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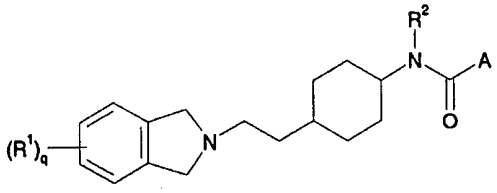
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(54) Title: 2,3–DIHYDRO–1H–ISOINDOLE DERIVATIVES USEFUL AS MODULATORS OF DOPAMINE D_3 RECEPTORS (ANTIPSYCHOTIC AGENTS)



(I)

(57) Abstract

0ompounds of formula (I), wherein R^2 represents a hydrogen atom or a C_{1-4} alkyl group; q is 1 or 2; A represents a group of formula (a), (b), (c) or (d), wherein Ar represents an optionally substituted phenyl ring or an optionally substituted 5– or 6–membered aromatic heterocyclic ring; or an optionally substituted bicyclic ring system; Ar^1 and Ar^2 each independently represent an optionally substituted phenyl ring or an optionally substituted 5– or 6–membered aromatic heterocyclic ring; and Y represents a bond, –NHCO–, –CONH–, $–CH_2–$, or $–(CH_2)_mY^1(CH_2)_n–$, wherein Y^1 represents O, S, SO_2 or CO and m and n each represent zero or (I) such that the sum of m + n is zero or 1; providing that when A represents a group of formula (a), any substituent present in Ar *ortho* to the carboxamide moiety is necessarily a hydrogen or methoxy group; r and s independently represent an integer from zero to 3 such that the sum of r and s is equal to an integer from 1 to 4; V represents a bond, O or S; and salts thereof.Compounds of formula (I) and their salts have affinity for dopamine receptors, in particular the D_3 receptor, and thus potential in the treatment of conditions wherein modulation of the D_3 receptor is beneficial, e.g. as antipsychotic agents.

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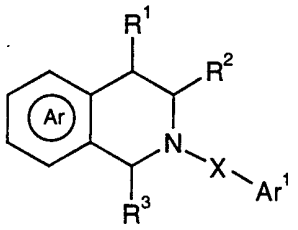
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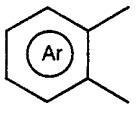
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2,3-DIHYDRO-1H-ISOINDOLE DERIVATIVES USEFUL AS MODULATORS OF DOPAMINE D_3 RECEPTORS (ANTIPSYCHOTIC AGENTS)

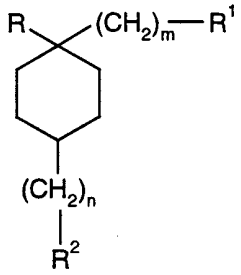
The present invention relates to novel 2,3-dihydro-1*H*-isoindole derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy, as modulators of dopamine D_3 receptors, in particular as antipsychotic agents.

US Patent No. 5,294,621 describes tetrahydropyridine derivatives of the formula:

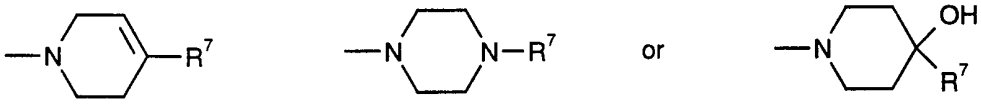


wherein  is an optionally substituted thienyl or optionally substituted phenyl ring; R^1, R^2 and R^3 are each *inter alia* hydrogen; X is *inter alia* $(CH_2)mNR^7CO$; m is 2-4; and Ar^1 is an optionally substituted heterocyclic ring or an optionally substituted phenyl ring. The compounds are said to be useful as antiarrhythmic agents.

EPA 431,580 describes compounds of formula



wherein R is OR^3, NR^4R^5, or $N(OR^4)R^5$, R^4 and R^5 are *inter alia* hydrogen, lower alkyl, aroyl or heteroaroyl; m is zero, 1 or 2; R^1 is hydrogen, aryl or various heteroaryl groups; n is zero or 1-4; and R^2 is:



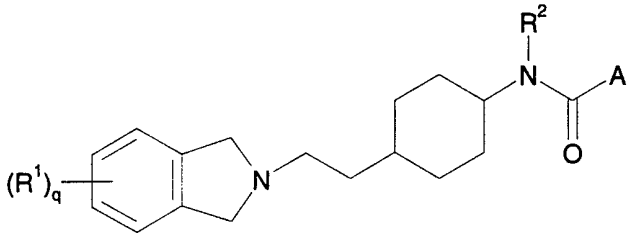
The compounds are said to be dopaminergic agents useful as antipsychotics, antihypertensives and also of use in the treatment of hyperprolactinaemia-related conditions and several central nervous system disorders.

WO 95/10513 describes benzothiophene derivatives and related compounds as estrogen agonists.

WO 97/43262 and WO 98/06699 describe tetrahydroisoquinoline derivatives as having affinity for the dopamine D_3 receptor.

We have now found a class of 2,3-dihydro-1*H*-isoindole derivatives which have affinity for dopamine receptors, in particular the D_3 receptor, and thus potential in the treatment of conditions wherein modulation of the D_3 receptor is beneficial, eg as antipsychotic agents.

In a first aspect the present invention provides compounds of formula (I) :



Formula (I)

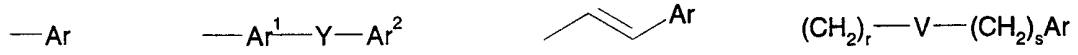
wherein:

R^1 represents a substituent selected from: a hydrogen or halogen atom; a hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-4}alkyl, C_{1-4}alkoxy, arylC_{1-4}alkoxy, C_{1-4}alkylthio, C_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkylC_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfonyloxy, C_{1-4}alkylsulfonylC_{1-4}alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-4}alkyl, C_{1-4}alkylsulfonamido, C_{1-4}alkylamido, C_{1-4}alkylsulfonamidoC_{1-4}alkyl, C_{1-4}alkylamidoC_{1-4}alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-4}alkyl, arylcarboxamidoC_{1-4}alkyl, aroyl, aroylC_{1-4}alkyl, or arylC_{1-4}alkanoyl group; a group $R^3OCO(CH_2)_p$, $R^3CON(R^4)(CH_2)_p$, $R^3R^4NCO(CH_2)_p$ or $R^3R^4NSO_2(CH_2)_p$ where each of R^3 and R^4 independently represents a hydrogen atom or a C_{1-4}alkyl group or R^3R^4 forms part of a C_{3-6}azacyloalkane or C_{3-6}(2-oxo)azacycloalkane ring and p represents zero or an integer from 1 to 4; or a group Ar^3-Z, wherein Ar^3 represents an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring and Z represents a bond, O, S , or CH_2;

R^2 represents a hydrogen atom or a C_{1-4}alkyl group;

q is 1 or 2;

A represents a group of the formula (a), (b), (c) or (d):



(a) (b) (c) (d)

wherein

Ar represents an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring; or an optionally substituted bicyclic ring system;

Ar^1 and Ar^2 each independently represent an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring; and

Y represents a bond, -NHCO-, -CONH-, $-CH_2-$, or $-(CH_2)_mY^1(CH_2)_n-$, wherein Y^1 represents O, S, SO_2, or CO and m and n each represent zero or 1 such that the sum of m+n is zero or 1; providing that when A represents a group of formula (a), any substituent present in Ar *ortho* to the carboxamide moiety is necessarily a hydrogen or a methoxy group;

r and s independently represent an integer from zero to 3 such that the sum of r and s is equal to an integer from 1 to 4;

V represents a bond, O or S;

and salts thereof.

In the compounds of formula (I) above an alkyl group or moiety may be straight or branched. Alkyl groups which may be employed include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl and any branched isomers thereof such as isopropyl, t-butyl, sec-butyl, and the like.

When R^1 represents an arylC_{1-4}alkoxy, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-4}alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-4}alkyl, arylcarboxamidoC_{1-4}alkyl, aroyl, aroylC_{1-4}alkyl, or arylC_{1-4}alkanoyl group, the aryl moiety may be selected from an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered heterocyclic ring. In the group R^1 an aryl moiety may be optionally substituted by one or more substituents selected from hydrogen, halogen, amino, cyano, C_{1-4}alkyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, C_{1-4}alkylamido, C_{1-4}alkanoyl, or R^5R^6NCO where each of R^5 and R^6 independently represents a hydrogen atom or C_{1-4}alkyl group.

A halogen atom present in the compounds of formula (I) may be fluorine, chlorine, bromine or iodine.

When q is 2, the substituents R^1 may be the same or different.

An optionally substituted 5- or 6-membered heterocyclic aromatic ring, as defined for any of the groups Ar, Ar^1, Ar^2 or Ar^3 may contain from 1 to 4 heteroatoms selected from O, N or S. When the ring contains 2-4 heteroatoms, one is preferably selected from O, N and S and the remaining heteroatoms are preferably N. Examples of 5 and 6-membered heterocyclic groups include furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl and pyrazolyl.

Examples of bicyclic, for example bicyclic aromatic or heteroaromatic, ring systems for Ar include naphthyl, indazolyl, indolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzisothiazolyl, quinolinyl, quinoxolinyl, quinazolinyl, cinnolinyl, isoquinolinyl, pyrazolo[1,5-a]pyrimidyl, pyrrolo[3,2-b]pyridyl, pyrrolo[3,2-c]pyridyl, thieno[3,2-b]thiophenyl, 1,2-dihydro-2-oxo-quinolinyl, 3,4-dihydro-2-oxo-4*H*-benzoxazinyl, 1,2-dihydro-2-oxo-3H-indolyl.

The rings Ar, Ar^1, or Ar^2 may each independently be optionally substituted by one or more substituents selected from: a hydrogen or halogen atom, or a hydroxy, oxo, cyano, nitro, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylenedioxy, C_{1-4}alkanoyl,

C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfinyl, C_{1-4}alkylthio, $R^7SO_2N(R^8)$-, $R^7R^8NSO_2$-, R^7R^8N-, R^7R^8NCO-, or $R^7CON(R^8)$- group wherein each of R^7 and R^8 independently represents a hydrogen atom or a C_{1-4} alkyl group, or R^7R^8 together form a C_{3-6} alkylene chain.

Alternatively, Ar and Ar^2 may be optionally substituted by one or more 5- or 6-membered heterocyclic rings, as defined above, optionally substituted by a C_{1-2} alkyl or R^7R^8N- group; wherein R^7 and R^8 are as defined above.

In the rings Ar and Ar^2 substituents positioned *ortho* to one another may be linked to form a 5- or 6- membered ring.

It will be appreciated that for use in medicine the salts of formula (I) should be physiologically acceptable. Suitable physiologically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts formed with inorganic acids eg. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids eg. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other non-physiologically acceptable salts eg. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

Certain of the compounds of formula (I) 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.

The compounds of formula (I) can exist in the form of *cis*- and *trans*- isomers with respect to the configuration at the cyclohexyl ring. When A represents a group (c) the compounds may also exist as geometric isomers around the double bond. The present invention includes within its scope all such isomers, including mixtures. Preferably the compounds of the invention are in the *trans* configuration with respect to the cyclohexyl ring. For compounds of formula (I) where A represents a group (c), *trans* geometry of the double bond is preferred.

In compounds of formula (I), it is preferred that R^1 represents a substituent selected from: a halogen atom, methyl, cyano, trifluoromethyl, pentafluoroethyl, methylsulfonyloxy or trifluoromethoxy group. Preferably q is 1. R^2 is preferably a hydrogen atom.

The group A is preferably a group of formula (a), (b) or (c). With regard to (a), preferred examples of Ar include optionally substituted indolyl, pyrazolo[1,5-a]pyrimidyl, cinnolinyl, quinolinyl, benzo[b]furanyl or pyrrolopyridyl. With regard to (c), preferred examples are optionally substituted phenyl groups.

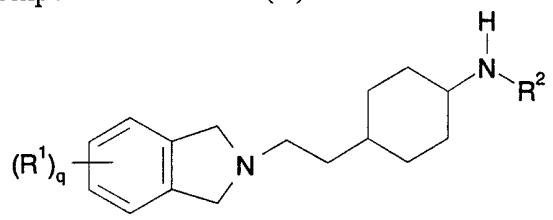
It is also preferred that the rings Ar, Ar^1, or Ar^2 are each independently optionally substituted by one or more substituents selected from: a hydrogen or halogen atom, cyano, methoxy, methylenedioxy, acetyl, acetylamino, methylsulfonyl, methylsulfonyloxy, methylaminosulfonyl, methylsulfonylamino, or methylaminocarbonyl group.

Certain of the substituted heteroaromatic ring systems 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.

Particular compounds according to the invention include those specifically exemplified and named hereinafter. These compounds may be in the form of their free base or physiologically acceptable salts thereof, particularly the monohydrochloride or monomesylate salts.

The present invention also provides a process for preparing compounds of formula (I) which process comprises :

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



Formula (II)

wherein R^1, R^2 and q are as hereinbefore defined, with a compound of formula (III):

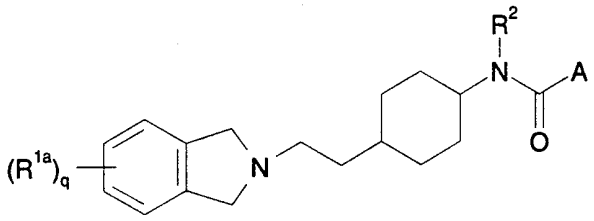
A-COX

Formula (III)

wherein A is as hereinbefore defined and X is a halogen atom or the residue of an activated ester;

(b) to prepare a compound of formula (I) by reacting a compound of formula (II) with a compound A-Br, or A-I, or A-OSO_2CF_3 in the presence of carbon monoxide and a catalyst such as *trans-bis*-triphenylphosphinepalladium(II)bromide;

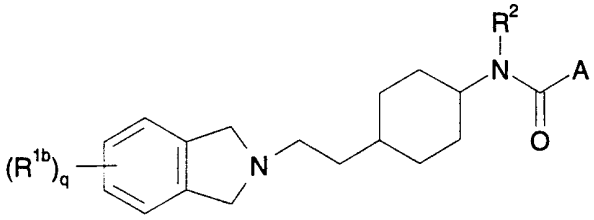
(c) to prepare a compound of formula (I) wherein R^1 is Ar^3-Z and Z is a bond, reacting a compound of formula (IV):



Formula (IV)

wherein R^2 and A are as hereinbefore defined and one R^{1a} represents a group W wherein W is a halogen atom or a trifluoromethylsulfonyloxy group, or W 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, and when q is 2 the other R^{1a} is R^1; with a compound Ar^3-W^1, wherein W^1 is a halogen atom or a trifluoromethylsulfonyloxy group when W is a group M or W^1 is a group M when W is a halogen atom or a trifluoromethylsulfonyloxy group;

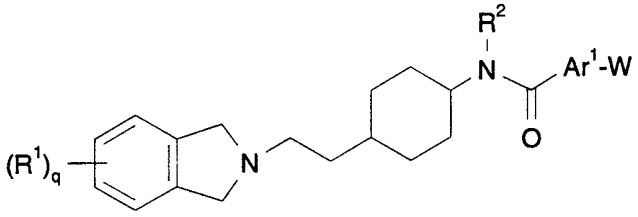
(d) to prepare a compound of formula (I) wherein R^1 is Ar^3-Z and Z is O or S, reacting a compound of formula (V):



Formula (V)

wherein R^2 and A are as hereinbefore defined and one R^{1b} represents a group ZH and when q is 2 the other R^{1b} represents R^1; with a reagent serving to introduce the group Ar^3;

(e) to prepare a compound of formula (I) where Y is a bond, reaction of a compound of formula (VI):



Formula (VI)

wherein R^1, R^2, Ar^1, W and q are as hereinbefore defined, with a compound Ar^2-W^1, wherein W^1 is a halogen atom or a trifluoromethylsulfonyloxy group when W is a group M, or W^1 is a group M when W is a halogen atom or a trifluoromethylsulfonyloxy group.

(f) interconversion of one compound of formula (I) to a different compound of formula (I) e.g. (i) alkylation of a compound (I) wherein R^2 represents hydrogen, (ii) conversion of one R^1 from alkoxy (e.g.methoxy) to hydroxy, or (iii) conversion of R^1 from hydroxy to sulfonyloxy, eg alkylsulfonyloxy or trifluoromethanesulfonyloxy; (iv) conversion of a compound wherein Y represents S to a compound wherein Y is SO_2 or (v) conversion of Y from CO to CH_2;

(g) separation of *cis*- and *trans*- isomers of compounds of formula (I) by conventional methods, e.g. chromatography or crystallisation;

and optionally thereafter forming a salt of formula (I).

Process (a) may be effected using conventional methods for the formation of an amide bond. When X is the residue of an activated ester this may be formed with e.g. a carbodiimide such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The reaction may be carried out in a solvent such as dichloromethane.

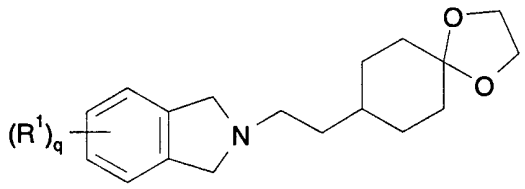
Reaction of a compound of formula (IV) with Ar^3W^1, according to process (c) or a compound of formula (VI) with Ar^2-W^1 according to process (e) may be effected in the presence of a transition metal eg palladium catalyst such as *bis*-triphenylphosphinepalladium dichloride or *tetrakis*-triphenylphosphinepalladium (0). When M represents 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. The substituent W is preferably a halogen atom such as bromine, or a sulfonyloxy group such as trifluoromethylsulfonyloxy; and W^1 is preferably a goup M, such as trialkylstannyl or $B(OH)_2$.

In process (d) the reagent serving to introduce the group Ar^3 is preferably a compound of formula Ar^3-Hal, wherein Hal is a halogen atom. The reaction may be effected in the presence of a base, such as potassium carbonate, in a solvent such as dimethylformamide.

Interconversion reactions according to process (f) may be effected using methods well known in the art.

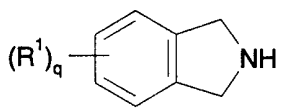
Compounds of formula (II) may be prepared by conversion of a compound of formula (VII), wherein R^1 and q are as hereinbefore defined,



Formula (VII)

into a corresponding ketone, followed by reductive amination. This may be effected by methods well known in the art for (i) conversion of a ketal to a ketone in the presence of aqueous acid; followed by (ii) reductive amination of the ketone with R^2NH_2 or ammonium acetate in the presence of a reducing agent. Suitable reducing agents which may be employed include sodium borohydride, cyanoborohydride or triacetoxyborohydride under acidic conditions, or catalytic hydrogenation. The reaction may conveniently be effected in a solvent such as methanol, ethanol or dichloroethane.

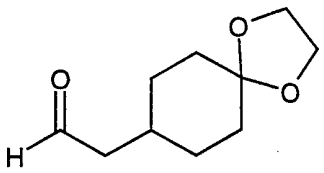
A compound of formula (VII) may itself be prepared by reacting a compound of formula (VIII):



Formula (VIII)

wherein R^1 and q are as hereinbefore defined;

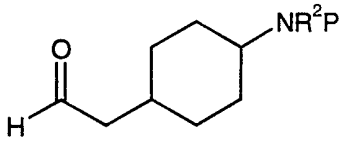
with a compound of formula (IX):



Formula (IX)

in the presence of a reducing agent. Suitable reducing agents which may be employed include sodium borohydride, cyanoborohydride or triacetoxyborohydride under acidic conditions, or catalytic hydrogenation. The reaction may conveniently be effected in a solvent such as ethanol or dichloroethane.

The individual *cis*- and *trans*- isomers of a compound of formula (II) may be prepared starting from *cis*- or *trans*- 4-amino-cyclohexaneacetic acid (T.P. Johnson, *et al.*, J. Med. Chem., 1997, (20), 279-290) followed by functional group interchange and/or protection using methods well known in the art, to give the individual *cis*- or *trans*- isomers of a compound of formula (X):



Formula (X)

wherein R^2 is as hereinbefore defined, and P is a protecting group, for example trifluoroacetyl or *tert*-butoxycarbonyl. Subsequent reaction of a compound of formula (X) with a compound of formula (VIII) in the presence of a reducing agent as described above followed by deprotection using standard methodology gives the individual isomers of a compound of formula (II) wherein R^2 is as hereinbefore defined.

Compounds of formula (III) are known or may be prepared using standard procedures.

Compounds of formula (IV), (V) or (VI) may be prepared by processes analogous to (a), (b), (c) and (d) described above. Compounds Ar^2W^1, Ar^3W^1 and Ar^3Hal are commercially available or may be prepared by standard methods. Compounds of formula (VIII) are known in the literature or may be prepared by known methods. The compound of formula (IX) is likewise known in the literature.

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. 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. Without wishing to be bound by theory, 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). Preferred compounds of the present invention are therefore those which have 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). Said compounds may advantageously be used as selective modulators of D_3 receptors.

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 (eg see Schwartz et al., Brain Res. Reviews, 1998, 26, 236-242). From the localisation of D3 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 D3 receptors are involved (eg see Levant, 1997, Pharmacol. Rev., 49, 231-252) . Examples of such substance abuse include alcohol, cocaine 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.

In a further aspect therefore the present invention provides a method of treating conditions which require modulation of dopamine D_3 receptors, for example psychoses such as schizophrenia, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a physiologically acceptable salt thereof.

The invention also provides the use of a compound of formula (I) or a physiologically acceptable salt thereof in the manufacture of a medicament for the treatment of conditions which require modulation of dopamine D_3 receptors, for example psychoses such as schizophrenia.

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The invention also provides the use of a compound of formula (I) or a physiologically acceptable salt thereof in the manufacture of a medicament for the treatment of conditions which require modulation of dopamine D_3 receptors, for example psychoses such as schizophrenia.

A preferred use for D_3 antagonists according to the present invention is in the treatment of psychoses such as schizophrenia.

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 pharmaceutical compositions comprising a novel compound of formula (I) or a physiologically acceptable salt thereof and a physiologically acceptable carrier.

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

The compounds of formula (I) and their physiologically 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.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically 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.

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.

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.

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically 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.

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 physiologically 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.

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.

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

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

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

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

The physiologically 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, preferably 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, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) or a physiologically 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

The ability of the compounds to bind selectively to human D_3 dopamine receptors can be demonstrated by measuring their binding to cloned receptors. The inhibition constants (K_i) of test compounds for displacement of [^{125}I] iodosulpride binding to human D_3 dopamine receptors expressed in CHO cells were determined as follows. The cell lines were shown to be free from bacterial, fungal and mycoplasmal contaminants, and stocks of each were stored frozen in liquid nitrogen. Cultures were grown as monolayers or in suspension in standard cell culture media. Cells were recovered by scraping (from monolayers) or by centrifugation (from suspension cultures), and were washed two or three times by suspension in phosphate buffered saline followed by collection by centrifugation. Cell pellets were stored frozen at -40°C. Crude cell membranes were prepared by homogenisation followed by high-speed centrifugation, and characterisation of cloned receptors achieved by radioligand binding.

Preparation of CHO cell membranes

Cell pellets were gently thawed at room temperature, and resuspended in about 20 volumes of ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), 20mM EDTA, 0.2 M sucrose. The suspension was homogenised using an Ultra-Turrax at full speed for 15 sec. The homogenate was centrifuged at 18,000 r.p.m for 20 min at 4°C in a Sorvall RC5C centrifuge. The membrane pellet was resuspended in ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), using an Ultra-Turrax, and recentrifuged at 18,000 r.p.m for 15 min at 4°C in a Sorvall RC5C. The membranes were washed two more times with ice-cold 50 mM Tris salts (pH 7.4 @ 37°C). The final pellet was resuspended in 50 mM Tris salts (pH 7.4 @

37°C), and the protein content determined using bovine serum albumin as a standard (Bradford, M. M. (1976) Anal. Biochem. 72, 248-254).

Binding experiments on cloned dopamine receptors

Crude cell membranes were incubated with 0.1 nM [^{125}I] iodosulpride (~2000 Ci/mmol; Amersham, U. K.), and the test compound in a buffer containing 50 mM Tris salts (pH 7.4 @ 37°C), 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% (w/v) bovine serum albumin, in a total volume of 1 ml for 30 min at 37°C. Following incubation, samples were filtered using a Brandel Cell Harvester, and washed three times with ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$. The radioactivity on the filters was measured using a Cobra gamma counter (Canberra Packard). Non-specific binding was defined as the radioligand binding remaining after incubation in the presence of 100 μM iodosulpride. For competition curves, 14 concentrations (half-log dilutions) of competing cold drug were used. Competition curves were analysed simultaneously whenever possible using non-linear least-squares fitting procedures, capable of fitting one, two or three site models.

Compounds of Examples tested according to this method had pKi values in the range 7.0 – 8.5 at the human cloned dopamine D_3 receptor.

Functional Activity at cloned dopamine receptors

The functional activity of compounds at human D2 and human D3 receptors (ie agonism or antagonism) may be determined using a Cytosensor Microphysiometer (McConnell HM et al Science 1992 257 1906-1912) In Microphysiometer experiments, cells (hD2_CHO or hD3_CHO) were seeded into 12mm Transwell inserts (Costar) at 300000 cells/cup in foetal calf serum (FCS)-containing medium. The cells were incubated for 6h at 37°C in 5%CO_2, before changing to FCS-free medium. After a further 16-18h, cups were loaded into the sensor chambers of the Cytosensor Microphysiometer (Molecular Devices) and the chambers perfused with running medium (bicarbonate-free Dulbecco's modified Eagles medium containing 2 mM glutamine and 44 mM NaCl) at a flow rate of 100 ul/min. Each pump cycle lasted 90s. The pump was on for the first 60s and the acidification rate determined between 68 and 88s, using the Cytosoft programme. Test compounds were diluted in running medium. In experiments to determine agonist activity, cells were exposed (4.5 min for hD2, 7.5 min for hD3) to increasing concentrations of putative agonist at half hour intervals. Seven concentrations of the putative agonist were used. Peak acidification rate to each putative agonist concentration was determined and concentration-response curves fitted using Robofit [Tilford, N.S., Bowen, W.P. & Baxter, G.S. Br. J. Pharmacol. (1995) in press]. In experiments to determine antagonist potency, cells were treated at 30 min intervals with five pulses of a submaximal concentration of quinpirole (100 nM for hD2 cells, 30 nM for hD3 cells), before exposure to the lowest concentration of putative antagonist. At the end of the next 30 min interval, cells were pulsed again with quinpirole (in the continued presence of the antagonist) before exposure to the next highest antagonist concentration. In all, five concentrations of antagonist were used in each experiment. Peak acidification rate to each

agonist concentration was determined and concentration-inhibition curves fitted using Robofit.

Pharmaceutical Formulations

The following represent typical pharmaceutical formulations according to the present invention, which may be prepared using standard methods.

IV Infusion

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Solvent/complexing agent	to 100 ml

Bolus Injection

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Co-Solvent	to 5 ml

Buffer : Suitable buffers include citrate, phosphate, sodium hydroxide/hydrochloric acid.

Solvent : Typically water but may also include cyclodextrins (1-100 mg) and co-solvents such as propylene glycol, polyethylene glycol and alcohol.

Tablet

Compound	1 - 40 mg
Diluent/Filler *	50 - 250 mg
Binder	5 - 25 mg
Disentegrant *	5 - 50 mg
Lubricant	1 - 5 mg
Cyclodextrin	1 - 100 mg

* may also include cyclodextrins

Diluent : e.g. Microcrystalline cellulose, lactose, starch

Binder : e.g. Polyvinylpyrrolidone, hydroxypropymethylcellulose

Disintegrant : e.g. Sodium starch glycollate, crospovidone

Lubricant : e.g. Magnesium stearate, sodium stearyl fumarate.

Oral Suspension

Compound	1 - 40 mg
Suspending Agent	0.1 - 10 mg
Diluent	20 - 60 mg

Preservative	0.01 - 1.0 mg
Buffer	to pH ca 5 - 8
Co-solvent	0 - 40 mg
Flavour	0.01 - 1.0 mg
Colourant	0.001 - 0.1 mg

Suspending agent : e.g. Xanthan gum, microcrystalline cellulose
Diluent : e.g. sorbitol solution, typically water
Preservative : e.g. sodium benzoate
Buffer : e.g. citrate
Co-solvent : e.g. alcohol, propylene glycol, polyethylene glycol, cyclodextrin

The invention is further illustrated by the following non-limiting examples :

Description 1

***trans*-2-(1-(4-(*N*- *tert*-Butyloxycarbonyl)amino)cyclohexyl)acetic acid, methyl ester**

A mixture of *trans*-(4-amino)cyclohexylacetic acid hydrogen sulfate (T.P. Johnston *et al*; J. Med Chem., 1977, 20 (2), 279-290), (27.0g, 106mmol), conc. H_2SO_4 (3ml), and methanol (300ml) was stirred at reflux for 5h. Resulting solution was filtered and the filtrate evaporated *in vacuo* to give a brown oil (36g). A mixture of this material, triethylamine (36ml; 26.1g, 259 mmol), dichloromethane (600ml) and di-*t*-butyl dicarbonate (25.5g, 117mmol) was stirred at 20°C for 18h. Resulting solution was partitioned between saturated aqueous $NaHCO_3$ (500ml) and dichloromethane (3x200ml), and the combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound (24.6g, 86%) as a colourless solid.

^{1}H NMR ($CDCl_3$) δ: 1.08 (4H, m), 1.43 (9H, s), 1.76 (3H, m), 2.00 (2H, m), 2.20 (2H, d, J = 7 Hz), 3.37 (1H, m), 3.66 (3H, s), 4.39 (1H, br s).

Description 2

***trans*-2-(1-(4-(*N*-*tert*-Butyloxycarbonyl)amino)cyclohexyl)acetaldehyde**

To a stirred solution of *trans*-2-(1-(4-(*N*-*tert*-butyloxycarbonyl)amino)cyclohexyl)acetic acid, methyl ester (46.0g, 170 mmol) in dry toluene (920ml) at -78°C under argon was added a solution of di-isobutylaluminium hydride (1M; 285 ml; 285 mmol), dropwise over 0.5h. Resulting solution was stirred for a further 0.3h and quenched with a mixture of methanol (28ml) in toluene (50ml) and then poured into saturated aqueous potassium sodium tartrate (1.2L). The resultant mixture was extracted with ether (4x1L). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give a waxy solid which was purified using silica gel, eluting with 10-50% ethyl acetate/hexane to give the title compound (21.77g, 53%) as a colourless solid.

^{1}H NMR ($CDCl_3$) δ: 1.12 (4H, m), 1.44 (9H, s), 1.78 (3H, m), 2.00 (2H, m), 2.33 (2H, dd, J = 7, 2 Hz), 3.37 (1H, m), 4.40 (1H, m), 9.75 (1H, m).

Description 3

***trans*-2-(2-(1-(4-(*N-tert*-Butyloxycarbonyl)amino)cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole**

A mixture of *trans*-2-(1-(4-(*N-tert*-butyloxycarbonyl)amino)cyclohexyl)acetaldehyde (6.8g, 25.2 mmol), 2,3-dihydro-1*H*-isoindole (3.00g, 25.2 mmol) (J. Borrstein, J.E. Shields and A.P. Boisselle; *Org. Syn. Coll. Vol. V.;* Baumgarten, H.E., Ed; Wiley: New York, **1973**; pp 406 – 408), sodium triacetoxyborohydride (8.0g, 37.8 mmol) in 1,2-dichloroethane (100ml) was stirred at 20°C for 16h. Resulting solution was partitioned between saturated $NaHCO_3$ (500ml) and dichloromethane (200ml), and the combined extracts were saturated $NaHCO_3$), dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel eluting with ethyl acetate hexane mixtures to afford the title compound (6.5g, 75%) as a pale pink solid.

^{1}H NMR ($CDCl_3$) δ: 1.00 – 1.11 (4H, m), 1.30 – 1.60 (3H, m), 1.44 (9H, s), 1.80 – 1.82 (2H, m), 1.98 – 2.04 (2H, m), 2.72 (2H, t, J = 8 Hz), 3.37 (1H, m), 3.90 (4H, s), 4.35 (1H, s) and 7.18 (4H, s).

Description 4

***trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole**

A mixture of *trans*-2-(2-(1-(4-(*N- tert*-butyloxycarbonyl)amino)cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole (6.4g, 18.6 mmol), trifluoroacetic acid (10ml) and dichloromethane (100ml) was stirred at *ca* 40°C for 45 min. Resulting solution was evaporated *in vacuo* and the residue partitioned between water (200ml) and ethyl acetate (100ml). The aqueous layer was washed with ethyl acetate (100 ml) then basified to pH 14 with 2M NaOH, and extracted with dichloromethane (3 x 300ml). The combined organic extracts, dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound (4.01g, 90%) as a pale brown solid.

Mass spectrum (API$^+$): Found 245 (MH^+). $C_{16}H_{24}N_2$ requires 244.

^{1}H NMR ($CDCl_3$) δ: 0.93 – 1.20 (4H, m), 1.20 – 1.40 (1H, m), 1.50 – 1.60 (4H, m), 1.70 – 1.90 (4H, m), 2.60 (1H, m), 2.73 (2H, t, J = 8 Hz), 3.90 (4H, s) and 7.18 (4H, s).

Description 5

2-(*tert*-Butyloxycarbonyl)-5-hydroxy-2,3-dihydro-1*H*-isoindole

5-Methoxy-2,3-dihydro-1*H*-isoindole (28.7 g) was dissolved in 48% hydrobromic acid (620 ml) and the mixture heated under reflux for 2h, then cooled and evaporated to give 5-hydroxy-2,3-dihydro-1*H*-isoindole hydrobromide (29.5 g) as a brown solid.
To the above hydrobromide salt (29.5 g) in tetrahydrofuran (215 ml) and water (215 ml) at 0°C was added triethylamine (48ml) followed by di-*tert*-butyl dicarbonate (33 g). The reaction was stirred for 18 h, then worked up as for Description 1 above and chromatographed on silica gel, to give the title compound (13.2 g, 29%) as a brown solid.

Mass spectrum (API$^+$): Found 136 [M-Boc]H$^+$. $C_{13}H_{17}NO_3$ requires 235.

Description 6

2-(*tert*-Butyloxycarbonyl)-5-cyano-2,3-dihydro-1*H*-isoindole

Trifluoromethanesulfonic anhydride (9.6 ml) was added to a solution of 2-(*tert*-butyloxycarbonyl)-5-hydroxy-2,3-dihydro-1*H*-isoindole (12.2 g) and triethylamine (8.7 ml) at -20°C under argon. The reaction was stirred overnight at room temperature, then the crude product isolated by extraction and chromatographed to give 2-(*tert*-butyloxycarbonyl)-5-trifluoromethanesulfonyloxy-2,3-dihydro-1*H*-isoindole (12.7 g), which was dissolved in DMF (180 ml). To this solution was added zinc cyanide (3.7 g) and *tetrakis*-triphenylphosphine palladium (0) (3.7 g) and the mixture was heated at 100°C for 4 h. Work-up and chromatography on silica gel gave the title compound as a solid (7.6 g, 83%).

Mass spectrum (API$^+$): Found 145 [M-Boc]H$^+$. $C_{14}H_{16}N_2O_2$ requires 244.

Description 7

5-Cyano-2,3-dihydro-1*H*-isoindole

A mixture of 2-(*tert*-butyloxycarbonyl)-5-cyano-2,3-dihydro-1*H*-isoindole (7.6 g) and trifluoroacetic acid (20 ml) in dichloromethane (200 ml) was heated at 40°C for 0.5 h, then cooled and evaporated *in vacuo* and the residue partitioned between dichloromethane and 2M sodium hydroxide. The aqueous phase was re-extracted with dichloromethane and the combined organics dried and evaporated to give the title compound as a pink solid (4.24 g, 94%).

Mass spectrum (API$^+$): Found 145 MH$^+$. $C_9H_8N_2$ requires 144.

Description 8

2-(*tert*-Butyloxycarbonyl)-5-methanesulfonyloxy-2,3-dihydro-1*H*-isoindole

The title compound (2.3 g, 69%) was prepared from 2-(*tert*-butyloxycarbonyl)-5-hydroxy-2,3-dihydro-1*H*-isoindole (2.5 g) and methanesulfonyl chloride (1.7 ml) using the method of Description 6.

Mass spectrum (API$^+$): Found 214 [M-Boc]H$^+$. $C_{14}H_{19}NO_5S$ requires 313.

Description 9

5-Methanesulfonyloxy-2,3-dihydro-1*H*-isoindole

The title compound (1.4 g, 90%) was prepared from 2-(*tert*-butyloxycarbonyl)-5-methanesulfonyloxy-2,3-dihydro-1*H*-isoindole using the method of Description 7.

Mass spectrum (API$^+$): Found 214 MH$^+$. $C_9H_{11}NO_3S$ requires 213.

Example 1

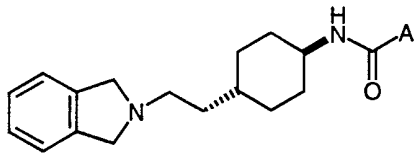
***trans*-2-(2-(1-(4-(4-quinolinyl)carboxamido)cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole**

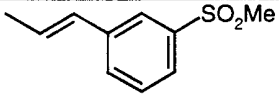
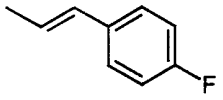
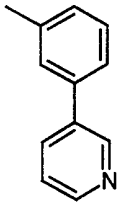
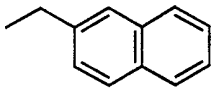
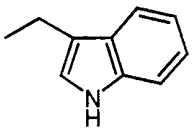
A mixture of *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole (0.1g : 0.35 mmol), 4-quinolinecarboxylic acid (0.061g ; 0.35 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.067g ; 0.35 mmol), 1-hydroxybenzotriazole (catalytic amount) and dichloromethane (4ml) was shaken for 16h. Saturated aqueous sodium bicarbonate (4ml) was added and the mixture shaken for 0.25h. Chromatography of the organic layer on silica eluting with 30 – 100% ethyl acetate in hexane and 0 – 10% methanol in ethyl acetate gradient elution gave the title compound as a solid.

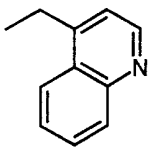
Mass spectrum (API$^+$): Found 400 (MH$^+$). $C_{26}H_{29}N_3O$ requires 399.

^{1}H NMR ($CDCl_3$) δ: 1.10 – 1.50 (5H, m), 1.50 – 1.60 (2H, m), 1.89 – 1.93 (2H, m), 2.18 – 2.22 (2H, m), 2.73 – 2.79 (2H, m), 3.92 (4H, s), 4.05 (1H, m), 5.94 (1H, J = 8 Hz), 7.20 (4H, s), 7.39 (1H, d, J = 4 Hz), 7.60 (1H, dt, J = 8, 1 Hz), 7.75 (1H, dt, J = 5, 1Hz), 8.14 (1H, d, J = 8 Hz), 8.16 (1H, d, J = 8 Hz) and 8.91 (1H, d, J = 4 Hz).

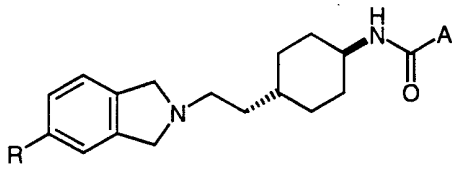
The following compounds were prepared according to the procedure of Example 1



Example	A	Characterising Data
		Mass spectrum (API^+) ^1H NMR δ ($CDCl_3$ or d_6-DMSO)
2		MH^+ 453. $C_{26}H_{32}N_2O_3S$ requires 452. 1.10 – 1.28 (4H, m), 1.40 – 1.50 (1H, m), 1.50 – 1.55 (2H, m), 1.85 – 1.90 (2H, m), 2.04 – 2.09 (2H, m), 2.75 (2H, t, J = 8 Hz), 3.07 (3H, s), 3.86 (1H, m), 3.91 (4H, s), 5.50 (1H, d, J = 8 Hz), 6.48 (1H, d, J = 16 Hz), 7.19 (4H, s), 7.58 (1H, t, J = 8 Hz), 7.62 (1H, d, J = 16 Hz), 7.72 (1H, d, J = 8 Hz), 7.89 (1H, d, J = 8 Hz) and 8.09 (1H, s).
3		MH^+ 393. $C_{25}H_{29}N_2FO$ requires 392. 1.10 – 1.20 (4h, M), 1.40 – 1.50 (1H, m), 1.50 – 1.55 (2H, m), 1.85 – 1.90 (2H, m), 2.04 – 2.08 (2H, m), 2.75 (2H, t, J = 8 Hz), 3.86 (1H, m), 3.92 (4H, s), 5.39 (1H, d, J = 8 Hz), 6.26 (1H, d, J = 16 Hz), 7.05 (2H, t, J = 8 Hz), 7.20 (4H, s), 7.45 – 7.49 (2H, m) and 7.57 (1H, d, J = 16 Hz).
4		MH^+ 426. $C_{28}H_{31}N_3O$ requires 425. 1.16 – 1.30 (4H, m), 1.40 – 1.50 (1H, m), 1.50 – 1.60 (2H, m), 1.88 – 1.91 (2H, m), 2.12 – 2.16 (2H, m), 2.76 (2H, t, J = 8 Hz), 3.92 (4H, s), 3.98 (1H, m), 5.94 (1H, d, J = 8 Hz), 7.19 (4H, s), 7.40 (1H, m), 7.65 (2H, m), 7.85 – 7.90 (3H, m), 8.60 – 8.65 (1H, m) and 8.85 – 8.88 (1H, m).
5		MH^+ 413. $C_{28}H_{32}N_2O$ requires 412. 0.93 – 1.11 (4H, m), 1.24 – 1.28 (1H, m), 1.42 – 1.48 (2H, m), 1.73 – 1.77 (2H, m), 1.88 – 1.91 (2H, m), 2.70 (2H, t, J = 8 Hz), 3.70 (2H, s), 3.74 (1H, m), 3.89 (4H, s), 5.17 (1H, d, J = 8 Hz), 7.17 (4H, s), 7.36 (1H, dd, J = 8, 2 Hz), 7.47 – 7.50 (2H, m), 7.70 (1H, s) and 7.80 – 7.90 (3H, m).
6		MH^+ 402. $C_{26}H_{31}N_3O$ requires 401. 0.86 – 0.94 (2H, m), 1.03 – 1.07 (2H, m), 1.24 – 1.28 (1H, m), 1.40 – 1.48 (2H, m), 1.70 – 1.74 (2H, m), 1.84 – 1.88 (2H, m), 2.67 (2H, t, J = 8 Hz), 3.70 (2H, s), 3.74 (1H, m), 3.86 (4H, s), 5.46 (1H, d, J = 8 Hz), 7.12 – 7.14 (1H, m), 7.16 (4H, s), 7.23 – 7.26 (2H, m), 7.39 (1H, d, J = 8 Hz), 7.54 (1H, d, J = 8 Hz) and

		8.21 (1H, s).
7		MH^+ 414. $C_{27}H_{31}N_3O$ requires 413. 0.85 – 0.94 (2H, m), 0.94 – 1.10 (2H, m), 1.20 – 1.30 (1H, m), 1.35 – 1.50 (2H, m), 1.68 – 1.80 (2H, m), 1.82 – 1.90 (2H, m), 2.68 (2H, t, J = 8 Hz), 3.74 (1H, m), 3.88 (4H, s), 3.97 (2H, s), 5.12 (1H, br s), 7.14 (4H, s), 7.33 (1H, d, J = 3 Hz), 7.60 (1H, m), 7.75 (1H, m), 7.97 (1H, d, J = 7 Hz), 8.14 (1H, d, J = 7 Hz), 8.88 (1H, d, J = 3 Hz).

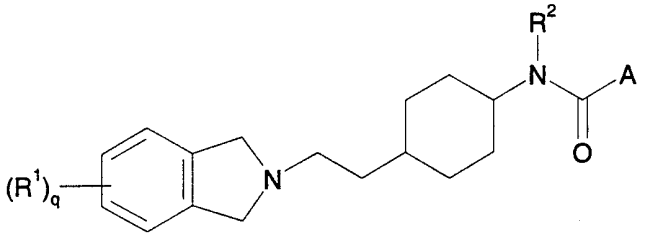
The following compounds were prepared according to the procedures of Descriptions 3 and 4 and Example 1



Example	R	A	Characterising Data
			Mass spectrum (API^+)
8	NC-	3-indolyl(7-aza)	Found 414. $C_{25}H_{27}N_5O$ requires 413.
9	NC-	-CH=CHPh(4-F)	Found 418. $C_{26}H_{28}FN_3O$ requires 417.
10	NC-	-CH=CHPh(3-OMe)	Found 430. $C_{27}H_{31}N_3O_2$ requires 429.
11	NC-	-CH=CHPh(2-OMe)	Found 430. $C_{27}H_{31}N_3O_2$ requires 429.
12	NC-	-CH=CHPh(2-CN)	Found 425. $C_{27}H_{28}N_4O$ requires 424.
13	NC-	-CH=CH(3-thienyl)	Found 406. $C_{24}H_{27}N_3OS$ requires 405.
14	NC-	-CH=CH(2-thienyl)	Found 406. $C_{24}H_{27}N_3OS$ requires 405.
15	$MeSO_2O$-	-CH=CHPh(4-F)	Found 487. $C_{26}H_{31}FN_2O_4S$ requires 486.
16	$MeSO_2O$-	5-quinolinyl(2-Me)	Found 508. $C_{28}H_{33}N_3O_4S$ requires 507.
17	$MeSO_2O$-	-Ph(3-(1-pyrazolyl))	Found 509. $C_{27}H_{32}N_4O_4S$ requires 508.

Claims :

1. A compound of formula (I) :



Formula (I)

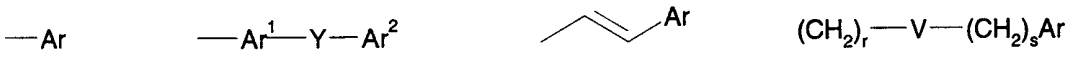
wherein:

R^1 represents a substituent selected from: a hydrogen or halogen atom; a hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-4}alkyl, C_{1-4}alkoxy, arylC_{1-4}alkoxy, C_{1-4}alkylthio, C_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkylC_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfonyloxy, C_{1-4}alkylsulfonylC_{1-4}alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-4}alkyl, C_{1-4}alkylsulfonamido, C_{1-4}alkylamido, C_{1-4}alkylsulfonamidoC_{1-4}alkyl, C_{1-4}alkylamidoC_{1-4}alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-4}alkyl, arylcarboxamidoC_{1-4}alkyl, aroyl, aroylC_{1-4}alkyl, or arylC_{1-4}alkanoyl group; a group $R^3OCO(CH_2)_p$, $R^3CON(R^4)(CH_2)_p$, $R^3R^4NCO(CH_2)_p$ or $R^3R^4NSO_2(CH_2)_p$ where each of R^3 and R^4 independently represents a hydrogen atom or a C_{1-4}alkyl group or R^3R^4 forms part of a C_{3-6}azacyloalkane or C_{3-6}(2-oxo)azacycloalkane ring and p represents zero or an integer from 1 to 4; or a group Ar^3-Z, wherein Ar^3 represents an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring and Z represents a bond, O, S , or CH_2;

R^2 represents a hydrogen atom or a C_{1-4}alkyl group;

q is 1 or 2;

A represents a group of the formula (a), (b), (c) or (d) :



(a) (b) (c) (d)

wherein

Ar represents an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring; or an optionally substituted bicyclic ring system;

Ar^1 and Ar^2 each independently represent an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring; and

Y represents a bond, -NHCO-, -CONH-, $-CH_2-$, or $-(CH_2)_mY^1(CH_2)_n-$, wherein Y^1 represents O, S, SO_2, or CO and m and n each represent zero or 1 such that the sum of m+n is zero or 1; providing that when A represents a group of formula (a), any substituent

present in Ar *ortho* to the carboxamide moiety is necessarily a hydrogen or a methoxy group;

r and s independently represent an integer from zero to 3 such that the sum of r and s is equal to an integer from 1 to 4;

V represents a bond, O or S;

and salts thereof.

2. A compound according to claim 1 wherein q represents 1.

3. A compound according to any of the preceding claims wherein rings Ar, Ar^1, or Ar^2 are each independently optionally substituted by one or more substituents selected from: a hydrogen or halogen atom, cyano, methoxy, methylenedioxy, acetyl, acetylamino, methylsulfonyl, methylsulfonyloxy, methylaminosulfonyl, methylsulfonylamino, or methylaminocarbonyl group.

4. A compound of formula (I) which is:

trans-2-(2-(1-(4-(4-quinolinyl)carboxamido)cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;

trans-(*E*)-2-(2-(1-(4-(3-(3-methanesulfonyl)phenylpropenoyl)amino)cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;

trans-(*E*)-2-(2-(1-(4-(3-(4-fluoro)phenylpropenoyl)amino)cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;

trans-2-(2-(1-(4-(3-(3-pyridyl)benzamido))cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;

trans-2-(2-(1-(4-(2-naphthyl)acetamido))cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;

trans-2-(2-(1-(4-(3-indolyl)acetamido))cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;

trans-2-(2-(1-(4-(4-quinolinyl)acetamido))cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;

trans-5-Cyano-2-(2-(1-(4-(3-pyrrolo[2,3-b]pyridyl)carboxamido)cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;

trans-(*E*)-5-Cyano-2-(2-(1-(4-(3-(4-fluoro)phenylpropenoyl)amino)cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;

trans-(*E*)-5-Cyano-2-(2-(1-(4-(3-(3-methoxy)phenylpropenoyl)amino)cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;

trans-(*E*)-5-Cyano-2-(2-(1-(4-(3-(2-methoxy)phenylpropenoyl)amino)cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;

trans-(*E*)-5-Cyano-2-(2-(1-(4-(3-(2-cyano)phenylpropenoyl)amino)cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;

trans-(*E*)-5-Cyano-2-(2-(1-(4-(3-(3-thiophenyl)propenoyl)amino)cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;

trans-(*E*)-5-Cyano-2-(2-(1-(4-(3-(2-thiophenyl)propenoyl)amino)cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;

trans-(*E*)-5-Methanesulfonyloxy-2-(2-(1-(4-(3-(4-fluoro)phenylpropenoyl)amino) cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;

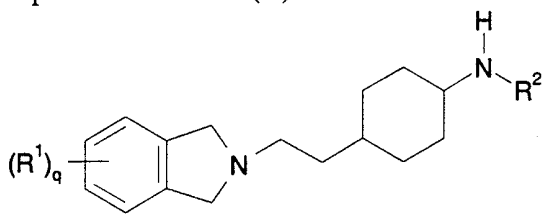
trans-5-Methanesulfonyloxy-2-(2-(1-(4-(5-(2-methyl)quinolinyl)carboxamido) cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;

trans-5-Methanesulfonyloxy-2-(2-(1-(4-(3-(3-(1-pyrazolyl)benzamido)))

cyclohexyl)ethyl)-2,3-dihydro-1*H*-isoindole;
or a salt thereof.

5. A process for preparing compounds of formula (I) which process comprises :

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



Formula (II)

wherein R^1, R^2, and q are as hereinbefore defined,
with a compound of formula (III):

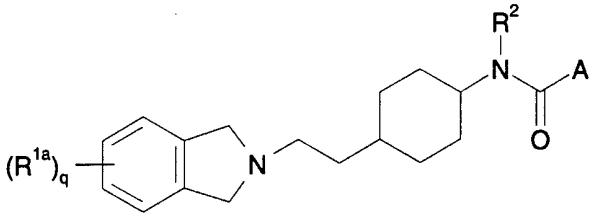
A-COX

Formula (III)

wherein A is as hereinbefore defined and X is a halogen atom or the residue of an activated ester;

(b) to prepare a compound of formula (I) by reacting a compound of formula (II) with a compound A-Br, or A-I, or A-OSO_2CF_3 in the presence of carbon monoxide and a catalyst;

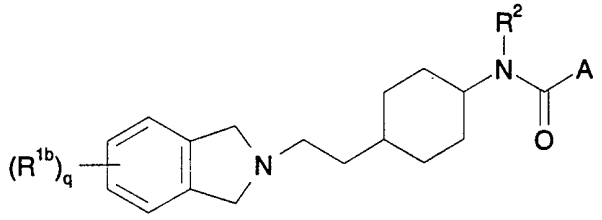
(c) to prepare a compound of formula (I) wherein R^1 is Ar^3-Z and Z is a bond, reacting a compound of formula (IV):



Formula (IV)

wherein A, R^2, and q are as hereinbefore defined, one R^{1a} represents a group W wherein W is a halogen atom or a trifluoromethylsulfonyloxy group, or W is a group M selected from a boron derivativeor a metal function, and when q is 2 the other R^{1a} is R^1; with a compound Ar^3-W^1, wherein W^1 is a halogen atom or a trifluoromethylsulfonyloxy group when W is a group M or W^1 is a group M when W is a halogen atom or a trifluoromethylsulfonyloxy group;

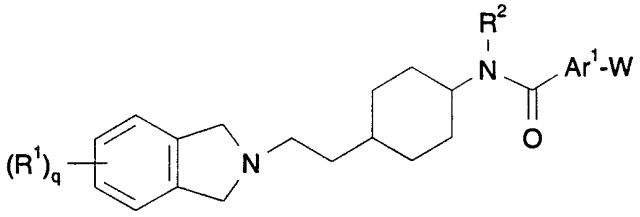
(d) to prepare a compound of formula (I) wherein R^1 is Ar^3-Z and Z is O or S, reacting a compound of formula (V):



Formula (V)

wherein A, R^2, and q are as hereinbefore defined, one R^{1b} represents a group ZH and when q is 2 the other R^{1b} represents R^1; with a reagent serving to introduce the group Ar^3;

(e) to prepare a compound of formula (I) where Y is a bond, reaction of a compound of formula (VI):



Formula (VI)

wherein R^1, R^2, q, Ar^1 and W are as hereinbefore defined, with a compound Ar^2-W^1, wherein W^1 is a halogen atom or a trifluoromethylsulfonyloxy group when W is a group M, or W^1 is a group M when W is a halogen atom or a trifluoromethylsulfonyloxy group.

(f) interconversion of one compound of formula (I) to a different compound of formula (I) e.g. (i) alkylation of a compound (I) wherein R^2 represents hydrogen, (ii) conversion of one R^1 from alkoxy (e.g.methoxy) to hydroxy, or (iii) conversion of R^1 from hydroxy to sulfonyloxy, eg alkylsulfonyloxy or trifluoromethanesulfonyloxy; (iv) conversion of a compound wherein Y represents S to a compound wherein Y is SO_2 or (v) conversion of Y from CO to CH_2;

(g) separation of *cis*- and *trans*- isomers of compounds of formula (I) by conventional methods;

and optionally thereafter forming a salt of formula (I).

6. A pharmaceutical composition comprising a compound of formula (I) as claimed in any of claims 1 to 4 or a physiologically acceptable salt thereof and a physiologically acceptable carrier therefor.

7. The use of a compound of formula (I) as claimed in any of claims 1 to 4 or a physiologically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition which requires modulation of a dopamine receptor.

8. Use acording to claim 7 wherein the dopamine receptor is a dopamine D_3 receptor.

9. Use according to claim 7 or claim 8 wherein a dopamine antagonist is required.

10. Use according to any of claims 7 to 9 wherein the condition is a psychotic condition.

11. Use according to claim 10 wherein the psychotic condition is schizophrenia.

12. A method of treating a condition which requires modulation of a dopamine receptor which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as claimed in claim 1 or a physiologically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/EP 99/07762

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 C07D209/44 C07D409/12 C07D403/12 A61K31/4709
A61K31/4427 A61K31/4035

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 98 50364 A (BRANCH CLIVE LESLIE ;JOHNSON CHRISTOPHER NORBERT (GB); STEMP GEOFF) 12 November 1998 (1998-11-12) the whole document ---	1,6-12
A	WO 98 06699 A (NASH DAVID JOHN ;STEMP GEOFFREY (GB); SMITHKLINE BEECHAM PLC (GB)) 19 February 1998 (1998-02-19) cited in the application the whole document ---	1,6-12
A	WO 97 43262 A (SMITHKLINE BEECHAM PLC ;STEMP GEOFFREY (GB); JOHNS AMANDA (GB)) 20 November 1997 (1997-11-20) cited in the application the whole document ---	1,6-12

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

[X] 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
31 January 2000	11/02/2000

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	Bosma, P

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INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/EP 99/07762

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 21628 A (MERCK SHARP & DOHME ;BROUGHTON HOWARD BARFF (GB); KULAGOWSKI JANUS) 29 September 1994 (1994-09-29) the whole document ---	1,6-12
A	EP 0 431 580 A (WARNER LAMBERT CO) 12 June 1991 (1991-06-12) cited in the application claims; examples -----	1,6-12

2

INTERNATIONAL SEARCH REPORT

...rnational application No.
PCT/EP 99/07762

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:

Remark: Although claim 12
is 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 compounds/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 II Observations where unity of invention is lacking (Continuation of item 2 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

Int. onal Application No
PCT/EP 99/07762

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		DE 69017606 T	06-07-1995
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		IE 66740 B	07-02-1996
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		NO 178262 B	13-11-1995
		NZ 236335 A	26-05-1992
		PT 96085 A,B	30-09-1991