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(54) **AZABICYCLO(3.1.0) HEXANE DERIVATIVES USEFUL AS MODULATORS OF DOPAMINE D3 RECEPTORS**

ALS MODULATEUREN DES DOPAMIN-D3-REZEPTORS GEEIGNETE AZABICYCLO[3.1.0]
HEXANDERIVATE

DERIVES AZABICYCLO (3.1.0) HEXANE UTILES COMME MODULATEURS DES RECEPTEURS
D3 DE LA DOPAMINE

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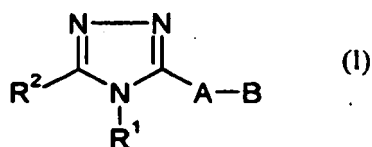
(56) References cited:
WO-A-00/42037 **WO-A-01/98267**
WO-A-02/40471 **WO-A-03/035622**

Description

[0001] The present invention relates to novel compounds, processes for their preparation, intermediates used in these processes, pharmaceutical compositions containing them and their use in therapy, as modulators of dopamine D₃ receptors.

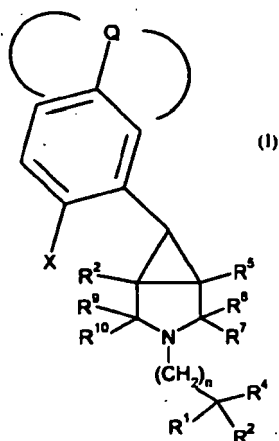
[0002] WO 2002/40471 (SmithKline Beecham) discloses certain benzazepine compounds having activity at the dopamine D₃ receptor.

[0003] WO 00/42037 (BASF AG) relates to triazole compounds of formula (I), in which R¹, R² and B have the meanings given in the description.



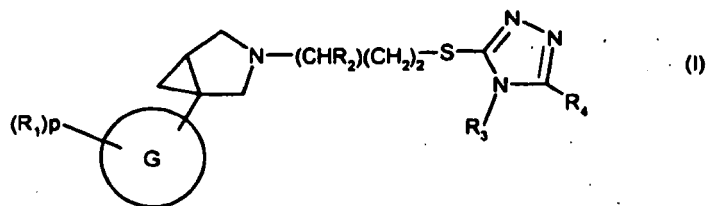
[0004] The compounds provided for in the invention have high affinity for the dopamine-D₃-receptor and can therefore be used for the treatment of diseases which respond to the influence of dopamine-D₃-ligands.

[0005] WO 03/035622 (PFIZER PRODUCTS INC.) discloses compounds of the formula (I) wherein X, Q, n, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are as defined. Compounds of formula (I) have activity as opioid antagonist, in particular substance abuse.



[0006] A new class of compounds which have affinity for dopamine receptors, in particular the dopamine D₃ receptor has been found. These compounds have potential in the treatment of conditions wherein modulation, especially antagonism/inhibition, of the D₃ receptor is beneficial, e.g. to treat drug dependency or as antipsychotic agents.

[0007] The present invention provides a compound of formula (I): 1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-({[4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4H-1,2,4-triazol-3-yl]thio}propyl)-3-azabicyclo[3.1.0]hexane or a pharmaceutically acceptable salt thereof,

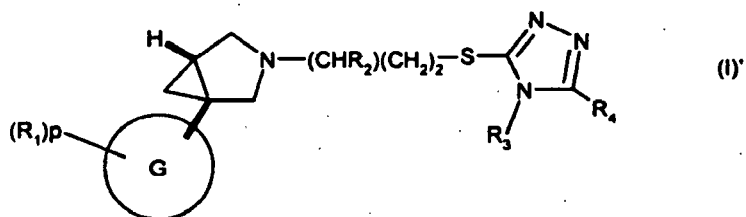


wherein

G is phenyl and $(R_1)_p$ is 2-fluoro-4-trifluoromethyl;
 R_2 is hydrogen;
 R_3 is methyl;
 R_4 is 4-methyl-1,3-oxazol-5-yl.

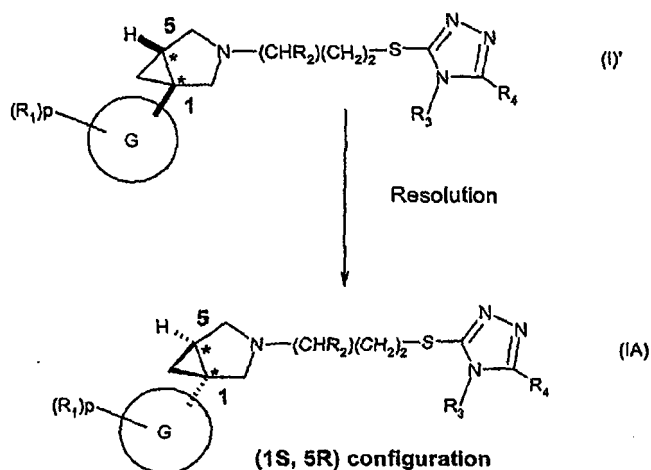
[0008] Because of the presence of the fused cyclopropane compounds of formula (I) are believed to have a "cis" disposition of the substituents (both groups linked to the bicyclic ring system are on the same face of this bicyclic ring system).

[0009] In another embodiment of the present invention compounds of formula (I)' are provided which correspond to the compounds of formula (I) having "cis" disposition, represented by the bold highlight of the bonds

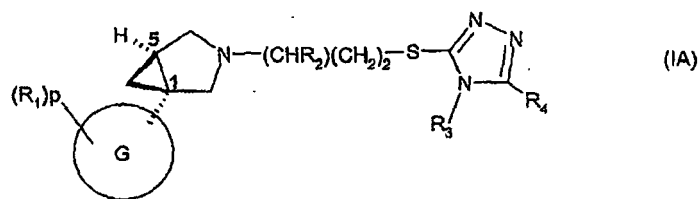


wherein G, p, R_1 , R_2 , R_3 , R_4 , and R_5 are defined as above for compounds of formula (I).

[0010] It will be appreciated that compounds of formula (I)' possess at least two chiral centres, namely at position 1 and 5 in the 3-azabicyclo[3.1.0]hexane portion of the molecule. Because of the fixed cis disposition, the compounds may exist in two stereoisomers which are enantiomers with respect to the chiral centres in the cyclopropane. It will also be appreciated, in common with most biologically active molecules that the level of biological activity may vary between the individual stereoisomers of a given molecule. It is intended that the scope of the invention includes all individual stereoisomers (diastereoisomers and enantiomers) and all mixtures thereof, including but not limited to racemic mixtures, which demonstrate appropriate biological activity with reference to the procedures described herein.



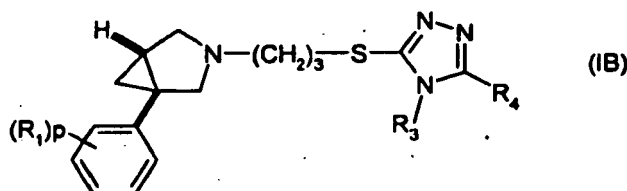
[0011] In a further embodiment of the present invention compounds of formula (IA) are provided that correspond to stereochemical isomers of compounds of formula (I)', enriched in configuration (1S,5R) or (1R,5R)



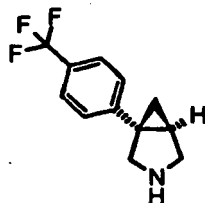
wherein G, p, R₁, R₂, R₃, R₄, and R₅ are defined as above for compounds of formula (I)' or a pharmaceutically acceptable salt thereof.

[0012] It is intended in the context of the present invention that stereochemical isomers enriched in configuration (1S, 5R) or (1R, 5R) of formula (IA) correspond in one embodiment to at least 90% e.e. In another embodiment the isomers correspond to at least 95% e.e. In another embodiment the isomers correspond to at least 99% e.e. As used herein, the term "salt" refers to any salt of a compound according to the present invention prepared from an inorganic or organic acid or base, quaternary ammonium salts and internally formed salts. Physiologically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compounds. Such salts must clearly have a physiologically acceptable anion or cation. Suitably physiologically acceptable salts of the compounds of the present invention include acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, phosphoric, metaphosphoric, nitric and sulfuric acids, and with organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, formic, propionic, glycolic, gluconic, maleic, succinic, camphorsulfuric, isothionic, mucic, gentisic, isonicotinic, saccharic, glucuronic, furoic, glutamic, ascorbic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, stearic, sulfinilic, alginic, galacturonic and arylsulfonic, for example benzenesulfonic and p-toluenesulfonic, acids; base addition salts formed with alkali metals and alkaline earth metals and organic bases such as N,N-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), lysine and procaine; and internally formed salts. Salts having a non-physiologically acceptable anion or cation are within the scope of the invention as useful intermediates for the preparation of physiologically acceptable salts and/or for use in non-therapeutic, for example, *in vitro*, situations.

[0013] In one embodiment, a compound of formula (IB) or a salt thereof is provided, wherein R₁, p, R₃ and R₄ are as defined for formula (I):

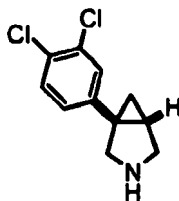


[0014] The strategy for determining the absolute configuration of the compounds of the present invention comprised as a first step the preparation of the chiral intermediate, (1S, 5R)-1-[4-(trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane,



(preparation 18), by using (S)-(+)-acetyl mandelic acid as resolving agent.

[0015] In the literature the absolute configuration of a series of compounds similar to this chiral intermediate is known, see J. Med Chem 1981, 24(5), 481-90. For some compounds disclosed in the reference the absolute configuration was proved by single crystal X-ray analysis.



[0016] Among them, 1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane was disclosed.

The absolute configuration of the optical isomers of the compounds of the present invention was assigned using comparative VCD (vibrational circular dichroism) and OR (optical rotation) analyses.

The configuration of (1*S*,5*R*)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane was assigned by comparing its experimental VCD spectrum and observed specific rotation to ab initio derived calculated data for (1*S*,5*R*)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane (see Preparation 48) as the reference sample.

[0017] The assignment of the absolute configuration of the title compound was confirmed by a single crystal X-ray structure obtained from a crystal of (1*S*,5*R*)-1-[4-(trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane, (*S*)-(+)-mandelic acid salt. Both the analysis based on the known configuration of the (*S*)-(+)-mandelic acid and on the basis of anomalous dispersion effects confirmed the assignment of the title compound as being (1*S*,5*R*)-1-[4-(trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane.

[0018] For those compounds which were subjected to detailed analysis (VCD; OR included in the experimental details) a common trend was recognised between absolute configuration of the 3-azabicyclo[3.1.0]hexane moiety and measured binding activity at the dopamine D3 receptor for each pair of enantiomers. For the remainder of the compounds of the present invention, where stereoisomers were evaluated separately, absolute configuration was assigned based on a reasonable assumption by a skilled person in the art, i.e. absolute configuration was then assigned based on measured binding activity at the dopamine D3 receptor for both enantiomers and comparison with the data of those compounds which were subjected to detailed analysis.

[0019] Chiral molecules exhibit vibrational circular dichroism (VCD). Vibrational circular dichroism (VCD) is the differential interaction of a chiral molecule with left and right circularly polarized infrared radiation during vibrational excitation.

[0020] The VCD spectrum of a chiral molecule is dependent on its three-dimensional structure. Most importantly, the VCD spectrum of a chiral molecule is a sensitive function of its absolute configuration and, in the case of flexible molecules, of its conformation. In principle, therefore, VCD permits the determination of the structure of a chiral molecule. VCD spectra were first measured in the 1970s. Subsequently, VCD instrumentation has developed enormously in spectral range and in sensitivity. Currently, VCD spectra of liquids and solutions can be measured over the majority of the fundamental infrared (IR) spectral range ($\nu \geq 650 \text{ cm}^{-1}$) with high sensitivity at acceptable resolution ($1\text{--}5 \text{ cm}^{-1}$) using both dispersive and Fourier Transform (FT) VCD instrumentation. Very recently, commercial FT VCD instrumentation has become available, greatly enhancing the accessibility of VCD spectra.

[0021] The use of VCD as a reliable method for the determination of absolute configuration of chiral molecules is now well established (see for example Shah RD, et al., Curr Opin Drug Disc Dev 2001;4:764-774; Freedman TB, et al., Helv Chim Acta 2002; 85:1160-1165; Dyatkin AB, et al. Chirality 2002;14:215-219; Solladie'-Cavallo A, Balaz Met al., Tetrahedron Assym 2001;12:2605-2611; Nafie LA, et al. Circular dichroism, principles and applications, 2nd ed. New York: John Wiley & Sons; 2000. p 97-131; Nafie LA, et al. in: Yan B, Gremlich H-U, editors. Infrared and Raman spectroscopy of biological materials. New York: Marcel Dekker; 2001. p 15-54; Polavarapu PL, et al., J Anal Chem 2000;366:727-734; Stephens PJ, et al., Chirality 2000;12:172-179; Solladie' -Cavallo A, et al., Eur J Org Chem 2002: 1788-1796).

[0022] The method entails comparison of observed IR and VCD spectra with calculations of the spectra for a specific configuration and provides information both on the absolute configuration and on the solution conformation.

[0023] Given an experimental spectrum of a chiral molecule whose absolute configuration and/or conformation are unknown and to be determined, the general procedure is as follows:

- 1) all possible structures are defined; 2) the spectra of these structures are predicted; and
- 3) predicted spectra are compared to the experimental spectrum. The correct structure will give a spectrum in agreement with experiment; incorrect structures will give spectra in disagreement with experiment.

[0024] VCD spectra are always measured simultaneously with vibrational unpolarized absorption spectra ("infrared (IR) spectra") and the two vibrational spectra together provide more information than does the VCD spectrum alone. In addition, vibrational unpolarized absorption spectra are automatically predicted simultaneously with VCD spectra.

[0025] For ab initio assignments, VCD and unpolarized IR spectra were calculated using the Gaussian 98 software package.

[0026] When chiral organic molecules are synthesized (or, if natural products, isolated) their optical rotations are routinely measured at one frequency or at a small number of discrete frequencies in the visible-near ultraviolet spectral region. Most commonly, the specific rotation at one frequency, that of the sodium D line, $[\alpha]_D$, is measured. The frequencies used lie below the threshold for electronic absorption, i.e., they are in the "transparent" spectral region. Optical rotation is a reflection of the enantiomeric excess (ee) of the sample and of the absolute configuration (AC) of the predominant enantiomer.

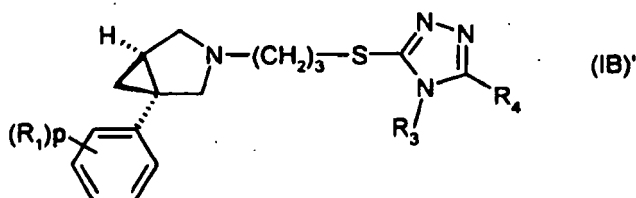
[0027] When the optical rotation at a given frequency for 100% ee is available, the measured optical rotation at the same frequency enables the sample ee to be determined. The determination of ee is the predominant application of discrete frequency, transparent spectral region optical rotations. In principle, the AC of the predominant enantiomer, if unknown, can also be determined. However, the determination of AC from optical rotation requires an algorithm which reliably predicts the optical rotations of molecules of known AC and a number of methodologies have been proposed for predicting discrete frequency, transparent spectral region optical rotations (Eliel EL, Wilen SH. Stereochemistry of organic compounds. New York: John Wiley & Sons; 1994. Chapter 13).

[0028] Very recently, developments in ab initio Density Functional Theory (DFT) have radically improved the accuracy of optical rotation calculation. As a result, for the first time it has become possible to routinely obtain ACs from optical rotations.

[0029] For ab initio OR assignments, the Dalton Quantum Chemistry Program was used.

[0030] Further embodiments of the present invention are compounds of formula (IB)' which, correspond to the stereochemical isomers of compounds of formula as defined above enriched in configuration (1S, 5R).

[0031] In one embodiment, a stereochemical isomer enriched in the (1S,5R) configuration of formula (IB)' or a salt thereof is provided, wherein R_1 , p, R_3 and R_4 are as defined for formula (I):



[0032] Certain of the compounds of the invention may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

[0033] Pharmaceutical acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compound of formula (I) using conventional methods.

[0034] Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of the compound of the invention are within the scope of the invention. The compounds of formula (I) may readily be isolated in association with solvent molecules by crystallisation or evaporation of an appropriate solvent to give the corresponding solvates.

[0035] In addition, prodrugs are also included within the context of this invention. As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, and in D. Fleisher, S. Ramon and H. Barbra "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Advanced Drug Delivery Reviews (1996) 19 (2) 115-130.

[0036] Prodrugs are any covalently bonded carriers that release a compound of structure (I) in vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or in vivo, yielding the parent compound. Prodrugs include, for example, compounds of this invention wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxy, amine or sulfhydryl groups. Thus, representative examples of prodrugs include (but are not limited to) acetate, formate and benzoate derivatives of alcohol, sulfhydryl and amine functional groups of the compounds of structure (I). Further, in the case of a carboxylic acid ($-\text{COOH}$), esters may be employed, such as methyl esters, ethyl esters, and the like. Esters may be active in their own right and/or be hydrolysable under *in vivo* conditions in the human body. Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt.

[0037] Furthermore, some of the crystalline forms of the compounds of structure (I) may exist as polymorphs.

[0038] Those skilled in the art will appreciate that in the preparation of the compound of the invention or a solvate thereof it may be necessary and/or desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions. Suitable protecting groups for use according to the present invention are well known to those skilled in the art and may be used in a conventional manner. See, for example, "Protective groups in organic synthesis" by T.W. Greene and P.G.M. Wuts (John Wiley & sons 1991) or "Protecting Groups" by P.J. Kocienski (Georg Thieme Verlag 1994). Examples of suitable amino protecting groups include acyl type protecting groups (e.g. formyl, trifluoroacetyl, acetyl), aromatic urethane type protecting groups (e.g. benzyloxycarbonyl (Cbz) and substituted Cbz), aliphatic urethane protecting groups (e.g. 9-fluorenylmethoxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), isopropylloxycarbonyl, cyclohexyloxycarbonyl) and alkyl type protecting groups (e.g. benzyl, trityl, chlorotriyl). Examples of suitable oxygen protecting groups may include for example alkyl silyl groups, such as trimethylsilyl or tert-butyldimethylsilyl; alkyl ethers such as tetrahydropyranyl or tert-butyl; or esters such as acetate

[0039] When a specific enantiomer of a compound of general formula (I) is required, this may be obtained for example by resolution of a corresponding enantiomeric mixture of a compound of formula (I) using conventional methods. Thus the required enantiomer may be obtained from the racemic compound of formula (I) by use of chiral HPLC procedure.

[0040] The subject invention also includes isotopically-labelled compounds, which are identical to those recited in formula (I) and following, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention and pharmaceutically acceptable salts thereof include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulphur, fluorine, iodine, and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I and ^{125}I .

[0041] Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H , ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are particularly useful in PET (positron emission tomography), and ^{125}I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of formula I and following of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

[0042] Certain groups/substituents included in the present invention may be present as isomers. The present invention includes within its scope all such isomers, including racemates, enantiomers, tautomers and mixtures thereof. Certain of the substituted heteroaromatic groups included in compounds of formula (I) may exist in one or more tautomeric forms. The present invention includes within its scope all such tautomeric forms, including mixtures.

[0043] In one embodiment of the present invention compounds are provided having a molecular weight of 800 or less. In another embodiment compounds are provided having a molecular weight of 600 or less. Generally, and without being limited thereto, such compounds may have higher oral bioavailability, and sometimes higher solubility and/or brain penetrancy. Molecular weight here refers to that of the unsolvated free base compound, excluding any molecular weight contributed by addition salts, solvent (e.g. water) molecules, prodrug molecular parts cleaved off *in vivo*, etc.

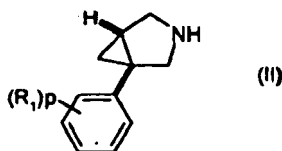
[0044] In general, the compounds or salts of the invention should be interpreted as excluding those compounds (if any) which are so chemically unstable, either per se or in water, that they are clearly unsuitable for pharmaceutical use through all administration routes, whether oral, parenteral or otherwise. Such compounds are known to the skilled chemist. Prodrugs or compounds which are stable *ex vivo* and which are convertible in the mammalian (e.g. human) body to the inventive compounds are however included.

[0045] Example compounds of the present invention include:

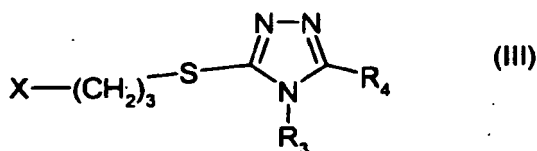
- (1*R*,5*S*/1*S*,5*R*)-1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-(3-[[4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio]propyl)-3-azabicyclo[3.1.0]hexane;
- (1*S*,5*R*)-1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-(3-[[4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio]propyl)-3-azabicyclo[3.1.0]hexane.

[0046] The process of the present invention for preparing compounds of formula (I) in which G is a phenyl derivative, comprises the steps of:

(a) reacting a compound of formula (II):

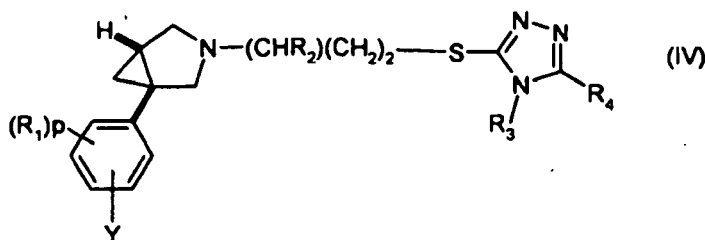


wherein R_1 and p are as defined for formula (I), with a compound of formula (III):



wherein R_2 , R_3 and R_4 are as defined for formula (I) and X is a leaving group, or

(b) for a compound of formula (I) wherein p is 1 or 2, reacting a compound of formula (IV):



wherein R_1 , R_2 , R_3 , and R_4 are as defined for formula (I), p is 0 or 1 and Y is halogen, a perfluoroalkylsulfonyloxy group (e.g. trifluoromethylsulfonyloxy), or Y is a group M selected from a boron derivative (e.g. a boronic acid function $B(OH)_2$) or a metal function such as trialkylstannyl (e.g. $SnBu_3$), zinc halide or magnesium halide; with a compound R_1-Y_1 , wherein Y_1 is halogen when Y is a group M ; or when Y is halogen or a perfluoroalkylsulfonyloxy group Y_1 is a group M as defined above or hydrogen that can be activated by a suitable base (e.g. Cs_2CO_3) in the presence of a suitable transition metal (e.g. Pd); "leaving group" is as understood by a skilled chemist, i.e. a group which can be displaced by a nucleophile in e.g. a S_N2 , S_N1 or S_NAr type reaction; and thereafter optionally for process (a) or process (b):

- (i) removing any protecting group(s); and/or
- (ii) forming a salt; and/or
- (iii) converting a compound of formula (I) or a salt thereof to another compound of formula (I) or a salt thereof.

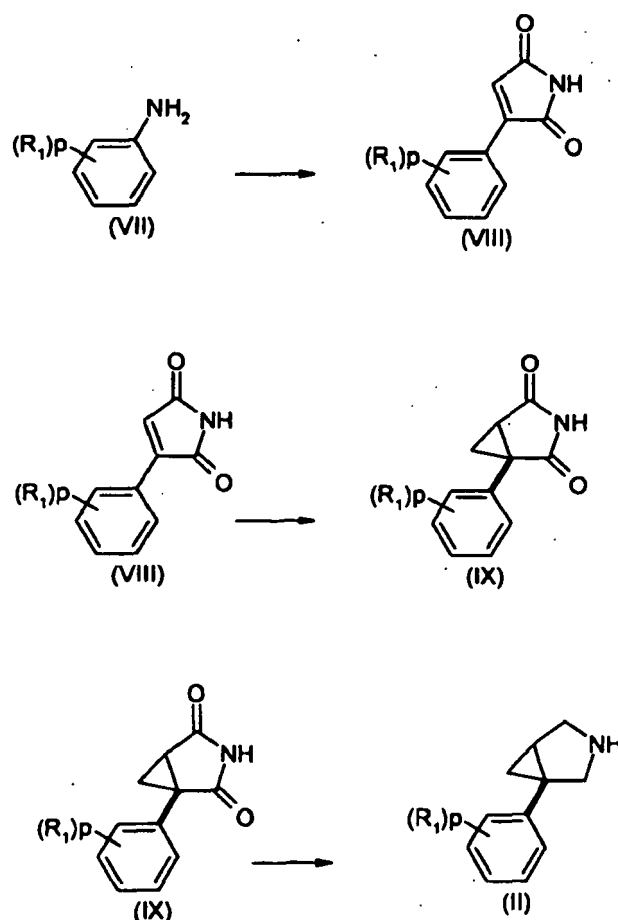
[0047] Process (a) may be performed using conventional methods for the formation of a tertiary amine. The leaving group X can be halogen such as chlorine. Alternatively X can be a sulfonyloxy group such C_{1-4} alkylsulfonyloxy (e.g. methanesulfonyloxy), C_{1-4} alkylsulfonyloxy or halo C_{1-4} alkylsulfonyloxy (e.g. trifluoromethanesulfonyloxy); or arylsulfonyloxy wherein aryl is optionally substituted phenyl, an optionally substituted 5- or 6- membered heteroaromatic group, or an optionally substituted bicyclic group, for example optionally substituted phenyl, wherein in each case the optional substituents are one or more C_{1-2} alkyl groups; e.g. para-toluenesulfonyloxy. When X is a halogen the reaction may be carried out using a base such as potassium carbonate in the presence of a source of iodide such as sodium iodide in a solvent such as N,N -dimethylformamide at a suitable temperature, e.g. 60 °C.

[0048] Compounds of formula (II) may be prepared by methods well known in the art (e.g. J. Med. Chem. 1981, 24, 481-490). Interconversion of groups R_1 may be affected by methodology well known in the art (e.g. demethylation of a methoxy group resulting in a hydroxy group using a suitable Lewis acidic reagent such as boron tribromide in an inert

solvent such as dichloromethane).

[0049] Reaction of a compound of formula (IV) with R1-Y1 according to process (b) may be effected in the presence of a transition metal e.g., palladium catalyst such as *bis*-triphenylphosphinepalladium dichloride, *tetrakis*-triphenylphosphinepalladium (0) or the complex formed *in situ* from tris(dibenzylideneacetone) dipalladium(0) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene. When M is a boronic acid function such as B(OH)₂ the reaction may be carried out under basic conditions, for example using aqueous sodium carbonate in a suitable solvent such as dioxane. When M is trialkylstannyl the reaction may be carried out in an inert solvent, such as xylene or dioxane optionally in the presence of LiCl. When M is a zinc or magnesium halide the reaction may be effected in an aprotic solvent such as tetrahydrofuran. When M is hydrogen that can be activated by a suitable base (e.g. Cs₂CO₃) in the presence of a suitable transition metal (e.g. Pd) the reaction may be carried out in an inert solvent such as dioxane in the presence of a suitable base such as Cs₂CO₃. The substituent Y may be halogen such as bromine, or a sulfonyloxy group such as trifluoromethylsulfonyloxy; and Y1 may be a group M, such as hydrogen that can be activated by a suitable base (e.g. Cs₂CO₃) in the presence of a suitable transition metal (e.g. Pd).

[0050] In one aspect of the present invention there is provided a synthetic process for the preparation of compounds of formula (II). This process comprises the following steps:



wherein:

step (a') means diazotation of an aniline (VII) followed by reaction with maleimide to give 3-arylmaleimide (VIII);

step (b') means cyclopropanation of (VIII) to provide bicyclic imide (IX);

step (c') means reduction of imide (IX) to give compounds of formula (II).

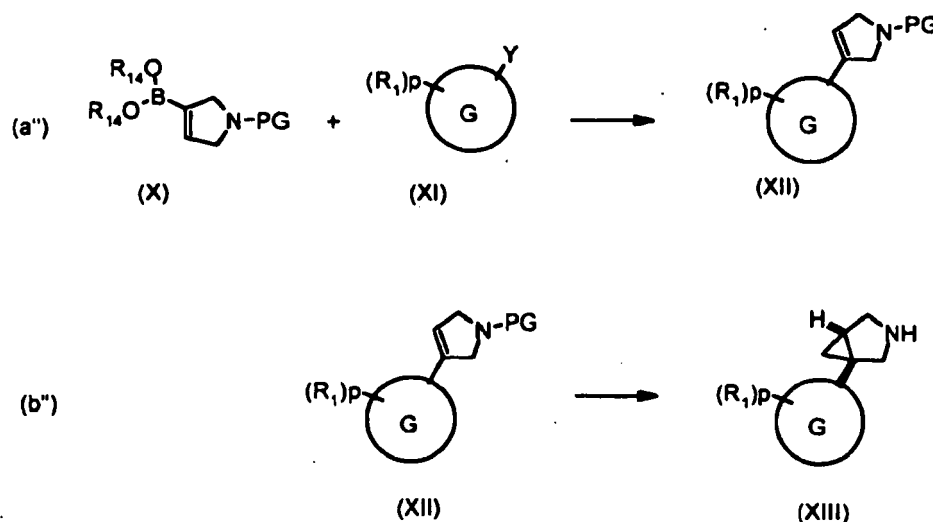
[0051] Step (a') may be effected using conventional methods for the Meerwein reaction (e.g. J. Am. Chem. Soc. 1955, 77, 2313 describes the formation of arylmaleimides using this approach). Alternatively, in many cases this step is suitably performed applying a procedure where to a mixture of maleimide, an appropriate copper (II) salt such as anhydrous CuCl₂, and a suitable organonitrite, such as *tert*-butyl nitrite, in a compatible solvent, such as acetonitrile, is slowly added a

solution of a compound of formula (VII). This is followed by allowing time to react as appropriate and a suitable workup. Preparation 8 exemplifies this process.

[0052] Step (b') consists of slow addition of a solution of purified compound of formula (VIII), or mixtures containing a compound of formula (VIII), dissolved in a suitable solvent such as dimethylsulfoxide, to a solution of trimethylsulfoxonium iodide in a suitable solvent such as dimethylsulfoxide and a suitable base, such as sodium hydride. This is followed by allowing time to react as appropriate and a suitable workup. Preparation 8 exemplifies this process.

[0053] Step (c') can be performed using a suitable reducing agent in a compatible solvent, such as borane in tetrahydrofuran or Red-Al® in toluene at an appropriate temperature, such as for example 65 °C in the case of borane as the reducing agent. This is followed by a suitable workup. Preparation 9 exemplifies this process.

[0054] In another aspect of the present invention an alternative synthetic process for the preparation of compounds of formula (II), or generally of formula (XIII), is provided. This process comprises the following steps:



wherein:

R_1 , p and G are as defined for formula (I), $R_{14}O$ is a suitable alkoxy group, PG is an appropriate protecting group and Y may be halogen such as bromine, or a sulfonyloxy group such as trifluoromethylsulfonyloxy and comprising the following steps:

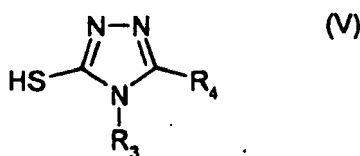
step (a'') means coupling reaction of a (2,5-dihydro-1H-pyrrol-3-yl)boronate (X) with the aromatic halogen or sulfonyloxy derivative (XI);

step (b'') means cyclization of (XII) followed by, if appropriate, deprotection to provide bicyclic amine (XIII).

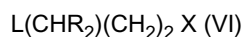
Step (a'') may be effected using conventional methods for the Suzuki coupling, e.g. using tetrakis(triphenylphosphine) palladium(0) as the source of catalytic palladium(0) in the presence of cesium fluoride in an appropriate solvent such as tetrahydrofuran at a suitable temperature. $(R_{14}O)_2B$ may suitably be 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl and PG benzyl, representing a compound of structure (X) as reported in Synlett 2002, 5, 829-831.

[0055] Step (b'') consists of a cyclopropanation reaction effected for example using the reagent generated from trimethylsulfoxonium iodide and a suitable base such as sodium hydride, in a compatible solvent, for example dimethylsulfoxide.

[0056] A compound of formula (III) may itself be prepared by reacting a compound of formula (V):

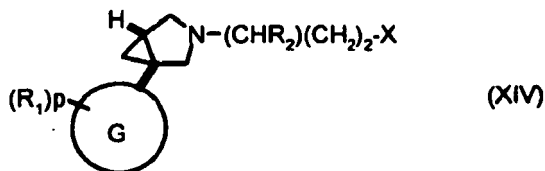


wherein R_3 and R_4 are as hereinbefore defined; with a compound of formula (VI):

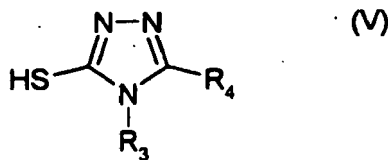


wherein X is defined as for formula (I) and L is a leaving group, e.g., a bromine atom. For typical reaction conditions, see Preparation 6 hereinafter.

[0057] Compounds of formula (I) where R_1 , R_2 , R_3 , R_4 , G and p are as above defined may be prepared by reacting a compound of formula (XIV):



wherein R_1 , R_2 , G and p are as defined for formula (I) and X is a leaving group, with a compound of formula (V):



wherein R_3 and R_4 are as hereinbefore defined.

[0058] A compound of formula (XIV) wherein R_1 , G and p are as defined for formula (I), X is a leaving group and R_2 is H (hydrogen) can be prepared by alkylation of a compound of formula (XIII) in the presence of a suitable base such as a tertiary amine, for example diisopropylethylamine, with a propyl derivative carrying two leaving groups of preferably differential reactivity in positions 1 and 3, for example 1-bromo-3-chloropropane.

[0059] A compound of formula (XIV) wherein R_1 , G and p are as defined for formula (I), X is a leaving group and R_2 is C_{1-4} alkyl can be prepared by the reaction between a beta-hydroxy ketone, for example 4-hydroxy-2-butanone if R_2 is methyl, with a compound of formula (XIII) in the presence of a suitable borohydride source such as $\text{NaBH}(\text{OAc})_3$, followed by conversion of the hydroxyl group into a leaving group by methods known to the person skilled in the art, for example by the action of thionyl chloride.

[0060] Interconversion reactions between compounds of formula (I) and salts thereof may be performed using methods well known in the art. Examples include:

- (i) converting one or more of R_1 from alkoxy (e.g. methoxy) to hydroxy,
- (ii) converting one or more of R_1 from hydroxy to sulfonyloxy, such as alkylsulfonyloxy or haloalkylsulfonyloxy, e.g. methanesulfonyloxy or alkylsulfonyloxy or trifluoromethanesulfonyloxy,
- (iii) converting one or more of R_1 from halogen or perfluoroalkylsulfonyloxy to cyano; and optionally thereafter forming a salt of formula (I).

[0061] Compounds of formula (I) have been found to exhibit affinity for dopamine receptors, in particular the D_3 receptor, and are expected to be useful in the treatment of disease states which require modulation of such receptors, such as psychotic conditions.

Such affinity is typically calculated from the IC_{50} as the concentration of a compound necessary to displace 50% of the radiolabeled ligand from the receptor, and is reported as a " K_i " value calculated by the following equation:

$$K_i = \frac{\text{IC}_{50}}{1 + L / K_D}$$

where L = radioligand and K_D = affinity of radioligand for receptor (Cheng and Prusoff, Biochem. Pharmacol. 22:3099,

1973).

[0062] In the context of the present invention pK_i (corresponding to the antilogarithm of K_i) is used instead of K_i and the compounds of the present invention typically show pK_i greater than 7. In one aspect the present invention provides compounds of formula (I) having a pK_i comprised between 7 and 8. In another aspect the present invention provides compounds of formula (I) having a pK_i comprised between 8 and 9. In a further aspect the present invention provides compounds of formula (I) having a pK_i greater than 9.

[0063] Many of the compounds of formula (I) have also been found to have greater affinity for dopamine D_3 than for D_2 receptors. The therapeutic effect of currently available antipsychotic agents (neuroleptics) is generally believed to be exerted via blockade of D_2 receptors; however this mechanism is also thought to be responsible for undesirable extrapyramidal side effects (eps) associated with many neuroleptic agents. It has been suggested that blockade of the recently characterised dopamine D_3 receptor may give rise to beneficial antipsychotic activity without significant eps. (see for example Sokoloff et al, Nature, 1990; 347: 146-151; and Schwartz et al, Clinical Neuropharmacology, Vol 16, No.4, 295-314, 1993). In one embodiment compounds of the present invention are provided which have higher (e.g. $\geq 10x$ or $\geq 100x$ higher) affinity for dopamine D_3 than dopamine D_2 receptors (such affinity can be measured using standard methodology for example using cloned dopamine receptors - see herein). Said compounds may suitably be used as selective modulators of D_3 receptors.

[0064] From the localisation of D_3 receptors, it could also be envisaged that the compounds could also have utility for the treatment of substance abuse where it has been suggested that D_3 receptors are involved (e.g. see Levant, 1997, Pharmacol: Rev., 49, 231-252). Examples of such substance abuse include alcohol, cocaine, heroin and nicotine abuse. Other conditions which may be treated by the compounds include dyskinetic disorders such as Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias; depression; anxiety, cognitive impairment including memory disorders such as Alzheimers disease, eating disorders, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders e.g. IBS.

[0065] Compounds of formula (I) may be used for treatment of all aspects of drug dependency including withdrawal symptoms from drugs of abuse such as alcohol, cocaine, opiates, nicotine, benzodiazepines and inhibition of tolerance induced by opioids. In addition, compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used to reduce craving and therefore will be useful in the treatment of drug craving. Drug craving can be defined as the incentive motivation to self-administer a psychoactive substance that was previously consumed. Three main factors are involved in the development and maintenance of drug craving: (1) Dysphoric states during drug withdrawal can function as a negative reinforcer leading to craving; (2) Environmental stimuli associated with drug effects can become progressively more powerful (sensitization) in controlling drug seeking or craving, and (3) A cognition (memory) of the ability of drugs to promote pleasurable effects and to alleviate a dysphoric state during withdrawal. Craving may account for the difficulty that individuals have in giving up drugs of abuse and therefore contributes significantly to the development and maintenance of drug dependence.

[0066] The compounds of formula (I) are of potential use as antipsychotic agents for example in the treatment of schizophrenia, schizo-affective disorders, psychotic depression, mania, paranoid and delusional disorders. Furthermore, they could have utility as adjunct therapy in Parkinsons Disease, particularly with compounds such as L-DOPA and possibly dopaminergic agonists, to reduce the side effects experienced with these treatments on long term use (e.g. see Schwartz et al., Brain Res. Reviews, 1998, 26, 236-242).

[0067] Within the context of the present invention, the terms describing the indications used herein are classified in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association (DSM-IV) and/or the International Classification of Diseases, 10th Edition (ICD-10). The various subtypes of the disorders mentioned herein are contemplated as part of the present invention. Numbers in brackets after the listed diseases below refer to the classification code in DSM-IV.

Within the context of the present invention, the term "psychotic disorder" includes :-

[0068] Schizophrenia including the subtypes Paranoid Type (295.30), Disorganised Type (295.10), Catatonic Type (295.20), Undifferentiated Type (295.90) and Residual Type (295.60); Schizophreniform Disorder (295.40); Schizoaffective Disorder (295.70) including the subtypes Bipolar Type and Depressive Type; Delusional Disorder (297.1) including the subtypes Erotomanic Type, Grandiose Type, Jealous Type, Persecutory Type, Somatic Type, Mixed Type and Unspecified Type; Brief Psychotic Disorder (298.8); Shared Psychotic Disorder (297.3); Psychotic Disorder Due to a General Medical Condition including the subtypes With Delusions and With Hallucinations; Substance-Induced Psychotic Disorder including the subtypes With Delusions (293.81) and With Hallucinations (293.82); and Psychotic Disorder Not Otherwise Specified (298.9).

[0069] Within the context of the present invention, the term "substance-related disorder" includes:-

Substance-related disorders including Substance Use Disorders such as Substance Dependence, Substance Craving and Substance Abuse; Substance-Induced Disorders such as Substance Intoxication, Substance Withdrawal, Substance-Induced Delirium, Substance-Induced Persisting Dementia, Substance-Induced Persisting Amnestic Disorder, Substance-Induced Psychotic Disorder, Substance-Induced Mood Disorder, Substance-Induced Anxiety Disorder, Substance-Induced Sexual Dysfunction, Substance-Induced Sleep Disorder and Hallucinogen Persisting Perception Disorder (Flashbacks); Alcohol-Related Disorders such as Alcohol Dependence (303.90), Alcohol Abuse (305.00), Alcohol Intoxication (303.00), Alcohol Withdrawal (291.81), Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnestic Disorder, Alcohol-Induced Psychotic Disorder, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder and Alcohol-Related Disorder Not Otherwise Specified (291.9); Amphetamine (or Amphetamine-Like)-Related Disorders such as Amphetamine Dependence (304.40), Amphetamine Abuse (305.70), Amphetamine Intoxication (292.89), Amphetamine Withdrawal (292.0), Amphetamine Intoxication Delirium, Amphetamine Induced Psychotic Disorder, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder and Amphetamine-Related Disorder Not Otherwise Specified (292.9); Caffeine Related Disorders such as Caffeine Intoxication (305.90), Caffeine-Induced Anxiety Disorder, Caffeine-Induced Sleep Disorder and Caffeine-Related Disorder Not Otherwise Specified (292.9); Cannabis-Related Disorders such as Cannabis Dependence (304.30), Cannabis Abuse (305.20), Cannabis Intoxication (292.89), Cannabis Intoxication Delirium, Cannabis-Induced Psychotic Disorder, Cannabis-Induced Anxiety Disorder and Cannabis-Related Disorder Not Otherwise Specified (292.9); Cocaine-Related Disorders such as Cocaine Dependence (304.20), Cocaine Abuse (305.60), Cocaine Intoxication (292.89), Cocaine Withdrawal (292.0), Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder and Cocaine-Related Disorder Not Otherwise Specified (292.9); Hallucinogen-Related Disorders such as Hallucinogen Dependence (304.50), Hallucinogen Abuse (305.30), Hallucinogen Intoxication (292.89), Hallucinogen Persisting Perception Disorder (flashbacks) (292.89), Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder and Hallucinogen-Related Disorder Not Otherwise Specified (292.9); Inhalant-Related Disorders such as Inhalant Dependence (304.60), Inhalant Abuse (305.90), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium, Inhalant-Induced Persisting Dementia, Inhalant-Induced Psychotic Disorder, Inhalant-Induced Mood Disorder, Inhalant-Induced Anxiety Disorder and Inhalant-Related Disorder Not Otherwise Specified (292.9); Nicotine-Related Disorders such as Nicotine Dependence (305.1), Nicotine Withdrawal (292.0) and Nicotine-Related Disorder Not Otherwise Specified (292.9); Opioid-Related Disorders such as Opioid Dependence (304.00), Opioid Abuse (305.50), Opioid Intoxication (292.89), Opioid Withdrawal (292.0), Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder, Opioid-Induced Mood Disorder, Opioid-Induced Sexual Dysfunction, Opioid-Induced Sleep Disorder and Opioid-Related Disorder Not Otherwise Specified (292.9); Phencyclidine (or Phencyclidine-Like)-Related Disorders such as Phencyclidine Dependence (304.60), Phencyclidine Abuse (305.90), Phencyclidine Intoxication (292.89), Phencyclidine Intoxication Delirium, Phencyclidine-Induced Psychotic Disorder, Phencyclidine-Induced Mood Disorder, Phencyclidine-Induced Anxiety Disorder and Phencyclidine-Related Disorder Not Otherwise Specified (292.9); Sedative-, Hypnotic-, or Anxiolytic-Related Disorders such as Sedative, Hypnotic, or Anxiolytic Dependence (304.10), Sedative, Hypnotic, or Anxiolytic Abuse (305.40), Sedative, Hypnotic, or Anxiolytic Intoxication (292.89), Sedative, Hypnotic, or Anxiolytic Withdrawal (292.0), Sedative, Hypnotic, or Anxiolytic Intoxication Delirium, Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium, Sedative-, Hypnotic-, or Anxiolytic-Persisting Dementia, Sedative-, Hypnotic-, or Anxiolytic-Persisting Amnestic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Psychotic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction, Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep Disorder and Sedative-, Hypnotic-, or Anxiolytic-Related Disorder Not Otherwise Specified (292.9); Polysubstance-Related Disorder such as Polysubstance Dependence (304.80); and Other (or Unknown) Substance-Related Disorders such as Anabolic Steroids, Nitrate Inhalants and Nitrous Oxide.

[0070] In a further aspect therefore the present invention provides a method of treating a condition for which modulation (especially antagonism/inhibition) of dopamine receptors (especially dopamine D₃ receptors) is beneficial, which comprises administering to a mammal (e.g. human) in need thereof an effective amount of a compound of formula (I) or a pharmaceutically (i.e. physiologically) acceptable salt thereof. Such conditions in particular include psychoses/psychotic conditions such as schizophrenia, and substance abuse.

[0071] The invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition in a mammal for which modulation (especially antagonism/inhibition) of dopamine receptors (especially dopamine D₃ receptors) is beneficial.

[0072] The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in

the treatment of a condition in a mammal for which modulation (especially antagonism/inhibition) of dopamine receptors (especially dopamine D₃ receptors) is beneficial.

[0073] In one embodiment, D₃ antagonists according to the present invention are used in the treatment of psychoses such as schizophrenia or in the treatment of substance abuse.

[0074] Thus, a still further aspect the invention provides a method of treating a psychotic condition (e.g. schizophrenia) or substance abuse which comprises administering to a mammal (e.g. human) in need thereof an effective amount of a compound of formula (I) as herein defined or a pharmaceutically acceptable salt thereof.

[0075] Also provided is the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a psychotic condition (e.g. schizophrenia) or substance abuse in a mammal.

[0076] Also provided is a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of a psychotic condition (e.g. schizophrenia) or substance abuse in a mammal.

[0077] Also provided is a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance in a mammal, e.g. for use in the treatment of any of the conditions described herein.

[0078] "Treatment" includes prophylaxis, where this is appropriate for the relevant condition(s).

[0079] For use in medicine, the compounds of the present invention are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically (i.e. physiologically) acceptable salt thereof and a pharmaceutically (i.e. physiologically) acceptable carrier. The pharmaceutical composition can be for use in the treatment of any of the conditions described herein.

[0080] The compounds of formula (I) may be administered by any convenient method, for example by oral, parenteral (e.g. intravenous), buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

[0081] The compounds of formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

[0082] A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

[0083] A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

[0084] A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

[0085] Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

[0086] Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluoro-chlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

[0087] Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

[0088] Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

[0089] Compositions suitable for transdermal administration include ointments, gels and patches.

[0090] In one embodiment, the composition is in unit dose form such as a tablet, capsule or ampoule.

[0091] Each dosage unit for oral administration contains for example from 1 to 250 mg (and for parenteral administration contains for example from 0.1 to 25 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

[0092] The pharmaceutically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, for example between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, for example between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

Biological Test Methods

[0093] Functional potency and intrinsic activity of compounds of this invention can be measured by the following GTP γ S scintillation proximity assay (GTP γ S-SPA). Cells used in the study are Chinese Hamster Ovary (CHO) Cells.

[0094] Cell Line

CHO_D2

CHO_D3

[0095] Cell membranes are prepared as follows. Cell pellets are resuspended in 10 volumes of 50mM HEPES, 1mM EDTA pH 7.4, using KOH. On the day the following proteases are added to the buffer just prior to giving the homogenisation buffer.

10⁻⁶M Leupeptin (Sigma L2884) - 5000 x stock = 5 mg/ml in buffer

25ug/ml Bacitracin (Sigma B0125) - 1000 x stock = 25 mg/ml in buffer

1mM PMSF - 1000 x stock = 17 mg/ml in 100% ethanol

2 \times 10⁻⁶M Pepstain A - 1000 x stock = 2 mM in 100% DMSO

[0096] The cells are homogenised by 2 x 15 second bursts in a 1 litre Glass Waring blender in a class two biohazard cabinet. The resulting suspension is spun at 500g for 20 mins (Beckman T21 centrifuge: 1550 rpm). The supernatant is withdrawn with a 25 ml pipette, aliquotted into pre-chilled centrifuge tubes and spun at 48,000g to pellet membrane fragments (Beckman T1270: 23,000 rpm for 30mins). The final 48,000g pellet is resuspended in Homogenisation Buffer, (4 x the volume of the original cell pellet). The 48,000g pellet is resuspended by vortexing for 5 seconds and homogenized in a dounce homogenizer 10-15 stokes. The prep is distributed into appropriate sized aliquots, (200-1000ul), in polypropylene tubes and store at -80° C. Protein content in the membrane preparations is evaluated with the Bradford protein assay.

[0097] The final top concentration of test drug is 3uM in the assay and 11 points serial dilution curves 1:4 in 100% DMSO are carried out using a Biomek FX. The test drug at 1% total assay volume (TAV) is added to a solid, white, 384 well assay plate. 50%TAV of precoupled (for 90 mins at 4°C) membranes, 5 μ g/well, and Wheatgerm Agglutinin Polystyrene Scintillation Proximity Assay beads (RPNQ0260, Amersham), 0.25mg/well, in 20mM HEPES pH 7.4, 100mM NaCl, 10mM MgCl₂, 60 μ g/ml saponin and 30 μ M GDP is added. The third addition was a 20% TAV addition of either buffer, (agonist format) or EC₈₀ final assay concentration of agonist, Quinelorane, prepared in assay buffer (antagonist format). The assay was started by the addition of 29%TAV of GTP γ [³⁵S] 0.38nM final (37MBq/ml, 1160Ci/mmol, Amersham). After all additions assay plates are spun down for 1 min at 1,000rpm. Assay plates are counted on a Viewlux, 613/55 filter, for 5 min., between 2-6 hours after the final addition.

[0098] The effect of the test drug over the basal generates EC₅₀ value by an iterative least squares curve fitting programme, expressed in the table as pEC₅₀ (i.e. -logEC₅₀). The ratio between the maximal effect of the test drug and the maximal effect of full agonist, Quinelorane, generates the Intrinsic Activity (IA) value (i.e. IA = 1 full agonist, IA < 1 partial agonist). fpKi values of test drug are calculated from the IC₅₀ generated by "antagonist format" experiment, using Cheng & Prusoff equation: fKi = IC₅₀ / 1+([A] / EC₅₀) where: [A] is the concentration of the agonist 5-HT in the assay and EC₅₀ is the 5-HT EC₅₀ value obtained in the same experiment. fpKi is defined as -logfki.

[0099] The compounds of the invention listed above have pKi values within the range of 7.0-10.5 at the dopamine D3 receptor pKi results are only estimated to be accurate to about \pm 0.3-0.5.

[0100] The compounds of the invention listed above have a selectivity over D2 greater than 30.

Examples

[0101] The invention is further illustrated by the following non-limiting examples. Preparations 1 to 5 were carried out in analogy to the synthetic route described in J.Med.Chem. 1981, 24, 481-490.

[0102] All temperatures refer to °C. Infrared spectra were measured on a FT-IR instrument. Compounds were analysed by direct infusion of the sample dissolved in acetonitrile into a mass spectra operated in positive electro spray (ES+)

ionisation mode. Proton Magnetic Resonance (^1H -NMR) spectra were recorded at 400 MHz, chemical shifts are reported in ppm downfield (d) from Me_4Si , used as internal standard, and are assigned as singlets (s), broad singlets (bs), doublets (d), doublets of doublets (dd), triplets (t), quartets (q) or multiplets (m).

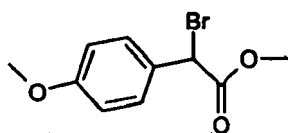
[0103] Experimental vibrational circular dichroism (VCD) spectra were measured using a ChiralIR™ VCD spectrometer operating in the 2000-800 cm^{-1} frequency range. Spectra were measured at room temperature (23°C) using a sealed transmission cell with barium fluoride windows and a path length of 100 microns. (Scan times varied from 60 to 120 minutes per isomer.) Sample solutions were typically prepared by dissolving 10 milligrams of each enantiomer in 100 microliters of deuterio-chloroform (CDCl_3). For ab initio assignments, VCD and unpolarized IR spectra were calculated using the Gaussian 98 software package. 1.

[0104] Optical rotations were measured using a (Perkin Elmer Model 241) polarimeter operating at 589 nm (Sodium source). Measurements were made using a 1 decimeter microcell thermostated at 23°C. Concentrations were typically 10 mg/ml ($c=0.01$). For ab initio OR assignments, the Dalton Quantum Chemistry Program was used.

[0105] Column chromatography was carried out over silica gel (Merck AG Darmstadt, Germany). The following abbreviations are used in the text: NBS = N-bromosuccinimide, Vitride = "Red-Al®", HOBT = 1-hydroxybenzotriazole, EtOAc = ethyl acetate, Et_2O = diethyl ether, DMF = N,N'-dimethylformamide, MeOH = methanol, TFA = trifluoroacetic acid, tetrahydrofuran = tetrahydrofuran, IPA = isopropanol, TEA = triethylamine, DCC = 1,3-dicyclohexylcarbodiimide, SCX = strong cation exchanger, Tic refers to thin layer chromatography on silica plates, and dried refers to a solution dried over anhydrous sodium sulphate, r.t. (RT) refers to room temperature, Rt = retention time, DMSO = dimethyl sulfoxide.

Preparation 1: Methyl bromo(4-methoxyphenyl)acetate

[0106]

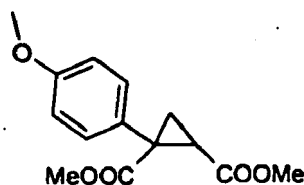


[0107] To a mixture of methyl 4-methoxyphenylacetate (20 g, 0.11 mol) and NBS (0.11 mol) in CCl_4 (0.2 l) were added 3 drops of 48% HBr and this mixture was heated to reflux for 8 h. The cooled solution was filtered through a pad of silica gel and the filtrate was evaporated *in vacuo* to give 29 g of the title compound as pale yellow oil, which was used in the subsequent step without further purification.

NMR (^1H , CDCl_3): δ 7.3 (d, 2H), 6.8 (d, 2H), 5.1 (s, 1H), 3.8 (s, 3H), 3.5 (s, 3H).

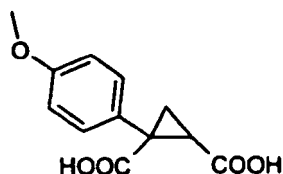
Preparation 2: Dimethyl 1-(4-methoxyphenyl)-1,2-cyclopropanedicarboxylate

[0108]



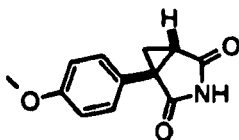
To a stirred slurry of NaH (4.4 g, 60% in mineral oil) in anhydrous Et_2O (0.3 l) was added methanol (10.3 mL) followed by a solution of bromo ester obtained in Prep. 1 methyl bromo(4-methoxyphenyl)acetate (29 g) in methyl acrylate (19.8 mL) (for examples starting from an ethyl phenylacetate derivative ethanol and ethyl acrylate were used, respectively) and methanol (3 mL) at 0 °C, over a 30 min.. The mixture was stirred at 25 °C for 24 h and then unreacted NaH was decomposed with 3 mL methanol. Water was added (75 mL), the organic phase separated, dried over Na_2SO_4 and filtered. Volatiles were evaporated *in vacuo* to give 31.5 g of the title compound as an oil, which was used in the subsequent step without further purification.

[0109] **NMR** (^1H , CDCl_3): δ 7.3 (d, 2H), 6.8 (d, 2H), 3.77 (s, 3H), 3.73 (s, 3H), 3.64 (s, 3H), 2.18 (dd, 1H), 2.05 (dd, 1H), 1.46 (dd, 1H). **MS** (m/z): 265.4 $[\text{MH}]^+$.

Preparation 3: 1-(4-Methoxyphenyl)-1,2-cyclopropanedicarboxylic acid**[0110]**

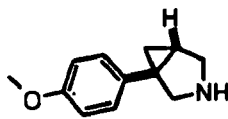
[0111] A mixture of diester obtained in Prep. 2 (31.5 g) and KOH (13.5 g) in 1:1 EtOH:H₂O (240 mL) was heated at reflux for 6 h and then concentrated to half the original volume. The aqueous solution was extracted with Et₂O, chilled in ice, and then made acidic with 25 mL of 12N HCl. White crystalline product was collected by filtration and dried under *vacuo* to give 12.8 g of the title compound (overall yield from methyl bromo(4-methoxyphenyl)acetate: 50%).

NMR (¹H, DMSO): δ 12.5 (bs, 2H), 7.25 (d, 2H), 6.85 (d, 2H), 3.7 (s, 3H), 2.0 (dd, 1H), 1.85 (dd, 1H), 1.38 (dd, 1H). **MS** (*m/z*): 235.0[M-H]⁺.

Preparation 4: (1*R*,5*S*/1*S*,5*R*)-1-[4-(Methoxy)phenyl]-3-azabicyclo[3.1.0]hexane-2,4-dione**[0112]**

[0113] A mixture of 12.8 g of the diacid obtained in Preparation 3 and 6.5 g of urea in 300 mL of *m*-xylene was heated at reflux for 8 h and then concentrated to dryness *in vacuo*. The crude was purified by column chromatography (AcOEt: cyclohexane=1 (?):10 to 4:6) to give 5.5 g of the title compound (*y*= 46%).

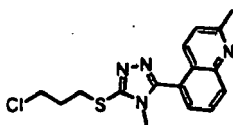
[0114] **MS** (*m/z*): 218.1 [MH]⁺.

Preparation 5: (1*R*,5*S*/1*S*,5*R*)-1-[4-(Methoxy)phenyl]-3-azabicyclo[3.1.0]hexane**[0115]**

[0116] To a stirred slurry of 5.5 g of the imide obtained in Preparation 4 in 170 mL of toluene was slowly added 45 mL of Vitride (3.4 M in toluene) under N₂. This solution was stirred at reflux for 2 h. To the cooled solution was cautiously added aqueous NaOH (10 M, 40 mL) and the organic layer was washed with two portions of water and dried over Na₂SO₄. This solution was filtered, and the filtrate was evaporated in *vacuo* to give 4.8 g of the title compound (*y*= 100%).

NMR (¹H, CDCl₃): δ 7.10 (d, 2H), 6.82 (d, 2H), 3.77 (s, 3H), 3.35-2.98 (m, 4H), 2.58 (dd, 1H), 0.87 (dd, 1H), 0.78 (dd, 1H), NH not observed. **MS** (*m/z*): 190.1[MH]⁺.

Preparation 6: 5-{5-[(3-Chloropropyl)thio]-4-methyl-4*H*-1,2,4-triazol-3-yl}-2-methylquinoline**[0117]**

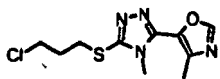


[0118] To 4-methyl-5-(2-methyl-5-quinoliny)-2,4-dihydro-3H-1,2,4-triazole-3-thione (3.6 g, prepared in analogy to the method described in WO200240471) in ethanol (60 mL) containing 1-bromo-3-chloropropane (2.0 mL) was carefully added with stirring sodium hydride (0.60 g, 60% in petroleum). The mixture was heated at reflux for 45 min. Volatiles were evaporated *in vacuo* and the residue submitted to column chromatography (EtOAc-acetone gradient). The material thus obtained was precipitated from hot EtOAc (20 mL) by adding petroleum ether (40-60, 50 mL), cooled and collected by filtration to provide the title compound as colourless crystals (2.1 g).

[0119] **NMR** (¹H, CDCl₃): δ 8.18 (d, 1H), 8.12 (d, 1H), 7.76 (t, 1H), 7.55 (d, 1H), 7.30 (d, 1H), 3.75 (t, 2H), 3.50 (t, 2H), 3.40 (s, 3H), 2.76 (s, 3H), 2.37 (m, 2H).

Preparation 7: 3-[(3-Chloropropyl)thio]-4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4H-1,2,4-triazole

[0120]



Ethyl-2-chloroacetoacetate (1 wt; 1 eq., 1000 g) was aged with formamide (0.68 vol; ca. 2.8 eq.) and the resulting solution was heated to 120 °C. After 5 hours the mixture was allowed to cool to room temperature and allowed to age under nitrogen over night. The mixture was treated with NaOH (3 M, 6 vol, reaction moderately exothermic) and stirred at room temperature for 4 hours. Ethyl acetate (6 vol) was added and the phases allowed to separate. The organic layer was discarded while the aqueous was acidified with conc. (32%) aqueous HCl to pH 2 (ca. 2.0 vol). A precipitate started to form. The suspension was treated with AcOEt (8 vol) and vigorously stirred until the bulk of the precipitate had dissolved. The aqueous phase was further extracted with AcOEt twice (6 vol each) and the combined organic layers distilled to low volume (again a suspension was observed at low volume). Fresh AcOEt (8 vol) was added and the mixture evaporated to dryness. The collected solid was placed in the oven at 40 °C over night under reduced pressure to give 4-methyl-1,3-oxazole-5-carboxylic acid (498 g, 64.5%).

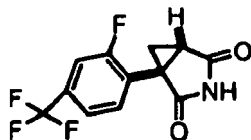
This material (498 g, 1 wt) was dissolved in dry tetrahydrofuran (5 vol), under nitrogen, cooled to 0 °C. DCC (1.62 wt, 1 eq) was added portionwise followed by HOBT (1.07 wt, 1 eq). The mixture was warmed to 25 ± 2 °C and stirred for 30 min. 4-Methyl-3-thiosemicarbazide (0.83 wt, 1 eq) was then added and the mixture further stirred for 2 h at 25 ± 2 °C. The mixture was filtered and the cake was washed with fresh tetrahydrofuran (1 vol) and dried on the filter for a few hours. The cake was suspended in 1 M aqueous NaOH (13 vol) and heated to 70 °C for 30 min. After this time, the mixture was cooled to 25 ± 2 °C and a solid was removed by filtration. The cake was washed with 1 M aqueous NaOH (10 vol). The combined mother liquors were cooled to 0 °C and acidified to ca. pH 5 with HCl (aqueous, 16%; NOTE: keep temperature while adding HCl below +10 °C). The suspended product was isolated by filtration washing with water (2x3 vol). The cake was dried at 40 °C for 18 h in high vacuum to obtain 4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (respectively a tautomeric form thereof; 290 g, 37%).

NaOEt (21% solution in EtOH, 2.08 vol, 1.1 eq) was added to EtOH (20 vol) under nitrogen atmosphere. 4-Methyl-5-(4-methyl-1,3-oxazol-5-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (respectively a tautomeric form thereof; 290 g, 1 wt) was added in one portion and the resulting mixture stirred at 25 ± 2 °C until a clear solution was obtained. Then 1-bromo-3-chloropropane (0.54 vol, 1.1 eq) was added and the solution stirred at 40 °C for 24 h then cooled to 25 °C. After filtration water (20 vol) was added and the ethanolic phase was removed by vacuum distillation (internal temperature ~40 °C). The mixture was extracted with EtOAc (41 vol). The aqueous layer was removed and the organic phase was evaporated to dryness. Dichloromethane (4 vol) was added. The organic solution is purified through a short silica gel column (18 wt of silica), eluting with EtOAc (200 vol) to give the title compound as a solid foam (267.64 g, 66%).

NMR (¹H, CDCl₃): δ 7.90 (s, 1H), 3.70 (s, 5H), 3.40 (t, 2H), 2.52 (s, 3H), 2.30 (m, 2H).

Preparation 8: 1 (1R,5S/1S,5R)-[2-Fluoro-4-(trifluoromethyl)phenyl]-3 azabicyclo[3.1.0]hexane-2,4-dione

[0121]



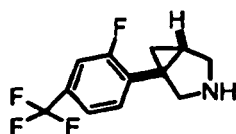
[0122] To a slurry of maleimide (1.7 eq), anhydrous CuCl_2 (1.2 eq) and *tert*-butyl nitrite (1.5 eq) in CH_3CN (35 mL) at 0 °C a solution of 2-fluoro-4-(trifluoromethyl)aniline (16.3 g) in CH_3CN (6.5 mL) was added dropwise. The reaction mixture was stirred at room temperature for 1 h and HCl (10%, aqueous, 196 mL) was added. The mixture was extracted with EtOAc, the organic layer was washed with saturated aqueous NaCl and dried over Na_2SO_4 . The solution was filtered and the filtrate was concentrated *in vacuo*. By NMR analysis the crude mixture resulted a 1:4 mixture of the arylated maleimide hydrogen chloride adduct (component A) and unreacted maleimide (component B).

A DMSO (140 mL) solution of this crude product was added dropwise to a preformed solution of trimethylsulfoxonium iodide (2 eq with respect to component A plus 2 eq with respect to component B) in anhydrous DMSO (412 mL) to which NaH (3 eq with respect to component A plus 2 eq with respect to component B) had been added portionwise. The reaction mixture was stirred for 30 min and AcOH (2 eq) was added followed by water. The reaction mixture was extracted with Et_2O and then with EtOAc, the combined organic layers were washed with saturated aqueous NaCl and dried over Na_2SO_4 . The solution was filtered and the filtrate was concentrated *in vacuo*. The crude product obtained was triturated with water and then with cyclohexanes to give the title compound as light brown solid (5.98 g).

NMR (^1H , CDCl_3): δ 7.55-7.3 (m, 3H), 2.8-2.7 (m, 1H), 2.1 (m, 1H), 2.0 (m, 1H), NH not observed. **MS** (m/z): 274 $[\text{MH}]^+$.

Preparation 9 (1*R*,5*S*/1*S*,5*R*)-1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane

[0123]

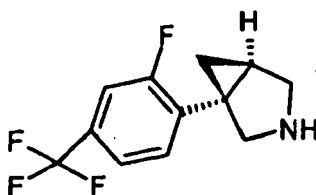


[0124] To a solution of (1*R*,5*S*/1*S*,5*R*)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-3-azabicyclo-[3.1.0]hexane-2,4-dione (2.6 g) in anhydrous tetrahydrofuran (56 mL), BH_3 in tetrahydrofuran (1 M, 4 eq) was added at 0 °C. The reaction mixture was stirred at 65 °C for 24 h, cooled to RT and MeOH was added until gas evolution ceased. Solvent was removed *in vacuo*, MeOH was added (200 mL) *p*-toluenesulfonic acid (3 eq) was added and the reaction mixture was stirred at 65 °C for 6 h, the reaction mixture was cooled to room temperature and a saturated solution of K_2CO_3 (1.7 eq) was added. The mixture was extracted with dichloromethane, the organic layer was washed with saturated aqueous NaCl and dried over Na_2SO_4 . The solution was filtered and the filtrate was concentrated *in vacuo* to give the title compound as colourless oil (2.1 g).

NMR (^1H , CDCl_3): δ 7.2-7.4 (m, 3H), 3.2 (m, 2H), 3.1 (m, 2H), 1.8 (m, 1H), 0.8 (m, 2H), NH not observed. **MS** (m/z): 246 $[\text{MH}]^+$.

Preparation 10: (1*S*,5*R*)-1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane

[0125]



[0126] (1*R*)-(-)-10-Camphorsulfonic acid (4.19 g) was added in portions to a stirred solution of (1*R*,5*S*/1*S*,5*R*)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane (4.4 g) in CH_3CN (44 mL). The resulting mixture was stirred

at room temperature for 20 min until a white precipitate formed. The mixture was then warmed up to reflux temperature, stirred for 45 minutes and then slowly allowed to cool to room temperature. The white solid was collected by filtration and dried *in vacuo*. This material was recrystallised 2 times from CH₃CN (25 mL per g solid) to give 1.57 g of a white solid. This material was then suspended in sodium hydroxide (1M solution, 1.1 eq) and dichloromethane (100 mL) and allowed to stir at room temperature until complete dissolution. After separation of the two phases, the aqueous layer was extracted again with dichloromethane. The combined organic layers were washed with sodium hydroxide and then dried over Na₂SO₄. Evaporation of solvent *in vacuo* gave the title compound (874 mg) as colorless liquid.

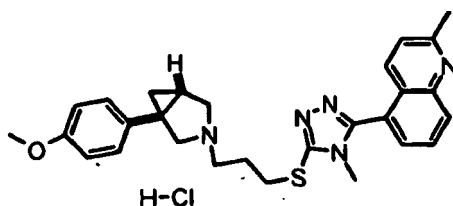
Analytical chromatography

Column: chiralcel OD 10 μ m, 250 x 4.6 mm
 Mobile phase: A: n-Hexane; B: Isopropanol +0.1% Isopropyl amine
 Gradient: isocratic 2% B
 Flow rate: 0.8 mL/min
 UV wavelength range: 200-400 nm
 Analysis

ret. time (min)	% a/a
17.18	>99.5 (1 <i>S</i> ,5 <i>R</i>)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane

Example 1: 5-[5-({3-[(1*R*,5*S*/1*S*,5*R*)-1-(4-Methoxyphenyl)-3-azabicyclo[3.1.0]hex-3-yl]propyl}thio)-4-methyl-4*H*-1,2,4-triazol-3-yl]-2-methylquinoline hydrochloride

[0127]



[0128] A mixture of (1*R*,5*S*/1*S*,5*R*)-1-[4-(methoxy)phenyl]-3-azabicyclo[3.1.0]hexane (Preparation 5, 42 mg), 5-{5-[(3-chloropropyl)thio]-4-methyl-4*H*-1,2,4-triazol-3-yl}-2-methylquinoline (0.26 mmol), Na₂CO₃ (0.44 mmol) and NaI (0.22 mmol) in DMF (anhydrous, 0.4 mL) was heated at 60 °C for 24 h. After elimination of the solvent under *vacuo*, the residue was dissolved in ethyl acetate and the organic layer was washed with saturated aqueous NaHCO₃ and dried over Na₂SO₄. This solution was filtered and the filtrate was concentrated *in vacuo*. The crude was purified by flash chromatography (dichloromethane to 10% MeOH in dichloromethane) to give 65 mg of the free base of the title compound. To a solution of this material in dichloromethane (0.2 mL) was added 0.14 mmol of HCl (1M in Et₂O), the solvent evaporated under *vacuo* and the material thus obtained triturated with Et₂O to give 69 mg of the title compound as a white slightly hygroscopic solid (59% yield).

[The procedure may in analogy be adapted to other combinations of 1-substituted 3-azabicyclo[3.1.0]hexanes and 3-substituted 5-[(3-chloropropyl)thio]-4-methyl-4*H*-1,2,4-triazols. An equivalent molar amount of K₂CO₃ may be used to replace Na₂CO₃.]

NMR (1H, DMSO): δ 10.57 (bs, 1H), 8.28 (bs, 1H), 8.2 (d, 1H), 7.94 (t, 1H), 7.82 (d, 1H), 7.56 (d, 1H), 7.25 (d, 2H), 6.91 (d, 2H), 4.01 (dd, 1H), 3.7 (m, 1H), 3.74 (s, 3H), 3.6-3.2 (m, 6H), 3.42 (s, 3H), 2.75 (s, 3H), 2.24 (quint, 2H), 2.08 (quint, 1H), 1.62/1.05 (t/t, 2H). **MS (m/z):** 486.3[MH]⁺.

[0129] Example 1 was separated to give the separated enantiomers by semipreparative Supercritical Fluid Chromatography (Gilson) using a chiral column Chiralpak AD-H, 25 x 2.1 cm, eluent CO₂ containing 20% (ethanol + 0.1% isopropanol), flow rate 25 mL/min, P 194 bar, T 35 °C, detection UV at 220 nm, loop 1 mL. Retention times given were obtained using an analytical Supercritical Fluid Chromatography (Gilson) using a chiral column Chiralpak AD-H, 25 x 0.46 cm, eluent CO₂ containing 20% (ethanol + 0.1% isopropanol), flow rate 2.5 mL/min, P 194 bar, T 35 °C, detection UV at 220 nm.

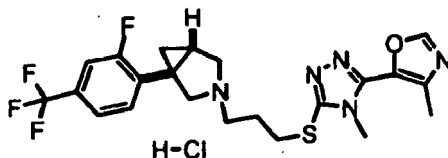
Enantiomer 1 was recovered in 15 mg yield as white solid (y=27%) from the racemate (60 mg). Rt. = 39.2 min.

Enantiomer 2 was recovered in 17 mg yield as white solid (y=30%) from the racemate (60 mg). Rt. = 43.4 min.

Enantiomer 1 showed fpKi (D3) > 1 log-unit higher than Enantiomer 2.

Example 2: (1*R*,5*S*/1*S*,5*R*)-1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-(3-[[4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio]propyl)-3-azabicyclo[3.1.0]hexane hydrochloride

[0130]



[0131] A mixture of (1*R*,5*S*/1*S*,5*R*)-1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane (Preparation 9, 700 mg, 2.8 mmol), 3-[(3-Chloropropyl)thiol-4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazole (Preparation 7, 3.4 mmol), Na₂CO₃ (3.4 mmol) and NaI (3.4 mmol) in DMF (anhydrous, 6 mL) was heated at 60 °C for 24 h. After elimination of the solvent under *vacuo*, the residue was dissolved in ethyl acetate and the organic layer was washed with saturated aqueous NaHCO₃ and dried over Na₂SO₄. This solution was filtered and the filtrate was concentrated *in vacuo*. The crude was purified by flash chromatography (dichloromethane to 10% MeOH in dichloromethane) to give 503 mg of the free base of the title compound.

NMR (¹H, CDCl₃): δ 7.89 (s, 1H), 7.32-7.2 (m, 3H), 3.70 (s, 3H), 3.30 (t, 2H), 3.26 (dd, 1H), 3.10 (dd, 1H), 2.60 (t, 2H), 2.52 (dd, 1H), 2.51 (s, 3H), 2.43 (dd, 1H), 1.94 (m, 2H), 1.74 (m, 1H), 1.40 (t, 1H), 0.76 (dd, 1H). **MS** (*m/z*): 482.2[MH]⁺. The title compound was obtained as a white solid following the method described for Example 15.

NMR (¹H, DMSO): δ 10.28 (bs, 1H), 8.58 (s, 1H), 7.73 (d, 1H), 7.6 (m, 2H), 4/ 3.57 (d/m, 2H), 3.79 (d, 1H), 3.69 (s, 3H), 3.5-3.2 (vbm, 1H), 3.27 (t, 2H), 2.5 (m, 2H), 2.4 (m, 1H), 2.38 (s, 3H), 2.14 (quint., 2H), 1.62/1.16 (2t, 2H). **MS** (*m/z*): 481[MH]⁺.

[0132] Example 2 was separated to give the separated enantiomers by semi-preparative HPLC using a chiral column Chiralpak AD 10 μm, 250 x 21 mm, eluent A: n-hexane; B: isopropanol + 0.1% isopropyl amine, gradient isocratic 9% B, flow rate 7 mL/min, detection UV at 200-400 nm. Retention times given were obtained using an analytical HPLC using a chiral column Chiralpak AD-H 5 μm, 250 x 4.6 mm, eluent A: n-hexane; B: isopropanol, gradient isocratic 15% B, flow rate 0.8 mL/min. detection UV at 200-400 nm.

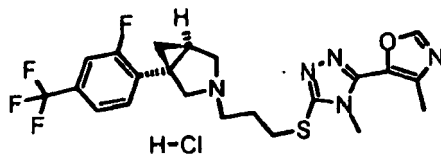
Enantiomer 1 was recovered as white solid, Rt. = 15.4 min.

Enantiomer 2 was recovered as white solid, Rt. = 16.3 min.

Enantiomer 2 showed fpK_i (D3) > 1 log-unit higher than Enantiomer 1.

Example 3: (1*S*,5*R*)-1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-(3-[[4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio]propyl)-3-azabicyclo[3.1.0]hexane hydrochloride

[0133]



[0134] The free base of the title compound was prepared in analogy to the method described in Example 1 from (1*S*,5*R*)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane. A mixture of (1*S*,5*R*)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane (Preparation 10, 727mg, 2.97mmol), 3-[(3-Chloropropyl)thiol-4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazole (Preparation 7, 3.6mmol.), K₂CO₃ (3.6mmol.) and NaI (2.97mmol) in DMF anhydrous was heated at 60 °C for 24 h. After elimination of the solvent under *vacuo*, the residue was dissolved in ethyl acetate and the organic layer was washed with saturated aqueous NaHCO₃ and dried over Na₂SO₄. This solution was filtered and the filtrate was concentrated *in vacuo*. The crude was purified by flash chromatography (dichloromethane to 10% MeOH in dichloromethane) to give 940 mg of the free base of the title compound.

[0135] This free base (886 mg) was converted to the hydrochloride salt (847 mg) according to the method described in Example 1. The title compound was obtained as a white solid.

Analytical Chiral HPLC confirmed the product to be identical to Enantiomer 2 of Example 16.

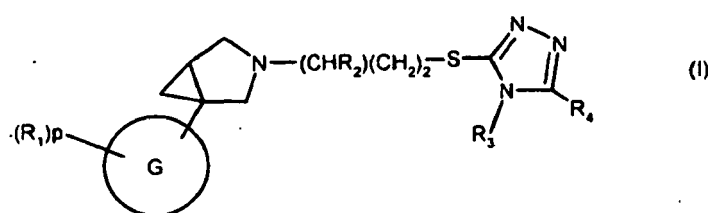
NMR and MS data corresponded to those reported for Example 2.

The absolute configuration of the title compound was confirmed using comparative VCD and comparative OR analyses of the corresponding free base to be (1*S*,5*R*)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-3-(3-[[4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio]propyl)-3-azabicyclo[3.1.0]hexane. (1*S*,5*R*)-3-(3-[[4-Methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio]propyl)-1-[4-(trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane (see Example 14) was used as the reference.

Specific Optical Rotation of the corresponding free base: $[\alpha]_D = -42^\circ$ (CDCl₃, T = 25 °C, c \equiv 0.005 g/0.8 mL).

Claims

1. 1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-(3-[[4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio]propyl)-3-azabicyclo[3.1.0]hexane or a pharmaceutically acceptable salt thereof, corresponding to a compound of formula (I),



wherein

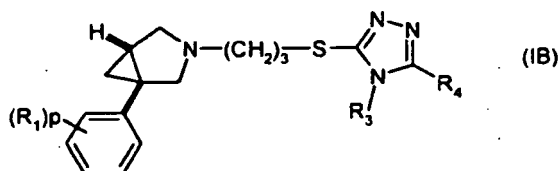
G is phenyl and (R₁)_p is 2-fluoro-4-trifluoromethyl;

R₂ is hydrogen;

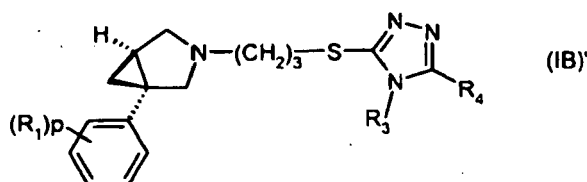
R₃ is methyl;

R₄ is 4-methyl-1,3-oxazol-5-yl.

2. A compound or a pharmaceutically acceptable salt thereof, corresponding to the compound of formula (IB) wherein R₁, p, R₃ and R₄ are as defined in claim 1.



3. A stereochemically isomer enriched in the (1*S*,5*R*) configuration of formula (IB)' or a pharmaceutically acceptable salt thereof, wherein R₁, p, R₃ and R₄ are as defined as in claim 1.



4. A compound or a pharmaceutically acceptable salt thereof according to any of claims 1-3 selected from a group consisting of:

(1*R*,5*S*/1*S*,5*R*)-1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-(3-{[4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio}propyl)-3-azabicyclo[3.1.0]hexane;

(1*R*,5*S*/1*S*,5*R*)-1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-(3-{[4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio}propyl)-3-azabicyclo[3.1.0]hexane hydrochloride

(1*S*,5*R*)-1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-(3-{[4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio}propyl)-3-azabicyclo[3.1.0]hexane;

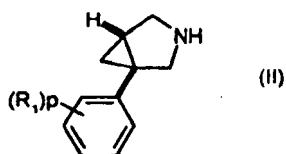
(1*S*,5*R*)-1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-(3-{[4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio}propyl)-3-azabicyclo[3.1.0]hexane hydrochloride.

5. (1*R*,5*S*/1*S*,5*R*)-1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-(3-{[4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio}propyl)-3-azabicyclo[3.1.0]hexane.

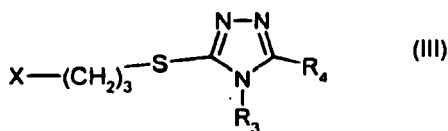
6. (1*S*,5*R*)-1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-(3-{[4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio}propyl)-3-azabicyclo[3.1.0]hexane.

7. A process for preparing a compound as claimed in claim 1, the process comprising the following steps:

reacting a compound of formula (II):



wherein $(R_1)_p$ is as defined for formula (I), with a compound of formula (III):



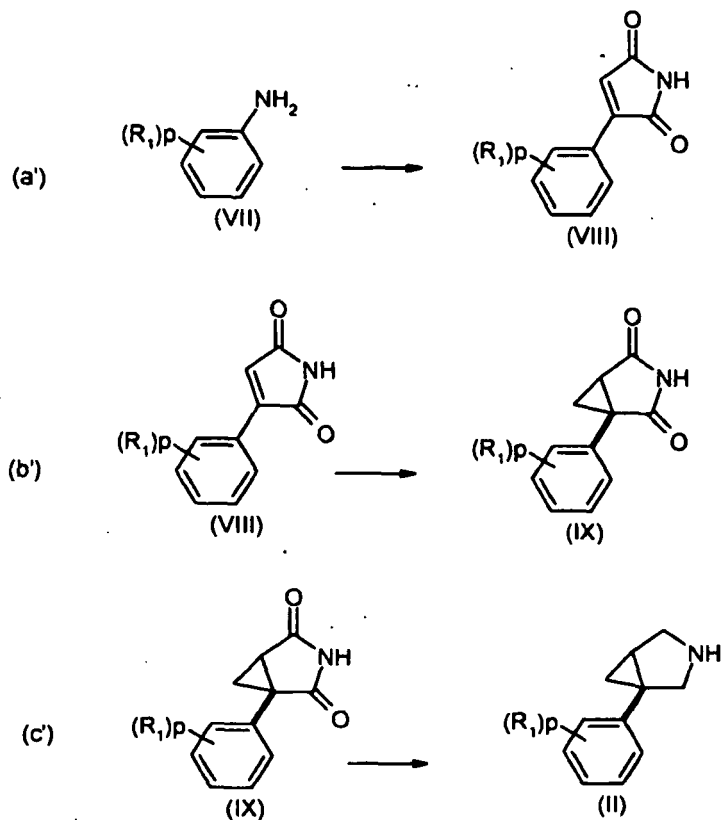
wherein R_3 and R_4 are as defined for formula (I) and X is a leaving group, and thereafter optionally:

(i) removing any protecting group(s); and/or

(ii) forming a salt; and/or

(iii) converting a compound of formula (I) or a salt thereof to another compound of formula (I) or a salt thereof.

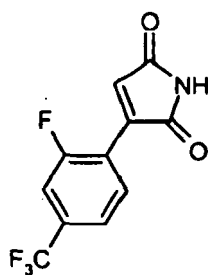
8. A process for preparing a compound of formula (II), according to claim 7 wherein $(R_1)_p$ is 2-fluoro-4-(trifluoromethyl)phenyl, the process comprising the following steps:



wherein:

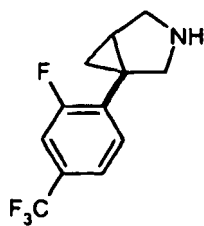
step(a') means diazotation of an aniline (VII) followed by reaction with maleimide to give 3-arylmaleimide (VIII);
 step (b') means cyclopropanation of (VIII) to provide bicyclic imide (IX);
 step (c') means reduction of imide (IX) to give compounds of formula (II).

9. 3-[2-fluoro-4-(trifluoromethyl)phenyl]-1H-pyrrole-2,5-dione



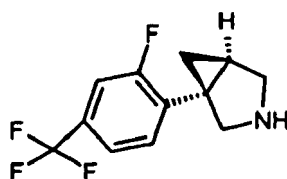
as intermediate in the preparation of the compound of formula (I) according to claim 8.

10. (1*R*,5*S*/1*S*,5*R*)-1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane,



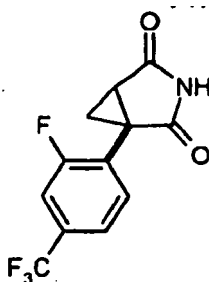
as intermediate in the preparation of the compound of formula (I) according to claim 8.

11. (1*S*,5*R*)-1-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane,



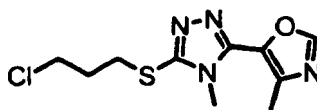
as intermediate in the preparation of the compound of formula (I) according to claim 8.

12. 1(1*R*,5*S*/1*S*,5*R*)-[2-Fluoro-4-(trifluoromethyl)phenyl]-3-azabicyclo[3.1.0]hexane-



2,4-dione, as intermediate in the preparation of the compound of formula (I) according to claim 8.

13. 3-[(3-Chloropropyl)thio]-4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazole,



as intermediate in the preparation of the compound of formula (I) according to claim 7.

14. Use of a compound as claimed in any of claims 1-6 in the manufacture of a medicament for the treatment of a condition in a mammal for which the modulation of dopamine D₃ receptors is beneficial, wherein the condition is psychosis or a psychotic condition, or is substance abuse.

15. Use as claimed in claim 14, wherein the condition is substance abuse.

16. Use as claimed in claim 14, wherein the psychotic condition is schizophrenia

17. A compound as claimed in any of claims 1-4 for use in therapy.

18. A compound as claimed in any of claims 1-6 for use in the treatment of a condition in a mammal for which modulation of dopamine D₃ receptors is beneficial, wherein the condition is psychosis or a psychotic condition, or is substance abuse..

19. A compound as claimed in any of claims 1-6 for use in the treatment of psychosis or a psychotic condition.

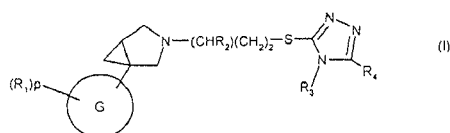
20. A compound as claimed in any of claims 1-6 for use in the treatment of substance abuse.

21. A compound as claimed in any of claims 1-5 for use in the treatment of schizophrenia.

22. A pharmaceutical composition comprising a compound as claimed in any of claims 1-6 and a pharmaceutically acceptable carrier.

Patentansprüche

1. 1-[2-Fluor-4-(trifluorinethyl)phenyl]-3-(3-([4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4H-1,2,4-triazol-3-yl]thio)propyl)-3-azabicyclo[3.1.0]hexan oder ein pharmazeutisch verträgliches Salz davon, welches einer Verbindung der Formel (I) entspricht



wobei

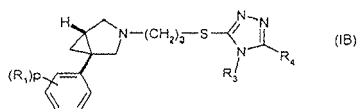
G für Phenyl steht und (R₁)_p für 2-Fluor-4-trifluormethyl steht;

R₂ für Wasserstoff steht;

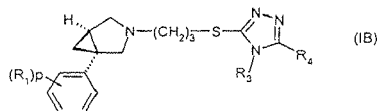
R₃ für Methyl steht;

R₄ für 4-Methyl-1,3-oxazol-5-yl steht.

2. Verbindung oder ein pharmazeutisch verträgliches Salz davon, welche der Verbindung der Formel (IB) entspricht, wobei R₁, p, R₃ und R₄ wie in Anspruch 1 definiert sind.



3. Stereochemisches Isomer, welches in der (1S,5R) Konfiguration der Formel (IB)' angereichert ist oder ein pharmazeutisch verträgliches Salz davon, wobei R₁, p, R₃ und R₄ wie in Anspruch 1 definiert sind.



4. Verbindung oder ein pharmazeutisch verträgliches Salz davon nach einem der Ansprüche 1 bis 3 ausgewählt aus einer Gruppe bestehend aus:

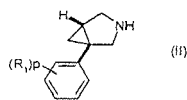
(1R,5S/1S,5R)-1-[2-Fluor-4-(trifluormethyl)phenyl]-3-(3-([4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4H-1,2,4-triazol-3-yl]thio)propyl)-3-azabicyclo[3.1.0]hexan;

(1R,5S/1S,5R)-1-[2-Fluor-4-(trifluormethyl)phenyl]-3-(3-([4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4H-1,2,4-triazol-3-yl]thio)propyl)-3-azabicyclo[3.1.0]hexan-Hydrochlorid;

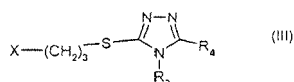
(1*S*,5*R*)-1-[2-Fluor-4-(trifluormethyl)phenyl]-3-(3-([4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio)propyl)-3-azabicyclo[3.1.0]hexan;
 (1*S*,5*R*)-1-[2-Fluor-4-(trifluormethyl)phenyl]-3-(3-([4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio)propyl)-3-azabicyclo[3.1.0]hexan-Hydrochlorid.

5. (1*R*,5*S*/1*S*,5*R*)-1-[2-Fluor-4-(trifluormethyl)phenyl]-3-(3-([4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio)propyl)-3-azabicyclo[3.1.0]hexan.
6. (1*S*,5*R*)-1-[2-Fluor-4-(trifluormethyl)phenyl]-3-(3-([4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol-3-yl]thio)propyl)-3-azabicyclo[3.1.0]hexan.
7. Verfahren zur Herstellung einer Verbindung wie in Anspruch 1 beansprucht, wobei das Verfahren die folgenden Schritte umfasst:

Umsetzen einer Verbindung der Formel (II):



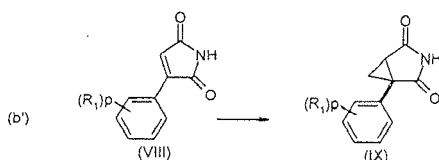
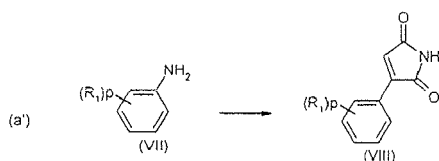
wobei $(R_1)_p$ wie für Formel (I) definiert ist, mit einer Verbindung der Formel (III):

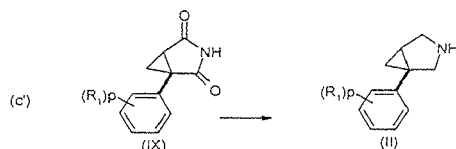


wobei R_3 und R_4 wie für Formel (I) definiert sind und X eine Abgangsgruppe ist und danach gegebenenfalls

- (i) Entfernen jeglicher Schutzgruppe(n); und/oder
 (ii) Bilden eines Salzes; und/oder
 (iii) Umwandeln einer Verbindung der Formel (I) oder eines Salzes davon in eine andere Verbindung der Formel (I) oder ein Salz davon.

8. Verfahren zur Herstellung einer Verbindung der Formel (II) nach Anspruch 7, wobei $(R_1)_p$ für 2-Fluor-4-(trifluormethyl)phenyl steht, wobei das Verfahren die folgenden Schritte umfasst:

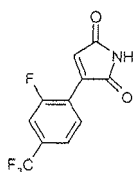




wobei:

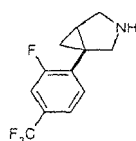
Schritt (a') Diazotierung eines Anilins (VII) bedeutet, gefolgt von der Reaktion mit Maleimid, um 3-Arylmaleimid (VIII) zu ergeben;
 Schritt (b') Cyclopropanierung von (VIII) bedeutet, um ein bicyclisches Imid (IX) bereitzustellen;
 Schritt (c') Reduktion von Imid (IX) bedeutet, um Verbindungen der Formel (II) zu ergeben.

9. 3-[2-Fluor-4-(trifluormethyl)phenyl]-1H-pyrrol-2,5-dion



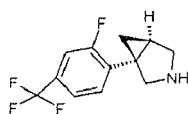
als Zwischenprodukt bei der Herstellung der Verbindung der Formel (I) nach Anspruch 8.

10. (1*R*,5*S*/1*S*,5*R*)-1-[2-Fluor-4-(trifluorinethyl)phenyl]-3-azabicyclo[3,1.0]hexan



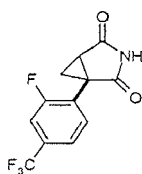
als Zwischenprodukt bei der Herstellung der Verbindung der Formel (I) nach Anspruch 8.

11. (1*R*,5*S*/1*S*,5*R*)-1-[2-Fluor-4-(trifluormethyl)phenyl]-3-azabicyao[3.1.0]hcxan

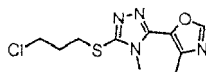


als Zwischenprodukt bei der Herstellung der Verbindung nach Formel (I) nach Anspruch 8.

12. 1(1*R*,5*S*/1*S*,5*R*)-[2-Fluor-4-(trifluormethyl)phenyl]-3-azabicyclo[3.1.0]hexan-2,4-dion



als Zwischenprodukt bei der Herstellung der Verbindung der Formel (I) nach Anspruch 8.

13. 3-[(3-Chlorpropyl)thio]-4-methyl-5-(4-methyl-1,3-oxazol-5-yl)-4*H*-1,2,4-triazol

als Zwischenprodukt bei der Herstellung der Verbindung der Formel (I) nach Anspruch 7.

14. Verwendung einer Verbindung wie in einem der Ansprüche 1 bis 6 beansprucht bei der Herstellung eines Medikaments zur Behandlung eines Zustands bei einem Säuger, für den die Regulierung von Dopamin D₃ Rezeptoren vorteilhaft ist, wobei der Zustand Psychose oder ein psychotischer Zustand ist oder Drogenmissbrauch ist.

15. Verwendung wie in Anspruch 14 beansprucht, wobei der Zustand Drogenmissbrauch ist.

16. Verwendung wie in Anspruch 14 beansprucht, wobei der psychotische Zustand Schizophrenie ist.

17. Verbindung wie in einem der Ansprüche 1 bis 4 beansprucht zur Verwendung in der Therapie.

18. Verbindung wie in einem der Ansprüche 1 bis 6 beansprucht zur Verwendung bei der Behandlung eines Zustands bei einem Säuger, für den die Regulierung von Dopamin D₃ Rezeptoren vorteilhaft ist, wobei der Zustand Psychose oder ein psychotischer Zustand ist oder Drogenmissbrauch ist.

19. Verbindung wie in einem der Ansprüche 1 bis 6 beansprucht zur Verwendung bei der Behandlung von Psychose oder eines psychotischen Zustands.

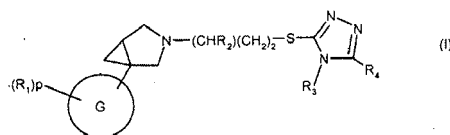
20. Verbindung wie in einem der Ansprüche 1 bis 6 beansprucht zur Verwendung bei der Behandlung von Drogenmissbrauch.

21. Verbindung wie in einem der Ansprüche 1 bis 5 beansprucht zur Verwendung bei der Behandlung von Schizophrenie.

22. Arzneimittel, umfassend eine Verbindung wie in einem der Ansprüche 1 bis 6 beansprucht und einen pharmazeutisch verträglichen Träger.

Revendications

1. 1-[2-fluoro-4-(trifluorométhyl)phényl]-3-(3-{[4-méthyl-5-(4-méthyl-1,3-oxazole-5-yl)-4*H*-1,2,4-triazole-3-yl]thio}propyl)-3-azabicyclo[3.1.0]hexane ou un de ses sels pharmaceutiquement acceptables, correspondant à un composé de formule (I) :



dans laquelle

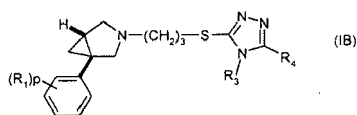
G représente un groupe phényle et (R₁)_p représente un groupe 2-fluoro-4-trifluorométhyle ;

R₂ représente un atome d'hydrogène ;

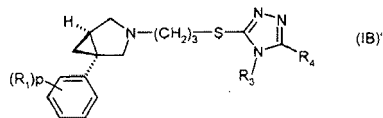
R₃ représente un groupe méthyle ;

R₄ représente un groupe 4-méthyl-1,3-oxazole-5-yle.

2. Composé ou un de ses sels pharmaceutiquement acceptables, correspondant au composé de formule (IB) dans laquelle R₁, p, R₃ et R₄ sont tels que définis dans la revendication 1.



3. Isomère stéréochimiquement enrichi en la configuration (1*S*,5*R*) de formule (IB)' ou un de ses sels pharmaceutiquement acceptables, dans lequel R_1 , p , R_3 et R_4 sont tels que définis dans la revendication 1.



4. Composé ou un de ses sels pharmaceutiquement acceptables suivant l'une quelconque des revendications 1 à 3, choisi dans un groupe consistant en :

le (1*R*,5*S*/1*S*,5*R*)-1-[2-fluoro-4-(trifluorométhyl)phényl]-3-(3-[[4-méthyl-5-(4-méthyl-1,3-oxazole-5-yl)-4*H*-1,2,4-triazole-3-yl]thio]propyl)-3-azabicyclo[3.1.0]hexane ;

le chlorhydrate de (1*R*,5*S*/1*S*,5*R*)-1-[2-fluoro-4-(tri-fluorométhyl)phényl]-3-(3-[[4-méthyl-5-(4-méthyl-1,3-oxazole-5-yl)-4*H*-1,2,4-triazole-3-yl]thio]propyl)-3-azabicyclo[3.1.0]hexane ;

le (1*S*,*S**R*)-1-[2-fluoro-4-(trifluorométhyl)phényl]-3-(3-[[4-méthyl-5-(4-méthyl-1,3-oxazole-5-yl)-4*H*-1,2,4-triazole-3-yl]thio]propyl)-3-azabicyclo[3.1.0]hexane ;

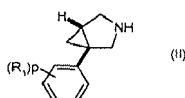
le chlorhydrate de (1*S*,5*R*)-1-[2-fluoro-4-(trifluoro-méthyl)phényl]-3-(3-[[4-méthyl-5-(4-méthyl-1,3-oxazole-5-yl)-4*H*-1,2,4-triazole-3-yl]thio]propyl)-3-azabicyclo[3.1.0]hexane.

5. (1*R*,5*S*/1*S*,5*R*)-1-[2-fluoro-4-(trifluorométhyl)phényl]-3-(3-[[4-méthyl-5-(4-méthyl-1,3-oxazole-5-yl)-4*H*-1,2,4-triazole-3-yl]thio]propyl)-3-azabicyclo[3.1.0]hexane.

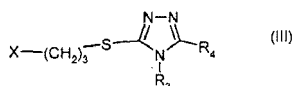
6. (1*S*,5*R*)-1-[2-fluoro-4-(trifluorométhyl)phényl]-3-(3-[[4-méthyl-5-(4-méthyl-1,3-oxazole-5-yl)-4*H*-1,2,4-triazole-3-yl]thio]propyl)-3-azabicyclo[3.1.0]hexane.

7. Procédé pour la préparation d'un composé suivant la revendication 1, le procédé comprenant les étapes suivantes :

réaction d'un composé de formule (II) :



dans laquelle $(R_1)_p$ est tel que défini pour la formule (I), avec un composé de formule (III) :



dans laquelle R_3 et R_4 sont tels que définis pour la formule (I) et X représente un groupe partant, et ensuite, facultativement :

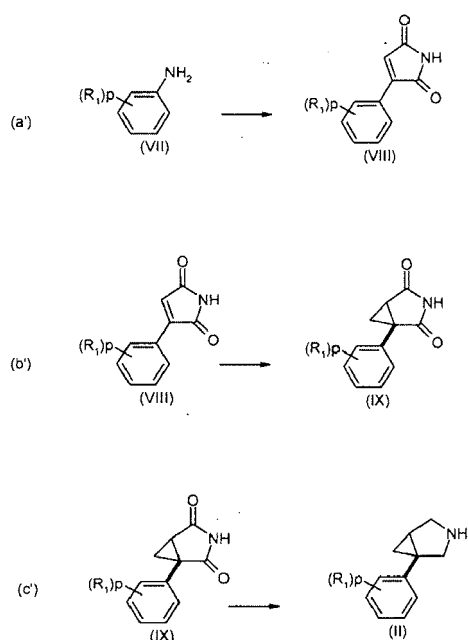
(i) élimination d'un ou plusieurs groupes protecteurs quelconques ; et/ou

(ii) formation d'un sel ; et/ou

(iii) conversion d'un composé de formule (I) ou d'un de ses sels en un autre composé de formule (I) ou un de ses sels.

8. Procédé pour la préparation d'un composé de formule (II) suivant la revendication 7, dans lequel $(R_1)_p$ représente

un groupe 2-fluoro-4-(trifluorométhyl)phényle, le procédé comprenant les étapes suivantes :



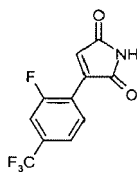
dans lesquelles :

l'étape (a') représente la diazotation d'une aniline (VII) suivie par la réaction avec un maléimide, pour donner un 3-arylmaléimide (VIII) ;

l'étape (b') représente la cyclopropanation du composé (VIII) pour fournir un imide bicyclique (IX) ;

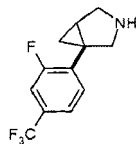
l'étape (c') représente la réduction de l'imide (IX) pour donner des composés de formule (II).

9. 3-[2-fluoro-4-(trifluorométhyl)phényl]-1H-pyrrole-2,5-dione



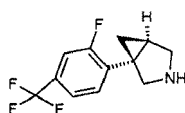
comme intermédiaire dans la préparation du composé de formule (I) suivant la revendication 8.

10. (1*R*,5*S*/1*S*,5*R*)-1-[2-fluoro-4-(trifluorométhyl)phényl]-3-azabicyclo[3.1.0]hexane



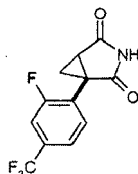
comme intermédiaire dans la préparation du composé de formule (I) suivant la revendication 8.

11. (1*S*,5*R*)-1-[2-fluoro-4-(trifluorométhyl)phényl]-3-azabicyclo[3.1.0]hexane



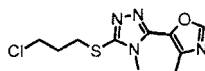
comme intermédiaire dans la préparation du composé de formule (I) suivant la revendication 8.

12. 1-(1*R*,5*S*/1*S*,5*R*)-1-[2-fluoro-4-(trifluorométhyl)-phényl]-3-azabicyclo[3.1.0]hexane-2,4-dione



comme intermédiaire dans la préparation du composé de formule (I) suivant la revendication 8.

13. 3-[(3-chloropropyl)thio]-4-méthyl-5-(4-méthyl-1,3-oxazole-5-yl)-4*H*-1,2,4-triazole



comme intermédiaire dans la préparation du composé de formule (I) suivant la revendication 7.

14. Utilisation d'un composé suivant l'une quelconque des revendications 1 à 6 dans la production d'un médicament destiné au traitement d'une affection pour laquelle la modulation des récepteurs de dopamine D₃ est bénéfique, dans laquelle l'affection est la psychose ou un état psychotique, ou bien est l'abus d'une substance.

15. Utilisation suivant la revendication 14, dans laquelle l'affection est l'abus d'une substance.

16. Utilisation suivant la revendication 14, dans laquelle l'état psychotique est la schizophrénie.

17. Composé suivant l'une quelconque des revendications 1 à 4, destiné à être utilisé en thérapie.

18. Composé suivant l'une quelconque des revendications 1 à 6, destiné à être utilisé dans le traitement chez un mammifère d'une affection pour laquelle la modulation des récepteurs de dopamine D₃ est bénéfique, l'affection étant la psychose ou un état psychotique, ou bien étant l'abus d'une substance.

19. Composé suivant l'une quelconque des revendications 1 à 6, destiné à être utilisé dans le traitement de la psychose ou d'un état psychotique.

20. Composé suivant l'une quelconque des revendications 1 à 6, destiné à être utilisé dans le traitement de l'abus d'une substance.

21. Composé suivant l'une quelconque des revendications 1 à 5, destiné à être utilisé dans le traitement de la schizophrénie.

22. Composition pharmaceutique comprenant un composé suivant l'une quelconque des revendications 1 à 6 et un support pharmaceutiquement acceptable.

REFERENCES CITED IN THE DESCRIPTION

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