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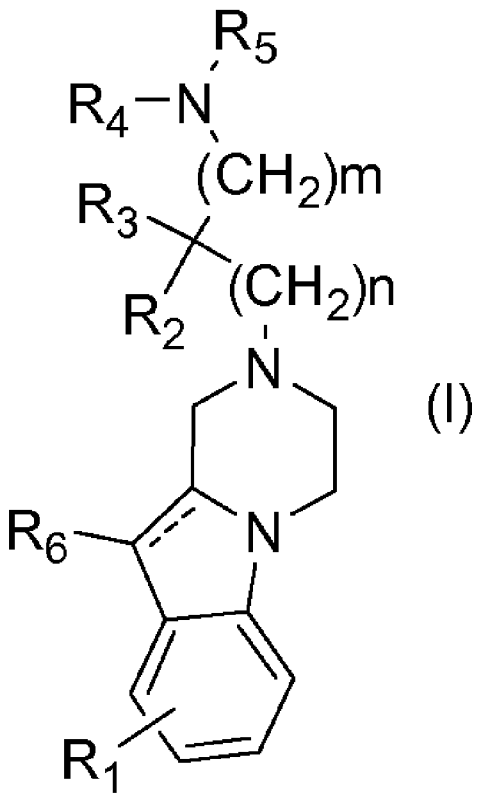

(I)

(57) Abstract: The invention refers to compounds of general formula (I) wherein the variables take the various meanings, pharmaceutical compositions containing them and their use in medicine, particularly in pain therapy.

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PYRAZINO[1,2-a]INDOLE COMPOUNDS, THEIR PREPARATION AND USE IN MEDICAMENTS

FIELD OF THE INVENTION

The present invention relates to compounds, pharmaceutical compositions containing them and their use in medicine, particularly in pain therapy.

BACKGROUND

The search for new therapeutic agents has been greatly aided in recent years by better understanding of the structure of proteins and other biomolecules associated with target diseases. One important class of these proteins are the sigma (σ) receptors, cell surface receptors of the central nervous system (CNS) which may be related to the dysphoric, hallucinogenic and cardiac stimulant effects of opioids. From studies of the biology and function of sigma receptors, evidence has been presented that sigma receptor ligands may be useful in the treatment of psychosis and movement disorders such as dystonia and tardive dyskinesia, and motor disturbances associated with Huntington's chorea or Tourette's syndrome and in Parkinson's disease (Walker, J.M. et al, Pharmacological Reviews, 1990, 42, 355). It has been reported that the known sigma receptor ligand rimcazole clinically shows effects in the treatment of psychosis (Snyder, S.H., Largent, B.L. J. Neuropsychiatry 1989, 1, 7). The sigma binding sites have preferential affinity for the dextrorotatory isomers of certain opiate benzomorphans, such as SKF-10047, (+)-cyclazocine, and (+)-pentazocine and also for some narcoleptics such as haloperidol.

"The sigma receptor/s" as used in this application is/are well known and defined using the following citation: This binding site represents a typical protein different from opioid, NMDA, dopaminergic, and other known neurotransmitter or hormone receptor families (G. Ronsisvalle et al. Pure Appl. Chem. 73, 1499-1509 (2001)).

The sigma receptor has at least two subtypes, which may be discriminated by stereoselective isomers of these pharmacoactive drugs. SKF-10047 has nanomolar affinity for the sigma 1 (σ-1) site, and has micromolar affinity for the sigma 2 (σ-2) site. Haloperidol has similar affinities for both subtypes.

The Sigma-1 receptor is a non-opiaceous type receptor expressed in numerous adult mammal tissues (e.g. central nervous system, ovary, testicle, placenta, adrenal gland, spleen, liver, kidney, gastrointestinal tract) as well as in embryo development from its earliest stages, and is apparently involved in a large number of physiological functions. Its high affinity for various pharmaceuticals has been described, such as for SKF-10047, (+)-pentazocine, haloperidol and rimcazole, among others, known ligands with analgesic, anxiolytic, antidepressive, antiamnesic, antipsychotic and neuroprotective activity. Sigma-1 receptor is of great interest in pharmacology in view of its possible physiological role in processes related to analgesia, anxiety, addiction, amnesia, depression, schizophrenia, stress, neuroprotection, psychosis and mood

disorders [Kaiser et al (1991) Neurotransmissions 7 (1): 1-5], [Walker, J.M. et al, Pharmacological Reviews, 1990, 42, 355], [Bowen W.D. (2000) Pharmaceutica Acta Helvetiae 74: 211-218] and Hayashi, T. et al, Drugs of the Future 2009, 34 (2), 137].

The Sigma-2 receptor is also expressed in numerous adult mammal tissues (e.g. nervous system, immune system, endocrine system, liver, kidney). Sigma-2 receptors can be components in a new apoptosis route that may play an important role in regulating cell proliferation or in cell development. This route seems to consist of Sigma-2 receptors joined to intracellular membranes, located in organelles storing calcium, such as the endoplasmic reticulum and mitochondria, which also have the ability to release calcium from these organelles. The calcium signals can be used in the signaling route for normal cells and/or in induction of apoptosis.

Sigma-2 receptor ligands, specially agonists, can be used as antineoplastic agents at doses inducing apoptosis or at sub-toxic doses in combination with other antineoplastic agents to revert the resistance to the drug, thereby allowing using lower doses of the antineoplastic agent and considerably reducing its adverse effects.

Additionally, Sigma-2 receptor ligands, specially antagonists, can be useful as agents for improving the weakening effects of delayed dyskinesia appearing in patients due to chronic treatment of psychosis with typical antipsychotic drugs, such as haloperidol. Sigma-2 receptors also seem to play a role in certain degenerative disorders in which blocking these receptors could be useful.

Endogenous sigma ligands are not known, although progesterone has been suggested to be one of them. Possible sigma-site-mediated drug effects include modulation of glutamate receptor function, neurotransmitter response, neuroprotection, behavior, and cognition (Quirion, R. et al. Trends Pharmacol. Sci., 1992, 13:85-86). Most studies have implied that sigma binding sites (receptors) are plasmalemmal elements of the signal transduction cascade. Drugs reported to be selective sigma ligands have been evaluated as antipsychotics (Hanner, M. et al. Proc. Natl. Acad. Sci., 1996, 93:8072-8077). The existence of sigma receptors in the CNS, immune and endocrine systems have suggested a likelihood that it may serve as link between the three systems.

In view of the potential therapeutic applications of agonists or antagonists of the sigma receptor, a great effort has been directed to find effective ligands. Different sigma receptor ligands have been reported.

For instance, WO2007098961A1 describes 4,5,6,7-tetrahydrobenzo[b]thiophene derivatives having pharmacological activity towards the sigma receptor.

Spiro[benzopyran] and spiro[benzofuran] derivatives with pharmacological activity on sigma receptors are disclosed in WO2007121976A1.

Pyrazole derivatives presenting a pyrazole group condensed with a cycloalkyl ring have been also reported as sigma ligands in WO2006021463A1.

WO2008055932A1 and WO2008055933A1 deal with 1,2,4-and 1,2,3-triazole compounds, respectively, having activity towards sigma receptors.

WO2009071657A1 also reports tricyclic triazolic compounds having activity towards sigma receptors.

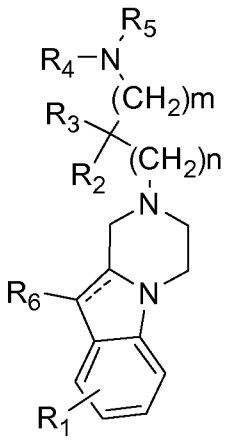
US3317524A discloses substituted 1,2,3,4-tetrahydropyrazino[1,2-a] indoles and intermediates in the preparation thereof, useful as anti-inflammatory agents, as central nervous system depressants, as analgesics and as anti-convulsants.

In spite of this background, there is still a need to find further compounds that have pharmacological activity towards the sigma receptor, preferably being both effective and selective as well as having potentially good "drugability" properties, i.e. good pharmaceutical properties related to administration, distribution, metabolism and excretion.

BRIEF DESCRIPTION OF THE INVENTION

The present invention discloses novel pyrazino[1,2-a]indole compounds with great affinity to sigma receptors which might be used for the treatment and/or prophylaxis of sigma related disorders or diseases.

Specifically, it is an object of the present invention a compound of general formula (I), or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof:



(I)

wherein

m is selected from 0,1, 2, 3 and 4;

n is selected from 0, 1, 2, 3 and 4;

⁻⁻⁻⁻⁻ represents a single or double bond;

$\mathbf{R_1}$ represents one or more optional and independent substitutions in the benzene moiety selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or

unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, -COR_8, -$C(O)OR_8$, -$C(O)NR_8R_9$, -$CH=NR_8$, -CN, -OR_8, -$OC(O)R_8$, -$S(O)_t$-R_8, -NR_8R_9, -$NR_8C(O)R_9$, -NO_2, -$N=CR_8R_9$, and halogen;

R_2 and **R_3** are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, -COR_8, -$C(O)OR_8$, -$C(O)NR_8R_9$, -$CH=NR_8$, -CN, -OR_8, -$OC(O)R_8$, -$S(O)_t$-R_8, -NR_8R_9, -$NR_8C(O)R_9$, and halogen;

or **R_2** and **R_3** together form a substituted or unsubstituted cycloalkyl or a substituted or unsubstituted heterocyclyl;

R_4 and **R_5** are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted, heterocyclyl, substituted or unsubstituted heterocyclylalkyl, -COR_8, -$C(O)OR_8$, and -$C(O)NR_8R_9$;

or **R_4** and **R_5** together with the bridging nitrogen atom form a substituted or unsubstituted heterocyclyl;

R_6 is selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, -COR_8, -$C(O)OR_8$, -$C(O)NR_8R_9$, -$CH=NR_8$, -CN, -OR_8, -$OC(O)R_8$, -$S(O)_t$-R_8, -NR_8R_9, -$NR_8C(O)R_9$, -NO_2, -$N=CR_8R_9$, and halogen;

t is selected from 0, 1 and 2;

R_8 and **R_9** are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl and halogen;

with the proviso that the following compounds are not included:

2-(2-dimethylaminoethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole,

2-(2-dimethylaminoethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole dichlorhydrate,

2-(3-dimethylaminopropyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole,

2-(3-dimethylaminopropyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole chlorhydrate,

2-(morpholinoethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole,

2-(morpholinoethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole chlorhydrate,

2-(morpholinoethyl)-1,2,3,4-tetrahydro-8-methoxypyrazino[1,2-a]indole,

2-(morpholinoethyl)-1,2,3,4-tetrahydro-8-methoxypyrazino[1,2-a]indole fumarate,

2-(2-piperidinoethyl)-1,2,3,4- tetrahydropyrazino[1,2-a]indole,

2-(2-piperidinoethyl)-1,2,3,4- tetrahydropyrazino[1,2-a]indole chlorhydrate, and

2-dimethylaminoethyl-1,2,3,4-tetrahydro-8-fluoropyrazino[1,2-a]indole,

2-(1H-1,2,3-benzotriazol-1-ylmethyl)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole,

2-(4-(2H-benzo[d][1,2,3]triazol-2-yl)butyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole,

2-(4-(3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)butyl)isoindoline-1,3-dione,

2-(4-(6-methoxy-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)butyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one,

N-(4-(6-methoxy-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)butyl)isoquinoline-3-carboxamide,

2-(3-dimethylaminopropyl)-8-chloro-10-phenyl-tetrahydropyrazino[1,2-a]indole,

8-chloro-2-diethylaminoethyl-10-phenyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole,

3-(10-(2-chlorophenyl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)propan-1-amine,

3-(10-(3-chlorophenyl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)propan-1-amine,

3-(10-(4-chlorophenyl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)propan-1-amine,

(10aR)-3-(9-bromo-3,4,10,10a-tetrahydro-1H-pyrazino[1,2-a]indol-2-ylmethyl)-oxazolidin-2-one, and

(10aS)-3-(9-bromo-3,4,10,10a-tetrahydro-1H-pyrazino[1,2-a]indol-2-ylmethyl)-oxazolidin-2-one.

Another object of the invention refers to different processes for the preparation of a compound of general formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof.

Another object of the invention refers to a medicament or pharmaceutical composition comprising at least one compound of general formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof and at least one pharmaceutically acceptable excipient.

Another object of the invention refers to a compound of general formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, for use as a medicament, particularly for the treatment and/or prophylaxis of a sigma receptor-mediated disease or condition.

Another object of the invention refers to the use of a compound of general formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, in the manufacture of a medicament for the treatment and/or prophylaxis of a sigma receptor-mediated disease or condition.

Another object of the invention refers to a method for the treatment and/or prophylaxis of a sigma receptor-mediated disease or condition, the method comprising administering to the subject in need of such a treatment or prophylaxis a therapeutically effective amount of a compound of general formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof.

In one embodiment, said sigma receptor-mediated disease or condition is specifically a sigma-1 mediated disease or condition. Within the group of diseases or conditions mediated by sigma receptor for which the compounds of the invention are useful, the following may be cited: pain, diarrhoea, lipoprotein disorders, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, obesity, migraine, arthritis, hypertension, arrhythmia, ulcer, glaucoma, learning, memory and attention deficits, cognition disorders, neurodegenerative diseases, demyelinating diseases, addiction to drugs and chemical substances including cocaine, amphetamine, ethanol and nicotine; tardive dyskinesia, stroke including ischemic stroke, epilepsy, stress, cancer, psychotic conditions, in particular depression, anxiety or schizophrenia; inflammation or autoimmune diseases. According to one preferred embodiment, the compounds of the invention are used for the treatment and/or prophylaxis of pain, especially neuropathic pain, inflammatory pain or other pain conditions involving allodynia and/or hyperalgesia.

These aspects and preferred embodiments thereof are additionally also defined hereinafter in the detailed description, as well as in the claims.

DETAILED DESCRIPTION OF THE INVENTION

In the context of the present invention, the following terms have the meaning detailed below.

"Alkyl" refers to a straight or branched hydrocarbon chain radical containing no unsaturation, and which is attached to the rest of the molecule by a single bond. Typical alkyl groups have from 1 to about 12, 1 to about 8, or 1 to about 6 carbon atoms, e. g., methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-pentyl, etc. If substituted by cycloalkyl, it corresponds to a “cycloalkylalkyl” radical, such as cyclopropyl methyl. If substituted by aryl, it corresponds to an "arylalkyl" radical, such as benzyl, benzhydryl or phenethyl. If substituted by heterocyclyl, it corresponds to a “heterocyclylalkyl” radical.

“Alkenyl” refers to a straight or branched hydrocarbon chain radical containing at least two carbon atoms and at least one unsaturation, and which is attached to the rest of the molecule by a single bond. Typical alkenyl radicals have from 2 to about 12, 2 to about 8 or 2 to about 6 carbon atoms. In a particular embodiment, the alkenyl group is vinyl, 1-methyl-ethenyl, 1-propenyl, 2-propenyl, or butenyl.

"Alkynyl" refers to a straight or branched hydrocarbon chain radical containing at least two carbon atoms and at least one carbon-carbon triple bond, and which is attached to the rest of the molecule by a single bond. Typical alkynyl radicals have from 2 to about 12, 2 to about 8 or 2 to about 6 carbon atoms. In a particular embodiment, the alkynyl group is ethynyl, propynyl (e.g. 1-propynyl, 2-propynyl), or butynyl (e.g. 1-butynyl, 2-butynyl, 3-butynyl).

"Cycloalkyl" refers to an alicyclic hydrocarbon. Typical cycloalkyl radicals contain from 1 to 4 separated and/or fused rings and from 3 to about 18 carbon atoms, preferably from 3 to 10 carbon atoms, such as cyclopropyl, cyclohexyl or adamantyl. In a particular embodiment, the cycloalkyl radical contains from 3 to about 6 carbon atoms.

"Aryl" refers to single and multiple ring radicals, including multiple ring radicals that contain separate and/or fused aryl groups. Typical aryl groups contain from 1 to 3 separated and/or fused rings and from 6 to about 18 carbon ring atoms, preferably from 6 to about 14 carbon ring atoms, such as phenyl, naphthyl, biphenyl, indenyl, fenanthryl or anthracyl radical.

"Heterocyclyl" include heteroaromatic and heteroalicyclic groups containing from 1 to 3 separated and/or fused rings and from 3 to about 18 ring atoms. Preferably heteroaromatic and heteroalicyclic groups contain from 5 to about 10 ring atoms. Suitable heteroaromatic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., coumarinyl including 8-coumarinyl, quinolyl including 8-quinolyl, isoquinolyl, pyridyl, pyrazinyl, pyrazolyl, pyrimidinyl, furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, isoxazolyl, oxazolyl, imidazolyl, indolyl, isoindolyl, indazolyl, indolizinyl, phthalazinyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, pyridazinyl, triazinyl, cinnolinyl, benzimidazolyl, benzofuranyl, benzofurazanyl, benzothienyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. Suitable heteroalicyclic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., pyrrolidinyl, tetrahydrofuryl, dihydrofuryl, tetrahydrothienyl, tetrahydrothiopyranyl, piperidyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, azepinyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridyl, 2-pyrrolinyl, 3- pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexyl, 3-azabicyclo[4.1.0]heptyl, 3H-indolyl, and quinolizinyl.

The groups above mentioned may be substituted at one or more available positions by one or more suitable groups such as OR', =O, SR', SOR', SO_2R', OSO_2R', OSO_3R', NO_2, NHR', $N(R')_2$, =N-R', N(R')COR', $N(COR')_2$, $N(R')SO_2R'$, N(R')C(=NR')N(R')R', N_3, CN, halogen, COR', COOR', OCOR', OCOOR', OCONHR', $OCON(R')_2$, CONHR', $CON(R')_2$, CON(R')OR', $CON(R')SO_2R'$, $PO(OR')_2$, PO(OR')R', PO(OR')(N(R')R'), C_1-C_{12} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, and heterocyclic group, wherein each of the R' groups is independently selected from

the group consisting of hydrogen, OH, NO_2, NH_2, SH, CN, halogen, COH, COalkyl, COOH, C_1-C_{12} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl and heterocyclic group. Where such groups are themselves substituted, the substituents may be chosen from the foregoing list.

"Halogen", "halo" or "hal" refers to bromo, chloro, iodo or fluoro.

The term "salt" must be understood as any form of a compound used in accordance with this invention in which said compound is in ionic form or is charged and coupled to a counter-ion (a cation or anion) or is in solution. This definition also includes quaternary ammonium salts and complexes of the molecule with other molecules and ions, particularly, complexes formed via ionic interactions. The definition includes in particular physiologically acceptable salts; this term must be understood as equivalent to "pharmacologically acceptable salts" or "pharmaceutically acceptable salts".

The term "pharmaceutically acceptable salts" in the context of this invention means any salt that is tolerated physiologically (normally meaning that it is not toxic, particularly, as a result of the counter-ion) when used in an appropriate manner for a treatment, applied or used, particularly, in humans and/or mammals. These physiologically acceptable salts may be formed with cations or bases and, in the context of this invention, are understood to be salts formed by at least one compound used in accordance with the invention –normally an acid (deprotonated)– such as an anion and at least one physiologically tolerated cation, preferably inorganic, particularly when used on humans and/or mammals. Salts with alkali and alkali earth metals are preferred particularly, as well as those formed with ammonium cations (NH_4^+). Preferred salts are those formed with (mono) or (di)sodium, (mono) or (di)potassium, magnesium or calcium. These physiologically acceptable salts may also be formed with anions or acids and, in the context of this invention, are understood as being salts formed by at least one compound used in accordance with the invention – normally protonated, for example in nitrogen – such as a cation and at least one physiologically tolerated anion, particularly when used on humans and/or mammals. This definition specifically includes in the context of this invention a salt formed by a physiologically tolerated acid, i.e. salts of a specific active compound with physiologically tolerated organic or inorganic acids – particularly when used on humans and/or mammals. Examples of this type of salts are those formed with: hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid or citric acid.

The term "solvate" in accordance with this invention should be understood as meaning any form of the compound in accordance with the invention in which said compound is bonded by a non-covalent bond to another molecule (normally a polar solvent), including especially hydrates and alcoholates, like for example, methanolate. A preferred solvate is the hydrate.

Any compound that is a prodrug of a compound of formula (I) is also within the scope of the invention. The term "prodrug" is used in its broadest sense and encompasses those derivatives that are converted in vivo to the compounds of the

invention. Examples of prodrugs include, but are not limited to, derivatives and metabolites of the compounds of formula (I) that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Preferably, prodrugs of compounds with carboxyl functional groups are the lower alkyl esters of the carboxylic acid. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid moieties present on the molecule. Prodrugs can typically be prepared using well-known methods, such as those described by Burger "Medicinal Chemistry and Drug Discovery 6th ed. (Donald J. Abraham ed., 2001, Wiley) and "Design and Applications of Prodrugs" (H. Bundgaard ed., 1985, Harwood Academic Publishers).

Any compound referred to herein is intended to represent such specific compound as well as certain variations or forms. In particular, compounds referred to herein may have asymmetric centres and therefore exist in different enantiomeric or diastereomeric forms. Thus, any given compound referred to herein is intended to represent any one of a racemate, one or more enantiomeric forms, one or more diastereomeric forms, and mixtures thereof. Likewise, stereoisomerism or geometric isomerism about the double bond is also possible, therefore in some cases the molecule could exist as (E)-isomer or (Z)-isomer (trans and cis isomers). If the molecule contains several double bonds, each double bond will have its own stereoisomerism, that could be the same as, or different to, the stereoisomerism of the other double bonds of the molecule. Furthermore, compounds referred to herein may exist as atropisomers. All the stereoisomers including enantiomers, diastereoisomers, geometric isomers and atropisomers of the compounds referred to herein, and mixtures thereof, are considered within the scope of the present invention.

Furthermore, any compound referred to herein may exist as tautomers. Specifically, the term tautomer refers to one of two or more structural isomers of a compound that exist in equilibrium and are readily converted from one isomeric form to another. Common tautomeric pairs are enamine-imine, amide-imidic acid, keto-enol, lactam-lactim, etc.

Unless otherwise stated, the compounds of the invention are also meant to include isotopically-labelled forms i.e. compounds which differ only in the presence of one or more isotopically-enriched atoms. For example, compounds having the present structures except for the replacement of at least one hydrogen atom by a deuterium or tritium, or the replacement of at least one carbon by ^{13}C- or ^{14}C-enriched carbon, or the replacement of at least one nitrogen by ^{15}N-enriched nitrogen are within the scope of this invention.

The compounds formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, having a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. Purity levels for the drug substance are preferably above 50%, more preferably above 70%, most

preferably above 90%. In a preferred embodiment it is above 95% of the compound of formula (I), or of its salts, solvates or prodrugs.

The skilled person can readily identify which substances fall under the definition of “leaving group”. For the purposes of the present invention, the term “leaving group” has its commonly accepted meaning; on page 275 of March, J. “Advanced Organic Chemistry: Reactions, Mechanism and Structure”, 5th Ed., Wiley-Interscience, a leaving group is defined as the part of the molecule which becomes cleaved in the reaction. Suitable leaving groups are therefore fragments of the molecule prone to being cleaved under certain reaction conditions. They may be present in the molecule from the beginning of the reaction, or may be generated in situ. For the processes disclosed herein, suitable leaving groups are commonly known and may be found in reference books, for example on pages 484-488, of March, J. “Advanced Organic Chemistry: Reactions, Mechanism and Structure”, 5th Ed., Wiley-Interscience. Examples of particular leaving groups include, but are not limited to, halogen, methylsulfonyl, *p*-toluenesulfonyl, trifluoromethylsulfonyl, p-nitrophenyl, ethyltrifluoroacetate and the like.

As used herein, the terms “treat”, “treating” and “treatment” include the eradication, removal, reversion, alleviation, modification, or control of a disease or condition after its onset.

As used herein, the terms “prevention”, “preventing”, “preventive” “prevent” and “prophylaxis” refer to the capacity of a therapeutic to avoid, minimize or difficult the onset or development of a disease or condition before its onset.

Therefore, by "treating" or "treatment" and/or “preventing” or “prevention”, as a whole, is meant at least a suppression or an amelioration of the symptoms associated with the condition afflicting the subject, where suppression and amelioration are used in a broad sense to refer to at least a reduction in the magnitude of a parameter, e.g., symptom associated with the condition being treated. As such, the method of the present invention also includes situations where the condition is completely inhibited, e.g., prevented from happening, or stopped, e.g., terminated, such that the subject no longer experiences the condition.

The inventors of the present invention have observed that pyrazino[1,2-a]indole compounds with general formula (I) as defined above unexpectedly show an affinity for Sigma receptor ranging from good to excellent. These compounds are therefore particularly suitable as pharmacologically active agents in medicaments for the prophylaxis and/or treatment of disorders or diseases related to Sigma receptors.

In particular, pyrazino[1,2-a]indole compounds with general formula (I) as defined above acting as Sigma-1 receptor ligands are preferred.

More particularly, pyrazino[1,2-a]indole compounds with general formula (I) as defined above acting as Sigma-1 receptor antagonist ligands are preferred.

In a particular embodiment, R_1 represents one or more optional and independent substitutions in the benzene moiety selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or

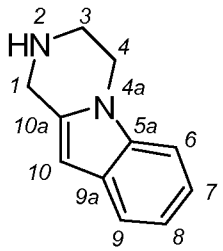
unsubstituted cycloalkylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heterocyclylalkyl.

In a more particular embodiment, R_1 represents one o more optional and independent substitutions in the benzene moiety selected from the group consisting of substituted or unsubstituted alkyl and halogen.

Preferably, R_1 represents one o more optional and independent substitutions in the benzene moiety selected from the group consisting of substituted or unsubstituted C_1-C_6 alkyl and halogen. More preferably, R_1 represents one o more optional and independent substitutions in the benzene moiety independently selected from methyl and fluoro.

According to a particular embodiment, R_1 in the compounds of general formula (I) represents from one to three (one, two or three) substitutions in the benzene moiety. Further, compounds substituted at position 8 of the pyrazino[1,2-a]indol ring have been found to be particularly appropriate.

For the sake of clarity, the usual numbering of the atoms of the pyrazino[1,2-a]indol ring is depicted below.



In a particular embodiment, m is selected from 0, 1 and 2 and/or n is selected from 0, 1, 2 and 3. In a more particular embodiment, m is 0 and/or n is selected from 0, 1, 2 and 3. Compounds of formula general (I) where the sum of m and n is 1, 2 or 3 are preferred.

In a particular embodiment, R_2 and R_3 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted, heterocyclyl, and substituted or unsubstituted heterocyclylalkyl.

In a particular embodiment, R_2 and R_3 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl and substituted or unsubstituted cycloalkyl, or R_2 and R_3 together form a substituted or unsubstituted cycloalkyl or a substituted or unsubstituted heterocyclyl.

In a more particular embodiment, R_2 and R_3 are independently selected from the group consisting of hydrogen and substituted or unsubstituted alkyl, or R_2 and R_3 together form a substituted or unsubstituted cycloalkyl.

Preferably, R_2 and R_3 are independently selected from the group consisting of hydrogen and substituted or unsubstituted C_1-C_6 alkyl. More preferably, R_2 and R_3 are independently selected from the group consisting of hydrogen, methyl and ethyl.

In a particular embodiment, R_4 and R_5 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted, heterocyclyl, and substituted or unsubstituted heterocyclylalkyl.

In a particular embodiment, R_4 and R_5 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, and substituted or unsubstituted cycloalkyl, or R_4 and R_5 together with the bridging nitrogen atom form a substituted or unsubstituted heterocyclyl.

In another particular embodiment, R_4 and R_5 together with the bridging nitrogen atom form a heterocyclyl group optionally substituted by a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, or halogen.

In a more particular embodiment, R_4 and R_5 are independently selected from the group consisting of hydrogen and substituted or unsubstituted C_1-C_6 alkyl, or R_4 and R_5 together with the bridging nitrogen atom form a substituted or unsubstituted 5- to 10-membered heterocyclyl, preferably a substituted or unsubstituted 5-, 6- or 7-membered heterocyclyl. Said substituted or unsubstituted 5-, 6- or 7-membered heterocyclyl is preferably non aromatic (heteroalicylic group).

Preferably, R_4 and R_5 are independently selected from the group consisting of hydrogen and substituted or unsubstituted methyl or ethyl, or R_4 and R_5 together with the bridging nitrogen atom form a substituted or unsubstituted azepanyl, piperidinyl or piperazinyl. Particular heterocyclyl radicals formed by R_4 and R_5 together with the bridging nitrogen atom are 4-methylpiperazin-1-yl, 4-cyclohexylpiperazin-1-yl, azepan-1-yl, piperidin-1-yl and 4-benzylpyperidin-1-yl.

According to one embodiment, R_4 and R_5 together with the bridging nitrogen atom form a 5-, 6- or 7-membered non aromatic heterocyclyl that, if substituted, said substitution is not =O.

In certain variants of the invention, R_4 and R_5 are independently not hydrogen or R_4 and R_5 are simultaneously not hydrogen.

In yet another embodiment, R_4 and R_5 are independently not COR_8. i.e. R_4 or R_5 together with the nitrogen atom do not form an amide or R_4 and R_5 together with the bridging nitrogen atom do not form a cyclic amide.

In yet another embodiment, R_4 and R_5 are independently not $C(O)OR_8$. i.e. R_4 or R_5 together with the nitrogen atom do not form a carbamate or R_4 and R_5 together with the bridging nitrogen atom do not form a cyclic carbamate.

In a particular embodiment, R_6 is selected from the group consisting of hydrogen and substituted or unsubstituted alkyl such as substituted or unsubstituted C_1-C_6 alkyl. Preferably, R_6 is selected from the group consisting of hydrogen and methyl.

In yet another embodiment, R_6 is not substituted or unsubstituted phenyl.

In additional preferred embodiments, the preferences described above for the different substituents are combined. The present invention is also directed to such combinations of preferred substitutions in the formula (I) above.

Particular individual compounds of the invention falling under formula (I) include the compounds listed below:

[1] 2-(2-(4-methylpiperazin-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[2] 2-(2-(azepan-1-yl)ethyl)-1,2,3,4,10,10a-hexahydropyrazino[1,2-a]indole

[3] 2-(2-(azepan-1-yl)ethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole hydrochloride

[4] 2-(2-(4-benzylpiperidin-1-yl)ethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole hydrochloride

[5] 2-(2-(4-methylpiperazin-1-yl)ethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole hydrochloride

[6] 2-(2-(4-benzylpiperidin-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole maleate

[7] 4-(3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-N,N-dimethylbutan-1-amine

[8] 2-(2-(azepan-1-yl)ethyl)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[9] 2-(2-(azepan-1-yl)ethyl)-8-fluoro-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[10] 2-(2-(azepan-1-yl)propyl)-8-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[11] 2-(2-(4-benzylpiperidin-1-yl)ethyl)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[12] 8-fluoro-2-(4-(piperidin-1-yl)butyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[13] 2-(3-(azepan-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[14] 2-(4-(piperidin-1-yl)butyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[15] 2-(4-(azepan-1-yl)butyl)-8-fluoro-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[16] 2-(4-(4-methylpiperazin-1-yl)butyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[17] 2-(2-(4-cyclohexylpiperazin-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[18] 8-fluoro-2-(2-(4-methylpiperazin-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[19] N,N-dimethyl-4-(3,4,10,10a-tetrahydropyrazino[1,2-a]indol-2(1H)-yl)butan-1-amine

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

The compounds listed below are disclosed by US3317524A and do not form part of the present invention:

2-(2-dimethylaminoethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole,

2-(2-dimethylaminoethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole dichlorhydrate,

2-(3-dimethylaminopropyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole,

2-(3-dimethylaminopropyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole chlorhydrate,

2-(morpholinoethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole,

2-(morpholinoethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole chlorhydrate,

2-(morpholinoethyl)-1,2,3,4-tetrahydro-8-methoxypyrazino[1,2-a]indole,

2-(morpholinoethyl)-1,2,3,4-tetrahydro-8-methoxypyrazino[1,2-a]indole fumarate,

2-(2-piperidinoethyl)-1,2,3,4- tetrahydropyrazino[1,2-a]indole,

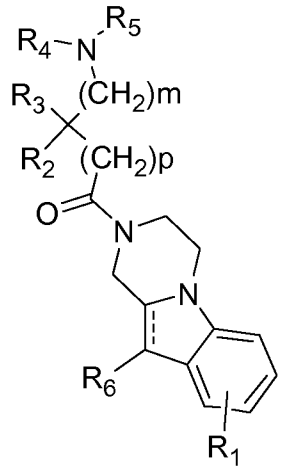
2-(2-piperidinoethyl)-1,2,3,4- tetrahydropyrazino[1,2-a]indole chlorhydrate, and

2-dimethylaminoethyl-1,2,3,4-tetrahydro-8-fluoropyrazino[1,2-a]indole.

The compounds of general formula (I) can be obtained by available synthetic procedures. For instance, they can be prepared in accordance with the following general procedures:

METHOD A

Process for the synthesis of a compound of general formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, the process comprising the reduction of a compound of general formula (II)



(II)

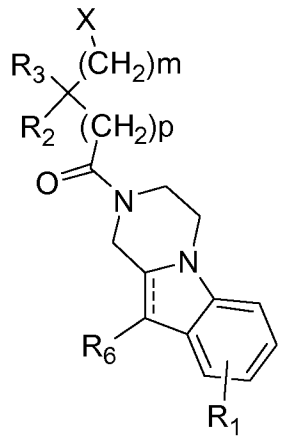
where m, -----, R_1, R_2, R_3, R_4 and R_6 have the meanings as in general formula (I) and p is selected from 0,1, 2, or 3.

The reduction of the amido group can be performed under conventional conditions known in the art. In a particular embodiment, the reaction is performed using a reducing agent selected from a metallic hydride such as lithium aluminium hydride, an alane or a borane or by catalytic hydrogenation. The reduction reaction can be performed in the presence of an organic solvent, such as a cyclic or acyclic ether (e.g. Et_2O, iPr_2O, 1,4-dioxane, tetrahydrofuran, methyltetrahydrofuran, dimethoxyethane), a hydrocarbonated solvent (e.g. pentane, hexane, heptane), an aromatic solvent (such as toluene, xylene), or mixtures thereof. In a particular embodiment, it is performed in dry polar aprotic solvent, such as tetrahydrofuran. These reactions can be conveniently performed at a temperature between -30 °C and a reflux temperature of the solvent used.

The compound of general formula (II) may be readily prepared in accordance with known chemical procedures, such as following one of the methods described beneath.

Method A1

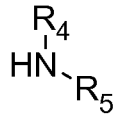
Process for the synthesis of a compound of general formula (II) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, the process comprising the reaction between a compound of general formula (III)



(III)

where m, p, -----, R_1, R_2, R_3 and R_6 have the meanings as in general formula (II) and X is a suitable leaving group,

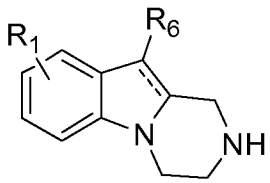
with a compound of general formula (IV)



(IV)

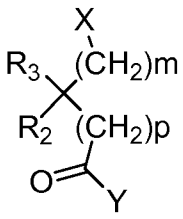
where R_4 and R_5 have the meanings as in general formula (I).

Compounds of general formula (III) may be prepared in turn by reaction between a compound of general formula (V)



(V)

where ⁻⁻⁻⁻⁻, R_1 and R_6 have the meanings as in general formula (I), with a compound of general formula (VI)



(VI)

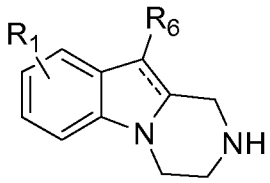
where m, p, R_2 and R_3 have the meanings as in general formula (II) and X and Y independently represent a suitable leaving group.

The above reactions can be performed in the presence of a suitable base and an organic solvent. Examples of bases include, but are not limited to, inorganic bases such as hydroxides, carbonates and sulfates of alkaline metals or alkaline earth metals, and organic bases such as mono(C_1-C_5 alkyl)amine, di(C_1-C_5 alkyl)amine, etc. Examples of solvents include, but are not limited to, organic solvents conventionally used in the art the present invention pertains to, preferably inert organic solvents. More specifically, examples of organic solvents to be used in the present invention are ethers such as diethyl ether, tetrahydrofuran; C_1-C_6 primary alcohols such as methanol, ethanol, propanol; halogenated compounds such as chloroform, methylene chloride; nitrile compounds such as acetonitrile, etc. These reactions can be conveniently performed at a temperature between -30 °C and a reflux temperature of the solvent used. Halogens are particularly suitable leaving groups for these reactions.

Compounds of general formula (IV), (V) and (VI) are commercially available or can be synthesized from commercially available products according to known methods or modified methods thereof.

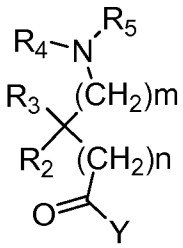
Method A2

Process for the synthesis of a compound of general formula (II) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, the process comprising the reaction between a compound of general formula (V):



(V)

where -----, R_1 and R_6 have the meanings as in general formula (I), with a compound of general formula (VII)



(VII)

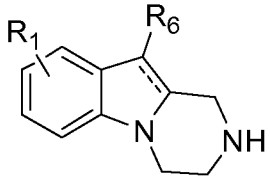
where m, n, R_2, R_3, R_4 and R_5 have the meanings as in general formula (I) an Y is OH or a suitable leaving group.

The amidation can be performed by different routes. For instance, the amidation may be achieved by activation of the carboxylic acid with a carbodiimide, such as 1,1-dicyclohexylcarbodiimide (DCC) or 1-ethyl 3-(3-dimethylaminopropyl)carbodiimide (EDC), in the presence of a catalytic amount of an organic base, such as DMAP or HOBT in an appropriate solvent, such as dichloromethane or N,N-dimethylformamide. The amidation can be achieved as well by using acyl chlorides in the presence of an aprotic solvent, such as dichloromethane, and an organic base, such as diisopropylethylamine or triethylamine. This reaction can also be performed starting from an ester (Y=OR), when R is a good leaving group, such as p-nitrophenyl or ethyltrifluoroacetate using catalytic basic conditions.

Compounds of general formula (V) and (VII) are commercially available or can be synthesized from commercially available products according to known methods or modified methods thereof.

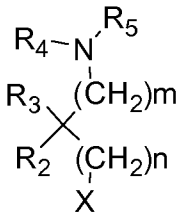
METHOD B

Process for the synthesis of a compound of general formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, the process comprising the reaction between a compound of general formula (V)



(V)

where -----, R_1 and R_6 have the meanings as in general formula (I) with a compound of general formula (VIII)



(VIII)

where m, n, R_2, R_3, R_4 and R_5 have the meanings as in general formula (I) and X is a suitable leaving group.

The above reaction can be performed in the presence of a suitable base and an organic solvent. Examples of bases include, but are not limited to, inorganic bases such as hydroxides, carbonates and sulfates of alkaline metals or alkaline earth metals, and organic bases such as mono(C_1-C_5 alkyl)amine, di(C_1-C_5 alkyl)amine, etc. Examples of solvents include, but are not limited to, organic solvents conventionally used in the art the present invention pertains to, preferably inert organic solvents. More specifically, examples of organic solvents to be used in the present invention are ethers such as diethyl ether, tetrahydrofuran; C_1-C_6 primary alcohols such as methanol, ethanol, propanol; halogenated compounds such as chloroform, methylene chloride; nitrile compounds such as acetonitrile, etc. The reaction can be conveniently performed at a temperature between -30 °C and a reflux temperature of the solvent used, preferably between room temperature and 120 °C, more preferably between 30 °C and 80 °C. Halogens are particularly suitable leaving groups for this reaction.

Compounds of general formula (V) and (VIII) are commercially available or can be synthesized from commercially available products according to known methods or modified methods thereof.

It is also an object of the invention to provide medicaments or pharmaceutical compositions comprising at least one compound of general formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof, and at least one pharmaceutically acceptable excipient.

The term “excipient” refers to components of a drug compound other than the active ingredient (definition obtained from the European Medicines Agency- EMA). They preferably include a "carrier, adjuvant and/or vehicle". Carriers are forms to which substances are incorporated to improve the delivery and the effectiveness of drugs. Drug carriers are used in drug-delivery systems such as the controlled-release technology to prolong in vivo drug actions, decrease drug metabolism, and reduce drug toxicity. Carriers are also used in designs to increase the effectiveness of drug delivery to the target sites of pharmacological actions (U.S. National Library of Medicine. National Institutes of Health). Adjuvant is a substance added to a drug product

formulation that affects the action of the active ingredient in a predictable way. Vehicle is an excipient or a substance, preferably without therapeutic action, used as a medium to give bulk for the administration of medicines (Stedman's Medical Spellchecker, © 2006 Lippincott Williams & Wilkins). Such pharmaceutical carriers, adjuvants or vehicles can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like, excipients, disgregants, wetting agents or diluents. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. The selection of these excipients and the amounts to be used will depend on the form of application of the pharmaceutical composition.

The pharmaceutical compositions in accordance with the invention can be adapted in order to be administered by any route of administration, be it orally or parenterally, such as pulmonarily, nasally, rectally and/or intravenously. Therefore, the formulation in accordance with the invention may be adapted for topical or systemic application, particularly for dermal, subcutaneous, intramuscular, intra-articular, intraperitoneal, pulmonary, buccal, sublingual, nasal, percutaneous, vaginal, oral or parenteral application. The preferred form of rectal application is by means of suppositories.

Suitable preparations for oral applications are tablets, pills, chewing gums, capsules, granules, drops or syrups. Suitable preparations for parenteral applications are solutions, suspensions, reconstitutable dry preparations or sprays.

The pharmaceutical composition of the invention may be formulated as deposits in dissolved form or in patches, for percutaneous application. Skin applications include ointments, gels, creams, lotions, suspensions or emulsions.

Another aspect of the invention is a method for the treatment and/or prophylaxis of a sigma receptor-mediated disease or condition, the method comprising administering to the subject in need of such a treatment or prophylaxis a therapeutically effective amount of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof.

Generally an effective administered amount of a compound used in the invention will depend on the relative efficacy of the compound chosen, the severity of the disorder being treated, or the age, weight or mode of administration. However, active compounds will typically be administered once or more times a day, for example 1, 2, 3 or 4 times daily, with typical total daily doses in the range of from 0.1 to 500 mg/kg/day.

Having described the present invention in general terms, it will be more easily understood by reference to the following examples which are presented as an illustration and are not intended to limit the present invention.

Examples

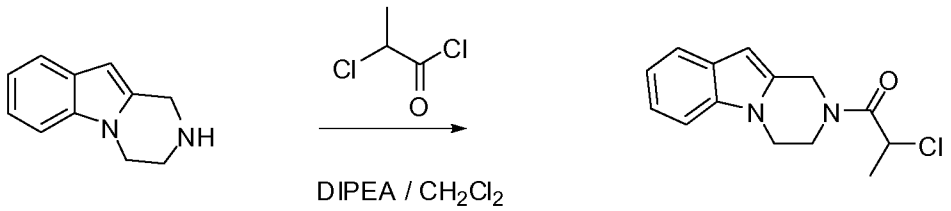
Method A

Example 1: 2-(2-(4-methylpiperazin-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole

1.1 Synthesis of 1-(3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-(4-methylpiperazin-1-yl)propan-1-one

Method A1

Synthesis of 2-chloro-1-(3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)propan-1-one

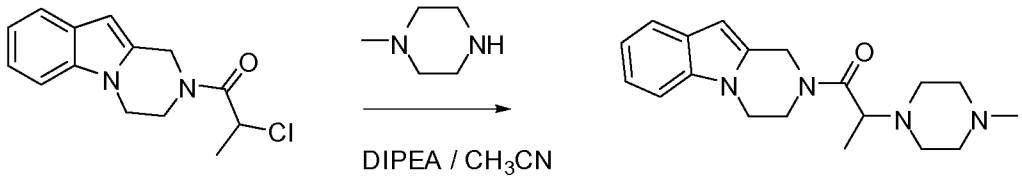


DIPEA / CH_2Cl_2

RT, 1h

To a mixture of 1,2,3,4-tetrahydropyrazino[1,2-a]indole (200 mg, 1.16 mmol) in methylene chloride (20 mL) diisopropylethylamine (300 mg, 2.,3 mmol) was added followed by drop-wise addition of 2-chloropropanoyl chloride (162 mg, 1.28 mmol) at 0 °C. The reaction was stirred for 1 h, quenched with water, and extracted with dichloromethane. The combined organic layers were washed with water and brine, dried over magnesium sulfate and evaporated to dryness, to provide the crude product (283 mg, 93% yield) as an orange oil.

Synthesis of 1-(3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-(4-methylpiperazin-1-yl)propan-1-one



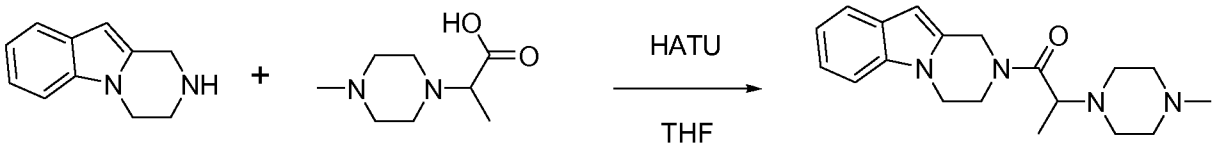
DIPEA / CH_3CN

reflux, 12h

To a mixture of 2-chloro-1-(3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)propan-1-one (170 mg, 0.65 mmol) in anhydrous acetonitrile (20 mL) diisopropylethylamine (167 mg, 1.3 mmol) was added followed by drop-wise addition of methylpiperazine (130 mg, 1.3 mmol). The reaction was stirred under reflux for 12 h. After cooling, the solvent was evaporated, water was added and the mixture was extracted with dichloromethane. The combined organic layers were washed with water, brine, dried over magnesium sulfate and then evaporated to dryness to provide the crude product (100 mg, 47% yield) as a brown oil.

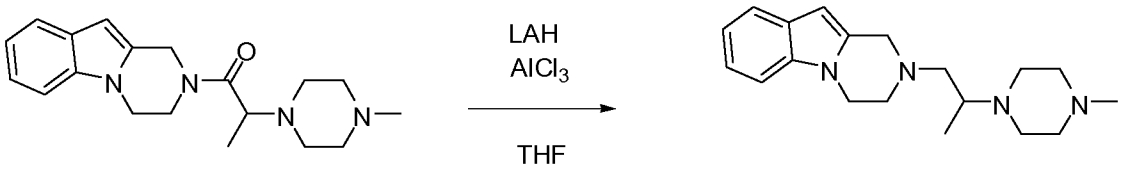
Method A2

Synthesis of 1-(3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-(4-methylpiperazin-1-yl)propan-1-one



To a suspension of 2-(4-methylpiperazin-1-yl)propanoic acid (103 mg, 0.6 mmol) in anhydrous THF (10 ml) diisopropylethylamine (150 mg, 1.16 mmol) was added and the mixture was stirred for 10 minutes. To the resulting white suspension 1,2,3,4- tetrahydro-pyrazino[1,2-a]indole (100 mg, 0.6 mmol) and 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate methanaminium (HATU) (350 mg, 0.92 mmol) were added and the mixture was stirred at 55-65 °C for 6 h and at rt overnight. The crude was concentrated, quenched with water and extracted with dichloromethane. The combined organic layers were sequentially washed with water and brine, dried over magnesium sulfate and then evaporated to dryness to provide a crude product that was chromatographed on silica gel to afford the title compound (94 mg, 48% yield).

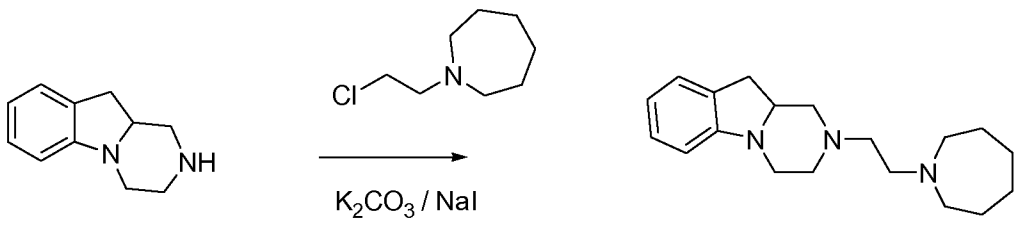
1.2 Synthesis of 2-(2-(4-methylpiperazin-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole



To a suspension of $AlCl_3$ (28 mg, 0.21 mmol) in anhydrous THF (15 ml), $LiAlH_4$ (24 mg, 0.63 mmol) was added at 0 °C, and the mixture was stirred at room temperature for 30 min. After this period a solution of 1-(3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-2-(4-methylpiperazin-1-yl)propan-1-one (68 mg, 0.21 mmol) in anhydrous THF (5ml) was slowly added at 0 °C, and the mixture was stirred at room temperature for 90 min. The reaction was quenched with a solution of aqueous NaOH (10%) and extracted with $CHCl_3$. The combined organic layers were washed with water and brine, dried over magnesium sulfate and then evaporated to dryness to provide the crude product (49 mg, 75% yield) as a solid.

Method B

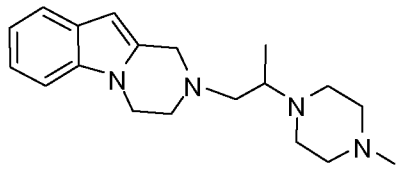
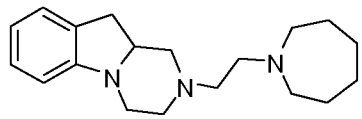
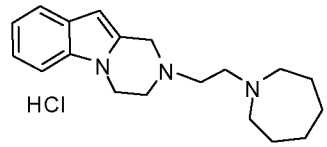
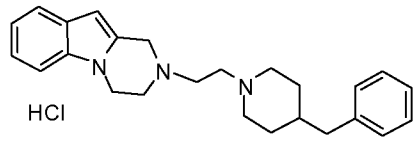
Example 2: 2-(2-(azepan-1-yl)ethyl)-1,2,3,4,10,10a-hexahydropyrazino[1,2-a]indole

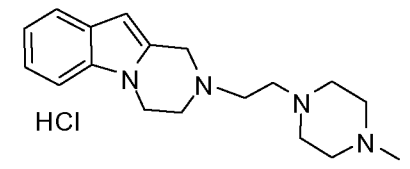
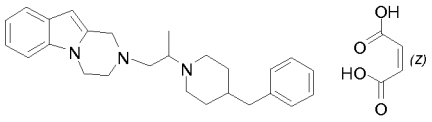
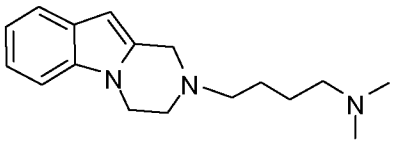
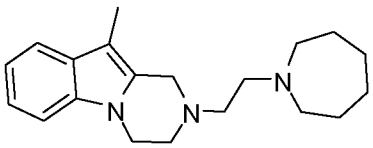
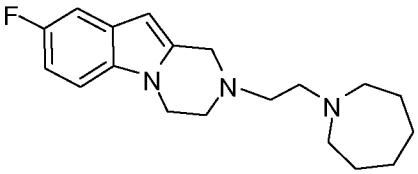
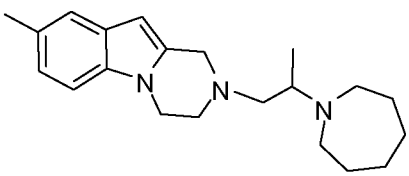


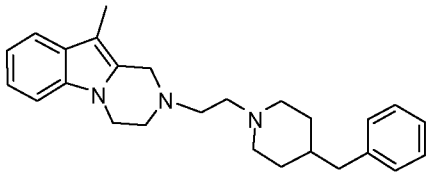
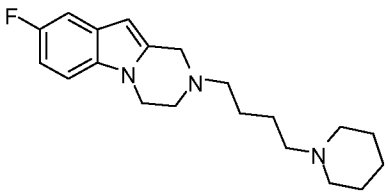
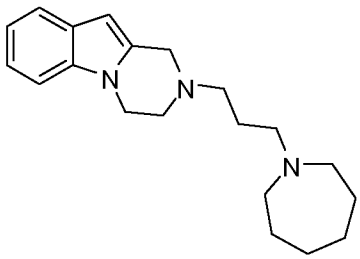
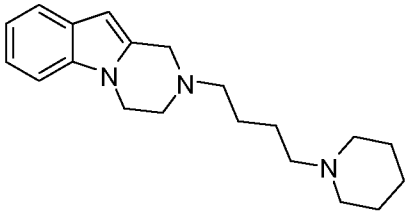
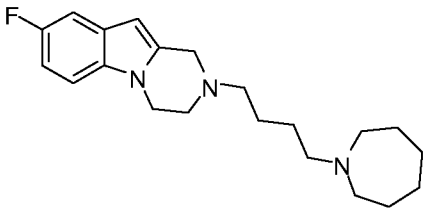
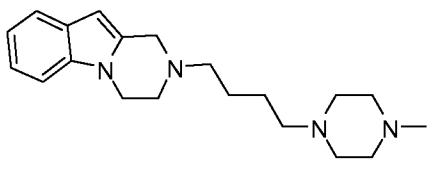
To a mixture of 1,2,3,4,10,10a-hexahydropyrazino[1,2-a]indole (100 mg, 0.57 mmol) in acetonitrile (20 mL), potassium carbonate (238 mg, 1.72 mmol), a catalytic amount of sodium iodide and 1-(2-chloroethyl)azepane hydrochloride (227 mg, 1.15 mmol) were successively added at 0 °C. The reaction was stirred under reflux for 18 h, filtered, and the organic solvent evaporated. The crude was treated with water and repeatedly extracted with dichloromethane. The combined organic layers were washed with water and brine, dried over magnesium sulfate and then evaporated to dryness to provide the crude product (58 mg, 34% yield) as an oil.

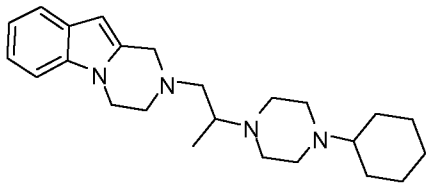
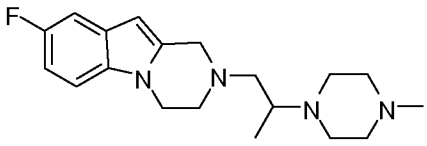
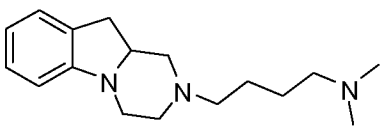
Particular compounds of formula (I) are listed in table (I) below.

Table I

Ex	Structure	Name	NMR
1		2-(2-(4-methylpiperazin-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole	^{1}H NMR ($CDCl_3$) δ: 7.54 (dd, J = 7.3, 1.6 Hz, 1H), 7.31 – 7.21 (m, 1H), 7.20 – 7.02 (m, 2H), 6.19 (s, 1H), 4.07 (t, J = 5.6 Hz, 2H), 3.94 (d, J = 14.7 Hz, 1H), 3.83 (d, J = 14.7 Hz, 1H), 3.10 (dt, J = 11.4, 5.5 Hz, 1H), 2.97 (dt, J = 11.8, 5.7 Hz, 1H), 2.86 (q, J = 6.5 Hz, 1H), 2.72 (ddd, J = 12.5, 5.5, 1.5 Hz, 1H), 2.64 (t, J = 4.9 Hz, 4H), 2.53 – 2.34 (m, 5H), 2.28 (s, 3H), 1.08 (d, J = 6.5 Hz, 3H).
2		2-(2-(azepan-1-yl)ethyl)-1,2,3,4,10,10a-hexahydropyrazino[1,2-a]indole	^{1}H NMR ($CDCl_3$) δ: 7.05 (t, J = 7.2 Hz, 2H), 6.63 (td, J = 7.4, 1.0 Hz, 1H), 6.42 (d, J = 7.7 Hz, 1H), 3.67 – 3.45 (m, 2H), 3.12 – 2.78 (m, 4H), 2.75 – 2.62 (m, 6H), 2.63 – 2.48 (m, 3H), 2.24 (td, J = 11.4, 3.3 Hz, 1H), 2.14 (t, J = 10.7 Hz, 1H), 1.70 – 1.50 (m, 8H).
3		2-(2-(azepan-1-yl)ethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole hydrochloride	^{1}H NMR (DMSO) δ: 10.65 (bs, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 6.39 (s, 1H), 4.84 – 4.48 (m, 2H), 4.46 – 4.24 (m, 2H), 3.87 – 3.46 (m, 5H), 3.46 – 3.20 (m, 5H), 2.03 – 1.73 (m, 4H), 1.77 – 1.53 (m, 4H).
4		2-(2-(4-benzylpiperidin-1-yl)ethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole hydrochloride	^{1}H NMR (DMSO) δ: 10.22 (bs, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.30 (t, J = 7.4 Hz, 2H), 7.26 – 7.10 (m, 4H), 7.08 (t, J = 7.5 Hz, 1H), 6.38 (s, 1H), 4.82 – 4.09 (m, 4H), 3.89 – 3.25 (m, 8H), 3.14 – 2.83 (m, 2H), 2.62 – 2.51 (m, 2H), 1.96 – 1.65 (m, 3H), 1.68 – 1.36 (m, 2H).

5		2-(2-(4-methylpiperazin-1-yl)ethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole hydrochloride	^{1}H NMR (DMSO) δ: 11.00 (bs, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 6.43 (s, 1H), 4.67 (s, 2H), 4.40 (t, J = 5.8 Hz, 2H), 3.83 (t, J = 6.0 Hz, 2H), 3.56 – 3.38 (m, 4H), 3.38 – 3.24 (m, 2H), 3.25 – 3.02 (m, 4H), 2.86 – 2.65 (m, 2H), 2.76 (s, 3H).
6		2-(2-(4-benzylpiperidin-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole maleate	^{1}H NMR (DMSO) δ: 7.47 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.28 (dd, J = 7.9, 6.4 Hz, 2H), 7.24 – 7.11 (m, 3H), 7.15 – 7.03 (m, 1H), 7.08 – 6.96 (m, 1H), 6.19 (s, 1H), 6.12 (d, J = 1.4 Hz, 4H), 4.08 (t, J = 5.6 Hz, 2H), 3.90 (s, 2H), 3.77 – 3.65 (m, 1H), 3.44 – 3.30 (m, 4H), 3.16 – 2.99 (m, 3H), 2.97 – 2.84 (m, 1H), 2.65 – 2.52 (m, 2H), 1.90 – 1.67 (m, 3H), 1.58 – 1.31 (m, 2H), 1.24 (d, J = 6.5 Hz, 3H).
7		4-(3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-N,N-dimethylbutan-1-amine	^{1}H NMR ($CDCl_3$) δ: 7.54 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.4 Hz, 1H), 7.19 – 7.10 (m, 1H), 7.08 (td, J = 7.5, 1.0 Hz, 1H), 6.20 (s, 1H), 4.16 – 4.04 (m, 2H), 3.82 (s, 2H), 3.06 – 2.91 (m, 2H), 2.65 – 2.54 (m, 2H), 2.54 – 2.42 (m, 2H), 2.35 (s, 6H), 1.69 – 1.56 (m, 4H).
8		2-(2-(azepan-1-yl)ethyl)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole	^{1}H NMR ($CDCl_3$) δ: 7.51 (d, J = 7.7 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 7.21 – 7.14 (m, 1H), 7.14 – 7.06 (m, 1H), 4.07 (t, J = 5.6 Hz, 2H), 3.84 (s, 2H), 3.44 (s, 4H), 3.29 (d, J = 3.4 Hz, 4H), 3.10 (t, J = 5.5 Hz, 2H), 2.21 (s, 3H), 2.03 (s, 4H), 1.75 (s, 4H).
9		2-(2-(azepan-1-yl)ethyl)-8-fluoro-1,2,3,4-tetrahydropyrazino[1,2-a]indole	^{1}H NMR ($CDCl_3$) δ: 7.23 – 7.09 (m, 2H), 6.88 (td, J = 9.0, 2.5 Hz, 1H), 6.15 (s, 1H), 4.15 – 4.01 (m, 2H), 3.87 (s, 2H), 3.04 (t, J = 5.6 Hz, 2H), 2.86 – 2.63 (m, 8H), 1.75 – 1.50 (m, 8H).
10		2-(2-(azepan-1-yl)propyl)-8-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole	^{1}H NMR ($CDCl_3$) δ: 7.32 (s, 1H), 7.15 (d, J = 8.2 Hz, 1H), 6.96 (dd, J = 8.4, 1.5 Hz, 1H), 6.10 (s, 1H), 4.13 – 3.98 (m, 2H), 3.93 (d, J = 14.6 Hz, 1H), 3.80 (d, J = 14.7 Hz, 1H), 3.21 – 3.04 (m, 1H), 3.05 – 2.86 (m, 2H), 2.78 – 2.54 (m, 5H), 2.43 (s, 3H), 2.41 – 2.22 (m, 1H),

			1.75 – 1.49 (m, 8H), 1.03 (d, J = 6.5 Hz, 3H).
11		2-(2-(4-benzylpiperidin-1-yl)ethyl)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole	^{1}H NMR ($CDCl_3$) δ: 7.50 (dd, J = 7.1, 1.7 Hz, 1H), 7.35 – 7.02 (m, 8H), 4.04 (t, J = 5.6 Hz, 2H), 3.80 (s, 2H), 3.13 – 2.91 (m, 4H), 2.79 (t, J = 7.0 Hz, 2H), 2.63 (t, J = 6.9 Hz, 2H), 2.55 (d, J = 6.7 Hz, 2H), 2.19 (s, 3H), 2.02 (t, J = 11.6 Hz, 2H), 1.76 – 1.59 (m, 2H), 1.60 – 1.46 (m, 1H), 1.46 – 1.21 (m, 2H).
12		8-fluoro-2-(4-(piperidin-1-yl)butyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole	^{1}H NMR ($CDCl_3$) δ: 7.23 – 7.05 (m, 2H), 6.87 (td, J = 9.1, 2.5 Hz, 1H), 6.15 (s, 1H), 4.06 (t, J = 5.7 Hz, 2H), 3.80 (s, 2H), 2.96 (t, J = 5.6 Hz, 2H), 2.67 – 2.50 (m, 2H), 2.43 – 2.24 (m, 6H), 1.75 – 1.49 (m, 8H), 1.49 – 1.31 (m, 2H).
13		2-(3-(azepan-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole	^{1}H NMR ($CDCl_3$) δ: 7.54 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 5.4 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 6.20 (s, 1H), 4.09 (t, J = 5.6 Hz, 2H), 3.82 (s, 2H), 3.00 (t, J = 5.7 Hz, 2H), 2.96 – 2.88 (m, 2H), 2.88 – 2.75 (m, 2H), 2.63 (t, J = 6.8 Hz, 2H), 2.08 – 1.90 (m, 2H), 1.90 – 1.75 (m, 4H), 1.75 – 1.58 (m, 4H), 1.39 – 1.29 (m, 2H).
14		2-(4-(piperidin-1-yl)butyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole	^{1}H NMR ($CDCl_3$) δ: 7.54 (d, J = 7.3 Hz, 1H), 7.26 (d, J = 7.9 Hz, 1H), 7.19 – 7.11 (m, 1H), 7.08 (td, J = 7.3, 1.3 Hz, 1H), 6.19 (s, 1H), 4.08 (t, J = 5.6 Hz, 2H), 3.82 (s, 2H), 2.97 (t, J = 5.6 Hz, 2H), 2.63 – 2.51 (m, 2H), 2.48 – 2.28 (m, 6H), 1.67 – 1.54 (m, 8H), 1.49 – 1.38 (m, 2H).
15		2-(4-(azepan-1-yl)butyl)-8-fluoro-1,2,3,4-tetrahydropyrazino[1,2-a]indole	^{1}H NMR (CD_3OD) δ: 7.28 (dd, J = 8.9, 4.4 Hz, 1H), 7.14 (dd, J = 9.7, 2.3 Hz, 1H), 6.87 (td, J = 9.1, 2.4 Hz, 1H), 6.21 (s, 1H), 4.12 (t, J = 5.7 Hz, 2H), 3.87 (s, 2H), 3.29 – 3.21 (m, 4H), 3.21 – 3.11 (m, 2H), 3.07 (t, J = 5.8 Hz, 2H), 2.68 (t, J = 6.7 Hz, 2H), 1.95 – 1.57 (m, 12H).
16		2-(4-(4-methylpiperazin-1-yl)butyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole	^{1}H NMR (CD_3OD) δ: 7.46 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.15 – 7.03 (m, 1H), 7.07 – 6.95 (m, 1H), 6.19 (s, 1H), 4.10 (t, J = 5.7 Hz, 2H), 3.85 (s, 2H), 3.04 (t, J = 5.7 Hz, 2H), 2.71 – 2.40 (m, 12H), 2.30 (s, 3H),

			1.75 – 1.53 (m, 4H).
17		2-(2-(4-cyclohexylpiperazin-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole	^{1}H NMR ($CDCl_3$) δ: 7.54 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 7.2 Hz, 1H), 7.14 (td, J = 7.9, 7.5, 1.5 Hz, 1H), 7.14 – 7.02 (m, 1H), 6.19 (s, 1H), 4.07 (t, J = 5.7 Hz, 2H), 3.93 (d, J = 14.6 Hz, 1H), 3.82 (d, J = 14.6 Hz, 1H), 3.10 (dt, J = 11.5, 5.6 Hz, 1H), 2.96 (dt, J = 11.9, 5.7 Hz, 1H), 2.90 – 2.80 (m, 1H), 2.79 – 2.53 (m, 8H), 2.42 (dd, J = 12.4, 7.7 Hz, 1H), 2.01 – 1.87 (m, 2H), 1.86 – 1.74 (m, 3H), 1.68 – 1.59 (m, 1H), 1.35 – 1.06 (m, 6H), 1.09 (d, J = 6.5 Hz, 3H).
18		8-fluoro-2-(2-(4-methylpiperazin-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole	^{1}H NMR (CD_3OD) δ: 7.25 (dd, J = 8.8, 4.4 Hz, 1H), 7.12 (dd, J = 9.9, 2.5 Hz, 1H), 6.84 (td, J = 9.1, 2.5 Hz, 1H), 6.16 (s, 1H), 4.07 (t, J = 5.7 Hz, 2H), 3.92 (d, J = 14.7 Hz, 1H), 3.84 (d, J = 14.7 Hz, 1H), 3.12 (dt, J = 11.5, 5.5 Hz, 1H), 3.07 – 2.91 (m, 2H), 2.82 – 2.64 (m, 5H), 2.65 – 2.41 (m, 5H), 2.30 (s, 3H), 1.10 (d, J = 6.6 Hz, 3H).
19		N,N-dimethyl-4-(3,4,10,10a-tetrahydropyrazino[1,2-a]indol-2(1H)-yl)butan-1-amine	^{1}H NMR ($CDCl_3$) δ: 7.13 – 6.98 (m, 2H), 6.63 (t, J = 7.3 Hz, 1H), 6.42 (d, J = 7.9 Hz, 1H), 3.68 – 3.44 (m, 2H), 3.10 – 2.92 (m, 2H), 2.92 – 2.72 (m, 2H), 2.56 (dd, J = 15.0, 8.0 Hz, 1H), 2.46 – 2.30 (m, 4H), 2.27 (s, 6H), 2.23 – 1.96 (m, 2H), 1.61 – 1.44 (m, 4H).

BIOLOGICAL ACTIVITY

Pharmacological study

Human Sigma 1 receptor radioligand assay

To investigate binding properties of sigma 1 receptor ligands to human sigma 1 receptor, transfected HEK-293 membranes and [^{3}H](+)-pentazocine (Perkin Elmer, NET-1056), as the radioligand, were used. The assay was carried out with 7 µg of membrane suspension, 5 nM of [^{3}H](+)-pentazocine in either absence or presence of either buffer or 10 µM Haloperidol for total and non-specific binding, respectively. Binding buffer contained Tris-HCl 50 mM at pH 8. Plates were incubated at 37 °C for 120 minutes. After the incubation period, the reaction mix was then transferred to MultiScreen HTS, FC plates (Millipore), filtered and plates were washed 3 times with ice-cold 10 mM Tris–HCL (pH7.4). Filters were dried and counted at approximately 40% efficiency in a MicroBeta scintillation counter (Perkin-Elmer) using EcoScint liquid scintillation cocktail.

Some of the results obtained are shown in table (II) below:

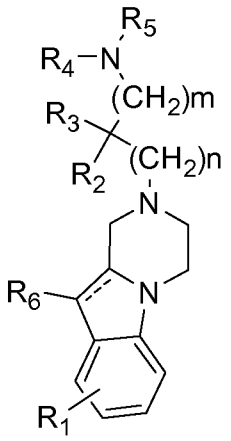
Table (II)

Ex	Ki (nM)
1	29.8
2	7.3
3	3.9
4	14.6
5	153
6	175
7	89.1
8	12.5
9	1.9
10	7.4

Ex	Ki (nM)
11	21.4
12	7.6
13	19.9
14	13.5
15	8.6
16	35.8
17	9.2
18	14.1
19	153

CLAIMS

1. A compound of general formula (I), or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate or solvate thereof:



(I)

wherein

m is selected from 0,1, 2, 3 and 4;

n is selected from 0, 1, 2, 3 and 4;

⁼⁼⁼⁼⁼ represents a single or double bond;

$\mathbf{R_1}$ represents one or more optional and independent substitutions in the benzene moiety selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, and halogen;

$\mathbf{R_2}$ and $\mathbf{R_3}$ are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, and halogen;

or $\mathbf{R_2}$ and $\mathbf{R_3}$ together form a substituted or unsubstituted cycloalkyl or a substituted or unsubstituted heterocyclyl;

$\mathbf{R_4}$ and $\mathbf{R_5}$ are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkenyl,

substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted, heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, and $-C(O)NR_8R_9$;

or R_4 and R_5 together with the bridging nitrogen atom form a substituted or unsubstituted heterocyclyl;

R_6 is selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$, $-CH=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, and halogen;

t is selected from 0, 1, and 2;

R_8 and R_9 are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl and halogen;

with the proviso that the following compounds are not included:

2-(2-dimethylaminoethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole,

2-(2-dimethylaminoethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole dichlorhydrate,

2-(3-dimethylaminopropyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole,

2-(3-dimethylaminopropyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole chlorhydrate,

2-(morpholinoethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole,

2-(morpholinoethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole chlorhydrate,

2-(morpholinoethyl)-1,2,3,4-tetrahydro-8-methoxypyrazino[1,2-a]indole,

2-(morpholinoethyl)-1,2,3,4-tetrahydro-8-methoxypyrazino[1,2-a]indole fumarate,

2-(2-piperidinoethyl)-1,2,3,4- tetrahydropyrazino[1,2-a]indole,

2-(2-piperidinoethyl)-1,2,3,4- tetrahydropyrazino[1,2-a]indole chlorhydrate, and

2-dimethylaminoethyl-1,2,3,4-tetrahydro-8-fluoropyrazino[1,2-a]indole,

2-(1H-1,2,3-benzotriazol-1-ylmethyl)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole,

2-(4-(2H-benzo[d][1,2,3]triazol-2-yl)butyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole,

2-(4-(3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)butyl)isoindoline-1,3-dione,

2-(4-(6-methoxy-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)butyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one,

N-(4-(6-methoxy-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)butyl)isoquinoline-3-carboxamide,

2-(3-dimethylaminopropyl)-8-chloro-10-phenyl-tetrahydropyrazino[1,2-a]indole,

8-chloro-2-diethylaminoethyl-10-phenyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole,

3-(10-(2-chlorophenyl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)propan-1-amine,

3-(10-(3-chlorophenyl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)propan-1-amine,

3-(10-(4-chlorophenyl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)propan-1-amine,

(10aR)-3-(9-bromo-3,4,10,10a-tetrahydro-1H-pyrazino[1,2-a]indol-2-ylmethyl)-oxazolidin-2-one, and

(10aS)-3-(9-bromo-3,4,10,10a-tetrahydro-1H-pyrazino[1,2-a]indol-2-ylmethyl)-oxazolidin-2-one.

2. The compound according to claim 1, wherein R_1 represents one o more optional and independent substitutions in the benzene moiety selected from the group consisting of substituted or unsubstituted alkyl and halogen.

3. The compound according to any one of claims 1 to 2, wherein m is selected from 0, 1 and 2 and/or n is selected from 0, 1, 2 and 3.

4. The compound according to any one of claims 1 to 3, wherein R_2 and R_3 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl and substituted or unsubstituted cycloalkyl, or R_2 and R_3 together form a substituted or unsubstituted cycloalkyl or a substituted or unsubstituted heterocyclyl.

5. The compound according to any one of claims 1 to 4, wherein R_4 and R_5 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, and substituted or unsubstituted cycloalkyl, or R_4 and R_5 together with the bridging nitrogen atom form a substituted or unsubstituted heterocyclyl.

6. The compound according to any one of claims 1 to 5, wherein R_6 is selected from the group consisting of hydrogen and substituted or unsubstituted alkyl.

7. A compound according to any one of claims 1 to 6, which is selected from:

[1] 2-(2-(4-methylpiperazin-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[2] 2-(2-(azepan-1-yl)ethyl)-1,2,3,4,10,10a-hexahydropyrazino[1,2-a]indole

[3] 2-(2-(azepan-1-yl)ethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole hydrochloride

[4] 2-(2-(4-benzylpiperidin-1-yl)ethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole hydrochloride

[5] 2-(2-(4-methylpiperazin-1-yl)ethyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole hydrochloride

[6] 2-(2-(4-benzylpiperidin-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole maleate

[7] 4-(3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-N,N-dimethylbutan-1-amine

[8] 2-(2-(azepan-1-yl)ethyl)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[9] 2-(2-(azepan-1-yl)ethyl)-8-fluoro-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[10] 2-(2-(azepan-1-yl)propyl)-8-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[11] 2-(2-(4-benzylpiperidin-1-yl)ethyl)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[12] 8-fluoro-2-(4-(piperidin-1-yl)butyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[13] 2-(3-(azepan-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[14] 2-(4-(piperidin-1-yl)butyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[15] 2-(4-(azepan-1-yl)butyl)-8-fluoro-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[16] 2-(4-(4-methylpiperazin-1-yl)butyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[17] 2-(2-(4-cyclohexylpiperazin-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole

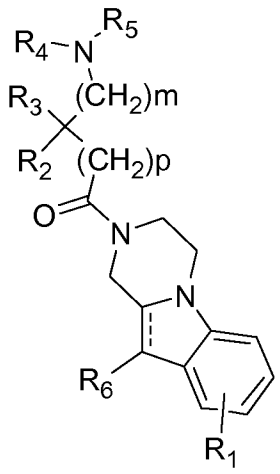
[18] 8-fluoro-2-(2-(4-methylpiperazin-1-yl)propyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[19] N,N-dimethyl-4-(3,4,10,10a-tetrahydropyrazino[1,2-a]indol-2(1H)-yl)butan-1-amine

or a pharmaceutically acceptable salt or solvate thereof.

8. A process for the preparation of a compound of formula general (I) as defined in claim 1, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate or solvate thereof, the process being selected from:

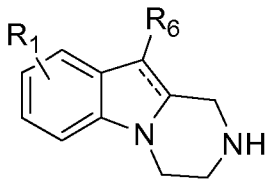
a) a process comprising the reduction of a compound of general formula (II)



(II)

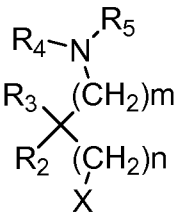
where m, ⁻⁻⁻⁻⁻, R_1, R_2, R_3, R_4 and R_6 have the meanings as in general formula (I) and p is selected from 0,1, 2, or 3; or

b) a process comprising the reaction a compound of general formula (V)



(V)

where ⁻⁻⁻⁻⁻, R_1 and R_6 have the meanings as in general formula (I) with a compound of general formula (VIII)



(VIII)

where m, n, R_2, R_3, R_4 and R_5 have the meanings as in general formula (I) and X is a suitable leaving group.

9. A pharmaceutical composition comprising at least one compound of general formula (I) as defined in claim 1, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate or solvate thereof and a pharmaceutically acceptable excipient.

10. A compound of general formula (I) as defined in claim 1, or a pharmaceutically acceptable salt, enantiomer, diastereomer, racemate or solvate thereof, for use as a medicament.

11. The compound for use according to claim 10, wherein the medicament is for the treatment and/or prophylaxis of a sigma receptor-mediated disease or condition.

12. The compound for use according to claim 11, wherein the sigma receptor-mediated disease or condition is selected from pain; diarrhoea; lipoprotein disorders; hyperlipidemia; hypertriglyceridemia; hypercholesterolemia; obesity; migraine; arthritis; hypertension; arrhythmia; ulcer; glaucoma; learning, memory and attention deficits; cognition disorders; neurodegenerative diseases; demyelinating diseases; addiction to drugs and chemical substances including cocaine, amphetamine, ethanol and nicotine; tardive dyskinesia; stroke including ischemic stroke; epilepsy; stress; cancer; psychotic conditions, in particular depression, anxiety or schizophrenia; inflammation and autoimmune diseases.

13. The compound for use according to claim 12, wherein the pain is selected from neuropathic pain, inflammatory pain or other pain conditions involving allodynia and/or hyperalgesia.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/058147

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/4985 A61K31/55 A61P29/00
ADD.

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

B. FIELDS SEARCHED

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

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

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

EPO-Internal, EMBASE, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ALAN R. KATRITZKY ET AL: "Novel Synthesis of 1,2,3,4-Tetrahydropyrazino[1,2- a]indoles", THE JOURNAL OF ORGANIC CHEMISTRY, vol. 68, no. 12, 1 June 2003 (2003-06-01), pages 4938-4940, XP055065668, ISSN: 0022-3263, DOI: 10.1021/jo026922x figure 2; compound 8 ----- -/--	1,3-6

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 July 2014	23/07/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Moriggi, J

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MATEUSZ NOWAK ET AL: "Homology Modeling of the Serotonin 5-HT 1A Receptor Using Automated Docking of Bioactive Compounds with Defined Geometry", JOURNAL OF MEDICINAL CHEMISTRY, vol. 49, no. 1, 1 January 2006 (2006-01-01), pages 205-214, XP055065669, ISSN: 0022-2623, DOI: 10.1021/jm050826h Compound 49 of the Supplementary Material, page S10	1,3-6, 9-13
X	& Mateusz Nowak ET AL: "Homology modeling of the serotonin 5-HT1A receptor using automated docking of bioactive compounds with defined geometry", J. Med. Chem., 25 November 2005 (2005-11-25), pages S1-S11, XP055065703, DOI: 10.1021/jm050826h Retrieved from the Internet: URL:http://pubs.acs.org/doi/suppl/10.1021/jm050826h/suppl_file/jm050826hsi20051025_122650.pdf [retrieved on 2013-06-06] Compound 49 of the Supplementary Material, page S10	1,3-6, 9-13

X	MOKROSZ, MARIA J. ET AL.: "Structure-activity relationship studies of CNS agents. 18. 1-(2-methoxyphenyl)-4-(4-succinimido)butyl]piperazine (MM-77): a new, potent, postsynaptic antagonist of 5-HT1A receptors", MEDICINAL CHEMISTRY RESEARCH, vol. 4, no. 3, 1994, pages 161-169, XP009170177, ISSN: 1054-2523 compound 11	1,3-6,8

X	US 3 317 524 A (FREED MEIER E) 2 May 1967 (1967-05-02) cited in the application column 1, line 10 - line 17; claim 1; examples 9, 10, 26-28, 32	1-6,9-13

X	US 2009/238761 A1 (CAMPIANI GIUSEPPE [IT] ET AL) 24 September 2009 (2009-09-24) claims 46, 85-87; table 1; compounds 1-2, 1-5	1,3-6, 8-13

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 022 778 A (FREED MEIER E) 10 May 1977 (1977-05-10) The first formula in column 1; column 10, line 41 - line 43; compounds 8, 11, 13a	1-6,9-13
X	US 2002/035110 A1 (BENTLEY JONATHAN M [GB] ET AL) 21 March 2002 (2002-03-21) claims 1, 130, 133; examples 3, 4	1-6,8-13
A	MICHAEL G N RUSSELL ET AL: "Benz[f]isoquinoline analogs as high-affinity .sigma. ligands", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 35, no. 11, 1 May 1992 (1992-05-01), pages 2025-2033, XP009139166, ISSN: 0022-2623, DOI: 10.1021/JM00089A012 introduction; table IV; compound 42	1-13
A	US 2003/171347 A1 (MATSUMOTO RAE R [US]) 11 September 2003 (2003-09-11) page 5, the two chemical structures; claim 2, formulae (E) and (D)	1-13

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/058147

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		DE 60113865 T2	20-07-2006
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		WO 0210169 A1	07-02-2002
		ZA 200300525 A	20-04-2004
US 2003171347 A1	11-09-2003	AU 4198299 A	06-12-1999
		US 2003171347 A1	11-09-2003
		WO 9959409 A1	25-11-1999