(19) DANMARK

(10) **DK/EP 3406609 T3**

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: ***C 07 D 401/14 (2006.01)*** ***A 61 K 31/454 (2006.01)*** ***C 07 D 401/04 (2006.01)***
***C 07 D 405/14 (2006.01)*** ***C 07 D 409/14 (2006.01)*** ***C 07 D 413/14 (2006.01)***
***C 07 D 417/14 (2006.01)*** ***C 07 D 471/04 (2006.01)*** ***C 07 D 491/107 (2006.01)***

(45) Oversættelsen bekendtgjort den: **2024-08-26**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2024-06-26**

(86) Europæisk ansøgning nr.: **18179258.1**

(86) Europæisk indleveringsdag: **2015-02-06**

(87) Den europæiske ansøgnings publiceringsdag: **2018-11-28**

(30) Prioritet: **2014-02-06 GB 201402013** **2014-09-19 GB 201416622**

(62) Stamansøgningsnr: **15703826.6**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

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(54) Benævnelse: **Bicykliske aza-forbindelser som muskariniske receptoragonister**

(56) Fremdragne publikationer:
**WO-A1-2007/100670**
**WO-A1-2013/072705**
**WO-A1-2014/045031**

**Fortsættes ...**

# DESCRIPTION

Description

**[0001]** This invention relates to compounds that are agonists of the muscarinic M1 receptor and/or M4 receptor and which are useful in the treatment of muscarinic M1/M4 receptor mediated diseases. Also provided are pharmaceutical compositions containing the compounds and the therapeutic uses of the compounds.

## Background of the Invention

**[0002]** Muscarinic acetylcholine receptors (mAChRs) 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 mAChR subtypes have been cloned, $M_1$ to $M_5$. The $M_1$ mAChR is predominantly expressed post-synaptically in the cortex, hippocampus, striatum and thalamus; $M_2$ mAChRs are located predominantly in the brainstem and thalamus, though also in the cortex, hippocampus and striatum where they reside on cholinergic synaptic terminals (Langmead et al., 2008 Br J Pharmacol). However, $M_2$ mAChRs are also expressed peripherally on cardiac tissue (where they mediate the vagal innervation of the heart) and in smooth muscle and exocrine glands. $M_3$ mAChRs are expressed at relatively low level in the CNS but are widely expressed in smooth muscle and glandular tissues such as sweat and salivary glands (Langmead et al., 2008 Br J Pharmacol).

**[0003]** Muscarinic receptors in the central nervous system, especially the $M_1$ mAChR, 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 (Whitehouse et al., 1982 Science). In schizophrenia, which also has cognitive impairment as an important component of the clinical picture, mAChR density is reduced in the pre-frontal cortex, hippocampus and caudate putamen of schizophrenic subjects (Dean et al., 2002 Mol Psychiatry). Furthermore, in animal models, blockade or damage to central cholinergic pathways results in profound cognitive deficits and non-selective mAChR antagonists have been shown to induce psychotomimetic effects in psychiatric patients. 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 dose-limiting adverse events resulting from stimulation of peripheral $M_2$ and $M_3$ mAChRs including disturbed gastrointestinal motility, bradycardia, nausea and vomiting (http://www.drugs.com/pro/donepezil.html; http://www.drugs.com/pro/rivastigmine.html).

**[0004]** Further discovery efforts have targeted the identification of direct $M_1$ mAChR agonists with the aim of inducing selective improvements in cognitive function with a favourable adverse effect profile. Such efforts resulted in the identification of a range of agonists, exemplified by compounds such as xanomeline, AF267B, sabcomeline, milameline and cevimeline. Many of these compounds have been shown to be highly effective in pre-clinical models of cognition in both rodents and / or non-human primates. Milameline has shown efficacy versus scopolamine-induced deficits in working and spatial memory in rodents; sabcomeline displayed efficacy in a visual object discrimination task in marmosets and xanomeline reversed mAChR antagonist-induced deficits in cognitive performance in a passive avoidance paradigm.

**[0005]** Alzheimer's disease (AD) is the most common neurodegenerative disorder (26.6 million people worldwide in 2006) that affects the elderly, resulting in profound memory loss and cognitive dysfunction. The aetiology of the disease is complex, but is characterised by two hallmark brain pathologies: aggregates of amyloid plaques, largely composed of amyloid-β peptide (Aβ), and neurofibrillary tangles, formed by hyperphosphorylated tau proteins. The accumulation of Aβ is thought to be the central feature in the progression of AD and, as such, many putative therapies for the treatment of AD are currently targeting inhibition of Aβ production. Aβ is derived from proteolytic cleavage of the membrane bound amyloid precursor protein (APP). APP is processed by two routes, nonamyloidgenic and amyloidgenic. Cleavage of APP by γ-secretase is common to both pathways, but in the former APP is cleaved by an α-secretase to yield soluble APPα. However, in the amyloidgenic route, APP is cleaved by β-secretase to yield soluble APPβ and also Aβ. *In vitro* studies have shown that mAChR agonists can promote the processing of APP toward the soluble, non-amyloidogenic pathway. *In vivo* studies showed that the mAChR agonist, AF267B, altered disease-like pathology in the 3xTgAD transgenic mouse, a model of the different components of Alzheimer's disease (Caccamo et al., 2006 Neuron). The mAChR agonist cevimeline has been shown to give a small, but significant, reduction in cerebrospinal fluid levels of Aβ in Alzheimer's patients, thus demonstrating potential disease modifying efficacy (Nitsch et al., 2000 Neurol).

**[0006]** Preclinical studies have suggested that mAChR agonists display an atypical antipsychotic-like profile in a range of pre-clinical paradigms. The mAChR agonist, xanomeline, reverses a number of dopamine mediated 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 (Mirza et al., 1999 CNS Drug Rev). Muscarinic receptors have also been implicated in the neurobiology of addicition. The reinforcing effects of cocaine and other addictive substances are mediated by the mesolimbic dopamine system where behavioral and neurochemical studies have shown that the cholinergic muscarinic receptor subtypes play important roles in regulation of dopaminergic neurotransmission. For example M(4) (-/-) mice demonstrated significantly enhanced reward driven behaviour as result of exposure to cocaine (Schmidt et al Psychopharmacology (2011) Aug;216(3):367-78). Furthermore xanomeline has

been dmoenstrated to block the effects of cocaine in these models.

**[0007]** Muscarinic receptors are also involved in the control of movement and potentially represent novel treatments for movement disorders such as Parkinson's disease, ADHD, Huntingdon's disease, tourette's syndrome and other syndromes associated with dopaminergic dysfunction as an underlying pathogenetic factor driving disease.

**[0008]** Xanomeline, sabcomeline, milameline and cevimeline have all progressed into various stages of clinical development for the treatment of Alzheimer's disease and/or schizophrenia. Phase II clinical studies with xanomeline demonstrated its efficacy versus various cognitive symptom domains, including behavioural disturbances and hallucinations associated with Alzheimer's disease (Bodick et al., 1997 Arch Neurol). This compound was also assessed in a small Phase II study of schizophrenics and gave a significant reduction in positive and negative symptoms when compared to placebo control (Shekhar et al., 2008 Am J Psych). However, in all clinical studies xanomeline and other related mAChR agonists have displayed an unacceptable safety margin with respect to cholinergic adverse events, including nausea, gastrointestinal pain, diahorrhea, diaphoresis (excessive sweating), hypersalivation (excessive salivation), syncope and bradycardia.

**[0009]** Muscarinic receptors are involved in central and peripheral pain. Pain can be divided into three different types: acute, inflammatory, and neuropathic. Acute pain serves an important protective function in keeping the organism safe from stimuli that may produce tissue damage; however management of post-surgical pain is required. Inflammatory pain may occur for many reasons including tissue damage, autoimmune response, and pathogen invasion and is triggered by the action of inflammatory mediators such as neuropeptides and prostaglandins which result in neuronal inflammation and pain. Neuropathic pain is associated with abnormal painful sensations to non-painful stimuli. Neuropathic pain is associated with a number of different diseases/traumas such as spinal cord injury, multiple sclerosis, diabetes (diabetic neuropathy), viral infection (such as HIV or Herpes). It is also common in cancer both as a result of the disease or a side effect of chemotherapy. Activation of muscarinic receptors has been shown to be analgesic across a number of pain states through the activation of receptors in the spinal cord and higher pain centres in the brain. Increasing endogenous levels of acetylcholine through acetylcholinesterase inhibitors, direct activation of muscarinic receptors with agonists or allosteric modulators has been shown to have analgesic activity. In contrast blockade of muscarinic receptors with antagonists or using knockout mice increases pain sensitivity. Evidence for the role of the M1 receptor in pain is reviewed by D. F. Fiorino and M. Garcia-Guzman, 2012.

**[0010]** More recently, a small number of compounds have been identified which display improved selectivity for the $M_1$ mAChR subtype over the peripherally expressed mAChR subtypes (Bridges et al., 2008 Bioorg Med Chem Lett; Johnson et al., 2010 Bioorg Med Chem Lett; Budzik et al., 2010 ACS Med Chem Lett). Despite increased levels of selectivity versus the $M_3$ mAChR subtype, some of these compounds retain significant agonist activity at both this subtype and the $M_2$ mAChR subtype. Herein we describe a series of compounds which

unexpectedly display high levels of selectivity for the $M_1$ and/or $M_4$ mAChR over the $M_2$ and $M_3$ receptor subtypes.

## Description of Figures

**[0011]** Description of the figures can be found in experimental sections B and C.

Figure 1 shows that Reference Example 1-33 Isomer 2 was found to reverse scopolamine-induced amnesia in a dose-dependent manner, with an approximate $ED_{50}$ of ca. 10 mg/kg (po). The effect of 30 mg/kg was similar to that produced by the cholinesterase inhibitor donepezil (0.1 mg/kg, ip) which served as a positive control.

Figure 2 shows the effect of novel test compounds on d-amphetamine induced hyperactivity in rats. Antipsychotic-like behaviour was assessed in rats by the inhibition of hyperactivity (or hyperlocomotion) elicited by d-amphetamine. Data for Example 1-21 Isomer 2, and Reference Examples 1-32 Isomer 2, 1-33 Isomer 2, 2-7 Isomer 2 and 2-17 Isomer 2 is shown.

## Summary Of The Invention

**[0012]** The technical disclosure set out below may in some respects go beyond the scope of the claims. Elements of the disclosure which do not fall within the scope of the claims are provided for information.

**[0013]** A first aspect of the invention is a compound which is ethyl 2-[4-(1-methyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate or a salt thereof.

**[0014]** A second aspect of the invention is a pharmaceutically acceptable salt of a compound according to the first aspect.

**[0015]** A third aspect of the invention is an acid addition salt of a compound according to the first aspect.

**[0016]** In one embodiment, the acid is citric acid, fumaric acid or hydrochloric acid.

**[0017]** A fourth aspect of the invention is a pharmaceutical composition comprising a compound or a salt as defined in any one of the first to third aspects and a pharmaceutically acceptable excipient.

**[0018]** A fifth aspect of the invention is a compound or a salt according to any one of the first to third aspects for use in the treatment of Alzheimer's Disease.

**[0019]** A sixth aspect of the invention is a compound or a salt according to any one of the first to third aspects for use in the treatment of schizophrenia.

**[0020]** A seventh aspect of the invention is a compound or a salt according to any one of the first to third aspects for use in the treatment of a bipolar disorder.

**[0021]** A eighth aspect of the invention is a compound or a salt according to any one of the first to third aspects for use in the treatment of dementia.

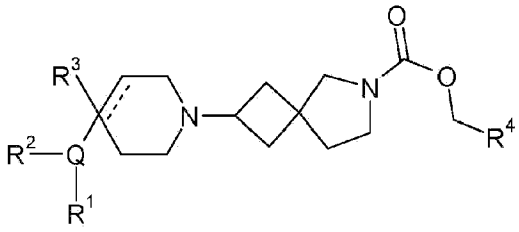
**[0022]** A ninth aspect of the invention is a compound or a salt according to any one of the first to third aspects for use in the treatment of dementia with Lewy bodies.

## Brief Description of the Invention

**[0023]** The present invention provides compounds having activity as muscarinic M1 and/or M4 receptor agonists. More particularly, the invention provides compounds that exhibit selectivity for the M1 receptor and/or the M4 receptor relative to the M2 and M3 receptor subtypes.

**[0024]** References to methods of treatment by therapy or surgery or in vivo diagnosis methods in this description are to be interpreted as references to compounds, pharmaceutical compositions and medicaments for use in those methods.

**[0025]** Generally described herein for the purposes of supporting the general synthetic methods are compounds of the formula (1):



(1)

or a salt thereof, wherein

Q is a five or six membered monocyclic heterocyclic ring containing 1, 2, 3 or 4 heteroatom ring members selected from N, O and S;

$R^1$ is selected from hydrogen; fluorine; chlorine; bromine; cyano; oxo; hydroxy; $OR^5$; $NR^5R^6$; $COR^s$; $COOR^6$; $OCOR^5$; $NR^7COR^5$; $CONR^5R^6$; $NR^7CONR^5R^6$; $NR^7COOR^5$; $OCONR^5R^6$; $SR^5$; $SOR^5$ and $SO_2R^5$; a $C_{1-6}$ non-aromatic hydrocarbon group which is optionally substituted with one to six fluorine atoms and wherein one or two, but not all, carbon atoms of the hydrocarbon group may optionally be replaced by a heteroatom selected from O, N and S and oxidized forms thereof; and an optionally substituted 5- or 6-membered ring containing 0, 1, 2 or 3 heteroatoms selected from O, N and S and oxidized forms thereof;

$R^2$ is selected from hydrogen; fluorine; chlorine; bromine; cyano; hydroxy; methoxy; $OR^5$; $NR^5R^6$; $COR^5$; $COOR^5$; $OCOR^5$; $NR^7COR^5$; $CONR^5R^6$; $NR^7CONR^5R^6$; $NR^7COOR^5$; $OCONR^5R^6$; $SR^5$; $SOR^5$ and $SO_2R^5$; a $C_{1-6}$ non-aromatic hydrocarbon group; or $R^1$ and $R^2$ can be joined together to form a 6 membered fused aromatic ring; $R^3$ is selected from hydrogen; fluorine; cyano; hydroxy; amino; and a $C_{1-9}$ non-aromatic hydrocarbon group which is optionally substituted with one to six fluorine atoms and wherein one, two or three, but not all, carbon atoms of the hydrocarbon group may optionally be replaced by a heteroatom selected from O, N and S and oxidized forms thereof;

$R^4$ is a hydrogen or a $C_{1-6}$ non-aromatic hydrocarbon group which is optionally substituted with one to six fluorine atoms and wherein one or two, but not all, carbon atoms of the hydrocarbon group may optionally be replaced by a heteroatom selected from O, N and S and oxidised forms thereof;

$R^5$, $R^6$ and $R^7$ are the same or different and each is independently selected from hydrogen, a non-aromatic $C_{1-4}$ hydrocarbon group optionally substituted with one or more fluorine atoms; or a group of formula $CH_2N(R^a)COOR^b$;

$R^a$ is selected from hydrogen and a non-aromatic $C_{1-4}$ hydrocarbon group;

$R^b$ is a non-aromatic $C_{1-4}$ hydrocarbon group which is optionally substituted with one or more groups selected from fluorine; chlorine; bromine; cyano; hydroxy; methoxy; amino; or a cycloalkyl, heterocycloalkyl, aryl or heteroaryl group;

and the dotted line indicates an optional second carbon-carbon bond, provided that when a second carbon-carbon bond is present, then $R^3$ is absent.

**[0026]** In one embodiment, a compound described herein is in the form of a salt.

**[0027]** In one embodiment, the salt is an acid addition salt.

**[0028]** In one embodiment, the salt is a pharmaceutically acceptable salt.

**Definitions**

**[0029]** In this application, the following definitions apply, unless indicated otherwise.

**[0030]** The term "treatment", in relation to the uses of the compounds of the formula (1), is used to describe any form of intervention where a compound is administered to a subject

suffering from, or at risk of suffering from, or potentially at risk of suffering from the disease or disorder in question. Thus, the term "treatment" covers both preventative (prophylactic) treatment and treatment where measurable or detectable symptoms of the disease or disorder are being displayed.

**[0031]** The term "effective therapeutic amount" as used herein (for example in relation to methods of treatment of a disease or condition) refers to an amount of the compound which is effective to produce a desired therapeutic effect. For example, if the condition is pain, then the effective therapeutic amount is an amount sufficient to provide a desired level of pain relief. The desired level of pain relief may be, for example, complete removal of the pain or a reduction in the severity of the pain.

**[0032]** The term "non-aromatic hydrocarbon group" as in "$C_{1-10}$ non-aromatic hydrocarbon group" or "acyclic $C_{1-5}$ non-aromatic hydrocarbon group" refers to a group consisting of carbon and hydrogen atoms and which contains no aromatic rings. The hydrocarbon group may be fully saturated or may contain one or more carbon-carbon double bonds or carbon-carbon triple bonds, or mixtures of double and triple bonds. The hydrocarbon group may be a straight chain or branched chain group or may consist of or contain a cyclic group. Thus the term non-aromatic hydrocarbon includes alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenyl alkyl and so on.

**[0033]** The terms "alkyl", "alkenyl", "alkynyl", "cycloalkyl" aryl, heteroaryl and "cycloalkenyl" are used in their conventional sense (e.g. as defined in the IUPAC Gold Book) unless indicated otherwise.

**[0034]** The term "saturated hydrocarbon group" as in "$C_{1-4}$ saturated hydrocarbon group" refers to a hydrocarbon group containing no carbon-carbon double bonds or triple bonds. The saturated hydrocarbon group can therefore be an alkyl group, a cycloalkyl group, a cycloalkylalkyl group, an alkylcycloalkyl group or a alkylcycloalkylalkyl group. Examples of $C_{1-4}$ saturated hydrocarbon groups include $C_{1-4}$ alkyl groups, cyclopropyl, cyclobutyl and cyclopropylmethyl.

**[0035]** The term "cycloalkyl" as used herein, where the specified number of carbon atoms permits, includes both monocyclic cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and bicyclic and tricyclic groups. Bicyclic cycloalkyl groups include bridged ring systems such as bicycloheptane, bicyclooctane and adamantane.

**[0036]** In the definitions of $R^1$,$R^2$, $R^3$ and $R^4$ above, where stated, one or two but not all, carbon atoms of the non-aromatic hydrocarbon group may optionally be replaced by a heteroatom selected from O, N and S and (in the case of $R^1$ and $R^4$) oxidised forms thereof. It will be appreciated that when a carbon atom is replaced by a heteroatom, the lower valencies of the heteroatoms compared to carbon means that fewer atoms will be bonded to the heteroatoms than would have been bonded to the carbon atom that has been replaced. Thus,

for example, replacement of of a carbon atom (valency of four) in a $CH_2$ group by oxygen (valency of two) will mean that the resulting molecule will contain two less hydrogen atoms and replacement of a carbon atom (valency of four) in a $CH_2$ group by nitrogen (valency of three) will mean that the resulting molecule will contain one less hydrogen atom.

**[0037]** Examples of a heteroatom replacements for carbon atoms include replacement of a carbon atom in a $-CH_2-CH_2-CH_2-$ chain with oxygen or sulfur to give an ether $-CH_2-O-CH_2-$ or thioether $-CH_2-S-CH_2-$, replacement of a carbon atom in a group $CH_2-C\equiv C-H$ with nitrogen to give a nitrile (cyano) group $CH_2-C\equiv N$, replacement of a carbon atom in a group $-CH_2-CH_2-CH_2-$ with C=O to give a ketone $-CH_2-C(O)-CH_2-$, replacement of a carbon atom in a group $-CH_2-CH_2-CH_2-$ with S=O or $SO_2$ to give a sulfoxide $-CH_2-S(O)-CH_2-$ or sulfone $-CH_2-S(O)_2-CH_2-$, replacement of a carbon atom in a $-CH_2-CH_2-CH_2-$chain with C(O)NH to give an amide $-CH_2-CH_2-C(O)-NH-$, replacement of a carbon atom in a $-CH_2-CH_2-CH_2-$ chain with nitrogen to give an amine $-CH_2-NH-CH_2-$, and replacement of a carbon atom in a $-CH_2-CH_2-CH_2-$ chain with C(O)O to give an ester (or carboxylic acid) $-CH_2-CH_2-C(O)-O-$. In each such replacement, at least one carbon atom of the hydrocarbon group must remain.

**Salts**

**[0038]** Many compounds of the formula (1) can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as carboxylate, sulfonate and phosphate salts.

**[0039]** The salts are typically acid addition salts.

**[0040]** The salts can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods such as methods described in Pharmaceutical Salts: Properties, Selection, and Use, P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor), ISBN: 3-90639-026-8, Hardcover, 388 pages, August 2002. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used.

**[0041]** Acid addition salts may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include mono- or di-salts formed with an acid selected from the group consisting of acetic, 2,2-dichloroacetic, adipic, alginic, ascorbic (e.g. L-ascorbic), L-aspartic, benzenesulfonic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric, camphor-sulfonic, (+)-(1S)-camphor-10-sulfonic, capric, caproic, caprylic, cinnamic, citric, cyclamic, dodecylsulfuric, ethane-1,2-disulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, formic, fumaric, galactaric, gentisic, glucoheptonic, D-gluconic, glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α-oxoglutaric, glycolic, hippuric, hydrohalic acids (e.g. hydrobromic,

hydrochloric, hydriodic), isethionic, lactic (e.g. (+)-L-lactic, (±)-DL-lactic), lactobionic, maleic, malic, (- )-L-malic, malonic, (±)-DL-mandelic, methanesulfonic, naphthalene-2-sulfonic, naphthalene-1,5-disulfonic, 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, pyruvic, L-pyroglutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulfuric, tannic, (+)-L-tartaric, thiocyanic, p-toluenesulfonic, undecylenic and valeric acids, as well as acylated amino acids and cation exchange resins.

**[0042]** Where the compounds of the formula (1) contain an amine function, these may form quaternary ammonium salts, for example by reaction with an alkylating agent according to methods well known to the skilled person.

**[0043]** The compounds of the invention may exist as mono- or di-salts depending upon the pKa of the acid from which the salt is formed.

**[0044]** The salt forms of the compounds of the invention are typically pharmaceutically acceptable salts, and examples of pharmaceutically acceptable salts are discussed in Berge et al., 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19. However, salts that are not pharmaceutically acceptable may also be prepared as intermediate forms which may then be converted into pharmaceutically acceptable salts. Such non-pharmaceutically acceptable salts forms may be useful, for example, in the purification or separation of the compounds described herein.

**Stereoisomers**

**[0045]** Stereoisomers are isomeric molecules that have the same molecular formula and sequence of bonded atoms but which differ only in the three-dimensional orientations of their atoms in space. The stereoisomers can be, for example, geometric isomers or optical isomers.

**Geometric Isomers**

**[0046]** With geometric isomers, the isomerism is due to the different orientations of an atom or group about a double bond, as in *cis* and *trans* (*Z* and *E)* isomerism about a carbon-carbon double bond, or *cis* and *trans* isomers about an amide bond, or *syn* and *anti* isomerism about a carbon nitrogen double bond (e.g. in an oxime), or rotational isomerism about a bond where there is restricted rotation, or *cis* and *trans* isomerism about a ring such as a cycloalkane ring.

**Optical Isomers**

**[0047]** Where compounds of the formula contain one or more chiral centres, and can exist in the form of two or more optical isomers, references to the compounds include all optical

isomeric forms thereof (e.g. enantiomers, epimers and diastereoisomers), either as individual optical isomers, or mixtures (e.g. racemic mixtures) or two or more optical isomers, unless the context requires otherwise.

**[0048]** The optical isomers may be characterised and identified by their optical activity (i.e. as + and - isomers, or d and l isomers) or they may be characterised in terms of their absolute stereochemistry using the "R and S" nomenclature developed by Cahn, Ingold and Prelog, see Advanced Organic Chemistry by Jerry March, 4th Edition, John Wiley & Sons, New York, 1992, pages 109-114, and see also Cahn, Ingold & Prelog, Angew. Chem. Int. Ed. Engl., 1966, 5, 385-415. Optical isomers can be separated by a number of techniques including chiral chromatography (chromatography on a chiral support) and such techniques are well known to the person skilled in the art. As an alternative to chiral chromatography, optical isomers can be separated by forming diastereoisomeric salts with chiral acids such as (+)-tartaric acid, (-)-pyroglutamic acid, (-)-di-toluoyl-L-tartaric acid, (+)-mandelic acid, (-)-malic acid, and (-)-camphorsulphonic, separating the diastereoisomers by preferential crystallisation, and then dissociating the salts to give the individual enantiomer of the free base.

**[0049]** Where compounds of the invention exist as two or more optical isomeric forms, one enantiomer in a pair of enantiomers may exhibit advantages over the other enantiomer, for example, in terms of biological activity. Thus, in certain circumstances, it may be desirable to use as a therapeutic agent only one of a pair of enantiomers, or only one of a plurality of diastereoisomers.

**[0050]** Accordingly, in another embodiment the invention provides compositions containing a compound described herein having one or more chiral centres, wherein at least 55% (e.g. at least 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95%) of the compound is present as a single optical isomer (e.g. enantiomer or diastereoisomer).

**[0051]** In one general embodiment, 99% or more (e.g. substantially all) of the total amount of the compound (or compound for use) is present as a single optical isomer.

**[0052]** For example, in one embodiment the compound is present as a single enantiomer.

**[0053]** In another embodiment, the compound is present as a single diastereoisomer.

**[0054]** The invention also provides mixtures of optical isomers, which may be racemic or non-racemic. Thus, the invention provides:
A compound described herein which is in the form of a racemic mixture of optical isomers.

**[0055]** A compound described herein which is in the form of a non-racemic mixture of optical isomers.

**isotopes**

**[0056]** The compounds described herein may contain one or more isotopic substitutions, and a reference to a particular element includes within its scope all isotopes of the element. For example, a reference to hydrogen includes within its scope $^{1}H$, $^{2}H$ (D), and $^{3}H$ (T). Similarly, references to carbon and oxygen include within their scope respectively $^{12}C$, $^{13}C$ and $^{14}C$ and $^{16}O$ and $^{18}O$.

**[0057]** In an analogous manner, a reference to a particular functional group also includes within its scope isotopic variations, unless the context indicates otherwise. For example, a reference to an alkyl group such as an ethyl group also covers variations in which one or more of the hydrogen atoms in the group is in the form of a deuterium or tritium isotope, e.g. as in an ethyl group in which all five hydrogen atoms are in the deuterium isotopic form (a perdeuteroethyl group).

**[0058]** The isotopes may be radioactive or non-radioactive. In one embodiment, the compound contains no radioactive isotopes. Such compounds are preferred for therapeutic use. In another embodiment, however, the compound may contain one or more radioisotopes. Compounds containing such radioisotopes may be useful in a diagnostic context.

**Solvates**

**[0059]** Compounds of the formula (1) as described herein may form solvates. Preferred solvates are solvates formed by the incorporation into the solid state structure (e.g. crystal structure) of the compounds described herein of molecules of a non-toxic pharmaceutically acceptable solvent (referred to below as the solvating solvent). Examples of such solvents include water, alcohols (such as ethanol, isopropanol and butanol) and dimethylsulphoxide. Solvates can be prepared by recrystallising the compounds described herein with a solvent or mixture of solvents containing the solvating solvent. Whether or not a solvate has been formed in any given instance can be determined by subjecting crystals of the compound to analysis using well known and standard techniques such as thermogravimetric analysis (TGE), differential scanning calorimetry (DSC) and X-ray crystallography. The solvates can be stoichiometric or non-stoichiometric solvates. Particularly preferred solvates are hydrates, and examples of hydrates include hemihydrates, monohydrates and dihydrates.

**[0060]** In one embodiment, a compound described herein is in the form of a solvate.

**[0061]** In one embodiment, the solvate is a hydrate.

**[0062]** For a more detailed discussion of solvates and the methods used to make and characterise them, see Bryn et al., Solid-State Chemistry of Drugs, Second Edition, published by SSCI, Inc of West Lafayette, IN, USA, 1999, ISBN 0-967-06710-3. Alternatively, rather than existing as a hydrate, the compound of the invention may be anhydrous. Therefore, also

described herein is a compound as described herein in an anhydrous form (e.g. anhydrous crystalline form).

**Crystalline and amorphous forms**

**[0063]** The compounds described herein may exist in a crystalline or non-crystalline (e.g. amorphous) state. Whether or not a compound exists in a crystalline state can readily be determined by standard techniques such as X-ray powder diffraction (XRPD). Crystals and their crystal structures can be characterised using a number of techniques including single crystal X-ray crystallography, X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and infra red spectroscopy, e.g. Fourier Transform infra-red spectroscopy (FTIR). The behaviour of the crystals under conditions of varying humidity can be analysed by gravimetric vapour sorption studies and also by XRPD. Determination of the crystal structure of a compound can be performed by X-ray crystallography which can be carried out according to conventional methods such as those described herein and as described in Fundamentals of Crystallography, C. Giacovazzo, H. L. Monaco, D. Viterbo, F. Scordari, G. Gilli, G. Zanotti and M. Catti, (International Union of Crystallography/ Oxford University Press, 1992 ISBN 0-19-855578-4 (p/b), 0-19-85579-2 (h/b)). This technique involves the analysis and interpretation of the X-ray diffraction of single crystal. In an amorphous solid, the three dimensional structure that normally exists in a crystalline form does not exist and the positions of the molecules relative to one another in the amorphous form are essentially random, see for example Hancock et al. J. Pharm. Sci. (1997), 86, 1).

**[0064]** In one embodiment, a compound described herein is in a crystalline form.

**[0065]** In one embodiment, a compound described herein is:

1. (a) from 50% to 100% crystalline, and more particularly is at least 50% crystalline, or at least 60% crystalline, or at least 70% crystalline, or at least 80% crystalline, or at least 90% crystalline, or at least 95% crystalline, or at least 98% crystalline, or at least 99% crystalline, or at least 99.5% crystalline, or at least 99.9% crystalline, for example 100% crystalline.

**[0066]** In one embodiment, a compound described herein is in an amorphous form.

**Prodrugs**

**[0067]** The compounds of the formula (1) as described herein may be presented in the form of a pro-drug. By "prodrugs" is meant for example any compound that is converted *in vivo* into a biologically active compound of the formula (1) as described herein.

**[0068]** For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any hydroxyl groups present in the parent compound with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

**[0069]** Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in ADEPT, GDEPT, LIDEPT, etc.). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

**[0070]** A compound described herein may contain a functional group which is convertable under physiological conditions to form a hydroxyl group or amino group.

**Complexes and clathrates**

**[0071]** Compounds of formula (1) may be in the form of complexes (e.g. inclusion complexes or clathrates with compounds such as cyclodextrins, or complexes with metals).

**[0072]** Accordingly, also described herein isa compound described herein in the form of a complex or clathrate.

**Biological activity and therapeutic uses**

**[0073]** The compounds described herein may have activity as muscarinic M1 receptor agonists. The muscarinic activity of the compounds can be determined using the Phospho-ERK1/2 assay described in Example A below.

**[0074]** A significant advantage of compounds described herein is that they are highly selective for the M1 receptor relative to the M2 and M3 receptor subtypes. For example, whereas compounds described herein typically have $pEC_{50}$ values of at least 6 (preferably at least 6.5) and $E_{max}$ values of greater than 80 (preferably greater than 95) against the M1 receptor in the functional assay described in Example A, they may have $pEC_{50}$ values of less than 5 and $E_{max}$ values of less than 20% when tested against the M2 and M3 subtypes in the functional assay of Example A.

**[0075]** Some compounds described herein are also highly selective for the M4 receptor relative to the M1 receptor. Examples of such compounds include the compound of Example 1-6(#), 1-9(#), 1-21 and 2-17(#). A hash sign (#) denotes a reference example.

**[0076]** Other compounds described herein have activity at both the M1 and M4 receptors. Examples of such compounds include compounds of Reference Examples 1-1 to 1-4 and 1-8 to 1-10 and 2-116.

**[0077]** In one embodiment, a compound described herein is for use in medicine.

**[0078]** In one embodiment, a compound described herein is for use as a muscarinic M1 and/or M4 receptor agonist.

**[0079]** In one embodiment, a compound described herein is a muscarinic M1 receptor agonist having a $pEC_{50}$ in the range from 6.0 to 8.1 and an $E_{max}$ of at least 90 against the M1 receptor in the assay of Example A herein or an assay substantially similar thereto.

**[0080]** In one embodiment, a compound described herein is a muscarinic M1 receptor agonist having a $pEC_{50}$ in the range from 6.5 to 7.5.

**[0081]** In one embodiment, a compound described herein has an $E_{max}$ of at least 95 against the M1 receptor.

**[0082]** In one embodiment, a compound described herein is a muscarinic M4 receptor agonist having a $pEC_{50}$ in the range from 6.0 to 9.0 and an $E_{max}$ of at least 90 against the M4 receptor in the assay of Example A herein or an assay substantially similar thereto.

**[0083]** In one embodiment, a compound described herein is a muscarinic M4 receptor agonist having a $pEC_{50}$ in the range from 6.5 to 9.0.

**[0084]** In one embodiment, a compound described herein has an $E_{max}$ of at least 95 against the M4 receptor.

**[0085]** In one embodiment, a compound described herein is selective for the M1 and/or M4 receptor compared to the muscarinic M2 and M3 receptors.

**[0086]** In one embodiment, a compound described herein is selective for the M1 receptor compared to the muscarinic M2 and M3 receptors.

**[0087]** In one embodiment, a compound described herein is selective for the M4 receptor compared to the muscarinic M2 and M3 receptors.

**[0088]** In one embodiment, a compound described herein is selective for the M1 receptor compared to the muscarinic M2, M3 and M4 receptors.

**[0089]** In one embodiment, a compound described herein is selective for the M4 receptor compared to the muscarinic M1, M2 and M3 receptors.

**[0090]** In one embodiment, a compound described herein is selective for the M1 and M4 receptor compared to the muscarinic M2 and M3 receptors.

**[0091]** In one embodiment, a compound described herein has a $pEC_{50}$ of less than 5 and an $E_{max}$ of less than 50 against the muscarinic M2 and M3 receptor subtypes.

**[0092]** In one embodiment, a compound described herein has a $pEC_{50}$ of less than 4.5 and/or an $E_{max}$ of less than 30 against the muscarinic M2 and M3 receptor subtypes.

**[0093]** In one embodiment, a compound described herein is for use in the treatment of a disease or condition mediated by the muscarinic M1 receptor.

**[0094]** By virtue of their muscarinic M1 and/or M4 receptor agonist activity, compounds described herein can be used in the treatment of Alzheimer's disease, schizophrenia and other psychotic disorders, cognitive disorders and other diseases mediated by the muscarinic M1 and /or M4 receptor, and can also be used in the treatment of various types of pain.

**[0095]** In one embodiment, a compound described herein is for use in the treatment of a cognitive disorder or psychotic disorder.

**[0096]** In one embodiment, the cognitive disorder or psychotic disorder comprises, arises from or is associated with a condition selected from cognitive impairment, Mild Cognitive Impairment, frontotemporal dementia, vascular dementia, dementia with Lewy bodies, presenile dementia, senile dementia, Friederich's ataxia, Down's syndrome, Huntington's chorea, hyperkinesia, mania, Tourette's syndrome, Alzheimer's disease, progressive supranuclear palsy, impairment of cognitive functions including attention, orientation, learning disorders, memory (i.e. memory disorders, amnesia, amnesic disorders, transient global amnesia syndrome and age-associated memory impairment) and language function; cognitive impairment as a result of stroke, Huntington's disease, Pick disease, Aids-related dementia or other dementia states such as Multiinfarct dementia, alcoholic dementia, hypotiroidism-related dementia, and dementia associated to other degenerative disorders such as cerebellar atrophy and amyotropic lateral sclerosis; other acute or sub-acute conditions that may cause cognitive decline such as delirium or depression (pseudodementia states) trauma, head trauma, age related cognitive decline, stroke, neurodegeneration, drug-induced states, neurotoxic agents, age related cognitive impairment, autism related cognitive impairment, Down's syndrome, cognitive deficit related to psychosis, and post-electroconvulsive treatment related cognitive disorders; cognitive disorders due to drug abuse or drug withdrawal including nicotine, cannabis, amphetamine, cocaine, Attention Deficit Hyperactivity Disorder (ADHD) and dyskinetic disorders such as Parkinson's disease, neuroleptic-induced parkinsonism, and tardive dyskinesias, schizophrenia, schizophreniform diseases, psychotic depression, mania, acute mania, paranoid, hallucinogenic and delusional disorders, personality disorders, obsessive compulsive disorders, schizotypal disorders, delusional disorders, psychosis due to

malignancy, metabolic disorder, endocrine disease or narcolepsy, psychosis due to drug abuse or drug withdrawal, bipolar disorders, epilepsy and schizo-affective disorder.

**[0097]** In one embodiment, a compound described herein is for use in the treatment of Alzheimer's disease.

**[0098]** In one embodiment, a compound described herein is for use in the treatment of Schizophrenia.

**[0099]** Also described herein is a method of treatment of a cognitive disorder in a subject (e.g. a mammalian patient such as a human, e.g. a human in need of such treatment), which method comprises the administration of a therapeutically effective dose of a compound described herein.

**[0100]** In one embodiment, the cognitive disorder comprises, arises from or is associated with a condition as defined in Embodiment 2.19.

**[0101]** In one embodiment, the cognitive disorder arises from or is associated with Alzheimer's disease.

**[0102]** In one embodiment, the cognitive disorder is Schizophrenia.

**[0103]** Also described herein is a compound described herein for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain.

**[0104]** Also described herein is a method of treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain, which method comprises the administration of a therapeutically effective dose of a compound described herein.

**[0105]** Also described herein is a compound described herein for the treatment of peripheral disorders such as reduction of intra ocular pressure in Glaucoma and treatment of dry eyes and dry mouth including Sjogren's Syndrome.

**[0106]** Also described herein is a method of treatment of peripheral disorders such as reduction of intra ocular pressure in Glaucoma and treatment of dry eyes and dry mouth including Sjogren's Syndrome, which method comprises the administration of a therapeutically

effective dose of a compound described herein.

**[0107]** Also described herein is the use of a compound described herein for the treatment of addicition.

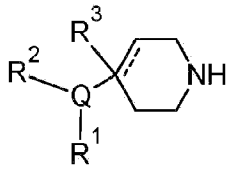
**[0108]** Also described herein is the use of a compound described herein for the treatment of movement disorders such as Parkinson's disease, ADHD, Huntingdon's disease, tourette's syndrome and other syndromes associated with dopaminergic dysfunction as an underlying pathogenetic factor driving disease.

**Methods for the Preparation of Compounds of the Formula (1)**

**[0109]** Compounds of the formula (1) can be prepared in accordance with synthetic methods well known to the skilled person and as described herein.

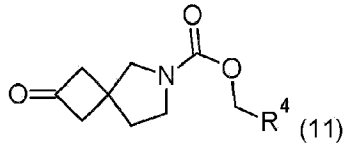
**[0110]** Also described herein is a process for the preparation of a compound described herein, which process comprises:

1. (A) the reaction of a compound of the formula (10)



(10)

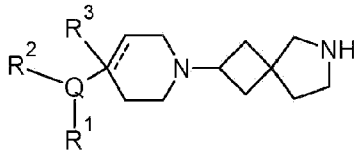
with a compound of the formula (11):



(11)

under reductive amination conditions; wherein $R^1$, $R^2$, $R^3$, $R^4$ and Q are as defined hereinabove; or

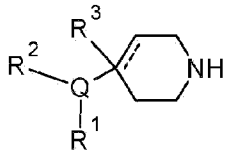
2. (B) the reaction of a compound of the formula (12):



(12)

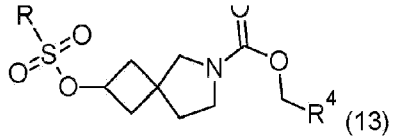
with a compound of the formula Cl-C(=O)-$CH_2$-$R^4$, in the presence of a base; or

3. (C) the reaction of a compound of the formula (10)



(10)

with a compound of the formula (13):


(13)

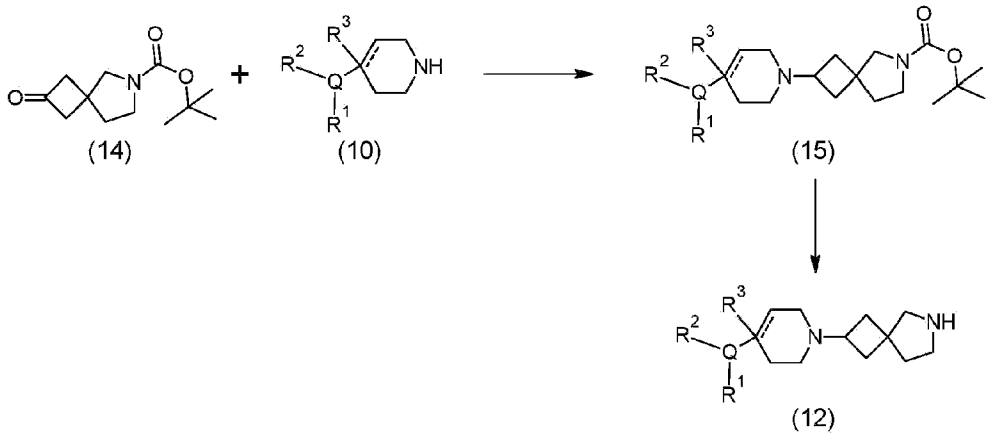
under nucleophilic substitution conditions; wherein $R^1$, $R^2$, $R^3$, $R^4$ and Q are as defined hereinabove; and optionally:

4. (D) converting one compound of the formula (1) to another compound of the formula (1).

**[0111]** In process variant (A), the piperidine heterocycle (10) is reacted with the substituted ketone (11) under reductive amination conditions. The reductive amination reaction is typically carried out at ambient temperature using a borohydride reducing agent such as sodium triacetoxy-borohydride in a solvent such as dichloromethane or dichloroethane containing acetic acid.

**[0112]** In process variant (C), the piperidine heterocycle (10) is reacted with the sulfonic ester (13, R = methyl, trifluoromethyl or 4-methylphenyl) in a nucleophilic substitution reaction which is typically carried out with mild heating (e.g. to a temperature of from about 40 °C to about 70° C) either neat, with no solvent, or in a suitable solvent such as tetrahydrofuran, acetonitrile or dimethylacetamide.

**[0113]** Intermediate compounds of the formula (12) can be prepared by the series of reactions shown in Scheme 1 below.

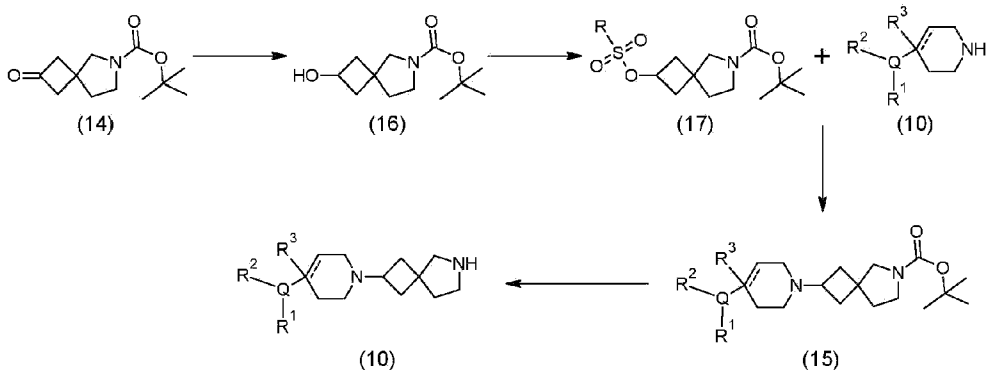

(14) (10) (15) (12)

Scheme 1

**[0114]** In reaction Scheme 1, the piperidine heterocycle (10) is reacted with the Boc-protected spiroketone (14) under reductive amination conditions. The reductive amination reaction is typically carried out with mild heating (e.g. to a temperature of from about 40 °C to about 70 °C) in the presence of either sodium cyanoborohydride in combination with zinc chloride or sodium triacetoxyborohydride in combination with titanium isopropoxide in a solvent such as dichloromethane or dichloroethane containing acetic acid to give an intermediate piperidine compound (15) which is then deprotected by removal of the Boc group by treatment with acid

(e.g. trifluoroacetic acid in dichloromethane) to give the compound (12).

**[0115]** Compounds of the formula (12) can also be prepared by the sequence of reactions shown in Scheme 2 below.




Scheme 2

**[0116]** In Scheme 2, the Boc-protected spiroketone (14) is reduced to the alcohol (16) using sodium borohydride in methanol. The alcohol (16) is then activated as the sulfonic ester (17, R = methyl, trifluoromethyl or 4-methylphenyl) using the corresponding sulfonyl chloride in dichloromethane in the presence of a tertiary amine such as triethylamine or *N,N*-diisopropylethylamine. The sulfonic ester (17) is reacted with the piperidine heterocycle (10) in a nucleophilic substitution reaction which is typically carried out with mild heating (e.g. to a temperature of from about 40 °C to about 70° C) either neat, with no solvent, or in a suitable solvent such as tetrahydrofuran, acetonitrile or dimethylacetamide to give compound (15) which is then deprotected by removal of the Boc group by treatment with acid (e.g. trifluoroacetic acid in dichloromethane) to give the compound (12).

**[0117]** Once formed, one compound of the formula (1), or a protected derivative thereof, can be converted into another compound of the formula (1) by methods well known to the skilled person. Examples of synthetic procedures for converting one functional group into another functional group are set out in standard texts such as Advanced Organic Chemistry and Organic Syntheses (see references above) or Fiesers' Reagents for Organic Synthesis, Volumes 1-17, John Wiley, edited by Mary Fieser (ISBN: 0-471-58283-2). Examples of these transformations include amide bond formation, urea formation, carbamate formation, alkylation reactions, N-arylation reaction and C-C bond coupling reactions.

**[0118]** In many of the reactions described above, it may be necessary to protect one or more groups to prevent reaction from taking place at an undesirable location on the molecule. Examples of protecting groups, and methods of protecting and deprotecting functional groups, can be found in Protective Groups in Organic Synthesis (T. Greene and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

**[0119]** Compounds made by the foregoing methods may be isolated and purified by any of a variety of methods well known to those skilled in the art and examples of such methods include

recrystallisation and chromatographic techniques such as column chromatography (e.g. flash chromatography) and HPLC.

**Pharmaceutical Formulations**

**[0120]** While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation).

**[0121]** Also described herein is a pharmaceutical composition comprising at least one compound described herein together with at least one pharmaceutically acceptable excipient.

**[0122]** In one embodiment, the composition is a tablet composition.

**[0123]** In another embodiment, the composition is a capsule composition.

**[0124]** The pharmaceutically acceptable excipient(s) can be selected from, for example, carriers (e.g. a solid, liquid or semi-solid carrier), adjuvants, diluents (e.g solid diluents such as fillers or bulking agents; and liquid diluents such as solvents and co-solvents), granulating agents, binders, flow aids, coating agents, release-controlling agents (e.g. release retarding or delaying polymers or waxes), binding agents, disintegrants, buffering agents, lubricants, preservatives, anti-fungal and antibacterial agents, antioxidants, buffering agents, tonicity-adjusting agents, thickening agents, flavouring agents, sweeteners, pigments, plasticizers, taste masking agents, stabilisers or any other excipients conventionally used in pharmaceutical compositions.

**[0125]** The term "pharmaceutically acceptable" as used herein means compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (e.g. a human subject) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each excipient must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

**[0126]** Pharmaceutical compositions containing compounds of the formula (1) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

**[0127]** The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, intrabronchial, sublingual, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration.

**[0128]** Pharmaceutical dosage forms suitable for oral administration include tablets (coated or uncoated), capsules (hard or soft shell), caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches such as buccal

patches.

**[0129]** Tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as microcrystalline cellulose (MCC), methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

**[0130]** Tablets may be designed to release the drug either upon contact with stomach fluids (immediate release tablets) or to release in a controlled manner (controlled release tablets) over a prolonged period of time or with a specific region of the GI tract.

**[0131]** The pharmaceutical compositions typically comprise from approximately 1% (w/w) to approximately 95%, preferably% (w/w) active ingredient and from 99% (w/w) to 5% (w/w) of a pharmaceutically acceptable excipient (for example as defined above) or combination of such excipients. Preferably, the compositions comprise from approximately 20% (w/w) to approximately 90% (w/w) active ingredient and from 80% (w/w) to 10% of a pharmaceutically excipient or combination of excipients. The pharmaceutical compositions comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, pre-filled syringes, dragées, powders, tablets or capsules.

**[0132]** Tablets and capsules may contain, for example, 0-20% disintegrants, 0-5% lubricants, 0-5% flow aids and/or 0-99% (w/w) fillers/ or bulking agents (depending on drug dose). They may also contain 0-10% (w/w) polymer binders, 0-5% (w/w) antioxidants, 0-5% (w/w) pigments. Slow release tablets would in addition typically contain 0-99% (w/w) release-controlling (e.g. delaying) polymers (depending on dose). The film coats of the tablet or capsule typically contain 0-10% (w/w) polymers, 0-3% (w/w) pigments, and/or 0-2% (w/w) plasticizers.

**[0133]** Parenteral formulations typically contain 0-20% (w/w) buffers, 0-50% (w/w) cosolvents, and/or 0-99% (w/w) Water for Injection (WFI) (depending on dose and if freeze dried). Formulations for intramuscular depots may also contain 0-99% (w/w) oils.

**[0134]** The pharmaceutical formulations may be presented to a patient in "patient packs" containing an entire course of treatment in a single package, usually a blister pack.

**[0135]** The compounds described herein will generally be presented in unit dosage form and,

as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation may contain from 1 nanogram to 2 grams of active ingredient, e.g. from 1 nanogram to 2 milligrams of active ingredient. Within these ranges, particular sub-ranges of compound are 0.1 milligrams to 2 grams of active ingredient (more usually from 10 milligrams to 1 gram, e.g. 50 milligrams to 500 milligrams), or 1 microgram to 20 milligrams (for example 1 microgram to 10 milligrams, e.g. 0.1 milligrams to 2 milligrams of active ingredient).

**[0136]** For oral compositions, a unit dosage form may contain from 1 milligram to 2 grams, more typically 10 milligrams to 1 gram, for example 50 milligrams to 1 gram, e.g. 100 miligrams to 1 gram, of active compound.

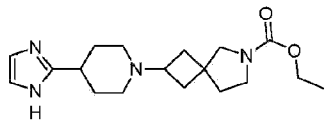
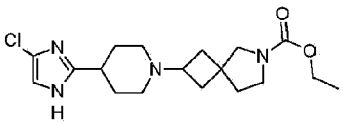
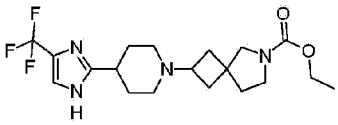
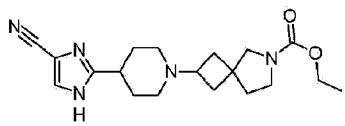
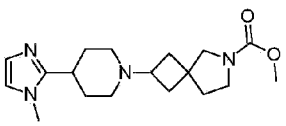
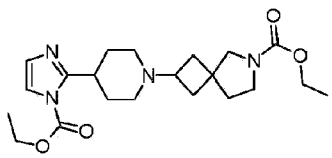
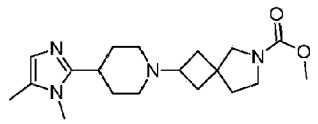
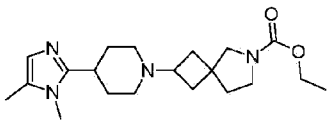
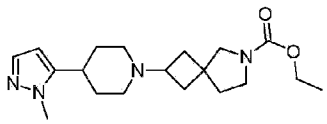
**[0137]** The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect (effective amount). The precise amounts of compound administered may be determined by a supervising physician in accordance with standard procedures.

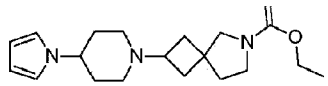
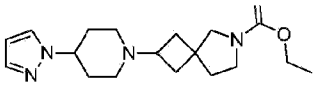
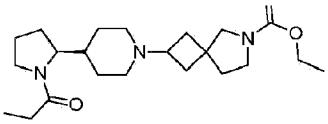
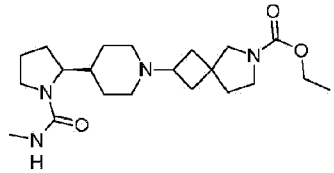
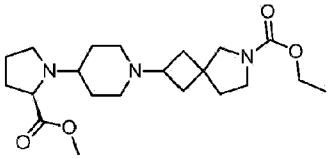
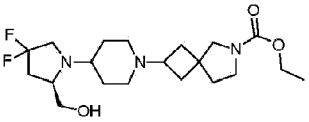
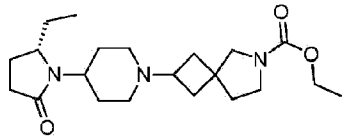
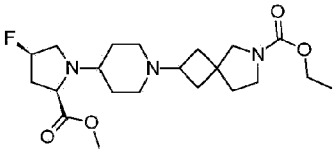
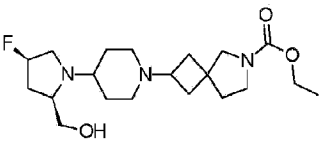
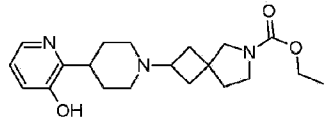
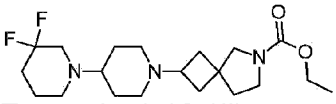
**EXAMPLES**

**[0138]** The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples.

**[0139]** The compounds of the Examples and Reference Examples shown in Table 1 below have been prepared. Their NMR and LCMS properties and the methods used to prepare them are set out in Table 3.

Table 1

| | | |
|---|---|---|
|  Example 1-1 (#) |  Example 1-2 (#) |  Example 1-3 (#) |
|  Example 1-4 (#) |  Example 1-6 (#) |  Example 1-8 (#) |
|  Example 1-9 (#) |  Example 1-10 (#) |  Example 1-21 |
|  |  |  |

| | | |
|---|---|---|
|  Example 1-32 (#) |  Example 1-33 (#) |  Example 2-7 (#) |
|  Example 2-17 (#) |  Example 2-84 (#) |  Example 2-107 (#) |
|  Example 2-116 (#) |  Example 2-134 (#) |  Example 2-136 (#) |
|  Example 3-4 (#) |  Example 4-13 (#) | |
| (#) Reference Example | | |

**General procedures**

**[0140]** Where no preparative routes are included, the relevant intermediate is commercially available. Commercial reagents were utilized without further purification. Room temperature (rt) refers to approximately 20-27°C. $^1$H NMR spectra were recorded at 400 MHz on either a Bruker or Jeol instrument. Chemical shift values are expressed in parts per million (ppm), i.e. (δ:)-values. The following abbreviations are used for the multiplicity of the NMR signals: s=singlet, br=broad, d=doublet, t=triplet, q=quartet, quint=quintet, td=triplet of doublets, tt= triplet of triplets, qd=quartet of doublets, ddd=doublet of doublet of doublets, ddt=doublet of doublet of triplets, m=multiplet. Coupling constants are listed as *J* values, measured in Hz. NMR and mass spectroscopy results were corrected to account for background peaks.

**[0141]** Chromatography refers to column chromatography performed using 60-120 mesh silica gel and executed under nitrogen pressure (flash chromatography) conditions. TLC for monitoring reactions refers to TLC run using the specified mobile phase and Silica gel F254 (Merck) as a stationary phase. Microwave-mediated reactions were performed in Biotage Initiator or CEM Discover microwave reactors.

**[0142]** LCMS experiments were typically carried out using electrospray conditions as specified for each compound under the following conditions:

**LCMS Methods A and B**

**[0143]** Instruments: Waters Alliance 2795, Waters 2996 PDA detector, Micromass ZQ; Column: Waters X-Bridge C-18, 2.5 micron, 2.1 × 20 mm or Phenomenex Gemini-NX C-18, 3 micron, 2.0 × 30 mm; Gradient [time (min)/solvent D in C (%)]: Method A: 0.00/2, 0.10/2, 2.50/95, 3.50/95, 3.55/2, 4.00/2 or Method B: 0.00/2, 0.10/2, 8.40/95, 9.40/95, 9.50/2, 10.00/2; Solvents: solvent C = 2.5 L $H_2O$ + 2.5 mL ammonia solution; solvent D = 2.5 L MeCN + 135 mL $H_2O$ + 2.5 mL ammonia solution); Injection volume 3 µL; UV detection 230 to 400 nM; column temperature 45 °C; Flow rate 1.5 mL/min.

**LCMS Method C**

**[0144]** Instruments: Agilent 1260 Infinity LC with Diode Array Detector, Agilent 6120B Single Quadrupole MS with API-ES Source; Column: Phenomenex Gemini-NX C-18, 3 micron, 2.0 × 30 mm; Gradient [time (min)/solvent B in A (%)]: Method: 0.00/5, 2.00/95, 2.50/95, 2.60/5, 3.00/5; Solvents: solvent A = 2.5 L $H_2O$ + 2.5 mL of (28% NH3 in $H_2O$); solvent B = 2.5 L MeCN + 129 mL $H_2O$ + 2.7 mL of (28% NH3 in $H_2O$); Injection volume 0.5 µL; UV detection 190 to 400 nM; column temperature 40 °C; Flow rate 1.5 mL/min.

**LCMS Methods D and E**

**[0145]** Instruments: HP 1100 with G1315A DAD, Micromass ZQ; Column: Waters X-Bridge C-18, 2.5 micron, 2.1 × 20 mm or Phenomenex Gemini-NX C-18, 3 micron, 2.0 × 30 mm; Gradient [time (min)/solvent D in C (%)]: Method D: 0.00/2, 0.10/2, 2.50/95, 3.50/95, 3.55/2, 4.00/2 or Method E: 0.00/2, 0.10/2, 8.40/95, 9.40/95, 9.50/2, 10.00/2; Solvents: solvent C = 2.5 L $H_2O$ + 2.5 mL 28% ammonia in $H_2O$ solution; solvent D = 2.5 L MeCN + 135 mL $H_2O$ + 2.5 mL 28% ammonia in $H_2O$ solution); Injection volume 1 µL; UV detection 230 to 400 nM; Mass detection 130 to 800 AMU (+ve and -ve electrospray); column temperature 45 °C; Flow rate 1.5 mL/min.

**LCMS Method F:**

**[0146]** Instruments: Waters Acquity H Class, Photo Diode Array, SQ Detector; Column: BEH C18, 1.7 micron, 2.1 × 50 mm; Gradient [time (min)/solvent B in A (%)]: 0.00/5, 0.40/5, 0.8/35, 1.20/55, 2.50/100, 3.30/100 4.00/5; Solvents: solvent A = 5mM mmmonium acetate and 0.1%

formic acid in $H_2O$; solvent B = 0.1% formic acid in MeCN; Injection volume 2 µL; UV detection 200 to 400 nM; Mass detection 100 to 1200 AMU (+ve electrospray); column at ambient temperature; Flow rate 0.5 mL/min.

**LCMS Method G:**

**[0147]** Instruments: Waters 2695, Photo Diode Array, ZQ-2000 Detector; Column: X-Bridge C18, 5 micron, 150 × 4.6mm; Gradient [time (min)/solvent B in A (%)]: 0.00/10, 5.00/90, 7.00/100, 11.00/100, 11.01/10 12.00/10; Solvents: solvent A = 0.1% ammonia in $H_2O$; solvent B = 0.1% ammonia in MeCN; Injection volume 10 µL; UV detection 200 to 400 nM; Mass detection 60 to 1000 AMU (+ve electrospray); column at ambient temperature; Flow rate 1.0 mL/min.

**[0148]** LCMS data in the experimental section are given in the format: Mass ion, retention time, UV activity.

**Abbreviations**

**[0149]**

AcOH
= acetic acid
CDI
= 1,1'-Carbonyldiimidazole
d
= day(s)
DAST
= diethylaminosulfur trifluoride
DCE
= dichloroethane
DCM
= dichloromethane
DIPEA
= diisopropylethylamine
DIAD
= diisopropyl azodicarboxylate
DMF
= dimethylformamide
DMP
= Dess-Martin periodinane
DMSO

= dimethylsulfoxide

ES

= electro spray ionisation

EtOAc

= ethyl acetate

h

= hour(s)

HATU

= 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b] pyridinium 3-oxid hexafluorophosphate

HPLC

= high performance liquid chromatography

LC

= liquid chromatography

$LiAlH_4$ / LAH

= Lithium aluminium hydride

MeCN

= acetonitrile

MeOH

= methanol

min

= minute(s)

MS

= mass spectrometry

$Et_3N$

= triethylamine

NMR

= nuclear magnetic resonance

rt

= room temperature

sat.

= saturated

sol.

= solution

STAB

= sodium triacetoxyborohydride

THF

= tetrahydrofuran

TLC

= thin layer chromatography

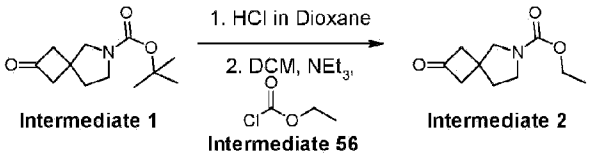
**[0150]** Prefixes *n*-, *s*-, *i*-, *t*- and *tert*- have their usual meanings: normal, secondary, *iso*, and

tertiary.

**Synthesis of intermediates:**

**Procedure for the preparation of Intermediate 2, ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate**

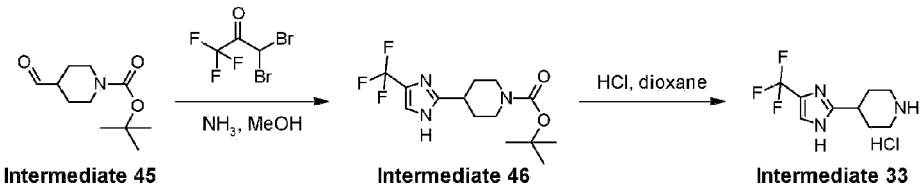
**[0151]**




**[0152]** 6-Boc-2-oxo-6-azaspiro[3.4]octane (3.37 g, 15 mmol) was added portionwise to hydrogen chloride (4 M dioxane solution, 50 mL, 210 mmol). Caution: effervescence. After 24 h, the reaction was concentrated *in vacuo* and the residual solid was dissolved in a mixture of $Et_3N$ (4.18 ml, 30 mmol) and DCM (66 mL). On completion of dissolution, the solution was immediately cooled to 0 °C, then ethyl chloroformate (1.57 mL, 16.5 mmol) was added dropwise. After 18 h, the mixture was poured into dichloromethane (100 mL) and NaHCOs (aq) (100 mL) and extracted (2 × 100 mL). The organic layers were collected, washed with brine (20 mL), dried over $MgSO_4$, then the residue after evaporation was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 100 g, 40-63 µm, 60 Å, 50 mL per min, gradient 0% to 4% MeOH in DCM]) to give **Intermediate 2,** ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate as a colourless oil (2.47 g, 83%). The data for the title compound are in Table 2.

**Procedure for the preparation of Intermediate 46, tert-butyl 4-(4-(trifluoromethyl)-1H-imidazol-2-yl)piperidine-1-carboxylate and Intermediate 33, 4-[4-(trifluoromethyl)-1H-imidazol-2-yl]piperidine**

**[0153]**




**[0154]** tert-Butyl 4-formylpiperidine-1-carboxylate (2.0 g, 9.4 mmol) was dissolved in MeOH (10mL) and followed by addition of 7M methanolic ammonia cooled at 0°C for 30 mins followed

by portion wise addition of 3,3-dibromo-1,1,1-trifluoropropan-2-one (5.07 g, 18.5 mmol). The resulting reaction mixture was stirred at 25°C for 2 h, solvents were removed *in vacuo* and the residue was partitioned between $H_2O$ (80 mL) and EtOAc (50 mL), the aqueous layer was extracted with EtOAc (2 × 50 mL), organic layers were combined, dried ($Na_2SO_4$), solvent was removed in vacuo and residue was purified by column chromatography (Activated basic Alumina at 0.5% MeOH in DCM) to give **Intermediate 46,** tert-butyl 4-(4-(trifluoromethyl)-1H-imidazol-2-yl)piperidine-1-carboxylate (1.80 g, 60%) as a white solid.

**[0155]** The data for the subtitle compound are in Table 2.

**[0156]** tert-Butyl 4-(4-(trifluoromethyl)-1H-imidazol-2-yl)piperidine-1-carboxylate (1 g, 3.13 mmol) was dissolved in 1,4-dioxane (5 mL) and followed by dropwise addition of HCl in 1,4-dioxane (20 mL, 3M solu.). The resulting reaction mixture was stirred at 30°C for 16 h, the solvents were removed *in vacuo* and the residue was purified by triturating with diethyl ether (3 × 5 mL) to give **Intermediate 33,** 4-(4-(trifluoromethyl)-1H-imidazol-2-yl)piperidine hydrochloride (650 mg, 95%) as a white solid. The data for the title compound are in Table 2.

**Procedure for the preparation of Intermediate 126, *tert*-butyl (2*R*)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate**

**[0157]**


**Intermediate 121** **Intermediate 126**

**[0158]** (R)-1-tert-Butyl 2-methyl 4-oxopyrrolidine-1,2-dicarboxylate (1.00 g,4.111 mmol) was dissolved in DCM (10 mL) at -78 °C and DAST was added (1.629 mL, 12.332 mmol). Reaction warmed to rt and stirred for 2 h. Reaction mixture diluted with DCM (100 mL) and washed with saturated $NaHCO_{3(aq)}$ (2 × 100 mL), combined aqueous layers washed with DCM (100 mL), combined organic layers washed with brine (25 mL) and passed through Biotage Phase separator. Sovent were removed *in vacuo* to give an orange oil (0.957 g, 90%).

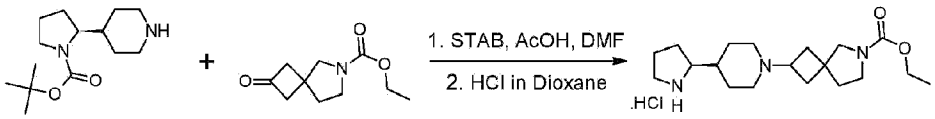
**[0159]** To (R)-1-tert-Butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate (500 mg, 1.885 mmol) in THF (5 mL) was added lithium borohydride as a 2.0M solution in THF (1.90 mL, 3.80 mmol) at 0°C and the reaction was warmed to RT and stirred for 1h. The solvents were removed *in vacuo,* and the reaction mixture diluted with DCM (50 mL) and washed with saturated $NaHCO_{3(aq)}$ (2 × 50 mL), combined aqueous layers washed with DCM (50 mL), combined organic layers washed with brine (50 mL) and passed through Biotage Phase separator. Volatiles removed under vacuum yielding **Intermediate 126,** *tert*-butyl (2*R*)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (452 mg, 92%).

**General Synthetic Procedures for Intermediates:**

**Route 6**

**Typical procedure for the preparation of pyrrolidines *via via* reductive amination and Boc-deprotection as exemplified by the preparation of Intermediate 127, mixture of diastereomers of ethyl 2-{4-[(2*S*)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate**

**[0160]**




Intermediate 51 Intermediate 2 Intermediate 127

**[0161]** *(S)-tert*-Butyl 2-(piperidin-4-yl)pyrrolidine-1-carboxylate (1.24 g, 6.29 mmol) and ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate (1.60 g, 6.29 mmol) were dissolved in DMF (15 mL) at rt and acetic acid (0.54 mL, 9.44 mmol) was added. The reaction mixture was stirred at rt for 3 h. STAB (2.67 g, 12.6 mmol) was then added and the reaction mixture was stirred overnight under nitrogen at rt. The solvents were removed *in vacuo,* and the residue was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 340g, 40-63 µm, 60 Å, 80 mL per min, gradient 0% to 10% 7N $NH_3$ in MeOH in DCM]) to give an inseparable mixture of isomers of ethyl 2-{4-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (2.46 g, 90%) as a yellow solid.

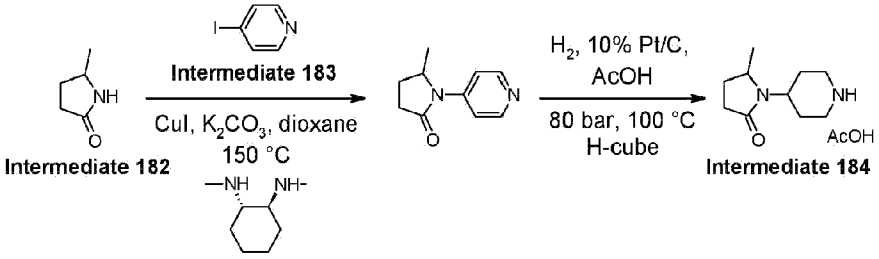
**[0162] LCMS (Method D):** m/z 436 $(M+H)^+$ $(ES^+)$, at 2.36 min, UV inactive.

**[0163]** A mixture of diastereomers of ethyl 2-{4-[(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (0.6 g, 1.4 mmol) was dissolved in 1,4-dioxane (10 mL) and treated dropwise with HCl in 1,4-dioxane (4M, 15 mL, 60 mmol). The resulting reaction mixture was stirred at 25 °C for 16 h, the solvents were removed and the residue was purified by triturating with diethyl ether (3 × 10 mL) to give a mixture of diastereomers of ethyl 2-{4-[(2*S*)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Intermediate 127** as a solid (0.45 g, 97%). The data for the title compound are in Table 2.

**Route 10**

**General procedure for the preparation of pyrrolidinone or oxadiazolone containing piperidines via copper catalyzed coupling to pyridine followed by hydrogenation as exemplified by the preparation of Intermediate 184, 5-methyl-1-(piperidin-4-yl)pyrrolidin-2-one acetate salt**

**[0164]**




**[0165]** A mixture of 5-methylpyrrolidin-2-one (0.050 g, 0.50 mmol), 4-iodopyridine (0.103 g, 0.50 mmol), (trans)-N,N'-dimethylcyclohexane-1,2-diamine (0.016 mL, 0.10 mmol), CuI (0.019 g, 0.10 mmol) and $K_2CO_3$ (0.209 g, 1.5 mmol) in dioxane (2 mL) was sealed in a nitrogen flushed glass tube and heated with stirring at 150 °C overnight. The cooled reaction mixture was concentrated onto flash silica (5 mL). The resulting powder was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 25 g, 40-63 µm, 60 Å], 30 mL per min, 0 to 5% Solvent A in DCM, where Solvent A is 10% of (7 M $NH_3$/MeOH) in MeOH) to give 5-methyl-1-(pyridin-4-yl)pyrrolidin-2-one (0.088 g, 99%) as an oil.

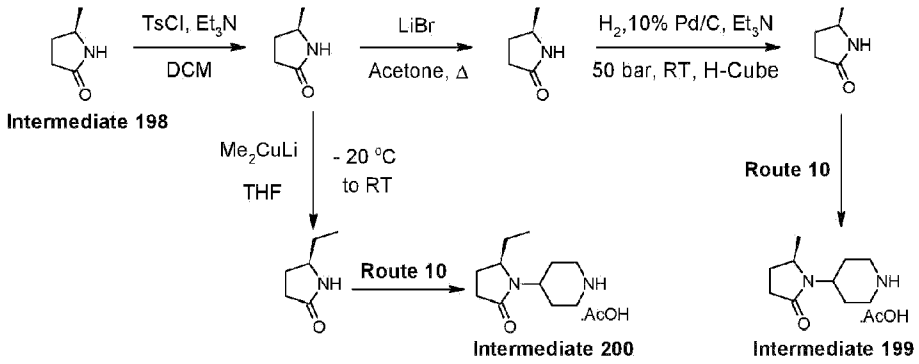
**LCMS (Method C):** m/z 177 $(M+H)^+$ $(ES^+)$, at 0.69 min, UV active

**[0166]** The 5-methyl-1-(pyridin-4-yl)pyrrolidin-2-one (0.080 g, 0.45 mmol ) was dissolved in AcOH (8 mL) and hydrogenated over 10% Pt/C catalyst at 80 bar pressure and 100 °C at a flow-rate of 1 mL/min using a H-Cube. The solution was then concentrated and the residue azeotroped with toluene (x2) to afford the crude **Intermediate 184,** 5-methyl-1-(piperidin-4-yl)pyrrolidin-2-one acetate salt (0.166 g, > 100%) as an oil. The data for the title compound are in Table 2.

**Route 11**

**Typical procedure for the preparation of piperidines *via* copper catalyzed coupling to pyridine followed by hydrogenation as exemplified by the preparation of Intermediate 199, (5R)-5-methyl-1-(piperidin-4-yl)pyrrolidin-2-one acetate salt and Intermediate 200, (5R)-5-ethyl-1-(piperidin-4-yl)pyrrolidin-2-one acetate salt**

**[0167]**




**Intermediate 199, (5R)-5-methyl-1-(piperidin-4-yl)pyrrolidin-2-one acetate salt:**

**[0168]** To a solution of (5S)-5-(hydroxymethyl)pyrrolidin-2-one (2.0 g, 17 mmol) and 4-methylbenzenesulfonyl chloride (5.3 g, 28 mmol) in DCM (24 mL) was added triethylamine (12 mL, 86 mmol). The resulting mixture was stirred at RT overnight then concentrated. The residue was dissolved in DCM and washed with 1 M aqueous HCl (x3) and brine (x1), then passed through a phase separator and concentrated to give a brown solid. The solid was recrystallized from DCM/isohexane to give a tan solid that was removed by filtration, washed with DCM/isohexane mixture and dried in air to give [(2S)-5-oxopyrrolidin-2-yl]methyl 4-methylbenzenesulfonate (3.13 g, 67%).

**[0169] LCMS (Method C):** m/z 270 $(M+H)^+$ $(ES^+)$, at 0.97 min, UV active A mixture of [(2S)-5-oxopyrrolidin-2-yl]methyl 4-methylbenzenesulfonate (0.50 g, 1.9 mmol) and lithium bromide (0.484 g, 5.6 mmol) in acetone (5 mL) was heated at reflux under $N_2$ overnight, then allowed to cool. The solvent was removed by concentration, the residue was distributed between DCM and $H_2O$ and the phases were separated. The aqueous phase was extracted with DCM (x3), then the organic phases were passed through a phase separator and concentrated to give (5S)-5-(bromomethyl)pyrrolidin-2-one (0.284 g, 86%) as a gum.

**[0170] LCMS (Method C):** m/z 178/180 $(M+H)^+$ $(ES^+)$, at 0.37 min, weakly UV active A solution of (5S)-5-(bromomethyl)pyrrolidin-2-one (0.284 g, 1.6 mmol) in triethylamine (0.267 mL, 1.9 mmol) and ethanol (32 mL) was hydrogenated over 10% Pd/C catalyst at 50 bar pressure and at RT at a flow-rate of 1 mL/min using a H-Cube. The solution was concentrated to give the crude (5R)-5-methylpyrrolidin-2-one (0.445 g, >100%) as a sticky solid.

**LCMS (Method C):** m/z 100 $(M+H)^+$ $(ES^+)$, at 0.34 min, weakly UV active

**[0171]** The crude (5R)-5-methylpyrrolidin-2-one (0.445 g, assumed 1.5 mmol) was reacted according to **Route 10** (coupling with **Intermediate 183**) to give the crude **Intermediate 199,** (5R)-5-methyl-1-(piperidin-4-yl)pyrrolidin-2-one acetate salt (0.125 g, 46%) as an oil. The data for the title compound are in Table 2.

**Intermediate 200, (5R)-5-ethyl-1-(piperidin-4-yl)pyrrolidin-2-one acetate salt:**

**[0172]** Methyllithium (1.5 M in ether, 7.4 mL, 11 mmol) was added quickly with stirring to a suspension of copper iodide (1.06 g, 5.6 mmol) in THF (6 mL), pre-cooled in ice-water under $N_2$. The pale brown solution was stirred in ice-water for 45 min, then cooled to - 20 °C. A solution of [(2S)-5-oxopyrrolidin-2-yl]methyl 4-methylbenzenesulfonate (0.50 g, 1.9 mmol) in THF (6 mL) was added portion-wise over 2 min and the resulting solution was stirred at - 20 °C for 45 min, then in ice-water overnight, allowing the cooling bath to slowly expire. The mixture was quenched with saturated aqueous $NH_4Cl$ (15 mL) and stirred for several hours. The two-phase mixture was extracted with ether (x3), the organic phases were washed with brine, passed through a phase separator and concentrated to give the crude (5R)-5-ethylpyrrolidin-2-one (0.124 g, 59%) as an oil.

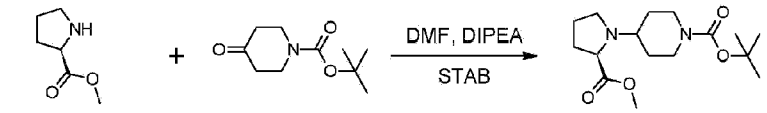
LCMS (Method C): m/z 114 $(M+H)^+$ $(ES^+)$, at 0.50 min, weakly UV active

**[0173]** The crude (5R)-5-ethylpyrrolidin-2-one (0.124 g, 1.10 mmol) was reacted according to **Route 10** (coupling with **Intermediate 183**) to give the crude **Intermediate 200**, (5R)-5-ethyl-1-(piperidin-4-yl)pyrrolidin-2-one acetate salt (0.156 g, 72%) as a gum. The data for the title compound are in Table 2.

**Route 13**

**Typical procedure for the preparation of piperidines *via* reductive aminations, as exemplified by the preparation of Intermediate 159, *tert*-butyl 4-[(2*R*)-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidine-1-carboxylate**

**[0174]**



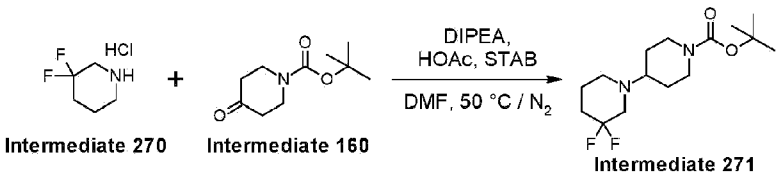

**Intermediate 115** **Intermediate 160** **Intermediate 159**

**[0175]** D-Proline methyl ester hydrochloride (0.200 g, 1.208 mmol) and 1-Boc-4-piperidinone (0.24 g, 1.208 mmol) were dissolved in DMF (2 mL) at rt and diisopropylethylamine (0.209 mL, 1.208 mmol) was added. The reaction mixture was stirred at rt for 3 h. STAB (0.512 g, 2.416 mmol) was then added and the reaction mixture was stirred overnight under nitrogen at rt. The solvents were removed *in vacuo,* and residue was partitioned between $H_2O$ (15 mL) and EtOAc (25 mL), aqueous layer was extracted with EtOAc (2 × 25 mL), organic layers were combined, dried over $Na_2SO_4$ and solvent was removed in vacuo to give tert-butyl 4-[(2R)-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidine-1-carboxylate, **Intermediate 159,** as a white solid (393 mg, >99%). The data for the title compound ares in Table 2

**Route 14**

**Typical procedure for the preparation of piperidines *via* reductive aminations, as exemplified by the preparation of Intermediate 271, *tert*-butyl 3,3-difluoro-1,4'-bipiperidine-1'-carboxylate**

**[0176]**




Intermediate 270 Intermediate 160 Intermediate 271

**[0177]** 3,3-difluoropiperidine. HCl (0.30 g, 1.90 mmol) and 1-Boc-4-piperidinone (0.379 g, 1.90 mmol) were dissolved in DMF (8 mL) at rt and diisopropylethylamine (0.246 g, 1.90 mmol) was added. The reaction mixture was stirred at 50°C under nitrogen for 2 h. The reaction mixture was cooled to rt, glacial acetic acid (0.114 g, 1.90 mmol) and STAB (1.01 g, 4.76 mmol) was then added and the reaction mixture was stirred overnight at 50°C under nitrogen. Water (2 mL) was added to the cooled reaction mixture and the solvents were removed *in vacuo.* The residue was diluted with sat. NaHCOs (aq) (10 mL) and extracted with DCM (2 × 10 mL) The combined organic layers were passed through a Biotage Phase Separator Cartridge to dry and the solvents were removed *in vacuo.* The residue was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 25g 40-63µm , 60Å, 25mL per min, gradient 0% to 10% MeOH / DCM]) to give *tert*-butyl 3,3-difluoro-1,4'-bipiperidine-1'-carboxylate, **Intermediate 271,** (0.347 g, 60%) as an amber oil. The data for the title compound are in Table 2

**General Synthetic Procedures for Examples:**

**Route a**

**Typical procedure for the preparation of piperidines *via* sodium triacetoxyborohydride reductive amination as exemplified by the preparation of Reference Example 1-1, ethyl 2-[4-(1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate**

**[0178]**

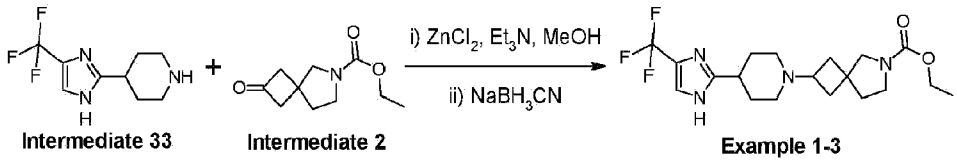

Intermediate 5 Intermediate 2 Example 1-1

**[0179]** 4-(1H-Imidazol-2-yl)piperidine dihydrochloride (1.43 g, 7.1 mmol) and ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate (1.60 g, 7.1 mmol) were dissolved in DCM (60 mL) at rt and titanium isopropoxide (2.31 mL, 7.81 mmol) was added. The reaction mixture was stirred at rt for 1 h. The reaction mixture was cooled to -5 °C, then STAB (3.01 g, 14.2 mmol) and acetic acid (350 µL, 4.26 mmol) were added and the reaction mixture was stirred overnight under nitrogen while warming to rt. The reaction mixture was quenched with the addition of $NaHCO_3$ (sat aq.) (10 mL) and diluted with DCM then filtered through a pad of celite. The layers were separated and the aqueous layer was extracted with DCM. The combined DCM layers were washed with brine, then dried over $MgSO_4$. The solvents were removed *in vacuo,* and the residue was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 50 g, 40-63 µm, 60 Å, 50 mL per min, gradient 1% to 10% MeOH in DCM with 0.5% NEts]) to give an inseparable mixture of diastereomers of ethyl 2-[4-(1*H*-imidazol-2-yl)piperidine]-6-azaspiro[3.4]octane-6-carboxylate (2.645g, 98.3%) as a white solid. Preparative HPLC was used to separate the diastereomers, using a Phenomenex Gemini-N C18 column, 150 × 21 mm, eluting with 28 to 38% MeCN/$H_2O$ at 18 mL/min and collecting fractions by monitoring at 218 nm to give isomer 1 ethyl 2-[4-(1*H*-imidazol-2-yl)piperidine]-6-azaspiro[3.4]octane-6-carboxylate (0.338 g, 14%) as a colourless solid and isomer 2 ethyl 2-[4-(1*H*-imidazol-2-yl)piperidine]-6-azaspiro[3.4]octane-6-carboxylate (0.369 g, 16%) as a colourless solid. The data for Isomer 2 are in Table 3.

**Route b**

**Typical procedure for the preparation of piperidines *via* sodium cyanoborohydride and zinc chloride reductive amination as exemplified by the preparation of Reference Example 1-3, ethyl 2-(4-(4-(trifluoromethyl)-1H-imidazol-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate**

**[0180]**




Intermediate 33 Intermediate 2 Example 1-3

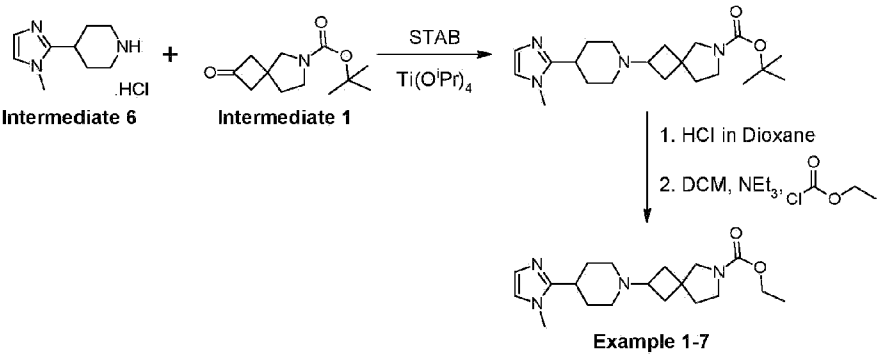
**[0181]** 4-(4-(Trifluoromethyl)-1H-imidazol-2-yl)piperidine (100 mg, 0.46 mmol), ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate (89 mg, 0.46 mmol), ZnCl2 (2 mg, 0.01 mmol) and

triethylamine (0.3 mL, 2.28 mmol) were dissolved in MeOH (5 mL) and the reaction mixture was stirred at 50°C for 2 h. The reaction mixture was cooled down to 0°C, and $NaBH_3CN$ (114 mg, 1.83 mmol) was added portion wise. The resulting reaction mixture was stirred at 25°C for 7 h and the solvents were removed in vacuo. The residue was partitioned between $H_2O$ (50 mL) and EtOAc (35 mL), the aqueous layer was extracted with EtOAc (2 × 35 mL), the organic layers were combined, dried ($Na_2SO_4$) and the solvent was removed in vacuo. The residue was purified by Prep HPLC [ reverse phase (X-BRIDGE, C-18, 250×19 mm, 5um, 18 mL per min, gradient 28.0% (over 40.0 mins), 100% (over 3.0 mins) then 28.0% ( over 5.0 min), 0.1% $NH_3$ in MeCN/water] to give ethyl 2-(4-(4-(trifluoromethyl)-1H-imidazol-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 1-3 Isomer 1**, (15 mg, 8.24%) as a yellow solid and ethyl 2-(4-(4-(trifluoromethyl)-1H-imidazol-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 1-3 Isomer 2,** (12 mg, 6.6%) as a yellow solid. The data for Isomer 2 are in Table 3

**Route d**

**Typical procedure for the preparation of piperidines *via* sodium triacetoxyborohydride reductive amination, Boc-deprotection and ethylcarbamate formation as exemplified by the preparation of Reference Example 1-7, ethyl 2-[4-(1-methyl-1*H*-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate**

**[0182]**




**[0183]** 4-(1-Methylimidazol-2-yl)piperidine hydrochloride (0.244 g, 1.21 mmol) and 6-Boc-2-oxo-6-azaspiro[3,4]octane (0.273 g, 1.21 mmol) were dissolved in DCM (10 mL) at rt and titanium isopropoxide (0.4 mL, 2.42 mmol) was added. The reaction mixture was stirred at rt for 1 h. The reaction mixture was cooled to -5 °C, then STAB (0.513 g, 2.42 mmol) and acetic acid (27 µL, 480 µmol) were added and the reaction mixture was stirred overnight under nitrogen while warming to rt. The reaction mixture was quenched with the addition of $NaHCO_3$ (sat aq.) (10 mL) and diluted with DCM then filtered through a pad of celite. The layers were separated and the aqueous layer was extracted with DCM. The combined DCM layers were

washed with brine, then dried over $MgSO_4$. The solvents were removed *in vacuo,* and the residue was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 25g, 40-63 µm, 60 Å, 50 mL per min, gradient 1% to 10% MeOH in DCM]) to give an inseparable mixture of isomers of *tert*-butyl 2-[4-(1-methyl-1*H*-imidazol-2-yl)piperidine]-6-azaspiro[3.4]octane-6-carboxylate (0.330 g, 72%) as a yellow gum.

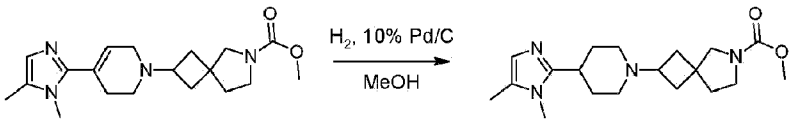
**LCMS (Method A):** m/z 374 $(M+H)^+$ $(ES^+)$, at 1.68 min, UV inactive.

**[0184]** *Tert*-butyl 2-[4-(1-methyl-1*H*-imidazol-2-yl)piperidine]-6-azaspiro[3.4]octane-6-carboxylate (0.326 g, 0.87 mmol) was dissolved in 4 M hydrogen chloride in dioxane (1.2 mL, 5.2 mmol). The reaction mixture was stirred at rt for 18 h. The volatiles were then removed *in vacuo* and the residue dissolved DCM (17 mL) and triethylamine (0.49 mL, 3.49 mmol). Ethyl chloroformate (125 µL, 1.31 mmol) was added dropwise and the solution stirred at rt for 18 h. The mixture was then poured into NaHCOs (aq) (75 mL) and DCM (75 mL), extracted (2 × 75 mL), and the combined DCM extracts washed with brine (20 mL) then dried over $MgSO_4$. After concentration, the residue was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 25 g, 40-63 µm, 60 Å, 50 mL per min, gradient 1% to 10% MeOH in DCM]) to provide ethyl 2-[4-(1-methyl-1*H*-imidazol-2-yl)piperidine]-6-azaspiro[3.4]octane-6-carboxylate as a brown oil as a mixture of diastereomers (0.25 g, 83%). Preparative HPLC was used to separate the diastereomers, using a Phenomenex Gemini-N C18 column, 150 × 21 mm, eluting with 38 to 48% $MeCN/H_2O$ at 18 mL/min and collecting fractions by monitoring at 218 nm to give ethyl 2-[4-(1-methyl-1*H*-imidazol-2-yl)piperidine]-6-azaspiro[3.4]octane-6-carboxylate, **Reference Example 1-7 Isomer 1,** (0.044 g, 15%) as a colourless oil and ethyl 2-[4-(1-methyl-1*H*-imidazol-2-yl)piperidine]-6-azaspiro[3.4]octane-6-carboxylate, **Reference Example 1-7 Isomer 2,** (0.031 g, 10%) as a colourless oil. The data for Isomer 2 are in Table 3

**Route e**

**Typical procedure for the hydrogenation of compounds containing 3,6-dihydropyridin-1(2H)-yl to give compounds containing piperidinyl as exemplified by the preparation of Reference Example 1-9, methyl 2-[4-(1,5-dimethyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate,**

**[0185]**




**Example 1-9**

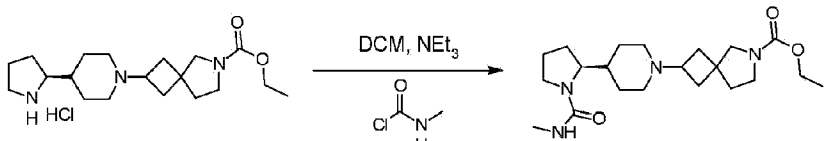
**[0186]** Methyl 2-(4-(1,5-dimethyl-1H-imidazol-2-yl)-3,6-dihydropyridin-1(2H)-yl)-6-azaspiro[3.4]octane-6-carboxylate (102 mg, 0.29 mmol) [synthesized via route d and

intermediates **3** and **34]** was dissolved in MeOH (10 mL) and 10% Pd/C (25 mg) was added. The reaction mixture was purged with $H_2$ gas then stirred at 25°C for 20 h under a balloon of $H_2$. The reaction mixture was filtered through celite and wash with MeOH, the solvents from the filtrate were removed *in vacuo,* and the residue was purified by preperative HPLC (X Bridge, C-18, 150×30 mm, 5um, 40 mL per min, gradient 30% ( over 12.00 mins ), 100% ( over 14.00 mins), then 30% ( over 14.01 mins), 0.1% Ammonia in Acetonitrile/ water] to give methyl 2-[4-(1,5-dimethyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Reference Example 1-9 Isomer 1,** (5.6 mg, 5.8%) as a colourless gum and methyl 2-[4-(1,5-dimethyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Reference Example 1-9 Isomer 2,** (11.6 mg, 11.7%) as a colourless gum. The data for Isomer 2 are in Table 3.

**Route m**

**Typical procedure for the preparation of piperidines *via* amide/carbamate/urea formation as exemplified by the preparation of Reference Example 2-17, ethyl 2-{4-[(2*S*)-1-(methylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate**

**[0187]**



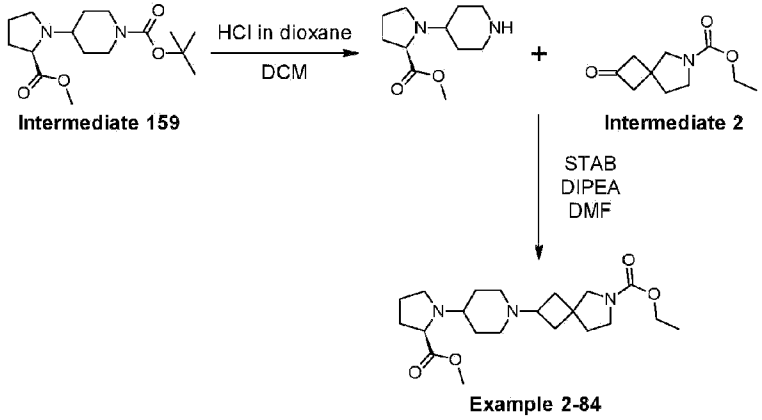

Intermediate 127 — Intermediate 57 — Example 2-17

**[0188]** A mixture of diastereomers of ethyl 2-{4-[(2S)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (2.10 g, 5.65 mmol) was dissolved DCM (20 mL) and triethylamine (1.54 mL, 11.1 mmol). Methylaminoformyl chloride (620 mg, 6.63 mmol) was added and the solution stirred at rt for 2 h. The mixture was then poured into 1M NaOH (aq) (50 mL), extracted with DCM (2 × 50 mL), and the combined DCM extracts washed with brine (50 mL) then passed through a Biotage phase separator and concentrated in vacuo, to provide ethyl 2-{4-[(2S)-1-(methylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate as a yellow solid and as a mixture of diastereomers (1.79 g, 82%). Preparative HPLC was used to separate the diastereomers, using a Phenomenex Gemini-NX C18 column, 100 × 30 mm, eluting with 25 to 35% MeCN/0.2% ammonia in $H_2O$ (*v*/*v*) at 18 mL/min and collecting fractions by monitoring at 210 nm to give **Reference Example 2-17 Isomer 1,** ethyl 2-{4-[(2*S*)-1-(methylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (0.78 g, 36%) as a colourless oil and **Reference Example 2-17 Isomer 2,** ethyl 2-{4-[(2*S*)-1-(methylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (0.67 g, 31%) as a colourless oil. The data for Isomer 2 are in Table 3

**Route aj**

**Typical procedure for the preparation of piperidines *via* deprotection and reductive aminations, as exemplified by the preparation of Reference Example 2-84, ethyl 2-{4-[(2R)-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate**

**[0189]**



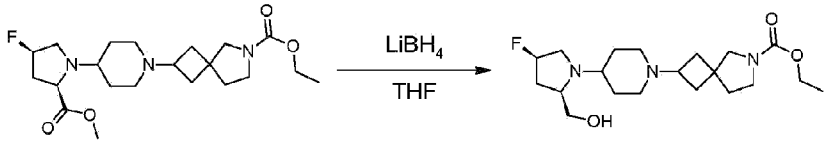

**[0190]** *tert*-Butyl 4-[(2R)-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidine-1-carboxylate (0.396 g, 1.26 mmol) was dissolved in DCM (1 mL), followed by the dropwise addition of HCl in dioxane (3 mL, 4.0 M solu.). The resulting reaction mixture was stirred at rt for 1 h, the solvents were removed in vacuo and the residue was carried on to the next step without further purification.

**[0191]** Methyl 1-piperidin-4-yl-D-prolinate.HCl (0.358 g, 1.26 mmol) and ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate (0.266 g, 1.26 mmol) were dissolved in DMF (4 mL) at rt and DIPEA (0.435 mL, 2.510 mmol) was added. The reaction mixture was stirred at rt for 3 h. STAB (0.533 g, 2.518 mmol) was then added and the reaction mixture was stirred overnight under nitrogen at rt. The solvents were removed *in vacuo,* and Preparative HPLC was used to separate the diastereomers, using a Phenomenex Gemini-NX C18 column, 100 × 30 mm, eluting with 25 to 45% MeCN/0.2% ammonia in $H_2O$ (v/v) at 18 mL/min and collecting fractions by monitoring at 210 nm to give **Reference Example 2-84 Isomer 1** ethyl 2-{4-[(2R)-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (18.4 mg, 4%) as a colourless oil and **Reference Example 2-84 Isomer 2,** ethyl 2-{4-[(2R)-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (13.9 mg, 3%) as a colourless oil. The data for Isomer 2 are in Table 3

**Route ar**

**Typical procedure for the preparation of piperidines *via* ester reduction, as exemplified by the preparation of Reference Example 2-136, ethyl 2-{4-[(2*R*,4*R*)-4-fluoro-2-(hydroxymethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate**

**[0192]**



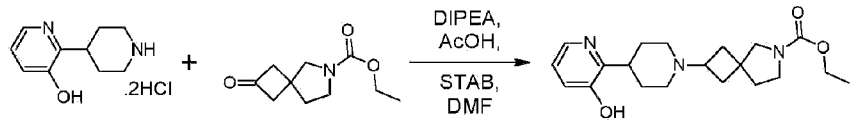

Example 2-134 Example 2-136

**[0193]** A mixture of diastereomers of ethyl 2-{4-[(2R,4R)-4-fluoro-2-(methoxycarbonyl) pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (0.140 g, 0.341 mmol) was dissolved in anhydrous THF (10 mL) and cooled to 0°C under nitrogen. 2.0M Lithium borohydride solution in THF (1.02 mL, 1.023 mmol) was added dropwise to the reaction mixture and then the reaction mixture was allowed to warm to rt overnight. The reaction mixture was quenched with sat. NaHCOs (aq) (15 mL) and then extracted with EtOAc (2 × 15mL), the organic layers were combined and dried ($MgSO_4$). The solvents were removed *in vacuo,* and the residue was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 10g 40-63µm, 60Å, 12 mL per min, gradient 0% to 10% MeOH / DCM]). The residue was further purified by preparative reversed phase HPLC (Phenomenex Gemini-NX 5 µm C18 110A Axia column, 100 × 30 mm, eluting with 20 to 50% MeCN/Solvent B over 14.4 min at 30 mL/min [where solvent B is 0.2% of (28% $NH_3/H_2O$) in $H_2O$] and collecting fractions by monitoring at 210 nm) to give ethyl 2-{4-[(2*R*,4*R*)-4-fluoro-2-(hydroxymethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Reference Example 2-136 Isomer 1,** (2.99 mg, 0.23%) as a white solid and ethyl 2-{4-[(2*R*,4*R*)-4-fluoro-2-(hydroxymethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Reference Example 2-136 Isomer 2,** (3.10 mg, 0.24%) as a white solid. The data for Isomer 2 are in Table 3.

**Route as**

**Typical procedure for the preparation of piperidines *via* sodium triacetoxyborohydride reductive amination in DMF as exemplified by the preparation of Reference Example 3-4, ethyl 2-[4-(3-hydroxypyridin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate**

**[0194]**



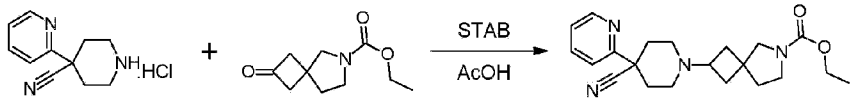

Intermediate 18 Intermediate 2 Example 3-4

**[0195]** 2-(Piperidin-4-yl)pyridin-3-ol dihydrochloride (0.20 g, 0.8 mmol) and ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate (0.157 g, 0.8 mmol) were mixed in DMF (8 mL) at rt. DIPEA (0.28 mL, 1.6 mmol) and AcOH (0.07 mL, 1.2 mmol) were added, followed by STAB (0.34 g, 1.6 mmol). The reaction mixture was stirred under nitrogen at rt overnight, then quenched with the addition of a small quantity of MeOH, and concentrated *in vacuo* to remove all the solvents. The residue was dissolved in a mixture of MeOH and DCM and concentrated onto flash silica (~10 mL) *in vacuo.* The resulting powder was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 25 g, 40-63 µm, 60 Å, 30 mL per min, gradient 0% to 15% Solvent A in DCM over 15 column volumes, where solvent A is 10% of (7 M $NH_3$/MeOH) in MeOH ]) to give a crude mixture of diastereomers (0.258 g). This mixture was dissolved in MeOH, a small quantity of 28% $NH_3/H_2O$ was added (~0.1 mL), and the solution was purified by preparative reversed phase HPLC using a Phenomenex Gemini-NX 5 µm C18 110A Axia column, 100 × 30 mm, eluted with 15 to 25% MeCN/Solvent B over 14.4 min at 30 mL/min [where solvent B is 0.2% of (28% $NH_3/H_2O$) in $H_2O$] and collecting fractions by monitoring at 230 nm to give ethyl 2-[4-(3-hydroxypyridin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Reference Example 3-4 Isomer 1,** (0.034 g, 12%) and ethyl 2-[4-(3-hydroxypyridin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Reference Example 3-4 Isomer 2**, (0.052 g, 18%). The data for Isomer 2 are in Table 3.

**Route at**

**Typical procedure for the preparation of piperidines *via* sodium triacetoxyborohydride reductive amination as exemplified by the preparation of Reference Example 3-10, ethyl 2-[4-cyano-(pyridine-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate**

**[0196]**




**Intermediate 14** **Intermediate 2** **Example 3-10**

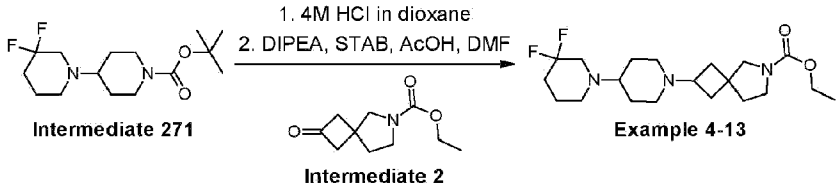
**[0197]** 4-(Pyridin-2-yl)piperidine-4-carbonitrile hydrochloride (0.187 g, 1.0 mmol) and ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate (0.197 g, 1.0 mmol) were dissolved in DCM (10 mL) under $N_2$ at rt and $NEt_3$ (0.15 mL, 1.1 mmol) was added. The reaction mixture was stirred at rt for 1 h, acetic acid (0.13 mL, 2.2 mmol) was added and the reaction mixture stirred at rt for 3 h. STAB (0.636 g, 3.0 mmol) was added and the reaction mixture stirred overnight. The reaction mixture was quenched with the addition of $NaHCO_3$ (sat aq.) (30 mL), extracted with DCM (4 × 25 mL) and the combined DCM layers passed through a Biotage phase separator.

The solvents were removed *in vacuo,* and the residue was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 25 g, 40-63 µm, 60 Å, 40 mL per min, gradient 0% to 10% MeOH in DCM) to give an inseparable mixture of diastereomers of ethyl 2-[4-cyano-(pyridine-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate. Preparative HPLC was used to separate the diastereomers, using a Phenomenex Gemini-N C18 column, 150 × 21 mm, eluting with 25 to 65% MeOH/$H_2O$ at 18 mL/min and collecting fractions by monitoring at 210 nm to give ethyl 2-[4-cyano-(pyridine-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Reference Example 3-10 Isomer 1,** (0.012 g, 3%) as a colourless solid and ethyl 2-[4-cyano-(pyridine-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Reference Example 3-10 Isomer 2,** (0.014 g, 4%) as a colourless solid. The data for both Isomers are in Table 3.

**Route aw**

**Typical procedure for the preparation of piperidines *via* deprotection and sodium triacetoxyborohydride reductive amination, as exemplified by the preparation of Reference Example 4-13, ethyl 2-(3,3-difluoro-1,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate**

**[0198]**




**[0199]** *tert*-Butyl 3,3-difluoro-1,4'-bipiperidine-1'-carboxylate (0.347 g, 1.14 mmol) was dissolved in 4.0M HCl in dioxane (5 mL) and the reaction mixture was stirred at rt overnight. The solvents were removed *in vacuo* and the residue was used in the next step without further purification. The crude reaction mixture and ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate (0.212 g, 1.14 mmol) were dissolved in DMF (6 mL) at rt and DIPEA (0.295 g, 2.28 mmol) was added. The reaction mixture was stirred at 50°C under nitrogen for 2 h. The reaction mixture was cooled to rt, glacial acetic acid (0.068 g, 1.14 mmol) and STAB (0.604 g, 2.85 mmol) were added and the reaction mixture was stirred overnight at 50°C under nitrogen. Water (2 mL) was added to the cooled reaction mixture and the solvents were removed *in vacuo.* The residue was partitioned between DCM (15 mL) and sat. NaHCOs (aq) (15 mL), the aqueous layer was washed with DCM (2 × 15 mL). The organic layers were combined and dried by passing through a Biotage Phase Separator Cartridge. The solvents were removed *in vacuo,* and the residue was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 10g 40-63µm, 60Å, 12mL per min, gradient 1% to 10% MeOH / DCM]). The residue was further purified by preparative reversed phase HPLC (Phenomenex Gemini-NX 5

µm C18 110A Axia column, 100 × 30 mm, eluting with 30 to 60% MeCN/Solvent B over 14.4 min at 30 mL/min [where solvent B is 0.2% of (28% $NH_3/H_2O$) in $H_2O$] and collecting fractions by monitoring at 210 nm) to give ethyl 2-(3,3-difluoro-1,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate, **Reference Example 4-13 Isomer** 1, (0.011 g, 2.6%) as a colourless oil and ethyl 2-(3,3-difluoro-1,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate, **Reference Example 4-13 Isomer 2,** (0.005 g, 1.3%) as a colourless oil. The data for Isomer 2 are in Table 3.

Table 2

Characterising data and commercial sources for starting materials and intermediates

**Table 2**

| **Intermediate** | **Route** | **Name** | **Data** |
|---|---|---|---|
| **1** | | 6-Boc-2-oxo-6-azaspiro[3.4]octane | Commercially available, CAS: 203661-71-6 |
| **2** | | ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate | **$^1$H NMR:** (400 MHz, $CDCl_3$) δ: 1.27 (t, J = 7.0 Hz, 3H), 2.08 (t, J = 6.2 Hz, 2H), 2.94 - 3.17 (m, 4H), 3.49 - 3.59 (m, 4H), 4.15 (q, J = 7.0 Hz, 2H) |
| **3** | | methyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate | **$^1$H NMR:** (400 MHz, CDsOD) δ:: 2.06 - 2.15 (m, 2 H), 2.94 - 3.04 (m, 2 H), 3.05 - 3.17 (m, 2 H), 3.47 (td, J = 6.8, 2.5 Hz, 2 H), 3.54 (d, J = 2.5 Hz, 2 H), 3.69 (s, 3 H) |
| **5** | | 4-(1H-imidazol-2-yl)piperidine dihydrochloride | Commercially available, CAS: 90747-46-9 |
| **6** | | 4-(1-methylimidazol-2-yl)piperidine hydrochloride | Commercially available, CAS: 1198420-89-1 |
| **9** | | 4-(1-methyl-1H-pyrazol-5-yl)piperidine | Commercially available, CAS: 640270-01-5 |
| **11** | | 4-(1*H*-pyrrol-1-yl)piperidine | Commercially available, CAS: 169751-01-3 |
| **12** | | 4-(1*H*-pyrazol-1-yl)piperidine | Commercially available, CAS: 762240-09-5 |
| **14** | | 4-(Pyridin-2-yl)piperidine-4-carbonitrile hydrochloride | Commercially available, CAS: 767263-33-2 |
| **15** | | 4-(1-Methylimidazol-2-yl)piperidine hydrochloride | Commercially available, CAS: 1198420-89-1 |
| **18** | | 4-(1*H*-1,2,3-Triazol-1- | Commercially available, |

Characterising data and commercial sources for starting materials and intermediates

**Table 2**

| Intermediate | Route | Name | Data |
|---|---|---|---|
| | | yl)piperidine hydrochloride | CAS: 690261-88-2 |
| **22** | | 4-(5-chloro-1H-imidazol-2-yl)piperidine dihydrobromide | **LCMS (Method C):** m/z 186/188 $(M+H)^+$ ($ES^+$), at 0.92 min, UV active |
| **33** | | 4-[4-(trifluoromethyl)-1H-imidazol-2-yl]piperidine hydrochloride | **LCMS (Method F):** m/z 220 $(M+H)^+$ ($ES^+$), at 2.16 min, UV active |
| **34** | | 4-(1,5-dimethyl-1H-imidazol-2-yl)-1,2,3,6-tetrahydropyridine hydrochloride | **LCMS (Method G):** m/z 178 $(M+H)^+$ ($ES^+$), at 3.90 min, UV active |
| **45** | | *tert*-butyl 4-formylpiperidine-1-carboxylate | Commercially available, CAS: 137076-22-3 |
| **46** | | *tert*-butyl 4-[4-(trifluoromethyl)-1*H*-imidazol-2-yl]piperidine-1-carboxylate | **LCMS (Method F):** m/z 320 $(M+H)^+$ ($ES^+$), at 2.16 min, UV active |
| **51** | | (*S*)-*Tert*-butyl 2-(piperidin-4-yl)pyrrolidine-1-carboxylate | Commercially available, CAS: 1449131-15-0 |
| **54** | | Propionyl Chloride | Commercially available, CAS: 79-03-8 |
| **57** | | Methylaminoformyl chloride | Commercially available, CAS: 6452-47-7 |
| **115** | | D-proline methyl ester hydrochloride | Commercially available, CAS: 65365-28-8 |
| **121** | | (*R*)-1-*tert*-Butyl 2-methyl 4-oxopyrrolidine-1,2-dicarboxylate | Commercially available, CAS: 256487-77-1 |
| **126** | **Intermediate 121** | *tert*-butyl (2*R*)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate | **LCMS (Method C):** m/z 238 $(M+H)^+$ (ES+), at 1.63 min, UV inactive |
| **127** | **Route 6 and intermediates 2 and 51** | Ethyl 2-{4-[(2*S*)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl | **LCMS (Method G):** m/z 336 $(M+H)^+$ ($ES^+$), at 6.23 min, UV inactive |
| **159** | **Route 13 and** | *tert*-butyl 4-[(2*R*)-2- | **LCMS (Method D):** m/z 313 |

Characterising data and commercial sources for starting materials and intermediates

**Table 2**

| Intermediate | Route | Name | Data |
|---|---|---|---|
| | **intermediates 115 and 160** | (methoxycarbonyl)pyrrolidin-1-yl]piperidine-1-carboxylate | $(M+H-^tBu)^+$ ($ES^+$), at 1.85 min, UV inactive |
| **160** | | tert-butyl 4-oxopiperidine-1-carboxylate | Commercially available, CAS: 79099-07-3 |
| **182** | | 5-methylpyrrolidin-2-one | Commercially available, CAS: 108-27-0 |
| **183** | | 4-iodopyridine | Commercially available, CAS: 15854-87-2 |
| **184** | **Route 10 and intermediates 182 and 183** | 5-methyl-1-(piperidin-4-yl)pyrrolidin-2-one acetate | **LCMS (Method C):** m/z 183 $(M+H)^+$ (ES+), at 0.53 min, UV active |
| **198** | | (5S)-5-(hydroxymethyl)pyrrolidin-2-one | Commercially available, CAS: 17342-08-4 |
| **199** | **Route 11 and intermediate 198** | (5R)-5-methyl-1-(piperidin-4-yl)pyrrolidin-2-one acetate | **LCMS (Method C):** m/z 183 $(M+H)^+$ (ES+), at 0.53 min, UV active |
| **200** | **Route 11 and intermediate 198** | (5R)-5-ethyl-1-(piperidin-4-yl)pyrrolidin-2-one acetate | **LCMS (Method C):** m/z 197 $(M+H)^+$ (ES+), at 0.69 min, UV active |
| **201** | | (5R)-5-(hydroxymethyl)pyrrolidin-2-one | Commercially available, CAS: 66673-40-3 |
| **203** | **Route 11 and intermediate 201** | (5S)-5-ethyl-1-(piperidin-4-yl)pyrrolidin-2-one acetate | **LCMS (Method C):** m/z 197 $(M+H)^+$ (ES+), at 0.69 min, UV active |
| **270** | | 3,3-difluoro-4-piperidine.HCl | Commercially available CAS:496807-97-7 |
| **271** | **Route 14 and intermediates 160 and 270** | tert-butyl 3,3-difluoro-1,4'-bipiperidine-1'-carboxylate | **LCMS (Method D):** m/z 305 $(M+H)^+$ (ES+) at 1.54 min, UV inactive |
| **279** | | 3-azabicyclo[3.1.0]hexane. HCl | Commercially available CAS: 73799-64-1 |
| **280** | **Route 14 and intermediates 160 and 279** | *tert*-butyl 4-(3-azabicyclo[3.1.0]hex-3-yl)piperidine-1-carboxylate | **LCMS (Method D):** m/z 267 $(M+H)^+$ (ES+) at 2.24 min, UV inactive |

Characterising data and commercial sources for starting materials and intermediates

**Table 2**

| Intermediate | Route | Name | Data |
|---|---|---|---|
| **309** | | 1-*tert*-butyl 2-methyl (2*R*,4*R*)-4-fluoropyrrolidine-1,2-dicarboxylate | Commercially available CAS 647857-43-0 |
| **311** | **Route 14 and intermediates 160 and 309** | *tert*-butyl 4-[(2*R*,4*R*)-4-fluoro-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidine-1-carboxylate | **LCMS (Method D):** m/z 331 $(M+H)^+$ (ES+) at 1.96 min, UV inactive |

**Table 3**

| Ex. No. | Name | Intermediate | Synthetic method | $^1$H NMR | LCMS Method | LCMS data |
|---|---|---|---|---|---|---|
| 1-1 (#) | Isomer 2: ethyl 2-[4-(1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate | **2 and 5** | **a** | (400 MHz, OMSO-$d_6$) δ: 1.14 (t, J = 6.6 Hz, 3H), 1.60 - 1.86 (m, 11H), 1.95 - 2.02 (m, 2H), 2.60 - 2.66 (m, 1H), 2.76 - 2.84 (m, 2H), 3.10 - 3.28 (m, 4H), 3.98 (q, J = 6.6 Hz, 2H), 6.78 - 6.83 (m, 2H), NH not observed | **B** | m/z 333 $(M+H)^+$ (ES+), at 2.69 min, UV inactive |
| 1-2 (#) | Isomer 2: ethyl 2-[4-(4-chloro-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate | **2 and 22** | **as** | (400 MHz, $CDCl_3$) δ: 1.24 (t, J = 7.0 Hz, 3H), 1.81 - 2.23 (m, 12H), 2.77 - 2.97 (m, 2H), 2.97 - 3.15 | **C** | m/z 367/369 $(M+H)^+$ (ES+), at 1.57 min, UV active |

**Table 3**

| Ex. No. | Name | Intermediate | Synthetic method | $^1$H NMR | LCMS Method | LCMS data |
|---|---|---|---|---|---|---|
| | | | | (m, 2H), 3.28 - 3.35 (m, 2H), 3.35 - 3.46 (m, 2H), 4.11 (q, J = 7.0 Hz, 2H), 6.82 (s, 1H), NH not observed | | |
| 1-3 (#) | Isomer 2: ethyl 2-{4-[4-(trifluoromethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate | **2 and 33** | **b** | (400 MHz, OMSO-$d_6$) δ: 1.18 (t, J = 7.0 Hz, 3H), 1.60 - 1.73 (m, 2H), 1.73 - 1.93 (m, 8H), 1.97 - 2.06 (m, 2H), 2.61 - 2.73 (m, 2H), 2.78 - 2.87 (m, 2H), 3.14 - 3.20 (m, 2H), 3.26 - 3.33 (m, 2H), 4.01 (q, J = 7.0 Hz, 2H), 7.64 (s, 1H), NH not observed. | **G** | m/z 401 $(M+H)^+$ (ES+), at 5.42 min, UV active |
| 1-4 (#) | Isomer 2: ethyl 2-[4-(4-cyano-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate | **Example 1-3** | **c** | (400 MHz, OMSO-$d_6$) δ:1.17 (t, J = 7.0 Hz, 3H), 1.58 - 1.71 (m, 2H), 1.73 - 1.92 (m, 8H), 1.95 - 2.05 (m, 2H), 2.62 - | **G** | m/z 358 $(M+H)^+$ (ES+), at 4.71 min, UV active |

| Table 3 | | | | | | |
|---|---|---|---|---|---|---|
| **Ex. No.** | **Name** | **Intermediate** | **Synthetic method** | **$^1$H NMR** | **LCMS Method** | **LCMS data** |
| | | | | 2.73 (m, 2H), 2.76 - 2.87 (m, 2H), 3.13 - 3.19 (m, 2H), 3.25 - 3.32 (m, 2H), 4.00 (q, J = 7.0 Hz, 2H), 8.02 (s, 1H), 12.66 (br, 1H). | | |
| 1-6 (#) | Isomer 2: methyl 2-[4-(1-methyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate | **3 and 15** | **at** | (400 MHz, $CDCl_3$) δ: 1.81 - 2.10 (m, 11H), 2.17 - 2.53 (m, 1H), 2.57 - 2.79 (m, 2H), 2.87 - 3.05 (m, 2H), 3.19 - 3.47 (m, 4H), 3.59 (s, 3H), 3.68 (s, 3H), 6.77 (s, 1H), 6.93 (s, 1H). | **B** | m/z 333 $(M+H)^+$ (ES+), at 2.78 min, UV inactive |
| 1-7 (#) | Isomer 2: ethyl 2-[4-(1-methyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate | **1 and 6** | **d** | (300 MHz, $CDCl_3$) δ: 1.22 (t, J = 7.0 Hz, 3H), 1.76 - 2.09 (m, 12H), 2.54 - 2.78 (m, 2H), 2.92 - 2.96 (m, 2H), 3.19 - 3.29 (m, 2H), 3.37 (dt, J = 13.6, 6.6 | **B** | m/z 347 $(M+H)^+$ (ES+), at 3.07 min, UV inactive |

**Table 3**

| Ex. No. | Name | Intermediate | Synthetic method | $^1$H NMR | LCMS Method | LCMS data |
|---|---|---|---|---|---|---|
| | | | | Hz, 2H), 3.57 (s, 3H), 4.08 (q, J = 7.0 Hz, 2H), 6.74 (s, 1H), 6.90 (s, 1H) | | |
| 1-8 (#) | Isomer 2: ethyl 2-{4-[1-(ethoxycarbonyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate | **1 and 5** | **d** | (400 MHz, $CDCl_3$) δ: 1.24 (t, J = 7.5 Hz, 3H), 1.42 (t, J = 7.0 Hz, 3H), 1.74 - 2.15 (m, 12H), 2.70 - 2.76 (m, 1H), 2.93 - 2.99 (m, 2H), 3.19 - 3.49 (m, 5H), 4.11 (q, J = 7.0 Hz, 2H), 4.42 (q, J = 7.5 Hz, 2H), 6.89 (s, 1H), 7.35 (s, 1H) | **B** | m/z 405 $(M+H)^+$ (ES+), at 3.94 min, weakly UV active |
| 1-9 (#) | Isomer 2: methyl 2-[4-(1,5-dimethyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate | **3 and 34** | **b and e** | 400 MHz, DMSO-$d_6$ δ: 1.60 - 1.85 (m, 10H), 1.99 - 2.08 (m, 2H), 2.11 (d, J = 1 Hz, 3H), 2.60 - 2.71 (m, 2H), 2.79 - 2.88 (m, 2H), 3.21 - 3.28 (m, 2H), 3.28 - 3.32 (m, 2H), | **G** | m/z 347 $(M+H)^+$ (ES+), at 4.83 min, UV active |

**Table 3**

| Ex. No. | Name | Intermediate | Synthetic method | $^1$H NMR | LCMS Method | LCMS data |
|---|---|---|---|---|---|---|
| | | | | 3.41 (s, 3H), 3.58 (s, 3H), 6.49 (s, 1H) | | |
| 1-10 (#) | Isomer 2: ethyl 2-[4-(1,5-dimethyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate | **2 and 34** | **b and e** | (400 MHz, $CD_3OD$) δ: 1.22 - 1.36 (m, 3H), 1.82 - 2.10 (m, 10H), 2.12 - 2.27 (m, 2H), 2.20 (s, 3H), 2.76 - 2.97 (m, 2H), 2.99 - 3.12 (m, 2H), 3.25 - 3.47 (m, 4H), 3.53 (s, 3H), 4.12 (q, J = 7.1 Hz, 2H), 6.61 (s, 1H) | **G** | m/z 361 $(M+H)^+$ (ES+), at 5.55 min, UV active |
| 1-21 | Isomer 2: ethyl 2-[4-(1-methyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate | **2 and 9** | **a** | (400 MHz, $CDCl_3$) δ: 1.18 - 1.30 (m, 3H), 1.67 - 2.30 (m, 12H), 2.57 - 2.63 (m, 1H), 2.70 - 2.84 (m, 1H), 3.00 - 3.15 (m, 2H), 3.22 - 3.61 (m, 4H), 3.81 (s, 3H), 4.11 (q, J = 6.4 Hz, 2H), 6.04 (s, 1H), 7.37 (s, 1H) | **B** | m/z 347 $(M+H)^+$ (ES+), at 3.18 min, UV inactive |

**Table 3**

| Ex. No. | Name | Intermediate | Synthetic method | $^1$H NMR | LCMS Method | LCMS data |
|---|---|---|---|---|---|---|
| 1-32 (#) | Isomer 2: ethyl 2-[4-(1H-pyrrol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate | **2 and 11** | **a** | (400 MHz, OMSO-$d_6$) δ: 1.27 (t, J = 7.0 Hz, 3H), 1.91 - 2.06 (m, 10H), 2.13 - 2.18 (m, 2H), 2.81 - 2.87 (m, 1H), 3.00 - 3.04 (m, 2H), 3.30 - 3.43 (m, 4H), 3.95 - 4.00 (m, 1H), 4.12 (q, J = 7.0 Hz, 2H), 6.05 (s, 2H), 6.77 (t, J = 2.0 Hz, 2H) | **B** | m/z 332 $(M+H)^+$ (ES+), at 3.90 min, UV inactive |
| 1-33 (#) | Isomer 2: ethyl 2-[4-(1H-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate | **1 and 12** | **a** | (400 MHz, $CDCl_3$) δ: 1.18 (t, J = 7.0 Hz, 3H), 1.78 - 2.13 (m, 12H), 2.63 - 2.73 (m, 1H), 2.88 - 2.95 (m, 2H), 3.19 - 3.40 (m, 4H), 4.05 (q, J = 7.0 Hz, 2H), 4.09 - 4.13 (m, 1H), 6.20 (t, J = 2.0 Hz, 1H), 7.37 (d, J = 2.0 Hz, 1H), 7.44 (s, 1H) | **B** | m/z 333 $(M+H)^+$ (ES+), at 3.14 min, UV inactive |
| 2-7 | Isomer 2: ethyl 2-{4- | **54 and** | **m** | (400 MHz, | **F** | m/z 392 |

**Table 3**

| Ex. No. | Name | Intermediate | Synthetic method | $^1$H NMR | LCMS Method | LCMS data |
|---|---|---|---|---|---|---|
| (#) | [(2S)-1-propanoylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate | **127** | | DMSO-$d_6$) δ: 0.92 - 1.00 (m, 3 H), 1.12 - 1.28 (m, 6 H), 1.32 - 1.63 (m, 4 H), 1.64 - 1.90 (m, 10 H), 1.92 - 2.03 (m, 2 H), 2.19 - 2.29 (m, 2 H), 2.73 - 2.88 (m, 2 H), 3.14 (d, J = 5.5 Hz, 2 H), 3.23 - 3.30 (m, 2 H), 3.38 - 3.47 (m, 1 H), 3.74 - 3.93 (m, 1 H), 4.00 (q, J = 7.0 Hz, 2 H) | | $(M+H)^+$ (ES+), at 1.69 min, UV active |
| 2-17 (#) | Isomer 1: ethyl 2-{4-[(2S)-1-(methylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate | **57 and 127** | **m** | (400 MHz, $CD_3OD$) δ: 1.25 (t, J = 7.0 Hz, 3 H), 1.28 - 1.43 (m, 2 H), 1.49 - 1.64 (m, 2 H), 1.66 - 1.95 (m, 12 H), 2.06 - 2.15 (m, 2 H), 2.65 - 2.78 (m, 4 H), 2.93 (d, J = 11.3 Hz, 2 H), 3.21 - 3.29 (m, 2 H), 3.33 - 3.38 (m, 3 | **E** | m/z 393 $(M+H)^+$ (ES+), at 2.99 min, UV inactive |

**Table 3**

| Ex. No. | Name | Intermediate | Synthetic method | $^1$H NMR | LCMS Method | LCMS data |
|---|---|---|---|---|---|---|
| | | | | H), 3.82 - 3.89 (m, 1 H), 4.10 (q, J = 7.0 Hz, 2 H) NH not observed | | |
| 2-84 (#) | Isomer 2: ethyl 2-{4-[(2R)-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate | **2 and 159** | **aj** | (400 MHz, $CD_3OD$) δ: 1.24 (t, *J* = 7.0 Hz, 3 H), 1.42 - 1.59 (m, 2 H), 1.72 - 1.97 (m, 11 H), 2.02 - 2.17 (m, 3 H), 2.43 (t, *J* = 10.9 Hz, 1 H), 2.58 - 2.78 (m, 2 H), 2.82 - 2.92 (m, 2 H), 3.01 - 3.11 (m, 1 H), 3.25 (s, 2 H), 3.37 (q, *J* = 6.6 Hz, 2 H), 3.49 (dd, *J* = 9.4, 3.51 Hz, 1 H), 3.68 (s, 3 H), 4.08 (q, *J* = 7.0 Hz, 2 H) | **E** | m/z 394 $(M+H)^+$ (ES+), at 3.29 min, UV inactive |
| 2-107 (#) | Isomer 2: ethyl 2-{4-[(2R)-4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate | **2 and 126** | **aj** | (400 MHz, $CD_3OD$) δ: 1.18 - 1.29 (m, 3 H), 1.43 - 1.60 (m, 2 H), 1.74 - 1.97 (m, 8 H), 2.04 - 2.23 (m, 3 H), | **E** | m/z 402 $(M+H)^+$ (ES+), at 3.23 min, UV inactive |

**Table 3**

| Ex. No. | Name | Intermediate | Synthetic method | $^1$H NMR | LCMS Method | LCMS data |
|---|---|---|---|---|---|---|
| | | | | 2.24 - 2.41 (m, 1 H), 2.66 - 2.81 (m, 2 H), 2.88 - 3.11 (m, 3 H), 3.14 - 3.28 (m, 5 H), 3.38 (q, J = 6.4 Hz, 2 H), 3.44 - 3.59 (m, 2 H), 4.09 (q, J = 7.2 Hz, 2 H) | | |
| 2-116 (#) | Isomer 2: ethyl 2-{4-[(2S)-2-ethyl-5-oxopyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate | **2 and 203** | **as** | (400 MHz, $CDCl_3$) δ: 0.86 (t, *J*=7.2 Hz, 3 H), 1.22 (td, *J*=7.0, 3.5 Hz, 3 H), 1.40 - 1.51 (m, 1 H), 1.61 (d, *J*=11.7 Hz, 1 H), 1.67 - 1.91 (m, 11 H), 1.91 - 2.11 (m, 3 H), 2.19 - 2.29 (m, 1 H), 2.38 - 2.48 (m, 1 H), 2.59 - 2.68 (m, 1 H), 2.83 - 2.94 (m, 2 H), 3.18 - 3.29 (m, 2 H), 3.31 - 3.42 (m, 2 H), 3.60 (t, *J*=8.2 Hz, 1 H), 3.78 - 3.89 (m, 1 | **B** | m/z 378 $(M+H)^+$ (ES+), at 3.73 min, UV active |

**Table 3**

| Ex. No. | Name | Intermediate | Synthetic method | $^1$H NMR | LCMS Method | LCMS data |
|---|---|---|---|---|---|---|
| | | | | H), 4.08 (q, *J*=7.0 Hz, 2 H) | | |
| 2-134 (#) | Isomer 2: ethyl 2-{4-[(2R,4R)-4-fluoro-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate | **2 and 311** | **aw** | (300 MHz, DMSO-$d_6$) δ: 1.16 (t, *J*=7.1 Hz, 3 H), 1.22 - 1.42 (m, 2 H), 1.56 - 1.89 (m, 8 H), 1.89 - 2.10 (m, 3 H), 2.31 - 2.48 (m, 2 H), 2.55 - 2.68 (m, 1 H), 2.68 - 2.94 (m, 3 H), 3.07 (d, *J*=11.4 Hz, 1 H), 3.10 - 3.19 (m, 2 H), 3.19 - 3.28 (m, 2 H), 3.51 (dd, *J*=9.9, 4.3 Hz, 1 H), 3.61 (s, 3 H), 3.99 (q, *J*=7.1 Hz, 2 H), 5.02 - 5.30 (m, 1 H) | **E** | m/z 412 $(M+H)^+$ (ES+), at 3.72 min, UV active |
| 2-136 (#) | Isomer 2: ethyl 2-{4-[(2R,4R)-4-fluoro-2-(hydroxymethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate | **Example 2-134** | **ar** | (300 MHz, DMSO-$d_6$) δ: 1.16 (t, *J*=7.1 Hz, 3 H), 1.25 - 1.51 (m, 2 H), 1.56 - 1.89 (m, 8 H), 1.89 - 2.06 (m, 3 H), 2.34 - | **E** | m/z 384 $(M+H)^+$ ($ES^+$), at 3.20 min, UV inactive |

**Table 3**

| Ex. No. | Name | Intermediate | Synthetic method | $^1$H NMR | LCMS Method | LCMS data |
|---|---|---|---|---|---|---|
| | | | | 2.45 (m, 2 H), 2.58 - 2.68 (m, 2 H), 2.70 - 2.82 (m, 3 H), 2.82 - 2.94 (m, 1 H), 2.96 - 3.10 (m, 1 H), 3.11 - 3.20 (m, 3 H), 3.39 - 3.49 (m, 2 H), 3.99 (q, *J*=7.2 Hz, 2 H), 4.39 (t, *J*=5.7 Hz, 1 H), 4.95 - 5.24 (m, 1 H) | | |
| 3-4 (#) | Isomer 2: ethyl 2-[4-(3-hydroxypyridin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate | **2 and 18** | **b** | (400 MHz, $CDCl_3$) δ: 1.21 - 1.29 (m, 3H), 1.75 - 2.38 (m, 12H), 2.87 - 3.23 (m, 4H), 3.24 - 3.48 (m, 4H), 4.05 - 4.21 (m, 2H), 6.97 - 7.06 (m, 1H), 7.12 - 7.21 (m, 1H), 8.02 - 8.10 (m, 1H), OH not observed | **C** | m/z 360 $(M+H)^+$ (ES+), at 1.29 min, UV active |
| 3-10 (#) | Isomer 1: ethyl 2-[4-cyano-4-(pyridin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate | **2 and 14** | **at** | (400 MHz, $CDCl_3$) δ: 1.17 - 1.37 (m, 4H), 1.45 - 1.72 | **B** | m/z 369 $(M+H)^+$ (ES+), at 3.33 min, UV |

| Table 3 | | | | | | |
|---|---|---|---|---|---|---|
| **Ex. No.** | **Name** | **Intermediate** | **Synthetic method** | **$^1$H NMR** | **LCMS Method** | **LCMS data** |
| | | | | (m, 2H), 1.75 - 2.02 (m, 3H), 2.06 - 2.51 (m, 7H), 2.72 - 3.15 (m, 2H), 3.26 - 3.48 (m, 4H), 4.06 - 4.22 (m, 2H), 7.21 - 7.32 (m, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.74 (dd, J = 7.2 + 7.2 Hz, 1H), 8.56 - 8.68 (m, 1H). | | active |
| 4-13 (#) | Isomer 2: ethyl 2-(3,3-difluoro-1,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate | **2 and 280** | **aw** | (300 MHz, DMSO-$d_6$) δ: 1.16 (t, *J*=7.1 Hz, 3 H), 1.29 - 1.48 (m, 2 H), 1.57 - 1.91 (m, 9 H), 1.92 - 2.00 (m, 2 H), 2.37 - 2.49 (m, 4 H), 2.53 - 2.71 (m, 5 H), 2.74 - 2.86 (m, 2 H), 3.06 - 3.22 (m, 4 H), 3.99 (q, *J*=7.0 Hz, 2 H) | **E** | m/z 386 $(M+H)^+$ $(ES^+)$, at 3.64 min, UV inactive |

**BIOLOGICAL ACTIVITY**

**EXAMPLE A**

**Phospho-ERK1/2 assays**

**[0200]** Functional assays were performed using the Alphascreen Surefire phospho-ERK1/2 assay (Crouch & Osmond, Comb. Chem. High Throughput Screen, 2008). ERK1/2 phosphorylation is a downstream consequence of both Gq/11 and Gi/o protein coupled receptor activation, making it highly suitable for the assessment of $M_1$, $M_3$ (Gq/11 coupled) and $M_2$, $M_4$ receptors (Gi/o coupled), rather than using different assay formats for different receptor subtypes. CHO cells stably expressing the human muscarinic $M_1$, $M_2$, $M_3$ or $M_4$ receptor were plated (25K / well) onto 96-well tissue culture plates in MEM-alpha + 10% dialysed FBS. Once adhered, cells were serum-starved overnight. Agonist stimulation was performed by the addition of 5 µL agonist to the cells for 5 min (37 °C). Media was removed and 50 µL of lysis buffer added. After 15 min, a 4 µL sample was transferred to 384-well plate and 7 µL of detection mixture added. Plates were incubated for 2 h with gentle agitation in the dark and then read on a PHERAstar plate reader.

**[0201]** $pEC_{50}$ and $E_{max}$ figures were calculated from the resulting data for each receptor subtype.

**[0202]** The results are set out in Table 4 below.

**[0203]** For each example two diastereomers exist which have been separated, unless stated otherwise, and assigned based on their retention time on LCMS analytical trace. In most examples, isomer 1 is not active. Analytical data for active isomers is reported in Table 3. Data for several weakly active compounds are included in Table 4 to highlight preference of absolute stereochemistry.

**Table 4**

| | **Muscarinic Activity** | | | |
|---|---|---|---|---|
| **Ex.No.** | **$pEC_{50}$ $M_1$ (% Emax cf. ACh)** | **$pEC_{50}$ $M_2$ (% Emax cf. ACh)** | **$pEC_{50}$ $M_3$ (% Emax cf. ACh)** | **$pEC_{50}$ $M_4$ (% Emax cf. ACh)** |
| ACh | 8.3 (102) | 7.8 (105) | 8.1 (115) | 8.1 (110) |
| 1-1 Isomer 2 (#) | 7.2 (121) | <4.7 (20) | <4.7 (26) | 8.1 (112) |
| 1-2 Isomer 2 (#) | 6.6 (93) | <4.7 (6) | <4.7 (4) | 7.6 (100) |
| 1-3 Isomer 2 (#) | 6.3 (30) | NT | NT | 6.7 (41) |

| Table 4 | | | | |
|---|---|---|---|---|
| | Muscarinic Activity | | | |
| Ex.No. | $pEC_{50}$ $M_1$ (% Emax cf. ACh) | $pEC_{50}$ $M_2$ (% Emax cf. ACh) | $pEC_{50}$ $M_3$ (% Emax cf. ACh) | $pEC_{50}$ $M_4$ (% Emax cf. ACh) |
| 1-4 Isomer 2 (#) | 6.0 (55) | NT | NT | 6.6 (67) |
| 1-6 Isomer 2 (#) | 5.9 (128) | <4.7 (57) | *7.2 (38) | 7.2 (71) |
| 1-7 Isomer 2 (#) | 6.8 (97) | <4.7 (15) | <4.7 (22) | 7.6 (97) |
| 1-8 Isomer 2 (#) | 6.5 (76) | <4.7 (34) | <4.7 (0) | 7.8 (98) |
| 1-9 Isomer 2 (#) | <4.7 (57) | NT | NT | 6.1 (48) |
| 1-10 Isomer 2 (#) | 5.3 (62) | NT | NT | 6.6 (106) |
| 1-21 Isomer 2 | <4.7 (11) | <4.7 (8) | <4.7 (0) | 7.4 (79) |
| 1-32 Isomer 2 (#) | 7.1 (113) | <4.7 (56) | <4.7 (16) | 8.2 (126) |
| 1-33 Isomer 2 (#) | 7.6 (11) | 4.7 (49) | <4.7 (7) | 8.4 (118) |
| 2-7 Isomer 2 (#) | 6.1 (41) | <4.7 (13) | *5.1 (27) | 7.9 (100) |
| 2-17 Isomer 2 (#) | 6.7 (72) | <4.7 (5) | <4.7 (4) | 8.5 (116) |
| 2-84 Isomer 2 (#) | 6.6 (36) | <4.7 | <4.7 | 7.7 (82) |
| 2-107 Isomer 2 (#) | 7.2 (87) | <4.7 (5) | <4.7 (46) | 8.2 (92) |
| 2-116 Isomer 2 (#) | 7.2 (109) | NT | NT | 8.2 (103) |
| 2-134 Isomer 2 (#) | <4.7 (18) | NT | NT | 7.2 (95) |
| 2-136 | 6.2 (105) | NT | NT | 7.9(110) |

| Table 4 | | | | |
|---|---|---|---|---|
| | Muscarinic Activity | | | |
| Ex.No. | $pEC_{50}$ $M_1$ (% Emax cf. ACh) | $pEC_{50}$ $M_2$ (% Emax cf. ACh) | $pEC_{50}$ $M_3$ (% Emax cf. ACh) | $pEC_{50}$ $M_4$ (% Emax cf. ACh) |
| Isomer 2 (#) | | | | |
| 3-10 Isomer 1 (#) | 5.9 (42) | <4.7 (3) | <4.7 (5) | 7.1 (71) |
| 3-10 Isomer 2 (#) | 8.0 (90) | 7.0 (96) | <4.7 (0) | 8.9 (103) |
| 4-13 Isomer 2 (#) | 6.2 (51) | <4.7 (10) | <4.7 (13) | 7.0 (59) |
| (#) - reference example, * - variable results, NT - Not tested | | | | |

**EXAMPLE B**

**Passive avoidance**

**[0204]** Studies were carried out as described previously by Foley et al., (2004) Neuropsychopharmacology. In the passive avoidance task scopolamine administration (1 mg/kg, i.p.) at 6 hours following training rendered animals amnesic of the paradigm. A dose range of 3, 10, and 30 mg/kg (po) free base, administered 90 minutes prior to the training period via oral gavage, was examined.

**[0205]** Reference Example 1-33 Isomer 2 was found to reverse scopolamine-induced amnesia of the paradigm in a dose-dependent manner, with an approximate $ED_{50}$ of ca. 10 mg/kg (po). The effect of 30 mg/kg was similar to that produced by the cholinesterase inhibitor donepezil (0.1 mg/kg, ip) which served as a positive control (Figure 1).

**EXAMPLE C**

**Effect of a novel test compound and xanomeline on d-amphetamine-induced hyperactivity in rats**

**[0206]** The aim of the study is to examine the effect of a novel test compound on d-amphetamine induced hyperactivity in rats. Schizophrenia is a complex multifactorial disease that cannot be fully represented by a single experimental procedure. Antipsychotic-like behaviour was assessed in rats by the inhibition of hyperactivity (or hyperlocomotion) elicited by d-amphetamine. This procedure is sensitive to clinically relevant dopamine receptor antagonists and is therefore considered suitable for comparing muscarinic agonists that influence dopaminergic signalling. A dose of xanomeline previously observed to significantly reduce d-amphetamine induced hyperactivity was employed as a positive control. Statistical analysis typically involved three-way analysis of covariance or robust regression with treatment, day and rack as factors and activity during the 30 minutes prior to treatment as a covariate, followed by appropriate multiple comparison tests. A P value of $<0.05$ was considered statistically significant and is marked accordingly in all subsequent figures.

**[0207]** Data for Example 1-21 Isomer 2, and Reference Examples 1-32 Isomer 2, 1-33 Isomer 2, 2-7 Isomer 2 and 2-17 Isomer 2 is shown in Figure 2.

**EXAMPLE D**

**PHARMACEUTICAL FORMULATIONS**

**(i) Tablet Formulation**

**[0208]** A tablet composition containing a compound described herein is prepared by mixing 50 mg of the compound with 197 mg of lactose (BP) as diluent, and 3 mg magnesium stearate as a lubricant and compressing to form a tablet in known manner.

**(ii) Capsule Formulation**

**[0209]** A capsule formulation is prepared by mixing 100 mg of a compound described herein with 100 mg lactose and optionally 1% by weight of magnesium stearate and filling the resulting mixture into standard opaque hard gelatin capsules.

# REFERENCES CITED IN THE DESCRIPTION

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## Patentkrav

**1.** Forbindelse, som er ethyl-2-[4-(1-methyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octan-6-carboxylat eller et salt deraf.

**2.** Farmaceutisk acceptabelt salt af en forbindelse ifølge krav 1.

**3.** Syreadditionssalt af en forbindelse ifølge krav 1.

**4.** Syreadditionssalt ifølge krav 3, hvor syren er citronsyre, fumarsyre eller saltsyre.

**5.** Farmaceutisk sammensætning omfattende en forbindelse eller et salt som defineret i et hvilket som helst af kravene 1 til 4 og en farmaceutisk acceptabel excipiens.

**6.** Forbindelse eller salt ifølge et hvilket som helst af kravene 1 til 4 til anvendelse i behandlingen af Alzheimers sygdom.

**7.** Forbindelse eller salt ifølge et hvilket som helst af kravene 1 til 4 til anvendelse i behandlingen af skizofreni.

**8.** Forbindelse eller salt ifølge et hvilket som helst af kravene 1 til 4 til anvendelse i behandlingen af en bipolar lidelse.

**9.** Forbindelse eller salt ifølge et hvilket som helst af kravene 1 til 4 til anvendelse i behandlingen af demens.

**10.** Forbindelse eller salt ifølge et hvilket som helst af kravene 1 til 4 til anvendelse i behandlingen af demens med Lewy-legemer.

# DRAWINGS

Drawing

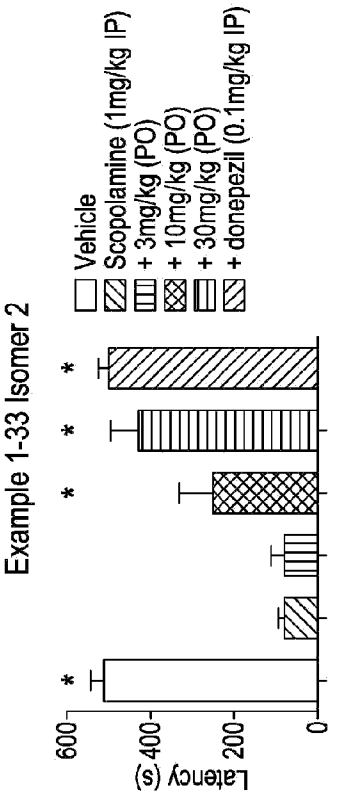


Fig. 1

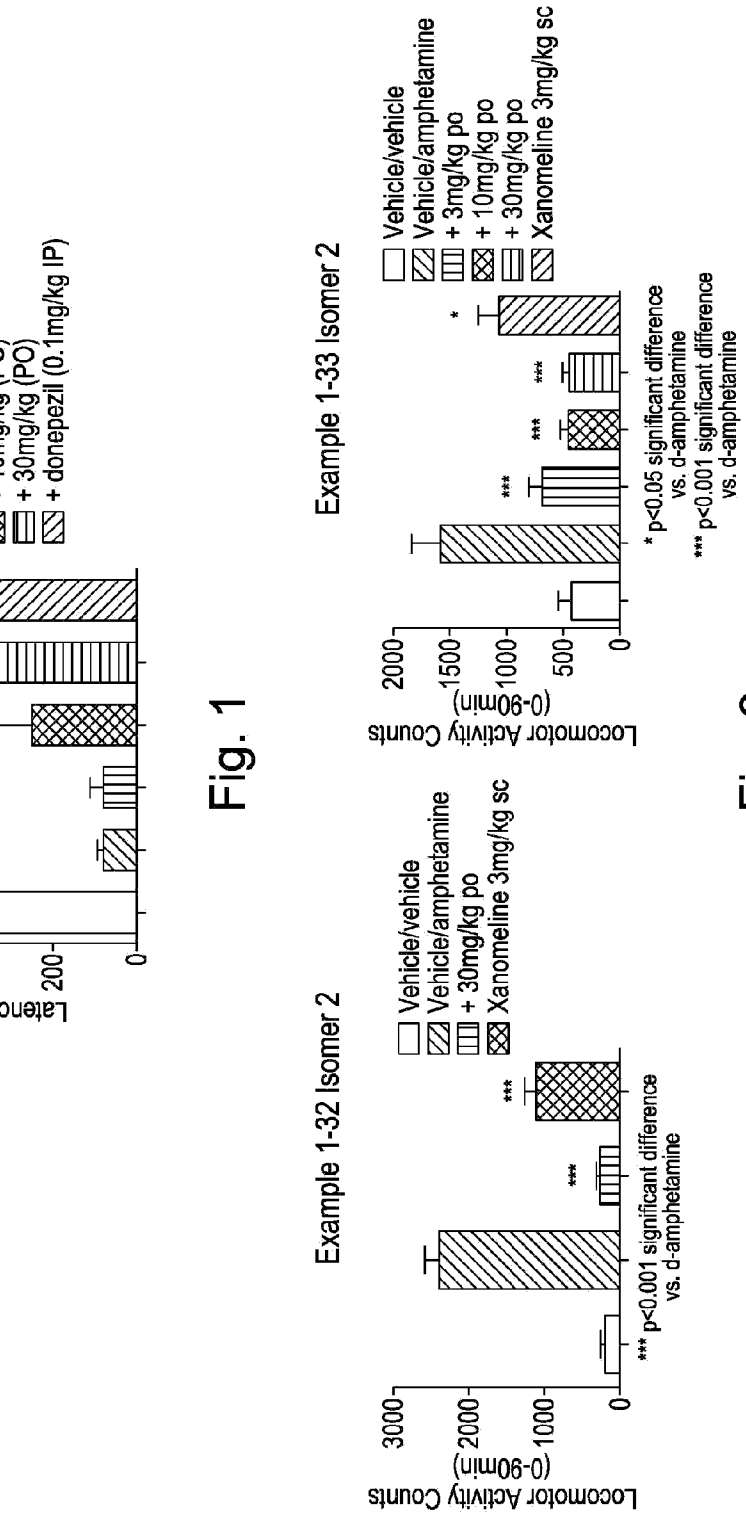


Fig. 2

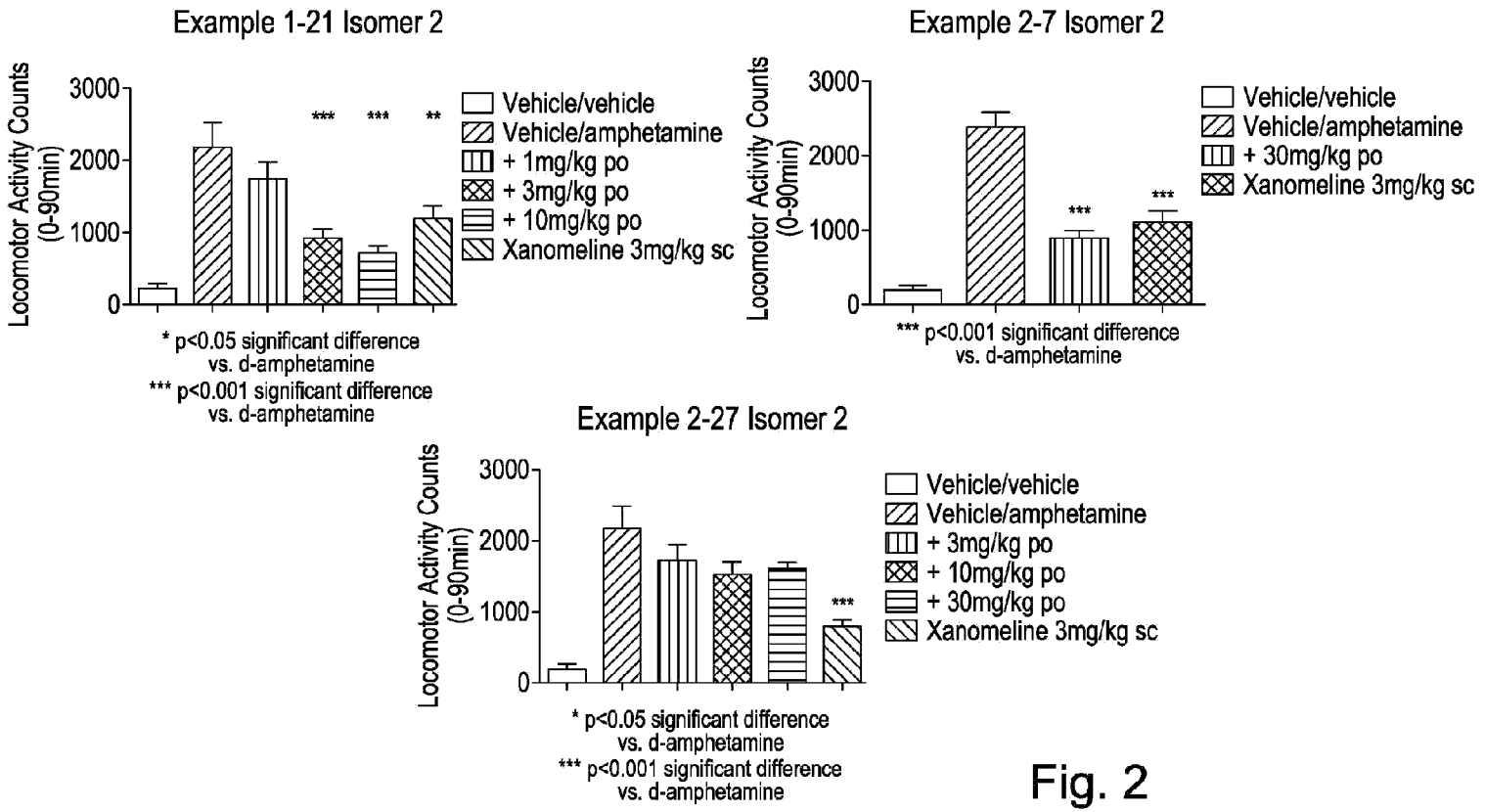


Fig. 2
(continued)