The present invention relates to compounds of the formula

and pharmaceutically acceptable salts and solvates thereof, and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such compounds as adenosine A2a receptor agonists.
PURINE DERIVATIVES

This invention relates to purine derivatives. More particularly, this invention relates to 9-(tetrahydro-2-furyl)-9H-purine-2-carboxamide derivatives and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives.

These derivatives are selective, functional agonists of the human adenosine A2a receptor and may be used as anti-inflammatory agents in the treatment of, inter alia, diseases of the respiratory tract.

Adenosine is a ubiquitous molecule having a central role in mammalian intermediary metabolism. Independently, adenosine acts on multiple surface receptors to produce a variety of responses. Adenosine receptor classification has revealed the presence of at least four subtypes: A1, A2a, A2b and A3. Stimulation of adenosine A2 receptors on the surface of human neutrophils has been reported to potently inhibit a range of neutrophil functions. Activated neutrophils can damage lung tissue by release of reactive oxygen species, for example, superoxide anion radicals (\(O_2^-\)), and granule products, for example, human neutrophil elastase (HNE), amongst other inflammatory mediators. In addition, activated neutrophils perform both de novo synthesis and release of arachidonic products such as leukotriene \(B_4\) (LTB\(_4\)). LTB\(_4\) is a potent chemo-attractant that recruits additional neutrophils to the inflammatory focus, whereas released \(O_2^-\) and HNE adversely affect the pulmonary extracellular matrix. The A2 receptor subtype mediating many of these responses (\(O_2^-\) and LTB\(_4\)/HNE release and cell adhesion) is established as A2a. The A2 subtype (A2a or A2b) mediating the other effects remains to be established.

Selective agonist activity at the A2a receptor is considered to offer greater therapeutic benefit than the use of non-selective adenosine receptor agonists because interaction with other subtypes is associated with detrimental effects in the lung in animal models and human tissue studies. For example, asthmatics, but not non-asthmatics, bronchoconstrict when challenged with inhaled adenosine. This response is at least in part due to the activation of the A1 receptor subtype. Activation of A1 receptors also promotes neutrophil chemotaxis and adherence to endothelial cells, thus promoting lung injury. Furthermore, many patients with respiratory disease will be co-prescribed \(\beta_2\)-agonists, and negative interaction has been shown in animal studies between isoprenaline and adenosine receptors negatively coupled to adenylate cyclase. Degranulation of human mast cells is promoted by activation of adenosine A2b receptors, thus selectivity over the A2b receptor is also advantageous.

We have now surprisingly found the present purine derivatives inhibit neutrophil function and are selective agonists of the adenosine A2a receptor. They may also have antagonist activity at the adenosine A3 receptor. The present compounds may be used to treat any disease for which an adenosine A2a receptor agonist is indicated. They can be used to treat a disease where leukocyte (e.g. neutrophil, eosinophil, basophil, lymphocyte, macrophage)—induced tissue damage is implicated. They are useful as anti-inflammatory agents in the treatment of diseases of the respiratory tract such as adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis. The present compounds may also be used in the treatment of septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, dermatitis, allergic dermatitis, eczema, ulcerative colitis, Crohn's disease, inflammatory bowel disease, Helicobacter pylori gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing.

Accordingly, the present invention provides a compound of the formula:

![Chemical Structure](image)

or a pharmaceutically acceptable salt or solvate thereof,

wherein \(R^1\) is hydrogen or \(C_1-C_6\) alkyl optionally substituted by 1 or 2 substituents each independently selected from phenyl and naphthyl, said phenyl and naphthyl being optionally substituted by \(C_1-C_6\) alkyl, \(C_1-C_6\) alkoxy, halo or cyano;

\([0009]\) \(R^2\) is \(H\) or \(C_1-C_6\) alkyl;

\([0010]\) \(A\) is \(C_1-C_6\) alkylene;

\([0011]\) \(R^3\) is (i) hydrogen, \(C_1-C_6\) alkyl, \(-COOR^4\), \(-CN\), \(-CONR^4R^5\), \(C_2-C_6\) cycloalkyl, phenyl or naphthyl, said \(C_2-C_6\) cycloalkyl, phenyl and naphthyl being optionally substituted by \(C_1-C_6\) alkyl, phenyl, \(C_1-C_6\) alkoxy(\(C_1-C_6\) alkyl), \(R^3\) \(N^1\)(\(C_1-C_6\) alkyl), halo(\(C_1-C_6\) alkyl), fluoro(\(C_1-C_6\) alkyl), \(-OR^4\), cyano, \(-COOR^4\), \(C_3-C_6\) cycloalkyl, \(-SO_2R^4\), \(-NR^4R^5\), \(-SO_2NR^4R^5\), \(-CONR^4R^5\), \(-NR^4COR^5\) or \(-NR^4SO_2R^4R^5\);

\([0012]\) or (ii) when \(A\) is \(C_1-C_6\) alkylene, \(-NR^4R^5\), \(-OR^4\), \(-OCOR^5\), \(-SO_2R^4\), \(-SO_2NR^4R^4\) or \(-NR^4COR^5\);

\([0013]\) or (iii) a C-linked, 4- to 11-membered ring, mono- or bicyclic, heterocycle having either from 1 to 4 ring nitrogen atom(s), or 1 or 2 nitrogen and 1 oxygen or 1 sulphur ring atoms, being optionally C-substituted by oxo, \(C_1-C_6\) alkyl(\(C_1-C_6\) alkyl), \(R^3\) \(NR^4\)(\(C_1-C_6\) alkyl), halo(\(C_1-C_6\) alkyl), fluoro(\(C_1-C_6\) alkyl), \(-OR^4\), cyano, \(-OR^4\), \(-COR^5\), \(-NR^4R^5\), \(-COOR^5\), \(-SO_2R^4\), \(-SO_2NR^4R^5\),...
—CONR'R"", —NR'SO_R" or —NR'COR" and optionally N-substituted by C_1-C_6 alkyl, phenyl, C_1-C_6 alkoxy(C_1-C_6)alkyl, fluoro(C_1-C_6)alkyl, C_2-C_6 alkanoyl, R', —COR'', —COOR', —SO_R'R or —CONR'R',

or (iv) when A is C_2-C_6 alkylene, N-linked azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, homopiperazinyl or morpholinyl, each being optionally C-substituted by C_1-C_6 alkyl, phenyl, C_1-C_6 alkoxy(C_1-C_6)alkyl, R'R''N(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, fluoro(C_1-C_6)alkoxy, C_2-C_6 alkanoyl, halo, —OR''', cyano, —COOR'', —C_2-C_6 cycloalkyl, —(SO_R)'' R'', —NR'COR'' or —NR'SO_R'R, and said piperazinyl and homopiperazinyl being optionally N-substituted by C_1-C_6 alkyl, phenyl, C_1-C_6 alkoxy(C_1-C_6)alkyl, R'R''N(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, fluoro(C_1-C_6)alkoxy, C_2-C_6 alkanoyl, halo, —OR''', cyano, —COOR'', —C_2-C_6 cycloalkyl, —(SO_R)'' R'', —SO_NR'R or —CONR'R',

[0015] R' is H, C_1-C_6 alkyl, C_2-C_6 cycloalkyl or phenyl;
[0016] R' is C_1-C_6 alkyl, C_2-C_6 cycloalkyl or phenyl;
[0017] R' is H, C_1-C_6 alkyl, C_2-C_6 cycloalkyl, phenyl, naphthyl or het;
[0018] R' is C_2-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl, naphthyl or het;
[0019] m is 0, 1 or 2; and
[0020] R, used in the definition of R' and R', means C-linked pyrrolyl, imidazolyl, triazolyl, thiienyl, furyl, thiophenyl, oxazolyl, thiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, quinolyl, isoquinolyl, benzimidazolyl, quinazolinyl, phthalazinyl, benzoazolyl or quinoxaliny, each being optionally substituted by C_1-C_6 alkyl, C_1-C_6 alkoxy, cyano or halo.

[0021] In the above definitions, halo means fluoro, chloro, bromo or iodo and alkyl, alkylene, alkanoyl and alkoxy groups containing the requisite number of carbon atoms can be unbranched or branched chain. The heterocycle as defined in R, part (iii), above may be aromatic or fully or partially saturated. The expression ‘C-linked’ used in the definitions of R' and het means that the group is linked to the adjacent atom by a ring carbon. The expression ‘N-linked’ used in the definition of R is means that the group is linked to the adjacent atom by a ring nitrogen. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and tert-butyl. Examples of alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and tert-butoxy. Examples of alkanoyl include acetyl and propionyl. Examples of aldehydes include methylene, 1,1-ethylen, 1,2-ethylen, 1,3-propylene and 1,2-propylene. Examples of cycloalkyl include cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[0022] Preferred heterocycles included within the definition of “heterocycle” for R (iii) are pyrrolyl, imidazolyl, triazolyl, thiienyl, furyl, thiophenyl, oxazolyl, thiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrazinyl, indolyl, isoindolyl, quinolyl, isoquinolyl, benzimidazolyl, quinazolinyl, phthalazinyl, benzoazolyl and quinoxaliny, together with partially or fully saturated versions thereof such as azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and morpholinyl.

[0023] In a second aspect, the present invention provides a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein

[0024] R'' is hydrogen or C_1-C_6 alkyl substituted by 1 or 2 substituents each independently selected from phenyl and naphthyl;
[0025] R'' is hydrogen or C_1-C_6 alkyl;
[0026] A is C_1-C_6 alkylene; and
[0027] R'' is phenyl, naphthyl, C_2-C_6 cycloalkyl, azetidinyl, pyrrolidinyl, piperidinyl, amino, —NH(C_1-C_6 alkyl) or —N(C_1-C_6 alkyl), said phenyl, naphthyl, C_2-C_6 cycloalkyl, azetidinyl, pyrrolidinyl and piperidinyl being optionally substituted by one or more substituents each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo(C_1-C_6)alkyl, halo and cyano;
[0028] with the proviso that when R'' is N-linked, optionally substituted-azetidinyl, -pyrrolidinyl or -piperidinyl, or is amino, —NH(C_1-C_6 alkyl) or —N(C_1-C_6 alkyl), A is C_2-C_6 alkylene.

[0029] The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and the base salts thereof.

[0030] Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, glucconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, p-toluenesulphonate and pamoate salts.

[0031] Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.


[0033] The pharmaceutically acceptable solvates of the compounds of the formula (I) include the hydrates thereof.

[0034] Also included within the present scope of the compounds of the formula (I) are polymorphs thereof.

[0035] A compound of the formula (I) may contain one or more additional asymmetric carbon atoms and therefore exist in two or more stereoisomeric forms. The present invention includes the individual stereoisomers of the compounds of the formula (I) together with mixtures thereof.

[0036] Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diaste-
reoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

Preferably, R is C1-C6 alkyl optionally substituted by 1 or 2 phenyl substituents.

Preferably, R is C1-C6 alkyl substituted by 1 or 2 phenyl substituents.

Preferably, R is C1-C4 alkyl substituted by 1 or 2 phenyl substituents.

Preferably, R is C1-C2 alkyl substituted by 1 or 2 phenyl substituents.

Preferably, R is phenylethyl or diphenylethyl.

Preferably, R is 2,2-diphenylethyl.

Preferably, R is H.

Preferably, A is C2-C4 alkylene.

Preferably, A is an unbranched C1-C4 alkylene.

Preferably, A is methylene, ethylene or propylene.

Preferably, A is methylene, 1,2-ethylene or 1,3-propylene.

Preferably, A is 1,2-ethylenylene.

Preferably, R is phenyl optionally substituted as previously defined for this definition for a compound of the formula (I).

Preferably, R is phenyl.

Preferably, when A is C2-C6 alkylene, R3 is —NR′R4.

Preferably, when A is C2-C6 alkylene, R3 is —NR′R4 wherein R′ is C1-C6 alkyl.

Preferably, when A is C2-C6 alkylene, R3 is —N(CH3)2.

Preferably, R is a C-linked, 5- to 7-membered ring monocyclic heterocycle having either from 1 to 4 ring nitrogen atom(s) or 1 or 2 nitrogen and 1 oxygen or 1 sulphur ring atoms, optionally substituted as previously defined for this definition for a compound of the formula (I).

Preferably, R is a C-linked, 5- or 6-membered ring monocyclic aromatic heterocycle having either from 1 to 4 ring nitrogen atom(s) or 1 or 2 nitrogen and 1 oxygen or 1 sulphur ring atoms, optionally substituted as previously defined for this definition for a compound of the formula (I).

Preferably, R is a C-linked, 5- or 6-membered ring monocyclic aromatic 30 heterocycle having from 1 to 4 ring nitrogen atom(s), optionally substituted as previously defined for this definition for a compound of the formula (I).

Preferably, R is C-linked pyridinyl optionally substituted by —OR′, R′, C1-C6 alkoxy(C1-C6)alkyl, R′R''N(C1-C6)alkyl or —NR′R4.

Preferably, R is 2-pyridinyl.

Preferably, when A is C2-C6 alkylene, R3 is N-linked pyrrolidinyl, piperidinyl or morpholinyl, each being optionally C-substituted as previously defined for this definition for a compound of the formula (I).

Preferably, when A is C2-C6 alkylene, R3 is pyrroloidin-1-yl, piperidin-1-yl, 4-isopropylpiperidin-1-yl or morpholin-4-yl.

Preferably, when A is C2-C6 alkylene, R3 is piperidin-1-yl.

Preferably, —A-R′ is phenethyl, 2-(dimethylamino)ethyl, 2-pyrrolidinylmethyl, 2-(2-pyrrolidinyl)ethyl, 3-(1-pyrrolidinyl)propyl, 2-(1-piperidinyl)ethyl, 2-(4-isopropyl-1-piperidinyl)ethyl or 2-(4-morpholinyl)ethyl.

Preferably, —A-R′ is 2-(1-piperidinyl)ethyl.

Particularly preferred examples of a compound of the formula (I) are

9-{[2(R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-N-[2-(1-piperidinyl)ethyl]-9H-purine-2-carboxamide;}

9-{[2(R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-N-phenethyl-9H-purine-2-carboxamide;}

9-{[2(R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-N-[2-(4-isopropyl-1-piperidinyl)ethyl]-9H-purine-2-carboxamide;}

9-{[2(R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-N-[3-(1-pyrrolidinyl)propyl]-9H-purine-2-carboxamide;}

9-{[2(R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-N-(2-pyrrolidinylmethyl)-9H-purine-2-carboxamide;}

9-{[2(R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-N-[2-(2-pyridinyl)ethyl]-9H-purine-2-carboxamide;}

9-{[2(R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-N-[2-(dimethylamino)ethyl]-6-[(2,2-diphenylethyl)amino]-9H-purine-2-carboxamide;}

together with pharmaceutically acceptable salts and solvates thereof.

The compounds of the formula (I) can be prepared using conventional procedures such as by the following illustrative methods in which R′, R″, R′′′ and A are as previously defined for a compound of the formula (I) unless otherwise stated.
1. All the compounds of the formula (I) can be prepared by aminocarbonylation reaction of a compound of the formula:

\[ R^1 \text{H} N \text{N} \overset{\text{II}}{\text{N}} \overset{\text{II}}{\text{N}} X \]

wherein \( X \) is a suitable leaving group such as bromo, iodo, \(-\text{Sn}(\text{C}_1-\text{C}_{12} \text{ alkyl})_3\) or \( \text{CF}_3\text{SO}_2-\), preferably iodo, with a compound of the formula:

\[ R^1 \text{N} \overset{\text{II}}{\text{A}}-R^3 \]

in the presence of carbon monoxide and a suitable coupling catalyst. Preferably, the catalyst is a palladium (II) catalyst, more preferably \( 1,1'\text{-bis(diphenylphosphino)ferrocenedichloropalladium} \) (II) (optionally as a 1:1 complex with dichloromethane). Alternatively, palladium (II) acetate may be used in the presence of a suitable ligand such as \( 1,1'\text{-bis(diphenylphosphino)ferrocene} \), triphenylphosphine, \( \text{tri(o-tolyl)}\text{phosphine} \) or \( \text{(R)-, (S)- or racemic 2,2'-bis(diphenylphosphino)-1,1'binaphthyl} \).

In a typical procedure the reaction is carried out in a sealed vessel in the presence of carbon monoxide at an elevated pressure, e.g. about 345 kPa (50 psi), at an elevated temperature, e.g. about 60°C, and in a suitable solvent, e.g. tetrahydrofuran, methanol or ethanol. Optionally, a suitable organic base may be present such as tertiary amine, e.g. triethylamine, N-ethylidisopropylamine or 4-methylmorpholine.

The intermediates of the formula (II) can be prepared as shown in Scheme 1.

\[ \text{Scheme 1} \]

\[ R^1 \text{N} \overset{\text{II}}{\text{A}}-\overset{\text{II}}{\text{OAc}} \]

-continued

2. All the compounds of the formula (I) can be prepared by deprotection of a compound of the formula:

\[ \overset{\text{II}}{\text{OAc}} \]

wherein \( R^8 \) and \( R^9 \) when taken separately are suitable protecting groups such as acetyl or benzoyl or when taken together are a suitable protecting group such as \( \text{C}_1-\text{C}_3 \) alkyne, e.g. \( 1,1\text{-dimethylmethylene} \).

In a typical procedure, where \( R^8 \) and \( R^9 \) taken together are \( 1,1\text{-dimethylmethylene}, \) a compound of the
formula (VI) is treated with a suitable acid such as hydrochloric acid, trifluoroacetic acid, sulphuric acid, p-toluenesulphonic acid, benzenesulphonic acid, methanesulphonic acid, acetic acid or formic acid, or a mixture thereof, optionally in the presence of a suitable solvent, e.g. ethanol, and optionally under aqueous conditions. The reaction may be carried out at an elevated temperature such as at the reflux temperature of the solvent.

[0087] The intermediates of the formula (VI) may be prepared as shown in Scheme 2.

[0088] wherein R8 and R9 are as previously defined for a compound of the formula (VI) and R10 is a suitable protecting group such as trialkylsilylethyl, e.g. t-butyldimethylsilyl, or t-butylidiphenylsilyl.

[0089] In a typical procedure a compound of the formula (VII) (that may be treated by a conventional procedure, e.g. where R8 and R9 taken together are 1,1-dimethylethylene and R10 is t-butyldimethylsilyl) is treated with a compound of the formula:

\[ \text{R}^{\text{N}} \text{H}^{\text{N}} \text{I} \]

[0090] in the presence of a suitable solvent, e.g. methanol, ethanol, acetonitrile or isopropanol, optionally in the presence of an additional acid acceptor, e.g. a tertiary amine such as triethylamine, N-ethylisopropylamine or 4-methylmorpholine. The reaction is preferably carried out at an elevated temperature such as at the reflux temperature of the solvent.

[0091] The compound of the formula (VIII) prepared may be treated with iodine in a suitable solvent such as tetrahydrofuran or dichloromethane at an elevated temperature, e.g. about 50°C, to provide an iodinated compound of the formula (IX)

[0092] The compound of the formula (IX) may be converted by aminocarbonylation to an amide of the formula (X) in the presence of an amine of the formula (III) and carbon monoxide under similar conditions to those described in Method 1 for the preparation of a compound of the formula (I) from a compound of the formula (II).

[0093] Selective removal of the R10 group under suitable deprotection conditions then provides a compound of the formula (VI). Where R10 is t-butylidemethylsilyl, the reaction may be carried out using a suitable fluoride source such as tetra-n-butylammonium fluoride or hydrogen fluoride/pyridine, and in a suitable solvent such as acetonitrile or tetrahydrofuran, at room temperature.

[0094] 3. All the compounds of the formula (I) can be prepared by deprotection of a compound of the formula:

\[ \text{R}^{\text{N}} \text{H}^{\text{N}} \text{I} \]

[0095] wherein R11, R12 and R13 are suitable protecting groups. Where R11, R12 and R13 are taken separately, examples include acetyl or benzyol. Alternatively, R12 and R13 may be taken together and examples include 1,1-dimethylethylene.

[0096] Conventional deprotection conditions may be used and will depend on the nature of the protecting groups to be removed. In a typical procedure where R11, R12 and R13 are
each acetyl the deprotection may be achieved using similar conditions to those described for the conversion of a compound of the formula (V) to a compound of the formula (II).

[0097] Deprotection of a compound of the formula (XII) to provide a compound of the formula (I) may also be accomplished in situ following the conversion of a compound of the formula (XIII) to a compound of the formula (XII) as described below. Here, where R<sup>13</sup>, R<sup>12</sup> and R<sup>15</sup> are each acetyl, the deprotection method using inorganic base is preferred, e.g. the reaction mixture containing a compound of the formula (XII) is treated with aqueous sodium hydroxide solution in 1,2-dimethoxyethane at from 5-20° C.

[0098] A compound of the formula (XII) may be prepared as shown in Scheme 3.

Scheme 3

\[
\begin{align*}
\text{Cl} & \quad \text{N} & \quad \text{N} & \quad \text{N} \\
\text{N} & \quad \text{Cl} & \quad \text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} & \quad \text{Cl} & \quad \text{N} \\
\text{XVI} & \quad \text{Cl} & \quad \text{N} & \quad \text{N} \\
\text{XV} & \quad \text{N} & \quad \text{N} & \quad \text{N} \\
\text{XIV} & \quad \text{Cl} & \quad \text{N} & \quad \text{N} \\
\text{XIII} & \quad \text{N} & \quad \text{N} & \quad \text{N} \\
\text{XII} & \quad \text{N} & \quad \text{N} & \quad \text{N} \\
\end{align*}
\]
[0099] wherein R\(^{14}\) is a suitable protecting group, e.g., tetrahydro-2H-pyran-2-yl, and R\(^{15}\) and R\(^{16}\) are each C\(_1\)-C\(_4\) alkyl, e.g. methyl or ethyl.

[0100] A compound of the formula (XIV) may be protected with a suitable protecting group R\(^{14}\) under conventional conditions. For example, where R\(^{14}\) is tetrahydro-2H-pyran-2-yl this may be obtained by reaction of a compound of the formula (XIV) with 2,3-dihydropyran in a suitable solvent such as ethyl acetate, toluene, dichloromethane, dimethylformamide, tert-butyl methyl ether, diisopropyl ether, tetrahydrofuran or acetonitrile, in the presence of a suitable acid catalyst such as p-toluenesulphonic acid, benzenesulphonic acid, camphorsulphonic acid, hydrochloric acid, sulphuric acid, methanesulphonic acid or pyridinium p-toluene sulphonate, at from 0°C to the reflux temperature of the solvent. Preferably, the reaction is carried out in ethyl acetate using p-toluenesulphonic acid.

[0101] Treatment of a compound of the formula (XV) with a compound of the formula

\[ R^2NH_2 \]
in a suitable solvent such as methanol, ethanol or isopropanol, and in the presence of a suitable acid acceptor such as a tertiary amine, e.g. triethylamine, N-ethylisopropylamine or 4-methylmorpholine, at up to the reflux temperature of the solvent provides a compound of the formula (XVI).

A compound of the formula (XVI) may be converted to a thioether of the formula (XVIII) by treatment with a suitable source such as sodium or potassium C1-C3 thiol dioxide in a suitable solvent such as dimethylsulphoxide, dimethylformamide or N-methylpyrrolidin-2-one, preferably at an elevated temperature, e.g. 100°C.

Oxidation of a thioether of the formula (XVIII) may be achieved using a suitable oxidant such as Oxone (trade mark) (potassium peroxymonosulphate), dimethyl dioxirane, m-chloroperbenzoic acid or peracetic acid, in a suitable solvent such as water, acetonitrile or dichloromethane, or a mixture thereof, optionally in the presence of a base such as sodium bicarbonate. The sulphoxide (XXIV) prepared may be treated with a suitable cyanide source such as potassium cyanide, zinc cyanide, sodium cyanide or copper cyanide, in a suitable solvent such as dimethylsulphoxide, dimethylformamide, N-methylpyrrolidin-2-one, tetrahydrofuran or acetonitrile, preferably at an elevated temperature, to provide a nitrile of the formula (XVII).

Direct conversion of a compound of the formula (XVI) to a nitrile of the formula (XVII) may be accomplished by treatment with a suitable cyanide source such as potassium cyanide, zinc cyanide, sodium cyanide or copper cyanide, in a suitable solvent such as dimethylsulphoxide, dimethylformamide, N-methylpyrrolidin-2-one, tetrahydrofuran or acetonitrile, in the presence of a suitable palladium catalyst such as tetrais(triphenylphosphine)palladium(0) or palladium(II) acetate in association with a suitable ligand such as triphenylphosphine, tri-o-tolylyphosphine, 1,1'-bis(diphenylphosphino)ferrocene or (R)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, and in the presence of a suitable base such as a tertiary amine, e.g. triethylamine, N-ethylisopropylamine or 4-methylmorpholine. The reaction may be carried out at up to the reflux temperature of the solvent and optionally under an inert gas pressure, e.g. argon. The reaction may also be carried out using a suitable cyanide source such as sodium or potassium cyanide in a suitable solvent such as dimethylsulphoxide, dimethylformamide or N-methylpyrrolidin-2-one, at a temperature of from 20 to 120°C.

A compound of the formula (XVII) may be deprotected to provide a compound of the formula (XXIII) using conventional conditions dependent on the protecting group to be removed. Where R14 is tetrahydro-2H-pyran-2-yl, deprotection may be achieved under acidic conditions such as by using a suitable acid, e.g. hydrochloric acid, trifluoroacetic acid, trichloroacetic acid, phosphoric acid, p-toluenesulphonic acid, benzenesulphonic acid, methanesulphonic acid or camphorsulphonic acid, and preferably in an alcoholic solvent, e.g. ethanol or isopropanol, that may optionally contain water, typically at room temperature to the reflux temperature of the solvent.

A nitrile of the formula (XXIII) may be hydrolysed to an acid of the formula (XXIV) under basic conditions such as by using an inorganic base, e.g. lithium hydroxide, sodium hydroxide or potassium hydroxide, in an aqueous C1-C3 alcohol solvent such as methanol, ethanol, isopropanol or industrial methylated spirits.

An acid of the formula (XXIV) may be converted to an amide of the formula (XIII) using conventional peptide coupling conditions, e.g. by activating the acid using a suitable reagent, optionally in the presence of a catalyst, and then by treatment of the activated intermediate with an amine of the formula (III) in a suitable solvent. Suitable activating agents include N,N'-carbonyldimidazole, thionyl chloride, oxalyl chloride or phosphorus oxychloride and suitable solvents include tetrahydrofuran, dimethylformamide, ethyl acetate, acetonitrile, toluene, acetonitrile or dichloromethane. Alternatively, the acid may be activated by treatment with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride or dicyclohexylcarbodiimide and 1-hydroxy-7-azabenzotriazole or 1-hydroxybenzotriazole hydrate and then treated with the amine of the formula (III) in the presence of an acid acceptor such as 4-methylmorpholine, triethylamine or N-ethylisopropylamine in a solvent such as tetrahydrofuran, dimethylformamide, ethyl acetate, acetonitrile, toluene, acetonitrile or dichloromethane, to provide an amide of the formula (XIII). Alternatively, the acid may be treated with benzotriazol-1-yloxytris(pyrrolidino) phosphonium hexafluorophosphate, bromo-tris-pyrrrolidino phosphonium hexafluorophosphate or 2-chloro-1-methylpyridinium iodide and the amine of the formula (III) in the presence of an acid acceptor such as 4-methylmorpholine, triethylamine or N-ethylisopropylamine in a solvent such as tetrahydrofuran, dimethylformamide, ethyl acetate or dichloromethane, to provide an amide of the formula (XIII). A compound of the formula (XIII) may be converted to a compound of the formula (XII) by reaction with a compound of the formula:

wherein Y is a suitable leaving group such as acetoxy, benzyloxy, methoxy or halo, e.g. chloro, and R11, R12 and R13 are suitable protecting groups as previously defined for a compound of the formula (XII), in the presence of a suitable acid or Lewis acid, e.g. trimethylsilyl trifluoromethanesulphonate. The reaction can be performed using a compound of the formula (XXVIII) in the form of a 2R- or 2S-diastereoisomer, or as an epimeric mixture thereof. The reaction is typically carried out in a suitable solvent, e.g. 1,2-dimethoxyethane, dichloromethane, acetonitrile, 1,1,1-trichloroethane or toluene, or a mixture thereof, preferably by pre-treating the compound of the formula (XIII) in situ with a suitable silylating agent, e.g. trimethylsilyl trifluoromethanesulphonate, N,O-bis(trimethylsilyl)acetamide, trimethylsilyl chloride or hexamethyldisilazane, before adding a compound of the formula (XXVIII). Elevated temperatures may be used in the reaction.

A compound of the formula (XXVIII) can be prepared by the conventional procedures.

A nitrile of the formula (XVII) may be converted to an ester of the formula (XX) by treatment with a catalytic or excess amount of an appropriate sodium or potassium C1-C4 alcohol such as sodium or potassium methoxide or ethoxide, in a corresponding C1-C4 alcohol solvent such as methanol or ethanol, followed by treatment with a suitable acid such as aqueous hydrochloric acid.
[0113] The ester of the formula (XX) may be converted to an amide of the formula (XXI) by treatment with an amine of the formula (III), optionally in a suitable solvent such as 1,2-dimethoxyethane or 2-methoxyethyl ether. The reaction may be carried out at elevated temperature and pressure.

[0114] An amide of the formula (XXI) may be converted to a compound of the formula (XIII) under conventional deprotection conditions dependent on the protecting group to be removed. Where R^14 is tetrahydro-2H-pyran-2-yl, this may be achieved under acidic conditions in a suitable solvent, typically using an acid such as hydrochloric acid, trifluoroacetic acid, sulphuric acid, trichloroacetic acid, phosphoric acid, p-toluenesulphonic acid, benzenesulphonic acid, methanesulphonic acid or camphorsulphonic acid, in an alcohol solvent, e.g. isopropanol, that may optionally also contain water. Elevated temperatures may be used in the reaction.

[0115] A compound of the formula (XVII) may be converted to an acid of the formula (XXII) under basic conditions, e.g. using an inorganic base such as lithium hydroxide, sodium hydroxide or potassium hydroxide, in an aqueous C_2-C_6 alcohol solvent such as methanol, ethanol, isopropanol or industrial methylated spirits. The reaction is preferably carried out at an elevated temperature.

[0116] An acid of the formula (XXII) may be converted to an amide of the formula (XXI) under similar conditions to those used for the conversion of a compound of the formula (XXIV) to a compound of the formula (XIII).

[0117] An ester of the formula (XX) may be converted to an acid of the formula (XXII) under basic conditions, e.g. using an inorganic base such as lithium hydroxide, sodium hydroxide or potassium hydroxide, in an aqueous solvent containing ethanol, methanol, isopropanol, butanol, industrial methylated spirits, tetrahydrofuran, dimethylformamide or 1,2-dimethoxyethane, optionally at an elevated temperature.

[0118] A compound of the formula (XVI) may be converted to an ester of the formula (XX) by alkyloxycarbonylation using carbon monoxide, a C_1-C_6 alcohol, a suitable palladium catalyst, optionally a further suitable solvent, and a suitable base such as a tertiary amine. In a typical reaction a catalytic quantity of palladium (II) acetate together with a suitable ligand such as 1,1'-bis(diphenylphosphino)ferrocene, triphenylphosphine, tri-o-tolylphosphine or (R), (S)- or racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, a suitable C_1-C_6 alcohol such as methanol, ethanol, 1-propanol, isopropanol or 1-butanol, and a tertiary amine, base such as triethylamine, N-ethylidisopropylamine or 4-methylmorpholine, are used under carbon monoxide at an elevated temperature and pressure.

[0119] A compound of the formula (XVI) may be converted to an acid of the formula (XXII) by hydroxyxocarbonylation using carbon monoxide, a suitable palladium catalyst and a suitable base under aqueous conditions. In a typical procedure, a catalytic quantity of palladium (II) acetate together with a suitable ligand such as 1,1'-bis(diphenylphosphino)ferrocene, triphenylphosphine, tri-o-tolylphosphine, or (R)-, (S)- or racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, a base such as an alkali metal hydroxide, e.g. sodium hydroxide, or a tertiary amine, and water, together with, optionally, a suitable water miscible solvent such as methanol, ethanol, 1-propanol, tetrahydrofuran, 1,2-dimethoxyethane, dimethylformamide or isopropanol, are used under an atmosphere of carbon monoxide at elevated temperature and pressure.

[0120] A compound of the formula (XVI) may be converted to a compound of the formula (XXII) by amination using carbon monoxide, an amine of the formula (III), a suitable palladium catalyst and a suitable solvent, optionally in the presence of a suitable base. In a typical procedure, a catalytic quantity of palladium (II) acetate together with a suitable ligand such as 1,1'-bis(diphenylphosphino)ferrocene, triphenylphosphine, tri-o-tolylphosphine or (R)-, (S)- or racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, a solvent such as tetrahydrofuran, dimethylformamide, 1,2-dimethoxyethane, ethyl acetate, N-methyl-2-pyrrolidinone, t-butyl methyl ether or diisopropyl ether, a tertiary amine base such as triethylamine, N-ethylidisopropylamine or 4-methylmorpholine, are used under an atmosphere of carbon monoxide at elevated temperature and pressure.

[0121] 4. All the compounds of the formula (I) can be prepared by reaction of a compound of the formula:

$$\text{(XXV)}$$

wherein R^17 is H or a suitable ester-forming group such as C_1-C_6 alkyl or benzyl, with an amine of the formula (III), and wherein R^17 is H in the presence of a suitable peptide coupling agent, under conventional conditions. In a typical procedure, the reagents are heated together, optionally in the presence of a suitable solvent such as 1,2-dimethoxyethane or 2-methoxyethyl ether, at elevated temperature, e.g. from 60 to 120° C., and optionally under pressure.

[0122] A compound of the formula (XXV) may be prepared as shown in Scheme 4.

[0123] A compound of the formula (XXV) may be prepared as shown in Scheme 4.
wherein R\textsuperscript{17} is a suitable ester-forming group such as C\textsubscript{1}-C\textsubscript{12} alkyl or benzyl and R\textsuperscript{12}, R\textsuperscript{13} and R\textsuperscript{14} are suitable protecting groups as previously defined for a compound of the formula (XXVIII).

In a typical procedure, a nitrile of the formula (XXIII) is converted to an ester of the formula (XXVII) under basic conditions, e.g. using a sodium or potassium C\textsubscript{1}-C\textsubscript{12} alkoxide such as sodium or potassium methoxide or ethoxide, in a corresponding C\textsubscript{1}-C\textsubscript{12} alkyl solvent such as methanol or ethanol, at from room temperature to the reflux temperature of the solvent, followed by treatment with a suitable acid such as aqueous hydrochloric acid.

An ester of the formula (XXVII) may be converted to a compound of the formula (XXVI) by reaction with a compound of the formula (XXVIII) under similar conditions to those used for the conversion of a compound of the formula (XIII) to a compound of the formula (XII).

A compound of the formula (XXVI) may be converted to a compound of the formula (XXVI) under similar conditions to those used for the conversion of a compound of the formula (XII) to a compound of the formula (I) such as by using sodium carbonate in methanol where R\textsuperscript{12}, R\textsuperscript{13} and R\textsuperscript{14} are each acetyl. An acid of the formula (XXV) (R\textsuperscript{2}H) may be prepared from the corresponding ester by conventional procedures.

All of the above reactions and the preparations of novel starting materials using in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the Examples and Preparations hereto. In particular, suitable protection and deprotection procedures are well-known in the art, e.g. as described in Greene et al, “Protective Groups in Organic Synthesis”, Third Edition, John Wiley & Sons Ltd.

A pharmaceutically acceptable salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of the formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

The anti-inflammatory properties of the compounds of the formula (I) are demonstrated by their ability to inhibit neutrophil function which indicates A2a receptor agonist activity. This is evaluated by determining the compound profile in an assay where superoxide production was measured from neutrophils activated by FMLP. Neutrophils were isolated from human peripheral blood using dextran sedimentation followed by centrifugation through Ficoll-Hypaque solution. Any contaminating erythrocytes in the granulocyte pellet were removed by lysis with ice-cold distilled water. Superoxide production from the neutrophils was induced by FMLP in the presence of a priming concentration of cytochalasin B. Adenosine deaminase was included in the assay to remove any endogenously produced adenosine that might suppress superoxide production. The effect of the compound on the FMLP-induced response was monitored colorometrically from the reduction of cytochrome C within the assay buffer. The potency of the compounds was assessed by the concentration giving 50% inhibition (IC\textsubscript{50}) compared to the control response to FMLP.

The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the compounds of the formula (I) can be administered orally, buccally or sublingually in the form of tablets, capsules, ointments, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, sustained-, pulsed- or controlled-release applications.

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycolate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or a high molecular weight polyethylene glycol. For aqueous suspensions and/or elixirs, the compounds of the formula (I) may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol or glycerin, and combinations thereof.

The compounds of the formula (I) can also be administered parenterally, for example, intravenously, intramuscularly, intraperitoneally, intratracheally, intraventricularly, intracisternally, intracranially or subcutaneously, or they may be administered by infusion techniques. They are best used in the form of sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the formula (I) will usually be from 0.01 to 100 mg/kg, preferably from 0.1 to 100 mg/kg (in single or divided doses).

Thus tablets or capsules of the compound of the formula (I) may contain from 5 to 500 mg of active
compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above doses are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

[0138] The compounds of formula (I) can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trifluorochloro
fluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3-heptafluoro propane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomiser or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the formula (I) and a suitable powder base such as lactose or starch.

[0139] Aerosol or dry powder formulations are preferably arranged so that each metered dose or “puff” contains from 20 to 4000 µg of a compound of the formula (I) for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 20 µg to 20 mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

[0140] Alternatively, the compounds of the formula (I) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. The compounds of the formula (I) may also be transdermally administered, for example, by the use of a skin patch.

[0141] For application topically to the skin, the compounds of the formula (I) can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polyethylene glycol 60, cetys esters wax, cetearyl alcohol, 2-octyllydocan, benzyl alcohol and water.

[0142] The compounds of the formula (I) may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/0251B and WO-A-98/55148.

[0143] It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

[0144] Thus the invention provides:

[0145] (i) a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;

[0146] (ii) a process for the preparation of a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;

[0147] (iii) a pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier;

[0148] (iv) a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;

[0149] (v) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament having Δ2 receptor agonist activity;

[0150] (vi) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of an anti-inflammatory agent;

[0151] (vii) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of a respiratory disease;

[0152] (viii) use as in (vii) where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis;

[0153] (ix) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, dermatitis, allergic dermatitis, eczema, ulcerative colitis, Crohn's disease, inflammatory bowel disease, Helicobacter pylori gastritis, non-Heliobacter pylori gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing;

[0154] (x) a method of treatment of a mammal, including a human being, with a Δ2 receptor agonist including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

[0155] (xi) a method of treatment of a mammal, including a human being, to treat an inflammatory disease including treating said mammal with an effective
amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

[0156] (xii) a method of treatment of a mammal, including a human being, to treat a respiratory disease including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

[0157] (xiii) a method as in (xii) where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis;

[0158] (xiv) a method of treatment of a mammal, including a human being, to treat septic shock, male erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, dermatitis, allergic dermatitis, eczema, ulcerative colitis, Crohn's disease, inflammatory bowel disease, Helicobacter pylori gastritis, non-Helicobacter pylori gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastrointestinal tract or a psychotic disorder, or for wound healing, including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof, and

[0159] (xv) certain novel intermediates disclosed herein.

[0160] The following Examples illustrates the preparation of the compounds of the formula (I):

**EXAMPLE 1**

9-[(2R,3R,4S,5R)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-{(2,2-diphenylethyl)amino}-N-[2-(1-piperidinyl)ethyl]-9H-purine-2-carboxamide

[0161]

**EXAMPLE 2**

9-[(2R,3R,4S,5R)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-{(2,2-diphenylethyl)amino}-N-phenethyl-9H-purine-2-carboxamide

[0164] A solution of 9-[(3aR,4R,6R,6aR)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]-6-{(2,2-diphenylethyl)amino}-N-phenethyl-9H-purine-2-carboxamide (0.58 g, 0.91 mmol) (Preparation 7) and formic acid (0.5 ml) in a mixture of acetic acid and water (1:1, by volume, 25 ml) was heated under reflux for 1 hour. The mixture was then cooled and basified to pH 8 with saturated aqueous sodium carbonate solution. The resulting precipitate was filtered off to give the crude product. This
solid was purified by column chromatography on silica gel eluting with a solvent system of dichloromethane:methanol:0.88 ammonia (90:10:1.5, by volume) to yield a solid which was triturated with diethyl ether, filtered and dried to afford the title compound as a solid (186 mg).

**EXAMPLE 3**

9-[[2R,3R,4S,5R]-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[[2,2-diphenylethylamino]-N-[2-(4-isopropyl-1-piperidinyl)ethyl]-9H-purine-2-carboxamide

A mixture of methyl 9-[[2R,3R,4S,5R]-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[[2,2-diphenylethylamino]-9H-purine-2-carboxylate (Preparation 18) (92 mg, 0.18 mmol) and 2-(4-isopropyl-1-piperidinyl)ethylamine (Preparation 20) (100 mg, 0.6 mmol) was heated at 120°C under a nitrogen atmosphere for 75 minutes. The reaction mixture was allowed to cool to room temperature and diethyl ether (2 ml) added to precipitate a crude product. The solvent was decanted off the gum which was then triturated with ethyl acetate (2 ml). The resulting white solid was filtered off and dried to give the title compound (59 mg).

**EXAMPLE 4**

9-[[2R,3R,4S,5R]-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[[2,2-diphenylethylamino]-N-[3-(1-pyrrolidinyl)propyl]-9H-purine-2-carboxamide

A mixture of methyl 9-[[2R,3R,4S,5R]-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[[2,2-diphenylethylamino]-9H-purine-2-carboxylate (Preparation 18) (92 mg, 0.18 mmol) and N-[3-(1-pyrrolidinyl)propyl]pyrrolidine (0.25 ml, 1.95 mmol) was heated at 120°C under a nitrogen atmosphere for 75 minutes. The reaction mixture was allowed to cool to room temperature and diethyl ether (2 ml) added to precipitate a crude product. The solvent was decanted off the gum which was purified by column chromatography on silica gel eluting with dichloromethane:methanol (60:20, by volume). Trituration with diethyl ether gave the title compound as a white solid (34 mg).
EXAMPLE 5

9-[(2R,3R,4S,5R)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-N-[2-(4-morpholinyethyl)]-9H-purine-2-carboxamide

[0173]

A mixture of methyl 9-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9H-purine-2-carboxylate (Preparation 18) (92 mg, 0.18 mmol) and N-(2-aminoethyl)morpholine (0.25 ml, 1.9 mmol) were heated at 120°C under a nitrogen atmosphere for 75 minutes. The reaction mixture was allowed to cool to room temperature and diethyl ether (2 ml) added to precipitate the title compound as a white solid which was filtered off and dried (68 mg).

[0174] ^1^H-NMR (300 MHz, CDCl₃) δ: 8.50 (1H, br s), 8.40 (1H, s), 7.40-7.70 (10H, m), 6.00 (2H, m), 4.65-4.60 (2H, m), 4.40-4.20 (4H, m), 4.15 (2H, m), 3.60-3.40 (6H, m), 2.60-2.50 (3H, m), 2.40-2.35 (4H, m). LRMS (thermospray): m/z [MH⁺] 604

EXAMPLE 6

9-[(2R,3R,4S,5R)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-N-[2-(pyridinylmethyl)]-9H-purine-2-carboxamide

[0176]

A mixture of methyl 9-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9H-purine-2-carboxylate (Preparation 18) (92 mg, 0.18 mmol) and 2-(aminomethyl)pyridine (0.25 ml, 2.4 mmol) was heated at 120°C under a nitrogen atmosphere for 75 minutes. The reaction mixture was allowed to cool to room temperature and diethyl ether (2 ml) added to precipitate a crude product. The solvent was decanted from the gum which was then triturated with ethyl acetate (2 ml). The resulting white solid was filtered off and dried to give the title compound (73 mg).

[0177] ^1^H-NMR (300 MHz, d₆-DMSO) δ: 9.15 (1H, m), 8.50-8.40 (2H, m), 8.05 (1H, m), 7.80 (1H, m), 7.40-7.10 (12H, m), 5.95 (1H, d), 5.45 (1H, br s), 5.20 (1H, br s), 5.10 (1H, br s), 4.70-4.50 (4H, m), 4.30 (2H, m), 4.20 (1H, m), 3.95 (1H, m), 3.70-3.50 (2H, m). LRMS (thermospray): m/z [MH⁺] 582
EXAMPLE 7

9-[(2R,3R,4S,5R)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-N-[2-(2-pyridinyl)ethyl]-9H-purine-2-carboxamide

A mixture of methyl 9-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9H-purine-2-carboxylate (Preparation 18) (92 mg, 0.18 mmol) and 2-(2-aminoethyl)pyridine (0.25 ml, 2.1 mmol) was heated at 120°C under a nitrogen atmosphere for 75 minutes. The reaction mixture was allowed to cool to room temperature and diethyl ether (2 ml) added to precipitate a crude product. The solvent was decanted from the gum which was purified by column chromatography on silica gel eluting with dichloromethane:methanol (95:5, by volume). Trituration with diethyl ether gave the title compound as a white solid (49 mg).

$^1$H-NMR (300 MHz, CD$_3$OD) δ: 8.40 (2H, m), 7.70 (1H, m), 7.40-7.10 (12H, m), 6.05 (1H, d), 4.60 (1H, m), 4.45 (1H, m), 4.35 (3H, m), 4.15 (1H, m), 3.95-3.70 (4H, m), 3.10 (2H, m). LRMS (thermospray): m/z [MH$^+$] 596

EXAMPLE 8

9-[(2R,3R,4S,5R)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-N-[2-(2-pyridinyl)ethyl]-6-[(2,2-diphenylethyl)amino]-9H-purine-2-carboxamide

A mixture of methyl 9-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-9H-purine-2-carboxylate (Preparation 18) (92 mg, 0.18 mmol) and N,N-dimethylethylenediamine (0.25 ml, 2.3 mmol) was heated at 120°C under a nitrogen atmosphere for 75 minutes. The reaction mixture was allowed to cool to room temperature and diethyl ether (2 ml) added to precipitate a crude product. The solvent was decanted off the gum which was purified by column chromatography on silica gel eluting with dichloromethane:methanol:concentrated aqueous ammonia (90:10:1, by volume). Trituration with diethyl ether gave the title compound as a white solid (51 mg).

$^1$H-NMR (400 MHz, CDCl$_3$) δ: 8.50 (1H, br s), 8.20 (1H, s), 7.30-7.15 (10H, m), 6.05 (1H, br s), 5.90 (1H, m), 5.70 (1H, m), 4.60 (1H, m), 4.40-4.30 (3H, m), 4.20 (1H, m); 4.00 (2H, m), 3.40 (2H, m), 2.50 (2H, m), 2.15 (6H, s). LRMS (thermospray): m/z [MH$^+$] 562
EXAMPLE 9

9-[(2R,3R,4S,5R)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-N-[2-(1-piperidinyl)ethyl]-9H-purine-2-carboxamide

[0185]

To a stirred solution of 6-(2,2-diphenylethyl)amino-N-[2-(1-piperidinyl)ethyl]-9-(2,3,5-tri-O-acetyl-B-D-ribofuranosyl)-9H-purine-2-carboxamide (assumed to be 310 g, 0.426 moles) (Preparation 24) and 1,2-dimethoxyethane (1600 ml) was added 5M aqueous sodium hydroxide solution (640 ml, 3.2 moles) over a 45 minute period with cooling in ice. The resultant mixture was stirred at ambient temperature for 3 hours, and then the layers were separated. The stirred organic phase was then diluted with deionised Water (1800 ml) with cooling. When the addition was complete, the resultant mixture was heated to 50-55°C whereupon crystallisation started. The heated and stirred suspension was added further deionised water (1800 ml) over a period of 50 minutes. Once the addition was complete, the resultant slurry was cooled to 10°C over a period of 45 minutes and the resulting solid was then collected by filtration. The solid was washed with a solution of 1,2-dimethoxyethane (400 ml) and deionised water (800 ml) and was then dried at 55°C, under reduced pressure to give the crude title compound as a brown solid (2039 g).

[0187] This material was combined with material obtained from processes carried out under similar conditions and was purified in the following manner. To a suspension of the crude title compound (398 g, 0.661 moles) in isopropanol (7050 ml) was added deionised water (1760 ml) and the resultant mixture was stirred and warmed until a clear solution was obtained. The solution was filtered and the filtrate was then distilled under nitrogen at atmospheric pressure with periodic addition of filtered isopropanol to maintain the distillation volume. Over the course of the distillation, a total of 29100 ml of distillate was collected, and a total of 26100 ml of filtered isopropanol was added. Towards the end of the distillation, the amount of water present in the distillate was measured by Karl-Fischer analysis to be <0.5% by weight. The mixture was then allowed to cool to 40°C over 3.5 hours with stirring during which time crystallisation occurred. The resultant slurry was stirred at ambient temperature for 12.5 hours and then cooled to 2°C in an ice-bath over 5.5 hours. The solid was collected by filtration, and the filter cake was washed with chilled, filtered isopropanol (2×1500 ml). The filter cake was dried at 60°C under reduced pressure to give the title compound as a pale beige-coloured solid (306 g, m.p. 182°C).

[0188] LRMS (positive atmospheric pressure chemical ionisation): m/z [MH+]+ 602. H-NMR (500 MHz, d6-DMSO) δ: 8.50 (1H, br t), 8.40 (1H, s), 8.00 (1H, br t), 7.35 (4H, d), 7.26 (4H, t), 7.15 (2H, t), 5.91 (1H, d), 5.39 (1H, d), 5.14 (1H, d), 5.06 (1H, t), 4.64-4.50 (2H, m), 4.28-4.18 (2H, m), 4.18-4.10 (1H, m), 3.96-3.90 (1H, m), 3.70-3.61 (1H, m), 3.60-3.50 (1H, m), 3.46-3.37 (2H, m), 2.50-2.44 (2H, m, partly obscured by DMSO peak), 2.40-2.32 (4H, m), 1.46-1.38 (4H, m), 1.36-1.28 (2H, m). [α]D25 (c=0.1 in methanol): −30°

[0189] The following Preparations describe the preparation of certain intermediates used in the preceding Examples.

Preparation 1

(2R,3R,4S,5R)-4-(Acetoxy)-3-[6-(2,2-diphenylethyl)amino]-2-iodo-9H-purin-9-yl)tetrahydro-3-furanyl acetate

[0190] A mixture (2R,3R,4S,5R)-4-(acetoxy)-2-[acetoxy)methyl]-5-(6-chloro-2-iodo-9H-purin-9-yl)tetrahydro-3-furanyl acetate (J. Med. Chem., 35, 248, (1992)) (15.2 g, 28.2 mmol), 2,2-diphenylethylamine (6 g 30.9 mmol), triethylamine (11.4 g, 112.8 mmol) and acetonitrile (200 ml) was stirred at room temperature, under a nitrogen atmosphere, for 24 hours, followed by heating under reflux for 90 minutes. The solvent was removed under reduced pressure and the residue partitioned between dichloromethane (500 ml) and water (200 ml). The organic phase was separated and the solvent removed under reduced pressure to give the title compound as a pale yellow foam (18.8 g).

[0191] 1H-NMR (CDCl3) δ: 7.70 (1H, s), 7.20-7.39 (10H, m), 6.11 (1H, d), 5.75 (2H, t), 5.61 (1H, m), 4.20-4.48 (6H, m), 2.19 (3H, s), 2.13 (3H, s), 2.09 (3H, s).
Preparation 2

(2R,3R,4S,5R)-2-[[2,2-Diphenylethyl)amino]-2-iodo-9H-purin-9-yl]-5-(hydroxymethyl)tetrahydro-3,4-furandiol

[0193]

Preparation 3

9-(3aR,4R,6R,6aR)-6-[[t-Butyl(dimethyl)silyloxymethyl]-2,2-dimethyltetrahydrofuro[3,4-d][3H]dioxol-4-yl]-6-chloro-2-(tributylstannyl)-9H-purine

[0194]

Preparation 4

9-(3aR,4R,6R,6aR)-6-[[t-Butyl(dimethyl)silyl]oxy)methyl]-2,2-dimethyltetrahydrofuro[3,4-d][3H]dioxol-4-yl]-N-(2,2-diphenylethyl)-2-(tributylstannyl)-9H-purin-6-amine

[0197]

A solution of 2,2,6,6-tetramethylpipercidine (17.6 g, 125 mmol) in dry tetrahydrofuran (350 ml) was cooled to 

-50° C, under an atmosphere of nitrogen gas, and treated with n-butyllithium (78 ml, 1.6M solution in hexanes, 125 mmol) over 15 minutes. The reaction mixture was then cooled to -70° C. and a solution of 9-[[3aR,4R,6R,6aR]-6-[[t-Butyl(dimethyl)silyl]oxy)methyl]-2,2-dimethyltetrahydrofuro[3,4-d][3H]dioxol-4-yl]-6-chloro-2-(tributylstannyl)-9H-purine (Bioorg. Med. Chem. Lett., 8, 695-698, (1998)) (11.0 g, 25 mmol) in dry tetrahydrofuran (150 ml) was added, dropwise, keeping the temperature below -70° C. The reaction mixture was stirred for 30 minutes. Tri-n-butyl tin chloride (40.7 g, 125 mmol) was then added to the reaction and the mixture stirred at -70° C. for 30 minutes. A saturated solution of ammonium chloride in water (100 ml) was added to the reaction which was then warmed to 0° C. A saturated aqueous solution of sodium hydroxide was added (150 ml) and the mixture extracted with ethyl acetate (3×100 ml). The combined organic extracts were washed with brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of hexane ethyl acetate (95:5, by volume) gradually changing to hexane:ethyl acetate (80:20, by volume) to afford the title compound (13.0 g).

[0198]

A mixture of 9-[[3aR,4R,6R,6aR]-6-[[t-Butyl(dimethyl)silyl]oxy)methyl]-2,2-dimethyltetrahydrofuro[3,4-d][3H]dioxol-4-yl]-6-chloro-2-(tributylstannyl)-9H-purine (12.0 g, 16.4 mmol) (Preparation 3), 2,2-diphenylethylamine (3.56 g, 18.0 mmol), triethylamine (3.30 g, 33.0 mmol) and acetonitrile (50 ml) was heated at
80°C for 18 hours. Further 2,2-diphenylethylamine (0.75 g, 3.8 mmol) was then added and the heating continued for 5 hours. The mixture was cooled, poured into water and extracted with ethyl acetate (3x50 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of hexane:ethyl acetate (4:1, by volume) gradually changing to hexane:ethyl acetate (2:1, by volume) to afford the title compound as an oil (10.3 g).

[0200] 1H-NMR (CDCl3): δ: 7.74 (1H, s), 7.14-7.37 (10H, m), 6.10 (1H, d), 5.52-5.62 (2H, m), 5.00 (1H, dd), 4.44 (1H, t), 4.25-4.38 (3H, m), 3.78 (1H, dd), 3.72 (1H, dd), 1.48-1.78 (9H, m), 1.30-1.44 (9H, m), 1.17 (6H, t), 0.88 (9H, o), 0.82 (9H, s), -0.06 (6H, s). LRMS (thermospray): m/z [MH+] 891

Preparation 5

9-[(3aR,4R,6R,6aR)-6-[[ tert-Butyl(dimethyl)silyl]oxy]methyl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]-N-(2,2-diphenylethyl)-2-iodo-9H-purin-6-amine

[0201]

[0202] A mixture of 9-[(3aR,4R,6R,6aR)-6-[[ tert-butyldimethylsilyl]oxy]methyl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]-N-(2,2-diphenylethyl)-2-(tributylstanny)-9H-purin-6-amine (1.09, 1.12 mmol) (Preparation 4), iodine (0.43 g, 1.68 mmol) and tetrahydrofuran (30 mL) was stirred at 50°C for 30 minutes. The mixture was cooled, dissolved in ethyl acetate and washed sequentially with saturated aqueous sodium thiosulphate solution followed by water. The organic phase was separated, dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of hexane:ethyl acetate (1:1, by volume) gradually changing to hexane:ethyl acetate (50:50, by volume) to afford the title compound (1.05 g).

[0203] 1H-NMR (CDCl3): δ: 7.77 (1H, br s), 7.16-7.36 (10H, m), 6.06 (1H, br s), 5.72 (1H, br s), 5.20 (1H, dd), 4.96 (1H, dd), 4.15-4.42 (4H, m), 3.84 (1H, dd), 3.78 (1H, dd), 1.62 (3H, s), 1.38 (3H, s), 0.86 (9H, s), 0.02 (6H, s). LRMS (thermospray): m/z [MH+] 728

Preparation 6

9-[(3aR,4R,6R,6aR)-6-[[ tert-Butyl(dimethyl)silyl]oxy]methyl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]-6-[(2,2-diphenylethyl)[amino]-N-phenethyl-9H-purine-2-carboxamide

[0204]

[0205] A mixture of 9-[(3aR,4R,6R,6aR)-6-[[ tert-butyldimethylsilyl]oxy]methyl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]-N-(2,2-diphenylethyl)-2-iodo-9H-purin-6-amine (1.0 g, 1.37 mmol) (Preparation 5), 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) (1:1 complex with dichloromethane) (0.1 g, 0.14 mmol), phenylethylamine (0.5 g, 4.1 mmol) and tetrahydrofuran (30 mL) was heated at 60°C under a carbon monoxide atmosphere at 345 kPa (50 psi) in a sealed vessel for 18 hours. The mixture was cooled and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of hexane:ethyl acetate (1:1, by volume) gradually changing to hexane:ethyl acetate (0:2 g) to afford the title compound as a foam (0.72 g).

[0206] 1H-NMR (CDCl3): δ: 7.90-8.10 (2H, m), 7.10-7.40 (15H, m), 6.26 (1H, d), 5.78 (1H, m), 5.14 (1H, m), 4.97 (1H, m), 4.10-4.44 (4H, m), 3.88 (1H, dd), 3.82 (1H, dd), 3.73 (2H, q), 2.94 (2H, t), 1.62 (3H, s), 1.36 (3H, s), 0.84 (9H, s), 0.02 (6H, s). LRMS (thermospray): m/z [MH+] 749
Preparation 7

9-{(3aR,4R,6R,6aR)-6-[Hydroxymethyl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]-6-[(2,2-diphenylethyl)amino]-N-phenethyl-9H-purine-2-carboxamide

[0207]

Preparation 8

2,6-Dichloro-(9-tetrahydro-2H-pyran-2-yl)-9H-purine

[0210]

[0208] A solution of 9-{(3aR,4R,6R,6aR)-6-[(tert-butyl(dimethyl)silyloxy)methyl]-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl]-6-[(2,2-diphenylethyl)amino]-N-phenethyl-9H-purine-2-carboxamide (0.72 g, 0.96 mmol) (Preparation 6) in acetonitrile (10 ml) was treated with tetra-n-butylammonium fluoride (1.44 ml, 1M solution in tetrahydrofuran, 1.4 mmol) and the resulting mixture stirred at room temperature for 1 hour. The solution was then partitioned between ethyl acetate and a saturated aqueous solution of sodium hydrogen carbonate. The organic phase was separated and the aqueous phase extracted again with ethyl acetate. The combined organic phases were then washed with brine, dried over anhydrous sodium sulphate and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane gradually changing to dichloromethane:methanol (95:5, by volume) to afford the title compound as an off-white foam (580 mg).

[0209] $^1$H-NMR (CDCl$_3$) δ: 7.92 (1H, t), 7.77 (1H, s), 7.02-7.40 (15H, m), 5.94 (1H, br s), 5.70-5.85 (2H, m), 5.18-5.26 (2H, m), 4.52 (1H, s), 3.96-4.38 (4H, m), 3.58-3.92 (3H, m), 2.92 (2H, t), 1.64 (3H, s), 1.37 (3H, s). LRMS (thermospray): m/z [MH$^+$] 635

Preparation 9

2-Chloro-N-(2,2-diphenylethyl)-(9-tetrahydro-2H-pyran-2-yl)-9H-purin-6-amine

[0213]

[0211] 2,6-Dichloro-9H-purine (20 g, 0.11 mol) and 4-toluene sulphonic acid monohydrate (0.2 g) were dissolved in ethyl acetate (300 ml), the mixture heated to 50°C and a solution of 2,3-dihydropyran (12.6 ml, 0.14 mol) in ethyl acetate (50 ml) added slowly over 30 minutes. The reaction mixture was cooled to room temperature, water (100 ml) added and the pH of the solution adjusted to 7 by addition of a saturated aqueous solution of sodium hydrogen carbonate. The organic layer was separated, washed sequentially with water and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was azeotroped twice with pentane to afford the slightly impure title compound as a white solid (30.9 g).

[0212] $^1$H-NMR (400 MHz, CDCl$_3$) δ: 8.30 (1H, s), 5.75 (1H, dd), 4.25-4.15 (1H, m), 3.85-3.70 (1H, m), 2.20-1.60 (6H, m).

A solution of 2,6-dichloro-(9-tetrahydro-2H-pyran-2-yl)-9H-purine (Preparation 8) (30.9 g, 0.11 mol) in
isopropyl alcohol (600 ml) was treated with N-ethyl-N-isopropyl-2-propanamine (47.5 ml, 0.27 mol) and 2,2-diphenylethylamine (24.8 g, 0.13 mol) and the resulting mixture heated under reflux for 3 hours. The solvent was removed under reduced pressure and the residue azeotroped with ethyl acetate. The residue was then purified by column chromatography on silica gel eluting with a gradient system of ethyl acetate:hexane (40:60, by volume) gradually changing to ethyl acetate:hexane (60:40, by volume) to afford the title compound as a foam (49.7 g).

[0215] 1H-NMR (400 MHz, CDCl₃) δ: 7.95-7.75 (1H, br s), 7.35-7.15 (10H, m), 5.80-5.70 (1H, br s), 5.65 (1H, d), 4.35 (1H, m), 4.30-4.18 (1H, br s), 4.10 (1H, d), 3.70 (1H, t), 2.05-1.95 (2H, m), 1.95-1.80 (1H, m), 1.80-1.55 (3H, m).

Preparation 10

N-(2,2-Diphenylethyl)-2-(methylsulfonyl)-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-amine

[0216]

[0217] A solution of 2-chloro-N-(2,2-diphenylethyl)-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-amine (Preparation 9) (49.7 g, 0.11 mol) and dry N,N-dimethylformamide (200 ml) was treated with sodium thiomethoxide (10 g, 0.14 mol) and the resulting mixture heated under an atmosphere of nitrogen at 100°C for 90 minutes. The mixture was stirred at room temperature for 72 hours and heated at 100°C for a further 2 hours. The reaction mixture was cooled and diluted with water (1000 ml). A suspension was formed which was extracted with diethyl ether (2×500 ml). The combined organic layers were washed sequentially with water and brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was azeotroped with diethyl ether then pentane to afford the title compound as a foam (48.9 g).

[0218] 1H-NMR (400 MHz, CDCl₃) δ: 7.80 (1H, s), 7.20-7.10 (10H, m), 5.70-5.55 (2H, d), 4.40-4.20 (3H, m), 4.20-4.05 (1H, m), 3.80-3.65 (1H, m), 2.60 (3H, s), 2.15-1.90 (3H, m), 1.90-1.60 (3H, m).

Preparation 11

N-(2,2-Diphenylethyl)-2-(methylsulfonyl)-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-amine

[0219]

[0220] A solution of Oxone (trade mark) (potassium peroxymonosulphate) (44 g, 71.7 mmol) in water (200 ml) was added dropwise over 2 hours to a solution of N-(2,2-diphenylethyl)-2-(methylsulfonyl)-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-amine (Preparation 10) (25 g, 56.2 mmol), sodium hydrogen carbonate (20 g, 238 mmol), acetone (1000 ml) and water (250 ml). The resultant mixture was stirred at room temperature for 24 hours, filtered and the residue washed with acetone. The acetone was removed from the filtrate by evaporation under reduced pressure and the resulting aqueous residue was extracted with ethyl acetate and then dichloromethane. The combined organic layers were washed with brine, dried using anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was triturated with diethyl ether, filtered, washed with diethyl ether and pentane and then dried to afford the title compound as a white solid (20.32 g).

[0221] 1H-NMR (CDCl₃) δ: 8.00 (1H, s), 7.35-7.15 (10H, m), 6.05-5.95 (1H, br s), 5.75 (1H, d), 4.40-4.35 (1H, m), 4.35-4.20 (2H, br s), 4.15-4.05 (1H, m), 3.75 (1H, t), 3.30 (3H, s), 2.18-2.05 (1H, m), 2.05-1.98 (1H, m), 1.98-1.80 (1H, m), 1.80-1.60 (3H, m).
Preparation 12
6-[(2,2-Diphenylethyl)amino]-9-(tetrahydro-2H-pyran-2-yl)-9H-purine-2-carbonitrile

A solution of N-(2,2-diphenylethyl)-2-(methylsulfonyl)-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-amine (Preparation 11) (20.1 g, 42.1 mmol) and dry N,N-dimethylformamide (100 ml) was treated with potassium cyanide (5.5 g, 84.6 mmol) and the mixture heated at 120\(^\circ\)C for 24 hours under a nitrogen atmosphere. The mixture was cooled to room temperature, poured into water (1000 ml) and stirring continued for a further 1 hour. The resultant solid was slowly filtered off and washed several times with water. The solid was dissolved in dichloromethane and the solution washed with water, dried with anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was azeotroped with diethyl ether (twice) to afford the title compound as an oil (17 g).

\[0223\]
\[0224\]
\[0225\]

Preparation 13
6-[(2,2-Diphenylethyl)amino]-9-(tetrahydro-2H-pyran-2-yl)-9H-purine-2-carbonitrile

A suspension of 6-[(2,2-diphenylethyl)amino]-9-(tetrahydro-2H-pyran-2-yl)-9H-purine-2-carbonitrile (Preparation 12 or 13) (1.00 g, 2.36 mmol) in methanol (20 ml) was treated with sodium methoxide (0.14 g, 2.59 mmol) and the resulting mixture heated under reflux under a nitrogen atmosphere for 20 hours. TLC analysis showed that some starting material still remained and therefore further sodium methoxide (64 mg, 1.18 mmol) was added and mixture heated under reflux under a nitrogen atmosphere for one hour. The mixture was cooled to room temperature and the solvent removed under reduced pressure. Tetrahydrofuran (30 ml) and water (10 ml) were added to the residue and the pH adjusted to 4 by addition of glacial acetic acid (1 ml). The mixture was heated under reflux for 1 hour. TLC analysis showed that some starting material still remained.

\[0226\]
\[0227\]
\[0228\]
\[0229\]
and therefore further acetic acid (0.5 ml) was added and heating under reflux continued for 18 hours. The reaction mixture was cooled to room temperature and partitioned between ethyl acetate and a saturated aqueous solution of sodium hydrogen carbonate. The organic phase was separated, washed with brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol (98.5:1.5, by volume) to afford the title compound (521 mg).

**Preparation 15**

6-[(2,2-Diphenylethyl)amino]-9H-purine-2-carbonitrile

**[0230]** 1H-NMR (400 MHz, CDCl₃) δ: 8.05 (1H, br s), 7.18-7.37 (10H, m), 5.84 (2H, m), 4.40 (3H, m), 4.14 (1H, d), 4.00 (3H, s), 3.78 (1H, t), 1.60-2.17 (6H, m). LRMS (thermospray): m/z [MH⁺] 458, [MN⁺] 480

**Preparation 16**

Methyl 6-[(2,2-diphenylethyl)amino]-9H-purine-2-carboxylate

**[0234]**

A solution of 6-[(2,2-diphenylethyl)amino]-9H-purine-2-carbonitrile (Preparation 15) (5.0 g, 14.7 mmol) and sodium metoxide (4.0 g, 74.1 mmol) in methanol (300 ml) was heated under reflux for 24 hours. Further sodium metoxide (2.0 g, 37 mmol) and methanol (100 ml) was then added and heating continued for a further 24 hours. The reaction mixture was cooled and the solvent removed under reduced pressure. The residue was dissolved in tetrahydrofuran (375 ml), 2 M aqueous hydrochloric acid solution (125 ml) added and the mixture stirred at room temperature for 24 hours. The tetrahydrofuran was removed under reduced pressure and the pH of the suspension adjusted to 7 with saturated aqueous sodium bicarbonate solution. Ethyl acetate (100 ml) was then added and the suspended white solid filtered off, washed with a little water then ethyl acetate and dried. Purification by column chromatography on silica gel eluting with a gradient system of dichloromethane:methanol (9:10, by volume) gradually changing to dichloromethane:methanol (75:25, by volume) afforded the title compound as a white solid (1.25 g) (n.b. evaporation of the ethyl acetate filtrate provided 2.0 g of the starting material).

**Preparation 17**

Methyl 6-[(2,2-diphenylethyl)amino]-9H-purine-2-carboxylate

**[0235]** 1H-NMR (400 MHz, CDCl₃) δ: 12.40 (1H, br s), 8.05 (1H, s), 7.55 (1H, s), 7.30-7.20 (10H, m), 4.80 (2H, m), 4.75 (1H, m), 3.80 (3H, s). LRMS (thermospray): m/z [MH⁺] 375

**[0236]** 1H-NMR (400 MHz, CDCl₃) δ: 8.20-8.05 (1H, br s), 7.40-7.10 (10H, m), 4.60-4.40 (1.4H, m), 4.20-4.00 (1.6H, m). LRMS (thermospray): m/z [MH⁺] 341
Preparation 17

Methyl 9\{(2R,3R,4R,5R)-3,4-bis(acetyloxy)-5-[(acetyloxy)methyl]tetrahydro-2-furanyl\}-6\{(2,2-diphenylethyl)amino\}-9H-purine-2-carboxylate

![Chemical Structure](image1)

[0238] A suspension of methyl 6\{(2,2-diphenylethyl)amino\}-9H-purine-2-carboxylate (Preparation 16) (1.5 g, 4.02 mmol) in 1,1,1-trichloroethane (40 ml) was treated with N,O-bis(trimethylsilyl)acetamide (4.8 ml, 19.6 mmol). The mixture was heated under reflux for two hours. The solution was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was taken up in anhydrous toluene (40 ml) and 1,2,3,5-tetra-O-acetyl-D-ribofuranose (1.65 g, 5.19 mmol) and trimethylsilyl trifluoromethanesulfonate (0.98 ml, 5.43 mmol) added. The resulting solution was heated under reflux under a nitrogen atmosphere for 3 hours. The mixture was cooled to room temperature, diluted with ethyl acetate (200 ml) and washed with a saturated aqueous solution of sodium hydrogen carbonate. The organic layer was separated, dried over anhydrous magnesium sulphate, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using gradient elution with ethyl acetate:pentane (70:30, by volume) then ethyl acetate:pentane (80:20, by volume) then ethyl acetate to afford the title compound as a foam (2.05 g).

[0239] \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.00 (1H, br s), 7.35-7.20 (1H, m), 6.25 (1H, m), 5.85-5.70 (3H, m), 4.50-4.30 (5H, m), 4.00 (3H, s), 2.15 (3H, s), 2.10 (3H, s), 2.05 (3H, s). LRMS (thermospray): m/z [MNa\(^+\)] 528

Preparation 18

Methyl 9\{(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl\}-6\{(2,2-diphenylethyl)amino\}-9H-purine-2-carboxylate

![Chemical Structure](image2)

[0240] A solution of methyl 9\{(2R,3R,4R,5R)-3,4-bis(acetyloxy)-5-[(acetyloxy)methyl]tetrahydro-2-furanyl\}-6\{(2,2-diphenylethyl)amino\}-9H-purine-2-carboxylate (Preparation 17) (2.0 g, 3.17 mmol), sodium carbonate (35 mg) and dry methanol (40 ml) was stirred at room temperature for 3.5 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using a gradient elution with dichloromethane:methanol (94:6, by volume) then dichloromethane:methanol (92:8, by volume) to afford the title compound as a white powder (1.5 g).

[0241] \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.80 (1H, br s), 7.35-7.20 (10H, m), 5.75 (2H, m), 5.10 (1H, m), 4.90 (1H, br s), 4.40 (3H, m), 4.30 (1H, s), 4.15 (1H, m), 3.90 (1H, m), 3.80-3.70 (4H, m), 3.15 (1H, s). LRMS (thermospray): m/z [MNa\(^+\)] 528

Preparation 19

2\{2-(4-Isopropyl-1-piperidinyl)ethyl\}-1H-isooindole-1,3(2H)-dione

![Chemical Structure](image3)

[0242] A solution of methyl 9\{(2R,3R,4R,5R)-3,4-bis(acetyloxy)-5-[(acetyloxy)methyl]tetrahydro-2-furanyl\}-6\{(2,2-diphenylethyl)amino\}-9H-purine-2-carboxylate (Preparation 17) (2.0 g, 3.17 mmol), sodium carbonate (35 mg) and dry methanol (40 ml) was stirred at room temperature for 3.5 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using a gradient elution with dichloromethane:methanol (94:6, by volume) then dichloromethane:methanol (92:8, by volume) to afford the title compound as a white powder (1.5 g).

[0243] \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.00 (1H, br s), 7.35-7.20 (11H, m), 6.25 (1H, m), 5.85-5.70 (3H, m), 4.50-4.30 (5H, m), 4.00 (3H, s), 2.15 (3H, s), 2.10 (3H, s), 2.05 (3H, s). LRMS (thermospray): m/z [MNa\(^+\)] 655

[0244] A solution of 4-isopropylpiperidine (3.3 g, 20.2 mmol), 2-bromophthalimide (5.4 g, 21.3 mmol), potassium carbonate (5.9 g, 45.4 mmol) and acetonitrile (100 ml)
and was heated under reflux for 2.5 hours then stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate (100 ml) and water (100 ml). The organic layer was separated and the aqueous layer extracted with further ethyl acetate (100 ml). The combined organic extracts were dried (Na₂SO₄) and the solvent removed by evaporation under reduced pressure. The resulting oil was purified by column chromatography on silica gel eluting with a gradient system of dichloromethane changing to dichloromethane:ethyl ether (50:50, by volume) changing to diethyl ether to afford the title compound (3.3 g).

**Preparation 20**

2-(4-Isopropyl-1-piperidinyl)ethylamine

**[0246]**

A solution of 2-(2-(4-isopropyl-1-piperidinyl)-ethyl]-1H-indole-1,3(2H)-dione (Preparation 19) (3.2 g, 10.6 mmol) in a 33% w/w solution of methanol in ethanol (60 ml) was heated under reflux for three hours. The solvent was removed under reduced pressure, further ethanol added (60 ml) and the solvent again removed under reduced pressure. The residue was suspended in dichloromethane (100 ml) and the solid filtered off. This was washed with dichloromethane (100 ml). The filtrate was evaporated under reduced pressure and the resulting oil purified by column chromatography on silica gel eluting with dichloromethane:methanol:aqueous NH₃ (90:10:1, by volume) to give a colourless oil. Bulb-to-bulb distillation (150-160°C, 30 mmHg) yielded the title compound (1.0 g, 55%).

**[0247]**

**[0250]** To a suspension of 6-(2,2-diphenylethyl)amino-9-(tetrahydro-2H-pyran-2-yl)-9H-purine-2-carboxylic acid (176 g, 0.415 moles) (Preparation 13) in industrial methylated spirits (770 ml) was added a solution of sodium hydroxide (33.3 g, 0.83 moles) in deionized water (110 ml). The resultant slurry was heated under reflux for 2.5 hours during which time a clear solution formed. The mixture was allowed to cool to ambient temperature over 16 hours which resulted in the formation of a precipitate. Water (200 ml) was then added, and the mixture was distilled at atmospheric pressure. Over the course of the distillation, water (500 ml) was added periodically to the mixture, and a total of 720 ml of distillate was collected. The resultant mixture was allowed to cool slowly to ambient temperature with stirring and a thick precipitate formed. The slurry was cooled in an ice-bath, and the solid was collected by filtration. The filter cake was washed with a solution of deionized water (225 ml) and industrial methylated spirits (25 ml). The dryer filter cake was suspended in a mixture of deionized water (965 ml) and dichloromethane (965 ml) and the pH of the mixture was adjusted to pH 1.2 by the addition of concentrated hydrochloric acid. The phases were separated and the aqueous layer was extracted with dichloromethane (300 ml). The organic phases were combined and the solvent was distilled at atmospheric pressure until 750 ml of distillate had collected. Ethyl acetate (1100 ml) was added and distillation was continued until further 750 ml of distillate had collected and an off-white precipitate had formed. The resulting slurry was allowed to cool to ambient temperature and the solid was collected by filtration. The cold filter cake was washed with chilled ethyl acetate (2×250 ml). The resultant solid was dried in an oven at 70°C under reduced pressure to give the title compound as an off-white solid (163 g), m.p. 155°C (with decomposition).

**Preparation 21**

6-[(2,2-diphenylethyl)amino]-9-(tetrahydro-2H-pyran-2-yl)-9H-purine-2-carboxylic acid

**[0249]**

**[0251]** LRMS (positive atmospheric pressure chemical ionization): m/z [M+H]+ 444. 1H-NMR (400 MHz, CDCl₃) δ: 8.10 (1H, s), 7.40-7.10 (10H, m), 6.30 (1H, br s), 5.90 (1H, d), 4.50-4.20 (3H, m), 4.15 (1H, br d), 3.80 (1H, br t), 2.20-1.60 (6H, m).
Preparation 22

6-[(2,2-Diphenylethyl)amino]-N-[2-(1-piperidinyl)-ethyl]-9-(tetrahydro-2H-pyran-2-yl)-9H-purine-2-carboxamide

To a suspension of 6-(2,2-diphenylethyl)amino-9-(tetrahydro-2H-pyran-2-yl)-9H-purine-2-carboxylic acid (249 g, 0.561 moles) (Preparation 21) in anhydrous tetrahydrofuran (2500 ml) was added N,N-carbonyldimidazole (109 g, 0.672 moles) in two portions over 10 minutes. The resulting mixture was stirred at ambient temperature under an atmosphere of nitrogen whereupon the solid gradually dissolved to give a cloudy pale orange solution. After stirring for 2.5 h, the reaction mixture was cooled in an ice-bath, and a solution of 2-(1-piperidinyl)ethylamine (86.4 g, 0.674 moles) in anhydrous tetrahydrofuran (100 ml) was added over a period of 55 minutes during which time a clear orange solution formed. The reaction mixture was stirred at room temperature for a further 17.5 hours. Deionised water (10 ml) was then added and the reaction mixture was then distilled at atmospheric pressure until approximately 2400 ml of distillate had collected. To the resultant amber oil was added isopropanol (2000 ml) and distillation at atmospheric pressure was continued until approximately 50 ml of distillate had collected. The resultant dark orange solution was allowed to cool to ambient temperature and further isopropanol (600 ml) was added to give a solution of the title compound in isopropanol that may be used directly without further purification.

Preparation 23

6-[(2,2-Diphenylethyl)amino]-N-[2-(1-piperidinyl)-ethyl]-9H-purine-2-carboxamide

[0252]

To a solution of 6-[(2,2-diphenylethyl)amino]-N-[2-(1-piperidinyl)-ethyl]-9-(tetrahydro-2H-pyran-2-yl)-9H-purine-2-carboxamide (206 g), m.p. 222°C. LRMS (positive atmospheric pressure chemical ionisation): m/z (MH+): 470. [1H-NMR (300 MHz, CDCl3) δ: 8.40 (1H, br s), 8.00 (1H, s), 7.40-7.15 (10H, m), 6.00-5.80 (2H, br d), 4.50-4.20 (3H, m), 4.10 (1H, br d), 3.80 (1H, br t), 3.55 (2H, q), 2.55 (2H, t), 2.50-2.25 (4H, m), 2.20-1.60 (6H, m), 1.60-1.25 (6H, m).

[0255] LRMS (positive atmospheric pressure chemical ionisation): m/z (MH+) 554. [1H-NMR (300 MHz, CDCl3) δ: 8.40 (1H, br s), 8.00 (1H, s), 7.40-7.15 (10H, m), 6.00-5.80 (2H, br d), 4.50-4.20 (3H, m), 4.10 (1H, br d), 3.80 (1H, br t), 3.55 (2H, q), 2.55 (2H, t), 2.50-2.25 (4H, m), 2.20-1.60 (6H, m), 1.60-1.25 (6H, m).

[0257] To a solution of 6-[(2,2-diphenylethyl)amino]-N-[2-(1-piperidinyl)-ethyl]-9-(tetrahydro-2H-pyran-2-yl)-9H-purine-2-carboxamide (assumed to be 311 g, 0.561 moles) in isopropanol (approximately 2600 ml), obtained from Preparation 22, was added deionised water (1320 ml) over a period of 5 minutes to form a cloudy pale amber solution. To this stirred mixture was added trifluoroacetic acid (257 ml, 3.34 moles) over a period of 30 minutes so that the pH of the reaction mixture was taken below 2. The resultant mixture was then heated under reflux for 1 hour during which time a slurry was formed. The mixture was allowed to cool to ambient temperature and was stirred for 16 hours. To the stirred slurry was slowly added aqueous sodium hydroxide solution (317 ml of a 10M solution, 3.17 moles) over a period of 30 minutes until the pH of the mixture reached 11. The pH was adjusted to pH 10 by the addition of trifluoroacetic acid (4 ml) and the resultant slurry was heated to 78°C. The mixture was cooled to ambient temperature over a period of 3 hours with stirring. The resultant slurry was filtered and the filtrate was washed with isopropanol (2×350 ml). The damp filtrate was then suspended in 1-propanol (5000 ml) and was heated under reflux during which time a solution was formed. The mixture was distilled at atmospheric pressure until 1800 ml of distillate had been collected. More 1-propanol (1800 ml) was added to the mixture and distillation was continued until 2200 ml of distillate had been collected. Distillation was stopped and the mixture was allowed to cool to ambient temperature over 16 hours with stirring during which time crystallisation occurred. The resultant slurry was cooled to 8°C in an ice-bath and the solid was collected by filtration. The filter cake was washed with 1-propanol (1000 ml) and was then dried at 70°C under reduced pressure to give the title compound as an off-white solid (206 g), m.p. 222°C.

[0258] LRMS (positive atmospheric pressure chemical ionisation): m/z (MH+) 470. [1H-NMR (300 MHz, CDCl3) δ:
15.25 (1H, br s), 8.55 (1H, br s), 8.30 (1H, s), 7.40-7.15 (10H, m), 5.90 (1H, br s), 4.50-4.25 (3H, m), 3.60 (2H, q), 2.55 (2H, t), 2.50-2.30 (4H, m), 1.50-1.20 (6H, m).

Preparation 24

6-[[2,2-Diphenylethyl]amino]-N-[2-(1-piperidinyl)-ethyl]-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine-2-carboxamide

To a stirred suspension of 6-(2,2-diphenylethyl)amino-N-2-(1-piperidinyl)ethyl-9H-purine-2-carboxamide (200 g, 0.426 moles) (Preparation 23) in anhydrous 1,2-dimethoxyethane (800 ml) under an atmosphere of nitrogen was added a solution of trimethylsilyl trifluoromethanesulfonate (200 g, 0.900 moles) in anhydrous 1,2-dimethoxyethane (200 ml) over a period of 15 minutes. During the addition, all the solid dissolved to give a deep red/amber solution and the reaction temperature rose from 20° C. to 31.5° C. The resultant mixture was heated to 55-60° C. and a solution of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (163 g, 0.512 moles) in anhydrous 1,2-dimethoxyethane (400 ml) was added over a period of 40 minutes. The addition apparatus was rinsed through into the reaction mixture with anhydrous 1,2-dimethoxyethane (200 ml). The reaction mixture was heated at 60° C. for 3 hours and was allowed to cool to ambient temperature. This crude reaction solution was held at ambient temperature for 18 hours. The resulting mixture containing the title compound may be used directly without further purification.

An analytical sample was obtained in the following manner. A sample of the aforementioned solution was added to saturated aqueous sodium bicarbonate solution and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, and the solvent was then removed under reduced pressure to give a light brown foam. The crude product was purified further using preparative chromatographic methods, for example by flash chromatography on silica gel using a gradient of 5:95 changing to 15:85, by volume, methanol: dichloromethane as the mobile phase, to give the title compound as a colourless foam.

Preparation 25

6-[[2,2-Diphenylethyl]amino]-9H-purine-2-carboxylic acid

To a suspension of 6-(2,2-diphenylethyl)amino]N-[2-(1-piperidinyl)ethyl]-9H-purine-2-carbonitrile (12.5 g, 0.0368 moles) (Preparation 15) in a mixture of industrial methylated spirits (80 ml) and deionised water (35 ml) was added sodium hydroxide (1.2 g, 0.03 moles) and the resultant mixture was heated under reflux for 17 hours during which time a clear solution was formed. The mixture was cooled to ambient temperature and was acidified by the addition of 1M aqueous hydrochloric acid solution (105 ml) to give a suspension. The solid was collected by filtration and was dried under reduced pressure at 50° C. to give the title compound as a colourless solid (13.5 g), m.p. 241-249° C.

LRMS (negative atmospheric pressure chemical ionisation): m/z [M-H]⁻ 358.

1H-NMR (300 MHz, d6-DMSO) δ: 8.20 (1H, br s), 7.75 (1H, br t), 7.40-7.00 (10H, m), 4.65-4.40 (1H, m), 4.25-4.05 (2H, m).
Preparation 26

6-{(2,2-Diphenylethyl)amino}-N-[2-(1-piperidinyl)ethyl]-9H-purine-2-carboxamide

To a suspension of 6-(2,2-diphenylethyl)amino 9H-purine-2-carboxylic acid (0.52 g, 1.45 mmol) (Preparation 25) in N,N-dimethylformamide (20 ml) was added N,N'-carbonyldimidazole (0.24 g, 1.48 mmol) and the resultant mixture was stirred at ambient temperature for 5 hours. To this mixture was added 2-(1-piperidinyl)ethylamine (0.206 ml, 1.45 mmol) and the resultant mixture was stirred at ambient temperature for 20 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give an oil that was partitioned between ethyl acetate (30 ml) and saturated aqueous sodium bicarbonate solution (20 ml). The layers were then separated and the aqueous phase was extracted with ethyl acetate (30 ml). The combined organic phases were then washed successively with saturated aqueous sodium bicarbonate solution (30 ml) and saturated aqueous sodium chloride solution (30 ml) and then dried (MgSO₄). The solvent was removed under reduced pressure to give the title compound as a brown solid (0.10 g). If required, purification of this material can be accomplished by recrystallisation from 1-propanol.

LRMS (positive atmospheric pressure chemical ionisation): m/z [MH⁺] 470. ¹H-NMR (300 MHz, CDCl₃) δ: 15.25 (1H, br s), 8.55 (1H, br s), 8.30 (1H, s), 7.40-7.15 (10H, m), 5.90 (1H, br s), 4.50-4.25 (3H, m), 3.60 (2H, q), 2.55 (2H, t), 2.50-2.30 (4H, m), 1.50-1.20 (6H, m).

Preparation 27

Ethyl 6-{(2,2-diphenylethyl)amino}-9-(tetrahydro-2H-pyran-2-yl)-9H-purine-2-carboxylate

A mixture of 2-chloro-N-(2,2-diphenylethyl)-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-amine (10 g, 23 mmol) (Preparation 9), triethylamine (9.6 ml, 69 mmol), palladium (II) acetate (0.0103 g, 0.046 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (0.376 g, 0.69 mmol) in ethanol (46 ml) was heated at 120°C under an atmosphere of carbon monoxide at 1725 kPa (250 psi) for 18 hours. The resulting slurry was cooled in an ice-bath for 2 hours and the solid was collected by filtration and washed with ethanol (20 ml). This material was then dried under reduced pressure to give an off-white solid (9.5 g). A portion of this solid (8.5 g) was suspended in ethyl acetate (170 ml) and the resultant mixture was stirred at ambient temperature for 60 hours. The mixture was filtered and the filter cake was rinsed with ethyl acetate (20 ml). The filtrate was then concentrated under reduced pressure to give the title compound as a tan coloured solid (6.45 g). A portion of this material (0.7 g) was crystallised from ethanol (3 ml) to give the title compound as a colourless solid (0.54 g), m.p. 138-140°C.

LRMS (positive atmospheric pressure chemical ionisation): m/z [MH⁺] 472.

¹H-NMR (300 MHz, CDCl₃) δ: 8.05 (1H, s), 7.45-7.15 (10H, m), 5.95-5.80 (2H, m), 4.60-4.30 (5H, m), 4.15 (1H, br d), 3.80 (1H, br t), 2.20-1.60 (6H, m), 1.50 (3H, t).
Preparation 28

6-[(2,2-Diphenylethyl)amino]-9-(tetrahydro-2H-pyran-2-yl)-9H-purine-2-carboxylic acid

[0272]

To a suspension of ethyl 6-[(2,2-diphenylethyl)amino]-9-(tetrahydro-2H-pyran-2-yl)-9H-purine-2-carboxylate (0.55 g, 1.16 mmol) (Preparation 27) in industrial methylated spirits (2.2 ml) was added deionised water (0.08 ml) followed by 10 M aqueous sodium hydroxide solution (0.23 ml, 2.3 mmol). The resulting mixture was stirred at 65°C for 30 minutes and then at ambient temperature for 18 hours during which time a thick paste was formed. To this mixture was added dichloromethane (10 ml) and the pH was adjusted to 2 by the addition of dilute aqueous hydrochloric acid solution. The phases were separated and the aqueous layer was extracted with dichloromethane (10 ml). The combined organic phases were then dried (MgSO₄) and the solvent was removed under reduced pressure to give the title compound as a tan coloured foam (0.43 g) that was identical by ¹H-NMR, high performance liquid chromatography, mass spectrometry and thin-layer chromatography to the compound prepared in Preparation 21.

Preparation 29

6-[(2,2-Diphenylethyl)amino]-9-(tetrahydro-2H-pyran-2-yl)-9H-purine-2-carboxylic acid

[0274]

[0275] A mixture of 2-chloro-N-(2,2-diphenylethyl)-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-amine (0.87 g, 2 mmol) (Preparation 9), palladium(II) acetate (0.002 g, 0.009 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.033 g, 0.06 mmol), 10 M aqueous sodium hydroxide solution (0.6 ml, 6 mmol) and tetrahydrofuran (4 ml) was heated at 140°C under an atmosphere of carbon monoxide at 1725 kPa (250 psi) for 12 hours. The mixture was allowed to cool and to stand at ambient temperature for 16 days during which time a suspension formed. The solid was collected by filtration and washed with tetrahydrofuran (10 ml). This material was added to a mixture of dichloromethane (35 ml) and water (25 ml) and the pH of the mixture was adjusted to 1 by the addition of dilute aqueous hydrochloric acid solution with stirring. The layers were separated and the aqueous phase was extracted with dichloromethane (25 ml). The combined organic phases were dried (MgSO₄) and the solvent was removed under reduced pressure to give the title compound as an amber foam (0.45 g) that was identical by ¹H-NMR, high performance liquid chromatography, mass spectrometry and thin-layer chromatography to the compound prepared in Preparation 21.

Pharmacological Activity

[0276] The compounds of the preceding Examples were tested for anti-inflammatory activity by their ability to inhibit neutrophil function (which indicates A2a receptor agonist activity) by the method described on page 26 and all had an IC₅₀ of less than 1 micromolar.

1-24. (canceled)

25. A method of agonising an A2a receptor in a mammal, said method comprising administering to said mammal in need of such treatment an effective amount of a compound of formula (I),

\[
\begin{align*}
\text{HN} & \quad \text{R} \\
\text{N} & \quad \text{R} \\
\text{O} & \quad \text{R} \\
\text{HN} & \quad \text{R}
\end{align*}
\]

or a pharmaceutically acceptable salt thereof,

wherein R¹ is hydrogen or C₁-C₆ alkyl optionally and independently substituted with 1 to 2 phenyl or naphthyl, said phenyl and naphthyl optionally and independently substituted with C₁-C₆ alkyl, C₁-C₆ alkoxy, halo or cyano;

R² is H or C₁-C₆ alkyl;

A is C₁-C₆ alkylene;

R³ is (i) hydrogen, C₁-C₆ alkyl, —COOR⁴, —CN, —CONR⁴R⁵, C₁-C₆ cycloalkyl, phenyl or naphthyl, said C₁-C₆ cycloalkyl, phenyl and naphthyl optionally and independently substituted with C₁-C₆ alkyl, phenyl, C₁-C₆ alkoxy(C₁-C₆)alkyl, R⁴R⁵N(C₁-C₆)alkyl,
halo(C1-C6)alkyl, fluoro(C1-C6)alkoxy, C2-C6 alkanoyl, halo, —OR4, cyano, COOR4, C2-C6 cycloalkyl, —(SO)nR2, —NR3R4, —SO3NR3R4, —CONR3R4, —NR3COR4 or —NR3SO3R4;

or (ii) when A is C2-C6 alkylene, R3 is —NR3R4, —OR4, —OCOR4, —SO3R4, —SO3NR3R4 or —NR3SO3R4;

or (iii) a C-linked, 4- to 11-membered ring, mono- or bicyclic, heterocycle comprising 1 to 4 ring nitrogen atoms, or 1 to 2 nitrogen and 1 oxygen or 1 sulfur ring atoms, said heterocycle optionally and independently C-substituted with oxo, C1-C6 alkoxy(C1-C6)alkyl, R2R4N(C1-C6)alkyl, halo(C1-C6)alkyl, fluoro(C1-C6)alkoxy, fluoro(C1-C6)alkanol, halo, cyano, —OR2, R², —COR2, —NR2R4, —COOR2, —SO3R4, —CONR2R4, —NR2SO3R4 or —NR2COR2, and said heterocycle optionally and independently N-substituted with C1-C6 alkoxy(C1-C6)alkyl, R2R4N(C1-C6)alkyl, halo(C1-C6)alkyl, fluoro(C1-C6)alkanol, halo, cyano, —OR2, R², —COR2, —NR2R4, —COOR2, —SO3R4, —CONR2R4 or —NR2SO3R4;

or (iv) when A is C2-C6 alkylene, R3 is an N-linked azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, homopiperazinyl or morpholinyl, said R3 is optionally and independently C-substituted with C1-C6 alkyl, phenyl, C1-C6 alkoxy(C1-C6)alkyl, R2R4N(C1-C6)alkyl, halo(C1-C6)alkyl, fluoro(C1-C6)alkoxy, C2-C6 alkanoyl, halo, —OR3, cyano, —COOR3, C2-C6 cycloalkyl, —(SO)nR3, —NR3R4, —SO3NR3R4, —CONR3R4, —NR3COR3 or —NR3SO3R3, and where said R3 is optionally and independently N-substituted with C1-C6 alkyl, phenyl, C1-C6 alkoxy(C2-C6)alkyl, R2R4N(C2-C6)alkyl, fluoro(C2-C6)alkyl C2-C6 alkanoyl, —COOR3, C2-C6 cycloalkyl, —SO3R3, —SO3NR3R3 or —CONR3R3;

R4 is H, C1-C6 alkyl, C2-C6 cycloalkyl or phenyl;

R5 is H, C1-C6 alkyl, C2-C6 cycloalkyl or phenyl;

R6 is H, C1-C6 alkyl, C2-C6 cycloalkyl, phenyl, naphthyl or het;

R7 is C1-C6 alkyl, C2-C6 cycloalkyl, phenyl, naphthyl or het;

m is 0, 1 or 2; and

“het” is a C-linked pyrrolyl, imidazolyl, triazolyl, thienyl, furyl, thiadiazolyl, oxadiazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, isindolyl, quinolinyl, isoquinolinyl, benzimidazolyl, quinazolyl, pyrazolyl, benzoxazolyl or quinoxalinyl, where said het is optionally and independently substituted with C1-C6 alkyl, C1-C6 alkoxy, cyano or halo.

26. A method of treating an inflammatory disease or a respiratory disease in a mammal, said method comprising administering to said mammal in need of such treatment an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof,

wherein R2 is hydrogen or C1-C6 alkyl optionally and independently substituted with 1 to 2 phenyl or naphthyl, said phenyl and naphthyl optionally and independently substituted with C1-C6 alkyl, C1-C6 alkoxy, halo or cyano;

R3 is H or C1-C6 alkyl;

A is C1-C6 alkylene;

R4 is (i) hydrogen, C1-C6 alkyl, —COOR4, —CN, —CONR2R4, C2-C6 cycloalkyl, phenyl or naphthyl, said C2-C6 cycloalkyl, phenyl and naphthyl optionally and independently substituted with C1-C6 alkyl, phenyl, C1-C6 alkoxy(C1-C6)alkyl, R2R4N(C1-C6)alkyl, halo(C1-C6)alkyl, fluoro(C1-C6)alkoxy, C2-C6 alkanoxy, halo, —OR4, cyano, COOR4, C2-C6 cycloalkyl, —(SO)nR4, —NR4R5, —SO3NR4R5, —CONR4R5, —NR4COR4 or —NR4SO3R4, and (ii) when A is C2-C6 alkylene, R3 is —NR3R4, —OR4, —OCOR4, —SO3R4, —SO3NR3R4 or —NR3SO3R4;

or (iii) a C-linked, 4- to 11-membered ring, mono- or bicyclic, heterocycle comprising 1 to 4 ring nitrogen atoms, or 1 to 2 nitrogen and 1 oxygen or 1 sulfur ring atoms, said heterocycle optionally and independently C-substituted with oxo, C1-C6 alkoxy(C1-C6)alkyl, R2R4N(C1-C6)alkyl, halo(C1-C6)alkyl, fluoro(C1-C6)alkoxy, fluoro(C1-C6)alkanol, halo, cyano, —OR3, R³, —COR3, —NR3R5, —COOR3, —SO3R5, —SO3NR3R5, —CONR3R5, —NR3SO3R5 or —NR3COR3, and said heterocycle optionally and independently N-substituted with C1-C6 alkoxy(C1-C6)alkyl, R2R4N(C1-C6)alkyl, halo(C1-C6)alkyl, fluoro(C1-C6)alkoxy, C2-C6 alkanoxy, halo, —OR4, cyano, COOR5, C2-C6 cycloalkyl, —(SO)nR5, —NR4R6, —SO3NR4R6, —CONR4R6, —NR4COR6 or —NR4SO3R6;

or (iv) when A is C2-C6 alkylene, R3 is —NR3R4, —OR4, —OCOR5, —SO3R5, —SO3NR3R5 or —NR3SO3R5;

or (i) hydrogen, C1-C6 alkyl, —COOR3, —CN, —CONR3R4, C2-C6 cycloalkyl, phenyl or naphthyl, said C2-C6 cycloalkyl, phenyl and naphthyl optionally and independently substituted with C1-C6 alkyl, phenyl, C1-C6 alkoxy(C1-C6)alkyl, R2R4N(C1-C6)alkyl, halo(C1-C6)alkyl, fluoro(C1-C6)alkoxy, C2-C6 alkanoxy, halo, —OR4, cyano, COOR4, C2-C6 cycloalkyl, —(SO)nR4, —NR4R5, —SO3NR4R5, —CONR4R5, —NR4COR4 or —NR4SO3R4, and (ii) when A is C2-C6 alkylene, R3 is —NR3R4, —OR4, —OCOR4, —SO3R4, —SO3NR3R4 or —NR3SO3R4;

or (iii) a C-linked, 4- to 11-membered ring, mono- or bicyclic, heterocycle comprising 1 to 4 ring nitrogen atoms, or 1 to 2 nitrogen and 1 oxygen or 1 sulfur ring atoms, said heterocycle optionally and independently C-substituted with oxo, C1-C6 alkoxy(C1-C6)alkyl, R2R4N(C1-C6)alkyl, halo(C1-C6)alkyl, fluoro(C1-C6)alkoxy, fluoro(C1-C6)alkanol, halo, cyano, —OR3, R³, —COR3, —NR3R5, —COOR3, —SO3R5, —SO3NR3R5, —CONR3R5, —NR3SO3R5 or —NR3COR3, and said heterocycle optionally and independently N-substituted with C1-C6 alkoxy(C1-C6)alkyl, R2R4N(C1-C6)alkyl, halo(C1-C6)alkyl, fluoro(C1-C6)alkoxy, C2-C6 alkanoxy, halo, —OR4, cyano, COOR5, C2-C6 cycloalkyl, —(SO)nR5, —NR4R6, —SO3NR4R6, —CONR4R6, —NR4COR6 or —NR4SO3R6;
R'R'N(C2-C6)alkyl, fluoro(C1-C4)alkyl, C1-C6 alkanoyl, —COOR2, C2-C6 cycloalkyl, —SO2R5, —SO2NR'R' or —CONR'R'; R' is H, C1-C6 alkyl, C2-C6 cycloalkyl or phenyl;
R5 is C1-C6 alkyl, C2-C6 cycloalkyl or phenyl;
R6 is H, C1-C6 alkyl, C2-C6 cycloalkyl, phenyl, naphthyl or het;
R7 is C1-C6 alkyl, C2-C6 cycloalkyl, phenyl, naphthyl or het;
m is 0, 1 or 2; and
“het” is a C-linked pyrrolyl, imidazolyl, triazolyl, thienyl, furyl, thiadiazolyl, oxadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, indolyl, isoindolyl, quinolinyl, isouquinolinyl, benzimidazolyl, quinazolinyl, phthalazinyl, benzoazoxolyl or quinoxalinyl, where said het is optionally and independently substituted with C1-C6 alkyl, C1-C6 alkoxy, cyano or halo.
27. (canceled)
28. The method of claim 26 where the disease is adult respiratory distress syndrome, bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis or rhinitis.
29. (canceled)
30. (canceled)
31. A compound of formula:

wherein R8 and R9 are taken separately and are each independently a protecting group, or R8 and R9 are taken together to form a protecting group; or
or (ii) when A is C$_2$-C$_6$ alkyne, R$^3$ is $-$NR$^4$R$^1$, $-$OR$^4$, $-$OCOR$^4$, $-$SO$_2$R$^4$, $-$SO$_2$NR$^4$R$^1$ or $-$NR$^4$COR$^4$,

or (iii) a C-linked, 4- to 11-membered ring, mono- or bicyclic, heterocycle comprising 1 to 4 ring nitrogen atoms, or 1 to 2 nitrogen and 1 oxygen or 1 sulfur ring atoms, said heterocycle optionally and independently C-substituted with oxo, C$_1$-C$_6$ alkoxy(C$_1$-C$_6$)alkyl, R$^4$R$^5$N(C$_1$-C$_6$)alkyl, halo(C$_1$-C$_6$)alkyl, fluoro(C$_1$-C$_6$)alkoxy, fluoro(C$_1$-C$_6$)alkanoyl, halo, cyano, $-$OR$^5$, R$^5$, $-$COR$^5$, $-$NR$^5$R$^5$, $-$CONR$^5$R$^5$, $-$SO$_2$NR$^5$R$^5$, $-$CONR$^5$R$^5$, $-$NR$^5$SO$_2$R$^5$ or $-$NR$^5$COR$^5$, and said heterocycle optionally and independently N-substituted with C$_1$-C$_6$ alkoxy(C$_1$-C$_6$)alkyl, R$^4$R$^5$N(C$_1$-C$_6$)alkyl, halo(C$_1$-C$_6$)alkyl, fluoro(C$_1$-C$_6$)alkanoyl, R$^5$, $-$COR$^5$, $-$SO$_2$R$^5$, $-$SO$_2$NR$^5$R$^5$, $-$CONR$^5$R$^5$, and where said R$^3$ is piperazinyl and homopiperazinyl, R$^3$ is optionally and independently N-substituted with C$_1$-C$_6$ alkyne, phenyl, C$_1$-C$_6$ alkoxy(C$_1$-C$_6$)alkyl, R$^4$R$^5$N(C$_1$-C$_6$)alkyl, halo(C$_1$-C$_6$)alkyl, fluoro(C$_1$-C$_6$)alkoxy, C$_2$-C$_5$ alkanoyl, halo, $-$OR$^4$, cyano, $-$COOR$^4$, C$_2$-C$_5$ cycloalkyl, $-$S(O)$_2$R$^5$, $-$NR$^5$R$^4$, $-$SO$_2$NR$^5$R$^4$, $-$CONR$^5$R$^4$, $-$NR$^4$COR$^4$ or $-$NR$^4$SO$_2$R$^4$, and where said R$^3$ is piperazinyl and homopiperazinyl, R$^3$ is optionally and independently N-substituted with C$_1$-C$_6$ alkyne, phenyl, C$_1$-C$_6$ alkoxy(C$_1$-C$_6$)alkyl, R$^4$R$^5$N(C$_1$-C$_6$)alkyl, halo(C$_1$-C$_6$)alkyl, fluoro(C$_1$-C$_6$)alkoxy, C$_2$-C$_5$ alkanoyl, $-$COOR$^4$, C$_2$-C$_5$ cycloalkyl, $-$SO$_2$R$^5$, $-$SO$_2$NR$^5$R$^4$ or $-$CONR$^5$R$^4$;

R$^4$ is H, C$_1$-C$_6$ alkyne, C$_2$-C$_5$ cycloalkyl or phenyl;

R$^5$ is H, C$_1$-C$_6$ alkyne, C$_2$-C$_5$ cycloalkyl or phenyl;

R$^5$ is H, C$_1$-C$_6$ alkyne, C$_2$-C$_5$ cycloalkyl, phenyl, naphthyl or het;

R$^7$ is C$_1$-C$_6$ alkyne, C$_2$-C$_5$ cycloalkyl, phenyl, naphthyl or het;

m is 0, 1 or 2; and

“het” is a C-linked pyrrolyl, imidazoyl, triazolyl, thiényl, furyl, thiadiazoyl, oxadiazoyl, pyridyl, pyrimidiny, pyridaziny, pyraziny, indoly, isoindolyl, quinolinyl, isquinolinyl, benzimidazoyl, quinazolinyl, phthalazinyl, benzoazoxyl or quinoxaliny, where said het is optionally and independently substituted with C$_1$-C$_6$ alkyne, C$_1$-C$_6$ alkoxy, cyano or halo.

32. A compound of formula:
wherein $R'$, $R''$ and $R'''$ are taken separately and are each independently a protecting group, or $R'$ is a protecting group taken together to form a protecting group, and $R''$ is an ester-forming group; or

(XXV)

wherein $R''$ is an ester-forming group; or

(XX)

wherein $R$ is $C_1$-$C_6$ alkyl optionally and independently substituted with 1 to 2 phenyl or naphthyl, said phenyl and naphthyl optionally and independently substituted with $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, halo or cyano.

33. A compound of claim 31 wherein $R'$ is 2,2-diphenylethyl, $R''$ is H and -A-$R^3$ is 2-(1-piperidinyl)ethyl.

34. A compound of claim 31 of formula (II) wherein X is iso.

35. A compound of claim 31 of formula (VI), (IX) or (X) wherein $R^6$ and $R^7$ are taken separately and are each independently acetyl or benzoyl or are taken together and are 1,1-dimethylmethylene.

36. A compound of claim 31 of formula (IX) or (X) wherein $R^10$ is a silyl protecting group.

37. A compound of claim 31 of formula (XII) wherein $R^{11}$, $R^{12}$ and $R^{13}$ are taken separately and are each independently acetyl or benzoyl, or $R^{12}$ and $R^{13}$ are taken together and are 1,1-dimethylmethylene.

38. A compound of claim 31 of formula (XXI) or (XXII) wherein $R^{14}$ is tetrahydro-2H-pyran-2-yl.

39. A compound of claim 32 of formula (XXV), (XXVI) or (XXVII) wherein $R^{17}$ is $C_1$-$C_6$ alkyl.

40. A compound of claim 32 of formula (XXVI) wherein $R^{11}$, $R^{12}$ and $R^{13}$ are taken separately and are each independently acetyl or benzoyl, or $R^{12}$ and $R^{13}$ are taken together and are 1,1-dimethylmethylene.

41. A compound of claim 32 wherein $R'$ is 2,2-diphenylethyl.

42. A compound of claim 32 of formula (XX) wherein $R^{14}$ is tetrahydro-2H-pyran-2-yl.

43. A method of inhibiting neutrophil function in a mammal, said method comprising administering to said mammal in need of such treatment an effective amount of a compound of formula (I),

(XXV)

or a pharmaceutically acceptable salt thereof,

wherein $R^2$ is hydrogen or $C_1$-$C_6$ alkyl optionally and independently substituted with 1 to 2 phenyl or naphthyl, said phenyl and naphthyl optionally and independently substituted with $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, halo or cyano;

$R^2$ is H or $C_1$-$C_6$ alkyl;

A is $C_1$-$C_6$ alkyne;

$R^2$ is (i) hydrogen, $C_1$-$C_6$ alkyl, —COOR', —CN, —CONR'R', $C_3$-$C_6$ cycloalkyl, phenyl or naphthyl, said $C_3$-$C_6$ cycloalkyl, phenyl and naphthyl optionally and independently substituted with $C_1$-$C_6$ alkyl, phe-
nyl, C₁₋₆ alkoxy(C₁₋₆)alkyl, R¹R²N(C₁₋₆)alkyl, halo(C₁₋₆)alkyl, fluoro(C₁₋₆)alkoxy, C₂₋₅ alkanoyl, halo, —OR⁴, cyano, COOR⁵, C₂₋₅ cycloalkyl, —SO₂R⁵, —NR⁵R⁶, —SO₂NR⁵R⁶, —CONR⁷R⁸, or —NR⁵COR⁹ or —NR⁵SO₂R⁹,

or (ii) when A is C₃₋₆ alkylene, R³ is —NR⁷R⁸, —OR⁹, —OCOR⁹, —SO₂R⁹, —SO₂NR⁹R¹⁰, or —NR⁵COR⁹,

or (iii) a C-linked, 4- to 11-membered ring, mono- or bicyclic, heterocycle comprising 1 to 4 ring nitrogen atoms, or 1 to 2 nitrogen and 1 oxygen or 1 sulfur ring atoms, said heterocycle optionally and independently C-substituted with oxo, C₁₋₆ alkoxy(C₁₋₆)alkyl, R¹R²N(C₁₋₆)alkyl, halo(C₁₋₆)alkyl, fluoro(C₁₋₆)alkoxy, fluoro(C₂₋₅)alkanoyl, halo, cyano, —OR⁹, R³, —COR⁶, —NR⁷R⁸, —COOR⁹, —S(O)₂R⁷, —SO₂NR⁹R¹⁰, —CONR⁷R⁸, —NR⁵SO₂R⁹ or —NR⁵COR⁹, and said heterocycle optionally and independently N-substituted with C₁₋₆ alkoxy(C₁₋₆)alkyl, R¹R²N(C₁₋₆)alkyl, halo(C₁₋₆)alkyl, fluoro(C₂₋₅)alkanoyl, R³, —COR⁶, —COOR⁹, —SO₂R⁷, —SO₂NR⁹R¹⁰ or —CONR⁷R⁸,

or (iv) when A is C₃₋₆ alkylene, R³ is an N-linked azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, homopiperazinyl or morpholino, said R³ is optionally and independently C-substituted with C₁₋₆ alkyl, phenyl, C₁₋₆ alkoxy(C₁₋₆)alkyl, R¹R²N(C₁₋₆)alkyl, halo(C₁₋₆)alkyl, fluoro(C₁₋₆)alkoxy, C₂₋₅ alkanoyl, halo, —OR⁴, cyano, —COOR⁵, C₂₋₅ cycloalkyl, —SO₂R⁵, —NR⁵R⁶, —SO₂NR⁵R⁶, —CONR⁷R⁸, —NR⁵COR⁹ or —NR⁵SO₂R⁹, and

where said R³ is piperazinyl and homopiperazinyl, R³ is optionally and independently N-substituted with C₂₋₅ alkyl, phenyl, C₁₋₆ alkoxy(C₂₋₅)alkyl, R¹R²N(C₂₋₅)alkyl, fluoro(C₁₋₆)alkyl, C₂₋₅ alkanoyl, —COOR⁹, C₂₋₅ cycloalkyl, —SO₂R⁵, —SO₂NR²R⁶ or —CONR⁷R⁸,

R⁵ is H, C₁₋₆ alkyl, C₂₋₅ cycloalkyl or phenyl;
R⁵ is C₁₋₆ alkyl, C₂₋₅ cycloalkyl or phenyl;
R⁵ is H, C₁₋₆ alkyl, C₂₋₅ cycloalkyl, phenyl, naphthyl or het;
R⁵ is C₁₋₆ alkyl, C₂₋₅ cycloalkyl, phenyl, naphthyl or het;
m is 0, 1 or 2; and

“het” is a C-linked pyrrolyl, imidazolyl, triazolyl, thiencyl, furyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, benzimidazolyl, quinoxazinyl, phthalazinyl, benzoxazolyl or quinoloxinyl, where said het is optionally and independently substituted with C₁₋₆ alkyl, C₁₋₆ alkoxy, cyano or halo.

44. The compound of claim 31 of formula (II), with the proviso that when X is bromo or iodo, R¹ is not H.

45. The compound of claim 44 of formula (IX), with the proviso that when R¹ is H, R⁵, R⁶ and R⁷ are not each i-butyldimethylsilylethyl or acetyl.

* * * * *