BICYCLIC AZA COMPOUNDS AS MUSCARINIC M1 RECEPTOR AGONISTS.

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

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*).

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).

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.

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*).

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.

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.

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.

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.

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

Description of the figures can be found in experimental sections B and C.

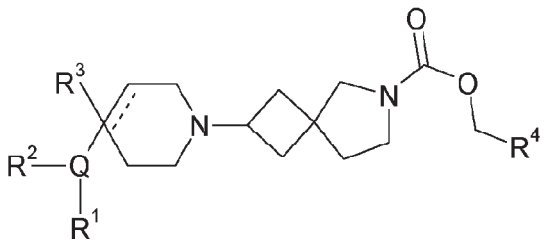
Figure 1 shows that Example 1-33 Isomer 2 was found to reverse scopolamine-induced amnesia in a dose-dependent manner, with an approximate ED_{50} of ca. 10 mg/kg (po). The effect of 30 mg/kg was similar to that produced by the cholinesterase inhibitor donepezil (0.1 mg/kg, ip) which served as a positive 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 Examples 1-21 Isomer 2, 1-32 Isomer 2, 1-33 Isomer 2, 2-7 Isomer 2 and 2-17 Isomer 2 is shown.

The Invention

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.

Accordingly, in one embodiment (Embodiment 1.1), the invention provides a compound 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^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 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_{1-6} 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;

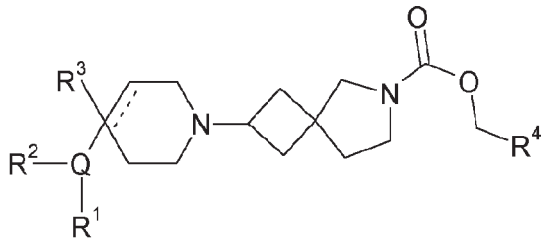
R^5, R^6 and R^7 are the same or different and each is independently selected from hydrogen, a non-aromatic C_{1-4} hydrocarbon group optionally substituted with one or more fluorine atoms; or a group of formula $CH_2N(R^a)COOR^b$;

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.

Accordingly, in one embodiment (Embodiment 1.1a), the invention provides a compound of the formula (1a):



(1a)

or a salt thereof, wherein

Q is a five or six or seven 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^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 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;

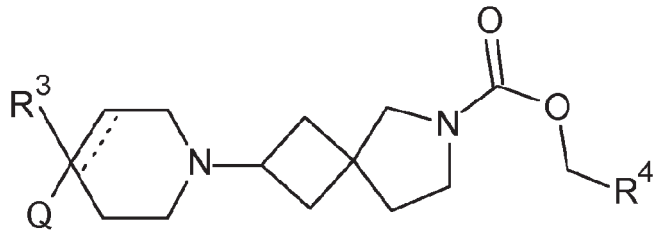
R^5, R^6 and R^7 are the same or different and each is independently selected from hydrogen, a non-aromatic C_{1-4} hydrocarbon group optionally substituted with one or more fluorine atoms; or a group of formula $CH_2N(R^a)COOR^b$;

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.

Accordingly, in one embodiment (Embodiment 1.1b), the invention provides a compound of the formula (1b):



(1b)

or a salt thereof, wherein

Q is an optionally substituted five or six or seven membered heterocyclic ring containing 1, 2, 3 or 4 heteroatom ring members selected from N, O and S;

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;

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.

Particular compounds of the formula (1), (1a) or (1b) are as defined in the Embodiments 1.2 to 1.180 set out below.

1.2 A compound according to Embodiment 1.1 wherein Q is an aromatic or unsaturated heterocyclic ring.

1.3 A compound according to Embodiment 1.2 wherein Q is an aromatic heterocyclic ring.

1.4 A compound according to Embodiment 1.3 wherein Q is an aromatic heterocyclic ring containing a nitrogen ring member and optionally one or two further ring members selected from O, N and S.

1.5 A compound according to Embodiment 1.4 wherein Q is an aromatic heterocyclic ring containing a nitrogen ring member and optionally one further ring member selected from O, N and S.

1.6 A compound according to Embodiment 1.5 wherein Q is an aromatic heterocyclic ring containing one or two nitrogen ring members.

1.7 A compound according to any one of Embodiments 1.1 to 1.6 wherein Q is a five membered heterocyclic ring linked to the adjacent six-membered ring by a carbon atom of the said five membered heterocyclic ring.

1.8 A compound according to any one of Embodiments 1.1 to 1.6 wherein Q is a five membered heterocyclic ring linked to the adjacent six-membered ring by a nitrogen atom of the said five membered heterocylic ring.

1.9 A compound according to Embodiment 1.1 wherein Q is selected from 1-pyrrolyl, 2-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 5-pyrazolyl, 2-thiazolyl, 2-oxazolyl, triazolyl, tetrazolyl, thiadiazolyl, oxadiazolyl, and tautomeric forms thereof.

1.10 A compound according to Embodiment 1.6 wherein Q is a pyrrole ring.

1.11 A compound according to Embodiment 1. 6 wherein Q is an imidazole ring

1.12 A compound according to Embodiment 1. 6 wherein Q is a pyrazole ring.

1.13 A compound according to Embodiment 1. 6 wherein Q is selected from 1-pyrazolyl, 3-pyrazolyl, 5-pyrazolyl and tautomeric forms thereof.

1.14 A compound according to Embodiment 1.1 wherein Q is a 6 membered ring containing one or more nitrogen atoms.

1.15 A compound according to Embodiment 1.14 wherein Q is pyridyl, pyrazyl or a 2-oxo-3N (3-piperidin-2-one) ring contining 0-2 C-C unsaturated bonds.

1.16 A compound according to Embodiment 1.1 wherein Q is a 5, 6 or 7 membered unsaturated heterocyclic ring.

1.17 A compound according to Embodiment 1.16 wherein Q is 5-pyrollidinyl.

1.18 A compound according to Embodiment 1.1 wherein Q is bicyclic; having a further ring attached to Q.

1.19 A compound according to Embodiment 1.1b wherein Q has one or more substituents, for example one, two or three substituents, which may be selected from one R^1 and/or R^2 wherein R^1 and R^2 may be the same or different. Further substituents for Q may include (L)-R^{10}, (L)-R^{11} and (L)-R^{12}, where L is a bond or a CH_2 group; R^{10}, R^{11} and R^{12} are independently selected from hydrogen; fluorine; chlorine; bromine; cyano; oxo; hydroxy; OR^{15}; $NR^{15}R^{16}$; COR^{15}; CSR^{15}; $COOR^{15}$; $COSR^{15}$; $OCOR^{15}$; $NR^{17}COR^{15}$; $CONR^{15}R^{16}$; $CSNR^{15}R^{16}$; $NR^{17}CONR^{15}R^{16}$; $R^{17}COOR^{15}$; $OCONR^{15}R^{16}$; SR^{15}; SOR^{15} and SO_2R^{15}; 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;

wherein the optional substituents for the optionally substituted 5- or 6-membered ring are selected from a group R^8 consisting of hydrogen; fluorine; chlorine; bromine; cyano; oxo; hydroxy; 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; and 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;

wherein R^{15}, R^{16} and R^{17} are the same or different, or may be joined together to form a ring, and each is independently selected from hydrogen, a non-aromatic C_{1-6} hydrocarbon group optionally substituted with one or more 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; or a group of formula $CH_2N(R^a)COOR^b$; or a group of formula (L)-R^{18} where L is a bond or a CH_2 group and R^{18} is 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;

wherein the optional substituents for the optionally substituted 5- or 6-membered ring are selected from a group R^8.

1.20 A compound according to any one of Embodiments 1.1 to 1.19 wherein R^1 is selected from hydrogen; fluorine; chlorine; bromine; cyano; oxo; hydroxy; 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 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;

wherein the optional substituents for the optionally substituted 5- or 6-membered ring are selected from a group R^8 consisting of hydrogen; fluorine; chlorine; bromine; cyano; oxo; hydroxy; 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; and 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.

1.21 A compound according to Embodiment 1.20 wherein R^1 is selected from hydrogen; fluorine; chlorine; bromine; cyano; oxo; hydroxy; 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_{1-5} 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 or 2 heteroatoms selected from O, N and S and oxidized forms thereof;

wherein the optional substituents for the optionally substituted 5- or 6-membered ring are selected from a group R^8 consisting of fluorine; chlorine; bromine; cyano; oxo; hydroxy; 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; and a C_{1-4} 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.

1.22 A compound according to Embodiment 1.21 wherein R^1 is selected from hydrogen; fluorine; chlorine; bromine; cyano; oxo; hydroxy; 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_{1-4} 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 aryl or heteroaryl ring containing 0, 1 or 2 heteroatoms selected from O, N and S and oxidized forms thereof;

wherein the optional substituents for the optionally substituted 5- or 6-membered aryl or heteroaryl ring are selected from a group R^8 consisting of fluorine; chlorine; bromine; cyano; oxo; hydroxy; 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; and a C_{1-4} 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.

1.23 A compound according to any one of Embodiments 1.1 to 1.19 wherein R^1 is selected from hydrogen; fluorine; chlorine; cyano; oxo; hydroxy; OR^5; NR^5R^6; COR^5; $COOR^5$; $OCOR^5$; NR^7COR^5; $CONR^5R^6$; $NR^7CONR^5R^6$; NR^7COOR^5; $OCONR^5R^6$; SO_2R^5; a C_{1-4} 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, wherein the optional substituents for the optionally substituted 5- or 6-membered ring are selected from a group R^8 consisting of fluorine; chlorine; bromine; cyano; oxo; hydroxy; 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; and a C_{1-4} 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.

1.24 A compound according to Embodiment 1.23 wherein R^1 is selected from hydrogen; fluorine; chlorine; cyano; hydroxy; OR^5; NR^5R^6; COR^5; $COOR^5$; $OCOR^5$; NR^7COR^5; $CONR^5R^6$; $NR^7CONR^5R^6$; NR^7COOR^5; $OCONR^5R^6$; SO_2R^5; and a C_{1-4} 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.

1.25 A compound according to Embodiment 1.24 wherein R^1 is selected from hydrogen; fluorine; chlorine; cyano; hydroxy; OR^5; NR^5R^6; COR^5; $COOR^5$; $OCOR^5$; NR^7COR^5; $CONR^5R^6$; $NR^7CONR^5R^6$; NR^7COOR^5; SO_2R^5; and a C_{1-4} non-aromatic hydrocarbon group which is optionally substituted with one to six fluorine atoms.

1.26 A compound according to Embodiment 1.25 wherein R^1 is selected from hydrogen; fluorine; chlorine; cyano; NR^5R^6; COR^5; $COOR^5$ and a C_{1-6} non-aromatic hydrocarbon group which is optionally substituted with one to six fluorine atoms.

1.27 A compound according to Embodiment 1.26 wherein R^1 is selected from hydrogen; fluorine; chlorine; cyano; NH_2, COR^5; $COOR^5$ and a C_{1-4} saturated non-aromatic hydrocarbon group which is optionally substituted with one to six fluorine atoms.

1.28 A compound according to Embodiment 1.27 wherein R^1 is selected from hydrogen; COR^5; $COOR^5$; $CONR^5R^6$ and a C_{1-4} alkyl group.

1.29 A compound according to Embodiment 1.28 wherein R^1 is selected from hydrogen; COR^5; $COOR^5$ and a C_{1-3} alkyl group.

1.30 A compound according to Embodiment 1.29 wherein R^1 is selected from hydrogen; methyl; ethyl and $COOR^5$.

1.31 A compound according to Embodiment 1.30 wherein R^1 is hydrogen.

1.32 A compound according to Embodiment 1.30 wherein R^1 is methyl or ethyl.

1.33 A compound according to Embodiment 1.20 to 1.30 wherein R^1 is COOMe; COOEt; COMe; COEt; $CONH_2$; CF_3; CONHMe; $CON(Me)_2$; $COCF_3$; CO-cyclopropyl; CO-cyclobutyl; CONHEt; COH; NH_2; OMe;

1.34 A compound according to any one of the Embodiments 1.1 to 1.33 wherein R^2 is selected from hydrogen; fluorine; chlorine; bromine; cyano; hydroxy; methoxy; and a C_{1-6} non-aromatic hydrocarbon group; or is joined together with R^1 to form a 6 membered fused aromatic ring.

1.35 A compound according to Embodiment 1.34 wherein R^2 is selected from hydrogen; fluorine; hydroxy; methoxy; and a C_{1-6} non-aromatic hydrocarbon group.

1.36 A compound according to Embodiment 1.35 wherein R^2 is selected from hydrogen; fluorine; methoxy; and a C_{1-4} saturated hydrocarbon group.

1.37 A compound according to Embodiment 1.36 wherein R^2 is selected from hydrogen; fluorine; methoxy; and a C_{1-4} alkyl group.

1.38 A compound according to Embodiment 1.37 wherein R^2 is selected from hydrogen and a C_{1-3} alkyl group.

1.39 A compound according to Embodiment 1.38 wherein R^2 is selected from hydrogen and methyl.

1.40 A compound according to Embodiment 1.34 wherein R^2 is joined together with R^1 to form a 6 membered fused aromatic ring which may be aryl or heteroaryl.

1.41 A compound according to any one of Embodiments 1.1 to 1.40 wherein the dotted line represents a second carbon-carbon bond and R^3 is absent.

1.42 A compound according to any one of Embodiments 1.1 to 1.40 wherein R^3 is present and the optional second carbon-carbon bond is absent.

1.43 A compound according to Embodiment 1.42 wherein R^3 is selected from hydrogen; fluorine; cyano; hydroxy; amino; and 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.

1.44 A compound according to Embodiment 1.43 wherein R^3 is selected from hydrogen; fluorine; cyano; hydroxy; amino; and a C_{1-6} non-aromatic hydrocarbon group which is optionally substituted with one to six fluorine atoms and wherein one, 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.

1.45 A compound according to Embodiment 1.44 wherein R^3 is selected from hydrogen; fluorine; cyano; hydroxy; amino; C_{1-4} alkyl and C_{1-4} alkoxy, wherein the C_{1-4} alkyl and C_{1-4} alkoxy are each optionally substituted with one to six fluorine atoms.

1.46 A compound according to Embodiment 1.45 wherein R^3 is selected from hydrogen; fluorine; hydroxy and methoxy.

1.47 A compound according to Embodiment 1.46 wherein R^3 is hydrogen.

1.48 A compound according to any one of Embodiments 1.1 to 1.47 wherein R^4 is hydrogen or an acyclic C_{1-6} hydrocarbon group.

1.49 A compound according to Embodiment 1.48 wherein R^4 is hydrogen or an acyclic C_{1-3} hydrocarbon group.

1.50 A compound according to Embodiment 1.49 wherein R^4 is hydrogen or a C_{1-3} alkyl group or a C_{2-3} alkynyl group.

1.51 A compound according to Embodiment 1.50 wherein R^4 is selected from hydrogen, methyl, ethyl, ethynyl and 1-propynyl.

1.52 A compound according to Embodiment 1.51 wherein R^4 is selected from hydrogen and methyl.

1.53 A compound according to Embodiment 1.52 wherein R^4 is methyl.

1.54 A compound according to any one of the preceding Embodiments wherein R^5, when present, is a non-aromatic C_{1-4} hydrocarbon group optionally substituted with one or more fluorine atoms; or a group of formula $CH_2N(R^a)COOR^b$.

1.55 A compound according to Embodiment 1.54 wherein the non-aromatic C_{1-4} hydrocarbon group is a saturated C_{1-4} hydrocarbon group.

1.56 A compound according to any one of Embodiments 1.1 to 1.53 wherein R^5, when present, is hydrogen.

1.57 A compound according to any one of Embodiments 1.1 to 1.53 wherein R^5, when present, is selected from hydrogen and a saturated C_{1-4} hydrocarbon group.

1.58 A compound according to Embodiment 1.55 or Embodiment 1.56 wherein the saturated C_{1-4} hydrocarbon group is a C_{1-4} alkyl group.

1.59 A compound according to Embodiment 1.58 wherein the saturated C_{1-4} hydrocarbon group is a C_{1-3} alkyl group.

1.60 A compound according to Embodiment 1.59 wherein the C_{1-3} alkyl group is selected from methyl, ethyl and isopropyl.

1.61 A compound according to Embodiment 1.60 wherein the C_{1-3} alkyl group is ethyl.

1.62 A compound according to any one of the preceding Embodiments wherein R^6, when present, is a non-aromatic C_{1-4} hydrocarbon group.

1.63 A compound according to Embodiment 1.62 wherein the non-aromatic C_{1-4} hydrocarbon group is a saturated C_{1-4} hydrocarbon group.

1.64 A compound according to any one of Embodiments 1.1 to 1.61 wherein R^6, when present, is hydrogen.

1.65 A compound according to Embodiment 1.63 wherein the saturated C_{1-4} hydrocarbon group is a C_{1-3} alkyl group.

1.66 A compound according to Embodiment 1.65 wherein the C_{1-3} alkyl group is selected from methyl, ethyl and isopropyl.

1.67 A compound according to any one of the preceding Embodiments wherein R^7, when present, is a non-aromatic C_{1-4} hydrocarbon group.

1.68 A compound according to Embodiment 1.67 wherein the non-aromatic C_{1-4} hydrocarbon group is a saturated C_{1-4} hydrocarbon group.

1.69 A compound according to any one of Embodiments 1.1 to 1.66 wherein R^7, when present, is hydrogen.

1.70 A compound according to any one of Embodiments 1.1 to 1.66 wherein R^7, when present, is selected from hydrogen and a saturated C_{1-4} hydrocarbon group.

1.71 A compound according to Embodiment 1.68 or Embodiment 1.70 wherein the saturated C_{1-4} hydrocarbon group is a C_{1-4} alkyl group.

1.72 A compound according to Embodiment 1.71 wherein the saturated C_{1-4} hydrocarbon group is a C_{1-3} alkyl group.

1.73 A compound according to Embodiment 1.72 wherein the C_{1-3} alkyl group is selected from methyl, ethyl and isopropyl.

1.74 A compound according to any one of the preceding Embodiments wherein, when R^1 is an optionally substituted 5- or 6-membered ring, it is selected from aromatic rings containing 0, 1 or 2 or 3 heteroatoms selected from O, N and S and oxidized forms thereof.

1.75 A compound according to Embodiment 1.74 wherein the aromatic ring is carbocyclic.

1.76 A compound according to Embodiment 1.74 wherein the aromatic ring is heterocyclic.

1.77 A compound according to any one of Embodiments 1.1 to 1.73 wherein, when R^1 is an optionally substituted 5- or 6-membered ring, it is selected from non-aromatic rings containing 0, 1 or 2 or 3 heteroatoms selected from O, N and S and oxidized forms thereof.

1.78 A compound according to Embodiment 1.77 wherein the non-aromatic ring is carbocyclic.

1.79 A compound according to Embodiment 1.77 wherein the non-aromatic ring is heterocyclic.

1.80 A compound according to any one of Embodiments 1.74 to 1.79 wherein the ring is a 5-membered ring.

1.81 A compound according to any one of Embodiments 1.74 to 1.79 wherein the ring is a 6-membered ring.

1.82 A compound according to any one of the preceding Embodiments wherein, when R^1 is an optionally substituted 5- or 6-membered ring, it is substituted with 0, 1, 2 or 3 substituents R^8.

1.83 A compound according to Embodiment 1.82 wherein there are 0, 1 or 2 substituents R^8 present.

1.84 A compound according to Embodiment 1.83 wherein there are 0 substituents R^8 present.

1.85 A compound according to Embodiment 1.82 wherein there is 1 substituent R^8 present.

1.86 A compound according to Embodiment 1.82 wherein there are 2 substituents R^8 present.

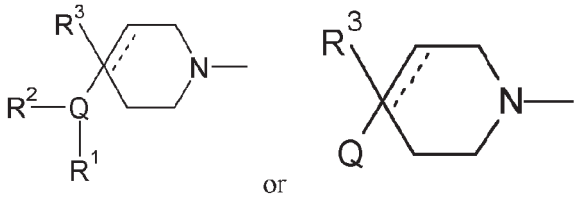
1.87 A compound according to any one of Embodiments 1.81, 1.82, 1.83, 1.85 and 1.86 wherein R^8 when present is selected from fluorine; cyano; oxo; hydroxy; OR^5; NR^5R^6; COR^5; $COOR^5$; $OCOR^5$; NR^7COR^5; $CONR^5R^6$; SR^5; SOR^5 and SO_2R^5; and a C_{1-6} non-aromatic hydrocarbon group which is 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.

1.88 A compound according to Embodiment 1.87 wherein R^8 is selected from fluorine; cyano; oxo; hydroxy; OR^5; NR^5R^6; COR^5; $COOR^5$; $OCOR^5$ and SO_2R^5; and a C_{1-4} 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.

1.89 A compound according to Embodiment 1.88 wherein R^8 is selected from fluorine; cyano; oxo; hydroxy; OR^5; NR^5R^6; and a C_{1-4} non-aromatic hydrocarbon group which is optionally substituted with one to six fluorine atoms.

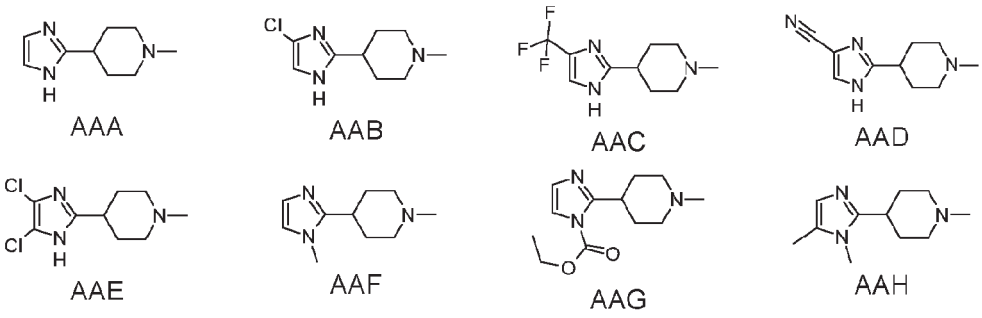
1.90 A compound according to Embodiment 1.89 wherein R^8 is selected from cyano; oxo; hydroxy; OR^5; NR^5R^6; and C_{1-4} alkyl.

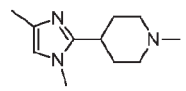
1.91 A compound according to any one of Embodiments 1.1 to 1.40 and 1.42 to 1.53 wherein the moiety:

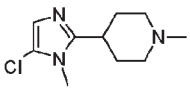


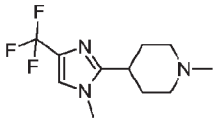
or

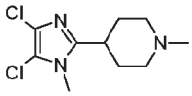
is selected from groups AAA to ACB below:

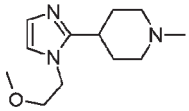


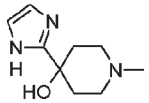

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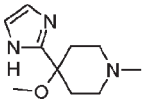

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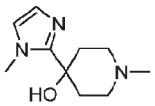

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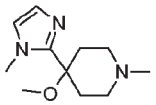

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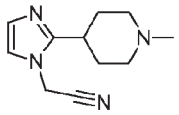

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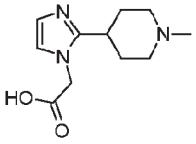

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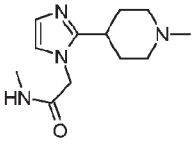

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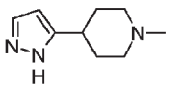

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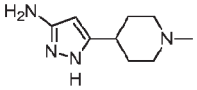

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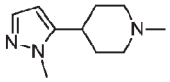

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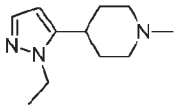

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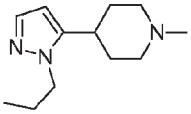

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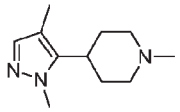

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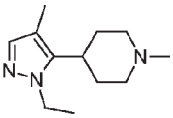

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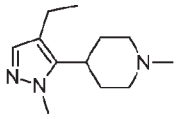

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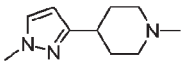

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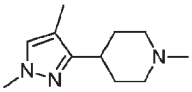

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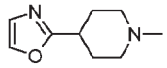

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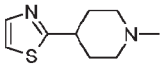

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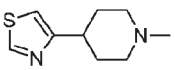

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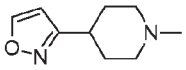

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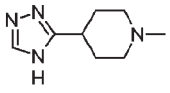

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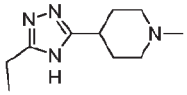

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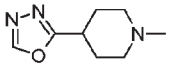

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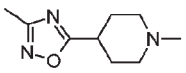

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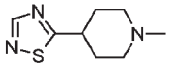

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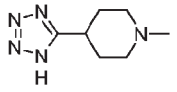

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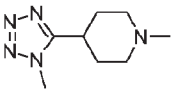

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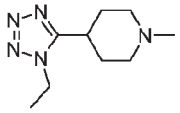

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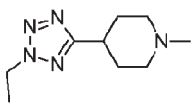

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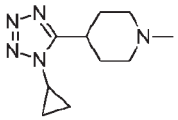

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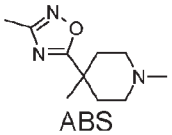

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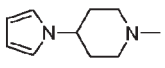

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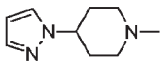

ABP

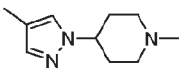

ABQ


ABR


ABS


ABT


ABU

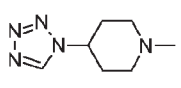

ABV

ABW

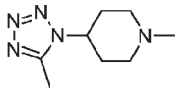
ABX

ABY

ABZ

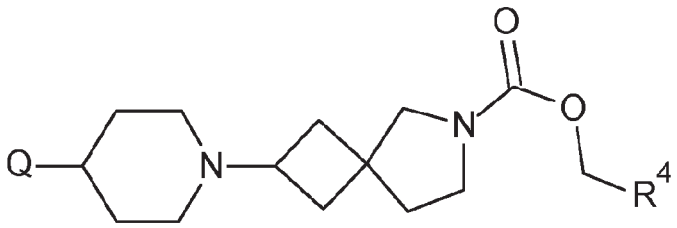


ACA



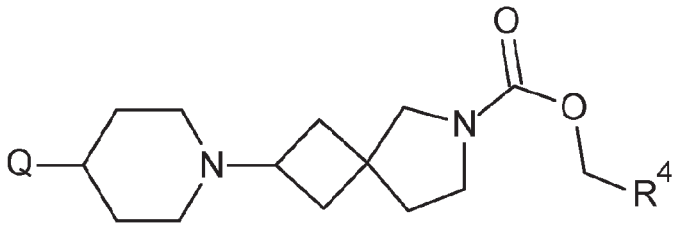
ACB

1.92 A compound according to having the formula (2) or formula 2a:



(2)

wherein Q is an optionally substituted 5 or 6 membered heterocyclic or heteraryl ring have one or more nitrogen atoms, and R^4 is as defined in any one of Embodiments 1.48 to 1.53; or



(2a)

wherein Q is an optionally substituted 5, 6 or 7 membered heterocyclic or heteraryl ring have one or more nitrogen atoms, and R^4 is as defined in any one of Embodiments 1.48 to 1.53.

1.93 A compound according to formula (2) or formula (2a) wherein Q has one or more substituents, for example one, two or three substituents which are selected from (L)-R^{10}, (L)-R^{11} and (L)-R^{12}, where L is a bond or a CH_2 group; R^{10}, R^{11} and R^{12} are independently selected from hydrogen; fluorine; chlorine; bromine; cyano; oxo; hydroxy; OR^{15}; $NR^{15}R^{16}$; COR^{15}; CSR^{15}; $COOR^{15}$; $COSR^{15}$; $OCOR^{15}$; $NR^{17}COR^{15}$; $CONR^{15}R^{16}$; $CSNR^{15}R^{16}$; $NR^{17}CONR^{15}R^{16}$; $R^{17}COOR^{15}$; $OCONR^{15}R^{16}$; SR^{15}; SOR^{15} and SO_2R^{15}; 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

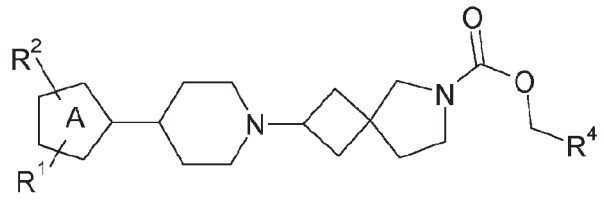
and S and oxidized forms thereof; and an optionally substituted 5- or 6-membered ring containing 0, 1, 2 or 3 heteroatoms selected from O, N and S and oxidized forms thereof;

wherein the optional substituents for the optionally substituted 5- or 6-membered ring are selected from a group R^8 consisting of hydrogen; fluorine; chlorine; bromine; cyano; oxo; hydroxy; 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; and 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;

wherein R^{15}, R^{16} and R^{17} are the same or different, or may be joined together to form a ring, and each is independently selected from hydrogen, a non-aromatic C_{1-6} hydrocarbon group optionally substituted with one or more 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; or a group of formula $CH_2N(R^a)COOR^b$; or a group of formula (L)-R^{18} where L is a bond or a CH_2 group and R^{18} is 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;

wherein the optional substituents for the optionally substituted 5- or 6-membered ring are selected from a group R^8.

1.94 A compound according to Embodiments 1.1 to 1.93 having the formula (3):



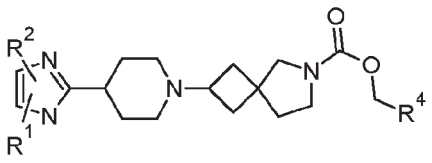
(3)

wherein R^1, R^2 and R^4 are as defined in any one of Embodiments 1.1 to 1.40 and 1.42 to 1.90 and the ring A is a five membered heterocyclic or heteroaryl ring containing one or two nitrogen ring members.

1.95 A compound according to Embodiment 1.94 wherein the ring A is a five membered heteroaryl ring containing two nitrogen ring members.

1.96 A compound according to Embodiment 1.95 wherein the ring A is an imidazole ring.

1.97 A compound according to Embodiment 1.96 having the formula (4):

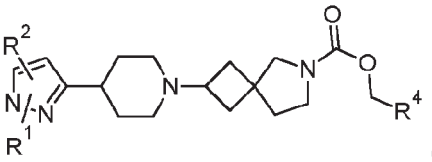


(4)

wherein R^1, R^2 and R^4 are as defined in any one of Embodiments 1.1 to 1.40 and 1.42 to 1.90.

1.98 A compound according to Embodiment 1.95 wherein the ring A is a pyrazole ring.

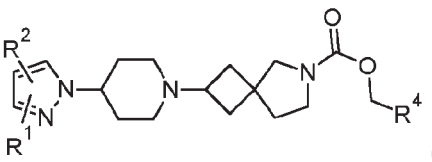
1.99 A compound according to Embodiment 1.98 having the formula (5):



(5)

wherein R^1, R^2 and R^4 are as defined in any one of Embodiments 1.1 to 1.40 and 1.42 to 1.90.

1.100 A compound according to Embodiment 1.98 having the formula (6):

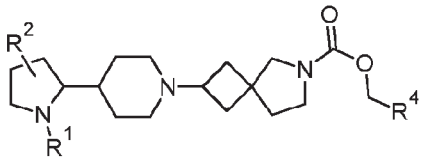


(6)

wherein R^1, R^2 and R^4 are as defined in any one of Embodiments 1.1 to 1.40 and 1.42 to 1.90.

1.101 A compound according to Embodiment 1.94 wherein ring A is a 5 membered heterocyclic ring containing one nitrogen atom.

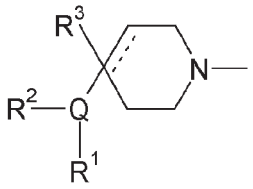
1.102 A compound according to Embodiment 1.101 having the formula (7):



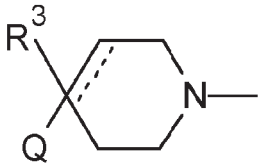
(7)

wherein R^1, R^2 and R^4 are as defined in any one of Embodiments 1.1 to 1.40 and 1.42 to 1.90.

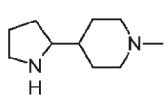
1.103 A compound according to embodiment 1.101 wherein moiety:



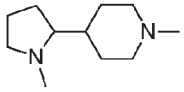
or



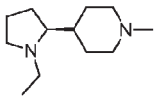
is selected from groups BAA to BCZ below:



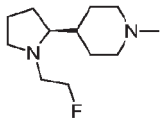
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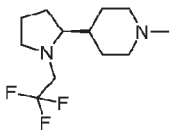
BAB



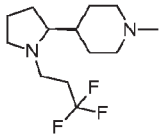
BAC



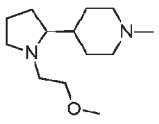
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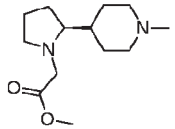
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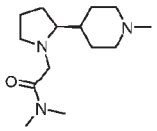
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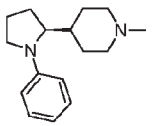
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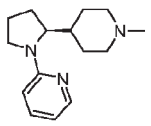
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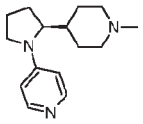
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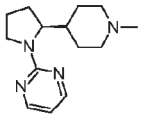
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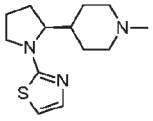
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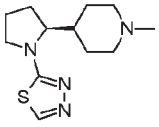
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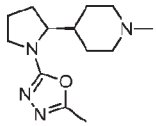
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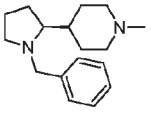
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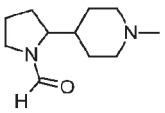
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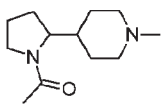
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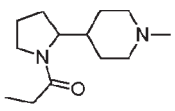
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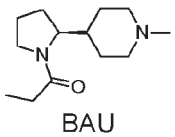
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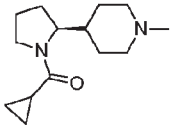
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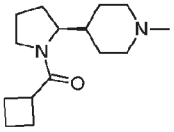
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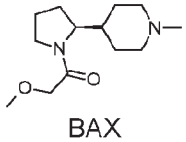
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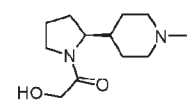
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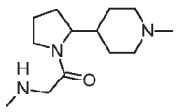


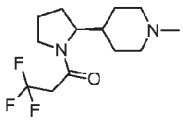
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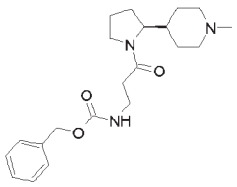


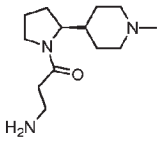
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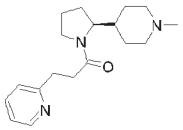

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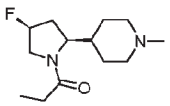

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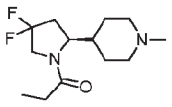

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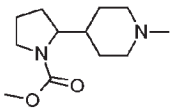

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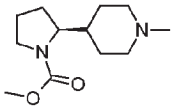

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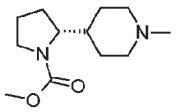

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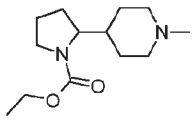

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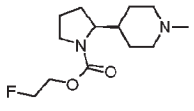

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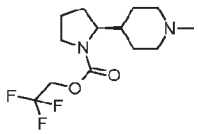

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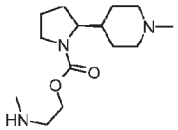

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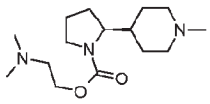

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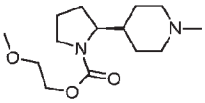

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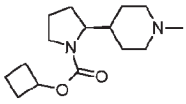

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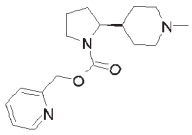

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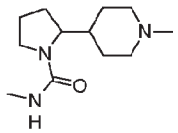

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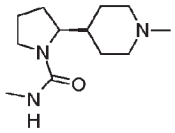

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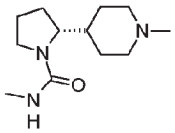

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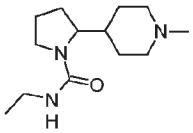

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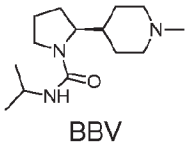

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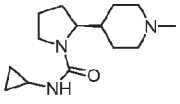

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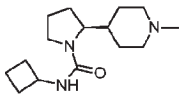

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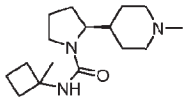

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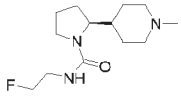

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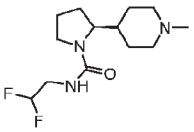

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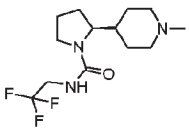

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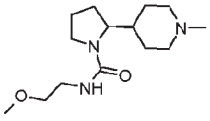

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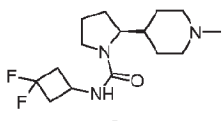

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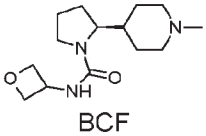

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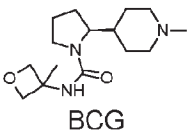

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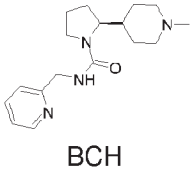

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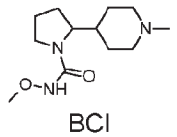

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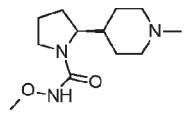

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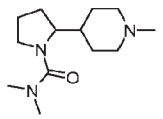

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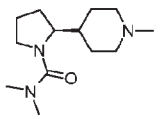

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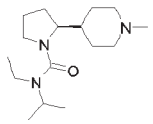

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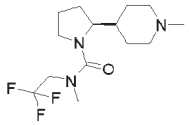

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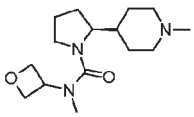

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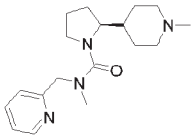

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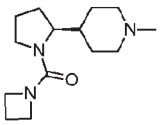

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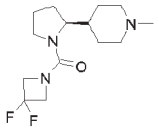

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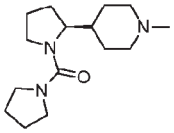

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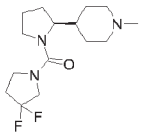

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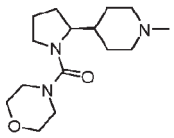

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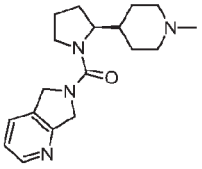

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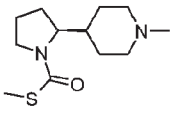

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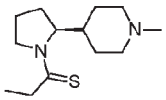

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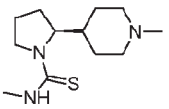

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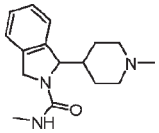

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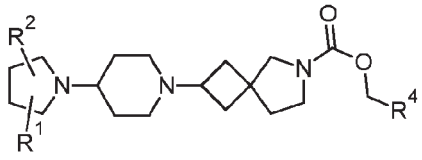

BCW


BCX


BCY

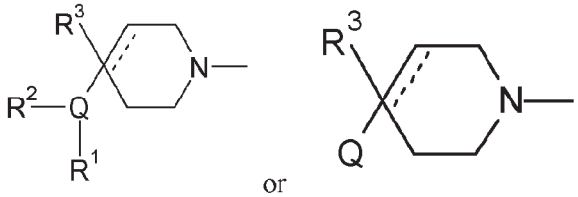

BCZ

1.104 A compound according to Embodiment 1.101 having the formula (8):

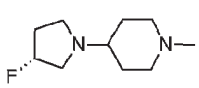

(8)

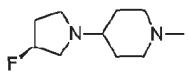
wherein R^1, R^2 and R^4 are as defined in any one of Embodiments 1.1 to 1.40 and 1.42 to 1.90.

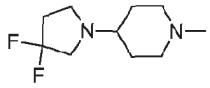
1.105 A compound according to embodiment 1.101 wherein moiety:

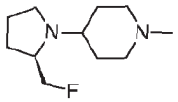

or

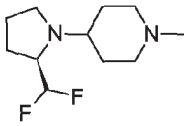
is selected from groups CAA to CBX below:

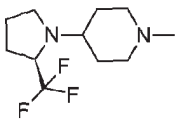

CAA

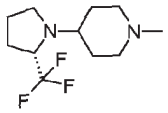

CAB

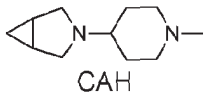

CAC

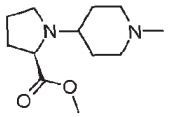

CAD

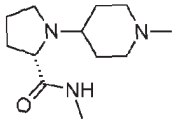

CAE

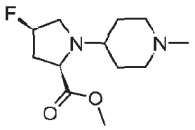

CAF

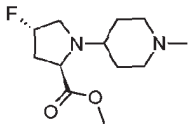

CAG

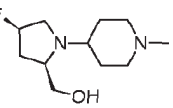

CAH

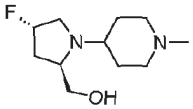

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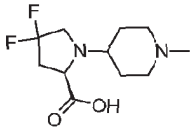

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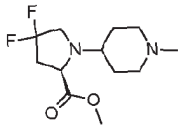

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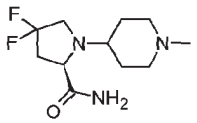

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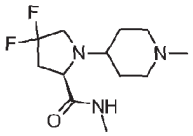

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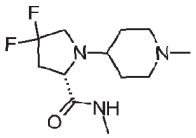

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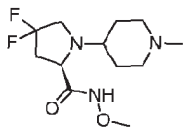

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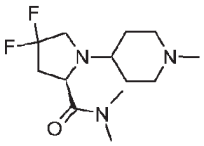

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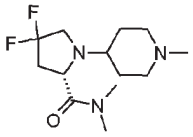

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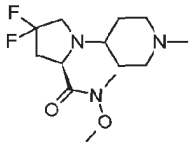

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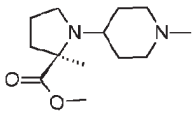

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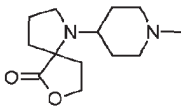

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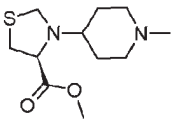

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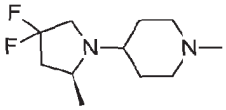

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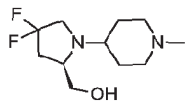

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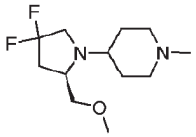

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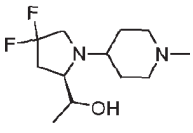

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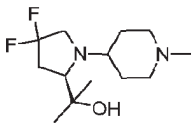

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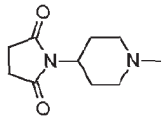

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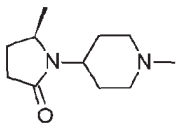

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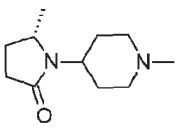

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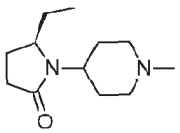

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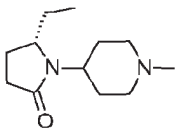

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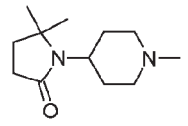

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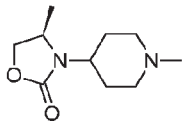

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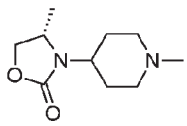

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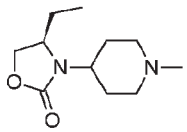

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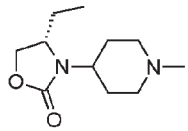

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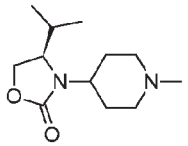

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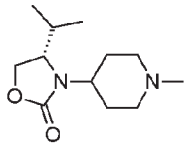

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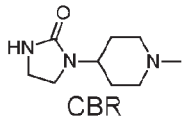

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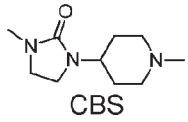

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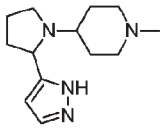

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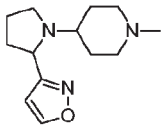

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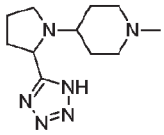

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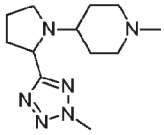

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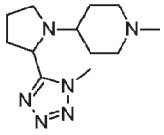

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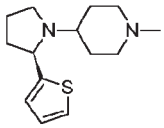

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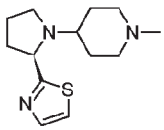

CBU


CBV


CBW

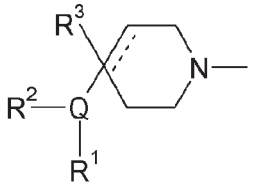

CBX

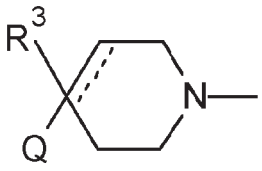

CBY


CBX

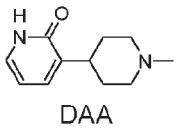
1.106 A compound according to embodiment 1.1 wherein Q is a six membered monocyclic heterocyclic ring containing 1, 2, 3 or 4 heteroatom ring members selected from N, O and S.

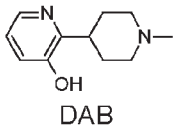
1.107 A compound according to Embodiment 1.106 wherein the moiety:

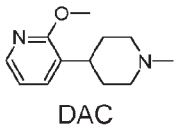

or

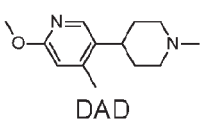


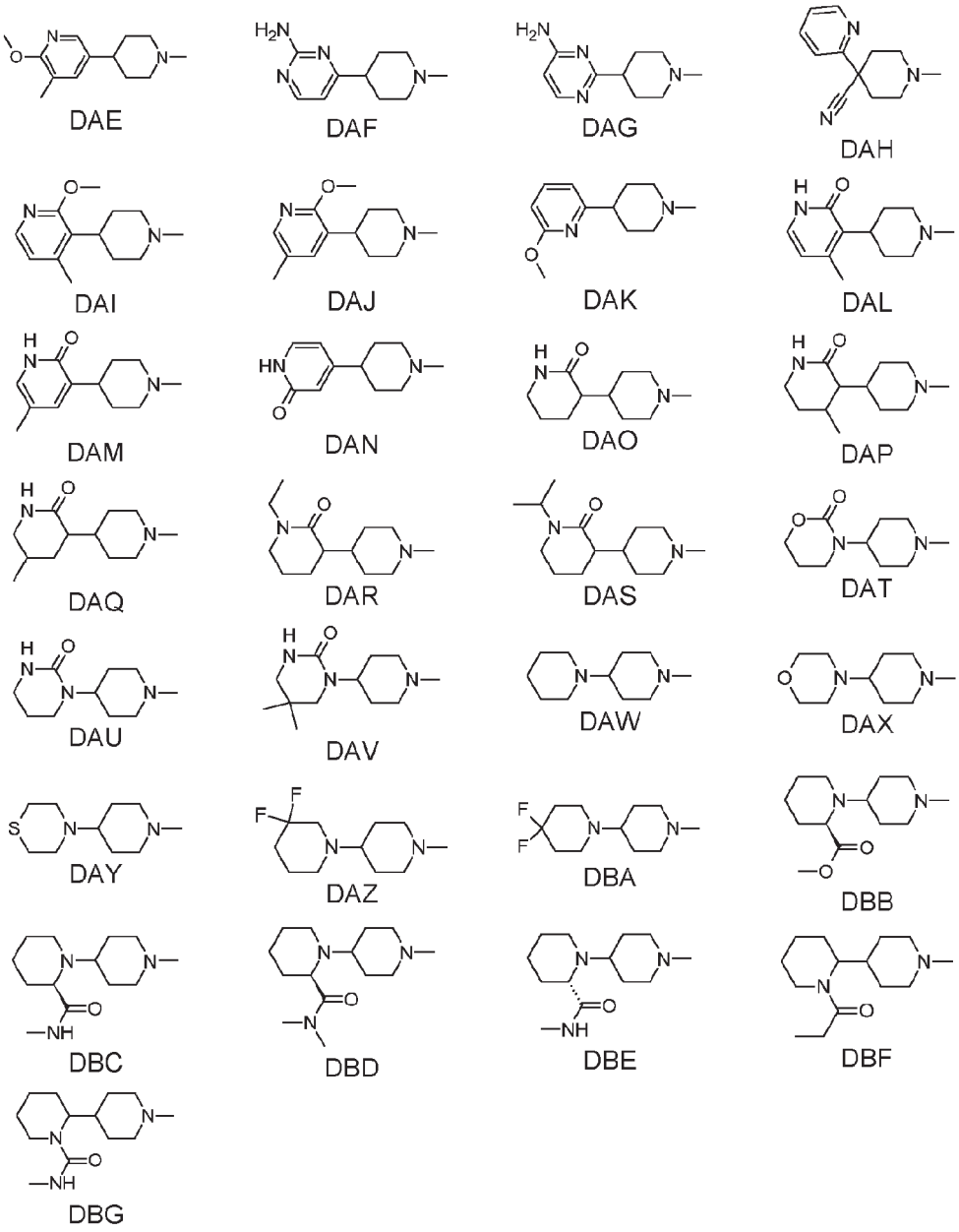
is selected from groups DAA to DBG below:


DAA


DAB

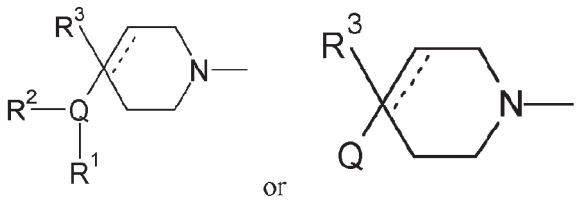

DAC


DAD

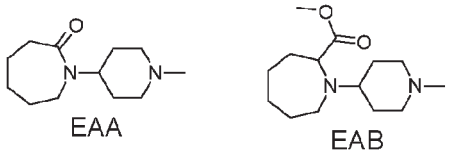


1.108 A compound according to embodiment 1.1 wherein Q is a seven membered monocyclic heterocyclic ring containing 1, 2, 3 or 4 heteroatom ring members selected from N, O and S.

1.109 A compound according to Embodiment 1.108 wherein the moiety:



is selected from groups EAA to EAB below:



1.110 A compound according to Embodiment 1.1 which is as defined in any one of Examples 1-1 to 1-73, 2-1 to 2-138, 3-1 to 3-16, 4-1 to 4-20 or 5-1 to 5-2.

1.111 A compound according to any one of Embodiments 1.1 to 1.110 having a molecular weight of less than 550.

1.112 A compound according to Embodiment 1.111 having a molecular weight of less than 500.

1.113 A compound according to Embodiment 1.112 having a molecular weight of, or less than 450.

1.114 A compound according to any one of Embodiments 1.1 to 1.113 which is in the form of a salt.

1.115 A compound according to Embodiment 1.114 wherein the salt is an acid addition salt.

1.116 A compound according to Embodiment 1.115 or Embodiment 1.115 wherein the salt is a pharmaceutically acceptable salt.

Definitions

In this application, the following definitions apply, unless indicated otherwise.

The term "treatment", in relation to the uses of the compounds of the formula (1), (1a) or (1b), 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.

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.

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.

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.

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.

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.

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.

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

Many compounds of the formula (1), (1a) or (1b) 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. All such salts are within the scope of this invention, and references to compounds of the formula (1), (1a) or (1b) include the salt forms of the compounds as defined in Embodiments 1.114 to 1.116.

The salts are typically acid addition salts.

The salts of the present invention 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.

Acid addition salts (as defined in Embodiment 1.120) may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts falling within Embodiment 1.120 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, (+)-(1*S*)-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.

Where the compounds of the formula (1), (1a) or (1b) 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. Such quaternary ammonium compounds are within the scope of formula (1), (1a) or (1b).

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.

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, which may be useful, for example, in the purification or separation of the compounds of the invention, also form part of the invention.

Stereoisomers

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

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.

Accordingly, in another embodiment (Embodiment 1.121), the invention provides a geometric isomer of a compound according to any one of Embodiments 1.1 to 1.116.

Optical Isomers

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.

Accordingly, in another embodiment (Embodiment 1.132) the invention provides a compound according to any one of Embodiments 1.1 to 1.121 which contains a chiral centre.

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.

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.

Accordingly, in another embodiment (Embodiment 1.133), the invention provides compositions containing a compound according to Embodiment 1.132 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 of Embodiment 1.108 is present as a single optical isomer (e.g. enantiomer or diastereoisomer).

In one general embodiment (Embodiment 1.134), 99% or more (e.g. substantially all) of the total amount of the compound (or compound for use) of Embodiment 1.132 is present as a single optical isomer.

For example, in one embodiment (Embodiment 1.135) the compound is present as a single enantiomer.

In another embodiment (Embodiment 1.136), the compound is present as a single diastereoisomer.

The invention also provides mixtures of optical isomers, which may be racemic or non-racemic. Thus, the invention provides:

1.137 A compound according to Embodiment 1.132 which is in the form of a racemic mixture of optical isomers.

1.138 A compound according to Embodiment 1.132 which is in the form of a non-racemic mixture of optical isomers.

Isotopes

The compounds of the invention as defined in any one of Embodiments 1.1 to 1.138 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.

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).

The isotopes may be radioactive or non-radioactive. In one embodiment of the invention (Embodiment 1.140), the compound of any one of Embodiments 1.1 to 1.138 contains no radioactive isotopes. Such compounds are preferred for therapeutic use. In another embodiment (Embodiment 1.141), however, the compound of any one of Embodiments 1.1 to 1.138may contain one or more radioisotopes. Compounds containing such radioisotopes may be useful in a diagnostic context.

Solvates

Compounds of the formula (1), (1a) or (1b) as defined in any one of Embodiments 1.1 to 1.141 may form solvates. Preferred solvates are solvates formed by the incorporation into the solid state structure (e.g. crystal structure) of the compounds of the invention 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 of the invention 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.

Accordingly, in further embodiments 1.150 and 1.151, the invention provides:

1.151 A compound according to any one of Embodiments 1.1 to 1.141 in the form of a solvate.

1.152 A compound according to Embodiment 1.151 wherein the solvate is a hydrate.

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, in another embodiment (Embodiment 1.153), the invention

provides a compound as defined in any one of Embodiments 1.1 to 1.141 in an anhydrous form (e.g. anhydrous crystalline form).

Crystalline and amorphous forms

The compounds of any one of Embodiments 1.1 to 1.153 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).

Accordingly, in further embodiments, the invention provides:

1.160 A compound according to any one of Embodiments 1.1 to 1.153 in a crystalline form.

1.161 A compound according to any one of Embodiments 1.1 to 1.153 which is:

(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.

1.162 A compound according to any one of Embodiments 1.1 to 1.153 which is in an amorphous form.

Prodrugs

The compounds of the formula (1), (1a) or (1b) as defined in any one of Embodiments 1.1 to 1.162 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), (1a) or (1b), as defined in any one of Embodiments 1.1 to 1.162.

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.

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.

Accordingly, in another embodiment (Embodiment 1.170), the invention provides a pro-drug of a compound as defined in any one of Embodiments 1.1 to 1.170 wherein the compound contains a functional group which is convertable under physiological conditions to form a hydroxyl group or amino group.

Complexes and clathrates

Also encompassed by formula (1), (1a) or (1b) in Embodiments 1.1 to 1.170 are complexes (e.g. inclusion complexes or clathrates with compounds such as cyclodextrins, or complexes with metals) of the compounds of Embodiments 1.1 to 1.170.

Accordingly, in another embodiment (Embodiment 1.180), the invention provides a compound according to any one of Embodiments 1.1 to 1.170 in the form of a complex or clathrate.

Biological activity and therapeutic uses

The compounds of the present invention 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.

A significant advantage of compounds of the invention is that they are highly selective for the M1 receptor relative to the M2 and M3 receptor subtypes. Compounds of the invention are not agonists of the M2 and M3 receptor subtypes. For example, whereas compounds of the invention 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.

Some compounds of the invention 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.

Other compounds of the invention have activity at both the M1 and M4 receptors. Examples of such compounds include compounds of Examples 1-1 to 1-4 and 1-8 to 1-10 and 2-116.

Accordingly, in Embodiments 2.1 to 2.9, the invention provides:

2.1 A compound according to any one of Embodiments 1.1 to 1.180 for use in medicine.

2.2 A compound according to any one of Embodiments 1.1 to 1.180 for use as a muscarinic M1 and/or M4 receptor agonist.

2.3 A compound according to any one of Embodiments 1.1 to 1.180 which 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.

2.4 A compound according to Embodiment 2.3 which is a muscarinic M1 receptor agonist having a pEC_{50} in the range from 6.5 to 7.5.

2.5 A compound according to Embodiment 2.3 or Embodiment 2.4 having an E_{max} of at least 95 against the M1 receptor.

2.6 A compound according to any one of Embodiments 1.1 to 1.180 which 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.

2.7 A compound according to Embodiment 2.6 which is a muscarinic M4 receptor agonist having a pEC_{50} in the range from 6.5 to 9.0.

2.8 A compound according to Embodiment 2.6 or Embodiment 2.7 having an E_{max} of at least 95 against the M4 receptor.

2.9 A compound according to any one of Embodiments 2.3 to 2.8 which is selective for the M1 and/or M4 receptor compared to the muscarinic M2 and M3 receptors.

2.10 A compound according to Embodiment 2.9 which is selective for the M1 receptor compared to the muscarinic M2 and M3 receptors.

2.11 A compound according to Embodiment 2.9 which is selective for the M4 receptor compared to the muscarinic M2 and M3 receptors.

2.12 A compound according to any one of Embodiments 2.3 to 2.5 which is selective for the M1 receptor compared to the muscarinic M2, M3 and M4 receptors.

2.13 A compound according to any one of Embodiments 2.6 to 2.8 which is selective for the M4 receptor compared to the muscarinic M1, M2 and M3 receptors.

2.14 A compound according to any one of Embodiments 2.3 to 2.8 which is selective for the M1 and M4 receptor compared to the muscarinic M2 and M3 receptors.

2.15 A compound according to any one of Embodiments 2.3 to 2.14 which has a pEC_{50} of less than 5 and an E_{max} of less than 50 against the muscarinic M2 and M3 receptor subtypes.

2.16 A compound according to Embodiment 2.15 which 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.

2.17 A compound according to any one of Embodiments 1.1 to 1.180 and Embodiments 2.3 to 2.16 for use in the treatment of a disease or condition mediated by the muscarinic M1 receptor.

By virtue of their muscarinic M1 and/or M4 receptor agonist activity, compounds of the invention 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.

Accordingly, in Embodiments 2.18 to 2.34, the invention provides:

2.18 A compound according to any one of Embodiments 1.1 to 1.180 for use in the treatment of a cognitive disorder or psychotic disorder.

2.19 A compound for use in according to Embodiment 2.18 wherein 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.

2.20 A compound according to any one of Embodiments 1.1 to 1.180 for use in the treatment of Alzheimer's disease.

2.21 A compound according to any one of Embodiments 1.1 to 1.180 for use in the treatment of Schizophrenia.

2.22 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 according to any one of Embodiments 1.1 to 1.180.

2.23 A method according to Embodiment 2.20 wherein the cognitive disorder comprises, arises from or is associated with a condition as defined in Embodiment 2.19.

2.24 A method according to Embodiment 2.23 wherein the cognitive disorder arises from or is associated with Alzheimer's disease.

2.25 A method according to Embodiment 2.24 wherein the cognitive disorder is Schizophrenia.

2.26 The use of a compound according to any one of Embodiments 1.1 to 1.180 for the manufacture of a medicament for the treatment of a cognitive disorder.

2.27 The use according to Embodiment 2.26 wherein the cognitive disorder comprises, arises from or is associated with a condition as defined in Embodiment 2.11.

2.28 The use according to Embodiment 2.27 wherein the cognitive disorder arises from or is associated with Alzheimer's disease.

2.29 The use according to Embodiment 2.29 wherein the cognitive disorder is Schizophrenia.

2.30 A compound according to any one of Embodiments 1.1 to 1.180 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.

2.31 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 according to any one of Embodiments 1.1 to 1.180.

2.32 A compound according to any one of Embodiments 1.1 to 1.180 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.

2.33 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 according to any one of Embodiments 1.1 to 1.180.

2.34 The use of a compound according to any one of Embodiments 1.1 to 1.180 for the manufacture of a medicament 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 or 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.

2.35 The use of a compound according to any one of Embodiments 1.1 to 1.180 for the treatment of addicition.

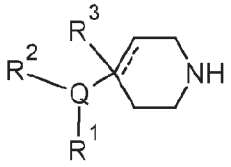
2.36 The use of a compound according to any one of Embodiments 1.1 to 1.180 for the treatment of movement disorders such as Parkinson's disease, ADHD, Huntingdon's disease, tourette's syndrome and other syndromes associated with dopaminergic dysfunction as an underlying pathogenetic factor driving disease.

Methods for the Preparation of Compounds of the Formula (1), (1a) or (1b)

Compounds of the formula (1), (1a) or (1b) can be prepared in accordance with synthetic methods well known to the skilled person and as described herein.

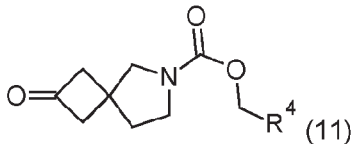
Accordingly, in another embodiment (Embodiment 3.1), the invention provides a process for the preparation of a compound as defined in any one of Embodiments 1.1 to 1.180, which process comprises:

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



(10)

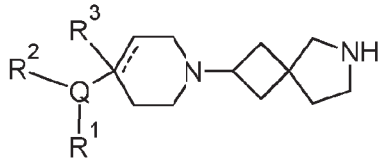
with a compound of the formula (11):



(11)

under reductive amination conditions; wherein R^1, R^2, R^3, R^4 and Q are as defined in any one of Embodiments 1.1 to 1.180; or

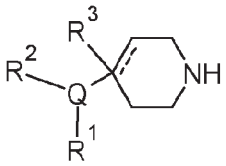
(B) the reaction of a compound of the formula (12):



(12)

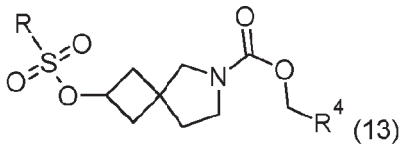
with a compound of the formula Cl-C(=O)-CH_2-R^4, in the presence of a base; or

(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 in any one of Embodiments 1.1 to 1.180; and optionally:

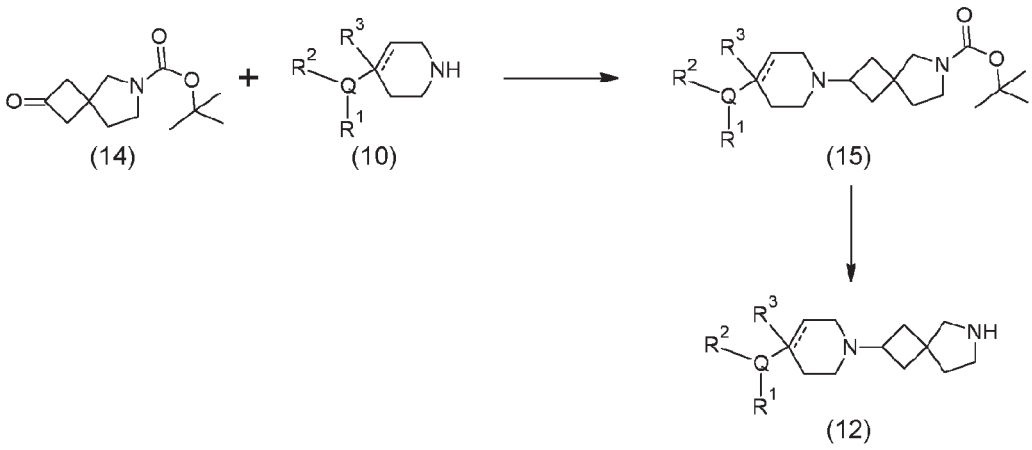
(D) converting one compound of the formula (1), (1a) or (1b) to another compound of the formula (1), (1a) or (1b).

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.

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.

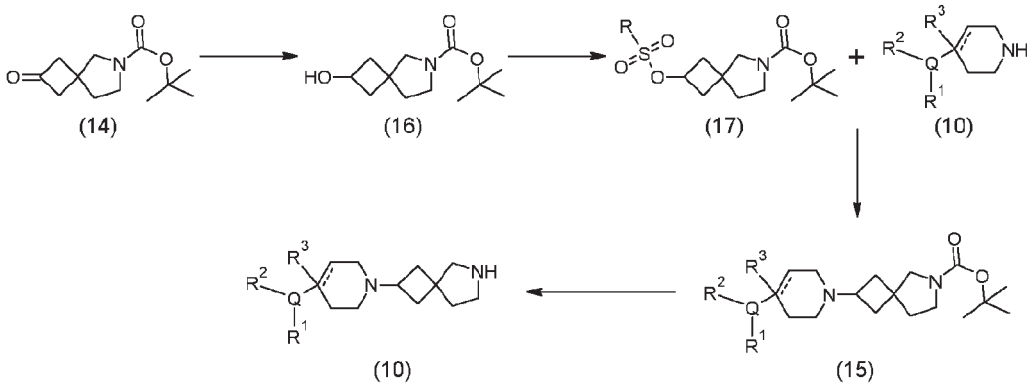
Intermediate compounds of the formula (12) can be prepared by the series of reactions shown in Scheme 1 below.



Scheme 1

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).

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



Scheme 2

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).

Once formed, one compound of the formula (1), (1a) or (1b), or a protected derivative thereof, can be converted into another compound of the formula (1), (1a) or (1b) 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.

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).

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

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).

Accordingly, in another embodiment (Embodiment 4.1) of the invention, there is provided a pharmaceutical composition comprising at least one compound of the formula (1), (1a) or (1b) as defined in any one of Embodiments 1.1 to 1.180 together with at least one pharmaceutically acceptable excipient.

In one embodiment (Embodiment 4.2), the composition is a tablet composition.

In another embodiment (Embodiment 4.3), the composition is a capsule composition.

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.

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.

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

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

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.

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.

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.

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.

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.

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.

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.

The compounds of the formula (1), (1a) or (1b) 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).

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.

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.

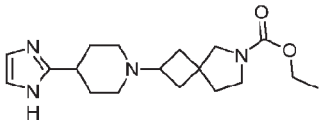
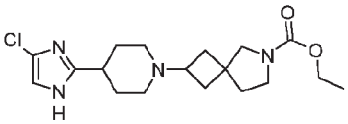
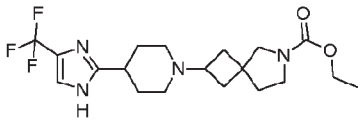
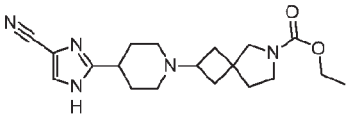
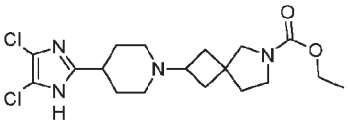
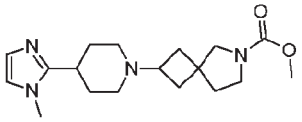
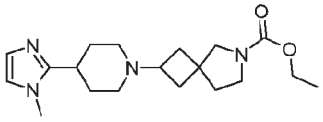
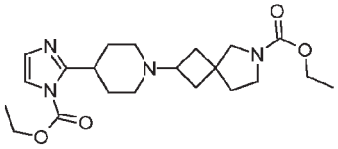
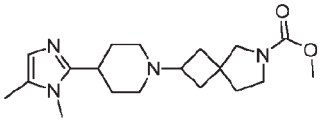
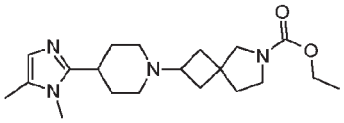
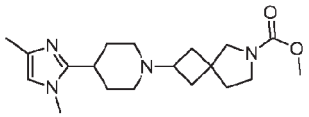
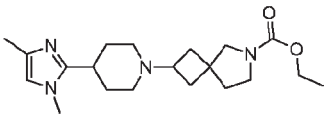
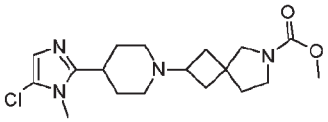
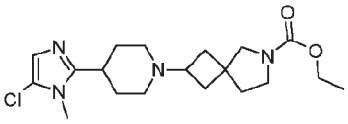
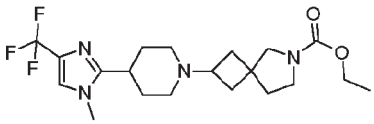
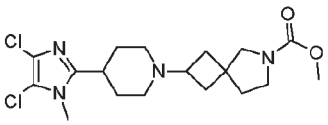
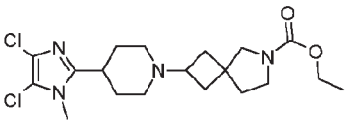
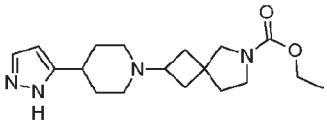
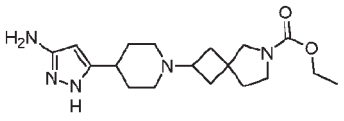
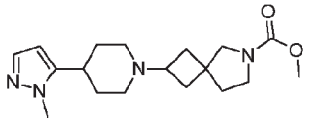
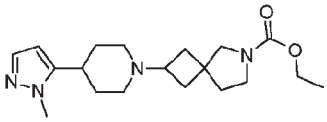
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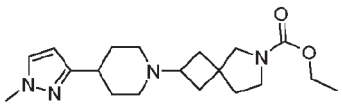
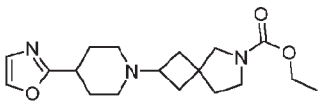
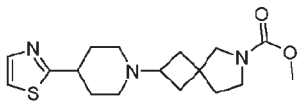
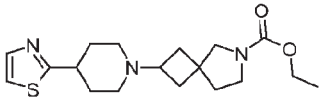
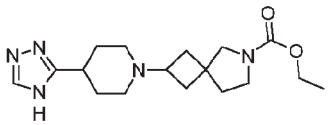
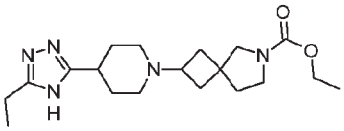
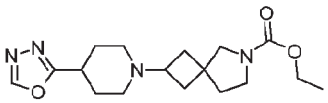
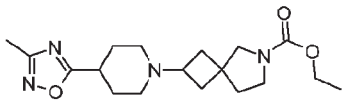
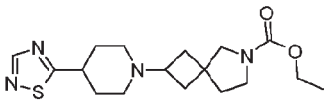
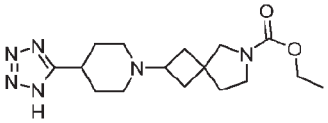
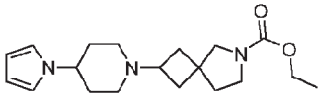
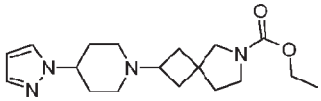
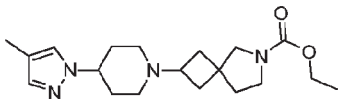
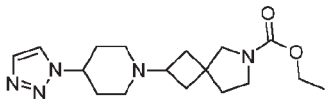
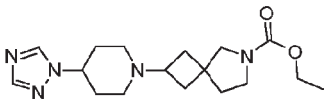
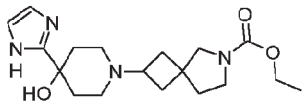
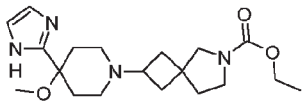
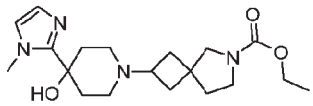
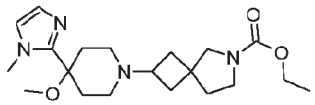
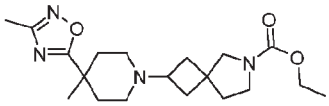
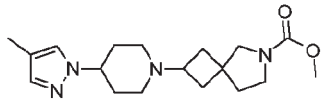
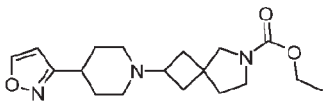
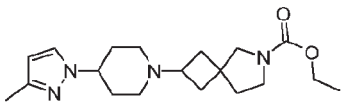
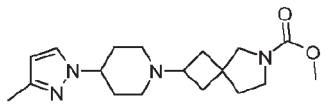
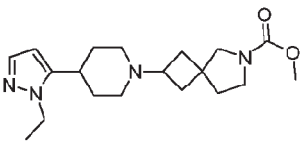
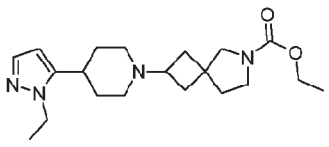
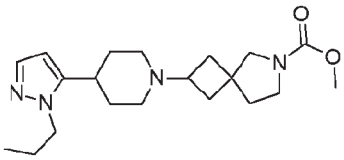
The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples.

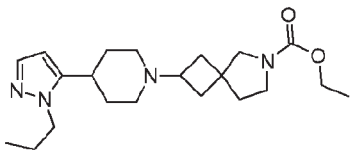
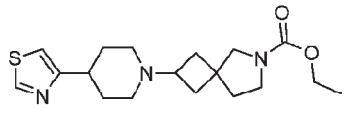
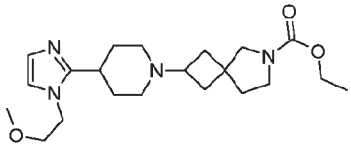
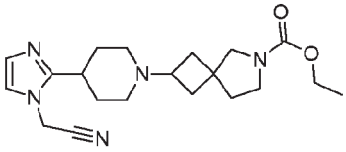
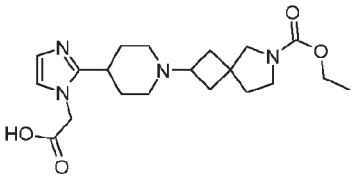
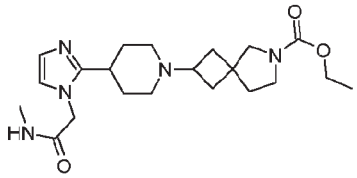
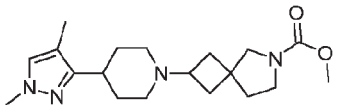
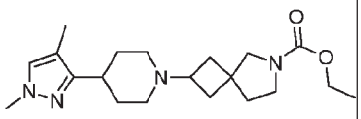
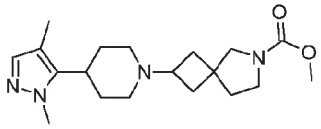
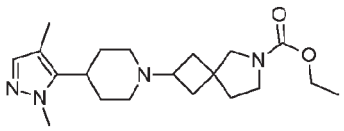
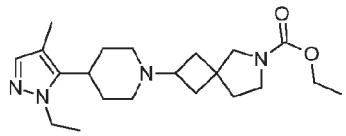
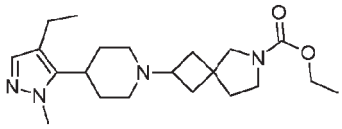
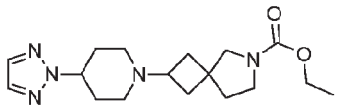
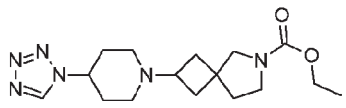
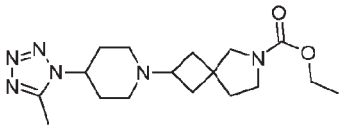
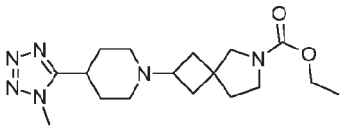
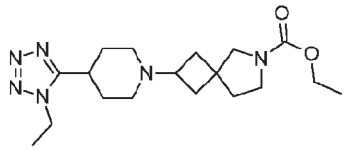
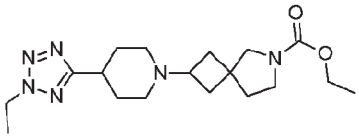
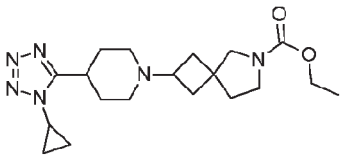
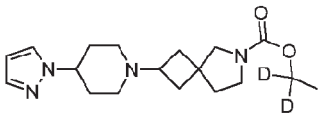
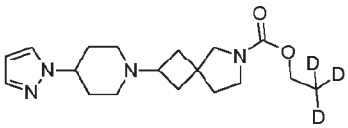
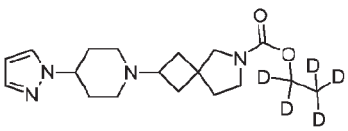
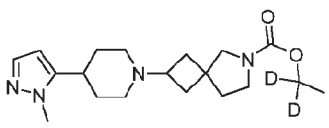
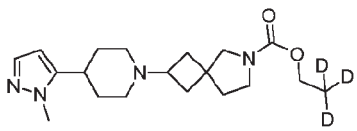
EXAMPLES 1-1 TO 5-2

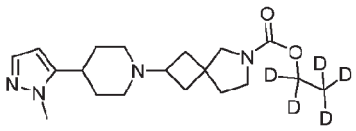
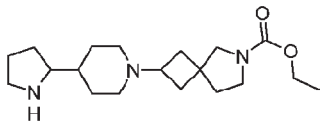
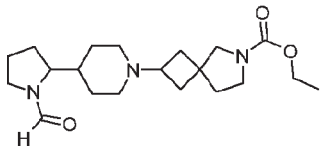
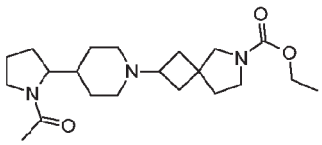
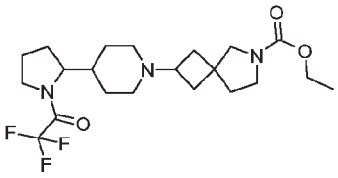
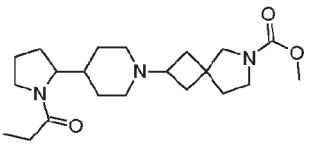
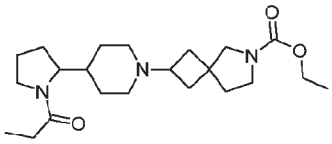
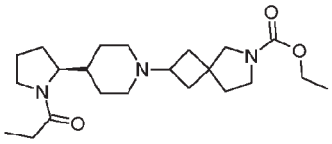
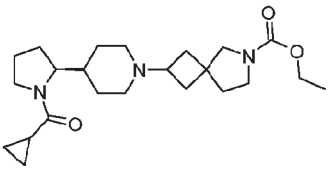
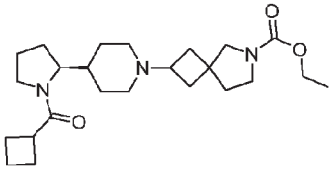
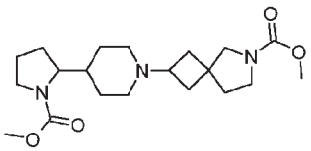
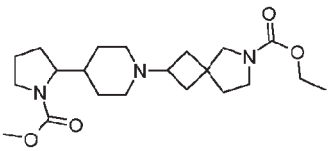
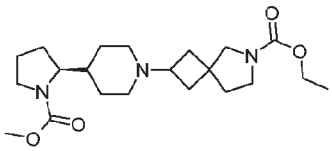
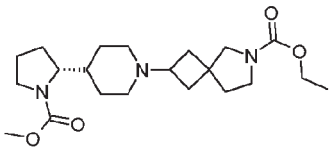
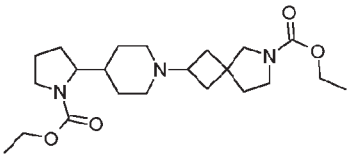
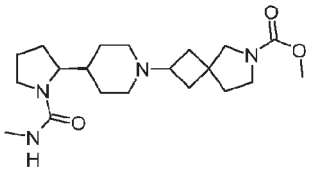
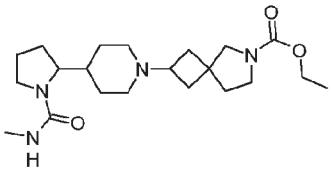
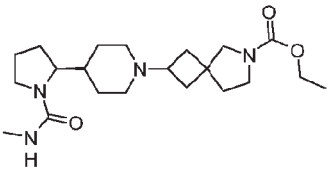
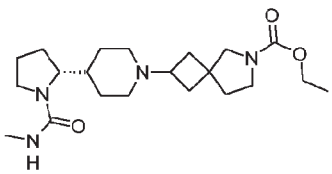
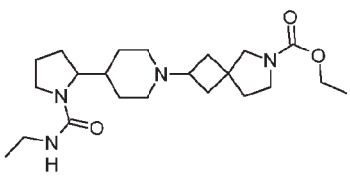
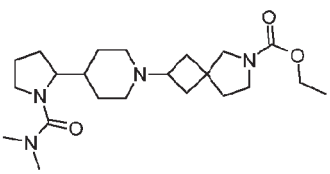
The compounds of Examples 1-1 to 5-2 shown in Table 1 below have been prepared. Their NMR and LCMS properties and the methods used to prepare them are set out in Table 3.

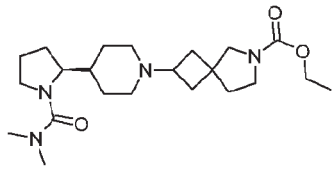
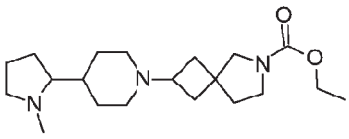
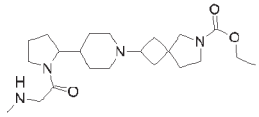
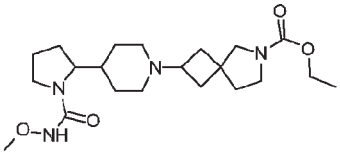
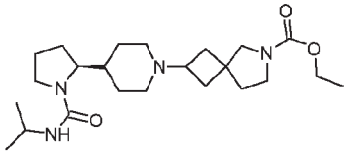
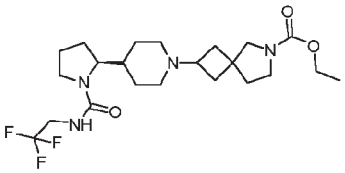
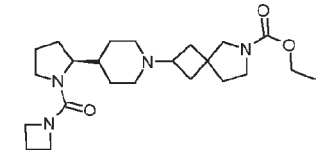
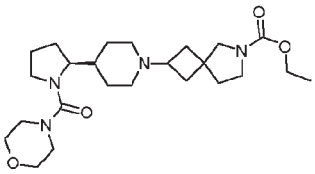
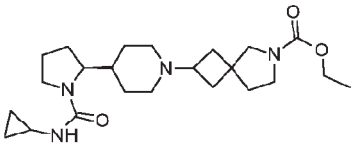
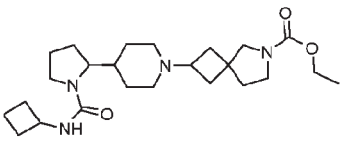
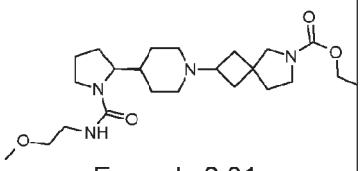
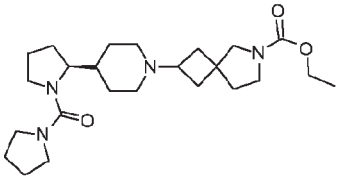
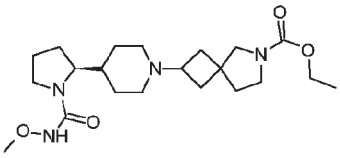
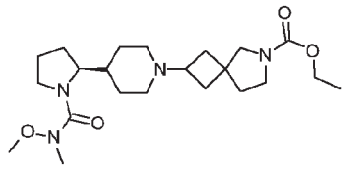
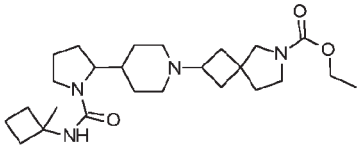
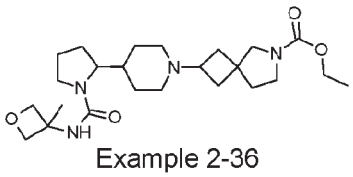
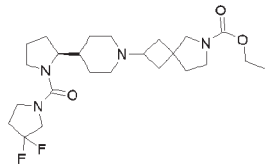
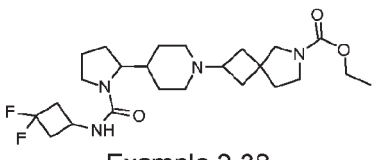
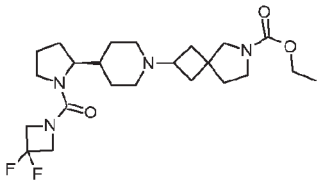
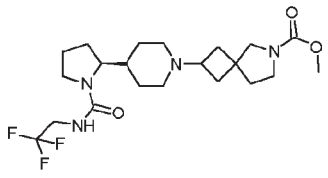
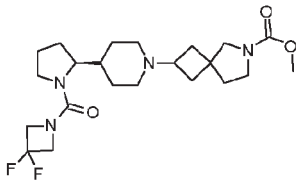
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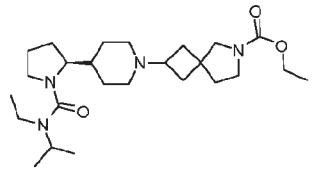
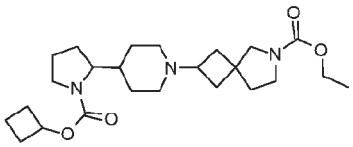
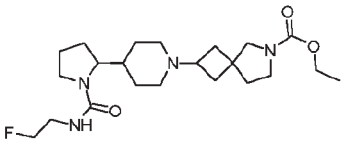
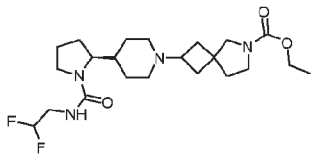
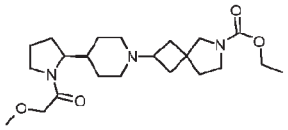
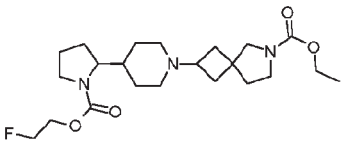
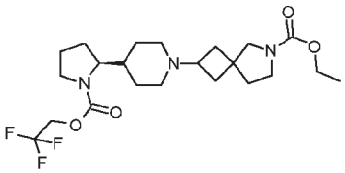
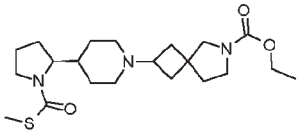
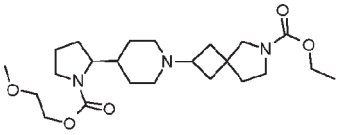
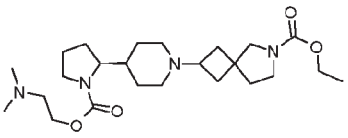
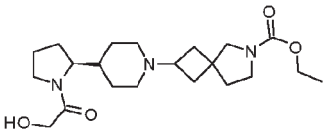
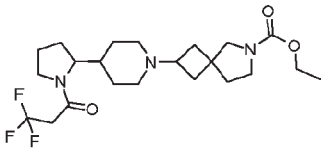
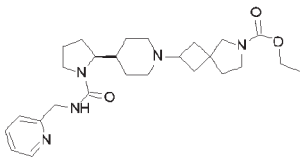
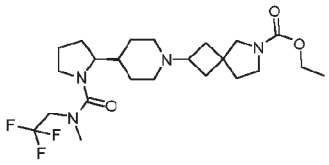
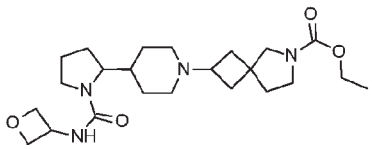
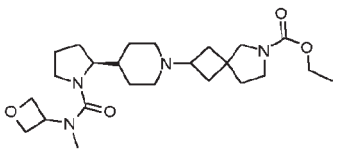
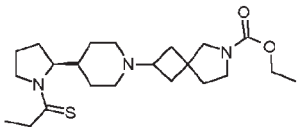
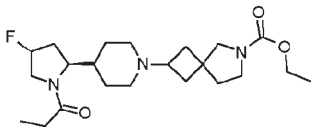
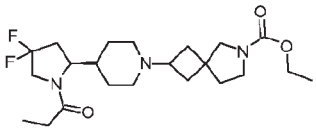
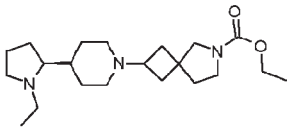
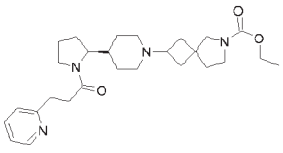
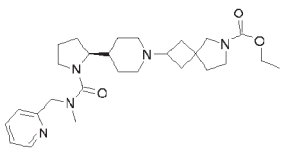
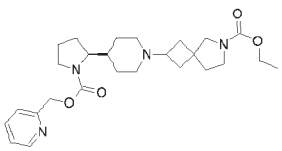
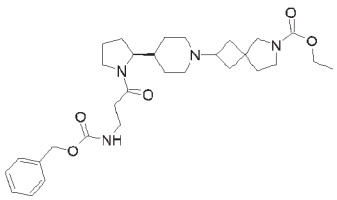
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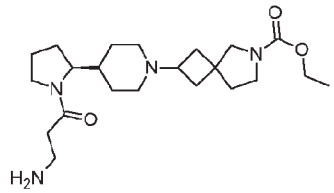
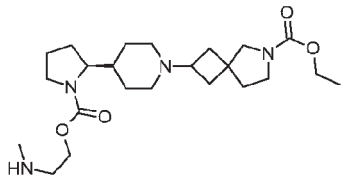
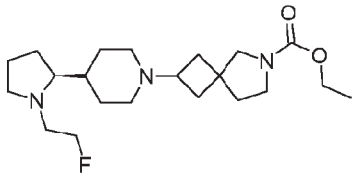
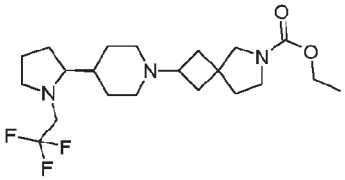
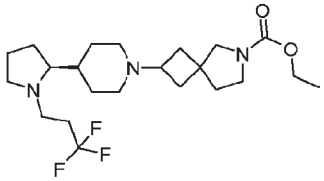
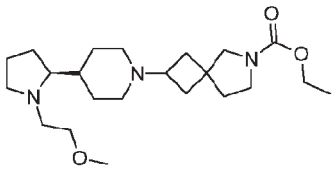
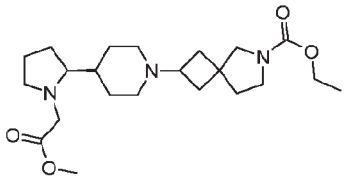
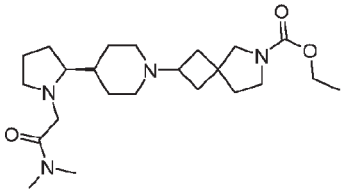
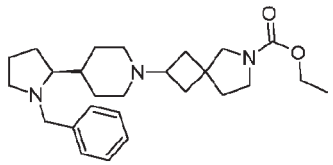
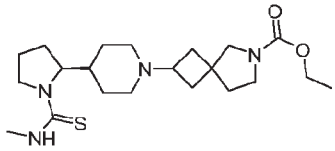
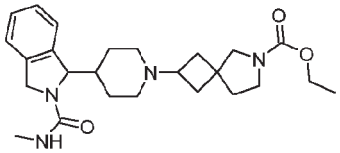
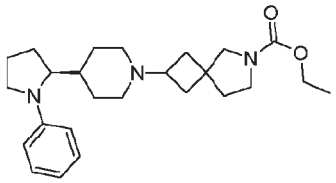
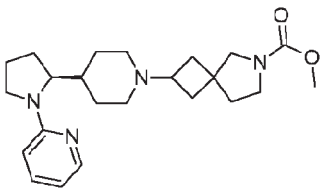
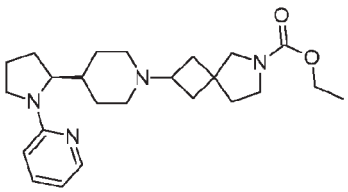
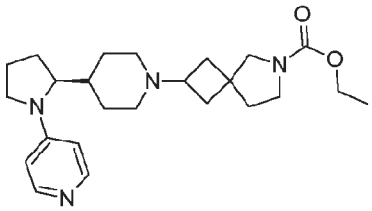
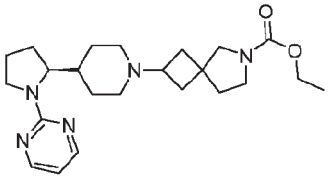
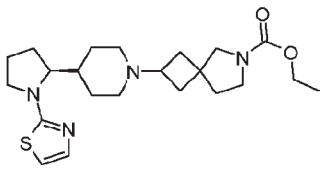
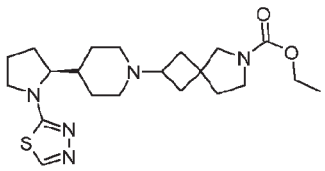
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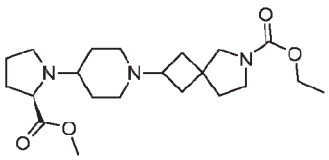
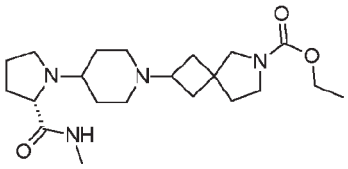
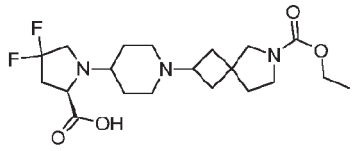
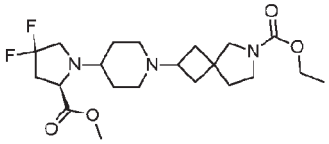
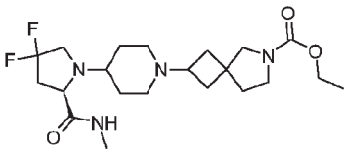
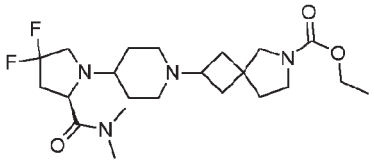
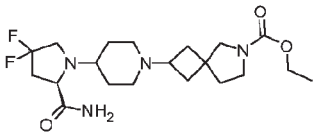
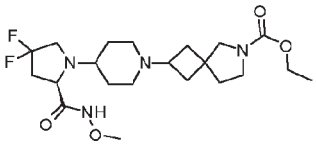
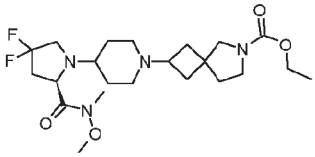
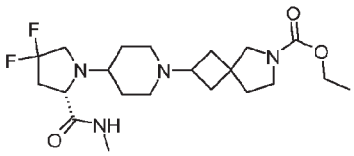
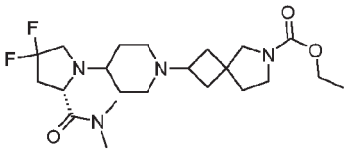
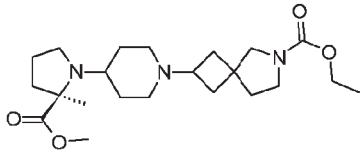
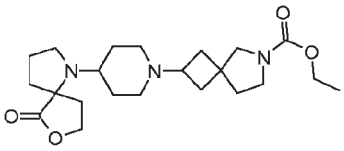
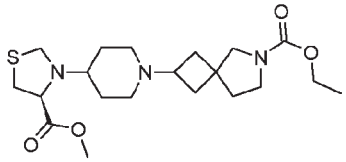
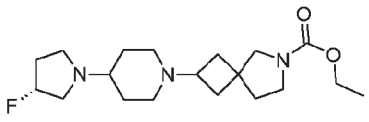
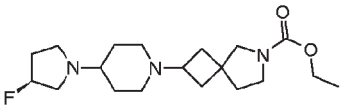
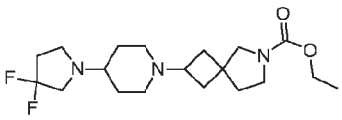
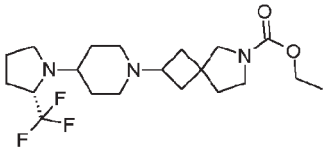
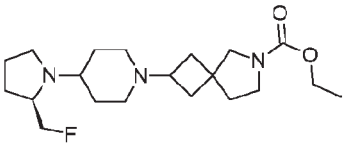
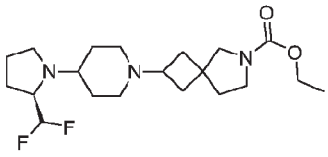
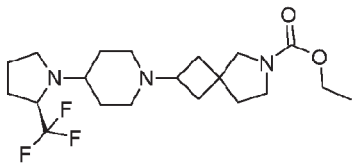
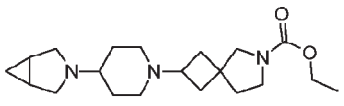
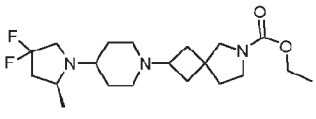
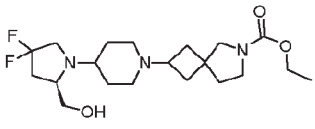
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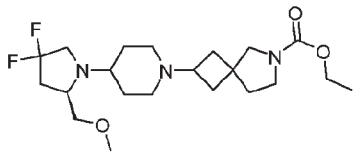
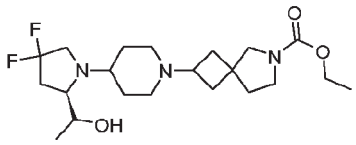
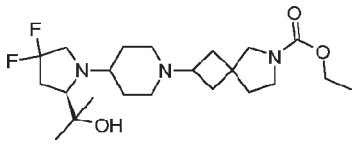
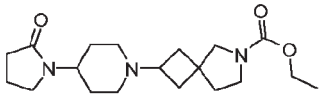
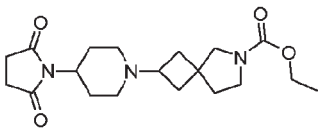
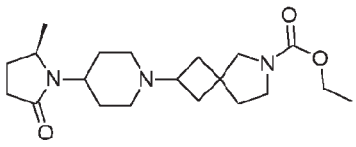
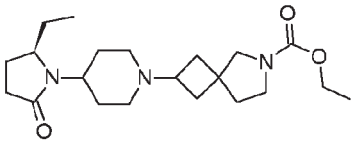
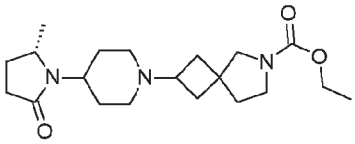
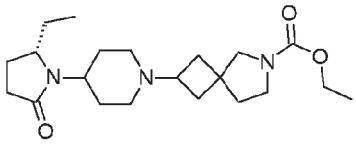
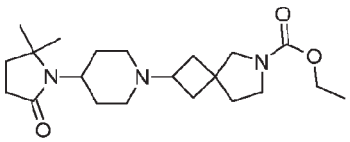
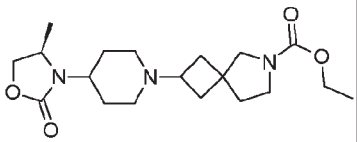
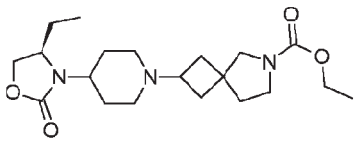
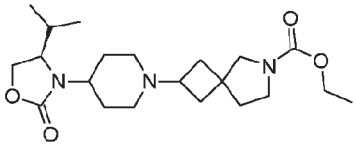
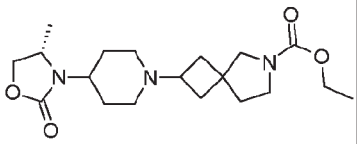
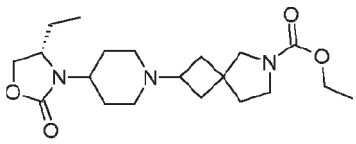
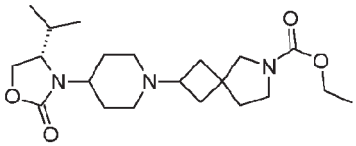
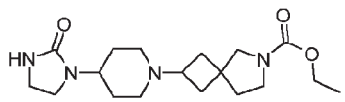
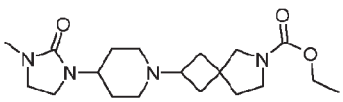
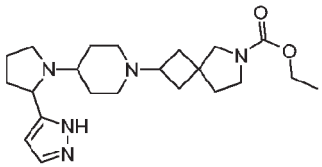
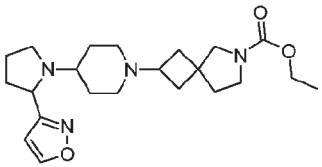
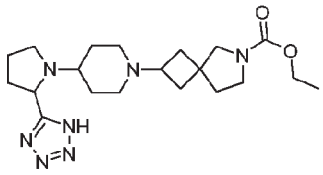
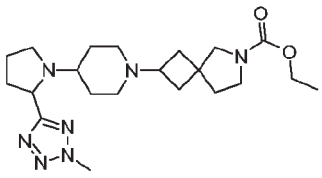
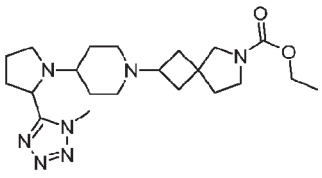
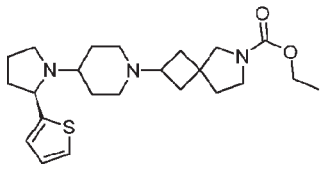
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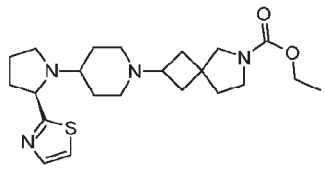
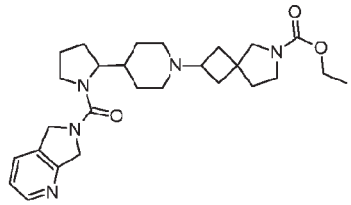
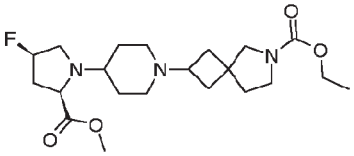
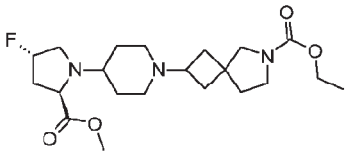
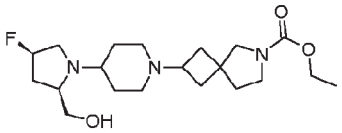
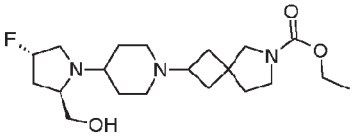
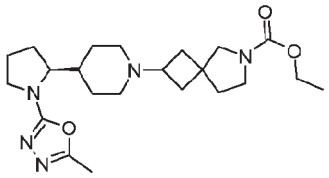
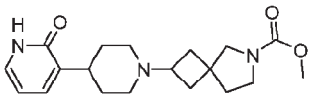
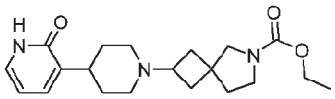
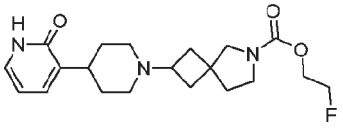
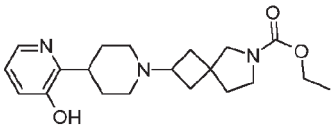
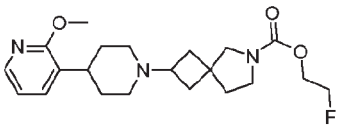
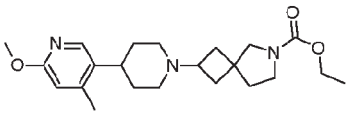
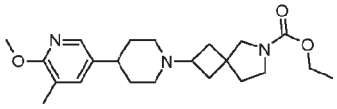
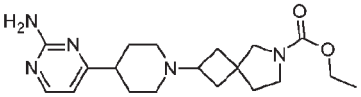
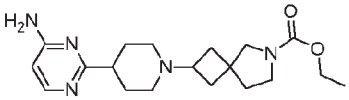
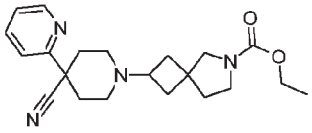
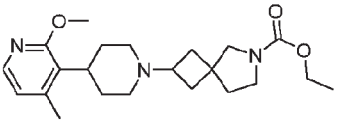
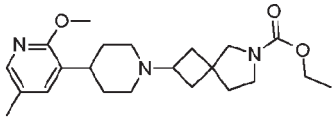
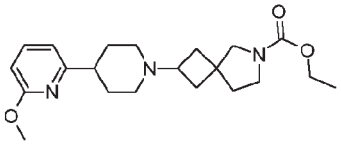
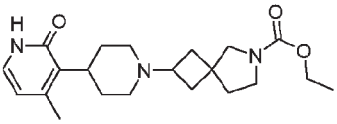
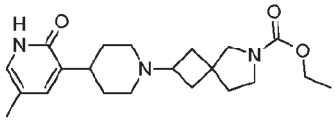
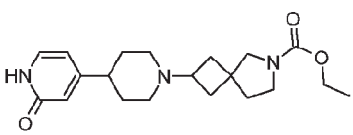
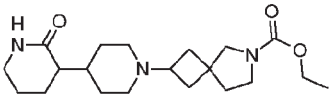
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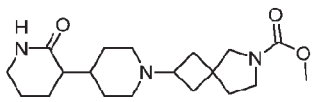
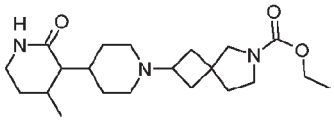
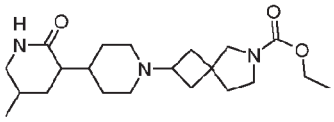
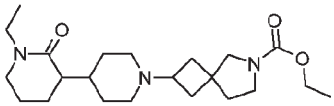
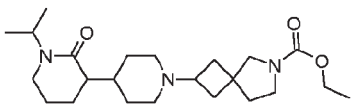
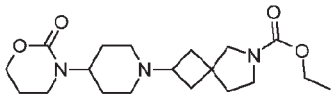
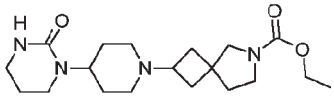
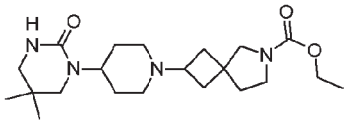
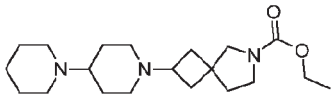
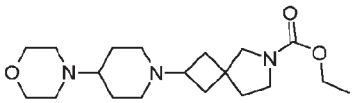
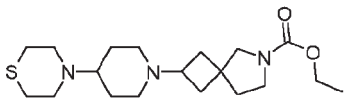
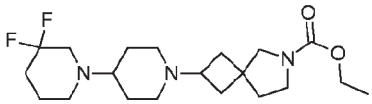
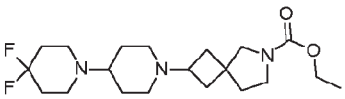
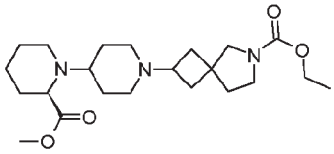
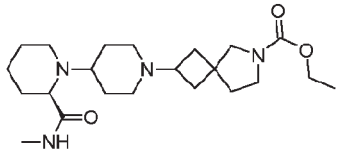
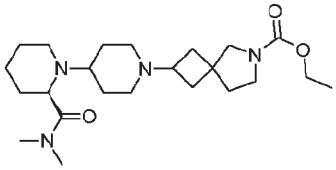
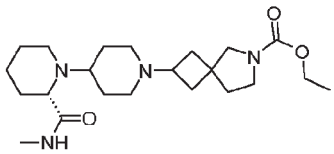
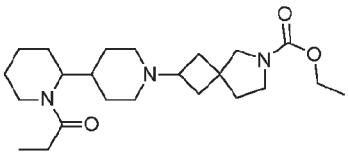
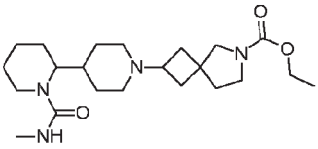
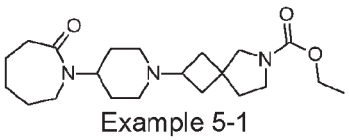
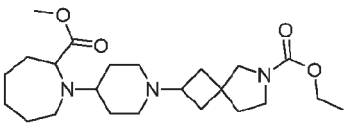
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 Example 2-60	 Example 2-61	 Example 2-62
 Example 2-63	 Example 2-64	

		Example 2-65
 Example 2-66	 Example 2-67	 Example 2-68
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 Example 2-78	 Example 2-79	 Example 2-80
 Example 2-81	 Example 2-82	 Example 2-83

 Example 2-84	 Example 2-85	 Example 2-86
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 Example 2-93	 Example 2-94	 Example 2-95
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 Example 2-99	 Example 2-100	 Example 2-101
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 Example 2-105	 Example 2-106	 Example 2-107

 Example 2-108	 Example 2-109	 Example 2-110
 Example 2-111	 Example 2-112	 Example 2-113
 Example 2-114	 Example 2-115	 Example 2-116
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 Example 2-120	 Example 2-121	 Example 2-122
 Example 2-123	 Example 2-124	 Example 2-125
 Example 2-126	 Example 2-127	 Example 2-128
 Example 2-129	 Example 2-130	 Example 2-131

 Example 2-132	 Example 2-133	 Example 2-134
 Example 2-135	 Example 2-136	 Example 2-137
 Example 2-138	 Example 3-1	 Example 3-2
 Example 3-3	 Example 3-4	 Example 3-5
 Example 3-6	 Example 3-7	 Example 3-8
 Example 3-9	 Example 3-10	 Example 3-11
 Example 3-12	 Example 3-13	 Example 3-14
 Example 3-15	 Example 3-16	 Example 4-1

 Example 4-2	 Example 4-3	 Example 4-4
 Example 4-5	 Example 4-6	 Example 4-7
 Example 4-8	 Example 4-9	 Example 4-10
 Example 4-11	 Example 4-12	 Example 4-13
 Example 4-14	 Example 4-15	 Example 4-16
 Example 4-17	 Example 4-18	 Example 4-19
 Example 4-20	 Example 5-1	 Example 5-2

General procedures

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. 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.

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

LCMS Methods A and B

Instruments: Waters Alliance 2795, Waters 2996 PDA detector, Micromass ZQ; Column: Waters X-Bridge C-18, 2.5 micron, 2.1 x 20 mm or Phenomenex Gemini-NX C-18, 3 micron, 2.0 x 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

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 x 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

Instruments: HP 1100 with G1315A DAD, Micromass ZQ; Column: Waters X-Bridge C-18, 2.5 micron, 2.1 x 20 mm or Phenomenex Gemini-NX C-18, 3 micron, 2.0 x 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:

Instruments: Waters Acquity H Class, Photo Diode Array, SQ Detector; Column: BEH C18, 1.7 micron, 2.1 x 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:

Instruments: Waters 2695, Photo Diode Array, ZQ-2000 Detector; Column: X-Bridge C18, 5 micron, 150 x 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.

LCMS Method H:

Instruments: Waters 2695, Photo Diode Array, ZQ-2000 Detector; Column: X-Bridge C18, 5 micron, 150 x 4.6mm; Gradient [time (min)/solvent B in A (%)]: 0.00/100, 7.00/50, 9.00/0, 11.00/0, 11.01/100, 12.00/100; 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.

LCMS Method I:

Instruments: Waters 2695, Photo Diode Array, ZQ-2000 Detector; Column: X-Bridge C18, 3.5 micron, 150 x 4.6mm; Gradient [time (min)/solvent B in A (%)]: 0.00/5, 5.00/90, 5.80/95, 10/95; 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.

LCMS Method J:

Instruments: Waters 2695, Photo Diode Array, ZQ-2000 Detector; Column: X-Bridge C18, 5 micron, 150 x 4.6mm; Gradient [time (min)/solvent B in A (%)]: 0.01/10, 5.00/90, 7.00/100, 11.00/100, 11.01/10, 12.00/10; Solvents: solvent A = 20mM ammonium acetate in H_2O; solvent B = MeOH; 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.

LCMS Method K:

Instruments: Waters 2695, Photo Diode Array, ZQ-2000 Detector; Column: X-Bridge C18, 3.5 micron, 50 x 4.6mm; Gradient [time (min)/solvent B in A (%)]: 0.01/0, 0.20/0, 5.00/90, 5.80/95, 7.20/95, 7.21/100, 10.00/100; 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.

LCMS Method L

Instruments: Waters Acquity UPLC, Waters 3100 PDA Detector, SQD; Column: Acquity BEH C-18, 1.7 micron, 2.1 x 100 mm; Gradient [time (min)/solvent B in A (%)]: 0.00/2, 2.00/2, 7.00/50, 8.50/80, 9.50/2, 10.0/2; Solvents: solvent A = 5 mM ammonium acetate in water; solvent B = acetonitrile; Injection volume 1μL; Detection wavelength 214 nm; Column temperature 30 °C; Flow rate 0.3 mL per min.

LCMS Method M

Instruments: Agilent 1260 Infinity series UHPLC; ELSD: Agilent 1260 infinity; Column: Acquity C-18, 1.7 micron, 2.1 x50 mm; Gradient [time (min)/solvent B in A (%)]: 0.00/10, 1.00/10, 2.00/15, 4.50/55, 6.00/90, 8.00/90, 9.00/10, 10.00/10; Solvents: A = 5 mM ammonium acetate in water, B = acetonitrile; Injection volume: 1 μL; Detection by ELSD; Column temperature: 40 °C; Flow rate: 0.6 mL per/min.

LCMS Method N

Instruments: Waters Acquity UPLC, Waters 3100 PDA Detector, SQD; Column: Acquity BEH C-18, 1.7 micron, 2.1 x 100 mm; Gradient [time (min)/solvent B in A (%)]: 0.00/2, 0.50/2, 1.50/20, 4.00/92, 5.00/92, 5.50/50, 6.00/2; Solvents: solvent A = 5 mM ammonium acetate in water; solvent B = acetonitrile; Injection volume 1μL; Detection wavelength 214 nm; Column temperature 35 °C; Flow rate 0.6 mL per min.

LCMS Method O

Instruments: Waters Acquity UPLC, Waters 3100 PDA Detector, SQD; Column: Acquity HSS-T3, 1.8 micron, 2.1 x 100 mm; Gradient [time (min)/solvent B in A (%)]: 0.00/10, 1.00/10, 2.00/15, 4.50/55, 6.00/90, 8.00/90, 9.00/10, 10.00/10; Solvents: solvent A = 0.1% trifluoroacetic acid in water; solvent B = acetonitrile; Injection volume 1μL; Detection wavelength 214 nm; Column temperature 30 °C; Flow rate 0.3 mL per min.

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

Abbreviations

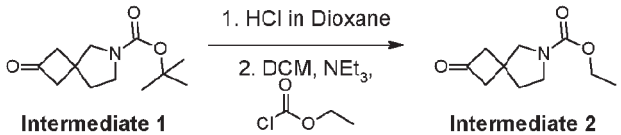
AcOH	=	acetic acid
CDI	=	1,1'-Carbonyldiimidazole
d	=	day(s)
DAST	=	diethylaminosulfur trifluoride

	DCE	=	dichloroethane
	DCM	=	dichloromethane
	DIPEA	=	diisopropylethylamine
	DIAD	=	diisopropyl azodicarboxylate
5	DMF	=	dimethylformamide
	DMP	=	Dess-Martin periodinane
	DMSO	=	dimethylsulfoxide
	ES	=	electro spray ionisation
	EtOAc	=	ethyl acetate
10	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
15	$LiAlH_4$ / LAH	=	Lithium aluminium hydride
	MeCN	=	acetonitrile
	MeOH	=	methanol
	min	=	minute(s)
	MS	=	mass spectrometry
20	Et_3N	=	triethylamine
	NMR	=	nuclear magnetic resonance
	rt	=	room temperature
	sat.	=	saturated
	sol.	=	solution
25	STAB	=	sodium triacetoxyborohydride
	THF	=	tetrahydrofuran
	TLC	=	thin layer chromatography

Prefixes *n*-, *s*-, *i*-, *t*- and *tert*- have their usual meanings: normal, secondary, *iso*, and tertiary.

Synthesis of intermediates:

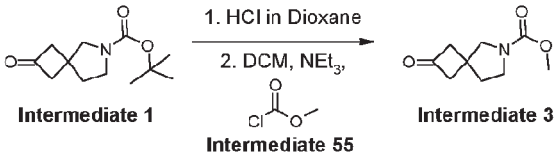
30 **Procedure for the preparation of Intermediate 2, ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate**



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
35 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 $NaHCO_3$ (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.

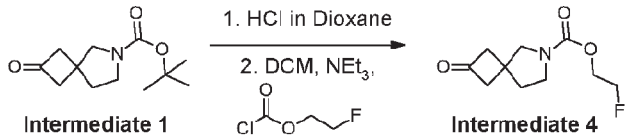
Procedure for the preparation of Intermediate 3, methyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate



Intermediate 1 Intermediate 55 Intermediate 3

6-Boc-2-oxo-6-azaspiro[3.4]octane (5.00 g, 22.2 mmol) was added portionwise to hydrogen chloride (4 M dioxane solution, 45 mL, 180 mmol) in dichloromethane (5 mL). Caution: effervescence. After 2 h, the reaction was concentrated *in vacuo* and 1.29 g of the residual solid dissolved in a mixture of triethylamine (2.23 ml, 16.0 mmol) and dichloromethane (10 mL). On completion of dissolution, the solution was immediately cooled to 0 °C, then methyl chloroformate (0.68 mL, 8.83 mmol) was added dropwise. After 3 h, the mixture was poured into dichloromethane (50 mL), washed with $NaHCO_3$ (aq) (2 × 50 mL) and extracted with DCM (50 mL). The organic layers were combined, washed with brine (50 mL), passed through a Biotage Phase Separator, the solvent was 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, 40 mL per min, gradient 0% to 10% MeOH in DCM]) to give **Intermediate 3**, methyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate as an orange oil (0.93 g, 66%). The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 4, 2-fluoroethyl 2-oxo-6-azaspiro [3.4]octane-6-carboxylate

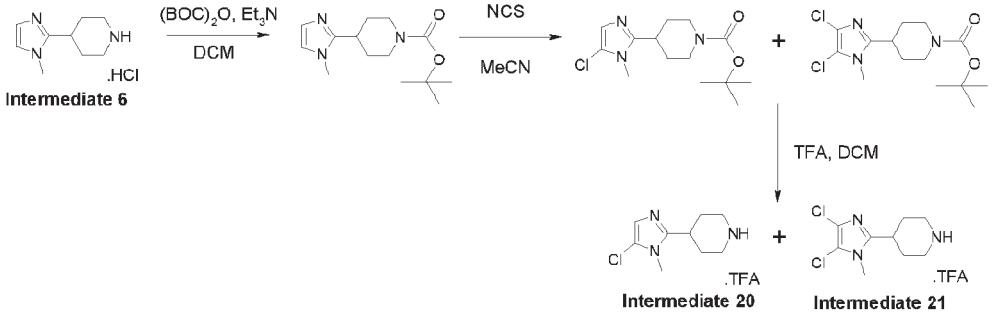


Intermediate 1 Intermediate 4

tert-Butyl 2-oxo-6-azaspiro [3.4] octane-6-carboxylate (5 g, 22.19 mmol) was stirred in HCl in 1,4-dioxane (25 mL) solution for 10 h at rt. The reaction mixture was was concentrated *in vacuo* and triturated with acetone (3 x 50 mL) to give 6-azaspiro[3.4]octan-2-one (2.77 g, 55.4%) as a

brown gum. The residue was dissolved in dry DCM (20mL) and Et_3N (0.7 mL, 4.8mmol) was added. The reaction mixture was cooled to 0°C and 2-fluoroethyl carbonochloridate (0.45 g, 3.6 mmol) was added. The reaction mixture to stir at 30°C for 5 h then diluted with water (50 mL), extracted with DCM (2 x 100 mL), organic layers were combined, dried (Na_2SO_4), and the solvent was removed *in vacuo*. The residue was purified by column chromatography (normal phase, 60-120 mesh silica, 0 to 10% EtOAc in Hexane) to give **Intermediate 4**, 2-fluoroethyl 2-oxo-6-azaspiro [3.4]octane-6-carboxylate (0.2 g, 38.8%) as a brown gum. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediates 20 and 21, 4-(5-chloro-1-methyl-1H-imidazol-2-yl)piperidine trifluoroacetate and 4-(4,5-dichloro-1-methyl-1H-imidazol-2-yl)piperidine trifluoroacetate respectively



4-(1-Methylimidazol-2-yl)piperidine hydrochloride (1 g, 4.96 mmol) was suspended in a mixture of anhydrous DCM (20 mL) and Et_3N (2.1 mL, 15.1 mmol) and cooled in an ice-water bath. $(BOC)_2O$ (1.19 g, 5.45 mmol) was added potion wise over 5 mins, the mixture was warmed to rt and stirred for 48 h. The mixture was diluted with DCM, washed with saturated aqueous $NaHCO_3$ (x2) and brine (x1), then passed through a phase separator and concentrated *in vacuo* to give *tert*-butyl 4-(1-methyl-1*H*-imidazol-2-yl)piperidine-1-carboxylate (1.34 g, quant.) as a solid.

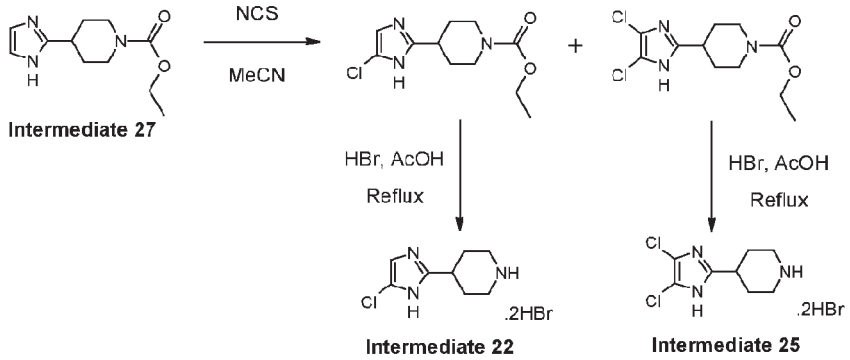
LCMS (Method C): m/z 266 $(M+H)^+$ (ES^+), at 1.43 min, UV active.

tert-Butyl 4-(1-methyl-1*H*-imidazol-2-yl)piperidine-1-carboxylate (0.250 g, 0.942 mmol) was dissolved in MeCN (7.5 mL), treated with NCS (0.314 g, 2.35 mmol) and stirred at rt overnight. The reaction mixture was concentrated onto flash silica (~15 mL) *in vacuo*. The resulting powder was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 50 g, 40-63 μm, 60 Å, 40 mL per min, gradient 2% to 10% Solvent A in DCM over 15 column volumes, where solvent A is 10% of (7 M NH_3/MeOH) in MeOH]) to give a mixture containing *tert*-butyl 4-(5-chloro-1-methyl-1H-imidazol-2-yl)piperidine-1-carboxylate and *tert*-butyl 4-(4,5-dichloro-1-methyl-1H-imidazol-2-yl)piperidine-1-carboxylate and succinimide (0.495 g).

LCMS (Method C): monochloro: m/z 300/302 $(M+H)^+$ (ES^+), at 1.68 min, UV active; dichloro: m/z 334/336/338 $(M+H)^+$ (ES^+), at 1.87 min, UV active. Ratio of monochloro;dichloro ~16:1 by LC-UV.

The mixture containing *tert*-butyl 4-(5-chloro-1-methyl-1H-imidazol-2-yl)piperidine-1-carboxylate and *tert*-butyl 4-(4,5-dichloro-1-methyl-1H-imidazol-2-yl)piperidine-1-carboxylate and succinimide (0.495 g) was dissolved in DCM (5 mL), treated with TFA (5 mL) and stirred at rt for 6 h. The reaction mixture was concentrated *in vacuo* and the residue azeotroped with toluene (x2) to afford a crude mixture of **Intermediate 20**, 4-(5-chloro-1-methyl-1H-imidazol-2-yl)piperidine trifluoroacetate and **Intermediate 21**, 4-(4,5-dichloro-1-methyl-1H-imidazol-2-yl)piperidine trifluoroacetate mixed with succinimide. Assumed quantitative yield. Used with no further purification. The data for the title compounds are in Table 2.

Procedure for the preparation of Intermediates 22 and 25, 4-(5-chloro-1H-imidazol-2-yl)piperidine dihydrobromide and 4-(4,5-dichloro-1H-imidazol-2-yl)piperidine dihydrobromide respectively



Ethyl 4-(1*H*-imidazol-2-yl)piperidine-1-carboxylate (0.40 g, 1.79 mmol) was dissolved in MeCN (12 mL), treated with NCS (0.360 g, 2.70 mmol) and stirred at rt for 5.5 h. The reaction mixture was concentrated onto flash silica (~10 mL) *in vacuo*. The resulting powder was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 50 g, 40-63 μm, 60 Å, 40 mL per min, gradient 0% to 5% Solvent A in DCM over 15 column volumes, then 5% Solvent A in DCM over 5 column volumes, where solvent A is 10% of (7 M NH_3/MeOH) in MeOH]) to give the separated ethyl 4-(5-chloro-1*H*-imidazol-2-yl)piperidine-1-carboxylate and ethyl 4-(4,5-dichloro-1*H*-imidazol-2-yl)piperidine-1-carboxylate, both mixed with succinimide. Each was dissolved in DCM, washed with H_2O (x3), passed through a phase separator and concentrated *in vacuo* to remove succinimide.

Ethyl 4-(5-chloro-1H-imidazol-2-yl)piperidine-1-carboxylate (0.12 g, 26%), **LCMS (Method C)**: m/z 258/260 $(M+H)^+$ (ES^+), at 1.34 min, UV active.

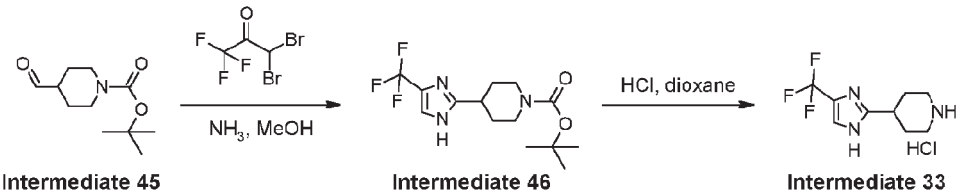
Ethyl 4-(4,5-dichloro-1H-imidazol-2-yl)piperidine-1-carboxylate (0.24 g, 45%), **LCMS (Method C)**: m/z 292/294/296 $(M+H)^+$ (ES^+), at 1.24 min, UV active.

Ethyl 4-(5-chloro-1H-imidazol-2-yl)piperidine-1-carboxylate (0.12 g, 0.47 mmol) was dissolved in AcOH (2 mL), treated with 48% aqueous HBr (2 mL) and heated at reflux at ~ 120° for 2 h. The reaction mixture was concentrated *in vacuo*, the residue was azeotroped with toluene (x1)

and concentrated *in vacuo* to afford a solid. Assumed to be **Intermediate 22**, 4-(5-chloro-1H-imidazol-2-yl)piperidine dihydrobromide salt in quantitative yield. Used immediately.

Ethyl 4-(4,5-dichloro-1H-imidazol-2-yl)piperidine-1-carboxylate (0.24 g, 0.82 mmol) was dissolved in AcOH (2 mL), treated with 48% aqueous HBr (2 mL) and heated ~ 120°C for 2 h. The reaction mixture was concentrated *in vacuo*, the residue was azeotroped with toluene (x1) and concentrated *in vacuo* to afford a solid. Assumed to be **Intermediate 25**, 4-(4,5-Dichloro-1H-imidazol-2-yl)piperidine dihydrobromide in quantitative yield. Used immediately. The data for the title compounds 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



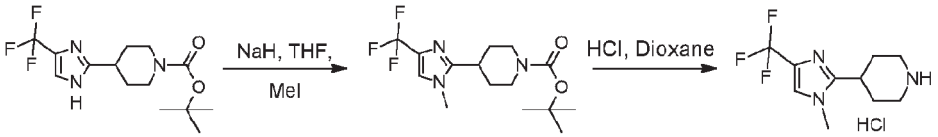
Intermediate 45 **Intermediate 46** **Intermediate 33**

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.

The data for the subtitle compound are in Table 2.

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 x 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 37, 4-[1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl]piperidine hydrochloride salt



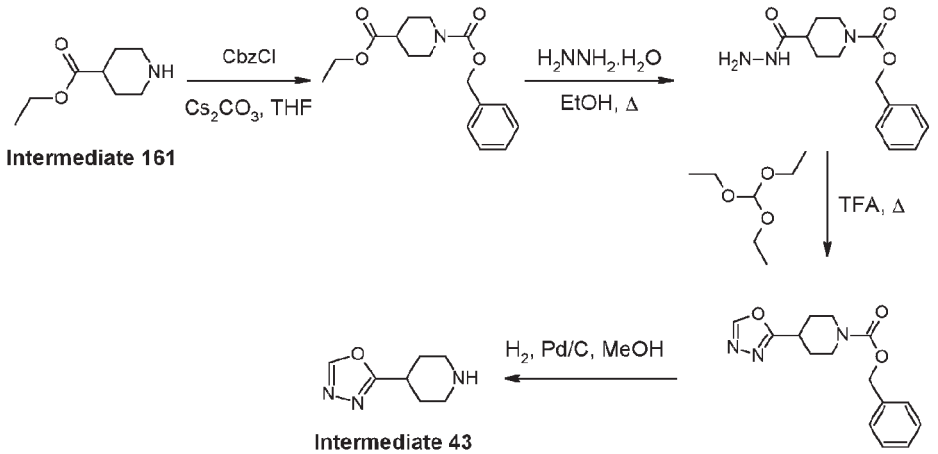
Intermediate 46 **Intermediate 37**

tert-Butyl 4-(4-(trifluoromethyl)-1H-imidazol-2-yl)piperidine-1-carboxylate (200 mg, 0.63 mmol) was dissolved in THF (5 mL) and 60% sodium hydride (74 mg, 1.88 mmol) added at 0°C. The reaction mixture was stirred at 0°C for 10 mins, then methyl iodide (0.06 mL, 0.96 mmol) was added and the resulting reaction mixture was stirred at 25°C for 2 h. The reaction mixture was partitioned between H_2O (60 mL) and EtOAc (45 mL), the aqueous layer was further extracted with EtOAc (2 x 45 mL), the organic layers were combined, dried (Na_2SO_4) and the solvents were removed in vacuo. The residue was purified by column chromatography (Normal silica, mesh size: 60-120, 0% to 2.0% to 3.5% MeOH in DCM) to give tert-butyl 4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)piperidine-1-carboxylate (190 mg, 91%) as a yellow gum.

LCMS (Method F): m/z 334 $(M+H)^+$ (ES^+), at 2.31 min, UV active

tert-Butyl 4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)piperidine-1-carboxylate (200 mg, 0.6 mmol) was dissolved in 1,4-dioxane (5 mL) and followed by dropwise addition of HCl in 1,4-dioxane (20 mL, 4M 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 x 5 mL) to give **Intermediate 37**, 4-[1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl]piperidine hydrochloride salt (140 mg, 86.8%) as a white solid. The data for the title compound are in Table 2

Procedure for the preparation of Intermediate 43, 4-(1,3,4-oxadiazol-2-yl)piperidine



Intermediate 161 **Intermediate 43**

Ethyl piperidine-4-carboxylate (3.0 g, 19.1 mmol) was dissolved in THF (15 mL) and Cs_2CO_3 (7.4 g, 22.9 mmol) added at 0°C. The resulting reaction mixture was stirred at 0 - 5°C for 10 mins, then benzyl chloroformate (3.2 g, 19.1 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was partitioned between

H_2O (100 mL) and EtOAc (200 mL), the aqueous layer was extracted with EtOAc (2 × 200 mL), the organic layers were combined, dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (Normal silica, mesh size: 60-120, 0% to 10% EtOAc in Hexane) to give 1-benzyl 4-ethyl piperidine-1,4-dicarboxylate (4.2 g, 76.4%) as a yellow solid.

LCMS (Method F): m/z 292 $(M+H)^+$ (ES^+), at 2.35 min, UV active

1-Benzyl 4-ethyl piperidine-1,4-dicarboxylate (4.2 g, 14.43 mmol) was dissolved in EtOH (10 mL), hydrazine monohydrate (10 mL, 5.41 mmol) was added and the resulting reaction mixture was stirred at 90°C overnight. The solvents were removed in vacuo and the crude product was triturated with pentane and hexane to give benzyl 4-(hydrazinylcarbonyl)piperidine-1-carboxylate (3.8 g, 95%) as a white solid.

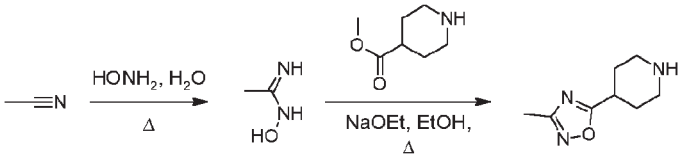
LCMS (Method H): m/z 278 $(M+H)^+$ (ES^+), at 1.76 min, UV active

Benzyl 4-(hydrazinylcarbonyl)piperidine-1-carboxylate (0.5 g, 1.79 mmol), was dissolved in triethylorthoformate (8 mL) and then TFA (0.1 mL) was added. The resulting reaction mixture was stirred at 80°C overnight. The reaction mixture was partitioned between H_2O (50 mL) and EtOAc (100 mL), the aqueous layer was extracted with EtOAc (2 × 100 mL), the organic layers were combined, dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (Normal silica, mesh size: 60-120, 50% to 60% EtOAc in Hexane) to give benzyl 4-(1,3,4-oxadiazol-2-yl)piperidine-1-carboxylate (0.19 g, 38%) as a yellow solid.

LCMS (Method H): m/z 288 $(M+H)^+$ (ES^+), at 2.03 min, UV active

Benzyl 4-(1,3,4-oxadiazol-2-yl)piperidine-1-carboxylate (0.15 g, 0.52 mmol) was dissolved in MeOH (10 mL). Dry 10% Pd on carbon catalyst (20 mg) was added and the reaction mixture was purged with H_2 gas at room temperature. The reaction mixture was stirred at room temperature for 12h under the H_2 atmosphere. The reaction mass was filtered through Celite and the was solvent removed *in vacuo* to give **Intermediate 43**, 4-(1,3,4-oxadiazol-2-yl)piperidine (0.078 g, 99%) as a colorless gum. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 44, 4-(3-methyl-1,2,4-oxadiazol-5-yl)piperidine



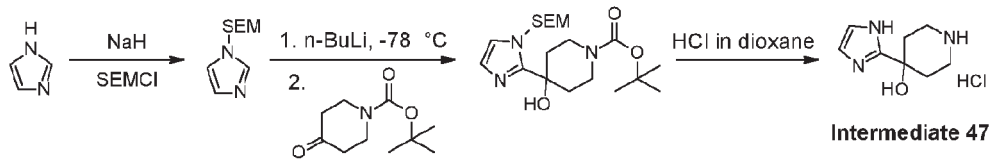
Intermediate 44

Acetonitrile (40.0 mL) and 50% hydroxylamine in water (4.20 mL) were heated at reflux at 90°C for 24 h. The reaction mixture was cooled to 0°C and filtered. The residue was dried to give (Z)-N-hydroxyethanimidamide (2.1 g, >100%) as a white crystalline solid.

LCMS (Method H): m/z 74 $(M+H)^+$ (ES^+), at 1.86 min, UV inactive

(Z)-N-hydroxyethanimidamide (0.50 g, 6.75 mmol) and methyl piperidine-4-carboxylate (1.17 g, 7.42 mmol) were dissolved in ethanol (20 mL). 21% Sodium ethoxide solution in ethanol (0.92 mL, 13.4 mmol) was added dropwise and the reaction mixture was stirred for 30 min at rt and then at 100°C for 16 h. The solvents were removed *in vacuo* and the residue was purified by column chromatography (normal-Phase Silica, 0 to 12% methanol in DCM) to give **Intermediate 44**, 4-(3-methyl-1,2,4-oxadiazol-5-yl)piperidine (380 mg, 34%) as a yellow gum. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 47, 4-(1*H*-imidazol-2-yl)piperidin-4-ol hydrochloride



Intermediate 160 **Intermediate 47**

1H-Imidazole (8.0 g, 117.5 mmol) was dissolved in DMF (100 mL), sodium hydride (4.7 g, 117.5 mmol, 60% in oil) was added at room temperature. The reaction mixture was stirred at rt for 2 h. 2-(trimethylsilyl) ethoxymethyl chloride (20.5 g, 123.38 mmol) was added dropwise to the reaction mixture at rt, after addition the reaction mixture was stirred at rt for 16 h. Reaction mixture was poured onto ice cold water (1000 mL) and extracted with EtOAc (500 mL), the aqueous layer was further extracted with EtOAc (2 x 500 mL), organic layers were combined, dried (Na_2SO_4) and the solvent were removed *in vacuo*. The residue was purified by column chromatography (normal phase silica, 0 to 1% methanol in DCM) to give 1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazole (16.2 g, 68.6%) as light green gum.

LCMS (Method F): m/z 199 $(M+H)^+$ (ES^+), at 1.73 min, UV active

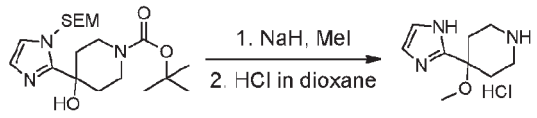
1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (5.0 g, 25.0 mmol) was dissolved in THF (50 mL) and cooled to -78°C. n-BuLi (19.0 mL, 30 mmol, 1.6M in hexane) was added dropwise at -78°C, the reaction mixture was then stirred at -78°C for 1 h. A solution of tert-butyl 4-oxopiperidine-1-carboxylate (5.53g, 27 mmol) in THF (10 mL) was added dropwise at -78°C to the reaction mixture. The reaction mixture was allowed to warm to rt over 2 h. The reaction mixture was quenched with saturated NH_4Cl solution (100 mL), extracted with EtOAc (50 mL), aqueous layer was further extracted with EtOAc (2 x 50 mL), the organic layers were combined, dried (Na_2SO_4), and the solvents were removed *in vacuo*. The residue was purified by column chromatography (normal phase silica, 0 to 20% EtOAc in hexane) to give tert-butyl 4-hydroxy-4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)piperidine-1-carboxylate (8g, 80.0%) as light yellow gum.

LCMS (Method F): m/z 398 $(M+H)^+$ (ES^+), at 2.16 min, UV active

tert-Butyl 4-hydroxy-4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)piperidine-1-carboxylate (2.0 g, 5.0 mmol) was dissolved in 4M HCl in 1,4-Dioxane (20 mL), the reaction

mixture was stirred at rt for 10 h. The solvents were removed *in vacuo*, and the residue was triturated with acetone (3 x 20 mL) to give **Intermediate 47**, 4-(1H-imidazol-2-yl)piperidin-4-ol (0.5 g, 60.2%) as brown gum. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 48, 4-(1*H*-imidazol-2-yl)-4-methoxypiperidine hydrochloride salt

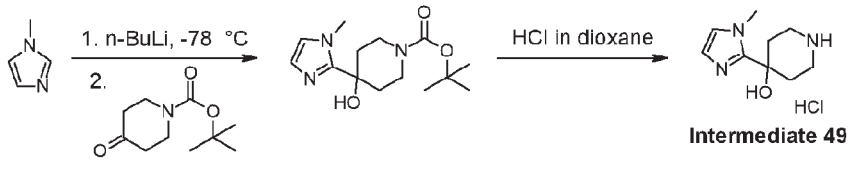


Intermediate 48

tert-Butyl 4-hydroxy-4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)piperidine-1-carboxylate (2.0 g, 5.0 mmol) was dissolved in DMF (20 mL). The solution was cooled to 0°C under N_2 and NaH (0.24 g, 10.0 mmol) was added. The reaction mixture was stirred at 0°C for 30 min then methyl iodide (1.07 g, 7.5 mmol) was added and the reaction mixture was stirred at rt for 2 h. The reaction mixture partitioned between water (50 mL) and EtOAc (50 mL), the aqeous layer was further extracted with EtOAc (3 x 100 mL), the organic layers were combined, dried (Na_2SO_4), and the solvents were removed *in vacuo*. The residue was purified by column chromatography (normal phase, 60-120 mesh silica, 0 to 10% EtOAc in Hexane) to give tert-butyl 4-methoxy-4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)piperidine-1-carboxylate (1.5 g, 75.0%) as yellow gum.

tert-butyl 4-methoxy-4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)piperidine-1-carboxylate (1.5 g, 3.6 mmol) was dissolved in 4M HCl in 1,4-Dioxane (20 mL), the reaction mixture was stirred at rt for 10 h. The solvents were removed *in vacuo*, and the residue was triturated with acetone (3 x 20 mL) to give **Intermediate 48**, 4-(1H-imidazol-2-yl)-4-methoxypiperidine (0.5 g, 76.0%) as brown solid. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 49, 4-(1-methyl-1*H*-imidazol-2-yl)piperidin-4-ol hydrochloride salt



Intermediate 160 **Intermediate 49**

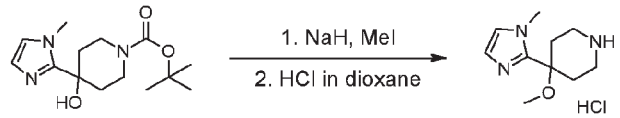
1-Methyl imidazole (6.0 g, 73.0 mmol) was dissolved in THF (100 mL) at rt and the reaction mixture was cooled to -78°C under nitrogen, *n*-BuLi in hexane (45.4 mL, 73.0 mmol) was slowly added. The reaction mixture was gradually warmed to 40°C and stirred for 4 h, then cooled to -78°C. *tert*-Butyl 4-oxopiperidine-1-carboxylate (14.56 g, 73.0 mmol) in THF (100 mL) was added. The reaction mixture was gradually warmed to 40°C and stirred for 10 h, then quenched

with water (50 mL). The reaction mixture was partitioned between EtOAc (200 mL) and water (150 mL), the aqueous layer was extracted with EtOAc (2 x 200 mL) and the organic layers were combined and dried (Na_2SO_4). The solvents were removed *in vacuo*, and the residue was washed with Methanol to give *tert*-butyl 4-hydroxy-4-(1-methyl-1*H*-imidazol-2-yl)piperidine-1-carboxylate (14.0 g, 68.1%) as a solid which was used crude in the subsequent reaction.

LCMS (Method F): m/z 282 $(M+H)^+$ (ES^+), at 2.05 min, UV active

tert-butyl 4-hydroxy-4-(1-methyl-1H-pyrrol-2-yl)piperidine-1-carboxylate (0.5 g, 1.7 mmol) was dissolved in 1,4 dioxane (30 mL) at rt and the reaction mixture was cooled to 0°C under nitrogen, HCl in dioxane (15 mL, 4M sol.) was slowly added. The reaction mixture was stirred at rt for 6 h, the solvents were removed *in vacuo*, and the residue purified by trituration from pentane (10 mL) and diethyl ether (10mL) to give **Intermediate 49**, 4-(1-methyl-1H-imidazol-2-yl)piperidin-4-ol (0.2g, 62.5%) as brown solid. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 50, 4-methoxy-4-(1-methyl-1*H*-imidazol-2-yl)piperidine hydrochloride salt



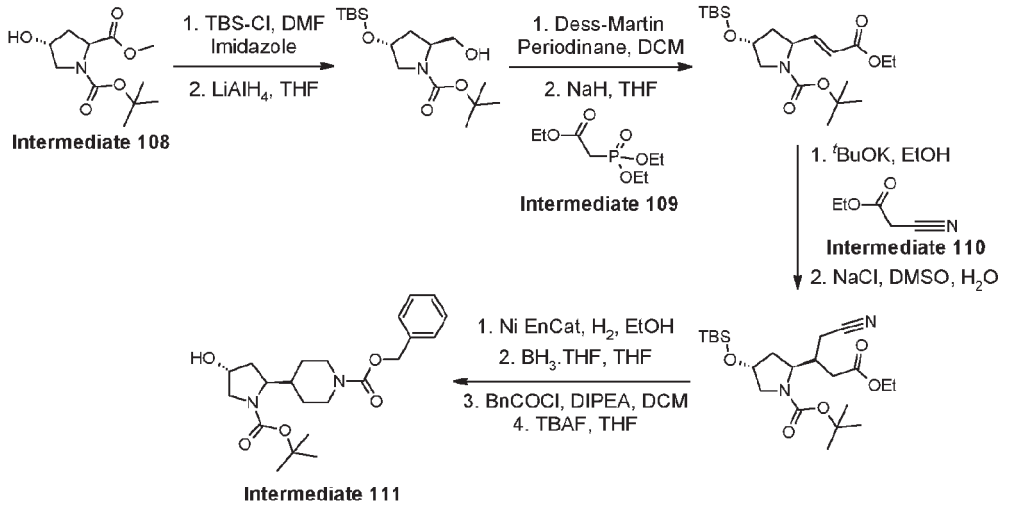
Intermediate 50

tert-Butyl 4-hydroxy-4-(1-methyl-1*H*-imidazol-2-yl)piperidine-1-carboxylate (3.0 g, 10.6 mmol) was dissolved in DMF (50 mL) at rt and the reaction mixture was cooled to 0°C under nitrogen, NaH (0.64 g, 16.0 mmol, 60% dispersion in oil) was added. The reaction mixture was stirred at 0°C for 1 hr and then methyliodide (1.8 g, 128 mmol) was added dropwise. The reaction mixture was warmed rt and stirred for 10 h, then quenched with water (50 mL). The reaction mixture was extracted with EtOAc (3 x 200 mL), and the organic layers were combined and dried (Na_2SO_4). The solvents were removed *in vacuo*, and the residue was purified by column chromatography (normal phase, silica, 60-120 mesh, gradient 0% to 50% EtOAc in Hexane) to give *tert*-butyl 4-methoxy-4-(1-methyl-1*H*-imidazol-2-yl)piperidine-1-carboxylate (1.3 g, 41.3%) as an pale yellow solid.

LCMS (Method F): m/z 296 $(M+H)^+$ (ES^+), at 2.36 min, UV active

tert-Butyl 4-methoxy-4-(1-methyl-1*H*-imidazol-2-yl)piperidine-1-carboxylate (1.3 g, 3.3 mmol) was dissolved in 1,4 dioxane (30 mL) at rt and the reaction mixture was cooled to 0°C under nitrogen, HCl in dioxane (15 mL, 4M sol.) was slowly added. The reaction mixture was stirred at rt for 6 h, the solvents were removed *in vacuo*, and the residue purified by trituration from pentane (10 mL) and diethyl ether (10mL) to give **Intermediate 50**, 4-methoxy-4-(1-methyl-1*H*-imidazol-2-yl)piperidine (0.80 g, 94.1%) as an off white solid. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 111, benzyl 4-[(2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl]piperidine-1-carboxylate



(2S,4R)-1-Boc-4-hydroxy pyrrolidine-2-carboxylic acid methyl ester (25 g, 101.93 mmol) and imidazole (34.687 g, 509.5 mmol) were dissolved in DMF (100 mL) and reaction cooled to 0 °C. *tert*-Butyldimethylsilyl chloride was then added (36.86 g, 244.56 mmol), reaction warmed to RT and stirred for 18 h. Volatiles removed on rotavap and reaction misture diluted with DCM (250 mL). Mixture washed with H_2O (2 x 250 mL), combined aqueous layers washed with DCM (250 mL), combined organic layers washed with saturated $NH_4Cl_{(aq)}$ (250 mL) and brine (250 mL) and passed through Biotage Phase separator. Volatiles removed under vacuum to give (2S,4R)-1-Boc-4-tert-butyldimethylsilyl ether-pyrrolidine-2-carboxylic acid methyl ester (35.812 g, 99%).

LCMS (Method D): m/z 260 $(M+H\text{-}Boc)^+$ (ES+), at 2.64 min, UV inactive

(2S,4R)-1-Boc-4-tert-butyldimethylsilyl ether-pyrrolidine-2-carboxylic acid methyl ester (42.7 g, 118.76 mmol) was dissolved in THF (100 mL) and reaction cooled to 0 °C. Lithium aluminium hydride was then added (120 mL of 1.0M solution in THF, 120.0 mmol) and reaction stirred at 0 °C for 1 h. Reaction quenched with H_2O (4.5 mL), 15% NaOH solution (4.5 mL) and H_2O (13.5 mL) and filtered thorugh a celite plug. Volatiles removed under vacuum to give (2S,4R)-1-Boc-4-tert-butyldimethylsilyl ether-pyrrolidine-2-hydroxy methyl (30.320 g, 77%).

LCMS (Method D): m/z 232 $(M+H\text{-}Boc)^+$ (ES+), at 2.00 min, UV inactive

(2S,4R)-1-Boc-4-tert-butyldimethylsilyl ether-pyrrolidine-2-hydroxy methyl (10.050 g, 30.362 mmol) was dissolved in DCM (100 mL) and Dess-Martin Periodinane (15.371 g, 36.253 mmol) was added. Reaction was stirred at rt for 2 hours, then volatiles removed on rotavap and crude product loaded directly onto Biotage SNAP column (100 g) for purification (10% to 50% EtOAc in n-hexane gradient) yielding (2S,4R)-1-Boc-4-tert-butyldimethylsilyl ether-pyrrolidine-2-carbaldehyde (2.150 g, 22%).

To a suspension of sodium hydride (135 mg of 60% dispersion in oil, 3.338 mmol) in THF (8 mL) at 0°C was added triethylphosphono acetate (0.665 mL, 3.338 mmol). After 10 mins, (2S,4R)-1-Boc-4-tert-butyldimethylsilyl ether-pyrrolidine-2-carbaldehyde (1.002 g, 3.034 mmol) in THF (2 mL) was added and reaction stirred at 0 °C for 30 mins. Volatiles removed on rotavap and reaction mixture diluted with DCM (20 mL). Mixture washed with H_2O (2 x 20 mL), combined aqueous layers washed with DCM (20 mL), combined organic layers washed with brine (20 mL) and passed through Biotage Phase separator. Volatiles removed under vacuum and crude mixture loaded onto Biotage SNAP column (100g) and purified by column chromatography (0 to 30% EtOAc in Hexane) yielding *tert*-butyl (2S,4R)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[(1E)-3-ethoxy-3-oxoprop-1-en-1-yl]pyrrolidine-1-carboxylate as a colourless oil (545 mg, 45%).

LCMS (Method D): m/z 300 $(M+H\text{-}Boc)^+$ (ES+), at 2.85 min, UV inactive.

To a solution of potassium *tert*-butoxide (421 mg, 3.753 mmol) and ethyl cyanoacetate (0.399 mL, 3.753 mmol) in EtOH (5 mL) was added *tert*-butyl (2S,4R)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[(1E)-3-ethoxy-3-oxoprop-1-en-1-yl]pyrrolidine-1-carboxylate (500 mg, 1.251 mmol) and reaction stirred at 78 °C for 18 h. AcOH was added (0.200 mL) and volatiles removed on rotavap. Reaction mixture diluted with DCM (50 mL) and washed with H_2O (2 x 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 and crude mixture loaded onto Biotage SNAP column (100g) and purified by column chromatography (0 to 30% EtOAc in Hexane) yielding diethyl 3-[(4R)-1-(tert-butoxycarbonyl)-4-{[tert-butyl(dimethyl)silyl]oxy}pyrrolidin-2-yl]-2-cyanopentanedioate as a yellow oil (567 mg, 89%).

To a solution of sodium chloride (71 mg, 1.212 mmol) and DMSO (0.040 mL, 2.204 mmol) in H_2O (3 mL) was added diethyl 3-[(4R)-1-(tert-butoxycarbonyl)-4-{[tert-butyl(dimethyl)silyl]oxy}pyrrolidin-2-yl]-2-cyanopentanedioate (565 mg, 1.102 mmol) and reaction stirred at 145 °C for 2 h. Ice water was added was added (50 mL) followed by EtOAc (50 mL) and organic layer washed with H_2O (2 x 50 mL). Combined organic layers washed with brine (50 mL) and passed through Biotage Phase separator. Volatiles removed under vacuum and crude mixture loaded onto Biotage SNAP column (50g) and purified by column chromatography (0 to 30% EtOAc in Hexane) yielding tert-butyl (4R)-4-{[tert-butyl(dimethyl)silyl]oxy}-2-(1-cyano-4-ethoxy-4-oxobutan-2-yl)pyrrolidine-1-carboxylate as a yellow oil (351 mg, 72%).

LCMS (Method D): m/z 341 $(M+H\text{-}Boc)^+$ (ES+), at 2.77 min, UV inactive

To a flask containing NiEnCat™ (65g wet beads, ~0.25 equiv.) was added tert-butyl (4R)-4-{[tert-butyl(dimethyl)silyl]oxy}-2-(1-cyano-4-ethoxy-4-oxobutan-2-yl)pyrrolidine-1-carboxylate (8.700 g, 19.7 mmol) in EtOH (75 mL) and reaction stirred at 78 °C under a hydrogen balloon atmosphere for 96 h. Reaction mixture filtered over a celite plug and volatiles removed under vacuum, the crude mixture was loaded onto Biotage SNAP column (340g) and purified by

column chromatography (2.5 to 10% MeOH in DCM) yielding *tert*-butyl (4R)-4-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-oxopiperidin-4-yl)pyrrolidine-1-carboxylate as a yellow oil (4.665 g, 59%).

LCMS (Method D): m/z 399 $(M+H)^+$ (ES+), at 1.90 min, UV inactive

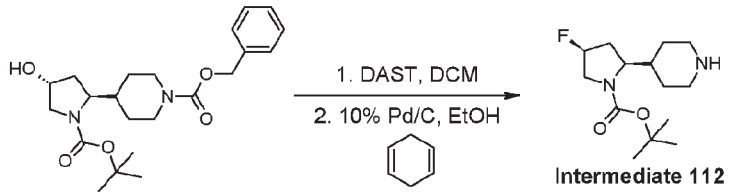
To a solution of *tert*-butyl (4R)-4-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-oxopiperidin-4-yl)pyrrolidine-1-carboxylate (1.850 g, 4.648 mmol) THF (30 mL) was added borane:tetrahydrofuran (9.3 mL of 1.0M solution in THF, 9.300 mmol) at 0°C and reaction stirred at 60 °C for 30 mins. Reaction cooled to rt and quenched with MeOH (10 mL) and volatiles removed on rotavap. Reaction mixture diluted with DCM (100 mL) and washed with 1M $NaOH_{(aq)}$ (2 x 100 mL), combined aqueous layers washed with DCM (100 mL), combined organic layers washed with brine (250 mL) and passed through Biotage Phase separator. Volatiles removed under vacuum yielding tert-butyl (2S,4R)-4-{[tert-butyl(dimethyl)silyl]oxy}-2-(piperidin-4-yl)pyrrolidine-1-carboxylate as a yellow oil (1.830 g, >99%).

LCMS (Method D): m/z 285 $(M+H\text{-}Boc)^+$ (ES+), at 3.00 min, UV inactive

To a solution of tert-butyl (2S,4R)-4-{[tert-butyl(dimethyl)silyl]oxy}-2-(piperidin-4-yl)pyrrolidine-1-carboxylate (1.830 g, 4.766 mmol) in DCM (20 mL) was added diisopropylethylamine (1.814 mL, 10.484 mmol) and benzyl chloroformate (0.816 mL, 5.719 mmol) at 0°C. Reaction warmed to rt and stirred for 18 h. Reaction mixture diluted with DCM (100 mL) and washed with 1M $NaOH_{(aq)}$ (2 x 100 mL), combined aqueous layers washed with DCM (100 mL), combined organic layers washed with brine (250 mL) and passed through Biotage Phase separator. Volatiles removed under vacuum and crude mixture loaded onto Biotage SNAP column (100g) and purified by column chromatography (10 to 40% EtOAc in Hexane) yielding benzyl 4-[(2S,4R)-1-(tert-butoxycarbonyl)-4-{[tert-butyl(dimethyl)silyl]oxy}pyrrolidin-2-yl]piperidine-1-carboxylate as a colourless oil (700 mg, 28%).

To a solution of benzyl 4-[(2S,4R)-1-(tert-butoxycarbonyl)-4-{[tert-butyl(dimethyl)silyl]oxy}pyrrolidin-2-yl]piperidine-1-carboxylate (0.780 g, 1.504 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (1.800 mL of 1.0 M THF solution, 1.800 mmol) and reaction stirred at rt for 1 h. Reaction mixture diluted with DCM (100 mL) and washed with H_2O (2 x 100 mL), combined aqueous layers washed with DCM (100 mL), combined organic layers washed with brine (250 mL) and passed through Biotage Phase separator. Volatiles removed under vacuum yielding **Intermediate 111**, benzyl 4-[(2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl]piperidine-1-carboxylate, as a colourless oil (500 mg, 82%). The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 112, *tert*-butyl (2*S*,4*S*)-4-fluoro-2-(piperidin-4-yl)pyrrolidine-1-carboxylate



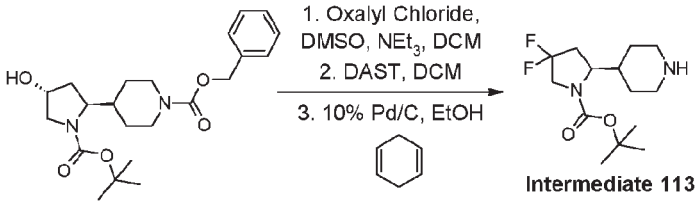
Intermediate 111 **Intermediate 112**

Benzyl 4-[(2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl]piperidine-1-carboxylate (100 mg, 0.247 mmol) was dissolved in DCM (1 mL) at -40 °C and DAST was added (0.049 mL, 0.371 mmol). Reaction warmed to rt and stirred for 2 h. Reaction mixture diluted with DCM (25 mL) and washed with saturated $NaHCO_{3(aq)}$ (2 x 25 mL), combined aqueous layers washed with DCM (25 mL), combined organic layers washed with brine (25 mL) and passed through Biotage Phase separator. Volatiles removed under vacuum to yield benzyl 4-[(2S,4S)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidin-2-yl]piperidine-1-carboxylate (0.090 g, 90%).

LCMS (Method D): m/z 307 $(M+H\text{-}Boc)^+$ (ES+), at 2.31 min, UV inactive

To a solution of benzyl 4-[(2S,4S)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidin-2-yl]piperidine-1-carboxylate (0.090 g, 0.221 mmol) dissolved in EtOH (2 mL) was added 10% Pd/C (10 mg) and 1,4 cyclohexadiene (0.147 mL, 1.530 mmol) and reaction stirred at 70 °C for 1 h. Reaction filtered thorugh a celite plug and volatiles removed under vacuum to yield **Intermediate 112**, *tert*-butyl (2*S*,4*S*)-4-fluoro-2-(piperidin-4-yl)pyrrolidine-1-carboxylate (55 mg, 92%). The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 113, *tert*-butyl (2*S*)-4,4-difluoro-2-(piperidin-4-yl)pyrrolidine-1-carboxylate



Intermediate 111 **Intermediate 113**

Oxalyl chloride (0.065 mL, 0.741 mmol) was dissolved in DCM (1 mL) at -78 °C and DMSO was added (0.100 mL). After 5 minutes at -78 °C, benzyl 4-[(2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl]piperidine-1-carboxylate (200 mg, 0.494 mmol) was added in DCM (2 mL) followed by triethylamine (0.345 mL, 2.47 mmol) after a further 5 mins at -78 °C. Reaction warmed to rt and stirred for 30 mins. Reaction mixture diluted with DCM (25 mL) and washed with saturated $NaHCO_{3(aq)}$ (2 x 25 mL), combined aqueous layers washed with DCM (25 mL), combined organic layers washed with brine (25 mL) and passed through Biotage Phase separator. Volatiles removed under vacuum to yield benzyl 4-[(2S)-1-(tert-butoxycarbonyl)-4-oxopyrrolidin-2-yl]piperidine-1-carboxylate (0.170 g, 85%).

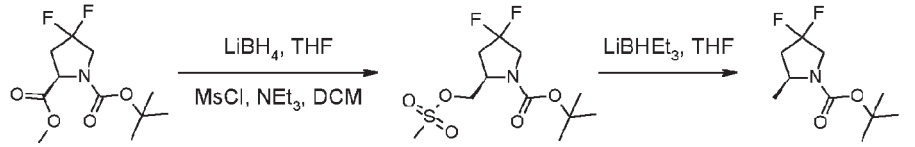
LCMS (Method D): m/z 303 $(M+H\text{-}Boc)^+$ (ES+), at 2.15 min, UV inactive

benzyl 4-[(2S)-1-(tert-butoxycarbonyl)-4-oxopyrrolidin-2-yl]piperidine-1-carboxylate (170 mg, 0.422 mmol) was dissolved in DCM (1 mL) at -78 °C and DAST was added (0.167 mL, 1.267 mmol). Reaction warmed to rt and stirred for 18 h. Reaction mixture diluted with DCM (25 mL) and washed with saturated $NaHCO_{3(aq)}$ (2 x 25 mL), combined aqueous layers washed with DCM (25 mL), combined organic layers washed with brine (25 mL) and passed through Biotage Phase separator. Volatiles removed under vacuum to yield benzyl 4-[(2S)-1-(tert-butoxycarbonyl)-4,4-difluoropyrrolidin-2-yl]piperidine-1-carboxylate (0.070 g, 39%).

LCMS (Method D): m/z 325 $(M+H\text{-}Boc)^+$ ($ES+$), at 2.41 min, UV inactive

To a solution of benzyl 4-[(2S)-1-(tert-butoxycarbonyl)-4,4-difluoropyrrolidin-2-yl]piperidine-1-carboxylate (0.067 g, 0.158 mmol) dissolved in EtOH (2 mL) was added 10% Pd/C (10 mg) and 1,4 cyclohexadiene (0.105 mL, 1.105 mmol) and reaction stirred at 70 °C for 1 h. Reaction filtered thorugh a celite plug and volatiles removed under vacuum to yield **Intermediate 113**, *tert*-butyl (2*S*)-4,4-difluoro-2-(piperidin-4-yl)pyrrolidine-1-carboxylate (30 mg, 65%). The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 125, tert-butyl (2S)-4,4-difluoro-2-methylpyrrolidine-1-carboxylate



Intermediate 257 **Intermediate 125**

To 1-tert-butyl 2-methyl (2R)-4,4-difluoropyrrolidine-1,2-dicarboxylate (2 g, 7.5 mmol) in THF (20 mL) was added lithium borohydride solution in THF (2.0 M, 7.5 mL, 15 mmol) at 0°C and the reaction was warmed to RT and stirred for 2 h. The reaction was quenched by the portion-wise addition of saturated aqueous $NaHCO_3$, and once effervescence had ceased, the mixture was concentrated to remove THF. The aqueous mixture was partitioned between saturated aqueous $NaHCO_3$ and DCM (x2), the organic phases were passed through a phase separator and concentrated to afford the crude tert-butyl (2R)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (1.98 g, > 100%) as an oil.

LCMS (Method C): m/z 260 $(M+Na)^+$ (ES^+), at 1.09 min, UV inactive.

To a solution of tert-butyl (2R)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (1 g, 4.2 mmol) in DCM (10 mL) and triethylamine (1.5 mL, 11 mmol) at 0 °C was added MsCl (0.42 mL, 5.4 mmol) portion-wise. The mixture was stirred at 0 °C for 100 min, then partitioned between ice cold saturated aqueous $NaHCO_3$ and ice cold DCM (x2), the organic phases were passed through a phase separator and concentrated to afford the crude tert-butyl (2R)-4,4-difluoro-2-{[(methylsulfonyl)oxy]methyl}pyrrolidine-1-carboxylate (1.55 g, > 100%) as an oil.

LCMS (Method C): m/z 338 $(M+Na)^+$ (ES^+), at 1.28 min, UV inactive.

To a solution of tert-butyl (2R)-4,4-difluoro-2-{[(methylsulfonyl)oxy]methyl}pyrrolidine-1-carboxylate (1.55 g, 4.9 mmol) in THF (15 mL) at 0°C was added $LiBHEt_3$ solution in THF (1.0 M, 9.8 mL, 9.8 mmol), potion-wise over 10 min. The mixture was then stirred for 3 days, allowing the cooling bath to expire. The mixture was cooled back to 0°C, quenched by the addition of H_2O, then concentrated to remove THF. The aqueous mixture was partitioned between saturated aqueous $NaHCO_3$ and DCM (x2), the organic phases were passed through a phase separator and concentrated to afford the crude **Intermediate 125**, tert-butyl (2S)-4,4-difluoro-2-methylpyrrolidine-1-carboxylate (0.89 g, 82%) as an oil. 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

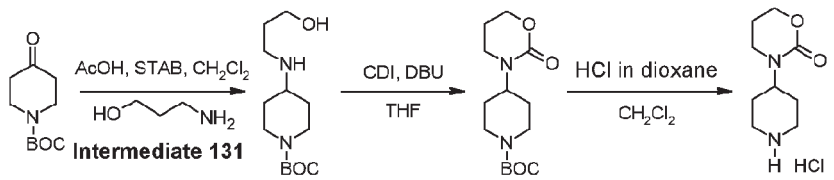


Intermediate 121 **Intermediate 126**

(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 x 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%).

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 x 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%).

Procedure for the preparation of Intermediate 132, 3-(piperidin-4-yl)-1,3-oxazinan-2-one hydrochloride



tert-Butyl 4-oxopiperidine-1-carboxylate (0.796 g, 4.00 mmol) and 3-aminopropan-1-ol (0.330 g, 4.4 mmol) were mixed in CH_2Cl_2 (20 mL) at rt, AcOH (0.68 mL, 12.0 mmol) was added and stirred for 3 h. STAB (2.34 g, 10.0 mmol) was added and the reaction mixture was stirred under nitrogen at rt overnight. The reaction mixture was quenched with the addition of $NaHCO_3$ (sat aq.) (40 mL) extracted with CH_2Cl_2 (4 x 45 mL) and the combined organic layers were washed with brine, then dried over $MgSO_4$ and filtered. The solvents were removed *in vacuo* to give crude *tert*-butyl 4-[(3-hydroxypropyl)amino]piperidine-1-carboxylate (1.03 g, 4.00 mmol) which was used without purification.

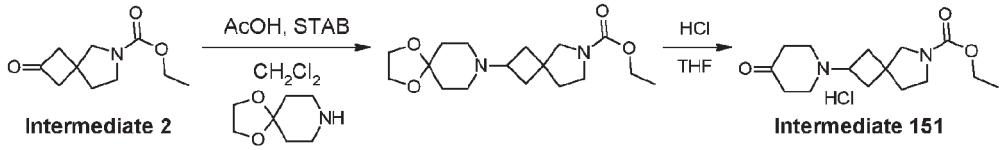
LCMS (Method B): m/z 259 $(M+H)^+$ (ES+), at 0.24 min, UV inactive.

tert-Butyl 4-[(3-hydroxypropyl)amino]piperidine-1-carboxylate (1.03 g, 4.00 mmol), CDI (1.36 g, 8.4 mmol) and DBU (0.24 mL, 1.60 mmol) were dissolved in THF (40 mL), the mixture heated to reflux and maintained for 72 h. The solvents were removed *in vacuo* and the residue purified by column chromatography [Biotage SNAP cartridge KP-sil 25g, 40-63 μm, 60 Å, 50 mL per min, gradient 0% to 10% MeOH in DCM]) to give *tert*-butyl 4-(2-oxo-1,3-oxazinan-3-yl)piperidine-1-carboxylate (0.60 g, 53%) as a colourless oil.

LCMS (Method B): m/z 307 $(M+Na)^+$ (ES+), at 0.16 min, UV inactive.

tert-Butyl 4-(2-oxo-1,3-oxazinan-3-yl)piperidine-1-carboxylate (0.60 g, 2.11 mmol) was dissolved in CH_2Cl_2 (21 mL), 4 M hydrogen chloride in dioxane (2.64 mL, 10.5 mmol) added and the reaction mixture stirred at rt overnight. The precipitate was collected by filtration, washed with CH_2Cl_2 (2 x 20 mL) and dried to give **Intermediate 132**, 3-(piperidin-4-yl)-1,3-oxazinan-2-one hydrochloride (0.352 g, 76%) as a colourless solid. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 151, ethyl 2-(4-oxopiperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate hydrochloride

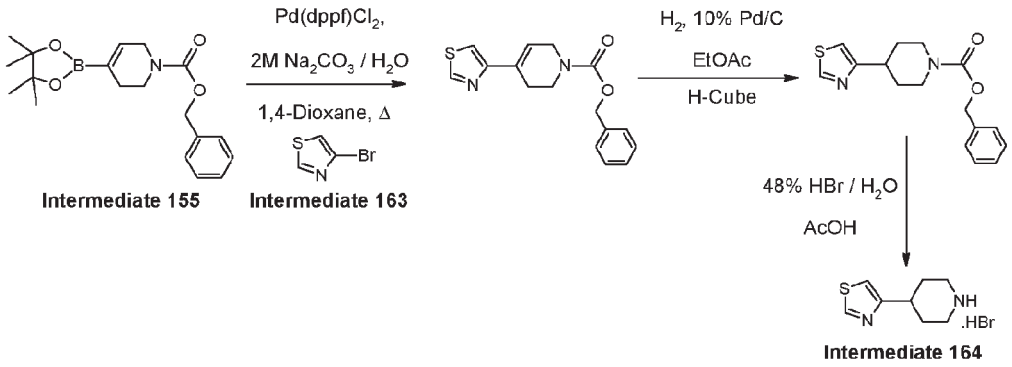


Ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate (0.985 g, 5.00 mmol) and 1,4-dioxa-8-azaspiro[4.5]decane (0.715 g, 5.00 mmol) were mixed in CH_2Cl_2 (50 mL) at rt, AcOH (0.31 mL, 5.50 mmol) was added and stirred for 3 h. STAB (2.65 g, 12.5 mmol) was added and the reaction mixture was stirred under nitrogen at rt overnight. The reaction mixture was quenched with the addition of $NaHCO_3$ (sat aq.) (40 mL) extracted with CH_2Cl_2 (4 x 45 mL) and the combined organic layers were washed with brine, then dried over $MgSO_4$ and filtered. The solvents were removed *in vacuo* to give crude ethyl 2-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-6-azaspiro[3.4]octane-6-carboxylate as a mixture of diastereomers which was used without further purification.

LCMS (Method D): m/z 325 $(M+H)^+$ (ES+), at 1.11 min and 1.16 min, UV inactive.

Crude ethyl 2-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-6-azaspiro[3.4]octane-6-carboxylate (1.62 g, 5.00 mmol) was dissolved in THF (10 mL), water (10 mL) and concentrated hydrochloric acid (10 mL) were added and the mixture stirred at rt overnight. The solvents were removed *in vacuo* and the residue tritiated from Et_2O to give **Intermediate 151**, ethyl 2-(4-oxopiperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate hydrochloride (1.30g, 82%) as a colourless solid. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 164, 4-(1,3-thiazol-4-yl)piperidine hydrobromide



Aqueous sodium carbonate solution (2M) and 1,4-dioxane were both degassed by passing a stream of nitrogen through a fritted glass tube into the liquids for 15 min. Benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (250 mg, 0.73 mmol), 4-bromo-1,3-thiazole (119 mg, 0.73 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (32 mg, 0.044 mmol), degassed aqueous sodium carbonate solution (2M, 1.1 mL, 2.2 mmol) and degassed 1,4-dioxane (3 mL) were placed into a nitrogen flushed tube, sealed and heated under pressure at 90 °C for 2.5 h. The cooled reaction mixture was diluted with H_2O and extracted with EtOAc. The organic phase was passed through a phase separator and concentrated onto flash silica (15 mL). The resulting powder was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 50 g, 40-63 μm, 60 Å], 40 mL per min, 65% Et_2O in isohexane isochratic) to give benzyl 4-(1,3-thiazol-4-yl)-3,6-dihydropyridine-1(2H)-carboxylate (173 mg, 79%).

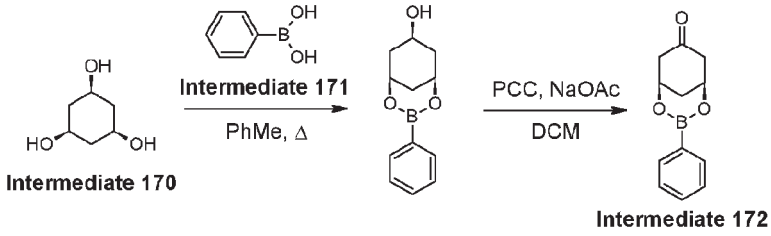
LCMS (Method C): m/z 301 $(M+H)^+$ (ES^+), at 1.46 min, UV active.

A solution of benzyl 4-(1,3-thiazol-4-yl)-3,6-dihydropyridine-1(2H)-carboxylate (150 mg, 0.50 mmol) in EtOAc (10 mL) was hydrogenated over 10% palladium on carbon catalyst at 100 bar pressure and at 50 °C at a flow rate of 1 mL / min using a H-Cube apparatus. The solution was concentrated to give benzyl 4-(1,3-thiazol-4-yl)piperidine-1-carboxylate (143 mg, 95%).

LCMS (Method A): m/z 303 $(M+H)^+$ (ES^+), at 1.92 min, UV active.

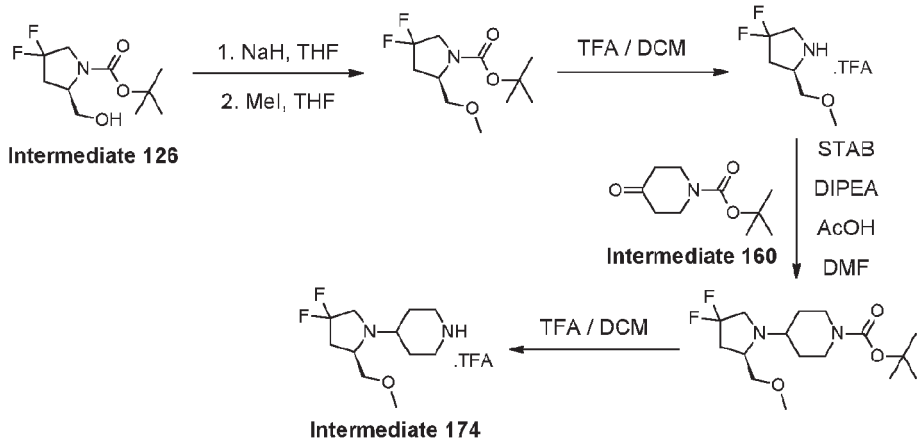
A solution of benzyl 4-(1,3-thiazol-4-yl)piperidine-1-carboxylate (127 mg, 0.42 mmol) in AcOH (1 mL) and 48% aqueous HBr (1 mL) was stirred at RT overnight. The mixture was then concentrated and the residue azeotroped with toluene to give **Intermediate 164**, 4-(1,3-thiazol-4-yl)piperidine hydrobromide (160 mg, >100%). The data for the title compound is in Table 2.

Procedure for the preparation of Intermediate 172, (1R,5S)-3-phenyl-2,4-dioxa-3-borabicyclo[3.3.1]nonan-7-one



(1S,3S,5S)-Cyclohexane-1,3,5-triol (1.0 g, 6.0 mmol) and phenylboronic acid (0.72 g, 6.0 mmol) were dissolved in toluene (35 mL) and heated at reflux at 120 °C for 16 h. The reaction mixture was concentrated to give the crude (1R, 5S, 7R)-3-phenyl-2,4-dioxa-3-borabicyclo[3.3.1]nonan-7-ol (1.43 g, 87%) as a solid, which was used immediately. (1R, 5S, 7R)-3-phenyl-2,4-dioxa-3-borabicyclo[3.3.1]nonan-7-ol (1.4 g, 6.4 mmol) was dissolved in DCM (50 mL). Sodium acetate (1.31 g, 16 mmol) and pyridinium chlorochromate (12.9 g, 11 mmol) were added and the reaction mixture was stirred for 16 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated to give the crude product which was recrystallization from DCM:hexane (1:4) to give **Intermediate 172**, (1R,5S)-3-phenyl-2,4-dioxa-3-borabicyclo[3.3.1]nonan-7-one (0.65 g, 38%) as a solid. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 174, 4-[(2R)-4,4-difluoro-2-(methoxymethyl)pyrrolidin-1-yl]piperidine trifluoroacetate salt



A solution of *tert*-butyl (2*R*)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (150 mg, 0.63 mmol) in THF (5 mL) was cooled in ice water and treated with 60% sodium hydride suspension in mineral oil (30 mg, 0.75 mmol). The mixture was stirred in ice for 30 min then at RT for 1.5 h before adding methyl iodide (0.118 mL, 1.9 mmol) and stirring at RT overnight. The mixture was quenched with a drop of H_2O then concentrated to remove THF. The residue was partitioned between sat. aqueous $NaHCO_3$ and DCM (x2), the organic phase was passed through a phase separator and concentrated to give the crude *tert*-butyl (2*R*)-4,4-difluoro-2-(methoxymethyl)pyrrolidine-1-carboxylate (110 mg, 69%) as an oil.

LCMS (Method C): m/z 274 $(M+Na)^+$ (ES^+), at 1.35 min, UV inactive.

A solution of the crude *tert*-butyl (2*R*)-4,4-difluoro-2-(methoxymethyl)pyrrolidine-1-carboxylate (110 mg, 0.44 mmol) in DCM (2 mL) and TFA (2 mL) was stirred at RT for 40 min then diluted with toluene and concentrated. The residue was azeotroped with toluene (x2) to give the crude (2*R*)-4,4-difluoro-2-(methoxymethyl)pyrrolidine trifluoroacetate salt as an oil (172 mg, >100%).

LCMS (Method C): m/z 152 $(M+H)^+$ (ES^+), at 0.73 min, UV inactive.

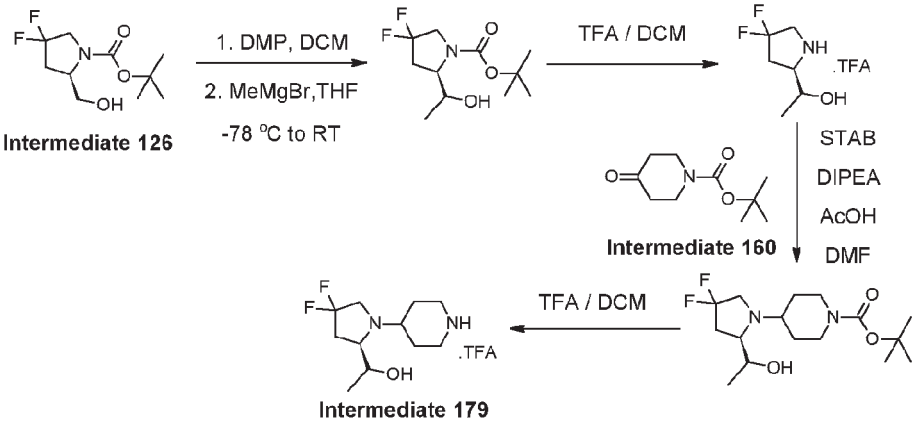
The crude (2*R*)-4,4-difluoro-2-(methoxymethyl)pyrrolidine trifluoroacetate salt (172 mg, assumed 0.44 mmol) was dissolved in DMF (5 mL). To the solution was added DIPEA (0.38 mL, 2.2 mmol), AcOH (0.038 mL, 0.66 mmol), *tert*-butyl 4-oxopiperidine-1-carboxylate (0.087 g, 0.44 mmol) and STAB (0.278 g, 1.3 mmol) in that order. The mixture was stirred at RT for 2 days, then concentrated to remove DMF. The residue was partitioned between sat. aqueous $NaHCO_3$ and DCM (x2) and the organic phase was passed through a phase separator and concentrated to give the crude *tert*-butyl 4-[(2*R*)-4,4-difluoro-2-(methoxymethyl)pyrrolidin-1-yl]piperidine-1-carboxylate (0.241 g, >100%) as an oil.

LCMS (Method C): m/z 335 $(M+H)^+$ (ES^+), at 1.43 min, UV inactive.

A solution of the crude *tert*-butyl 4-[(2*R*)-4,4-difluoro-2-(methoxymethyl)pyrrolidin-1-yl]piperidine-1-carboxylate (0.241 g, assumed 0.44 mmol) in DCM (2 mL) and TFA (2 mL) was stirred at RT for 45 min then diluted with toluene and concentrated. The residue was azeotroped with toluene (x2) to give the crude **Intermediate 174**, 4-[(2R)-4,4-difluoro-2-(methoxymethyl)pyrrolidin-1-yl]piperidine trifluoroacetate salt as an oil.

The data for the title compound is in Table 2.

Procedure for the preparation of Intermediate 179, 1-[(2R)-4,4-difluoro-1-(piperidin-4-yl)pyrrolidin-2-yl]ethanol trifluoroacetate salt



Intermediate 126

Intermediate 160

Intermediate 179

A solution of *tert*-butyl (2*R*)-4,4-difluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (150 mg, 0.63 mmol) in DCM (5 mL) was cooled in ice water and treated with Dess-Martin Periodinane (402 mg, 0.95 mmol). The cooling bath was removed and the mixture was stirred at RT for 3 h. Sat. aqueous $NaHCO_3$ (5 mL), sat. aqueous sodium thiosulphate (5 mL) and EtOAc (10 mL) were added and the mixture was stirred vigorously for 30 min. The phases were separated and the aqueous was re-extracted with EtOAc. The combined organic phases were passed through a phase separator and concentrated to give the crude aldehyde, which was immediately dissolved in THF (5 mL), cooled to -78 °C and treated with methylmagnesium bromide in ether (3M, 0.42 mL, 1.3 mmol). The mixture was removed from the cooling bath, stirred for 2.75 h and then quenched by the addition of sat. aqueous NH_4Cl. The mixture was concentrated to remove THF and then partitioned between sat. NH_4Cl and DCM (x2). The organic phase was passed through a phase separator and concentrated onto flash silica (10 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, 20 to 50% EtOAc in isohexane, to give *tert*-butyl (*2R*)-4,4-difluoro-2-(1-hydroxyethyl)pyrrolidine-1-carboxylate (0.106 g, 67%) as an oil.

LCMS (Method C): m/z 152 $(M\text{-}BOC+H)^+$, 196 $(M\text{-}tBu+H)^+$ (ES^+), at 1.24 min, UV inactive.

A solution of the *tert*-butyl (*2R*)-4,4-difluoro-2-(1-hydroxyethyl)pyrrolidine-1-carboxylate (102 mg, 0.41 mmol) in DCM (2 mL) and TFA (2 mL) was stirred at RT for 30 min then diluted with toluene and concentrated. The residue was azeotroped with toluene to give the crude 1-[(2R)-4,4-difluoropyrrolidin-2-yl]ethanol trifluoroacetate salt as a gum. Used immediately.

LCMS (Method C): m/z 152 $(M+H)^+$ (ES^+), at 0.27 min, UV inactive.

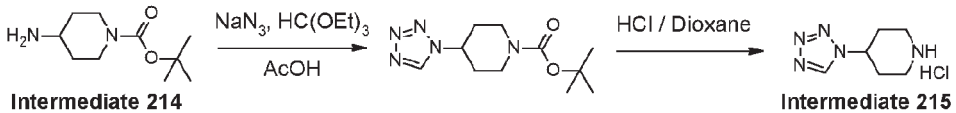
The crude 1-[(2R)-4,4-difluoropyrrolidin-2-yl]ethanol trifluoroacetate salt from above (assumed 0.41 mmol) was dissolved in DMF (5 mL). To the solution was added DIPEA (0.38 mLm, 2.0 mmol), AcOH (0.035 mL, 0.61 mmol), *tert*-butyl 4-oxopiperidine-1-carboxylate (0.081 g, 0.41 mmol) and STAB (0.258 g, 1.2 mmol) in that order. The mixture was stirred at RT for 3 days, then concentrated to remove DMF. The residue was azeotroped with toluene, dissolved in MeOH and 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 15% Solvent A in DCM, where Solvent A is 10% of (7 M NH3/MeOH) in MeOH) to give tert-butyl 4-[(2R)-4,4-difluoro-2-(1-hydroxyethyl)pyrrolidin-1-yl]piperidine-1-carboxylate (0.301 g, >100%) as an oil.

LCMS (Method C): m/z 335 $(M+H)^+$ (ES^+), at 1.41 min, UV inactive.

A solution of tert-butyl 4-[(2R)-4,4-difluoro-2-(1-hydroxyethyl)pyrrolidin-1-yl]piperidine-1-carboxylate (0.301 g, assumed 0.41 mmol) in DCM (2 mL) and TFA (2 mL) was stirred at RT for 30 min then diluted with toluene and concentrated. The residue was azeotroped with toluene to give the crude **Intermediate 179**, 1-[(2R)-4,4-difluoro-1-(piperidin-4-yl)pyrrolidin-2-yl]ethanol trifluoroacetate salt as an oil (0.553 g, >100%). The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 215, 4-(1H-tetrazol-1-yl)piperidine hydrochloride salt



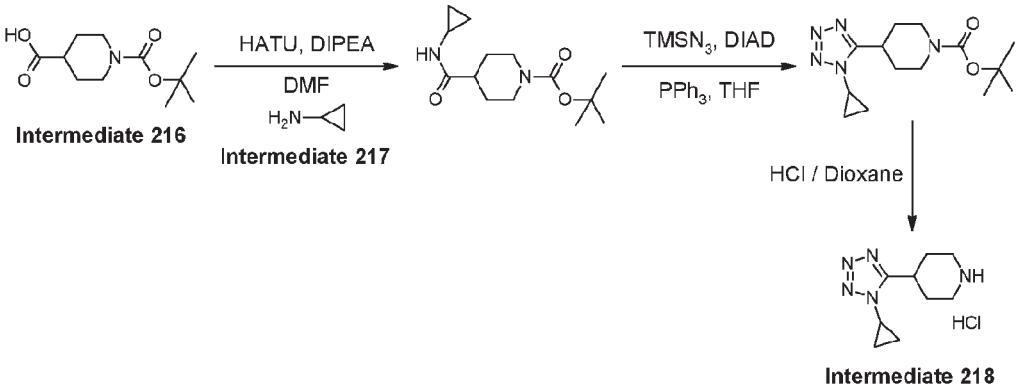
Intermediate 214 **Intermediate 215**

Triethylorthoformate (3.5 g, 23 mmol), tert-butyl 4-aminopiperidine-1-carboxylate (0.80 g, 3.9 mmol) and sodium azide (1.52 g, 23 mmol) were dissolved in acetic acid (50 mL). The resulting reaction mixture was stirred at 100 °C for 6 h, then cooled to RT. The volatiles were removed by concentration and the residue was partitioned between H_2O (100 mL) and ethyl acetate (150 mL). The aqueous layer was further extracted with ethyl acetate (2 x 100 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed by concentration to give the crude product, which was triturated with diethyl ether to give tert-butyl 4-(1H-tetrazol-1-yl) piperidine-1-carboxylate (0.51 g, 9 %) as a solid.

LCMS (Method F): m/z 254 $(M+H)^+$ (ES^+), at 1.92 min, weakly UV active.

tert-Butyl 4-(1H-tetrazol-1-yl) piperidine-1-carboxylate (0.51 g, 2.0 mmol) was dissolved in 1, 4-dioxane (10 mL). A solution of HCl in 1, 4-dioxane (4M, 5 mL, 20 mmol) was added dropwise and the resulting mixture was stirred at RT for 16 h. The solvents were removed by concentration and the residue was purified by triturating with diethyl ether (3 x 10 mL) to give **Intermediate 215**, 4-(1H-tetrazol-1-yl)piperidine hydrochloride (0.30 g, 97 %) as a solid. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 218, 4-(1-cyclopropyl-1H-tetrazol-5-yl)piperidine hydrochloride salt



Intermediate 216

Intermediate 217

Intermediate 218

1-(tert-Butoxycarbonyl) piperidine-4-carboxylic acid (2.0 g, 8.7 mmol) and cyclopropylamine (0.6 mL, 8.7 mL) were dissolved in DMF (45 mL). HATU (3.3 g, 8.7 mmol) was added at room temperature followed by DIPEA (3.1 mL, 17 mmol). The reaction mixture was stirred at room temperature for 3h. The reaction mixture was diluted with cold water (250 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give the crude product, which was purified by column chromatography (Normal phase, Neutral silica gel, 60-120 mesh, 0 to 35 % EtOAC in hexanes) to give tert-butyl 4-(cyclopropylcarbamoyl)piperidine-1-carboxylate (1.5 g, 64 %) as a solid.

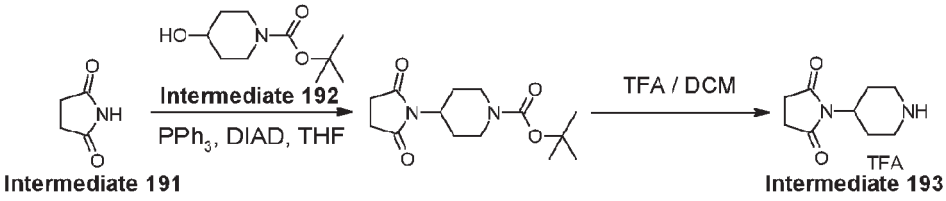
LCMS (Method F): m/z 269 $(M+H)^+$ (ES^+), at 1.80 min, weakly UV active.

tert-Butyl 4-(cyclopropylcarbamoyl)piperidine-1-carboxylate (1.5 g, 5.6 mmol) and triphenyl phosphine (2.9 g, 11 mmol) were dissolved in THF (160 mL). DIAD (2.26 g, 11 mmol) was added at room temperature over 15 min. Trimethylsilyl azide (1.3 g, 11 mmol) was added and the reaction mixture was allowed to stir at room temperature for 24 h. The reaction mixture was diluted with water (250 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give the crude product, which was purified by column chromatography (Normal phase, Neutral silica gel, 60-120 mesh, 0 to 30 % EtOAC in hexane) to give tert-butyl 4-(1-cyclopropyl-1H-tetrazol-5-yl)piperidine-1-carboxylate (400 mg, 24 %) as a solid..

LCMS (Method F): m/z 294 $(M+H)^+$ (ES^+), at 1.96 min, weakly UV active.

tert-Butyl 4-(1-cyclopropyl-1H-tetrazol-5-yl)piperidine-1-carboxylate (400 mg, 1.4 mmol) was dissolved in dioxane (5 mL). A solution of HCl in dioxane (4M, 5 mL, 20 mmol) was added at 0 °C and the mixture was stirred at room temperature for 5 h. The solvent was removed by concentration and the residue was triturated with diethyl ether (10 mL) to give **Intermediate 218** 4-(1-cyclopropyl-1H-tetrazol-5-yl)piperidine hydrochloride (260 mg, 98 %) as a solid. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 193, 1-(piperidin-4-yl)pyrrolidine-2,5-dione trifluoroacetate salt

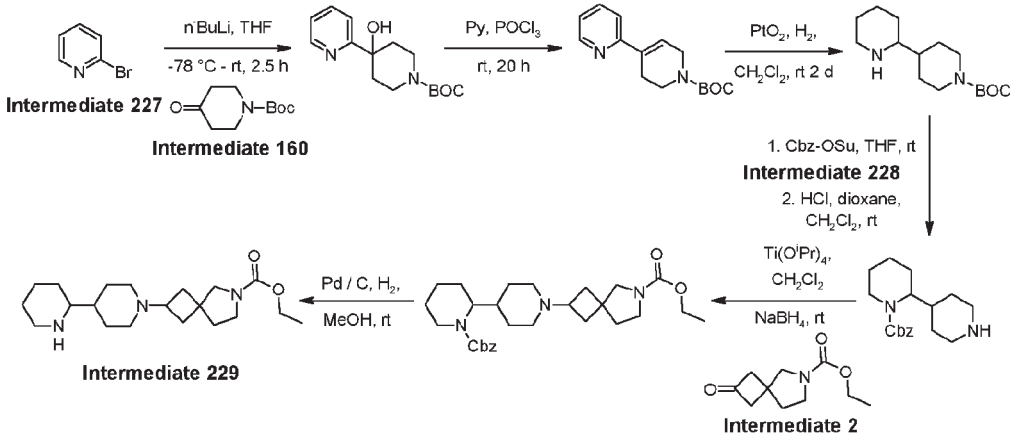


Succinimide (0.099 g, 1.0 mmol), tert-butyl 4-hydroxypiperidine-1-carboxylate (0.221 g, 1.10 mmol and triphenylphosphine (0.314 g, 1.20 mmol) were dissolved in THF (5 mL) then treated with diisopropyl azodicarboxylate (0.236 mL, 1.20 mmol) and stirred at RT overnight. The reaction mixture was concentrated 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, 20% to 100% EtOAc in isohexane) to give tert-butyl 4-(2,5-dioxopyrrolidin-1-yl)piperidine-1-carboxylate (0.253 g, 90%) as a solid.

LCMS (Method C): m/z 305 $(M+Na)^+$ (ES^+), at 1.11 min, UV inactive

A solution of tert-butyl 4-(2,5-dioxopyrrolidin-1-yl)piperidine-1-carboxylate (0.141 g, 0.50 mmol) in DCM (3 mL) and TFA (3 mL) was stirred at RT for 30 min then diluted with toluene and concentrated. The residue was azeotroped with toluene to give **Intermediate 193**, 1-(piperidin-4-yl)pyrrolidine-2,5-dione trifluoroacetate salt as a gum. Used immediately. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 229, ethyl 2-([2,4'-bipiperidin]-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate



To a solution of 2-bromopyridine (10.0 g, 63.3 mmol) in dry THF (60 mL), n-BuLi (79.1 mL, 2.5 M in hexane, 126 mmol) was slowly added at -78 °C. After stirring at this temperature for 30 min, *tert*-butyl 4-oxopiperidine-1-carboxylate (13.8 g, 69.6 mmol) in THF (40 mL) was slowly added. The reaction temperature was gradually brought to room temperature and stirred for 2 h. After cooling to 0 °C, the reaction mixture was carefully quenched with ice cold water (50 mL). After removal of the volatiles, the aq layer was extracted with ethyl acetate (3 x 50 mL).

The organic layers were combined and washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography [normal phase, silica gel (100-200 mesh), gradient 0% to 30% ethyl acetate in hexane] to give *tert*-butyl 4-hydroxy-4-(pyridin-2-yl)piperidine-1-carboxylate (11.4 g, 65%) as a yellow oil.

^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.48 (s, 9H), 1.56 - 1.63 (m, 2H), 1.90 - 2.0 (m, 2H), 3.25 - 3.46 (m, 2H), 4.05 - 4.22 (m, 2H), 5.29 (br.s., 1H), 7.20 - 7.25 (m, 1H), 7.32 (d, *J* = 8.0, Hz, 1H), 7.73 (dt, *J* = 1.6, 8.4 Hz, 1H), 8.53 (d, *J* = 4.8 Hz, 1H).

To a solution of *tert*-butyl 4-hydroxy-4-(pyridin-2-yl)piperidine-1-carboxylate (11.4 g, 41.0 mmol) in pyridine (100 mL), $POCl_3$ (5.7 mL, 61.5 mmol) was added and stirred at room temperature for 20 h. After removal of pyridine *in vacuo*, the reaction mixture was quenched with aq NaOH (10%, 30 mL) and extracted with chloroform (2 x 30 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography [normal phase, silica gel (100-200 mesh), gradient 0% to 30% ethyl acetate in hexane] to give *tert*-butyl 3',6'-dihydro-[2,4'-bipyridine]-1'(2'*H*)-carboxylate (2.3 g, 21%) as a yellow oil.

^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.48 (s, 9H), 2.61 - 2.70 (m, 2H), 3.60 - 3.70 (m, 2H), 4.10 - 4.19 (m, 2H), 6.58 - 6.62 (m, 1H), 7.11 - 7.19 (m, 1H), 7.36 (d, *J* = 7.88 Hz, 1H), 7.62 - 7.66 (m, 1H), 8.55 (d, *J* = 4.4 Hz, 1H).

To a solution of *tert*-butyl 3',6'-dihydro-[2,4'-bipyridine]-1'(2'*H*)-carboxylate (2.3 g, 8.84 mmol) in CH_2Cl_2 (20 mL), PtO_2 (200 mg, 0.88 mmol) was added and the reaction mixture was stirred at room temperature for 2 d under H_2 atmosphere. The reaction mixture was filtered through a pad of celite, washed with MeOH and concentrated *in vacuo.* The residue was purified by flash column chromatography [normal phase, silica gel (100-200 mesh), gradient 0% to 15% MeOH in DCM having 0.1% aq ammonia] to give *tert*-butyl [2,4'-bipiperidine]-1'-carboxylate (1.05 g, 44%) as a colorless oil.

^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.30 - 1.40 (m, 1H), 1.48 (s, 9H), 1.60 - 1.91 (m, 8H), 2.45 - 2.55 (m, 2H), 2.58 - 2.75 (m, 4H), 3.24 - 3.31 (m, 1H), 4.14 - 4.24 (m, 2H).

To a solution of *tert*-butyl [2,4'-bipiperidine]-1'-carboxylate (1.05 g, 3.91 mmol) in THF (5 mL), Cbz-OSu (975 mg, 3.91 mmol) in THF (5 mL) was added and stirred at room temperature for 2 h. The reaction mixture was quenched with water (20 mL) and the aq layer was extracted with ethyl acetate (2 x 20 mL). The organic layers were combined and washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography [normal phase, silica gel (100-200 mesh), gradient 0% to 20% ethyl acetate in hexane] to give 1-benzyl 1'-(*tert*-butyl) [2,4'-bipiperidine]-1,1'-dicarboxylate (840 mg, 53%) as a colorless oil.

^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.44 (s, 9H), 1.50 - 1.63 (m, 2H), 1.68 - 1.92 (m, 4H), 1.95 - 2.14 (m, 2H), 2.55 - 2.80 (m, 2H), 2.81 - 2.95 (m, 4H), 2.98 - 3.10 (m, 1H), 3.75 - 4.24 (m, 3H), 5.11 (s, 2H), 7.34 - 7.37 (m, 5H).]

To a solution of 1-benzyl 1'-(*tert*-butyl) [2,4'-bipiperidine]-1,1'-dicarboxylate (840 mg, 2.1 mmol)

in CH_2Cl_2 (10 mL), HCl in dioxane (10 mL, 4 M) was slowly added at 0 °C and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated $NaHCO_3$ (20 mL) and the aq layer was extracted with CH_2Cl_2 (2 x 20 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography [normal phase, silica gel (100-200 mesh), gradient 0% to 15% MeOH in DCM having 0.1% aq ammonia] to give benzyl [2,4'-bipiperidine]-1-carboxylate (570 mg, 90%) as a colorless sticky solid.

^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.35 - 1.70 (m, 6H), 1.71 - 1.98 (m, 4H), 2.46 - 2.63 (m, 2H), 2.68 - 2.73 (m, 1H), 3.03 - 3.18 (m, 1H), 3.65 - 3.80 (m, 2H), 3.86 - 4.16 (m, 2H), 5.11 (s, 2H), 7.34 - 7.37 (m, 5H).

To a solution of benzyl [2,4'-bipiperidine]-1-carboxylate (520 mg, 1.72 mmol) and ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate (305 mg, 1.55 mmol) in CH_2Cl_2 (15 mL), $Ti(O^iPr)_4$ (1.6 mL, 5.16 mmol) was added and stirred at 0 °C for 40 min. To this reaction mixture $NaBH_4$ (1.1 g, 5.16 mmol) was added and stirring continued at this temperature for 2 h. The reaction mixture was quenched with water (20 mL) and the aq layer was extracted with CH_2Cl_2 (2 x 20 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by prep-HPLC (reverse phase, X BRIDGE, C-18, 19 x 250 mm, 5µ, gradient 68% to 90% ACN in water containing 0.1% NH_4OH, 214 nm, RT: 7.45 min for **Isomer-1** and 8.37 min for **Isomer-2** to give ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate **Isomer 1**, (120 mg, 15%) and ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate **Isomer-2**, (160 mg, 19%) as colorless sticky solids.

Isomer-1:

LCMS (Method L): m/z 484 $(M+H)^+$ (ES+), at 5.70 min, UV active.

^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.10 - 1.32 (m, 6H), 1.36 - 1.95 (m, 14H), 2.00 - 2.18 (m, 2H), 2.52 - 3.05 (m, 4H), 3.20 - 3.45 (m, 4H), 3.87 - 4.18 (m, 4H), 5.11 (s, 2H), 7.30 - 7.35 (m, 5H).

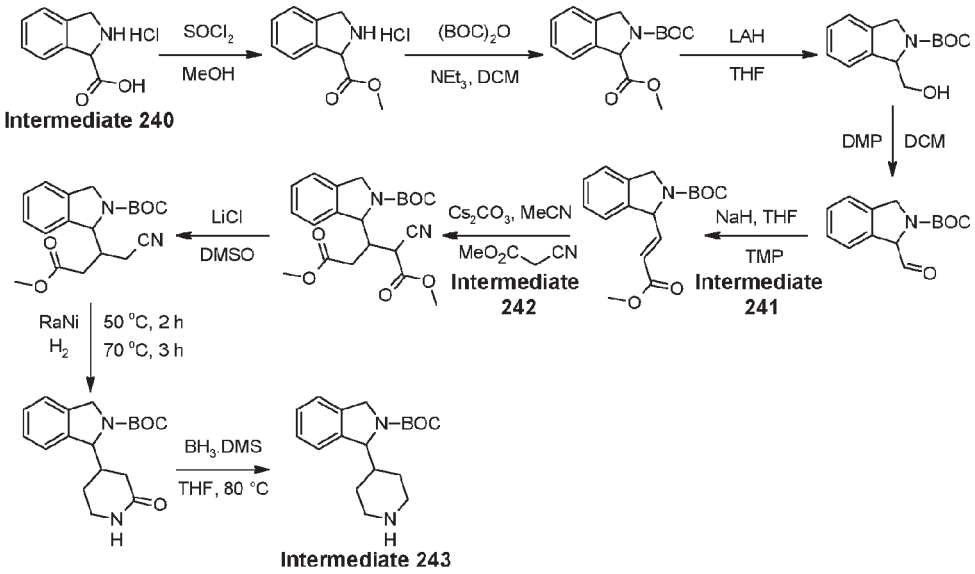
Isomer-2:

LCMS (Method L): m/z 484 $(M+H)^+$ (ES+), at 5.81 min, UV active.

^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.10 - 1.32 (m, 6H), 1.35 - 1.53 (m, 5H), 1.62 - 1.80 (m, 5H), 1.81 - 1.97 (m, 4H), 2.00 - 2.18 (m, 2H), 2.52 - 3.00 (m, 4H), 3.18 - 3.52 (m, 4H), 3.88 - 4.20 (m, 4H), 5.11 (s, 2H), 7.32 - 7.37 (m, 5H).

To a solution of a mixture of isomers of ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate (1.0 g, 2.06 mmol) in MeOH (20 mL), 10% Pd on charcoal (320 mg, 50% wet) was added and the reaction mixture was stirred at rt for 16 h under H_2 atmosphere. The reaction mixture was filtered through a pad of celite, washed with MeOH and concentrated *in vacuo,* and triturated with pentane to give **Intermediate 229**, ethyl 2-([2,4'-bipiperidin]-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate (445 mg, 92%) as a colorless liquid. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 243, *tert*-butyl 1-(piperidin-4-yl)-1,3-dihydro-2*H*-isoindole-2-carboxylate



To a solution of isoindoline-1-carboxylic acid hydrochloride (5.0 g, 25.0 mmol) in methanol (60 mL), $SOCl_2$ (2.7 mL, 37.5 mmol) was slowly added at 0 °C and the reaction mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was concentrated *in vacuo*. The residue was triturated with diethyl ether to give methyl isoindoline-1-carboxylate hydrochloride (4.9 g, 92%) as an off white solid. The residue was used for the next step without further purification.

^{1}H-NMR (400 MHz; DMSO-d_6) δ: 3.81 (s, 3H), 4.52 - 4.63 (m, 2H), 5.70 (s, 1H), 7.44 - 7.50 (m, 4H), 9.77 (br.s., 2H).

To a solution of methyl isoindoline-1-carboxylate hydrochloride (4.9 g, 23.0 mmol) in DCM (50 mL), Et_3N (9.9 mL, 69.0 mmol) and $(Boc)_2O$ (8.0 mL, 34.0 mmol) were sequentially added at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with water (20 mL). After separating the organic layer, the aq layer was extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were combined and washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography [normal phase, silica gel (100-200 mesh), gradient 10% to 30% ethyl acetate in hexane] to give 2-(*tert*-butyl) 1-methyl isoindoline-1,2-dicarboxylate (6.5 g, 90%) as a colorless liquid.

^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.52 (s, 9H), 3.75 (s, 3H), 4.65 - 4.85 (m, 2H), 5.45 (s, 1H), 7.25 - 7.43 (m, 4H).

To a solution 2-(*tert*-butyl) 1-methyl isoindoline-1,2-dicarboxylate (6.5 g, 23.0 mmol) in THF (60 mL), LAH (2M, 11.5 mL, 23.0 mmol) was slowly added at 0 °C and stirred for 30 min. After completion, the reaction mixture was quenched with sat aq Na_2SO_4 (20 mL). The reaction mixture was filtered through a pad of celite and washed with ethyl acetate (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give *tert*-butyl 1-(hydroxymethyl)isoindoline-2-

carboxylate (5.2 g, 91%) as an off white solid. The crude residue was used for the next step without further purification.

^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.52 (s, 9H), 3.70 - 3.78 (m, 1H), 3.98 - 4.03 (m, 1H), 4.60 - 4.69 (m, 1H), 4.70 - 4.85 (m, 2H), 5.22 (br.s., 1H), 7.25 - 7.40 (m, 4H).

To a solution of *tert*-butyl 1-(hydroxymethyl)isoindoline-2-carboxylate (5.2 g, 20.0 mmol) in DCM (100 mL), Dess-Mertin periodinane (27 g, 62.0 mmol) was added portion wise at 0 °C and stirred at room temperature for 48 h. After completion, the reaction mixture was filtered through a pad of celite and washed with diethyl ether (3 x 20 mL). The filtrate was washed with sat aq $NaHCO_3$ solution, brine, dried (Na_2SO_4) and concentrated *in vacuo* to give *tert*-butyl 1-formylisoindoline-2-carboxylate (4.5 g, 88%) as a brown liquid. The crude residue was used for the next step without further purification.

^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.48 (s, 9H), 4.65 - 4.90 (m, 2H), 5.29 - 5.35 (s, 1H), 7.25 - 7.35 (m, 4H), 9.51 (s, 1H).

To a solution of NaH (874 mg, 18.2 mmol) in THF, trimethylphosphonoacetate (3.3 mL, 18.2 mmol) was added at -78 °C. After stirring for 1 h at -78 °C, *tert*-butyl 1-formylisoindoline-2-carboxylate (4.5 g, 18.2 mmol) was slowly added and the reaction mixture was allowed to 0 °C. After completion, the reaction mixture was quenched with sat aq NH_4Cl solution (10 mL) and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo* to give *tert*-butyl (*E*)-1-(3-methoxy-3-oxoprop-1-en-1-yl)isoindoline-2-carboxylate (5.2 g, 92%) as a brown liquid. The residue was used for the next step without further purification.

MS (ESI +ve): 304

To a solution of *tert*-butyl (*E*)-1-(3-methoxy-3-oxoprop-1-en-1-yl)isoindoline-2-carboxylate (5.2 g, 17.2 mmol) in MeCN (20 mL), Cs_2CO_3 (11.1 g, 34.4 mmol) was added portion wise at room temperature. After stirring for 20 min, methyl cyanoacetate (3.0 mL, 34.4 mmol) was slowly added and the reaction mixture was stirred at 70 °C for 16 h. After completion, the reaction mixture was filtered through a pad of celite and thoroughly washed with hexane (3 x 20 mL). The filtrate was concentrated *in vacuo* to give dimethyl 3-(2-(*tert*-butoxycarbonyl)isoindolin-1-yl)-2-cyanopentanedioate) (5.5 g, cr) as a brown sticky solid. The crude residue was used for the next step without further purification.

MS (ESI +ve): 403

To a solution of dimethyl 3-(2-(tert-butoxycarbonyl)isoindolin-1-yl)-2-cyanopentanedioate) (1.6 g, crude) in DMSO (15 mL), LiCl (500 mg, 11.7 mmol) was added followed by addition of water (0.1 mL, cat.) and the reaction mixture was stirred at 135 °C for 16 h. After completion, the reaction mixture was quenched with water (20 mL) and the aq layer was extracted with diethyl ether (3 x 20 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo* to give *tert*-butyl 1-(1-cyano-4-methoxy-4-oxobutan-2-yl)isoindoline-2-carboxylate (1.5 g, cr) as a brown semisolid. The crude residue was used for the next step without further purification.

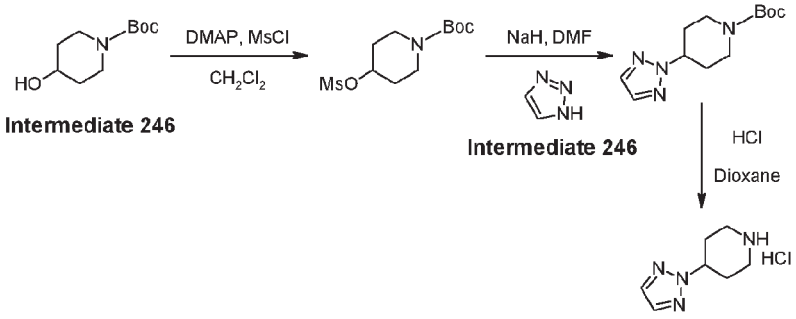
MS (ESI +ve): 345

To a solution of *tert*-butyl 1-(1-cyano-4-methoxy-4-oxobutan-2-yl)isoindoline-2-carboxylate (300 mg, 0.8 mmol) in MeOH (30 mL), Raney-Ni (0.30 g, wet) was added and the reaction mixture was heated to 50 °C for 2 h under H_2 atmosphere at 50 psi. Then the reaction temperature was increased to 70 °C and stirred for 3 h. After completion, the reaction mixture was filtered through a pad of celite, washed with MeOH (25 mL) and concentrated in *vacuo.* The residue was triturated with diethyl ether (30 mL) to give *tert*-butyl 1-(2-oxopiperidin-4-yl)isoindoline-2-carboxylate (0.21 g, 76%) as a brown solid.

MS (ESI +ve): 317

To a solution of *tert*-butyl 1-(2-oxopiperidin-4-yl)isoindoline-2-carboxylate (210 mg, 0.60 mmol) in THF (5 mL), BH_3-DMS (0.5 mL, 6.60 mmol) was slowly added at 0 °C and the reaction mixture was stirred at 78 °C for 8 h. After cooling at 0 °C, the reaction mass was quenched with methanol (0.5 mL) followed by water (1 mL). To the crude reaction mass 5% MeOH/ DCM (30 mL) was added and filtered. The filtrate was concentrated *in vacuo.* The residue was triturated with diethyl ether (20 mL) to give *tert*-butyl 1-(piperidin-4-yl)isoindoline-2-carboxylate, **Intermediate 243** (200 mg, 99%) as a brown solid. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 247, 4-(2*H*-1,2,3-triazol-2-yl)piperidine



Intermediate 247

tert-Butyl 4-hydroxypiperidine-1-carboxylate (0.500 g, 2.4 mmol) was dissolved in CH_2Cl_2 then DMAP (0.302 g, 2.4 mmol) and methane sulfonyl chloride (0.284 g, 2.48 mmol) added dropwise at 0°C.The resulting reaction mixture was stirred at RT for 6 h then partitioned between H_2O (70 mL) and CH_2Cl_2 (70 mL), the aqueous layer was further extracted with CH_2Cl_2 (2 x 70 mL), the organic layers were combined, dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give crude *tert*-butyl 4-((methylsulfonyl) oxy) piperidine-1-carboxylate (0.520 g, 75.0%) as a white solid which was used directly without any further purification.

^{1}H-NMR (400 MHz; DMSO) δ: 1.23 (d, J = 9.38 Hz, 2H) 1.54 - 1.69 (m, 4H) 1.86 - 1.96 (m, 2H) 2.35 (s, 1H) 2.85 - 3.00 (m, 2H) 3.18 (d, J = 5.42 Hz, 5H) 3.54 - 3.67 (m, 4H) 4.83 (s, 1H).

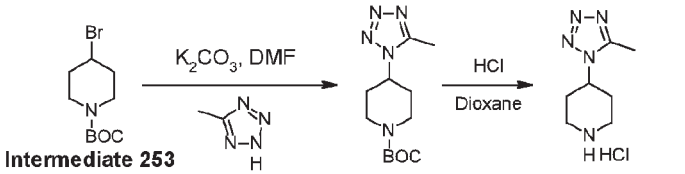
1*H*-1,2,3-Triazole (0.098 g, 1.4 mmol) was dissolved in DMF (5 mL), NaH (0.037 g, 1.5 mmol) was added and stirred at 0°C for 30 min. *tert*-Butyl 4-((methylsulfonyl)oxy)piperidine-1-

carboxylate (0.400 g, 1.4 mmol) was added and stirred at 150°C for 1 h. The reaction mixture was partitioned between H_2O (50 mL) and EtOAc (50 mL), the aqueous layer was further extracted with EtOAc (2 x 50 mL), the organic layers were combined, dried (Na_2SO_4), filtered and the solvent was removed *in vacuo* to give crude *tert*-butyl 4-(2*H*-1,2,3-triazol-2-yl) piperidine-1-carboxylate (0.350 g, 97.0%) as a colorless gum which was used directly without any further purification.

LCMS (Method F): m/z 253 $(M+H)^+$ (ES+), at 1.95 min, UV active.

tert-Butyl 4-(2*H*-1,2,3-triazol-2-yl)piperidine-1-carboxylate (0.500 g, 1.9 mmol) was dissolved in 1,4-dioxane (10 mL) followed by drop wise addition of HCl in 1,4-dioxane (5 mL, 4M). The resulting reaction mixture was stirred at 25°C for 16 h, the solvents were removed *in vacuo* and the residue was purified by triturating with diethyl ether (3 x 10 mL) to give 4-(2*H*-1,2,3-triazol-2-yl)piperidine hydrochloride, **Intermediate 247**, (0.290 g, 96.3%) as a light white solid. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 255, 4-(5-methyl-1*H*-tetrazol-1-yl)piperidine hydrochloride



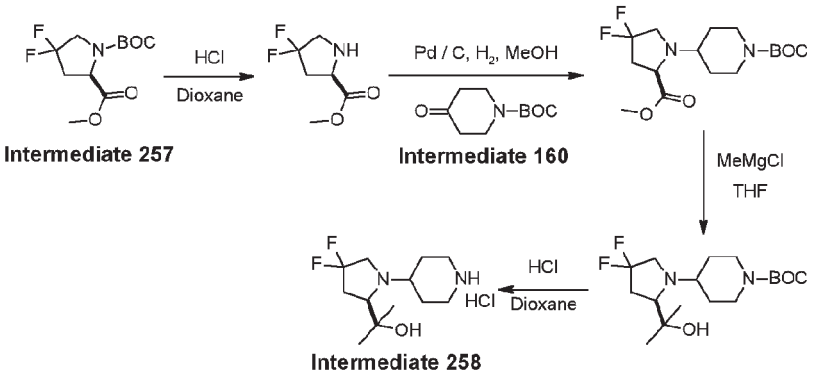
Intermediate 253 **Intermediate 254** **Intermediate 255**

5-Methyl-2*H*-tetrazole (0.500 g, 5.9 mmol) and *tert*-butyl 4-bromopiperidine-1-carboxylate (1.29 g, 4.8 mmol) were dissolved in DMF. K_2CO_3 (1.64 g, 11.8 mmol) was added, the resulting reaction mixture was stirred at 100°C for 6 h then partitioned between H_2O (100 mL) and ethyl acetate (150 mL). The aqueous layer was further extracted with ethyl acetate (2 x 100 mL), the organic layers were combined, dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was purified by combi-flash column chromatography (normal phase, neutral silica gel, 60-120 mesh, 10 to 20% EtOAc in hexane) to give *tert*-butyl 4-(5-methyl-1H-tetrazol-1-yl)piperidine-1-carboxylate (0.280 g, 34.6 %) as a white solid.

^{1}H-NMR (400 MHz, DMSO) δ: 1.43 (s, 9H), 1.73 - 1.88 (m, 2H), 2.01 (br. s., 2H), 2.68 - 2.75 (m, 3H), 2.88 - 2.91 (m, 2H), 4.03 - 4.10 (m, 2H), 4.60 - 4.70 (m, 1H).

tert-Butyl 4-(5-methyl-1*H*-tetrazol-1-yl) piperidine-1-carboxylate (0.280 g, 1.04 mmol) was dissolved in 1, 4-dioxane (10 mL) followed by drop wise addition of HCl in 1, 4-dioxane (5 mL, 4M). The resulting reaction mixture was stirred at 25°C for 16 h, the solvents were removed *in vacuo* and the residue was purified by triturating with diethyl ether (3 x 10 mL) to give 4-(5-methyl-1*H*-tetrazol-1-yl)piperidine hydrochloride, **Intermediate 255** (0.170 g, 97.6 %) as a white solid. The data for the title compound are in Table 2.

Procedure for the preparation of Intermediate 258, give (*R*)-2-(4,4-difluoro-1-(piperidin-4-yl)pyrrolidin-2-yl)propan-2-ol hydrochloride



To a solution of 1-(*tert*-butyl) 2-methyl (*R*)-4,4-difluoropyrrolidine-1,2-dicarboxylate (500 mg, 1.89 mmol) in dioxane (15 mL), HCl in dioxane (4 M, 15 mL) was slowly added at 0 °C and stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was triturated with hexane (10 mL). This residue was basified with aq sat $NaHCO_3$ (10 mL) and concentrated. To the crude reaction mass CDM (30 mL) was added and filtered. The filtrate was concentrated *in vacuo* to give methyl (*R*)-4,4-difluoropyrrolidine-2-carboxylate (**2**, 320 mg, 84%) as a brown liquid. This crude residue was used for the next step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.40 - 1.51 (m, 1H), 2.58 - 2.84 (m, 3H), 3.52 - 3.62 (m, 1H), 3.84 (s, 3H), 4.40 - 4.52 (m, 1H).

To a solution of methyl (*R*)-4,4-difluoropyrrolidine-2-carboxylate (200 mg, 1.21 mmol) and *tert*-butyl 4-oxopiperidine-1-carboxylate (240 mg, 1.21 mmol) in methanol (20 mL), 10% palladium on carbon (300 mg, 50% wet) was added and the reaction mixture was stirred under H_2 (1 atm) at room temperature for 24 h. After completion, the reaction mixture was filtered through a pad of celite, thoroughly washed with methanol and concentrated *in vacuo* to give *tert*-butyl (*R*)-4-(4,4-difluoro-2-(methoxycarbonyl)pyrrolidin-1-yl)piperidine-1-carboxylate (400 mg, 95%) as a colour less liquid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.32 - 1.45 (m, 1H), 1.45 (s, 9H), 1.61 - 1.80 (m, 4H), 2.39 - 2.49 (m, 1H), 2.50 - 2.83 (m, 2H), 3.19 (s, 3H), 3.35 - 3.49 (m, 2H), 3.61 - 3.82 (m, 3H), 3.94 - 4.05 (m, 1H).

To a solution *tert*-butyl (*R*)-4-(4,4-difluoro-2-(methoxycarbonyl)pyrrolidin-1-yl)piperidine-1-carboxylate (375 mg, 1.07 mmol) in THF (10 mL), MeMgBr (3M, 1.07 mL, 3.21 mmol) was slowly added at 0 °C and stirred for 4 h at room temperature. After completion, the reaction mixture was quenched with sat aq NH_4Cl solution (10 mL) and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography [normal phase, silica gel (100-200 mesh), gradient 10% to 30% ethyl acetate in hexane] to give

tert-butyl (*R*)-4-(4,4-difluoro-2-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)piperidine-1-carboxylate (240 mg, 64%) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.11 (s, 3H), 1.21 (s, 3H), 1.21 - 1.40 (m, 2H), 1.46 (s, 9H), 1.61 - 1.80 (m, 2H), 2.15 - 2.30 (m, 3H), 2.50 - 2.83 (m, 3H), 3.02 - 3.23 (m, 2H), 4.09 - 4.30 (m, 2H). O-H not observed.

To a solution of (*R*)-4-(4,4-difluoro-2-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)piperidine-1-carboxylate (240 mg, 0.69 mmol) in dioxane (10 mL), HCl in dioxane (4 M, 10 mL) was slowly added at 0 °C and stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* and the residue triturated with hexane (10 mL). To the crude reaction mass CH_2Cl_2 (30 mL) was added and filtered. The filtrate was concentrated *in vacuo* to give (*R*)-2-(4,4-difluoro-1-(piperidin-4-yl)pyrrolidin-2-yl)propan-2-ol hydrochloride, **Intermediate 258** (150 mg, 87%) as a brown liquid. The data for the title compound are in Table 2.

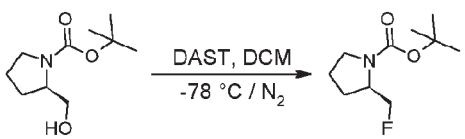
Procedure for the preparation of Intermediate 282, *tert*-butyl (2*R*)-2-(dimethylcarbamoyl)piperidine-1-carboxylate



Intermediate 281 **Intermediate 282**

(R)–(tert-butoxycarbonyl)piperidine-2-carboxylic acid (0.500 g, 2.18 mmol) was dissolved in anhydrous DCM (8 mL) and the reaction mixture was cooled to 0°C under nitrogen. 1- ethyl-3-(3-dimethylaminopropyl)-carbodiimide HCl (0.628 g, 3.275 mmol), hydroxybenzotriazole (0.334 g, 2.183 mmol), N-methylmorpholine (1.104 g, 10.915 mmol) and dimethylamine hydrochloride (0.356 g, 4.36 mmol) was added and the reaction mixture was stirred at rt under nitrogen overnight. The reaction mixture was diluted with DCM (20 mL) and washed with sat. $NaHCO_3$ (aq) (20mL) and sat. NaCl (aq) (20mL). The organic layer was passed through a Biotage Phase Separator Cartridge 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 (2*R*)-2-(dimethylcarbamoyl)piperidine-1-carboxylate, **Intermediate 282**, (0.241 g, 43%) as an amber oil. The data for the title compound are in Table 2

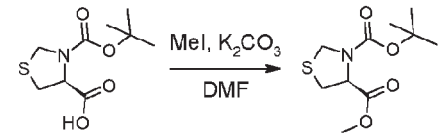
Procedure for the preparation of Intermediate 295, *tert*-butyl (2R)-2-(fluoromethyl)pyrrolidine-1-carboxylate



Intermediate 294 **Intermediate 295**

(2R)-(+)-1-Boc-2-pyrolidinemethanol (0.300 g, 1.49 mmol) was dissolved in DCM (8 mL) and cooled under nitrogen to -78°C. *N,N*-Diethylaminosulfur trifluoride (0.360 g 2.24 mmol) was added to the reaction mixture dropwise, the reaction mixture was stirred at -78°C under nitrogen for 4 h and then warmed to rt overnight. The reaction mixture was quenched by addition of sat. $NaHCO_3$ (aq) (20mL) and extracted with DCM (2 x 15 mL), the organic layers were combined and dried by passing through a Biotage Phase Separator Cartridge and the solvents were removed *in vacuo*. The residue was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 10g 40-63μm, 60Å, 12mL per min, gradient 0% to 4% MeOH / DCM]) to give *tert*-butyl (2R)-2-(fluoromethyl)pyrrolidine-1-carboxylate, **Intermediate 295**, (0.104 g, 34%), as an amber oil. The data for the title compound are in Table 2

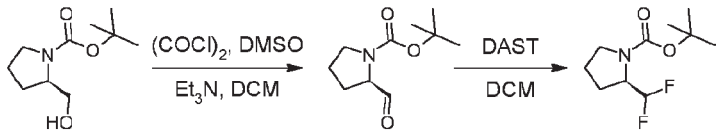
Procedure for the preparation of Intermediate 285, methyl (4S)-1,3-thiazolidine-4-carboxylate hydrochloride



Intermediate 284 **Intermediate 285**

(S)-3-Boc-thiazolidine-4-carboxylic acid (1.00 g, 4.29 mmol) was dissolved in anhydrous DMF (4 mL), potassium carbonate (2.372 g, 17.16 mmol) and iodomethane (0.730 g, 5.14 mmol) were added. The reaction mixture was stirred at rt under nitrogen overnight. The solvents were removed *in vacuo* and the residue was dissolved in EtOAc (40 mL) and washed with water (3 x 20mL) and sat. NaCl (aq) (20mL), dried ($MgSO_4$). The solvents were removed *in vacuo* give 3-*tert*-butyl-4-methyl (4S)-1,3-thiazolidine-3,4-dicarboxylate, **Intermediate 285**, (0.812 g, 77%) as a pale yellow oil. The data for the title compound are in Table 2

Procedure for the preparation of Intermediate 297, *tert*-butyl (2R)-2-(difluoromethyl)pyrrolidine-1-carboxylate



Intermediate 294 **Intermediate 297**

DMSO (0.698 g, 8.94 mmol) was added dropwise to a solution of oxalyl chloride (0.566 g, 2.93 mmol) in anhydrous DCM (12 mL) at -78°C under nitrogen. The reaction mixture was stirred at -78°C under nitrogen for 15 min then a solution of (2R)-(+)-1-Boc-2-pyrrolidinemethanol (0.600 g, 2.98 mmol) in anhydrous DCM (4 mL) was added dropwise. The reaction mixture was stirred at -78°C under nitrogen for 15 min then Et_3N (1.06 g, 11.92 mmol) was added and the reaction mixture was stirred at 0°C under nitrogen for 1 h. The reaction mixture was quenched with sat. $NaHCO_3$ (aq) (20 mL) and extracted with DCM (2 x 20 mL), the organic layers were combined

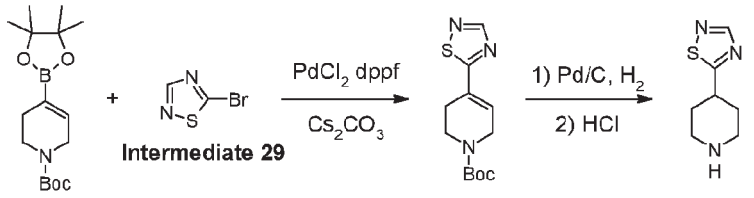
and dried by passing through a Biotage Phase Separator Cartridge and the solvents were removed *in vacuo*. The residue was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 10g 40-63μm, 60Å, 12mL per min, gradient 0% to 4% MeOH / DCM]) to give *tert*-butyl(2R)-2-formylpyrrolidine-1-carboxylate (0.435 g, 73%).

tert-butyl(2R)-2-formylpyrrolidine-1-carboxylate (0.435 g, 2.19 mmol) was dissolved in anhydrous DCM (8 mL) and cooled under nitrogen to -78°C. *N,N*-Diethylaminosulfur trifluoride (0.528 g, 3.28 mmol) was added to the reaction mixture dropwise, the reaction mixture was stirred at -78°C under nitrogen for 3 h and then warmed to rt overnight. The reaction mixture was quenched by addition of sat. $NaHCO_3$ (aq) (20mL) and extracted with DCM (2 x 15 mL), the organic layers were combined and dried by passing through a Biotage Phase Separator Cartridge and the solvents were removed *in vacuo*. The residue was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 10g 40-63μm, 60Å, 12mL per min, gradient 0% to 4% MeOH / DCM]) to give *tert*-butyl (2R)-2-(difluoromethyl)pyrrolidine-1-carboxylate, **Intermediate 297**, (0.217 g, 45%) as an amber oil. The data for the title compound are in Table 2

General Synthetic Procedures for Intermediates:

Route 1

Typical procedure for the preparation of piperidines *via* Suzuki reaction, hydrogenation and Boc-deprotection as exemplified by the preparation of Intermediate 30, 5-(piperidin-4-yl)-1,2,4-thiadiazole



Intermediate 28 **Intermediate 30**

2-5-Bromo-1,2,4-thiadiazole (108 mg, 0.65 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (200 mg, 0.65 mmol) and Cs_2CO_3 (632 mg, 1.94 mmol) were dissolved in Dioxane : water (10: 2 mL). The reaction mixture was degassed for 30 mins followed by addition of $PdCl_2$dppf (24 mg, 0.03 mmol) then stirred for 16 h at 90°C. The reaction mixture was partitioned between H_2O (80 mL) and EtOAc (50 mL), the aqueous layer was further extracted with EtOAc (2 x 50 mL), the organic layers were combined, dried (Na_2SO_4), solvents were removed *in vacuo* and the residue was purified by column chromatography (normal phase silica, mesh size: 60-120, 16% to 20% EtOAc in Hexane) to give *tert*-butyl 4-(1,2,4-thiadiazol-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (158 mg, 92.0%) as an off white solid.

LCMS (Method F): m/z 212 $(M+H-56)^+$ (ES+), at 2.37 min, UV active

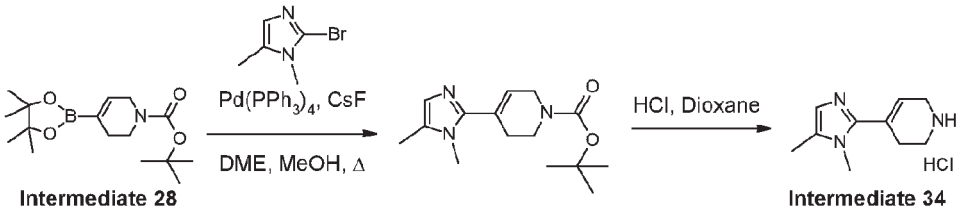
tert-Butyl 4-(1,2,4-thiadiazol-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (200 mg, 0.74 mmol) was dissolved in MeOH (15 mL) and 10% Pd/C (20 mg) was added. The reaction mixture was purged with H_2 gas and stirred at 25°C for 8 h under H_2 pressure. The reaction mixture was filtered through celite, the residue was washed with MeOH, and the solvents were removed *in vacuo* and the residue was purified by column chromatography (normal phase silica, mesh size: 60-120, 20% to 24% EtOAc in Hexane) to give *tert*-butyl 4-(1,2,4-thiadiazol-5-yl)piperidine-1-carboxylate (150 mg, 74.6%) as a dark green gum.

LCMS (Method F): m/z 214 $(M+H)^+$ (ES+), at 2.14 min, UV active

tert-Butyl 4-(1,2,4-thiadiazol-5-yl)piperidine-1-carboxylate (150 mg, 0.56 mmol) was dissolved in 1,4-dioxane (5 mL), HCl in dioxane (10 mL, 3.0M solu.) was added dropwise and the reaction was stirred at 30°C for 16 h. Solvents were removed *in vacuo* and the residue was purified by triturating with diethyl ether (3 x 3 mL) to give **Intermediate 30**, 5-(piperidin-4-yl)-1,2,4-thiadiazole (102 mg, 89.5%) as a dark green gum. The data for the title compound are in Table 2.

Route 2

Procedure for the preparation of Intermediate 34, 4-(1,5-dimethyl-1H-imidazol-2-yl)-1,2,3,6-tetrahydropyridine



Intermediate 28 **Intermediate 34**

tert-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2.0 g, 6.55 mmol), 2-bromo-1,5-dimethyl-1H-imidazole (1.13 g, 6.45 mmol) and CsF (2.9 g, 1.85 mmol) were dissolved in DME: MeOH (2:1, 30 mL). The reaction mixture was degassed for 5 mins, then $Pd(PPh_3)_4$ (73 mg, 0.064 mmol) was added and the resulting reaction mixture was stirred for 5 h at 100°C. The reaction mixture was partitioned between H_2O (100 mL) and EtOAc (100 mL), the aqueous layer was further extracted with EtOAc (2 x 100 mL), the organic layers were combined, dried (Na_2SO_4) and the solvents were removed in vacuo. The residue was purified by column chromatography (normal silica, mesh size: 60-120, 13% to 17% Ethyl acetate in Hexane) to give tert-butyl 4-(1,5-dimethyl-1H-imidazol-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1 g, 55%) as a yellow gum.

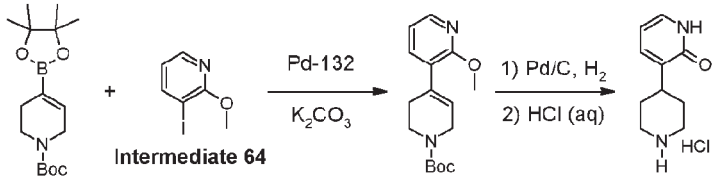
LCMS (Method F): m/z 278 $(M+H)^+$ (ES^+), at 1.70 min, UV active

tert-Butyl 4-(1,5-dimethyl-1H-imidazol-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.0 g, 3.61 mmol) was dissolved in 1,4-dioxane (20 mL) 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

x 5 mL) to give **Intermediate 34**, 4-(1,5-dimethyl-1H-imidazol-2-yl)-1,2,3,6-tetrahydropyridine hydrochloride (0.5 g, 65%) as a white solid. The data for the title compound are in Table 2.

Route 3

Typical procedure for the preparation of piperidines *via* Suzuki reaction, hydrogenation and Boc-deprotection as exemplified by the preparation of Intermediate 65, 3-(piperidin-4-yl)pyridin-2(1*H*)-one hydrochloride



Intermediate 28 **Intermediate 65**

tert-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2.5 g, 10.0 mmol), 3-iodo-2-methoxypyridine (8.21 g, 26.0 mmol) and K_2CO_3 (4.3 g, 31.8 mmol) were dissolved in 1-4 dioxane (10 mL) and water (5 mL). The reaction mixture was degassed using N_2 for 15 min; Pd-132 (0.376 g, 0.53 mmol) was added and the reaction mixture was stirred at 80°C for 2 h. The reaction mixture was diluted with water (50 mL), extracted with EtOAc (2 x 100 mL), the organic layers were combined, dried (Na_2SO_4), solvent was removed in *vacuo* and crude product was purified by column chromatography (Normal phase, 60-120 mesh silica, 0 to 20% EtOAc in Hexane) to give *tert*-butyl 2-methoxy-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate (2.0 g, 69.0%) as off white solid.

LCMS (Method F): m/z 291 $(M+H)^+$ (ES+), at 2.39 min, UV active

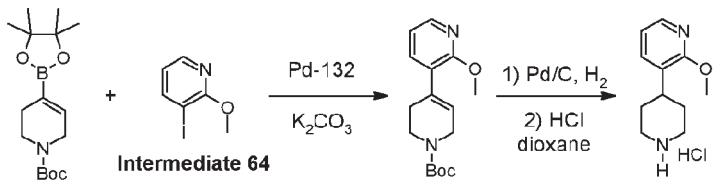
tert-Butyl 2-methoxy-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate (1.89 g, 6.51 mmol) was dissolved in MeOH (10 mL) and 10% Pd/C (0.2 g) was added. The reaction mixture was purged with H_2 gas and stirred at rt for 12 h under H_2. The reaction mixture was filtered through celite and solvents were removed *in vacuo* to give *tert*-butyl 4-(2-methoxypyridin-3-yl) piperidine-1-carboxylate (0.91 g, 47.9%) as a colorless gum.

LCMS (Method F): m/z 293 $(M+H)^+$ (ES+), at 2.50 min, UV active

tert-Butyl 4-(2-methoxypyridin-3-yl) piperidine-1-carboxylate (0.200 g, 0.6 mmol) was dissolved in 1,4-dioxane (4.0 mL) and water (2.0 mL) and conc. HCl was added, the reaction mixture was stirred for 10 h at 100°C. The solvents were removed in *vacuo* and the residue was triturated with acetone (3 x 10 mL) to give **Intermediate 65**, 3-(piperidin-4-yl)pyridin-2(1*H*)-one hydrochloride (0.100 g, 82.6%) as a brown solid. The data for the title compound are in Table 2.

Route 4

Typical procedure for the preparation of piperidines *via* Suzuki reaction, hydrogenation and Boc-deprotection as exemplified by the preparation of Intermediate 66, 2-methoxy-3-(piperidin-4-yl)pyridine hydrochloride



Intermediate 28 Intermediate 64 Intermediate 66

tert-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2.5 g, 10.0 mmol), 3-iodo-2-methoxypyridine (8.21 g, 26.0 mmol) and K_2CO_3 (4.3 g, 31.8 mmol) were dissolved in 1-4 dioxane (10 mL) and water (5 mL). The reaction mixture was degassed using N_2 for 15 min; Pd-132 (0.376 g, 0.53 mmol) was added and the reaction mixture was stirred at 80°C for 2 h. The reaction mixture was diluted with water (50 mL), extracted with EtOAc (2 x 100 mL), the organic layers were combined, dried (Na_2SO_4), solvent was removed in *vacuo* and crude product was purified by column chromatography (Normal phase, 60-120 mesh silica, 0 to 20% EtOAc in Hexane) to give *tert*-butyl 2-methoxy-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate (2.0 g, 69.0%) as off white solid.

LCMS (Method F): m/z 291 $(M+H)^+$ (ES+), at 2.39 min, UV active

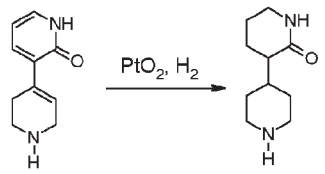
tert-Butyl 2-methoxy-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate (1.89 g, 6.51 mmol) was dissolved in MeOH (10 mL) and 10% Pd/C (0.2 g) was added. The reaction mixture was purged with H_2 gas and stirred at rt for 12 h under H_2. The reaction mixture was filtered through celite and solvents were removed *in vacuo* to give *tert*-butyl 4-(2-methoxypyridin-3-yl) piperidine-1-carboxylate (0.91 g, 47.9%) as a colorless gum.

LCMS (Method F): m/z 293 $(M+H)^+$ (ES+), at 2.50 min, UV active

tert-Butyl 4-(2-methoxypyridin-3-yl)piperidine-1-carboxylate (0.8 g, 2.7mmol) was stirred in HCl in 1,4-dioxane (4.0 mL, 4.0M solu.) for 10 h at rt. The solvents were removed in *vacuo* and the residue was triturated by acetone (3 x 10 mL) to give **Intermediate 66**, 2-methoxy-3-(piperidin-4-yl)pyridine hydrochloride (0.135 g, 25.7%) as white solid. The data for the title compound are in Table 2.

Route 5

Typical procedure for the preparation of piperidines *via* hydrogenation as exemplified by the preparation of Intermediate 69, 3,4'-bipiperidin-2-one



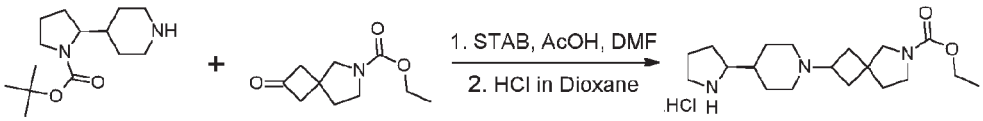
Intermediate 65 Intermediate 69

3-(Piperidin-4-yl)-1,6-dihydropyridin-2-ol (0.5g, 2.8mmol) was dissolved in MeOH (10 mL) and PtO_2 (0.2 g) was added. The reaction mixture was purged with H_2 gas and stirred at rt for 12 h under H_2 gas. The reaction mixture was filtered through celite and the solvents were removed

in *vacuo* to give **Intermediate 69**, 3,4'-bipiperidin-2-one (0.4 g,78.3%) as a brown gum. The data for the title compound are in Table 2.

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



Intermediate 51 **Intermediate 2** **Intermediate 127**

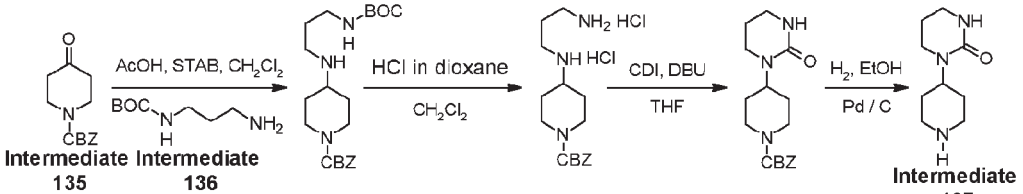
(S)-tert-Butyl 2-(piperidin-4-yl)pyrrolidine-1-carboxylate (1.24 g, 6.29 mmol) and ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate (1.60 g, 6.29 mmol) were dissolved in DMF (15 mL) at rt and acetic acid (0.54 mL, 9.44 mmol) was added. The reaction mixture was stirred at rt for 3 h. STAB (2.67 g, 12.6 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.

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

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 x 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 7

Typical procedure for the preparation of piperidines *via* reductive amination, Boc-deprotection, urea formation, and hydrogenolysis as exemplified by the preparation of Intermediate 137, 1-(piperidin-4-yl)tetrahydropyrimidin-2(1*H*)-one



Benzyl 4-oxopiperidine-1-carboxylate (0.932 g, 4.00 mmol) and *tert*-butyl (3-aminopropyl)carbamate (0.766 g, 4.4 mmol) were mixed in CH_2Cl_2 (20 mL) at rt, AcOH (0.68 mL, 12.0 mmol) was added and stirred for 3 h. STAB (2.59 g, 12.0 mmol) was added and the reaction mixture was stirred under nitrogen at rt overnight. The reaction mixture was quenched with the addition of $NaHCO_3$ (sat aq.) (40 mL) extracted with CH_2Cl_2 (4 x 45 mL) and the combined organic layers were washed with brine, then dried over $MgSO_4$ and filtered. The solvents were removed *in vacuo* and the residue purified by column chromatography [Biotage SNAP cartridge KP-sil 25g, 40-63 μm, 60 Å, 50 mL per min, gradient 0% to 10% MeOH in DCM]) to give benzyl 4-({3-[(*tert*-butoxycarbonyl)amino]propyl}amino)piperidine-1-carboxylate (1.54 g, 98%) as a colourless oil.

LCMS (Method B): m/z 392 $(M+H)^+$ (ES+), at 1.73 min, UV active.

Benzyl 4-({3-[(*tert*-butoxycarbonyl)amino]propyl}amino)piperidine-1-carboxylate (1.54 g, 3.92 mmol) was dissolved in CH_2Cl_2 (19.5 mL), 4 M hydrogen chloride in dioxane (4.90 mL, 19.6 mmol) added and the reaction mixture stirred at rt overnight. The solvents were removed *in vacuo*, the residue washed with CH_2Cl_2 (2 x 20 mL) and dried to give crude benzyl 4-[(3-aminopropyl)amino]piperidine-1-carboxylate dihydrochloride (1.41 g, 99%) as an off-white solid.

LCMS (Method B): m/z 292 $(M+H)^+$ (ES+), at 1.46 min, UV active.

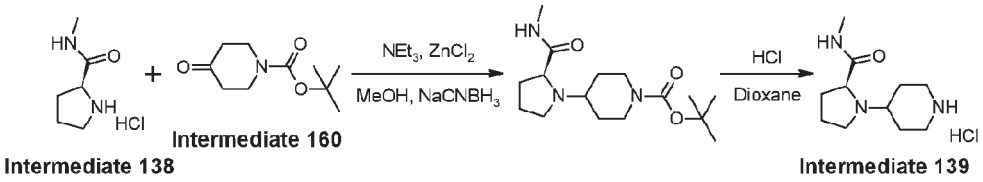
Crude benzyl 4-[(3-aminopropyl)amino]piperidine-1-carboxylate dihydrochloride (1.41 g, 3.88 mmol), CDI (0.778 g, 4.80 mmol) and pyridine (0.24 mL, 12.0 mmol) were dissolved in THF (39 mL), the mixture heated to reflux and maintained for 18 h. The solvents were removed *in vacuo* and the residue purified by column chromatography [Biotage SNAP cartridge KP-sil 50g, 40-63 μm, 60 Å, 50 mL per min, gradient 0% to 10% MeOH in DCM]) to give benzyl 4-(2-oxotetrahydropyrimidin-1(2H)-yl)piperidine-1-carboxylate (0.82 g, 65%) as a colourless solid.

LCMS (Method B): m/z 318 $(M+H)^+$ (ES+), at 2.62 min, UV active.

Benzyl 4-(2-oxotetrahydropyrimidin-1(2H)-yl)piperidine-1-carboxylate (0.82 g, 2.59 mmol) was dissolved in EtOH (100 mL) and passed through a 10% Pd / C cartridge using a H-Cube set at 50 °C, 40 Bar H_2 at 1 mL / min. The eluted solution was concentrated *in vacuo* to give **Intermediate 137**, 1-(piperidin-4-yl)tetrahydropyrimidin-2(1*H*)-one (0.470 g, 99%) as a colourless solid. The data for the title compound are in Table 2.

Route 8

Typical procedure for the preparation of piperidines *via* reductive amination, and Boc-deprotection as exemplified by the preparation of Intermediate 139, (2*S*)-*N*-methyl-1-(piperidin-4-yl)pyrrolidine-2-carboxamide



(*S*)-*N*-methylpyrrolidine-2-carboxamide (0.5g, 3.8 mmol), NEt_3 (1.5 mL, 11.0 mmol), *tert*-butyl 4-oxopiperidine-1-carboxylate (0.38 g, 3.9 mmol) and $ZnCl_2$ (0.15 g, 4.5 mmol) were dissolved in MeOH (15 mL) under nitrogen and stirred for 1 h at 50-60°C. $NaCNBH_3$ (0.16 g, 0.67 mmol) was added portion wise at 0-10°C and the mixture stirred for 3 hrs at room temperature. The reaction mixture was partitioned between EtOAc (2 x 100 mL) and water (50 mL), the organic layers were combined, dried (Na_2SO_4), filtered, the solvent was removed *in vacuo* and the crude product was purified by column chromatography (normal phase silica, 0 to 20 % EtOAc in hexane) to give *tert*-butyl (*S*)-4-(2-(methylcarbamoyl) pyrrolidin-1-yl) piperidine-1-carboxylate (0.3g, 25.0 %) as a light brown liquid.

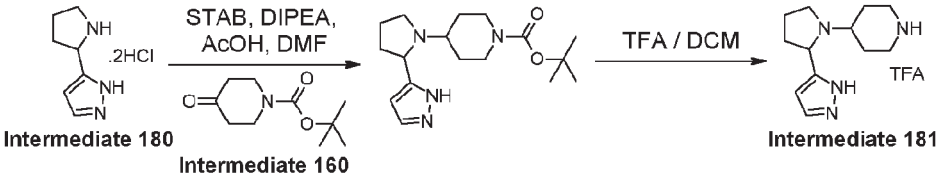
TLC observation: RF value: 0.5 (EA: Hex, 5: 5).

LCMS (Method G): m/z 312 $(M+H)^+$ (ES+), at 1.61 min, UV inactive.

tert-Butyl (*S*)-4-(2-(methylcarbamoyl) pyrrolidin-1-yl) piperidine-1-carboxylate (0.3 g, 0.96mmol) was stirred in HCl in 1,4-dioxane (5.00 mL) solution for 10 hrs at room temperature. The reaction mixture was concentrated under high vaccum and triturated by acetone (3 x 10 mL) to give **Intermediate 139**, (*S*)-*N*-methyl-1-(piperidin-4-yl)pyrrolidine-2-carboxamide dihydrochloride (0.135 g, 67.16%) as a colourless solid. The data for the title compound are in Table 2.

Route 9

General procedure for the preparation of piperidines carrying a N-linked cyclic amine at the 4-position via reductive alkylation and deprotection as exemplified by the preparation of Intermediate 181, 4-[2-(1H-pyrazol-5-yl)pyrrolidin-1-yl]piperidine trifluoroacetate salt



5-(Pyrrolidin-2-yl)-1H-pyrazole dihydrochloride (0.105 g, 0.50 mmol) was dissolved in DMF (5 mL). To the solution was added DIPEA (0.435 mL, 2.5 mmol), AcOH (0.043 mL, 0.75 mmol), *tert*-butyl 4-oxopiperidine-1-carboxylate (0.100 g, 0.50 mmol) and STAB (0.318 g, 1.50 mmol) in that order. The mixture was stirred at rt for 2 days, then concentrated to remove DMF. The residue was partitioned between sat. aqueous $NaHCO_3$ and DCM (x2) and the organic phase

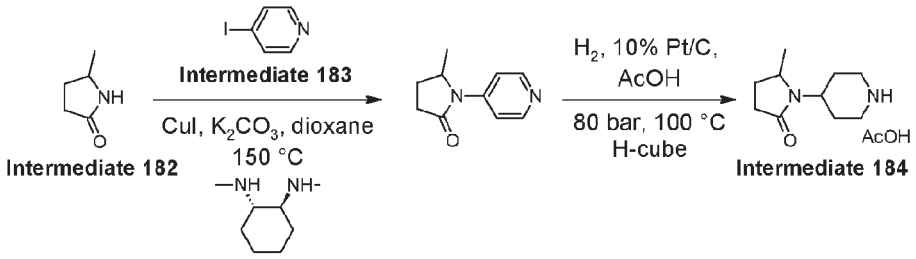
was passed through a phase separator and concentrated to give the crude tert-butyl 4-[2-(1H-pyrazol-5-yl)pyrrolidin-1-yl]piperidine-1-carboxylate (0.271 g, > 100%) as an oil.

LCMS (Method C): m/z 321 $(M+H)^+$ (ES^+), at 1.18 min, UV active

A solution of the crude tert-butyl 4-[2-(1H-pyrazol-5-yl)pyrrolidin-1-yl]piperidine-1-carboxylate (0.271 g, assumed 0.50 mmol) in DCM (3 mL) and TFA (3 mL) was stirred at RT for 110 min then diluted with toluene and concentrated. The residue was azeotroped with toluene to give the crude **Intermediate 181**, 4-[2-(1H-pyrazol-5-yl)pyrrolidin-1-yl]piperidine trifluoroacetate salt (0.598 g, > 100%) as an oil. Used immediately. 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



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.

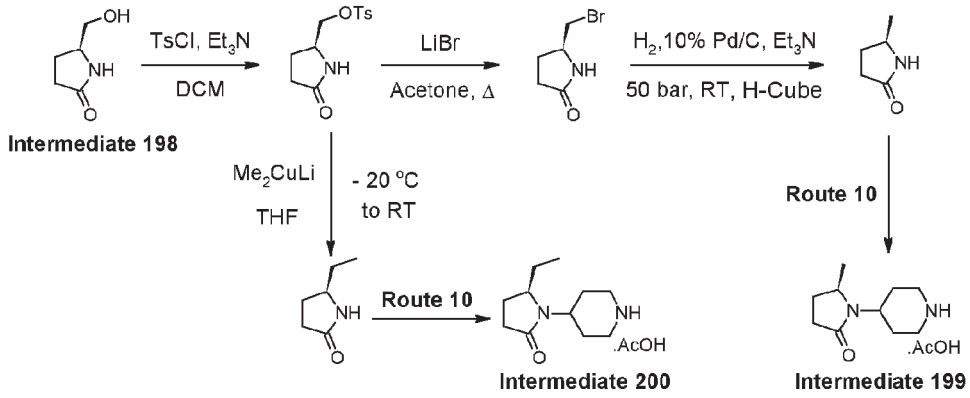
LCMS (Method C): m/z 177 $(M+H)^+$ (ES^+), at 0.69 min, UV active

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



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

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%).

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.

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

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:

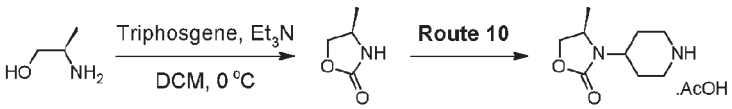
Methyllithium (1.5 M in ether, 7.4 mL, 11 mmol) was added quickly with stirring to a suspension of copper iodide (1.06 g, 5.6 mmol) in THF (6 mL), pre-cooled in ice-water under N_2. The pale brown solution was stirred in ice-water for 45 min, then cooled to - 20 °C. A solution of [(2S)-5-oxopyrrolidin-2-yl]methyl 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

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 12

Typical procedure for the preparation of piperidines *via* carbamate formation, copper catalyzed coupling to pyridine followed by hydrogenation as exemplified by the preparation of Intermediate 205, (4R)-4-methyl-3-(piperidin-4-yl)-1,3-oxazolidin-2-one acetate salt



Intermediate 206 **Intermediate 205**

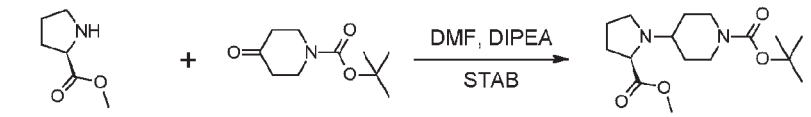
A solution of triphosgene (0.297 g, 1.0 mmol) in DCM (5 mL) was added portion-wise over 1 h to a solution of (2R)-2-aminopropan-1-ol (0.156 mL, 2.0 mmol) and triethylamine (0.56 mL, 4.0 mmol) in DCM (5 mL), precooled in ice-water. The mixture was stirred in ice-water for a further 2 h, then ether (6 mL) was added. The thick suspension was filtered through a sinter, washing the solid with more ether (6 mL). The filtrate was concentrated onto flash silica (5 mL) and 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, 100% EtOAc) to give (4R)-4-methyl-1,3-oxazolidin-2-one (192 mg, 95%) as a solid.

LCMS (Method C): m/z 102 $(M+H)^+$ (ES^+), at 0.14 min, UV inactive

(4R)-4-Methyl-1,3-oxazolidin-2-one (0.188 g, 1.9 mmol) was reacted according to **Route 10** (coupling with **Intermediate 183**) to give the crude **Intermediate 205**, (4R)-4-methyl-3-(piperidin-4-yl)-1,3-oxazolidin-2-one acetate salt (0.343 g, 100%) as a solid. 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-[(2R)-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidine-1-carboxylate

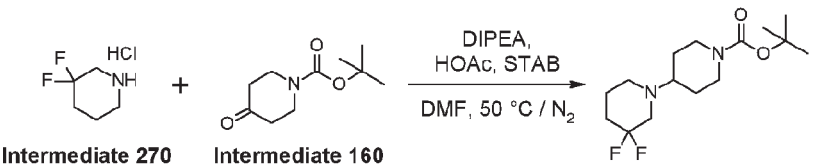


Intermediate 115 **Intermediate 160** **Intermediate 159**

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



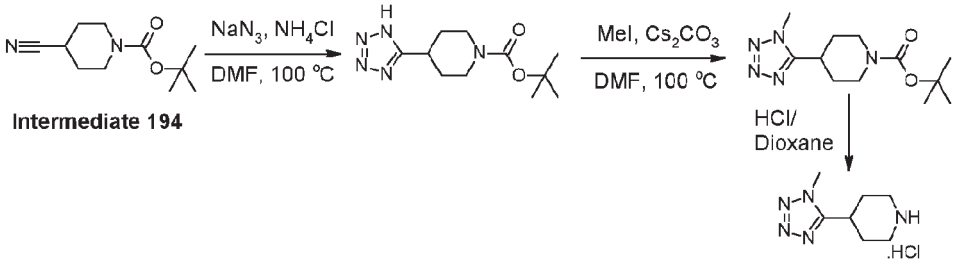
Intermediate 270 **Intermediate 160** **Intermediate 271**

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. $NaHCO_3$ (aq) (10 mL) and extracted with DCM (2 x 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

Route 15

Typical procedure for the preparation of piperidines *via* tetrazole formation, followed by alkylation as exemplified by the preparation of Intermediate 195, 4-(1-methyl-1H-tetrazol-5-yl)piperidine hydrochloride salt



Intermediate 194

Intermediate 195

tert-Butyl 4-cyanopiperidine-1-carboxylate (2.1 g, 10 mmol), sodium azide (1.95 g, 30 mmol) and ammonium chloride (1.6 g, 30 mmol) were dissolved in DMF (20 mL). The reaction mixture was stirred at 100 °C for 24 h, then diluted with water (250 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give the crude product, which was purified by column chromatography (Normal phase, Neutral silica gel, 60-120 mesh, 0 to 5 % MeoH in DCM) to give tert-butyl 4-(1H-tetrazol-5-yl)piperidine-1-carboxylate (1.25 g, 50%) as a solid.

LCMS (Method F): m/z 198 $(M\text{-}tBu+H)^+$ (ES^+), at 1.69 min, UV inactive

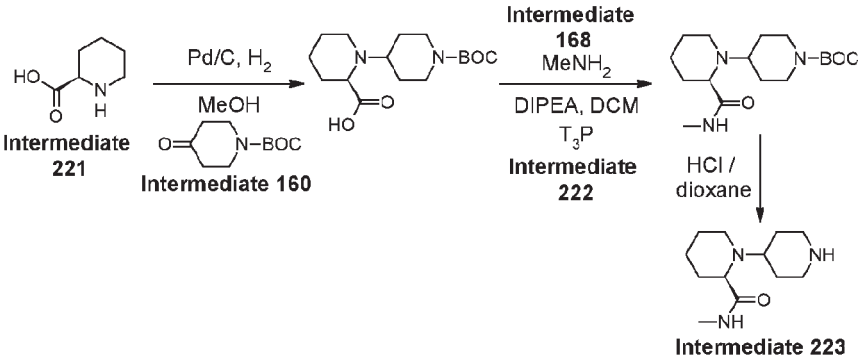
tert-Butyl 4-(1H-tetrazol-5-yl)piperidine-1-carboxylate (1.2 g, 4.7 mmol), iodomethane (2.0 g, 14 mmol) and Cs_2CO_3 (9.6 g, 28 mmol) were dissolved in dry DMF (36 mL). The reaction mixture was stirred at 100 °C for 2 h, then diluted with water (250 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give the crude product, which was purified by column chromatography (Normal phase, Neutral silica gel, 60-120 mesh, 0 to 35 % EtOAc in hexane and then 45 to 60 % EtOAc in hexane to separate the two regioisomers. The required regioisomer, tert-butyl 4-(1-methyl-1H-tetrazol-5-yl)piperidine-1-carboxylate (0.160 g, 13%), was the second to elute from the column and was obtained as a solid.

LCMS (Method F): m/z 212 $(M\text{-}tBu+H)^+$ (ES^+), at 1.79 min, UV inactive

tert-Butyl 4-(1-methyl-1H-tetrazol-5-yl)piperidine-1-carboxylate (0.160 g, 0.60 mmol) was dissolved in dioxane (3 mL). HCl in dioxane (4M, 3 mL, 12 mmol) was added at 0 °C and the mixture was stirred at room temperature for 5 h. The solvent was removed and the mixture was triturated with diethyl ether (5 mL) to give 4-(1-methyl-1H-tetrazol-5-yl)piperidine hydrochloride salt, **Intermediate 195**, (0.130 g, > 100%) as solid. The data for the title compound are in Table 2.

Route 16

Typical procedure for the preparation of piperidines *via* reductive amination, amide formation and Boc-deprotection as exemplified by the preparation of Intermediate 223, (2*R*)-*N*-methyl-1,4'-bipiperidine-2-carboxamide



To a solution of *R*-pipecolinic acid (1 g, 7.75 mmol) and *tert*-butyl 4-oxopiperidine-1-carboxylate (2.31 g, 11.6 mmol) in MeOH (40 mL), 10% Pd on charcoal (1 g, 50% wet) was added and the reaction mixture was stirred at room temperature under H_2 (1 atm) for 48 h. The reaction mixture was filtered through a celite bed and the filtrate was evaporated *in vacuo*. This crude residue was triturated in DCM (50 mL) to give (*R*)-1'-(*tert*-butoxycarbonyl)-[1,4'-bipiperidine]-2-carboxylic acid (1.2 g, 50%) as a white solid. This crude residue was used for the next step without further purification.

^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1.46 (s, 9H), 1.50 - 1.59 (m, 1H), 1.75 - 1.91 (m, 4H), 1.93 - 2.05 (m, 2H), 2.10 - 2.19 (m, 2H), 2.35 - 2.41 (m, 1H), 2.51 - 2.69 (m, 3H), 3.41 - 3.49 (m, 1H), 3.55 - 3.61 (m, 1H), 3.70 - 3.79 (m, 1H), 4.25 - 4.36 (m, 2H).

To a solution of (*R*)-1'-(*tert*-butoxycarbonyl)-[1,4'-bipiperidine]-2-carboxylic acid (1.0 g, 3.20 mmol) and $MeNH_2$ (2 M in THF, 3.2 mL, 6.41 mmol) in DCM (20 mL), DIPEA (1.75 mL, 9.60 mmol) was added at 0 °C. After stirring for 10 min, 1-propane phosphonic anhydride [50% solution in ethyl acetate (4.07 mL, 6.41 mmol)] was added and stirred at room temperature for 3 h. After completion, the reaction mixture was quenched with saturated aq $NaHCO_3$ and extracted with DCM (3 x 30 mL). The organic layers were combined and washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give *tert*-butyl (*R*)-2-(methylcarbamoyl)-[1,4'-bipiperidine]-1'-carboxylate (4, 1 g, 97%) as a colorless gummy liquid. This crude residue was used for the next step without further purification.

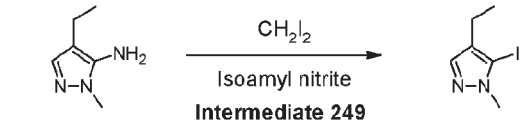
^{1}H-NMR (400 MHz, DMSO) δ: 1.46 (s, 9H), 1.61 - 1.80 (m, 4H), 1.91 - 2.08 (m, 4H), 2.25 - 2.33 (m, 2H), 2.61 - 2.71 (m, 4H), 2.82 (d, J = 4.8 Hz, 3H), 3.32 - 3.45 (m, 2H), 4.25 - 4.36 (m, 2H), 6.85 (br.s., 1H).

To a solution of *tert*-butyl (*R*)-2-(methylcarbamoyl)-[1,4'-bipiperidine]-1'-carboxylate (700 mg, 2.15 mmol) in dioxane (10 mL), HCl in dioxane (4 M, 10 mL) was slowly added at 0 °C and

stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo.* This was basified with aq sat $NaHCO_3$ (10 mL) and concentrated. To the crude reaction mass 5% MeOH/ DCM (30 mL) was added, stirred for 10 min and filtered. The filtrate was concentrated *in vacuo* to give **Intermediate 223**, (*R*)-*N*-methyl-[1,4'-bipiperidine]-2-carboxamide (400 mg, 83%) as a brown gummy liquid. The data for the title compound are in Table 2.

Route 17

Typical procedure for the preparation of iodo pyrazoles *via* sandmeyer reaction as exemplified by the preparation of Intermediate 250, 4-ethyl-5-iodo-1-methyl-1*H*-pyrazole

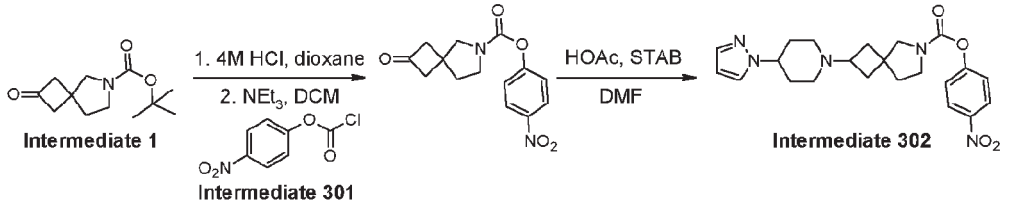


Intermediate 248 **Intermediate 250**

1-Ethyl4-methyl-1*H* pyrazole amine (0.5 g, 3.932 mmol), was dissolved in di iodo methane (9.0 mL) at 0-5°c under nitrogen atmosphere followed by the dropwise addition of isoamyl nitrite and the mixture was stirred for 2 h at 80°C then 2 h at room temperature. The reaction mixture was partitioned between H_2O (100 mL) and EtOAc (250 mL), the aqueous layer was further extracted with EtOAc (2 x 250 mL), the combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography (normal phase, neutral silica gel, 60-120 mesh, 30 to 50 % ethyl acetate in hexane) to give 4-ethyl-5-iodo-1-methyl-1*H*-pyrazole **Intermediate 250** (0.5 g, 53.23 %) as a light yellowish gum. The data for the title compound are in Table 2.

Route 18

Typical procedure for the preparation of activated carbamates *via* deprotection, carbamate formation followed by reductive amination as exemplified by the preparation of Intermediate Intermediate 302, *tert*-butyl (2R)-2-(difluoromethyl)pyrrolidine-1-carboxylate



Intermediate 1 **Intermediate 301** **Intermediate 302**

6-Boc-2-oxo-6-aza-spiro [3.4]octane (4.00 g, 0.017mol) was dissolved in 4M HCl in dioxane (25 mL) and stirred at rt under nitrogen overnight. The solvents were removed *in vacuo* to give an off white solid which was suspended in DCM (40 mL), reaction mixture was cooled under nitrogen to 0°C. Et_3N (3.60 g, 0.036 mol) and 4-nitrophenyl chloroformate (3.767 g, 0.0187 mol) were added and the reaction mixture was and stirred at rt overnight. The reaction mixture was quenched with sat. $NaHCO_3$ (aq) (30 mL) and extracted with DCM (3 x 20 mL). The organic

layers were combined and dried by passing through a Biotage Phase Separator Cartridge and the solvents were removed *in vacuo*. The residue was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 50g 40-63μm, 60Å, 50mL per min, gradient 0% to 6% MeOH / DCM]) to give 4-nitrophenyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate as a yellow solid (1.40 g, 27%).

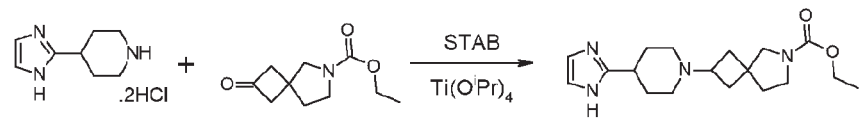
LCMS (Method C): m/z 291 (M+H)+ (ES+) at 1.167 min

4-nitrophenyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate (0.700 g, 2.41 mmol) was dissolved in DMF (15 mL). 4-(1H-pyrazole-1-yl)piperidine (0.365 g, 2.41 mmol), glacial acetic acid (0.144 g, 2.41 mmol) and STAB (1.535 g, 7.24 mmol) were added, the reaction mixture was stirred at 50°C under nitrogen overnight. Reaction mixture quenched with water (2 mL) and the solvents were removed *in vacuo*. The residue was partitioned between DCM (20 mL) and sat. $NaHCO_3$ (aq) (20 mL), aqueous layer was extracted with DCM (2 x 20mL), the organic layers were combined and dried by passing through a Biotage Phase Separator Cartridge 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 4-nitrophenyl 2-[4-(1*H*-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Intermediate 302**, (0.738 g, 72%). 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 Example 1-1, ethyl 2-[4-(1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate



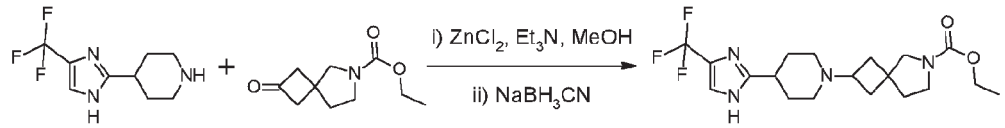
Intermediate 5 **Intermediate 2** **Example 1-1**

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% NEt_3]) 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 x 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 Example 1-3, ethyl 2-(4-(4-(trifluoromethyl)-1H-imidazol-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

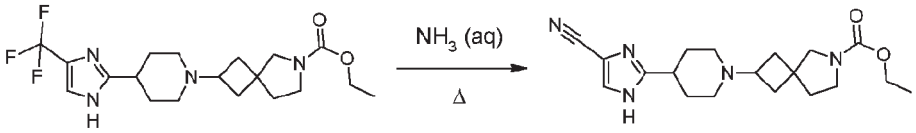


Intermediate 33 **Intermediate 2** **Example 1-3**

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 c

Typical procedure for the conversion of trifluoromethyl substituted imidazoles to cyano substituted imidazoles as exemplified by the preparation of Example 1-4, ethyl 2-[4-(4-cyano-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

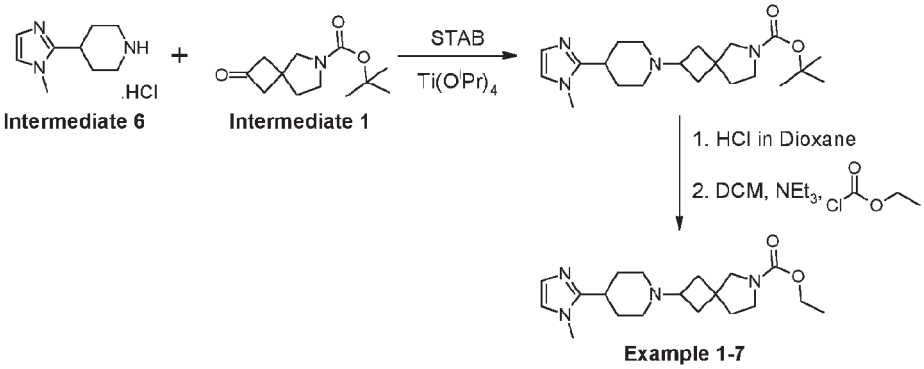


Example 1-3 **Example 1-4**

Ethyl 2-(4-(4-(trifluoromethyl)-1H-imidazol-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate (200 mg, 0.50 mmol) was dissolved in NH_3 solution (20 mL) and stirred at 60°C for 8 h. The solvents were removed *in vacuo* and the residue was partitioned between H_2O (60 mL) and EtOAc (40 mL), aqueous layer was extracted with EtOAc (2 × 40 mL), organic layers were combined, dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by Prep HPLC [reverse phase (DURASHELL, C-18, 250×21.2 mm, 5um, 22 mL per min, gradient 25.0% (over 30.0 mins), 100% (over 3.0 mins) then 25.0% (over 7.0 min), 0.1% NH3 in MeCN/water] to give ethyl 2-(4-(4-cyano-1H-imidazol-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate, **Example 1-4 Isomer 1**, (26 mg, 14.6%) as a yellow solid and ethyl 2-[4-(4-cyano-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Example 1-4 Isomer 2**, (25 mg, 14.06%) 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 Example 1-7, ethyl 2-[4-(1-methyl-1*H*-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate



Intermediate 6 **Intermediate 1** **Example 1-7**

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

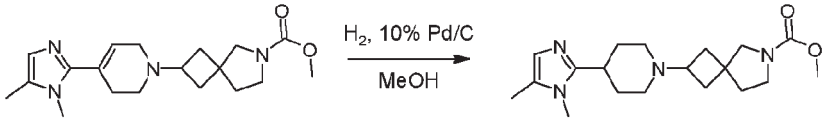
the aqueous layer was extracted with DCM. The combined DCM layers were washed with brine, then dried over $MgSO_4$. The solvents were removed *in vacuo*, and the residue was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 25g, 40-63 μm, 60 Å, 50 mL per min, gradient 1% 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.

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 $NaHCO_3$ (aq) (75 mL) and DCM (75 mL), extracted (2 x 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 x 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, **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, **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 Example 1-9, methyl 2-[4-(1,5-dimethyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate,



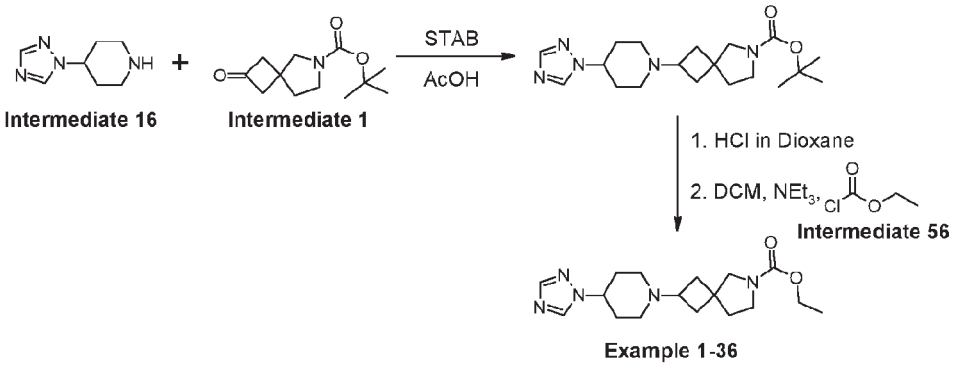
Example 1-9

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, **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, **Example 1-9 Isomer 2**, (11.6 mg, 11.7%) as a colourless gum. The data for Isomer 2 are in Table 3.

Route f

Typical procedure for the preparation of piperidines *via* sodium triacetoxyborohydride reductive amination, Boc-deprotection and ethylcarbamate formation as exemplified by the preparation of Example 1-36, ethyl 2-[4-(1*H*-1,2,4-triazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate



4-(1*H*-1,2,4-Triazol-1-yl)piperidine (0.152 g, 1.0 mmol) and 6-Boc-2-oxo-6-azaspiro[3,4]octane (0.222 g, 1.05 mmol) were dissolved in DCM (10 mL) under N_2 at rt and acetic acid (0.13 mL, 2.22 mmol) was added. The reaction mixture was stirred at rt for 2 h, STAB (0.53 g, 2.50 mmol) added and the reaction mixture stirred overnight at rt. The reaction mixture was quenched with the addition of $NaHCO_3$ (sat aq.) (30 mL), extracted with DCM (4 x 25 mL) and the combined DCM layers passed through a Biotage phase separator. The solvents were removed *in vacuo*, to give a crude mixture of diastereomers of *tert*-butyl 2-[4-(1*H*-1,2,4-triazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate which was used without purification.

LCMS (Method C): m/z 362 $(M+H)^+$ (ES^+), at 1.58 min and 1.61 min, UV inactive.

Crude *tert*-butyl 2-[4-(1*H*-1,2,4-triazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate (assumed 1.0 mmol) was dissolved in 4 M hydrogen chloride in dioxane (1.2 mL, 5.2 mmol) and the reaction mixture stirred at rt overnight. The volatiles were removed *in vacuo* and the residue dissolved in DCM (10 mL) and NEt_3 (0.70 mL, 5.0 mmol) added. Ethyl chloroformate (0.14 mL, 1.5 mmol) was added dropwise and the solution stirred at rt overnight. The mixture was poured into $NaHCO_3$ (aq) (40 mL) extracted with DCM (4 x 40 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-(1*H*-1,2,4-triazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate. Preparative HPLC was used to separate the diastereomers, using a Phenomenex Gemini-NX 5 μm C18 110A Axia column, 100 x 30 mm, eluting with 25 to 55% MeCN/Solvent B over 14.4 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-(1*H*-1,2,4-triazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Example 1-36 Isomer 1**, (0.026 g, 8%) as a colourless solid and ethyl 2-[4-(1*H*-1,2,4-triazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Example 1-36 Isomer 2**, (0.026 g, 8%) as a colourless solid. The data for Isomer 2 are in Table 3.

Route g

Typical procedure for the alkylation of imidazole containing compounds using sodium hydride in DMF as exemplified by the preparation of Example 1-51, ethyl 2-{4-[1-(2-methoxyethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

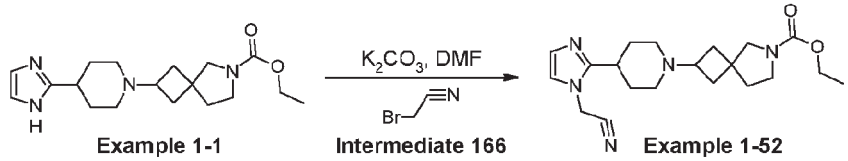


Mixture of diastereomers of ethyl 2-[4-(1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate (150 mg, 0.45 mmol) was dissolved in anhydrous DMF (3 mL), treated with a 60% suspension of sodium hydride in mineral oil (27 mg, 0.68 mmol) and stirred at RT for 2 h. 2-Bromoethyl methyl ether (0.051 mL, 0.54 mmol) was added and the mixture was stirred at RT overnight. The mixture was concentrated to remove DMF. The residue was dissolved in MeOH and 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 20% Solvent A in DCM, where Solvent A is 10% of (7 M NH3/MeOH) in MeOH) to give a mixture of diastereomers of ethyl 2-{4-[1-(2-methoxyethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (159 mg, 90%). This mixture was dissolved in MeOH and the solution was purified by preparative reversed phase HPLC using a Phenomenex Gemini-NX 5 μm C18 110A Axia column, 100 x 30 mm, eluted with 15 to 45% 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-[1-(2-methoxyethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Example 1-51 Isomer 1,** (54 mg, 31%) and ethyl 2-{4-[1-(2-methoxyethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Example 1-51 Isomer 2,** (27 mg, 15%).

The data for Isomer 2 are in Table 3

Route h

Typical procedure for the alkylation of imidazole containing compounds using potassium carbonate in DMF as exemplified by the preparation of Example 1-52, ethyl 2-{4-[1-(cyanomethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

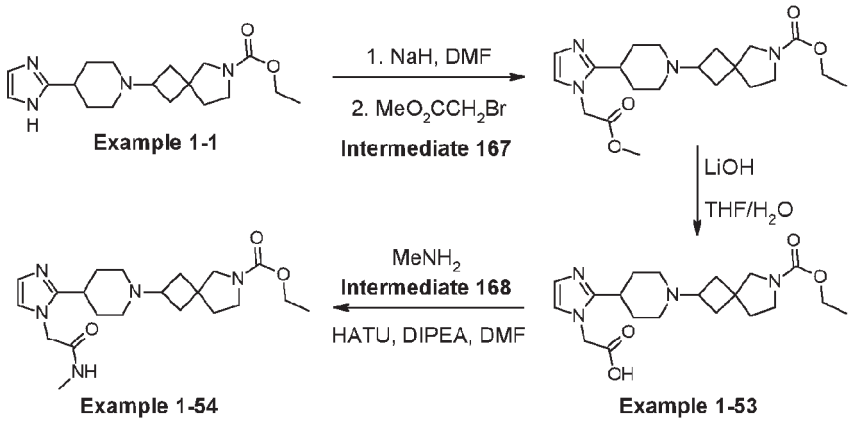


Example 1-1 **Intermediate 166** **Example 1-52**

Mixture of diastereomers of ethyl 2-[4-(1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate (150 mg, 0.45 mmol) was dissolved in anhydrous DMF (3 mL). Potassium carbonate (187 mg, 1.4 mmol) and bromoacetonitrile (0.114 mL, 1.6 mmol) were added and the mixture was stirred at RT over two nights. The mixture was concentrated to remove DMF. The residue was dissolved in MeOH and 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 20% Solvent A in DCM, where Solvent A is 10% of (7 M NH3/MeOH) in MeOH) to give a mixture of diastereomers of ethyl 2-{4-[1-(cyanomethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (91 mg, 54%). This mixture was dissolved in MeOH and the solution was purified by preparative reversed phase HPLC using a Phenomenex Gemini-NX 5 μm C18 110A Axia column, 100 x 30 mm, eluted with 15 to 45% 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-[1-(cyanomethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Example 1-52 Isomer 1**, (8 mg, 5%) and ethyl 2-{4-[1-(cyanomethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Example 1-52 Isomer 2,** (5 mg, 3%). The data for Isomer 2 are in Table 3

Route i

Procedure for the preparation of Example 1-53, (2-{1-[6-(ethoxycarbonyl)-6-azaspiro[3.4]oct-2-yl]piperidin-4-yl}-1H-imidazol-1-yl)acetic acid and Example 1-54, ethyl 2-(4-{1-[2-(methylamino)-2-oxoethyl]-1H-imidazol-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate



Mixture of diastereomers of ethyl 2-[4-(1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate (500 mg, 1.5 mmol) was reacted with 60% dispersion of sodium hydride in mineral oil (90 mg, 2.3 mmol) and methyl bromoacetate (0.171 mL, 1.8 mmol) in DMF (10 mL) using the method of **Route g** to give a mixture of diastereomers of ethyl 2-{4-[1-(2-methoxy-2-oxoethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (393 mg, 65%).

LCMS (Method C): m/z 405 $(M+H)^+$ (ES^+), at 1.12 & 1.17 min, weakly UV active.

The mixture of diastereomers of ethyl 2-{4-[1-(2-methoxy-2-oxoethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (180 mg, 0.45 mmol) was stirred with lithium hydroxide monohydrate (75 mg, 1.8 mmol) in THF (4 mL) and H_2O (1 mL) at rt for 5 days. The mixture was concentrated to remove THF, acidified with 1M aqueous HCl and concentrated to afford the crude mixture of diastereomers of (2-{1-[6-(ethoxycarbonyl)-6-azaspiro[3.4]oct-2-yl]piperidin-4-yl}-1H-imidazol-1-yl)acetic acid (0.4 g, > 100%). Approximately 0.2 g of this mixture was dissolved in MeOH and the solution was purified by preparative reversed phase HPLC using a Phenomenex Gemini-NX 5 μm C18 110A Axia column, 100 x 30 mm, eluted with 5 to 15% 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 (2-{1-[6-(ethoxycarbonyl)-6-azaspiro[3.4]oct-2-yl]piperidin-4-yl}-1H-imidazol-1-yl)acetic acid, **Example 1-53 Isomer 1,** (30 mg, 17%) and (2-{1-[6-(ethoxycarbonyl)-6-azaspiro[3.4]oct-2-yl]piperidin-4-yl}-1H-imidazol-1-yl)acetic acid, **Example 1-53 Isomer 2,** (22 mg, 13%).

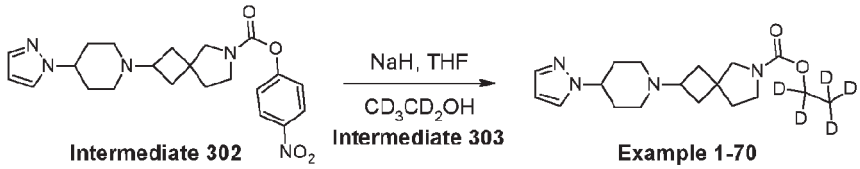
The data for Isomer 2 are in Table 3.

The remaining crude mixture of diastereomers of (2-{1-[6-(ethoxycarbonyl)-6-azaspiro[3.4]oct-2-yl]piperidin-4-yl}-1H-imidazol-1-yl)acetic acid, **Example 1-53**, (0.2 g, assumed 0.22 mmol) was dissolved in DMF (3 mL) and treated with diisopropylethylamine (0.155 mL, 0.89 mmol) and a solution of methylamine in methanol (2M, 0.33 mL, 0.66 mmol). HATU (0.127 g, 0.33 mmol) was then added and the mixture was stirred at RT overnight. The mixture was concentrated to remove DMF, the residue was dissolved in a mixture of DCM and MeOH and concentrated onto flash silica (10 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 20% Solvent A in DCM, where Solvent A is 10% of (7 M NH3/MeOH) in MeOH) to give a mixture of diastereomers of ethyl 2-(4-{1-[2-(methylamino)-2-oxoethyl]-1H-imidazol-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate. This mixture was dissolved in MeOH and the solution was purified by preparative reversed phase HPLC using a Phenomenex Gemini-NX 5 μm C18 110A Axia column, 100 x 30 mm, eluted with 15 to 45% 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-{1-[2-(methylamino)-2-oxoethyl]-1H-imidazol-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate, **Example 1-54 Isomer 1,** (9 mg, 4%) and ethyl 2-(4-{1-[2-(methylamino)-2-oxoethyl]-1H-imidazol-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate, **Example 1-54 Isomer 2,** (6 mg, 3%). The data for Isomer 2 are in Table 3

Route j

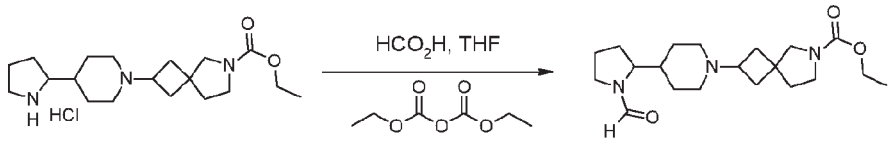
Typical procedure for the preparation of piperidines *via* carbamate formation, as exemplified by the preparation of Example 1-70, ethyl 2-{4-[(2*R*)-4,4-difluoro-2-(methylcarbamoyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate



4-nitrophenyl 2-[4-(1*H*-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate (0.125g, 0.294 mmol) was suspended in anhydrous THF (4 mL) and sonicated to cause dissolution. Sodium hydride, 60 % dispersion in mineral oil, (0.026 g, 0.647 mmol) was added and the reaction mixture was stirred at rt under nitrogen for 10 mins. Ethanol-1,1-2,2,2-d5 (0.150 g, 2.94 mmol) was added and the reaction mixture was stirred at rt under nitrogen overnight. Water (1 mL) was added to the reaction mixture and the solvents were removed *in vacuo*. The residue was partitioned between DCM (20 mL) and sat. $NaHCO_3$ (aq) (10 mL), aqueous layer was extracted with DCM (2 x 10 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 40-63∟m, 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 x 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 ($^2H_5$)ethyl 2-[4-(1*H*-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Example 1-70 Isomer 1**, (0.017 g, 17%) as a white solid and ($^2H_5$)ethyl 2-[4-(1*H*-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Example 1-70 Isomer 2**, (0.013 g, 13%) as a white solid. The data for Isomer 2 are in Table 3.

Route k

Typical procedure for the preparation of piperidines *via* formamide formation as exemplified by the preparation of Example 2-2, ethyl 2-[4-(1-formylpyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate



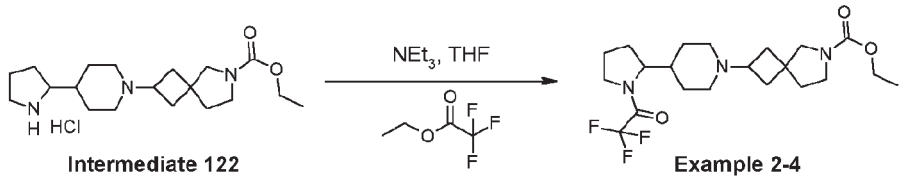
Intermediate 122 **Intermediate 63** **Example 2-2**

A mixture of formic acid (2 mL) and acetic anhydride (0.1 mL, 1.43 mmol) were stirred at 60°C for 1h, then the reaction was cooled to 0°C, and a mixture of diastereomers of ethyl 2-(4-(pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate.HCl (100 mg, 0.30 mmol) in THF (2 mL) was added dropwise. The resulting reaction mixture was stirred at 60°C for 8 h, adjusted to basic pH then the reaction mixture was partitioned between H_2O (40 mL) and EtOAc (25 mL). The aqueous layer was further extracted with EtOAc (2 x 25 mL) and the organic layers were combined and dried over Na_2SO_4. Solvents 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 ethyl 2-[4-(1-formylpyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate **Example 2-2 isomer 1** (14.6 mg, 13.0%) as a yellow gum

and ethyl 2-[4-(1-formylpyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate **Example 2-2 isomer 2** (12.5 mg, 11.1%) as a yellow gum. The data for Isomer 2 are in Table 3

Route L

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

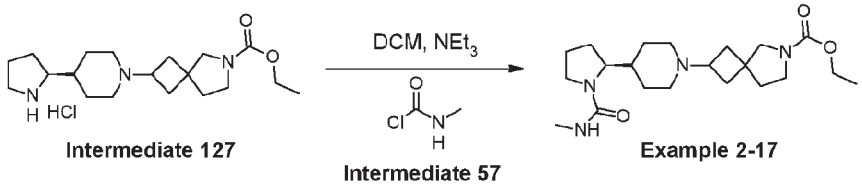


Intermediate 122 Intermediate 62 Example 2-4

Ethyl 2-(4-(pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate (50 mg, 0.15 mmol) and NEt_3 (0.06 mL, 0.45 mmol) were dissolved in THF (3 mL) at rt. Ethyl 2,2,2-trifluoroacetate (0.03 mg, 0.22 mmol) was added dropwise, and the resulting reaction mixture was stirred at rt for 8 h. The reaction mixture was partitioned between H_2O (40 mL) and EtOAc (25 mL), the aqueous layer was further extracted with EtOAc (2 x 25 mL), the organic layers were combined and dried ove Na_2SO_4. Solvents were removed *in vacuo* and 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 ethyl 2-{4-[1-(trifluoroacetyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate **Example 2-4 isomer-1** (5.5 mg, 8.0%) as a yellow gum and ethyl 2-{4-[1-(trifluoroacetyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-4 isomer-2** (6.2 mg, 9.7%) as a yellow 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 Example 2-17, ethyl 2-{4-[(2*S*)-1-(methylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate



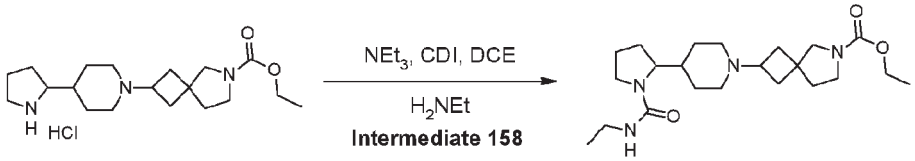
Intermediate 127 Intermediate 57 Example 2-17

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 x 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-[(2*S*)-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 x 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 **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 **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 n

Typical procedure for the preparation of piperidines *via* urea / carbamate formation as exemplified by the preparation of Example 2-19, ethyl 2-{4-[1-(ethylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

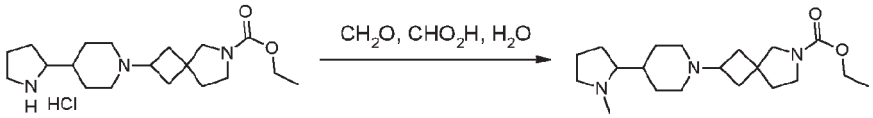


Intermediate 122 **Example 2-19**

A mixture of diastereomers of ethyl 2-(4-(pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate.HCl (100 mg, 0.30 mmol), diethyl amine (0.3 mL, 0.60 mmol) and NEt_3 (0.1 mL, 0.90 mmol) were dissolved in DCE (5 mL) at rt. CDI (145 mg, 0.60 mmol) was added and the reaction mixture was stirred at rt for 15 h. The reaction mixture was partitioned between H_2O (40 mL) and EtOAc (25 mL), the aqueous layer was further extracted with EtOAc (2 x 25 mL), the organic layers were combined, dried (Na_2SO_4), the solvents were removed *in vacuo* and residue was purified by Prep HPLC [reverse phase HPLC (X-BRIDGE, C-18, 250×19 mm, 5um, 15 mL per min, gradient 30.0% to 38.0% (over 25.0 mins),100.0% (over 3.0 mins) then 30.0% (over 2.0 mins),0.1% NH_3 in MeCN/water] to give ethyl 2-(4-(1-(ethylcarbamoyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate, **Example 2 19 isomer-1**, (7.5 mg, 6.20%) as a yellow gum and ethyl 2-(4-(1-(ethylcarbamoyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-19 isomer 2**, (8.1 mg, 6.60%) as a yellow gum. The data for Isomer 2 are in Table 3

Route o

Typical procedure for the preparation of piperidines *via* alkylation as exemplified by the preparation of Example 2-22, ethyl 2-[4-(1-methylpyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

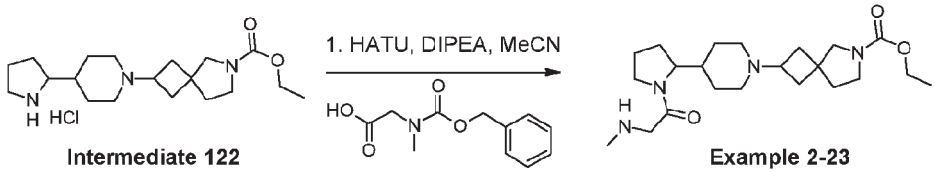


Intermediate 122 **Example 2-22**

A mixture of diastereomers of ethyl 2-(4-(pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate.HCl (200 mg, 0.60 mmol) and formaldehyde (40 % soln, 1.01 mL, 3.60 mmol) were dissolved in H_2O (2 mL) at 25°C. Formic acid (0.303 mL, 0.90 mmol) was added dropwise and the resulting mixture was stirred at 70°C for 14 h. The reaction mixture was quenched with $NaHCO_3$ solution (5 mL), then the reaction mixture was partitioned between H_2O (50 mL) and EtOAc (35 mL). The aqueous layer was further extracted with EtOAc (2 x 35 mL), organic layers were combined and dried over Na_2SO_4. Solvents were removed in vacuo and the residue was purified by Prep HPLC [reverse phase HPLC (X-Bridge,C-18, 250×19.0 mm, 5um, 14 mL per min, gradient 37 % (over 28.0 mins), 100 % (over 4.0 mins) then 37 %(over 3.0 mins),0.1% NH3 in MeCN/water] to give ethyl 2-(4-(1-methylpyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-22 isomer 1** (12 mg, 5.80 %) as a yellow gum and ethyl 2-(4-(1-methylpyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-22 isomer 2** (11 mg, 5.30 %) as a yellow gum. The data for Isomer 2 are in Table 3

Route p

Typical procedure for the preparation of piperidines *via* amide formation as exemplified by the preparation of Example 2-23, ethyl 2-{4-[1-(N-methylglycyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate



Intermediate 122 **Intermediate 75** **Example 2-23**

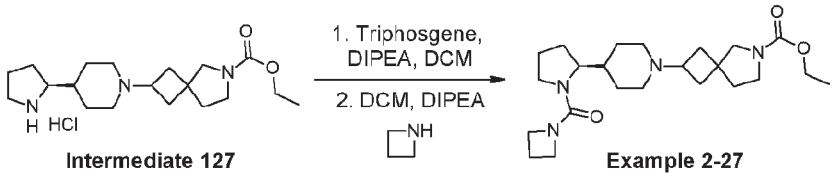
N-[(benzyloxy)carbonyl]-N-methylglycine (73 mg, 0.33 mmol) was dissolved in acetonitrile (5 mL) followed by addition of HATU (170 mg, 0.45 mmol) and DIPEA (0.2 mL, 0.90 mmol). The reaction mixture was stirred at 0°C for 10 minutes, followed by addition of a mixture of diastereomers of ethyl 2-(4-(pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate.HCl (100 mg, 0.30 mmol) and resulting reaction mixture was stirred at 25°C for 3 h. The reaction mixture was partitioned between H_2O (50 mL) and EtOAc (35 mL), the aqueous layer was further extracted with EtOAc (2 x 35 mL), the organic layers were combined, dried over Na_2SO_4 and solvents were removed in vacuo. Finally, the residue was purified by column chromatography (normal basic alumina, activated, 0.5 % to 1.0 % MeOH in DCM) to give ethyl 2-(4-(1-(N-((benzyloxy)carbonyl)-N-methylglycyl) pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate (130 mg, 80.74 %) as a brown gum. Ethyl 2-(4-(1-(N-

((benzyloxy)carbonyl)-N-methylglycyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate (130 mg, 0.24 mmol) was dissolved in

MeOH (10 mL) followed by addition of Pd/C (dry basis, 13 mg). The reaction was then purged with H_2 gas and resulting reaction mixture was stirred at 25°C for 10 h. The reaction mixture was filtered through a celite plug and washed with methanol, then the filtrate dried over Na_2SO_4 and solvents were removed in vacuo. The residue was purified by Prep HPLC [reverse phase HPLC (X-BRIDGE, C-18, 250×19 mm, 5um, 15 mL per min, gradient 20.0 % to 35.0 % (over 30.0 mins), 100.0 % (over 3.0 mins) then 20.0 % (over 2.0 mins), 0.1 % NH3 in MeCN/water] to give ethyl 2-(4-(1-(methylglycyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-23 isomer 1**, (9.0 mg, 9.27%) as a yellow gum and ethyl 2-(4-(1-(ethylcarbamoyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-23 isomer 2**, (8.0 mg, 8.50%) as a yellow gum. The data for Isomer 2 are in Table 3

Route q

Typical procedure for the preparation of piperidines *via* urea formation as exemplified by the preparation of Example 2-27, ethyl 2-{4-[(2S)-1-(azetidin-1-ylcarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate



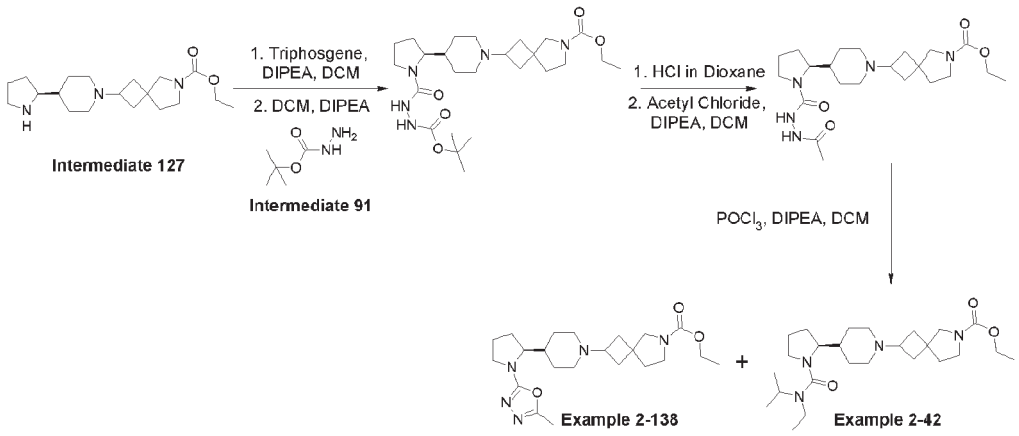
Intermediate 127 **Intermediate 79** **Example 2-27**

A mixture of diastereomers of ethyl 2-{4-[(2S)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (100 mg, 0.291 mmol) were dissolved DCM (5 mL) and diisopropylethylamine (0.099 mL, 0.58 mmol). Triphosgene (88 mg, 0.291 mmol) was added at 0°C and the solution warmed to rt and stirred for 1h. The mixture was then diluted with DCM (50 mL) and washed with H_2O (70 mL). The aqueous layer was extracted with DCM (2x 50 mL), and the combined DCM extracts dried with Na_2SO_4 and concentrated in vacuo. The residue was dissolved in DCM (5 mL) and azetidine (0.020 mL, 0.291 mmol) and diisopropylethylamine (0.256 mL, 1.48 mmol) were added. The reaction was stirred at rt for 1 h. The mixture was then diluted with DCM (50 mL) and washed with H_2O (70 mL). The aqueous layer was extracted with DCM (2x 50 mL), and the combined DCM extracts dried with Na_2SO_4 and concentrated in vacuo, to provide ethyl 2-{4-[(2*S*)-1-(azetidin-1-ylcarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate as a yellow solid and as a mixture of diastereomers. The residue was purified by Prep HPLC [reverse phase HPLC (CHIRALPAK AD-H, C-18, 250 × 20 mm, 5 um, 18.0 mL per min, gradient 0 % to 50 % (over 15.0 mins),0.1% Ammonia in acetonitrile and 0.1% ammonia in H_2O to give ethyl (*S*)-2-(4-(1-(azetidine-1-carbonyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-27**

isomer 1 (20 mg, 16.12 %) as a colorless gum, and **Example 2-27 isomer 2** (20 mg, 16.12 %) as a colorless gum. The data for Isomer 2 are in Table 3

Route r

Typical procedure for the preparation of piperidines *via* urea formation and dehydration as exemplified by the preparation of Example 2-42, ethyl 2-(4-{(2S)-1-[ethyl(propan-2-yl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate and Example 2-138, ethyl 2-{4-[(2S)-1-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate



A mixture of diastereomers of ethyl 2-{4-[(2S)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (164 mg, 0.403 mmol) was dissolved in DCM (2 mL) and diisopropylethylamine (0.209 mL, 1.21 mmol). Triphosgene (43 mg, 0.145 mmol) was added at 0°C and the solution warmed to rt and stirred for 18h. To this mixture was added *tert*-butyl carbazate (108 mg, 0.82 mmol) and diisopropylethylamine (0.142 mL, 0.82 mmol) and the reaction was stirred at rt for 18 h. The mixture was then diluted with DCM (20 mL) and washed with saturated $NaHCO_3$ (aq) (2 x 20 mL). The aqueous layers were extracted with DCM (20 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-(*tert*-butyl carbazoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate as a yellow oil and as a mixture of diastereomers (192 mg, 97%).

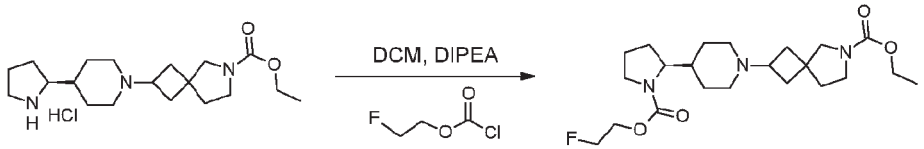
LCMS (Method D): m/z 494 $(M+H)^+$ (ES^+), at 1.83 and 1.87 min, UV inactive.

The crude product was dissolved in 4 M hydrogen chloride in dioxane (2.0 mL, 8.0 mmol) and DCM (1 mL). The reaction mixture was stirred at rt for 1 h. The volatiles were then removed *in vacuo*, before the reaction mixture was redissolved in DCM (2 mL) and diisopropylethylamine (0.142 mL, 0.82 mmol). Acetyl chloride (0.031 mL, 0.428 mmol) was added at 0°C, and the solution warmed to rt and stirred for 2h. The volatiles were removed in vacuo and carried through to next step without further purification. The residue was dissolved in toluene (2 mL) and diisopropylethylamine (0.135 mL, 0.78 mmol) and cooled to 0°C. Phosphorus oxychloride

was added (0.182 mL, 1.945 mmol) and reaction stirred at 110°C for 30 minutes, before the reaction was cooled to rt and quenched with ice water (20 mL). The mixture was then diluted with DCM (20 mL) and washed with 1M $NaOH_{(aq)}$ (2 x 20 mL). The aqueous layers were extracted with DCM (3x20 mL), and the combined DCM extracts washed with brine (50 mL) then passed through a Biotage phase separator and concentrated in vacuo. The residue was purified by preparative HPLC, using a Phenomenex Gemini-NX C18 column, 100 x 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 **Example 2-42 Isomer 1**, ethyl 2-(4-{(2*S*)-1-[ethyl(propan-2-yl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate (1.7 mg, 1%) as a colourless oil, **Example 2-42 Isomer 2**, ethyl 2-(4-{(2*S*)-1-[ethyl(propan-2-yl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate (1.6 mg, 1%) as a colourless oil, **Example 2-138 Isomer 1**, ethyl 2-{4-[(2*S*)-1-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (3.9 mg, 2.5%) as a colourless oil and **Example 2-138 Isomer 2**, ethyl 2-{4-[(2*S*)-1-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (3.0 mg, 2%) as a colourless oil. The data for Isomers 2 are in Table 3

Route s

Typical procedure for the preparation of piperidines *via* carbamate formation as exemplified by the preparation of Example 2-47, ethyl 2-(4-{(2S)-1-[(2-fluoroethoxy)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate



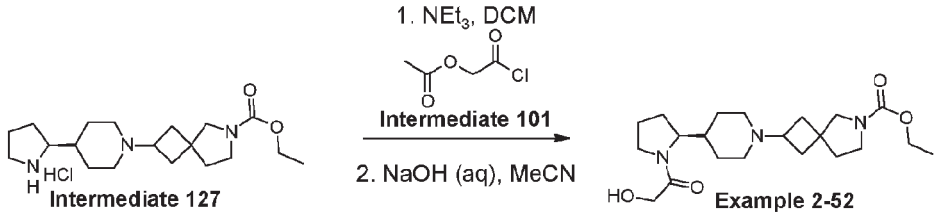
Intermediate 127 **Intermediate 96** **Example 2-47**

A mixture of diastereomers of ethyl 2-{4-[(2S)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (0.15 g, 0.44 mmol) and diisopropylethylamine (0.152 mL, 0.89 mmol) were dissolved in DCM (5 mL), then reaction mixture was cooled to 0°C. 2-fluoroethyl chloroformate (0.062 g, 0.492 mmol) was added and the resulting reaction mixture was stirred at 25°C for 16 h. The reaction mixture was partitioned between H_2O (70 mL) and DCM (50 mL), aqueous layer was further extracted with DCM (2 x 50 mL), organic layers were combined, dried over Na_2SO_4, and solvent was removed in vacuo. The residue was purified by Prep HPLC [reverse phase HPLC (CHIRALPAK AD-H, C-18, 250 × 20 mm, 5 um, 18.0 mL per min, gradient 0 % to 35 % (over 52 mins), 0.1% ammonia in acetonitrile and 0.1% ammonia in Water to give ethyl 2-(4-{(2S)-1-[(2-fluoroethoxy)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-47 isomer-1** (17 mg, 8.9 %) as a yellow gum, and ethyl 2-(4-{(2S)-1-[(2-fluoroethoxy)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-

azaspiro[3.4]octane-6-carboxylate **Example 2-47 isomer-2** (19 mg, 10 %) as a yellow gum. The data for Isomer 2 are in Table 3

Route t

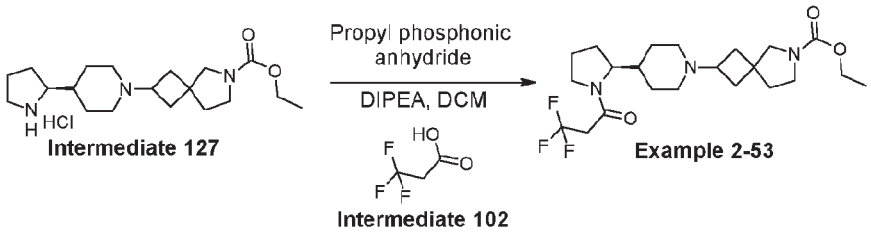
Typical procedure for the preparation of piperidines *via* amide formation as exemplified by the preparation of Example 2-52, ethyl 2-{4-[(2S)-1-(hydroxyacetyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate



A mixture of diastereomers of ethyl 2-{4-[(2S)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (0.2 g, 0.541 mmol) and triethylamine (0.152 mL, 1.1 mmol) were dissolved in DCM (5 mL), then reaction mixture was cooled to 0°C and acetoxy acetyl chloride (0.080 g, 0.591 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. The volatiles were removed *in vacuo*, then the residue was dissolved in acetonitrile (25 mL) and 20% NaOH solution in water (10 mL) and stirred it at room temperature for 1h. The reaction mixture was partitioned between H_2O (70 mL) and DCM (50 mL), aqueous layer was further extracted with DCM (2 x 50 mL), the organic layers were combined, dried over Na_2SO_4, the solvent was removed under vacuum and residue was purified by Prep HPLC [reverse phase HPLC (CHIRALPAK AD-H, C-18, 250 × 20 mm, 5 um, 18.0 mL per min, gradient 0 % to 30 % (over 35.0mins),0.1% Ammonia in Acetonitril and 0.1% Ammonia in Water to give ethyl (S)-2-(4-(1-(2-hydroxyacetyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-52 isomer 1** (8 mg, 8.3 %) as a colorless gum, and ethyl (S)-2-(4-(1-(2-hydroxyacetyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-52 isomer 2** (12 mg, 12.24 %) as a colorless gum. The data for Isomer 2 are in Table 3

Route u

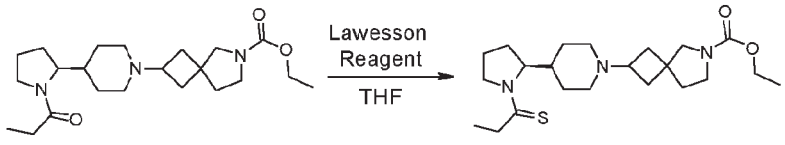
Typical procedure for the preparation of piperidines *via* amide formation as exemplified by the preparation of Example 2-53, ethyl 2-{4-[(2S)-1-(3,3,3-trifluoropropanoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate



(A mixture of diastereomers of ethyl 2-{4-[(2S)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (0.12 g, 0.36 mmol) and diisopropylethylamine (0.123 mL, 0.71 mmol) were dissolved in DCM (10 mL) followed by the addition of trifluoropropanioic acid (0.045 g, 0.394 mmol). The reaction mixture was cooled to 0°C, and propyl phosphonic anhydride was added (0.140 g, 0.462 mmol 50% EtOAc solution) was added and the resulting reaction mixture was stirred at 25°C for 2 h. The reaction mixture was partitioned between H_2O (20 mL) and DCM (50 mL), aqueous layer was further extracted with DCM (2 x 50 mL), organic layers were combined, dried over Na_2SO_4, and solvent was removed in vacuo. The residue was purified by Prep HPLC [reverse phase HPLC (CHIRALPAK AD-H, C-18, 250 × 20 mm, 5 um, 18.0 mL per min, gradient 0 % to 30 % (over 27.0mins),0.1% Ammonia in Acetonitrile and 0.1% Ammonia in Water to ethyl (S)-2-(4-(1-(3,3,3-trifluoropropanoyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-53 isomer 1** (9 mg, 6.0 %) as a colorless gum, and ethyl (S)-2-(4-(1-(3,3,3-trifluoropropanoyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-53 isomer 2** (9 mg, 6.0 %) as a colorless gum. The data for Isomer 2 are in Table 3

Route v

Typical procedure for the preparation of thioamides *via* Lawesson reagent as exemplified by the preparation of Example 2-58, ethyl 2-{4-[(2S)-1-propanethioylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

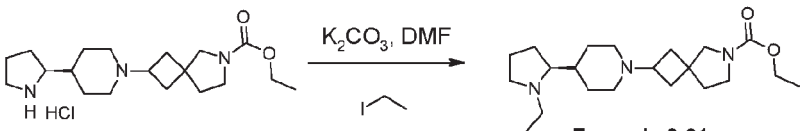


Ethyl 2-{4-[(2S)-1-propanoylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (0.341 g, 0.87 mmol) was dissolved in THF (4 mL) followed by the addition of Lawesson Reagent (0.265 g, 0.65 mmol). The reaction mixture was stirred at 70°C for 24 hours. The volatiles were removed in vacuo, and the reaction mixture was partitioned between 1M NaOH $_{(aq)}$ (50 mL) and DCM (30 mL), aqueous layer was further extracted with DCM (2 x 50 mL), organic layers were combined, washed with 5% sodium metabisulfite $_{(aq)}$, dried over Na_2SO_4, and solvents were removed in vacuo. The residue was purified by Preparative HPLC, using a Phenomenex Gemini-NX C18 column, 100 x 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 **Example 2-58 Isomer 1** ethyl 2-{4-[(2S)-1-propanethioylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (14.1 mg, 4%) as a yellow oil and **Example 2-58 Isomer 2**, ethyl 2-{4-[(2S)-1-propanethioylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (7.6 mg, 2%) as a yellow oil. The data for Isomer 2 are in Table 3

Route w

Typical procedure for the preparation of piperidines *via* alkylation as exemplified by the preparation of Example 2-61, ethyl 2-{4-[(2S)-1-ethylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

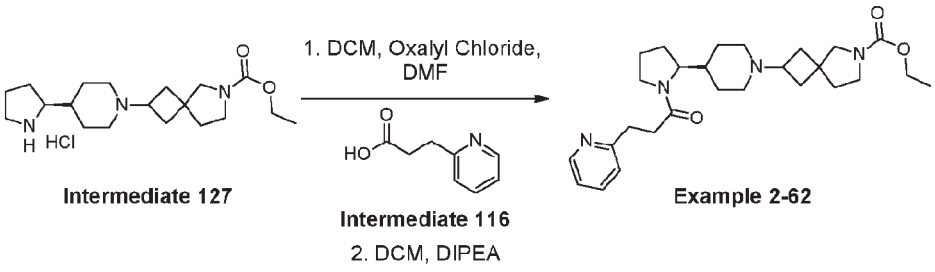


Intermediate 127 **Intermediate 114** **Example 2-61**

A mixture of diastereomers of ethyl 2-{4-[(2S)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (0.100 g, 0.29 mmol) and potassium carbonate (0.123 mg, 0.89 mmol) were dissolved in DMF (5 mL) and the reaction mixture was stirred at 60°C for 2 hours. Iodoethane was then added (0.049 g, 0.31 mmol and the reaction mixture was stirred at 100°C for 62 hours. The reaction mixture was partitioned between H_2O (70 mL) and EtOAc (50 mL), aqueous layer was further extracted with EtOAc (2 x 50 mL), organic layers were combined, dried over Na_2SO_4, and solvent was removed in vacuo. The residue was purified by Prep HPLC (X Bridge, C-18, 150×19 mm, 5um, 20 mL per min, gradient 35 % (over 0.01 mins), 100 % (over 25.01 mins), then 35 % (over 30.00 mins), 0.1% ammonia in acetonitrile/ water] to give ethyl (S)-2-(4-(1-ethylpyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-61 isomer 1** (43 mg, 38.8 %) as a colourless gum, and ethyl (S)-2-(4-(1-ethylpyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-61 isomer 2** (26 mg, 23.1 %) as a colourless gum. The data for Isomer 2 are in Table 3

Route x

Typical procedure for the preparation of piperidines *via* s amide formation as exemplified by the preparation of Example 2-62, ethyl 2-(4-{(2S)-1-[3-(pyridin-2-yl)propanoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

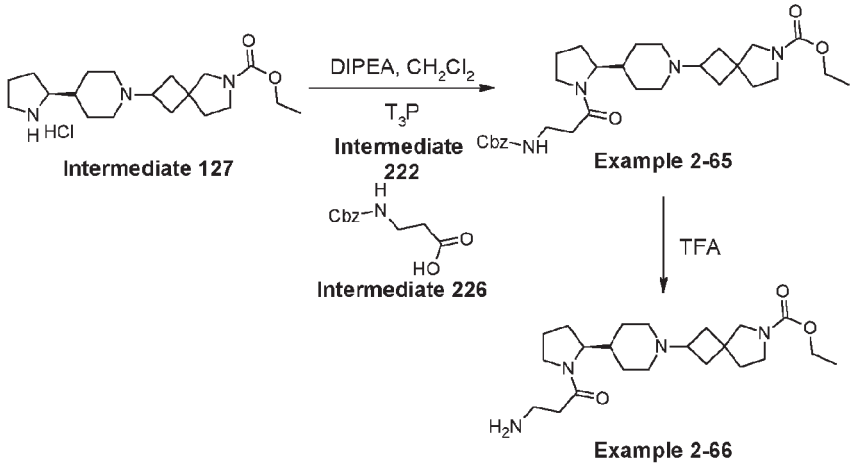


Intermediate 127 **Intermediate 116** **Example 2-62**

To a solution of oxalyl chloride (0.065 mL, 0.768 mmol) in DCM (2mL) at 0°C was added 2-pyridinepropionic acid (106 mg, 0.704 mmol) and DMF (1 drop). A mixture of diastereomers of ethyl 2-{4-[(2S)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (262 mg, 0.640 mmol) was dissolved in DCM (1 mL) and diisopropylethylamine (0.355 mL, 2.049 mmol) and added to the solution, which was stirred at rt for 2 h. The mixture was then poured into 1M NaOH (aq) (50 mL), extracted with DCM (2 x 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-[3-(pyridin-2-yl)propanoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate as a black oil and as a mixture of diastereomers (0.245 g, 82%). Preparative HPLC was used to separate the diastereomers, using a Phenomenex Gemini-NX C18 column, 100 x 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 **Example 2-62 Isomer 1**, ethyl 2-(4-{(2S)-1-[3-(pyridin-2-yl)propanoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate (0.042 g, 14%) as a colourless oil and **Example 2-62 Isomer 2**, ethyl 2-(4-{(2S)-1-[3-(pyridin-2-yl)propanoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate (0.030 g, 10%) as a colourless oil. The data for 2 are in Table 3

Route y

Typical procedure for the preparation of piperidines *via* amide formation and CBZ-deprotection as exemplified by the preparation of Example 2-65, ethyl 2-{4-[(2*S*)-1-{*N*-[(benzyloxy)carbonyl]-β-alanyl}pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate and Example 2-66, ethyl 2-{4-[(2*S*)-1-(β-alanyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate



A mixture of diastereomers of ethyl 2-{4-[(2S)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (100 mg, 0.298 mmol) and DIPEA (0.102 mL, 0.597 mmol) were dissolved in CH_2Cl_2 (5 mL), cooled to 0°C and Z-β-ala-OH (0.066 g, 0.298 mmol)

added followed by propane phosphonic anhydride (0.123 g, 0.388 mmol,50% In ethyl acetate). The resulting reaction mixture was stirred at 25°C for 3 h, partitioned between H_2O (70 mL) and CH_2Cl_2 (50 mL) and the aqueous layer further extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give ethyl 2-{4-[(2*S*)-1-{*N*-[(benzyloxy)carbonyl]-β-alanyl}pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (100 mg, 71.4 %) as a colorless gum which was used directly without purification for the synthesis of **Example 2-66**.

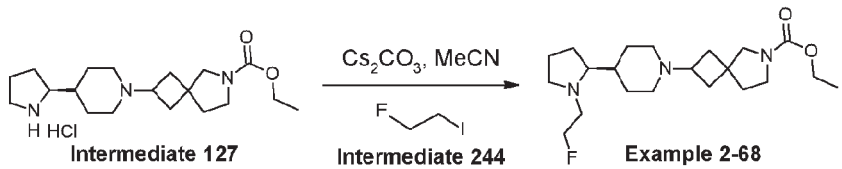
LCMS (Method I): m/z 541 $(M+H)^+$ (ES+) at 4.38 and 4.51 min, UV inactive.

The residue could be purified by Prep HPLC [reverse phase HPLC (CHIRALPAK AD-H, C-18, 250 × 20 mm, 5 um, 18.0 mL per min, gradient 0% to 50% (over 15.0 mins), 0.1% ammonia in acetonitrile and 0.1% ammonia in water to give ethyl 2-{4-[(2*S*)-1-{*N*-[(benzyloxy)carbonyl]-β-alanyl}pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate **Example 2-65 Isomer 1** (20 mg, 12.5 %) as a colourless gum, and ethyl 2-{4-[(2*S*)-1-{*N*-[(benzyloxy)carbonyl]-β-alanyl}pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate **Example 2-65 Isomer 2** (20 mg, 12.5 %) as a colourless gum. The data for Isomer 2 are in Table 3.

A mixture of diastereomers of ethyl 2-{4-[(2*S*)-1-{*N*-[(benzyloxy)carbonyl]-β-alanyl}pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (100 mg, 0.185 mmol) was dissolved in TFA (2.0 mL).The resulting solution was stirred at 80°C for 3 h, concentrated *in vacuo* and the residue purified by Prep HPLC [reverse phase HPLC (CHIRALPAK AD-H, C-18, 250 × 19 mm, 5 um, 13.0 mL per min, gradient 0 % to 30 % (over 30.0 mins), 0.1% ammonia in acetonitrile and 0.1% ammonia in water to give ethyl (*S*)-2-(4-(1-(3-aminopropanoyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4] octane-6-carboxylate **Example 2-66 Isomer 1** (2 mg, 2.63 %) as a colorless gum and ethyl (*S*)-2-(4-(1-(3-aminopropanoyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane -6-carboxylate **Example 2-66 Isomer 2** (3 mg, 4.0 %) as a colorless gum. The data for Isomer 2 are in Table 3.

Route z

Typical procedure for the preparation of piperidines *via* alkylation as exemplified by the preparation of Example 2-68, ethyl 2-{4-[(2*S*)-1-(2-fluoroethyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate



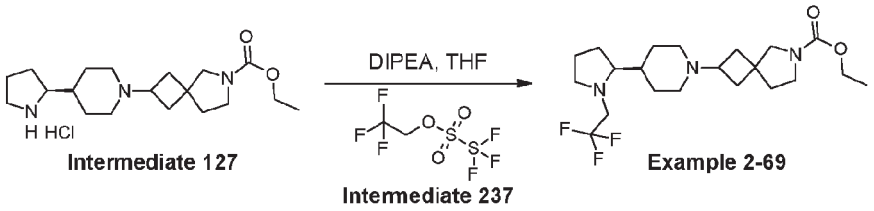
Intermediate 127 **Intermediate 244** **Example 2-68**

A mixture of diastereomers of ethyl 2-{4-[(2S)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (100 mg, 0.27mmol) was dissolved in MeCN (5 mL), CS_2CO_3 (290mg, 0.89 mmol) was added followed by the addition of 2-iodo-1-fluoroethane (56 mg g, 0.32 mmol) and the reaction mixture was stirred at 50°C for 16 h. The reaction mixture

was partitioned between H_2O (70 mL) and ethyl acetate (50 mL), the aqueous layer was further extracted with ethyl acetate (2 x 50 mL), the organic layers were combined, dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was purified by prep HPLC [reverse phase HPLC (CHIRALPAK AD-H, C-18, 250 × 19 mm, 5 um, 15.0 mL per min, gradient 0% to 40% (over 19.0mins), 0.1% ammonia in acetonitrile and 0.1% ammonia in water] to give ethyl (*S*)-2-(4-(1-(2-fluoroethyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-68 Isomer 1** (25 mg, 25%) as a yellowish gum and ethyl (*S*)-2-(4-(1-(2-fluoroethyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-68 Isomer 2** (20 mg, 20.3 %) as a yellowish gum. The data for Isomer 2 are in Table 3.

Route aa

Typical procedure for the preparation of piperidines *via* alkylation as exemplified by the preparation of Example 2-69, ethyl 2-{4-[(2S)-1-(2,2,2-trifluoroethyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

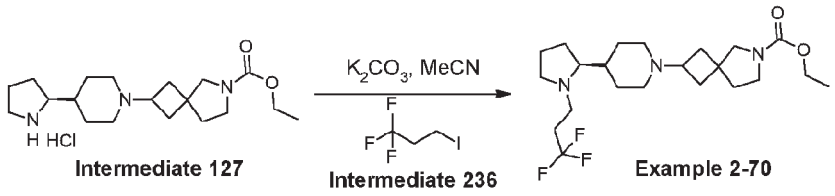


Intermediate 127 **Intermediate 237** **Example 2-69**

A mixture of diastereomers of ethyl 2-{4-[(2S)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (0.100 g, 0.29 mmol) and DIPEA (0.112 g, 0.87 mmol) were dissolved in THF (5 mL) and stirred at 60°C for 2 hrs. 2,2,2-Trifluoroethyl trifluoromethanesulfonate (0.067 g, 0.29 mmol) was added dropwise at 0°C and the resulting reaction mixture was stirred at room temperature for 24 h. The reaction mixture was partitioned between H_2O (70 mL) and EtOAc (50 mL), the aqueous layer was further extracted with EtOAc (2 x 50 mL), the organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by prep HPLC (X Bridge, C-18, 250×19 mm, 5um, 12 mL per min, gradient 45 % (over 0.01 mins), 100 % (over 30.00 mins), then 45 % (over 32.00 mins), 0.1% ammonia in acetonitrile/water to give ethyl (*S*)-2-(4-(1-(2,2,2-trifluoroethyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-69 Isomer 1** (0.003g, 2.4 %) as a colorless gum and ethyl (*S*)-2-(4-(1-(2,2,2-trifluoroethyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-69 Isomer 2** (0.002 mg, 1.6 %) as a colorless gum. The data for Isomer 2 are in Table 3.

Route ab

Typical procedure for the preparation of piperidines *via* alkylation as exemplified by the preparation of Example 2-70, ethyl 2-{4-[(2S)-1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

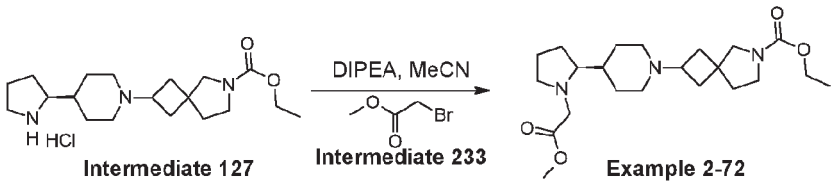


Intermediate 127 Intermediate 236 Example 2-70

A mixture of diastereomers of ethyl 2-{4-[(2S)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (0.100 g, 0.29 mmol) and K_2CO_3 (0.123 g, 0.89 mmol) were dissolved in MeCN (5 mL) and reaction mixture was stirred at 60°C for 2 hrs. 1,1,1-Trifluoro-3-iodopropane (0.066 g, 0.29 mmol) was added dropwise at 0°C and the resulting mixture was stirred at room temperature for 8 h. The reaction mixture was partitioned between H_2O (70 mL) and EtOAc (50 mL), the aqueous layer was further extracted with EtOAc (2 x 50 mL), the organic layers were combined, dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was purified by prep HPLC (X Bridge, C-18, 250×19 mm, 5um, 15 mL per min, gradient 60 % (over 0.01 mins), 100 % (over 14.01 mins), then 60 % (over 23.00 mins), 0.1% ammonia in acetonitrile/water to give ethyl (*S*)-2-(4-(1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-70 Isomer 1** (0.005 g, 3.9 %) as a colorless gum, and ethyl (*S*)-2-(4-(1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-70 Isomer 2** (0.005 mg, 3.9 %) as a colorless gum. The data for Isomer 1 and Isomer 2 are in Table 3.

Route ac

Typical procedure for the preparation of piperidines *via* alkylation as exemplified by the preparation of Example 2-72, ethyl (*S*)-2-(4-(1-(2-methoxy-2-oxoethyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate



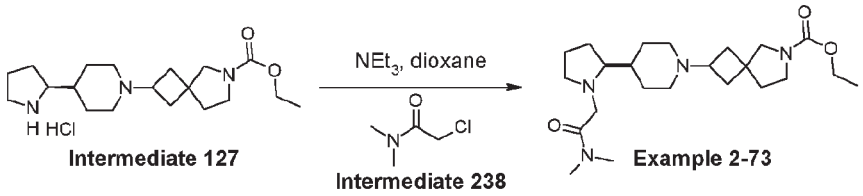
Intermediate 127 Intermediate 233 Example 2-72

A mixture of diastereomers of ethyl 2-{4-[(2S)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (0.100 g, 0.29 mmol) and DIPEA (0.14 mL, 0.87 mmol) were dissolved in MeCN (5 mL) and reaction mixture was stirred at RT for 1 h. Methyl bromoacetate (0.044 g, 0.29 mmol) was added dropwise and the resulting reaction mixture was stirred at 100°C for 3h. The reaction mixture was partitioned between H_2O (70 mL) and EtOAc (50 mL), aqueous layer was further extracted with EtOAc (2 x 50 mL), the organic layers were combined, dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was purified by prep HPLC (X Bridge, C-18, 250×19 mm, 5um, 15 mL per min, gradient 48 % (over

0.01 mins), 100 % (over 11.1 mins), 48 % (over 48.00 mins), 0.1% ammonia in acetonitrile/water] to give ethyl (*S*)-2-(4-(1-(2-methoxy-2-oxoethyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-72 Isomer 1** (0.012 g, 9.9 %) as a colorless gum, and ethyl (*S*)-2-(4-(1-(2-methoxy-2-oxoethyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-72 Isomer 2** (0.013 mg, 10.7 %) as a colorless gum. The data for Isomer 2 are in Table 3.

Route ad

Typical procedure for the preparation of piperidines *via* alkylation as exemplified by the preparation of Example 2-72, ethyl 2-(4-{(2*S*)-1-[2-(dimethylamino)-2-oxoethyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

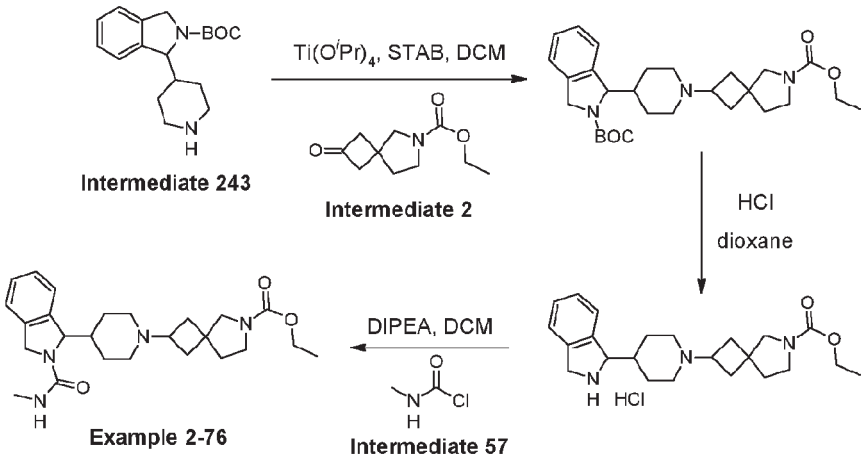


Intermediate 127 **Intermediate 238** **Example 2-73**

A mixture of diastereomers of ethyl 2-{4-[(2S)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (0.100 g, 0.29 mmol) and NEt_3 (0.087 g, 0.85 mmol) were dissolved in dioxane (5 mL) and the reaction mixture was stirred at 60°C for 30 min. 2-Chloro-*N*,*N*-dimethylacetamide (0.036 g, 0.29 mmol) was added dropwise at 0°C and the resulting mixture was stirred at room temperature for 12 h. The reaction mixture was partitioned between H_2O (70 mL) and EtOAc (50 mL), the aqueous layer was further extracted with EtOAc (2 x 50 mL), the organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by prep HPLC (X Bridge, C-18, 250×19 mm, 5um, 14 mL per min, gradient 20 % (over 0.01 mins), 40 % (over 36.00 mins), 100 % (over 44.00 mins), then 20 % (over 52.00 mins), 0.1% ammonia in acetonitrile/water] to give ethyl (*S*)-2-(4-(1-(2-(dimethylamino)-2-oxoethyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-72 Isomer 1** (0.002g, 1.6 %) as a yellow gum and ethyl (*S*)-2-(4-(1-(2-(dimethylamino)-2-oxoethyl)pyrrolidin-2-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-72 Isomer 2** (0.002 mg, 1.6 %) as a yellow gum. The data for Isomer 2 are in Table 3.

Route ae

Typical procedure for the preparation of piperidines *via* reductive amination, Boc-deprotection and urea / amide formation as exemplified by the preparation of Example 2-76, ethyl 2-{4-[2-(methylcarbamoyl)-2,3-dihydro-1*H*-isoindol-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate



To a solution of *tert*-butyl 1-(piperidin-4-yl)isoindoline-2-carboxylate (135 mg, 0.45 mmol) and ethyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (88 mg, 0.890 mmol) in DCM (5 mL), Ti(O^{i}Pr)$_4$ (0.40 mL, 1.34 mmol) was added at 0 °C and the reaction mixture was stirred for 1 h. $Na(OAc)_3BH$ (283 mg, 1.34 mmol) was added portion wise to the reaction mixture and stirred at 0 °C for 2 h. After completion, the reaction mixture was quenched with aq sat $NaHCO_3$ and extracted with DCM (3 x 30 mL). The organic layers were combined and washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography [normal phase, silica gel (100-200 mesh), gradient 5% to 10% methanol in DCM] to give *tert*-butyl 1-(1-(6-(ethoxycarbonyl)-6-azaspiro[3.4]octan-2-yl)piperidin-4-yl)isoindoline-2-carboxylate (35 mg, 75%) as a colourless liquid.

MS (ESI +ve): 484

To a solution of *tert*-butyl 1-(1-(6-(ethoxycarbonyl)-6-azaspiro[3.4]octan-2-yl)piperidin-4-yl)isoindoline-2-carboxylate (290 mg, 0.61 mmol) in 1,4-dioxane (10 mL), HCl in dioxane (4 M, 5 mL) was slowly added at 0 °C and the mixture was stirred at room temperature for 5 h. The solvent was evaporated *in vacuo.* The solid residue was triturated with diethyl ether to give ethyl 2-(4-(isoindolin-1-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate hydrochloride (250 mg, cr) as an off white solid.

MS (ESI +ve): 384

^{1}H-NMR (400 MHz; DMSO-d_6) δ: 1.15 (t, J = 6.9 Hz, 3H), 1.16 - 1.26 (m, 1H), 1.70 - 1.90 (m, 5H), 1.95 - 2.28 (m, 5H), 3.49 - 3.72 (m, 4H), 3.60 - 3.72 (m, 4H), 3.98 - 4.15 (m, 2H), 4.13 (q, J = 6.9 Hz, 2H), 4.45 - 4.59 (m, 2H), 7.37 - 7.49 (m, 5H), 9.54, 10.19 (2br.s., 2H).

To a solution of ethyl 2-(4-(isoindolin-1-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate hydrochloride (240 mg, 0.40 mmol) in DCM (5 mL), DIPEA (0.43 mL, 2.38 mmol) was added at 0 °C. To this reaction mixture methylcarbamic chloride (67 mg, 0.72 mmol) was added and stirred at room temperature for 16 h. The reaction mixture was quenched with water (10 mL) and the aq layer was extracted with DCM (2 x 20 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column

chromatography [normal phase, silica gel (100-200 mesh), gradient 5% to 10% methanol in DCM] to give ethyl 2-(4-(2-(methylcarbamoyl)-isoindolin-1-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate as a mixture of diastereomers (130 mg, 48%) as a gummy liquid.

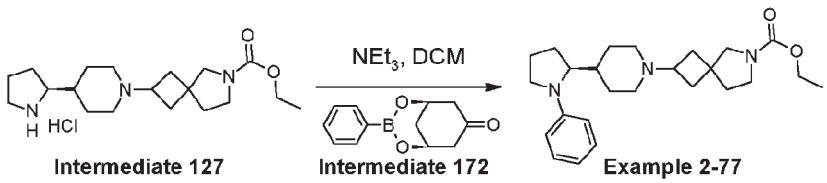
LCMS (Method M): m/z 441 $(M+H)^+$ (ES+), at 1.97 and 1.99 min, UV active.

^{1}H-NMR (400 MHz; DMSO-d_6): δ: 1.15 (t, J = 6.9 Hz, 3H), 1.16 - 1.26 (m, 4 H), 1.49 - 1.90 (m, 5H), 1.91 - 2.01 (m, 2H), 2.62 (d, J = 3.9 Hz, 3 H), 2.70 -2.90 (m, 2H), 3.09 - 3.25 (m, 4H), 3.97 (q, J = 6.8 Hz, 2H), 4.45 - 4.59 (m, 2H), 5.01 - 5.09 (m, 1H), 6.27 (br.s., 1H), 7.22 - 7.32 (m, 4H).

Separation of diastereomers using prep HPLC (73.0 mg submitted, Gilson Semi Preparative HPLC system- including Dual Piston Pumps 331 and 332, a 171 Diode Array Detector and a GX-271 Liquid Handler, solvents: aqueous = water + 0.2% ammonia (28% ammonia solution) and organic = acetonitrile, gradient: 20-50% organic in aqueous, flow Rate: 30ml/min, column: Gemini-NX, C18,5 µ, 100x30mm) gave ethyl 2-(4-(2-(methylcarbamoyl)-isoindolin-1-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-76 Isomer 1** (8.99 mg, 12.3 %) as a colourless gum and ethyl 2-(4-(2-(methylcarbamoyl)-isoindolin-1-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 2-76 Isomer 2** (10.9 mg, 14.9 %) as a colourless gum. The data for Isomer 1 and Isomer 2 are in Table 3.

Route af

Typical procedure for the arylation of pyrrolidine as exemplified by the preparation of Example 2-77, ethyl 2-{4-[(2S)-1-phenylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate



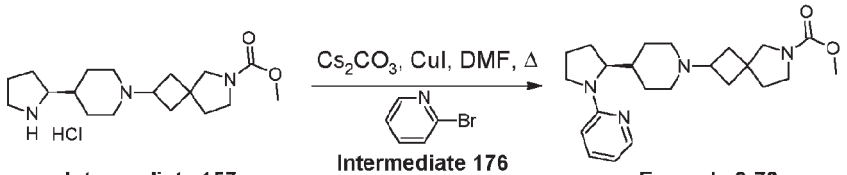
Intermediate 127 **Intermediate 172** **Example 2-77**

A mixture of diastereomers of ethyl 2-{4-[(2S)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (0.100 g, 0.27 mmol) was dissolved in DCM (5 mL), and triethylamine (54 mg, 0.54 mmol) was added followed by (1R,5S)-3-phenyl-2,4-dioxa-3-borabicyclo[3.3.1]nonan-7-one (see J. Luo et al. Tetrahedron Letters 54 (2013), 4505–4508, 58 mg, 0.53 mmol). The reaction mixture was stirred at room temperature for 16h, then partitioned between H_2O (70 mL) and DCM (100 mL). The aqueous layer was further extracted with DCM (2 x 50 mL), and the organic layers were combined, dried (Na_2SO_4), the solvent was removed and the residue was purified by Prep HPLC [reverse phase HPLC (CHIRALPAK AD-H, C-18, 250 × 19 mm, 5 um, 15.0 mL per min, gradient 0 % to 30 % (over 21.0mins), 0.1% Ammonia in Acetonitrile and 0.1% Ammonia in Water to give ethyl 2-{4-[(2S)-1-phenylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-77 Isomer 1** (10 mg, 13 %)

as a gum, and ethyl 2-{4-[(2S)-1-phenylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-77 Isomer 2** (10 mg, 13 %) as a gum. The data for Isomer 2 are in Table 3.

Route ag

Typical procedure for the arylation of pyrrolidine containing compounds with heterocycles using cesium carbonate and copper iodide in DMF as exemplified by the preparation of Example 2-78, methyl 2-{4-[(2S)-1-(pyridin-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

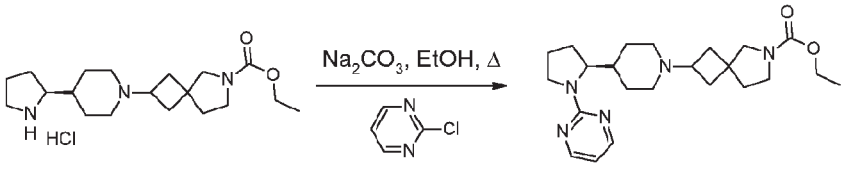


Intermediate 157 **Intermediate 176** **Example 2-78**

A mixture of diastereomers of methyl 2-{4-[(2*S*)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (0.120 g, 0.37 mmol), Cs_2CO_3 (0.361 g, 1.1 mmol) and CuI (0.105 g, 0.50 mmol) were dissolved in DMF (5 mL) and stirred at RT for 30 min. 2-Bromopyridine (0.058 g, 0.37 mmol) was then added and the resulting mixture was stirred at 100 °C for 18 h. The reaction mixture was partitioned between H_2O (70 mL) and EtOAc (50 mL). The aqueous layer was further extracted with EtOAc (2 x 50 mL). The organic layers were combined, dried (Na_2SO_4), the solvent was removed by concentration and the residue was purified Prep HPLC (X Bridge, C-18, 150×19 mm, 5um, 13 mL per min, gradient 40 % to 100% (over 20 mins), 0.1% Ammonia in Acetonitrile/ water] to give methyl 2-{4-[(2S)-1-(pyridin-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate **Example 2-78 Isomer 1** (0.011 g, 2 %) as a gum, and methyl 2-{4-[(2S)-1-(pyridin-2-yl)pyrrolidin-2- yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate **Example 2-78 Isomer 2** (0.09 mg, 2 %) as a gum. The data for Isomer 2 are in Table 3.

Route ah

Typical procedure for the arylation of pyrrolidine containing compounds with heterocycles using sodium carbonate in ethanol as exemplified by the preparation of Example 2-81, ethyl 2-{4-[(2S)-1-(pyrimidin-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

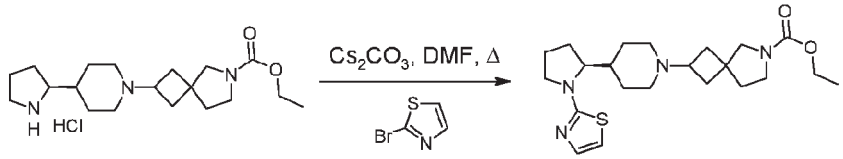


Intermediate 127 **Intermediate 169** **Example 2-81**

A mixture of diastereomers of ethyl 2-{4-[(2S)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl (0.100 g, 0.29 mmol) and Na_2CO_3 (0.092 g, 0.87 mmol) were dissolved in ethanol (10 mL) and stirred at RT for 30 min. 2-Chloropyrimidine (0.034 g, 0.29 mmol) was then added at 0 °C. The resulting reaction mixture was stirred at 80 °C for 6 h. The reaction mixture was concentrated and dichloromethane was added. The mixture was filtered, and the filtrate was concentrated and purified by Prep HPLC (X Bridge, C-18, 150×19 mm, 5um, 15 mL per min, gradient 38 % (over 0.01 mins), 42 % (over 15.00 mins), 100 % (over 19.00 mins), then 38 % (over 23.00 mins), 0.1% Ammonia in Acetonitrile/ water] to give ethyl 2-{4-[(2S)-1-(pyrimidin-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-81 Isomer 1** (0.031g, 25 %) as a gum, and ethyl 2-{4-[(2S)-1-(pyrimidin-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-81 Isomer 2** (0.017 mg, 14 %) as a gum. The data for Isomer 2 are in Table 3.

Route ai

Typical procedure for the arylation of pyrrolidine containing compounds with heterocycles using cesium carbonate in DMF as exemplified by the preparation of Example 2-82, ethyl 2-{4-[(2S)-1-(1,3-thiazol-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

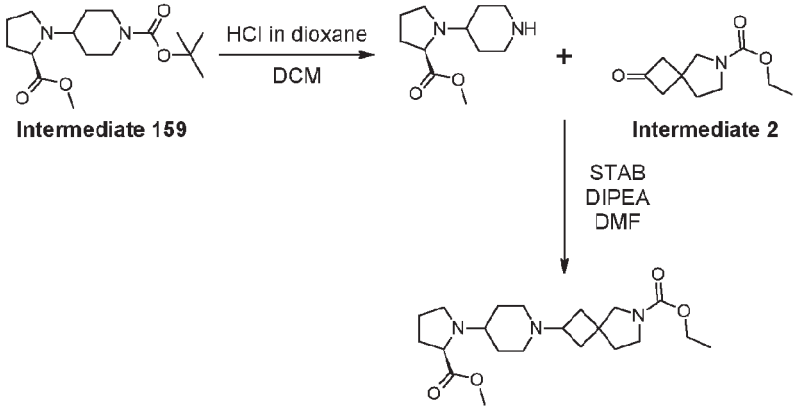


Intermediate 127 **Intermediate 40** **Example 2-82**

The mixture of diastereomers of ethyl 2-{4-[(2*S*)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl, **Intermediate 127**, (100 mg, 0.27 mmol) was dissolved in DMF (5 mL) and CS_2CO_3 (260 mg, 0.81 mmol) was added to it, followed by the addition of 2-bromothiazole (58 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 16h. The reaction mixture was partitioned between H_2O (70 mL) and EtOAc (50 mL). The aqueous layer was further extracted with EtOAc (2 x 50 mL). The organic layers were combined, dried (Na_2SO_4), the solvent was removed by concentration and the residue was purified by Prep HPLC [reverse phase HPLC (CHIRALPAK AD-H, C-18, 250 × 19 mm, 5 um, 15.0 mL per min, gradient 0 % to 30 % (over 21.0mins),0.1% Ammonia in Acetonitrile and 0.1% Ammonia in Water to give ethyl 2-{4-[(2S)-1-(1,3-thiazol-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-82 Isomer 1** (20 mg, 18 %) as a colorless gum, and ethyl 2-{4-[(2S)-1-(1,3-thiazol-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-82 Isomer 2** (6 mg, 6 %) as a colorless gum. The data for Isomer 1 and 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 Example 2-84, ethyl 2-{4-[(2R)-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate



Intermediate 159 **Intermediate 2**

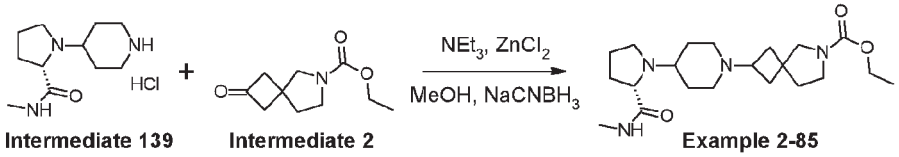
Example 2-84

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.

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 x 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 **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 **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 ak

Typical procedure for the preparation of piperidines *via* reductive amination as exemplified by the preparation of Example 2-85, ethyl 2-{4-[(2*S*)-2-(methylcarbamoyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

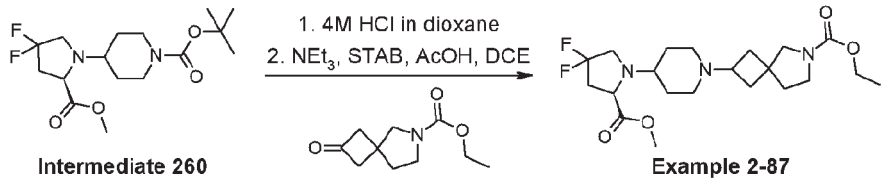


Intermediate 139 **Intermediate 2** **Example 2-85**

(*S*)-*N*-methyl-1-(piperidin-4-yl)pyrrolidine-2-carboxamide dihydrochloride (0.2g, 0.94 mmol), NEt_3 (0.75 mL, 5.0 mmol), 6-(ethoxycarbonyl)-2-oxo-6-azaspiro[3.4]octan-8-ylium (0.188 g, 0.93 mmol) and $ZnCl_2$ (30 mg, 0.02 mmol) were dissolved in MeOH (15.00 mL) under nitrogen and stirred for 1 h at 50-60°C. $NaCNBH_3$ (0.069 g, 1.0 mmol) was added portion wise at 0-10°C and the reaction mixture stirred for 3 h at room temperature. The reaction mixture was partitioned between EtOAc (2 x 50 mL) and water (30 mL), the organic layers were combined, dried (Na_2SO_4), filtered and the solvent was removed *in vacuo* and the crude product was purified by PREP-HPLC [reverse phase HPLC (X-Bridge PREP C18, 250 × 19 mm, 5um, 15 mL per min, gradient 30% to 100 % (over 22 min), then 100 % (2 min), 0.1 % NH_3 in Acetonitrile to give **Example 2-85 Isomer** 1, ethyl (*S*)-2-(4-(2-(methylcarbamoyl)pyrrolidin-1-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate (0.09 g, 24.32%) as a white solid and **Example 2-85 Isomer 2**, ethyl (*S*)-2-(4-(2-(methylcarbamoyl)pyrrolidin-1-yl)piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate (0.089 g, 24.10%) as a white solid. The data for Isomer 2 are in Table 3.

Route ap

Typical procedure for the preparation of piperidines *via* deprotection and sodium triacetoxyborohydride reductive amination, as exemplified by the preparation of Example 2-87, ethyl 2-{4-[(2R)-4,4-difluoro-2-(methoxycarbonyl)pyrrolidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate



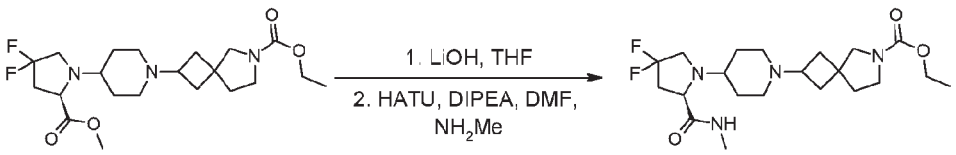
Intermediate 260 **Intermediate 2** **Example 2-87**

tert-butyl 4-[(2R)-4,4-difluoro-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidine-1-carboxylate (0.36 g, 1.03 mmol) was dissolved in 4.0M HCl in dioxane (10 mL) and the reaction mixture was stirred at rt for 6 h. 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 (0.243 g, 1.233 mmol) were dissolved in DCE (10 mL) at rt and Et_3N (0.249 g, 2.47 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 (0.784 g, 3.69 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. $NaHCO_3$ (aq) (15 mL), the aqueous layer was washed with DCM (2 x 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 x 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-[(2R)-4,4-difluoro-2-(methoxycarbonyl)pyrrolidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-87 Isomer 1** (0.020 g, 4.5%) and ethyl 2-{4-[(2R)-4,4-difluoro-2-(methoxycarbonyl)pyrrolidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-87 Isomer 2** (0.020 g, 4.5%). The data for Isomer 2 are in Table 3.

Route am

Typical procedure for the preparation of piperidines *via* deprotection and amide formation, as exemplified by the preparation of Example 2-88, ethyl 2-{4-[(2*R*)-4,4-difluoro-2-(methylcarbamoyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate



Example 2-87 **Example 2-88**

A mixture of diastereomers of ethyl 2-{4-[(2*R*)-4,4-difluoro-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-87**, (0.400 g, 0.932 mmol) was dissolved in THF (8 mL) and 1M LiOH (aq) (1.9mL) was added, the reaction mixture was stirred at rt overnight. The reaction mixture was neutralised using 2.0M HCl solution and solvents were removed *in vacuo*. The residue was azeotroped with toluene to give 1-{1-[6-(ethoxycarbonyl)-6-azaspiro[3.4]oct-2-yl]piperidin-4-yl}-4,4-difluoro-D-proline (0.440 g, 100%) as a yellow glass.

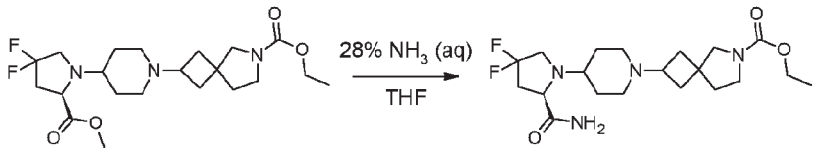
LCMS (Method C): m/z 416 (M+H)+ (ES+) at 0.71min, UV inactive

1-{1-[6-(ethoxycarbonyl)-6-azaspiro[3.4]oct-2-yl]piperidin-4-yl}-4,4-difluoro-D-proline (0.193 g, 0.466 mmol), was dissolved in anhydrous DMF (5 mL) and HATU (0.533 g, 1.398 mmol), 2.0M methylamine solution in THF (2.3 mL, 2.33 mmol) and DIPEA (0.301 g, 2.33 mmol) were added, the reaction mixture was stirred overnight at rt. The solvents were removed *in vacuo*, and the residue was partitioned between DCM (20 mL) and sat. $NaHCO_3$ (aq) (20 mL), aqueous layer was extracted with DCM (2 x 15 mL). The organic layers were combined, washed with brine (20 mL) 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 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 x 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*)-4,4-difluoro-2-(methylcarbamoyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-88 Isomer 1**, (0.038 g, 18%) as a colourless oil and ethyl 2-{4-[(2*R*)-4,4-difluoro-2-(methylcarbamoyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-88 Isomer 2**, (0.037g, 18%) as a colourless oil. The data for Isomer 2 are in Table 3.

Route an

Typical procedure for the preparation of piperidines *via* amide formation, as exemplified by the preparation of Example 2-90, ethyl 2-{4-[(2R)-2-carbamoyl-4,4-difluoropyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

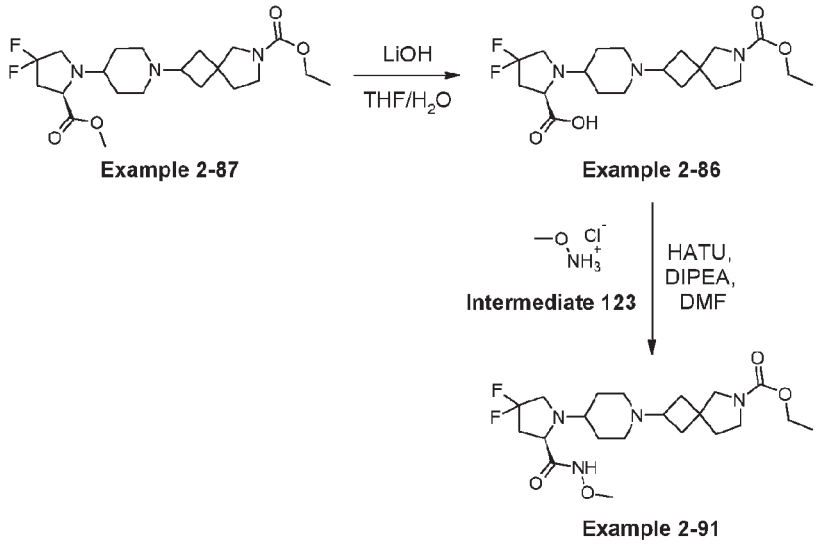


Intermediate 122 **Example 2-90**

Mixture of diastereomers of ethyl 2-{4-[(2R)-2-methoxycarbonyl-4,4-difluoropyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (456 mg,1.062 mmol) was dissolved in THF (1 mL) and 28% NH_3 solution (9 mL) at 60°C and reaction stirred for 18 h. Reaction mixture neutralized with 1M $HCl_{(aq)}$ diluted with DCM (25 mL) and washed with H_2O (2 x 25 mL), combined aqueous layers washed with DCM (25 mL), combined organic layers washed with brine (25 mL) and passed through Biotage Phase separator. Volatiles removed under vacuum to yield an orange oil (0.290 g, 65%). Preparative HPLC was used to separate the diastereomers, using a Phenomenex Gemini-NX C18 column, 100 x 30 mm, eluting with 20 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 **Example 2-90 Isomer 1** ethyl 2-{4-[(2R)-2-carbamoyl-4,4-difluoropyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (16.8 mg, 4%) as a colourless oil and **Example 2-90 Isomer 2**, ethyl 2-{4-[(2R)-2-carbamoyl-4,4-difluoropyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (12.4 mg, 3%) as a colourless oil. The data for Isomer 2 are in Table 3

Route ao

Typical procedure for the preparation of piperidines *via* hydrolysis and amide formation, as exemplified by the preparation of Example 2-91, ethyl 2-{4-[(2R)-4,4-difluoro-2-(methoxycarbamoyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

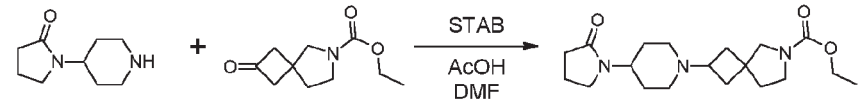


Mixture of diastereomers of ethyl 2-{4-[(2R)-2-methoxycarbonyl-4,4-difluoropyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (230 mg,0.536 mmol) was dissolved in THF (6.5 mL) and 1.0M LiOH solution (1.1 mL, 1.1 mmol) at rt and reaction stirred for 18 h. Volatiles removed under vacuum and compound carried through without further purification.

1-{1-[6-(ethoxycarbonyl)-6-azaspiro[3.4]oct-2-yl]piperidin-4-yl}-4,4-difluoro-D-proline (125 mg, 0.300 mmol) was dissolved in DMF (1 mL) followed by addition of HATU (228 mg, 0.60 mmol) and DIPEA (0.260 mL, 1.50 mmol). The reaction mixture was stirred at 0°C for 10 minutes, followed by addition of methoxyamine hydrochloride (25 mg, 0.30 mmol) and resulting reaction mixture was stirred at rt for 18 h. The reaction mixture was concentrated in vacuo, then was partitioned between saturated $NaHCO_{3(aq)}$ (50 mL) and DCM (50 mL), the aqueous layer was further extracted with DCM (2 x 50 mL), the organic layers were combined, washed with brine (50 mL) and passed through Biotage Phase separator. Volatiles removed under vacuum to yield an orange oil (0.102 g, 77%). Preparative HPLC was used to separate the diastereomers, using a Phenomenex Gemini-NX C18 column, 100 x 30 mm, eluting with 20 to 50% MeCN/0.2% ammonia in H_2O (*v/v*) at 18 mL/min and collecting fractions by monitoring at 210 nm to give **Example 2-91 Isomer 1** ethyl 2-{4-[(2R)-4,4-difluoro-2-(methoxycarbamoyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (12.2 mg, 4%) as a colourless oil and **Example 2-91 Isomer 2**, ethyl 2-{4-[(2R)-4,4-difluoro-2-(methoxycarbamoyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate (7.2 mg, 3%) as a colourless oil. The data for Isomer 2 are in Table 3

Route ap

Typical procedure for the preparation of piperidines *via* deprotection and sodium triacetoxyborohydride reductive amination, as exemplified by the preparation of Example 2-111, ethyl 2-[4-(2-oxopyrrolidin-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate



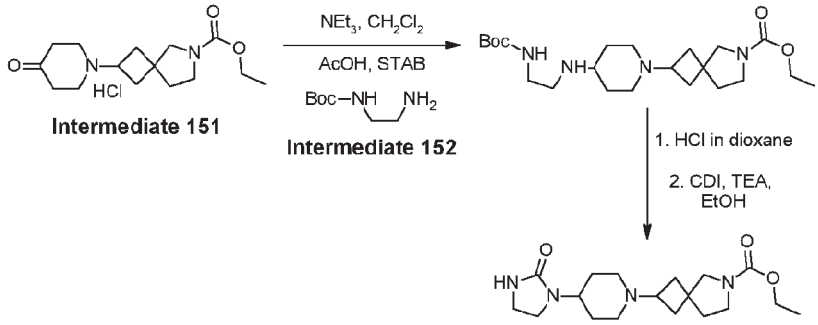
Intermediate 269 **Intermediate 2** **Example 2-111**

1-Piperidin-4-yl pyrrolidine-2-one (0.200 g, 1.19 mmol) 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, the reaction mixture was stirred at 40°C under nitrogen for 3 h. The reaction mixture was cooled to rt, STAB (0.630 g, 2.97 mmol) and glacial acetic acid (0.071 g, 1.189 mmol) were added and the reaction mixture was stirred overnight at 40°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. $NaHCO_3$ (aq) (15 mL), the aqueous layer was washed with DCM (2 x 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 x 30 mm, eluting with 20 to 35% 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-oxopyrrolidin-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-111 Isomer 1**, (0.008 g, 2%) as a colourless oil and ethyl 2-[4-(2-oxopyrrolidin-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-111 Isomer 2**, (0.009 g, 2%) as a colourless oil. The data for Isomer 2 are in Table 3.

If amine used in the reductive amination contains a second amine group which is protected (with standard amine protecting groups such as BOC or Cbz). Then standard methods for deprotection can be used to remove these protecting groups once the reductive amination has been performed to allow further functionalization of the target.

Route aq

Typical procedure for the preparation of piperidines *via* reductive amination, Boc deprotection and urea formation as exemplified by the preparation of Example 2-124, ethyl 2-[4-(2-oxo-1,2-dihydropyridin-4-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate



Intermediate 151 **Intermediate 152** **Example 2-124**

Ethyl 2-(4-oxopiperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate hydrochloride (0.316 g, 1.00 mmol) and *tert*-butyl (2-aminoethyl)carbamate (0.320 g, 2.00 mmol) were dissolved in DCM (10 mL) under N_2 at rt, NEt_3 (0.15 mL, 1.10 mmol) was added and the reaction mixture was stirred at rt for 0.5 h. Acetic acid (0.13 mL, 2.20 mmol) was added, the reaction mixture stirred at rt for 2 h, STAB (0.530 g, 2.50 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 x 25 mL), the combined DCM layers were passed through a Biotage phase separator and concentrated *in vacuo* to give crude ethyl 2-[4-({2-[(*tert*-butoxycarbonyl)amino]ethyl}amino)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate as a mixture of diastereomers which was used without any further purification.

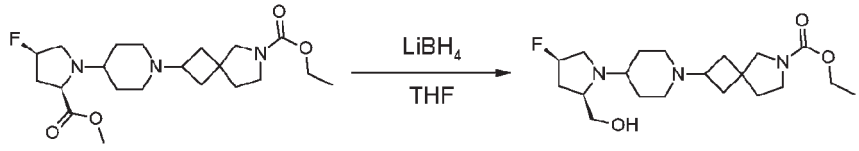
LCMS (Method D): m/z 425 $(M+H)^+$ (ES+), at 1.30 and 1.35 min, UV inactive.

Crude ethyl 2-[4-({2-[(*tert*-butoxycarbonyl)amino]ethyl}amino)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate (0.424 g, 1.00 mmol) was dissolved in CH_2Cl_2 (10 mL), 4 M hydrogen chloride in dioxane (1.25 mL, 5.0 mmol) added and the reaction mixture stirred at rt overnight. The volatiles were removed *in vacuo*, the residue dissolved in EtOH (10 mL), NEt_3 (1.40 mL, 10.0 mmol) and CDI (0.244 g, 1.50 mmol) added and the mixture heated to reflux and maintained overnight. The solvent was removed *in vacuo*, the resiude partitioned between CH_2Cl_2 (20 mL) and water (20 mL) and the aqueous layer extracted with CH_2Cl_2 (4 x 20 mL). The combined organics were concentrated *in vacuo* to give crude ethyl 2-[4-(2-oxoimidazolidin-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate as a mixture of diastereomers. Preparative HPLC was used to separate the diastereomers, using a Phenomenex Gemini-N C18 column, 150 x 21 mm, eluting with 25 to 45% MeCN in 0.2% NH_3/H_2O at 18 mL/min and collecting fractions by monitoring at 210 nm to give ethyl 2-[4-(2-oxo-1,2-dihydropyridin-4-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Example 2-124 Isomer 1**, (0.008 g, 2.3%) as a colourless solid and ethyl 2-[4-(2-oxo-1,2-dihydropyridin-4-yl)piperidin-1-yl]-6-

azaspiro[3.4]octane-6-carboxylate **Example 2-124 Isomer 2**, (0.008 g, 2.3%) as a colourless solid. 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 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

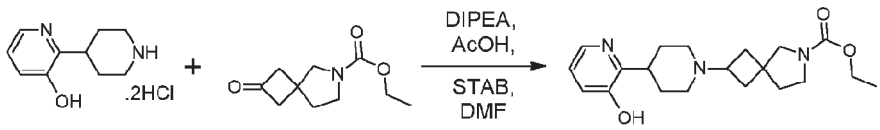


Example 2-134 **Example 2-136**

A mixture of diastereomers of ethyl 2-{4-[(2*R*,4*R*)-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. $NaHCO_3$ (aq) (15 mL) and then extracted with EtOAc (2 x 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 x 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, **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, **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 Example 3-4, ethyl 2-[4-(3-hydroxypyridin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

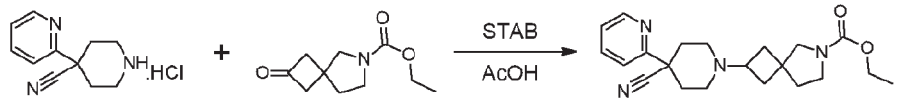


Intermediate 18 **Intermediate 2** **Example 3-4**

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 x 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, **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, **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 Example 3-10, ethyl 2-[4-cyano-(pyridine-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate



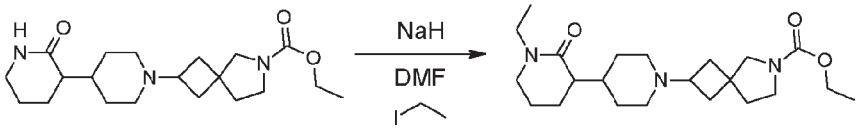
Intermediate 14 **Intermediate 2** **Example 3-10**

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 x 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 x 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, **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, **Example 3-10 Isomer 2**, (0.014 g, 4%) as a colourless solid. The data for both Isomers are in Table 3.

Route au

Typical procedure for the preparation of piperidines *via* alkylation as exemplified by the preparation of Example 4-5, ethyl 2-(1-ethyl-2-oxo-3,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate

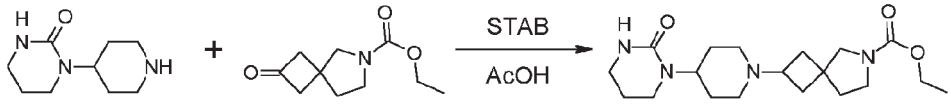


Example 4-1 **Intermediate 114** **Example 4-5**

Ethyl 2-(2-oxo-[3,4'-bipiperidin]-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate, **Example 4-1**, (0.2 g, 0.55 mmol), was dissolved in DMF (3mL) and cooled to 0-5°C. Sodium hydride (0.080 g, 1.6 mmol) and iodoethane (0.139 g, 0.8 mmol), were added and the reaction mixture stirred at room temperature for 3 h. The reaction was quenched with water (50 mL), extracted with EtOAc (3 x 30 mL), and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give crude ethyl 2-(1-ethyl-2-oxo-3,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate as a mixture of diastereomers. The crude product was purified by prep. HPLC [X-Bridge C18 (150 X 19 mm, 5um, 17 mL per min, gradient 27% to 100 % (over 30min), then 100 % (4 min), 0.1 % NH_3 in acetonitrile to give ethyl 2-(1-ethyl-2-oxo-[3,4'-bipiperidin]-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 4-5 Isomer-1** (0.011 g, 5.11%) as a colorless gum and ethyl 2-(1-ethyl-2-oxo-[3,4'-bipiperidin]-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate **Example 4-5 Isomer-2** (0.012 g, 5.80%) as a colorless gum. The data for Isomer 2 are in Table 3.

Route av

Typical procedure for the preparation of piperidines *via* sodium triacetoxyborohydride reductive amination as exemplified by the preparation of Example 4-8, ethyl 2-[4-(2-oxotetrahydropyrimidin-1(2H)-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate



Intermediate 137 **Intermediate 2** **Example 4-8**

1-(Piperidin-4-yl)tetrahydropyrimidin-2(1*H*)-one (0.183 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, acetic acid (0.13 mL, 2.2 mmol) was added and the reaction mixture stirred at rt for 3 h.

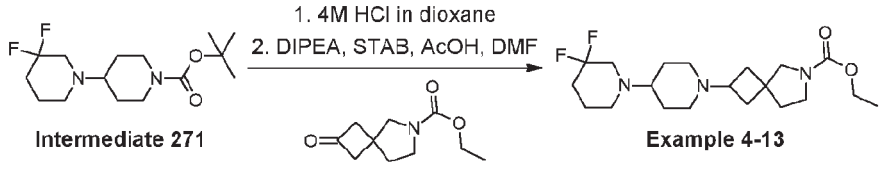
STAB (0.530 g, 2.5 mmol) was added and the reaction mixture stirred overnight. The reaction mixture was quenched with the addition of $NaHCO_3$ (sat aq.) (30 mL), extracted with DCM (4 x 25 mL) and the combined DCM layers passed through a Biotage phase separator. The solvents were removed *in vacuo*, 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-(2-oxotetrahydropyrimidin-1(2*H*)-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 x 21 mm, eluting with 15 to 30% MeCN in 0.2% NH_3/H_2O at 18 mL/min and collecting fractions by monitoring at 210 nm to give ethyl 2-[4-(2-oxotetrahydropyrimidin-1(2*H*)-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Example 4-8 Isomer 1**, (0.028 g, 7.7%) as a colourless solid and ethyl 2-[4-(2-oxotetrahydropyrimidin-1(2*H*)-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate **Example 4-8 Isomer 2**, (0.025 g, 6.9%) 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 Example 4-13, ethyl 2-(3,3-difluoro-1,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate



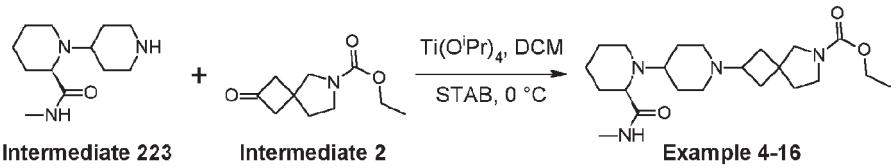
Intermediate 271 Intermediate 2 Example 4-13

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. $NaHCO_3$ (aq) (15 mL), the aqueous layer was washed with DCM (2 x 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 x 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, **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, **Example 4-13 Isomer 2**, (0.005 g, 1.3%) as a colourless oil. The data for Isomer 2 are in Table 3.

Route ax

Typical procedure for the preparation of piperidines *via* reductive amination as exemplified by the preparation of Example 4-16, ethyl 2-[(2*R*)-2-(methylcarbamoyl)-1,4'-bipiperidin-1'-yl]-6-azaspiro[3.4]octane-6-carboxylate

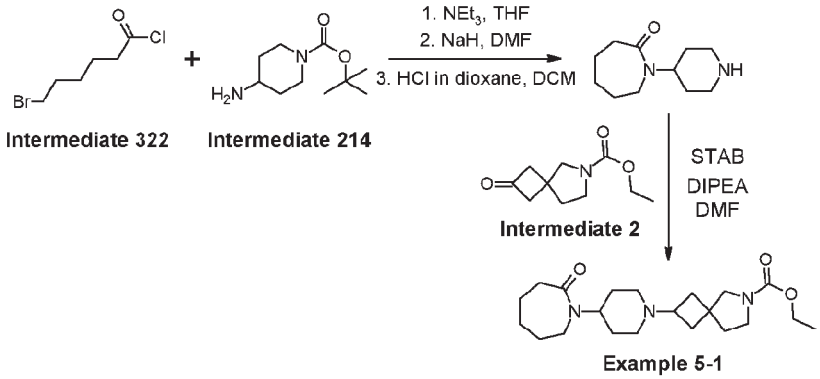


Intermediate 223 **Intermediate 2** **Example 4-16**

To a solution of (*R*)-*N*-methyl-[1,4'-bipiperidine]-2-carboxamide (200 mg, 0.890 mmol) and ethyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (175 mg, 0.890 mmol) in DCM (7.5 mL), $Ti(OiPr)_4$ (0.80 mL, 2.67 mmol) was added at 0 °C and the reaction mixture was stirred for 1 h. $Na(OAc)_3BH$ (562 mg, 2.67 mmol) was added portion wise to the reaction mixture and stirred at 0 °C for 2 h. After completion, the reaction mixture was quenched with aq sat $NaHCO_3$ and extracted with DCM (3 x 30 mL). The organic layers were combined and washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by prep-HPLC (reverse phase, X BRIDGE, C-18, 19 x 250 mm, 5μ, gradient 10% to 90% ACN in water containing 5 mM NH_4OAc, to give 25 mg (7%) of ethyl 2-[(2*R*)-2-(methylcarbamoyl)-1,4'-bipiperidin-1'-yl]-6-azaspiro[3.4]octane-6-carboxylate **Example 4-16 Isomer-1** and 25 mg (7%) of ethyl 2-[(2*R*)-2-(methylcarbamoyl)-1,4'-bipiperidin-1'-yl]-6-azaspiro[3.4]octane-6-carboxylate **Example 4-16 Isomer-2** as colorless semisolids. The data for Isomer 2 are in Table 3.

Route ay

Typical procedure for the preparation of piperidines *via* alkylation, cyclisation and sodium triacetoxyborohydride reductive aminations, as exemplified by the preparation of Example 5-1, ethyl 2-[4-(2-oxoazepan-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate



To a solution of 4-Amino-1-Boc-piperidine (200 mg, 1.0 mmol) in THF (2 mL) was added triethylamine (0.153 mL, 1.1 mmol) and 6-Bromohexanoyl chloride (0.168 mL, 1.098 mmol) and cloudy suspension was stirred at rt for 2h. 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-[(6-bromohexanoyl)amino]piperidine-1-carboxylate (378 mg, >99%) as an orange oil.

tert-butyl 4-[(6-bromohexanoyl)amino]piperidine-1-carboxylate (378 mg, 1.0 mmol) was dissolved in DMF (25 mL) and sodium hydride was added (48 mg, 1.2 mmol). The reaction mixture was stirred at 80°C for 1h, the solvent was removed *in vacuo* and the residue was was purified by column chromatography (normal phase, [Biotage SNAP cartridge KP-sil 10 g, 40-63μm, 60Å, 25 mL per min, 1% to 10% MeOH in DCM]) to give tert-butyl 4-(2-oxoazepan-1-yl)piperidine-1-carboxylate (178 mg, 60%). The residue 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. 1-(piperidin-4-yl)azepan-2-one.HCl (0.182 g, 0.738 mmol) and ethyl 2-oxo-6-azaspiro[3.4]octane-6-carboxylate (0.155 g, 0.785 mmol) were dissolved in DMF (2 mL) at rt and DIPEA (0.136 mL, 0.790 mmol) was added. The reaction mixture was stirred at rt for 3 h. STAB (0.332 g, 1.569 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 preparative reversed phase HPLC (Phenomenex Gemini-NX 5 μm C18 110A Axia column, 100 x 30 mm, eluting with 25 to 45% 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-oxoazepan-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Example 5-1 Isomer 1** (6.2 mg, 2%) as a colourless oil and ethyl 2-[4-(2-oxoazepan-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate, **Example 5-1 Isomer 2** (3.9 mg, 1%) 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, CD_3OD) 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)
4		2-fluoroethyl 2-oxo-6-azaspiro [3.4]octane-6-carboxylate	**LCMS (Method F)**: m/z 216 $(M+H)^+$ (ES+) at 1.79 min, UV inactive
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
7		4-(1*H*-pyrazol-5-yl)piperidine	Commercially available, CAS: 278798-08-6
8		5-(piperidin-4-yl)-1H-pyrazol-3-amine	Commercially available, CAS: 1325671-21-3
9		4-(1-methyl-1H-pyrazol-5-yl)piperidine	Commercially available, CAS: 640270-01-5
10		4-(1-methyl-1*H*-pyrazol-3-yl)piperidine	Commercially available, CAS: 1211527-48-8
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
13		4-(4-methyl-1*H*-pyrazol-1-yl)piperidine	Commercially available, CAS: 1211520-55-6
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
16		4-(1*H*-1,2,4-Triazol-1-yl)piperidine	Commercially available, CAS: 158655-26-6
17		4-(1*H*-1,2,4-Triazol-3-yl)piperidine hydrochloride	Commercially available, CAS: 1417359-91-1
18		4-(1*H*-1,2,3-Triazol-1-yl)piperidine hydrochloride	Commercially available, CAS: 690261-88-2
19		2-(piperidin-4-yl)pyridin-3-ol dihydrochloride	Commercially available, CAS: 1260650-52-9
20		4-(5-chloro-1-methyl-1H-imidazol-2-yl)piperidine trifluoroacetate	**LCMS (Method C):** m/z 200/202 $(M+H)^+$ (ES+), at 1.33 min, UV active
21		4-(4,5-dichloro-1-methyl-1H-imidazol-2-yl)piperidine trifluoroacetate	**LCMS (Method C):** m/z 234/236/238 $(M+H)^+$ (ES+), at 1.53 min, UV active
22		4-(5-chloro-1H-imidazol-2-	**LCMS (Method C):** m/z 186/188

		yl)piperidine dihydrobromide	$(M+H)^+$ (ES+), at 0.92 min, UV active
23		4-(5-ethyl-1H-1,2,4-triazol-3-yl)piperidine hydrochloride	Commercially available, CAS: 1432680-84-6
24		4-methyl-4-(3-methyl-1,2,4-oxadiazol-5-yl)piperidine hydrochloride	Commercially available, CAS: 1361112-08-4
25		4-(4,5-dichloro-1H-imidazol-2-yl)piperidine dihydrobromide	m/z 220/222/224 $(M+H)^+$ (ES+), at 0.54 min, UV active
26		2-(piperidin-4-yl)pyrimidin-4-amine dihydrochloride	Commercially available, CAS: 1461714-43-1
27		ethyl 4-(1H-imidazol-2-yl)piperidine-1-carboxylate	Commercially available, CAS: 1198420-87-9
28		tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate	Commercially available, CAS: 286961-14-6
29		2-5-bromo-1,2,4-thiadiazole	Commercially available, CAS: 43201-13-4
30	**Route 1 and intermediates 28 and 29**	5-(piperidin-4-yl)-1,2,4-thiadiazole	**LCMS (Method G):** m/z 170 $(M+H)^+$ (ES+), at 3.761 min, UV active
31		4-(1H-tetrazol-5-yl) piperidine	Commercially available, CAS: 112626-97-8
32		4-(1*H*-pyrazol-1-yl)piperidine	Commercially available, CAS: 762240-09-5
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
35		2-bromo-1,4-dimethyl-1H-imidazole	Commercially available, CAS: 235426-30-9
36	**Route 2 and intermediate 35**	4-(1,4-dimethyl-1H-imidazol-2-yl)-1,2,3,6-tetrahydropyridine	**LCMS (Method G):** m/z 178 $(M+H)^+$ (ES^+), at 3.80 min, UV active
37		4-[1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl]piperidine hydrochloride salt	**LCMS (Method F):** m/z 234 $(M+H)^+$ (ES^+), at 1.48 min, UV active
38		4-(1-methyl-1*H*-pyrazol-5-yl)piperidine	Commercially available, CAS: 640270-01-5
39		2-bromooxazole	Commercially available, CAS: 125533-82-6
40		2-bromothiazole	Commercially available, CAS: 3034-53-5
41	**Route 1 and intermediate 39**	4-(1,3-oxazol-2-yl)piperidine	**LCMS (Method H):** m/z 153 $(M+H)^+$ (ES^+), at 7.92 min, UV active
42	**Route 1 and intermediate 40**	4-(1,3-thiazol-2-yl)piperidine	**LCMS (Method H):** m/z 169 $(M+H)^+$ (ES^+), at 7.58 min, UV active
43		4-(1,3,4-oxadiazol-2-yl)piperidine	**^{1}H NMR:** (400 MHz, $CDCl_3$) δ: 1.78 – 1.90 (m, 2H), 1.99 – 2.16 (m, 2H), 2.70 – 2.85 (m, 2H), 3.02 – 3.16 (m, 1H), 3.16 – 3.27 (m, 2H), 8.35 (s, 1H), NH not observed
44		4-(3-methyl-1,2,4-oxadiazol-5-	**LCMS (Method H):** m/z 168 $(M+H)^+$

		yl)piperidine	(ES^+), at 5.80 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
47		4-(1*H*-imidazol-2-yl)piperidin-4-ol hydrochloride salt	**LCMS (Method G)**: m/z 168 $(M+H)^+$ (ES^+), at 2.46 min, UV active
48		4-(1*H*-imidazol-2-yl)-4-methoxypiperidine hydrochloride salt	**LCMS (Method G)**: m/z 182 $(M+H)^+$ (ES^+), at 2.87 min, UV active
49		4-(1-methyl-1*H*-imidazol-2-yl)piperidin-4-ol hydrochloride salt	**LCMS (Method G)**: m/z 182 $(M+H)^+$ (ES^+), at 3.09 min, UV active
50		4-methoxy-4-(1-methyl-1*H*-imidazol-2-yl)piperidine hydrochloride salt	**LCMS (Method G)**: m/z 196 $(M+H)^+$ (ES^+), at 3.35 min, UV active
51		(*S*)-*Tert*-butyl 2-(piperidin-4-yl)pyrrolidine-1-carboxylate	Commercially available, CAS: 1449131-15-0
52		(*R*)-*Tert*-butyl 2-(piperidin-4-yl)pyrrolidine-1-carboxylate	Commercially available, CAS: 1451390-44-5
53		*Tert*-butyl 2-(piperidin-4-yl)pyrrolidine-1-carboxylate	Commercially available, CAS: 929974-12-9
54		Propionyl Chloride	Commercially available, CAS: 79-03-8
55		Methyl chloroformate	Commercially available, CAS: 79-22-1
56		Ethyl chloroformate	Commercially available, CAS: 541-41-3
57		Methylaminoformyl chloride	Commercially available, CAS: 6452-47-7
58		Dimethylaminoformyl chloride	Commercially available, CAS: 79-44-7
59		Cyclopropanecarbonyl chloride	Commercially available, CAS: 4023-34-1
60		Cyclobutanecarbonyl chloride	Commercially available, CAS: 5006-22-4
61		Acetyl chloride	Commercially available, CAS: 75-36-5
62		Ethyl 2,2,2-trifluoroacetate	Commercially available, CAS: 383-63-1
63		Acetic Anhydride	Commercially available, CAS: 108-24-7
64		3-iodo-2-methoxypyridine	Commercially available, CAS: 112197-15-6
65	**Route 3 and intermediates 28 and 64**	3-(piperidin-4-yl) pyridin-2-ol	**^{1}H NMR:** (400 MHz, DMSO-d_6) δ: 1.70 – 2.00 (m, 4H), 2.84 - 3.15 (m, 3H), 3.32 (d, J = 12.5 Hz, 2H),7.00 (dd, J = 7.3 and 5.2 Hz, 1H), 7.53 (dd, J = 7.3 and 1.5 Hz, 1H), 8.06 (dd, J = 5.2 and 1.5 Hz, 1H), 8.93 - 9.39 (m, 2H)
66	**Route 4 and intermediates 28 and 64**	2-methoxy-3-(piperidin-4-yl)pyridine	**LCMS (Method F):** m/z 193 $(M+H)^+$ (ES+), at 6.19 min, UV active
67		5-bromo-2-methoxy-4-methylpyridine	Commercially available, CAS: 164513-39-7

68		5-bromo-2-methoxy-3-methylpyridine	Commercially available, CAS: 760207-87-2
69	**Route 5 and intermediate 65**	3,4'-bipiperidin-2-one	**LCMS (Method F)**: m/z 183 $(M+H)^+$ (ES+), at 0.32 min, UV active
70		4-(piperidin-4-yl)pyrimidin-2-amine	Commercially available, CAS: 1211532-88-5
71	**Route 4 and intermediates 28 and 67**	2-methoxy-4-methyl-5-(piperidin-4-yl)pyridine	**LCMS (Method F)**: m/z 207 $(M+H)^+$ (ES+), at 1.44 min, UV active
72	**Route 4 and intermediates 28 and 68**	2-methoxy-3-methyl-5-(piperidin-4-yl)pyridine	**LCMS (Method F)**: m/z 207 $(M+H)^+$ (ES+), at 1.59 min, UV active
73		4-(4-methyl-1H-pyrazol-1-yl)piperidine	Commercially available, CAS: 1211520-55-6
74		4-Isoxazol-3-yl-piperidine	Commercially available, CAS: 1060814-32-5
75		*N*-[(benzyloxy)carbonyl]-N-methylglycine	Commercially available, CAS: 39608-31-6
76		Methoxyamine hydrochloride	Commercially available, CAS: 593-56-6
77		Isopropylamine	Commercially available, CAS: 75-31-0
78		2,2,2-Trifluoroethylamine	Commercially available, CAS: 753-90-2
79		Azetidine	Commercially available, CAS: 503-29-7
80		Morpholine	Commercially available, CAS: 110-91-8
81		Cyclopropylamine	Commercially available, CAS: 765-30-0
82		Cyclobutylamine	Commercially available, CAS: 2516-34-9
83		2-methoxyethylamine	Commercially available, CAS: 109-85-3
84		Pyrrolidine	Commercially available, CAS: 123-75-1
85		N,O-dimethylhydroxylamine hydrochloride	Commercially available, CAS: 6638-79-5
86		1-methylcyclobutan-1-amine hydrochloride	Commercially available, CAS: 174886-05-6
87		3-amino-3-methyloxetane	Commercially available, CAS: 874473-14-0
88		3,3-difluoropyrrolidine hydrochloride	Commercially available, CAS: 163457-23-6
89		3,3-difluorocyclobutanamine hydrochloride	Commercially available, CAS: 637031-93-7
90		3,3-difluoroazetidine hydrochloride	Commercially available, CAS: 288315-03-7
91		*tert*-Butyl carbazate	Commercially available, CAS: 870-46-2
92		cyclobutanol	Commercially available, CAS: 2919-23-5
93		2-fluoroethylamine hydrochloride	Commercially available, CAS: 460-08-2
94		2,2-difluoroethylamine	Commercially available, CAS: 430-67-1

95		methoxyacetyl chloride	Commercially available, CAS: 38870-89-2
96		2-fluoroethyl chloroformate	Commercially available, CAS: 462-27-1
97		2,2,2-trifluoroethyl chloroformate	Commercially available, CAS: 27746-99-2
98		methyl chlorothiolformate	Commercially available, CAS: 18369-83-0
99		2-methoxyethanol	Commercially available, CAS: 109-86-4
100		2-dimethylaminoethanol	Commercially available, CAS: 108-01-0
101		acetoxy acetyl chloride	Commercially available, CAS: 13831-31-7
102		3,3,3-trifluoropropionic acid	Commercially available, CAS: 2516-99-6
103		2-(aminomethyl)pyridine	Commercially available, CAS: 3731-51-9
104		2,2,2-Trifluoro-N-methylethanamine hydrochloride	Commercially available, CAS: 2730-52-1
105		oxetan-3-ylamine	Commercially available, CAS: 21635-88-1
106		N-methyl-3-aminooxetane	Commercially available, CAS: 952182-03-5
107		Lawesson Reagent	Commercially available, CAS: 19172-47-5
108		(2S,4R)-1-Boc-4-hydroxy pyrrolidine-2-carboxylic acid methyl ester	Commercially available, CAS: 102195-79-9
109		triethyl phosphono acetate	Commercially available, CAS: 867-13-0
110		ethyl cyanoacetate	Commercially available, CAS: 105-56-6
111	**Intermediates 108, 109 and 110**	benzyl 4-[(2S,4R)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidin-2-yl]piperidine-1-carboxylate	**LCMS (Method D)**: m/z 405 $(M+H)^+$ (ES+), at 1.98 min, UV active
112	**Intermediate 111**	*tert*-butyl (2S,4S)-4-fluoro-2-(piperidin-4-yl)pyrrolidine-1-carboxylate	**LCMS (Method D)**: m/z 273 $(M+H)^+$ (ES+), at 1.80 min, UV active
113	**Intermediate 111**	*tert*-butyl (2S)-4,4-difluoro-2-(piperidin-4-yl)pyrrolidine-1-carboxylate	**LCMS (Method D)**: m/z 291 $(M+H)^+$ (ES+), at 1.88 min, UV active
114		iodoethane	Commercially available, CAS: 75-03-6
115		D-proline methyl ester hydrochloride	Commercially available, CAS: 65365-28-8
116		2-pyridine propionic acid	Commercially available, CAS: 15197-75-8
117		2-[(methylamino)methyl]pyridine	Commercially available, CAS: 21035-59-6
118		2-pyridinemethanol	Commercially available, CAS: 586-98-1
119		piperidine, 4-(3-methyl-1H-pyrazol-1-yl)-	Commercially available, CAS: 1138819-53-0
120		piperidine, 4-(1-ethyl-1H-	Commercially available,

		pyrazol-5-yl)-	CAS: 442876-34-8
121		(*R*)-1-*tert*-Butyl 2-methyl 4-oxopyrrolidine-1,2-dicarboxylate	Commercially available, CAS: 256487-77-1
122	**Route 6 and intermediates 2 and 53**	Ethyl 2-[4-(pyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate.HCl	**LCMS (Method D)**: m/z 350 $(M+H)^+$ (ES^+), at 2.64 min, UV inactive
123		O-Methylhydroxylamine hydrochloride	Commercially available, CAS: 593-56-6
124		N,O-Dimethylhydroxylamine hydrochloride	Commercially available, CAS: 6638-79-5
125	**Intermediate 257**	*tert*-butyl (2S)-4,4-difluoro-2-methylpyrrolidine-1-carboxylate	**LCMS (Method C)**: m/z 222 $(M+H)^+$ (ES+), at 1.97 min, UV inactive
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-[(2S)-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
128		3-bromo-2-methoxy-5-methylpyridine	Commercially available, CAS: 717843-56-6
129	**Route 4 and intermediate 28 and 127**	2-methoxy-5-methyl-3-(piperidin-4-yl)pyridine hydrochloride	**LCMS (Method C)**: m/z 207 $(M+H)^+$ (ES+), at 1.62 min, UV active
130		Iodomethane	Commercially available, CAS: 79099-07-3
131		3-aminopropan-1-ol	Commercially available, CAS: 156-87-6
132	**Intermediates 131 and 160**	3-(piperidin-4-yl)-1,3-oxazinan-2-one hydrochloride	**LCMS (Method D)**: m/z 185 $(M+H)^+$ (ES+), at 0.29 min, UV inactive
133		3-bromo-2-methoxy-4-methylpyridine	Commercially available, CAS: 717843-51-1
134	**Intermediates 28 and 133**	2-methoxy-4-methyl-3-(piperidin-4-yl)pyridine hydrochloride	**LCMS (Method F)**: m/z 207 $(M+H)^+$ (ES+), at 1.56 min, UV active
135		benzyl 4-oxopiperidine-1-carboxylate	Commercially available, CAS: 185847-84-1
136		*tert*-butyl (3-aminopropyl)carbamate	Commercially available, CAS: 75178-96-0
137	**Route 7 and intermediates 135 and 136**	1-(piperidin-4-yl)tetrahydropyrimidin-2(1*H*)-one	**LCMS (Method B)**: m/z 184 $(M+H)^+$ (ES+), at 4.28 min, UV inactive
138		(*S*)-*N*-methylpyrrolidine-2-carboxamide hydrochloride	Commercially available, CAS: 33208-98-9
139	**Route 8 and intermediates 138 and 160**	(*S*)-*N*-methyl-1-(piperidin-4-yl)pyrrolidine-2-carboxamide dihydrochloride	**LCMS (Method G)**: m/z 212 $(M+H)^+$ (ES+), at 6.65 min, UV inactive
140		2-bromo-6-methoxypyridine	Commercially available, CAS: 40473-07-2
141	**Route 4 and intermediates 28 and 140**	2-methoxy-6-(piperidin-4-yl)pyridine hydrochloride	**LCMS (Method G)**: m/z 193 $(M+H)^+$ (ES+), at 0.65 min, UV active
142		3-bromo-2-methoxy-5-methylpyridine	Commercially available, CAS: 717843-56-6
143	**Route 3 and**	5-methyl-3-(piperidin-4-	**LCMS (Method F)**: m/z 193 $(M+H)^+$

	intermediates 28 and 142	yl)pyridin-2(1*H*)-one hydrochloride	(ES+), at 0.276 min, UV active
144	**Route 5 and intermediate 143**	5-methyl-[3,4'-bipiperidin]-2-one	**LCMS (Method J)**: m/z 197 $(M+H)^+$ (ES+), at 4.05 min, UV inactive
145		3-bromo-2-methoxy-4-methylpyridine	Commercially available, CAS: 717843-51-1
146	**Route 3 and intermediates 28 and 145**	4-methyl-3-(piperidin-4-yl)pyridin-2(1*H*)-one hydrochloride	**LCMS (Method I)**: m/z 193 $(M+H)^+$ (ES+), at 2.82 min, UV active
147	**Route 5 and intermediate 146**	4-methyl-[3,4'-bipiperidin]-2-one	**LCMS (Method I)**: m/z 197 $(M+H)^+$ (ES+), at 3.14 min, UV inactive
148		*tert*-butyl (3-amino-2,2-dimethylpropyl)carbamate	Commercially available, CAS: 292606-35-0
149	**Route 7 and intermediates 135 and 148**	5,5-dimethyl-1-(piperidin-4-yl)tetrahydropyrimidin-2(1*H*)-one	**LCMS (Method D)**: m/z 212 $(M+H)^+$ (ES+), at 0.70 min, UV inactive
150		1,4-dioxa-8-azaspiro[4.5]decane	Commercially available, CAS: 74-88-4
151	**Intermediates 2 and 150**	ethyl 2-(4-oxopiperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**LCMS (Method D)**: m/z 281 $(M+H)^+$ (ES+), at 0.992 min and 1.04 min, UV inactive
152		*tert*-butyl (2-aminoethyl)carbamate	Commercially available, CAS: 57260-73-8
153		4-bromo-2-methoxypyridine	Commercially available, CAS: 100367-39-3
154	**Route 3 and intermediates 28 and 153**	4-(piperidin-4-yl) pyridin-2(1*H*)-one hydrochloride	**LCMS (Method I)**: m/z 179 $(M+H)^+$ (ES+), at 2.57 min, UV active
155		benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate	Commercially available, CAS: 286961-15-7
156		isopropyl iodide	Commercially available, CAS: 75-30-9
157	**Route 6 and intermediates 3 and 51**	methyl 2-{4-[(2*S*)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate.HCl	**LCMS (Method J)**: m/z 322 $(M+H)^+$ (ES^+), at 4.37 min, UV inactive
158		Diethylamine	Commercially available, CAS: 109-89-7
159	**Route 13 and intermediates 115 and 160**	*tert*-butyl 4-[(2*R*)-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidine-1-carboxylate	**LCMS (Method D)**: m/z 313 $(M+H-{}^tBu)^+$ (ES^+), at 1.85 min, UV inactive
160		tert-butyl 4-oxopiperidine-1-carboxylate	Commercially available, CAS: 79099-07-3
161		Ethyl 4-piperidinecarboxylate	Commercially available, CAS: 1126-09-6
162	**Route 6 and intermediates 2 and 52**	ethyl 2-{4-[(2*R*)-pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**LCMS (Method E)**: m/z 336 $(M+H)^+$ (ES+), at 5.16 min, UV inactive
163		4-bromo-1,3-thiazole	Commercially available, CAS: 34259-99-9
164	**Intermediates 155 and 163**	4-(1,3-thiazol-4-yl)piperidine hydrobromide	**^{1}H NMR:** (400 MHz, D_2O) δ: 1.82 - 2.10 (m, 2H), 2.15 - 2.44 (m 2H), 3.05 - 3.72 (m, 5H), 7.72 (s, 1H),

			9.62 (s, 1H), Two exchangeable protons not observed
165		2-bromoethyl methyl ether	Commercially available, CAS: 6482-24-2
166		bromoacetonitrile	Commercially available, CAS: 590-17-0
167		methyl bromoacetate	Commercially available, CAS: 96-32-2
168		Methylamine solution (2.0 M in THF)	Commercially available CAS:74-89-5
169		2-chloropyrimidine	Commercially available, CAS: 1722-12-9
170		(1S,3S,5S)-Cyclohexane-1,3,5-triol	Commercially available, CAS: 50409-12-6
171		phenylboronic acid	Commercially available, CAS 98-80-6
172	**Intermediates 170 and 171**	(1R,5S)-3-phenyl-2,4-dioxa-3-borabicyclo[3.3.1]nonan-7-one	**^{1}H NMR:** (400 MHz, $CDCl_3$) δ: 2.29 (d, *J*=13.7 Hz, 1 H), 2.47 (d, *J*=12.8 Hz, 1 H), 2.63 (d, *J*=16.2 Hz, 2 H), 2.95 (d, *J*=15.9 Hz, 2 H), 4.85 (br. s., 2 H), 7.30 - 7.48 (m, 3 H), 7.73 (d, *J*=7.0 Hz, 2 H)
173		4-(1-propyl-1H-pyrazol-5-yl)piperidine	Commercially available, CAS: 1342846-65-4
174	**Intermediates 126 and 160**	4-[(2R)-4,4-difluoro-2-(methoxymethyl)pyrrolidin-1-yl]piperidine trifluoroacetate	**LCMS (Method C)**: m/z 235 $(M+H)^+$ (ES+), at 1.02 min, UV inactive
175		4-chloropyridine	Commercially available, CAS: 626-61-9
176		2-bromopyridine	Commercially available, CAS: 109-04-6
177		4-(1,4-dimethyl-1*H*-pyrazol-3-yl)piperidine	Commercially available, CAS: 1511937-89-5
178		4-(1,4-dimethyl-1*H*-pyrazol-5-yl)piperidine	Commercially available, CAS: 1540203-24-4
179	**intermediates 126 and 160**	1-[(2R)-4,4-difluoro-1-(piperidin-4-yl)pyrrolidin-2-yl]ethanol trifluoroacetate	**LCMS (Method C)**: m/z 235 $(M+H)^+$ (ES+), at 0.79 min, UV inactive
180		5-(pyrrolidin-2-yl)-1H-pyrazole dihydrochloride	Commercially available, CAS: 1361114-72-8
181	**Route 9 and intermediates 180 and 160**	4-[2-(1H-pyrazol-5-yl)pyrrolidin-1-yl]piperidine trifluoroacetate	**LCMS (Method C)**: m/z 221 $(M+H)^+$ (ES+), at 0.87 min, UV active
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
185		5,5-dimethylpyrrolidin-2-one	Commercially available, CAS: 5165-28-6
186	**Route 10 and intermediate 185**	5,5-dimethyl-1-(piperidin-4-yl)pyrrolidin-2-one acetate	**LCMS (Method C)**: m/z 197 $(M+H)^+$ (ES+), at 0.78 min, UV active
187		(4S)-4-(propan-2-yl)-1,3-oxazolidin-2-one	Commercially available, CAS: 17016-83-0

188	**Route 10 and intermediate 187**	(4S)-3-(piperidin-4-yl)-4-(propan-2-yl)-1,3-oxazolidin-2-one acetate	**LCMS (Method C)**: m/z 213 $(M+H)^+$ (ES+), at 0.74 min, UV active
189		methyl azepane-2-carboxylate	Commercially available, CAS: 5228-33-1
190	**Route 9 and intermediate 189**	methyl 1-(piperidin-4-yl)azepane-2-carboxylate trifluoroacetate	**LCMS (Method C)**: m/z 241 $(M+H)^+$ (ES+), at 1.20, UV inactive
191		pyrrolidine-2,5-dione	Commercially available, CAS: 123-56-8
192		tert-butyl 4-hydroxypiperidine-1-carboxylate	Commercially available, CAS: 109384-19-2
193		1-(piperidin-4-yl)pyrrolidine-2,5-dione trifluoroacetate	**LCMS (Method C)**: m/z 183 $(M+H)^+$ (ES+), at 0.29 min, UV inactive
194		tert-butyl 4-cyanopiperidine-1-carboxylate	Commercially available, CAS: 91419-52-2
195	**Route 15 and intermediates 130 and 194**	4-(1-methyl-1H-tetrazol-5-yl)piperidine hydrochloride	**LCMS (Method K)**: m/z 168 $(M+H)^+$ (ES+), at 2.41 min, UV inactive
196		(4R)-4-(propan-2-yl)-1,3-oxazolidin-2-one	Commercially available, CAS: 95530-58-8
197	**Route 10 and intermediate 196**	(4R)-3-(piperidin-4-yl)-4-(propan-2-yl)-1,3-oxazolidin-2-one acetate	**LCMS (Method C)**: m/z 213 $(M+H)^+$ (ES+), at 0.78 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
202	**Route 11 and intermediate 201**	(5S)-5-methyl-1-(piperidin-4-yl)pyrrolidin-2-one acetate	**LCMS (Method C):** m/z 183 $(M+H)^+$ (ES+), at 0.54 min, weakly UV active
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
204		(2R)-2-aminopropan-1-ol	Commercially available, CAS: 35320-23-1
205	**Route 12 and intermediate 204**	(4R)-4-methyl-3-(piperidin-4-yl)-1,3-oxazolidin-2-one acetate	**LCMS (Method C)**: m/z 185 $(M+H)^+$ (ES+), at 0.37 min, UV active
206		(2R)-2-aminobutan-1-ol	Commercially available, CAS: 5856-63-3
207	**Route 12 and intermediate 206**	(4R)-4-ethyl-3-(piperidin-4-yl)-1,3-oxazolidin-2-one acetate	**LCMS (Method C)**: m/z 199 $(M+H)^+$ (ES+), at 0.59 min, UV active
208		(2S)-2-aminopropan-1-ol	Commercially available, CAS: 2749-11-3
209	**Route 12 and intermediate 208**	(4S)-4-methyl-3-(piperidin-4-yl)-1,3-oxazolidin-2-one acetate	**LCMS (Method C)**: m/z 185 $(M+H)^+$ (ES+), at 0.39 min, UV active
210		(2S)-2-aminobutan-1-ol	Commercially available,

			CAS: 5856-62-2
211	**Route 12 and intermediate 210**	(4S)-4-ethyl-3-(piperidin-4-yl)-1,3-oxazolidin-2-one acetate	**LCMS (Method C)**: m/z 199 $(M+H)^+$ (ES+), at 0.60 min, UV active
212		1-methylimidazolidin-2-one	Commercially available, CAS: 694-32-6
213	**Route 12 and intermediate 212**	1-methyl-3-(piperidin-4-yl)imidazolidin-2-one acetate	**LCMS (Method C)**: m/z 184 $(M+H)^+$ (ES+), at 0.40 min, UV active
214		tert-butyl 4-aminopiperidine-1-carboxylate	Commercially available, CAS: 87120-72-7
215	**Intermediate 214**	4-(1H-tetrazol-1-yl)piperidine hydrochloride	**LCMS (Method K)**: m/z 154 $(M+H)^+$ (ES+), at 2.22 min, weakly UV active
216		1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid	Commercially available, CAS: 84358-13-4
217		cyclopropanamine	Commercially available, CAS: 765-30-0
218	**Intermediates 216 and 217**	4-(1-cyclopropyl-1H-tetrazol-5-yl)piperidine hydrochloride	**LCMS (Method F)**: m/z 194 $(M+H)^+$ (ES+), at 0.46 min, weakly UV active
219		1-ethyl-4-methyl-1H-pyrazol-5-amine	Commercially available, CAS: 3702-13-4
220	**Route 1 and intermediates 28 and 252**	4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)piperidine hydrochloride	**LCMS (Method I)**: m/z 194 $(M+H)^+$ (ES+), at 3.13 min, UV active
221		*R*-pipecolinic acid	Commercially available, CAS: 1723-00-8
222		propylphosphonic anhydride solution ≥50 wt. % in ethyl acetate	Commercially available, CAS: 68957-94-8
223	**Route 16 and intermediates 160, 221 and 222**	(*R*)-*N*-methyl-[1,4'-bipiperidine]-2-carboxamide	**^{1}H-NMR** (400 MHz, DMSO) δ: 1.75 - 1.91 (m, 4H), 2.21 - 2.29 (m, 4H), 2.69 (d, J = 4.8 Hz, 3H), 2.94 - 3.07 (m, 3H), 3.30 - 3.49 (m, 4H), 3.62 - 3.80 (m, 2H), 4.10 - 4.12 (m, 1H), 9.03 (br.s., 1H), 10.01 (br.s., 1H).
224		*S*-pipecolinic acid	Commercially available, CAS: 3105-95-1
225	**Route 16 and intermediates 160, 221 and 224**	(*S*)-*N*-methyl-[1,4'-bipiperidine]-2-carboxamide	**^{1}H-NMR** (400 MHz; $CDCl_3$) δ: 1.25 - 1.40 (m, 2H), 1.55 - 1.69 (m, 4H), 1.82 - 2.10 (m, 4H), 2.32 - 2.38 (m, 1H), 2.51 - 2.65 (m, 3H), 2.79 - 2.85 (m, 1H), 2.82 (d, J = 4.8 Hz, 3H), 3.12 - 3.19 (m, 3H), 6.75 (br.s., 1H).
226		Z-β-ala-OH	Commercially available, CAS: 2304-94-1
227		2-bromopyridine	Commercially available, CAS: 109-04-6
228		Cbz-OSu	Commercially available, CAS: 13139-17-8
229	**Intermediates 160, 227 and 228**	ethyl 2-([2,4'-bipiperidin]-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate	**^{1}H-NMR** (400 MHz; $CDCl_3$) δ: 1.22 (t, *J* = 6.8 Hz, 3H), 1.32 - 1.49 (m, 4H), 1.60 - 2.90 (m, 12H), 2.08 (bs, 1H), 2.51 - 2.75 (m, 4H), 2.91 - 2.98 (m, 3H), 3.25 - 3.50 (m, 6H), 4.12 (q, *J* = 6.8 Hz, 2H).
230		propionic acid	Commercially available, CAS: 79-09-4

231		2-bromo ethyl methyl ether	Commercially available, CAS: 6482-24-2
232		benzyl bromide	Commercially available, CAS: 202-847-3
233		methyl bromoacetate	Commercially available, CAS: 96-32-2
234		1,1′-carbonyldiimidazole	Commercially available, CAS: 530-62-1
235		*tert*-butyl (2-hydroxyethyl)methylcarbamate	Commercially available, CAS: 57561-39-4
236		1,1,1-trifluoro-3-iodopropane	Commercially available, CAS: 460-37-7
237		2,2,2-trifluoroethyl trifluoromethanesulfonate	Commercially available, CAS: 6226-25-1
238		2-chloro-*N*,*N*-dimethylacetamide	Commercially available, CAS: 2675-89-0
239		methyl isothiocyanate	Commercially available, CAS: 556-61-6
240		isoindoline-1-carboxylic acid hydrochloride	Commercially available, CAS: 96016-96-5
241		trimethylphosphonoacetate	Commercially available, CAS: 5927-18-4
242		methyl cyanoacetate	Commercially available, CAS: 105-34-0
243	**Intermediates 240, 241 and 242**	*tert*-butyl 1-(piperidin-4-yl)isoindoline-2-carboxylate	**^{1}H-NMR** (400 MHz; $CDCl_3$) δ: 1.42 (s, 9H), 1.51 - 1.62 (m, 3H), 3.15 - 3.18 (m, 2 H), 3.37 - 3.42 (m, 4 H), 4.08 - 4.11 (m, 1H), 4.32 - 4.38 (m, 2H), 7.18 - 7.34 (m, 4H).
244		1-iodo-2-fluoroethane	Commercially available, CAS: 762-51-6
245		*tert*-butyl 4-hydroxypiperidine-1-carboxylate	Commercially available, CAS: 109384-19-2
246		1*H*-1,2,3-triazole	Commercially available, CAS: 288-36-8
247	**Intermediates 245 and 246**	4-(2*H*-1,2,3-triazol-2-yl)piperidine hydrochloride	**LCMS (Method K)**: m/z 153 $(M+H)^+$ (ES+), at 2.94 min, UV active
248		1-ethyl-4-methyl-1*H* pyrazole amine	Commercailly available CAS: 354795-57-6
249		isoamyl nitrite	Commercailly available CAS: 110-46-3
250	**Route 17 and intermediates 248 and 249**	4-ethyl-5-iodo-1-methyl-1*H*-pyrazole	**LCMS (Method I)**: m/z 236 $(M+H)^+$ (ES+), at 4.36 min, UV active
251	**Route 1 and intermediates 28 and 250**	4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)piperidine hydrochloride	**LCMS (Method I)**: m/z 194 $(M+H)^+$ (ES+), at 3.37 min, UV active
252	**Route 17 and intermediates 219 and 249**	4-methyl-5-iodo-1-ethyl-1*H*-pyrazole	**LCMS (Method I)**: m/z 236 $(M+H)^+$ (ES+), at 4.40 min, UV active
253		*tert*-butyl 4-bromopiperidine-1-carboxylate	Commercailly available CAS: 180695-79-8
254		5-methyl-2*H*-tetrazole	Commercailly available CAS: 4076-36-2
255	**Intermediates 253 and 254**	4-(5-methyl-1*H*-tetrazol-1-yl)piperidine hydrochloride	**^{1}H-NMR:** (400 MHz, DMSO) δ: 2.15 - 2.29 (m, 4H), 2.56 (s, 3H), 3.08 (d, J = 10.2 Hz, 2H), 3.42 (d, J = 12.6 Hz,

			2H), 4.74 - 4.87 (m, 1H), 6.33 - 6.38 (m, 1H).
256		2-bromo-1,3,4-thiadiazole	Commercailly available CAS: 61929-24-6
257		1-(*tert*-butyl) 2-methyl (*R*)-4,4-difluoropyrrolidine-1,2-dicarboxylate	Commercailly available CAS: 647857-74-7
258	**Intermediates 160 and 257**	(*R*)-2-(4,4-difluoro-1-(piperidin-4-yl)pyrrolidin-2-yl)propan-2-ol hydrochloride	**^{1}H-NMR:** (400 MHz, $CDCl_3$) δ: 1.11 (s, 3H), 1.21 (s, 3H), 1.21 - 1.31 (m, 1H), 1.49 - 1.52 (m, 2H), 1.71 - 1.89 (m, 2H), 2.19 - 2.30 (m, 2H), 2.50 - 2.83 (m, 3H), 3.02 - 3.43 (m, 4H). N-H and O-H not observed.
259		(R)-Methyl 4,4-difluoropyrrolidine-2-carboxylate. HCl	Commercially available CAS: 1408057-39-5
260	**Route 14 and intermediates 160 and 259**	*tert*-butyl 4-[(2*R*)-4,4-difluoro-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidine-1-carboxylate	**LCMS (Method D)**: m/z 349 $(M+H)^+$ (ES+) at 2.03 min, UV inactive
261		(S)- Methyl 4,4-difluoropyrrolidine-2-carboxylate. HCl	Commercially available CAS: 136046-05-8
262	**Route 14 and intermediates 160 and 261**	*tert*-butyl 4-[(2*S*)-4,4-difluoro-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidine-1-carboxylate	**LCMS (Method D)**: m/z 349 $(M+H)^+$ (ES+) at 2.04 min, UV inactive
263		(R)-(-)-3-Fluoropyrrolidine. HCl	Commercially available CAS: 136725-55-8
264		(S)-(+)-3-Fluoropyrrolidine. HCl	Commercially available CAS: 136725-53-6
265		4,4-difluoropiperidine. HCl	Commercially available CAS: 144230-52-4
266	**Route 14 and intermediates 160 and 265**	*tert*-butyl 4,4-difluoro-1,4'-bipiperidine-1'-carboxylate	**LCMS (Method D)**: m/z 305 $(M+H)^+$ (ES+) at 1.97 min, UV inactive
267		Thiomorpholine	Commercially available CAS:123-90-0
268	**Route 13 and intermediates 160 and 267**	*tert*-butyl 4-(thiomorpholin-4-yl)piperidine-1-carboxylate	**LCMS (Method D)**: m/z 287 $(M+H)^+$ (ES+) at 1.86 min, UV inactive
269		1-piperidin-4-yl pyrolidin-2-one	Commercially available CAS: 91596-61-1
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
272	**Route 13 and intermediates 80 and 160**	*tert*-butyl 4-(morpholin-4-yl)piperidine-1-carboxylate	**LCMS (Method D)**: m/z 271 $(M+H)^+$ (ES+) at 1.54 min, UV inactive
273		2-(R)- 2 Trifluoromethylpyrrolidine	Commercially available CAS: 1073556-31-6
274	**Route 13 and intermediates 160 and 273**	*tert*-butyl 4-[(2*R*)-2-(trifluoromethyl)pyrrolidin-1-yl]piperidine-1-carboxylate	**LCMS (Method D)**: m/z 267 (M+H)+ (ES+) at 2.27 and 2.30 min, UV inactive
275		piperidine	Commercially available CAS:110-89-4

276	**Route 13 and intermediates 160 and 275**	*tert*-butyl 1,4'-bipiperidine-1'-carboxylate	**LCMS (Method D)**: m/z 269 $(M+H)^+$ (ES+) at 2.06 min, UV inactive
277		2-(S)- 2 Trifluoromethylpyrrolidine	Commercially available CAS: 119580-41-5
278	**Route 13 and intermediates 160 and 277**	*tert*-butyl 4-[(2*S*)-2-(trifluoromethyl)pyrrolidin-1-yl]piperidine-1-carboxylate	**LCMS (Method D)**: m/z 323 $(M+H)^+$ (ES+) at 2.27 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
281		(R)-1-(tert-Butoxycarbonyl)piperidine-2-carboxylic acid	Commercially available CAS: 28697-17-8
282	**Intermediate 281**	*tert*-butyl (2*R*)-2-(dimethylcarbamoyl)piperidine-1-carboxylate	**^{1}H NMR:** (400 MHz, DMSO-*d*6) δ: 1.22 - 1.42 (m, 12 H), 1.46 - 1.83 (m, 4 H), 2.79 (s, 3 H), 2.95 (s, 3 H), 3.70 (d, *J*=12.5 Hz, 1 H), 4.74 - 4.94 (m, 1 H)
283	**Route 14 and intermediates 160 and 282**	*tert*-butyl (2*R*)-2-(dimethylcarbamoyl)-1,4'-bipiperidine-1'-carboxylate	**LCMS (Method D)**: m/z 340 $(M+H)^+$ (ES+) at 1.89 min, UV inactive
284		(S)-3-Boc-thiazolidine-4-carboxylic acid	Commercially available CAS: 63091-82-7
285	**Intermediate 284**	3-*tert*-butyl 4-methyl (4*S*)-1,3-thiazolidine-3,4-dicarboxylate	**^{1}H NMR:** (400 MHz, $CDCl_3$) δ: 1.47 (s, 5 H), 1.43 (s, 4 H), 3.13 - 3.22 (m, 1 H), 3.22 - 3.37 (m, 1 H), 3.75 (s, 3 H), 4.34 - 4.52 (m, 1 H), 4.57-4.60 (m, 0.5 H), 4.61 - 4.70 (m, 1H), 4.84 - 4.92 (m, 0.5 H)
286	**Route 14 and intermediates 160 and 284**	*tert*-butyl 4-[(4*S*)-4-(methoxycarbonyl)-1,3-thiazolidin-3-yl]piperidine-1-carboxylate	**LCMS (Method D)**: m/z 331 $(M+H)^+$ (ES+) at 2.16 min, UV inactive
287		5-(Pyrrolidin-2-yl)-1H-1,2,3,4-tetrazole	Commercially available CAS: 758710-03-1
288	**Route 13 and intermediates 160 and 287**	*tert*-butyl 4-[2-(2*H*-tetrazol-5-yl)pyrrolidin-1-yl]piperidine-1-carboxylate	**LCMS (Method D)**: m/z 323 $(M+H)^+$ (ES+) at 1.90 min, UV inactive
289		(R)-2-Piperidinecarboxylic acid methyl ester hydrochloride	Commercially available CAS: 18650-38-9
290	**Route 14 and intermediates 160 and 289**	1'-*tert*-butyl 2-methyl (2*R*)-1,4'-bipiperidine-1',2-dicarboxylate	**LCMS (Method C)**: m/z 327 $(M+H)^+$ (ES+) at 1.43 min, UV inactive
291		(2R,4R)-4-Hydroxypyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester	Commercially available CAS: 114676-69-6
292		D-proline, 2-methyl-, methyl ester, hydrochloride (1:1)	Commercially available CAS: 1286768-32-8
293	**Route 14 and intermediates 160 and 292**	*tert*-butyl 4-[(2*R*)-2-(methoxycarbonyl)-2-methylpyrrolidin-1-yl]piperidine-1-carboxylate	**LCMS (Method D)**: m/z 271 $(M+H)^+$ (ES+) at 2.36 min, UV inactive
294		(2R)-(+)-1-Boc-2-pyrrolidinemethanol	Commercially available CAS: 83435-58-9
295	**Intermediate**	*tert*-butyl (2*R*)-2-	**^{1}H NMR:** (400 MHz, $CDCl_3$) δ: 1.46

	294	(fluoromethyl)pyrrolidine-1-carboxylate	(s, 5 H), 1.57 (s, 4 H), 1.80 - 2.00 (m, 2 H), 2.01 - 2.15 (m, 2 H), 3.09 - 3.23 (m, 1 H), 3.65 (dt, *J*=11.4, 7.8 Hz, 1 H), 3.80 - 3.96 (m, 1 H), 4.17 (dd, *J*=8.8, 3.3 Hz, 1 H), 4.51 (t, *J*=8.4 Hz, 1 H)
296	**Route 14 and intermediates 160 and 295**	*tert*-butyl 4-[(2*R*)-2-(fluoromethyl)pyrrolidin-1-yl]piperidine-1-carboxylate	**LCMS (Method D)**: m/z 287 $(M+H)^+$ (ES+) at 2.56 min, UV inactive
297	**Intermediate 294**	*tert*-butyl (2*R*)-2-(difluoromethyl)pyrrolidine-1-carboxylate	**^{1}H NMR:** (400 MHz, $CDCl_3$) δ: 1.36 - 1.45 (m, 1 H), 1.47 (s, 3 H), 1.57 (s, 6 H), 3.16 (dt, *J*=11.0, 6.8 Hz, 1 H), 3.22 - 3.32 (m, 1 H), 3.34 - 3.54 (m, 1 H) 3.59 - 3.73 (m, 2 H), 3.77 - 3.99 (m, 1 H), 4.12 - 4.29 (m, 1 H)
298	**Route 14 and intermediates 160 and 297**	*tert*-butyl 4-[(2*R*)-2-(difluoromethyl)pyrrolidin-1-yl]piperidine-1-carboxylate	**LCMS (Method D)**: m/z 305 $(M+H)^+$ (ES+) at 2.80 min, UV inactive
299		7-Oxa-1-azaspiro[4.4]nonan-6-one.HCl	Commercially available CAS:1018670-73-9
300	**Route 14 and intermediates 160 and 299**	*tert*-butyl 4-(6-oxo-7-oxa-1-azaspiro[4.4]non-1-yl)piperidine-1-carboxylate	**LCMS (Method D)**: m/z 325 $(M+H)^+$ (ES+) at 2.08 min, UV inactive
301		4-Nitrophenyl chloroformate	Commercially available CAS: 7693-46-1
302	**Route 18 and intermediates 1, 32 and 301**	4-nitrophenyl 2-[4-(1*H*-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**LCMS (Method D)**: m/z 426 $(M+H)^+$ (ES+) at 2.12 min, UV active
303		Ethanol-1,1,2,2,2-d_5	Commercially available CAS: 1859-08-1
304		Ethanol-1,1-d_2	Commercially available CAS: 1859-09-2
305		Ethanol-2,2,2-d_3	Commercially available CAS: 1759-87-1
306	**Route 18 and intermediates 1, 9 and 301**	4-nitrophenyl 2-[4-(1-methyl-1*H*-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**LCMS (Method D)**: m/z 440 $(M+H)^+$ (ES+) at 2.11 min, UV active
307		Dimethylamine hydrochloride	Commercially available CAS: 506-59-2
308	**Route 15 and intermediates 130 and 288**	Mixture of *tert*-butyl 4-[2-(1-methyl-1*H*-tetrazol-5-yl)pyrrolidin-1-yl]piperidine-1-carboxylate and *tert*-butyl 4-[2-(2-methyl-2*H*-tetrazol-5-yl)pyrrolidin-1-yl]piperidine-1-carboxylate	**LCMS (Method D)**: m/z 337 $(M+H)^+$ (ES+) at 2.43 min, UV inactive
309		1-*tert*-butyl 2-methyl (2*R*,4*R*)-4-fluoropyrrolidine-1,2-dicarboxylate	Commercially available CAS 647857-43-0
310		1-*tert*-butyl 2-methyl (2*R*,4*S*)-4-fluoropyrrolidine-1,2-dicarboxylate	Commercially available CAS 647857-39-4
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
312	**Route 14 and**	*tert*-butyl 4-[(2*R*,4*S*)-4-fluoro-2-	**LCMS (Method D)**: m/z 331 $(M+H)^+$

	intermediates 160 and 310	(methoxycarbonyl)pyrrolidin-1-yl]piperidine-1-carboxylate	(ES+) at 2.04 min, UV inactive
313		(R)-2-(pyrrolidin-2-yl)thiazole	Commercially available CAS: 1228558-20-0
314	**Route 9 and intermediates 160 and 313**	4-[(2*R*)-2-(1,3-thiazol-2-yl)pyrrolidin-1-yl]piperidine dihydrochloride	**LCMS (Method K)**: m/z 238 $(M+H)^+$ (ES+) at 7.00 min, UV active
315		(2*R*)-2-(thiophen-2-yl)pyrrolidine	Commercially available CAS: 154777-22-7
316	**Route 9 and intermediates 160 and 315**	4-[(2*R*)-2-(thiophen-2-yl)pyrrolidin-1-yl]piperidine dihydrochloride	**LCMS (Method K)**: m/z 237 $(M+H)^+$ (ES+) at 7.80 min, UV active
317		3-[(2*R*)-pyrrolidin-2-yl]-1,2-oxazole	Commercially available CAS: 1255147-67-1
318	**Route 9 and intermediates 160 and 317**	4-[2-(1,2-oxazol-3-yl)pyrrolidin-1-yl]piperidine dihydrochloride	**LCMS (Method K)**: m/z 222 $(M+H)^+$ (ES+) at 6.24 min, UV active
319	**Route 15 and intermediates 114 and 194**	4-(2-ethyl-2*H*-tetrazol-5-yl)piperidine hydrochloride	**LCMS (Method I):** m/z $(M+H)^+$ (ES+) at 3.128min, UV active
320	**Route 15 and intermediates 114 and 194**	4-(1-ethyl-1*H*-tetrazol-5-yl)piperidine hydrochloride	**LCMS (Method I)**: m/z 182 $(M+H)^+$ (ES+) at 2.54 min, UV active
321		6,7-dihydro-5H-pyrrolo[3,4-b]pyridine dihydrochloride	Commercially available CAS: 147740-02-1
322		6-Bromohexanoyl chloride	Commercially available CAS: 22809-37-6
323	**Route 6 and intermediates 3 and 53**	Mthyl 2-[4-(pyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate.HCl	**LCMS (Method J)**: m/z 322 $(M+H)^+$ (ES^+), at 4.37 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, DMSO-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 (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	**C**	m/z 367/369 $(M+H)^+$ (ES+), at 1.57 min, UV active
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, DMSO-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, DMSO-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 – 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).	**G**	m/z 358 $(M+H)^+$ (ES+), at 4.71 min, UV active
1-5	Isomer 2: ethyl 2-[4-(4,5-dichloro-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 25**	**as**	(400 MHz, CD_3OD) δ: 1.20 – 1.31 (m, 3H), 1.67 – 1.82 (m, 2H), 1.87 - 2.02 (m, 8H), 2.10 – 2.18 (m, 2H), 2.61 – 2.72 (m, 1H), 2.76 – 2.88 (m, 1H), 2.90 – 3.04 (m, 2H), 3.25 – 3.29 (m, 2H), 3.36 – 3.46 (m, 2H), 4.10 (q, J = 7.0 Hz, 2H), NH not observed	**C**	m/z 401/403/405 $(M+H)^+$ (ES+), at 1.57 min, UV active
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-	**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	**B**	m/z 347 $(M+H)^+$ (ES+), at 3.07 min, UV inactive

	yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate			(m, 2H), 3.37 (dt, J = 13.6, 6.6 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), 3.41 (s, 3H), 3.58 (s, 3H), 6.49 (s, 1H)	**G**	m/z 347 $(M+H)^+$ (ES+), at 4.83 min, UV active
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
1-11	Isomer 2: methyl 2-[4-(1,4-dimethyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**3 and 36**	**b and e**	(400 MHz, DMSO-d_6) δ: 1.57 – 1.93 (m, 10H), 1.96 – 2.06 (m, 2H), 2.02 (s, 3H), 2.59 – 2.79 (m, 2H), 2.81 – 2.92 (m, 2H), 3.15 – 3.22 (m, 2H), 3.26 – 3.33 (m, 2H), 3.50 (s, 3H), 3.57 (s, 3H), 6.66 (s, 1H)	**G**	m/z 347 $(M+H)^+$ (ES+), at 4.54 min, UV active
1-12	Isomer 2: ethyl 2-[4-(1,4-dimethyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 36**	**b and e**	(400 MHz, DMSO-d_6) δ: 1.18 (t, J = 7.0 Hz, 3H), 1.59 – 1.91 (m, 10H), 1.98 – 2.05 (m, 2H), 2.02 (s, 3H), 2.67 – 2.75 (m, 2H), 2.82 – 2.90 (m, 2H), 3.16 – 3.22 (m, 2H), 3.27 – 3.32 (m, 2H), 3.49 (s, 3H), 4.01 (q, J = 7.0 Hz, 2H), 6.66 (s, 1H)	**G**	m/z 361 $(M+H)^+$ (ES+), at 5.34 min, UV active
1-13	Isomer 2: methyl 2-[4-(5-chloro-1-methyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**3 and 20**	**as**	(400 MHz, $CDCl_3$) δ: 1.81 - 2.01 (m, 10H), 2.01 - 2.11 (m, 2H), 2.55 – 2.66 (m, 1H), 2.66 – 2.79 (m, 1H), 2.91 – 3.00 (m, 2H), 3.25 (s, 1H), 3.32 (s, 1H),), 3.34 – 3.40 (m, 1H), 3.41 – 3.46 (m, 1H), 3.52 (s, 3H), 3.68 (s, 3H), 6.86 (s, 1H)	**C**	m/z 367/369 $(M+H)^+$ (ES+), at 1.61 min, UV active
1-14	Isomer 2: ethyl 2-[4-(5-chloro-1-methyl-1H-imidazol-2-yl)piperidin-1-	**2 and 20**	**as**	(400 MHz, $CDCl_3$) δ: 1.25 (t, J = 7.0 Hz, 3H), 1.81 - 2.01 (m, 10H), 2.01 - 2.11 (m, 2H), 2.55 – 2.66 (m, 1H), 2.66 – 2.78 (m, 1H), 2.90 – 3.00 (m, 2H), 3.26 (s, 1H), 3.31 (s, 1H),),	**C**	m/z 381/383 $(M+H)^+$ (ES+), at 1.69 min, UV active

	yl]-6-azaspiro[3.4]octane-6-carboxylate			3.34 – 3.47 (m, 2H), 3.52 (s, 3H), 4.12 (q, J = 7.0 Hz, 2H), 6.86 (s, 1H)		
1-15	Isomer 2: ethyl 2-{4-[1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 37**	**b**	(400 MHz, DMSO-d_6) δ: 1.18 (t, J = 7.0 Hz, 3H), 1.58 – 1.72 (m, 2H), 1.73 – 1.93 (m, 8H), 1.95 – 2.08 (m, 2H), 2.65 – 2.81 (m, 2H), 2.82 – 2.92 (m, 2H), 3.14 – 3.23 (m, 2H), 3.25 – 3.34 (m, 2H), 3.65 (s, 3H), 4.02 (q, J = 7.0 Hz, 2H), 7.67 (s, 1H)	**G**	m/z 415 $(M+H)^+$ (ES+), at 4.95 min, UV active
1-16	Isomer 2: methyl 2-[4-(4,5-dichloro-1-methyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**3 and 21**	**as**	(400 MHz, $CDCl_3$) δ: 1.79 - 2.00 (m, 10H), 2.00 - 2.11 (m, 2H), 2.56 – 2.66 (m, 1H), 2.67 – 2.76 (m, 1H), 2.89 – 3.00 (m, 2H), 3.25 (s, 1H), 3.31 (s, 1H),), 3.33 – 3.40 (m, 1H), 3.41 – 3.46 (m, 1H), 3.53 (s, 3H), 3.69 (s, 3H)	**C**	m/z 401/403/405 $(M+H)^+$ (ES+), at 1.70 min, UV active
1-17	Isomer 2: ethyl 2-[4-(4,5-dichloro-1-methyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 21**	**as**	(400 MHz, $CDCl_3$) δ: 1.25 (t, J = 7.0 Hz, 3H), 1.79 - 2.00 (m, 10H), 2.01 - 2.10 (m, 2H), 2.55 – 2.66 (m, 1H), 2.66 – 2.79 (m, 1H), 2.90 – 2.99 (m, 2H), 3.26 (s, 1H), 3.31 (s, 1H),), 3.34 – 3.47 (m, 2H), 3.53 (s, 3H), 4.12 (q, J = 7.0 Hz, 2H)	**C**	m/z 415/417/419 $(M+H)^+$ (ES+), at 1.79 min, UV active
1-18	Isomer 2: ethyl 2-[4-(1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 7**	**a**	(400 MHz, $CDCl_3$) δ: 1.24 (t, J = 7.0 Hz, 3H), 1.68 - 2.13 (m, 12H), 2.69 – 2.75 (m, 2H), 2.91 – 2.98 (m, 2H), 3.18 - 3.52 (m, 4H), 4.11 (q, J = 7.0 Hz, 2H), 6.11 (s, 1H), 7.48 (s, 1H), NH not observed	**B**	m/z 333 $(M+H)^+$ (ES+), at 3.16 min, UV inactive
1-19	Isomer 2: ethyl 2-[4-(3-amino-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 8**	**a**	(400 MHz, $CDCl_3$) δ: 1.25 (t, J = 6.2 Hz, 3H), 1.60 - 2.20 (m, 12H), 2.53 – 2.59 (m, 1H), 2.70 – 2.75 (m, 1H), 2.92 – 2.98 (m, 2H), 3.21 - 3.47 (m, 4H), 4.01 - 4.20 (m, 2H), 5.45 (s, 1H), 3xNH not observed	**B**	m/z 348 $(M+H)^+$ (ES+), at 2.75 min, UV inactive
1-20	Mixture of diastereomers: methyl 2-[4-(1-methyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**3 and 38**	**b**	400 MHz, $CDCl_3$) δ: 1.56 - 1.70 (m, 2H), 1.79 - 2.01 (m, 8H), 2.05 – 2.25 (m, 2H), 2.51 – 2.83 (m, 2H), 2.88 – 3.14 (m, 2H), 3.23 - 3.51 (m, 4H), 3.71 (s, 3H), 3.83 (s, 3H), 6.03 (br, 1H), 7.34 – 7.43 (m, 1H)	**B**	m/z 333 $(M+H)^+$ (ES+), at 2.70 min, UV inactive
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

1-22	Isomer 2: ethyl 2-[4-(1-methyl-1H-pyrazol-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 10**	**a**	(400 MHz, $CDCl_3$) δ: 1.14 - 1.32 (m, 3H), 1.54 - 1.71 (m, 2H), 1.78 - 2.12 (m, 10H), 2.43 – 2.49 (m, 1H), 2.60 - 2.78 (m, 1H), 2.84 - 2.96 (m, 2H), 3.16 - 3.46 (m, 4H), 3.84 (s, 3H), 4.03 - 4.20 (m, 2H), 7.13 (s, 1H), 7.32 (s, 1H)	**B**	m/z 347 $(M+H)^+$ (ES+), at 3.51 min, UV inactive
1-23	Isomer 2: ethyl 2-[4-(1,3-oxazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 41**	**b**	(400 MHz, DMSO-d_6) δ: 1.18 (t, J = 7.0 Hz, 3H), 1.57 – 1.73 (m, 2H), 1.73 – 1.91 (m, 6H), 1.92 – 2.05 (m, 4H), 2.63 – 2.72 (m, 2H), 2.73 – 2.85 (m, 2H), 3.13 – 3.21 (m, 2H), 3.25 – 3.34 (m, 2H), 4.01 (q, J = 7.0 Hz, 2H), 8.01 (s, 1H), 7.12 (s, 1H).	**G**	m/z 334 $(M+H)^+$ (ES+), at 5.37 min, UV active
1-24	Isomer 2: methyl 2-[4-(1,3-thiazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**3 and 42**	**b**	(400 MHz, DMSO-d_6) δ: 1.58 – 1.73 (m, 2H), 1.73 – 1.92 (m, 6H), 1.96 – 2.10 (m, 4H), 2.65 – 2.74 (m, 1H), 2.79 – 2.89 (m, 2H), 2.91 – 3.03 (m, 1H), 3.20 – 3.32 (m, 4H), 3.58 (s, 3H), 7.61 (d, J = 3.4 Hz, 1H), 7.72 (d, J = 3.4 Hz, 1H).	**G**	m/z 336 $(M+H)^+$ (ES+), at 5.15 min, UV active
1-25	Isomer 2: ethyl 2-[4-(1,3-thiazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 42**	**b**	(400 MHz, DMSO-d_6) δ: 1.18 (t, J = 7.0 Hz, 3H), 1.59 – 1.74 (m, 2H), 1.76 – 1.92 (m, 6H), 1.97 – 2.09 (m, 4H), 2.63 – 2.75 (m, 1H), 2.80 – 2.90 (m, 2H), 2.92 – 3.05 (m, 1H), 3.14 – 3.20 (m, 2H), 3.25 – 3.34 (m, 2H), 4.01 (q, J = 7.0 Hz, 2H), 7.60 (d, J = 3.0 Hz, 1H), 7.72 (d, J = 3.0 Hz, 1H)	**F**	m/z 350 $(M+H)^+$ (ES+), at 1.61 min, UV active
1-26	Isomer 2: ethyl 2-[4-(4H-1,2,4-triazol-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**1 and 17**	**f**	(400 MHz, $CDCl_3$) δ: 1.15 – 1.38 (m, 3H), 1.77 – 3.21 (m, 15H), 3.23 – 3.78 (m, 5H), 4.00 – 4.27 (m, 2H), 8.42 (s, 1H), NH not observed	**E**	m/z 334 $(M+H)^+$ (ES+), at 2.78 min, UV inactive
1-27	Isomer 2: ethyl 2-[4-(5-ethyl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 23**	**as**	(400 MHz, $CDCl_3$) δ: 1.25 (t, J = 7.0 Hz, 3H), 1.34 (t, J = 7.5 Hz, 3H), 1.73 - 2.35 (m, 12H), 2.79 (q, J = 7.5 Hz, 2H), 2.84 – 3.15 (m, 4H), 3.31 – 3.46 (m, 4H), 4.11 (q, J = 7.0 Hz, 2H), NH not observed	**C**	m/z 362 $(M+H)^+$ (ES+), at 1.43 min, UV active
1-28	Isomer 2: ethyl 2-[4-(1,3,4-oxadiazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 43**	**b**	(400 MHz, DMSO-d_6) δ: 1.18 (t, J = 7.0 Hz, 3H), 1.62 – 1.74 (m, 2H), 1.75 – 1.94 (m, 6H), 1.95 – 2.06 (m, 4H), 2.65 – 2.74 (m, 1H), 2.74 – 2.83 (m, 2H), 2.93 – 3.01 (m, 1H), 3.14 – 3.21 (m, 2H), 3.26 – 3.32 (m, 2H), 4.00 (q, J = 7.0 Hz, 2H), 9.15 (s, 1H)	**G**	m/z 335 $(M+H)^+$ (ES+), at 4.89 min, UV active
1-29	Isomer 2: ethyl 2-[4-(3-methyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]-6-	**2 and 44**	**b**	(400 MHz, DMSO-d_6) δ: 1.18 (t, J = 7.0 Hz, 3H), 1.62 – 1.74 (m, 2H), 1.75 – 1.95 (m, 6H), 1.95 – 2.05 (m, 4H), 2.33 (s, 3H), 2.65 – 2.72 (m, 1H), 2.72 – 2.81 (m, 2H), 2.93 – 3.03	**F**	m/z 349 $(M+H)^+$ (ES+), at 1.63 min, UV active

	azaspiro[3.4]octane-6-carboxylate			(m, 1H), 3.14 – 3.20 (m, 2H), 3.25 – 3.33 (m, 2H), 4.01 (q, J = 7.0 Hz, 2H)		
1-30	Isomer 2: ethyl 2-[4-(1,2,4-thiadiazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2, 28, 29 and 30**	**b**	(400 MHz, DMSO-d_6) δ: 1.17 (t, J = 7.0, 3H), 1.59 – 1.95 (m, 8H), 1.95 – 2.20 (m, 4H), 2.39 – 2.93 (m, 4H), 3.09 – 3.53 (m, 4H), 4.00 (q, J = 7.0 Hz, 2H), 8.82 (s, 1H)	**G**	m/z 351 $(M+H)^+$ (ES+), at 5.47 min, UV active
1-31	Isomer 2: ethyl 2-[4-(1H-tetrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 31**	**b**	(400 MHz, DMSO-d_6) δ: 1.03 – 1.27 (m, 3H), 1.88 – 1.92 (m, 4H), 1.92 – 2.26 (m, 6H), 2.39 – 2.63 (m, 2H), 2.66 – 2.87 (m, 3H), 3.00 – 3.40 (m, 4H), 3.99 (q, J = 7.0 Hz, 2H), 4.80 – 4.96 (m, 1H), 8.93 (s, 1H)	**F**	m/z 335 $(M+H)^+$ (ES+), at 1.56 min, UV active
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, DMSO-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
1-34	Isomer 1: ethyl 2-[4-(4-methyl-1H-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**1 and 13**	**d**	(400 MHz, $CDCl_3$) δ: 1.25 (t, J = 7.0 Hz, 3H), 1.79 - 2.01 (m, 9H), 2.06 (s, 3H), 2.07 – 2.18 (m, 3H), 2.65 - 2.78 (m, 1H), 2.92 – 2.98 (m, 2H), 3.28 - 3.43 (m, 4H), 4.03 – 4.11 (m, 1H), 4.12 (q, J = 7.0 Hz, 2H), 7.18 (s, 1H), 7.28 (s, 1H)	**B**	m/z 347 $(M+H)^+$ (ES+), at 3.43 min, UV inactive
1-34	Isomer 2: ethyl 2-[4-(4-methyl-1H-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**1 and 11**	**d**	(400 MHz, $CDCl_3$) δ: 1.25 (t, J = 7.0 Hz, 3H), 1.81 - 2.19 (m, 9H), 2.07 (s, 3H), 2.10 – 2.16 (m, 3H), 2.65 - 2.81 (m, 1H), 2.93 – 2.99 (m, 2H), 3.21 - 3.49 (m, 4H), 4.10 – 4.12 (m, 1H), 4.12 (q, J = 7.0 Hz, 2H), 7.20 (s, 1H), 7.28 (s, 1H)	**B**	m/z 347 $(M+H)^+$ (ES+), at 3.55 min, UV inactive
1-35	Isomer 2: ethyl 2-[4-(1H-1,2,3-triazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**1 and 18**	**f**	(400 MHz, $CDCl_3$) δ: 1.19 (t, 3H), 1.76 – 2.10 (m, 10H), 2.10 – 2.24 (m, 2H), 2.62 – 2.79 (m, 1H), 2.84 – 3.02 (m, 2H), 3.17 – 3.28 (m, 2H), 3.28 – 3.42 (m, 2H), 3.98 – 4.12 (q, J = 7.0 Hz, 2H), 4.38 – 4.59 (m, 1H), 7.54 (s, 1H) 7.64 (s, 1H).	**E**	m/z 334 $(M+H)^+$ (ES+), at 2.90 min, UV inactive
1-36	Isomer 2: ethyl 2-[4-(1H-1,2,4-triazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**1, 16 and 56**	**f**	(400 MHz, $CDCl_3$) δ: 1.21 – 1.81 (m, 3H), 1.84 – 2.12 (m, 10H), 2.13 – 2.30 (m, 2H), 2.62 – 2.88 (m, 1H), 2.88 – 3.08 (m, 2H), 3.22 – 3.33 (m, 2H), 3.34 – 3.47 (m, 2H), 4.06 – 4.15 (m, 2H), 4.16 – 4.25 (m, 1H), 7.93 (s, 1H), 8.10 (s, 1H).	**E**	m/z 334 $(M+H)^+$ (ES+), at 2.88 min, UV inactive

1-37	Isomer 2: ethyl 2-[4-hydroxy-4-(1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 47**	**b**	(400 MHz, DMSO-d_6) δ: 1.17 (t, J = 7.0 Hz, 3 H), 1.65 – 1.88 (m, 6 H), 1.93 – 2.04 (m, 4 H), 2.14 – 2.26 (m, 2H), 2.36 – 2.47 (m, 2 H), 2.62 – 2.72 (m, 1 H), 3.12 – 3.20 (m, 2 H), 3.23 – 3.31 (m, 2H), 4.00 (q, J = 7.0 Hz, 2H), 5.04 (s, 1 H), 6.77 (s, 1 H), 6.94 (s, 1 H), 11.71 (s, 1 H)	H	m/z 349 (M+H)+ (ES+) at 7.05 min, UV active
1-38	Isomer 2: ethyl 2-[4-(1H-imidazol-2-yl)-4-methoxypiperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 48**	**b**	(400 MHz, DMSO-d_6) δ: 1.16 (t, J = 7.0 Hz, 3 H), 1.71 – 1.86 (m, 6 H), 1.89 – 2.08 (m, 6 H), 2.53 – 2.58 (m, 2 H), 2.59 – 2.71 (m, 1 H), 2.84 (s, 3 H), 3.11 – 3.20 (m, 2 H), 3.22 – 3.29 (m, 2H), 4.00 (q, J = 7.0 Hz, 2H), 6.82 (s, 1 H), 7.09 (s, 1 H), 11.94 (s, 1 H)	F	m/z 363 (M+H)+ (ES+) at 1.41 min, UV active
1-39	Isomer 2: ethyl 2-[4-hydroxy-4-(1-methyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 49**	**b**	(400 MHz, DMSO-d_6) δ: 1.17 (t, J = 7.0 Hz, 3 H), 1.70 – 1.90 (m, 6 H), 1.93 – 2.04 (m, 4 H), 2.11 – 2.24 (m, 2H), 2.42 – 2.47 (m, 2 H), 2.63 – 2.72 (m, 1 H), 3.11 – 3.18 (m, 2 H), 3.24 – 3.30 (m, 2H), 3.77 (s, 3H), 4.00 (q, J = 7.0 Hz, 2H), 5.09 (s, 1 H), 6.70 (s, 1 H), 7.00 (s, 1 H)	G	m/z 363 (M+H)+ (ES+) at 4.05 min, UV active
1-40	Isomer 2: ethyl 2-[4-methoxy-4-(1-methyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 50**	**b**	(400 MHz, DMSO-d_6) δ: 1.17 (t, J = 7.0 Hz, 3 H), 1.72 – 2.21 (m, 12 H), 2.60 – 2.72 (m, 1 H), 2.87 (s, 3 H), 3.11 – 3.18 (m, 2 H), 3.24 – 3.30 (m, 4H), 3.77 (s, 3H), 4.00 (q, J = 7.0 Hz, 2H), 6.78 (s, 1 H), 7.11 (s, 1 H)	F	m/z 377 (M+H)+ (ES+) at 1.50 min, UV active
1-41	Isomer 2: ethyl 2-[4-methyl-4-(3-methyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 24**	**as**	(400 MHz, $CDCl_3$) δ: 1.24 (t, J = 7.0 Hz, 3H), 1.35 – 1.40 (m, 3H), 1.56 - 2.12 (m, 11H), 2.30 – 2.39 (m, 2H), 2.40 (s, 3H), 2.57 – 2.78 (m, 2H), 3.21 – 3.45 (m, 4H), 4.11 (q, J = 7.0 Hz, 2H)	C	m/z 363 $(M+H)^+$ (ES+), at 1.70 min, UV active
1-42	Isomer 2: methyl 2-[4-(4-methyl-1*H*-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**3 and 73**	**at**	(400 MHz, CD_3OD) δ: 1.82 - 2.19 (m, 15 H), 2.82 (quin, *J* = 7.9 Hz, 1 H), 2.92 - 3.05 (m, 2 H), 3.27 (s, 2 H), 3.34 - 3.44 (m, 2 H), 3.66 (s, 3 H), 4.02 - 4.16 (m, 1 H), 7.27 (s, 1 H), 7.44 (s, 1 H)	E	m/z 333 $(M+H)^+$ (ES+), at 2.77 min, UV active
1-43	Isomer 2: ethyl 2-[4-(1,2-oxazol-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 74**	**at**	(400 MHz, methanol-d_4) δ: 1.24 (t, *J* = 7.0 Hz, 3 H), 1.65 - 1.82 (m, 2 H), 1.84 - 2.20 (m, 10 H), 2.72 - 3.02 (m, 4 H), 3.27 (s, 2 H), 3.39 (q, *J* = 6.6 Hz, 2 H), 4.09 (q, *J* = 7.0 Hz, 2 H), 6.18 (s, 1 H), 8.27 (s, 1 H)	E	m/z 334 $(M+H)^+$ (ES+), at 3.14 min, UV active
1-44	Isomer 2: ethyl 2-[4-(3-methyl-1H-pyrazol-1-	**2 and 119**	**at**	(400 MHz, CD_3OD) δ: 1.24 (t, J = 7.2 Hz, 3 H), 1.82 - 2.17 (m, 12 H), 2.22 (s, 3 H), 2.83 (quin, J = 7.9 Hz, 1 H), 3.00 (d,	E	m/z 347 $(M+H)^+$ (ES+), at 3.11 min, UV active

	yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate			J = 9.4 Hz, 2 H), 3.27 (s, 2 H), 3.39 (q, J = 6.5 Hz, 2 H), 4.01 - 4.15 (m, 3 H), 6.04 (d, J = 2.3 Hz, 1 H), 7.52 (d, J = 2.3 Hz, 1 H)		
1-45	Isomer 2: methyl 2-[4-(3-methyl-1H-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**3 and 119**	**at**	(400 MHz, CD_3OD) δ: 1.81 - 2.17 (m, 12 H), 2.22 (s, 3 H), 2.83 (quin, J = 7.9 Hz, 1 H), 2.95 - 3.05 (m, 2 H), 3.27 (s, 2 H), 3.39 (t, J = 6.4 Hz, 2 H), 3.66 (s, 3 H), 4.00 - 4.13 (m, 1 H), 6.04 (d, J = 2.3 Hz, 1 H), 7.52 (d, J = 2.3 Hz, 1 H)	**E**	m/z 333 $(M+H)^+$ (ES+), at 2.84 min, UV active
1-46	Isomer 2: methyl 2-[4-(1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**3 and 120**	**at**	(400 MHz, CD_3OD) δ: 1.37 (t, J = 7.2 Hz, 3 H), 1.60 - 1.78 (m, 2 H), 1.84 - 2.01 (m, 8 H), 2.07 - 2.18 (m, 2 H), 2.67 - 2.88 (m, 2 H), 2.99 (d, J = 11.7 Hz, 2 H), 3.27 (s, 2 H), 3.39 (t, J = 6.4 Hz, 2 H), 3.66 (s, 3 H), 4.12 (q, J = 7.3 Hz, 2 H), 6.09 (d, J = 2.0 Hz, 1 H), 7.38 (d, J = 2.0 Hz, 1 H)	**E**	m/z 347 $(M+H)^+$ (ES+), at 2.89 min, UV active
1-47	Isomer 2: ethyl 2-[4-(1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 120**	**at**	(400 MHz, CD_3OD) δ:1.24 (t, J = 7.2 Hz, 3 H), 1.37 (t, J = 7.22 Hz, 3 H), 1.60 - 1.78 (m, 2 H), 1.82 - 2.04 (m, 8 H), 2.07 - 2.19 (m, 2 H), 2.67 - 2.87 (m, 2 H), 2.99 (d, J = 11.7 Hz, 2 H), 3.27 (s, 2 H), 3.39 (q, J = 6.6 Hz, 2 H), 4.05 - 4.18 (m, 4 H), 6.09 (d, J = 1.6 Hz, 1 H), 7.38 (d, J = 1.6 Hz, 1 H)	**E**	m/z 361 $(M+H)^+$ (ES+), at 3.23 min, UV active
1-48	Isomer 2: methyl 2-[4-(1-propyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**3 and 173**	**as**	(400 MHz, $CDCl_3$) δ: 0.93 (t, J=7.4 Hz, 3 H), 1.58 - 2.19 (m, 13 H), 2.52 - 2.87 (m, 2 H), 2.93 - 3.12 (m, 2 H), 3.23 - 3.51 (m, 5 H), 3.68 (s, 3 H), 4.00 (t, J=7.3 Hz, 2 H), 6.05 (br. s., 1 H), 7.42 (s, 1 H)	**B**	m/z 361 $(M+H)^+$ (ES+), at 3.66 min, UV active
1-49	Isomer 2: ethyl 2-[4-(1-propyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 173**	**as**	(400 MHz, $CDCl_3$) δ: 0.93 (t, J=7.4 Hz, 3 H), 1.25 (t, J=7.0 Hz, 3 H), 1.56 - 2.20 (m, 13 H), 2.51 - 2.83 (m, 2 H), 2.90 - 3.12 (m, 2 H), 3.25 - 3.50 (m, 5 H), 4.00 (t, J=7.4 Hz, 2 H), 4.12 (q, J=7.3 Hz, 2 H), 6.05 (br. s., 1 H), 7.42 (s, 1 H)	**B**	m/z 375 $(M+H)^+$ (ES+), at 4.16 min, UV active
1-50	Isomer 2: ethyl 2-[4-(1,3-thiazol-4-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 164**	**as**	(400 MHz, $CDCl_3$) δ: 1.25 (t, *J*=7.0 Hz, 3 H), 1.51 - 2.31 (m, 11 H), 2.63 - 3.16 (m, 4 H), 3.20 - 3.47 (m, 5 H), 4.12 (q, *J*=7.3 Hz, 2 H), 6.90 - 7.05 (br. s., 1 H), 8.76 (s, 1 H)	**B**	m/z 350 $(M+H)^+$ (ES+), at 1.39 min, weakly UV active
1-51	Isomer 2: ethyl 2-{4-[1-(2-methoxyethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-	**Example 1-1 and 165**	**g**	(400 MHz, $CDCl_3$) δ: 1.25 (t, J=7.2 Hz, 3 H), 1.74 - 2.15 (m, 12 H), 2.72 (br. s., 2 H), 3.01 (br. s., 2 H), 3.28 - 3.46 (m, 4 H), 3.32 (s, 3 H), 3.61 (t, J=5.5 Hz, 2 H), 4.04 (t, J=5.5 Hz, 2 H), 4.11 (q, J=7.2 Hz, 2 H), 6.89 (s, 1 H), 6.96 (s, 1 H)	**B**	m/z 391 $(M+H)^+$ (ES+), at 3.56 min, weakly UV active

	carboxylate					
1-52	Isomer 2: ethyl 2-{4-[1-(cyanomethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**Example 1-1 and 166**	**h**	(400 MHz, $CDCl_3$) δ: 1.25 (t, J=7.0 Hz, 3 H), 1.47 - 2.32 (m, 11 H), 2.64 - 3.26 (m, 4 H), 3.27 - 3.50 (m, 5 H), 4.06 - 4.17 (m, 2 H), 4.90 (s, 2 H), 6.97 (br. s., 1 H), 7.02 (s, 1 H)	**B**	m/z 372 $(M+H)^+$ (ES+), at 3.24 min, weakly UV active
1-53	Isomer 2: (2-{1-[6-(ethoxycarbonyl)-6-azaspiro[3.4]oct-2-yl]piperidin-4-yl}-1H-imidazol-1-yl)acetic acid	**Example 1-1 and 167**	**i**	(400 MHz, DMSO-d_6) δ: 1.18 (t, J=7.2 Hz, 3 H), 1.59 - 1.94 (m, 10 H), 1.95 - 2.08 (m, 2 H), 2.80 - 2.93 (m, 2 H), 3.95 - 4.07 (q, J=7.0 Hz, 2 H), 4.29 - 4.38 (br. s., 2 H), 6.70 (s, 1 H), 6.89 (s, 1 H). 7 protons obscured by water peak.	**B**	m/z 391 $(M+H)^+$ (ES+), at 1.57 min, UV inactive
1-54	Isomer 2: ethyl 2-(4-{1-[2-(methylamino)-2-oxoethyl]-1H-imidazol-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**Example 1-53 and 168**	**i**	(400 MHz, $CDCl_3$) δ: 1.25 (t, J=7.2 Hz, 3 H), 1.71 - 2.33 (m, 11 H), 2.68 - 3.20 (m, 4 H), 2.81 (d, J=4.7 Hz, 3 H), 3.27 - 3.48 (m, 5 H), 4.11 (q, J=7.0 Hz, 2 H), 4.66 (s, 2 H), 6.01 (br. s, 1 H), 6.91 (d, J=5.5 Hz, 1 H), 7.05 (s, 1 H)	**B**	m/z 404 $(M+H)^+$ (ES+), at 2.18 min, weakly UV active
1-55	Isomer 2: methyl 2-[4-(1,4-dimethyl-1H-pyrazol-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**3 and 177**	**as**	(300 MHz, CDCl3) δ: 1.51 - 2.26 (m, 15 H), 2.56 - 2.82 (m, 2 H), 2.92 - 3.14 (m, 2 H), 3.20 - 3.53 (m, 4 H), 3.69 (s, 3 H), 3.83 (s, 3 H), 7.18 (s, 1 H)	**B**	m/z 347 $(M+H)^+$ (ES+), at 4.22 min, UV active
1-56	Isomer 2: ethyl 2-[4-(1,4-dimethyl-1H-pyrazol-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 177**	**as**	(400 MHz, $CDCl_3$) δ: 1.27 (t, J=7.0 Hz, 3 H), 1.63 (s, 5 H), 1.68 - 2.25 (m, 10 H), 2.43 - 2.75 (m, 2 H), 2.84 - 3.06 (m, 2 H), 3.29 - 3.43 (m, 4 H), 3.82 (br. s., 3 H), 4.10 - 4.18 (m, 2 H), 7.18 (s, 1 H)	**B**	m/z 361 $(M+H)^+$ (ES+), at 3.70 min, UV active
1-57	Isomer 2: methyl 2-[4-(1,4-dimethyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**3 and 178**	**as**	(300 MHz, $CDCl_3$) δ: 1.53 - 2.20 (m, 15 H), 2.54 - 2.90 (m, 2 H), 2.94 - 3.17 (m, 2 H), 3.27 - 3.50 (m, 4 H), 3.68 (s, 3 H), 3.77 (s, 3 H), 7.04 (s, 1 H)	**B**	m/z 347 $(M+H)^+$ (ES+), at 4.74 min, UV active
1-58	Isomer 2: ethyl 2-[4-(1,4-dimethyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-	**2 and 178**	**as**	(400 MHz, $CDCl_3$) δ: 1.25 (t, J=7.0 Hz, 3 H), 1.67 - 2.19 (m, 15 H), 2.54 - 2.82 (m, 2 H), 2.93 - 3.12 (m, 2 H), 3.25 - 3.48 (m, 4 H), 3.77 (s, 3 H), 4.11 (q, J=7.3 Hz, 2 H), 7.04 (s, 1 H)	**B**	m/z 361 $(M+H)^+$ (ES+), at 4.07 min, UV active

	carboxylate					
1-59	Isomer 2: ethyl 2-[4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 173**	**b**	(400 MHz, CD_3OD) δ: 1.25 (t, *J*=7.2 Hz, 3 H), 1.33 (t, *J*=7.2 Hz, 3 H), 1.77 (d, *J*=10.7 Hz, 2 H), 1.90 - 2.10 (m, 8 H), 2.10 - 2.24 (m, 2 H), 2.13 (s, 3 H), 2.79 - 2.96 (m, 2 H), 3.08 (d, *J*=8.9 Hz, 2 H), 3.28 - 3.30 (m, 2 H), 3.37 - 3.45 (m, 2 H), 4.07 - 4.18 (m, 4 H), 7.18 (s, 1 H)	**I**	m/z 375 $(M+H)^+$ (ES+), at 4.22 min, weakly UV active
1-60	Isomer 2: ethyl 2-[4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 251**	**b**	(400 MHz, CD_3OD) δ: 1.18 - 1.40 (m, 6 H), 1.96 – 2.10 (m, 3H), 2.11 - 2.31 (m, 5H), 2.33 – 2.46 (m, 2H), 2.59 (q, J = 7.5 Hz, 2H), 2.67 – 2.84 (m, 2H), 3.07 – 3.23 (m, 1H), 3.37 - 3.61 (m, 6H), 3.85 (s, 3H), 4.13 (q, J = 6.8 Hz, 3H), 7.28 (s, 1H).	**I**	m/z 375 $(M+H)^+$ (ES+), at 4.36 min, UV active
1-61	Isomer 2: ethyl 2-[4-(2*H*-1,2,3-triazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 247**	**ak**	(400 MHz, CD_3OD) δ: 1.27 (t, J = 7.1 Hz, 3H), 1.88 - 2.02 (m, 4H), 2.12 – 2.28 (m, 8H), 2.81 - 2.92 (m, 1H), 2.93 - 3.05 (m, 2H), 3.27 – 3.36 (m, 2H), 3.37 - 3.46 (m, 2H), 4.12 (q, J=7.1 Hz, 2H), 4.51 - 4.61 (m, 1H), 7.69 (s, 2H).	**I**	m/z 334 $(M+H)^+$ (ES+), at 3.90 min, UV active
1-62	Isomer 2: ethyl 2-[4-(1H-tetrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 215**	**b**	(400 MHz, CD_3OD) δ: 1.25 (t, J=7.0 Hz, 3 H), 1.90 - 2.00 (m, 4 H), 2.05 - 2.21 (m, 6 H), 2.21 - 2.32 (m, 2 H), 2.81 - 2.91 (m, 1 H), 3.02 (d, J=7.3 Hz, 2 H), 3.28 (s, 2 H), 3.36 - 3.44 (m, 2 H), 4.10 (q, J=7.1 Hz, 2 H), 4.60 - 4.71 (m, 1 H), 9.26 (s, 1 H)	**I**	m/z 335 $(M+H)^+$ (ES+), at 3.47 min, weakly UV active
1-63	Isomer 2: ethyl 2-[4-(5-methyl-1*H*-tetrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 255**	**b**	(400 MHz, CD_3OD) δ: 1.20 - 1.34 (m, 4H), 1.90 – 2.03 (m, 4H), 2.04 - 2.32 (m, 9H), 2.61 (s, 3H), 2.84 - 2.93 (m, 1H), 3.02 – 3.13 (m, 2H), 3.30 - 3.52 (m, 2H), 4.12 (q, J = 7.1 Hz, 2H), 4.42 – 4.54 (m, 1H).	**I**	m/z 349 $(M+H)^+$ (ES+), at 3.44 min, UV active
1-64	Isomer 2: ethyl 2-[4-(1-methyl-1H-tetrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 195**	**b**	(400 MHz, $CDCl_3$) δ: 1.25 (t, J=7.2 Hz, 3 H), 1.82 - 2.31 (m, 8 H), 2.74 - 3.72 (m, 12 H), 4.02 - 4.16 (m, 5 H)	**I**	m/z 349 $(M+H)^+$ (ES+), at 3.40 min, UV active
1-65	Isomer 2: ethyl 2-[4-(1-ethyl-1*H*-tetrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 320**	**ak**	(400 MHz, DMSO-d_6) δ: 1.17 (t, *J*=7.0 Hz, 3 H), 1.42 (t, *J*=7.3 Hz, 3 H), 1.62 - 1.96 (m, 10 H), 1.96 - 2.07 (m, 2 H), 2.66 - 2.76 (m, 1 H), 2.82 - 2.91 (m, 2 H), 2.95 - 3.06 (m, 1 H), 3.17 (d, *J*=7.0 Hz, 2 H), 3.25 - 3.32 (m, 2 H), 4.00 (q, *J*=7.2 Hz, 2 H), 4.39 (q, *J*=7.3 Hz, 2 H)	**I**	m/z 363 $(M+H)^+$ (ES^+), at 3.75 min, UV active

1-66	Isomer 2: ethyl 2-[4-(2-ethyl-2*H*-tetrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 319**	**ak**	(400 MHz, DMSO-d_6) δ: 1.17 (t, *J*=7.2 Hz, 3 H), 1.49 (t, *J*=7.3 Hz, 3 H), 1.61 - 1.75 (m, 2 H), 1.75 - 1.92 (m, 6 H), 1.92 - 2.06 (m, 4 H), 2.63 - 2.74 (m, 1 H), 2.79 (d, *J*=11.3 Hz, 2 H), 2.88 (tt, *J*=11.4, 4.0 Hz, 1 H), 3.16 (d, *J*=6.7 Hz, 2 H), 3.28 (q, *J*=7.0 Hz, 2 H), 4.00 (q, *J*=7.0 Hz, 2 H), 4.64 (q, *J*=7.3 Hz, 2 H)	**I**	m/z 363 $(M+H)^+$ (ES^+), at 4.06 min, UV active
1-67	Isomer 2: ethyl 2-[4-(1-cyclopropyl-1H-tetrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 218**	**b**	(400 MHz, DMSO-d_6) δ: 1.12 - 1.26 (m, 7 H), 1.66 - 1.94 (m, 8 H), 1.94 - 2.06 (m, 4 H), 2.66 - 2.79 (m, 1 H), 2.89 (d, J=11.6 Hz, 2 H), 3.03 - 3.14 (m, 1 H), 3.18 (d, J=7.0 Hz, 2 H), 3.26 - 3.35 (m, 2 H), 3.84 (s, 1 H), 3.96 - 4.07 (m, 2 H)	**I**	m/z 375 $(M+H)^+$ (ES+), at 3.88 min, weakly UV active
1-68	Isomer 2: (1,1-$^2H_2$)ethyl 2-[4-(1*H*-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**302 and 304**	**j**	(400 MHz, DMSO-d_6) δ: 1.13 (s, 3 H), 1.73 - 2.03 (m, 12 H), 2.61 - 2.74 (m, 1 H), 2.78 - 2.88 (m, 2 H), 3.14 (d, *J*=6.2 Hz, 2 H), 3.26 (q, *J*=6.6 Hz, 2 H), 4.08 - 4.17 (m, 1 H), 6.20 (t, *J*=2.0 Hz, 1 H), 7.37 - 7.44 (m, 1 H), 7.71 - 7.81 (m, 1 H)	**E**	m/z 335 $(M+H)^+$ (ES^+), at 3.59 min, UV inactive
1-69	Isomer 2: (2,2,2-$^2H_3$)ethyl 2-[4-(1*H*-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**302 and 305**	**j**	(400 MHz, DMSO-d_6) δ: 1.73 - 2.03 (m, 12 H), 2.61 - 2.74 (m, 1 H), 2.84 (d, *J*=7.8 Hz, 2 H), 3.14 (d, *J*=6.2 Hz, 2 H), 3.26 (q, *J*=6.6 Hz, 2 H), 3.96 (s, 2 H), 4.07 - 4.17 (m, 1 H), 6.20 (t, *J*=2.0 Hz, 1 H), 7.35 - 7.45 (m, 1 H), 7.68 - 7.80 (m, 1 H)	**E**	m/z 336 $(M+H)^+$ (ES^+), at 3.58 min, UV inactive
1-70	Isomer 2: ($^2H_5$)ethyl 2-[4-(1*H*-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**302 and 303**	**j**	(400 MHz, DMSO-d_6) δ: 1.73 - 2.03 (m, 12 H), 2.68 (t, *J*=7.4 Hz, 1 H), 2.84 (d, *J*=7.8 Hz, 2 H), 3.14 (d, *J*=6.2 Hz, 2 H), 3.22 - 3.29 (m, 2 H), 4.07 - 4.15 (m, 1 H), 6.20 (t, *J*=2.0 Hz, 1 H), 7.36 - 7.43 (m, 1 H), 7.75 (m, 1 H)	**E**	m/z 338 $(M+H)^+$ (ES^+), at 3.58 min, UV inactive
1-71	Isomer 2: (1,1-$^2H_2$)ethyl 2-[4-(1-methyl-1*H*-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**306 and 304**	**j**	(400 MHz, DMSO-d_6) δ: 1.13 (s, 3 H), 1.47 (q, *J*=11.8 Hz, 2 H), 1.65 - 1.94 (m, 8 H), 1.94 - 2.03 (m, 2 H), 2.56 - 2.72 (m, 2 H), 2.82 (d, *J*=11.3 Hz, 2 H), 3.13 (d, *J*=6.2 Hz, 2 H), 3.23 - 3.28 (m, 2 H), 3.68 - 3.74 (s, 3 H), 6.02 (s, 1 H), 7.25 (d, *J*=1.6 Hz, 1 H)	**E**	m/z 349 $(M+H)^+$ (ES^+), at 3.59 min, UV inactive
1-72	Isomer 2: (2,2,2-$^2H_3$)ethyl 2-[4-(1-methyl-1*H*-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**306 and 305**	**j**	(400 MHz, DMSO-d_6) δ: 1.47 (q, *J*=12.0 Hz, 2 H), 1.72 - 1.93 (m, 8 H), 1.93 - 2.03 (m, 2 H), 2.56 - 2.71 (m, 2 H), 2.82 (d, *J*=10.2 Hz, 2 H), 3.13 (d, *J*=5.9 Hz, 2 H), 3.22 - 3.29 (m, 2 H), 3.68 - 3.75 (s, 3 H), 3.96 (s, 2 H), 6.02 (s, 1 H), 7.25 (d, *J*=1.6 Hz, 1 H)	**E**	m/z 350 $(M+H)^+$ (ES^+), at 3.58 min, UV inactive

1-73	Isomer 2: ($^2H_5$)ethyl 2-[4-(1-methyl-1*H*-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**306 and 303**	**j**	(400 MHz, DMSO-d_6) δ: 1.40 - 1.54 (m, 2 H), 1.67 - 1.93 (m, 8 H), 1.94 - 2.05 (m, 2 H), 2.57 - 2.71 (m, 2 H), 2.82 (d, *J*=10.9 Hz, 2 H), 3.13 (d, *J*=5.9 Hz, 2 H), 3.22 - 3.28 (m, 2 H), 3.72 (s, 3 H), 6.02 (s, 1 H), 7.23 - 7.28 (m, 1 H)	**E**	m/z 352 $(M+H)^+$ (ES^+), at 3.56 min, UV inactive
2-1	Isomer 2: ethyl 2-[4-(pyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 53**	**m**	(400 MHz, DMSO-d_6) δ: 1.16 (t, J = 7.1 Hz, 3 H), 1.49 - 1.87 (m, 13 H), 1.97 (t, J = 9.2 Hz, 2 H), 2.55 - 2.85 (m, 9 H), 3.14 (d, J = 6.1 Hz, 2 H), 3.24 - 3.27 (m, 1 H), 4.00 (q, J = 7.1 Hz, 2 H), NH not observed	**F**	m/z 336 $(M+H)^+$ (ES+), at 1.70 min, UV inactive
2-2	Isomer 2: ethyl 2-[4-(1-formylpyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**122 and 63**	**k**	(400 MHz, $CDCl_3$) δ: 1.17 - 1.57 (m, 5 H), 1.59 - 2.30 (m, 14 H), 2.57 - 2.73 (m, 1 H), 2.84 - 3.01 (m, 2 H), 3.17 - 3.51 (m, 6 H), 3.55 - 3.75 (m, 2 H), 4.12 (q, J = 7.0 Hz, 2 H), 8.19 - 8.31 (m, 1 H)	**G**	m/z 364 $(M+H)^+$ (ES+), at 5.07 min, UV active
2-3	Isomer 2: ethyl 2-[4-(1-acetylpyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**122 and 60**	**m**	(400 MHz, $CDCl_3$) δ: 1.22 - 1.31 (m, 3 H), 1.53 - 1.77 (m, 11 H), 1.78 - 1.99 (m, 6 H), 2.00 - 2.12 (m, 5 H), 2.58 - 2.69 (m, 1 H), 2.84 - 2.99 (m, 2 H), 3.22 - 3.33 (m, 2 H), 3.34 - 3.53 (m, 3 H), 4.13 (q, J = 7.2 Hz, 2 H)	**G**	m/z 378 $(M+H)^+$ (ES+), at 5.22 min, UV active
2-4	Isomer 2: ethyl 2-{4-[1-(trifluoroacetyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**122 and 62**	**L**	(400 MHz, CD_3OD) δ: 1.27 (t, J = 7.1 Hz, 3 H), 1.30 - 1.68 (m, 6 H), 1.74 - 2.21 (m, 12 H), 2.75 - 2.90 (m, 1 H), 3.00 (d, J = 10.4 Hz, 2 H), 3.39 - 3.45 (m, 2 H), 3.51 - 3.61 (m, 1 H), 3.75 - 3.87 (m, 1 H), 4.11 (q, J = 7.1 Hz, 2 H), 4.15 - 4.23 (m, 1 H), 4.64 (br. s., 1 H)	**G**	m/z 432 $(M+H)^+$ (ES+), at 6.50 min, UV active
2-5	Isomer 2: methyl 2-[4-(1-propanoylpyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**323 and 54**	**m**	(400 MHz, DMSO-d_6) δ: 0.97 (t, J = 7.1 Hz, 3 H), 1.11 - 1.27 (m, 2 H), 1.36 - 1.62 (m, 4 H), 1.66 - 1.89 (m, 9 H), 1.93 - 2.02 (m, 2 H), 2.24 (q, J = 7.1 Hz, 2 H), 2.56 - 2.65 (m, 1 H), 2.74 - 2.86 (m, 2 H), 3.14 (d, J = 2.8 Hz, 2 H), 3.22 - 3.30 (m, 3 H), 3.39 - 3.47 (m, 1 H), 3.56 (s, 3 H), 3.84 - 3.92 (m, 1 H)	**G**	m/z 378 $(M+H)^+$ (ES+), at 5.21 min, UV active
2-6	Isomer 2: ethyl 2-[4-(1-propanoylpyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**122 and 54**	**m**	(400 MHz, DMSO-d_6) δ: 0.93 - 0.99 (m, 3 H), 1.16 (t, J = 7.0 Hz, 3 H), 1.20 - 1.27 (m, 1 H), 1.35 - 1.44 (m, 2 H), 1.45 - 1.62 (m, 2 H), 1.64 - 1.89 (m, 7 H), 1.90 - 2.01 (m, 2 H), 2.19 - 2.29 (m, 2 H), 2.54 - 2.63 (m, 3 H), 2.78 (d, J = 11.3 Hz, 2 H), 3.14 (d, J = 6.1 Hz, 2 H), 3.22 - 3.30 (m, 2 H), 3.39 - 3.48 (m, 3 H), 3.76 - 3.91 (m, 1 H), 3.99 (q, J = 7.0 Hz, 2	**G**	m/z 392 $(M+H)^+$ (ES+), at 5.27 min, UV active

				H)		
2-7	Isomer 2: ethyl 2-{4-[(2S)-1-propanoylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**54 and 127**	**m**	(400 MHz, 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)	**F**	m/z 392 $(M+H)^+$ (ES+), at 1.69 min, UV active
2-8	Isomer 2: ethyl 2-{4-[(2S)-1-(cyclopropylcarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**59 and 127**	**m**	(400 MHz, CD_3OD) δ: 0.73 - 0.87 (m, 3 H), 0.88 - 1.03 (m, 1 H), 1.24 (t, J = 7.2 Hz, 3 H), 1.30 - 1.46 (m, 2 H), 1.49 - 2.03 (m, 15 H), 2.04 - 2.15 (m, 2 H), 2.67 - 2.82 (m, 1 H), 2.89 - 3.01 (m, 2 H), 3.25 (s, 2 H), 3.34 - 3.42 (m, 2 H), 3.63 (s, 1 H), 4.01 - 4.15 (m, 3 H)	**E**	m/z 404 $(M+H)^+$ (ES+), at 3.49 min, UV inactive
2-9	Isomer 2: ethyl 2-{4-[(2S)-1-(cyclobutylcarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**60 and 127**	**m**	(400 MHz, CD_3OD) δ: 1.24 (t, J = 7.1 Hz, 3 H), 1.28 - 1.61 (m, 5 H), 1.66 - 2.28 (m, 20 H), 2.67 - 2.78 (m, 1 H), 2.88 - 2.99 (m, 2 H), 3.25 (s, 2 H), 3.35 - 3.52 (m, 3 H), 3.99 - 4.05 (m, 1 H), 4.09 (q, J = 7.1 Hz, 2 H)	**E**	m/z 418 $(M+H)^+$ (ES+), at 3.67 min, UV inactive
2-10	Isomer 2: methyl 2-{4-[1-(methoxycarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**55 and 323**	**m**	(400 MHz, DMSO-d_6) δ: 1.07 - 1.26 (m, 2 H), 1.38 - 1.49 (m, 2 H), 1.50 - 1.62 (m, 2 H), 1.69 - 1.78 (m, 6 H), 1.78 - 1.88 (m, 2 H), 1.93 - 2.01 (m, 2 H), 2.54 - 2.65 (m, 2 H), 2.80 (d, J = 10.1 Hz, 2 H), 3.15 (d, J = 2.8 Hz, 2 H), 3.24 – 3.31 (m, 2 H), 3.37 - 3.43 (m, 2 H), 3.53 - 3.60 (m, 6 H), 3.62 - 3.70 (m, 1 H)	**G**	m/z 380 $(M+H)^+$ (ES+), at 5.62 min, UV active
2-11	Isomer 2: ethyl 2-{4-[1-(methoxycarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**55 and 122**	**m**	(400 MHz, DMSO-d_6) δ: 1.09 - 1.28 (m, 6 H), 1.40 - 1.52 (m, 2 H), 1.70 - 1.88 (m, 8 H), 1.93 - 2.05 (m, 2 H), 2.53 - 2.59 (m, 3 H), 2.76 - 2.89 (m, 1 H), 3.10 - 3.31 (m, 7 H), 3.56 (s, 3 H), 3.63 - 3.70 (m, 1 H), 4.00 (q, J = 7.0 Hz, 2 H)	**G**	m/z 394 $(M+H)^+$ (ES+), at 5.74 min, UV active
2-12	Isomer 2: ethyl 2-{4-[(2S)-1-(methoxycarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**55 and 127**	**m**	(400 MHz, DMSO-d_6) δ: 1.07 - 1.29 (m, 6 H), 1.38 - 1.50 (m, 2 H), 1.50 - 1.63 (m, 2 H), 1.69 - 1.87 (m, 8 H), 1.92 - 2.03 (m, 2 H), 2.57 - 2.66 (m, 1 H), 2.80 (d, J = 10.4 Hz, 2 H), 3.14 (d, J = 5.8 Hz, 2 H), 3.27 (q, J = 6.5 Hz, 2 H), 3.38 - 3.43 (m, 2 H), 3.56 (s, 3 H), 3.67 (br. s., 1 H), 4.00 (q, J = 7.0 Hz, 2 H)	**F**	m/z 394 $(M+H)^+$ (ES+), at 1.73 min, UV active

2-13	Isomer 2: ethyl 2-{4-[(2R)-1-(methoxycarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**55 and 162**	**m**	(400 MHz, CD_3OD) δ: 1.24 (t, J = 7.1 Hz, 3 H), 1.29 - 1.46 (m, 2 H), 1.51 - 1.63 (m, 2 H), 1.66 - 1.97 (m, 11 H), 2.04 - 2.15 (m, 2 H), 2.73 (quin, J = 8.0 Hz, 1 H), 2.93 (d, J = 11.4 Hz, 2 H), 3.25 (app s, 3 H), 3.33 - 3.43 (m, 2 H), 3.44 - 3.55 (m, 1 H), 3.66 (s, 3 H), 3.72 - 3.84 (m, 1 H), 4.09 (q, J = 7.1 Hz, 2 H)	**E**	m/z 394 $(M+H)^+$ (ES+), at 4.30 min, UV inactive
2-14	Isomer 2: ethyl 2-{4-[1-(ethoxycarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**56 and 122**	**m**	(400 MHz, DMSO-d_6) δ: 1.11 - 1.21 (m, 6 H), 1.38 - 1.63 (m, 6 H), 1.67 - 1.87 (m, 9 H), 1.92 - 2.00 (m, 2 H), 2.55 - 2.67 (m, 2 H), 2.75 – 2.84 (m, 2 H), 3.09 – 3.22 (m, 3 H), 3.24 – 3.30 (m, 2 H), 3.62 – 3.69 (m, 1 H), 4.00 (m, 4 H)	**G**	m/z 408 $(M+H)^+$ (ES+) at 6.01 min, UV active
2-15	Isomer 2: methyl 2-{4-[(2S)-1-(methylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**57 and 157**	**m**	(400 MHz, CD_3OD) δ: 1.24 - 1.42 (m, 2 H), 1.51 - 1.64 (m, 2 H), 1.67 - 1.98 (m, 12 H), 2.09 (dd, J = 11.0, 7.6 Hz, 2 H), 2.68 - 2.77 (m, 4 H), 2.93 (d, J = 11.0 Hz, 2 H), 3.22 - 3.26 (m, 2 H), 3.35 - 3.41 (m, 3 H), 3.66 (s, 3 H), 3.82 - 3.91 (m, 1 H), NH not observed	**E**	m/z 379 $(M+H)^+$ (ES+), at 2.23 min, UV inactive
2-16	Isomer 2: ethyl 2-{4-[1-(methylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**57 and 122**	**m**	(400 MHz, DMSO-d_6) δ: 1.16 (t, J = 7.0 Hz, 3 H), 1.37 - 1.47 (m, 2 H), 1.49 - 1.63 (m, 3 H), 1.64 - 1.88 (m, 9 H), 1.92 – 2.03 (m, 2 H), 2.53 - 2.64 (m, 4 H), 2.73 – 2.85 (m, 2 H), 3.08 - 3.30 (m, 7 H), 3.67 - 3.76 (m, 1 H), 3.99 (q, J = 7.0 Hz, 2 H), 5.93 – 6.02 (m, 1 H)	**G**	m/z 393 $(M+H)^+$ (ES+) at 5.46 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 H), 3.82 - 3.89 (m, 1 H), 4.10 (q, J = 7.0 Hz, 2 H) NH not observed	**E**	m/z 393 $(M+H)^+$ (ES+), at 2.99 min, UV inactive
2-17	Isomer 2: 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: 1.24 (t, J = 7.1 Hz, 3 H), 1.27 - 1.42 (m, 2 H), 1.50 - 1.63 (m, 2 H), 1.67 - 1.96 (m, 12 H), 2.04 - 2.13 (m, 2 H), 2.66 - 2.78 (m, 4 H), 2.93 (d, J = 11.3 Hz, 2 H), 3.23 - 3.27 (m, 2 H), 3.34 - 3.41 (m, 3 H), 3.83 - 3.89 (m, 1 H), 4.09 (q, J = 7.1 Hz, 2 H)	**E**	m/z 393 $(M+H)^+$ (ES+), at 3.16 min, UV inactive
2-18	Isomer 2: ethyl 2-{4-[(2R)-1-	**57 and 162**	**m**	(400 MHz, CD_3OD) δ: 1.24 (t, J = 7.0 Hz, 3 H), 1.29 - 1.43 (m, 2 H), 1.50 - 1.65 (m, 2 H), 1.66 - 1.98 (m, 11 H), 2.09	**E**	m/z 393 $(M+H)^+$ (ES+), at 2.20 min, UV inactive

	(methylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate			(dd, J = 11.1, 7.6 Hz, 2 H), 2.67 - 2.77 (m, 4 H), 2.93 (d, J = 11.0 Hz, 2 H), 3.22 - 3.27 (m, 4 H), 3.35 - 3.42 (m, 2 H), 3.82 - 3.89 (m, 1 H), 4.09 (q, J = 7.0 Hz, 2 H), NH not observed		
2-19	Isomer 2: ethyl 2-{4-[1-(ethylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**122 and 158**	**q**	(400 MHz, $CDCl_3$) δ: 1.16 (t, J = 7.3 Hz, 3 H), 1.22 - 1.41 (m, 5 H), 1.50 - 1.74 (m, 4 H), 1.76 - 1.96 (m, 9 H), 1.99 – 2.10 (m, 2 H), 2.56 - 2.69 (m, 1 H), 2.82 – 2.98 (m, 2 H), 3.18 - 3.47 (m, 8 H), 3.86 - 3.97 (m, 1 H), 4.06 – 4.25 (m, 3 H)	**G**	m/z 407 $(M+H)^+$ (ES+) at 5.46 min, UV active
2-20	Isomer 2: ethyl 2-{4-[1-(dimethylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**58 and 122**	**m**	(400 MHz, DMSO-d_6) δ: 1.08 – 1,15 (m, 2 H), 1.16 (t, J = 7.0 Hz, 3 H), 1.36 - 1.63 (m, 7 H), 1.70 - 1.88 (m, 6 H), 1.93 – 2.01 (m, 2 H), 2.73 (s, 6 H), 2.78 - 2.87 (m, 2 H), 3.12 - 3.30 (m, 7 H), 3.87 - 3.95 (m, 1 H), 4.00 (q, J = 7.0 Hz, 2 H)	**G**	m/z 407 $(M+H)^+$ (ES+) at 5.81 min, UV active
2-21	Isomer 2: ethyl 2-{4-[(2S)-1-(dimethylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**58 and 127**	**m**	(400 MHz, DMSO-d_6) δ: 1.09 – 1,15 (m, 2 H), 1.16 (t, J = 7.0 Hz, 3 H), 1.38 - 1.69 (m, 7 H), 1.72 - 1.89 (m, 6 H), 1.93 – 2.03 (m, 2 H), 2.72 (s, 6 H), 2.78 - 2.82 (m, 2 H), 3.11 - 3.30 (m, 7 H), 3.86 - 3.95 (m, 1 H), 3.99 (q, J = 7.0 Hz, 2 H)	**G**	m/z 407 $(M+H)^+$ (ES+) at 5.92 min, UV active
2-22	Isomer 2: ethyl 2-[4-(1-methylpyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**122**	**o**	(400 MHz, CD_3OD) δ: 1.22 - 1.45 (m, 7 H), 1.54 - 1.87 (m, 8 H), 1.88 - 2.01 (m, 4 H), 2.08 - 2.17 (m, 2 H), 2.17 - 2.32 (m, 1 H), 2.35 (s, 3 H), 2.72 - 2.84 (m, 1 H), 2.93 - 3.02 (m, 2 H), 3.03 - 3.12 (m, 1 H), 3.28 (s, 2 H), 3.37 - 3.46 (m, 2 H), 4.11 (q, *J* = 7.0 Hz, 2 H)	**H**	m/z 350 $(M+H)^+$ (ES+), at 6.86 min, UV active at 202 nm
2-23	Isomer 2: ethyl 2-{4-[1-(*N*-methylglycyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**75 and 122**	**n**	(400 MHz, $CDCl_3$) δ: 1.16 - 1.39 (m, 4 H), 1.40 - 1.52 (m, 1 H), 1.54 - 1.75 (m, 3 H), 1.76 - 2.13 (m, 12 H), 2.45 (s, 3 H), 2.56 - 2.71 (m, 1 H), 2.82 - 2.97 (m, 2 H), 3.20 - 3.48 (m, 8 H), 4.07 - 4.20 (m, 3 H) NH not observed.	**H**	m/z 407 $(M+H)^+$ (ES+), at 5.77 min, UV inactive
2-24	Isomer 2: ethyl 2-{4-[1-(methoxycarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**76 and 122**	**m**	(400 MHz, $CDCl_3$) δ: 1.17 - 1.47 (m, 5 H), 1.48 - 2.27 (m, 15 H), 2.56 - 2.76 (m, 1 H), 2.85 - 3.02 (m, 2 H), 3.14 - 3.53 (m, 6 H), 3.74 (s, 3 H), 3.91 - 4.03 (m, 1 H), 4.06 - 4.19 (m, 2 H) NH not observed.	**H**	m/z 409 $(M+H)^+$ (ES+), at 5.23 min, UV active

2-25	Isomer 2: ethyl 2-{4-[(2*S*)-1-(propan-2-ylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**77 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.09 - 1.17 (m, 6 H), 1.24 (t, *J* = 7.0 Hz, 3 H), 1.28 - 1.44 (m, 2 H), 1.50 - 1.65 (m, 2 H), 1.66 - 1.99 (m, 11 H), 2.04 - 2.15 (m, 2 H), 2.68 - 2.79 (m, 1 H), 2.93 (d, *J* = 10.9 Hz, 2 H), 3.22 - 3.28 (m, 4 H), 3.38 (q, *J* = 6.6 Hz, 2 H), 3.85 - 3.94 (m, 2 H), 4.08 (q, *J* = 7.0 Hz, 2 H) NH not observed.	**E**	m/z 421 $(M+H)^+$ (ES+), at 4.15 min, UV inactive
2-26	Isomer 2: ethyl 2-(4-{(2*S*)-1-[(2,2,2-trifluoroethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**78 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.24 (t, *J* = 7.0 Hz, 3 H), 1.29 - 1.43 (m, 2 H), 1.48 - 1.65 (m, 2 H), 1.66 - 2.00 (m, 11 H), 2.04 - 2.14 (m, 2 H), 2.67 - 2.79 (m, 1 H), 2.94 (d, *J* = 11.3 Hz, 2 H), 3.25 (s, 3 H), 3.33 - 3.42 (m, 3 H), 3.63 - 3.78 (m, 1 H), 3.85 - 3.98 (m, 2 H), 4.09 (q, *J* = 7.0 Hz, 2 H) NH not observed.	**E**	m/z 461 $(M+H)^+$ (ES+), at 4.03 min, UV inactive
2-27	Isomer 2: ethyl 2-{4-[(2*S*)-1-(azetidin-1-ylcarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**79 and 127**	**q**	(400 MHz, DMSO-d_6) δ: 1.08 - 1.22 (m, 6 H), 1.38 - 1.89 (m, 13 H), 1.98 (br. s., 2 H), 2.07 - 2.20 (m, 2 H), 3.03 - 3.31 (m, 7 H), 3.67 (q, *J* = 7.6 Hz, 2 H), 3.79 - 3.88 (m, 1 H), 3.91 - 4.07 (m, 5 H)	**H**	m/z 419 $(M+H)^+$ (ES+), at 5.88 min, UV active at 202 nm
2-28	Isomer 2: ethyl 2-{4-[(2*S*)-1-(morpholin-4-ylcarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**80 and 127**	**q**	(400 MHz, DMSO-d_6) δ: 1.02 - 1.19 (m, 5 H), 1.33 - 1.61 (m, 7 H), 1.64 - 1.86 (m, 6 H), 1.93 (t, *J* = 9.2 Hz, 2 H), 2.52 - 2.62 (m, 1 H), 2.75 (d, *J* = 9.8 Hz, 2 H), 2.96 - 3.06 (m, 2 H), 3.08 - 3.28 (m, 7 H), 3.44 - 3.61 (m, 4 H), 3.87 - 4.00 (m, 3 H), 4.05 - 4.13 (m, 1 H)	**E**	m/z 449 $(M+H)^+$ (ES+), at 3.29 min, UV inactive
2-29	Isomer 2: ethyl 2-{4-[(2*S*)-1-(cyclopropylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**81 and 127**	**q**	(400 MHz, DMSO-d_6) δ: 0.28 - 0.40 (m, 2 H), 0.43 - 0.53 (m, 2 H), 1.02 - 1.24 (m, 5 H), 1.39 (t, *J* = 11.3 Hz, 2 H), 1.43 - 1.58 (m, 2 H), 1.58 - 1.85 (m, 6 H), 1.94 (t, *J* = 9.2 Hz, 2 H), 2.52 - 2.61 (m, 1 H), 2.76 (d, *J* = 11.3 Hz, 2 H), 3.07 - 3.19 (m, 7 H), 3.19 - 3.28 (m, 1 H), 3.66 - 3.76 (m, 1 H), 3.97 (q, *J* = 7.0 Hz, 2 H), 4.04 - 4.15 (m, 2 H), 6.09 (d, *J* = 2.7 Hz, 1 H)	**E**	m/z 419 $(M+H)^+$ (ES+), at 3.24 min, UV inactive
2-30	Isomer 2: ethyl 2-{4-[(2*S*)-1-(cyclobutylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-	**82 and 127**	**q**	(400 MHz, DMSO-d_6) δ: 1.02 - 1.22 (m, 5 H), 1.29 - 1.57 (m, 6 H), 1.58 - 1.98 (m, 10 H), 1.99 - 2.12 (m, 2 H), 2.51 - 2.60 (m, 1 H), 2.75 (d, *J* = 10.5 Hz, 2 H), 3.07 - 3.27 (m, 8 H), 3.71 (br. s., 1 H), 3.97 (q, *J* = 7.0 Hz, 2 H), 4.04 - 4.15 (m, 2 H), 6.13 (d, *J* = 8.2 Hz, 1 H)	**E**	m/z 433 $(M+H)^+$ (ES+), at 3.65 min, UV inactive

	carboxylate					
2-31	Isomer 2: ethyl 2-(4-{(2*S*)-1-[(2-methoxyethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**83 and 127**	**q**	(400 MHz, DMSO-d_6) δ: 1.01 - 1.26 (m, 5 H), 1.32 - 1.58 (m, 5 H), 1.59 - 1.86 (m, 8 H), 1.94 (t, *J* = 9.2 Hz, 2 H), 2.52 - 2.61 (m, 1 H), 2.76 (d, *J* = 10.5 Hz, 2 H), 3.02 - 3.28 (m, 13 H), 3.64 - 3.74 (m, 1 H), 3.97 (q, *J* = 7.0 Hz, 2 H), 6.01 (t, *J* = 5.5 Hz, 1 H)	E	m/z 437 $(M+H)^+$ (ES+), at 3.06 min, UV inactive
2-32	Isomer 2: ethyl 2-{4-[(2*S*)-1-(pyrrolidin-1-ylcarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**84 and 127**	**q**	(400 MHz, DMSO-d_6) δ: 1.01 - 1.18 (m, 5 H), 1.32 - 1.86 (m, 17 H), 1.93 (t, *J* = 9.2 Hz, 2 H), 2.52 - 2.61 (m, 1 H), 2.75 (d, *J* = 9.0 Hz, 2 H), 3.02 - 3.30 (m, 9 H), 3.84 - 3.92 (m, 1 H), 3.97 (q, *J* = 7.0 Hz, 2 H), 4.06 - 4.12 (m, 1 H)	E	m/z 433 $(M+H)^+$ (ES+), at 3.85 min, UV inactive
2-33	Isomer 1: ethyl 2-{4-[(2*S*)-1-(methoxycarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**76 and 127**	**q**	(400 MHz, $CDCl_3$) δ: 1.03 - 1.45 (m, 5 H), 1.47 - 2.24 (m, 16 H), 2.56 - 2.77 (m, 1 H), 2.92 (br. s., 2 H), 3.14 - 3.53 (m, 5 H), 3.75 (s, 3 H), 3.89 - 4.04 (m, 1 H), 4.12 (q, *J* = 6.8 Hz, 2 H) NH not observed.	I	m/z 409 $(M+H)^+$ (ES+), at 3.50 min, UV active at 202 nm
2-33	Isomer 2: ethyl 2-{4-[(2*S*)-1-(methoxycarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**76 and 127**	**q**	(400 MHz, $CDCl_3$) δ: 1.27 (t, *J* = 6.50 Hz, 3 H), 1.36 - 2.22 (m, 17 H), 2.76 (br. s., 1 H), 2.93 - 3.10 (m, 2 H), 3.16 - 3.26 (m, 1 H), 3.28 - 3.48 (m, 5 H), 3.74 (s, 3 H), 3.99 (d, *J* = 5.49 Hz, 1 H), 4.14 (q, *J* = 6.50 Hz, 2 H) NH not observed.	I	m/z 409 $(M+H)^+$ (ES+), at 3.64 min, UV active at 202 nm
2-34	Isomer 1: ethyl 2-(4-{(2*S*)-1-[methoxy(methyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**85 and 127**	**q**	(400 MHz, $CDCl_3$) δ: 1.15 - 1.48 (m, 8 H), 1.56 - 2.07 (m, 11 H), 2.09 - 2.39 (m, 5 H), 2.95 - 3.11 (m, 3 H), 3.19 - 3.54 (m, 6 H), 3.57 - 3.73 (m, 3 H), 4.04 - 4.20 (m, 2 H)	I	m/z 423 $(M+H)^+$ (ES+), at 4.17 min, UV active at 202 nm
2-34	Isomer 2: ethyl 2-(4-{(2*S*)-1-[methoxy(methyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-	**85 and 127**	**q**	(400 MHz, $CDCl_3$) δ: 1.19 - 1.37 (m, 7 H), 1.53 - 2.01 (m, 12 H), 2.10 - 2.27 (m, 2 H), 2.99 (s, 3 H), 3.29 - 3.45 (m, 6 H), 3.46 - 3.54 (m, 1 H), 3.59 - 3.67 (m, 3 H), 4.07 - 4.21 (m, 4 H)	I	m/z 423 $(M+H)^+$ (ES+), at 4.30 min, UV active at 202 nm

	yl)-6-azaspiro[3.4]octane-6-carboxylate					
2-35	Isomer 2: ethyl 2-(4-{(2*S*)-1-[(1-methylcyclobutyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**86 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.24 (t, *J* = 7.0 Hz, 3 H), 1.28 - 1.39 (m, 2 H), 1.43 (s, 3 H), 1.49 - 2.02 (m, 17 H), 2.03 - 2.14 (m, 2 H), 2.15 - 2.32 (m, 2 H), 2.73 (quin, *J* = 7.8 Hz, 1 H), 2.93 (d, *J* = 11.3 Hz, 2 H), 3.20 - 3.28 (m, 3 H), 3.33 - 3.44 (m, 3 H), 3.81 - 3.91 (m, 1 H), 4.09 (q, *J* = 7.0 Hz, 2 H) NH not observed.	**E**	m/z 447 $(M+H)^+$ (ES+), at 4.06 min, UV inactive
2-36	Isomer 2: ethyl 2-(4-{(2*S*)-1-[(3-methyloxetan-3-yl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**87 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.24 (t, *J* = 7.1 Hz, 3 H), 1.28 - 1.44 (m, 2 H), 1.50 - 1.65 (m, 5 H), 1.66 - 1.98 (m, 11 H), 2.04 - 2.14 (m, 2 H), 2.67 - 2.79 (m, 1 H), 2.93 (d, *J* = 11.3 Hz, 2 H), 3.21 - 3.27 (m, 3 H), 3.33 - 3.42 (m, 3 H), 3.81 - 3.89 (m, 1 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 4.38 (d, *J* = 7.0 Hz, 2 H), 4.72 (dd, *J* = 14.8, 7.0 Hz, 2 H) NH not observed.	**E**	m/z 449 $(M+H)^+$ (ES+), at 3.09 min, UV inactive
2-37	Isomer 2: ethyl 2-(4-{(2*S*)-1-[(3,3-difluoropyrrolidin-1-yl)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**88 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.24 (t, *J* = 7.0 Hz, 3 H), 1.27 - 1.40 (m, 2 H), 1.51 - 1.80 (m, 7 H), 1.81 - 1.98 (m, 6 H), 2.05 - 2.14 (m, 2 H), 2.28 - 2.45 (m, 2 H), 2.73 (quin, *J* = 7.9 Hz, 1 H), 2.93 (d, *J* = 10.9 Hz, 2 H), 3.25 (s, 3 H), 3.34 - 3.43 (m, 3 H), 3.43 - 3.57 (m, 2 H), 3.68 - 3.77 (m, 1 H), 3.82 - 3.97 (m, 1 H), 4.00 - 4.13 (m, 3 H)	**E**	m/z 469 $(M+H)^+$ (ES+), at 2.44 min, UV inactive
2-38	Isomer 2: ethyl 2-(4-{(2*S*)-1-[(3,3-difluorocyclobutyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**89 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.24 (t, *J* = 7.0 Hz, 3 H), 1.27 - 1.44 (m, 2 H), 1.49 - 1.64 (m, 2 H), 1.65 - 2.00 (m, 12 H), 2.02 - 2.14 (m, 2 H), 2.46 - 2.63 (m, 2 H), 2.73 (quin, *J* = 7.9 Hz, 1 H), 2.78 - 2.89 (m, 2 H), 2.93 (d, *J* = 11.7 Hz, 2 H), 3.22 - 3.28 (m, 2 H), 3.34 - 3.42 (m, 3 H), 3.84 - 3.92 (m, 1 H), 4.00 - 4.13 (m, 3 H) NH not observed.	**E**	m/z 469 $(M+H)^+$ (ES+), at 2.83 min, UV inactive
2-39	Isomer 2: ethyl 2-(4-{(2*S*)-1-[(3,3-difluoroazetidin-1-yl)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**90 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.24 (t, *J* = 7.0 Hz, 3 H), 1.27 - 1.40 (m, 2 H), 1.52 - 1.66 (m, 2 H), 1.67 - 1.98 (m, 11 H), 2.04 - 2.14 (m, 2 H), 2.74 (quin, *J* = 8.0 Hz, 1 H), 2.93 (d, *J* = 10.9 Hz, 2 H), 3.16 - 3.27 (m, 3 H), 3.34 - 3.43 (m, 3 H), 3.99 (q, *J* = 6.1 Hz, 1 H), 4.04 - 4.22 (m, 4 H), 4.36 - 4.49 (m, 2 H)	**E**	m/z 455 $(M+H)^+$ (ES+), at 2.83 min, UV inactive
2-40	Isomer 2: methyl 2-(4-{(2*S*)-1-[(2,2,2-trifluoroethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-	**78 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.26 - 1.44 (m, 2 H), 1.49 - 1.65 (m, 2 H), 1.66 - 1.99 (m, 12 H), 2.04 - 2.14 (m, 2 H), 2.67 - 2.82 (m, 1 H), 2.94 (d, *J* = 10.9 Hz, 2 H), 3.17 - 3.27 (m, 3 H), 3.35 - 3.43 (m, 2 H), 3.62 - 3.78 (m, 4 H), 3.86 - 4.00 (m, 2	**E**	m/z 447 $(M+H)^+$ (ES+), at 2.45 min, UV inactive

	azaspiro[3.4]octane-6-carboxylate			H) NH not observed.		
2-41	Isomer 2: methyl 2-(4-{(2*S*)-1-[(3,3-difluoroazetidin-1-yl)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**90 and 157**	**q**	(400 MHz, CD_3OD) δ: 1.26 - 1.42 (m, 2 H), 1.52 - 1.66 (m, 2 H), 1.68 - 1.99 (m, 11 H), 2.04 - 2.15 (m, 2 H), 2.73 (quin, *J* = 7.9 Hz, 1 H), 2.93 (d, *J* = 10.9 Hz, 2 H), 3.17 - 3.28 (m, 3 H), 3.34 - 3.44 (m, 3 H), 3.67 (s, 3 H), 3.94 - 4.04 (m, 1 H), 4.09 - 4.24 (m, 2 H), 4.36 - 4.51 (m, 2 H)	**E**	m/z 441 ($(M+H)^+$ (ES+), at 2.22 min, UV inactive
2-42	Isomer 1: ethyl 2-(4-{(2*S*)-1-[ethyl(propan-2-yl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**91 and 127**	**r**	(400 MHz, CD_3OD) δ: 1.02 - 1.12 (m, 6 H), 1.17 - 1.26 (m, 6 H), 1.28 - 1.40 (m, 2 H), 1.49 - 1.98 (m, 15 H), 2.05 - 2.15 (m, 3 H), 2.67 - 2.79 (m, 2 H), 2.85 - 2.96 (m, 3 H), 3.33 - 3.41 (m, 3 H), 3.88 - 4.00 (m, 1 H), 4.02 - 4.15 (m, 3 H)	**E**	m/z 449 $(M+H)^+$ (ES+), at 3.42 min, UV inactive
2-42	Isomer 2: ethyl 2-(4-{(2*S*)-1-[ethyl(propan-2-yl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**91 and 127**	**r**	(400 MHz, CD_3OD) δ: 1.00 - 1.12 (m, 6 H), 1.18 - 1.27 (m, 6 H), 1.27 - 1.43 (m, 3 H), 1.43 - 1.99 (m, 13 H), 2.04 - 2.14 (m, 2 H), 2.68 - 2.78 (m, 1 H), 2.85 - 2.98 (m, 3 H), 3.25 (br. s., 3 H), 3.37 (t, *J* = 6.8 Hz, 3 H), 3.88 - 4.00 (m, 1 H), 4.01 - 4.13 (m, 3 H)	**E**	m/z 449 $(M+H)^+$ (ES+), at 3.61 min, UV inactive
2-43	Isomer 2: ethyl 2-(4-{(2*S*)-1-[(cyclobutyloxy)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**92 and 127**	**m**	400 MHz, $CDCl_3$) δ: 0.78 - 0.95 (m, 5 H), 1.20 - 1.42 (m, 6 H), 1.49 - 2.17 (m, 15 H), 2.28 - 2.43 (m, 2 H), 2.57 - 2.71 (m, 1 H), 2.83 - 3.00 (m, 2 H), 3.19 - 3.61 (m, 4 H), 3.72 - 3.88 (m, 1 H), 4.13 (q, *J* = 7.02 Hz, 2 H), 4.88 - 5.04 (m, 1 H)	**I**	m/z 434 $(M+H)^+$ (ES+), at 5.19 min, UV active at 202 nm
2-44	Isomer 2: ethyl 2-(4-{(2*S*)-1-[(2-fluoroethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**93 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.24 (t, *J* = 7.0 Hz, 3 H), 1.28 - 1.45 (m, 2 H), 1.58 (t, *J* = 15.6 Hz, 2 H), 1.67 - 1.99 (m, 12 H), 2.04 - 2.15 (m, 2 H), 2.73 (quin, *J* = 7.9 Hz, 1 H), 2.93 (d, *J* = 11.3 Hz, 2 H), 3.25 (s, 2 H), 3.33 - 3.53 (m, 5 H), 3.84 - 3.92 (m, 1 H), 4.09 (q, *J* = 7.0 Hz, 2 H), 4.35 (t, *J* = 5.2 Hz, 1 H), 4.47 (t, *J* = 5.2 Hz, 1 H) NH not observed.	**E**	m/z 425 $(M+H)^+$ (ES+), at 3.24 min, UV inactive
2-45	Isomer 2: ethyl 2-(4-{(2*S*)-1-[(2,2-difluoroethyl)carbamoyl]pyr	**94 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.24 (t, *J* = 7.0 Hz, 3 H), 1.28 - 1.44 (m, 2 H), 1.50 - 1.64 (m, 2 H), 1.65 - 2.01 (m, 12 H), 2.02 - 2.15 (m, 2 H), 2.73 (quin, *J* = 7.8 Hz, 1 H), 2.93 (d, *J* = 11.3	**E**	m/z 443 $(M+H)^+$ (ES+), at 3.45 min, UV inactive

	rolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate			Hz, 2 H), 3.25 (s, 3 H), 3.33 - 3.60 (m, 4 H), 3.88 (d, *J* = 5.1 Hz, 1 H), 4.09 (q, *J* = 7.0 Hz, 2 H), 5.66 - 6.01 (m, 1 H) NH not observed.		
2-46	Isomer 2: ethyl 2-{4-[(2*S*)-1-(methoxyacetyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**95 and 127**	**m**	(400 MHz, $CDCl_3$) δ: 1.15 - 1.29 (m, 3 H), 1.30 - 1.52 (m, 4 H), 1.51 - 1.98 (m, 12 H), 2.00 - 2.15 (m, 3 H), 2.56 - 2.74 (m, 1 H), 2.80 - 3.00 (m, 2 H), 3.12 - 3.53 (m, 8 H), 3.94 - 4.20 (m, 4 H)	**I**	m/z 408 $(M+H)^+$ (ES+), at 3.58 min, UV active
2-47	Isomer 2: ethyl 2-(4-{(2*S*)-1-[(2-fluoroethoxy)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**96 and 127**	**s**	(400 MHz, $CDCl_3$) δ: 1.16 - 1.49 (m, 5 H), 1.50 - 2.17 (m, 17 H), 2.83 - 3.05 (m, 1 H), 3.16 - 3.64 (m, 6 H), 3.78 - 3.94 (m, 1 H), 4.13 (q, *J* = 6.5 Hz, 2 H), 4.24 - 4.48 (m, 2 H), 4.52 - 4.76 (m, 2 H)	**I**	m/z 426 $(M+H)^+$ (ES+), at 4.50 min, UV active at 202 nm
2-48	Isomer 2: ethyl 2-(4-{(2*S*)-1-[(2,2,2-trifluoroethoxy)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**97 and 127**	**s**	(400 MHz, $CDCl_3$) δ: 1.17 - 1.47 (m, 5 H), 1.49 - 2.33 (m, 15 H), 2.66 (d, *J* = 7.32 Hz, 1 H), 2.84 - 3.09 (m, 2 H), 3.19 - 3.46 (m, 5 H), 3.47 - 3.71 (m, 1 H), 3.84 (dd, *J* = 18.16, 4.4 Hz, 1 H), 4.11 (q, *J* = 7.0 Hz, 2 H), 4.32 - 4.67 (m, 2 H)	**I**	m/z 462 $(M+H)^+$ (ES+), at 5.07 min, UV active at 202 nm
2.49	Isomer 2: ethyl 2-(4-{(2*S*)-1-[(methylsulfanyl)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**98 and 127**	**s**	(400 MHz, $CDCl_3$) δ: 1.15 - 1.45 (m, 5 H), 1.46 - 1.76 (m, 9 H), 1.79 - 2.13 (m, 9 H), 2.35 (s, 3 H), 2.58 - 2.72 (m, 1 H), 2.85 - 3.02 (m, 2 H), 3.21 - 3.57 (m, 4 H), 4.13 (q, *J* = 6.8 Hz, 2 H)	**I**	m/z 410 $(M+H)^+$ (ES+), at 4.74 min, UV active at 202 nm
2-50	Isomer 2: ethyl 2-(4-{(2*S*)-1-[(2-methoxyethoxy)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**99 and 127**	**m**	(400 MHz, $CDCl_3$) δ: 1.17 - 1.31 (m, 3 H), 1.35 - 1.51 (m, 2 H), 1.52 - 2.17 (m, 18 H), 2.90 - 3.14 (m, 2 H), 3.21 - 3.47 (m, 7 H), 3.48 - 3.65 (m, 2 H), 3.76 - 3.91 (m, 1 H), 4.13 (q, *J* = 6.8 Hz, 2 H), 4.18 - 4.33 (m, 2 H)	**I**	m/z 438 $(M+H)^+$ (ES+), at 4.33 min, UV active at 202 nm
2-51	Isomer 2: ethyl 2-{4-[(2*S*)-1-{[2-(dimethylamino)ethoxy]car	**100 and 127**	**m**	(400 MHz, $CDCl_3$) δ: 1.15 - 1.49 (m, 6 H), 1.51 - 2.18 (m, 14 H), 2.32 (s, 6 H), 2.52 - 2.80 (m, 3 H), 2.85 - 3.05 (m, 2 H), 3.14 - 3.63 (m, 7 H), 4.07 - 4.27 (m, 4 H)	**I**	m/z 451 $(M+H)^+$ (ES+), at 4.22 min, UV active at 202 nm

	bonyl}pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate					
2-52	Isomer 2: ethyl 2-{4-[(2*S*)-1-(hydroxyacetyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**101 and 127**	**t**	(400 MHz, $CDCl_3$) δ: 1.14 - 1.51 (m, 7 H), 1.52 - 1.77 (m, 3 H), 1.77 - 2.21 (m, 10 H), 2.62 (d, *J* = 10.1 Hz, 1 H), 2.90 (d, *J* = 10.1 Hz, 2 H), 3.16 - 3.69 (m, 7 H), 3.98 - 4.28 (m, 4 H) OH not observed.	**I**	m/z 394 $(M+H)^+$ (ES+), at 3.66 min, UV active at 202 nm
2-53	Isomer 2: ethyl 2-{4-[(2*S*)-1-(3,3,3-trifluoropropanoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**102 and 127**	**u**	(400 MHz, CD_3OD) δ: 1.21 - 1.36 (m, 4 H), 1.44 - 1.66 (m, 2 H), 1.77 (d, *J* = 12.8 Hz, 2 H), 1.85 - 2.08 (m, 8 H), 2.10 - 2.23 (m, 2 H), 2.23 - 2.32 (m, 2 H), 2.39 (br. s., 2 H), 3.25 - 3.31 (m, 2 H), 3.38 - 3.70 (m, 7 H), 4.06 - 4.17 (m, 3 H)	**I**	m/z 446 $(M+H)^+$ (ES+), at 4.42 min, UV active at 202 nm
2-54	Isomer 1: ethyl 2-(4-{(2*S*)-1-[(pyridin-2-ylmethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**103 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.20 - 1.28 (m, 3 H), 1.29 - 1.47 (m, 2 H), 1.60 (t, *J* = 12.3 Hz, 2 H), 1.67 - 2.03 (m, 12 H), 2.04 - 2.18 (m, 2 H), 2.65 - 2.79 (m, 1 H), 2.94 (d, *J* = 9.0 Hz, 2 H), 3.33 - 3.51 (m, 5 H), 3.91 (q, *J* = 5.5 Hz, 1 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 4.36 - 4.55 (m, 2 H), 7.28 (dd, *J* = 7.4, 5.1 Hz, 1 H), 7.38 (d, *J* = 7.4 Hz, 1 H), 7.79 (ddd, *J* = 7.4, 1.6 Hz, 1 H), 8.45 (d, *J* = 5.1 Hz, 1 H) NH not observed.	**E**	m/z 470 $(M+H)^+$ (ES+), at 2.99 min, UV inactive
2-54	Isomer 2: ethyl 2-(4-{(2*S*)-1-[(pyridin-2-ylmethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**103 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.24 (t, *J* = 7.0 Hz, 3 H), 1.28 - 1.46 (m, 2 H), 1.60 (t, *J* = 12.3 Hz, 1 H), 1.67 - 2.02 (m, 11 H), 2.09 (t, *J* = 9.6 Hz, 2 H), 2.73 (quin, *J* = 7.9 Hz, 1 H), 2.94 (d, *J* = 8.6 Hz, 2 H), 3.25 (s, 2 H), 3.33 - 3.52 (m, 5 H), 3.91 (d, *J* = 5.5 Hz, 1 H), 4.03 - 4.14 (m, 2 H), 4.36 - 4.55 (m, 2 H), 7.28 (dd, *J* = 7.6, 5.27 Hz, 1 H), 7.38 (d, *J* = 7.6 Hz, 1 H), 7.79 (ddd, *J* = 7.6, 1.6 Hz, 1 H), 8.45 (d, *J* = 5.3 Hz, 1 H) NH not observed.	**E**	m/z 470 $(M+H)^+$ (ES+), at 3.17 min, UV inactive
2-55	Isomer 1: ethyl 2-(4-{(2*S*)-1-[methyl(2,2,2-trifluoroethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**104 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.16 - 1.28 (m, 3 H), 1.29 - 1.49 (m, 2 H), 1.51 - 1.80 (m, 6 H), 1.81 - 2.02 (m, 8 H), 2.10 (t, *J* = 8.2 Hz, 2 H), 2.65 - 2.79 (m, 1 H), 2.87 - 2.98 (m, 2 H), 3.01 - 3.16 (m, 3 H), 3.25 (s, 1 H), 3.33 - 3.51 (m, 5 H), 3.96 - 4.18 (m, 3 H), 4.47 - 4.70 (m, 1 H)	**E**	m/z 475 $(M+H)^+$ (ES+), at 4.02 min, UV inactive

2-55	Isomer 2: ethyl 2-(4-{(2*S*)-1-[methyl(2,2,2-trifluoroethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**104 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.24 (t, *J* = 7.2 Hz, 3 H), 1.28 - 1.42 (m, 2 H), 1.51 - 1.80 (m, 6 H), 1.82 - 2.03 (m, 6 H), 2.09 (t, *J* = 9.8 Hz, 2 H), 2.66 - 2.79 (m, 1 H), 2.93 (d, *J* = 9.8 Hz, 2 H), 3.04 (s, 3 H), 3.25 (s, 2 H), 3.33 - 3.50 (m, 6 H), 4.01 - 4.15 (m, 3 H), 4.53 - 4.68 (m, 1 H)	**E**	m/z 475 $(M+H)^+$ (ES+), at 4.17 min, UV inactive
2-56	Isomer 2: ethyl 2-{4-[(2*S*)-1-(oxetan-3-ylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**105 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.24 (t, *J* = 7.0 Hz, 3 H), 1.27 - 1.42 (m, 2 H), 1.48 - 1.64 (m, 2 H), 1.66 - 1.99 (m, 11 H), 2.02 - 2.14 (m, 2 H), 2.72 (quin, *J* = 7.9 Hz, 1 H), 2.93 (d, *J* = 11.3 Hz, 2 H), 3.25 (s, 2 H), 3.33 - 3.43 (m, 4 H), 3.89 (q, *J* = 5.3 Hz, 1 H), 4.08 (q, *J* = 7.0 Hz, 2 H), 4.55 - 4.63 (m, 2 H), 4.78 - 4.86 (m, 3 H) NH not observed.	**E**	m/z 435 $(M+H)^+$ (ES+), at 2.82 min, UV inactive
2-57	Isomer 2: ethyl 2-(4-{(2*S*)-1-[methyl(oxetan-3-yl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**106 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.24 (t, *J* = 7.2 Hz, 3 H), 1.27 - 1.43 (m, 2 H), 1.48 - 1.79 (m, 7 H), 1.81 - 2.00 (m, 7 H), 2.03 - 2.15 (m, 2 H), 2.72 (quin, *J* = 7.8 Hz, 1 H), 2.81 - 2.99 (m, 4 H), 3.25 (s, 2 H), 3.33 - 3.45 (m, 4 H), 3.97 - 4.13 (m, 3 H), 4.56 - 4.84 (m, 5 H) NH not observed.	**E**	m/z 449 $(M+H)^+$ (ES+), at 3.20 min, UV inactive
2-58	Isomer 2: ethyl 2-{4-[(2*S*)-1-propanethioylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**Example 2-7 and 107**	**v**	(400 MHz, CD_3OD) δ: 1.18 - 1.32 (m, 6 H), 1.36 - 1.62 (m, 4 H), 1.62 - 1.82 (m, 2 H), 1.83 - 2.16 (m, 10 H), 2.54 (br. s., 1 H), 2.65 - 2.82 (m, 3 H), 2.93 (d, *J* = 10.9 Hz, 2 H), 3.25 (s, 2 H), 3.38 (q, *J* = 6.6 Hz, 2 H), 3.56 - 3.67 (m, 1 H), 3.75 - 3.86 (m, 1 H), 4.09 (q, *J* = 7.0 Hz, 2 H), 4.62 - 4.73 (m, 1 H)	**E**	m/z 408 $(M+H)^+$ (ES+), at 3.82 min, UV inactive
2-59	Isomer 2: ethyl 2-{4-[(2*S*,4*S*)-4-fluoro-1-propanoylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2, 54 and 112**	**ap and m**	(400 MHz, CD_3OD) δ: 1.05 - 1.15 (m, 3 H), 1.24 (t, *J* = 7.0 Hz, 3 H), 1.27 - 1.51 (m, 2 H), 1.52 - 1.97 (m, 9 H), 1.98 - 2.27 (m, 4 H), 2.27 - 2.48 (m, 2 H), 2.66 - 2.79 (m, 1 H), 2.87 - 3.01 (m, 2 H), 3.25 (s, 2 H), 3.34 - 3.45 (m, 2 H), 3.61 - 3.75 (m, 1 H), 3.83 - 4.00 (m, 1 H), 4.03 - 4.21 (m, 3 H), 5.19 - 5.40 (m, 1 H)	**E**	m/z 410 $(M+H)^+$ (ES+), at 3.32 min, UV inactive
2-60	Isomer 2: ethyl 2-{4-[(2*S*)-4,4-difluoro-1-propanoylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2, 54 and 113**	**ap and m**	(400 MHz, CD_3OD) δ: 1.04 - 1.16 (m, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.27 - 1.43 (m, 3 H), 1.51 - 1.82 (m, 4 H), 1.83 - 2.01 (m, 5 H), 2.04 - 2.15 (m, 2 H), 2.23 - 2.54 (m, 4 H), 2.67 - 2.80 (m, 1 H), 2.87 - 3.02 (m, 2 H), 3.25 (s, 2 H), 3.38 (q, *J* = 6.6 Hz, 2 H), 3.71 - 4.05 (m, 1 H), 4.09 (q, *J* = 7.0 Hz, 2 H), 4.14 - 4.36 (m, 1 H)	**E**	m/z 428 $(M+H)^+$ (ES+), at 3.52 min, UV inactive

2-61	Isomer 2: ethyl 2-{4-[(2*S*)-1-ethylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**114 and 127**	**w**	(400 MHz, DMSO-d_6) δ: 0.99 (t, *J* = 7.2 Hz, 3 H), 1.06 - 1.26 (m, 5 H), 1.30 - 1.41 (m, 1 H), 1.42 - 1.66 (m, 7 H), 1.67 - 1.89 (m, 4 H), 1.90 - 2.10 (m, 4 H), 2.13 - 2.22 (m, 1 H), 2.55 - 2.64 (m, 1 H), 2.65 - 2.85 (m, 3 H), 3.02 (t, *J* = 7.5 Hz, 1 H), 3.14 (d, *J* = 6.1 Hz, 2 H), 3.27 (q, *J* = 6.8 Hz, 2 H), 3.54 - 3.67 (m, 1 H), 4.00 (q, *J* = 7.2 Hz, 2 H)	**K**	m/z 364 $(M+H)^+$ (ES+), at 5.60 min, UV active at 202 nm
2-62	Isomer 2: ethyl 2-(4-{(2*S*)-1-[3-(pyridin-2-yl)propanoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**116 and 127**	**x**	(400 MHz, CD_3OD) δ: 1.17 - 1.42 (m, 5 H), 1.43 - 1.59 (m, 2 H), 1.60 - 1.98 (m, 11 H), 2.08 (t, *J* = 9.6 Hz, 2 H), 2.65 - 2.97 (m, 5 H), 3.01 - 3.17 (m, 2 H), 3.17 - 3.28 (m, 2 H), 3.38 (q, *J* = 6.6 Hz, 3 H), 3.49 - 3.65 (m, 1 H), 3.96 - 4.04 (m, 1 H), 4.09 (q, *J* = 7.2 Hz, 2 H), 7.21 - 7.28 (m, 1 H), 7.30 - 7.36 (m, 1 H), 7.73 (ddd, *J* = 7.6, 1.6 Hz, 1 H), 8.40 - 8.48 (m, 1 H)	**E**	m/z 469 $(M+H)^+$ (ES+), at 3.32 min, UV inactive
2-63	Isomer 2: ethyl 2-(4-{(2*S*)-1-[methyl(pyridin-2-ylmethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**117 and 127**	**q**	(400 MHz, CD_3OD) δ: 1.24 (t, *J* = 7.0 Hz, 3 H), 1.27 - 1.42 (m, 2 H), 1.51 (d, *J* = 11.7 Hz, 1 H), 1.57 - 1.80 (m, 6 H), 1.82 - 2.02 (m, 7 H), 2.04 - 2.14 (m, 2 H), 2.73 (quin, *J* = 7.9 Hz, 1 H), 2.84 - 2.97 (m, 5 H), 3.25 (s, 2 H), 3.38 (q, *J* = 6.6 Hz, 2 H), 3.47 (t, *J* = 7.8 Hz, 1 H), 4.09 (q, *J* = 7.0 Hz, 3 H), 4.42 (d, *J* = 16.4 Hz, 1 H), 4.64 (d, *J* = 16.4 Hz, 1 H), 7.31 (dd, *J* = 7.2, 5.00 Hz, 1 H), 7.37 (d, *J* = 7.8 Hz, 1 H), 7.82 (dd, *J* = 7.8, 7.20 Hz, 1 H), 8.49 (d, *J* = 5.0 Hz, 1 H)	**E**	m/z 484 $(M+H)^+$ (ES+), at 3.72 min, UV inactive
2-64	Isomer 2: ethyl 2-(4-{(2*S*)-1-[(pyridin-2-ylmethoxy)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**118 and 127**	**q**	(300 MHz, CD_3OD) δ: 1.20 - 1.47 (m, 5 H), 1.50 - 2.02 (m, 12 H), 2.04 - 2.19 (m, 2 H), 2.66 - 2.82 (m, 1 H), 2.94 (d, *J* = 10.4 Hz, 2 H), 3.26 (s, 2 H), 3.37 - 3.46 (m, 3 H), 3.51 - 3.68 (m, 1 H), 3.79 - 3.95 (m, 1 H), 3.99 - 4.19 (m, 3 H), 5.20 (s, 2 H), 7.31 - 7.41 (m, 1 H), 7.48 (d, *J* = 7.8 Hz, 1 H), 7.87 (dd, *J* = 7.8, 7.7 Hz, 1 H), 8.47 - 8.57 (m, 1 H)	**E**	m/z 471 $(M+H)^+$ (ES+), at 3.69 min, UV inactive
2-65	Isomer 2: ethyl 2-{4-[(2*S*)-1-{*N*-[(benzyloxy)carbonyl]-β-alanyl}pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**127, 222 and 226**	**y**	(400 MHz, $CDCl_3$) δ: 1.25 (t, J = 8.2 Hz, 3H), 1.34 - 1.48 (m, 4H), 1.52 - 2.21 (m, 9H), 2.37 – 2.71 (m, 4H), 2.91 – 3.05 (m, 3H), 3.19 - 3.59 (m, 9H), 4.04 – 4.19 (m, 4H), 5.10 (s, 2H), 5.64 (s, 1H), 7.28 - 7.42 (m, 5H).	**I**	m/z 541 $(M+H)^+$ (ES+), at 4.51 min, UV active
2-66	Isomer 2: ethyl 2-{4-[(2*S*)-1-(β-alanyl)pyrrolidin-2-yl]piperidin-1-yl}-6-	**127, 222 and 226**	**y**	(400 MHz, DMSO-d_6) δ: 1.14 - 1.26 (m, 6H), 1.35 - 1.63 (m, 4H), 1.65 - 1.88 (m, 9H), 1.97 - 1.99 (m, 2H), 2.32 - 2.69 (m, 4H), 2.76 - 2.83 (m, 3H), 3.08 – 3.56 (m, 7H), 3.91 - 3.96	**I**	m/z 407 $(M+H)^+$ (ES+), at 3.70 min, UV inactive

	azaspiro[3.4]octane-6-carboxylate			(m, 1H), 3.99 (q, J = 7.0 Hz, 2H).		
2-67	Isomer 2: ethyl 2-{4-[(2*S*)-1-{[2-(methylamino)ethoxy]carbonyl}pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**127, 234 and 235**	**n**	(400 MHz, CD_3OD) δ: 1.31 - 1.34 (m, 3H), 1.41 - 1.47 (m, 2H), 1.85 - 2.01 (m, 9H), 2.34 - 2.36 (m, 5H), 2.77 - 2.79 (m, 6H), 3.32 - 3.34 (m, 6H), 3.33 - 3.37 (m, 2H), 3.41 - 3.43 (m, 2H), 3.62 - 3.73 (m, 1H), 3.86 - 3.90 (m, 2H), 4.12 - 4.14 (m, 2H).	**I**	m/z 437 $(M+H)^+$ (ES+), at 4.10 min, UV inactive
2-68	Isomer 2: ethyl 2-{4-[(2*S*)-1-(2-fluoroethyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**127 and 240**	**z**	(400 MHz, DMSO-d_6) δ: 1.03 - 1.22 (m, 5H), 1.30 - 1.41 (m, 1H), 1.42 - 1.68 (m, 8H), 1.69 - 1.78 (m, 2H), 1.78 - 1.88 (m, 2H), 1.92 – 2.01 (m, 2H), 2.09 – 2.20 (m, 1H), 2.24 - 2.43 (m, 2H), 2.44 – 2.69 (m, 2H), 2.74 - 2.85 (m, 2H), 2.88 – 3.17 (m, 3H), 3.23 – 3.31 (m, 2H), 3.99 (q, J = 7.0 Hz, 2H), 4.33 - 4.66 (m, 2H).	**I**	m/z 382 $(M+H)^+$ (ES+), at 4.71 min, UV inactive
2-69	Isomer 2: ethyl 2-{4-[(2*S*)-1-(2,2,2-trifluoroethyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**127 and 237**	**aa**	(400 MHz, CD_3OD) δ: 1.27 (t, J = 7.2 Hz, 3H), 1.29 – 1.54 (m, 2H), 1.60 - 1.71 (m, 3H), 1.72 - 1.85 (m, 5H), 1.90 - 2.01 (m, 4H), 2.09 - 2.17 (m, 2H), 2.42 - 2.50 (m, 1H), 2.55 - 2.65 (m, 1H), 2.76 - 2.83 (m, 1H), 2.95 - 3.05 (m, 3H), 3.20 - 3.31 (m, 3H), 3.36 - 3.39 (m, 2H), 3.39 - 3.44 (m, 2H), 4.11 (q, J = 7.2 Hz, 2H).	**I**	m/z 418 $(M+H)^+$ (ES+), at 5.11 min, UV inactive
2-70	Isomer 1: ethyl 2-{4-[(2*S*)-1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**127 and 236**	**ab**	(400 MHz, CD_3OD) δ: 1.23 - 1.40 (m, 6H), 1.45 - 1.54 (m, 1H), 1.62 - 1.71 (m, 3H), 1.72 - 1.83 (m, 4H), 1.85 - 1.97 (m, 5H), 2.08 - 2.21 (m, 3H), 2.35 - 2.46 (m, 3H), 2.73 - 2.80 (m, 1H), 2.92 - 3.02 (m, 3H), 3.09 – 3.15 (m, 1H), 3.32 – 3.44 (m, 4H), 4.13 (q, J = 7.0 Hz, 2H).	**I**	m/z 432 $(M+H)^+$ (ES+), at 5.54 min, UV inactive
2-70	Isomer 2: ethyl 2-{4-[(2*S*)-1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**127 and 236**	**ab**	(400 MHz, CD_3OD) δ: 1.27 (t, J = 7.2 Hz, 3H), 1.30 - 1.39 (m, 3H), 1.46 - 1.55 (m, 1H), 1.61 – 1.69 (m, 2H), 1.74 - 1.84 (m, 4H), 1.90 - 1.99 (m, 4H), 2.09 - 2.23 (m, 3H), 2.31 - 2.47 (m, 4H), 2.73 - 2.82 (m, 1H), 2.95 - 3.03 (m, 3H), 3.09 - 3.16 (m, 1H), 3.28 (s, 2H), 3.37 – 3.43 (m, 3H), 4.11 (q, J = 7.2 Hz, 2H).	**I**	m/z 432 $(M+H)^+$ (ES+), at 5.39 min, UV inactive
2-71	Isomer 2: ethyl 2-{4-[(2*S*)-1-(2-methoxyethyl)pyrrolidin-2-yl]piperidin-1-yl}-6-	**127 and 231**	**w**	(400 MHz, CD_3OD) δ: 1.21 – 1.42 (m, 9H), 1.54 - 1.99 (m, 12H), 2.07 – 2.18 (m, 2H), 2.26 - 2.51 (m, 2H), 2.76 – 2.85 (m, 1H), 2.95 – 3.09 (m, 2H), 3.16 – 3.44 (m, 7H) 3.52 - 3.59 (m, 2H), 4.11 (q, J=7.0 Hz, 2H).	**I**	m/z 394 $(M+H)^+$ (ES+), at 4.55 min, UV inactive

	azaspiro[3.4]octane-6-carboxylate					
2-72	Isomer 2: ethyl 2-{4-[(2*S*)-1-(2-methoxy-2-oxoethyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**127 and 233**	**ac**	(400 MHz, CD_3OD) δ: 1.22 - 1.29 (m, 4H), 1.30 - 1.38 (m, 2H), 1.45 - 1.54 (m, 2H), 1.64 - 1.85 (m, 7H), 1.92 - 2.00 (m, 3H), 2.09 - 2.17 (m, 2H), 2.40 - 2.48 (m, 2H), 2.54 - 2.59 (m, 2H), 2.88 - 3.04 (m, 3H), 3.18 - 3.22 (m, 2H), 3.23 - 3.25 (m, 2H), 3.38 - 3.45 (m, 1H), 3.53 - 3.60 (m, 2H), 3.69 - 3.73 (m, 1H), 4.08 - 4.15 (m, 2H).	**I**	m/z 408 $(M+H)^+$ (ES+), at 4.56 min, UV inactive
2-73	Isomer 1: ethyl 2-(4-{(2*S*)-1-[2-(dimethylamino)-2-oxoethyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**127 and 238**	**ad**	(400 MHz, CD_3OD) δ: 1.20 – 1.43 (m, 9H), 1.52 - 1.81 (m, 7H), 1.84 - 1.98 (m, 5H), 2.12 - 2.22 (m, 1H), 2.33 - 2.41 (m, 1H), 2.53 - 2.57 (m, 1H), 2.84 - 2.90 (m, 1H), 2.94 (s, 2H), 3.00 - 3.06 (m, 2H), 3.13 (s, 1H), 3.19 - 3.21 (m, 2H), 3.22 - 3.27 (m, 1H), 3.36 - 3.42 (m, 4H), 3.55 - 3.63 (m, 1H), 4.13 (d, J = 7.1 Hz, 2H).	**I**	m/z 421 $(M+H)^+$ (ES+), at 3.94 min, UV inactive
2-73	Isomer 2: ethyl 2-(4-{(2*S*)-1-[2-(dimethylamino)-2-oxoethyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate	**127 and 238**	**ad**	(400 MHz, CD_3OD) δ: 1.21 – 1.44 (m, 8H), 1.54 – 2.03 (m, 12H), 2.10 - 2.24 (m, 2H), 2.31 - 2.43 (m, 1H), 2.53 - 2.59 (m, 1H), 2.84 - 2.90 (m, 1H), 2.94 (s, 2H), 3.02 - 3.12 (m, 2H), 3.13 (s, 1H), 3.23 - 3.30 (m, 3H), 3.36 - 3.46 (m, 4H), 3.54 - 3.63 (m, 1H), 4.11 (d, J = 7.10 Hz, 2H).	**I**	m/z 421 $(M+H)^+$ (ES+), at 4.06 min, UV inactive
2-74	Isomer 2: ethyl 2-{4-[(2*S*)-1-benzylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**127 and 232**	**w**	(400 MHz, DMSO-d_6) δ: 1.07 - 1.22 (m, 5H), 1.44 - 1.72 (m, 9H), 1.73 - 1.76 (m, 4H), 1.93 - 2.07 (m, 2H), 2.32 - 2.88 (m, 6H), 3.05 - 3.28 (m, 5H), 3.87- 4.17 (m, 3H), 7.18 - 7.37 (m, 5H).	**I**	m/z 426 $(M+H)^+$ (ES+), at 6.30 min, UV active
2-75	Isomer 2: ethyl 2-{4-[(2*S*)-1-(methylcarbamothioyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**127 and 239**	**m**	(400 MHz, DMSO-d_6) δ: 1.16 (t, J = 7.17, 3H), 1.22 - 1.54 (m, 5H), 1.70 - 1.86 (m, 9H), 1.90 – 2.03 (m, 3H), 2.64 - 2.75 (m, 6H), 3.11 - 3.45 (m, 6H), 4.00 (q, J = 7.0 Hz, 2H) 4.29 (s, 1H), 7.23 (s, 1H).	**I**	m/z 409 $(M+H)^+$ (ES+), at 4.10 min, UV inactive
2-76	Isomer 1: ethyl 2-{4-[2-(methylcarbamoyl)-2,3-dihydro-1*H*-isoindol-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-	**2, 243 and 244**	**ae**	(400 MHz, DMSO-d_6) δ: 1.13 (t, J = 7.1 Hz, 3H), 1.27 - 1.57 (m, 5H), 1.56 - 1.76 (m, 4H), 1.83 - 2.01 (m, 3H), 2.57 - 2.70 (m, 5H), 2.70 – 2.81 (m, 1H), 3.10 - 3.25 (m, 4H), 3.97 (q, *J* = 7.1 Hz, 2H), 4.36 - 4.48 (m, 1H), 4.51 – 4.65 (m, 1H), 4.96 - 5.09 (m, 1H), 6.19 – 6.30 (m, 1H), 7.16 - 7.37 (m, 4H).	**M**	m/z 441 $(M+H)^+$ (ES+), at 1.97 min, UV active

	carboxylate					
2-76	Isomer 2: ethyl 2-{4-[2-(methylcarbamoyl)-2,3-dihydro-1*H*-isoindol-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2, 243 and 244**	**ae**	(400 MHz, DMSO-d_6) δ: 1.12 (t, J = 7.1 Hz, 3H), 1.28 - 1.57 (m, 4H), 1.57 - 1.72 (m, 2H), 1.72 – 1.83 (m, 2H), 1.83 - 2.01 (m, 3H), 2.27 – 2.34 (m, 1H), 2.57 - 2.69 (m, 6H), 2.71 – 2.80 (m, 1H), 3.01 – 3.12 (m, 2H), 3.16 - 3.28 (m, 2H), 3.95 (q, *J* = 7.1 Hz, 2H), 4.38 - 4.49 (m, 1H), 4.52 – 4.64 (m, 1H), 4.97 - 5.10 (m, 1H), 6.20 – 6.31 (m, 1H), 7.20 - 7.37 (m, 4H).	**M**	m/z 441 $(M+H)^+$ (ES+), at 1.99 min, UV active
2-77	Isomer 2: ethyl 2-{4-[(2S)-1-phenylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**127 and 172**	**af**	(400 MHz, CD_3OD) δ: 1.24 (td, J=7.0, 1.5 Hz, 3 H), 1.32 - 1.49 (m, 2 H), 1.53 - 1.62 (m, 1 H), 1.63 - 1.73 (m, 2 H), 1.75 - 1.85 (m, 2 H), 1.85 - 2.03 (m, 8 H), 2.04 - 2.15 (m, 2 H), 2.68 - 2.81 (m, 1 H), 2.89 - 3.02 (m, 2 H), 3.06 - 3.17 (m, 1 H), 3.26 (s, 2 H), 3.33 - 3.43 (m, 2 H), 3.45 - 3.54 (m, 1 H), 3.68 - 3.76 (m, 1 H), 4.09 (q, J=7.0 Hz, 2 H), 6.56 - 6.64 (m, 3 H), 7.08 - 7.19 (m, 2 H)	**I**	m/z 412 $(M+H)^+$ (ES+), at 6.19 min, UV active
2-78	Isomer 2: methyl 2-{4-[(2S)-1-(pyridin-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**157 and 176**	**ag**	(400 MHz, CD_3OD) δ: 1.25 - 2.14 (m, 18 H), 2.66 - 2.79 (m, 1 H), 2.88 - 3.00 (m, 2 H), 3.25 (d, J=1.5 Hz, 2 H), 3.33 - 3.45 (m, 2 H), 3.47 - 3.56 (m, 1 H), 3.66 (s, 3 H), 4.01 - 4.10 (m, 1 H), 6.51 - 6.58 (m, 2 H), 7.45 - 7.53 (m, 1 H), 7.97 - 8.01 (m, 1 H)	**I**	m/z 399 $(M+H)^+$ (ES+), at 4.56 min, UV active
2-79	Isomer 2: ethyl 2-{4-[(2*S*)-1-(pyridin-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**127 and 176**	**ag**	(400 MHz, $CDCl_3$) δ: 1.19 - 1.21 (m, 1H), 1.29 - 1.31 (m, 6H), 2.05 - 2.12 (m, 4H), 2.13 - 2.14 (m, 8H), 2.51 - 2.53 (m, 1H), 2.97 - 2.98 (m, 3H), 3.14 - 3.18 (m, 2H), 3.24 - 3.28 (m, 3H), 3.41 - 3.43 (m, 1H), 4.02 - 4.05 (m, 1H), 4.12 - 4.15 (m, 2H), 6.40 (d, J = 7.0 Hz, 1H), 6.54 (dd, J = 7.0 and 7.0, Hz, 1H), 7.41 (dd, J = 7.0 and 7.0 Hz, 1H), 8.17 (d, J = 7.0 Hz, 1H).	**I**	m/z 413 $(M+H)^+$ (ES+), at 5.05 min, UV active
2-80	Isomer 1: ethyl 2-{4-[(2S)-1-(pyridin-4-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**127 and 175**	**ah**	(400 MHz, CD_3OD) δ: 1.15 - 2.18 (m, 18 H), 1.25 (t, J=7.2 Hz, 3 H), 2.69 - 2.81 (m, 1 H), 2.90 - 3.00 (m, 2 H), 3.32 - 3.41 (m, 2 H), 3.46 - 3.54 (m, 1 H), 3.85 - 3.92 (m, 1 H), 4.05 - 4.15 (m, 2 H), 6.60 (d, J=6.4 Hz, 2 H), 8.04 (d, J=4.9 Hz, 2 H). 2 protons obscured by MeOH peak.	**I**	m/z 413 $(M+H)^+$ (ES+), at 4.49 min, UV active
2-80	Isomer 2: ethyl 2-{4-[(2S)-1-(pyridin-4-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-	**127 and 175**	**ah**	(400 MHz, CD_3OD) δ: 1.13 - 2.18 (m, 21 H), 2.72 - 2.83 (m, 1 H), 2.93 - 3.02 (m, 2 H), 3.26 (s, 2 H), 3.34 - 3.43 (m, 2 H), 3.47 - 3.59 (m, 1 H), 3.88 - 3.96 (m, 1 H), 4.09 (q, J=7.0 Hz,	**I**	m/z 413 $(M+H)^+$ (ES+), at 4.65 min, UV active

	azaspiro[3.4]octane-6-carboxylate			2 H), 6.64 (d, J=6.7 Hz, 2 H), 8.04 (d, J=6.4 Hz, 2 H).		
2-81	Isomer 2: ethyl 2-{4-[(2*S*)-1-(pyrimidin-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**127 and 169**	**ah**	(400 MHz, CD_3OD) δ:1.21 - 1.28 (m, 3 H), 1.35 - 1.82 (m, 6 H), 1.86 - 2.14 (m, 10 H), 2.68 - 2.79 (m, 1 H), 2.90 - 2.99 (m, 2 H), 3.26 (s, 2 H), 3.34 - 3.43 (m, 2 H), 3.46 - 3.67 (m, 2 H), 4.09 (q, J=7.0 Hz, 2 H), 4.17 - 4.26 (m, 1 H), 4.56 - 4.70 (m, 1 H), 6.57 (t, J=4.9 Hz, 1 H), 8.29 (d, J=4.9 Hz, 2 H)	**I**	m/z 414 $(M+H)^+$ (ES+), at 4.54 min, UV active
2-82	Isomer 2: ethyl 2-{4-[(2*S*)-1-(1,3-thiazol-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**40 and 127**	**ai**	(400 MHz, DMSO-d_6) δ: 1.17 (t, 3 H), 1.21 - 1.36 (m, 4 H), 1.39 - 1.65 (m, 4 H), 1.67 - 1.82 (m, 4 H), 1.83 - 2.05 (m, 6 H), 2.76 - 2.86 (m, 2 H), 3.16 - 3.31 (m, 5 H), 3.38 - 3.45 (m, 1 H), 3.73 - 3.80 (m, 1 H), 4.00 (q, J=7.0 Hz, 2 H), 6.70 (d, J=3.7 Hz, 1 H), 7.13 (d, J=3.7 Hz, 1 H)	**E**	m/z 419 $(M+H)^+$ (ES+), at 4.67 min, UV active
2-83	Isomer 2: ethyl 2-{4-[(2*S*)-1-(1,3,4-thiadiazol-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**127 and 256**	**ai**	(400 MHz, DMSO-d_6) δ: 1.39 - 1.41 (m, 4H), 1.42 - 1.43 (m, 3H), 1.60 - 1.71 (m, 3H), 1.80 - 1.83 (m, 3H), 1.97 - 2.02 (m, 9H), 3.11 - 3.13 (m, 2H), 3.21- 3.23 (m, 4H), 3.31-3.36 (m, 1H), 3.91 - 3.93 (m, 1H), 4.12 - 4.13 (q, 2H, J = 6.2 Hz), 8.62 (s, 1H).	**I**	m/z 420 $(M+H)^+$ (ES+), at 4.08 min, UV active
2-84	Isomer 2: ethyl 2-{4-[(2*R*)-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
2-85	Isomer 2: ethyl 2-{4-[(2*S*)-2-(methylcarbamoyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 139**	**ak**	(400 MHz, DMSO-d_6) δ: 1.16 (t, J = 7.0 Hz, 3 H), 1.28 - 1.44 (m, 2 H), 1.50 - 2.03 (m, 11 H), 2.15 - 2.30 (m, 1 H), 2.33 - 2.64 (m, 5 H), 2.68 – 2.81 (m, 2 H), 2.97 - 3.19 (m, 4 H), 3.22 - 3.39 (m, 5 H), 3.99 (q, J = 7.0 Hz, 2 H), 7.67 (q, J = 4.6 Hz, 1 H).	**G**	m/z 393 $(M+H)^+$ (ES^+) at 5.15 min, UV inactive
2-86	Mixture of diasteromers: 1-{1-[6-(ethoxycarbonyl)-6-azaspiro[3.4]oct-2-yl]piperidin-4-yl}-4,4-difluoro-D-proline	**Example 2-87**	**ao**	(400 MHz, CD_3OD) δ: 1.18 - 1.30 (m, 3 H), 1.75 (br. s., 2 H), 1.85 - 2.04 (m, 4 H), 2.06 - 2.22 (m, 2 H), 2.23 - 2.42 (m, 3 H), 2.45 - 2.72 (m, 3 H), 2.79 - 2.91 (m, 1 H), 2.99 (dt, J = 17.4, 10.6 Hz, 1 H), 3.17 - 3.27 (m, 2 H), 3.33 - 3.55 (m, 7 H), 4.03 - 4.16 (m, 2 H) OH not observed.	**E**	m/z 416 $((M+H)^+$ (ES+), at 1.62 min, UV inactive

2-87	Isomer 2: ethyl 2-{4-[(2*R*)-4,4-difluoro-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 260**	**aL**	(400 MHz, DMSO-d_6) δ: 1.13 (t, *J*=7.0 Hz, 3 H), 1.20 - 1.33 (m, 2 H), 1.62 - 1.83 (m, 8 H), 1.90 - 1.97 (m, 3 H), 2.53 - 2.62 (m, 4 H), 3.11 (d, *J*=6.2 Hz, 2 H), 3.19 - 3.26 (m, 5 H), 3.61 (s, 3 H), 3.81 - 3.86 (m, 1 H), 3.97 (q, *J*=7.0 Hz, 2 H)	**E**	m/z 430 $(M+H)^+$ (ES^+), at 3.64 min, UV inactive
2-88	Isomer 2: ethyl 2-{4-[(2*R*)-4,4-difluoro-2-(methylcarbamoyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**Example 2-87 and 168**	**am**	(400 MHz, DMSO-d_6) δ: 1.13 (t, *J*=7.0 Hz, 3 H), 1.32 (q, *J*=12.0 Hz, 2 H), 1.49 - 1.66 (m, 3 H), 1.66 - 1.75 (m, 3 H), 1.75 - 1.86 (m, 2 H), 1.94 (dd, *J*=10.9, 7.4 Hz, 2 H), 2.03 - 2.22 (m, 1 H), 2.33 - 2.38 (m, 1 H), 2.52 - 2.63 (m, 5 H), 2.68 - 2.79 (m, 2 H), 2.91 - 3.07 (m, 1 H), 3.11 (d, *J*=5.9 Hz, 2 H), 3.18 - 3.29 (m, 3 H), 3.48 (dd, *J*=9.8, 5.5 Hz, 1 H), 3.97 (q, *J*=7.0 Hz, 2 H), 7.82 (q, *J*=4.7 Hz, 1 H)	**E**	m/z 429 $(M+H)^+$ (ES^+), at 2.96 min, UV inactive
2-89	Isomer 2: ethyl 2-{4-[(2*R*)-2-(dimethylcarbamoyl)-4,4-difluoropyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**Example 2-87 and 307**	**am**	(400 MHz, DMSO-d_6) δ: 1.13 (t, *J*=7.0 Hz, 3 H), 1.19 - 1.33 (m, 2 H), 1.51 - 1.75 (m, 6 H), 1.75 - 1.84 (m, 2 H), 1.88 - 1.99 (m, 2 H), 2.08 - 2.22 (m, 1 H), 2.53 - 2.62 (m, 3 H), 2.67 - 2.73 (m, 2 H), 2.77 (s, 3 H), 2.97 (s, 3 H), 3.11 (d, *J*=6.2 Hz, 2 H), 3.24 (q, *J*=6.8 Hz, 2 H), 3.37 - 3.47 (m, 2 H), 3.97 (q, *J*=7.2 Hz, 2 H), 4.14 (dd, *J*=9.0, 4.7 Hz, 1 H)	**E**	m/z 443 $(M+H)^+$ (ES^+), at 3.03 min, UV inactive
2-90	Isomer 2: ethyl 2-{4-[(2R)-2-carbamoyl-4,4-difluoropyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**Example 2-87**	**an**	(400 MHz, CD_3OD) δ: 1.24 (t, J = 7.0 Hz, 3 H), 1.44 - 1.61 (m, 2 H), 1.74 - 1.98 (m, 9 H), 2.04 - 2.14 (m, 2 H), 2.17 - 2.31 (m, 1 H), 2.51 (t, J = 10.9 Hz, 1 H), 2.57 - 2.80 (m, 2 H), 2.91 (t, J = 9.5 Hz, 2 H), 2.98 - 3.15 (m, 1 H), 3.25 (s, 3 H), 3.34 - 3.50 (m, 3 H), 3.55 (dd, J = 9.5, 5.5 Hz, 1 H), 4.08 (q, J = 7.0 Hz, 2 H)	**E**	m/z 415 $(M+H)^+$ (ES+), at 3.20 min, UV inactive
2-91	Isomer 2: ethyl 2-{4-[(2R)-4,4-difluoro-2-(methoxycarbamoyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**Example 2-87 and 123**	**ao**	(400 MHz, CD_3OD) δ: 1.24 (t, J = 7.2 Hz, 3 H), 1.43 - 1.58 (m, 2 H), 1.75 - 1.98 (m, 8 H), 2.09 (t, J = 9.8 Hz, 2 H), 2.20 - 2.37 (m, 1 H), 2.43 - 2.53 (m, 1 H), 2.54 - 2.78 (m, 2 H), 2.84 - 2.96 (m, 2 H), 2.96 - 3.15 (m, 1 H), 3.25 (s, 2 H), 3.34 - 3.45 (m, 3 H), 3.61 (dd, J = 9.6, 5.3 Hz, 1 H), 3.68 (s, 3 H), 4.08 (q, J = 7.2 Hz, 2 H) NH not observed.	**E**	m/z 445 $(M+H)^+$ (ES+), at 2.62 min, UV inactive
2-92	Isomer 2: ethyl 2-(4-{(2R)-4,4-difluoro-2-[methoxy(methyl)carbamoyl]pyrrolidin-1-yl}piperidin-1-	**Example 2-87 and 124**	**ao**	(400 MHz, CD_3OD) δ: 1.24 (t, J = 7.0 Hz, 3 H), 1.51 (d, J = 10.9 Hz, 2 H), 1.72 - 1.97 (m, 8 H), 2.03 - 2.13 (m, 2 H), 2.24 (qd, J = 14.3, 6.1 Hz, 1 H), 2.56 - 2.78 (m, 3 H), 2.86 (d, J = 9.4 Hz, 2 H), 3.07 - 3.21 (m, 4 H), 3.25 (s, 2 H), 3.33	**E**	m/z 459 $(M+H)^+$ (ES+), at 3.63 min, UV inactive

	yl)-6-azaspiro[3.4]octane-6-carboxylate			- 3.51 (m, 3 H), 3.73 (s, 3 H), 4.08 (q, J = 7.0 Hz, 2 H), 4.20 - 4.30 (m, 1 H)		
2-93	Isomer 2: ethyl 2-{4-[(2*S*)-4,4-difluoro-2-(methylcarbamoyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2, 167 and 262**	**aL and am**	(400 MHz, DMSO-d_6) δ: 1.13 (t, *J*=7.0 Hz, 3 H), 1.26 - 1.38 (m, 2 H), 1.54 - 1.66 (m, 3 H), 1.66 - 1.75 (m, 3 H), 1.75 - 1.85 (m, 2 H), 1.89 - 1.99 (m, 2 H), 2.06 - 2.19 (m, 1 H), 2.33 - 2.38 (m, 1 H), 2.54 - 2.61 (m, 5 H), 2.71 - 2.78 (m, 2 H), 2.96 - 3.06 (m, 1 H), 3.11 (d, *J*=5.9 Hz, 2 H), 3.21 - 3.27 (m, 3 H), 3.45 - 3.51 (m, 1 H), 3.97 (q, *J*=7.0 Hz, 2 H), 7.74 - 7.88 (m, 1 H)	**E**	m/z 429 $(M+H)^+$ (ES^+), at 2.97 min, UV inactive
2-94	Isomer 2: ethyl 2-{4-[(2*S*)-2-(dimethylcarbamoyl)-4,4-difluoropyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2, 262 and 307**	**aL and am**	(400 MHz, DMSO-d_6) δ: 1.13 (t, *J*=7.0 Hz, 3 H), 1.20 - 1.32 (m, 2 H), 1.52 - 1.75 (m, 6 H), 1.75 - 1.84 (m, 2 H), 1.93 (dd, *J*=10.5, 8.2 Hz, 2 H), 2.08 - 2.20 (m, 1 H), 2.52 - 2.62 (m, 3 H), 2.67 - 2.72 (m, 2 H), 2.77 (s, 3 H), 2.97 (s, 3 H), 3.11 (d, *J*=6.2 Hz, 2 H), 3.21 - 3.27 (m, 2 H), 3.36 - 3.44 (m, 2 H), 3.93 - 4.01 (m, 2 H), 4.14 (dd, *J*=9.0, 4.7 Hz, 1 H)	**E**	m/z 443 $(M+H)^+$ (ES^+), at 3.03 min, UV inactive
2-95	Isomer 2: ethyl 2-{4-[(2*R*)-2-(methoxycarbonyl)-2-methylpyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 293**	**aw**	(400 MHz, DMSO-d_6) δ:1.13 (t, *J*=7.0 Hz, 3 H), 1.19 (s, 3 H), 1.27 - 1.38 (m, 2 H), 1.40 - 1.51 (m, 3 H), 1.52 - 1.74 (m, 7 H), 1.75 - 1.85 (m, 2 H), 1.87 - 1.98 (m, 2 H), 1.98 - 2.08 (m, 1 H), 2.52 - 2.62 (m, 1 H), 2.67 - 2.85 (m, 3 H), 2.89 (q, *J*=7.5 Hz, 1 H), 3.11 (d, *J*=6.6 Hz, 2 H), 3.24 (q, *J*=6.8 Hz, 2 H), 3.55 (s, 3 H), 3.97 (q, *J*=7.0 Hz, 2 H)	**E**	m/z 408 $(M+H)^+$ (ES^+), at 4.06 min, UV inactive
2-96	Isomer 2: ethyl 2-[4-(6-oxo-7-oxa-1-azaspiro[4.4]non-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 300**	**aw**	(400 MHz, DMSO-d_6) δ:1.13 (t, *J*=7.0 Hz, 3 H), 1.25 - 1.50 (m, 3 H), 1.50 - 1.68 (m, 4 H), 1.68 - 1.86 (m, 8 H), 1.86 - 2.02 (m, 4 H), 2.18 - 2.35 (m, 1 H), 2.53 - 2.67 (m, 1 H), 2.67 - 2.85 (m, 2 H), 2.95 - 3.07 (m, 1 H), 3.11 (d, *J*=6.6 Hz, 2 H), 3.24 (q, *J*=6.6 Hz, 2 H), 3.97 (q, *J*=7.0 Hz, 2 H), 4.06 - 4.18 (m, 1 H), 4.32 (t, *J*=8.6 Hz, 1 H)	**E**	m/z 406 $(M+H)^+$ (ES^+), at 5.24 min, UV inactive
2-97	Isomer 1: ethyl 2-{4-[(4*S*)-4-(methoxycarbonyl)-1,3-thiazolidin-3-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 286**	**aw**	(400 MHz, DMSO-d_6) δ: 1.08 - 1.18 (m, 3 H), 1.32 (quin, *J*=11.9 Hz, 2 H), 1.58 - 1.87 (m, 8 H), 1.96 (t, *J*=9.4 Hz, 2 H), 2.32 - 2.38 (m, 1 H), 2.59 (t, *J*=7.2 Hz, 1 H), 2.72 (d, *J*=8.2 Hz, 2 H), 2.93 - 3.13 (m, 2 H), 3.14 - 3.26 (m, 4 H), 3.60 (s, 3 H), 3.93 (d, *J*=9.8 Hz, 1 H), 3.98 (q, *J*=7.0 Hz, 2 H), 4.26 (d, *J*=9.4 Hz, 1 H), 4.41 (d, *J*=5.5 Hz, 1 H)	**E**	m/z 412 $(M+H)^+$ (ES^+), at 3.62 min, UV inactive
2-97	Isomer 2: ethyl 2-{4-[(4*S*)-4-(methoxycarbonyl)-1,3-thiazolidin-3-yl]piperidin-1-	**2 and 286**	**aw**	(400 MHz, DMSO-d_6) δ: 1.13 (t, *J*=7.0 Hz, 3 H), 1.24 - 1.43 (m, 2 H), 1.57 - 1.86 (m, 8 H), 1.88 - 2.01 (m, 2 H), 2.33 - 2.38 (m, 1 H), 2.58 (t, *J*=6.8 Hz, 1 H), 2.72 (d, *J*=9.0 Hz, 2	**E**	m/z 412 $(M+H)^+$ (ES^+), at 3.78 min, UV inactive

	yl}-6-azaspiro[3.4]octane-6-carboxylate			H), 2.93 - 3.03 (m, 1 H), 3.06 (d, *J*=2.3 Hz, 1 H), 3.08 - 3.17 (m, 2 H), 3.24 (q, *J*=6.8 Hz, 2 H), 3.60 (s, 3 H), 3.88 - 4.04 (m, 3 H), 4.26 (d, *J*=9.4 Hz, 1 H), 4.41 (d, *J*=5.9 Hz, 1 H)		
2-98	Isomer 2: ethyl 2-{4-[(3*R*)-3-fluoropyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**151 and 262**	**ap**	(400 MHz, DMSO-d_6) δ: 1.13 (t, *J*=7.2 Hz, 3 H), 1.26 - 1.35 (m, 2 H), 1.59 - 1.86 (m, 10 H), 1.88 - 1.99 (m, 6 H), 2.71 - 2.88 (m, 3 H), 3.12 (d, *J*=7.0 Hz, 2 H), 3.20 - 3.29 (m, 3 H), 3.97 (q, *J*=7.0 Hz, 2 H), 5.02 - 5.13 (m, 1 H)	**E**	m/z 354 $(M+H)^+$ (ES^+), at 3.06 min, UV inactive
2-99	Isomer 2: ethyl 2-{4-[(3*S*)-3-fluoropyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**151 and 263**	**ap**	(400 MHz, DMSO-d_6) δ: 1.13 (t, *J*=7.0 Hz, 3 H), 1.25 - 1.37 (m, 2 H), 1.54 - 1.84 (m, 10 H), 1.86 - 1.99 (m, 6 H), 2.71 - 2.85 (m, 3 H), 3.12 (d, *J*=7.0 Hz, 2 H), 3.20 - 3.26 (m, 3 H), 3.97 (q, *J*=7.0 Hz, 2 H), 5.03 - 5.16 (m, 1 H)	**E**	m/z 354 $(M+H)^+$ (ES^+), at 3.03 min, UV inactive
2-100	Isomer 2: ethyl 2-[4-(3,3-difluoropyrrolidin-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**88 and 151**	**ap**	(400 MHz, DMSO-d_6) δ: 1.13 (t, *J*=7.0 Hz, 3 H), 1.24 - 1.31 (m, 2 H), 1.57 - 1.87 (m, 7 H), 1.89 - 2.06 (m, 3 H), 2.11 - 2.27 (m, 1 H), 2.44 (br. s., 1 H), 2.55 - 2.61 (m, 4 H), 2.68 - 2.71 (m, 2 H), 2.87 (t, *J*=14.1 Hz, 2 H), 3.12 (d, *J*=7.0 Hz, 2 H), 3.20 - 3.27 (m, 2 H), 3.97 (q, *J*=7.0 Hz, 2 H)	**E**	m/z 372 $(M+H)^+$ (ES^+), at 3.38 min, UV inactive
2-101	Isomer 2: ethyl 2-{4-[(2*S*)-2-(trifluoromethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 278**	**aw**	(400 MHz, DMSO-d6) δ:1.13 (t, *J*=7.0 Hz, 3 H), 1.29 - 1.47 (m, 2 H), 1.55 - 1.85 (m, 12 H), 1.89 - 2.00 (m, 2 H), 2.54 - 2.68 (m, 2 H), 2.70 - 2.90 (m, 3 H), 3.11 (d, *J*=5.9 Hz, 2 H), 3.19 - 3.27 (m, 3 H), 3.49 - 3.61 (m, 1 H), 3.96 (q, *J*=7.0 Hz, 2 H)	**E**	m/z 404 $(M+H)^+$ (ES^+), at 4.22 min, UV inactive
2-102	Isomer 2: ethyl 2-{4-[(2*R*)-2-(fluoromethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 296**	**aw**	(400 MHz, DMSO-d_6) δ:1.10 - 1.16 (m, 3 H), 1.21 (s, 2 H), 1.27 - 1.50 (m, 3 H), 1.50 - 1.56 (m, 2 H), 1.56 - 1.72 (m, 3 H), 1.72 - 1.92 (m, 5 H), 1.92 - 2.03 (m, 2 H), 2.09 - 2.21 (m, 1 H), 2.23 - 2.45 (m, 4 H), 2.69 - 2.94 (m, 1 H), 3.09 - 3.21 (m, 2 H), 3.21 - 3.29 (m, 4 H), 3.98 (q, *J*=7.0 Hz, 2 H)	**E**	m/z 368 $(M+H)^+$ (ES^+), at 5.04 min, UV inactive
2-103	Isomer 2: ethyl 2-{4-[(2*R*)-2-(difluoromethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 298**	**aw**	(400 MHz, DMSO-d_6) δ:1.14 (t, *J*=7.0 Hz, 3 H), 1.18 - 1.28 (m, 2 H), 1.32 - 1.49 (m, 2 H), 1.57 - 1.87 (m, 11 H), 1.89 (s, 1 H), 1.92 - 2.09 (m, 2 H), 2.10 - 2.23 (m, 1 H), 2.67 - 2.94 (m, 3 H), 3.06 - 3.21 (m, 3 H), 3.21 - 3.28 (m, 2 H), 3.98 (q, *J*=7.2 Hz, 2 H), 5.63 - 5.78 (m, 1 H)	**E**	m/z 386 $(M+H)^+$ (ES^+), at 5.62 min, UV inactive
2-104	Isomer 2: ethyl 2-{4-[(2*R*)-2-(trifluoromethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-	**2 and 274**	**aw**	(300 MHz, DMSO-d_6) δ: 1.16 (t, *J*=7.0 Hz, 3 H), 1.31 - 1.54 (m, 2 H), 1.54 - 1.91 (m, 12 H), 1.97 (t, *J*=9.2 Hz, 2 H), 2.58 - 2.75 (m, 2 H), 2.75 - 2.92 (m, 3 H), 3.14 (br. s., 2 H), 3.20-	**E**	m/z 404 $(M+H)^+$ (ES^+), at 4.22 min, UV inactive

	azaspiro[3.4]octane-6-carboxylate			3.25 (m, 3 H) 3.49 - 3.66 (m, 1 H), 3.99 (q, *J*=7.1 Hz, 2 H)		
2-105	Isomer 2: ethyl 2-[4-(3-azabicyclo[3.1.0]hex-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 280**	**aw**	(400 MHz, DMSO-d_6) δ: 0.27 (br. s., 1 H), 0.45 - 0.54 (m, 1 H), 1.13 (t, *J*=7.0 Hz, 3 H), 1.22 - 1.40 (m, 4 H), 1.57 - 1.86 (m, 8 H), 1.94 (t, *J*=8.2 Hz, 2 H), 1.98 - 2.14 (m, 1 H), 2.19 - 2.36 (m, 2 H), 2.59 - 2.73 (m, 3 H), 2.93 (d, *J*=8.2 Hz, 2 H), 3.11 (d, *J*=5.5 Hz, 2 H), 3.20 - 3.25 (m, 2 H), 3.96 (q, *J*=7.2 Hz, 2 H)	**E**	m/z 348 $(M+H)^+$ (ES^+), at 3.78 min, UV inactive
2-106	Isomer 2: ethyl 2-{4-[(2S)-4,4-difluoro-2-methylpyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 125**	**aj**	(400 MHz, CD_3OD) δ: 1.11 (d, J = 5.9 Hz, 3 H), 1.19 - 1.35 (m, 4 H), 1.41 - 1.63 (m, 2 H), 1.71 - 1.97 (m, 9 H), 2.05 - 2.15 (m, 2 H), 2.31 - 2.46 (m, 1 H), 2.63 - 2.82 (m, 2 H), 2.89 - 3.00 (m, 2 H), 3.08 - 3.22 (m, 2 H), 3.25 (s, 2 H), 3.34 - 3.42 (m, 2 H), 4.09 (q, J = 7.0 Hz, 2 H)	**E**	m/z 386 $(M+H)^+$ (ES+), at 3.98 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), 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)	**E**	m/z 402 $(M+H)^+$ (ES+), at 3.23 min, UV inactive
2-108	Isomer 2: ethyl 2-{4-[(2R)-4,4-difluoro-2-(methoxymethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 174**	**as**	(400 MHz, $CDCl_3$) δ: 1.25 (t, J=7.0 Hz, 3 H), 1.41 - 1.99 (m, 10 H), 2.01 - 2.24 (m, 3 H), 2.24 - 2.44 (m, 1 H), 2.57 - 2.78 (m, 1 H), 2.83 - 3.11 (m, 3 H), 3.14 - 3.47 (m, 9 H), 3.35 (s, 3H), 4.11 (q, J=7.2 Hz, 2 H)	**B**	m/z 416 $(M+H)^+$ (ES+), at 4.04 min, UV inactive
2-109	Isomer 2: ethyl 2-{4-[(2R)-4,4-difluoro-2-(1-hydroxyethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 179**	**as**	(400 MHz, $CDCl_3$) δ: 1.14 (d, J=6.2 Hz, 3 H), 1.24 (t, J=7.0 Hz, 3 H), 1.40 - 2.20 (m, 13 H), 2.25 - 2.43 (m, 1 H), 2.58 - 2.83 (m, 2 H), 2.83 - 3.10 (m, 4 H), 3.10 - 3.34 (m, 4 H), 3.34 - 3.44 (m, 2 H), 3.49 - 3.57 (m, 1 H), 4.11 (q, J=7.0 Hz, 2 H)	**B**	m/z 416 $(M+H)^+$ (ES+), at 4.20 min, UV inactive
2-109	Isomer 4: ethyl 2-{4-[(2R)-4,4-difluoro-2-(1-hydroxyethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-	**2 and 179**	**as**	(400 MHz, $CDCl_3$) δ:1.08 (d, J=6.6 Hz, 3 H), 1.24 (t, J=6.6 Hz, 3 H), 1.47 - 2.19 (m, 13 H), 2.20 - 2.37 (m, 1 H), 2.60 - 2.72 (m, 2 H), 2.89 - 3.02 (m, 4 H), 3.02 - 3.17 (m, 2 H), 3.18 - 3.44 (m, 4 H), 3.85 - 3.94 (m, 1 H), 4.11 (q, J=6.8 Hz,	**B**	m/z 416 $(M+H)^+$ (ES+), at 3.99 min, UV inactive

	azaspiro[3.4]octane-6-carboxylate			2 H)		
2-110	Mixture of diasteremomers: ethyl 2-{4-[(2*R*)-4,4-difluoro-2-(2-hydroxypropan-2-yl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 258**	**ax**	(400 MHz, DMSO-d_6) δ: 0.85 – 1.08 (m, 5H), 1.09 – 1.21 (m, 4H), 1.21 – 1.44 (m, 2H), 1.44 – 1.88 (m, 6H), 1.88 – 2.35 (m, 4H), 2.55 – 3.17 (m, 6H), 3.17 – 3.39 (m, 3H), 3.42 – 3.76 (m, 3H), 3.94 – 4.09 (m, 3H), 4.23 (s, 1H).	**N**	m/z 430 $(M+H)^+$ (ES+), at 2.14 + 2.16 min, UV inactive
2-111	Isomer 2: ethyl 2-[4-(2-oxopyrrolidin-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 269**	**ap**	^{1}H NMR (400 MHz, DMSO-d_6) δ:1.14 (t, *J*=7.2 Hz, 3 H), 1.46 (d, *J*=10.2 Hz, 2 H), 1.52 - 1.66 (m, 2 H), 1.66 - 1.77 (m, 4 H), 1.77 - 1.91 (m, 5 H), 1.96 (t, *J*=9.0 Hz, 2 H), 2.14 - 2.21 (m, 2 H), 2.80 (d, *J*=10.2 Hz, 2 H), 3.12 (d, *J*=5.5 Hz, 2 H), 3.22 - 3.28 (m, 4 H), 3.60 - 3.74 (m, 1 H), 3.97 (q, *J*=7.0 Hz, 2 H)	**E**	m/z 350 $(M+H)^+$ (ES^+), at 2.33 min, UV inactive
2-112	Isomer 2: ethyl 2-[4-(2,5-dioxopyrrolidin-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 193**	**as**	(400 MHz, $CDCl_3$) δ: 1.25 (t, J=7.0 Hz, 3 H), 1.47 - 1.63 (m, 2 H), 1.76 - 2.11 (m, 8 H), 2.41 - 2.56 (m, 2 H), 2.58 - 2.78 (m, 1H), 2.67 (s, 4 H), 2.90 - 3.03 (m, 2 H), 3.19 - 3.48 (m, 4 H), 3.92 - 4.06 (m, 1 H), 4.11 (q, J=6.9 Hz, 2 H)	**B**	m/z 364 $(M+H)^+$ (ES+), at 3.70 min, UV active
2-113	Isomer 2: ethyl 2-{4-[(2R)-2-methyl-5-oxopyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 199**	**as**	(400 MHz, $CDCl_3$) δ: 1.21 - 1.30 (m, 6 H), 1.57 - 1.72 (m, 2 H), 1.74 - 1.95 (m, 9 H), 1.96 - 2.07 (m, 2 H), 2.10 - 2.20 (m, 1 H), 2.21 - 2.33 (m, 1 H), 2.44 - 2.54 (m, 1 H), 2.59 - 2.76 (m, 1 H), 2.82 - 3.01 (m, 2 H), 3.27 (d, *J*=19.9 Hz, 2 H), 3.32 - 3.45 (m, 2 H), 3.75 - 3.95 (m, 2 H), 4.10 (q, *J*=6.6 Hz, 2 H)	**B**	m/z 364 $(M+H)^+$ (ES+), at 3.53 min, UV active
2-114	Isomer 2: ethyl 2-{4-[(2R)-2-ethyl-5-oxopyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 200**	**as**	(400 MHz, $CDCl_3$) δ: 0.86 (t, *J*=7.2 Hz, 3 H), 1.22 (td, *J*=7.0, 3.1 Hz, 3 H), 1.40 - 1.53 (m, 1 H), 1.61 (d, *J*=12.1 Hz, 1 H), 1.68 - 1.92 (m, 11 H), 2.03 (d, *J*=8.2 Hz, 3 H), 2.18 - 2.30 (m, 1 H), 2.37 - 2.48 (m, 1 H), 2.58 - 2.71 (m, 1 H), 2.82 - 2.97 (m, 2 H), 3.18 - 3.29 (m, 2 H), 3.30 - 3.42 (m, 2 H), 3.60 (t, *J*=8.4 Hz, 1 H), 3.76 - 3.92 (m, 1 H), 4.08 (q, *J*=6.9 Hz, 2 H)	**B**	m/z 378 $(M+H)^+$ (ES+), at 3.73 min, UV active
2-115	Isomer 2: ethyl 2-{4-[(2S)-2-methyl-5-oxopyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-	**2 and 202**	**as**	(400 MHz, $CDCl_3$) δ: 1.20 - 1.30 (m, 6 H), 1.54 - 1.67 (m, 2 H), 1.72 - 1.96 (m, 9 H), 1.98 - 2.09 (m, 2 H), 2.09 - 2.20 (m, 1 H), 2.20 - 2.32 (m, 1 H), 2.43 - 2.54 (m, 1 H), 2.59 - 2.74 (m, 1 H), 2.82 - 3.01 (m, 2 H), 3.26 (d, *J*=19.9 Hz, 2 H), 3.31	**B**	m/z 364 $(M+H)^+$ (ES+), at 3.53 min, UV active

	carboxylate			- 3.44 (m, 2 H), 3.75 - 3.95 (m, 2 H), 4.10 (q, *J*=6.8 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 H), 4.08 (q, *J*=7.0 Hz, 2 H)	**B**	m/z 378 $(M+H)^+$ (ES+), at 3.73 min, UV active
2-117	Isomer 2: ethyl 2-[4-(2,2-dimethyl-5-oxopyrrolidin-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 186**	**as**	(400 MHz, $CDCl_3$) δ: 1.18 - 1.32 (m, 9 H), 1.42 - 1.57 (m, 2 H), 1.63 - 2.11 (m, 10 H), 2.29 - 2.39 (m, 2 H), 2.50 - 2.82 (m, 3 H), 2.86 - 3.14 (m, 3 H), 3.21 - 3.32 (m, 2 H), 3.32 - 3.46 (m, 2 H), 4.11 (q, J=6.9 Hz, 2 H)	**B**	m/z 378 $(M+H)^+$ (ES+), at 5.41 min, UV active
2-118	Isomer 2: ethyl 2-{4-[(4R)-4-methyl-2-oxo-1,3-oxazolidin-3-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 205**	**as**	(400 MHz, $CDCl_3$) δ: 1.17 - 1.23 (m, 3 H), 1.30 (d, *J*=6.2 Hz, 3 H), 1.66 - 1.88 (m, 10 H), 1.95 - 2.06 (m, 2 H), 2.58 - 2.68 (m, 1 H), 2.82 - 2.95 (m, 2 H), 3.17 - 3.27 (m, 2 H), 3.28 - 3.39 (m, 2 H), 3.53 - 3.67 (m, 1 H), 3.79 (dd, *J*=8.2, 5.1 Hz, 1 H), 3.86 - 3.94 (m, 1 H), 4.06 (q, *J*=7.0 Hz, 2 H), 4.30 (t, *J*=8.2 Hz, 1 H)	**B**	m/z 366 $(M+H)^+$ (ES+), at 3.30 min, UV active
2-119	Isomer 2: ethyl 2-{4-[(4R)-4-ethyl-2-oxo-1,3-oxazolidin-3-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 207**	**as**	(400 MHz, $CDCl_3$) δ: 0.85 (t, *J*=7.4 Hz, 3 H), 1.21 (td, *J*=6.9, 3.3 Hz, 3 H), 1.52 - 1.65 (m, 1 H), 1.67 - 1.90 (m, 11 H), 1.98 - 2.07 (m, 2 H), 2.58 - 2.68 (m, 1 H), 2.89 (dd, *J*=18.9, 9.2 Hz, 2 H), 3.18 - 3.28 (m, 2 H), 3.35 (dt, *J*=19.6, 6.8 Hz, 2 H), 3.55 - 3.66 (m, 1 H), 3.77 (dt, *J*=7.6, 4.0 Hz, 1 H), 3.95 (dd, *J*=8.6, 4.7 Hz, 1 H), 4.04 - 4.11 (m, 2 H), 4.26 (t, *J*=8.4 Hz, 1 H)	**B**	m/z 380 $(M+H)^+$ (ES+), at 3.73 min, UV active
2-120	Isomer 2: ethyl 2-{4-[(4R)-2-oxo-4-(propan-2-yl)-1,3-oxazolidin-3-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 197**	**as**	(300 MHz, $CDCl_3$) δ: 0.89 (dd, J=10.1, 6.9 Hz, 6 H), 1.25 (t, J=7.1 Hz, 3 H), 1.51 - 2.25 (m, 13 H), 2.60 - 2.78 (m, 1 H), 2.85 - 3.05 (m, 2 H), 3.21 - 3.49 (m, 4 H), 3.54 - 3.74 (m, 1 H), 3.74 - 3.83 (m, 1 H), 4.05 - 4.21 (m, 4 H)	**B**	m/z 394 $(M+H)^+$ (ES+), at 3.93 min, UV active
2-121	Isomer 2: ethyl 2-{4-[(4S)-4-methyl-2-oxo-1,3-oxazolidin-3-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 209**	**as**	(400 MHz, $CDCl_3$) δ: 1.18 - 1.25 (m, 3 H), 1.32 (d, *J*=5.9 Hz, 3 H), 1.65 - 1.93 (m, 10 H), 1.97 - 2.09 (m, 2 H), 2.58 - 2.71 (m, 1 H), 2.82 - 2.98 (m, 2 H), 3.18 - 3.29 (m, 2 H), 3.36 (dt, *J*=19.7, 6.7 Hz, 2 H), 3.55 - 3.69 (m, 1 H), 3.80 (dd, *J*=8.2, 5.5 Hz, 1 H), 3.86 - 3.97 (m, 1 H), 4.08 (q, *J*=6.9 Hz, 2 H),	**B**	m/z 366 $(M+H)^+$ (ES+), at 3.43 min, UV active

				4.32 (t, *J*=8.2 Hz, 1 H)		
2-122	Isomer 2: ethyl 2-{4-[(4S)-4-ethyl-2-oxo-1,3-oxazolidin-3-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 211**	**as**	(300 MHz, $CDCl_3$) δ: 0.90 (t, *J*=7.5 Hz, 3 H), 1.25 (t, *J*=7.1 Hz, 3 H), 1.52 - 2.20 (m, 14 H), 2.62 - 2.78 (m, 1 H), 2.84 - 3.06 (m, 2 H), 3.22 - 3.55 (m, 4 H), 3.58 - 3.72 (m, 1 H), 3.72 - 3.88 (m, 1 H), 3.99 (dd, *J*=8.6, 4.7 Hz, 1 H), 4.05 - 4.19 (m, 2 H), 4.29 (t, *J*=8.6 Hz, 1 H)	**B**	m/z 380 $(M+H)^+$ (ES+), at 3.72 min, UV active
2-123	Isomer 2: ethyl 2-{4-[(4S)-2-oxo-4-(propan-2-yl)-1,3-oxazolidin-3-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 188**	**as**	(400 MHz, $CDCl_3$) δ: 0.82 - 0.96 (m, 6 H), 1.25 (s, 3 H), 1.56 - 2.24 (m, 13 H), 2.61 - 2.78 (m, 1 H), 2.85 - 3.03 (m, 2 H), 3.21 - 3.48 (m, 4 H), 3.55 - 3.74 (m, 1 H), 3.74 - 3.83 (m, 1 H), 4.05 - 4.20 (m, 4 H)	**B**	m/z 394 $(M+H)^+$ (ES+), at 5.16 min, UV active
2-124	Isomer 2: ethyl 2-[4-(2-oxoimidazolidin-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**151 and 152**	**aq**	(400 MHz, $CDCl_3$) δ: 1.16 - 1.36 (m, 3 H), 1.45 - 2.23 (m, 13 H), 2.56 - 2.80 (m, 1 H), 2.83 – 3.08 (m, 2 H), 3.17 - 3.52 (m, 7 H), 3.63 - 3.90 (m, 1 H), 4.10 (q, J = 7.0 Hz, 2 H), 4.24 – 4.42 (m, 1 H).	**B**	m/z 351 $(M+H)^+$ (ES^+), at 2.12 min, UV inactive
2-125	Isomer 2: ethyl 2-[4-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 213**	**ac**	(300 MHz, $CDCl_3$) δ: 1.20 - 1.30 (m, 3 H), 1.61 - 1.98 (m, 10 H), 2.00 - 2.15 (m, 2 H), 2.62 - 2.73 (m, 1 H), 2.77 (s, 3 H), 2.86 - 2.98 (m, 2 H), 3.21- 3.48 (m, 5 H), 3.26 (s, 3 H), 3.69 - 3.85 (m, 1 H), 4.05 - 4.19 (m, 2 H)	**B**	m/z 365 $(M+H)^+$ (ES+), at 3.07 min, UV active
2-126	Isomer 2: ethyl 2-{4-[2-(1H-pyrazol-5-yl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 181**	**as**	(400 MHz, $CDCl_3$) δ:1.24 (t, J=7.0 Hz, 3 H), 1.48 - 2.28 (m, 16 H), 2.38 - 2.73 (m, 4 H), 2.76 - 3.02 (m, 2 H), 3.07 - 3.22 (m, 1 H), 3.22 - 3.43 (m, 4 H), 4.10 (q, J=7.0 Hz, 2 H), 6.15 (br. s., 1 H), 7.52 (d, J=2.0 Hz, 1 H). One exchangeable proton not observed.	**B**	m/z 402 $(M+H)^+$ (ES+), at 3.62 min, UV active
2-127	Isomer 2: ethyl 2-{4-[2-(1,2-oxazol-3-yl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 318**	**ak**	(400 MHz, DMSO-d_6) δ: 1.16 (t, *J*=7.2 Hz, 3 H), 1.33 (dd, *J*=12.1, 11.4 Hz, 2 H), 1.49 - 1.68 (m, 2 H), 1.68 - 1.89 (m, 9 H), 1.90 - 2.02 (m, 2 H), 2.03 - 2.17 (m, 1 H), 2.25 (t, *J*=11.6 Hz, 1 H), 2.55 - 2.83 (m, 4 H), 2.83 - 3.01 (m, 1 H), 3.06 - 3.19 (m, 2 H), 3.26 (q, *J*=7.0 Hz, 2 H), 3.99 (q, *J*=7.0 Hz, 2 H), 4.11 - 4.24 (m, 1 H), 6.22 - 6.35 (m, 1 H), 8.39 - 8.48 (m, 1 H)	**I**	m/z 403 $(M+H)^+$ (ES^+), at 4.20 min, UV active
2-128	Isomer 2: ethyl 2-{4-[2-(1*H*-tetrazol-5-yl)pyrrolidin-1-	**2 and 288**	**aw**	(400 MHz, DMSO-d_6) δ:1.13 (t, *J*=7.2 Hz, 3 H), 1.25 - 1.50 (m, 2 H), 1.55 - 1.67 (m, 2 H), 1.67 - 1.84 (m, 5 H), 1.86 -	**E**	m/z 404 $(M+H)^+$ (ES^+), at 1.78 min, UV inactive

	yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate			2.05 (m, 6 H), 2.15 - 2.26 (m, 1 H), 2.62 (br. s., 1 H), 2.68 - 2.83 (m, 2 H), 2.94 - 3.05 (m, 1 H), 3.11 (d, *J*=5.9 Hz, 2 H), 3.14 - 3.19 (m, 2 H), 3.21 - 3.27 (m, 3 H), 3.96 (q, *J*=7.0 Hz, 2 H), 4.62 (br. s., 1 H)		
2-129	Isomer 2: ethyl 2-{4-[2-(2-methyl-2*H*-tetrazol-5-yl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 308**	**aw**	(400 MHz, DMSO-d_6) δ: 1.13 (t, *J*=7.0 Hz, 3 H), 1.19 - 1.33 (m, 2 H), 1.44 (d, *J*=12.1 Hz, 1 H), 1.49 - 1.60 (m, 2 H), 1.63 - 1.72 (m, 3 H), 1.73 - 1.94 (m, 7 H), 2.11 - 2.28 (m, 2 H), 2.51 - 2.64 (m, 3 H), 2.68 (d, *J*=10.2 Hz, 1 H), 3.05 - 3.16 (m, 3 H), 3.23 (q, *J*=6.6 Hz, 2 H), 3.96 (q, *J*=7.0 Hz, 2 H), 4.10 (s, 3 H), 4.35 (dd, *J*=9.2, 5.3 Hz, 1 H)	**E**	m/z 418 $(M+H)^+$ (ES^+), at 3.72 min, UV inactive
2-130	Isomer 1: ethyl 2-{4-[2-(1-methyl-1*H*-tetrazol-5-yl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 308**	**aw**	(400 MHz, DMSO-d_6) δ: 0.43 (t, *J*=6.4 Hz, 3 H), 0.60 - 0.82 (m, 2 H), 0.91 - 1.21 (m, 11 H), 1.24 - 1.31 (m, 3 H), 1.38 - 1.50 (m, 2 H), 1.79 - 1.95 (m, 2 H), 1.95 - 2.13 (m, 5 H), 2.13 - 2.24 (m, 1 H), 3.28 (q, *J*=7.2 Hz, 2 H), 3.52 (s, 3 H), 3.57 (dd, *J*=8.2, 3.9 Hz, 1 H)	**E**	m/z 418 $(M+H)^+$ (ES^+), at 3.61 min, UV inactive
2-130	Isomer 2: ethyl 2-{4-[2-(1-methyl-1*H*-tetrazol-5-yl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 308**	**aw**	(400 MHz, DMSO-d_6) δ: 0.43 (t, *J*=7.0 Hz, 3 H), 0.66 - 0.83 (m, 2 H), 0.93 - 1.00 (m, 2 H), 1.02 - 1.31 (m, 12 H), 1.38 - 1.54 (m, 2 H), 1.83 - 2.13 (m, 7 H), 2.13 - 2.24 (m, 1 H), 3.27 (q, *J*=7.0 Hz, 2 H), 3.52 (s, 3 H), 3.55 - 3.61 (m, 1 H)	**E**	m/z 418 $(M+H)^+$ (ES^+), at 3.80 min, UV inactive
2-131	Isomer 2: ethyl 2-{4-[(2*R*)-2-(thiophen-2-yl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 316**	**ak**	(400 MHz, CD_3OD) δ: 1.21 - 1.30 (m, 3 H), 1.51 - 1.66 (m, 2 H), 1.69 - 1.81 (m, 3 H), 1.81 - 2.03 (m, 7 H), 2.04 - 2.16 (m, 2 H), 2.16 - 2.30 (m, 1 H), 2.41 - 2.55 (m, 1 H), 2.64 - 2.75 (m, 2 H), 2.82 - 2.99 (m, 2 H), 3.08 (t, *J*=10.1 Hz, 1 H), 3.36 - 3.43 (m, 3 H), 4.10 (q, *J*=7.0 Hz, 2 H), 4.16 - 4.29 (m, 1 H), 4.66 (br. s., 2 H), 6.90 - 6.97 (m, 2 H), 7.21 - 7.33 (m, 1 H)	**I**	m/z 418 $(M+H)^+$ (ES^+), at 5.32 min, UV active
2-132	Isomer 2: ethyl 2-{4-[(2*R*)-2-(1,3-thiazol-2-yl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 314**	**ak**	(400 MHz, DMSO-d_6) δ: 1.16 (t, *J*=7.2 Hz, 3 H), 1.28 - 1.48 (m, 2 H), 1.51 - 1.65 (m, 3 H), 1.65 - 1.88 (m, 7 H), 1.88 - 2.03 (m, 2 H), 2.08 - 2.25 (m, 1 H), 2.36 - 2.47 (m, 1 H), 2.55 - 2.63 (m, 3 H), 2.65 - 2.86 (m, 2 H), 3.01 - 3.20 (m, 3 H), 3.20 - 3.30 (m, 2 H), 3.99 (q, *J*=7.0 Hz, 2 H), 4.16 - 4.31 (m, 1 H), 7.50 (d, *J*=3.4 Hz, 1 H), 7.67 (d, *J*=3.1 Hz, 1 H)	**I**	m/z 419 $(M+H)^+$ (ES^+), at 4.60 min, UV active
2-133	Isomer 1: ethyl 2-{4-[(2*S*)-1-(5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-	**127 and 321**	**q**	(400 MHz, CD_3OD) δ: 0.36 - 0.66 (m, 7H), 0.76 - 1.38 (m, 15H), 1.87 – 2.02 (m, 1H), 2.09 – 2.23 (m, 2H), 2.62 - 2.81 (m, 2H), 3.22 - 3.43 (m, 3H), 3.68 - 3.96 (m, 3H), 3.96 - 4.34	**E**	m/z 482 $(M+H)^+$ (ES+), at 3.90 min, UV active

	ylcarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate			(m, 3H), 6.48 - 6.61 (m, 1H), 7.01 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 4.9 Hz, 1H).		
2-133	Isomer 2: ethyl 2-{4-[(2*S*)-1-(5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-ylcarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**127 and 321**	**q**	(400 MHz, CD_3OD) δ: 1.13 - 1.49 (m, 7H), 1.55 - 2.24 (m, 14H), 2.67 - 2.83 (m, 1H), 2.88 – 3.04 (m, 2H), 3.21 - 3.77 (m, 3H), 4.02 - 4.24 (m, 3H), 4.45 - 5.15 (m, 6H), 7.37 (dd, J = 7.7, 5.0 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 8.45 (d, J = 3.4 Hz, 1H).	**E**	m/z 482 $(M+H)^+$ (ES+), at 4.04 min, UV active
2-134	Isomer 2: ethyl 2-{4-[(2*R*,4*R*)-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
2-135	Isomer 2: ethyl 2-{4-[(2*R*,4*S*)-4-fluoro-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 312**	**aw**	(300 MHz, DMSO-d_6) δ: 1.16 (t, *J*=7.1 Hz, 3 H), 1.21 - 1.42 (m, 2 H), 1.57 - 1.88 (m, 8 H), 1.89 - 2.01 (m, 2 H), 2.02 - 2.31 (m, 2 H), 2.34 - 2.46 (m, 1 H), 2.55 - 2.65 (m, 1 H), 2.65 - 2.79 (m, 2 H), 2.85 - 3.05 (m, 1 H), 3.07 - 3.22 (m, 3 H), 3.22 - 3.27 (m, 2 H), 3.61 (s, 3 H), 3.76 (t, *J*=7.0 Hz, 1 H), 3.99 (q, *J*=7.1 Hz, 2 H), 5.08 - 5.40 (m, 1 H)	**E**	m/z 412 $(M+H)^+$ (ES+), at 3.96 min, UV active
2-136	Isomer 2: ethyl 2-{4-[(2*R*,4*R*)-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 - 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)	**E**	m/z 384 $(M+H)^+$ (ES^+), at 3.20 min, UV inactive
2-137	Isomer 2: ethyl 2-{4-[(2*R*,4*S*)-4-fluoro-2-(hydroxymethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**Example 2-135**	**ar**	(300 MHz, DMSO-d_6) δ: 1.16 (t, *J*=7.1 Hz, 3 H), 1.26 - 1.45 (m, 2 H), 1.57 - 1.88 (m, 8 H), 1.91 - 2.09 (m, 3 H), 2.56 - 2.65 (m, 4 H), 2.69 - 2.84 (m, 3 H), 2.99 - 3.17 (m, 4 H), 3.18 - 3.24 (m, 1 H), 3.36 - 3.45 (m, 2 H), 3.99 (q, *J*=7.1 Hz, 2 H), 4.35 (t, *J*=5.7 Hz, 1 H), 4.98 - 5.25 (m, 1 H)	**E**	m/z 384 $(M+H)^+$ (ES^+), at 3.33 min, UV active

2-138	Isomer 2: ethyl 2-{4-[(2*S*)-1-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**91 and 127**	**r**	(400 MHz, CD_3OD) δ: 1.24 (t, *J*=7.0 Hz, 3H), 1.28 – 1.45 (m, 1H), 1.58 – 1.68 (m, 2H), 1.69 – 1.86 (m, 3H), 1.86 - 2.01 (m, 8H), 2.07 – 2.13 (m, 2H), 2.37 (s, 3H), 2.67 – 2.98 (m, 3H), 3.24 – 3.42 (m, 4H), 3.43 – 3.52 (m, 3H), 3.78 – 3.88 (m, 1H), 4.09 (q, J = 7.3 Hz, 2H).	**E**	m/z 418 $(M+H)^+$ (ES+), at 2.57 min, UV active
3-1	Isomer 1: methyl 2-[4-(2-oxo-1,2-dihydropyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**3 and 65**	**b**	(400 MHz, DMSO-d_6) δ: 1.35 – 1.51 (m, 2H), 1.66 – 1.83 (m, 8H), 1.98 – 2.09 (m, 2H), 2.40 – 2.72 (m, 2H), 2.81 – 2.91 (m, 2H), 3.15 – 3.48 (m, 4H), 3.57 (s, 3H), 6.12 (dd, J = 6.5 and 6.5 Hz, 1H), 7.16 – 7.26 (m, 2H), NH not observed	**G**	m/z 346 $(M+H)^+$ (ES+), at 4.34 min, UV active
3-1	Isomer 2: methyl 2-[4-(2-oxo-1,2-dihydropyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**3 and 65**	**b**	(400 MHz, DMSO-d_6) δ: 1.34 – 1.52 (m, 2H), 1.66 – 1.93 (m, 8H), 1.94 – 2.11 (m, 2H), 2.45 – 2.75 (m, 2H), 2.78 – 2.94 (m, 2H), 3.09 – 3.21 (m, 2H), 3.21 – 3.44 (m, 2H), 3.56 (s, 3H), 6.13 (dd, J = 6.5 and 6.5 Hz, 1H), 7.18 – 7.33 (m, 2H), NH not observed	**G**	m/z 346 $(M+H)^+$ (ES+), at 4.43 min, UV active
3-2	Isomer 1: ethyl 2-[4-(2-oxo-1,2-dihydropyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 65**	**b**	(400 MHz, DMSO-d_6) δ: 0.99 – 1.23 (m, 3H), 1.30 – 1.49 (m, 2H), 1.59 – 1.84 (m, 6H), 1.95 – 2.11 (m, 2H), 2.45 – 2.74 (m, 5H), 2.75 – 2.89 (m, 2H), 3.15 – 3.31 (m, 3H), 3.93 – 4.07 (m, 2H), 6.18 (dd, J = 6.5 and 6.5 Hz, 1H), 7.21 (d, J = 6.5 Hz, 1H), 7.26 (d, J = 6.5 Hz, 1H), NH not observed	**F**	m/z 360 $(M+H)^+$ (ES+), at 1.54 min, UV active
3-2	Isomer 2: ethyl 2-[4-(2-oxo-1,2-dihydropyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 65**	**b**	(400 MHz, DMSO-d_6) δ: 1.08 – 1.27 (m, 3H), 1.32 – 1.58 (m, 2H), 1.59 – 1.76 (m, 2H), 1.76 (m, 4H), 1.93 – 2.20 (m, 2H), 2.45 – 2.97 (m, 6H), 3.08 – 3.20 (m, 2H), 3.22 – 3.36 (m, 2H), 3.95 – 4.11 (m, 2H), 6.17 (dd, J = 6.5 and 6.5 Hz, 1H), 7.21 (d, J = 6.5 Hz, 1H), 7.25 (d, J = 6.5 Hz, 1H), NH not observed	**F**	m/z 360 $(M+H)^+$ (ES+), at 1.58 min, UV active
3-3	Isomer 2: 2-fluoroethyl 2-[4-(2-oxo-1,2-dihydropyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**4 and 65**	**b**	(400 MHz, DMSO-d_6) δ: 1.35 – 1.57 (m, 2H), 1.58 – 1.92 (m, 5H), 1.91 – 2.13 (m, 2H), 2.32 – 3.02 (m, 7H), 3.20 – 3.44 (m, 4H), 4.07 – 4.32 (m, 2H), 4.47 – 4.72 (m, 2H), 6.13 (dd, J = 6.5 and 6.5 Hz, 1H), 7.18 – 7.43 (m, 2H), 11.49 (s, 1H)	**F**	m/z 378 $(M+H)^+$ (ES+), at 1.57 min, UV active
3-4	Isomer 2: ethyl 2-[4-(3-hydroxypyridin-2-yl)piperidin-1-yl]-6-	**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 –	**C**	m/z 360 $(M+H)^+$ (ES+), at 1.29 min, UV active

	azaspiro[3.4]octane-6-carboxylate			8.10 (m, 1H), OH not observed		
3-5	Isomer 2: 2-fluoroethyl 2-[4-(2-methoxypyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**4 and 66**	**b**	(400 MHz, DMSO-d_6) δ: 1.48 – 2.08 (m, 11H), 2.65 – 2.79 (m, 2H), 2.84 – 2.94 (m, 2H), 3.14 – 3.24 (m, 2H), 3.26 – 3.40 (m, 3H), 3.86 (m, 3H), 4.15 – 4.21 (m, 1H), 4.21 – 4.30 (m, 1H), 4.48 – 4.57 (m, 1H), 4.61 – 4.69 (m, 1H), 6.94 (dd, J = 7.0 & 5.0 Hz, 1H), 7.58 (d, J = 7.0 Hz, 1H), 8.01 (d, J = 5.0, 1H)	F	m/z 392 $(M+H)^+$ (ES+), at 1.73 min, UV active
3-6	Isomer 2: ethyl 2-[4-(6-methoxy-4-methylpyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 71**	**b**	(400 MHz, DMSO-d_6) δ: 1.16 (t, J = 7.0 Hz, 3H), 1.48 – 1.89 (m, 9H), 1.93 – 2.04 (m, 2H), 2.24 (s, 3H), 2.41 – 2.55 (m, 3H), 2.82 – 2.95 (m, 2H), 3.05 – 3.23 (m, 2H), 3.23 – 3.36 (m, 2H), 3.77 (m, 3H), 3.99 (q, J = 7.0 Hz, 2H), 6.60 (s, 1H), 7.94 (s, 1H)	F	m/z 388 $(M+H)^+$ (ES+), at 1.73 min, UV active
3-7	Isomer 2: ethyl 2-[4-(6-methoxy-5-methylpyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 72**	**b**	(400 MHz, DMSO-d_6) δ: 1.18 (t, J = 7.0 Hz, 3H), 1.54 – 2.10 (m, 12H), 2.12 (s, 3H), 2.70 – 3.10 (m, 2H), 3.15 – 3.23 (m, 2H), 3.24 – 3.36 (m, 2H), 3.37 – 3.52 (m, 2H), 3.84 (m, 3H), 4.00 (q, J = 7.0 Hz, 2H), 7.43 (s, 1H), 7.86 (s, 1H)	F	m/z 388 $(M+H)^+$ (ES+), at 1.77 min, UV active
3-8	Isomer 2: ethyl 2-[4-(2-aminopyrimidin-4-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**1 and 70**	**d**	^{1}H NMR (400 MHz, CD_3OD) δ: 1.18 - 1.32 (m, 3 H), 1.68 - 2.03 (m, 10 H), 2.07 - 2.18 (m, 2 H), 2.49 (t, J=11.7 Hz, 1 H), 2.80 (quin, J=8.0 Hz, 1 H), 3.00 (d, J=11.3 Hz, 2 H), 3.33 - 3.45 (m, 4 H), 4.09 (q, J=7.0 Hz, 2 H), 6.56 (d, J=5.5 Hz, 1 H), 8.12 (d, J=5.5 Hz, 1 H), two NH not observed	B	m/z 360 $(M+H)^+$ (ES+), at 2.98 min, UV active
3-9	Isomer 2: ethyl 2-[4-(4-aminopyrimidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 26**	**as**	(400 MHz, CD_3OD) δ: 1.23 – 1.28 (m, 3H), 1.88 – 1.99 (m, 10H), 2.07 – 2.21 (m, 2H), 2.52 – 2.66 (m, 1H), 2.73 – 2.90 (m, 1H), 2.96 – 3.07 (m, 2H), 3.28 (s, 2H), 3.36 – 3.46 (m, 2H), 4.09 – 4.13 (m, 2H), 6.33 (d, J = 6.0 Hz, 1H), 7.97 (d, J = 6.0 Hz, 1H), 2 x NH not observed	C	m/z 360 $(M+H)^+$ (ES+), at 1.56 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 (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).	B	m/z 369 $(M+H)^+$ (ES+), at 3.33 min, UV active
3-10	Isomer 2: ethyl 2-[4-cyano-4-(pyridin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-	**2 and 14**	**at**	(400 MHz, $CDCl_3$) δ: 1.16 – 1.39 (m, 4H), 1.48 – 1.70 (m, 2H), 1.78 – 2.47 (m, 10H), 2.74 – 3.09 (m, 2H), 3.20 – 3.50	B	m/z 369 $(M+H)^+$ (ES+), at 3.40 min, UV active

	carboxylate			(m, 4H), 4.03 – 4.20 (m, 2H), 7.20 – 7.32 (m, 1H), 7.48 – 7.61 (m, 1H), 7.67 – 7.82 (m, 1H), 8.55 – 8.69 (m, 1H).		
3-11	Isomer 2: ethyl 2-[4-(2-methoxy-4-methylpyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 134**	**b**	(400 MHz, DMSO-d_6) δ: 1.17 (t, J = 7.0 Hz, 3 H), 1.40 (d, J = 12.2 Hz, 2 H), 1.67 - 1.94 (m, 6 H), 2.00 (ddd, J = 9.2, 7.1, 2.6 Hz, 2 H), 2.11 - 2.26 (m, 2 H), 2.29 (s, 3 H), 2.61 - 2.70 (m, 1 H), 2.73 – 2.81 (m, 1 H), 2.86 (d, J = 11.0 Hz, 2 H), 3.26 - 3.38 (m, 2 H), 3.84 (s, 3 H), 4.01 (q, J = 7.0 Hz, 2 H), 4.11 (q, J = 5.2 Hz, 2 H), 6.78 (d, J = 5.2 Hz, 1 H), 7.85 (d, J = 4.9 Hz, 1 H).	**F**	m/z 388 $(M+H)^+$ (ES^+) at 1.86 min, UV active
3-12	Isomer 2: ethyl 2-[4-(2-methoxy-5-methylpyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 129**	**b**	(400 MHz, DMSO-d_6) δ: 1.14-1.19 (m, 4H), 1.57 (d, J = 9.6 Hz, 2H), 1.66 (s, 3H), 1.77-1.85 (m, 4H), 1.86 (s, 2H), 2.01 (d, J = 7.6 Hz, 2H), 2.19 (s, 3H), 2.88 (d, J = 10.0 Hz, 2H), 3.16 (d, J = 5.2 Hz, 2H), 3.26-3.34 (m, 2H), 3.82 (s, 3H), 4.00 (d, J = 6.8 Hz, 2H), 7.40 (s, 1H), 7.80 (s, 1H).	**G**	m/z 388 $(M+H)^+$ (ES^+) at 7.10 min, UV active
3-13	Isomer 2: ethyl 2-[4-(6-methoxypyridin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 141**	**b**	(400 MHz, DMSO-d_6) δ: 1.16 (s, 3 H), 1.57 – 1.89 (m, 11 H), 1.93 – 2.07 (m, 2 H), 2.63 – 2.70 (m, 1 H), 2.86 – 2.95 (m, 2H), 3.08 – 3.18 (m, 2 H), 3.25 – 3.45 (m, 2 H), 3.83 (s, 3 H), 4.00 (d, J = 4.0 Hz, 2 H), 6.60 (d, J = 7.6 Hz, 1 H), 6.80 – 6.90 (m, 1 H), 7.55 – 7.70 (m, 1 H).	**G**	m/z 374 $(M+H)^+$ (ES^+) at 7.15 min, UV active
3-14	Isomer 1: ethyl 2-[4-(4-methyl-2-oxo-1,2-dihydropyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 146**	**b**	(400 MHz, CD_3OD) δ: 0.91 (d, J = 7.3 Hz, 4 H), 1.04 - 1.65 (m, 8 H), 1.84 - 2.21 (m, 4 H), 2.31 (s, 3 H), 2.58 (d, J = 13.7 Hz, 2 H), 2.77 - 3.09 (m, 3 H), 3.25 - 3.47 (m, 2 H), 4.06 - 4.19 (m, 2 H), 6.22 (d, J = 6.7 Hz, 1 H), 7.17 (d, J = 6.4 Hz, 1 H), NH not observed.	**II**	m/z 374 $(M+H)^+$ (ES^+) at 3.85 min, UV active
3-14	Isomer 2: ethyl 2-[4-(4-methyl-2-oxo-1,2-dihydropyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 146**	**b**	(400 MHz, CD_3OD) δ: 0.92 (d, J = 7.3 Hz, 4 H), 1.18 - 1.60 (m, 8 H), 1.88 - 2.25 (m, 4 H), 2.31 (s, 3 H), 2.50 - 3.20 (m, 5 H), 3.28 - 3.50 (m, 2 H), 4.12 (q, J = 7.0 Hz, 2 H), 6.23 (d, J = 6.7 Hz, 1 H), 7.18 (d, J = 6.4 Hz, 1 H), NH not observed.	**I**	m/z 374 $(M+H)^+$ (ES^+) at 4.04 min, UV active
3-15	Isomer 1: ethyl 2-[4-(5-methyl-2-oxo-1,2-dihydropyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-	**2 and 143**	**b**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.17 (t, J = 7.0 Hz, 3H), 1.40 - 1.62 (m, 2H), 1.65 - 1.78 (m, 4H), 1.78 - 1.95 (m, 5H), 1.95 – 2.09 (m, 5H), 2.57 – 2.73 (m, 1H), 2.81 – 3.06 (m, 2H), 3.08 – 3.23 (m, 2H), 3.24 - 3.46 (m, 2H), 4.00 (q, J = 7.0 Hz, 2H), 7.00 (s, 1H), 7.10 (s, 1H), 11.30 (s, 1H).	**E**	m/z 374 $(M+H)^+$ (ES^+) at 3.27 min, UV active

	carboxylate					
3-15	Isomer 2: ethyl 2-[4-(5-methyl-2-oxo-1,2-dihydropyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 143**	**b**	(400 MHz, DMSO-d_6) δ: 1.18 (td, J = 7.1, 2.9 Hz, 3 H), 1.38 - 1.96 (m, 10 H), 2.04 - 2.28 (m, 3 H), 2.57 - 2.77 (m, 1 H), 2.84 - 3.10 (m, 2 H), 3.12 - 3.45 (m, 7 H), 4.01 (q, J = 7.2 Hz, 2 H), 7.00 (s, 1 H), 7.10 (s, 1 H), 11.31 (br. s., 1 H).	**E**	m/z 374 $(M+H)^+$ (ES^+) at 3.33 min, UV active
3-16	Isomer 2: ethyl 2-[4-(2-oxo-1,2-dihydropyridin-4-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 154**	**b**	(400 MHz, DMSO-d_6) δ: 1.16 (t, J = 6.9 Hz, 3 H), 1.41 - 2.09 (m, 12 H), 2.28 - 2.44 (m, 1 H), 2.61 - 2.76 (m, 1 H), 2.86 (d, J = 10.7 Hz, 1 H), 3.03 - 3.44 (m, 5 H), 4.00 (q, J = 7.0 Hz, 2 H), 6.00 (d, J = 7.0 Hz, 1 H), 6.13 (d, J = 8.5 Hz, 1 H), 7.35 (dd, J = 9.2, 7.0 Hz, 1 H), 11.20 - 11.58 (m, 1 H).	**I**	m/z 360 $(M+H)^+$ (ES^+) at 3.26 min, UV active
4-1	Isomer 2: ethyl 2-(2-oxo-3,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate	**2 and 69**	**b**	(400 MHz, DMSO-d_6) δ: 1.17 (t, J = 6.7 Hz, 3 H), 1.22 – 2.11 (m, 18 H), 2.57 - 2.69 (m, 1 H), 2.80 (t, J = 11.6 Hz, 2 H), 2.96 - 3.15 (m, 2 H), 3.16 - 3.30 (m, 4 H), 4.01 (q, J = 7.0 Hz, 2 H), 7.39 (br. s., 1 H).	**G**	m/z 364 $(M+H)^+$ (ES^+) at 4.86 min, UV inactive
4-1	Isomer 3: ethyl 2-(2-oxo-3,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate	**2 and 69**	**b**	(400 MHz, DMSO-d_6) δ: 1.16 (t, J = 7.0 Hz, 3 H), 1.21 - 2.12 (m, 18 H), 2.55 - 2.70 (m, 1 H), 2.72 - 2.86 (m, 2 H), 3.00 - 3.17 (m, 4 H), 3.27 (d, J = 7.0 Hz, 2 H), 4.00 (q, J = 7.2 Hz, 2 H), 7.39 (br. s., 1 H).	**G**	m/z 364 $(M+H)^+$ (ES^+) at 4.95 min, UV inactive
4-1	Isomer 4: ethyl 2-(2-oxo-3,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate	**2 and 69**	**b**	(400 MHz, DMSO-d_6) δ: 1.16 (t, J = 7.0 Hz, 3 H), 1.21 - 1.89 (m, 14 H), 1.89 - 2.02 (m, 3 H), 2.02 - 2.12 (m, 1 H), 2.55 – 2.64 (m, 1 H), 2.65 - 2.85 (m, 2 H), 2.98 - 3.18 (m, 4 H), 3.20 - 3.39 (m, 2 H), 4.00 (q, *J*=7.2 Hz, 2 H), 7.39 (br. s., 1 H).	**G**	m/z 364 $(M+H)^+$ (ES^+) at 4.97 min, UV inactive
4-2	Isomer 4: methyl 2-(2-oxo-3,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate	**3 and 69**	**b**	(400 MHz, DMSO-d_6) δ: 1.07 - 2.20 (m, 18 H), 2.99 - 3.21 (m, 4 H), 3.23 - 3.43 (m, 5 H), 3.56 (s, 3 H), 7.44 (br. s., 1 H).	**G**	m/z 350 $(M+H)^+$ (ES^+) at 3.23 min, UV inactive
4-3	Isomer 2: ethyl 2-(4-methyl-2-oxo-3,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate	**2 and 147**	**b**	(400 MHz, CD_3OD) δ: 0.98 (d, J = 7.0 Hz, 2 H), 1.19 - 1.70 (m, 7 H), 1.71 - 1.84 (m, 2 H), 1.84 - 2.10 (m, 6 H), 2.11 – 2.43 (m, 4 H), 2.83 - 3.09 (m, 2 H), 3.23 - 3.46 (m, 9 H), 4.13 (q, J =7.0 Hz, 2 H).	**E**	m/z 378 $(M+H)^+$ (ES^+) at 3.75 min, UV inactive
4-4	Isomer 1: ethyl 2-(5-methyl-2-oxo-3,4'-bipiperidin-1'-yl)-	**2 and 144**	**b**	(400 MHz, $CDCl_3$) δ: 1.02 (d, J = 6.7 Hz, 2 H), 1.24 - 1.35 (m, 3 H), 1.48 - 2.42 (m, 14 H), 2.76 - 3.30 (m, 10 H), 3.38	**I**	m/z 378 $(M+H)^+$ (ES^+) at 3.59 min, UV inactive

	6-azaspiro[3.4]octane-6-carboxylate			(d, J = 19.8 Hz, 3 H), 4.14 (q, J = 7.0 Hz, 2 H), 6.38 (br. s., 1 H).		
4-4	Isomer 2: ethyl 2-(5-methyl-2-oxo-3,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate	**2 and 144**	**b**	(400 MHz, $CDCl_3$) δ: 1.03 (d, J = 6.4 Hz, 2 H), 1.22 - 1.36 (m, 3 H), 1.48 - 2.19 (m, 14 H), 2.20 – 2.45 (m, 3 H), 2.79 - 3.67 (m, 10 H), 4.13 (q, J = 6.7 Hz, 2 H), 6.58 (br. s., 1 H).	**I**	m/z 378 $(M+H)^+$ (ES^+) at 3.67 min, UV inactive
4-5	Isomer 2: ethyl 2-(1-ethyl-2-oxo-3,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate	**Example 4-1 and 114**	**au**	(400 MHz, CD_3OD) δ: 1.13 (t, J = 7.2 Hz, 3 H), 1.19 (t, J = 7.2 Hz, 3 H), 1.23 - 2.39 (m, 17 H), 2.63 - 3.04 (m, 3 H), 3.25 - 3.52 (m, 9 H), 4.11 (q, J = 7.2 Hz, 2 H).	**I**	m/z 392 $(M+H)^+$ (ES^+) at 3.91 min, UV inactive
4-6	Isomer 2: ethyl 2-[2-oxo-1-(propan-2-yl)-3,4'-bipiperidin-1'-yl]-6-azaspiro[3.4]octane-6-carboxylate	**Example 4-1 and 156**	**au**	(400 MHz, CD_3OD) δ: 1.14 (dd, J = 7.0, 5.2 Hz, 6 H), 1.21 - 1.74 (m, 8 H), 1.79 - 2.01 (m, 7 H), 2.08 - 2.22 (m, 3 H), 2.35 (ddd, J = 10.5, 6.6, 4.3 Hz, 1 H), 2.74 - 3.08 (m, 3 H), 3.10 - 3.23 (m, 1 H), 3.24 - 3.46 (m, 7 H), 4.12 (q, J = 7.2 Hz, 2 H), 4.78 (sept, J = 6.8 Hz, 1 H).	**E**	m/z 406 $(M+H)^+$ (ES^+) at 4.12 min, UV inactive
4-7	Isomer 2: ethyl 2-[4-(2-oxo-1,3-oxazinan-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 132**	**at**	(400 MHz, $CDCl_3$) δ: 1.22 (td, J = 7.0, 3.9 Hz, 3 H), 1.66 – 1.76 (m, 4 H), 1.76 - 1.92 (m, 6 H), 1.92 - 2.12 (m, 4 H), 2.58 - 2.76 (m, 1 H), 2.91 (d, J = 10.2 Hz, 2 H), 3.17 - 3.31 (m, 4 H), 3.31 - 3.44 (m, 2 H), 4.09 (q, J = 7.0 Hz, 2 H), 4.14 - 4.29 (m, 3 H).	**B**	m/z 366 $(M+H)^+$ (ES^+), at 2.35 min, UV inactive
4-8	Isomer 1: ethyl 2-[4-(2-oxotetrahydropyrimidin-1(2*H*)-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 137**	**av**	(400 MHz, $CDCl_3$) δ: 1.24 (td, J = 7.0, 3.1 Hz, 3 H), 1.58 – 1.74 (m, 4 H), 1.74 - 2.01 (m, 8 H), 2.02 - 2.21 (m, 2 H), 2.52 - 2.78 (m, 1 H), 2.78 – 3.03 (m, 2 H), 3.10 - 3.41 (m, 8 H), 4.10 (q, J = 7.3 Hz, 2 H), 4.22 - 4.42 (m, 1 H), 4.67 – 4.82 (m, 1 H).	**E**	m/z 365 $(M+H)^+$ (ES^+), at 2.68 min, UV inactive
4-8	Isomer 2: ethyl 2-[4-(2-oxotetrahydropyrimidin-1(2*H*)-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 137**	**av**	(400 MHz, $CDCl_3$) δ: 1.17 – 1.31 (m, 3H), 1.49 – 1.77 (m, 4H), 1.77 - 1.97 (m, 7H), 1.97 - 2.19 (m, 3H), 2.52 – 3.02 (m, 3H), 3.09 - 3.31 (m, 6H), 3.31 - 3.48 (m, 2H), 4.01 - 4.17 (m, 2H), 4.23 – 4.46 (m, 1H), 4.57 – 4.92 (m, 1H).	**E**	m/z 365 $(M+H)^+$ (ES^+), at 2.81 min, UV inactive
4-9	Mixture of diastereomers: ethyl 2-[4-(5,5-dimethyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 149**	**av**	(400 MHz, $CDCl_3$) δ: 0.96 - 1.12 (m, 5 H), 1.25 (td, J = 7.0, 3.9 Hz, 3 H), 1.46 - 1.96 (m, 8 H), 1.96 - 2.71 (m, 5 H), 2.79 - 3.00 (m, 5 H), 3.16 - 3.60 (m, 5 H), 4.03 - 4.19 (m, 2 H), 4.25 - 4.73 (m, 2 H).	**B**	m/z 393 $(M+H)^+$ (ES^+), at 2.67 min, UV inactive

4-10	Isomer 2: ethyl 2-(1,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate	**2 and 276**	**aw**	(400 MHz, DMSO-d_6) δ: 1.13 (t, *J*=7.0 Hz, 3 H), 1.28 - 1.50 (m, 8H), 1.54 - 1.67 (m, 4 H), 1.67 - 1.86 (m, 4 H), 1.86 - 2.01 (m, 2 H), 2.34 - 2.44 (m, 3 H), 2.50 - 2.62 (m, 2 H), 2.76 (d, *J*=11.7 Hz, 2 H), 3.10 (d, *J*=6.2 Hz, 2 H), 3.19 - 3.26 (m, 3 H), 3.96 (q, *J*=7.0 Hz, 2 H)	E	m/z 350 $(M+H)^+$ (ES^+), at 3.62 min, UV inactive
4-11	Isomer 2: ethyl 2-[4-(morpholin-4-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 272**	**aw**	(400 MHz, DMSO-d_6) δ: 1.14 (t, *J*=7.0 Hz, 3 H), 1.23 - 1.37 (m, 2 H), 1.52 - 1.83 (m, 7 H), 1.92 - 2.12 (m, 3 H), 2.36 - 2.45 (m, 6 H), 2.52 - 2.57 (m, 2 H), 2.76 (d, *J*=10.2 Hz, 2 H), 3.13 - 3.26 (m, 3 H), 3.48 - 3.57 (m, 3 H), 3.98 (q, *J*=7.0 Hz, 2 H)	E	m/z 352 $(M+H)^+$ (ES^+), at 2.70 min, UV inactive
4-12	Isomer 2: ethyl 2-[4-(thiomorpholin-4-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 268**	**aw**	(400 MHz, DMSO-d_6) δ:1.13 (t, *J*=7.0 Hz, 3 H), 1.39 (q, *J*=10.9 Hz, 2 H), 1.49 - 1.66 (m, 5 H), 1.66 - 1.85 (m, 5 H), 1.89 - 2.00 (m, 3 H), 2.22 (t, *J*=12.1 Hz, 2 H), 2.68 - 2.74 (m, 5 H), 2.78 (d, *J*=10.5 Hz, 2 H), 3.11 (d, *J*=5.9 Hz, 2 H), 3.20 - 3.27 (m, 2 H), 3.97 (q, *J*=7.0 Hz, 2 H)	E	m/z 368 $(M+H)^+$ (ES^+), at 3.18 min, UV inactive
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
4-14	Isomer 2: ethyl 2-(4,4-difluoro-1,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate	**2 and 266**	**aw**	(400 MHz, DMSO-d_6) δ: 1.13 (t, *J*=7.0 Hz, 3 H), 1.28 - 1.44 (m, 2 H), 1.56 - 1.67 (m, 4 H), 1.67 - 1.75 (m, 2 H), 1.75 - 2.01 (m, 8 H), 2.20 - 2.30 (m, 1 H), 2.51 - 2.63 (m, 5 H), 2.77 (d, *J*=11.7 Hz, 2 H), 3.11 (d, *J*=6.2 Hz, 2 H), 3.24 (q, *J*=6.9 Hz, 2 H), 3.97 (q, *J*=7.0 Hz, 2 H)	E	m/z 386 $(M+H)^+$ (ES^+), at 3.49 min, UV inactive
4-15	Isomer 2: methyl (2*R*)-1'-[6-(ethoxycarbonyl)-6-azaspiro[3.4]oct-2-yl]-1,4'-bipiperidine-2-carboxylate	**2 and 290**	**aw**	(400 MHz, DMSO-d_6) δ: 1.13 (t, *J*=7.0 Hz, 3 H), 1.23 - 1.50 (m, 7 H), 1.57 - 1.67 (m, 5 H), 1.67 - 1.87 (m, 5 H), 1.95 (t, *J*=8.4 Hz, 2 H), 2.38 - 2.42 (m, 1 H), 2.70 - 2.94 (m, 3 H), 3.11 (d, *J*=5.9 Hz, 2 H), 3.24 (q, *J*=6.8 Hz, 3 H), 3.42 - 3.45 (m, 1 H), 3.58 (s, 3 H), 3.97 (q, *J*=7.0 Hz, 2 H)	E	m/z 408 $(M+H)^+$ (ES^+), at 3.86 min, UV inactive
4-16	Isomer 2: ethyl 2-[(2*R*)-2-(methylcarbamoyl)-1,4'-bipiperidin-1'-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 223**	**ax**	(400 MHz, $CDCl_3$) δ: 1.22 (t, J = 6.8 Hz, 3H), 1.41 - 1.50 (m, 2H), 1.61 - 1.75 (m, 4H), 1.81 - 1.95 (m, 6H), 2.51 - 2.61 (m, 1H), 2.70 - 2.75 (m, 1H), 2.82 (d, J = 4.6 Hz, 3H), 2.95 - 3.45 (m, 11H), 3.10 - 3.27 (m, 4H), 4.12 (q, J = 6.8 Hz, 2H), 7.06 (br.s., 1H).	M	m/z 407 $(M+H)^+$ (ES+), at 1.69 min, UV inactive
4-17	Isomer 2: ethyl 2-[(2*R*)-2-	**2 and**	**aw**	(400 MHz, DMSO-d_6) δ: 1.13 (t, *J*=7.0 Hz, 3 H), 1.29 - 1.41	E	m/z 421 $(M+H)^+$ (ES^+), at

	(dimethylcarbamoyl)-1,4'-bipiperidin-1'-yl]-6-azaspiro[3.4]octane-6-carboxylate	**283**		(m, 2 H), 1.43 - 1.53 (m, 3 H), 1.53 - 1.66 (m, 5 H), 1.66 - 1.74 (m, 2 H), 1.74 - 1.87 (m, 3 H), 1.87 - 1.99 (m, 3 H), 2.41 - 2.45 (m, 3 H), 2.76 (s, 6 H), 3.10 (d, *J*=6.2 Hz, 4 H), 3.12 - 3.15 (m, 4 H), 3.97 (q, *J*=7.0 Hz, 2 H)		4.13 min, UV inactive
4-18	Isomer 2: ethyl 2-[(2*S*)-2-(methylcarbamoyl)-1,4'-bipiperidin-1'-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2 and 225**	**ax**	(400 MHz, $CDCl_3$) δ: 1.25 (t, J = 6.8 Hz, 3H), 1.41 - 1.50 (m, 2H), 1.61 - 1.75 (m, 4H), 1.81 - 1.95 (m, 6H), 2.51 - 2.61 (m, 1H), 2.70 - 2.75 (m, 1H), 2.82 (d, J = 4.6 Hz, 3H), 2.95 - 3.45 (m, 11H), 3.10 - 3.27 (m, 4H), 4.12 (q, J = 6.8 Hz, 2H), 7.22 (br.s., 1H).	**M**	m/z 407 $(M+H)^+$ (ES+), at 1.67 min, UV inactive
4-19	Isomer 2: ethyl 2-(1-propanoyl-2,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate	**222, 229 and 230**	**y**	(400 MHz, $CDCl_3$) δ: 1.10 - 1.15 (m, 3H), 1.22 - 1.25 (m, 3H), 1.34 - 1.54 (m, 4H), 1.55 - 1.68 (m, 4H), 1.70 - 1.80 (m, 3H), 1.81 - 1.90 (m, 4H), 1.98 - 2.20 (m, 6H), 2.27 - 2.40 (m, 2H), 2.42 - 3.10 (m, 3H), 3.22 - 3.34 (m, 2H), 3.34 - 3.45 (m, 2H), 4.05 - 4.15 (m, 2H), 4.53 - 4.64 (m, 1H).	**O**	m/z 406 $(M+H)^+$ (ES+), at 4.48 min, UV inactive
4-20	Isomer 2: ethyl 2-[1-(methylcarbamoyl)-2,4'-bipiperidin-1'-yl]-6-azaspiro[3.4]octane-6-carboxylate	**57 and 229**	**m**	(400 MHz, $CDCl_3$) δ: 1.22 - 1.27 (m, 3H), 1.31 - 1.47 (m, 3H), 1.48 - 1.62 (m, 5H), 1.72 - 1.79 (m, 2H), 1.82 - 1.91 (m, 4H), 2.02 - 2.12 (m, 5H), 2.61 - 2.82 (m, 5H), 2.90 - 3.06 (m, 2H), 3.25 - 3.33 (m, 2H), 3.34 - 3.44 (m, 2H), 3.48 - 3.64 (m, 1H), 3.88 - 4.00 (m, 1H), 4.05 - 4.13 (m, 2H), 4.37 (br.s., 1H).	**O**	m/z 407 $(M+H)^+$ (ES+), at 4.29 min, UV inactive
5-1	Isomer 2: ethyl 2-[4-(2-oxoazepan-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate	**2, 214 and 322**	**ay**	(400 MHz, CD_3OD) δ: 1.24 (t, *J* = 7.0 Hz, 3 H), 1.52 - 1.79 (m, 10 H), 1.80 - 1.99 (m, 6 H), 2.04 - 2.17 (m, 2 H), 2.48 - 2.61 (m, 2 H), 2.72 - 2.88 (m, 1 H), 2.96 (d, *J* = 11.7 Hz, 2 H), 3.26 (s, 2 H), 3.33 - 3.46 (m, 4 H), 4.09 (q, *J* = 7.0 Hz, 2 H), 4.40 (tt, *J* = 12.01, 4.20 Hz, 1 H)	**E**	m/z 378 (M+H)+ (ES+), at 2.85 min, UV inactive
5-2	Isomer 2: ethyl 2-{4-[2-(methoxycarbonyl)azepan-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate	**2 and 190**	**as**	(400 MHz, $CDCl_3$) δ: 1.24 (t, J = 7.0 Hz, 3 H), 1.28 - 2.14 (m, 20 H), 2.46 - 2.70 (m, 2 H), 2.73 - 2.92 (m, 3 H), 2.94 - 3.05 (m, 1 H), 3.21 - 3.46 (m, 4 H), 3.52 - 3.61 (m, 1 H), 3.67 (s, 3 H), 4.06 - 4.16 (m, 2 H)	**B**	m/z 422 $(M+H)^+$ (ES+), at 5.54 min, UV active

BIOLOGICAL ACTIVITY

EXAMPLE A

Phospho-ERK1/2 assays

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.

pEC_{50} and E_{max} figures were calculated from the resulting data for each receptor subtype.

The results are set out in Table 4 below.

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)
1-4 Isomer 2	6.0 (55)	NT	NT	6.6 (67)
1-5 Isomer 2	6.9 (94)	<4.7 (19)	<4.7 (2)	7.7 (81)
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)
1-11 Isomer 2	5.8 (98)	NT	NT	6.6 (85)
1-12 Isomer 2	6.0 (85)	<4.7 (11)	<4.7 (15)	6.9 (128)
1-13 Isomer 2	5.8 (61)	NT	NT	6.4 (86)
1-14 Isomer 2	6.2 (66)	<4.7 (27)	<4.7 (5)	7.3 (99)
1-15 Isomer 2	7.0 (70)	<4.7 (4)	<4.7 (6)	NT
1-16 Isomer 2	5.8 (80)	*5.1 (34)	<4.7 (1)	6.8 (82)
1-17 Isomer 2	6.2 (53)	<4.7 (14)	<4.7 (0)	7.2 (90)
1-18 Isomer 2	6.9 (65)	<4.7 (3)	<4.7 (56)	7.3 (89)
1-19 Isomer 2	6.1 (83)	NT	NT	*5.1 (48)
1-20 Mixture of diastereomers	<4.7 (62)	NT	NT	6.0 (56)
1-21 Isomer 2	<4.7 (11)	<4.7 (8)	<4.7 (0)	7.4 (79)
1-22 Isomer 2	6.7 (47)	NT	NT	<4.7 (20)
1-23 Isomer 2	6.4 (55)	<4.7 (7)	<4.7 (9)	7.5 (105)
1-24 Isomer 2	6.6 (102)	*5.2 (32)	<4.7 (0)	7.6 (78)
1-25 Isomer 2	7.3 (110)	<4.7 (15)	<4.7 (13)	8.4 (128)
1-26 Isomer 2	5.6 (46)	<4.7 (99)	6.1 (53)	6.7 (76)
1-27 Isomer 2	6.0 (27)	NT	NT	6.4 (41)
1-28 Isomer 2	5.7 (57)	NT	NT	6.3 (60)
1-29 Isomer 2	6.1 (44)	NT	NT	6.9 (36)
1-30 Isomer 2	6.5 (37)	<4.7 (9)	<4.7 (5)	7.9 (101)
1-31 Isomer 2	5.6 (34)	NT	NT	7.0 (40)
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)
1-34 Isomer 1	6.3 (49)	<4.7 (10)	<4.7 (0)	6.8 (48)
1-34 Isomer 2	8.1 (130)	<4.7 (43)	<4.7 (0)	8.6 (117)
1-35 Isomer 2	6.4 (80)	NT	NT	6.7 (61)
1-36 Isomer 2	5.3 (73)	NT	NT	6.6 (47)
1-37 Isomer 2	5.6 (78)	NT	NT	6.3 (126)
1-38 Isomer 2	7.0 (31)	<4.7 (14)	<4.7 (19)	6.1 (98)
1-39 Isomer 2	6.0 (49)	NT	NT	6.4 (97)
1-40 Isomer 2	<4.7 (904)	NT	NT	6.8 (50)
1-41 Isomer 2	6.0 (52)	NT	NT	6.6 (35)
1-42 Isomer 2	7.4 (123)	6.5 (27)	<4.7 (16)	8.2 (76)
1-43 Isomer 2	6.8 (32)	<4.7 (7)	<4.7 (8)	7.5 (61)
1-44 Isomer 2	7.1 (126)	<4.7 (80)	<4.7 (7)	8.2 (126)
1-45 Isomer 2	6.5 (80)	5.8 (56)	<4.7 (26)	7.7 (80)
1-46 Isomer 2	<4.7 (35)	NT	NT	6.7 (63)
1-47 Isomer 2	<4.7 (7)	4.7 (82)	<4.7 (19)	7.8 (81)
1-48 Isomer 2	<4.7 (63)	NT	NT	6.2 (68)
1-49 Isomer 2	5.2 (71)	<4.7 (21)	<4.7 (9)	7.1 (92)
1-50 Isomer 2	8.1 (124)	<4.7 (20)	<4.7 (8)	8.7 (122)
1-51 Isomer 2	5.9 (74)	NT	NT	6.8 (106)
1-52 Isomer 2	6.8 (102)	<4.7 (15)	<4.7 (20)	7.8 (106)
1-53 Isomer 2	5.3 (38)	NT	NT	5.9 (80)
1-54 Isomer 2	<4.7 (51)	NT	NT	6.1 (74)
1-55 Isomer 2	5.3 (40)	NT	NT	6.3 (64)

1-56 Isomer 2	6.0 (30)	<4.7 (0)	<4.7 (3)	6.9 (89)
1-57 Isomer 2	5.7 (63)	<4.7 (7)	<4.7 (7)	6.9 (69)
1-58 Isomer 2	6.1 (55)	<4.7 (13)	<4.7 (2)	7.5 (93)
1-59 Isomer 2	6.4 (38)	NT	NT	7.0 (76)
1-60 Isomer 2	6.5 (82)	NT	NT	7.4 (88)
1-61 Isomer 2	6.5 (66)	<4.7 (1)	<4.7 (2)	7.6 (97)
1-62 Isomer 2	5.9 (73)	NT	NT	<4.7 (10)
1-63 Isomer 2	<4.7 (82)	NT	NT	6.0 (24)
1-64 Isomer 2	5.3 (40)	NT	NT	6.5 (78)
1-65 Isomer 2	<4.7 (60)	NT	NT	6.6 (73)
1-66 Isomer 2	<4.7 (14)	NT	NT	6.6 (32)
1-67 Isomer 2	5.5 (37)	NT	NT	6.5 (75)
1-68 Isomer 2	7.1 (91)	NT	NT	8.2 (98)
1-69 Isomer 2	7.1 (99)	NT	NT	8.3 (104)
1-70 Isomer 2	7.1 (92)	NT	NT	8.3 (101)
1-71 Isomer 2	<4.7 (6)	NT	NT	7.0 (69)
1-72 Isomer 2	<4.7 (17)	NT	NT	6.8 (69)
1-73 Isomer 2	<4.7 (11)	NT	NT	6.9 (72)
2-1 Isomer 2	<4.7 (6)	<4.7	<4.7	6.5 (63)
2-2 Isomer 2	6.1 (39)	<4.7 (53)	<4.7 (16)	7.2 (79)
2-3 Isomer 2	*5.0 (32)	<4.7 (14)	<4.7 (4)	7.3 (89)
2-4 Isomer 2	6.5 (102)	<4.7 (2)	<4.7 (3)	7.3 (110)
2-5 Isomer 2	*5.2 (34)	NT	NT	6.8 (66)
2-6 Isomer 2	5.5 (57)	<4.7 (30)	<4.7 (16)	7.8 (132)
2-7 Isomer 2	6.1 (41)	<4.7 (13)	*5.1 (27)	7.9 (100)
2-8 Isomer 2	6.2 (36)	<4.7 (3)	<4.7 (4)	7.8 (86)
2-9 Isomer 2	6.0 (43)	<4.7 (4)	<4.7 (6)	8.0 (104)
2-10 Isomer 2	<4.7 (19)	NT	NT	6.7 (50)
2-11 Isomer 2	*4.7 (39)	<4.7 (7)	<4.7 (7)	7.6 (100)
2-12 Isomer 2	<4.7 (9)	<4.7 (9)	<4.7 (6)	8.0 (57)
2-13 Isomer 2	*5.0 (69)	<4.7 (7)	<4.7 (24)	6.8 (57)
2-14 Isomer 2	<4.7 (43)	<4.7 (3)	<4.7 (7)	7.8 (91)
2-15 Isomer 2	6.4 (72)	<4.7 (9)	<4.7 (9)	7.8 (111)
2-16 Isomer 2	6.6 (41)	<4.7 (53)	<4.7 (7)	8.2 (114)
2-17 Isomer 2	6.7 (72)	<4.7 (5)	<4.7 (4)	8.5 (116)
2-18 Isomer 2	<4.7 (8)	<4.7 (1)	<4.7 (4)	7.1 (56)
2-19 Isomer 2	6.2 (44)	<4.7 (3)	<4.7 (10)	8.1 (113)
2-20 Isomer 2	<4.7 (24)	<4.7 (1)	<4.7 (6)	7.5 (106)
2-21 Isomer 2	6.2 (46)	<4.7 (4)	<4.7 (2)	8.1 (113)
2-22 Isomer 2	<4.7 (7)	NT	NT	6.5 (31)
2-23 Isomer 2	5.9 (65)	<4.7 (3)	<4.7 (9)	7.3 (104)
2-24 Isomer 2	6.2 (37)	<4.7 (5)	<4.7 (9)	7.7 (121)
2-25 Isomer 2	6.2 (74)	<4.7 (6)	<4.7 (2)	8.0 (86)
2-26 Isomer 2	*7.9 (92)	<4.7 (66)	<4.7 (4)	8.2 (99)
2-27 Isomer 2	*7.5 (24)	<4.7 (0.4)	<4.7 (15)	8.0 (73)
2-28 Isomer 2	<4.7 (7)	<4.7 (3)	<4.7 (5)	7.6 (63)
2-29 Isomer 2	6.3 (60)	<4.7 (5)	<4.7 (13)	7.8 (110)
2-30 Isomer 2	6.3 (34)	<4.7 (52)	<4.7 (13)	7.8 (97)
2-31 Isomer 2	6.9 (93)	<4.7 (7)	<4.7 (7)	8.5 (108)
2-32 Isomer 2	5.6 (69)	<4.7 (52)	<4.7 (11)	7.9 (110)
2-33 Isomer 1	6.4 (86)	<4.7 (8)	<4.7 (3)	8.1 (109)

2-33 Isomer 2	<4.7 (4)	<4.7 (5)	<4.7 (5)	7.7 (65)
2-34 Isomer 1	5.7 (74)	<4.7 (16)	<4.7 (8)	7.6 (89)
2-34 Isomer 2	5.5 (56)	<4.7 (3)	<4.7 (39)	6.6 (58)
2-35 Isomer 2	6.4 (108)	<4.7 (1)	<4.7 (4)	7.8 (92)
2-36 Isomer 2	6.8 (89)	<4.7 (3)	<4.7 (5)	8.2 (113)
2-37 Isomer 2	5.5 (106)	<4.7 (33)	<4.7 (58)	7.7 (83)
2-38 Isomer 2	6.8 (110)	<4.7 (1)	<4.7 (2)	8.3 (115)
2-39 Isomer 2	5.6 (41)	<4.7 (1)	<4.7 (1)	7.8 (76)
2-40 Isomer 2	6.1 (78)	<4.7 (2)	<4.7 (1)	7.5 (90)
2-41 Isomer 2	5.6 (36)	NT	NT	7.0 (91)
2-43 Isomer 2	*5.5 (19)	<4.7 (4)	<4.7 (5)	7.3 (47)
2-44 Isomer 2	6.5 (71)	<4.7 (4)	<4.7 (8)	8.3 (100)
2-45 Isomer 2	6.6 (67)	<4.7 (5)	<4.7 (5)	8.3 (111)
2-46 Isomer 2	*5.8 (32)	<4.7 (5)	<4.7 (8)	7.8 (85)
2-47 Isomer 2	5.2 (45)	NT	NT	6.0 (63)
2-48 Isomer 2	6.5 (34)	<4.7 (3)	<4.7 (5)	8.0 (81)
2-50 Isomer 2	6.6 (63)	<4.7 (4)	<4.7 (2)	7.6 (73)
2-51 Isomer 2	<4.7(237)	<4.7 (1)	<4.7 (3)	7.2 (53)
2-52 Isomer 2	6.2 (49)	<4.7 (4)	<4.7 (4)	7.7 (85)
2-53 Isomer 2	7.1 (109)	<4.7 (10)	*5.2 (21)	8.1 (126)
2-54 Isomer 1	<4.7 (1)	<4.7 (50)	<4.7 (0)	7.8 (45)
2-54 Isomer 2	7.3 (86)	<4.7 (8)	<4.7 (23)	8.9 (134)
2-55 Isomer 1	<4.7 (15)	NT	NT	6.8 (67)
2-55 Isomer 2	<4.7 (7)	<4.7 (22)	<4.7 (12)	7.6 (52)
2-56 Isomer 2	6.2 (96)	<4.7 (8)	<4.7 (0)	8.3 (134)
2-57 Isomer 2	<4.7 (16)	<4.7 (25)	<4.7 (4)	7.5 (117)
2-58 Isomer 2	6.0 (66)	<4.7 (45)	<4.7 (9)	7.5 (156)
2-59 Isomer 2	*5.5 (28)	<4.7 (11)	<4.7 (7)	6.6 (67)
2-61 Isomer 2	<4.7 (10)	NT	NT	6.3 (40)
2-62 Isomer 2	<4.7 (20)	<4.7 (6)	<4.7 (8)	7.8 (65)
2-63 Isomer 2	6.6 (34)	<4.7 (0)	<4.7 (4)	7.2 (60)
2-64 Isomer 2	<4.7 (12)	<4.7 (6)	<4.7 (8)	8.5 (41)
2-65 Isomer 2	6.8 (60)	<4.7 (1)	<4.7 (1)	8.1 (107)
2-66 Isomer 2	7.4 (96)	<4.7 (18)	<4.7 (8)	8.9 (115)
2-67 Isomer 2	<4.7 (19)	<4.7 (67)	<4.7 (1)	7.7 (79)
2-68 Isomer 2	6.0 (32)	<4.7 (4)	<4.7 (6)	7.2 (73)
2-69 Isomer 2	6.4 (87)	<4.7 (3)	<4.7 (2)	7.9 (110)
2-70 Isomer 1	5.4 (37)	NT	NT	6.8 (52)
2-70 Isomer 2	5.8 (93)	<4.7 (1)	<4.7 (3)	7.5 (111)
2-71 Isomer 2	5.3 (39)	NT	NT	6.9 (56)
2-72 Isomer 2	6.1 (30)	<4.7 (13)	<4.7 (10)	7.1 (52)
2-73 Isomer 2	<4.7 (14)	NT	NT	6.5 (43)
2-74 Isomer 2	<4.7 (18)	<4.7 (16)	<4.7 (8)	7.1 (54)
2-75 Isomer 2	6.5 (80)	<4.7 (6)	<4.7 (4)	8.6 (109)
2-76 Isomer 1	6.9 (82)	<4.7 (10)	<4.7 (35)	7.4 (114)
2-76 Isomer 2	7.3 (88)	<4.7 (16)	<4.7 (14)	7.9 (107)
2-77 Isomer 2	6.6 (51)	<4.7 (14)	<4.7 (47)	8.2 (105)
2-78 Isomer 2	<4.7 (11)	4.9 (27)	<4.7 (5)	6.9 (49)
2-79 Isomer 2	6.3 (37)	<4.7 (2)	<4.7 (19)	7.5 (70)
2-80 Isomer 2	6.9 (98)	<4.7 (16)	<4.7 (18)	7.7 (107)
2-81 Isomer 2	<4.7 (12)	NT	NT	7.2 (33)

2-82 Isomer 2	6.3 (52)	<4.7 (1)	<4.7 (0)	7.7 (70)
2-83 Isomer 2	5.4 (55)	NT	NT	8.0 (100)
2-84 Isomer 2	6.6 (36)	<4.7	<4.7	7.7 (82)
2-85 Isomer 2	5.6 (66)	NT	NT	<4.7 (3)
2-87 Isomer 2	6.4 (46)	<4.7 (54)	<4.7 (3)	7.8 (100)
2-88 Isomer 2	6.5 (25)	<4.7 (80)	<4.7 (5)	7.4 (44)
2-89 Isomer 2	5.2 (37)	<4.7 (68)	<4.7 (8)	6.7 (102)
2-90 Isomer 2	6.8 (54)	<4.7 (4)	<4.7 (1)	7.9 (53)
2-91 Isomer 2	6.3 (40)	<4.7 (12)	<4.7 (10)	7.1 (67)
2-92 Isomer 2	5.5 (50)	<4.7 (2)	<4.7 (5)	7.5 (82)
2-93 Isomer 2	<4.7 (7)	NT	NT	<4.7 (3)
2-94 Isomer 2	<4.7 (7)	NT	NT	5.17 (80)
2-95 Isomer 2	<4.7 (19)	<4.7 (16)	<4.7 (9)	7.2 (49)
2-96 Isomer 2	<4.7 (2)	<4.7 (1)	<4.7 (5)	6.9 (63)
2-97 Isomer 2	<4.7 (5)	<4.7 (3)	<4.7 (3)	7.4 (37)
2-98 Isomer 2	<4.7 (10)	NT	NT	6.9 (45)
2-99 Isomer 2	<4.7 (18)	NT	NT	6.8 (54)
2-100 Isomer 2	<4.7 (16)	<4.7 (4)	<4.7 (5)	6.7 (55)
2-101 Isomer 2	5.0 (70)	NT	NT	6.2 (98)
2-102 Isomer 2	5.3 (23)	<4.7 (1)	<4.7 (11)	6.5 (45)
2-103 Isomer 2	6.7 (26)	<4.7 (4)	<4.7 (3)	7.7 (100)
2-104 Isomer 2	7.1 (102)	<4.7 (8)	<4.7 (8)	7.8 (111)
2-105 Isomer 2	<4.7 (26)	NT	NT	6.7 (38)
2-106 Isomer 2	6.9 (97)	<4.7 (10)	<4.7 (5)	7.7 (102)
2-107 Isomer 2	7.2 (87)	<4.7 (5)	<4.7 (46)	8.2 (92)
2-109 Isomer 2	6.4 (50)	<4.7 (9)	5.0 (26)	7.8 (91)
2-109 Isomer 4	6.5 (42)	<4.7 (15)	<4.7 (9)	7.7 (82)
2-111 Isomer 2	6.3 (31)	<4.7 (1)	<4.7 (0)	7.5 (62)
2-112 Isomer 2	<4.7 (7)	NT	NT	6.6 (63)
2-113 Isomer 2	6.9 (100)	NT	NT	7.8 (113)
2-114 Isomer 2	6.9 (103)	NT	NT	8.1 (114)
2-115 Isomer 2	6.7 (68)	NT	NT	7.6 (78)
2-116 Isomer 2	7.2 (109)	NT	NT	8.2 (103)
2-117 Isomer 2	5.2 (99)	<4.7 (4)	<4.7 (7)	7.2 (96)
2-118 Isomer 2	<4.7 (33)	NT	NT	6.9 (84)
2-119 Isomer 2	5.6 (85)	NT	NT	6.9 (84)
2-120 Isomer 2	6.4 (96)	NT	NT	6.5 (87)
2-121 Isomer 2	6.0 (31)	NT	NT	6.7 (60)
2-122 Isomer 2	6.0 (59)	NT	NT	6.8 (60)
2-123 Isomer 2	6.5 (114)	<4.7 (8)	<4.7 (29)	6.5 (93)
2-124 Isomer 2	6.2 (45)	<4.7 (2)	<4.7 (0)	7.1 (77)
2-125 Isomer 2	5.4 (32)	NT	NT	6.5 (81)
2-126 Isomer 2	<4.7 (15)	NT	NT	7.1 (60)
2-127 Isomer 2	<4.7 (11)	NT	NT	8.0 (72)
2-128 Isomer 2	5.0 (89)	NT	NT	5.8 (104)
2-129 Isomer 2	<4.7 (12)	NT	NT	7.0 (55)
2-130 Isomer 1	6.5(42)	NT	NT	7.9 (20)
2-130 Isomer 2	<4.7 (11)	NT	NT	7.2 (66)
2-131 Isomer 2	6.3 (61)	NT	NT	6.8 (108)
2-132 Isomer 2	<4.7 (18)	NT	NT	7.9 (72)
2-133 Isomer 1	<4.7 (37)	NT	NT	8.0 (70)

2-133 Isomer 2	7.1 (69)	NT	NT	9.2 (118)
2-134 Isomer 2	<4.7 (18)	NT	NT	7.2 (95)
2-135 Isomer 2	<4.7 (15)	NT	NT	7.9 (90)
2-136 Isomer 2	6.2 (105)	NT	NT	7.9(110)
2-137 Isomer 2	6.0(78)	NT	NT	7.4 (111)
2-138 Isomer 2	<4.7 (17)	NT	NT	7.4 (44)
3-2 Isomer 1	7.5 (97)	<4.7 (7)	<4.7 (0)	8.2 (115)
3-3 Isomer 2	7.6 (81)	*5.0 (50)	<4.7 (56)	8.2 (106)
3-5 Isomer 2	<4.7 (20)	<4.7 (65)	<4.7 (11)	7.8 (80)
3-6 Isomer 2	<4.7 (74)	<4.7 (0)	<4.7 (4)	7.4 (58)
3-7 Isomer 2	<4.7 (40)	NT	NT	7.0 (39)
3-8 Isomer 2	<4.7 (19)	<4.7 (2)	<4.7 (0)	7.6 (54)
3-9 Isomer 2	6.6 (103)	<4.7 (2)	<4.7 (4)	7.6 (96)
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)
3-11 Isomer 2	7.4 (36)	NT	NT	7.6 (58)
3-12 Isomer 2	6.6 (34)	<4.7 (2)	<4.7 (5)	8.4 (110)
3-13 Isomer 2	7.9 (97)	<4.7 (2)	<4.7 (1)	7.9 (82)
3-14 Isomer 1	5.5 (65)	NT	NT	6.3 (65)
3-14 Isomer 2	5.5 (29)	NT	NT	6.6 (75)
3-15 Isomer 2	6.6 (60)	NT	NT	7.4 (36)
3-16 Isomer 2	5.1 (39)	NT	NT	5.6 (47)
4-1 Isomer 2	<4.7 (10)	NT	NT	7.16 (47)
4-1 Isomer 4	6.4 (58)	<4.7 (3)	<4.7 (5)	7.3 (68)
4-2 Isomer 4	6.1 (94)	NT	NT	7.1 (42)
4-3 Isomer 2	6.8 (103)	<4.7 (9)	<4.7 (4)	7.9 (88)
4-4 Isomer 2	7.5 (97)	<4.7 (19)	<4.7 (21)	8.3 (73)
4-5 Isomer 2	6.3 (52)	<4.7 (9)	<4.7 (9)	7.8 (60)
4-6 Isomer 2	6.9 (66)	<4.7 (75)	<4.7 (9)	7.3 (77)
4-7 Isomer 2	5.4 (73)	<4.7 (1)	<4.7 (10)	6.6 (67)
4-8 Isomer 1	6.3 (42)	<4.7 (3)	<4.7 (8)	7.2 (74)
4-10 Isomer 2	<4.7 (7)	NT	NT	6.6 (31)
4-11 Isomer 2	<4.7 (54)	NT	NT	6.7 (55)
4-12 Isomer 2	<4.7 (19)	<4.7 (7)	<4.7 (14)	7.4 (32)
4-13 Isomer 2	6.2 (51)	<4.7 (10)	<4.7 (13)	7.0 (59)
4-14 Isomer 2	6.7 (28)	<4.7 (55)	<4.7 (0)	7.7 (48)
4-15 Isomer 2	6.6 (82)	<4.7 (7)	<4.7 (13)	7.2 (113)
4-16 Isomer 2	6.0 (94)	NT	NT	6.8 (105)
4-17 Isomer 2	<4.7 (27)	NT	NT	6.6 (106)
4-18 Isomer 2	5.5 (76)	NT	NT	6.2 (79)
4-19 Isomer 2	<4.7 (7)	NT	NT	6.6 (38)
4-20 Isomer 2	<4.7 (11)	NT	NT	6.8 (34)
5-2 Isomer 2	6.0 (58)	<4.7 (5)	<4.7 (4)	7.3 (96)

* – variable results, NT – Not tested

EXAMPLE B

Passive avoidance

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.

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

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.

Data for Examples 1-21 Isomer 2, 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

A tablet composition containing a compound of the formula (1), (1a) or (1b) 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

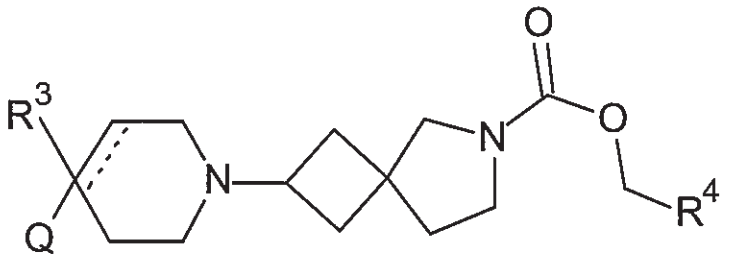
A capsule formulation is prepared by mixing 100 mg of a compound of the formula (1), (1a) or (1b) with 100 mg lactose and optionally 1% by weight of magnesium stearate and filling the resulting mixture into standard opaque hard gelatin capsules.

Equivalents

The foregoing examples are presented for the purpose of illustrating the invention and should not be construed as imposing any limitation on the scope of the invention. It will readily be apparent that numerous modifications and alterations may be made to the specific embodiments of the invention described above and illustrated in the examples without departing from the principles underlying the invention. All such modifications and alterations are intended to be embraced by this application.

CLAIMS

1. A compound of the formula (1b):



(1b)

or a salt thereof, wherein

Q is an optionally substituted five or six or seven membered heterocyclic ring containing 1, 2, 3 or 4 heteroatom ring members selected from N, O and S; wherein Q may be substituted with one, two or three substituents, which may be selected from R^1 and/or R^2 wherein R^1 and R^2 may be the same or different or Q may be substituted with (L)-R^{10}, (L)-R^{11} and (L)-R^{12}, where L is a bond or a CH_2 group; R^{10}, R^{11} and R^{12} are independently selected from hydrogen; fluorine; chlorine; bromine; cyano; oxo; hydroxy; OR^{15}; $NR^{15}R^{16}$; COR^{15}; CSR^{15}; $COOR^{15}$; $COSR^{15}$; $OCOR^{15}$; $NR^{17}COR^{15}$; $CONR^{15}R^{16}$; $CSNR^{15}R^{16}$; $NR^{17}CONR^{15}R^{16}$; $R^{17}COOR^{15}$; $OCONR^{15}R^{16}$; SR^{15}; SOR^{15} and SO_2R^{15}; 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, wherein the optional substituents for the optionally substituted 5- or 6-membered ring are selected from group R^8;

R^1 is selected from hydrogen; fluorine; chlorine; bromine; cyano; oxo; hydroxy; 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 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, wherein the optional substituents for the optionally substituted 5- or 6-membered ring are selected from group R^8;

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; and 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^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;

R^8 is selected from hydrogen; fluorine; chlorine; bromine; cyano; oxo; hydroxy; 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; and 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;

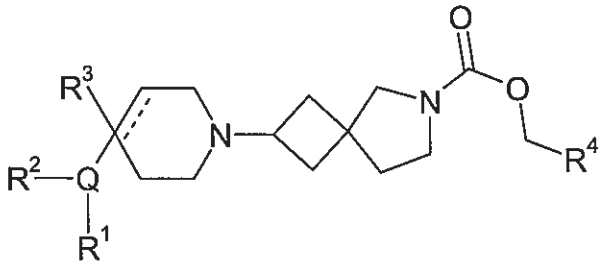
R^{15}, R^{16} and R^{17} are the same or different, or may be joined together to form a ring, and each is independently selected from hydrogen, a non-aromatic C_{1-6} hydrocarbon group optionally substituted with one or more fluorine atoms and wherein one or two, but not all, carbon atoms of the hydrocarbon group may optionally be replaced by a heteroatom selected from O, N and S and oxidized forms thereof; or a group of formula $CH_2N(R^a)COOR^b$; or a group of formula (L)-R^{18} where L is a bond or a CH_2 group and R^{18} is 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, wherein the optional substituents for the optionally substituted 5- or 6-membered ring are selected from group R^8;

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;
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.

2. A compound according to claim 1 represented by 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^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 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; and 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;

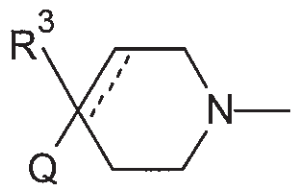
and the dotted line indicates an optional second carbon-carbon bond, provided that when a second carbon-carbon bond is present, then R^3 is absent.

3. A compound according to claims 1 or 2 wherein Q is an aromatic heterocyclic ring containing one or two nitrogen atoms.

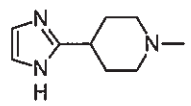
4. A compound according to claim 3 wherein Q is (i) an imidazole ring or (ii) a pyrazole ring or wherein Q is (i) a piperidin-2-one ring or (ii) a pyrrolidine ring.

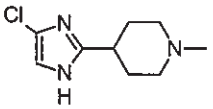
5. The compound according to claim 1 wherein Q is a 5, 6 or 7 membered unsaturated heterocyclic ring.

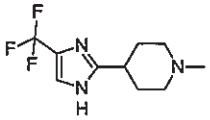
6. The compound according to claim 1 wherein the moiety:

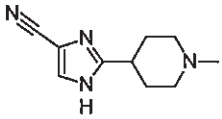


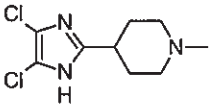
is selected from groups AAA to ACB, BAA to BCZ, CAA to CBZ, DAA to DBG or EAA to EAB:

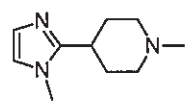

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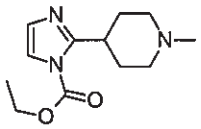

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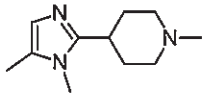

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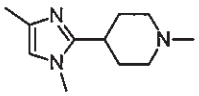

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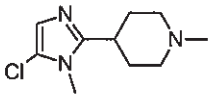

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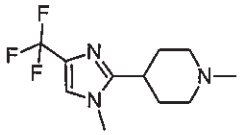

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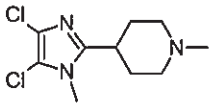

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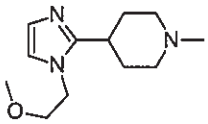

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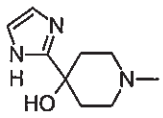

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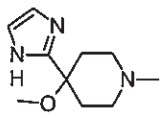

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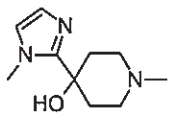

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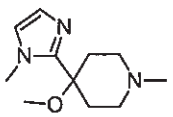

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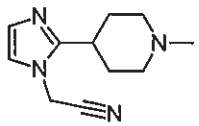

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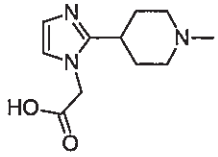

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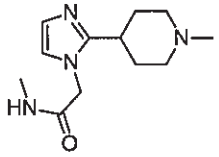

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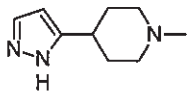

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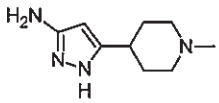

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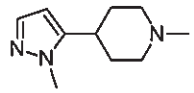

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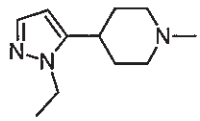

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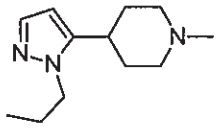

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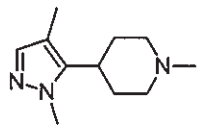

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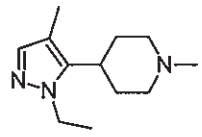

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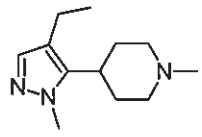

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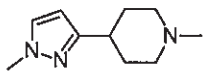

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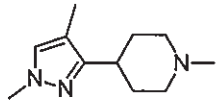

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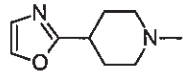

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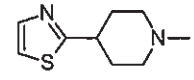

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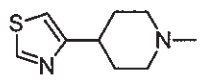

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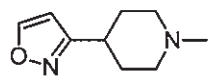

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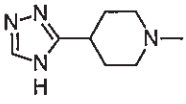

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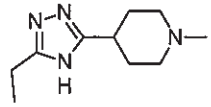

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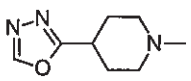

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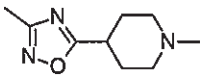

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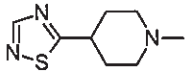

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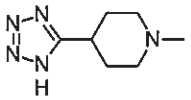
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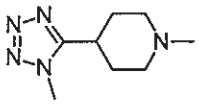
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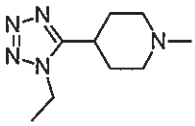
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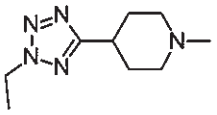
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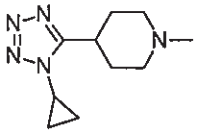
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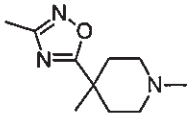
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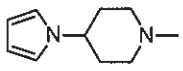
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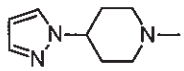
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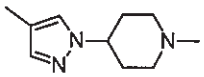
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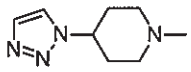
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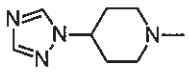
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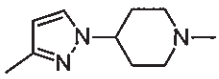
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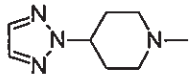
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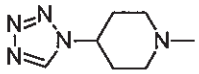
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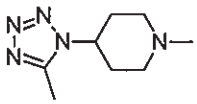
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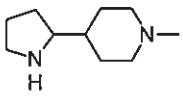
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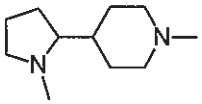
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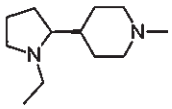
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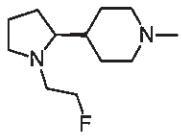
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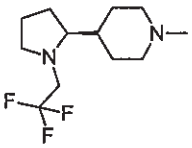
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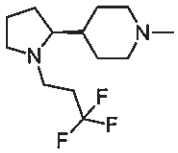
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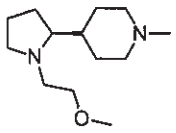
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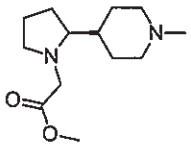
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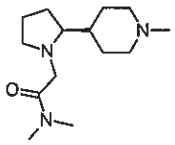
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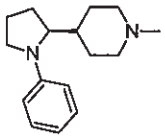
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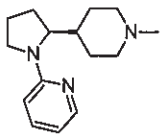
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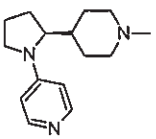
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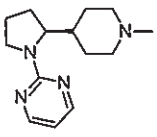
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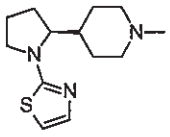
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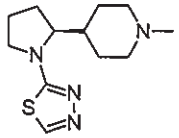
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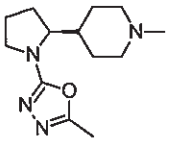
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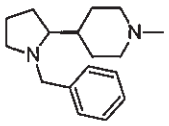
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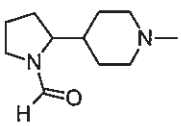


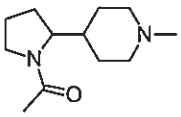
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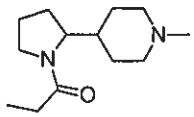


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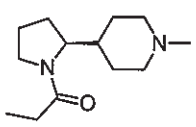




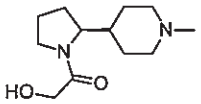




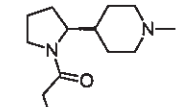
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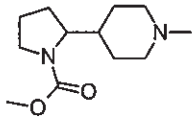
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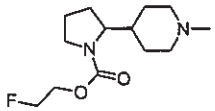
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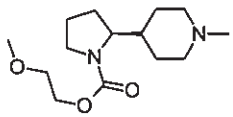
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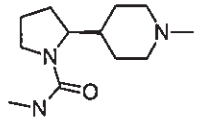
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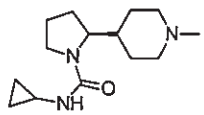
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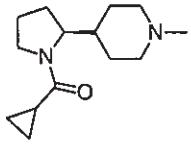


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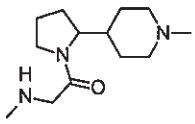


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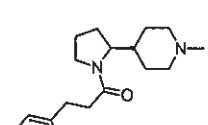
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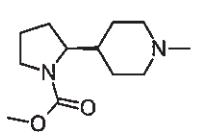
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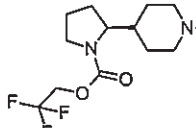
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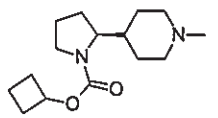
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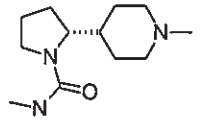
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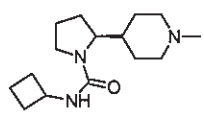
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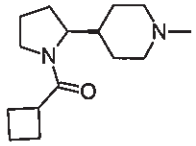


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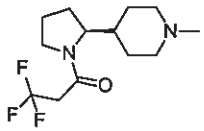


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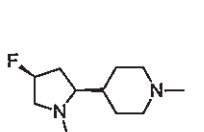
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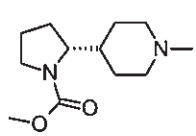
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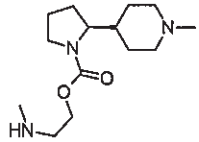
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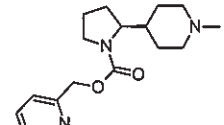
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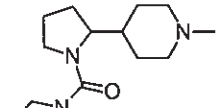
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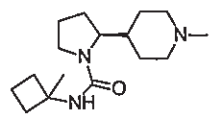
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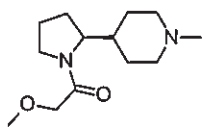


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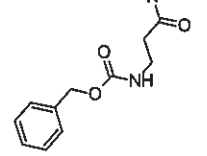


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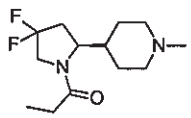


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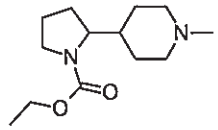


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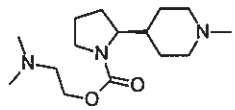
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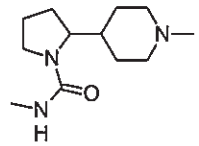
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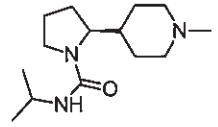
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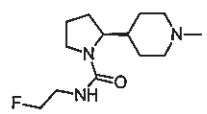
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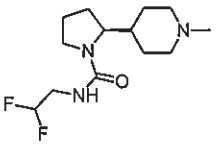


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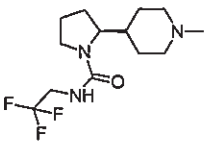


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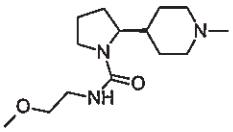




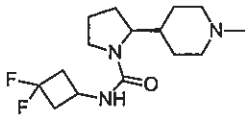
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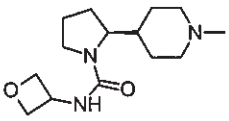
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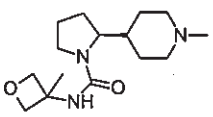
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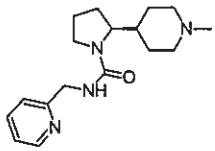
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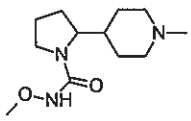
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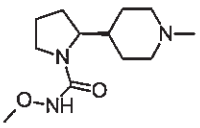
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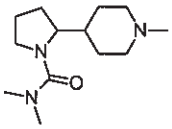
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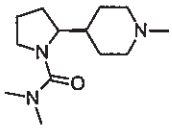
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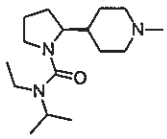
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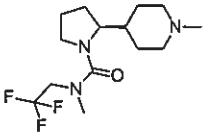
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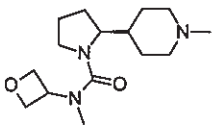
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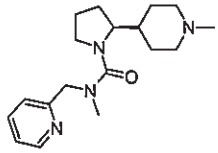
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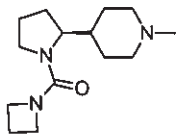
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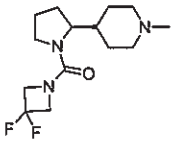
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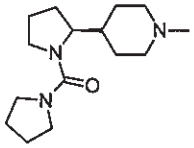
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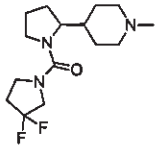
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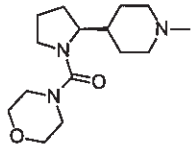
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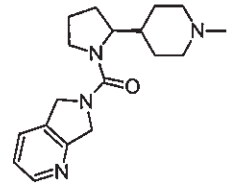
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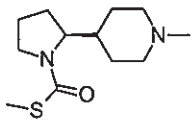
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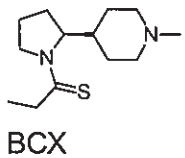
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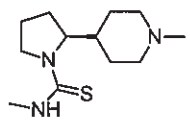
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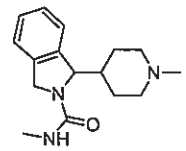
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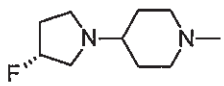
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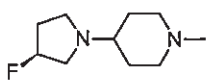
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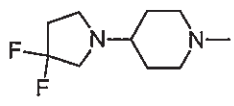
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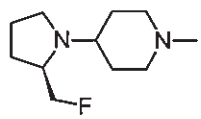
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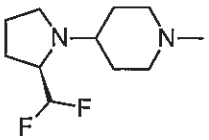
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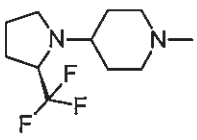
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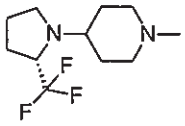
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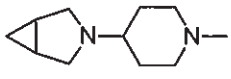
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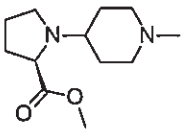
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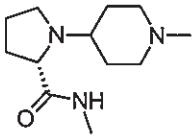
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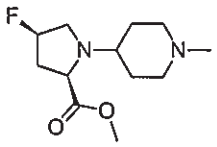
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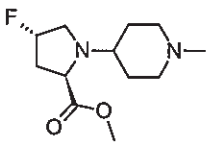
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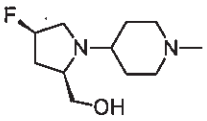
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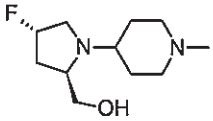
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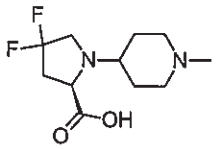
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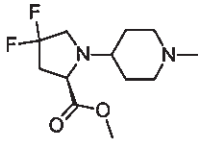
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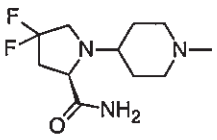
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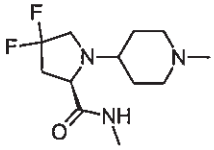
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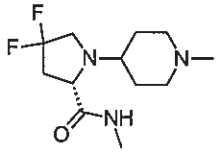
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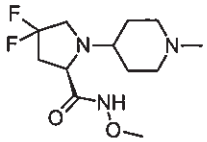
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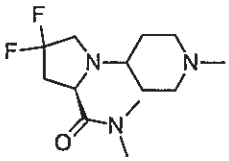
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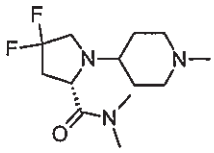
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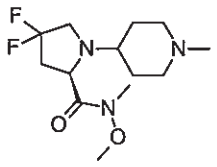
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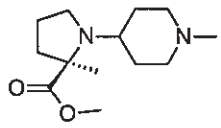
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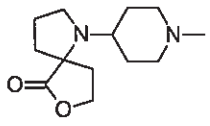
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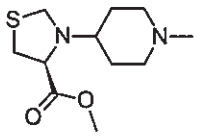
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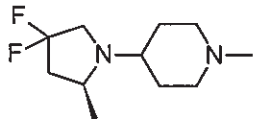
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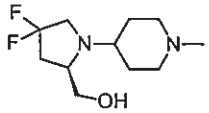
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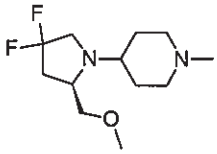
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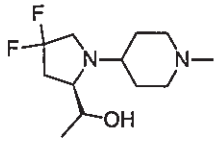
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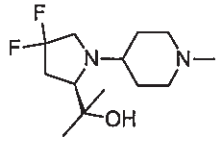
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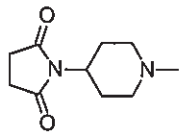
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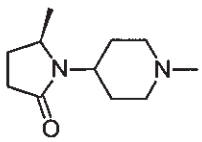
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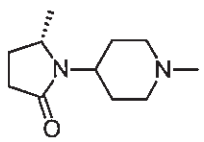
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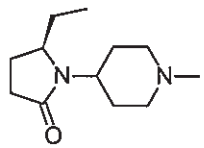
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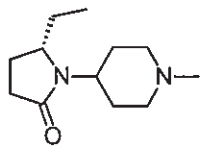
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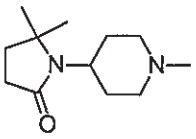
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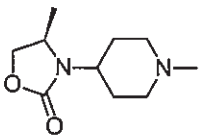


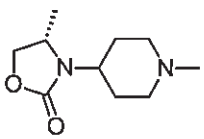
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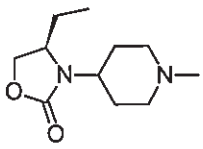


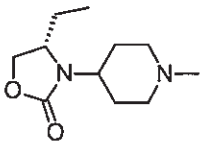
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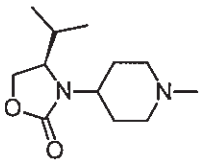

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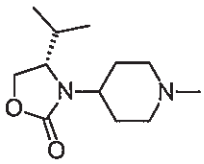

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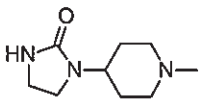

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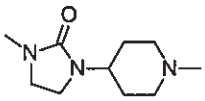

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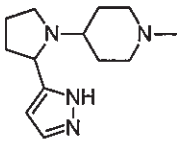

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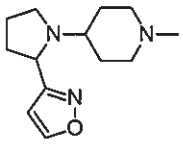

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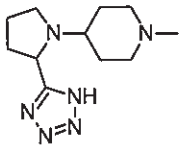

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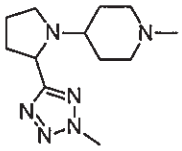

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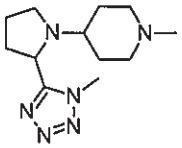

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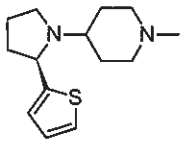

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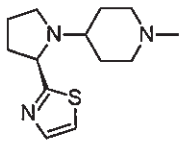

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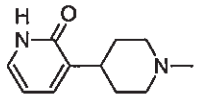

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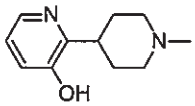

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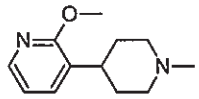

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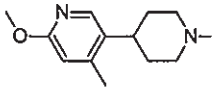

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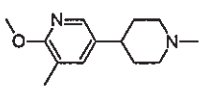

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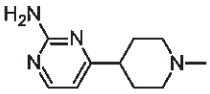

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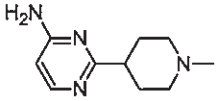

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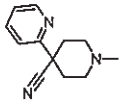

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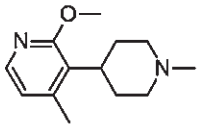

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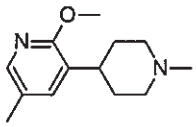

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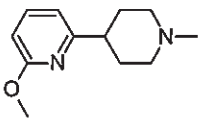

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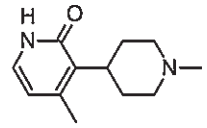

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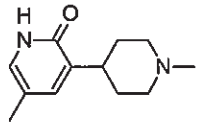

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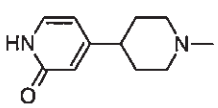

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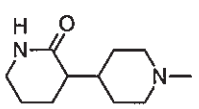

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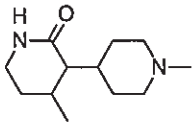

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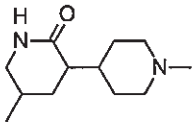

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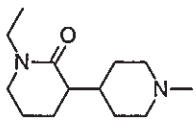

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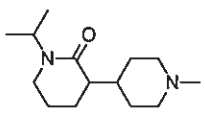

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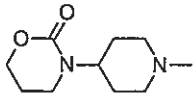

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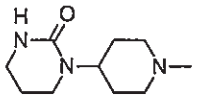

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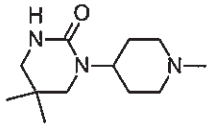

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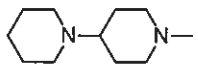

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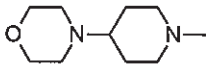

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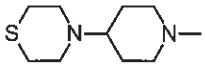

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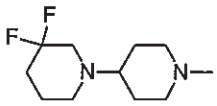

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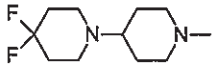

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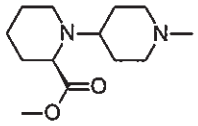

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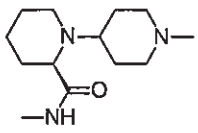

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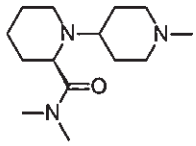

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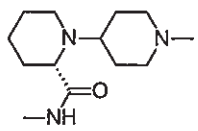

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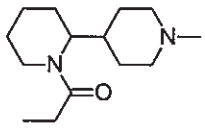

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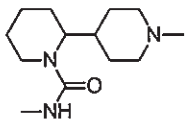

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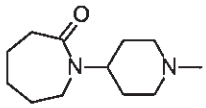

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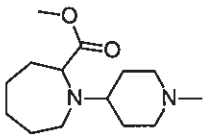

DBD


DBE


DBF


DBG


EAA


EAB

7. A compound according to claim 1 wherein Q is bicyclic or is substituted with one or more groups selected from (L)-R^{10}, (L)-R^{11} and (L)-R^{12}, where L is a bond or a CH_2 group; R^{10}, R^{11} and R^{12} are independently selected from hydrogen; fluorine; chlorine; bromine; cyano; oxo; hydroxy; OR^{15}; $NR^{15}R^{16}$; COR^{15}; CSR^{15}; $COOR^{15}$; $COSR^{15}$; $OCOR^{15}$; $NR^{17}COR^{15}$; $CONR^{15}R^{16}$; $CSNR^{15}R^{16}$; $NR^{17}CONR^{15}R^{16}$; $R^{17}COOR^{15}$; $OCONR^{15}R^{16}$; SR^{15}; SOR^{15}; SO_2R^{15}; 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;

wherein the optional substituents for the optionally substituted 5- or 6-membered ring are selected from a group R^8 consisting of hydrogen; fluorine; chlorine; bromine; cyano; oxo; hydroxy; 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; and 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;

wherein R^{15}, R^{16} and R^{17} are the same or different, or may be joined together to form a ring, and each is independently selected from hydrogen, a non-aromatic C_{1-6} hydrocarbon group optionally substituted with one or more 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; or a group of formula $CH_2N(R^a)COOR^b$; or a group of formula (L)-R^{18} where L is a bond or a CH_2 group and R^{18} is 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;

wherein the optional substituents for the optionally substituted 5- or 6-membered ring are selected from a group R^8.

8. A compound according to any one of claims 2 to 5 wherein wherein R^1 is selected from hydrogen; fluorine; cyano; hydroxy; OR^5; NR^5R^6; COR^5; $COOR^5$; $OCOR^5$; NR^7COR^5; $CONR^5R^6$; $NR^7CONR^5R^6$; NR^7COOR^5; SO_2R^5; and a C_{1-4} non-aromatic hydrocarbon group which is optionally substituted with one to six fluorine atoms.

9. A compound according to any one of claims 2 to 8 wherein R^2 is hydrogen.

10. A compound according to any one of claims 1 to 9 wherein R^3 is present and the optional second carbon-carbon bond is absent, and wherein R^3 is selected from hydrogen; fluorine; hydroxyl, methoxy and cyano.

11. A compound according to any one of claims 1 to 10 wherein R^4 is selected from hydrogen and methyl.

12. A compound according to claim 1 which is

Ethyl 2-[4-(1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(4-chloro-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[4-(trifluoromethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(4-cyano-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(4,5-dichloro-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-[4-(1-methyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1-methyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[1-(ethoxycarbonyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-[4-(1,5-dimethyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1,5-dimethyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-[4-(1,4-dimethyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1,4-dimethyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

methyl 2-[4-(5-chloro-1-methyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(5-chloro-1-methyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-[4-(4,5-dichloro-1-methyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(4,5-dichloro-1-methyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(3-amino-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-[4-(1-methyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1-methyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1-methyl-1H-pyrazol-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1,3-oxazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Methyl 2-[4-(1,3-thiazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(1,3-thiazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(4H-1,2,4-triazol-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(5-ethyl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(1,3,4-oxadiazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(3-methyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(1,2,4-thiadiazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(1H-tetrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(1H-pyrrol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(1H-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(4-methyl-1H-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(1H-1,2,3-triazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(1H-1,2,4-triazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-hydroxy-4-(1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(1H-imidazol-2-yl)-4-methoxypiperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-hydroxy-4-(1-methyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-methoxy-4-(1-methyl-1H-imidazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-methyl-4-(3-methyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Methyl 2-[4-(4-methyl-1*H*-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(1,2-oxazol-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(3-methyl-1H-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-[4-(3-methyl-1H-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-[4-(1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-[4-(1-propyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1-propyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1,3-thiazol-4-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[1-(2-methoxyethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[1-(cyanomethyl)-1H-imidazol-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

(2-{1-[6-(ethoxycarbonyl)-6-azaspiro[3.4]oct-2-yl]piperidin-4-yl}-1H-imidazol-1-yl)acetic acid

Ethyl 2-(4-{1-[2-(methylamino)-2-oxoethyl]-1H-imidazol-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-[4-(1,4-dimethyl-1H-pyrazol-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1,4-dimethyl-1H-pyrazol-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-[4-(1,4-dimethyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1,4-dimethyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(2*H*-1,2,3-triazol-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1H-tetrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(5-methyl-1*H*-tetrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1-methyl-1H-tetrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1-ethyl-1*H*-tetrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(2-ethyl-2*H*-tetrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1-cyclopropyl-1H-tetrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

(1,1-$^{2}H_{2}$)Ethyl 2-[4-(1*H*-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

(2,2,2-$^{2}H_{3}$)Ethyl 2-[4-(1*H*-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

($^{2}H_{5}$)Ethyl 2-[4-(1*H*-pyrazol-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

(1,1-$^{2}H_{2}$)Ethyl 2-[4-(1-methyl-1*H*-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

(2,2,2-$^{2}H_{3}$)Ethyl 2-[4-(1-methyl-1*H*-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

($^{2}H_{5}$)Ethyl 2-[4-(1-methyl-1*H*-pyrazol-5-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(pyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1-formylpyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1-acetylpyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[1-(trifluoroacetyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-[4-(1-propanoylpyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1-propanoylpyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2S)-1-propanoylpyrrolidin-2-yl]piperidin-1-yl}-6-

azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2S)-1-(cyclopropylcarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2S)-1-(cyclobutylcarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-{4-[1-(methoxycarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[1-(methoxycarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2S)-1-(methoxycarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2R)-1-(methoxycarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[1-(ethoxycarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-{4-[(2S)-1-(methylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[1-(methylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2S)-1-(methylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2R)-1-(methylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[1-(ethylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[1-(dimethylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2S)-1-(dimethylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(1-methylpyrrolidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[1-(*N*-methylglycyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[1-(methoxycarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(propan-2-ylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[(2,2,2-trifluoroethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(azetidin-1-ylcarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(morpholin-4-ylcarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(cyclopropylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(cyclobutylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[(2-methoxyethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(pyrrolidin-1-ylcarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(methoxycarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[methoxy(methyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[(1-methylcyclobutyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[(3-methyloxetan-3-yl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[(3,3-difluoropyrrolidin-1-yl)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[(3,3-difluorocyclobutyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[(3,3-difluoroazetidin-1-yl)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-(4-{(2*S*)-1-[(2,2,2-trifluoroethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-(4-{(2*S*)-1-[(3,3-difluoroazetidin-1-yl)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[ethyl(propan-2-yl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-

azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[(cyclobutyloxy)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[(2-fluoroethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[(2,2-difluoroethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(methoxyacetyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[(2-fluoroethoxy)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[(2,2,2-trifluoroethoxy)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[(methylsulfanyl)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[(2-methoxyethoxy)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-{[2-(dimethylamino)ethoxy]carbonyl}pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(hydroxyacetyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(3,3,3-trifluoropropanoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

ethyl 2-(4-{(2*S*)-1-[(pyridin-2-ylmethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[methyl(2,2,2-trifluoroethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(oxetan-3-ylcarbamoyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[methyl(oxetan-3-yl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-propanethioylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*,4*S*)-4-fluoro-1-propanoylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-4,4-difluoro-1-propanoylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-ethylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[3-(pyridin-2-yl)propanoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[methyl(pyridin-2-ylmethyl)carbamoyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[(pyridin-2-ylmethoxy)carbonyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-{*N*-[(benzyloxy)carbonyl]-β-alanyl}pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(β-alanyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-{[2-(methylamino)ethoxy]carbonyl}pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(2-fluoroethyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(2,2,2-trifluoroethyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(2-methoxyethyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(2-methoxy-2-oxoethyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2*S*)-1-[2-(dimethylamino)-2-oxoethyl]pyrrolidin-2-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-benzylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(methylcarbamothioyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[2-(methylcarbamoyl)-2,3-dihydro-1*H*-isoindol-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2S)-1-phenylpyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-

carboxylate

Methyl 2-{4-[(2S)-1-(pyridin-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(pyridin-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2S)-1-(pyridin-4-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2S)-1-(pyrimidin-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2S)-1-(1,3-thiazol-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(1,3,4-thiadiazol-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*R*)-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-2-(methylcarbamoyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

1-{1-[6-(ethoxycarbonyl)-6-azaspiro[3.4]oct-2-yl]piperidin-4-yl}-4,4-difluoro-D-proline

Ethyl 2-{4-[(2*R*)-4,4-difluoro-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*R*)-4,4-difluoro-2-(methylcarbamoyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*R*)-2-(dimethylcarbamoyl)-4,4-difluoropyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2R)-2-carbamoyl-4,4-difluoropyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2R)-4,4-difluoro-2-(methoxycarbamoyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-{(2R)-4,4-difluoro-2-[methoxy(methyl)carbamoyl]pyrrolidin-1-yl}piperidin-1-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-4,4-difluoro-2-(methylcarbamoyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-2-(dimethylcarbamoyl)-4,4-difluoropyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*R*)-2-(methoxycarbonyl)-2-methylpyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(6-oxo-7-oxa-1-azaspiro[4.4]non-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(4*S*)-4-(methoxycarbonyl)-1,3-thiazolidin-3-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(3*R*)-3-fluoropyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(3*S*)-3-fluoropyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(3,3-difluoropyrrolidin-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-2-(trifluoromethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*R*)-2-(fluoromethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*R*)-2-(difluoromethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*R*)-2-(trifluoromethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(3-azabicyclo[3.1.0]hex-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2S)-4,4-difluoro-2-methylpyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2R)-4,4-difluoro-2-(hydroxymethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2R)-4,4-difluoro-2-(methoxymethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2R)-4,4-difluoro-2-(1-hydroxyethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2R)-4,4-difluoro-2-(1-hydroxyethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*R*)-4,4-difluoro-2-(2-hydroxypropan-2-yl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(2-oxopyrrolidin-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-

carboxylate

Ethyl 2-[4-(2,5-dioxopyrrolidin-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2R)-2-methyl-5-oxopyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2R)-2-ethyl-5-oxopyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2S)-2-methyl-5-oxopyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2S)-2-ethyl-5-oxopyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(2,2-dimethyl-5-oxopyrrolidin-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(4R)-4-methyl-2-oxo-1,3-oxazolidin-3-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(4R)-4-ethyl-2-oxo-1,3-oxazolidin-3-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(4R)-2-oxo-4-(propan-2-yl)-1,3-oxazolidin-3-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(4S)-4-methyl-2-oxo-1,3-oxazolidin-3-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(4S)-4-ethyl-2-oxo-1,3-oxazolidin-3-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(4S)-2-oxo-4-(propan-2-yl)-1,3-oxazolidin-3-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(2-oxoimidazolidin-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(3-methyl-2-oxoimidazolidin-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[2-(1H-pyrazol-5-yl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[2-(1,2-oxazol-3-yl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[2-(1*H*-tetrazol-5-yl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[2-(2-methyl-2*H*-tetrazol-5-yl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[2-(1-methyl-1*H*-tetrazol-5-yl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*R*)-2-(thiophen-2-yl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*R*)-2-(1,3-thiazol-2-yl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-ylcarbonyl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*R*,4*R*)-4-fluoro-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*R*,4*S*)-4-fluoro-2-(methoxycarbonyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*R*,4*R*)-4-fluoro-2-(hydroxymethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*R*,4*S*)-4-fluoro-2-(hydroxymethyl)pyrrolidin-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-{4-[(2*S*)-1-(5-methyl-1,3,4-oxadiazol-2-yl)pyrrolidin-2-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-[4-(2-oxo-1,2-dihydropyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(2-oxo-1,2-dihydropyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

2-Fluoroethyl 2-[4-(2-oxo-1,2-dihydropyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(3-hydroxypyridin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

2-Fluoroethyl 2-[4-(2-methoxypyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(6-methoxy-4-methylpyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(6-methoxy-5-methylpyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

ethyl 2-[4-(2-aminopyrimidin-4-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-

carboxylate

Ethyl 2-[4-(4-aminopyrimidin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

ethyl 2-[4-cyano-4-(pyridin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(2-methoxy-4-methylpyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(2-methoxy-5-methylpyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(6-methoxypyridin-2-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(4-methyl-2-oxo-1,2-dihydropyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(4-methyl-2-oxo-1,2-dihydropyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(5-methyl-2-oxo-1,2-dihydropyridin-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(2-oxo-1,2-dihydropyridin-4-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(2-oxo-3,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate

Methyl 2-(2-oxo-3,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(4-methyl-2-oxo-3,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(5-methyl-2-oxo-3,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(1-ethyl-2-oxo-3,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[2-oxo-1-(propan-2-yl)-3,4'-bipiperidin-1'-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(2-oxo-1,3-oxazinan-3-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(2-oxotetrahydropyrimidin-1(2*H*)-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-[4-(5,5-dimethyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate

Ethyl 2-(1,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(morpholin-4-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(thiomorpholin-4-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-(3,3-difluoro-1,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-(4,4-difluoro-1,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate
Methyl (2*R*)-1'-[6-(ethoxycarbonyl)-6-azaspiro[3.4]oct-2-yl]-1,4'-bipiperidine-2-carboxylate
Ethyl 2-[(2*R*)-2-(methylcarbamoyl)-1,4'-bipiperidin-1'-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[(2*R*)-2-(dimethylcarbamoyl)-1,4'-bipiperidin-1'-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[(2*S*)-2-(methylcarbamoyl)-1,4'-bipiperidin-1'-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-(1-propanoyl-2,4'-bipiperidin-1'-yl)-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[1-(methylcarbamoyl)-2,4'-bipiperidin-1'-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-[4-(2-oxoazepan-1-yl)piperidin-1-yl]-6-azaspiro[3.4]octane-6-carboxylate
Ethyl 2-{4-[2-(methoxycarbonyl)azepan-1-yl]piperidin-1-yl}-6-azaspiro[3.4]octane-6-carboxylate
or a salt thereof.

13. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 12 and a pharmaceutically acceptable excipient.

14. A compound according to claims 1 to 12 for use in the treatment of a cognitive disorder or psychotic disorder or for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain or for the treatment of addiction, or for the treatment of movement disorders.

15. A compound according to claim 14 for use in the treatment of Alzheimer's Disease, dementia with Lewy bodies or schizophrenia.