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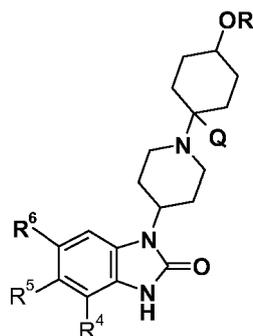
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(54) Title: BENZIMIDAZOLES WHICH HAVE ACTIVITY AT M1 RECEPTOR AND THEIR USES IN MEDICINE



(I)

(57) Abstract: Compounds of formula (I), salts and solvates are provided, wherein Q, R, R₄ - R₆ are as defined in the Claims. Uses of the Compounds for therapy, for example in the treatment of psychotic disorders and cognitive impairment, are also disclosed.

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BENZIMIDAZOLES WHICH HAVE ACTIVITY AT M1 RECEPTOR AND THEIR USES IN MEDICINE

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

5

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, M₁ to M₅. The muscarinic M₁ receptor is predominantly expressed in the cerebral cortex and hippocampus, although it is also expressed in the periphery e.g. exocrine glands.

10

Muscarinic receptors in the central nervous system, especially M₁, 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.

15

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.

20

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.

25

30

M₁ 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.

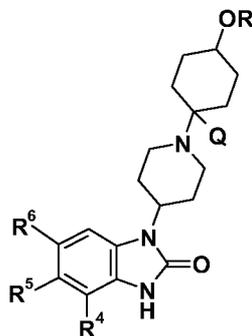
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Xanomeline has also been shown to reduce psychotic symptoms such as suspiciousness, hallucinations and delusions in Alzheimer's patients. However, the relatively non-selective nature of the compound gives rise to dose-limiting peripheral cholinergic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

- 5 Certain M₁ receptor agonists are known, for example in PCT/GB2006/003585. We have now found a novel group of compounds which are M₁ receptor agonists.

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



10

(I)

wherein:

- R⁴ is fluoro;
- R⁵ is selected from hydrogen, cyano, halogen, C₁₋₆alkyl, C₁₋₆alkyl substituted with one or more fluorine atoms, C₁₋₆ alkoxy, and C₁₋₆ alkoxy substituted with one or more fluorine atoms;
- 15 - R⁶ is selected from hydrogen, halogen, cyano, C₁₋₆alkyl, C₁₋₆alkyl substituted with one or more fluorine atoms, C₁₋₆alkylsulfonyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl substituted with one or more fluorine atoms, C₁₋₆alkoxy and C₁₋₆alkoxy substituted with one or more fluorine atoms;
- 20 - R is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl/C₁₋₆alkyl and C₂₋₆alkynyl, any alkyl or cycloalkyl group being optionally substituted with one or more fluorine atoms; and
- Q is hydrogen or C₁₋₆alkyl.

25 As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C₁₋₆alkyl means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms. Examples include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isobutyl, isopropyl, t-butyl and 1,1-dimethylpropyl.

30 As used herein, the term "alkoxy" refers to a straight or branched alkoxy group containing the specified number of carbon atoms. For example, C₁₋₆alkoxy means a straight or branched alkoxy group containing at least 1, and at most 6, carbon atoms. Examples of "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.

5 As used herein, the term "cycloalkyl" refers to a non-aromatic hydrocarbon ring containing the specified number of carbon atoms. For example, C₃₋₆cycloalkyl means a non-aromatic carbocyclic ring containing at least three, and at most six, ring carbon atoms. Examples of "cycloalkyl" as used herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

10 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, C₂₋₆alkynyl 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
15 ethynyl, propynyl, butynyl, pentynyl and hexynyl.

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
20 (which may be abbreviated to "iodo" or "I"). Examples of halogens are fluorine, chlorine and bromine.

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.
25 Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol and acetic acid. The solvent used may be water and the solvate may also be referred to as a hydrate.

30 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, 3 or 4 substituents on a given substituted group. For example, if R⁶ is a C₁₋₆alkyl group, it may be substituted by 1, 2, 3 or 4 fluoro groups; and if R⁶ is a C₁₋₆alkoxy group, it may be substituted by 1, 2, 3 or 4 fluoro groups. For
35 example, R⁶ may be a C₁₋₆alkyl group substituted by 3 fluoro groups; and R⁶ may be a C₁₋₆alkoxy group substituted by 3 fluoro groups. For example, R⁶ may be CF₃. Similarly, if R⁵ is a C₁₋₆alkyl group substituted by one or more fluoro groups, it may be substituted by 1, 2, 3 or 4 fluoro groups; and if R⁵ is a C₁₋₆alkoxy group, it may be substituted by 1, 2, 3 or 4
40 fluoro groups. For example, R⁵ may be a C₁₋₆alkyl group substituted by 3 fluoro groups; and R⁵ may be a C₁₋₆alkoxy group substituted by 3 fluoro groups. For example, R⁵ may be CF₃ or CH₂F. Similarly, if R is a C₁₋₆alkyl group substituted by one or more fluoro groups, it may be substituted by 1, 2, 3 or 4 fluoro groups; and if R is a C₃₋₆cycloalkyl

group, it may be substituted by 1, 2, 3 or 4 fluoro groups. For example, R may be a C₁₋₆alkyl group substituted by 3 fluoro groups; and R may be a C₃₋₆cycloalkyl group substituted by 3 fluoro groups. For example, R may be CF₃ or CH₂F.

5 In one embodiment, R⁵ is selected from hydrogen, chloro, bromo, fluoro, C₁₋₄alkyl, C₁₋₄alkyl substituted with one or more fluorine atoms, and C₁₋₄alkoxy.

10 In one embodiment, R⁵ is selected from hydrogen, cyano, halogen, C₁₋₆alkyl, C₁₋₆alkyl substituted with one, two or three fluorine atoms, C₁₋₆alkoxy, and C₁₋₆alkoxy substituted with one, two or three fluorine atoms.

15 In one embodiment, R⁵ is selected from hydrogen, cyano, halogen, C₁₋₄alkyl, C₁₋₄alkyl substituted with one, two or three fluorine atoms, C₁₋₄alkoxy, and C₁₋₄alkoxy substituted with one, two or three fluorine atoms.

In one embodiment, R⁵ is selected from hydrogen, cyano, halogen, C₁₋₂alkyl, C₁₋₂alkyl substituted with one or more fluorine atoms, C₁₋₂alkoxy, and C₁₋₂alkoxy substituted with one or more fluorine atoms.

20 In one embodiment, R⁵ is selected from hydrogen, cyano, halogen, C₁₋₂alkyl, C₁₋₂alkyl substituted with one or more fluorine atoms, C₁₋₂alkoxy, and C₁₋₂alkoxy substituted with one, two or three fluorine atoms.

25 In a further embodiment of the invention, R⁵ is selected from hydrogen, chloro, bromo, fluoro, methyl, ethyl, methoxy and trifluoromethyl. For example, R⁵ is hydrogen or fluoro. For example R⁵ is hydrogen.

30 In one embodiment, R⁶ is selected from hydrogen, halogen, cyano, C₁₋₆alkyl, C₁₋₆alkyl substituted with one, two or three fluorine atoms, C₁₋₆alkylsulfonyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl substituted with one, two or three fluorine atoms, C₁₋₆alkoxy and C₁₋₆alkoxy substituted with one, two or three fluorine atoms.

35 In one embodiment, R⁶ is selected from halogen, cyano, C₁₋₄alkyl, C₁₋₄alkyl substituted with one or more fluorine atoms, C₁₋₄alkylsulfonyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl substituted with one, two or three fluorine atoms, C₁₋₄alkoxy and C₁₋₄alkoxy substituted with one, two or three fluorine atoms.

40 In one embodiment, R⁶ is selected from, chloro, bromo, fluoro, methyl, ethyl, isopropyl, methoxy, trifluoromethoxy and trifluoromethyl.

In a further embodiment, R⁶ is selected from chloro, bromo, fluoro, methyl, ethyl, isopropyl, methoxy, trifluoromethoxy and trifluoromethyl. In a further embodiment of the invention, R⁶ is selected from chloro, methyl and methoxy, for example methyl.

5 In one embodiment, R is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₆alkyl and C₂₋₆alkynyl, any alkyl or cycloalkyl group being optionally substituted with one, two or three fluorine atoms.

10 In one embodiment, R is selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₄alkyl and C₂₋₄alkynyl, any alkyl or cycloalkyl group being optionally substituted with one, two or three fluorine atoms.

15 In one embodiment of the invention, R is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl and C₃₋₆cycloalkylC₁₋₆alkyl, any alkyl group being optionally substituted with one or more fluorine atoms.

In one embodiment of the invention, R is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl and C₃₋₆cycloalkylC₁₋₆alkyl, any alkyl group being optionally substituted with one, two or three fluorine atoms.

20 In one embodiment of the invention, R is selected from C₁₋₃alkyl and C₃₋₆cycloalkylC₁₋₃alkyl, any alkyl or cycloalkyl group (for example any alkyl group) being optionally substituted with one or more fluorine atoms.

25 In one embodiment of the invention, R is selected from C₁₋₃alkyl and C₃₋₆cycloalkylC₁₋₃alkyl, any alkyl or cycloalkyl group (for example any alkyl group) being optionally substituted with one, two or three fluorine atoms.

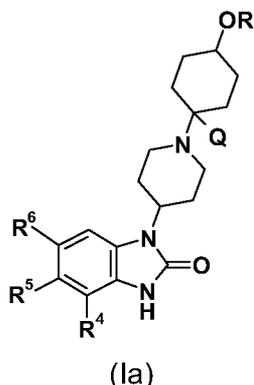
30 In a further embodiment, R is selected from methyl, ethyl, propyl, isopropyl and cyclopropylmethyl. For example R is methyl.

In one embodiment of the invention Q is selected from hydrogen and C₁₋₃alkyl. In a further embodiment, Q is selected from hydrogen, methyl, ethyl and propyl. For example, Q represents hydrogen or methyl, for example hydrogen.

35 It will be appreciated that compounds of formula (I) can exist in *cis* or *trans* isomeric forms (the OR group on the cyclohexane ring in relation to the piperidine substituent). The individual isomers (*cis* and *trans*) and mixtures of these are included within the scope of the present invention. In one embodiment, the compounds of formula (I) are *trans* isomers.

40

The present invention also provides a compound of formula (Ia):



wherein:

- 5 - R⁴ is fluoro;
 - R⁵ is selected from hydrogen, halogen, C₁₋₆alkyl, C₁₋₆alkyl substituted with one or more fluorine atoms, C₁₋₆ alkoxy, and C₁₋₆ alkoxy substituted with one or more fluorine atoms;
 - R⁶ is selected from halogen, C₁₋₆alkyl, C₁₋₆alkyl substituted with one or more fluorine atoms, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl substituted with one or more fluorine atoms, C₁₋₆
 10 alkoxy and C₁₋₆ alkoxy substituted with one or more fluorine atoms;
 - R is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₆alkyl, any alkyl or cycloalkyl group being optionally substituted with one or more fluorine atoms; and
 - Q is hydrogen or C₁₋₆alkyl;
 or a pharmaceutically acceptable salt or solvate thereof.

15

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

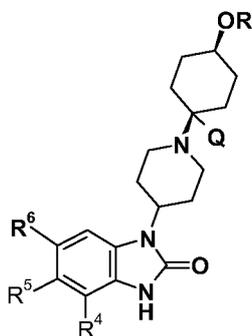
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It will be appreciated that for use in medicine the salts of formula (I) should be pharmaceutically acceptable. Suitable salts will be apparent to those skilled in the art and include for example mono- or di- basic salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric, sulfamic phosphoric, hydroiodic, phosphoric or metaphosphoric acid; and with organic acids, such as tartaric, acetic, trifluoroacetic, citric,
 25 malic, lactic, fumaric, benzoic, formic, propionic, glycolic, gluconic, maleic, succinic, (1S)-(-)-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-
 30 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,
 35 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.

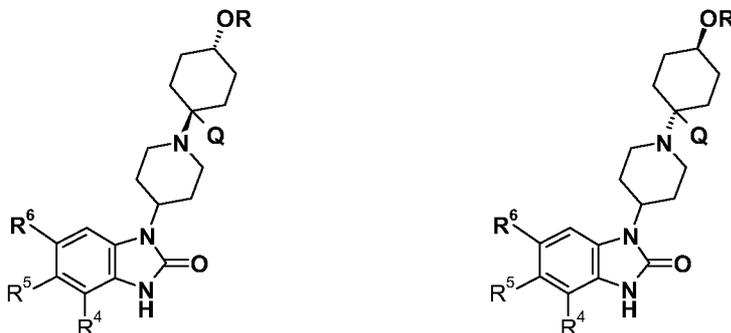
It will be appreciated that compounds of formula (I) can exist in *cis* or *trans* isomeric forms (the OR group on the cyclohexane ring in relation to the piperidine substituent).

10 *Cis* form:



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

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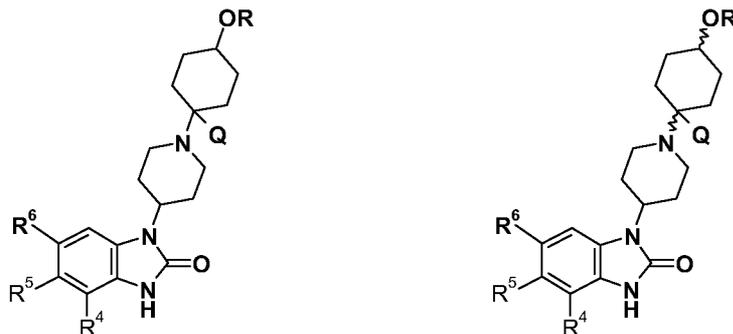
The individual isomers (*cis* and *trans*) and mixtures of these are included within the scope of the present invention. The isomers may be separated one from the other by the usual methods or by methods detailed for the example compounds below. Any given isomer may also be obtained by stereospecific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

25

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:



5

Compounds according to the invention include those specifically exemplified in the Examples section and named hereinafter including, without limitation:-

1. 4-Fluoro-6-methyl-1-[1-(*cis*-4-methoxycyclohexyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one
- 10 2. 4-Fluoro-6-methyl-1-[1-(*trans*-4-methoxycyclohexyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one

and salts and solvates thereof, for example the hydrochloride salt, the trifluoroacetate salt or the formate salt.

15 Further examples of the compounds of the invention include:

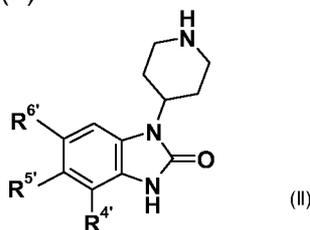
1. 4-Fluoro-6-methyl-1-[1-(*trans*-4-ethoxycyclohexyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one
2. 4-Fluoro-6-methyl-1-[1-(*trans*-4-propoxycyclohexyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one
- 20 3. 4-Fluoro-6-methyl-1-{1-[*trans*-1-methyl-4-(propyloxy)cyclohexyl]-4-piperidinyl}-1,3-dihydro-2*H*-benzimidazol-2-one
4. 1-{1-[*trans*-4-(Ethoxy)-1-methylcyclohexyl]-4-piperidinyl}-4-fluoro-6-methyl-1,3-dihydro-2*H*-benzimidazol-2-one
5. 1-{1-[*trans*-4-(Ethoxy)-1-methylcyclohexyl]-4-piperidinyl}-4,6-difluoro-1,3-dihydro-2*H*-benzimidazol-2-one
- 25 6. 4-Fluoro-6-methyl-1-{1-[*trans*-1-methyl-4-(methyloxy)cyclohexyl]-4-piperidinyl}-1,3-dihydro-2*H*-benzimidazol-2-one
7. 4,6-Difluoro-1-{1-[*trans*-1-methyl-4-(methyloxy)cyclohexyl]-4-piperidinyl}-1,3-dihydro-2*H*-benzimidazol-2-one
- 30 8. 4-Fluoro-1-{1-[*trans*-1-methyl-4-(methyloxy)cyclohexyl]-4-piperidinyl}-1,3-dihydro-2*H*-benzimidazol-2-one
9. 1-{1-[*trans*-4-(ethoxy)-1-methylcyclohexyl]-4-piperidinyl}-4-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one

35 and salts and solvates thereof, for example the hydrochloride salt, the trifluoroacetate salt or the formate salt.

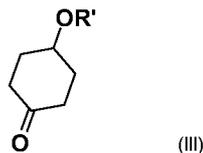
It will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula (I), which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter 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 “promoieties”, 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. Suitable prodrugs for compounds of the invention include : esters, carbonate esters, hemiesters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides, carbamates, azo-compounds, phosphamides, glycosides, ethers, acetals and ketals.

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)



with a compound of formula (III)



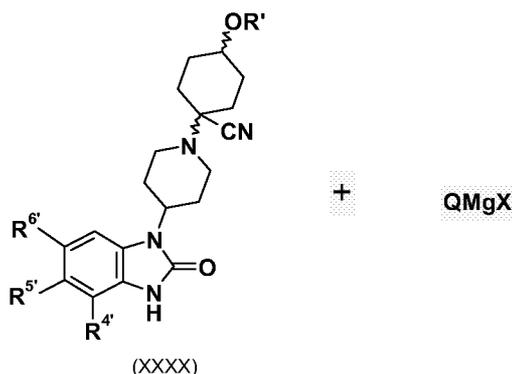
wherein

R^{4'} is a group R⁴ as previously defined, or a group convertible to R⁴, R^{5'} is a group R⁵ as previously defined, or a group convertible to R⁵, R^{6'} is a group R⁶ as previously defined, or a group convertible to R⁶, and R' is a group R as previously defined, 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 C₁₋₆ alkyl. Thus, in general process (A2), a compound of formula (II) can be reacted with a compound of formula (III) in the presence of a source of cyanide, e.g. acetone cyanohydrin, to form the cyano intermediate (XXXX) which can be reacted with an alkyl Grignard reagent QMgX to form compounds of formula (I) in which Q is C₁₋₆ alkyl.



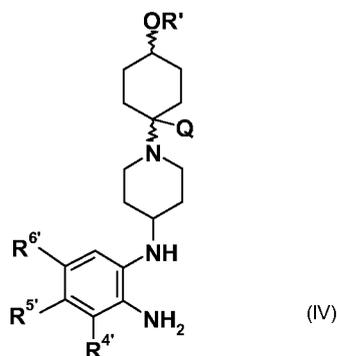
wherein

R^{4'} is a group R⁴ as previously defined, or a group convertible to R⁴, R^{5'} is a group R⁵ as previously defined, or a group convertible to R⁵, R^{6'} is a group R⁶ as previously defined, or a group convertible to R⁶, and R' is a group R as previously defined, or a group convertible to R, Q is C₁₋₆ alkyl, and X is bromo or iodo or chloro.

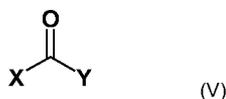
This reaction can generate a mixture of *cis* and *trans* isomers which can be separated by chromatography or crystallisation.

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)



with a compound of formula (V)



5

wherein $R^{4'}$ is a group R^4 as previously defined, or a group convertible to R^4 , $R^{5'}$ is a group R^5 as previously defined, or a group convertible to R^5 , $R^{6'}$ is a group R^6 as previously defined, or a group convertible to R^6 , R^1 is a group R as previously defined, or a group convertible to R , Q is as previously defined, and X and Y both represent leaving groups. X and Y can be the same or different and examples are Cl , PhO , EtO , imidazole. When X and Y are both Cl , i.e. phosgene, this reagent can be generated *in situ* e.g. from diphosgene or triphosgene.

10

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, diisopropylethylamine, or potassium carbonate, and optionally with heating.

15

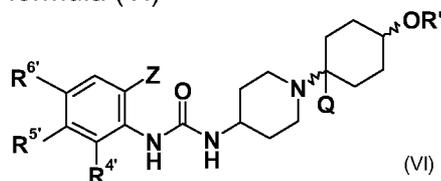
It will be appreciated that compounds of formula (IV) can be pure *cis* or *trans* isomers, or a mixture of isomers. If necessary, separation of pure *cis* and *trans* isomers after the reaction with (V) can be achieved by chromatography or crystallisation.

20

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

25

treatment of a compound of formula (VI)



with a palladium or copper catalyst (VII) to effect an intramolecular cyclisation

30

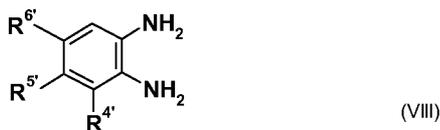
wherein $R^{4'}$ is a group R^4 as previously defined, or a group convertible to R^4 , $R^{5'}$ is a group R^5 as previously defined, or a group convertible to R^5 , $R^{6'}$ is a group R^6 as previously defined, or a group convertible to R^6 , R' is a group R as previously defined, or a group convertible to R , Q is as previously defined, and Z is a leaving group such as bromo, iodo, chloro or triflate.

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.)

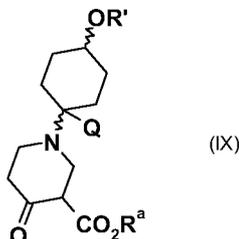
It will be appreciated that compounds of formula (VI) can be pure *cis* or *trans* isomers, or a mixture of isomers. If necessary, separation of pure *cis* and *trans* isomers after the intramolecular cyclisation can be achieved by chromatography or crystallisation.

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

coupling a compound of formula (VIII):



with a compound of formula (IX)



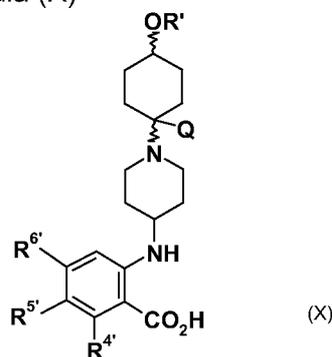
wherein $R^{4'}$ is a group R^4 as previously defined, or a group convertible to R^4 , $R^{5'}$ is a group R^5 as previously defined, or a group convertible to R^5 , $R^{6'}$ is a group R^6 as previously defined, or a group convertible to R^6 , R' is a group R as previously defined, or a group convertible to R , Q is as previously defined, 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 pure *cis* or *trans* isomers, or a mixture of isomers. If necessary, separation of pure *cis* and *trans* isomers after the intramolecular cyclisation can be achieved by chromatography or crystallisation.

- 5 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)



10

with diphenylphosphoryl azide or other reagent/combination of reagents to effect the Curtius rearrangement of compound (X), followed by intramolecular cyclisation.

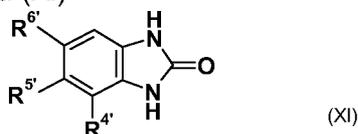
- 15 wherein $R^{4'}$ is a group R^4 as previously defined, or a group convertible to R^4 , $R^{5'}$ is a group R^5 as previously defined, or a group convertible to R^5 , $R^{6'}$ is a group R^6 as previously defined, or a group convertible to R^6 , R' is a group R as previously defined, or a group convertible to R , and Q is as previously defined.

- 20 The Curtius rearrangement is typically carried out by mixing the two reactants in an inert solvent such as toluene, optionally with heating.

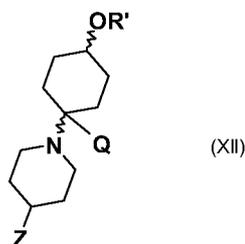
It will be appreciated that compounds of formula (X) can be pure *cis* or *trans* isomers, or a mixture of isomers. If necessary, separation of pure *cis* and *trans* isomers after the intramolecular cyclisation can be achieved by chromatography or crystallisation.

- 25 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)



- 30 with a compound of formula (XII)



wherein $R^{4'}$ is a group R^4 as previously defined, or a group convertible to R^4 , $R^{5'}$ is a group R^5 as previously defined, or a group convertible to R^5 , $R^{6'}$ is a group R^6 as previously defined, or a group convertible to R^6 , R' is a group R as previously defined, or a group convertible to R , Q is as previously defined, 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 pure *cis* or *trans* isomers, or a mixture of isomers. If necessary, separation of pure *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 alkoxy 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 trifluoromethyl 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 .

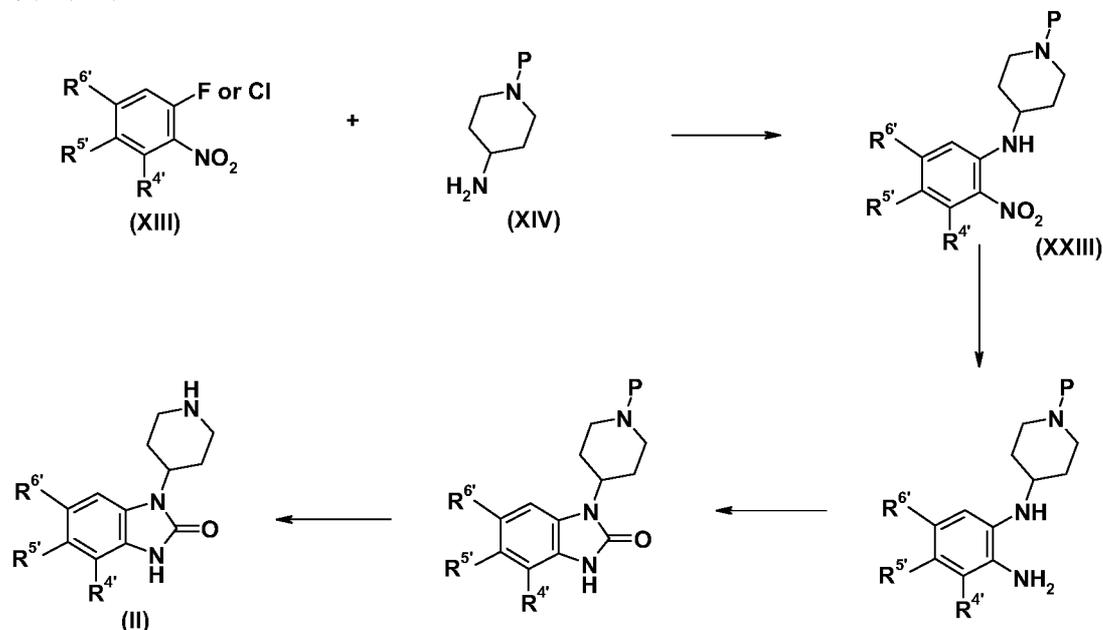
Conversion of R' to R or interconversions of R may be accomplished as indicated below. For example when R' is benzyl, the benzyl group can be removed using standard methodology, e.g. catalytic hydrogenation over palladium on carbon, to provide the alcohol. Alkylation of the resultant alcohol using a strong base e.g. sodium hydride and a C₁₋₆ alkylating agent e.g. methyl iodide or propyl iodide, will afford the desired product.

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 nitrobenzene intermediate (XIII) with the amine (XIV), wherein R^{4'} is a group R⁴ as previously defined, or a group convertible to R⁴, R^{5'} is a group R⁵ as previously defined, or a group convertible to R⁵, R^{6'} is a group R⁶ as previously defined, or a group convertible to R⁶, 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).

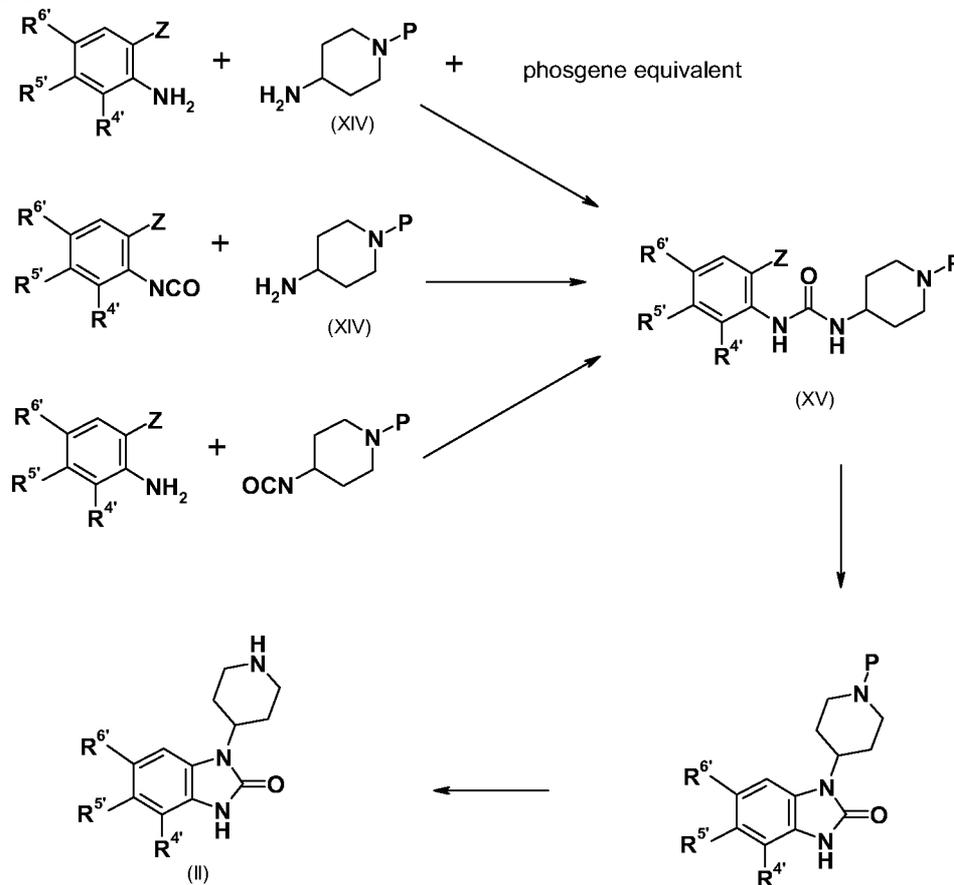
Scheme 1.



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 previously defined, or a group convertible to R^4 , $R^{5'}$ is a group R^5 as previously defined, or a group convertible to R^5 , $R^{6'}$ is a group R^6 as previously defined, 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.

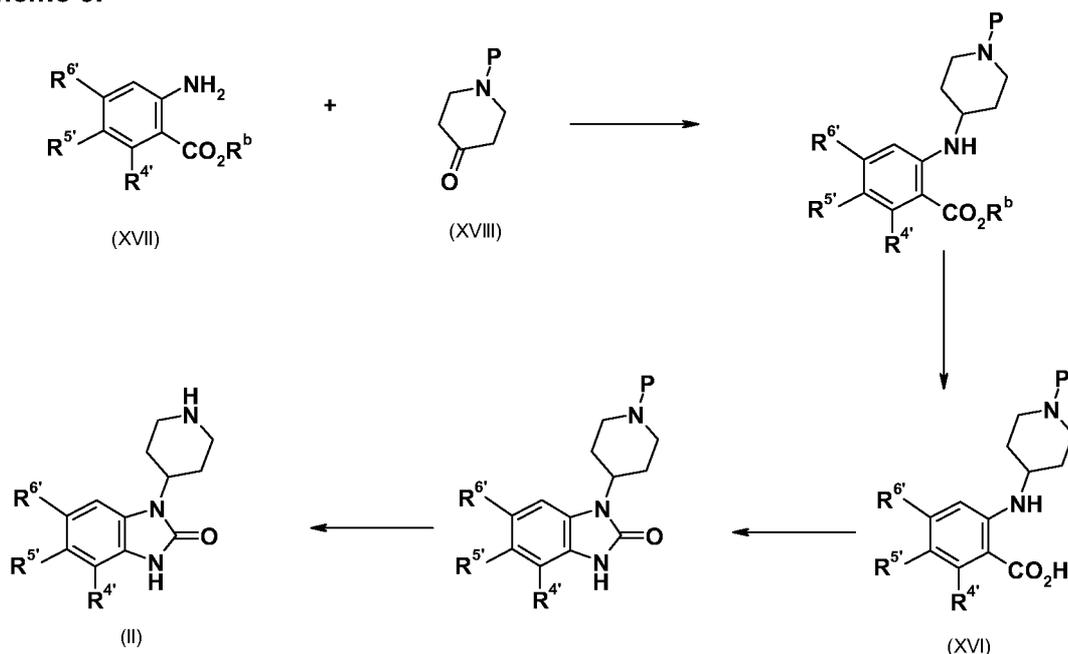
Scheme 2.



(c) Curtius rearrangement of an intermediate (XVI), wherein $R^{4'}$ is a group R^4 as previously defined, or a group convertible to R^4 , $R^{5'}$ is a group R^5 as previously defined, or a group convertible to R^5 , $R^{6'}$ is a group R^6 as previously defined, 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.

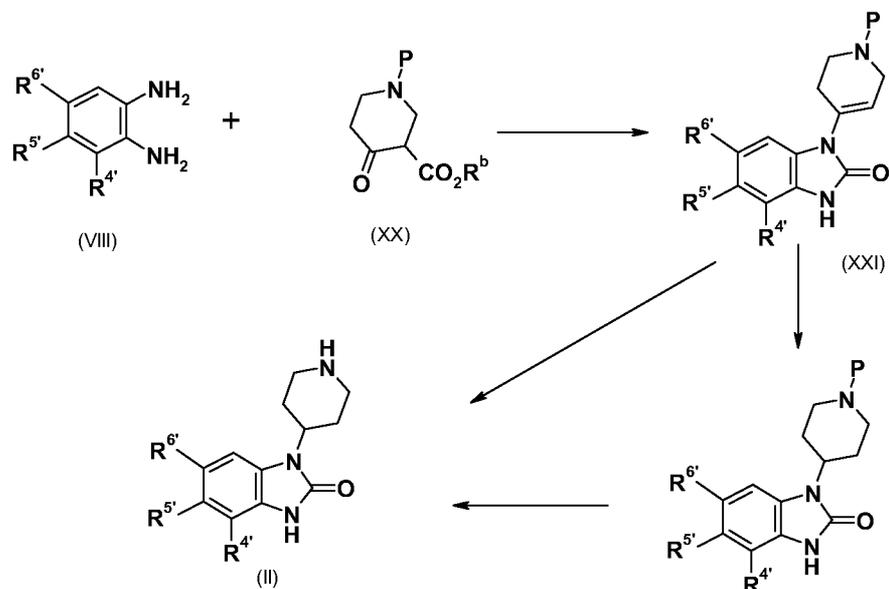
Scheme 3.



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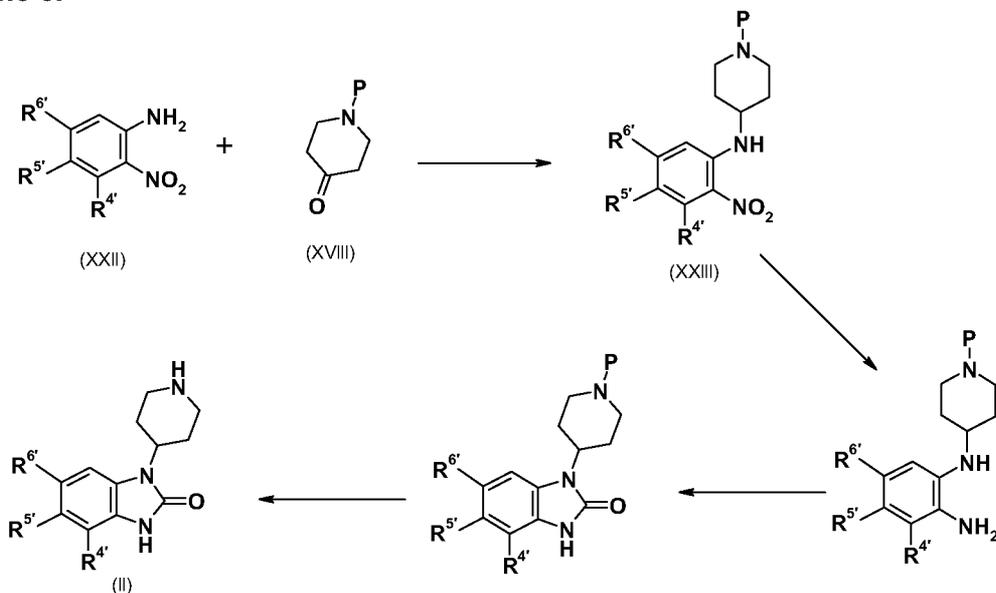
(d) Condensation of an orthophenylenediamine (VIII) with a 3-alkoxycarbonyl-4-piperidone (XX), wherein R^{4'} is a group R⁴ as previously defined, or a group convertible to R⁴, R^{5'} is a group R⁵ as previously defined, or a group convertible to R⁵, R^{6'} is a group R⁶ as previously defined, or a group convertible to R⁶, P represents a nitrogen protecting group e.g. Boc, acetyl, trifluoroacetyl, benzyloxycarbonyl and R^b is a C₁₋₅ 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.

20 Scheme 4.



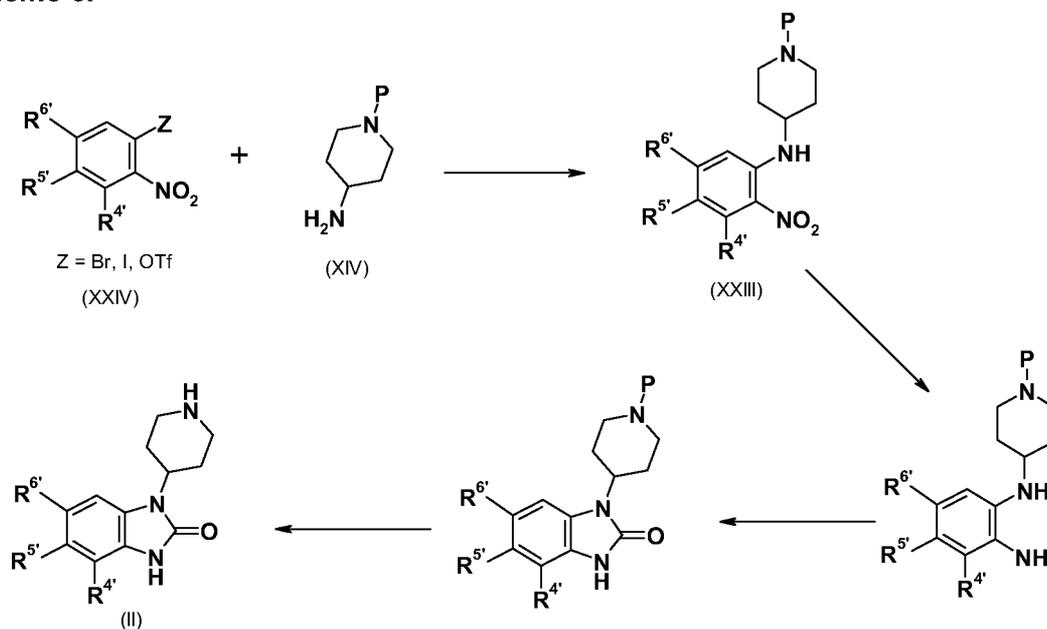
- (e) Reductive alkylation of an ortho nitroaniline (XXII) with an N-protected 4-piperidone (XVIII), wherein R^4 is a group R^4 as previously defined, or a group convertible to R^4 , R^5 is a group R^5 as previously defined, or a group convertible to R^5 , R^6 is a group R^6 as previously defined, or 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.



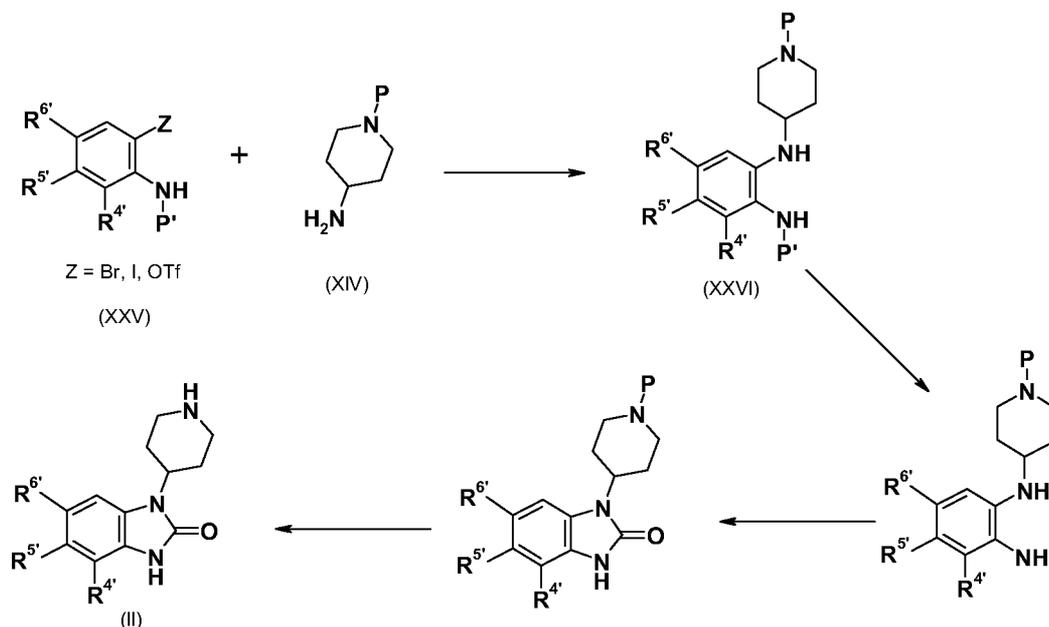
- (f) metal catalysed reaction between the amine (XIV) and a suitably substituted nitrobenzene compound (XXIV) wherein $R^{4'}$ is a group R^4 as previously defined, or a group convertible to R^4 , $R^{5'}$ is a group R^5 as previously defined, or a group convertible to R^5 , $R^{6'}$ is a group R^6 as previously defined, 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 previously defined, or a group convertible to R^4 , $R^{5'}$ is a group R^5 as previously defined, or a group convertible to R^5 , $R^{6'}$ is a group R^6 as previously defined, 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.



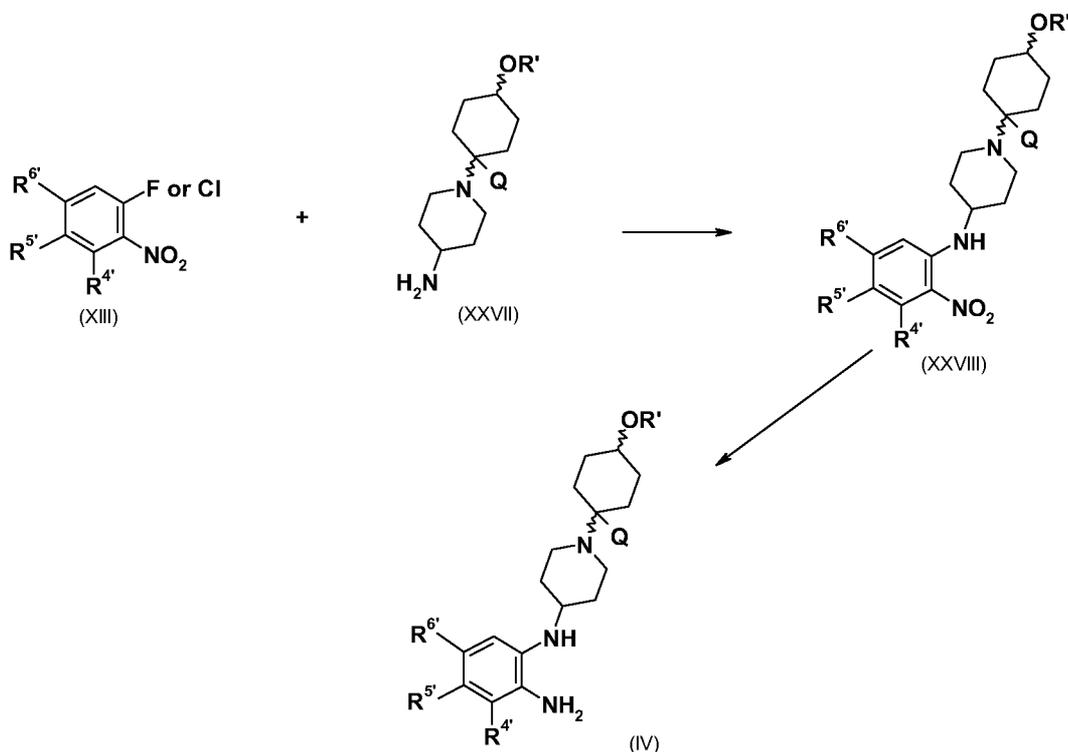
The compounds of formula (II) can be prepared by standard literature methodology.

5

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

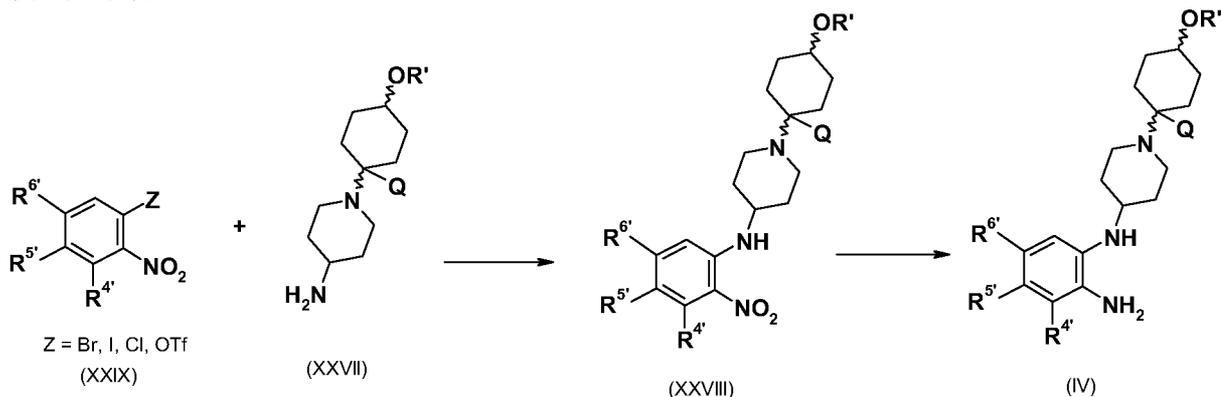
- (h) displacement of an ortho-fluoro or ortho-chloro nitrobenzene intermediate (XIII) with the amine (XXVII) wherein R^{4'} is a group R⁴ as previously defined, or a group convertible to R⁴, R^{5'} is a group R⁵ as previously defined, or a group convertible to R⁵, R^{6'} is a group R⁶ as previously defined, or a group convertible to R⁶, R' is a group R as previously defined, or a group convertible to R, and Q is as previously defined, 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.
- 10
- 15

Scheme 8.



- (i) metal catalysed reaction of the amine (XXVII) with the ortho substituted nitrobenzene (XXIX), wherein R^{4'} is a group R⁴ as previously defined, or a group convertible to R⁴, R^{5'} is a group R⁵ as previously defined, or a group convertible to R⁵, R^{6'} is a group R⁶ as previously defined, or a group convertible to R⁶, R' is a group R as previously defined, or a group convertible to R, and Q is as previously defined, 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.

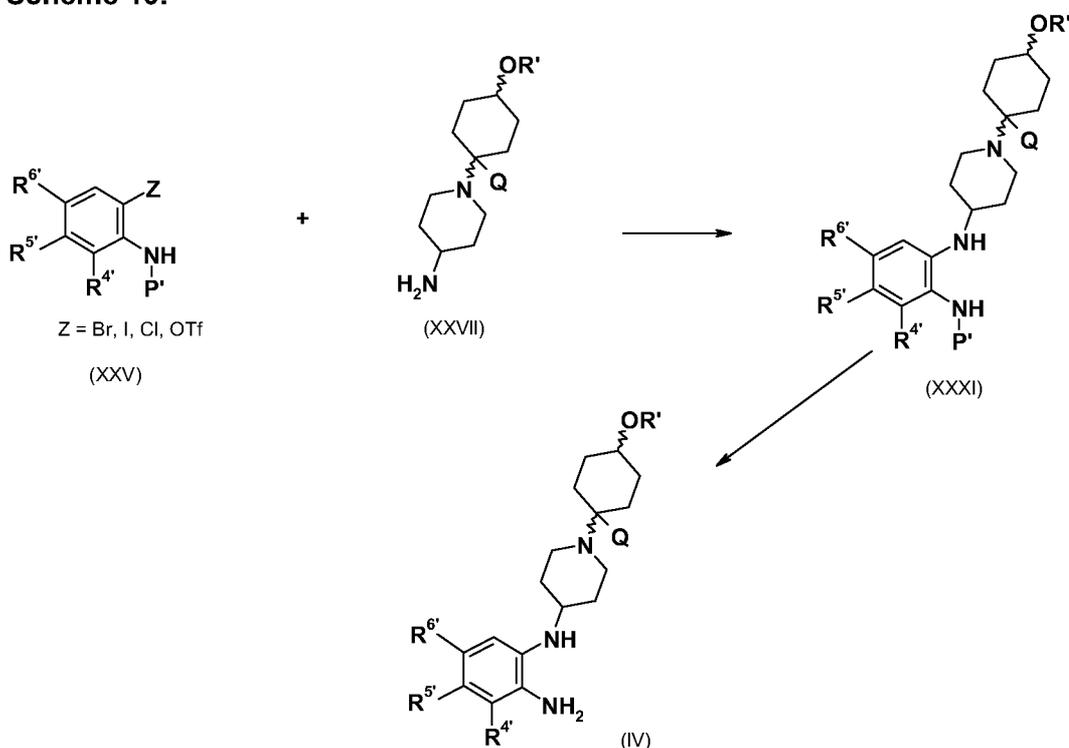


15

- (j) metal catalysed reaction of the amine (XXVII) with the protected aniline derivative (XXV), wherein R^{4'} is a group R⁴ as previously defined, or a group convertible to R⁴, R^{5'} is

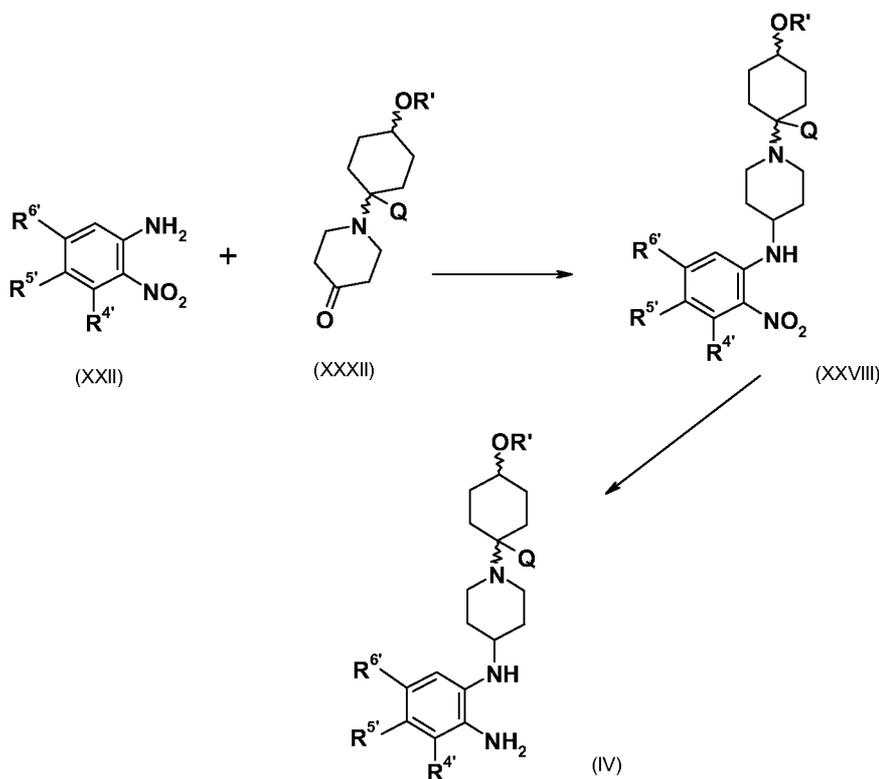
a group R^5 as previously defined, or a group convertible to R^5 , $R^{6'}$ is a group R^6 as previously defined, or a group convertible to R^6 , R' is a group R as previously defined, or a group convertible to R , and Q is as previously defined, and P' represents a nitrogen protecting group such as 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.

10 **Scheme 10.**



(k) Reductive alkylation of an ortho nitroaniline (XXII) with the piperidone (XXXII) wherein $R^{4'}$ is a group R^4 as previously defined, or a group convertible to R^4 , $R^{5'}$ is a group R^5 as previously defined, or a group convertible to R^5 , $R^{6'}$ is a group R^6 as previously defined, or a group convertible to R^6 , R' is a group R as previously defined, or a group convertible to R , and Q is as previously defined, 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.

5

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

- 10
- 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)
 - reacting the amine (XXXIV) with the isocyanate (XXXVI)

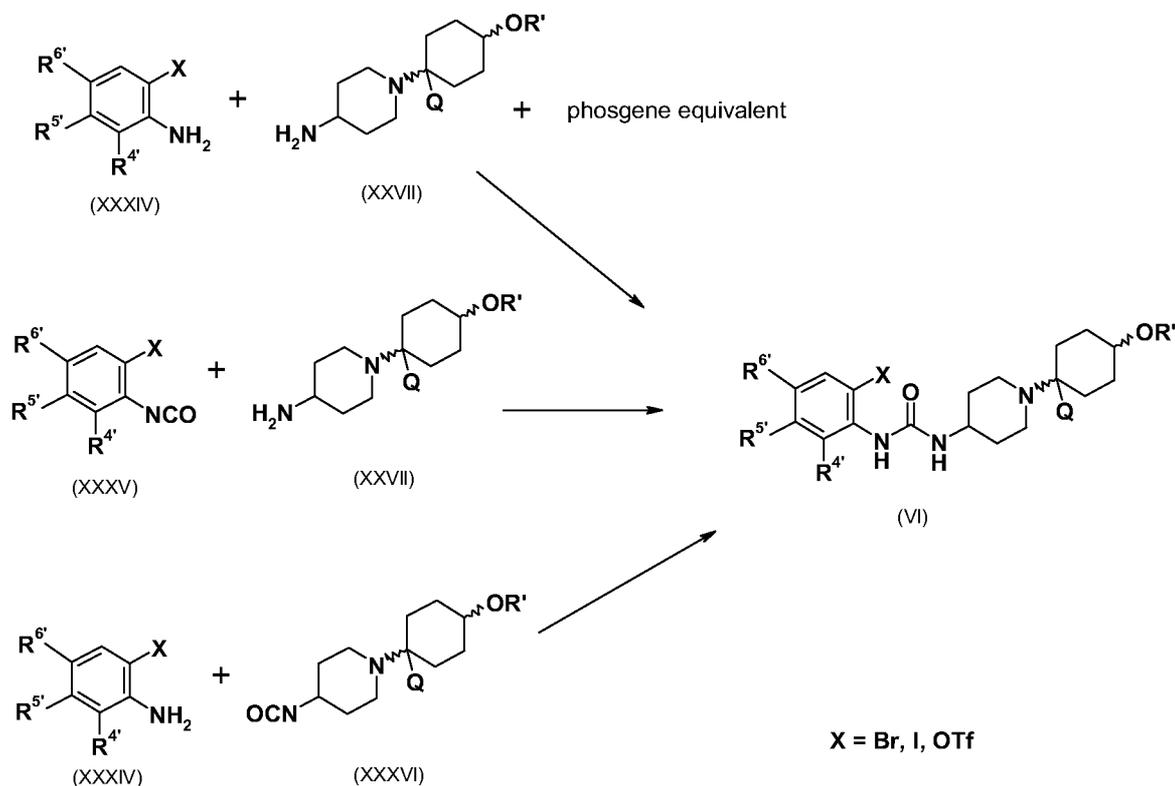
15

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.

20

Scheme 12.



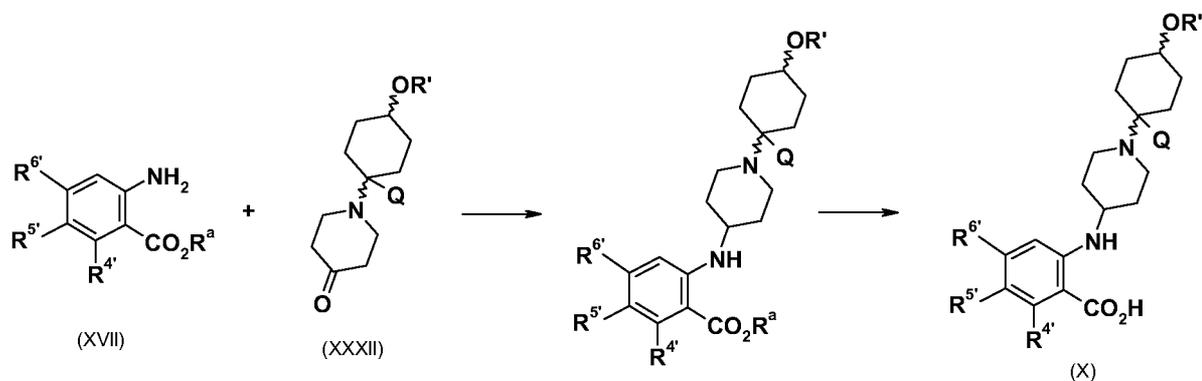
5 Palladium and copper catalysts (VII) are commercially available or can be prepared as described in the literature (see references in Process C).

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

10 Compounds of formula (IX) can be prepared by reductive alkylation of the 3-alkoxycarbonyl-4-piperidone with the appropriate substituted cyclohexanone.

15 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.



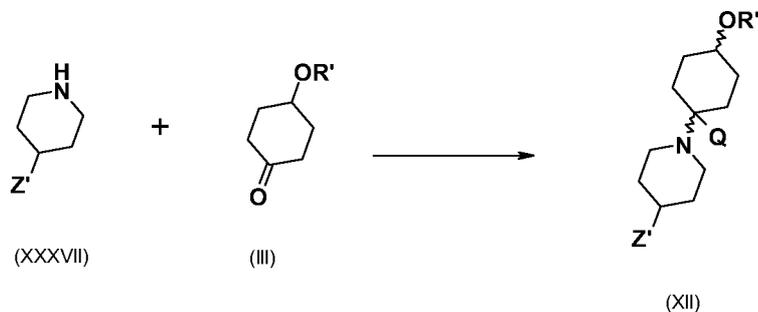
Compounds of formula (XI) are commercially available or can be prepared by literature processes.

5

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.

10

Scheme 14.

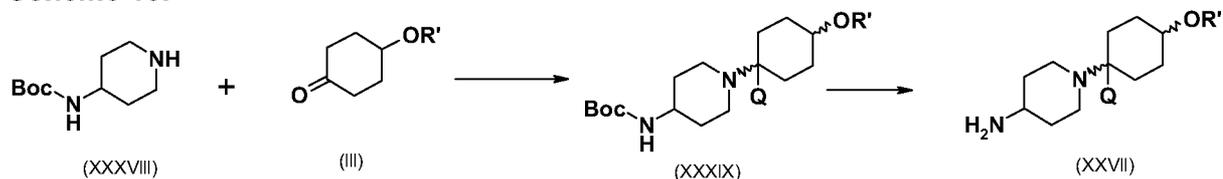


15

The compound (XXVII) where Q = H can be prepared as shown in Scheme 15. Reductive alkylation of the commercially available amine (XXXVIII) with the cyclohexanone (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.

20

Scheme 15.



25

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

5 Compounds of the present invention are M₁ receptor agonists. Selective M₁ 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
10 peripheral cholinergic side effects mediated predominantly through M₂ and M₃ receptors. M₁ 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.

15

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

In another aspect, the invention provides a compound of formula (I) or a salt or solvate
20 thereof for use in the treatment of a condition which requires agonism of a muscarinic M₁ receptor.

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
25 Association (DSM-IV) and/or the International Classification of Diseases, 10th Edition (ICD-10). The various subtypes of the disorders mentioned herein are contemplated as part of the present invention. Numbers in brackets after the listed diseases below refer to the classification code in DSM-IV.

30 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
35 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
40 Hallucinations (293.82); and Psychotic Disorder Not Otherwise Specified (298.9);

Other conditions the treatment of which require agonism of a muscarinic M₁ receptor include:

- 5 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
- 10 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);
- 15 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
- 20 General Medical Condition (293.84), Substance-Induced Anxiety Disorder and Anxiety Disorder Not Otherwise Specified (300.00);
- 25 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,
- 30 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-
- 35 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
- 40 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
5 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
10 (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),
15 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
20 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
25 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
30 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
35 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
40 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;

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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
10 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
15 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
20 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
25 /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);
30

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),
35 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

40 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),
5 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).

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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
15 impairment.

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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
20 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 amyotrophic lateral sclerosis; other
25 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
30 treatment related cognitive disorders; and dyskinetic disorders such as Parkinson's
disease, neuroleptic-induced parkinsonism, and tardive dyskinesias.

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The therapy of the present invention may also be used as a memory and/or cognition enhancer in healthy humans with no cognitive and/or memory deficit.

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In another aspect, the invention provides a compound of formula (I) as hereinbefore described or a salt or solvate 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 salt or solvate thereof for use in the treatment of schizophrenia.

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The invention also provides a compound of formula (I) as hereinbefore described or a salt or solvate 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 salt or solvate thereof in the manufacture of a medicament for the treatment of a condition which requires agonism of a muscarinic M₁ receptor.

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

10

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

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In another aspect, the invention provides a method of treating a condition which requires agonism of a muscarinic M₁ receptor, which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) as hereinbefore described or a salt or solvate thereof. In one embodiment, the mammal is a human.

20

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 salt or solvate 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 salt or solvate thereof. In one embodiment, the mammal is a human.

25

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 salt or solvate thereof. In one embodiment, the mammal is a human.

30

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

35

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

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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 salt or solvate thereof and at least one
5 antipsychotic agent, a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyramidal 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
10 component. The compounds of formula (I) or a salt or solvate 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 extrapyramidal side effects or a cognitive enhancer, but the scope of the invention also includes the adjunctive therapeutic administration of at least one
15 antipsychotic agent, a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyramidal side effects or a cognitive enhancer to patients who are receiving administration of compounds of formula (I) or a salt or solvate thereof.

The combination therapies of the invention may also be administered simultaneously. By
20 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
25 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 salt or solvate thereof to a patient receiving therapeutic administration of at least one
30 antipsychotic agent. In a further aspect, the invention provides the use of compounds of formula (I) or a salt or solvate 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. The invention further provides compounds of formula (I) or a salt or solvate thereof for use for adjunctive
35 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
40 receiving therapeutic administration of compounds of formula (I) or a salt or solvate 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 salt or solvate 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 salt or solvate 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 salt or solvate 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 salt or solvate 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 the use of compounds of formula (I) or a 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 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 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 salt or solvate thereof and one or more further dosage forms each comprising a 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 extrapyramidal 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 extrapyramidal 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 extrapyramidal side effects and a cognitive enhancer.

5 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 extrapyramidal side effects and a cognitive enhancer.

10 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 extrapyramidal side effects and a cognitive enhancer to a patient receiving therapeutic administration of a compound of the present invention.

15 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 extrapyramidal 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
20 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 extrapyramidal side effects and a cognitive enhancer for adjunctive therapeutic administration for the
25 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
30 combination with an active ingredient selected from the group consisting of: a mood stabiliser, an antidepressant, an anxiolytic, a drug for extrapyramidal 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 extrapyramidal side effects and a
35 cognitive enhancer in the manufacture of a medicament for simultaneous therapeutic administration in the treatment of a psychotic disorder.

40 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 extrapyramidal side effects and a

cognitive enhancer for simultaneous therapeutic administration in the treatment of a psychotic disorder.

5 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 extrapyramidal side effects and a cognitive enhancer in the treatment of a psychotic disorder.

10 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 extrapyramidal side effects and a cognitive enhancer in the treatment of a psychotic disorder.

15 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 extrapyramidal side effects and a cognitive enhancer in the treatment of a psychotic disorder.

20 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 extrapyramidal 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.

25 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 extrapyramidal side effects and a cognitive enhancer for simultaneous therapeutic administration with a compound of the present invention in the treatment of a psychotic disorder.

30 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,
35 a drug for extrapyramidal side effects and a cognitive enhancer for simultaneous therapeutic administration.

In one embodiment, the patient is a human.

40 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 antagonists; nicotinic alpha-7

modulators; glycine transporter GlyT1 inhibitors; D2 partial agonist/D3 antagonist/H3 antagonists; AMPA modulators; NK3 antagonists such as osanetant and talnetant; an atypical antipsychotic, for example clozapine, olanzapine, risperidone, quetiapine, aripiprazole, 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-piperaziny)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 Alpha) ; 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®), triflupromazine (available under the tradename VESPRIN®), chlorprothixene (available under the tradename TARACTAN®), droperidol (available
5 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.

10 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, aripiprazole, haloperidol, clozapine, ziprasidone, talnetant and
15 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.
20

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
25 (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,
30 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).
35

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
40 invention include anticholinergics (such as bengtropine, 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 M1 agonists (such as cevimeline).

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In one embodiment, the active ingredient for use in combination with a compound of the present invention, is an atypical antipsychotic, for example clozapine, olanzapine, risperidone, quetiapine, aripirazole, ziprasidone or amisulpride.

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In one embodiment, the active ingredient for use in combination with a compound of the present invention is a typical antipsychotic, for example chlorpromazine, thioridazine, mesoridazine, fluphenazine, perphenazine, prochlorperazine, trifluoperazine, thiothixine, haloperidol, thiflurpromazine, pimozide, droperidol, chlorprothixene, molindone or loxapine.

15

In another embodiment, the active ingredient for use in combination with a compound of the present invention is a mood stabiliser, for example lithium, sodium valproate/valproic acid/divalproex, carbamazepine, lamotrigine, gabapentin, topiramate, oxcarbazepine or tiagabine.

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In another embodiment, the active ingredient for use in combination with a compound of the present invention is an antidepressant, for example a serotonin agonist (such as rauwolscine, yohimbine or metoclopramide); a serotonin reuptake inhibitor (such as citalopram, escitalopram, fluoxetine, fluvoxamine, femoxetine, indalpine, zimeldine, paroxetine or sertraline); a dual serotonin/noradrenaline reuptake inhibitor (such as venlafaxine, reboxetine, duloxetine or milnacipran); a noradrenaline reuptake inhibitors (such as reboxetine); a tricyclic antidepressants (such as amitriptyline, clomipramine, imipramine, maprotiline, nortriptyline or trimipramine); a monoamine oxidase inhibitor (such as isocarboxazide, moclobemide, phenelzine or tranylcypromine); or other (such as bupropion, amineptine, radafaxine, mianserin, mirtazapine, nefazodone or trazodone).

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In another embodiment, the active ingredient for use in combination with a compound of the present invention is an anxiolytic, for example a benzodiazepine such as alprazolam or lorazepam.

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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 salt or solvate thereof and a pharmaceutically acceptable carrier. The pharmaceutical composition can be for use in the treatment of any of the conditions described herein.

40

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

- 5 The compounds of formula (I) as hereinbefore described and their salts or solvates which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

10 A liquid formulation will generally consist of a suspension or solution of the compound or salt or solvate 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.

15 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.

20 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.

25 Typical parenteral compositions consist of a solution or suspension of the compound or salt or solvate 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
30 administration.

35 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
40 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.

5

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.

10 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 salt thereof calculated as the free base.

15

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 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.

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For adjunctive therapeutic administration according to the invention, compounds of formula (I) or salts or solvates 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.

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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 salts or solvates 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

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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).

15 Biological Test Methods

FLIPR experiments on M₁ receptor to determine agonist/antagonist potency

Assay A

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 (20,000/well) and allowed to grow overnight at 37 degrees. Media was removed and 30uL loading buffer (HBSS with 20mM HEPES, pH 7.4) containing FLIPR Calcium 3 dye (Molecular Devices Co., Sunnyvale, CA) was added according to manufacturer's instructions. After incubation at 37 degrees for 45-60 minutes, 10uL of the assay buffer (HBSS with 20mM HEPES and 2.5 mM probenecid, pH 7.4) containing test compounds was added to each well on FLIPR instrument. Calcium response was monitored to determine agonism. Plates were then incubated for another 30 minutes before 10uL of assay buffer containing acetylcholine was added at an EC₈₀, 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 M1 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 pEC₅₀/pIC₅₀ were calculated. The intrinsic activities of agonist compounds were calculated as percentage of maximum FLIPR response induced by acetylcholine (ie using acetylcholine at EC₁₀₀ as the control).

Assay B

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 30uL loading buffer (HBSS with 2.5mM probenecid, 2uM Fluo-4, 500uM Brilliant Black, pH 7.4) was added. After incubation at 37 degrees for 90 minutes, 10uL 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 10uL of assay buffer containing acetylcholine was added at an EC80, 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 M1 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 pEC50/fpKi 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 (ie calculated using a 100% max response from a fitted acetylcholine standard curve, containing multiple concentrations, as control).

Examples 1-10 below were tested in one or both of the above assays and were found to have a pEC₅₀ value of > 6.0 at the muscarinic M₁ receptor, and intrinsic activity > 50%.

FLIPR experiments on M₁ receptor to determine agonist intrinsic activity

Assay A

To determine the intrinsic activities of M1 agonist compounds, compounds of the invention were characterized in FLIPR experiments on U2OS cells with transient expression of human muscarinic M1 receptors. Briefly, U2OS 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) in 2x10⁵/mL cell suspension with 0.1% virus/cell ratio (v/v). 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 (10,000/well) and allowed to grow overnight at 37 degrees. FLIPR experiment was then carried out 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 pEC50 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 (ie calculated using a 100%max response from a fitted acetylcholine standard curve, containing multiple concentrations, as control).

Assay B

To determine the intrinsic activities of M1 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 4.8×10^7 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 pEC50 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 (ie calculated using a 100% max response from a fitted acetylcholine standard curve, containing multiple concentrations, as control).

Examples 1-10 below were tested in this assay and were found to have a pEC₅₀ value of > 6.0 at the muscarinic M₁ receptor, and intrinsic activity of greater than or equal to 0.3.

FLIPR experiments on M₂₋₅ receptor to determine receptor subtype selectivity

Assay A

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, M2, M3, M4 or M5. In the case of M2 and M4 receptors, chimeric G-protein Gqj5 was also co-expressed to couple receptors to the calcium signaling pathway. Briefly, cells were plated (20,000/well) and allowed to grow overnight at 37 degrees. FLIPR experiment was then carried out 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 pEC50/pIC50 values were calculated.

Assay B

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, M2, M3, M4 or M5. In the case of M2 and M4 receptors, chimeric G-protein Gqj5 was also co-expressed to couple receptors to the

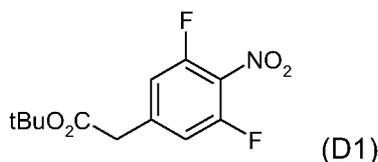
calcium signaling pathway. Briefly, cells were plated (15,000/well) and allowed to grow overnight at 37 degrees. The FLIPR experiment was then carried out on the next day using the same protocol as described above for CHO-M1 cells. Results were imported into ActivityBase data analysis suite where the curves were analysed by non-linear curve fitting and the resulting pEC50/fpKi values were calculated.

Examples 1-10 below were tested in this assay and were found to be selective for the M1 receptor over M2, M3, M4 and M5 receptors, with typical selectivity (ratio of pEC50's) of ≥ 10 -fold, and in certain cases ≥ 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.

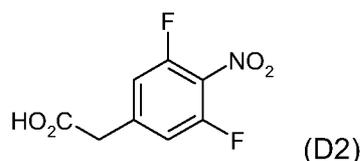
All reactions were either done under argon or can be done under argon, unless stated otherwise (for example hydrogenation reactions).

Description 1. t-Butyl 3,5-difluoro-4-nitrophenylacetate (D1)

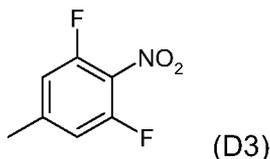


A mixture of 2,6-difluoronitrobenzene (2.5g), t-butyl chloroacetate (3.8ml) and N-methyl pyrrolidone (50ml) was added over 20min at -10°C to -20°C to a solution of potassium t-butoxide (4.2g) in N-methyl pyrrolidone (50ml). After 30min more at the same temperature the reaction was poured onto a mixture of ice and 2M hydrochloric acid and then extracted twice with hexane. Drying, evaporation and chromatography (20g silica, 1:1 hexane:dichloromethane) gave the title compound as a yellow oil, 1.3g.

Description 2. 3,5-Difluoro-4-nitrophenylacetic acid (D2)

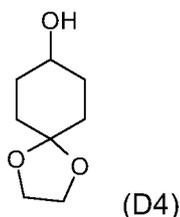


A mixture of t-butyl 3,5-difluoro-4-nitrophenylacetate (D1, 1.3g) and 4M HCl in dioxane (10ml) was stirred at room temperature for 18h then evaporated to give the title compound, 1.0g.

Description 3. 3,5-Difluoro-4-nitrotoluene (D3)

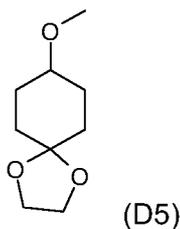
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A mixture of 3,5-difluoro-4-nitrophenylacetic acid (D2, 1.0g), potassium carbonate (0.6g), and dimethylformamide (5ml) was stirred at 50°C for 30min then cooled and partitioned between 2M hydrochloric acid and hexane. Drying, evaporation and chromatography (20g silica, 0-20% ethyl acetate in hexane) gave the title compound as a yellow oil, 0.65g.

10 Description 4. 1,4-Dioxaspiro[4.5]decan-8-ol (D4)

1,4-Dioxaspiro[4.5]decan-8-one (64 mmol, 10 g) was dissolved in ethanol (125 ml) and treated with NaBH₄ (1.2eq., 76.8 mmol, 2.9 g), at 0°C and the mixture was stirred at room temperature for 1 hour. Reaction was quenched with NaOH (25 ml, 2N aqueous solution). The aqueous solution was extracted with dichloromethane (2x). The organics were combined, dried over Na₂SO₄, filtered and the solvent was evaporated to afford the title compound, 8.3 g, 82%, as a colourless oil.

¹HNMR □ (d⁶DMSO, 400 MHz): 1.44 (4H, m), 1.65 (4H, m), 3.55 (1H, d broad), 3.83 (4H, m), 4.48 (1H, d).

Description 5. 8-(Methoxy)-1,4-dioxaspiro[4.5]decane (D5)

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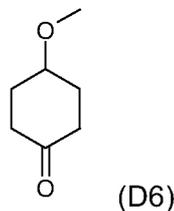
1,4-dioxaspiro[4.5]decan-8-ol (D4, 52.5 mmol, 8.3g) was dissolved in dimethylformamide (200 ml) and sodium hydride (2eq., 105 mmol, 4.2 g) was added at 0°C portionwise. The mixture was stirred at 0°C for 10 minutes and iodomethane (2 eq., 6.5 ml) was added at room temperature. The mixture was stirred at room temperature for 2 hours, then it was

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quenched with methanol, partitioned between ethyl acetate and water and the two phases were separated. The aqueous phase was extracted with ethyl acetate (2x), the combined organics were washed with brine, dried over Na₂SO₄, filtered and the solvent was evaporated to afford the crude compound. Chromatography (ethyl acetate/n-hexane) afforded title compound, 7.3 g, 80%, as a colourless oil.

¹HNMR □ (d⁶DMSO, 400 MHz): 1.46 (2H, m), 1.55 (2H, m), 1.64 (2H, m), 1.73 (2H, m), 3.21 (3H, s), 3.24 (1H, m), 3.83 (4H, m)

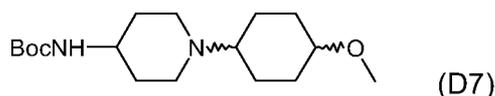
Description 6. 4-(Methoxy)cyclohexanone (D6)



8-(Methoxy)-1,4-dioxaspiro[4.5]decane (D5, 62.2 mmol, 11.9g) was dissolved in 10 ml of tetrahydrofuran and HCl (50 ml of 5M aqueous solution) was added at room temperature; the mixture was stirred at room temperature for one overnight. The tetrahydrofuran was then evaporated, mixture was basified to pH = 10 and it was extracted with ethyl acetate (3x); the organic phases were combined and washed with brine, dried over Na₂SO₄, filtered and the solvent was evaporated to afford the title compound, 8.2g, complete conversion.

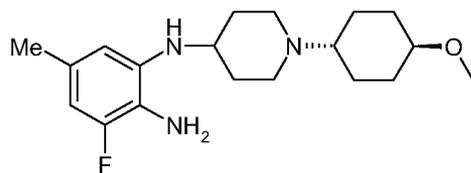
¹HNMR □ (d⁶DMSO, 400 MHz): 1.92 (4H, m), 2.20 (2H, m), 2.348 (2H, m), 3.29 (3H, s), 3.53 (1H, m)

Description 7. *cis/trans*-1,1-Dimethylethyl [1-(4-methoxycyclohexyl)-4-piperidinyl]carbamate (D7)



A solution of 4-methoxycyclohexanone (D6, 4.5g) in dichloromethane (200ml) at room temperature under argon was treated with 1,1-dimethylethyl 4-piperidinylcarbamate (9.0g) and sodium triacetoxyborohydride (16.0g) then stirred at room temperature for 18h, then partitioned between dichloromethane and water at pH9. Drying, evaporation, and chromatography (50g silica, 0-10% methanol in dichloromethane) gave the title compound as a mixture of *cis* and *trans* isomers, 7.0g.

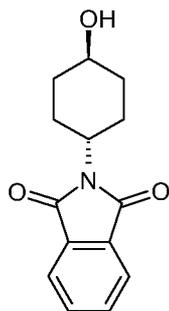
Description 8. *cis/trans*-1-(4-Methoxycyclohexyl)-4-piperidinamine dihydrochloride (D8)



(D11)

A stirred suspension of *trans*-N-(3-fluoro-5-methyl-2-nitrophenyl)-1-(4-methoxycyclohexyl)-4-piperidinamine (D9b, 140mg) in ethanol (8ml) at 50°C was treated with Raney nickel (0.8ml of 10% aqueous suspension) followed by dropwise addition of hydrazine hydrate (0.2ml). The mixture was heated at the same temperature for 1h, then filtered through Kieselguhr and the filtrate evaporated and re-evaporated from toluene to afford the title compound, 130mg.

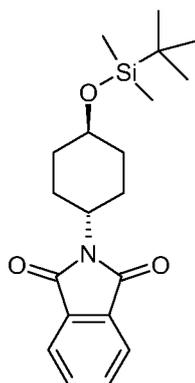
Description 12. *trans*-N-(4-Hydroxycyclohexyl)phthalimide (D12)



(D12)

N-Ethoxycarbonylphthalimide (100g) was added to a mixture of *trans*-4-hydroxycyclohexylamine hydrochloride (69g), potassium carbonate (158g) and water (1l) at room temperature. After 3h the title compound was isolated by filtration, washing with water then ethyl acetate, 95g.

Description 13. *trans*-N-(4-tert-Butyldimethylsilyloxycyclohexyl)phthalimide (D13)

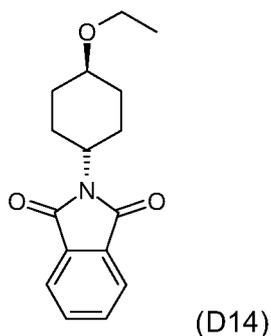


(D13)

Tert-butyldimethylsilyl chloride (60g) was added in portions to a mixture of *trans*-N-(4-hydroxycyclohexyl)phthalimide (D12, 95g), imidazole (55g), and dimethylformamide (200ml) at

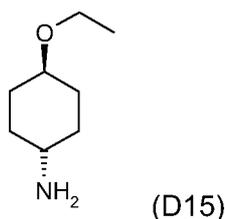
20-30°C (internal, ice cooling). After stirring for 3h more at 40°C the mixture was partitioned water / hexane. Drying and evaporation of the organic layer gave the title compound crystallised from pentane, 92g.

5 **Description 14. *trans*-N-(4-Ethoxycyclohexyl)phthalimide (D14)**



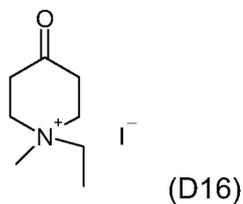
10 Acetaldehyde (10ml) in acetonitrile (50ml) was added over 30 minutes to a solution of *trans*-N-(4-tert-butyldimethylsilyloxycyclohexyl)phthalimide (D13, 50.0g), bismuth tribromide (6.7g), triethylsilane (27ml) in acetonitrile (500ml) stirred at ice bath temperature and the mixture was allowed to warm to room temperature overnight. The mixture was filtered and the resulting grey solid and filtrate were worked up separately. The filtrate was evaporated and treated with hexane to give the title compound as a white solid (16.35g). The grey solid washed with dichloromethane, the dichloromethane extract was evaporated and the residue was stirred with hexane (200ml) to give a second crop of the title compound as a white solid (17.47g).

20 **Description 15. *trans*-4-Ethoxycyclohexylamine (D15)**



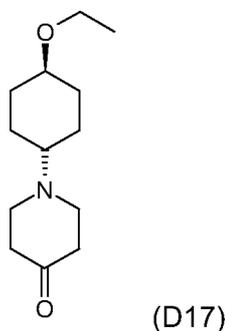
A solution of *trans*-N-(4-ethoxycyclohexyl)phthalimide (D14, 16.35g), hydrazine hydrate (12ml) in ethanol (300ml) and methanol (200ml) was stirred at reflux for 3 hours. The solvent was removed to give a slurry, which was treated with diethyl ether and filtered. The filtrate was evaporated to afford the title compound as a viscous oil contaminated with ether (8.16g).

Description 16. 1-Ethyl-1-methyl-4-oxopiperidinium iodide (D16)



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 17. *trans*-1-(4-Ethoxycyclohexyl)-4-piperidone (D17)



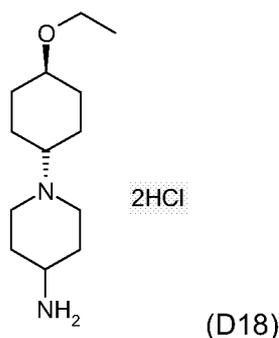
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A mixture of 1-ethyl-4-piperidone methiodide (D16, 27g), *trans*-4-ethoxycyclohexylamine (D15, 8.16g), potassium carbonate (13.5g), water (100ml), and ethanol (200ml) was heated for 3 hours at 80°C, then cooled overnight. The mixture was partitioned with aqueous sodium bicarbonate and dichloromethane. The dichloromethane layer was separated, washed with brine and solvent removed to give the title compound as a amber coloured oil (13.2g).

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Description 18. *trans*-1-(4-Ethoxycyclohexyl)-4-piperidinamine dihydrochloride (D18)

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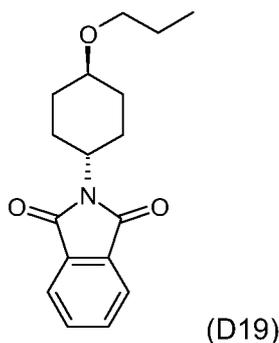


A mixture of *trans*-1-(4-ethoxycyclohexyl)-4-piperidone (D17, 13.2g), 2M ammonia in methanol (300ml), and 10% palladium on carbon paste (4g) was hydrogenated at 50psi at

room temperature for 18h, then filtered and evaporated to give the title compound (9.5g) as a oil.

Description 19. *trans*-N-(4-Propoxycyclohexyl)phthalimide (D19)

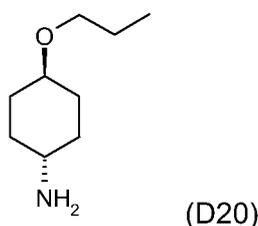
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10 A solution of *trans*-N-(4-tert-butyldimethylsilyloxycyclohexyl)phthalimide (D13, 45g) in acetonitrile (500ml) at room temperature was treated sequentially with triethylsilane (24ml), bismuth tribromide (6g), and (dropwise) propanal (11ml) at 20-30°C (internal, ice cooling). After 30min more the solution was partitioned aqueous sodium bicarbonate / ethyl acetate. Drying and evaporation of the organic layer gave the title compound crystallised from pentane, 20g.

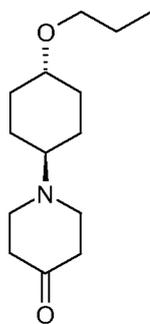
Description 20. *trans*-4-Propoxycyclohexylamine (D20)

15



20 A mixture of *trans*-N-(4-propoxycyclohexyl)phthalimide (D19, 20g), hydrazine hydrate (15ml), and ethanol (400ml) was heated at 80°C for 2h then cooled and filtered. The filtrate was evaporated and the resulting residue redissolved in diethyl ether, filtered and again evaporated to give the title compound, 11g.

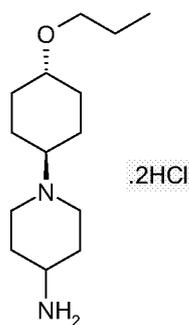
Description 21. *trans*-1-(4-Propoxycyclohexyl)-4-piperidone (D21)



(D21)

1-Ethyl-4-piperidone methiodide (D16, 26g) was added to a refluxing mixture of *trans*-4-propoxycyclohexylamine (D20, 11g), potassium carbonate (1g), water (75ml), and ethanol (150ml) over 30min, and the mixture was then heated for another 30min at 80°C, then cooled, partitioned aqueous sodium bicarbonate / dichloromethane, and purified by chromatography (40+M Biotage silica column, 0 to 10% methanol in dichloromethane containing 0.2M ammonia) to give the title compound, 8g.

10 **Description 22. *trans*-1-(4-Propoxycyclohexyl)-4-piperidinamine dihydrochloride (D22)**

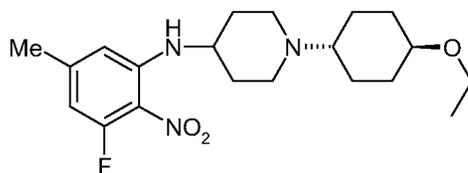


(D22)

15 A mixture of *trans*-1-(4-propoxycyclohexyl)-4-piperidone (D21, 7.5g), 2M ammonia in methanol (100ml), and 10% palladium on carbon paste (100mg) was hydrogenated at 50psi at room temperature for 18h then filtered and evaporated. The residue was converted to the dihydrochloride salt to give the title compound, crystallised from diethyl ether, 7.5g.

20

Description 23. *trans*-N-(3-Fluoro-5-methyl-2-nitrophenyl)-1-(4-ethoxycyclohexyl)-4-piperidinamine (D23)

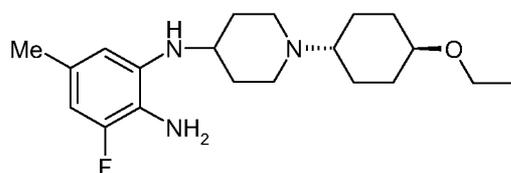


(D23)

25

A stirred solution of 3,5-difluoro-4-nitrotoluene (D3, 0.17g) in dimethylformamide (5ml) at room temperature under argon was treated with diisopropylethylamine (0.7ml) and *trans*-1-[4-(ethoxy)cyclohexyl]-4-piperidinamine dihydrochloride (D18, 0.3g) and heated at 80°C for 18h. The cooled reaction was diluted with ethyl acetate and washed three times with water then dried, evaporated and chromatographed (Biotage KP-NH™-silica column eluting with 0-15% ethyl acetate/hexane) to give the title compound (0.12g).

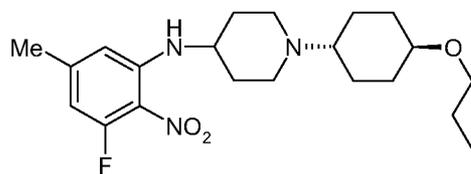
Description 24. *trans*-3-Fluoro-5-methyl-*N*-[1-(4-ethoxycyclohexyl)-4-piperidinyl]-1,2-benzenediamine (D24)



(D24)

A stirred suspension of *trans-N*-(3-fluoro-5-methyl-2-nitrophenyl)-1-(4-ethoxycyclohexyl)-4-piperidinamine (D23, 120mg) in ethanol (10ml) at 50°C was treated with Raney nickel (2.0ml of 10% aqueous suspension) followed by dropwise addition of hydrazine hydrate (0.17ml). The mixture was heated at the same temperature for 1h, then filtered through Kieselguhr and the filtrate evaporated and re-evaporated from toluene to afford the title compound, 120mg.

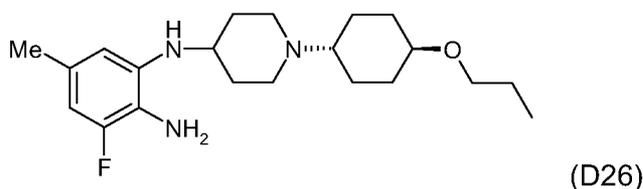
Description 25. *trans-N*-(3-Fluoro-5-methyl-2-nitrophenyl)-1-(4-propoxycyclohexyl)-4-piperidinamine (D25)



(D25)

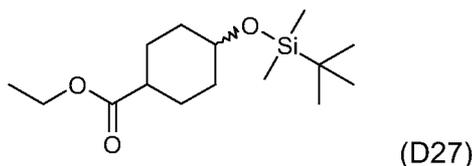
A stirred solution of 3,5-difluoro-4-nitrotoluene (D3, 0.17g) in dimethylformamide (5ml) at room temperature under argon was treated with diisopropylethylamine (0.7ml) and *trans*-1-[4-(propoxy)cyclohexyl]-4-piperidinamine dihydrochloride (D22, 0.31g) and heated at 80°C for 18h. The cooled reaction was diluted with ethyl acetate and washed three times with water then dried, evaporated and chromatographed (Biotage KP-NH™-silica column eluting with 0-15% ethyl acetate/hexane) to give the title compound (0.12g).

Description 26. *trans*-3-Fluoro-5-methyl-*N*-[1-(4-propoxycyclohexyl)-4-piperidinyl]-1,2-benzenediamine (D26)



A stirred suspension of *trans*-*N*-(3-fluoro-5-methyl-2-nitrophenyl)-1-(4-propoxycyclohexyl)-4-piperidinamine (D25, 120mg) in ethanol (10ml) at 50°C was treated with Raney nickel (2.0ml of 10% aqueous suspension) followed by dropwise addition of hydrazine hydrate (0.17ml). The mixture was heated at the same temperature for 1h, then filtered through Kieselguhr and the filtrate evaporated and re-evaporated from toluene to afford the title compound, 100mg.

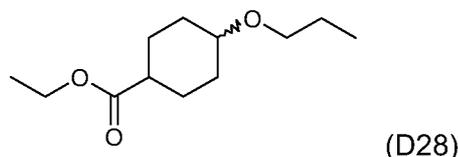
10 **Description 27. Ethyl 4-[(1,1-dimethylethyl)(dimethyl)silyloxy]cyclohexanecarboxylate (D27)**



Chloro(1,1-dimethylethyl)dimethylsilane (115g) was added in portions over 1 hour to a solution of ethyl 4-hydroxycyclohexanecarboxylate (118g), imidazole (103g) and dimethylformamide (400ml) stirred under an atmosphere of argon. A small exotherm was observed resulting in the reaction mixture temperature increasing to ~40°C. The mixture was stirred at room temperature overnight then poured into 10% citric acid solution (2000ml) and extracted with diethyl ether (2 x 800ml). The ether extracts were washed with water, brine and then dried (Na₂SO₄) and the solvent was removed to give the title compound as a oil (198.4g)

¹H NMR \square (CDCl₃, 400 MHz): 0.01 (6H, m), 0.85 (9H, s), 1.2 (3H, m), 1.3-1.5 (2H, m), 1.6 (2H, m), 1.85-2 (3H, m), 2.15-2.3 (1H, m) 3.5 (0.4H, m) 3.86 (1H, m) 4.1 (1H, m).

25 **Description 28. *cis,trans*-Ethyl 4-(propyloxy)cyclohexanecarboxylate (D28)**

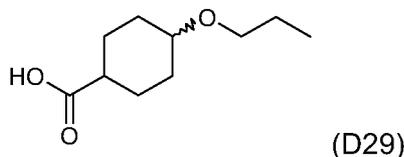


Propionaldehyde (6.4g) in acetonitrile (50ml) was added over 30 minutes to a solution of *cis/trans* ethyl 4-[(1,1-dimethylethyl)(dimethyl)silyloxy]cyclohexanecarboxylate (D27, 25.2g), bismuth tribromide (4.4g), triethylsilane (17.5ml) in acetonitrile (300ml) and the mixture was stirred for a further 1.5 hours. The solvent was partially removed then the

residue was treated with ethyl acetate and saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried with anhydrous sodium sulphate and the solvent was removed to give the title compound contaminated with silicone residues (39.1g).

5

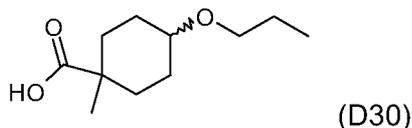
Description 29. *cis,trans*-4-(Propyloxy)cyclohexanecarboxylic acid (D29)



The crude product from Description 28 containing *cis,trans*-ethyl 4-(propyloxy)cyclohexanecarboxylate (D28, 39.1g), 40% w/w sodium hydroxide solution (150ml), tetrahydrofuran (200ml) and methanol (150ml) were stirred together for approx. 72 hours. The solvent was partially removed then the resulting mixture was treated with ethyl acetate and water. The aqueous layer was separated, acidified with concentrated hydrochloric acid and extracted with diethyl ether. The ether layer was washed with brine, dried with anhydrous sodium sulphate and the solvent was removed to give the title compound as a oil (15.42g).

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Description 30. *cis,trans*-1-Methyl-4-(propyloxy)cyclohexanecarboxylic acid (D30)



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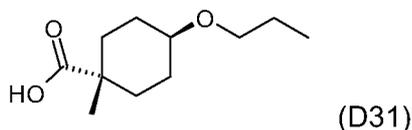
A stirred solution of diisopropylamine (24ml, 0.17mole) in tetrahydrofuran (300ml) at -20°C under argon was treated over 10 mins with 2.5M n-butyllithium in hexane (68ml, 0.17mole), then allowed to warm to 0°C and stir for 15 mins. The mixture was recooled to -10°C and treated over 10 mins with a solution of 4-(propyloxy)cyclohexanecarboxylic acid (D29, 13.8g, 0.074mole) in tetrahydrofuran. The resulting yellow solution was heated at 50°C for 2.5hrs, then cooled to 0°C and treated with iodomethane (13.8ml, 0.22mole). The mixture was allowed to warm to room temperature and stir for 20hrs when a yellow precipitate had formed. The mixture was cooled to 10°C, treated with 10% citric acid solution (200ml), then concentrated under vacuum to approx. 250ml volume. The residual mixture was diluted with water (200ml) and extracted with Et₂O (3x250ml). The combined extract was dried (Na₂SO₄) and concentrated under vacuum to leave a yellow oil (15.0g) which was approx. 60:40 mixture of *cis:trans* isomers.

25

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Description 31. *trans*-1-Methyl-4-(propyloxy)cyclohexanecarboxylic acid (D31)

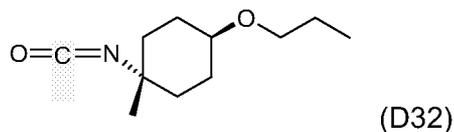
35



cis/trans-1-Methyl-4-(propyloxy)cyclohexanecarboxylic acid (D30, 13g, 0.070mole) was added to stirred thionyl chloride (50ml), 0.68mole) at 10°C and then allowed to warm to room temperature, followed by heating at 85°C for 3 hrs. The mixture was concentrated under vacuum and the residue concentrated twice with toluene to remove excess thionyl chloride. The residue was dissolved in tetrahydrofuran (100ml), treated with dil. NaHCO₃ solution (250ml) and stirred well at room temperature for 24 hrs, followed by standing at room temperature for 3 days. The mixture from the same stage of a smaller scale reaction on 2g of *cis/trans*-1-methyl-4-(propyloxy)cyclohexanecarboxylic acid was combined at this time. The combined mixture was concentrated under vacuum to approx. 300ml and the aqueous residue washed with Et₂O (2x120ml), then acidified with 2M HCl acid and extracted with EtOAc (2x150ml). The combined extract was dried (Na₂SO₄) and concentrated under vacuum to leave the title compound as a pale yellow solid (5.1g, 34%).

¹H NMR \square (CDCl₃, 400 MHz): 0.92 (3H, t), 1.24 (3H, s), 1.54-1.74 (8H, m), 1.78-1.88 (2H, m), 3.33-3.40 (3H, m). 1H not discernible from spectrum.

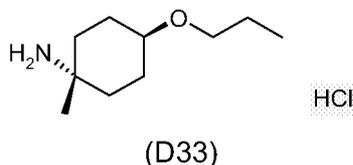
Description 32. *trans*-1-Isocyanato-1-methyl-4-(propyloxy)cyclohexane (D32)



A stirred solution of *trans*-1-methyl-4-(propyloxy)cyclohexanecarboxylic acid (D31, 5.1g, 0.027mole) in toluene (120ml) at room temperature under argon was treated with triethylamine (4.9ml, 0.035mole) and diphenylphosphoryl azide (5.8ml, 0.027mole) and heated at 85°C for 1 hr. The mixture was allowed to cool to room temperature, then treated with 1M NaOH solution (200ml) and extracted with Et₂O (2x150ml). The combined extract was dried (Na₂SO₄) and concentrated under vacuum to leave the title compound as a yellow oil (5.0g, 100%).

¹H NMR \square (CDCl₃, 400 MHz): 0.91 (3H, t), 1.36 (3H, s), 1.50-1.60 (4H, m), 1.65-1.80 (6H, m), 3.33 (2H, t), 3.46-3.52 (1H, m).

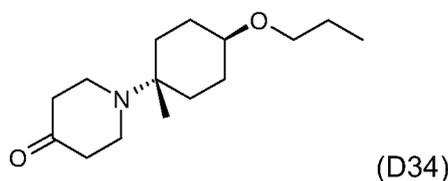
Description 33. [*trans*-1-Methyl-4-(propyloxy)cyclohexyl]amine hydrochloride (D33)



35

A solution of *trans*-1-isocyanato-1-methyl-4-(propyloxy)cyclohexane (D32, 5.0g, 0.027mole) in tetrahydrofuran (100ml) was treated with 5M HCl acid (25ml) and stirred at room temperature under argon for 20hrs, then concentrated under vacuum and the residue azeotroped with toluene to remove traces of water. The residual semi-solid was triturated with Et₂O (120ml) to give a solid, which was filtered off, washed with Et₂O and dried at 50°C under vacuum to afford the title compound as a white solid (4.5g, 85%).
¹H NMR \square (CDCl₃, 400 MHz): 0.91 (3H, t), 1.47 (3H, s), 1.45-1.70 (4H, m), 1.75-2.00 (6H, m), 3.52 (2H, t), 3.40-3.48 (1H, m), 8.38 (3H, br s).

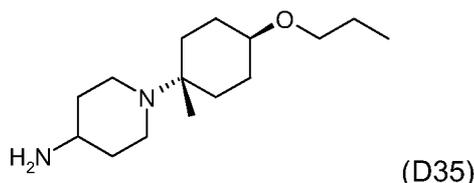
Description 34. 1-[*trans*-1-Methyl-4-(propyloxy)cyclohexyl]-4-piperidinone (D34)



A stirred solution of [*trans*-1-methyl-4-(propyloxy)cyclohexyl]amine hydrochloride (D33, 4.5g, 0.022mole) in a mixture of ethanol (100ml) and water (60ml) at room temperature under argon was treated with potassium carbonate (3.31g, 0.024mole) followed by 1-ethyl-1-methyl-4-oxopiperidinium iodide (D16, 8.91g, 0.033mole), then heated at 80°C for 2.5hrs. The mixture was allowed to cool, concentrated under vacuum to approx. 60ml, then the aqueous residue was treated with sat. NaHCO₃ solution and extracted with dichloromethane (3x80ml). The combined extract was dried (Na₂SO₄) and concentrated under vacuum to leave an orange oil (6.1g), which was chromatographed on silica gel eluting with 0-10% MeOH/dichloromethane to afford the title compound as a yellow oil (3.45g, 63%).

¹H NMR \square (CDCl₃, 400 MHz): 0.93 (3H, s + 3H, t), 1.48-1.72 (8H, m), 1.80-1.92 (2H, m), 2.41 (4H, t), 2.82 (4H, t), 3.35-3.45 (3H, t + m).

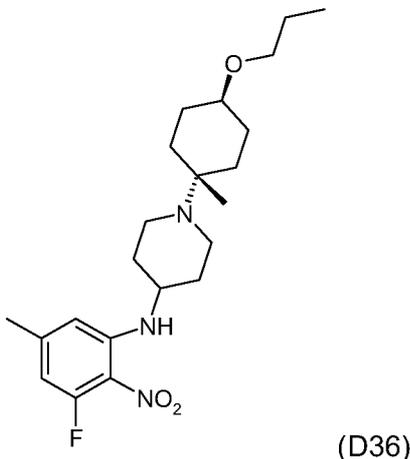
Description 35. 1-[*trans*-1-Methyl-4-(propyloxy)cyclohexyl]-4-piperidinamine (D35)



A solution of 1-[*trans*-1-methyl-4-(propyloxy)cyclohexyl]-4-piperidinone (D34, 2.0g, 0.0079mole) in 2M NH₃/MeOH (60ml) was treated with 10% Pd/C (150mg) and shaken under hydrogen atmosphere at 55psi initial pressure for 3.5 days at room temperature. The mixture was filtered through Kieselguhr to remove catalyst and the filtrate concentrated under vacuum to leave the title compound as a white solid (1.82g, 91%).

$^1\text{H NMR}$ \square (CDCl_3 , 400 MHz): 0.91 (3H, t), 1.08 (3H, br s), 1.32-1.45 (2H, m), 1.5-1.60 (2H, m), 1.62-2.60 (assume 12H, set of broad signals), 2.70-3.10 (1H, br), 3.40-3.45 (3H, m), 3.40-4.40 (2H, v br).

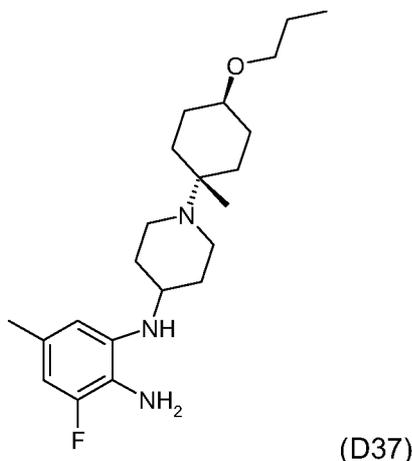
5 **Description 36. *N*-(3-Fluoro-5-methyl-2-nitrophenyl)-1-[*trans*-1-methyl-4-(propyloxy)cyclohexyl]-4-piperidinamine (D36)**



10 A stirred mixture of 3,5-difluoro-4-nitrotoluene (D3, 170mg, 0.98mmole), 1-[*trans*-1-methyl-4-(propoxy)cyclohexyl]-4-piperidinamine (D35, 250mg, 0.98mmole) and diisopropylethylamine (0.2ml, 1.17mmole) in dimethylformamide (20ml) was heated at 50°C overnight under an argon atmosphere. The mixture was washed with sat. NaHCO_3 solution then extracted with dichloromethane. The organic phase was eluted through an

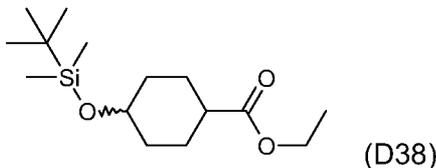
15 SCX cartridge, washed with methanol and the compound was collected by elution with 2M NH_3 in MeOH. The solvent was removed under vacuum to leave a red solid, which was chromatographed on silica eluting with 20-60% EtOAc/DCM to afford the title compound (320mg, 79%). $\text{MH}^+ = 408$.

20 **Description 37. 3-Fluoro-5-methyl-*N*¹-{1-[*trans*-1-methyl-4-(propyloxy)cyclohexyl]-4-piperidinyl}-1,2-benzenediamine (D37)**



A stirred solution of *N*-(3-fluoro-5-methyl-2-nitrophenyl)-1-[*trans*-1-methyl-4-(propyloxy)cyclohexyl]-4-piperidinamine (D36, 320mg, 0.85mmole) in ethanol (70ml) at room temperature under argon was treated with Raney Nickel (100mg) and dropwise addition of hydrazine hydrate (1ml) and maintained for 45 mins. The solution was filtered through Kieselguhr and the filtrate concentrated under vacuum to leave the title compound as a colourless oil (288mg, 90%). $MH^+ = 378$.

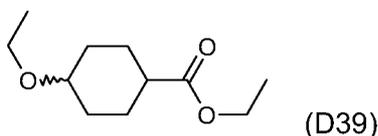
10 **Description 38. *cis/trans*-Ethyl 4-[[1,1-dimethylethyl)(dimethyl)silyl]oxy}cyclohexanecarboxylate (D38)**



15 Chloro(1,1-dimethylethyl)dimethylsilane (115g) was added in portions over 1 hour to a solution of ethyl 4-hydroxycyclohexanecarboxylate (118g), imidazole (103g) and dimethylformamide (400ml) stirred under an atmosphere of argon. A small exotherm was observed resulting in the reaction mixture temperature increasing to $\sim 40^\circ\text{C}$. The mixture was stirred at room temperature overnight then poured into 10% citric acid solution (2000ml) and extracted with diethyl ether (2 x 800ml). The ether extracts were washed with water, brine and then dried (Na_2SO_4) and the solvent was removed to give the title compound as a oil (198.4g).

20 $^1\text{H NMR } \delta$ (CDCl_3 , 400 MHz): 0.01 (6H, m), 0.85 (9H, s), 1.2 (3H, m), 1.3-1.5 (2H, m), 1.6 (2H, m), 1.85-2 (3H, m), 2.15-2.3 (1H, m) 3.5 (0.4H, m) 3.86 (1H, m) 4.1 (1H, m).

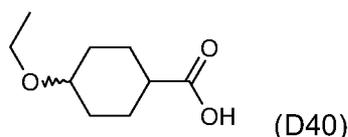
25 **Description 39. *cis/trans*-Ethyl 4-(ethyloxy)cyclohexanecarboxylate (D39)**



cis/trans Ethyl 4-[[[(1,1-dimethylethyl)(dimethyl)silyl]oxy]cyclohexanecarboxylate (D38, 35g, 122 mmol) was dissolved in CH₃CN (250 ml) and Et₃SiH (1.2 eq., 0.146 mol, 23ml) and BiBr₃ (4% mol, 4.9 mmol, 2.2 g) were added at room temperature followed by acetaldehyde (1.2 eq., 8.2 ml), which was slowly added at 25°C. The mixture was stirred at room temperature for 1 hour. The mixture was subsequently poured onto an aqueous saturated solution of NaHCO₃ and the mixture obtained was then extracted with EtOAc (3x). Organics were combined, dried over Na₂SO₄, filtered and the solvent was evaporated to afford the crude mixture that was purified by silica chromatography (Biotage 65i column, EtOAc-nhex) to afford the title compound (21 g, 87%).

¹H NMR δ (DMSO, 400 MHz): 1.1 (3H, m), 1.15 (3H, m), 1.492-3.212 (assume 10 H, set of broad signals and multiplets), 3.312 (2 H, m), 4.041 (2H, m).

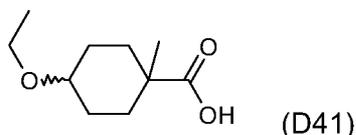
15 **Description 40. *cis/trans*-4-(Ethoxy)cyclohexanecarboxylic acid (D40)**



cis/trans-ethyl 4-(Ethoxy)cyclohexanecarboxylate (D39, 21g, 105 mmol) was dissolved in MeOH/tetrahydrofuran (100 ml/100 ml) and NaOH (5 eq., 0.5 mol, 40 ml, 12.5N aqueous solution) was slowly added at room temperature. The mixture was stirred at room temperature for one overnight. The tetrahydrofuran/MeOH was then evaporated and the crude was washed with Et₂O. The aqueous was acidified and extracted with EtOAc (2x); organics were dried over Na₂SO₄, filtered and the solvent was evaporated to afford the title compound as a pale-yellow oil (17.3 g, 96%).

¹H NMR δ (DMSO, 400 MHz): 1.1 (3H, m), 1.3-3.201 (assume 10 H, set of broad signals and multiplets), 3.417 (2H, m), 12.1 (1H, s broad).

30 **Description 41. *cis/trans*-4-(Ethoxy)-1-methylcyclohexanecarboxylic acid (D41)**



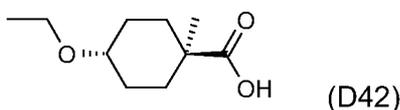
A stirred solution of diisopropylamine (2.3 eq., 0.231mol, 33 ml) in tetrahydrofuran (300ml) at -20°C under argon was treated over 10 min with 2.5M n-butyllithium in hexane (2.3 eq., 93 ml), then allowed to warm to 0°C and stir for 15 mins. The mixture was recooled to -10°C and treated over 10 min with a solution of *cis/trans*-4-

(ethyloxy)cyclohexanecarboxylic acid (D40, 17.3g, 0.1 mol) in 50 ml of tetrahydrofuran. The resulting yellow solution was heated at 50°C for 2.5hrs, then cooled to 0°C and treated with iodomethane (3 eq., 0.3 mol, 19 ml). The mixture was allowed to warm to room temperature and stir for 20 hrs when a yellow precipitate had formed. The mixture

5 was cooled to 10°C, treated with 10% citric acid solution (200ml), and then concentrated under vacuum. The residual mixture was diluted with water (200ml) and extracted with Et₂O (2x). The combined extracts were dried (Na₂SO₄) and concentrated under vacuum to leave the title compound as a yellow oil (16.2 g, 87%), a mixture of *cis:trans* isomers.

10 ¹H NMR δ (DMSO, 400 MHz): 1.086 (assume 8H, m), 1.510 (3H, m), 1.698 (1H, m), 1.781 (1H, m), 2.005 (1H, m), 3.191 (0.5H, m), 3.392 (2H, m), 3.606 (0.5H, m), 12.2 (1H, s br).

Description 42. *trans*-4-(Ethyloxy)-1-methylcyclohexanecarboxylic acid (D42)



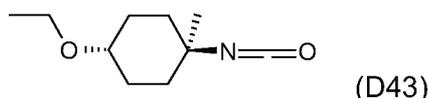
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cis/trans-4-(Ethyloxy)-1-methylcyclohexanecarboxylic acid (D41, 16.2 g, 87.1 mmol) was dissolved in thionyl chloride (15 eq., 1.31 mol, 95 ml) at room temperature and subsequently heated to 85°C for 4 hrs. The mixture was allowed to cool to room temperature and the thionyl chloride was azeotropically evaporated with toluene. The residue was dissolved in tetrahydrofuran (100ml), treated with a 5% aqueous solution of Na₂CO₃ (500 ml) and stirred well at room temperature for 20 minutes. The aqueous residue washed with Et₂O (2x), then acidified and extracted with EtOAc (3x). The combined extracts were dried (Na₂SO₄), filtered and concentrated under vacuum to leave the title compound (6.5 g, 40%).

20

25 ¹H NMR δ (DMSO, 400 MHz): 1.076 (6H, m), 1.505 (6H, m), 1.693 (2H, m), 3.331 (1H, m), 3.394 (2H, q), 12.1 (1H, s br).

Description 43. *trans*-4-(Ethyloxy)-1-isocyanato-1-methylcyclohexane (D43)

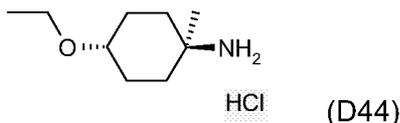


30

A stirred solution of *trans*-4-(ethyloxy)-1-methylcyclohexanecarboxylic acid (D42, 5.5g, 29.5mmol) in toluene (120ml) at room temperature under argon was treated with triethylamine (1.3 eq., 37.7 mmol, 5.3 ml) and diphenylphosphoryl azide (1eq., 29.5 mmol, 6.4 ml) and heated at 85°C for 1 hr. The mixture was allowed to cool to room temperature, then treated with 1M NaOH solution (300ml) and extracted with Et₂O (3x). The combined extract was dried (Na₂SO₄), filtered and concentrated under vacuum to leave the title compound (5 g, 94 %).

35

40 ¹H NMR δ (DMSO, 400 MHz): 1.092 (3H, t), 1.330 (3H, s), 1.487-1.691 (8H, m), 3.392 (2H, q), 3.477 (1H, m).

Description 44. [*trans*-4-(Ethyloxy)-1-methylcyclohexyl]amine mono hydrochloride (D44)

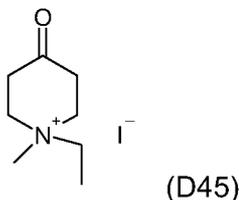
5

A solution of *trans*-4-(ethyloxy)-1-isocyanato-1-methylcyclohexane (D43, 5.0g, 27.3 mmol) in tetrahydrofuran (100ml) was treated with 5M aqueous HCl acid (5.5 eq., 150 mmol, 30 ml) and stirred at room temperature under argon for one overnight, then concentrated under vacuum. The residual semi-solid was triturated with Et₂O to give a first batch of title compound as a white solid (2.8 g). The mother liquors were evaporated, dissolved in tetrahydrofuran again (50 ml) and treated with 5M aqueous HCl acid (15 ml) and the mixture stirred for one week-end at room temperature. The solvent was then evaporated and the solid obtained was dried in the oven at 50°C before trituration with Et₂O. This final trituration afforded further 646 mg of title compound. The two batches were combined to afford 3.4 g, 66%.

10

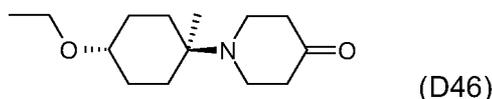
15

¹H NMR δ (DMSO, 400 MHz): 1.084 (3H, t), 1.256 (3H, s), 1.378 (2H, m), 1.619 (4H, m), 1.847 (2H, m), 3.243 (1H, m), 3.424 (2H, q), 8.090 (3H, br s).

20 Description 45. 1-Ethyl-1-methyl-4-oxopiperidinium iodide (D45)

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).

25

Description 46. 1-[*trans*-4-(Ethyloxy)-1-methylcyclohexyl]-4-piperidinone (D46)

30

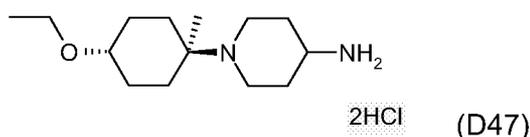
A stirred solution of [*trans*-4-(ethyloxy)-1-methylcyclohexyl]amine mono hydrochloride (D44, 3.4 g, 17.8 mmol) in a mixture of ethanol (216 ml) and water (108 ml) at room temperature under argon was treated with potassium carbonate (1.1 eq., 19.6 mmol, 2.7g) followed by 1-ethyl-1-methyl-4-oxopiperidinium iodide (D45, 1.5 eq., 26.7 mmol, 7.1g), then heated at 80°C for 2 hours. The mixture was allowed to cool to room temperature

35

then the aqueous residue was treated with sat. NaHCO₃ solution and extracted with dichloromethane (3x). The combined extracts were dried (Na₂SO₄) and concentrated under vacuum to leave the crude compound which was chromatographed on silica gel (Biotage 65i column) eluting with 0-10% MeOH/DCM to afford the title compound (2.3 g 54%).

¹H NMR δ (DMSO, 400 MHz): 0.855 (3H, s), 1.099 (3H, t), 1.421 (2H, m), 1.544 (4H, m), 1.793 (2H, m), 2.297 (4H, t), 2.726 (4H, t), 3.377-3.430 (3H, t + m).

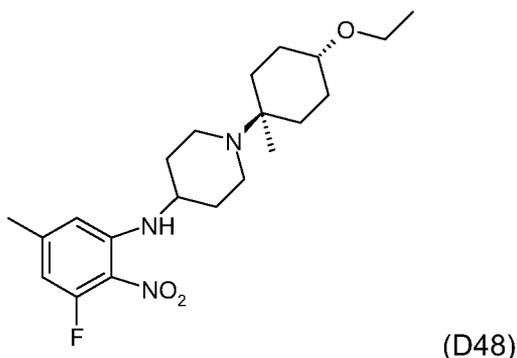
Description 47. 1-[*trans*-4-(Ethyloxy)-1-methylcyclohexyl]-4-piperidinamine dihydrochloride (D47)



A solution of 1-[*trans*-4-(ethyloxy)-1-methylcyclohexyl]-4-piperidinone (D46, 2.3g, 9.62 mmol) in 2M NH₃/MeOH (200ml) was treated with 10% Pd/C (510 mg) and shaken under hydrogen atmosphere at 50psi initial pressure for one overnight at room temperature. The mixture was filtered through Kieselguhr to remove catalyst and the filtrate concentrated under vacuum to leave the free base of the title compound. This was treated with 10 ml of HCl (1M solution of in Et₂O) and dissolved in MeOH (20 ml) and for 10 min. Solvent was subsequently evaporated to afford the title compound as a white solid (2.8 g, complete conversion).

¹H NMR δ (DMSO, 250 MHz, at 352.2K): 1.091 (6H, m br), 1.336 (2H, m), 1.695-1.865 (7H, m), 2.067 (2H, d br), 2.531 (1H, br), 3.187-3.317 (assume 6H, set of broad signals and multiplets), 3.434 (2H, q), 8.496 (2H, s br).

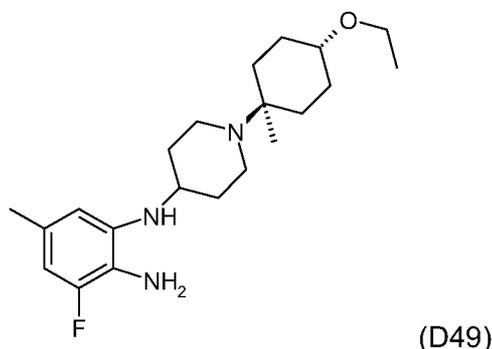
Description 48. 1-[*trans*-4-(Ethyloxy)-1-methylcyclohexyl]-N-(3-fluoro-5-methyl-2-nitrophenyl)-4-piperidinamine (D48)



A solution of 1,3-difluoro-5-methyl-2-nitrobenzene (183mg, 1.06mmole) and 1-[*trans*-4-(ethyloxy)-1-methylcyclohexyl]-4-piperidinamine dihydrochloride (D47, 300mg, 0.962mmole) in N,N-dimethylformamide (5ml) under argon was treated with

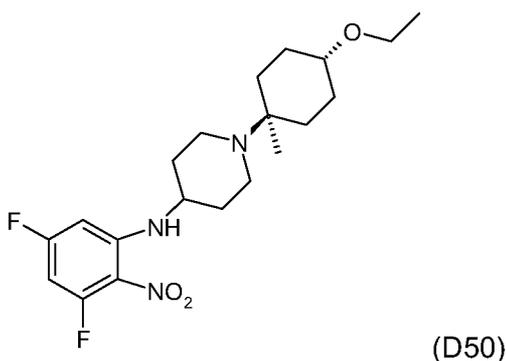
diisopropylethylamine (0.49ml, 2.88 mmole) and the reaction mixture heated at 110°C for 60mins in a microwave reactor. The resulting mixture was then concentrated under vacuum, the residue treated using dil. NaHCO₃ solution (50ml) and then extracted using ethyl acetate (3x50ml). The combined extract was dried (MgSO₄) and concentrated under vacuum to give crude material as an orange residue. The residue was then chromatographed on silica eluting 0-10% methanol/dichloromethane to yield the title compound (150mg, 40%) as an orange residue. MH⁺ = 394.

Description 49. (2-Amino-3-fluoro-5-methylphenyl){1-[*trans*-4-(ethoxy)-1-methylcyclohexyl]-4-piperidiny}amine (D49)



A stirred solution of the 1-[*trans*-4-(ethoxy)-1-methylcyclohexyl]-*N*-(3-fluoro-5-methyl-2-nitrophenyl)-4-piperidinamine (D48, 120mg, 0.305mmole) in EtOH (10ml) at room temperature under argon was treated with Raney Nickel (25mg), followed by hydrazine hydrate (148μL, 3.05mmole). The reaction mixture left to stir for 2h when the initial yellow colour had been lost. The catalyst was removed by filtration through Kieselguhr and the filtrate concentrated under vacuum to leave the title compound as an off-white residue (90mg, 81%). MH⁺ = 364.

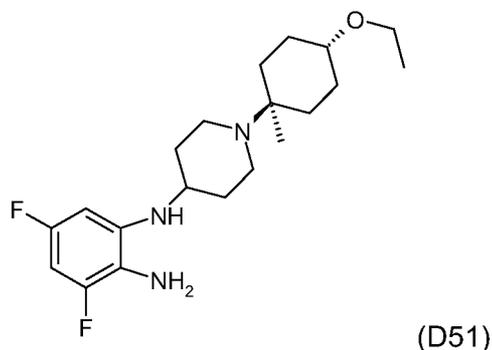
Description 50. *N*-(3,5-Difluoro-2-nitrophenyl)-1-[*trans*-4-(ethoxy)-1-methylcyclohexyl]-4-piperidinamine (D50)



A solution of 1,3,5-trifluoro-2-nitrobenzene (187mg, 1.06mmole) and 1-[*trans*-4-(ethoxy)-1-methylcyclohexyl]-4-piperidinamine dihydrochloride (D47, 300mg, 0.962mmole) in N,N-

dimethylformamide (7ml) under argon was treated with diisopropylethylamine (0.49ml, 2.88 mmole) and the reaction mixture heated at 110°C for 50mins in a microwave reactor. The resulting mixture was then concentrated under vacuum, the residue treated using dil. NaHCO₃ solution (50ml) and then extracted using dichloromethane (2x30ml). The combined extract was dried (MgSO₄) and concentrated under vacuum to give crude material as an orange residue. The residue was chromatographed on silica gel eluting with 0-10% methanol/dichloromethane to afford the title compound (140mg, 34%) as an orange residue. MH⁺ = 398.

10 **Description 51. (2-Amino-3,5-difluorophenyl){1-[*trans*-4-(ethoxy)-1-methylcyclohexyl]-4-piperidinyl}amine (D51)**

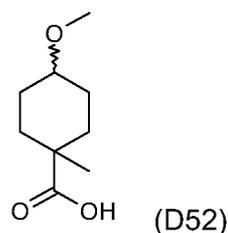


15 A stirred solution of the *N*-(3,5-difluoro-2-nitrophenyl)-1-[*trans*-4-(ethoxy)-1-methylcyclohexyl]-4-piperidinamine (D50, 140mg, 0.328mmole) in EtOH (10ml) at room temperature under argon was treated with Raney Nickel (25mg), followed by hydrazine hydrate (159μL, 3.28mmole). The reaction mixture left to stir for 2h when the initial yellow colour had been lost. The catalyst was removed by filtration through Kieselguhr and the filtrate concentrated under vacuum to leave the title compound as an off-white residue (110mg, 91%).

20 ¹H NMR δ (CDCl₃, 400 MHz): 0.93 (3H, s), 1.20-1.23 (3H, t), 1.44-1.59 (4H, m), 1.59-1.68 (2H, m), 1.82-1.87(2H, m), 2.00-2.07 (2H, m), 2.23-2.34 (2H, m), 3.18 (1H, m), 3.33-3.38 (1H, m), 3.45-3.51 (2H, m), 3.69-3.75 (1H, m), 3.89 (1H, m), 6.12-6.22 (2H, m).

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Description 52. *cis/trans*-1-Methyl-4-(methoxy)cyclohexanecarboxylic acid (D52)



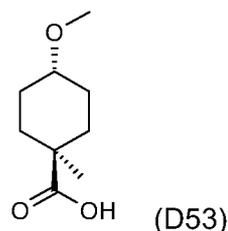
30 A stirred solution of diisopropylamine (16.1ml, 115 mmol, 2.1 eq.) in tetrahydrofuran (200ml) at 0°C under argon was treated with 2.5M *n*-butyllithium in hexane (1.05 eq., 110

mmol, 44ml) and it was then stirred at the same temperature for 10 minutes. The mixture was then treated with a solution of 4-(methyloxy)cyclohexanecarboxylic acid (1 eq., 55 mmol, 8.7g) in 50 ml of dry tetrahydrofuran. The resulting yellow solution was heated at 50°C for 2.0 hrs, then cooled to 0°C and treated with iodomethane (3 eq., 12 ml). The mixture was allowed to warm to room temperature and stir for 2 hrs. The mixture was partitioned between citric acid (10% aqueous solution) and Et₂O, the two phases were separated and the aqueous was extracted with Et₂O (2x). Organics were combined, dried (Na₂SO₄), filtered and concentrated under vacuum to leave a yellow solid (9.8g) a mixture of *cis:trans* isomers.

¹H NMR δ (d⁶DMSO, 400MHz): 1.078-2.018 (11 H, *cis/trans* isomers), 3.074 (1H, m single isomer), 3.193 (3H, s single isomer), 3.213 (3H, s single isomer), 3.606 (1H, s broad, single isomer), >12.5 (1H, s broad, *cis/trans* isomers).

Description 53. *trans*-1-Methyl-4-(methyloxy)cyclohexanecarboxylic acid (D53)

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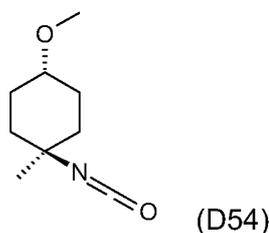


cis/trans-1-Methyl-4-(methyloxy)cyclohexanecarboxylic acid (D52, 41.3 mmol, 7.7 g) was dissolved in thionyl chloride (15.3 eq., 631 mmol, 46 ml) and the mixture was refluxed at 90°C for 4 hours. The solvent was evaporated and the crude product treated with toluene and concentrated in vacuo. The residual brown oil was treated with 5% Na₂CO₃ solution (400 ml) and tetrahydrofuran (40 ml) and the mixture was stirred at room temperature for 30 minutes. The aqueous solution was washed with Et₂O (2x) and the aqueous phase was acidified with 2M HCl acid and extracted with ethyl acetate (2x). The combined organics were dried over Na₂SO₄, filtered and the solvent was evaporated to afford the titled compound (2.8 g, 40%).

¹H NMR δ (d⁶DMSO, 400MHz): 1.085 (3H, s), 1.419 (2H, m), 1.485 (4H, m), 1.701 (2H, m), 3.225 (4H, m), 3.342 (1H, s).

Description 54. *trans*-1-Isocyanato-1-methyl-4-(methyloxy)cyclohexane (D54)

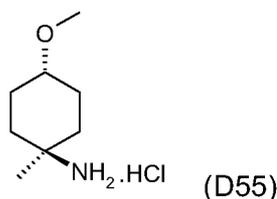
30



To a solution of *trans*-1-methyl-4-(methoxy)cyclohexanecarboxylic acid (D53, 15.0 mmol, 2.8 g) in dry toluene (70 ml), Et₃N (1.3 eq., 19.6 mmol, 2.7 ml), and diphenylphosphoryl azide (1.0 eq., 15.0 mmol, 3.2 ml) were added at room temperature. The mixture was refluxed at 80°C for 2 hours. The mixture was cooled to room temperature and poured onto 1M NaOH (70 ml) and the aqueous solution was extracted with EtOAc (2x). The organics were combined, dried over Na₂SO₄, filtered and the solvent was evaporated to afford the crude compound. The crude product was then purified by chromatography (EtOAc-nhex) on silica column to afford the title compound (1.33 g, 48%).

¹H NMR δ (d⁶DMSO, 400MHz): 1.327 (3H, s), 1.61 (8H, m), 3.197 (3H, s) 3.355 (1H, m).

Description 55. *trans*-1-Methyl-4-(methoxy)cyclohexanamine monohydrochloride (D55)



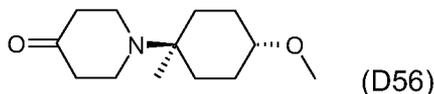
15

To a solution of *trans*-1-isocyanato-1-methyl-4-(methoxy)cyclohexane (D54, 7.27 mmol, 1.33 g) in tetrahydrofuran (30 ml), concentrated HCl acid (6 ml) was added at room temperature. The mixture was stirred for 4 hours at room temperature and concentrated HCl acid (a few drops) was added. The reaction was left overnight and the solvent evaporated to afford the title compound (0.9 g, 69%).

20

¹H NMR δ (d⁶DMSO, 400MHz): 1.260 (3H, s), 1.39 (2H, m), 1.632 (4H, m), 1.87 (2H, m), 3.157 (1H, m), 3.217 (3H, s).

25 Description 56. 1-[*trans*-1-Methyl-4-(methoxy)cyclohexyl]-4-piperidinone (D56)



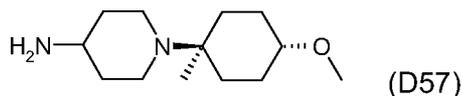
trans-1-Methyl-4-(methoxy)cyclohexanamine monohydrochloride (D55, 7.69 mmol, 1.1 g), 1-ethyl-1-methyl-4-oxopiperidinium iodide (D45, 1.7 eq., 13.1 mmol, 3.5 g) potassium carbonate (1.5 eq., 11.5 mmol, 1.5 g), water (40 ml) and ethanol (80 ml) were refluxed at 80°C until the starting material was not observed on TLC. The mixture was partitioned between NaHCO₃ solution and dichloromethane. Some product was lost due to mechanical spillage. The work up was repeated. The dichloromethane solution was dried, concentrated under vacuum and the crude product was then purified by chromatography (MeOH-NH₃-dichloromethane) on silica column to afford the title compound (650 mg, 35 %).

35

^1H NMR δ (d^6DMSO , 400MHz) 0.85 (3H, s), 1.50 (8H, m), 1.762 (2H, t), 2.301 (4H, t), 2.725 (4H, t), 3.207 (3H, s), 3.274 (1H, m).

Description 57. 1-[*trans*-1-Methyl-4-(methoxy)cyclohexyl]-4-piperidinamine (D57)

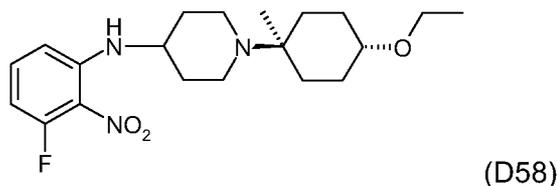
5



To a solution of 1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinone (D56, 2.67 mmol, 650 mg) in 2M NH_3 in methanol (15.0 eq., 40.0 mmol, 20 ml), 10% Pd/C paste (65 mg) was added. The mixture hydrogenated at 50psi for 24 hours at room temperature. The mixture filtered through Kieselguhr and washed with ethanol (100 ml). The solvent was evaporated to afford the crude product. The reaction was repeated on the crude product and left for 24 hours. The mixture was filtered through celite and washed with ethanol and the solvent was evaporated to afford the title compound (390 mg, 68%). $\text{M}^+ + \text{H} = 227$.

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Description 58. 1-[*trans*-4-(Ethoxy)-1-methylcyclohexyl]-*N*-(3-fluoro-2-nitrophenyl)-4-piperidinamine (D58)

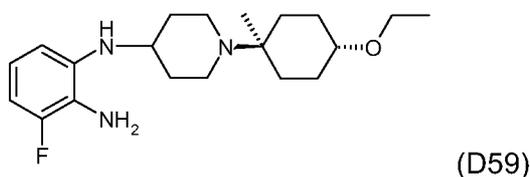


20

A microwave vessel was charged with 2,6-difluoro-1-nitrobenzene (0.318g), 1-[*trans*-1-methyl-4-(ethoxy)cyclohexyl]-4-piperidinamine dihydrochloride (D47, 0.318g), dimethylformamide (3ml) and diisopropylethylamine (1.0ml) and heated at 200°C for 20 minutes in a microwave reactor. The cooled reaction was evaporated, dissolved in methanol and loaded onto a SCX cartridge which was eluted with methanol, then with 2M methanolic ammonia. The methanolic ammonia fraction was evaporated and the residue was chromatographed on silica gel eluted with 0-5% dichloromethane – methanolic ammonia to give the title compound as a yellow glass (0.114g). $\text{MH}^+ = 380$.

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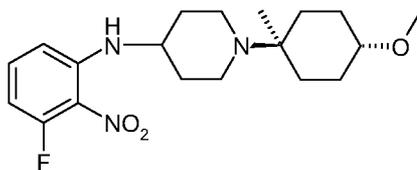
Description 59. 3-Fluoro-*N*-{1-[*trans*-1-methyl-4-(ethoxy)cyclohexyl]-4-piperidinyl}-1,2-benzenediamine (D59)



35

A solution of 1-[*trans*-4-(ethoxy)-1-methylcyclohexyl]-*N*-(3-fluoro-2-nitrophenyl)-4-piperidinamine (D58, 0.114g) in ethanol (20ml) was treated with Raney-nickel (~0.2ml) and hydrazine hydrate (1ml). The mixture was stirred at 40°C for 1 hour then cooled, filtered and the filtrate was evaporated to give the title compound as a brown solid
5 (0.097g). $MH^+ = 350$.

Description 60. *N*-(3-Fluoro-2-nitrophenyl)-1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinamine (D60)



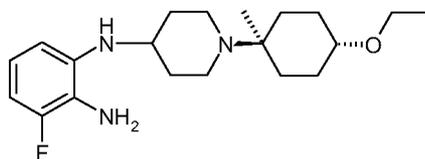
(D60)

10

A microwave vessel was charged with 2,6-difluoro-1-nitrobenzene (0.318g), 1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinamine dihydrochloride (diHCl salt of D57, 0.318g), dimethylformamide (3ml) and diisopropylethylamine (1.0ml) and heated at 200°C
15 for 20 minutes in a microwave reactor. The cooled reaction was evaporated, dissolved in methanol and loaded onto a SCX cartridge which was eluted with methanol then 2M methanolic ammonia. The methanolic ammonia fraction was evaporated and the residue was chromatographed on silica gel eluted with dichloromethane – methanolic ammonia 0-5% to give the title compound as a yellow glass (0.249g). $MH^+ = 366$.

20

Description 61. 3-Fluoro-*N*-{1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinyl}-1,2-benzenediamine (D61)

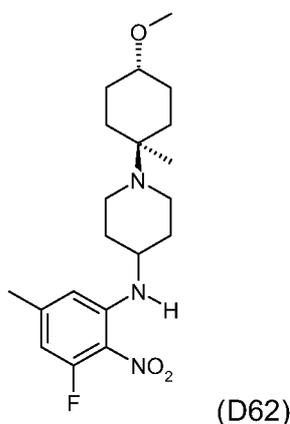


(D61)

25

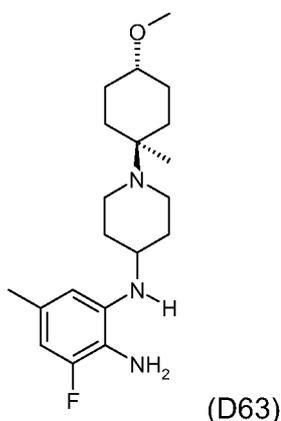
A solution of *N*-(3-fluoro-2-nitrophenyl)-1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinamine (D60, 0.249g) in ethanol (30ml) was treated with Raney-nickel (~1ml) and hydrazine hydrate (1ml). The mixture was stirred at 45°C for 0.5 hours then cooled, filtered and the filtrate was evaporated, dissolved in dichloromethane and evaporated to
30 give the title compound as a solid (0.202g). $MH^+ = 336$.

Description 62. *N*-(3-Fluoro-5-methyl-2-nitrophenyl)-1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinamine (D62)



Diisopropylethylamine (0.55mL, 3.23mmole) and 2,6-difluoro-4-methyl-1-nitrobenzene (206mg, 1.19mmole) were added to a solution of 1-[*trans*-4-(methoxy)-1-methylcyclohexyl]-4-piperidinamine dihydrochloride (di HCl salt of D57, 306mg, 1.02mmole) in N,N-dimethylformamide (5ml) under argon. The reaction was heated at 100°C in a microwave reactor for 30min and then for a further 30min. The mixture was poured on to sat. NaHCO₃ solution (50mL) and extracted with EtOAc (3x). The combined organics were washed sequentially with brine, H₂O and brine, dried (Na₂SO₄) and concentrated via rotary evaporation. The crude residue was purified by SCX (5g) and then chromatographed (silica, CH₂Cl₂-0.5% NH₃ /9.5% MeOH /90% CH₂Cl₂) to yield the title compound (157mg, 41%) as an orange oil which solidified on standing to give an orange solid. MH⁺ 380.

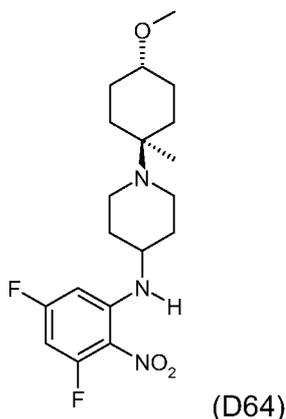
15 **Description 63. (2-Amino-3-fluoro-5-methylphenyl){1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinyl}amine (D63)**



20 Raney Nickel (0.25mL, 10% sol. in H₂O) was added to a vigorously stirred solution of *N*-(3-fluoro-5-methyl-2-nitrophenyl)-1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinamine (D62, 150mg, 0.40mmole) in EtOH (10mL) under argon. Hydrazine hydrate (220μL, 7.06mmole) was added dropwise followed by a second portion of Raney Nickel (0.25mL, 10% sol. in H₂O). The reaction was stirred for 1h and then filtered

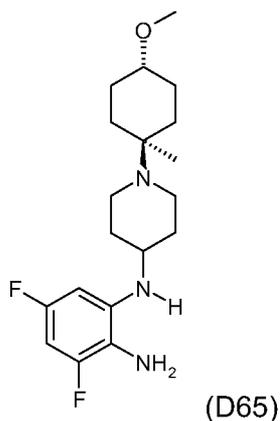
through Kieselguhr using EtOH. The solvent was removed via rotary evaporation to give the title compound (113mg, 81%) as a white solid. MH^+ 350.

5 **Description 64. *N*-(3,5-Difluoro-2-nitrophenyl)-1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinamine (D64)**



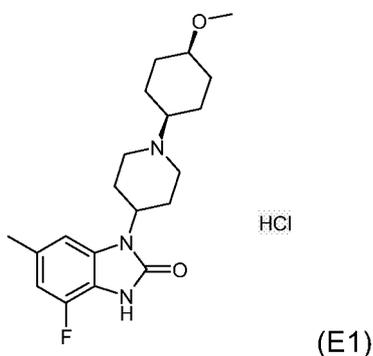
Diisopropylethylamine (0.56mL, 3.29mmole) and 2,4,6-trifluoro-1-nitrobenzene (533mg, 3.01mmole) were added to a solution of 1-[*trans*-4-(methoxy)-1-methylcyclohexyl]-4-piperidinamine dihydrochloride (diHCl salt of D57, 318mg, 1.06mmole) in *N,N*-dimethylformamide (5ml) at r.t. under argon. The reaction was heated at 110°C in a microwave reactor for 30min and then for a further 30min. The reaction was poured on to sat. $NaHCO_3$ solution (50mL) and extracted with EtOAc (3x). The combined organics were washed sequentially with brine, H_2O and brine, dried (Na_2SO_4) and concentrated via rotary evaporation. The crude residue was purified by SCX (5g) and then chromatographed (silica, CH_2Cl_2 -0.5% NH_3 /9.5% MeOH /90% CH_2Cl_2) to yield the title compound (221mg, 54%) as a yellow solid. MH^+ 384.

20 **Description 65. (2-Amino-3,5-difluorophenyl){1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinyl}amine (D65)**



N-(3,5-Difluoro-2-nitrophenyl)-1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinamine (D64, 221mg, 0.58mmole) was dissolved in EtOH (10mL) and stirred vigorously at r.t. under argon. Raney Nickel (0.25mL, 10% sol. in H₂O) was added, followed by the hydrazine hydrate (180μL, 5.78mmole). A second portion of Raney Nickel (0.25mL, 10% sol. in H₂O) was added and the reaction was stirred vigorously for 45min. The mixture was filtered through Kieselguhr using EtOH and concentrated by rotary evaporation to give the title compound (229mg) as a brown oil which solidified on standing to a brown solid. MH⁺ 354.

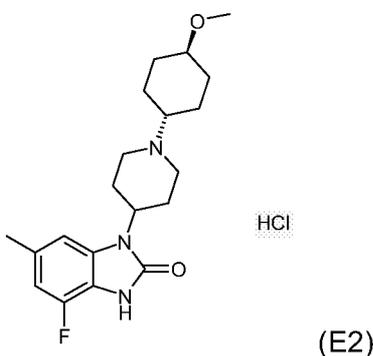
10 **Example 1. 4-Fluoro-6-methyl-1-[1-(*cis*-4-methoxycyclohexyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (E1)**



15 A solution of *cis* 3-fluoro-5-methyl-*N*-[1-(4-methoxycyclohexyl)-4-piperidinyl]-1,2-benzenediamine (D10, 210mg) in dichloromethane (12ml) at 0°C was treated with triphosgene (70mg) then diisopropylethylamine (0.15ml), and then maintained at 0°C for 1h. The mixture was partitioned between dichloromethane and water at pH9. Drying, evaporation and chromatography (20g silica, 2-10% methanol in dichloromethane) gave the title compound isolated as the hydrochloride salt from diethyl ether, 100mg.

20 ¹HNMR (d⁶DMSO): 1.4 (2H, m), 1.7 (2H, m), 1.8-2.1 (6H, m), 2.35 (3H, s), 2.8 (2H, m), 3.25 (3H, s), 3.3-3.8 (6H, m), 4.6 (1H, m), 6.7 (1H, d, J=11Hz), 7.4 (1H, s), 10.5 (1H, br s), 11.4 (1H, s), MH⁺ 362.

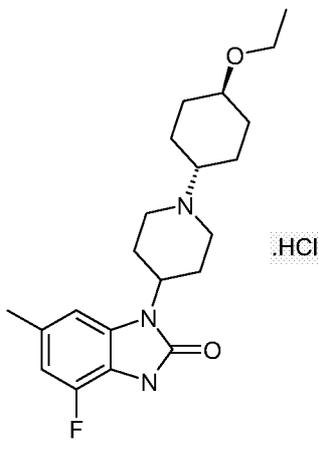
25 **Example 2. 4-Fluoro-6-methyl-1-[1-(*trans*-4-methoxycyclohexyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (E2)**



A solution of trans 3-fluoro-5-methyl-N-[1-(4-methoxycyclohexyl)-4-piperidiny]-1,2-benzenediamine (D11, 130mg) in dichloromethane (8ml) at 0°C was treated with triphosgene (50mg) then diisopropylethylamine (0.10ml), and then maintained at 0°C for 1h. The mixture was partitioned between dichloromethane and water at pH9. Drying, evaporation and chromatography (20g silica, 2-10% methanol in dichloromethane) gave the title compound isolated as the hydrochloride salt from diethyl ether, 100mg.

¹HNMR (d⁶DMSO): 1.2 (2H, m), 1.6 (2H, m), 1.9 (2H, m), 2.2 (4H, m), 2.35 (3H, s), 2.8 (2H, m), 3.3 (3H, s), 3.1-3.6 (6H, m), 4.6 (1H, m), 6.75 (1H, d, J=11Hz), 7.4 (1H, s), 10.6 (1H, br s), 11.3 (1H, s), MH+ 362.

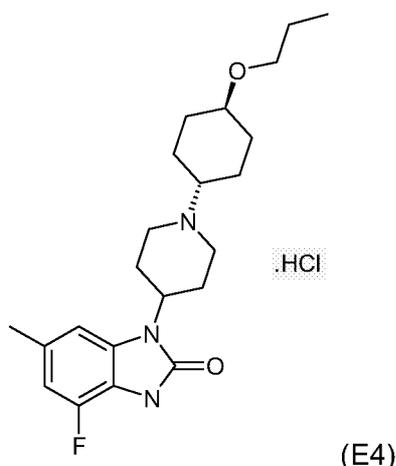
Example 3. 4-Fluoro-6-methyl-1-[1-(*trans*-4-ethoxycyclohexyl)-4-piperidiny]-1,3-dihydro-2H-benzimidazol-2-one hydrochloride (E3)



A solution of trans 3-fluoro-5-methyl-N-[1-(4-ethoxycyclohexyl)-4-piperidiny]-1,2-benzenediamine (D24, 120mg) in dichloromethane (6ml) at 0°C was treated with triphosgene (40mg) then diisopropylethylamine (0.08ml), and then maintained at 0°C for 1h. The mixture was partitioned between dichloromethane and aqueous sodium bicarbonate. Drying, evaporation and chromatography (10g silica, 0-10% methanol in dichloromethane) gave the title compound isolated as the hydrochloride salt from diethyl ether, 95mg.

¹HNMR (HCl salt) (d⁶DMSO): 1.1 (3H, t), 1.2 (2H, m), 1.55 (2H, m), 1.9 (2H, m), 2.15 (4H, m), 2.35 (3H, s), 2.8 (2H, m), 3.2-3.5 (12H, m), 4.6 (1H, m), 6.7 (1H, d, J=11Hz), 7.4 (1H, s), 10.5 (1H, br s), 11.35 (1H, s), MH+ 376.

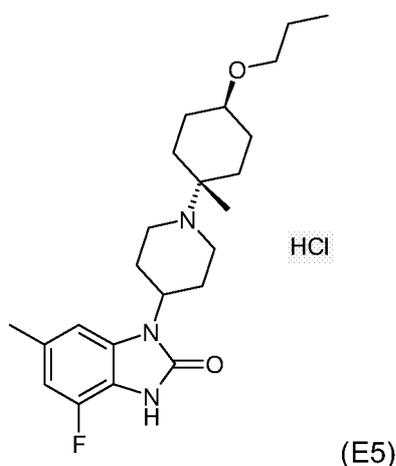
Example 4. 4-Fluoro-6-methyl-1-[1-(*trans*-4-propoxycyclohexyl)-4-piperidiny]-1,3-dihydro-2H-benzimidazol-2-one hydrochloride (E4)



A solution of *trans* 3-fluoro-5-methyl-*N*-[1-(4-propoxycyclohexyl)-4-piperidinyl]-1,2-benzenediamine (D26, 100mg) in dichloromethane (6ml) at 0°C was treated with triphosgene (35mg) then diisopropylethylamine (0.07ml), and then maintained at 0°C for 1h. The mixture was partitioned between dichloromethane and aqueous sodium bicarbonate. Drying, evaporation and chromatography (10g silica, 0-10% methanol in dichloromethane) gave the title compound isolated as the hydrochloride salt from diethyl ether, 65mg.

¹HNMR (HCl salt) □ (d⁶DMSO): 0.85 (3H, t), 1.2 (2H, m), 1.5 (4H, m), 1.9 (2H, m), 2.15 (4H, m), 2.35 (3H, s), 2.8 (2H, m), 3.2-3.5 (15H, m), 4.6 (1H, m), 6.7 (1H, d, J=11Hz), 7.4 (1H, s), 10.2 (1H, br s), 11.35 (1H, s), MH⁺ 390.

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

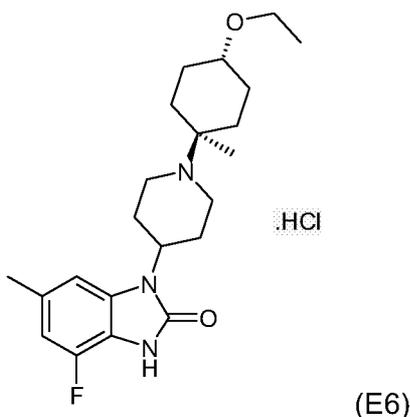


A stirred mixture of 3-fluoro-5-methyl-*N*¹-{1-[*trans*-1-methyl-4-(propyloxy)cyclohexyl]-4-piperidinyl}-1,2-benzenediamine (D37, 288mg, 0.76mmole) in dichloromethane (50ml) was treated with diisopropylethylamine (0.4ml, 2.2mmole) and portionwise addition of triphosgene (89mg, 0.3mmole) at 0°C under argon for 15 minutes. The mixture was

allowed to warm to room temperature, then washed with sat. NaHCO₃ solution and extracted with dichloromethane. The extract was dried (Na₂SO₄) and concentrated under vacuum, then crystallised from diethyl ether and collected by filtration to afford the free base of the title compound (165mg, 56%). This was dissolved in dichloromethane (10ml), treated with 1M HCl/Et₂O (5ml) and stirred for 5 mins. The precipitate was filtered off to afford the title compound as a white solid (147mg). MH⁺ = 404.

¹H NMR δ (d⁶DMSO, 400MHz): 0.87 (3H, t), 1.20-1.40 (5H, s + m), 1.41-1.54 (2H, m), 1.80-2.03 (assume 6H, m), 2.33 (3H, s), 2.83-3.00 (2H, m), 3.10-3.26 (3H, m), 3.30-3.70 (assume 6H, several signals), 4.55-4.67 (1H, m), 6.73 (1H, d), 7.53 (1H, s), 10.4 (1H, br s), 11.33 (1H, s).

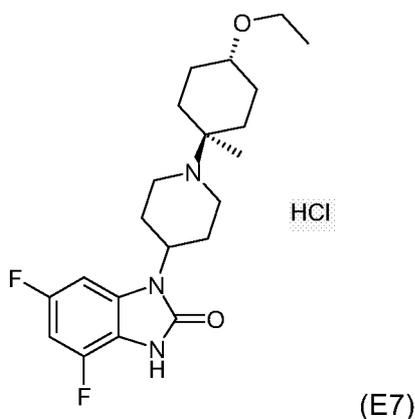
Example 6. 1-{1-[*trans*-4-(Ethyloxy)-1-methylcyclohexyl]-4-piperidinyl}-4-fluoro-6-methyl-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (E6)



A stirred solution of the (2-amino-3-fluoro-5-methylphenyl){1-[*trans*-4-(ethyloxy)-1-methylcyclohexyl]-4-piperidinyl}amine (D49, 90mg, 0.25mmole) in dichloromethane (7ml) at 0°C under argon was treated with diisopropylethylamine (63μL, 0.375mmole) followed by solid triphosgene (30mg, 0.10mmole) and maintained at 0°C for 1h. The mixture was treated with dil. NaHCO₃ solution (20ml) and extracted with dichloromethane (2 x 25ml). The combined extract was dried (phase separation cartridge) and concentrated under vacuum to afford the free base of the title compound as an off-white residue. This was then treated with 1M HCl/diethyl ether (0.25ml) and the solid filtered to yield the hydrochloride salt (38mg, 36%) as a white solid. MH⁺ 390.

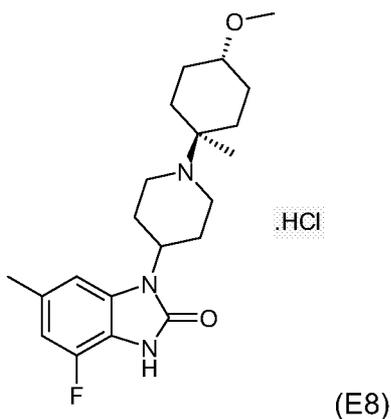
¹H NMR (free base) δ (CDCl₃, 400 MHz): 0.95 (3H, s), 1.19-1.28 (3H, m), 1.43-1.58 (4H, m), 1.66-1.72 (2H, m), 1.80-1.83 (2H, m), 1.88-1.93 (2H, m), 2.23-2.36 (4H, m), 2.39 (3H, s), 3.14-3.16 (2H, m), 3.39-3.43 (1H, m), 3.47-3.53 (2H, m), 4.22-4.26 (1H, m), 6.25-6.65 (1H, d), 6.83 (1H, s), 7.98 (1H, s).

Example 7. 1-{1-[*trans*-4-(Ethyloxy)-1-methylcyclohexyl]-4-piperidinyl}-4,6-difluoro-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (E7)



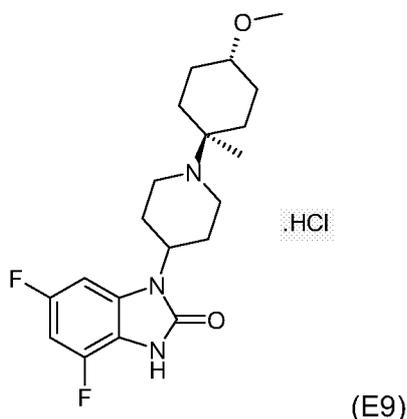
- A stirred solution of the (2-amino-3,5-difluorophenyl){1-[*trans*-4-(ethoxy)-1-methylcyclohexyl]-4-piperidinyl}amine (D51, 110mg, 0.29mmole) in dichloromethane (5ml) at 0°C under argon was treated with diisopropylethylamine (60μL, 0.435mmole) followed by solid triphosgene (34mg, 0.12mmole) and maintained at 0°C for 1h. The mixture was treated with dil. NaHCO₃ solution (20ml) and extracted with dichloromethane (2 x 30ml). The combined extract was dried (phase separation cartridge) and concentrated under vacuum to afford crude material as an off white solid. The crude material was then purified using a Waters Xbridge chromatography column and solvent gradient using aqueous ammonium bicarbonate (10mmolar) adjusted to pH10 with ammonia and acetonitrile as the mobile phase to give the free base of the title compound (27mg) as a white solid. This was treated with 1M HCl/diethyl ether (0.25ml) and the solid filtered to afford the title compound (31mg, 36%) as a white solid. MH⁺ 394.
- ¹H NMR (free base) δ (CDCl₃, 400 MHz): 0.94 (3H, s), 1.20-1.23 (3H, t), 1.44-1.59 (4H, m), 1.64-1.69 (2H, m), 1.80-1.91 (4H, m), 1.80-1.91 (4H, m), 3.14-3.15 (2H, d), 3.42-3.44 (1H, m), 3.46-3.53 (2H, q), 4.25 (1H, m), 6.56-6.64 (1H, m), 6.82-6.85 (1H, m), 8.48 (1H, s).

- Example 8. 4-Fluoro-6-methyl-1-{1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinyl}-1,3-dihydro-2H-benzimidazol-2-one hydrochloride (E8)**



Diisopropylethylamine (100 μ L, 0.58mmole) was added to a solution of (2-amino-3-fluoro-5-methylphenyl){1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinyl}amine (D63, 113mg, 0.30mmole) in CH₂Cl₂ (10mL) at room temperature under argon. The reaction was cooled to 0°C and triphosgene (30mg, 0.10mmole) was added portion-wise. The reaction was stirred for 1h before the addition of 2M NaOH (10mL). The mixture was then diluted with CH₂Cl₂ (20mL) and sat. NaHCO₃ solution (20mL). The aqueous layer was extracted with CH₂Cl₂ (2x) and the combined organics were dried and concentrated via rotary evaporation. The crude residue was triturated with EtOAc-Et₂O (1:1) to give a pale purple solid which was azeotroped with toluene (2x5mL) and then chromatographed (silica, CH₂Cl₂-0.5% NH₃ /9.5% MeOH /90% CH₂Cl₂) to give the free base of the title compound as a white solid. The free base was treated with MeOH (2mL) and then 1M HCl in Et₂O (0.30mL). The mixture was stirred for 1h and then the solvent was removed by rotary evaporation to give the title compound (103mg, 42%) as a white solid. MH⁺ 376. ¹H NMR δ (DMSO-*d*₆, 400 MHz): 1.23-1.38 (5 H, m), 1.75-2.07 (8 H, m), 2.33 (3 H, s), 2.79 (2 H, m), 3.06-3.26 (3 H, m), 3.26 (3 H, s), 3.65 (2 H, m), 4.57 (1 H, m), 6.75 (1 H, d, *J* 11), 7.24 (1 H, s), 9.57 (1 H, m), 11.35 (1 H, s)

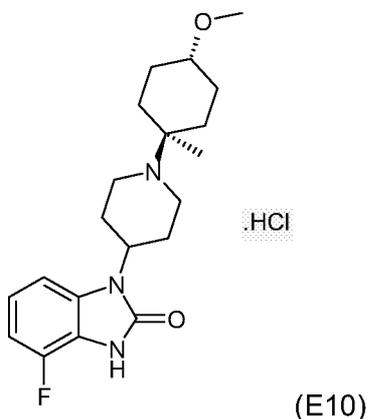
Example 9. 4,6-Difluoro-1-{1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinyl}-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (E9)



Diisopropylethylamine (200 μ L, 1.18mmole) was added to a solution of (2-amino-3,5-difluorophenyl){1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinyl}amine (D65, 204mg, 0.58mmole) in CH₂Cl₂ (10mL) at room temperature under argon. The reaction was cooled to 0°C and triphosgene (63mg, 0.21mmole) was added portion-wise. The reaction was stirred for 1h before the addition of 2M NaOH (10mL). The mixture was then diluted with CH₂Cl₂ (20mL) and sat. NaHCO₃ solution (20mL). The aqueous layer was extracted with CH₂Cl₂ (3x) and the combined organics were dried and concentrated via rotary evaporation. The crude residue was chromatographed (silica, CH₂Cl₂-0.5% NH₃ /9.5% MeOH /90% CH₂Cl₂) to give the free base of the title compound as a white solid. The free base was treated with MeOH (2mL) and then 1M HCl in Et₂O (0.20mL). The mixture was stirred for 30min and then the solvent was removed by rotary evaporation to give the title compound (97mg, 40%) as a pale yellow solid. MH⁺ 380.

^1H NMR δ (DMSO- d_6 , 400 MHz): 1.24-1.38 (5 H, m), 1.77 (2 H, m), 1.90-2.08 (6 H, m), 2.70 (2 H, m), 3.06-3.25 (3 H, m), 3.26 (3 H, m), 3.66 (2 H, m), 4.59 (1 H, m), 6.98 (1 H, m), 7.38 (1 H, m), 9.45 (1 H, m), 11.55 (1 H, s).

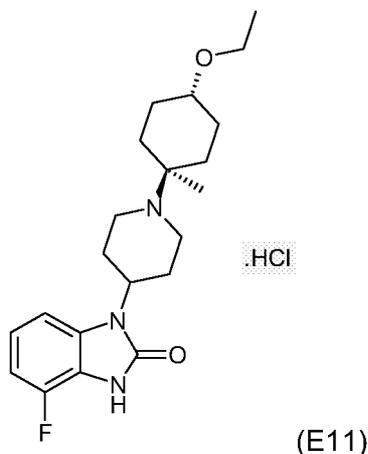
5 **Example 10. 4-Fluoro-1-{1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinyl}-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (E10)**



10 Triphoshene (0.072g) was added to a solution of 3-fluoro-*N*-{1-[*trans*-1-methyl-4-(methoxy)cyclohexyl]-4-piperidinyl}-1,2-benzenediamine (D61, 0.202g.), dichloromethane (15ml) and diisopropylethylamine (0.5ml) stirred at ice bath temperature. The solution was stirred to room temperature overnight then washed with saturated sodium bicarbonate solution and dried with hydromatrix and the solvent was removed. The residue was chromatographed on silica gel eluted with 0-10% dichloromethane –
 15 methanolic ammonia to give the free base of the title compound as a white solid. This was dissolved in dichloromethane, treated with hydrogen chloride in ether and the solvent was removed to give the title compound as a white solid (0.090g). $\text{MH}^+ = 362$.

20 ^1H NMR δ (d^6 DMSO, 250 MHz): 0.95 (3H, s), 1.15-1.45 (5H, m), 1.8-2.1 (8H, m), 2.75-3.0 (2H, m), 3.0-3.3 (~10H, m), 3.34 (3H, m), 3.1-3.25 (2H, m), 4.6 (1H, m), 6.9 (2H, m) 7.6 (1H, d), 10.3 (1H, m), 11.5 (1H, s).

25 **Example 11. 1-{1-[*trans*-4-(ethoxy)-1-methylcyclohexyl]-4-piperidinyl}-4-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (E11)**



Triphoshene (0.032g) was added to a solution of 3-fluoro-*N*-{1-[*trans*-1-methyl-4-(ethoxy)cyclohexyl]-4-piperidinyl}-1,2-benzenediamine (D59, 0.096g,) dichloromethane (15ml) and diisopropylethylamine (0.2ml) stirred at ice bath temperature. The solution was stirred at room temperature overnight, then washed with saturated sodium bicarbonate solution and the solvent was removed. The residue was chromatographed on silica gel eluted with 0-10% dichloromethane – methanolic ammonia to give the free base of the title compound as a white solid. This was dissolved in dichloromethane, treated with hydrogen chloride in ether and the solvent was removed to give the title compound as a white solid (0.049g). $MH^+ = 376$.

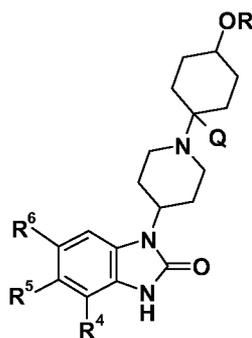
1H NMR δ (d^6 DMSO, 400 MHz) (free base): 0.95 (3H, s), 1.23 (3H, t), 1.45-1.6 (4H, m), 1.65-1.8 (4H, m), 1.85-2.0 (4H, m), 2.2-2.4 (4H, m), 3.15 (2H, m), 3.43 (1H, m), 3.5 (2H, m), 4.3 (1H, m), 6.81 (1H, d), 6.96 (1H, m), 9.63 (1H, m), 7.03 (1H, m), 9.2 (1H, s).

^{19}F NMR δ (d^6 DMSO) -134.19ppm

All 1H NMR are consistent with the structures shown.

CLAIMS

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



(I)

5

wherein:

- R⁴ is fluoro;
- R⁵ is selected from hydrogen, cyano, halogen, C₁₋₆alkyl, C₁₋₆alkyl substituted with one or more fluorine atoms, C₁₋₆alkoxy, and C₁₋₆alkoxy substituted with one or more fluorine atoms;
- 10 - R⁶ is selected from hydrogen, halogen, cyano, C₁₋₆alkyl, C₁₋₆alkyl substituted with one or more fluorine atoms, C₁₋₆alkylsulfonyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl substituted with one or more fluorine atoms, C₁₋₆alkoxy and C₁₋₆alkoxy substituted with one or more fluorine atoms;
- 15 - R is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl/C₁₋₆alkyl and C₂₋₆alkynyl, any alkyl or cycloalkyl group being optionally substituted with one or more fluorine atoms; and
- Q is hydrogen or C₁₋₆alkyl.

2. A compound as claimed in claim 1, wherein R⁵ is selected from hydrogen, cyano, halogen, C₁₋₂alkyl, C₁₋₂alkyl substituted with one or more fluorine atoms, C₁₋₂alkoxy, and C₁₋₂alkoxy substituted with one or more fluorine atoms.

3. A compound as claimed in claim 1 or claim 2, wherein R⁶ is selected from hydrogen, halogen, cyano, C₁₋₄alkyl, C₁₋₄alkyl substituted with one or more fluorine atoms, C₁₋₄alkylsulfonyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl substituted with one, two or three fluorine atoms, C₁₋₄alkoxy and C₁₋₄alkoxy substituted with one, two or three fluorine atoms.

4. A compound as claimed in claim 1, 2 or 3, wherein R is selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl/C₁₋₄alkyl and C₂₋₄alkynyl, any alkyl or cycloalkyl group being optionally substituted with one, two or three fluorine atoms.

5. A compound as claimed in any of claims 1-4, wherein Q is selected from hydrogen and C₁₋₃alkyl.

6. A compound as claimed in claim 1, which is:

1. 4-Fluoro-6-methyl-1-[1-(*cis*-4-methoxycyclohexyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one
2. 4-Fluoro-6-methyl-1-[1-(*trans*-4-methoxycyclohexyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one
3. 4-Fluoro-6-methyl-1-[1-(*trans*-4-ethoxycyclohexyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one
4. 4-Fluoro-6-methyl-1-[1-(*trans*-4-propoxycyclohexyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one
5. 4-Fluoro-6-methyl-1-{1-[*trans*-1-methyl-4-(propyloxy)cyclohexyl]-4-piperidinyl}-1,3-dihydro-2*H*-benzimidazol-2-one
6. 1-{1-[*trans*-4-(Ethyloxy)-1-methylcyclohexyl]-4-piperidinyl}-4-fluoro-6-methyl-1,3-dihydro-2*H*-benzimidazol-2-one
7. 1-{1-[*trans*-4-(Ethyloxy)-1-methylcyclohexyl]-4-piperidinyl}-4,6-difluoro-1,3-dihydro-2*H*-benzimidazol-2-one
8. 4-Fluoro-6-methyl-1-{1-[*trans*-1-methyl-4-(methyloxy)cyclohexyl]-4-piperidinyl}-1,3-dihydro-2*H*-benzimidazol-2-one
9. 4,6-Difluoro-1-{1-[*trans*-1-methyl-4-(methyloxy)cyclohexyl]-4-piperidinyl}-1,3-dihydro-2*H*-benzimidazol-2-one
10. 4-Fluoro-1-{1-[*trans*-1-methyl-4-(methyloxy)cyclohexyl]-4-piperidinyl}-1,3-dihydro-2*H*-benzimidazol-2-one
11. 1-{1-[*trans*-4-(ethyloxy)-1-methylcyclohexyl]-4-piperidinyl}-4-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one

or a salt or solvate thereof.

7. A pharmaceutical composition comprising a compound claimed in any one of claims 1 to 6 and a pharmaceutically acceptable carrier.

8. A compound as claimed in any one of claim 1 to 6 for use in therapy.

9. A compound as claimed in any one of claims 1 to 6 for use in the treatment of a condition which requires agonism of a muscarinic M₁ receptor.

10. A compound as claimed in any one of claims 1 to 6 for use in the treatment of a psychotic disorder or cognitive impairment.

11. Use of a compound as claimed in any one of claims 1 to 6 in the manufacture of a medicament for the treatment of a condition which requires agonism of a muscarinic M₁ receptor.

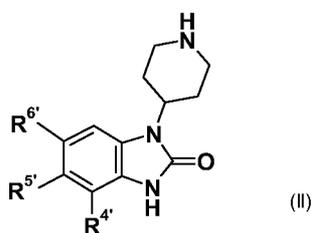
12. Use of a compound as claimed in any one of claims 1 to 6 in the manufacture of a medicament for the treatment of a psychotic disorder or cognitive impairment.

13. A method of treating a condition which requires agonism of a muscarinic M₁ receptor, which comprises administering to a mammal in need thereof an effective amount of a compound as claimed in any one of claims 1 to 6.

5 14. A method of treating a psychotic disorder or cognitive impairment, which comprises administering to a mammal in need thereof an effective amount of a compound as claimed in any of claims 1 to 6.

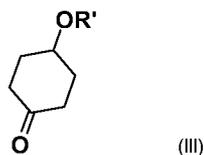
10 15. A process for preparing a compound as claimed in claim 1, which process is selected from:

- process (A1) which comprises coupling a compound of formula (II):



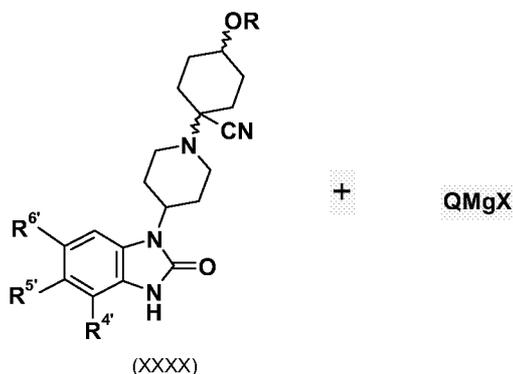
15

with a compound of formula (III):



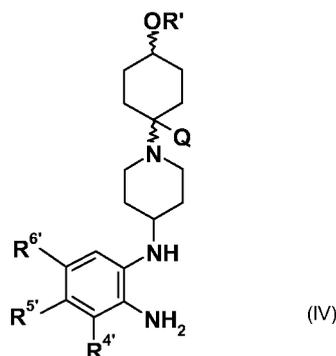
20 wherein R^{4'} is a group R⁴ as defined in claim 1, or a group convertible to R⁴, R^{5'} is a group R⁵ defined in claim 1, or a group convertible to R⁵, R^{6'} is a group R⁶ as defined in claim 1, or a group convertible to R⁶, R' is a group R as defined in claim 1, or a group convertible to R, under conditions suitable for reductive alkylation;

25 - process (A2) which comprises reacting a compound of formula (II) with a compound of formula (III) in the presence of a source of cyanide to form the cyano intermediate (XXXX) which can be reacted with an alkyl Grignard reagent QMgX to form compounds of formula (I):



5 wherein R^{4'} is a group R⁴ as previously defined, or a group convertible to R⁴, R^{5'} is a group R⁵ defined in claim 1, or a group convertible to R⁵, R^{6'} is a group R⁶ as defined in claim 1, or a group convertible to R⁶, R' is a group R as defined in claim 1, or a group convertible to R; Q is C₁₋₆alkyl, and X is bromo, iodo or chloro under conditions suitable for Grignard reactions;

10 - process (B) which comprises coupling a compound of formula (IV):



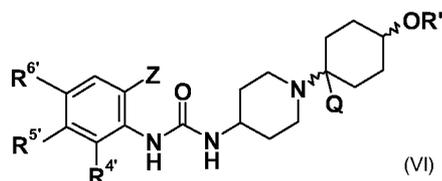
with a compound of formula (V):



15 wherein R^{4'} is a group R⁴ as previously defined, or a group convertible to R⁴, R^{5'} is a group R⁵ defined in claim 1, or a group convertible to R⁵, R^{6'} is a group R⁶ as defined in claim 1, or a group convertible to R⁶, R' is a group R as defined in claim 1, or a group convertible to R, Q is as defined in claim 1, and X and Y both represent leaving groups, optionally in an inert solvent, optionally in the presence of a base, and optionally with heating;

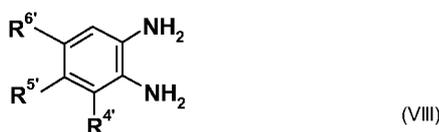
20

- process (C) which comprises treatment of a compound of formula (VI):

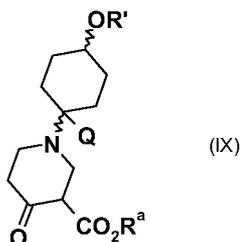


with a palladium or copper catalyst (VII) to effect an intramolecular cyclisation; wherein R^{4'} is a group R⁴ as previously defined, or a group convertible to R⁴, R^{5'} is a group R⁵ defined in claim 1, or a group convertible to R⁵, R^{6'} is a group R⁶ as defined in claim 1, or a group convertible to R⁶, R' is a group R as defined in claim 1, or a group convertible to R, Q is as defined in claim 1, and Z is a leaving group such as bromo, iodo, chloro or triflate;

- process (D) which comprises coupling a compound of formula (VIII)

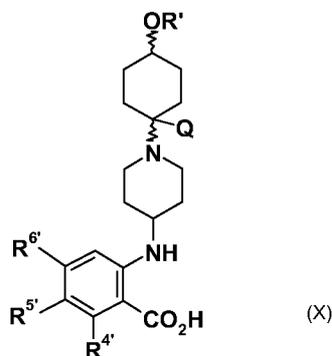


with a compound of formula (IX):



wherein R^{4'} is a group R⁴ as previously defined, or a group convertible to R⁴, R^{5'} is a group R⁵ defined in claim 1, or a group convertible to R⁵, R^{6'} is a group R⁶ as defined in claim 1, or a group convertible to R⁶, R' is a group R as defined in claim 1, or a group convertible to R, Q is as defined in claim 1, and R^a is a C1-5 alkyl group, by heating in an inert solvent, for example xylene, followed by reduction of the piperidine double bond;

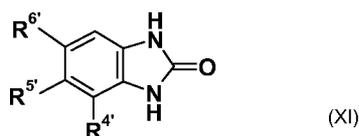
- process (E) which comprises reaction of a compound of formula (X):



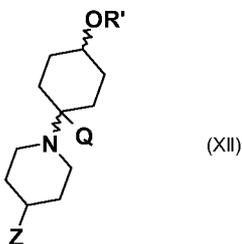
with a reagent/combination of reagents to effect the Curtius rearrangement of compound (X), followed by intramolecular cyclisation; wherein $R^{4'}$ is a group R^4 as previously defined, or a group convertible to R^4 , $R^{5'}$ is a group R^5 defined in claim 1, or a group convertible to R^5 , $R^{6'}$ 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 , Q is as defined in claim 1;

and

- process (F) which comprises coupling a compound of formula (XI):



with a compound of formula (XII):



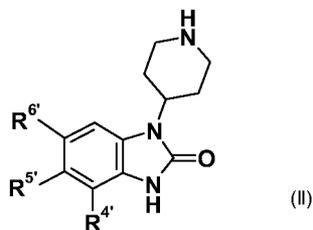
wherein $R^{4'}$ is a group R^4 as previously defined, or a group convertible to R^4 , $R^{5'}$ is a group R^5 defined in claim 1, or a group convertible to R^5 , $R^{6'}$ is a group R^6 as defined in claim 1, or a group convertible to R^6 , R' is a group R as defined in claim 1, or a group convertible to R , Q is as defined in claim 1, and Z is hydroxy or a leaving group under alkylation or Mitsunobu reaction conditions;

and optionally thereafter, for any of the above processes:

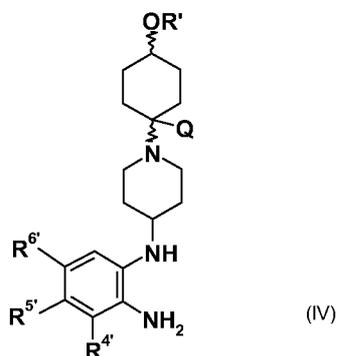
- removing any protecting groups; and/or

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

17. A compound of formula (II):

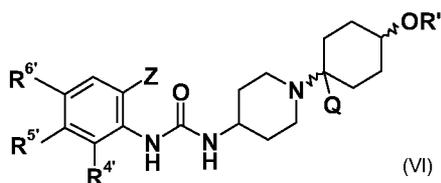


a compound of formula (IV)

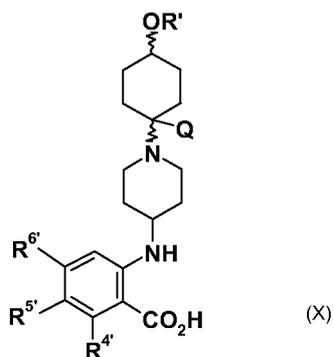


5

a compound of formula (VI)



10 or a compound of formula (X)



15 wherein R^{4'} is a group R⁴ as defined in claim 1, or a group convertible to R⁴, R^{5'} is a group R⁵ defined in claim 1, or a group convertible to R⁵, R^{6'} is a group R⁶ as defined in claim 1, or a group convertible to R⁶, R' is a group R as defined in claim 1, or a group convertible to R, and Z is a leaving group.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/052640

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4184 C07D235/26 A61P25/18

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

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97/16186 A (MERCK & CO INC [US]; THOMPSON WAYNE J [US]; RANSOM RICHARD W [US]; MAL) 9 May 1997 (1997-05-09) page 8; claims; examples -----	1-17
Y	WO 96/13262 A (MERCK & CO INC [US]; THOMPSON WAYNE J [US]; SUGRUE MICHAEL F [US]; RAN) 9 May 1996 (1996-05-09) claims; examples; table 6 -----	1-17
Y	WO 03/105781 A (MERCK & CO INC [US]; BANYU PHARMA CO LTD [JP]; OGIDIGBEN MILLER J [US]) 24 December 2003 (2003-12-24) the whole document -----	1-17
	-/--	

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

18 June 2007

Date of mailing of the international search report

25/06/2007

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Authorized officer

Gavriliu, Daniela

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/052640

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 221 443 A1 (BANYU PHARMA CO LTD [JP]) 10 July 2002 (2002-07-10) claims; examples 18,26; table 1 -----	1-17
X	HENNING R ET AL: "SYNTHESIS AND NEUROLEPTIC OF A SERIES OF 1-1-(BENZO-1,4-DIOXAN-2-YLM ETHYL)-4-PIPERIDINYLBENZIMIDAZOLONE DERIVATIVES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 30, no. 5, 1987, pages 814-819, XP001084049 ISSN: 0022-2623 scheme III examples 44b-44f,44h,44j-44n; tables II,III -----	17
P,X	BURGEY ET AL: "Benzodiazepine calcitonin gene-related peptide (CGRP) receptor antagonists: Optimization of the 4-substituted piperidine" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 16, no. 19, 1 October 2006 (2006-10-01), pages 5052-5056, XP005611693 ISSN: 0960-894X scheme I figure 1; table i -----	17
E	WO 2007/036715 A (GLAXO GROUP LTD [GB]; BUDZIK BRIAN [US]; COOPER DAVID GWYN [GB]; FORBE) 5 April 2007 (2007-04-05) see descriptions examples 5, 9, 14, 23 and 29; schemes 2-7 -----	17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/052640

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

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

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

Although claims 13, 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2007/052640

Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
WO 9716186	A	09-05-1997	AU 7478396 A	22-05-1997
WO 9613262	A	09-05-1996	AU 701127 B2 AU 3967495 A CA 2200468 A1 EP 0786997 A1 JP 2002515008 T	21-01-1999 23-05-1996 09-05-1996 06-08-1997 21-05-2002
WO 03105781	A	24-12-2003	AU 2003245565 A1 CA 2488845 A1 EP 1515722 A2 JP 2005532361 T	31-12-2003 24-12-2003 23-03-2005 27-10-2005
EP 1221443	A1	10-07-2002	AT 275141 T AU 766233 B2 AU 7686500 A CA 2387535 A1 DE 60013464 D1 DE 60013464 T2 ES 2223588 T3 WO 0127104 A1 US 6699880 B1	15-09-2004 09-10-2003 23-04-2001 19-04-2001 07-10-2004 15-09-2005 01-03-2005 19-04-2001 02-03-2004
WO 2007036715	A	05-04-2007	NONE	