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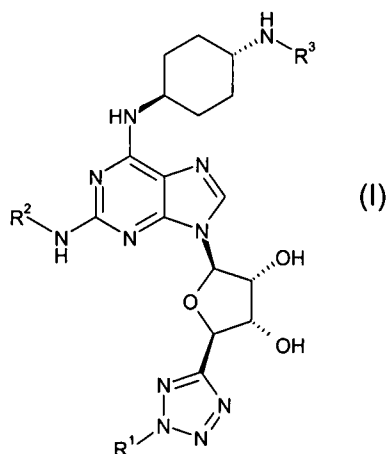
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(54) Title: PURINE DERIVATIVES AS AGONISTS OF THE ADENOSINE A2A RECEPTOR



(57) Abstract: The invention relates to novel adenosine receptor agonists of formula (I), methods for their manufacture and their use as medicaments.

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PURINE DERIVATIVES AS AGONISTS OF THE ADENOSINE A_{2A} RECEPTOR

This invention relates to new chemical compounds, processes for their preparation, pharmaceutical formulations containing them and to their use in therapy.

Inflammation is a primary response to tissue injury or microbial invasion and is characterised by leukocyte adhesion to the endothelium, diapedesis and activation within the tissue. Leukocyte activation can result in the generation of toxic oxygen species (such as superoxide anion), and the release of granule products (such as peroxidases and proteases). Circulating leukocytes include neutrophils, eosinophils, basophils, monocytes and lymphocytes. Different forms of inflammation involve different types of infiltrating leukocytes, the particular profile being regulated by the profile of adhesion molecule, cytokine and chemotactic factor expression within the tissue.

The primary function of leukocytes is to defend the host from invading organisms such as bacteria and parasites. Once a tissue is injured or infected a series of events occurs which causes the local recruitment of leukocytes from the circulation into the affected tissue. Leukocyte recruitment is controlled to allow for the orderly destruction and phagocytosis of foreign or dead cells, followed by tissue repair and resolution of the inflammatory infiltrate. However, in chronic inflammatory states, recruitment is often inappropriate, resolution is not adequately controlled and the inflammatory reaction causes tissue destruction.

There is evidence from both *in vitro* and *in vivo* studies to suggest that compounds active at the adenosine A_{2A} receptor will have anti-inflammatory actions. The area has been reviewed by Cronstein (Cronstein BN, (1994), J. Appl. Physiol. 76, pp 5-13) and Jacobson (Jacobson KA & Gao Z-A (2006), Nature Reviews Drug Discovery, 5, pp 247-264). Studies on isolated neutrophils show an A₂ receptor-mediated inhibition of superoxide generation, degranulation, aggregation and adherence (Cronstein BN, Kramer SB, Weissmann G, Hirschhorn R, (1983), Trans. Assoc. Am. Physicians 96, pp 384-391; Cronstein BN, Kramer SB, Rosenstein ED, Weissmann G, Hirschhorn R, (1985), Ann N.Y. Acad. Sci. 451, pp 291-301; Burkey TH, Webster RO, (1993), Biochem. Biophys. Acta 1175, pp 312-318; Richter J, (1992), J. Leukocyte Biol. 51, pp 270-275; Skubitz KM, Wickman NW, Hammerschmidt DE, (1988), Blood 72, pp 29-33). When agents selective for the A_{2A} receptor over the A_{2B} receptor (e.g. CGS21680) have been used, the profile of inhibition appears consistent with an action on the A_{2A} receptor subtype (Dianzani C, Brunelleschi S, Viano I, Fantozzi R, (1994), Eur. J. Pharmacol. 263, pp 223-226).

Adenosine agonists may also down-regulate other classes of leucocytes (Elliot KRF, Leonard EJ, (1989), FEBS Letters 254, pp 94-98; Peachell PT, Lichtenstein LM, Schleimer RP, (1989), Biochem. Pharmacol. 38, pp 1717-1725). Studies on whole animals have shown the anti-inflammatory effects of methotrexate to be mediated through

5 adenosine and A₂ receptor activation (Asako H, Wolf RE, Granger DN, (1993), Gastroenterology 104, pp 31-37; Cronstein BN, Naime D, Ostad E, (1993), J. Clin. Invest. 92, pp 2675-2682; Cronstein BN, Naime D, Ostad E, (1994), Adv. Exp. Med. Biol. 370, pp 411-416). The selective A_{2A} agonist, CGS-21680 has shown anti-inflammatory activity in rats in pulmonary inflammation induced by allergen challenge and is blocked by pre-

10 treatment with selective A_{2A} receptor antagonist ZM241385 (Fozard, John R.; Ellis, Karen M.; Villela Dantas, Maria F.; Tigani, Bruno; Mazzoni, Lazzaro, European Journal of Pharmacology (2002), 438(3), 183-188). Adenosine itself, and compounds that raise circulating levels of adenosine also show anti-inflammatory effects *in vivo* (Green PG, Basbaum AI, Helms C, Levine JD, (1991), Proc. Natl. Acad. Sci. 88, pp 4162-4165;

15 Rosengren S, Bong GW, Firestein GS, (1995), J. Immunol. 154, pp 5444-5451). In addition raised levels of circulating adenosine in man (as a result of adenosine deaminase deficiency) results in immunosuppression (Hirschorn R, (1993), Pediatr. Res. 33, pp S35-41) and the crucial role A_{2A} receptors play in limiting and terminating inflammation has been reported by Ohta (Ohta, A & Sitkovsky, M, Nature, (2001), 414, pp916-920;

20 Sitkovsky, MV & Ohta, A, Trends in Immunology, (2005), 26, pp299-304).

We have now found novel compounds which inhibit leukocyte recruitment and activation and which are potent agonists of the adenosine 2_A (hereinafter A_{2A}) receptor. The compounds are therefore of potential therapeutic benefit in providing protection from leukocyte-induced tissue damage in diseases where leukocytes are implicated at the site

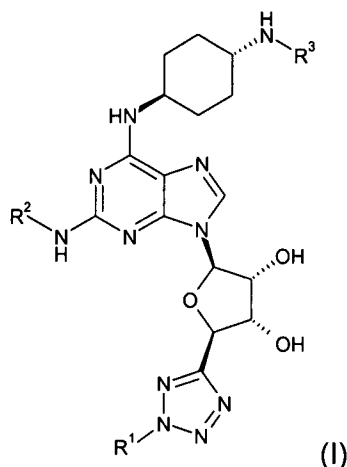
25 of inflammation. The compounds of the invention may also represent a safer alternative to corticosteroids in the treatment of inflammatory diseases, whose uses may be limited by their side-effect profiles.

Further, the compounds of the invention may show an improved profile over known A_{2A}-selective agonists in that they may possess one or more of the following properties:

- 30
- (I) approximately 100 fold more selective for A_{2A} over the human A₃ receptor;
 - (II) approximately 100 fold more selective for A_{2A} over the human A_{2B} receptor;
 - (III) approximately 100 fold more selective for A_{2A} over the human A₁ receptor;
 - (IV) greater than approximately 90% binding to human serum albumin; and
 - (V) less pronounced cardiovascular effects, in particular reduced tachycardia.

This profile can be considered of benefit as A₃ receptors are also found on leucocytes (e.g. eosinophils) and other inflammatory cells (e.g. mast cells) and activation of these receptors may have pro-inflammatory effects (Kohno Y, Xiao-duo J, Mawhorter SD, Koshiba M, Jacobson KA, (1996), Blood 88 pp 3569-3574; 1996; Van Schaick EA, Jacobson KA, Kim HO, Ijzerman AP, Danhof M, (1996), Eur. J. Pharmacol. 308 pp 311-314). It is even considered that the bronchoconstrictor effects of adenosine in asthmatics may be mediated via the adenosine A₃ receptor (Kohno Y, Xiao-duo J, Mawhorter SD, Koshiba M, Jacobson KA, (1996), Blood 88 pp 3569-3574). A_{2B} receptors are also found on mast cells and may thus be implicated in mast cell activation. A₁ receptors have a wide tissue distribution and can be found on *inter alia* heart, adipocytes, respiratory smooth muscle, neutrophils, kidney, hippocampus and cortex. A₁ receptor activation may thus cause decreased lipolysis, diuresis and CNS activation (Fozard JR, McCarthy C, (2002), Current Opinion in Investigational Drugs 3 pp 69-77). A compound that exhibits greater than approximately 90% binding to human serum albumin may be expected to have a reduced free fraction in whole blood.

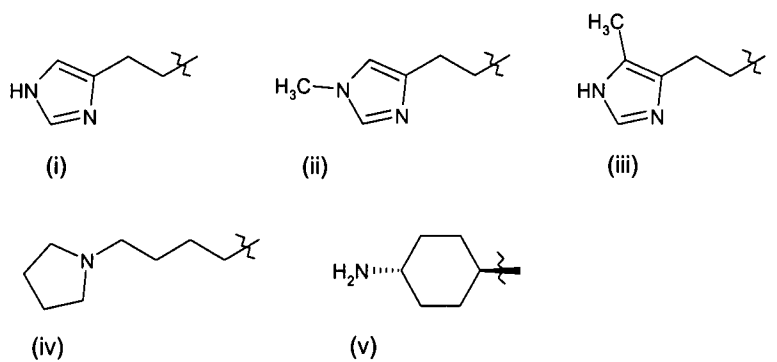
Thus according to the invention we provide compounds of formula (I):



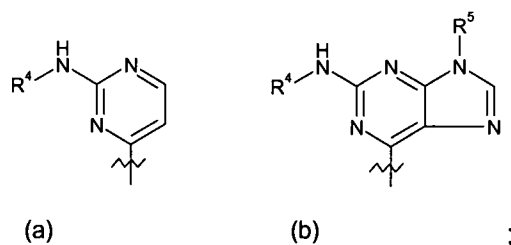
wherein:

R¹ represents methyl or ethyl;

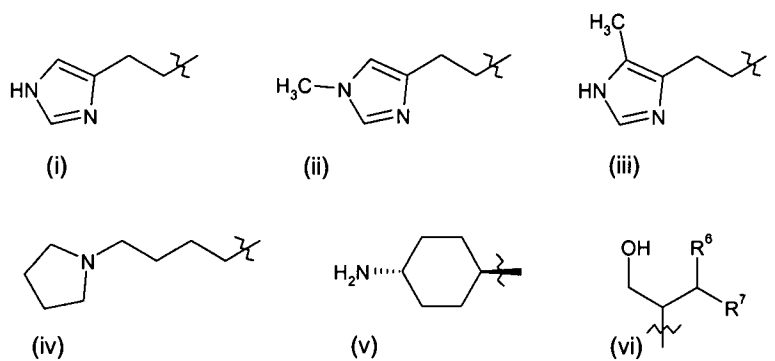
R² represents a group selected from the list consisting of:



R^3 represents a group selected from the list consisting of:



wherein R^4 represents a group selected from the list consisting of:



5

R^5 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkylaryl, C_{1-4} alkylheteroaryl or C_{1-4} hydroxyalkyl;

R^6 and R^7 independently represent hydrogen, methyl or phenyl;

and salts and solvates thereof.

- 10 By the term C_{1-4} alkyl as used herein is meant an alkyl function having between one to four carbon atoms in total, which may optionally be branched. Exemplary C_{1-4} alkyl groups include methyl, ethyl, propyl (n-propyl and iso-propyl) and butyl (n-butyl, sec-butyl and tert-butyl).

By the term C₁₋₄alkylaryl is meant a C₁₋₄alkyl function as described above, which is substituted by an aryl group. By the term aryl is meant a phenyl or naphthyl group which may optionally be substituted. An exemplary aryl group is phenyl. Exemplary C₁₋₄alkylaryl groups include benzyl.

- 5 By the term C₁₋₄alkylheteroaryl is meant a C₁₋₄alkyl function as described above, which is substituted by a heteroaryl group. By the term heteroaryl is meant a 5 or 6 membered aromatic group containing heteroatoms e.g. 1-4 heteroatoms selected from nitrogen, oxygen and sulphur. Exemplary heteroaryl groups include 5 membered rings (e.g. pyrrole, furan, thiophene) and 6 membered rings (e.g. pyridine, pyrimidine and pyrazine).
- 10 By the term C₁₋₄hydroxyalkyl is meant a C₁₋₄alkyl function as described above which is substituted with one or more (eg 1) hydroxyl groups.

Alkyl groups, whether as a group or part of a group, may optionally be substituted by one or more (e.g. one) fluorine atoms. Exemplary fluorine substituted alkyl groups include fluoromethyl and trifluoromethyl.

- 15 Aryl and heteroaryl groups may optionally be substituted, for example by one or more groups selected from amino, cyano, halo (e.g. fluorine or chlorine), nitro, thio and methoxy (optionally substituted by halo, e.g. trifluoromethoxy).

R¹ may for example represent ethyl.

- 20 R² may for example represent group (i), (ii), (iii) or (iv), e.g. group (iv). In one embodiment of the invention R² represents group (ii) or (iv). In another embodiment of the invention R² represents group (ii). In a further embodiment of the invention R² represents group (iv).

In one embodiment of the invention R³ represents group (a). In a second embodiment of the invention R³ represents group (b).

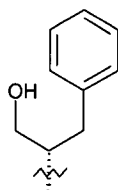
- 25 R⁴ may for example represent group (i), (ii), (iii), (iv) or (v) e.g. group (i), (ii), (iii) or (iv), e.g. group (iv). In one embodiment of the invention R⁴ represents group (ii) or (iv). In another embodiment of the invention R⁴ represents group (ii). In a further embodiment of the invention R⁴ represents group (iv).

R⁵ may, for example, represent hydrogen.

R⁶ may, for example, represent phenyl.

R⁷ may, for example, represent hydrogen.

An example of the group (vi) moiety is the following group, derived from L-phenylalaninol:



In one embodiment of the invention R² and R⁴ are the same. In a second embodiment of the invention R² and R⁴ are not the same.

In one embodiment of the invention the compound of formula (I) is:

(2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{{2-(1*H*-imidazol-4-yl)ethyl}amino}-6-({*trans*-4-[(2-{{2-(1*H*-imidazol-4-yl)ethyl}amino)-1*H*-purin-6-yl]amino]cyclohexyl}amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

10 (2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{{2-(1-methyl-1*H*-imidazol-4-yl)ethyl}amino}-6-({*trans*-4-[(2-{{2-(1-methyl-1*H*-imidazol-4-yl)ethyl}amino)-1*H*-purin-6-yl]amino]cyclohexyl}amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

(2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{{2-(5-methyl-1*H*-imidazol-4-yl)ethyl}amino}-6-({*trans*-4-[(2-{{2-(5-methyl-1*H*-imidazol-4-yl)ethyl}amino)-1*H*-purin-6-yl]amino]cyclohexyl}amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

15 (2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{{4-(1-pyrrolidinyl)butyl}amino}-6-({*trans*-4-[(2-{{4-(1-pyrrolidinyl)butyl}amino)-1*H*-purin-6-yl]amino]cyclohexyl}amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-(2-[(*trans*-4-aminocyclohexyl)amino]-6-{{*trans*-4-({2-[(*trans*-4-aminocyclohexyl)amino]-9*H*-purin-6-yl]amino)cyclohexyl}amino)-9*H*-purin-9-yl)-5-(2-ethyl-2*H*-tetrazol-5-yl)tetrahydro-3,4-furandiol;

20 (2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{{2-(1*H*-imidazol-4-yl)ethyl}amino}-6-({*trans*-4-[(2-{{2-(1*H*-imidazol-4-yl)ethyl}amino)-4-pyrimidinyl]amino]cyclohexyl}amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

(2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino}-6-({*trans*-4-[(2-{[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino}-4-pyrimidinyl)amino]cyclohexyl)amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

5 (2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{[2-(5-methyl-1*H*-imidazol-4-yl)ethyl]amino}-6-({*trans*-4-[(2-{[2-(5-methyl-1*H*-imidazol-4-yl)ethyl]amino}-4-pyrimidinyl)amino]cyclohexyl)amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

(2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{[4-(1-pyrrolidinyl)butyl]amino}-6-({*trans*-4-[(2-{[4-(1-pyrrolidinyl)butyl]amino}-4-pyrimidinyl)amino]cyclohexyl)amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

10

(2*R*,3*R*,4*S*,5*R*)-2-(2-[(*trans*-4-aminocyclohexyl)amino]-6-({*trans*-4-[(2-[(*trans*-4-aminocyclohexyl)amino]-4-pyrimidinyl)amino]cyclohexyl)amino)-9*H*-purin-9-yl)-5-(2-ethyl-2*H*-tetrazol-5-yl)tetrahydro-3,4-furandiol;

15 or a salt or solvate of any one thereof.

In a further embodiment of the invention the compound of formula (I) is:

(2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino}-6-({*trans*-4-[(2-{[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino}-1*H*-purin-6-yl)amino]cyclohexyl)amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

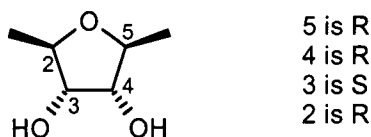
20 (2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{[4-(1-pyrrolidinyl)butyl]amino}-6-({*trans*-4-[(2-{[4-(1-pyrrolidinyl)butyl]amino}-1*H*-purin-6-yl)amino]cyclohexyl)amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

(2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino}-6-({*trans*-4-[(2-{[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino}-4-pyrimidinyl)amino]cyclohexyl)amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

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or a salt or solvate of any one thereof.

Compounds of formula (I) require absolute stereochemistry about the tetrahydrofuran ring such that the stereochemistry about each stereocentre in the tetrahydrofuran ring is as follows:

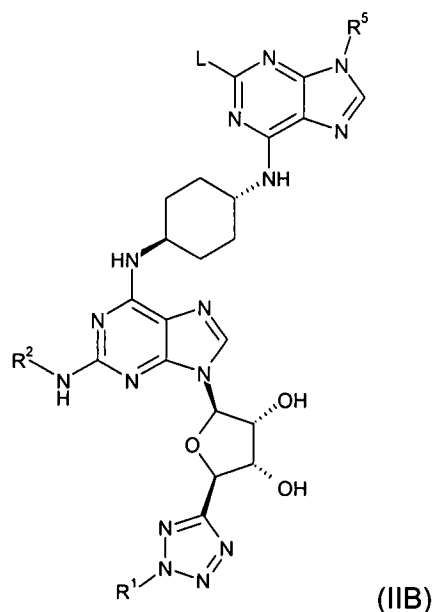
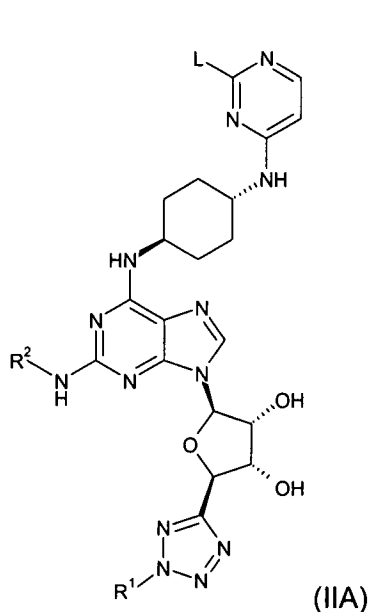


The stereochemistry about the cyclohexyl ring in the conserved core and the substituent groups where R^2 represents (v) or R^4 represents (v) are defined in relative terms. Within this requirement the invention encompasses all stereoisomers of the compounds of formula (I) (e.g. enantiomers or diastereoisomers) whether as individual stereoisomers isolated such as to be substantially free of the other stereoisomer (i.e. pure) or as mixtures thereof. An individual stereoisomer isolated such as to be substantially free of the other stereoisomer (i.e. pure) will be isolated such that less than about 10%, for example less than about 1% or less than about 0.1% of the other stereoisomer is present.

Salts of the compounds of the present invention are also encompassed within the scope of the invention. Because of their potential use in medicine, the salts of the compounds of formula (I) are preferably pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts can include acid addition salts. A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, formic, sulfuric, nitric, phosphoric, succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, xinafoate, *p*-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid), optionally in a suitable solvent such as an organic solvent, to give the salt which may be isolated for example by crystallisation and filtration. Thus, a pharmaceutically acceptable acid addition salt of a compound of formula (I) can be for example a hydrobromide, hydrochloride, formate, sulfate, nitrate, phosphate, succinate, maleate, acetate, fumarate, citrate, tartrate, benzoate, *p*-toluenesulfonate, methanesulfonate or naphthalenesulfonate salt. Other non-pharmaceutically acceptable salts, e.g. oxalates or trifluoroacetates, may be used, for example in the isolation of compounds of the invention, and are included within the scope of this invention. The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of formula (I).

Also included within the scope of the invention are all solvates, for example hydrates, and complexes of compounds and salts of the invention.

Compounds of formula (I), or a protected derivative thereof, may be prepared by the reaction of a compound of formula (IIA) or (IIB), or a protected derivative thereof:



wherein the groups R^1 , R^2 and R^5 are as defined above for compounds of formula (I) and L represents a leaving group;

by reaction with an amine of formula (III), or a protected derivative thereof:

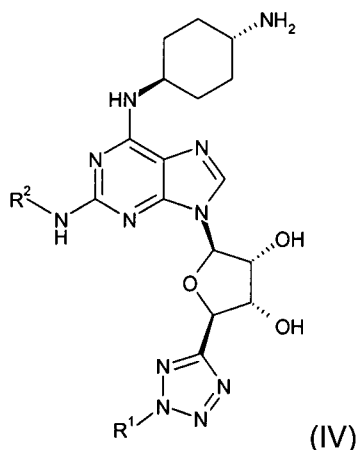


wherein R^4 is as defined above for compounds of formula (I).

L suitably represents halogen, for example bromine or chlorine, in particular chlorine. The reaction will generally involve heating the reagents to an elevated temperature of 50°C to 150°C, such as 100°C to 130°C, particularly about 120°C to 130°C, in the presence of an
 10 inert solvent such as DMSO and a base, such as an amine base (e.g. diisopropylethylamine).

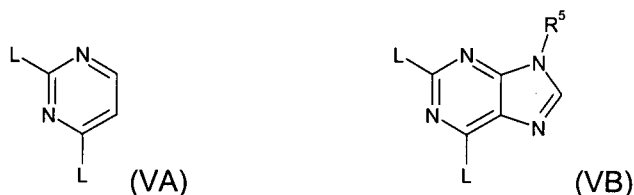
When R^5 represents hydrogen, the nitrogen to which it is attached (i.e. the 9 position of the purine ring) may suitably be protected, for example as the tetrahydropyran-2-yl derivative. Following the reaction described above for the formation of a protected
 15 derivative of a compound of formula (I), the nitrogen may then be deprotected. Suitable conditions for deprotection will depend upon the chosen protecting group, for example, where the protecting group is tetrahydropyran-2-yl suitable deprotection conditions include treatment with formic acid in methanol/water.

Compounds of formula (IIA) or (IIB), or a protected derivative thereof may be prepared by
 20 the reaction of a compound of formula (IV), or a protected derivative thereof:



wherein the groups R^1 and R^2 are as defined above for compounds of formula (I);

with a compound of formula (VA) or (VB), or a protected derivative thereof:

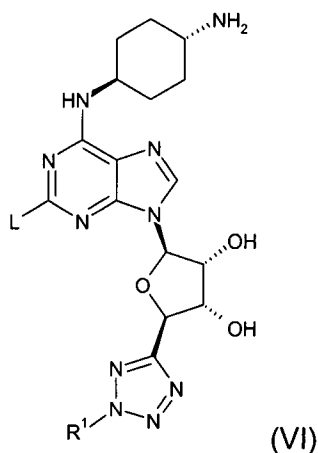


- 5 wherein R^5 is as defined above for compounds of formula (I) and L represents a leaving group.

L suitably represents halogen, for example bromine or chlorine, in particular chlorine. The reaction will generally be performed in the presence of a base, such as an amine base (e.g. diisopropylethylamine), in a suitable solvent, such as an alcohol (e.g. isopropanol), at
 10 an elevated temperature (e.g. 50°C to 70°C).

As noted above, when R^5 represents hydrogen, the nitrogen to which it is attached (i.e. the 9 position of the purine ring) may suitably be protected, for example as the tetrahydropyran-2-yl derivative. Following the reaction described above for the formation of a protected derivative of a compound of formula (IIB), the nitrogen may then be
 15 deprotected. Suitable conditions for deprotection will depend upon the chosen protecting group, for example, where the protecting group is tetrahydropyran-2-yl suitable deprotection conditions include treatment with formic acid in methanol/water.

Compounds of formula (IV), or a protected derivative thereof, may be prepared by the reaction of a compound of formula (VI), or a protected derivative thereof:



wherein R¹ is as defined above for compounds of formula (I) and L represents a leaving group;

with an amine of formula (VII), or a protected derivative thereof:



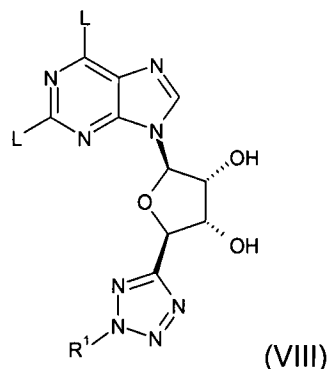
wherein R² is as defined above for compounds of formula (I).

L suitably represents halogen, for example bromine or chlorine, in particular chlorine. The reaction will generally involve heating the reagents to an elevated temperature of 50°C to 150°C, such as 100°C to 130°C, particularly about 120°C to 130°C, in the presence of an
 10 inert solvent such as DMSO and a base, such as an amine base (e.g. diisopropylethylamine).

Suitably the primary amine group attached to the cyclohexyl ring in compounds of formula (VI) is protected, for example as the dimethylethyloxycarbonyl (Boc) derivative. Following the reaction to yield a protected derivative of a compound of formula (IV) the amine
 15 protecting group may be removed, for example, where the protecting group represents dimethylethyloxycarbonyl this may be removed, for example, by treatment with trifluoroacetic acid in dichloromethane.

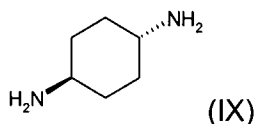
When R² represents a group of formula (v), the amine function of R² may suitably be protected by a different protecting group employed to that employed to protect the amine
 20 function of the compound of formula (VI). For example the former may be protected using Cbz (which may subsequently be removed by catalytic hydrogenation) and the latter may be protected using Boc.

Compounds of formula (VI), or protected derivatives thereof, may be prepared by the reaction of a compound of formula (VIII), or a protected derivative thereof:



wherein R¹ is as defined above for compounds of formula (I) and L represents a leaving group;

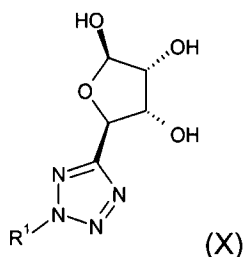
with the compound of formula (IX), or a protected derivative thereof:



L suitably represents halogen, for example bromine or chlorine, in particular chlorine. The reaction will typically be performed in the presence of a base, such as an amine base (e.g. diisopropylethylamine), in a suitable solvent, such as an alcohol (e.g. isopropanol), at an elevated temperature (e.g. 50°C to 70°C).

Compounds of formula (IX) will typically be utilised in the form in which one primary amine group is protected, for example as the dimethylethyloxycarbonyl derivative.

Compounds of formula (VIII) wherein L represents chlorine, R¹ represents ethyl and the hydroxyl functions are protected with acetyl groups are disclosed in WO98/28319 (referred to as Intermediate 7 therein). Other compounds of formula (VIII) may be prepared by analogous means. Briefly, a compound of formula (VIII) may be prepared by reacting a compound of formula (X), or a protected derivative thereof:



wherein R¹ is as defined above for compounds of formula (I);

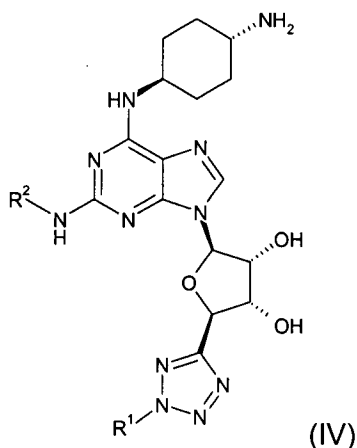
- with a compound such as 2,6-dichloropurine in a suitable solvent (e.g. acetonitrile), under inert conditions and in the presence of a Lewis acid (such as trimethylsilyl triflate) and optionally with a catalyst (e.g. 1,8-diazabicyclo[5.4.0]undec-7-ene).

Compounds of formula (III), (VII), (IX) and (X) are known *per se* or may be prepared by known methods.

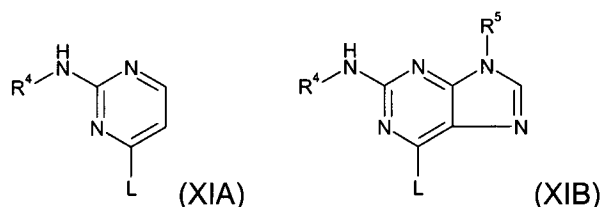
Compounds of formula (VA), for example 2,4-dichloropyrimidine, are available commercially or may be prepared by known methods.

- 10 The compound of formula (VB) wherein L represent chlorine and which is protected by a tetrahydropyran-2-yl group (i.e. 2,6-dichloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine) and a method for its synthesis are disclosed in WO2003/080604A1 (referred to as Intermediate 11 therein). Other compounds of formula (VB) may be prepared by analogous means.

- 15 In a second process, compounds of formula (I), or a protected derivative thereof, may be prepared by reacting a compound of formula (IV) as described above, or a protected derivative thereof:



with a compound of formula (XIA) or (XIB), or a protected derivative thereof:

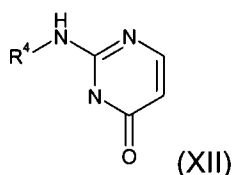


wherein the groups R^4 and R^5 are as defined above for compounds of formula (I) and L is a leaving group.

L suitably represents halogen, for example bromine or chlorine, in particular chlorine. Said reaction will generally involve heating the reagents to a temperature of 50°C to 150°C, in the presence of an inert solvent such as ethanol, propan-2-ol or DMSO and a base, such as an amine base (e.g. diisopropylethylamine).

In compounds of formula (XIB) when R^5 represents H the nitrogen to which it is attached (i.e. the 9-position of the purine ring) may optionally be protected by a tetrahydropyran-2-yl (THP) moiety. The THP group may subsequently be removed following the reaction with a compound of formula (IV). Suitable deprotection conditions include treatment with formic acid in methanol/water.

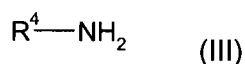
Compounds of formula (XIA) may be prepared according to Manley PJ et al. (2003) Bioorganic Med. Chem. Lett., 13 pp 1673-1677. Briefly, a compound of formula (XII), or a protected derivative thereof:



wherein R^4 is as defined above for compounds of formula (I);

may be reacted with POCl_3 under reflux.

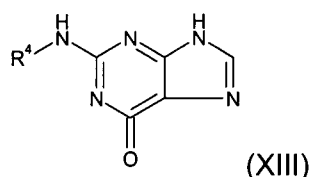
Compounds of formula (XII) may be prepared by the reacting 2-(methylthio)-pyrimidin-4(3H)-one (commercially available) with an amine of formula (III) as described above, or a protected derivative thereof:



wherein R^4 is as defined above for compounds of formula (I).

The reaction is typically performed in diglyme at a temperature of approximately 170 °C.

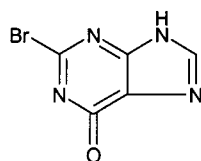
Compounds of formula (XIB) wherein R⁵ represents H may be prepared by means described in Wright GE et al. (1987) J. Med. Chem., 30 pp 109-116. Briefly, a compound
 5 of formula (XIII):



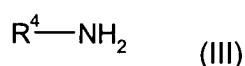
wherein R⁴ is as defined above for compounds of formula (I);

may be reacted with POCl₃ in the presence of N,N-dimethylaniline under reflux.

Compounds of formula (XIII) may be prepared by the reaction of a compound such as 2-
 10 bromohypoxanthine, which is commercially available:



with an amine of formula (III) as described above, or a protected derivative thereof:



wherein R⁴ is as defined above for compounds of formula (I);

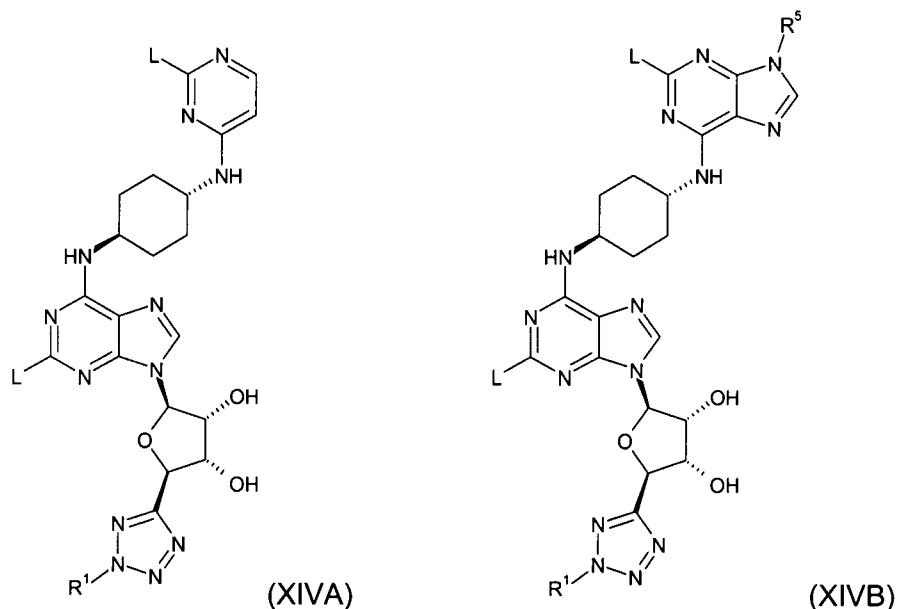
15 under reflux in a mixture of water and 2-methoxyethanol. Further details of this reaction may be obtained by reference to WO99/38877.

Compounds of formula (XIB) wherein R⁵ does not represent H, may be prepared by the alkylation of compounds of formula (XIB) wherein R⁵ represents H. Alkylation may be performed using an alkylating agent such as R⁵-I, in the presence of a base (e.g. potassium carbonate) and a suitable solvent (e.g. DMF), for example see Langli, G et al.
 20 (1996) Tetrahedron, 52 pp5625-5638. Alternatively, alkylation may be performed using an alcohol R⁵-OH in the presence of diethylazodicarboxylate and triphenylphosphine in

THF (see Maruyama, T et al. (2000) Nucleosides, Nucleotides and Nucleic Acids, 19 pp1193-1203).

In a third process, compounds of formula (I) wherein R^2 and R^4 are the same, or a protected derivative thereof, may be prepared by reacting a compound of formula (XIVA)

5 or (XIVB), or a protected derivative thereof:



wherein R^1 and R^5 are as defined above for compounds of formula (I) and L represents a leaving group;

with a compound of formula (VII), as described above, or a protected derivative thereof:



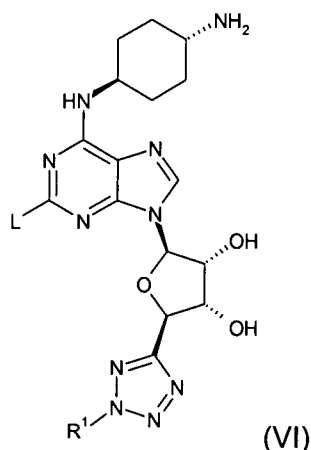
wherein R^2 is as defined above for compounds of formula (I).

L suitably represents halogen, for example bromine or chlorine, in particular chlorine. Said reaction will generally involve heating the reagents to a temperature of 50°C to 150°C, such as 100°C to 130°C, particularly about 120°C to 130°C, in the presence of an inert
 15 solvent such as DMSO and a base, such as an amine base (e.g. diisopropylethylamine).

When R^5 represents hydrogen, the nitrogen to which it is attached (i.e. the 9 position of the purine ring) may suitably be protected, for example as the tetrahydropyran-2-yl derivative. Following the reaction described above for the formation of a protected derivative of a compound of formula (I), the nitrogen may then be deprotected. Suitable

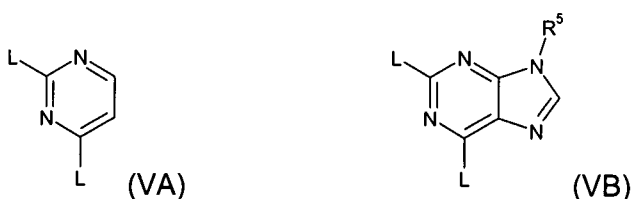
conditions for deprotection will depend upon the chosen protecting group, for example, where the protecting group is tetrahydropyran-2-yl suitable deprotection conditions include treatment with formic acid in methanol/water.

- Compounds of formula (XIVA) or (XIVB), or protected derivatives thereof, may be prepared by reacting a compound of formula (VI), as described above, or a protected derivative thereof:



wherein R^1 is as defined above for compounds of formula (I) and L represents a leaving group;

- with a compound of formula (VA) or (VB), as described above:



wherein R^5 is as defined above for compounds of formula (I) and L represents a leaving group.

- As noted above, for compounds of formula (VB) where R^5 represents hydrogen, the nitrogen to which it is attached (i.e. the 9 position of the purine ring) may suitably be protected, for example as the tetrahydropyran-2-yl derivative.

- L suitably represents halogen, for example bromine or chlorine, especially chlorine. The compound of formula (VA) may, for example, be 2,4-dichloropyrimidine. The compound of formula (VB) may, for example, be 2,6-dichloro-9-(tetrahydropyran-2-yl)purine. The reaction will generally be performed in the presence of a base, such as an amine base

(e.g. diisopropylethylamine), in a suitable solvent, such as an alcohol (e.g. isopropanol), at an elevated temperature (e.g. 50°C to 70°C).

Following the reaction described above for the formation of a protected derivative of a compound of formula (XIVB), the purine nitrogen may be then deprotected. Suitable conditions for deprotection will depend upon the chosen protecting group, for example, where the protecting group is tetrahydropyran-2-yl suitable deprotection conditions include the use of formic acid in methanol/water.

Compounds of formula (IIA), (IIB), (IV), (VI), (VIII), (X), (XIVA) and (XIVB) may be used in a form in which the hydroxyl groups are protected with suitable protecting groups, e.g. with acetonide or acetyl groups, in particular acetyl groups.

As described above protected derivatives of compounds of the invention or intermediates for preparing compounds of the invention may be used. Examples of protecting groups and the means for their removal can be found in TW Greene "Protective Groups in Organic Synthesis" (J Wiley and Sons, 1991). Suitable hydroxyl protecting groups include alkyl (e.g. methyl), acetal (e.g. acetonide) and acyl (e.g. acetyl or benzoyl) which may be removed by hydrolysis, and arylalkyl (e.g. benzyl) which may be removed by catalytic hydrogenolysis. Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl) which may be removed by hydrolysis or hydrogenolysis as appropriate.

The processes described above for the production of compounds of formula (I) and salts and solvates thereof constitute one aspect of the present invention. Novel intermediates, for example compounds of formulae (IIA), (IIB), (IV), (XIVA), (XIVB) and protected derivatives thereof, also form an aspect of the invention.

The potential for compounds of formula (I) to inhibit leukocyte function may be demonstrated, for example, by their ability to inhibit superoxide (O_2^-) generation from neutrophils stimulated with chemoattractants such as N-formylmethionyl-leucyl-phenylalanine (fMLP). Accordingly, compounds of formula (I) are of potential therapeutic benefit in providing protection from leukocyte-induced tissue damage in diseases where leukocytes are implicated at the site of inflammation.

Examples of disease states in which the compounds of the invention have potentially beneficial anti-inflammatory effects include diseases of the respiratory tract such as adult respiratory distress syndrome (ARDS), bronchitis (including chronic bronchitis), cystic

fibrosis, asthma (including allergen-induced asthmatic reactions), emphysema, rhinitis and septic shock. Other relevant disease states include diseases of the gastrointestinal tract such as intestinal inflammatory diseases including inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), *Helicobacter pylori* induced gastritis and intestinal inflammatory diseases secondary to radiation exposure or allergen exposure, and non-steroidal anti-inflammatory drug-induced gastropathy. Furthermore, compounds of the invention may be used to treat skin diseases such as psoriasis, allergic dermatitis and hypersensitivity reactions and diseases of the central nervous system which have an inflammatory component e.g. Alzheimer's disease and multiple sclerosis.

- 10 Further examples of disease states in which compounds of the invention have potentially beneficial effects include cardiac conditions such as peripheral vascular disease, post-ischaemic reperfusion injury and idiopathic hypereosinophilic syndrome.

Compounds of the invention which inhibit lymphocyte function may be useful as immunosuppressive agents and so have use in the treatment of auto-immune diseases such as rheumatoid arthritis and diabetes.

Compounds of the invention may also be useful in inhibiting metastasis.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

More preferably the treatment and/or prophylaxis is of asthma or COPD including chronic bronchitis and emphysema in a mammal (e.g. human).

As mentioned above, compounds of formula (I) are useful in human or veterinary medicine, in particular as anti-inflammatory agents.

There is thus provided as a further aspect of the invention a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in human or veterinary medicine, particularly in the treatment of patients with an inflammatory condition and/or allergic condition who are susceptible to leukocyte-induced tissue damage.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of patients with an inflammatory condition and/or allergic condition who are susceptible to leukocyte-induced tissue damage.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with an inflammatory condition and/or allergic condition who is susceptible to leukocyte-induced tissue damage, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

For use in medicine, the compounds of the present invention are usually administered as a pharmaceutical composition.

The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof optionally with one or more pharmaceutically acceptable carriers and/or excipients.

The pharmaceutical composition may be for use in the treatment and/or prophylaxis of any of the conditions described herein.

Compounds of formula (I) and salts and solvates thereof and/or the pharmaceutical composition containing them may be administered, for example, by parenteral (eg. intravenous, subcutaneous, or intramuscular), inhaled, nasal, transdermal or rectal administration, or as topical treatments (eg. ointments or gels). Routes of administration of particular interest include inhaled and intra-nasal. Inhaled administration involves topical administration to the lung, eg. by aerosol or dry powder composition.

The compound of formula (I) and salts and solvates thereof and/or the pharmaceutical composition may be administered by a controlled or sustained release formulation as described in WO 00/50011.

A parenteral composition may comprise a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil. Alternatively, the solution may be lyophilised; the lyophilised parenteral pharmaceutical composition may be reconstituted with a suitable solvent just prior to administration.

Compositions for nasal or inhaled administration may conveniently be formulated as aerosols, solutions, suspensions, drops, gels or dry powders, with aqueous or non-aqueous vehicles optionally with the addition of agents such as thickening agents, buffer

salts or acid or alkali to adjust the pH, isotonicity adjusting agents, antioxidants and/or preservatives.

5 Capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

There is also provided a process for preparing such a pharmaceutical formulation which comprises mixing the ingredients.

10

For compositions suitable and/or adapted for inhaled administration, the compound or salt or solvate of formula (I) is typically in a particle-size-reduced form, and particularly the size-reduced form is obtained or obtainable by micronisation. Generally, the particle size of the size-reduced (e.g. micronised) compound or salt can be defined by a D50 value of
15 about 0.5 to about 10 microns (for example as measured using laser diffraction).

Aerosol formulations, e.g. for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities
20 in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

25

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide or an organic propellant such as a chlorofluorocarbon (CFC) or hydrofluorocarbon (HFC). Suitable CFC propellants include dichlorodifluoromethane, trichlorofluoromethane and
30 dichlorotetrafluoroethane. Suitable HFC propellants include 1,1,1,2,3,3,3-heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser.

Optionally, in particular for dry powder inhalable compositions, a pharmaceutical
35 composition for inhaled administration can be incorporated into a plurality of sealed dose containers (e.g. containing the dry powder composition) mounted longitudinally in a strip

or ribbon inside a suitable inhalation device. The container is rupturable or peel-openable on demand and the dose of e.g. the dry powder composition can be administered by inhalation via the device such as the DISKUSTM device, marketed by GlaxoSmithKline. The DISKUSTM inhalation device is for example described in GB 2242134 A, and in such

5 a device at least one container for the pharmaceutical composition in powder form (the container or containers preferably being a plurality of sealed dose containers mounted longitudinally in a strip or ribbon) is defined between two members peelably secured to one another; the device comprises: a means of defining an opening station for the said container or containers; a means for peeling the members apart at the opening station to

10 open the container; and an outlet, communicating with the opened container, through which a user can inhale the pharmaceutical composition in powder form from the opened container. Alternatively, the formulation may be presented if desired together with one or more other therapeutic agents in an inhalation device wherein the individual therapeutic agents are administrable simultaneously but are stored separately (or wholly or partly

15 stored separately for triple combinations), e.g. in separate pharmaceutical compositions, for example as described in WO 03/061743.

The proportion of the active compound of formula (I) or salt or solvate thereof in the topical compositions according to the invention depends on the precise type of formulation

20 to be prepared but may generally be within the range of from 0.001 to 20% by weight, for example 0.001 to 10% by weight. Generally, however for most types of preparations the proportion used may be within the range of from 0.005 to 1% such as 0.01 to 0.5%. However, in powders for inhalation or insufflation the proportion used may be within the range of from 0.1 to 5%.

25 Aerosol formulations are preferably arranged so that each metered dose or "puff" of aerosol contains 10 μ g-2000 μ g, for example 20 μ g-2000 μ g, preferably about 20 μ g-500 μ g of a compound of formula (I). Administration may be once daily or several times daily, for example 2, 3, 4 or 8 times, giving for example 1, 2 or 3 doses each time. The overall daily

30 dose with an aerosol will be within the range 20 μ g-10mg, for example 100 μ g-10mg, preferably 200 μ g-2000 μ g. The overall daily dose and the metered dose delivered by capsules and cartridges in an inhaler or insufflator will generally be double those with aerosol formulations.

35 The compound (or salts and solvates thereof) and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic

agents, for example selected from anti-inflammatory agents, anticholinergic agents (particularly an M_1 , M_2 , M_1/M_2 or M_3 receptor antagonist), β_2 -adrenoreceptor agonists, antiinfective agents (e.g. antibiotics, antivirals), or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a
5 pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with one or more other therapeutically active agents, for example selected from an anti-inflammatory agent (for example a corticosteroid or an NSAID), an anticholinergic agent, a β_2 -adrenoreceptor agonist, an antiinfective agent (e.g. an antibiotic or an antiviral), or an antihistamine. Particular combinations of the invention include a
10 compound of formula (I) or a physiologically acceptable salt or solvate thereof together with a steroid, a β_2 -adrenoreceptor agonist, an anticholinergic, and/or a PDE-4 inhibitor. Preferred combinations are those comprising one or two other therapeutic agents.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic
15 ingredient(s) may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts), or prodrugs, or as esters (e.g. lower alkyl esters), or as solvates (e.g. hydrates) to optimise the activity and/or stability and/or physical characteristics (e.g. solubility) of the therapeutic ingredient. It will be clear also that where appropriate, the therapeutic ingredients may be used in optically pure form.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof with one or more other therapeutically active agents, for example, a β_2 -adrenoreceptor agonist, an anti-histamine, an anti-allergic agent, an anti-inflammatory agent (including a steroid or a PDE-4
25 inhibitor), an anticholinergic agent or an antiinfective agent (eg. antibiotics or antivirals).

Examples of β_2 -adrenoreceptor agonists include salmeterol (e.g. as the racemate or a single enantiomer, such as the *R*-enantiomer), salbutamol (e.g. as the racemate or a single enantiomer such as the *R*-enantiomer), formoterol (e.g. as the racemate or a single
30 diastereomer such as the *R,R*-diastereomer), salmefamol, fenoterol, carmoterol, etanterol, naminterol, clenbuterol, pirbuterol, flerobuterol, reproterol, bambuterol, indacaterol or terbutaline and salts thereof, for example the xinafoate (1-hydroxy-2-naphthalenecarboxylate) salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol. For example, salmeterol (which may be a racemate or
35 a single enantiomer, such as the *R*-enantiomer), salbutamol, formoterol, salmefamol,

fenoterol or terbutaline and salts thereof, for example the xinafoate salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol. Long-acting β_2 -adrenoreceptor agonists, for example those which provide bronchodilation for 12 hours or longer, may be preferred. Examples include salmeterol and formoterol.

5

Other long acting β_2 -adrenoreceptor agonists include those described in WO02/66422A, WO02/270490, WO02/076933, WO03/024439, WO03/072539, WO 03/091204, WO04/016578, WO04/022547, WO04/037807, WO04/037773, WO04/037768, WO04/039762, WO04/039766, WO01/42193 and WO03/042160.

10

Particular long-acting β_2 -adrenoreceptor agonists are:

3-(4-{{6-(((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl}oxy}butyl)benzenesulfonamide;

3-(3-{{7-(((2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl)phenyl]ethyl)-amino)heptyl}oxy}propyl)benzenesulfonamide;

15

4-((1R)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol;

4-((1R)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol;

20

N-[2-hydroxyl-5-[(1R)-1-hydroxy-2-[[2-4-[(2R)-2-hydroxy-2-phenylethyl]amino]phenyl]ethyl]amino]ethyl]phenyl]formamide,

N-2{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1H)-quinolinon-5-yl)ethylamine, and

5-[(R)-2-(2-{4-[4-(2-amino-2-methyl-propoxy)-phenylamino]-phenyl}-ethylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, and salts thereof.

25

The β_2 -adrenoreceptor agonist may be in the form of a salt formed with a pharmaceutically acceptable acid selected from sulphuric, hydrochloric, fumaric, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), cinnamic, substituted cinnamic, triphenylacetic, sulphamic, sulphanilic, naphthaleneacrylic, benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic and 4-phenylbenzoic acid.

30

Anti-inflammatory agents that may be incorporated in a combination include corticosteroids particularly inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples of corticosteroids include methyl prednisolone,

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prednisolone, dexamethasone, fluticasone propionate, 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carbothioic acid S-(2-oxo-tetrahydro-furan-3S-yl) ester, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methylcyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(2,2,3,3-tetramethylcyclopropylcarbonyl)oxy-androsta-1,4-diene-17 β -carboxylic acid cyanomethyl ester, beclomethasone esters (such as the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (such as the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, (16 α ,17-[[*(R)*-cyclohexylmethylene]bis(oxy)]-11 β ,21-dihydroxy-pregna-1,4-diene-3,20-dione), butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester and 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester, more preferably 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester.

Non-steroidal compounds that may have glucocorticoid activity include those covered in the following patent applications WO03/082827, WO01/10143, WO98/54159, WO04/005229, WO04/009016, WO04/009017, WO04/018429, WO03/104195, WO03/082787, WO03/082280, WO03/059899, WO03/101932, WO02/02565, WO01/16128, WO00/66590, WO03/086294, WO04/026248, WO03/061651, WO03/08277.

Anti-inflammatory agents include non-steroidal anti-inflammatory drugs (NSAID's).

Possible NSAID's that may be used in a combination include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (for example, theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis (for example, montelukast), iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (for example, adenosine 2a agonists), cytokine antagonists (for example, chemokine antagonists, such as a CCR3 antagonist) or inhibitors of cytokine synthesis, or 5-

lipooxygenase inhibitors. An iNOS (inducible nitric oxide synthase inhibitor) is preferably for oral administration. Other iNOS inhibitors include those disclosed in WO93/13055, WO98/30537, WO02/50021, WO95/34534 and WO99/62875. Suitable CCR3 inhibitors include those disclosed in WO02/26722.

5

Phosphodiesterase 4 (PDE4) inhibitors that may be used in a combination include any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family, such as PDE3 and PDE5, as well as PDE4.

10

Compounds include *cis*-4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]. Another compound of interest is *cis*-4-cyano-4-

15 [3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomilast) and its salts, esters, pro-drugs or physical forms, which is described in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference.

20 Other PDE4 inhibitors include AWD-12-281 from Elbion (Hofgen, N. et al. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa

25 Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. et al. Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden;; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from

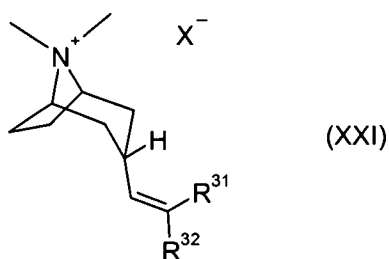
30 Vernalis; or T-440 (Tanabe Seiyaku; Fuji, K. et al. J Pharmacol Exp Ther, 1998, 284(1): 162), and T2585.

Further compounds are disclosed in the published international patent application WO04/024728 (Glaxo Group Ltd), PCT/EP2003/014867 (Glaxo Group Ltd) and

35 PCT/EP2004/005494 (Glaxo Group Ltd).

Anticholinergic agents are those compounds that act as antagonists at the muscarinic receptors, in particular those compounds which are antagonists of the M₁ or M₃ receptors, dual antagonists of the M₁/M₃ or M₂/M₃ receptors or pan-antagonists of the M₁/M₂/M₃ receptors. Exemplary compounds for administration via inhalation include ipratropium (for example, as the bromide, CAS 22254-24-6, sold under the name Atrovent), oxitropium (for example, as the bromide, CAS 30286-75-0) and tiotropium (for example, as the bromide, CAS 136310-93-5, sold under the name Spiriva). Also of interest are revatropate (for example, as the hydrobromide, CAS 262586-79-8) and LAS-34273 which is disclosed in WO01/04118. Exemplary compounds for oral administration include pirenzepine (for example, CAS 28797-61-7), darifenacin (for example, CAS 133099-04-4, or CAS 133099-07-7 for the hydrobromide sold under the name Enablex), oxybutynin (for example, CAS 5633-20-5, sold under the name Ditropan), terodiline (for example, CAS 15793-40-5), tolterodine (for example, CAS 124937-51-5, or CAS 124937-52-6 for the tartrate, sold under the name Detrol), otilonium (for example, as the bromide, CAS 26095-59-0, sold under the name Spasmomen), trospium chloride (for example, CAS 10405-02-4) and solifenacin (for example, CAS 242478-37-1, or CAS 242478-38-2, or the succinate also known as YM-905 and sold under the name Vesicare).

Other anticholinergic agents include compounds of formula (XXI), which are disclosed in US patent application 60/487981:



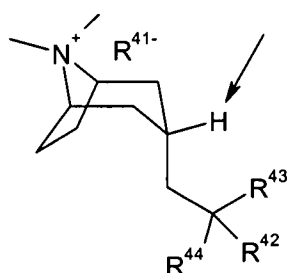
in which the preferred orientation of the alkyl chain attached to the tropane ring is endo; R³¹ and R³² are, independently, selected from the group consisting of straight or branched chain lower alkyl groups having preferably from 1 to 6 carbon atoms, cycloalkyl groups having from 5 to 6 carbon atoms, cycloalkyl-alkyl having 6 to 10 carbon atoms, 2-thienyl, 2-pyridyl, phenyl, phenyl substituted with an alkyl group having not in excess of 4 carbon atoms and phenyl substituted with an alkoxy group having not in excess of 4 carbon atoms;

X⁻ represents an anion associated with the positive charge of the N atom. X⁻ may be but is not limited to chloride, bromide, iodide, sulfate, benzene sulfonate, and toluene sulfonate, including, for example:

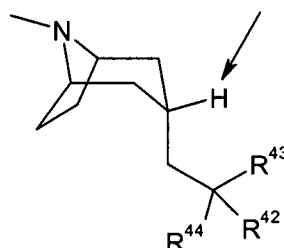
- (3-*endo*)-3-(2,2-di-2-thienylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;
 5 (3-*endo*)-3-(2,2-diphenylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide;
 (3-*endo*)-3-(2,2-diphenylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane 4-methylbenzenesulfonate;
 (3-*endo*)-8,8-dimethyl-3-[2-phenyl-2-(2-thienyl)ethenyl]-8-azoniabicyclo[3.2.1]octane bromide; and/or
 10 (3-*endo*)-8,8-dimethyl-3-[2-phenyl-2-(2-pyridinyl)ethenyl]-8-azoniabicyclo[3.2.1]octane bromide.

Further anticholinergic agents include compounds of formula (XXII) or (XXIII), which are disclosed in US patent application 60/511009:

15



(XXII)



(XXIII)

wherein:

the H atom indicated is in the exo position;

- 20 R⁴¹⁻ represents an anion associated with the positive charge of the N atom. R⁴¹⁻ may be but is not limited to chloride, bromide, iodide, sulfate, benzene sulfonate and toluene sulfonate;

- R⁴² and R⁴³ are independently selected from the group consisting of straight or branched chain lower alkyl groups (having preferably from 1 to 6 carbon atoms), cycloalkyl groups (having from 5 to 6 carbon atoms), cycloalkyl-alkyl (having 6 to 10 carbon atoms), heterocycloalkyl (having 5 to 6 carbon atoms) and N or O as the heteroatom, heterocycloalkyl-alkyl (having 6 to 10 carbon atoms) and N or O as the heteroatom, aryl, optionally substituted aryl, heteroaryl, and optionally substituted heteroaryl;

- R⁴⁴ is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₁₂)cycloalkyl, (C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl(C₃-C₁₂)cycloalkyl, (C₁-C₆)alkyl(C₃-C₇)heterocycloalkyl, aryl, heteroaryl, (C₁-C₆)alkyl-aryl, (C₁-C₆)alkyl-heteroaryl, -OR⁴⁵, -CH₂OR⁴⁵, -CH₂OH, -CN,

-CF₃, -CH₂O(CO)R⁴⁶, -CO₂R⁴⁷, -CH₂NH₂, -CH₂N(R⁴⁷)SO₂R⁴⁵, -SO₂N(R⁴⁷)(R⁴⁸), -CON(R⁴⁷)(R⁴⁸), -CH₂N(R⁴⁸)CO(R⁴⁶), -CH₂N(R⁴⁸)SO₂(R⁴⁶), -CH₂N(R⁴⁸)CO₂(R⁴⁵), -CH₂N(R⁴⁸)CONH(R⁴⁷);

R⁴⁵ is selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)alkyl(C₃-C₁₂)cycloalkyl,

5 (C₁-C₆)alkyl(C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl-aryl, (C₁-C₆)alkyl-heteroaryl;

R⁴⁶ is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₁₂)cycloalkyl, (C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl(C₃-C₁₂)cycloalkyl, (C₁-C₆)alkyl(C₃-C₇)heterocycloalkyl, aryl, heteroaryl, (C₁-C₆)alkyl-aryl, (C₁-C₆)alkyl-heteroaryl;

R⁴⁷ and R⁴⁸ are, independently, selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₁₂)cycloalkyl, (C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl(C₃-C₁₂)cycloalkyl, (C₁-C₆)alkyl(C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl-aryl, and (C₁-C₆)alkyl-heteroaryl, including, for example:

(endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;

3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile;

15 (endo)-8-methyl-3-(2,2,2-triphenyl-ethyl)-8-aza-bicyclo[3.2.1]octane;

3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide;

3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionic acid;

(endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;

(endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide;

20 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propan-1-ol;

N-benzyl-3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide;

(endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;

1-benzyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;

25 1-ethyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;

N-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-acetamide;

N-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzamide;

3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-di-thiophen-2-yl-propionitrile;

(endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane

30 iodide;

N-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzenesulfonamide;

[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;

N-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-

35 methanesulfonamide; and/or

(endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.

Further compounds include:

- (endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
- 5 (endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
- (endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide;
- (endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
- 10 (endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide; and/or
- (endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.
- 15 Antihistamines (also referred to as H1-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H1-receptors, and are safe for human use. First generation antagonists, include derivatives of ethanolamines, ethylenediamines, and alkylamines, such as diphenylhydramine, pyrilamine, clemastine, chlorpheniramine. Second generation antagonists, which are non-sedating, include loratidine, desloratidine,
- 20 terfenadine, astemizole, acrivastine, azelastine, levocetirizine fexofenadine, cetirizine and efletirizine.
- The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof together with a PDE4
- 25 inhibitor.
- The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof together with a β_2 -adrenoreceptor agonist.
- 30 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof together with an anticholinergic.
- 35 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof together with an antihistamine.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention.

5

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Preferably, the individual compounds will be administered simultaneously in a combined pharmaceutical formulation. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

10

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus a pharmaceutical composition comprising a combination as defined above optionally together with one or more pharmaceutically acceptable carriers and/or excipients represent a further aspect of the invention.

15

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or in combined pharmaceutical compositions.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention.

20

The compounds of the invention may be more efficacious, show greater selectivity, have fewer side effects, have a longer duration of action, show less systemic activity when administered by inhalation or have other more desirable properties than similar known compounds.

25

In particular the compounds of the invention may be highly potent at the A_{2A} receptor, show greater selectivity for the adenosine 2_A receptor subtype over other adenosine receptor subtypes (especially the A₁ and A₃ receptor subtypes), be capable of being highly bound to human serum albumin (greater than about 90%) and/or may exhibit less pronounced cardiac effects than hitherto known compounds.

30

The various aspects of the invention will now be described by reference to the following Examples. These Examples are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

EXAMPLES

Synthetic Examples

General Experimental Details

All reactions were carried out under an atmosphere of nitrogen unless specified otherwise

5 All temperatures are given in degrees centigrade.

Where products were purified by column chromatography, 'flash silica' refers to silica gel for chromatography, 0.035 to 0.070mm (220 to 440mesh) (e.g. Fluka silica gel 60), where column elution was accelerated by an applied pressure of nitrogen at up to 10 p.s.i. Where thin layer chromatography (TLC) has been used, it refers to silica gel TLC using
10 plates, typically 4 x 10 cm silica gel on aluminium foil plates with a fluorescent indicator (254nm), (e.g. Fluka 60778). Biotage refers to prepacked silica gel cartridges containing KP-Sil run on a flash 12i chromatography module. Solid Phase Extraction (SPE) columns are pre-packed cartridges used in parallel purifications, normally under vacuum. These are commercially available from Varian. SCX cartridges are Ion Exchange SPE columns
15 where the stationary phase is polymeric benzene sulfonic acid. These are used to isolate amines.

The Liquid Chromatography/Mass Spectrometry (LC/MS) systems used:

LCMS was conducted on Phenomenex Luna 3micron C18(2) 30 x 4.6mm column eluting
20 with 0.1 % HCO₂H in water (solvent A) and 0.1% HCO₂H in acetonitrile (solvent B), using the following elution gradient:

0-0.5 min 5%B, 0.5-4.5 min 5-95%B, 4.5-5.5 min 95%B, 5.5-6.0min 95-5%B at a flow rate of 2mL/min. The mass spectra were recorded on a Micromass Platform LC quadrupole mass spectrometer using electro spray positive and negative mode (ES+ve and ES-ve).

25 For the alternative preparations of Examples 2, 4 and 7, the LC/MS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% HCO₂H and 0.01M ammonium acetate in water (solvent A) and 0.05% HCO₂H 5% water in acetonitrile (solvent B), using the following elution gradient 0.0-7min 0%B, 0.7-4.2min 100%B, 4.2-
30 5.3min 0%B, 5.3-5.5min 0%B at a flow rate of 3ml/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

Preparative HPLC conditions:

Where products were purified by preparative HPLC, this was carried out on a Genesis C18 reverse-phase column with 7micron packing and of dimension 21mm id x 100mm.

- 5 Elution was carried out on a gradient of MeOH: Water, buffered with 0.1% formic acid, starting at 5% MeOH and increasing the MeOH at 1% per minute until the compound had eluted. The concentration of the MeOH in the eluent at the time of elution was 20-30%. The flow rate was 5mL/min and UV detection at 254nm was used.

NMR:

- 10 ¹H NMR spectra were recorded using a Bruker DPX 250MHz, referenced to tetramethylsilane.

ISCO Companion XL:

- 15 The Companion XL is an automated single user flash chromatography system which utilises disposable cartridges (120gm to 1500gm). It provides binary on-line solvent mixing to enable gradient methods to be run. Samples are logged in using the multi functional open access software which manages flow rates, gradient profile and collection conditions. The system is equipped with a variable wavelength uv detector and two Foxy 200 fraction collectors enabling automated peak cutting, collection and tracking.

20

Abbreviations used:

	IPA	isopropanol
	DCM	dichloromethane
	THF	tetrahydrofuran
25	MeOH	methanol
	DMF	dimethylformamide
	DIPEA	diisopropylethylamine
	EtOAc	ethyl acetate
	ACN	acetonitrile
30	CHC	cyclohexane
	DMSO	dimethylsulphoxide
	DMAP	4-dimethylaminopyridine
	HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
35	NBS	N-bromosuccinimide
	IMS and IMS-G	industrial methylated spirit

TFA	trifluoroacetic acid
Boc	tert-butyloxycarbonyl
Rt	retention time
h	hour(s)
5 min	minute(s)
HPLC	High pressure liquid chromatography
K	Kelvin
TBME	tertiary butyl methyl ether
NMR	nuclear magnetic resonance

10

Flash silica gel refers to Merck ART No. 9385; silica gel refers to Merck ART No. 7734

Amine starting materials:

The amine in Examples 1 and 6 is commercially available from, for example, Sigma.

15 The amine in Examples 2 and 7 was used as the free base. The free base may be derived from the dihydrochloride salt which is commercially available from, for example, Sigma. Preparation of the free base is described in, for example, Intermediate 5 below.

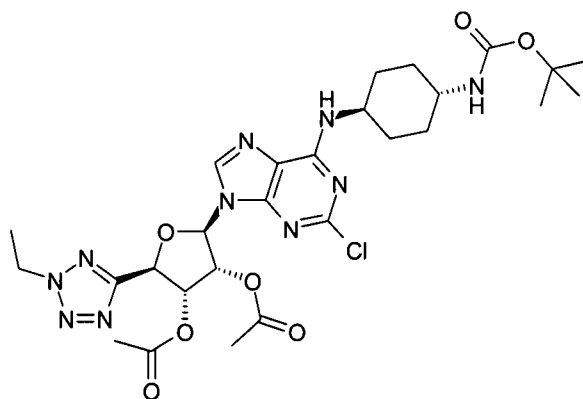
The amine in Examples 3 and 8 may be prepared by, for example, the method describe in J. Het. Chem., (1981), 18(4), 831 to 832.

The amine in Examples 4 and 9 is commercially available from, for example, Apin.

20 The amine in Examples 5 and 10 is commercially available from, for example, Aldrich.

Intermediate 1

(2R,3R,4R,5R)-2-(2-Chloro-6-([trans-4-(((1,1-dimethylethyl)oxy)carbonyl)amino)cyclohexyl]amino)-9H-purin-9-yl)-5-(2-ethyl-2H-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate



To stirred (2*R*,3*R*,4*R*,5*R*)-2-(2,6-dichloro-9*H*-purin-9-yl)-5-(2-ethyl-2*H*-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate (ref WO98/28319A1) (15g) in propan-2-ol (100ml) was added N,N-diisopropylethylamine (7.7ml) and 1,1-dimethylethyl (*trans*-4-aminocyclohexyl)carbamate (6.82g). The mixture was stirred at 65°C for 24h before cooling to room temperature and concentrating *in vacuo*. The crude product was purified by column chromatography (silica) eluting with 30% cyclohexane in ethyl acetate. The appropriate fractions were combined and concentrated *in vacuo* and triturated with diethyl ether to yield the title compound as a white solid, 8.56g.

10 LC-MS: Rt 3.88min.

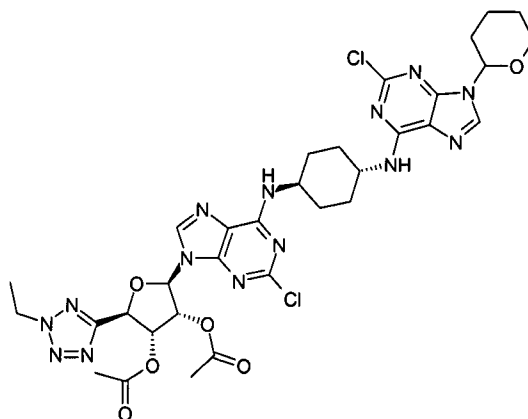
Alternative Preparation of Intermediate 1

(2*R*,3*R*,4*R*,5*R*)-2-(2,6-Dichloro-9*H*-purin-9-yl)-5-(2-ethyl-2*H*-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate (10g) (ref WO98/28319A1) was suspended in isopropanol (100ml). 1,1-Dimethylethyl (*trans*-4-aminocyclohexyl)carbamate (4.56g) and N,N-diisopropylethylamine (5.6ml) were added and the mixture heated at 65°C under nitrogen overnight. The reaction mixture was allowed to cool to room temperature and evaporated down *in vacuo*. The residue was partitioned between ethyl acetate and water. The organic phase was separated and the aqueous extracted twice with ethyl acetate. The organic phases were combined, washed with water, dried (Na₂SO₄), and evaporated down *in vacuo*, dried under high vacuum overnight, to give the title compound, 12.49g.

LCMS; Rt 3.38min, MH⁺ 649.

Intermediate 2

(2R,3R,4R,5R)-2-{2-Chloro-6-[(trans-4-[(2-chloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-yl]amino)cyclohexyl]amino]-9H-purin-9-yl}-5-(2-ethyl-2H-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate



- 5 (2R,3R,4R,5R)-2-(2-Chloro-6-[(trans-4-[(1,1-dimethylethyl)oxy]carbonyl)amino]cyclohexyl]amino)-9H-purin-9-yl)-5-(2-ethyl-2H-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate (Intermediate 1) (5.2 mmol) was treated with 1:1 trifluoroacetic acid/dichloromethane (20ml) for ca. 2h. This was concentrated *in vacuo* and the residue was purified by SPE (SCX, 50g), eluting sequentially with dichloromethane, methanol, 40% (2M ammonia in methanol): dichloromethane and 2M ammonia in methanol. The appropriate fraction was concentrated *in vacuo* and suspended in propan-2-ol (60ml). To this was added N,N-diisopropylethylamine (4m.eq.) and 2,6-dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine (prepared according to the method disclosed in WO2003080604A1) (1m.eq.) and this was heated at 60°C overnight. After cooling to room temperature, further 2,6-dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine (0.5m.eq.) and N,N-diisopropylethylamine (4ml) were added and this was heated at 60°C for a further ca. 5h. After cooling to room temperature, the reaction mixture was then concentrated *in vacuo* and the residue was partitioned between dichloromethane (ca. 60ml) and water (ca. 60ml). The organics were washed with water (ca. 60ml), dried over magnesium sulfate and concentrated *in vacuo* to yield the title compound as an off-white crystalline solid, 4g.

LC-MS: Rt 3.67 min.

Alternative Preparation of Intermediate 2

- 25 (2R,3R,4R,5R)-2-{6-[(trans-4-Aminocyclohexyl)amino]-2-chloro-9H-purin-9-yl}-5-(2-ethyl-2H-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate (Intermediate 4) (7.9g) was dissolved in

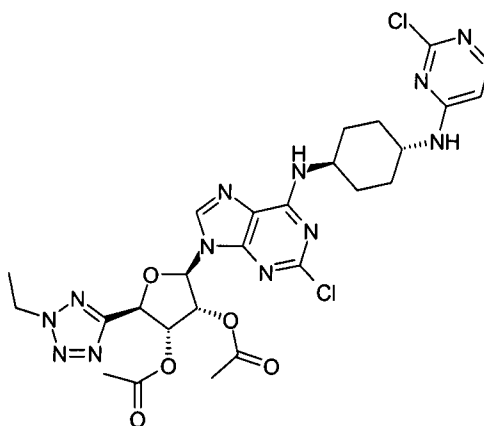
isopropanol (200ml) and stirred at room temperature under nitrogen. N,N-diisopropylethylamine (10ml) was added followed by 2,6-dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine (3.92g). The mixture was stirred at 60°C under nitrogen for 18h. The reaction mixture was allowed to cool to room temperature and evaporated down *in vacuo*.

- 5 The residue was partitioned between ethyl acetate and water. The organic phase was separated and the aqueous extracted twice with ethyl acetate. The organic phases were combined, dried (MgSO₄), and evaporated down *in vacuo* to give the title compound (10.35g). Used without purification.

LCMS; Rt 3.44 min, (MH)⁺ 785.

10 Intermediate 3

(2R,3R,4R,5R)-2-[2-Chloro-6-({trans-4-[(2-chloro-4-pyrimidinyl)amino]cyclohexyl)amino}-9H-purin-9-yl]-5-(2-ethyl-2H-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate



- (2R,3R,4R,5R)-2-(2-Chloro-6-[(1,1-dimethylethyl)oxy]carbonyl)amino)cyclohexyl]amino)-9H-purin-9-yl)-5-(2-ethyl-2H-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate (Intermediate 1) (5.4mmol) was treated with 1:1 trifluoroacetic acid/dichloromethane (20ml) at room temperature for ca. 1h. This was concentrated *in vacuo* and the residue was partitioned between dichloromethane (50ml) and aqueous sodium bicarbonate (50ml). The organics were washed with aqueous sodium bicarbonate (50ml), dried over sodium sulfate and concentrated *in vacuo* to give a white solid. This was dissolved in propan-2-ol (100ml). To this was added N,N-diisopropylethylamine (4m.eq.) and 2,4-dichloropyrimidine (1m.eq.). The reaction mixture was heated at 60°C overnight. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (50ml) and water (50ml). The organics were washed with water (50ml), dried over sodium sulfate and concentrated *in vacuo*. The

crude product was purified by SPE (50g, silica) eluting with x% ethyl acetate in dichloromethane where x=25,50,75. Fractions containing desired product were combined and concentrated *in vacuo* to yield the title compound as a colourless gum, 1.49g.

LC-MS: Rt 3.44 min.

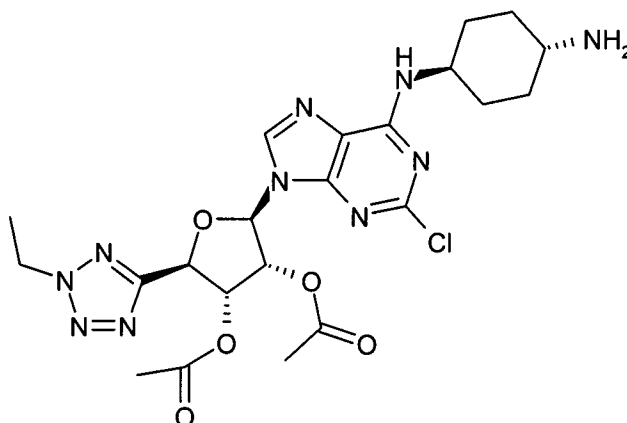
5 Alternative Preparation of Intermediate 3

(2R,3R,4R,5R)-2-{6-[(trans-4-Aminocyclohexyl)amino]-2-chloro-9H-purin-9-yl}-5-(2-ethyl-2H-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate (Intermediate 4) (3.2g) was dissolved in isopropanol (100ml) and stirred at room temperature under nitrogen. N,N-diisopropylethylamine (4ml) was added followed by 2,4-dichloropyrimidine (0.86g). The mixture was heated at 60°C for 18h. The reaction mixture was allowed to cool to room temperature and evaporated down *in vacuo*. The residue was partitioned between ethyl acetate and water. The organic phase was separated and the aqueous extracted twice with ethyl acetate. The organic phases were combined, dried (MgSO₄), and evaporated down *in vacuo*. The residue was purified on a silica SPE cartridge (100g), eluting with 0 to 100% ethyl acetate - dichloromethane gradient over 60 min. The appropriate fractions were combined and evaporated down *in vacuo* to give the title compound, 1.53g.

LCMS; Rt 3.24 min, MH⁺ 661.

Intermediate 4

(2R,3R,4R,5R)-2-{6-[(trans-4-Aminocyclohexyl)amino]-2-chloro-9H-purin-9-yl}-5-(2-ethyl-2H-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate

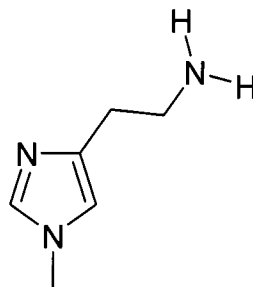


(2*R*,3*R*,4*R*,5*R*)-2-(2-Chloro-6-([*trans*-4-(((1,1-dimethylethyl)oxy)carbonyl} amino)cyclohexyl]amino)-9*H*-purin-9-yl)-5-(2-ethyl-2*H*-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate (Intermediate 1) (12.49g), was dissolved in trifluoroacetic acid – dichloromethane mixture (50:50; 40ml). The mixture was stirred at room temperature for 1-2h and then evaporated down *in vacuo*. The residue was partitioned between ethyl acetate and 2N aq.sodium bicarbonate solution, making sure the trifluoroacetic acid was neutralised. The organic phase was separated, washed with brine, dried (MgSO₄), and evaporated down *in vacuo*, to give the title compound, 11.2g.

LCMS; Rt 2.3 min, MH⁺ 549.

10 Intermediate 5

[2-(1-Methyl-1*H*-imidazol-4-yl)ethyl]amine



15 a) 7,8-Dihydroimidazo[1,5-*c*]pyrimidin-5(6*H*)-one

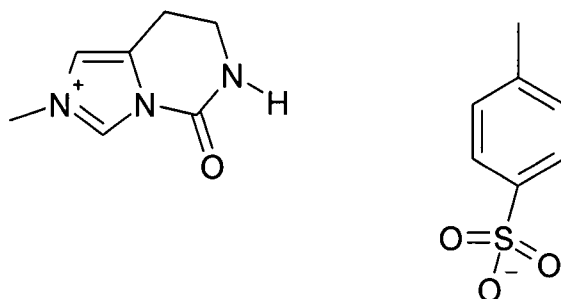
Carbonyldiimidazole (970.2g) was added to a stirred suspension of [2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amine dihydrochloride (999.9g) (commercial eg Sigma) and imidazole (37g) in dichloromethane (5.3 litres) at ca 22°C. The resulting white suspension was heated at reflux until reaction was complete by nmr (4h.). Solvent (8 litres) was distilled off at atmospheric pressure whilst adding IMS-G (8 litres). Additional IMS-G (2 litres) was added and the suspension cooled to ca. 22°C and aged at this temperature for at 2h. The solid was collected by filtration, washed with IMS-G (2 x 0.5 litres), pulled dry and dried in *vacuo* at ca. 60°C to yield the title compound, 478g.

25 NMR (d₆-DMSO) 300K:

8.22δ (1H, br.s), 8.06δ (1H, s), 6.80δ (1H, s), 3.35δ (2H, m), 2.87δ (2H, m).

b) 2-Methyl-5-oxo-5,6,7,8-tetrahydroimidazo[1,5-*c*]pyrimidin-2-ium 4-methylbenzenesulfonate

30

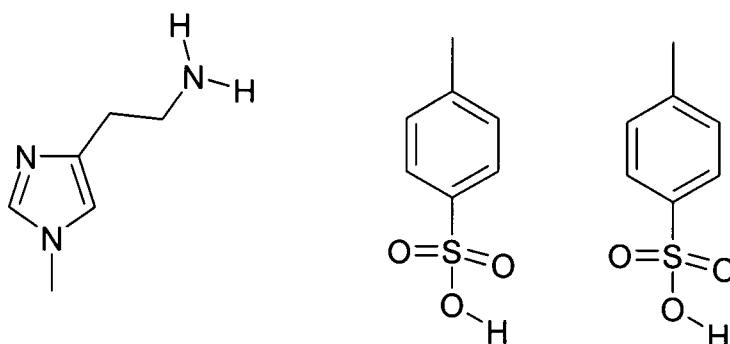


A stirred suspension of 7,8-dihydroimidazo[1,5-c]pyrimidin-5(6H)-one (699.7g) in DMF (2.45 litres) was heated to ca. 60°C. A solution of methyl 4-methylbenzenesulfonate (1058.2g.) in DMF (0.7 litres) was added over 100 min at ca. 60°C, and rinsed in with DMF (0.35 litres). The white suspension was stirred at ca. 60°C. for 200 min. when the reaction was complete by nmr. The reaction mixture was allowed to cool to ca. 40°C and TBME (5.25 litres) was added. The product was cooled to ca. 22°C, aged at this temperature for 17h, and filtered. The cake was washed with TBME-DMF (3:1, 1.4 litres), then with TBME (2 X 1.4 litres), the cake was pulled dry, and the product was dried in vacuo at ca. 50°C to yield the title compound, 1583.5g.

NMR (d6-DMSO) 300K:

9.83δ (1H, s), 9.04δ (1H, br. s), 7.59δ (1H, s), 7.48δ (2H, d), 7.11δ (2H, d), 3.89δ (3H, s), 3.46δ (2H, m), 3.00δ (2H, t), 2.29δ (3H, s).

c) [2-(1-methyl-1H-imidazol-4-yl)ethyl]amine bis(4-methylbenzenesulfonate)



A mixture of 2-methyl-5-oxo-5,6,7,8-tetrahydroimidazo[1,5-c]pyrimidin-2-ium 4-methylbenzenesulfonate (625.1g) , 4-methylbenzenesulfonic acid hydrate (406.6g), 1,4-dioxan (9.38 litres) and water (625ml) was heated at reflux (ca. 90°C) for 2.5h. when the reaction was complete by nmr. The reaction mixture was concentrated by distillation at atmospheric pressure collecting 7.03 litres. The concentrate was allowed to cool to ca.

77°C, and IMS-G (1.56 litres) was added. The resulting bright solution was allowed to cool and was seeded with [2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amine bis(4-methylbenzenesulfonate) (0.625g) at ca. 54°C. The suspension was allowed to cool to ca. 22°C and aged for 40 min. The solid was filtered off and washed successively with 1,4-dioxan-IMS (3:1, 1.25 litres), and then 1,4-dioxan (2 X 1.25 litres), pulled dry and dried in vacuo at ca. 50°C to yield the title compound, 866.3g.

NMR (d6-DMSO) 300K:

8.80δ (1H, s), 7.69δ (4H, d), 7.45δ (1H, s), 7.25δ (4H, d), 3.87δ (3H, s), 3.26δ (2H, t), 3.09δ (2H, t), 2.36δ (6H, s).

d) [2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amine

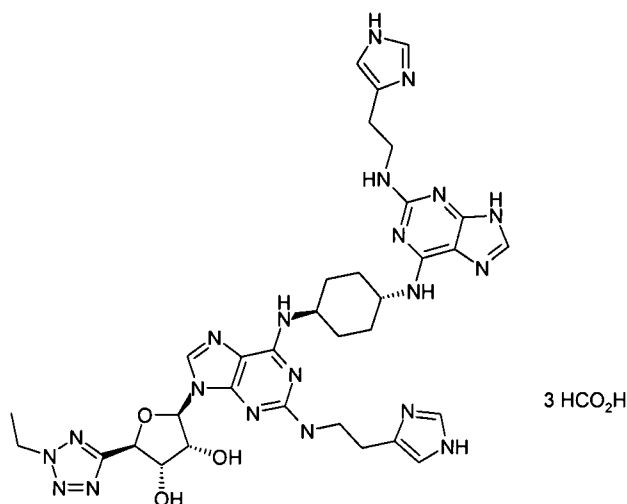
[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amine bis(4-methylbenzenesulfonate) (50g) was dissolved in IMS (200ml)/ water (200ml). This was passed through a DOWEX550A column (600g), eluting with IMS (ca. 4 litres). Appropriate fractions were combined and concentrated in vacuo to yield the title compound, 13.4g.

NMR (CDCl₃) 298K:

7.34δ (1H, s), 6.66δ (1H, s), 3.63δ (3H, s), 2.97δ (2H, t), 2.69δ (2H, t).

Example 1

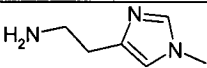
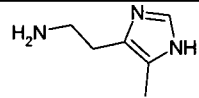
(2*R*,3*S*,4*R*,5*R*)-2-(2-Ethyl-2*H*-tetrazol-5-yl)-5-[2-{[2-(1*H*-imidazol-4-yl)ethyl]amino}-6-({*trans*-4-[(2-{[2-(1*H*-imidazol-4-yl)ethyl]amino}-1*H*-purin-6-yl)amino]cyclohexyl)amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol, triformate

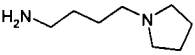
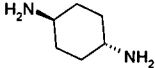


- 5 A mixture of (2*R*,3*R*,4*R*,5*R*)-2-{2-chloro-6-[(*trans*-4-{[2-chloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-yl]amino}cyclohexyl)amino]-9*H*-purin-9-yl]-5-(2-ethyl-2*H*-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate (Intermediate 2) (0.19mmole), amine (histamine) (20m. eq.) and *N,N*-diisopropylethylamine (20m.eq.) in dimethylsulfoxide (1ml) was heated at 125°C overnight. The cooled reaction mixture was washed with tert-butyl methyl ether (2 X ca. 10ml), dissolved in methanol (2ml) / water (4ml) /formic acid (0.5ml) and heated with a heat gun. It was purified by preparative hplc to give the title compound as an off-white solid, 58mg.

LC-MS: Rt 4.41 min, MH⁺ =767.

- 10 Examples 2, 3, 4 and 5 were synthesised in an analogous manner to Example 1:

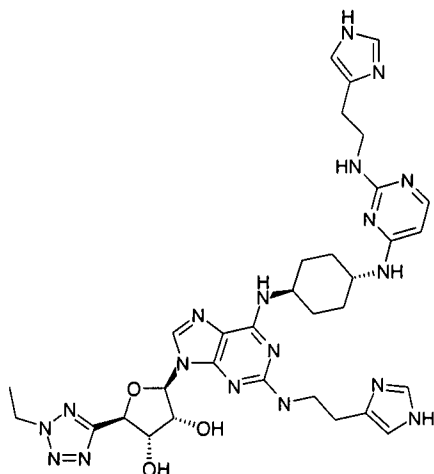
Example	Amine	Product	Product mass	LC-MS Rt	MH ⁺
2		(2 <i>R</i> ,3 <i>S</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(2-ethyl-2 <i>H</i> -tetrazol-5-yl)-5-[2-[[2-(1-methyl-1 <i>H</i> -imidazol-4-yl)ethyl]amino]-6-({ <i>trans</i> -4-[(2-[[2-(1-methyl-1 <i>H</i> -imidazol-4-yl)ethyl]amino)-1 <i>H</i> -purin-6-yl]amino]cyclohexyl)amino)-9 <i>H</i> -purin-9-yl]tetrahydro-3,4-furandiol, diformate	45mg	4.41 min	795
3		(2 <i>R</i> ,3 <i>S</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(2-ethyl-2 <i>H</i> -tetrazol-5-yl)-5-[2-[[2-(5-methyl-1 <i>H</i> -imidazol-4-yl)ethyl]amino]-6-({ <i>trans</i> -4-[(2-[[2-(5-methyl-1 <i>H</i> -imidazol-4-yl)ethyl]amino)-1 <i>H</i> -purin-6-yl]amino]cyclohexyl)amino)-9 <i>H</i> -purin-9-yl]tetrahydro-3,4-furandiol, triformate	74mg	4.60 min	795

Example	Amine	Product	Product mass	LC-MS Rt	MH+
4	 *	(2 <i>R</i> ,3 <i>S</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(2-ethyl-2 <i>H</i> -tetrazol-5-yl)-5-[2-[[4-(1-pyrrolidinyl)butyl]amino]-6-({ <i>trans</i> -4-[(2-[[4-(1-pyrrolidinyl)butyl]amino)-1 <i>H</i> -purin-6-yl]amino]cyclohexyl)amino)-9 <i>H</i> -purin-9-yl]tetrahydro-3,4-furandiol, triformate	40mg	4.56 min	829
5		(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(2-[(<i>trans</i> -4-aminocyclohexyl)amino]-6-{{ <i>trans</i> -4-[(2-[(<i>trans</i> -4-aminocyclohexyl)amino]-9 <i>H</i> -purin-6-yl]amino)cyclohexyl]amino)-9 <i>H</i> -purin-9-yl)-5-(2-ethyl-2 <i>H</i> -tetrazol-5-yl)tetrahydro-3,4-furandiol, triformate	55mg	4.38 min	773

* in Example 2 the amine was used as the free base which may be derived from the commercially available dihydrochloride salt.

Example 6

- 5 (2*R*,3*S*,4*R*,5*R*)-2-(2-Ethyl-2*H*-tetrazol-5-yl)-5-[2-[[2-(1*H*-imidazol-4-yl)ethyl]amino]-6-({*trans*-4-[(2-[[2-(1*H*-imidazol-4-yl)ethyl]amino)-4-pyrimidinyl]amino]cyclohexyl)amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol, tetraformate



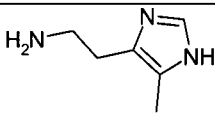
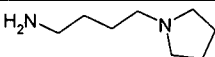
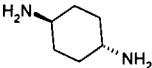
A mixture of (2*R*,3*R*,4*R*,5*R*)-2-[2-chloro-6-({*trans*-4-[(2-chloro-4-pyrimidinyl)amino]cyclohexyl)amino)-9*H*-purin-9-yl]-5-(2-ethyl-2*H*-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate (Intermediate 3) (0.23mmol), amine (histamine)

- 5 (20m.eq.) and *N,N*-diisopropylethylamine (20m.eq.) in dimethylsulfoxide (1ml) was heated at 125°C overnight. The cooled reaction solution was washed with tert-butyl methyl ether (2 x ca. 10ml) and the residue was dissolved in methanol (2ml) / water (4ml) / formic acid (0.5ml) and purified by preparative hplc. The appropriate fractions were combined and concentrated *in vacuo* and freeze-dried to give the title compound, 93mg.

- 10 LC-MS: Rt 4.72 min, MH⁺ = 727

Examples 7, 8, 9 and 10 were synthesised in an analogous manner to Example 6:

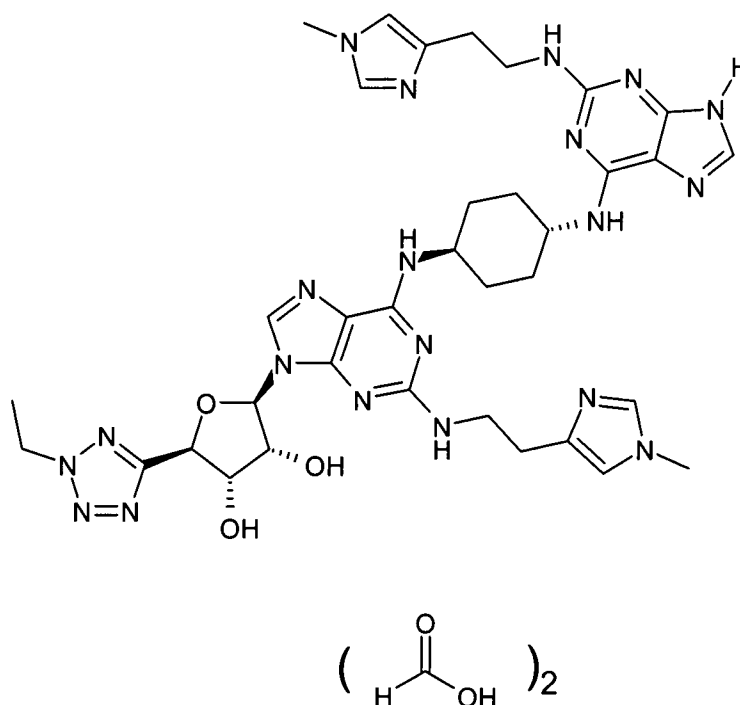
Example	Amine	Product	Product mass	LC-MS Rt	MH ⁺
7		(2 <i>R</i> ,3 <i>S</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(2-ethyl-2 <i>H</i> -tetrazol-5-yl)-5-[2-[(1-methyl-1 <i>H</i> -imidazol-4-yl)ethyl]amino]-6-({ <i>trans</i> -4-[(2-[(1-methyl-1 <i>H</i> -imidazol-4-yl)ethyl]amino)-4-pyrimidinyl]amino]cyclohexyl)amino)-9 <i>H</i> -purin-9-yl]tetrahydro-3,4-furandiol, diformate	84mg	4.25 min	755

Example	Amine	Product	Product mass	LC-MS Rt	MH+
8		(2 <i>R</i> ,3 <i>S</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(2-ethyl-2 <i>H</i> -tetrazol-5-yl)-5-[2-[[2-(5-methyl-1 <i>H</i> -imidazol-4-yl)ethyl]amino]-6-({ <i>trans</i> -4-[(2-[[2-(5-methyl-1 <i>H</i> -imidazol-4-yl)ethyl]amino)-4-pyrimidinyl]amino]cyclohexyl)amino)-9 <i>H</i> -purin-9-yl]tetrahydro-3,4-furandiol, diformate	84mg	4.40 min	755
9		(2 <i>R</i> ,3 <i>S</i> ,4 <i>R</i> ,5 <i>R</i>)-2-(2-ethyl-2 <i>H</i> -tetrazol-5-yl)-5-[2-[[4-(1-pyrrolidinyl)butyl]amino]-6-({ <i>trans</i> -4-[(2-[[4-(1-pyrrolidinyl)butyl]amino)-4-pyrimidinyl]amino]cyclohexyl)amino)-9 <i>H</i> -purin-9-yl]tetrahydro-3,4-furandiol, tetraformate	69mg	4.43 min	789
10		(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-2-(2-[(<i>trans</i> -4-aminocyclohexyl)amino]-6-[[<i>trans</i> -4-({2-[(<i>trans</i> -4-aminocyclohexyl)amino]-4-pyrimidinyl)amino]cyclohexyl)amino)-9 <i>H</i> -purin-9-yl)-5-(2-ethyl-2 <i>H</i> -tetrazol-5-yl)tetrahydro-3,4-furandiol, triformate	61mg	4.19 min	733

* in Example 7 the amine was used as the free base which may be derived from the commercially available dihydrochloride salt.

Alternative Preparation of Example 2

- 5 Formic acid - (2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]-6-({*trans*-4-[(2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]-1*H*-purin-6-yl]amino]cyclohexyl)amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol (2:1)



(2*R*,3*R*,4*R*,5*R*)-2-{2-Chloro-6-[(*trans*-4-[[2-chloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-yl]amino}cyclohexyl)amino]-9*H*-purin-9-yl]-5-(2-ethyl-2*H*-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate (Intermediate 2) (2.85g) was added to a solution of [2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amine (8.2g) and *N,N*-diisopropylethylamine (11.8ml) in dimethylsulphoxide (15ml) and heated at 125°C under nitrogen for 20h. The mixture was allowed to cool to room temperature and washed with diethyl ether (2 x 50ml). The mixture was poured onto water (200ml) and stirred for 30 min. The sticky solid that formed was filtered, washed with water, dissolved in methanol and evaporated down *in vacuo*. This was dissolved in methanol (30ml) and 2*N* HCl (10ml) added. The mixture was stirred at room temperature under nitrogen for 4h. The methanol was removed *in vacuo* and the residue diluted with water (15ml). The solution was basified with 2*N* aq. sodium bicarbonate solution, a solid precipitated which was filtered, washed with water and dried under vacuum to give the free base (2.19g). A portion of the solid (1g) was dissolved in 0.1% formic acid in water and loaded onto a C18 SPE cartridge (50g) and washed on with 0.1% formic acid in water. The product was eluted with 10% acetonitrile / 0.1% formic acid in water. The appropriate fractions were combined and the solvent removed *in vacuo*. The residue was then freeze-dried from water to give the title compound, 0.76g.

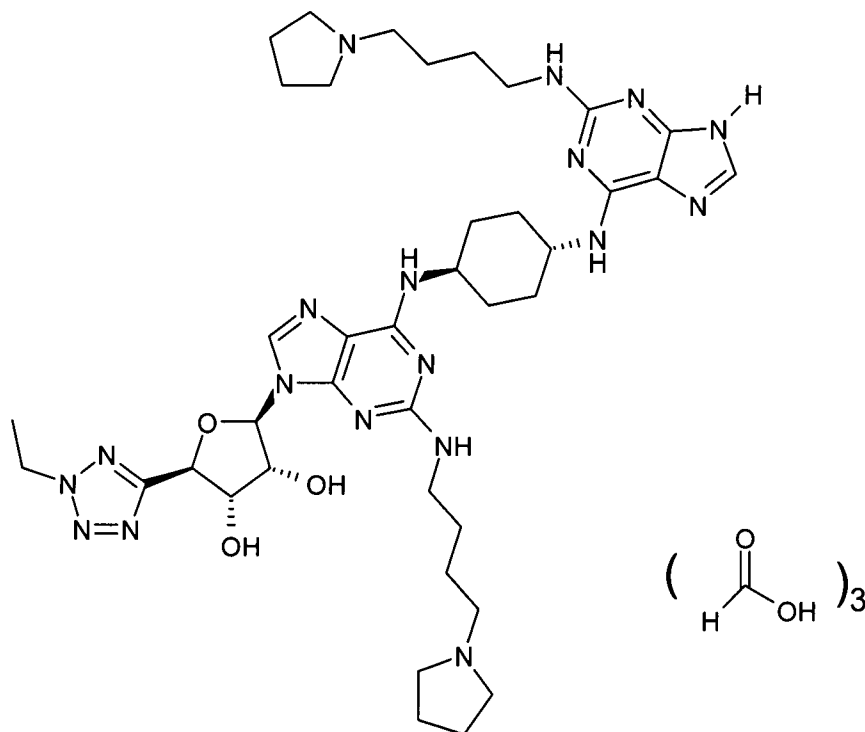
LCMS; *R*_t 1.98 min, (MH)⁺ 795.

NMR (D6-DMSO + D₂O, 392K):

7.81δ (1H, s), 7.60δ (1H, s), 7.45δ (2H, br. s), 6.84,6.82δ (2H, 2 X s), 6.00δ (1H, d), 5.18δ (1H, d), 4.80δ (2H, m), 4.65δ (2H, q), 4.15δ (2H, m), 3.55δ (4H, t), 2.75δ (4H, 2 X t), 2.10δ (4H, br. d), 1.60-1.40δ (7H, m + t).

5 Alternative Preparation of Example 4

Formic acid - (2R,3S,4R,5R)-2-(2-ethyl-2H-tetrazol-5-yl)-5-[2-{[4-(1-pyrrolidinyl)butyl]amino}-6-({trans-4-[(2-{[4-(1-pyrrolidinyl)butyl]amino}-1H-purin-6-yl)amino]cyclohexyl}amino)-9H-purin-9-yl]tetrahydro-3,4-furandiol (3:1)



10

(2R,3R,4R,5R)-2-{2-Chloro-6-[(trans-4-{[2-chloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-yl]amino}cyclohexyl)amino]-9H-purin-9-yl}-5-(2-ethyl-2H-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate (Intermediate 2) (3.0g), [4-(1-pyrrolidinyl)butyl]amine (10.84g) and N,N-diisopropylethylamine (13.45ml) were stirred with dimethylsulphoxide (20ml) at 125°C under nitrogen for 20h. The mixture was allowed to cool to room temperature and washed with diethyl ether (2 x 100ml). The mixture was poured onto water (200ml), stirred for 25min and the precipitated solid was filtered, washed with water, and dried under vacuum. The solid was dissolved in methanol (30ml) and 2N HCl added (30ml). The mixture was heated at 60°C for 1-2h. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane and 2N aq. sodium bicarbonate solution. The product went into the aqueous layer. The aqueous layer was evaporated down *in vacuo* and the residue

15

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triturated with methanol. The solid was filtered and the filtrate evaporated down to give a residue (5g) which was purified by reverse phase chromatography. The solid (~4g) was dissolved in water /formic acid solution (20ml / 0.5ml), loaded onto a C18 SPE cartridge (70g) and eluted with a stepped gradient of 0 to 20% acetonitrile / 0.1% formic acid in water (~200ml of each). The appropriate fractions were combined and acetonitrile removed *in vacuo*. The solution was then freeze-dried to give the title compound (0.769g).

LCMS; Rt 1.98 min, (MH)⁺ 829.

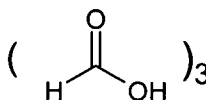
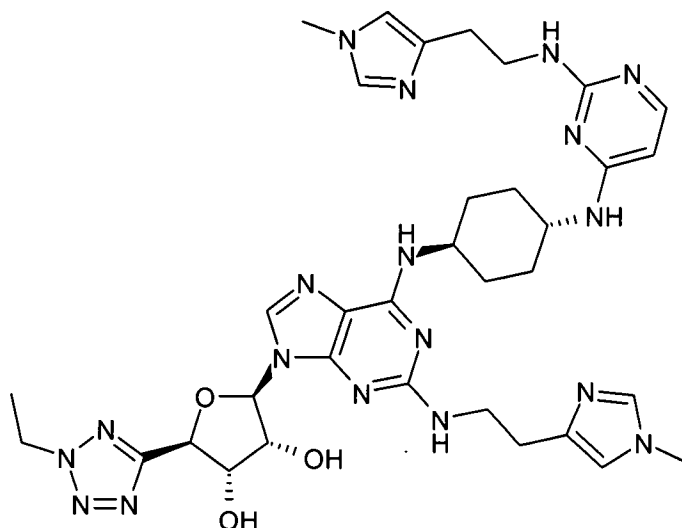
NMR (D6-DMSO + D₂O, 392K):

10 7.85δ (1H, s), 7.58δ (1H, s), 5.98δ (1H, d), 5.15δ (1H, d), 4.80δ (1H, t), 4.70-4.60δ (3H, m), 4.10δ (2H, br. m), 3.30δ (4H, 2 X t, partially hidden by water), 3.0δ (8H, m), 2.95δ (4H, m), 2.05δ (4H, br. d), 1.85δ (8H, m), 1.75-1.30δ (15H, m + t).

Alternative Preparation of Example 7

15

Formic acid - (2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino}-6-({*trans*-4-[(2-{[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino}-4-pyrimidinyl)amino]cyclohexyl)amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol (3:1)



20

(2*R*,3*R*,4*R*,5*R*)-2-[2-Chloro-6-({*trans*-4-[(2-chloro-4-pyrimidinyl)amino] cyclohexyl)amino)-9*H*-purin-9-yl]-5-(2-ethyl-2*H*-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate (Intermediate 3) (1.53g), [2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amine (5.7g) and *N,N*-diisopropylethylamine (8ml) were stirred with dimethylsulphoxide (10ml) at 125°C under nitrogen for 18h. The mixture was allowed to cool to room temperature and washed with *tert*-butyl methyl ether (2 x 100ml). The mixture was diluted with water, a sticky solid precipitated which was triturated and the water decanted. The sticky solid/gum was dissolved in methanol and evaporated down *in vacuo*. The residue was split into two batches and purified by reverse phase chromatography using the Companion XL. Each solid was dissolved in water /acetonitrile /formic acid solution (2.5ml / 0.5ml / 0.3 ml), loaded onto a reverse phase cartridge (330g) and eluted with a gradient of 5 to 50% acetonitrile / 0.1% formic acid in water over 8 column volumes. The appropriate fractions from both runs were combined and evaporated down *in vacuo*. The residue was taken up in water and freeze-dried to give the title compound (1.08g).

LCMS; Rt 1.99 min, $([M+2H]/2)^{2+}$ 378.

NMR (D6-DMSO + D₂O, 392K):

7.80δ (1H, s), 7.58δ (1H, d), 7.40δ (1H, s), 6.78δ (2H, 2 X s), 5.95δ (1H, d), 5.80δ (1H, d), 5.15δ (1H, d), 4.78δ (2H, m), 4.60δ (2H, q), 4.05δ (1H, m), 3.70δ (1H, m), 3.50δ (6H, s), 3.45δ (4H, 2 X t), 2.70δ (4H, 2 X t), 2.00δ (4H, m), 1.45δ (3H, t), 1.40δ (4H, m).

Biological Examples

Biological activity of compounds may be assessed using the following assays or similar assays:

Biological Example 1

In Vitro agonist activity against human adenosine A₁, A_{2A}, and A_{2B} receptors

The agonist potency and selectivity of compounds against human adenosine receptors is determined using Chinese hamster ovary (CHO) cells transfected with the gene for the relevant receptor. These cells are used to measure the production of cAMP in response to compound stimulation.

The DiscoverX assay is an enzyme complementation assay based on CHO cells that involves two fragments of β -galactosidase, enzyme acceptor (EA) and enzyme donor (ED). Following the production of cAMP EA binds to ED, active enzyme is produced and a luminescent product is formed following the addition of substrate. For both methods the effect of test compounds is determined by their effects on basal levels of cAMP (A_{2A} and A_{2B}) or on forskolin enhanced cAMP (A_1).

In all of the *in vitro* assays the activity of test compounds is expressed as a ratio to that of the non-selective adenosine receptor agonist, N-ethyl carboxamide adenosine (NECA).

In certain embodiments of the invention compounds demonstrating activity at the A_{2A} receptor of at least two times that of NECA may be preferred. On testing, the compounds of Examples 1 – 9 were found to meet this criteria.

In other embodiments of the invention compounds demonstrating greater than 100-fold selectivity for the A_{2A} receptor over the A_1 receptor may be preferred. On testing, the compounds of Examples 1 - 9 were found to meet this criteria.

In further embodiments of the invention compounds demonstrating greater than 100-fold selectivity for the A_{2A} receptor over the A_{2B} receptor may be preferred. On testing, the compounds of Examples 4 and 6 - 9 were found to meet this criteria.

An alternative assay system was also used for Examples 2, 4 & 7, where as in DiscoverX, the agonist potency and selectivity of compounds against human adenosine receptors is determined using Chinese hamster ovary (CHO) cells transfected with the gene for the relevant receptor. These cells are used to measure the production of cAMP in response to compound stimulation.

A cAMP tracer is formed by the interaction between Biotin-cAMP and Streptavidin labelled with Europium-W8044 Chelate. This tracer then competes with cellular cAMP for binding to cAMP specific antibodies labelled with the dye Alexa Fluor 647.

Light pulses at 340nm excite the Europium Chelate molecules of the cAMP tracer and, if the tracer is bound to the antibody, the energy emitted by the Eu-chelate is transferred to the Alexa Fluor molecule on the antibody. This results in an emission of light from the Alexa molecule at 665nm which is measured.

Therefore the greater the levels of cellular cAMP produced by receptor stimulation, the less cAMP tracer can bind to the antibodies and the less energy transfer is observed, hence the fluorescent signal will be decreased.

- 5 For G_S-coupled receptors such as the Adenosine A2a and A2b receptors, agonist stimulation results in an increase in cAMP levels and hence a decrease in fluorescence at 665nm. Antagonist addition will have the reverse effect.

- 10 For G_I-coupled receptors such as the Adenosine A1 receptor, agonist addition inhibits forskolin induced cAMP production and hence leads to an increase in fluorescence at 665nm. Antagonism blocks the effect of the agonist and hence increases cellular cAMP and decreases the fluorescent signal.

- 15 In certain embodiments of the invention compounds demonstrating activity at the A2_A receptor of at least two times that of NECA may be preferred. On testing, the compounds of Examples 2, 4 and 7 were found to meet this criteria.

- 20 In other embodiments of the invention compounds demonstrating greater than 100-fold selectivity for the A2_A receptor over the A1 receptor may be preferred. On testing, the compounds of Examples 2, 4 and 7 were found to meet this criteria.

In further embodiments of the invention compounds demonstrating greater than 100-fold selectivity for the A2_A receptor over the A2_B receptor may be preferred. On testing, the compounds of Examples 2, 4 and 7 were found to meet this criteria.

25 **Biological Example 2**

Human Serum Albumin (HSA) binding

Instrument: Agilent HP1100 HPLC instruments were used throughout.

HPLC columns: Chromtech Immobilised HSA HPLC column 50 x 3 mm was purchased from Chromtech (Cheshire, UK).

- 30 *Mobile phase and detection:* The mobile phase A was 50 mM pH 7.4 ammonium acetate solution, while mobile phase B was 2-Propanol (HPLC grade, Runcorn, UK). The mobile phase flow rate was 1.8 ml/min. The column temperature was kept at 30 °C. The gradient profile and run time were the same with each column, the linear gradient from 0 to 30% 2-

propanol was applied from 0 to 3 minutes. From 3 to 5 minutes, the mobile phase composition was constant 30% 2-propanol and 70% 50-mM ammonium acetate. From 5 min to 5.2 min the mobile phase composition was change to 100% ammonium acetate buffer only and remained the same until the end of the run. Each separation was stopped after 6 minutes. The column temperature was kept at 30°C.

Detection: Chromatograms were recorded at 230 and 254 nm by a diode array UV absorption detector at room temperature.

Calibration of the protein columns: The column performance check and the calibration have been performed before the analysis of every 96 well plate. The compounds used for the column calibrations were dissolved separately in 0.5 mg/ml concentration in 50% 2-propanol and 50% pH 7.4 ammonium acetate solution mixtures. The calibration set of compounds their literature % plasma protein binding and its linear conversion value (logK_{lit}), as well as typical retention times, their logarithmic values, log K derived from the calibration curve and % binding data are listed in Table 1.

Table 1. Calibration set of compounds with their literature and typical measured chromatographic data obtained with the HSA column. (Literature data were obtained from ref. Valko K, Nunhuck S, Bevan C, Abraham MC, Reynolds DP, (2003) J. Pharm. Sci. 92 p2236-2248.

Compound	Literature % PPB	tR	logtR	lit logK	logK measured	%HSA measured
Warfarin2	98	3.42	0.53	1.51	1.433	97.4
Nizatidine	35	0.40	-0.039	-0.28	-0.49	24.6
Bromazepam	60	1.16	0.06	0.17	0.45	74.7
Carbamazepine	75	1.35	0.13	0.46	0.59	80.5
Budesonide	88	1.6	0.20	0.83	0.75	85.6
Piroxicam	94.5	3.1	0.49	1.16	1.34	96.6

Compound	Literature % PPB	tR	logtR	lit logK	logK measured	%HSA measured
Nicardipine	95	2.7	0.43	1.20	1.22	95.0
Ketoprofen	98.7	3.8	0.58	1.63	1.53	9.1
Indomethacin	99	4.5	0.66	1.69	1.69	98.9
Diclofenac	99.8	5.0	0.70	1.92	1.78	99.3

The literature % PPB (bound in plasma) values were converted to the linear free energy related logK values (logarithm of apparent affinity constant) using the following equation.

$$\text{Log K} = \log \left[\frac{\% \text{ PPB}}{(101 - \% \text{ PPB})} \right] - [\text{Plasma Protein}]$$

In one embodiment of the invention compounds demonstrating HSA binding greater than 90% may be preferred. The compounds of Examples 1 - 10 were found to meet this criteria on testing.

10 **Biological Example 3**

Inhibition of neutrophilia

Rats are lightly anaesthetized (isofluorane in oxygen) and vehicle or test substance administered intratracheally using a cannula placed trans-orally (200 µl). Following intratracheal administration, rats are returned to their cages and allowed free access to both food and water. Thirty min later, rats are placed in a perspex box and exposed to aerosolized lipopolysaccharide (LPS) (0.15 mg/ml, serotype 0127:B8) for 15 min (Devilbiss nebuliser) at a flow rate of 15 ml/min. Animals are killed 4 h later with pentobarbital (250 mg/kg i.p.). The lungs are lavaged using 3 aliquots (5 ml) of phosphate-buffered saline (Sigma catalogue no. P3813, pH 7.4) containing heparin (10 units/ml); recovered cells are pooled (pooled volume of recovered fluid will be recorded) and centrifuged (1300 rpm for 7 min). The supernatant is removed by aspiration and the cell pellet resuspended in 1 ml phosphate-buffered saline. Total cells are counted

(Sysmex Microcell Counter F-500, TOA Medical Electronics Ltd., Japan). Smears are made by diluting recovered fluid (to approximately 10^6 cells/ml) and spinning an aliquot (100 μ l) in a centrifuge (Cytospin, Shandon, UK). Smears are air dried, fixed using a solution of methanol for 10 s and stained with buffered eosin (10 s) and methylene blue/Azur 1 (5 s) (Speedy-Diff, ClinTech Ltd, Essex, UK) in order to differentiate eosinophils, neutrophils, macrophages and lymphocytes. A total of 300 cells per smear are counted by light microscopy under oil immersion (x1000).

In one embodiment of the invention compounds demonstrating inhibition of neutrophilia of (>50%) may be preferred. On testing at a concentration of 100 μ g/kg, the compounds of Examples 1, 2, 3, 4, 6 and 7 were found to meet this criteria. The compounds of Examples 5, 8, 9 and 10 were not tested.

Examples 2, 4 and 7 were retested at 30 μ g/kg using a method similar to that described above. Of these 3 compounds only Example 4 gave > 50% inhibition.

Biological Example 4

In Vitro agonist activity against human adenosine A_3 receptors

The adenosine A_3 agonist potency of compounds are determined using Chinese Hamster ovary cells stably expressing the human adenosine A_3 receptor and the cAMP response element SPAP (secreted placental alkaline phosphatase). Increasing the level of cAMP in these cell causes an increase in the transcription of the SPAP reporter gene, which can be quantified by addition of a colour substrate to measure a coloured product. The adenosine A_3 receptor is G_i linked so levels cAMP have to be enhanced by forskolin in these cells. Activation of the adenosine A_3 receptor is determined by the reduction of forskolin enhanced cAMP, which is measured as a decrease in the coloured product. The Adenosine A_3 activity of the test compounds is expressed as a ratio to that of the non-selective adenosine receptor agonist, N-ethyl carboxamide adenosine (NECA).

Examples 2, 8, 9, and 10 were functionally inactive over the concentration range of the assay. Examples 1, 3, 6 and 7 were greater than 100-fold selective over A_{2A} . Examples 4 and 5 were greater than 10-fold selective over A_{2A} .

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were

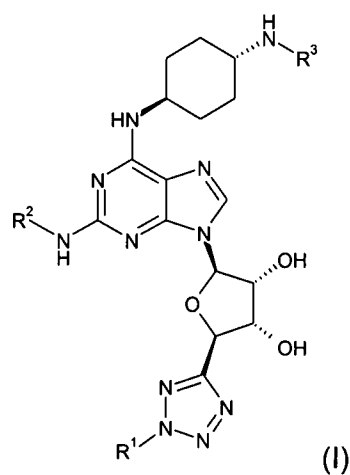
specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will
5 be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein.
10 They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

Claims

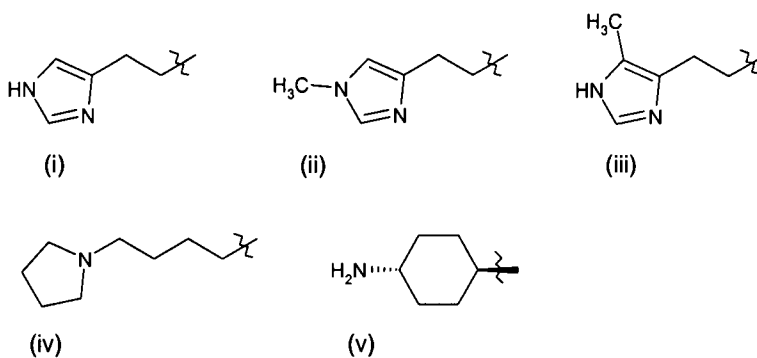
1. A compound of formula (I):



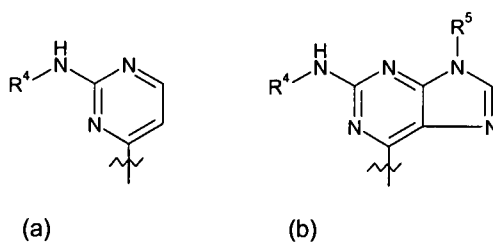
wherein:

- 5 R¹ represents methyl or ethyl;

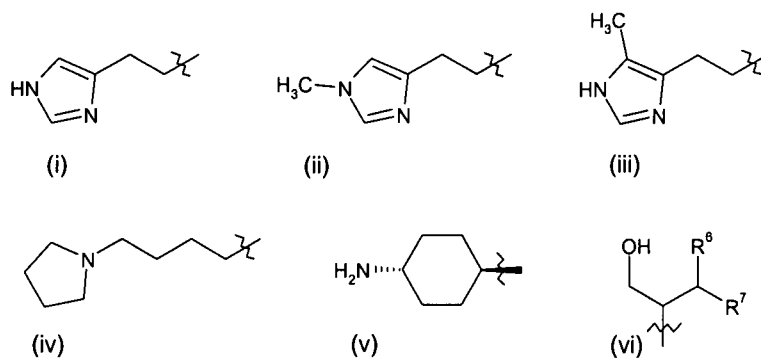
R² represents a group selected from the list consisting of:



R³ represents a group selected from the list consisting of:



- 10 wherein R⁴ represents a group selected from the list consisting of:



R⁵ represents hydrogen, C₁₋₄alkyl, C₁₋₄alkylaryl, C₁₋₄alkylheteroaryl or C₁₋₄hydroxyalkyl;

R⁶ and R⁷ independently represent hydrogen, methyl or phenyl;

- 5 and salts and solvates thereof.
2. A compound according to claim 1, wherein R¹ represents ethyl.
3. A compound according to either claim 1 or claim 2, wherein R² represents group (i), (ii), (iii) or (iv).
4. A compound according to claim 3, wherein R² represents group (ii).
- 10 5. A compound according to claim 3, wherein R² represents group (iv).
6. A compound according to any one of claims 1 to 5, wherein R³ represents group (a).
7. A compound according to any one of claims 1 to 5, wherein R³ represents group (b).
- 15 8. A compound according to any one of claims 1 to 7, wherein R⁵ represents H.
9. A compound according to any one of claims 1 to 8, wherein R⁴ represents group (i), (ii), (iii), (iv) or (v).
10. A compound according to claim 9, wherein R⁴ represents group (ii).
11. A compound according to claim 9, wherein R⁴ represents group (iv).
- 20 12. A compound of formula (I) which is:

(2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{{2-(1*H*-imidazol-4-yl)ethyl}amino}-6-({*trans*-4-[(2-{{2-(1*H*-imidazol-4-yl)ethyl}amino)-1*H*-purin-6-yl]amino]cyclohexyl}amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

5 (2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{{2-(1-methyl-1*H*-imidazol-4-yl)ethyl}amino}-6-({*trans*-4-[(2-{{2-(1-methyl-1*H*-imidazol-4-yl)ethyl}amino)-1*H*-purin-6-yl]amino]cyclohexyl}amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

(2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{{2-(5-methyl-1*H*-imidazol-4-yl)ethyl}amino}-6-({*trans*-4-[(2-{{2-(5-methyl-1*H*-imidazol-4-yl)ethyl}amino)-1*H*-purin-6-yl]amino]cyclohexyl}amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

10 (2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{{4-(1-pyrrolidinyl)butyl}amino}-6-({*trans*-4-[(2-{{4-(1-pyrrolidinyl)butyl}amino)-1*H*-purin-6-yl]amino]cyclohexyl}amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-(2-[(*trans*-4-aminocyclohexyl)amino]-6-{{*trans*-4-({2-[(*trans*-4-aminocyclohexyl)amino]-9*H*-purin-6-yl]amino)cyclohexyl}amino)-9*H*-purin-9-yl)-5-(2-ethyl-2*H*-tetrazol-5-yl)tetrahydro-3,4-furandiol;

15

(2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{{2-(1*H*-imidazol-4-yl)ethyl}amino}-6-({*trans*-4-[(2-{{2-(1*H*-imidazol-4-yl)ethyl}amino)-4-pyrimidinyl]amino]cyclohexyl}amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

(2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{{2-(1-methyl-1*H*-imidazol-4-yl)ethyl}amino}-6-({*trans*-4-[(2-{{2-(1-methyl-1*H*-imidazol-4-yl)ethyl}amino)-4-pyrimidinyl]amino]cyclohexyl}amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

20

(2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{{2-(5-methyl-1*H*-imidazol-4-yl)ethyl}amino}-6-({*trans*-4-[(2-{{2-(5-methyl-1*H*-imidazol-4-yl)ethyl}amino)-4-pyrimidinyl]amino]cyclohexyl}amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

25 (2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{{4-(1-pyrrolidinyl)butyl}amino}-6-({*trans*-4-[(2-{{4-(1-pyrrolidinyl)butyl}amino)-4-pyrimidinyl]amino]cyclohexyl}amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

(2*R*,3*R*,4*S*,5*R*)-2-(2-[(*trans*-4-aminocyclohexyl)amino]-6-{{*trans*-4-({2-[(*trans*-4-aminocyclohexyl)amino]-4-pyrimidinyl]amino)cyclohexyl}amino)-9*H*-purin-9-yl)-5-(2-ethyl-2*H*-tetrazol-5-yl)tetrahydro-3,4-furandiol;

30

or a salt or solvate of any one thereof.

13. A compound of formula (I) which is:

5 (2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino}-6-({*trans*-4-[(2-{[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino}-1*H*-purin-6-yl)amino]cyclohexyl}amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

(2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{[4-(1-pyrrolidinyl)butyl]amino}-6-({*trans*-4-[(2-{[4-(1-pyrrolidinyl)butyl]amino}-1*H*-purin-6-yl)amino]cyclohexyl}amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

10

(2*R*,3*S*,4*R*,5*R*)-2-(2-ethyl-2*H*-tetrazol-5-yl)-5-[2-{[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino}-6-({*trans*-4-[(2-{[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino}-4-pyrimidinyl)amino]cyclohexyl}amino)-9*H*-purin-9-yl]tetrahydro-3,4-furandiol;

or a salt or solvate of any one thereof.

15 14. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 13, which further comprises one or more pharmaceutically acceptable diluents or carriers.

15. A compound according to any one of claims 1 to 13 for use as a medicament.

20 16. Use of a compound according to any one of claims 1 to 13 in the manufacture of a medicament for the treatment of inflammatory diseases.

17. A method of treatment or prophylaxis of inflammatory diseases which comprises administering to a patient an effective amount of a compound according to any one of claims 1 to 13.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/007078

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07H19/16 A61K31/70 A61P29/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07H C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/67265 A (GLAXO GROUP LIMITED; ALLEN, DAVID, GEORGE; CHAN, CHUEN; COUSINS, RICHARD) 29 December 1999 (1999-12-29) page 9, line 5	1-17
A	WO 98/28319 A (GLAXO GROUP LIMITED; COX, BRIAN; KEELING, SUZANNE, ELAINE; ALLEN, DAVID) 2 July 1998 (1998-07-02) page 7, line 9; examples 1,35,53,67	1-17
A	WO 03/080613 A (GLAXO GROUP LIMITED; BLATCHER, PHILIP) 2 October 2003 (2003-10-02) claims	1-17
P,X	WO 2005/116037 A (GLAXO GROUP LIMITED; BLATCHER, PHILIP; COUSINS, RICHARD, PETER, CHARLES) 8 December 2005 (2005-12-08) claims	1-17

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

23 August 2006

Date of mailing of the international search report

30/08/2006

Name and mailing address of the ISA/

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Authorized officer

De Jong, B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/007078

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 17 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/007078

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