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(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ALLEN, David, George [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). CHAN, Chuen [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). COOK, Caroline, Mary [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). COUSINS, Richard, Peter, Charles [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). COX, Brian [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). DYKE, Hazel, Joan [GB/GB]; Chiroscience Ltd., Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). ELLIS, Frank [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). GEDEN, Joanna, Victoria [GB/GB]; OSI Pharmaceuticals (Aston Molecules), 10 Holt Court South, Aston Science Park, Birmingham B7 4EJ (GB). HOBBS, Heather [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). KEELING, Suzanne, Elaine [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). REDGRAVE, Alison, Judith [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). SWANSON, Stephen [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). BAYS, David [GB/GB]; 9 Windmill Field, Ware, Hertfordshire SG12 9PE (GB).

(74) Agent: TEUTEN, Andrew, J.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

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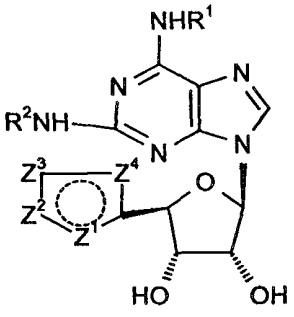
(54) Title: 2-(PURIN-9-YL)-TETRAHYDROFURAN-3,4-DIOL DERIVATIVES



(I)

(57) Abstract

There are provided according to the invention, novel compounds of formula (I), wherein R^1, R^2, Z^1, Z^2, Z^3 and Z^4 are as defined in the specification, processes for preparing them, formulations containing them and their use in therapy for the treatment of inflammatory diseases.

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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 leucocytes (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).

Certain substituted 4'-carboxamido and 4'-thioamido adenosine derivatives which are useful for the treatment of inflammatory diseases are described in International Patent Application Nos. WO94/17090, WO96/02553, WO96/02543 (Glaxo Group). Substituted 4'-carboxamidoadenosine derivatives useful in the treatment of dementia are described in AU 8771946 (Hoechst Japan). Substituted 4'-hydroxymethyl adenosine derivatives which are useful for the treatment of gastrointestinal motility disorders are described in EP-A-423776 and EP-A-423777 (Searle). Substituted 4'-hydroxymethyl adenosine derivatives which are useful as platelet aggregation inhibitors are described in BE-768925 (Takeda). 4'-Hydroxymethyl adenosine derivatives and 4'-esters thereof which are useful as anti-hypertensive agents or have other cardiovascular activity are described in US 4663313, EP 139358 and US 4767747 (Warner Lambert), US 4985409 (Nippon Zoki) and US 5043325 (Whitby Research). 4-Hydroxymethyladenosine derivatives useful in the treatment of autoimmune

disorders are described in US 5106837 (Scripps Research Institute). 4'-Hydroxymethyladenosine derivatives useful as anti-allergic agents are described in US 4704381 (Boehringer Mannheim). Certain 4'-tetrazolylalkyl adenosine derivatives which are useful in the treatment of heart and circulatory disorders are generically described in DT-A-2621470 (Pharma-Waldhof). Other 4'-carboxamidoadenosine derivatives useful in the treatment of cardiovascular conditions are described in US 5219840, GB 2203149 and GB 2199036 (Sandoz), WO94/02497 (US Dept. Health), US 4968697 and EP 277917 (Ciba Geigy), US 5424297 (Univ. Virginia) and EP 232813 (Warner Lambert). Other 4'-carboxamidoadenosine derivatives lacking substitution on the purine ring in the 2-position are described in DT 2317770, DT 2213180, US 4167565, US 3864483 and US 3966917 (Abbott Labs), DT 2034785 (Boehringer Mannheim), JP 58174322 and JP 58167599 (Tanabe Seiyaku), WO92/05177 and US 5364862 (Rhone Poulenc Rorer), EP 66918 (Procter and Gamble), WO86/00310 (Nelson), EP 222330, US 4962194, WO88/03147 and WO88/03148 (Warner Lambert) and US 5219839, WO95/18817 and WO93/14102 (Lab UPSA). 4'-Hydroxymethyladenosine derivatives lacking substitution on the purine ring in the 2-position are described in WO95/11904 (Univ Florida). 4'-Substituted adenosine derivatives useful as adenosine kinase inhibitors are described in WO94/18215 (Gensia). Other 4'-halomethyl, methyl, thioalkylmethyl or alkoxymethyl adenosine derivatives are described in EP 161128 and EP 181129 (Warner Lambert) and US 3983104 (Schering). Other 4'-carboxamidoadenosine derivatives are described in US 7577528 (NIH), WO91/13082 (Whitby Research) and WO95/02604 (US Dept Health).

Certain tetrazole containing deoxynucleotides which were found to lack anti-infective activity are described in Baker et al (1974) Tetrahedron 30, 2939-2942. Other tetrazole containing adenosine derivatives which show activity as platelet aggregation inhibitors are described in Mester and Mester (1972)

Pathologie-Biologie, 20 (Suppl) 11-14. Certain nitrile containing ribose derivatives are described in Schmidt et al (1974) Liebigs. Ann. Chem. 1856-1863.

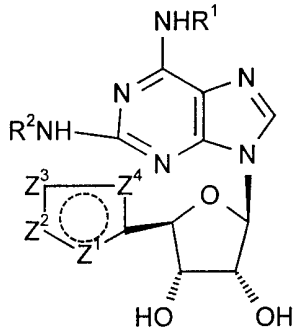
Other publications include: WO 98/16539 (Novo Nordisk A/S) which describes adenosine derivatives for the treatment of myocardial and cerebral ischaemia and epilepsy; WO 98/01426 (Rhone-Poulenc Rorer Pharmaceuticals Inc.) which relates to adenosine derivatives possessing antihypertensive, cardioprotective, anti-ischaemic and antilipolytic properties; and WO 98/01459 (Novo Nordisk A/S) which describes *N*,9-disubstituted adenine derivatives which are substituted in the 4' position by unsubstituted oxazolyl or isoxazolyl and the use of such compounds for the treatment of disorders involving cytokines in humans. WO 98/28319 (Glaxo Group Limited) was published subsequent to the earliest priority date of this application and describes 4'-substituted tetrazole 2-(purin-9-yl)-tetrahydrofuran-3,4-diol derivatives;

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. This profile can be considered of benefit as A3 receptors are also found on leucocytes (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-$CH(CH_2OH)$-;

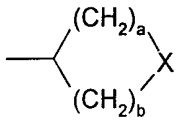
(ix) arylC_{1-5}alkyl-$CH(CH_2OH)$-;

(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

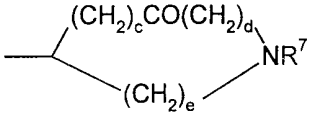


or such a group in which one methylene carbon atom adjacent to X, or both if such exist, is substituted by methyl;

(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 $-(CH_2)_fSO_2NH_g(arylC_{1-4}alkyl-)_{2-g}$ where f is 2 or 3 and g is an integer 0 to 2;

Z^1, Z^2, Z^3 and Z^4 together with the carbon atom form a 5-membered heterocyclic aromatic ring;

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;

p represents 0 or 1;

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;

and salts and solvates thereof.

Z^1, Z^2, Z^3 and Z^4 will independently represent C, N, O or S and, in the case of C and N, together with a sufficient number of hydrogen atoms to provide the ring with aromatic character. At least one of Z^1, Z^2, Z^3 and Z^4 will represent a heteroatom. Preferably at least one of Z^1, Z^2, Z^3 and Z^4 will represent a nitrogen atom. More preferably at least one of Z^1, Z^2, Z^3 and Z^4 will represent a nitrogen atom, two of the remainder independently will represent C or N and the fourth will represent C, N or O. In each case sufficient hydrogen atoms will be provided to give the ring aromatic character. However, we prefer that Z^1, Z^2, Z^3 and Z^4 do not all represent nitrogen

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.

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.

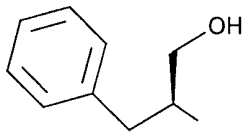
Examples of C_{1-8}alkyl for R^1 and R^2 include $-(CH_2)_2C(Me)_3$, $-CH(Et)_2$ and $CH_2=C(Me)CH_2CH_2-$.

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 imidazoyl 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

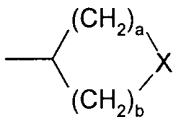


Examples of arylC_{1-5}alkyl-$C(CH_2OH)_2$- for R^1 and R^2 include $PhCH_2C(CH_2OH)_2$-.

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 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

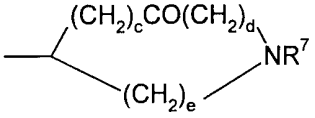


for R^1 and R^2 include pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, tetrahydro-1,1-dioxide thiophen-3-yl, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl and 1,1-dioxo-hexahydro-1.lamda.6-thiopyran-4-yl, or a derivative in which the ring nitrogen is substituted by C_{1-6}alkyl (e.g. methyl), C_{1-6}alkylacyl (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 $aryl_2CHCH_2$-, C_{1-8}alkyl-, hydrogen or $arylC_{1-6}$alkyl.

We prefer R^2 to represent ethyl-piperidin-1-yl, $PhCH_2CH(CH_2OH)$-, -$CH(CH_2OH)CH(CH_3)_2$, trans-4-amino-cyclohexyl, 2-(1-methyl-1H-imidazoyl-4-yl)CH_2CH_2-, pyrrolidin-3-yl, ethyl-pyridin-2-yl, $H_2NC(=NH)NH(CH_2)_2$-, or cyclopentyl.

We 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.

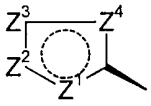
We prefer that a represents 2 and that b represents 1 or 2. We prefer X to represent NR^7 (e.g. NH), O, S or SO_2, particularly O, S or NH.

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.

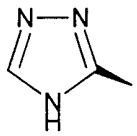
We particularly prefer R^1 to represent Ph_2CHCH_2-, hydrogen, $CH(Et_2)$ or $PhCH_2CH_2$-, especially Ph_2CHCH_2.

We particularly prefer R^2 to represent $-CH(CH_2OH)CH(CH_3)_2$ or 2-(1-methyl-1H-imidazoyl-4-yl)CH_2CH_2-.

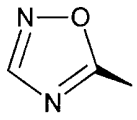
We prefer that the moiety



represents one of the following groups:



(i)



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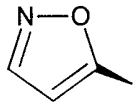
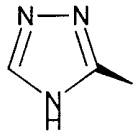


(iii)

wherein the group:



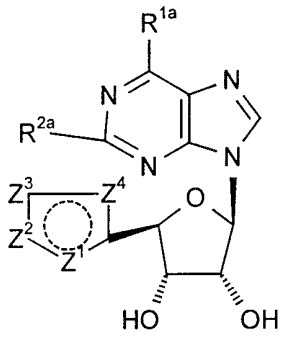
(i)

is particularly preferred.

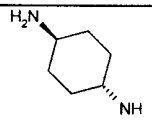
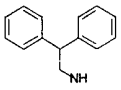
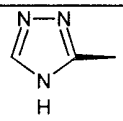
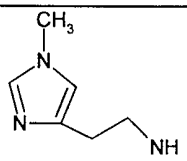
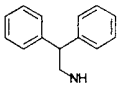
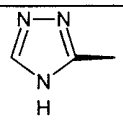
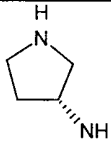
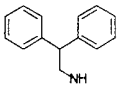
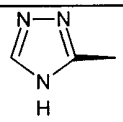
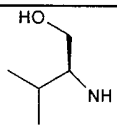
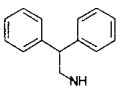
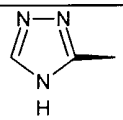
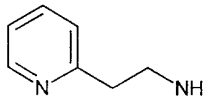
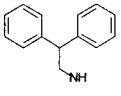
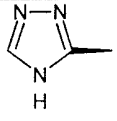
The representation of formula (I) indicates the absolute stereochemistry. When sidechains contain chiral centres the invention extends to mixtures of enantiomers (including racemic mixtures) and diastereoisomers as well as

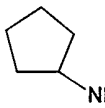
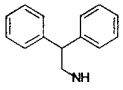
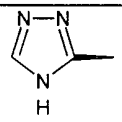
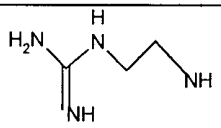
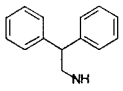
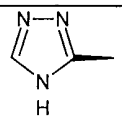
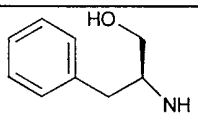
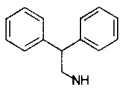
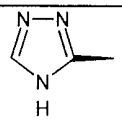
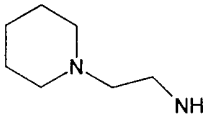
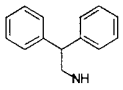
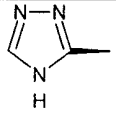
individual enantiomers. Generally it is preferred to use a compound of formula (I) in the form of a purified single enantiomer.

Particularly preferred compounds herein have formula (Ia) in which R^{2a}, R^{1a} and the Z^1-Z^4 comprising ring are as defined in the table below:

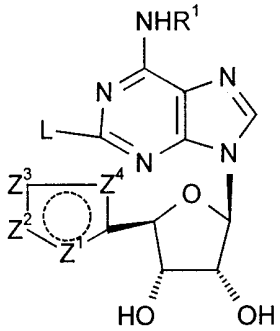


(Ia)

R^{2a}	R^{1a}	Ring comprising Z^1-Z^4
		
		
		
		
		

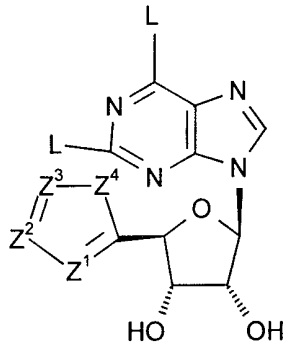
We also provide a first process for the preparation of compounds of formula (I) including the step of reacting a compound of formula (II)



(II)

wherein L represents a leaving group, e.g. halogen, particularly 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*.

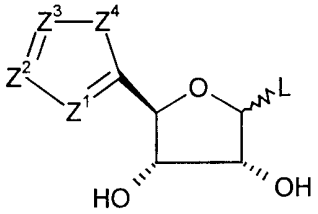
Compounds of formula (II) or a protected derivative thereof may be prepared by reacting a compound of formula (III)



(III)

or a protected 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. diisopropyl ethylamine in a solvent such as an alcohol (e.g. isopropanol) at elevated temperature (e.g. 50°C).

The compound of formula (III) wherein L represents chlorine or a protective derivative thereof may be prepared by reacting a compound of formula (IV)



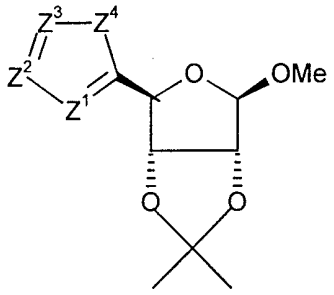
(IV)

wherein L represents a leaving group, or a protected derivative thereof with 2,6,dichloropurine.

We prefer to use the compound of formula (IV) 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.

The compounds of formula (IV) or a protected derivatives thereof may be prepared from a compound of formula (V)



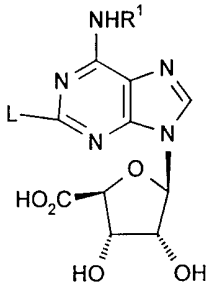
(V)

by treating the compound of formula (V) with trifluoroacetic acid in water followed by acetic anhydride in a solvent such as pyridine, DMAP, Et_3N, DCM or a combination of these.

Compounds of formula (IV) in which L represents halogen may be prepared for the corresponding 1'-alcohol or a 1'-ester such as the acetate. Reaction will generally occur on treatment with anhydous HCl or HBr. 1'-Iodides may be prepared directly on treatment with trimethylsilyliodide and 1'-fluorides may be prepared on treatment with DAST. An inert solvent, e.g. diethylether, DCM, THF or CCl_4 will generally be suitable.

Compounds of formula (V) may be prepared from D-ribose using methods analogous to those described at Scheme 1 of PCT Application No. PCT/EP97/07197, wherein the heterocyclic ring formation is achieved by conventional methods known *per se*.

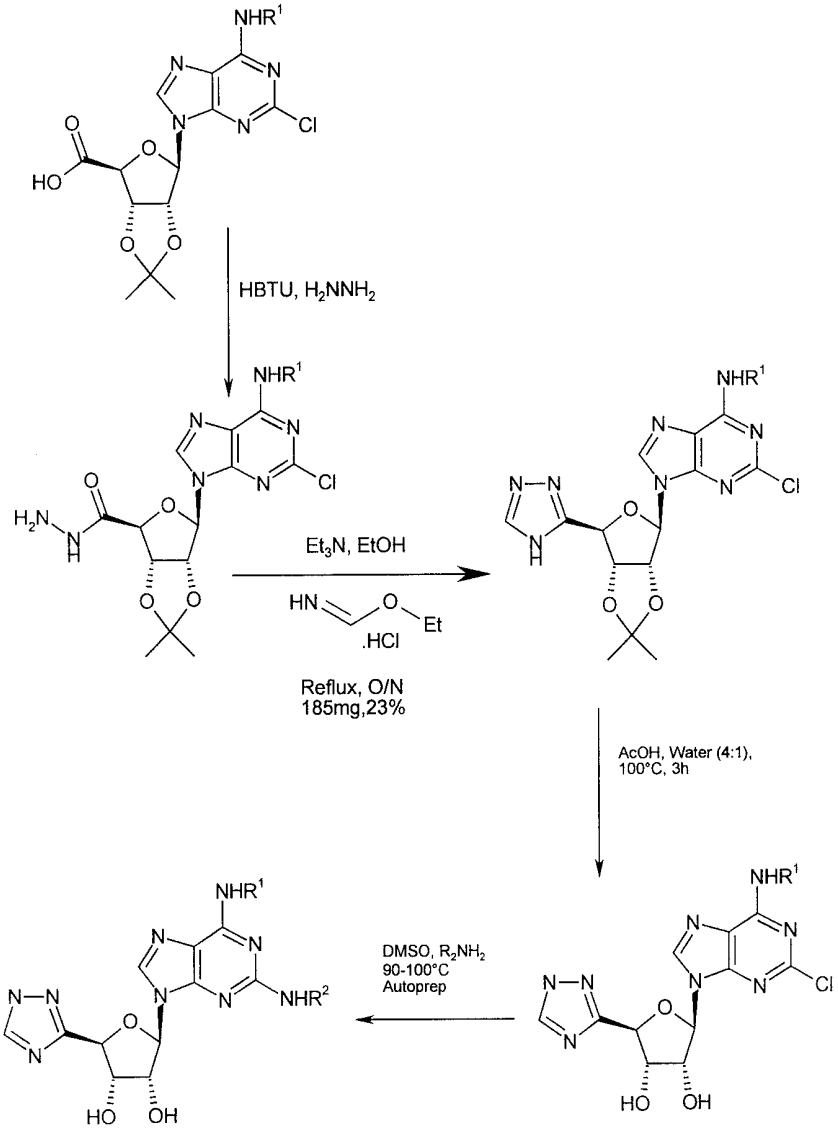
We also provide a second process for the preparation of compounds of formula (II) including the step of reacting a compound of formula (VI)



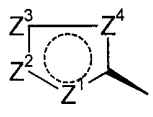
(VI)

with reagents to enable formation of the appropriate heterocyclic ring (comprising Z^1, Z^2, Z^3, and Z^4) using conventional heterocyclic ring formation methods known *per se*. The compound of formula (VI) wherein R^1 represents Ph_2CHCH_2 and L represents chlorine is known and described at preparation 4. of PCT Patent Application No. WO94/17090. Other compounds of formula (VI) may be prepared by analogous or conventional methods.

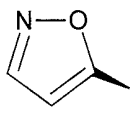
This second process is particularly suitable for making compounds herein where the heterocyclic ring is a triazolyl. A preferred reaction scheme of this type comprises:



In a third process, where the moiety:

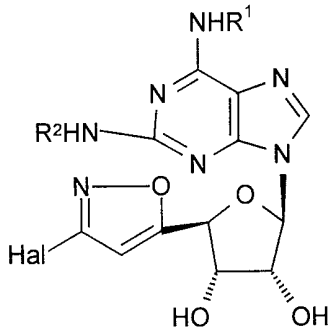


is represented by:



(iii)

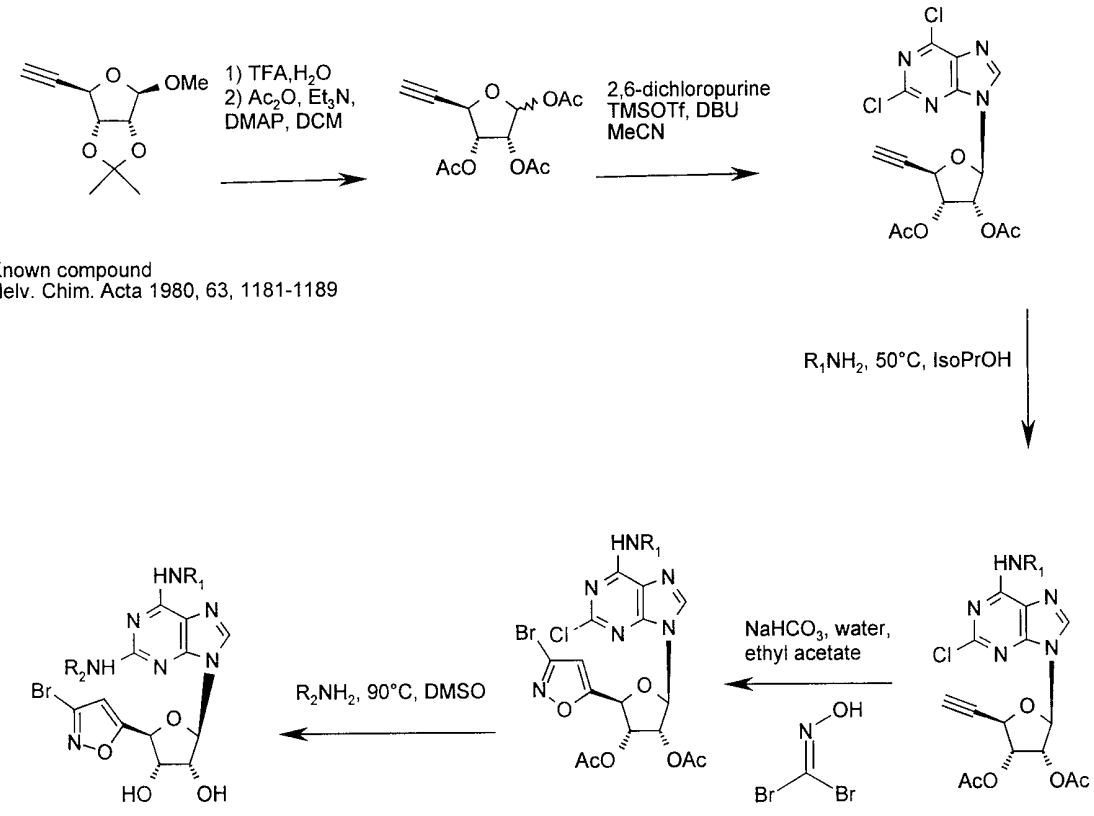
the compounds of formula (I) may be obtained by dehalogenating a compound of formula (VII):



(VII)

The dehalogenation can, for example, be achieved by known catalytic hydrogenation processes.

Compounds of formula (VII) wherein Hal represents Br may be prepared according to the following scheme:



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

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

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

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

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

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 (e.g. 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 were 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 was 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 were also transfected with cyclic AMP response elements promoting the gene for secreted placental alkaline phosphatase (SPAP) (Wood, 1995). The effect of test compounds was

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 were then determined as a ratio to that of the non-selective agonist N-ethyl carboxamide adenosine (NECA).

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Throughout the 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 but not to the exclusion of any other integer or step or group of integers or steps.

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. 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). 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.

Intermediate 1: (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 hydrazide

(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 WO94/17090] (200mg, 0.4mmol) in dry dimethylformamide (2mL) was treated with HBTU (152mg, 0.4mmol) and di-isopropylethylamine (129mg, 0.18mL, 1mmol) and the reaction stirred at room temperature under nitrogen for 15 minutes. Hydrazine hydrate (20mg, 0.019mmol) was added and the reaction stirred at room temperature for a further 20 hours. The reaction mixture was partitioned between ethyl acetate (100mL) and saturated ammonium chloride solution (100mL). The organic phase was washed with a further portion of saturated ammonium chloride solution, 2N citric acid (2 x 100mL), saturated sodium bicarbonate (2 x 100mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the titled compound as pale coloured foam (0.158g).
LC-MS System A Rt.= 4.73 min., *m/z* 550 (MH^+)

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

Intermediate 1 (2.500g), ethyl formimidate hydrochloride (0.748g, 6.8mmol) and triethylamine (25.8ml) in ethanol (20ml) were heated to reflux for 68 hrs.. Solvent was removed *in vacuo* and the residue was purified by column chromatography on flash silica twice firstly with ethylacetate-cyclohexane (1:1 to neat ethyl acetate), then with cyclohexane-ethyl acetate (10:1, 5:1, 2:1, 1:1, 1:2 and then neat ethyl acetate) to give the title compound as a crisp orange foam (0.185g).
TLC SiO_2 (neat ethylacetate, visualised by UV light) Rf = 0.27

Intermediate 3: (2R,3R,4S,5R)-2-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(4H-[1,2,4]triazol-3-yl)-tetrahydro-furan-3,4-diol acetate

Intermediate 2 (0.450g, 0.82mmol), acetic acid (20ml) and water (5ml) were heated at 100° C for 3 hrs.. Upon cooling the solvent was removed *in vacuo*

and azeotroped with ethyl acetate (50ml). Purification using column chromatography on flash silica eluted with dichloromethane, ethanol and 880 ammonia (100:10:1) furnished the title compound as a cream coloured solid (0.317g) TLC SiO_2 (dichloromethane, methanol and 880 ammonia (100:8:1), visualised by UV light) Rf = 0.14

Example 1: (2R,3R,4S,5R)-2-[2-(trans-4-Amino-cyclohexylamino)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(4H-[1,2,4]triazol-3-yl)-tetrahydro-furan-3,4-diol formate

Intermediate 3 (0.026g, 0.05mmol) and *trans*-1,4-diaminocyclohexane (0.029g, 0.25mmol) in anhydrous DMSO (1.2ml) in a sealed vial (e.g. Reacti-vial™) were heated at 100° C for 71 hrs.. The reaction mixture was diluted with acetonitrile and water (2ml, 1:1) containing 0.1% formic acid. and purified with using Autoprep. HPLC to afford the title compound after freeze drying as a brown coloured solid (0.010g). LC/MS system A R_t = 3.51 mins, *m/z* = 597 MH^+

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

Example 2 was prepared in an analogous manner to Example 1 with 1-methylhistamine (0.031g, 0.25mmol) heating for 69 hrs. to afford the title compound after freeze drying as a cream coloured solid (0.012g).
LC/MS system A R_t = 3.56 mins, *m/z* = 608 MH^+

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

Example 3 was prepared in an analogous manner to Example 1 with (3R)-(+)-3-aminopyrrolidine (0.027g, 0.25mmol) to afford the title compound after freeze drying as a cream coloured solid (0.010g).

LC/MS system A R_t = 3.55 mins, *m/z* = 569 MH^+

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

Example 4 was prepared in an analogous manner to Example 1 with L-2-amino-3-methylbutanol (0.026g, 0.25mmol) but heated for a further 69 hrs.. Further valinol (0.026g, 0.25mmol) was added and heated at 100° C for 20 hrs. to afford the title compound after freeze drying as a cream coloured solid (0.007g).

LC/MS system A R_t = 4.06 mins, *m/z* = 586 MH^+

Example 5: (2R,3R,4S,5R)-2-[6-(2,2-Diphenyl-ethylamino)-2-(2-pyridin-2-yl-ethylamino)-purin-9-yl]-5-(4H-[1,2,4]triazol-3-yl)-tetrahydro-furan-3,4-diol formate

Example 5 was prepared in an analogous manner to Example 1 with 2-(2-amino ethyl)pyridine (0.031g, 0.25mmol) to afford the title compound after freeze drying as a cream coloured solid (0.011g). LC/MS system A R_t = 3.73 mins, *m/z* = 605 MH^+

Example 6: (2R,3R,4S,5R)-2-[2-Cyclopentylamino-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(4H-[1,2,4]triazol-3-yl)-tetrahydro-furan-3,4-diol formate

Example 6 was prepared in an analogous manner to Example 1 with cyclopentylamine (0.021g, 0.25mmol) followed by a second addition of cyclopentylamine (0.021g, 0.25mmol) heated for a further 69 hrs. to afford the title compound after freeze drying as a cream coloured solid (0.003g).

LC/MS system B R_t = 3.21 mins, *m/z* = 568 MH^+

Example 7: N-{2-[9-[3R,4S-Dihydroxy-5R-(4H-[1,2,4]triazol-3-yl)-tetrahydro-furan-2R-yl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-ylamino]-ethyl}-guanidine formate

Example 7 was prepared in an analogous manner to Example 1 with ethylenediamine (0.015g, 0.25mmol). To the reaction mixture was added 1H-pyrazole-1-carboxamidine monohydrochloride (0.073g, 0.5mmol) and imidazole (0.034g, 0.5mmol) and heated at 50°C for 24 hrs.. The reaction mixture was diluted with acetonitrile and water (2ml, 1:1) containing 0.1% formic acid. and purified with using Autoprep. HPLC to afford the title compound after freeze drying as a cream coloured solid (0.008g). LC/MS system B R_t = 2.41 mins, *m/z* = 585 MH^+

Example 8: (2R,3R,4S,5R)-2-[6-(2,2-Diphenyl-ethylamino)-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(4H-[1,2,4]triazol-3-yl)-tetrahydro-furan-3,4-diol formate

Example 8 was prepared in an analogous manner to Example 1 with 3-(S)-(-)2-amino-3-phenyl propanol (0.038g, 0.25mmol) to afford the title compound after freeze drying as a cream coloured solid (0.010g). LC/MS system A R_t = 4.20 mins, *m/z* = 634 MH^+

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

Example 9 was prepared in an analogous manner to Example 1 2-piperidinoethylamine (0.032g, 0.25mmol) to afford the title compound after freeze drying as a cream coloured solid (0.013g).
LC/MS system A R_t = 3.59 mins, *m/z* = 611 MH^+

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	11.37	> 353	1098

2	1.08	> 430	1003.4
3	10.49	> 306	586.92
4	3.79	> 306	670.92
5	19.3	> 397	3329
6	16.96	> 305	1627
7	19.01	> 368	2577
8	26.74	> 326	280.97
9	8.13	> 472	969.8

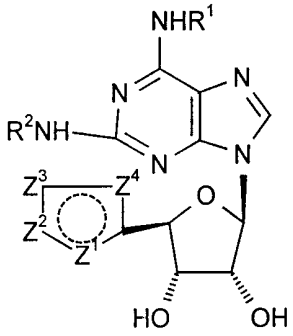
Values given in the Table are EC_{50} values as a ratio of that of NECA.

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
HBTU	2-(IH-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
DMSO	dimethylsulphoxide
DEAD	diethylazocarboxylate

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-$CH(CH_2OH)$-;

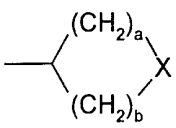
(ix) arylC_{1-5}alkyl-$CH(CH_2OH)$-;

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

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

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

(xiii) a group of formula

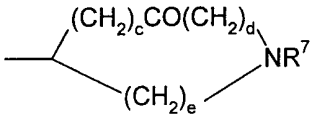


or such a group in which one methylene carbon atom adjacent to X, or both if such exist, is substituted by methyl;

(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 $-(CH_2)_fSO_2NH_g(arylC_{1-4}alkyl-)_{2-g}$ where f is 2 or 3 and g is an integer 0 to 2;

Z^1, Z^2, Z^3 and Z^4 together with the carbon atom form a 5-membered heterocyclic aromatic ring;

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;

p represents 0 or 1;

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;

and salts and solvates thereof.

2. A compound according to claim 1 wherein R^1 and R^2 do not both represent hydrogen.

3. A compound according to claim 1 or claim 2 wherein R^1 represents $aryl_2CHCH_2$-, C_{1-8}alkyl-, hydrogen or $arylC_{1-6}$alkyl.

4. A compound according to any one of claims 1 to 3 wherein R^1 represents Ph_2CHCH_2.

5. A compound according to any one of claims 1 to 4 wherein R^2 represents ethyl-piperidin-1-yl, $PhCH_2CH(CH_2OH)$-, $-CH(CH_2OH)CH(CH_3)_2$, trans-4-amino-cyclohexyl, 2-(1-methyl-1H-imidazoyl-4-yl)CH_2CH_2-, pyrrolidin-3-yl, ethyl-pyridin-2-yl, $H_2NC(=NH)NH(CH_2)_2$-, or cyclopentyl.

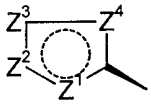
6. A compound according to any one of claims 1 to 5 wherein R^2 represents $-CH(CH_2OH)CH(CH_3)_2$ or 2-(1-methyl-1H-imidazoyl-4-yl)CH_2CH_2-.

7. A compound according to any one of claims 1 to 6 wherein R^4 and R^5 independently represent hydrogen or aryl or NR^4R^5 together may represent pyrrolidinyl, piperidinyl, morpholinyl, azetidinyl, azepinyl, piperazinyl or N-methylpiperazinyl.

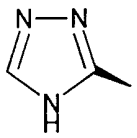
8. A compound according to any one of claims 1 to 7 wherein R^6 represents OH or NH_2.

9. A compound according to any one of claims 1 to 8 wherein X represents NR^7, O, S or SO_2.

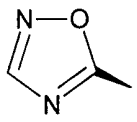
10. A compound according to any one of claims 1 to 9 wherein the moiety



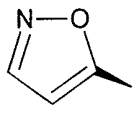
represents one of the following groups:



(i)

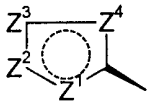


(ii)

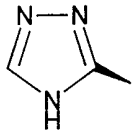


(iii)

11. A compound according to any one of claims 1 to 10 wherein the moiety



represents



(i)

12. A compound of formula (I) which is

(2R,3R,4S,5R)-2-[2-(trans-4-Amino-cyclohexylamino)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(4H-[1,2,4]triazol-3-yl)-tetrahydro-furan-3,4-diol;

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

(2R,3R,4S,5R)-2-[6-(2,2-Diphenyl-ethylamino)-2-(pyrrolidin-3R-ylamino)-purin-9-yl]-5-(4H-[1,2,4]triazol-3-yl)-tetrahydro-furan-3,4-diol;

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

(2R,3R,4S,5R)-2-[6-(2,2-Diphenyl-ethylamino)-2-(2-pyridin-2-yl-ethylamino)-purin-9-yl]-5-(4H-[1,2,4]triazol-3-yl)-tetrahydro-furan-3,4-diol;

(2R,3R,4S,5R)-2-[2-Cyclopentylamino-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(4H-[1,2,4]triazol-3-yl)-tetrahydro-furan-3,4-diol;

N-{2-[9-[3R,4S-Dihydroxy-5R-(4H-[1,2,4]triazol-3-yl)-tetrahydro-furan-2R-yl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-ylamino]-ethyl}-guanidine;

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

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

or a salt or solvate of any one thereof.

13. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 12 or a pharmaceutically acceptable salt or

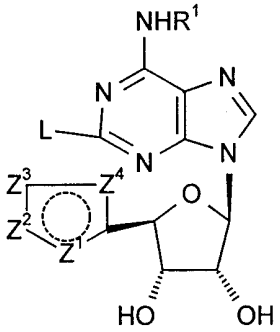
solvate thereof in admixture with one or more pharmaceutically acceptable diluents or carriers.

14. A compound of formula (I) as defined in any one of claims 1 to 12 or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical.

15. Use of a compound of formula (I) as defined in any one of claims 1 to 12 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of inflammatory diseases.

16. A method of treatment or prophylaxis of inflammatory diseases eg asthma which comprises administering to a patient an effective amount of a compound of formula (I) as defined in any one of claims 1 to 12 or a pharmaceutically acceptable salt or solvate thereof.

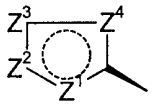
17. A process for preparation of compounds of formula (I) as defined in any one of claims 1 to 12 which comprises reacting a compound of formula (II)



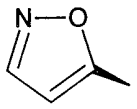
(II)

wherein L represents a leaving group or a protected derivative thereof with a compound of formula R^2NH_2 or a protected derivative thereof, wherein R^1, R^2, Z^1, Z^2, Z^3 and Z^4 are as defined in any one of claims 1 to 12.

18. A process for preparation of compounds of formula (I) where the moiety:

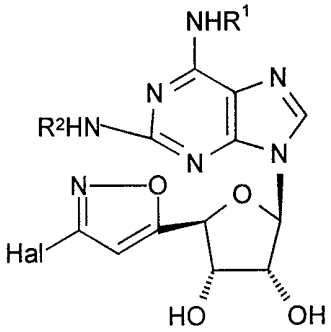


is represented by:



(iii)

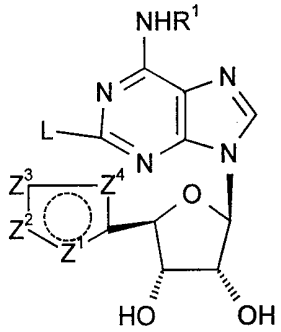
which comprises dehalogenating a compound of formula (VII):



(VII)

wherein R^1 and R^2 are as defined in any one of claims 1 to 12 and Hal represents halogen.

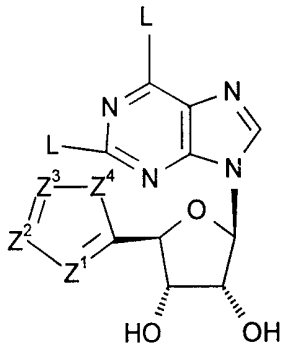
19. A compound of formula (II)



(II)

wherein L represents a leaving group or a protected derivative thereof, wherein R^1, R^2, Z^1, Z^2, Z^3 and Z^4 are as defined in any one of claims 1 to 12.

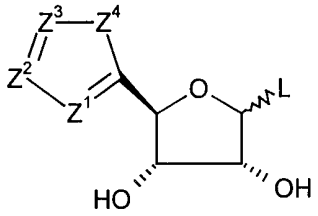
20. A compound of formula (III)



(III)

or a protected derivative thereof, wherein L represents a leaving group or a protected derivative thereof and Z^1, Z^2, Z^3 and Z^4 are as defined in any one of claims 1 to 12.

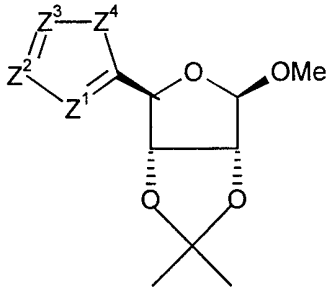
21. A compound of formula (IV)



(IV)

wherein L represents a leaving group, or a protected derivative thereof and Z^1, Z^2, Z^3 and Z^4 are as defined in any one of claims 1 to 12.

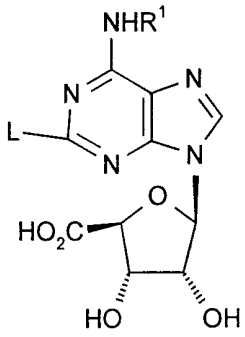
22. A compound of formula (V)



(V)

wherein Z^1, Z^2, Z^3 and Z^4 are as defined in any one of claims 1 to 12.

23. A compound of formula (VI)



(VI)

wherein L represents a leaving group or a protected derivative thereof and R^1 is as defined in any one of claims 1 to 12, with the proviso that when R^1 represents Ph_2CHCH_2, L does not represent chlorine.

INTERNATIONAL SEARCH REPORT

Interna: ,ial Application No
PCT/EP 99/04271

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H19/16 A61K31/70 C07H19/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 01459 A (NOVONORDISK AS) 15 January 1998 (1998-01-15) claim 1 ---	1,13-20
A	WO 96 02553 A (GLAXO GROUP LTD ;AYRES DIANA SALLY & HF (GB); GREGSON MICHAEL (GB)) 1 February 1996 (1996-02-01) abstract ---	1,13-20
A	WO 94 17090 A (GLAXO GROUP LTD ;GREGSON MICHAEL (GB); AYRES BARRY EDWARD (GB); EW) 4 August 1994 (1994-08-04) abstract ---	1,13-20
A	DE 26 21 470 A (PHARMA WALDHOF GMBH & CO) 1 December 1977 (1977-12-01) claim 1 --- -/--	1,13-20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 October 1999	13/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Scott, J

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/04271

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 167 565 A (STEIN HERMAN H ET AL) 11 September 1979 (1979-09-11) column 5, line 17, 2-chloroadenosine-5'-carboxylic acid; column 7, line 18, 2-acetamido adenosine-5'-carboxylic acid	23
X	WO 93 22328 A (SCHERING PLOUGH S P A ;CRISTALLI GLORIA (IT)) 11 November 1993 (1993-11-11) page 16, line 10, 1'-deoxy-1'-(6-amino-2-iodo-9H-purin-9-yl)-B-D-ribofuranuronic acid	23
A	KOBE J ET AL: "PREPARATION AND UTILITY OF 5-BETA-D-RIBOFURANOSYL-1H-TETRAZOLE AS A KEY SYNTHON FOR C-NUCLEOSIDE SYNTHESIS" NUCLEOSIDES & NUCLEOTIDES, vol. 13, no. 10, 1 January 1994 (1994-01-01), pages 2209-2244, XP002064181 ISSN: 0732-8311 the whole document	21,22
P,X	WO 98 28319 A (GEDEN JOANNA VICTORIA ;COX BRIAN (GB); HOBBS HEATHER (GB); GLAXO G) 2 July 1998 (1998-07-02) the whole document, but especially claims 1-41	1-23
E	WO 99 38877 A (COUSINS RICHARD PETER CHARLES ;COX BRIAN (GB); CHAN CHUEN (GB); GL) 5 August 1999 (1999-08-05) the whole document, but especially the claims and the examples	1-10, 13-23

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/04271

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. [X] Claims Nos.: 16
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 16 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

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

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Internat ...nal Application No
PCT/EP 99/04271

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