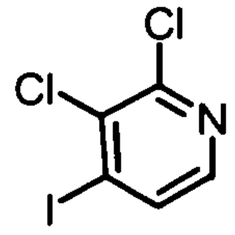


A mixture of compounds **D8** (2 g, 10.1 mmol) and **D4** (2.898 g, 14.14 mmol) in EtOH (10 ml) was subjected to microwave heating at 150 °C for 40 min. After cooling to room temperature, the solvent was evaporated *in vacuo*. The residue thus obtained was diluted with EtOAc and washed with water. The organic layer was separated and washed with water, then with 1M HCl (aqueous solution), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product thus obtained was triturated with diethylether to yield compound **D9** (1.5 g, 48.8%).

LCMS: MW (theor): 303; [MH$^+$]: 304; RT (min): 2.48. Method 14.

Description 10

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

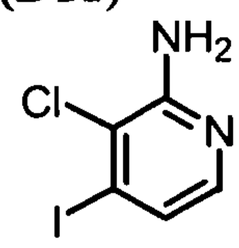


To a solution of *n*-butyllithium (27.6 ml, 69 mmol, 2.5 M in hexanes) in dry Et_2O (150 ml) cooled at –78 °C under a nitrogen atmosphere, 2,2,6,6-tetramethylpiperidine (11.64 ml, 69 mmol) was added dropwise. The resulting reaction mixture was stirred at –78 °C for 10 min. and a solution of 2,3-dichloropyridine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

LCMS: MW (theor): 273; [MH^+]: do not ionise; RT (min): 2.73. (Method 12)

Description 11

3-Chloro-4-iodo-pyridin-2-ylamine (D11)

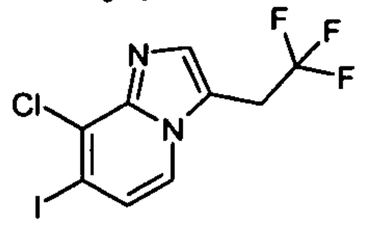


A mixture of compound **D10** (6 g, 21.9 mmol) in aqueous NH_4OH (12 ml, 11 N) was heated at 129 °C for 12 h. After cooling to room temperature, DCM was added. The organic layer was separated, washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue thus obtained was purified by column chromatography (silica gel; DCM/MeOH(NH_3) up to 2% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **D11** (2.88 g, 52%) as a white solid.

LCMS: MW (theor): 254; [MH^+]: 255; RT (min): 2.22. (Method 13)

Description 12

8-Chloro-7-iodo-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine (D12)

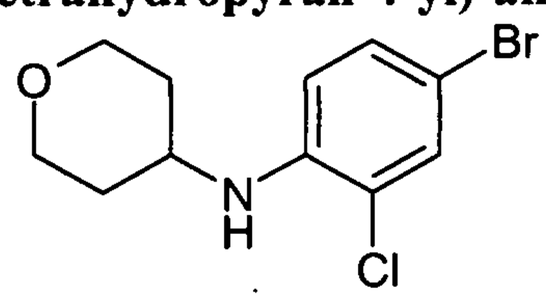


To a mixture of compound **D11** (0.507 g, 1.992 mmol) in EtOH (7 ml) was added compound **D4** (0.817 g, 3.985 mmol). The reaction mixture was subjected to microwave heating at 150 °C for 30 min. The mixture was cooled to room temperature and the volatiles were evaporated *in vacuo*. The residue was taken up in DCM and washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; DCM/EtOAc up to 6% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **D12** (0.5 g, 69.6%) as yellow solid.

LCMS: MW (theor): 360; [MH^+]: 361; RT (min): 2.31 (Method 8)

Description 13

(4-Bromo-2-chlorophenyl)-(tetrahydropyran-4-yl)-amine (D13)

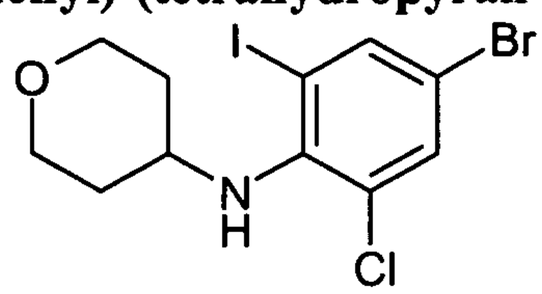


A mixture of 4-bromo-2-chloro-phenylamine (0.5 g, 2.422 mmol), tetrahydropyran-4-one (1.308 ml, 10.898 mmol), and sodium triacetoxyborohydride (2.31 g, 10.898 mmol) in DCE (20 ml) was stirred at room temperature for 16 h. The reaction mixture was washed with $NaHCO_3$ (aqueous sat. solution), dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; heptane/DCM up to 40% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **D13** (0.383 g, 52%) as white solid.

LCMS: MW (theor): 289; [MH^+]: 290; RT (min): 4.39 (Method 1).

Description 14

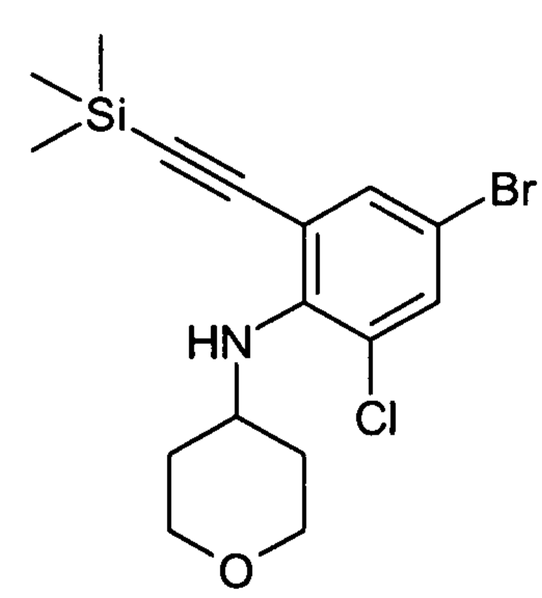
(4-Bromo-2-chloro-6-iodo-phenyl)-(tetrahydropyran-4-yl)-amine (D14)



To a solution of **D13** (0.380 g, 1.308 mmol) in $CHCl_3$ (20 ml) and acetic acid (10 ml) was added N-iodosuccinimide (0.324 mg, 1.438 mmol). The resulting suspension was stirred at room temperature for 3 h. The reaction mixture was diluted with DCM, and sequentially washed with $Na_2S_2O_3$ (aqueous sat. solution), $NaHCO_3$ (aqueous sat. solution) and brine. The washed organic layer was dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; heptane/DCM up to 50% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **D14** (0.145 g, 26.6%) as a colorless oil.

Description 15

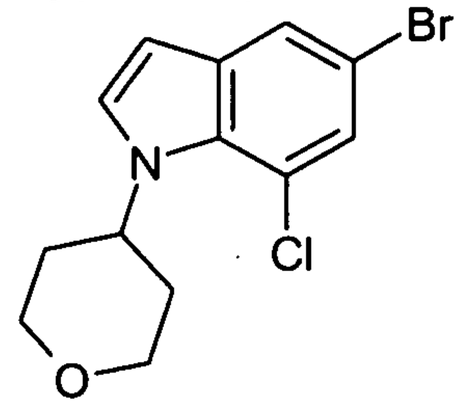
(4-Bromo-2-chloro-6-trimethylsilanylethynyl-phenyl)-(tetrahydro-pyran-4-yl)-amine (D15)



D14 (0.145 g, 0.348 mmol), $Pd(PPh_3)_2Cl_2$ (12.219 mg, 0.0174 mmol) and CuI (3.315 mg, 0.0174 mmol) were placed in a oven-dried flask under a nitrogen atmosphere. Dry Et_3N (10 ml) was added, and the resulting suspension was cooled to 0 °C and stirred. After dropwise addition of trimethylsilylacetylene (0.0541 ml, 0.383 mmol), the mixture was stirred at room temperature overnight under a nitrogen atmosphere. The reaction mixture was diluted with DCM, washed with brine and dried (Na_2SO_4). The solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; heptane/DCM up to 60% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **D15** (0.11 g, 81.6%) as a colorless oil. LCMS: MW (theor): 285; [MH^+]: 286; RT (min): 4.26 (Method 11).

Description 16

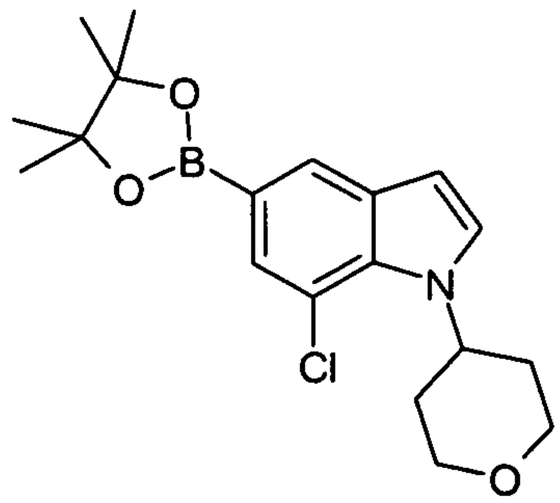
5-Bromo-7-chloro-1-(tetrahydro-pyran-4-yl)-*1H*-indole (D16)



A mixture of **D15** (0.11 g, 0.284 mmol) and CuI (0.108 mg, 0.569 mmol) in DMF (10 ml) was subjected to microwave heating at 180 °C for 15 min. After cooling to room temperature, the reaction was diluted with DCM and filtered over a pad of diatomaceous earth. The filtrate was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; heptane as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **D16** (0.071 g, 79%).
GCMS: MW (theor): 313; [M^+]: 313; RT (min): 13.6 (Method 21).

Description 17

7-Chloro-1-(tetrahydro-pyran-4-yl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-*1H*-indole (D17)

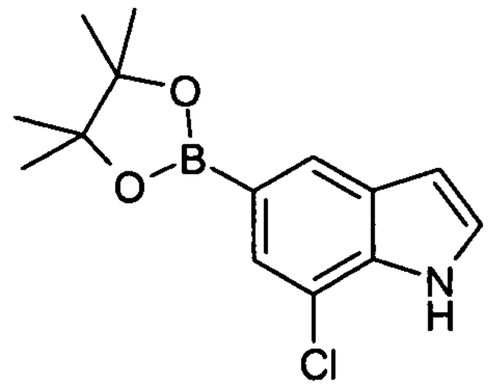


Bis(pinacolato)diboron (0.275 g, 1.083 mmol) and potassium acetate (0.199 g, 2.031 mmol) were added to a solution of intermediate **D16** (0.071 g, 0.226 mmol) in 1,4-dioxane (10 ml) and DMF (4 ml). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (14.9 mg, 0.0203 mmol) was added. The reaction mixture was subjected to microwave heating at 150 °C for 40 min. Only minor conversion to the desired product was observed by LCMS. Two additional microwave irradiations were required to complete the conversion to the desired product, first at 170 °C for 50 min and second at 175 °C for 1h, with their corresponding additional amounts of bis(pinacolato)diboron (1.6 eq), potassium acetate (3 eq), [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (0.03 eq) and DMF (2 ml) for each of

the additional irradiations. After cooling to room temperature, the reaction mixture was filtered through a pad of diatomaceous earth. The filtrate was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent: heptane/DCM up to 50% as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield **D17** (0.072 g, 88 %) as a colorless oil.

Description 18

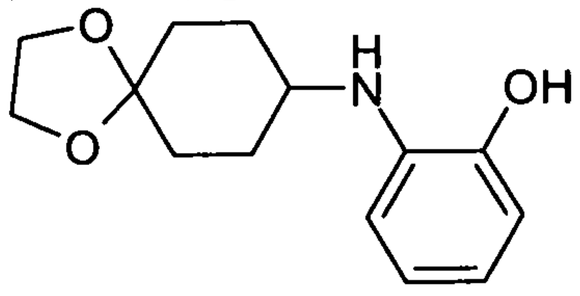
7-Chloro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-*1H*-indole (D18)



Bis(pinacolato)diboron (1.058 g, 4.165 mmol) and potassium acetate (0.383 g, 3.905 mmol) were added to a solution of 5-bromo-7-chloro-*1H*-indole (0.3 g, 1.302 mmol) [C.A.S.180623-89-6] in dioxane (10 ml) and DMF (2 ml). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (47.75 mg, 0.0651 mmol) was added. The reaction mixture was subjected to microwave heating at 150 ºC for 30 min. Only minor conversion to the desired product was observed by LCMS. Then, the reaction was charged with an additional amount of [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (48 mg) and subjected to microwave irradiation again at 150ºC for 30 min. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth. The filtrate was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel: Heptane/EtOAc up to 10% as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield **D18** (0.08 g, 22 %) as a white solid.
LCMS: MW (theor): 277; $[M-H^+]$: 276; RT (min): 4.66 (Method 9).

Description 19

2-(1,4-Dioxa-spiro[4.5]dec-8-ylamino)-phenol (D19)

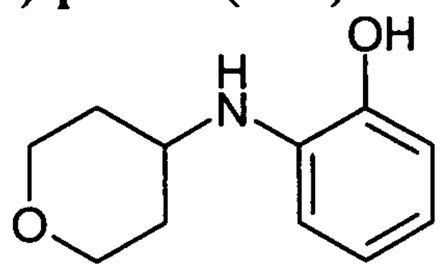


A mixture of 2-aminophenol (2 g, 18.327 mmol), 1,4-dioxa-spiro[4.5]decan-8-one (3.721 g, 23.825 mmol), and sodium triacetoxyborohydride (5.826 g, 27.491 mmol) in

DCE (20 ml) and acetic acid (0.2 ml) was stirred at room temperature for 3 h. The reaction mixture was diluted with DCM and washed with $NaHCO_3$ (aqueous sat. solution), dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The solid residue was triturated with diisopropyl ether to yield **D19** (3.78 g) as a white solid.
LCMS: MW (theor): 327; [MH^+]: 328; RT (min): 3.92 (Method 9).

Description 20

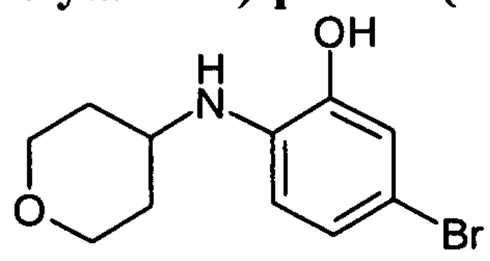
2-(Tetrahydro-pyran-4-ylamino)-phenol (D20)



A mixture of 2-aminophenol (1 g, 9.164 mmol), tetrahydropyran-4-one (1.099 ml, 11.913 mmol), and sodium triacetoxyborohydride (0.71 g, 3.42 mmol) in DCE (50 ml) was stirred at room temperature for 16 h. The crude mixture was filtered over diatomaceous earth, washed with DCM and the filtrate was evaporated *in vacuo* to yield **D20** (0.69 g) which was used as such in the next reaction step without further purification.
LCMS: MW (theor): 193; [MH^+]: 194; RT (min): 2.19 (Method 9).

Description 21

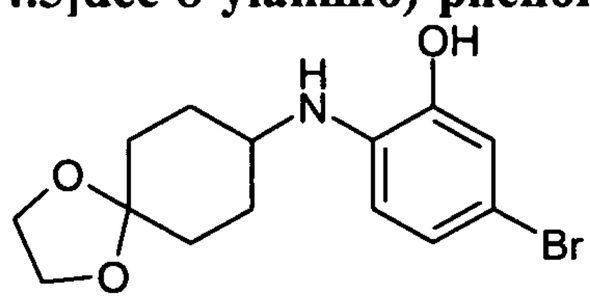
5-Bromo-2-(tetrahydro-pyran-4-ylamino)-phenol (D21)



A solution of intermediate **D20** (0.66 g, 3.415 mmol) and *N*-bromosuccinimide (0.669 g, 3.757 mmol) in DMF (10 ml) was stirred at room temperature for 1 h. Subsequently, the reaction mixture was washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/EtOAc 8:2 as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **D21** (0.433 g, 46.6 %) as a reddish solid.
LCMS: MW (theor): 271; [MH^+]: 272; RT (min): 3.33 (Method 9).

Description 22

5-Bromo-2-(1,4-dioxa-spiro[4.5]dec-8-ylamino)-phenol (D22)

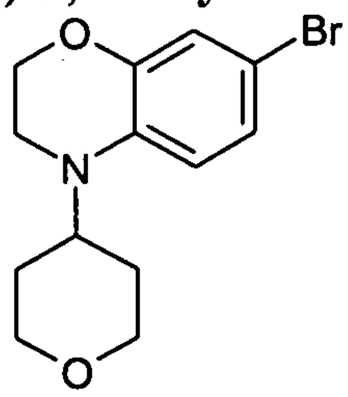


A solution of intermediate **D19** (1 g, 4.011 mmol) and *N*-bromosuccinimide (0.785 g, 4.412 mmol) in DMF (15 ml) was stirred at room temperature for 1 h. Subsequently, the reaction mixture was washed with $NaHCO_3$ (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/EtOAc 8:2 as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **D22** (0.433 g, 32.89 %) as a reddish solid.

LCMS: MW (theor): 327; [MH^+]: 328; RT (min): 2.82 (Method 15)

Description 23

7-Bromo-4-(tetrahydropyran-4-yl)-3,4-dihydro-*2H*-benzo[1,4]oxazine (D23)



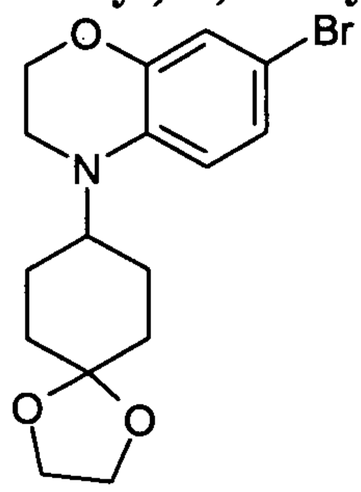
A mixture of intermediate **D21** (0.433 g, 1.591 mmol), 1,2-dibromoethane (0.411 ml, 4.773 mmol and K_2CO_3 (1.099 g, 7.955 mmol) in DMF (10 ml) was subjected to microwave heating at 180 °C for 15 min. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth. The filtrate was evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield a colorless oil that crystallized to yield **D23** (0.267 g, 56 %) as a white solid.

M.P.: 66.2 °C.

LCMS: MW (theor): 297; [MH^+]: 298; RT (min): 4.24 (Method 9).

Description 24

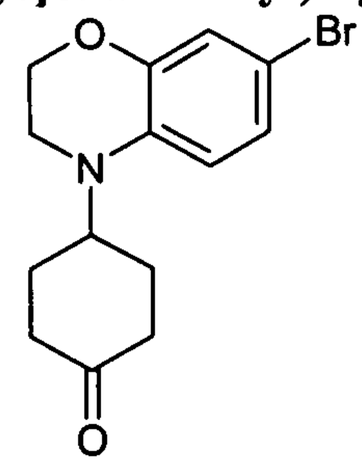
7-Bromo-4-(1,4-dioxa-spiro[4.5]dec-8-yl)-3,4-dihydro-*2H*-benzo[1,4]oxazine (D24)



A mixture of intermediate **D22** (0.433 g, 1.319 mmol), 1,2-dibromoethane (0.341 ml, 3.958 mmol and potassium carbonate (0.912 g, 6.596 mmol) in DMF (10 ml) was subjected to microwave heating at 180 °C for 15 min. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth. The filtrate was evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield a colorless oil that crystallized to yield **D24** (0.271 g, 58 %).
LCMS: MW (theor): 353; [MH^+]: 354; RT (min): 4.71 (Method 9)

Description 25

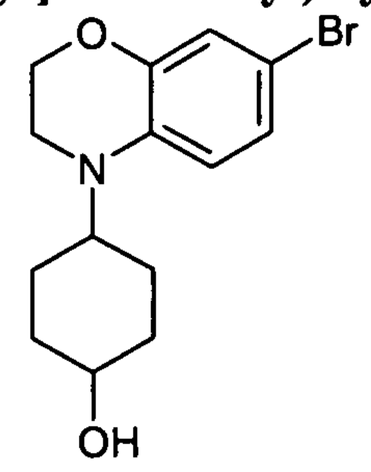
4-(7-Bromo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-cyclohexanone (D25)



A mixture of intermediate **D24** (0.250 g, 0.706 mmol), *p*-toluenesulfonic acid (13.424 mg, 0.0706 mmol) in H_2O (5 ml) and acetone (2.5 ml) was subjected to microwave heating at 100 °C for 15 min. After cooling to room temperature the reaction mixture was diluted with DCM and washed with $NaHCO_3$ (aqueous sat. solution), dried (Na_2SO_4) and evaporated *in vacuo*. The reaction mixture was purified by column chromatography (silica gel; DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **D25** (0.172 g, 78 %) as white solid. M.P.: 101.8 °C.
LCMS: MW (theor): 309; [MH^+]: 310; RT (min): 3.77 (Method 16).

Description 26

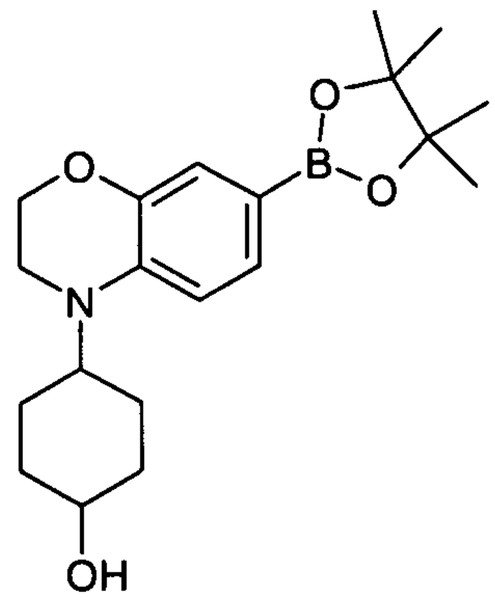
4-(7-Bromo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-cyclohexanol (D26)



A mixture of intermediate **D25** (1.3 g, 4.191 mmol) and sodium borohydride (0.476 g, 12.573 mmol) in MeOH (15 ml) was stirred at room temperature for 3 h. Then, the resulting mixture was carefully quenched with NH_4Cl (aqueous sat. solution) and extracted with DCM. The organic layer was separated, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was triturated with a mixture of diisopropylether/diethylether to yield **D26** (1.045 g, 63 %) as *cis/trans* mixture of isomers (34% and 66% respectively) LCMS: MW (theor): 311; [MH^+]: 312; RT (min): 2.83. (Method 15)

Description 27

4-[7-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-cyclohexanol (D27)

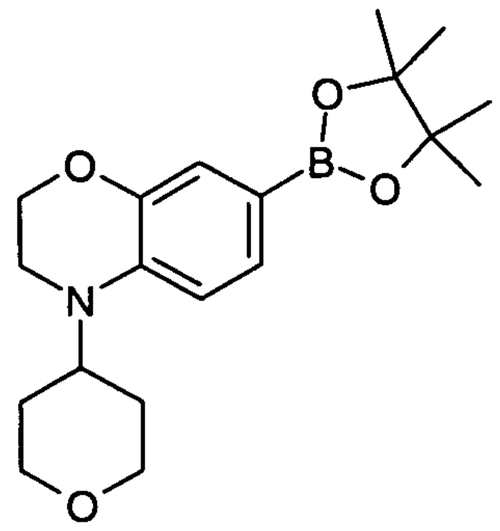


Bis(pinacolato)diboron (0.552 g, 2.174 mmol) and potassium acetate (0.492 g, 5.016 mmol) were added to a solution of intermediate **D26** (*cis/trans* mixture) (0.522 g, 1.672 mmol) in 1,4-dioxane (5 ml). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) - complex with DCM (1:1) (0.0736 g, 0.1 mmol) was added. The reaction mixture was heated overnight at 95 °C in a sealed tube. After cooling to room temperature, the reaction mixture was filtered through a pad of diatomaceous earth and the pad was further washed with 1,4-dioxane. The combined filtrates were evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; DCM/EtOAc gradient up to 5% as eluent). The desired fractions were collected and evaporated *in vacuo* to afford

a colorless oily residue that crystallized upon standing to yield **D27** (0.6 g, 99 %) as cis/trans mixture of isomers. By LCMS (67% *trans* and 33% *cis*)
LCMS: MW (theor): 359; [MH^+]: 360; RT (min): 2.74. (Method 17)

Description 28

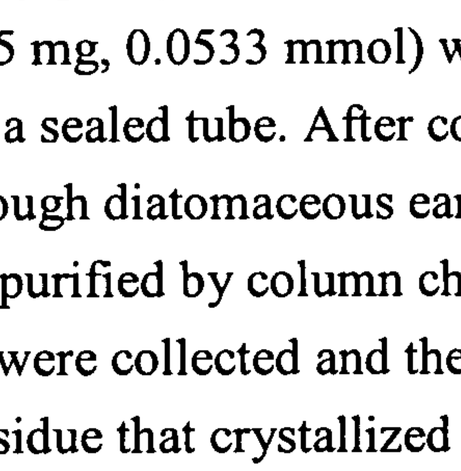
4-(Tetrahydro-pyran-4-yl)-7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-*2H*-benzo[1,4]oxazine (D28)



Bis(pinacolato)diboron (315.956 mg, 1.244 mmol mmol) and potassium acetate (261.659 mg, 2.666 mmol) were added to a solution of intermediate **D23** (265 mg, 0.889 mmol) in 1,4-dioxane (12 ml). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) - complex with DCM (1:1) (39.125 mg, 0.0533 mmol) was added. The reaction mixture was heated overnight at 95 °C in a sealed tube. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth. The filtrate was evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; DCM as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield a colorless oily residue that crystallized upon standing to yield **D28** (0.61 g, 19.88 %) as a white solid.
LCMS: MW (theor): 345; [MH^+]: 346; RT (min): 4.52 (Method 9).

Description 29

5-Bromo-1-(1,4-dioxa-spiro[4.5]dec-8-yl)-*1H*-indole (D29)

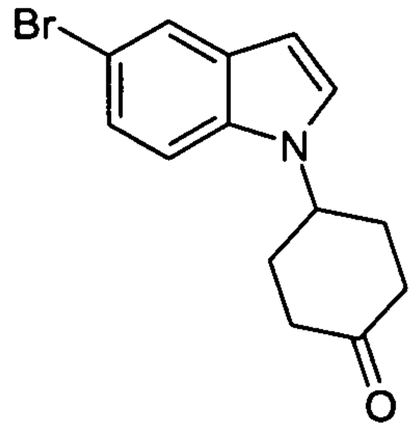


A mixture of 5-bromoindole (8.472 g, 43.216 mmol), toluene-4-sulfonic acid 1,4-dioxa-spiro[4.5]dec-8-yl ester (13.5 g, 43.216 mmol) (prepared according to the

procedure described in Journal of the Chemical Society, Perkin Transactions 1 (2002), (20), 2251-2255) and powdered potassium hydroxide (13.239 g, 235.958 mmol) in DMSO (300 ml) was stirred at 80 °C for 6 h. Subsequently, the mixture was cooled to room temperature and poured into ice water. The resulting aqueous mixture was extracted with Et_2O, dried (Na_2SO_4), and the volatiles were evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; DCM/heptane 1:1 as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **D29** (2.897 g, 19.93 %) as a white solid.
LCMS: MW (theor): 335; [MH^+]: 336; RT (min): 4.38 (Method 18)

Description 30

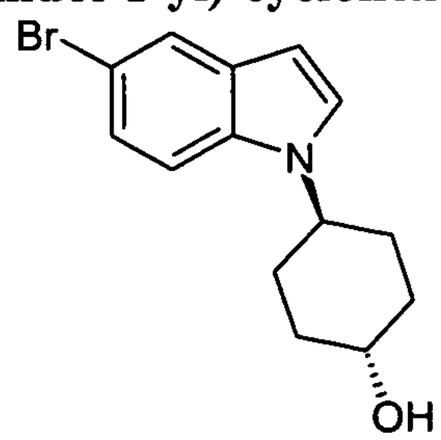
4-(5-Bromo-*1H*-indol-1-yl)-cyclohexanone (D30)



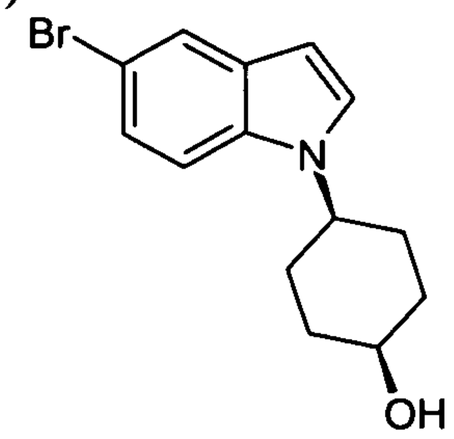
A mixture of intermediate **D29** (24 g, 71.38 mmol) and p-toluenesulfonic acid (0.679 mg, 3.569 mmol) in water (72 ml) and acetone (168 ml) was subjected to microwave heating at 100 °C for 15 min. After cooling to room temperature, the reaction mixture was diluted with DCM and washed with $NaHCO_3$ (aqueous sat. solution), dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The residue was triturated with a mixture of Et_2O (100 ml)/acetone (30 ml). The solid was filtered off and the filtrate was evaporated *in vacuo* to yield **D30** (18.13 g, 73 %) as yellow oil.
GCMS: MW (theor): 291; [M^+]: 291; RT (min): 14.5.

Description 31

4-(5-Bromo-*1H*-indol-1-yl)-cyclohexanol (D31)



trans-**D31**



cis-**D31**

Sodium borohydride (62.198 mg, 1.644 mmol) was added to a mixture of intermediate **D30** (2.074 g, 7.098 mmol) in MeOH (50 ml) stirred at 0 °C. The resulting reaction mixture was warmed to room temperature and further stirred for 1 h. Subsequently, the mixture was concentrated *in vacuo* and the residue was dissolved in DCM. This solution was washed with NH_4Cl (aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; EtOAc/heptane gradient from 0:100 to 30:70 as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield *trans*-**D31** (1.809 g, 86.6 %) and *cis*-**D31** (0.110 g, 5.27 %).

trans-**D31**

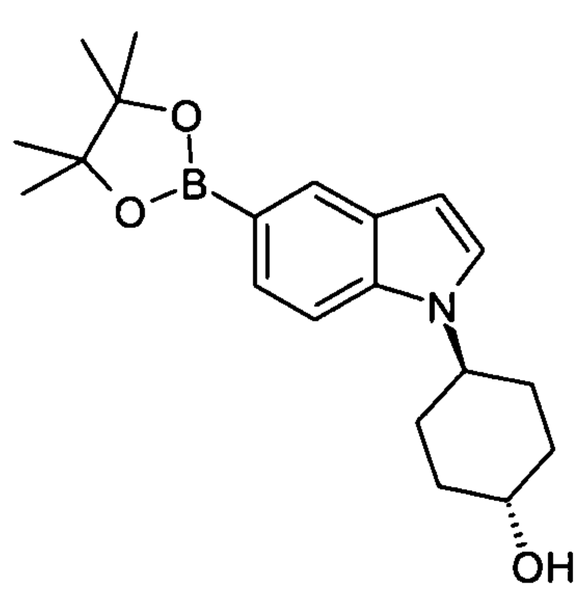
LCMS: MW (theor): 293; [MH^+]: 294; RT (min): 3.88 (Method 19)

cis-**D31**

LCMS: MW (theor): 293; [MH^+]: 294; RT (min): 3.88 (Method 19)

Description *trans*-32

***trans*-4-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-*1H*-indol-1-yl]-cyclohexanol (*trans*-D32)**

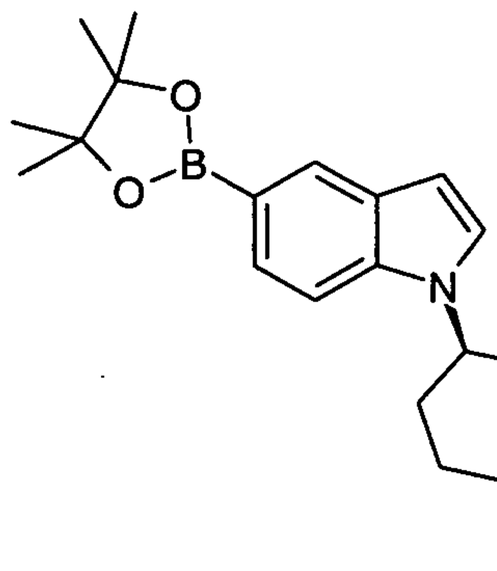


Bis(pinacolato)diboron (0.829 g, 3.263 mmol) and potassium acetate (0.300 g, 3.059 mmol) were added to a solution of intermediate *trans*-**D31** (0.300 g, 1.02 mmol) in 1,4-dioxane (12 ml) and DMF (2 ml). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)-complex with DCM (1:1) (0.0374 g, 0.051 mmol) was added. The reaction mixture was subjected to microwave heating at 160 °C for 1 h. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth. The filtrate was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent: DCM/EtOAc gradient from 100:0 to 60:40). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield *trans*-**D32** (0.260 g, 74.6 %).

LCMS: MW (theor): 341; [MH^+]: 342; RT (min): 4.74 (Method 10).

Description *cis*-32

***cis*-4-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-*1H*-indol-1-yl]-cyclohexanol (*cis*-D32)**

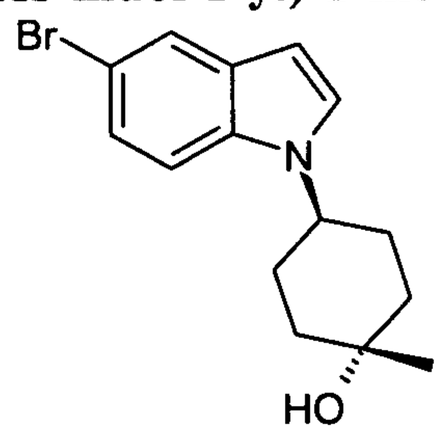


Bis(pinacolato)diboron (0.265 g, 1.042 mmol) and potassium acetate (0.219 g, 2.233 mmol) were added to a solution of intermediate *cis*-**D31** (0.219 g, 0.744 mmol) in 1,4-dioxane (4 ml). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) - complex with DCM (1:1) (0.033 g, 0.045 mmol) was added. The reaction mixture was heated for 2 h. at 95 °C. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth. The filtrate was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; heptane/EtOAc gradient from 100:0 to 80:20 as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield intermediate *cis*-**D32** (0.213 g, 83.8 %). M.P.: 187.7 °C.

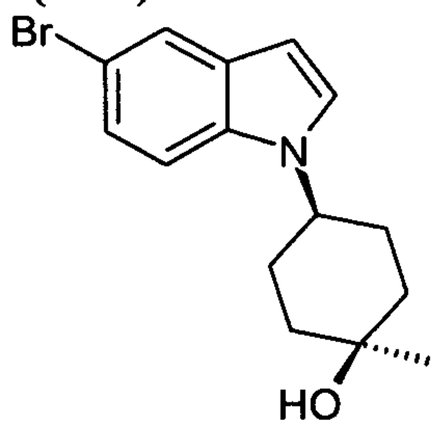
LCMS: MW (theor): 341; $[MH^+]$: 342; RT (min): 4.74 (Method 3)

Description 33

4-(5-Bromo-*1H*-indol-1-yl)-1-methyl-cyclohexanol (D33)



trans-**D33**



cis-**D33**

Methylmagnesium bromide (1.4 M solution in toluene/THF) (3.667 ml, 5.134 mmol) was added dropwise to a cooled solution (at 0 °C) of intermediate **D30** (0.5 g, 1.711 mmol) in THF (20 ml) under a N_2 atmosphere. The resulting reaction mixture was warmed to room temperature and further stirred for 4 h. After cooling in an ice bath, the mixture was carefully quenched with NH_4Cl (aqueous sat. solution), and was

subsequently extracted with DCM. The organic layer was separated, dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; 0-30% EtOAc/heptane as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield *cis*-**D33** (0.096 g, 18.2 %) and *trans*-**D33** (0.12 g, 22.7 %).

M.P. *cis*-**D33:** 111 °C.

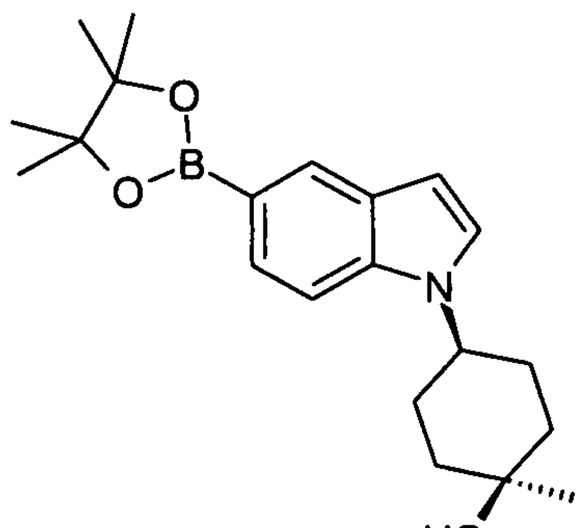
LCMS: MW (theor): 307; [MH^+]: 308; RT (min): 4.06 (Method 20)

M.P. *trans*-**D33:** 95.9 °C.

LCMS: MW (theor): 307; [MH^+]: 308; RT (min): 4.30 (Method 18)

Description *cis*-34

***cis*-1-Methyl-4-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-*1H*-indol-1-yl]-cyclohexanol (*cis*-D34)**

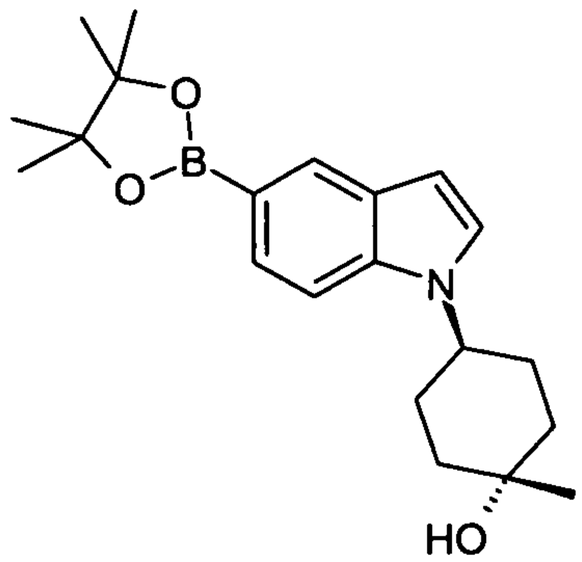


Bis(pinacolato)diboron (0.111 g, 0.436 mmol) and potassium acetate (0.0917 g, 0.934 mmol) were added to a solution of intermediate *cis*-**D33** (0.096 g, 0.311 mmol) in 1,4-dioxane (4 ml). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) - complex with DCM (1:1) (0.0137 g, 0.0187 mmol) was added. The reaction mixture was heated at 100 °C for 1.5 h. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth. The filtrate was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; heptane/EtOAc gradient from 100:0 to 80:20 as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield *cis*-**D34** (0.074 g, 66.87 %).

LCMS: MW (theor): 355; [MH^+]: 356; RT (min): 3.86 (Method 6)

Description *trans*-34

***trans*-1-Methyl-4-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-*1H*-indol-1-yl]-cyclohexanol (*trans*-D34)**

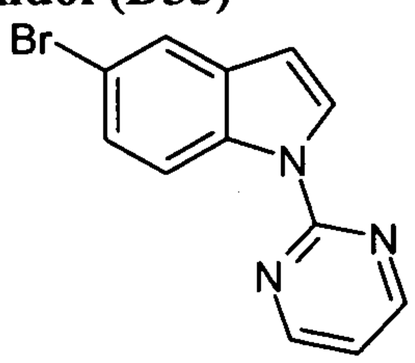


Bis(pinacolato)diboron (0.130 g, 0.513 mmol) and potassium acetate (0.108 g, 1.1 mmol) were added to a solution of intermediate *trans*-**D33** (0.113 g, 0.367 mmol) in 1,4-dioxane (5 ml). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) - complex with DCM (1:1) (0.0161 g, 0.022 mmol) was added. The reaction mixture was heated at 100 °C for 2.5 h. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth. The filtrate was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; heptane/EtOAc gradient from 100:0 to 80:20 as eluent). The desired fractions were collected and evaporated *in vacuo* to yield *trans*-**D34** (0.096 g, 74 %).

LCMS: MW (theor): 355; [MH^+]: 356; RT (min): 3.97 (Method 6)

Description 35

5-Bromo-1-pyrimidin-2-yl-*1H*-indol (D35)

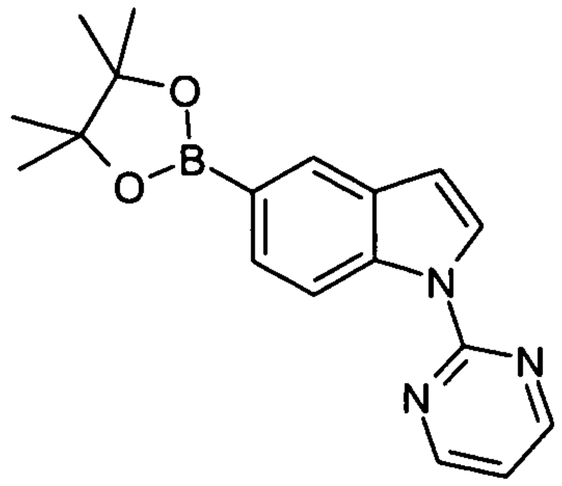


A nitrogen stream was bubbled through a mixture of 5-bromoindole (2 g, 10.201 mmol) in DMSO (10 mL). Then, K_2CO_3 (4.23 g, 30.604 mmol), Copper (I) iodine (0.097 g, 0.51 mmol), L-proline.trifluoric acetic acid (0.234 g, 1.02 mmol) and 2-bromopyrimidine (1.622 g, 10.201 mmol) were added. The resulting reaction mixture was stirred in a sealed tube at 90 °C for 48 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc and water and filtered through diatomaceous earth. The filtrate was evaporated *in vacuo*. The residue was purified by column

chromatography (silica gel; DCM as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **D35** (2.6 g, 92 %).

Description 36

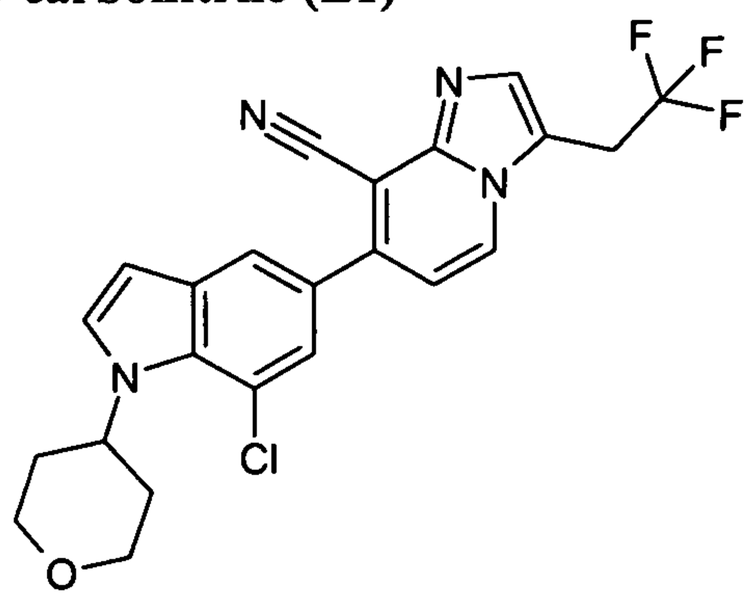
1-Pyrimidin-2-yl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-*1H*-indole (D36)



Bis(pinacolato)diboron (2 g, 7.88 mmol) and potassium acetate (1.933 g, 19.699 mmol) were added to a solution of intermediate **D35** (1.8 g, 6.566 mmol) in DMSO (13 ml). A nitrogen stream was bubbled through the mixture and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) - complex with DCM (1:1) (0.145 g, 0.197 mmol) was added. The reaction mixture was heated at 100 °C for 16 h. Only partial conversion towards the desired product was observed by LCMS. Then, the reaction vessel was charged with an additional amount of tetrakis(triphenylphosphine) palladium(0) (0.145 g) and heated again at 110 °C for 4.5 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc and filtered through diatomaceous earth. The filtrate was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; heptane/EtOAc gradient from 100:0 to 90:10 as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **D36** (2.19 g, 73 %).

Example 1

7-[7-Chloro-1-(tetrahydro-pyran-4-yl)-*1H*-indol-5-yl]-3-(2,2,2-trifluoroethyl) imidazo[1,2-a]pyridine-8-carbonitrile (E1)

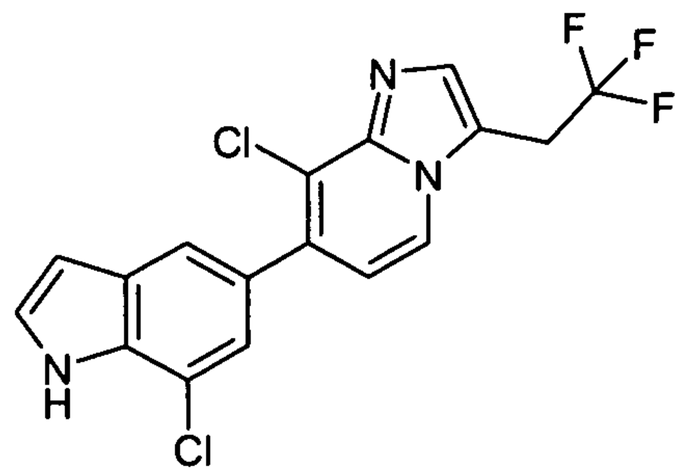


A mixture of intermediate **D17** (0.07 g, 0.194 mmol), intermediate **D9** (0.107 g, 0.194 mmol), tetrakis(triphenylphosphine)palladium(0) (0.011 g, 0.00968 mmol) and an aqueous saturated $NaHCO_3$ solution (5 ml) in 1,4-dioxane (5 ml) was subjected to microwave heating at 150 °C for 10 min. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth, the filtrate was diluted with DCM and the organic layer was washed first with water and subsequently with brine. The organic fraction was dried (Na_2SO_4), filtered and the solvent was evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; DCM/EtOAc up to 30% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **E1** (9.1 mg, 9.6 %) as a yellow syrup.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.03 - 2.13 (m, 2 H), 2.14 - 2.20 (m, 2 H), 3.64 (td, J=11.8, 1.6 Hz, 2 H), 3.80 (q, J=9.9 Hz, 2 H), 4.17 (dd, J=11.7, 4.2 Hz, 2 H), 5.55 (tt, J=11.6, 4.0 Hz, 1 H), 6.69 (d, J=3.5 Hz, 1 H), 7.15 (d, J=7.2 Hz, 1 H), 7.39 (d, J=3.2 Hz, 1 H), 7.47 (d, J=1.4 Hz, 1 H), 7.79 (s, 1 H), 7.91 (d, J=1.7 Hz, 1 H), 8.22 (d, J=7.2 Hz, 1 H).

Example 2

8-Chloro-7-(7-chloro-*1H*-indol-5-yl)-3-(2,2,2-trifluoroethyl)-imidazo[1,2-a]-pyridine (E2)



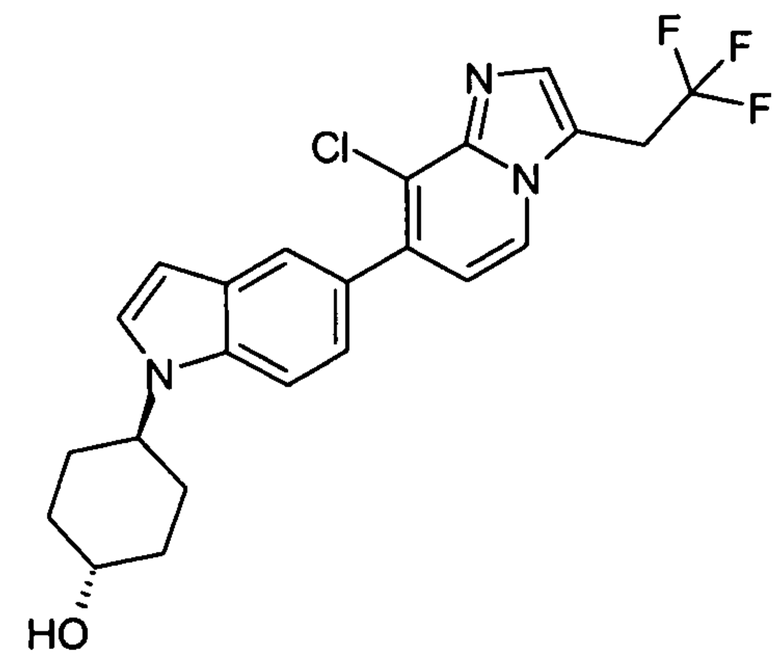
A mixture of intermediate **D18** (0.09 g, 0.324 mmol), intermediate **D12** (0.106 g, 0.295 mmol), K_3PO_4 (0.187 g, 0.884 mmol) and DAPCy (8.624 mg, 0.0147 mmol) in EtOH (2 ml) was stirred at room temperature overnight. The reaction mixture was filtered through diatomaceous earth and the filtrate was evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; DCM/EtOAc up to 5% as eluent). The desired fractions were collected and evaporated *in vacuo*. The residue was triturated with heptane to give a solid that was filtered off and dried in the oven to yield **E2** (0.07 g, 61.8 %) as a white solid.

M.P. decomposed

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.78 (q, J=9.9 Hz, 1 H), 6.68 (dd, J=3.2, 2.3 Hz, 1 H), 7.01 (d, J=7.2 Hz, 1 H), 7.35 (dd, J=2.8, 2.8 Hz, 1 H), 7.39 (d, J=1.4 Hz, 1 H), 7.70 - 7.73 (m, 1 H), 7.74 (s, 1 H), 8.00 (d, J=6.9 Hz, 1 H), 8.57 (br. s., 1 H).

Example 3

***trans*-4-[5-[8-Chloro-3-(2,2,2-trifluoroethyl)-imidazo[1,2-a]pyridin-7-yl]-*1H*-indol-1-yl]-cyclohexanol (E3)**



A mixture of intermediate *trans*-**D32** (0.255 g, 0.748 mmol), intermediate **D12** (0.35 g, 0.68 mmol), tetrakis(triphenylphosphine)palladium(0) (0.039 g, 0.034 mmol) and an aqueous saturated $NaHCO_3$ solution (1.5 ml) in 1,4-dioxane (3 ml) was subjected to

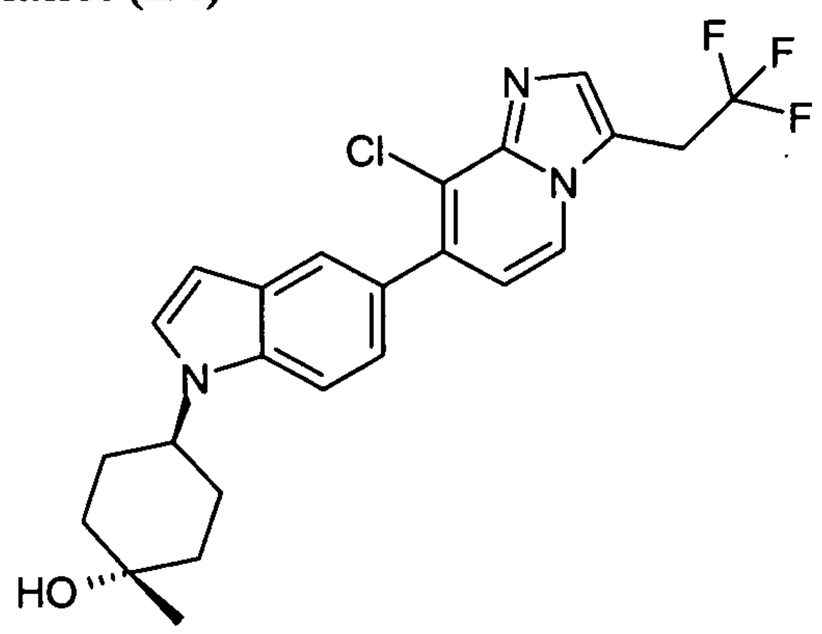
microwave heating at 150 °C for 10 min. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth, the diatomaceous earth was further washed with EtOAc and the combined filtrates were washed with water and brine. The organic layer was separated, dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel; DCM/MeOH(NH_3) up to 10 % followed by heptane/EtOAc as eluent). The desired fractions were collected and evaporated *in vacuo*. The residue was triturated with diethyl ether. The white precipitate was filtered off and dried *in vacuo* to yield **E3** (0.14 g, 46 %) as a white solid.

M.P. 129.4°C

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.53 - 1.68 (m, 3 H), 1.80 - 1.95 (m, 2 H), 2.21 (br. d, J=10.9 Hz, 4 H), 3.78 (q, J=9.9 Hz, 2 H), 3.79 - 3.89 (m, 1 H), 4.25 - 4.37 (m, 1 H), 6.60 (d, J=3.2 Hz, 1 H), 7.04 (d, J=7.2 Hz, 1 H), 7.27 (d, 1 H), 7.40 (dd, J=8.6, 1.6 Hz, 1 H), 7.48 (d, J=8.6 Hz, 1 H), 7.72 (s, 1 H), 7.80 (d, J=1.4 Hz, 1 H), 7.99 (d, J=6.9 Hz, 1 H).

Example 4

***trans*-4-[5-[8-Chloro-3-(2,2,2-trifluoroethyl)-imidazo[1,2-a]pyridin-7-yl]-*1H*-indol-1-yl]-1-methyl-cyclohexanol (E4)**



A mixture of intermediate *trans*-**D34** (0.221 g, 0.373 mmol), **D12** (0.112 g, 0.311 mmol), tetrakis(triphenylphosphine)palladium(0) (0.018 g, 0.0155 mmol) and a saturated aqueous $NaHCO_3$ solution (2 ml) in 1,4-dioxane (8 ml) was subjected to microwave heating at 150 °C for 10 min. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth, the diatomaceous earth was further washed with EtOAc and the combined filtrates were washed with water and brine. The organic fraction was dried (Na_2SO_4), filtered and the solvent was evaporated *in vacuo*. The crude residue was purified by column chromatography (silica gel;

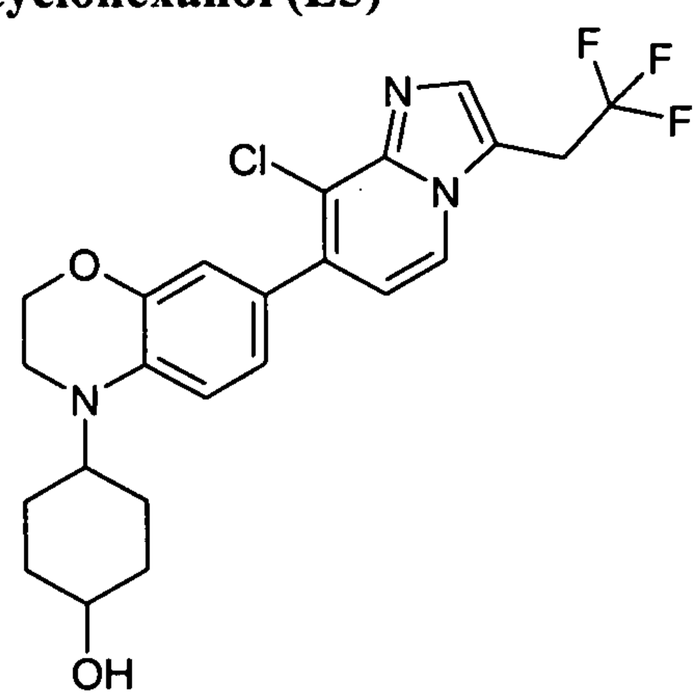
DCM/EtOAc up to 15% as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo*. The residue was triturated with Et_2O. A white precipitate was filtered off and dried *in vacuo* to yield a residue that was triturated with DIPE, filtered off and dried in the oven to yield **E4** (0.75 g, 52 %) as a white solid.

M.P.162.2°C

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.11 (br. s, 1 H), 1.36 (s, 3 H), 1.69 (td, J=13.9, 3.9 Hz, 2 H), 1.83 - 1.93 (m, 2 H), 1.94 - 2.04 (m, 2 H), 2.25 (qd, J=13.2, 3.7 Hz, 2 H), 3.77 (q, J=9.9 Hz, 2 H), 4.26 (tt, J=12.3, 3.9 Hz, 1 H), 6.59 (d, J=3.2 Hz, 1 H), 7.04 (d, J=6.9 Hz, 1 H), 7.35 (d, J=3.2 Hz, 1 H), 7.39 (dd, J=8.8, 1.6 Hz, 1 H), 7.48 (d, J=8.6 Hz, 1 H), 7.71 (s, 1 H), 7.80 (d, J=1.4 Hz, 1 H), 7.98 (d, J=6.9 Hz, 1 H).

Example 5

4-[7-[8-Chloro-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridin-7-yl]-2,3-dihydro-*4H*-1,4-benzoxazin-4-yl]-cyclohexanol (E5)



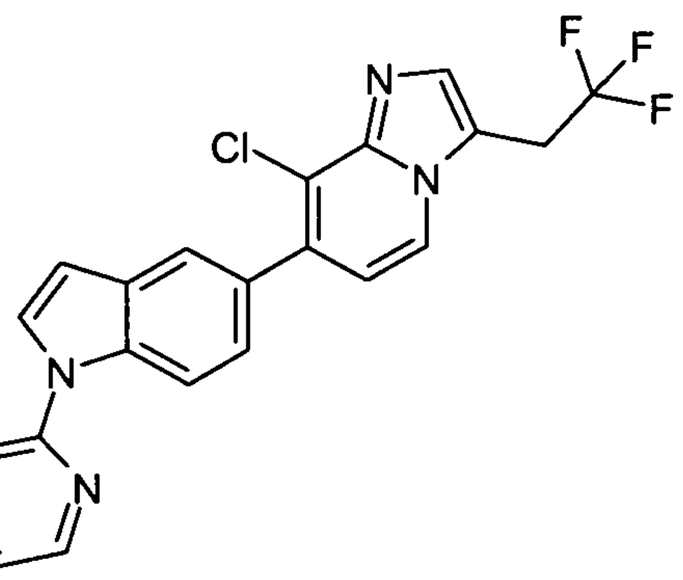
A mixture of intermediate **D27** (0.3 g, 0.835 mmol), **D12** (0.301 g, 0.835 mmol), tetrakis(triphenylphosphine)palladium(0) (0.0482 g, 0.0418 mmol) and $NaHCO_3$ (aqueous sat. solution) (1.5 ml) in 1,4-dioxane (5 ml) was heated at 150 °C for 10 min. under microwave irradiation. After cooling to room temperature, the reaction mixture was further subjected to microwave heating at 150°C for an additional 10 min. Only partial conversion towards the desired product was observed by LCMS. Then, the reaction vessel was charged with an additional amount of tetrakis(triphenylphosphine) palladium(0) (0.0482 g) and a saturated aqueous $NaHCO_3$ solution (0.5 ml) and heated again at 150 °C for 10 min under microwave irradiation. After cooling to room temperature, the reaction mixture was filtered through diatomaceous earth and the diatomaceous earth was further washed with 1,4-dioxane. The combined filtrates were evaporated *in vacuo*. The residue was purified by column chromatography (silica gel:

DCM/EtOAc up to 50% as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo* to yield **E5** as mixture of diastereoisomers as determined by ^{1}HNMR. *trans /cis* = 88:12 (0.097 g, 10 %)

(trans-**E5)** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.11 (br. s, 1 H), 1.38 - 1.73 (m, 4 H), 1.90 (br. d, J=12.3 Hz, 2 H), 2.13 (br. d, J=12.5 Hz, 2 H), 3.29 - 3.36 (m, 2 H), 3.60 - 3.73 (m, 2 H), 3.74 (q, J=9.9 Hz, 2 H), 4.20 - 4.29 (m, 2 H), 6.80 (d, J=8.6 Hz, 1 H), 6.95 (d, J=7.2 Hz, 1 H), 7.04 (d, J=1.4 Hz, 1 H), 7.10 (br. d, J=8.6 Hz, 1 H), 7.68 (s, 1 H), 7.94 (d, J=7.2 Hz, 1 H).

Example 25

8-Chloro-7-(1-pyrimidin-2-yl-*1H*-indol-5-yl)-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine



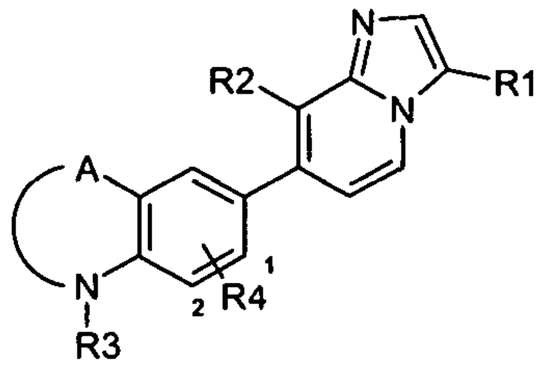
A mixture of intermediate **D36** (0.267 g, 0.832 mmol), **D12** (0.25 g, 0.693 mmol), tetrakis(triphenylphosphine)palladium(0) (0.0401 g, 0.0347 mmol) and $NaHCO_3$ (aqueous sat. solution) (1.7 ml) in 1,4-dioxane (6.8 ml) was heated at 150 °C for 5 min. under microwave irradiation. After cooling to room temperature, the reaction mixture was diluted with EtOAc and water and filtered through diatomaceous earth. The filtrate was extracted with EtOAc, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel: DCM/EtOAc up to 15% as eluent). The desired fractions were collected and the solvent was evaporated *in vacuo*. to yield a residue that was triturated with DIPE, filtered off and dried in the oven to yield **E25** (0.135 g, 46 %)

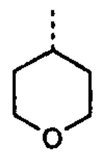
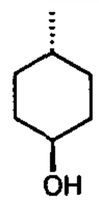
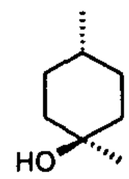
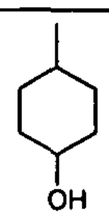
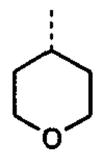
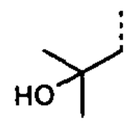
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.78 (q, *J*=9.9 Hz, 2 H), 6.78 (d, *J*=3.5 Hz, 1 H), 7.06 (d, *J*=6.9 Hz, 1 H), 7.10 (t, *J*=4.7 Hz, 1 H), 7.51 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.73 (s, 1 H), 7.80 (d, *J*=1.8 Hz, 1 H), 8.01 (d, *J*=6.9 Hz, 1 H), 8.36 (d, *J*=3.5 Hz, 1 H), 8.74 (d, *J*=4.6 Hz, 2 H), 8.93 (d, *J*=8.6 Hz, 1 H).

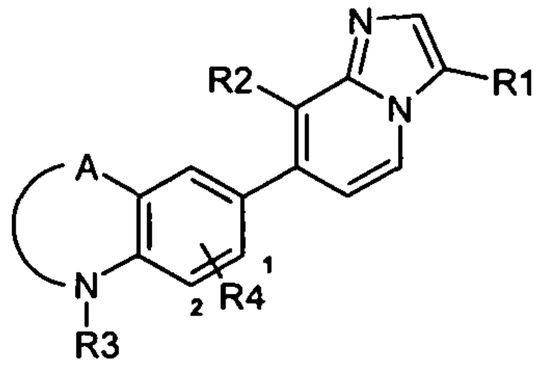
M.P. Decomposed

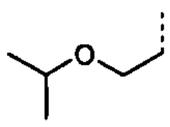
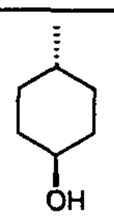
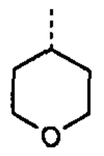
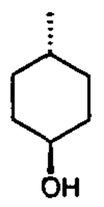
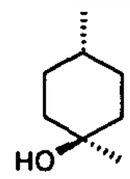
Table 1 lists compounds of Formula (I) that were prepared according to one of the above Examples (Ex. No.).

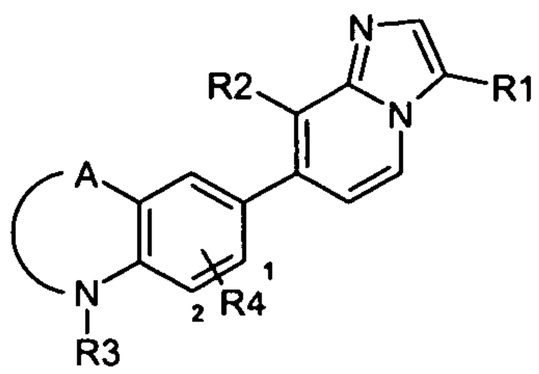
Table 1:

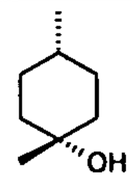
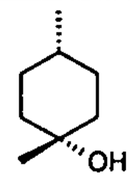
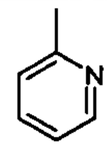
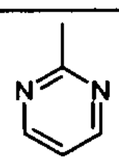
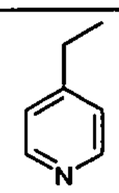
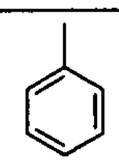
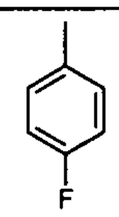
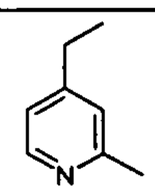


Co.nr.	Exp nr.	R^1	R^2	R^3	R^4	A
1	E1	--CH_2-CF_3	--CN		2-Cl	-CH=CH-
2	E2	--CH_2-CF_3	--Cl	H	2Cl	-CH=CH-
3	E3	--CH_2-CF_3	--Cl		H	-CH=CH-
4	E4	--CH_2-CF_3	--Cl		H	-CH=CH-
5	E5	--CH_2-CF_3	--Cl		H	-CH_2-CH_2-O-
6	E1	--CH_2-CF_3	--CN		H	-CH=CH-
7	E1	--CH_2-CF_3	--CN	Me	H	-CH=CH-
8	E1	--CH_2-CF_3	--CN	H	2-Cl	-CH=CH-
9	E1	--CH_2-CF_3	--CN		H	-CH=CH-



Co.nr.	Exp nr.	R^1	R^2	R^3	R^4	A
10	E1	--CH_2-CF_3	--CN	Me	2-Cl	-CH=CH-
11	E1	--CH_2-CF_3	--CN		2-Cl	-CH=CH-
12	E1	--CH_2-CF_3	--CN		H	-CH_2-CH_2-O-
13	E1	--CH_2-CF_3	--CN		H	-CH=CH-
14	E1	--CH_2-CF_3	--CN		H	-CH=CH-
15	E1	--CH_2-CF_3	--CN	Me	H	-CH_2-CH_2-O-
16	E1	--CH_2-CF_3	--CN		H	-CH=CH-
17	E1	--CH_2-CF_3	--CN		H	-CH_2-CH_2-O-
18	E1	--CH_2-CF_3	--Cl		2-Cl	-CH=CH-
19	E1	--CH_2-CF_3	--CN		H	-CH_2-CH_2-O-
20	E1	--CH_2-CF_3	--CN	H	H	-CH_2-CH_2-O-
21	E1	--CH_2-CF_3	--CN		H	-CH=CH-



Co.nr.	Exp nr.	R^1	R^2	R^3	R^4	A
22	E1	--CH_2-CF_3	--CN		H	-CH=CH-
23	E1	--CH_2-CF_3	--Cl		H	-CH=CH-
24	E2	--CH_2-CF_3	--Cl		H	-CH=CH-
25	E2	--CH_2-CF_3	--Cl		H	-CH=CH-
26	E1	--CH_2-CF_3	--CN	H	H	-CH=CMe-
27	E1	--CH_2-CF_3	--CN		H	-CH=CH-
28	E1	--CH_2-CF_3	--CN		H	-CH=CH-
29	E1	--CH_2-CF_3	--CN		H	-CH=CH-
30	E1	--CH_2-CF_3	--CN		H	-CH=CH-

Physico-Chemical Data

General procedure for Waters MS instruments (TOF, ZQ, SQD, Platform)

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

General procedure for Agilent MS instrument (MSD)

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

General procedure for Waters MS instruments (Acquity-SQD)

The UPLC measurement was performed using an Acquity system from Waters comprising a sampler organizer, a binary pump with degasser, a four column's oven, a diode-array detector (DAD) and a column as specified in the respective methods below. Column flow is used without split to the MS detector. The MS detector is configured with an ESCI dual ionization source (electrospray combined with atmospheric pressure chemical ionization). Nitrogen was used as the nebulizer gas. The source temperature was maintained at 140 °C. Data acquisition was performed with MassLynx-Openlynx software.

General procedure for Agilent GC/MSD instrument

The GC measurement was performed using a 6890 Series Gas Chromatograph (Agilent Technologies) system comprising a 7683 Series injector and autosampler, a column

oven and a column as specified in the respective methods below, coupled to a 5973N MSD Mass Selective Detector (single quadrupole, Agilent Technologies). The MS detector was configured with an electronic impact ionization source / chemical ionization source (EI/CI). EI low-resolution mass spectra were acquired by scanning from 50 to 550 at a rate of 14.29 scans/s. The source temperature was maintained at 230°C. Helium was used as the nebulizer gas. Data acquisition was performed with Chemstation-Open Action software.

Method 1

In addition to the general procedure: Reversed phase HPLC was carried out on an XDB-C18 cartridge (1.8 µm, 2.1 x 30 mm) from Agilent, at 60°C with a flow rate of 1 ml/min, at 60°C. The gradient conditions used are: 90 % A (0.5 g/l 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 by scanning from 100 to 750 in 0.5 seconds using a dwell time of 0.3 seconds. The capillary needle voltage was 2.5 kV for positive ionization mode and 2.9 kV for negative ionization mode. The cone voltage was 20 V for both positive and negative ionization modes. Leucine-Enkephaline was the standard substance used for the lock mass calibration.

Method 2

In addition to the general procedure: Reversed phase HPLC was carried out on an XDB-C18 cartridge (1.8 µm, 2.1 x 30 mm) from Agilent, at 60°C with a flow rate of 1 ml/min, at 60°C. The gradient conditions used are: 90 % A (0.5 g/l 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.

Method 3

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, 50 % C in 6.5 minutes, kept till 7.0 minutes and equilibrated to initial conditions at 7.3 minutes until 9.0 minutes. Injection volume 2 µl. High-resolution mass spectra (Time of Flight, TOF) were acquired by scanning from 100 to 750 in 0.5 seconds using a dwell time of 0.3 seconds. The capillary needle voltage was 2.5 kV for positive ionization mode and 2.9 kV for negative ionization mode. The cone voltage was 20 V for both positive and negative ionization modes. Leucine-Enkephaline was the standard substance used for the lock mass calibration.

Method 4

In addition to the general procedure: Reversed phase HPLC was carried out on a Sunfire-C18 column (2.5 µm, 2.1 x 30 mm) from Waters, with a flow rate of 1.0 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l ammonium acetate solution + 5 % acetonitrile), 5 % B (mixture of acetonitrile / methanol, 1/1), to 100 % B at 6.5 minutes, kept till 7.0 minutes and equilibrated to initial conditions at 7.3 minutes until 9.0 minutes. Injection volume 2 µl. Low-resolution mass spectra (quadrupole, SQD) were acquired by scanning from 100 to 1000 in 0.1 seconds using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 20 V for positive ionization mode and 30 V for negative ionization mode.

Method 5

In addition to the general procedure: Reversed phase UPLC was carried out on a BEH-C18 column (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 0.8 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 90 % A (0.5 g/l ammonium acetate solution), 10 % B (mixture of acetonitrile / methanol, 1/1), to 20 % A, 80 % B in 6.3 minutes, to 100 % B in 6.85 minutes, kept till 7.50 minutes and equilibrated to initial conditions at 7.75 minutes until 9.0 minutes. Injection volume 0.5 µl. Low-resolution mass spectra (quadrupole, SQD) were acquired by scanning from 100 to 1000 in 0.1 seconds using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 20 V for positive ionization mode and 30 V for negative ionization mode.

Method 6

In addition to the general procedure: Reversed phase UPLC was carried out on a BEH-C18 column (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 0.8 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l

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

Method 7

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: 90 % A (0.5 g/l ammonium acetate solution), 10 % B (mixture of acetonitrile / methanol, 1/1), kept 0.20 minutes, to 100 % B 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. Low-resolution mass spectra (Quadrupole, MSD) were acquired in electrospray mode by scanning from 100 to 1000 in 0.99 seconds, step size of 0.30 and peak width of 0.10 minutes. The capillary needle voltage was 1.0 kV and the fragmentor voltage was 70V for both positive and negative ionization modes

Method 8

In addition to the general procedure: Reversed phase UPLC was carried out on a BEH-C18 column (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 0.8 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 90 % A (0.5 g/l ammonium acetate solution), 10 % B (mixture of acetonitrile / methanol, 1/1), kept 0.2 minutes, to 20 % A, 80 % B in 3.5 minutes, to 100 % B in 3.8 minutes, kept till 4.15 minutes and equilibrated to initial conditions at 4.3 minutes until 5.0 minutes. Injection volume 0.5 µl. Low-resolution mass spectra (quadrupole, SQD) were acquired by scanning from 100 to 1000 in 0.1 seconds using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 20 V for positive ionization mode and 30 V for negative ionization mode

Method 9

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 (quadrupole, SQD) were acquired 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. The cone voltage was 20 V and 50V for positive ionization mode and 30V for negative ionization mode.

Method 10

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, 50 % C in 6.5 minutes, kept till 7.0 minutes and equilibrated to initial conditions at 7.3 minutes until 9.0 minutes. Injection volume 2 µl. High-resolution mass spectra (Time of Flight, TOF) were acquired by scanning from 100 to 750 in 0.5 seconds using a dwell time of 0.3 seconds. The capillary needle voltage was 2.5 kV for positive ionization mode and 2.9 kV for negative ionization mode. The cone voltage was 20 V for both positive and negative ionization modes. Leucine-Enkephaline was the standard substance used for the lock mass calibration.

Method 11

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), kept 0.2 minutes, to 100 % B in 3.0 minutes, kept till 3.15 minutes and equilibrated to initial conditions at 3.3 minutes until 5.0 minutes. Injection volume 2 µl. Low-resolution mass spectra (quadrupole, SQD) were acquired by scanning from 100 to 1000 in 0.1 second using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 20 V and 50 V for positive ionization mode and 30 V for negative ionization mode.

Method 12

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 1.0 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), kept 0.2 minutes, to 100 % B 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. Low-resolution mass spectra (single quadrupole,

ZQ detector) were acquired by scanning from 100 to 1000 in 0.5 second using a dwell time of 0.1 second. The capillary needle voltage was 3 kV. The cone voltage was 20 V and 50 V for positive ionization mode and 20 V for negative ionization mode.

Method 13

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 1.0 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), kept 0.20 minutes, to 100 % B 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. Low-resolution mass spectra (single quadrupole, MSD detector) were acquired in electrospray mode by scanning from 100 to 1000 in 0.99 seconds, step size of 0.30 and peak width of 0.10 minutes. The capillary needle voltage was 1.0 kV and the fragmentor voltage was 70V for both positive and negative ionization modes.

Method 14

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: 90 % A (0.5 g/l ammonium acetate solution), 10 % B (mixture of acetonitrile / methanol, 1/1), kept 0.20 minutes, to 100 % B 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. Low-resolution mass spectra (Quadrupole, MSD) were acquired in electrospray mode by scanning from 100 to 1000 in 0.99 seconds, step size of 0.30 and peak width of 0.10 minutes. The capillary needle voltage was 1.0 kV and the fragmentor voltage was 70V for both positive and negative ionization modes

Method 15

In addition to the general procedure: Reversed phase HPLC was carried out on a Sunfire-C18 column (2.5 µm, 2.1 x 30 mm) from Waters, with a flow rate of 1.0 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l ammonium acetate solution + 5 % acetonitrile), 5 % B (mixture of acetonitrile / methanol, 1/1), kept 0.2 minutes, to 100 % B in 3.0 minutes, kept till 3.15 minutes and equilibrated to initial conditions at 3.30 minutes until 5.0 minutes. Injection volume 2 µl. Low-resolution mass spectra (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 second using an inter-channel delay

of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 20 V and 50 V for positive ionization mode and 30 V for negative ionization mode.

Method 16

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), 10 % B (mixture of acetonitrile / methanol, 1/1), to 100 % B in 5.2 minutes, kept till 5.6 minutes and equilibrated to initial conditions at 5.8 minutes until 7.0 minutes. Injection volume 2 µl. Low-resolution mass spectra (single quadrupole, MSD detector) were acquired in electrospray mode by scanning from 100 to 1000 in 0.99 seconds, step size of 0.30 and peak width of 0.10 minutes. The capillary needle voltage was 1.0 kV and the fragmentor voltage was 70V for both positive and negative ionization modes

Method 17

In addition to the general procedure: Reversed phase UPLC was carried out on a BEH-C18 column (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 0.8 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l ammonium acetate solution + 5 % acetonitrile), 5 % B (mixture of acetonitrile / methanol, 1/1), kept 0.2 minutes, to 20 % A, 80 % B in 3.5 minutes, to 100 % B in 3.8 minutes, kept till 4.15 minutes and equilibrated to initial conditions at 4.3 minutes until 5.0 minutes. Injection volume 0.5 µl. Low-resolution mass spectra (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 seconds using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 20 V for positive ionization mode and 30 V for negative ionization mode.

Method 18

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 0.8 ml/min, at 60°C. 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 100 % B in 5.0 minutes, kept till 5.15 minutes and equilibrated to initial conditions at 5.3 minutes until 7.0 minutes. Injection volume 2 µl. Low-resolution mass spectra (single quadrupole, MSD detector) were acquired in electrospray mode by scanning from 100 to 1000 in 0.99 seconds, step size of 0.30 and peak width of 0.10 minutes. The capillary needle voltage was 1.0 kV and the fragmentor voltage was 70V for both positive and negative ionization modes.

Method 19

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 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 5.0 minutes, kept till 5.4 minutes and equilibrated to initial conditions at 5.6 minutes until 7.0 minutes. Injection volume 2 µl. Low-resolution mass spectra (single quadrupole, MSD detector) were acquired in electrospray mode by scanning from 100 to 1000 in 0.99 seconds, step size of 0.30 and peak width of 0.10 minutes. The capillary needle voltage was 1.0 kV and the fragmentor voltage was 70V for both positive and negative ionization modes.

Method 20

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 % acetonitrile), 5 % B (mixture of acetonitrile / methanol, 1/1), to 100 % B in 5.0 minutes, kept till 5.15 minutes and equilibrated to initial conditions at 5.3 minutes until 7.0 minutes. Injection volume 2 µl. Low-resolution mass spectra (single quadrupole, MSD detector) were acquired in electrospray mode by scanning from 100 to 1000 in 0.99 seconds, step size of 0.30 and peak width of 0.10 minutes. The capillary needle voltage was 1.0 kV and the fragmentor voltage was 70V for both positive and negative ionization modes.

Method 21

In addition to the general procedure: GC was carried out on an J&W HP-5MS column (0.25 µm, 0.25 mm x 30 m) from Agilent Technologies, with a constant flow rate of 1.2 ml/min. The temperature gradient applied was: initial temperature 50°C, hold for 3 min, then a 20°C/min ramp was applied for 10min until 250°C which was hold for 2 min in a 15min run. Front inlet temperature was 250°C. Split injection mode was used, 1 µl injection volume, with a 50/1 ratio into the GC-MS system.

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/min. Maximum temperature was 300 °C. The M.P. 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 on a Bruker DPX-400 and on a Bruker AV-500 spectrometer with standard pulse sequences, operating at 400 MHz and 500 MHz respectively, using $CDCl_3$ and C_6D_6 as solvents. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard.

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

Co.Nr	Melting point (°C)	MW (theor)	[MH$^+$]	RT (min)	LCMS Method
1	n.d.	458	459	4.53	2
2	182.8	383	384	4.2	3
3	131.6	447	448	4.0	5
4	262.2	461	462	3.64	6
5	n.d.	465	466	4.15/4.28	4
6	232.9	424	425	4.08	2
7	n.d.	354	355	3.93	2
8	n.d.	374	375	3.77	2
9	n.d.	412	413	3.85	1
10	172	388	389	4.38	2
11	175.3	428	429	4.98	2
12	n.d.	412	413	4.57	2
13	117.9	394	395	4.57	2
14	n.d.	426	427	4.47	2
15	n.d.	372	373	3.83	2

Co.Nr	Melting point (°C)	MW (theor)	[MH$^+$]	RT (min)	LCMS Method
16	n.d.	438	439	4.07	3
17	n.d.	442	443	4.01	2
18	151.3	437	438	5.35	2
19	n.d.	456	457	3.83	2
20	decomp	358	359	2.52	6
21	138.6	452	453	4.39	4
22	171.1	452	453	4.28	4
23	261.9	461	462	3.53	6
24	decomp	426	427	4.55	6
25	decomp	427	428	3.85	6
26	decomp	354	355	3.76	2
27	decomp	431	432	3.85	2
28	decomp	416	417	4.88	2
29	197.3	434	435	4.93	2
30	decomp	445	446	4.06	2

n.d.: not determined

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 4.

[^{35}S]GTPγS binding assay

The [^{35}S]GTPγS binding assay is a functional membrane-based assay used to study G-protein coupled receptor (GPCR) function whereby incorporation of a non-hydrolysable form of GTP, [^{35}S]GTPγS (guanosine 5'-triphosphate, labelled with gamma-emitting ^{35}S), is measured. The G-protein α subunit catalyzes the exchange of guanosine 5'-diphosphate (GDP) by guanosine triphosphate (GTP) and on activation of the GPCR by an agonist, [^{35}S]GTPγS, becomes incorporated and cannot be cleaved to continue the exchange cycle (Harper (1998) Current Protocols in Pharmacology 2.6.1-10, John Wiley & Sons, Inc.). The amount of radioactive [^{35}S]GTPγS incorporation is a direct measure of the activity of the G-protein and hence the activity of the agonist can be determined. mGluR2 receptors are shown to be preferentially coupled to Gαi-protein, a preferential coupling for this method, and hence it is widely used to study receptor activation of mGluR2 receptors both in recombinant cell lines and in tissues (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 hs, prior to washing in PBS (phosphate-buffered saline), and then collection by scraping in homogenisation buffer (50 mM Tris-HCl buffer, pH 7.4, 4 °C). Cell lysates were homogenized briefly (15 s) using an ultra-turrax homogenizer. The homogenate was centrifuged at 23 500 x g for 10 min. 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 homogenised 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 was 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 was then calculated as EC_{50}.

Table 3: 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 5.78 (weak activity) to 7.07 (very high activity). The error of determination of a pEC_{50} value for a single experiment is estimated to be about 0.3 log-units.

Co.Nr	GTPγS - hR2 PAM pEC_{50}
1	6.42
2	7.07
3	6.78
4	6.89
5	6.95
6	6.30
7	6.64
8	6.50
9	5.97
10	6.93
11	6.96
12	6.93
13	6.73
14	6.09
15	6.24
16	6.61
17	6.24

Co.Nr	GTPγS - hR2 PAM pEC_{50}
18	6.60
19	6.72
20	5.78
21	6.51
22	6.30
23	6.39
24	6.33
25	6.48
26	6.27
27	6.93
28	6.66
29	6.70
30	7.47

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

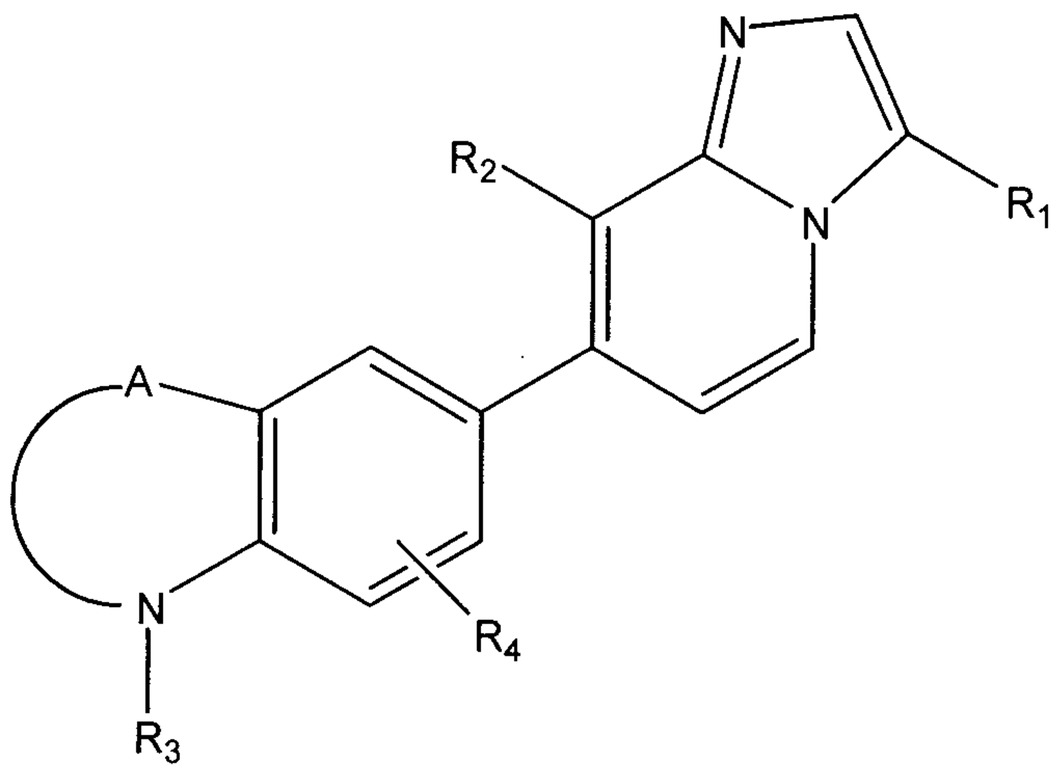
In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

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.

61200-90

CLAIMS:

1. A compound of Formula (I)



(I)

or a stereochemically isomeric form thereof, wherein

R^1 is C_{1-6}alkyl; C_{3-7}cycloalkyl; trifluoromethyl; C_{1-3}alkyl substituted with trifluoromethyl, 2,2,2-trifluoroethoxy, C_{3-7}cycloalkyl, phenyl, or phenyl substituted with halo, trifluoromethyl, or trifluoromethoxy; phenyl; phenyl substituted with 1 or 2 substituents selected from the group consisting of halo, trifluoromethyl, and trifluoromethoxy; or 4-tetrahydropyranyl;

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

R^3 is hydrogen; C_{1-3}alkyl; C_{1-3}alkyl substituted with C_{3-7}cycloalkyl, phenyl, phenyl substituted with 1 or 2 substituents selected from the group consisting of halo, cyano, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl; pyridinyl or pyridinyl substituted with 1 or 2 C_{1-3}alkyl groups; hydroxyC_{2-4}alkyl; C_{1-3}alkyloxyC_{2-4}alkyl; 4-tetrahydropyranyl; 1-oxa-spiro[3,5]non-7-yl; 2-oxa-spiro[3,5]non-7-yl; 1-oxa-spiro[4,5]dec-8-yl; 2-oxa-spiro[4,5]dec-8-yl; 4-(hydroxy)-cyclohexanyl; 4-(hydroxy)-4-(C_{1-3}alkyl)cyclohexanyl; 4-(hydroxy)-4-(C_{3-7}cycloalkyl)-cyclohexanyl; 4-(C_{1-3}alkyloxy)cyclohexanyl; phenyl; pyridinyl; pyridinylmethyl; or phenyl, pyridinyl or pyridinylmethyl substituted with one or two substituents selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl;

R^4 is hydrogen or halo;

A is a radical of formula

-CH=CH- (a), or

$-CH_2-CH_2-O-$ (b);

wherein one or two hydrogen atoms may be replaced by C_{1-3}alkyl or polyhaloC_{1-3}alkyl;

or a pharmaceutically acceptable salt or a solvate thereof.

2. The compound of formula (I) according to claim 1, wherein

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

R^2 is cyano or halo;

R^3 is hydrogen; C_{1-3}alkyl; C_{1-3}alkyl substituted with C_{3-7}cycloalkyl; hydroxyC_{2-4}alkyl; C_{1-3}alkyloxyC_{2-4}alkyl; 4-tetrahydropyranyl; 4-(hydroxy)-cyclohexanyl; or 4-(hydroxy)-4-(C_{1-3}alkyl)cyclohexanyl;

R^4 is hydrogen, chloro or fluoro;

A is a radical of formula

-CH=CH- (a), or

$-CH_2-CH_2-O-$ (b);

or a pharmaceutically acceptable salt or a solvate thereof.

3. The compound of formula (I) according to claim 1, wherein

R^1 is C_{1-3}alkyl substituted with trifluoromethyl;

R^2 is cyano or chloro;

R^3 is hydrogen; methyl; methylyl substituted with cyclopropyl; 2-hydroxy-2,2-dimethylethyl; 1-methylethyloxyethyl; 4-tetrahydropyranyl; 4-(hydroxy)-cyclohexanyl; or 4-(hydroxy)-4-(methyl)cyclohexanyl;

R^4 is hydrogen or chloro;

A is a radical of formula

-CH=CH- (a), or

$-CH_2-CH_2-O-$ (b);

or a pharmaceutically acceptable salt or a solvate thereof.

4. The compound of formula (I) according to claim 1, wherein

R^1 is 2,2,2-trifluoroethyl;

R^2 is cyano or chloro;

A is a radical of formula -CH=CH- (a);

or a pharmaceutically acceptable salt or a solvate thereof.

5. The compound of formula (I) according to claim 1, wherein

R^1 is 2,2,2-trifluoroethyl;

R^2 is cyano or chloro;

A is a radical of formula $-CH_2-CH_2-O-$ (b);

or a pharmaceutically acceptable salt or a solvate thereof.

61200-90

6. A pharmaceutical composition comprising a compound according to any one of claims 1 to 5 and a pharmaceutically acceptable carrier.

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

8. A compound according to any one of claims 1 to 5 or a pharmaceutical composition according to claim 6 for use in treating or preventing a central nervous system disorder selected from the group consisting 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. A compound for use according to claim 8, wherein the central nervous system disorder is an anxiety disorder, selected from the group consisting of agoraphobia, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, posttraumatic stress disorder (PTSD) and social phobia.

10. A compound for use according to claim 8, wherein the central nervous system disorder is a psychotic disorder selected from the group consisting of schizophrenia, delusional disorder, schizoaffective disorder, schizophreniform disorder and substance-induced psychotic disorder or a personality disorder selected from the group consisting of obsessive-compulsive personality disorder, schizoid personality disorder and schizotypal personality disorder.

11. A compound for use according to claim 8, wherein the central nervous system disorder is a substance-related disorder selected from the group consisting 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.

61200-90

12. A compound for use according to claim 8, wherein the central nervous system disorder is a mood disorder selected from the group consisting of bipolar disorders (I & II), cyclothymic disorder, depression, dysthymic disorder, major depressive disorder and substance-induced mood disorder.

13. A compound for use according to claim 8, wherein the central nervous system disorder is epilepsy or a convulsive disorder selected from the group consisting 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 and epilepsy partialis continua.

14. A compound for use according to claim 8, wherein the childhood disorder is attention-deficit/hyperactivity disorder.

15. A compound for use according to claim 8, wherein the central nervous system disorder is a cognitive disorder selected from the group consisting 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.