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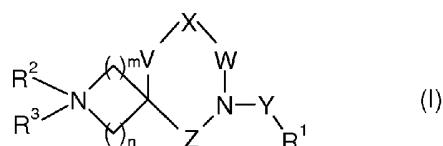
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(54) Title: DIAZASPIRO [5.5] UNDECANE DERIVATIVES AND RELATED COMPOUNDS AS MUSCARINIC-RECEPTOR ANTAGONISTS AND BETA-ADRENORECEPTOR AGONISTS FOR THE TREATMENT OF PULMONARY DISORDERS



(57) Abstract: Spirocyclicmorpholine-substituted amides of formula (I); processes for their preparation, pharmaceutical compositions containing them, a process for preparing pharmaceutical compositions, their use in therapy and intermediates of use in their preparation.

**DIAZASPIRO [5.5] UNDECANE DERIVATIVES AND RELATED COMPOUNDS AS
MUSCARINIC-RECEPTOR ANTAGONISTS AND BETA-ADRENORECEPTOR
AGONISTS FOR THE TREATMENT OF PULMONARY DISORDERS**

The present invention relates to spirocyclicmorpholine-substituted amides, a process for their preparation, pharmaceutical compositions containing them, a process for preparing pharmaceutical compositions, their use in therapy and intermediates of use in their preparation.

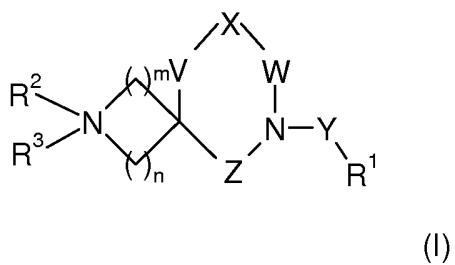
Muscarinic receptors are a G-protein coupled receptor (GPCR) family having five family members M₁, M₂, M₃, M₄ and M₅. Of the five muscarinic subtypes, three (M₁, M₂ and M₃) are known to exert physiological effects on human lung tissue.

Parasympathetic nerves are the main pathway for reflex bronchoconstriction in human airways and mediate airway tone by releasing acetylcholine onto muscarinic receptors. Airway tone is increased in patients with respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD), and for this reason muscarinic receptor antagonists have been developed for use in treating airway diseases. Muscarinic receptor antagonists, often called anticholinergics in clinical practice, have gained widespread acceptance as a first-line therapy for individuals with COPD, and their use has been extensively reviewed in the literature (e.g. Lee et al, Current Opinion in Pharmacology 2001,1, 223-229).

When used to treat respiratory disorders, muscarinic receptor antagonists are typically administered by inhalation. However, when administered by inhalation a significant proportion of the muscarinic receptor antagonist is often absorbed into the systemic circulation resulting in reported side effects such as dry mouth. Additionally, the majority of muscarinic antagonists have a relatively short duration of action requiring that they be administered several times a day. Such a multiple-daily dosing regime is not only inconvenient to the patient but also creates a significant risk of inadequate treatment due to patient non-compliance associated with the frequent repeat dosing schedule.

There therefore remains a need for novel compounds that are capable of blocking muscarinic receptors. In particular, a need exists for new muscarinic antagonists that have high potency and reduced systemic side effects when administered by inhalation. Moreover, a need exists for new muscarinic antagonists that exhibit a long duration of action when dosed by inhalation, and which are amenable to either once or twice daily dosing.

In accordance with one aspect of the present invention there is provided a compound of formula (I):



wherein

R¹ is selected from the following;

(i) an optionally substituted 4-8 membered ring, said ring being aromatic or fully or partially saturated and wherein up to four of the ring atoms may be replaced by heteroatoms independently selected from N, O and S. Examples of such rings include phenyl, thiazolyl, thienyl, isoxazolyl, furyl, cyclohex-3-enyl, cyclohexyl, cycloheptyl and the like.

(ii) an optionally substituted fused bicyclic ring system of up to 10 atoms, said rings being aromatic or fully or partially saturated, and wherein up to four of the ring atoms may be replaced by heteroatoms independently selected from N, O and S. Examples of such rings include benzo[b]thienyl, benzofuranyl, benzo[d]imidazolyl, quinoxaliny1, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyridinyl, dihydrobenzo[b][1,4]dioxinyl, 4,5,6,7-tetrahydro-2H-indazolyl, benzo[d][1,3]dioxolyl and the like.

(iii) an optionally substituted C₁₋₆ alkyl group wherein one or two of the carbon atoms can be replaced by O, S or N and wherein said alkyl group may be substituted once or twice by a ring system independently selected from (i) and (ii) above, and wherein the C₁₋₆ alkyl chain may be substituted by up to five substituents selected from halogen, cyano, S(O)₀₋₂R¹⁰, NR⁸R⁹, S(O)₂NR⁸R⁹, C(O)NR⁸R⁹, C(O)OR¹⁰, NR¹⁰S(O)₂R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(O)OR¹¹, NR¹⁰C(O)NR⁸R⁹, OR¹⁰, C₁₋₆ alkyl and C₃₋₆ cycloalkyl (wherein two C₁₋₃ alkyl chains may be joined to form a cycloalkyl ring of up to eight ring atoms), wherein any ring may be optionally substituted by up to three substituents independently selected from halogen, cyano, SH, S(O)₀₋₂R¹⁰, NR⁸R⁹, S(O)₂NR⁸R⁹, C(O)NR⁸R⁹, C(O)OR¹⁰, NR¹⁰S(O)₂R¹¹, NR¹⁰C(O)R¹¹, NR¹⁰C(O)OR¹¹, NR¹⁰C(O)NR⁸R⁹, OR¹⁰).

and wherein for the ring systems in (i) and (ii) above “optionally substituted” means optionally substituted by up to four substituents independently selected from halogen, cyano, nitro, SH, S(O)₀₋₂R¹⁰, NR⁸R⁹, S(O)₂NR⁸R⁹, C(O)NR⁸R⁹, C(O)OR¹⁰, NR¹⁰S(O)₂R¹¹,

$\text{NR}^{10}\text{C(O)R}^{10}$, $\text{NR}^{10}\text{C(O)OR}^{11}$, $\text{NR}^{10}\text{C(O)NR}^8\text{R}^9$, OR^{10} , C_{1-6} alkyl or C_{3-6} cycloalkyl (wherein a carbon atom of alkyl or cycloalkyl may be optionally replaced by N, O or S) and alkyl or cycloalkyl may be optionally substituted by up to five substituents selected from C_{1-6} alkyl, halogen, cyano, SH, $\text{S(O)}_{0-2}\text{R}^{10}$, NR^8R^9 , $\text{S(O)}_2\text{NR}^8\text{R}^9$, $\text{C(O)NR}^8\text{R}^9$, C(O)OR^{10} , $\text{NR}^{10}\text{S(O)}_2\text{R}^{11}$, $\text{NR}^{10}\text{C(O)R}^{10}$, $\text{NR}^{10}\text{C(O)OR}^{11}$, $\text{NR}^{10}\text{C(O)NR}^8\text{R}^9$, OR^{10}), phenyl or a 4-8 membered heterocyclic ring (containing up to 4 heteroatoms selected from N, O or S) and wherein the phenyl or 4-8 membered heterocyclic rings may be optionally substituted by up to 3 substituents independently selected from halogen, cyano, nitro, SH, $\text{S(O)}_{0-2}\text{R}^{10}$, NR^8R^9 , $\text{S(O)}_2\text{NR}^8\text{R}^9$, $\text{C(O)NR}^8\text{R}^9$, C(O)OR^{10} , $\text{NR}^{10}\text{S(O)}_2\text{R}^{11}$, $\text{NR}^{10}\text{C(O)R}^{10}$, $\text{NR}^{10}\text{C(O)OR}^{11}$, $\text{NR}^{10}\text{C(O)NR}^8\text{R}^9$, OR^{10} , C_{1-6} alkyl or C_{3-6} cycloalkyl (wherein alkyl or cycloalkyl may be optionally substituted by up to 3 substituents selected from halogen or OR^{10});

and wherein the saturated ring systems in (i) and (iii) may also be substituted by up to three C_{1-6} alkyl groups that can be joined to form bridged ring structures, optionally substituted by halogen or OR^{10} . Examples of these ring systems include adamantyl and bicyclo[2.2.1]heptyl;

X represents O, S(O)_{0-2} or $\text{CR}^{12}\text{R}^{13}$;

m = 0, 1, 2 or 3;

n = 1, 2, 3 or 4; provided that **m + n** is greater than or equal to 2;

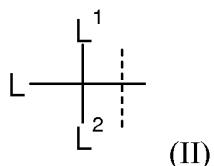
W represents $\text{CR}^{12}\text{R}^{13}-\text{CR}^{12}\text{R}^{13}$ or $\text{CR}^{12}\text{R}^{13}-\text{CR}^{12}\text{R}^{13}-\text{CR}^{12}\text{R}^{13}$;

V and **Z** independently represent a bond, $\text{CR}^{12}\text{R}^{13}$ or $\text{CR}^{12}\text{R}^{13}-\text{CR}^{12}\text{R}^{13}$, provided that when X represents either O or S(O)_{0-2} then m, V and Z are such that all the heteroatoms in the rings are separated by at least two carbon atoms;

Y represents C(O) , C(O)NR^{10} , SO_2 or $\text{SO}_2\text{NR}^{10}$;

R² is a lone pair, or C_{1-6} alkyl, in which cases the nitrogen atom to which it is attached is a quaternary nitrogen and carries a positive charge; or

R³ is a group of formula (II)



wherein L¹ and L² independently represent hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl, wherein the C₁₋₆ alkyl and C₃₋₆ cycloalkyl may be optionally substituted by up to three substituents independently selected from halogen, hydroxyl and C₁₋₆ alkoxy;

or

L¹ and/or L² may be linked to carbon atoms in the group L, or L¹ and L² may be linked to each other, to form aliphatic rings of up to 6 ring atoms, wherein each ring may comprise up to three heteroatoms independently selected from N, O and S;

and wherein L represents a straight or branched hydrocarbyl chain of up to 15 carbon atoms;

wherein up to three of the carbon atoms in the chain are optionally substituted once or twice by groups independently selected from halogen, cyano, S(O)₀₋₂R¹⁰, NR¹⁴R¹⁵, S(O)₂NR⁸R⁹, C(O)NR⁸R⁹, C(O)OR¹⁰, NR¹⁰S(O)₂R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(O)OR¹¹, NR¹⁰C(O)NR⁸R⁹, OR¹⁰, C₁₋₆ alkyl and C₃₋₆ cycloalkyl, and wherein alkyl and cycloalkyl may be optionally substituted by up to three substituents independently selected from halogen, hydroxyl and C₁₋₆ alkoxy;

wherein up to three carbon atoms of the chain may be replaced by groups independently selected from O, NR¹⁰, S, S(O), S(O)₂, C(O)O, OC(O), , NR¹⁰C(O)NR¹⁰, NR¹⁰S(O)₂NR¹⁰, OC(O)NR¹⁰, NR¹⁰C(O)O, provided that any such groups in the chain are separated by at least two chain carbon atoms; and

wherein up to six carbon atoms of the chain may form part of an aryl, heteroaryl, fused bicyclic, alicyclic, or heteroaliphatic ring having up to four heteroatoms independently selected from N, O or S, said ring comprising up to 10 ring atoms, and wherein the ring is optionally substituted by up to three substituents independently selected from halogen, cyano, S(O)₀₋₂R¹⁰, NR⁸R⁹, S(O)₂NR⁸R⁹, C(O)NR⁸R⁹, C(O)OR¹⁰, NR¹⁰S(O)₂R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(O)OR¹¹, NR¹⁰C(O)NR⁸R⁹, =O, OR¹⁰, C₁₋₆ alkyl and C₃₋₆ cycloalkyl, and wherein alkyl and cycloalkyl may be optionally substituted by up to three substituents independently selected from halogen, hydroxyl and C₁₋₆ alkoxy, with the proviso that L does not comprise an optionally substituted para- or meta-hydroxy phenyl-1-hydroxy-ethylamino- group (or fused bicyclic derivative thereof) or an optionally substituted 4-hydroxy-2-pyridyl-1-hydroxy-ethylamino- group;

R⁸ and R⁹ are independently hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl, or R⁸ and R⁹ may be joined together to form a heterocyclic ring comprising up to 9 ring atoms (optionally

containing a further heteroatom selected from O, N or S) wherein the ring may be optionally substituted by up to three substituents independently selected from halogen, hydroxyl, C₁₋₆ alkyl or C₃₋₆ cycloalkyl, and wherein alkyl and cycloalkyl may be optionally substituted by up to three substituents independently selected from halogen, hydroxyl and C₁₋₆ alkoxy;

R¹⁰ represents hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl, wherein alkyl and cycloalkyl may be optionally substituted by up to three substituents independently selected from halogen, hydroxyl and C₁₋₆ alkoxy;

R¹¹ represents C₁₋₆ alkyl or C₃₋₆ cycloalkyl, wherein the C₁₋₆ alkyl and C₃₋₆ cycloalkyl may be optionally substituted by up to three substituents independently selected from halogen, hydroxyl or C₁₋₆ alkoxy;

R¹² and **R**¹³ each independently represent hydrogen, fluorine, C₁₋₆ alkyl or C₃₋₆ cycloalkyl; or R¹² and R¹³ when attached to the same carbon atom, together with the carbon atom to which they are both attached, may additionally form a 3 to 6 membered aliphatic ring;

R¹⁴ represents hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl, and;

R¹⁵ represents

(i) hydrogen or;

(ii) an optionally substituted aryl, heteroaryl, fused bicyclic, alicyclic or heteroaliphatic ring, or;

(iii) a C₁₋₆ straight- or branched chain alkyl optionally containing an oxygen or sulfur atom in the chain and optionally substituted by up to 3 substituents selected from halogen, hydroxyl, OR¹⁰, -COOR¹⁰, C(=O)NR⁸R⁹, NR¹⁰C(=O)R¹⁰ (wherein R⁸, R⁹, and R¹⁰ are as defined above and each independently may additionally represent an optionally substituted aryl, heteroaryl, fused bicyclic, alicyclic or heteroaliphatic ring), or an optionally substituted aryl, heteroaryl, fused bicyclic, alicyclic or heteroaliphatic ring, or;

(iv) a C₃₋₈ cycloalkyl group optionally substituted by up to 3 substituents selected from halogen, hydroxyl, OR¹⁰, -COOR¹⁰, C(=O)NR⁸R⁹, NR¹⁰C(=O)R¹⁰ (wherein R⁸, R⁹, and R¹⁰ are as defined above and each independently may additionally represent an optionally substituted aryl, heteroaryl, fused bicyclic, alicyclic or heteroaliphatic ring), or an optionally substituted aryl, heteroaryl, fused bicyclic, alicyclic or heteroaliphatic ring;

or R¹⁴ and R¹⁵ are joined together with the nitrogen atom to which they are attached to form a heterocyclic ring (optionally fused to an aryl or heteroaryl ring), optionally containing a further heteroatom selected from O, N, or S, and optionally substituted by C₁₋₆alkyl, =O, -C(=O)NR⁸R⁹, -NR¹⁰C(=O)R¹⁰, -C(=O)R¹⁰(wherein R⁸, R⁹, and R¹⁰ are as defined above and each independently may additionally represent an optionally substituted aryl, heteroaryl, fused bicyclic, alicyclic or heteroaliphatic ring), or an optionally substituted aryl, heteroaryl, fused bicyclic, alicyclic or heteroaliphatic ring;

and pharmaceutically acceptable salts thereof.

The Group R¹

Conveniently R¹ represents

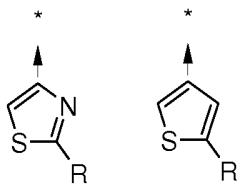
- (i) a phenyl ring or a 5- or 6-membered heteroaryl ring;
- (ii) a fused bicyclic ring ;
- (iii) R¹ may also conveniently represent an optionally substituted C₁₋₆ alkyl group wherein one or two of the carbon atoms can be replaced by O, S or N and wherein said alkyl group may be substituted by the ring systems described in (i) and (ii),

and a convenient C₁₋₆ alkyl group is methylene or ethylene or propylene;

wherein each ring in (i), (ii) and (iii) is optionally substituted by up to three substituents independently selected from halogen, cyano, OR¹⁰, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, or an optionally substituted phenyl ring.

Conveniently R¹ is selected from thiophene or thiazole or benzofuran or pyrazolo[1,5-a]pyridine each optionally substituted by one or two substituents. One of the optional substituents is conveniently selected from H, Cl, F and C₁₋₃ alkyl. The other optional substituent is selected from methyl, ethyl, propyl, n-butyl, CF₃, CH₂CF₃, CH(CH₃)₂, CH(CH₂CH₃)₂, CH(CH₃)CH₂CH₃, CH₂CH(CH₃)₂, C(CH₃)₃, cyclopropyl, cyclobutyl and cyclopentyl;

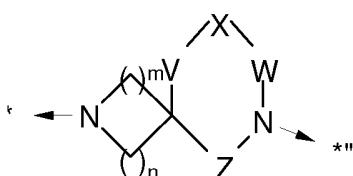
Conveniently R¹ is selected from



wherein the arrow marks the attachment point to the group Y and R is selected from methyl, ethyl, propyl, n-butyl, CF_3 , CH_2CF_3 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_2\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{C}(\text{CH}_3)_3$, cyclopropyl, cyclobutyl and cyclopentyl;

The Group R^2

Conveniently R^2 represents a lone pair;



The group Y and the group

Y represents $\text{C}(\text{O})$, $\text{C}(\text{O})\text{NR}^{10}$, SO_2 or $\text{SO}_2\text{NR}^{10}$; Conveniently Y represents $\text{C}(\text{O})$;

Conveniently

X represents O or S.

$m = 1$ or 2 ;

$n = 1$ or 2 ;

W represents $\text{CR}^{12}\text{R}^{13}\text{CR}^{12}\text{R}^{13}$ or $\text{CR}^{12}\text{R}^{13}\text{CR}^{12}\text{R}^{13}\text{CR}^{12}\text{R}^{13}$;

V and Z independently represent a bond or $\text{CR}^{12}\text{R}^{13}$

V and Z are such that all the heteroatoms in the rings are separated by at least two carbon atoms (e.g. When V is a bond then Z is $\text{CR}^{12}\text{R}^{13}$).

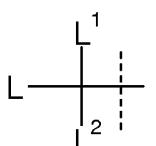
Conveniently

- (i) m and $n = 2$, V = bond, Z = CH_2 , X = O and W = CH_2CH_2
- (ii) m and $n = 2$, V = bond, Z = CH_2 , X = O and W = CF_2CH_2
- (iii) m and $n = 1$, V = bond, Z = CH_2 , X = O and W = CH_2CH_2
- (iv) m and $n = 2$, V = bond, Z = CH_2CH_2 , X = O and W = CH_2CH_2

Conveniently the spirocycle is selected from (i), (ii) or (iii) above.

Conveniently the spirocycle is (i)

The Group

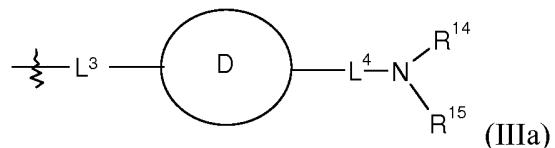


Conveniently the group

(II)

is represented by a group selected from

(i). A group of formula (IIIa)



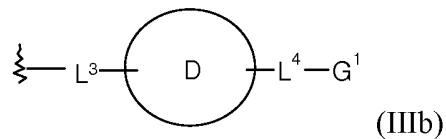
wherein L^3 represents a bond or a C_{1-10} -alkylene, C_{1-10} -alkenylene group, or C_{1-10} -alkynylene group, optionally containing an oxygen or sulfur atom in the chain, (conveniently the group has a chain of up to 8, up to 6 or up to 4 atoms) and;

D is an optionally substituted aryl, heteroaryl, fused bicyclic, alicyclic or heteroaliphatic ring (such as an optionally substituted aryl or heteroaryl ring), and;

L^4 represents a bond or a C_{1-6} -alkylene group optionally containing an oxygen or sulfur atom in the chain (such as a chain of up to 4 atoms), and R^{14} and R^{15} are as defined above;

or

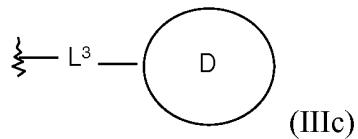
(ii) A group of Formula (IIIb)



wherein L^3 , L^4 and D , are as defined in (i) above and G^1 is the group OR^{10} or $C(O)OR^{10}$;

or;

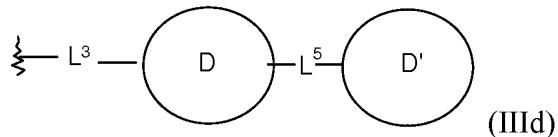
(iii) A group of Formula (IIIc)



wherein L^3 and D are as defined in (i) above. Convenient compounds are for example of formula $(CH_2)_m-(O)_p-(CH_2)_n-Ar$ (wherein Ar is as defined above and optionally substituted by halogen or C_{1-6} alkyl, m is 1-3, p is 0 or 1, and n is 0-2), such as phenoxypropyl, 4-halobenzoyloxyethyl (eg. 4-chlorobenzoyloxyethyl) or 4-halophenethyl (eg. 4-fluorophenethyl);

or;

(iv) A group of formula (IIId)



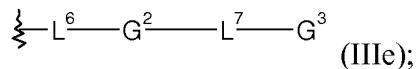
wherein L^3 and D are as defined in (i) above, and;

L^5 is a bond, C_{1-6} alkylene group, or an oxygen or sulfur atom, and;

Ring D' is an optionally substituted aryl, heteroaryl, fused bicyclic, alicyclic or heteroaliphatic ring;

or:

(v) A group of formula (IIIe)



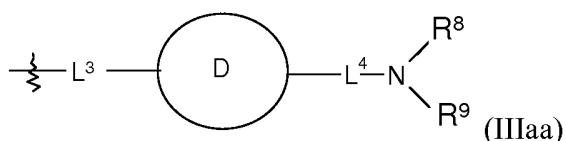
wherein L^6 and L^7 are independently each a C_{1-10} -alkylene, C_{1-10} -alkenylene, or C_{1-10} -alkynylene group (conveniently the group has a chain of up to 8, up to 6 or up to 4 atoms), and;

G^2 is a bond, or an oxygen or sulfur atom, and;

G^3 is a group $-NR^{14}R^{15}$, $-C(=O)N^{14}R^{15}$ or OR^{10} , and R^{10} , R^{14} and R^{15} are as defined above.

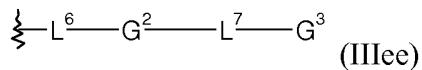
Wherein in groups of formula (IIIa-d) rings D and D' are optionally substituted by up to three substituents independently selected from halogen, $S(O)_{0-2}R^{10}$, NR^8R^9 , $S(O)_2NR^8R^9$, $C(O)NR^8R^9$, $C(O)OR^{10}$, $NR^{10}S(O)_2R^{11}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)OR^{11}$, $NR^{10}C(O)NR^8R^9$, $=O$, OR^{10} , C_{1-6} alkyl and C_{3-6} cycloalkyl, and wherein alkyl and cycloalkyl may be optionally substituted by up to three substituents independently selected from halogen, hydroxyl and C_{1-6} alkoxy;

Conveniently the group of Formula (IIIa) is a group of Formula (IIIaa);



wherein L^3 , D , and L^4 are as defined in Formula (IIIa), and R^8 and R^9 are as defined above

Conveniently the group of formula (IIIe) is a group of formula (IIIee);



wherein L^6 , G^2 and L^7 are as defined in Formula (IIIe) and G^3 is a group $-NR^8R^9$, $-C(=O)NR^8R^9$ or OR^{10} , and R^8 , R^9 , and R^{10} are as defined above

Conveniently

R^{14} represents hydrogen or C_{1-6} alkyl

R^{15} represents independently

(i) hydrogen or;

(ii) an optionally substituted aryl or heteroaryl ring, or;

(iii) a C_{1-6} straight- or branched chain alkyl optionally containing an oxygen or sulfur atom in the chain and optionally substituted by up to 3 substituents selected from halogen, hydroxyl, OR^{10} , $-COOR^{10}$, $C(=O)NR^8R^9$, $NR^{10}C(=O)R^{10}$ (wherein R^8 , R^9 , and R^{10} are as defined above and each independently may additionally represent an optionally substituted aryl or heteroaryl ring), or an optionally substituted aryl or heteroaryl ring; or

(iv) a C_{3-8} cycloalkyl group optionally substituted by up to 3 substituents selected from halogen, hydroxyl, OR^{10} , $-COOR^{10}$, $C(=O)NR^8R^9$, $NR^{10}C(=O)R^{10}$ (wherein R^8 , R^9 , and R^{10} are as defined above and each independently may additionally represent an optionally substituted aryl or heteroaryl ring), or an optionally substituted aryl or heteroaryl ring; or

R^{14} and R^{15} are joined together with the nitrogen atom to which they are attached to form a heterocyclic ring (optionally fused to an aryl or heteroaryl ring), optionally containing a further heteroatom selected from O, N, or S, and optionally substituted by C_{1-6} alkyl, $=O$, $-C(=O)NR^8R^9$, $-NR^{10}C(=O)R^{10}$, $-C(=O)R^{10}$ (wherein R^8 , R^9 , and R^{10} are as defined above and each independently may additionally represent an optionally substituted aryl or heteroaryl ring), or an optionally substituted aryl or heteroaryl ring;

When the compounds of formula (I) is a quaternary ammonium salt, it comprises an anion "A" associated with the positive charge on the quaternary nitrogen atom. The anion "A" may be any pharmaceutically acceptable anion of a mono or polyvalent (e.g. bivalent) acid. In an embodiment of the invention "A" may be an anion of a mineral acid, for example chloride, bromide, iodide, sulfate, nitrate or phosphate; or an anion of a suitable organic acid, for example acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, methanesulphonate, p-toluenesulphonate, benzenesulphonate, napadisylate

(naphthalene-1,5-disulphonate) (e.g. a heminapadisylate), 2,5-dichlorobenzenesulphonate, xinafoate (1-hydroxy-2-naphthoate) or 1-hydroxynaphthalene-2-sulphonate.

It will be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms. Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

It is also to be understood that the present invention encompasses the replacement of any quaternary carbon, more specifically the quaternary carbon present in the spirocyclic system, by a silicon atom for example as disclosed in "Silicon switches of Marketed Drugs: Mini-reviews in Med. Chem.", 2006, 6, 1169-1177.

Definitions

The term 'heteroaryl' means an aromatic ring system of 5 to 7 atoms, conveniently from 5-6 atoms, having up to three heteroatoms selected from N, O and S. Examples of such heteroaryl rings include thiazolyl, thienyl, isoxazolyl, furyl, isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, tetrazolyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl, triazolyl and the like. The heteroaryl group may be attached by any available carbon or nitrogen atom.

The term 'fused bicyclic ring' means a ring system of up to 12 atoms wherein 2 rings are fused together. The system may optionally contain up to 4 heteroatoms selected from N, S and O. The rings may independently be aromatic, partially saturated or fully saturated. Examples of such fused bicyclic ring systems include benzo[b]thienyl, benzofuranyl, benzo[d]imidazolyl, quinoxaliny, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyridinyl, dihydrobenzo[b][1,4]dioxinyl, 4,5,6,7-tetrahydro-2H-indazolyl, benzo[d][1,3]dioxolyl, benzoxazolyl, benzothiazolyl, benzofuranyl, benzothienyl, naphthyl, indanyl, 1,2,3,4-tetrahydronaphthyl, 1,2,3,4-tetraydroquinolinyl, 5,6,7,8-tetrahydroquinolinyl and the like. The ring system may be joined to the rest of the molecule by any convenient nitrogen or carbon atom.

The term 'aryl' means an aromatic carbocyclic ring. Examples are phenyl, naphthyl and the like.

The term ‘alicyclic’ means a group having a carbocyclic ring structure which may be saturated or unsaturated, but may not be a benzenoid or other aromatic system.

The term ‘aliphatic’ means a non-aromatic group.

The term ‘heteroaliphatic ring’ means a heterocyclic ring that is wholly or partially saturated, but not aromatic. The ring has up to 10 atoms with up to 4 heteroatoms selected from N, O or S. Examples are piperidine, morpholine, tetrahydrofuran, pyrrolidine and the like.

The groups ‘aryl’, ‘heteroaryl’, ‘fused bicyclic’, ‘alicyclic’ and ‘heteroaliphatic’ ring may be substituted by one or more substituent groups selected from C₁₋₆ alkyl, C₃₋₆ cycloalkyl, halogen, cyano, nitro, SH, S(O)₀₋₂R¹⁰, NR⁸R⁹, S(O)₂NR⁸R⁹, C(O)NR⁸R⁹, C(O)OR¹⁰, NR¹⁰S(O)₂R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(O)OR¹¹, NR¹⁰C(O)NR⁸N⁹, OR¹⁰.

Unless otherwise stated, in the context of the present specification alkyl groups and moieties may be straight or branched chain and include, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl or tert-butyl. ‘C₁₋₈ alkyl’ means a straight or branched chain alkyl group having from one to eight carbon atoms; similarly ‘C₁₋₆ alkyl’ means a straight or branched alkyl chain having from one to six carbon atoms. Cycloalkyl groups are monocyclic, for example cyclopentyl or cyclohexyl. ‘C₃₋₈ cycloalkyl’ means a cycloalkyl group having from three to eight carbon atoms. Alkyl, alkylene and cycloalkyl groups may be optionally substituted by up to three groups selected from halogen, hydroxy, hydroxy-C₁₋₆alkyl or C₁₋₆ alkoxy.

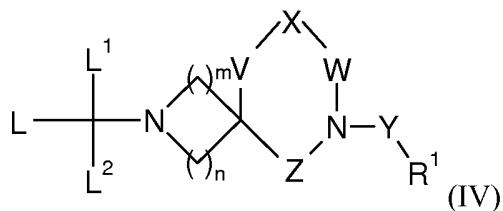
‘Halogen’ is for example, fluoride, chloride or bromide.

‘Alkoxy’ means an alkyl or cycloalkyl group attached to an oxygen atom. Examples are methoxy, ethoxy and cyclopropyloxy.

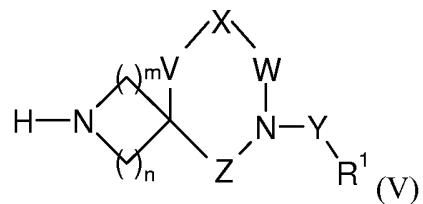
In the context of the present specification, where it is stated that a group may be optionally substituted with up to three substituents, the group may be unsubstituted or substituted; when substituted the group will generally be substituted with one, two or three substituents. In general, a hydroxyl moiety will not be attached to a carbon atom which is adjacent to a nitrogen atom, another oxygen atom or a sulfur atom.

The invention further provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined above which comprises reacting a compound of formula (IV) with an C₁₋₆alkyl halide eg. methyl iodide or ethyl iodide.

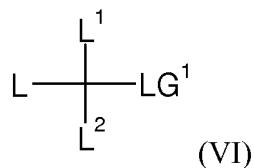
Compounds of formula (IV)



wherein R^1 , m , n , V , W , X , Y and Z are as defined in formula (I) and L , L^1 and L^2 are as defined in formula (II) can be prepared by reacting a compound of formula (V) or a suitable salt thereof (e.g. hydrobromide, acetate or hydrochloride),

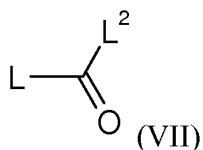


wherein R^1 , m , n , V , W , X , Y and Z are as defined in formula (I) with a compound of formula (VI)



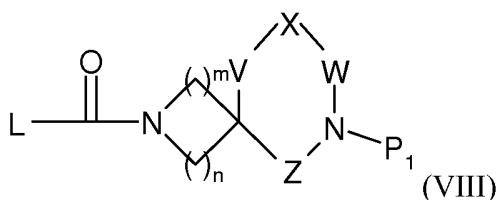
wherein LG^1 represents a leaving group (e.g. chloride, bromide, iodide, methanesulfonate or *para*-toluenesulfonate) and L , L^1 and L^2 are as defined in formula (II) in the presence of a base (e.g. potassium carbonate, triethylamine or diisopropylethylamine) in an organic solvent, for example, *N,N*-dimethylformamide or dichloromethane, at a temperature, for example in the range from 0 to 60°C.

Compounds of the formula (IV), wherein L^1 equals hydrogen and R^1 , m , n , V , W , X and Z are as defined in formula (I) and, L and L^2 are as defined in formula (II), can be prepared by reacting a compound of formula (V) or a suitable salt thereof (e.g. hydrobromide, acetate or hydrochloride), with a compound of formula (VII)

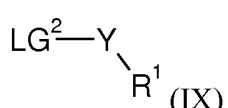


wherein L and L² are as defined in formula (II) above in the presence of a suitable reducing agent (e.g. sodium cyanoborohydride, sodium triacetoxyborohydride, or hydrogen in the presence of a palladium on carbon or palladium oxide catalyst) in an organic solvent, for example, N-methyl-2-pyrrolidinone or ethanol, at a temperature, for example in the range from 0 to 60°C.

Compounds of formula (IV) in which both L¹ and L² equals hydrogen may be prepared by contacting a corresponding compound of formula (VIII).



wherein m, n, V, W, X, Y and Z are as defined in formula (I), L is as defined in formula (II) and P¹ is a suitable nitrogen protective group, with a reducing agent, for example, lithium aluminium hydride or borane tetrahydrofuran complex in an organic solvent, for example, tetrahydrofuran at a temperature, for example in the range from 0 to 60°C, followed by removal of the protective group and reaction with a compound of formula (IX), or a suitable salt thereof,

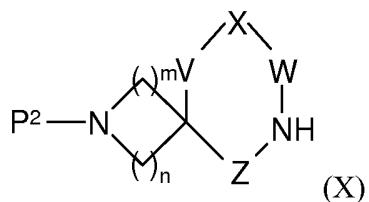


wherein R¹ and Y are as defined in formula (I) and LG² represents hydroxyl or a leaving group (e.g. halide, chloride), followed by removal of the protective groups (e.g. treatment with hydrochloric or trifluoroacetic acid);

When LG² represents hydroxyl, the reaction is conveniently carried out in the presence of an activating reagent, for example, carbonyldiimidazole, 1-Propanephosphonic acid cyclic anhydride (T3P) or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HATU), in an organic solvent, for example, N,N-dimethylformamide or dichloromethane, optionally in a presence of a base (e.g. triethylamine), at a temperature, for example in the range from 0 to 60 °C,

When LG^2 represents a halide (e.g. chloride), the reaction is conveniently carried out in the presence of a base, for example, triethylamine, diisopropylethylamine or pyridine in an organic solvent, for example, dichloromethane or tetrahydrofuran at a temperature, for example, in the range from 0 to 25 °C;

Compound of formula (V) wherein R^1 , V, X, W, and Z are as defined in formula (I) can be prepared by contacting a compound of formula (X)

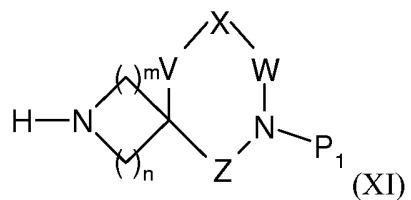


wherein P^2 is a suitable nitrogen protective group (e.g. *tert*-Butylcarbonate), with a compound of formula (IX), or a suitable salt thereof, wherein R^1 , Y and LG^2 are as defined in formula (IX),

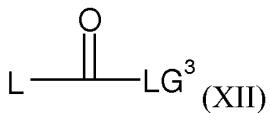
When LG^2 represents hydroxyl, the reaction is conveniently carried out in the presence of an activating reagent, for example, carbonyldiimidazole, 1-Propanephosphonic acid cyclic anhydride (T3P) or O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluroniumhexafluorophosphate (HATU), in an organic solvent, for example, *N,N*-dimethylformamide or dichloromethane, optionally in a presence of a base (e.g. triethylamine), at a temperature, for example in the range from 0 to 60 °C,

When LG^2 represents a halide (e.g. chloride), the reaction is conveniently carried out in the presence of a base, for example, triethylamine, diisopropylethylamine or pyridine in an organic solvent, for example, dichloromethane or tetrahydrofuran at a temperature, for example, in the range from 0 to 25 °C;

Compound of formula (VIII) wherein m, n, V, W, X, Y and Z are as defined in formula (I), L is as defined in formula (II) and P^1 is a suitable nitrogen protective group, can be prepared by contacting a compound of formula (XI)



with a compound of formula (XII), or a suitable salt thereof,

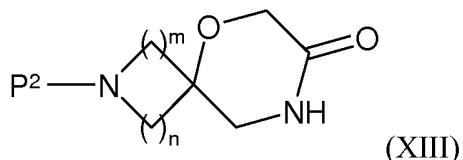


wherein LG^3 is a suitable leaving group;

When LG^3 represents hydroxyl, the reaction is conveniently carried out in the presence of an activating reagent, for example, carbonyldiimidazole, 1-Propanephosphonic acid cyclic anhydride (T3P) or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HATU), in an organic solvent, for example, *N,N*-dimethylformamide or dichloromethane, optionally in a presence of a base (e.g. triethylamine), at a temperature, for example in the range from 0 to 60 °C,

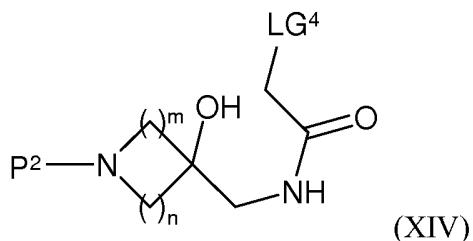
When LG^3 represents a halide (e.g. chloride), the reaction is conveniently carried out in the presence of a base, for example, triethylamine, diisopropylethylamine or pyridine in an organic solvent, for example, dichloromethane or tetrahydrofuran at a temperature, for example, in the range from 0 to 25 °C;

A compound of general formula (X), wherein V represents a bond, X represents O, W represents $\text{CR}^{27}\text{R}^{28}\text{CR}^{29}\text{R}^{30}$, Z represents $\text{CR}^{37}\text{R}^{38}$, R^{27} , R^{28} , R^{29} , R^{30} , R^{37} , R^{38} each represent hydrogen, and P^2 is as defined in formula (X), can be prepared from a compound of formula (XIII)



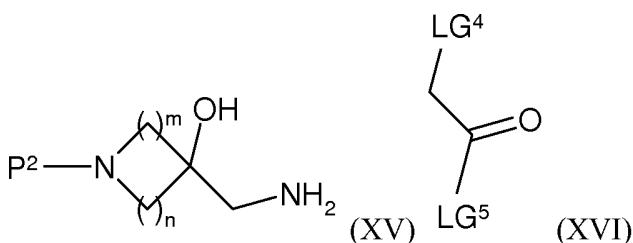
wherein P^2 , m and n are as defined in compound of formula (X), by treatment with a suitable reducing agent such as borane-THF complex in a suitable solvent such as tetrahydrofuran at 30-70°C with the resulting boron complex decomposed with a suitable amine such as *N,N*2-dimethyleneamine-1,2-diamine in methanol at 60-90°C

A compound of formula (XIII) can be prepared from a compound of formula (XIV)



wherein LG^4 is a suitable leaving group such as halogen or tosylate and P^2 , m and n are as defined in compound of formula (XIII), by treatment with a suitable base such as potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran at 50-90°C.

A compound of formula (XIV) can be prepared by reacting a compound of formula (XV) with a compound of formula (XVI)

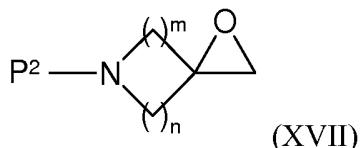


wherein LG^5 represents a hydroxyl or halogen group such as chloride and P^2 , m, n and LG^4 are as defined in compound of formula (XIV);

For the case where LG^5 represents hydroxyl, the reaction is conveniently carried out in the presence of an activating reagent, for example, carbonyldiimidazole, 1-Propanephosphonic acid cyclic anhydride (T3P) or O-(7-azabenzotriazol-1-yl)- N,N,N',N' -tetramethyluroniumhexafluorophosphate (HATU), in an organic solvent, for example, N,N -dimethylformamide or dichloromethane, optionally in a presence of a base (e.g. triethylamine), at a temperature, for example in the range from 0 to 60 °C;

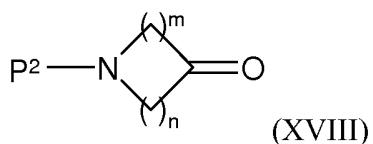
For the case where LG^5 represents chloride, the reaction is conveniently carried out in the presence of a base, for example, triethylamine or diisopropylethylamine in an organic solvent, for example, dichloromethane or tetrahydrofuran at a temperature, for example, in the range from 0 to 25 °C;

A compound of formula (XV) can be prepared by reacting a compound of formula (XVII)



wherein P^2 , m and n are as defined in compound of formula (XV), with ammonia in a suitable solvent such as methanol at a temperature in the range from 20-60°C;

A compound of formula (XVII) can be prepared by reacting a compound of formula (XVIII)



wherein P^2 , m and n are as defined in compound of formula (XVII), with trimethyl sulfoxonium iodide in the presence of a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as dimethylsulfoxide at a temperature in the range from 0-20°C;

Also the process above refers to simple oxidation and reduction steps, these are performed under standard conditions well established in the literature (e.g. Dess-Martin, Swern, pyridinium chlorochromate, pyridinium sulfur trioxide complex oxidations). They can be conveniently performed in an organic solvent such as dichloromethane, in a range of temperature from -78 to 50 °C (Annual Reports on the Progress of Chemistry, Section B: Organic Chemistry, 2004, 100, 51-70).

Compounds of formula (VI), (VII), (IX), (XII), (XVI), and are either commercially available, known in the literature, or can be readily prepared by those skilled in the art using one of the process described above or using known techniques.

Other intermediate compounds are novel and represent independent aspects of the invention.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the reagents may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the addition or removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

Compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures.

The compounds of the invention have activity as pharmaceuticals, in particular as anticholinergic agents including muscarinic receptor (M1, M2, and M3) antagonists, in

particular M3 antagonists. Diseases and conditions which may be treated with the compounds include:

1. *respiratory tract*: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;
2. *bone and joints*: arthritides associated with or including osteoarthritis/osteoarthrosis, both primary and secondary to, for example, congenital hip dysplasia; cervical and lumbar spondylitis, and low back and neck pain; rheumatoid arthritis and Still's disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondarthropathy; septic arthritis and other infection-related arthropathies and bone disorders such as tuberculosis, including Potts' disease and Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositis and polymyositis; polymalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever

and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthralgias, tendonitides, and myopathies;

3. *pain and connective tissue remodelling of musculoskeletal disorders due to injury [for example sports injury] or disease:* arthritides (for example rheumatoid arthritis, osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as osteoporosis, Paget's disease or osteonecrosis), polychondritis, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as periodontitis);

4. *skin:* psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;

5. *eyes:* blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial;

6. *gastrointestinal tract:* glossitis, gingivitis, periodontitis; oesophagitis, including reflux; eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis including ulcerative colitis, proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, and food-related allergies which may have effects remote from the gut (for example migraine, rhinitis or eczema);

7. *abdominal*: hepatitis, including autoimmune, alcoholic and viral; fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic;
8. *genitourinary*: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female);
9. *allograft rejection*: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;
10. *CNS*: Alzheimer's disease and other dementing disorders including CJD and nvCJD; amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; acute and chronic pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain, pain arising from cancer and tumor invasion, neuropathic pain syndromes including diabetic, post-herpetic, and HIV-associated neuropathies; neurosarcoidosis; central and peripheral nervous system complications of malignant, infectious or autoimmune processes;
11. other auto-immune and allergic disorders including Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome;
12. other disorders with an inflammatory or immunological component; including acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and paraneoplastic syndromes;
13. *cardiovascular*: atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis , inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (for example syphilitic); vasculitides; disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins;
14. *oncology*: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting

the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and,

15. *gastrointestinal tract:* Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, microscopic colitis, indeterminant colitis, irritable bowel disorder, irritable bowel syndrome, non-inflammatory diarrhea, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema.

Accordingly, the present invention further provides a compound of formula (I), as hereinbefore defined for use in therapy.

In another aspect, the invention provides the use of a compound of formula (I), as hereinbefore defined, in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

A further aspect of the invention provides a method of treating a disease state in a mammal suffering from, or at risk of, said disease, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I) as hereinbefore defined.

The present invention also provides a compound of formula (I) as hereinbefore defined, for treating chronic obstructive pulmonary disease (COPD) (such as irreversible COPD).

The present invention also provides a compound of formula (I) as hereinbefore defined, for treating asthma.

The present invention also provides the use of a compound of formula (I) as hereinbefore defined, in the treatment of chronic obstructive pulmonary disease (COPD) (such as irreversible COPD).

The present invention also provides the use of a compound of formula (I) as hereinbefore defined, in the treatment of asthma.

The present invention also provides the use of a compound of formula (I) as hereinbefore defined, in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease (COPD) (such as irreversible COPD).

The present invention also provides the use of a compound of formula (I) as hereinbefore defined, in the manufacture of a medicament for use in the treatment of asthma.

The present invention further provides a method of treating chronic obstructive pulmonary disease (COPD) (such as irreversible COPD), in a warm-blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I) as hereinbefore defined.

The present invention further provides a method of treating asthma in a warm-blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I) as hereinbefore defined.

In order to use a compound of the invention for the therapeutic treatment of a warm-blooded animal, such as man, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition that comprises a compound of the invention as hereinbefore defined and a pharmaceutically acceptable adjuvant, diluent or carrier. In a further aspect the present invention provides a process for the preparation of said composition, which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will, for example, comprise from 0.05 to 99%w (per cent by weight), such as from 0.05 to 80%w, for example from 0.10 to 70%w, such as from 0.10 to 50%w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, aerosols, dry powder formulations, tablets, capsules, syrups, powders, granules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule, which contains between 0.1mg and 1g of active ingredient.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection. Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of 0.01mgkg^{-1} to 100mgkg^{-1} of the compound, for example in the range of 0.1mgkg^{-1} to 20mgkg^{-1} of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose, which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day

Another suitable pharmaceutical composition of this invention is one suitable for inhaled administration, inhalation being a particularly useful method for administering the compounds of the invention when treating respiratory diseases such as chronic obstructive pulmonary disease (COPD) or asthma. When administered by inhalation the compounds of formula (I) may be used effectively at doses in the μg range, for example 0.1 to 500 μg , 0.1 to 50 μg , 0.1 to 40 μg , 0.1 to 30 μg , 0.1 to 20 μg , 0.1 to 10 μg , 5 to 10 μg , 5 to 50 μg , 5 to 40 μg , 5 to 30 μg , 5 to 20 μg , 5 to 10 μg , 10 to 50 μg , 10 to 40 μg 10 to 30 μg , or 10 to 20 μg of active ingredient.

In an embodiment of the invention, there is provided a pharmaceutical composition comprising a compound of the invention as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier, which is formulated for inhaled administration.

When administered by inhalation, metered dose inhaler devices may be used to administer the active ingredient, dispersed in a suitable propellant and with or without additional excipients such as ethanol, surfactants, lubricants or stabilising agents. Suitable propellants include hydrocarbon, chlorofluorocarbon and hydrofluoroalkane (e.g. heptafluoroalkane) propellants, or mixtures of any such propellants. Preferred propellants are P134a and P227, each of which may be used alone or in combination with other propellants and/or surfactant and/or other excipients. Nebulised aqueous suspensions or,

preferably, solutions may also be employed, with or without a suitable pH and/or tonicity adjustment, either as a unit-dose or multi-dose formulations.

Dry powder inhalers may be used to administer the active ingredient, alone or in combination with a pharmaceutically acceptable carrier, in the later case either as a finely divided powder or as an ordered mixture. The dry powder inhaler may be single dose or multi-dose and may utilise a dry powder or a powder-containing capsule.

Metered dose inhaler, nebuliser and dry powder inhaler devices are well known and a variety of such devices are available.

The invention further relates to combination therapies wherein a compound of the invention or a pharmaceutical composition or formulation comprising a compound of the invention, is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

In particular, for the treatment of the inflammatory diseases such as (but not restricted to) rheumatoid arthritis, osteoarthritis, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), psoriasis, and inflammatory bowel disease, the compounds of the invention may be combined with agents listed below.

Non-steroidal anti-inflammatory agents (hereinafter NSAIDs) including non-selective cyclo-oxygenase COX-1 / COX-2 inhibitors whether applied topically or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin); selective COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarcoxib, parecoxib and etoricoxib); cyclo-oxygenase inhibiting nitric oxide donors (CINODs); glucocorticosteroids (whether administered by topical, oral, intramuscular, intravenous, or intra-articular routes); methotrexate; leflunomide; hydroxychloroquine; d-penicillamine; auranofin or other parenteral or oral gold preparations; analgesics; diacerein; intra-articular therapies such as hyaluronic acid derivatives; and nutritional supplements such as glucosamine.

The present invention still further relates to the combination of a compound of the invention together with a cytokine or agonist or antagonist of cytokine function, (including agents which act on cytokine signalling pathways such as modulators of the SOCS system)

including alpha-, beta-, and gamma-interferons; insulin-like growth factor type I (IGF-1); interleukins (IL) including IL1 to 17, and interleukin antagonists or inhibitors such as anakinra; tumour necrosis factor alpha (TNF- α) inhibitors such as anti-TNF monoclonal antibodies (for example infliximab; adalimumab, and CDP-870) and TNF receptor antagonists including immunoglobulin molecules (such as etanercept) and low-molecular-weight agents such as pentoxyfylline.

In addition the invention relates to a combination of a compound of the invention with a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax Il-15).

The present invention still further relates to the combination of a compound of the invention with a modulator of chemokine receptor function such as an antagonist of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX₃CR1 for the C-X₃-C family.

The present invention further relates to the combination of a compound of the invention with an inhibitor of matrix metalloprotease (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12, including agents such as doxycycline.

The present invention still further relates to the combination of a compound of the invention and a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAY x 1005.

The present invention further relates to the combination of a compound of the invention and a receptor antagonist for leukotrienes (LT) B4, LTC4, LTD4, and LTE4 selected from the group consisting of the phenothiazin-3-1s such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast;

benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention and a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

The present invention further relates to the combination of a compound of the invention and a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine; applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention and a proton pump inhibitor (such as omeprazole) or a gastroprotective histamine type 2 receptor antagonist.

The present invention further relates to the combination of a compound of the invention and an antagonist of the histamine type 4 receptor.

The present invention still further relates to the combination of a compound of the invention and an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

The present invention still further relates to the combination of a compound of the invention and a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, pirbuterol, or indacaterol or a chiral enantiomer thereof.

The present invention further relates to the combination of a compound of the invention and a chromone, such as sodium cromoglycate or nedocromil sodium.

The present invention still further relates to the combination of a compound of the invention with a glucocorticoid, such as flunisolide, triamcinolone acetonide,

beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

The present invention further relates to the combination of a compound of the invention with an agent that modulates a nuclear hormone receptor such as PPARs.

The present invention still further relates to the combination of a compound of the invention together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (for example omalizumab).

The present invention further relates to the combination of a compound of the invention and another systemic or topically-applied anti-inflammatory agent, such as thalidomide or a derivative thereof, a retinoid, dithranol or calcipotriol.

The present invention still further relates to the combination of a compound of the invention and combinations of aminosalicylates and sulfapyridine such as sulfasalazine, mesalazine, balsalazide, and olsalazine; and immunomodulatory agents such as the thiopurines, and corticosteroids such as budesonide.

The present invention further relates to the combination of a compound of the invention together with an antibacterial agent such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral agent including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir, ritonavir, and saquinavir; a nucleoside reverse transcriptase inhibitor such as didanosine, lamivudine, stavudine, zalcitabine or zidovudine; or a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz.

The present invention still further relates to the combination of a compound of the invention and a cardiovascular agent such as a calcium channel blocker, a beta-adrenoceptor blocker, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-2 receptor antagonist; a lipid lowering agent such as a statin or a fibrate; a modulator of blood cell morphology such as pentoxyfylline; thrombolytic, or an anticoagulant such as a platelet aggregation inhibitor.

The present invention further relates to the combination of a compound of the invention and a CNS agent such as an antidepressant (such as sertraline), an anti-Parkinsonian drug (such as deprenyl, L-dopa, ropinirole, pramipexole, a MAOB inhibitor such as selegiline and rasagiline, a comP inhibitor such as tasmar, an A-2 inhibitor, a

dopamine reuptake inhibitor, an NMDA antagonist, a nicotine agonist, a dopamine agonist or an inhibitor of neuronal nitric oxide synthase), or an anti-Alzheimer's drug such as donepezil, rivastigmine, tacrine, a COX-2 inhibitor, propentofylline or metrifonate.

The present invention still further relates to the combination of a compound of the invention and an agent for the treatment of acute or chronic pain, such as a centrally or peripherally-acting analgesic (for example an opioid or derivative thereof), carbamazepine, phenytoin, sodium valproate, amitryptyline or other anti-depressant agent-s, paracetamol, or a non-steroidal anti-inflammatory agent.

The present invention further relates to the combination of a compound of the invention together with a parenterally or topically-applied (including inhaled) local anaesthetic agent such as lignocaine or a derivative thereof.

A compound of the present invention can also be used in combination with an anti-osteoporosis agent including a hormonal agent such as raloxifene, or a biphosphonate such as alendronate.

The present invention still further relates to the combination of a compound of the invention together with a: (i) tryptase inhibitor; (ii) platelet activating factor (PAF) antagonist; (iii) interleukin converting enzyme (ICE) inhibitor; (iv) IMPDH inhibitor; (v) adhesion molecule inhibitors including VLA-4 antagonist; (vi) cathepsin; (vii) kinase inhibitor such as an inhibitor of tyrosine kinase (such as Btk, Itk, Jak3 or MAP, for example Gefitinib or Imatinib mesylate), a serine / threonine kinase (such as an inhibitor of a MAP kinase such as p38, JNK, protein kinase A, B or C, or IKK), or a kinase involved in cell cycle regulation (such as a cyclin dependent kinase); (viii) glucose-6 phosphate dehydrogenase inhibitor; (ix) kinin-B1. - or B2. -receptor antagonist; (x) anti-gout agent, for example colchicine; (xi) xanthine oxidase inhibitor, for example allopurinol; (xii) uricosuric agent, for example probenecid, sulfinpyrazone or benzboromarone; (xiii) growth hormone secretagogue; (xiv) transforming growth factor (TGF β); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor for example basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) capsaicin cream; (xix) tachykinin NK1 or NK3 receptor antagonist such as NKP-608C, SB-233412 (talnetant) or D-4418; (xx) elastase inhibitor such as UT-77 or ZD-0892; (xxi) TNF-alpha converting enzyme inhibitor (TACE); (xxii) induced nitric oxide synthase (iNOS) inhibitor; (xxiii) chemoattractant receptor-homologous molecule expressed on TH2

cells, (such as a CRTH2 antagonist); (xxiv) inhibitor of P38; (xxv) agent modulating the function of Toll-like receptors (TLR), (xxvi) agent modulating the activity of purinergic receptors such as P2X7; or (xxvii) inhibitor of transcription factor activation such as NFkB, API, or STATS.

A compound of the invention can also be used in combination with an existing therapeutic agent for the treatment of cancer, for example suitable agents include:

- (i) an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin);
- (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5 α -reductase such as finasteride;
- (iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function);
- (iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbB2 antibody trastuzumab, or the anti-erbB1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-

bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family;

- (v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin $\alpha v\beta 3$ function or an angiostatin);
- (vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213;
- (vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense;
- (viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or
- (ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

In a further embodiment the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is a compound of formula (I) as hereinbefore described, and at least one further active ingredient selected from:-

- a phosphodiesterase inhibitor,
- a $\beta 2$. adrenoceptor agonist,
- a modulator of chemokine receptor function,
- an inhibitor of kinase function,
- a protease inhibitor,

- a steroidal glucocorticoid receptor agonist, and a
- a non-steroidal glucocorticoid receptor agonist.

The pharmaceutical product according to this embodiment may, for example, be a pharmaceutical composition comprising the first and further active ingredients in admixture. Alternatively, the pharmaceutical product may, for example, comprise the first and further active ingredients in separate pharmaceutical preparations suitable for simultaneous, sequential or separate administration to a patient in need thereof.

The pharmaceutical product of this embodiment is of particular use in treating respiratory diseases such as asthma, COPD or rhinitis.

Examples of a phosphodiesterase inhibitor that may be used in the pharmaceutical product according to this embodiment include a PDE4 inhibitor such as an inhibitor of the isoform PDE4D, a PDE3 inhibitor and a PDE5 inhibitor. Examples include the compounds (Z)-3-(3,5-dichloro-4-pyridyl)-2-[4-(2-indanyloxy-5-methoxy-2-pyridyl)propenenitrile, N-[9-amino-4-oxo-1-phenyl-3,4,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepin-3(R)-yl]pyridine-3-carboxamide (CI-1044)

3-(benzyloxy)-1-(4-fluorobenzyl)-N-[3-(methylsulphonyl)phenyl]-1H-indole-2-carboxamide,

(1S-exo)-5-[3-(bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]tetrahydro-2(1H)-pyrimidinone (Atizoram),

N-(3,5,dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide (AWD-12-281),

β -[3-(cyclopentyloxy)-4-methoxyphenyl]-1,3-dihydro-1,3-dioxo-2H-isoindole-2-propanamide (CDC-801),

N-[9-methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepin-3(R)-yl]pyridine-4-carboxamide (CI-1018),

cis-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid (Cilomilast)

8-amino-1,3-bis(cyclopropylmethyl)xanthine (Cipamfylline)

N-(2,5-dichloro-3-pyridinyl)-8-methoxy-5-quinolinecarboxamide (D-4418),

5-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-iminothiazolidin-4-one (Darbufelone),

2-methyl-1-[2-(1-methylethyl)pyrazolo[1,5-a]pyridin-3-yl]-1-propanone (Ibudilast),

2-(2,4-dichlorophenylcarbonyl)-3-ureidobenzofuran-6-yl methanesulphonate (Lirimilast),

(-)-(R)-5-(4-methoxy-3-propoxyphenyl)-5-methyloxazolidin-2-one (Mesopram),
(-)-cis-9-ethoxy-8-methoxy-2-methyl-1,2,3,4,4a,10b-hexahydro-6-(4-diisopropylaminocarbonylphenyl)-benzo[c][1,6]naphthyridine (Pumafentrine),
3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridyl)-4-(difluoromethoxy)benzamide (Roflumilast),
the N-oxide of Roflumilast,
5,6-diethoxybenzo[b]thiophene-2-carboxylic acid (Tibenelast)
2,3,6,7-tetrahydro-2-(mesitylimino)-9,10-dimethoxy-3-methyl-4H-pyrimido[6,1-a]isoquinolin-4-one (trequinsin) and
3-[[3-(cyclopentyloxy)-4-methoxyphenyl]-methyl]-N-ethyl-8-(1-methylethyl)-3H-purine-6-amine (V-11294A).

Examples of a β_2 -adrenoceptor agonist that may be used in the pharmaceutical product according to this embodiment include metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol (e.g. as sulphate), formoterol (e.g. as fumarate), salmeterol (e.g. as xinafoate), terbutaline, orciprenaline, bitolterol (e.g. as mesylate), pirbuterol or indacaterol. The β_2 -adrenoceptor agonist of this embodiment may be a long-acting β_2 -agonists, for example salmeterol (e.g. as xinafoate), formoterol (e.g. as fumarate), bambuterol (e.g. as hydrochloride), carmoterol (TA 2005, chemically identified as 2(1H)-Quinolone, 8-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxy-phenyl)-1-methylethyl]-amino]ethyl]-monohydrochloride, [R-(R*,R*)] also identified by Chemical Abstract Service Registry Number 137888-11-0 and disclosed in U.S. Patent No 4,579,854), indacaterol (CAS no 312753-06-3; QAB-149), formanilide derivatives e.g. 3-(4-{[6-((2R)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}-butyl)-benzenesulfonamide as disclosed in WO 2002/76933, benzenesulfonamide derivatives e.g. 3-(4-{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxy-methyl)phenyl]ethyl}amino)-hexyl]oxy}butyl)benzenesulfonamide as disclosed in WO 2002/88167, aryl aniline receptor agonists as disclosed in WO 2003/042164 and WO 2005/025555, indole derivatives as disclosed in WO 2004/032921 and US 2005/222144, and compounds GSK 159797, GSK 159802, GSK 597901, GSK 642444 and GSK 678007.

Examples of a modulator of chemokine receptor function that may be used in the pharmaceutical product according to this embodiment include a CCR1 receptor antagonist.

Examples of an inhibitor of kinase function that may be used in the pharmaceutical product according to this embodiment include a p38 kinase inhibitor and an IKK inhibitor.

Examples of a protease inhibitor that may be used in the pharmaceutical product according to this embodiment include an inhibitor of neutrophil elastase or an inhibitor of MMP12.

Examples of a steroidal glucocorticoid receptor agonist that may be used in the pharmaceutical product according to this embodiment include budesonide, fluticasone (e.g. as propionate ester), mometasone (e.g. as furoate ester), beclomethasone (e.g. as 17-propionate or 17,21-dipropionate esters), ciclesonide, loteprednol (as e.g. etabonate), etiprednol (as e.g. dicloacetate), triamcinolone (e.g. as acetonide), flunisolide, zoticasone, flumoxonide, rofleponide, butixocort (e.g. as propionate ester), prednisolone, prednisone, tipredane, steroid esters e.g. 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carbothioic acid S-(2-oxo-tetrahydro-furan-3S-yl) ester and 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester, steroid esters according to DE 4129535, steroids according to WO 2002/00679, WO 2005/041980, or steroids GSK 870086, GSK 685698 and GSK 799943.

Examples of a modulator of a non-steroidal glucocorticoid receptor agonist that may be used in the pharmaceutical product according to this embodiment include those described in WO2006/046916.

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt thereof, for example an acid addition salt such as a hydrochloride (for example a mono- or di-hydrochloride), hydrobromide (for example a mono- or di-hydrobromide), trifluoroacetate (for example a mono- or di-trifluoroacetate), sulphate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate, pyruvate, succinate, oxalate, methanesulphonate or *p*-toluenesulphonate.

The present invention will now be illustrated with the following non-limiting Examples.

General Methods

Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were of laboratory grade and were used as received. All operations were carried out at ambient temperature, *i.e.* in the range 17 to 28°C and, where appropriate, under an atmosphere of an inert gas such as nitrogen. ‘Microwave’ heating refers to heating to constant temperature, using variable power microwave irradiation in a CEM Discover® microwave reactor. Hydrogenation reactions were carried out using a Büchi Peteric® system or a ThalesNano H-Cube® system, as detailed. Concentration of all solutions was carried out by evaporation under reduced pressure (*in vacuo*), *e.g.* using a Büchi Rotavapor® rotary evaporator.

Thin Layer Chromatography (TLC) was carried out using aluminium- or glass-backed plates coated with silica (particle size <63 µm; porosity 60 Å; surface area ~500 m²/g), with a fluorescent (UV₂₅₄) indicator. Following elution, the plates were visualized by either UV₂₅₄ irradiation, or development with a suitable indicator, such as iodine (pre-absorbed onto silica), an aqueous solution of potassium permanganate, or an aqueous solution of cerium (IV) ammonium nitrate. Examples of indicator preparations can be found in ‘Experimental Organic Chemistry: Preparative and Microscale’ 2nd Ed. (Harwood, L., Moody, C. and Percy, J.), WileyBlackwell, 1998.

Analytical HPLC was carried out using either a Waters XBridge™ C8 3.5 µm column eluting with a gradient of acetonitrile in either 0.1% aqueous trifluoroacetic acid, 0.1% aqueous formic acid, 0.1% aqueous ammonium acetate or 0.1% aqueous ammonia; a Waters XBridge™ C18 3.5 µm column with a gradient of acetonitrile in 0.1% aqueous ammonia; a Waters Symmetry™ C18 3.5 µm column with a gradient of acetonitrile in 0.1% aqueous trifluoroacetic acid; a Waters Sunfire™ C8 3.5 µm column with a gradient of acetonitrile in 0.1% aqueous trifluoroacetic acid; or a Phenomenex Gemini™ C18 3 µm column with a gradient of acetonitrile in 0.1% aqueous trifluoroacetic acid. UV spectra of the eluted peaks were measured using a diode array on an Agilent 1100® system, or equivalent.

Compounds in the tables below were characterised using the following analytical HPLC conditions: SunFire™ C18 2.5 µm 4.6 x 30 mm column (Waters Corporation), MeCN/0.1%aq TFA, gradient 5-95% MeCN).

Time (min)	% aqueous	% MeCN	Flow (mL/min)
0.3	95	5	2.5
2.7	5	95	2.5
2.8	5	95	2.5
2.9	95	5	2.5

Medium pressure liquid chromatography (MPLC) on silica (particle size <63 µm; porosity 60 Å; surface area ~500 m²/g) was carried out using pre-packed Biotage FLASH™ columns or equivalent, *e.g.* Thomson SINGLE StEP™, Biotage Isolute™, Teledyne Isco RediSep™, or Silicycle UltraPure silica columns at recommended solvent flow rates and sample loadings. Fraction purity was determined by either TLC or analytical HPLC.

Preparative HPLC was carried out using a gradient of acetonitrile or methanol in 0.1% or 0.2% aqueous TFA, aqueous formic acid or aqueous ammonia solution, using a Phenomenex Gemini™ NX C18 (30 x 100 mm, 5 µm) column, a Waters Sunfire™ Prep C8 (30 x 100 mm, 10 µm) column, a Waters Sunfire™ Prep C18 (30 x 100 mm, 5 µm) column or a Waters XBridge™ C8 (30 x 100 mm, 5 µm) column as stationary phase at a flow rate of 30 – 35 mL/min, as detailed. Fractions were collected following detection by UV spectroscopy at a wavelength such as 220 or 254 nm. Fraction purity was determined by either TLC or analytical HPLC.

¹H NMR spectra were recorded on Bruker Avance 600 (600 MHz), a Bruker DRX 500 (500 MHz) or a Varian UnityInova 500 MHz, 400 MHz or 300 MHz instrument. Either the central peaks of chloroform-*d* (CDCl₃; δ_H 7.27 ppm), dimethylsulfoxide-*d*₆ (d₆-DMSO; δ_H 2.50 ppm) or methanol-*d*₄ (CD₃OD; δ_H 3.31 ppm), or an internal standard of tetramethylsilane (TMS; δ_H 0.00 ppm) were used as references. Mass spectra were recorded on an Agilent MSD (+ve and -ve APCI and/or electrospray (*e.g.* in multimode)) following analytical HPLC.

All other processes were carried out using standard laboratory techniques, *e.g.* as detailed in ‘Experimental Organic Chemistry: Preparative and Microscale’ 2nd Ed. (Harwood, L., Moody, C. and Percy, J.), WileyBlackwell, 1998.

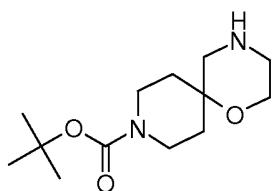
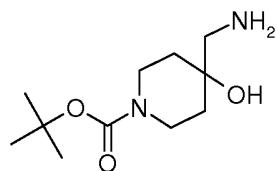
The abbreviations or terms used in the examples have the following meanings:

g grammes

h	hour(s)
min	minute(s)
mL	millilitres
AIBN	azobisisobutyronitrile
CDI	1,1'-carbonyldiimidazole
DCM	dichloromethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulphoxide
HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HCl	hydrogen chloride / hydrochloric acid
HPLC	high performance liquid chromatography
Hunig's base	<i>N,N</i> -diisopropylethylamine
IPA	isopropanol
MeCN	acetonitrile
MeOH	methanol
MTBE	methyl <i>tert</i> -butyl ether
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NMP	1-methylpyrrolidin-2-one
RT	room temperature
SCX	strong cation exchange - silica based solid phase extraction with a sulfonic acid sorbent
T3P	2-propanephosphonic acid anhydride
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Tosic-65	macroporous polymer bound ion exchange resin supplied by Biotage AB.
Triton-B	Benzyltrimethylammonium hydroxide
<i>tert</i> -Butyl 1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate hydrochloride salt was made using Preparation 1 described below.	

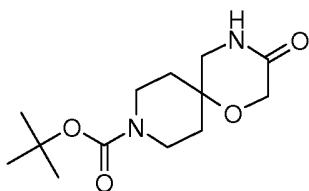
Naming package for title/subtitled compounds:

Struct=Name 9.0.7 from CambridgeSoft Corporation

Preparation of Synthetic Intermediates**Preparation 1*****tert*-Butyl 1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate****a) *tert*-Butyl 4-(aminomethyl)-4-hydroxypiperidine-1-carboxylate**

A solution of *tert*-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (9.6 g) in ammonia solution (7N in methanol, 220 mL) was stirred for 3 days at 20°C. The solvent was evaporated under reduced pressure to yield the subtitled compound as a gum which crystallised on standing. Yield 10.4 g.

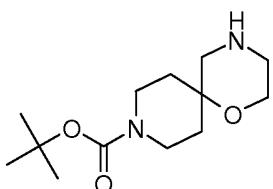
¹H NMR (400 MHz, CD₃OD) δ 3.81 - 3.73 (m, 2H), 3.22 - 3.09 (m, 2H), 2.56 (s, 2H), 1.58 - 1.36 (m, 4H), 1.43 (s, 9H). Three exchangeable protons not observed.

b) *tert*-Butyl 3-oxo-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate

Chloroacetyl chloride (4.88 mL) was added dropwise to a vigorously stirred mixture at 0°C of potassium carbonate (17.4 g) in water (78 mL) and *tert*-butyl 4-(aminomethyl)-4-hydroxypiperidine-1-carboxylate [Preparation 1, step a] (10.4 g) in ethyl acetate (92 mL). After 30 minutes at 0°C, the mixture was extracted with ethyl acetate and the organic layer dried, filtered and the solvent evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (200 mL) and added dropwise over 3 hours to a stirred

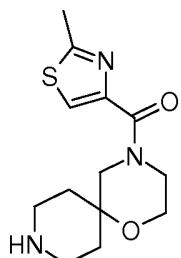
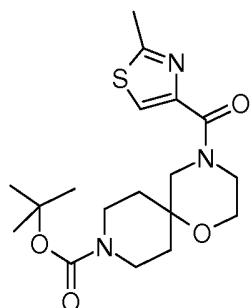
solution under nitrogen and at reflux of potassium *tert*-butoxide (1M in *tert*-butanol, 75 mL) and THF (250 mL). The mixture was removed from reflux and allowed to stir for 18 hours at room temperature. Most of the solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and brine, the aqueous layer was re-extracted with ethyl acetate and the combined organics were dried, filtered and the solvent removed under reduced pressure. The residue was purified by trituration with a mixture of ether (30 mL) and isohexane (20 mL) to give the subtitled compound as a white solid. Yield 8.2 g.
¹H NMR (400 MHz, D₆-DMSO) δ 7.95 (s, 1H), 3.97 (s, 2H), 3.72 - 3.62 (m, 2H), 3.10 (d, J = 6.6 Hz, 2H), 3.05 - 2.93 (m, 2H), 1.77 - 1.69 (m, 2H), 1.53 - 1.43 (m, 2H), 1.40 (s, 9H).

c) *tert*-Butyl 1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate



A solution of *tert*-butyl 3-oxo-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate [Preparation 1, step b] (8.2 g) in tetrahydrofuran (100 mL) was treated dropwise with borane tetrahydrofuran complex (1M in THF, 91 mL) and the resultant mixture heated at 55°C for 2 hours. Borane dimethyl sulphide complex (2M in THF, 15.2 mL) was added and the resultant mixture heated at 55°C for 2 hours. The mixture was cooled to room temperature and quenched with methanol and the solvents were evaporated under reduced pressure. The residue was dissolved in methanol (250 mL) and the solution treated with N₁,N₂-dimethylethane-1,2-diamine (10 g), the resultant mixture was refluxed for 6 hours, further N₁,N₂-dimethylethane-1,2-diamine (3 g) was added and refluxing was continued for 6 hours. The mixture was cooled to room temperature and the solvents evaporated under reduced pressure. The residue was purified by flash silica chromatography, using 1% triethylamine and 5% methanol in dichloromethane as solvent. Fractions containing the product were evaporated to dryness to afford the titled compound as a white solid. Yield 7.4 g.

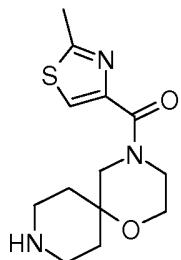
¹H NMR (400 MHz, CDCl₃) δ 3.72 (s, 2H), 3.68 - 3.64 (m, 2H), 3.14 (t, J = 20.0 Hz, 2H), 2.87 - 2.81 (m, 2H), 2.68 (s, 2H), 1.97 - 1.88 (m, 2H), 1.46 (s, 9H), 1.44 - 1.36 (m, 2H). One exchangeable proton not observed.

Preparation 2**(2-Methylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone hydrochloride****a) *tert*-Butyl 4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate**

1-Propanephosphonic acid cyclic anhydride (1.57M in THF, 4.18 mL) was added to a solution of *tert*-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate hydrochloride (WuXi PharmaTech) (1.92 g), 2-methylthiazole-4-carboxylic acid (0.94 g) and triethylamine (5.48 mL) in DMF (70 mL) and the resulting mixture stirred for 16 h. The reaction mixture was poured into water (500 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic solutions were washed with water (2 x 100 mL) and brine (100 mL), dried over magnesium sulphate, filtered and evaporated *in vacuo*. Purification was by silica gel chromatography eluting with ethyl acetate to give the subtitled compound as a clear oil. Yield 2.30 g.

¹H NMR (400 MHz, D₆-DMSO, 90°C) δ 7.95 (s, 1H), 3.80-3.45 (m, 8H), 3.18-2.96 (m, 2H), 2.67 (s, 3H), 1.77-1.62 (m, 2H), 1.43-1.31 (m, 11H).

b) (2-Methylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone hydrochloride



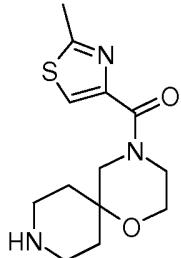
Trifluoroacetic acid (10 mL) was added to a solution of *tert*-butyl 4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate [Preparation 2, step a] (2.3 g) in DCM (50 mL) at 0°C and the resulting mixture was stirred for 16 h. The solvent was evaporated *in vacuo*. Toluene (50 mL) was added and the mixture evaporated *in vacuo*. The residue was dissolved in methanol (20 mL) and applied to a SCX cartridge pre-wetted with methanol. The cartridge was washed with methanol (250 mL) and eluted with ammonia solution (3M in methanol, 150 mL). The eluent was evaporated *in vacuo*, and the residue dissolved in MeCN (100 mL). HCl (1M in diethyl ether, 10 mL) was added and the solvent was evaporated *in vacuo* to give the titled compound as a yellow solid.

Yield 1.90 g.

¹H NMR (400 MHz, D₆-DMSO, 90°C) δ 9.16 (s, 2H), 7.92 (s, 1H), 4.25 (s, 4H), 3.66-3.58 (m, 2H), 3.12-2.90 (m, 4H), 2.69 (s, 3H), 2.01-1.89 (m, 2H), 1.85-1.73 (m, 2H).

Preparation 3

(2-Methylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate



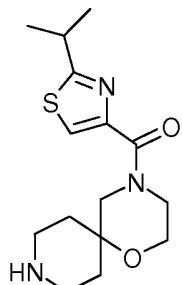
1-Propanephosphonic acid cyclic anhydride (1.57M in THF, 2.49 mL) was added to a solution of *tert*-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate hydrochloride (WuXi PharmaTech) (1.0 g), 2-methylthiazole-4-carboxylic acid (0.56 g) and triethylamine (3.26 mL) in DMF (30 mL) and the resulting mixture stirred for 16 hours at room temperature. The reaction was partitioned between water (500 mL) and ethyl acetate (200

mL). The layers were separated and the aqueous layer extracted with ethyl acetate (2 x 150 mL). The combined organic solutions were washed with water (2 x 100 mL), and brine (100 mL), then dried over magnesium sulphate, filtered and evaporated *in vacuo*. Purification was by silica gel chromatography eluting with ethyl acetate. The resulting oil was dissolved in dichloromethane (30 mL) and trifluoroacetic acid (3 mL) was added dropwise. This was then stirred for 1 hour and concentrated *in vacuo*. The residue was azeotroped twice with toluene (20 mL). The resulting gum was triturated with ether to give the subtitled compound as a white solid. Yield 1.20 g.
m/z 282 (M+H)⁺ (APCI).

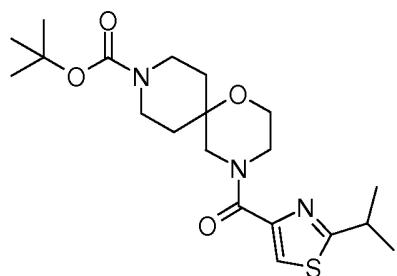
¹H NMR (300 MHz, D₆-DMSO) δ 8.59-8.18 (m, 2H), 8.00 (s, 1H), 3.86-3.49 (m, 6H), 3.22-2.86 (m, 4H), 2.69 (s, 3H), 2.00-1.90 (m, 2H), 1.74-1.58 (m, 2H).

Preparation 4

(2-Isopropylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate



a) *tert*-Butyl 4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate

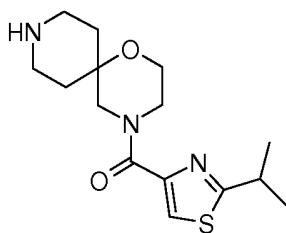


A solution of 2-isopropylthiazole-4-carboxylic acid (1 g) and *tert*-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate hydrochloride (WuXi PharmaTech) (1.71 g) in DMF (30 mL) was cooled in an ice bath and treated with triethylamine (2.44 mL) followed

by HATU (2.89 g). The ice bath was removed and the mixture was stirred at 20°C for 1 hour. The mixture was partitioned between ethyl acetate and brine, the organic layer was washed twice with brine, dried over sodium sulphate, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash silica chromatography using 70% ethyl acetate in isohexane as solvent. Pure fractions were evaporated to dryness to afford the subtitled compound. Yield 2.0 g.

¹H NMR (400 MHz, D₆-DMSO, 90°C) δ 7.93 (s, 1H), 3.71 - 3.63 (m, 6H), 3.51 - 3.44 (m, 2H), 3.35 - 3.26 (m, 1H), 3.18 - 3.10 (m, 2H), 1.74 - 1.67 (m, 2H), 1.49 - 1.41 (m, 2H), 1.39 (s, 9H), 1.34 (d, J = 7.6 Hz, 6H).

b) (2-Isopropylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate

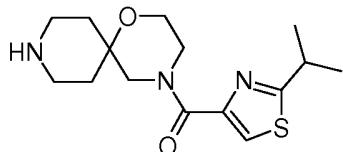


A solution of *tert*-butyl 4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate [Preparation 4, step a] (2.3 g) in a mixture of dichloromethane (40 mL) and trifluoroacetic acid (10 mL) was allowed to stand at 20°C for 30 minutes. Toluene (50 mL) was added and the solvents were evaporated, then this process was repeated with more toluene (50 mL). The residue was triturated with ether. The gum was then dissolved in acetonitrile and the solvent evaporated to afford the titled compound. Yield 1.64 g.

m/z 310 (M+H)⁺ (APCI).

Preparation 5

a) (2-Isopropylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone hydrochloride

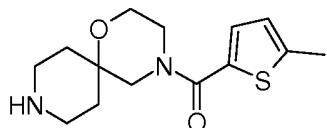


A solution of 2-isopropylthiazole-4-carboxylic acid (12 g) and *tert*-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate hydrochloride [WuXi PharmaTech] (20 g) in 2-methyltetrahydrofuran (140 mL) was cooled in ice-water and treated with triethylamine (47 mL), followed by T3P (1.6M in THF, 54 mL). The mixture was allowed to warm to RT and was stirred for 1 h. Water (140 mL) was added with stirring, then the phases were separated. The organic phase was washed with water (80 mL), and then concentrated to a volume of (~100 mL) under reduced pressure using a temperature of <30°C. IPA (75 mL) was added, and the mixture was concentrated to a volume of (~100 mL). More IPA (75 mL) was added, and the mixture was again concentrated to a volume of (~100 mL). A solution of hydrogen chloride in IPA (~6M, 81 mL) was added with cooling in ice-water, then the mixture was warmed to 40°C and stirred for 3.5 h. The mixture was cooled to RT, diluted with MTBE (34 mL) and stirred for 30 min. The resulting precipitated solid was removed by filtration and dried in a vacuum oven at 55°C overnight to give the titled compound. Yield 20.5 g.

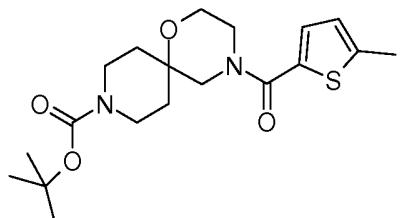
¹H NMR (400 MHz, D₆-DMSO) δ 8.88 (d, J = 41.0 Hz, 2H), 8.05 (s, 1 H), 3.86 - 3.46 (m, 6 H), 3.32 (quintet, J = 6.7 Hz, 1 H), 3.17 - 3.02 (m, 2 H), 3.01 - 2.85 (m, 2 H), 1.96 (d, J = 14.1 Hz, 2 H), 1.81 - 1.55 (m, 2 H), 1.35 (d, J = 6.9 Hz, 6 H).

Preparation 6

(5-Methylthiophen-2-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate



a) *tert*-Butyl 4-(5-methylthiophene-2-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate

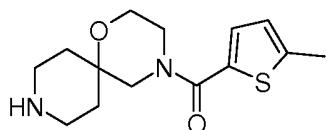


1-Propanephosphonic acid cyclic anhydride (1.57M in THF, 0.64 mL) was added to a

solution of *tert*-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate hydrochloride (WuXi PharmaTech) (0.26 g), 5-methylthiophene-2-carboxylic acid (0.14 g) and triethylamine (0.84 mL) in DMF (8 mL) and the resulting mixture stirred for 16 h. The reaction mixture was poured into water (100 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic solutions were washed with water (2 x 100 mL) and brine (100 mL), then dried over magnesium sulphate, filtered and evaporated *in vacuo*. Purification was by silica gel chromatography eluting with ethyl acetate:isohexane, 1:1, to give the subtitled compound as a clear oil. Yield 0.32 g.

¹H NMR (400 MHz, CDCl₃) δ 7.11 (d, J = 3.6 Hz, 1H), 6.72-6.69 (m, 1H), 3.78 - 3.67 (m, 8H), 3.60 - 3.51 (m, 2H), 3.19 - 3.10 (m, 2H), 2.51 (s, 3H), 1.86 - 1.79 (m, 2H), 1.45 (s, 9H).

b) (5-Methylthiophen-2-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate

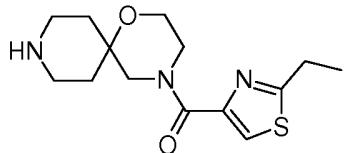


tert-Butyl 4-(5-methylthiophene-2-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate [Preparation 6, step a] (0.32 g) in DCM (3 mL) was treated with trifluoroacetic acid (1.0 g). After 2 h, the reaction mixture was evaporated *in vacuo* and azeotroped twice with toluene to yield the titled compound which was used directly. Yield 0.32 g.

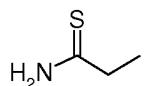
m/z 281 (M+H)⁺ (APCI).

Preparation 7

(2-Ethylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate



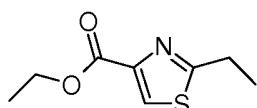
a) Propanethioamide



Phosphorus pentasulfide (15.2 g) was added to a suspension of propionamide (20 g) in methyl *t*-butyl ether (900 mL) and the mixture stirred for 18 hours. The mixture was filtered through Celite and concentrated *in vacuo* to afford the subtitled compound as a yellow oil. Yield 15.8 g.

¹H NMR (300 MHz, CDCl₃) δ 7.59 (s, 1H), 6.88 (s, 1H), 2.70 (q, J = 7.5 Hz, 2H), 1.32 (t, J = 7.5 Hz, 3H).

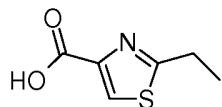
b) Ethyl 2-ethylthiazole-4-carboxylate



Ethyl 3-bromo-2-oxopropanoate (24.7 mL) was added dropwise over 10 min to a solution of propanethioamide [Preparation 7, step a] (15.8 g) in ethanol (150 mL) at 0-10°C under nitrogen. When the addition was complete the mixture was stirred at ambient temperature for 18 hours. The mixture was concentrated *in vacuo*, the residue diluted with water and extracted into ethyl acetate (x 3). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and the solvent removed. The crude product was purified by flash silica chromatography, elution gradient 10, 15 and 20% ethyl acetate in isohexane. Fractions containing the product were evaporated to dryness to afford the subtitled compound as a pale green solid. Yield 16.0 g.

¹H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 4.42 (q, J = 7.1 Hz, 2H), 3.10 (q, J = 7.5 Hz, 2H), 1.44 - 1.38 (m, 6H).

c) 2-Ethylthiazole-4-carboxylic acid

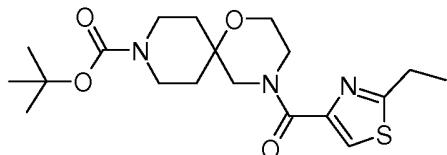


Concentrated HCl (75 mL) was added to a suspension of ethyl 2-ethylthiazole-4-carboxylate [Preparation 7, step b] (16 g) in water (75 mL) and the mixture stirred at 100°C for 24 hours. The mixture was cooled and concentrated *in vacuo*. The residue was triturated with acetone, the solid collected by filtration and dried *in vacuo* to afford the subtitled compound as a grey solid. Yield 14.4 g.

m/z 158 (M+H)⁺ / 156 (M-H)⁻ (APCI).

¹H NMR (400 MHz, D₆-DMSO) δ 8.31 (s, 1H), 3.01 (q, J = 7.5 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H). One exchangeable proton not observed.

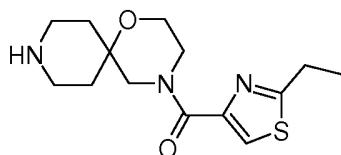
d) *tert*-Butyl 4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate



T3P (1.6M in THF, 51.3 mL) was added dropwise to a stirred suspension of *tert*-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate hydrochloride (WuXi PharmaTech) (18.1 g), 2-ethylthiazole-4-carboxylic acid [Preparation 7, step c] (12 g) and triethylamine (52 mL) in DMF (120 mL) under nitrogen, and the mixture stirred at ambient temperature for 20 hours. It was diluted with water and extracted into ethyl acetate (x 3). The combined extracts were washed successively with 10% brine, 30% brine and saturated brine, dried over magnesium sulfate, filtered and the solvent removed. The crude product was purified by flash silica chromatography, eluting with ethyl acetate. Fractions containing the product were evaporated to dryness to afford the subtitled compound as a yellow oil. Yield 24.0 g.

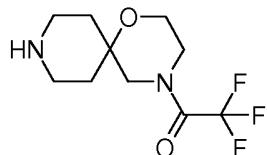
m/z 340 (M-tBu+H)⁺ (APCI).

e) (2-Ethylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate



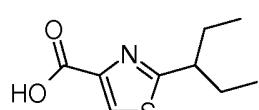
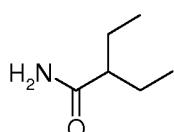
Prepared by the method of Preparation 6, step b using *tert*-butyl 4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate [Preparation 7, step d] (24.0 g) in place of *tert*-butyl 4-(5-methylthiophene-2-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate. Trituration with ether afforded a white solid, which was collected by filtration and dried to give the titled compound. Yield 27.7 g.

¹H NMR (400 MHz, D₆-DMSO) δ 8.55 (s, 1H), 8.39 (s, 1H), 8.04 - 8.00 (m, 1H), 3.81 - 3.51 (m, 6H), 3.18 - 2.91 (m, 6H), 2.00 - 1.90 (m, 2H), 1.72 - 1.56 (m, 2H), 1.32 (t, J = 7.2 Hz, 3H).

Preparation 8**2,2,2-Trifluoro-1-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)ethanone trifluoroacetate**

A solution of trifluoroacetic anhydride (9.6 mL) in DCM (10 mL) was added dropwise, over a period of 15 minutes, to a stirred solution of triethylamine (15.2 mL) and *tert*-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate hydrochloride [WuXi PharmaTech] (9.95 g) in DCM (100 mL) at 0°C under nitrogen. The resulting solution was stirred at 0°C for 30 minutes. More triethylamine (2.5 mL) was added, followed by more trifluoroacetic anhydride (1.6 mL) in DCM (10 mL), and stirring at 0°C was continued for 1 hour. Water (100 mL) was added and the mixture was vigorously stirred for 10 minutes. The organic layer was separated, dried, and the solvent evaporated under reduced pressure. The residue was dissolved in DCM (100 mL) and the solution treated with trifluoroacetic acid (25 mL). This mixture was allowed to stand at 20°C for 10 minutes and then diluted with toluene (40 mL). The solvents were removed under reduced pressure and the residue azeotroped with more toluene (x 2) to yield the titled compound. Yield 14.0 g.

m/z 253 (M+H)⁺ (APCI).

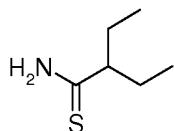
Preparation 9**2-(Pentan-3-yl)thiazole-4-carboxylic acid****a) 2-Ethylbutanamide**

2-Ethylbutanoyl chloride (5 g) was cautiously added dropwise to ice cold 35% aqueous ammonia (50 mL) and the resulting suspension stirred for 1 h. The reaction mixture was extracted with DCM (3 x 100 mL). The combined organic phases were washed with brine

(100 mL), dried over sodium sulphate, filtered and evaporated to give the subtitled compound as a white solid. Yield 3.4 g.

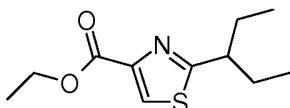
¹H NMR (400 MHz, D₆-DMSO) δ 7.23 (s, 1H), 6.71 (s, 1H), 1.98 - 1.88 (m, 1H), 1.50 - 1.27 (m, 4H), 0.81 (t, J = 7.4 Hz, 6H).

b) 2-Ethylbutanethioamide



Prepared by the method of Preparation 7, step a using 2-ethylbutanamide [Preparation 9, step a] (3.4 g) in place of propionamide. Yield 3.8 g. Used directly.

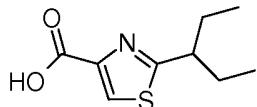
c) Ethyl 2-(pentan-3-yl)thiazole-4-carboxylate



Prepared by the method of Preparation 7, step b using 2-ethylbutanethioamide [Preparation 9, step b] (3.8 g) in place of propanethioamide. Yield 2.8 g.

¹H NMR (400 MHz, D₆-DMSO) δ 8.42 (s, 1H), 4.29 (q, J = 7.1 Hz, 2H), 2.99 - 2.89 (m, 1H), 1.82 - 1.58 (m, 4H), 1.30 (t, J = 7.0 Hz, 3H), 0.81 (t, J = 7.4 Hz, 6H).

d) 2-(Pentan-3-yl)thiazole-4-carboxylic acid

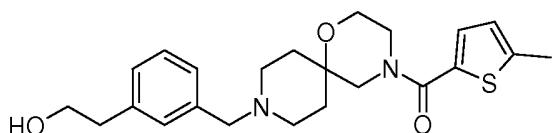
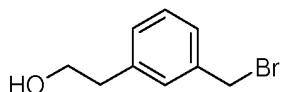


Lithium hydroxide (2.07 g) was added to a solution of ethyl 2-(pentan-3-yl)thiazole-4-carboxylate [Preparation 9, step c] (2.8 g) in a mixture of THF (80 mL) and water (20 mL). The resulting mixture was stirred overnight. The reaction was acidified with concentrated hydrochloric acid (~6 mL) and the THF evaporated. The resulting aqueous mixture was saturated with sodium chloride and extracted with ethyl acetate (3 x 100 mL). The combined organics were dried over sodium sulphate, filtered and evaporated to give the titled compound as a white solid. Yield 2.3 g.

¹H NMR (300 MHz, D₆-DMSO) δ 12.91 (s, 1H), 8.34 (s, 1H), 2.98 - 2.86 (m, 1H), 1.84 - 1.56 (m, 4H), 0.81 (t, J = 7.3 Hz, 6H).

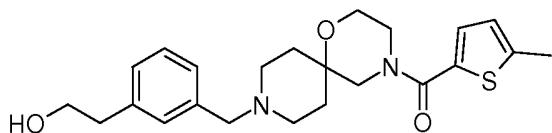
Example 1

(9-(3-(2-Hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(5-methylthiophen-2-yl)methanone

**a) 2-(3-(Bromomethyl)phenyl)ethanol**

Borane dimethyl sulphide complex (2M in THF, 5.78 mL) was added dropwise to a solution of 2-(3-(bromomethyl)phenyl)acetic acid (1.06 g) in THF (10 mL) at 0°C and the resulting mixture stirred for 10 min. The reaction was then allowed to warm to room temperature and stirred overnight. Methanol (5 mL) was then added and the mixture concentrated *in vacuo*. Purification was by silica gel chromatography eluting with isohexane to diethyl ether gradient to give the subtitled compound as a white solid. Yield 1.0 g.

¹H NMR (300 MHz, CDCl₃) δ 7.34-7.24 (m, 3H), 7.22-7.12 (m, 1H), 4.48 (s, 2H), 3.87 (t, J = 6.5 Hz, 2H), 2.87 (t, J = 6.5 Hz, 2H). One exchangeable proton not observed.

b) (9-(3-(2-Hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(5-methylthiophen-2-yl)methanone

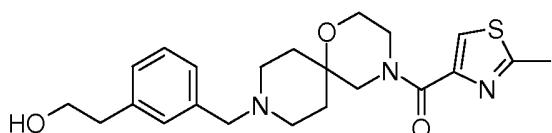
2-(3-(Bromomethyl)phenyl)ethanol [Example 1, step a] (0.136 g) was added to a stirred solution of (5-methylthiophen-2-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate [Preparation 6] (0.250 g) and triethylamine (0.278 mL) in MeCN (5 mL). After 1 h, the reaction mixture was concentrated and applied to a silica gel column eluting with ethyl acetate:triethylamine, 95:5 to give the titled compound. Yield 0.24 g.

m/z 415 (M+H)⁺ (APCI).

¹H NMR (400 MHz, CDCl₃) δ 7.28-7.24 (m, 2H), 7.18-7.15 (m, 1H), 7.11-7.08 (m, 2H), 6.70-6.67 (m, 1H), 3.86 (t, J = 6.6 Hz, 2H), 3.77-3.69 (m, 4H), 3.56 (s, 2H), 3.48 (s, 2H), 2.86 (t, J = 7.0 Hz, 2H), 2.55-2.48 (m, 5H), 2.40-2.32 (m, 2H), 1.89-1.82 (m, 2H), 1.70-1.50 (2Hs under water peak). One exchangeable proton not observed.

Example 2

9-(3-(2-Hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone



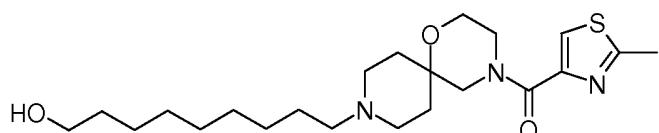
(2-Methylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate [Preparation 3] (2.2 g) was added to a solution of 2-(3-(bromomethyl)phenyl)ethanol [Example 1, step a] (1.2 g) and triethylamine (2.3 mL) in acetonitrile (30 mL). The resulting mixture was stirred overnight at RT under nitrogen. The solvent was evaporated and the residue purified by silica gel chromatography, gradient elution 99:1:0.1 to 97:3:0.3 DCM:MeOH:'880' aqueous ammonia to give the titled compound as a clear foam. Yield 1.72 g.

m/z 416 (M+H)⁺ (APCI).

¹H NMR (400 MHz, D₆-DMSO) δ 7.85 (s, 1H), 7.18 (t, J = 7.4 Hz, 1H), 7.12-7.04 (m, 3H), 4.24 (t, J = 5.1 Hz, 1H), 3.71-3.54 (m, 8H), 3.42 (s, 2H), 2.71 (t, J = 6.9 Hz, 2H), 2.68 (s, 3H), 2.38-2.27 (m, 4H), 1.74-1.64 (m, 2H), 1.57-1.47 (m, 2H).

Example 3

(9-(9-Hydroxynonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone



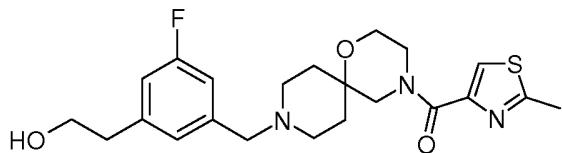
9-Bromononan-1-ol (0.29 g) was added to a suspension of (2-methylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone hydrochloride [Preparation 2] (0.4 g) in a mixture of triethylamine (0.41 mL) and acetonitrile (10 mL). The resulting mixture was stirred for 16 h at 50°C. The solvent was evaporated *in vacuo* and the residue partitioned

between ethyl acetate (30 mL) and saturated sodium bicarbonate solution (30 mL). The layers were separated and the aqueous extracted with ethyl acetate (2 x 30 mL). The combined organic solutions were washed with brine (30 mL), dried over sodium sulphate, filtered and evaporated *in vacuo*. The residue was dissolved in methanol (10 mL) and applied to a SCX cartridge pre-wetted with methanol. The cartridge was washed with methanol (10 mL) and eluted with ammonia solution (3M in methanol, 100 mL). The eluent was evaporated *in vacuo* to give the titled compound a yellow oil. Yield 0.32 g. m/z 424 (M+H)⁺ (APCI).

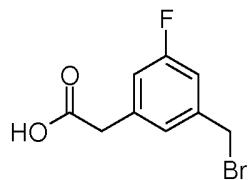
¹H NMR (300 MHz, D₆-DMSO) δ 7.95 (s, 1H), 4.30 (t, J = 5.1Hz, 1H), 3.78-3.44 (m, 8H), 3.42-3.33 (m, 2H), 2.69 (s, 3H), 2.35-2.14 (m, 8H), 1.71-1.57 (m, 2H), 1.55-1.19 (m, 12H).

Example 4

(9-(3-Fluoro-5-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone



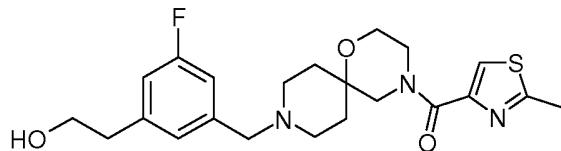
a) 2-(3-(Bromomethyl)-5-fluorophenyl)acetic acid



Benzoyl peroxide (0.05 g) was added to a mixture of 2-(3-fluoro-5-methylphenyl)acetic acid (0.518 g) and N-bromosuccinimide (0.6 g) in DCM (10 mL). The reaction was heated at reflux for 1 h. DCM (10 mL) and water (20 mL) were added and the organic phase separated. The organic layer was washed with brine (20 mL), dried over sodium sulphate, filtered and evaporated *in vacuo*. The residue was triturated with toluene and the resulting white solid removed by filtration. The mother liquors were evaporated *in vacuo* to give the subtitled compound as a white solid which was used in the next step without further purification. Yield 0.38 g.

¹H NMR (400 MHz, D₆-DMSO) δ 7.22 - 7.17 (m, 2H), 7.09 - 7.05 (m, 1H), 4.68 (s, 2H), 3.61 (s, 2H). One exchangeable proton not observed.

b) (9-(3-Fluoro-5-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone



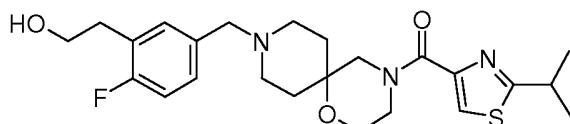
A solution of borane dimethyl sulfide complex (2M in THF, 3.85 mL) was added dropwise to a solution of 2-(3-(bromomethyl)-5-fluorophenyl)acetic acid [Example 4, step a] (0.38 g) in THF (10 mL) at 0°C. The resulting mixture was allowed to warm to RT and stirred for 1 h. The reaction was cooled to 0°C and methanol (1 mL) was added dropwise until bubbling ceased. The solvent was evaporated *in vacuo* and the residue redissolved in MeCN (10 mL). (2-Methylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate [Preparation 3] (0.61 g) was then added followed by triethylamine (0.54 mL) and the resulting mixture stirred for 70 h. The solvent was then evaporated *in vacuo*. Purification was by silica gel chromatography eluting with 99:1:0.1 to 94.5:5:0.5 DCM:methanol:'880' aqueous ammonia gradient. The fractions containing the product were combined and evaporated *in vacuo* to give the titled compound as a yellow foam. Yield 0.57 g.

m/z 434 (M+H)⁺ (APCI).

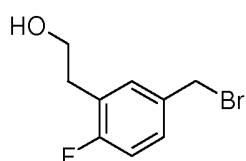
¹H NMR (400 MHz, D₆-DMSO) δ 7.87 (s, 1H), 7.30 - 6.75 (m, 3H), 4.47 - 4.20 (m, 1H), 3.73 - 3.56 (m, 8H), 3.06 - 2.96 (m, 4H), 2.74 (t, J = 6.5 Hz, 2H), 2.68 (s, 3H), 2.50 - 2.27 (m, 2H), 1.93 - 1.47 (m, 4H).

Example 5

(9-(4-Fluoro-3-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone



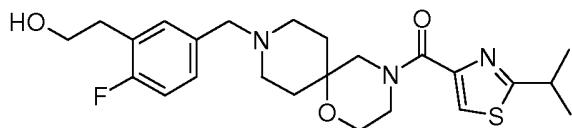
a) 2-(5-(Bromomethyl)-2-fluorophenyl)ethanol



Dibenzoyl peroxide (1 g) was added to a solution of NBS (10.6 g) and 2-(2-fluoro-5-methylphenyl)acetic acid (10 g) in DCM (250 mL) and the resulting mixture was heated under reflux for 12 h. The solvent was evaporated and the white solid partitioned between ethyl acetate (250 mL) and 10% sodium chloride solution (500 mL). The layers were separated and the organic phase washed with 10% sodium chloride solution (500 mL), dried over magnesium sulphate, filtered and evaporated. The white solid obtained was redissolved in tetrahydrofuran (150 mL) and cooled in an ice bath. A solution of borane dimethyl sulfide complex (2M in THF, 89 mL) was added cautiously and the mixture was then allowed to warm to RT and stirred overnight. The reaction was cooled in an ice bath and cautiously quenched with methanol. Once bubbling had ceased the solvent was evaporated and the residue was triturated with a 4:1 mixture of isohexane:ether. Purification was by silica gel chromatography eluting with 9:1 to 4:1 ethyl acetate:isohexane gradient to give the subtitled compound as a clear oil. Yield 6.5 g.

¹H NMR (300 MHz, CDCl₃) δ 7.32 - 7.21 (m, 2H), 7.04 - 6.97 (m, 1H), 4.46 (s, 2H), 3.87 (t, J = 6.5 Hz, 2H), 2.93 - 2.87 (m, 2H). One exchangeable proton not observed.

b) (9-(4-Fluoro-3-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone

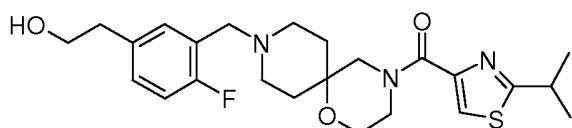


A solution of 2-(5-(bromomethyl)-2-fluorophenyl)ethanol [Example 5, Step a] (5.17 g) in ethanol (20 mL) was added dropwise to a suspension of (2-isopropylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate [Preparation 4] (9.4 g) and potassium carbonate (6.75 g) in ethanol (75 mL) and the resulting mixture stirred overnight. The mixture was filtered, the filter cake was washed with ethanol (50 mL), and the filtrate and washings combined and evaporated. The residue was partitioned between water (100 mL) and ethyl acetate (250 mL). The phases were separated and the organic phase washed with brine (100 mL), dried over sodium sulphate, filtered and evaporated. The residue was purified by flash silica chromatography using 95:5 ethyl acetate:triethylamine as solvent to give the titled compound as a clear oil. Yield 7.9 g. m/z 462 (M+H)⁺ (APCI).

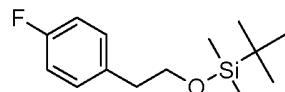
¹H NMR (500 MHz, D₆-DMSO) δ 7.90 (s, 1H), 7.18 (dd, J = 7.5, 1.8 Hz, 1H), 7.12 - 7.08 (m, 1H), 6.99 (dd, J = 10.0, 8.4 Hz, 1H), 4.34 (t, J = 5.3 Hz, 1H), 3.69 - 3.57 (m, 8H), 3.39 (s, 2H), 3.31 (septet, J = 6.9 Hz, 1H), 2.74 (t, J = 7.0 Hz, 2H), 2.40 - 2.33 (m, 2H), 2.33 - 2.24 (m, 2H), 1.73 - 1.65 (m, 2H), 1.58 - 1.50 (m, 2H), 1.36 (d, J = 7.0 Hz, 6H).

Example 6

(9-(2-Fluoro-5-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone



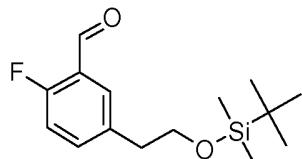
a) *tert*-Butyl(4-fluorophenethoxy)dimethylsilane



tert-Butyldimethylsilyl chloride (9.03 g) was added portionwise to a stirred solution of 2-(4-fluorophenyl)ethanol (7 g) and imidazole (4.08 g) in DMF (100 mL) at 20°C. The reaction mixture was stirred for 3 hours at room temperature and then partitioned between ethyl acetate and brine. The organic layer was washed twice with brine, dried, filtered and the solvent concentrated under reduced pressure. The crude product was purified by flash silica chromatography eluting with 2% ethyl acetate in isohexane. Fractions containing the product were evaporated to dryness to afford the subtitled compound. Yield 11.60 g.

¹H NMR (400 MHz, CDCl₃) δ 7.18-7.13 (m, 2H), 6.98-6.93 (m, 2H), 3.77 (t, J = 6.9 Hz, 2H), 2.78 (t, J = 6.8 Hz, 2H), 0.86 (s, 9H), -0.03 (s, 6H).

b) 5-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-2-fluorobenzaldehyde

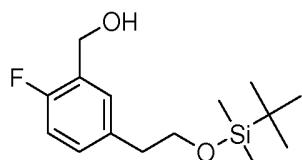


To a solution of 2,2,6,6-tetramethylpiperidine (10.77 g) in THF (200 mL) at 0°C was added over 25 minutes butyllithium (1.6M in hexanes, 48 mL). The mixture was cooled to -78°C and a solution of *tert*-butyl(4-fluorophenethoxy)dimethylsilane [Example 6, step a] (9.7 g) in THF (50 mL) was added dropwise over 25 minutes. The reaction mixture was stirred at -78°C for 90 minutes. DMF (9.3 mL) was then added dropwise over 10 minutes.

The reaction mixture was stirred at 0°C for 1 hour and then poured into ice-cold aqueous HCl (0.5M, 500 mL). The mixture was extracted with ethyl acetate and the organic layer washed twice with water, dried, filtered and the solvent concentrated under reduced pressure to give the subtitled compound. Yield 10.00 g.

¹H NMR (400 MHz, CDCl₃) δ 10.36 (s, 1H), 7.72-7.69 (m, 1H), 7.48-7.43 (m, 1H), 7.11-7.06 (m, 1H), 3.80 (t, J = 6.5 Hz, 2H), 2.83 (t, J = 6.4 Hz, 2H), 0.85 (s, 9H), 0.04 (s, 6H).

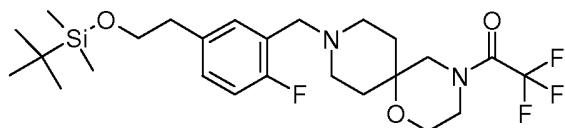
c) (5-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-2-fluorophenyl)methanol



Sodium borohydride (1.33 g) was added portionwise over 30 minutes to a solution at 0°C of 5-(2-(*tert*-butyldimethylsilyloxy)ethyl)-2-fluorobenzaldehyde [Example 6, step b] (9.9 g) in ethanol (120 mL). The reaction mixture was then stirred at room temperature for 30 minutes before being reduced to half the initial volume by concentration under reduced pressure. The residue was partitioned between ethyl acetate and brine, the organic layer was washed with brine, dried, filtered and the solvent concentrated under reduced pressure. The crude product was purified by flash silica chromatography using 12% ethyl acetate in isohexane as solvent. Fractions containing the product were concentrated to dryness to afford the subtitled compound. Yield 7.30 g.

¹H NMR (400 MHz, CDCl₃) δ 7.26-7.23 (m, 1H), 7.13-7.08 (m, 1H), 6.98-6.93 (m, 1H), 4.73 (d, J = 6.2 Hz, 2H), 3.78 (t, J = 6.9 Hz, 2H), 2.79 (t, J = 6.9 Hz, 2H), 1.71 (t, J = 6.5 Hz, 1H), 0.87 (s, 9H), -0.02 (s, 6H).

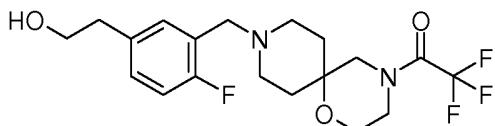
d) 1-(9-(5-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-2-fluorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2,2,2-trifluoroethanone



Methanesulphonyl chloride (1.3 mL) in DCM (20 mL) was added dropwise to a solution at 0°C of (5-(2-(*tert*-butyldimethylsilyloxy)ethyl)-2-fluorophenyl)methanol [Example 6, step c] (4.66 g) and triethylamine (2.5 mL) in DCM (100 mL). The mixture was stirred at 0°C for 1 hour and then washed with water. The organic layer was dried, filtered and the

solvent evaporated under reduced pressure. The resultant intermediate (5.9 g) was added portionwise over 30 minutes to a stirred solution at 20°C of 2,2,2-trifluoro-1-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)ethanone trifluoroacetate [Preparation 8] (6 g) and triethylamine (9.1 mL) in acetonitrile (130 mL). The reaction mixture was stirred for 4 hours at 20°C. The solvent was evaporated under reduced pressure and the residue partitioned between ethyl acetate and brine. The organic layer was dried, filtered and the solvent evaporated under reduced pressure to give the subtitled compound. Yield 8.5 g. m/z 519 (M+H)⁺ (APCI).

e) 2,2,2-Trifluoro-1-(9-(2-fluoro-5-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)ethanone



TBAF (1M in THF, 16.4 mL) was added to a solution of 1-(9-(5-(*tert*-butyldimethylsilyloxy)ethyl)-2-fluorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2,2,2-trifluoroethanone [Example 6, step d] (8.5 g) in THF (100 mL) and the resultant solution allowed to stand at 20°C for 18 hours. The solvent was evaporated under reduced pressure and the residue was purified by flash silica chromatography, using 2% methanol in dichloromethane containing 1% triethylamine as solvent. Fractions containing the product were evaporated to dryness to afford the subtitled compound. Yield 4.2 g. m/z 405 (M+H)⁺ (APCI).

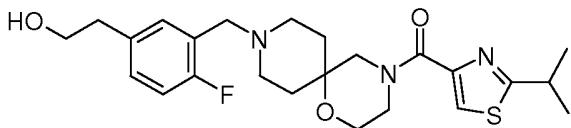
f) 2-(3-(1-Oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl)-4-fluorophenyl)ethanol



A solution of sodium carbonate (1.4 g) in water (40 mL) was added to a solution of 2,2,2-trifluoro-1-(9-(2-fluoro-5-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)ethanone [Example 6, step e] (4.2 g) in acetonitrile (40 mL). The reaction mixture was stirred at 20°C for 20 hours. The acetonitrile was removed under reduced pressure and the remaining aqueous solution was extracted with DCM (x 9). The combined DCM extracts were dried, filtered and the solvent removed under reduced pressure to yield the subtitled compound. Yield 2.7 g.

m/z 309 ($M+H$)⁺ (APCI).

g) (9-(2-Fluoro-5-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone



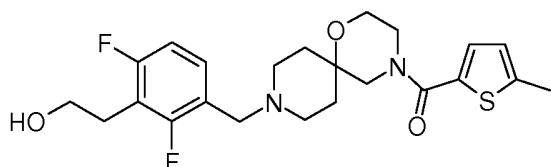
HATU (1.1 g) was added in one portion to a cooled solution of 2-(3-(1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl)-4-fluorophenyl)ethanol [Example 6, step f] (0.7 g) and 2-isopropylthiazole-4-carboxylic acid (0.39 g) and triethylamine (0.95 mL) in DMF (15 mL). The reaction mixture was stirred at 20°C for 1 hour and then partitioned between ethyl acetate and brine. The organic layer was washed with brine (x 2), dried, filtered and the solvent removed under reduced pressure. The crude product was purified by flash silica chromatography, using 3% methanol in ethyl acetate containing 1% triethylamine as solvent. Fractions containing the product were evaporated to dryness to afford the titled compound. Yield 0.61 g.

m/z 462 ($M+H$)⁺ (APCI).

¹H NMR (400 MHz, D₆-DMSO) δ 7.90 (s, 1H), 7.19 (d, J = 7.3 Hz, 1H), 7.13 - 7.07 (m, 1H), 6.97 (t, J = 9.3 Hz, 1H), 4.28 - 4.24 (m, 1H), 3.71 - 3.55 (m, 6H), 3.46 (s, 2H), 3.35 - 3.26 (m, 1H), 3.00 (s, 2H), 2.70 (t, J = 6.7 Hz, 2H), 2.45 - 2.26 (m, 4H), 1.74 - 1.65 (m, 2H), 1.59 - 1.49 (m, 2H), 1.36 (d, J = 7.0 Hz, 6H).

Example 7

(9-(2,4-Difluoro-3-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(5-methylthiophen-2-yl)methanone



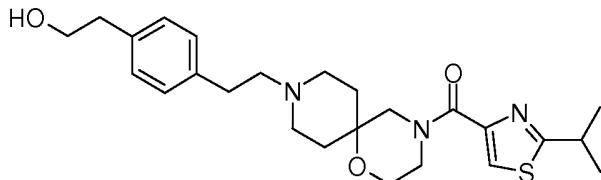
Dibenzoyl peroxide (0.03 g) was added to a mixture of NBS (0.53 g) and 2-(2,6-difluoro-3-methylphenyl)acetic acid (0.50 g) in DCM (10 mL). The reaction was heated at reflux for 4 h. DCM (10 mL) and water (20 mL) were added and the organic phase separated. The organic phase was washed with brine (20 mL), dried over sodium sulphate, filtered and evaporated. The residue was redissolved in THF (10 mL) and cooled in an ice bath. A

solution of borane dimethyl sulfide complex (2M in THF, 4 mL) was added dropwise and the mixture stirred for 1 h. Methanol (2 mL) was cautiously added dropwise and once bubbling had ceased the solvent was evaporated. The residue was redissolved in acetonitrile (10 mL) and (5-methylthiophen-2-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate [Preparation 6] (0.8 g) was added followed by triethylamine (1.12 mL). The resulting mixture was stirred overnight, evaporated and purified by silica gel chromatography eluting with 99:1:0.1 to 97:3:0.3 DCM:methanol:'880' aqueous ammonia gradient to give the titled compound as a clear foam. Yield 0.37 g. m/z 451(M+H)⁺ (APCI).

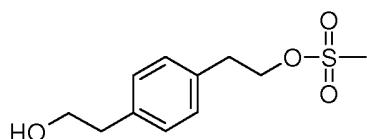
¹H NMR (400 MHz, D₆-DMSO) δ 7.28 - 7.17 (m, 2H), 6.97 - 6.91 (m, 1H), 6.81 - 6.78 (m, 1H), 4.53 - 4.40 (m, 1H), 3.69 - 3.43 (m, 10H), 2.79 (t, J = 7.0 Hz, 2H), 2.47 - 2.32 (m, 7H, obscured by solvent peak), 1.77 - 1.65 (m, 2H), 1.55 - 1.43 (m, 2H).

Example 8

(9-(4-(2-Hydroxyethyl)phenethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone



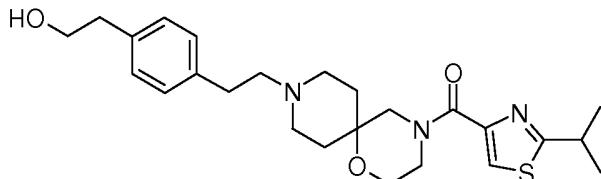
a) 4-(2-Hydroxyethyl)phenethyl methanesulfonate



Methanesulfonyl chloride (0.67 mL) in DCM (2 mL) was added dropwise to a stirred solution at 0°C of 2,2'-(1,4-phenylene)diethanol (1.30 g) and triethylamine (1.36 mL) in DCM (30 mL). The reaction mixture was stirred for 1 hour at 0°C and then washed with water. The aqueous layer was re-extracted with DCM and the combined organic phases were dried, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash silica chromatography using 3% methanol in dichloromethane as solvent. Fractions containing the product were evaporated to dryness to afford the subtitled compound. Yield 0.56 g.

¹H NMR (400 MHz, D₆-DMSO) δ 7.21 - 7.14 (m, 4H), 4.60 (t, J = 5.3 Hz, 1H), 4.38 (t, J = 6.8 Hz, 2H), 3.60 - 3.55 (m, 2H), 3.10 (s, 3H), 2.95 (t, J = 6.8 Hz, 2H), 2.69 (t, J = 7.2 Hz, 2H).

b) (9-(4-(2-Hydroxyethyl)phenethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone



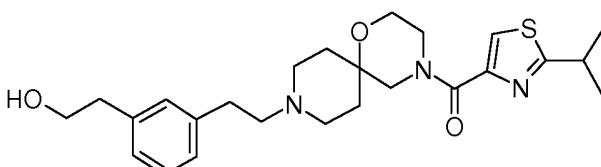
Potassium carbonate (0.634 g) was added to a solution of (2-isopropylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate [Preparation 4] (0.971 g) and 4-(2-hydroxyethyl)phenethyl methanesulfonate [Example 8, step a] (0.56 g) in acetonitrile (20 mL) and water (0.3 mL). The reaction mixture was heated at 60°C for 1 day. The solvent was evaporated under reduced pressure and the residue partitioned between water and ethyl acetate. The aqueous layer was re-extracted with ethyl acetate and the combined organic phases were dried, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash silica chromatography, using 2% methanol in dichloromethane with 1% triethylamine as solvent. Fractions containing the product were evaporated to dryness to afford the titled compound. Yield 0.68 g.

m/z 458 (M+H)⁺ (APCI).

¹H NMR (500 MHz, D₆-DMSO, 90°C) δ 7.91 (s, 1H), 7.08 (s, 4H), 4.20 (t, J = 4.7 Hz, 1H), 3.70 - 3.58 (m, 8H), 3.35 - 3.27 (m, 1H), 2.71 - 2.65 (m, 4H), 2.57 - 2.32 (m, 6H), 1.75 - 1.67 (m, 2H), 1.59 - 1.52 (m, 2H), 1.36 (d, J = 6.8 Hz, 6H).

Example 9

a) (9-(3-(2-Hydroxyethyl)phenethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone



A mixture of (2-isopropylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone hydrochloride [Preparation 5] (10 g) and 2-(3-(2-bromoethyl)phenyl)ethanol

[*Organometallics* 2002, **21**(20), 4217] (10 g) and potassium carbonate (16 g) in acetonitrile (600 mL) and water (10 mL) was heated at 60°C for 36 hours. The solvent was decanted off and evaporated under reduced pressure. The residue was partitioned between ethyl acetate and brine, the aqueous layer was re-extracted with ethyl acetate, and the combined organic layers were dried, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash silica chromatography, using 5% methanol in ethyl acetate containing 1% triethylamine as solvent. Fractions containing the product were evaporated to dryness to afford the titled compound. Yield 11 g.

m/z 458 (M+H)⁺ (APCI).

¹H NMR (500 MHz, D₆-DMSO 90°C) δ 7.91 (s, 1H), 7.13 (t, *J* = 8.5 Hz, 1H), 7.05 - 6.98 (m, 3H), 4.20 (t, *J* = 5.4 Hz, 1H), 3.71 - 3.59 (m, 8H), 3.35 - 3.27 (m, 1H), 2.73 - 2.64 (m, 4H), 2.55 - 2.33 (m, 6H), 1.74 - 1.66 (m, 2H), 1.58 - 1.51 (m, 2H), 1.36 (d, *J* = 6.9 Hz, 6H).

Example 9a

(9-(3-(2-Hydroxyethyl)phenethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone toxic acid salt

A solution of (9-(3-(2-hydroxyethyl)phenethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone (1.12 g, 2.45 mmol) in ethanol (50 mL) was treated with ToxicAcid monohydrate (0.466 g, 2.45 mmol) and the solvent was evaporated under reduced pressure. The residue was triturated with ether to yield 1.58 g of (9-(3-(2-hydroxyethyl)phenethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone toxic acid salt as a white crystalline solid.

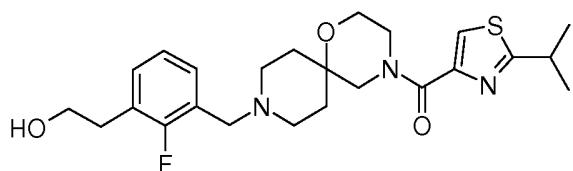
1H NMR (400 MHz, DMSO, 90°C) δ 9.06 (s, 1H), 7.98 (s, 1H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.15 - 7.03 (m, 5H), 3.77 - 3.59 (m, 8H), 3.50 - 3.26 (m, 5H), 3.18 - 2.88 (m, 4H), 2.72 (t, *J* = 6.9 Hz, 2H), 2.28 (s, 3H), 2.20 - 2.02 (m, 2H), 1.77 - 1.62 (m, 2H), 1.36 (d, *J* = 6.8 Hz, 6H).

plus 1 exchangeable not observed

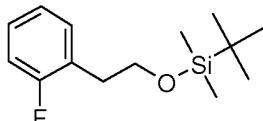
m/z 458.1 (M+H)⁺

Example 10

(9-(2-Fluoro-3-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone



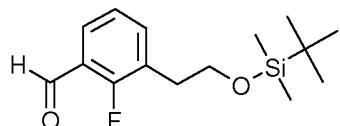
a) ***tert*-Butyl(2-fluorophenethoxy)dimethylsilane**



A solution of 2-(2-fluorophenyl)ethanol (5.5 g) and imidazole (8.0 g) in DMF (50 mL) was cooled in ice-water, treated with *tert*-butyldimethylchlorosilane (6.52 g), then removed from the cooling bath and stirred at room temperature for 3.5 hours. The solution was poured into water and extracted three times with diethyl ether. The combined organic extracts were washed three times with water, once with brine, then dried over anhydrous magnesium sulphate and concentrated under reduced pressure to afford the subtitled compound as a colourless oil. Yield 9.9 g.

¹H NMR (400 MHz, CDCl₃) δ 7.25 - 7.14 (m, 2H), 7.07 - 6.97 (m, 2H), 3.81 (t, *J* = 7.0 Hz, 2H), 2.87 (t, *J* = 6.9 Hz, 2H), 0.86 (s, 9H), -0.03 (s, 6H).

b) 3-(*tert*-Butyldimethylsilyloxy)ethyl)-2-fluorobenzaldehyde

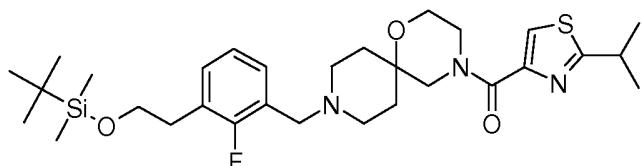


A solution of 2,2,6,6-tetramethylpiperidine (11.0 g) in anhydrous THF (200 mL) was cooled to -78° and treated with butyllithium (37.5 mL), added steadily over 5 minutes via a syringe. The solution was stirred at -78° for 15 minutes and then treated with a solution of *tert*-butyl(2-fluorophenethoxy)dimethylsilane [Example 10, step a] (9.9 g) in THF (25 mL), added dropwise over 15 minutes. The solution that was stirred at -78° for 2 hours, then treated with a solution of DMF (9.0 mL) in THF (25 mL), added dropwise over 10 minutes. The solution was stirred at -78° for 1 hour, then the cooling bath was removed and the solution was allowed to warm to room temperature overnight. The reaction mixture was poured into aqueous HCl (0.5M) and extracted three times with ethyl acetate. The combined organic phases were washed three times with water, once with brine, then

dried over magnesium sulphate, filtered and concentrated under reduced pressure to afford the subtitled compound. Yield 10.1 g.

¹H NMR (400 MHz, CDCl₃) δ 10.41 (s, 1H), 7.79 - 7.74 (m, 1H), 7.55 (td, *J* = 7.4, 1.6 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 3.88 (t, *J* = 6.5 Hz, 2H), 2.96 (t, *J* = 6.6 Hz, 2H), 0.88 (s, 9H), 0.00 (s, 6H).

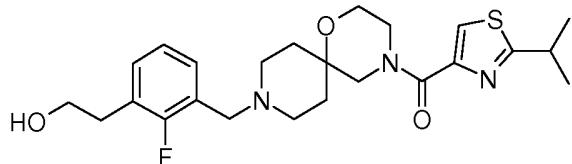
c) (9-(3-(*tert*-Butyldimethylsilyloxy)ethyl)-2-fluorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone



3-(*tert*-Butyldimethylsilyloxy)ethyl)-2-fluorobenzaldehyde [Example 10, step b] (4.07 g) was added to (2-isopropylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate [Preparation 4] (6.10 g) in a mixture of *N*-methyl-2-pyrrolidinone (50 mL) and acetic acid (0.83 mL) and stirred for 30 min. Sodium triacetoxyborohydride (4.58 g) was then added and the mixture stirred overnight. The reaction mixture was poured into water (100 mL), the pH was adjusted to 8 using saturated sodium bicarbonate solution, and the mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic phases were washed with water (3 x 100 mL) and brine (100 mL), dried over sodium sulphate, filtered and evaporated. The residue was purified by flash silica chromatography using 77.5:17.5:5 isohexane:ethyl acetate:triethylamine as solvent to give the subtitled compound as a clear oil. Yield 5.35 g.

¹H NMR (400 MHz, D₆-DMSO, 90°C) δ 7.96 (s, 1H), 7.29 - 7.18 (m, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 3.85 (t, *J* = 6.5 Hz, 2H), 3.74 - 3.67 (m, 6H), 3.54 (s, 2H), 3.37 (septet, *J* = 6.9 Hz, 1H), 2.88 - 2.82 (m, 2H), 2.50 - 2.34 (m, 4H), 1.79 - 1.71 (m, 2H), 1.63 - 1.54 (m, 2H), 1.42 (d, *J* = 6.9 Hz, 6H), 0.87 (s, 9H), 0.00 (s, 6H).

d) (9-(2-Fluoro-3-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone



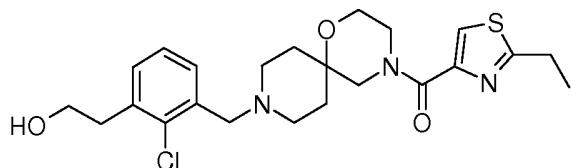
TBAF (1M in THF, 13.9 mL) was added to a solution of (9-(3-(*tert*-butyldimethylsilyloxy)ethyl)-2-fluorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone [Example 10, step c] (5.35 g) in THF (50 mL) and the resulting mixture was stirred for 1 h. The solvent was evaporated and the residue partitioned between ethyl acetate (100 mL) and water (100 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (2 x 100 mL). The combined organic phases were washed with brine (100 mL), dried over sodium sulphate, filtered and evaporated. The crude material was purified by flash silica chromatography, elution gradient 4:1 isohexane:ethyl acetate to 100% ethyl acetate to give the titled compound as a clear oil. Yield 3.90 g.

m/z 462 (M+H)⁺ (APCI).

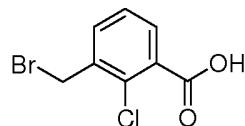
¹H NMR (300 MHz, D₆-DMSO) δ 7.93 (s, 1H), 7.23 - 7.14 (m, 2H), 7.03 (t, J = 7.5 Hz, 1H), 4.48 - 4.40 (m, 1H), 3.69 - 3.56 (m, 8H), 3.48 (s, 2H), 3.38 - 3.24 (m, 1H), 2.75 (t, J = 6.9 Hz, 2H), 2.45 - 2.23 (m, 4H), 1.76 - 1.62 (m, 2H), 1.60 - 1.47 (m, 2H), 1.35 (d, J = 6.9 Hz, 6H).

Example 11

(9-(2-Chloro-3-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-ethylthiazol-4-yl)methanone



a) 3-(Bromomethyl)-2-chlorobenzoic acid

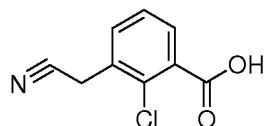


Benzoyl peroxide (1.33 g) was added to a suspension of 2-chloro-3-methylbenzoic acid (25 g) and *N*-bromosuccinimide (28.7 g) in chlorobenzene (250 mL) and the resulting mixture was heated to 85°C for 4 h. The mixture was diluted with ethyl acetate (100 mL) and washed with 10% aqueous brine (3 x 100 mL). The organic layer was dried over magnesium sulphate, filtered and evaporated. The beige solid was recrystallised from

ethyl acetate (~75 mL)/isohexane (~250 mL) to give the subtitled compound as a white solid. Yield 25.3 g.

¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, J = 7.7 Hz, 1H), 7.66 (d, J = 7.4 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 4.67 (s, 2H). One exchangeable proton not observed.

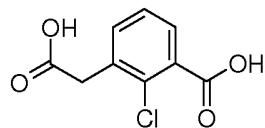
b) 2-Chloro-3-(cyanomethyl)benzoic acid



A solution of 3-(bromomethyl)-2-chlorobenzoic acid [Example 11, step a] (13.2 g) in DMF (150 mL) was treated with a solution of potassium cyanide (7.23 g) in water (50 mL) and the resulting solution was stirred at room temperature overnight. The mixture was diluted with water (200 mL) and carefully acidified with concentrated hydrochloric acid (25 mL), venting any liberated HCN through bleach solution via a stream of nitrogen. After being stirred for 2 hours, the aqueous phase was extracted with ethyl acetate (3 x 250 mL). The combined organic phases were washed with water (3 x 250 mL) and brine (250 mL), dried over magnesium sulphate, filtered and evaporated to give the subtitled compound as a white solid. Yield 10.3 g.

¹H NMR (300 MHz, D₆-DMSO) δ 13.54 (s, 1H), 7.75 - 7.67 (m, 2H), 7.48 (t, J = 7.7 Hz, 1H), 4.16 (s, 2H).

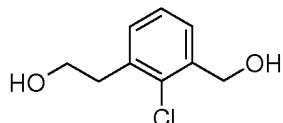
c) 3-(Carboxymethyl)-2-chlorobenzoic acid



Concentrated sulfuric acid (60 mL) was added dropwise to ice-cold water (75 mL) and the resulting solution was added to 2-chloro-3-(cyanomethyl)benzoic acid [Example 11, step b] (14 g). The resulting suspension was heated to reflux (165°C) for 30 min during which the starting material dissolved and a new precipitate was observed. The reaction was allowed to cool and was diluted with water (250 mL) and extracted with ethyl acetate (3 x 500 mL). The combined organic phases were washed with water (250 mL) and brine (250 mL), then dried over magnesium sulphate and evaporated to give the subtitled compound as a white solid. Yield 13.7 g.

¹H NMR (400 MHz, D₆-DMSO) δ 7.62 (dd, J = 7.7, 1.8 Hz, 1H), 7.54 (dd, J = 7.7, 1.8 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 3.78 (s, 2H). Two exchangeable protons not observed.

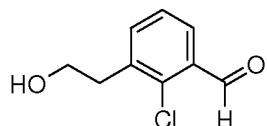
d) 2-(2-Chloro-3-(hydroxymethyl)phenyl)ethanol



A solution of borane dimethyl sulfide complex (2M in THF, 220 mL) was added portionwise over 5 minutes to a suspension of 3-(carboxymethyl)-2-chlorobenzoic acid [Example 11, step c] (18.9 g) in dry THF (800 mL) at room temperature. The resulting effervescent suspension was stirred at room temperature for 30 minutes, then heated to reflux for 60 minutes, and allowed to cool to room temperature overnight. The mixture was quenched by the portionwise addition of methanol (100 mL) over 15 minutes and stirred until bubbling ceased. Concentrated aqueous HCl (25 mL) was added, the mixture was stirred for 30 min and concentrated under reduced pressure. The gummy residue was partitioned between ethyl acetate (500 mL) and aqueous HCl (2M, 200 mL). The phases were separated and the aqueous phase extracted with ethyl acetate (2 x 300 mL). The combined organic phases were washed with brine (300 mL), dried over magnesium sulphate, filtered and evaporated to give the subtitled compound as a yellow oil. Yield 17.8 g.

¹H NMR (400 MHz, D₆-DMSO) δ 7.40 (dd, J = 7.0, 2.2 Hz, 1H), 7.29 - 7.21 (m, 2H), 5.34 (t, J = 5.5 Hz, 1H), 4.71 (t, J = 4.9 Hz, 1H), 4.55 (d, J = 5.1 Hz, 2H), 3.63 - 3.56 (m, 2H), 2.87 (t, J = 7.2 Hz, 2H).

e) 2-Chloro-3-(2-hydroxyethyl)benzaldehyde

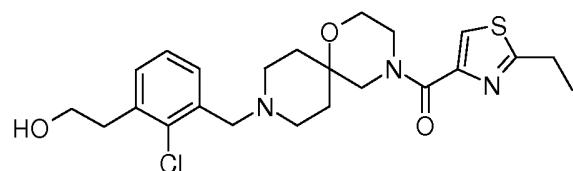


Manganese (IV) dioxide (43.1 g) was added to a slight suspension of 2-(2-chloro-3-(hydroxymethyl)phenyl)ethanol [Example 11, step d] (18.5 g) in chloroform (500 mL), and the resulting suspension was heated at reflux for 2 h. The reaction mixture was cooled, filtered through Celite and the filter pad washed with DCM (3 x 300 mL). The combined washings and filtrate were evaporated and the residue purified by flash silica chromatography eluting with 3:1 to 1:1 isohexane:ethyl acetate gradient. The fractions

containing product were combined and evaporated to give the subtitled compound as a white solid. Yield 12.0 g.

¹H NMR (400 MHz, CDCl₃) δ 10.55 (s, 1H), 10.54 (t, J = 5.6 Hz, 1H), 7.83 (dd, J = 7.7, 1.8 Hz, 1H), 7.55 (dd, J = 7.4, 1.8 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 3.94 (q, J = 6.4 Hz, 2H), 3.11 (t, J = 6.5 Hz, 2H).

f) (9-(2-Chloro-3-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-ethylthiazol-4-yl)methanone



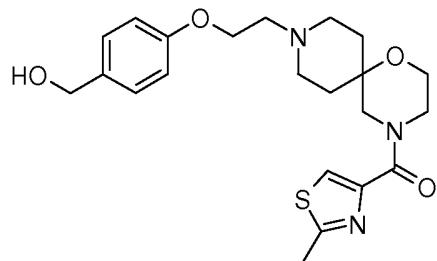
To a suspension of 2-chloro-3-(2-hydroxyethyl)benzaldehyde [Example 9, step e] (1.5 g) and (2-ethylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate [Preparation 7] (4.25 g) in tetrahydrofuran (50 mL) was added triethylamine (2.5 mL) in one portion. The mixture was stirred for 0.5 h, sodium triacetoxyborohydride (2.58 g) was then added in one portion and the resultant solution was stirred for 2 h. The reaction mixture was partitioned between ethyl acetate (100 mL) and saturated sodium bicarbonate solution (50 mL). The mixture was shaken vigorously for 10 min and the layers were separated. The aqueous phase was extracted with ethyl acetate (100 mL). The combined organic solutions were washed with brine, dried over sodium sulphate, filtered and evaporated. The residue was purified by flash silica chromatography using 95:5 ethyl acetate:triethylamine as solvent. The fractions containing the product were combined and evaporated to give the titled compound as a clear oil. Yield 3.40 g.

m/z 464/466 (M+H)⁺ (APCI).

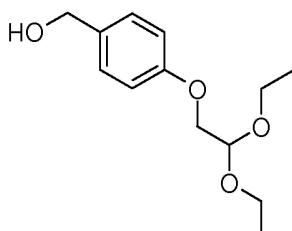
¹H NMR (400 MHz, D₆-DMSO, 90°C) δ 7.89 (s, 1H), 7.33 - 7.28 (m, 1H), 7.24 - 7.16 (m, 2H), 4.35 (t, J = 5.4 Hz, 1H), 3.68 - 3.60 (m, 8H), 3.55 (s, 2H), 3.02 (q, J = 7.5 Hz, 2H), 2.89 (t, J = 6.9 Hz, 2H), 2.46 - 2.31 (m, 4H), 1.75 - 1.67 (m, 2H), 1.59 - 1.51 (m, 2H), 1.33 (t, J = 7.6 Hz, 3H).

Example 12

(9-(2-(4-(Hydroxymethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone



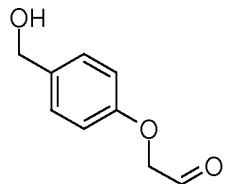
a) [4-(2,2-Diethoxy-ethoxy)-phenyl]-methanol



Caesium carbonate (39.4 g) was added to a solution of 4-hydroxymethyl-phenol (10 g) and 2-bromo-1,1-diethoxyethane (12.73 mL) in DMF (200 mL) and the resulting mixture stirred at 90°C for 16 h. The reaction was poured into water (500 mL) and extracted with ethyl acetate (3 x 250 mL). The combined organic solutions were washed with water (250 mL) and brine (250 mL), then dried over sodium sulphate, filtered and evaporated *in vacuo*. Purification was by silica gel chromatography eluting with an isohexane to diethyl ether gradient to give the subtitled compound as a yellow oil. Yield 9.5 g.

¹H NMR (400 MHz, CDCl₃) δ 7.29-7.25 (m, 2H), 6.93-6.88 (m, 2H), 4.83 (t, J = 5.2Hz, 1H), 4.61 (s, 2H), 4.00 (d, J = 5.2Hz, 2H), 3.81-3.72 (m, 2H), 3.68-3.58 (m, 2H), 1.25 (t, J = 7.0Hz, 6H). One exchangeable proton not observed.

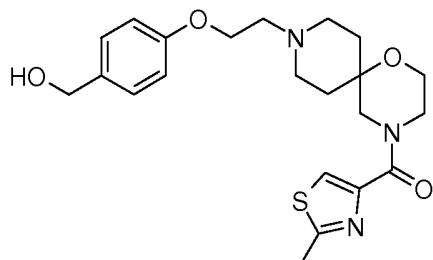
b) 2-(4-(Hydroxymethyl)phenoxy)acetaldehyde



Aqueous HCl (2M, 4 mL) was added to a solution of (4-(2,2-diethoxyethoxy)phenyl)methanol [Example 12, step a] (0.9 g) in acetone (20 mL) and the resulting mixture was stirred for 16 h at room temperature. The reaction was concentrated *in vacuo* and the resulting aqueous solution extracted with ethyl acetate (3 x 20 mL). The combined organic solutions were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give the subtitled compound as a clear gum, which was used directly in the

next step. Yield 0.50 g.

c) (9-(2-(4-(Hydroxymethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone



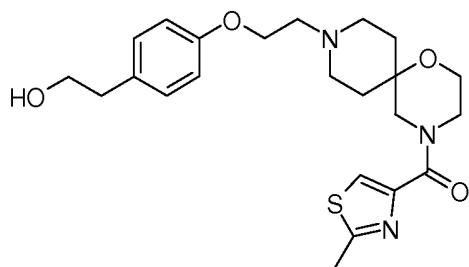
(2-Methylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone hydrochloride [Preparation 2] (0.38 g) was added to a solution of 2-(4-hydroxymethyl)phenoxyacetaldehyde [Example 12, step b] (0.17 g) in NMP (10 mL) and acetic acid (0.06 mL). The resulting mixture was stirred for 30 min then cooled in an ice bath. Sodium triacetoxyborohydride (0.32 g) was then added and the reaction allowed to warm to room temperature and stirred for 16 h. The reaction was diluted with methanol (30 mL) and applied to a SCX cartridge pre-wetted with methanol. The cartridge was washed with methanol (250 mL) and eluted with ammonia solution (3M in methanol, 150 mL). The eluent was evaporated *in vacuo* and the residue purified by silica gel chromatography eluting with 95:5 ethyl acetate:triethylamine to give the titled compound as a gum. Yield 0.32 g.

m/z 432 (M+H)⁺ (APCI).

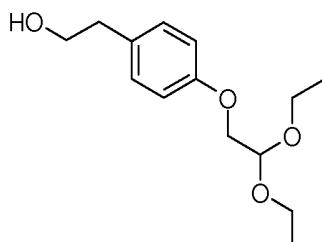
¹H NMR (300 MHz, D₆-DMSO) δ 7.86 (s, 1H), 7.23-7.16 (m, 2H), 6.85 (dt, J = 8.7, 1.1 Hz, 2H), 4.72-4.62 (m, 1H), 4.44-4.38 (m, 2H), 4.10-3.99 (m, 2H), 3.66 (d, J = 6.7 Hz, 4H), 3.61-3.55 (m, 2H), 2.71-2.64 (m, 5H), 2.47-2.42 (m, 4H), 1.76-1.64 (m, 2H), 1.59-1.45 (m, 2H).

Example 13

(9-(2-(4-(2-Hydroxyethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone



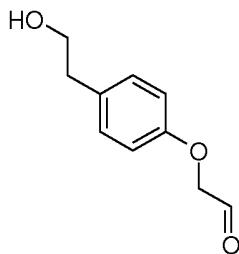
a) 2-(4-(2,2-Diethoxyethoxy)phenyl)ethanol



Caesium carbonate (28.3 g) was added to a solution of 4-(2-hydroxyethyl)phenol (10 g) and 2-bromo-1,1-diethoxyethane (11.79 mL) in DMF (150 mL). The resulting suspension was heated at 90°C for 16 h. The reaction was poured into water (500 mL). The aqueous phase was extracted with ethyl acetate (3 x 200 mL). The combined organic solutions were washed with water (200 mL) and brine (200 mL), then dried over magnesium sulfate, filtered and evaporated *in vacuo*. Purification was by silica gel chromatography eluting with isohexane to 1:1 ethyl acetate:isohexane gradient to give the subtitled compound as a yellow oil. Yield 10 g.

¹H NMR (300 MHz, CDCl₃) δ 7.14 (d, J = 6.9 Hz, 2H), 6.88 (d, J = 6.9 Hz, 2H), 4.83 (t, J = 5.0 Hz, 1H), 4.00 (d, J = 5.0 Hz, 2H), 3.87-3.70 (m, 4H), 3.70-3.56 (m, 2H), 2.81 (t, J = 6.4 Hz, 2H), 1.25 (t, J = 6.9 Hz, 6H). One exchangeable proton not observed.

b) 2-(4-(2-Hydroxyethyl)phenoxy)acetaldehyde

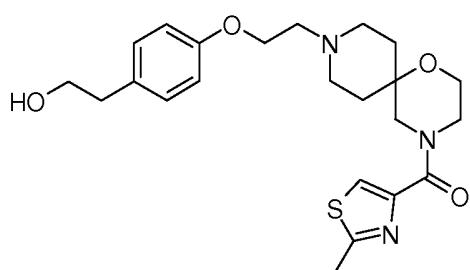


Concentrated hydrochloric acid (5 mL) was added to a solution of 2-(4-(2,2-diethoxyethoxy)phenyl)ethanol [Example 13, step a] (0.76 g) in 1,4-dioxane (10 mL) and the resulting mixture was stirred for 1 h. The reaction was diluted with water (50 mL) and

extracted with ethyl acetate (3 x 50 mL). The combined organic solutions were washed with water (50 mL) and brine (50 mL), then dried over sodium sulphate, filtered and evaporated *in vacuo* to give the subtitled compound, which was used directly.

Yield 0.35 g.

c) (9-(2-(4-(2-Hydroxyethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone



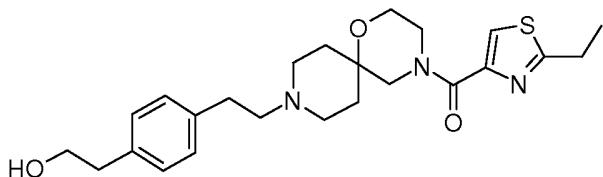
(2-Methylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone hydrochloride [Preparation 2] (0.63 g) was added to a solution of 2-(4-(2-hydroxyethyl)phenoxy)acetaldehyde [Example 13, step b] (0.541 g) in a mixture of NMP (10 mL) and acetic acid (0.11 mL). The resulting mixture was stirred at room temperature for 30 min then cooled in an ice bath. Sodium triacetoxyborohydride (0.64 g) was then added and the reaction was allowed to warm to room temperature and stirred for 16 h. The reaction was diluted with methanol (30 mL) and applied to a SCX cartridge pre-wetted with methanol. The cartridge was washed with methanol (100 mL) and eluted with ammonia solution (3M in methanol, 100 mL). The eluent was evaporated *in vacuo* and the residue purified by silica gel chromatography, eluting with 95:5 ethyl acetate:triethylamine to give the titled compound as a brown oil. Yield 0.74 g.

m/z 446 (M+H)⁺ (APCI).

¹H NMR (300 MHz, D₆-DMSO) δ 7.86 (s, 1H), 7.09 (d, J = 8.4 Hz, 2H), 6.84-6.77 (m, 2H), 4.24-4.15 (m, 1H), 4.02 (t, J = 6.0 Hz, 2H), 3.68-3.54 (m, 8H), 3.00 (s, 2H), 2.71 - 2.61 (m, 5H), 2.51-2.42 (m, 4H), 1.75-1.65 (m, 2H), 1.59-1.45 (m, 2H).

Example 14

(2-Ethylthiazol-4-yl)(9-(4-(2-hydroxyethyl)phenethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone

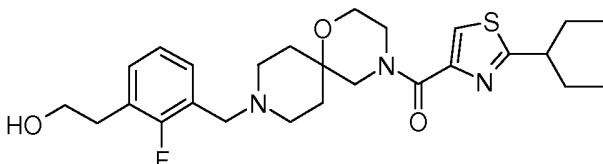


A solution of 2-(4-(2-bromoethyl)phenyl)ethanol [Organometallics 2002, 21(20), 4217] (1.71 g) in NMP (5 mL) was added to a suspension of (2-ethylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate [Preparation 7] (3.0 g) and cesium carbonate (5.60 g) in NMP (10 mL) and the mixture stirred at 75°C under nitrogen for 4 hours. More 2-(4-(2-bromoethyl)phenyl)ethanol (0.65 g) was added and the mixture stirred at 75°C for 18 hours. The mixture was cooled, diluted with water and extracted into ethyl acetate (x 3). The combined extracts were washed with 10% brine, 30% brine and saturated brine, dried over magnesium sulfate, filtered and the solvent removed. The crude product was purified by flash silica chromatography, successively eluted with 50% ethyl acetate in isohexane with 5% triethylamine, then 100% ethyl acetate with 5% triethylamine, then 10% methanol in ethyl acetate with 5% triethylamine. Fractions containing the product were evaporated to dryness to afford the titled compound as a yellow oil. Yield 1.90 g.

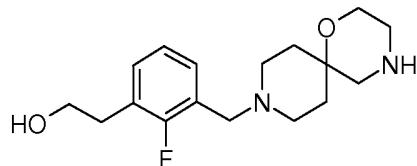
m/z 444 (M+H)⁺ (APCI).

Example 15

(9-(2-Fluoro-3-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-(pentan-3-yl)thiazol-4-yl)methanone



a) 2-(3-(1-Oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl)-2-fluorophenyl)ethanol

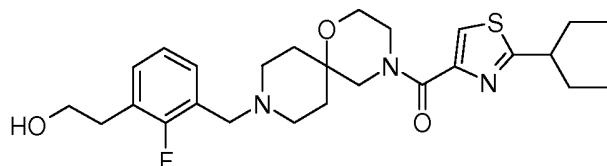


3-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-2-fluorobenzaldehyde [Example 10, Step b] (5.0 g) was added to a solution of 2,2,2-trifluoro-1-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)ethanone trifluoroacetate [Preparation 8] (9.3 g) and acetic acid (1.0 mL) in *N*-methyl-2-

pyrrolidinone (50 mL). The resulting mixture was stirred for 15 min, then cooled in an ice bath. Sodium triacetoxyborohydride (5.64 g) was then added and the mixture was stirred overnight. The reaction mixture was quenched by the addition of saturated sodium bicarbonate solution:brine (1:5) and extracted four times with ethyl acetate. The combined organic phases were dried (MgSO_4), filtered and concentrated *in vacuo* to afford an oil. The oil was dissolved in THF (100 mL) and treated with TBAF (1M in THF, 18.0 mL). The resulting solution was stirred at room temperature for 50 minutes, then more TBAF (1M in THF, 18.0 mL) was added and the mixture was stirred for a further 100 minutes. The solution was then concentrated *in vacuo* to afford an oil. The oil was dissolved in methanol (100 mL), the solution was treated with '880' aqueous ammonia (20 mL), stirred at room temperature for 50 minutes, then concentrated *in vacuo* to give an oil. The oil was dissolved in methanol and concentrated onto flash silica *in vacuo*. The resulting powder was purified by flash chromatography on silica eluted with '880' aqueous ammonia:methanol:dichloromethane (1:10:89) to afford the subtitled compound as a yellow oil. Yield 5.8 g, 60% pure. Used crude.

m/z 309 ($\text{M}+\text{H}$)⁺ (APCI).

b) (9-(2-Fluoro-3-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-(pentan-3-yl)thiazol-4-yl)methanone



HATU (0.35 g) was added to a colourless solution of 2-(3-(1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl)-2-fluorophenyl)ethanol [Example 15, step a] (0.364 g), 2-(pentan-3-yl)thiazole-4-carboxylic acid [Preparation 9] (0.141 g) and triethylamine (0.30 mL) in DMF (10 mL), pre-cooled in ice-water. The resulting yellow mixture was stirred in ice-water for 1 hour, then at room temperature for 1 hour. The solution was poured into a mixture of water and brine and extracted twice with ethyl acetate. The combined organic extracts were washed three times with water, once with brine, then dried (MgSO_4), filtered and concentrated onto flash silica *in vacuo*. The resulting powder was purified by flash chromatography on silica eluted with

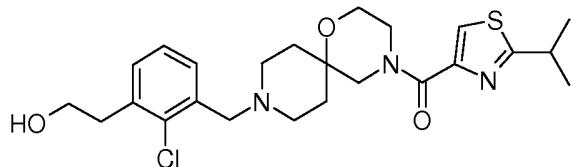
triethylamine:methanol:dichloromethane (1:2:97) to afford the titled compound. Yield 0.324 g.

m/z 490 (M+H)⁺ (APCI).

¹H NMR (400 MHz, DMSO) δ 7.93 (s, 1H), 7.22 - 7.14 (m, 2H), 7.03 (t, J = 7.6 Hz, 1H), 4.39 - 4.32 (m, 1H), 3.69 - 3.58 (m, 6H), 3.52 - 3.46 (m, 2H), 2.97 - 2.90 (m, 1H), 2.75 (t, J = 7.3 Hz, 2H), 2.70 (s, 2H), 2.46 - 2.29 (m, 4H), 1.82 - 1.66 (m, 6H), 1.58 - 1.47 (m, 2H), 0.85 (t, J = 7.3 Hz, 6H).

Example 16

(9-(2-Chloro-3-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone



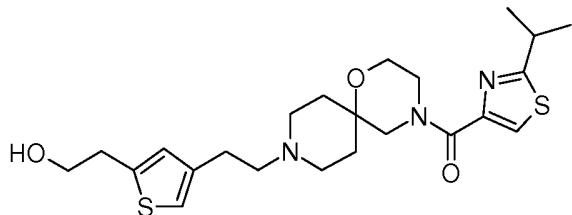
Prepared by the method of Example 11, step f using (2-isopropylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone hydrochloride [Preparation 5] (1.37 g) in place of (2-ethylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate, and 2-methyltetrahydrofuran (50 mL) in place of tetrahydrofuran. Yield 1.00 g.

m/z 478/480 (M+H)⁺ (APCI).

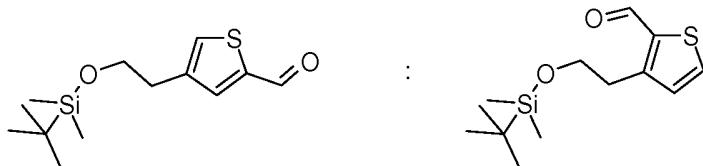
¹H NMR (400 MHz, D₆-DMSO 90°C) δ 7.91 (d, J = 1.3 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.24 - 7.16 (m, 2H), 4.36 (t, J = 5.1 Hz, 1H), 3.73 - 3.59 (m, 8H), 3.55 (s, 2H), 3.32 (septet, J = 6.8 Hz, 1H), 2.89 (t, J = 7.0 Hz, 2H), 2.46 - 2.40 (m, 1H), 2.40 - 2.28 (m, 1H), 2.17 (t, J = 8.1 Hz, 1H), 1.91 (quintet, J = 7.5 Hz, 1H), 1.77 - 1.65 (m, 2H), 1.62 - 1.50 (m, 2H), 1.36 (d, J = 6.5 Hz, 6H).

Example 17

(9-(2-(5-(2-Hydroxyethyl)thiophen-3-yl)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone



a) Mixture of 4-(*tert*-butyldimethylsilyloxy)ethyl)thiophene-2-carbaldehyde with 3-(*tert*-butyldimethylsilyloxy)ethyl)thiophene-2-carbaldehyde



Butyllithium (36.1 mL) was added dropwise to stirred solution of *tert*-butyldimethyl(2-thiophen-3-yl)ethoxy silane [J. Med. Chem. 2000, 43(8), 1508] (10.0 g) in THF (200 mL) cooled to -78°C. After the addition the reaction mixture was stirred in an ice bath for 1h and then cooled to -78°C. DMF (31.9 mL) was added dropwise over 5 min, and after a further 10 min the cooling bath was removed. After 1h, the reaction mixture was partitioned between water and ethyl acetate and the ethyl acetate solution was washed twice with water and brine, dried over sodium sulphate, filtered and evaporated under reduced pressure. Purification by silica gel chromatography eluting with ethyl acetate:isohexane, 1:20, gave a 5:1 mixture of 4-(*tert*-butyldimethylsilyloxy)ethyl)thiophene-2-carbaldehyde and 3-(*tert*-butyldimethylsilyloxy)ethyl)thiophene-2-carbaldehyde by ¹H NMR as an oil. Yield 8.1 g.

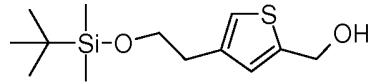
4-(*tert*-butyldimethylsilyloxy)ethyl)thiophene-2-carbaldehyde:

¹H NMR (400 MHz, CDCl₃) δ 9.93 (d, J = 1.2 Hz, 1H), 7.71 (d, J = 1.5 Hz, 1H), 7.52 (s, 1H), 3.92 - 3.84 (m, 2H), 2.91 (t, J = 6.5 Hz, 2H), 0.92 (s, 9H), 0.04 (s, 6H).

3-(*tert*-butyldimethylsilyloxy)ethyl)thiophene-2-carbaldehyde:

¹H NMR (400 MHz, CDCl₃) δ 10.08 (s, 1H), 7.69 (d, J = 5.0 Hz, 1H), 7.09 (d, J = 5.0 Hz, 1H), 3.92 - 3.84 (m, 2H), 3.22 (t, J = 6.5 Hz, 2H), 0.89 (s, 9H), -0.01 (s, 6H).

b) (4-(*tert*-Butyldimethylsilyloxy)ethyl)thiophen-2-yl)methanol

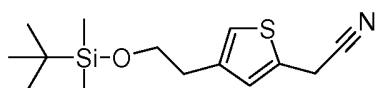


Sodium borohydride (1.40 g) was added portionwise to a stirred solution at 0°C of 4-(*tert*-butyldimethylsilyloxy)ethyl)thiophene-2-carbaldehyde [Example 17, Step a] (10 g) in ethanol (70 mL). The reaction mixture was stirred for 1 hour at 0°C and then partitioned between ethyl acetate and aqueous brine and separated. The organic layer was dried, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash silica chromatography using 12% ethyl acetate in isohexane as solvent.

Fractions containing the product were evaporated to dryness to afford the subtitled compound. Yield 6.00 g.

¹H NMR (400 MHz, D₆-DMSO) δ 7.04 (s, 1H), 6.82 (s, 1H), 5.35 (t, J = 5.6 Hz, 1H), 4.55 (d, J = 5.6 Hz, 2H), 3.73 (t, J = 7.0 Hz, 2H), 2.69 (t, J = 6.9 Hz, 2H), 0.85 (s, 9H), 0.00 (s, 6H).

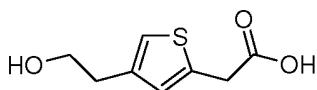
c) 2-(4-(*tert*-Butyldimethylsilyloxy)ethyl)thiophen-2-yl)acetonitrile



Triphenylphosphine (7.16 g) followed by carbon tetrabromide (8.62 g) were added in one portion to (4-(*tert*-butyldimethylsilyloxy)ethyl)thiophen-2-yl)methanol [Example 17, Step b] (6.00 g) in DCM (50 mL) at 0°C under nitrogen. The resulting solution was stirred at room temperature for 1 hour. The reaction mixture was cooled to 0°C and treated with tetraethylammonium cyanide (4.92 g), added in one portion. The mixture was diluted further with dichloromethane (20 mL) and stirred at room temperature for 40 minutes. The reaction mixture was partitioned between dichloromethane and aqueous brine, the organic layer was separated, dried over sodium sulphate and the solvent removed under reduced pressure. The crude product was purified by flash silica chromatography, elution gradient 2 to 6% ethyl acetate in isohexane. Fractions containing the product were evaporated to dryness to afford the subtitled compound. Yield 4.20 g.

¹H NMR (400 MHz, CDCl₃) δ 6.93 (s, 1H), 6.92 (s, 1H), 3.86 (s, 2H), 3.78 (t, J = 6.7 Hz, 2H), 2.78 (t, J = 6.7 Hz, 2H), 0.88 (s, 9H), 0.00 (s, 6H).

d) 2-(4-(2-Hydroxyethyl)thiophen-2-yl)acetic acid

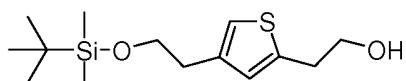


A solution of 2-(4-(*tert*-butyldimethylsilyloxy)ethyl)thiophen-2-yl)acetonitrile [Example 17, step c] (4.20 g) dissolved in ethanol (30 mL) was added to a stirred solution of potassium hydroxide (1.67 g) in water (30 mL). The resulting mixture was stirred at 100°C for 3 hours. The mixture was partitioned between aqueous brine and ethyl acetate, and the phases separated. The aqueous layer was cooled with ice and acidified by dropwise addition of concentrated hydrochloric acid. The aqueous layer was then extracted with ethyl acetate (x 2), the combined organic phases were washed with aqueous

brine, dried over sodium sulphate and the solvent evaporated under reduced pressure to give a yellow solid which was triturated with ether (20 mL) to give the subtitled compound. Yield 2.33 g.

¹H NMR (400 MHz, D₆-DMSO) δ 12.46 (s, 1H), 7.00 (s, 1H), 6.81 (s, 1H), 4.61 (t, J = 4.9 Hz, 1H), 3.73 (s, 2H), 3.60 - 3.54 (m, 2H), 2.66 (t, J = 7.0 Hz, 2H).

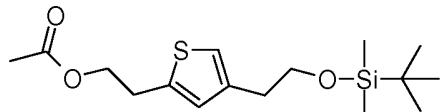
e) 2-(4-(*tert*-Butyldimethylsilyloxy)ethyl)thiophen-2-yl)ethanol



tert-Butyldimethylsilyl chloride (2.21 g) was added portionwise to a mixture of imidazole (1.00 g) and 2-(4-(2-hydroxyethyl)thiophen-2-yl)acetic acid [Example 17, step d] (1.3 g) in DMF (15 mL) at 20°C over a period of 20 minutes. The resulting solution was stirred at 20°C for 1 hour. The reaction mixture was diluted with THF (15 mL), cooled in ice-water, and treated with a solution of potassium carbonate (1.35 g) in water (15 mL). This mixture was stirred at 0°C for 20 minutes. The mixture was partitioned between ethyl acetate and aqueous brine, and the phases separated. The organic layer was washed twice with aqueous brine, dried, filtered and the solvent removed under reduced pressure. The residue was dissolved in THF (40 mL), cooled in an ice bath and treated with borane tetrahydrofuran complex (1M in THF, 21 mL), added dropwise. The resultant solution was stirred at 20°C for 2 hours. The reaction mixture was quenched by dropwise addition of methanol (10 mL) and the solvents were removed under reduced pressure. The crude product was purified by flash silica chromatography using 17% ethyl acetate in isohexane as solvent. Fractions containing the product were evaporated to dryness to afford the subtitled compound. Yield 1.25 g.

¹H NMR (400 MHz, D₆-DMSO) δ 6.94 (s, 1H), 6.75 (s, 1H), 4.75 (t, J = 5.3 Hz, 1H), 3.74 (t, J = 6.9 Hz, 2H), 3.62 - 3.56 (m, 2H), 2.86 (t, J = 6.9 Hz, 2H), 2.69 (t, J = 6.8 Hz, 2H), 0.85 (s, 9H), 0.00 (s, 6H).

f) 2-(4-(*tert*-Butyldimethylsilyloxy)ethyl)thiophen-2-yl)ethyl acetate

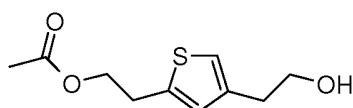


A solution of acetyl chloride (0.36 mL) in dry THF (3 mL) was added dropwise over 10 minutes to a stirred solution at 20°C of 2-(4-(*tert*-butyldimethylsilyloxy)ethyl)thiophen-

2-yl)ethanol [Example 17, Step e] (1.10 g) and triethylamine (1.18 mL) in dry THF (30 mL). The mixture was stirred at 20°C for 20 minutes and then partitioned between ethyl acetate and brine. The organic layer was dried, filtered and the solvent evaporated under reduced pressure to give the subtitled compound. Yield 1.20 g.

¹H NMR (400 MHz, CDCl₃) δ 6.81 (s, 1H), 6.72 (s, 1H), 4.27 (t, J = 6.9 Hz, 2H), 3.78 (t, J = 6.9 Hz, 2H), 3.09 (t, J = 6.8 Hz, 2H), 2.77 (t, J = 6.9 Hz, 2H), 2.06 (s, 3H), 0.88 (s, 9H), 0.00 (s, 6H).

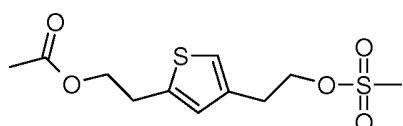
g) 2-(4-(2-Hydroxyethyl)thiophen-2-yl)ethyl acetate



TBAF (1M in THF, 3.65 mL) was added dropwise to a solution of 2-(4-(*tert*-butyldimethylsilyloxy)ethyl)thiophen-2-yl)ethyl acetate [Example 17, Step f] (1.2 g) in dry THF (30 mL). This solution was allowed to stand at 20°C for 1 hour, then the solvents were evaporated under reduced pressure and the residue was purified by flash silica chromatography, using 40% ethyl acetate in isohexane as solvent. Fractions containing the product were evaporated to dryness to afford the subtitled compound. Yield 0.63 g.

¹H NMR (400 MHz, D₆-DMSO) δ 6.97 (s, 1H), 6.80 (s, 1H), 4.60 (t, J = 5.3 Hz, 1H), 4.17 (t, J = 6.7 Hz, 2H), 3.60 - 3.54 (m, 2H), 3.04 (t, J = 6.5 Hz, 2H), 2.65 (t, J = 7.0 Hz, 2H), 2.01 (s, 3H).

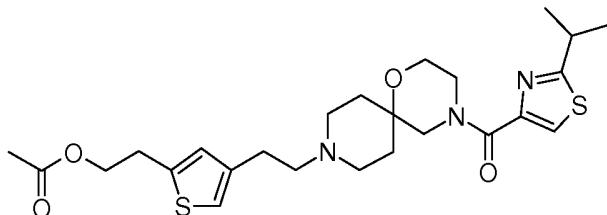
h) 2-(4-(2-(Methylsulfonyloxy)ethyl)thiophen-2-yl)ethyl acetate



A solution of 2-(4-(2-hydroxyethyl)thiophen-2-yl)ethyl acetate [Example 17, Step g] (0.6 g) and triethylamine (0.47 mL) in DCM (30 mL) at 0°C was treated dropwise over 20 minutes with a solution of methanesulphonyl chloride (0.24 mL) in DCM (3 mL). The mixture was stirred at 20°C for 1 hour and then washed with water. The organic layer was dried, filtered and the solvent evaporated under reduced pressure to afford the titled compound. Yield 0.80 g.

¹H NMR (500 MHz, CDCl₃) δ 6.91 (s, 1H), 6.74 (s, 1H), 4.40 (t, J = 6.7 Hz, 2H), 4.27 (t, J = 6.7 Hz, 2H), 3.11 (t, J = 6.5 Hz, 2H), 3.02 (t, J = 6.8 Hz, 2H), 2.91 (s, 3H), 2.07 (s, 3H).

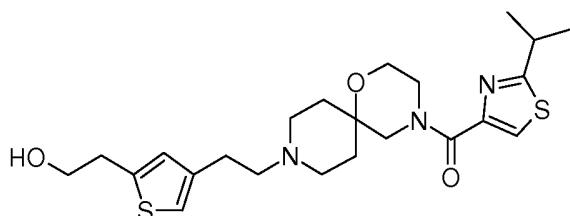
i) 2-(4-(4-(2-Isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethyl)thiophen-2-yl)ethyl acetate



Prepared by the method of Example 8, step b using the hydrochloride salt of (2-isopropylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone [Preparation 5] (1 g) in place of its trifluoroacetate salt, and 2-(4-(2-(methylsulfonyloxy)ethyl)thiophen-2-yl)ethyl acetate [Example 17, Step h] (0.8 g) in place of 4-(2-hydroxyethyl)phenethyl methanesulfonate. Yield 1.0 g.

m/z 506 (M+H)⁺ (APCI).

j) (9-(2-(5-(2-Hydroxyethyl)thiophen-3-yl)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone



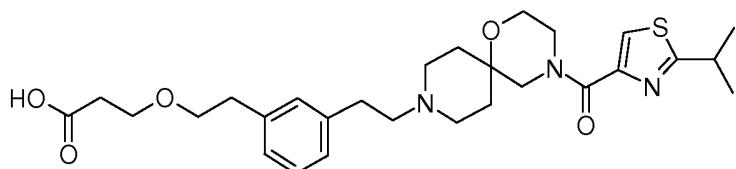
Aqueous sodium hydroxide (1M, 4.9 mL) was added to a solution of 2-(4-(2-(4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethyl)thiophen-2-yl)ethyl acetate [Example 17, Step i] (1.0 g) in methanol (20 mL) and the resulting mixture was stirred for 1 hour at 20°C. The mixture was partitioned between ethyl acetate and brine and separated. The organic phase was dried, filtered and the solvent evaporated under reduced pressure to afford the titled compound. Yield 0.92 g.

m/z 464 (M+H)⁺ (APCI).

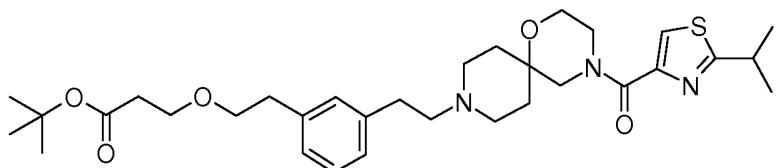
¹H NMR (400 MHz, D₆-DMSO, 90°C) δ 7.91 (s, 1H), 6.86 (s, 1H), 6.70 (s, 1H), 4.39 (t, J = 5.3 Hz, 1H), 3.70 - 3.58 (m, 8H), 3.35 - 3.27 (m, 1H), 2.86 (t, J = 6.8 Hz, 2H), 2.63 (t, J = 7.7 Hz, 2H), 2.52 - 2.30 (m, 6H), 1.73 - 1.65 (m, 2H), 1.58 - 1.50 (m, 2H), 1.36 (d, J = 6.9 Hz, 6H).

Example 18

3-(3-(2-(4-(2-Isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethyl)phenethoxy)propanoic acid

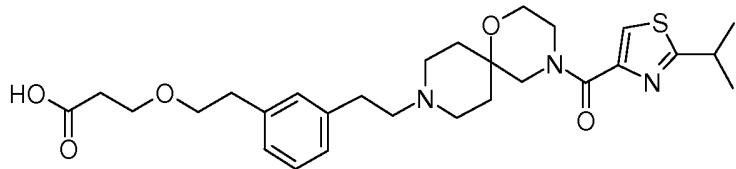


a) *tert*-Butyl 3-(3-(2-(4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethyl)phenethoxy)propanoate



(9-(3-(2-Hydroxyethyl)phenethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone [Example 9] (2.4 g) was dissolved in acetonitrile (2 mL) and *tert*-butyl acrylate (1.7 mL) added, followed by benzyltrimethylammonium hydroxide (40% in water, 0.72 mL). The mixture was stirred at ambient temperature for 3 hours. The volatiles were removed under reduced pressure and the residue purified by flash silica chromatography eluting with 3% methanol in dichloromethane containing 1% ‘880’ aqueous ammonia to afford the subtitled compound. Yield 2.7 g.
m/z 586 (M+H)⁺ (APCI).

b) 3-(3-(2-(4-(2-Isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethyl)phenethoxy)propanoic acid

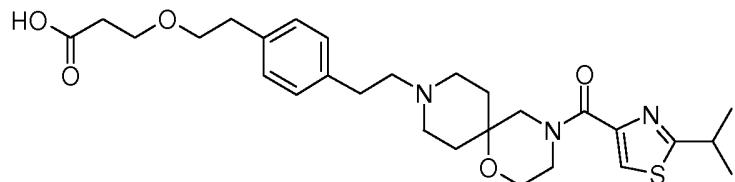


tert-Butyl 3-(3-(2-(4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethyl)phenethoxy)propanoate [Example 18, step a] (0.70 g) was stirred in dichloromethane (8 mL) and trifluoroacetic acid (2 mL) was added. The solution was stirred for 18 hours, then the volatiles were removed under reduced pressure to afford the titled compound. Yield 1.0 g.

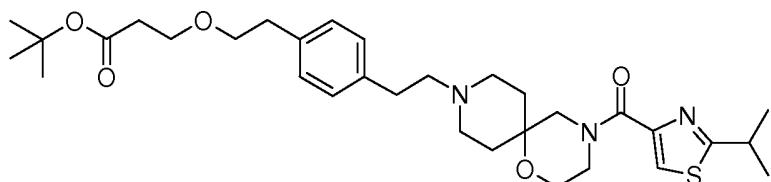
m/z 530 (M+H)⁺ (APCI).

Example 19

3-(4-(2-(4-(2-Isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethyl)phenethoxy)propanoic acid



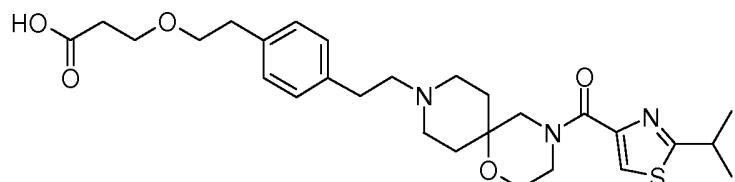
a) *tert*-Butyl 3-(4-(2-(4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethyl)phenethoxy)propanoate



Benzyltrimethylammonium hydroxide (40% in methanol, 0.031 mL) was added to a solution of (9-(4-(2-hydroxyethyl)phenethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone [Example 8] (0.62 g) in toluene (20 mL). The solvent was removed under reduced pressure and the residue azeotroped with toluene. The resultant liquid, which was just mobile with traces of toluene, was treated dropwise with *tert*-butyl acrylate (0.225 g). The reaction mixture was stirred at 20°C for 18 hours. The mixture was purified by flash silica chromatography using 2% methanol in dichloromethane with 1% triethylamine as solvent. Fractions containing the product were evaporated to dryness to afford the subtitled compound. Yield 0.550 g.

m/z 586 (M+H)⁺ (APCI).

b) 3-(4-(2-(4-(2-Isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethyl)phenethoxy)propanoic acid



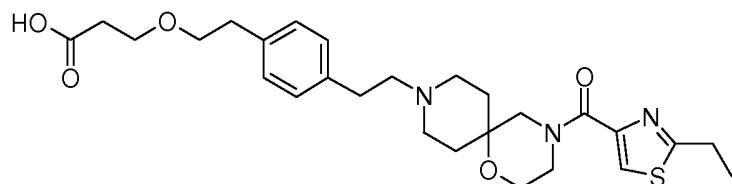
Trifluoroacetic acid (10 mL) was added to a solution of *tert*-butyl 3-(4-(2-(4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethyl)phenethoxy)propanoate [Example 19, step a] (0.55 g) in DCM (20 mL) and the

resultant solution allowed to stand at 20°C for 1 hour. Toluene (30 mL) was added and the solvents were evaporated under reduced pressure. The residue was azeotroped with acetonitrile (x 2) to yield the titled compound. Yield 0.60 g.

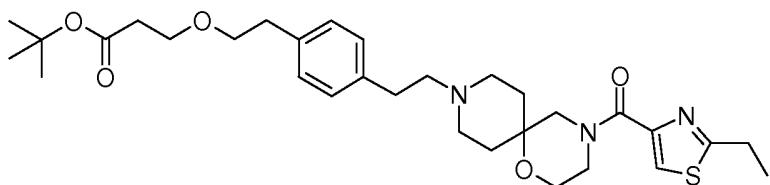
m/z 530 (M+H)⁺ (APCI).

Example 20

3-(4-(2-(4-(2-Ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethyl)phenethoxy)propanoic acid



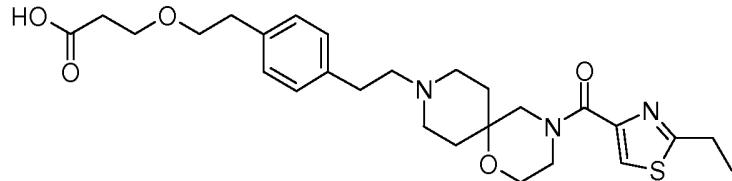
a) *tert*-Butyl 3-(4-(2-(4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethyl)phenethoxy)propanoate



Benzyltrimethylammonium hydroxide (40% in water, 0.51 mL) was added to a solution of (2-ethylthiazol-4-yl)(9-(4-(2-hydroxyethyl)phenethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone [Example 14] (1.9 g) and *tert*-butyl acrylate (1.32 mL) in acetonitrile (1.5 mL) and the mixture stirred at ambient temperature for 4 hours. The mixture was concentrated *in vacuo* and the crude product purified by flash silica chromatography, elution gradient 50 to 75% ethyl acetate in isohexane with 5% triethylamine. Fractions containing the product were evaporated to dryness to afford the subtitled compound as a colourless oil. Yield 2.19 g.

m/z 572 (M+H)⁺ (APCI).

b) 3-(4-(2-(4-(2-Ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethyl)phenethoxy)propanoic acid



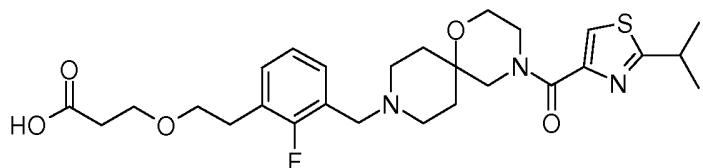
Prepared by the method of Example 19, step b using *tert*-butyl 3-(4-(2-(4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethyl)phenethoxy)propanoate [Example 20, step a] (2.2 g) in place of *tert*-butyl 3-(4-(2-(4-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethyl)phenethoxy)propanoate. Yield 3.36 g.

m/z 516 (M+H)⁺ (APCI).

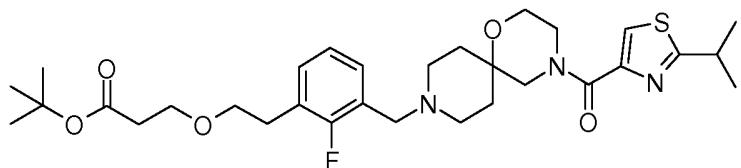
¹H NMR (400 MHz, CDCl₃) δ 7.90 (s, 1H), 7.13 (dd, J = 29.9, 8.1 Hz, 4H), 3.97 - 3.92 (m, 1H), 3.82 - 3.77 (m, 3H), 3.74 - 3.67 (m, 4H), 3.64 - 3.56 (m, 1H), 3.35 - 3.27 (m, 1H), 3.10 - 3.00 (m, 6H), 2.85 (t, J = 6.5 Hz, 2H), 2.61 - 2.55 (m, 2H), 2.21 - 2.13 (m, 2H), 2.03 - 1.92 (m, 6H), 1.45 - 1.34 (m, 3H). One exchangeable proton not observed.

Example 21

3-(2-Fluoro-3-((4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)propanoic acid



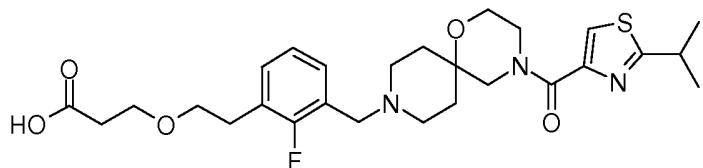
a) *tert*-Butyl 3-(2-fluoro-3-((4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)propanoate



Prepared by the method of Example 18, step a using (9-(2-fluoro-3-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone [Example 10] (3.85 g) in place of (9-(3-(2-hydroxyethyl)phenethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone. The crude product was purified by flash silica chromatography, elution gradient 1:1 ethyl acetate:isohexane with 5% triethylamine to 95:5 ethyl acetate:triethylamine. Fractions containing the product were evaporated to dryness to afford the subtitled compound. Yield 3.95 g.

m/z 590 (M+H)⁺ (APCI).

b) 3-(2-Fluoro-3-((4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)propanoic acid



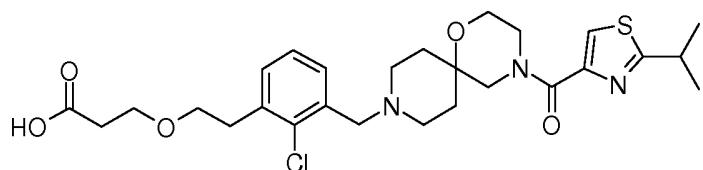
TFA (10 mL) was cautiously added to a solution of *tert*-butyl 3-(2-fluoro-3-((4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)propanoate [Example 21, step a] (3.95 g) in DCM (40 mL). The resulting mixture was stirred for 2 h. The solvent was evaporated and the residue azeotroped twice with acetonitrile. The residue was dissolved in freshly distilled 2-methyltetrahydrofuran (100 mL) and washed 3 times with a mixture of brine and saturated sodium bicarbonate solution (10:1, 100 mL). The organic phase was dried over sodium sulphate, filtered and evaporated. The residue was azeotroped 3 times with isohexane to give the titled compound as a white foam. Yield 2.92 g.

m/z 534 (M+H)⁺ (APCI).

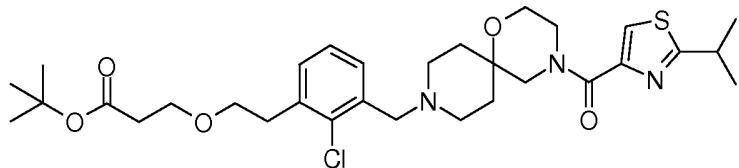
¹H NMR (300 MHz, D₆-DMSO) δ 8.00 (s, 1H), 7.58 - 7.01 (m, 3H), 3.75 - 3.54 (m, 12H), 3.42 - 3.25 (m, 5H), 2.83 (t, J = 6.6 Hz, 2H), 2.42 (t, J = 6.3 Hz, 2H), 1.87 - 1.47 (m, 4H), 1.34 (d, J = 6.9 Hz, 6H). One exchangeable proton not observed.

Example 22

3-(2-Chloro-3-((4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)propanoic acid



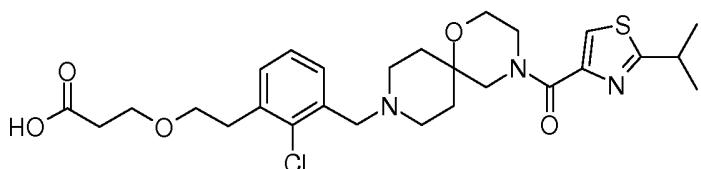
a) *tert*-Butyl 3-(2-chloro-3-((4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)propanoate



Prepared by the method of Example 19, step a using (9-(2-chloro-3-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-

yl)methanone [Example 16] (1.0 g) in place of (9-(4-(2-hydroxyethyl)phenethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone. Yield 0.93 g. m/z 606 M⁺ (APCI).

b) 3-(2-chloro-3-((4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)propanoic acid



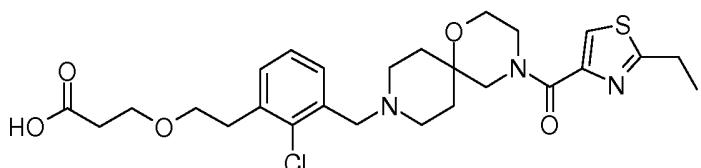
Prepared by the method of Example 21, step b using *tert*-butyl 3-(2-chloro-3-((4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)propanoate [Example 22, step a] (0.93 g) in place of *tert*-butyl 3-(2-fluoro-3-((4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)propanoate. Yield 0.76 g.

m/z 550 M⁺ (APCI).

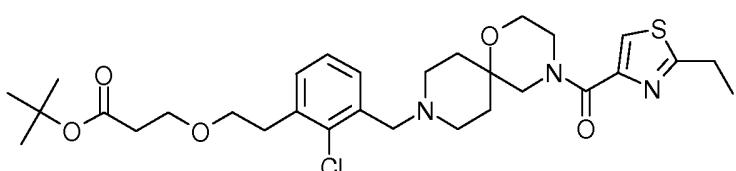
¹H NMR (400 MHz, D₆-DMSO) δ 7.94 (s, 1H), 7.51 (ddd, J = 20.1, 7.6, 1.6 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.26 - 7.08 (m, 1H), 4.47 (s, 2H), 3.76 - 3.60 (m, 10H), 3.37 - 3.13 (m, 5H), 3.00 (t, J = 6.8 Hz, 2H), 2.42 (t, J = 6.3 Hz, 2H), 2.11 - 1.96 (m, 2H), 1.88 - 1.67 (m, 2H), 1.35 (d, J = 7.3 Hz, 6H). One exchangeable proton not observed.

Example 23

3-(2-Chloro-3-((4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)propanoic acid



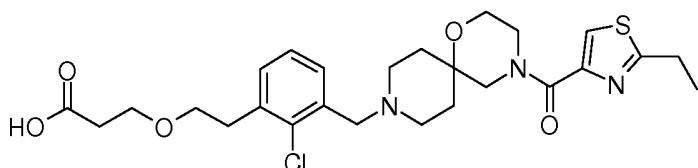
a) *tert*-Butyl 3-(2-chloro-3-((4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)propanoate



Triton-B (40% in water, 0.94 mL) was added to a solution of (9-(2-chloro-3-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-ethylthiazol-4-yl)methanone [Example 11] (3.2 g) and *tert*-butyl acrylate (1.5 mL) in acetonitrile (1 mL) and the resulting mixture stirred overnight at RT. The solvent was evaporated and the residue was purified by flash silica chromatography, elution gradient 1:1:0.05 ethyl acetate:isohexane:triethylamine to 95:5 ethyl acetate:triethylamine to give the subtitled compound as a clear oil. Yield 3.2 g.

m/z 592 M⁺ (APCI).

b) 3-(2-Chloro-3-((4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)propanoic acid



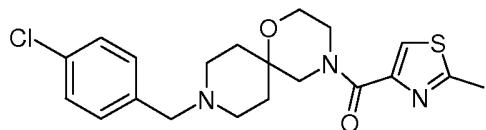
TFA (10 mL) was added to a solution of *tert*-butyl 3-(2-chloro-3-((4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)propanoate [Example 23, step a] (3.1 g) in DCM (30 mL) and the resulting mixture stirred for 2 h, then evaporated. The residue was partitioned between ethyl acetate (100 mL) and saturated sodium bicarbonate solution (50 mL). The phases were separated and the aqueous phase was washed with more ethyl acetate (2 x 100 mL). The aqueous phase was then acidified with acetic acid and extracted with ethyl acetate (3 x 100 mL). The combined organic solutions were dried over sodium sulphate, filtered and evaporated to give the titled compound as a white foam. Yield 2.7 g.

m/z 536 M⁺ (APCI).

¹H NMR (400 MHz, D₆-DMSO, 90°C) δ 7.92 (s, 1H), 7.60 - 7.53 (m, 1H), 7.44 - 7.39 (m, 1H), 7.32 (t, J = 7.6 Hz, 1H), 3.76 - 3.56 (m, 12H), 3.12 - 2.92 (m, 8H), 2.42 (t, J = 6.4 Hz, 2H), 2.01 - 1.73 (m, 4H), 1.33 (t, J = 7.6 Hz, 3H). One exchangeable proton not observed.

Example 24

(9-(4-Chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone hydrochloride salt

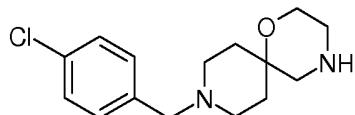


To a stirred solution of 4-chlorobenzaldehyde (0.17 g) and (2-methylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone hydrochloride [Preparation 2] (0.28 g) in NMP (2 mL) was added sodium triacetoxyborohydride (0.32 g) and the reaction was stirred overnight. The reaction was diluted with methanol (2 mL) and the mixture was passed through a SCX column flushing with methanol. The product was eluted with ammonia solution (7N in methanol) and the resulting residue after concentration was purified by chromatography on silica gel eluting with 1-5% (0.7N ammonia in methanol) in dichloromethane. Fractions containing the product were concentrated and the residue was dissolved in diethyl ether (5 mL), treated with HCl (4N in 1,4-dioxane, 2 mL), and the resulting white solid removed by filtration to afford the titled compound. Yield 0.33 g. m/z 406 ($M+H$)⁺ (APCI).

¹H NMR (300 MHz, CD₃OD) δ 7.90 (s, 1H), 7.64 (d, 2H), 7.49 (d, 2H), 4.28 (s, 2H), 3.69 (s, 4H), 3.63-3.57 (m, 1H), 3.22-3.14 (m, 3H), 3.08-2.93 (m, 2H), 2.69 (s, 3H), 2.10-1.80 (4, 4H).

Examples 25-89

a) 9-(4-Chlorophenylmethyl)- 1-oxa-4,9-diazaspiro[5.5]undecane

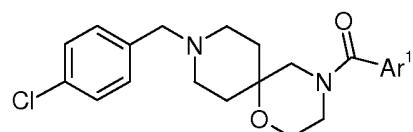


To a solution of 1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylic acid, 1,1-dimethylethyl ester (WuXi PharmaTech) (6.5 g) in THF (200 mL) was added 4-chlorophenylbenzaldehyde (2.56 g) followed by sodium triacetoxyborohydride (4.87 g) and the mixture stirred for 24 hours. The mixture was evaporated to dryness and the residue taken up into DCM (300 mL), washed well with water and dried over magnesium sulfate. Filtration and evaporation gave a crude residue which was redissolved in a mixture of DCM (30 mL) and TFA (30 mL) and the mixture allowed to stand for 1 hour. The mixture was evaporated to dryness and the residue was dissolved in methanol and applied to a SCX cartridge pre-wetted with methanol. The cartridge was washed with

methanol and the product eluted with ammonia solution (3M in methanol). The eluent was evaporated *in vacuo* to give the subtitled compound as a colourless foam. Yield 7.1 g. m/z 281(M+H)⁺ (APCI).

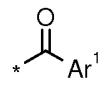
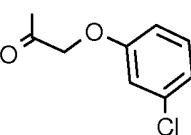
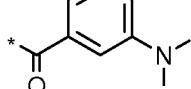
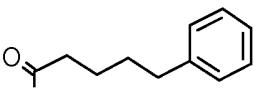
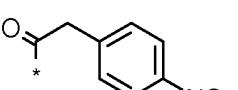
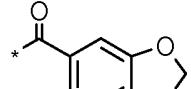
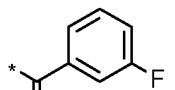
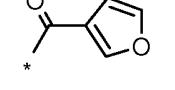
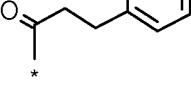
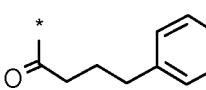
b) General procedure for preparation of Examples 25-89:

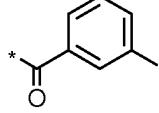
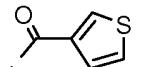
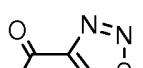
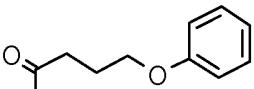
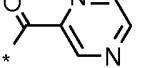
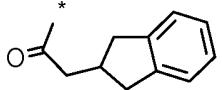
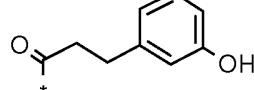
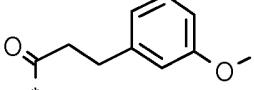
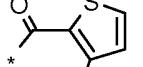
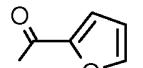
To a solution of the carboxylic acid (0.1 mmol) in NMP (0.5 mL) was added Hunig's base (0.1 mL) followed by a solution of bromo-tris-pyrrolidinophosphoniumhexafluorophosphate (PYBROP, 0.1 mmol) dissolved in NMP (0.2 mL). This mixture was shaken for 1 minute, then added to 9-(4-chlorophenylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecane [Examples 25-89, step a] (0.1 mmol) dissolved in NMP (0.2 mL) and the mixture shaken overnight. The crude mixture was then evaporated to dryness and purified (HPLC, Waters XTerra®, 0.1% aqueous ammonium acetate:acetonitrile, gradient elution 95:05 to 5-95 over 15 mins) to give the following compounds:

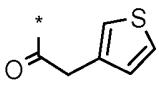
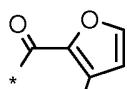
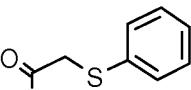
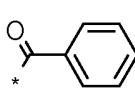
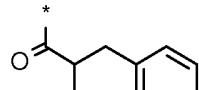
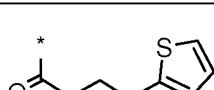
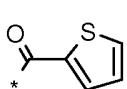
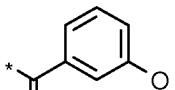
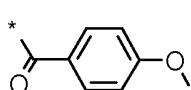


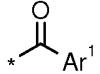
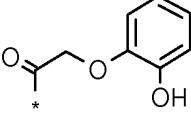
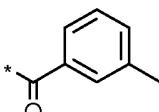
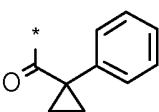
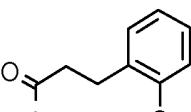
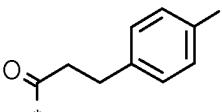
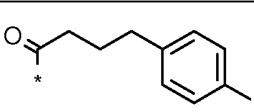
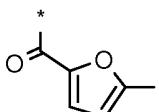
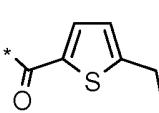
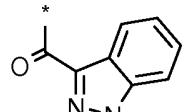
The title compounds of Examples 25 to 89 were purified using ammonium acetate. It will be understood that, for each individual Example the purification process used may have produced the title compound as an acetate salt, a partial acetate salt or the free base.

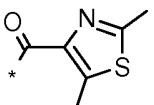
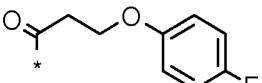
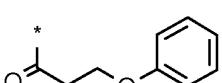
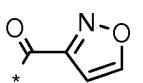
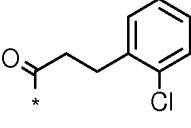
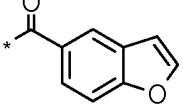
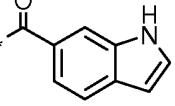
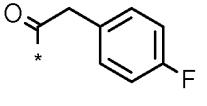
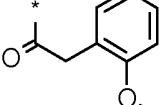
Ex. No.	Name	* 	Observed (M+H) ⁺	Retention time (min)
25	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(5-methylthiophen-2-yl)methanone		404	1.36
26	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(4-(methylthio)phenyl)methanone		430	1.44
27	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(p-tolyl)methanone		398	1.46

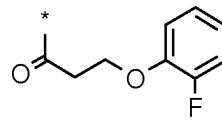
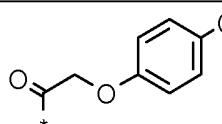
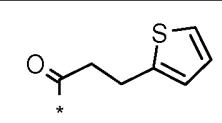
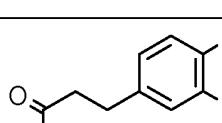
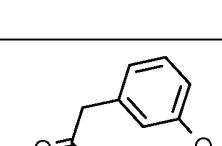
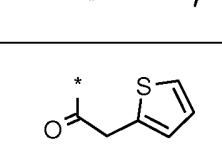
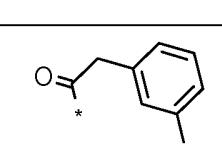
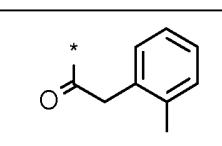
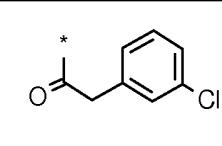
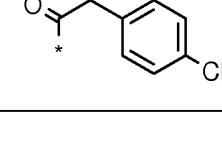
Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
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29	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(3-(dimethylamino)phenyl)methanone		427	1.17
30	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-5-phenylpentan-1-one		440	1.57
31	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-(4-nitrophenyl)ethanone		443	1.39
32	benzo[d][1,3]dioxol-5-yl(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone		428	1.37
33	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(3-fluorophenyl)methanone		402	1.33
34	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)furan-3-methanone		374	1.29
35	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-3-phenylpropan-1-one		412	1.53
36	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-4-phenylbutan-1-one		426	1.62

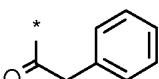
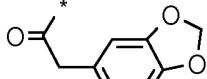
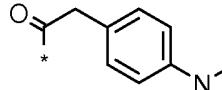
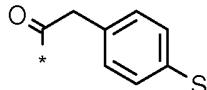
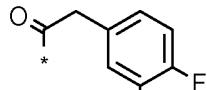
Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
37	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(m-tolyl)methanone		398	1.39
38	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(thiophen-3-yl)methanone		390	1.34
39	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(1,2,3-thiadiazol-4-yl)methanone		392	1.20
40	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-4-phenoxybutan-1-one		442	1.57
41	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyrazin-2-yl)methanone		386	1.14
42	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-(2,3-dihydro-1H-inden-2-yl)ethanone		438	1.52
43	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-3-(3-hydroxyphenyl)propan-1-one		428	1.36
44	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-3-(3-methoxyphenyl)propan-1-one		442	1.49
45	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(3-methylthiophen-2-yl)methanone		404	1.42
46	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(furan-2-		374	1.24

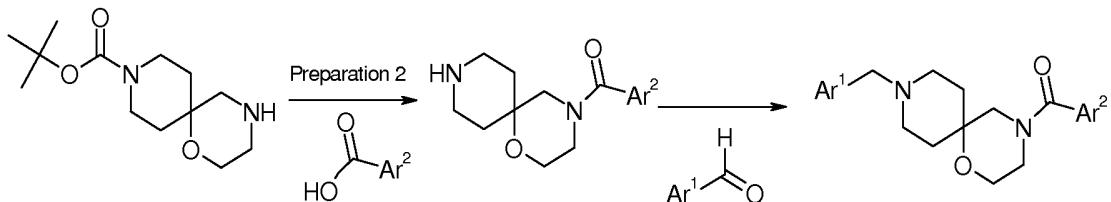
Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
	yl)methanone			
47	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-(thiophen-3-yl)ethanone		404	1.41
48	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(3-methylfuran-2-yl)methanone		388	1.32
49	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-(phenylthio)ethanone		430	1.44
50	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(phenyl)methanone		384	1.30
51	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(1,2,3,4-tetrahydronaphthalen-2-yl)methanone		438	1.53
52	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-4-(thiophen-2-yl)butan-1-one		432	1.47
53	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(thiophen-2-yl)methanone		390	1.29
54	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(3-methoxyphenyl)methanone		414	1.35
55	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(4-methoxyphenyl)methanone		414	1.34

Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
56	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-(2-hydroxyphenoxy)ethanone		430	1.31
57	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(3-ethylphenyl)methanone		412	1.47
58	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(1-phenylcyclopropyl)methanone		424	1.45
59	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-3-(2-methoxyphenyl)propan-1-one		442	1.46
60	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-3-p-tolylpropan-1-one		426	1.56
61	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-4-p-tolylbutan-1-one		440	1.65
62	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(5-methylfuran-2-yl)methanone		388	1.31
63	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(5-ethylthiophen-2-yl)methanone		418	1.48
64	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(1H-indazol-3-yl)methanone		424	1.31

Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
65	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2,5-dimethylthiazol-4-yl)methanone		419	1.26
66	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-3-(4-fluorophenoxy)propan-1-one		446	1.55
67	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-3-phenoxypropan-1-one		428	1.43
68	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(isoxazol-3-yl)methanone		375	1.28
69	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-3-(2-chlorophenyl)propan-1-one		446	1.51
70	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(5-(hydroxymethyl)furan-2-yl)methanone		404	1.23
71	benzofuran-5-yl(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone		424	1.39
72	(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(1H-indol-6-yl)methanone		423	1.36
73	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-(4-fluorophenyl)ethanone		416	1.40
74	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-(2-methoxyphenyl)ethanone		428	1.40

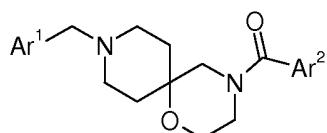
Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
75	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-3-(2-fluorophenoxy)propan-1-one		446	1.45
76	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-(4-chlorophenoxy)ethanone		448	1.59
77	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-3-(thiophen-2-yl)propan-1-one		418	1.40
78	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-3-(3,4-difluorophenyl)propan-1-one		448	1.58
79	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-(3-methoxyphenyl)ethanone		428	1.38
80	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-(thiophen-2-yl)ethanone		404	1.34
81	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-m-tolylethanone		412	1.45
82	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-o-tolylethanone		412	1.42
83	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-(3-chlorophenyl)ethanone		432	1.54
84	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-(4-chlorophenyl)ethanone		432	1.48

Ex. No.	Name		Observed (M+H)⁺	Retention time (min)
	chlorophenyl)ethanone			
85	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-phenylethanone		398	1.36
86	2-(benzo[d][1,3]dioxol-5-yl)-1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)ethanone		442	1.44
87	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-(4-(dimethylamino)phenyl)ethanone		441	1.05
88	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-(4-(methylthio)phenyl)ethanone		444	1.46
89	1-(9-(4-chlorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-(3,4-difluorophenyl)ethanone		434	1.43

Examples 90-170**General Procedure for preparation of Examples 90 to 170:**

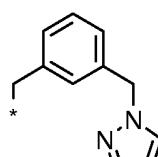
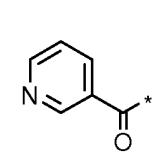
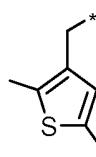
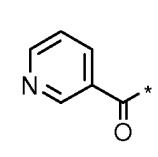
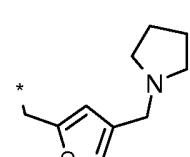
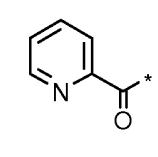
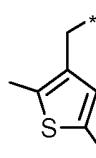
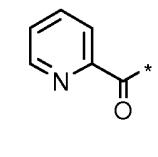
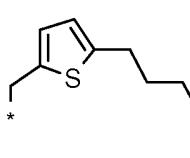
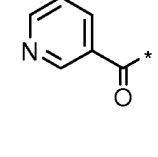
A solution of aldehyde (195 µmol) in dichloromethane (0.5 mL) was treated with a solution of the amine [prepared according to the procedure used in Preparation 2] (150 µmol) in DMSO (0.5 mL). [N.B. If any of the reactants were used as salts, triethylamine (20 µL, 150 µmol) was added]. The resulting reaction was stirred on a Vortex stirrer. The reaction was treated with a solution of sodium triacetoxyborohydride (255 µmol) in dichloromethane (0.5 mL) and acetic acid (25 µL) was added. The reaction mixture was

stirred for 24 h at room temperature. The completeness of the reaction was monitored by LCMS. Dichloromethane was evaporated and residue was purified directly by reverse phase HPLC using a gradient of acetonitrile in 0.1% aqueous TFA solution using a SunFire™ prep C18 OBD™ 5µm 19 x 50 mm column (Waters Corporation) at a flow rate of 20 mL/min to give the following compounds:

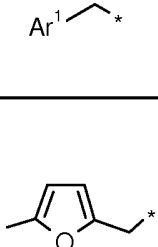
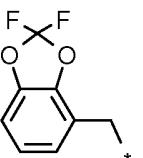
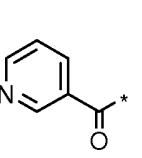
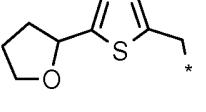
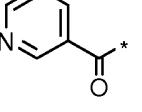
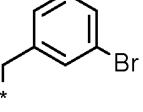
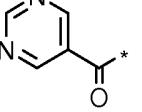
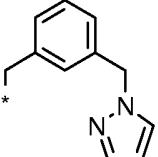
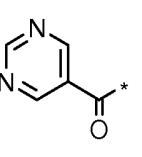


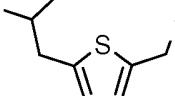
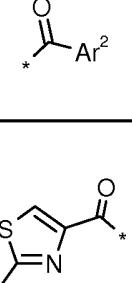
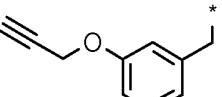
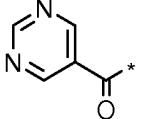
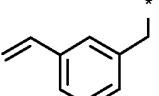
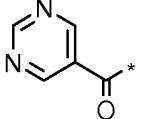
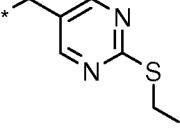
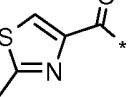
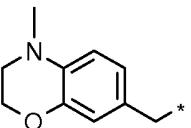
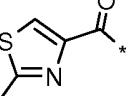
It will be understood that the compounds of Examples 90-170 are produced as trifluoroacetate salts.

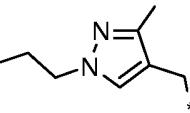
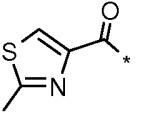
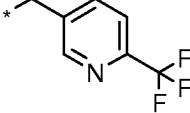
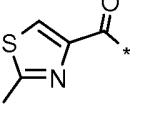
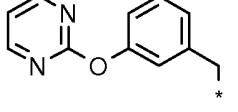
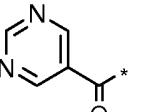
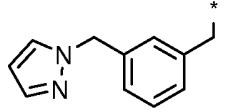
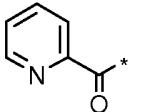
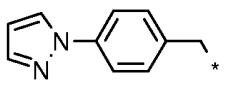
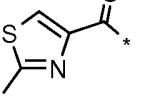
Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*$	$^* \text{---} \text{Ar}^2$	Observed (M+H) ⁺	Retention time (min)
90	(9-((5-cyclopentylthiophen-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-3-yl)methanone			425	1.30
91	pyridin-3-yl(9-(3-(pyrimidin-2-yloxy)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone			445	0.93
92	(9-(3-(1H-pyrazol-1-yl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-3-yl)methanone			417	0.99

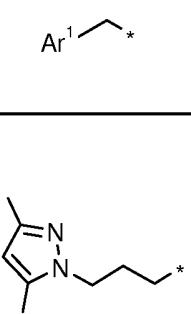
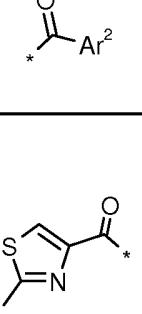
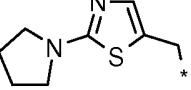
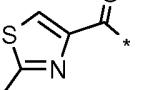
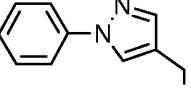
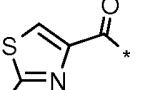
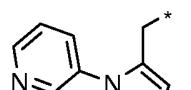
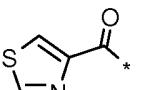
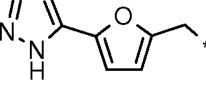
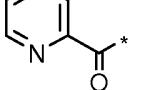
Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*$	$^* \text{---} \text{C(=O)---Ar}^2$	Observed (M+H) ⁺	Retention time (min)
93	(9-((1 <i>H</i> -pyrazol-1-yl)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-3-yl)methanone			431	0.98
94	(9-((2,5-dimethylthiophen-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-3-yl)methanone			385	1.08
95	pyridin-2-yl(9-((4-(pyrrolidin-1-ylmethyl)thiophen-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone			440	0.98
96	(9-((2,5-dimethylthiophen-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-2-yl)methanone			385	1.19
97	(9-((5-butylthiophen-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-3-yl)methanone			413	1.29

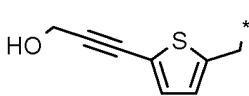
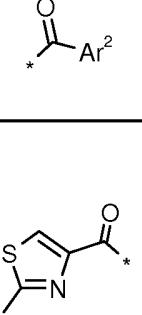
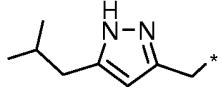
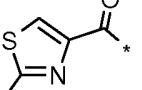
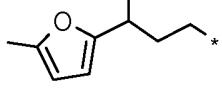
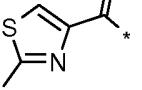
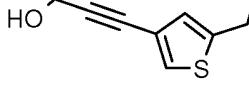
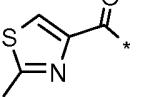
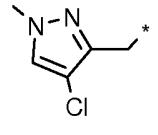
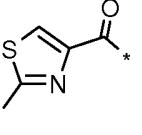
Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*\text{---} \text{Ar}^2$	${}^*\text{---} \text{C}(=\text{O})\text{---} \text{Ar}^2$	Observed (M+H) ⁺	Retention time (min)
98	(9-((1-ethyl-5-methyl-1H-pyrazol-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-2-yl)methanone			383	0.95
99	(9-(benzo[b]thiophen-2-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-2-yl)methanone			407	1.23
100	(9-((5-methylthiophen-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-2-yl)methanone			371	1.10
101	(9-((1-(2-fluorophenyl)-1H-pyrazol-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-2-yl)methanone			435	1.14
102	(9-(3-(1H-pyrazol-1-yl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-2-yl)methanone			417	1.11

Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*\text{---} \text{Ar}^2$	${}^*\text{---} \text{C}(=\text{O})\text{---} \text{Ar}^2$	Observed (M+H) ⁺	Retention time (min)
103	(9-((5-methylfuran-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-2-yl)methanone			355	1.03
104	(9-((2,2-difluorobenzo[d][1,3]dioxol-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-3-yl)methanone			431	1.10
105	pyridin-3-yl(9-((5-(tetrahydrofuran-2-yl)thiophen-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone			427	1.00
106	(9-(3-bromobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyrimidin-5-yl)methanone			430	1.12
107	(9-(3-((1H-pyrazol-1-yl)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyrimidin-5-yl)methanone			432	1.03

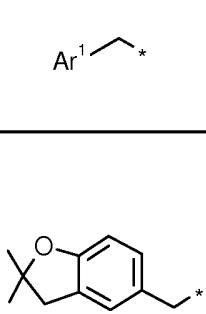
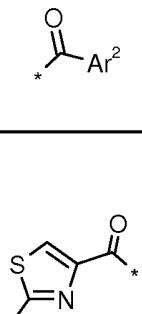
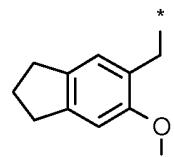
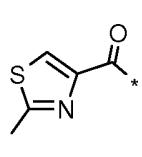
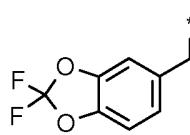
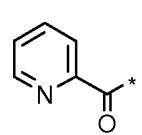
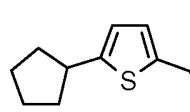
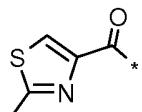
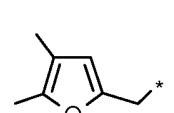
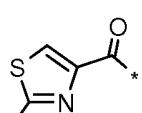
Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*\text{---} \text{Ar}^2$	${}^*\text{---} \text{C(=O)}\text{---} \text{Ar}^2$	Observed (M+H) ⁺	Retention time (min)
108	(9-((5-isobutylthiophen-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			433	1.43
109	(9-(3-(prop-2-ynyloxy)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyrimidin-5-yl)methanone			406	1.10
110	pyrimidin-5-yl(9-(3-vinylbenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone			378	1.13
111	(9-((2-(ethylthio)pyrimidin-5-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			433	1.16
112	(9-((4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			442	1.19

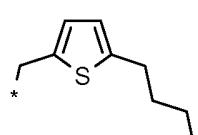
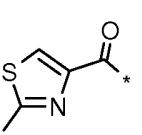
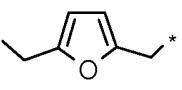
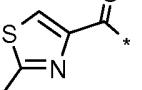
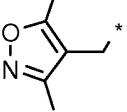
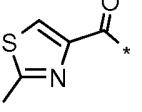
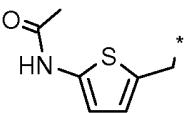
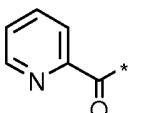
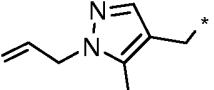
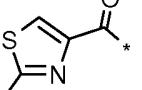
Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*\text{---} \text{Ar}^2$	${}^*\text{---} \text{C(=O)}\text{---} \text{Ar}^2$	Observed (M+H) ⁺	Retention time (min)
113	(9-((3-methyl-1-propyl-1H-pyrazol-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			417	1.08
114	(2-methylthiazol-4-yl)(9-((6-(trifluoromethyl)pyridin-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone			440	1.14
115	(9-(3-(pyrimidin-2-yloxy)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyrimidin-5-yl)methanone			446	0.97
116	(9-(3-((1H-pyrazol-1-yl)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-2-yl)methanone			431	1.10
117	(9-(4-(1H-pyrazol-1-yl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			437	1.17

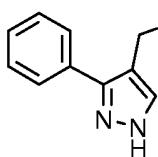
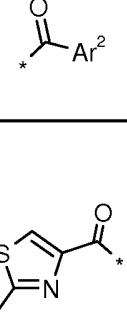
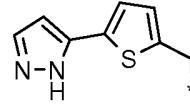
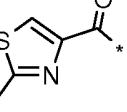
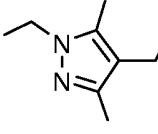
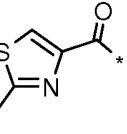
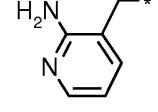
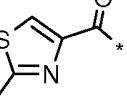
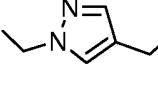
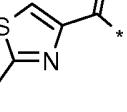
Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*\text{---} \text{Ar}^2$	Observed (M+H) ⁺	Retention time (min)	
118	(9-(3-(3,5-dimethyl-1H-pyrazol-1-yl)propyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			417	1.05
119	(2-methylthiazol-4-yl)(9-((2-(pyrrolidin-1-yl)thiazol-5-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone			447	0.91
120	(2-methylthiazol-4-yl)(9-((1-phenyl-1H-pyrazol-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone			437	1.22
121	(2-methylthiazol-4-yl)(9-((1-(pyridin-3-yl)-1H-pyrrol-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone			437	1.02
122	(9-((5-(1H-pyrazol-5-yl)furan-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-2-yl)methanone			407	0.99

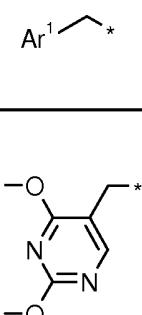
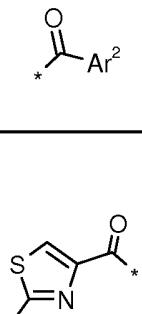
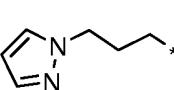
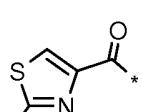
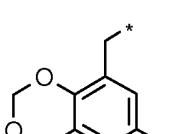
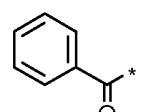
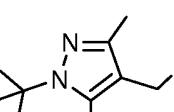
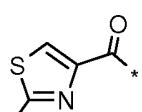
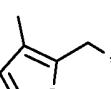
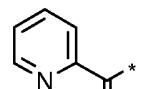
Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*$	$^* \text{---} \text{Ar}^2$	Observed (M+H) ⁺	Retention time (min)
123	(9-((5-(3-hydroxyprop-1-ynyl)thiophen-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			431	1.06
124	(9-((5-isobutyl-1H-pyrazol-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			417	1.20
125	(9-(3-(5-methylfuran-2-yl)butyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			417	1.31
126	(9-((4-(3-hydroxyprop-1-ynyl)thiophen-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			431	1.04
127	(9-((4-chloro-1-methyl-1H-pyrazol-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			409	1.04

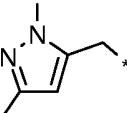
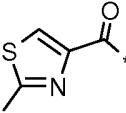
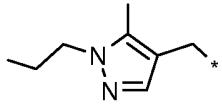
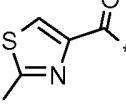
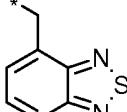
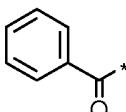
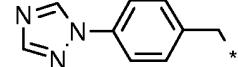
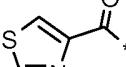
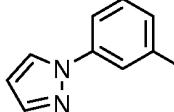
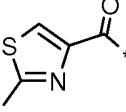
Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*\text{---}$	$^*\text{---} \text{C}(=\text{O})\text{---}\text{Ar}^2$	Observed (M+H) ⁺	Retention time (min)
128	(9-(2-(furan-2-yl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			437	1.27
129	(9-((3-methyl-1-vinyl-1H-pyrazol-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			401	1.04
130	(9-((2,2-dimethyl-2,3-dihydrobenzofuran-7-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			441	1.35
131	pyrimidin-5-yl(9-(3-(trifluoromethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone			420	1.17
132	(2-methylthiazol-4-yl)(9-((1-(thiazol-2-yl)-1H-pyrrol-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone			443	1.18

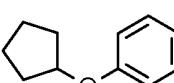
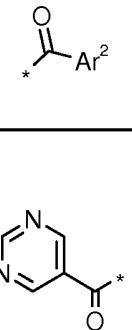
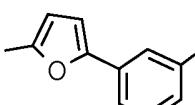
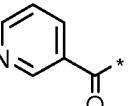
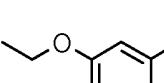
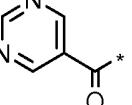
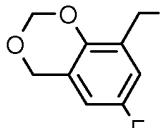
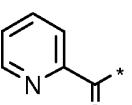
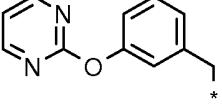
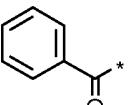
Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*\text{---} \text{Ar}^2$	Observed (M+H) ⁺	Retention time (min)	
133	(9-((2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			441	1.30
134	(9-((6-methoxy-2,3-dihydro-1H-inden-5-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			441	1.36
135	(9-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-2-yl)methanone			431	1.25
136	(9-((5-cyclopentylthiophen-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			445	1.48
137	(9-((4,5-dimethylfuran-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			389	1.21

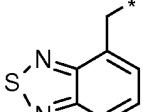
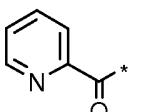
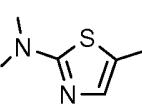
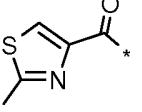
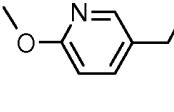
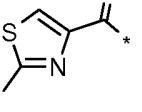
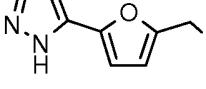
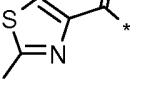
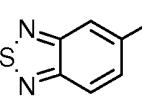
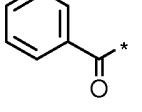
Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*\text{---} \text{Ar}^2$	${}^*\text{---} \text{C(=O)}\text{---} \text{Ar}^2$	Observed (M+H) ⁺	Retention time (min)
138	(9-((5-butylthiophen-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			433	1.47
139	(9-((5-ethylfuran-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			389	1.20
140	(9-((3,5-dimethylisoxazol-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			390	0.99
141	N-(5-((4-picolinoyl-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)thiophen-2-yl)acetamide			414	0.94
142	(9-((1-allyl-5-methyl-1H-pyrazol-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			415	1.06

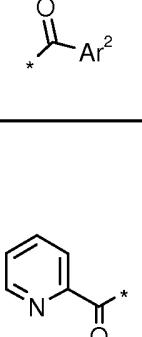
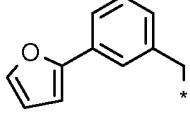
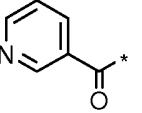
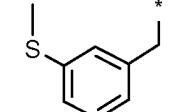
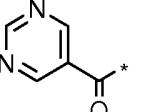
Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*$	$^* \text{---} \text{C(=O) --- Ar}^2$	Observed (M+H) ⁺	Retention time (min)
143	(2-methylthiazol-4-yl)(9-((3-phenyl-1H-pyrazol-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone			437	1.12
144	(9-((5-(1H-pyrazol-5-yl)thiophen-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			443	1.09
145	(9-((1-ethyl-3,5-dimethyl-1H-pyrazol-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			417	1.03
146	(9-((2-aminopyridin-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			387	0.77
147	(9-((1-ethyl-1H-pyrazol-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			389	0.97

Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*\text{---} \text{Ar}^2$	${}^*\text{---} \text{C(=O)}\text{---} \text{Ar}^2$	Observed (M+H) ⁺	Retention time (min)
148	(9-((2,4-dimethoxypyrimidin-5-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			433	1.04
149	(9-(3-(1H-pyrazol-1-yl)propyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			389	0.99
150	(9-((6-fluoro-4H-benzo[d][1,3]dioxin-8-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(phenyl)methanone			426	1.22
151	(9-((1-tert-butyl-3,5-dimethyl-1H-pyrazol-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			445	1.18
152	(9-((3-methylthiophen-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-2-yl)methanone			371	1.07

Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*$	$^* \text{---} \text{C(=O)} \text{---} \text{Ar}^2$	Observed (M+H) ⁺	Retention time (min)
153	(9-((1,3-dimethyl-1H-pyrazol-5-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			389	0.97
154	(9-((5-methyl-1-propyl-1H-pyrazol-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			417	1.10
155	(9-(benzo[c][1,2,5]thiadiazol-4-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(phenyl)methanone			408	1.19
156	(9-(4-(1H-1,2,4-triazol-1-yl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			438	1.03
157	(9-(3-(1H-pyrazol-1-yl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			437	1.16

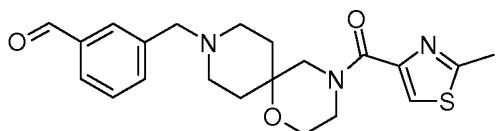
Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*\text{---} \text{Ar}^2$	${}^*\text{---} \text{C}(=\text{O})\text{---} \text{Ar}^2$	Observed (M+H) ⁺	Retention time (min)
158	(9-(3-(cyclopentyloxy)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyrimidin-5-yl)methanone			436	1.35
159	(9-(3-(5-methylfuran-2-yl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-3-yl)methanone			431	1.26
160	(9-(3-ethoxybenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyrimidin-5-yl)methanone			396	1.12
161	(9-((6-fluoro-4H-benzo[d][1,3]dioxin-8-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-2-yl)methanone			427	1.09
162	phenyl(9-(3-(pyrimidin-2-yloxy)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone			444	1.18

Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*\text{---} \text{Ar}^2$	${}^*\text{---} \text{C(=O)}\text{---} \text{Ar}^2$	Observed (M+H) ⁺	Retention time (min)
163	(9-(benzo[c][1,2,5]thiadiazol-4-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-2-yl)methanone			409	1.05
164	(9-((2-(dimethylamino)thiazol-5-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			421	0.87
165	(9-((6-methoxypyridin-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			402	1.04
166	(9-((5-(1H-pyrazol-5-yl)furan-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone			427	1.06
167	(9-(benzo[c][1,2,5]thiadiazol-5-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(phenyl)methanone			408	1.18

Ex. No.	NAME	$\text{Ar}^1 \text{---} ^*\text{---} \text{Ar}^2$	${}^*\text{---} \text{C(=O)}\text{---} \text{Ar}^2$	Observed (M+H) ⁺	Retention time (min)
168	(9-((4-((dimethylamino)methyl)thiophen-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-2-yl)methanone			414	0.75
169	(9-(3-(furan-2-yl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyridin-3-yl)methanone			417	1.17
170	(9-(3-(methylthio)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(pyrimidin-5-yl)methanone			398	1.12

Examples 171-202

a) 3-((4-(2-Methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)benzaldehyde



A solution of (2-methylthiazol-4-yl)(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone trifluoroacetate [Preparation 3] (0.408 g), 3-(bromomethyl)benzaldehyde (0.205 g) and triethylamine (0.36 mL) in acetonitrile (10 mL) was stirred at room temperature overnight. The solution was concentrated *in vacuo* and the residue partitioned between ethyl acetate and saturated sodium bicarbonate. The organic phase was washed twice with water, once with brine, then dried over anhydrous magnesium sulphate and purified by flash

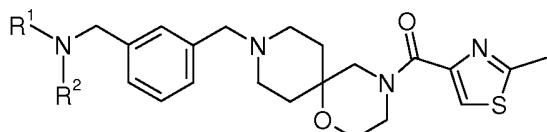
chromatography on silica eluted with 5% methanol in dichloromethane to afford the subtitled compound as a yellow gum. Yield 0.325 g.

m/z 400 (M+H)⁺ (APCI).

¹H NMR (400 MHz, D₆-DMSO, 90°C) δ 10.01 (s, 1H), 7.85 (d, J = 0.8 Hz, 1H), 7.80 (s, 1H), 7.76 (d, J = 7.4 Hz, 1H), 7.61 (d, J = 7.4 Hz, 1H), 7.52 (t, J = 7.4 Hz, 1H), 3.71 - 3.46 (m, 8H), 2.68 (s, 3H), 2.44 - 2.29 (m, 4H), 1.78 - 1.65 (m, 2H), 1.61 - 1.46 (m, 2H).

b) General procedure for preparation of Examples 171 to 202:

A suitable amine (0.05 mmol) was treated with solutions of 3-((4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)benzaldehyde [Examples 171-202, step a] (19 mg) and acetic acid (6 mg) in methanol (0.4 mL) and shaken until dissolved. The solutions were then treated with solutions of sodium triacetoxyborohydride (32 mg) in ethanol (0.4 mL) and stirred overnight. They were then applied to a pre-washed bed of Tosic-65 resin and washed with methanol. The products were eluted with methanolic ammonia solution and allowed to evaporate. The residues were taken up in DMSO (0.4 mL) and purified by reverse phase HPLC using a gradient of acetonitrile in 0.1% aqueous TFA solution using a SunFire™ prep C18 OBD™ 5μm 19 x 50mm column (Waters Corporation) at a flow rate of 20 mL/min to give the following compounds:

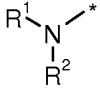
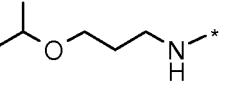
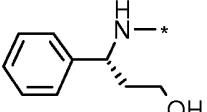
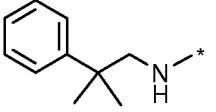
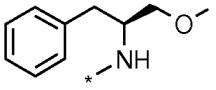
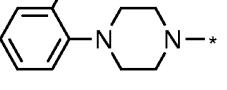
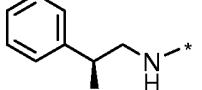


It will be understood that the compounds of Examples 171-202 are produced as trifluoroacetate salts.

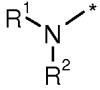
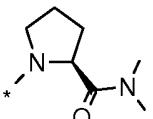
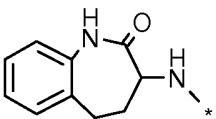
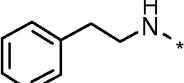
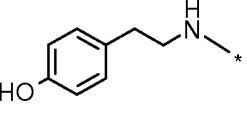
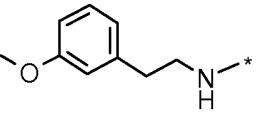
Ex. No.	Name	R ¹ N R ²	Observed (M+H) ⁺	Retention time (min)
171	(9-((3-hydroxy-2,2-dimethylpropylamino)methyl)b enzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		486	0.94

Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
172	(9-(3-((2-methoxyethylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		458	0.90
173	(R)-(9-(3-((2-hydroxy-1-phenylethylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		520	1.02
174	(9-(3-((3-chlorobenzylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		524	1.11
175	(2-methylthiazol-4-yl)(9-(3-((2-phenoxyethylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone		520	1.09
176	(9-(3-((3-chloro-4-methylbenzylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		538	1.18
177	(9-(3-((2,6-dichlorobenzylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		558	1.08

Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
178	(S)-(9-(3-((1-hydroxy-3-phenylpropan-2-ylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		534	1.07
179	(R)-1-((4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)benzyl)pyrrolidine-2-carboxamide		497	0.84
180	N-methyl-N-(1-(3-((4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)benzyl)pyrrolidin-3-yl)acetamide		525	0.91
181	(9-((2-methoxyethyl)(methyl)amino)ethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		472	0.90
182	N-ethyl-2-((4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)benzylamino)acetamide		485	0.90

Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
183	(9-(3-((3-isopropoxypropylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		500	1.03
184	(R)-(9-(3-((3-hydroxy-1-phenylpropylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		534	1.03
185	(9-(3-((2-methyl-2-phenylpropylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		532	1.15
186	(S)-(9-(3-((1-methoxy-3-phenylpropan-2-ylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		548	1.14
187	(2-methylthiazol-4-yl)(9-(3-((4-o-tolylpiperazin-1-yl)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone		559	1.19
188	(S)-(9-(3-((2-hydroxy-2-phenylethylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		520	1.03

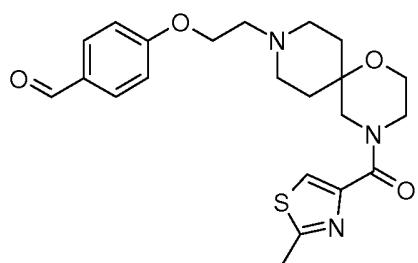
Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
189	(9-(3-((1-(4-chlorophenyl)ethylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		538	1.17
190	(9-(3-((3-chloro-2-methylbenzylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		538	1.15
191	(9-(3-((2-chloro-6-methylbenzylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		538	1.10
192	(9-(3-(((1 <i>R</i> ,2 <i>R</i>)-2-hydroxy-2,3-dihydro-1 <i>H</i> -inden-1-ylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		532	1.01
193	(9-(3-((2-(3,5-dimethylisoxazol-4-yl)ethylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		523	1.00

Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
194	(S)-N,N-dimethyl-1-(3-((4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)benzyl)pyrrolidine-2-carboxamide		525	0.86
195	3-((4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)benzylamino)-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one		559	1.03
196	(2-methylthiazol-4-yl)(9-((phenethylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone		504	1.08
197	(9-((4-hydroxyphenethylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		520	0.99
198	(9-((3-methoxyphenethylamino)methyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		534	1.11

Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
199	(9-(3-((2-fluorophenethylamino)methyl)b enzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		522	1.09
200	(9-(3-((3-chlorophenethylamino)methyl)b enzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		538	1.17
201	(9-(3-((4-chlorophenethylamino)methyl)b enzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		538	1.19
202	(9-(3-((3-fluorophenethylamino)methyl)b enzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		522	1.11

Examples 203-228

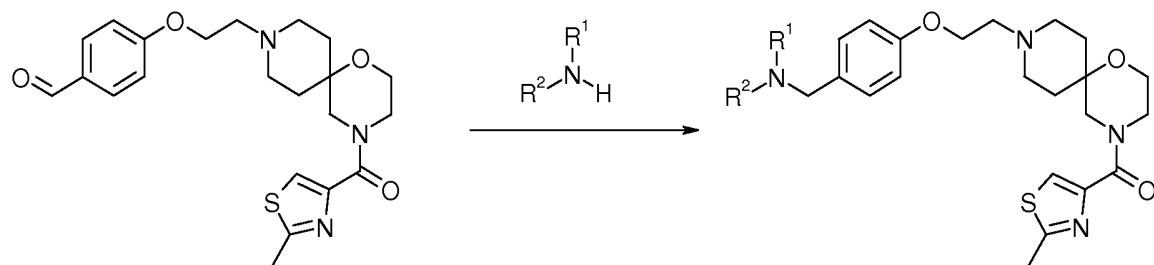
a) 4-(2-(4-(2-Methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)benzaldehyde



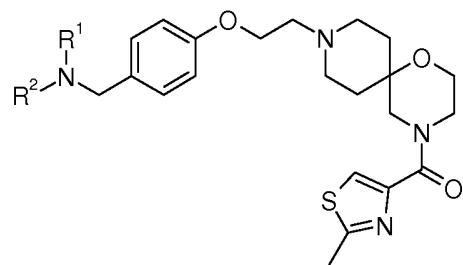
Manganese dioxide (0.65 g) was added to a solution of (9-(2-(4-(hydroxymethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone [Example 12] (0.32 g) in DCM (20 mL) and the resulting black suspension was heated under reflux for 1 h. After cooling, the reaction mixture was passed through a pad of Celite. The pad was washed with DCM (2 x 30 mL) and the combined filtrate and washings evaporated *in vacuo* to give the subtitled compound as a gum. Yield 0.25 g. m/z 430 (M+H)⁺ (APCI).

¹H NMR (300 MHz, D₆-DMSO) δ 9.86 (s, 1H), 7.96 (s, 1H), 7.88-7.83 (m, 2H), 7.13 (d, J = 8.5 Hz, 2H), 4.26-4.11 (m, 2H), 3.77-3.46 (m, 6H), 2.78 - 2.65 (m, 5H), 2.48-2.34 (m, 4H), 1.76-1.36 (m, 4H).

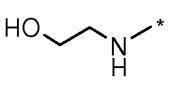
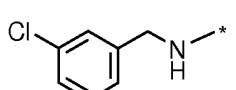
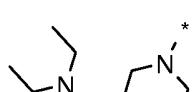
b) General procedure for preparation of Examples 203-228:

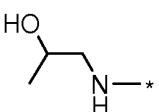
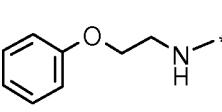
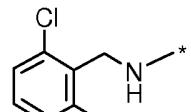
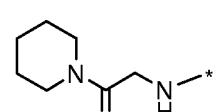
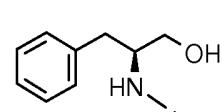
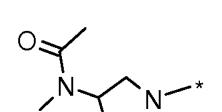


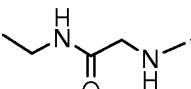
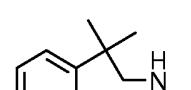
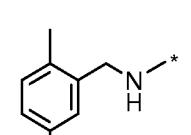
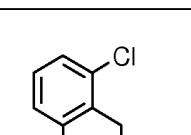
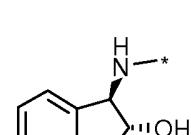
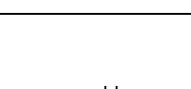
The amine (0.025 mmol) was treated with solutions of 4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)benzaldehyde [Example 201, step a] (4.5 mg) and acetic acid (3 mg) in methanol (0.4 mL) and shaken until dissolved. The resulting mixture was then treated with a solution of sodium triacetoxyborohydride (16 mg) in methanol (0.2 mL) and allowed to stand over the weekend. The solution was then treated with a solution of sodium triacetoxyborohydride (16 mg) in ethanol (0.2 mL) and allowed to stand overnight. The reaction mixture was applied to a pre-washed bed of Tosic-65 resin and washed with methanol. The product was eluted with methanolic ammonia solution and allowed to evaporate. The residue was taken up in DMSO (0.4 mL) and purified by reverse phase HPLC using a gradient of acetonitrile in 0.1% aqueous TFA solution using a SunFire™ prep C18 OBD™ 5μm 19 x 50mm column (Waters Corporation) at a flow rate of 20 mL/min.

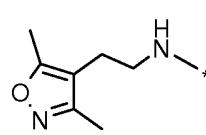
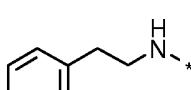
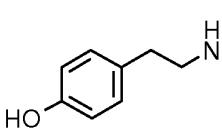
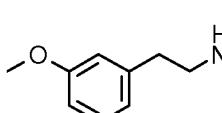
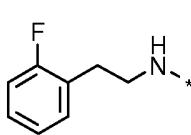
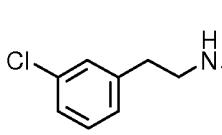


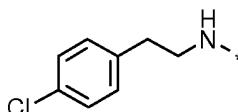
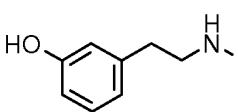
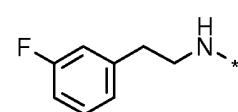
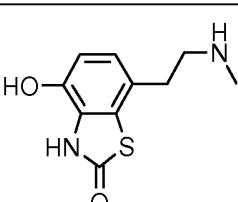
It will be understood that the compounds of Examples 203-228 are produced as trifluoroacetate salts.

Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
203	(9-(2-(4-((3-hydroxy-2,2-dimethylpropylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		516	0.95
204	(9-(2-(4-((2-hydroxyethylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		474	0.86
205	(9-(2-(4-((3-chlorobenzylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		554	1.12
206	N,N-diethyl-1-(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)benzyl)piperidine-3-carboxamide		597	1.10

Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
207	(9-(2-(4-((2-hydroxypropylamino)methyl)phenoxyethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		488	0.91
208	(2-methylthiazol-4-yl)(9-(2-(4-((2-phenoxyethylamino)methyl)phenoxyethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone		550	1.11
209	(9-(2-(4-((2,6-dichlorobenzylamino)methyl)phenoxyethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		588	1.11
210	2-(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)benzylamino)-1-(piperidin-1-yl)ethanone		555	1.01
211	(S)-(9-(2-(4-((1-hydroxy-3-phenylpropan-2-ylamino)methyl)phenoxyethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		564	1.09
212	N-methyl-N-(1-(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)benzyl)pyrrolidin-3-yl)acetamide		555	0.93

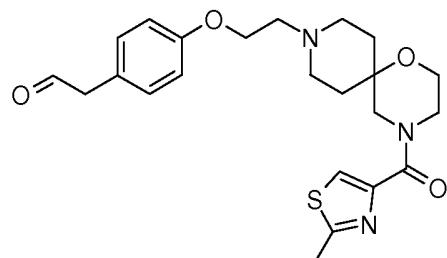
Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
213	N-ethyl-2-(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)benzylamino)acetamide		515	0.92
214	(9-(2-(4-((2-methyl-2-phenylpropylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		562	1.15
215	(9-(2-(4-((5-chloro-2-methylbenzylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		568	1.17
216	(9-(2-(4-((2-chloro-6-methylbenzylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		568	1.13
217	(9-(2-(4-(((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-ylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		562	1.03
218	(2-methylthiazol-4-yl)(9-(2-(4-((oxetan-3-ylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone		486	1.02

Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
219	(9-(2-(4-((2-(3,5-dimethylisoxazol-4-yl)ethylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		553	1.01
220	(2-methylthiazol-4-yl)(9-(2-(4-((phenethylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone		534	1.11
221	(9-(2-(4-((4-hydroxyphenethylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		550	1.02
222	(9-(2-(4-((3-methoxyphenethylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		564	1.13
223	(9-(2-(4-((2-fluorophenethylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		552	1.10
224	(9-(2-(4-((3-chlorophenethylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		568	1.19

Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
225	(9-(2-(4-((4-chlorophenethylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		568	1.20
226	9-(2-(4-((3-hydroxyphenethylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		550	0.99
227	(9-(2-(4-((3-fluorophenethylamino)methyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		552	1.13
228	4-hydroxy-7-(2-(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)benzylamino)ethyl)benzo[d]thiazol-2(3H)-one		624	1.08

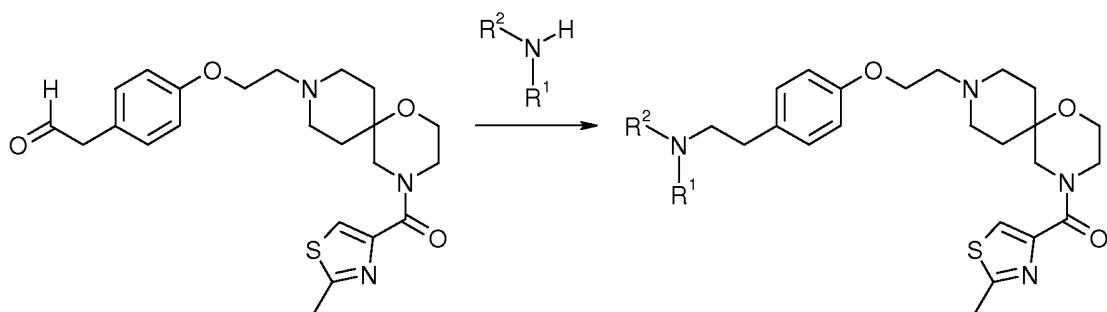
Example 229-254

a) 2-(4-(2-(4-(2-Methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)phenyl)acetaldehyde

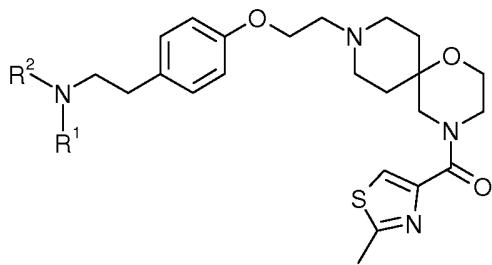


Trifluoroacetic acid (0.04 mL) was added to a solution of (9-(2-(4-(2-hydroxyethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone [Example 13] (0.22 g) in DCM (3 mL) and the resulting mixture was stirred for 5 min. Dess-Martin periodinane (0.31 g) was then added and the resulting mixture stirred for 5 min. A mixture of saturated sodium thiosulphate solution (0.5 mL), sodium bicarbonate solution (0.5 mL) and ether (5 mL) was then added and the resulting mixture stirred for 5 min. The organic layer was separated and washed with sodium bicarbonate solution (1 mL) and water (1 mL), then dried over sodium sulphate, filtered and evaporated *in vacuo* to give the subtitled compound as a clear oil which was used immediately. Yield 0.19 g.

b) General procedure for preparation of Examples 229-254:

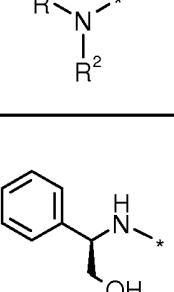
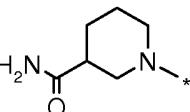
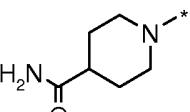
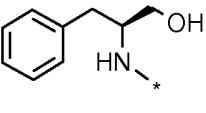
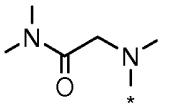
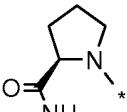


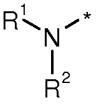
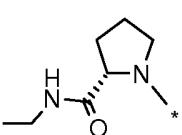
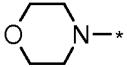
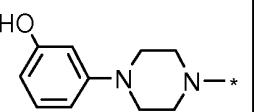
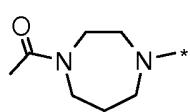
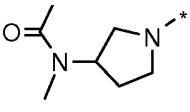
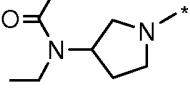
The amine (0.025 mmol) was treated with solutions of 2-(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)phenyl)acetaldehyde [Example 227, step a] (4.5 mg) and acetic acid (3 mg) in methanol (0.4 mL) and shaken until dissolved. The resulting solution was then treated with a solution of sodium triacetoxyborohydride (16 mg) in methanol (0.2 mL) and allowed to stand over the weekend. The reaction mixture was then treated with a solution of sodium triacetoxyborohydride (16 mg) in ethanol (0.2 mL) and allowed to stand overnight. The reaction mixture was applied to a pre-washed bed of Toscic-65 resin and washed with methanol. The product was eluted with methanolic ammonia solution and allowed to evaporate. The residue was taken up in DMSO (0.4 mL) and purified by reverse phase HPLC using a gradient of acetonitrile in 0.1% aqueous TFA solution using a SunFire™ prep C18 OBD™ 5µm 19 x 50mm column (Waters Corporation) at a flow rate of 20 mL/min.



It will be understood that the compounds of Examples 229-254 are produced as trifluoroacetate salts.

Ex. No.	Name	$\text{R}^1-\overset{*}{\text{N}}-\text{R}^2$	Observed (M+H) ⁺	Retention time (min)
229	(9-(2-(4-(2-(dimethylamino)ethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone	$\text{N}^{\cdot*}$	472	0.91
230	(2-methylthiazol-4-yl)(9-(2-(4-(2-(piperidin-1-yl)ethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone	$\text{C}_4\text{H}_9\text{N}^{\cdot*}$	512	0.98
231	(9-(2-(4-(2-(3-hydroxy-2,2-dimethylpropylamino)ethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone	$\text{HO}(\text{CH}_2)_2\text{N}^{\cdot*}\text{H}$	530	0.99
232	2-(methyl(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)phenethyl)amino)acetic acid	$\text{CH}_3\text{CH}(\text{OH})\text{C}(=\text{O})\text{N}^{\cdot*}\text{H}$	516	0.91

Ex. No.	Name	$\text{R}^1\text{N}^*\text{---}\text{R}^2$	Observed (M+H) ⁺	Retention time (min)
233	(R)-(9-(2-(4-(2-(2-hydroxy-1-phenylethylamino)ethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		564	1.08
234	1-(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)phenethyl)piperidine-3-carboxamide		555	0.92
235	1-(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)phenethyl)piperidine-4-carboxamide		555	0.93
236	(S)-(9-(2-(4-(2-(1-hydroxy-3-phenylpropan-2-ylamino)ethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		578	1.11
237	N,N-dimethyl-2-(methyl(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)phenethyl)amino)acetamide		543	0.94
238	(R)-1-(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)phenethyl)pyrrolidine-2-carboxamide		541	0.92

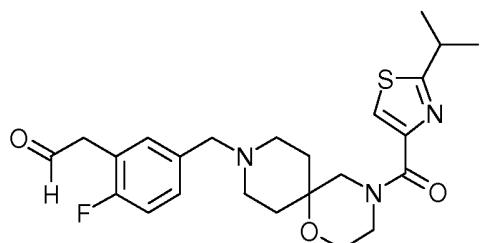
Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
239	(S)-N-ethyl-1-(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)phenethyl)pyrrolidine-2-carboxamide		569	1.00
240	(2-methylthiazol-4-yl)(9-(2-(4-(2-morpholinoethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone		514	0.92
241	(9-(2-(4-(2-(4-(3-hydroxyphenyl)piperazin-1-yl)ethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		605	1.06
242	1-(4-(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)phenethyl)-1,4-diazepan-1-yl)ethanone		569	0.94
243	N-methyl-N-(1-(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)phenethyl)pyrrolidin-3-yl)acetamide		569	1.01
244	N-ethyl-N-(1-(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)phenethyl)pyrrolidin-3-yl)acetamide		583	1.02

Ex. No.	Name	$\begin{array}{c} \text{R}^1 \\ \\ \text{N}^{*} \\ \\ \text{R}^2 \end{array}$	Observed (M+H) ⁺	Retention time (min)
245	(R)-(9-(2-(4-(2-(methoxymethyl)pyrrolidin-1-yl)ethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		542	1.00
246	(R)-(9-(2-(4-(2-(3-hydroxy-1-phenylpropylamino)ethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		578	1.08
247	1-isopropyl-4-(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)phenethyl)piperazin-2-one		569	1.00
248	1-(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)phenethyl)-1,4-diazepan-5-one		541	0.89
249	(S)-(9-(2-(4-(2-(hydroxymethyl)pyrrolidin-1-yl)ethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		528	0.93
250	2-(methyl(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)phenethyl)amino)acetamide		515	0.90

Ex. No.	Name	$\text{R}^1\text{N}^*\text{R}^2$	Observed (M+H) ⁺	Retention time (min)
251	(2-methylthiazol-4-yl)(9-(2-(4-(2-oxetan-3-ylamino)ethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)methanone		500	0.9
252	(S)-N,N-dimethyl-1-(4-(2-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)phenethyl)pyrrolidine-2-carboxamide		569	0.97
253	(9-(2-(4-(2-(methyl(phenethyl)amino)ethyl)phenoxy)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-methylthiazol-4-yl)methanone		562	1.14
254	4-hydroxy-7-(2-(4-(2-(4-(2-methylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)ethoxy)phenethylamino)ethyl)benzo[d]thiazol-2(3H)-one		638	1.09

Example 255-273

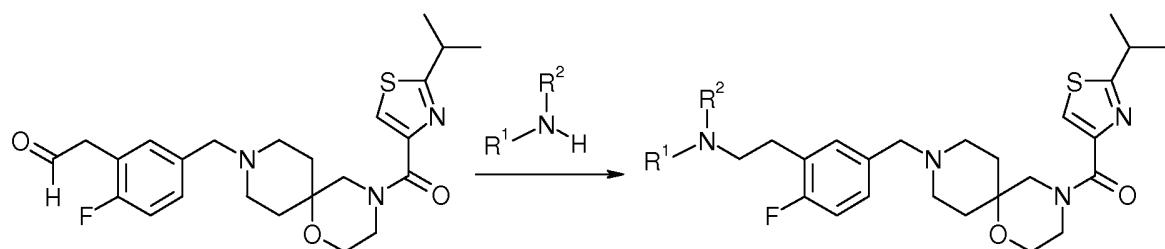
a). 2-Isopropyl-thiazole-4-carboxylic acid ethyl-(2-{1-[4-fluoro-3-(2-oxo-ethyl)-benzyl]-piperidin-4-yloxy}-ethyl)-amide



Trifluoroacetic acid (0.178 mL, 2.31 mmol) was added to a solution of (9-(4-fluoro-3-(2-hydroxyethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone (1.066 g, 2.31 mmol) in DCM (20 mL) at 0°C and the resulting mixture stirred for 5min. Dess-MartinPeriodinane (1.470 g, 3.47 mmol) was then added and the mixture stirred at RT until consumption of the alcohol by LC-MS (45min). saturated sodium thiosulphate solution (5mL), saturated sodium bicarbonate solution (5mL) and ethyl acetate (20mL) was then added and the mixture stirred for 10mIn. The aqueous was separated and extracted with ethyl acetate (20mL). The combined organics were washed with brine. AcOH (~0.1mL) was then added and the mixture dried over sodium sulphate, filtered and evaporated. The crude aldehyde, still a bit wet so weight slightly high, was dissolved in methanol (2mL) and used immediately in the following experiments.

m/z 460 (M+H)+ (APCI)

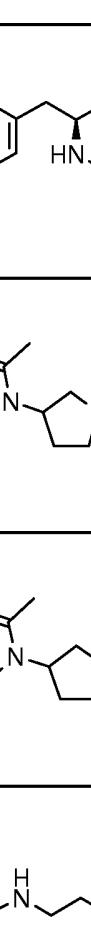
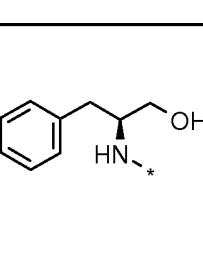
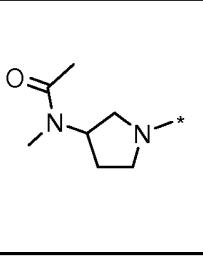
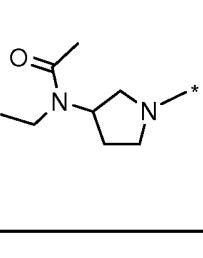
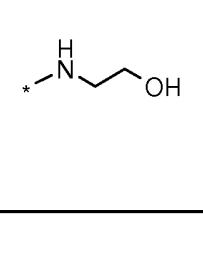
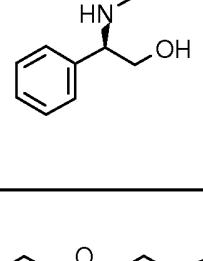
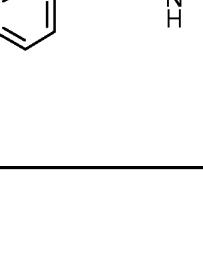
b) General reductive amination procedure for Examples 255-273

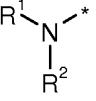
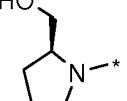
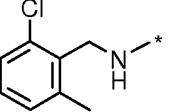
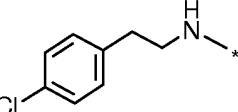
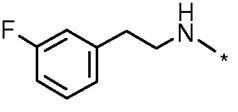
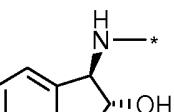
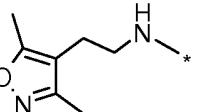


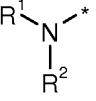
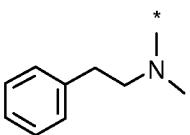
Amine (0.05mmol) was treated with solutions of 2-(2-fluoro-5-((4-((2-isopropylthiazol-4-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenyl)acetaldehyde (23mg) and acetic acid (6mg) in methanol (0.4ml) and shaken until dissolved. The solutions were then treated with solutions of sodium triacetoxyborohydride (32mg) in ethanol (0.4ml) and stirred overnight. They were then applied to a pre-washed bed of tosic 65 resin and washed with methanol. The products were eluted with methanolic ammonia solution and allowed to evaporate. The residues were taken up in DMSO (0.4ml) and purified by reverse phase HPLC using a gradient of acetonitrile in 0.1% aqueous TFA solution using a SunFire™ prep C18 OBD™ 5µm 19 x 50mm column (Waters Corporation) at a flow rate of 20 mL/min.

It will be understood that the compounds of Examples 255-273 are produced as trifluoroacetate salts.

Ex. No.	Name	$\text{R}^1\text{N}(\text{R}^2)^*$	Observed (M+H) ⁺	Retention time (min)
255	(<i>R</i>)-(9-(4-fluoro-3-(2-(3-hydroxy-1-phenylpropylamino)ethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone		594	1.29
256	(9-(4-fluoro-3-(2-(4-(piperidine-1-carbonyl)piperidin-1-yl)ethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone		639	1.29
257	(9-(4-fluoro-3-(2-(4-otolylpiperazin-1-yl)ethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone		619	1.45
258	(9-(3-(2-(2-chlorobenzyl)(methyl)amino)ethyl)-4-fluorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone		598	1.32
259	(9-(3-(2-(2-chlorobenzylamino)ethyl)-4-fluorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone		584	1.33
260	(<i>R</i>)-(9-(4-fluoro-3-(2-(2-hydroxy-2-phenylethylamino)ethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-		580	1.29

Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
	yl)methanone			
261	(S)-(9-(4-fluoro-3-(2-(1-hydroxy-3-phenylpropylamino)ethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone		594	1.33
262	<i>N</i> -(1-(2-fluoro-5-((4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethyl)pyrrolidin-3-yl)- <i>N</i> -methylacetamide		585	1.15
263	<i>N</i> -ethyl- <i>N</i> -(1-(2-fluoro-5-((4-(2-isopropylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethyl)pyrrolidin-3-yl)acetamide		599	1.21
264	(9-(4-fluoro-3-(2-(2-hydroxyethylamino)ethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone		504	0.93
265	(R)-(9-(4-fluoro-3-(2-(2-hydroxy-1-phenylethylamino)ethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone		580	1.28
266	(9-(4-fluoro-3-(2-(2-phenoxyethylamino)ethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone		580	1.37

Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
267	(S)-(9-(4-fluoro-3-(2-(2-hydroxymethyl)pyrrolidin-1-yl)ethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone		544	1.14
268	(9-(3-(2-(2-chloro-6-methylbenzylamino)ethyl)-4-fluorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone		598	1.37
269	(9-(3-(2-(4-chlorophenethylamino)ethyl)-4-fluorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone		598	1.46
270	(9-(4-fluoro-3-(2-(3-fluorophenethylamino)ethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone		582	1.39
271	(9-(4-fluoro-3-(2-((1 <i>R</i> ,2 <i>R</i>)-2-hydroxy-2,3-dihydro-1 <i>H</i> -inden-1-ylamino)ethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone		592	1.26
272	(9-(3-(2-(3,5-dimethylisoxazol-4-yl)ethylamino)ethyl)-4-fluorobenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone		583	1.23

Ex. No.	Name		Observed (M+H) ⁺	Retention time (min)
273	(9-(4-fluoro-3-(2-(methyl(phenethyl)amino)ethyl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)(2-isopropylthiazol-4-yl)methanone		578	1.38

The following experimental procedures were used to determine the muscarinic activity of the compounds from the invention:

Assay 1:

Muscarinic 3 receptor calcium mobilisation assay, Spot Test @ 10µM

The activity (% inhibition of fluorescence) of compounds on the M₃ receptor is determined by hrM3 mediated intracellular calcium mobilisation in Fluo-4 loaded CHO (Chinese hamster ovary) cells expressing the human muscarinic acetylcholine M₃ receptor (M₃-ACh) using a FLIPR (fluorescence imaging plate reader).

CHO M₃-ACh cells (Euroscreen ES-212-C) in Hams F12 nutrient mixture containing glutamine (Sigma H6658) supplemented with 10% Foetal Calf Serum (PAA), 1% Non-essential Amino Acid Solution (Sigma), 0.5mg/ml geneticin (Invitrogen), are distributed into the wells of a 384 well plate at a density of 2.0 x 10⁵ cells/ml. The cells are incubated at 37°C at 95%/5 % (v/v) air/CO₂ in 95% relative humidity for 18hrs. The Molecular Devices Calcium assay kit (R8033-BLA4) is used to determine the calcium mobilisation response. Briefly, the culture medium is removed and the cells loaded with fluorescent dye for 60 minutes at 37°C, according to the manufacturers instructions. Candidate compounds are then added to the cells at a final concentration of 10 µM in Dimethyl sulfoxide and incubated for 15 minutes at 37°C. The cell plates are then transferred to the FLIPR; an EC100 of Acetyl-β-methylcholine bromide (Sigma A2126) is added to the cells and fluorescence measured. The compound activity at 10 µM, defined as % inhibition of fluorescent response, is determined.

Assay 2:

Muscarinic 3 receptor binding assay, Spot Test @ 1 and 10µM

The activity (% inhibition specific binding) of compounds on the M₃ receptor is determined by competition binding of [³H]N-methyl scopolamine (NMS) to CHO-K1 (Chinese Hamster Ovary) cell membranes expressing the human muscarinic acetylcholine M₃ receptor (M₃-ACh) in a scintillation proximity assay (SPA) format.

SPA beads are precoated with membranes and then incubated at 2mg of beads per well with 1 or 10 µM compound of the invention, [³H]NMS at 0.1 nM, quarter Kd (experimentally determined dissociation constant) and assay buffer (20 mM HEPES pH 7.4 containing 5 mM MgCl₂ and 0.1% (w/v) bovine serum albumin). The assay is conducted in a final volume of 200 µL, in the presence of 1% (v/v) dimethyl sulphoxide (DMSO). Total binding of [³H]NMS is determined in the absence of competing compound and non-specific binding of [³H]NMS is determined in the presence of 1 µM atropine. The plates are incubated for 16 hours at room temperature and then read on Wallac Microbeta™ using a normalised ³H protocol. The compound activity at 1 or 10 µM, defined as % inhibition specific [³H]-NMS binding, is determined.

Assay 3

Muscarinic 3 receptor binding assay pIC₅₀

The affinity (pIC₅₀) of compounds binding to the M₃ receptor is determined by competition binding of [³H]N-methyl scopolamine (NMS) to CHO-K1 (Chinese Hamster Ovary) cell membranes expressing the human muscarinic acetylcholine M₃ receptor (M₃-ACh) in a scintillation proximity assay (SPA) format.

SPA beads are precoated with membranes and then incubated at 2mg of beads per well with serial dilutions of compounds of the invention, [³H]NMS at 0.1nM, quarter Kd (experimentally determined dissociation constant) and assay buffer (20 mM HEPES pH 7.4 containing 5 mM MgCl₂ and 0.1% (w/v) bovine serum albumin). The assay is conducted in a final volume of 200 µL, in the presence of 1% (v/v) dimethyl sulphoxide (DMSO). Total binding of [³H]NMS is determined in the absence of competing compound and non-specific binding of [³H]NMS is determined in the presence of 1 µM atropine. The plates are incubated for 16 hours at room temperature and then read on Wallac Microbeta™ using a normalised ³H protocol. The pIC₅₀, defined as the negative logarithm of the molar concentration of compound required for 50% reduction in specific [³H]-NMS binding, is determined.

Assay 4**Methacholine Induced Bronchoconstriction in vivo**

Dunkin-Hartley guinea-pigs (300 – 600g) are supplied by a designated breeding establishment. Animals are dosed with test compound or vehicle either by inhalation in conscious guinea-pigs or by intratracheal instillation (0.5ml/kg) under recoverable gaseous anaesthesia (5% halothane). Animals are allowed to recover from the anaesthesia prior to the measurement of bronchoconstriction. Up to 48 hours post-dosing guinea-pigs are terminally anaesthetized with sodium pentobarbitone (60 mg/kg), the trachea cannulated for artificial ventilation and the jugular vein is cannulated for intravenous administration of methacholine. The guinea-pigs are ventilated using a constant volume respiratory pump (Harvard Rodent Ventilator model 683) at a rate of 60 breath/min and a tidal volume of 5 ml/kg during surgical preparation. Lung function (lung resistance and compliance) is measured in anaesthetised and ventilated guinea-pigs using a pulmonary measurement Flexivent system (SCIREQ, Montreal, Canada) connected to the tracheal cannulae. The animals are ventilated (quasi-sinusoidal ventilation pattern) at 60 breaths/min at a tidal volume of 5 ml/kg. A positive end expiratory pressure of 2-3 cmH₂O is applied. Respiratory resistance is measured using the Flexivent “snapshot” facility (1 second duration, 1 Hz frequency). Lung resistance and compliance is measured before and after intravenous administration of methacholine (3, 10 and 30 ug/kg). The peak increase in resistance following methacholine challenge is calculated and the effect of the test compound on methacholine-induced lung function changes is calculated.

Percentage inhibition of bronchoconstriction is calculated at each dose of methacholine as follows:

$$\frac{[\text{Change in resistance in vehicle treated group} - \text{Change in resistance in compound treated group}]}{\text{Change in resistance in vehicle treated group}} \times 100$$

Assay 5**Inhibition of pilocarpine induced salivation by i.n. administered compounds.**

Guinea pigs (450-550g) supplied by Harlan UK or David Hall, Staffs UK and acclimatised to the in-house facilities for a minimum of three days before use. Guinea pigs are randomly assigned into treatment groups and weighed. Each animal is lightly anaesthetised (4% Halothane) and administered compound or vehicle intranasally (0.5ml/kg) at up to 24 hours before challenge with pilocarpine. At the test time point,

guinea pigs are terminally anaesthetised with urethane (25% solution in H₂O, 1.5g/kg). Once sufficient anaesthesia had developed (absence of toe pinch reflex) each animal had an absorbent pad placed in the mouth for 5 minutes to dry residual saliva, this pad is removed and replaced with a new pre-weighed pad for 5 minutes to establish a reading of baseline saliva production. At the end of this 5 minute period the pad is removed and weighed. A new pre-weighed pad is inserted into the mouth before each animal received s.c. pilocarpine administered under the skin at the back of the neck (0.6mg/kg @ 2ml/kg). The pad is removed, weighed and replaced with a new pre-weighed pad every 5 minutes up to 15 minutes.

Saliva production is calculated by subtracting the pre-weighed weight of the pad from each 5 minute period post weighed pad and these numbers added together to produce an accumulation of saliva over 15 minutes. Each 5 minute period may be analysed in addition to the whole 15 minute recording period. Baseline production of saliva is assumed to be constant and multiplied by three to produce a reading for baseline saliva production over 15 minutes.

Inhibition of saliva produced by the compound may be calculated by using the following equation: (1-(Test-baseline)/(Veh-baseline))*100.

Biological Results:

Example Number	Assay 1 % inhibition @10µM	Assay 2 % inhibition @1µM	Assay 2 % inhibition @10µM	Assay 3 pIC₅₀
3				8.6
4				8.0
7				7.0
8				7.0
9				7.0
17				7.6
20				6.7
25	98.2			7.1
26	97.7			6.6
27	84.8			6.3

28		22.4	67.0	
29	98.8			6.2
30		12.2	53.6	
31		39.3	78.5	
32	99.5			6.2
33	93.6			6.4
34	96.1			6.9
35	52.2			
36	89.1	29.5		
37	96.3			6.5
38	95.1			6.9
39	90.7			6.7
40	74.8	26.1	79.4	
41	95.2			6.4
42	70.7	30.4	78.1	
43		7.6	52.9	
44		14.0	60.3	
45	98.2			6.4
46				7.2
47	79.9	46.4	83.9	
48	99.4			6.9
49		11.6	56.1	
50	99.2			6.6
51	45.5	12.5	60.9	
52	99.5	66.1	95.1	
53	75.1			7.1
54				6.2
55	96.2			6.5
56			91.4	
57	97.0			6.2
58	89.6	32.8	83.9	

59		10.9	60.0	
60		6.9	50.7	
61	99.9	44.9	87.4	
62	47.7			7.3
63	97.4			7.2
64			94.1	6.0
65	98.4			6.7
66	70.5	28.2	82.9	
67	67.6	31.9	79.4	
68	78.8			6.4
69	59.4	20.8	71.1	
70	94.8			7.0
71	100.2			7.5
72	101.6			8.0
72	83.5			6.0
73	49.3	22.4	74.3	
74		4.5	45.9	
75	57.5	20.8	69.8	
76	57.0	19.0	62.8	
77	62.4	35.9	79.7	
78	55.1	15.6	56.8	
79	45.4	21.1	64.4	
80	62.5	27.3	75.9	
81	38.0	23.3	67.9	
82	54.2	37.8	72.4	
83	32.9	13.7	64.4	
84	80.6	40.5	81.3	
85		39.9	81.7	
86	77.0	47.9	84.2	
87	58.8	29.4	65.4	
88	61.8	24.2	76.2	

89	57.3	24.5	76.2	
90			61.6	5.6
91			64.1	5.6
92			53.0	
93			80.1	6.0
94			54.5	5.6
95			87.4	6.4
96			83.5	6.4
97			65.0	5.7
98			60.4	
99			56.8	5.5
100			82.9	6.0
101			51.2	
102			91.5	6.8
103			80.7	6.3
104			94.5	5.7
105			74.2	5.8
106			69.3	5.9
107			51.1	
108			98.7	7.6
109			55.3	5.6
110			64.1	5.7
111			60.1	5.6
112			85.7	6.2
113			77.0	6.1
114			81.8	6.2
115			55.2	5.6
116			98.0	7.0
117			85.3	5.7
118			90.5	6.4
119			71.5	5.9

120			85.7	6.1
121			91.5	6.7
122			58.4	5.6
123			93.2	6.9
124			50.4	
125			98.7	8.0
126			97.4	8.0
127			57.4	5.6
128			63.9	5.6
129			85.9	6.3
130			96.8	7.4
131			61.0	5.7
132			56.6	5.7
133			86.9	6.2
134			98.3	7.0
135			53.2	
136			99.5	7.9
137			95.0	7.0
138			98.1	7.8
139			100.4	7.9
140			65.3	5.8
141			89.7	6.7
142			96.6	6.9
143			69.2	5.8
144			90.1	6.5
145			82.0	6.2
146			93.8	6.9
147			92.3	7.0
148			80.8	6.1
149			91.3	6.6
150			62.8	5.8

151			53.8	
152			85.4	6.4
153			60.3	5.6
154			91.8	6.8
155			84.5	6.4
156			75.5	6.0
157			97.6	8.0
158			53.9	5.4
159			75.5	5.8
160			51.7	
161			59.3	5.6
162			85.3	6.6
163			88.8	6.5
164			52.7	
165			86.1	6.3
166			97.1	7.1
167			74.8	5.8
168			83.3	6.1
169			69.2	5.7
170			55.8	5.5
171		98.7		
172		100.0		
173		99.3		
174		99.0		
175		100.9		
176		100.6		
177		99.0		
178		97.5		
179		98.7		
180		98.1		
181		97.2		

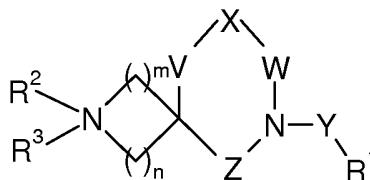
182		99.6		
183		98.1		
184		98.7		
185		97.8		
186		99.0		
187		100.0		
188		100.9		
189		100.3		
190		99.3		
191		99.0		
192		100.0		
193		99.3		
194		98.1		
195		99.0		
196		100.0		
197		99.3		
198		100.0		
199		98.4		
200		100.0		
201		99.0		
202		98.4		
203		96.5		
204		90.0		
205		96.8		
206		96.2		
207		91.9		
208		95.3		
209		95.0		
210		98.7		
211		99.6		
212		94.7		

213		94.4		
214		95.9		
215		98.4		
216		99.0		
217		99.0		
218		92.5		
219		97.8		
220		95.6		
221		97.5		
222		96.8		
223		97.2		
224		98.0		
225		97.7		
226		95.3		
227		96.8		
228				8.1
229		91.2		
230		95.9		
231		93.4		
232		85.0		
233		99.0		
234		97.5		
235		96.8		
236		95.9		
237		93.7		
238		94.7		
239		96.5		
240		96.2		
241		97.5		
242		95.9		
243		95.9		

244		96.8		
245		98.4		
246		98.7		
247		94.7		
248		97.8		
249		96.2		
250		96.2		
251		95.6		
252		93.1		
253		97.2		
254				8.4
255		100.0		
256		99.8		
257		100.0		
258		99.0		
259		100.0		
260		98.8		
261		98.5		
262		100.0		
263		100.0		
264		101.0		
265		101.0		
266		99.8		
267		96.6		
268		98.6		
269		99.8		
270		99.3		
271		100.0		
272		99.8		
273		97.8		

CLAIMS

1. A compound of formula (I):



(I)

wherein

R¹ is selected from the following;

- (i) an optionally substituted 4-8 membered ring, said ring being aromatic or fully or partially saturated and wherein up to four of the ring atoms may be replaced by heteroatoms independently selected from N, O and S;
- (ii) an optionally substituted fused bicyclic ring system of up to 10 atoms, said rings being aromatic or fully or partially saturated, and wherein up to four of the ring atoms may be replaced by heteroatoms independently selected from N, O and S;
- (iii) an optionally substituted C₁₋₆ alkyl group wherein one or two of the carbon atoms can be replaced by O, S or N and wherein said alkyl group may be substituted once or twice by a ring system independently selected from (i) and (ii) above, and wherein the C₁₋₆ alkyl chain may be substituted by up to five substituents selected from halogen, cyano, S(O)₀₋₂R¹⁰, NR⁸R⁹, S(O)₂NR⁸R⁹, C(O)NR⁸R⁹, C(O)OR¹⁰, NR¹⁰S(O)₂R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(O)OR¹¹, NR¹⁰C(O)NR⁸R⁹, OR¹⁰, C₁₋₆ alkyl and C₃₋₆ cycloalkyl (wherein two C₁₋₃ alkyl chains may be joined to form a cycloalkyl ring of up to eight ring atoms), wherein any ring may be optionally substituted by up to three substituents independently selected from halogen, cyano, SH, S(O)₀₋₂R¹⁰, NR⁸R⁹, S(O)₂NR⁸R⁹, C(O)NR⁸R⁹, C(O)OR¹⁰, NR¹⁰S(O)₂R¹¹, NR¹⁰C(O)R¹¹, NR¹⁰C(O)OR¹¹, NR¹⁰C(O)NR⁸R⁹, OR¹⁰).

and wherein for the ring systems in (i) and (ii) above “optionally substituted” means optionally substituted by up to four substituents independently selected from halogen, cyano, nitro, SH, S(O)₀₋₂R¹⁰, NR⁸R⁹, S(O)₂NR⁸R⁹, C(O)NR⁸R⁹, C(O)OR¹⁰, NR¹⁰S(O)₂R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(O)OR¹¹, NR¹⁰C(O)NR⁸R⁹, OR¹⁰, C₁₋₆ alkyl or C₃₋₆ cycloalkyl (wherein a carbon atom of alkyl or cycloalkyl may be optionally replaced by N, O or S) and alkyl or cycloalkyl may be optionally substituted by up to five substituents selected

from C₁₋₆ alkyl, halogen, cyano, SH, S(O)₀₋₂R¹⁰, NR⁸R⁹, S(O)₂NR⁸R⁹, C(O)NR⁸R⁹, C(O)OR¹⁰, NR¹⁰S(O)₂R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(O)OR¹¹, NR¹⁰C(O)NR⁸R⁹, OR¹⁰), phenyl or a 4-8 membered heterocyclic ring (containing up to 4 heteroatoms selected from N, O or S) and wherein the phenyl or 4-8 membered heterocyclic rings may be optionally substituted by up to 3 substituents independently selected from halogen, cyano, nitro, SH, S(O)₀₋₂R¹⁰, NR⁸R⁹, S(O)₂NR⁸R⁹, C(O)NR⁸R⁹, C(O)OR¹⁰, NR¹⁰S(O)₂R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(O)OR¹¹, NR¹⁰C(O)NR⁸R⁹, OR¹⁰), C₁₋₆ alkyl or C₃₋₆ cycloalkyl (wherein alkyl or cycloalkyl may be optionally substituted by up to 3 substituents selected from halogen or OR¹⁰);

and wherein the saturated ring systems in (i) and (iii) may also be substituted by up to three C₁₋₆ alkyl groups that can be joined to form bridged ring structures, optionally substituted by halogen or OR¹⁰;

X represents O, S(O)₀₋₂ or CR¹²R¹³;

m = 0, 1, 2 or 3;

n = 1, 2, 3 or 4; provided that **m** + **n** is greater than or equal to 2;

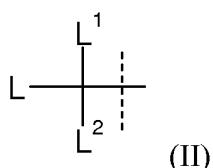
W represents CR¹²R¹³-CR¹²R¹³ or CR¹²R¹³-CR¹²R¹³-CR¹²R¹³;

V and **Z** independently represent a bond, CR¹²R¹³ or CR¹²R¹³-CR¹²R¹³, provided that when X represents either O or S(O)₀₋₂ then m, V and Z are such that all the heteroatoms in the rings are separated by at least two carbon atoms;

Y represents C(O), C(O)NR¹⁰, SO₂ or SO₂NR¹⁰;

R² is a lone pair, or C₁₋₆ alkyl, in which cases the nitrogen atom to which it is attached is a quaternary nitrogen and carries a positive charge; or

R³ is a group of formula (II)



wherein L¹ and L² independently represent hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl, wherein the C₁₋₆ alkyl and C₃₋₆ cycloalkyl may be optionally substituted by up to three substituents independently selected from halogen, hydroxyl and C₁₋₆ alkoxy;

or

L^1 and/or L^2 may be linked to carbon atoms in the group L, or L^1 and L^2 may be linked to each other, to form aliphatic rings of up to 6 ring atoms, wherein each ring may comprise up to three heteroatoms independently selected from N, O and S;

and wherein **L** represents a straight or branched hydrocarbyl chain of up to 15 carbon atoms;

wherein up to three of the carbon atoms in the chain are optionally substituted once or twice by groups independently selected from halogen, cyano, $S(O)_{0-2}R^{10}$, $NR^{14}R^{15}$, $S(O)_2NR^8R^9$, $C(O)NR^8R^9$, $C(O)OR^{10}$, $NR^{10}S(O)_2R^{11}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)OR^{11}$, $NR^{10}C(O)NR^8R^9$, OR^{10} , C_{1-6} alkyl and C_{3-6} cycloalkyl, and wherein alkyl and cycloalkyl may be optionally substituted by up to three substituents independently selected from halogen, hydroxyl and C_{1-6} alkoxy;

wherein up to three carbon atoms of the chain may be replaced by groups independently selected from O, NR^{10} , S, $S(O)$, $S(O)_2$, $C(O)O$, $OC(O)$, $NR^{10}C(O)NR^{10}$, $NR^{10}S(O)_2NR^{10}$, $OC(O)NR^{10}$, $NR^{10}C(O)O$, provided that any such groups in the chain are separated by at least two chain carbon atoms; and

wherein up to six carbon atoms of the chain may form part of an aryl, heteroaryl, fused bicyclic, alicyclic, or heteroaliphatic ring having up to four heteroatoms independently selected from N, O or S, said ring comprising up to 10 ring atoms, and wherein the ring is optionally substituted by up to three substituents independently selected from halogen, cyano, $S(O)_{0-2}R^{10}$, NR^8R^9 , $S(O)_2NR^8R^9$, $C(O)NR^8R^9$, $C(O)OR^{10}$, $NR^{10}S(O)_2R^{11}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)OR^{11}$, $NR^{10}C(O)NR^8R^9$, =O, OR^{10} , C_{1-6} alkyl and C_{3-6} cycloalkyl, and wherein alkyl and cycloalkyl may be optionally substituted by up to three substituents independently selected from halogen, hydroxyl and C_{1-6} alkoxy, with the proviso that L does not comprise an optionally substituted para- or meta-hydroxy phenyl-1-hydroxy-ethylamino- group (or fused bicyclic derivative thereof) or an optionally substituted 4-hydroxy-2-pyridyl-1-hydroxy-ethylamino- group;

R^8 and R^9 are independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, or R^8 and R^9 may be joined together to form a heterocyclic ring comprising up to 9 ring atoms (optionally containing a further heteroatom selected from O, N or S) wherein the ring may be optionally substituted by up to three substituents independently selected from halogen, hydroxyl, C_{1-6} alkyl or C_{3-6} cycloalkyl, and wherein alkyl and cycloalkyl may be optionally

substituted by up to three substituents independently selected from halogen, hydroxyl and C₁₋₆ alkoxy;

R¹⁰ represents hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl, wherein alkyl and cycloalkyl may be optionally substituted by up to three substituents independently selected from halogen, hydroxyl and C₁₋₆ alkoxy;

R¹¹ represents C₁₋₆ alkyl or C₃₋₆ cycloalkyl, wherein the C₁₋₆ alkyl and C₃₋₆ cycloalkyl may be optionally substituted by up to three substituents independently selected from halogen, hydroxyl or C₁₋₆ alkoxy;

R¹² and **R**¹³ each independently represent hydrogen, fluorine, C₁₋₆ alkyl or C₃₋₆ cycloalkyl; or R¹² and R¹³ when attached to the same carbon atom, together with the carbon atom to which they are both attached, may additionally form a 3 to 6 membered aliphatic ring;

R¹⁴ represents hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl, and;

R¹⁵ represents

(i) hydrogen or;

(ii) an optionally substituted aryl, heteroaryl, fused bicyclic, alicyclic or heteroaliphatic ring, or;

(iii) a C₁₋₆ straight- or branched chain alkyl optionally containing an oxygen or sulfur atom in the chain and optionally substituted by up to 3 substituents selected from halogen, hydroxyl, OR¹⁰, -COOR¹⁰, C(=O)NR⁸R⁹, NR¹⁰C(=O)R¹⁰ (wherein R⁸, R⁹, and R¹⁰ are as defined above and each independently may additionally represent an optionally substituted aryl, heteroaryl, fused bicyclic, alicyclic or heteroaliphatic ring), or an optionally substituted aryl, heteroaryl, fused bicyclic, alicyclic or heteroaliphatic ring, or;

(iv) a C₃₋₈ cycloalkyl group optionally substituted by up to 3 substituents selected from halogen, hydroxyl, OR¹⁰, -COOR¹⁰, C(=O)NR⁸R⁹, NR¹⁰C(=O)R¹⁰ (wherein R⁸, R⁹, and R¹⁰ are as defined above and each independently may additionally represent an optionally substituted aryl, heteroaryl, fused bicyclic, alicyclic or heteroaliphatic ring), or an optionally substituted aryl, heteroaryl, fused bicyclic, alicyclic or heteroaliphatic ring; or R¹⁴ and R¹⁵ are joined together with the nitrogen atom to which they are attached to form a heterocyclic ring (optionally fused to an aryl or heteroaryl ring), optionally containing a further heteroatom selected from O, N, or S, and optionally substituted by C₁₋₆ alkyl, =O, -C(=O)NR⁸R⁹, -NR¹⁰C(=O)R¹⁰, -C(=O)R¹⁰ (wherein R⁸, R⁹, and R¹⁰ are as

defined above and each independently may additionally represent an optionally substituted aryl, heteroaryl, fused bicyclic, alicyclic or heteroaliphatic ring), or an optionally substituted aryl, heteroaryl, fused bicyclic, alicyclic or heteroaliphatic ring;
and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof and wherein R¹ represents

- (i) an optionally substituted phenyl or 5-6-membered heteroaryl ring;
- (ii) an optionally fused bicyclic ring ; or
- (iii) an optionally substituted C₁₋₆ alkyl group wherein one or two of the carbon atoms can be replaced by O, S or N and wherein said alkyl group may be substituted by the ring systems described in (i) and (ii), and

wherein each ring in (i), (ii) and (iii) is optionally substituted by up to three substituents independently selected from halogen, cyano, OR¹⁰, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, or an optionally substituted phenyl ring.

3. A compound of formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof as hereinbefore defined for use in therapy.

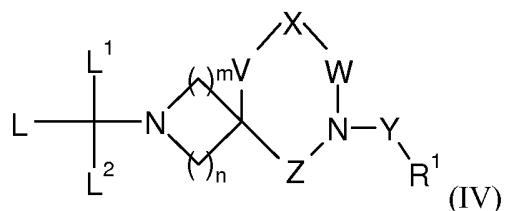
4. The use of a compound of formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in therapy.

5. A method of treating, or reducing the risk of, an inflammatory disease or condition (including a reversible obstructive airways disease or condition) which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition comprising a compound of formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

7. A process for the preparation of a pharmaceutical composition which comprises mixing a compound of formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable adjuvant, diluent or carrier.

8. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined above which comprises reacting a compound of formula (IV)



wherein R¹, m, n, V, W, X, Y and Z are as defined in formula (I) and L, L¹ and L² are as defined in formula (II), with an C₁₋₆alkyl halide.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/051657

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D498/10 A61K31/537 A61P11/06 A61P11/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/102771 A (ASTRAZENECA AB [SE]) 13 September 2007 (2007-09-13) compounds page 170 – page 178 claims 1,13-15 -----	1-8
P, X	WO 2009/098448 A (ASTRAZENECA AB [SE]) 13 August 2009 (2009-08-13) examples claims 1,13 -----	1-8



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

26 January 2010

Date of mailing of the international search report

02/02/2010

Name and mailing address of the ISA/

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Authorized officer

Cortés, José

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2009/051657

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claim 5 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: -

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2009/051657

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 2007102771 A	13-09-2007	AR EP JP UY	059956 A1 2013197 A1 2009529042 T 30195 A1	14-05-2008 14-01-2009 13-08-2009 31-10-2007
WO 2009098448 A	13-08-2009	US UY	2009298807 A1 31639 A1	03-12-2009 30-09-2009