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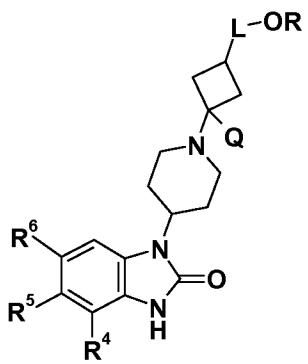
(54) Title: 1-(1-CYCLOBUTYL-4-PIPERIDINYL)-1,3-DIHYDRO-2H-BENZIMIDAZOL-2-ONE DERIVATIVES WHICH HAVE ACTIVITY ON THE ML RECEPTOR AND THEIR USE IN MEDICINE



(I)

(57) Abstract: Compounds of formula I or a salt thereof are provided wherein R^4, R^5, R^6, Q, L and R are as defined in the description. Uses of the compounds as medicaments and in the manufacture of medicaments for treating psychotic disorders and cognitive impairments are disclosed. The invention further discloses pharmaceutical compositions comprising the compounds.

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(1-BUTYL-4-PIPERIDINYL)-1,3-DIHYDRO-2H-BENZIMIDAZOL-2-ONE DERIVATIVES WHICH HAVE ACTIVITY ON THE ML RECEPTOR AND THEIR USE IN MEDICINE

This invention relates to novel compounds, pharmaceutical compositions containing them and their use in therapy, in particular as antipsychotic agents.

Muscarinic acetylcholine receptors are members of the G protein coupled receptor superfamily which mediate the actions of the neurotransmitter acetylcholine in both the central and peripheral nervous system. Five muscarinic receptor subtypes have been cloned, M_1 to M_5. The muscarinic M_1 receptor is predominantly expressed in the cerebral cortex and hippocampus, although it is also expressed in the periphery e.g. exocrine glands.

Muscarinic receptors in the central nervous system, especially M_1, play a critical role in mediating higher cognitive processing. Diseases associated with cognitive impairments, such as Alzheimer's disease, are accompanied by loss of cholinergic neurons in the basal forebrain. Furthermore, in animal models, blockade or lesion of central cholinergic pathways results in profound cognitive deficits.

Cholinergic replacement therapy has largely been based on the use of acetylcholinesterase inhibitors to prevent the breakdown of endogenous acetylcholine. These compounds have shown efficacy versus symptomatic cognitive decline in the clinic, but give rise to side effects resulting from stimulation of peripheral muscarinic receptors including disturbed gastrointestinal motility and nausea.

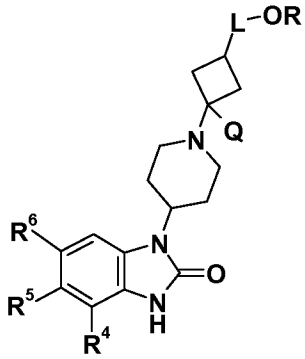
The dopamine hypothesis of schizophrenia suggests that excess dopaminergic stimulation is responsible for the positive symptoms of the disease, hence the utility of dopamine receptor antagonists to reduce psychotic symptoms. However, conventional dopamine receptor antagonists can cause extrapyramidal side effects (EPS) in patients, including tremor and tardive dyskinesias.

M_1 receptor agonists have been sought for the symptomatic treatment of cognitive decline. More recently, a number of groups have shown that muscarinic receptor agonists display an atypical antipsychotic-like profile in a range of pre-clinical paradigms. The muscarinic agonist, xanomeline, reverses a number of dopamine driven behaviours, including amphetamine induced locomotion in rats, apomorphine induced climbing in mice, dopamine agonist driven turning in unilateral 6-OH-DA lesioned rats and amphetamine-induced motor unrest in monkeys (without EPS liability). It also has been shown to inhibit A10, but not A9, dopamine cell firing and conditioned avoidance and induces *c-fos* expression in prefrontal cortex and nucleus accumbens, but not in striatum in rats. These data are all suggestive of an atypical antipsychotic-like profile.

Xanomeline has also been shown to reduce psychotic symptoms such as suspiciousness, hallucinations and delusions in Alzheimer's patients. However, the relatively non-selective nature of the compound gives rise to dose-limiting peripheral cholinergic side effects.

Certain M_1 receptor agonists are known, for example in WO2007/036718, WO2007/036715, WO2007/036711, WO2007/107566, WO2007/107567 and WO2007/107565. We have now found a novel group of compounds which are M_1 receptor agonists.

In a first aspect therefore, the invention provides a compound of formula (I) or a salt thereof:



(I)

wherein:

- R^4 is selected from the group consisting of hydrogen and fluoro;
- R^5 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6}alkyl (optionally substituted with one or more fluorine atoms), and C_{1-6}alkoxy (optionally substituted with one or more fluorine atoms);
- R^6 is selected from the group consisting of hydrogen, halogen, cyano, C_{1-6}alkyl (optionally substituted with one or more fluorine atoms), C_{1-6}alkylsulfonyl, C_{3-6}cycloalkyl (optionally substituted with one or more fluorine atoms), and C_{1-6}alkoxy (optionally substituted with one or more fluorine atoms);
- Q is selected from the group consisting of hydrogen and C_{1-6}alkyl;
- L is selected from the group consisting of a bond, CH_2 and $(CH_2)_2$; and
- R is selected from the group consisting of C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkyl and C_{2-6}alkynyl, any alkyl or cycloalkyl group being optionally substituted by one or more fluorine atoms.

As used herein, the term “alkyl” refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C_{1-6}alkyl means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms. C_{1-4}alkyl means a straight or branched alkyl containing at least 1, and at most 4, carbon atoms. C_{1-2}alkyl means a straight or branched alkyl containing at least 1, and at most 2, carbon atoms. Examples of “C_{1-6}alkyl” groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isobutyl, isopropyl, t-butyl and 1,1-dimethylpropyl.

As used herein, the term "alkoxy" refers to a straight or branched alkoxy group containing the specified number of carbon atoms. For example, C_{1-6}alkoxy means a straight or branched alkoxy group containing at least 1, and at most 6, carbon atoms. C_{1-4}alkoxy means a straight or branched alkoxy group containing at least 1, and at most 4, carbon atoms. C_{1-2}alkoxy means a straight or branched alkoxy group containing at least 1, and at most 2, carbon atoms. Examples of "C_{1-6}alkoxy" as used herein include, but are not limited to, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 1-methylethyl-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy or hexyloxy.

As used herein, the term "cycloalkyl" refers to a non-aromatic hydrocarbon ring containing the specified number of carbon atoms. For example, C_{3-6}cycloalkyl means a non-aromatic carbocyclic ring containing at least three, and at most six, ring carbon atoms. Examples of "C_{3-6}cycloalkyl" as used herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

As used herein, the term "halogen" (or the abbreviated form "halo") refers to the elements fluorine (which may be abbreviated to "fluoro" or "F"), chlorine (which may be abbreviated to "chloro" or "Cl"), bromine (which may be abbreviated to "bromo" or "Br") and iodine (which may be abbreviated to "iodo" or "I"). Examples of halogens are fluorine, chlorine and bromine.

As used herein, the term "alkynyl" refers to a linear or branched hydrocarbon group containing one or more carbon-carbon triple bonds and the specified number of carbon atoms. For example, C_{2-6}alkynyl means a linear or branched hydrocarbon group containing one or more carbon-carbon triple bonds and at least two, and at most six, carbon atoms. Examples of "alkynyl" as used herein include, but are not limited to, include ethynyl, propynyl, butynyl, pentynyl and hexynyl.

As used herein, the term "C_{1-6}alkylsulfonyl" refers to a group -SO_2-C_{1-6}alkyl wherein the term "alkyl" is as hereinbefore defined.

As used herein, the term "C_{3-6}cycloalkylC_{1-6}alkyl" refers to a group C_{3-6}cycloalkyl-C_{1-6}alkyl, wherein the terms "alkyl" and "cycloalkyl" are as hereinbefore defined.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated. For example, there may be 1, 2 or 3 substituents on a given substituted group. For example, if R is a C_{1-6}alkyl group, it may be substituted by 1, 2, 3 or 4 fluoro groups; and if R is a C_{1-6}alkoxy group, it may be substituted by 1, 2, 3 or 4 fluoro groups.

In one embodiment, R^6 is selected from hydrogen, halogen, cyano, C_{1-6}alkyl (optionally substituted with one, two or three fluorine atoms), C_{1-6}alkylsulfonyl, C_{3-6}cycloalkyl (optionally substituted with one, two or three fluorine atoms), and C_{1-6}alkoxy (optionally substituted with one, two or three fluorine atoms).

In one embodiment, R^6 is C_{1-6}alkyl.

In one embodiment of the invention, R^6 is selected from chloro, bromo, fluoro, methyl, ethyl, isopropyl, methoxy, cyclopropyl, trifluoromethoxy and trifluoromethyl, for example chloro, fluoro, methyl, cyclopropyl, methoxy, trifluoromethoxy and trifluoromethyl.

In one embodiment, R^6 is selected from chloro, fluoro, methyl, methoxy, trifluoromethoxy, cyclopropyl and trifluoromethyl.

In one embodiment, R^6 is selected from methyl, fluoro, chloro, methoxy and cyclopropyl.

In one embodiment, R^6 is selected from chloro, methyl and methoxy. In one embodiment, R^6 is methyl.

In one embodiment, R^5 is selected from hydrogen and halogen.

In one embodiment, R^5 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6}alkyl (optionally substituted with one, two or three fluorine atoms), and C_{1-6}alkoxy (optionally substituted with one, two or three fluorine atoms).

In one embodiment, R^5 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-4}alkyl (optionally substituted with one or more fluorine atoms), and C_{1-4}alkoxy (optionally substituted with one or more fluorine atoms).

In one embodiment, R^5 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-2}alkyl (optionally substituted with one, two or three fluorine atoms), and C_{1-2}alkoxy (optionally substituted with one, two or three fluorine atoms).

In one embodiment, R^5 is selected from hydrogen and fluorine. In one embodiment, R^5 is hydrogen. In one embodiment, R^5 is fluorine.

In one embodiment, R^4 is hydrogen. In one embodiment, R^4 is fluoro.

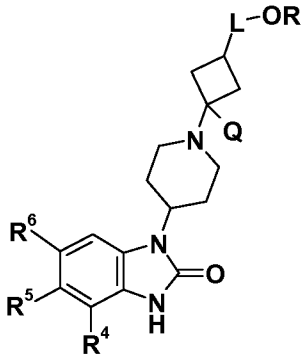
In an embodiment, Q is selected from hydrogen and C_{1-3}alkyl. In one embodiment, Q is selected from hydrogen or methyl. In one embodiment, Q is hydrogen. In one embodiment, Q is methyl.

In one embodiment, L is CH_2.

In one embodiment, R is C_{1-6}alkyl.

In one embodiment, R is selected from methyl and ethyl. In one embodiment, R is methyl. In one embodiment, R is ethyl.

In one embodiment, the invention provides a compound of formula (I') or a salt or solvate thereof:



(I')

wherein:

- R^4 is selected from the group consisting of hydrogen and fluoro;
- R^5 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6}alkyl, C_{1-6}alkyl substituted with one or more fluorine atoms, C_{1-6}alkoxy, and C_{1-6}alkoxy substituted with one or more fluorine atoms;
- R^6 is selected from the group consisting of hydrogen, halogen, cyano, C_{1-6}alkyl, C_{1-6}alkyl substituted with one or more fluorine atoms, C_{1-6}alkylsulfonyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl substituted with one or more fluorine atoms, C_{1-6}alkoxy and C_{1-6}alkoxy substituted with one or more fluorine atoms;

Q is selected from the group consisting of hydrogen and C_{1-6}alkyl;

L is selected from the group consisting of a bond, CH_2 and $(CH_2)_2$;

R is selected from the group consisting of C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkyl and C_{2-6}alkynyl, any alkyl or cycloalkyl group being optionally substituted by one or more fluorine atoms.

All features and embodiments for formula (I) apply to compounds of formula (I') mutatis mutandis. Hereinafter, all references to compounds of formula (I) include compounds of formula (I').

In one embodiment the salt of the compound of formula (I) is a pharmaceutically acceptable salt. In one embodiment, the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof.

It will be appreciated that for use in medicine the salts of formula (I) should be pharmaceutically acceptable. Suitable salts will be apparent to those skilled in the art and

include for example mono- or di- basic salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric, sulfamic phosphoric, hydroiodic, phosphoric or metaphosphoric acid; and with organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, formic, propionic, glycolic, gluconic, maleic, succinic, (1R)-(-)-10-camphorsulphonic, (1S)-(+)-10-camphorsulphonic, isothionic, mucic, gentisic, isonicotinic, saccharic, glucuronic, furoic, glutamic, ascorbic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, stearic, sulfinilic, alginic, galacturonic and arylsulfonic, for example naphthalene-1,5-disulphonic, naphthalene-1,3-disulphonic, benzenesulfonic, and p-toluenesulfonic, acids. Other non-pharmaceutically acceptable salts e.g. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. The compounds of the present invention may be in the form of their free base or pharmaceutically acceptable salts thereof, particularly the monohydrochloride, monoformate or monotrifluoroacetate salts. Certain of the compounds of formula (I) may form acid addition salts with less than one (for example, 0.5 equivalent of a dibasic acid) or one or more equivalents of an acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms thereof.

Solvates of the compounds of formula (I) and solvates of the salts of compounds of formula (I) are included within the scope of the present invention. As used herein, the term “solvate” refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Those skilled in the art of organic chemistry will appreciate that many organic componds can form such complexes with solvents in which they are reacted or from which they are precipitated or crystallised. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvant. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water. Where the solvent used is water such a solvate may then also be referred to as a hydrate.

The compounds of formula (I) may have the ability to crystallise in more than one form. This is a characteristic known as polymorphism, and it is understood that such polymorphic forms (“polymorphs”) are within the scope of formula (I). Polymorphism generally can occur as a response to changes in temperature or pressure or both and can also result from variations in the crystallisation process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility, and melting point.

It will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula (I), which may be made prior to a final deprotection stage, may not

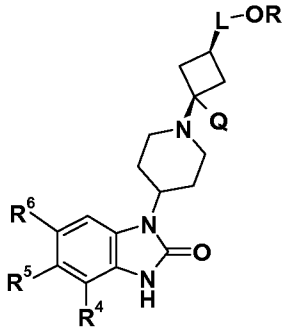
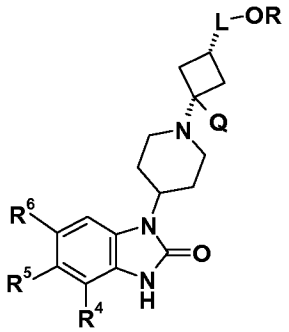
possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". Further, certain compounds of the invention may act as prodrugs of other compounds of the invention. All protected derivatives and prodrugs of compounds of the invention are included within the scope of the invention. Examples of suitable protecting groups for the compounds of the present invention are described in Drugs of Today, Volume 19, Number 9, 1983, pp 499 – 538 and in Topics in Chemistry, Chapter 31, pp 306 – 316 and in "Design of Prodrugs" by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference). It will further be appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties", for example as described by H. Bundgaard in "Design of Prodrugs" (the disclosure in which document is incorporated herein by reference) may be placed on appropriate functionalities when such functionalities are present within compounds of the invention. Possible prodrugs for some compounds of the invention include: esters, carbonate esters, hemi-esters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides, carbamates, azo-compounds, phosphamides, glycosides, ethers, acetals and ketals.

Hereinafter, compounds of formula (I) (whether in solvated or unsolvated form) or their pharmaceutically acceptable salts (whether in solvated or unsolvated form) or prodrugs thereof defined in any aspect of the invention (except intermediate compounds in chemical processes) are referred to as "compounds of the invention".

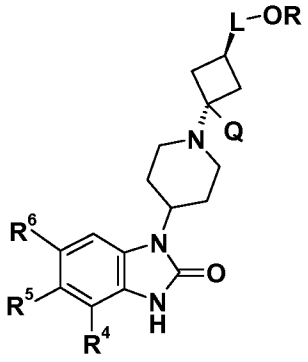
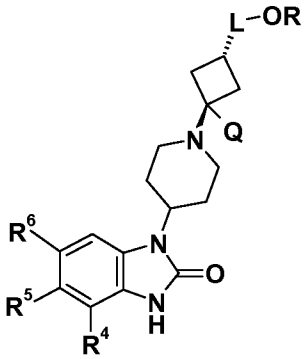
The invention also includes all suitable isotopic variations of a compound of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine and chlorine such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Certain isotopic variations of the invention, for example, those in which a radioactive isotope such as ^{3}H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e., ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the compounds of the invention can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Examples hereafter using appropriate isotopic variations of suitable reagents.

It will be appreciated that compounds of formula (I) can exist in *cis* or *trans* isomeric forms (the L-OR group on the cyclobutane ring in relation to the piperidine substituent).

It will be appreciated that the *cis* form may be drawn in the following different ways, although both represent the same isomeric form:

It will be appreciated that the *trans* form may be drawn in the following different ways, although both represent the same isomeric form:

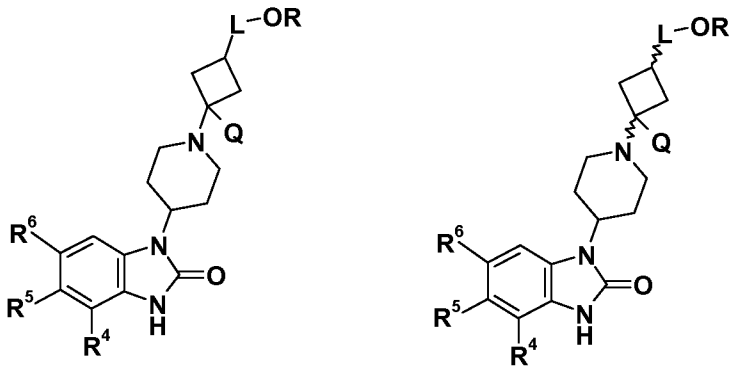



The individual isomers (*cis* and *trans*) and mixtures of these are included within the scope of the present invention. The isomers may be separated one from the other by the usual methods or by methods detailed for the example compounds below. Any given isomer may also be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

In one embodiment, the compounds of formula (I) are *trans* isomers.

In another embodiment, the compounds of formula (I) are *cis* isomers.

Mixtures of *cis*- and *trans*- compounds, or compounds in which the cis/trans conformation have not been determined, are drawn herein as shown below:

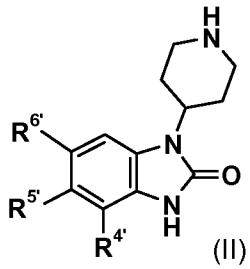


Compounds according to the invention include:
6-Methyl-1-(1-{3-[(methoxymethyl)cyclobutyl}-4-piperidinyl)-1,3-dihydro-2H-benzimidazol-2-one;
1-(1-{cis-3-[(Ethyloxy)methyl]cyclobutyl}-4-piperidinyl)-6-methyl-1,3-dihydro-2H-benzimidazol-2-one;
1-(1-{cis-3-[(Ethyloxy)methyl]cyclobutyl}-4-piperidinyl)-5-fluoro-6-methyl-1,3-dihydro-2H-benzimidazol-2-one;
5-Fluoro-6-methyl-1-(1-{cis-3-[(methyloxy)methyl]cyclobutyl}-4-piperidinyl)-1,3-dihydro-2H-benzimidazol-2-one;
4-Fluoro-6-methyl-1-{1-[4-(methoxymethyl)cyclobutyl]-4-piperidinyl}-1,3-dihydro-2H-benzimidazol-2-one;
cis 6-Methyl-1-(1-{3-[(methoxymethyl)cyclobutyl}-4-piperidinyl)-1,3-dihydro-2H-benzimidazol-2-one;
and salts thereof.

Compounds of the invention may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthesis schemes. In the following reaction schemes and hereafter, unless otherwise stated, all the groups are as defined in the first aspect. It is also recognised that in all of the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Greene and P. G. M. Wuts (1991) *Protecting Groups in Organic Synthesis*, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of the invention.

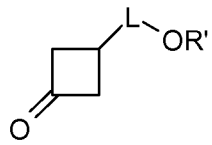
In a further aspect, the invention provides a general process (A1) for preparing compounds of formula (I) in which Q =H, which process comprises:

coupling a compound of formula (II):



(II)

wherein $R^{4'}$ is a group R^4 as defined for formula (I), or a group convertible to R^4, $R^{5'}$ is a group R^5 as defined for formula (I), or a group convertible to R^5, $R^{6'}$ is a group R^6 as defined for formula (I), or a group convertible to R^6;
with a compound of formula (III):

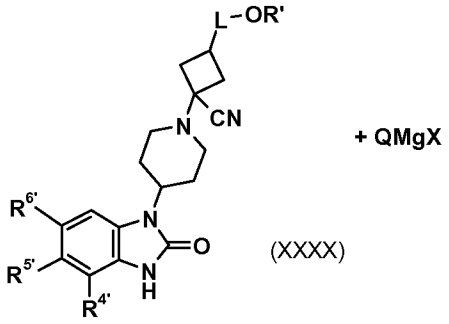


(III)

wherein L is as defined for formula (I), and R' is a group R as defined for formula (I), or a group convertible to R.

The reaction is carried out under conditions suitable for reductive alkylation. The reductive alkylation reaction is typically carried out using sodium triacetoxyborohydride in dichloroethane, optionally in the presence of triethylamine, and optionally in the presence of titanium tetraisopropoxide. Alternatively sodium cyanoborohydride can be used as the reducing reagent in solvents such as methanol or ethanol, or the reductive alkylation can be effected under catalytic hydrogenation conditions using a palladium catalyst. In a further variation, the compounds (II) and (III) can be condensed under dehydrating conditions e.g. molecular sieves or magnesium sulfate, and the resultant imine or enamine reduced using for example sodium borohydride or by catalytic hydrogenation. This reaction can generate a mixture of *cis* and *trans* isomers which can be separated by chromatography or crystallisation.

A modification of general process (A1) is required where Q is C_{1-6} alkyl. Thus, in general process (A2), a compound of formula (II) as defined above is reacted with a compound of formula (III) as defined above, in the presence of a source of cyanide, e.g. acetone cyanohydrin, to form the cyano intermediate (XXXX) (wherein L is as defined for formula (I) and $R^{4'}$, $R^{5'}$, $R^{6'}$ and R' are as defined above for formula (II), Q is C_{1-6}alkyl, and X is bromo or iodo or chloro) which can be reacted with an alkyl Grignard reagent, QMgX, to form compounds of formula (I) in which Q is C_{1-6}alkyl.

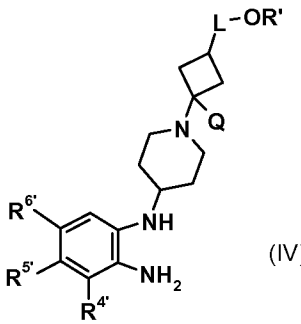


(XXXX)

In one aspect, the invention provides a compound of formula (XXXX) or salts thereof, wherein $R^{4'}$, $R^{5'}$, $R^{6'}$, L and R' are as hereinbefore defined.

This reaction can generate a mixture of *cis* and *trans* isomers which can be separated by chromatography or crystallisation.

In a further aspect, the invention provides a general process (B) for preparing compounds of formula (I) which process comprises coupling a compound of formula (IV):



(IV)

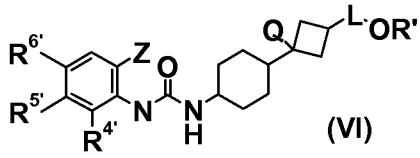
wherein L and Q are as defined for formula (I) and $R^{4'}$, $R^{5'}$, $R^{6'}$ and R' are as defined above for formula (II), with a compound of formula (V):

(V)

wherein X and Y and both represent leaving groups. X and Y can be the same or different and examples are Cl, PhO, EtO and imidazole. When X and Y are both Cl, i.e. phosgene, this reagent can be generated *in situ* e.g. from diphosgene or triphosgene. The above reaction is carried out using standard methodology e.g. reacting the diamine (IV) with the reagent (V) in an inert solvent for example dichloromethane or toluene, optionally in the presence of a base such as triethylamine or potassium carbonate, and optionally with heating. It will be appreciated that compounds of formula (IV) can be *cis* or *trans* isomers, or a mixture of isomers. If necessary, separation of *cis* and *trans* isomers after the reaction with (V) can be achieved by chromatography or crystallisation.

In one aspect, the invention provides a compound of formula (IV) or salts thereof, wherein $R^{4'}$, $R^{5'}$, $R^{6'}$, Q, L and R' are as hereinbefore defined.

In a further aspect, the invention provides a general process (C) for preparing compounds of formula (I) which process comprises treatment of a compound of formula (VI):

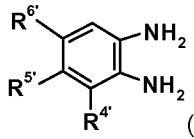


(VI)

wherein L and Q are as defined for formula (I) and $R^{4'}$, $R^{5'}$, $R^{6'}$ and R' are as defined above for formula (II), and Z is a leaving group such as bromo, iodo, chloro or triflate, with a palladium or copper catalyst (VII) to effect an intramolecular cyclisation. The cyclisation reaction can be carried out using a variety of palladium or copper reagents as described in the literature (JACS, 2003, 125, 6653; Tet. Lett., 2004, 45, 8535; or JACS, 2002, 124, 7421.) It will be appreciated that compounds of formula (VI) can be *cis* or *trans* isomers, or a mixture of isomers. If necessary, separation of *cis* and *trans* isomers after the intramolecular cyclisation can be achieved by chromatography or crystallisation.

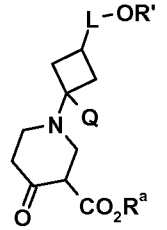
In one aspect, the invention provides a compound of formula (VI) or salts thereof, wherein $R^{4'}$, $R^{5'}$, $R^{6'}$, Q, L, R' and Z are as hereinbefore defined.

In a further aspect, the invention provides a general process (D) for preparing compounds of formula (I) which process comprises coupling a compound of formula (VIII):



(VIII)

wherein $R^{4'}$, $R^{5'}$, $R^{6'}$ and R' are as defined above for formula (II), with a compound of formula (IX):

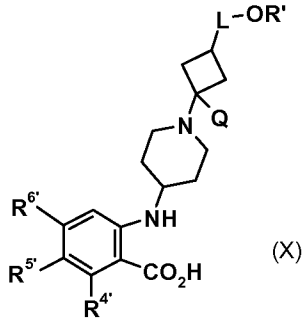


(IX)

wherein L and Q are as defined for formula (I), R' is as defined for formula (II) and R^a is a C_{1-5}alkyl group. The condensation and cyclisation reactions can be carried out under reaction conditions similar to those described in the literature for an analogous process

(US 3161645) (for example heating in an inert solvent such as xylene) followed by reduction of the piperidine double bond using for example catalytic hydrogenation over palladium or Raney nickel. It will be appreciated that compounds of formula (IX) can be *cis* or *trans* isomers, or a mixture of isomers. If necessary, separation of *cis* and *trans* isomers after the intramolecular cyclisation can be achieved by chromatography or crystallisation.

In a further aspect, the invention provides a general process (E) for preparing compounds of formula (I) which process comprises reaction of a compound of formula (X):

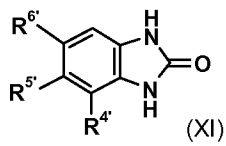


(X)

wherein L and Q are as defined for formula (I) and $R^{4'}$, $R^{5'}$, $R^{6'}$ and R' are as defined above for formula (II), with diphenylphosphoryl azide or other reagent/combination of reagents to effect the Curtius rearrangement of compound (X), followed by intramolecular cyclisation. The Curtius rearrangement is typically carried out by mixing the two reactants in an inert solvent such as toluene, optionally with heating. It will be appreciated that compounds of formula (X) can be *cis* or *trans* isomers, or a mixture of isomers. If necessary, separation of *cis* and *trans* isomers after the intramolecular cyclisation can be achieved by chromatography or crystallisation.

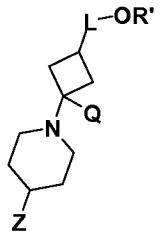
In one aspect, the invention provides a compound of formula (X) or salts thereof, wherein $R^{4'}$, $R^{5'}$, $R^{6'}$, Q, L and R' are as hereinbefore defined.

In a further aspect, the invention provides a general process (F) for preparing compounds of formula (I) which process comprises coupling a compound of formula (XI):



(XI)

wherein $R^{4'}$, $R^{5'}$, $R^{6'}$ and R' are as defined above for formula (II), with a compound of formula (XII):



(XII)

wherein L and Q are as defined for formula (I) and R' is as defined above for formula (II), and Z is hydroxy or a leaving group such as chloro, bromo or iodo, or alkyl/aryl sulfonate. The alkylation reaction can be carried out under classical alkylation (Z = a leaving group) or Mitsunobu reaction (Z = OH) conditions. Using classical alkylation conditions, the benzimidazolone intermediate (XI) can be deprotonated using a base such as sodium hydride in an inert solvent such as dimethylformamide, and then treated with the alkylating reagent (XII), optionally with heating. The Mitsunobu reaction with (XII) Z = OH can be carried out using standard conditions e.g. triphenylphosphine and diethylazodicarboxylate in an inert solvent such as dichloromethane or tetrahydrofuran at room temperature. It will be appreciated that compounds of formula (X) can be *cis* or *trans* isomers, or a mixture of isomers. If necessary, separation of *cis* and *trans* isomers after the intramolecular cyclisation can be achieved by chromatography or crystallisation.

Conversion of $R^{6'}$ to R^6 or interconversions of R^6 may be accomplished as indicated below. For example, when $R^{6'}$ is a halogen, it can be converted to an alkoxy or trifluoromethyl group by copper catalysed reaction, using an alcohol, or methyl fluorosulfonyl(difluoro)acetate, respectively. It may also be converted to an alkyl group with an organometallic reagent, for example an alkylstannane.

As another example, when $R^{6'}$ is hydroxy, it may be converted to an alkoxy group by reaction with an alkyl halide or sulfonate, or to trifluoromethoxy by conversion to the xanthate followed by oxidation in the presence of fluoride ion.

As a further example, when $R^{6'}$ is methyl, it may be converted to a trifluoromethyl group by chlorination or bromination followed by displacement of the introduced halogens with fluoride.

Similarly, conversion of $R^{5'}$ to R^5 or interconversions of R^5 may be accomplished as described for R^6.

Conversion of R' to R or interconversions of R may be accomplished as indicated below. For example when R' is benzyl, the benzyl group can be removed using standard methodology, e.g. catalytic hydrogenation over palladium on carbon, to provide the alcohol. Alkylation of the resultant alcohol using a strong base e.g. sodium hydride and a C_{1-6} alkylating agent e.g. methyl iodide or ethyl iodide or propyl iodide, will afford the

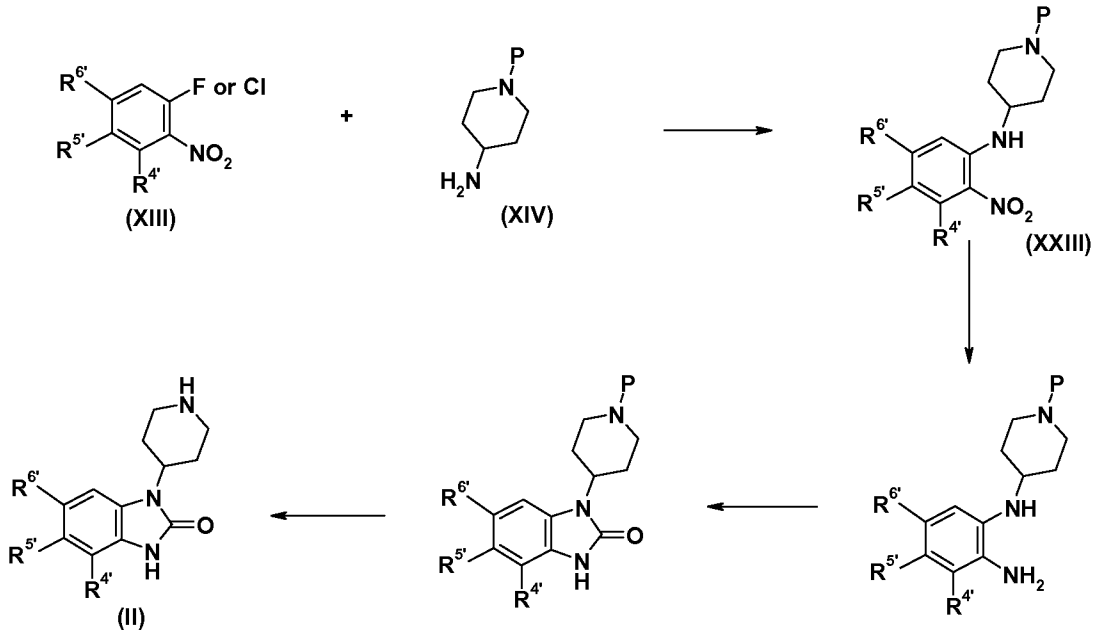
desired product. It will be appreciated that protection of any NH functionality present in the molecule may be necessary

As another example, when R is methyl, the methyl group can be removed by treatment with a dealkylating agent such as boron tribromide to afford the alcohol intermediate, which can be alkylated in a similar manner to that described above.

Compounds of formula (II) are generally known in the literature or can be prepared by a range of different processes for example:

(a) displacement of an ortho-fluoro or ortho-chloro of the nitrobenzene intermediate (XIII) with the amine (XIV), wherein $R^{4'}$ is a group R^4 as defined for formula (I), or a group convertible to R^4, $R^{5'}$ is a group R^5 as defined for formula (I), or a group convertible to R^5, $R^{6'}$ is a group R^6 as defined for formula (I), or a group convertible to R^6, and P represents a nitrogen protecting group (e.g. Boc, acetyl, trifluoroacetyl, ethoxycarbonyl, benzyloxycarbonyl), to give (XXIII), followed by reduction of the nitro group, cyclisation using phosgene or a phosgene equivalent, and deprotection of the piperidine nitrogen using standard literature conditions (Scheme 1).

Scheme 1.

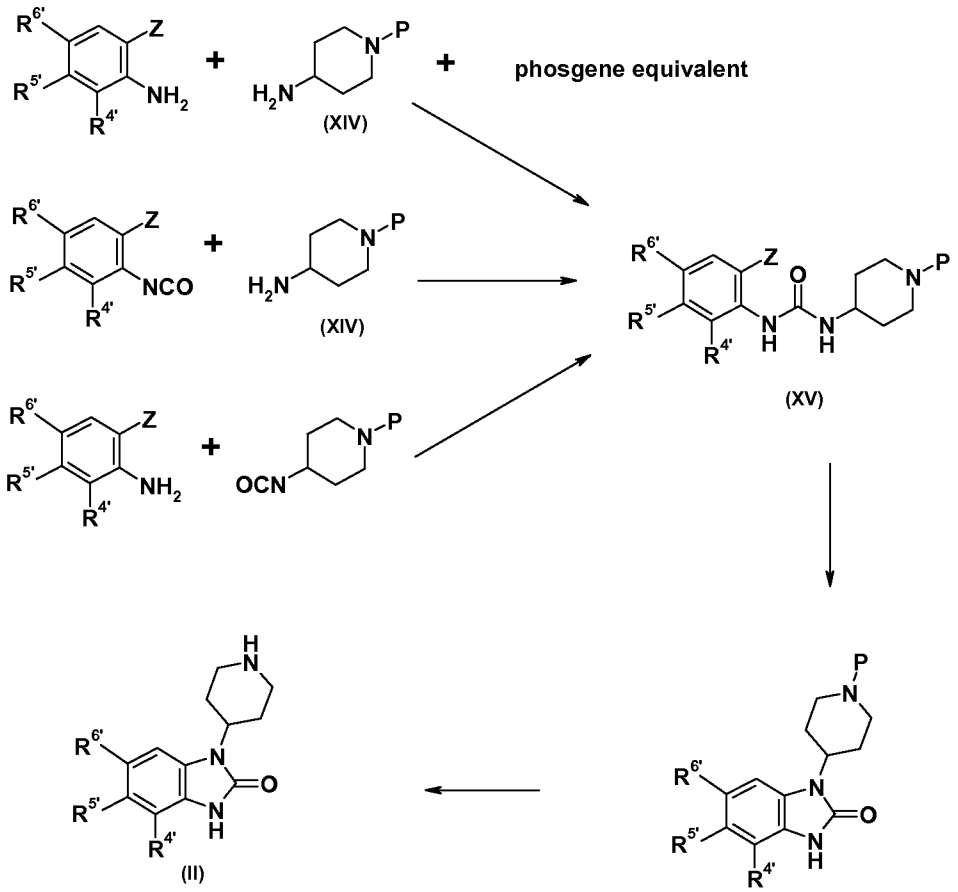


Compounds of formula (XIII) are commercially available or can be prepared by standard methodology. The compound (XIV) in which P = Boc is commercially available.

(b) metal catalysed cyclisation of an intermediate (XV) followed by deprotection of the piperidine nitrogen, wherein $R^{4'}$ is a group R^4 as defined for formula (I), or a group convertible to R^4, $R^{5'}$ is a group R^5 as defined for formula (I), or a group convertible to R^5,

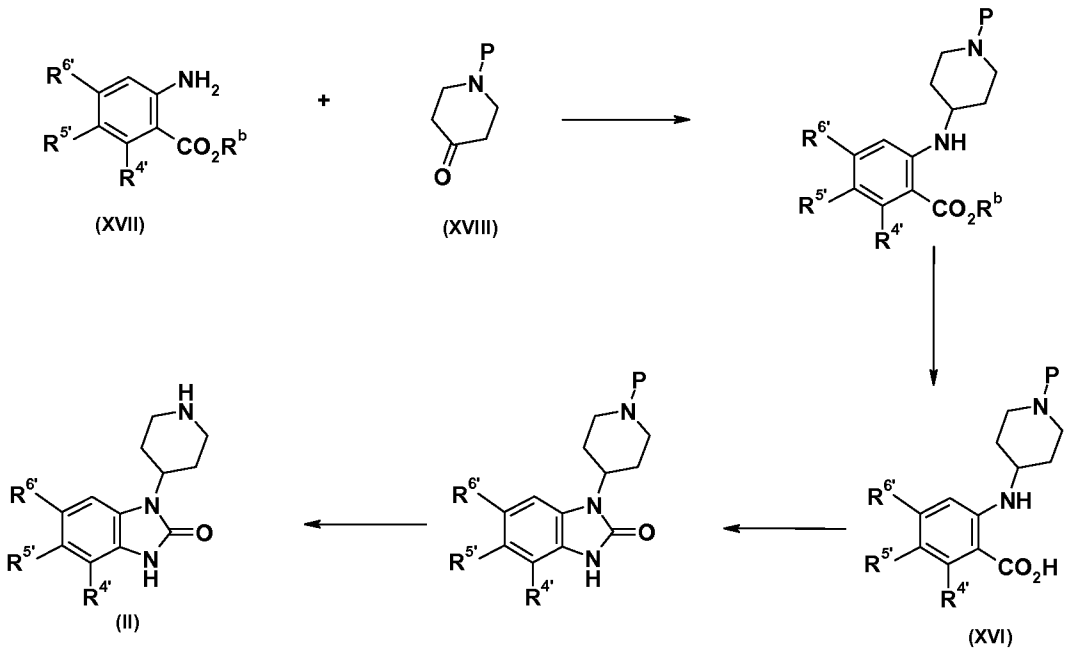
$R^{6'}$ is a group R^6 as defined for formula (I), or a group convertible to R^6, P represents a nitrogen protecting group (e.g. Boc, acetyl, trifluoroacetyl, benzyloxycarbonyl), and Z represents a leaving group such as bromo, iodo, chloro or triflate. Reaction conditions for the metal catalysed cyclisation are summarised in Process C. The urea (XV) can be prepared using any of the classical methods for urea formation as illustrated in Scheme 2. The starting materials for this process are commercially available or can be prepared using standard methodology.

Scheme 2.



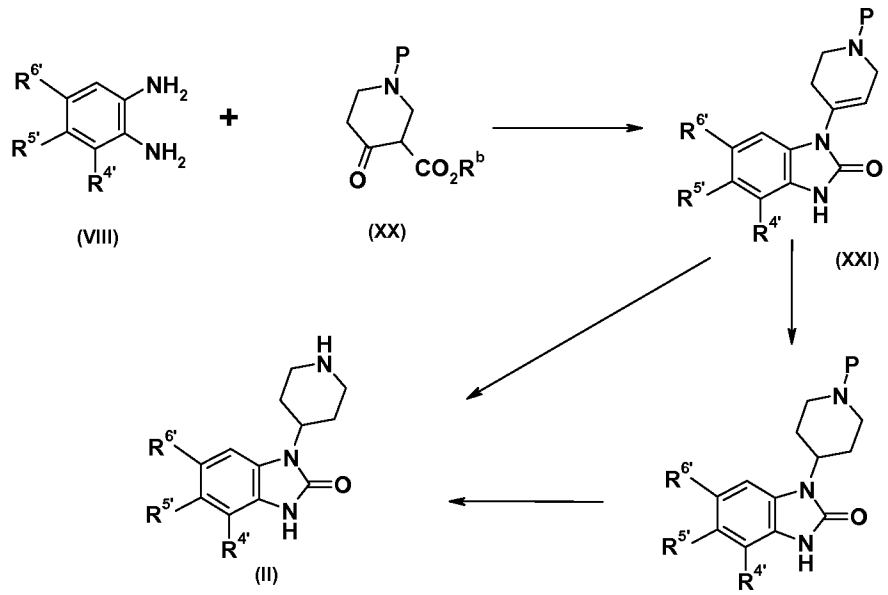
(c) Curtius rearrangement of an intermediate (XVI), wherein $R^{4'}$ is a group R^4 as defined for formula (I), or a group convertible to R^4, $R^{5'}$ is a group R^5 as defined for formula (I), or a group convertible to R^5, $R^{6'}$ is a group R^6 as defined for formula (I), or a group convertible to R^6, P represents a nitrogen protecting group (e.g. Boc, acetyl, trifluoroacetyl, benzyloxycarbonyl), and R^b represents H or a C_{1-5} alkyl group e.g. methyl or ethyl, followed by intramolecular cyclisation and deprotection of the piperidine nitrogen (Scheme 3). The anthranilic acid or ester starting materials (XVII) are commercially available or can be made by standard methodology. The piperidone starting material (P = Boc or benzyl) is commercially available. The Curtius rearrangement can be effected using the conditions described under process E.

Scheme 3.



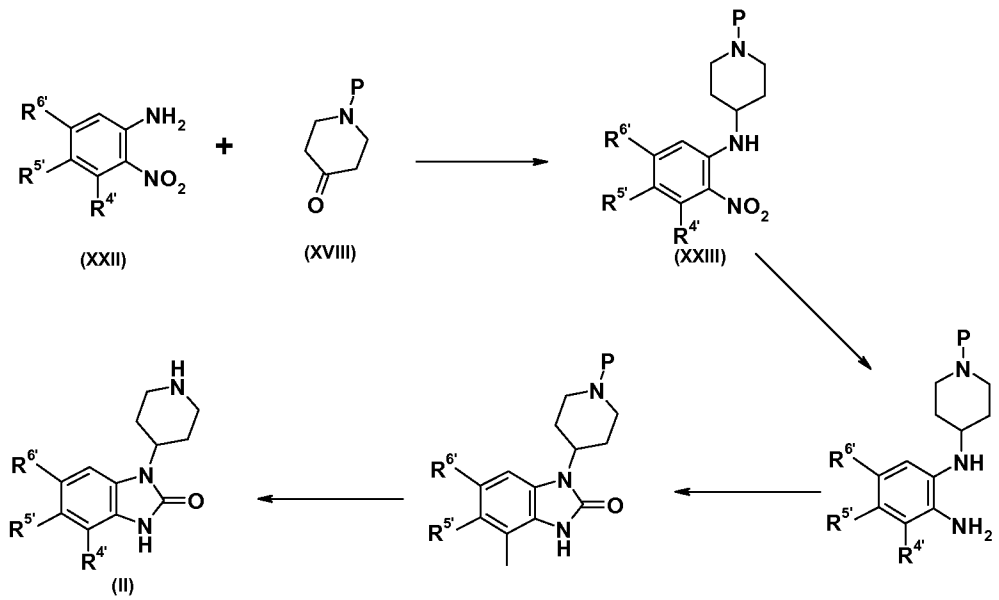
(d) Condensation of an orthophenylenediamine (VIII) with a 3-alkoxycarbonyl-4-piperidone (XX), wherein $R^{4'}$ is a group R^4 as defined for formula (I), or a group convertible to R^4, $R^{5'}$ is a group R^5 as defined for formula (I), or a group convertible to R^5, $R^{6'}$ is a group R^6 as defined for formula (I), or a group convertible to R^6, P represents a nitrogen protecting group (e.g. Boc, acetyl, trifluoroacetyl, benzyloxycarbonyl) and R^b is a C_{1-5}alkyl group (Scheme 4), by heating in an inert solvent at elevated temperature, to afford the tetrahydropyridine intermediate (XXI). Hydrogenation of the double bond and deprotection of the piperidine nitrogen can be accomplished separately or concomitantly dependent on the precise nature of the protecting group P, to afford the desired product (II). Compounds of formula (VIII) are commercially available or can be prepared by standard methodology. Compounds of formula (XX) are commercially available or can be prepared by standard methodology.

Scheme 4.



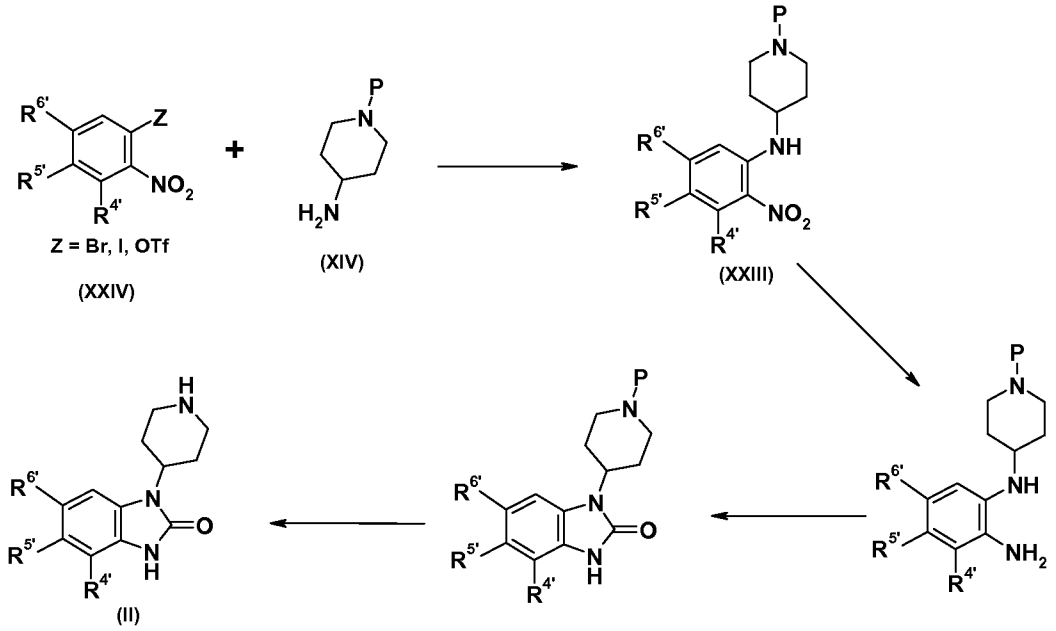
(e) Reductive alkylation of an ortho nitroaniline (XXII) with an N-protected 4-piperidone (XVIII), wherein $R^{4'}$ is a group R^4 as defined for formula (I), or a group convertible to R^4, $R^{5'}$ is a group R^5 as defined for formula (I), or a group convertible to R^5, $R^{6'}$ is a group R^6 as defined for formula (I), or a group convertible to R^6, and P represents a nitrogen protecting group (e.g. Boc, acetyl, trifluoroacetyl, benzyloxycarbonyl), using for example sodium triacetoxyborohydride to give the intermediate (XXIII). Reduction of the nitro group, followed by cyclisation and deprotection as described hereinbefore provides the desired product (II) (Scheme 5). Compounds of formula (XXII) and (XVIII) are commercially available or can be prepared by standard methodology.

Scheme 5.



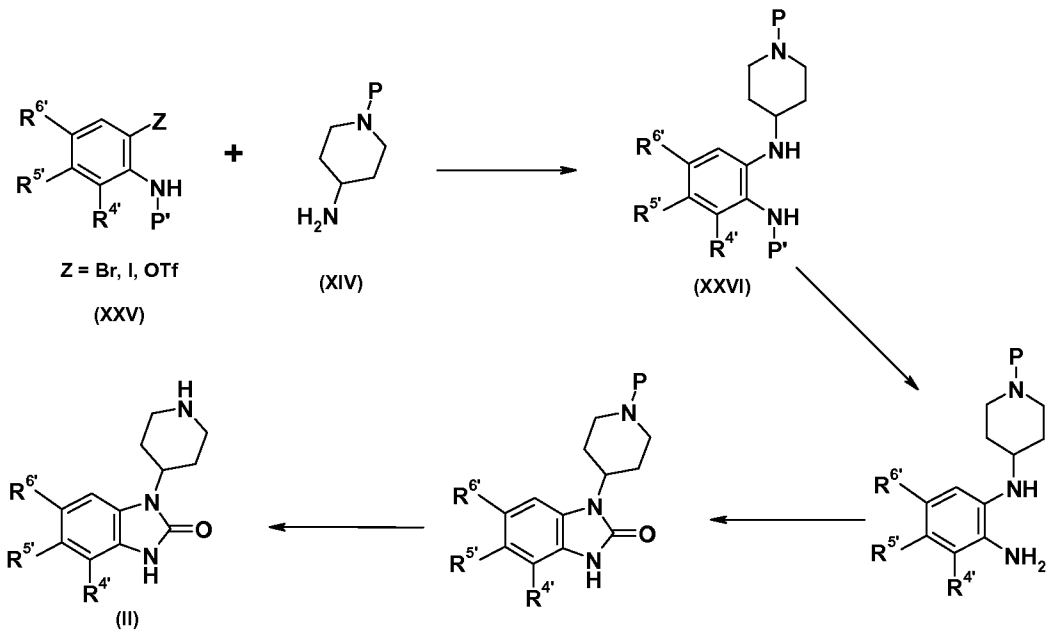
(f) metal catalysed reaction between the amine (XIV) and a suitably substituted nitrobenzene compound (XXIV) wherein $R^{4'}$ is a group R^4 as defined for formula (I), or a group convertible to R^4, $R^{5'}$ is a group R^5 as defined for formula (I), or a group convertible to R^5, $R^{6'}$ is a group R^6 as defined for formula (I), or a group convertible to R^6, P represents a nitrogen protecting group (e.g. Boc, acetyl, trifluoroacetyl, benzyloxycarbonyl), and Z represents a leaving group such as bromo, iodo, chloro or triflate (Scheme 6). This process generates intermediates of formula (XXIII) and subsequent reactions are similar to that for Scheme 5. Compounds of formula (XXIV) are commercially available or can be prepared by known methodology. The compound (XIV) in which P = Boc is commercially available.

Scheme 6.



(g) metal catalysed reaction between the amine (XIV) and the protected aniline (XXV), wherein $R^{4'}$ is a group R^4 as defined for formula (I), or a group convertible to R^4, $R^{5'}$ is a group R^5 as defined for formula (I), or a group convertible to R^5, $R^{6'}$ is a group R^6 as defined for formula (I), or a group convertible to R^6, P and P' independently represent a nitrogen protecting group (e.g. Boc, acetyl, trifluoroacetyl, benzyloxycarbonyl), and Z represents a leaving group such as bromo, iodo, chloro or triflate, to give the intermediate (XXVI) (Scheme 7). Deprotection of the aniline followed by the same reaction sequence as in Scheme 6 affords the desired intermediate (II). Compounds of formula (XXV) are commercially available or can be prepared by known methodology e.g. halogenation ortho to the optionally protected aniline group. The compound (XIV) in which P = Boc is commercially available.

Scheme 7.

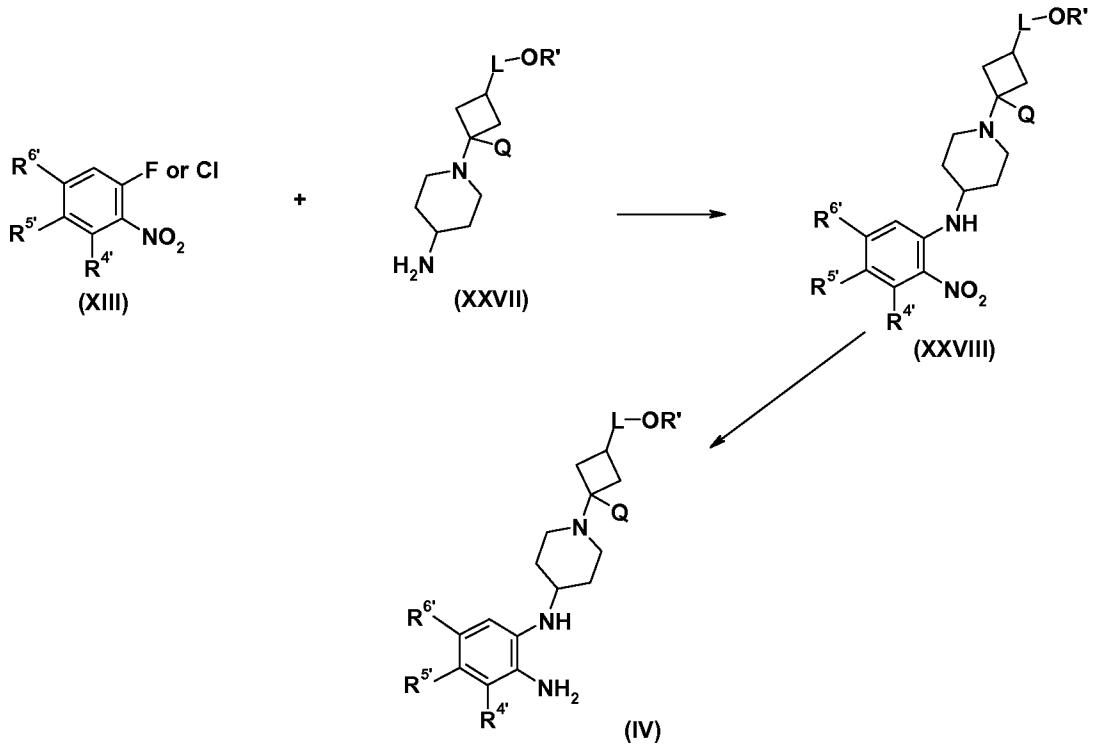


The compounds of formula (III) can be prepared by standard literature methodology.

Compounds of formula (IV) can be prepared by a number of different processes e.g.

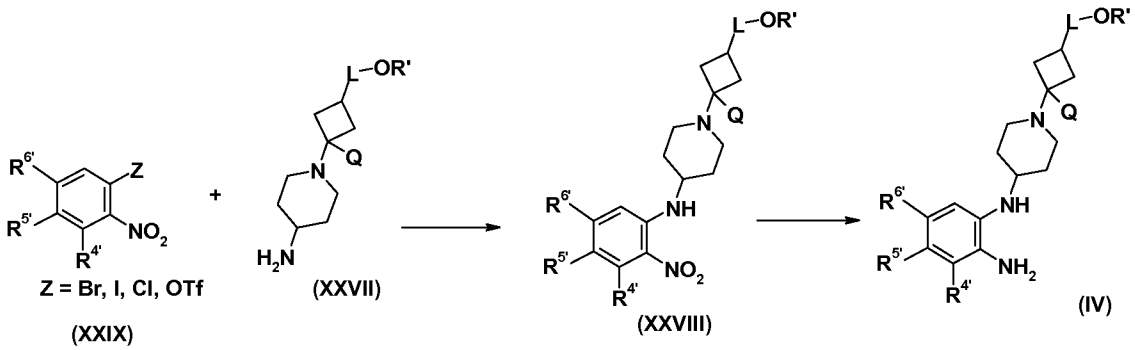
(h) displacement of an ortho-fluoro or ortho-chloro nitrobenzene intermediate (XIII) with the amine (XXVII) wherein $R^{4'}$ is a group R^4 as defined for formula (I), or a group convertible to R^4, $R^{5'}$ is a group R^5 as defined for formula (I), or a group convertible to R^5, $R^{6'}$ is a group R^6 as defined for formula (I), or a group convertible to R^6, R' is a group R as defined for formula (I), or a group convertible to R, and Q is as defined for formula (I), to afford compound (XXVIII) followed by reduction of the nitro group using standard conditions e.g. hydrogenation over palladium or Raney nickel (Scheme 8). Compounds of formula (XIII) are commercially available or can be prepared by standard methodology. It will be appreciated that separation of the *cis* and *trans* isomers can be achieved at any suitable stage in the synthesis.

Scheme 8.



(i) metal catalysed reaction of the amine (XXVII) with the ortho substituted nitrobenzene (XXIX), wherein L is a bond or $(CH_2)_{1-2}$; $R^{4'}$ is a group R^4 as defined for formula (I), or a group convertible to R^4, $R^{5'}$ is a group R^5 as defined for formula (I), or a group convertible to R^5, $R^{6'}$ is a group R^6 as defined for formula (I), or a group convertible to R^6, R' is a group R as defined for formula (I), or a group convertible to R, and Q is as defined for formula (I), to afford compound (XXVIII) (Scheme 9) followed by the same reactions as illustrated in Scheme 8. Compounds of formula (XXIX) are commercially available or can be prepared by standard methodology. It will be appreciated that separation of the *cis* and *trans* isomers can be achieved at any suitable stage in the synthesis.

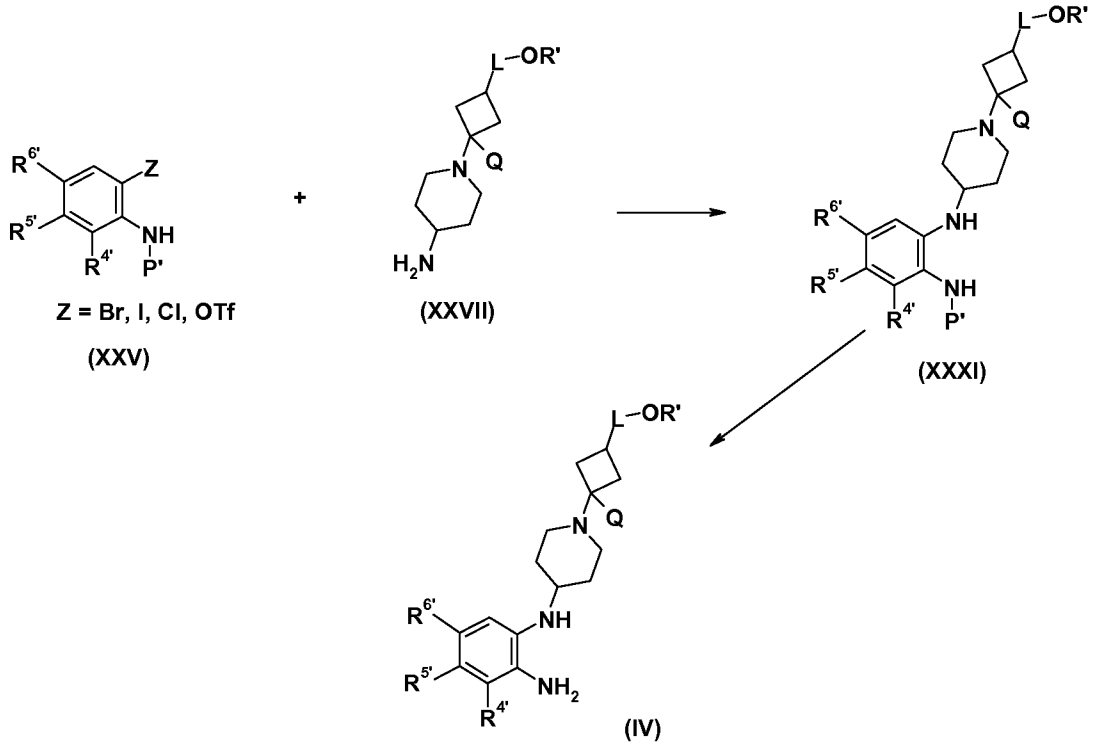
Scheme 9.



(j) metal catalysed reaction of the amine (XXVII) with the protected aniline derivative (XXV), wherein L is a bond or $(CH_2)_{1-2}$; $R^{4'}$ is a group R^4 as defined for formula (I), or a group convertible to R^4, $R^{5'}$ is a group R^5 as defined for formula (I), or a group convertible to R^5, $R^{6'}$ is a group R^6 as defined for formula (I), or a group convertible to R^6, R' is a

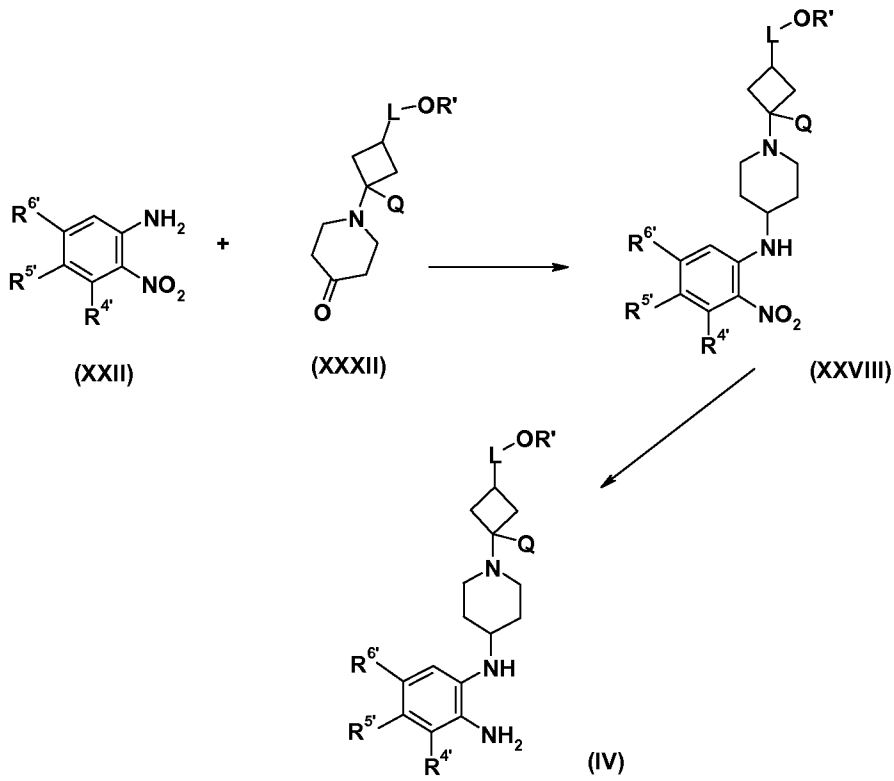
group R as defined for formula (I), or a group convertible to R, and Q is as defined for formula (I), and P' represents a nitrogen protecting group (such as acetyl, trifluoroacetyl, Boc, phthalimide), to afford compound (XXXI) (Scheme 10) followed by deprotection of the aniline group. Compounds of formula (XXV) are commercially available or can be prepared by standard methodology. It will be appreciated that separation of the *cis* and *trans* isomers can be achieved at any suitable stage in the synthesis.

Scheme 10.



(k) Reductive alkylation of an ortho nitroaniline (XXII) with the piperidone (XXXII) wherein L is a bond or $(CH_2)_{1-2}$; $R^{4'}$ is a group R^4 as defined for formula (I), or a group convertible to R^4, $R^{5'}$ is a group R^5 as defined for formula (I), or a group convertible to R^5, $R^{6'}$ is a group R^6 as defined for formula (I), or a group convertible to R^6, R' is a group R as defined for formula (I), or a group convertible to R, and Q is as defined for formula (I), using for example sodium triacetoxyborohydride in dichloroethane to give the intermediate (XXVIII) (Scheme 11). Reduction of the nitro group using, for example, palladium on carbon or Raney nickel affords the desired intermediate (IV). It will be appreciated that separation of the *cis* and *trans* isomers can be achieved at any suitable stage in the synthesis.

Scheme 11.



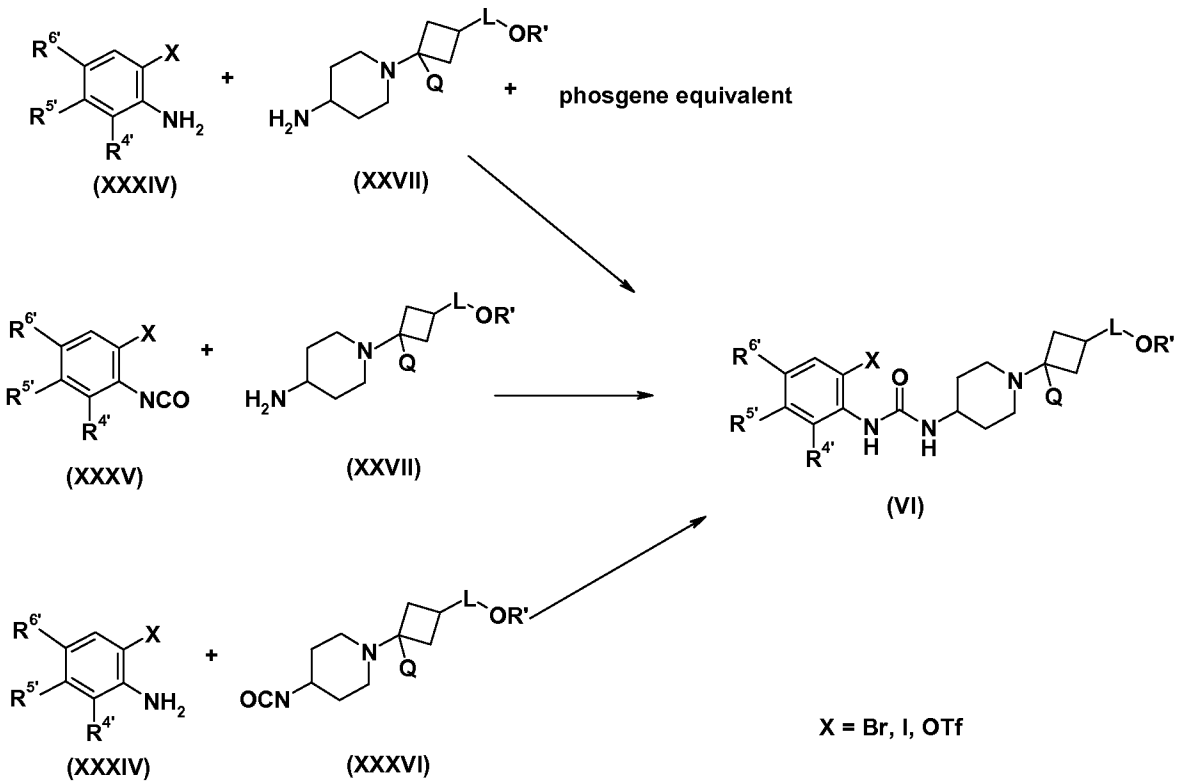
Compounds of formula (V) are commercially available e.g. carbonyl diimidazole, phosgene, phosgene solution in toluene, diphosgene, triphosgene, phenyl chloroformate, diethyl carbonate.

Compounds of formula (VI) can be prepared by a variety of processes e.g. urea formation as shown in Scheme 12 by:

- combining the two amines (XXXIV) and (XXVII) with phosgene or a phosgene equivalent using standard conditions Phosgene equivalents include carbonyl diimidazole, diphosgene, triphosgene, phenyl chloroformate;
- reacting the amine (XXVII) with the isocyanate (XXXV); or
- reacting the amine (XXXIV) with the isocyanate (XXXVI).

Both isocyanates can be prepared from the corresponding amines using standard methodology for isocyanate formation. It will be appreciated that separation of the *cis* and *trans* isomers can be achieved at any suitable stage in the synthesis.

Scheme 12.



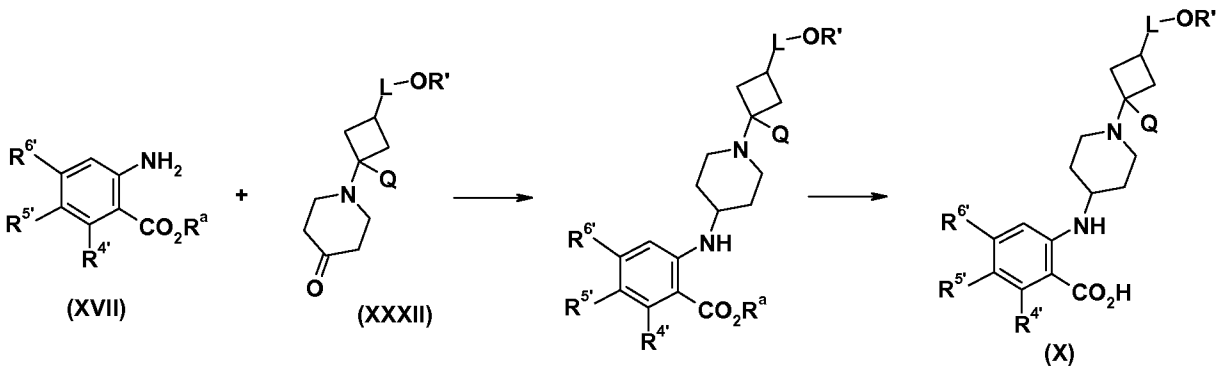
Palladium and copper catalysts (VII) are commercially available or can be prepared as described in the literature (see references in Process C).

Compounds of formula (VIII) are commercially available or can be prepared by known literature routes e.g. reduction of a mono or dinitrobenzene precursor.

Compounds of formula (IX) where Q = H can be prepared by reductive alkylation of the 3-alkoxycarbonyl-4-piperidone with the approriatelly substituted cyclobutanone.

Compounds of formula (X) can be prepared as shown in Scheme 13. Reductive alkylation of an anthranilic acid or ester (XVII) with the ketone (XXXII), followed if appropriate by hydrolysis of the ester group. It will be appreciated that separation of the *cis* and *trans* isomers can be achieved at any suitable stage in the synthesis.

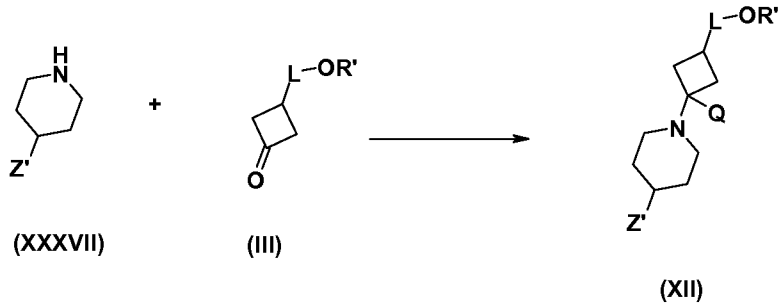
Scheme 13.



Compounds of formula (XI) are commercially available or can be prepared by literature processes.

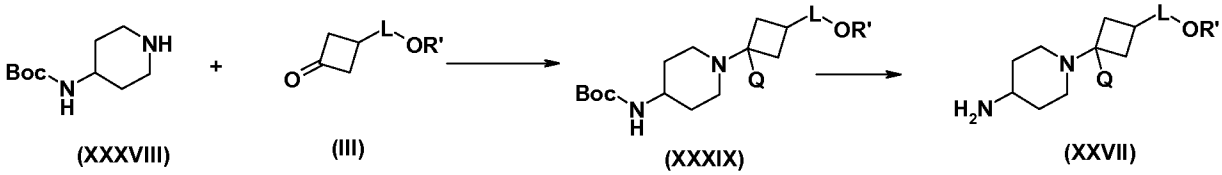
Compounds of formula (XII) where Q = H can be prepared as shown in Scheme 14, by reductive alkylation of (XXXVII) where Z' represents Z or a group convertible to Z, with the ketone (III). Conversion of a Z' = hydroxy group to Z = chloro or bromo can be accomplished using standard methodology e.g. treatment with thionyl chloride or triphenylphosphine/carbon tetrabromide. It will be appreciated that separation of the *cis* and *trans* isomers can be achieved at any suitable stage in the synthesis.

Scheme 14.



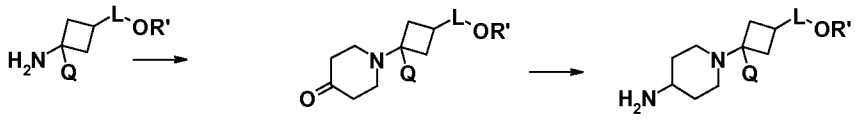
The compound (XXVII) where Q = H can be prepared as shown in Scheme 15. Reductive alkylation of the commercially available amine (XXXVIII) with cyclobutanone (III) using for example sodium triacetoxyborohydride in dichloroethane provides the intermediate (XXXIX) which is deprotected using HCl in ethanol or trifluoroacetic acid to afford the primary amine (XXVII). It will be appreciated that separation of the *cis* and *trans* isomers can be achieved at any suitable stage in the synthesis.

Scheme 15.



Compound (XXVII) can also be prepared as shown in Scheme 16. Amine (XXXXI) may be converted to the aforementioned piperidone (XXXII) with, for example, 1-methyl-1-ethyl-4-piperidonium iodide, and this can be converted to (XXVII) by reductive amination by, for example, hydrogenation over palladium on carbon in the presence of ammonia.

Scheme 16



(XXXXI) (XXXII) (XXVII)

The compound (XXVII) where Q = alkyl can be prepared as in process A2, followed by deprotection.

In one embodiment, the group $R^{4'}$ in the above described processes is the group R^4 as hereinbefore defined.

In one embodiment, the group $R^{5'}$ in the above described processes is the group R^5 as hereinbefore defined.

In one embodiment, the group $R^{6'}$ in the above described processes is the group R^6 as hereinbefore defined.

In one embodiment, the group R' in the above described processes is the group R as hereinbefore defined.

Compounds of the present invention are M_1 receptor agonists. Selective M_1 receptor agonists are said to be useful to ameliorate positive and cognitive symptoms of psychotic disorders such as schizophrenia, schizo-affective disorders, schizophreniform diseases, psychotic depression, mania, acute mania, paranoid and delusional disorders, and cognitive impairment including memory disorders such as Alzheimer's disease without peripheral cholinergic side effects mediated predominantly through M_2 and M_3 receptors. M_1 receptor agonists may also be suitable for combination with other typical and atypical antipsychotics and other actives such as mood stabilisers, antidepressants, anxiolytics, drugs for extrapyramidal side effects and cognitive enhancers, to provide improved treatment of psychotic disorders.

Thus in a further aspect, the invention provides a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof for use in therapy.

In another aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of a condition wherein agonism of a muscarinic M_1 receptor would be beneficial.

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

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

Other conditions wherein agonism of the M_1 receptor would be beneficial in their treatment include:

Depression and mood disorders including Major Depressive Episode, Manic Episode, Mixed Episode and Hypomanic Episode; Depressive Disorders including Major Depressive Disorder, Dysthymic Disorder (300.4), Depressive Disorder Not Otherwise Specified (311); Bipolar Disorders including Bipolar I Disorder, Bipolar II Disorder (Recurrent Major Depressive Episodes with Hypomanic Episodes) (296.89), Cyclothymic Disorder (301.13) and Bipolar Disorder Not Otherwise Specified (296.80); Other Mood Disorders including Mood Disorder Due to a General Medical Condition (293.83) which includes the subtypes With Depressive Features, With Major Depressive-like Episode, With Manic Features and With Mixed Features), Substance-Induced Mood Disorder (including the subtypes With Depressive Features, With Manic Features and With Mixed Features) and Mood Disorder Not Otherwise Specified (296.90);

Anxiety disorders including Social Anxiety Disorder, Panic Attack, Agoraphobia, Panic Disorder, Agoraphobia Without History of Panic Disorder (300.22), Specific Phobia (300.29) including the subtypes Animal Type, Natural Environment Type, Blood-Injection-Injury Type, Situational Type and Other Type), Social Phobia (300.23), Obsessive-

Compulsive Disorder (300.3), Posttraumatic Stress Disorder (309.81), Acute Stress Disorder (308.3), Generalized Anxiety Disorder (300.02), Anxiety Disorder Due to a General Medical Condition (293.84), Substance-Induced Anxiety Disorder and Anxiety Disorder Not Otherwise Specified (300.00);

Substance-related disorders including Substance Use Disorders such as Substance Dependence, Substance Craving and Substance Abuse; Substance-Induced Disorders such as Substance Intoxication, Substance Withdrawal, Substance-Induced Delirium, Substance-Induced Persisting Dementia, Substance-Induced Persisting Amnestic Disorder, Substance-Induced Psychotic Disorder, Substance-Induced Mood Disorder, Substance-Induced Anxiety Disorder, Substance-Induced Sexual Dysfunction, Substance-Induced Sleep Disorder and Hallucinogen Persisting Perception Disorder (Flashbacks); Alcohol-Related Disorders such as Alcohol Dependence (303.90), Alcohol Abuse (305.00), Alcohol Intoxication (303.00), Alcohol Withdrawal (291.81), Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnestic Disorder, Alcohol-Induced Psychotic Disorder, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder and Alcohol-Related Disorder Not Otherwise Specified (291.9); Amphetamine (or Amphetamine-Like)-Related Disorders such as Amphetamine Dependence (304.40), Amphetamine Abuse (305.70), Amphetamine Intoxication (292.89), Amphetamine Withdrawal (292.0), Amphetamine Intoxication Delirium, Amphetamine Induced Psychotic Disorder, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder and Amphetamine-Related Disorder Not Otherwise Specified (292.9); Caffeine Related Disorders such as Caffeine Intoxication (305.90), Caffeine-Induced Anxiety Disorder, Caffeine-Induced Sleep Disorder and Caffeine-Related Disorder Not Otherwise Specified (292.9); Cannabis-Related Disorders such as Cannabis Dependence (304.30), Cannabis Abuse (305.20), Cannabis Intoxication (292.89), Cannabis Intoxication Delirium, Cannabis-Induced Psychotic Disorder, Cannabis-Induced Anxiety Disorder and Cannabis-Related Disorder Not Otherwise Specified (292.9); Cocaine-Related Disorders such as Cocaine Dependence (304.20), Cocaine Abuse (305.60), Cocaine Intoxication (292.89), Cocaine Withdrawal (292.0), Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder and Cocaine-Related Disorder Not Otherwise Specified (292.9); Hallucinogen-Related Disorders such as Hallucinogen Dependence (304.50), Hallucinogen Abuse (305.30), Hallucinogen Intoxication (292.89), Hallucinogen Persisting Perception Disorder (Flashbacks) (292.89), Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder and Hallucinogen-Related Disorder Not Otherwise Specified (292.9); Inhalant-Related Disorders such as Inhalant Dependence (304.60), Inhalant Abuse (305.90), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium,

Inhalant-Induced Persisting Dementia, Inhalant-Induced Psychotic Disorder, Inhalant-Induced Mood Disorder, Inhalant-Induced Anxiety Disorder and Inhalant-Related Disorder Not Otherwise Specified (292.9); Nicotine-Related Disorders such as Nicotine Dependence (305.1), Nicotine Withdrawal (292.0) and Nicotine-Related Disorder Not Otherwise Specified (292.9); Opioid-Related Disorders such as Opioid Dependence (304.00), Opioid Abuse (305.50), Opioid Intoxication (292.89), Opioid Withdrawal (292.0), Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder, Opioid-Induced Mood Disorder, Opioid-Induced Sexual Dysfunction, Opioid-Induced Sleep Disorder and Opioid-Related Disorder Not Otherwise Specified (292.9); Phencyclidine (or Phencyclidine-Like)-Related Disorders such as Phencyclidine Dependence (304.60), Phencyclidine Abuse (305.90), Phencyclidine Intoxication (292.89), Phencyclidine Intoxication Delirium, Phencyclidine-Induced Psychotic Disorder, Phencyclidine-Induced Mood Disorder, Phencyclidine-Induced Anxiety Disorder and Phencyclidine-Related Disorder Not Otherwise Specified (292.9); Sedative-, Hypnotic-, or Anxiolytic-Related Disorders such as Sedative, Hypnotic, or Anxiolytic Dependence (304.10), Sedative, Hypnotic, or Anxiolytic Abuse (305.40), Sedative, Hypnotic, or Anxiolytic Intoxication (292.89), Sedative, Hypnotic, or Anxiolytic Withdrawal (292.0), Sedative, Hypnotic, or Anxiolytic Intoxication Delirium, Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium, Sedative-, Hypnotic-, or Anxiolytic-Persisting Dementia, Sedative-, Hypnotic-, or Anxiolytic- Persisting Amnestic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Psychotic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorder Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction, Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep Disorder and Sedative-, Hypnotic-, or Anxiolytic-Related Disorder Not Otherwise Specified (292.9); Polysubstance-Related Disorder such as Polysubstance Dependence (304.80); and Other (or Unknown) Substance-Related Disorders such as Anabolic Steroids, Nitrate Inhalants and Nitrous Oxide;

Sleep disorders including primary sleep disorders such as Dyssomnias such as Primary Insomnia (307.42), Primary Hypersomnia (307.44), Narcolepsy (347), Breathing-Related Sleep Disorders (780.59), Circadian Rhythm Sleep Disorder (307.45) and Dyssomnia Not Otherwise Specified (307.47); primary sleep disorders such as Parasomnias such as Nightmare Disorder (307.47), Sleep Terror Disorder (307.46), Sleepwalking Disorder (307.46) and Parasomnia Not Otherwise Specified (307.47); Sleep Disorders Related to Another Mental Disorder such as Insomnia Related to Another Mental Disorder (307.42) and Hypersomnia Related to Another Mental Disorder (307.44); Sleep Disorder Due to a General Medical Condition; and Substance-Induced Sleep Disorder including the subtypes Insomnia Type, Hypersomnia Type, Parasomnia Type and Mixed Type;

Eating disorders such as Anorexia Nervosa (307.1) including the subtypes Restricting Type and Binge-Eating/Purging Type; Bulimia Nervosa (307.51) including the subtypes

Purging Type and Nonpurging Type; Obesity; Compulsive Eating Disorder; and Eating Disorder Not Otherwise Specified (307.50);

Autistic Disorder (299.00); Attention-Deficit /Hyperactivity Disorder including the subtypes Attention-Deficit /Hyperactivity Disorder Combined Type (314.01), Attention-Deficit /Hyperactivity Disorder Predominantly Inattentive Type (314.00), Attention-Deficit /Hyperactivity Disorder Hyperactive-Impulse Type (314.01) and Attention-Deficit /Hyperactivity Disorder Not Otherwise Specified (314.9); Hyperkinetic Disorder; Disruptive Behaviour Disorders such as Conduct Disorder including the subtypes childhood-onset type (321.81), Adolescent-Onset Type (312.82) and Unspecified Onset (312.89), Oppositional Defiant Disorder (313.81) and Disruptive Behaviour Disorder Not Otherwise Specified; and Tic Disorders such as Tourette's Disorder (307.23);

Personality Disorders including the subtypes Paranoid Personality Disorder (301.0), Schizoid Personality Disorder (301.20), Schizotypal Personality Disorder (301,22), Antisocial Personality Disorder (301.7), Borderline Personality Disorder (301,83), Histrionic Personality Disorder (301.50), Narcissistic Personality Disorder (301,81), Avoidant Personality Disorder (301.82), Dependent Personality Disorder (301.6), Obsessive-Compulsive Personality Disorder (301.4) and Personality Disorder Not Otherwise Specified (301.9); and

Sexual dysfunctions including Sexual Desire Disorders such as Hypoactive Sexual Desire Disorder (302.71), and Sexual Aversion Disorder (302.79); sexual arousal disorders such as Female Sexual Arousal Disorder (302.72) and Male Erectile Disorder (302.72); orgasmic disorders such as Female Orgasmic Disorder (302.73), Male Orgasmic Disorder (302.74) and Premature Ejaculation (302.75); sexual pain disorder such as Dyspareunia (302.76) and Vaginismus (306.51); Sexual Dysfunction Not Otherwise Specified (302.70); paraphilias such as Exhibitionism (302.4), Fetishism (302.81), Frotteurism (302.89), Pedophilia (302.2), Sexual Masochism (302.83), Sexual Sadism (302.84), Transvestic Fetishism (302.3), Voyeurism (302.82) and Paraphilia Not Otherwise Specified (302.9); gender identity disorders such as Gender Identity Disorder in Children (302.6) and Gender Identity Disorder in Adolescents or Adults (302.85); and Sexual Disorder Not Otherwise Specified (302.9).

The compounds of formula (I) may also be useful for the enhancement of cognition, including both the treatment of cognitive impairment on its own and the treatment of cognition impairment in other diseases such as schizophrenia, bipolar disorder, depression, other psychiatric disorders and psychotic conditions associated with cognitive impairment. Where cognitive impairment results from a treatment of a disease, M_1 agonists may be beneficial. For example, when the treatment of epilepsy with anticonvulsants results in cognitive impairment, an M_1 agonist may be useful for the alleviation or treatment of the cognitive impairment.

Within the context of the present invention, the term cognitive impairment includes, for example, impairment of cognitive functions including attention, orientation, learning disorders, memory (i.e. memory disorders, amnesia, amnesic disorders, transient global amnesia syndrome and age-associated memory impairment) and language function; cognitive impairment as a result of stroke, Alzheimer's disease, Huntington's disease, Pick disease, Aids-related dementia or other dementia states such as Multiinfarct dementia, alcoholic dementia, hypotiroidism-related dementia, and dementia associated to other degenerative disorders such as cerebellar atrophy and amyotropic lateral sclerosis; other acute or sub-acute conditions that may cause cognitive decline such as delirium or depression (pseudodementia states) trauma, head trauma, age related cognitive decline, stroke, neurodegeneration, drug-induced states, neurotoxic agents, mild cognitive impairment, age related cognitive impairment, autism related cognitive impairment, Down's syndrome, cognitive deficit related to psychosis, and post-electroconvulsive treatment related cognitive disorders; and dyskinetic disorders such as Parkinson's disease, neuroleptic-induced parkinsonism, and tardive dyskinesias.

Compounds of formula (I) or pharmaceutically accepatble salts thereof may also be used as memory and/or cognition enhancers in healthy humans with no cognitive and/or memory deficit.

In another aspect, the invention provides a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof for use in the treatment of a psychotic disorder. In one embodiment, the invention provides a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof for use in the treatment of schizophrenia.

The invention also provides a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof for use in the treatment of cognitive impairment.

In another aspect, the invention provides the use of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition wherein agonism of the M_1 receptor would be beneficial.

In another aspect, the invention provides the use of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a psychotic disorder. In one embodiment, the invention provides the use of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of schizophrenia.

In another aspect, the invention provides a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof in the treatment of a psychotic disorder. In one embodiment, the invention provides a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof for the treatment of schizophrenia.

The invention also provides the use of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cognitive impairment.

The invention also provides a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof for the treatment of cognitive impairment.

In another aspect, the invention provides a method of treating a condition where agonism of the M_1 receptor would be beneficial, which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof. In one embodiment, the mammal is a human.

In another aspect, the invention provides a method of treating a psychotic disorder which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof. In one embodiment, the invention provides a method of treating schizophrenia, which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof. In one embodiment, the mammal is a human.

The invention also provides a method of treating cognitive impairment, which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof. In one embodiment, the mammal is a human.

The compounds of formula (I) and pharmaceutically acceptable salts thereof may also be suitable for combination with other actives, such as typical and atypical antipsychotics, mood stabilisers, antidepressants, anxiolytics, drugs for extrapyrimidal side effects and cognitive enhancers to provide improved treatment of psychotic disorders.

The combination therapies of the invention are, for example, administered adjunctively. By adjunctive administration is meant the coterminous or overlapping administration of each of the components in the form of separate pharmaceutical compositions or devices. This regime of therapeutic administration of two or more therapeutic agents is referred to generally by those skilled in the art and herein as adjunctive therapeutic administration; it

is also known as add-on therapeutic administration. Any and all treatment regimes in which a patient receives separate but coterminous or overlapping therapeutic administration of the compounds of formula (I) or a pharmaceutically acceptable salt thereof and at least one antipsychotic agent, a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects or a cognitive enhancer are within the scope of the current invention. In one embodiment of adjunctive therapeutic administration as described herein, a patient is typically stabilised on a therapeutic administration of one or more of the components for a period of time and then receives administration of another component. The compounds of formula (I) or a pharmaceutically acceptable salt thereof may be administered as adjunctive therapeutic treatment to patients who are receiving administration of at least one antipsychotic agent, a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects or a cognitive enhancer, but the scope of the invention also includes the adjunctive therapeutic administration of at least one antipsychotic agent, a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects or a cognitive enhancer to patients who are receiving administration of compounds of formula (I) or a pharmaceutically acceptable salt thereof.

The combination therapies of the invention may also be administered simultaneously. By simultaneous administration is meant a treatment regime wherein the individual components are administered together, either in the form of a single pharmaceutical composition or device comprising or containing both components, or as separate compositions or devices, each comprising one of the components, administered simultaneously. Such combinations of the separate individual components for simultaneous combination may be provided in the form of a kit-of-parts.

In a further aspect therefore, the invention provides a method of treatment of a psychotic disorder by adjunctive therapeutic administration of compounds of formula (I) or a pharmaceutically acceptable salt thereof to a patient receiving therapeutic administration of at least one antipsychotic agent. In a further aspect, the invention provides the use of compounds of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of at least one antipsychotic agent. In a further aspect, the invention provides compounds of formula (I) or a pharmaceutically acceptable salt thereof for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of at least one antipsychotic agent. The invention further provides compounds of formula (I) or a pharmaceutically acceptable salt thereof for use for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of at least one antipsychotic agent.

In a further aspect, the invention provides a method of treatment of a psychotic disorder by adjunctive therapeutic administration of at least one antipsychotic agent to a patient receiving therapeutic administration of compounds of formula (I) or a pharmaceutically acceptable salt thereof. In a further aspect, the invention provides the use of at least one antipsychotic agent in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of compounds of formula (I) or a pharmaceutically acceptable salt thereof. In a further aspect, the invention provides at least one antipsychotic agent for adjunctive therapeutic administration for the treatment of a psychotic disorder in a pateient recieving therapeutic administration of compounds of formula (I) or a pharmaceutically acceptable salt thereof. The invention further provides at least one antipsychotic agent for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of compounds of formula (I) or a pharmaceutically acceptable salt thereof.

In a further aspect, the invention provides a method of treatment of a psychotic disorder by simultaneous therapeutic administration of compounds of formula (I) or a pharmaceutically acceptable salt thereof in combination with at least one antipsychotic agent. The invention further provides the use of a combination of compounds of formula (I) or a pharmaceutically acceptable salt thereof and at least one antipsychotic agent in the manufacture of a medicament for simultaneous therapeutic administration in the treatment of a psychotic disorder. The invention further provides a combination of compounds of formula (I) or a pharmaceutically acceptable salt thereof and at least one antipsycotic agent for simultaneous therapeutic administration in the treatment of a psychotic disorder. The invention further provides the use of compounds of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for simultaneous therapeutic administration with at least one antipsychotic agent in the treatment of a psychotic disorder. The invention further provides compounds of formula (I) or a pharmaceutically acceptable salt thereof for use for simultaneous therapeutic administration with at least one antipsychotic agent in the treatment of a psychotic disorder. The invention further provides the use of at least one antipsychotic agent in the manufacture of a medicament for simultaneous therapeutic administration with compounds of formula (I) or a pharmaceutically acceptable salt thereof in the treatment of a psychotic disorder. The invention further provides at least one antipsychotic agent for simultaneous therapeutic administration with compounds of formula (I) or a pharmaceutically acceptable salt thereof in the treatment of a psychotic disorder.

In a further aspect, the invention provides a kit-of-parts for use in the treatment of a psychotic disorder comprising a first dosage form comprising compounds of formula (I) or a pharmaceutically acceptable salt thereof and one or more further dosage forms each comprising an antipsychotic agent for simultaneous therapeutic administration.

In another aspect, the invention provides a method of treatment of a psychotic disorder by adjunctive therapeutic administration of a compound of the present invention to a patient receiving therapeutic administration of an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer.

In a further aspect, the invention provides the use of a compound of the present invention in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer.

The invention also provides a compound of the present invention for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer.

The invention also provides the use of a compound of the present invention in adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer.

The invention further provides the use of a compound of the present invention for use for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer.

In a further aspect, the invention provides a method of treatment of a psychotic disorder by adjunctive therapeutic administration of an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer to a patient receiving therapeutic administration of a compound of the present invention.

In a further aspect, the invention provides the use of an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of a compound of the present invention.

The invention also provides an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of a compound of the present invention

The invention also provides the use of an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of a compound of the present invention

In a further aspect, the invention provides a method of treatment of a psychotic disorder by simultaneous therapeutic administration of a compound of the present invention in combination with an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer.

The invention further provides the use of a combination of a compound of the present invention and an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer in the manufacture of a medicament for simultaneous therapeutic administration in the treatment of a psychotic disorder.

The invention further provides a combination of a compound of the present invention and an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer for simultaneous therapeutic administration for the treatment of a psychotic disorder.

The invention further provides the use of a combination of a compound of the present invention and an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer for simultaneous therapeutic administration in the treatment of a psychotic disorder.

The invention further provides the use of a compound of the present invention in the manufacture of a medicament for simultaneous therapeutic administration with an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer in the treatment of a psychotic disorder.

The invention further provides a compound of the present invention for simultaneous therapeutic administration with an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer for the treatment of a psychotic disorder.

The invention further provides the use of a compound of the present invention for simultaneous therapeutic administration with an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer in the treatment of a psychotic disorder.

The invention further provides a compound of the present invention for use for simultaneous therapeutic administration with an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer in the treatment of a psychotic disorder.

The invention further provides the use of an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer in the manufacture of a medicament for simultaneous therapeutic administration with a compound of the present invention in the treatment of a psychotic disorder.

The invention further provides an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer for simultaneous therapeutic administration with a compound of the present invention for the treatment of a psychotic disorder.

The invention further provides the use of an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer for simultaneous therapeutic administration with a compound of the present invention in the treatment of a psychotic disorder.

In a further aspect, the invention provides a kit-of-parts for use in the treatment of a psychotic disorder comprising a first dosage form comprising a compound of the present invention and one or more further dosage forms each comprising an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyrimidal side effects and a cognitive enhancer for simultaneous therapeutic administration.

In one embodiment, the patient is a human.

Examples of antipsychotic drugs that may be useful in the present invention include, but are not limited to: sodium channel blockers; mixed 5HT/dopamine receptor antagonists; mGluR5 positive modulators; D3 antagonists; 5HT6 angatonists; nicotinic alpha-7 modulators; glycine transporter GlyT1 inhibitors; D2 partial agonist/D3 antanogist/H3 antagonists; AMPA modulators; NK3 antagonists such as osanetant and talnetant; an atypical antipsychotic, for example clozapine, olanzapine, risperidone, quetiapine, aripirazole, ziprasidone and amisulpride; butyrophenones, such as haloperidol, pimozide, and droperidol; phenothiazines, such as chlorpromazine, thioridazine, mesoridazine, trifluoperazine, perphenazine, fluphenazine, thiflupromazine, prochlorperazine, and acetophenazine; thioxanthenes, such as thiothixene and chlorprothixene; thienobenzodiazepines; dibenzodiazepines; benzisoxazoles; dibenzothiazepines; imidazolidinones; benzisothiazolyl-piperazines; triazine such as lamotrigine; dibenzoxazepines, such as loxapine; dihydroindolones, such as molindone; aripiprazole; and derivatives thereof that have antipsychotic activity.

Examples of tradenames and suppliers of selected antipsychotic drugs that may be suitable for use in the present invention are as follows : clozapine (available under the tradename CLOZARIL®, from Mylan, Zenith Goldline, UDL, Novartis); olanzapine (available under the tradename ZYPREXA®, from Lilly); ziprasidone (available under the tradename GEODON®, from Pfizer); risperidone (available under the tradename RISPERDAL®, from Janssen); quetiapine fumarate (available under the tradename SEROQUEL®, from AstraZeneca); sertindole (available under the tradename SERLECT®); amisulpride (available under the tradename SOLION®, from Sanofi-Synthelabo); haloperidol (available under the tradename HALDOL®, from Ortho-McNeil); haloperidol decanoate (available under the tradename HALDOL decanoate®); haloperidol lactate (available under the tradenames HALDOL® and INTENSOL®); chlorpromazine (available under the tradename THORAZINE®, from SmithKline Beecham (GSK)); fluphenazine (available under the tradename PROLIXIN®, from Apothecon, Copley, Schering, Teva, and American Pharmaceutical Partners, Pasadena); fluphenazine decanoate (available under the tradename PROLIXIN decanoate®); fluphenazine enanthate (available under the tradename PROLIXIN®); fluphenazine hydrochloride (available under the tradename PROLIXIN®); thiothixene (available under the tradename NAVANE®, from Pfizer); thiothixene hydrochloride (available under the tradename NAVANE®); trifluoperazine (10-[3-(4-methyl-1-piperazinyl)propyl]-2-(trifluoromethyl)phenothiazine dihydrochloride, available under the tradename STELAZINE®, from SmithKline Beckman); perphenazine (available under the tradename TRILAFON®, from Schering); perphenazine and amitriptyline hydrochloride (available under the tradename ETRAFON TRILAFON®); thioridazine (available under the tradename MELLARIL®; from Novartis, Roxane, HiTech, Teva, and Alpharma); molindone (available under the tradename MOBAN®, from Endo); molindone hydrochloride (available under the tradename MOBAN®); loxapine (available under the tradename LOXITANE®; from Watson); loxapine hydrochloride (available under the

tradename LOXITANE®); and loxapine succinate (available under the tradename LOXITANE®). Furthermore, benperidol (Glianimon®), perazine (Taxilan®) or melperone (Eunerpan®)) may be used.

Other suitable antipsychotic drugs include promazine (available under the tradename SPARINE®), triflurpromazine (available under the tradename VESPRIN®), chlorprothixene (available under the tradename TARACTAN®), droperidol (available under the tradename INAPSINE®), acetophenazine (available under the tradename TINDAL®;), prochlorperazine (available under the tradename COMPAZINE®), methotrimeprazine (available under the tradename NOZINAN®), pipotiazine (available under the tradename PIPOTRIL®), iloperidone, pimozide and flupenthixol.

The antipsychotic drugs listed above by Tradename may also be available from other suppliers under a different Tradename.

In one further aspect of the invention, suitable antipsychotic agents include olanzapine, risperidone, quetiapine, amisulpride, aripiprazole, haloperidol, clozapine, olanzepine, ziprasidone, talnetant and osanetant.

Mood stabilisers which may be used in the therapy of the present invention include lithium, sodium valproate/valproic acid/divalproex, carbamazepine, lamotrigine, gabapentin, topiramate, oxcarbazepine and tiagabine.

Antidepressant drugs which may be used in the therapy of the present invention include serotonin antagonists, CRF-1 antagonists, Cox-2 inhibitor/SSRI dual antagonists; dopamine/noradrenaline/serotonin triple reuptake inhibitors; NK1 antagonists; NK1 and NK2 dual antagonists; NK1/SSRI dual antagonists; NK2 antagonists; serotonin agonists (such as rauwolscine, yohimbine and metoclopramide); serotonin reuptake inhibitors (such as citalopram, escitalopram, fluoxetine, fluvoxamine, femoxetine, indalpine, zimeldine, paroxetine and sertraline); dual serotonin/noradrenaline reuptake inhibitors (such as venlafaxine, reboxetine, duloxetine and milnacipran); Noradrenaline reuptake inhibitors (such as reboxetine); tricyclic antidepressants (such as amitriptyline, clomipramine, imipramine, maprotiline, nortriptyline and trimipramine); monoamine oxidase inhibitors (such as isocarboxazide, moclobemide, phenelzine and tranylcypromine); 5HT3 antagonists (such as example ondansetron and granisetron); and others (such as bupropion, amineptine, radafaxine, mianserin, mirtazapine, nefazodone and trazodone).

Anxiolytics which may be used in the therapy of the present invention include V1b antagonists, 5HT7 antagonists and benzodiazepines such as alprazolam and lorazepam.

Drugs for extrapyramidal side effects which may be used in the therapy of the present invention include anticholinergics (such as benztropine, biperiden, procyclidine and trihexyphenidyl), antihistamines (such as diphenhydramine) and dopaminergics (such as amantadine).

Cognitive enhancers which may be used in the therapy of the present invention include example cholinesterase inhibitors (such as tacrine, donepezil, rivastigmine and galantamine), H3 antagonists and muscarinic M_1 agonists (such as cevimeline).

For use in medicine, the compounds of the present invention are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. The pharmaceutical composition can be for use in the treatment of any of the conditions described herein. In a further aspect, the invention provides a process for preparing a pharmaceutical composition, the process comprising mixing a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers. In a further aspect, the invention provides a pharmaceutical composition comprising a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof in combination with at least 1 antipsychotic, and one or more pharmaceutically acceptable carriers. In a further aspect, the invention provides a process for preparing a pharmaceutical composition, the process comprising mixing a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt thereof, at least 1 antipsychotic, and one or more pharmaceutically acceptable carriers.

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

The compounds of the invention 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 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 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 pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochloro-hydrocarbon. 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. The composition may be in unit dose form such as a tablet, capsule or ampoule.

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

It will be appreciated that the precise dose administered will depend on the age and condition of the patient and the frequency and route of administration and will be at the ultimate discretion of the attendant physician.

The antipsychotic agent component or components used in the adjunctive therapy of the present invention may also be administered in their basic or acidic forms as appropriate or, where appropriate, in the form of a pharmaceutically acceptable salt or other derivative. All solvates and all alternative physical forms of the antipsychotic agent or agents or their salts or derivatives as described herein, including but not limited to alternative crystalline forms, amorphous forms and polymorphs, are also within the scope of this invention. In the case of the antipsychotic agent or agents, the forms and derivatives are, for example, those which are approved for therapeutic administration as monotherapies, including those mentioned above, but all references to antipsychotic agents herein include all salts or other derivatives thereof, and all solvates and alternative physical forms thereof.

For adjunctive therapeutic administration according to the invention, compounds of formula (I) or pharmaceutically acceptable salts thereof and the antipsychotic agent or agents or their salts, derivatives or solvates may each be administered in pure form, but each of the components will, for example, be formulated into any suitable pharmaceutically acceptable and effective composition which provides effective levels of the respective component in the body. The choice of the most appropriate pharmaceutical compositions for each component is within the skill of the art, and may be the same form or different forms for each of the components. Suitable formulations include, but are not limited to tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions.

For simultaneous administration as a combined composition of compounds of formula (I) and the antipsychotic agent or agents according to the invention, compounds of formula (I) or their pharmaceutically acceptable salts and the antipsychotic agent or agents and their salts, derivatives or solvates may be administered together in pure form, but the combined components will, for example, be formulated into any suitable pharmaceutically acceptable and effective composition which provides effective levels of each of the components in the body. The choice of the most appropriate pharmaceutical compositions for the combined components is within the skill of the art. Suitable formulations include, but are not limited to tablets, sub-lingual tablets, buccal compositions, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions.

In order to obtain consistency of adjunctive administration, the compositions of each of the components, or of the combination of the components is, for example, in the form of a unit dose.

The term "treatment" includes prophylaxis, where this is appropriate for the relevant condition(s).

Biological Test Methods

FLIPR experiments on M_1 receptor to determine agonist/antagonist potency

Compounds of the invention were characterized in a functional assay to determine their ability to activate the intracellular calcium pathway in CHO cells with stable expression of human muscarinic receptors using FLIPR (Fluorometric Imaging Plate Reader) technology. Briefly, CHO-M1 cells were plated (15,000/well) and allowed to grow overnight at 37 degrees. Media was removed and 30μL loading buffer (HBSS with 2.5mM probenicid, 2μM Fluo-4, 500μM Brilliant Black, pH 7.4) was added. After incubation at 37 degrees for 90 minutes, 10μL of the assay buffer (HBSS with 2.5 mM probenecid, pH 7.4) containing test compounds was added to each well on the FLIPR instrument. Calcium response was monitored to determine agonism. Plates were then incubated for another 30 minutes before 10μL of assay buffer containing acetylcholine was added at an EC_{80}, as the agonist challenge. Calcium response was then monitored again to determine compound's antagonism to acetylcholine. Concentration-response curves of both agonism and antagonism on M_1 receptors were performed for each compound. Results were imported into ActivityBase data analysis suite (ID Business Solution Inc., Parsippany, NJ) where the curves were analysed by non-linear curve fitting and the resulting pEC_{50}/fpK_i were calculated. The intrinsic activities of agonist compounds were calculated as percentage of maximum FLIPR response induced by acetylcholine added as control on the same compound plates, and converted to a fraction between 0 and 1 (i.e. calculated using a 100% max response from a fitted acetylcholine standard curve, containing multiple concentrations, as control).

The example compounds below were tested in the above assay and were each found to have an average pEC_{50} value of > 6.0 at the muscarinic M_1 receptor, and intrinsic activity > 50%.

FLIPR experiments on M_1 receptor to determine agonist intrinsic activity

To determine the intrinsic activities of M_1 agonist compounds, compounds of the invention were characterized in FLIPR experiments on CHO cells with transient expression of human muscarinic M1 receptors. Briefly, CHO cells were transduced with M1 BacMam virus (Ames, R S; Fornwald, J A; Nuthulaganti, P; Trill, J J; Foley, J J; Buckley, P T; Kost, T A; Wu, Z and Romanos, M A. (2004) *Use of BacMam recombinant baculoviruses to support G protein-coupled receptor drug discovery*. Receptors and Channels 10 (3-4): 99-109) at a multiplicity of infection of 6. The virus to cell ratio was determined in separate

experiments by functional titration to be most appropriate to measure intrinsic activities of partial agonists. After mixing with virus in suspension, cells were then plated (15,000/well) and allowed to grow overnight at 37 degrees. Alternatively, cells were then frozen in 1ml vials at a concentration of $4.8x10^7$ cells/ml in 90% dialysed Foetal Bovine Serum, 10% DimethylSulphoxide at -140 degrees. Cells could then be thawed on the day prior to assay, plated (15,000/well) and allowed to grow overnight at 37 degrees.

The FLIPR experiment was carried out on the day following plating using the same protocol as described above for CHO-M1 cells. Results were imported into ActivityBase data analysis suite where the curves were analysed by non-linear curve fitting and the resulting pEC_{50} values were calculated. The intrinsic activities of agonist compounds were calculated as percentage of maximum FLIPR response induced by acetylcholine added as control on the same compound plates, and converted to a fraction between 0 and 1 (i.e. calculated using a 100% max response from a fitted acetylcholine standard curve, containing multiple concentrations, as control).

The example compounds below were tested in the above assay, and were found to have average pEC_{50} values of > 6.0 at the muscarinic M_1 receptor, and intrinsic activity of greater than or equal to 0.3.

FLIPR experiments on M_{2-5} receptor to determine receptor subtype selectivity

To determine selectivity of compounds of the invention against other muscarinic receptor subtypes, compounds were characterized in FLIPR experiments in CHO cells with stable expression of human muscarinic receptors, M_2, M_3, M_4 or M_5. In the case of M_2 and M_4 receptors, chimeric G-protein Gqi5 was also co-expressed to couple receptors to the calcium signaling pathway. Briefly, cells were plated (15,000/well) and allowed to grow overnight at 37 degrees. The FLIPR experiment was then carried out on the next day using the same protocol as described above for CHO-M1 cells. Results were imported into ActivityBase data analysis suite where the curves were analysed by non-linear curve fitting and the resulting pEC_{50}/fpK_i values were calculated.

The example compounds below were tested in the above assay and were found to be selective for the M_1 receptor over M_2, M_3, M_4 and M_5 receptors, with typical selectivity (ratio of pEC_{50}'s) of $\geq$10-fold, and in certain cases $\geq$ 100-fold.

The invention is further illustrated by the following non-limiting examples. In the procedures that follow, after each starting material, reference to a Description by number is typically provided. This is provided merely for assistance to the skilled chemist.

The starting material may not necessarily have been prepared from the batch referred to.

SCX refers to a sulfonic acid ion exchange resin supplied by Varian. All reactions were either done under argon or can be done under argon, unless stated otherwise (for example hydrogenation reactions).

NMR spectra were run on either a Brucker DPX250A or DPX400B spectrometer at 250 or 400MHz frequency respectively at 295K and run as a dilute solution of d_6-DMSO unless otherwise stated. All NMR spectra were referenced to tetramethylsilane (TMS δH 0, δC 0). All coupling constants are reported in hertz (Hz) and multiplicities are labelled s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets) and m (multiplet).

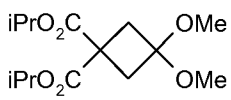
Mass spectra were recorded on an Agilent 1100 LCMS system using a Sunfire C18 3.5 micron reverse phase column eluted with acetonitrile - aqueous ammonium bicarbonate. Total ion current traces were obtained for electrospray positive and negative ionisation (ES+ / ES-) and/or atmospheric pressure chemical positive and negative ionisation (AP+ / AP-).

Starting materials, reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise stated. Unless otherwise stated, all compounds with chiral centres are racemic. Where reactions are described as having been carried out in a similar manner to earlier, more completely described reactions, the general reaction conditions used were essentially the same. Work up conditions used were of the types standard in the art, but may have been adapted from one reaction to another. The starting material may not necessarily have been prepared from the batch referred to. Compounds synthesised may have various purities ranging from for example 85% to 98%. However, calculations of number of moles and yield are generally not adjusted for this.

Abbreviations

dil. Dilute
DMA dimethylacetamide
MDAP mass directed auto purification
PS polystyrene

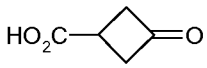
Description 1. Diisopropyl 3,3-dimethoxycyclobutane-1,1-dicarboxylate (D1)



Diisopropyl malonate (108ml) was added dropwise to a suspension of sodium hydride (25g, 60%) in DMF (400ml) at <40°C, followed by 1,3-dibromo-2,2-dimethoxypropane (80g) in one portion. After 24h at 140°C, the mixture was cooled then partitioned between

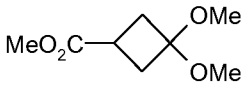
hexane and aqueous ammonium chloride. The organic layer was dried, evaporated, and distilled to give the title compound (41g), b.pt. 100-115°C/0.9mmHg.

Description 2. 3-Oxocyclobutanecarboxylic acid (D2)



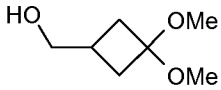
A mixture of diisopropyl 3,3-dimethoxycyclobutane-1,1-dicarboxylate (D1, 17g) and 5M hydrochloric acid (100ml) was heated for 84h at 100°C, then concentrated under vacuum and partitioned between ethyl acetate and brine. Drying and evaporation gave the title compound (4.1g).

Description 3. Methyl 3,3-dimethoxycyclobutanecarboxylate (D3)



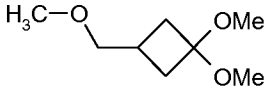
A mixture of 3-oxocyclobutanecarboxylic acid (D2, 4.1g), methanol (20ml), dichloromethane (20ml), trimethyl orthoformate (20ml), and polymer supported p-toluenesulphonic acid (1g, 4mmol/g) was stirred at room temperature for 18h, then filtered and evaporated to give the title compound (5.5g).

Description 4. 3,3-Dimethoxycyclobutanemethanol (D4)



Lithium aluminium hydride (30ml, 1M in THF) was added to a solution of methyl 3,3-dimethoxycyclobutanecarboxylate (D3, 6.6g) in more THF at reflux. After a further 1h at reflux, the mixture was cooled, and treated dropwise with aqueous sodium sulphate (6ml, saturated), then filtered, evaporated, and chromatographed (50g silica, 25-100% ethyl acetate in hexane) to give the title compound (3.2g).

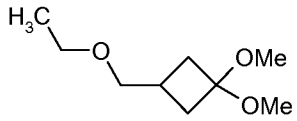
Description 5. 1,1-Dimethoxy-3-(methoxymethyl)cyclobutane (D5)



A stirred solution of 3,3-dimethoxycyclobutanemethanol (D4, 3.2g) in N,N-dimethylformamide (20ml) was treated with sodium hydride (1.4g of 60% oil dispersion), then with iodomethane (4.5ml). After 2h at room temperature the mixture was partitioned

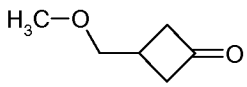
between aqueous ammonium chloride and diethyl ether, dried, evaporated, and chromatographed (50g silica, 0-50% ethyl acetate in hexane) to give the title compound (1.3g).

Description 6. 1,1-Dimethoxy-3-(ethoxymethyl)cyclobutane (D6)



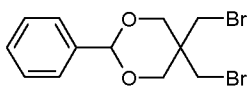
A stirred solution of [3,3-bis(methyloxy)cyclobutyl]methanol (D4, 2.0g, 0.014mole) in N,N-dimethylformamide (15ml) at 0°C under argon was treated with sodium hydride (0.80g of 60% oil dispersion, 0.021mole), then allowed to warm to room temperature and stir for 1.5 hours. The mixture was treated with iodoethane (2.24ml, 0.028mole) and maintained at room temperature for 2 hours, then the mixture was poured into water (100ml) and extracted with ether (2 x 70ml). The combined extract was dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a colourless oil (2.4g, 100%). ^{1}H NMR δ ($CDCl_3$, 400MHz): 1.21 (3H, t), 1.80-1.90 (2H, m), 2.25-2.40 (3H, m), 3.14 (3H, s), 3.15 (3H, s), 3.43 (2H, d), 3.50 (2H, q).

Description 7. 3-(Methoxymethyl)cyclobutanone (D7)



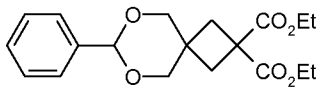
A mixture of 1,1-dimethoxy-3-(methoxymethyl)cyclobutane (D5, 450mg), water (1ml), ethanol (10ml), and polymer supported p-toluenesulphonic acid (250mg, 4mmol/g) was stirred at room temperature for 4h, then filtered, dried, and carfully evaporated. Chromatography (5g silica, 25-50% ethyl acetate in hexane) gave the title compound (150mg).

Description 8. 5,5-Bis(bromomethyl)-2-phenyl-1,3-dioxane (D8)



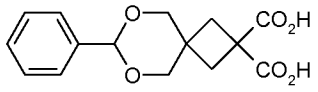
A mixture of 1,3-dibromo-2,2-bis(hydroxymethyl)propane (33g), benzaldehyde (14g), benzene (50ml) and p-toluenesulphonic acid (cat.) was refluxed in a Dean and Stark apparatus until water removal was complete, then washed with aqueous sodium bicarbonate, dried, evaporated, and crystallised from methanol at -10°C to give the title compound (70g).

Description 9. Diethyl 7-phenyl-6,8-dioxaspiro[3.5]nonane-2,2-dicarboxylate (D9)



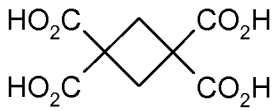
Diethyl malonate (65g) was added carefully to a suspension of sodium hydride (16g, 60%) in DMF (400ml). When reaction ceased, 5,5-bis(bromomethyl)-2-phenyl-1,3-dioxane (D8, 70g) was added and the reaction heated for 4h at 140°C, then cooled and partitioned between aqueous ammonium chloride and ethyl acetate/hexane. The organic layer was dried, evaporated, and crystallised from hexane to give the title compound (45g).

Description 10. 7-Phenyl-6,8-dioxaspiro[3.5]nonane-2,2-dicarboxylic acid (D10)



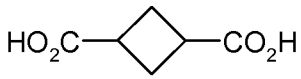
Diethyl 7-phenyl-6,8-dioxaspiro[3.5]nonane-2,2-dicarboxylate (D9, 45g) was added to a solution of potassium hydroxide (24g) in ethanol (500ml). The mixture was heated for 30min at 80°C, then cooled to 0°C, and the dipotassium salt of the title compound isolated by filtration. This was partitioned between water at pH4 and diethyl ether to give the title compound (32g).

Description 11. 1,1,3,3-Cyclobutanetetracarboxylic acid (D11)



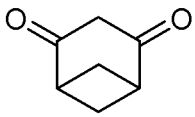
A mixture of 7-phenyl-6,8-dioxaspiro[3.5]nonane-2,2-dicarboxylic acid (D10, 32g) and 2M nitric acid (25ml) was heated for 5min at 100°C, then cooled and washed with diethyl ether. The residual solution was briefly boiled then added to a mixture of concentrated nitric acid (100ml) and fuming nitric acid (1ml) at 100°C. After 1h more evaporated to small volume and formic acid (25ml) added, then evaporated to dryness and extracted with diethyl ether. Addition of hexane precipitated the title compound (10.6g).

Description 12. 1,3-Cyclobutanedicarboxylic acid (D12)



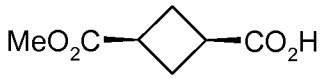
1,1,3,3-Cyclobutanetetracarboxylic acid (D11, 10.6g) was heated at 165°C/20mmHg until evolution of gas ceased and then cooled to give the title compound as a mixture of isomers (5.4g)

Description 13. Bicyclo[3.1.1]heptane-2,4-dione (D13)



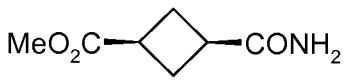
A mixture of 1,3-cyclobutanedicarboxylic acid (D12, 5.4g) and acetyl chloride (10ml) was heated for 2h at 50°C, then evaporated and distilled at 200°C/2mmHg to give the title compound (600mg). The pot residue was extracted with dichloromethane, which was filtered through Celite® and evaporated, then extracted with hot hexane to give further title compound (200mg).

Description 14. *cis*-3-(Methoxycarbonyl)cyclobutanecarboxylic acid (D14)



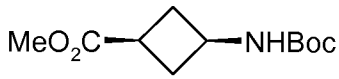
A mixture of bicyclo[3.1.1]heptane-2,4-dione (D13, 600mg), methanol (5ml), THF (5ml), and triethylamine (0.9ml) was combined at 0°C, stirred 2h at room temperature, then evaporated and partitioned between aqueous citric acid and diethyl ether to give the title compound (700mg).

Description 15. *cis*-Methyl 3-(aminocarbonyl)cyclobutanecarboxylate (D15)



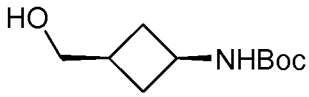
Ethyl chloroformate (0.55ml) was added to a mixture of *cis*-3-(methoxycarbonyl)cyclobutanecarboxylic acid (D14, 760mg), triethylamine (0.8ml), and dichloromethane (50ml) at 0°C, after 30min more ammonia (40ml of 0.3M in dichloromethane) was added, and after another 1h at 0°C and 2h at room temperature, filtration, evaporation, and trituration with diethyl ether gave the title compound (550mg).

Description 16. *cis*-Methyl 3-(tert-butoxycarbonylamino)cyclobutanecarboxylate (D16)



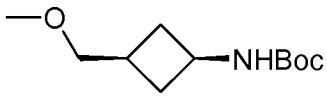
To *cis*-methyl 3-(aminocarbonyl)cyclobutanecarboxylate (D15, 550mg) in t-butanol (20ml) and DMF (10ml) at 40°C was added lead tetraacetate (7.9g). The solution was then refluxed at 100°C for 20min, cooled, evaporated, and filtered through silica (10g), eluting with diethyl ether. The resulting solution was washed with aqueous sodium hydroxide, then water, dried and evaporated. Chromatography (50g silica, 0-50% ethyl acetate in hexane) gave the title compound (350mg).

Description 17. *cis*-3-(tert-Butoxycarbonylamino)cyclobutanemethanol (D17)



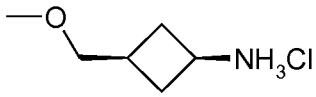
A solution of *cis*-methyl 3-(tert-butoxycarbonylamino)cyclobutanecarboxylate (D16, 350mg) in ethanol (15ml) was treated with calcium chloride (430mg) then sodium borohydride (220mg). After 18h at room temperature, evaporation and partition between water and dichloromethane gave the title compound (250mg).

Description 18. *cis*-1,1-Dimethylethyl 3-[(methoxymethyl)cyclobuty]carbamate (D18)



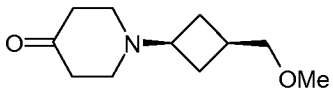
A mixture of *cis*-3-(tert-butoxycarbonylamino)cyclobutanemethanol (D17, 230mg), acetonitrile (12ml), iodomethane (12ml), and silver oxide (1.4g)) was heated for 18h at 40°C, then cooled, filtered and evaporated to give the title compound (230mg).

Description 19. *cis*-3-(Methoxymethyl)cyclobutylamine hydrochloride (D19)



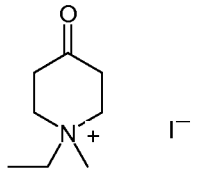
A mixture of *cis*-1,1-dimethylethyl 3-[(methoxymethyl)cyclobuty]carbamate (D18, 230mg) 4M hydrogen chloride in dioxan (5ml), and dichloromethane (5ml) was stirred at room temperature for 4h then evaporated to give the title compound (160mg).

Description 20. *cis*-1-[3-(methoxymethyl)cyclobutyl]-4-piperidone (D20)



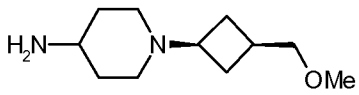
A mixture of *cis*-3-(methoxymethyl)cyclobutylamine hydrochloride (D19, 160mg), ethanol (10ml), water (5ml), potassium carbonate (200mg), and 1-ethyl-1-methyl-4-piperidonium iodide (D21, 400mg) was heated at 80°C for 1h, then partitioned between water and dichloromethane, then dried, evaporated, and chromatographed (5g silica, 0-10% methanol in dichloromethane containing ammonia) to afford the title compound (140mg).

Description 21. 1-Ethyl-4-piperidone methiodide (D21)



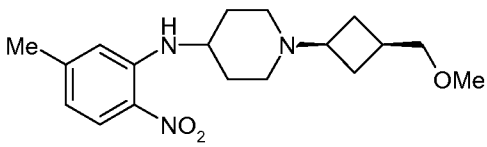
Iodomethane (65ml) was added in portions to a solution of 1-ethyl-4-piperidone (100g) in acetone (1l) at 20-30°C (internal, ice cooling). After stirring for 3h more, the title compound was obtained by filtration (189g).

Description 22. *cis*-1-[3-(methoxymethyl)cyclobutyl]-4-piperidinamine (D22)



A solution of *cis*-1-[3-(methoxymethyl)cyclobutyl]-4-piperidone (D20, 140mg) in 2M ammonia/methanol (50ml) was treated with 10% Pd/C paste (50mg) and shaken under hydrogen atmosphere at initial pressure of 50psi for 18 hours. The catalyst was removed by filtration and the filtrate concentrated under vacuum then purified by SCX chromatography to afford the title compound (100mg).

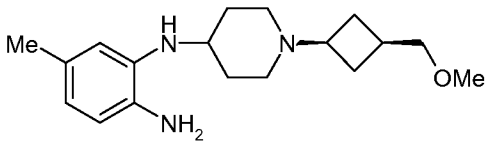
Description 23. *cis*-N-(5-Methyl-2-nitrophenyl)-1-[3-(methoxymethyl)cyclobutyl]-4-piperidinamine (D23)



A mixture of *cis*-1-[3-(methoxymethyl)cyclobutyl]-4-piperidinamine (D22, 100mg), N,N-dimethylformamide (5ml), diisopropylethylamine (0.34ml), and 3-fluoro-4-nitrotoluene (120mg) was heated at 50°C for 66h. The solution was then cooled, diluted with ethyl acetate and washed three times with water, then dried, and concentrated under vacuum

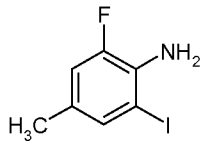
and chromatographed (5g silica, 0-10% methanol in dichloromethane containing ammonia) to afford the title compound (90mg).

Description 24. *cis*-N-(5-Methyl-2-aminophenyl)-1-[3-(methoxymethyl)cyclobutyl]-4-piperidinamine (D24)



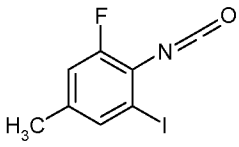
A solution of *cis*-N-(5-methyl-2-nitrophenyl)-1-[3-(methoxymethyl)cyclobutyl]-4-piperidinamine (D23, 90mg) in ethanol (10ml) at 50°C was treated with Raney nickel (0.5ml of 10% aq. suspension) then hydrazine hydrate (0.5ml). After 1h more at the same temperature the catalyst was removed by filtration through Celite® and the filtrate evaporated and re-evaporated from toluene then diethyl ether to afford the title compound (75mg).

Description 25. 2-Fluoro-6-iodo-4-methylaniline (D25)



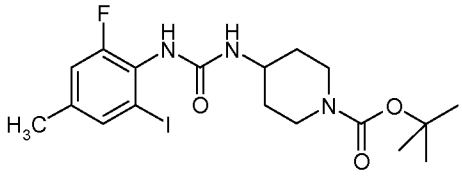
A solution of 2-fluoro-4-methylaniline (1.0 g, 8 mmol) in glacial acetic acid (10 ml) was treated with sodium acetate trihydrate (2.2 g, 16 mmol) then iodine monochloride (1.3 g). After 30min at room temperature aqueous sodium bicarbonate / sodium sulfite and diethyl ether were added, and the organic phase was dried ($MgSO_4$), evaporated and chromatographed on silica eluting with 0 to 30% ethyl acetate in hexane to give the title compound (370 mg).

Description 26. 1-Fluoro-3-iodo-2-isocyanato-5-methylbenzene (D26)



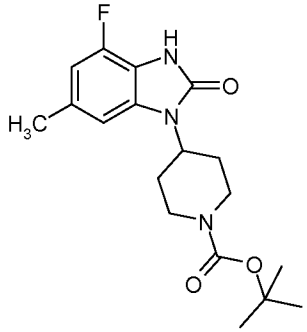
A mixture of 2-fluoro-6-iodo-4-methylaniline (D25) (370 mg, 1.5 mmol), triphosgene (150 mg, 0.05mmol), and dioxan (3 ml) was heated at reflux for 1h 15min then cooled and evaporated to give the crude title compound.

Description 27. 1,1-Dimethylethyl 4-({[(2-fluoro-6-iodo-4-methylphenyl)amino]-carbonyl}amino)-1-piperidinecarboxylate (D27)



A mixture of crude 1-fluoro-3-iodo-2-isocyanato-5-methylbenzene (D26), 4-amino-1-N-Boc piperidine (200 mg, 1mmol), and dichloromethane (3 ml) was stirred at room temperature for 1h then directly purified by chromatography on silica gel eluting with 0 to 10% methanol in dichloromethane. Further purification by MDAP (mass-directed auto-purification) gave the title compound (300 mg).

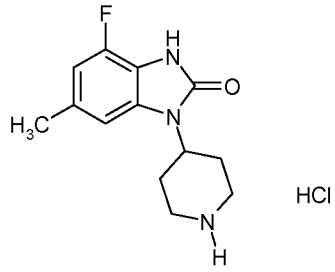
Description 28. 1,1-Dimethylethyl 4-(4-fluoro-6-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-piperidinecarboxylate (D28)



Under an argon atmosphere, a mixture of 1,4-dioxane (3 ml), palladium 1,1'-bis(diphenylphosphino)ferrocene dichloride (10% mol, 0.0623 mmol, 50 mg), and NaO^tBu (2 eq., 1.26 mmol, 121 mg), was sonicated for 10 minutes at room temperature and 1,1-dimethylethyl 4-({[(2-fluoro-6-iodo-4-methylphenyl)amino]carbonyl}amino)-1-piperidine-carboxylate (D27) (1 eq., 0.623 mmol, 300 mg) was added at room temperature and the mixture was refluxed at 80 °C overnight. The reaction mixture was cooled to room temperature, poured onto NH_4Cl (saturated solution) and the aqueous solution obtained was extracted with ethyl acetate repeatedly; the organics were combined, dried over Na_2SO_4, filtered and the solvent was evaporated to afford the crude compound (250 mg) that was purified by MDAP to yield the title compound, (30mg , 11%).

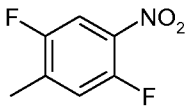
^1H NMR δ (d_6-DMSO, 400 MHz) 1.44 (9H, s), 1.68 (2H, d broad), 2.20 (2H, dddd), 2.32 (3H, s), 2.85 (2H, s broad), 4.05 (2H, m broad), 4.30 (1H, m broad), 6.72 (1H, d), 6.90 (1H, s), 11.3 (1H, s broad).

Description 29. 4-Fluoro-6-methyl-1-(4-piperidinyl)-1,3-dihydro-2H-benzimidazol-2-one hydrochloride (D29).



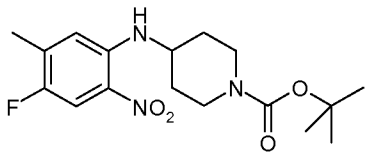
1,1-Dimethylethyl 4-(4-fluoro-6-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-piperidinecarboxylate D28 (0.072 mmol, 25 mg) was dissolved in dichloromethane (5 ml) and was treated with HCl (3 ml of a 4M solution in 1,4-dioxane) at room temperature; the mixture was stirred at room temperature for two hours. Solvent was evaporated to afford the title compound as the mono hydrochloride salt, $M^+ + H = 250$.

Description 30. 2,5-difluoro-4-nitrotoluene (D30)



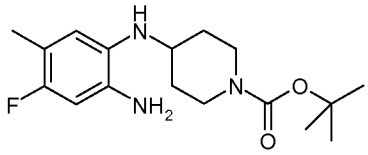
A solution of 2,5-difluorotoluene (10g) in concentrated sulphuric acid (50ml) at 20°-30°C was treated portionwise with potassium nitrate (7.9g). After 15min, the mixture was poured onto ice and extracted with hexane:diethyl ether (1:1), washed with water, dried, and evaporated to give the title compound (8.9g).

Description 31. 1,1-Dimethylethyl 4-[(4-fluoro-5-methyl-2-nitrophenyl)amino]-1-piperidine-carboxylate (D31).



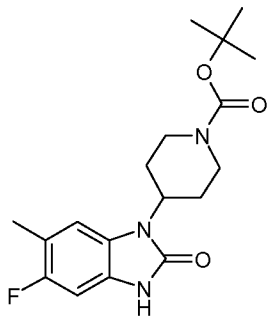
1,4-Difluoro-2-methyl-5-nitrobenzene (D30, 1.5 mol, 260 mg) in dimethylformamide (10 mL) was treated under argon at room temperature with 1,1-dimethylethyl 4-amino-1-piperidinecarboxylate (1.5 mmol, 300.5 mg, 1 eq) and diisopropylethylamine (1.5 mmol, 260 µL, 1 eq) then stirred at 70-80 °C for 38h. The mixture was concentrated under reduced pressure, treated with water and extracted twice with ether. Organics were combined, dried over $MgSO_4$ and concentrated under reduced pressure to give a red-brown residue which was chromatographed (0-25% ethyl acetate/petrol ether) to give the title compound as a red solid (0.96 mmol, 340 mg, 64% yield). M+H-^{t}Bu = 298.07, main fragment.

Description 32. 1,1-Dimethylethyl 4-[(2-amino-4-fluoro-5-methylphenyl)amino]-1-piperidinecarboxylate (D32).



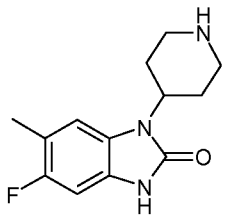
1,1-Dimethylethyl 4-[(4-fluoro-5-methyl-2-nitrophenyl)amino]-1-piperidinecarboxylate (D31) (0.96 mmol, 340 mg) in ethanol (10 mL) was treated under argon at room temperature with Raney Nickel (50% in water, 0.5 mL) then dropwise with hydrazine hydrate (9.6 mmol, 10 eq) in ethanol over 15min. The mixture was heated at 45°C for 50min. The Raney nickel was filtered off and washed with ethanol. The filtrate was concentrated under reduced pressure to give the title compound (0.88 mmol, 284 mg, 92% yield). M+H = 324.16

Description 33. 1,1-Dimethylethyl 4-(5-fluoro-6-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-piperidine-carboxylate (D33).



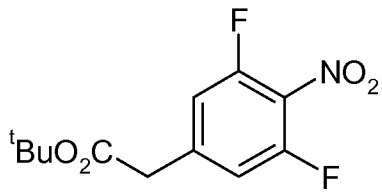
1,1-Dimethylethyl 4-[(2-amino-4-fluoro-5-methylphenyl)amino]-1-piperidinecarboxylate (D32) (0.88 mmol, 284 mg) in tetrahydrofuran (5 mL) was treated with N,N'-carbonyldiimidazole (0.88 mmol, 141 mg, 1 eq) under argon and was stirred at room temperature for 3h then heated at 45 °C for 45 min, then N,N'-carbonyldiimidazole (0.44 mmol, 70 mg, 0.5 eq) was added and allowed to react for 45 min. The mixture was concentrated, partitioned between 10% Na_2CO_3 aqueous solution and ethyl acetate. The organic extracts were dried on $MgSO_4$, concentrated and chromatographed to give the title compound (0.68 mmol, 239 mg, 77% yield). M-H = 348.3

Description 34. 5-Fluoro-6-methyl-1-(4-piperidinyl)-1,3-dihydro-2H-benzimidazol-2-one (D34).



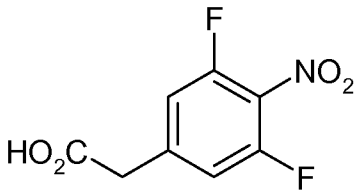
1,1-Dimethylethyl 4-(5-fluoro-6-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-piperidine-carboxylate (D33) (0.68 mmol, 239 mg) in dichloromethane (5 mL) was treated under argon at room temperature with trifluoroacetic acid (1 mL) and allowed to stir for 1h. The mixture was concentrated, treated with 10% Na_2CO_3 aqueous solution, extracted 3 times with ethyl acetate. Organics were combined, dried on $MgSO_4$, and concentrated under reduced pressure to give the title compound (0.64 mmol, 160 mg, 94% yield). M+H = 250.2

Description 35. 1,1-dimethylethyl (3,5-difluoro-4-nitrophenyl)acetate (D35)



A mixture of potassium *tert*-butoxide (248g) in N-methyl-2-pyrrolidinone (2000ml) was cooled under nitrogen to -20°C. A mixture of 2,6-difluoronitrobenzene (100g) and *tert*-butylchloroacetate (160g) in N-methyl-2-pyrrolidinone (2000ml) was added slowly at -10°C to -20°C over 1.5 hours. After 30 minutes, a further portion of potassium *tert*-butoxide (88g) was added. The reaction mass was quenched into 1600ml of 2M HCl and 1kg crushed ice, then 2000ml hexane was added and the mixture stirred for 10 minutes. The layers were separated and the aqueous layer was extracted with hexane (2 x 1500ml). The combined hexane layers were washed with saturated brine (2 x 1000ml), then dried over anhydrous sodium sulphate, then filtered and washed with 200ml hexane. The solution was then evaporated to give the title compound as a brown liquid (152g).

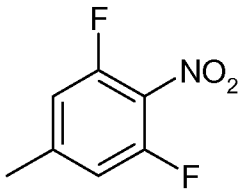
Description 36. (3,5-difluoro-4-nitrophenyl)acetic acid (D36)



1,1-Dimethylethyl (3,5-difluoro-4-nitrophenyl)acetate (D35, 150g) and 4M HCl in 1,4-dioxane (1150ml) was stirred for 18 h at about 25°C. Nitrogen was bubbled through the mixture to remove excess HCl over 7 hours, then the mixture was concentrated. Toluene (300ml) was distilled off then the residue was stirred with hexane (300ml) for 10 minutes. The hexane was decanted off, and the residue stirred with hexane (150ml) for 10 minutes, then the hexane was decanted off. The residue was stirred with toluene (450ml) for 2 hours at around 25°C. The solid was filtered and washed with 1:1 toluene/hexane (300ml), then dried under vacuum to give the title compound as a brown fine powder (41.5g).

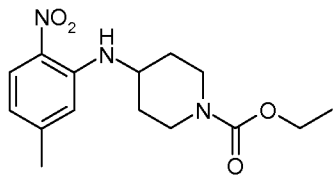
^{1}H NMR δ (d_6-DMSO, 300 MHz, d_5-DMSO as reference at 2.5 ppm): 3.78 (2H) s; 7.44 (2H) d.

Description 37. 1,3-difluoro-5-methyl-2-nitrobenzene (D37)



A mixture of (3,5-difluoro-4-nitrophenyl)acetic acid (D36, 41g), potassium carbonate (24.6g) and DMF (205ml) was slowly heated to about 50°C for 30 minutes. The reaction was then cooled to about 25°C and quenched into 2M HCl (1025ml) and hexane (400ml) and stirred for 10 minutes. The layers were separated and the aqueous layer was extracted with hexane (400ml). The combined hexane layers were washed with saturated brine (2 x 200ml), then dried with anhydrous sodium sulphate and the solution was concentrated to give the title compound as a low melting solid (26g).

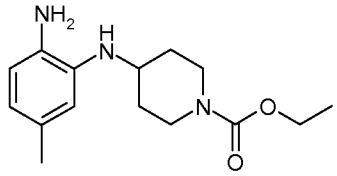
Description 38. Ethyl 4-[(5-methyl-2-nitrophenyl)amino]-1-piperidinecarboxylate (D38).



Ethyl-4-amino-1-piperidine-carboxylate (18.3 g, 106 mmol) was added to a stirred suspension of 3-fluoro-4-nitrotoluene (15.0g g, 97 mmol), sodium carbonate (10.3 g, 97 mmol) and potassium iodide (0.16 g, 0.97 mmol) in dimethylformamide (150 mL). The mixture was heated to 50 °C, stirred for 15 hours and then allowed to cool. The reaction mixture was diluted with water (200 mL) and ethyl acetate (200 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 x 200 mL). The organic extracts were combined, extracted with a 10% aqueous solution of citric acid

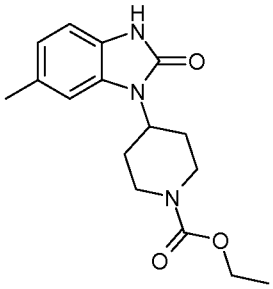
(250 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica, eluting with dichloromethane and then ethyl acetate/hexane (7:8) to give the title compound (25.0 g, 84 % yield) as a yellow solid. (R_f: 0.3 (ethyl acetate/hexane 7:8))

Description 39. Ethyl 4-[(2-amino-5-methylphenyl)amino]-1-piperidinecarboxylate (D39)



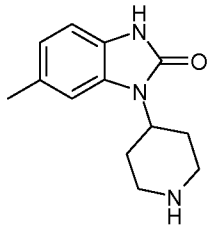
A suspension of D38 (20.0 g, 65 mmol) and 5% Pd/C (3.0g) in methanol (400 mL) in an autoclave (1000 mL) was put under an atmosphere of hydrogen (~ 50 atm). The mixture was stirred at room temperature for 3 hours and then filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure to give the title compound (18.0 g, 100% yield) as a purple oil that was used without further purification. (R_f: 0.1 (ethyl acetate/hexane 7:8))

Description 40. Ethyl 4-(6-methyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-piperidinecarboxylate (D40).



A solution of 1,1´-carbonyldiimidazole (12.2 g, 75 mmol) in acetonitrile (150 mL) was added portionwise over 10 minutes to a stirred solution of D39 (13.0 g, 47 mmol) in acetonitrile (150 mL) at 40 °C. The reaction mixture was heated at 40 °C for 36 hours and then allowed to cool. The precipitate was collected by filtration and washed with acetonitrile (2 x 50 mL) to give the title compound (10.8 g, 76% yield) as a light purple solid that was used without further purification (R_f: 0.5 (ethyl acetate/hexane 7:8)). m.p. 222 – 224 °C.

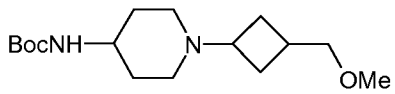
Description 41. 6-Methyl-1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one (D41).



D40 (12.5 g, 41 mmol) was suspended in a 2.5 M aqueous solution of sodium hydroxide (150 mL). The suspension was refluxed for 15 hours and then allowed to cool. The solution was acidified with 6 M HCl (~ 70 mL) until no more effervescence was observed (~ pH 2) and then the pH was carefully adjusted to pH 8.5 using 2.5 M aqueous NaOH. The resulting precipitate was collected by filtration, washed with cold water (20 mL) and then dried under vacuum at 40 °C for 15 hours to give the title compound (9.5 g, 100% yield) as a beige solid (R_f: Baseline (ethyl acetate/hexane 2:3)).

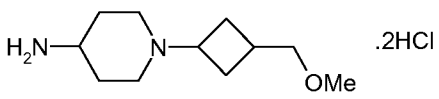
^{1}H NMR (300 MHz, d_6-DMSO): δ 10.77 (1H, br s), 9.00 (1H, br s), 7.29 (1H, s), 6.84 (1H, d), 6.78 (1H, d), 4.51 – 4.47 (1H, m), 3.33 – 3.30 (2H, m), 3.03 – 2.99 (2H, m), 2.61 – 2.58 (2H, m), 2.46 (3H, s), 1.76 – 1.72 (2H,m); m.p. >300 °C.

Description 42. N-Boc 1-[3-(methoxymethyl)cyclobutyl]-4-piperidinamine (D42)



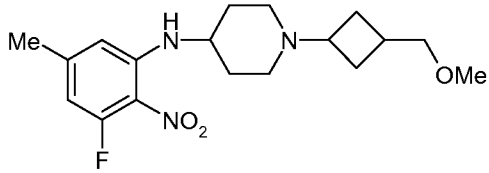
A mixture of 3-(methoxymethyl)cyclobutanone (D7, 1.0ml, 1M in dichloromethane), 4-(t-butyloxycarbonylamino)piperidine (100mg), acetic acid (0.05ml), dichloromethane (1.5ml), and polymer supported sodium cyanoborohydride (600mg, 2.04 mmol/g) was heated in the microwave for 10min at 110 °C, then filtered and the solvent evaporated. Chromatography (10g silica, 0-10% methanol in dichloromethane containing ammonia) afforded the title compound as a mixture of isomers (70mg).

Description 43. 1-[3-(methoxymethyl)cyclobutyl]-4-piperidinamine dihydrochloride (D43)



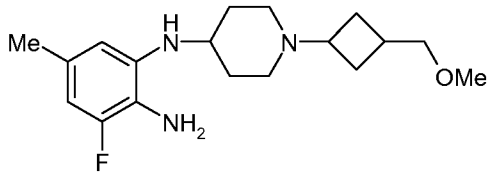
A mixture of N-Boc 1-[3-(methoxymethyl)cyclobutyl]-4-piperidinamine (D42, 70mg), dichloromethane (2ml), and HCl in dioxan (1ml, 4M) was stirred at room temperature for 4h then the solvent was evaporated to give the title compound (55mg).

Description 44. N-(5-Methyl-3-fluoro-2-nitrophenyl)-1-[3-(methoxymethyl)cyclobutyl]-4-piperidinamine (D44)



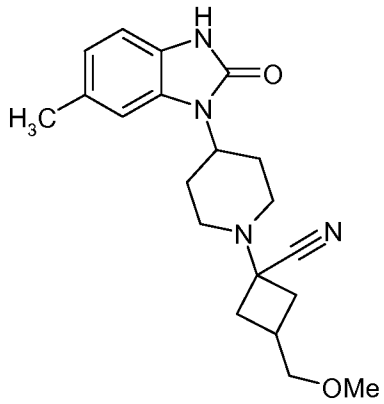
A mixture of 1-[3-(methoxymethyl)cyclobutyl]-4-piperidinamine (D43, 180mg), N,N-dimethylformamide (5ml), diisopropylethylamine (0.5ml), and 3,5-difluoro-4-nitrotoluene (D37, 120mg) was heated at 50°C for 18h. The solution was then cooled, diluted with ethyl acetate and washed three times with water, then dried, and concentrated under vacuum and chromatographed (12+M Biotage NH column, 0-15% ethyl acetate in hexane) to afford the title compound as a mixture of isomers (100mg).

Description 45. N-(5-Methyl-3-fluoro-2-aminophenyl)-1-[3-(methoxymethyl)cyclobutyl]-4-piperidinamine (D45)



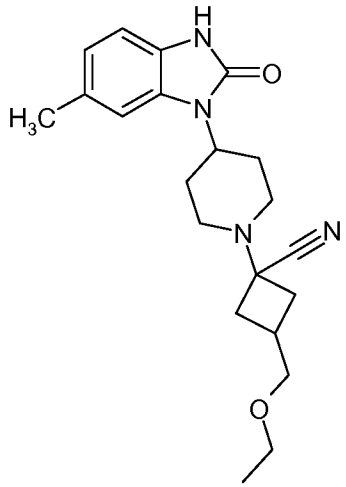
A solution of, N-(5-methyl-3-fluoro-2-nitrophenyl)-1-[3-(methoxymethyl)cyclobutyl]-4-piperidinamine (D44, 100mg) in ethanol (10ml) at 50°C was treated with Raney nickel (0.5ml of 10% aq. suspension) and hydrazine hydrate (0.2ml). After 1h more at the same temperature the catalyst was removed by filtration through Celite® and the filtrate evaporated and reevaporated from toluene to afford the title compound as a mixture of isomers (80mg).

Description 46. 1-[4-(6-methyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-piperidinyl]-3-(methoxymethyl)cyclobutanecarbonitrile (D46)



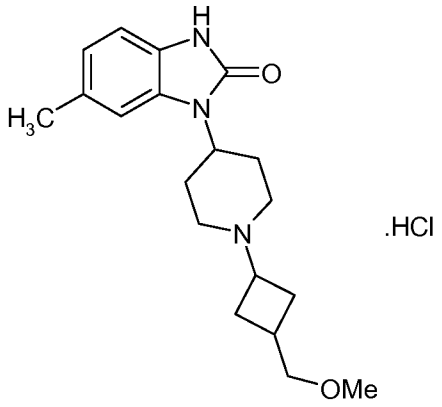
1,1-Dimethoxy-3-(methoxymethyl)cyclobutane (D5, 160mg) was converted to 3-(methoxymethyl)cyclobutanone by stirring for 4h with diethyl ether (10 ml), water (1 ml), and polymer supported toluenesulphonic acid (4mm0l/g, 100mg) followed by filtration, drying, and careful evaporation. A mixture of this ketone, 6-methyl-1-(4-piperidinyl)-1,3-dihydro-2H-benzimidazol-2-one (D41, 110mg), acetone cyanohydrin (100 mg), magnesium sulphate (300 mg), and DMA (1 ml) was then strirred at 60°C overnight under a slow stream of argon, partitioned between dichloromethane and water and crystallised from diethyl ether to give the title compound (85mg).

Description 47. 1-[4-(6-methyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-piperidinyl]-3-(ethoxymethyl)cyclobutanecarbonitrile (D47)



1,1-Dimethoxy-3-(ethoxymethyl)cyclobutane (D6, 170mg) was converted to 3-(methoxymethyl)cyclobutanone by stirring overnight with diethyl ether (10 ml), water (1 ml), and polymer supported toluenesulphonic acid (4mm0l/g, 100mg) followed by filtration, drying, and careful evaporation. A mixture of this ketone, 6-methyl-1-(4-piperidinyl)-1,3-dihydro-2H-benzimidazol-2-one (D41, 110mg), acetone cyanohydrin (100 mg), magnesium sulphate (300 mg), and DMA (1 ml) was then strirred at 60°C overnight under a slow stream of argon, partitioned between dichloromethane and water and crystallised from diethyl ether to give the title compound (120mg).

Example 1. 6-Methyl-1-(1-{3-[(methoxymethyl)cyclobutyl}-4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (E1)

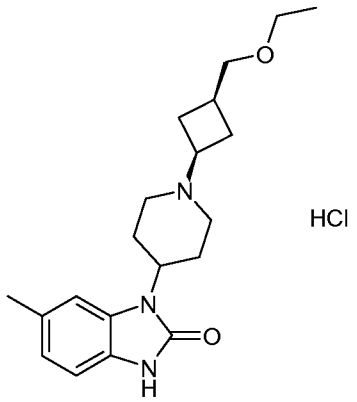


A mixture of 3-(methoxymethyl)cyclobutanone (D7, 75mg), dichloromethane (2.5ml), 6-methyl-1-(4-piperidinyl)-1,3-dihydro-2H-benzimidazol-2-one (D41, 110mg), acetic acid (0.15ml), and PS-cyanoborohydride (600mg of 2.04 mmole/g loading) was heated in a microwave reactor at 110°C for 10 minutes. The mixture was filtered and the filtrate loaded onto an SCX cartridge, washed with methanol and eluted with 2M ammonia in methanol. Purification by high pH MDAP gave the title compound as a mixture of cis/trans isomers, isolated as the hydrochloride salt from diethyl ether (20mg)).

MH^+ 330.

^1H NMR (HCl salt) δ (d_6-DMSO): 1.8 (2H, m), 2.1 (2H, m), 2.3 (2H, m), 2.4 (3H, s), 2.7 (2H, m), 3.0 (2H, m), 3.2-3.7 (12H,m), 4.5 (1H, m), 6.8 (2H, m), 7.4 (1H, 2s), 10.5 and 10.7 (1H, 2bs), 10.8 (1H, s).

Example 2. 1-(1-{*cis*-3-[(Ethyloxy)methyl]cyclobutyl}-4-piperidinyl)-6-methyl-1,3-dihydro-2H-benzimidazol-2-one hydrochloride (E2)



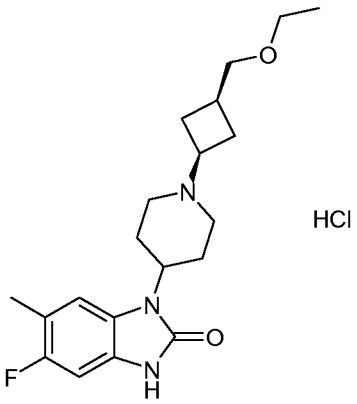
A solution of 1,1-dimethoxy-3-(ethoxymethyl)cyclobutane (D6, 200mg, 1.15mmole) in dichloromethane (5ml) was treated with 5M HCl acid (4ml) and stirred vigorously for 1.5 hours. The dichloromethane layer was separated, dried (Na_2SO_4) and diluted further with dichloromethane (2ml), then treated with 6-methyl-1-(4-piperidinyl)-1,3-dihydro-2H-benzimidazol-2-one (D41, 231mg, 1.0mmole), acetic acid (0.17ml, 3.0mmole), and PS-cyanoborohydride (1g of 2.04 mmole/g loading, 2.04 mmole) and heated in a microwave

reactor at 100°C for 10 minutes. The mixture was filtered and the filtrate loaded onto an SCX cartridge (2g), washed with dichloromethane and then eluted with 2M ammonia/methanol to remove the product. Recrystallisation of product from ethyl acetate afforded a white solid which was approx. 2:1 mixture of isomers. The mother liquors were concentrated under vacuum and shown to be the same 2:1 mixture of isomers (75mg). This latter material was chromatographed on silica gel (40g) eluting with 4% methanol/ethyl acetate to afford cis isomer in the early fractions. Combination of fractions containing cis isomer and concentration under vacuum, followed by crystallisation of the residue from ether (8ml) afforded the free base of the title compound as a white solid (29mg) (>90% cis isomer). This material was dissolved in mixture of dichloromethane (2ml) and methanol (0.5ml), treated with 1M HCl/ether (0.17ml) and concentrated under vacuum to afford the title compound as a white solid (32mg).

MH+ 343.

^{1}H NMR (free base) δ ($CDCl_3$, 400MHz): 1.21 (3H, t), 1.58-1.70 (2H, m), 1.83 (2H, br d), 1.96 (2H, br t), 2.20-2.32 (3H, m), 2.35-2.50 (2H, m), 2.38 (3H, s), 2.62-2.72 (1H, m), 3.06 (2H, br d), 3.43 (2H, d), 3.48 (2H, q), 3.30-3.40 (1H, m), 6.85 (1H, d), 6.97 (1H, d), 7.14 (1H, s), 9.44 (1H, br s).

Example 3. 1-(1-{*cis*-3-[(Ethyloxy)methyl]cyclobutyl}-4-piperidinyl)-5-fluoro-6-methyl-1,3-dihydro-2H-benzimidazol-2-one hydrochloride (E3)



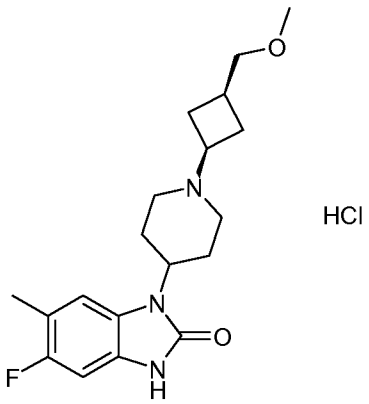
A solution of 1,1-dimethoxy-3-(ethoxymethyl)cyclobutane (D6, 300mg, 1.72mmole) in dichloromethane (5ml) was treated with 5M HCl acid (5ml) and stirred vigorously for 2.5 hours. The dichloromethane layer was separated then treated with 5-fluoro-6-methyl-1-(4-piperidinyl)-1,3-dihydro-2H-benzimidazol-2-one hydrochloride (D34, 428mg, 1.5mmole), acetic acid (0.29ml, 5.1mmole), anhydrous sodium acetate (205mg, 2.5mmole) and PS-cyanoborohydride (700mg of 4.3 mmole/g loading, 3.0mmole) and heated in a microwave reactor at 100°C for 10 minutes. The mixture was filtered and the filtrate loaded onto an SCX cartridge (5g), washed with dichloromethane and methanol, then eluted with 2M ammonia/methanol to remove the product. This latter solution was concentrated under vacuum and the residue crystallisation from ethyl acetate afforded a white solid (310mg)

which was approx. 2:1 mixture of cis:trans isomers. This material was chromatographed on silica gel (100g) eluting with 3% methanol/ethyl acetate to afford the cis isomer in the early fractions. Combination of fractions containing cis isomer and concentration under vacuum, followed by crystallisation of the residue from ether afforded the free base of the title compound as a white solid (41mg) (>95% cis isomer). This material was dissolved in mixture of dichloromethane (2ml) and methanol (0.3ml), treated with 1M HCl/ether (0.30ml) and concentrated to afford the title compound as a white solid (41mg).

MH^+ 361.

^1H NMR (free base) δ ($CDCl_3$, 400MHz): 1.20 (3H, t), 1.57-1.70 (2H, m), 1.83 (2H, br d), 1.97 (2H, br t), 2.18-2.32 (3H, m + 3H, s), 2.32-2.50 (2H, m), 2.63-2.73 (1H, m), 3.07 (2H, br d), 3.43 (2H, d), 3.49 (2H, q), 4.25-4.40 (1H, m), 6.81 (1H, d), 7.07 (1H, d), 9.88 (1H, br s).

Example 4. 5-Fluoro-6-methyl-1-(1-{*cis*-3-[(methyloxy)methyl]cyclobutyl}-4-piperidinyl)-1,3-dihydro-2H-benzimidazol-2-one hydrochloride (E4)



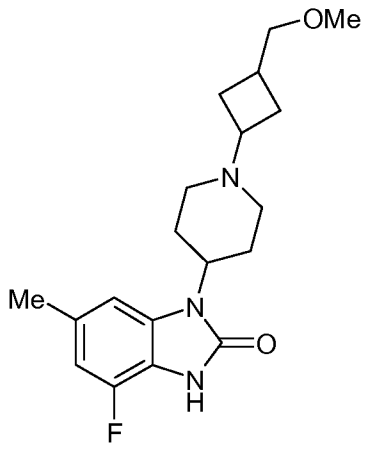
A solution of 3,3-dimethoxycyclobutanemethanol (D5, 200mg, 1.25mmole) in dichloromethane (4ml) was treated with 5M HCl acid (3ml) and stirred vigorously at room temperature for 2 hours. The dichloromethane layer was separated, more dichloromethane added (4ml) , followed by 5-fluoro-6-methyl-1-(4-piperidinyl)-1,3-dihydro-2H-benzimidazol-2-one hydrochloride (D34, 200mg, 1.25mmole), acetic acid (0.21ml, 3.7mmole), anhydrous sodium acetate (150mg, 1.8mmole) and PS-cyanoborohydride (510mg of 4.3 mmole/g loading, 2.2mmole) and heated in a microwave reactor at 100°C for 10 minutes. The mixture was filtered and the filtrate diluted with dichloromethane (10ml), washed with 10% Na_2CO_3 solution (15ml), dried (Na_2SO_4) and concentrated under vacuum. The residue was chromatographed on silica gel (100g) eluting with 5% methanol/ethyl acetate to afford mainly cis isomer in the early fractions. Combination of fractions containing >85% cis isomer and concentration under vacuum, followed by crystallisation of the residue from ether afforded the free base of the title compound as a white solid (35mg) (approx. 90% cis isomer). This material was dissolved in

dichloromethane (2ml), treated with 1M HCl/ether (0.3ml) and concentrated to afford the title compound as a white solid (37mg).

MH^+ 361.

^1H NMR (free base) δ ($CDCl_3$, 400MHz): 1.60-1.72 (2H, m), 1.80 (2H, br d), 1.95 (2H, br t), 2.18-2.32 (2H, m), 2.29 (3H, s), 2.32-2.48 (2H, m), 2.62-2.73 (1H, m), 3.05 (2H, br d), 3.34 (3H, s), 3.38 (2H, d), 4.27-4.40 (1H, m), 6.82 (1H, d), 7.07 (1H, d), 10.10 (1H, br s).

Example 5. 4-Fluoro-6-methyl-1-{1-[4-(methoxymethyl)cyclobutyl]-4-piperidinyl}-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (E5)

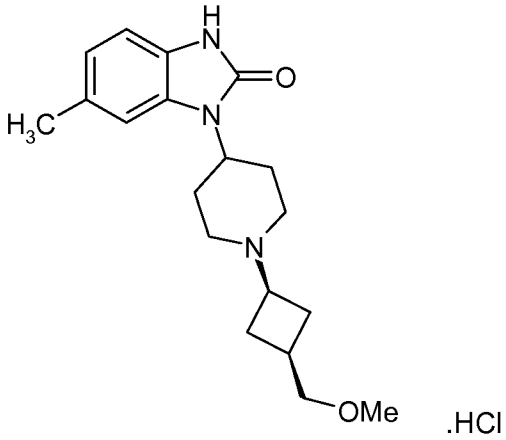


.HCl

A stirred solution of N-(5-methyl-3-fluoro-2-aminophenyl)-1-[3-(methoxymethyl)cyclobutyl]-4-piperidinamine (D45, 80mg) in dichloromethane (8ml) at 0°C was treated with triphosgene (30mg) then diisopropylethylamine (0.08ml). After 30min at 0°C the mixture was partitioned between dil. $NaHCO_3$ solution and dichloromethane. Drying, evaporation, crystallisation from diethyl ether, conversion to the hydrochloride salt and purification by MDAP gave the title compound as a mixture of isomers, isolated as the hydrochloride salt from diethyl ether (7mg). MH^+ = 348.

^1H NMR (HCl salt) δ (DMSO-d^6): 1.8 (2H, m), 2.1 (2H, m), 2.3 (2H, m), 2.4 (3H, s), 2.7 (2H, m), 3.0 (2H, m), 3.2-3.7 (12H,m), 4.5 (1H, m), 6.8 (2H, m), 7.3 (1H, 2s), 10.3 and 10.6 (1H, 2bs), 11.4 (1H, s).

Example 6. *cis*-6-Methyl-1-(1-{3-[(methoxymethyl)cyclobutyl}-4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (E6)

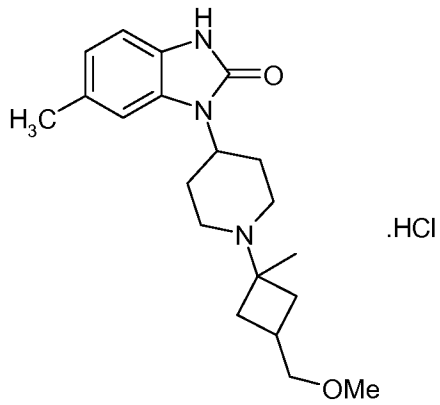


.HCl

A stirred solution of *cis*-N-(5-methyl-2-aminophenyl)-1-[3-(methoxymethyl)cyclobutyl]-4-piperidinamine (D24, 75mg) in dichloromethane (5ml) at 0°C was treated with triphosgene (30mg) then diisopropylethylamine (0.08ml). After 30min at 0°C the mixture was partitioned between dil. $NaHCO_3$ solution and dichloromethane. Drying, evaporation, and crystallisation from diethyl ether gave the title compound, isolated as the hydrochloride salt from diethyl ether (48mg). MH^+ = 330.

^1H NMR (HCl salt) δ (d_6-DMSO): 1.9 (2H, d), 2.1 (2H, m), 2.3 (2H, m), 2.4 (3H, s), 2.7 (2H, q), 3.0 (2H, q), 3.3 (3H, s), 3.4 (2H,d), 3.5 (3H, m), 4.5 (1H, m), 6.7 (1H, d), 6.8 (1H, d), 7.3 (1H, s), 10.6 (1H, bs), 10.8 (1H, s).

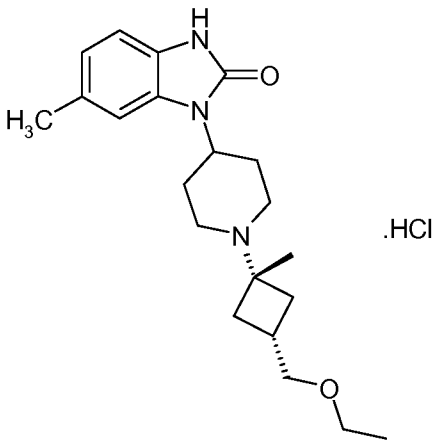
Example 7. cis and trans 6-Methyl-1-(1-{1-methyl-3-[(methoxymethyl)cyclobutyl}-4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (E7)



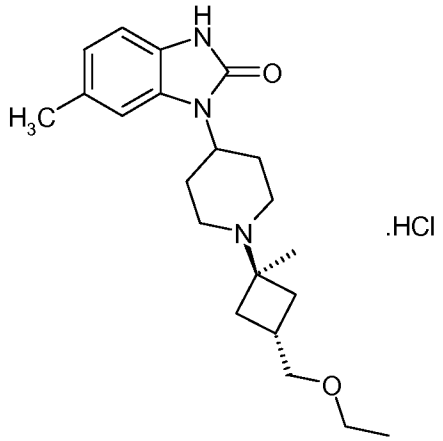
.HCl

A mixture of 1-[4-(6-methyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-piperidinyl]-3-(methoxymethyl)cyclobutanecarbonitrile (D46, 85mg), methylmagnesium bromide (3M in diethyl ether, 0.7 ml), and THF (5 ml) was stirred at room temperature for 2h then partitioned between aqueous sodium potassium tartrate and dichloromethane. Isolation by SCX chromatography, and then isomer separation by HPLC gave the trans isomer, (3mg, MH^+ 344), and cis isomer, (20mg, MH^+ 344).

Examples 8a & 8b. cis 6-Methyl-1-(1-{1-methyl-3-[(ethoxymethyl)cyclobutyl}-4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (E8a) and trans 6-Methyl-1-(1-{1-methyl-3-[(ethoxymethyl)cyclobutyl}-4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (E8b)



(E8a)



(E8b)

A mixture of 1-[4-(6-methyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-piperidinyl]-3-(ethoxymethyl)cyclobutanecarbonitrile (D47, 120mg), methylmagnesium bromide (3M in diethyl ether, 1.0 ml), and THF (5 ml) was stirred at room temperature for 3h then partitioned between aqueous sodium potassium tartrate and dichloromethane. Isolation by SCX chromatography followed by purification by preparative HPLC afforded the cis and trans isomers.

The faster eluting component was the trans isomer isolated as its TFA salt (20mg) (98.8% w\w purity). This was dissolved in methanol (1ml) and loaded onto a SCX cartridge (1g), then washed with MeOH followed by elution with 2M NH_3/MeOH solution. The NH_3 solution was concentrated under vacuum to afford the free base as a pale brown oil (6.5mg). A 5.5mg sample was dissolved in a mixture of DCM (2ml) and MeOH (0.5ml), treated with 1M HCl/Et_2O (0.06ml) and concentrated to afford the title compound E8b as a pale brown solid (5mg).

MH^+ 358.

^{1}H NMR free base ($CDCl_3$) δ: 1.12 (3H, s), 1.18-1.35 (t + m), 1.52-2.00 (m), 2.17-2.30 (4H, m), 2.30-2.47 (5H, s + m), 2.47-2.60 (1H, m), 2.95 (2H, br d), 3.46-3.55 (4H, m), 4.27-4.40 (1H, m), 6.85 (1H, d), 6.95 (1H, d), 7.13 (1H, s), 8.74 (1H, s).

The slower eluting component was the cis isomer isolated as its TFA salt (58mg) (97.3% w\w purity). This was converted to the free base as above to afford a pale brown solid (28mg). A 25.8mg sample was dissolved in a mixture of DCM (2ml) and MeOH (0.5ml), treated with 1M HCl/Et_2O (0.12ml) and concentrated to afford title compound E8a as a pale brown solid (25mg).

MH^+ 358.

^1H NMR free base ($CDCl_3$) d: 1.05 (3H, s), 1.20 (3H, t), 1.68-1.73 (2H, m), 1.75-1.87 (2H, m), 1.90-2.00 (2H, m), 2.20-2.47 (8H, m), 2.84 (2H, br d), 3.43-3.55 (4H, m), 4.23-4.37 (1H, m), 6.85 (1H, d), 6.97 (1H, m), 7.11 (1H, s), 9.37 (1H, s).

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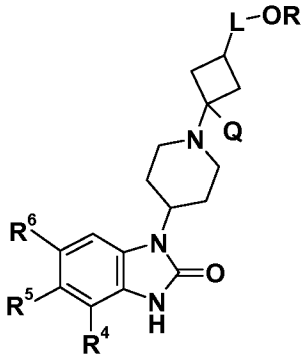
CLAIMS

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



(I)

wherein:

- R^4 is selected from the group consisting of hydrogen and fluoro;
- R^5 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6}alkyl (optionally substituted with one or more fluorine atoms), and C_{1-6}alkoxy (optionally substituted with one or more fluorine atoms);
- R^6 is selected from the group consisting of hydrogen, halogen, cyano, C_{1-6}alkyl (optionally substituted with one or more fluorine atoms), C_{1-6}alkylsulfonyl, C_{3-6}cycloalkyl (optionally substituted with one or more fluorine atoms), and C_{1-6}alkoxy (optionally substituted with one or more fluorine atoms);
- Q is selected from the group consisting of hydrogen and C_{1-6}alkyl;
- L is selected from the group consisting of a bond, CH_2 and $(CH_2)_2$; and
- R is selected from the group consisting of C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkyl and C_{2-6}alkynyl, any alkyl or cycloalkyl group being optionally substituted by one or more fluorine atoms.

2. A compound as claimed in claim 1 wherein the salt is a pharmaceutically acceptable salt.

3. A compound as claimed in claim 1 or claim 2 wherein R^6 is methyl.

4. A compound as claimed in any of claims 1-3 wherein R^5 is selected from hydrogen and fluorine.

5. A compound as claimed in any of claims 1-4 wherein Q is selected from hydrogen or methyl.

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

7. A compound as claimed in any of claims 1-6 wherein R is selected from methyl and ethyl.

8. A compound as claimed in claim 1, which is selected from the group consisting of:
6-Methyl-1-(1-{3-[(methoxymethyl)cyclobutyl}-4-piperidinyl)-1,3-dihydro-2H-benzimidazol-2-one;
1-(1-{cis-3-[(Ethyloxy)methyl]cyclobutyl}-4-piperidinyl)-6-methyl-1,3-dihydro-2H-benzimidazol-2-one;
1-(1-{cis-3-[(Ethyloxy)methyl]cyclobutyl}-4-piperidinyl)-5-fluoro-6-methyl-1,3-dihydro-2H-benzimidazol-2-one;
5-Fluoro-6-methyl-1-(1-{cis-3-[(methyloxy)methyl]cyclobutyl}-4-piperidinyl)-1,3-dihydro-2H-benzimidazol-2-one;
4-Fluoro-6-methyl-1-{1-[4-(methoxymethyl)cyclobutyl]-4-piperidinyl}-1,3-dihydro-2H-benzimidazol-2-one;
cis 6-Methyl-1-(1-{3-[(methoxymethyl)cyclobutyl}-4-piperidinyl)-1,3-dihydro-2H-benzimidazol-2-one;
and salts thereof.

9. A compound as claimed in claim 8 wherein the salt is a pharmaceutically acceptable salt.

10. A pharmaceutical composition comprising a compound claimed in any of claims 2-9 and a pharmaceutically acceptable carrier, diluent or excipient.

11. A compound as claimed in any of claims 2-9 for use in therapy.

12. A compound as claimed in any of claims 2-9 for use in the treatment of a condition wherein agonism of a muscarinic M_1 receptor would be beneficial.

13. A compound as claimed in any of claims 2-9 for use in the treatment of a psychotic disorder or cognitive impairment.

14. Use of a compound as claimed in any of claims 2-9 in the manufacture of a medicament for the treatment of a condition wherein agonism of a muscarinic M_1 receptor would be benefical.

15. Use of a compound as claimed in any of claims 2-9 in the manufacture of a medicament for the treatment of a psychotic disorder or cognitive impairment.

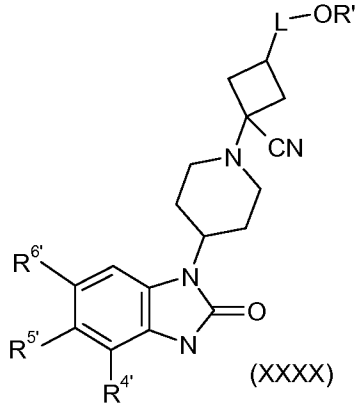
16. A compound as claimed in any of claims 2-9 for the treatment of a condition wherein agonism of a muscarinic M_1 receptor would be benefical.

17. A compound as claimed in any of claims 2-9 for the treatment of a psychotic disorder or cognitive impairment.

18. A method of treating a condition wherein agonism of a muscarinic M_1 receptor would be beneficial, which method comprises administering to a mammal in need thereof an effective amount of a compound as claimed in any of claims 2-9.

19. A method of treating a psychotic disorder or cognitive impairment, which method comprises administering to a mammal in need thereof an effective amount of a compound as claimed in any of claims 2-9.

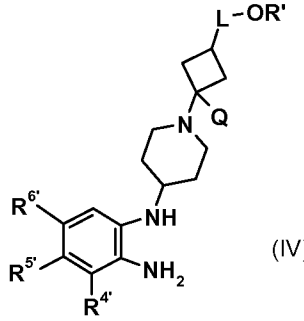
20. A compound of formula (XXXX) or salts thereof:



(XXXX)

wherein:
L is as defined in claim 1;
$R^{4'}$ is a group R^4 as defined in claim 1 or a group convertible to R^4;
$R^{5'}$ is a group R^5 as defined in claim 1 or a group convertible to R^5;
$R^{6'}$ is a group R^6 as defined in claim 1 or a group convertible to R^6; and
R' is a group R as defined in claim 1 or a group convertible to R.

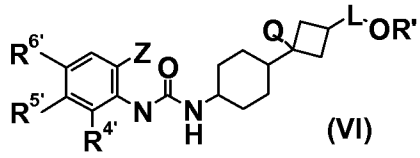
21. A compound of formula (IV) or salts thereof:



(IV)

wherein:
L is as defined in claim 1;
Q is as defined in claim 1;
$R^{4'}$ is a group R^4 as defined in claim 1 or a group convertible to R^4;
$R^{5'}$ is a group R^5 as defined in claim 1 or a group convertible to R^5;
$R^{6'}$ is a group R^6 as defined in claim 1 or a group convertible to R^6; and
R' is a group R as defined in claim 1 or a group convertible to R.

22. A compound of formula (VI) or salts thereof:



(VI)

wherein:

L is as defined in claim 1;

Q is as defined in claim 1;

$R^{4'}$ is a group R^4 as defined in claim 1 or a group convertible to R^4;

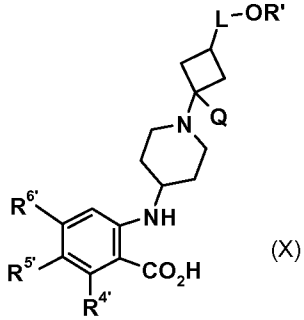
$R^{5'}$ is a group R^5 as defined in claim 1 or a group convertible to R^5;

$R^{6'}$ is a group R^6 as defined in claim 1 or a group convertible to R^6;

R' is a group R as defined in claim 1 or a group convertible to R; and

Z is a leaving group.

23. A compound of formula (X) or salts thereof:



(X)

wherein:

L is as defined in claim 1;

Q is as defined in claim 1;

$R^{4'}$ is a group R^4 as defined in claim 1 or a group convertible to R^4;

$R^{5'}$ is a group R^5 as defined in claim 1 or a group convertible to R^5;

$R^{6'}$ is a group R^6 as defined in claim 1 or a group convertible to R^6; and

R' is a group R as defined in claim 1 or a group convertible to R.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/053600

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 A61K31/454 A61P25/00

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)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96/13262 A (MERCK & CO INC [US]; THOMPSON WAYNE J [US]; SUGRUE MICHAEL F [US]; RAN) 9 May 1996 (1996-05-09) page 4, line 15 - line 25; claim 1	1-23

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

☒ See patent family annex.

* Special categories of cited documents :

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

"E" earlier 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
8 July 2008	16/07/2008

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	Moriggi, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/053600

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9613262 A	09-05-1996	AU 701127 B2	21-01-1999
		AU 3967495 A	23-05-1996
		CA 2200468 A1	09-05-1996
		EP 0786997 A1	06-08-1997
		JP 2002515008 T	21-05-2002