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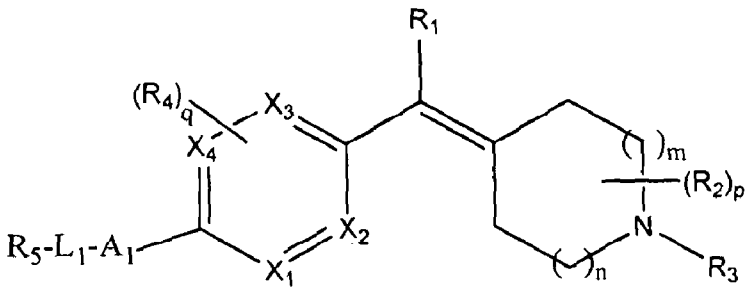
(54) **Title**: COMPOUNDS AND THEIR USE TO TREAT HISTAMINE H3 RELATED DISORDERS



(1)

(57) **Abstract**: The present invention provides compounds of formula (1) and pharmaceutically acceptable salts thereof, wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, m, n, p, q, Q_1, Q_2, Q_3, Q_4, Q_5, Q_6, X_1, X_2, X_3, X_4, A_1 and L_1, are as defined in the specification, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

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COMPOUNDS AND THEIR USE TO TREAT HISTAMINE H3 RELATED DISORDERS

The present invention relates to compounds and their uses, and in particular to compounds having a piperidinylalkene scaffold and their therapeutic use in the treatment or prevention of conditions having an association with the histamine H3 receptor.

The H3 receptor was first identified pharmacologically in 1983 as an autoreceptor that regulates the production of histamine (**1**). The receptor was later cloned in 1999 (**2**). It is a constitutively active G protein-coupled receptor that is expressed predominantly in the central nervous system (CNS) and modulates a variety of CNS functions both centrally and peripherally. It is expressed on the presynaptic terminals of CNS neurones and acts as a negative modulator of release of neurotransmitters such as histamine, acetylcholine, norepinephrine, serotonin and dopamine (**3**). Consequently, the ability of the H3 receptor to regulate the release of a wide range of neurotransmitters has fuelled research into the development of antagonists / inverse agonists which have potential in behavioural and physiological conditions, for example CNS disorders such as narcolepsy, disorders of wakefulness, cognition or attention, pain and in suppression of food intake.

Histaminergic neurones are located in the tuberomammillary nucleus of the posterior hypothalamus and project their axons into brain regions including the hypothalamus, thalamus, cerebral cortex, amygdala, and septum. Activity of histaminergic neurons is closely linked with the sleep / wake cycle and numerous reports in the literature have established that the H3 receptor plays a role in cognition and sleep / wake related processes, based on studies with known H3 receptor antagonists and their effects in animal models (**4**, **5**, **6**). H3 antagonist compound A-349821 is currently in preclinical development and has been shown to demonstrate cognition-enhancing effects in the rat (**7**).

The histaminergic system is one of the targets of leptin signalling in the hypothalamus. Known H3 antagonist clobenpropit increases histamine release in the hypothalamus of mice and has the effect of reducing energy intake in both lean and obese mice (**8**). The role of the H3 receptor in obesity has been further substantiated through studies with

antagonists thioperamide and ciproxifan and more recently with non-imidazole compounds (**10**).

The non-selective antagonist thioperamide has an antinociceptive effect in a number of acute pain models (**11**). H3 antagonists have been suggested for the treatment of neuropathic pain (**12**). In addition GSK207040 and GSK334429 are selective non-imidazole H3 antagonist compounds that display high affinity for both rat and human H3 receptors. Both compounds reduced tactile allodynia in the rat, suggesting H3 antagonists have therapeutic potential in the treatment of neuropathic pain (**13**).

In an attempt to identify compounds with improved drug-like properties, non-imidazole compounds have been at the forefront of research, for example A-349821 (**7**) and GSK207040 / GSK334429 (**13**). ABT-239 is currently being investigated for use in attention deficit hyperactivity disorder, Alzheimer's Disease and schizophrenia (**14**).

International patent application WO2007113249 discloses 1-[4-[(1-methyl-4-piperidinylidene)methyl]phenyl]ethanone as an intermediate towards the synthesis of a class of N-hydroxycinnamoylamides.

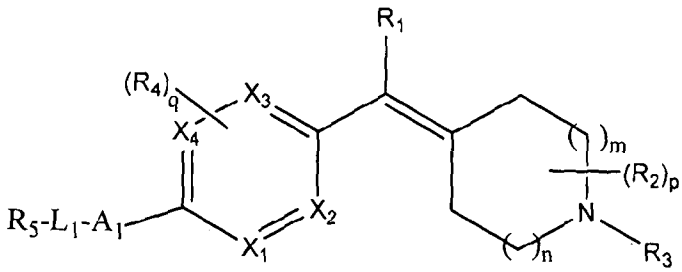
International patent application WO2003031412 discloses a series of [4-(1-methylethoxy)phenyl]ethylidene]piperidine derivatives as muscarinic antagonists.

Wang D *et al*, Life Sciences (1997), 60(15), 1271-1277 discloses 4-[(4-methoxyphenyl)methylene]-1,2,2,6,6-pentamethylpiperidine as an intermediate towards the synthesis of [^{3}H]benzylpempidine.

US patent US 4,166,814 discloses a series of piperidine derivatives, including 4,4'-(1,4-phenylenedimethylidyne)bis[1,2,2,6,6-pentamethyl]-piperidine, as light stabilisers for plastics.

There exists a clinical need to generate further classes of H3 antagonist and/or inverse agonist compounds that demonstrate improved drug-like properties (**9**).

In accordance with a first aspect of the present invention, there is provided a compound having the Formula (1):



(1)

wherein:

R_1 represents H or C_{1-6} alkyl;

R_2 represents C_{1-6} alkyl, wherein each R_2 may be the same or different;

p represents 0, 1, 2, 3 or 4;

m represents 1 or 2;

n represents 1 or 2; provided that both and m and n do not represent 2;

R_3 represents C_{1-6} alkyl, -Q_1-C_{3-6} cycloalkyl or -Q_2-3-6 membered monocyclic heterocyclyl, wherein each may be optionally substituted by one or more substituents, independently selected from halogen, C_{1-6} alkyl or C_{1-6} alkoxy;

Q_1 and Q_2 independently represent a covalent bond or C_{1-3} alkylene;

X_1, X_2, X_3 and X_4 independently represent CH or N; wherein no more than 2 of X_1, X_2, X_3 and X_4 represent N;

R_4, independently represents halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{1-6} alkoxy or haloC_{1-6} alkoxy;

q represents 0, 1 or 2;

A_1 represents a covalent bond or C_{1-6} alkylene optionally substituted by one or more hydroxy or C_{1-6} alkoxy;

L_1 represents a covalent bond or –NR_6-, -O-, ^{b}-NR_7CO-^{a}, ^{b}-$CONR_8$-^{a}, -C(O)-, ^{b}-NR_7SO_2-^{a}, ^{b}-SO_2NR_8-^{a}, -$S(O)_2$-, in which ^{a} represents the point of attachment to A_1 and ^{b} represents the point of attachment to R_5;

R_6, R_7 and R_8 independently represent H or C_{1-6} alkyl;

R_5 represents -$(CH_2)_{1-3}OC_{1-6}$ alkyl, or –Q_3-C_{3-8} cycloalkyl, -Q_4-heteroaryl, -Q_5-heterocyclyl, -Q_6-aryl; in which the C_{3-8} cycloalkyl, heteroaryl, heterocyclyl and aryl are

optionally substituted with one or more R_9; wherein each R_9 may be the same or different;

when A_1 represents optionally substituted C_{1-6} alkylene, R_5 also represents H or C_{1-6} alkyl;

Q_3, Q_4, Q_5 and Q_6 independently represent a covalent bond or C_{1-3} alkylene;

R_9 represents halogen, -CN, -NO_2, =O, -OR_{10}, -$NR_{11}R_{12}$, -COR_{11}, -CO_2R_{12}, -$CONR_{13}R_{14}$, -$SO_2NR_{13}R_{14}$, -$NR_{15}COR_{16}$, -$NR_{15}SO_2R_{16}$, -$OCONR_{13}R_{14}$, -$NR_{13}CO_2R_{14}$, -$NR_{13}CONR_{13}R_{14}$, -SR_{14}, -SOR_{14}, -SO_2R_{14}, -OSO_2R_{14}, -C_{3-6}cycloalkyl, -aryl, -heteroaryl, -heterocyclyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OR_{10}, -$NR_{11}R_{12}$, -COR_{11}, -CO_2R_{12}, -$CONR_{13}R_{14}$, -$SO_2NR_{13}R_{14}$, -$NR_{15}COR_{16}$, -$NR_{15}SO_2R_{16}$, -$OCONR_{13}R_{14}$, -$NR_{13}CO_2R_{14}$, -$NR_{13}CONR_{13}R_{14}$, -SR_{14}, -SOR_{14}, -SO_2R_{14}, -OSO_2R_{14}, -C_{3-6}cycloalkyl, -aryl, -heteroaryl or –heterocyclyl; in which each C_{1-6} alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl or heterocyclyl present as or as part of R_9 is optionally substituted with one or more R_{17}, wherein each R_{17} may be the same or different;

R_{10} represents H, C_{1-3} alkyl or haloC_{1-3} alkyl;

R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} independently represent H or C_{1-3} alkyl;

R_{17} represents halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, - CN, -NO_2, =O, -OR_{18}, -CO_2R_{19}, -COR_{19}, -$NR_{19}R_{20}$, -$CONR_{19}R_{20}$, -$NR_{19}COR_{20}$, -$NR_{19}SO_2R_{20}$ or -$SO_2NR_{19}R_{20}$;

R_{18} represents H, C_{1-6}alkyl or -haloC_{1-6} alkyl;

R_{19} and R_{20} independently represent H or C_{1-6}alkyl;

excluding 4,4'-(1,4-phenylenedimethylidyne)bis[1,2,2,6,6-pentamethyl]-piperidine;

or a pharmaceutically acceptable salt thereof.

The compounds of the invention have been found to modulate the histamine H3 receptor. In particular, the compounds possess antagonist or inverse agonist properties at this receptor. Based on the high affinity for the receptor, the compounds may have the potential to display useful selectivity for the H3 receptor.

Where any group in the compound of formula (1) above is referred to as being optionally substituted, this group may be unsubstituted or substituted by one or more

substituents. Typically any such group will be unsubstituted, or substituted by one, two or three substituents.

In the compounds of the invention as represented by formula (1) and the more detailed description hereinafter certain of the general terms used in relation to groups or substituents thereon are to be understood to include the following atoms or groups unless otherwise specified.

The term 'halogen' as used herein refers to a fluorine, chlorine, bromine or iodine atom, unless otherwise specified.

The term 'hydroxyl' as used herein refers to –OH.

The term 'C_{x-y} alkyl' as used herein refers to a linear or branched saturated hydrocarbon group containing from x to y carbon atoms. For example, C_{1-6} alkyl refers to a linear or branched saturated hydrocarbon group containing from 1 to 6 carbon atoms. Examples of C_{1-6} alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert butyl, n-pentyl, isopentyl, neopentyl and hexyl. C_0alkyl indicates that the group is absent i.e. there is a direct bond between the groups.

The term 'C_{x-y} alkylene' as used herein refers to a divalent hydrocarbon group obtained by removing one hydrogen atom from 'C_{x-y} alkyl' above. Examples of C_{1-6} alkylene groups include methylene, methylmethylene, dimethylmethylene, ethylene, propylene and methylpropylene.

The term 'C_{x-y}alkoxy' as used herein refers to an -O-C_{x-y} alkyl group wherein C_{x-y} alkyl is as defined herein. Examples of C_{1-6}alkoxy groups include methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy.

The term 'haloC_{x-y}alkyl' as used herein refers to a C_{x-y}alkyl group as defined herein wherein at least one hydrogen atom is replaced with halogen. Examples of such groups include fluoroethyl, trifluoromethyl and trifluoroethyl.

The term 'C_{1-3} hydroxyalkyl' as used herein refers to a C_{1-3}alkyl group as defined herein wherein at least one hydrogen atom is replaced with hydroxyl. Examples of C_{1-3} hydroxyalkyl groups include hydroxymethyl and hydroxyethyl.

The term 'C_{x-y} cycloalkyl' as used herein refers to a saturated monocyclic hydrocarbon ring of x to y carbon atoms. For example, C_{3-8} cycloalkyl refers to a saturated monocyclic hydrocarbon ring of 3 to 8 carbon atoms. Examples of C_{3-8} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term 'heterocyclyl' refers to a 4-7 membered monocyclic ring or a 8-12 membered bicyclic, bridged or spiro-fused ring, any of which may be saturated or partially unsaturated, which monocyclic or bicyclic ring contains 1 to 4 heteroatoms selected from oxygen, nitrogen, silicon or sulphur.

Examples of such monocyclic groups include pyrrolidinyl, azetidinyl, pyrazolidinyl, oxazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dioxolanyl, dioxanyl, oxathiolanyl, oxathianyl, dithianyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl, tetrahydropyridinyl, dihydropyridinyl, tetrahydropyrimidinyl, dihydropyrimidinyl, tetrahydropyridazinyl, dihydropyridazinyl, tetrahydropyrazinyl, dihydropyrazinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, diazepanyl, azepanyl and oxazepanyl.

Examples of N-linked 4-7 membered monocyclic heterocyclyl groups include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl.

Examples of such 8-12 membered bicyclic, bridged or spiro-fused rings include indolinyl, isoindolinyl, benzopyranyl, quinuclidinyl, 2,3,4,5-tetrahydro-1H-3-benzazepine, tetrahydroisoquinolinyl, octahydrocyclopenta[c]pyrrolyl, octahydrocyclopenta[b]pyrrolyl, octahydro-1H-isoindolyl, octahydro-1H-indolyl, octahydro-1H-cyclopenta[b]pyridinyl, octahydro-1H-cyclopenta[c]pyridinyl, azabicyclo[3.2.1]octyl, azabicyclo[2.2.1]heptanyl, oxaspiro[4.5]decanyl and oxaspiro[4.4]nonanyl.

It will be appreciated that any heterocyclyl ring may be attached to the rest of the molecule through any available C or N atom. Optional substituents may be present on any available C or N atom.

The term 'heteroaryl' as used herein refers to a 5-6 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring which monocyclic or bicyclic ring contains

1 to 4 heteroatoms selected from oxygen, nitrogen and sulphur. Examples of such monocyclic aromatic rings include thienyl, furyl, furazanyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazolyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyridinyl, triazinyl, tetrazinyl and the like. Examples of such bicyclic aromatic rings include quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pteridinyl, cinnolinyl, phthalazinyl, naphthyridinyl, indolyl, isoindolyl, azaindolyl, indolizinyl, indazolyl, purinyl, pyrrolopyridinyl, furopyridinyl, benzofuranyl, isobenzofuranyl, benzothienyl, benzoimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and imidazopyridyl.

It will be appreciated that any heteroaryl ring may be attached to the rest of the molecule through any available C or N atom. Optional substituents may be present on any available C or N atom.

When the 'heteroaryl' contains a nitrogen atom, the nitrogen atom may be oxidized. For instance, pyridyl as the 'heteroaryl' may be its N-oxide.

The term 'aryl' as used herein refers to a C_{6-12} monocyclic or bicyclic hydrocarbon ring wherein at least one ring is aromatic. Examples of such groups include phenyl, naphthyl and tetrahydronaphthalenyl.

'Pharmaceutically acceptable salts' of compounds of Formula (1) of the present invention include salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids and salts with basic or acidic amino acids. Salts with acids may, in particular, be employed in some instances. In particular, 'pharmaceutically acceptable salts' of compounds of Formula (1) of the present invention include but are not limited to acid addition salts (for example, phosphates, nitrates, sulphates, borates acetates, maleates, citrates, fumarates, succinates, methanesulfonates, benzoates, salicylates and hydrohalides), and salts of amino acids (such as glycine, alanine, valine, leucine, isoleucine, cysteine, methionine, proline). Further pharmaceutically acceptable salts include quaternary ammonium salts of the compounds of formula (1).

Compounds of formula (1) and their salts may be in the form of a solvate, which is included in the scope of the invention. Such solvates may be formed with common organic solvents, including but not limited to, alcoholic solvents e.g. methanol, ethanol or isopropanol.

The compound of Formula (1) of the present invention may be in either hydrate or non-hydrate form.

General methods for the preparation of salts are well known to the person skilled in the art. Pharmaceutical acceptability of salts will depend on a variety of factors, including formulation processing characteristics and *in vivo* behaviour, and the skilled person would readily be able to assess such factors having regard to the present disclosure.

Where compounds of the invention exist in different enantiomeric and/or diastereoisomeric forms (including geometric isomerism about a double bond), these compounds may be prepared as isomeric mixtures or racemates, although the invention relates to all such enantiomers or isomers, whether present in an optically pure form or as mixtures with other isomers. Individual enantiomers or isomers may be obtained by methods known in the art, such as optical resolution of products or intermediates (for example chiral chromatographic separation (e.g. chiral HPLC)), or an enantiomeric synthesis approach. Similarly, where compounds of the invention may exist as alternative tautomeric forms (e.g. keto/enol, amide/imidic acid), the invention relates to the individual tautomers in isolation, and to mixtures of the tautomers in all proportions. The invention also extends to all conformational ring isomers.

In certain embodiments, the compounds of the invention bear one or more radiolabels. Such radiolabels may be introduced by using radiolabel-containing reagents in the synthesis of the compounds of formula (1), or may be introduced by coupling the compounds of formula (1) to chelating moieties capable of binding to a radioactive metal atom. Such radiolabeled versions of the compounds may be used, for example, in diagnostic imaging studies.

In certain embodiments, R_1 represents H. In other certain embodiments, R_1 represents C_{1-3} alkyl, typically methyl.

In certain embodiments, p represents 0.

In some embodiments, p represents 1. R_2, when present generally represents C_{1-3} alkyl, typically methyl or ethyl.

Typically, p represents 0 or 1.

In some embodiments, m represents 1. In other embodiments, m represents 2.

In some embodiments, n represents 1. In other embodiments, n represents 2.

In certain embodiments, m represents 1 and n represents 1. In other certain embodiments, m represents 1 and n represents 2. In one embodiment, m represents 1 and n represents 1 or 2.

In further certain embodiments, m represents 2 and n represents 1.

Q_1 typically represents a covalent bond or $-CH_2-$.

Q_2 typically represents a covalent bond.

In certain embodiments, R_3 represents C_{1-6} alkyl, C_{3-6} cycloalkyl, $-CH_2-C_{3-6}$ cycloalkyl or 3-6 membered heterocycloalkyl, each of which may be optionally substituted.

Representative examples of R_3 3-6 membered heterocycloalkyl include pyrrolidinyl, azetidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl, tetrahydrothiophenyl, and tetrahydrothiopyranyl.

Suitable R_3 optional substituents include halogen, typically fluorine.

Typical examples of R_3 include ethyl, isopropyl, isobutyl, cyclobutyl, cyclopentyl, $-CH_2$-cyclopropyl and tetrahydrofuranyl, each of which may be optionally substituted.

Specific examples of R_3 include ethyl, isopropyl, isobutyl, cyclobutyl, 3-fluorocyclobutyl, cyclopentyl, $-CH_2$-cyclopropyl and tetrahydrofuran-3-yl.

In one embodiment, R_3 represents C_{1-6} alkyl or optionally substituted C_{3-6} cycloalkyl.

In a particular embodiment, R_3 represents optionally substituted C_{3-6} cycloalkyl, typically cyclobutyl or cyclopropyl. In a further particular embodiment, R_3 represents cyclobutyl.

In some embodiments, X_1 represents CH. In other embodiments, X_1 represents N.

In some embodiments, X_2 represents CH. In other embodiments, X_2 represents N.

In some embodiments, X_3 represents CH. In other embodiments, X_3 represents N.

In some embodiments, X_4 represents CH. In other embodiments, X_4 represents N.

In some embodiments X_1, X_2, X_3 and X_4 each represent CH.

In some embodiments, one of the groups X_1, X_2, X_3 or X_4 represents N and the rest represent CH.

In one embodiment, R_4 represents halogen.

In certain embodiments, q represents 0. Typically, q represents 0 or 1. When q is other than 0, specific R_4 examples include fluoro or chloro.

In some embodiments A_1 represents a covalent bond or a straight or branched C_{1-4} alkylene optionally substituted by one or more hydroxy.

Typical examples of A_1 include a covalent bond or optionally substituted methylene, (methyl)methylene, (dimethyl)methylene, ethylene and (methyl)propylene.

Specific examples of A_1 include a covalent bond, $-CH_2-$, $-CH(OH)-$, $-C(CH_3)_2-$, $-C(CH_3)(OH)-$, $-CH(OH)CH_2-^d$, $-CH_2CH(OH)-^d$ and $-(CH_2)_2-C(CH_3)(OH)-^d$, wherein ^{d} represents the point of attachment to the X_1, X_2, X_3, X_4 containing ring.

In one embodiment, A_1 represents a covalent bond or $-CH_2-$.

Specific examples of L_1 include a covalent bond, $-NH-$, $-N(CH_3)-$, $-O-$, $^b-NHCO-^a$, $^b-CONH-^a$, $-C(O)-$, $^b-N(CH_3)SO_2-^a$, $^b-NHSO_2-^a$, $^b-SO_2NH-^a$ and $-S(O)_2$.

In one embodiment, L_1 represents a covalent bond.

Typical examples of $-L_1-A_1-$ include a covalent bond, C_{1-6} alkylene, $-NR_6-C_{1-6}$ alkylene-, $-O-C_{1-6}$alkylene-, $-NR_7CO-$, $-NR_7CO-C_{1-6}$alkylene-, $-CONR_8-C_{1-6}$ alkylene-, $-C(O)-$, $-NR_7SO_2-$, $-NR_7SO_2-C_{1-6}$alkylene-, $-SO_2NR_8-$, $-S(O)_2-C_{1-6}$alkylene-and -S(O), wherein C_{1-6} alkylene, when present, is optionally substituted.

Specific examples of $-L_1-A_1-$ include a covalent bond, $-CH_2-$, -CH(OH)-, $-C(CH_3)(OH)-$, $-CH(OH)CH_2-$, $-(CH_2)_2-C(CH_3)(OH)-$, $-NH-CH_2-$, $-N(CH_3)-CH_2-$, $-O-CH_2-$, $-O-C(CH_3)_2-$, $-O-(CH_2)_2-C(CH_3)(OH)-$, -NHCO-, $-NHCO-CH_2-$, $-CONH-CH_2-$, -C(O)-, $-NHSO_2-$, $-NHSO_2-CH_2-$, $-N(CH_3)SO_2-CH_2-$,$-SO_2NH-$, $-S(O)_2-$, CH_2- and $-S(O)_2$.

In one embodiment, R_5 represents $-(CH_2)_{1-3}OC_{1-6}$ alkyl, or $-Q_3-C_{3-8}$ cycloalkyl, $-Q_4$-monocyclic heteroaryl, $-Q_5$-heterocyclyl or $-Q_6$-monocyclic aryl; in which the C_{3-8} cycloalkyl, heteroaryl, heterocyclyl and aryl are optionally substituted with one or more R_9; wherein each R_9 may be the same or different; and when A_1 represents optionally substituted C_{1-6} alkylene, R_5 also represents H or C_{1-6} alkyl.

In a further embodiment, R_5 represents $-Q_3-C_{3-8}$ cycloalkyl, $-Q_4$-heteroaryl or $-Q_5$-heterocyclyl; in which the C_{3-8} cycloalkyl, heteroaryl and heterocyclyl are optionally substituted with one or more R_9, each of which may be the same or different.

In certain embodiments Q_3, Q_4 and Q_5 independently represent a covalent bond or methylene.

Typical examples of R_5 C_{3-8}cycloalkyl, heteroaryl and heterocyclyl groups present when R_5 represents $-Q_3-C_{3-8}$ cycloalkyl, $-Q_4$-heteroaryl or $-Q_5$-heterocyclyl respectively include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, pyrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyridazinyl, tetrahydrofuranyl, tetrahydropyranyl, oxazolidinyl, imidazolidinyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, azepanyl, oxepanyl, octahydrocyclopenta[c]pyrrolyl, azabicyclo[3.2.1]octanyl or oxaspiro[4.5]decanyl, each of which may be optionally substituted.

R_5 is typically unsubstituted or mono- or di-substituted. R_5 may also be tri-substituted. In one embodiment R_5 is unsubstituted. In another embodiment R_5 is monosubstituted. In another embodiment R_5 is disubstituted. In a further embodiment, R_5 is tri-substituted.

In one embodiment, R_9 represents halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, =O, -C_{0-6} alkyl-OR_{10}, -C_{0-6} alkyl-COR_{11}, -C_{0-6} alkyl-CO_2R_{12}, -C_{0-6} alkyl-$CONR_{13}R_{14}$, -C_{0-6} alkyl-$NR_{15}COR_{16}$, or -C_{0-6}alkyl-heteroaryl, wherein said C_{1-6} alkyl or -C_{0-6}alkyl-heteroaryl is optionally substituted with one or more R_{17}, each of which may be the same or different.

Suitable heteroaryl groups present when R_9 represents -C_{0-6}alkyl-heteroaryl include monocyclic heteroaryl groups, including thienyl, furyl, furazanyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazolyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyridinyl, triazinyl and tetrazinyl, each of which may be substituted with one or more R_{17}, each of which may be the same or different.

R_{17} typically represents C_{1-6} alkyl, generally methyl.

Specific examples of R_9 C_{0-6}alkyl-heteroaryl include pyrimidin-2-yl, 3-methyl-1,2,4-oxadiazolyl or pyrazol-1-yl.

Specific examples of R_9 include F, -CH_3, -$CH_2CH(CH_3)_2$, -CF_3, =O, -OH, -OCH_3, -OCH_2CH_3, -$OCH(CH_3)_2$, -$C(CH_3)_2OH$, –CH_2OCH_3, -CH_2OH, -$C(O)CH_3$, -CO_2CH_3, -$CO_2CH_2CH_3$, -$CON(CH_3)_2$, -$NHCOCH_3$, pyrimidin-2-yl, 3-methyl-1,2,4-oxadiazolyl and pyrazol-1-yl.

Specific examples of R_5 include –$(CH_2)_2$-OCH_3, –$(CH_2)_2$-OCH_2CH_3, -$(CH_2)_3$-OCH_3, cyclopropyl, 3-ethylcarboxylate-1-hydroxycyclobutan-1-yl, 3-methoxymethyl-1-hydroxycyclobutan-1-yl, cyclopentyl, 1-hydroxycyclopentan1-yl, 2-(methoxymethyl)-1-hydroxy-cyclopentan-1-yl, 4-methoxy-1-hydroxy-cycloheptan-1-yl, 1-hydroxycyclohexan-1-yl, 4-methoxy-1-hydroxycyclohexan-1-yl, 3-methoxy-1-hydroxycyclohexan-1-yl, 2-methoxy-1-hydroxycyclohexan-1-yl, 4-isopropoxy-1-hydroxycyclohexan-1-yl, 4-methoxy-1-fluorocyclohexan-1-yl, 4-acetylamino-1-hydroxycyclohexan-1-yl, 4-ethylcarboxylate-1-hydroxycyclohexan-1-yl, 4-(hydroxymethyl)-1-hydroxycyclohexan-1-yl, 4-(methoxymethyl)-1-hydroxycyclohexan-1-yl, 4-hydroxy-4-methyl-1-hydroxycyclohexan-1-yl, 4-methoxy-4-methyl-1-hydroxycyclohexan-1-yl, 1,4-dimethoxycyclohexan-1-yl, 4-N,N-dimethylcarbamoyl-1-hydroxycyclohexan-1-yl, 4-(3-methyl-1,2,4-oxadiazol-5-yl)-1-hydroxycyclohexan-1-yl, 4-(1H-pyrazol-1-yl)-1-hydroxycyclohexan-1-yl, 4-ethoxy-1-hydroxycyclohexan-1-yl, 3-methoxy-1-hydroxycycloheptan-1-yl, cyclopentyl-methylene-, 1-methylpyrazol-4-yl, 1-methylpyrazol-5-yl, 1,5-dimethyl-1H-pyrazol-4-yl, 2-methylpropylpyrazol-4-yl, 1,3,5-trimethyl-1H-pyrazol-4-yl, 1-methyl-5-

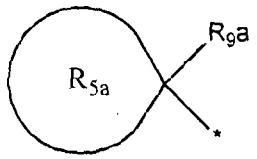
trifluoromethyl-1H-pyrazol-3-yl, 1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl, 1,2-oxazol-4-yl, 3,5-dimethyl-1,2-oxazol-4-yl, 5-methyl-1,2-oxazol-3-yl, 5-N,N-dimethylcarbamoyl-1,2-oxazol-3-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 5-methyl-1,3,4-oxadiazol-2-yl, 5-methyl-1,2,4-oxadiazol-3-yl, 2,4-diemthyl-1,3-thiazol-5-yl, pyridin-3-yl, pyridazin-3-yl, (2-methyl-1,3-oxazol-4-yl)-methylene-, (5-methyl-1,2-oxazol-3-yl)-methylene-, pyridin-2(1H)-on-1-yl, 3-methoxy-pyridin-2(1H)-on-1-yl, 3-methyl-pyridin-2(1H)-on-1-yl, 6-methyl-3-(trifluoromethyl)pyridin-2(1H)-on-1-yl, 3-(trifluoromethyl)pyridin-2(1H)-on-1-yl, 5-(methoxymethyl)pyridin-2(1H)-on-1-yl, 3-methylcarboxylate-6-oxo-1,6-dihydropyridin-1-yl, pyridazin-3(2H)-on-2-yl, tetrahydrofuran-3-yl, 3-hydroxytetrahydrofuran-3-yl, 4-hydroxytetrahydrofuran-3-yl, tetrahydropyran-4-yl, 4-hydroxytetrahydropyran-4-yl, 2,6-dimethyl-4-hydroxytetrahydropyran-4-yl, 4-fluorotetrahydropyran-4-yl, 3-methylimidazolidin-2-onyl, 1,3-oxazolidin-2-onyl, pyrrolidin-1-yl, 2-oxopyrrolidin-1-yl, 3-methoxy-2-oxopyrrolidin-1-yl, 4-methoxy-2-oxopyrrolidin-1-yl, 1-acetyl-4-hydroxypiperidin-4-yl, 1-(pyrimidin-2-yl)-4-hydroxypiperidin-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-methoxypiperidin-1-yl, 2-oxopiperidin-1-yl, morpholin-4-yl, 2,6-dimethylmorpholin-4-yl, 3-oxomorpholin-4-yl, 1-acetyl-4-hydroxyazepan-4-yl, 4-hydroxyoxepan-4-yl, 5-oxo-1,4-oxazepan-4-yl, 3-methoxy-3-methyl-azetidin-1-yl, 3-methoxy-3-methyl-azetidin-1-yl, 4-methoxytetrahydro-2H-pyran-2-yl, 4-(methoxymethyl)tetrahydro-2H-pyran-4-yl, 4-ethylcarboxylate-tetrahydropyran-4-yl, 1-(propan-2-ol)tetrahydro-2H-pyran-4-yl, (tetrahydrofuran-3-yl)-methylene, 2-acetyl-4-hydroxyoctahydrocyclopenta[c]pyrrol-4-yl, 8-acetyl-3-hydroxy-8-azabicyclo[3.2.1]octan-3-yl, 8-hydroxy-oxaspiro[4.5]decan-8-yl; and when A_1 is C_{1-6} alkylene, H, or methyl, isopropyl or isobutyl.

In one particular embodiment, R_5 represents 4-methoxy-1-hydroxycyclohexan-1-yl, 4-ethoxy-1-hydroxycyclohexan-1-yl, 4-methoxy-4-methyl-1-hydroxycyclohexan-1-yl, 4-isopropoxy-1-hydroxycyclohexan-1-yl, 4-methoxy-1-fluorocyclohexan-1-yl, 4-(methoxymethyl)-1-hydroxycyclohexan-1-yl, 4-hydroxytetrahydropyran-4-yl, 4-fluorotetrahydropyran-4-yl and 1,5-dimethyl-1H-pyrazol-4-yl.

In one particular subgroup of compounds according to the invention, A_1 represents a covalent bond or $-CH_2-$, L_1 represents a covalent bond and R_5 represents $-Q_3$-C_{3-8} cycloalkyl, $-Q_4$-heteroaryl or $-Q_5$-heterocyclyl; in which the C_{3-8} cycloalkyl, heteroaryl

and heterocyclyl are optionally substituted with one or more R_9, each of which may be the same or different.

In a further particular subgroup of compounds according to the invention, A_1 represents a covalent bond or $-CH_2-$, L_1 represents a covalent bond and R_5 represents an optionally substituted 5 to 6 membered monocyclic heteroaryl or a ring of formula R_{5a}:



wherein R_{5a} represents a C_{3-8} cycloalkyl or heterocyclyl ring, each optionally substituted with one or more R_9; R_{9a} represents $-C_{0-6}$ alkyl-OR_{10} or –F and * represents the point of attachment to A_1.

In one embodiment R_{5a} represents optionally substituted cyclohexyl or optionally substituted tetrahydropyran-4-yl.

R_{9a} typically represents –OH, $-OCH_3$, $-C(CH_3)_2OH$, $-CH_2OCH_3$ or -F. In one embodiment R_{9a} represents –OH or –F.

In a further aspect of the invention, specific novel compounds include each of the novel compounds whose preparation is described in the accompanying Examples, and pharmaceutically acceptable salts thereof.

In particular embodiments the compound of formula (1) is selected from the group consisting of:

1-cyclobutyl-4-[4-(1-methyl-1H-pyrazol-4-yl)benzylidene]piperidine;

1-cyclobutyl-4-{4-[1-(2-methylpropyl)-1H-pyrazol-4-yl]benzylidene}piperidine;

1-cyclobutyl-4-[4-(3,5-dimethyl-1,2-oxazol-4-yl)benzylidene]piperidine;

1-cyclobutyl-4-[4-(1-methyl-1H-pyrazol-5-yl)benzylidene]piperidine;

1-cyclobutyl-4-[4-(2,4-dimethyl-1,3-thiazol-5-yl)benzylidene]piperidine;

1-cyclobutyl-4-[4-(1,5-dimethyl-1H-pyrazol-4-yl)benzylidene]piperidine;

1-cyclobutyl-4-[4-(1,2-oxazol-4-yl)benzylidene]piperidine;

1-cyclobutyl-4-[4-(1,3,5-trimethyl-1H-pyrazol-4-yl)benzylidene]piperidine;

4-[2-chloro-4-(1-methyl-1H-pyrazol-4-yl)benzylidene]-1-cyclobutylpiperidine;

1-cyclobutyl-4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)benzylidene]piperidine;
1-cyclobutyl-4-[4-(5-methyl-1,3,4-oxadiazol-2-yl)benzylidene]piperidine;
1-cyclobutyl-4-[4-(5-methyl-1,2,4-oxadiazol-3-yl)benzylidene]piperidine;
{4-[(1-cyclopentylpiperidin-4-ylidene)methyl]phenyl}methanol;
(4-{[1-(2-methylpropyl)piperidin-4-ylidene]methyl}phenyl)methanol;
N-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}cyclopentanecarboxamide;
N-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}tetrahydrofuran-3-carboxamide;
2-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-N-cyclopentylacetamide;
2-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-N-(tetrahydrofuran-3-yl)acetamide;
2-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(pyrrolidin-1-yl)ethanone;
{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}(pyrrolidin-1-yl)methanone;
4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-N-cyclopentylbenzamide;
4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-N-(tetrahydrofuran-3-yl)benzamide;
4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-N-(cyclopentylmethyl)benzamide;
4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-N-(tetrahydrofuran-3-ylmethyl)benzamide;
4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-N-(pyridin-3-yl)benzamide;
N-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}pyridin-3-amine;
{3-chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}(pyrrolidin-1-yl)methanone;
{2-chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}(pyrrolidin-1-yl)methanone;
{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-2-fluorophenyl}(pyrrolidin-1-yl)methanone;
{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-3-fluorophenyl}(pyrrolidin-1-yl)methanone;
{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-3-fluorophenyl}methanol;
{3-chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}methanol;
{6-[(1-cyclobutylpiperidin-4-ylidene)methyl]pyridin-3-yl}(pyrrolidin-1-yl)methanone;
{6-[(1-cyclobutylpiperidin-4-ylidene)methyl]pyridin-3-yl}methanol;
{5-[(1-cyclobutylpiperidin-4-ylidene)methyl]pyridin-2-yl}(pyrrolidin-1-yl)methanone;
pyrrolidin-1-yl(4-{[1-(tetrahydrofuran-3-yl)piperidin-4-ylidene]methyl}phenyl)methanone;

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}pyridin-2(1H)-one;
2-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}pyridazin-3(2H)-one;
3-({4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}oxy)pyridazine;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-3-methoxypyridin-2(1H)-one;
methyl 1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-6-oxo-1,6-dihydropyridine-3-carboxylate;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-3-methylpyridin-2(1H)-one;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-6-methyl-3-(trifluoromethyl)pyridin-2(1H)-one;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-3-(trifluoromethyl)pyridin-2(1H)-one;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}piperidin-2-one;
4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}morpholin-3-one;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}pyrrolidin-2-one;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-5-(methoxymethyl)pyridin-2(1H)-one;
(3S)-1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-3-methoxypyrrolidin-2-one;
(4R)-1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-4-methoxypyrrolidin-2-one;
4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-1,4-oxazepan-5-one;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-3-methylimidazolidin-2-one;
3-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-1,3-oxazolidin-2-one;
1-cyclobutyl-4-{4-[(cyclopentyloxy)methyl]benzylidene}piperidine;
1-cyclobutyl-4-{4-[(tetrahydrofuran-3-ylmethoxy)methyl]benzylidene}piperidine;
1-cyclobutyl-4-{4-[(cyclopentylmethoxy)methyl]benzylidene}piperidine;
1-cyclobutyl-4-{4-[(tetrahydro-2H-pyran-4-yloxy)methyl]benzylidene}piperidine;
1-cyclobutyl-4-(4-{[(2-methyl-1,3-oxazol-4-yl)methoxy]methyl}benzylidene) piperidine;
1-cyclobutyl-4-(4-{[(5-methyl-1,2-oxazol-3-yl)methoxy]methyl}benzylidene) piperidine;
3-({4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}oxy)pyridine;
1-cyclobutyl-4-(4-{[(5-methyl-1,2-oxazol-3-yl)oxy]methyl}benzylidene)piperidine;

1-cyclobutyl-4-[4-({[1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]oxy}methyl)benzylidene]piperidine;

1-cyclobutyl-4-[4-({[1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]oxy}methyl) benzylidene]piperidine;

3-({4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}oxy)-N,N-dimethyl-1,2-oxazole-5-carboxamide;

1-cyclobutyl-4-[4-(piperidin-1-ylmethyl)benzylidene]piperidine;

4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}morpholine;

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-4,4-difluoropiperidine;

4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-2,6-dimethylmorpholine;

1-cyclobutyl-4-{4-[(4-methoxypiperidin-1-yl)methyl]benzylidene}piperidine;

N-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-2-methoxy-N-methylethanamine;

N-(4-((1-ethylpiperidin-4-ylidene)methyl)benzyl)cyclopentanamine dihydrochloride;

1-(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)ethanol;

(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)(cyclopentyl)methanol;

1-(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)-3-methylbutan-1-ol;

(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)methanol;

2-(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)propan-2-ol;

1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)-2-methylpropan-1-ol;

(3-Chloro-4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)(cyclopentyl)methanol;

1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)-2-cyclopentylethanol;

1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)-2-cyclopropylethanol;

Cyclopentyl(4-{[1-(2-methylpropyl)piperidin-4-ylidene]methyl}phenyl)methanol;

Cyclopentyl(4-((1-ethylpiperidin-4-ylidene)methyl)phenyl)methanol;

Cyclopentyl(4-((1-(cyclopropylmethyl)piperidin-4-ylidene)methyl)phenyl)methanol;

1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)cyclopentanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}cyclohexanol;

3-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydrofuran-3-ol;

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;

1-(4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxypiperidin-1-yl)ethanone;

N-(4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxycyclohexyl)acetamide;

Ethyl 4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxycyclohexanecarboxylate;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methoxycyclohexanol;

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(pyrimidin-2-yl)piperidin-4-ol;

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-(hydroxymethyl)cyclohexanol;

1-[4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxyhexahydrocyclopenta[c]pyrrol-2(1H)-yl]ethanone;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-(3-methyl-1,2,4-oxadiazol-5-yl)cyclohexanol;

1-(4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxyazepan-1-yl)ethanone;

1-(3-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl)ethanone;

Ethyl 3-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-3-hydroxycyclobutanecarboxylate;

{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}(tetrahydro-2H-pyran-4-yl)methanol;

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxy-N,N-dimethylcyclohexanecarboxamide;

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(1-methyl-1H-pyrazol-4-yl)ethanol;

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-2,6-dimethyltetrahydro-2H-pyran-4-ol;

4-{3-Chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methoxy-4-methylcyclohexanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methylcyclohexane-1,4-diol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-(methoxymethyl)cyclohexanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-ethoxycyclohexanol;

8-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-oxaspiro[4.5]decan-8-ol;

1-{3-Chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methoxycyclohexanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-(propan-2-yloxy)cyclohexanol;

2-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methoxybutan-2-ol;

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-3-(methoxymethyl)cyclobutanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-3-methoxycyclohexanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-(1H-pyrazol-1-yl)cyclohexanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-2-methoxycyclohexanol;

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}oxepan-4-ol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-3-methoxycycloheptanol;

{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(tetrahydrofuran-3-yl)ethanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-2-(methoxymethyl)cyclopentanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methoxycycloheptanol;

1-{4-[(1-cyclopentylpiperidin-4-ylidene)methyl]phenyl}-4-methoxycyclohexanol;

4-{4-[(1-Cyclopentylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;

4-Methoxy-1-(4-{[1-(propan-2-yl)piperidin-4-ylidene]methyl}phenyl)cyclohexanol;

4-(4-{[1-(propan-2-yl)piperidin-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol;

1-(4-{[1-(Cyclopropylmethyl)piperidin-4-ylidene]methyl}phenyl)-4-methoxycyclohexanol;

1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)propan-2-ol;

2-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)-1-cyclopentylethanol;

1-(4-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)benzyl)-4-hydroxypiperidin-1-yl)ethanone;

1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)benzyl)cyclopentanol;

1-Cyclopentyl-2-(4-((1-ethylpiperidin-4-ylidene)methyl)phenyl)ethanol;

2-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(tetrahydrofuran-3-yl)ethanol;

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}tetrahydro-2H-pyran-4-ol;

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-3-fluorobenzyl}tetrahydro-2H-pyran-4-ol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}-4-methoxycyclohexanol;

4-(4-{[1-(Tetrahydrofuran-3-yl)piperidin-4-ylidene]methyl}benzyl)tetrahydro-2H-pyran-4-ol

4-(4-{[1-(3-Fluorocyclobutyl)piperidin-4-ylidene]methyl}benzyl)tetrahydro-2H-pyran-4-ol;

2-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(tetrahydro-2H-pyran-4-yl)ethanol;

3-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}tetrahydrofuran-3-ol;

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydrofuran-3-ol;

1-{4-[(E)-(1-Cyclobutylazepan-4-ylidene)methyl]phenyl}-4-methoxycyclohexanol;

1-{4-[(Z)-(1-Cyclobutylazepan-4-ylidene)methyl]phenyl}-4-methoxycyclohexanol;

4-{4-[(E)-(1-Cyclobutylazepan-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;

4-{4-[(Z)-(1-Cyclobutylazepan-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;

4-(4-{(E)-[1-(Propan-2-yl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol;

4-(4-{(Z)-[1-(Propan-2-yl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol;

4-{4-[(E)-(1-Cyclobutylazepan-4-ylidene)methyl]benzyl}tetrahydro-2H-pyran-4-ol;

4-{4-[(E)-(1-Cyclopentylazepan-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;

4-{4-[(Z)-(1-cyclopentylazepan-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;

4-(4-{(E)-[1-(Cyclopropylmethyl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol;

4-(4-{(Z)-[1-(Cyclopropylmethyl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol;

4-(4-{(E)-[1-(2-Methylpropyl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol;

4-(4-{(Z)-[1-(2-Methylpropyl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol;

4-{4-[(E)-(1-Ethylazepan-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;

1-{6-[(1-Cyclobutylpiperidin-4-ylidene)methyl]pyridin-3-yl}-4-methoxycyclohexanol;

4-({5-[(1-Cyclobutylpiperidin-4-ylidene)methyl]pyridin-2-yl}methyl)tetrahydro-2H-pyran-4-ol;

1-{5-[(1-Cyclobutylpiperidin-4-ylidene)methyl]pyridin-2-yl}-4-methoxycyclohexanol;

1-Cyclobutyl-4-{4-[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]benzylidene}piperidine;

1-Cyclobutyl-4-[4-(4-fluorotetrahydro-2H-pyran-4-yl)benzylidene]piperidine;

1-Cyclobutyl-4-[4-(1-fluoro-4-methoxycyclohexyl)benzylidene]piperidine;

N-(4-(1-(1-Cyclobutylpiperidin-4-ylidene)ethyl)benzyl)cyclopentanamine;

{4-[1-(1-Cyclobutylpiperidin-4-ylidene)ethyl]phenyl}methanol;

1-Cyclobutyl-4-{1-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]ethylidene}piperidine;

4-{4-[(E)-(1-Cyclobutyl-3-methylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;

1-Cyclobutyl-4-[4-(tetrahydro-2H-pyran-4-ylsulfonyl)benzylidene]piperidine;

1-Cyclobutyl-4-{4-[(2-methoxyethyl)sulfonyl]benzylidene}piperidine;

1-Cyclobutyl-4-{4-[(3-methoxypropyl)sulfonyl]benzylidene}piperidine;

1-Cyclobutyl-4-{4-[(tetrahydro-2H-pyran-4-ylmethyl)sulfonyl]benzylidene}piperidine;

1-Cyclobutyl-4-{4-[(2-ethoxyethyl)sulfonyl]benzylidene}piperidine;

1-Cyclobutyl-4-(4-{[(2-ethoxyethyl)sulfonyl]methyl}benzylidene)piperidine;

4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-N-methyl-N-(tetrahydro-2H-pyran-4-yl)benzenesulfonamide;

4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-N-(tetrahydro-2H-pyran-4-yl)benzenesulfonamide;

4-({4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}sulfonyl)morpholine;

1-Cyclobutyl-4-{4-[(3-methoxyazetidin-1-yl)sulfonyl]benzylidene}piperidine;

1-Cyclobutyl-4-{4-[(4-methoxypiperidin-1-yl)sulfonyl]benzylidene}piperidine;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-N-methyl-N-(tetrahydro-2H-pyran-4-yl)methanesulfonamide;

4-({4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}sulfonyl)morpholine;

1-Cyclobutyl-4-(4-{[(3-methoxy-3-methylazetidin-1-yl)sulfonyl]methyl}benzylidene)piperidine;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-N-(tetrahydro-2H-pyran-4-yl)methanesulfonamide;

1-Cyclobutyl-4-[4-(1,4-dimethoxycyclohexyl)benzylidene]piperidine;

1-Cyclobutyl-4-[4-(4-methoxytetrahydro-2H-pyran-2-yl)benzylidene]piperidine;

1-Cyclobutyl-4-{4-[4-(methoxymethyl)tetrahydro-2H-pyran-4-yl]benzylidene}piperidine;

Ethyl 4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-carboxylate;

2-(4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-yl)propan-2-ol;

and pharmaceutically acceptable salts thereof.

Particularly useful compounds in accordance with the invention include each of the compounds described in the accompanying examples, and pharmaceutically acceptable salts thereof.

In accordance with a second aspect of the invention, there is provided a pharmaceutical composition comprising a compound according to the first aspect of the invention, together with one or more pharmaceutically acceptable excipients.

Pharmaceutical compositions of this invention comprise any of the compounds of the first aspect of the present invention, or pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention are those conventionally employed in the field of pharmaceutical formulation, and include, but are not limited to, sugars, sugar alcohols, starches, ion exchangers, alumina, aluminium stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycerine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulphate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, rectally, nasally, buccally, vaginally or via an implanted reservoir. Oral administration is preferred. The pharmaceutical

compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as that described in Ph. Helv, or a similar alcohol.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, powders, granules, and aqueous suspensions and solutions. These dosage forms are prepared according to techniques well-known in the art of pharmaceutical formulation. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavouring and/or colouring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by

mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilising or dispersing agents known in the art.

The compounds of the present invention may be administered in a dose of around 1 to around 20,000 μg/kg per dose, depending on the condition to be treated or prevented, and the characteristics of the subject being administered with the compound. In many instances, the dose may be around 1 to around 1500 μg/kg per dose. The dosing regimen for a given compound could readily be determined by the skilled person having access to this disclosure.

In one particular embodiment, the pharmaceutical composition of the invention additionally comprises one or more additional active pharmaceutical ingredients. These additional active ingredients may be agents known to the skilled person to be useful in the treatment or prevention of the diseases mentioned in the present disclosure, or co-morbidities thereof.

In a third aspect, the present invention provides a compound according to the first aspect of the invention, or a composition according to the second aspect, for use in therapy.

In a fourth aspect, the invention provides a compound according to the first aspect of the invention, or a composition according to the second aspect, for use in the treatment or prevention of a condition whose development or symptoms are linked to histamine H3 receptor activity.

A number of conditions whose development or symptoms are linked to histamine H3 receptor activity are known to the skilled person.

In a fifth aspect, the invention also provides a method of treatment or prevention of a condition whose development or symptoms are linked to histamine H3 receptor activity, the method comprising the administration, to a subject in need of such treatment or prevention, of a therapeutically effective amount of a compound according to the first aspect of the invention, or a composition according to the second aspect.

In particular, there is provided a compound according to the fourth aspect, or a method according to the fifth aspect, wherein the condition is a disorder of the central nervous system.

In certain embodiments, the condition to be treated may be selected from sleep disorders (such as narcolepsy and hypersomnia), cognitive disorders (such as dementia and schizophrenia), attentional disorders (such as attention deficit hyperactivity disorder), neurodegenerative disorders (such as AD), schizophrenia, epilepsy, pain (such as neuropathic pain) and obesity.

In preferred embodiments the condition may be selected from schizophrenia, Alzheimer's Disease (AD) and dementia. In an alternative embodiment, the condition may be selected from narcolepsy, pain and obesity.

In particular embodiments, the condition may be selected from narcolepsy, neuropathic pain and obesity.

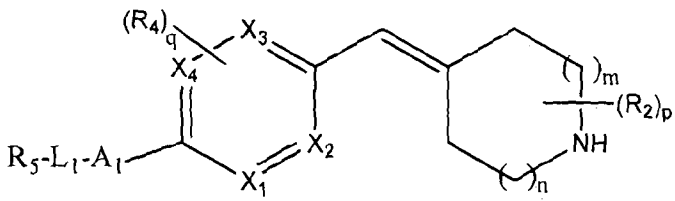
In a sixth aspect, the present invention provides the use of a compound according to the first aspect of the invention in the preparation of a medicament for the treatment or prevention of a condition whose development or symptoms are linked to histamine H3 receptor activity. Such conditions may be selected from those described above.

In the following process description, the symbols R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, m, n, p, q, Q_1, Q_2, Q_3, Q_4, Q_5, Q_6, X_1, X_2, X_3, X_4, A_1 and L_1 when used in the formulae depicted are to be understood to represent those groups as described above in relation to formula (1) unless otherwise indicated. During any of the synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. The methods of addition and removal of such protecting groups are those which would conventionally be used in relation to the particular molecule-type or group being protected, for example

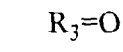
the methods described in standard works of reference in synthetic methodology, such as Kocienski (2004) *Protecting Groups*. 4th Edn. Georg Thieme Verlag. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

The following processes together with the intermediates are provided as further aspects of the invention.

Thus in another aspect of the invention, compounds according to formula (1), wherein R_1 represents H, may be prepared by a process which comprises reacting a compound of formula (I) with a compound of formula (II):



(I)

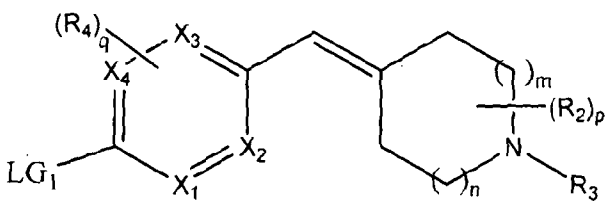


(II)

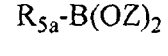
wherein R_2, R_3, R_4, R_5, n, m, p, q, A_1, L_1, X_1, X_2, X_3 and X_4 are as herein defined.

The reaction may be achieved by treatment with a suitable reducing agent, for example, sodium triacetoxyborohydride under acidic conditions e.g. in the presence of an organic acid such as acetic acid in a suitable solvent, such as a halogented hydrocarbon e.g. dichloromethane.

In a further process, compounds of formula (1), wherein R_1 represents H, A_1 and L_1 each represent a covalent bond and R_5 represents an aryl or heteroaryl group, may be prepared by a process which comprises reacting a compound of formula (III) with a compound of formula (IV):



(III)



(IV)

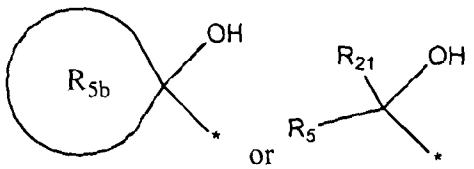
Wherein R_2, R_3, R_4, n, m, p, q, X_1, X_2, X_3 and X_4 are as herein defined, LG_1 represents a suitable leaving group, R_{5a} represents R_5 aryl or heteroaryl and $-B(OZ)_2$ represents boronic acid or a ester derivative thereof.

LG_1 typically represents halogen e.g. bromine.

$B(OZ)_2$ typically represents boronic acid or boronic acid pinacol ester.

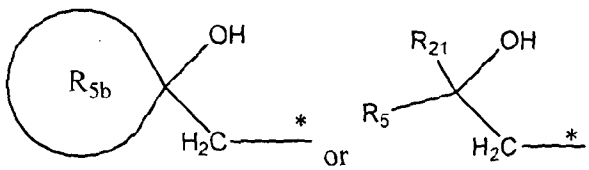
The reaction may conveniently be achieved by reaction in the presence of a suitable catalyst, such as palladium under basic conditions e.g. in the presence of an inorganic base such as sodium carbonate in an approriate solvent such as a cylic ether e.g. dioxane at elevated temperature.

In another process, compounds of formula (1), where L_1 represents a covalent bond and–A_1- R_5 represents:



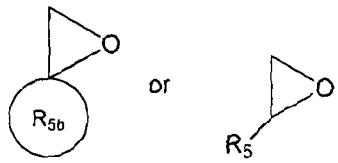
wherein R_{21} represents H or C_{1-3} alkyl, R_5 is as herein defined, R_{5b} represents an optionally substituted C_{3-8} cycloalkyl or optionally substituted heterocyclyl ring and * represents the point of attachment, may be prepared by a process which comprises initial conversion of a compound of formula (III) to a Grignard reagent followed by reaction with R_{5b}=O or $(R_5)(R_{21})C$=O in a suitable solvent e.g. a cyclic ether such as THF.

In a further process, compounds of formula (1), where L_1 represents a covalent bond and–A_1-R_5 represents:



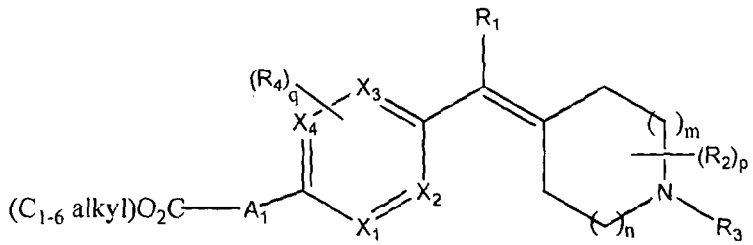
wherein R_{21} represents H or C_{1-3} alkyl, R_5 is as herein defined, R_{5b} represents an optionally substituted C_{3-8} cycloalkyl or optionally substituted heterocyclyl ring and *

represents the point of attachment, may be prepared by a process which comprises reacting a compound of formula (III) with an epoxide of formula:



The reaction may conveniently be effected by initial reaction of a compound (III) with alkyllithium in the presence of an acid e.g. a Lewis acid such as borontrifluoride, followed by treatment with an epoxide in an appropriate solvent e.g. a cyclic ether such as THF.

In a further process, compounds of formula (1), where L_1 represents a covalent bond and R_5 represents an oxadiazolyl group, may be prepared by conversion of an intermediate of formula (V):



(V)

wherein R_1, R_2, R_3, R_4, n, m, p, q, A_1, X_1, X_2, X_3 and X_4 are as herein defined.

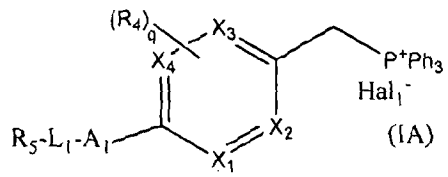
Suitable conditions include treatment under basic conditions e.g. an inorganic base such as sodium hydride, with acetamidoxime in an appropriate solvent e.g. THF. Alternative conditions include treatment with acetylhydrazide in the presence of trimethylaluminium, followed by treatment with $POCl_3$ under reflux.

Alternatively, compounds of formula (1) wherein A_1 represents C_{1-6} alkylene, L_1 represents –O- and R_5 represents H, may be prepared by treating a compound of formula (V) with a suitable reducing agent e.g. lithium aluminium hydride in an appropriate solvent e.g. a cyclic ether such as THF.

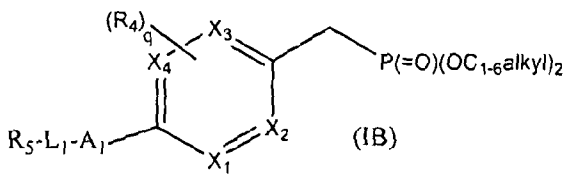
In a further process, compounds of formula (1), wherein L_1 represents $-NR_7CO-$ may be prepared by process which comprises reacting a compound of formula (V) with R_5R_7NH. Suitable conditions include reaction in the presence of trimethylaluminium or

bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct in a suitable solvent such as a cyclic ether e.g. THF. Compounds according to formula (1) wherein L_1 represents –CO- and R_5 represents N-linked heterocyclyl may be prepared in an analogous method. Alternatively an intermediate of formula (V) may be converted to the corresponding acid chloride using standard techniques such as reaction with LiOH followed by treatment with oxalyl chloride, which may then be reacted with R_5R_7NH in a suitable solvent e.g. a halogented hydrocarbon e.g. dichloromethane.

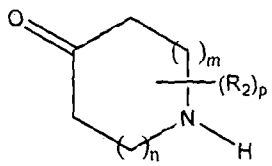
Intermediates of formula (I) may be prepared using methods known to those skilled in the art, or using the methods as described in the examples hereinafter. For example, an intermediate of formula (I) may be prepared by a process which comprises reacting a compound of formula (IA) or (IB) with a compound of formula (VI):



(IA)



(IB)



(VI)

wherein R_2, R_4, R_5, n, m, p, q, A_1, L_1, X_1, X_2, X_3 and X_4 are as herein defined and Hal_1 represents halogen.

Hal_1 typically represents bromine.

The reaction is conventiently effected by the treatment under basic conditions e.g. an inorganic base such as potassium carbonate or sodium hydride in a suitable solvent such as a halogented hydrocarbon e.g. dichloromethane or an ether such as tetrahydrofuran. Reaction may be achieved at elevated temperature in the presence of catalyst such as a crown ether e.g. 18-crown-6 or 15-crown-5.

Intermediates of formula (IA) and (IB) may be prepared by using methods known to those skilled in the art, for example, using methods as described in the Examples hereinafter.

Similarly, intermediates of formula (III), (V) and any other intermediates as used in the above processes, where not commercially available, may be prepared by using methods known to those skilled in the art, for example, using methods as described in the Examples hereinafter.

It will be understood that any compound of formula (1) initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula (1) by techniques known from the art. For example, suitable examples are provided in the examples hereinafter.

It will be further understood that a deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups. The protecting groups may be removed using methods well known to those skilled in the art.

The compounds of formula (1) above may be converted to a pharmaceutically acceptable salt thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, benzenesulphonate (besylate), saccharin (e.g. monosaccharin), trifluoroacetate, sulphate, nitrate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate, pyruvate, succinate, valerate, propanoate, butanoate, malonate, oxalate, 1-hydroxy-2-napthoate (xinafoate), methanesulphonate or *p*-toluenesulphonate salt.

Novel intermediates form a further aspect of the invention.

The invention will now be described in more detail by way of example only.

1. Synthetic Methodologies

The methods used for synthesis of the compounds of the invention are illustrated by the general schemes below and the preparative examples that follow. All compounds and intermediates were characterised at least by liquid chromatography-mass spectroscopy (LCMS). The starting materials and reagents used in preparing these compounds are

available from commercial suppliers. These general schemes are merely illustrative of methods by which the compounds of this invention can be synthesised, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

Nuclear magnetic resonance (NMR) spectra were recorded at either 400 MHz or 300 MHz; the chemical shifts (δ) are reported in parts per million. Spectra were recorded using a Bruker 400 Avance instrument fitted with a 5 mm BBFO probe or DUL probe. Instrument control was by Bruker TopSpin 2.1 software. Alternatively, spectra were recorded on a JEOL ECX 300 instrument.

Purity was assessed using UPLC with UV (photodiode array) detection over a wide range of wavelengths, normally 220-450 nm, using a Waters Acquity UPLC system.

Compounds were purified using normal phase chromatography on silica or alumina, or by reverse phase chromatographic methods, using Biotage or Isolute KPNH Cartridge, SCX cartridge and SCX-2 solid phase extraction cartridges.

Preparative HPLC was performed using an Agilent Technologies 1100 Series system typically using Waters 19 mm id x 100 mm long C18 columns such as XBridge or SunFire 5μm materials at room temperature. Mobile phases typically consisted of acetonitrile or methanol mixed with water containing either 0.1 % formic acid or 0.1 % ammonia.

Room temperature in the following schemes means the temperature ranging from 20 °C to 25 °C.

Abbreviations:

Ac	Acetyl
Ac_2O	Acetic anhydride
AcOH	Acetic acid
Aq.	Aqueous
Boc	tert-Butoxy carbonyl
n-Bu	n-butyl
cat	Catalytic

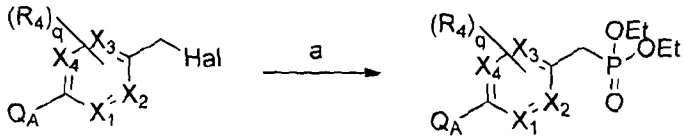
$CDCl_3$	Deuterated chloroform
CDI	Carbonyl diimidazole
DAST	Diethylaminosulfur trifluoride
dba	Dibenzylideneacetone
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DBU	1,8-Diazabicycloundec-7-ene
DCM	Dichloromethane
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diiospropylethylamine
DMAP	Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
DMF	Dimethyl formamide
EDC	1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride
Et	Ethyl
EtOAc	Ethyl acetate
h	Hours
HOAt	1-Hydroxy-7-azabenzotriazole
KOAc	Potassium acetate
KHMDS	Potassium bis(trimethylsilyl)amide
KOtBu	Potassium tert-butoxide
LCMS	Liquid Chromatography Mass Spectrum
mCPBA	meta-Chloroperbenzoic acid
Me	Methyl
min	Minutes
MS	Mass Spectrum
MW	Microwave
NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	N-Bromosuccinimide
NMM	N-Methylmorpholine
NMR	Nuclear Magnetic Resonance
PhMe	Toluene
pTSA	para-Toluenesulfonic acid
r.t.	Room temperature

sat.	Saturated
TBAF	Tetrabutylammonium fluoride
TBDMS	tert-Butyldimethyl silyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

In the following experimental section the symbols R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, m, n, p, q, Q_1, Q_2, Q_3, Q_4, Q_5, Q_6, X_1, X_2, X_3, X_4, A_1 and L_1 are as herein defined, unless otherwise specified.

1. INTERMEDIATES

Scheme 1

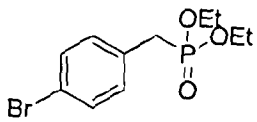


Q_A represents $-CO_2C_{1-6}$ alkyl, CN, C_{1-6} alkyl, halogen or $-A_1-L_1-R_5$
Hal represents halogen

Reagents and conditions: a) $P(OEt)_3$, 150 °C

Intermediate 1

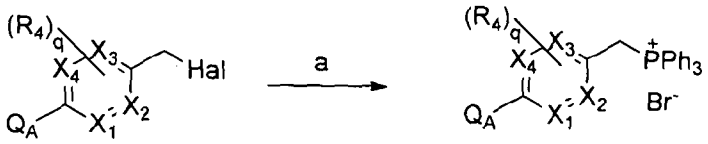
Diethyl 4-bromobenzylphosphonate



4-Bromobenzyl bromide (22.5g, 90mmol) and triethylphosphite (16.45g, 99mmol) were heated to 150°C for 3 h. The mixture was purifed by flash chromatography (1/4 EtOAc/hexane) to give diethyl 4-bromobenzylphosphonate (25.2g, 91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ ?7.45 (m, 2H), 7.15 (m, 2H), 4.00 (m, 4H), 3.05 (m, 2H), 1.25 (m, 6H)

Scheme 2

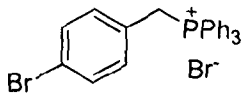


Q_A represents $-CO_2C_{1-6}$ alkyl,CN, C_{1-6} alkyl, halogen or $-A_1-L_1-R_5$
Hal represents halogen

Reagents and conditions: a) PPh_3, toluene, reflux

Intermediate 2

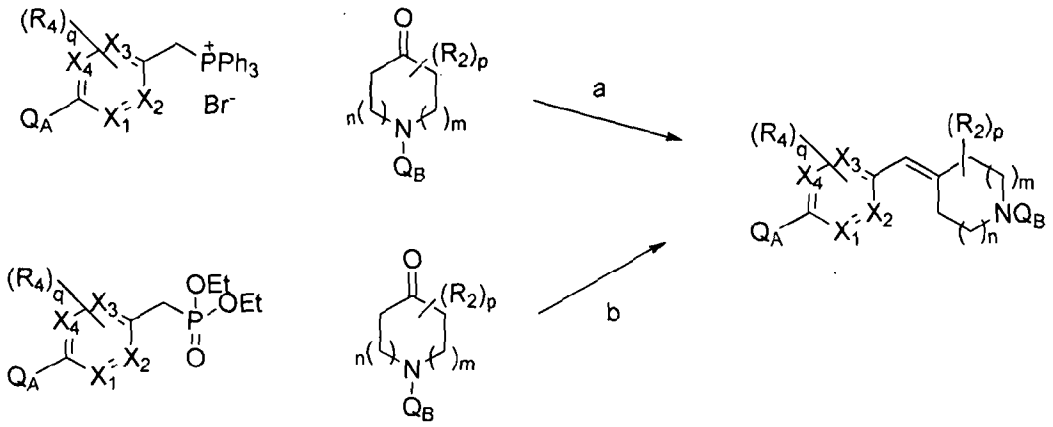
(4-Bromobenzyl)(triphenyl)phosphonium bromide



To a stirred solution of 1-bromo-4-(bromomethyl)benzene (8g, 32mmol) in toluene (160 ml) was added triphenylphosphine (8.4g, 32mmol). The reaction was stirred at 120°C under an atmoshpere of nitrogen for 17 hours after which time a white precipitate had formed. The reaction was then cooled to room temperature and the solid was collected by filtration, washing with a minimum amount of cold toluene to give (4-bromobenzyl)(triphenyl)phosphonium bromide as a white solid (15.4 g, 89 %)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 - 8.01 (m, 2 H), 7.57 - 7.84 (m, 8 H), 7.33 - 7.55 (m, 1 H), 6.79 - 7.02 (m, 1 H), 5.04 - 5.28 (m, 2 H)
MS ES^+ 433, 435

Scheme 3



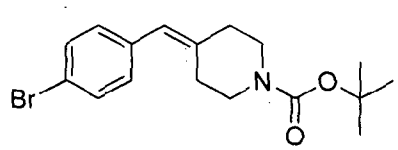
Q_A= $-CO_2C_{1-6}$ alkyl, C_{1-6} alkyl, CN, halogen or $-A_1-L_1-R_5$

Q_B= H or R_3

Reagents and conditions: a) Potassium carbonate, 18-crown-6, DCM, reflux; b) NaH, 15-crown-5, 50 °C, 1 h

Intermediate 3

tert-Butyl 4-(4-bromobenzylidene)piperidine-1-carboxylate



Method A

To a suspension of (4-bromobenzyl)triphenylphosphonium bromide (**Int 2**) (49.3 g, 96 mmol) in DCM (300 ml) were added tert-butyl 4-oxopiperidine-1-carboxylate (19.2 g, 96 mmol), potassium carbonate (13.3 g, 96 mmol) and 18-crown-6 (2.5 g, 9.6 mmol). The reaction was stirred at 45°C under an atmosphere of nitrogen for 34 h. The reaction mixture was partitioned between DCM (300 ml) and water (200 ml). The aqueous layer was further extracted with DCM (200 ml). The combined organics were washed with brine (200 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give an off white solid. Purification by column chromatography (SiO_2; 0-20 % EtOAc

in petrol) gave *tert*-butyl 4-(4-bromobenzylidene)piperidine-1-carboxylate as a colourless oil (26.3 g, 74 %).

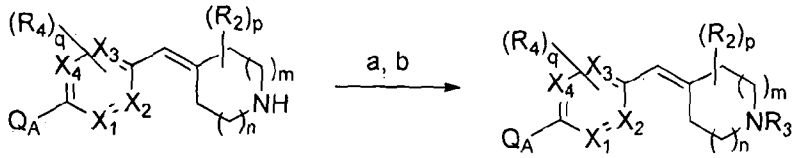
Method B

Diethyl 4-bromobenzylphosphonate (**Int 1**) (1.69 g, 5.5 mmol) in THF (3 ml) was added dropwise to a stirred suspension of sodium hydride (60 % dispersion in oil, 0.32 g, 8.0 mmol) in THF (20 ml) and 15-crown-5 (2 drops) at rt. The reaction was warmed to 65 °C for 15 minutes and then cooled to rt. *tert*-Butyl 4-oxopiperidine-1-carboxylate (1 g, 5 mmol) was added and the reaction was warmed to 50 °C for 1 h. The reaction mixture was poured onto ice water and extracted with ethyl acetate. The organic extract was washed with brine, dried over $MgSO_4$ and evaporated. Purification by column chromatography (SiO_2; 0-15 % EtOAc in petrol) gave *tert*-butyl 4-(4-bromobenzylidene)piperidine-1-carboxylate as colourless oil (1.19 g, 69 %).

^{1}H NMR (400 MHz, MeOD) δ 7.41 - 7.50 (m, 2H), 7.05 - 7.17 (m, 2H), 6.35 (s, 1H), 3.45 - 3.56 (m, 2H), 3.37 - 3.45 (m, 2H), 2.39 - 2.48 (m, 2H), 2.29 - 2.38 (m, 2H), 1.39 - 1.54 (m, 9H)

MS ES^+ 252

Scheme 4

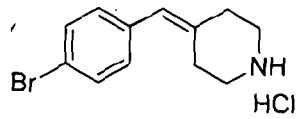


Q_A = $-CO_2C_{1-6}$ alkyl, C_{1-6} alkyl, CN, halogen or $-A_1-L_1-R_5$

Reagents and conditions: a) HCl, dioxane; b) Triethylamine, acetic acid, sodium triacetoxyborohydride, $R_3C{=}O$, DCM

Intermediate 4

4-(4-bromobenzylidene)piperidine hydrochloride

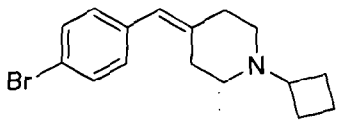


To a stirred solution of tert-butyl 4-(4-bromobenzylidene)piperidine-1-carboxylate (**Int 3**) (5 g, 14.2 mmol) in dioxane (14 ml) was added HCl (4M in dioxane, 17.7 ml, 71 mmol). The reaction was stirred at r.t. under an atmosphere of nitrogen for 4 hours. The reaction mixture was concentrated under reduced pressure to give 4-(4-bromobenzylidene)piperidine hydrochloride as a white solid (4.1 g, 95 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (br. s., 2H), 7.47 - 7.64 (m, 2H), 7.14 - 7.26 (m, 2H), 6.42 (s, 1H), 3.01 - 3.21 (m, 4H), 2.56 - 2.67 (m, 4H)
MS ES$^+$ 252 and 254

Intermediate 5

4-(4-bromobenzylidene)-1-cyclobutylpiperidine

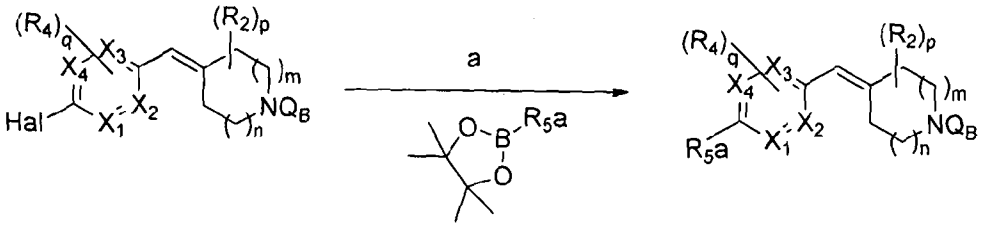


To a solution of 4-(4-bromobenzylidene)piperidine hydrochloride (**Int 4**) (8.4 g, 29 mmol), triethylamine (4.0 ml, 29.0 mmol) and cyclobutanone (6.1 g, 87 mmol), in DCM (100 ml) was added sodium triacetoxyborohydride (18.5 g, 87 mmol) and acetic acid (8.3 ml, 145 mmol). The mixture was stirred under nitrogen at r.t. for 4.5 h. The mixture was diluted with DCM (50 ml) and NaOH (2M aq., 150 ml) and the phases separated. The aqueous layer was further extracted with DCM (2 x 100 ml) and the organic extracts were combined, washed with brine (200 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (SiO_2; 0-15% (2% ammonium hydroxide in MeOH) in DCM) gave 4-(4-bromobenzylidene)-1-cyclobutylpiperidine as an off white solid (4.9 g, 16.2 mmol, 56% yield).

^{1}H NMR (400 MHz, MeOD) δ 7.40 - 7.51 (m, 2 H), 7.05 - 7.16 (m, 2 H), 6.30 (s, 1 H), 2.69 - 2.87 (m, 1 H), 2.25 - 2.57 (m, 8 H), 2.03 - 2.16 (m, 2 H), 1.85 - 2.03 (m, 2 H), 1.66 - 1.82 (m, 2 H)

MS ES$^+$ 306 and 308

Scheme 5

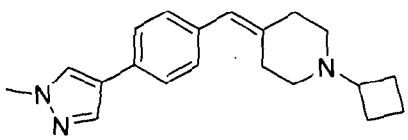


Reagents and conditions: a) $PdCl_2(dppf)$, dioxane, 2M $Na_2CO_3(aq)$, 120 °C, microwave

2. Examples

2.1 Example 1

1-Cyclobutyl-4-[4-(1-methyl-1H-pyrazol-4-yl)benzylidene]piperidine



Prepared according to **Scheme 5**

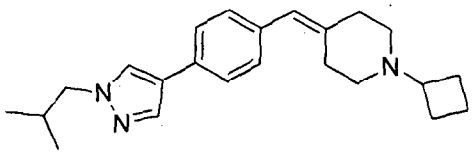
A mixture of 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) (250 mg, 0.82 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (170 mg, 0.82 mmol) and $PdCl_2(dppf)$ (59.7 mg, 0.08 mmol) in Na_2CO_3 aq. (2M, 2 ml) and dioxane (10 ml) was purged with nitrogen for 20 min. The reaction was then heated in the microwave for 2 h at 120°C. The reaction was filtered through a pad of celite and the filtrate concentrated. The residue was dissolved in DCM and washed with water and brine, dried ($MgSO_4$) and evaporated. Purification by column chromatography (NH-

silica 0-35% EtOAc / petrol) gave 1-cyclobutyl-4-(4-(1-methyl-1H-pyrazol-4-yl)benzylidene)piperidine as a pale brown solid (90 mg, 36%)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.71 (s, 1H), 7.62 (s, 1H), 7.38 - 7.45 (m, 2H), 7.16 - 7.23 (m, 2H), 6.26 (s, 1H), 3.86 - 3.94 (m, 3H), 2.63 - 2.75 (m, 1H), 2.47 - 2.54 (m, 2H), 2.36 (s, 4H), 2.22 - 2.30 (m, 2H), 1.96 - 2.07 (m, 2H), 1.79 - 1.92 (m, 2H), 1.60 - 1.74 (m, 2H)
MS (ES^+) 308.

2.2 Example 2

1-Cyclobutyl-4-{4-[1-(2-methylpropyl)-1H-pyrazol-4-yl]benzylidene}piperidine

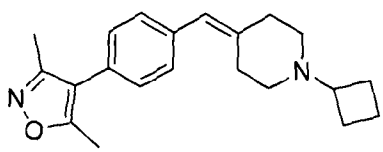


Prepared in an analogous manner to **Example 1** via **Scheme 5** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 1-isobutylpyrazole-4-boronic acid pinacol ester.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 - 8.17 (m, 1 H), 7.80 - 7.89 (m, 1 H), 7.47 - 7.56 (m, 2 H), 7.12 - 7.22 (m, 2 H), 6.20 - 6.30 (m, 1 H), 3.84 - 3.98 (m, 2 H), 2.62 - 2.74 (m, 1 H), 2.41 - 2.47 (m, 2 H), 2.31 (m, 4 H), 2.19 - 2.26 (m, 2 H), 2.06 - 2.19 (m, 1 H), 1.91 - 2.02 (m, 2 H), 1.73 - 1.86 (m, 2 H), 1.55 - 1.68 (m, 2 H), 0.84 - 0.88 (m, 6 H)
MS ES+ 350

2.3 Example 3

1-Cyclobutyl-4-[4-(3,5-dimethyl-1,2-oxazol-4-yl)benzylidene]piperidine



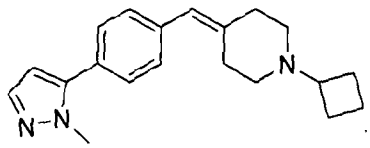
Prepared in an analogous manner to **Example 1** via **Scheme 5** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 3,5-dimethylisoxazole-4-boronic acid pinacol ester.

^{1}H NMR (400 MHz, MeOD) δ 7.13 - 7.24 (m, 4 H), 6.27 (s, 1 H), 2.69 (quin, J = 7.96 Hz, 1 H), 2.42 - 2.52 (m, 2 H), 2.35 (d, J = 4.29 Hz, 2 H), 2.30 (s, 3 H), 2.21 - 2.29 (m, 2 H), 2.15 (s, 3 H), 1.93 - 2.05 (m, 2 H), 1.76 - 1.92 (m, 2 H), 1.56 - 1.69 (m, 2 H)

MS ES+ 323

2.4 Example 4

1-Cyclobutyl-4-[4-(1-methyl-1H-pyrazol-5-yl)benzylidene]piperidine



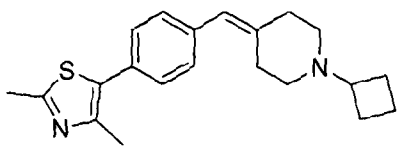
Prepared in an analogous manner to **Example 1** via **Scheme 5** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 1-methyl-1H-pyrazol-5-yl)boronic acid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 - 7.54 (m, 3 H), 7.28 - 7.39 (m, 2 H), 6.36 - 6.43 (m, 1 H), 6.27 - 6.36 (m, 1 H), 3.86 (s, 3 H), 2.61 - 2.75 (m, 1 H), 2.46 (m, 2 H), 2.34 (s, 4 H), 2.21 - 2.28 (m, 2 H), 1.92 - 2.02 (m, 2 H), 1.73 - 1.86 (m, 2 H), 1.56 - 1.68 (m, 2 H)

MS ES+ 308

2.5 Example 5

1-Cyclobutyl-4-[4-(2,4-dimethyl-1,3-thiazol-5-yl)benzylidene]piperidine



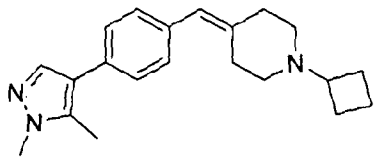
Prepared in an analogous manner to **Example 1** via **Scheme 5** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 2,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-thiazole.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39 (s, 2 H), 7.24 - 7.32 (m, 2 H), 6.23 - 6.34 (m, 1 H), 2.64 - 2.74 (m, 1 H), 2.59 - 2.64 (m, 3 H), 2.42 - 2.48 (m, 2 H), 2.39 (s, 3 H), 2.29 - 2.35 (m, 4 H), 2.21 - 2.26 (m, 2 H), 1.92 - 2.02 (m, 2 H), 1.74 - 1.86 (m, 2 H), 1.61 (m, 2 H)

MS ES+ 339

2.6 Example 6

1-Cyclobutyl-4-[4-(1,5-dimethyl-1H-pyrazol-4-yl)benzylidene]piperidine



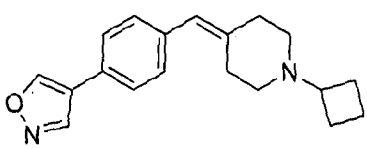
Prepared in an analogous manner to **Example 1** via **Scheme 5** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 1,5-dimethyl-1H-pyrazole-4-boronic acid pinacol ester.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (s, 1 H), 7.30 - 7.39 (m, 2 H), 7.15 - 7.28 (m, 2 H), 6.22 - 6.31 (m, 1 H), 3.78 (s, 3 H), 2.61 - 2.73 (m, 1 H), 2.41 - 2.48 (m, 2 H), 2.37 (s, 3 H), 2.32 (s, 4 H), 2.17 - 2.28 (m, 2 H), 1.88 - 2.03 (m, 2 H), 1.71 - 1.89 (m, 2 H), 1.53 - 1.71 (m, 2 H)

MS ES+ 322

2.7 Example 7

1-Cyclobutyl-4-[4-(1,2-oxazol-4-yl)benzylidene]piperidine

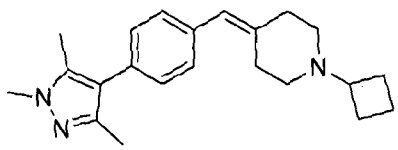


Prepared in an analogous manner to **Example 1** via **Scheme 5** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-oxazole.

^{1}H NMR (400 MHz, MeOD) δ9.06 (s, 1 H), 8.84 (s, 1 H), 7.59 (d, 2 H), 7.27 (d, 2 H), 6.37 (s, 1 H), 2.73 - 2.89 (m, 1 H), 2.57 (s, 2 H), 2.41 - 2.53 (m, 4 H), 2.32 - 2.42 (m, 2 H), 2.04 - 2.20 (m, 2 H), 1.88 - 2.04 (m, 2 H), 1.63 - 1.84 (m, 2 H)
MS ES+ 294

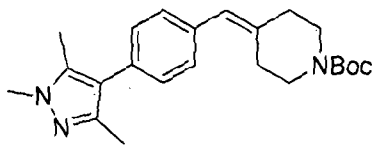
2.8 Example 8

1-Cyclobutyl-4-[4-(1,3,5-trimethyl-1H-pyrazol-4-yl)benzylidene]piperidine



Step a **Intermediate 6**

tert-butyl 4-[4-(1,3,5-trimethyl-1H-pyrazol-4-yl)benzylidene]piperidine-1-carboxylate



Prepared in an analogous manner to **Example 1** via **Scheme 5** starting with *tert*-butyl 4-(4-bromobenzylidene)piperidine-1-carboxylate (**Int 3**) and using 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.
MS ES+ 382

Step b **Example 8**

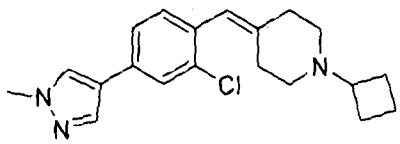
Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with tert-butyl 4-[4-(1,3,5-trimethyl-1H-pyrazol-4-yl)benzylidene]piperidine-1-carboxylate (**Int 6**) and using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12 - 7.29 (m, 4 H), 6.23 - 6.33 (m, 1 H), 3.69 (s, 3 H), 2.62 - 2.75 (m, 1 H), 2.42 - 2.48 (m, 2 H), 2.29 - 2.38 (m, 4 H), 2.22 (s, 5 H), 2.13 (s, 3 H), 1.90 - 2.05 (m, 2 H), 1.71 - 1.89 (m, 2 H), 1.62 (m, 2 H)

MS ES+ 336

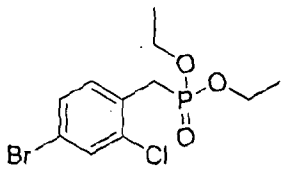
2.9 Example 9

4-[2-Chloro-4-(1-methyl-1H-pyrazol-4-yl)benzylidene]-1-cyclobutylpiperidine



Step a **Intermediate 7**

Diethyl (4-bromo-2-chlorobenzyl)phosphonate

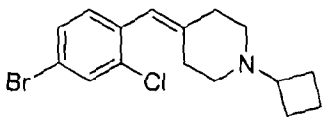


Prepared in an analogous manner to **Intermediate 1** via **Scheme 1** starting with 4-bromo-1-(bromomethyl)-2-chlorobenzene (CAS 89720-77-4).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.31 (m, 2H), 4.04 (q, 4H), 3.26 (d, 2H), 1.25 (t, 6H).

Step b **Intermediate 8**

4-(4-bromo-2-chlorobenzylidene)-1-cyclobutylpiperidine



Prepared in an analogous manner to **Intermediate 3** via **Scheme 3**, method B using diethyl (4-bromo-2-chlorobenzyl)phosphonate (**Int 7**) and 1-cyclobutyl-4-piperidone (CAS 359880-05-0).

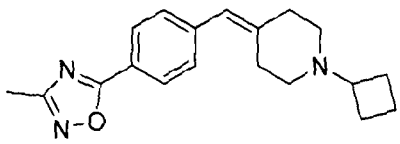
Step c **Example 9**

Prepared in an analogous fashion to **Example 1** via **Scheme 5** starting with 4-(4-bromo-2-chlorobenzylidene)-1-cyclobutylpiperidine (**Int 8**) and using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.

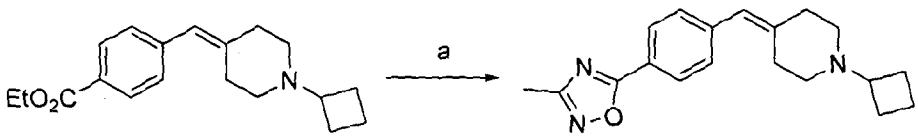
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.75 (s, 1 H), 7.65 (s, 1 H), 7.50 (s, 1 H), 7.21 – 7.37 (m, 2 H), 6.30 (s, 1 H), 3.90 (m, 3 H), 2.70 – 2.80 (m, 1 H), 2.38 – 2.43 (m, 6 H), 2.26 - 2.32 (m, 2 H), 2.00 – 2.10 (m, 2 H), 1.85 – 1.98 (m, 2 H), 1.65 – 1.77 (m, 2H)
MS (ES^+) 342

2.10 Example 10

1-Cyclobutyl-4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)benzylidene]piperidine



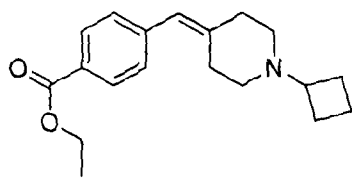
Scheme 6



Reagents and conditions: a) Acetamidoxime, NaH, THF

Step a **Intermediate 9**

Ethyl 4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzoate



Prepared in an analogous manner to **Intermediate 5** via **Scheme 5** starting with *tert*-butyl 4-(4-(ethoxycarbonyl)benzylidene)piperidine-1-carboxylate (CAS: 726185-65-5) and using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 - 7.96 (m, 2 H), 7.29 - 7.38 (m, 2 H), 6.34 (s, 1 H), 4.18 - 4.38 (m, 2 H), 2.61 - 2.75 (m, 1 H), 2.38 - 2.47 (m, 2 H), 2.28 - 2.36 (m, 4 H), 2.15 - 2.27 (m, 2 H), 1.89 - 2.03 (m, 2 H), 1.68 - 1.89 (m, 2 H), 1.52 - 1.68 (m, 2 H), 1.21 - 1.40 (m, 3 H)
MS ES$^+$ 300

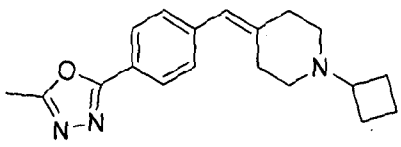
Step b **Example 10**

To a solution of acetamidoxime (74 mg, 1 mmol) in THF (10 ml) was added NaH (60% dispersion in oil, 42 mg, 1.1 mmol) and the mixture heated to reflux for 15 min. To this mixture was added a solution of ethyl 4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzoate (**Int 9**) (100 mg, 0.33 mmol) in THF (5 ml) and the reaction heated to reflux for 10 h. The reaction was allowed to cool to r.t. and was concentrated under reduced pressure. The residue was partitioned between DCM and water and the layers separated. The aqueous phase was further extracted with DCM and the combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (2% MeOH in DCM) to give 1-cyclobutyl-4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)benzylidene]piperidine as yellow oil that crystallised on standing (60 mg, 58%).

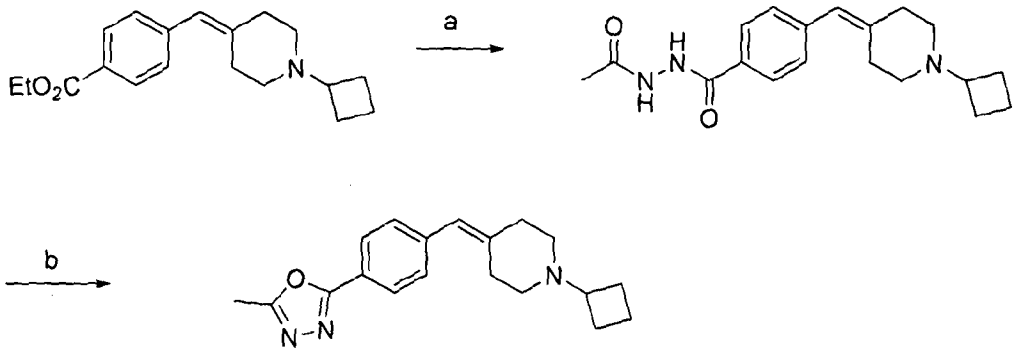
^{1}H NMR (400 MHz, MeOD) δ 7.99 - 8.13 (m, 2 H), 7.34 - 7.50 (m, 2 H), 6.43 (s, 1 H), 2.73 - 2.88 (m, 1 H), 2.53 - 2.64 (m, 2 H), 2.47 - 2.52 (m, 3 H), 2.45 (s, 3 H), 2.35 - 2.42 (m, 2 H), 2.04 - 2.16 (m, 2 H), 1.88 - 2.04 (m, 2 H), 1.64 - 1.85 (m, 2 H)
MS ES+ 310

2.11 Example 11

1-Cyclobutyl-4-[4-(5-methyl-1,3,4-oxadiazol-2-yl)benzylidene]piperidine



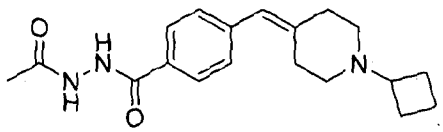
Scheme 7



Reagents and conditions: a) Acetylhydrazide, Me_3Al in PhMe, THF; b) $POCl_3$, reflux

Step a **Intermediate 10**

N'-Acetyl-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzohydrazide



To a solution of ethyl 4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzoate (**Int 9**) (200 mg, 0.67 mmol) and acetyl hydrazide (50 mg, 0.67 mmol) in THF (10 ml) was added Me_3Al (2.0 M in toluene, 835 µl, 1.67 mmol) and the reaction stirred at r.t. for 72 h. The reaction was then heated to 60°C for 12 h. Further acetyl hydrazide (50 mg, 0.67 mmol) and Me_3Al (2.0 M in toluene, 835 µl, 1.67 mmol) were added and the reaction heated for 12 h. The reaction was allowed to cool to r.t. and $Na_2SO_4.10H_2O$ was added. The mixture was filtered and the filtrate concentrated under reduced pressure. The residue was triturated from heptane/EtOAc to give N'-acetyl-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzohydrazide (80 mg, 37%) which was used directly in the next step.

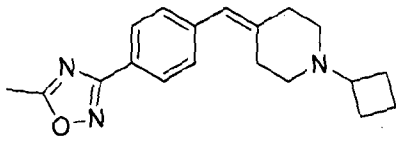
Step b **Example 11**

N'-Acetyl-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzohydrazide (**Int 10**) (67 mg, 0.2 mmol) was heated to reflux in $POCl_3$ (2 ml) for 1h. The reaction was allowed to cool to r.t. and was then concentrated under reduced pressure. The residue was partitioned between DCM and sat. aq. $NaHCO_3$ and the layers separated. The organic phase was dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (SiO_2; DCM to 10% MeOH (NH_3)) to give 1-cyclobutyl-4-[4-(5-methyl-1,3,4-oxadiazol-2-yl)benzylidene]piperidine as a cream solid (50 mg, 81 %).

^{1}H NMR (400MHz, $CDCl_3$) δ ?7.97 (d, 2H, J = 8.0 Hz), 7.31 (d, 2H, J = 8.0 Hz), 6.35 (s, 1H), 2.96-2.19 (m, 7H), 2.61 (s, 3 H), 2.09 (m, 3H), 1.84-1.53 (m, 4H), 1.25 (m, 1H)
MS ES+ 310

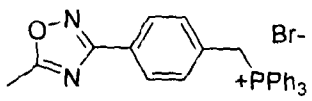
2.12 Example 12

1-Cyclobutyl-4-[4-(5-methyl-1,2,4-oxadiazol-3-yl)benzylidene]piperidine



Step a **Intermediate 11**

[4-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl](triphenyl)phosphonium bromide



Prepared in an analogous manner to **Intermediate 2** via **Scheme 2** starting from 3-(4-(bromomethyl)phenyl)-5-methyl-1,2,4-oxadiazole.

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.65 (s, 3 H), 5.09 - 5.38 (m, 2 H), 7.10 - 7.21 (m, 3 H), 7.56 - 8.08 (m, 16 H)

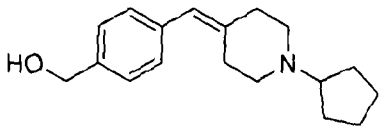
Step b **Example 12**

Prepared in an analogous manner to **Intermediate 5** via **Scheme 3**, method A and **Scheme 4** starting with [4-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl](triphenyl) phosphonium bromide (**Int 11**) and using cyclobutanone in step b of **Scheme 3**.

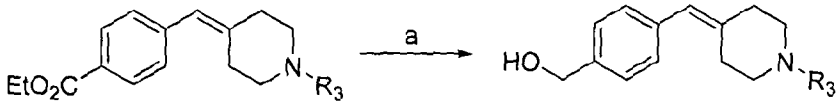
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 - 8.00 (m, 2 H), 7.33 - 7.43 (m, 2 H), 6.28 - 6.38 (m, 1 H), 2.66 (s, 4 H), 2.42 - 2.47 (m, 2 H), 2.34 (s, 4 H), 2.18 - 2.27 (m, 2 H), 1.89 - 2.04 (m, 2 H), 1.69 - 1.87 (m, 2 H), 1.54 - 1.68 (m, 2 H)
MS ES+ 310

2.13 Example 13

{4-[(1-Cyclopentylpiperidin-4-ylidene)methyl]phenyl}methanol



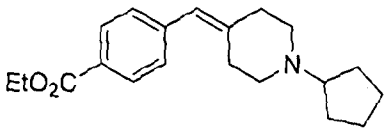
Scheme 8



Reagents and conditions: a) $LiAlH_4$, THF

Step a **Intermediate 12**

Ethyl 4-[(1-cyclopentylpiperidin-4-ylidene)methyl]benzoate



Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with *tert*-butyl 4-(4-(ethoxycarbonyl)benzylidene)piperidine-1-carboxylate (CAS: 726185-65-5) and using cyclopentanone in step b.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, 2H), 7.21 (d, 2H), 6.23 (s, 1H), 4.29 (q, 2H), 2.44 (m, 8H), 2.08 (m, 1H), 1.9-1.3 (m, 10H), 1.30 (t, 3H)

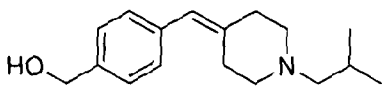
Step b **Example 13**

To a solution of ethyl 4-[(1-cyclopentylpiperidin-4-ylidene)methyl]benzoate (**Int 12**) (3 g, 9.6 mmol) in THF (100 ml) at 0°C was added $LiAlH_4$ (1.1 g. 28 mmol) portionwise. The reaction was stirred for 72 h. $NaSO_4.10H_2O$ was then added and the mixture stirred for 30 min. The mixture was filtered through Celite and the filtrate concentrated under reduced pressure. The crude material was purified via column chromatography (SiO_2;EtOAc) to give {4-[(1-cyclopentylpiperidin-4-ylidene)methyl]phenyl}methanol as a white solid (1.1 g, 42 %).

^{1}H NMR (400 MHz, MeOD) δ 7.18 (d, J = 8.08 Hz, 2 H), 7.07 (d, J = 8.08 Hz, 2 H), 6.19 (s, 1 H), 4.47 (s, 2 H), 2.37 - 2.61 (m, 7 H), 2.26 - 2.36 (m, 2 H), 1.72 - 1.89 (m, 2 H), 1.55 - 1.69 (m, 2 H), 1.41 - 1.53 (m, 2 H), 1.25 - 1.40 (m, 2 H)
MS ES+ 272

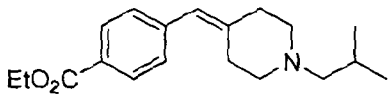
2.14 Example 14

(4-{[1-(2-Methylpropyl)piperidin-4-ylidene]methyl}phenyl)methanol



Step a **Intermediate 13**

Ethyl 4-{[1-(2-methylpropyl)piperidin-4-ylidene]methyl}benzoate



Prepared in an analogous manner to **Intermediate 3** via **Scheme 3**, method B using ethyl 4-[(diethoxyphosphoryl)methyl]benzoate (CAS 71441-08-2) and 1-(2-methylpropyl)piperidin-4-one (CAS 72544-16-2)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, 2H), 7.25 (d, 2H), 6.25 (s, 1H), 4.33 (q, 2H), 2.48 (m, 4H), 2.36 (m, 4H), 2.06 (d, 2H), 1.75 (m, 1H),)1.36 (q, 3H), 0.88 (d, 6H)

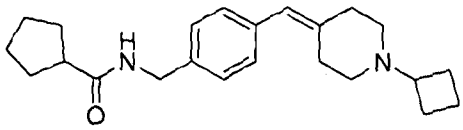
Step b **Example 14**

Prepared in an analogous manner to **Example 13** via **Scheme 8** starting with ethyl 4-{[1-(2-methylpropyl)piperidin-4-ylidene]methyl}benzoate (**Int 13**)

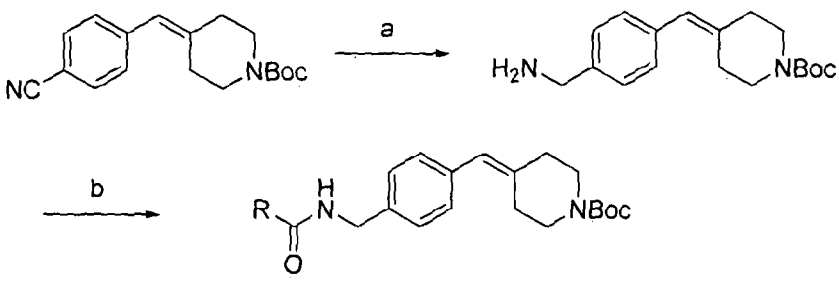
^{1}H NMR (400 MHz, MeOD) δ 7.18 (d, J = 8.08 Hz, 2 H), 7.05 (d, J = 8.08 Hz, 2 H), 6.18 (s, 1 H), 4.47 (s, 2 H), 2.36 - 2.47 (m, 4 H), 2.25 - 2.34 (m, 4 H), 2.03 (d, J = 7.33 Hz, 2 H), 1.64 - 1.81 (m, 1 H), 0.83 (d, J = 6.57 Hz, 6 H)
MS ES+ 260

2.15 Example 15

N-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}cyclopentanecarboxamide



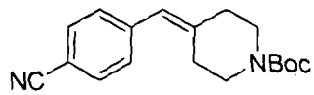
Scheme 9



Reagents and conditions: a) $LiAlH_4$, THF; b) RCO_2H, EDC, NMM, DCM

Step a **Intermediate 14**

tert-Butyl 4-(4-cyanobenzylidene)piperidine-1-carboxylate

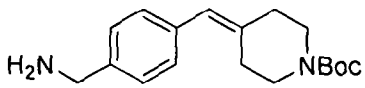


Prepared in an analogous manner to Intermediate 2 by method B, scheme 3, using diethyl (4-cyanobenzyl)phosphonate (CAS: 1552-41-6) and tert-butyl 4-oxopiperidine-1-carboxylate.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (m, 2H), 7.26 (m, 2H), 6.34 (s, 1H), 3.45 (m, 4H), 2.40 (m, 4H), 1.46 (s, 9H)

Step b **Intermediate 15**

tert-Butyl 4-[4-(aminomethyl)benzylidene]piperidine-1-carboxylate

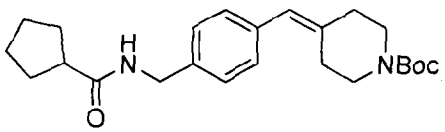


tert-Butyl 4-(4-cyanobenzylidene)piperidine-1-carboxylate (**Int 14**) (3 g, 0.01 mol) was added portionwise to a suspension of $LiAlH_4$ (3 g, 0.08 mol) in THF (200 ml) at 0°C. The reaction was allowed to warm to r.t. and stirred for 18 h. The reaction was cooled to 0°C and excess $Na_2SO_4.10H_2O$ was added. The mixture was stirred for 30 minutes and was then filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2; 5% to 20% MeOH containing 2% NH_4OH, in DCM) gave *tert*-butyl 4-[4-(aminomethyl)benzylidene]piperidine-1-carboxylate as a white solid (0.98 g, 32 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.26 (d, J = 8 Hz, 2H), 7.15 (d, J = 8 Hz, 2H), 6.33 (s, 1H), 3.84 (s, 2H), 3.49 (t, J = 5.5.Hz, 2H), 3.38 (t, J = 5.5 Hz, 2H), 2.45 (t, J = 5.5 Hz, 2H), 2.32 (t, J = 5.5 Hz, 2H), 1.47 (s, 9H)
MS ES+ 230

Step c **Intermediate 16**

tert-Butyl-4-(4-{[(cyclopentylcarbonyl)amino]methyl}benzylidene)piperidine-1-carboxylate



To a mixture of cyclopentanecarboxylic acid (120 µl, 1.1 mmol) and EDC (220 mg, 1.15 mmol) in DCM (5 ml) was added N-methyl morpholine (240 µl, 2.2 mmol) and the reaction stirred for 5 min. A solution of *tert*-butyl 4-[4-(aminomethyl)

benzylidene]piperidine-1-carboxylate (**Int 15**) (300 mg, 1. mmol) in DCM (5 ml) was then added and the reaction stirred for 18 h. The DCM was removed under reduced pressure and the residue partitioned between EtOAc and 10% aq. citric acid. The layers were separated and the aq. phase further extracted with EtOAc (×3). The combined organic extracts were washed with sat. aq. $NaHCO_3$, water then brine, dried ($MgSO_4$) and concentrated under reduced pressure to give *tert*-butyl 4-(4-{[(cyclopentylcarbonyl)amino]methyl}benzylidene)piperidine-1-carboxylate as an off-white solid (285 mg, 62 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 8 Hz, 2H), 7.14 (d, J = 8 Hz, 2H), 6.32 (s, 1H), 5.73 (m, 1H), 4.42 (d, J = 6 Hz, 2H), 3.50 (t, J = 6 Hz), 3.39 (t, J = 6 Hz, 2H), 2.54 (quintet, J = 8 Hz, 1H), 2.44 (t, J = 6 Hz, 2H), 2.32 (t, J = 6 Hz, 2H), 1.93-1.68 (m, 6H), 1.64-1.52 (m, 2H), 1.47 (s, 9H)

Step d **Example 15**

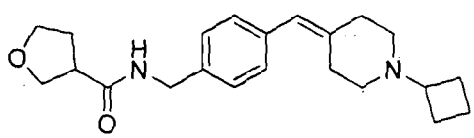
Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with **Intermediate 16** and using cyclobutanone in step b.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, J = 8 Hz, 2H), 7.15 (d, J = 8 Hz, 2H), 6.25 (s, 1H), 5.68 (m, 1H), 4.42 (d, J = 5.5 Hz, 2H), 2.71 (quin, J = 8 Hz, 1H), 2.54- 2.46 (m, 3H), 2.41 (s, 4H), 2.30 (m, 2H), 2.06- 1.56 (m, 14H)

MS ES+ 351

2.16 Example 16

N-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}tetrahydrofuran-3-carboxamide



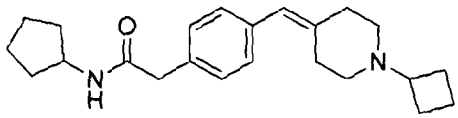
Prepared in an analogous manner to **Example 15** via **Scheme 9** starting from **Intermediate 16** using tetrahydrofuran-3-carboxylic acid in step b, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 8 Hz, 2H), 7.15 (d, J = 8 Hz, 2H), 6.25 (s, 1H), 5.90 (m, 1H), 4.42 (d, J = 8 Hz, 2H), 3.99- 3.87 (m, 3H), 3.81 (q, J = 7.5 Hz, 1H), 2.92 (quin, J = 6 Hz, 1H), 2.72 (quin, J = 7.5 Hz, 1H), 2.52 (t, J = 5.5 Hz, 2H), 2.41 (s, 4H), 2.30 (m, 2H), 2.24- 2.14 (m, 2H), 2.10- 2.00 (m, 2H), 2.00- 1.94 (m, 2H), 1.74-1.64 (m, 2H)

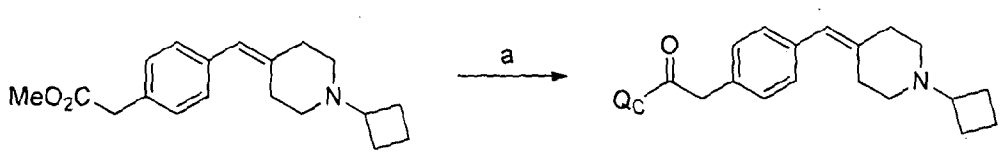
MS ES^+ 355

2.17 Example 17

2-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-N-cyclopentylacetamide



Scheme 10



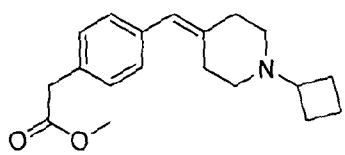
wherein Q_C represents R_5R_7NH or R_5 N-linked optionally substituted heterocyclyl.

Reagents and conditions: a) Bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct, R_5R_7NH or R_5 N-linked optionally substituted heterocyclyl, THF, reflux

-NR7-R5 or R_5 N-linked optionally substituted heterocyclyl

Step a **Intermediate 17**

Methyl {4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}acetate



Prepared in an analogous manner to **Intermediate 5** via **Scheme 3**, method B starting with 2-(4-((diethoxyphosphoryl)methyl)phenyl)acetic acid (CAS 177712-50-4) and tert-butyl 4-oxopiperidine-1-carboxylate, and **Scheme 4**, using cyclobutanone in step b, followed by esterification with methanol using standard conditions.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 8 Hz, 2H), 7.10 (d, J = 8 Hz, 2H), 6.37 (s, 1H), 3.69 (s, 3H), 3.60 (s, 2H), 3.13 (quintet, J = 8 Hz, 1H), 2.94-2.54 (m, 10H), 2.18-2.09 (m, 2H), 1.88 (q, J = 9 Hz, 1H), 1.76-1.62 (m, 1H)

Step b **Example 17**

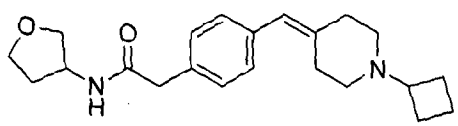
To bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct (154 mg, 0.6 mmol) in THF (5 ml) was added cyclopentylamine (60 µl, 0.6 mmol) and the mixture stirred at 40°C for 1 h. A solution of methyl {4-[(1-cyclobutylpiperidin-4-ylidene)methyl] phenyl}acetate (120 mg, 0.40 mmol) in THF (5 ml) was then added and the reaction heated at reflux for 18 h. The reaction was cooled, diluted with THF (5 ml) and quenched with $Na_2SO_4.10H_2O$. The mixture was filtered, washing with EtOAc, and the filtrate concentrated under reduced pressure. Purification by column chromatography (SiO_2; 5% NH_3/MeOH in DCM) gave 2-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-N-cyclopentylacetamide as a cream solid (47 mg, 33%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (s, 4H), 6.26 (s, 1H), 5.28 (br. s, 1H), 4.18 (sextet, J = 7 Hz, 1H), 3.51 (s, 2H), 2.73 (m, 1H), 2.54 (m, 2H), 2.43 (m, 4H), 2.32 (m, 2H), 2.07-2.01 (m, 3H), 1.98- 1.86 (m, 3H), 1.74- 1.60 (m, 3H), 1.58-1.51 (m, 3H), 1.24 (sextet, J = 6.5 Hz, 2H)

MS ES+ 353

2.18 Example 18

2-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-N-(tetrahydrofuran-3-yl)acetamide

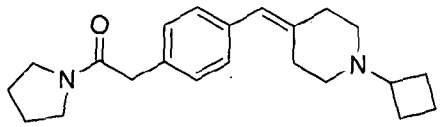


Prepared in an analogous manner to **Example 17** via **Scheme 10** starting with **Intermediate 17** and using tetrahydrofuran-3-amine.

^{1}H NMR (400 MHz, MeOD) δ 7.09 - 7.17 (m, 2H), 6.99 - 7.07 (m, 2H), 6.21 (s, 1H), 4.21 - 4.29 (m, 1H), 3.63 - 3.85 (m, 3H), 3.45 - 3.52 (m, 1H), 3.37 (s, 2H), 2.61 - 2.73 (m, 1H), 2.27 - 2.45 (m, 6H), 2.20 - 2.27 (m, 2H), 2.04 - 2.16 (m, 1H), 1.92 - 2.02 (m, 2H), 1.77 - 1.91 (m, 2H), 1.68 - 1.78 (m, 1H), 1.56 - 1.67 (m, 2H)
MS ES+ 355

2.19 Example 19

2-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(pyrrolidin-1-yl)ethanone

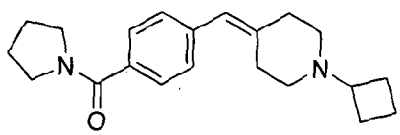


Prepared in an analogous manner to **Example 17** via **Scheme 10** starting with **Intermediate 17** and using pyrrolidine.

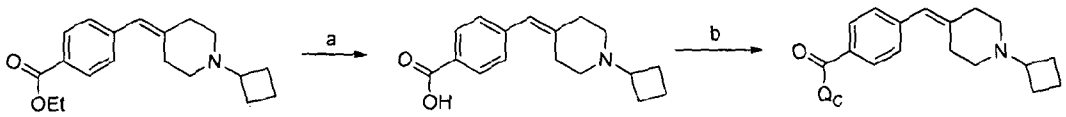
^{1}H NMR (400 MHz, MeOD) δ 7.13 (d, J = 8.08 Hz, 2 H), 7.05 (d, J = 8.08 Hz, 2 H), 6.21 (s, 1 H), 3.58 (s, 2 H), 3.42 (d, J = 6.57 Hz, 2 H), 3.33 (t, J = 6.82 Hz, 2 H), 2.59 - 2.82 (m, 1 H), 2.15 - 2.50 (m, 9 H), 1.91 - 2.06 (m, 2 H), 1.71 - 1.91 (m, 6 H), 1.54 - 1.71 (m, 2 H)
MS ES+ 339

2.20 Example 20

{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}(pyrrolidin-1-yl)methanone



Scheme 11

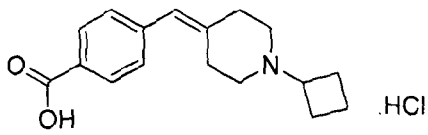


Wherein Q_C represents R_5R_7NH or R_5 N-linked optionally substituted heterocyclyl.

Reagents and conditions: a) LiOH, EtOH, THF, H_2O; b)i) $(COCl)_2$, DMF, DCM ii) R_5R_7NH or R_5 N-linked optionally substituted heterocyclyl, DCM

Step a **Intermediate 18**

4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzoic acid hydrochloride



Ethyl 4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzoate (**Intermediate 9**) (1.34 g, 4.5 mmol) was dissolved in ethanol (20 ml) and THF (20 ml) and lithium hydroxide (0.94 g, 22.4 mmol) in water (40 ml) was added. The reaction was stirred for 16 hours at rt. The reaction was concentrated and the resulting mixture was extracted with DCM and the aqueous phase acidified with 6M HCl (aq.). The mixture was concentrated until a white solid precipitated; this was collected by filtration to yield 4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzoic acid hydrochloride (1.0 g, 73 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.90 (br s, 1H), 11.24 (br s, 1H), 7.88 (d, J = 8 Hz, 2H), 7.32 (d, J = 8 Hz, 2H), 6.51 (s, 1H), 3.56 (quin, J = 7 Hz, 1H), 3.32 (br s, 4H), 2.84-2.64 (m, 2H), 2.47 (quin, J = 1.5 Hz, 2H), 2.36 (quin, J = 10 Hz, 2H), 2.11 (br m, 2H), 1.74-1.62 (m, 2H)

MS (ES^+) 272

Step b **Example 20**

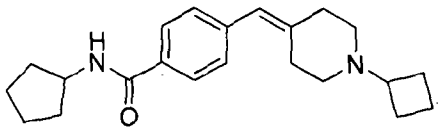
To a mixture of 4-((1-cyclobutylpiperidin-4-ylidene)methyl)benzoic acid (**Int 18**) (205 mg, 0.67 mmol) in DCM (5 ml) at 0 °C was added oxalyl chloride (64 µl, 0.73 mmol) followed by DMF (1 drop, catalytic). The reaction was allowed to warm to r.t. and was stirred for 2.5 h. The reaction was cooled to 0°C and pyrrolidine (195 µl, 2.33 mmol) was added. The reaction was stirred at 0°C for 30 min. The reaction was diluted with

DCM and washed with water then brine. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in MeOH (2 ml) and loaded onto a 2 g SCX-2 column. The column was eluted with MeOH then 10 % 2M NH_3/MeOH in DCM and the appropriate fractions concentrated under reduced pressure. The residue was triturated from diethyl ether to give {4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}(pyrrolidin-1-yl)methanone as an off-white solid (163 mg, 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 8 Hz, 2H), 7.20 (d, J = 8 Hz, 2H), 6.28 (s, 1H), 3.64 (t, J = 7 Hz, 2H), 3.46 (t, J = 7 Hz, 2H), 2.71 (br. s, 1H), 2.53 (br. s, 2H), 2.41 (br. s, 3H), 2.29 (br. s, 2H), 2.06-1.85 (m, 8H), 1.74-1.61 (m, 3H)
MS ES+ 335

2.21 Example 21

4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-N-cyclopentylbenzamide

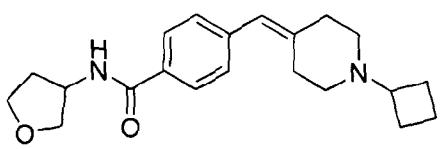


Prepared in an analogous manner to **Example 20** via **Scheme 11** starting with **Intermediate 18** and using cyclopentylamine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8 Hz, 2H), 7.22 (d, J = 8Hz, 2H), 6.28 (s, 1H), 6.02 (d, J = 7 Hz, 1H), 4.39 (sextet, J = 7Hz, 1H), 2.72 (quin, J = 7.5 Hz, 1H), 2.56- 2.47 (m, 2H), 2.46- 2.34 (s, 4H), 2.32- 2.24 (m, 2H), 2.17- 1.85 (m, 6H), 1.81-1.58 (m, 6H), 1.55- 1.40 (m, 2H)
MS ES+ 339

2.22 Example 22

4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-N-(tetrahydrofuran-3-yl)benzamide



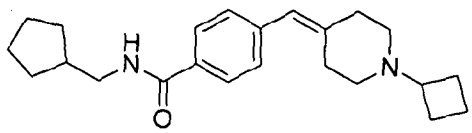
Prepared in an analogous manner to **Example 20** via **Scheme 11** starting with **Intermediate 18** and using 3-aminotetrahydrofuranyl.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 8 Hz, 2H), 7.24 (d, J = 8 Hz, 2H), 6.28 (s, 1H), 6.24 (br. s, 1H), 4.76- 4.69 (m, 1H), 3.99 (q, J = 8 Hz, 1H), 3.90 (dd, J = 9.5, 5 Hz, 1H), 3.84 (dd, J = 8.5, 6 Hz, 1H), 3.81- 3.76 (m, 1H), 2.51 (t, J = 5.5 Hz, 2H), 2.41 (s, 4H), 2.39- 2.34 (m, 1H), 2.71 (quin, J = 7.5 Hz, 1H), 2.30 (t, J = 5.5 Hz, 2H), 2.08- 1.89 (m, 5H), 1.76- 1.60 (m, 2H).

MS ES+ 341

2.23 Example 23

4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-N-(cyclopentylmethyl)benzamide



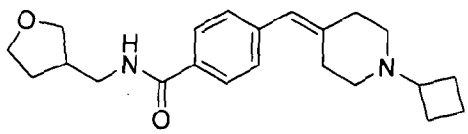
Prepared in an analogous manner to **Example 20** via **Scheme 11** starting with **Intermediate 18** and using 1-cyclopentylmethanamine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 8 Hz, 2H), 7.24 (d, J = 8 Hz, 2H), 6.29 (s, 1H), 6.10 (m, 1H), 3.39 (dd, J = 7 Hz, 5 Hz, 2H), 2.72 (quin, J = 7.5 Hz, 1H), 2.54- 2.50 (m, 2H), 2.42 (br. s, 4H), 2.30 (br. s, 2H), 2.15 (septet, J = 7.5 Hz, 1H), 2.08- 2.05 (m, 2H), 2.03- 1.86 (m, 1H), 1.85- 1.50 (m, 8H), 1.33- 1.21 (m, 3H).

MS ES+ 353

2.24 Example 24

4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-N-(tetrahydrofuran-3-ylmethyl)benzamide



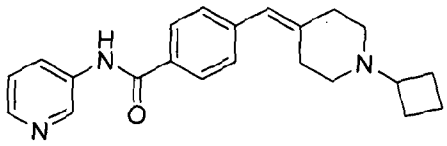
Prepared in an analogous manner to **Example 20** via **Scheme 11** starting with **Intermediate 18** and using 1-(tetrahydrofuran-3-yl)methanamine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 8 Hz, 2H), 7.20 (d, J = 8 Hz, 2H), 6.61 (t, J = 5.5 Hz, 1H), 6.26 (s, 1H), 3.88 (td, J = 8 Hz, 5.5 Hz, 1H), 3.79 (dd, J = 8.5, 7 Hz, 1H), 3.71 (q, J = 8 Hz, 1H), 3.60 (dd, J = 8.5, 5 Hz, 1H), 3.43 (td, J = 6.5, 2 Hz, 2H), 2.71 (quin, J = 7.5 Hz, 1H), 2.58 (septet, J = 7 Hz, 1H), 2.51 (t, J = 5.5 Hz, 2H), 2.42 (s, 4H), 2.30 (t, J = 5.5 Hz, 2H), 2.10- 1.90 (m, 5H), 1.73- 1.58 (m, 3H).

MS ES+ 355

2.25 Example 25

4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-N-(pyridin-3-yl)benzamide



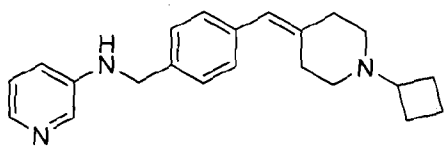
Prepared in an analogous manner to **Example 15** via **Scheme 9** starting with **Intermediate 18** and using pyridin-3-amine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 2.5 Hz, 1H), 8.39 (d, J = 4.54 Hz, 1H), 8.31 (dd, J = 4.5 Hz, 2.5 Hz, 1H), 7.92 (s, 1H), 7.83 (d, J = 8 Hz, 2H), 7.35 (s, 1H), 7.33 (d, J = 8 Hz, 2H), 6.32 (s, 1H), 2.71 (quin, J = 7.5 Hz, 1H), 2.53 (t, J = 6 Hz, 2H), 2.42 (s, 4H), 2.31 (t, J = 6 Hz, 2H), 2.10- 2.00 (m, 2H), 1.91 (quin, J = 9 Hz, 2H), 1.74- 1.62 (m, 2H).

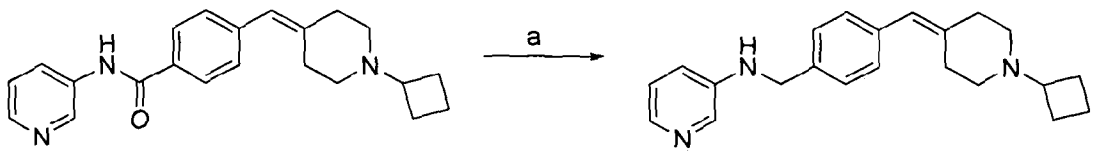
MS ES+ 348

2.26 Example 26

N-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}pyridin-3-amine



Scheme 12



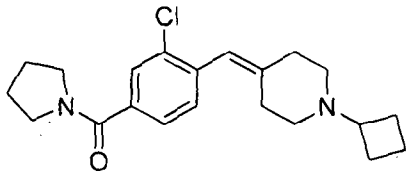
Reagents and conditions: a) $LiAlH_4$, THF

To a solution of 4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-N-(pyridin-3-yl)benzamide (Example 25, 180 mg, 0.52 mmol) in THF (8 ml) at 0 °C was added $LiAlH_4$ (1M solution on THF, 2.1 ml, 2.1 mmol) dropwise. The reaction was stirred for 2 h whilst allowing to warm to r.t. The reaction was cooled in ice/water, quenched via the addition of $Na_2SO_4.10H_2O$, diluted with THF (10 ml) and stirred for 30 min whilst allowing to warm to r.t. The mixture was filtered, washing with EtOAc, and the filtrate concentrated under reduced pressure. Purification by column chromatography (SiO_2; 5 % 2M NH_3/MeOH in DCM) gave N-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}pyridin-3-amine as a white solid (88 mg, 51 %).

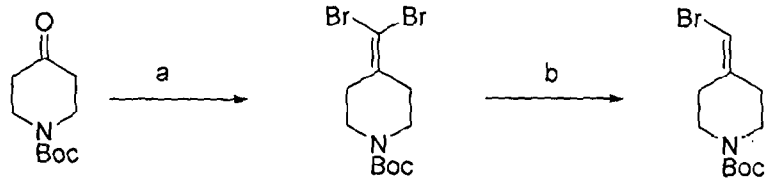
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 3 Hz, 1H), 7.97 (dd, J = 4.5, 1.5 Hz, 1H), 7.29 (d, J = 8 Hz, 2H), 7.18 (d, J = 8 Hz, 2H), 7.07 (dd, J = 8, 4.5 Hz, 1H), 6.88 (ddd, J = 8, 3, 1.5 Hz, 1H), 6.26 (s, 1H), 4.32 (d, J = 5.5 Hz, 2H), 4.09 (t, J = 5.5 Hz, 1H), 2.70 (quin, J = 8Hz, 1H), 2.52 (t, J = 5.5 Hz, 2H), 2.40 (s, 4H), 2.29 (t, J = 5.5 Hz, 2H), 2.08-2.00 (m, 2H), 1.95 (quin, J = 10 Hz, 2H), 1.86- 1.66 (m, 2H).
MS (ES^+) 334

2.27 Example 27

{3-Chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}(pyrrolidin-1-yl)methanone



Scheme 13

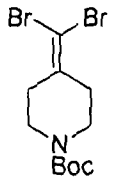


Int 19 Int 20

Reagents and conditions: a) PPh_3, CBr_4, DCM; b) NH_4Cl, Zn, MeOH, THF

Step a **Intermediate 19**

tert-Butyl 4-(dibromomethylidene)piperidine-1-carboxylate



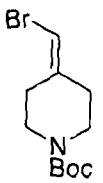
A solution of tert-butyl 4-oxopiperidine-1-carboxylate (30 g, 151 mmol) and triphenylphosphine (79 g, 301 mmol) in DCM (300 ml) cooled to 0°C under nitrogen was treated portionwise with carbon tetrabromide (100 g, 301 mmol) and stirred at 0° C for 3 h before allowing to warm to r.t. and stirring for 3 days. The reaction mixture was filtered and the filtrate evaporated to dryness. Et_2O was added, the mixture stirred for 1 h and filtered. The filtrate was concentrated to give *tert*-butyl 4-(dibromomethylidene)piperidine-1-carboxylate contaminated with triphenylphosphine oxide as a white solid (53.9 g, quantitative).

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.34 - 3.41 (m, 4 H), 2.37 - 2.45 (m, 4 H), 1.41 (s, 9 H)

MS ES^+ 339, 341, 343

Step b **Intermediate 20**

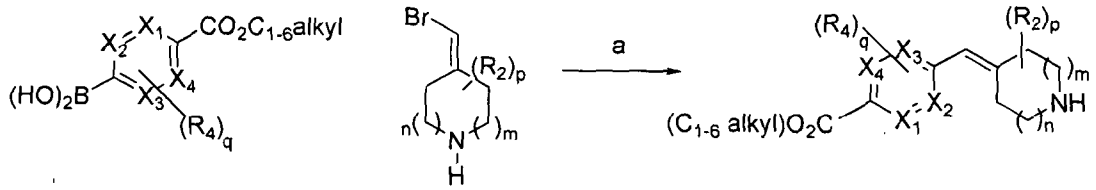
tert-Butyl 4-(bromomethylidene)piperidine-1-carboxylate



To a stirred solution of tert-butyl 4-(dibromomethylene)piperidine-1-carboxylate (12 g, 33.8 mmol) in MeOH (80 ml) and THF (40 ml) at 0°C under an atmosphere of nitrogen was added ammonium chloride (14.46 g, 270 mmol). The reaction was stirred at 0°C for 30 minutes. After this time zinc dust (8.85 g, 135 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. The mixture was then filtered, washing the solids with MeOH. The organics were concentrated under reduced pressure to give a white solid which was taken up in EtOAc/water. The layers were separated and the org phase dried ($MgSO_4$) and concentrated under reduced pressure to give *tert*-butyl 4-(bromomethylidene)piperidine-1-carboxylate (9 g, 96 %).

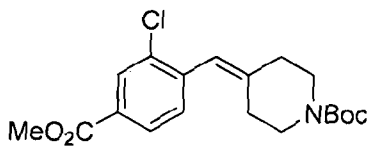
^{1}H NMR (400 MHz, DMSO-d_6) δ 6.26 (s, 1 H), 3.19 - 3.43 (m, 4 H), 2.15 - 2.35 (m, 4 H), 1.41 (s, 9 H)
MS ES+ 220, 222

Scheme 14



Reagents and conditions: a) $PdCl_2$(dppf), sat, aq. Na_2CO_3, dioxane, 80 °C

Step c **Intermediate 21**
tert-Butyl 4-[2-chloro-4-(methoxycarbonyl)benzylidene]piperidine-1-carboxylate



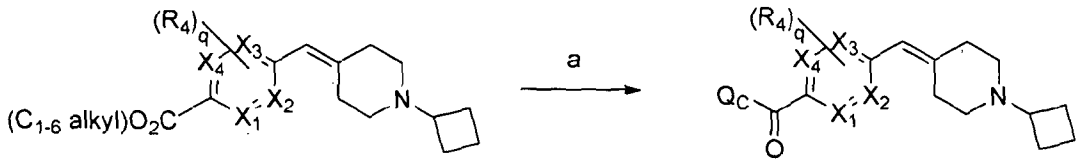
To a solution of *tert*-butyl 4-(bromomethylidene)piperidine-1-carboxylate (**Int 20**) (1.0 g, 3.62 mmol) and [2-chloro-4-(methoxycarbonyl)phenyl]boronic acid (813 mg, 3.80 mmol) in dioxane (10 ml) was added sat. aq. Na_2CO_3 (1 ml) and the mixture degassed for 10 min. $PdCl_2$(dppf) (263 mg, 0.36 mmol) was added and reaction heated to 80°C

for 18 h. The reaction was allowed to cool to r.t. and filtered through a pad of Celite, washing with EtOAc. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2; heptane to 5 % EtOAc in heptane) to give *tert*-butyl 4-[2-chloro-4-(methoxycarbonyl)benzylidene] piperidine-1-carboxylate as a white solid (580 mg, 45%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 6.42 (s, 1H), 3.90 (s, 3H). 3.52 (t, J = 6.0 Hz, 2H), 3.40 (t, J = 6.0 Hz, 2H). 2.37 (t, J = 6.0 Hz, 2H), 2.30 (t, J = 6.0 Hz, 2H), 1.46 (s, 9H)

MS ES+ 310

Scheme 15

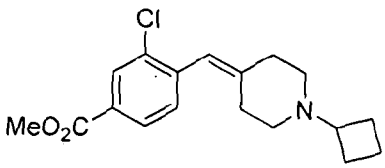


Q_C represents $-NR_7-R_5$ or R_5 N-linked optionally substituted heterocyclyl

Reagents and conditions: a) Q_C-H, Me_3Al in PhMe, THF

Step d **Intermediate 22**

Methyl 3-chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzoate



Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with *tert*-butyl 4-[2-chloro-4-(methoxycarbonyl)benzylidene]piperidine-1-carboxylate (**Int 21**) and using cyclobutanone in step b.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 6.29 (s, 1H), 3.90 (s, 3H), 2.71 (m, 1H), 2.43-2.30 (m, 6H), 2.30-2.20 (m, 2H), 2.04-2.02 (m, 2H), 1.89-1.85 (m, 2H), 1.69-1.67 (m, 2H)

MS ES+ 320

Step e **Example 27**

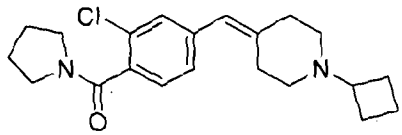
To Me_3Al (2M in toluene, 1.75 ml, 3.5 mmol) at 0 °C was added pyrrolidine (293 µl, 3.5 mmol) and the mixture stirred for 10 min. A solution of methyl 3-chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzoate (225 mg, 0.70 mmol) in THF (5 ml) was then added and the reaction allowed to warm to r.t. and stirred for 18 h. Further Me_3Al (2 M in toluene, 1.75 ml, 3.5 mmol) was added and the reaction stirred for 24 h. The reaction was poured onto sat. aq. Na_2SO_4 and EtOAc and the mixture stirred for 10 min. The layers were separated and the organic phase washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by prep HPLC gave {3-chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}(pyrrolidin-1-yl)methanone as an orange gum (101 mg, 40 %)

^{1}H NMR (400 MHz, MeOD) δ 7.40 (d, J = 1.52 Hz, 2 H), 7.25 (dd, J = 7.96, 1.39 Hz, 2 H), 7.16 (d, J = 8.08 Hz, 1 H), 6.17 (s, 1 H), 3.42 (t, J = 6.95 Hz, 2 H), 3.31 (t, J = 6.57 Hz, 2 H), 2.64 (quin, J = 7.89 Hz, 1 H), 2.26 - 2.38 (m, 4 H), 2.14 - 2.26 (m, 4 H), 1.86 - 1.99 (m, 2 H), 1.65 - 1.87 (m, 6 H), 1.46 - 1.64 (m, 2 H)

MS ES+ 385, 361

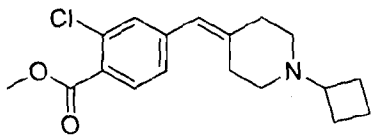
2.28 Example 28

{2-Chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}(pyrrolidin-1-yl)methanone



Step a **Intermediate 23**

Methyl 2-chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzoate



Prepared in an analogous manner to **Intermediate 22** via **Scheme 14** starting with [3-chloro-4-(methoxycarbonyl)phenyl]boronic acid and t-butyl 4-(bromomethylidene) piperidine-1-carboxylate (**Int 20**) and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.69 (d, J = 8.08 Hz, 2 H), 7.22 (s, 2 H), 7.12 (d, J = 8.08 Hz, 2 H), 6.23 (s, 1 H), 3.80 (s, 3 H), 2.69 (quin, J = 7.96 Hz, 1 H), 2.15 - 2.49 (m, 8 H), 1.92 - 2.05 (m, 2 H), 1.75 - 1.91 (m, 2 H), 1.53 - 1.70 (m, 2 H)
MS ES+ 320

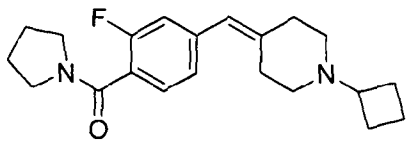
Step b **Example 28**

Prepared in an analogous manner to **Example 27** via **Scheme 15** starting with methyl 2-chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzoate (**Int 23**) and using pyrrolidine.

^{1}H NMR (400 MHz, MeOD) δ 7.17 - 7.25 (m, 2 H), 7.13 (d, J = 8.59 Hz, 1 H), 6.23 (s, 1 H), 3.50 (t, J = 6.82 Hz, 2 H), 3.14 (t, J = 6.57 Hz, 2 H), 2.61 - 2.83 (m, 1 H), 2.19 - 2.50 (m, 8 H), 1.94 - 2.05 (m, 2 H), 1.75 - 1.94 (m, 6 H), 1.51 - 1.71 (m, 2 H)
MS ES+ 359, 361

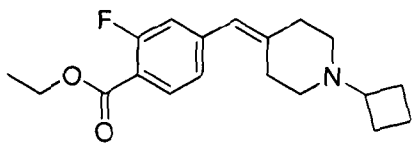
2.29 Example 29

{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-2-fluorophenyl}(pyrrolidin-1-yl)methanone



Step a **Intermediate 24**

Ethyl 4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-2-fluorobenzoate



Prepared in an analogous manner to **Intermediate 22** via **Scheme 14** starting with [3-fluoro-4-(methoxycarbonyl)phenyl]boronic acid and t-butyl 4-(bromomethylidene) piperidine-1-carboxylate (**Int 20**) and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 - 7.81 (m, 1H), 7.02 - 7.12 (m, 2H), 6.25 (s, 1H), 4.18 - 4.29 (m, 2H), 2.56 - 2.66 (m, 1H), 2.31 - 2.40 (m, 2H), 2.21 - 2.30 (m, 4H), 2.12 - 2.21 (m, 2H), 1.83 - 1.95 (m, 2H), 1.66 - 1.79 (m, 2H), 1.49 - 1.61 (m, 2H), 1.18 - 1.28 (m, 3H)

MS ES+ 318

Step b **Example 29**

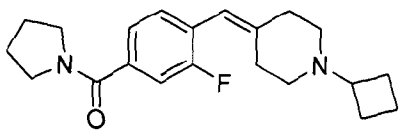
Prepared in an analogous manner to **Example 27** via **Scheme 15** starting with ethyl 4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-2-fluorobenzoate (**Int 24**) and using pyrrolidine.

^{1}H NMR (400 MHz, MeOD) δ 7.26 (t, *J* =7.45 Hz, 1 H), 7.01 (d, J = 7.83 Hz, 1 H), 6.94 (d, J =11.12 Hz, 1 H), 6.26 (s, 1 H), 3.49 (t, J = 6.82 Hz, 2 H), 3.25 (d, J = 6.82 Hz, 2 H), 2.64 - 2.86 (m, 1 H), 2.19 - 2.53 (m, 9 H), 1.95 - 2.08 (m, 2 H), 1.76 - 1.95 (m, 7 H)

MS ES+ 343

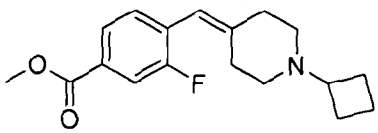
2.30 Example 30

{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-3-fluorophenyl}(pyrrolidin-1-yl)methanone



Step a **Intermediate 25**

Methyl 4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-3-fluorobenzoate



Prepared in an analogous manner to **Intermediate 22** via **Scheme 14** starting with [2-fluoro-4-(methoxycarbonyl)phenyl]boronic acid and t-butyl 4-(bromomethylidene) piperidine-1-carboxylate (**Int 20**) and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.68 (dd, J = 7.96, 1.39 Hz, 3 H), 7.57 (dd, J = 10.48, 1.39 Hz, 3 H), 7.25 (t, J = 7.71 Hz, 3 H), 6.18 (s, 1 H), 3.81 (s, 3 H), 2.69 (quin, J = 7.96 Hz, 1 H), 2.14 - 2.47 (m, 8 H), 1.90 - 2.05 (m, 2 H), 1.74 - 1.91 (m, 2 H), 1.50 - 1.70 (m, 2 H)

MS ES+ 304

Step b **Example 30**

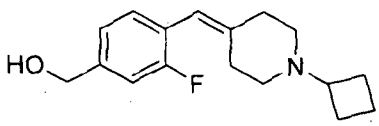
Prepared in an analogous manner to **Example 27** via **Scheme 15** starting with methyl 4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-3-fluorobenzoate (**Int 25**) and using pyrrolidine.

^{1}H NMR (400 MHz, MeOD) δ 7.06 - 7.29 (m, 3 H), 6.17 (s, 1 H), 3.49 (t, J = 6.95 Hz, 2 H), 3.39 (t, J = 6.44 Hz, 2 H), 2.64 - 2.82 (m, 1 H), 2.19 - 2.53 (m, 8 H), 1.94 - 2.06 (m, 2 H), 1.74 - 1.94 (m, 6 H), 1.56 - 1.70 (m, 2 H)

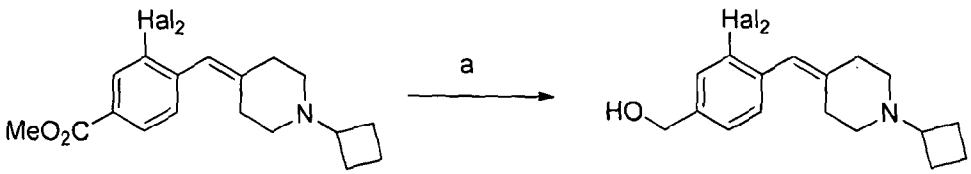
MS ES+ 343

2.31 Example 31

{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-3-fluorophenyl}methanol



Scheme 16



Hal_2 represents Cl or F

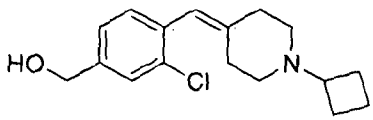
Reagents and conditions: a) $LiAlH_4$, THF, 0 °C to r.t.

To a stirred solution of methyl 4-((1-cyclobutylpiperidin-4-ylidene)methyl)-3-fluorobenzoate (**Int 25**) (78 mg, 0.257 mmol) in THF (1.2 ml) at 0°C under an atmosphere of nitrogen was added dropwise $LiAlH_4$ (1M in THF, 514 µl, 0.51 mmol). The reaction was then allowed to warm to room temperature and stirred under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to 0°C and quenched by the addition of Na_2SO_4. $10H_2O$. The mixture was allowed to warm to room temperature and then filtered through a bed of celite. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2; 0-10 % MeOH containing 2% NH_4OH, in DCM) to give {4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-3-fluorophenyl}methanol as a clear oil (39 mg, 55 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.14 - 7.25 (m, 1H), 7.02 - 7.14 (m, 2H), 6.16 (s, 1H), 5.19 - 5.35 (m, 1H), 4.48 (d, J = 5.81 Hz, 2H), 2.58 - 2.75 (m, 1H), 2.15 - 2.38 (m, 8H), 1.88 - 2.05 (m, 2H), 1.71 - 1.87 (m, 2H), 1.49 - 1.69 (m, 2H)
MS ES+ 276

2.32 Example 32

{3-Chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}methanol

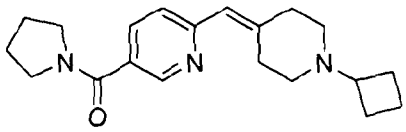


Prepared in an analogous manner to **Example 31** via **Scheme 16** starting with methyl 3-chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzoate (**Int 22**).

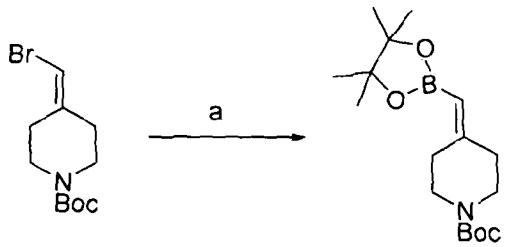
^{1}H NMR (400 MHz, MeOD) δ 7.29 (s, 1 H), 7.01 - 7.17 (m, 2 H), 6.20 (s, 1 H), 4.47 (s, 2 H), 2.68 (quin, J = 7.96 Hz, 1 H), 2.13 - 2.46 (m, 7 H), 1.89 - 2.03 (m, 2 H), 1.75 - 1.90 (m, 2 H), 1.54 - 1.70 (m, 2 H)
MS ES+ 292, 294

2.33 Example 33

{6-[(1-Cyclobutylpiperidin-4-ylidene)methyl]pyridin-3-yl}(pyrrolidin-1-yl)methanone



Scheme 17

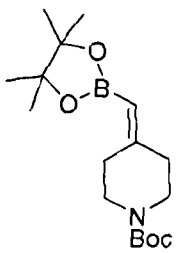


Int 20 **Int 26**

Reagents and conditions: a) Bis(pinacolato)diboron, KOAc, PPh_3, Pd_2dba_3, dioxane, reflux

Step a **Intermediate 26**

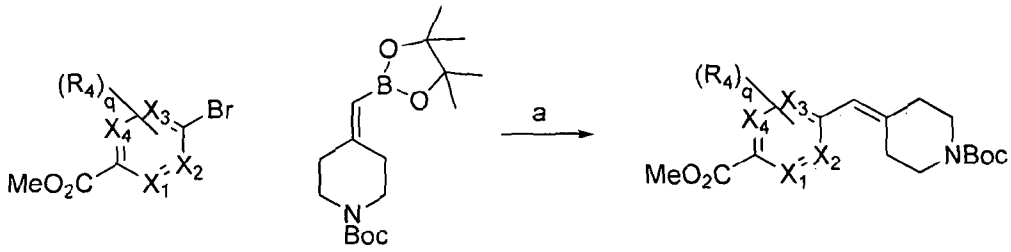
tert-Butyl 4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylidene]piperidine-1-carboxylate



tert-Butyl 4-(bromomethylidene)piperidine-1-carboxylate (3.00 g, 10.9 mmol), bis(pinacolato)diboron (4.1 g, 16 mmol), KOAc (1.9 g, 19.6 mmol), triphenylphosphine (185 mg, 0.65 mmol) and Pd_2dba_3 (300 mg, 0.33 mmol) were stirred in dioxane (50 ml) and degassed by bubbling Ar through the mixture for 20 min. The mixture was then heated at reflux overnight. The solution was cooled and the dioxane removed under reduced pressure. The residue was purified by column chromatography (SiO_2; 20:1 heptane/ethyl acetate) to give *tert*-butyl 4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylidene]piperidine-1-carboxylate as a white solid (1.45 g, 41 %).

^1H NMR (300 MHz, $CDCl_3$) δ 5.14 (s, 1H), 3.43 (m, 4H), 2.59 (m, 2H), 1.41 (s, 9H), 1.25 (s, 18 H)

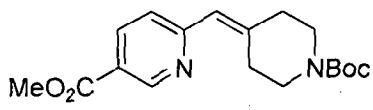
Scheme 18



Reagents and conditions: a) $PdCl_2(dppf)$, sat. aq. Na_2CO_3, dioxane, 80 °C

Step b **Intermediate 27**

Methyl-6-{[1-(tert-butoxycarbonyl)piperidin-4-ylidene]methyl}pyridine-3-carboxylate

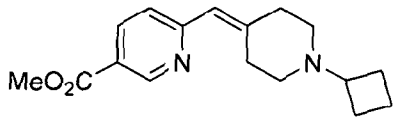


A mixture of *tert*-butyl 4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylidene]piperidine-1-carboxylate (**Int 26**) (660 mg, 2.04 mmol) and methyl 6-bromopyridine-3-carboxylate (563mg, 2.14mmol) in dioxane (5 ml) and sat. aq. Na_2CO_3 (1 ml) was degassed for 10 min. $PdCl_2(dppf)$ (149 mg, 0.02 mmol) was then added and the reaction heated to 80 °C for 18 h. The reaction mixture was allowed to cool to r.t. and was filtered through a pad of celite, washing with EtOAc. The filtrate was concentrated under reduced pressure and purified by column chromatography (SiO_2; 10 % diethyl ether in DCM) to give methyl 6-{[1-(tert-butoxycarbonyl)piperidin-4-ylidene]methyl}pyridine-3-carboxylate as a pale yellow oil (223 mg, 33 %).

^1H NMR (300MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.09 (d, J = 6.8 Hz, 1H), 7.64 (d, J = 6.8 Hz, 1H), 6.34 (s, 1H), 3.99 (s, 3H), 3.52 (t, J = 4.5 Hz, 2H), 3.41 (t, J = 4.5 Hz, 2H), 2.43 (t, J = 4.5 Hz, 2H), 2.36 (t, J = 4.5 Hz, 2H), 1.46 (s, 9H)

Step c **Intermediate 28**

Methyl 6-[(1-cyclobutylpiperidin-4-ylidene)methyl]pyridine-3-carboxylate



Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with methyl 6-{[1-(tert-butoxycarbonyl)piperidin-4-ylidene]methyl}pyridine-3-carboxylate (**Int 27**) using cyclobutanone in step b.

^{1}H NMR (300MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.08 (d, 1H), 7.63 (d, 1H), 6.27 (s, 1H), 4.00 (s, 3H), 2.6-1.2 (m, 15H)

MS ES+ 287.5

Step d **Example 33**

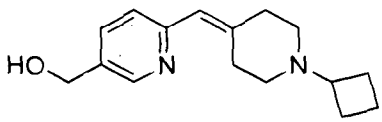
Prepared in an analogous manner to **Example 27** via **Scheme 15** starting with methyl 6-[(1-cyclobutylpiperidin-4-ylidene)methyl]pyridine-3-carboxylate (**Int 28**) and using pyrrolidine.

^{1}H NMR (300MHz, $CDCl_3$) δ8.73 (s, 1H), 7.78 (d, 1H), 7.18 (d, 1H), 6.34 (s, 1H), 3.65 (t, 2H), 3.48 (t, 2H), 2.99 (t, 2H), 2.85 (m, 1H), 2.61 (m, 2H), 2.52 (s, 4H), 1.6-2.2 (m, 10H)

MS ES+ 326

2.34 Example 34

{6-[(1-Cyclobutylpiperidin-4-ylidene)methyl]pyridin-3-yl}methanol



Prepared in an analogous manner to **Example 31** via **Scheme 16** starting with methyl 6-[(1-cyclobutylpiperidin-4-ylidene)methyl]pyridine-3-carboxylate (**Int 28**).

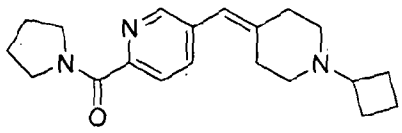
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 - 8.56 (m, 1 H), 7.62 - 7.77 (m, 1 H), 7.18 - 7.29 (m, 1 H), 6.31 (s, 1 H), 5.21 - 5.34 (m, 1 H), 4.44 - 4.63 (m, 2 H), 2.85 - 2.99 (m, 2 H),

2.67 - 2.82 (m, 1 H), 2.38 (d, J = 2.53 Hz, 5 H), 1.95 - 2.08 (m, 2 H), 1.78 - 1.94 (m, 2 H), 1.58 - 1.75 (m, 2 H)

MS ES+ 259

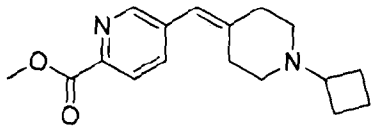
2.35 Example 35

{5-[(1-Cyclobutylpiperidin-4-ylidene)methyl]pyridin-2-yl}(pyrrolidin-1-yl)methanone



Step a **Intermediate 29**

Methyl 5-[(1-cyclobutylpiperidin-4-ylidene)methyl]pyridine-2-carboxylate



Prepared in an analogous manner to **Intermediate 28** via **Scheme 18** starting with methyl 5-bromopyridine-2-carboxylate and *tert*-butyl 4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylidene]piperidine-1-carboxylate (**Int 26**) and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 - 8.58 (m, 1 H), 7.97 - 8.04 (m, 1 H), 7.75 - 7.85 (m, 1 H), 6.36 (s, 1 H), 3.87 (s, 3 H), 3.31 (s, 1 H), 2.41 - 2.46 (m, 2 H), 2.31 - 2.40 (m, 4 H), 2.23 - 2.31 (m, 2 H), 1.90 - 2.02 (m, 2 H), 1.70 - 1.88 (m, 2 H), 1.51 - 1.68 (m, 2 H)

Step b **Example 35**

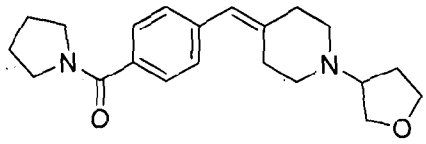
Prepared in an analogous manner to **Example 27** via **Scheme 15** starting with methyl 5-[(1-cyclobutylpiperidin-4-ylidene)methyl]pyridine-2-carboxylate (**Int 29**) and using pyrrolidine.

^{1}H NMR (300MHz, $CDCl_3$) δ 8.40 (d, 1H, J = 2 Hz), 7.77 (d, 1H, J = 8 Hz), 7.57 (dd, 1H, J = 8, 2 Hz), 6.23 (s, 1H), 3.75 (m, 2H), 3.67 (m, 2H), 2.70 (m, 1H), 2.35-2.58 (m, 6H), 2.30 (m, 2H), 1.80-2.10 (m, 8H), 1.69 (m, 2H)

MS ES+ 326

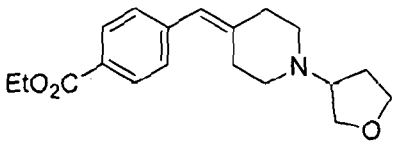
2.36 Example 36

Pyrrolidin-1-yl(4-{[1-(tetrahydrofuran-3-yl)piperidin-4-ylidene]methyl}phenyl) methanone



Step a **Intermediate 30**

Ethyl 4-{[1-(tetrahydrofuran-3-yl)piperidin-4-ylidene]methyl}benzoate



Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with *tert*-butyl 4-(4-(ethoxycarbonyl)benzylidene)piperidine-1-carboxylate (CAS: 726185-65-5) and using dihydrofuran-3(2H)-one in step b.

^{1}H NMR (300MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.25 (m, 2H), 6.31 (s, 1H), 4.37 (q, 2H), 3.99-3.67 (m, 2H), 3.79 (m, 1H), 3.67 (m, 1H), 3.01 (quin, 1H), 2.62 (m, 1H), 2.53 (m, 4H), 2.43 (m, 3H), 2.06 (m, 1H0, 1.89 (m, 1H), 1.39 (t, 3H).

Step b **Example 36**

Prepared in an analogous manner to **Example 27** via **Scheme 15** starting with ethyl 4-{[1-(tetrahydrofuran-3-yl)piperidin-4-ylidene]methyl}benzoate (**Int 30**) and using pyrrolidine.

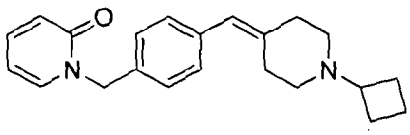
^{1}H NMR (400 MHz, MeOD) δ 7.39 (d, J = 8.08 Hz, 2 H), 7.19 (d, J = 8.08 Hz, 2 H), 6.26 (s, 1 H), 3.84 (td, J = 8.59, 4.04 Hz, 1 H), 3.74 - 3.81 (m, 1 H), 3.65 (q, J = 8.34 Hz, 1 H), 3.56 (dd, J = 8.72, 6.95 Hz, 1 H), 3.49 (t, J = 6.95 Hz, 2 H), 3.39 (t, J = 6.69

Hz, 2 H), 2.93 (quin, J = 7.26 Hz, 1 H), 2.50 - 2.62 (m, 1 H), 2.40 - 2.50 (m, 4 H), 2.27 - 2.39 (m, 3 H), 1.95 - 2.08 (m, 1 H), 1.64 - 1.95 (m, 6 H)

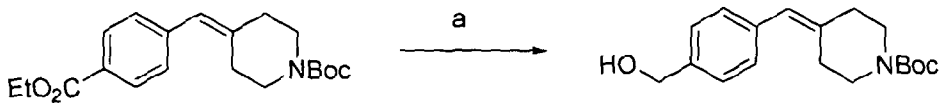
MS (ES^+) 341

2.37 Example 37

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}pyridin-2(1H)-one



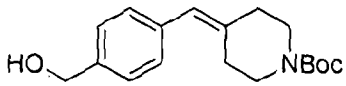
Scheme 19



Reagents and conditions: a) $LiAlH_4$, THF, 0 °C to r.t.

Step a **Intermediate 31**

tert-Butyl 4-(4-(hydroxymethyl)benzylidene)piperidine-1-carboxylate

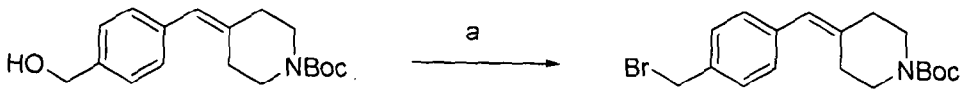


A solution of ethyl 4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzoate (**Int 9**) (3.45 g, 10 mmol) in THF (30 ml) was stirred at 0°C under argon. $LiAlH_4$ (0.76 g, 20 mmol) was added in portions and the mixture was stirred overnight, allowing it to warm to room temperature. It was then cooled back to 0°C before finely ground $Na_2SO_4 \cdot H_2O$ (2 g) was added potionwise while stirring vigorously. After 1 hour the mixture was filtered, rinsing the solid well with THF (100 ml). Evaporation of the solvents afforded *tert*-butyl 4-(4-(hydroxymethyl)benzylidene)piperidine-1-carboxylate (2.5 g, 83 %) which was used without further purification.

^{1}H NMR (400 MHz, MeOD-d_4) δ 7.28 - 7.37 (m, 2H), 7.14 - 7.24 (m, 2H), 6.42 (s, 1H), 4.55 - 4.65 (m, 2H), 3.48 - 3.56 (m, 2H), 3.38 - 3.48 (m, 2H), 2.41 - 2.55 (m, 2H), 2.31 - 2.41 (m, 2H), 1.42 - 1.54 (m, 9H)

MS $(ES)^+$ 326 $(M + Na^+)$

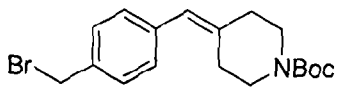
Scheme 20



Reagents and conditions: a) CBr_4, PPh_3, DCM

Step b **Intermediate 32**

tert-Butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate

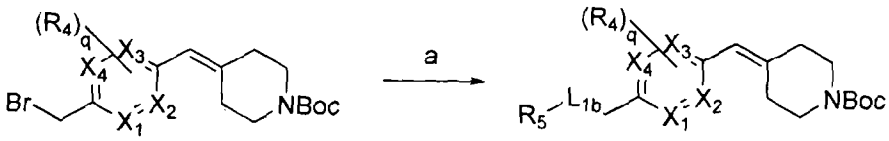


tert-Butyl 4-(4-(hydroxymethyl)benzylidene)piperidine-1-carboxylate (**Int 31**) (4.1 g, 13.5 mmol) and triphenylphosphine (4.3 g, 16.2 mmol) were dissolved in DCM (50 ml) to give a colourless solution. Carbon tetrabromide (5.4 g, 16.2 mmol) was added in portions and the reaction mixture was stirred at r.t. for 20 h. The reaction was concentrated and purified by column chromatography (SiO_2; 0-15 % EtOAc / petrol) to give *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate as a clear oil which solidified on standing (2.7 g, 53 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ7.36 - 7.48 (m, 2H), 7.17 - 7.26 (m, 2H), 6.36 (s, 1H), 4.70 (s, 2H), 3.36 - 3.48 (m, 2H), 3.27 - 3.37 (m, 2H), 2.36 - 2.43 (m, 2H), 2.25 - 2.34 (m, 2H), 1.41 (s, 9H)

MS ES+ 310, 312

Scheme 21

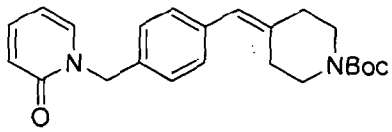


L_{1b} represents a covalent bond or –O-.

Reagents and conditions: a) NaH, DMF, R_5-L_{1b}-H; or a); Cs_2CO_3, DMF, R_5-L_{1b}-H; or a) K_2CO_3, THF, R_5-L_{1b}-H; or a) LiHMDS, DMF R_5-L_{1b}-H or a) KHMDS, DMF, R_5-L_{1b}-H

Step c **Intermediate 33**

tert-Butyl 4-{4-[(2-oxopyridin-1(2H)-yl)methyl]benzylidene}piperidine-1- carboxylate



To a solution of 2-hydroxypyridine (93 mg, 0.98 mmol) in THF (5 ml) at 0°C was added sodium hydride (60% dispersion in oil, 50 mg, 1.23 mmol) and the mixture was stirred for 30 min. *tert*-Butyl-4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) (300 mg, 0.82 mmol) was added and the ice bath removed and the mixture was diluted with DMF (0.5 ml) and stirred for 2.5 days. The mixture was then poured into water (10 ml) and extracted with diethyl ether (3 x 10 ml). The combined extracts were washed with water (2 x 10 ml) and brine (10 ml) and dried over $MgSO_4$. After evaporation of the solvents the residue was purified by column chromatography (SiO_2, 3% 2M NH_3/MeOH in DCM) to afford the desired material as a pale yellow-brown solid (260 mg, 83 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.25 (2H, m), 7.24 (2H, d, J = 8 Hz), 7.14 (2H, d, J = 8 Hz), 7.00 (1H, d, J = 9 Hz), 6.30 (1H, s), 6.14 (1H, td, J = 6.5 Hz, 1.5 Hz), 5.33 (2H, s), 3.48 (2H, t, J = 5.5 Hz), 3.37 (2H, t, J = 5.5 Hz), 2.42 (2H, t, J = 5.5 Hz), 2.31 (2H, t, J = 5.5 Hz), 1.46 (9H, s).

Step d **Example 37**

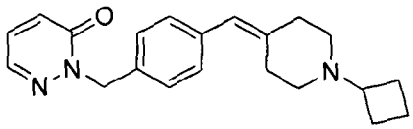
Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with *tert*-butyl 4-{4-[(2-oxopyridin-1(2H)-yl)methyl]benzylidene}piperidine-1-carboxylate (**Int 33**) using cyclobutanone in step b.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34- 7.26 (m, 2H), 7.23 (d, J = 8 Hz, 2H), 7.16 (d, J = 8 Hz, 2H), 6.61 (d, J = 9 Hz, 1H), 6.24 (s, 1H), 6.14 (td, J = 6.5 Hz, 1 Hz, 1H), 5.12 (s, 2H), 2.70 (quin, J = 7.5 Hz, 1H), 2.50 (t, J = 5.5 Hz, 2H), 2.40 (s, 4H), 2.28 (m, 2H), 2.06- 1.99 (m, 2H), 1.96- 1.90 (m, 1H), 1.74- 1.63 (m, 3H)

MS ES+ 335

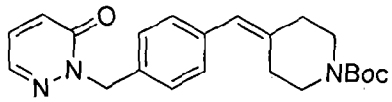
2.38 Example 38

2-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}pyridazin-3(2H)-one



Step a **Intermediate 34**

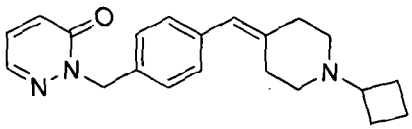
tert-Butyl 4-{4-[(6-oxopyridazin-1(6H)-yl)methyl]benzylidene}piperidine-1-carboxylate



Intermediate 34 was prepared in an analogous manner to **Intermediate 33** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using pyridazin-3(2H)-one. Used as isolated in next step.

Step b **Example 38**

2-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}pyridazin-3(2H)-one



Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with tert-butyl 4-{4-[(6-oxopyridazin-1(6H)-yl)methyl]benzylidene}piperidine-1-carboxylate (**Int 34**) and using cyclobutanone in step b.

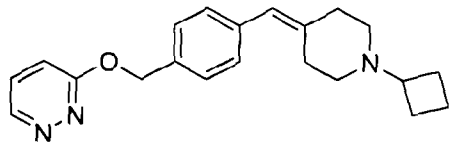
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (dd, J = 4 Hz, 1.5 Hz, 1H), 7.36 (d, J = 8 Hz, 2H), 7.15 (dd, J = 6 Hz, 4 Hz, 1H), 7.14 (d, J = 8 Hz, 2H), 6.93 (dd, J = 9 Hz, 1.5 Hz, 1H),

6.24 (s, 1H), 5.30 (s, 2H), 2.71 (quin, J = 7 Hz, 1H), 2.51 (m, 2H), 2.39 (s, 4H), 2.28 (m, 2H), 2.08- 1.99 (m, 2H), 1.74- 1.60 (m, 4H).

MS (ES^+) 336

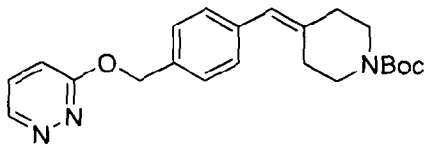
2.39 Example 39

3-({4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}oxy)pyridazine



Step a **Intermediate 35**

tert-Butyl 4-{4-[(pyridazin-3-yloxy)methyl]benzylidene}piperidine-1-carboxylate



Intermediate 35 was prepared in an analogous manner to **Intermediate 33** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using pyridazin-3-ol. Used as isolated in next step.

Step b **Example 39**

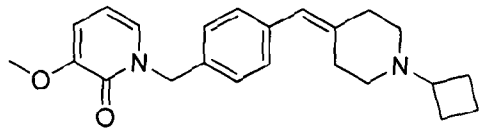
Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with tert-butyl 4-{4-[(pyridazin-3-yloxy)methyl]benzylidene}piperidine-1-carboxylate (**Int 35**) and using cyclobutanone in step b.

^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 5 Hz, 1H), 7.38 (d, J = 8 Hz, 2H), 7.25 (dd, J = 9, 5 Hz, 1H), 7.22 (d, J = 8 Hz, 2H), 6.95 (d, J = 9 Hz, 1H), 6.25 (s, 1H), 5.32 (s, 2H), 2.71 (quin, J = 8 Hz, 1H), 2.50 (t, J =5.5 Hz, 2H), 2.41 (s, 4H), 2.29 (t, J = 5.5 Hz, 2H), 2.06-1.98 (m, 2H), 1.96-1.89 (m, 2H), 1.73-1.63 (m, 2H).

MS (ES^+) 336

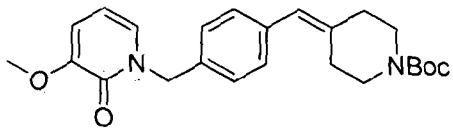
2.40 Example 40

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-3-methoxypyridin-2(1H)-one



Step a **Intermediate 36**

tert-Butyl 4-{4-[(3-methoxy-2-oxopyridin-1(2H)-yl)methyl]benzylidene}piperidine-1-carboxylate



To a solution of 3-methoxypyridin-2(1H)-one (123 mg, 0.98 mmol) in DMF (3 ml) was added cesium carbonate (534 mg, 1.64 mmol) at 0 °C and the reaction stirred for 45 min. Tert-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (300 mg, 0.82 mmol) was added and the reaction allowed to warm to r.t and stirred for 16 h. The reaction was quenched with brine and extracted with EtOAc (x 3). The combined organics were washed with brine (x 5), dried over $MgSO_4$ and evaporated to dryness. Purification by column chromatography (SiO_2 0-100 % EtOAc/petrol then 0-10 % MeOH/EtOAc) gave tert-butyl 4-(4-((3-methoxy-2-oxopyridin-1(2H)-yl)methyl)benzylidene)piperidine-1-carboxylate as a white gum (271 mg, 81 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.26 - 7.42 (m, 1 H), 7.05 - 7.28 (m, 4 H), 6.74 - 6.85 (m, 1 H), 6.34 (s, 1 H), 6.08 - 6.22 (m, 1 H), 5.09 (s, 2 H), 3.70 (s, 3 H), 3.37 - 3.46 (m, 2 H), 2.31 - 2.41 (m, 2 H), 2.24 - 2.31 (m, 2 H), 1.41 (s, 9 H)
MS ES+ 411

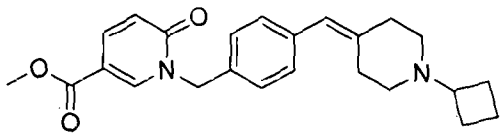
Step b **Example 40**

Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with tert-butyl 4-{4-[(3-methoxy-2-oxopyridin-1(2H)-yl)methyl]benzylidene}piperidine-1-carboxylate (**Int 36**) and using cyclobutanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.07 - 7.17 (m, 3H), 6.97 - 7.06 (m, 2H), 6.72 - 6.79 (m, 1H), 6.12 - 6.22 (m, 2H), 5.05 (s, 2H), 3.67 (s, 3H), 2.55 - 2.69 (m, 1H), 2.21 - 2.37 (m, 6H), 2.10 - 2.21 (m, 2H), 1.86 - 1.97 (m, 2H), 1.71 - 1.84 (m, 2H), 1.51 - 1.62 (m, 2H)
MS (ES^+) 365

2.41 Example 41

Methyl 1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-6-oxo-1,6-dihydropyridine-3-carboxylate

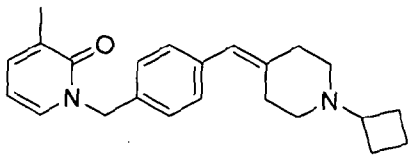


Prepared in an analogous manner to **Example 40** (using Cs_2CO_3 as base) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using methyl 6-oxo-1,6-dihydropyridine-3-carboxylate and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 7.76 - 7.86 (m, 1H), 7.22 - 7.32 (m, 2H), 7.12 - 7.21 (m, 2H), 6.43 - 6.54 (m, 1H), 6.23 (s, 1H), 5.17 (s, 2H), 3.79 (s, 3H), 2.60 - 2.72 (m, 1H), 2.24 - 2.42 (m, 6H), 2.13 - 2.24 (m, 2H), 1.90 - 2.00 (m, 2H), 1.71 - 1.85 (m, 2H), 1.54 - 1.67 (m, 2H)
MS (ES^+) 393

2.42 Example 42

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-3-methylpyridin-2(1H)-one

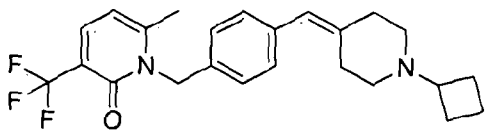


Prepared in an analogous manner to **Example 40** (using Cs_2CO_3 as base) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using 3-methylpyridin-2(1H)-one and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.52 - 7.60 (m, 1H), 7.37 - 7.45 (m, 1H), 7.23 - 7.31 (m, 2H), 7.14 - 7.22 (m, 2H), 6.28 - 6.35 (m, 2H), 5.19 (s, 2H), 2.75 - 2.86 (m, 1H), 2.31 - 2.55 (m, 8H), 2.03 - 2.18 (m, 5H), 1.87 - 2.01 (m, 2H), 1.66 - 1.81 (m, 2H)
MS (ES$^+$) 348

2.43 Example 43

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-6-methyl-3-(trifluoromethyl)pyridin-2(1H)-one

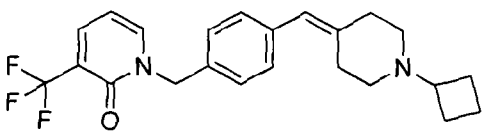


Prepared in an analogous manner to **Example 40** (using Cs_2CO_3 as base) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using 6-methyl-3-(trifluoromethyl)pyridin-2(1H)-one and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.16 - 7.25 (m, 2H), 7.10 - 7.16 (m, 2H), 6.77 - 6.83 (m, 1H), 6.48 - 6.54 (m, 1H), 6.29 - 6.35 (m, 1H), 5.43 (s, 2H), 2.73 - 2.84 (m, 1H), 2.38 - 2.55 (m, 9H), 2.29 - 2.38 (m, 2H), 2.02 - 2.13 (m, 2H), 1.89 - 2.01 (m, 2H), 1.65 - 1.80 (m, 2H)
MS (ES$^+$) 417

2.44 Example 44

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-3-(trifluoromethyl)pyridin-2(1H)-one



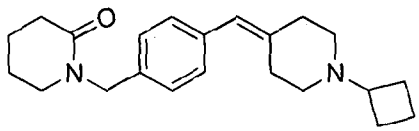
Prepared in an analogous manner to **Example 40** (using Cs_2CO_3 as base) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate

(**Int 32**) and using 3-(trifluoromethyl)pyridin-2(1H)-one and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.91 - 8.03 (m, 2H), 7.28 - 7.36 (m, 2H), 7.16 - 7.24 (m, 2H), 6.43 - 6.50 (m, 1H), 6.32 (s, 1H), 5.22 (s, 2H), 2.74 - 2.86 (m, 1H), 2.39 - 2.57 (m, 6H), 2.30 - 2.39 (m, 2H), 2.03 - 2.16 (m, 2H), 1.88 - 2.00 (m, 2H), 1.65 - 1.82 (m, 2H)
MS (ES$^+$) 403

2.45 Example 45

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}piperidin-2-one

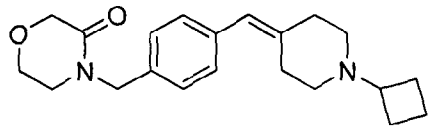


Prepared in an analogous manner to **Example 37** (NaH) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using piperidin-2-one and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.14 - 7.27 (m, 4H), 6.33 (s, 1H), 4.59 (s, 2H), 3.25 - 3.31 (m, 2H), 2.75 - 2.88 (m, 1H), 2.32 - 2.58 (m, 10H), 2.05 - 2.14 (m, 2H), 1.90 - 2.01 (m, 2H), 1.69 - 1.87 (m, 6H)
MS (ES$^+$) 339

2.46 Example 46

4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}morpholin-3-one



Prepared in an analogous manner to **Example 37** (NaH) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using morpholin-3-one and **Scheme 4** using cyclobutanone in step b.

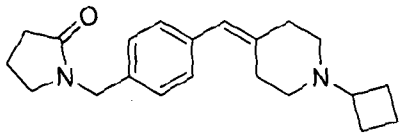
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 - 7.26 (m, 4H), 6.25 - 6.32 (m, 1H), 4.63 (s, 2H), 4.27 (s, 2H), 3.80 - 3.91 (m, 2H), 3.25 - 3.34 (m, 2H), 2.67 - 2.79 (m, 1H), 2.48 - 2.59

(m, 2H), 2.37 - 2.47 (m, 4H), 2.26 - 2.37 (m, 2H), 2.01 - 2.11 (m, 2H), 1.85 - 2.00 (m, 2H), 1.65 - 1.79 (m, 2H)

MS (ES^+) 341

2.47 Example 47

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}pyrrolidin-2-one



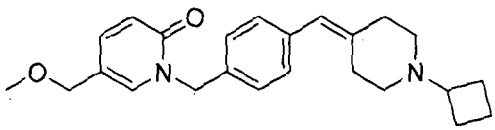
Prepared in an analogous manner to **Example 37** (NaH) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using pyrrolidin-2-one and **Scheme 4** using cyclobutanone in step b.

^1H NMR (400 MHz, DMSO-d_6) δ 7.14 - 7.20 (m, 4H), 6.26 (s, 1H), 4.34 (s, 2H), 3.19 - 3.28 (m, 2H), 2.61 - 2.71 (m, 1H), 2.36 - 2.43 (m, 2H), 2.25 - 2.36 (m, 6H), 2.15 - 2.25 (m, 2H), 1.88 - 2.01 (m, 4H), 1.72 - 1.85 (m, 2H), 1.56 - 1.69 (m, 2H)

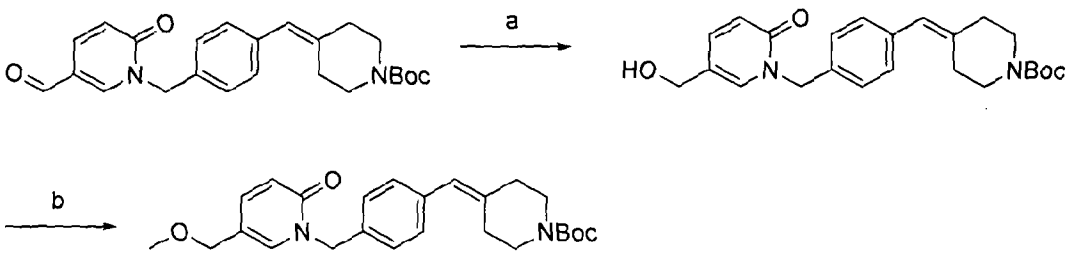
MS (ES^+) 325

2.48 Example 48

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-5-(methoxymethyl)pyridin-2(1H)-one



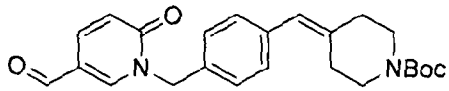
Scheme 22



Reagents and conditions: a) DIBAL-H, THF, -78 °C; b) NaH, MeI, DMF

Step a **Intermediate 37**

tert-butyl 4-{4-[(5-formyl-2-oxopyridin-1(2H)-yl)methyl]benzylidene}piperidine-1-carboxylate



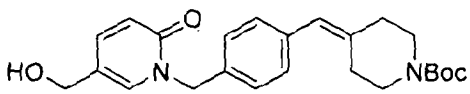
Prepared in an analogous manner to **Example 40** (Cs_2CO_3) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using 6-oxo-1,6-dihydropyridine-3-carbaldehyde.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 8.70 - 8.79 (m, 1H), 7.75 - 7.84 (m, 1H), 7.26 - 7.38 (m, 2H), 7.19 - 7.26 (m, 2H), 6.48 - 6.59 (m, 1H), 6.35 (s, 1H), 5.18 (s, 2H), 3.37 - 3.44 (m, 2H), 3.30 - 3.35 (m, 2H), 2.32 - 2.40 (m, 2H), 2.22 - 2.31 (m, 2H), 1.41 (s, 9H)

MS (ES^+) 353

Step b **Intermediate 38**

tert-butyl 4-(4-{[5-(hydroxymethyl)-2-oxopyridin-1(2H)-yl]methyl}benzylidene) piperidine-1-carboxylate



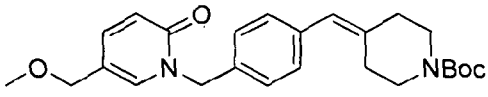
To a solution of tert-butyl 4-(4-((5-formyl-2-oxopyridin-1(2H)-yl)methyl)benzylidene)piperidine-1-carboxylate (**Int 37**) (500 mg, 1.22 mmol) in THF (8 ml) at -78°C was added DIBAL-H (3.67 ml, 1 M solution in hexanes, 3.67 mmol) and the reaction stirred at this temperature for 1 h. The reaction was quenched with a sat. aq. solution of sodium potassium tartrate, diluted with EtOAc and filtered through a pad of celite washing with EtOAc. The filtrate was concentrated under reduced pressure to give tert-butyl 4-(4-((5-(hydroxymethyl)-2-oxopyridin-1(2H)-yl)methyl)benzylidene)piperidine-1-carboxylate as an orange gum (501 mg, quantitiative).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 - 7.61 (m, 1H), 7.27 - 7.36 (m, 1H), 7.14 - 7.21 (m, 2H), 7.06 - 7.14 (m, 2H), 6.30 - 6.37 (m, 1H), 6.25 (s, 1H), 4.93 - 5.03 (m, 3H), 4.09 - 4.15 (m, 2H), 3.27 - 3.37 (m, 2H), 3.20 - 3.25 (m, 2H), 2.24 - 2.31 (m, 2H), 2.14 - 2.21 (m, 2H), 1.32 (s, 9H)

MS (ES^+) 411

Step c **Intermediate 39**

tert-butyl 4-(4-{[5-(methoxymethyl)-2-oxopyridin-1(2H)-yl]methyl}benzylidene) piperidine-1-carboxylate



To a solution of tert-butyl 4-(4-((5-(hydroxymethyl)-2-oxopyridin-1(2H)-yl)methyl)benzylidene)piperidine-1-carboxylate (**Int 38**) (585 mg, 1.42 mmol) in DMF (5 ml) at 0°C was added sodium hydride (114 mg, 60 % dispersion in oil, 2.85 mmol). The reaction was stirred at this temperature for 1 hour. Methyl iodide (0.11 ml, 1.7 mmol) was added and the reaction allowed to warm to r.t. and stirred for 16 h. The reaction was cooled to 0°C and quenched with brine and extracted with EtOAc (x 2). The organics were combined and washed with brine (x 5), dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography (SiO_2; 50-100 % EtOAc/petrol) to give tert-butyl 4-(4-((5-(methoxymethyl)-2-oxopyridin-1(2H)-yl)methyl)benzylidene)piperidine-1-carboxylate (223 mg, 37%).

^{1}H NMR (400 MHz, MeOD) δ 7.67 - 7.73 (m, 1H), 7.51 - 7.59 (m, 1H), 7.25 - 7.33 (m, 2H), 7.15 - 7.24 (m, 2H), 6.57 - 6.63 (m, 1H), 6.40 (s, 1H), 5.19 (s, 2H), 4.25 (s, 2H), 3.46 - 3.58 (m, 2H), 3.37 - 3.45 (m, 2H), 3.35 (s, 3H), 2.40 - 2.49 (m, 2H), 2.29 - 2.39 (m, 2H), 1.48 (s, 9H)

MS (ES^+) 425

Step d **Example 48**

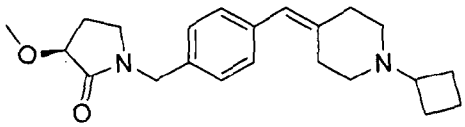
Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with tert-butyl 4-(4-{[5-(methoxymethyl)-2-oxopyridin-1(2H)-yl]methyl}benzylidene) piperidine-1-carboxylate (**Int 39**) and using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (s, 1H), 7.37 - 7.46 (m, 1H), 7.21 - 7.30 (m, 2H), 7.12 - 7.20 (m, 2H), 6.39 - 6.47 (m, 1H), 6.24 (s, 1H), 5.06 (s, 2H), 4.13 (s, 2H), 3.23 (s, 3H), 2.59 - 2.72 (m, 1H), 2.25 - 2.42 (m, 6H), 2.15 - 2.24 (m, 2H), 1.90 - 2.00 (m, 2H), 1.71 - 1.84 (m, 2H), 1.53 - 1.67 (m, 2H)

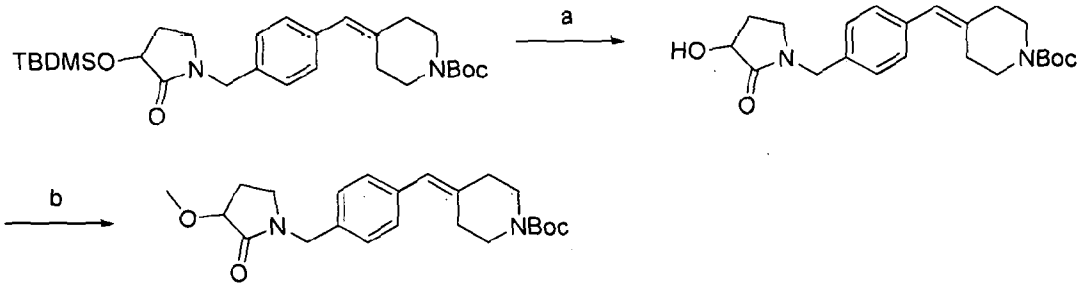
MS (ES^+) 380

2.49 Example 49

(3S)-1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-3-methoxypyrrolidin-2-one



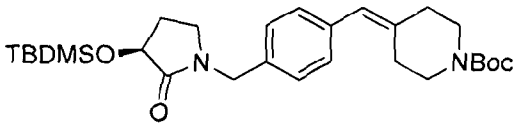
Scheme 23



Reagents and conditions: a) TBAF, THF; b) NaH, MeI, DMF or NaHMDS, MeI, DMF

Step a **Intermediate 40**

tert-butyl 4-(4-{[(3S)-3-{[tert-butyl(dimethyl)silyl]oxy}-2-oxopyrrolidin-1-yl]methyl}benzylidene)piperidine-1-carboxylate

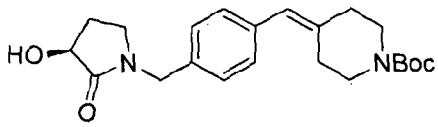


Prepared in an analogous manner to **Example 37** (NaH) via **Scheme 21** starting from *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using (3S)-3-{[tert-butyl(dimethyl)silyl]oxy}pyrrolidin-2-one.

^{1}H NMR (400 MHz, MeOD) δ 6.97 - 7.10 (m, 4H), 6.23 (s, 1H), 4.16 - 4.36 (m, 3H), 3.29 - 3.39 (m, 2H), 3.19 - 3.28 (m, 2H), 3.09 - 3.13 (m, 1H), 2.99 - 3.08 (m, 1H), 2.24 - 2.32 (m, 2H), 2.11 - 2.23 (m, 3H), 1.62 - 1.75 (m, 1H), 1.31 (s, 9H), 0.77 (s, 9H), 0.01 (br. s., 6H)
MS (ES$^+$) 445

Step b **Intermediate 41**

tert-butyl 4-(4-{[(3S)-3-hydroxy-2-oxopyrrolidin-1-yl]methyl}benzylidene) piperidine-1-carboxylate

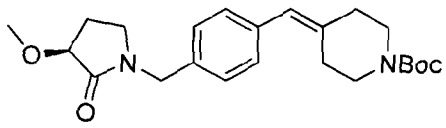


To a solution of (S)-tert-butyl 4-(4-((3-(tert-butyldimethylsilyloxy)-2-oxopyrrolidin-1-yl)methyl)benzylidene)piperidine-1-carboxylate (**Int 40**) (1.65 g, 3.29 *mmol*) in THF (10 ml) at 0°C was added TBAF (1.0 M in THF, 6.58 ml, 6.58 mmol) and the reaction allowed to warm to r.t. Water and EtOAc were added and the layers separated. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2; 80-100 % EtOAc/petrol to 0-10 % MeOH/EtOAc to give (S)-tert-butyl 4-(4-((3-hydroxy-2-oxopyrrolidin-1-yl)methyl)benzylidene)piperidine-1-carboxylate (0.90 g, 71 %).

^{1}H NMR (400 MHz, MeOD) δ 7.17 - 7.28 (m, 4H), 6.41 (s, 1H), 4.32 - 4.54 (m, 3H), 3.48 - 3.56 (m, 2H), 3.37 - 3.46 (m, 2H), 3.18 - 3.29 (m, 2H), 2.32 - 2.50 (m, 5H), 1.79 - 1.92 (m, 1H), 1.43 - 1.53 (m, 9H)
MS (ES$^+$) 331

Step c **Intermediate 42**

tert-butyl 4-(4-{[(3S)-3-methoxy-2-oxopyrrolidin-1-yl]methyl}benzylidene) piperidine-1-carboxylate



To a solution of (S)-tert-butyl 4-(4-((3-hydroxy-2-oxopyrrolidin-1-yl)methyl)benzylidene)piperidine-1-carboxylate (**Int 41**) (904 mg, 2.339 mmol) in DMF (7mL) at 0 °C was added NaH (60% dispersion on oil, 187 mg, 4.68 mmol). The reaction was stirred at this temperature for 1 h. To this suspension was added methyl iodide (0.176 ml, 2.81 mmol) and the reaction allowed to warm slowly to r.t. and stirred overnight. The reaction was cooled to 0°C and quenched with brine and extracted with EtOAc (x 2). The organics were combined and washed with brine (x 5), dried over $MgSO_4$ and concentrated under reduced pressure to give an orange oil which solidified on standing (~1g). Purification by column chromatography (SiO_2; 80-100 % EtOAc/petrol) gave tert-butyl 4-(4-{[(3S)-3-methoxy-2-oxopyrrolidin-1-yl]methyl}benzylidene)piperidine-1-carboxylate which solidified on standing to give a pale yellow solid (659 mg, 70 %).

^{1}H NMR (400 MHz, MeOD) δ 7.05 - 7.31 (m, 4 H), 6.41 (s, 1 H), 4.30 - 4.57 (m, 2 H), 3.95 - 4.19 (m, 1 H), 3.48 - 3.57 (m, 5 H), 3.38 - 3.46 (m, 2 H), 3.29 - 3.37 (m, 1 H), 3.17 - 3.29 (m, 1 H), 2.27 - 2.50 (m, 5 H), 1.82 - 1.97 (m, 1 H), 1.49 (s, 9 H)
MS ES+ 345

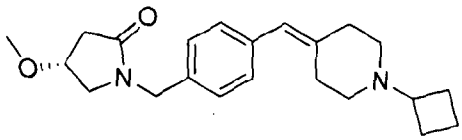
Step d **Example 49**

Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with tert-butyl 4-(4-{[(3S)-3-methoxy-2-oxopyrrolidin-1-yl]methyl}benzylidene)piperidine-1-carboxylate (**Int 42**) using cyclobutanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.13 - 7.26 (m, 4H), 6.33 (s, 1H), 4.36 - 4.55 (m, 2H), 4.03 - 4.14 (m, 1H), 3.53 (s, 3H), 3.18 - 3.29 (m, 1H), 2.74 - 2.88 (m, 1H), 2.31 - 2.56 (m, 10H), 2.04 - 2.14 (m, 2H), 1.85 - 2.01 (m, 3H), 1.68 - 1.82 (m, 2H)
MS (ES^+) 355

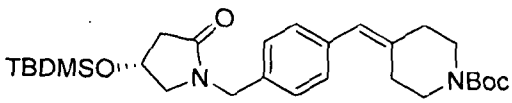
2.50 Example 50

(4R)-1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-4-methoxypyrrolidin-2-one



Step a **Intermediate 43**

tert-Butyl 4-(4-{[(4R)-4-{[tert-butyl(dimethyl)silyl]oxy}-2-oxopyrrolidin-1-yl]methyl}benzylidene)piperidine-1-carboxylate



To a solution of (R)-4-(tert-butyldimethylsilyloxy)pyrrolidin-2-one (0.71 g, 3.28 mmol) in DMF (5 ml) was added NaHMDS (1 M solution in THF, 4.10 ml, 4.10 mmol) at 0 °C and the reaction stirred at this temperature for 10 min and then allowed to warm to r.t. for 1 h. *tert*-Butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) (1.0 g, 2.73 mmol) was added at 0 °C and the reaction allowed to warm to r.t. slowly in the ice bath and stirred for 3 h. The reaction was quenched by the careful drop-wise addition of brine at 0 °C and extracted with EtOAc (x 2) and washed combined organics with brine (x 5), dried over $MgSO_4$ and evaporated under reduced pressure to give a brown oil. Purification by column chromatography (SiO_2; 30-70% EtOAc/petrol) gave the *tert*-butyl 4-(4-{[(4R)-4-{[tert-butyl(dimethyl)silyl]oxy}-2-oxopyrrolidin-1-yl]methyl}benzylidene)piperidine-1-carboxylate as a bright yellow oil which solidified on standing.

^{1}H NMR (400 MHz, MeOD) δ 7.20 - 7.26 (m, 2 H), 7.13 - 7.20 (m, 2 H), 6.39 (s, 1 H), 4.62 - 4.74 (m, 1 H), 4.43 - 4.54 (m, 1 H), 4.17 - 4.27 (m, 1 H), 3.54 - 3.64 (m, 1 H), 3.44 - 3.54 (m, 2 H), 3.35 - 3.44 (m, 2 H), 3.07 - 3.18 (m, 1 H), 2.69 - 2.83 (m, 1 H), 2.39 - 2.48 (m, 2 H), 2.22 - 2.39 (m, 3 H), 1.47 (s, 10 H), 0.86 (s, 10 H), 0.08 (s, 3 H), 0.02 (s, 3 H)

MS (ES+) 445

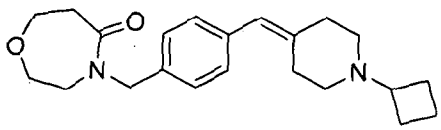
Step b **Example 50**

Prepared in an analogous manner to **Example 49** via **Scheme 23** starting with tert-butyl 4-(4-{[(4R)-4-{[tert-butyl(dimethyl)silyl]oxy}-2-oxopyrrolidin-1-yl]methyl} benzylidene)piperidine-1-carboxylate (**Int 43**) and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 6.97 - 7.09 (m, 4H), 6.17 (s, 1H), 4.20 - 4.38 (m, 2H), 3.81 - 3.94 (m, 1H), 3.32 - 3.44 (m, 1H), 3.12 (s, 3H), 2.52 - 2.67 (m, 3H), 2.11 - 2.40 (m, 9H), 1.86 - 1.96 (m, 2H), 1.71 - 1.84 (m, 2H), 1.50 - 1.62 (m, 2H)
MS (ES$^+$) 355

2.51 Example 51

4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-1,4-oxazepan-5-one

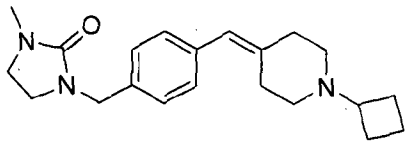


Prepared in an analogous manner to **Example 37** (NaH) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using 1,4-oxazepan-5-one and via **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.22 - 7.30 (m, 2H), 7.15 - 7.23 (m, 2H), 6.33 (s, 1H), 4.60 (s, 2H), 3.74 - 3.82 (m, 2H), 3.56 - 3.63 (m, 2H), 3.49 - 3.57 (m, 2H), 2.75 - 2.86 (m, 3H), 2.31 - 2.57 (m, 8H), 2.04 - 2.14 (m, 2H), 1.88 - 2.01 (m, 2H), 1.70 - 1.83 (m, 2H)
MS (ES$^+$) 355

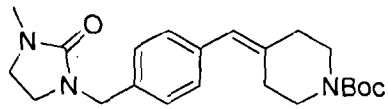
2.52 Example 52

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}-3-methylimidazolidin-2-one



Step a **Intermediate 44**

tert-Butyl 4-{4-[(3-methyl-2-oxoimidazolidin-1-yl)methyl]benzylidene}piperidine-1-carboxylate



A suspension of tert-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) (0.25 g, 0.68 mmol), potassium carbonate (0.47 g, 3.41 mmol) and 1-methylimidazolidin-2-one (68 mg, 0.68 mmol) in acetonitrile (5 ml) was stirred at r.t. overnight. The reaction mixture was then heated to reflux for 24 h. The reaction mixture was quenched with water and partitioned between EtOAc and brine. The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and the residue purified by dry flash column chromatography (SiO_2;10-70 % EtOAc/petrol) to give tert-butyl 4-{4-[(3-methyl-2-oxoimidazolidin-1-yl)methyl]benzylidene}piperidine-1-carboxylate as a colourless gum (0.104 g, 40 % yield).

^{1}H NMR (400 MHz, MeOD) δ 7.19 (m, 4 H) 6.39 (s, 1 H) 4.31 (s, 2 H) 3.50 (t, J = 5.56 Hz, 2 H) 3.41 (t, J =5.56 Hz, 2 H) 3.32 - 3.36 (m, 2 H) 3.19 - 3.25 (m, 2 H) 2.80 (s, 3 H) 2.45 (t, J = 5.68 Hz, 2 H) 2.34 (t, J = 5.68 Hz, 2 H) 1.47 (s, 9 H)
MS ES+ 330

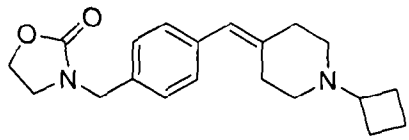
Step b **Example 52**

Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with tert-butyl 4-{4-[(3-methyl-2-oxoimidazolidin-1-yl)methyl]benzylidene}piperidine-1-carboxylate (**Int 44**) and using cyclobutanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.23 (d, 2 H), 7.18 (d, 2 H), 6.34 (s, 1 H), 4.34 (s, 2 H), 3.34 - 3.39 (m, 3 H), 3.20 - 3.27 (m, 2 H), 2.81 (s, 3 H), 2.31 - 2.59 (m, 8 H), 2.03 - 2.15 (m, 2 H), 1.96 (t, *J* =9.47 Hz, 2 H), 1.67 - 1.81 (m, 2 H)
MS (ES^+) 340

2.53 Example 53

3-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-1,3-oxazolidin-2-one



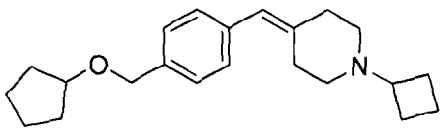
Prepared in an analogous manner to **Example 52** via Scheme 21 starting with tert-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using 1,3-oxazolidin-2-one and via **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12 - 7.27 (m, 4 H), 6.26 (s, 1 H), 4.32 (s, 2 H), 4.22 - 4.29 (m, 2 H), 3.37 - 3.45 (m, 2 H), 2.61 - 2.72 (m, 1 H), 2.37 - 2.43 (m, 2 H), 2.26 - 2.35 (m, 4 H), 2.16 - 2.24 (m, 2 H), 1.90 - 2.00 (m, 2 H), 1.71 - 1.84 (m, 2 H), 1.54 - 1.67 (m, 2 H)

MS (ES^+) 327

2.54 Example 54

1-Cyclobutyl-4-{4-[(cyclopentyloxy)methyl]benzylidene}piperidine



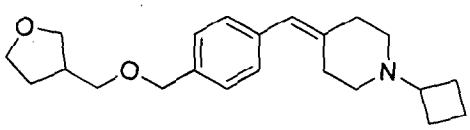
Prepared in an analogous manner to **Example 37** (NaH) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using cyclopentanol and via **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8 Hz, 2H), 7.19 (d, J = 8 Hz, 2H), 6.27 (s, 1H), 4.44 (s, 2H), 4.02- 3.97 (m, 1H), 2.72 (quin, J = 7.5 Hz, 1H), 2.54 (t, J = 5.5 Hz, 2H), 2.42 (br. s, 4H), 2.31 (t, J = 5.5 Hz, 2H), 2.09- 1.90 (m, 4H), 1.78- 1.66 (m, 8H), 1.57- 1.48 (m, 2H).

MS (ES^+) 326

2.55 Example 55

1-cyclobutyl-4-{4-[(tetrahydrofuran-3-ylmethoxy)methyl]benzylidene}piperidine



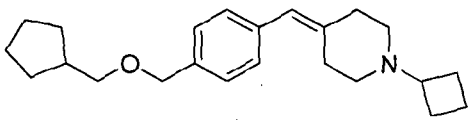
Prepared in an analogous manner to **Example 37** (NaH) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using tetrahydrofuran-3-ylmethanol and via **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.17 (d, J = 8.08 Hz, 2 H), 7.08 (d, J = 8.08 Hz, 2 H), 6.23 (s, 1 H), 4.39 (s, 2 H), 3.66 - 3.76 (m, 2 H), 3.55 - 3.65 (m, 1 H), 3.42 - 3.51 (m, 1 H), 3.25 - 3.41 (m, 2 H), 2.63 - 2.81 (m, 1 H), 2.17 - 2.53 (m, 9 H), 1.75 - 2.05 (m, 5 H), 1.45 - 1.71 (m, 3 H)

MS (ES^+) 342

2.56 Example 56

1-cyclobutyl-4-{4-[(cyclopentylmethoxy)methyl]benzylidene}piperidine



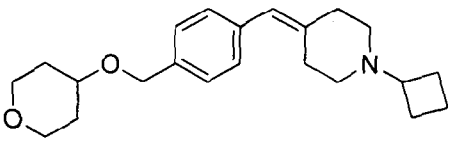
Prepared in an analogous manner to **Example 37** (NaH) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using cyclopentylmethanol, and via **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8 Hz, 2H), 7.16 (d, J = 8 Hz, 2H), 6.27 (s, 1H), 4.48 (s, 2H), 3.33 (d, J = 7 Hz, 2H), 2.72 (quin, J = 6.5 Hz, 1H), 2.55 (br. s, 2H), 2.42 (br. s, 4H), 2.31 (br. s, 2H), 2.20 (septet, J = 7.5 Hz, 1H), 2.06- 1.88 (m, 4H), 1.79-1.50 (m, 8H), 1.27- 1.21 (m, 2H).

MS (ES^+) 340

2.57 Example 57

1-cyclobutyl-4-{4-[(tetrahydro-2H-pyran-4-yloxy)methyl]benzylidene}piperidine



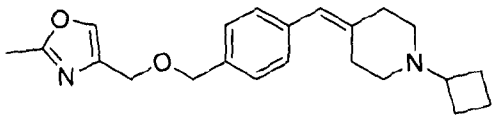
Prepared in an analogous manner to **Example 37** (NaH) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using tetrahydro-2H-pyran-4-ol, and via **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8 Hz, 2H), 7.16 (d, J = 8 Hz, 2H), 6.27 (s, 1H), 4.53 (s, 2H), 3.96 (dt, J = 12 Hz, 4 Hz, 2H), 3.59 (tt, J = 9, 4 Hz, 1H), 3.43 (ddd, J = 12, 9, 3 Hz, 2H), 2.73 (quin, J = 8 Hz, 1H), 2.55 (t, J = 5.5 Hz, 2H), 2.43 (s, 4H), 2.32 (t, J = 5.5 Hz, 2H), 2.06- 1.90 (m, 6H), 1.75-1.59 (m, 4H).

MS (ES^+) 342

2.58 Example 58

1-Cyclobutyl-4-(4-{[(2-methyl-1,3-oxazol-4-yl)methoxy]methyl}benzylidene) piperidine

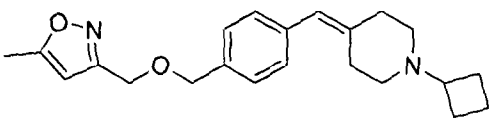


Prepared in an analogous manner to **Example 37** (NaH) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using (2-methyl-1,3-oxazol-4-yl)methanol, and via **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO) δ 7.93 (s, 1H), 7.28 (d, 2H), 7.18 (d, 2H), 6.27 (s, 1H), 4.49 (s, 2H), 4.35 (s, 2H), 2.62-2.74 (m, 1H), 2.36-2.45 (m, 5H), 2.26-2.35 (m, 4H), 2.17-2.26 (m, 2H), 1.90-2.01 (m, 2H), 1.72-1.85 (m, 2H), 1.52-1.68 (m, 2H).
MS (ES^+) 353

2.59 Example 59

1-Cyclobutyl-4-(4-{[(5-methyl-1,2-oxazol-3-yl)methoxy]methyl}benzylidene) piperidine



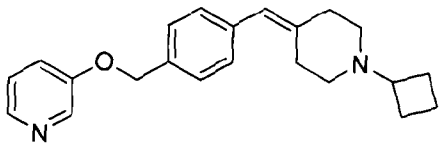
Prepared in an analogous manner to **Example 37** (NaH) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using (5-methyl-1,2-oxazol-3-yl)methanol, and via **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO) δ 7.29 (d, 2H), 7.18 (d, 2H), 6.28 (s, 2H), 4.53 (s, 2H), 4.50 (s, 2H), 2.61-2.72 (m, 1H), 2.36-2.44 (m, 5H), 2.27-2.35 (m, 4H), 2.18-2.25 (m, 2H), 1.86-2.01 (m, 2H), 1.71-1.86 (m, 2H), 1.52-1.70 (m, 2H).

MS (ES^+) 353

2.60 Example 60

3-({4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}oxy)pyridine



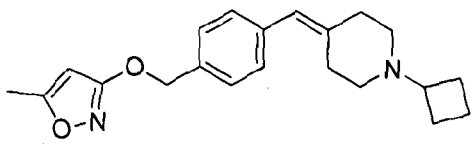
Prepared in an analogous manner to **Example 37** (NaH) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using pyridin-3-ol, and via **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO) δ 8.36 (d, 1H), 8.18 (d, 1H), 7.46 (dd, 1H), 7.42 (d, 2H), 7.30-7.37 (m, 1H), 7.23 (d, 2H), 6.29 (s, 1H), 5.16 (s, 2H), 2.60-2.76 (m, 1H), 2.38-2.46 (m, 2H), 2.27-2.37 (m, 4H), 2.17-2.27 (m, 2H), 1.89-2.02 (m, 2H), 1.72-1.87 (m, 2H), 1.53-1.68 (m, 2H).

MS (ES^+) 335

2.61 Example 61

1-Cyclobutyl-4-(4-{[(5-methyl-1,2-oxazol-3-yl)oxy]methyl}benzylidene)piperidine

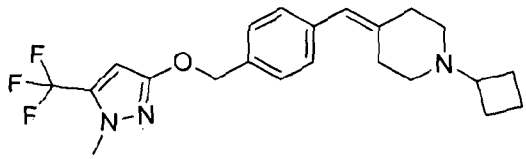


Prepared in an analogous manner to **Example 52** (K_2CO_3 in DMF instead of MeCN) via **Scheme 21** starting with tert-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using 5-methyl-1,2-oxazol-3-ol, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO) δ 7.40 (d, 2H), 7.22 (d, 2H), 6.29 (s, 1H), 6.00 (s, 1H), 5.17 (s, 2H), 2.58-2.77 (m, 1H), 2.37-2.45 (m, 2H), 2.27-2.37 (m, 7H), 2.11-2.27 (m, 2H), 1.90-2.02 (m, 2H), 1.71-1.87 (m, 2H), 1.53-1.69 (m, 2H).
MS (ES^+) 339

2.62 Example 62

1-cyclobutyl-4-[4-({[1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]oxy}methyl)benzylidene]piperidine

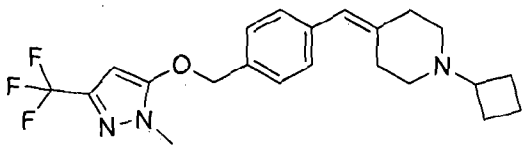


Prepared in an analogous manner to **Example 40** (Cs_2CO_3 in DMF) via **Scheme 21** starting with tert-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using 1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-ol, and via **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO) δ 7.38 (d, 2H), 7.21 (d, 2H), 6.42 (s, 1H), 6.28 (s, 1H), 5.14 (s, 2H), 3.81 (s, 3H), 2.62-2.73 (m, 1H), 2.37-2.45 (m, 2H), 2.26-2.37 (m, 4H), 2.17-2.26 (m, 2H), 1.89-2.02 (m, 2H), 1.71-1.86 (m, 2H), 1.53-1.69 (m, 2H).
MS (ES^+) 406

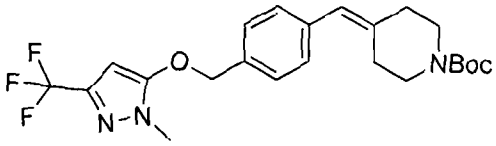
2.63 Example 63

1-Cyclobutyl-4-[4-({[1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]oxy}methyl) benzylidene]piperidine



Step a **Intermediate 45**

tert-butyl 4-[4-({[1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]oxy}methyl)benzylidene]piperidine-1-carboxylate



To a solution of 1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-ol (350 mg, 2.107 mmol) in dry DMF (3 ml) cooled to 0° C under nitrogen was added KHMDS (0.5M in toluene, 4.23 ml, 2.12 mmol) and the reaction mixture stirred at 0 °C for 1 h. *tert*-Butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) (500 mg, 1.37 mmol) was added and the reaction mixture stirred at 0°C for 1 h, then at r.t. for 20 h. Water (20 ml) was added and the organics extracted with EtOAc (3 x 20 ml). The combined organics were washed with brine (2 x 15 ml), dried (H frit) and evaporated to dryness. The crude product was purified by column chromatography (SiO_2; 0-35 % EtOAc / petrol) to give tert-butyl 4-[4-({[1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]oxy}methyl)benzylidene]piperidine-1-carboxylate (97 mg, 16 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.40 (m, 2 H), 7.19 - 7.27 (m, 2 H), 6.37 (s, 1 H), 5.84 (s, 1 H), 5.09 (s, 2 H), 3.70 (s, 3 H), 3.32 - 3.61 (m, 4 H), 2.41 - 2.53 (m, 2 H), 2.28 - 2.41 (m, 2 H), 1.49 (s, 9 H)
MS ES+ 452

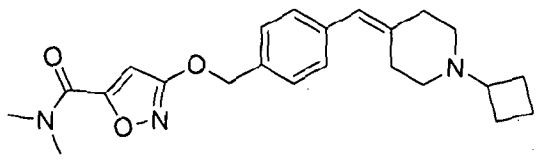
Step b **Example 63**

Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting from tert-butyl 4-[4-({[1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]oxy}methyl)benzylidene] piperidine-1-carboxylate (**Int 45**) and using cyclobutanone in step b.

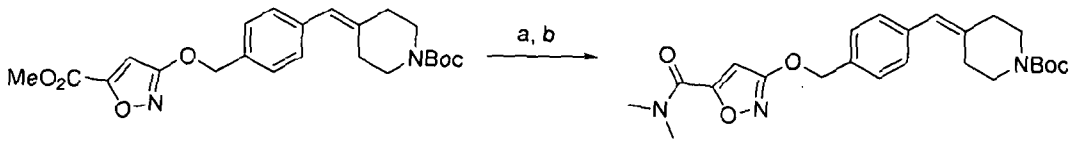
^{1}H NMR (400 MHz, DMSO) δ 7.44 (d, 2H), 7.24 (d, 2H), 6.29 (s, 2H), 5.21 (s, 2H), 3.64 (s, 3H), 2.62-2.73 (m, 1H), 2.37-2.45 (m, 2H), 2.27-2.36 (m, 4H), 2.18-2.26 (m, 2H), 1.90-2.02 (m, 2H), 1.73-1.86 (m, 2H), 1.51-1.69 (m, 2H).
MS (ES^+) 406

2.64 Example 64

3-({4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}oxy)-N,N-dimethyl-1,2-oxazole-5-carboxamide



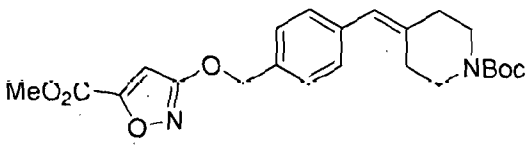
Scheme 24



Reagents and conditions: a) LiOH, THF, MeOH, H_2O; b) $Me_2NH.HCl$, EDC.HCl, HOAt, DIPEA, DCM

Step a **Intermediate 46**

tert-Butyl 4-[4-({[5-(methoxycarbonyl)-1,2-oxazol-3-yl]oxy}methyl)benzylidene] piperidine-1-carboxylate

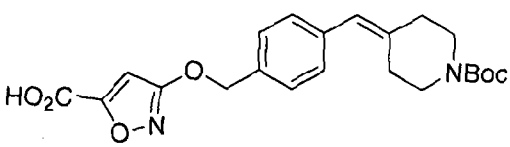


Prepared in an analogous manner to **Example 40** (Cs_2CO_3 in DMF) via **Scheme 21** starting with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using methyl 3-hydroxy-1,2-oxazole-5-carboxylate.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 - 7.49 (m, 2H), 7.22 - 7.30 (m, 2H), 7.13 (s, 1H), 6.39 (s, 1H), 5.30 (s, 2H), 3.89 (s, 3H), 3.39 - 3.48 (m, 2H), 3.32 - 3.37 (m, 2H), 2.35 - 2.44 (m, 2H), 2.25 - 2.33 (m, 2H), 1.42 (s, 9H)

Step b **Intermediate 47**

3-[(4-{[1-(tert-Butoxycarbonyl)piperidin-4-ylidene]methyl}benzyl)oxy]-1,2-oxazole-5-carboxylic acid

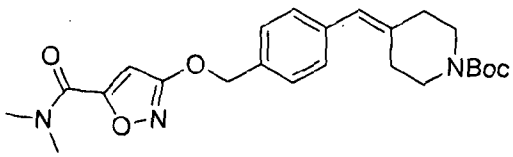


A mixture of methyl 3-(4-((1-(tert-butoxycarbonyl)piperidin-4-ylidene)methyl)benzyloxy)isoxazole-5-carboxylate (**Int 46**) (258 mg, 0.60 mmol) and LiOH (2.0 ml, 4.00 mmol) in THF (1 ml) and MeOH (2 ml) was stirred at r.t. for 5 h. The reaction mixture was evaporated to dryness and 2M HCl (5 ml) was added. The organics were extracted with DCM (3 x 20 ml), dried (H frit) and evaporated to dryness to give 3-[(4-{[1-(tert-butoxycarbonyl)piperidin-4-ylidene]methyl} benzyl)oxy]-1,2-oxazole-5-carboxylic acid (246 mg, 99 %).

MS (ES^-) 413

Step c **Intermediate 48**

tert-Butyl 4-[4-({[5-(dimethylcarbamoyl)-1,2-oxazol-3-yl]oxy}methyl)benzylidene] piperidine-1-carboxylate



A mixture of 3-(4-((1-(tert-butoxycarbonyl)piperidin-4-ylidene)methyl) benzyloxy)isoxazole-5-carboxylic acid (**Int 47**) (246 mg, 0.59 mmol), dimethylamine hydrochloride (145 mg, 1.78 mmol), EDC (171 mg, 0.89 mmol) and HOAt (121 mg, 0.89 mmol) in DCM (10 ml) was treated with DIPEA (0.31 ml, 1.78 mmol) and the solution stirred at r.t. for 20 h. Sodium bicarbonate solution (20 ml) was added and extracted with DCM (3 x 20 ml), dried (H frit) and evaporated to dryness. The residue was purified by column chromatography (SiO_2; 0-60 % EtOAc/petrol) to give tert-butyl 4-[4-({[5-(dimethylcarbamoyl)-1,2-oxazol-3-yl]oxy}methyl)benzylidene] piperidine-1-carboxylate (270 mg, quantitative).

MS (ES^+) 442

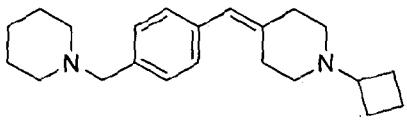
Step d **Example 64**

Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting from tert-butyl 4-[4-({[5-(dimethylcarbamoyl)-1,2-oxazol-3-yl]oxy}methyl)benzylidene] piperidine-1-carboxylate (**Int 48**) and using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO) δ 7.43 (d, 2H), 7.23 (d, 2H), 6.75 (s, 1H), 6.29 (s, 1H), 5.27 (s, 2H), 3.09 (s, 3H), 2.99 (s, 3H), 2.62-2.74 (m, 1H), 2.37-2.46 (m, 2H), 2.27-2.36 (m, 4H), 2.17-2.27 (m, 2H), 1.89-2.02 (m, 2H), 1.71-1.86 (m, 2H), 1.52-1.69 (m, 2H).
MS (ES^+) 396

2.65 Example 65

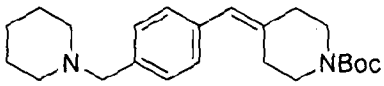
1-Cyclobutyl-4-[4-(piperidin-1-ylmethyl)benzylidene]piperidine



Step a **Intermediate 49**

(Scheme 21)

tert-Butyl 4-[4-(piperidin-1-ylmethyl)benzylidene]piperidine-1-carboxylate



A mixture of tert-butyl 4-[4-(bromomethyl)benzylidene]piperidine-1-carboxylate (**Int 32**) (350 mg, 0.96 mmol), piperidine (115 µl, 1.15 mmol) and potassium carbonate (400 mg, 2.9 mmol) in THF (10 ml) was stirred at r.t. for 72 h. The reaction was diluted with EtOAc and washed with water. The organic phase was washed further with water (x 2) and brine then dried ($MgSO_4$) and concentrated under reduced pressure to give tert-butyl 4-[4-(piperidin-1-ylmethyl)benzylidene]piperidine-1-carboxylate as a white solid (297 mg, 83 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8 Hz, 2H), 7.13 (d, J = 8 Hz, 2H), 6.33 (s, 1H), 3.50 (t, J = 6 Hz, 2H), 3.46 (s, 2H), 3.40 (t, J = 6 Hz, 2H), 2.47 (t, J = 5.5 Hz, 2H), 2.38 (m, 4H), 2.32 (t, J = 5.5 Hz, 2H), 1.62-1.52 (m, 6H), 1.47 (s, 9H)
MS ES^+ 371

Step b **Example 65**

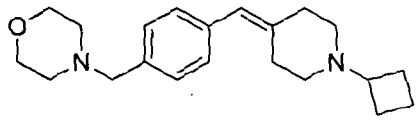
Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting from tert-butyl 4-[4-(piperidin-1-ylmethyl)benzylidene]piperidine-1-carboxylate (**Int 49**) and using cyclobutanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.17 (d, J = 7.83 Hz, 4H), 7.05 (d, J = 8.08 Hz, 4H), 6.22 (s, 1H), 3.38 (s, 2H), 2.67 (quin, J = 7.96 Hz, 1H), 2.11 - 2.49 (m, 25H), 1.91 - 2.05 (m, 2H), 1.74 - 1.90 (m, 5H), 1.55 - 1.70 (m, 5H), 1.42 - 1.56 (m, 11H), 1.33 - 1.42 (m, 5H)

MS ES$^+$ 325

2.66 Example 66

4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}morpholine



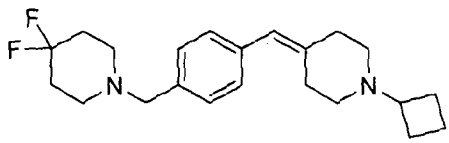
Prepared in an analogous manner to **Example 65** via **Scheme 21** startng with tert-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using morpholine, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8 Hz, 2H), 7.14 (d, J = 8 Hz, 2H), 6.26 (s, 1H), 3.70 (t, J = 5 Hz, 4H), 3.47 (s, 2H), 2.71 (quin, J = 8 Hz, 1H), 2.54 (t, J = 5 Hz, 2H), 2.46-2.38 (m, 6H), 2.30 (t, J = 5 Hz, 2H), 2.07- 1.98 (m, 2H), 1.98- 1.88 (m, 2H), 1.74- 1.61 (m, 4H).

MS ES$^+$ 327

2.67 Example 67

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}-4,4-difluoropiperidine



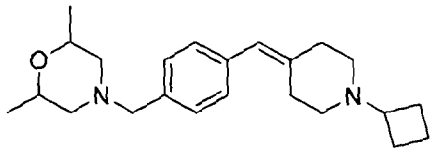
Prepared in an analogous manner to **Example 65** via **Scheme 21** startng with tert-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using 4,4-difluoropiperidine, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8 Hz, 2H), 7.14 (d, J = 8 Hz, 2H), 6.26 (s, 1H), 3.52 (s, 2H), 2.71 (quin, J = 8 Hz, 1H), 2.54 (t, J = 5.5 Hz, 6H), 2.41 (s, 4H), 2.30 (t, J = 5.5 Hz, 2H), 2.05- 1.90 (m, 6H), 1.74- 1.62 (m, 4H).

MS ES$^+$ 361

2.68 Example 68

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}-2,6-dimethylmorpholine



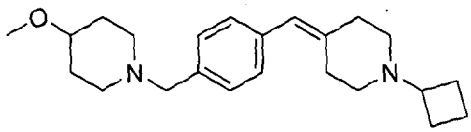
Prepared in an analogous manner to **Example 65** via **Scheme 21** startng with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using 2,6-dimethylmorpholine, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8 Hz, 2H), 7.14 (d, J = 8 Hz, 2H), 6.27 (s, 1H), 3.74- 3.64 (m, 2 H), 3.44 (s, 2H), 2.78- 2.69 (m, 1H), 2.70 (d, J = 10.5 Hz, 2H), 2.56 (t, J = 5.5 Hz, 2H), 2.43 (s, 4H), 2.33 (t, J = 5.5 Hz, 2H), 2.06- 1.93 (m, 4H), 1.74 (t, J = 10.5 Hz, 2H), 1.75- 1.64 (m, 2H), 1.13 (d, J = 6 Hz, 6H).

MS ES^+ 355

2.69 Example 69

1-Cyclobutyl-4-{4-[(4-methoxypiperidin-1-yl)methyl]benzylidene}piperidine



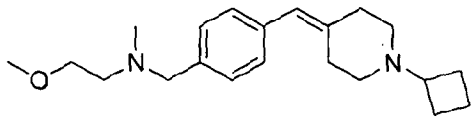
Prepared in an analogous manner to **Example 65** via **Scheme 21** startng with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using 4-methoxypiperidine, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8 Hz, 2H), 7.13 (d, J = 8 Hz, 2H), 6.25 (s, 1H), 3.46 (s, 2H), 3.33 (s, 3H), 3.21 (tt, J = 8.5, 5 Hz, 1H), 2.76- 2.66 (m, 3H), 2.53 (t, J = 5.5 Hz, 2H), 2.39 (s, 4H), 2.29 (t, J = 5.5 Hz, 2H), 2.18- 2.09 (m, 2H), 2.08- 1.99 (m, 2H), 1.95- 1.84 (m, 4H), 1.77- 1.59 (m, 4H)

MS ES^+ 355

2.70 Example 70

N-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}-2-methoxy-N-methylethanamine



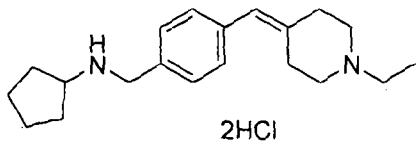
Prepared in an analogous manner to **Example 65** via **Scheme 21** startng with *tert*-butyl 4-(4-(bromomethyl)benzylidene)piperidine-1-carboxylate (**Int 32**) and using 2-methoxy-N-methylethanamine, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.17 (d, J =7.83 Hz, 2H), 7.05 (d, J =8.08 Hz, 2H), 6.22 (s, 1H), 3.35 - 3.49 (m, 4H), 3.22 (s, 3H), 2.68 (quin, J =7.96 Hz, 1H), 2.50 (t, J =5.68 Hz, 2H), 2.19 - 2.47 (m, 8H), 2.15 (s, 3H), 1.90 - 2.03 (m, 2H), 1.76 - 1.89 (m, 2H), 1.55 - 1.69 (m, 2H)

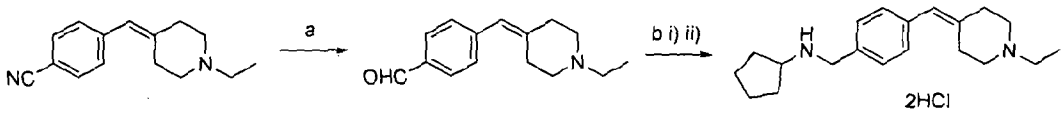
MS ES$^+$ 329

2.71 Example 71

N-(4-((1-ethylpiperidin-4-ylidene)methyl)benzyl)cyclopentanamine dihydrochloride



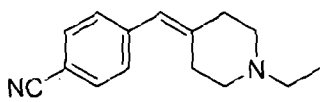
Scheme 25



Reagents and conditions: a) DIBAL, DCM, 0 °C; b)i) cyclopentylamine, $NaBH_4$, AcOH, THF ii) HCl, MeOH

Intermediate 50

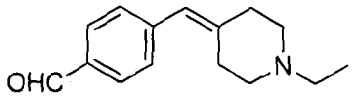
4-[(1-ethylpiperidin-4-ylidene)methyl]benzonitrile



Prepared in an analogous manner to **Intermediate 3** via **Scheme 3**, method B using diethyl (4-cyanobenzyl)phosphonate (CAS: 1552-41-6) and 1-ethylpiperidin-4-one.

Step a **Intermediate 51**

4-[(1-ethylpiperidin-4-ylidene)methyl]benzaldehyde



To a solution of 4-[(1-ethylpiperidin-4-ylidene)methyl]benzonitrile (**Int 50**) (6.0 g, 26.5 mmol) in DCM (60 ml) at 0 °C was added DIBAL (21.2 ml, 1.25 M, 26.5 mmol). The reaction was stirred at this temperature for 1 h. Further DIBAL (11 ml, 1.25 M, 7.3 mmol) was added and the reaction stirred for 1 h. Saturated aq. sodium potassium tartrate was added and the mixture stirred at r.t. for 1 h. The layers were separated. 10 % aq. HCl was added to the organic phase and the mixture stirred for 1 h. The mixture was then basified by the addition of 2 M NaOH (aq.) and extracted into DCM. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography gave 4-[(1-ethylpiperidin-4-ylidene)methyl]benzaldehyde (520 mg, 9 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.82 (d, J = 7.2 Hz, 2H), 7.33 (d, J = 7.2 Hz, 2H), 6.32 (s, 1H), 2.57 (m, 4H), 2.47 (m, 6H), 1.12 (t, J = 7.2, Hz, 3H)

Step b **Example 71**

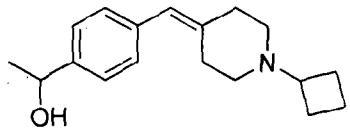
To a solution of 4-[(1-ethylpiperidin-4-ylidene)methyl]benzaldehyde (**Int 51**) (416 mg, 1.81 mmol) in THF (5 ml) at r.t. was added cyclopentylamine (0.18 ml, 1.81 mmol) and the reaction stirred for 18 h. The mixture was concentrated under reduced pressure and the residue taken up into MeOH. $NaBH_4$ (137 mg, 3.63 mmol) and AcOH (2 drops) were added and the reaction stirred at r.t. for 72 h. Saturated aq. $NaHCO_3$ (10 ml) was added and the mixture extracted with DCM. The organic phase was dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (SiO_2, 1/20 saturated NH_3 in MeOH/DCM) to give N-(4-((1-ethylpiperidin-4-ylidene)methyl)benzyl)cyclopentanamine as a clear oil. This was dissolved in MeOH (5 ml) and a solution of HCl in MeOH (5 ml) was added. The mixture was stirred at r.t. for 2 h then concentrated under reduced pressure to give N-(4-((1-ethylpiperidin-4-ylidene)methyl)benzyl)cyclopentanamine dihydrochloride as a white solid (220 mg, 36 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (br. s., 1 H), 9.22 (br. s., 2 H), 7.45 - 7.57 (m, 2 H), 7.19 - 7.32 (m, 2 H), 6.43 (s, 1 H), 3.95 - 4.15 (m, 2 H), 3.31 - 3.62 (m, 3 H), 2.94 - 3.11 (m, 2 H), 2.63 - 2.94 (m, 4 H), 2.46 - 2.62 (m, 2 H), 1.77 - 2.01 (m, 2 H), 1.55 - 1.77 (m, 4 H), 1.36 - 1.55 (m, 2 H), 1.09 - 1.30 (m, 3 H)

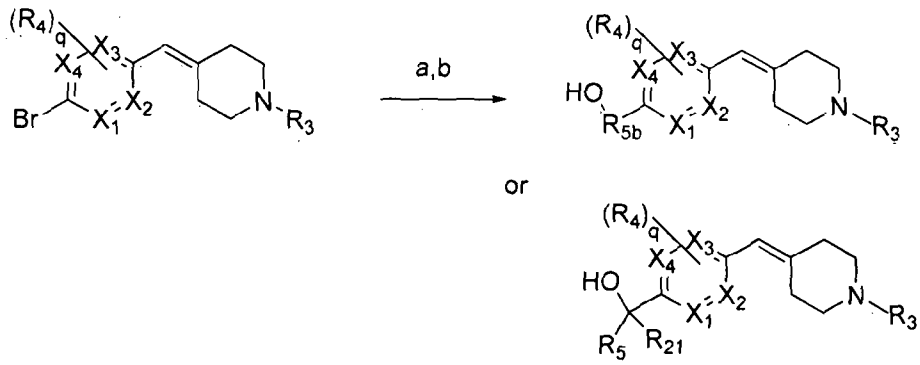
MS ES$^+$ 299

2.72 Example 72

1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)ethanol



Scheme 26

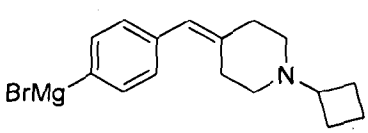


R_{5b} represents R_5 cycloalkyl or heterocyclyl, each of which may be optionally substituted, R_{21} represents H or C_{1-3} alkyl.

Reagents and conditions: a) *n*-Butyllithium, THF, -78 °C; or Mg, reflux, THF; b) R_{5b}=O or $R_5R_{21}C$=O

Step a **Intermediate 52**

Bromo{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}magnesium



Into a dry flask fitted with condensor and dropping funnel was added Mg (397 mg, 16.3 mmol) and iodine (2 crystals). A solution of 4-(4-bromobenzylidene)-1-

cyclobutylpiperidine (5 g, 16.3 mmol) in THF (20 ml) was added dropwise to the magensium and iodine with heating to give a THF solution of bromo{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}magnesium.

Step b **Example 72**

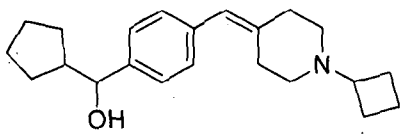
To a solution of acetaldehyde (108 mg, 2.46 mmol) in THF (5 ml) at r.t. was added a THF solution of bromo{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl} magnesium (**Int 52**) (4.25 ml, 2.05 mmol). The mixture became warm (~ 30 °C). The reaction was stirred for 30 min. The reaction mixture was evaporated, treated with 2 M HCl (5 ml) and EtOAc (20 ml). The layers were separated and the aqueous layer basified and extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (SiO_2, 5% MeOH in DCM with 1% NH_4OH) to give 1-(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)ethanol (132 mg, 24 %).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.29 (d, J = 8.26 Hz, 2H), 7.14 (d, J = 8.26 Hz, 2H), 6.23 (s, 1H), 4.85 (q, J = 6.16 Hz, 1H), 2.67 (br s, 1H), 2.66 (quin, J = 7.91 Hz, 1H), 2.45 (t, J = 5.85 Hz, 2H), 2.35 (m, 4H), 2.23 (t, J = 5.85 Hz, 2H), 1.98 (m, 2H), 1.86 (m, 2H), 1.63 (m, 2H), 1.46 (d, J = 6.54 Hz, 3H)

MS ES^+ 272

2.73 Example 73

(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)(cyclopentyl)methanol



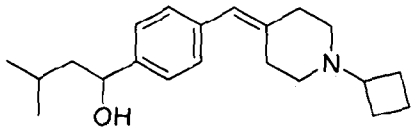
Prepared in an analogous manner to **Example 72** via **Scheme 26** using bromo{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}magnesium (**Int 52**) and cyclopentane carbaldehyde.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 - 7.30 (m, 2H), 7.07 - 7.17 (m, 2H), 6.25 (s, 1H), 5.00 - 5.07 (m, 1H), 4.20 - 4.28 (m, 1H), 2.62 - 2.74 (m, 1H), 2.37 - 2.45 (m, 2H), 2.18 -

2.36 (m, 6H), 2.01 - 2.12 (m, 1H), 1.89 - 2.00 (m, 2H), 1.72 - 1.86 (m, 2H), 1.35 - 1.70 (m, 8H), 1.23 - 1.33 (m, 1H), 1.11 - 1.22 (m, 1H)
MS ES^+ 326

2.74 Example 74

1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)-3-methylbutan-1-ol

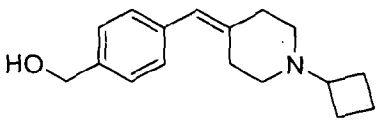


Prepared in an analogous manner to **Example 72** via **Scheme 26** starting with bromo{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}magnesium (**Int 52**) and using 3-methylbutanal.

^1H NMR (300MHz, $CDCl_3$) δ 7.29 (d, J = 8.26 Hz, 2H), 7.14 (d, J = 8.26 Hz, 2H), 6.23 (s, 1H), 4.85 (q, J = 6.16 Hz, 1H), 2.67 (br s, 1H), 2.66 (quin, J = 7.91 Hz, 1H), 2.45 (t, J = 5.85 Hz, 2H), 2.35 (m, 4H), 2.23 (t, J = 5.85 Hz, 2H), 1.98 (m, 2H), 1.86 (m, 2H), 1.63 (m, 2H), 1.46 (d, J = 6.54 Hz, 3H)
MS ES+ 314

2.75 Example 75

(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)methanol



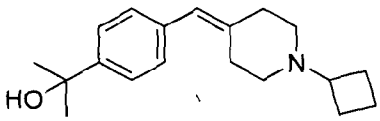
To DMF (0.19 ml, 2.45 mmol) under argon was added a solution of bromo{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}magnesium (**Int 52**) (0.674 g, 2.04 mmol) in THF (4.4 ml). The reaction was stirred for 10 min and was then concentrated under reduced pressure. The residue was taken up in MeOH (5 ml) and $NaBH_4$ (116 mg, 3.06 mmol) was added. The reaction was concentrated under reduced pressure and 2 M HCl (aq.) was added. The mixture was basified and EtOAc was added. The mixture was filtered through Celite and the layers separated. The organic phase was dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (SiO_2; 5-

10 % MeOH (NH_3) in DCM) to give (4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)methanol (53 mg, 10 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 - 7.36 (m, 2H), 7.12 - 7.25 (m, 2H), 6.32 (s, 1H), 5.09 - 5.23 (m, 1H), 4.44 - 4.61 (m, 2H), 2.64 - 2.81 (m, 1H), 2.19 - 2.50 (m, 8H), 1.94 - 2.09 (m, 2H), 1.75 - 1.94 (m, 2H), 1.54 - 1.75 (m, 2H)
MS ES$^+$ 258

2.76 Example 76

2-(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)propan-2-ol

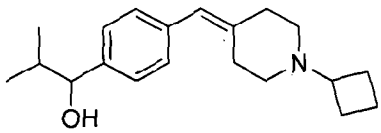


Prepared in an analogous manner to **Example 72** via **Scheme 26** starting with bromo{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}magnesium (**Int 52**) and using acetone.

^{1}H NMR (400 MHz, MeOD) δ 7.39 - 7.48 (m, 2H), 7.11 - 7.19 (m, 2H), 6.33 (s, 1H), 2.73 - 2.86 (m, 1H), 2.31 - 2.61 (m, 8H), 2.04 - 2.15 (m, 2H), 1.87 - 2.02 (m, 2H), 1.67 - 1.83 (m, 2H), 1.46 - 1.60 (m, 6H)
MS ES$^+$ 286

2.77 Example 77

1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)-2-methylpropan-1-ol



Prepared in an analogous manner to **Example 72** via **Scheme 26** starting with bromo{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}magnesium (**Int 52**) and using 2-methylpropanal.

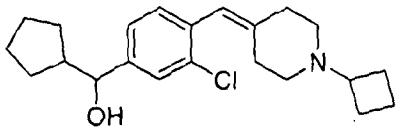
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.17 - 7.26 (m, 2H), 7.08 - 7.16 (m, 2H), 6.19 - 6.27 (m, 1H), 4.97 - 5.06 (m, 1H), 4.15 - 4.25 (m, 1H), 2.61 - 2.73 (m, 1H), 2.36 - 2.46 (m,

2H), 2.25 - 2.36 (m, 4H), 2.16 - 2.25 (m, 2H), 1.89 - 2.02 (m, 2H), 1.70 - 1.86 (m, 3H), 1.52 - 1.68 (m, 2H), 0.81 - 0.91 (m, 3H), 0.73 (m, 3H)

MS ES^+ 300

2.78 Example 78

(3-Chloro-4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)(cyclopentyl)methanol



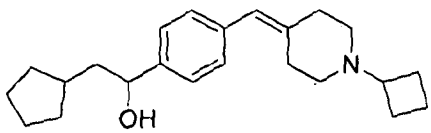
Prepared in an analogous manner to **Example 72** via **Scheme 26** starting with 4-(4-bromo-2-chlorobenzylidene)-1-cyclobutylpiperidine in step a and using cyclopentanecarbaldehyde in step b.

^1H NMR (400 MHz, DMSO-d_6) δ 7.37 (s, 1H), 7.13 - 7.28 (m, 2H), 6.23 (s, 1H), 5.19 - 5.24 (m, 1H), 4.24 - 4.32 (m, 1H), 2.63 - 2.76 (m, 1H), 2.18 - 2.40 (m, 7H), 1.92 - 2.11 (m, 3H), 1.73 - 1.87 (m, 2H), 1.36 - 1.68 (m, 8H), 1.15 - 1.36 (m, 3H)

MS ES^+ 360

2.79 Example 79

1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)-2-cyclopentylethanol



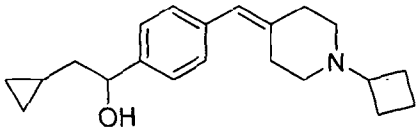
Prepared in an analogous manner to **Example 72** via **Scheme 26** starting with bromo{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}magnesium (**Int 52**) and using cyclopentylacetaldehyde.

^1H NMR (300MHz, $CDCl_3$) δ 7.27 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 6.24 (s, 1H), 4.65 (t, J = 5.5 Hz, 1H), 2.67 (m, 1H), 2.49 (m, 2H), 2.40 (m, 6H), 2.27 (m, 2H), 1.99-1.40 (m, 16H)

MS ES^+ 340

2.80 Example 80

1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)-2-cyclopropylethanol



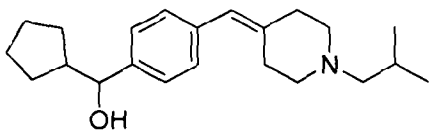
Prepared in an analogous manner to **Example 72** via **Scheme 26** starting with bromo{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}magnesium (**Int 52**) and using cyclopropylacetaldehyde.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 - 7.31 (m, 2H), 7.10 - 7.17 (m, 2H), 6.27 (br. s., 1H), 5.06 - 5.12 (m, 1H), 4.51 - 4.58 (m, 1H), 3.32 (s, 1H), 2.68 (br. s., 1H), 2.41 (br. s., 2H), 2.31 (br. s., 4H), 2.19 - 2.27 (m, 1H), 1.97 (br. s., 2H), 1.72 - 1.89 (m, 2H), 1.55 - 1.70 (m, 3H), 1.27 - 1.37 (m, 1H), 0.63 - 0.75 (m, 1H), 0.28 - 0.43 (m, 2H), -0.07 - 0.08 (m, 2H)

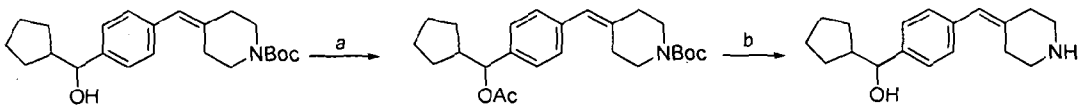
MS ES$^+$ 312

2.81 Example 81

Cyclopentyl(4-{[1-(2-methylpropyl)piperidin-4-ylidene]methyl}phenyl)methanol



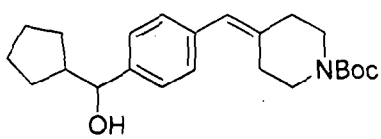
Scheme 27



Reagents and conditions: a) Ac_2O, DMAP, pyridine; b) TFA, DCM

Step a **Intermediate 53**

tert-Butyl 4-{4-[cyclopentyl(hydroxy)methyl]benzylidene}piperidine-1-carboxylate



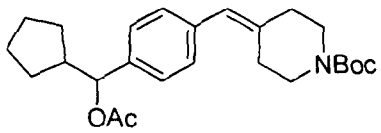
To a solution of *tert*-butyl 4-(4-bromobenzylidene)piperidine-1-carboxylate (**Int 3**) (5 g, 14.2 mmol) in THF (200 ml) at -78 °C was added n-BuLi (9.3 ml, 2.3 M in hexanes, 21.3 mmol) and the reaction stirred at this temperature for 10 min. A solution of cyclopentanecarbaldehyde (1.7 g, 17 mmol) in THF (10 ml) was added and the reaction stirred for 3 h whilst allowing to warm to r.t. The reaction was quenched *via* the addition of 20 % aq. citric acid and extracted twice with EtOAc. The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (SiO_2; 5/1 hexane/EtOAc) to give tert-butyl 4-{4-[cyclopentyl(hydroxy)methyl]benzylidene}piperidine-1-carboxylate as a clear oil (3.78 g, 59 %).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.29 (d, 2H), 7.15 (d, 2H), 6.33 (s, 1H), 4.39 (d, 1H), 3.50 (t, 2H), 3.40 (t, 2H), 2.48 (t, 2H), 2.32 (t, 2H), 2.20 (m, 1H), 1.90 (m, 2H), 1.60-1.40 (m, 16H).

MS ES^+ 339

Step b **Intermediate 54**

tert-Butyl 4-{4-[(acetyloxy)(cyclopentyl)methyl]benzylidene}piperidine-1-carboxylate



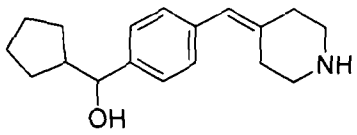
To a solution of *tert*-butyl 4-{4-[cyclopentyl(hydroxy)methyl]benzylidene}piperidine-1-carboxylate (**Int 53**) (500 mg, 1.35 mmol) in pyridine (7 ml) at r.t. was added acetic anhydride (0.14 ml, 1.48 ml) and DMAP (2 mg, cat.). The reaction was stirred at r.t. for 3 h and was then concentrated under reduced pressure. The residue was taken up in EtOAc, washed with water (x 3), dried ($MgSO_4$) and concentrated under reduced pressure to give *tert*-butyl 4-{4-[(acetyloxy)(cyclopentyl)methyl]benzylidene} piperidine-1-carboxylate (535 mg, 96 %).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.27 (d, 2H), 7.13 (d, 2H), 6.31 (s, 1H), 5.51 (d, 1H), 3.49 (t, 4H), 3.39 (t, 4H), 2.45 (t, 4H), 2.32 (t, 4H), 2.05 (s, 3H), 1.8 (m, 1H), 1.57 (m, 8H), 1.46 (s, 9H).

MS ES$^+$ 354

Step c **Intermediate 55**

Cyclopentyl[4-(piperidin-4-ylidenemethyl)phenyl]methanol



To a solution of *tert*-butyl 4-{4-[(acetyloxy)(cyclopentyl)methyl] benzylidene}piperidine-1-carboxylate (**Int 55**) (535 mg, 1.30 mmol) in DCM (10 ml) was added TFA (2 ml) and the reaction stirred at r.t. for 1.5 h. The reaction was quenched *via* the addition of aq. Na_2CO_3 and the layers were separated. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was taken up in MeOH (2 ml) and 1 M NaOH (aq., 2 ml) and the reaction stirred at r.t. for 1 h. The solvent was removed under reduced pressure and the resultant residue partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organics dried ($MgSO_4$) and concentrated under reduced pressure to give cyclopentyl[4-(piperidin-4-ylidenemethyl)phenyl]methanol as a yellow solid (256 mg, 73 %).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.28 (d, 2H), 7.16 (d, 2H), 6.26 (s, 1H), 4.38 (d, 1H), 2.95 (t, 2H), 2.83 (t, 2H), 2.45 (t, 2H), 2.32 (t, 2H), 2.22 (m, 1H).
MS ES$^+$ 272

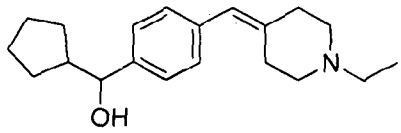
Step d **Example 81**

Prepared in an analogous manner to Intermediate 5 via step b of **Scheme 4** starting with cyclopentyl[4-(piperidin-4-ylidenemethyl)phenyl]methanol (**Int 55**) and using isobutyraldehyde.

^{1}H NMR (300MHz, $CDCl_3$) δ7.29 (d, 2H), 7.14 (d, 2H), 6.34 (d, 1H), 4.38 (d, 1H), 2.4 - 2.84 (m, 4H), 2.19 (m, 1H), 1.88 (m, 7H), 1.4 - 1.68 (m, 6H), 1.02 - 1.25 (m, 8H)
MS ES$^+$ 328

2.82 Example 82

Cyclopentyl(4-((1-ethylpiperidin-4-ylidene)methyl)phenyl)methanol

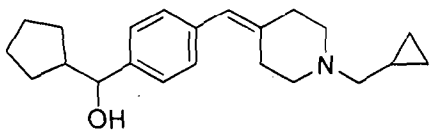


Prepared in an analogous manner to Intermediate 5 via step b of **Scheme 4** starting with cyclopentyl[4-(piperidin-4-ylidenemethyl)phenyl]methanol (**Int 55**) and using acetaldehyde.

^{1}H NMR (300MHz, $CDCl_3$) δ7.28 (d, 2H), 7.16 (d, 2H), 6.26 (s, 1H), 4.38 (d, 1H), 2.53 (m, 4H), 2.42 (m, 6H), 2.22 (m, 1H), 1.88 (m, 2H), 1.37 - 1.7 (m, 6H), 1.10 (t, 3H)
MS ES^+ 300

2.83 Example 83

Cyclopentyl(4-((1-(cyclopropylmethyl)piperidin-4-ylidene)methyl)phenyl)methanol

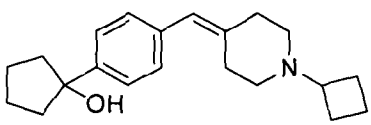


Prepared in an analogous manner to Intermediate 5 via step b of **Scheme 4** starting with cyclopentyl[4-(piperidin-4-ylidenemethyl)phenyl]methanol (**Int 55**) and using cyclopropanecarbaldehyde.

^{1}H NMR (300MHz, $CDCl_3$) δ 7.28 (d, 2H), 7.17 (d, 2H), 6.26 (s, 1H), 4.38 (d, 1H), 2.40-2.64 (m, 8H), 2.17-2.29 (m, 3H), 1.91 (s, 2H), 1.37-1.70 (m, 6H), 0.89 (m, 1H), 0.51 (q, 2H), 0.4 (q, 2H)
MS ES^+ 326

2.84 Example 84

1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)cyclopentanol

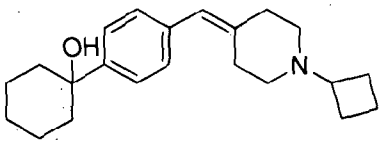


Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using cyclopentanone. (BuLi method).

^{1}H NMR (300MHz, $CDCl_3$) δ7.44 (d, 2H), 7.17 (d, 2H), 6.30 (s, 1H), 2.68 (m, 1H), 2.58 (m, 2H), 2.38 (s, 4H), 2.28 (m, 2H), 1.6-2.1 (m, 14H)
MS ES^+ 312

2.85 Example 85

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}cyclohexanol

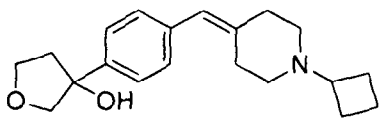


Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using cyclohexanone. (BuLi method).

^{1}H NMR (400 MHz, MeOD) δ 7.29 - 7.37 (m, 2H), 7.00 - 7.07 (m, 2H), 6.22 (s, 1H), 2.60 - 2.79 (m, 1H), 2.14 - 2.54 (m, 9H), 1.90 - 2.06 (m, 2H), 1.77 - 1.91 (m, 2H), 1.55 - 1.77 (m, 9H), 1.37 - 1.55 (m, 2H)
MS ES^+ 326

2.86 Example 86

3-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydrofuran-3-ol



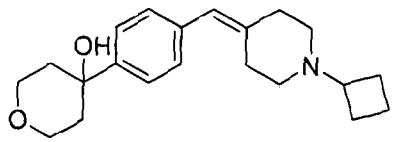
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using dihydrofuran-3(2H)-one. (BuLi method).

^{1}H NMR (400MHz, $CDCl_3$) δ7.43 (d, J = 8Hz, 2H), 7.21 (d, J = 8 Hz, 2H), 6.26 (s, 1H), 4.19 (m, 2H), 3.97 (dd, J = 9.1, 1.4 Hz, 1H), 3.90 (d, J = 9.6 Hz, 1H), 2.70 (m, 1H), 1.50-2.50 (m, 16H)

MS ES$^+$ 314

2.87 Example 87

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol

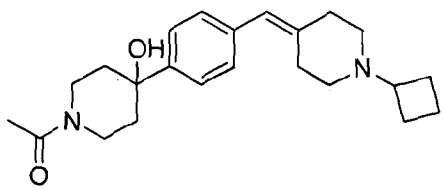


Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using tetrahydro-4H-pyran-4-one. (BuLi method).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 - 7.51 (m, 2H), 7.08 - 7.25 (m, 2H), 6.25 (s, 1H), 4.97 (br. s., 1H), 3.59 - 3.89 (m, 4H), 2.58 - 2.78 (m, 1H), 2.37 - 2.46 (m, 2H), 2.13 - 2.38 (m, 6H), 1.87 - 2.04 (m, 4H), 1.71 - 1.87 (m, 2H), 1.44 - 1.70 (m, 4H)
MS ES$^+$ 328

2.88 Example 88

1-(4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxypiperidin-1-yl)ethanone

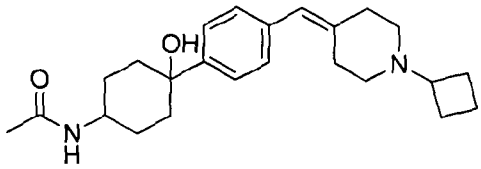


Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 1-acetylpiperidine-4-one. (BuLi method).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 - 7.51 (m, 2H), 7.07 - 7.28 (m, 2H), 6.26 (br. s., 1H), 5.07 (br. s., 1H), 4.21 - 4.39 (m, 1H), 3.58 - 3.78 (m, 1H), 3.37 - 3.53 (m, 1H), 2.81 - 2.99 (m, 1H), 2.57 - 2.79 (m, 1H), 2.37 - 2.47 (m, 2H), 2.26 - 2.38 (m, 4H), 2.14 - 2.27 (m, 2H), 2.03 (s, 3H), 1.93 - 1.99 (m, 2H), 1.54 - 1.93 (m, 8H)
MS ES$^+$ 369

2.89 Example 89

N-(4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxycyclohexyl)acetamide



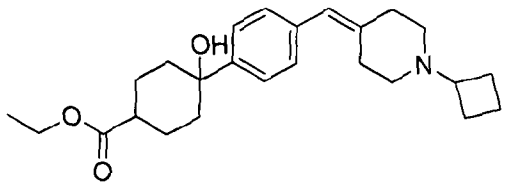
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using N-(4-oxocyclohexyl)acetamide. (BuLi method). A mixture of ring isomers was obtained.

^{1}H NMR (400 MHz, MeOD) δ 7.40 - 7.57 (m, 2H), 7.11 - 7.25 (m, 2H), 6.34 (s, 1H), 3.64 - 4.05 (m, 1H), 2.74 - 2.90 (m, 1H), 2.32 - 2.62 (m, 8H), 2.01 - 2.33 (m, 3H), 1.88 - 2.02 (m, 8H), 1.66 - 1.88 (m, 8H)

MS ES$^+$ 383

2.90 Example 90

Ethyl 4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxycyclohexanecarboxylate



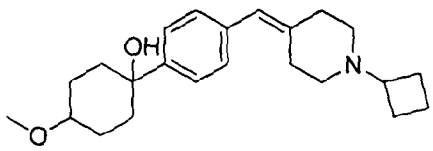
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using ethyl 4-oxocyclohexanecarboxylate. (BuLi method). A mixture of ring isomers was obtained.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.51 (m, 2H), 7.15 - 7.26 (m, 2H), 6.28 (s, 1H), 4.10 - 4.26 (m, 2H), 2.60 - 2.84 (m, 1H), 2.48 - 2.61 (m, 2H), 2.15 - 2.48 (m, 7H), 1.80 - 2.13 (m, 11H), 1.57 - 1.80 (m, 3H), 1.22 - 1.38 (m, 3H)

MS ES$^+$ 398

2.91 Example 91

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methoxycyclohexanol



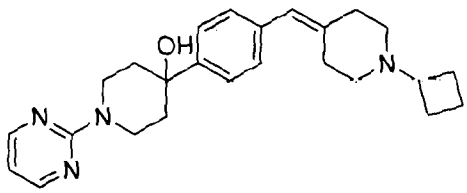
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 4-methoxycyclohexanone. (BuLi method). One ring isomer was isolated.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.08 Hz, 2H), 7.21 (d, J = 8.08 Hz, 2H), 6.28 (s, 1H), 3.42 (s, 3H), 3.21 - 3.33 (m, 1H), 2.65 - 2.79 (m, 1H), 2.50 - 2.62 (m, 2H), 2.35 - 2.47 (m, 4H), 2.24 - 2.35 (m, 2H), 1.52 - 2.14 (m, 15H)

MS ES^+ 357

2.92 Example 92

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(pyrimidin-2-yl)piperidin-4-ol



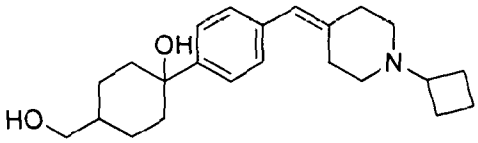
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 1-(pyrimidin-2-yl)piperidin-4-one. (BuLi method).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 4.55 Hz, 2H), 7.42 (d, J = 8.34 Hz, 2H), 7.14 (d, J = 8.34 Hz, 2H), 6.58 (t, J = 4.67 Hz, 1H), 6.24 (s, 1H), 5.09 (br. s., 1H), 4.48 - 4.65 (m, 2H), 3.16 - 3.39 (m, 2H), 2.60 - 2.76 (m, 1H), 2.36 - 2.45 (m, 2H), 2.24 - 2.37 (m, 4H), 2.13 - 2.25 (m, 2H), 1.90 - 2.04 (m, 2H), 1.72 - 1.90 (m, 4H), 1.52 - 1.72 (m, 4H)

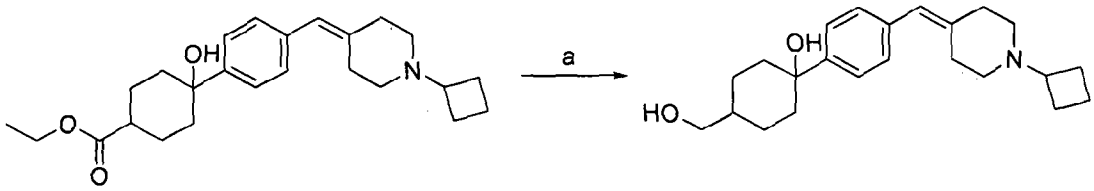
MS ES^+ 405

2.93 Example 93

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-(hydroxymethyl)cyclohexanol



Scheme 28



Reagents and conditions: a) $LiAlH_4$, THF, 0 °C to r.t.

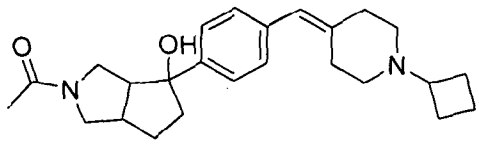
To a stirred solution of ethyl 4-(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)-4-hydroxycyclohexanecarboxylate (**Ex 90**) (81 mg, 0.204 mmol) in dry THF (10 ml) at 0 °C under an atmosphere of nitrogen was added dropwise $LiAlH_4$ (1M in THF, 407 µL, 0.407 mmol). The reaction was stirred at 0 °C for 30 minutes, then allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched with water (10 ml). The organics were extracted using EtOAc (2 x 50 ml). The combined organics were washed with brine (25 ml), dried over $MgSO_4$, filtered and concentrated to give a colourless oil. Purification via column chromatography (NH silica, 0-100 % EtOAc in petrol) afforded 1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-(hydroxymethyl)cyclohexanol as a white solid (39 mg, 51 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 - 7.52 (m, 2H), 7.03 - 7.21 (m, 2H), 6.24 (s, 1H), 4.53 - 4.73 (m, 1H), 4.27 - 4.46 (m, 1H), 3.21 - 3.28 (m, 2H), 2.60 - 2.75 (m, 1H), 2.36 - 2.46 (m, 2H), 2.25 - 2.36 (m, 4H), 2.16 - 2.27 (m, 2H), 1.73 - 2.10 (m, 5H), 1.13 - 1.73 (m, 10H)

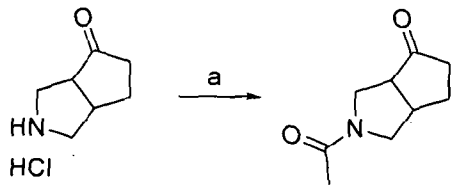
MS ES^+ 356

2.94 Example 94

1-[4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxyhexahydrocyclopenta[c]pyrrol-2(1H)-yl]ethanone



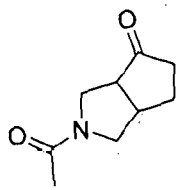
Scheme 29



Reagents and conditions: a) AcCl, Na_2CO_3 (aq.), DCM

Step a **Intermediate 56**

2-Acetylhexahydrocyclopenta[c]pyrrol-4(1H)-one



To a solution of hexahydrocyclopenta[c]pyrrol-4(5H)-one hydrochloride (2.9 g, 17.8 mmol) in sodium carbonate (aq.) (35.5 ml, 71.0 mmol) at 0 °C under an atmosphere of nitrogen was added dropwise a solution of acetyl chloride (1.22 ml, 17.8 mmol) in dry DCM (36 ml). The reaction was then allowed to warm to room temperature and stirred for 2 h. The reaction mixture was separated and the organic layer was washed with brine (50 ml), dried over $MgSO_4$ and concentrated to give an orange oil (1.83 g, 62 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 - 3.87 (m, 3H), 3.18 - 3.27 (m, 1H), 3.01 - 3.17 (m, 1H), 2.75 - 2.86 (m, 1H), 2.30 - 2.48 (m, 2H), 2.13 - 2.30 (m, 1H), 2.01 - 2.07 (m, 3H), 1.79 - 1.96 (m, 1H)

Step b **Example 94**

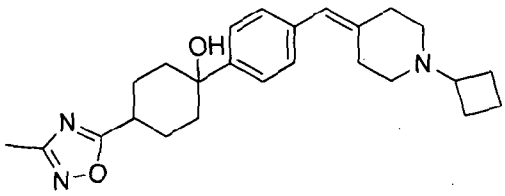
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 2-acetylhexahydrocyclopenta[c]pyrrol-4(1H)-one (**Int 56**). (BuLi method).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 - 7.47 (m, 2H), 7.17 - 7.27 (m, 2H), 6.17 - 6.37 (m, 1H), 3.68 - 3.88 (m, 2H), 3.28 - 3.60 (m, 2H), 2.86 - 3.16 (m, 2H), 2.64 - 2.82 (m, 1H), 2.48 - 2.61 (m, 2H), 2.37 - 2.49 (m, 4H), 2.27 - 2.39 (m, 2H), 2.11 - 2.26 (m, 2H), 2.01 - 2.12 (m, 6H), 1.80 - 2.00 (m, 3H), 1.64 - 1.79 (m, 2H)

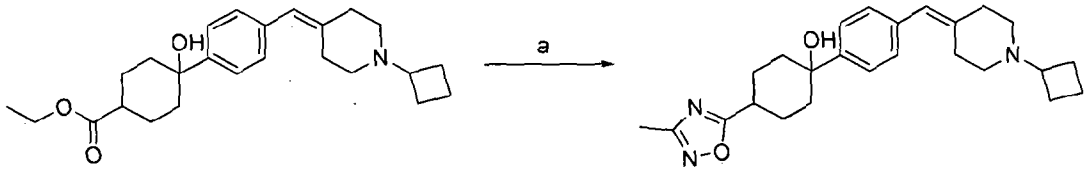
MS ES^+ 395

2.95 Example 95

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-(3-methyl-1,2,4-oxadiazol-5-yl)cyclohexanol



Scheme 30



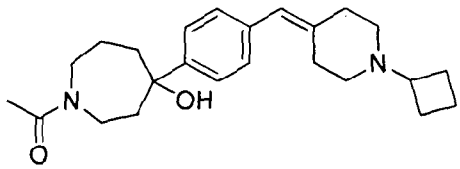
Reagents and conditions: a) Acetamidoxime, NaH, THF

Prepared in an analogous manner to **Example 10** starting with ethyl 4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxycyclohexanecarboxylate (**Example 90**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.53 (m, 2H), 7.14 - 7.25 (m, 2H), 6.19 - 6.35 (m, 1H), 2.90 - 3.37 (m, 1H), 2.64 - 2.84 (m, 1H), 2.49 - 2.63 (m, 2H), 2.37 - 2.51 (m, 6H), 2.16 - 2.38 (m, 5H), 1.88 - 2.16 (m, 7H), 1.78 - 1.88 (m, 1H), 1.57 - 1.78 (m, 5H)
MS ES^+ 408

2.96 Example 96

1-(4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxyazepan-1-yl)ethanone



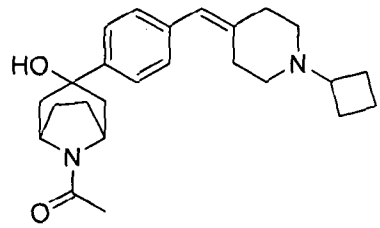
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 1-acetylazepan-4-one (CAS 50492-23-4).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.45 (m, 2H), 7.16 - 7.24 (m, 2H), 6.23 - 6.34 (m, 1H), 3.85 - 4.21 (m, 1H), 3.48 - 3.74 (m, 2H), 3.25 - 3.47 (m, 1H), 2.65 - 2.81 (m, 1H), 2.48 - 2.62 (m, 2H), 2.37 - 2.47 (m, 4H), 2.26 - 2.35 (m, 2H), 2.12 - 2.18 (m, 3H), 1.80 - 2.13 (m, 9H), 1.47 - 1.78 (m, 4H)

MS ES^+ 383

2.97 Example 97

1-(3-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl)ethanone



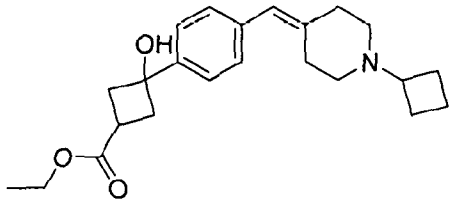
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 8-acetyl-8-azabicyclo[3.2.1]octan-3-one (CAS 56880-02-5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 - 7.40 (m, 2H), 7.14 - 7.23 (m, 2H), 6.18 - 6.33 (m, 1H), 4.80 - 4.89 (m, 1H), 4.19 - 4.31 (m, 1H), 2.66 - 2.80 (m, 1H), 2.49 - 2.58 (m, 3H), 2.36 - 2.48 (m, 5H), 2.26 - 2.38 (m, 3H), 2.15 - 2.26 (m, 1H), 2.13 (s, 3H), 2.00 - 2.10 (m, 4H), 1.84 - 1.99 (m, 4H), 1.63 - 1.81 (m, 2H), 1.56 - 1.62 (m, 1H)

MS ES^+ 395

2.98 Example 98

Ethyl 3-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-3-hydroxycyclobutanecarboxylate



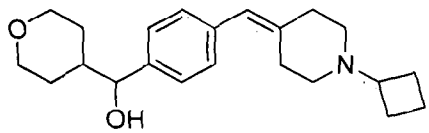
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using ethyl 3-oxocyclobutanecarboxylate (CAS 87121-89-9). A mixture of ring isomers was obtained.

^{1}H NMR (400 MHz, MeOD) δ 7.35 - 7.42 (m, 2H), 7.06 - 7.16 (m, 2H), 6.20 - 6.30 (m, 1H), 3.98 - 4.11 (m, 2H), 2.61 - 2.82 (m, 4H), 2.21 - 2.58 (m, 10H), 1.94 - 2.06 (m, 2H), 1.77 - 1.94 (m, 2H), 1.56 - 1.71 (m, 2H), 1.16 (m, 3H)

MS ES$^+$ 370

2.99 Example 99

{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}(tetrahydro-2H-pyran-4-yl)methanol



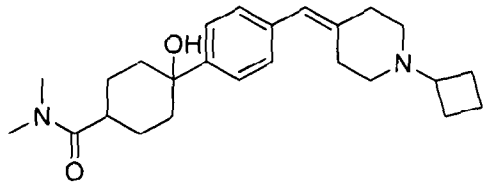
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using tetrahydro-2H-pyran-4-carbaldehyde.

^{1}H NMR (400 MHz, MeOD) δ 7.27 (s, 2H), 7.19 (s, 2H), 6.29 - 6.38 (m, 1H), 4.24 - 4.35 (m, 1H), 3.93 - 4.06 (m, 1H), 3.81 - 3.94 (m, 1H), 3.36 - 3.44 (m, 1H), 3.34 - 3.36 (m, 1H), 2.71 - 2.85 (m, 1H), 2.49 - 2.56 (m, 2H), 2.39 - 2.50 (m, 4H), 2.30 - 2.39 (m, 2H), 2.03 - 2.15 (m, 2H), 1.78 - 2.02 (m, 4H), 1.67 - 1.78 (m, 2H), 1.25 - 1.48 (m, 2H), 1.13 - 1.24 (m, 1H)

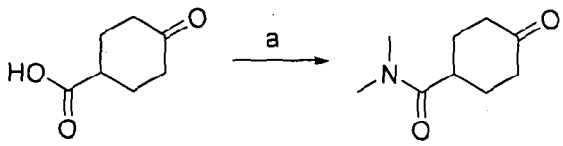
MS ES$^+$ 342

2.100 Example 100

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxy-N,N-dimethylcyclohexanecarboxamide



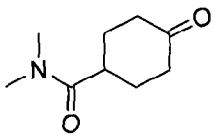
Scheme 31



Reagents and conditions: a) $Me_2NH.HCl$, EDC, HOAt, DIPEA, DCM

Step a **Intermediate 57**

N,N-dimethyl-4-oxocyclohexanecarboxamide



To a stirred solution of 4-oxocyclohexanecarboxylic acid (1 g, 7.03 mmol) in dry DCM (24 ml) was added dimethylamine hydrochloride (1.72 g, 21.1 mmol), HOAt (1.436 g, 10.6 mmol), EDC (2.02 g, 10.6 mmol) and DIPEA (3.69 ml, 21.1 mmol). The solution was stirred at r.t. for 17 h. The reaction mxiture was partitioned between DCM (50 ml) and water (25 ml). The organics were further extracted with DCM (50 ml) and the combined organics washed with brine (25 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified by SCX ion-exchange chromatography, eluting with MeOH and concentrated under reduced pressure to give a colourless oil. The crude oil was further purified by column chromatography (SiO_2, 0-100% EtOAc in petrol then 0-15% MeOH in EtOAc) to give N,N-dimethyl-4-oxocyclohexanecarboxamide as a colourless oil (0.693 g, 55%).

^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.14 (s, 3H), 3.00 (s, 3H), 2.92 - 2.98 (m, 1H), 2.53 - 2.63 (m, 2H), 2.30 - 2.45 (m, 2H), 2.01 - 2.15 (m, 4H)

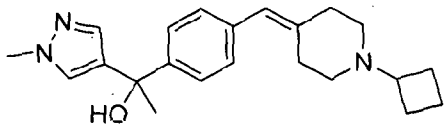
Step b **Example 100**

Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using N,N-dimethyl-4-oxocyclohexanecarboxamide (**Int 57**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.53 (m, 2H), 7.12 - 7.25 (m, 2H), 6.15 - 6.34 (m, 1H), 3.11 (s, 3H), 2.99 (s, 3H), 2.66 - 2.78 (m, 1H), 2.50 - 2.66 (m, 3H), 2.37 - 2.47 (m, 4H), 2.25 - 2.36 (m, 2H), 2.00 - 2.19 (m, 4H), 1.82 - 2.00 (m, 6H), 1.63 - 1.81 (m, 5H)
MS ES^+ 398

2.101 Example 101

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(1-methyl-1H-pyrazol-4-yl)ethanol

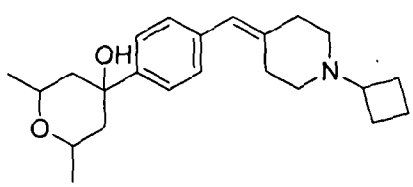


Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 1-(1-methyl-1H-pyrazol-4-yl)ethanone.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.47 (m, 3H), 7.15 - 7.26 (m, 3H), 6.20 - 6.36 (m, 1H), 3.87 (s, 3H), 2.65 - 2.79 (m, 1H), 2.48 - 2.63 (m, 2H), 2.36 - 2.48 (m, 4H), 2.25 - 2.36 (m, 2H), 2.01 - 2.16 (m, 3H), 1.86 - 2.00 (m, 5H), 1.55 - 1.85 (m, 2H)
MS ES^+ 352

2.102 and 2.103 Examples 102 and 103

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-2,6-dimethyltetrahydro-2H-pyran-4-ol



Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 2,6-dimethyltetrahydro-4H-pyran-4-one. Two isomers were isolated, isomer A and isomer B:

ISOMER A

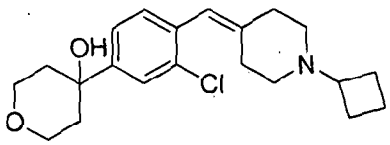
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.50 (m, 2H), 7.15 - 7.26 (m, 2H), 6.21 - 6.32 (m, 1H), 3.38 - 3.58 (m, 2H), 2.63 - 2.80 (m, 1H), 2.50 - 2.60 (m, 2H), 2.37 - 2.50 (m, 6H), 2.25 - 2.36 (m, 2H), 2.01 - 2.13 (m, 2H), 1.85 - 2.01 (m, 2H), 1.53 - 1.85 (m, 5H), 1.16 - 1.33 (m, 6H)
MS ES^+ 357

ISOMER B

^{1}H NMR (400 MHz, $CDCl_3$) δ?7.38 - 7.51 (m, 2H), 7.17 - 7.25 (m, 2H), 6.15 - 6.34 (m, 1H), 3.96 - 4.11 (m, 2H), 2.66 - 2.82 (m, 1H), 2.48 - 2.63 (m, 2H), 2.36 - 2.48 (m, 4H), 2.22 - 2.36 (m, 2H), 2.00 - 2.14 (m, 2H), 1.84 - 2.00 (m, 2H), 1.63 - 1.81 (m, 5H), 1.48 - 1.63 (m, 2H), 1.18 - 1.33 (m, 6H)
MS ES^+ 357

2.104 Example 104

4-{3-Chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol



Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromo-2-chlorobenzylidene)-1-cyclobutylpiperidine (**Int 8**) and using tetrahydro-4H-pyran-4-one.

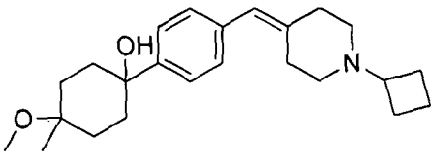
^{1}H NMR (400 MHz, MeOD) δ 7.55 (d, J =1.52 Hz, 1H), 7.39 (dd, J =8.08, 1.52 Hz, 1H), 7.22 (d, J =8.08 Hz, 1H), 6.33 (s, 1H), 3.89 - 4.01 (m, 2H), 3.77 - 3.88 (m, 2H),

2.67 - 2.98 (m, 1H), 2.44 - 2.63 (m, 4H), 2.29 - 2.44 (m, 4H), 2.04 - 2.19 (m, 4H), 1.88 - 2.04 (m, 2H), 1.70 - 1.83 (m, 2H), 1.59 - 1.68 (m, 2H)

MS ES^+ 363

2.105 Example 105

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methoxy-4-methylcyclohexanol



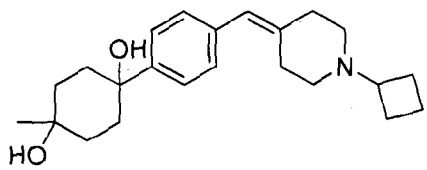
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 4-methoxy-4-methylcyclohexanone (CAS 23438-15-5).

^1H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.53 (m, 2H), 7.13 - 7.25 (m, 2H), 6.19 - 6.32 (m, 1H), 3.30 (s, 3H), 2.64 - 2.79 (m, 1H), 2.50 - 2.60 (m, 2H), 2.37 - 2.46 (m, 4H), 2.27 - 2.37 (m, 2H), 1.85 - 2.12 (m, 10H), 1.62 - 1.82 (m, 2H), 1.47 - 1.62 (m, 5H)

MS ES^+ 370

2.106 Example 106

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methylcyclohexane-1,4-diol



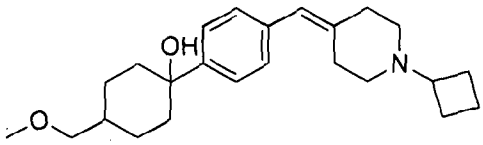
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 4-hydroxy-4-methylcyclohexanone.

^1H NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.42 (m, 2H), 7.09 - 7.16 (m, 2H), 6.06 - 6.24 (m, 1H), 2.55 - 2.74 (m, 1H), 2.40 - 2.53 (m, 2H), 2.27 - 2.38 (m, 4H), 2.16 - 2.27 (m, 2H), 1.74 - 2.06 (m, 10H), 1.40 - 1.74 (m, 8H), 1.24 - 1.34 (m, 1H)

MS ES^+ 356

2.107 and 2.108 Examples 107 and 108

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-(methoxymethyl)cyclohexanol



Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 4-(methoxymethyl)cyclohexanone (CAS 17159-84-1). Two isomers were separated, Isomer A and Isomer B:

ISOMER A

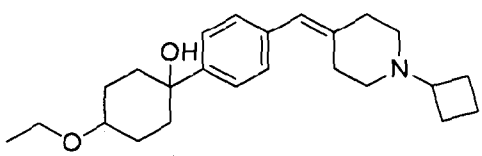
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 - 7.50 (m, 2H), 7.05 - 7.26 (m, 2H), 6.05 - 6.31 (m, 1H), 4.70 (s, 1H), 3.31 (s, 3H), 3.26 (d, J = 6.32 Hz, 2H), 2.61 - 2.77 (m, 1H), 2.37 - 2.46 (m, 2H), 2.25 - 2.36 (m, 4H), 2.14 - 2.25 (m, 2H), 1.89 - 2.11 (m, 4H), 1.70 - 1.88 (m, 5H), 1.55 - 1.70 (m, 2H), 1.40 - 1.55 (m, 2H), 1.12 - 1.34 (m, 2H)
MS ES$^+$ 370

ISOMER B

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 - 7.50 (m, 2H), 6.92 - 7.18 (m, 2H), 6.16 - 6.31 (m, 1H), 4.62 (s, 1H), 3.25 (s, 3H), 3.19 (d, J = 6.32 Hz, 2H), 2.59 - 2.74 (m, 1H), 2.37 - 2.45 (m, 2H), 2.26 - 2.37 (m, 4H), 2.11 - 2.26 (m, 2H), 1.88 - 2.03 (m, 2H), 1.36 - 1.88 (m, 13H)
MS ES$^+$ 370

2.109 Example 109

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-ethoxycyclohexanol



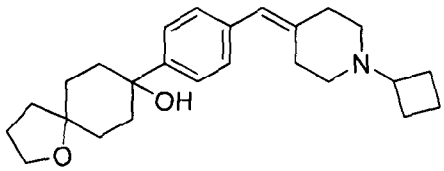
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 4-ethoxycyclohexanone.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.51 (m, 2H), 7.14 - 7.24 (m, 2H), 6.19 - 6.35 (m, 1H), 3.59 (q, J = 7.07 Hz, 2H), 3.27 - 3.42 (m, 1H), 2.63 - 2.81 (m, 1H), 2.48 - 2.62 (m, 2H), 2.36 - 2.47 (m, 4H), 2.23 - 2.36 (m, 2H), 1.62 - 2.12 (m, 14H), 1.26 (t, J = 6.95 Hz, 3H)

MS ES^+ 370

2.110 Example 110

8-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-oxaspiro[4.5]decan-8-ol



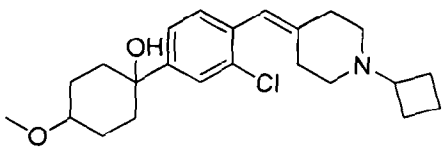
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 1-oxaspiro[4.5]decan-8-one

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 - 7.49 (m, 2H), 7.00 - 7.20 (m, 2H), 6.16 - 6.31 (m, 1H), 4.74 (br. s., 1H), 3.71 (t, J = 6.57 Hz, 2H), 2.56 - 2.79 (m, 1H), 2.36 - 2.45 (m, 2H), 2.24 - 2.36 (m, 4H), 2.14 - 2.26 (m, 2H), 1.73 - 2.06 (m, 12H), 1.52 - 1.71 (m, 4H), 1.32 - 1.45 (m, 2H)

MS ES^+ 383

2.111 and 2.112 Examples 111 and 112

1-{3-Chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methoxycyclohexanol



Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromo-2-chlorobenzylidene)-1-cyclobutylpiperidine (**Int 8**) and using 4-methoxycyclohexanone. Two isomers were separated, Isomer A and Isomer B:

ISOMER A

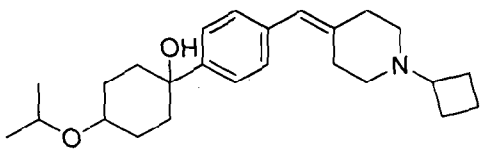
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (d, J =1.52 Hz, 2 H), 7.36 (dd, J = 8.08, 1.26 Hz, 1 H), 7.19 (d, J = 8.08 Hz, 1 H), 6.21 (s, 1 H), 4.93 (s, 1 H), 3.26 (s, 3 H), 3.15 - 3.24 (m, 1 H), 2.60 - 2.75 (m, 1 H), 2.30 - 2.39 (m, 4 H), 2.16 - 2.29 (m, 4 H), 1.88 - 2.02 (m, 2 H), 1.69 - 1.88 (m, 6 H), 1.48 - 1.69 (m, 6 H)
MS ES$^+$ 390, 392

ISOMER B

^{1}H NMR (400 MHz, MeOD) δ 7.52 (d, J =1.52 Hz, 1 H), 7.34 (dd, J = 8.08, 1.77 Hz, 1 H), 7.19 (d, J = 8.08 Hz, 1 H), 6.31 (s, 1 H), 3.50 - 3.59 (m, 1 H), 3.38 (s, 3 H), 2.78 (d, J = 8.59 Hz, 1 H), 2.42 - 2.53 (m, 4 H), 2.30 - 2.42 (m, 4 H), 2.03 - 2.16 (m, 4 H), 1.88 - 2.03 (m, 4 H), 1.79 - 1.88 (m, 2 H), 1.66 - 1.79 (m, 2 H), 1.47 - 1.60 (m, 2 H)
MS ES$^+$ 390, 392

2.113 and 2.114 Examples 113 and 114

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-(propan-2-yloxy)cyclohexanol



Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 4-(propan-2-yloxy)cyclohexanone (CAS 69697-46-7). The 2 ring isomers were separated and isolated.

ISOMER A

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 - 7.48 (m, 2H), 7.03 - 7.19 (m, 2H), 6.10 - 6.30 (m, 1H), 4.71 (br. s., 1H), 3.64 - 3.85 (m, 1H), 3.33 - 3.46 (m, 1H), 2.59 - 2.78 (m, 1H),

2.36 - 2.46 (m, 2H), 2.25 - 2.36 (m, 4H), 2.13 - 2.25 (m, 2H), 1.88 - 2.05 (m, 2H), 1.54 - 1.86 (m, 12H), 1.08 (d, J = 6.06 Hz, 6H)

MS ES^+ 385

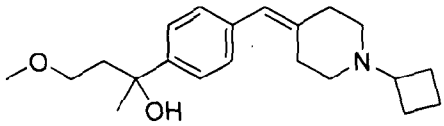
ISOMER B

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 - 7.49 (m, 2H), 7.06 - 7.18 (m, 2H), 6.12 - 6.34 (m, 1H), 4.62 - 4.75 (m, 1H), 3.53 - 3.80 (m, 1H), 3.36 - 3.46 (m, 1H), 2.58 - 2.76 (m, 1H), 2.37 - 2.45 (m, 2H), 2.26 - 2.36 (m, 4H), 2.13 - 2.26 (m, 2H), 1.88 - 2.05 (m, 2H), 1.50 - 1.88 (m, 12H), 0.92 - 1.19 (m, 6H)

MS ES^+ 385

2.115 Example 115

2-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methoxybutan-2-ol



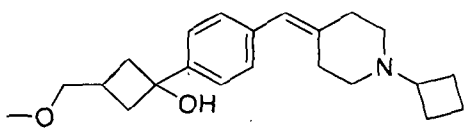
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 4-methoxybutan-2-one.

^{1}H NMR (400MHz, CD_2Cl_2) δ 7.39 (d, 2H), 7.21 (d, 2H), 6.30 (s, 1H), 3.98 (s, 1H), 3.53 (quint, 1H), 3.20-3.33 (m, 4H), 2.66-2.80 (m, 1H), 2.48-2.60 (m, 2H), 2.35-2.46 (m, 4H), 2.22-2.35 (m, 2H), 1.99-2.18 (m, 4H), 1.81-1.97 (m, 2H), 1.57-1.81 (m, 2H), 1.51 (s, 3H).

MS ES^+ 330

2.116 Example 116

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-3-(methoxymethyl)cyclobutanol



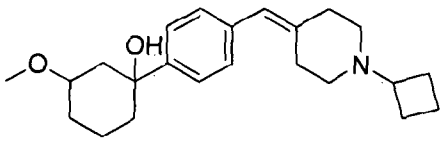
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 3-(methoxymethyl)cyclobutanone (CAS 1068160-23-5). A mixture of ring isomers was obtained.

^{1}H NMR (400 MHz, DMSO-d_6) δ7.31 - 7.49 (m, 2H), 7.10 - 7.22 (m, 2H), 6.22 - 6.28 (m, 1H), 5.43 (s, 1H), 3.37 - 3.46 (m, 2H), 3.25 (s, 3H), 2.60 - 2.82 (m, 2H), 2.37 - 2.47 (m, 3H), 2.31 (s, 4H), 2.09 - 2.27 (m, 4H), 1.88 - 2.08 (m, 3H), 1.71 - 1.86 (m, 2H), 1.62 (m, 2H)

MS ES$^+$ 342

2.117 and 2.118 Examples 117 and 118

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-3-methoxycyclohexanol



Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 3-methoxycyclohexanone. The 2 ring isomers were separated and isolated.

ISOMER A

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 - 7.51 (m, 2H), 7.07 - 7.23 (m, 2H), 6.16 - 6.30 (m, 1H), 4.78 (s, 1H), 3.37 - 3.46 (m, 1H), 3.27 (s, 3H), 2.61 - 2.77 (m, 1H), 2.38 - 2.47 (m, 2H), 2.26 - 2.38 (m, 4H), 2.12 - 2.26 (m, 3H), 1.88 - 2.10 (m, 3H), 1.48 - 1.89 (m, 9H), 1.18 - 1.40 (m, 1H)

MS ES$^+$ 357

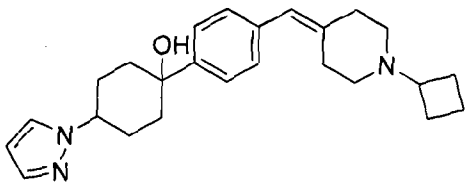
ISOMER B

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 - 7.54 (m, 2H), 7.07 - 7.21 (m, 2H), 6.09 - 6.34 (m, 1H), 4.79 (s, 1H), 3.43 - 3.63 (m, 1H), 3.23 (s, 3H), 2.60 - 2.74 (m, 1H), 2.36 - 2.46 (m, 2H), 2.25 - 2.36 (m, 4H), 2.14 - 2.25 (m, 2H), 1.89 - 2.12 (m, 4H), 1.50 - 1.87 (m, 8H), 1.35 - 1.50 (m, 1H), 0.99 - 1.22 (m, 1H)

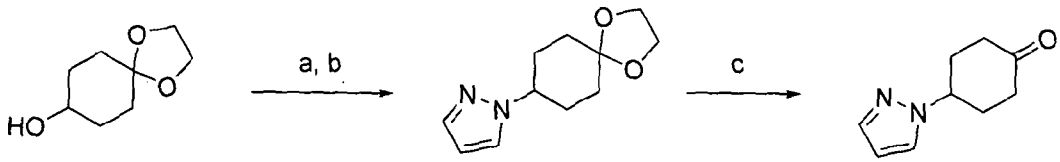
MS ES$^+$ 357

2.119 Example 119

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-(1H-pyrazol-1-yl)cyclohexanol



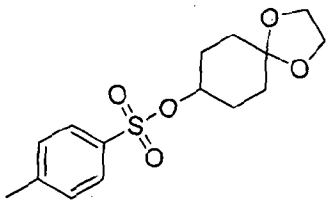
Scheme 32



Reagents and conditions: a) TsCl, pyridine; b) NaH, 1H-pyrazole, DMF, 60 °C; c) HCl, THF

Step a **Intermediate 58**

1,4-Dioxaspiro[4.5]dec-8-yl 4-methylbenzenesulfonate

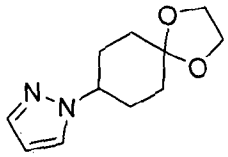


A solution of 1,4-dioxaspiro[4.5]decan-8-ol (1.00 g, 6.32 mmol) in pyridine (10 ml) was treated with 4-methylbenzenesulfonyl chloride (1.45 g, 7.59 mmol) and the reaction mixture stirred at r.t. under nitrogen for 18 h. The reaction mixture was quenched with brine and extracted with EtOAc (x2). The combined organics were washed with 0.5 M HCl, sat. sodium bicarbonate and brine (20 ml), dried (hydrophobic frit) and concentrated under reduced pressure to give a clear liquid. The crude product was purified by column chromatography (KPNH, 0-50 % EtOAc in petrol) to give the desired product as a clear liquid, which crystallised upon standing to give a white solid (1.85 g, 94 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 - 7.86 (m, 2H), 7.41 - 7.53 (m, 2H), 4.56 - 4.67 (m, 1H), 3.76 - 3.88 (m, 4H), 2.42 (s, 3H), 1.45 - 1.75 (m, 8H)

Step b **Intermediate 59**

1-(1,4-Dioxaspiro[4.5]dec-8-yl)-1H-pyrazole

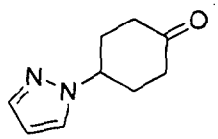


To a mixture of sodium hydride (60% dispersion in mineral oil, 70 mg, 1.76 mmol) in DMF (5 ml) at 0° C was added 1H-pyrazole (109 mg, 1.60 mmol) and the reaction mixture stirred under nitrogen for 30 min. 1,4-Dioxaspiro[4.5]decan-8-yl 4-methylbenzenesulfonate (**Int 58**) (500 mg, 1.60 mmol) was added and the reaction mixture stirred at 0° C for 10 min then heated to 60° C for 5 h. The reaction mixture was cooled, quenched with water and partitioned between EtOAc and water. The organic layer separated, washed with brine, dried (hydrophobic frit) and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 0-100 % EtOAc in petrol) to give 1-(1,4-dioxaspiro[4.5]dec-8-yl)-1H-pyrazole as a white solid (112 mg, 34 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 - 7.77 (m, 1H), 7.35 - 7.45 (m, 1H), 6.13 - 6.27 (m, 1H), 4.17 - 4.33 (m, 1H), 3.80 - 3.94 (m, 4H), 1.89 - 2.05 (m, 4H), 1.59 - 1.85 (m, 4H)

Step c **Intermediate 60**

4-(1H-Pyrazol-1-yl)cyclohexanone



A solution of 1-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-pyrazole (**Int 59**) (110 mg, 0.528 mmol), HCl (5 M, 0.5 ml, 2.50 mmol) and THF (2 ml) was stirred at room temperature for 20 h. The mixture was quenched with water, extracted with EtOAc (x 3), and the combined organics dried (hydrophobic frit) and concentrated under reduced pressure to give 4-(1H-pyrazol-1-yl)cyclohexanone (82 mg, 95 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.51 (m, 2H), 6.17 - 6.27 (m, 1H), 4.52 - 4.65 (m, 1H), 2.45 - 2.58 (m, 3H), 2.33 - 2.45 (m, 2H), 2.19 - 2.33 (m, 2H), 1.96 - 2.14 (m, 1H)

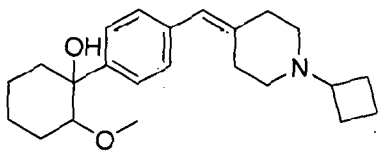
Step d **Example 119**

Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 4-(1H-pyrazol-1-yl)cyclohexanone (**Int 60**).

^{1}H NMR (400MHz, DMSO-d_6) δ 7.75 (d, 1H), 7.48 (d, 2H), 7.44 (s, 1H), 7.15 (d, 2H), 6.25 (d, 2H), 4.92 (s, 1H), 4.22 - 4.35 (m, 1H), 2.60 - 2.73 (m, 1H), 2.38 - 2.46 (m, 2H), 2.27-2.36 (m, 4H), 2.13 - 2.27 (m, 4H), 1.70 - 2.05 (m, 10H), 1.53 - 1.68 (m, 2H).
MS ES^+ 392

2.120 Example 120

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-2-methoxycyclohexanol

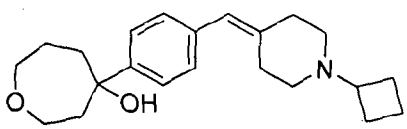


Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 2-methoxycyclohexanone.

^{1}H NMR (400 MHz, MeOD) δ 7.50 (d, J = 8.34 Hz, 2H), 7.14 (d, J = 8.34 Hz, 2H), 6.33 (s, 1H), 3.25 - 3.29 (m, 1H) 2.99 (s, 3H), 2.73 - 2.87 (m, 1H), 2.23 - 2.61 (m, 9H), 1.36 - 2.02 (m, 11H)
MS ES^+ 356

2.121 and 2.120 Examples 121 and 122

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}oxepan-4-ol



Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using oxepan-4-one (CAS 62643-19-0). The 2 ring isomers were separated and isolated

ISOMER A:

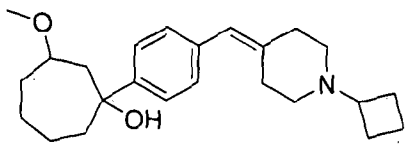
^{1}H NMR (400 MHz, MeOD) δ 7.45 (d, J = 8.08 Hz, 2H), 7.16 (d, J = 8.08 Hz, 2H), 6.32 (s, 1H), 3.85 - 3.97 (m, 2H), 3.75 - 3.85 (m, 1H), 3.66 - 3.75 (m, 1H), 2.69 - 2.89 (m, 1H), 2.27 - 2.62 (m, 9H), 2.14 - 2.27 (m, 2H), 2.02 - 2.15 (m, 2H), 1.60 - 2.02 (m, 7H)
MS ES$^+$ 342

ISOMER B:

^{1}H NMR (400 MHz, MeOD) δ 7.47 (d, J = 8.34 Hz, 2H), 7.14 (d, J = 8.08 Hz, 2H), 6.33 (s, 1H), 3.55 (dd, J =10.86, 4.29 Hz, 1H), 2.69 - 2.88 (m, 1H), 2.51 - 2.61 (m, 2H), 2.39 - 2.50 (m, 4H), 2.28 - 2.39 (m, 2H), 2.03 - 2.16 (m, 2H), 1.89 - 2.03 (m, 3H), 1.74 (d, J = 2.27 Hz, 7H), 1.35 - 1.56 (m, 2H)
MS ES$^+$ 342

2.123 and 2.124 Examples 123 and 124

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-3-methoxycycloheptanol



Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 3-methoxycycloheptanone (CAS 17159-70-5). The 2 ring isomers were separated and isolated

ISOMER A:

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 - 7.51 (m, 2H), 7.04 - 7.21 (m, 2H), 6.14 - 6.34 (m, 1H), 4.91 (s, 1H), 3.50 - 3.69 (m, 1H), 3.18 (s, 3H), 2.57 - 2.79 (m, 1H), 2.36 - 2.46 (m, 2H), 2.25 - 2.36 (m, 4H), 2.16 - 2.26 (m, 2H), 1.86 - 2.09 (m, 6H), 1.73 - 1.86 (m, 2H), 1.48 - 1.73 (m, 7H), 1.38 - 1.48 (m, 1H)
MS ES$^+$ 370

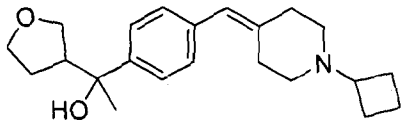
ISOMER B:

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.34 - 7.51 (m, 2H), 6.99 - 7.26 (m, 2H), 6.16 - 6.32 (m, 1H), 4.85 (s, 1H), 3.25 - 3.29 (m, 1H), 3.10 (s, 3H), 2.58 - 2.79 (m, 1H), 2.37 - 2.46 (m, 2H), 2.15 - 2.36 (m, 7H), 1.87 - 2.09 (m, 4H), 1.57 - 1.87 (m, 8H), 1.25 - 1.58 (m, 3H)

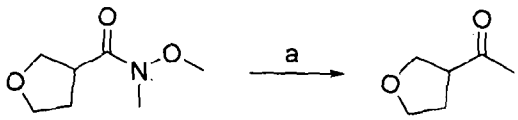
MS ES$^+$ + 1 371

2.125 Example 125

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(tetrahydrofuran-3-yl)ethanol



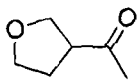
Scheme 33



Reagents and conditions: a) MeMgBr, THF

Step a **Intermediate 61**

1-(Tetrahydrofuran-3-yl)ethanone



To a solution of N-methoxy-N-methyltetrahydrofuran-3-carboxamide (CAS 766539-67-7, 1 g, 6.28 mmol) in THF (10 ml) at -78 °C was added methylmagnesium bromide (3 M in THF, 2.51 ml, 7.54 mmol) dropwise. The reaction was then stirred at -78 °C for 1.5 h. The mixture was quenched with water and extracted with EtOAc. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give 1-(tetrahydrofuran-3-yl)ethanone as a pale yellow oil (320 mg, 45 %). Used crude in the next step.

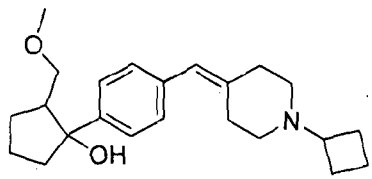
Step b **Example 125**

Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 1-(tetrahydrofuran-3-yl)ethanone (**Int 61**)

^{1}H NMR (400 MHz, MeOD) δ 7.39 - 7.49 (m, 2H), 7.09 - 7.22 (m, 2H), 6.32 (s, 1H), 3.60 - 3.95 (m, 3H), 3.40 - 3.58 (m, 1H), 2.65 - 2.89 (m, 2H), 2.25 - 2.62 (m, 8H), 1.84 - 2.18 (m, 5H), 1.57 - 1.83 (m, 3H), 1.52 (d, J =13.14 Hz, 3H)
MS ES$^+$ 342

2.126 Example 126

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-2-(methoxymethyl)cyclopentanol

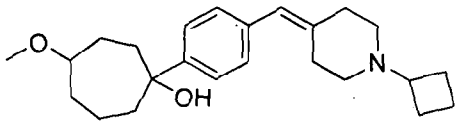


Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 2-(methoxymethyl)cyclopentanone (CAS 35457-02-4).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 - 7.50 (m, 2H), 7.05 - 7.22 (m, 2H), 6.25 (s, 1H), 4.67 (s, 1H), 3.13 - 3.26 (m, 2H), 3.08 (s, 3H), 2.59 - 2.75 (m, 1H), 2.39 - 2.44 (m, 2H), 2.08 - 2.35 (m, 8H), 1.50 - 2.08 (m, 12H)
MS ES$^+$ 356

2.127 and 2.128 Examples 127 and 128

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methoxycycloheptanol



Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 4-methoxycycloheptanone (CAS 17429-01-5). The 2 ring isomers were separated and isolated

ISOMER A:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.52 (m, 2H), 7.12 - 7.23 (m, 2H), 6.15 - 6.37 (m, 1H), 3.43 - 3.62 (m, 1H), 3.35 (s, 3H), 2.66 - 2.83 (m, 1H), 2.48 - 2.61 (m, 2H), 2.24 - 2.45 (m, 7H), 1.85 - 2.20 (m, 8H), 1.49 - 1.85 (m, 8H)

MS ES^+ 370

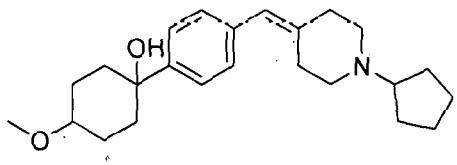
ISOMER B:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.50 (m, 2H), 7.09 - 7.23 (m, 2H), 6.19 - 6.36 (m, 1H), 3.51 - 3.67 (m, 1H), 3.39 (s, 3H), 2.96 - 3.10 (m, 1H), 2.62 - 2.81 (m, 1H), 2.49 - 2.62 (m, 2H), 2.35 - 2.47 (m, 4H), 2.21 - 2.35 (m, 2H), 1.82 - 2.16 (m, 12H), 1.63 - 1.83 (m, 3H), 1.47 - 1.63 (m, 1H)

MS ES^+ 370

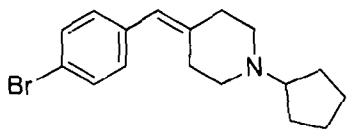
2.129 Example 129

1-{4-[(1-cyclopentylpiperidin-4-ylidene)methyl]phenyl}-4-methoxycyclohexanol



Step a **Intermediate 62**

4-(4-Bromobenzylidene)-1-cyclopentylpiperidine



Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with *tert*-butyl 4-(4-bromobenzylidene)piperidine-1-carboxylate (**Int 3**) and using cyclopentanone in step b.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, J =8.34 Hz, 2H), 7.16 (d, J = 8.34 Hz, 2H), 6.22 (s, 1H), 2.45 - 2.50 (m, 3H), 2.42 (s, 4H), 2.26 - 2.35 (m, 2H), 1.77 (d, J = 6.32 Hz, 2H), 1.54 - 1.66 (m, 2H), 1.49 (dd, 2H), 1.26 - 1.41 (m, 2H)

MS ES$^+$ 320, 322

Step b **Example 129**

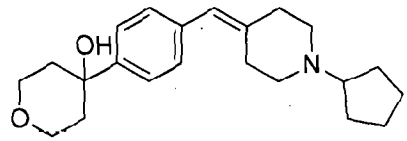
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclopentylpiperidine (**Int 62**) and using 4-methoxycyclohexanone.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.51 (m, 2H), 7.16 - 7.25 (m, 2H), 6.16 - 6.34 (m, 1H), 3.42 (s, 3H), 3.12 - 3.35 (m, 1H), 2.34 - 2.70 (m, 9H), 1.95 - 2.09 (m, 2H), 1.65 - 1.95 (m, 10H), 1.35 - 1.64 (m, 5H)

MS ES$^+$ 371

2.130 Example 130

4-{4-[(1-Cyclopentylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol



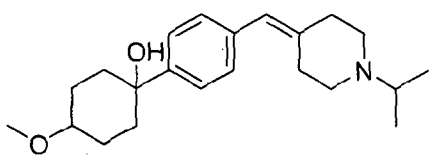
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-cyclopentylpiperidine (**Int 62**) and using tetrahydro-4H-pyran-4-one.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 - 7.49 (m, 2H), 7.05 - 7.21 (m, 2H), 6.24 (s, 1H), 4.97 (s, 1H), 3.78 (s, 4H), 2.45 - 2.49 (m, 3H), 2.35 - 2.45 (m, 4H), 2.25 - 2.35 (m, 2H), 1.86 - 2.05 (m, 2H), 1.70 - 1.85 (m, 2H), 1.41 - 1.70 (m, 6H), 1.22 - 1.40 (m, 2H)

MS ES$^+$ 342

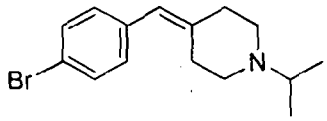
2.131 Example 131

4-Methoxy-1-(4-{[1-(propan-2-yl)piperidin-4-ylidene]methyl}phenyl)cyclohexanol



Step a **Intermediate 63**

4-(4-Bromobenzylidene)-1-(propan-2-yl)piperidine



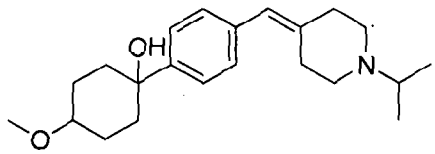
Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with *tert*-butyl 4-(4-bromobenzylidene)piperidine-1-carboxylate (**Int 3**) and using acetone in step b.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.46 (m, 2H), 7.03 - 7.11 (m, 2H), 6.19 (s, 1H), 2.72 - 2.82 (m, 1H), 2.56 - 2.64 (m, 2H), 2.49 (s, 4H), 2.34 - 2.42 (m, 2H), 1.05 (d, J =6.57 Hz, 6H)

MS ES^+ 294, 296

Step b **Example 131**

4-Methoxy-1-(4-{[1-(propan-2-yl)piperidin-4-ylidene]methyl}phenyl)cyclohexanol



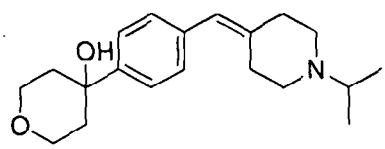
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-(propan-2-yl)piperidine (**Int 63**) and using 4-methoxycyclohexanone.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 - 7.49 (m, 2H), 7.04 - 7.20 (m, 2H), 6.11 - 6.32 (m, 1H), 4.74 (s, 1H), 3.31 (s, 3H), 3.15 - 3.24 (m, 1H), 2.63 - 2.80 (m, 1H), 2.34 - 2.46 (m, 4H), 2.21 - 2.36 (m, 2H), 1.50 - 1.88 (m, 8H), 0.96 (d, 6H)

MS ES^+ 345

2.132 Example 132

4-(4-{[1-(propan-2-yl)piperidin-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol



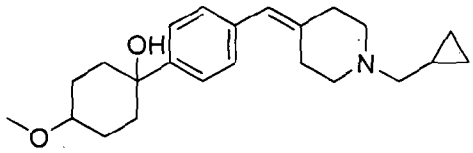
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-(propan-2-yl)piperidine (**Int 63**) and using tetrahydro-4H-pyran-4-one.

^{1}H NMR (400 MHz, MeOD) δ 7.43 - 7.51 (m, 2H), 7.15 - 7.25 (m, 2H), 6.33 (s, 1H), 3.91 - 4.02 (m, 2H), 3.78 - 3.87 (m, 2H), 2.78 - 2.88 (m, 1H), 2.64 - 2.74 (m, 2H), 2.53 - 2.64 (m, 4H), 2.42 - 2.49 (m, 2H), 2.09 - 2.21 (m, 2H), 1.65 - 1.73 (m, 2H), 1.06 - 1.15 (m, 6H)

MS ES$^+$ 316

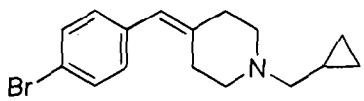
2.133 Example 133

1-(4-{[1-(Cyclopropylmethyl)piperidin-4-ylidene]methyl}phenyl)-4-methoxycyclohexanol



Step a **Intermediate 64**

4-(4-Bromobenzylidene)-1-(cyclopropylmethyl)piperidine



Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with *tert*-butyl 4-(4-bromobenzylidene)piperidine-1-carboxylate (**Int 3**) and using cyclopropanecarbaldehyde in step b.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.47 (m, 2H), 6.99 - 7.14 (m, 2H), 6.21 (s, 1H), 2.60 - 2.70 (m, 2H), 2.52 (s, 4H), 2.36 - 2.47 (m, 2H), 2.20 - 2.33 (m, 2H), 0.82 - 0.97 (m, 1H), 0.41 - 0.57 (m, 2H), 0.00 - 0.16 (m, 2H)

MS ES$^+$ 306, 308

Step b **Example 133**

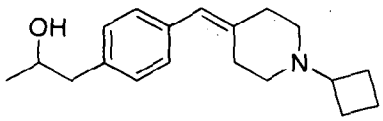
Prepared in an analogous manner to **Intermediate 53** via **Scheme 26** starting with 4-(4-bromobenzylidene)-1-(cyclopropylmethyl)piperidine (**Int 64**) and using 4-methoxycyclohexanone.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.22 - 7.43 (m, 2H), 6.99 - 7.18 (m, 2H), 6.06 - 6.25 (m, 1H), 4.67 (s, 1H), 3.20 (s, 3H), 3.09 - 3.17 (m, 1H), 2.43 - 2.51 (m, 2H), 2.31 - 2.39 (m, 4H), 2.17 - 2.30 (m, 2H), 2.01 - 2.18 (m, 2H), 1.45 - 1.80 (m, 8H), 0.64 - 0.87 (m, 1H), 0.30 - 0.48 (m, 2H), -0.13 - 0.07 (m, 2H)

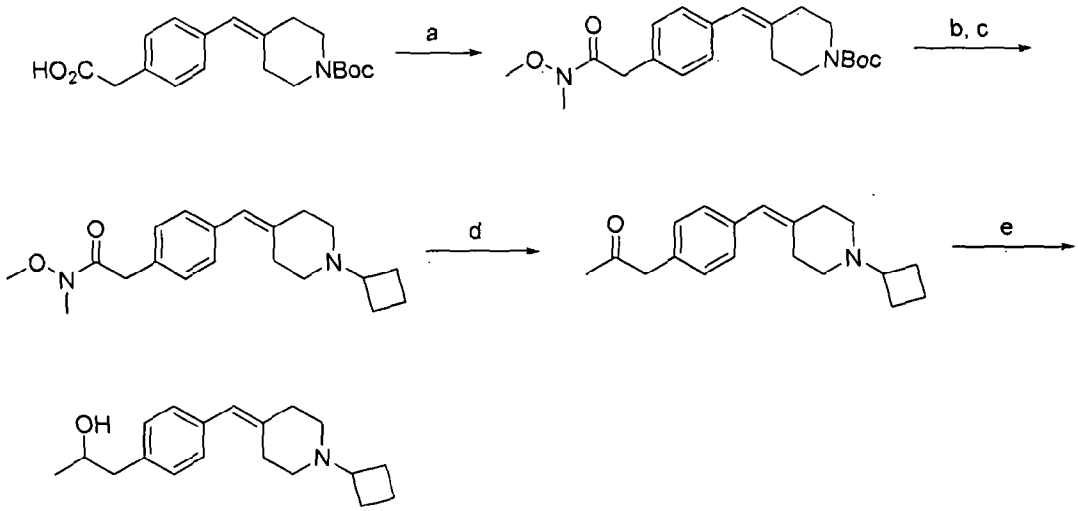
MS ES$^+$ 356

2.134 Example 134

1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)propan-2-ol



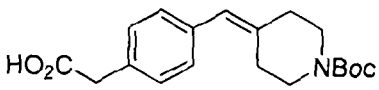
Scheme 34



Reagents and conditions: a) CDI, dimethyl N,O-hydroxylamine HCl, Et_3N, DCM; b) TFA, DCM; c) cyclobutanone, triethylamine, acetic acid, sodium triacetoxyborohydride, DCM; d) MeMgBr, Et_2O, THF; e) $NaBH_4$, MeOH

Intermediate 65

(4-{[1-(tert-butoxycarbonyl)piperidin-4-ylidene]methyl}phenyl)acetic acid

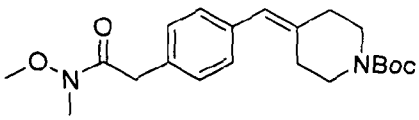


Prepared in an analogous manner to **Intermediate 3** via **Scheme 3**, method B, starting from 2-(4-((diethoxyphosphoryl)methyl)phenyl)acetic acid (CAS 177712-50-4) and using tert-butyl 4-oxopiperidine-1-carboxylate.

^{1}H NMR (300MHz, $CDCl_3$) δ 10.5 (br s, 1H), 7.22 (d, 2H), 7.15 (d, 2H), 6.32 (s, 1H), 3.62 (s, 2H), 3.49 (m, 2H), 3.38 (m, 2H), 2.44 (m, 2H), 2.30 (m, 2H), 1.44 (s, 9H).
No LCMS

Step a **Intermediate 66**

tert-Butyl 4-(4-{2-[methoxy(methyl)amino]-2-oxoethyl}benzylidene)piperidine-1-carboxylate

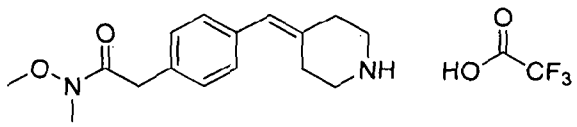


To a solution of (4-{[1-(tert-butoxycarbonyl)piperidin-4-ylidene]methyl}phenyl)acetic acid (**Int 65**) (2.5 g, 7.5 mmol) in DCM (50 ml) was added CDI (1.3 g, 8.3 mmol) and the reaction stirred for 20 min. Dimethyl N,O-hydroxylamine hydrochloride (0.9 g, 9.1 mmol) and Et_3N (3 ml) were added and the reaction stirred for 1 h. The reaction was diluted with DCM and washed with 2 % citric acid (aq.) then brine, dried (Na_2SO_4) and concentrated under reduced pressure to give tert-butyl 4-(4-{2-[methoxy(methyl)amino]-2-oxoethyl}benzylidene)piperidine-1-carboxylate as a brown oil (2.46 g, 87 %).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.24 (d, 2H), 7.13 (d, 2H), 6.31 (s, 1H), 3.75 (s, 2H), 3.65 (s, 3H), 3.48 (t, 2H), 3.38 (t, 2H), 3.18 (s, 3H), 2.45 (t, 2H), 2.31 (t, 2H), 1.43 (s, 9H).

Step b **Intermediate 67**

N-Methoxy-N-methyl-2-[4-(piperidin-4-ylidenemethyl)phenyl]acetamide trifluoroacetate

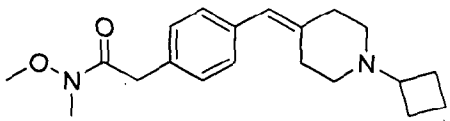


To a solution of tert-butyl 4-(4-{2-[methoxy(methyl)amino]-2-oxoethyl}benzylidene)piperidine-1-carboxylate (**Int 66**) (2.46 g, 6.6 mmol) in DCM (10 ml) at r.t. was added TFA (5 ml, 66 mmol) and the reaction stirred for 1 h. The reaction was then concentrated under reduced pressure and azeotroped with toluene to give N-methoxy-N-methyl-2-[4-(piperidin-4-ylidenemethyl)phenyl]acetamide trifluoroacetate (4.78 g, 100 %)

^{1}H NMR (300MHz, $CDCl_3$) δ 7.17-7.30 (m, 4H), 6.50 (s, 1H), 3.76 (s, 2H), 3.68 (s, 3H), 3.30 (s, 3H), 3.10 - 3.30 (m, 4H), 2.72 (t, 2H), 2.62 (t, 2H).

Step c **Intermediate 68**

2-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-N-methoxy-N-methylacetamide



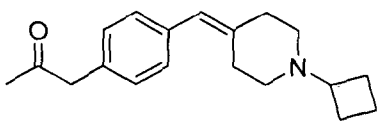
Prepared in an analogous manner to **Intermediate 5** via **Scheme 4**, step b, starting from N-methoxy-N-methyl-2-[4-(piperidin-4-ylidenemethyl)phenyl]acetamide trifluoroacetate (**Int 67**) and using cyclobutanone.

^{1}H NMR (300MHz, $CDCl_3$) δ7.17 (d, 2H), 7.08 (d, 2H), 6.19 (s, 1H), 3.68 (s, 2H), 3.58 (s, 3H), 3.12 (s, 3H), 2.65 (quin, 1H), 2.47 (t, 2H), 2.34 (s, 4H), 2.23 (t, 2H), 1.95 (m, 2H), 1.85 (m, 2H), 1.65 (m, 2H).

MS ES^+ 329

Step d **Intermediate 69**

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}propan-2-one



To a solution of 2-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-N-methoxy-N-methylacetamide (**Int 68**) (180 mg, 0.54 mmol) in THF (4 ml) at r.t. was added methyl magnesium bromide (2 ml, 3 M solution in Et_2O, 6.0 mmol) and the reaction stirred for 1 h. The reaction was poured onto 2 M HCl (aq.) (10 ml), basified and then extracted into EtOAc (2 x 20 ml). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to give 1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}propan-2-one (120 mg, 78 %).

^{1}H NMR (300MHz, $CDCl_3$) δ7.13 (m, 4H), 6.22 (s, 1H), 3.66 (s, 2H), 2.68 (q, 1H), 2.50 (t, 2H), 2.38 (s, 4H), 2.27 (t, 2H), 2.13 (s, 3H), 2.0 (m, 2H), 1.88 (m, 2H), 1.66 (m, 2H).

Step e **Example 134**

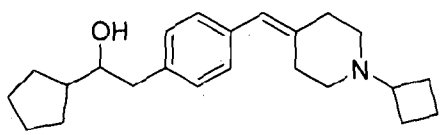
To a solution of 1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}propan-2-one (**Int 69**) (120 mg, 0.42 mmol) in MeOH (3 ml) at r.t. was added $NaBH_4$ (40 mg, 1.05 mmol) and the reaction stirred for 1 h. The reaction was concentrated under reduced pressure then treated with 20 % citric acid (aq.) then basified with 2.5 M NaOH (aq.) and extracted with EtOAc (x 2). The combined organics were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (SiO_2; 10 % MeOH in DCM) to give 1-(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)propan-2-ol as a clear oil (100 mg, 83 %).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.12 (m, 4H), 6.25 (s, 1H), 3.98 (m, 1H), 2.80-2.35 (m, 11H), 2.04 (m, 4H), 1.69 (m, 2H), 1.23 (m, 3H)

MS ES^+ 286

2.135 Example 135

2-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)-1-cyclopentylethanol



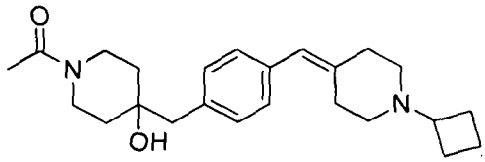
Prepared in an analogous manner to **Example 134** via **Scheme 34**, using cyclopentyl magnesium bromide in step d.

^{1}H NMR (300MHz, $CDCl_3$) δ 7.15 (m, 4H), 6.25 (s, 1H), 3.61 (m, 1H), 2.90-1.20 (m, 26H)

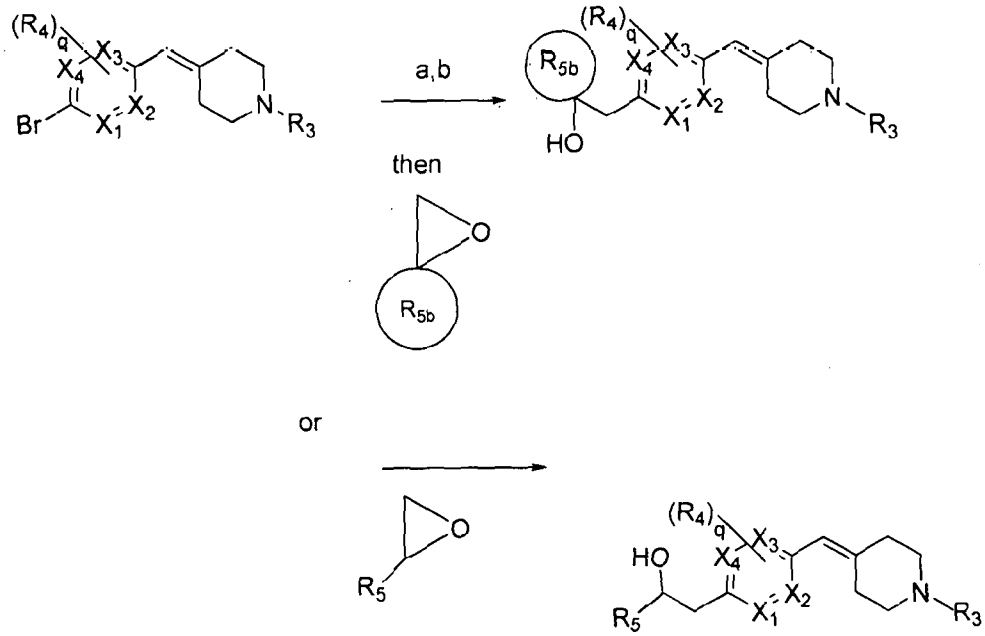
MS ES^+ 340

2.136 Example 136

1-(4-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)benzyl)-4-hydroxypiperidin-1-yl)ethanone



Scheme 35

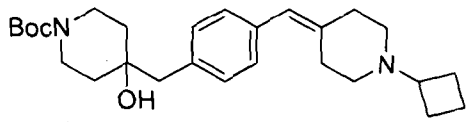


R_{5b} represents R_5 cycloalkyl or heterocyclyl, each of which may be optionally substituted.

Reagents and conditions: a) n-Butyllithium, THF, -78 °C; or Mg, reflux, THF; b) $BF_3.Et_2O$, -78 °C to r.t.

Step a **Intermediate 170**

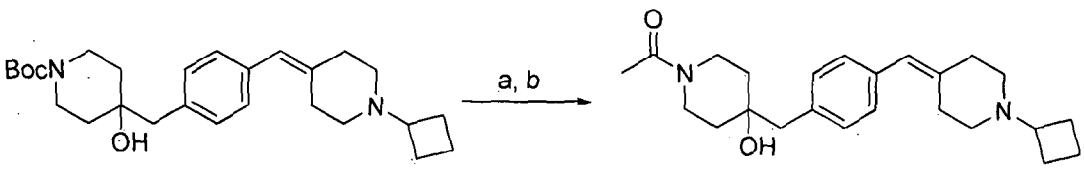
tert-Butyl-4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-4-hydroxypiperidine-1-carboxylate



To a solution of 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) (500 mg, 1.63 mmol) in THF (10 ml) at – 78 °C was added *n*-BuLi (0.81 ml, 2 M in hexanes, 1.63 mmol). The reaction was stirred for 10 min then $BF_3.OEt_2$ (200 μL, 1.63 mmol) was added and the reaction stirred for a further 5 min. A solution of *tert*-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (348 mg, 1.63 mmol) in THF (2 ml) was added dropwise and the reaction stirred for 1 h. The reaction was quenched via the addition of sat. aq. NH_4Cl and basified with K_2CO_3. The mixture was extracted with EtOAc (x 3), dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (SiO_2; 0 to 5 % MeOH in DCM) to give *tert*-butyl 4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-4-hydroxypiperidine-1-carboxylate (300 mg, 42 %) as a yellow gum.

^{1}H NMR (300MHz, $CDCl_3$) δ 7.13 (s, 4H), 6.32 (s, 1H), 3.87 (s, 2H), 3.08 (t, 2H), 2.96 (s, 1H), 2.60 - 2.76 (m, 6H), 2.12 (m, 2H), 1.50 - 1.90 (m, 8H), 1.45 (s, 9H).
MS ES^+ 441.5

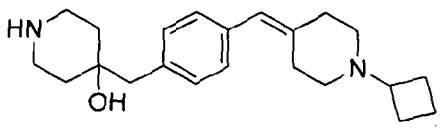
Scheme 36



Reagents and conditions: a) TFA, DCM; b) Ac_2O, Et_3N, DCM

Step b **Intermediate 171**

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}piperidin-4-ol



Prepared in an analogous manner to **Intermediate 67** starting from **Intermediate 170** (TFA dep). The free base was obtained *via* loading the TFA salt onto an SCX column and eluting with NH_3 in MeOH. The filtrate was concentrated under reduced pressure to give 4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}piperidin-4-ol.

^{1}H NMR (300MHz, $CDCl_3$): δ 7.13 (s, 4H), 6.24 (s, 1H), 2.91 (m, 5H), 2.67 - 2.73 (m, 3H), 2.52 (t, 2H), 2.39 (s, 4H), 2.28 (t, 1H), 1.82 - 2.08 (m, 4H), 1.67 (m, 6H), 1.52 (m, 2H).

Step c **Example 136**

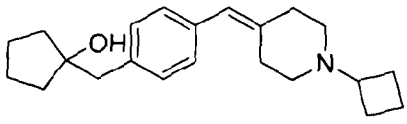
To a solution of 4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}piperidin-4-ol (**Int 171**) (100 mg, 0.29 mmol) and Et_3N (82 µl, 0.59 mmol) in DCM (2 ml) at 0 °C was added Ac_2O (33 µl, 0.35 mmol). The reaction was allowed to warm to r.t. and stirred for 2 h. The reaction was diluted with DCM, washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (SiO_2; 0 to 5 % MeOH in DCM) to give 1-(4-(4-((1-cyclobutylpiperidin-4-ylidene)methyl)benzyl)-4-hydroxypiperidin-1-yl)ethanone as a beige solid (110 mg, 99 %).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.13 (m, 4H), 6.27 (s, 1H), 4.38 (d, 1H), 3.59 (d, 1H), 3.39 (m, 1H), 2.93 (t, 1H), 2.77 (s, 3H), 2.4 - 2.6 (m, 10H), 2.0 - 2.1 (m, 6H), 1.5 - 1.73 (m, 5H)

MS ES^+ 383

2.137 Example 137

1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)benzyl)cyclopentanol

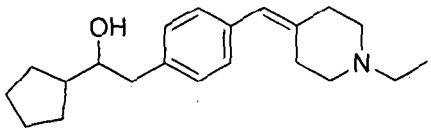


Prepared in an analogous manner to **Intermediate 170** via **Scheme 35** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 1-oxaspiro[2.4]heptane (CAS 185-60-4).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.24 (d, 2H), 7.09 (d, 2H), 6.46 (s, 1H), 3.38 (m, 1H), 2.68 - 3.00 (m, 6H), 2.56 (m, 2H), 2.26 (m, 2H), 1.99 (m, 2H), 1.48 - 1.88 (m, 12H)
MS ES^+ 326

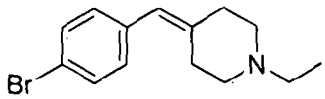
2.138 Example 138

1-Cyclopentyl-2-(4-((1-ethylpiperidin-4-ylidene)methyl)phenyl)ethanol



Step a **Intermediate 172**

4-(4-Bromobenzylidene)-1-ethylpiperidine



Prepared in an analogous manner to **Intermediate 3** via **Scheme 3**, method B using diethyl 4-bromobenzylphosphonate and 1-ethylpiperidin-4-one.

^{1}H NMR (300MHz, $CDCl_3$) δ 7.41 (d, 2H), 7.05 (d, 2H), 6.17 (s, 1H), 2.48 (m, 4H), 2.38 (m, 6H), 1.10 (t, 3H).
MS ES^+ 309.

Step b **Example 138**

Prepared in an analogous manner to **Intermediate 170** via **Scheme 35** starting with 4-(4-bromobenzylidene)-1-ethylpiperidine (**Int 172**) and using 1-oxaspiro[2.4]heptane (CAS 185-60-4).

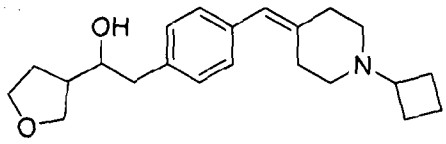
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.13 - 7.19 (m, 2H), 7.03 - 7.12 (m, 2H), 6.18 - 6.28 (m, 1H), 4.36 - 4.45 (m, 1H), 3.42 - 3.51 (m, 1H), 2.63 - 2.74 (m, 1H), 2.40 - 2.48 (m,

4H), 2.24 - 2.40 (m, 6H), 1.72 - 1.86 (m, 1H), 1.35 - 1.70 (m, 8H), 1.20 - 1.36 (m, 1H), 1.01 (m, 3H)

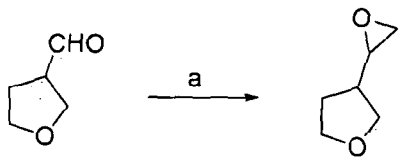
MS ES^+ 314

2.139 Example 139

2-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(tetrahydrofuran-3-yl)ethanol



Scheme 37



Reagents and conditions: a) Trimethylsulfoxonium iodide, KOtBu, DME

Step a **Intermediate 173**

3-(oxiran-2-yl)tetrahydrofuran

To a suspension of trimethylsulfoxonium iodide (2.1 g, 9.4 mmol) in DME (20 ml) was added KO'Bu (1.15 g, 9.4 mmol). The reaction was stirred for 30 min at r.t. and was then cooled to 0 °C. A solution of tetrahydrofuran-3-carbaldehyde (858 mg, 8.6 mmol) in DME was added dropwise and the reaction stirred for 1 h. The reaction was quenched via the addition of sat. aq. NH_4Cl and extracted with EtOAc. The organics were washed with sat. aq. $NaHCO_3$ and brine then dried ($MgSO_4$) and concentrated under reduced pressure to give 3-(oxiran-2-yl)tetrahydrofuran (140 mg, 14 %).

^1H NMR (300MHz, $CDCl_3$) δ 3.70 (m, 4H), 2.92 (m, 1H), 2.80 (q, 1H), 2.53 (m, 1H), 1.80 (m, 3H)

Step b **Example 139**

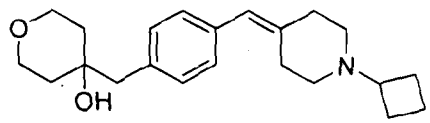
Prepared in an analogous manner to **Intermediate 170** via **Scheme 35** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 3-(oxiran-2-yl)tetrahydrofuran (**Int 173**).

^{1}H NMR (300MHz, $CDCl_3$) δ7.15 (s, 4H), 6.24 (s, 1H), 3.59 - 3.97 (m, 5H), 1.53 - 2.92 (m, 20H)

MS ES^+ 342

2.140 Example 140

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}tetrahydro-2H-pyran-4-ol



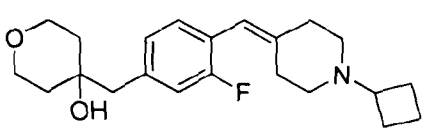
Prepared in an analogous manner to **Intermediate 170** via **Scheme 35** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 1,6-dioxaspiro[2.5]octane.

^{1}H NMR (400 MHz, MeOD) δ 7.08 (d, 2H, J = 8.08 Hz), 7.07 (m, 2H), 7.01 (d, 2H, J = 8.08 Hz), 6.21 (s, 1H), 3.51 - 3.71 (m, 4H), 2.61 - 2.73 (m, 1H), 2.64 (s, 2H), 2.38 - 2.47 (m, 2H), 2.26 - 2.38 (m, 4H), 2.17 - 2.26 (m, 2H), 1.90 - 2.02 (m, 2H), 1.74 - 1.90 (m, 2H), 1.52 - 1.69 (m, 4H), 1.26 - 1.38 (m, 2H)

MS ES^+ 342

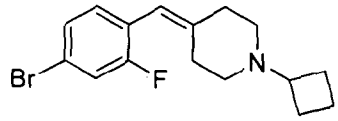
2.141 Example 141

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-3-fluorobenzyl}tetrahydro-2H-pyran-4-ol



Step a **Intermediate 174**

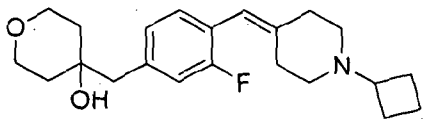
4-(4-Bromo-2-fluorobenzylidene)-1-cyclobutylpiperidine



Prepared in an analogous manner to **Intermediate 5** via **Scheme 3**, method A, starting from (4-bromo-2-fluorobenzyl)(triphenyl)phosphonium bromide and *tert*-butyl 4-oxopiperidine-1-carboxylate, and **Scheme 4** using cyclobutanone in step b.

Step b **Example 144**

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-3-fluorobenzyl}tetrahydro-2H-pyran-4-ol



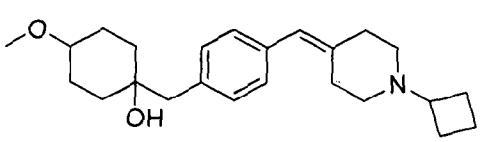
Prepared in an analogous manner to **Intermediate 170** via **Scheme 35** starting with 4-(4-bromo-2-fluorobenzylidene)-1-cyclobutylpiperidine (**Int 174**) and using 1,6-dioxaspiro[2.5]octane.

^{1}H NMR (400 MHz, MeOD) δ 7.08 - 7.21 (m, 1H), 6.91 - 7.07 (m, 2H), 6.24 (s, 1H), 3.67 - 3.81 (m, 4H), 2.78 - 2.89 (m, 1H), 2.77 (s, 2H), 2.25 - 2.55 (m, 8H), 2.03 - 2.19 (m, 2H), 1.85 - 2.03 (m, 2H), 1.61 - 1.83 (m, 4H), 1.43 (m, 2H), 1.36 - 1.50 (m, 2H)

MS ES$^+$ 360

2.142 Example 142

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}-4-methoxycyclohexanol



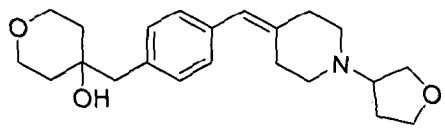
Prepared in an analogous manner to **Intermediate 170** via **Scheme 35** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 6-methoxy-1-oxaspiro[2.5]octane. A mixture of ring isomers was obtained.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.11 - 7.21 (m, 2H), 7.00 - 7.11 (m, 2H), 6.23 (s, 1H), 4.08 (br. s., 1H), 3.19 (s, 3H), 2.92 - 3.09 (m, 1H), 2.63 - 2.76 (m, 1H), 2.55 - 2.64 (m, 2H), 2.36 - 2.47 (m, 2H), 2.26 - 2.35 (m, 4H), 2.15 - 2.26 (m, 2H), 1.89 - 2.03 (m, 2H), 1.72 - 1.88 (m, 2H), 1.56 - 1.72 (m, 4H), 1.38 - 1.51 (m, 4H), 1.17 - 1.33 (m, 2H)

MS ES$^+$ 370

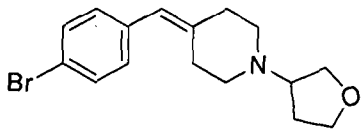
2.143 Example 143

4-(4-{[1-(Tetrahydrofuran-3-yl)piperidin-4-ylidene]methyl}benzyl)tetrahydro-2H-pyran-4-ol



Step a **Intermediate 175**

4-(4-Bromobenzylidene)-1-(tetrahydrofuran-3-yl)piperidine



Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with *tert*-butyl 4-(4-bromobenzylidene)piperidine-1-carboxylate (Intermediate 3) and using dihydrofuran-3(2H)-one in step b.

^{1}H NMR (300MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.05 (m, 2H), 6.21 (s, 1H), 3.62 - 3.99 (m, 4H), 2.98 - 3.03 (m, 1H), 2.40 - 2.60 (m, 8H), 1.81 - 2.12 (m, 2H)

Step b **Example 143**

Prepared in an analogous manner to **Intermediate 170** via **Scheme 35** starting with 4-(4-bromobenzylidene)-1-(tetrahydrofuran-3-yl)piperidine (**Int 175**) and using 1,6-dioxaspiro[2.5]octane.

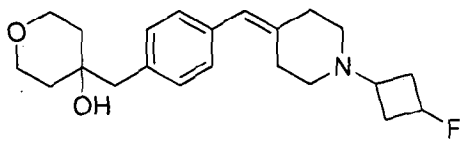
^{1}H NMR (400 MHz, MeOD) δ 7.17 - 7.24 (m, 2H), 7.08 - 7.16 (m, 2H), 6.33 (s, 1H), 3.84 - 4.01 (m, 2H), 3.62 - 3.84 (m, 6H), 3.00 - 3.13 (m, 1H), 2.76 (s, 2H), 2.62 - 2.74

(m, 1H), 2.52 - 2.62 (m, 4H), 2.39 - 2.52 (m, 3H), 2.03 - 2.22 (m, 1H), 1.81 - 1.99 (m, 1H), 1.60 - 1.80 (m, 2H), 1.39 - 1.52 (m, 2H)

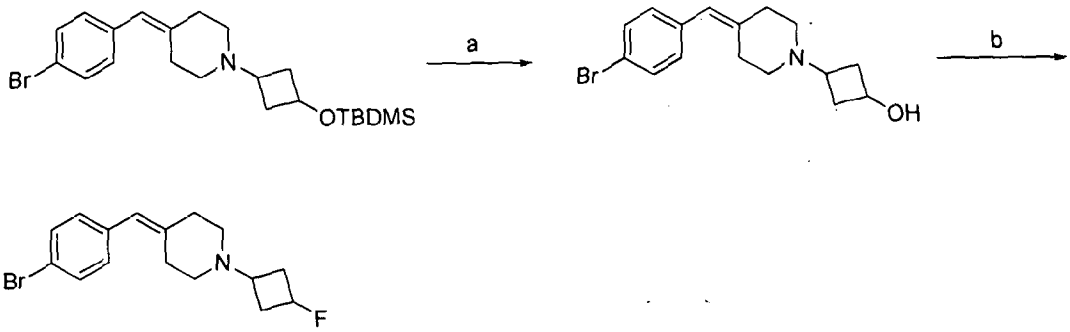
MS ES^+ 358

2.144 Example 144

4-(4-{[1-(3-Fluorocyclobutyl)piperidin-4-ylidene]methyl}benzyl)tetrahydro-2H-pyran-4-ol



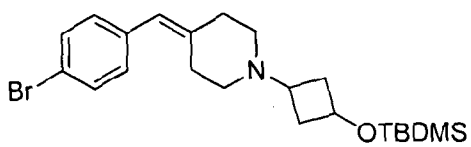
Scheme 38



Reagents and conditions: a) TBAF, THF; b)i) BH_3.THF, THF ii) $C_4F_9SO_2F$, DBU, PhMe

Step a **Intermediate 176**

4-(4-Bromobenzylidene)-1-(3-{[*tert*-butyl(dimethyl)silyl]oxy}cyclobutyl)piperidine

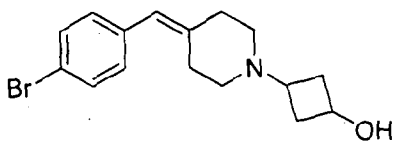


Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with *tert*-butyl 4-(4-bromobenzylidene)piperidine-1-carboxylate (Intermediate 3) and using 3-{[*tert*-butyl(dimethyl)silyl]oxy}cyclobutanone (CAS 929913-18-8) in step b.

^{1}H NMR (300MHz, $CDCl_3$): δ 7.42 (m, 2H), 7.05 (m, 2H), 6.20 (s, 1H), 3.97 (m, 1H), 2.20 - 2.45 (m, 9H), 2.04 (m, 2H), 1.27 (m, 2H), 0.85 (s, 9H), 0.02 (s, 6H)

Step b **Intermediate 177**

3-[4-(4-Bromobenzylidene)piperidin-1-yl]cyclobutanol

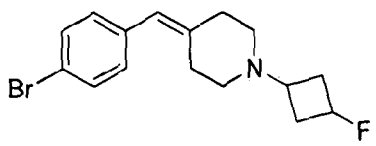


To a solution of 4-(4-bromobenzylidene)-1-(3-{[*tert*-butyl(dimethyl)silyl] oxy}cyclobutyl)piperidine (**Int 176**) (0.88 g, 2.0 mmol) in THF (10 ml) was added TBAF (2.0 ml, 1 M solution in THF, 2.0 mmol) and the reaction stirred at r.t. for 18 h. Sat. aq. $NaHCO_3$ was added and the mixture extracted into DCM (x 3). The organics were washed with brine, dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (SiO_2; 50 % EtOAc in petrol) to yield 3-[4-(4-bromobenzylidene)piperidin-1-yl]cyclobutanol as a white solid (612 mg, 94 %).

^{1}H NMR (300MHz, $CDCl_3$): δ7.42 (m, 2H), 7.05 (m, 2H), 6.23 (s, 1H), 4.01 (m, 1H), 2.30 - 2.64 (m, 11H), 2.10 (m, 1H), 1.91 - 2.00 (m, 2H)

Step c **Intermediate 178**

4-(4-bromobenzylidene)-1-(3-fluorocyclobutyl)piperidine



To a solution of 3-[4-(4-bromobenzylidene)piperidin-1-yl]cyclobutanol (**Int 177**) (355 mg, 1.1 mmol) in THF (10 ml) at -78 °C was added borane.THF (1.1 ml, 1 M solution in THF, 1.1 mmol). The reaction was stirred at this temperature for 2 h and was then allowed to warm to r.t. The solvent was removed under reduced pressure to give a white foam (405 mg). This dissolved in toluene (10 ml) and DBU (0.54 ml, 2.6 mmol) and nonafluorobutanesulfonyl fluoride (0.31 ml, 1.8 mmol) were added. The reaction was stirred for 18 h. Sat. aq. $NaHCO_3$ was added and the mixture extracted into EtOAc (x 3). The organics were washed with brine, dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (SiO_2; 5 % MeOH in DCM) to give 4-(4-bromobenzylidene)-1-(3-fluorocyclobutyl)piperidine (120 mg, 31 %).

^{1}H NMR (300MHz, $CDCl_3$): δ 7.42 (m, 2H), 7.05 (m, 2H), 6.21 (s, 1H), 5.15 (m, 1H), 3.05 (m, 1H), 2.24 - 2.47 (m, 8H), 1.55 - 1.70 (m, 4H)

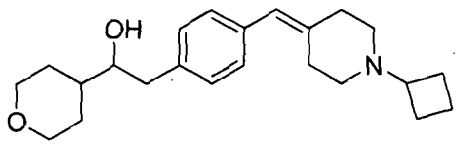
Step d **Example 144**

Prepared in an analogous manner to **Intermediate 170** via **Scheme 35** starting with 4-(4-bromobenzylidene)-1-(3-fluorocyclobutyl)piperidine (**Int 178**) and using 1,6-dioxaspiro[2.5]octane.

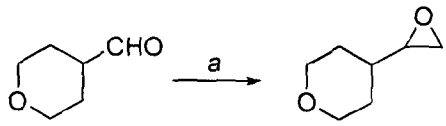
^{1}H NMR (400 MHz, DMSO-d_6) δ 6.93 - 7.25 (m, 4 H), 6.26 (s, 1 H), 4.93 - 5.30 (m, 1 H), 4.32 (s, 1 H), 3.45 - 3.67 (m, 4 H), 2.81 - 3.08 (m, 1 H), 2.66 (s, 2 H), 2.44 (br. s., 2 H), 2.07 - 2.40 (m, 9 H), 1.37 - 1.61 (m, 2 H), 1.09 - 1.37 (m, 3 H)
MS ES^+ 360

2.145 Example 145

2-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(tetrahydro-2H-pyran-4-yl)ethanol



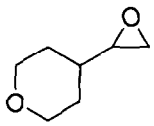
Scheme 39



Reagents and conditions: a) Trimethylsulfoxonium iodide, NaH, DMSO

Step a **Intermediate 179**

4-(Oxiran-2-yl)tetrahydro-2H-pyran



To a suspension of trimethylsulfoxonium iodide (1.778 g, 8.08 mmol) and NaH (0.308 g, 7.71 mmol) in DMSO (14 ml) was added dropwise tetrahydro-2H-pyran-4-carbaldehyde (0.8 g, 7.01 mmol). The resultant solution was stirred at r.t. for 20 min and then heated for 30 min at 60 °C. The mixture was poured into water and extracted with DCM (x 3). The organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a colourless oil. The oil was dissolved into diethyl ether and washed with half saturated brine (x 5).The organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield 4-(oxiran-2-yl)tetrahydro-2H-pyran as a colourless oil (236 mg, 26 %). Used without further purification in next step.

Step b **Example 145**

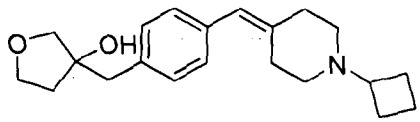
Prepared in an analogous manner to **Intermediate 170** via **Scheme 35** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 4-(oxiran-2-yl)tetrahydro-2H-pyran (**Int 179**).

^{1}H NMR (400 MHz, MeOD) δ7.16 - 7.25 (m, 2H), 7.09 - 7.16 (m, 2H), 6.28 - 6.35 (m, 1H), 3.92 - 4.04 (m, 2H), 3.52 - 3.61 (m, 1H), 3.35 - 3.42 (m, 2H), 2.71 - 2.92 (m, 2H), 2.58 - 2.68 (m, 1H), 2.29 - 2.58 (m, 8H), 2.03 - 2.16 (m, 2H), 1.89 - 2.03 (m, 2H), 1.68 - 1.84 (m, 3H), 1.39 - 1.67 (m, 4H)

MS ES$^+$ 356

2.146 Example 146

3-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}tetrahydrofuran-3-ol

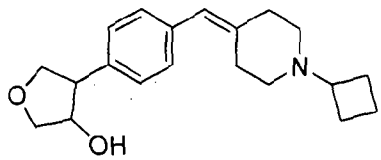


Prepared in an analogous manner to **Intermediate 170** via **Scheme 35** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 1,5-dioxaspiro[2.4]heptane (CAS 185-61-5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 - 7.25 (m, 4H), 6.23 - 6.33 (m, 1H), 3.89 - 4.13 (m, 2H), 3.72 - 3.80 (m, 1H), 3.59 - 3.72 (m, 1H), 2.97 (s, 2H), 2.65 - 2.80 (m, 1H), 2.47 - 2.61 (m, 2H), 2.38 - 2.47 (m, 4H), 2.23 - 2.38 (m, 2H), 2.00 - 2.15 (m, 3H), 1.84 - 2.00 (m, 3H), 1.62 - 1.84 (m, 3H)
MS ES^+ 328

2.147 Example 147

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydrofuran-3-ol



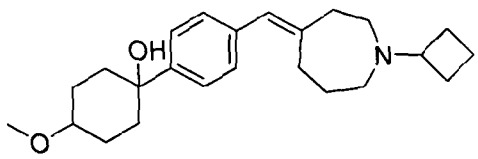
Prepared in an analogous manner to **Intermediate 170** via **Scheme 35** starting with 4-(4-bromobenzylidene)-1-cyclobutylpiperidine (**Int 5**) and using 3,6-dioxabicyclo[3.1.0]hexane.

^{1}H NMR (400MHz, DMSO-d_6) δ 7.21 (m, 2H), 7.14 (m, 2H), 6.24 (s, 1H), 5.24 (m, 1H), 4.21 (m, 1H), 4.14 (m, 1H), 3.94 (m, 1H), 3.70 (m, 1H), 3.56 (m, 1H), 3.12 - 3.19 (m, 1H), 2.67 (m, 1H), 2.36 - 2.44 (m, 2H), 2.25 - 2.35 (m, 4H), 2.17 - 2.25 (m, 2H), 1.90 - 2.02 (m, 2H), 1.72 - 1.85 (m, 2H), 1.49 - 1.68 (m, 2H)
MS ES^+ 314

2.148 and 2.149 Examples 148 and 149

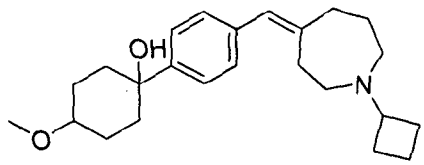
Example 148

1-{4-[(E)-(1-Cyclobutylazepan-4-ylidene)methyl]phenyl}-4-methoxycyclohexanol



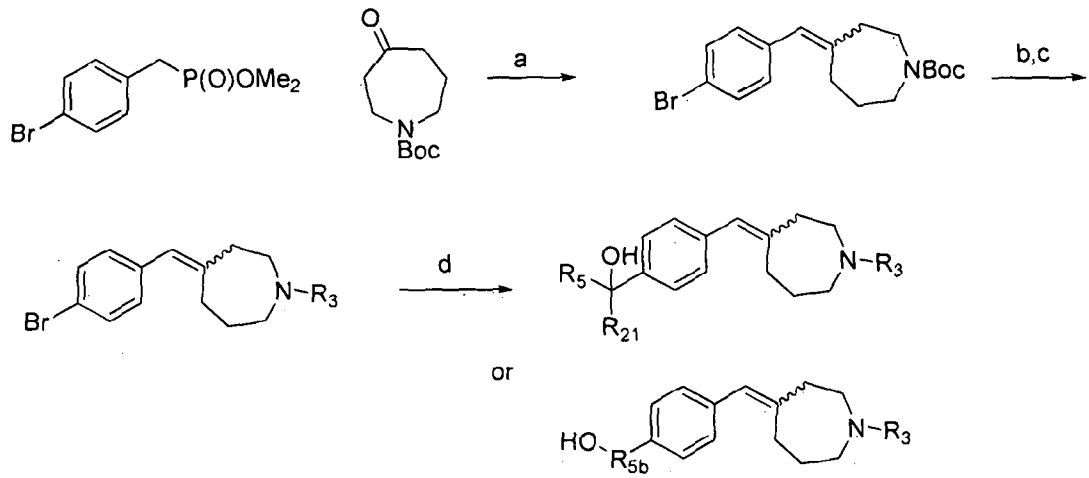
Example 149

1-{4-[(Z)-(1-Cyclobutylazepan-4-ylidene)methyl]phenyl}-4-methoxycyclohexanol



Examples 148 and 149 were prepared as a mixture of alkene isomers and separated at the end of the synthesis.

Scheme 40

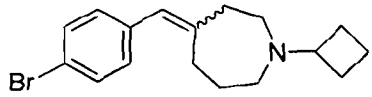


R_{5b} represents R_5 cycloalkyl or heterocyclyl, each of which may be optionally substituted, R_{21} represents H or C_{1-3} alkyl.

Reagents and conditions: a) NaH, EtOH, THF 75 °C, 3 h; b) HCl, dioxane; c) triethylamine, acetic acid, sodium triacetoxyborohydride, R_3=O, DCM; d) *n*-Butyllithium, THF, -78 °C, R_{5b}=O or $R_5R_{21}C$=O

Step a **Intermediate 180**

(4E/Z)-4-(4-Bromobenzylidene)-1-cyclobutylazepane



Prepared in an analogous manner to **Intermediate 5** via **Scheme 3**, method B, starting from *tert*-butyl 4-oxoazepane-1-carboxylate and diethyl (4-bromobenzyl)phosphonate, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 - 7.36 (m, 2 H), 6.90 - 7.07 (m, 2 H), 6.12 (s, 1 H), 2.66 - 2.91 (m, 1 H), 2.23 - 2.58 (m, 8 H), 1.84 - 2.05 (m, 2 H), 1.41 - 1.84 (m, 6 H)
MS (ES^+) 320.5, 322.5

Step b **Examples 148 and 149**

Prepared in an analogous manner to **Intermediate 53** via **Scheme 40** starting with (4E/Z)-4-(4-bromobenzylidene)-1-cyclobutylazepane (**Int 180**) and using 4-methoxycyclohexanone. The crude material was purified by column chromatography (NH SiO_2; 20 - 100 % EtOAc in petrol) and then by reverse phase HPLC to give the separate alkene isomers.

Example 148

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.50 (m, 2H), 7.19 - 7.27 (m, 2H), 6.28 (s, 1H), 3.42 (s, 3H), 3.19 - 3.36 (m, 1H), 2.78 - 2.93 (m, 1H), 2.59 - 2.68 (m, 2H), 2.48 - 2.59 (m, 4H), 2.40 - 2.48 (m, 2H), 1.58 - 2.13 (m, 16H)
MS ES^+ 371

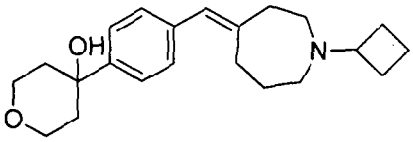
Example 149

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.50 (m, 2H), 7.18 - 7.26 (m, 2H), 6.29 (s, 1 H), 3.42 (s, 3H), 3.21 - 3.33 (m, 1H), 2.82 - 3.01 (m, 1H), 2.61 - 2.74 (m, 2H), 2.39 - 2.61 (m, 6H), 1.95 - 2.12 (m, 4H), 1.60 - 1.95 (m, 12H)

MS ES$^+$ 371

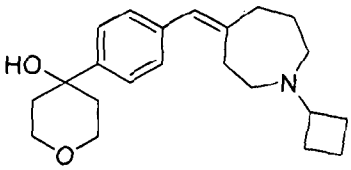
2.150 Example 150

4-{4-[(E)-(1-Cyclobutylazepan-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol



2.151 Example 151

4-{4-[(Z)-(1-Cyclobutylazepan-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol



Examples 150 and **151** were prepared in an analogous manner to **Examples 148** and **149** via **Scheme 40** starting from (4E/Z)-4-(4-bromobenzylidene)-1-cyclobutylazepane (**Int 180**) and using tetrahydro-4H-pyran-4-one.

Example 150

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.52 (m, 2H), 7.22 - 7.28 (m, 2H), 6.19 - 6.38 (m, 1H), 3.80 - 4.04 (m, 4H), 2.79 - 2.94 (m, 1H), 2.37 - 2.68 (m, 8H), 2.14 - 2.27 (m, 2H), 1.99 - 2.12 (m, 2H), 1.77 - 1.96 (m, 4H), 1.49 - 1.77 (m, 5H)

MS ES$^+$ 343

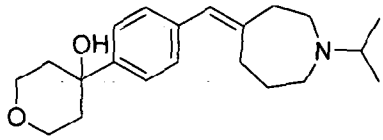
Example 151

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.50 (m, 2 H), 7.22 - 7.28 (m, 2 H), 6.29 (s, 1 H), 3.83 - 4.02 (m, 4 H), 2.84 - 2.97 (m, 1 H), 2.62 - 2.71 (m, 2 H), 2.44 - 2.61 (m, 6 H), 2.13 - 2.25 (m, 2 H), 1.98 - 2.12 (m, 2 H), 1.51 - 1.93 (m, 10 H)

MS ES$^+$ 343

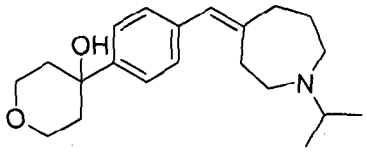
2.152 Example 152

4-(4-{(E)-[1-(Propan-2-yl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol



2.153 Example 153

4-(4-{(Z)-[1-(Propan-2-yl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol



Examples 152 and 153 were prepared as a mixture of alkene isomers and separated at the end of the synthesis.

Step a **Intermediate 181**

(4E/Z)-4-(4-bromobenzylidene)-1-(propan-2-yl)azepane

Prepared in an analogous manner to **Intermediate 5** via **Scheme 3**, method B, starting from tert-butyl 4-oxoazepane-1-carboxylate and diethyl (4-bromobenzyl)phosphonate, and **Scheme 4** using acetone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.39 - 7.52 (m, 2H), 7.07 - 7.22 (m, 2H), 6.24 - 6.33 (m, 1H), 2.84 - 3.03 (m, 1H), 2.41 - 2.84 (m, 8H), 1.70 - 1.88 (m, 2H), 1.07 (m, 6H)

MS ES$^+$ 308/310

Step b **Examples 152 and 153**

Examples 152 and **153** were prepared in an analogous manner to **Examples 148** and **149** via **Scheme 40** starting from (4E/Z)-4-(4-bromobenzylidene)-1-(propan-2-yl)azepane (**Int 181**) and using tetrahydro-4H-pyran-4-one.

Example 152

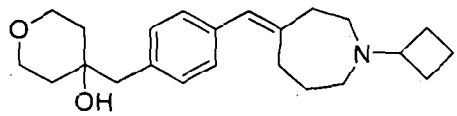
^{1}H NMR (400 MHz, MeOD) δ 7.41 - 7.51 (m, 2H), 7.18 - 7.28 (m, 2H), 6.30 - 6.39 (m, 1H), 3.90 - 4.01 (m, 2H), 3.75 - 3.89 (m, 2H), 2.97 - 3.13 (m, 1H), 2.69 - 2.94 (m, 4H), 2.47 - 2.69 (m, 4H), 2.06 - 2.22 (m, 2H), 1.78 - 1.92 (m, 2H), 1.60 - 1.74 (m, 2H), 1.12 (m, 6H)
MS ES$^+$ 330

Example 153

^{1}H NMR (400 MHz, MeOD) δ7.42 - 7.51 (m, 2H), 7.18 - 7.29 (m, 2H), 6.26 - 6.37 (m, 1H), 3.89 - 4.03 (m, 2H), 3.76 - 3.88 (m, 2H), 2.87 - 2.99 (m, 1H), 2.72 - 2.85 (m, 4H), 2.63 - 2.73 (m, 2H), 2.46 - 2.55 (m, 2H), 2.07 - 2.23 (m, 2H), 1.77 - 1.88 (m, 2H), 1.58 - 1.73 (m, 2H), 1.05 (m, 6H)
MS ES$^+$ 330

2.154 Example 154

4-{4-[(E)-(1-Cyclobutylazepan-4-ylidene)methyl]benzyl}tetrahydro-2H-pyran-4-ol

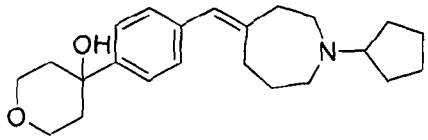


Prepared in an analogous manner to **Intermediate 170** via **Scheme 40** starting with (4E/Z)-4-(4-bromobenzylidene)-1-cyclobutylazepane (**Int 180**) and using 1,6-dioxaspiro[2.5]octane.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 - 7.25 (m, 4H), 6.24 - 6.32 (m, 1H), 3.70 - 3.84 (m, 4H), 2.83 - 2.91 (m, 1H), 2.77 (s, 2H), 2.49 - 2.67 (m, 6H), 2.39 - 2.49 (m, 2H), 2.00 - 2.13 (m, 2H), 1.74 - 1.94 (m, 6H), 1.61 - 1.73 (m, 2H), 1.40 - 1.52 (m, 2H), 1.26 (s, 1H)
MS ES$^+$ 356

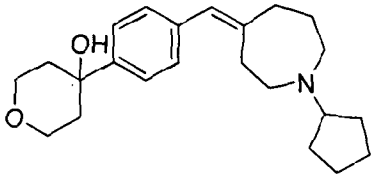
2.155 Example 155

4-{4-[(E)-(1-Cyclopentylazepan-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol



2.156 Example 156

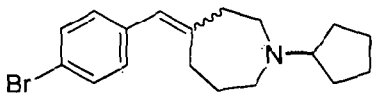
4-{4-[(Z)-(1-cyclopentylazepan-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol



Examples 155 and 156 were prepared as a mixture of alkene isomers and separated at the end of the synthesis.

Step a **Intermediate 182**

(4E/Z)-4-(4-Bromobenzylidene)-1-cyclopentylazepane



Prepared in an analogous manner to **Intermediate 5** via **Scheme 3**, method B, starting from tert-butyl 4-oxoazepane-1-carboxylate and diethyl (4-bromobenzyl)phosphonate, and **Scheme 4** using cyclopentanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.39 - 7.51 (m, 2H), 7.10 - 7.22 (m, 2H), 6.24 - 6.32 (m, 1H), 2.71 - 3.01 (m, 5H), 2.47 - 2.70 (m, 4H), 1.68 (m, 12H)

MS ES$^+$ 334/336

Step b **Examples 155 and 156**

Examples 155 and **156** were prepared in an analogous manner to **Examples 148** and **149** via **Scheme 40** starting from (4E/Z)-4-(4-bromobenzylidene)-1-cyclopentylazepane (**Int 182**) and using tetrahydro-4H-pyran-4-one.

Example 155

^{1}H NMR (400 MHz, MeOD) δ 7.43 - 7.51 (m, 2H), 7.21 - 7.28 (m, 2H), 6.32 - 6.38 (m, 1H), 3.91 - 4.02 (m, 2H), 3.77 - 3.87 (m, 2H), 2.90 - 3.03 (m, 1H), 2.82 - 2.91 (m, 2H), 2.71 - 2.81 (m, 2H), 2.56 - 2.64 (m, 4H), 2.08 - 2.22 (m, 2H), 1.80 - 1.97 (m, 4H), 1.54 - 1.79 (m, 6H), 1.46 (m, 2H)

MS ES$^+$ 356

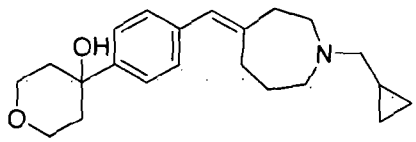
Example 156

^{1}H NMR (400 MHz, MeOD) δ7.42 - 7.50 (m, 2H), 7.20 - 7.29 (m, 2H), 6.29 - 6.39 (m, 1H), 3.89 - 4.04 (m, 2H), 3.75 - 3.89 (m, 2H), 2.94 - 3.04 (m, 1H), 2.86 - 2.94 (m, 2H), 2.77 - 2.86 (m, 2H), 2.65 - 2.76 (m, 2H), 2.47 - 2.59 (m, 2H), 2.07 - 2.20 (m, 2H), 1.79 - 1.94 (m, 4H), 1.62 - 1.77 (m, 4H), 1.49 - 1.62 (m, 2H), 1.42 (m, 2H)

MS ES$^+$ 356

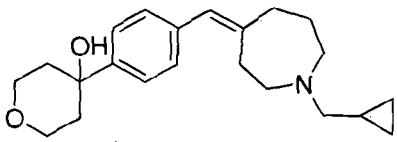
2.157 Example 157

4-(4-{(E)-[1-(Cyclopropylmethyl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol



2.158 Example 158

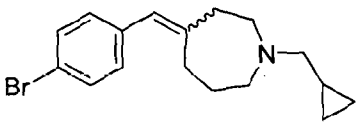
4-(4-{(Z)-[1-(Cyclopropylmethyl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol



Examples 157 and 158 were prepared as a mixture of alkene isomers and separated at the end of the synthesis.

Step a **Intermediate 183**

(4E/Z)-4-(4-Bromobenzylidene)-1-(cyclopropylmethyl)azepane



Prepared in an analogous manner to **Intermediate 5** via **Scheme 3**, method B, starting from tert-butyl 4-oxoazepane-1-carboxylate and diethyl (4-bromobenzyl)phosphonate, and **Scheme 4** using cyclopropanecarboxaldehyde in step b.

^{1}H NMR (400 MHz, MeOD) δ7.44 (m, 2H), 7.06 - 7.21 (m, 2H), 6.21 - 6.35 (m, 1H), 2.70 - 2.91 (m, 4H), 2.46 - 2.70 (m, 4H), 2.39 (s, 2H), 1.73 - 1.91 (m, 2H), 0.80 - 0.96 (m, 1H), 0.46 - 0.62 (m, 2H), 0.04 - 0.21 (m, 2H)

MS ES$^+$ 320/322

Step b **Examples 157 and 158**

Examples 157 and **158** were prepared in an analogous manner to **Examples 148** and **149** via **Scheme 40** starting from (4E/Z)-4-(4-bromobenzylidene)-1-(cyclopropylmethyl)azepane (**Int 183**) and using tetrahydro-4H-pyran-4-one.

Example 157

^{1}H NMR (400 MHz, MeOD) δ 7.39 - 7.49 (m, 2H), 7.17 - 7.26 (m, 2H), 6.27 - 6.36 (m, 1H), 3.87 - 4.00 (m, 2H), 3.74 - 3.87 (m, 2H), 2.83 - 2.92 (m, 2H), 2.73 - 2.83 (m, 2H), 2.55 - 2.67 (m, 4H), 2.39 - 2.48 (m, 2H), 2.04 - 2.20 (m, 2H), 1.79 - 1.93 (m, 2H), 1.60 - 1.73 (m, 2H), 0.84 - 1.00 (m, 1H), 0.50 - 0.60 (m, 2H), 0.08 - 0.21 (m, 2H)

MS ES$^+$ 342

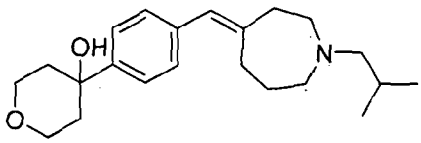
Example 158

^{1}H NMR (400 MHz, MeOD) δ 7.42 - 7.48 (m, 2H), 7.19 - 7.28 (m, 2H), 6.30 - 6.35 (m, 1H), 3.89 - 3.99 (m, 2H), 3.76 - 3.86 (m, 2H), 2.86 - 2.94 (m, 2H), 2.78 - 2.86 (m, 2H), 2.66 - 2.73 (m, 2H), 2.50 - 2.58 (m, 2H), 2.37 - 2.46 (m, 2H), 2.07 - 2.20 (m, 2H), 1.79 - 1.87 (m, 2H), 1.61 - 1.71 (m, 2H), 0.84 - 0.94 (m, 1H), 0.49 - 0.57 (m, 2H), 0.12 (m, 2H)

MS ES$^+$ 342

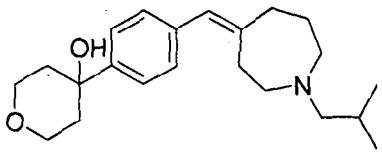
2.159 Example 159

4-(4-{(E)-[1-(2-Methylpropyl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol



2.160 Example 160

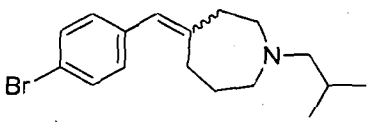
4-(4-{(Z)-[1-(2-Methylpropyl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol



Examples 159 and 160 were prepared as a mixture of alkene isomers and separated at the end of the synthesis.

Step a **Intermediate 184**

(4E/Z)-4-(4-Bromobenzylidene)-1-(2-methylpropyl)azepane



Prepared in an analogous manner to **Intermediate 5** via **Scheme 3**, method B, starting from tert-butyl 4-oxoazepane-1-carboxylate and diethyl (4-bromobenzyl)phosphonate, and **Scheme 4** using isobutyraldehyde in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.45 (m, 2H), 7.07 - 7.22 (m, 2H), 6.19 - 6.32 (m, 1H), 2.41 - 2.82 (m, 8H), 2.13 - 2.34 (m, 2H), 1.65 - 1.87 (m, 3H), 0.92 (m, 6H)
MS ES$^+$ 322/324

Step b **Examples 159 and 160**

Examples 159 and **160** were prepared in an analogous manner to **Examples 148** and **149** via **Scheme 40** starting from (4E/Z)-4-(4-Bromobenzylidene)-1-(cyclopropylmethyl)azepane (**Int 184**) and using tetrahydro-4H-pyran-4-one.

Example 159

^{1}H NMR (400 MHz, MeOD) δ 7.43 - 7.51 (m, 2H), 7.16 - 7.30 (m, 2H), 6.27 - 6.34 (m, 1H), 3.91 - 4.00 (m, 2H), 3.74 - 3.88 (m, 2H), 2.71 - 2.81 (m, 2H), 2.63 - 2.71 (m, 2H), 2.53 - 2.63 (m, 4H), 2.22 - 2.35 (m, 2H), 2.08 - 2.21 (m, 2H), 1.76 - 1.89 (m, 3H), 1.61 - 1.73 (m, 2H), 0.95 (m, 6H)

MS ES$^+$ 344

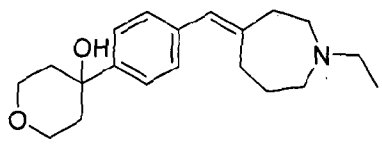
Example 160

^{1}H NMR (400 MHz, MeOD) δ7.43 - 7.49 (m, 2H), 7.18 - 7.28 (m, 2H), 6.29 - 6.35 (m, 1H), 3.89 - 4.01 (m, 2H), 3.77 - 3.88 (m, 2H), 2.77 - 2.87 (m, 2H), 2.69 - 2.77 (m, 2H), 2.61 - 2.69 (m, 2H), 2.46 - 2.55 (m, 2H), 2.22 - 2.34 (m, 2H), 2.06 - 2.22 (m, 2H), 1.63 - 1.86 (m, 5H), 0.90 (m, 6H)

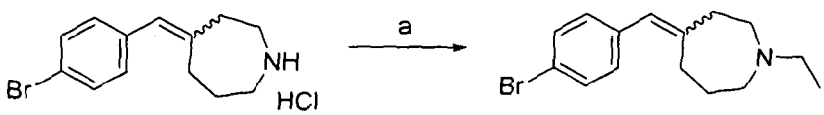
MS ES$^+$ 344

2.161 Example 161

4-{4-[(E)-(1-Ethylazepan-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol



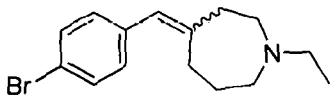
Scheme 41



Reagents and conditions: a) EtI, K_2CO_3, DMF

Step a **Intermediate 185**

(4E/Z)-4-(4-Bromobenzylidene)-1-ethylazepane



To a stirred suspension of 4-(4-bromobenzylidene)azepane hydrochloride (2.23 g, 7.36 mmol) in DMF (25 ml) was added K_2CO_3 (2.54 g, 18.40 mmol) and iodoethane (0.589 ml, 7.36 mmol) and mixture stirred at r.t. for 18 h.

Sat. NH_4Cl and EtOAc were added and phases separated and aqueous was further extracted with EtOAc (x 3). The organics were washed with brine (x 4), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified via column chromatography (NH SiO_2, 0 - 60 % EtOAc in petrol) to yield (4E/Z)-4-(4-bromobenzylidene)-1-ethylazepane as a yellow oil (1.86 g, 86 %).

^{1}H NMR (400 MHz, MeOD) δ 7.40 - 7.53 (m, 2H), 7.10 - 7.24 (m, 2H), 6.22 - 6.36 (m, 1H), 2.42 - 2.86 (m, 10H), 1.75 - 1.94 (m, 2H), 1.13 (m, 3H)

MS ES$^+$ 294/296

Step b **Example 161**

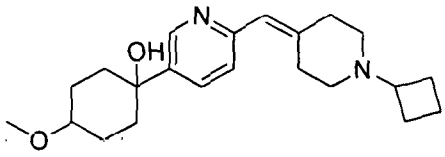
Example 161 was prepared in an analogous manner to **Examples 148** and **149** via **Scheme 40** starting from (4E/Z)-4-(4-bromobenzylidene)-1-ethylazepane (**Int 185**) and using tetrahydro-4H-pyran-4-one.

^{1}H NMR (400 MHz, MeOD) δ 7.43 - 7.51 (m, 2H), 7.21 - 7.28 (m, 2H), 6.32 - 6.38 (m, 1H), 3.90 - 4.01 (m, 2H), 3.78 - 3.88 (m, 2H), 2.75 - 2.85 (m, 2H), 2.68 - 2.75 (m, 2H), 2.55 - 2.68 (m, 6H), 2.09 - 2.21 (m, 2H), 1.81 - 1.92 (m, 2H), 1.62 - 1.73 (m, 2H), 1.15 (s, 3H)

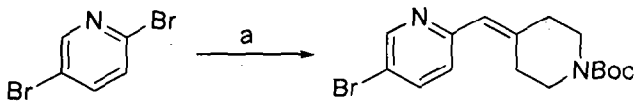
MS ES$^+$ 316

2.162 Example 162

1-{6-[(1-Cyclobutylpiperidin-4-ylidene)methyl]pyridin-3-yl}-4-methoxycyclohexanol



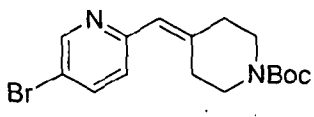
Scheme 42



Reagents and conditions: a) **Int 26**, K_3PO_4, $PdCl_2(dppf)$, dioxane, water, 100 °C MW

Step a **Intermediate 186**

tert-Butyl 4-[(5-bromopyridin-2-yl)methylidene]piperidine-1-carboxylate



A mixture of 2,5-dibromopyridine (1.61 g, 6.81 mmol), tert-butyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)piperidine-1-carboxylate (**Int 26**) (2.20 g, 6.81 mmol), potassium phosphate (1.45 g, 6.81 mmol) and $PdCl_2(dppf)$ (0.498 g, 0.681 mmol) in 1, 4-dioxane (7 ml) and water (7 ml) was heated in the microwave at 100 °C for 20 min. Water was added and the mixture extracted with EtOAc, dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (SiO_2; 0 - 20 % EtOAc in petrol) to give tert-butyl 4-[(5-bromopyridin-2-yl)methylidene]piperidine-1-carboxylate as a yellow solid (645 mg, 27 %).

^1H NMR (400 MHz, DMSO-d_6) δ 8.64 (m, 1H), 7.98 (m, 1H), 7.26 (m, 1H), 6.35 (s, 1H), 3.44 (m, 2H), 3.37 (m, 2H), 2.87 (m, 2H), 2.31 (m, 2H), 1.42 (s, 9H)

MS ES^+ 253/255

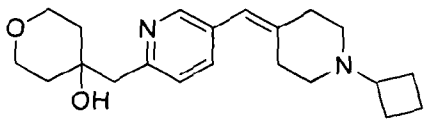
Step b **Example 162**

Prepared via **Scheme 4** starting from tert-butyl 4-[(5-bromopyridin-2-yl)methylidene]piperidine-1-carboxylate (**Int 186**) using cyclobutanone and **Scheme 26** using nBuLi starting from 5-bromo-2-[(1-cyclobutylpiperidin-4-ylidene)methyl]pyridine and using 4-methoxycyclohexanone.

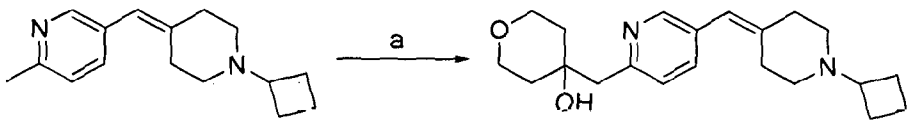
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 - 8.67 (m, 1H), 7.67 - 7.79 (m, 1H), 7.07 - 7.20 (m, 1H), 6.24 (s, 1H), 4.93 (s, 1H), 3.13 - 3.28 (m, 4H), 2.81 - 2.93 (m, 2H), 2.57 - 2.72 (m, 1H), 2.27 - 2.38 (m, 5H), 2.17 - 2.27 (m, 2H), 1.91 - 2.02 (m, 2H), 1.69 (m, 12H)
MS ES$^+$ 357

2.163 Example 163

4-({5-[(1-Cyclobutylpiperidin-4-ylidene)methyl]pyridin-2-yl}methyl)tetrahydro-2H-pyran-4-ol



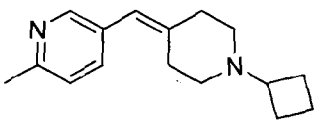
Scheme 43



Reagents and conditions: a) n-BuLi, THF, -20 °C, tetrahydro-4H-pyran-4-one

Step a **Intermediate 187**

5-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-2-methylpyridine



Prepared in an analogous manner to **Intermediate 3** via **Scheme 3** method B starting from 5-(bromomethyl)-2-methylpyridine hydrobromide and using tert-butyl 4-oxopiperidine-1-carboxylate then **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (300MHz, $CDCl_3$) δ8.34 (d, 1H, J = 2.0 Hz), 7.39 (dd, 1H, J = 8.0, 2.0 Hz), 7.09 (d, 1H, J = 8.0 Hz), 6.19 (s, 1H), 2.73 (quin, 1H, J = 8.0 Hz), 2.53 (br. s., 2H), 2.49 (m, 2H), 2.43 (br. s., 2H), 2.31 (m, 2H), 2.08 - 1.89 (m, 4H), 1.77 - 1.59 (m, 2H)

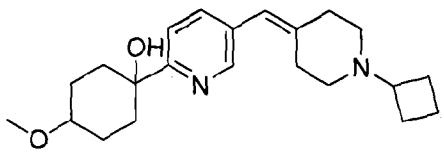
Step b **Example 163**

To a solution of 5-[(1-cyclobutylpiperidin-4-ylidene)methyl]-2-methylpyridine (**Int 187**) (80 mg, 0.33 mmol) in THF (5 ml) at -20 °C was added *n*-BuLi (155 µl, 2.35 M in hexanes, 0.36 mmol). Tetrahydro-4H-pyran-4-one (34 µl, 0.36 mmol) was added immediately and the reaction allowed to warm to r.t. and stirred for 72 h. The reaction was quenched *via* the addition of AcOH and was then concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2; 0 to 10 % MeOH (1 % NH_3) in DCM then 10 % MeOH in toluene) to give 4-({5-[(1-cyclobutylpiperidin-4-ylidene)methyl]pyridin-2-yl}methyl)tetrahydro-2H-pyran-4-ol (38 mg, 34 %).

^{1}H NMR (400 MHz, MeOD) δ 8.20 (s, 1H), 7.41 - 7.55 (m, 1H), 7.13 - 7.27 (m, 1H), 6.21 (s, 1H), 3.52 - 3.74 (m, 4H), 2.83 (s, 2H), 2.63 - 2.78 (m, 1H), 2.14 - 2.47 (m, 8H), 1.92 - 2.07 (m, 2H), 1.75 - 1.91 (m, 2H), 1.53 - 1.74 (m, 4H), 1.30 - 1.43 (m, 2H)
MS ES^+ 343

2.164 and 2.165 Examples 164 and 165

1-{5-[(1-Cyclobutylpiperidin-4-ylidene)methyl]pyridin-2-yl}-4-methoxycyclohexanol



Prepared via **Scheme 2** starting from 2-bromo-5-(bromomethyl)pyridine to give [(6-bromopyridin-3-yl)methyl](triphenyl)phosphonium bromide then **Scheme 3** method A to give tert-butyl 4-[(6-bromopyridin-3-yl)methylidene]piperidine-1-carboxylate then **Scheme 4** using cyclobutanone in step b to give 2-bromo-5-[(1-cyclobutylpiperidin-4-ylidene)methyl]pyridine then **Scheme 26** using nBuLi and 4-methoxycyclohexanone. The 2 ring isomers were separated and isolated.

Example 164 ISOMER 1

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 7.50 - 7.67 (m, 2H), 6.24 (s, 1H), 5.00 (s, 1H), 3.26 (s, 3H), 3.10 - 3.24 (m, 1H), 2.60 - 2.75 (m, 1H), 2.35 - 2.43 (m, 2H), 2.28 - 2.36 (m, 4H), 2.17 - 2.26 (m, 2H), 1.87 - 2.02 (m, 4H), 1.69 - 1.87 (m, 4H), 1.48 - 1.69 (m, 6H)

MS ES^+ 357

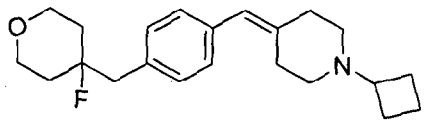
Example 165 ISOMER 2

^1H NMR (400 MHz, DMSO-d_6) δ 8.33 (s, 1H), 7.48 - 7.65 (m, 2H), 6.24 (s, 1H), 4.94 (s, 1H), 3.37 - 3.47 (m, 1H), 3.23 (s, 3H), 2.59 - 2.76 (m, 1H), 2.36 - 2.43 (m, 2H), 2.33 (s, 4H), 2.08 - 2.29 (m, 4H), 1.91 - 2.06 (m, 2H), 1.48 - 1.91 (m, 8H), 1.25 - 1.39 (m, 2H)

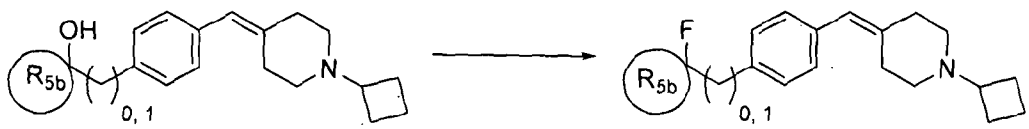
MS ES^+ 357

2.166 Example 166

1-Cyclobutyl-4-{4-[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]benzylidene}piperidine



Scheme 44



R_{5b} is as defined in Scheme 35

Reagents and conditions: a) DAST, DCM, -78 °C

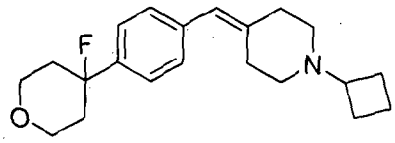
To a solution of 4-(4-((1-cyclobutylpiperidin-4-ylidene)methyl)benzyl)tetrahydro-2H-pyran-4-ol (**Example 143**) (226 mg, 0.66 mmol) in DCM (3.31 ml) at -78 °C was added DAST (437 µl, 3.31 mmol). The reaction was stirred at this temperature for 5 h. Water was added and reaction allowed to warm to r.t. Sat. aq. $NaHCO_3$ and DCM were added and the layers separated. The organics were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (NH silica; 0 - 40 % EtOAc in petrol). The residue was purified by prep. HPLC to give 1-cyclobutyl-4-{4-[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]benzylidene}piperidine as a white solid (26 mg, 11 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.17 (m, 2H, J = 8.08 Hz), 7.13 (d, 2H, J =8.08 Hz), 6.25 (s, 1H), 3.61 - 3.79 (m, 2H), 3.40 - 3.57 (m, 2H), 2.91 (d, 2H, J = 22.99 Hz), 2.57 - 2.75 (m, 1H), 2.41 (t, 2H, J = 5.43 Hz), 2.25 - 2.36 (m, 4H), 2.22 (t, 2H, J = 5.68 Hz), 1.90 - 2.04 (m, 2H), 1.69 - 1.90 (m, 3H), 1.44 - 1.69 (m, 5H)

MS ES$^+$ 344

2.167 Example 167

1-Cyclobutyl-4-[4-(4-fluorotetrahydro-2H-pyran-4-yl)benzylidene]piperidine

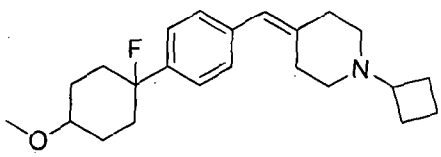


Prepared in an analogous manner to **Example 166** via **Scheme 44** starting from 4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol (**Example 88**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.41 (m, 2H), 7.18 - 7.27 (m, 2H), 6.21 - 6.37 (m, 1H), 3.82 - 4.03 (m, 4H), 2.64 - 2.81 (m, 1H), 2.50 - 2.62 (m, 2H), 2.37 - 2.50 (m, 4H), 2.28 - 2.37 (m, 2H), 2.00 - 2.27 (m, 4H), 1.84 - 2.01 (m, 4H), 1.63 - 1.82 (m, 2H)
MS ES$^+$ 331

2.168 Example 168

1-Cyclobutyl-4-[4-(1-fluoro-4-methoxycyclohexyl)benzylidene]piperidine



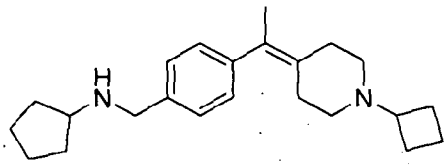
Prepared in an analogous manner to **Example 166** via Scheme 44 starting from 1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methoxycyclohexanol (**Example 91**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.38 (m, 2H), 7.14 - 7.24 (m, 2H), 6.22 - 6.32 (m, 1H), 3.43 (s, 3H), 3.23 - 3.37 (m, 1H), 2.66 - 2.80 (m, 1H), 2.48 - 2.61 (m, 2H), 2.37 - 2.46 (m, 4H), 2.27 - 2.37 (m, 2H), 2.00 - 2.23 (m, 6H), 1.84 - 1.99 (m, 3H), 1.62 - 1.84 (m, 5H)

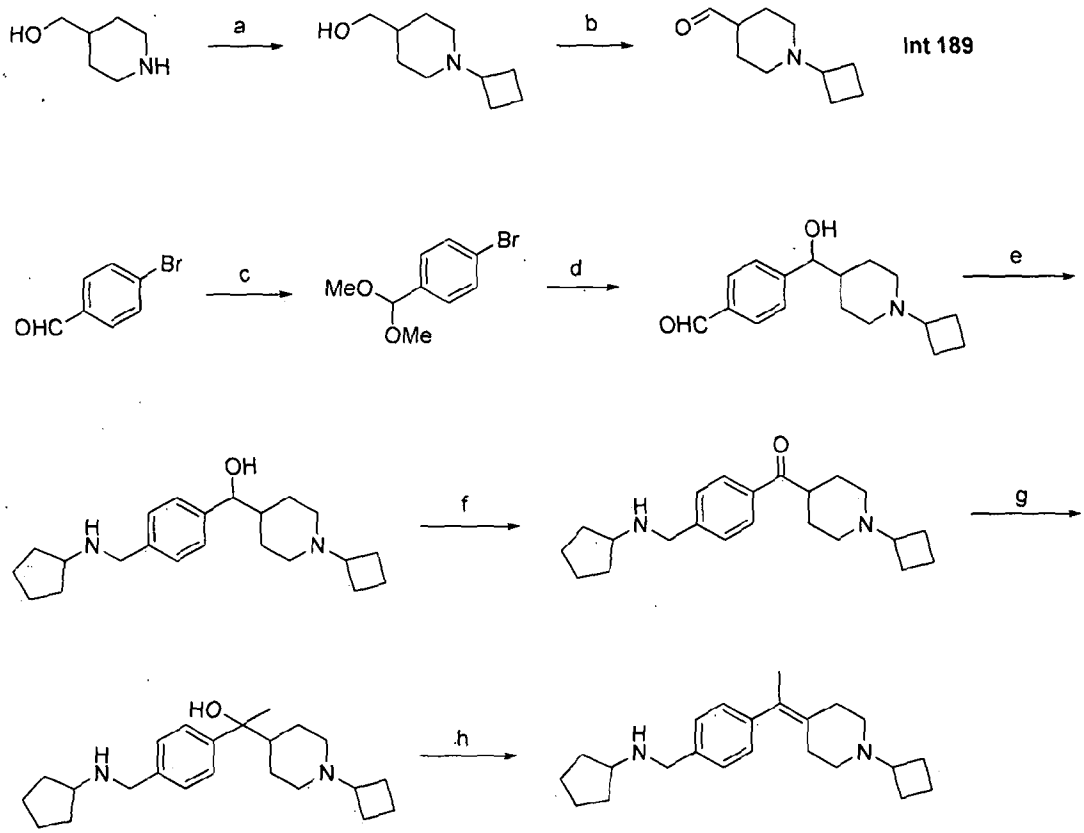
MS ES$^+$ 358

2.169 Example 169

N-(4-(1-(1-Cyclobutylpiperidin-4-ylidene)ethyl)benzyl)cyclopentanamine



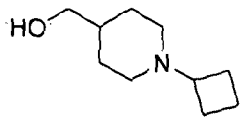
Scheme 45



Reagents and conditions: a) cyclobutanone, sodium triacetoxyborohydride, DCM; b) $(COCl)_2$, DMSO, Et_3N, DCM, -78 °C to r.t.; c) trimethylorthoformate, pTSA, MeOH; d)i) Mg, I_2, THF, reflux then **Int 189**, THF, 0 °C to r.t. then HCl (aq.); e) cyclopentylamine, THF then $NaBH_4$, MeOH; f) $(COCl)_2$, DMSO, Et_3N, DCM, -78 °C to r.t.; g) MeMgBr, THF; h) 2N H_2SO_4

Step a **Intermediate 188**

(1-Cyclobutylpiperidin-4-yl)methanol



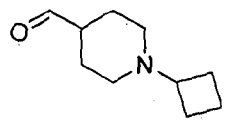
To a stirring solution of piperidin-4-ylmethanol (5.42 g, 47.6 mmol) in DCM was added cyclobutanone (5 g, 71.3 mmol) at r.t. Sodium triacetoxyborohydride (15.1 g, 71.3 mmol) was added portionwise. The resulting suspension was allowed to stir for 40 min. NaOH (10 g, 250 mmol) was then added to brine (100 ml) and added to the reaction mixture. The layers were separated and the aqueous layer back extracted with EtOAc (x 2). The organics were washed with brine, dried (sodium sulfate), filtered and concentrated under reduced pressure to yield 1-cyclobutylpiperidin-4-yl)methanol as a crude yellow oil (7.98 g, 100 %).

^{1}H NMR (300MHz, $CDCl_3$) δ3.50 (m, 2H), 2.85 (m, 2H), 2.70 – 2.50 (m, 2H), 2.00 (m, 2H), 1.90 – 1.60 (m, 7H), 1.40 (m, 1H), 1.20 (m, 2H)

MS ES^+ 170

Step b **Intermediate 189**

1-Cyclobutylpiperidine-4-carbaldehyde



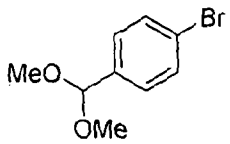
Oxalyl chloride (7.19 g, 47.2 mmol) was dissolved in DCM and cooled to -78 °C. DMSO (8.85 g, 113.3 mmol) was added dropwise and the mixture stirred for 5 min before a solution of (1-cyclobutylpiperidin-4-yl)methanol (**Int 188**) (7.98 g, 47.2 mmol) was added dropwise and mixture stirred at -78 °C for 15 min. Triethylamine (23.84 g, 236 mmol) was added dropwise. The resulting off-white suspension was allowed to warm to r.t. for 1 h. The reaction mixture was filtered through celite, dried (sodium sulfate), filtered, concentrated under reduced pressure and azeotroped with toluene to yield 1-cyclobutylpiperidine-4-carbaldehyde as an orange oil (7.02 g, 88 %).

^{1}H NMR (300MHz, $CDCl_3$) δ 9.60 (s, 1H), 2.75 (m, 2H), 2.25 (m, 1H), 2.10 – 1.80 (m, 9H), 1.70 (m, 4H)

MS ES^+ 168

Step c **Intermediate 190**

1-Bromo-4-(dimethoxymethyl)benzene



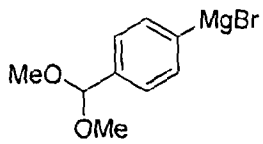
4-Bromobenzaldehyde (30 g, 162 mmol) trimethylorthoformate (51.62 g, 486 mmol) and para-toluenesulfonic acid (3.0 g, 16.2 mmol) were stirred in MeOH (300 ml) at r.t. for 20 h. A further portion of trimethylorthoformate (25.81 g, 243 mmol) was added and the water azeotroped with toluene under reduced pressure. The residue was diluted with toluene and washed with 15 % aqueous sodium hydroxide, dried (sodium sulfate), filtered and concentrated under reduced pressure. It was purified by vacuum distillation to give 1-bromo-4-(dimethoxymethyl)benzene as a colourless liquid (23.92 g, 64 %).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.35 (m, 2H), 5.35 (s, 1H), 3.30 (s, 6H)

MS ES^+ 168

Step d i) **Intermediate 191**

Bromo[4-(dimethoxymethyl)phenyl]magnesium

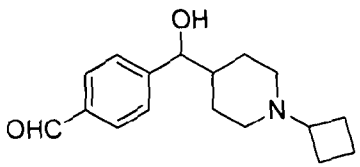


Magnesium turnings (1.22 g, 50.2 mmol) were charged to dried glassware in anhydrous THF (20 ml) with an iodine crystal. A solution of 1-bromo-4-(dimethoxymethyl)benzene (**Int 190**) (11.57 g, 50.3 mmol) in anhydrous THF was

added dropwise with heating. The bromo[4-(dimethoxymethyl)phenyl]magnesium solution was used directly in the subsequent reactions.

Step d ii) **Intermediate 192**

4-((1-Cyclobutylpiperidin-4-yl)(hydroxy)methyl)benzaldehyde

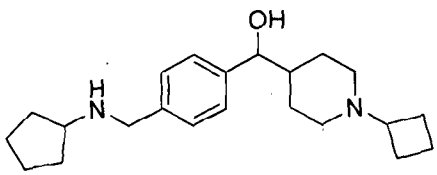


A solution of 1-cyclobutylpiperidine-4-carbaldehyde (**Int 189**) (6.54 g, 0.39 mmol) in anhydrous THF was added dropwise to a suspension of bromo[4-(dimethoxymethyl)phenyl]magnesium (**Int 191**) (50.3 mmol) in anhydrous THF at 0 °C with stirring and the mixture was allowed to warm to r.t. After stirring for 1 h the reaction mixture was concentrated under reduced pressure and treated with 2N aqueous HCl (30 ml) and stirred for 5 min before washing with DCM (x 2). The aqueous layer was then basified with 50 % aqueous NaOH and extracted with EtOAc (x 2). The organics were combined and dried (sodium sulfate) and concentrated under reduced pressure to yield 4-((1-cyclobutylpiperidin-4-yl)(hydroxy)methyl)benzaldehyde as an off-white solid (9.31 g, 75 %).

^{1}H NMR (300MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.85 (m, 2H), 7.45 (m, 2H), 4.50 (m, 1H), 2.85 (m, 2H), 2.60 (m, 1H), 2.00 – 1.20 (m, 13H)
MS ES^+ 274

Step e **Intermediate 193**

(1-Cyclobutylpiperidin-4-yl)(4-((cyclopentylamino)methyl)phenyl)methanol

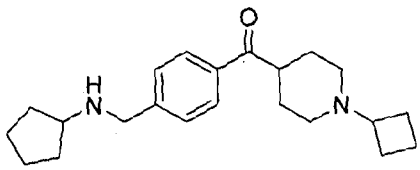


To a solution of 4-((1-cyclobutylpiperidin-4-yl)(hydroxy)methyl)benzaldehyde (**Int 192**) (4.67 g, 17.18 mmol) in anhydrous THF (50 ml) was added cyclopentylamine

(2.19 g, 25.8 mmol) and mixture was stirred at r.t. for 1 h. Further cyclopentylamine (0.73 g, 8.59 mmol) was added and stirred at 60 °C for 1 h. The reaction mixture was concentrated under reduced pressure and diluted with MeOH (50 ml). Sodium borohydride (1.94 g, 51.5 mmol) was added portionwise and stirred at r.t. for 1 h. The reaction mixture was concentrated under reduced pressure and treated with 2 N aqueous HCl, basified with 2.5 N aqueous NaOH and extracted into EtOAc (x 2). The organics were dried (sodium sulfate) and concentrated under reduced pressure to yield (1-cyclobutylpiperidin-4-yl)(4-((cyclopentylamino)methyl)phenyl)methanol as a crude yellow oil (5.54 g, 95 %).

^{1}H NMR (300MHz, $CDCl_3$) δ7.25 (m, 4H), 4.30 (m, 1H), 3.70 (s, 2H), 3.10 (m, 1H), 2.90 (m, 1H), 2.75 (m, 1H), 2.60 (m, 1H), 2.00 – 1.20 (m, 22H)
MS ES^+ 343

Step f **Intermediate 194**
(1-Cyclobutylpiperidin-4-yl){4-[(cyclopentylamino)methyl]phenyl}methanone



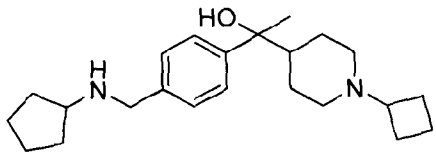
To a solution of oxalyl chloride (2.47 g, 19.4 mmol) in DCM (30 ml) at -78 °C was added dropwise DMSO (3 g, 38.9 mmol). The resultant mixture was stirred at -78 °C for 5 min then (1-cyclobutylpiperidin-4-yl)(4-((cyclopentylamino)methyl) phenyl)methanol (**Int 193**) (5.54 g, 16.2 mmol) in DCM was added dropwise. The mixture was stirred for 15 min then NEt_3 (8.2 g, 81 mmol) was added dropwise and the mixture allowed to warm to r.t. The reaction mixture was poured into sat. aq. $NaHCO_3$ and the aqueous was extracted with DCM (x 2). The organics were dried (sodium sulfate) and concentrated under reduced pressure to yield (1-cyclobutylpiperidin-4-yl)(4-((cyclopentylamino)methyl)phenyl)methanone as a yellow waxy solid (4.3 g, 78 %).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.89 (m, 2H), 7.40 (m, 2H), 3.81 (s, 2H), 3.20 (m, 1H), 3.10 (m, 1H), 2.90 (m, 2H), 2.70 (m, 1H), 2.10 -1.10 (m, 21H)

MS ES$^+$ 341

Step g **Intermediate 195**

1-(1-Cyclobutylpiperidin-4-yl)-1-{4-[(cyclopentylamino)methyl]phenyl}ethanol



To a solution of (1-cyclobutylpiperidin-4-yl)(4-((cyclopentylamino)methyl)phenyl) methanone (**Int 194**) (1.0 g, 2.94 mmol) in anhydrous THF (15 ml) was added methylmagnesium bromide (4.9 ml, 14.71 mmol) dropwise and stirred at r.t. for 1 h. The reaction mixture was concentrated under reduced pressure and treated with 2N aqueous HCl (10 ml) then basified with 50 % aqueous NaOH and extracted with EtOAc. The organics were dried, (sodium sulfate) and concentrated under reduced pressure. The crude material was purified by column chromatography (SiO_2; 5 % MeOH (1% NH_3)/ DCM) to yield 1-(1-cyclobutylpiperidin-4-yl)-1-{4-[(cyclopentylamino)methyl]phenyl}ethanol (530 mg, 43 %).

^{1}H NMR (300MHz, $CDCl_3$) δ7.30 (m, 2H), 7.20 (m, 2H), 3.70 (s, 2H), 3.10 (m, 1H), 2.85 (d, 2H), 2.55 (m, 1H), 2.00 – 1.20 (m, 24H)

MS ES$^+$ 357

Step h **Example 169**

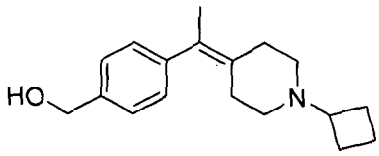
1-(1-cyclobutylpiperidin-4-yl)-1-{4-[(cyclopentylamino)methyl]phenyl}ethanol (**Int 195**) (450 mg, 1.26 mmol) was treated with 2N aqueous sulfuric acid (15 ml) and heated to 80 °C for 18 h. The reaction was basified using brine / NaOH and extracted into EtOAc, dried (sodium sulphate) and concentrated under reduced pressure. The crude material was purified by column chromatography (SiO_2; 5 % MeOH (1 % NH_3) / DCM) to yield N-{4-[1-(1-cyclobutylpiperidin-4-ylidene)ethyl]benzyl} cyclopentanamine (109 mg, 26 %).

^{1}H NMR (300MHz, $CDCl_3$?)δ7.25 (m, 2H), 7.05 (m,? 2H), 3.70 (s, 2H), 3.10 (m, 1H), 2.65 (m, 1H), 2.45 – 2.30 (m, 4H), 2.15 (m, 4H), 1.95 (m, 2H), 1.90 (s, 3H), 1.85 (m, 4H), 1.70 (m, 4H), 2.50 (m, 2H), 1.35 (m, 2H)

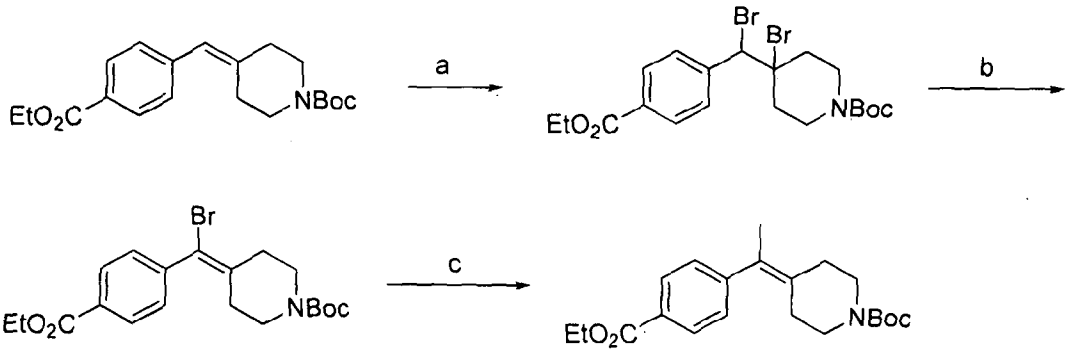
MS ES^+ 339

2.170 Example 170

{4-[1-(1-Cyclobutylpiperidin-4-ylidene)ethyl]phenyl}methanol



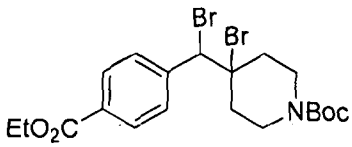
Scheme 46



Reagents and conditions: a) Br_2, K_2CO_3, DCM; b) DBU, DCM; c) $MeB(OH)_2$, K_3PO_4, $PdCl_2(dppf)$, THF, H_2O, 60 °C MW

Step a **Intermediate 196**

tert-Butyl 4-bromo-4-{bromo[4-(ethoxycarbonyl)phenyl]methyl}piperidine-1-carboxylate



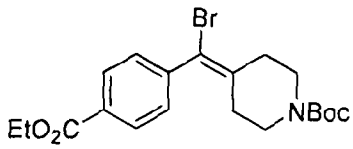
Potassium carbonate (1 g, 7 mmol) was added to a solution of ethyl 4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzoate (**Int 9**) (5.53 g, 16 mmol) in DCM (250 ml) and the suspension was stirred at r.t. A solution of bromine (2.9 g, 18 mmol) in DCM (50 ml) was added over 5 min and the mixture was then stirred for 2 h. The

mixture was filtered and the solvent evaporated to afford a white solid which was triturated with heptane and dried to yield *tert*-butyl 4-bromo-4-{bromo[4-(ethoxycarbonyl)phenyl]methyl}piperidine-1-carboxylate (6.2 g, 76 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.58 (m, 2H), 5.12 (s, 1H), 4.39 (m, 2H), 4.10 (m, 2H), 3.10 (m, 2H), 2.13 (m, 2H), 1.90 – 1.70 (m, 2H), 1.41 (s, 9H), 1.38 (m, 3H)

Step b **Intermediate 197**

tert-Butyl 4-{bromo[4-(ethoxycarbonyl)phenyl]methylidene}piperidine-1-carboxylate

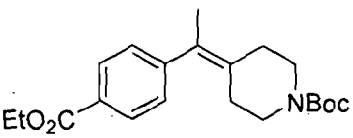


A solution of *tert*-butyl 4-bromo-4-{bromo[4-(ethoxycarbonyl)phenyl]methyl}piperidine-1-carboxylate (**Int 196**) (2.52 g, 5 mmol) in DCM (75 ml) was stirred at r.t. and DBU (0.91 g, 6 mmol) in DCM (25 ml) was added over 5 min. The solution was allowed to stand overnight before a further aliquot of DBU (0.40 g, 2.5 mmol) was added and the solution warmed to 40 °C for 1 h. After cooling to r.t., the mixture was washed with water (x 3), dried ($MgSO_4$) and concentrated under reduced pressure. This was stirred with cold diethyl ether and the supernatant decanted. Evaporation of the ether yielded tert-butyl 4-{bromo[4-(ethoxycarbonyl)phenyl]methylidene}piperidine-1-carboxylate as a yellow solid (1.7 g, 80 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ8.02 (m, 2H), 7.32 (m, 2H), 4.37 (m, 2H), 3.54 (m, 2H), 3.32 (m, 2H), 2.64 (m, 2H), 2.22 (m, 2H), 1.41 (s, 9H), 1.38 (m, 3H)

Step c **Intermediate 198**

tert-Butyl 4-{1-[4-(ethoxycarbonyl)phenyl]ethylidene}piperidine-1-carboxylate

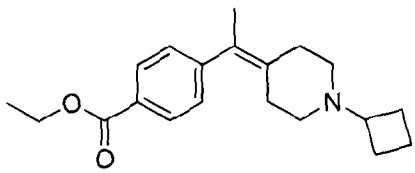


To a stirred solution of the *tert*-butyl 4-{bromo[4-(ethoxycarbonyl)phenyl]methylidene}piperidine-1-carboxylate (**Int 197**) (1.5 g, 3.5 mmol) and methylboronic acid (630 mg, 10.5 mmol) in THF (15 ml) was added K_3PO_4 (2.23 g, 10.5 mmol) in water (3 ml). The mixture was degassed by bubbling argon through it for 10 min and then $Pd(dppf)Cl_2$ (292 mg, 0.4 mmol) was added and it was irradiated at 60°C in a microwave for 2 h. The mixture was filtered through celite and silica and concentrated under reduced pressure then purified by column chromatography (SiO_2; 5 % EtOAc in heptane) to yield *tert*-butyl 4-{1-[4-(ethoxycarbonyl)phenyl]ethylidene}piperidine-1-carboxylate
as a colourless oil (990 mg, 79 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ7.99 (d, 2H, J = 6.8 Hz), 7.14 (d, 2H, J = 6.8 Hz), 4.37 (q, 2H, J = 7.4 Hz), 3.48 (t, 2H, J = 6 Hz), 3.29 (t, 2H, J = 6 Hz), 2.39 (t, 2H, J = 6 Hz), 2.09 (t, 2H, J = 6 Hz), 1.97 (s, 3H), 1.46 (s, 9H), 1.40 (t, 3H, J = 7.4 Hz)

Step d **Intermediate 199**

Ethyl 4-[1-(1-cyclobutylpiperidin-4-ylidene)ethyl]benzoate



Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting with tert-butyl 4-{1-[4-(ethoxycarbonyl)phenyl]ethylidene}piperidine-1-carboxylate (**Int 198**) and using cyclobutanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.88 (d, 2H, J = 8.08 Hz), 7.13 (d, 2H, J = 8.08 Hz), 4.26 (q, 2H, J = 7.07 Hz), 2.84 - 3.00 (m, 1H), 2.51 - 2.63 (m, 2H), 2.43 - 2.51 (m, 2H), 2.31 - 2.42 (m, 2H), 1.98 - 2.16 (m, 4H), 1.84 - 1.98 (m, 5H), 1.58 - 1.73 (m, 2H), 1.29 (t, 3H, J = 7.07 Hz)
MS ES^+ 314

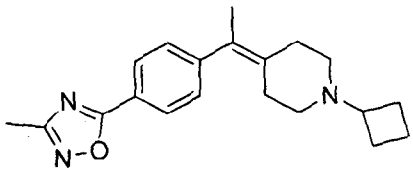
Step e **Example 170**

Prepared in analogous manner to **Intermediate 31** via **Scheme 16** starting from ethyl 4-[1-(1-cyclobutylpiperidin-4-ylidene)ethyl]benzoate (**Int 199**).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, 2H, J = 8 Hz), 7.13 (d, 2H, J = 8 Hz), 6.25 (s, 1H), 3.46 (s, 2H), 3.33 (s, 3H), 3.21 (tt, 1H, J = 8.5 Hz, 5 Hz), 2.76- 2.66 (m, 3H), 2.53 (t, 2H, J = 5.5 Hz), 2.39 (s, 4H), 2.29 (t, 2H, J = 5.5 Hz), 2.18 - 2.09 (m, 2H), 2.08 - 1.99 (m, 2H), 1.95 - 1.84 (m, 4H), 1.77 - 1.59 (m, 4H)
MS ES^+ 272

2.171 Example 171

1-Cyclobutyl-4-{1-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]ethylidene}piperidine

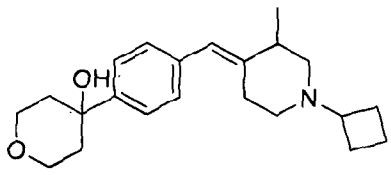


Prepared in analogous manner to **Example 10** via **Scheme 6** starting from ethyl 4-[1-(1-cyclobutylpiperidin-4-ylidene)ethyl]benzoate (**Example 199**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, 2H, J = 8.34 Hz), 7.19 (m, 2H), 2.57 - 2.71 (m, 1H), 2.37 - 2.45 (m, 5H), 2.28 - 2.37 (m, 2H), 2.06 - 2.22 (m, 4H), 1.77 - 2.02 (m, 7H), 1.52 - 1.72 (m, 2H)
MS ES^+ 324

2.172 Example 172

4-{4-[(E)-(1-Cyclobutyl-3-methylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol (racemic)



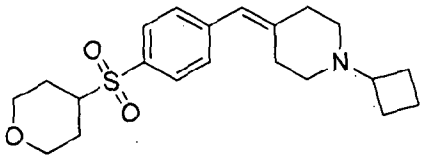
Prepared via **Scheme 3** Method A starting from *tert*-butyl 3-methyl-4-oxopiperidine-1-carboxylate and (4-bromobenzyl)(triphenyl)phosphonium bromide then **Scheme 4** using

cyclobutanone in step b then **Scheme 26** starting from (4E)-4-(4-bromobenzylidene)-1-cyclobutyl-3-methylpiperidine and using BuLi and tetrahydro-4H-pyran-4-one.

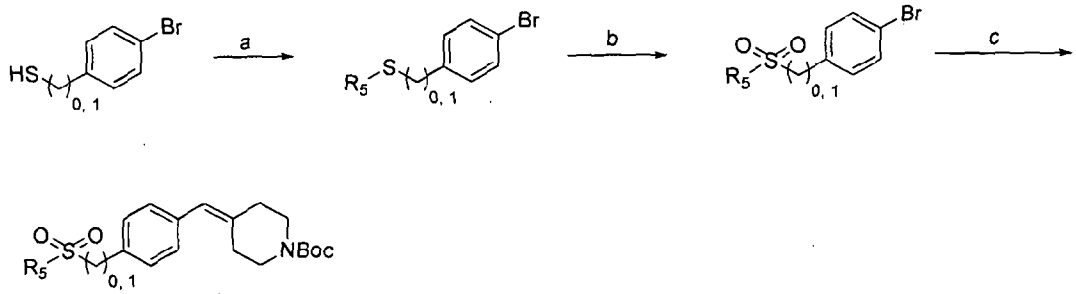
^{1}H NMR (400 MHz, MeOD) δ 7.44 (d, 2H, J = 8.08 Hz) 7.17 (d, 2H, J = 8.08 Hz) 6.31 (s, 1H) 3.89 - 4.01 (m, 2H) 3.77 - 3.88 (m, 2H) 2.69 - 2.93 (m, 4H) 2.42 - 2.56 (m, 1H) 2.01 - 2.30 (m, 5H) 1.83 - 2.01 (m, 3H) 1.71 - 1.81 (m, 3H) 1.64 - 1.82 (m, 6H) 1.68 (d, 3H, J = 12.88 Hz) 1.18 (d, 3H, J = 6.82 Hz)
MS ES$^+$ 342

2.173 Example 173

1-Cyclobutyl-4-[4-(tetrahydro-2H-pyran-4-ylsulfonyl)benzylidene]piperidine



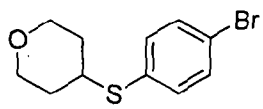
Scheme 47



Reagents and conditions: a) NaH, R_5Br, DMF; b) mCPBA, DCM; c) **Int 26**, $Pd(PPh_3)_4$, K_2CO_3, dioxane, H_2O, 100 °C MW or **Int 26**, $PdCl_2(dppf)$, sat. aq. Na_2CO_3, dioxane, 80 °C MW

Step a) **Intermediate 200**

4-[(4-Bromophenyl)sulfanyl]tetrahydro-2H-pyran

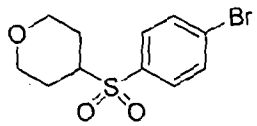


To a solution of 4-bromobenzenethiol (2 g, 10.58 mmol) in DMF (20 ml) was added NaH (0.635 g, 15.87 mmol) at 0 °C and the reaction stirred for 1 h. To this was added 4-bromotetrahydro-2H-pyran (1.92 g, 11.64 mmol) in DMF and the reaction allowed to warm to r.t. and stirred for 67 h. Reaction was quenched by addition of water and extracted with EtOAc (x 2). The organics were washed with brine (x 5), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2; 0 -100 % DCM in petrol) to yield 4-[(4-bromophenyl)sulfanyl]tetrahydro-2H-pyran (2.18 g, 75 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ7.52 (m, 2H), 7.35 (m, 2H), 3.73 - 3.88 (m, 2H), 3.44 - 3.56 (m, 1H), 3.39 (m, 2H), 1.84 (m, 2H), 1.49 (m, 2H)

Step b) **Intermediate 201**

4-[(4-Bromophenyl)sulfonyl]tetrahydro-2H-pyran

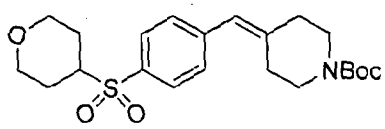


To a solution of 4-[(4-bromophenyl)sulfanyl]tetrahydro-2H-pyran (**Int 200**) (2.18 g, 8 mmol) in DCM (25 ml) was added 3-chlorobenzoperoxoic acid (4.13 g, 37 mmol). Mixture was quenched by addition of sodium hydrogen carbonate and extracted with DCM (x 2). The organics were dried ($MgSO_4$) and concentrated under reduced pressure to yield 4-(4-bromophenylsulfonyl)tetrahydro-2H-pyran (2.66 g, 100 %). Taken on as crude material in the next step.

MS ES^+ 309

Step c **Intermediate 202**

tert-Butyl 4-[4-(tetrahydro-2H-pyran-4-ylsulfonyl)benzylidene]piperidine-1-carboxylate



A microwave vial was charged with 4-(4-bromophenylsulfonyl)tetrahydro-2H-pyran (**Int 201**) (598 mg, 2.0 mmol), *tert*-butyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)methylene)piperidine-1-carboxylate (**Int 26**) (950 mg, 2.9 mmol), and potassium carbonate (1.083 g, 7.84 mmol) in 1,4-Dioxane : H_2O (4 ml : 4 ml). The vial was sealed and purged with nitrogen then $Pd(PPh_3)_4$ (226 mg, 0.2 mmol) was added and mixture irradiated in the microwave for 45 min at 100 °C. Mixture was quenched by the addition of sat. aq. $NaHCO_3$ and extracted with EtOAc (x 2). The organics were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Residue was purified by column chromatography (SiO_2; 0 – 50 % EtOAc in petrol) to yield *tert*-butyl 4-[4-(tetrahydro-2H-pyran-4-ylsulfonyl)benzylidene]piperidine-1-carboxylate as a white solid.

MS ES^+ 422

Step d **Example 173**

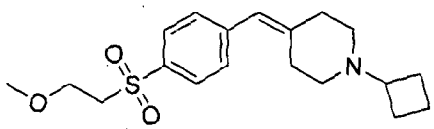
Prepared in an analogous manner to **Intermediate 5** via **Scheme 4** starting from *tert*-butyl 4-[4-(tetrahydro-2H-pyran-4-ylsulfonyl)benzylidene]piperidine-1-carboxylate (**Int 202**) using cyclobutanone in step b

^1H NMR (400 MHz, DMSO-d_6) δ 7.74 - 7.85 (m, 2H), 7.46 - 7.55 (m, 2H), 6.40 (s, 1H), 3.84 - 3.95 (m, 2H), 3.45 - 3.60 (m, 1H), 3.22 - 3.30 (m, 2H), 2.65 - 2.76 (m, 1H), 2.40 - 2.47 (m, 2H), 2.31 - 2.40 (m, 4H), 2.20 - 2.29 (m, 2H), 1.92 - 2.05 (m, 2H), 1.67 - 1.85 (m, 4H), 1.45 - 1.67 (m, 4H)

MS ES^+ 376

2.174 Example 174

1-cyclobutyl-4-{4-[(2-methoxyethyl)sulfonyl]benzylidene}piperidine

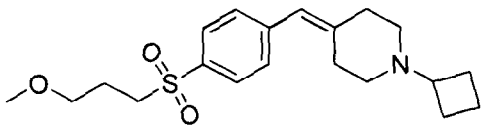


Prepared in an analogous manner to **Example 173** via **Scheme 47** starting from 4-bromobenzenethiol and 2-methoxyethanethiol using $PdCl_2dppf$ and Na_2CO_3 in step c, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 - 7.88 (m, 2H), 7.32 - 7.51 (m, 2H), 6.37 (s, 1H), 3.51 - 3.68 (m, 4H), 3.10 (s, 3H), 2.59 - 2.76 (m, 1H), 2.40 - 2.46 (m, 2H), 2.34 (s, 4H), 2.19 - 2.30 (m, 2H), 1.91 - 2.03 (m, 2H), 1.71 - 1.91 (m, 2H), 1.50 - 1.71 (m, 2H)
MS ES$^+$ 350

2.175 Example 175

1-Cyclobutyl-4-{4-[(3-methoxypropyl)sulfonyl]benzylidene}piperidine

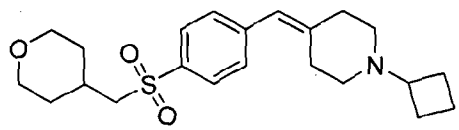


Prepared in an analogous manner to **Example 173** via **Scheme 47** starting from 4-bromobenzenethiol and 3-methoxypropane-1-thiol using $PdCl_2dppf$ and Na_2CO_3 in step c, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 - 7.88 (m, 2H), 7.39 - 7.53 (m, 2H), 6.38 (s, 1H), 3.22 - 3.42 (m, 7H), 2.59 - 2.78 (m, 1H), 2.40 - 2.47 (m, 2H), 2.34 (s, 4H), 2.17 - 2.29 (m, 2H), 1.88 - 2.04 (m, 2H), 1.70 - 1.88 (m, 4H), 1.51 - 1.70 (m, 2H)
MS ES$^+$ 364

2.176 Example 176

1-Cyclobutyl-4-{4-[(tetrahydro-2H-pyran-4-ylmethyl)sulfonyl]benzylidene} piperidine

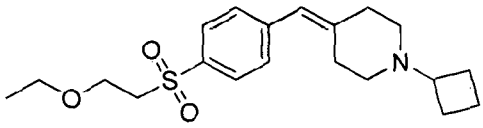


Prepared in an analogous manner to **Example 173** via **Scheme 47** starting from 4-bromobenzenethiol and tetrahydro-2H-pyran-4-ylmethanethiol using $Pd(PPh_3)_4$ and K_2CO_3 in step c, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, MeOD) δ 7.87 (m, 2H, J = 8.34 Hz), 7.46 (m, 2H, J = 8.34 Hz), 6.42 (s, 1H), 3.78 - 3.91 (m, 2H), 3.39 (td, 2H, J = 11.81, 1.89 Hz), 3.18 (d, 2H, J = 6.32 Hz), 2.74 - 2.84 (m, 1H), 2.51 - 2.57 (m, 2H), 2.46 (s, 4H), 2.36 (t, 2H, J = 5.56 Hz), 2.02 - 2.21 (m, 3H), 1.87 - 2.00 (m, 2H), 1.68 - 1.82 (m, 4H), 1.34 - 1.49 (m, 2H)
MS ES$^+$ 390

2.177 Example 177

1-Cyclobutyl-4-{4-[(2-ethoxyethyl)sulfonyl]benzylidene}piperidine



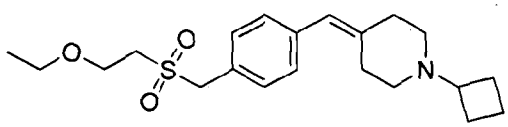
Prepared in an analogous manner to **Example 173** via **Scheme 47** starting from 4-bromobenzenethiol and 2-ethoxyethanethiol using $PdCl_2dppf$ and Na_2CO_3 in step c, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 - 7.92 (m, 2H), 7.34 - 7.59 (m, 2H), 6.59 (s, 1H), 3.52 - 3.71 (m, 5H), 3.43 - 3.52 (m, 1H), 3.34 - 3.43 (m, 1H), 3.21 - 3.29 (m, 2H), 2.66 - 2.91 (m, 4H), 2.54 - 2.66 (m, 2H), 2.26 - 2.46 (m, 2H), 2.04 - 2.26 (m, 2H), 1.53 - 1.86 (m, 2H), 0.77 - 0.92 (m, 3H)

MS ES^+ 364

2.178 Example 178

1-Cyclobutyl-4-(4-{[(2-ethoxyethyl)sulfonyl]methyl}benzylidene)piperidine



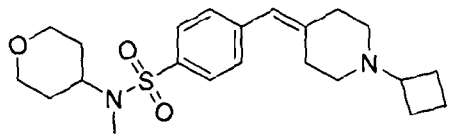
Prepared in an analogous manner to **Example 173** via **Scheme 47** using appropriate starting materials and using $PdCl_2dppf$ and Na_2CO_3 in step c, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 - 7.48 (m, 2H), 7.18 - 7.26 (m, 2H), 6.29 (s, 1H), 4.36 (s, 2H), 3.76 - 3.96 (m, 2H), 3.51 - 3.68 (m, 2H), 3.02 - 3.13 (m, 2H), 2.66 - 2.84 (m, 1H), 2.48 - 2.62 (m, 2H), 2.43 (m, 4H), 2.20 - 2.36 (m, 2H), 2.01 - 2.13 (m, 2H), 1.81 - 2.01 (m, 2H), 1.49 - 1.81 (m, 2H), 1.13 - 1.44 (m, 3H)

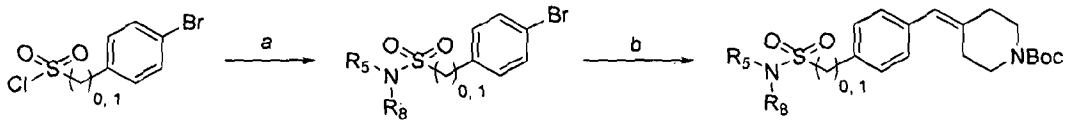
MS ES^+ 378

2.179 Example 179

4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-N-methyl-N-(tetrahydro-2H-pyran-4-yl)benzenesulfonamide



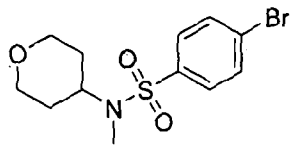
Scheme 48



Reagents and conditions: a) R_5R_8NH, Et_3N, DCM or R_5R_8NH, Na_2CO_3, MeCN; b) **Int 26**, $Pd(PPh_3)_4$, K_2CO_3, dioxane, H_2O, 100 °C MW or **Int 26**, $PdCl_2(dppf)$, sat. aq. Na_2CO_3, dioxane, 80 °C MW or **Int 26**, $Pd(PPh_3)_4$, Na_2CO_3, dioxane, H_2O, 100 °C MW

Step a **Intermediate 203**

4-Bromo-N-methyl-N-(tetrahydro-2H-pyran-4-yl)benzenesulfonamide



To a solution of N-methyltetrahydro-2H-pyran-4-amine (0.710 g, 6.16 mmol) and Et_3N (1.227 ml, 8.81 mmol) in DCM (10 ml) cooled to 0 °C was added dropwise a solution of 4-bromobenzene-1-sulfonyl chloride (1.5 g, 5.87 mmol) in DCM (10 ml). The reaction was allowed to warm to r.t. and stirred for 20 h. The reaction was concentrated under reduced pressure and the resultant white solid dissolved in EtOAc and filtered. The filtrate was concentrated under reduced pressure and the resulting solid dried under high vacuum to yield 4-bromo-N-methyl-N-(tetrahydro-2H-pyran-4-yl)benzenesulfonamide as an off-white solid (1.94 g, 99 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ7.79 (m, 4H), 3.87 - 4.01 (m, 1H), 3.73 - 3.86 (m, 2H), 3.33 - 3.37 (m, 1H), 3.29 (m, 1H), 2.70 (s, 3H), 1.54 - 1.70 (m, 2H), 1.11 - 1.27 (m, 2H)

Step b **Example 179**

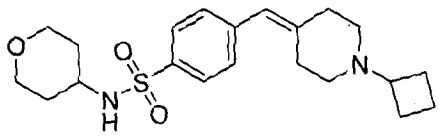
Prepared in an analogous manner to **Example 173** via **Scheme 48** starting from 4-bromo-N-methyl-N-(tetrahydro-2H-pyran-4-yl)benzenesulfonamide (**Int 203**) in step b and using $PdCl_2dppf$ and Na_2CO_3, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 - 7.79 (m, 2H), 7.34 - 7.46 (m, 2H), 6.34 (s, 1H), 3.87 - 4.00 (m, 1H), 3.75 - 3.87 (m, 2H), 3.31 (m, 2H), 2.61 - 2.74 (m, 4H), 2.38 - 2.45 (m, 2H), 2.30 - 2.38 (m, 4H), 2.21 - 2.29 (m, 2H), 1.88 - 2.05 (m, 2H), 1.72 - 1.88 (m, 2H), 1.54 - 1.72 (m, 4H), 1.14 - 1.26 (m, 2H)

MS ES$^+$ 405

2.180 Example 180

4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-N-(tetrahydro-2H-pyran-4-yl)benzenesulfonamide



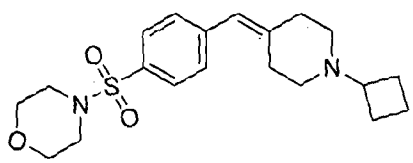
Prepared in an analogous manner to **Example 179** via **Scheme 48** starting with 4-bromobenzene-1-sulfonyl chloride and tetrahydro-2H-pyran-4-amine and using $Pd(PPh_3)_4$ and Na_2CO_3 in step b, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 - 7.78 (m, 2H), 7.29 - 7.48 (m, 2H), 6.34 (br. s., 1H), 3.65 - 3.81 (m, 2H), 3.09 - 3.27 (m, 3H), 2.61 - 2.75 (m, 1H), 2.33 (br. s., 9H), 1.87 - 2.05 (m, 2H), 1.70 - 1.87 (m, 2H), 1.56 - 1.70 (m, 2H), 1.41 - 1.56 (m, 2H), 1.32 (m, 2H)

MS ES$^+$ 391

2.181 Example 181

4-({4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}sulfonyl)morpholine



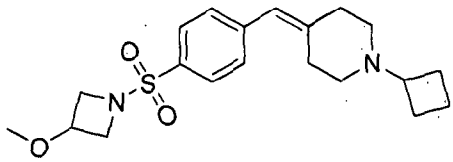
Prepared in an analogous manner to **Example 179** via **Scheme 48** starting with 4-bromobenzene-1-sulfonyl chloride and morpholine and using $PdCl_2dppf$ and Na_2CO_3 in step b, and **Scheme 4** using cyclobutanone in step b.

^1H NMR (400 MHz, DMSO-d_6) δ 7.62 - 7.72 (m, 2H), 7.41 - 7.51 (m, 2H), 6.38 (s, 1H), 3.55 - 3.68 (m, 4H), 2.79 - 2.93 (m, 4H), 2.63 - 2.78 (m, 1H), 2.40 - 2.47 (m, 2H), 2.34 (s, 4H), 2.17 - 2.29 (m, 2H), 1.90 - 2.03 (m, 2H), 1.71 - 1.90 (m, 2H), 1.53 - 1.71 (m, 2H)

MS ES^+ 377

2.182 Example 182

1-Cyclobutyl-4-{4-[(3-methoxyazetidin-1-yl)sulfonyl]benzylidene}piperidine



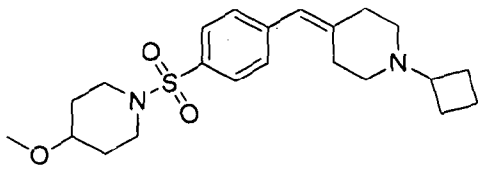
Prepared in an analogous manner to **Example 179** via **Scheme 48** starting with 4-bromobenzene-1-sulfonyl chloride and 3-methoxyazetidine hydrochloride and using $PdCl_2dppf$ and Na_2CO_3 in step b, and **Scheme 4** using cyclobutanone in step b.

^1H NMR (400 MHz, DMSO-d_6) δ 7.67 - 7.80 (m, 2H), 7.40 - 7.57 (m, 2H), 6.39 (s, 1H), 3.97 - 4.08 (m, 1H), 3.86 - 3.97 (m, 2H), 3.39 - 3.51 (m, 2H), 3.05 (s, 3H), 2.62 - 2.76 (m, 1H), 2.41 - 2.48 (m, 2H), 2.35 (s, 3H), 2.19 - 2.32 (m, 2H), 1.89 - 2.04 (m, 2H), 1.71 - 1.89 (m, 2H), 1.51 - 1.71 (m, 2H)

MS ES^+ 377

2.183 Example 183

1-Cyclobutyl-4-{4-[(4-methoxypiperidin-1-yl)sulfonyl]benzylidene}piperidine



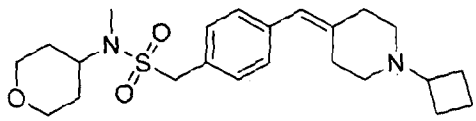
Prepared in an analogous manner to **Example 179** via **Scheme 48** starting with 4-bromobenzene-1-sulfonyl chloride and 4-methoxypiperidine and using $PdCl_2dppf$ and Na_2CO_3 in step b, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 - 7.74 (m, 2H), 7.36 - 7.51 (m, 2H), 6.36 (s, 1H), 3.19 - 3.27 (m, 1H), 3.15 (s, 3H), 2.99 - 3.11 (m, 2H), 2.73 - 2.83 (m, 2H), 2.63 - 2.73 (m, 1H), 2.41 - 2.48 (m, 2H), 2.34 (s, 4H), 2.20 - 2.29 (m, 2H), 1.89 - 2.04 (m, 2H), 1.70 - 1.89 (m, 4H), 1.45 - 1.70 (m, 4H)

MS ES$^+$ 405

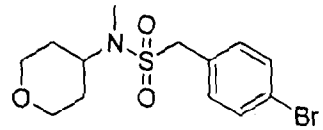
2.184 Example 184

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-N-methyl-N-(tetrahydro-2H-pyran-4-yl)methanesulfonamide



Step a) **Intermediate 204**

1-(4-Bromophenyl)-N-methyl-N-(tetrahydro-2H-pyran-4-yl)methanesulfonamide



To a suspension of N-methyltetrahydro-2H-pyran-4-amine (0.507 g, 4.40 mmol) and sodium carbonate (0.467 g, 4.40 mmol) in MeCN (10 ml) was added (4-bromophenyl)methanesulfonyl chloride (0.593 g, 2.201 mmol) and the reaction mixture was stirred at r.t. for 1.5 h. The mixture was quenched with water and extracted with EtOAc (x 2). The organics were dried ($MgSO_4$) and concentrated under reduced pressure to yield 1-(4-bromophenyl)-N-methyl-N-(tetrahydro-2H-pyran-4-yl)methanesulfonamide as a white solid (0.634 g, 83 %).

^{1}H NMR (400 MHz, MeOD) δ 7.56 (m, 2H, J = 8.34 Hz), 7.38 (m, 2H, J = 8.34 Hz), 4.34 (s, 2H), 3.95 (dd, 2H, J = 11.62, 4.55 Hz), 3.69 - 3.82 (m, 1H), 3.35 - 3.43 (m, 2H), 2.72 (s, 3H), 1.74 - 1.87 (m, 2H), 1.45 - 1.53 (m, 2H)

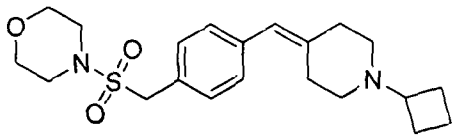
Step b **Example 187**

Prepared in an analogous manner to **Example 179** via **Scheme 48**, step b starting with 1-(4-bromophenyl)-N-methyl-N-(tetrahydro-2H-pyran-4-yl)methanesulfonamide (**Int 204**) and using $Pd(PPh_3)_4$ and K_2CO_3, and **Scheme 4** using cyclobutanone in step b.

^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 2H J = 7.83 Hz), 7.20 (m, 2H, J = 8.08 Hz), 6.27 (s, 1H), 4.20 (s, 2H), 3.92 (dd, 2H, J = 11.37, 4.29 Hz), 3.60 - 3.75 (m, 1H), 3.29 (t, 2H, J = 11.37 Hz), 2.59 - 2.76 (m, 4H), 2.44 - 2.54 (m, 2H), 2.41 (s, 4H), 2.20 - 2.32 (m, 2H), 1.99 - 2.10 (m, 2H), 1.81 - 1.99 (m, 2H), 1.62 - 1.79 (m, 4H), 1.29 - 1.41 (m, 2H)
MS ES^+ 419

2.185 Example 185

4-({4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}sulfonyl)morpholine

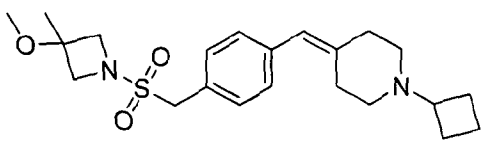


Prepared in an analogous manner to **Example 184** via **Scheme 48** starting with (4-bromophenyl)methanesulfonyl chloride and morpholine and using $Pd(PPh_3)_4$ and K_2CO_3 in step b, and **Scheme 4** using cyclobutanone in step b.

^1H NMR (400 MHz, MeOD) δ 7.42 (m, 2H, J = 8.08 Hz), 7.24 (m, 2H, J = 8.08 Hz), 6.36 (s, 1H), 4.36 (s, 2H), 3.59 - 3.70 (m, 4H), 3.10 - 3.21(m, 4H), 2.73 - 2.87 (m, 1H), 2.51 - 2.59 (m, 2H), 2.41 - 2.51 (m, 4H), 2.36 (t, 2H, J = 5.43 Hz), 2.02 - 2.16 (m, 2H), 1.89 - 2.02 (m, 2H), 1.65 - 1.84 (m, 2H)
MS ES^+ 391

2.186 Example 186

1-Cyclobutyl-4-(4-{[(3-methoxy-3-methylazetidin-1-yl)sulfonyl]methyl} benzylidene)piperidine



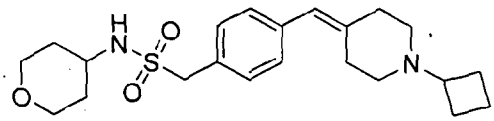
Prepared in an analogous manner to **Example 184** via **Scheme 48** starting with (4-bromophenyl)methanesulfonyl chloride and 3-methoxy-3-methylazetidine hydrochloride and using $Pd(PPh_3)_4$ and K_2CO_3 in step b, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 (d, 2H, J = 8.08 Hz), 7.20 (d, 2H, J = 8.08 Hz), 6.27 (s, 1H), 4.48 (s, 2H), 3.85 (d, 2H, J = 8.34 Hz), 3.56 (d, 2H, J = 8.34 Hz), 3.13 (s, 3H), 2.62 - 2.74 (m, 1H), 2.35 - 2.45 (m, 2H), 2.31 (s, 4H), 2.22 (t, 2H, J = 5.56 Hz), 1.86 - 2.06 (m, 2H), 1.69 - 1.83 (m, 2H), 1.53 - 1.67 (m, 2H), 1.39 (s, 3H)

MS ES^+ 405

2.187 Example 187

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-N-(tetrahydro-2H-pyran-4-yl)methanesulfonamide



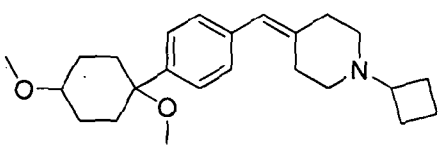
Prepared in an analogous manner to **Example 184** via **Scheme 48** starting with (4-bromophenyl)methanesulfonyl chloride and tetrahydro-2H-pyran-4-amine and using $Pd(PPh_3)_4$ and K_2CO_3 in step b, and **Scheme 4** using cyclobutanone in step b.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 (d, 2H, J = 8.08 Hz), 7.13 - 7.25 (m, 3H), 6.27 (s, 1H), 4.30 (s, 2H), 3.67 - 3.83 (m, 2H), 3.14 - 3.27 (m, 3H), 2.60 - 2.73 (m, 1H), 2.40 (t, 2H, J = 5.31 Hz), 2.31 (br. s., 4H), 2.13 - 2.25 (m, 2H), 1.87 - 2.00 (m, 2H), 1.66 - 1.87 (m, 4H), 1.49 - 1.66 (m, 2H), 1.28 - 1.48 (m, 2H)

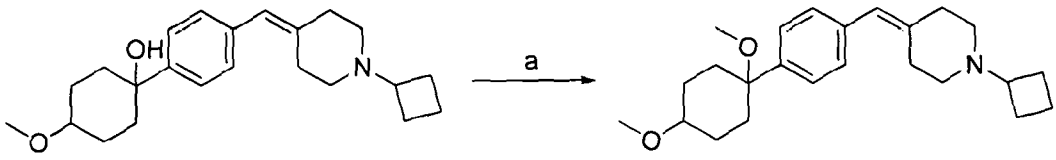
MS ES^+ 405

2.188 Example 188

1-Cyclobutyl-4-[4-(1,4-dimethoxycyclohexyl)benzylidene]piperidine



Scheme 49



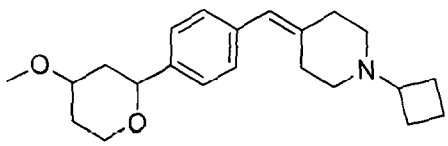
Reagents and conditions: a)i) BH_3.THF, THF, -78 °C ii) NaHMDS, MeI, THF iii) 2M NaOH (aq.)

To a stirred solution of 1-(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)-4-methoxycyclohexanol (**Example 91**) (700 mg, 1.969 mmol) in dry THF (19.7 ml) at -78 °C, under an atmosphere of nitrogen, was added dropwise borane.THF complex (2.166 ml, 2.166 mmol) and the reaction was stirred at -78 °C for 2 h. The reaction was then allowed to warm to r.t. and then concentrated under reduced pressure. To a solution of the resultant oil dissolved in dry THF (10 ml), cooled to 0 °C under nitrogen, was added dropwise NaHMDS in THF (2.166 ml, 2.166 mmol). The reaction was stirred at 0 °C for 15 min. Iodomethane was then added dropwise (148 µl, 2.363 mmol) and the reaction was stirred at 0 °C for 1 h and then allowed to warm to r.t. and stirred for 17 h. 2M sodium hydroxide (10 ml) was added and the reaction was stirred at r.t. for 5 days. The mixture was extracted with EtOAc (x 2). The organics were washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude oil was purified by column chromatography (NH silica; 0 – 30 % EtOAc in petrol) to yield a colourless oil which was dried in the high vacuum oven at 60 °C for 3 h to yield 1-cyclobutyl-4-[4-(1,4-dimethoxycyclohexyl)benzylidene]piperidine as a yellow solid (274 mg, 36 %).

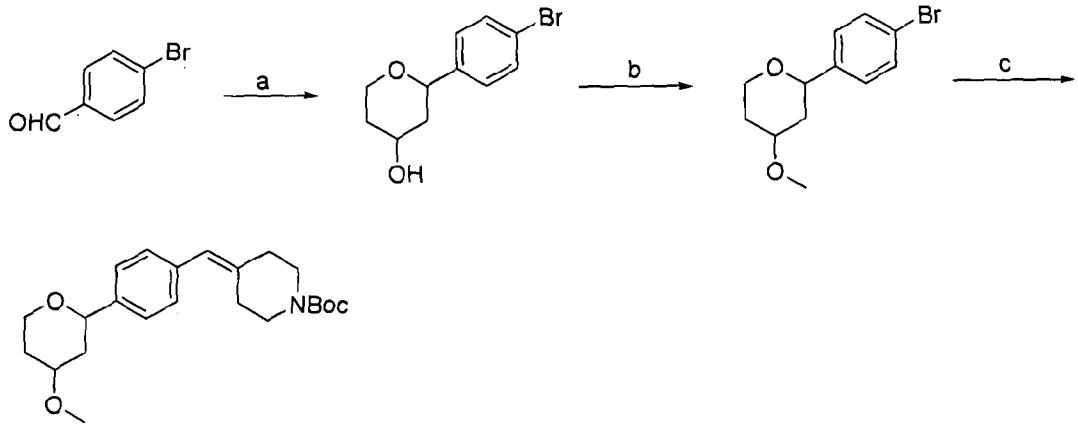
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.26 - 7.39 (m, 2H), 7.07 - 7.26 (m, 2H), 6.18 - 6.31 (m, 1H), 3.26 (s, 3H), 3.10 - 3.23 (m, 1H), 2.87 (s, 3H), 2.61 - 2.73 (m, 1H), 2.38 - 2.46 (m, 2H), 2.26 - 2.36 (m, 4H), 2.16 - 2.26 (m, 2H), 1.89 - 2.04 (m, 4H), 1.72 - 1.89 (m, 4H), 1.56 - 1.72 (m, 4H), 1.39 - 1.55 (m, 2H)
MS ES^+ 370

2.189 Example 189

1-Cyclobutyl-4-[4-(4-methoxytetrahydro-2H-pyran-2-yl)benzylidene]piperidine



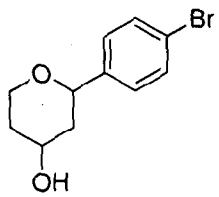
Scheme 50



Reagents and conditions: a) But-3-en-1-ol, H_2SO_4; b) NaH, MeI, THF; c) **Int 26**, $Pd(PPh_3)_4$, K_2CO_3, dioxane/water, 100 °C, MW

Step a **Intermediate 205**

2-(4-Bromophenyl)tetrahydro-2H-pyran-4-ol

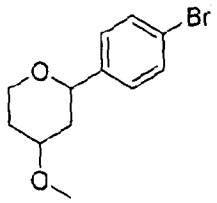


To a mixture of 4-bromobenzaldehyde (5 g, 27.0 mmol) and but-3-en-1-ol (5.85 g, 81 mmol) was added dropwise sulfuric acid (4.32 ml, 81 mmol) and the reaction mixture was stirred at r.t. for 18 h. The reaction was poured onto ice water, basified to pH 8 with 1M NaOH, extracted with EtOAc and dried ($MgSO_4$), and concentrated under reduced pressure. The crude oil was purified by column chromatography (SiO_2; 0 – 55 % EtOAc in petrol) and concentrated under reduced pressure to yield 2-(4-bromophenyl)tetrahydro-2H-pyran-4-ol as a white solid (2.5 g, 36 %).

^{1}H NMR (400 MHz,MeOD) δ7.49 (m, 2H), 7.30 (s, 2H), 4.28 - 4.40 (m, 1H), 4.04 - 4.18 (m, 1H), 3.81 - 3.96 (m, 1H), 3.54 - 3.71 (m, 1H), 2.07 - 2.18 (m, 1H), 1.85 - 2.00 (m, 1H), 1.49 - 1.66 (m, 1H), 1.39 (m, 1H)

Step b **Intermediate 206**

2-(4-bromophenyl)-4-methoxytetrahydro-2H-pyran



To a solution of 2-(4-bromophenyl)tetrahydro-2H-pyran-4-ol (**Int 205**) (2.5 g, 9.72 mmol) in THF, under a nitrogen atmosphere, was added sodium hydride (0.506 g, 12.64 mmol) at 0 °C and the resultant slurry stirred for 1 h at 0 °C. Iodomethane (0.790 ml, 12.64 mmol) was added dropwise and the reaction mixture allowed to warm to r.t. and stirred for 18 h. The reaction was quenched with sat. NH_4Cl and extracted with Et_2O (x 3). The organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO_2; 5 - 40 % EtOAc in petrol) to yield the 2-(4-bromophenyl)-4-methoxytetrahydro-2H-pyran as a clear, colourless oil (1.2 g, 46 %).

^{1}H NMR (400 MHz, CD_2Cl_2) δ1.39 (m, 1H), 1.48 - 1.60 (m, 1H), 2.00 - 2.09 (m, 1H), 2.24 (dt, 1H, J = 12.57, 2.05 Hz), 3.38 (s, 3H), 3.45 - 3.62 (m, 2H), 4.12 - 4.25 (m, 1H), 4.31 (dd, 1H, J = 11.49, 1.39 Hz); 7.28 (d, 2H, J = 8.34 Hz), 7.51 (d, 2H, J = 8.59 Hz)

Step c **Example 189**

Prepared in an analogous manner to **Example 179** via **Scheme 48**, step b starting with 2-(4-bromophenyl)-4-methoxytetrahydro-2H-pyran (**Int 206**) and using $Pd(PPh_3)_4$ and K_2CO_3, and **Scheme 4** using cyclobutanone in step b.

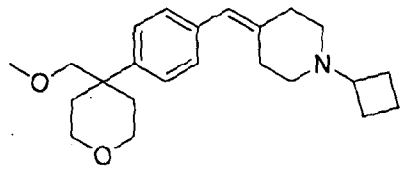
^{1}H NMR (400 MHz, MeOD) δ 7.25 - 7.41 (m, 2H), 7.12 - 7.23 (m, 2H), 6.34 (s, 1H), 4.28 - 4.41 (m, 1H), 4.08 - 4.20 (m, 1H), 3.51 - 3.68 (m, 2H), 3.40 (s, 3H), 2.70 - 2.87

(m, 1H), 2.29 - 2.60 (m, 8H), 2.17 - 2.29 (m, 1H), 2.02 - 2.16 (m, 3H), 1.84 - 2.02 (m, 2H), 1.63 - 1.84 (m, 2H), 1.29 - 1.59 (m, 2H)

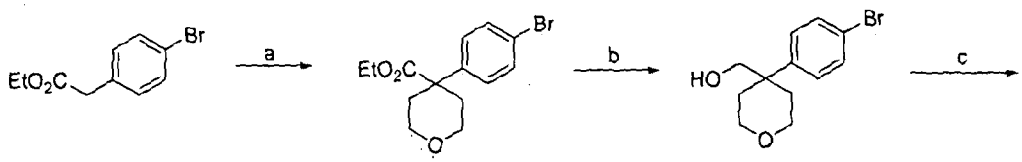
MS ES^+ 342

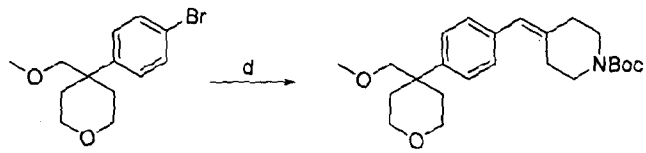
2.190 Example 190

1-Cyclobutyl-4-{4-[4-(methoxymethyl)tetrahydro-2H-pyran-4-yl]benzylidene}piperidine



Scheme 51

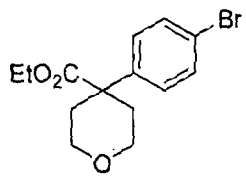




Reagents and conditions: a) NaH, 1-bromo-2-(2-bromoethoxy)ethane, DMF, Et_2O; b) $LiAlH_4$, THF; c) NaH, MeI, DMF; d) **Int 26**, $Pd(PPh_3)_4$, K_2CO_3, dioxane, H_2O, 100 °C MW

Step a **Intermediate 207**

4-Bromophenyl 2-ethyltetrahydro-2H-pyran-4-carboxylate



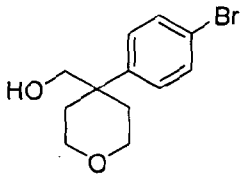
A mixture of NaH (60% in mineral oil) (2.057 g, 51.4 mmol) in DMF (67 ml) stirred at 0 °C was treated dropwise with a mixture of ethyl 2-(4-bromophenyl)acetate (5 g, 20.57 mmol) and 1-bromo-2-(2-bromoethoxy)ethane (2.59 ml, 20.57 mmol) in 3 ml of diethyl

ether. The mixture was allowed to warm to r.t. and stirred for 17 h. Mixture was quenched with water and sat. NH_4Cl. The mixture was extracted with EtOAc (x 3) and then organics washed with brine (x 3) and dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2; 0 – 100 % EtOAc in petrol) to yield 4-bromophenyl 2-ethyltetrahydro-2H-pyran-4-carboxylate as a pale yellow oil (2.88 g, 45 %).

^{1}H NMR (400 MHz, CD_2Cl_2) δ7.46 - 7.56 (m, 2H), 7.32 (m, 2H), 4.15 (m, 2H), 3.84 - 3.98 (m, 2H), 3.50 - 3.63 (m, 2H), 2.38 - 2.56 (m, 2H), 1.95 (m, 2H), 1.21 (m, 3H)

Step b **Intermediate 208**

[4-(4-Bromophenyl)tetrahydro-2H-pyran-4-yl]methanol



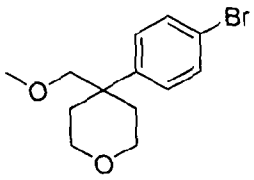
To a solution of ethyl 4-(4-bromophenyl)tetrahydro-2H-pyran-4-carboxylate (2.88 g, 9.19 mmol) in THF (30 ml) at 0°C was added $LiAlH_4$ (1 M solution on THF, 9.19 ml, 9.19 mmol) dropwise. The reaction was left to stir at 0°C for an hour and was then quenched via the dropwise addition of sat. sodium sulphate and the mixture stirred for 1 hour. The mixture was then filtered through celite washing with THF and EtOAc and the filtrate was concentrated.

Purification via column chrmoatography (SiO_2 0-100 % EtOAc/petrol,). Gave (4-(4-bromophenyl)tetrahydro-2H-pyran-4-yl)methanol (2.5838 g, 9.53 mmol, 104 % yield) as a colourless oil (2.5 g, quantitative).

^{1}H NMR (400 MHz, CD_2Cl_2) δ7.50 - 7.59 (m, 2H), 7.28 (m, 2H), 3.77 (m, 2H), 3.61 (s, 2H), 3.47 - 3.58 (m, 2H), 2.06 - 2.15 (m, 2H), 1.91 (m, 2H)

Step c **Intermediate 209**

4-(4-Bromophenyl)-4-(methoxymethyl)tetrahydro-2H-pyran



A round-bottomed flask was charged with (4-(4-bromophenyl)tetrahydro-2H-pyran-4-yl)methanol (2.5838 g, 9.53 mmol) in DMF (32 ml) and cooled to 0°C in an ice bath. Sodium hydride (0.419 g, 10.48 mmol) was added and mixture stirred under nitrogen for 10 mins. MeI (0.715 ml, 11.43 mmol) was added dropwise and mixture was allowed to warm to RT and stirred overnight under nitrogen.

Water (50 ml) was added to quench reaction.The aqueous layer was backextracted with EtOAc (3 x 100 ml). Combined the organic layers and wash with brine (3 x 100 ml). The organic was dried $MgSO_4$, filtered and concentrated. The residue was purified via Biotage (0-100% EtOAc/Petrol, 100G silica SNAP column), yielding 4-(4-bromophenyl)-4-(methoxymethyl)tetrahydro-2H-pyran (1.745 g, 6.12 mmol, 64.2 % yield) as a colourless oil.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.44 - 7.54 (m, 2H), 7.22 - 7.31 (m, 2H), 3.69 - 3.83 (m, 2H), 3.47 - 3.59 (m, 2H), 3.39 (m, 2H), 3.22 (m, 3H), 2.01 - 2.13 (m, 2H), 1.93 (m, 2H)
MS ES^+ 285/287

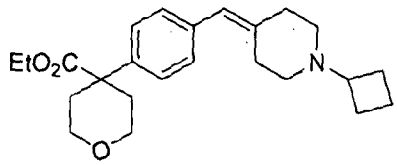
Step d **Example 190**

Prepared in an analogous manner to **Example 179** via **Scheme 51**, step c starting with 4-(4-bromophenyl)-4-(methoxymethyl)tetrahydro-2H-pyran (**Int 209**) and using $Pd(PPh_3)_4$ and K_2CO_3, and **Scheme 4** using cyclobutanone in step b.

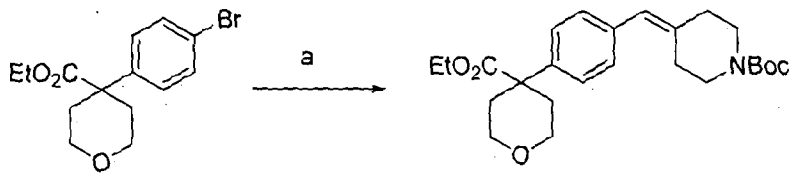
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.29 - 7.40 (m, 2H), 7.17 - 7.27 (m, 2H), 6.44 - 6.54 (m, 1H), 3.69 - 3.82 (m, 2H), 3.44 - 3.64 (m, 4H), 3.41 (s, 2H), 3.24 (s, 5H), 2.97 - 3.10 (m, 2H), 2.75 - 2.90 (m, 2H), 2.35 - 2.64 (m, 3H), 2.18 - 2.31 (m, 2H), 2.05 - 2.14 (m, 2H), 1.90 - 2.03 (m, 3H), 1.72 - 1.86 (m, 1H)
MS ES^+ 356

2.191 Example 191

Ethyl 4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-carboxylate



Scheme 52



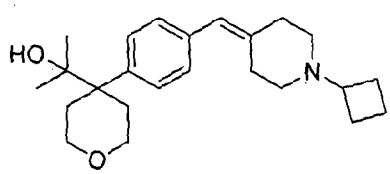
Reagents and conditions: a) Int 26, $Pd(PPh_3)_4$, K_3PO_4, THF, H_2O, 100 °C MW

Prepared in an analogous manner to **Example 179** via **Scheme 52** starting with ethyl 4-(4-bromophenyl)tetrahydro-2H-pyran-4-carboxylate (**Int 207**) and using $Pd(PPh_3)_4$ and K_3PO_4, and **Scheme 4** using cyclobutanone in step b.

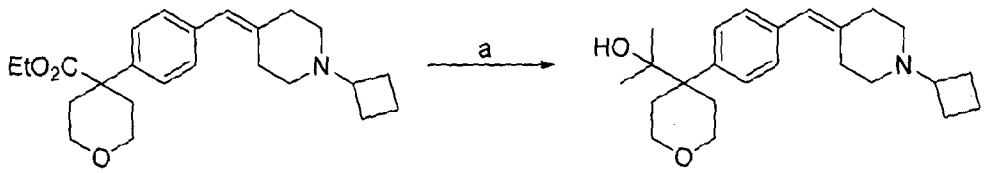
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.38 (m, 2H), 7.13 - 7.23 (m, 2H), 6.26 (s, 1H), 4.06 - 4.24 (m, 2H), 3.89 - 4.06 (m, 2H), 3.51 - 3.64 (m, 2H), 2.64 - 2.81 (m, 1H), 2.48 - 2.60 (m, 4H), 2.41 (s, 4H), 2.22 - 2.36 (m, 2H), 1.81 - 2.13 (m, 6H), 1.66 - 1.81 (m, 2H), 1.11 - 1.26 (m, 3H)
MS ES^+ 384

2.192 Example 192

2-(4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-yl)propan-2-ol



Scheme 53



Reagents and conditions: a) MeMgBr, Et_2O, THF

To a stirred solution of ethyl 4-(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)tetrahydro-2H-pyran-4-carboxylate (**Example 191**) (91 mg, 0.237 mmol) in dry THF (791 µl) at 0 °C, under an atmosphere of nitrogen, was added dropwise methylmagnesium bromide in diethyl ether (174 µl, 0.522 mmol) and the reaction was stirred at 0 °C for 30 min. Reaction was allowed to warm to r.t. for 2 h. Further methylmagnesium bromide in diethyl ether (174 µl, 0.522 mmol) was added at r.t. The reaction was stirred under nitrogen for 2 h. To this mixture was added methylmagnesium bromide in diethyl ether (174 µl, 0.522 mmol) and the reaction was stirred at r.t. for 17 h. The reaction mixture was quenched with water (10 ml). The organics were extracted with EtOAc (x 2). The organics were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude oil was purified by column chromatography (NH silica; 10 – 100 % DCM in petrol), oil was dried in a high vacuum oven at 50 °C for 17 h to yield 2-(4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-yl)propan-2-ol as a colouless oil (18 mg, 20 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 - 7.34 (m, 2H), 7.08 - 7.22 (m, 2H), 6.25 (s, 1H), 4.25 (s, 1H), 3.59 - 3.78 (m, 2H), 2.99 - 3.16 (m, 2H), 2.60 - 2.74 (m, 1H), 2.41 - 2.47 (m, 2H), 2.27 - 2.36 (m, 4H), 2.21 - 2.27 (m, 2H), 2.11 - 2.21 (m, 2H), 1.88 - 2.08 (m, 4H), 1.73 - 1.87 (m, 2H), 1.55 - 1.69 (m, 2H), 0.92 (s, 6H)

MS ES^+ 370

3. Biological efficacy of compounds of the invention

3.1 In Vitro H3 Binding Assay

The ability of compounds to bind to the H3 receptor was determined by measuring the reduction in tritiated N-α-methyl-histamine (^{3}H-NαMH) binding in a competition binding assay. Changes in the levels of bound radio-label were monitored by scintillation counting with a Trilux Microbeta (Perkin Elmer).

Membranes were prepared from CHO-K1 cells stably expressing human H3 receptor; routinely grown as monolayers in Ham's F12 medium (Invitrogen) supplemented with 10% Foetal Clone III (Hyclone), 500μg/ml G418 (Invitrogen), 5 μg/ml blasticidine S (Invivogen) and 50 μg/ml Gentamicin (Sigma) in 5% CO_2 at 37°C. Cells were grown to 80-95% confluency, rinsed once with 1x PBS (Invitrogen) and detached by incubating with 1x PBS containing 0.02% EDTA (Sigma) for 10 minutes at room temperature. Cells were collected by centrifugation at 900 xg, 4°C for 10 minutes. Cells were rinsed once with 1x PBS and re-suspended in ice cold homogenisation buffer (50mM Tris-HCl (pH 7.4), 2.5mM EDTA, 5mM $MgCl_2$, 200mM Sucrose) at $1x10^7$ cells/ml and kept on ice. Cells were homogenised on ice and debris removed by centrifugation at 500 x *g*, 4°C for 5 minutes. The resulting supernatant was centrifuged at 75,600 xg, 4°C for 60 minutes. Membranes were suspended in homogenisation buffer, protein concentration was determined (BCA Protein Assay kit (Pierce)), diluted to 2.2 mg/ml, dispensed into 1ml aliquots and stored at -80 °C.

Membranes were thawed on ice, sonicated with 4 cycles of 20 pulses (50% amplitude, 0.5 pulse) (UP200S Hielscher) on ice, diluted in assay buffer (50mM Tris-HCl (pH7.4), 5mM $MgCl_2$) to 62.5 μg/ml. Compound was serially diluted in DMSO before being diluted 1:10 with assay buffer. 5μg of membrane in 80 μl of assay buffer was added per well of a 96 well polystyrene plate (Corning). 10 μl of compound was added per well. The assay was initiated by the addition of 10 μl of 20nM ^{3}H-NαMH per well and incubated for one hour at room temperature with shaking. Total binding was determined in the presence of 1% DMSO and non-specific binding was determined by the inclusion of 1 μM R-α-methyl-histamine (RαMH). Incubations were then filtered through filtermat A (Perkin Elmer) and washed three times with assay buffer. Filtermats were dried at 42°C for two hours, scintillant added and the level of bound radioactivity determined.

IC50 values for compounds were determined from seven point log scale dose-response studies and represent the concentration of compound required to inhibit 50% of the specific binding of 2nM ^{3}H-NαMH (difference between total and non-specific binding). Curves were generated using the average of duplicate wells for each data point and analyzed using nonlinear regression of sigmoidal dose response (variable slope).

3.2 In Vitro H3 Functional Assay

The functional activity of compounds at the H3 receptor was determined by measuring changes in the level of intracellular cAMP using a cAMP response element driven luciferase reporter assay. The changes in luciferase expression were monitored by a luminescence plate reader, Analyst HT (MDS Analytical). Increases in intracellular cAMP were readily detected upon activation of protein kinase A by forskolin (Sigma) and suppression of this response observed with the application of the H3 receptor agonist RαMH (Sigma).

CHO(dhfr^{+})-cre-luc cells stably expressing human H3 receptor were routinely grown as monolayers in Minimal Essential Medium α (MEMα) (Invitrogen) supplemented with 10% dialysed FBS (Hyclone), in 5% CO_2 at 37°C. 48 hours prior to assay, cells were seeded in clear-base white walled 384-well plates (Corning) at a density of 5000 cells/well. On the day of assay, growth media was removed and replaced with 15 µl of assay buffer (MEMα, 5 mg/ml fatty acid free BSA (Sigma)) per well. Cells were then incubated for 30 minutes at 37°C, 5% CO_2. Compound was serially diluted in DMSO before being diluted 1:10 with assay buffer. 2.5 µl of compound diluted in assay buffer was added and cells incubated for 5 minutes at 37°C, 5% CO_2. 2.5 µl of each reagent was then added in the following order: RαMH (10 nM), isobutylmethylxanthine (1-methyl-3-(2-methylpropyl)-7H-purine-2,6-dione; IBMX) (500 µM) (Sigma) and forskolin (1 µM). Cells were then incubated for 90 minutes at 37°C, 5% CO_2, followed by 30 minutes at room temperature. At the end of incubation 25 µl of Steadylite reagent (Perkin Elmer) was added, plates were sealed and placed on a shaker for 5 minutes. The level of light output to determine the level of luciferase expression was then measured.

IC50 values for compounds were determined from ten point half log scale dose-response studies and represent the concentration of compound required to prevent 50%

inhibition of forskolin stimulated cells in the presence of RαMH alone. Curves were generated using the average of duplicate wells for each data point and analyzed using nonlinear regression of four parameter dose response.

3.3 Results

Example Compound	hH3 binding IC_{50}/nM	hH3 functional IC_{50}/nM
Example 1	15	5
Example 6	10	4
Example 16	73	
Example 19	51	
Example 25	19	
Example 30	180	
Example 35	310	
Example 37	11	4
Example 40	26	5
Example 43	20	
Example 51	67	
Example 55	84	19
Example 60	16	
Example 68	9	
Example 70	3	
Example 77	54	25
Example 83	190	150
Example 87	39	4
Example 91	7	3
Example 92	8	4
Example 98	37	
Example 105	7	
Example 109	6	2
Example 111/112	7	3
Example 113/114	12 / 22	
Example 126	33	
Example 136	55	13

Example 140	16	5
Example 142	37	5
Example 148	3	2
Example 150	21	2
Example 155	4	1
Example 159	35	
Example 162	56	
Example 167	12	
Example 168	29	6
Example 173	37	3
Example 175	320	14
Example 179	160	8
Example 185	150	3
Example 191	85	

These results indicate that compounds of the invention have potent antagonist or inverse agonist activity at the H3 receptor, both in terms of binding and, where tested, in terms of inhibition of the functional response caused by receptor activation. The compounds tested above exhibit IC_{50} values significantly less than 1 μM, with the compounds showing low nanomolar affinity at the H3 receptor. Accordingly, the compounds of the invention are expected to have usefulness in the prevention or treatment of conditions, such as those discussed above, in which H3 receptor activity is implicated.

In addition, the compounds of the present invention may possess variously advantageous pharmacological and/or toxicological profiles, when tested in a variety of standard tests for such parameters. For example, the compounds of the invention may exhibit one or more potentially useful properties for *in vivo* use, when characterised by pharmacological and/or toxicological tests including: HERG interaction (which is an indication of potential cardiotoxicity, and measures the effects of the compounds on the human ether-a-go-go-related gene, using for example the PatchXpress 7000A platform); $CypP_{450}$ interactions (which may be measured in accordance with the FDA draft guidelines for drug interaction studies (study design, data analysis and implications for dosing and labeling) (Sep. 2006), see *www.fda.gov*); phototoxicity (for example using a

protocol in accordance with assay details outlined in the OECD guidelines for testing of chemicals: 432 In Vitro 3T3 Neutral Red Uptake phototoxicity test, April 2004); determination of pharmacokinetic parameters (for example following *in vivo* dosing via multiple routes, with plasma concentrations of compounds being determined from venous blood samples using an LC-MS/MS protocol); and *in vivo* receptor occupancy (determined, for example, using protocols based on Medhurst *et al.*, *Journal of Pharmacology and Experimental Therapeutics*, 2007, **321**, 1032). These standard tests for the characterisation of drug molecules are well known to the skilled person.

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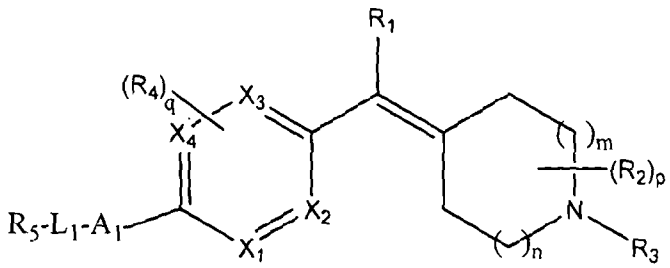
CLAIMS

1. A compound of formula (1):



(1)

wherein:

R_1 represents H or C_{1-6} alkyl;

R_2 represents C_{1-6} alkyl, wherein each R_2 may be the same or different;

p represents 0, 1, 2, 3 or 4;

m represents 1 or 2;

n represents 1 or 2; provided that both and m and n do not represent 2;

R_3 represents C_{1-6} alkyl, -Q_1-C_{3-6} cycloalkyl or -Q_2-3-6 membered monocyclic heterocyclyl, wherein each may be optionally substituted by one or more substituents, independently selected from halogen, C_{1-6} alkyl or C_{1-6} alkoxy;

Q_1 and Q_2 independently represent a covalent bond or C_{1-3} alkylene;

X_1, X_2, X_3 and X_4 independently represent CH or N; wherein no more than 2 of X_1, X_2, X_3 and X_4 represent N;

R_4, independently represents halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{1-6} alkoxy or haloC_{1-6} alkoxy;

q represents 0, 1 or 2;

A_1 represents a covalent bond or C_{1-6} alkylene optionally substituted by one or more hydroxy or C_{1-6} alkoxy;

L_1 represents a covalent bond or –NR_6-, -O-, ^{b}-NR_7CO-^{a}, ^{b}-$CONR_8$-^{a}, -C(O)-, ^{b}-NR_7SO_2-^{a}, ^{b}-SO_2NR_8-^{a}, -$S(O)_2$-, in which ^{a} represents the point of attachment to A_1 and ^{b} represents the point of attachment to R_5;

R_6, R_7 and R_8 independently represent H or C_{1-6} alkyl;

R_5 represents -$(CH_2)_{1-3}OC_{1-6}$ alkyl, or –Q_3-C_{3-8} cycloalkyl, -Q_4-heteroaryl, -Q_5-heterocyclyl, -Q_6-aryl; in which the C_{3-8} cycloalkyl, heteroaryl, heterocyclyl and aryl are

optionally substituted with one or more R_9; wherein each R_9 may be the same or different;

when A_1 represents optionally substituted C_{1-6} alkylene, R_5 also represents H or C_{1-6} alkyl;

Q_3, Q_4, Q_5 and Q_6 independently represent a covalent bond or C_{1-3} alkylene;

R_9 represents halogen, -CN, $-NO_2$, =O, $-OR_{10}$, $-NR_{11}R_{12}$, $-COR_{11}$, $-CO_2R_{12}$, $-CONR_{13}R_{14}$, $-SO_2NR_{13}R_{14}$, $-NR_{15}COR_{16}$, $-NR_{15}SO_2R_{16}$, $-OCONR_{13}R_{14}$, $-NR_{13}CO_2R_{14}$, $-NR_{13}CONR_{13}R_{14}$, $-SR_{14}$, $-SOR_{14}$, $-SO_2R_{14}$, $-OSO_2R_{14}$, $-C_{3-6}$cycloalkyl, -aryl, -heteroaryl, -heterocyclyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, $-OR_{10}$, $-NR_{11}R_{12}$, $-COR_{11}$, $-CO_2R_{12}$, $-CONR_{13}R_{14}$, $-SO_2NR_{13}R_{14}$, $-NR_{15}COR_{16}$, $-NR_{15}SO_2R_{16}$, $-OCONR_{13}R_{14}$, $-NR_{13}CO_2R_{14}$, $-NR_{13}CONR_{13}R_{14}$, $-SR_{14}$, $-SOR_{14}$, $-SO_2R_{14}$, $-OSO_2R_{14}$, $-C_{3-6}$cycloalkyl, -aryl, -heteroaryl or –heterocyclyl; in which each C_{1-6} alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl or heterocyclyl present as or as part of R_9 is optionally substituted with one or more R_{17}, wherein each R_{17} may be the same or different;

R_{10} represents H, C_{1-3} alkyl or haloC_{1-3} alkyl;

R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} independently represent H or C_{1-3} alkyl;

R_{17} represents halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, - CN, $-NO_2$, =O, $-OR_{18}$, $-CO_2R_{19}$, $-COR_{19}$, $-NR_{19}R_{20}$, $-CONR_{19}R_{20}$, $-NR_{19}COR_{20}$, $-NR_{19}SO_2R_{20}$ or $-SO_2NR_{19}R_{20}$;

R_{18} represents H, C_{1-6}alkyl or -haloC_{1-6} alkyl;

R_{19} and R_{20} independently represent H or C_{1-6}alkyl;

excluding 4,4'-(1,4-phenylenedimethylidyne)bis[1,2,2,6,6-pentamethyl]-piperidine;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R_1 represents H.

3. A compound according to claim 1 or claim 2, wherein p represents 0.

4. A compound according to any of claims 1 to 3, wherein m represents 1 and n represents 1 or 2.

5. A compound according to any of claims 1 to 4, wherein R_3 represents optionally substituted C_{3-6} cycloalkyl.

6. A compound according to any one of claims 1 to 5, wherein X_1, X_2, X_3 and X_4 each represent CH.

7. A compound according to any one of claims 1 to 6, wherein $-L_1-A_1-$ represents a covalent bond, C_{1-6} alkylene, $-NR_6-C_{1-6}$ alkylene-, $-O-C_{1-6}$ alkylene-, $-NR_7CO-$, $-NR_7CO-C_{1-6}$alkylene-, $-CONR_8-C_{1-6}$ alkylene-, $-C(O)-$, $-NR_7SO_2-$, $-NR_7SO_2-C_{1-6}$alkylene-, $-SO_2NR_8-$, $-S(O)_2-C_{1-6}$alkylene-and $-S(O)_2$, wherein C_{1-6} alkylene, when present, is optionally substituted.

8. A compound according to any one of claims 1 to 7, wherein R_5 represents $-Q_3-C_{3-8}$ cycloalkyl, $-Q_4$-heteroaryl or $-Q_5$-heterocyclyl; in which the C_{3-8} cycloalkyl, heteroaryl and heterocyclyl are optionally substituted with one or more R_9, each of which may be the same or different.

9. A compound according to claim 8, wherein R_5 C_{3-8}cycloalkyl, heteroaryl and heterocyclyl groups present when R_5 represents $-Q_3-C_{3-8}$ cycloalkyl, $-Q_4$-heteroaryl or $-Q_5$-heterocyclyl respectively are selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, pyrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyridazinyl, tetrahydrofuranyl, tetrahydropyranyl, oxazolidinyl, imidazolidinyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, azepanyl, oxepanyl, octahydrocyclopenta[c]pyrrolyl, azabicyclo[3.2.1]octanyl or oxaspiro[4.5]decanyl, each of which may be optionally substituted with one or more R_9, each of which may be the same or different.

10. A compound according to any preseding claim, wherein R_9 represents halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, =O, $-C_{0-6}$ alkyl-OR_{10}, $-C_{0-6}$ alkyl-COR_{11}, $-C_{0-6}$ alkyl-CO_2R_{12}, $-C_{0-6}$ alkyl-$CONR_{13}R_{14}$, $-C_{0-6}$ alkyl-$NR_{15}COR_{16}$, or $-C_{0-6}$alkyl-heteroaryl, wherein said

C_{1-6} alkyl or -C_{0-6}alkyl-heteroaryl is optionally substituted with one or more R_{17}, each of which may be the same or different.

11. A compound of formula (1) as defined in claim 1 selected from the group consisting of:

1-cyclobutyl-4-[4-(1-methyl-1H-pyrazol-4-yl)benzylidene]piperidine;
1-cyclobutyl-4-{4-[1-(2-methylpropyl)-1H-pyrazol-4-yl]benzylidene}piperidine;
1-cyclobutyl-4-[4-(3,5-dimethyl-1,2-oxazol-4-yl)benzylidene]piperidine;
1-cyclobutyl-4-[4-(1-methyl-1H-pyrazol-5-yl)benzylidene]piperidine;
1-cyclobutyl-4-[4-(2,4-dimethyl-1,3-thiazol-5-yl)benzylidene]piperidine;
1-cyclobutyl-4-[4-(1,5-dimethyl-1H-pyrazol-4-yl)benzylidene]piperidine;
1-cyclobutyl-4-[4-(1,2-oxazol-4-yl)benzylidene]piperidine;
1-cyclobutyl-4-[4-(1,3,5-trimethyl-1H-pyrazol-4-yl)benzylidene]piperidine;
4-[2-chloro-4-(1-methyl-1H-pyrazol-4-yl)benzylidene]-1-cyclobutylpiperidine;
1-cyclobutyl-4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)benzylidene]piperidine;
1-cyclobutyl-4-[4-(5-methyl-1,3,4-oxadiazol-2-yl)benzylidene]piperidine;
1-cyclobutyl-4-[4-(5-methyl-1,2,4-oxadiazol-3-yl)benzylidene]piperidine;
{4-[(1-cyclopentylpiperidin-4-ylidene)methyl]phenyl}methanol;
(4-{[1-(2-methylpropyl)piperidin-4-ylidene]methyl}phenyl)methanol;
N-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}cyclopentanecarboxamide;
N-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}tetrahydrofuran-3-carboxamide;
2-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-N-cyclopentylacetamide;
2-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-N-(tetrahydrofuran-3-yl)acetamide;
2-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(pyrrolidin-1-yl)ethanone;
{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}(pyrrolidin-1-yl)methanone;
4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-N-cyclopentylbenzamide;
4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-N-(tetrahydrofuran-3-yl)benzamide;
4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-N-(cyclopentylmethyl)benzamide;
4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-N-(tetrahydrofuran-3-ylmethyl)benzamide;
4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-N-(pyridin-3-yl)benzamide;
N-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}pyridin-3-amine;
{3-chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}(pyrrolidin-1-yl)methanone;

{2-chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}(pyrrolidin-1-yl)methanone;
{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-2-fluorophenyl}(pyrrolidin-1-yl)methanone;
{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-3-fluorophenyl}(pyrrolidin-1-yl)methanone;
{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]-3-fluorophenyl}methanol;
{3-chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}methanol;
{6-[(1-cyclobutylpiperidin-4-ylidene)methyl]pyridin-3-yl}(pyrrolidin-1-yl)methanone;
{6-[(1-cyclobutylpiperidin-4-ylidene)methyl]pyridin-3-yl}methanol;
{5-[(1-cyclobutylpiperidin-4-ylidene)methyl]pyridin-2-yl}(pyrrolidin-1-yl)methanone;
pyrrolidin-1-yl(4-{[1-(tetrahydrofuran-3-yl)piperidin-4-ylidene]methyl}phenyl) methanone;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}pyridin-2(1H)-one;
2-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}pyridazin-3(2H)-one;
3-({4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}oxy)pyridazine;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-3-methoxypyridin-2(1H)-one;
methyl 1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-6-oxo-1,6-dihydropyridine-3-carboxylate;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-3-methylpyridin-2(1H)-one;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-6-methyl-3-(trifluoromethyl)pyridin-2(1H)-one;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-3-(trifluoromethyl)pyridin-2(1H)-one;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}piperidin-2-one;
4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}morpholin-3-one;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}pyrrolidin-2-one;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-5-(methoxymethyl)pyridin-2(1H)-one;
(3S)-1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-3-methoxypyrrolidin-2-one;
(4R)-1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-4-methoxypyrrolidin-2-one;

4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-1,4-oxazepan-5-one;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-3-methylimidazolidin-2-one;
3-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-1,3-oxazolidin-2-one;
1-cyclobutyl-4-{4-[(cyclopentyloxy)methyl]benzylidene}piperidine;
1-cyclobutyl-4-{4-[(tetrahydrofuran-3-ylmethoxy)methyl]benzylidene}piperidine;
1-cyclobutyl-4-{4-[(cyclopentylmethoxy)methyl]benzylidene}piperidine;
1-cyclobutyl-4-{4-[(tetrahydro-2H-pyran-4-yloxy)methyl]benzylidene}piperidine;
1-cyclobutyl-4-(4-{[(2-methyl-1,3-oxazol-4-yl)methoxy]methyl}benzylidene) piperidine;
1-cyclobutyl-4-(4-{[(5-methyl-1,2-oxazol-3-yl)methoxy]methyl}benzylidene) piperidine;
3-({4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}oxy)pyridine;
1-cyclobutyl-4-(4-{[(5-methyl-1,2-oxazol-3-yl)oxy]methyl}benzylidene)piperidine;
1-cyclobutyl-4-[4-({[1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]oxy}methyl)benzylidene]piperidine;
1-cyclobutyl-4-[4-({[1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]oxy}methyl) benzylidene]piperidine;
3-({4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}oxy)-N,N-dimethyl-1,2-oxazole-5-carboxamide;
1-cyclobutyl-4-[4-(piperidin-1-ylmethyl)benzylidene]piperidine;
4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}morpholine;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-4,4-difluoropiperidine;
4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-2,6-dimethylmorpholine;
1-cyclobutyl-4-{4-[(4-methoxypiperidin-1-yl)methyl]benzylidene}piperidine;
N-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]benzyl}-2-methoxy-N-methylethanamine;
N-(4-((1-ethylpiperidin-4-ylidene)methyl)benzyl)cyclopentanamine dihydrochloride;
1-(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)ethanol;
(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)(cyclopentyl)methanol;
1-(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)-3-methylbutan-1-ol;
(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)methanol;
2-(4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)propan-2-ol;
1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)-2-methylpropan-1-ol;

(3-Chloro-4-((1-cyclobutylpiperidin-4-ylidene)methyl)phenyl)(cyclopentyl)methanol;
1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)-2-cyclopentylethanol;
1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)-2-cyclopropylethanol;
Cyclopentyl(4-{[1-(2-methylpropyl)piperidin-4-ylidene]methyl}phenyl)methanol;
Cyclopentyl(4-((1-ethylpiperidin-4-ylidene)methyl)phenyl)methanol;
Cyclopentyl(4-((1-(cyclopropylmethyl)piperidin-4-ylidene)methyl)phenyl)methanol;
1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)cyclopentanol;
1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}cyclohexanol;
3-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydrofuran-3-ol;
4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;
1-(4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxypiperidin-1-yl)ethanone;
N-(4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxycyclohexyl)acetamide;
Ethyl 4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxycyclohexanecarboxylate;
1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methoxycyclohexanol;
4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(pyrimidin-2-yl)piperidin-4-ol;
1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-(hydroxymethyl)cyclohexanol;
1-[4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxyhexahydrocyclopenta[c]pyrrol-2(1H)-yl]ethanone;
1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-(3-methyl-1,2,4-oxadiazol-5-yl)cyclohexanol;
1-(4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxyazepan-1-yl)ethanone;
1-(3-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl)ethanone;
Ethyl 3-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-3-hydroxycyclobutanecarboxylate;
{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}(tetrahydro-2H-pyran-4-yl)methanol;

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-hydroxy-N,N-dimethylcyclohexanecarboxamide;

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(1-methyl-1H-pyrazol-4-yl)ethanol;

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-2,6-dimethyltetrahydro-2H-pyran-4-ol;

4-{3-Chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methoxy-4-methylcyclohexanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methylcyclohexane-1,4-diol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-(methoxymethyl)cyclohexanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-ethoxycyclohexanol;

8-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-oxaspiro[4.5]decan-8-ol;

1-{3-Chloro-4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methoxycyclohexanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-(propan-2-yloxy)cyclohexanol;

2-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methoxybutan-2-ol;

1-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}-3-(methoxymethyl)cyclobutanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-3-methoxycyclohexanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-(1H-pyrazol-1-yl)cyclohexanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-2-methoxycyclohexanol;

4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}oxepan-4-ol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-3-methoxycycloheptanol;

{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(tetrahydrofuran-3-yl)ethanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-2-(methoxymethyl)cyclopentanol;

1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-4-methoxycycloheptanol;

1-{4-[(1-cyclopentylpiperidin-4-ylidene)methyl]phenyl}-4-methoxycyclohexanol;

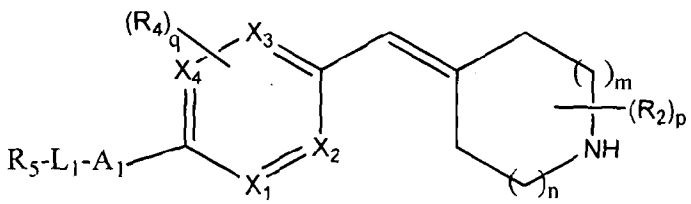
4-{4-[(1-Cyclopentylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;
4-Methoxy-1-(4-{[1-(propan-2-yl)piperidin-4-ylidene]methyl}phenyl)cyclohexanol;
4-(4-{[1-(propan-2-yl)piperidin-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol;
1-(4-{[1-(Cyclopropylmethyl)piperidin-4-ylidene]methyl}phenyl)-4-methoxycyclohexanol;
1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)propan-2-ol;
2-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)phenyl)-1-cyclopentylethanol;
1-(4-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)benzyl)-4-hydroxypiperidin-1-yl)ethanone;
1-(4-((1-Cyclobutylpiperidin-4-ylidene)methyl)benzyl)cyclopentanol;
1-Cyclopentyl-2-(4-((1-ethylpiperidin-4-ylidene)methyl)phenyl)ethanol;
2-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(tetrahydrofuran-3-yl)ethanol;
4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}tetrahydro-2H-pyran-4-ol;
4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-3-fluorobenzyl}tetrahydro-2H-pyran-4-ol;
1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}-4-methoxycyclohexanol;
4-(4-{[1-(Tetrahydrofuran-3-yl)piperidin-4-ylidene]methyl}benzyl)tetrahydro-2H-pyran-4-ol
4-(4-{[1-(3-Fluorocyclobutyl)piperidin-4-ylidene]methyl}benzyl)tetrahydro-2H-pyran-4-ol;
2-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-1-(tetrahydro-2H-pyran-4-yl)ethanol;
3-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}tetrahydrofuran-3-ol;
4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydrofuran-3-ol;
1-{4-[(E)-(1-Cyclobutylazepan-4-ylidene)methyl]phenyl}-4-methoxycyclohexanol;
1-{4-[(Z)-(1-Cyclobutylazepan-4-ylidene)methyl]phenyl}-4-methoxycyclohexanol;
4-{4-[(E)-(1-Cyclobutylazepan-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;
4-{4-[(Z)-(1-Cyclobutylazepan-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;
4-(4-{(E)-[1-(Propan-2-yl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol;
4-(4-{(Z)-[1-(Propan-2-yl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol;
4-{4-[(E)-(1-Cyclobutylazepan-4-ylidene)methyl]benzyl}tetrahydro-2H-pyran-4-ol;
4-{4-[(E)-(1-Cyclopentylazepan-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;

4-{4-[(Z)-(1-cyclopentylazepan-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;
4-(4-{(E)-[1-(Cyclopropylmethyl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol;
4-(4-{(Z)-[1-(Cyclopropylmethyl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol;
4-(4-{(E)-[1-(2-Methylpropyl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol;
4-(4-{(Z)-[1-(2-Methylpropyl)azepan-4-ylidene]methyl}phenyl)tetrahydro-2H-pyran-4-ol;
4-{4-[(E)-(1-Ethylazepan-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;
1-{6-[(1-Cyclobutylpiperidin-4-ylidene)methyl]pyridin-3-yl}-4-methoxycyclohexanol;
4-({5-[(1-Cyclobutylpiperidin-4-ylidene)methyl]pyridin-2-yl}methyl)tetrahydro-2H-pyran-4-ol;
1-{5-[(1-Cyclobutylpiperidin-4-ylidene)methyl]pyridin-2-yl}-4-methoxycyclohexanol;
1-Cyclobutyl-4-{4-[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]benzylidene}piperidine;
1-Cyclobutyl-4-[4-(4-fluorotetrahydro-2H-pyran-4-yl)benzylidene]piperidine;
1-Cyclobutyl-4-[4-(1-fluoro-4-methoxycyclohexyl)benzylidene]piperidine;
N-(4-(1-(1-Cyclobutylpiperidin-4-ylidene)ethyl)benzyl)cyclopentanamine;
{4-[1-(1-Cyclobutylpiperidin-4-ylidene)ethyl]phenyl}methanol;
1-Cyclobutyl-4-{1-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]ethylidene}piperidine;
4-{4-[(E)-(1-Cyclobutyl-3-methylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-ol;
1-Cyclobutyl-4-[4-(tetrahydro-2H-pyran-4-ylsulfonyl)benzylidene]piperidine;
1-Cyclobutyl-4-{4-[(2-methoxyethyl)sulfonyl]benzylidene}piperidine;
1-Cyclobutyl-4-{4-[(3-methoxypropyl)sulfonyl]benzylidene}piperidine;
1-Cyclobutyl-4-{4-[(tetrahydro-2H-pyran-4-ylmethyl)sulfonyl] benzylidene}piperidine;
1-Cyclobutyl-4-{4-[(2-ethoxyethyl)sulfonyl]benzylidene}piperidine;
1-Cyclobutyl-4-(4-{[(2-ethoxyethyl)sulfonyl]methyl}benzylidene)piperidine;
4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-N-methyl-N-(tetrahydro-2H-pyran-4-yl)benzenesulfonamide;
4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]-N-(tetrahydro-2H-pyran-4-yl)benzenesulfonamide;
4-({4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}sulfonyl)morpholine;

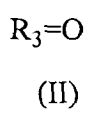
1-Cyclobutyl-4-{4-[(3-methoxyazetidin-1-yl)sulfonyl]benzylidene}piperidine;
1-Cyclobutyl-4-{4-[(4-methoxypiperidin-1-yl)sulfonyl]benzylidene}piperidine;
1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-N-methyl-N-(tetrahydro-2H-pyran-4-yl)methanesulfonamide;
4-({4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]benzyl}sulfonyl)morpholine;
1-Cyclobutyl-4-(4-{[(3-methoxy-3-methylazetidin-1-yl)sulfonyl]methyl}benzylidene)piperidine;
1-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}-N-(tetrahydro-2H-pyran-4-yl)methanesulfonamide;
1-Cyclobutyl-4-[4-(1,4-dimethoxycyclohexyl)benzylidene]piperidine;
1-Cyclobutyl-4-[4-(4-methoxytetrahydro-2H-pyran-2-yl)benzylidene]piperidine;
1-Cyclobutyl-4-{4-[4-(methoxymethyl)tetrahydro-2H-pyran-4-yl]benzylidene}piperidine;
Ethyl 4-{4-[(1-cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-carboxylate;
2-(4-{4-[(1-Cyclobutylpiperidin-4-ylidene)methyl]phenyl}tetrahydro-2H-pyran-4-yl)propan-2-ol;
and pharmaceutically acceptable salts thereof.

12. A process for the preparation of a compound of formula (1) or a pharmaceutically acceptable salt thereof as defined in claim 1 which comprises:

(i) when R_1 represents H, reacting a compound of formula (I) with a compound of formula (II):



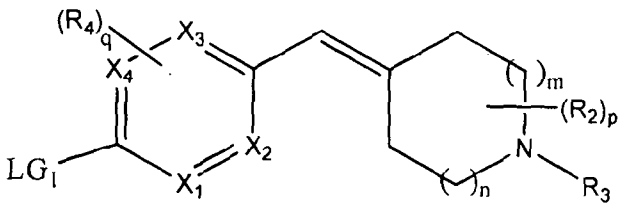
(I)



(II)

wherein R_2, R_3, R_4, R_5, n, m, p, q, A_1, L_1, X_1, X_2, X_3 and X_4 are as herein defined; or

(ii) when R_1 represents H, A_1 and L_1 each represent a covalent bond and R_5 represents an aryl or heteroaryl group, reacting a compound of formula (III) with a compound of formula (IV):



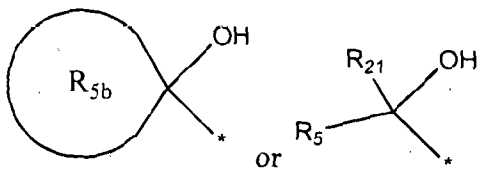
(III)

R_{5a}-$B(OZ)_2$

(IV)

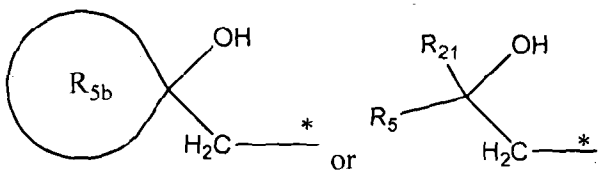
wherein R_2, R_3, R_4, n, m, p, q, X_1, X_2, X_3 and X_4 are as herein defined, LG_1 represents a suitable leaving group, R_{5a} represents R_5 aryl or heteroaryl and $-B(OZ)_2$ represents boronic acid or a ester derivative thereof; or

(iii) when R_1 represents H, L_1 represents a covalent bond and $-A_1$- R_5 represents:

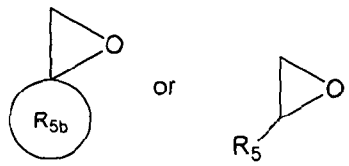


conversion of a compound of formula (III) to a Grignard reagent followed by reaction with R_{5b}=O or $(R_5)(R_{21})C$=O; wherein R_{21} represents H or C_{1-3} alkyl, R_5 is as herein defined, R_{5b} represents an optionally substituted C_{3-8} cycloalkyl or optionally substituted heterocyclyl ring and * represents the point of attachment; or

(iv) when R_1 represents H, L_1 represents a covalent bond and $-A_1$-R_5 represents:

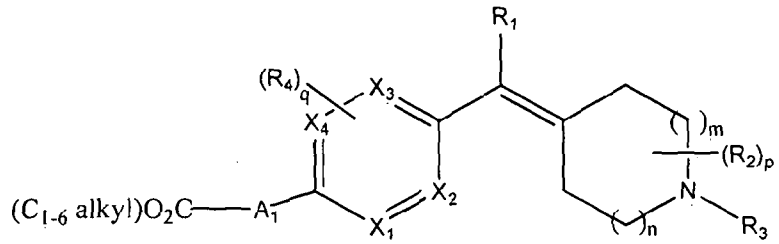


reacting a compound of formula (III) with an epoxide of formula:



wherein R_{21} represents H or C_{1-3} alkyl, R_5 is as herein defined, R_{5b} represents an optionally substituted C_{3-8} cycloalkyl or optionally substituted heterocyclyl ring and * represents the point of attachment; or

(v) when L_1 represents a covalent bond and R_5 represents an oxadiazolyl group, conversion of an intermediate of formula (V):



(V)

wherein R_1, R_2, R_3, R_4, n, m, p, q, A_1, X_1, X_2, X_3 and X_4 are as herein defined; or

(vi) when R_1 represents H, A_1 represents C_{1-6} alkylene, L_1 represents –O- and R_5 represents H, reacting a compound of formula (V) with a suitable reducing agent; or

(vii) when R_1 represents H, L_1 represents $-NR_7CO-$, reacting a compound of formula (V) with R_5R_7NH; or

(viii) when R_1 represents H, L_1 represents –CO- and R_5 represents N-linked heterocyclyl; reacting a compound of formula (V) with a N containing heterocyclyl;

and optionally thereafter carrying out one or more of the following procedures:

- converting a compound of formula (1) into another compound of formula (1)
- removing any protecting groups
- forming a pharmaceutically acceptable salt.

13. A pharmaceutical composition comprising a compound of formula (1) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 11, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

14. A composition according to claim 13, comprising one or more additional, pharmaceutically active ingredients.

15. A compound according to any of claims 1 to 11, or a composition according to claim 13 or 14, for use in therapy.

16. A compound according to any of claims 1 to 11, or a composition according to claim 13 or 14, for use in the treatment or prevention of a condition whose development or symptoms are linked to histamine H3 receptor activity.

17. A method of treatment or prevention of a condition whose development or symptoms are linked to histamine H3 receptor activity, the method comprising the administration, to a subject in need of such treatment or prevention, of a therapeutically effective amount of a compound according to any of claims 1 to 11.

18. A compound for use according to claim 16, or a method according to claim 17, wherein the condition is a disorder of the central nervous system.

19. A compound for use or a method according to any of claims 16 to 18, wherein the disorder is selected from schizophrenia, neurodegenerative disorders (such as Alzheimer's Disease), cognitive disorders (such as dementia and schizophrenia), sleep disorders (such as narcolepsy and hypersomnia), pain, obesity, attentional disorders and epilepsy.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2012/000673

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/82 C07D401/10 C07D401/12 C07D401/14 C07D407/12
C07D407/14 C07D413/10 C07D417/10 A61K31/435 A61P25/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/207917 A1 (WANG YUGUANG [US] ET AL) 6 November 2003 (2003-11-06) page 18; compound G	1-17
X	WO 02/12190 A2 (ORTHO MCNEIL PHARM INC [US]) 14 February 2002 (2002-02-14) page 111; example 60	1-17
X	US 2 739 968 A (NATHAN SPERBER ET AL) 27 March 1956 (1956-03-27) column 6; compound VII	1-17

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

☒ See patent family annex.

* Special categories of cited documents :

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

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 September 2012	01/10/2012

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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