

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 May 2009 (22.05.2009)

PCT

(10) International Publication Number
WO 2009/062676 A2

(51) International Patent Classification:
C07D 471/04 (2006.01)

[ES/ES]; Calle Jarama, 75, Poligono Industrial, E-45007 Toledo (ES).

(21) International Application Number:
PCT/EP2008/009534

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

(22) International Filing Date:
12 November 2008 (12.11.2008)

(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, 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, 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.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
07120647.8 14 November 2007 (14.11.2007) EP

(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, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicants (*for all designated States except US*): **ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC.** [US/US]; 1000 U.S. Route 202, Raritan, NJ 08869 (US). **ADDEX PHARMA S.A.** [CH/CH]; 12, chemin des Aulx, CH-1228 Plan-les-Ouates/Geneva (CH).

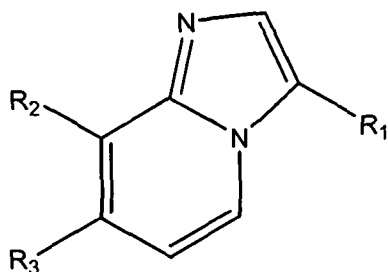
(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **TRABANCO-SUAREZ, Andrés, Avelino** [ES/ES]; Calle Jarama, 75, Poligono Industrial, E-45007 Toledo (ES). **TRESADERN, Gary, John** [GB/ES]; Calle Jarama, 75, Poligono Industrial, E-45007 Toledo (ES). **VEGA RAMIRO, Juan, Antonio** [ES/ES]; Calle Jarama, 75, Poligono Industrial, E-45007 Toledo (ES). **CID-NUNEZ, Jose, Maria**

Published:

— *without international search report and to be republished upon receipt of that report*

(54) Title: IMIDAZO[1,2-A]PYRIDINE DERIVATIVES AND THEIR USE AS POSITIVE ALLOSTERIC MODULATORS OF MGLUR2 RECEPTORS



(I)

(57) Abstract: The present invention relates to novel compounds, in particular novel imidazo[1,2-a]pyridine derivatives according to Formula (I) wherein all radicals are as defined in the application and claims. The compounds according to the invention are positive allosteric modulators of metabotropic receptors - subtype 2 ("mGluR2") which are useful for the treatment or prevention of neurological and psychiatric disorders associated with glutamate dysfunction and diseases in which the mGluR2 subtype of metabotropic receptors is involved. In particular, such diseases are central nervous system disorders selected from the group of anxiety, schizophrenia, migraine, depression, and epilepsy. The invention is also directed to phar-

maceutical compositions and processes to prepare such compounds and compositions, as well as to the use of such compounds for the prevention and treatment of such diseases in which mGluR2 is involved.

IMIDAZO[1,2-a]PYRIDINE DERIVATIVES AND THEIR USE AS POSITIVE ALLOSTERIC MODULATORS OF MGLUR2 RECEPTORS

5

Field of the Invention

The present invention relates to novel imidazo[1,2-a]pyridine derivatives which are positive allosteric modulators of the metabotropic glutamate receptor subtype 2 ("mGluR2") and which are useful for the treatment or prevention of neurological and psychiatric disorders associated with glutamate dysfunction and diseases in which the mGluR2 subtype of metabotropic receptors is involved. The invention is also directed to pharmaceutical compositions comprising such compounds, to processes to prepare such compounds and compositions, and to the use of such compounds for the prevention or treatment of neurological and psychiatric disorders and diseases in which mGluR2 is involved.

15

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.

20

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.

25

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

30

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

The mGluR2 subtype is negatively coupled to adenylate cyclase via activation of G α i-protein, and its activation leads to inhibition of glutamate release in the synapse.

35

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

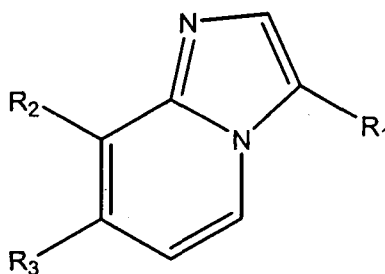
inhibition of the acoustic startle effect models of schizophrenia (J. Pharmacol. Exp. Ther. **2006**, 318, 173-185; Psychopharmacology **2005**, 179, 271-283).

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)



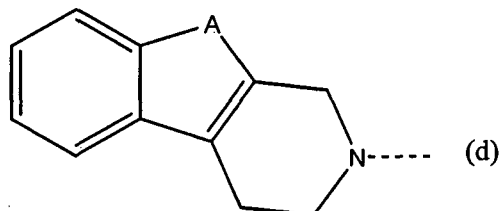
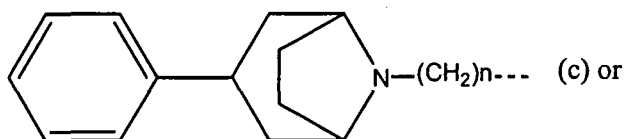
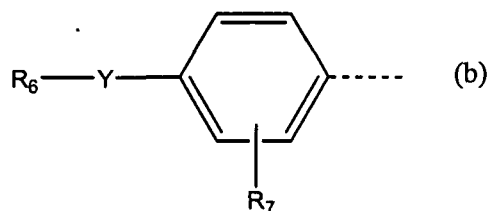
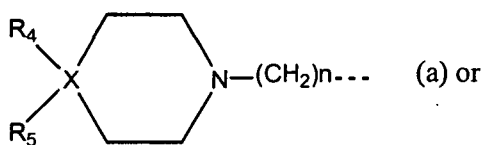
(I)

and the stereochemically isomeric forms thereof, wherein

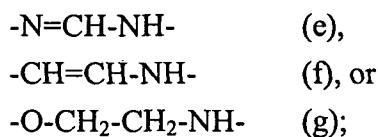
R¹ is C₁₋₆alkyl; C₃₋₆cycloalkyl; trifluoromethyl; C₁₋₃alkyl substituted with trifluoromethyl, 2,2,2-trifluoroethoxy, C₃₋₇cycloalkyl, phenyl, or phenyl substituted with C₁₋₃alkyl, C₁₋₃alkyloxy, cyano, halo, trifluoromethyl, or trifluoromethoxy; phenyl; phenyl substituted with 1 or 2 substituents selected from the group consisting of C₁₋₃alkyl, C₁₋₃alkyloxy, cyano, halo, trifluoromethyl, and trifluoromethoxy; or 4-tetrahydropyranyl;

R² is cyano, halo, trifluoromethyl, C₁₋₃alkyl or cyclopropyl;

R^3 is a radical of formula (a) or (b) or (c) or (d)



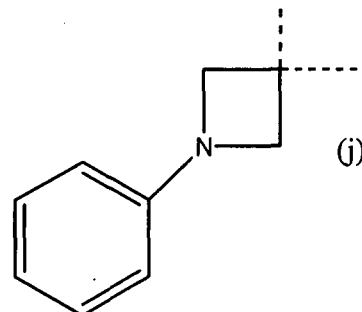
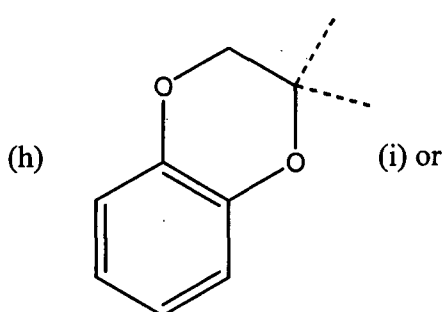
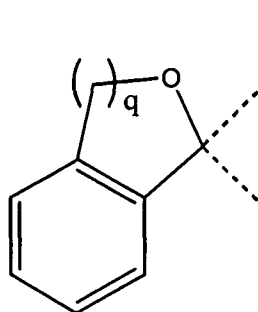
R^4 is hydrogen; hydroxy C_{3-6} cycloalkyl; pyridinyl; pyridinyl substituted with one or two C_{1-3} alkyl groups; pyrimidinyl; pyrimidinyl substituted with one or two C_{1-3} alkyl groups; phenyl; phenyl substituted with 1 or 2 substituents selected from the group consisting of halo, C_{1-3} alkyl, hydroxy C_{1-3} alkyl, mono- or polyhalo C_{1-3} alkyl, cyano, hydroxyl, amino, carboxyl, C_{1-3} alkyloxy C_{1-3} alkyl, C_{1-3} alkyloxy, mono- or polyhalo- C_{1-3} alkyloxy, C_{1-3} alkylcarbonyl, mono- and di(C_{1-3} alkyl)amino, and morpholinyl; or phenyl with two vicinal substituents which taken together form a bivalent radical of formula



R^5 is hydrogen, fluoro, hydroxyl, hydroxy C_{1-3} alkyl, hydroxy C_{1-3} alkyloxy, fluoro C_{1-3} alkyl, fluoro C_{1-3} alkyloxy, morpholinyl or cyano;

X is C or N in which case R^5 represent the electron pair on N; or

R^4 -X- R^5 represents a radical of formula (h) or (i) or (j)

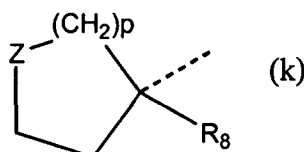


n is 0 or 1;

q is 1 or 2;

R^6 is C_{1-3} alkyl; C_{3-6} cycloalkyl; hydroxy C_{2-4} alkyl; (C_{3-6} cycloalkyl) C_{1-3} alkyl; phenyl; pyridinyl; or phenyl or pyridinyl substituted with one or two substituents selected from the group consisting of halo, C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy C_{1-3} alkyl, trifluoromethyl and $(CH_2)_m-CO_2H$, wherein $m = 0, 1, \text{ or } 2$; or

R^6 is a cyclic radical of formula (k)



wherein R^8 is hydrogen, C_{1-3} alkyl, C_{1-3} alkyloxy, hydroxy C_{1-3} alkyl;

p is 1 or 2 ;

Z is O, CH_2 or $CR^9(OH)$ wherein R^9 is hydrogen or C_{1-3} alkyl; or

R^8 and R^9 form a radical $-CH_2-CH_2-$;

R^7 is hydrogen, halo or trifluoromethyl;

Y is a covalent bond, O, NH, S, SO, SO_2 , $C(OH)(CH_3)$, $-CH_2-O-$, $-O-CH_2-$, CHF or CF_2 ; or

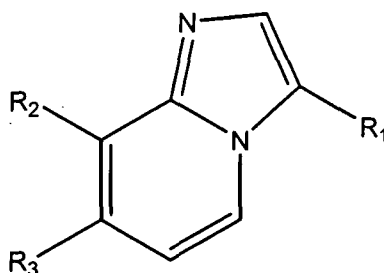
R^6-Y is morpholinyl, pyrrolidinyl, or piperidinyl optionally substituted with hydroxyl or hydroxy C_{1-3} alkyl; and

A is O or NH;

or a pharmaceutically acceptable salt or a solvate thereof.

In one embodiment, the invention relates to a compound according to Formula

(I)



(I)

or a stereochemically isomeric form thereof, wherein

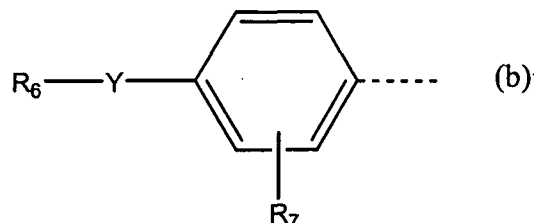
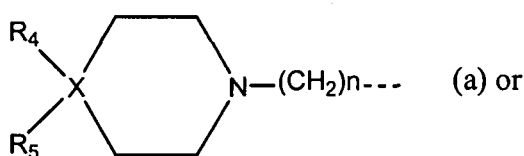
R^1 is C_{1-6} alkyl; trifluoromethyl; C_{1-3} alkyl substituted with trifluoromethyl, 2,2,2-trifluoroethoxy, C_{3-7} cycloalkyl, phenyl, or phenyl substituted with halo,

trifluoromethyl, or trifluoromethoxy; phenyl; phenyl substituted with halo, trifluoromethyl, or trifluoromethoxy; or 4-tetrahydropyranyl;

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

R^3 is a radical of formula (a) or (b)

5



R^4 is hydrogen; pyridinyl; pyrimidinyl; pyrimidinyl substituted with one or two C_{1-3} alkyl groups; phenyl; phenyl substituted with 1 or 2 substituents selected from the group consisting of halo, C_{1-3} alkyl, hydroxy C_{1-3} alkyl, polyhalo C_{1-3} alkyl, cyano, hydroxyl, amino, carboxyl, C_{1-3} alkyloxy C_{1-3} alkyl, C_{1-3} alkyloxy, polyhalo C_{1-3} alkyloxy, C_{1-3} alkylcarbonyl, mono- and di(C_{1-3} alkyl)amino, and morpholinyl; or phenyl with two vicinal substituents which taken together form a bivalent radical of formula

-N=CH-NH- (e),

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

15 -O-CH₂-CH₂-NH- (g);

R^5 is hydrogen, fluoro, hydroxyl, hydroxy C_{1-3} alkyl, hydroxy C_{1-3} alkyloxy, fluoro C_{1-3} alkyl, fluoro C_{1-3} alkyloxy or cyano;

X is C or N in which case R^5 represent the electron pair on N;

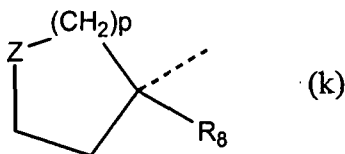
n is 0 or 1;

20

R^6 is phenyl; pyridinyl; or phenyl or pyridinyl substituted with one or two substituents selected from the group consisting of halo, C_{1-3} alkyl, C_{1-3} alkoxy, trifluoromethyl and $(CH_2)_m$ -CO₂H, wherein m = 0, 1, or 2; or

R^6 is a cyclic radical of formula (k)

25



wherein R^8 is hydrogen, C_{1-3} alkyl, C_{1-3} alkyloxy, hydroxy C_{1-3} alkyl;

p is 1 or 2 ;

Z is O or CR⁹(OH) wherein R^9 is hydrogen or C_{1-3} alkyl; or

R^8 and R^9 form a radical -CH₂-CH₂-;

30 R^7 is hydrogen, halo or trifluoromethyl;

Y is a covalent bond, O, NH, S, SO, SO₂, or CF₂; or
a pharmaceutically acceptable salt or a solvate thereof.

In one embodiment, the invention relates to a compound according to Formula (I)

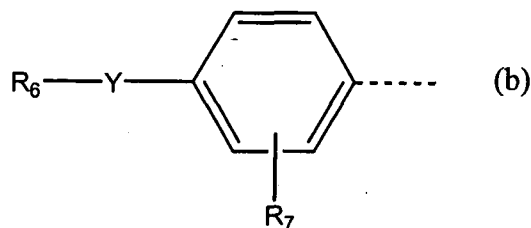
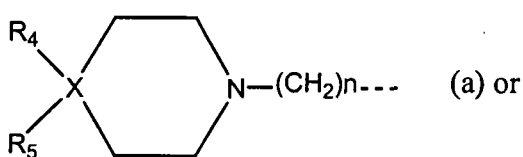
5 wherein

R¹ is C₁₋₆alkyl; trifluoromethyl; C₁₋₃alkyl substituted with trifluoromethyl, or phenyl; or phenyl;

R² is cyano or halo;

R³ is a radical of formula (a) or (b)

10



R⁴ is pyrimidinyl; pyrimidinyl substituted with one or two C₁₋₃alkyl groups; phenyl; phenyl substituted with 1 or 2 substituents selected from the group consisting of halo, polyhaloC₁₋₃alkyl;

15 R⁵ is hydrogen or hydroxyl;

X is C or N in which case R⁵ represent the electron pair on N;

n is 0 or 1;

20 R⁶ is pyridinyl substituted with one or two substituents selected from the group consisting of C₁₋₃alkyl;

R⁷ is hydrogen or halo;

Y is O; or

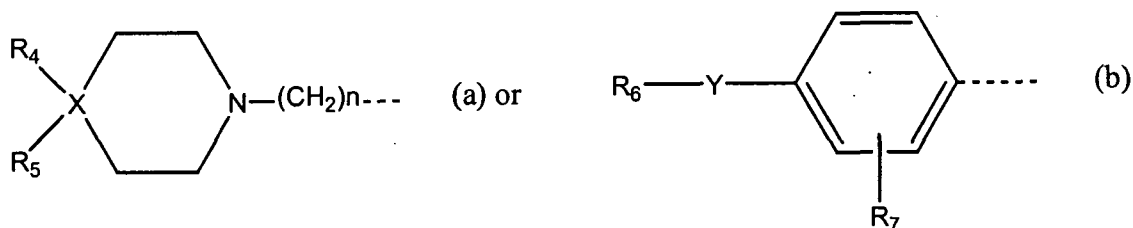
a pharmaceutically acceptable salt or a solvate thereof.

25 In one embodiment, the invention relates to a compound according to Formula (I) wherein

R¹ is methyl; ethyl, 1-propyl, trifluoromethyl; 2,2,2-trifluoroethyl, 4,4,4-trifluorobutyl, phenylmethyl or phenyl;

R² is cyano;

30 R³ is a radical of formula (a) or (b)



R^4 is pyrimidinyl; pyrimidinyl substituted with one or two C_{1-3} alkyl groups; phenyl; phenyl substituted with 1 or 2 substituents selected from the group consisting of fluoro, chloro and trifluoromethyl;

5 R^5 is hydrogen or hydroxyl;

X is C or N in which case R^5 represent the electron pair on N;

n is 0 or 1;

10 R^6 is pyridinyl substituted with one or two substituents selected from the group consisting of methyl;

R^7 is hydrogen, fluoro or chloro;

Y is O; or

a pharmaceutically acceptable salt or a solvate thereof.

15 In a further embodiment, the invention relates to a compound according to formula (I) or a stereochemically isomeric form thereof, wherein the compound is 8-Chloro-7-(4-fluoro-4-phenyl-piperidin-1-yl)-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine (E50),

20 2-(2-{1-[8-Chloro-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridin-7-yl]-piperidin-4-yl}-phenyl)-propan-2-ol (E65),

7-{4-[2-(1-Hydroxy-1-methyl-ethyl)-phenyl]-piperidin-1-yl}-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (E67),

7-(4-Fluoro-4-phenyl-piperidin-1-yl)-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (E68),

25 (*cis*)-7-[3-Chloro-4-(4-hydroxy-cyclohexylamino)-phenyl]-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (E95),

(*trans*)-7-[3-Chloro-4-(4-hydroxy-cyclohexylamino)-phenyl]-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (E96),

30 (*trans*)-4-{2-Chloro-4-[8-chloro-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridin-7-yl]-phenylamino}-1-methyl-cyclohexanol (E100),

4-{2-Chloro-4-[8-chloro-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridin-7-yl]phenylamino}-cyclohexanol (E101), or

7-(3-Chloro-4-cyclopropylamino-phenyl)-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (E105).

The notation C₁₋₃alkyl 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 C₁₋₆alkyl 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 cycloC₃₋₇alkyl 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.

- 5 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.

- 10 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
15 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
20 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
25 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
30 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
35 (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 ^3H , ^{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 ^3H , ^{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.

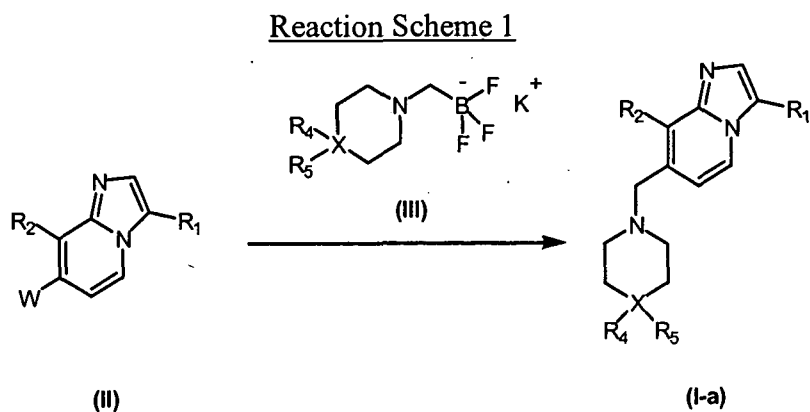
The compounds of Formula (I) may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable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

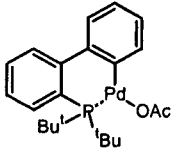
The final compounds according to Formula (I-a), can be prepared by reacting an intermediate compound of Formula (II) with a compound of Formula (III) according to reaction scheme (1), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, 1,4-dioxane or mixtures of inert solvents such as, for example,

1,4-dioxane/DMF, in the presence of a suitable base, such as, for example, K_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 alkyltrifluoroborates, such as, for example, halo.



Experimental procedure 2

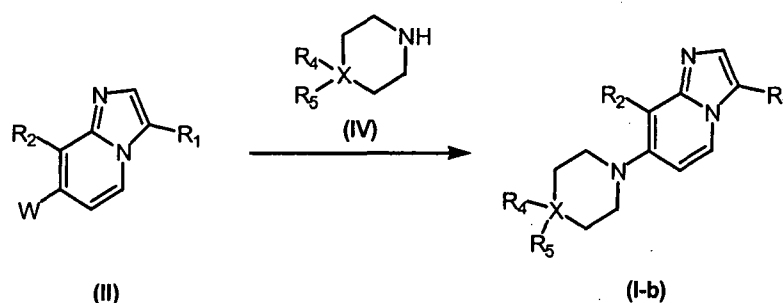
10 The final compounds according to Formula (I-b), can be prepared by reacting an intermediate compound of Formula (II) with a compound of Formula (IV) according to reaction scheme (2), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, 1,4-dioxane, in the presence of a suitable base, such as, for

example, K_3PO_4 , a Pd-complex catalyst such as, for example, , under thermal conditions such as, for example, heating the reaction mixture for example at 80 °C for 12 hours. In reaction scheme (2), all variables are defined as in Formula (I) and W is a suitable group for Pd-mediated coupling with amines, such as, for example, halo.

Alternatively, compounds according to Formula (I-b) can be prepared by reacting an intermediate compound of Formula (II) with a compound of Formula (IV) according to reaction scheme (2), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, 1,2-dimethoxyethane or acetonitrile, in the presence of a suitable base, such as, for example, CS_2CO_3 or *N,N*-diisopropylethylamine, under thermal conditions such as, for example, heating the reaction mixture for example at 180 °C under microwave irradiation for 45 minutes.

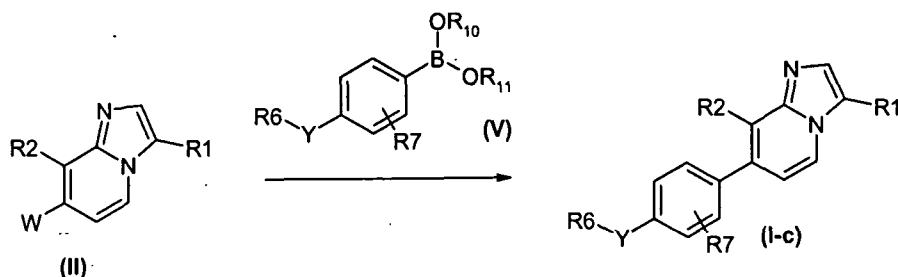
Alternatively, compounds according to Formula (I-b) can be prepared by reacting an intermediate compound of Formula (II) with a compound of Formula (IV) according to reaction scheme (2), a reaction that is performed in a suitable reaction-inert solvent such as, for example, toluene, in the presence of 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 hours in a sealed tube.

Reaction Scheme 2

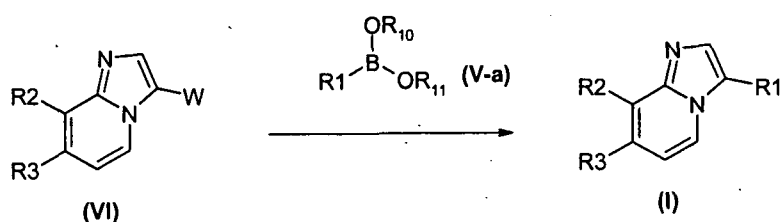


Experimental procedure 3

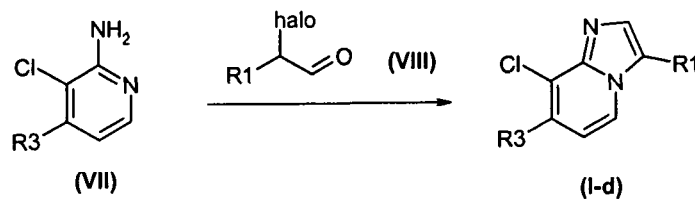
The final compounds according to Formula (I-c), can be prepared by reacting an intermediate compound of Formula (II) with a compound of Formula (V) according to reaction scheme (3), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, 1,4-dioxane or mixtures of inert solvents such as, for example, 1,4-dioxane/DMF, in the presence of a suitable base, such as, for example, aqueous NaHCO₃ or Na₂CO₃, a Pd-complex catalyst such as, for example, Pd(PPh₃)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 (3), 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, triflate or a pyridinium moiety. R¹⁰ and R¹¹ may be hydrogen or alkyl, or may be taken together to form for example a bivalent radical of formula -CH₂CH₂-, -CH₂CH₂CH₂-, or -C(CH₃)₂C(CH₃)₂-.

Reaction Scheme 3Experimental procedure 4

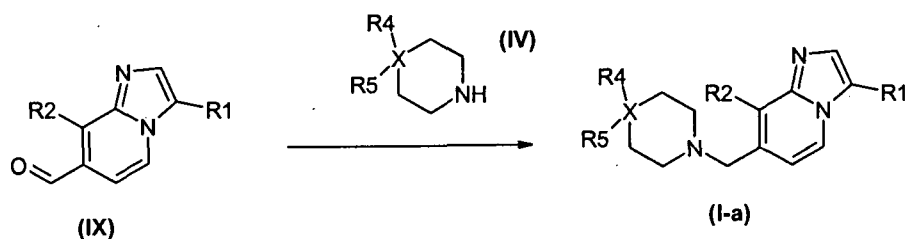
- 5 The final compounds according to Formula (I), can be prepared by reacting an intermediate compound of Formula (VI) with a compound of Formula (V-a) according to reaction scheme (4), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, 1,4-dioxane or mixtures of inert solvents such as, for example, 1,4-dioxane/DMF, in the presence of a suitable base, such as, for example, aqueous
- 10 NaHCO₃ or Na₂CO₃, a Pd-complex catalyst such as, for example, Pd(PPh₃)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 (4), 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. R¹⁰ and R¹¹ may be
- 15 hydrogen or alkyl, or may be taken together to form for example a bivalent radical of formula -CH₂CH₂-, -CH₂CH₂CH₂-, or -C(CH₃)₂C(CH₃)₂-.

Reaction Scheme 420 Experimental procedure 5

- The final compounds according to Formula (I-d) can be prepared by reacting an intermediate of Formula (VII) with an intermediate compound of Formula (VIII) according to reaction scheme (5). This reaction is performed in a suitable reaction-inert solvent such as, for example, ethanol under thermal conditions such as, for example,
- 25 heating the reaction mixture for example at 150 °C under microwave irradiation for 50 minutes. In reaction scheme (5), all variables are defined as in Formula (I).

Reaction Scheme 5Experimental procedure 6

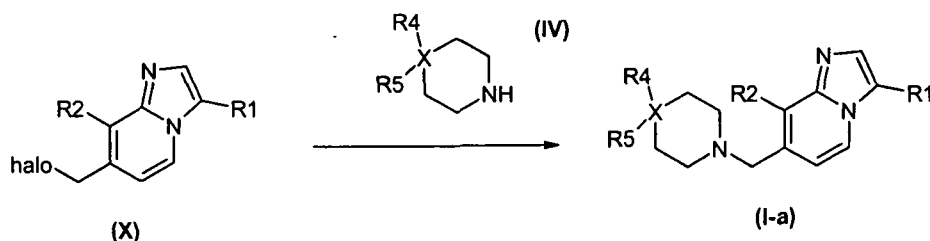
5 The final compounds according to Formula (I-a) can be prepared by reacting an intermediate of Formula (IX) with an intermediate of Formula (IV) under reductive amination conditions that are known by those skilled in the art. This is illustrated in reaction scheme (6) wherein all variables are defined as in Formula (I). The reaction may be performed, for example, in the presence of sodium triacetoxy borohydride in a
 10 suitable reaction-inert solvent such as, for example, 1,2-dichloroethane, at a suitable temperature, typically at room temperature, for a suitable period of time that allows the completion of the reaction.

Reaction Scheme 6

15

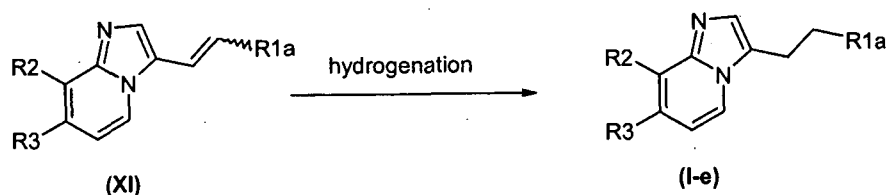
Experimental procedure 7

20 Alternatively, final compounds according to Formula (I-a) can be prepared by reacting an intermediate of Formula (X) with an intermediate of Formula (IV) under alkylating conditions that are known by those skilled in the art. This is illustrated in reaction scheme (7) wherein all variables are defined as in mentioned hereabove. The reaction may be performed, for example, in the presence of a base such as for example diisopropylethylamine in a suitable reaction solvent such as, for example, DMF for a suitable period of time that allows the completion of the reaction at suitable temperature such as for example 120°C.

Reaction Scheme 7Experimental procedure 8

5 The final compounds according to Formula (I-e) can be prepared by reacting an intermediate of Formula (XI) under reductive conditions that are known by those skilled in the art. This is illustrated in reaction scheme (8) wherein all variables are defined as in Formula (I). The reaction may be performed, for example, in the presence of a catalyst such as, for example palladium on activated carbon, for a period of time

10 that ensures the completion of the reaction, typically at room temperature and 1 atmosphere of hydrogen for 16 hours. R^{1a} is C₁₋₄alkyl or C₁₋₄alkyl substituted with trifluoromethyl.

Reaction Scheme 8

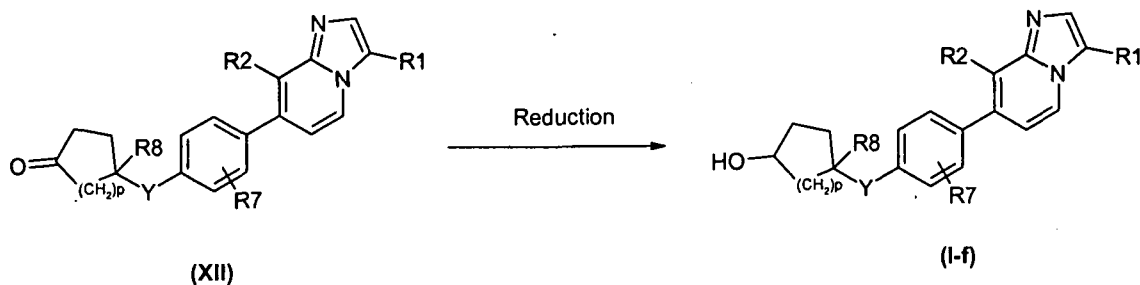
15

Experimental procedure 9

 The final compounds according to Formula (I-f) can be prepared by reacting an intermediate of Formula (XII) under reductive conditions that are known by those skilled in the art. The reaction is illustrated in reaction scheme (9) wherein all

20 substituents are defined as in Formula (I). The reaction can be carried out in the presence of, for example, sodium borohydride in a suitable solvent such as, for example, methanol. The reaction may be performed at a suitable temperature, typically room temperature, for a suitable period of time that allows the completion of the reaction. R⁸ and p are as defined in a radical of Formula (k) in the R⁶ definition.

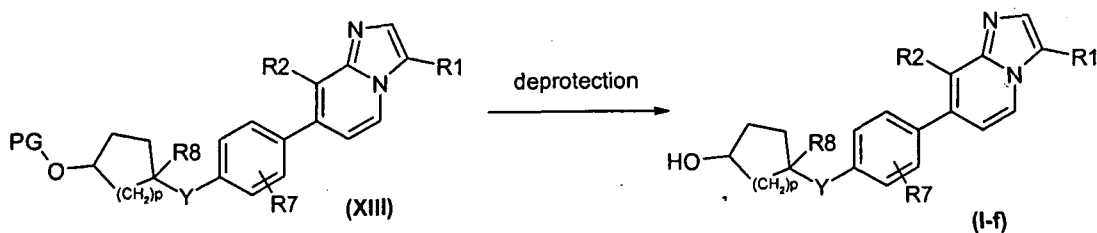
Reaction Scheme 9



Experimental procedure 10

Alternatively, final compounds according to Formula (I-f) can be prepared by art known procedures by treating an intermediate of Formula (XIII) under suitable deprotection conditions. In reaction scheme (10), all variables are defined as in Formula (I) and PG is a suitable protecting group for the alcohol function, such as for example trimethylsilyl and tert-butyldimethylsilyl.

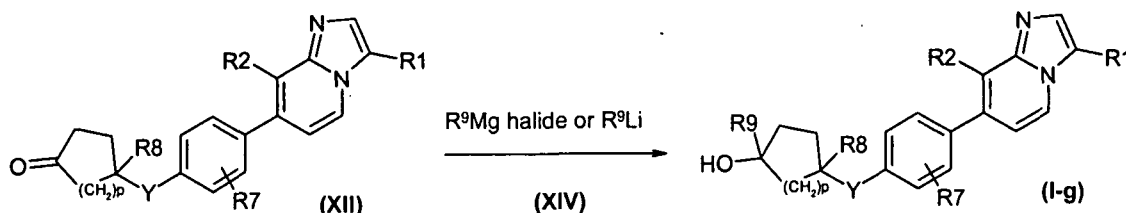
Reaction Scheme 10



PG = Protecting group (i.e. alkylsilylether)

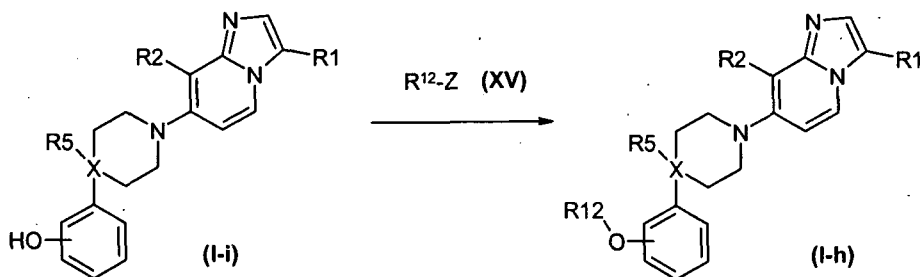
Experimental procedure 11

The final compounds according to Formula (I-g) can be prepared by art known procedures by reacting an organometallic compound of Formula (XIV) with an intermediate compound of Formula (XII) according to reaction scheme (11). The reaction can be carried out in an inert solvent such as, for example, THF, diethyl ether or dioxane. Typically, the mixture can be stirred for 1 up to 48 hours at a temperature between 0-100 °C. In reaction scheme (11), all variables are defined as in Formula (I).

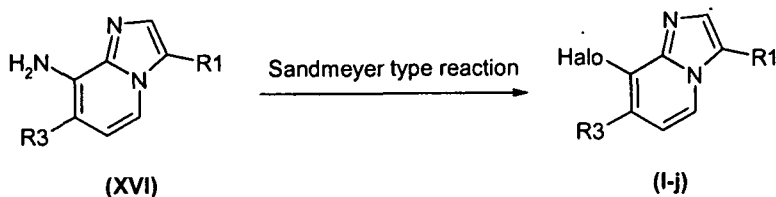
Reaction Scheme 11Experimental procedure 12

5 The final compounds according to Formula (I-h) can be prepared by art known procedures by treating final compounds of Formula (I-i) with an intermediate compound of Formula (XV). The reaction can be carried out in an inert solvent such as DMF, with an alkylating reagent such as iodomethane in presence of a base such as for example potassium carbonate under thermal conditions such as microwave irradiation
10 at 150 °C for 10 min.

 Likewise, final compounds of Formula (I-h) can be prepared according to the experimental procedure (2). In reaction scheme (12), all variables are defined as in Formula (I) and Z is a suitable leaving group in alkylation reactions such as for example halo, triflate, 4-methylphenylsulfonyl, methylsulfonyl and R¹² is C₁₋₃alkyl or
15 mono- or polyhaloC₁₋₃alkyl.

Reaction Scheme 12Experimental procedure 13

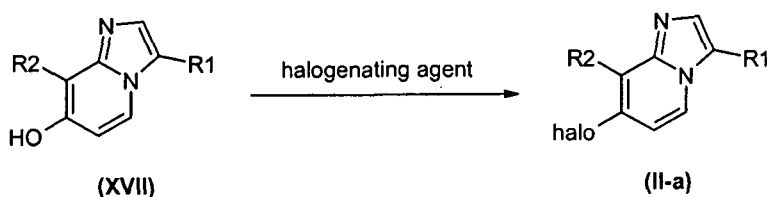
20 The final compounds according to Formula (I-j) can be prepared by art known procedures from intermediate compounds of Formula (XVI) via a Sandmeyer type reaction applying methods known by the person skilled in the art. In reaction scheme (13), all variables are defined as in Formula (I) and halo- may be chloro-, bromo- or iodo-.

Reaction Scheme 13

The transformation of functional groups present in the final compounds according to Formula (I) into other functional groups can be performed by synthesis methods well known to a person skilled in the art. For example, compounds of Formula (I) that contain an ester can be hydrolysed following art known procedures.

B. Preparation of the intermediate compoundsExperimental procedure 14

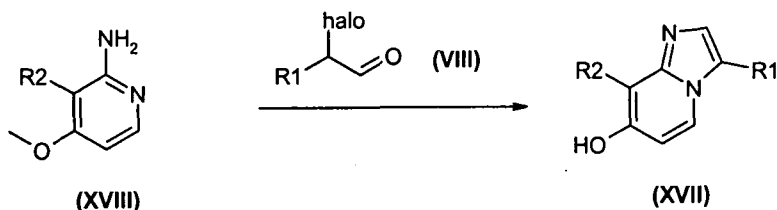
Intermediate compounds of Formula (II) wherein W represents halo, hereby named (II-a), can be prepared by reacting an intermediate compound of Formula (XVII) with a suitable halogenating agent such as, for example, phosphorus(V) oxychloride, a reaction that is performed in a suitable reaction-inert solvent 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 hour. In reaction scheme (14), all variables are defined as in Formula (I) and halo- may be chloro-, bromo- or iodo-.

Reaction Scheme 14Experimental procedure 15

Intermediate compounds of Formula (XVII) can be prepared by reacting an intermediate of Formula (XVIII) with an intermediate compound of Formula (VIII) according to reaction scheme (15). 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 (15), all variables are defined as in Formula (I).

Reaction Scheme 15

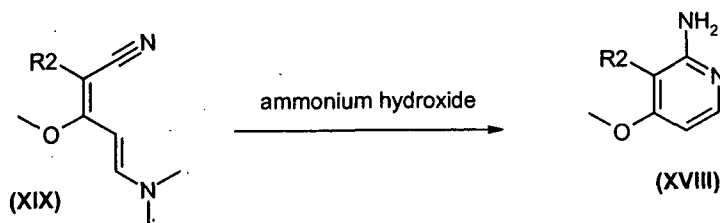


5

Experimental procedure 16

Intermediate compounds of Formula (XVIII) can be prepared by reacting an intermediate compound of Formula (XIX) 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 hours. In reaction scheme (16), R² is defined as in Formula (I).

Reaction Scheme 16



Experimental procedure 17

Intermediate compounds of Formula (XIX) can be prepared by reacting an intermediate of Formula (XX) with *N,N*-dimethylformamide dimethyl acetal according to reaction scheme (17). 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 at reflux for 2 hours. In reaction scheme (17), R² is defined as in Formula (I).

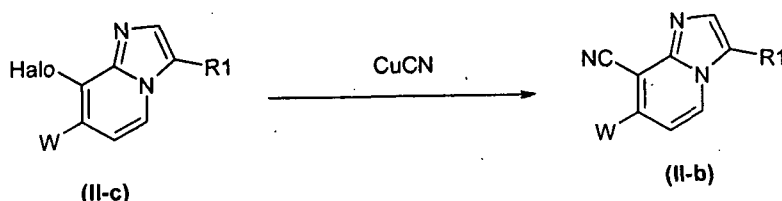
20

Reaction Scheme 17

Intermediate compounds of Formula (XX) 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. Thus for example intermediate compounds of Formula (XX) where R^2 = halo, can be prepared according to the procedure described in *Chemische Berichte* (1976), 109(8), 2908-13.

Experimental procedure 18

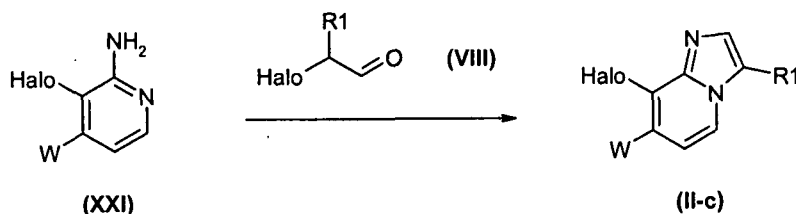
Intermediate compounds of Formula (II) wherein R^2 is cyano, hereby named (II-b), can be prepared by art known procedures from an intermediate of Formula (II) wherein R^2 is halo, hereby named (II-c), by treatment with Copper cyanide. This reaction is performed in a suitable reaction-inert solvent such as, for example, acetonitrile under microwave irradiation, for example, heating the reaction mixture for example at 160 °C for 30 minutes. In reaction scheme (18), all variables are defined as in Formula (I), halo- may be chloro-, bromo- or iodo- and W is as defined in Formula (II).

Reaction Scheme 18Experimental procedure 19

Intermediate compounds of Formula (II) wherein R^2 is halo, hereby named (II-c) can be prepared by reacting an intermediate of Formula (XXI) with an intermediate compound of Formula (VIII) according to reaction scheme (19). 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 (19), all variables are defined as in Formula (I) and W is defined as in Formula (II).

Reaction Scheme 19



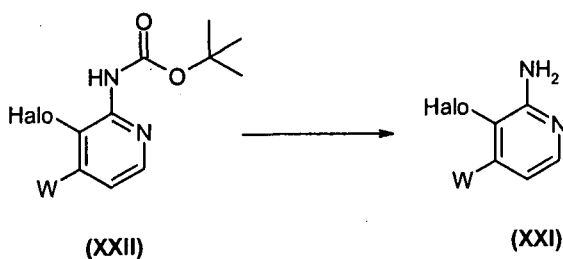
5

Experimental procedure 20

Intermediate compounds of Formula (XXI) can be prepared by treating an intermediate of Formula (XXII) with an acid such as for example trifluoroacetic acid according to reaction scheme (20). 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 hours. In reaction scheme (20), all variables are defined as in Formula (I), halo- may be chloro-, bromo- or iodo- and W is as defined in Formula (II).

10

Reaction Scheme 20



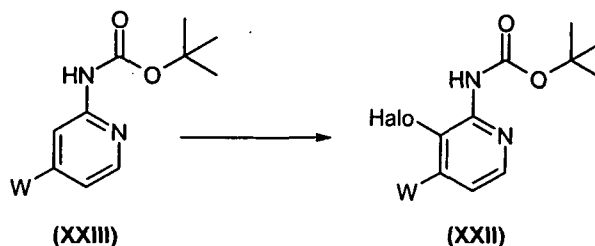
15

Experimental procedure 21

Intermediate compounds of Formula (XXII) can be prepared by reacting intermediate compound of Formula (XXIII) with a strong base such as for example butyllithium and further treatment with a halogenating agent such as for example iodine according to reaction scheme (21). 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 hours. In reaction scheme (21), halo- may be chloro-, bromo- or iodo- and W is as defined in Formula (II).

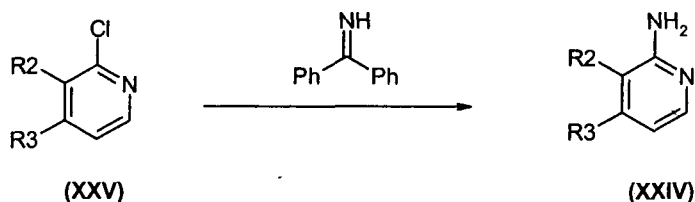
20

25

Reaction Scheme 21Experimental procedure 22

5 Intermediate compounds according to Formula (XXIV) can be prepared by reacting an intermediate compound of Formula (XXV) with diphenylmethanimine according to reaction scheme (22), 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

10 suitable period of time that allows the completion of the reaction, for example at 100 °C for 16 hours in a sealed tube. In reaction scheme (22), all variables are defined as in Formula (I).

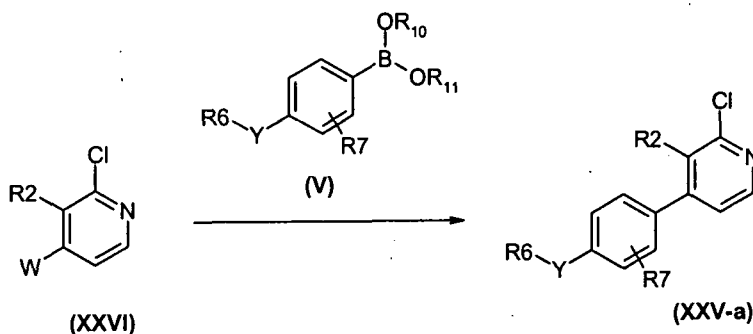
Reaction Scheme 22Experimental procedure 23

20 Intermediate compounds of Formula (XXV) wherein R³ is a radical of Formula (b) defined as in Formula (I), hereby named (XXV-a), can be prepared by reacting an intermediate compound of Formula (XXVI) with a compound of Formula (V) according to reaction scheme (23), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, 1,4-dioxane or mixtures of inert solvents such as, for example, 1,4-dioxane/DMF, in the presence of a suitable base, such as, for example,

25 aqueous NaHCO₃ or Na₂CO₃, a Pd-complex catalyst such as, for example, Pd(PPh₃)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 (23) all

variables are defined as in Formula (I) and W is as defined in Formula (II). R¹⁰ and R¹¹ are as defined in Formula (V).

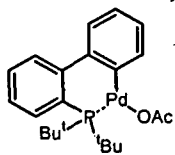
Reaction Scheme 23



5

Experimental procedure 24

Intermediate compounds according to Formula (XXV) wherein R³ is a radical of Formula (a) defined as in Formula (I) wherein n is 0, hereby named (XXV-b), can be prepared by reacting an intermediate compound of Formula (XXVI) with a compound of Formula (IV) according to reaction scheme (24), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, 1,4-dioxane, in the presence of a suitable base, such as, for example, K₃PO₄, a Pd-complex catalyst such as, for example,



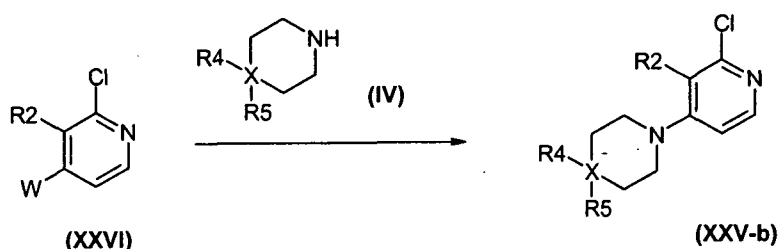
, under thermal conditions such as, for example, heating the reaction mixture for example at 80 °C for 12 hours. In reaction scheme (24), all variables are defined as in Formula (I) and W is a suitable group for Pd-mediated coupling with amines, such as, for example, halo.

Alternatively, compounds according to Formula (XXV-b) can be prepared by reacting an intermediate compound of Formula (XXVI) with a compound of Formula (IV) according to reaction scheme (2), a reaction that is performed in a suitable reaction-inert solvent, such as, for example, 1,2-dimethoxyethane or acetonitrile, in the presence of a suitable base, such as, for example, Cs₂CO₃ or *N,N*-diisopropylethylamine, under thermal conditions such as, for example, heating the reaction mixture for example at 180 °C under microwave irradiation for 45 minutes.

Alternatively, compounds according to Formula (XXV-b) can be prepared by reacting an intermediate compound of Formula (XXVI) with a compound of Formula (IV) according to reaction scheme (24), 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 hours in a sealed tube.

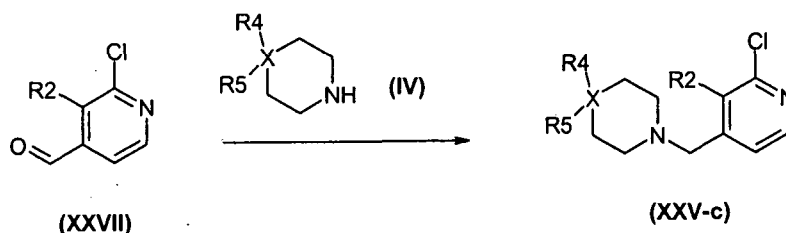
Reaction Scheme 24



Experimental procedure 25

Intermediate compounds according to Formula (XXV) wherein R³ is a radical of Formula (a) defined as in Formula (I) wherein n is 1, hereby named (XXV-c) can be prepared by reacting an intermediate of Formula (XXVII) with an intermediate of Formula (IV) under reductive amination conditions that are known by those skilled in the art. This is illustrated in reaction scheme (25) The reaction may be performed, for example, in the presence of sodium triacetoxyborohydride in a suitable reaction-inert solvent such as, for example, 1,2-dichloroethane, at a suitable temperature, typically at room temperature, for a suitable period of time that allows the completion of the reaction. In reaction scheme (25) all variables are defined as in Formula (I).

Reaction Scheme 25

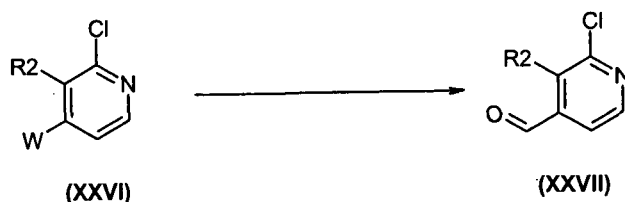


Experimental procedure 26

Intermediate compounds according to Formula (XXVII) can be prepared by reacting an intermediate of Formula (XXVI) using conditions that are known by those

skilled in the art. This is illustrated in reaction scheme (26) wherein all variables are defined as mentioned hereabove. The reaction may be performed, for example, by first converting the aryl halide of Formula (XXVI), where W = halo, into an aryl metal derivative, where W = metal; where the metal may be lithium, magnesium, boron or zinc followed by reaction with an appropriate carbonyl source, such as for example DMF. Reaction methods accomplishing these reactions are well known to those skilled in the art and include halogen-metal exchange with a Grignard reagent such as isopropylmagnesium chloride or with a strong base such as for example BuLi in a suitable reaction inert solvent such as THF, diethyl ether or toluene, preferably THF at a temperature between -78°C and room temperature, followed by the reaction with a carbonyl source such as for example DMF at temperatures between -78°C and 100 °C.

Reaction Scheme 26



Experimental procedure 27

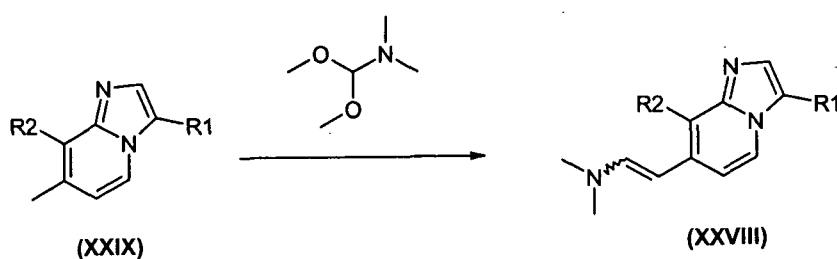
Intermediate compounds according to Formula (IX) can be prepared by reacting an intermediate of Formula (XXVIII) with at least a stoichiometric amount of oxidant, under conditions that are known by those skilled in the art. The reaction can be conducted in a suitable reaction inert solvent such as for example THF in the presence of water. Preferably, the reaction is conducted at a moderate high temperature such as for example from room temperature to 50 °C. The reaction is continued until it is substantially completed which typically occurs within about 0.5 to 5 hours. Suitable oxidants are well known in the art and include, for example, sodium periodate (NaIO₄). In reaction scheme (27) all variables are defined as in Formula (I).

Reaction Scheme 27



Experimental procedure 28

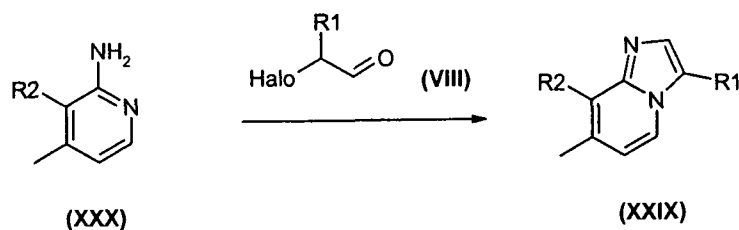
Intermediate compounds according to Formula (XXVIII) can be prepared by reacting an intermediate of Formula (XXIX) with at least a stoichiometric amount of dimethoxymethyl-dimethyl-amine [C.A.S. 4637-24-5]. The reaction is preferably conducted in a reaction inert solvent such as for example 1,4-dioxane at a moderately high temperature such as for example from about 100 °C to 160 °C. This is illustrated in reaction scheme (28) wherein all variables are defined as in Formula (I).

Reaction Scheme 28

10

Experimental procedure 29

Intermediate compounds of Formula (XXIX), can be prepared by reacting an intermediate of Formula (XXX) with an intermediate of Formula (VIII) according to reaction scheme (29). 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 (29), all variables are defined as in Formula (I).

Reaction Scheme 29

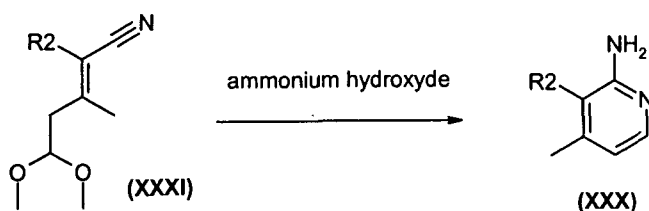
20

Experimental procedure 30

Intermediate compounds of Formula (XXX) can be prepared by reacting an intermediate compound of Formula (XXXI) with an ammonia source such as for example ammonium hydroxide under thermal conditions such as, for example, heating

the reaction mixture at reflux for 3 hours. In reaction scheme (30), R² is defined as in Formula (I).

Reaction Scheme 30

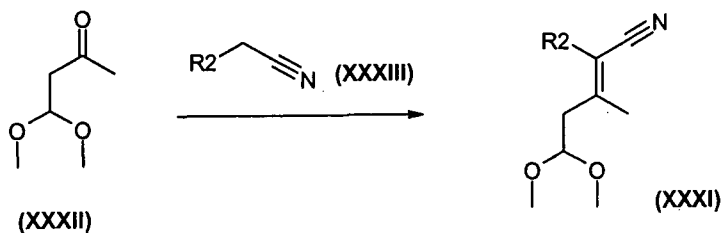


5

Experimental procedure 31

Intermediate compounds according to Formula (XXXI) can be prepared by reacting an intermediate of Formula (XXXII) with an intermediate of Formula (XXXIII) under Knoevenagel conditions that are known by those skilled in the art. This is illustrated in reaction scheme 31 wherein all variables are defined as mentioned hereabove.

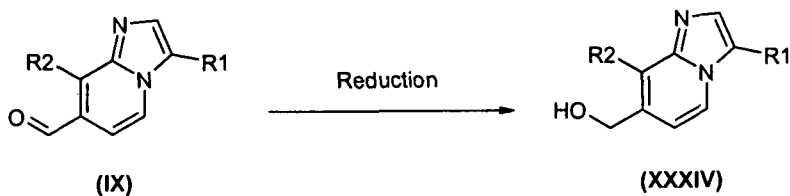
Reaction Scheme 31



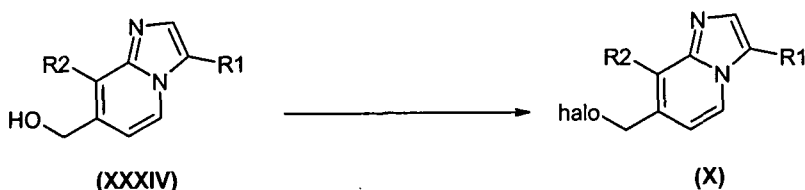
Experimental procedure 32

Intermediate compounds of Formula (XXXIV) can be prepared by reduction of the carbonyl function present in intermediate compound of Formula (IX) under reduction conditions that are well known by those skilled in the art. This is illustrated in reaction scheme (32) wherein all variables are defined as in Formula (I). The reaction may be performed, for example, in the presence of sodium triacetoxy borohydride in a suitable reaction-inert solvent such as, for example, dichloroethane, at a suitable temperature, typically at room temperature, for a suitable period of time that allows the completion of the reaction.

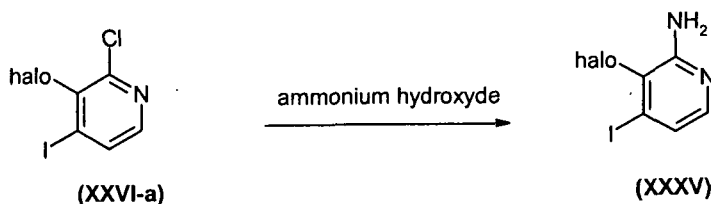
20

Reaction Scheme 32Experimental procedure 33

- 5 Intermediate compounds according to Formula (X) can be prepared from an intermediate of Formula (XXXIV) by conversion of the hydroxy group present in the structure into a halogen under reaction conditions that are known by those skilled in the art. This is illustrated in reaction scheme (33) wherein all variables are defined as mentioned hereabove and halo is chloro, bromo or iodo. The reaction may be performed, for example, in the presence of a halogenating reagent such as for example P(O)Br₃ in a suitable reaction-inert solvent such as, for example, DCM or DMF or mixtures of both, at a suitable temperature, typically at room temperature, for a suitable period of time that allows the completion of the reaction.

Reaction Scheme 33Experimental procedure 34

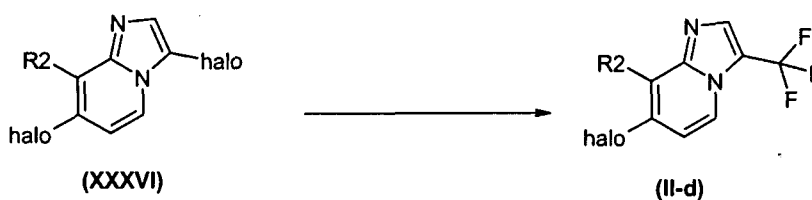
- 20 Intermediate compounds of Formula (XXXV) can be prepared by reacting an intermediate of Formula (XXVI), wherein R² is halo and W is iodine, hereby named (XXVI-a), with ammonium hydroxide according to reaction scheme (34). This reaction is performed under thermal conditions such as, for example, heating the reaction mixture for example at 130 °C for 12 hours into a sealed vessel.

Reaction Scheme 34

Experimental procedure 35

Intermediate compounds of Formula (II) wherein R¹ is trifluoromethyl and W is halo, hereby named (II-d) can be prepared by reacting an intermediate of Formula (XXXVI) with a suitable trifluoromethylating agent, such as for example fluorosulfonyl(difluoro)acetic acid methyl ester, according to reaction scheme (35). This reaction is performed in a suitable reaction-inert solvent such as, for example, *N,N*-dimethylformamide in the presence of a suitable coupling agent such as for example, copper iodide, under thermal conditions such as, for example, heating the reaction mixture for example at 160 °C under microwave irradiation for 45 minutes. In reaction scheme (35), all variables are defined as in Formula (I).

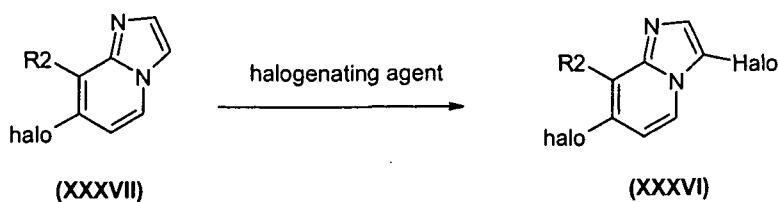
Reaction Scheme 35



Experimental procedure 36

Intermediate compounds of Formula (XXXVI) can be prepared by reacting an intermediate of Formula (XXXVII) with a suitable halogenating reagent as, for example, *N*-iodosuccinimide according to reaction scheme (36). This reaction is performed in a suitable reaction-inert solvent such as, for example, acetonitrile stirring the mixture for example at room temperature for 3 hours. In reaction scheme (36), all variables are defined as in Formula (I).

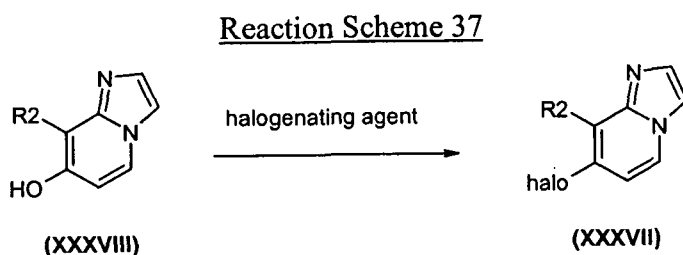
Reaction Scheme 36



Experimental procedure 37

Intermediate compounds of Formula (XXXVII) can be prepared by reacting an intermediate compound of Formula (XXXVIII) 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 hour. In reaction scheme (37), all variables are defined as in Formula (I) and halo- may be chloro-, bromo- or iodo-.

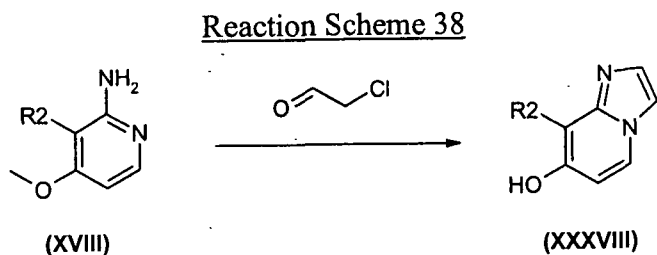
10



Experimental procedure 38

Intermediate compounds of Formula (XXXVIII) can be prepared by reacting an intermediate of Formula (XVIII) with chloroacetaldehyde according to reaction scheme (38). 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 (38), R² is defined as in Formula (I).

20



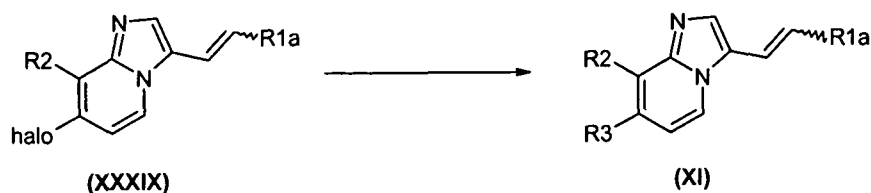
Experimental procedure 39

Intermediate compounds of Formula (XI) can be prepared by reacting an intermediate compound of Formula (XXXIX) as defined in experimental procedures 2

25

and 3. All variables are defined as in Formula (I) and halo- may be chloro-, bromo- or iodo- and R^{1a} is C₁₋₄alkyl or C₁₋₄alkyl substituted with trifluoromethyl.

Reaction Scheme 39

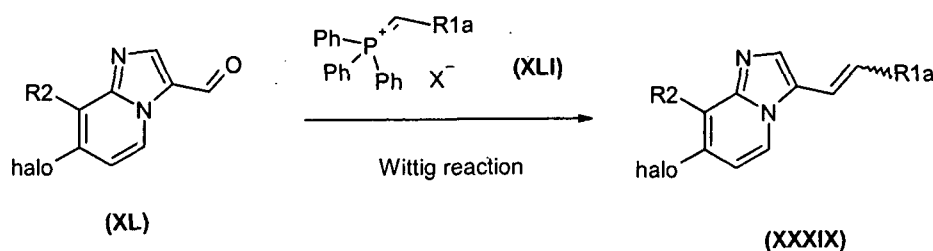


5

Experimental procedure 40

Intermediate compounds of Formula (XXXIX) can be prepared by reacting an intermediate compound of Formula (XL) with intermediate of Formula (XLI) under standard Wittig reaction conditions. This reaction is performed in a suitable reaction-inert solvent such as, for example, THF at a temperature between -78 °C and room temperature in the presence of a Wittig-type reagent of formula (XLI), for example prepared in situ from alkyltriphenylphosphonium halide and a base such as for example lithium bis(trimethylsilyl)amide for a suitable period of time that allows the completion of the reaction, such as for example 1 hour. In reaction scheme (40), all variables are defined as in Formula (I) and halo- may be chloro-, bromo- or iodo- and R^{1a} is C₁₋₄alkyl or C₁₋₄alkyl substituted with trifluoromethyl.

Reaction Scheme 40



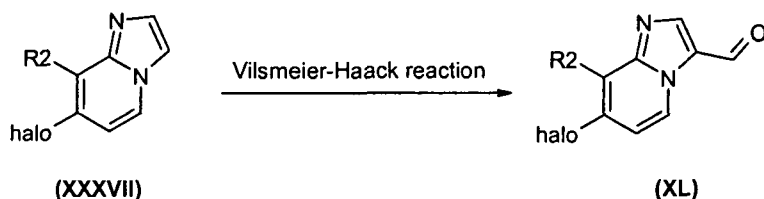
Experimental procedure 41

Intermediate compounds of Formula (XL) can be prepared by reacting an intermediate compound of Formula (XXXVII) under standard Vilsmeier-Haack reaction conditions such as, for example, DMF and phosphoryl chloride (POCl₃) from room temperature to 140 °C under classical thermal heating or under microwave irradiation, for a suitable period of time that allows the completion of the reaction, as

25

for example 1 hour. In reaction scheme (41), R^2 is defined as in Formula (I) and halo- may be chloro-, bromo- or iodo-.

Reaction Scheme 41

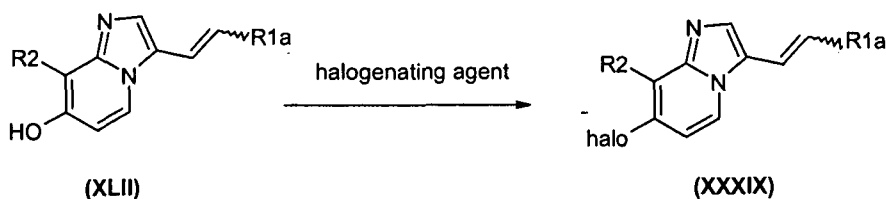


5

Experimental procedure 42

Alternatively, intermediate compounds of Formula (XXXIX) can be prepared by reacting an intermediate of Formula (XLII) with a suitable halogenating agent such as, for example, phosphorus(V) oxychloride. This reaction is performed at a moderately elevated temperature such as, for example, 130 °C for 15 minutes under microwave irradiation. In reaction scheme (42), all variables are defined as in Formula (I) and halo- may be chloro-, bromo- or iodo- and R^{1a} is C₁₋₄alkyl or C₁₋₄alkyl substituted with trifluoromethyl.

Reaction Scheme 42

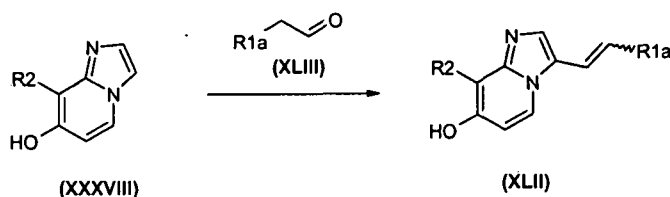


15

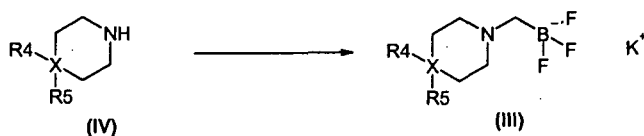
Experimental procedure 43

Intermediate compounds of Formula (XLII) can be prepared by reacting an intermediate compound of Formula (XXXVIII) with an aldehyde of Formula (XLIII) according to reaction scheme (43). The reaction is performed in acid media such as for example acetic acid media, at a moderately high temperature, as for example 155 °C, under microwave irradiation for a suitable period of time, as for example 1 h. In reaction scheme (43), all variables are defined as in Formula (I) and R^{1a} is C₁₋₄alkyl or C₁₋₄alkyl substituted with trifluoromethyl..

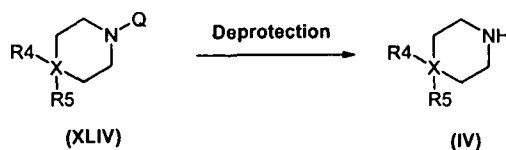
20

Reaction Scheme 43Experimental procedure 44

- 5 Intermediate compounds of Formula (III) can be prepared by reacting an intermediate of Formula (IV) with potassium (bromomethyl)trifluoroborate according to reaction scheme (44). This reaction is performed in a suitable reaction-inert solvent such as, for example, acetonitrile under thermal conditions such as, for example, heating the reaction mixture for example at 80 °C for 2 hours. In reaction scheme (44),
- 10 all variables are defined as in Formula (I).

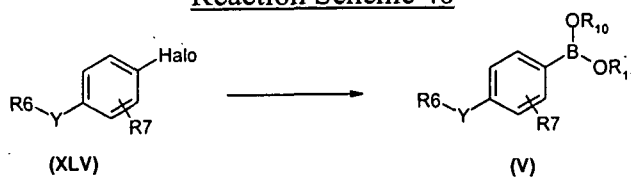
Reaction Scheme 44Experimental procedure 45

- 15 Intermediate compounds of Formula (IV) can be prepared by deprotection of the nitrogen atom in an intermediate compound of formula (XLIV), wherein Q represents a suitable protecting group for the nitrogen atom of a derivative, such as for example tert-butoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, benzyl and methyl, according to reaction scheme (45) applying art known procedures. For example, when
- 20 Q represents benzyl, then the deprotection reaction may be performed in a suitable reaction inert solvent, such as for example an alcohol, i.e. methanol, and 1,4-cyclohexadiene, in the presence of a suitable catalyst, such as for example palladium on charcoal, at a moderately high temperature such as, for example, 100 °C into a sealed vessel. Alternatively, when Q represents an alkyloxycarbonyl group, the deprotection
- 25 reaction can be performed by reaction with a suitable acid, such as for example hydrochloric acid, in a suitable reaction-inert solvent, such as for example 1,4-dioxane at a moderately high temperature, such as for example reflux temperature. In reaction scheme (45), all variables are defined as in formula (I).

Reaction Scheme 45Experimental procedure 46

5 Intermediate compounds of Formula (V) can be prepared by art known procedures by reacting an intermediate of Formula (XLV) 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)ferrocene]dichloropalladium(II) in a inert solvent such as, for example, dichloromethane, in the presence of a suitable salt
10 such as, for example, potassium acetate at moderately high temperature such as, for example, 110 °C for as, for example, 16 hours.

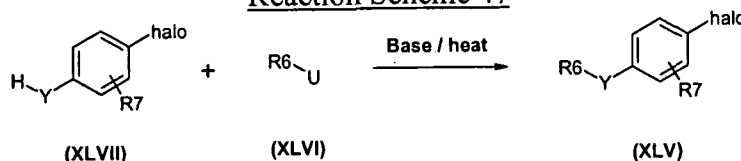
Additionally, compounds of Formula (V) can be prepared from compounds of Formula (XLV) by art known procedures of halogen-metal exchange and subsequent reaction with an appropriate boron source. Thus, for example, reaction of an
15 intermediate compound of Formula (XLV) with an organolithium compound such as, for example, *n*-butyllithium at a moderately low temperature such as, for example, -40 °C in an inert solvent such as, for example, THF followed by subsequent reaction with an appropriate boron source such as, for example, trimethoxyborane. In reaction scheme (46), all variables are defined as in Formula (I) and R¹⁰ and R¹¹ are defined as
20 in Formula (V).

Reaction Scheme 46Experimental procedure 47

25 Intermediate compounds of Formula (XLV) can be prepared by nucleophilic substitution art known procedures by reacting a halogenated intermediate of Formula (XLVI) with a suitable intermediate of Formula (XLVII) according to reaction scheme (47). This reaction is performed in the presence of a suitable base such as, for example, sodium hydride in a inert solvent such as, for example, DMF, at moderately high

temperature such as, for example, 180 °C, either under classical or microwave irradiation heating, for a suitable period of time to ensure completion of the reaction. In reaction scheme (47), all variables are defined as in Formula (I), halo may be chloro, bromo or iodo and U is a suitable leaving group in nucleophilic substitution reactions such as a halogen or nitro.

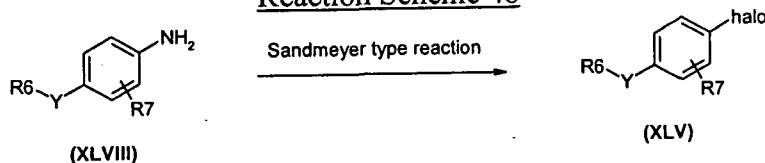
Reaction Scheme 47



Experimental procedure 48

Additionally, compounds of Formula (XLV) can be prepared by art known procedures from intermediate aniline-like compounds of Formula (XLVIII) via a Sandmeyer type reaction following reaction condition well known by the person skilled in the art. In reaction scheme (48), all variables are defined as in Formula (I), halo may be chloro, bromo or iodo.

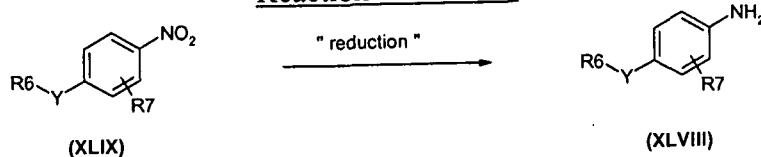
Reaction Scheme 48



Experimental procedure 49

Intermediate compounds of Formula (XLVIII) can be prepared from intermediate nitro compounds of Formula (XLIX) via reduction of the nitro group to the amino function by art known procedures, such as catalytic hydrogenation or the use of tin(II) chloride dihydrate as a reducing agent. In reaction scheme (49), all variables are defined as in Formula (I).

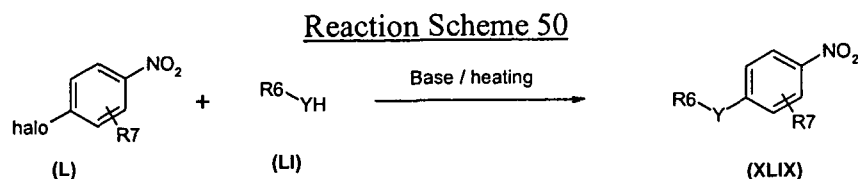
Reaction Scheme 49



Experimental procedure 50

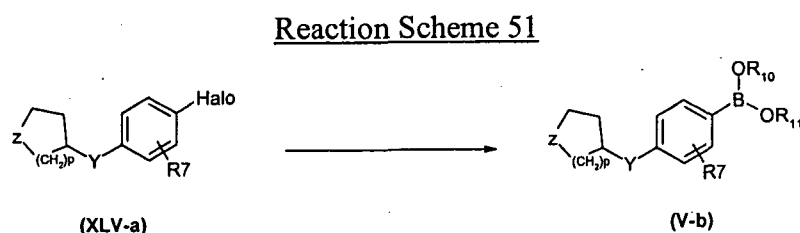
Intermediate compounds of Formula (XLIX) can be prepared by art known procedures by reacting an intermediate of Formula (L) with a suitable intermediate of

Formula (LI) according to reaction scheme (50), a reaction that is performed in the presence of a suitable base such as, for example, cesium carbonate in an inert solvent such as, for example, tetrahydrofuran, heating at an appropriate temperature and for a suitable period of time that allows the completion of the reaction, either under
 5 traditional heating or under microwave irradiation. In reaction scheme (50), all variables are defined as in Formula (I) and Y is O or NH.



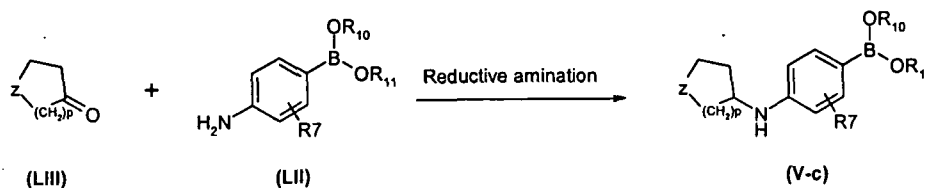
10 Experimental procedure 51

Intermediate compounds of Formula (V) wherein R^6 is a cyclic radical of Formula (k), hereby named (V-b) can be prepared by art known procedures by reacting an intermediate of Formula (XLV) wherein R^6 is a cyclic radical of formula (k), hereby named (XLV-a) with a suitable boron source according to reaction scheme (51), a
 15 reaction that is performed following art know conditions such as the ones cited above in reaction scheme (46).

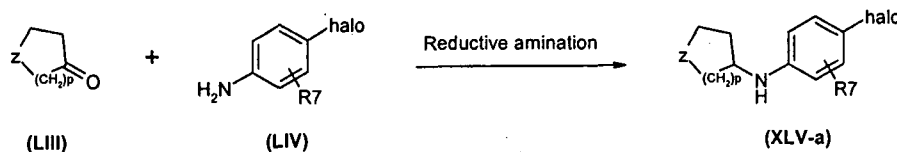


20 Experimental procedure 52

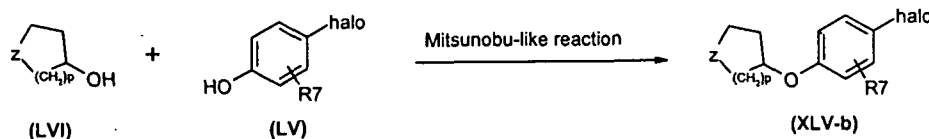
Additionally, compounds of Formula (V), wherein R^6 is a cyclic radical of Formula (k) and Y is NH hereby named (V-c) can be prepared by reacting an intermediate compound of Formula (LII) with a cyclic ketone derivative of Formula (LIII) under reductive amination conditions that are known by those skilled in the art,
 25 according to reaction scheme (52), a reaction that is performed using a reduction agent such as for example, sodium triacetoxy borohydride in a suitable reaction-inert solvent, such as for example 1,2-dichloroethane, at a suitable temperature, typically room temperature, for a suitable period of time that allows the completion of the reaction. In reaction scheme (52) all variables are defined as in Formula (I) and R^{10} and R^{11} are
 30 defined as in Formula (V).

Reaction Scheme 52Experimental procedure 53

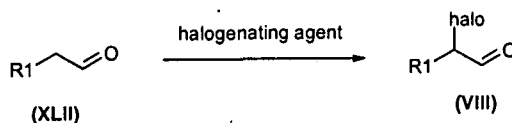
5 Intermediate compounds of Formula (XLV) wherein R⁶ is a cyclic radical of formula (k) and Y is NH, hereby named (XLV-a) can be prepared by art known procedures by reacting an aniline intermediate of Formula (LIV) with a cyclic ketone derivative of Formula (LIII), under reductive amination conditions that are known by those skilled in the art, according to reaction scheme (53), a reaction that is performed
 10 using a reductive agent such as for example, sodium triacetoxy borohydride in a suitable reaction-inert solvent, such as for example 1,2-dichloroethane, at a suitable temperature, typically room temperature, for a suitable period of time that allows the completion of the reaction. In reaction scheme (53), all variables are defined as in Formula (I), R¹⁰ and R¹¹ are defined as in Formula (V) and halo- may be chloro-,
 15 bromo- or iodo-.

Reaction Scheme 53Experimental procedure 54

20 Intermediate compounds of Formula (XLV) wherein R⁶ is a cyclic radical of formula (k) and Y is O, hereby named (XLV-b) can be prepared by art known procedures by reacting a phenol intermediate of Formula (LV) with a cyclic alcohol of Formula (LVI) according to reaction scheme (54), a reaction that is performed in the presence of a phosphine, such as for example triphenylphosphine and a suitable
 25 coupling agent for Mitsunobu-like couplings, such as for example di-*tert*-butyl azadicarboxylate in a inert solvent such as, for example, dichloromethane, at moderately low temperature such as, for example, 25 °C for example 2 hours. In reaction scheme (54), all variables are defined as in Formula (I) and halo- may be chloro-, bromo- or iodo-.

Reaction Scheme 54Experimental procedure 55

Intermediate compounds of Formula (VIII) can be prepared by reacting an intermediate compound of Formula (XLII) with a 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 (55), all variables are defined as in Formula (I).

Reaction Scheme 55

The starting materials according to Formulas (V-a), (XIV), (XV), (XXIII), (XXVI), (XXXII), (XXXIII), (XLII), (XLIII), (XLIV), (XLVI), (L), (LI), (LII) (LIII) (LIV) (LV) and (LVI) are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known by those skilled in the art.

Thus intermediate compounds of Formula (IV) can be prepared as for example as it is described in *Organic Letters* **2007**, 9(8), 1505; *Tetrahedron Letters* **2000**, 41(46), 8853; *Toso Kenkyu Hokoku* **1999**, 43, 37, or are commercially available.

Thus intermediate compounds of Formula (VIII) can be prepared as for example as it is described in *J. Org. Chem.* **1966**, 31, or are commercially available.

Thus intermediate compounds of Formula (XIX) can be prepared as for example as it is described in *Synthesis* (1984), (9), 768-70; *Heterocycles* **1986**, 24(8), 2111 or are commercially available.

Thus intermediate compounds of Formula (XXIII) can be prepared as for example as it is described in WO 2008051197 A2 or are commercially available.

Thus intermediate compounds of Formula (XLII) can be prepared as for example as it is described in *Journal of the American Chemical Society* **1987**, 109(25), 7714 and *Synthetic Communications* **2007**, 37(4), 599-605.

Thus intermediate compounds of Formula, (LIII), (LIV), (LV) and (LVI) can be prepared following procedures generally known by those skilled in the art, thus for example can be prepared as it is described in WO 2003029209-A2. Additionally some of these intermediates are commercially available.

Pharmacology

10 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
15 an agonist of mGluR2, the compounds of this invention increase the mGluR2 response. The compounds provided in this invention are expected to have their effect at mGluR2 by virtue of their ability to increase the response of such receptors to glutamate or mGluR2 agonists, enhancing the response of the receptor. Hence, the present invention relates to a compound according to the present invention for use as a medicine, as well
20 as to the use of a compound according to the invention or a pharmaceutical composition according to the invention for the manufacture of a medicament for treating or preventing, in particular treating, a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of allosteric modulators of mGluR2, in particular positive
25 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
30 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
35 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),
5 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

10 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,
15 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.

20 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.

25 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.

30 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.

5 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
10 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.

15 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.

20 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.

25

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
30 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
5 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
10 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.

15

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 %
20 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
25 diseases or conditions for which compounds of Formula (I) or the other drugs may have utility as well as to the use of such a composition for the manufacture of a medicament. The present invention also relates to a combination of a compound according to the present invention and a mGluR2 orthosteric agonist. The present invention also relates to such a combination for use as a medicine. The present invention also relates to a
30 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
35 effect of mGluR2 allosteric modulators, in particular positive mGluR2 allosteric

modulators.. The different drugs of such a combination or product may be combined in a single preparation together with pharmaceutically acceptable carriers or diluents, or they may each be present in a separate preparation together with pharmaceutically acceptable carriers or diluents.

5

The following examples are intended to illustrate but not to limit the scope of the present invention.

Chemistry

10

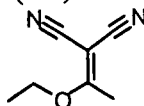
Several methods for preparing the compounds of this invention are illustrated in the following Examples. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification.

Hereinafter, "THF" means tetrahydrofuran; "DMF" means *N,N*-dimethylformamide; "EtOAc" means ethyl acetate; "DCM" means dichloromethane; "BINAP" means 1,1'-[1,1'-binaphthalene]-2,2'-diylbis[1,1-diphenyl-phosphine]; "DBU" means 1,8-diaza-7-bicyclo[5.4.0]undecene; "NH₄OH" means ammonium hydroxide; "NaHCO₃" means sodium hydrogencarbonate; "Et₂O" means diethyl ether; "MgSO₄" means magnesium sulphate; "EtOH" means ethanol; "Na₂SO₄" means sodium sulphate; "CH₃CN" means acetonitrile; "NaH" means sodium hydride; "MeOH" means methanol; "NH₃" means ammonia; "Na₂S₂O₃" means sodium thiosulphate; "AcOH" means acetic acid; "Et₃N" means triethylamine; "NH₄Cl" means ammonium chloride; "K₂CO₃" means potassium carbonate; "Pd(PPh₃)₄" means tetrakis(triphenylphosphine)palladium(0); "r.t." means room temperature

Microwave assisted reactions were performed in a single-mode reactor: InitiatorTM Sixty EXP microwave reactor (Biotage AB), or in a multimode reactor: MicroSYNTH Labstation (Milestone, Inc.).

Description 1

30 2-(1-Ethoxy-ethylidene)-malononitrile (D1)



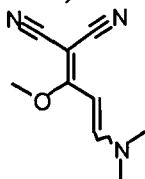
A mixture of malononitrile (17 g, 257.57 mmol) and triethylorthoacetate (45.95 g, 283.25 mmol) was heated at 95 °C for 1.5 h. The mixture was then evaporated *in vacuo*

to give a solid that was filtered off yielding 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.

5 Description 2

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



To a mixture of **D1** (34 g, 250 mmol) in methanol (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* yielding compound **D2** (16.2 g, 38%) as a red solid.

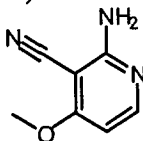
LCMS: MW (theor): 177; [MH⁺]: 178; RT (min): 2.25.

Compound **D2** is also commercially available CAS: 95689-38-6.

15

Description 3

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

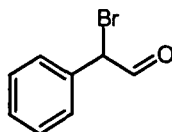


A mixture of **D2** (16 g, 90.39 mmol) in NH₄OH (100 ml, 30% in water) was heated at reflux for 3 h. After cooling in an ice bath a yellow solid precipitated. The solid was filtered off, washed with cold isopropanol and dried *in vacuo* to yield compound **D3** (10 g, 76%) as a white solid.

LCMS: MW (theor): 149; [MH⁺]: 150; RT (min): 0.41.

Compound **D3** is also commercially available CAS: 98651-70-8.

25

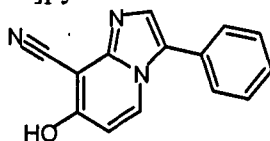
Description 4**Bromo-phenyl-acetaldehyde (D4)**

- 5 To a solution of phenylacetaldehyde (4.03 g, 33.5 mmol) in 1,4-dioxane (1 ml) cooled to 0 °C, was added bromine (1.80 ml, 35 mmol) dropwise over 15 min. The reaction mixture was further stirred at 0 °C for 10 min., allowed to warm to room temperature and then further stirred for 10 min. This mixture containing compound **D4** (yield assumed to be quantitative) was used in the next reaction step without further
- 10 purification.

Compound **D4** can also be prepared as described in: Bulletin of the Korean Chemical Society 1995, 16(4), 371-374.

Description 5

- 15 7-Hydroxy-3-phenyl-imidazo[1,2-a]pyridine-8-carbonitrile (D5)

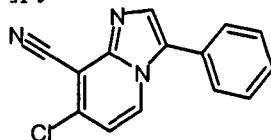


- A mixture of compounds **D3** (2 g, 13.41 mmol) and **D4** (6.69g, 33.5 mmol) in EtOH (10 ml) was subjected to microwave heating at 160 °C for 45 min. The reaction mixture was cooled to room temperature and then diluted with DCM, causing a solid to
- 20 precipitate. The solid obtained was filtered off, washed thoroughly with DCM and dried *in vacuo* to yield compound **D5** (2.65 g, 84%) as a pale yellow solid.

LCMS: MW (theor): 235; [MH⁺]: 236; RT (min): 1.63 (Method 21).

Description 6

- 25 7-Chloro-3-phenyl-imidazo[1,2-a]pyridine-8-carbonitrile (D6)



- A mixture of compound **D5** (2.3 g, 9.77 mmol) and phosphorus(V) oxychloride (50 ml) was heated at 120 °C for 5 h. After cooling to room temperature the solvents were evaporated *in vacuo*. The residue thus obtained was carefully poured into a mixture of
- 30 crushed ice and NaHCO₃ (aqueous sat. solution). Then EtOAc was added and the

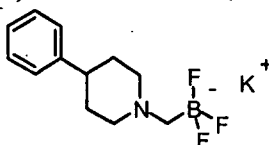
mixture was stirred for 2 h. until complete hydrolysis of the remaining phosphorus oxychloride had occurred. The organic layer was then separated, washed with brine, dried (Na_2SO_4) and the solvent evaporated *in vacuo* to give a residue that forms a precipitate upon the addition of Et_2O . The solid was filtered off and dried *in vacuo* to yield compound **D6** (0.82 g, 33%) as yellow solid.

LCMS: MW (theor): 253; $[\text{MH}^+]$: 254; RT (min): 3.44 (Method 1).

MP: decomposed.

Description 7

10 Potassium (phenylpiperidylmethyl)trifluoroborate (D7)

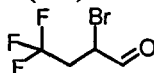


To a solution of potassium (bromomethyl)trifluoroborate (0.1 g, 0.5 mmol) in CH_3CN (1 ml) was added 4-phenylpiperidine (0.241 g, 1.5 mmol). The reaction mixture was heated at 80 °C for 2 h. After cooling, the solvent was evaporated *in vacuo* to give a residue that precipitated after treatment with Et_2O . The solid was filtered off and dried *in vacuo* to yield compound **D7** (0.108 g, 89%).

LCMS: MW (theor): 281; $[\text{M}]$: 242; RT (min): 2.64.

Description 8

20 2-Bromo-4,4,4-trifluoro-butylaldehyde (D8)

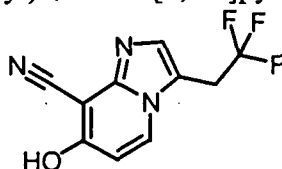


To a mixture of 4,4,4-trifluorobutylaldehyde (5 g, 39.68 mmol) in 1,4-dioxane (5 ml) cooled to 0 °C, was added bromine (2.24 ml, 43.65 mmol), dropwise. The reaction mixture was stirred at 0 °C for 2 h. The resulting reaction mixture was filtered through a pad of diatomaceous earth and the filtrate was washed with NaHCO_3 (aqueous sat. solution). The organic layer was separated, dried (MgSO_4) and evaporated *in vacuo* to yield compound **D8** (6.2 g, 76%) that was used in the next reaction step without further purification.

$^1\text{H-NMR}$ (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 9

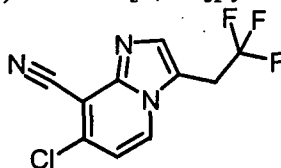
7-Hydroxy-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (D9)



- 5 A mixture of compounds **D3** (3.31 g, 22.19 mmol) and **D8** (6.2 g, 21.86 mmol, 72% purity, calculated by $^1\text{H-NMR}$) 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 Et₂O and a solid precipitated out. The solid thus obtained was filtered off, washed with EtOAc and dried *in vacuo* to yield compound **D9** (1 g, 18%).
- 10 LCMS: MW (theor): 241; [MH^+]: 242; RT (min): 1.06.

Description 10

7-Chloro-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (D10)



- 15 A mixture of compound **D9** (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 thus obtained was then treated with NaHCO₃ (aqueous sat. solution) and extracted with DCM. The organic layer was separated, dried (MgSO₄) and evaporated *in vacuo*. The crude product was
- 20 purified by column chromatography (silica gel; Et₂O as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **D10** (0.6 g, 56%) as yellow solid.

LCMS: MW (theor): 259; [MH^+]: 260; RT (min): 2.66 (Method 16).**Description 11**

2,4-Dibromo-nicotinonitrile (D11)



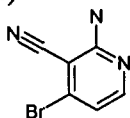
To a solution of commercially available 4-methoxy-2-oxo-1,2-dihydro-3-pyridinecarbonitrile (95.47 g, 333 mmol) [C.A.S. 21642-98-8] in acetonitrile (670 ml),

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 NaHCO₃ (aqueous sat. solution), dried (MgSO₄) and
5 evaporated *in vacuo*. The crude product thus obtained was triturated with diisopropyl ether to yield compound **D11** (34.5 g, 79%) as a white solid.

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

Description 12

10 2-Amino-4-bromo-nicotinonitrile (D12)

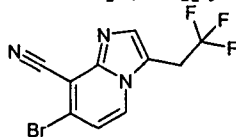


A mixture of compound **D11** (32 g, 122.2 mmol) in NH₄OH (200 ml) and THF (200 ml) was heated at 100 °C for 12 h. in a PARR pressure vessel. After cooling, EtOAc was added. The organic layer was separated, washed with brine, dried (Na₂SO₄) and
15 evaporated *in vacuo*. The residue thus obtained was triturated with DCM. The solid thus obtained was filtered off. The filtrate was evaporated *in vacuo* to yield compound **D12** (6.5 g, 26.8%) as a white solid.

LCMS: MW (theor): 197; [MH⁺]: 198; RT (min): 1.14 (Method 1).

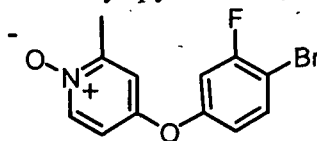
20 Description 13

7-Bromo-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (D13)



A mixture of compounds **D12** (2 g, 10.1 mmol) and **D8** (2.898 g, 14.14 mmol) in EtOH
25 (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 (MgSO₄) and evaporated *in vacuo*. The crude product thus obtained was triturated with diethylether
30 to yield compound **D13** (1.5 g, 48.8%)

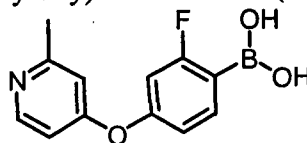
LCMS: MW (theor): 303; [MH⁺]: 304; RT (min): 2.48. (Method 14).

Description 14**4-(4-Bromo-3-fluorophenoxy)-2-methyl-pyridine *N*-oxide (D14)**

To a mixture of 4-bromo-3-fluorophenol (6 g, 31.41 mmol) in DMF (20 ml) was added
5 NaH (0.81 g, 56 mmol, 60% in mineral oil) at room temperature. The resulting reaction
mixture was stirred for 10 min., then, 4-nitro-2-picoline *N*-oxide (5.6 g, 36.12 mmol)
was added. The resulting solution was subjected to microwave heating at 180 °C for 1
h. The mixture was cooled to room temperature and diluted with EtOAc and H₂O.
Layers were separated and the aqueous layer was extracted twice with EtOAc. The
10 combined organic extracts were dried (Na₂SO₄) and evaporated *in vacuo*. The residue
thus obtained was purified by column chromatography (silica gel; DCM/MeOH(NH₃)
up to 2% as eluent). The desired fractions were collected and evaporated *in vacuo* to
yield compound **D14** (3.61 g, 39%) as dark orange solid.

LCMS: MW (theor): 297; [MH⁺]: 298; RT (min): 2.54 (Method 12).

15

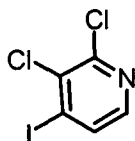
Description 15**2-Fluoro-4-(2-methyl-pyridin-4-yloxy)-boronic acid (D15)**

To a solution of compound **D14** (1.05 g, 3.52 mmol) in a mixture of 1,4-dioxane (9 ml)
20 and DMF (4 ml) were added bis(pinacolato)diboron (2.68 g, 10.56 mmol) and
potassium acetate (1.035 g, 10.56 mmol). The resulting mixture was degassed using a
stream of nitrogen and to this was added [1,1'-bis(diphenylphosphino)
ferrocene]dichloropalladium(II) (0.115 g, 0.141 mmol). The reaction mixture was then
heated at 110 °C for 3 h. The mixture was cooled to room temperature, diluted with
25 H₂O and extracted twice with EtOAc. The combine organic layers were evaporated *in*
vacuo to yield compound **D15** (0.87 g, quant.) as dark brown oil that was used in the
next reaction step without further purification.

LCMS: MW (theor): 247; [MH⁺]: 248; RT (min): 2.22 (Method 22).

Description 16

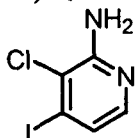
2,3-Dichloro-4-iodo-pyridine (D16)



- Reaction performed under nitrogen atmosphere. To a solution of n-butyllithium (27.6 ml, 69 mmol, 2.5 M in hexanes) in dry Et₂O (150 ml) cooled at -78 °C, was added 2,2,6,6-tetramethylpiperidine (11.64 ml, 69 mmol) dropwise. The resulting reaction mixture was stirred at -78 °C for 10 min. and then a solution of 2,3-dichloropyridine (10 g, 67.57 mmol) in dry THF (75 ml) was added dropwise. The mixture was stirred at -78 °C for 30 minutes and then a solution of iodine (25.38 g, 100 mmol) in dry THF (75 ml) was added. The mixture was allowed to warm to room temperature overnight, quenched with Na₂S₂O₃ (aqueous sat. solution) and extracted twice with EtOAc. The combined organic extracts were washed with NaHCO₃ (aqueous sat. solution), dried (Na₂SO₄) and evaporated *in vacuo*. The crude residue was precipitated with heptane, filtered off and dried to yield compound **D16** (8.21 g, 44%) as a pale cream solid.
- LCMS: MW (theor): 273; [MH⁺]: did not ionise; RT (min): 2.73 (Method 21).

Description 17

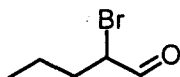
3-Chloro-4-iodo-pyridin-2-ylamine (D17)



- A mixture of compound **D16** (6 g, 21.9 mmol) in NH₄OH (12 ml, 11 N) was heated at 129 °C for 12 h. After cooling DCM was added, the organic layer was separated, washed with brine, dried (Na₂SO₄) and evaporated *in vacuo*. The residue thus obtained was purified by column chromatography (silica gel; DCM/MeOH(NH₃) up to 2% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **D17** (2.88 g, 52%) as a white solid.
- LCMS: MW (theor): 254; [MH⁺]: 255; RT (min): 2.22 (Method 22).

Description 18

2-Bromo-pentanal (D18)



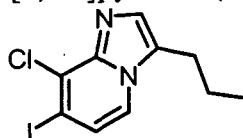
To a solution of valeraldehyde (4.27 g, 49.57 mmol) in 1,4-dioxane (1 ml) cooled to 0 °C, was added bromine (2.46 ml, 49.57 mmol), dropwise over 15 min. The reaction mixture was further stirred at 0 °C for 10 minutes, allowed to warm to room temperature and stirred for a further 10 minutes. This mixture was then quenched with
5 NaHCO₃ (aqueous sat. solution) and extracted with Et₂O. The organic layer was separated, dried (MgSO₄) and evaporated *in vacuo* to yield compound **D18** (6 g, 30%) that was used in the next reaction step without further purification.

Compound **D18** can also be prepared as described in: *Helvetica Chimica Acta* **1949**, 32 35-38.

10

Description 19

8-Chloro-7-iodo-3-propyl-imidazo[1,2-a]pyridine (**D19**)

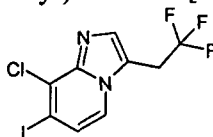


To a mixture of compound **D17** (0.76 g, 2.98 mmol) in EtOH (8 ml) was added
15 compound **D18** (2.55 g, 15.5 mmol). The reaction mixture was subjected to microwave heating at 150 °C for 45 min. The mixture was cooled to room temperature and the solvents were evaporated *in vacuo*. The residue was treated with DCM. The precipitate thus obtained was filtered off and dried to yield compound **D19** (0.7 g, 73%) as a pale cream solid.

20 LCMS: MW (theor): 320; [MH⁺]: 321; RT (min): 2.55 (Method 23).

Description 20

8-Chloro-7-iodo-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine (**D20**)



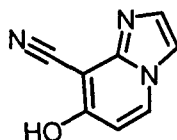
25 To a mixture of compound **D17** (0.507 g, 1.992 mmol) in EtOH (7 ml) was added compound **D8** (0.817 g, 3.985 mmol). The reaction mixture was subjected to microwave heating at 150 °C for 30 min. The mixture was cooled to room temperature and the solvents were evaporated *in vacuo*. The residue was then taken up in DCM and washed with NaHCO₃ (aqueous sat. solution). The organic layer was separated, dried
30 (Na₂SO₄) and the solvent evaporated *in vacuo*. The residue thus obtained 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 **D20** (0.5 g, 69.6%) as yellow solid.

LCMS: MW (theor): 360; $[MH^+]$: 361; RT (min): 2.31 (Method 15).

5 Description 21

7-Hydroxy-imidazo[1,2-a]pyridine-8-carbonitrile (D21)



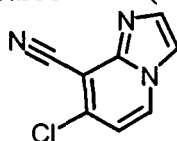
To a mixture of compound **D3** (2 g, 13.404 mmol) in EtOH (5 ml) was added chloroacetaldehyde (1.58 g, 20.11 mmol). The reaction mixture was subjected to
10 microwave heating at 150 °C for 45 min. After cooling to room temperature, the solvent was evaporated *in vacuo*. The residue thus obtained was then treated with Et₂O and a solid precipitated. The solid thus obtained was filtered off, washed with EtOAc and dried *in vacuo* to yield compound **D21** (1.5 g, 70%).

LCMS: MW (theor): 159; $[MH^+]$: 160; RT (min): 0.21.

15

Description 22

7-Chloro-imidazo[1,2-a]pyridine-8-carbonitrile (D22)



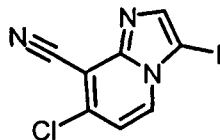
A mixture of compound **D21** (1.5 g, 9.425 mmol) and phosphorus(V) oxychloride (3.5
20 ml) was subjected to microwave heating at 130 °C for 15 min. After cooling to room temperature, the solvent was evaporated *in vacuo*. The residue thus obtained was treated with NaHCO₃ (aqueous sat. solution) and extracted with DCM. The organic layer was separated, dried (MgSO₄) and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; Et₂O as eluent). The desired fractions
25 were collected and evaporated *in vacuo* to yield compound **D22** (1.6 g, 95%) as yellow solid.

LCMS: MW (theor): 177; $[MH^+]$: 178; RT (min): 1.45.

MP: decomposed.

Description 23

7-Chloro-3-iodo-imidazo[1,2-a]pyridine-8-carbonitrile (D23)

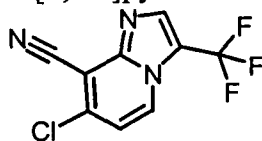


To a mixture of compound **D22** (0.5 g, 2.81 mmol) in CH₃CN (5 ml) was added *N*-iodosuccinimide (0.696 g, 3.09 mmol). The reaction mixture was stirred for 3 h. at room temperature. After cooling, the solvent was evaporated *in vacuo*. The residue was treated with aqueous Na₂S₂O₃ (2 N) and extracted with DCM. The organic layer was separated, dried (MgSO₄) and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; heptane/EtOAc 1:1 as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **D23** (0.7 g, 82%) as brown solid.

LCMS: MW (theor): 303; [MH⁺]: 304; RT (min): 2.14 (Method 17).

Description 24

7-Chloro-3-trifluoromethyl-imidazo[1,2-a]pyridine-8-carbonitrile (D24)

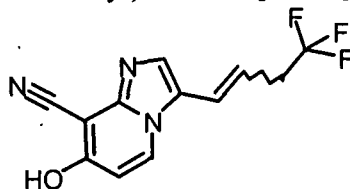


To a mixture of compound **D23** (0.2 g, 0.659 mmol) in DMF (3 ml) were added fluorosulfonyl(difluoro)acetic acid methyl ester (0.633 g, 3.295 mmol) and copper(I) iodide (0.63 g, 3.295 mmol). The reaction mixture was subjected to microwave heating at 160 °C for 45 min. After cooling, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; heptane/EtOAc as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **D24** (0.1 g, 62%) as yellow solid.

LCMS: MW (theor): 259; [MH⁺]: 260; RT (min): 2.56 (Method 16).

Description 25

7-Hydroxy-3-(4,4,4-trifluoro-but-1-enyl)-imidazo[1,2-a]pyridine-8-carbonitrile (D25)

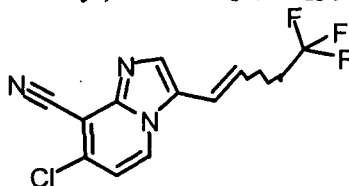


To a mixture of compound **D21** (0.25 g, 1.57 mmol) in AcOH (3 ml) was added 4,4,4-trifluorobutylaldehyde (1.38 g, 10.99 mmol). The reaction mixture was subjected to microwave heating at 155 °C for 45 min. After cooling to room temperature, the solvent was evaporated *in vacuo*. The residue was treated with NaHCO₃ (aqueous sat. solution) and extracted with DCM. The organic layer was separated, dried (MgSO₄) and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH 0.5 % as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **D25** (0.1 g, 24%) as an oil.

LCMS: MW (theor): 267; [MH⁺]: 268; RT (min): 2.16 (Method 24).

Description 26

7-Chloro-3-(4,4,4-trifluoro-but-1-enyl)-imidazo[1,2-a]pyridine-8-carbonitrile (D26)



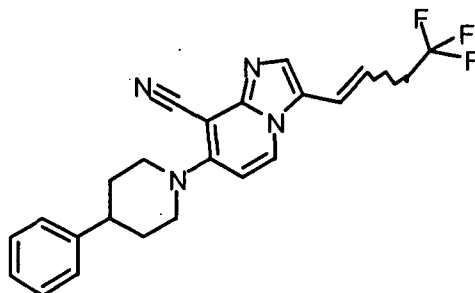
A mixture of compound **D25** (0.1 g, 0.374 mmol) and phosphorus(V) oxychloride (1.5 ml) was subjected to microwave heating at 130 °C for 15 min. After cooling to room temperature, the solvent was evaporated *in vacuo*. The residue was treated with NaHCO₃ (aqueous sat. solution) and extracted with DCM. The organic layer was separated, dried (Mg₂SO₄) and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH 0.5 % as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **D26** (0.85 g, 80%) as yellow solid.

LCMS: MW (theor): 285; [MH⁺]: 286; RT (min): 2.85.

MP: 158 °C.

Description 27

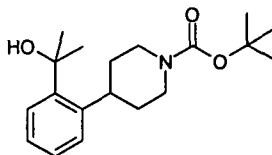
7-(4-Phenyl-piperidin-1-yl)-3-(4,4,4-trifluoro-but-1-enyl)-imidazo[1,2-a]pyridine-8-carbonitrile (D27)



- To a mixture of compound **D26** (0.12 g, 0.42 mmol) in DMF (3 ml) were added 4-phenylpiperidine (0.081 g, 0.504 mmol) and Et₃N (0.064 g, 0.63 mmol). The reaction mixture was subjected to microwave heating at 150 °C for 45 min. After cooling to room temperature, the solvent was evaporated *in vacuo* and the residue thus obtained was treated with NH₄Cl (aqueous sat. solution) and extracted with DCM. The organic layer was separated, dried (MgSO₄) and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; heptane/EtOAc 7:3 as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **D27** (0.12 g, 70%) as yellow oil.
- LCMS: MW (theor): 410; [MH⁺]: 411; RT (min): 3.49 (Method 17).

Description 28

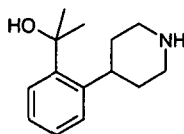
4-[2-(1-Hydroxy-1-methyl-ethyl)-phenyl]-piperidine-1-carboxylic acid tert-butyl ester (D28)



- To a solution of 4-(2-Methoxycarbonyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester (2.6 g, 8.14 mmol) [C.A.S. 732275-95-5] in THF (150 ml) cooled at 0 °C and under nitrogen atmosphere, was added dropwise methylmagnesium bromide – 1.4 M solution in toluene/THF (17.443 ml, 24.421 mmol) and the resulting reaction mixture was stirred at 45 °C for 2 h. After cooling in an ice bath the mixture was carefully quenched with a saturated aqueous solution of ammonium chloride, and then extracted with EtOAc. The combined organic phase was dried (Na₂SO₄) and the solvent evaporated *in vacuo* to yield **D28** (2.77 g, 69 %).
- LCMS: MW (theor): 319; [MH⁺]: 320; RT (min): 3.01 (Method 20).

Description 29

2-(2-Piperidin-4-yl-phenyl)-propan-2-ol (D29)



- A solution of intermediate **D28** (27 g, 5.636 mmol) and potassium hydroxide (2.433 g, 43.357 mmol) in isopropyl alcohol (13.5 ml) and water (27 ml) was subjected to microwave heating at 180 °C for 60 min. After cooling to room temperature, the

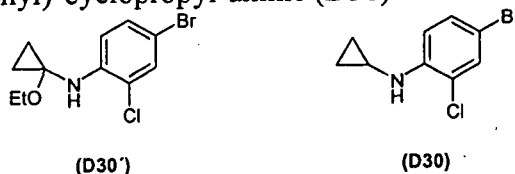
5 mixture was washed with water and sodium chloride (aqueous saturated solution). The organic phase was dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH(NH_3) up to 10% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **D29** as yellow solid (1.041 g, %).

M.P. 219.5°C.

LCMS: MW (theor): 220; [M^+]: 220; RT (min): 1.29 (Method 11).

Description 30

10 (4-Bromo-2-chloro-phenyl)-cyclopropyl-amine (D30)

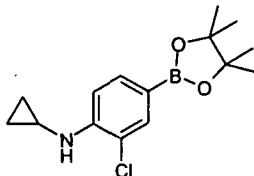


To a solution of 4-bromo-2-chloroaniline [C.A.S. 38762-41-3], (1 g, 4.843 mmol) in AcOH (19 ml) and MeOH (10 mL) stirred at room temperature and under nitrogen atmosphere was added dropwise (1-ethoxycyclopropyloxy-trimethylsilane [C.A.S. 27374-25-0] (1.199 ml, 5.57 mmol). The reaction mixture was then refluxed at 67–69 °C for 3 h. The mixture was then concentrated *in vacuo* to yield intermediate **D30'**.

15 In another flask, NaBH_4 (0.366 g, 9.687 mmol) was suspended in THF (10 mL) and cooled to 5°C. Then, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ complex (1.228 ml, 9.687 mmol) was added dropwise. The resulting reaction mixture was stirred under a N_2 atmosphere at 5 °C for 1 h. Then, to this mixture was added a solution of **D30'** in THF (5 mL) dropwise at 5–10 °C over 20 min. After stirring at r.t. for 5 h., at reflux temperature for 2 h., and then removing THF by distillation, the mixture was cooled to r.t. and poured into water. The resulting mixture was extracted with Et_2O . The organic layer was washed with water and dried (Na_2SO_4) followed by the removal of the volatiles under vacuo. The crude product thus obtained was purified by column chromatography (silica gel; Heptane/ EtOAc 99:1 as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate compound **D30** (0.390 g, 32.6%).

Description 31

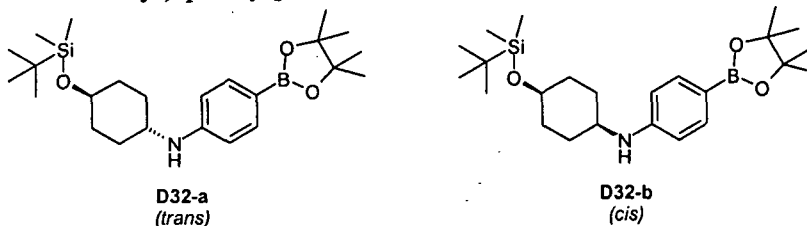
[2-Chloro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropyl-amine (D31)



- 5 Bis(pinacolato)diboron (0.643 g, 2.531 mmol) and potassium acetate (0.466 g, 4.746 mmol) were added to a solution of intermediate **D30** (0.390 g, 1.582 mmol) in 1,4-dioxane (2 ml) and DMF (0.5 ml). The mixture was degassed and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) - complex with DCM (1:1) (0.0348 g, 0.0475 mmol) was added. The reaction mixture was heated at 150 °C for 10
- 10 min. under microwave irradiation. 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; heptane as eluent). The desired fractions were collected and evaporated *in vacuo* to afford intermediate compound **D31** (0.269 g, 49%).
- 15 GCMS: MW (theor): 293; [M⁺]: 293; RT (min): 12.7.

Description 32

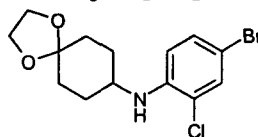
[4-(tert-Butyl-dimethyl-silanyloxy)-cyclohexyl]-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amine (D32)



- 20 A mixture of 4-(tert-Butyl-dimethyl-silanyloxy)-cyclohexanone (1.72 ml, 6.85 mmol) [C.A.S.55145-45-4], 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (1 g, 4.56 mmol) and sodium triacetoxy-borohydride (1.44 g, 6.85 mmol) in DCM (25 ml) was stirred at r.t. for 1 day. Then, the mixture was washed with NH₄Cl (aqueous sat.
- 25 solution). The organic layer was collected, dried (MgSO₄) and evaporated *in vacuo*. The crude product thus obtained was purified by column chromatography (silica gel; heptane/EtOAc up to 5% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate compound **D32-a** (*trans*) (0.566 g, 31%) and **D32-b** (*cis*) (1.089 g, 61%).

Description 33

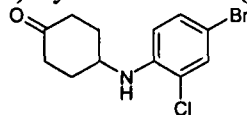
(4-Bromo-2-chloro-phenyl)-(1,4-dioxa-spiro[4.5]dec-8-yl)-amine (D33)



A mixture of 4-bromo-2-chloro-phenylamine (6 g, 29.06 mmol), 1,4-cyclohexanedione
5 monoethyleneketal (6.908 g, 43.59 mmol), and sodium triacetoxy-borohydride (9.239
g, 43.59 mmol) in DCE (100 ml) and acetic acid (0.2 ml) was stirred at r.t. for 2 days.
The mixture was then filtered through a pad of diatomaceous earth and washed with
dichloromethane. The filtrate was washed with NaHCO₃ (aqueous sat. solution),
sodium chloride (aqueous sat. solution), dried (MgSO₄) and evaporated *in vacuo*. The
10 crude product thus obtained was purified by column chromatography (silica gel;
DCM/EtOAc 4:1 as eluent). The desired fractions were collected and evaporated *in vacuo*
to yield intermediate compound **D33** (8.57 g, 85%).

Description 34

15 4-(4-Bromo-2-chloro-phenylamino)-cyclohexanone (D34)

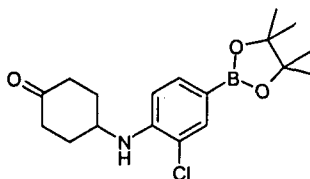


A mixture of intermediate **D33** (4 g, 11.539 mmol), p-toluenesulfonic acid (21.949 mg,
0.115 mmol) in H₂O (6 ml) and acetone (3 ml) was heated at 110 °C for 45 min. under
microwave irradiation. After cooling to r.t. the reaction mixture was diluted with DCM
20 and washed with a saturated aqueous NaCl solution, dried (Na₂SO₄) and evaporated *in vacuo*.
The reaction mixture was purified by column chromatography (silica gel;
DCM/MeOH(NH₃) up to 0.1% as eluent). The desired fractions were collected and
evaporated *in vacuo* to yield intermediate compound **D34** (2.17 g, 62 %) as a white
solid.

25

Description 35

4-[2-Chloro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamino]-
cyclohexanone (D35)

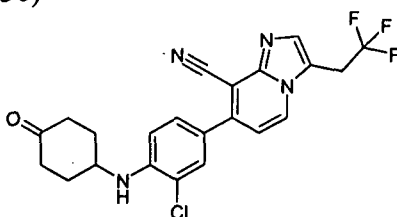


Bis(pinacolato)diboron (2.028g, 7.984 mmol) and potassium acetate (1.469 g, 14.97 mmol) were added to a solution of intermediate **D34** (1.51 g, 4.99 mmol) in 1,4-dioxane (4 ml) and DMF (1 ml). The mixture was degassed and then [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) - complex with DCM (1:1) (0.110 g, 0.15 mmol) was added. The reaction mixture was heated at 150 °C for 10 min. under microwave irradiation. 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; heptane/EtOAc up to 10% as eluent). The desired fractions were collected and evaporated *in vacuo* to afford intermediate compound **D35** (1.09 g, 62.4%).

LCMS: MW (theor): 349; [MH⁺]: 350; RT (min): 3.46 (Method 16).

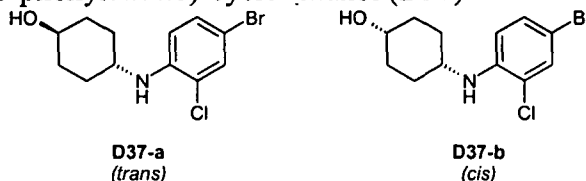
Description 36

7-[3-Chloro-4-(4-oxo-cyclohexylamino)-phenyl]-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (**D36**)



To a mixture of compound **D10** (0.25 g, 0.963 mmol) in 1,4-dioxane (4 ml) under a nitrogen atmosphere were added compound **D35** (0.404 g, 1.156 mmol), Pd(PPh₃)₄ (0.111 g, 0.0963 mmol) and finally NaHCO₃ (1 ml, aqueous sat. solution). The reaction mixture was subjected to microwave heating at 150 °C for 10 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and the pad washed with EtOAc. The combined filtrates were washed with NaCl (aqueous sat. solution). The organic layer was separated, dried (Na₂SO₄) and evaporated *in vacuo* and the residue was purified by column chromatography (silica gel; starting from DCM/MeOH(NH₃) up to 10% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate compound **D36** (0.419 g, 97 %).

LCMS: MW (theor): 446; [MH⁺]: 447; RT (min): 3.06 (Method 17).

Description 37**4-(4-Bromo-2-chloro-phenylamino)-cyclohexanol (D37)**

To a mixture of intermediate **D34** (2 g, 5.288 mmol) in MeOH (40 ml) stirred at -78°C ,
 5 was added sodium borohydride (220 mg, 5.816 mmol). The mixture was gradually
 warmed to r.t. and further stirred for 16 h. Then, the resulting mixture was quenched
 with an aqueous saturated ammonium chloride solution, washed with sodium chloride
 (aqueous sat. solution), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue
 thus obtained was purified by circular chromatography (silica gel; DCM/MeOH(NH_3)
 10 up to 5% as eluent). The desired fractions were collected and evaporated *in vacuo* to
 yield **D37-a** (trans) (0.380 g, 23.6 %) and **D37-b** (cis) (0.710 g, 44 %).

D37-a (trans)M.P. $> 300^{\circ}\text{C}$.

15 LCMS: MW (theor): 303; $[\text{MH}^+]$: 304; RT (min): 4.17 (Method 12).

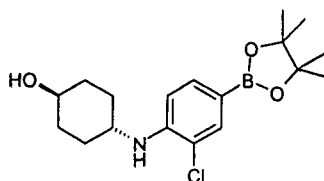
D37-b (cis)M.P. $> 300^{\circ}\text{C}$

LCMS: MW (theor): 303; $[\text{MH}^+]$: 304; RT (min): 2.93 (Method 18).

20

Description D38

(trans)-4-[2-Chloro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamino]
 cyclohexanol (**D38**)



25 Bis(pinacolato)diboron (0.947 g, 3.729 mmol) and potassium acetate (0.686 g, 6.992
 mmol) were added to a solution of intermediate **D37-a** (0.710 g, 2.331 mmol) in 1,4-
 dioxane (5 ml). The mixture was degassed and then [1,1'-bis(diphenylphosphino)-
 ferrocene]-dichloropalladium(II) - complex with DCM (1:1) (0.051 g, 0.0699 mmol)
 was added. The reaction mixture was heated at 150°C for 10 min. under microwave
 30 irradiation. After cooling to r.t., the reaction mixture was filtered through diatomaceous
 earth. The filtrate was evaporated *in vacuo*. The crude residue was purified by column

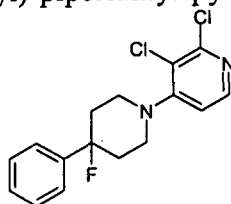
chromatography (silica gel; DCM/MeOH(NH₃) up to 2% as eluent). The desired fractions were collected and evaporated *in vacuo* to afford a colourless oily residue that crystallized to yield intermediate compound *trans*-**D38** (0.950 g) as a white solid.

LCMS: MW (theor): 351; [MH⁺]: 352; RT (min): 3.09 (Method 18).

5

Description 39

2,3-Dichloro-4-(4'-fluoro-4'-phenyl)-piperidiny-pyridine (D39)

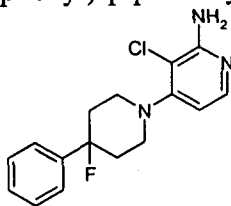


10 A mixture of **D16** (2g, 7.302 mmol), 4-fluoro-4-phenylpiperidine hydrochloride (2.048 g, 9.493 mmol) [C.A.S. 1056382-25-2] and DMF (5.055 ml, 29.209 mmol) in acetonitrile (10 ml) was heated in a sealed tube at 110 °C for 16 h. The mixture was then treated with NaHCO₃ (aqueous sat. solution). The organic layer was separated, dried (Na₂SO₄) and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; Heptane/DCM from 4:1 up to 1:4 as eluent). The desired
15 fractions were collected and evaporated *in vacuo* to yield compound **D39** (0.88 g, 37%) as a white solid.

LCMS: MW (theor): 324; [MH⁺]: 325; RT (min): 5.08 (Method 2).

Description 40

20 2-Amino-3-chloro-4-(4'-fluoro-4'-phenyl)-piperidiny-pyridine (D40)



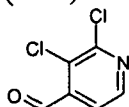
To a stirred solution of compound **D39** (0.88 g, 2.709 mmol) in toluene (14 ml) previously degassed, were added sodium *tert*-butoxide (0.496 g, 3.842 mmol), racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.269 g, 0.433 mmol),
25 tris(dibenzylideneacetone)dipalladium(0) (0.161 g, 0.176 mmol) and benzophenone imine (0.559 ml, 3.328 mmol). The reaction mixture was heated at 80 °C for 16 h. in a sealed tube. Then, a solution of hydroxylamine hydrochloride (1.116 g, 16.06 mmol) and triethylamine (2.4 ml, 17.219 mmol) in MeOH (14 ml) was added and then stirred for 5 h. The reaction mixture was diluted with NaHCO₃ (aqueous sat. solution). The

residue was taken up in DCM. The precipitated solid obtained was filtered off and dried in vacuum to give 0.3 g of **D40**. The mother liquors were evaporated *in vacuo*. The residue thus obtained was purified by column chromatography (silica gel; DCM/AcOEt up to 20% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **D40** (0.270 g). Total amount of **D40** = 570 mg).

LCMS: MW (theor): 305; [MH⁺]: 306; RT (min): 4.55 (Method 6).

Description 41

2,3-Dichloro-pyridine-4-carbaldehyde (**D41**)



10

To a solution of 2,3-dichloropyridine (10 g, 67.57 mmol) [C.A.S. 2402-77-9] in dry THF (200 ml) cooled at -78°C under a nitrogen atmosphere, n-butyllithium (37.165 ml, 74 mmol, 2 M in hexanes) was dropwise added. The resulting reaction mixture was stirred at -78 °C for 20 min. Then dry DMF (6.28 ml, 81.087 mmol) was added dropwise. After 15 min stirring at -78°C, the mixture was allowed to warm to room temperature, quenched with water and extracted with DCM. The combined organic extracts were dried (Na₂SO₄) and evaporated *in vacuo*. The crude residue was purified by short open column chromatography (DCM as eluent). The desired product fractions were collected and evaporated *in vacuo* to give a residue that was further purified by column chromatography (silica gel; DCM/heptane up to 50% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate compound **D41** (4.15 g, 34.9%) as a white solid.

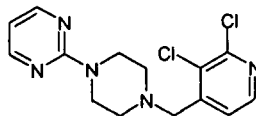
15

20

GCMS = RT (min): 7.9.

25 Description 42

2-[4-(2,3-Dichloro-pyridin-4-ylmethyl)-piperazin-1-yl]-pyrimidine



30

A solution of 2-piperazin-1-yl-pyrimidine hydrochloride (1.132 g, 4.773 mmol), in DCE (25 ml) was added to **D41** (0.7 g, 3.977 mmol), sodium triacetoxy-borohydride (1.264 g, 5.966 mmol) and acetic acid (0.4 ml). The resulting mixture was stirred at r.t. for 1 day. Then, DMF (5 ml) was added and the reaction stirred for a further 16 h. at r.t. The reaction mixture was then diluted with NaHCO₃ (aqueous sat. solution) and extracted with DCM. The organic layer was dried (MgSO₄) and evaporated *in vacuo*.

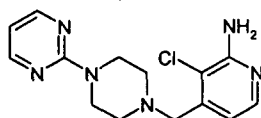
The crude product thus obtained was purified by column chromatography (silica gel; DCM/MeOH up to 4% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate compound **D42** (0.865 g, 67%) as a white solid.

LCMS: MW (theor): 323; [MH⁺]: 324; RT (min): 4.18 (Method 1).

5

Description 43

3-Chloro-4-(4-pyrimidin-2-yl-piperazin-1-ylmethyl)-pyridin-2-ylamine (**D43**)



To a stirred solution of compound **D42** (0.835 g, 2.575 mmol) in toluene (16 ml) previously degassed, were added sodium tert-butoxide (0.351 g, 3.657 mmol), racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.257 g, 0.412 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.153 g, 0.167 mmol) and benzophenone imine (0.532 ml, 3.168 mmol). The reaction mixture was heated at 80 °C for 16 h. in a sealed tube. Then, after cooling, a solution of 1N HCl (40 ml) and THF (40 ml) were added and the mixture stirred for 1 h. Then, the resulting aqueous mixture was washed with EtOAc. The aqueous layer was basified with NaHCO₃ (aqueous sat. solution) and extracted with EtOAc. The organic layer was dried (MgSO₄) and evaporated *in vacuo*. The crude product thus obtained was purified by column chromatography (silica gel; DCM/MeOH up to 2% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate compound **D43** (0.607 g, 77%) as a yellow solid.

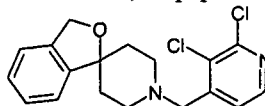
20

M.P. 185 °C.

LCMS: MW (theor): 304; [MH⁺]: 305; RT (min): 3.03 (Method 1).

Description 44

25 2,3-Dichloro-4-[3'H-spiro[2'-benzofuran-1,4'-piperidinylmethyl]-pyridine (**D44**)



30

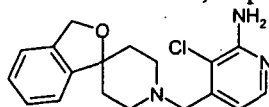
A solution of spiro[isobenzofuran-1(3H),4'-piperidine], hydrochloride (0.155 g, 0.818 mmol), in DCE (2 ml) was added to **D41** (0.12 g, 0.682 mmol), sodium triacetoxyborohydride (0.159 g, 0.75 mmol) and acetic acid (0.4 ml). The resulting mixture was stirred at r.t. for 1 day. The reaction mixture was diluted with NaHCO₃ (aqueous sat. solution) and extracted with DCM. The organic layer was dried (MgSO₄) and evaporated *in vacuo*. The crude product thus obtained was purified by column chromatography (silica gel; DCM/AcOEt up to 6% as eluent). The desired fractions

were collected and evaporated *in vacuo* to yield intermediate compound **D44** (0.15 g, 63%) as a white solid

LCMS: MW (theor): 348; [MH⁺]: 349; RT (min): 4.33 (Method 13)

5 Description 45

2-Amino-3-chloro-4-[3'H-spiro[2'-benzofuran-1,4'-piperidinylmethyl]-pyridine (D45)



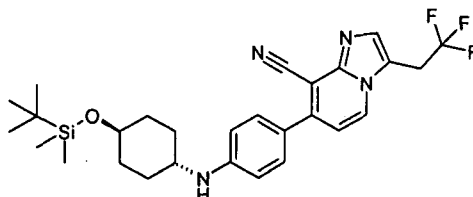
To a stirred solution of compound **D44** (0.154 g, 0.429 mmol) in toluene (3 ml) previously degassed, were added sodium tert-butoxide (0.059 g, 0.61 mmol), racemic-
 10 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.043 g, 0.0687 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.0255 g, 0.0279 mmol) and benzophenone imine (0.0886 ml, 0.528 mmol). The reaction mixture was heated at 80 °C for 16 h. in a sealed tube. Then, after cooling, a solution of 1N HCl (40 ml) and THF (40 ml) were added and the mixture stirred for 1 h. Then, the resulting aqueous mixture was washed
 15 with EtOAc. The aqueous layer was basified with NaHCO₃ (aqueous sat. solution) and extracted with EtOAc. The organic layer was dried (MgSO₄) and evaporated *in vacuo*. The crude product thus obtained was purified by column chromatography (silica gel; DCM/MeOH up to 2% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate compound **D45** (0.1 g, 71%) as a yellow solid.

20 LCMS: MW (theor): 329; [MH⁺]: 330; RT (min): 3.13 (Method 4).

Description 46

7-{4-[4-(tert-Butyl-dimethyl-silanyloxy)-cyclohexylamino]-phenyl}-3-(2,2,2-trifluoroethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (D46)

25



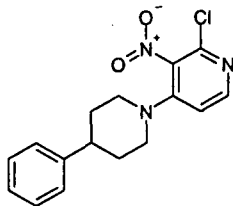
To a mixture of compound **D13** (0.048 g, 0.158 mmol) in 1,4-dioxane (2 ml) under nitrogen atmosphere were added compound **D32-a** (0.082 g, 0.19 mmol), Pd(PPh₃)₄ (9.15 g, 0.00792 mmol) and NaHCO₃ (0.5 ml, aqueous sat. solution). The reaction
 30 mixture was subjected to microwave heating at 150 °C for 10 min. After cooling, the mixture was washed with DCM. The organic layer was separated, dried (Na₂SO₄) and evaporated *in vacuo* and the residue was purified by column chromatography (silica

gel; starting from DCM/EtOAc up to 6% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate compound **D46** (0.06 g, 72 %).

LCMS: MW (theor): 528; $[MH^+]$: 529; RT (min): 3.18 (Method 15).

5 Description 47

2-Chloro-3-nitro-4(4'-phenylpiperidine)pyridine (D47)



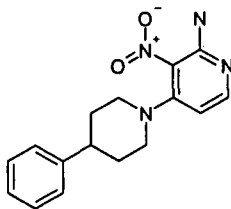
- To a solution of 2,4-dichloro-3-nitro-pyridine (2 g, 10.363 mmol) [CAS No. 5975-12-2] in acetonitrile (40 ml) was cooled at 0°C, was added triethylamine (2.873 ml, 20.727 mmol) and phenylpiperidine (1.671 mg, 10.363 mmol), [CAS No. 771-99-3]. The resulting mixture was stirred at 0 °C for 1.5 h. Then NaHCO₃ (aqueous sat. solution) was added. The resulting aqueous solution was extracted with DCM. The organic layer was separated, dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; starting from DCM/heptane up to 20% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate compound **D47** (2.67 g, 81 %) as a yellow solid.

M.P. 131.0 °C.

LCMS: MW (theor): 317; $[MH^+]$: 318; RT (min): 4.57 (Method 1).

20 Description 48

2-Amino-3-nitro-4(4'-phenylpiperidine)pyridine (D48)



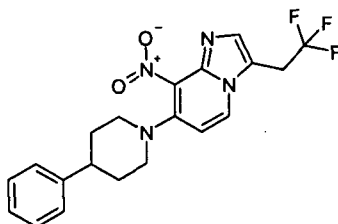
- A mixture of intermediate compound **D47** (1.5 g, 4.72 mmol) in ammonium hydroxide (40 ml) was heated in a PARR reactor vessel at 140°C for 16 h. Then the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; starting from DCM/MeOH up to 2% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate compound **D48** (0.4 g, 28.4 %) as a solid.

M.P. 205.6°C.

LCMS: MW (theor): 298; $[MH^+]$: 299; RT (min): 4.01 (Method 1).

Description 49

8-Nitro-7-(4-phenyl-piperidin-1-yl)-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine
(D49)



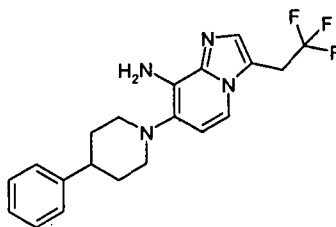
A mixture of intermediate compounds **D48** (0.4 g, 1.341 mmol) and **D8** (2 g, 9.757 mmol) in EtOH (2 ml) was subjected to microwave heating at 150 °C for 50 min. After cooling to room temperature, the solvent was evaporated *in vacuo*. The residue thus
10 obtained was purified by column chromatography (silica gel; DCM/MeOH(NH₃) up to 2% as eluent). The desired fractions were collected and evaporated *in vacuo*. The residue was triturated with diisopropylether yielding to intermediate compound **D49** (130 g, 24%) as an orange oil.

LCMS: MW (theor): 404; $[MH^+]$: 405; RT (min): 4.51 (Method 1).

15

Description 50

7-(4-Phenyl-piperidin-1-yl)-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridin-8-ylamine
(D50)

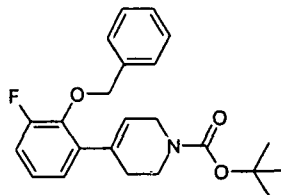


20 To a mixture of intermediate compound **D49** (0.075 g, 0.185 mmol) in EtOH (0.6 ml), H₂O (0.1 ml) and HCl (0.1 ml), was added Fe (103.6 mg, 1.855 mmol) portionwise. The mixture was heated at 80°C for 1 h. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with DCM. The filtrate was then washed with NaHCO₃ (aqueous sat. solution). The organic layer was separated, dried (Na₂SO₄) and
25 evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; starting from DCM/MeOH(NH₃) up to 2% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **D50** (0.057 g, 82 %).

LCMS: MW (theor): 374; $[MH^+]$: 375; RT (min): 5.13 (Method 19).

Description 51

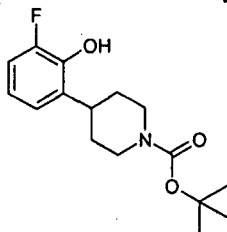
4-(2-benzyloxy-3-fluoro-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (D51)



- 5 To a solution of 1,2,3,6-tetrahydro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyridine-1-carboxylic acid *ter*-butylester (0.75 g, 2.426 mmol) [CAS 375853-82-0] (synthesis described in WO 2004072025 A2 20040826) in 1,4-dioxane (7 ml) and an aqueous saturated solution of K_2CO_3 (3.5 ml), was added 2-benzyloxy-1-bromo-3-fluoro-benzene (1.023 mg, 3.638 mmol) [1036724-55-6]. The resulting solution was
- 10 degassed using a stream of nitrogen and to this was added $Pd(PPh_3)_4$ (0.14 g, 0.121 mmol). The reaction was then subjected to microwave heating in a sealed tube at 150 °C for 10 min. After cooling to room temperature, the reaction mixture was diluted with water and washed with EtOAc. The organic layer was separated, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel;
- 15 starting from Heptane/DCM up to 100% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield intermediate compound **D51** (0.727 g, 78 %)

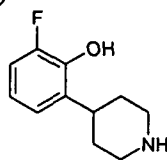
Description 52

4-(3-Fluoro-2-hydroxy-phenyl)-piperidine-1-carboxylic acid tert-butyl ester (D52)

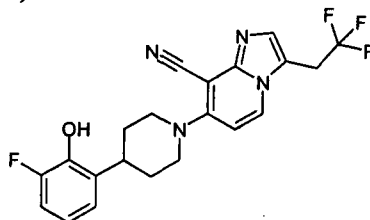


- 20 A solution of intermediate **D51** (0.727 g, 1.896 mmol) in EtOH (40 ml) was hydrogenated in a H-CUBE™ using Pd/C 10% column (CatCart 70mm) at full hydrogen, at 80°C and 1.5 ml/min flow. The solvent was evaporated *in vacuo* to give intermediate compound **D52** (0.56 g, 100 %).

25

Description 53**2-Fluoro-6-piperidin-4-yl-phenol (53)**

- Intermediate **D52** (3.067 g, 7.852 mmol) was dissolved in a mixture of trifluoroacetic acid (5 ml) in DCM (5 ml). The resulting solution was stirred for 30 min. at room temperature. Then Na_2CO_3 (aqueous sat. solution) was carefully added and the resulting aqueous mixture was washed with a mixture of DCM/n-BuOH 1:3. The combined organic phase was dried (Na_2SO_4) and the solvent evaporated *in vacuo* to yield intermediate compound **D53** (0.37 g, 100 %).
- LCMS: MW (theor): 195, $[\text{MH}^+]$: 196; RT (min): 0.36 (Method 16).

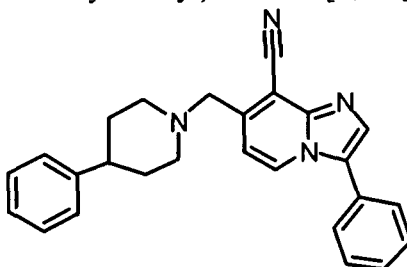
Description 54**7-[4-(3-Fluoro-2-hydroxy-phenyl)-piperidin-1-yl]-3-(2,2,2-trifluoro-ethyl) imidazo[1,2-a]pyridine-8-carbonitrile (D54)**

- A mixture of compound **D10** (0.31 g, 1.194 mmol), **D53** (0.349 g, 1.79 mmol), *N,N*-diisopropylethylamine (0.416 ml, 2.388 mmol) in CH_3CN (3 ml) was subjected to microwave heating in a sealed tube at 180 °C for 10 min. The mixture was cooled to room temperature, diluted with Na_2CO_3 (aqueous sat. solution) and washed with DCM.
- The organic layer was separated, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was treated with DCM. The solid thus obtained was collected to yield intermediate compound **D54** (0.32 g, 64 %).

LCMS: MW (theor): 418, $[\text{MH}^+]$: 419; RT (min): 4.05 (Method 2).

Example 1

3-Phenyl-7-(4-phenyl-piperidin-1-ylmethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (E1)

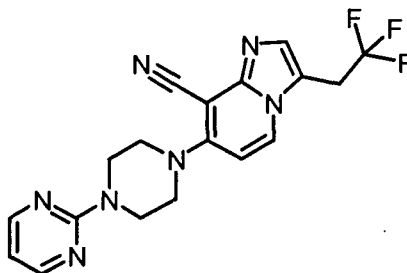


To a mixture of compound **D6** (0.15 g, 0.593 mmol) and K_2CO_3 (0.35 g, 2.55 mmol) in
5 1,4-dioxane (4 ml) and DMF (1.5 ml) was added compound **D7** (0.237 g, 0.85 mmol).
The resulting mixture was degassed using a stream of nitrogen and to this was added
 $Pd(PPh_3)_4$ (0.098 g, 0.085 mmol). The reaction mixture was then subjected to
microwave heating in a sealed tube at 150 °C for 10 min. The reaction mixture was
cooled to room temperature and filtered through a pad of diatomaceous earth. The
10 filtrate was concentrated *in vacuo*. The residue thus obtained was purified by
preparative reverse phase HPLC to yield compound **E1** (0.072 g, 31%).

1H NMR (500 MHz, $CDCl_3$) δ ppm 1.74 - 1.83 (m, 2 H), 1.83 - 1.90 (m, 2 H), 2.32 (td,
 $J=11.6, 2.6$ Hz, 2 H), 2.55 (tt, $J=11.9, 3.8$ Hz, 1 H), 2.99 (br. d, $J=11.3$ Hz, 2 H), 3.86
15 (s, 2 H), 7.18 - 7.22 (m, 2 H), 7.22 - 7.25 (m, 2 H), 7.28 - 7.34 (m, 2 H), 7.44 - 7.51 (m,
1 H), 7.51 - 7.58 (m, 4 H), 7.78 (s, 1 H), 8.43 (d, $J=7.2$ Hz, 1 H).

Example 2

7-(4-Pyrimidin-2-yl-piperazin-1-yl)-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-
20 carbonitrile (E2)



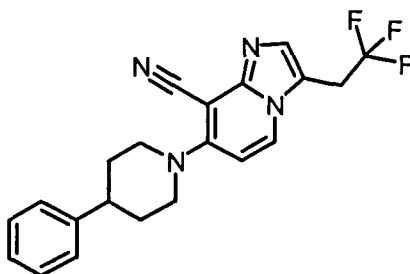
A mixture of compound **D10** (0.1 g, 0.38 mmol), 1-(2-pyrimidyl)piperazine
dihydrochloride (0.101 g, 0.50 mmol), *N,N*-diisopropylethylamine (0.21 ml, 1.2 mmol)
in CH_3CN (5 ml) was subjected to microwave heating in a sealed tube at 180 °C for 45
25 min. The mixture was then cooled to room temperature and the solvents evaporated *in vacuo*.
The residue thus obtained was taken up in DCM and washed with $NaHCO_3$
(aqueous sat. solution). The organic layer was separated, dried (Na_2SO_4) and

evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH(NH₃) up to 2% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **E2** as yellow solid (0.089 g, 60%).

- 5 ¹H NMR (500 MHz, CDCl₃) δ ppm 3.67 (q, J=10.1 Hz, 2 H), 3.71 - 3.76 (m, 4 H), 4.02 - 4.10 (m, 4 H), 6.57 (t, J=4.6 Hz, 1 H), 6.65 (d, J=7.8 Hz, 1 H), 7.53 (s, 1 H), 7.94 (d, J=7.8 Hz, 1 H), 8.35 (d, J=4.9 Hz, 1 H).

Example 3

- 10 7-(4-Phenyl-piperidin-1-yl)-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (**E3**)

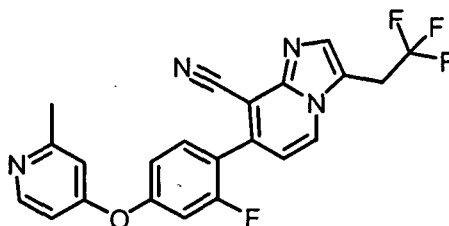


- 15 A mixture of compound **D10** (0.1 g, 0.38 mmol), 4-phenylpiperidine (0.073 g, 0.45 mmol), *N,N*-diisopropylethylamine (0.21 ml, 1.2 mmol) in CH₃CN (5 ml) was subjected to microwave heating in a sealed tube at 180 °C for 45 min. The mixture was then cooled to room temperature and the solvents evaporated *in vacuo*. The residue thus obtained was taken up in DCM and washed with NaHCO₃ (aqueous sat. solution). The organic layer was separated, dried (Na₂SO₄) and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH(NH₃) up to 20 2% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield a pre-purified fraction that was further purified by preparative reverse phase HPLC to give compound **E3** as yellow solid (0.102 g, 70%).

- 25 ¹H NMR (400 MHz, CDCl₃) δ ppm 1.87 - 2.00 (m, 2 H), 2.00 - 2.09 (m, 2 H), 2.74 - 2.87 (m, 1 H), 3.31 (td, J=12.6, 2.3 Hz, 1 H), 3.66 (q, J=9.8 Hz, 2 H), 4.22 (br. d, J=13.2 Hz, 2 H), 6.65 (d, J=7.9 Hz, 1 H), 7.21 - 7.28 (m, 3 H), 7.30 - 7.38 (m, 2 H), 7.51 (s, 1 H), 7.89 (d, J=7.6 Hz, 1 H).

Example 4

7-[2-Fluoro-4-(2-methyl-pyridin-4-yloxy)-phenyl]-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (E4)

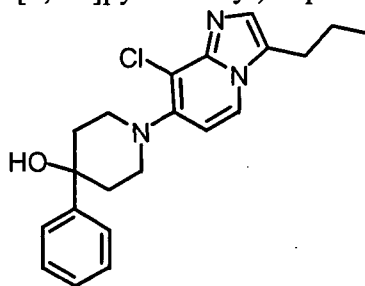


5 To a mixture of compound **D10** (0.24 g, 0.98 mmol) in 1,4-dioxane (2 ml) under nitrogen atmosphere were added compound **D15** (0.483 g, 1.96 mmol), Pd(PPh₃)₄ (0.045 g, 0.039 mmol) and NaHCO₃ (2 ml, aqueous sat. solution). The reaction mixture was subjected to microwave heating at 150 °C for 10 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with dioxane. The filtrate was evaporated *in vacuo* and the residue was purified by column chromatography (silica gel; DCM/MeOH(NH₃) up to 2% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **E4** (0.039 g, 9%).

15 ¹H NMR (400 MHz, CDCl₃) δ ppm 2.57 (s, 3 H), 3.82 (q, J=9.7 Hz, 2 H), 6.81 (dd, J=5.8, 2.3 Hz, 1 H), 6.85 (d, J=2.1 Hz, 1 H), 7.00 (dd, J=10.9, 2.3 Hz, 1 H), 7.05 (dd, J=8.3, 2.3 Hz, 1 H), 7.10 (dd, J=7.2, 1.6 Hz, 1 H), 7.63 (t, J=8.3 Hz, 1 H), 7.84 (s, 1 H), 8.26 (d, J=7.2 Hz, 1 H), 8.46 (d, J=5.8 Hz, 1 H).

20 **Example 21**

1-(8-Chloro-3-propyl-imidazo[1,2-a]pyridin-7-yl)-4-phenyl-piperidin-4-ol (E21)



To a stirred solution of compound **D19** (0.3 g, 0.94 mmol) in toluene (10 ml) were added 4-hydroxy-4-phenylpiperidine (0.166 g, 0.95 mmol), palladium (II) acetate (0.011 g, 0.047 mmol), sodium *tert*-butoxide (0.23 g, 2.35 mmol) and BINAP (0.0437 g, 0.071 mmol). The reaction mixture was heated at 100 °C for 16 h in a sealed tube. After cooling to room temperature the mixture was filtered through a pad of diatomaceous earth. The filtrate was evaporated *in vacuo*. The residue thus obtained

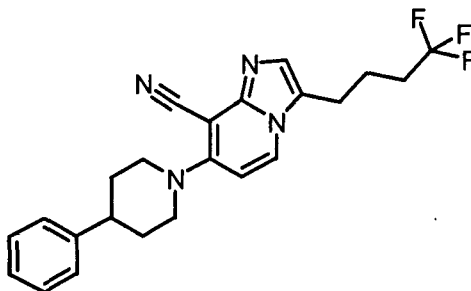
was purified by column chromatography (silica gel; DCM/MeOH(NH₃) up to 2% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **E21** (0.014 g, 4 %) as a pale yellow solid.

- 5 ¹H NMR (500 MHz, CDCl₃) δ ppm 1.04 (t, J=7.2 Hz, 3 H), 1.87 (br. s., 1 H), 1.73 - 1.82 (m, 2 H), 1.88 - 1.94 (m, 2 H), 2.39 (td, J=13.3, 4.9 Hz, 2 H), 2.77 (t, J=7.5 Hz, 2 H), 3.33 (td, J=11.8, 2.0 Hz, 2 H), 3.36 - 3.43 (m, 2 H), 6.81 (d, J=7.2 Hz, 1 H), 7.28 - 7.32 (m, 1 H), 7.33 (s, 1 H), 7.40 (t, J=7.7 Hz, 2 H), 7.56 - 7.61 (m, J=8.1, 1.2 Hz, 2 H), 7.79 (d, J=7.5 Hz, 1 H).

10

Example 28

7-(4-Phenyl-piperidin-1-yl)-3-(4,4,4-trifluoro-butyl)-imidazo[1,2-a]pyridine-8-carbonitrile (**E28**)

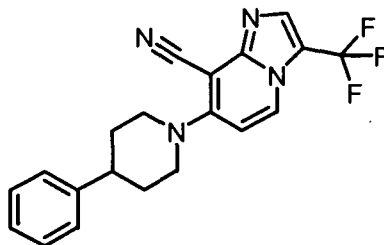


- 15 A mixture of compound **D27** (0.12 g, 0.292 mmol) in EtOAc (10 ml) was hydrogenated at room temperature in the presence of 10% palladium on activated carbon (0.002 g, 0.02 mmol). The reaction mixture was stirred at room temperature for 15 min. Then the mixture was filtered through a pad of diatomaceous earth and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; 20 heptane/EtOAc 1:1 as eluent) and then by preparative reverse phase HPLC to give compound **E28** (0.02 g, 17%) as yellow solid.

- 25 ¹H NMR (500 MHz, CDCl₃) δ ppm 1.94 (qd, J=12.1, 3.8 Hz, 2 H), 1.98 - 2.07 (m, 4 H), 2.15 - 2.27 (m, 2 H), 2.79 (tt, J=12.1, 3.8 Hz, 1 H), 2.88 (t, J=7.5 Hz, 2 H), 3.29 (td, J=12.7, 2.3 Hz, 2 H), 4.18 (br.d, J=13.0 Hz, 2 H), 6.61 (d, J=7.8 Hz, 1 H), 7.21 - 7.26 (m, 3 H), 7.29 (s, 1 H), 7.31 - 7.36 (m, 2 H), 7.79 (d, J=7.8 Hz, 1 H).

Example 29

7-(4-Phenyl-piperidin-1-yl)-3-trifluoromethyl-imidazo[1,2-a]pyridine-8-carbonitrile (E29)

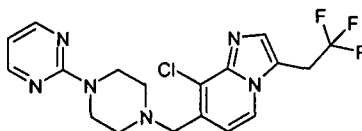


- 5 To a mixture of compound **D24** (0.08 g, 0.326 mmol) in DMF (3 ml) were added 4-phenylpiperidine (0.058 g, 0.358 mmol) and Et₃N (0.05 g, 0.489 mmol). The reaction mixture was subjected to microwave heating at 150 °C for 45 min. After cooling, the solvent was evaporated *in vacuo*. The crude product was pre-purified by column chromatography (silica gel; heptane/EtOAc 1:1 as eluent) and then by preparative
- 10 radial chromatography. The desired fractions were collected and evaporated *in vacuo* to yield a yellow oil that treated with isopropanol to give a precipitate that was filtered off and dried affording compound **E29** (0.005 g, 4%).

- ¹H NMR (400 MHz, CDCl₃) δ ppm 1.85 - 2.00 (m, 2 H), 2.02 - 2.12 (m, 2 H), 2.84 (tt, J=12.0, 3.8 Hz, 1 H), 3.36 (td, J=12.7, 2.3 Hz, 2 H), 4.29 (dt, J=13.2, 2.0 Hz, 2 H), 6.72 (d, J=7.9 Hz, 1 H), 7.21 - 7.28 (m, 3 H), 7.30 - 7.38 (m, 2 H), 7.82 (d, J=1.2 Hz, 1 H), 8.03 (d, J=7.9 Hz, 1 H).

Example 36

- 20 8-Chloro-7-(4-pyrimidin-2-yl-piperazin-1-ylmethyl)-3-(2,2,2-trifluoro-ethyl)imidazo[1,2-a]pyridine (E36)



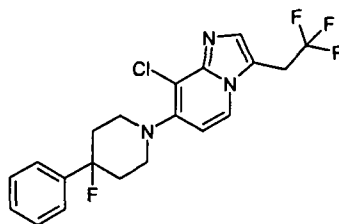
- A mixture of compounds **D43** (0.51 g, 1.673 mmol) and **D8** (0.686 g, 3.347 mmol) in EtOH (8 ml) was subjected to microwave heating at 150 °C for 50 min. After cooling to
- 25 room temperature, the solvent was evaporated *in vacuo*. The residue thus obtained was taken up in NaHCO₃ (aqueous sat. solution) and extracted with DCM. The organic layer was separated, dried (Na₂SO₄) and evaporated *in vacuo* and the residue was purified by column chromatography (silica gel; starting from DCM/MeOH(NH₃) up to 1% and followed by DCM/MeOH up to 2% as eluent). The desired fractions were
- 30 collected and evaporated *in vacuo* to yield a residue that was triturated with diisopropylether to yield compound **E36** (0.40 g, 58 %) as cream solid.

¹H NMR (500 MHz, CDCl₃) δ ppm 2.56 - 2.63 (m, 4 H), 3.74 (q, J=10.1 Hz, 2 H), 3.78 (s, 2 H), 3.82 - 3.88 (m, 4 H), 6.49 (t, J=4.9 Hz, 1 H), 7.21 (d, J=6.9 Hz, 1 H), 7.67 (s, 1 H), 7.94 (d, J=6.9 Hz, 1 H), 8.31 (d, J=4.6 Hz, 2 H).

5

Example 50

8-Chloro-7-(4-fluoro-4-phenyl-piperidin-1-yl)-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine (E50)

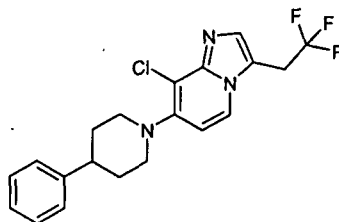


- 10 To a mixture of compounds **D40** (0.56 g, 1.831 mmol) and DMF (0.638 ml, 3.663 mmol) in iPrOH (8 ml) was added **D8** (0.751 g, 3.663 mmol). The resulting mixture was subjected to microwave heating at 150 °C for 50 min. After cooling to room temperature, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by column chromatography (silica gel; DCM/EtOAc up to 20% as eluent). The
- 15 desired fractions were collected and evaporated *in vacuo*. The residue was purified by preparative Superfluid Critical (pyridine 20 mm; mobile phase, isocratic 85% CO₂, 15% MeOH) yielding compound **E50** (221 g, 29%).

- ¹H NMR (500 MHz, CDCl₃) δ ppm 2.15 (br. t, J=11.8 Hz, 2 H), 2.33 (td, J=13.6, 4.9 Hz, 1 H), 2.42 (td, J=13.6, 4.9 Hz, 1 H), 3.31 (br. t, J=11.8 Hz, 2 H), 3.44 - 3.52 (m, 2 H), 3.71 (q, J=9.8 Hz, 2 H), 6.87 (d, J=7.2 Hz, 1 H), 7.31 - 7.36 (m, 1 H), 7.39 - 7.45 (m, 2 H), 7.46 - 7.50 (m, 2 H), 7.60 (s, 1 H), 7.91 (d, J=7.2 Hz, 1 H).
- 20

Example 51

- 25 8-Chloro-7-(4-phenyl-piperidin-1-yl)-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine (E51)



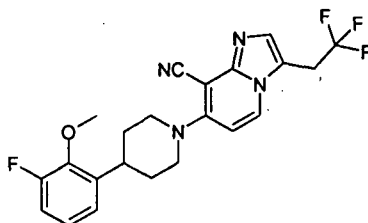
A solution of intermediate **D50** (0.05 g, 0.134 mmol) in chlorhydric acid 12N was stirred at room temperature for 10 min. Then after cooling to 0°C, NaNO₂ (0.184 mg,

2.671 mmol) was slowly added, followed by CuCl (104.024 mg, 0.14 mmol). The reaction mixture was then stirred at room temperature for 16 h. The reaction was further heated at 80°C for 90 min., cooled, poured into a mixture of NH₄OH:H₂O 1:1 and then extracted with DCM. The combined organic phase was dried (Na₂SO₄) and the solvent evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; starting from DCM/EtOAc up to 10% as eluent). The desired fractions were collected and evaporated *in vacuo*. The residue thus obtained was triturated with diisopropylether to yield **E51** (19 mg, 36%) as a brown solid

¹H NMR (400 MHz, CDCl₃) δ ppm 1.93 - 2.09 (m, 4 H), 2.69 (tt, J=11.3, 4.6 Hz, 1 H), 2.95 (td, J=11.6, 2.9 Hz, 2 H), 3.66 (br. d, J=11.6 Hz, 2 H), 3.70 (q, J=9.8 Hz, 2 H), 6.82 (d, J=7.5 Hz, 1 H), 7.20 - 7.26 (m, 1 H), 7.28 - 7.32 (m, 2 H), 7.32 - 7.38 (m, 2 H), 7.59 (s, 1 H), 7.88 (d, J=7.5 Hz, 1 H).

Example 61

7-[4-(3-Fluoro-2-methoxy-phenyl)-piperidin-1-yl]-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (**E61**)

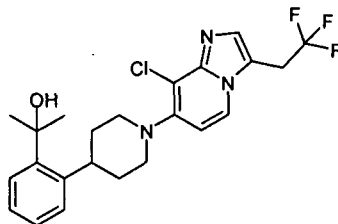


To a suspension of intermediate **D54** (0.090 g, 0.215 mmol) and potassium carbonate (0.054 mg, 0.43 mmol) in DMF (1 ml) was added methyl iodide (0.037 mg, 0.258 mmol). The resulting reaction mixture was heated at 150°C for 10 min. under microwave irradiation. After cooling to room temperature, water was added and the resulting aqueous mixture was extracted with EtOAc. The combined organic phase was dried (Na₂SO₄) and the solvent evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; starting from DCM/EtOAc up to 25% as eluent). The desired fractions were collected and evaporated *in vacuo*. The residue thus obtained was triturated with diisopropylether to yield **E61** (7.8 mg, 8.4%) as a solid

¹H NMR (400 MHz, CDCl₃) δ ppm 1.82 - 2.04 (m, 4 H), 3.24 (tt, J=11.7, 4.1 Hz, 1 H), 3.34 (td, J=12.9, 2.8 Hz, 2 H), 3.66 (q, J=9.9 Hz, 2 H), 3.96 (d, J=1.8 Hz, 3 H), 4.21 (br. d, J=12.9 Hz, 2 H), 6.65 (d, J=7.9 Hz, 1 H), 6.93 - 7.05 (m, 3 H), 7.51 (s, 1 H), 7.90 (d, J=7.6 Hz, 1 H).

Example 65

2-(2-{1-[8-Chloro-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridin-7-yl]-piperidin-4-yl}-phenyl)-propan-2-ol (E65)



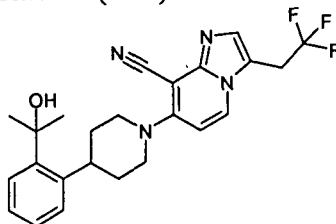
5 To a stirred solution of compound **D20** (0.4 g, 1.11 mmol) in toluene (13 ml) were added **D29** (0.365 g, 1.664 mmol), palladium (II) acetate (0.0126 g, 0.0555 mmol), cesium carbonate (0.904 g, 2.774 mmol) and BINAP (0.0518 g, 0.0832 mmol). The reaction mixture was heated at 100 °C for 16 h. in a sealed tube. The reaction mixture
10 was then charged with an additional amount of cesium carbonate (0.05 eq.) and BINAP (0.075 eq.) and heating continued at 100°C for a further 16 h. After this period, a further amount of cesium carbonate (0.05 eq.) and BINAP (0.075 eq.) was added and the reaction heated at 80°C for two days. The mixture was then cooled to room temperature, filtered through a pad of diatomaceous earth and the filtrate evaporated *in vacuo*. The residue thus obtained was purified by column chromatography (silica gel;
15 DCM/EtOAc from 100:0 to 50:50). The desired fractions were collected and evaporated *in vacuo*. The residue thus obtained was triturated with diethylether to yield **E65** (0.195 g, 39 %)

20 ¹H NMR (500 MHz, CDCl₃) δ ppm 1.72 (s, 6 H), 1.81 (s, 1 H), 1.91 (br. d, J=11.8 Hz, 2 H), 2.08 (qd, J=12.7, 3.5 Hz, 2 H), 2.92 - 3.02 (m, 2 H), 3.64 (d, J=11.6 Hz, 2 H), 3.70 (q, J=9.8 Hz, 2 H), 3.81 (tt, J=11.8, 3.8 Hz, 1 H), 6.82 (d, J=7.5 Hz, 1 H), 7.13 - 7.22 (m, 1 H), 7.30 (t, J=7.4 Hz, 1 H), 7.43 (d, J=7.8 Hz, 1 H), 7.49 (d, J=7.5 Hz, 1 H), 7.58 (s, 1 H), 7.88 (d, J=7.5 Hz, 1 H).

25

Example 67

7-{4-[2-(1-Hydroxy-1-methyl-ethyl)-phenyl]-piperidin-1-yl}-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (E67)

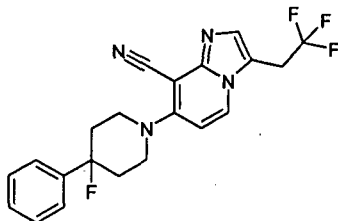


A mixture of compound **D10** (0.23 g, 0.62 mmol), **D29** (0.163 g, 0.744 mmol) and *N,N*-diisopropylethylamine (0.162 ml, 0.93 mmol) in CH₃CN (10 ml) was subjected to microwave heating in a sealed tube at 160 °C for 60 min. The reaction mixture was charged with additional **D29** (0.0598 g; 0.44 eq) and *N,N*-diisopropylethylamine (0.054 ml, 0.5 equ.) and irradiated again at 160 °C for 45 min. The mixture was cooled to room temperature and the solvents were evaporated *in vacuo*. The residue thus obtained was purified by column chromatography (silica gel; DCM/MeOH(NH₃) up to 3% as eluent) to give compound **E67** (0.212 g, 77%).

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.57 (s, 6 H), 1.76 - 1.92 (m, 4 H), 3.20 - 3.29 (m, 2 H), 3.91 - 4.00 (m, 1 H), 4.14 (q, J=11.0 Hz, 2 H), 4.20 (br. d, J=13.6 Hz, 2 H), 5.07 (s, 1 H), 7.00 (d, J=7.8 Hz, 1 H), 7.11 (t, J=7.2 Hz, 1 H), 7.19 (t, J=7.4 Hz, 1 H), 7.31 (d, J=7.5 Hz, 1 H), 7.39 (d, J=7.5 Hz, 1 H), 7.40 (s, 1 H), 8.51 (d, J=7.8 Hz, 1 H).

Example 68

7-(4-Fluoro-4-phenyl-piperidin-1-yl)-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-*a*]pyridine-8-carbonitrile (**E68**)

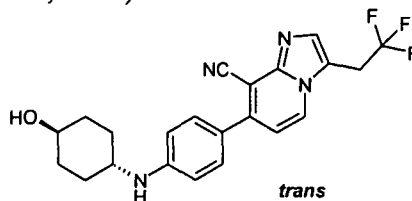


A mixture of compound **D10** (0.626 g, 0.250 mmol), 4-fluoro-4-phenylpiperidine [C.A.S. 1056382-25-2] (0.1234 g, 0.689 mmol), *N,N*-diisopropylethylamine (0.161 mg, 1.252 mmol) in CH₃CN (5 ml) was subjected to microwave heating in a sealed tube at 150 °C for 25 min. The reaction mixture was cooled to room temperature and the solvents were evaporated *in vacuo*. The residue thus obtained was taken up in DCM and washed with NaHCO₃ (aqueous sat. solution). The organic layer was separated, dried (Na₂SO₄) and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel; DCM/MeOH(NH₃) up to 10% as eluent) to give compound **E68** (0.065 g, 24.5%).

¹H NMR (500 MHz, CDCl₃) δ ppm 2.14 - 2.24 (m, 2 H), 2.29 (td, J=13.9, 4.6 Hz, 1 H), 2.36 (td, J=13.9, 4.9 Hz, 1 H), 3.63 (td, J=13.0, 2.6 Hz, 2 H), 3.67 (q, J=9.8 Hz, 2 H), 4.03 (ddd, J=12.7, 2.3 Hz, 2 H), 6.69 (d, J=7.8 Hz, 1 H), 7.31 - 7.36 (m, 1 H), 7.37 - 7.45 (m, 4 H), 7.54 (s, 1 H), 7.94 (d, J=7.8 Hz, 1 H).

Example 91

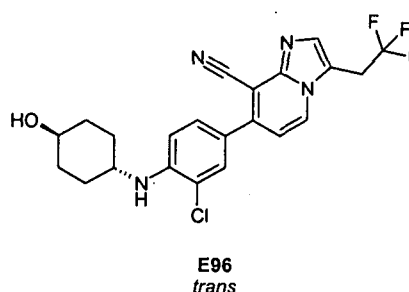
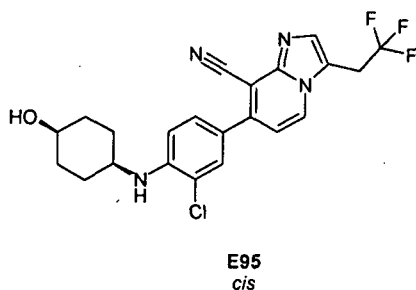
7-[4-(4-hydroxy-cyclohexylamino)-phenyl]-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile. (E91, *trans*)



- 5 To a solution of intermediate **D46** (0.060 g, 0.113 mmol) in THF (3 ml) stirred at room temperature and under a nitrogen atmosphere, was added tetramethylammonium fluoride – 1.0 M solution in toluene/THF (0.170, 0.17 mmol) dropwise and the resulting reaction mixture was stirred at room temperature for 16 h. The solvent was then evaporated *in vacuo*. The residue thus obtained was taken up in DCM and the resulting
- 10 solution washed with water. The combined organic phase was dried (Na₂SO₄) and the solvent evaporated *in vacuo*. The residue was purified by column chromatography (silica gel; starting from DCM/MeOH(NH₃) up to 2% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **E91** (0.016 g, 34%) as a yellow solid.
- 15 ¹H NMR (400 MHz, CDCl₃) δ ppm 1.19 - 1.35 (m, 2 H), 1.38 - 1.55 (m, 3 H), 1.99 - 2.12 (m, 2 H), 2.13 - 2.24 (m, 2 H), 3.27 - 3.44 (m, 1 H), 3.67 - 3.75 (m, 1 H), 3.76 (q, J=9.8 Hz, 2 H), 3.90 (br. s., 1 H), 6.69 (d, J=8.8 Hz, 2 H), 7.07 (d, J=7.2 Hz, 1 H), 7.58 (d, J=8.8 Hz, 2 H), 7.72 (s, 1 H), 8.13 (d, J=7.4 Hz, 1 H).

20 **Example 95 and Example 96**

7-[3-Chloro-4-(4-hydroxy-cyclohexylamino)-phenyl]-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile. (E95-*cis*) (E96, *trans*)



- 25 To a mixture of intermediate **D36** (0.419 g, 0.938 mmol) in MeOH (40 ml) stirred at 0°C, was added sodium borohydride (0.039 mg, 1.031 mmol). The mixture was gradually warmed to room temperature and stirred for 30 min. The resulting mixture was then evaporated *in vacuo*. The residue thus obtained was taken up in AcOEt, washed with sodium chloride (aqueous sat. solution), dried (Na₂SO₄), filtered and

evaporated *in vacuo*. The residue thus obtained was purified column chromatography (silica gel; DCM/EtOAc up to 20% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **E95** (*cis*) (0.05 g, 11,9 %) and **E96** (*trans*) (0.075 g, 17.8 %).

5

E95, cis

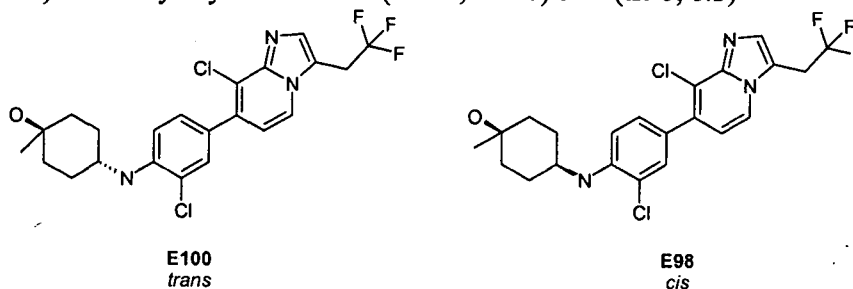
¹H NMR (400 MHz, CDCl₃) δ ppm 1.37 (br. s., 1 H), 1.70 - 1.92 (m, 8 H), 3.48 - 3.57 (m, 1 H), 3.77 (q, J=9.9 Hz, 2 H), 3.98 (br. s., 1 H), 4.69 (br. d, J=7.6 Hz, 1 H), 6.79 (d, J=9.0 Hz, 1 H), 7.05 (d, J=7.2 Hz, 1 H), 7.60 (dd, J=9.3, 2.1 Hz, 1 H), 7.62 (s, 1 H),
10 7.75 (s, 1 H), 8.15 (d, J=7.2 Hz, 1 H).

E96, trans

¹H NMR (400 MHz, CDCl₃) δ ppm 1.26 (br. s., 1 H), 1.30 - 1.42 (m, 2 H), 1.42 - 1.54 (m, 2 H), 2.03 - 2.13 (m, 2 H), 2.20 (br. d, J=12.0 Hz, 2 H), 3.35 - 3.47 (m, 1 H), 3.70 -
15 3.80 (m, 1 H), 3.77 (q, J=9.7 Hz, 2 H), 4.51 (br. d, J=7.2 Hz, 1 H), 6.79 (d, J=8.6 Hz, 1 H), 7.04 (d, J=7.2 Hz, 1 H), 7.59 (dd, J=8.6, 2.1 Hz, 1 H), 7.62 (d, J=2.1 Hz, 1 H), 7.75 (s, 1 H), 8.16 (d, J=7.2 Hz, 1 H).

Example 98 and Example 100

20 4-{2-Chloro-4-[8-chloro-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridin-7-yl]-phenylamino}-1-methyl-cyclohexanol. (**E100, trans**) and (**E98, cis**)



To a solution of intermediate **D36** (0.238 g, 0.449 mmol) in THF (50 ml), cooled at -78 °C and under nitrogen atmosphere, was added methylmagnesium bromide - 1.4 M solution in toluene/THF (0.352 ml, 0.493 mmol) dropwise and the resulting reaction mixture was stirred for 10 min. The reaction was then gradually warmed to room temperature and stirred for 16 h. The reaction mixture was then charged with additional methylmagnesium bromide - 1.4 M solution in toluene/THF (0.801, 0.572 mmol ml). The reaction was heated at 60°C for 3 h. After cooling in an ice bath the mixture was
25 carefully quenched with a saturated aqueous solution of ammonium chloride, and was then extracted with EtOAc. The combined organic phase was dried (Na₂SO₄) and the solvent evaporated *in vacuo*. The residue was purified by column chromatography
30

(silica gel; starting from DCM/EtOAc 1:1 as eluent). The desired fractions were collected and evaporated *in vacuo* to yield **E98** (*cis*) (0.021 g) as a cream solid and **E100** (*trans*) (0.052 g) as a white solid.

5 **E98** (*cis*)

¹H NMR (400 MHz, CDCl₃) δ ppm 1.27 (br. s., 1 H), 1.33 (s, 3 H), 1.49 - 1.67 (m, 4 H), 1.71 - 1.81 (m, 2 H), 2.05 - 2.15 (m, 2 H), 3.51 - 3.60 (m, 1 H), 3.75 (q, J=9.9 Hz, 2 H), 4.50 (br. d, J=7.4 Hz, 1 H), 6.76 (d, J=8.6 Hz, 1 H), 6.92 (d, J=6.9 Hz, 1 H), 7.37 (dd, J=8.6, 2.1 Hz, 1 H), 7.49 (d, J=2.1 Hz, 1 H), 7.70 (s, 1 H), 7.95 (d, J=6.9 Hz, 1 H).

10

E100 (*trans*)

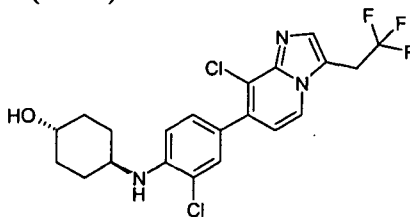
M.P. 205.1°C

¹H NMR (400 MHz, CDCl₃) δ ppm 1.14 (br. s., 1 H), 1.30 (s, 3 H), 1.51 - 1.64 (m, 2 H), 1.62 - 1.73 (m, 2 H), 1.73 - 1.81 (m, 2 H), 1.93 - 2.03 (m, 2 H), 3.29 - 3.40 (m, 1 H), 3.75 (q, J=9.9 Hz, 2 H), 4.45 (br. d, J=7.9 Hz, 1 H), 6.75 (d, J=8.6 Hz, 1 H), 6.92 (d, J=7.2 Hz, 1 H), 7.37 (dd, J=8.6, 2.1 Hz, 1 H), 7.48 (d, J=2.1 Hz, 1 H), 7.70 (s, 1 H), 7.95 (d, J=6.9 Hz, 1 H).

15

Example 101

20 4-{2-Chloro-4-[8-chloro-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridin-7-yl]phenylamino}-cyclohexanol. (**E101**)



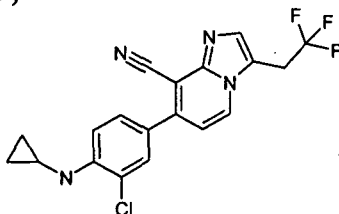
To a mixture of compound **D20** (0.480 g, 0.934 mmol) in 1,4-dioxane (2 ml) under a nitrogen atmosphere were added compound **D38** (0.394 g, 1.12 mmol), Pd(PPh₃)₄ (0.00539 g, 0.0467 mmol) and NaHCO₃ (1 ml, aqueous sat. solution). The reaction mixture was subject to microwave heating at 150 °C for 10 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with EtOAc. The filtrate washed with NaCl (aqueous sat. solution). The organic layer was separated, dried (Na₂SO₄) and evaporated *in vacuo* and the residue was purified by column chromatography (silica gel; starting from DCM/MeOH(NH₃) up to 1% and followed by DCM/EtOAc 7:3 as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **E101** (0.240 g, 56.1 %).

30

¹H NMR (500 MHz, CDCl₃) δ ppm 1.31 - 1.40 (m, 2 H), 1.43 - 1.53 (m, 2 H), 1.47 (s, 1 H), 2.08 (br. d, J=10.4 Hz, 2 H), 2.21 (br. d, J=11.6 Hz, 2 H), 3.33 - 3.43 (m, 1 H), 3.71 - 3.78 (m, 1 H), 3.75 (q, J=9.8 Hz, 2 H), 4.37 (br. d, J=7.8 Hz, 1 H), 6.76 (d, J=8.7 Hz, 1 H), 6.92 (d, J=6.9 Hz, 1 H), 7.37 (dd, J=8.4, 2.0 Hz, 1 H), 7.49 (d, J=2.3 Hz, 1 H), 7.70 (s, 1 H), 7.96 (d, J=7.2 Hz, 1 H).

Example 105

7-(3-Chloro-4-cyclopropylamino-phenyl)-3-(2,2,2-trifluoro-ethyl)-imidazo[1,2-a]pyridine-8-carbonitrile (E105)



10

To a mixture of compound **D13** (0.150 g, 0.321 mmol) in 1,4-dioxane (2 ml) under a nitrogen atmosphere were added compound **D31** (0.113 g, 3.85 mmol), Pd(PPh₃)₄ (0.0185 g, 0.016 mmol) and NaHCO₃ (0.5 ml, aqueous sat. solution). The reaction mixture was subjected to microwave heating at 150 °C for 10 min. After cooling, the mixture was filtered through a pad of diatomaceous earth and washed with 1,4-dioxane. The filtrate was evaporated *in vacuo* and the residue was purified by column chromatography (silica gel; DCM/MeOH(NH₃) up to 10% as eluent). The desired fractions were collected and evaporated *in vacuo* to yield compound **E105** (0.017 g, 13.9%).

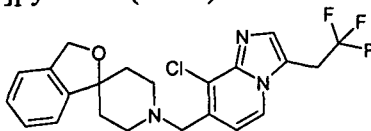
20

¹H NMR (400 MHz, CDCl₃) δ ppm 0.61 - 0.67 (m, 2 H), 0.84 - 0.90 (m, 2 H), 2.50 - 2.58 (m, 1 H), 3.78 (q, J=9.9 Hz, 2 H), 5.03 (br. s., 1 H), 7.06 (d, J=7.2 Hz, 1 H), 7.21 (d, J=8.6 Hz, 1 H), 7.60 (d, J=2.1 Hz, 1 H), 7.63 (dd, J=8.6, 2.1 Hz, 1 H), 7.76 (s, 1 H), 8.16 (d, J=7.4 Hz, 1 H).

25

Example 123

8-Chloro-7-(4-spiro-[3-(2,3-dihydro-benzofuran)] piperidin-1-ylmethyl)-3-(2,2,2-trifluoro-ethyl) imidazo[1,2-a]pyridine (E123)



30

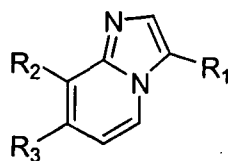
A mixture of **D45** (0.1 g, 0.303 mmol) and **D8** (0.124 g, 0.606 mmol) in EtOH (2 ml) was subjected to microwave heating at 150 °C for 50 min. After cooling to room

temperature, the solvent was evaporated *in vacuo*. The residue thus obtained was taken up in NaHCO₃ (aqueous sat. solution) and extracted with DCM. The organic layer was separated, dried (Na₂SO₄) and evaporated *in vacuo*. The residue thus obtained was purified by column chromatography (silica gel; starting from DCM/MeOH up to 3%.

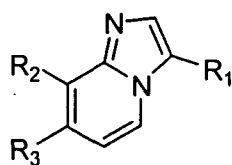
- 5 The desired fractions were collected and evaporated *in vacuo* to yield a residue that was triturated with diisopropylether to yield compound **E123** (0.059 g, 44.7 %) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ ppm 1.78 (br. d, J=11.8 Hz, 2 H), 1.99 (td, J=13.0, 4.6 Hz, 2 H), 2.57 - 2.67 (m, 2 H), 2.83 (br. d, J=11.3 Hz, 2 H), 3.73 (q, J=9.9 Hz, 2 H), 3.81 (s, 2 H), 5.08 (s, 2 H), 7.13 - 7.18 (m, 1 H), 7.19 - 7.24 (m, 2 H), 7.24 - 7.31 (m, 2 H), 7.66 (s, 1 H), 7.93 (d, J=6.9 Hz, 1 H).

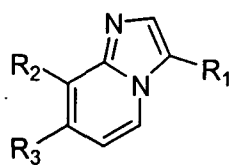
- 15 **Table 1**: Compounds prepared according to Formula (I).



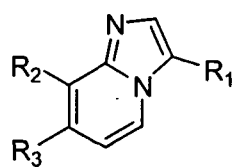
Co.nr.	Exp nr.	R ¹	R ²	R ³
1	E1*		--CN	
2	E2*	--CH ₂ -CF ₃	--CN	
3	E3*	--CH ₂ -CF ₃	--CN	
4	E4*	--CH ₂ -CF ₃	--CN	
5	E3	--CH ₂ -CH ₂ -CH ₃	--CN	



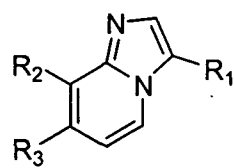
Co.nr.	Exp nr.	R ¹	R ²	R ³
6	E3	--CH ₂ -CH ₂ -CH ₃	--CN	
7	E3		--CN	
8	E3	--CH ₂ -CH ₂ -CH ₃	--CN	
9	E4	--CH ₂ -CH ₂ -CH ₃	--CN	
10	E2		--CN	
11	E4	--CH ₂ -CH ₂ -CH ₃	--CN	
12	E2	--CH ₂ -CH ₃	--CN	
13	E4	--CH ₂ -CF ₃	--CN	
14	E2	--CH ₂ -CH ₂ -CH ₃	--CN	
15	E2	--CH ₂ -CH ₂ -CH ₃	--CN	
16	E2	--CH ₂ -CH ₃	--CN	
17	E4	--CH ₂ -CF ₃	--CN	
18	E4	--CH ₂ -CH ₃	--CN	



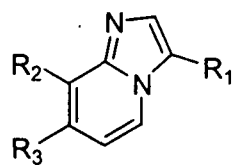
Co.nr.	Exp nr.	R ¹	R ²	R ³
19	E2	--CH ₂ -CH ₃	--CN	
20	E2		--CN	
21	E21*	--CH ₂ -CH ₂ -CH ₃	--Cl	
22	E2	--CH ₂ -CH ₂ -CH ₃	--CN	
23	E2	--CH ₂ -CH ₃	--CN	
24	E4	--CH ₃	--CN	
25	E4	--CH ₂ -CH ₃	--CN	
26	E3	--CH ₃	--CN	
27	E2	--CH ₂ -CF ₃	--CN	
28	E28*	--CH ₂ -CH ₂ -CH ₂ -CF ₃	--CN	
29	E29*	--CF ₃	--CN	
30	E3	--CH ₂ -CF ₃	--CN	
31	E3	--CH ₂ -CF ₃	--CN	



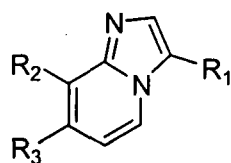
Co.nr.	Exp nr.	R ¹	R ²	R ³
32	E3	--CH ₂ -CF ₃	--CN	
33	E3	--CH ₂ -CF ₃	--CN	
34	E2	--CH ₂ -CF ₃	--CN	
35	E36	--CH ₂ -CF ₃	--Cl	
36	E36*	--CH ₂ -CF ₃	--Cl	
37	E36	--CH ₂ -CF ₃	--Cl	
38	D42	--CH ₂ -CF ₃	--CN	
39	E2	--CH ₂ -CF ₃	--CN	
40	D42	--CH ₂ -CF ₃	--CN	
41	E36	--CH ₂ -CF ₃	--Cl	
42	E36	--CH ₂ -CF ₃	--Cl	
43	E2	--CH ₂ -CF ₃	--CN	
44	E2	--CH ₂ -CF ₃	--CN	



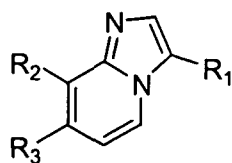
Co.nr.	Exp nr.	R ¹	R ²	R ³
45	E2	--CH ₂ -CF ₃	--CN	
46	E36	--CH ₂ -CF ₃	--Cl	
47	E4		--CN	
48	E2		--CN	
49	E4		--CN	
50	E50*	--CH ₂ -CF ₃	--Cl	
51	E51*	--CH ₂ -CF ₃	--Cl	
52	E2	--CH ₂ -CF ₃	--CN	
53	E2	--CH ₂ -CF ₃	--CN	
54	E2	--CH ₂ -CF ₃	--CN	
55	E28		--CN	
56	E2	--CH ₂ -CF ₃	--CN	



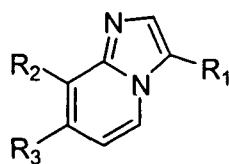
Co.nr.	Exp nr.	R ¹	R ²	R ³
57	E2	--CH ₂ -CF ₃	--CN	
58	E2	--CH ₂ -CF ₃	--CN	
59	E2	--CH ₂ -CF ₃	--CN	
60	E2	--CH ₂ -CF ₃	--CN	
61	E61*	--CH ₂ -CF ₃	--CN	
62	E2	--CH ₂ -CF ₃	--CN	
63	E65	--CH ₂ -CF ₃	--Cl	
64	E4	--CH ₂ -CF ₃	--Me	
65	E65*	--CH ₂ -CF ₃	--Cl	
66	E50	--CH ₂ -CF ₃	--Cl	
67	E67*	--CH ₂ -CF ₃	--CN	
68	E68*	--CH ₂ -CF ₃	--CN	



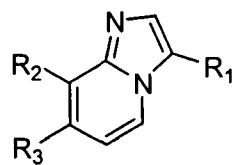
Co.nr.	Exp nr.	R ¹	R ²	R ³
69	E2	--CH ₂ -CF ₃	--CN	
70	E50	--CH ₂ -CF ₃	--Cl	
71	E4	--CH ₂ -CF ₃	--CN	
72	E4	--CH ₂ -CF ₃	--CN	
73	E28	--CH ₂ -CH ₂ -CH ₂ -CF ₃	--CN	
74	E4	--CH ₂ -CF ₃	--CN	
75	E28		--CN	
76	E4	--CH ₂ -CF ₃	--CN	
77	E4	--CH ₂ -CF ₃	--CN	
78	E4	--CH ₂ -CF ₃	--CN	
79	E4	--CH ₂ -CF ₃	--CN	
80	E4	--CH ₂ -CF ₃	--CN	
81	E4	--CH ₂ -CF ₃	--CN	
82	E4	--CH ₂ -CF ₃	--CN	



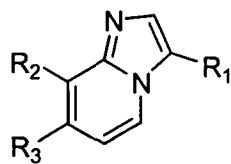
Co.nr.	Exp nr.	R ¹	R ²	R ³
83	E4	--CH ₂ -CF ₃	--CN	
84	E4	--CH ₂ -CF ₃	--CN	
85	E4	--CH ₂ -CF ₃	--CN	
86	E4	--CH ₂ -CF ₃	--CN	
87	E4	--CH ₂ -CF ₃	--CN	
88	E4	--CH ₂ -CF ₃	--CN	
89	E4	--CH ₂ -CF ₃	--CN	
90	E4	--CH ₂ -CF ₃	--CN	
91	E91*	--CH ₂ -CF ₃	--CN	
92	E4	--CH ₂ -CF ₃	--CN	
93	E91	--CH ₂ -CF ₃	--CN	
94	E4	--CH ₂ -CF ₃	--CN	
95	E95*	--CH ₂ -CF ₃	--CN	
96	E96*	--CH ₂ -CF ₃	--CN	



Co.nr.	Exp nr.	R ¹	R ²	R ³
97	E98	--CH ₂ -CF ₃	--CN	
98	E98*	--CH ₂ -CF ₃	--Cl	
99	E4	--CH ₂ -CF ₃	--Cl	
100	E100*	--CH ₂ -CF ₃	--Cl	
101	E101*	--CH ₂ -CF ₃	--Cl	
102	E96	--CH ₂ -CF ₃	--CN	
103	E95	--CH ₂ -CF ₃	--CN	
104	E98	--CH ₂ -CF ₃	--CN	
105	E105*	--CH ₂ -CF ₃	--CN	
106	E4	--CH ₂ -CF ₃	--CN	
107	E4	--CH ₂ -CF ₃	--CN	
108	E4	--CH ₂ -CF ₃	--CN	
109	E50	--CH ₂ -CF ₃	--Cl	



Co.nr.	Exp nr.	R^1	R^2	R^3
110	E4	--CH ₂ -CF ₃	--CN	
111	E4	--CH ₂ -CF ₃	--CN	
112	E4	--CH ₂ -CF ₃	--CN	
113	E4	--CH ₂ -CF ₃	--CN	
114	E4	--CH ₂ -CF ₃	--CN	
115	E2	--CH ₂ -CF ₃	--CN	
116	E2	--CH ₂ -CF ₃	--CN	
117	E2	--CH ₂ -CF ₃	--CN	
118	E2	--CH ₂ -CF ₃	--CN	
119	E2	--CH ₂ -CF ₃	--CN	
120	E4	--CH ₂ -CF ₃	--CN	
121	E2	--CH ₂ -CF ₃	--CN	



Co.nr.	Exp nr.	R^1	R^2	R^3
122	E95	--CH ₂ -CF ₃	--CN	
123	E123*	--CH ₂ -CF ₃	--Cl	
124	E123	--CH ₂ -CF ₃	--Cl	
125	E21	--CH ₂ -CF ₃	--Cl	

Physico-Chemical Data

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

5 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)

15 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)

25 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

30

was maintained at 140 °C. Data acquisition was performed with MassLynx-Openlynx software.

Method 1.

5 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
10 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.

15

Method 2.

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),
20 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
25 was 20 V and 50V for positive ionization mode and 30V for negative ionization mode.

Method 3.

In addition to the general procedure: Reversed phase UPLC was carried out on a BEH-C18 column (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 0.8 ml/min, at
30 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.

5

Method 4.

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.

15

Method 5.

This method was used in Beerse for purity/concentration validation (CLND) after SFC separation. Afterwards, we have validated the purity in Toledo using S6009S6001 method.

20

Method 6.

In addition to the general procedure: Reversed phase UPLC was carried out on a HSS-T3 column (1.8 μm, 2.1 x 50 mm) from Waters, with a flow rate of 0.8 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l ammonium acetate solution + 5 % acetonitrile), 5 % 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.

30

Method 7.

In addition to the general procedure: Reversed phase HPLC was carried out on a XBridge-C18 column (2.5 μ m, 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 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 μ l. 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 8

In addition to the general procedure: Reversed phase HPLC was carried out on a Sunfire-C18 column (2.5 μ m, 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 μ l. 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 9.

In addition to the general procedure: Reversed phase HPLC was carried out on a Sunfire-C18 column (2.5 μ m, 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 μ l. 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
5 30 V 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 μ m, 2.1 x 30 mm) from Waters, with a flow rate of
10 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 in 5.0 minutes, kept till 5.15 minutes and equilibrated to initial conditions at 5.30 minutes until 7.0 minutes. Injection volume 2 μ l. Low-resolution mass spectra (SQD detector; quadrupole) were acquired in positive
15 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 11.

In addition to the general procedure: Reversed phase HPLC was carried out on an XDB-C18 cartridge (1.8 μ m, 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 (1 g/l ammonium bicarbonate solution), 5 % B (acetonitrile), 5 % C (methanol) to 50 % B and 50 % C in
20 6.0 minutes, to 100 % B at 6.5 minutes and equilibrated to initial conditions at 7.0 minutes until 9.0 minutes. Injection volume 2 μ l. High-resolution mass spectra (Time of Flight, TOF) were acquired only in positive ionization mode by scanning from 100 to 750 in 0.5 seconds using a dwell time of 0.1 seconds. The capillary needle voltage was 2.5 kV for positive ionization mode and the cone voltage was 20 V. Leucine-Enkephaline was the standard substance used for the lock mass calibration.

Method 12.

In addition to the general procedure: Reversed phase HPLC was carried out on a Eclipse Plus-C18 column (3.5 μ m, 2.1 x 30 mm) from Agilent, with a flow rate of 1.0 ml/min, at 60°C without split to the MS detector. The gradient conditions used are: 95
5 % 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 5.30 minutes until 7.0 minutes. Injection volume 2 μ l. 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
10 needle voltage was 3 kV. The cone voltage was 20 V for positive ionization mode and 30 V for negative ionization mode.

Method 13.

In addition to the general procedure: Reversed phase HPLC was carried out on a
15 Sunfire-C18 column (2.5 μ m, 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), 2.5 % B (acetonitrile), 2.5% C (methanol), to 50 % B, 50 % C 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 μ l. High-resolution mass spectra (Time
20 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.

25

Method 14.

In addition to the general procedure: Reversed phase HPLC was carried out on a Sunfire-C18 column (2.5 μ m, 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
30 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 μ l. 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

5

Method 15.

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.

15 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 16.

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)

25 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 17.

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

5 % B (acetonitrile), 5 % C (methanol), kept 0.2 minutes, to 50 % B, 50 % C in 3.5 minutes, kept till 3.65 minutes and equilibrated to initial conditions at 3.8 minutes until 5.0 minutes. Injection volume 2 μ l. 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.

10 Method 18.

In addition to the general procedure: Reversed phase HPLC was carried out on a Eclipse Plus-C18 column (3.5 μ m, 2.1 x 30 mm) from Agilent, 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), 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 μ l. 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 19.

In addition to the general procedure: Reversed phase HPLC was carried out on an XDB-C18 cartridge (1.8 μ m, 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 μ l. 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 20.

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: 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
10 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.

15

Method 21.

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),
20 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
25 and 50 V for positive ionization mode and 20 V for negative ionization mode.

Method 22.

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
30 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 μ l. 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 23.

In addition to the general procedure: Reversed phase HPLC was carried out on a XDB-C18 cartridge (1.8 μ m, 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), 5 % B (acetonitrile), 5 % C (methanol), kept 0.2 minutes, to 50 % B, 50 % C in 3.5 minutes, kept till 3.65 minutes and equilibrated to initial conditions at 3.8 minutes until 5.0 minutes. Injection volume 2 μ l. Low-resolution mass spectra (single quadrupole, Platform detector) were acquired by scanning from 100 to 750 in 1.5 second using a dwell time of 0.3 second. The capillary needle voltage was 3 kV. The cone voltage was 30 V and 70 V for positive ionization mode and 30 V for negative ionization mode.

Method 24.

In addition to the general procedure: Reversed phase HPLC was carried out on a XDB-C18 cartridge (1.8 μ m, 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 μ l. 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.

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

Co.Nr	Melting point (°C)	MW (theor)	[MH ⁺]	RT (min)	LCMS Method
1	nd	392	393	5.32	1
2	239	387	388	3.34	1
3	nd	384	385	4.41	1
4	nd	426	427	4.11	1
5	126.8-131	412	413	5.13	1
6	161	344	345	4.73	1
7	nd	392	393	5.08	1
8	201.1	360	361	3.93	1
9	159	368	369	4.28	1
10	nd	378	379	5.01	1
11	181.8	368	369	4.25	1
12	150	330	331	4.39	1
13	nd	408	409	4.03	1
14	194.4	375	376	4.41	1
15	148.2	345	346	4.31	1
16	265	346	347	3.55	1
17	nd	426	427	4.02	1
18	nd	354	355	3.91	1
19	231.4	361	362	4.07	1
20	220	379	380	4.64	1
21	nd	369	370	4.17	1
22	176.4	347	348	3.56	1
23	nd	333	334	3.13	1
24	nd	340	341	3.55	1
25	197.6	372	373	3.92	1

Co.Nr	Melting point (°C)	MW (theor)	[MH ⁺]	RT (min)	LCMS Method
26	nd	316	317	3.98	1
27	nd	398	399	4.74	1
28	128.5	412	413	4.9	1
29	nd	370	371	4.68	1
30	272.1	400	401	3.64	1
31	139.3	402	403	4.45	1
32	>300	452	453	4.80	1
33	186.5	420	421	4.65	2
34	>300	415	416	4.15	1
35	154.8	425	426	4.9	1
36	161.4	410	411	3.8	1
37	156.9	444	445	4.7	1
38	181.2	432	433	3.7	1
39	nd	435	436	4.5	1
40	145	416	417	4.6	1
41	161.1	425	426	5.1	1
42	decompose	407	408	5.1	1
43	196	444	445	3.7	1
44	152	416	417	4.9	1
45	nd	432	433	3.9	1
46	150.2	426	427	4.8	1
47	267	414	415	5.1	1
48	145.4	370	371	5.0	1
49	nd	342	343	4.5	1
50	220.7	411	412	5.2	1,5,6
51	263.1	393	394	4.9	1
52	nd	421	422	4.2	1

Co.Nr	Melting point (°C)	MW (theor)	[MH ⁺]	RT (min)	LCMS Method
53	decompose	400	401	4.0	1
54	155.4	442	443	4.1	2
55	decompose	373	374	4.0	1
56	decompose	401	402	3.7	1
57	nd	469	470	4.3	1
58	212.9	412	413	4.4	2
59	decompose	428	429	3.8	1
60	decompose	401	402	3.7	1
61	nd	432	433	4.6	1
62	289.8	418	419	3.8	3
63	189.3	451	452	4.3	7
64	213.9	373	374	5.2	1
65	234.7	451	452	4.7	8
66	174.4	421	422	3.8	4
67	227.5	442	443	3.4	4
68	214	402	403	4.4	1
69	nd	432	433	4.4	8
70	decompose	420	421	5.0	1
71	195.6	409	410	5.0	1
72	nd	427	428	4.8	1
73	234.1	454	455	4.4	1
74	163	411	412	4.7	1
75	277.2	412	413	4.6	1
76	decompose	411	412	4.8	1
77	177.9	411	412	4.6	1
78	176	411	412	4.7	1
79	173.4	409	410	4.6	1

Co.Nr	Melting point (°C)	MW (theor)	[MH ⁺]	RT (min)	LCMS Method
80	174.3	393	394	4.7	1
81	102.7	421	422	4.1	1
82	143.2	451	452	4.4	1
83	decompose	437	438	3.0	1
84	nd	419	420	5.2	1
85	decompose	405	406	4.8	1
86	nd	423	424	4.1	1
87	decompose	393	394	4.7	1
88	nd	357	358	4.7	1
89	161.6	462	463	4.4	1
90	decompose	435	436	4.2	1
91	137.5	414	415	3.4	1
92	230.7	434	435	4.3	1
93	155	414	415	3.6	1
94	202.6	462	463	4.4	1
95	nd	448	449	4.1	2
96	123.7	448	449	4.1	1
97	nd	463	464	3.3	4
98	nd	471	472	4.7	8
99	149.7	443	444	4.6	9
100	205.1	471	472	4.7	8
101	183.1	457	458	4.3	8
102	nd	449	450	3.3	4
103	210.2	449	450	3.1	4
104	nd	463	464	3.5	4
105	nd	390	391	4.5	1
106	nd	374	375	4.2	1

Co.Nr	Melting point (°C)	MW (theor)	[MH ⁺]	RT (min)	LCMS Method
107	decompose	384	385	4.8	1
108	decompose	404	405	4.9	1
109	decompose	393	394	5.1	1
110	decompose	420	421	4.2	1
111	nd	400	401	3.4	1
112	174	442	443	3.3	4
113	decompose	425	426	4.8	1
114	207.1	425	426	4.7	1
115	198.7	426	427	4.7	1
116	252.5	396	397	4.35	2
117	decompose	395	396	4.04	2
118	nd	430	431	4.55	2
119	nd	464	465	4.57	2
120	nd	407	408	4.75	2
121	decompose	469	470	4.22	2
122	nd	406	407	2.77	4
123	164.2	435	436	4.63	9
124	nd	451	452	3.07	20
125	decompose	434	435	4.17	12

n.d. means not determined

D. Pharmacological examples

5 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 [³⁵S]GTPγS binding assay method described below and which is suitable for the identification of such compounds, and more particularly the compounds according to Formula (I), are shown in Table 3

5

[³⁵S]GTPγS binding assay

The [³⁵S]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, [³⁵S]GTPγS (guanosine 5'-triphosphate, labelled with gamma-emitting ³⁵S), 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, [³⁵S]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 [³⁵S]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 [³⁵S]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.

25

Membrane preparation

CHO-cells were cultured to pre-confluence and stimulated with 5 mM butyrate for 24 hours, prior to washing in PBS, and then collection by scraping in homogenisation buffer (50 mM Tris-HCl buffer, pH 7.4, 4 °C). Cell lysates were homogenized briefly (15s) using an ultra-turrax homogenizer. The homogenate was centrifuged at 23 500 x g for 10 minutes and the supernatant discarded. The pellet was resuspended in 5 mM Tris-HCl, pH 7.4 and centrifuged again (30 000 x g, 20 min, 4 °C). The final pellet was resuspended in 50 mM HEPES, pH 7.4 and stored at -80 °C in appropriate aliquots before use. Protein concentration was determined by the Bradford method (Bio-Rad, USA) with bovine serum albumin as standard.

35

[³⁵S]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 MgCl₂, 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 EC₂₅ 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 [³⁵S]GTPγS (0.1 nM, f.c.) to achieve a total reaction volume of 200 µl, microplates were shaken briefly and further incubated to allow [³⁵S]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 (Na₂PO₄·2H₂O 10 mM, NaH₂PO₄·H₂O 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 [³⁵S]GTPγS was measured in a 96-well scintillation plate reader (Top-Count, Perkin-Elmer, USA). Non-specific [³⁵S]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.

25 Data analysis

The concentration-response curves of representative compounds of the present invention in the presence of added EC₂₅ 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 ($Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogEC}_{50} - X) * \text{Hill Slope}))}$) allowing determination of EC₅₀ values. The EC₅₀ is the concentration of a compound that causes a half-maximal potentiation of the glutamate response. This is calculated by subtracting the maximal responses of glutamate in presence of a fully saturating concentration of a positive allosteric modulator from the response of glutamate in absence of a positive allosteric modulator. The concentration producing the half-maximal effect is then calculated as EC₅₀

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

Co.Nr	GTP γ S - hR2 PAM
	pEC ₅₀
1	6.29
2	6.07
3	6.91
4	6.16
5	6.97
6	6.81
7	6.75
8	6.50
9	6.50
10	6.40
11	6.37
12	6.30
13	6.23
14	6.19
15	6.01
16	6.00
17	5.95
18	5.88
19	5.64
20	n.c.
21	n.c.
22	n.c.
23	n.c.
24	n.c.
25	n.c.

Co.Nr	GTP γ S - hR2 PAM
	pEC ₅₀
26	n.c.
27	6.53
28	6.88
29	6.11
30	6.38
31	7.09
32	7.09
33	7.21
34	6.35
35	6.22
36	n.c.
37	5.52
38	n.c.
39	5.86
40	5.89
41	6.36
42	6.25
43	n.c.
44	6.49
45	n.c.
46	5.76
47	6.64
48	7.03
49	6.17
50	6.71
51	6.80
52	6.56

Co.Nr	GTP γ S - hR2 PAM
	pEC ₅₀
53	5.87
54	6.62
55	5.96
56	6.19
57	6.32
58	7.01
59	6.43
60	6.28
61	7.43
62	6.78
63	6.41
64	5.81
65	6.75
66	6.55
67	6.84
68	7.03
69	8.01
70	6.57
71	6.74
72	6.67
73	5.98
74	6.77
75	6.43
76	6.57
77	6.98
78	6.66
79	6.59

Co.Nr	GTP γ S - hR2 PAM
	pEC ₅₀
80	6.73
81	6.28
82	7.35
83	6.17
84	6.52
85	6.12
86	5.50
87	6.51
88	6.35
89	6.56
90	6.17
91	5.95
92	6.15
93	5.87
94	6.76
95	6.73
96	6.53
97	6.22
98	6.31
99	6.20
100	6.90
101	6.81
102	6.07
103	6.03
104	5.98
105	6.85
106	5.2

Co.Nr	GTP γ S - hR2 PAM
	pEC ₅₀
107	6.63
108	6.34
109	6.56
110	5.67
111	5.98
112	6.17
113	6.81
114	6.85
115	6.67
116	6.76
117	6.16
118	7.20
119	7.24
120	6.80
121	5.68
122	6.26
123	n.c.
124	6.1
125	5.75

n.c. means that the EC₅₀ could not be calculated

EC50 values were not calculated in case the concentration-response curve did not reach a plateau level. By definition, the EC50 value of a compound is the concentration needed to reach 50% of the maximal response reached by that compound.

All compounds were tested in presence of mGluR2 agonist, glutamate at a predetermined EC_{25} concentration, to determine positive allosteric modulation (GTP γ S-PAM). Values shown are averages of duplicate values of 11-concentration response curves, from at least one experiment. All compounds except compound No. 20 to 26 (for which no maximal response could be obtained) showed a pEC_{50} value of more than 5.0, from 5.6 (weak activity) to 7.2 (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.

10 E. Composition examples

"Active ingredient" as used throughout these examples relates to a final compound of formula (I), the pharmaceutically acceptable salts thereof, the solvates and the stereochemically isomeric forms thereof.

Typical examples of recipes for the formulation of the invention are as follows:

15

1. Tablets

Active ingredient	5 to 50 mg
Di-calcium phosphate	20 mg
Lactose	30 mg
20 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.

25

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.

30

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.

35

4. Ointment

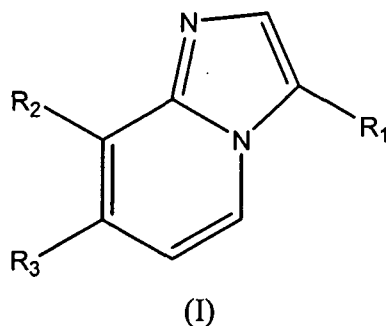
	Active ingredient	5 to 1000 mg
	Stearyl alcohol	3 g
	Lanoline	5 g
5	White petroleum	15 g
	Water	ad 100 g

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

Reasonable variations are not to be regarded as a departure from the scope of the invention. It will be obvious that the thus described invention may be varied in many ways by those skilled in the art.

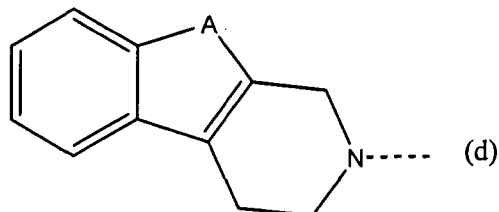
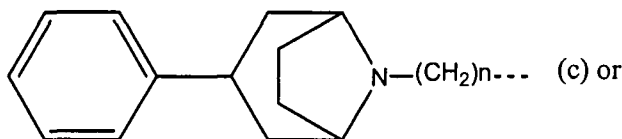
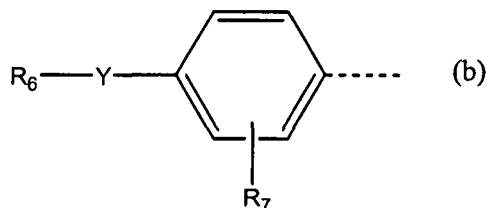
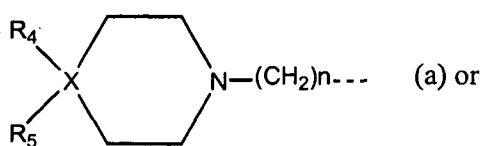
CLAIMS

1. A compound having the formula (I)



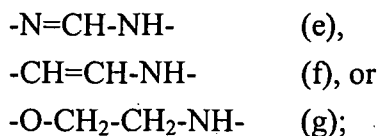
or a stereochemically isomeric form thereof, wherein

- R^1 is C_{1-6} alkyl; C_{3-6} cycloalkyl; trifluoromethyl; C_{1-3} alkyl substituted with trifluoromethyl, 2,2,2-trifluoroethoxy, C_{3-7} cycloalkyl, phenyl, or phenyl substituted with C_{1-3} alkyl, C_{1-3} alkyloxy, cyano, halo, trifluoromethyl, or trifluoromethoxy; phenyl; phenyl substituted with 1 or 2 substituents selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkyloxy, cyano, halo, trifluoromethyl, and trifluoromethoxy; or 4-tetrahydropyranyl;
- R^2 is cyano, halo, trifluoromethyl, C_{1-3} alkyl or cyclopropyl;
- R^3 is a radical of formula (a) or (b) or (c) or (d)

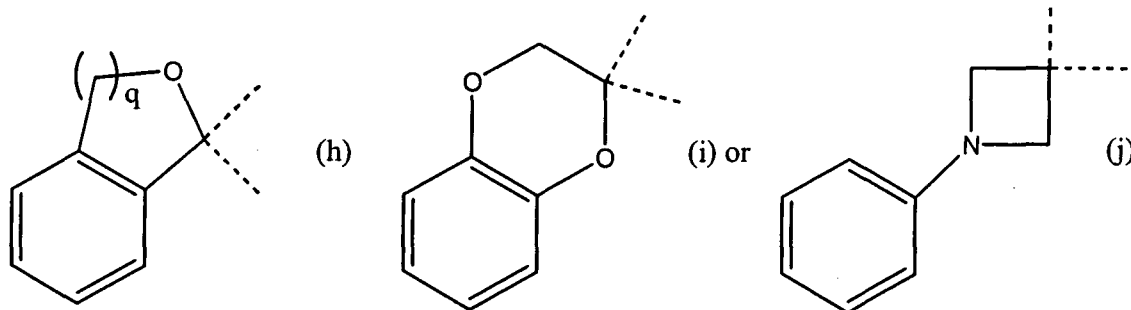


R^4 is hydrogen; hydroxy C_{3-6} cycloalkyl; pyridinyl; pyridinyl substituted with one or two C_{1-3} alkyl groups; pyrimidinyl; pyrimidinyl substituted with one or two C_{1-3} alkyl groups; phenyl; phenyl substituted with 1 or 2 substituents selected from the group

consisting of halo, C₁₋₃alkyl, hydroxyC₁₋₃alkyl, mono- or polyhaloC₁₋₃alkyl, cyano, hydroxyl, amino, carboxyl, C₁₋₃alkyloxyC₁₋₃alkyl, C₁₋₃alkyloxy, mono- or polyhalo-C₁₋₃alkyloxy, C₁₋₃alkylcarbonyl, mono- and di(C₁₋₃alkyl)amino, and morpholinyl; or phenyl with two vicinal substituents which taken together form a bivalent radical of formula



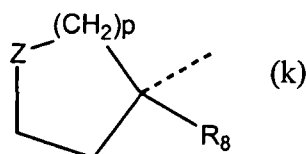
R⁵ is hydrogen, fluoro, hydroxyl, hydroxyC₁₋₃alkyl, hydroxyC₁₋₃alkyloxy, fluoroC₁₋₃alkyl, fluoroC₁₋₃alkyloxy, morpholinyl or cyano;
 X is C or N in which case R⁵ represent the electron pair on N; or
 R⁴-X-R⁵ represents a radical of formula (h) or (i) or (j)



n is 0 or 1;
 q is 1 or 2;

R⁶ is C₁₋₃alkyl; C₃₋₆cycloalkyl; hydroxyC₂₋₄alkyl; (C₃₋₆cycloalkyl)C₁₋₃alkyl; phenyl; pyridinyl; or phenyl or pyridinyl substituted with one or two substituents selected from the group consisting of halo, C₁₋₃alkyl, C₁₋₃alkoxy, hydroxyC₁₋₃alkyl, trifluoromethyl and (CH₂)_m-CO₂H, wherein m = 0, 1, or 2; or

R⁶ is a cyclic radical of formula (k)



wherein R⁸ is hydrogen, C₁₋₃alkyl, C₁₋₃alkyloxy, hydroxyC₁₋₃alkyl;
 p is 1 or 2 ;
 Z is O, CH₂ or CR⁹(OH) wherein R⁹ is hydrogen or C₁₋₃alkyl; or
 R⁸ and R⁹ form a radical -CH₂-CH₂-;

R⁷ is hydrogen, halo or trifluoromethyl;

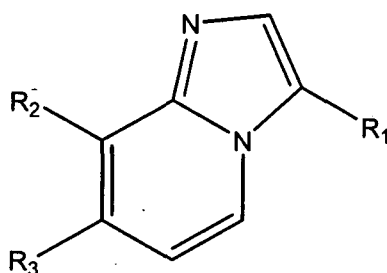
Y is a covalent bond, O, NH, S, SO, SO₂, C(OH)(CH₃), -CH₂-O-, -O-CH₂-, CHF or CF₂; or

R⁶-Y is morpholinyl, pyrrolidinyl, or piperidinyl optionally substituted with hydroxyl or hydroxyC₁₋₃alkyl; and

5 A is O or NH;

or a pharmaceutically acceptable salt or a solvate thereof.

2. The compound according to claim 1 having the formula (I)



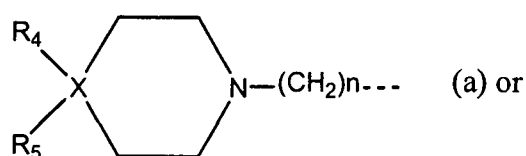
(I)

or a stereochemically isomeric form thereof, wherein

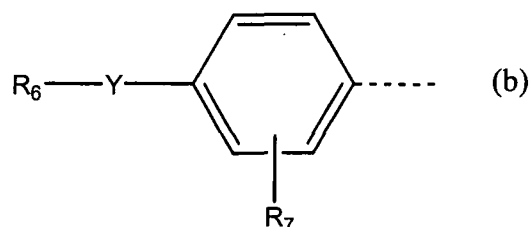
R¹ is C₁₋₆alkyl; trifluoromethyl; C₁₋₃alkyl substituted with trifluoromethyl, 2,2,2-trifluoroethoxy, C₃₋₇cycloalkyl, phenyl, or phenyl substituted with halo, trifluoromethyl, or trifluoromethoxy; phenyl; phenyl substituted with halo, trifluoromethyl, or trifluoromethoxy; or 4-tetrahydropyranyl;

R² is cyano, halo, trifluoromethyl, C₁₋₃alkyl or cyclopropyl;

R³ is a radical of formula (a) or (b)



(a) or



(b)

R⁴ is hydrogen; pyridinyl; pyrimidinyl; pyrimidinyl substituted with one or two C₁₋₃alkyl groups; phenyl; phenyl substituted with 1 or 2 substituents selected from the group consisting of halo, C₁₋₃alkyl, hydroxyC₁₋₃alkyl, polyhaloC₁₋₃alkyl, cyano, hydroxyl, amino, carboxyl, C₁₋₃alkyloxyC₁₋₃alkyl, C₁₋₃alkyloxy, polyhaloC₁₋₃alkyloxy, C₁₋₃alkylcarbonyl, mono- and di(C₁₋₃alkyl)amino, and morpholinyl; or phenyl with two vicinal substituents which taken together form a bivalent radical of formula

-N=CH-NH- (e),

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

-O-CH₂-CH₂-NH- (g);

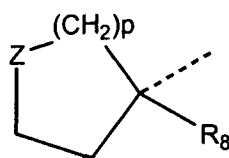
R⁵ is hydrogen, fluoro, hydroxyl, hydroxyC₁₋₃alkyl, hydroxyC₁₋₃alkyloxy, fluoroC₁₋₃alkyl, fluoroC₁₋₃alkyloxy or cyano;

- 5 X is C or N in which case R⁵ represent the electron pair on N;
n is 0 or 1;

R⁶ is phenyl; pyridinyl; or phenyl or pyridinyl substituted with one or two substituents selected from the group consisting of halo, C₁₋₃alkyl, C₁₋₃alkoxy, trifluoromethyl and

- 10 (CH₂)_m-CO₂H, wherein m = 0, 1, or 2; or

R⁶ is a cyclic radical of formula (k)



wherein R⁸ is hydrogen, C₁₋₃alkyl, C₁₋₃alkyloxy, hydroxyC₁₋₃alkyl;

- 15 p is 1 or 2 ;

Z is O or CR⁹(OH) wherein R⁹ is hydrogen or C₁₋₃alkyl; or

R⁸ and R⁹ form a radical -CH₂-CH₂-;

R⁷ is hydrogen, halo or trifluoromethyl;

Y is a covalent bond, O, NH, S, SO, SO₂, or CF₂; or

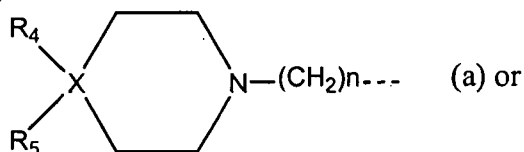
- 20 a pharmaceutically acceptable salt or a solvate thereof.

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

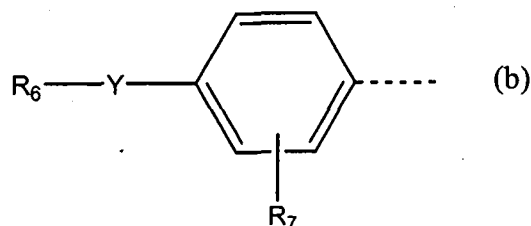
- 25 R¹ is C₁₋₆alkyl; trifluoromethyl; C₁₋₃alkyl substituted with trifluoromethyl, or phenyl; or phenyl;

R² is cyano or halo;

R³ is a radical of formula (a) or (b)



(a) or



(b)

R^4 is pyrimidinyl; pyrimidinyl substituted with one or two C_{1-3} alkyl groups; phenyl; phenyl substituted with 1 or 2 substituents selected from the group consisting of halo, polyhalo C_{1-3} alkyl,

R^5 is hydrogen or hydroxyl;

- 5 X is C or N in which case R^5 represent the electron pair on N;
n is 0 or 1;

R^6 is pyridinyl substituted with one or two substituents selected from the group consisting of C_{1-3} alkyl;

- 10 R^7 is hydrogen or halo;

Y is O; or

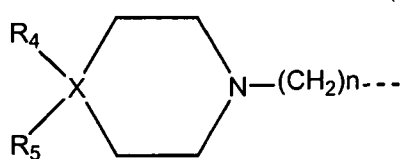
a pharmaceutically acceptable salt or a solvate thereof.

4. The compound according to claim 1 wherein

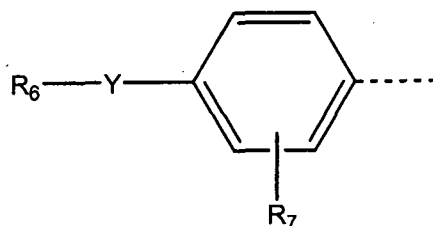
- 15 R^1 is methyl; ethyl, 1-propyl, trifluoromethyl; 2,2,2-trifluoroethyl, 4,4,4-trifluorobutyl, phenylmethyl or phenyl;

R^2 is cyano;

R^3 is a radical of formula (a) or (b)



(a) or



(b)

20

R^4 is pyrimidinyl; pyrimidinyl substituted with one or two C_{1-3} alkyl groups; phenyl; phenyl substituted with 1 or 2 substituents selected from the group consisting of fluoro, chloro and trifluoromethyl;

R^5 is hydrogen or hydroxyl;

- 25 X is C or N in which case R^5 represent the electron pair on N;
n is 0 or 1;

R^6 is pyridinyl substituted with one or two substituents selected from the group consisting of methyl;

- 30 R^7 is hydrogen, fluoro or chloro;

Y is O; or

a pharmaceutically acceptable salt or a solvate thereof.

5. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 4 and a pharmaceutically acceptable carrier or excipient.
- 5 6. A compound according to any one of claims 1 to 4 for use as a medicament.
7. Use of a compound according to any one of claims 1 to 4 or a pharmaceutical composition according to claim 5 for the manufacture of a medicament for treating or preventing a condition in a mammal, including a human, the treatment
10 or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR2 positive allosteric modulators.
8. Use of a compound according to any one of claims 1 to 4 or a pharmaceutical composition according to claim 5 for the manufacture of a medicament for treating
15 or preventing a central nervous system disorder selected from the group of anxiety disorders, psychotic disorders, personality disorders, substance-related disorders, eating disorders, mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, neurotoxicity and ischemia.
- 20 9. Use according to claim 8, wherein the central nervous system disorder is an anxiety disorder, selected from the group of agoraphobia, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, posttraumatic stress disorder (PTSD), social phobia and other phobias.
- 25 10. Use according to claim 8, wherein the central nervous system disorder is a psychotic disorder selected from the group of schizophrenia, delusional disorder, schizoaffective disorder, schizophreniform disorder and substance-induced psychotic disorder.
- 30 11. Use according to claim 8, wherein the central nervous system disorder is a personality disorder selected from the group of obsessive-compulsive personality disorder and schizoid, schizotypal disorder.
- 35 12. Use according to claim 8, wherein the central nervous system disorder is a substance-related disorder selected from the group of alcohol abuse, alcohol dependence, alcohol withdrawal, alcohol withdrawal delirium, alcohol-induced

psychotic disorder, amphetamine dependence, amphetamine withdrawal, cocaine dependence, cocaine withdrawal, nicotine dependence, nicotine withdrawal, opioid dependence and opioid withdrawal.

- 5 13. Use according to claim 8, wherein the central nervous system disorder is an eating disorder selected from the group of anorexia nervosa and bulimia nervosa.
- 10 14. Use according to claim 8, wherein the central nervous system disorder is a mood disorder selected from the group of bipolar disorders (I & II), cyclothymic disorder, depression, dysthymic disorder, major depressive disorder and substance-induced mood disorder.
- 15 15. Use according to claim 8, wherein the central nervous system disorder is migraine.
- 20 16. Use according to claim 8, wherein the central nervous system disorder is epilepsy or a convulsive disorder selected from the group of generalized nonconvulsive epilepsy, generalized convulsive epilepsy, petit mal status epilepticus, grand mal status epilepticus, partial epilepsy with or without impairment of consciousness, infantile spasms, epilepsy partialis continua, and other forms of epilepsy.
- 25 17. Use according to claim 8, wherein the childhood disorder is attention-deficit/hyperactivity disorder.
- 30 18. Use according to claim 8, wherein the central nervous system disorder is a cognitive disorder selected from the group of delirium, substance-induced persisting delirium, dementia, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, dementia of the Alzheimer's type, substance-induced persisting dementia and mild cognitive impairment.
- 35 19. Use according to claim 8, wherein the central nervous system disorder is selected from the group of anxiety, schizophrenia, migraine, depression, and epilepsy.
20. Use of a compound according to any one of claims 1 to 4 in combination with an orthosteric agonist of mGluR2 for the manufacture of a medicament for treating or preventing a condition as cited in any one of claims 7 to 19.

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