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2-(purin-9-yl) -tetrahydrofuran-3, 4-diol derivatives

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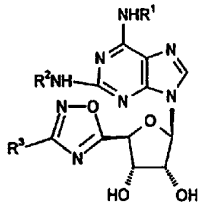


(I)

(57) Abstract

There are provided according to the invention, novel compounds of formula (I) wherein R^1, R^2 and R^3 are as described in the specification, processes for preparing them, formulations containing them and their use in therapy for the treatment of inflammatory diseases.

2-(Purin-9-yl)-tetrahydrofuran-3,4-diol derivatives

This invention relates to new chemical compounds, processes for their preparation, pharmaceutical formulations containing them and 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 A2a receptor will have anti-inflammatory actions. The area has been reviewed by Cronstein (1994). Studies on isolated

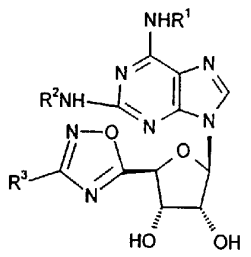
neutrophils show an A2 receptor-mediated inhibition of superoxide generation, degranulation, aggregation and adherence (Cronstein et al, 1983 and 1985; Burkey and Webster, 1993; Richter, 1992; Skubitz et al, 1988. When agents selective for the A2a receptor over the A2b receptor (eg CGS21680) have been used, the profile of inhibition appears consistent with an action on the A2a receptor subtype (Dianzani et al, 1994). Adenosine agonists may also down-regulate other classes of leukocytes (Elliot and Leonard, 1989; Peachell et al, 1989). Studies on whole animals have shown the anti-inflammatory effects of methotrexate to be mediated through adenosine and A2 receptor activation (Asako et al, 1993; Cronstein et al, 1993 and 1994). Adenosine itself, and compounds that raise circulating levels of adenosine also show anti-inflammatory effects *in vivo* (Green et al, 1991; Rosengren et al, 1995). In addition raised levels of circulating adenosine in man (as a result of adenosine deaminase deficiency) results in immunosuppression (Hirschorn, 1993).

We have now found a novel group of compounds with broad anti-inflammatory properties which inhibit leukocyte recruitment and activation and which are agonists of the adenosine 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 of inflammation. The compounds of the invention may also represent a safer alternative to corticosteroids in the treatment of inflammatory diseases, whose uses are severely limited by their side-effect profiles.

More particularly, the compounds of this invention may show an improved profile over known A2a-selective agonists in that they generally lack agonist activity at the human A3 receptor. They may even possess antagonist activity at the human A3 receptor. This profile can be considered of benefit as A3 receptors are also found on leukocytes (eg eosinophil) and other inflammatory cells (eg

mast cell) and activation of these receptors may have pro-inflammatory effects (Kohno et al, 1996; Van Schaick et al 1996). It is even considered that the bronchoconstrictor effects of adenosine in asthmatics may be mediated via the adenosine A3 receptor (Kohno et al, 1996).

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



(I)

wherein R^1 and R^2 independently represent a group selected from:

(i) C_{3-8}cycloalkyl-;

(ii) hydrogen;

(iii) $aryl_2CHCH_2$-;

(iv) C_{3-8}cycloalkylC_{1-6}alkyl-;

(v) C_{1-8}alkyl-;

(vi) arylC_{1-6}alkyl-;

(vii) R^4R^5N-C_{1-6}alkyl-;

(viii) C_{1-6}alkyl-$CH(CH_2OH)$-;

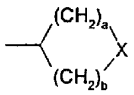
(ix) arylC_{1-5}alkyl-$CH(CH_2OH)$-;

(x) arylC_{1-5}alkyl-$C(CH_2OH)_2$-;

(xi) C_{3-8}cycloalkyl independently substituted by one or more (e.g. 1, 2 or 3) $-(CH_2)_pR^6$ groups;

(xii) $H_2NC(=NH)NHC_{1-6}$alkyl-;

(xiii) a group of formula

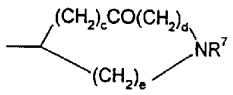


or such a group in which one methylene carbon atom adjacent to X, or both if such exist, is substituted by methyl;

(xiv) $-C_{1-6}$alkyl-OH;

(xv) $-C_{1-8}$haloalkyl;

(xvi) a group of formula



(xvii) aryl; and

(xviii) $-(CH_2)_fSO_2NH_g(C_{1-4}alkyl-)_{2-g}$ or $-(CH_2)_fSO_2NH_g(arylC_{1-4}alkyl-)_{2-g}$;

R^3 represents methyl, ethyl, $-CH=CH_2$, n-propyl, $-CH_2CH=CH_2$, $-CH=CHCH_3$, isopropenyl, cyclopropyl, cyclopropenyl, $-CH(OH)CH_3$, $-(CH_2)_q$halogen, $-(CH_2)_hY(CH_2)_iH$, $-COO(CH_2)_iH$, $-CON(CH_2)_mH((CH_2)_nH)$, $-CO(CH_2)_oH$, or $-C((CH_2)_uH)=NO(CH_2)_vH$;

Y represents O, S or $N(CH_2)_jH$;

a and b independently represent an integer 0 to 4 provided that a + b is in the range 3 to 5;

c, d and e independently represent an integer 0 to 3 provided that c + d + e is in the range 2 to 3;

f represents 2 or 3 and g represents an integer 0 to 2;

p represents 0 or 1;

q represents 1 or 2;

h represents 1 or 2 and i represents an integer 0 to 1; such that h+i is in the range 1 to 2;

j represents an integer 0 to 1 such that h+i+j is in the range 1 to 2;

l represents 1 or 2;

m and n independently represent an integer 0 to 2 such that m+n is in the range 0 to 2;

o represents an integer 0 to 2;

u and v independently represent 0 or 1 such that u+v is in the range 0 to 1;

R^4 and R^5 independently represent hydrogen, C_{1-6}alkyl, aryl, arylC_{1-6}alkyl- or NR^4R^5 together may represent pyridinyl, pyrrolidinyl, piperidinyl, morpholinyl, azetidinyl, azepinyl, piperazinyl or N-C_{1-6}alkylpiperazinyl;

R^6 represents OH, NH_2, $NHCOCH_3$ or halogen;

R^7 represents hydrogen, C_{1-6}alkyl, -C_{1-6}alkylaryl or -COC_{1-6}alkyl;

X represents NR^7, O, S, SO or SO_2;

and salts and solvates thereof.

References to C_{x-y}alkyl include references to an aliphatic hydrocarbon grouping containing x to y carbon atoms which may be straight chain or branched and may be saturated or unsaturated. References to alkoxy may also be interpreted similarly. Preferably these groups will be saturated.

References to aryl include references to mono- and bicyclic carbocyclic aromatic rings (e.g. phenyl, naphthyl) and heterocyclic aromatic rings, for example containing 1-3 hetero atoms selected from N, O and S (e.g. pyridinyl,

pyrimidinyl, thiophenyl, imidazolyl, quinolinyl, furanyl, pyrrolyl, oxazolyl) all of which may be optionally substituted, e.g. by C_{1-6}alkyl, halogen, hydroxy, nitro, C_{1-6}alkoxy, cyano, amino, SO_2NH_2 or $-CH_2OH$.

Examples of C_{3-8}cycloalkyl for R^1 and R^2 include monocyclic alkyl groups (e.g. cyclopentyl, cyclohexyl) and bicyclic alkyl groups (e.g. norbornyl such as exo-norborn-2-yl).

Examples of $(aryl)_2CHCH_2$- for R^1 and R^2 include Ph_2CHCH_2- or such a group in which one or both phenyl moieties is substituted, e.g. by halogen or C_{1-4}alkyl.

Examples of C_{3-8}cycloalkylC_{1-6}alkyl- for R^1 and R^2 include ethylcyclohexyl.

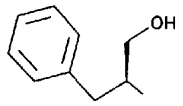
Examples of C_{1-6}alkyl for R^1 and R^2 include $-(CH_2)_2C(Me)_3$, $-CH(Et)_2$ and $CH_2=C(Me)CH_2CH_2$-.

Examples of arylC_{1-6}alkyl- for R^1 and R^2 include $-(CH_2)_2Ph$, $-CH_2Ph$ or either in which Ph is substituted (one or more times) by halogen (e.g. iodine), amino, methoxy, hydroxy, $-CH_2OH$ or SO_2NH_2; $-(CH_2)_2$ pyridinyl (e.g. $-(CH_2)_2$pyridin-2-yl) optionally substituted by amino; $(CH_2)_2$imidazolyl (e.g. 1H-imidazol-4-yl) or this group in which imidazole is N-substituted by C_{1-6}alkyl (especially methyl).

Examples of R^4R^5N-C_{1-6}alkyl- for R^1 and R^2 include ethyl-piperidin-1-yl, ethyl-pyrrolidin-1-yl, ethyl-morpholin-1-yl, $-(CH_2)_2NH$(pyridin-2-yl) and $-(CH_2)_2NH_2$.

Examples of C_{1-6}alkyl-$CH(CH_2OH)$- for R^1 and R^2 include $Me_2CHCH(CH_2OH)$-.

Examples of arylC_{1-5}alkyl-$CH(CH_2OH)$- for R^1 and R^2 include $PhCH_2CH(CH_2OH)$- particularly

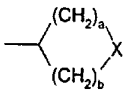


Examples of arylC_{1-5}alkyl-$C(CH_2OH)_2$- for R^1 and R^2 include $PhCH_2C(CH_2OH)_2$-.

Examples of C_{3-8} cycloalkyl independently substituted by one or more $-(CH_2)_pR^6$ groups (eg 1, 2 or 3 such groups) for R^1 and R^2 include 2-hydroxy-cyclopentyl (especially trans- 2-hydroxy-cyclopentyl) and 4-aminocyclohexyl (especially trans-4-amino-cyclohexyl).

Examples of $H_2NC(=NH)NHC_{1-6}$alkyl for R^1 and R^2 include $H_2NC(=NH)NH(CH_2)_2$-

Examples of groups of formula

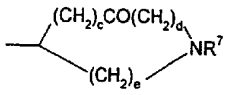


for R^1 and R^2 include pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, tetrahydro-1,1-dioxide thiophen-3-yl, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl and 1,1-dioxo-hexahydro-1.lamda.6-thiopyran-4-yl, or a derivative in which the ring nitrogen is substituted by C_{1-6}alkyl (e.g. methyl), C_{1-6}alkylacyl (e.g. acetyl), arylC_{1-6}alkyl- (e.g. benzyl).

Examples of -C_{1-6}alkyl-OH groups for R^1 and R^2 include $-CH_2CH_2OH$ and $-CH(CH_2OH)CH(CH_3)_2$.

Examples of C_{1-8}haloalkyl for R^1 and R^2 include $-CH_2CH_2Cl$ and $(CH_3)_2ClC(CH_2)_3$-.

Examples of groups of formula



for R^1 and R^2 include 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-3-yl or a derivative in which the ring nitrogen is substituted by C_{1-6}alkyl (e.g. methyl) or benzyl.

Examples of aryl for R^1 and R^2 include phenyl optionally substituted by halogen (e.g. fluorine, especially 4-fluorine).

An example of a $-(CH_2)_fSO_2NH_g(C_{1-4}alkyl)_{2-g}$ group for R^1 and R^2 is $-(CH_2)_2SO_2NHMe$, and an example of a $-(CH_2)_fSO_2NH_g(arylC_{1-4}alkyl)_{2-g}$ group for R^1 and R^2 is $-(CH_2)_2SO_2NHCH_2Ph$.

An example of C_{1-6}alkyl for R^7 is methyl, an example of C_{1-6}alkylaryl for R^7 is benzyl, and an example of $-COC_{1-6}$alkyl for R^7 is acetyl.

We prefer that R^1 and R^2 do not both represent hydrogen.

We prefer R^1 to represent $aryl_2CHCH_2$-.
We also prefer R^1 to represent C_{1-8}alkyl, C_{3-8}cycloalkylC_{1-6}alkyl- , arylC_{1-6}alkyl- or hydrogen.

We prefer R^2 to represent $-CH(CH_2OH)C_{1-3}$alkyl, 4-aminocyclohexyl, pyrrolidinyl (particularly pyrrolidin-3-yl) or arylCH_2CH_2-, especially where aryl represents (1-C_{1-3}alkyl-1H-imidazol-4-yl).

We also prefer R^2 to represent pyrrolidin-3-yl N-substituted by C_{1-6}alkyl or benzyl, $R^4R^5NC_{1-6}$alkyl, C_{1-6}alkyl-OH, aryl (especially where aryl represents phenyl substituted by halogen), arylC_{1-5}alkyl-$CH(CH_2OH)$-, C_{3-8}cycloalkyl, aryl$(CH_2)_2$ (especially where aryl represents pyridinyl (particularly pyridin-2-yl), 1H-imidazol-

4-yl, phenyl or phenyl disubstituted by methoxy) or C_{3-8}cycloalkyl independently substituted by one or more (e.g. 1, 2 or 3) $-(CH_2)_pR^6$ groups.

We prefer R^3 to represent methyl, ethyl, n-propyl, cyclopropyl, $-CH_2OH$, $-COOCH_3$ or -CH=NOH, more preferably methyl, ethyl, n-propyl, cyclopropyl or $-CH_2OH$.

We particularly prefer R^3 to represent methyl, ethyl, n-propyl or cyclopropyl, most particularly methyl, ethyl or cyclopropyl, especially methyl or ethyl, most especially ethyl.

We prefer R^4 and R^5 independently to represent hydrogen, C_{1-6}alkyl, aryl, arylC_{1-6}alkyl- or NR^4R^5 together may represent pyrrolidinyl, piperidinyl, morpholinyl, azetidinyl, azepinyl, piperazinyl or N-C_{1-6}alkylpiperazinyl;

We particularly prefer R^4 and R^5 independently to represent hydrogen or aryl or NR^4R^5 together to represent pyrrolidinyl, piperidinyl, morpholinyl, azetidinyl, azepinyl, piperazinyl or N-methylpiperazinyl.

We prefer that p represents 0. We prefer that R^6 represents OH or NH_2.

We prefer q to represent 1. We prefer h to represent 1. We prefer i to represent 0. We prefer j to represent 1. We prefer l to represent 1. We prefer m and n to represent 0. We prefer o to represent 1. We prefer u to represent 0. We prefer v to represent 0. We prefer Y to represent O.

We prefer that a represents 2 and that b represents 1 or 2. We prefer X to represent NR^7 (e.g. NH), O, S or SO_2, particularly O, S or NH.

We prefer that c represents 0, and either that d represents 1 and e represents 1 or d represents 0 and e represents 2. We prefer that R^7 represents hydrogen.

We particularly prefer R^1 to represent Ph_2CHCH_2-.

We also particularly prefer R^1 to represent $CH(CH_2CH_3)_2$, phenylethyl, cyclohexylethyl, $-(CH_2)_2C(CH_3)_3$ or hydrogen.

We particularly prefer R^2 to represent $-CH(CH_2OH)CH(CH_3)_2$ (particularly 1S-hydroxymethyl-2-methyl-propyl), trans-4-amino-cyclohexyl, 2-(1-methyl-1H-imidazol-4-yl)CH_2CH_2- or pyrrolidin-3-yl.
We also particularly prefer R^2 to represent 2-(1H-imidazol-4-yl) ethyl, morpholin-1-ylethyl, pyrrolidin-1-ylethyl, pyridin-2-ylaminoethyl, (+)-exonorborn-2-yl, 3,4-dimethoxy phenylethyl, 2-hydroxyethyl, 4-fluorophenyl, N-benzyl-pyrrolidin-3-yl, pyridin-2ylethyl, 1S-hydroxymethyl-2-phenylethyl, cyclopentyl, phenylethyl, piperidin-1-ylethyl or 2-hydroxypentyl (particularly trans-2-hydroxypentyl).

We especially prefer R^1 to represent Ph_2CHCH_2-, $-CH(CH_2CH_3)_2$, hydrogen or phenylethyl-.

We especially prefer R^2 to represent 2-(1-methyl-1H-imidazol-4-yl)CH_2CH_2-, 1S-hydroxymethyl-2-phenylethyl, phenylethyl or 1S-hydroxymethyl-2-methyl-propyl.

The most preferred compounds of formula (I) are

(2R,3R,4S,5S)-2-{6-(2,2-Diphenyl-ethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2S,3S,4R,5R)-2-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-5-{6-(1-ethyl-propylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-{6-(1-Ethyl-propylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-{6-(2,2-Diphenyl-ethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-{6-Amino-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-[6-Amino-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-(6-Amino-2-phenethylamino-purin-9-yl)-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2-(1-methyl-1H-imidazol-4-yl)-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-{6-Phenethylamino-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-[6-(2,2-Diphenyl-ethylamino)-2-(1S-hydroxymethyl-2-methyl-propylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

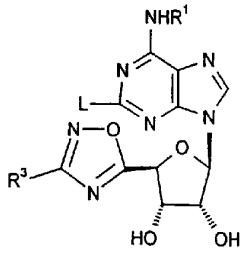
(2R,3R,4S,5S)-2-[6-(1-Ethyl-propylamino)-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

and salts and solvates thereof.

The representation of formula (I) indicates the absolute stereochemistry. When sidechains contain chiral centres the invention extends to mixtures of enantiomers (including racemic mixtures) and diastereoisomers as well as

individual enantiomers. Generally it is preferred to use a compound of formula (I) in the form of a purified single enantiomer.

We also provide a first process for the preparation of compounds of formula (I) including the step of reacting a compound of formula (II)



(II)

wherein L represents a leaving group eg halogen, especially chlorine, or a protected derivative thereof ;

with a compound of formula R^2NH_2 or a protected derivative thereof.

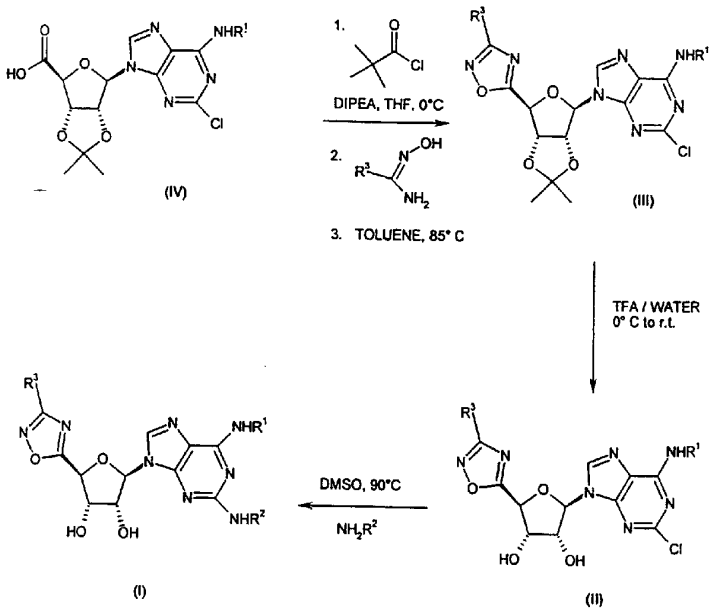
Said reaction will generally involve heating the reagents to a temperature of 50 °C-150 °C in the presence of an inert solvent such as DMSO. The compound of formula (II) may be used in a form which the two hydroxyl groups are protected e.g. with acetonide or acetyl groups. Compounds of formula R^2NH_2 are either known or may be prepared by conventional methods known *per se*.

Compounds of formula (II) may be prepared from compounds of formula (IV) a first process involving activation of the carboxyl group on the compound of formula (IV) followed by reaction with an amidoxime of formula $OH\text{-}N{=}C(R^3)NH_2$ in a solvent such as tetrahydrofuran and then cyclisation at temperature of 20 °C-150 °C in a solvent such as toluene. Methods of carboxyl activation include reaction with an acid chloride, such as pivalolyl chloride, or an acid anhydride in the presence of a base such as a tertiary amine, for example di-

isopropylethylamine. Activating agents used in peptide chemistry such as EEDQ may also be used. Hydroxyl protecting groups may be removed under conditions know to those practising in the art. For example, the acetonide may be removed by treatment with aqueous acid such as trifluoroacetic acid or acetic acid at a temperature of 0 °C-150 °C.

One preferred reaction scheme involving this first process is provided below:

Scheme 1

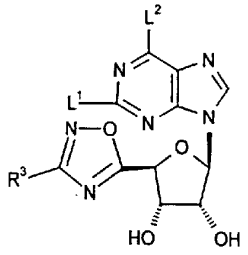


Preferred leaving group L is halogen (particularly chlorine).

The isopropylidine protecting group for the two ribose hydroxy groups in compounds of formula (III) and (IV) are illustrative, and other protecting groups may be contemplated.

Compounds of formula (IV) may be prepared by a method analogous to that described at Preparation 4 (R^1 = Ph_2CHCH_2-) in International Patent Application No. WO 94/17090 or by processes analogous to those described herein. The synthesis of amidoximes is described in Flora et al, 1978 and Bedford et al, 1986.

Compounds of formula (II) may also be prepared by a process comprising reacting a compound of formula (V)

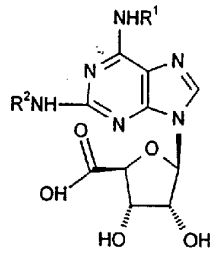


(V)

wherein L^1 and L^2 independently represent a leaving group especially halogen (e.g. chlorine) or a protective derivative thereof
with a compound of formula R^1NH_2.

This reaction will preferably be performed in the presence of a base such as an amine base (e.g. diisopropylethylamine) in a solvent such as an alcohol (e.g. isopropanol) at elevated temperature (e.g. 50 °C).

We also provide a second process for the preparation of compounds of formula (I) including the step of reacting a compound of formula (VI)



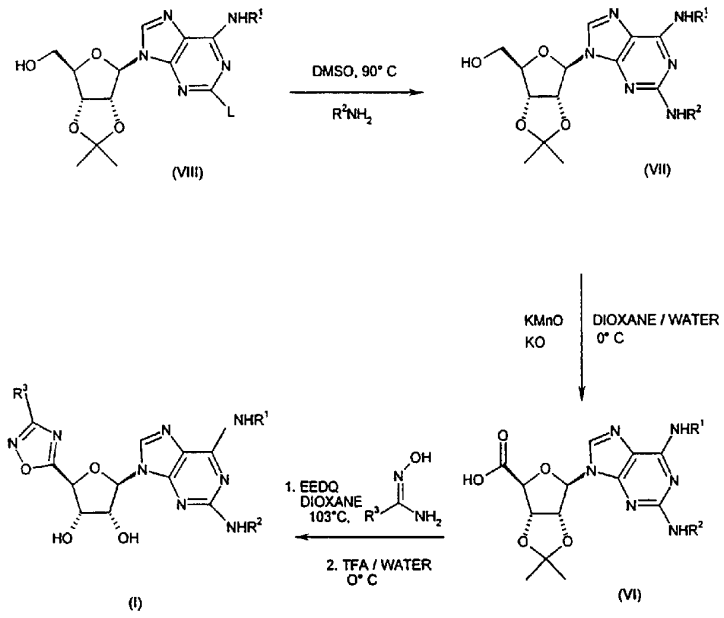
(VI)

or a protected derivative thereof with a carboxyl activating agent, such as EEDQ, and an amidoxime compound of formula OH-N=C(R^3)NH_2. This reaction may generally be performed at a temperature of 50 °C-150 °C in the presence of an inert solvent such as dioxan.

Compound of formula (VI) may be prepared by oxidation of the hydroxymethyl group of a compound of formula (VII). Suitable methods of oxidation include reaction of the compound of formula (VII) with a permanganate, such as potassium permanganate, in the presence of a base, such as aqueous potassium hydroxide, in an inert water-miscible solvent such as dioxan at a temperature of 0 °C-50 °C. Further suitable oxidation methods include the use of TEMPO in the presence of a hypochlorite, such as sodium hypochlorite, and a metal bromide, such as potassium bromide, in the presence of a base, such as sodium hydrogen carbonate, in a biphasic aqueous solvent, such as ethyl acetate, and water at 0 °C-50 °C. Other methods of oxidation known to persons skill in the art may also be used.

One preferred reaction scheme involving this second process is provided below:

Scheme 2



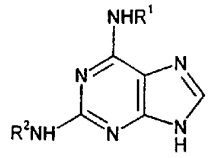
(VIII) (VII) (I) (VI)

Preferred leaving group L is halogen (particularly chlorine).

Compounds of formula (VII) may be prepared by reacting a compound of formula (VIII) with an amine of formula R^2NH_2 in an inert solvent such as DMSO at 50 °C-150 °C. Amines of formula R^2NH_2 may be obtained commercially or prepared by methods known in the art.

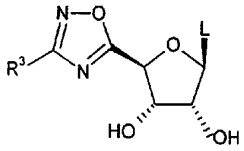
Compounds of formula (VIII) may be prepared by a method analogous to that described at Preparation 3 (R^1 = Ph_2CHCH_2-) in International Patent Application No. WO 94/17090.

We also provide a third process for preparation of compounds of formula I which comprises reacting a compound of formula (IX)



(IX)

with a compound of formula (X)



(X)

wherein L is a leaving group
or a protected derivative thereof.

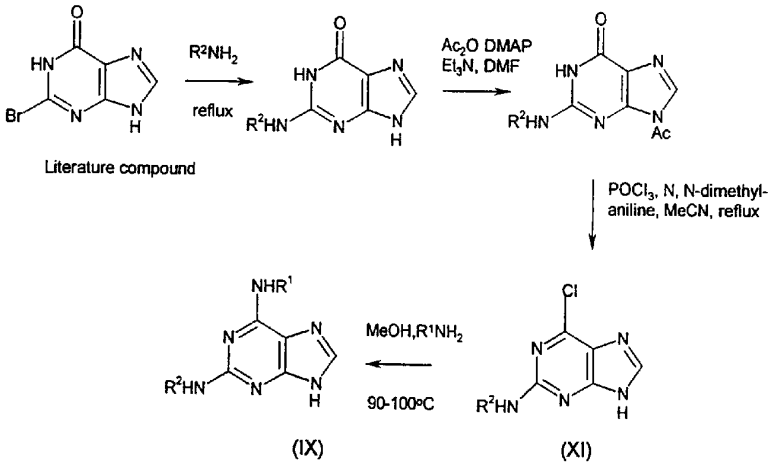
We prefer to use the compound of formula (X) when the ribose 2- and 3-hydroxyl groups are protected for example by acetyl. Leaving group L may represent OH but will preferably represent C_{1-6}alkoxy (e.g. methoxy or ethoxy) an ester moiety (e.g. acetyloxy or benzoyloxy) or halogen. The preferred group L is acetyloxy. The reaction may be formed by combining the reactants in an inert solvent such as MeCN in the presence of a Lewis Acid (e.g. TMSOTf) and DBU.

This process is also suitable for preparation of compounds of formula (II) in which case a derivative compound of formula (IX) wherein the moiety R^2NH is replaced by L will be used. An analogous process is also suitable for preparation of compounds of formula (V).

Compounds of formula (IX) (and the above mentioned derivatives) are either known or may be prepared by known methods.

For example, compounds of formula (VIII) may be prepared, for example following Scheme 3:

Scheme 3



Compounds of formula (X) may be prepared by methods analogous to those described herein for the preparation of compounds of formula (III).

We also provide a fourth process for the preparation of compounds of formula (I) which involves reacting a compound of formula (IIa)

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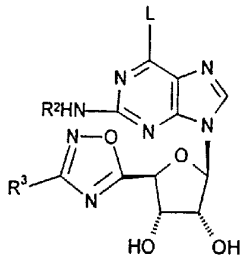
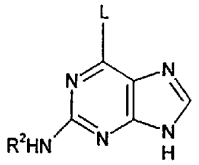


(IIa)

wherein L represents a leaving group eg. chlorine or a protected derivative thereof, with a compound of formula R^1NH_2, under conditions analogous to those described for the first process above.

Compounds of formula (IIa) may be prepared by reacting a compound of formula (XI)'

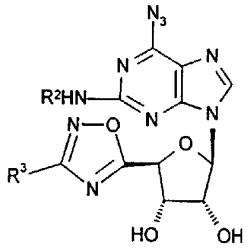


(XI)'

(especially where L represents halogen eg. chlorine) with a compound of formula (X) under conditions analogous to those described for the third process.

Compounds of formula (XI)' may be prepared following Scheme 3 or by an analogous process.

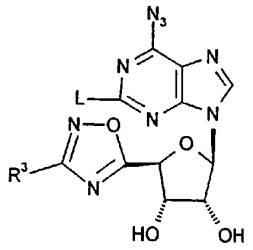
We also provide a fifth process for the preparation of compounds of formula (I) in which R^1 represents hydrogen, which comprises conversion of a compound of formula (IIb)



(IIb)

for example under treatment with PPh_3 followed by water.

Compounds of formula (IIb) may be prepared by reacting a compound of formula (Va)



(Va)

with a compound of formula R^2NH_2 under conditions analogous to those described for the first process above.

Compounds of formula (Va) may be prepared by reacting a compound of formula (V) wherein L^1 and L^2 independently represent a leaving group especially halogen (e.g. chlorine) or a protective derivative thereof with a compound of formula NaN_3.

We further provide a sixth process for the preparation of compounds of formula (I) including the step of deprotecting a compound of formula (I) which is protected and where desired or necessary converting a compound of formula (I) or a salt thereof into another salt thereof

Compounds of formula R^1NH_2, R^2NH_2 and $OH\text{-}N=C(R^3)NH_2$ are either known or may be prepared by known methods.

Examples of protecting groups where referred to in this patent application and the means for their removal can be found in T W 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.

Suitable salts of the compounds of formula (I) include physiologically acceptable salts such as acid addition salts derived from inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, methanesulphonates, and if appropriate, inorganic base salts such as alkali metal salts, for example sodium salts. Other salts of the compounds of formula (I) include salts which are not physiologically acceptable but may be useful in the preparation of compounds of formula (I) and physiologically acceptable salts thereof. Examples of such salts include trifluoroacetates and formates.

Examples of suitable solvates of the compounds of formula (I) include hydrates.

Acid-addition salts of compounds of formula (I) may be obtained by treating a free-base of formula (I) with an appropriate acid.

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 chronic obstructive pulmonary disease and diseases of the gastrointestinal tract such as intestinal inflammatory diseases including inflammatory bowel diseases (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 eg Alzheimer's disease and multiple sclerosis.

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 or in promoting wound healing.

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.

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 physiologically acceptable salt or solvate thereof for use in human or veterinary medicine, particularly in the treatment of patients with inflammatory conditions 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 physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of patients with inflammatory conditions 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 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 physiologically acceptable salt or solvate thereof.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in anti-inflammatory therapy, comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together, if desirable, with one or more physiologically acceptable carriers or excipients.

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

The compounds according to the invention may, for example, be formulated for oral, buccal, parenteral, topical or rectal administration, preferably for parenteral or topical (e.g. by aerosol) administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example,

aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p- hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically

into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

By topical administration as used herein, we include administration by insufflation and inhalation. Examples of various types of preparation for topical administration include ointments, creams, lotions, powders, pessaries, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator, solutions for nebulisation or drops (e.g. eye or nose drops).

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil or a solvent such as a polyethylene glycol. Thickening agents which may be used include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, microcrystalline wax and beeswax.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents or suspending agents.

Spray compositions may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane,

dichlorotetra-fluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2-tetrafluoroethane, carbon dioxide or other suitable gas.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Capsules and cartridges of for example gelatin, 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.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example anti-inflammatory agents (such as corticosteroids (eg fluticasone propionate, beclomethasone dipropionate, mometasone furoate, triamcinolone acetonide or budesonide) or NSAIDs (eg sodium cromoglycate)) or beta adrenergic agents (such as salmeterol, salbutamol, formoterol, fenoterol or terbutaline and salts thereof) or antiinfective agents (eg antibiotics, antivirals).

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together with another therapeutically active agent, for example an anti-inflammatory agent such as a corticosteroid or NSAID.

The combination 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 carrier thereof represent a further aspect of the invention.

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

Compounds of the invention may conveniently be administered in amounts of, for example, 0.01 to 500mg/kg body weight, preferably 0.01 to 100mg/kg body weight, 1 to 4 times daily. The precise dose will of course depend on the age and condition of the patient and the particular route of administration chosen.

Certain intermediate compounds described herein are new and these are also provided as an aspect of the invention.

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

In particular the compounds of the invention have the advantage that they may show greater selectivity for the adenosine 2a receptor subtype over other adenosine receptor subtypes (especially the A1 and A3 receptor subtypes) than hitherto known compounds.

Compounds of the invention may be tested for in vitro and in vivo biological activity in accordance with the following screens:

(1) Agonist activity against adenosine 2a, adenosine 1 and adenosine 3 receptor subtypes.

Agonist selectivity of compounds against other human adenosine receptors is determined using Chinese hamster ovary (CHO) cells transfected with the gene for the relevant human adenosine receptor following a method based on that of Castanon and Spevak, 1994. The CHO cells are also transfected with cyclic AMP response elements promoting the gene for secreted placental alkaline phosphatase (SPAP) (Wood, 1995). The effect of test compounds may be determined by their effects on basal levels of cAMP (A2a) or on forskolin-enhanced cAMP (A1 and A3) as reflected by changes in levels of SPAP. EC_{50} values for compounds may then be determined as a ratio to that of the non-selective agonist N-ethyl carboxamide adenosine (NECA).

(2) Antigen-induced lung eosinophil accumulation in sensitised guinea pigs.

Ovalbumin sensitised guinea pigs are dosed with mepyramine (1mg/kg ip) to protect against anaphylactic bronchospasm. A compound of the invention is then given by the inhaled route (30min breathing of an aerosol of the compound) immediately prior to ovalbumin challenge (30min breathing of an aerosol generated from a 50ug/ml solution of ovalbumin). Twenty four hours after challenge, the guinea pigs are killed and the lungs lavaged. Total and differential leukocyte counts are then obtained for the bronchoalveolar lavage fluid and the dose of test compound giving a 50% reduction in eosinophil accumulation (ED_{50}) is determined (Sanjar et al. 1992).

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The invention is illustrated by the following Examples:

Examples

General experimental details

Where products were purified by column chromatography, 'flash silica' refers to silica gel for chromatography, 0.040 to 0.063mm mesh (e.g. Merck Art 9385), where column elution was accelerated by an applied pressure of nitrogen at up to 5 p.s.i. 'Biotage' refers to the use of the Biotage Flash 40 system using pre-packed normal phase silica columns where solvent elution was accelerated by an applied pressure of nitrogen upto 20 p.s.i.. Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using 5 x 10 cm silica gel 60 F_{254} plates (e.g. Merck Art 5719), visualised by UV light unless otherwise indicated.

Where products were purified by preparative HPLC, this was carried out on a C18-reverse-phase column (1" Dynamax™), eluting with a gradient of acetonitrile (containing 0.1% trifluoroacetic acid) in water (containing 0.1% trifluoroacetic acid) and the compounds isolated as their trifluoroacetate salts unless otherwise specified.

Standard Automated Preparative HPLC column, conditions & eluent

Automated preparative high performance liquid chromatography (autoprep. HPLC) was carried out using a Supelco™ ABZ+ 5μm 100mmx22mm i.d. column

eluted with a mixture of solvents consisting of i) 0.1% formic acid in water and ii) 0.05% formic acid in acetonitrile, the eluent being expressed as the percentage of ii) in the solvent mixture, at a flow rate of 4ml per minute. Unless otherwise stated the eluent was used as a gradient of 5-95 % over 20 minutes.

LC/MS System

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

LC/MS System A - A Supelco™ ABZ+, 3.3cm x 4.6mm i.d. column eluting with solvents: A - 0.1%v/v formic acid + 0.077% w/v ammonium acetate in water, and B - 95:5 acetonitrile:water + 0.05% v/v formic acid. The following gradient protocol was used: 100% A for 0.7 mins; A+B mixtures, gradient profile 0 - 100% B over 3.5mins; hold at 100% B for 3.5mins; return to 0% B over 0.3mins. Positive and negative electrospray ionization was employed.

LC/MS System B - A Supelco™ ABZ+, 5cm x 2.1mm i.d. column eluting with solvents: A - 0.1%v/v formic acid + 0.077% w/v ammonium acetate in water, and B - 95:5 acetonitrile:water + 0.05% v/v formic acid. The following gradient protocol was used: 0 - 100% B over 3.5mins; hold at 100% B for 1.50mins; return to 0% B over 0.50mins. Positive and negative electrospray ionization was employed.

LC/MS System C - A Supelco™ ABZ+, 3.3cm x 4.6mm i.d. column eluting with solvents: A - 0.1%v/v formic acid + 10mmol ammonium acetate in water, and B - 95:5 acetonitrile:water + 0.05% v/v formic acid. The following gradient protocol was used: 100% A for 0.7 mins; A+B mixtures, gradient profile 0 - 100% B over 3.7mins; hold at 100% B for 0.9mins; return to 0% B over 0.2mins. Positive and negative electrospray ionization was employed.

Intermediates

Intermediate 1: (6R-{6-(2,2-Diphenyl-ethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl)-methanol.

2-Chloro-N-(2,2diphenylethyl)-2,3,O-(1-methylethylidene)-adenosine, [Preparation 3. from International Patent Application No. WO 94/17090], (0.20g, 0.384mmol) was added to 2-(1-methyl-1H-imidazol-4-yl)ethylamine (0.24g, 1.92mmol, generated from the corresponding bis-hydrochloride by neutralisation with a slight deficiency of solid sodium hydroxide in methanol), and the solvent was removed by evaporation. DMSO (0.7 ml) was added to the residue to form a slurry, which was heated at 90°C for 25h. The cooled reaction mixture was purified by column chromatography on flash silica (200:5:1 -200:10:1,DCM : MeOH : NH_3) to give the title compound as a white solid (0.226g).

LC/MS SYSTEM A R_t = 3.97mins, *m/z* = 611 MH^+

Intermediate 2: (3aS,4S,6R,6aR)-6-{6-(2,2-Diphenyl-ethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid.

A solution of Intermediate 1 (0.226g, 0.370mmol) in 1,4 dioxan (3ml), and water (1ml) was added dropwise to a stirring purple solution of potassium permanganate (0.292g, 1.85mmol), and potassium hydroxide (0.166g, 2.96mmol) in water (1ml) at 0°C. The resultant solution was stirred at 0°C for 3h, then treated with solid sodium metabisulphite until the purple colour was discharged. The resultant grey slurry was acidified to pH3, with hydrochloric acid solution (2N), and the product was extracted into ethylacetate (3x 20ml). The organics were washed with brine (20ml), and dried ($MgSO_4$), then concentrated *in vacuo* to afford the title compound as a white solid (0.100g).

LC/MS SYSTEM A R_t = 3.96mins, *m/z* = 625 MH^+

Intermediate 3: {2-Chloro-9-[6S-(3-ethyl-[1,2,4]oxadiazol-5-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl}-(2,2-diphenyl-ethyl)-amine.

Diisopropylethylamine (0.218ml, 1.214mmol) was added a stirring mixture of (3aS,4S,6R,6aR)-6-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,2-dimethyl- tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid [Preparation 4. from International Patent Application No. WO 94/17090] (0.50g, 0.935mmol), in dry tetrahydrofuran (10ml), at 0 °C. Pivaloyl chloride (0.150ml, 1.214mmol) was added to the cooled stirring mixture, and it was stirred for at 0 °C for 1h. The mixture was cooled to -10°C, and N-hydroxy-propionamidine, (0.160g, 1.87mmol) in dry tetrahydrofuran (3ml) was added dropwise, and the resultant solution stirred for 1h. The mixture was allowed to warm to room temperature and stirred for a further 20h. The solution was concentrated *in vacuo*, then azeotroped with toluene (2 x 10ml). The yellow residue was re-dissolved in toluene (15ml), and heated at 80°C with stirring for 1h. Once cool the reaction mixture was concentrated *in vacuo* to give a yellow oil, which was purified by column chromatography on flash silica (35-50% ethylacetate-cyclohexane) to give the title compound as a white solid (0.430g).

TLC (35% ethylacetate - cyclohexane) rf = 0.58

Intermediate 4: (2R,3R,4S,5S)-2-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol.

A solution of Intermediate 3 (0.375mg, 0.638mmol) in a mixture of trifluoroacetic acid (5.6ml) and water (1.4ml), was stirred at 5-10°C under nitrogen for 8.5h, then concentrated in vacuo. The residue was azeotroped with toluene (2X), to produce the title compound as a cream coloured solid (0.340mg).

LC/MS system B R_t = 3.36mins, *m/z* = 548 MH^+

Intermediate 5: 2-Chloro-N-(1-Ethylpropyl)-adenosine

A mixture of 2,6-dichloro-9-(2,3,5-tri-O-acetyl-ß-D-ribofuranosyl)-9H-purine ** (10.1g, 22.6mM), iso-propanol (300ml), K_2CO_3 (5g) and 1-ethylpropylamine (2.17g, 24.84mM) was stirred at 20 C for 24hrs. The reaction mixture was heated at 54 °C for 73 hrs. Solvent was removed in vacuo, water (50ml) was added, extracted with ethyl acetate (3 x 80ml), the combined extracts were dried ($MgSO_4$) affording the title compound as a creamy light brown foam (9.44g). LC/MS system A R_t = 2.66 min, *m/z* = 372 MH^+.

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Intermediate 6: {6R-[2-Chloro-6-(1-ethyl-propylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl}-methanol

A mixture of Intermediate 5 (9.3g, 22.6mmol), 2,2-dimethoxypropane (35ml), acetone (250ml) and para-toluenesulfonic acid (8.1g) was stirred for 22 hrs. at 20 °C. The solvent was removed in vacuo and the residue taken up in ethyl acetate (200ml), washed with sodium bicarbonate (aqueous, saturated, 3 x 70ml). The aqueous washings were back extracted with ethyl acetate (50ml). The combined organic layers were dried ($MgSO_4$) and solvent was removed in vacuo. The residue was purified by column chromatography on flash silica (50%, 60% and then 70% ethyl acetate – cyclohexane) to afford the title compound as a white foam (5.67g). TLC SiO_2 (50% ethyl acetate in cyclohexane) Rf = 0.17

Intermediate 7: (3aS,4S,6R,6aR)-6-[2-Chloro-6-(1-ethyl-propylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid

A mixture of Intermediate 6 (5.431g, 13.2mmol), KBr (0.157g, 1.32mmol), TEMPO, (0.010g, 0.07mmol) in ethyl acetate (205ml) and saturated aqueous $NaHCO_3$ (138ml) was vigorously stirred for 20 mins. at 0 °C. A mixture made up of sodium hypochlorite (13% active chloride, 7.3ml) solid $NaHCO_3$ (0.420g) and

water (2ml) was added dropwise over 5 mins. After 30 mins. more reagents (KBr, TEMPO, sodium hypochlorite, solid $NaHCO_3$ and water in the same quantities as above) were added. This addition was repeated after a further 30 mins had elapsed. One hour later the reaction mixture was poured into aqueous solution of Na_2SO_3 (28g) in water (400ml), diluted with ethyl acetate (100ml). The mixture was vigorously shaken and the organic phase washed with water (100ml). The combined aqueous layers were cooled to 0 °C and acidified to pH 3 with 2M hydrochloric acid, extracted with ethyl acetate (3 x 200ml), dried ($MgSO_4$) and solvent was removed in vacuo leaving the title compound as a white foam (5.03g). LC/MS system B R_t = 3.25min, *m/z* = 426 MH^+.

Intermediate 8: {2-Chloro-9-[6S-(3-ethyl-[1,2,4]oxadiazol-5-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl}-(1-ethyl-propyl)-amine

Intermediate 7 (0.7g, 1.647mmol), in anhydrous tetrahydrofuran (12ml) at 0 °C was treated with diisopropylethylamine (0.372ml, 2.14mmol), and pivaloyl chloride (0.263ml, 2.14mmol). The resultant solution was stirred at 1.5h at 0 °C, then was cooled further to (-10 °C), and N-hydroxy-propionamidine (0.289g, 3.29mmol) was added in tetrahydrofuran (5ml) over 15mins. The solution was stirred at 0-5 °C for 1h, then at room temperature for 20h. The reaction mixture was concentrated *in vacuo* then azeotroped with toluene (2x 20ml). The residue was dissolved in toluene (15ml), then heated at 80°C for 1h. Once cool the solution was concentrated *in vacuo*, then purified by column chromatography on flash silica (35% ethyl acetate – cyclohexane) to give the title compound as a clear oil (0.780g). TLC SiO_2 (30% ethyl acetate in cyclohexane) Rf = 0.26. LC/MS system B R_t = 3.53min, *m/z* = 478 MH^+.

Intermediate 9: (2R,3R,4S,5S)-2-[2-Chloro-6-(1-ethyl-propylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol

Intermediate 8 (0.78g, 1.63mmol) in trifluoroacetic acid / water (10:1, 5ml), was stirred at 0 °C for 4.5h. The mixture was concentrated *in vacuo*, azeotroped with toluene (3 x 10ml), to afford the title compound as a pink solid (0.705g). LC/MS system B R_t = 3.05min, *m/z* = 438 MH^+.

Intermediate 10: {2-Chloro-9-[2,2-dimethyl-6S-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl}-(1-ethyl-propyl)-amine

Intermediate 7 (0.7g, 1.647mmol), in anhydrous tetrahydrofuran (12ml) at 0 °C was treated with diisopropylethylamine (0.372ml, 2.14mmol), and pivaloyl chloride (0.263ml, 2.14mmol). The resultant solution was stirred at 1.5h at 0 °C, then was cooled further to (- 10°C), and N-hydroxy-acetamidine (0.244g, 3.29mmol) was added in tetrahydrofuran (5ml) over 15mins. The solution was stirred at 0-5 °C for 1h, then at room temperature for 20h. The reaction mixture was concentrated *in vacuo* then azeotroped with toluene (2x 20ml). The residue was dissolved in toluene (15ml), then heated at 80 °C for 1h. Once cool the solution was concentrated *in vacuo*, then purified by column chromatography on flash silica (35% ethyl acetate – cyclohexane) to give the title compound as a clear oil (0.762g). TLC SiO_2 (30% ethyl acetate in cyclohexane) Rf = 0.24. LC/MS system B R_t = 3.41min, *m/z* = 464 MH^+.

Intermediate 11: (2R,3R,4S,5S)-2-[2-Chloro-6-(1-ethyl-propylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol

Intermediate 10 (0.76g, 1.64mmol) in trifluoroacetic acid / water (10:1), (5ml), was stirred at 0 °C for 4.5h. The mixture was concentrated *in vacuo*, azeotroped with toluene (3 x 10ml), to afford the title compound as a pale pink solid (0.692g). LC/MS system B R_t = 2.92min, *m/z* = 424 MH^+.

Intermediate 12: 2-Chloroadenosine

A stream of ammonia was bubbled through anhydrous methanol (25ml) for 30 mins. at 0 °C. The solution was added to a mixture of 2,6-dichloro-9-(2,3,5-tri-O-acetyl-ß-D-ribofuranosyl)-9H-purine ** (2.000g, 4.5mmol) in dry methanol (5ml) and allowed to warm to 20 °C over 24 h. More ammonia was bubbled through the solution after a further 6h and subsequently after a further 20h. Solvent was removed in vacuo and the residue was purified by column chromatography on flash silica (neat ethyl acetate) to afford the title compound as a white solid (1.152g). TLC SiO_2 (neat ethylacetate) Rf = 0.15

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Intermediate 13: [6R-(6-Amino-2-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-methanol

To a stirred solution of Intermediate 12 (0.700g, 2.3mmol) in acetone (70ml) was added 2,2-dimethoxypropane (1.70m, 13.8mmol) and para-toluenesulfonic acid (0.438g, 2.3mmol) and the reaction mixture was stirred overnight at 20 °C. The solvent was removed in vacuo and taken up in ethyl acetate (150ml). The suspension was shaken with sodium bicarbonate (aqueous, saturated, 3 x 50ml)and water. The aqueous washings were back extracted with ethyl acetate (50ml). The combined organic layers were dried ($MgSO_4$) and solvent was removed in vacuo to afford the title compound as a white solid (0.651g).
TLC SiO_2 (neat ethyl acetate) Rf = 0.33

Intermediate 14: (3aS,4S,6R,6aR)-6-(6-Amino-2-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid

A solution of Intermediate 13 (0.400g, 1.2mmol) in 1,4-dioxane (12ml) and water (4ml) was added dropwise over 20 mins to a stirred solution of $KMnO_4$ (0.924g, 5.8mmol) and potassium hydroxide (0.524g, 9.4mmol) in water (4ml) at 0 °C. The mixture was stirred at 0 °C for a further 3h. Solid sodium metabisulphite was added to discharge the purple colour and then acidified to pH 3 with 2N

HCl. The mixture was extracted with ethyl acetate (3 x 50ml), the combined organic solutions were washed with brine, dried ($MgSO_4$), solvent was removed in vacuo to afford the title compound as a white solid (0.316g).
TLC SiO_2 (neat ethyl acetate) Rf = 0.10

Intermediate 15: 2-Chloro-9-[2,2-dimethyl-6S-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-ylamine

Intermediate 14 (0.400g), diisopropylethylamine (0.154ml) in tetrahydrofuran (10ml) were stirred for 15min under nitrogen at room temperature then cooled to 0 °C. Pivaloylchloride (0.18ml) was added and the mixture stirred at 0 °C for 1hr. The mixture was treated with N-hydroxy-acetamidine (0.196g), stirred at 0 °C for 1hr, then allowed to warm up to room temperature overnight. The reaction mixture was concentrated *in vacuo,* toluene (20ml) added and the mixture heated at 80 °C for 3hrs. The cooled mixture was evaporated *in vacuo.* Purification by column chromatography on flash silica eluted with [dichloromethane:ethanol: 880 ammonia (100:8:1)] furnished the title compound as a white solid (0.328g). TLC SiO_2 (Dichloromethane: ethanol: 880 NH_3 100:8:1) Rf = 0.47

Intermediate 16: 2-Chloro-9-[6S-(3-ethyl-[1,2,4]oxadiazol-5-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-ylamine

Intermediate 14 (0.500g), diisopropylethylamine (0.318ml) in tetrahydrofuran (10ml) were cooled to 0 °C and stirred for 15min under nitrogen. Pivaloylchloride (0.225ml) was added and the mixture stirred for 1hr at 0 °C .The mixture was treated with N-hydroxy-propionamidine (0.246g) in tetrahydrofuran (2ml), stirred for 1hr at 0 °C, then allowed to warm up to room temperature overnight. The cooled reaction mixture was evaporated *in vacuo.* Purification by column chromatography on flash silica eluted with dichloromethane:ethanol: 880 ammonia (100:8:1) to afford the title compound as a pale yellow foam (0.389g)

TLC SiO_2 (Dichloromethane: ethanol: 880 NH_3 100:8:1) Rf = 0.5

Intermediate 17: (2R,3R,4S,5S)-2-(6-Amino-2-chloro-purin-9-yl)-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol acetate

Intermediate 15 (0.488g) in acetic acid (20ml) and water (5ml) was heated at 100 °C for 16hrs. The cooled reaction mixture was evaporated *in vacuo* to afford the title compound as a brown oil (0.537g)

TLC SiO_2 (Dichloromethane: ethanol: 880 NH_3 100:8:1) Rf = 0.14

Intermediate 18: (2R,3R,4S,5S)-2-(6-Amino-2-chloro-purin-9-yl)-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol acetate

Intermediate 16 (0.381g) in acetic acid (15ml) and water(3ml) was heated at 100 °C for 4.5hrs, then at 119 °C for 3hrs. More acetic acid (5ml) and water (1ml) was added and the reaction mixture heated at 119 °C for 8hrs. The cooled reaction mixture was evaporated *in vacuo* to furnish the title compound as a light brown solid (0.410g). TLC SiO_2 (Dichloromethane: ethanol: 880 NH_3 100:8:1) Rf = 0.15.

Intermediate 19: [6R-(6-Amino-2-phenylethylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl]-methanol

A solution of Intermediate 13 (10.0g, 19.5mmol) and phenylethylamine (12.2ml, 97.3mmol) was heated to 110 °C for 7 hrs. The reaction mixture was diluted with ethyl acetate (400ml), washed with 1M HCl. The aqueous layer was re-extracted with ethyl acetate (3 x 200ml) and the combined organic extracts were dried ($MgSO_4$), solvent was removed *in vacuo* and purified by column chromatography on flash silica eluted with 5% methanol in dichloromethane to afford the title compound as a brown oil (7.61g)

TLC SiO_2 (Dichloromethane: methanol, 10:1) Rf = 0.28

Intermediate 20: (3aS,4S,6R,6aR)-6-(6-Amino-2-phenylethylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid

A solution of Intermediate 19 (4.0g, 9.38mmol) in 1,4-dioxane (54ml) and water (13.3ml) was added dropwise over 30 mins. to a stirred solution of $KMnO_4$ (7.5g, 46.9mmol) and potassium hydroxide (4.24g, 75mmol) in water (84ml) at 0 °C. The mixture was stirred at 0 °C for a further 1 h. Excess $KMnO_4$ was destroyed by the portionwise addition of solid sodium metabisulphite, the solution was filtered through a pad of Celite and washed with further 1,4-dioxan. The filtrate was concentrated *in vacuo* to a volume of 20ml, acidified with concentrated HCl. The solid formed was filtered and dried overnight over P_2O_5 to afford the title compound as a white solid (2.25g).

TLC SiO_2 (Dichloromethane: methanol, 5:1) Rf = 0.44

Intermediate 21: 2-Phenylethylamino-9-[6S-(3-ethyl-[1,2,4]oxadiazol-5-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-ylamine

To Intermediate 20 (0.500g, 1.14mmol) in DME (10ml) was added N-hydroxy-acetamidine (0.168g, 2.28mmol) and EEDQ (0.654g, 2.28mmol) and was heated to reflux for 2hrs. Further N-hydroxy-acetamidine (0.168g, 2.28mmol) and EEDQ (0.654g, 2.28mmol) were added and the reaction was heated at reflux for 4 days, the solvent was removed *in vacuo* and the residue was purified by column chromatography on flash silica eluted with 5% methanol in ethyl acetate to afford the title compound as a yellow foam (0.256g).

TLC SiO_2 (Ethyl acetate: methanol, 19:1) Rf = 0.33

Intermediate 22: {2-Chloro-9-[2,2-dimethyl-6R-(3-propyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-(3aS,6aR)-furo[3,4-d][1,3]dioxol-4S-yl]-9H-purin-6-yl}-(2,2-diphenyl-ethyl)-amine

Diisopropylethylamine (0.181ml, 1.04mmol) was added to a stirring mixture of (3aS,4S,6R,6aR)-6-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,2-

dimethyl- tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid [Preparation 4, International Patent Application No. WO94/17090] (0.428g, 0.8mmol), in dry tetrahydrofuran (8ml), at 0 °C. Pivaloyl chloride (0.128ml, 1.04mmol) was added to the cooled mixture, and it was stirred at 0 °C for 1h. N-Hydroxy-butyramidine, (0.163g, 1.6mmol) in dry tetrahydrofuran (7ml) was added dropwise, over ten minutes, and the resultant solution stirred for 1h at 0 °C. The mixture was allowed to warm to room temperature and stirred for a further 20h. The solution was concentrated *in vacuo*, then azeotroped with toluene (2 x 10ml). The yellow residue was re-dissolved in toluene (15ml), and heated at 80°C with stirring for 1h. Once cool the reaction mixture was concentrated *in vacuo* then purified by column chromatography on flash silica (40% ethylacetate-cyclohexane) to give the title compound as a clear oil (0.392g).

LC/MS system A R_t = 5.27mins, *m/z* = 602 MH^+

Intermediate 23: (2R,3R,4S,5S)-2-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(3-propyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol

A solution of Intermediate 22 (0.392g, 0.652mmol) in a mixture of acetic acid (10ml) and water (2.5ml), was stirred at 100 °C under nitrogen for 26h, then concentrated *in vacuo*. The residue was azeotroped with toluene (2x 10ml), to produce the title compound as a beige foam (0.355g).

LC/MS system B R_t = 3.41mins, *m/z* = 562 MH^+

Intermediate 24: {2-Chloro-9-[2,2-dimethyl-6S-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl}-(2,2-diphenyl-ethyl)-amine

Diisopropylethylamine (0.063ml, 0.364mmol) was added to a stirring mixture of (3aS,4S,6R,6aR)-6-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,2-dimethyl- tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid [Preparation 4 in International Patent Application No. WO94/17090] (0.15g, 0.28mmol), in dry

tetrahydrofuran (4ml), at 0 °C. Pivaloyl chloride (0.045ml, 0.364mmol) was added to the cooled stirring mixture, and it was stirred at 0 °C for 1.5h. N-Hydroxy-acetamidine, (0.042g, 0.56mmol) was added portion-wise over 10mins, and the resultant solution stirred for 1h at 0 °C. The mixture was allowed to warm to room temperature and stirred for a further 20h. The solution was concentrated *in vacuo*, then azeotroped with toluene (2 x 10ml). The yellow residue was re-dissolved in toluene (7ml), and heated at 80 °C with stirring for 1h. Once cool the reaction mixture was concentrated *in vacuo* to give the title compound as a yellow oil (0.146g).

LC/MS system B R_t = 3.58mins, *m/z* = 574 MH^+

Intermediate 25: (2R,3R,4S,5S)-2-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol

A solution of Intermediate 24 (0.146g, 0.255mmol) in a mixture of acetic acid (10ml) and water (2.5ml), was stirred at 100 °C under nitrogen for 37h, then concentrated *in vacuo*. The residue was azeotroped with toluene (2x 10ml), to produce the title compound as a yellow solid (0.132g).

LC/MS system B R_t = 3.23mins, *m/z* = 534 MH^+

Intermediate 26: {2-Chloro-9-[6S-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-2,2-dimethyl-tetrahydro-(3aR,6aS)-furo[3,4-d][1,3]dioxol-4R-yl]-9H-purin-6-yl}-(1-ethyl-propyl)-amine

Intermediate 7 (2.13g, 5mmol) dissolved in tetrahydrofuran(33ml) under nitrogen was cooled to 5 °C, N,N-diisopropylethylamine (1.9ml, 11mmol) and trimethylacetyl chloride (0.67ml, 5.5mmol) were added and mixture allowed to warm to room temperature over 1h. After cooling to 5 °C N-Hydroxy-cyclopropanecarboxamidine** (0.61g, 6 mmol) was added and the reaction mixture stirred for 16h allowing warming to room temperature. Solvent was removed *in vacuo* and the residue was dissolved in toluene (100ml) and heated

to reflux (120 °C) under nitrogen for 24h. Toluene was removed *in vacuo* and product purified by Solid Phase Extraction using Varian Mega Bonded Elut cartridge (10g SiO_2) eluted with ethyl acetate / cyclohexane (1:2) to afford title compound as yellow gum (2.170g).

LCMS SYSTEM A R_t=4.80mins *m/z*=490 MH^+

** W.J. Fanshawe, V.J. Bauer, S.R. Safir, D.A. Blickens and S.J.Riggi, J. Med. Chem., 1969, 12, 381

Intermediate 27: (2R,3R,4S,5S)-2-[2-Chloro-6-(1-ethyl-propylamino)-purin-9-yl]-5-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol

Intermediate 26 (2.1g,4.5mmol) was dissolved in trifluoroacetic acid/ water (9:1, 25ml) at 0 °C under nitrogen with stirring for 6h. and left in refrigerator (4 °C) for 16h. The mixture was concentrated *in vacuo* and poured slowly on to saturated sodium bicarbonate solution (150ml), extracting with dichloromethane(3x 50ml), washing with brine, drying with sodium sulphate, filtering and concentrating to afford the title compound as a yellow-white solid (2g).

LCMS SYSTEM B R_t = 3.22mins *m/z* = 450 MH^+

Intermediate 28: {6R-(2-Chloro-6-phenethylamino-purin-9-yl)-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl}-methanol

A mixture of acetic acid 4R-acetoxy-5R-acetoxymethyl-2R-(2,6-dichloro-purin-9-yl)-tetrahydro-furan-3R-yl ester** (0.1g, 0.224mmol), 2-phenylethylamine (0.034ml, 0.27mmol) and di-isopropylethylamine (0.047ml, 0.27mmol) in isopropanol (2ml) was heated at 52 °C for 17.5h in a sealed vial (e.g. Reacti-vial™). The reaction was then diluted with methanol (1ml). A solution of sodium methoxide (25wt% in methanol, 0.077ml, 0.336mmol) was added and stirred for 3.5h at room temperature. Acetic acid (0.2ml) was then added to the reaction mixture. Removal of volatile matters gave a residue which was dissolved in

acetone (2.5ml) and treated with 2,2-dimethoxypropane (0.35ml) and para-toluenesulfonic acid (0.081g). More reagents were added at 66h [acetone (3ml) and 2,2-dimethoxypropane (0.35ml)] and 90h [para-toluenesulfonic acid (81mg)]. After a further 21h reaction mixture was evaporated under a jet of air. The resultant mixture was stirred with saturated aqueous sodium carbonate (4ml) for 10 mins., extracted with ethyl acetate (3X3ml), dried ($MgSO_4$) and evaporated *in vacuo* to give the titled compound as a light brown gum (0.118g).
LC/MS system A R_t = 4.50 mins, *m/z* = 446 MH^+ for $C_{21}H_{24}{}^{35}ClN_5O_4$.

** M.J. Robins and B. Uznanski, Canad. J. Chem., 1981, 59(17), 2608

Intermediate 29: {6R-[2-Chloro-6-(2-cyclohexyl-ethylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl}-methanol
Intermediate 29 was prepared in an analogous manner to Intermediate 28 using 2-cyclohexylethylamine (0.034g, 0.27mmol). The title compound was obtained as a light brown foam (0.116g).
LC/MS system A R_t = 4.93 mins, *m/z* = 452 MH^+ for $C_{21}H_{30}{}^{35}ClN_5O_4$.

Intermediate 30: {6R-[2-Chloro-6-(3,3-dimethyl-butylamino)-purin-9-yl]-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl}-methanol
Intermediate 30 was prepared in an analogous manner to Intermediate 28 using 3,3-dimethylbutylamine (0.036ml, 0.27mmol). The title compound was obtained as a white solid (0.111g) in 88% purity.
LC/MS system A R_t = 4.93 mins, *m/z* = 452 MH^+ for $C_{21}H_{30}{}^{35}ClN_5O_4$.

Intermediate 31: {6R-(6-phenethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl) methanol

A mixture of Intermediate 28 (0.118g, 0.265mmol) and 2-(1-methyl-1H-imidazol-4-yl)ethylamine (0.168g, 1.344mmol) generated from the corresponding bis-hydrochloride by neutralisation with a slight deficiency of solid sodium hydroxide in methanol) in a mixture of di-isopropylethylamine (0.3ml) and DMSO (0.3ml) was heated in a sealed vial (e.g. Reacti-vial™) for 20h at 104 °C. The cooled reaction mixture was diluted with aqueous sodium hydroxide (0.5M, 5ml), extracted with dichloromethane (4X5ml). Combined extracts were filtered through a Varian Mega Bond Elut cartridge (5g Si, 20ml size), eluted with dichloromethane, 50% EtOAc-cyclohexane, EtOAc and then 10% MeOH-EtOAc. Fractions containing the desired product were combined and evaporated *in vacuo* affording the titled product as a clear gum (0.107g).

TLC (10% MeOH-EtOAc, visualised by UV light) rf = 0.13

Intermediate 32: {6R-{6-(2-cyclohexyl-ethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl) methanol

Intermediate 32 was prepared in an analogous manner to Intermediate 31 using Intermediate 29 (0.116g, 0.257mmol). The title compound was obtained as a clear gum (0.09g).

TLC (10% MeOH-EtOAc, visualised by UV light) rf = 0.13

Intermediate 33: {6R-{6-(3,3-dimethyl-butylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4R-yl) methanol

Intermediate 33 was prepared in an analogous manner to Intermediate 31 using Intermediate 30 (0.111g, 0.261mmol). The title compound was obtained as a clear gum (0.097g).

TLC (10% MeOH-EtOAc, visualised by UV light) rf = 0.13

Intermediate 34: (3aS,4S,6R,6aR)-6-{6-phenethylamino-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid

To a stirring mixture of potassium hydroxide (0.1g) and potassium permanganate (0.158g, 1mmol) in water (1ml) at 0 °C, a solution of Intermediate 31 (0.107g, 0.2mmol) in dioxan (1.6ml) was added dropwise over 5 mins. Mixture was stirred in ice-water bath for 4h. Solid sodium metabisulphite was added until all purple coloration disappeared. Mixture was filtered through a short and compressed pad of Harbourlite. The resultant aqueous solution was carefully acidified to pH3 – 4 with 2M aqueous hydrochloric acid and washed with EtOAc (3X5ml). The resultant aqueous solution was freeze-dried to give a white solid which was extracted with methanol (3ml then 2X1ml) to give the titled product as a creamy white solid (0.084g).

LC/MS system C R_t = 2.43 mins, *m/z* = 549 MH^+

Intermediate 35: (3aS,4S,6R,6aR)-6-{6-(2-cyclohexyl-ethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid

Intermediate 35 was prepared in an analogous manner to Intermediate 34 using Intermediate 32 (0.09g, 0.17mmol). The title compound was obtained as a creamy white solid (0.081g).

LC/MS system C R_t = 2.61 mins, *m/z* = 555 MH^+

Intermediate 36: (3aS,4S,6R,6aR)-6-{6-(3,3-Dimethyl-butylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid

Potassium hydroxide (0.09g, 1.52mmol) was crushed and dissolved in water (0.5ml) with stirring. Potassium permanganate (0.158g, 0.95mmol) was added with stirring and the mixture cooled to 0 °C. to this was added Intermediate 33 (0.097g, 0.19mmol) dissolved in 1,4-dioxane (1.6ml) and water (0.5ml), pre-

cooled to 0 °C. The reaction mixture was stirred for 3h at 0 °C then treated with solid sodium metabisulphite (0.15g) until the purple colour discharged. Insolubles were filtered off through a pad of Harborlite washing with water (10ml). The aqueous mixture was extracted with dichloromethane (2 x 20ml). Combined organics were concentrated *in vacuo* to afford title compound as a yellow oil (0.064g).

LCMS SYSTEM C Rt=2.44min *m/z*=529 MH^+

Intermediate 37: 2-(Pyridin-2-ylamino)-ethylamine

2-Bromopyridine (10.00g, 63.3mmol) was added dropwise to 1,2-diaminoethane (76.00g, 126.6mmol) under nitrogen at 20 °C with stirring. The reaction mixture was stirred at 20 °C for 4h. and then under reflux for 24h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography on flash silica eluting with dichloromethane, ethanol and ammonia (30:8:1) to afford the title compound as a red oil (1.23g).

TLC SiO_2, (Dichloromethane, ethanol, ammonia; 30:8:1) Rf = 0.14

Mass Spectrum *m/z* 138 (MH^+ for $C_7H_{11}N_3$).

Intermediate 38: N-Hydroxy-propionamidine

A mixture of propionitrile (20ml, 280mmol), potassium carbonate (78g, 560mmol) and hydroxylamine hydrochloride (19.000g, 280mmol) in ethanol (400ml) was stirred at room temperature for 15min and slowly heated to reflux over 1 hour and refluxed for 7 hours. On cooling the mixture was filtered through Harbolite filter aid, washed with ethanol (100ml). The solvent was evaporated *in vacuo* and the residue was azeotroped with toluene (3x100ml) to afford the title compound as a light coloured oil (17g)

TLC SiO_2 (5%methanol/ chlorofrom/1% ammonia) Rf = 0.21

Intermediate 39: 3-Ethyl-5-(6R-methoxy-2,2-dimethyl-tetrahydro-(3aR,6aR)-furo[3,4-d][1,3]dioxol-4S-yl)-[1,2,4]oxadiazole

A mixture of (3aS,4S,6R,6aR)-Methoxy-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxole-4-carboxylic acid, prepared by following the method of Intermediate 1 in International Patent Application No. WO98/28319, (14.800g, 68mmol), 1-hydroxybenzatriazole (9.200g, 68mmol), and 1(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (13.000g, 68mmol) in DMF (200ml) was stirred at room temperature overnight. Intermediate 38 (6.000g, 68mmol) in DMF (10ml) was then added and the mixture heated to 70°C overnight. Upon cooling the solvent was removed *in vacuo*. The residue was taken up into ethyl acetate (100ml) and washed with 10% citric acid (2x100ml), water (1x100ml) and the organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to afford the title compound as a colourless gum (17.00g). LC/MS SYSTEM C R_t = 1.77 mins, m/z = 271 MH^+

Intermediate 40: Acetic acid 4S-acetoxy-2R-(3-ethyl-[1,2,4]oxadiazol-5-yl)-5S-methoxy-tetrahydro-furan-3R-yl ester

A mixture of Intermediate 39 (17g, 62mmol) and concentrated hydrochloric acid (3ml) in methanol (200ml) was heated to reflux overnight. On cooling the mixture was evaporated *in vacuo* to 50% volume, and pyridine (50ml) was added. The mixture was then evaporated *in vacuo* to approximately 25% of original volume. Additional pyridine (100ml) was added and the mixture was evaporated *in vacuo*. The residue was taken up into anhydrous pyridine (150ml) and treated with acetic anhydride (50ml, excess) followed DMAP (0.38g 3mmol). The mixture was stirred at room temperature overnight. The mixture was evaporated, the residue was taken up into ethyl acetate (200ml) and washed with 10% citric acid (2x100ml), water (100ml), dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification using flash column chromatography with a Biotage column

(3x90g, SiO_2) eluted with 30% cyclohexane, ethyl acetate furnished the title compound as a colourless solid (17.500g).

TLC SiO_2 (50% cyclohexane/ ethyl acetate) Rf = 0.52

Intermediate 41: Acetic acid 4S-acetoxy-2R-(2,6-dichloro-purin-9-yl)-5S-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3R-yl ester

A mixture of 2,6-dichloropurine (0.829g, 4.3mmol) in 1,1,1,3,3,3,hexamethyldisilazane (5ml) was heated to reflux overnight, then the solvent was removed *in vacuo*. The residue obtained was azeotroped with anhydrous toluene (3x5ml). To the residue in anhydrous acetonitrile (2ml) was added Intermediate 40 (0.500g, 1.6mmol) and DBU (0.65ml, 4.3mmol). The mixture was then cooled to 0°C and the TMSOTf (0.9ml, 4.8mmol) was added. The mixture was allowed to warm to room temperature, and the heated to reflux overnight giving a deep red coloured solution. On cooling the mixture was poured into saturated bicarbonate solution (5ml) and extracted with ethyl acetate (3x10ml). The combined organic layers was washed with water (20ml), dried ($MgSO_4$) and the solvent removed *in vacuo* . The residue obtained was purified using flash column chromatography with a Biotage column (8g, SiO_2) eluting with 60% cyclohexane, ethyl acetate to afford the title compound as an off white solid (0.599g).

LC/MS SYSTEM C R_t = 3.32 mins, m/z = 472 MH^+

Intermediate 42: Acetic acid 4S-acetoxy-2R-[6-azido-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5S-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetra hydro-furan-3R-yl ester

To a cooled mixture of Intermediate 41 (0.600g, 1.27mmol) in anhydrous DMF at −10 to −15°C was added sodium azide (0.088g, 1.35mmol) . The mixture was stirred at −10°C for 2 hours and 3-(S)-(-)2-amino-3-phenyl propanol (0.388g, 2.8mmol) in anhydrous DMF (1ml) was added. The mixture was allowed to warm

to room temperature and stirred overnight. Water(15ml) was added and the mixture was extracted with ethyl acetate (3x15ml). The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo*. Purification using flash column chromatography with a Biotage column (8g, SiO_2) eluting with 30% cyclohexane, ethyl acetate, furnished the title compound as a colourless gum (0.450g).

LC/MS SYSTEM C R_t = 3.25 min, m/z = 593 MH^+

Intermediate 43: Acetic acid 4S-acetoxy-2R-[6-amino-2-(1S-hydroxy methyl-2-phenyl-ethylamino)-purin-9-yl]-5S-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3R-yl ester

A mixture of Intermediate 42 (0.440g, 0.74mmol) and triphenylphosphine (0.220g, 0.84mmol) in tetrahydrofuran (5ml) was stirred at room temperature overnight. The solvent was evaporated *in vacuo*. Purification using Autoprep. HPLC afforded the title compound as an off-white solid (0.410g).

LC/MS SYSTEM C R_t = 2.77 min, m/z = 567 MH^+

Examples

Example 1: (2R,3R,4S,5S)-2-[6-(2,2-Diphenyl-ethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol bis(trifluoroacetate).

A solution of Intermediate 2 (0.050g, 0.08mmol) in 1,4-dioxane (2ml) was treated with EEDQ (0.024g, 0.096mmol), and N-hydroxy-acetamidine (0.012g, 0.16mmol). The resultant mixture was heated at 103 °C with stirring for 6 days. The solution was concentrated *in vacuo* to afford a yellow oil. A cooled solution of trifluoroacetic acid (0.9ml) and water (0.1ml), was added to the yellow oil. The resultant solution was stirred at 0 °C for 6h, then concentrated *in vacuo*, and

azeotroped with toluene (3X). Purification by preparative HPLC (30-70% acetonitrile in water) gave the title compound as a white solid (0.006g).
LC/MS SYSTEM A R_t = 3.98mins, *m/z* = 623 MH^+

Example 2: (2R,3R,4S,5S)-2-{6-(2,2-Diphenyl-ethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol bis(difluoroacetate).

Example 2 was prepared in an analogous manner to Example 1 using N-hydroxy-propionamidine (0.014g, 0.16mmol). A solution of Intermediate 2 (0.050g, 0.08mmol) in 1,4-dioxan (2ml) was treated with EEDQ (0.024g, 0.096mmol), and N-hydroxy-propionamidine (0.014g, 0.16mmol). The resultant mixture was heated at 103 °C with stirring for 6 days. The solution was concentrated *in vacuo* to afford a yellow oil. A cooled solution of trifluoroacetic acid (0.9ml) and water (0.1ml), was added to the yellow oil. The resultant solution was stirred at 0 °C for 6h, then concentrated *in vacuo*, and azeotroped with toluene (3X). Purification by preparative HPLC (30-70% acetonitrile in water) gave the title compound as a white solid (0.012g).
LC/MS SYSTEM A R_t = 4.02mins, *m/z* = 637 MH^+

Example 3: (2R,3R,4S,5S)-2-[6-(2,2-Diphenyl-ethylamino)-2-(pyrrolidin-3R-ylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate.

A mixture of Intermediate 4 (0.034g, 0.062mmol), (3R)-(+ -3-aminopyrrolidine) (0.030 ml, 0.311mmol) and DMSO (0.03ml), in a sealed vial (e.g. Reacti-vial™) was heated at 80 °C for 28h. The resultant crude product was purified by Autoprep. HPLC to afford the title compound after freeze drying as a white solid (0.017g).
LC/MS system A R_t = 3.65mins, *m/z* = 598 MH^+

Example 4: (2R,3R,4S,5S)-2-[2-(trans-4-Amino-cyclohexylamino)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol diformate.

Example 4 was formed in an analogous manner to Example 3 using *trans*-1,4,-diaminocyclohexane (0.035g, 0.311mmol). The title compound was obtained after freeze-drying as a white solid (0.013g).

LC/MS system B R_t = 2.58mins, *m/z* = 626 MH^+

Example 5: (2R,3R,4S,5S)-2-[6-(2,2-Diphenyl-ethylamino)-2-(1S-hydroxymethyl-2-methyl-propylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate.

Example 5 was formed in an analogous manner to Example 3 using (S)-2-amino-3-methyl-1-butanol (0.032g, 0.311mmol), and heating the reaction mixture for 3 days, at 80-95 °C. The title compound was obtained after freeze-drying as a white solid (0.005g).

LC/MS system B R_t = 3.16mins, *m/z* = 615 MH^+

Example 6: (2R,3R,4S,5S)-2-[6-(1-Ethyl-propylamino)-2-(2-morpholin-4-yl-ethylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Intermediate 11 (0.069g, 0.163mmol) and 4-(2-aminoethyl)morpholine (0.107ml, 0.815mmol) were dissolved in DMSO (0.03ml) and heated at 80 ° C for 26h in a sealed vial (eg Reacti vial™), a further portion of 4-(2-aminoethyl)morpholine (0.053ml, 0.407mmol) was added after the first 20h. The product was purified by Autoprep. HPLC to give the title compound after freeze drying as a brown solid (0.059g).

LC/MS system B R_t = 2.19min, *m/z* = 517MH^+.

Example 7: (2R,3R,4S,5S)-2-{6-Amino-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol bis(trifluoroacetate)

Intermediate 17 (0.048g), 2-(1-methyl-1H-imidazol-4-yl)ethylamine (0.06g) in DMSO (0.05ml) were heated in a sealed vial (eg Reacti vial™) at 90 °C for 20hrs. The crude material was purified twice by Autoprep HPLC then by preparative HPLC (10-60% Acetonitrile over 22min), solvent was removed *in vacuo* and the residue freeze-dried to give the title compound as a brown solid (0.007g)

LC/MS system A R_t =1.8min, *m/z* 443 (MH^+)

Example 8: (2R,3R,4S,5S)-2-[6-Amino-2-(2-pyridin-2-yl-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol diformate

Intermediate 18 (0.041g), 2-(2-aminoethyl)pyridine(0.06ml), DMSO (0.05ml), were heated in a sealed vial (eg Reacti vial™) at 90 °C for 16hrs. The sample was purified by Autoprep HPLC. Solvent was removed *in vacuo* and the residue freeze-dried to give the title compound as a pale brown solid (0.011g).

LC/MS system B R_t = 1.92min, *m/z* 454 (MH^+)

Example 9: (2R,3R,4S,5S)-2-[6-Amino-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Intermediate 18 (0.041g), (S)-(-)-2-amino-3-phenyl-1-propanol (0.06g), DMSO (0.05ml), were heated in a sealed vial (eg Reacti vial™) at 90 °C for 32hrs, then at 110 °C for 16hrs. The sample was purified twice by Autoprep. HPLC. Solvent was removed *in vacuo* and the residue freeze-dried to give the title compound as a white solid (0.003g).

LC/MS system B R_t = 2.36min, *m/z* = 483 (MH^+)

Example 9 (Alternative Procedure): 2R-[6-Amino-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5S-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3R,4S-diol formate

A mixture of Intermediate 43 (0.160g, 0.28mmol) and potassium cyanide (0.009g, 0.14mmol) in methanol (3ml) was stirred at room temperature for 30min. The solvent was evaporated *in vacuo* and the residue was purified using to Autoprep. HPLC to furnish the title compound as a white solid (0.050g).

LC/MS SYSTEM C R_t = 2.35 min, m/z = 483 MH^+

Example 10: (2R,3R,4S,5S)-2-{6-Amino-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol diformate

Intermediate 18 (0.041g), 2-(1-methyl-1H-imidazol-4-yl)ethylamine (0.06g), DMSO (0.05ml) were heated in a sealed vial (eg Reacti vial™) at 90 °C for 32hrs, then at 110 °C for 16hrs. The sample was purified by Autoprep. HPLC, solvent was removed *in vacuo* and the residue freeze-dried to give the title compound as a brown solid (0.014g).

LC/MS system B R_t = 1.88min, *m/z* = 457 (MH^+)

Example 11: (2R,3R,4S,5S)-2-(6-Amino-2-cyclopentylamino-purin-9-yl)-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Intermediate 17 (0.048g), cyclopentylamine (0.06ml) in DMSO (0.05ml) were heated in a sealed vial (eg Reacti vial™) at 90 °C for 20hrs. The crude material was purified by Autoprep HPLC, solvent was removed *in vacuo* and the residue freeze-dried to give the title compound as a pale yellow solid (0.006g)

LC/MS system A R_t =2.2min, *m/z* = 403(MH^+)

Example 12: (2R,3R,4S,5S)-2-[6-Amino-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Intermediate 17 (0.048g), (S)-(-)-2-amino-3-phenyl-1-propanol (0.06g) in DMSO (0.05ml) were heated in a sealed vial (eg Reacti vial™) at 90 °C for 20hrs. The crude material was purified twice by Autoprep HPLC, solvent was removed *in vacuo* and the residue freeze-dried to give the title compound as a white solid(0.002g)

LC/MS system A R_t=2.24 min, *m/z* = 469 (MH^+)

Example 13: (2S,3S,4R,5R)-2-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-5-{6-(1-ethyl-propylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-tetrahydro-furan-3,4-diol formate

Intermediate 9 (0.070g, 0.161mmol) and 2-(1-methyl-1H-imidazol-4-yl)ethylamine (0.101g, 0.807mmol) were dissolved in DMSO (0.03ml) and heated at 85 -100 °C under nitrogen for 8 days, a further portion of 2-(1-methyl-1H-imidazol-4-yl)ethylamine (0.101g, 0.807mmol) was added after the first 5 days. The product was purified by Autoprep. HPLC to give the title compound after freeze drying as a cream solid (0.010g).

LC/MS system A R_t = 3.36min, *m/z* = 526 MH^+.

Example 14: (2R,3R,4S,5S)-2-{6-(1-Ethyl-propylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Intermediate 11 (0.069g, 0.163mmol) and 2-(1-methyl-1H-imidazol-4-yl)ethylamine (0.102g, 0.815mmol) were dissolved in DMSO (0.03ml) and heated at 85 -100 °C under nitrogen for 7 days, a further portion of 2-(1-methyl-1H-imidazol-4-yl)ethylamine (0.102g, 0.815mmol) was added after the first 5

days. The product was purified by Autoprep. HPLC to give the title compound after freeze drying as a beige solid (0.013g).

LC/MS system A R_t = 3.32min, *m/z* = 512MH^+.

Example 15: (2R,3R,4S,5S)-2-(6-Amino-2-phenethylamino-purin-9-yl)-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol trifluoroacetate

Intermediate 21 (0.210g, 0.44mmol) was dissolved in trifluoroacetic acid and water 9:1, 2ml) and the solution was stirred at 20 °C for 3 hrs., and solvent was removed *in vacuo*. Purification by preparative HPLC (10-90% acetonitrile in water) afforded the title compound after freeze drying as a pale yellow solid (0.088g).

Mass spectrum m/z 439 (MH+ for $C_{20}H_{23}N_8O_4$)

Analysis found: C, 46.70; H, 4.05; N, 19.51; $C_{20}H_{22}N_8O_4.C_2HF_3O_2.0.5H_2O$ requires C, 46.54; H, 4.24; N, 19.56

Example 16: (2R,3R,4S,5S)-2-[2-(trans-4-Amino-cyclohexylamino)-6-(1-ethyl-propylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Intermediate 11 (0.069g, 0.163mmol) and *trans* -1,4-diaminocyclohexane (0.093g, 0.815mmol) were dissolved in DMSO (0.03ml) and heated at 80-90 °C for 66h in a sealed vial (eg Reacti vial™), a further portion of *trans* -1,4-diaminocyclohexane (0.093g, 0.815mmol) was added after the first 20h. The product was purified by Autoprep. to give the title compound after freeze drying as a brown solid (0.063g).

LC/MS system B R_t = 2.12min, *m/z* = 502 MH^+.

Example 17: (2R,3R,4S,5S)-2-[6-(1-Ethyl-propylamino)-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Intermediate 11 (0.069g, 0.163mmol) and 3-(S)-(-)2-amino-3-phenyl propanol (0.123g, 0.815mmol) were dissolved in DMSO (0.03ml) and heated at 80-95 °C for 5.5 days in a sealed vial (eg Reacti vial™). The product was purified by Autoprep. HPLC to give the title compound after freeze drying as a yellow solid (0.014g).

LC/MS system B R_t = 2.80min, *m/z* = 539 MH^+.

Example 18: (2R,3R,4S,5S)-2-[6-(1-Ethyl-propylamino)-2-(2-piperidin-1-yl-ethylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Intermediate 11 (0.069g, 0.163mmol) and 2-piperidinoethylamine (0.116ml, 0.815mmol) were dissolved in DMSO (0.03ml) and heated at 80 °C for 40h in a sealed vial (Reacti vial™) a further portion of 2-piperidinoethylamine (0.058ml, 0.407mmol) was added after the first 20h. The product was purified by Autoprep. HPLC to give the title compound after freeze drying as a brown solid (0.031g).

LC/MS system B R_t = 2.25min, *m/z* = 516 MH^+.

Example 19: (2S,3S,4R,5R)-2-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2-morpholin-4-yl-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol formate

Intermediate 9 (0.070g, 0.161mmol) and 4-(2-aminoethyl)morpholine (0.106ml, 0.807mmol) were dissolved in DMSO (0.03ml) and heated at 80 °C in a sealed vial (eg Reacti vial™), for 26h, a further portion of 4-(2-aminoethyl)morpholine (0.053ml, 0.403mmol) was added after the first 6h. The product was purified by Autoprep. HPLC to give the title compound after freeze drying as a beige solid (0.049g).

LC/MS system B R_t = 2.27min, *m/z* = 532 MH^+.

Example 20: (2S,3S,4R,5R)-2-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2-piperidin-1-yl-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol formate

Intermediate 9 (0.070g, 0.161mmol) and 2-piperidinoethylamine (0.115ml, 0.807mmol) were dissolved in DMSO (0.03ml) and heated at 80 °C in a sealed vial (eg Reacti vial™), for 40h, a further portion of 2-piperidinoethylamine (0.057ml, 0.403mmol) was added after the first 20h. The product was purified by Autoprep. HPLC to give the title compound after freeze drying as a brown gum (0.035g).

LC/MS system B R_t = 2.33min, *m/z* = 530 MH^+.

Example 21: (2S,3S,4R,5R)-2-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2-pyridin-2-yl-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol formate

Intermediate 9 (0.070g, 0.161mmol) and 2-(2-aminoethyl) pyridine (0.096ml, 0.807mmol) were dissolved in DMSO (0.03ml) and heated at 80 °C in a sealed vial (eg Reacti vial™), for 46h, a further portion of 2-(2-aminoethyl) pyridine (0.096ml, 0.807mmol) was added after the first 20h. The product was purified by Autoprep. HPLC to give the title compound after freeze drying as a beige solid (0.035g).

LC/MS system B R_t = 2.38min, *m/z* = 524 MH^+.

Example 22: (2R,3R,4S,5S)-2-[2-Cyclopentylamino-6-(1-ethyl-propylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Intermediate 11 (0.069g, 0.163mmol) and cyclopentylamine (0.08 ml, 0.815mmol) were dissolved in DMSO (0.03ml) and heated at 80 °C for 20h in a sealed vial (eg Reacti vial™). The product was purified by Autoprep. HPLC to give the title compound after freeze drying as a beige solid (0.007g).

LC/MS system B R_t = 2.87min, *m/z* = 472 MH^+.

Example 23: (2R,3R,4S,5S)-2-[2-Cyclopentylamino-6-(1-ethyl-propylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Intermediate 9 (0.070g, 0.161mmol) and cyclopentylamine (0.08ml, 0.807mmol) were dissolved in DMSO (0.03ml) and heated at 80 °C in a sealed vial (eg Reacti vial™), for 20h. The product was purified by Autoprep. HPLC to give the title compound after freeze drying as a cream solid (0.008g).
LC/MS system B R_t = 3.01min, *m/z* = 486 MH^+.

Example 24: (2R,3R,4S,5S)-2-[6-(1-Ethyl-propylamino)-2-(2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Intermediate 11 (0.069g, 0.163mmol) and (R,R)-aminocyclopentan-2-ol[~] (0.082g, 0.815mmol) were dissolved in DMSO (0.03ml) and heated at 80-95 °C for 68h in a sealed vial (eg Reacti vial™). The product was purified by Autoprep. HPLC to give the title compound after freeze drying as a brown solid (0.005g).
LC/MS system B R_t = 2.57min, *m/z* = 489 MH^+.

[~] L.E. Overman and S. Sugai, J. Org. Chem., 1985, 50, 4154

Example 25: (2S,3S,4R,5R)-2-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol formate

Intermediate 9 (0.070g, 0.161mmol) and (R,R)-aminocyclopentan-2-ol[~] (0.082g, 0.807mmol) were dissolved in DMSO (0.03ml) and heated at 80-95 °C in a sealed vial (eg Reacti vial™), for 68h. The product was purified by Autoprep. HPLC to give the title compound after freeze drying as a brown solid (0.005g).
LC/MS system B R_t = 2.68min, *m/z* = 503 MH^+.

[~] L.E. Overman and S. Sugai, J. Org. Chem., 1985, 50, 4154

Example 26: (2R,3R,4S,5S)-2-[6-(1-Ethyl-propylamino)-2-(pyrrolidin-3R-ylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Intermediate 11 (0.069g, 0.163mmol) and (3R)-(+)-3-aminopyrrolidine (0.070g, 0.815mmol) were dissolved in DMSO (0.03ml) and heated at 80 °C for 6h in a sealed vial (eg Reacti vial™). The product was purified by Autoprep. HPLC to give the title compound after freeze drying as a cream solid (0.041g).
LC/MS system B R_t = 2.24min, *m/z* = 474 MH^+.

Example 27: (2S,3S,4R,5R)-2-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(pyrrolidin-3R-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol formate

Intermediate 9 (0.070g, 0.161mmol) and (3R)-(+)-3-aminopyrrolidine (0.07g, 0.807mmol) were dissolved in DMSO (0.03ml) and heated at 80 °C in a sealed vial (eg Reacti vial™), for 6h. The product was purified by Autoprep. HPLC to give the title compound after freeze drying as a cream solid (0.041g).
LC/MS system B R_t = 2.31min, *m/z* = 488 MH^+.

Example 28: (2R,3R,4S,5S)-2-[6-(1-Ethyl-propylamino)-2-(1S-hydroxymethyl-2-methyl-propylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Intermediate 11 (0.069g, 0.163mmol) and L-2-amino-3-methylbutanol (0.084g, 0.815mmol) were dissolved in DMSO (0.03ml) and heated at 80-95 °C for 5.5 days in a sealed vial (eg Reacti vial™). The product was purified by Autoprep. HPLC to give the title compound after freeze drying as a yellow gum (0.030g).
LC/MS system B R_t = 2.59min, *m/z* = 491 MH^+.

Example 29: (2R,3R,4S,5S)-2-[2-(trans-4-Amino-cyclohexylamino)-6-(1-ethyl-propylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Intermediate 9 (0.070g, 0.161mmol) and *trans* -1,4-diaminocyclohexane (0.092g, 0.807mmol) were dissolved in DMSO (0.03ml) and heated at 80-90 °C in a sealed vial (eg Reacti vial™), for 66h, a further portion of *trans* -1,4-diaminocyclohexane (0.092mg, 0.807mmol) was added after the first 20h. The product was purified by Autoprep. HPLC to give the title compound after freeze drying as a brown solid (0.082g).

LC/MS system B R_t = 2.21min, *m/z* = 516 MH^+.

Example 30: (2R,3R,4S,5S)-2-[6-Amino-2-(2-pyridin-2-yl-ethylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol diformate

Intermediate 17 (0.048g), 2-(2-aminoethyl)pyridine (0.06ml) in DMSO (0.05ml) were heated in a sealed vial (eg Reacti vial™) at 90 °C for 20hrs. 2-(2-aminoethyl)pyridine (0.05ml) was added and the mixture heated at 110 °C for 16h. Purification by Autoprep. HPLC followed by freeze-drying gave the title compound as a pale brown solid (0.0015g)

LC/MS system B R_t = 1.88 min, *m/z* = 440 MH^+.

Example 31: (2R,3R,4S,5S)-2-[6-(2,2-Diphenyl-ethylamino)-2-(2-morpholin-4-yl-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

A mixture of Intermediate 4 (0.034g, 0.062mmol), 4-(2-aminoethyl)morpholine (0.041ml, 0.31mmol) and DMSO (0.03ml), in a sealed vial (e.g. Reacti-vial™) was heated at 80 °C for 28h. Purification by Autoprep. HPLC afforded the title compound after freeze drying as a white solid (0.015g).

LC/MS system A R_t = 3.67mins, *m/z* = 642MH^+

Example 32: (2R,3R,4S,5S)-2-[6-(2,2-Diphenyl-ethylamino)-2-(2-piperidin-1-yl-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

A mixture of Intermediate 4 (0.034g, 0.062mmol), 2-piperidinoethylamine (0.044ml, 0.311mmol) and DMSO (0.03ml), in a sealed vial (e.g. Reacti-vial™) was heated at 80 °C for 28h. Purification by Autoprep. HPLC afforded the title compound after freeze drying as a white solid (0.010g).

LC/MS system A R_t = 3.72mins, *m/z* = 640MH$^+$

Example 33: (2R,3R,4S,5S)-2-{6-(2,2-Diphenyl-ethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-propyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

A mixture of Intermediate 23 (0.075g, 0.135mmol), and 2-(1-methyl-1H-imidazol-4-yl)ethylamine (0.085g, 0.677mmol) in diisopropylethylamine (0.04ml) and DMSO (0.04ml), in a sealed vial (e.g. Reacti-vial™) was heated at 85 °C for 40h. A further portion of 2-(1-methyl-1H-imidazol-4-yl)ethylamine (0.085g, 0.677mmol) was added after the first 20h. Purification by Autoprep. HPLC afforded the title compound after freeze drying as a cream solid (0.037g).

LC/MS system B R_t = 2.71mins, *m/z* = 651 MH$^+$

Example 34: (2R,3R,4S,5S)-2-{6-(2,2-Diphenyl-ethylamino)-2-[2-(1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

A mixture of Intermediate 25 (0.132g, 0.248mmol), and histamine (0.138g, 1.24mmol) in diisopropylethylamine (0.04ml) and DMSO (0.04ml), in a sealed vial (e.g. Reacti-vial™) was heated at 85-90 °C for 40h. The resultant crude product was purified by Autoprep. HPLC to afford the title compound after freeze drying as a cream solid (0.032g).

LC/MS system B R_t = 2.59mins, *m/z* = 609 MH$^+$.

Example 35: (2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2-piperidin-1-yl-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diolldiformate

A mixture of Intermediate 27 (70mg, 0.15mmol) and 2-piperidinoethylamine (0.117ml, 0.83mmol) in dimethylsulphoxide (0.3ml) in a sealed vial (e.g. Reacti-vial™) was heated with stirring to 90 °C for 4h. The resultant crude product was purified by Autoprep. HPLC to afford the title compound after freeze-drying as a brown solid (0.015g)

LCMS SYSTEM C R_t=2.32mins *m/z*=542 MH^+

Example 36: (2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2-morpholin-4-yl-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol diformate

Example 36 prepared in an analogous method to Example 35 using 4-(2-aminoethyl)morpholine (0.108ml, 0.825mmol) at 90 °C for 4h. The title compound was afforded after freeze-drying as a brown solid (0.009g)

LCMS SYSTEM C R_t=2.32mins *m/z*=544 MH^+

Example 37: (2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2-(2-pyridinyl)-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol diformate

Example 37 prepared in an analogous manner to Example 35 using 2-(2-aminoethyl)pyridine (0.104g, 0.825mmol) at 90 °C for 4h. The title compound was afforded after freeze-drying as a brown solid (0.012g)

LCMS SYSTEM C R_t=2.18mins *m/z*=535 MH^+

Example 38: (2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2-(1-methyl-1H-imidazol-4-yl)-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol diformate

Example 38 prepared in an analogous method to Example 35 using 2-(1-methyl-1H-imidazol-4-yl)-ethylamine (0.14g, 0.825mmol; generated from the corresponding bishydrochloride by neutralization with slight deficient of solid sodium hydroxide in methanol and evaporation of any volatile matters under a jet of nitrogen) at 90 °C for 4h. The title compound was afforded after freeze-drying as a brown solid (0.015g)

LCMS SYSTEM C R_t=2.32mins *m/z*=542 MH^+

Example 39: (2R,3R,4S,5S)-2-[6-(2,2-Diphenyl-ethylamino)-2-(2-pyrrolidin-1-yl-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol diformate

A mixture of Intermediate 3 (70mg, 0.15mmol) and 1-(2-aminoethyl)pyrrolidine (0.114g,1mmol) in dimethylsulphoxide (0.2ml) in a sealed vial (e.g. Reacti-vial™) was heated with stirring to 90 °C for 4h. The resultant crude product was purified by Autoprep. HPLC to afford the title compound after freeze-drying as a brown solid (0.008g)

LCMS SYSTEM B R_t=2.67mins *m/z*=626 MH^+

Example 40: (2R,3R,4S,5S)-2-{6-(2,2-Diphenyl-ethylamino)-2-[2-(pyridin-2-ylamino)-ethylamino]-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol diformate

Example 40 was prepared in an analogous manner to Example 39 using Intermediate 37 (0.137g,1mmol) at 90 °C for 4h. The title compound was afforded after freeze-drying as a brown solid (0.003g)

LCMS SYSTEM A R_t=2.74mins *m/z*=649 MH^+

Example 41: (2R,3R,4S,5S)-2-{2-(Bicyclo[2.2.1]hept-2-ylamino)-6-(2,2-diphenyl-ethylamino)-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Example 41 was prepared in an analogous manner to Example 39 using (±)-exo-2-aminonorbornane (0.110g,1mmol) at 90 °C for 4h. The title compound was afforded after freeze-drying as a brown solid (0.008g)
LCMS SYSTEM B R_t=3.77mins *m/z*=623 MH^+

Example 42: (2R,3R,4S,5S)-2-{2-(2-[3,4-Dimethoxy-phenyl]-ethylamino)-6-(2,2-diphenyl-ethylamino)-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Example 42 was prepared in an analogous manner to Example 39 using 2-(3,4-dimethoxyphenyl)-ethylamine (0.181,1mmol) at 90 °C for 4h. The title compound was afforded after freeze-drying as a brown solid (0.002g)
LCMS SYSTEM B R_t=3.42mins *m/z*=693 MH^+

Example 43: (2R,3R,4S,5S)-2-[6-(2,2-Diphenyl-ethylamino)-2-(2-hydroxy-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

Example 39 was prepared in an analogous manner to Example 39 using 2-hydroxy-ethylamine (0.061g,1mmol) at 90 °C for 4h. The title compound was afforded after freeze-drying as a brown solid (0.013g)
LCMS SYSTEM B R_t=3.02mins *m/z*=573 MH^+

Example 44: (2R,3R,4S,5S)-2-[6-(2,2-Diphenyl-ethylamino)-2-(4-fluoro-phenylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol formate

A mixture of Intermediate 3 (50mg, 0.09mmol) and 4-fluoroaniline (0.11g, 1mmol) in DMSO (0.2ml) in a sealed vial (e.g. Reacti-vial™) was heated with stirring to 90 °C for 20h. and heated for another 20h. at 110 °C. The resultant crude product was purified by Autoprep. HPLC to afford the title compound after freeze-drying as a brown solid (0.005g)

LCMS SYSTEM C Rt=3.60 min *m/z*=623 MH^+

Example 45: (2R,3R,4S,5S)-2-[2-(1-Benzyl-pyrrolidin-3S-ylamino)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol diformate

Example 45 was prepared in an analogous manner to Example 35 using 1-benzyl-3S-amino-pyrrolidine(0.18g,1mmol) at 90 °C for 20h. The title compound was afforded after freeze-drying as a brown solid (0.003g)

LCMS SYSTEM C Rt=2.75min *m/z*=688 MH^+

Example 46: (2R,3R,4S,5S)-2-{6-phenethylamino-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol diformate

Intermediate 34 (0.083mg, 0.15mmol) was dissolved in DCM/THF (9:1, 3ml) using sonication by ultrasound. N, N-diisopropylethylamine (0.057ml, 3.32mmol) and trimethylacetyl chloride (0.021ml, 0.16mmol) were added at 0 °C with stirring under nitrogen. The reaction was allowed to warm to room temperature over 2h, cooled again to 0 °C and N-hydroxy-propionamidine (0.015g, 0.18mmol in 0.5ml tetrahydrofuran) added with stirring. The reaction was allowed to warm to room temperature and stirred for 16h. The solvents were evaporated *in vacuo* and the reaction mixture dissolved in toluene (10ml). The reaction was heated to reflux (120 °C) for 8h. The product was purified on a Varian Mega Bond Elut cartridge (5g Si, 20ml size) eluting with ethyl acetate/methanol (50:1-1:1) to afford crude product as a yellow oil (0.01g). The product dissolved in trifluoroacetic acid/ water (4ml, 9:1) at 0 °C with stirring under nitrogen for 4h. The solvents were evaporated *in vacuo*, azeotroped with toluene (2x 50ml) and purification using Autoprep. HPLC afforded title compound as yellow gum (0.004 g)

LCMS SYSTEM C Rt=2.39min *m/z*=561 MH^+

Example 47: (2R,3R,4S,5S)-2-{6-(2-cyclohexylethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol diformate

Example 47 was prepared in an analogous manner to Example 46 using Intermediate 35 (0.081g, 0.146mmol), trimethylacetyl chloride (0.02ml, 0.16mmol), N, N-diisopropylethylamine (0.056ml, 0.32mmol) in DCM/THF (9:1,2ml) and N-hydroxy-propionamidine (0.014g, 0.175mmol). Purification using Autoprep. HPLC afforded title compound as yellow gum (0.003 g)

LCMS SYSTEM C Rt=2.54min *m/z*=567 MH^+

Example 48: (2R,3R,4S,5S)-2-{6-(3,3-Dimethyl-butylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol diformate

Example 48 was prepared in an analogous manner to Example 46 using Intermediate 36 (0.05g, 0.09mmol), trimethylacetyl chloride (0.012ml, 0.1mmol), N, N-diisopropylethylamine (0.035ml, 0.2mmol) in DCM/THF (9:1,2ml) and N-hydroxy-propionamidine (0.0087g, 0.11mmol). Purification using Autoprep. HPLC afforded title compound as yellow gum (0.002 g)

LCMS SYSTEM C Rt=2.42min *m/z*=541 MH^+

Biological data

The compounds of the Examples were tested in screen (1) (agonist activity against receptor sub-types) and the results obtained were as follows:

Example No.	A2a	A3	A1
1	1.19	>197	1306
2	0.64	>197	1823
3*	4.63	>304	6719

Example No.	A2a	A3	A1
4	5.37	>383	>=3996
5	6.12	>309	1391.2
6*	41.35	>642	>4833
7*	11.02	>117	1013.4
8*	14.05	>215	>=3865
9*	0.81	>231	1692.4
9**	0.086	>287	3006
10*	7.66	>269	3449.6
11*	6.66	>266	145.5
12*	4.54	>302	1863.5
13	0.61	>289	>=4370
14	0.66	>239	>4587
15	2.29	>130	>5511
16*	11.87	>362	>6244
17*	3.97	>362	>6244
18*	8.16	>314	>6244
19*	34.52	>694	>5860
20*	17.08	>694	>=1853
21*	9.39	>303	>5090
22	22.25	>193	78.28
23	12.72	>163	17.02
24	18.13	>284	>5264
25	19.35	>163	515.35
26*	5.18	>284	>5264
27*	10.5	>284	263.14
28*	5.49	>284	>5263
29*	8.92	>117	989.5

Example No.	A2a	A3	A1
30*	19.54	>215	1460.7
31	30.6	>262	6452
32	31.4	>258	7521
33*	8.35	>259	≥815.9
34*	8.31	231.1	3270.8
35	7.89	>194	912.1
36	20.13	>194	>9364
37	49.45	>87	>10402
38	2.02	>87	670.04
39	30.21	>130	4505.4
40	4.89	>130	>=3311.7
41	23.93	>130	2033.2
42	32.77	>130	>6064
43	6.85	>130	1367.6
44	94.39	>165	>6131
45	29.82	>165	>3738.84
46	0.90	>165	3560.13
47	6.93	>165	4993.28
48	4.40	>165	16.84

* Data are minimum values since preparation was found, after testing, to contain an inactive impurity.

** Data on retested purified compound.

Values given in the Table are EC_{50} values as a ratio of that of NECA.

ABBREVIATIONS

TMS	trimethylsilyl
TFA	trifluoroacetic acid
DMF	N,N-dimethylformamide
NECA	N-ethylcarboxamideadenosine
DMAP	4-dimethylaminopyridine
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
TMSOTf	Trimethylsilyltrifluoromethylsulphonate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
BSA	bistrimethylsilylacetamide
DCM	dichloromethane
DAST	diethylaminosulphur trifluoride
Ph	phenyl
CDI	carbonyldiimidazole
EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2 dihydroquinone
NSAID	non-steroidal antiinflammatory drug
DMSO	dimethylsulphoxide
Me	methyl
Et	ethyl
THF	tetrahydrofuran

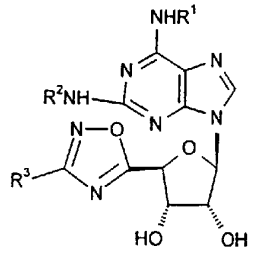
Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any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

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form or suggestion that that prior art forms part of the common general knowledge in Australia.

It would be appreciated by a person skilled in the art the numerous variations and/or modifications may be made to the invention as shown the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

CLAIMS:

1. A compound of formula (I):



(I)

wherein R^1 and R^2 independently represent a group selected from:

(i) C_{3-8}cycloalkyl-;

(ii) hydrogen;

(iii) $aryl_2CHCH_2$-;

(iv) C_{3-8}cycloalkylC_{1-6}alkyl-;

(v) C_{1-8}alkyl-;

(vi) arylC_{1-6}alkyl-;

(vii) R^4R^5N-C_{1-6}alkyl-;

(viii) C_{1-6}alkyl-$CH(CH_2OH)$-;

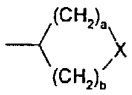
(ix) arylC_{1-5}alkyl-$CH(CH_2OH)$-;

(x) arylC_{1-5}alkyl-$C(CH_2OH)_2$-;

(xi) C_{3-8}cycloalkyl independently substituted by one or more -$(CH_2)_pR^6$ groups;

(xii) $H_2NC(=NH)NHC_{1-6}$alkyl-;

(xiii) a group of formula

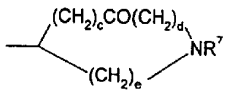


or such a group in which one methylene carbon atom adjacent to X, or both if such exist, is substituted by methyl;

(xiv) $-C_{1-6}$alkyl-OH;

(xv) $-C_{1-8}$haloalkyl;

(xvi) a group of formula



(xvii) aryl; and

(xviii) $-(CH_2)_fSO_2NH_g(C_{1-4}alkyl-)_{2-g}$ or $-(CH_2)_fSO_2NH_g(arylC_{1-4}alkyl-)_{2-g}$;

R^3 represents methyl, ethyl, $-CH=CH_2$, n-propyl, $-CH_2CH=CH_2$, $-CH=CHCH_3$, isopropenyl, cyclopropyl, cyclopropenyl, $-CH(OH)CH_3$, $-(CH_2)_q$halogen, $-(CH_2)_hY(CH_2)_iH$, $-COO(CH_2)_iH$, $-CON(CH_2)_mH((CH_2)_nH)$, $-CO(CH_2)_oH$, or $-C((CH_2)_uH)=NO(CH_2)_vH$;

Y represents O, S or $N(CH_2)_iH$;

a and b independently represent an integer 0 to 4 provided that a + b is in the range 3 to 5;

c, d and e independently represent an integer 0 to 3 provided that c + d + e is in the range 2 to 3;

f represents 2 or 3 and g represents an integer 0 to 2;

p represents 0 or 1;

q represents 1 or 2;

h represents 1 or 2 and i represents an integer 0 to 1; such that h+i is in the range 1 to 2;

j represents an integer 0 to 1 such that h+i+j is in the range 1 to 2;

l represents 1 or 2;

m and n independently represent an integer 0 to 2 such that m+n is in the range 0 to 2;

o represents an integer 0 to 2;

u and v independently represent 0 or 1 such that u+v is in the range 0 to 1;

R^4 and R^5 independently represent hydrogen, C_{1-6}alkyl, aryl, arylC_{1-6}alkyl- or NR^4R^5 together may represent pyridinyl, pyrrolidinyl, piperidinyl, morpholinyl, azetidinyl, azepinyl, piperazinyl or N-C_{1-6}alkylpiperazinyl;

R^6 represents OH, NH_2, $NHCOCH_3$ or halogen;

R^7 represents hydrogen, C_{1-6}alkyl, -C_{1-6}alkylaryl or -COC_{1-6}alkyl;

X represents NR^7, O, S, SO or SO_2;

and salts and solvates thereof.

2. A compound of formula (I) according to claim 1 wherein R^3 represents methyl, ethyl, n-propyl, cyclopropyl or -CH_2OH.

3. A compound of formula (I) according to claim 2 wherein R^3 represents methyl, ethyl or n-propyl.

4. A compound of formula (I) according to claim 2 wherein R^3 represents ethyl.

5. A compound of formula (I) according to any one of claims 1 to 4 wherein R^1 and R^2 do not both represent hydrogen.

6. A compound of formula (I) according to any one of claims 1 to 5 wherein R^1 represents C_{1-8}alkyl, C_{3-8}cycloalkylC_{1-6}alkyl-, arylC_{1-6}alkyl- or hydrogen.

7. A compound of formula (I) according to any one of claims 1 to 5 wherein R^1 represents aryl$_2$CHCH$_2$-.

8. A compound of formula (I) according to claim 6 wherein R^1 represents -CH(CH$_2$CH$_3$)$_2$, phenylethyl, cyclohexylethyl, -(CH$_2$)$_2$C(CH$_3$)$_3$ or hydrogen.

9. A compound of formula (I) according to any one of claims 1 to 5 wherein R^1 represents Ph$_2$CHCH$_2$-, -CH(CH$_2$CH$_3$)$_2$, hydrogen or phenylethyl-.

10. A compound of formula (I) according to claim 7 wherein R^1 represents Ph$_2$CHCH$_2$-.

11. A compound of formula (I) according to any one of claims 1 to 10 wherein R^2 represents -CH(CH$_2$OH)C_{1-3}alkyl, 4-aminocyclohexyl, pyrrolidinyl or arylCH$_2$CH$_2$-.

12. A compound of formula (I) according to any one of claims 1 to 10 wherein R^2 represents pyrrolidin-3-yl N-substituted by C_{1-6}alkyl or benzyl, $R^4R^5NC_{1-6}$alkyl, C_{1-6}alkyl-OH, aryl, arylC_{1-5}alkyl-CH(CH$_2$OH)-, C_{3-8}cycloalkyl, aryl(CH$_2$)$_2$- or C_{3-8}cycloalkyl independently substituted by one or more -(CH$_2$)$_p$R^6 groups.

13. A compound of formula (I) according to claim 12 wherein R^2 represents 2-(1H-imidazol-4-yl) ethyl, morpholin-1-ylethyl, pyrrolidin-1-ylethyl, pyridin-2-ylaminoethyl, (+)-exonorborn-2-yl, 3,4-dimethoxy phenylethyl, 2-hydroxyethyl, 4-fluorophenyl, N-benzyl-pyrrolidin-3-yl, pyridin-2ylethyl, 1S-hydroxymethyl-2-phenylethyl, cyclopentyl, phenylethyl, piperidin-1-ylethyl or 2-hydroxypentyl.

14. A compound of formula (I) according to claim 11 wherein R^2 represents $-CH(CH_2OH)CH(CH_3)_2$, trans-4-amino-cyclohexyl, 2-(1-methyl-1H-imidazol-4-yl)CH_2CH_2- or pyrrolidin-3-yl.

15. A compound of formula (I) according to any one of claims 1 to 10 wherein R^2 represents 2-(1-methyl-1H-imidazol-4-yl)CH_2CH_2-, 1S-hydroxymethyl-2-phenylethyl, phenylethyl or 1S-hydroxymethyl-2-methyl-propyl.

16. A compound of formula (I) according to any one of claims 1 to 15 wherein R^4 and R^5 independently represent hydrogen, C_{1-6}alkyl, aryl, arylC_{1-6}alkyl- or NR^4R^5 together represent pyrrolidinyl, piperidinyl, morpholinyl, azetidinyl, azepinyl, piperazinyl or N-C_{1-6}alkylpiperazinyl.

17. A compound of formula (I) according to claim 16 wherein R^4 and R^5 independently represent hydrogen, aryl or NR^4R^5 together represent pyrrolidinyl, piperidinyl, morpholinyl, azetidinyl, azepinyl, piperazinyl or N-methylpiperazinyl.

18. A compound of formula (I) according to claim 1 which is (2R,3R,4S,5S)-2-{6-(2,2-Diphenyl-ethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol or a salt or solvate thereof.

19. A compound of formula (I) according to claim 1 which is

(2R,3R,4S,5S)-2-[6-Amino-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol or a salt or solvate thereof.

20. A compound of formula (I) according to claim 1 which is
(2R,3R,4S,5S)-2-{6-(2,2-Diphenyl-ethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-[6-(2,2-Diphenyl-ethylamino)-2-(pyrrolidin-3R-ylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-[2-(trans-4-Amino-cyclohexylamino)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-[6-(2,2-Diphenyl-ethylamino)-2-(1S-hydroxymethyl-2-methyl-propylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-[6-(1-Ethyl-propylamino)-2-(2-morpholin-4-yl-ethylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-{6-Amino-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-[6-Amino-2-(2-pyridin-2-yl-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-{6-Amino-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-(6-Amino-2-cyclopentylamino-purin-9-yl)-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-[6-Amino-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2S,3S,4R,5R)-2-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-5-{6-(1-ethyl-propylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-[6-(1-Ethyl-propylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-(6-Amino-2-phenethylamino-purin-9-yl)-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-[2-(trans-4-Amino-cyclohexylamino)-6-(1-ethyl-propylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-[6-(1-Ethyl-propylamino)-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-[6-(1-Ethyl-propylamino)-2-(2-piperidin-1-yl-ethylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2S,3S,4R,5R)-2-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2-morpholin-4-yl-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;

(2S,3S,4R,5R)-2-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2-piperidin-1-yl-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;

(2S,3S,4R,5R)-2-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2-pyridin-2-yl-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-[2-Cyclopentylamino-6-(1-ethyl-propylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-[2-Cyclopentylamino-6-(1-ethyl-propylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-[6-(1-Ethyl-propylamino)-2-(2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2S,3S,4R,5R)-2-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-[6-(1-Ethyl-propylamino)-2-(pyrrolidin-3R-ylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2S,3S,4R,5R)-2-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(pyrrolidin-3R-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-[6-(1-Ethyl-propylamino)-2-(1S-hydroxymethyl-2-methyl-propylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-[2-(trans-4-Amino-cyclohexylamino)-6-(1-ethyl-propylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-[6-Amino-2-(2-pyridin-2-yl-ethylamino)-purin-9-yl]-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-[6-(2,2-Diphenyl-ethylamino)-2-(2-morpholin-4-yl-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-[6-(2,2-Diphenyl-ethylamino)-2-(2-piperidin-1-yl-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-{6-(2,2-Diphenyl-ethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-propyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-{6-(2,2-Diphenyl-ethylamino)-2-[2-(1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-methyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;

(2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2-piperidin-1-yl-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;

(2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2-morpholin-4-yl-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;

(2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2-(2-pyridinyl)-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;

(2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(1-ethyl-propylamino)-2-(2-(1-methyl-1H-imidazol-4-yl)-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5S)-2-[6-(2,2-Diphenyl-ethylamino)-2-(2-pyrrolidin-1-yl-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-{6-(2,2-Diphenyl-ethylamino)-2-[2-(pyridin-2-ylamino)-ethylamino]-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-{2-(Bicyclo[2.2.1]hept-2-ylamino)-6-(2,2-diphenyl-ethylamino)-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-{2-(2-[3,4-Dimethoxy-phenyl]-ethylamino)-6-(2,2-diphenyl-ethylamino)-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-[6-(2,2-Diphenyl-ethylamino)-2-(2-hydroxy-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-[6-(2,2-Diphenyl-ethylamino)-2-(4-fluoro-phenylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-[2-(1-Benzyl-pyrrolidin-3S-ylamino)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-{6-phenethylamino-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-{6-(2-cyclohexylethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
(2R,3R,4S,5S)-2-{6-(3,3-Dimethyl-butylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-5-(3-ethyl-[1,2,4]oxadiazol-5-yl)-tetrahydro-furan-3,4-diol;
or a salt or solvate of any one thereof

21. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 20 or a pharmaceutically acceptable salt or solvate thereof in admixture with one or more pharmaceutically acceptable diluents or carriers.

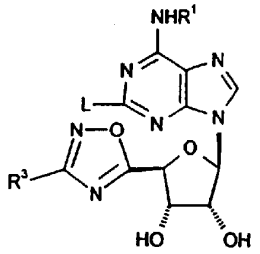
22. A compound of formula (I) as defined in any one of claims 1 to 20 or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical.

23. Use of a compound of formula (I) as defined in any one of claims 1 to 20 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of inflammatory diseases.

24. A method of treatment or prophylaxis of inflammatory diseases which comprises administering to a patient an effective amount of a compound of formula (I) as defined in any one of claims 1 to 20 or a pharmaceutically acceptable salt or solvate thereof.

25. A process for preparation of a compound of formula (I) as defined in any one of claims 1 to 20 which comprises:

(i) reacting a compound of formula (II)



(II)

wherein R^1 is as defined in any one of claims 1, 5 to 10 and 18 to 20 and R^3 is as defined in any one of claims 1 to 4 and 18 to 20 and L represents a leaving group eg halogen, especially chlorine, or a protected derivative thereof with a compound of formula R^2NH_2 or a protected derivative thereof, wherein R^2 is as defined in any one of claims 1, 5, 11 to 15 and 18 to 20;

(ii) reacting a compound of formula (VI)

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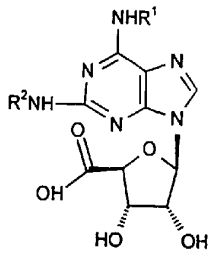
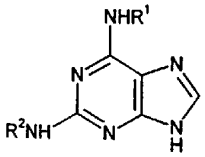


(VI)

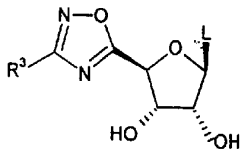
wherein R^1 is as defined in any one of claims 1, 5 to 10 and 18 to 20 and R^2 is as defined in any one of claims 1, 5, 11 to 15 and 18 to 20 or a protected derivative thereof with a carboxyl activating agent, and an amidoxime compound of formula $OH\text{-}N{=}C(R^3)NH_2$, wherein R^3 is as defined in any one of claims 1 to 4 and 18 to 20;

(iii) reacting a compound of formula (IX)



(IX)

wherein R^1 is as defined in any one of claims 1, 5 to 10 and 18 to 20 and R^2 is as defined in any one of claims 1, 5, 11 to 15 and 18 to 20 with a compound of formula (X)



(X)

wherein R^3 is as defined in any one of claims 1 to 4 and 18 to 20 and L is a leaving group

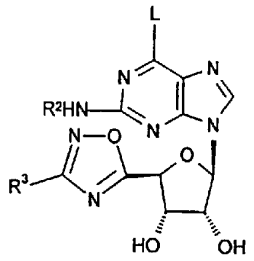
or a protected derivative thereof; or

(iv) deprotecting a protected compound of formula (I)

and where desired or necessary converting a compound of formula (I) or a salt thereof into another salt thereof.

26. A process for preparation of a compound of formula (I) as defined in any one of claims 1 to 20 which comprises:

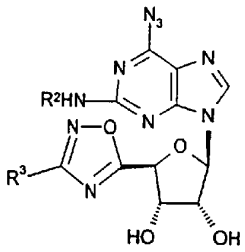
(i) reacting a compound of formula (IIa)



(IIa)

wherein R^2 is as defined in any one of claims 1, 5, 11 to 15 and 18 to 20 and R^3 is as defined in any one of claims 1 to 4 and 18 to 20 and L represents a leaving group eg. chlorine or a protected derivative thereof, with a compound of formula R^1NH_2, wherein R^1 is as defined in any one of claims 1, 5 to 10 and 18 to 20; or

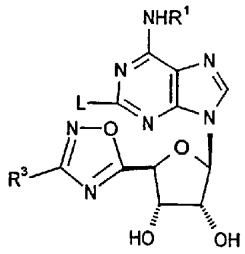
(ii) preparing a compound of formula (I) wherein R^1 represents hydrogen by conversion of a compound of formula (IIb)



(IIb)

wherein R^2 is as defined in any one of claims 1, 5, 11 to 15 and 18 to 20 and R^3 is as defined in any one of claims 1 to 4 and 18 to 20.

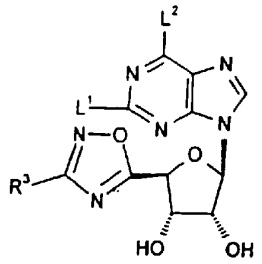
27. A compound of formula (II)



(II)

wherein R^1 is as defined in any one of claims 1, 5 to 10 and 18 to 20 and R^3 is as defined in any one of claims 1 to 4 and 18 to 20 and L represents a leaving group, or a protected derivative thereof.

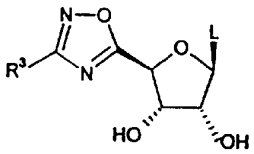
28. A compound of formula (V)



(V)

wherein R^3 is as defined in any one of claims 1 to 4 and 18 to 20 and L^1 and L^2 independently represent a leaving group or a protected derivative thereof.

29. A compound of formula (X)



(X)

wherein R^3 is as defined in any one of claims 1 to 4 and 18 to 20 and L represents a leaving group, or a protected derivative thereof.

30. Use of a compound of formula (I) as defined in any one of claims 1 to 20 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of asthma or chronic obstructive pulmonary disease (COPD).

31. A method of treatment of treatment or prophylaxis of asthma or COPD which comprises administering to a patient an effective amount of a compound of formula (I) as defined in any one of claims 1 to 20 or a pharmaceutically acceptable salt or solvate thereof.

32. A compound of formula (I) according to claim 1 substantially as hereinbefore described with reference to the Examples.

DATED this 15th day of November, 2002

Glaxo Group Limited

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