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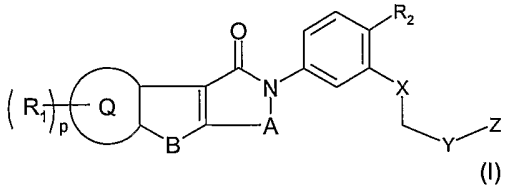
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(54) Title: COMPOUNDS HAVING ACTIVITY AT 5HT2C RECEPTOR AND USES THEREOF



(I)

(57) Abstract: Compounds of formula (I) and pharmaceutically acceptable salts thereof are disclosed: wherein Q is phenyl or a 6-membered heteroaromatic group containing at least one nitrogen atom; A is $-(CH_2-CH_2)-$, $-(CH=CH)-$, $-(CH_2)_3-$, $-C(CH_3)_2-$, $-(CH=CH-CH_2)-$, or a group $-(CHR_3)-$ wherein R_3 is hydrogen, halogen, hydroxy, cyano, nitro, C_1-6alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, haloC_1-6alkyl, C_1-6alkoxy, haloC_1-6alkoxy or C_{1-6}alkylthio; B is O, S or NR_{11}, wherein R_{11} is hydrogen, C_{1-6}alkyl optionally substituted by C_{1-6}alkoxy, or is C_{1-6}alkanoyl optionally substituted by C_{1-6}alkoxy; R_1 is halogen, cyano, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy, amino, mono- or di-C_{1-6}alkylamino, an N-linked 4 to 7 membered heterocyclic group, nitro, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, arylC_{1-6}alkylthio, COR_4 (wherein R_4 is amino, mono- or di-C_{1-6}alkylamino or an N-linked 4 to 7 membered heterocyclic group), $COOR_5$ or COR_6 (wherein R_5 and R_6 are independently hydrogen or C_{1-6}alkyl); p is 0, 1 or 2 or 3; R_2 is hydrogen, halogen, hydroxy, cyano, nitro, C_{1-6}alkyl, C_{1-6}alkanoyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, C_{1-6}alkylthio, amino, mono- or di-C_{1-6}alkylamino or an N-linked 4 to 7 membered heterocyclic group; X is oxygen, sulfur, $-CH_2-$ or NR_8 wherein R_8 is hydrogen or C_{1-6}alkyl; Y is a single bond, $-CH_2-$, $-(CH_2)_2-$ or $-CH=CH-$; and Z is an optionally substituted N-linked heterocyclic group or a C-linked 4 to 7 membered heterocyclic group containing at least one nitrogen, or Z is $-NR_9R_{10}$ where R_9 and R_{10} are independently hydrogen or C_{1-6}alkyl. Method of preparation and uses thereof in therapy, such as for example in treatment of depression and anxiety, are also disclosed.

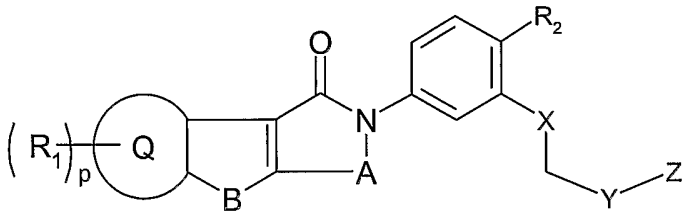
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Compounds having activity at 5HT2c receptor and uses thereof

This invention relates to novel compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment and/or prevention of CNS disorders and other disorders.

WO 96/23783, WO 97/46699 and WO 97/48700 all disclose a series of indoline derivatives which are 5-HT_{2C} receptor antagonists and which are claimed to be useful in the treatment of various CNS disorders.

A novel class of compounds possessing 5-HT_{2C} receptor activity has been found. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

Q is phenyl or a 6-membered heteroaromatic group containing at least one nitrogen atom;

A is $-(CH_2-CH_2)-$, $-(CH=CH)-$, $-(CH_2)_3-$, $-C(CH_3)_2-$, $-(CH=CH-CH_2)-$, or a group $-(CHR_3)-$ wherein R_3 is hydrogen, halogen, hydroxy, cyano, nitro, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy or C_{1-6}alkylthio;

B is O, S or NR_{11}, wherein R_{11} is hydrogen, C_{1-6}alkyl optionally substituted by C_{1-6}alkoxy, or is C_{1-6}alkanoyl optionally substituted by C_{1-6}alkoxy;

R_1 is halogen, cyano, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy, amino, mono- or di-C_{1-6}alkylamino, an N-linked 4 to 7 membered heterocyclic group, nitro, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, arylC_{1-6}alkylthio, COR_4 (wherein R_4 is amino, mono- or di-C_{1-6}alkylamino or an N-linked 4 to 7 membered heterocyclic group), $COOR_5$ or COR_6 (wherein R_5 and R_6 are independently hydrogen or C_{1-6}alkyl);

p is 0, 1 or 2 or 3;

R_2 is hydrogen, halogen, hydroxy, cyano, nitro, C_{1-6}alkyl, C_{1-6}alkanoyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, C_{1-6}alkylthio, amino, mono- or di-C_{1-6}alkylamino or an N-linked 4 to 7 membered heterocyclic group;

X is oxygen, sulfur, $-CH_2-$ or NR_8 wherein R_8 is hydrogen or C_{1-6}alkyl;

Y is a single bond, $-CH_2-$, $-(CH_2)_2-$ or $-CH=CH-$; and

Z is an optionally substituted N-linked heterocyclic group or a C-linked 4 to 7 membered heterocyclic group containing at least one nitrogen, or Z is $-NR_9R_{10}$ where R_9 and R_{10} are independently hydrogen or C_{1-6}alkyl.

The following terms, whether used alone or as part of another group are to be given the following meanings, unless otherwise stated.

The term "6-membered heteroaromatic group containing at least one nitrogen atom" refers to groups such as pyridyl, pyridazinyl, pyrinidinyl, pyrazinyl and triazinyl.

The term "halogen" and its abbreviated form "halo" are used herein to describe fluorine, chlorine, bromine or iodine.

The term "alkyl" is used herein to describe a straight chain or branched fully saturated hydrocarbon group. "C_{1-6}alkyl" refers to alkyl groups having from one to six carbon atoms, including all isomeric forms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, sec-pentyl, n-pentyl, isopentyl, tert-pentyl and hexyl.

The term "C_{1-6}alkanoyl" refers to an alkanoyl group having from 1 to 6 carbon atoms, such as methanoyl (or "formyl"), ethanoyl (or "acetyl"), propanoyl, isopropanoyl, butanoyl, isobutanoyl, sec-butanoyl, pentanoyl, neopentanoyl, sec-pentanoyl, isopentanoyl, tertpentanoyl and hexanoyl.

The term "C_{1-6}alkoxy" refers to a straight chain or branched chain alkoxy (or "alkyloxy") group having from one to six carbon atoms, including all isomeric forms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy, sec-pentoxy, n-pentoxy, isopentoxy, tert-pentoxy and hexoxy.

The term "C_{3-7}cycloalkyl" refers to a cycloalkyl group consisting of from 3 to 7 carbon atoms, such as cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane. Optional substituents for C_{3-7}cycloalkyl includes one or more halogen, hydroxy, oxo, C_{1-6}alkyl, cyano, CF_3, OCF_3, C_{1-6}alkoxy and C_{1-6}alkanoyl.

The term "C_{1-6}alkylthio" refers to a straight chain or branched chain alkylthio group having from one to six carbon atoms, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, neopentylthio, sec-pentylthio, n-pentylthio, isopentylthio, tert-pentylthio and hexylthio.

The term "mono- or di-C_{1-6}alkylamino" refers to an amino group which is substituted by one C_{1-6}alkyl group or an amino group which is substituted by two C_{1-6}alkyl groups, the two amino groups being the same or different. Examples of monoC1-6alkylamino include

methylamine, ethylamine, propylamine, isopropylamine, butylamine, isobutylamine, sec-butylamine, tert-butylamine, pentylamine, neopentylamine, sec-pentylamine, n-pentylamine, isopentylamine, tert-pentylamine and hexylamine. Examples of di-C1-6alkylamino include dimethylamine, diethylamine, dipropylamine, diisopropylamine, dibutylamine, diisobutylamine, disec-butylamine, ditert-butylamine, dipentylamine, dineopentylamine, dihexylamine, butylmethylamino, isopropylmethylamino, ethylisopropylamino, ethylmethylamino, etc.

The term "aryl" is used herein to describe 5 to 7-membered monocyclic or 9 to 11-membered bicyclic aromatic carbocyclic groups such as phenyl or naphthyl, or monocyclic or bicyclic heteroaromatic groups such as pyrrolyl, furyl, thienyl, pyrrolinyl, imidazolyl, pyrazolyl, pyrazolinyl, thiazolyl, isoxazolyl, furazanyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, indazolyl, indolinyl, isoindolinyl, benzimidazolyl, benzoxazolyl, benzothienyl, quinolyl, quinoxalinyl, quinazolinyl and isoquinolyl; all of which may be optionally substituted by one or more of C_{1-6}alkyl (to form "arylC_{1-6}alkyl"), halogen, CF_3 or C_{1-6}alkoxy (to form "arylC_{1-6}alkoxy").

The terms "halo C_{1-6}alkoxy" or "haloC_{1-6}alkyl" are used to describe a C_{1-6}alkoxy or a C_{1-6}alkyl group, respectively, substituted with one or more halogens. Examples include -$CHCl_2$, -CF_3, -OCF_3, etc.

The term "heterocyclic group" is used herein to describe an aromatic or non-aromatic ring containing 1, 2 or 3 heteroatoms selected from nitrogen, sulphur and oxygen. Suitable examples of 4 to 7 membered heterocyclic groups include azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolinyl, isothiazolidinyl, thiazolidinyl, pyrrolyl, pyrrolinyl, pyrazolinyl, imidazolyl, pyrazolyl, isothiazolyl, thiazolyl, piperidyl, piperazinyl, morpholinyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, azepinyl, azepanyl, dioxolanyl, thienyl, tetrahydrothienyl, tetrahydrofuryl, dioxanyl and dithianyl.

The term "N-linked heterocyclic group" is used herein to describe a heterocyclic group which is linked to the remainder of the molecule via a nitrogen atom. Suitable examples of 4 to 7 membered N-linked heterocyclic groups include azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolinyl, isothiazolidinyl, thiazolidinyl, pyrrolyl, pyrrolinyl, pyrazolinyl, imidazolyl, pyrazolyl, piperidyl, piperazinyl, morpholinyl and azepanyl.

The term "C-linked heterocyclic group containing at least one nitrogen" is used herein to describe a heterocyclic group which is contains at least one nitrogen atom and is linked to the remainder of the molecule via a carbon atom. Suitable examples of 4 to 7 membered C-linked heterocyclic groups containing at least one nitrogen include azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, pyrrolyl, pyrrolinyl, pyrazolinyl, imidazolyl, pyrazolyl, piperidyl, piperazinyl, morpholinyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, azepinyl and azepanyl.

More than one optional substituent may be present in the N-linked or C-linked heterocycle, which may be the same or different, and may be attached to any carbon atom of the heterocycle or an available nitrogen atom.

Suitable optional substituents for the N-linked or C-linked heterocycle include C_{1-6}alkyl, amino, mono- or di- C_{1-6}alkylamino, aryl, arylC_{1-6}alkyl, arylamino, hydroxy, C_{1-6}alkylamido, hydroxyC_{1-6}alkyl, C_{1-6}alkoxycarbonyl, halogen, haloC1-6alkyl, a heteroaromatic group (such as indole or benzimidazole), an aromatic or non-aromatic N-linked or C-linked heterocycle or an aromatic or non-aromatic heterocycleC_{1-6}alkyl optionally substituted by C_{1-6}alkyl. Examples of aromatic or non-aromatic heterocycleC_{1-6}alkyl include heterocycle-methyl (such as pyridinyl-methyl and benzimidazolyl-methyl) and heterocycle-ethyl (such as morpholinyl-ethyl and indolyl-ethyl).

Substituents in the N-linked or C-linked heterocycle may form a bridge structure, to form a group such as for example 2-oxa-5-azabicyclo[2.2.1]heptyl. Such a bicyclic group may be further substituted by the substituents listed above. More than one substituent may be present on the same carbon atom to form spiro structures such as 1,4 and 1,5 dioxa spiro compounds.

When A is a group -(CHR_3)-, preferably R_3 is hydrogen. Preferably A is -CH_2-.

When p is 2 or 3, R_1 may be the same or different. Preferably p is 1 or 2 and R_1 is/are halogen, particularly chloro or fluoro.

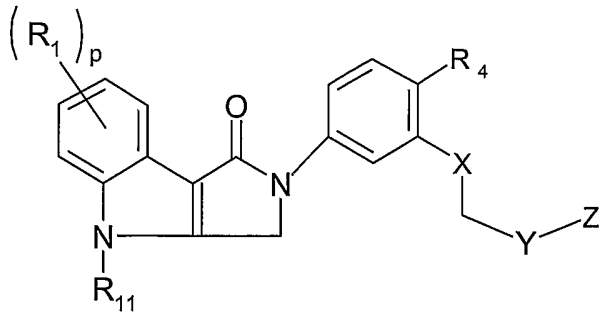
Preferably R_2 is C_{1-6}alkoxy (particularly methoxy), halogen or cyano.

Preferably X is oxygen.

Preferably Y is -CH_2-.

Preferably Z is an optionally substituted N-linked 4 to 7 membered heterocycle, in particular piperidyl. Preferred substituents include halogen (particularly fluoro) and C_{1-6}alkyl (particularly methyl).

Preferred compounds are compounds of formula (Ia):



(Ia)

wherein R_1, p, R_{11}, R_4, X, Y and Z, are as defined for formula (I). Preferred features of formula (I) also apply to formula (Ia).

Preferred compounds include:

6-Bromo-5-methoxy-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride

5-Methoxy-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride

5,6-Dichloro-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride

5-Chloro-2-{4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride

2-[4-Methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-1,2-dihydro-8-thia-2-aza-cyclopenta[a]inden-3-one hydrochloride

2-{4-Methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-1,2-dihydro-8-thia-2-aza-cyclopenta[a]inden-3-one hydrochloride

2-[4-Methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride

5-Chloro-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride

6-Chloro-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride

6-Fluoro-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride

2-{4-Methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-1,8-dimethyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride

2-{4-Methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride

6-Chloro-2-{4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride

5-Fluoro-2-{4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride
6-Fluoro-2-{4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride
7-Fluoro-2-{4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride

and pharmaceutically acceptable salts thereof.

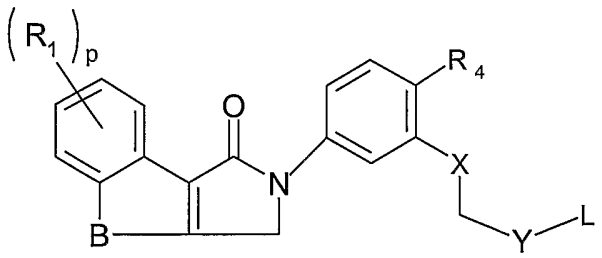
The compounds of formula (I) can form acid addition salts. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid.

The compounds of this invention may be in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. geometric or ("*cis-trans*") isomers, diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

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

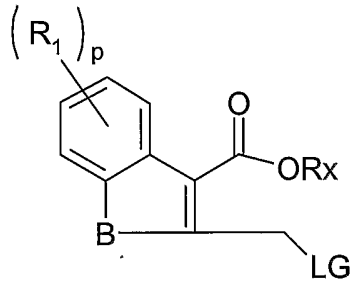


(II)

wherein R_1, R_2, p, A, X, and Y are as defined for formula (I), and L is a leaving group, with a compound of formula (III):

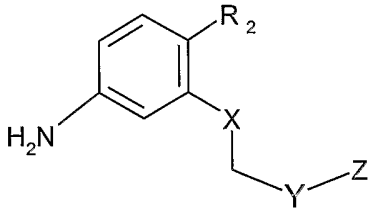
Z-H
(III)

wherein Z is as defined for formula (I); or
(b) reacting a compound of formula (III):



(III)

with a compound of formula (IV) or a salt thereof:



(IV)

followed, as appropriate, with a treatment of the intermediate obtained with $AlMe_3$ or a similar oxophilic reagent;

and for either process (a) or process (b), optionally followed by:

- removing any protecting groups; and/or
- converting a compound of formula (I) into another compound of formula (I); and/or
- forming a pharmaceutically acceptable salt.

For the reaction of process (a), suitably L is mesylate. The reaction may take place in a solvent such as DMF in the presence of sodium iodide and potassium carbonate.

For the reaction of process (b), LG is a leaving group such as halogen, for example chloro or bromo, or a sulfonate ester, for example mesyl or tosyl. Rx is alkyl, for example Me. The reaction may take place in a solvent such as DMF at elevated temperature,

suitably 100 °C. Where this reaction does not lead to spontaneous cyclisation of the intermediate alkylation product this material is treated with $AlMe_3$ or a similar oxophilic reagent.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard techniques. For example, and by way of illustration rather than limitation, a compound wherein A is -(HCOH)- may be converted to a compound wherein A is -(CH_2)- by using a suitable reducing agent such as triethylsilane-trifluoroacetic acid using dichloromethane as solvent;

Compounds of formulae (II), (III) and (IV) are commercially available or may be prepared according to methods described herein or may be prepared according to known methods or by analogous methods thereto.

Those skilled in the art will appreciate that it may be necessary to protect certain groups to carry out the above processes. Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981).

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

In a further aspect, the present invention provides a process for preparing a pharmaceutical composition, the process comprising mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose);, fillers (e.g. lactose,

microcrystalline cellulose or calcium hydrogen phosphate);, tabletting lubricants lubricants (e.g. magnesium stearate, talc or silica);, disintegrants (e.g. potato starch or sodium starch glycollate); and acceptable wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents (e.g. lecithin or acacia), non-aqueous vehicles (which may include edible oils e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid), and, if desired, conventional flavourings or colorants, buffer salts and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose, utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle, optionally with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-

aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device. Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

The compounds of the present invention have affinity for the 5-HT_{2C} receptor. The affinity can be determined by assessing their ability to displace [^{3}H]-mesulergine from rat or human 5-HT_{2C} clones expressed in 293 cells *in vitro*, as described in WO 94/04533.

All the Example compounds were tested according to this assay and were found to have pKi values >5.8. Some compounds show a considerably higher affinity in the range of 7.0 to >9.0 in human cells.

The intrinsic activity of the compounds of this invention can be determined according to the [^{35}S]GTPγS functional assay which is described in WO 99/07700.

Compounds of formula (I) and their pharmaceutically acceptable salts are of use in the treatment of certain CNS disorders such as depression (which term is used herein to include bipolar depression, unipolar depression, single or recurrent major depressive

episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder, dysthymic disorders with early or late onset and with or without atypical features, neurotic depression and social phobia, depression accompanying dementia for example of the Alzheimer's type, vascular dementia with depressed mood, schizoaffective disorder or the depressed type, and depressive disorders resulting from general medical conditions including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, *etc*), anxiety including generalised anxiety and social anxiety disorder, schizophrenia, panic disorder, agoraphobia, social phobia, epilepsy, obsessive compulsive disorder and post-traumatic stress disorder, pain (particularly neuropathic pain), migraine, memory disorders, including dementia, amnesic disorders and age-associated memory impairment, disorders of eating behaviours including anorexia nervosa and bulimia nervosa, sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy), withdrawal from abuse of drugs such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine (phencyclidine-like compounds), opiates (e.g. cannabis, heroin, morphine), sedative ipnotic, amphetamine or amphetamine-related drugs (e.g. dextroamphetamine, methylamphetamine) or a combination thereof, Alzheimer's disease, motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders, disorders associated with spinal trauma and/or head injury such as hydrocephalus, gastrointestinal disorders such as IBS (Irritable Bowel Syndrome), Crohn's disease, ulcerative colitis, non-steroidal anti-inflammatory drug induced damage) as well as microvascular diseases such as macular oedema and retinopathy.

It is to be understood that, as used herein, the term "treatment" refers to alleviation of established symptoms as well as prophylaxis.

Thus the present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance. In particular, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of the above disorders. In particular the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as a therapeutic substance in the treatment of a CNS disorder. Preferably the CNS disorder is depression and/or anxiety.

Compounds of the invention may be administered in combination with other active substances such as 5HT3 antagonists, NK-1 antagonists, serotonin agonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants and/or dopaminergic antidepressants.

Suitable 5HT3 antagonists which may be used in combination of the compounds of the inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

Suitable SSRIs which may be used in combination with the compounds of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

Suitable SNRIs which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptiline, chlomipramine and nortriptiline.

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

The invention further provides a method of treatment of the above disorders in mammals including humans, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. In particular the invention provides a a method of treatment of a CNS disorder in mammals including humans, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. Preferably the disorder is depression and/or anxiety.

In another aspect, the invention provides for the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders. In particular the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of a CNS disorder. Preferably the CNS disorder is depression and/or anxiety.

The composition of the present invention may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned

disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three times a day. Such therapy may extend for a number of weeks or months. When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrate the preparation of compounds of the present invention.

General Procedure 1 (G1): Hydrochloride salt formation

To a solution of the free base in CH_2Cl_2 was added excess HCl (1M in Et_2O). The resulting mixture was evaporated to dryness and the residue triturated using a mixture of EtOAc:Et_2O *ca.* 1:1 and dried to give the respective hydrochloride salt.

General Procedure 2 (G2): Bromination to form substituted bromomethyl heterobicyclic compounds

A mixture of the substituted methyl heterocyclic compound, *N*-bromosuccinimide (typically 1.1 eq.) and benzoyl peroxide (0.05 eq.) in dry CCl_4 (2 ml per mmol substituted toluene) was heated at reflux. After complete conversion (typically 5 h; NMR control) the mixture was allowed to cool, filtered (washing with CH_2Cl_2 :petroleum ether *ca.* 1:1), concentrated and submitted to column chromatography to give the respective substituted bromomethyl heterocyclic compound.

General Procedure 3 (G3): Methyl ester formation

To the substituted heterobicyclic carboxylic acid in dry CH_2Cl_2 (*ca.* 0.2-0.5 M) containing catalytic DMF (*ca.* 0.1 eq.) at 0 °C was added with stirring oxalyl chloride (*ca.* 1.3 eq.). The ice bath was removed. After gas evolution had ceased (typically 1-2 h) volatiles were removed *in vacuo*. To the residue was added dry methanol (to give a *ca.* 0.2 - 1 M solution; CAUTION: on scales above *ca.* 5 mmol this involved a significant exotherme) and the mixture was kept for 16 h or alternatively heated at 60 °C for 2 h. The material obtained after evaporation of the volatiles was used as such or purified by column chromatography.

General Procedure 4 (G4): *N*-Methylation

To the substituted indole in dry DMF (*ca.* 0.5 M) was added methyl iodide (1 eq.) followed by sodium hydride (60% in mineral oil, 1.2 eq.). CAUTION: on scales above *ca.* 2 mmol this involved a significant exotherme. After 3 h water was added with stirring and the product of acceptable purity for further conversion, as appropriate, either
collected by filtration and washed subsequently with water, a few drops of MeOH, and petroleum ether or
obtained from the extraction of this mixture using petroleum ether:EtOAc:CH_2Cl_2 2:1:1, evaporation of the volatiles, and trituration of the residue with petroleum ether.

General Procedure 5 (G5): Chlorination to form substituted chloromethyl heterobicyclic compounds

A mixture of the substituted methyl heterocyclic compound was treated as described in Procedure G2 but using *N*-chlorosuccinimide instead of *N*-bromosuccinimide to give the respective substituted chloromethyl heterocyclic compound.

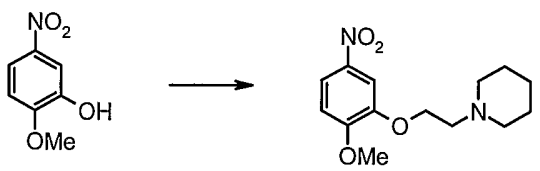
General Procedure 6 (G6): Preparation of substituted 2-(2-nitro-phenyl)-3-hydroxy-but-2-enoic acid methyl ester compounds

Typical scale 5 mmol: To NaH (60% in mineral oil, 2.3 eq.) in dry DMF (20 ml per 1 g 60% NaH) at 0 °C was added portionwise over 20 min *via* syringe with vigorous stirring acetylacetate methyl ester (2.1 eq.). After 10 min this mixture was allowed to warm to 25 °C and added to a stirred reaction vessel cooled in an ice bath containing the substituted 2-nitro-fluorobenzene (1.0 eq.). After 45 min the mixture was allowed to warm to 25 °C. After 16 h excess aqueous HCl (2 M) was added followed by water and Et_2O. The layers were mixed, to give the substituted 2-(2-nitro-phenyl)-3-hydroxy-but-2-enoic acid methyl ester compounds.

General Procedure 7 (G7): Preparation of substituted indoles using $TiCl_3$

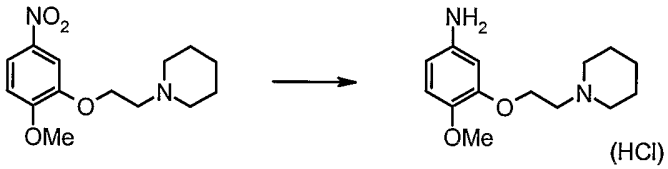
To a stirred mixture of the substituted 2-(2-nitro-phenyl)-3-hydroxy-but-2-enoic acid methyl ester compound in HOAc (6.5 ml per mmol) was added a solution of $TiCl_3$ (15% in 20-30% aqueous HCl, 6.5 ml per mmol). The resulting mixture was heated to 90 °C for 1.5 h, then cooled in an ice bath. Water and CH_2Cl_2 :MeOH 9:1 were added with stirring. The organic layer was collected, diluted with EtOAc:petroleum ether 1:1, washed (brine *2) and concentrated. The desired substituted indoles were obtained in adequate purity for further conversion following either trituration (Et_2O:petroleum ether 1:5) or column chromatography.

Preparation 1 (P1): 1-[2-(2-Methoxy-5-nitro-phenoxy)-ethyl]-piperidine



To a solution of 2-methoxy-5-nitrophenol (10 g) in DMF (45 ml) at room temperature were added K_2CO_3 (23 g) and 1-(2-chloroethyl)piperidin hydrochloride (12 g). The suspension was stirred at room temperature for 3 days. The suspension was diluted with water and twice extracted with EtOAc: Et_2O 1:2, the combined organic phases were washed with brine, concentrated to dryness *in vacuo*, to obtain the title product as a brown oil (99%).
NMR (^{1}H, $CDCl_3$): δ 7.85 (dd, 1H), 7.75 (d, 1H), 6.90 (d, 1H), 4.20 (t, 2H), 3.90 (s, 3H), 2.80 (t, 2H), 2.45-2.60 (m, 4H), 1.55-1.65 (m, 4H) (m, 4H), 1.35-1.50 (m, 2H).
MS (*m/z*): 281$[MH]^+$.

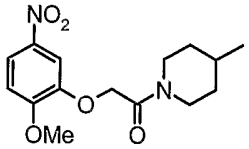
Preparation 2 (P2): 4-Methoxy-3-(2-piperidin-1-yl-ethoxy)-phenylamine (hydrochloride)



(HCl)

To 1-[2-(2-methoxy-5-nitro-phenoxy)-ethyl]-piperidine (59 mmol) in a mixture of MeOH (140 ml), NH_4Cl (17.1 g), water (140 ml) and conc. aqueous HCl (4.9 ml) was added iron powder (10.6 g). The mixture was heated at reflux with vigorous stirring for 90 min. and concentrated to *ca.* half volume *in vacuo*. EtOAc was added, filtered (Celite), washing with water. Et_2O was added, the layers were mixed and the aqueous layer collected. K_2CO_3 was added until pH *ca.* 9-10 and the mixture was twice extracted with EtOAc:Et_2O 1:1. The combined organic layers were dried (K_2CO_3), filtered and concentrated to give the free base of the title compound as a red oil (56 mmol). **NMR (^{1}H, $CDCl_3$):** δ 6.67 (d, 1H), 6.30 (d, 1H), 6.20 (dd, 1H), 4.07 (t, 2H), 3.75 (s, 3H), 3.40 (bs, 2H), 2.80 (t, 2H), 2.40-2.55 (m, 4H), 1.51-1.62 (m, 4H), 1.35-1.46 (m, 2H).
Batches of this material were converted to the hydrochloride salt as required by treating a solution of the free base in dichloromethane with 1 eq. HCl (1 M solution in Et_2O), followed by evaporation to dryness.

Preparation 3 (P3): 2-(2-Methoxy-5-nitro-phenoxy)-1-(4-methyl-piperidin-1-yl)-ethanone



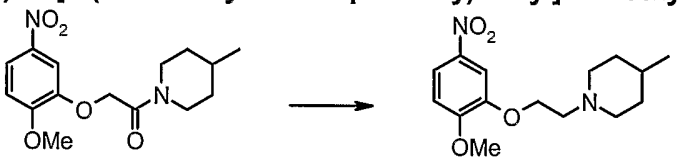
To a NaOH solution (14 g of NaOH, 350 mmol, in 300 ml of water) at 0 °C containing 4-metylpiperidine (36 ml, 310 mmol) chloroacetylchloride (23.7 ml, 305 mmol) was added in 10 min under vigorous stirring at 0 °C. After 3 h the mixture was acidified using HCl (2M aqueous) and the acqueous phase was extracted twice with CH_2Cl_2 (2 x 150 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated

to dryness *in vacuo* to give 37 g of intermediate which was dissolved in *N*-methyl pyrrolidone (120 ml).

To this solution 2-methoxy-5-nitrophenol (24 g, 156 mmol), K_2CO_3 (21 g, 152 mmol) and NaI (2 g, 13 mmol) were added. The suspension was mechanically stirred and heated at 120 °C. After 16 h the reaction was cooled and diluted with Et_2O (500 ml), the organic phase was washed twice with water (2x 150 ml), then with NaOH (aqueous, 1M, 100 ml) and finally with brine (150 ml).

The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness *in vacuo* to give 35 g of the title compound as a yellow solid. **NMR (^{1}H, $CDCl_3$):** δ 8.00 (dd, 1H), 7.76 (d, 1H), 6.98 (d, 1H), 4.87 (s, 2H), 4.55 (d, 1H), 4.02 (s, 3H), 3.85 (d, 1H), 3.13 (t, 1H), 2.68 (t, 1H), 1.55-1.85 (m, 4H), 1.10-1.30 (m, 1H), 1.01 (d, 3H). **MS (*m/z*):** 309 $[MH]^+$.

Preparation 4 (P4): 1-[2-(2-Methoxy-5-nitro-phenoxy)-ethyl]-4-methyl-piperidine



2-(2-Methoxy-5-nitro-phenoxy)-1-(4-methyl-piperidin-1-yl)-ethanone (11 g, 35.7 mmol) was dissolved in anh. THF (20 ml), 1M BH_3.THF (2.2eq, 78.5 ml) was added dropwise to the solution, and the mixture was heated at reflux for 4 hours. The solution was cooled to room temperature, CH_3OH (100 ml) was added, and the solvent was removed under reduced pressure. The residue was dissolved in CH_3OH (100 ml) , 6N HCl (200 ml) was added, and the solution was heated to reflux for 30'. The CH_3OH was removed under reduced pressure and the remaining aqueous solution was made basic (pH>10) with 2.5 M NaOH. The basic solution was extracted with ethyl acetate (3x80 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give 9.4 g of the title product as a red oil. (yield: 90%). **NMR (^{1}H, $CDCl_3$):** δ 7.91 (dd, 1H), 7.80 (d, 1H), 6.90 (d, 1H), 4.21 (t, 2H), 3.96 (s, 3H), 2.97 (m, 2H), 2.85 (t, 2H), 2.12 (m, 2H), 1.64 (m, 2H), 1.4 (m, 1H), 1.29 (m, 2H), 0.92 (d, 3H). **MS (*m/z*):** 295 $[MH]^+$.

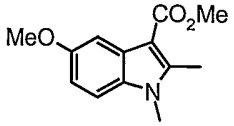
Preparation 5 (P5): 4-Methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenylamine (hydrochloride)



To a solution of 1-[2-(2-methoxy-5-nitro-phenoxy)-ethyl]-4-methyl-piperidine (9.5 g, 32.3 mmol) in abs. EtOH (200 ml) were added Pd/C 10% (1 g) and the reaction mixture was hydrogenated at room temperaturature at 1 atm. After 5 hrs the reaction mixture was filtered on a Celite pad and the solution was concentrated *in vacuo* to give 8.5 g of the

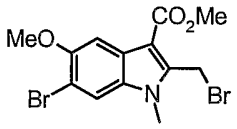
title product as a brown solid (yield: 99%). **NMR (^{1}H, $CDCl_3$):** δ 6.61 (d, 1H), 6.26 (d, 1H), 6.04 (dd, 1H), 4.60 (bs, 2H), 3.91 (t, 2H), 3.58 (s, 3H), 2.85 (m, 2H), 2.61 (t, 2H), 1.97 (m, 2H), 1.52 (m, 2H), 1.3 (m, 1H), 1.1 (m, 2H), 0.86 (d, 3H).
Batches of this material were converted to the hydrochloride salt as required as described for Preparation 2.

Preparation 6 (P6): 5-Methoxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid methyl ester



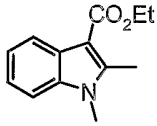
The title compound was obtained from 5-methoxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid according to Procedure G3 (quant. yield): **NMR (^{1}H, $CDCl_3$):** δ 7.60 (s, 1H), 7.15 (d, 1H), 6.84 (d, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.64 (s, 3H), 2.72 (s, 3H). **m.p.:** 123-126 °C.

Preparation 7 (P7): 6-Bromo-2-bromomethyl-5-methoxy-2-methyl-1*H*-indole-3-carboxylic acid methyl ester



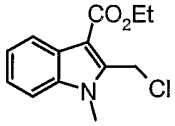
The title compound was obtained from 5-methoxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid methyl ester according to Procedure G2 (using 1.2 eq. *N*-bromosuccinimide, 8% yield): **NMR (^{1}H, $CDCl_3$):** δ 7.65 (s, 1H), 7.55 (s, 1H), 5.09 (s, 2H), 3.94 (s, 6H), 3.73 (s, 3H).

Preparation 8 (P8): 1,2-Dimethyl-1*H*-indole-3-carboxylic acid ethyl ester



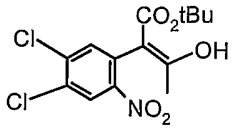
The title compound was obtained from 2-methyl-1*H*-indole-3-carboxylic acid ethyl ester according to Procedure G4 (yellow powder, 87% yield): **NMR (^{1}H, $CDCl_3$):** δ 8.08-8.12 (m, 1H), 7.16-7.31 (m, 3H), 4.37 (q, 2H), 3.70 (s, 3H), 2.77 (s, 3H), 1.44 (t, 3H).

Preparation 9 (P9): 2-Chloromethyl-1-methyl-1*H*-indole-3-carboxylic acid ethyl ester



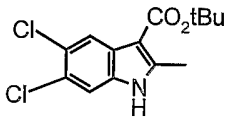
The title compound was obtained from 1,2-dimethyl-1*H*-indole-3-carboxylic acid ethyl ester (P8, 0.45 g) according to Procedure G5 (yellow oil that solidified on cooling, 94% yield): **NMR (^{1}H, $CDCl_3$):** δ 8.15 (d, 1H), 7.23-7.36 (m, 3H), 5.28 (s, 2H), 4.40 (q, 2H), 3.83 (s, 3H), 1.44 (t, 3H).

Preparation 10 (P10): 2-(4,5-Dichloro-2-nitro-phenyl)-3-hydroxy-but-2-enoic acid *tert*-butyl ester



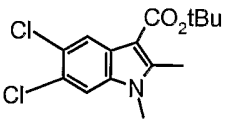
To acetylacetate *tert*-butyl ester (1.6 ml) in dry DMF (10 ml) at 0 °C was added portionwise with vigorous stirring NaH (60% in mineral oil, 0.46 g). After 15 min at 25 °C the mixture was again cooled in an ice bath and 1,2-dichloro-4-fluoro-5-nitrobenzene was added in a single portion resulting in a dark purple solution. This was allowed to warm in the defrosting ice bath over 2.5 h. Aqueous HCl (1 M, 7.5 ml) was added followed by water and Et_2O. The layers were mixed, the organic layer collected, washed (brine), concentrated and submitted to column chromatography to give the title compound as a yellow oil (1.7 g): **NMR (^{1}H, $CDCl_3$):** δ 13.2 (s, 1H), 8.08 (s, 1H), 7.35 (s, 1H), 1.88 (s, 3H), 1.32 (s, 9H). **MS (*m/z*):** 346 $[M-H]^-$ (2Cl).

Preparation 11 (P11): 5,6-Dichloro-2-methyl-1*H*-indole-3-carboxylic acid *tert*-butyl ester



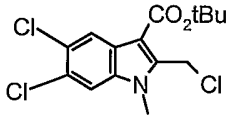
To 2-(4,5-dichloro-2-nitro-phenyl)-3-hydroxy-but-2-enoic acid *tert*-butyl ester (P10, 4.8 mmol) in a mixture of MeOH (12 ml), NH_4Cl (1.4 g), water (12 ml) and ethanol (10 ml) was added iron powder (0.86 g). The mixture was heated at reflux with vigorous stirring for 2.5 h and concentrated to *ca.* half volume *in vacuo*. EtOAc was added, filtered (Celite), washing with water and EtOAc. The organic layer was collected, volatiles evaporated *in vacuo* and the residue submitted to column chromatography to give, besides the corresponding *N*-hydroxy indole derivative (major product, 64%), the title compound as a yellow solid (0.19 g, 13%). **NMR (^{1}H, $CDCl_3$):** δ 8.27 (bs, 1H), 8.13 (s, 1H), 7.32 (s, 1H), 2.69 (s, 3H), 1.62 (s, 9H). **MS (*m/z*):** 298 $[M-H]^-$ (2Cl).

Preparation 12 (P12): 5,6-Dichloro-1,2-dimethyl-1*H*-indole-3-carboxylic acid *tert*-butyl ester



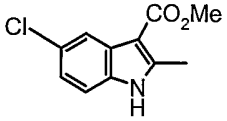
The title compound was obtained from 5,6-dichloro-2-methyl-1*H*-indole-3-carboxylic acid *tert*-butyl ester (P11, 0.19 g) according to Procedure G4 (colourless solid, 86% yield): **NMR (^{1}H, $CDCl_3$):** δ 8.17 (s, 1H), 7.35 (s, 1H), 3.64 (s, 3H), 2.71 (s, 3H), 1.62 (s, 9H).

Preparation 13 (P13): 2-Chloromethyl-5,6-dichloro-1-methyl-1*H*-indole-3-carboxylic acid *tert*-butyl ester



The title compound was obtained from 5,6-dichloro-1,2-dimethyl-1*H*-indole-3-carboxylic acid *tert*-butyl ester (P12, 0.17 g) according to Procedure G5 (yellow solid that solidified on cooling, 96%): **NMR (^{1}H, $CDCl_3$):** δ 8.23 (s, 1H), 7.43 (s, 1H), 5.21 (s, 2H), 3.77 (s, 3H), 1.64 (s, 9H).

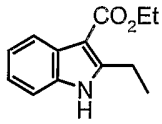
Preparation 14 (P14): 5-Chloro-2-methyl-1*H*-indole-3-carboxylic acid methyl ester



The title compound was obtained by:

1. Procedure G6 but using 2,4-dichloronitrobenzene (5 mmol) instead of a substituted 2-nitro-fluorobenzene. The reaction required heating (2 h at 60 °C followed by 5 h at 85 °C). The product was obtained as a yellow oil (0.88 g) containing impurities as judged by NMR.
2. Treating this material as described in Procedure G7 to give the title compound as an off-white solid (0.31 g): **NMR (^{1}H, $CDCl_3$):** δ 8.32 (bs, 1H), 8.02 (s, 1H), 7.10-7.22 (m, 2H), 3.91 (s, 3H), 2.71 (s, 3H). **MS (*m/z*):** 222 $[M-H]^-$ (1Cl).

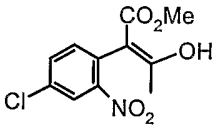
Preparation 15 (P15): 2-Ethyl-1*H*-indole-3-carboxylic acid ethyl ester



The title compound (5 mmol scale) was obtained by:

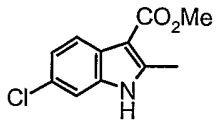
1. Procedure G6 but using 3-oxo-valeric acid ethyl ester instead of acetylacetate methyl ester to give the product as a yellow oil (0.90 g).
2. Treating this material as described in Procedure G7 to give the title compound as an off-white solid (0.12 g): **NMR (^{1}H, $CDCl_3$):** δ 8.52 (bs, 1H), 8.15 (s, 1H), 7.15-7.37 (m, 3H), 4.44 (q, 2H), 3.23 (q, 2H), 1.47 (t, 3H), 1.36 (t, 3H). **MS (*m/z*):** 216 $[M-H]^-$.

Preparation 16 (P16): 2-(4-Chloro-2-nitro-phenyl)-3-hydroxy-but-2-enoic acid methyl ester



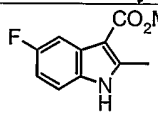
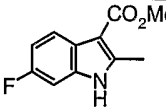
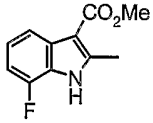
The title compound was obtained as a yellow oil (1.3 g) following Procedure G6 using 5-chloro-2-fluoronitrobenzene (5 mmol). **NMR (^{1}H, $CDCl_3$):** δ 7.97 (d, 1H), 7.56 (dd, 1H), 7.23 (d, 1H), 3.62 (s, 3H), 1.82 (s, 3H) (enol-OH not monitored). **MS (*m/z*):** 270 $[M-H]^-$ (1Cl).

Preparation 17 (P17): 6-Chloro-2-methyl-1*H*-indole-3-carboxylic acid methyl ester

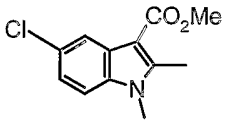


The title compound was obtained as a colourless solid (0.60 g) by treating 2-(4-chloro-2-nitro-phenyl)-3-hydroxy-but-2-enoic acid methyl ester (4.7 mmol) as described in Procedure G7. **NMR (^{1}H, $CDCl_3$):** δ 8.25 (bs, 1H), 7.96 (d, 1H), 7.12-7.27 (m, 2H), 3.94 (s, 3H), 2.70 (s, 3H). **MS (*m/z*):** 222 $[M-H]^-$ (1Cl).

The following substituted indoles (P18-P20) were prepared in analogy to Preparations 16 and 17 using Procedures G6 followed by G7.

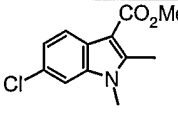
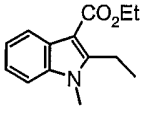
Preparation 18 (P18): 5-Fluoro-2-methyl-1*H*-indole-3-carboxylic acid methyl ester		**NMR (^{1}H, $CDCl_3$):** δ 8.30 (bs, 1H), 7.72 (d, 1H), 7.15-7.22 (m, 1H), 6.90 (t, 1H), 3.91 (s, 3H), 2.73 (s, 3H). **MS (*m/z*):** 206 $[M-H]^-$.
Preparation 19 (P19): 6-Fluoro-2-methyl-1*H*-indole-3-carboxylic acid methyl ester		**NMR (^{1}H, $CDCl_3$):** δ 8.30 (bs, 1H), 7.99 (dd, 1H), 7.90-7.03 (m, 2H), 3.91 (s, 3H), 2.73 (s, 3H). **MS (*m/z*):** 206 $[M-H]^-$.
Preparation 20 (P20): 7-Fluoro-2-methyl-1*H*-indole-3-carboxylic acid methyl ester		**NMR (^{1}H, $CDCl_3$):** δ 8.46 (bs, 1H), 7.82 (d, 1H), 7.04-7.16 (m, 1H), 6.89 (t, 1H), 3.94 (s, 3H), 2.77 (s, 3H). **MS (*m/z*):** 206 $[M-H]^-$.

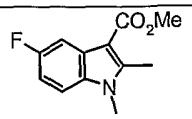
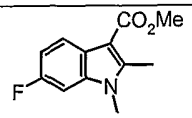
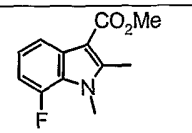
Preparation 21 (P21): 5-Chloro-1,2-dimethyl-1*H*-indole-3-carboxylic acid methyl ester



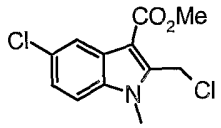
The title compound was obtained as a yellow powder (0.29 g) following Procedure G4 using 5-chloro-2-methyl-1*H*-indole-3-carboxylic acid methyl ester (0.28 g). **NMR (^{1}H, $CDCl_3$):** δ 8.05 (s, 1H), 7.05-7.20 (m, 2H), 3.92 (s, 3H), 3.67 (s, 3H), 2.74 (s, 3H). **MS (*m/z*):** 238 $[M+H]^+$ (1Cl).

The following substituted indoles (P22-P26) were prepared in analogy to Preparation 21 using Procedure G4.

Preparation 22 (P22): 6-Chloro-1,2-dimethyl-1*H*-indole-3-carboxylic acid methyl ester		**NMR (^{1}H, $CDCl_3$):** δ 7.98 (d, 1H), 7.26 (d, 1H), 7.16 (dd, 1H), 3.90 (s, 3H), 3.66 (s, 3H), 2.74 (s, 3H). **MS (*m/z*):** 238 $[M+H]^+$ (1Cl).
Preparation 23 (P23): 2-Ethyl-1-methyl-1*H*-indole-3-carboxylic acid		**NMR (^{1}H, $CDCl_3$):** δ 8.08-8.16 (m, 1H), 7.16-7.32 (m, 3H), 4.37 (q, 2H), 3.72 (s, 3H), 3.23 (q, 2H), 1.42

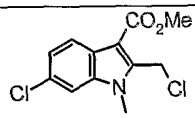
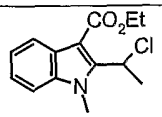
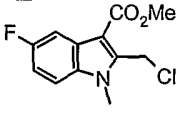
ethyl ester		(t, 3H), 1.24 (t, 3H). **MS (*m/z*):** 232 $[M+H]^+$.
Preparation 24 (P24): 5-Fluoro-1,2-dimethyl-1*H*-indole-3-carboxylic acid methyl ester		**NMR (^{1}H, $CDCl_3$):** δ 7.73 (dd, 1H), 7.18 (dd, 1H), 6.94 (td, 1H), 3.89 (s, 3H), 3.68 (s, 3H), 2.74 (s, 3H). **MS (*m/z*):** 222 $[M+H]^+$.
Preparation 25 (P25): 6-Fluoro-1,2-dimethyl-1*H*-indole-3-carboxylic acid methyl ester		**NMR (^{1}H, $CDCl_3$):** δ 8.00 (dd, 1H), 6.91-7.00 (m, 2H), 3.89 (s, 3H), 3.65 (s, 3H), 2.73 (s, 3H). **MS (*m/z*):** 222 $[M+H]^+$.
Preparation 26 (P26): 7-Fluoro-1,2-dimethyl-1*H*-indole-3-carboxylic acid methyl ester		**NMR (^{1}H, $CDCl_3$):** δ 7.84 (d, 1H), 7.06 (dd, 1H), 6.85 (dd, 1H), 3.90 (s, 6H), 2.73 (s, 3H). **MS (*m/z*):** 222 $[M+H]^+$.

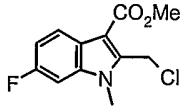
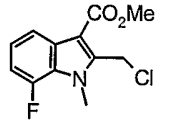
Preparation 27 (P27): 5-Chloro-2-chloromethyl-1-methyl-1*H*-indole-3-carboxylic acid methyl ester



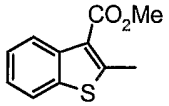
The title compound (0.25 g off-white solid) was obtained from 5-chloro-1,2-dimethyl-1*H*-indole-3-carboxylic acid methyl ester (1.2 mmol) according to Procedure G5: **NMR (^{1}H, $CDCl_3$):** δ 8.11 (s, 1H), 7.11-7.28 (m, 2H), 5.25 (s, 2H), 3.96 (s, 3H), 3.83 (s, 3H).

The following substituted indoles (P28-P32) were prepared in analogy to Preparation 27 using Procedure G5.

Preparation 28 (P28): 6-Chloro-2-chloromethyl-1-methyl-1*H*-indole-3-carboxylic acid methyl ester		**NMR (^{1}H, $CDCl_3$):** δ 8.04 (d, 1H), 7.34 (s, 1H), 7.20 (d, 1H), 5.24 (s, 2H), 3.94 (s, 3H), 3.80 (s, 3H).
Preparation 29 (P29): 2-(1-Chloroethyl)-1-methyl-1*H*-indole-3-carboxylic acid ethyl ester		**NMR (^{1}H, $CDCl_3$):** δ 8.02 (d, 1H), 7.10-7.28 (m, 3H), 6.80 (q, 1H), 4.32 (q, 2H), 3.91 (s, 3H), 1.85 (d, 3H), 1.35 (t, 3H).
Preparation 30 (P30): 2-Chloromethyl-5-fluoro-1-methyl-1*H*-indole-3-carboxylic acid methyl ester		**NMR (^{1}H, $CDCl_3$):** δ 7.78 (dd, 1H), 7.25 (dd, 1H), 7.03 (td, 1H), 5.26 (s, 2H), 3.95 (s, 3H), 3.83 (s, 3H).

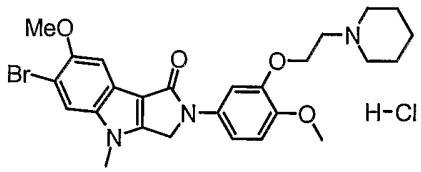
Preparation 31 (P31): 2-Chloromethyl-6-fluoro-1-methyl-1*H*-indole-3-carboxylic acid methyl ester		**NMR (^{1}H, $CDCl_3$):** δ 8.06 (dd, 1H), 6.95-7.05 (m, 2H), 5.24 (s, 2H), 3.92 (s, 3H), 3.79 (s, 3H).
Preparation 32 (P32): 2-Chloromethyl-7-fluoro-1-methyl-1*H*-indole-3-carboxylic acid methyl ester		**NMR (^{1}H, $CDCl_3$):** δ 7.89 (d, 1H), 7.10 (td, 1H), 6.94 (dd, 1H), 5.24 (s, 2H), 4.06 (s, 3H), 3.93 (s, 3H).

Preparation 33 (P33): 2-Methyl-benzo[*b*]thiophene-3-carboxylic acid methyl ester



To a stirred suspension of $AlCl_3$ (0.93 g) in dry 1,2-dichloroethane (2 ml) at 0 °C was added oxalyl chloride (0.61 ml). After 20 min 2-methyl-benzo[*b*]thiophene (0.62 g) in dry 1,2-dichloroethane (1 ml) was added dropwise *via* syringe. After an additional 15 min the mixture was poured onto ice and conc. aqueous HCl (2 ml). This was extracted twice with CH_2Cl_2 . Evaporation of the volatiles *in vacuo* gave a residue which was vigorously stirred with NaOH (*ca.* 1.5 g) in water until a clear solution was obtained. This was washed with Et_2O, acidified using excess HCl and extracted with Et_2O. This extract was washed (brine) and concentrated to give a cream solid (0.6 g). This was dissolved in dry CH_2Cl_2 (15 ml) containing catalytic DMF (2 drops) and at 0 °C was added with stirring oxalyl chloride (0.41 ml). The ice bath was removed. After gas evolution had ceased (2 h) volatiles were removed *in vacuo*. To the residue was added dry methanol (5 ml) and the mixture was kept for 16 h. The material obtained after evaporation of the volatiles was submitted to column chromatography to give the title compound (0.12 g) as a yellow oil. **NMR (^{1}H, $CDCl_3$):** δ 8.41 (d, 1H), 7.75 (t, 1H), 7.42 (t, 1H), 7.35 (d, 1H), 3.98 (s, 3H), 2.85 (s, 3H) [n.b. in a major by-product these protons are shifted to 2.75 (s, 3H)].

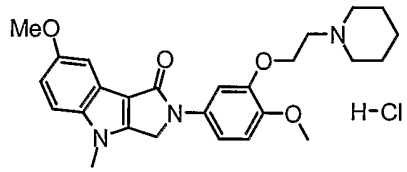
Example 1: 6-Bromo-5-methoxy-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2*H*-2,8-diazacyclopenta[*a*]inden-3-one hydrochloride



6-Bromo-2-bromomethyl-5-methoxy-2-methyl-1*H*-indole-3-carboxylic acid methyl ester (P6, 29 mg) and 4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenylamine hydrochloride (P2, 1.1 eq.) were heated in dry DMF (0.5 ml) for 2 h at 120 °C. $NaHCO_3$ (*ca.* 100 mg) was added and heating continued for additional 2 h. The mixture was concentrated *in vacuo* and the residue submitted to column chromatography. From this was obtained a mixture

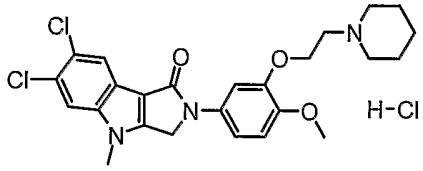
of compounds (28 mg) that was dissolved tn dry CH_2Cl_2 (1 ml) and allowed to react with Me_3Al (2 M in toluene, 0.08 ml) for 6 h. The solution was partitioned between aqueous NaOH (1 M) and CH_2Cl_2 :iPrOH 3:1. The organic layer was collected, volatiles evaporated and the residue submitted to column chromatography, follwed by conversion to the hydrochloride salt (G1). Trituration with MeOH (1 ml *2) gave the title compound as an off-white solid (6 mg): **NMR (^{1}H, d4-MeOH):** δ 7.75 (s, 1H), 7.72 (d, 1H), 7.53 (s, 1H), 7.18 (dd, 1H), 7.09 (d, 1H), 4.95 (s, 2H), 4.42 (t, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 3.83 (s, 3H), 3.74 (d, 2H), 3.58 (t, 2H), 3.10 (t, 2H), 2.04 (d, 2H), 1.80-1.93 (m, 3H), 1.52-1.63 (m, 1H). **MS (*m/z*):** 528/530 $[MH]^+$ (1Br). **m.p.** 227-229 °C.

Example 2: 5-Methoxy-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2*H*-2,8-diazacyclopenta[*a*]inden-3-one hydrochloride



6-Bromo-5-methoxy-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2*H*-2,8-diazacyclopenta[*a*]inden-3-one (38 mg) in EtOAc (5 ml) and EtOH (*ca.* 0.2 ml) was hydrogenated at atmospheric pressure on Pd/C (10%, 10 mg) for 16 h and on Pd/C (10%, 100 mg) for 8 h. The mixture was filtered through Celite, volatiles evaporated and the residue submitted to column chromatography followed by preparative reverse phase HPLC, follwed by conversion to the hydrochloride salt (G1) to give the product as an orange gum (2 mg). **NMR (^{1}H, d4-MeOH):** δ 7.64 (d, 1H), 7.28-7.35 (m, 2H), 7.09 (d, 1H), 6.99 (d, 1H), 6.85 (d, 1H), 4.86 (s, 2H), 4.32 (t, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 3.58-3.68 (m, 2H), 3.49 (t, 2H), 2.93-3.08 (m, 2H), 1.84-1.99 (m, 2H), 1.63-1.84 (m, 3H), 1.40-1.60 (m, 1H). **MS (*m/z*):** 450 $[MH]^+$.

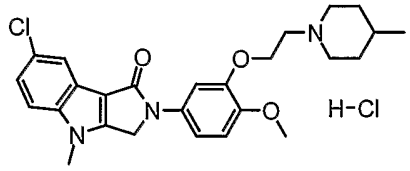
Example 3: 5,6-Dichloro-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2*H*-2,8-diazacyclopenta[*a*]inden-3-one hydrochloride



2-Chloromethyl-5,6-dichloro-1-methyl-1*H*-indole-3-carboxylic acid *tert*-butyl ester (P13, 91 mg) and 4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenylamine hydrochloride (P2, 75 mg) were heated in dry DMF (0.7 ml) and dry dioxane (0.5 ml) for 2 h at 100 °C. The mixture was concentrated *in vacuo* and the residue submitted to column chromatography. From this was obtained an *N*-alkylation product which was exposed to trifluoroacetic acid (2 ml) in CH_2Cl_2 (2 ml) for 3 h. The volatiles were evaporated *in vacuo* and the residue heated in HCl/dioxane (4 M, *ca.* 30 min). Again, volatiles were evaporated *in vacuo* and to the

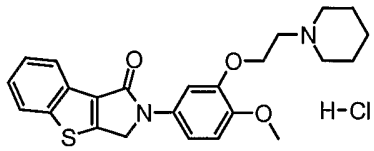
residue in dry CH_2Cl_2 (*ca.* 1 ml) containing catalytic DMF (*ca.* 0.1 eq.) at 0 °C was added with stirring oxalyl chloride (9 µl). The ice bath was removed and after 2 h volatiles were evaporateded *in vacuo*. The residue was treated with NEt_3 in dioxane and subsequently partitioned between aqueous NaOH (*ca.* 0.5 M) and EtOAc. The organic layer was collected, volatiles evaporated and the residue submitted to column chromatography, follwed by conversion to the hydrochloride salt (G1) to give the title compound as an off-white solid (5 mg): **NMR (^{1}H, d4-MeOH):** δ 7.99 (s, 1H), 7.70 (d, 1H), 7.18 (dd, 1H), 7.09 (d, 1H), 6.80 (s, 1H), 4.99 (s, 2H), 4.40 (t, 2H), 3.90 (s) and 3.85 (s, 6H), 3.70-3.76 (m, 2H), 3.57 (t, 2H), 3.05-3.15 (m, 2H), 1.50-1.63 and 1.66-2.05 (m, 5H). **MS (*m/z*):** 488 $[MH]^+$ (2Cl).

Example 4: 5-Chloro-2-{4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2*H*-2,8-diazacyclopenta[*a*]inden-3-one hydrochloride



5-Chloro-2-chloromethyl-1-methyl-1*H*-indole-3-carboxylic acid methyl ester (P27, 0.46 mmol) and 4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenylamine hydrochloride (P5, 1.2 eq.) were heated in dry DMF (0.55 ml) for 5 h at 100 °C. Volatiles were evaporated *in vacuo* and the residue submitted to column chromatography. From this was obtained an *N*-alkylation product (38%) a solution of which in CH_2Cl_2 (0.05 M) was allowed to react with Me_3Al (2 M in hexanes, 3 eq.) for 5 h. Silica gel, water (few drops), 10% conc. aqueous NH_3/MeOH:CH_2Cl_2 1:10 were added with vigorous stirring, the resulting slurry removed by filtration and washed well with 10% conc. aqueous NH_3/MeOH:CH_2Cl_2 1:10. The solution thus obtained was concentrated *in vacuo* and the residue submitted to column chromatography, follwed by conversion to the hydrochloride salt (G1) to give the title compound as an off-white solid (55 mg): **NMR (^{1}H, d4-MeOH):** δ 7.86 (d, 1H), 7.72 (d, 1H), 7.55 (d, 1H), 7.32 (dd, 1H), 7.23 (dd, 1H), 7.11 (d, 1H), 4.97 (s, 2H), 4.45 (t, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 3.80 (d, 2H), 3.62 (t, 2H), 3.18 (t, 2H), 2.01 (d, 2H), 1.78 (m, 1H), 1.56 (m, 2H), 1.08 (d, 3H) (only data for the major isomer resulting from protonation reported). **MS (*m/z*):** 468 $[MH]^+$ (1Cl).

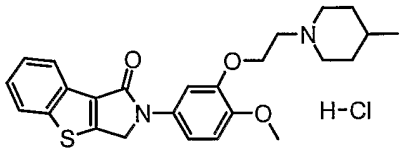
Example 5: 2-[4-Methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-1,2-dihydro-8-thia-2-aza-cyclopenta[a]inden-3-one hydrochloride



2-Methyl-benzo[*b*]thiophene-3-carboxylic acid methyl ester (P33) was treated as described in G5 to give material (0.17 g) which contained *ca.* 35% of the chloromethyl

derivative. Half of this material and 4-methoxy-3-(2-piperidin-1-yl-ethoxy)-phenylamine hydrochloride (P2, 0.45 mmol) were heated in dry DMF (0.5 ml) for 5 h at 100 °C. The mixture was concentrated *in vacuo* and the residue submitted to column chromatography, follwed by conversion to the hydrochloride salt (G1) to give the title compound as an orange film (31 mg). **NMR (^{1}H, d4-MeOH):** δ 8.24 (d, 1H), 8.04 (d, 1H), 7.75 (d, 1H), 7.46-7.58 (m, 2H), 7.29 (dd, 1H), 7.15 (d, 1H), 5.16 (s, 2H), 4.46 (t, 2H), 3.94 (s, 3H), 3.78 (d, 2H), 3.61 (t, 2H), 3.14 (t, 2H), 2.02 (d, 2H), 1.80-1.96 (m, 3H), 1.53-1.66 (m, 1H). **MS (*m/z*):** 423 $[MH]^+$.

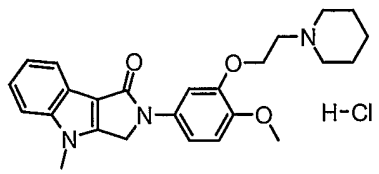
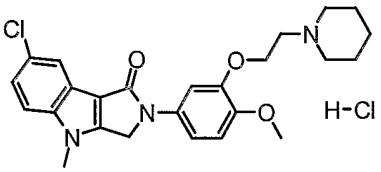
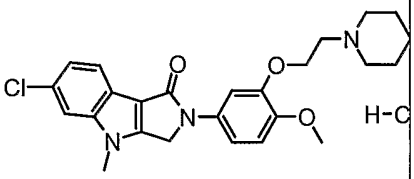
Example 6: 2-{4-Methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-1,2-dihydro-8-thia-2-aza-cyclopenta[a]inden-3-one hydrochloride

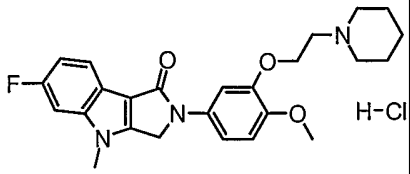
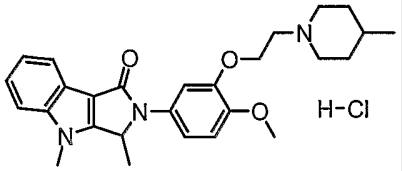
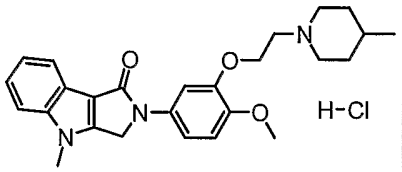


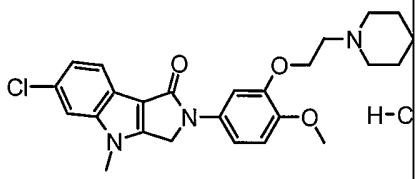
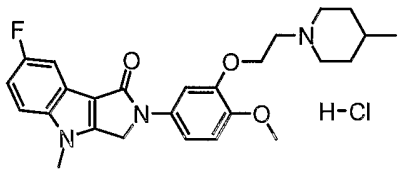
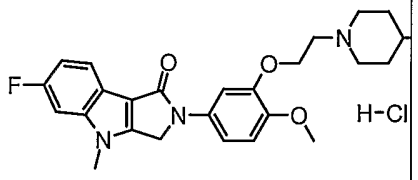
The title compound was obtained as described for Example 5 but using 4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenylamine hydrochloride (P5) to give the product as an orange film (35 mg). **NMR (^{1}H, d4-MeOH):** δ 8.24 (d, 1H), 8.04 (d, 1H), 7.75 (d, 1H), 7.46-7.58 (m, 2H), 7.29 (dd, 1H), 7.15 (d, 1H), 5.16 (s, 2H), 4.46 (t, 2H), 3.94 (s, 3H), 3.78 (d, 2H), 3.61 (t, 2H), 3.14 (t, 2H), 2.00 (d, 2H), 1.70-1.82 (m, 1H), 1.54 (dq, 2H), 1.08 (d, 3H). **MS (*m/z*):** 437 $[MH]^+$.

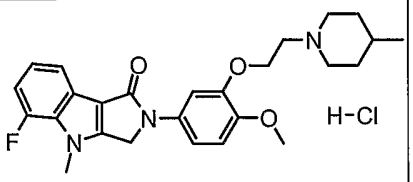
The following examples were prepared in analogy to Example 4 from the respective substituted 2-chloromethyl indoles and the respectlive substituted phenylamine hydrochlorides (P2 respectively P5):

5

Example 7: 2-[4-Methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2*H*-2,8-diazacyclopenta[*a*]inden-3-one hydrochloride		**NMR (^{1}H, d4-MeOH):** δ 7.88 (d, 1H), 7.74 (d, 1H), 7.56 (d, 1H), 7.34 (dt, 1H), 7.28 (dt, 1H), 7.21 (dd, 1H), 7.11 (d, 1H), 4.99 (s, 2H), 4.29 (t, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.60 (t, 2H), 3.72-3.78 (m, 2H), 3.08-3.15 (d, 2H), 1.97-2.05 (m, 2H), 1.80-1.93 (m, 3H), 1.53-1.62 (m, 1H). **MS (*m/z*):** 420 $[MH]^+$.
Example 8: 5-Chloro-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2*H*-2,8-diazacyclopenta[*a*]inden-3-one hydrochloride		**NMR (^{1}H, d4-MeOH):** δ 7.86 (d, 1H), 7.72 (d, 1H), 7.55 (d, 1H), 7.32 (dd, 1H), 7.23 (dd, 1H), 7.11 (d, 1H), 4.98 (s, 2H), 4.45 (t, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 3.77 (d, 2H), 3.62 (t, 2H), 3.14 (t, 2H), 2.01 (d, 2H), 1.80-1.95 (m, 3H), 1.54-1.68 (m, 1H). **MS (*m/z*):** 454 $[MH]^+$ (1Cl).
Example 9: 6-Chloro-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2*H*-2,8-diazacyclopenta[*a*]inden-3-one hydrochloride		**NMR (^{1}H, d4-MeOH):** δ 7.85 (d, 1H), 7.74 (d, 1H), 7.64 (d, 1H), 7.28 (dd, 1H), 7.22 (dd, 1H), 7.12 (d, 1H), 5.01 (s, 2H), 4.45 (t, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 3.77 (d, 2H), 3.62 (t, 2H), 3.14 (t, 2H), 2.01

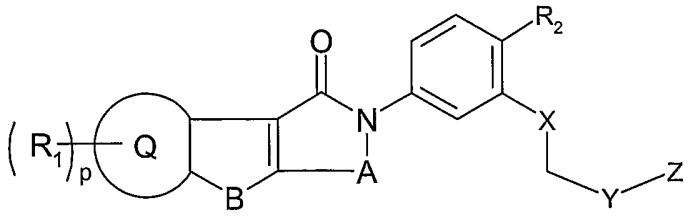
		(d, 2H), 1.80-1.95 (m, 3H), 1.54-1.68 (m, 1H). **MS (*m/z*):** 454 $[MH]^+$ (1Cl).
Example 10: 6-Fluoro-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2*H*-2,8-diazacyclopenta[*a*]inden-3-one hydrochloride		**NMR (^{1}H, d4-MeOH):** δ 7.83 (m, 1H), 7.68 (d, 1H), 7.32 (dd, 1H), 7.20 (dd, 1H), 6.88-7.00 (m, 2H), 4.94 (s, 2H), 4.30 (t, 2H), 3.91 (s, 3H), 3.83 (s, 3H), 3.76 (d, 2H), 3.59 (t, 2H), 3.13 (t, 2H), 1.95 (d, 2H), 1.65-1.83 (m, 3H), 1.37-1.53 (m, 1H).
Example 11: 2-{4-Methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-1,8-dimethyl-1,8-dihydro-2*H*-2,8-diazacyclopenta[*a*]inden-3-one hydrochloride		**NMR (^{1}H, d4-MeOH):** δ 7.86 (d, 1H), 7.54 (d, 1H), 7.35 (d, 1H), 7.33 (t, 1H), 7.25 (t,1H), 7.13 (d, 1H), 7.07 (d, 1H), 5.42 (q, 1H), 4.35-4.45 (m, 2H), 3.90 (s, 6H), 3.74-3.80 (m, 2H), 3.55-3.61 (m, 2H), 3.11 (t, 2H), 1.88-2.03 (m, 2H), 1.65-1.83 (m, 1H), 1.42-1.58 (m, 5H), 1.04 (d, 3H) (only data for the major isomer resulting from protonation reported). **MS (*m/z*):** 448 $[MH]^+$.
Example 12: 2-{4-Methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2*H*-2,8-diazacyclopenta[*a*]inden-3-one hydrochloride		**NMR (^{1}H, d4-MeOH):** δ 7.83 (d, 1H), 7.51 (d, 1H), 7.30 (dt, 1H), 7.22 (dt, 1H), 7.16 (dd,1H), 7.10 (d, 1H), 7.06 (d, 1H), 4.95 (s, 2H), 4.38 (t, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.74 (d, 2H), 3.54 (t, 2H), 3.08 (dt, 2H), 1.96 (bd, 2H),

		1.65-1.80 (m, 1H), 1.48 (dq, 2H), 1.02 (d, 3H) (only data for the major isomer resulting from protonation reported). **MS (*m/z*):** 434 $[MH]^+$.
Example 13: 6-Chloro-2-{4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2*H*-2,8-diazacyclopenta[*a*]inden-3-one hydrochloride		**NMR (^{1}H, d4-MeOH):** δ 7.84 (d, 1H), 7.72 (d, 1H), 7.63 (d, 1H), 7.28 (dd, 1H), 7.22 (dd, 1H), 7.12 (d, 1H), 4.98 (s, 2H), 4.44 (t, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 3.77 (d, 2H), 3.62 (t, 2H), 3.14 (t, 2H), 2.01 (d, 2H), 1.70-1.84 (m, 1H), 1.55 (dq, 2H), 1.04 (d, 3H) (only data for the major isomer resulting from protonation reported). **MS (*m/z*):** 468 $[MH]^+$.
Example 14: 5-Fluoro-2-{4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2*H*-2,8-diazacyclopenta[*a*]inden-3-one hydrochloride		**NMR (^{1}H, d4-MeOH):** δ 7.73 (d, 1H), 7.54-7.57 (m, 2H), 7.18 (dd, 1H), 7.08-7.13 (m, 2H), 4.99 (s, 2H), 4.43 (t, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.76 (d, 2H), 3.58 (t, 2H), 3.12 (t, 2H), 2.01 (d, 2H), 1.66-1.82 (m, 1H), 1.46-1.58 (m, 2H), 1.06 (d, 3H) (only data for the major isomer resulting from protonation reported).
Example 15: 6-Fluoro-2-{4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2*H*-2,8-diazacyclopenta[*a*]inden-3-		**NMR (^{1}H, d4-MeOH):** δ 7.83 (m, 1H), 7.68 (d, 1H), 7.32 (dd, 1H), 7.20 (dd, 1H), 6.87-6.98 (m, 2H), 4.94 (s, 2H), 4.43 (t, 2H), 3.91 (s, 3H),

one hydrochloride		3.83 (s, 3H), 3.76 (d, 2H), 3.59 (t, 2H), 3.13 (t, 2H), 2.01 (d, 2H), 1.53-1.73 (m, 1H), 1.33-1.53 (m, 2H), 1.06 (d, 3H) (only data for the major isomer resulting from protonation reported).
Example 16: 7-Fluoro-2-{4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2*H*-2,8-diazacyclopenta[*a*]inden-3-one hydrochloride		**NMR (^{1}H, d4-MeOH):** δ 7.75 (dd, 1H), 7.68 (d, 1H), 6.90-7.15 (m, 4H), 4.94 (s, 2H), 4.43 (t, 2H), 3.95 (s, 3H), 3.80 (s, 3H), 3.76 (d, 2H), 3.59 (t, 2H), 3.05 (t, 2H), 1.99 (d, 2H), 1.55-1.75 (m, 1H), 1.32-1.50 (m, 2H), 1.06 (d, 3H) (only data for the major isomer resulting from protonation reported).

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:
Q is phenyl or a 6-membered heteroaromatic group containing at least one nitrogen atom;
A is $-(CH_2-CH_2)-$, $-(CH=CH)-$, $-(CH_2)_3-$, $-C(CH_3)_2-$, $-(CH=CH-CH_2)-$, or a group $-(CHR_3)-$ wherein R_3 is hydrogen, halogen, hydroxy, cyano, nitro, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy or C_{1-6}alkylthio;
B is O, S or NR_{11}, wherein R_{11} is hydrogen or C_{1-6}alkyl or C_{1-6}alkanoyl optionally substitued by C_{1-6}alkoxy;
R_1 is halogen, cyano, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxy, amino, mono- or di-C_{1-6}alkylamino, an N-linked 4 to 7 membered heterocyclic group, nitro, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, arylC_{1-6}alkylthio or $COOR_4$ or COR_5 wherein R_4, and R_5 are independently hydrogen or C_{1-6}alkyl or COR_6 wherein R_6 is amino, mono- or di-C_{1-6}alkylamino or an N-linked 4 to 7 membered heterocyclic group;
p is 0, 1 or 2 or 3;
R_2 is hydrogen, halogen, hydroxy, cyano, nitro, C_{1-6}alkyl, C_{1-6}alkanoyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, C_{1-6}alkylthio, amino, mono- or di-C_{1-6}alkylamino or an N-linked 4 to 7 membered heterocyclic group;
X is oxygen, sulfur, $-CH_2-$ or NR_8 wherein R_8 is hydrogen or C_{1-6}alkyl;
Y is a single bond, $-CH_2-$, $-(CH_2)_2-$ or $-CH=CH-$; and
Z is an optionally substituted N-linked heterocyclic group or a C-linked 4 to 7 membered heterocyclic group containing at least one nitrogen, or Z is $-NR_9R_{10}$ where R_9 and R_{10} are independently hydrogen or C_{1-6}alkyl.

2. A compound as claimed in claim 1, wherein A is $-CH_2-$.

3. A compound as claimed in claim 1 or 2, wherein p is 1 or 2 and R_1 is/are halogen, particularly chloro or fluoro.

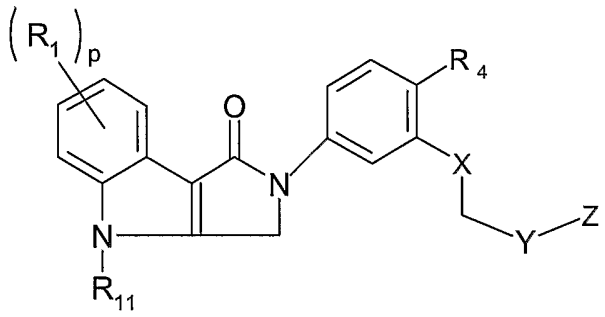
4. A compound as claimed in claim 1, 2 or 3, wherein R_2 is C_{1-6}alkoxy (particularly methoxy), halogen or cyano.

5. A compound as claimed in any of claims 1-4, wherein X is oxygen.

6. A compound as claimed in any of claims 1-5, wherein Y is $-CH_2-$.

7. A compound as claimed in any of claims 1-6, wherein Z is an optionally substituted N-linked 4 to 7 membered heterocycle, in particular piperidyl.

8. A compound as claimed in claim 1 having the formula (Ia):



(Ia)

wherein R_1, p, R_{11}, R_4, X, Y and Z, are as defined in claim 1.

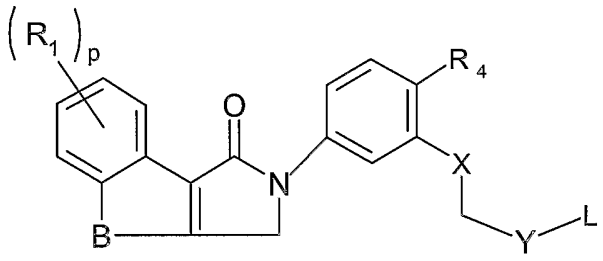
9. A compound as claimed in claim 1 which is:

6-Bromo-5-methoxy-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride
5-Methoxy-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride
5,6-Dichloro-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride
5-Chloro-2-{4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride
2-[4-Methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-1,2-dihydro-8-thia-2-aza-cyclopenta[a]inden-3-one hydrochloride
2-{4-Methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-1,2-dihydro-8-thia-2-aza-cyclopenta[a]inden-3-one hydrochloride
2-[4-Methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride
5-Chloro-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride
6-Chloro-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride

6-Fluoro-2-[4-methoxy-3-(2-piperidin-1-yl-ethoxy)phenyl]-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride
2-{4-Methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-1,8-dimethyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride
2-{4-Methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride
6-Chloro-2-{4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride
5-Fluoro-2-{4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride
6-Fluoro-2-{4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride
7-Fluoro-2-{4-methoxy-3-[2-(4-methyl-piperidin-1-yl)-ethoxy]-phenyl}-8-methyl-1,8-dihydro-2H-2,8-diazacyclopenta[a]inden-3-one hydrochloride
or a pharmaceutically acceptable salt thereof.

10. A process for the preparation of a compound as claimed in claim 1, which process comprises:

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

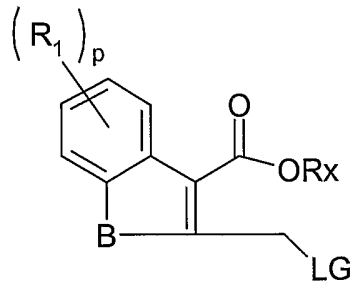


(II)

wherein R_1, R_2, p, A, X, and Y are as defined for formula (I), and L is a leaving group, with a compound of formula (III):

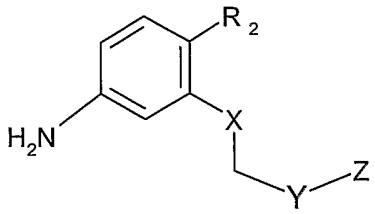
Z-H
(III)

wherein Z is as defined for formula (I); or
(b) reacting a compound of formula (III):



(III)

with a compound of formula (IV) or a salt thereof:



(IV)

followed, as appropriate, with a treatment of the intermediate obtained with $AlMe_3$ or a similar oxophilic reagent;

and for either process (a) or process (b), optionally followed by:

- removing any protecting groups; and/or
- converting a compound of formula (I) into another compound of formula (I); and/or
- forming a pharmaceutically acceptable salt.

11. A pharmaceutical composition comprising a compound as defined in any of claims 1-9 and a pharmaceutically acceptable carrier or excipient.

12. A process for preparing a pharmaceutical composition, the process comprising mixing a compound as claimed in any of claims 1-9 and a pharmaceutically acceptable carrier or excipient.

13. A compound as claimed in any of claims 1-9 for use as a therapeutic substance.

14. A compound as claimed in any of claims 1-9 for use in the treatment of a CNS disorder.

15. A compound as claimed in claim 14, wherein the disorder is depression or anxiety.

16. A method of treatment of a CNS disorder in mammals including humans, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound as defined in any of claims 1-9.

17. A method as claimed in claim 16, wherein the disorder is depression or anxiety.

18. Use of a compound as claimed in any of claims 1-9 in the manufacture of a medicament for use in the treatment of a CNS disorder.

19. The use as claimed in claim 18, wherein the disorder is depression or anxiety.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/001844

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 C07D495/04 A61K31/407 A61P25/00
//(C07D487/04,209:00,209:00),(C07D495/04,333:00,209:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 03/089409 A (GLAXO GROUP LTD ; JAXA-CHAMIEC ALBERT ANDRZEJ (IT); DAMIANI FEDERICA () 30 October 2003 (2003-10-30) page 1, line 10 - page 2, line 3 claims 1-21	1-19
A	WO 97/48700 A (BROMIDGE STEVEN MARK ; SMITHKLINE BEECHAM PLC (GB)) 24 December 1997 (1997-12-24) cited in the application the whole document	1-19
A	WO 94/04533 A (SMITHKLINE BEECHAM PLC ; FORBES IAN THOMSON (GB); MARTIN ROGER THOMAS) 3 March 1994 (1994-03-03) cited in the application page 45 - page 47; claim 1	1-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 August 2004	25/08/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Goss, I

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/001844

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16 and 17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/001844

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