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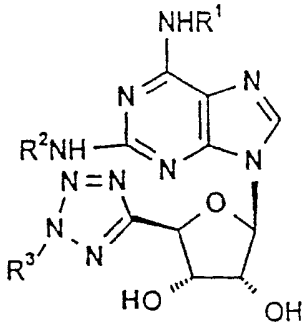
(54) Title: 2-(Purin-9-yl)-tetrahydrofuran-3,4-diol derivatives

(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.



(I)

56) Documents Cited: WO 96 92553 A; WO 94 17090 A; DE 2621470 A

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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).

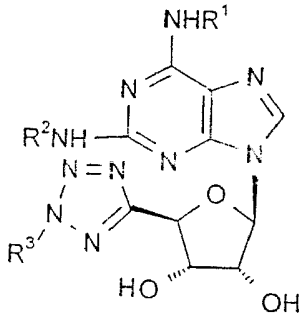
Certain tetrazole containing deoxynucleotides which were found to lack anti-infective activity are described in Baker et al (1974) Tetrahedron 30, 2939-2942. Other tetrazole containing adenosine derivatives which show activity as platelet aggregation inhibitors are described in Mester and Mester (1972) Pathologie-Biologie, 20 (Suppl) 11-14.

Certain nitrile containing ribose derivatives are described in Schmidt et al (1974) Liebigs. Ann. Chem. 1856-1863.

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 may be 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 significant agonist activity at the human A3 receptor. Furthermore they may even possess A3 antagonist activity. 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:

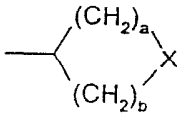


(I)

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 $-(CH_2)_pR^6$ groups;
(xii) $H_2NC(=NH)NHC_{1-6}$alkyl-;

(xiii) a group of formula

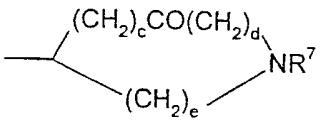


or such a group in which one methylene carbon atom adjacent to X, or both if such exist, is substituted by methyl;

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

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

(xvi) a group of formula



and

(xvii) aryl;

R^3 represents methyl, ethyl or isopropyl;

R^4 and R^5 independently 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;

R^6 represents OH, NH_2 or halogen;

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

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.

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References to C_{1-6}alkyl include references to an aliphatic hydrocarbon grouping containing 1 to 6 carbon atoms which may be straight chain or branched and may be saturated or unsaturated. References to C_{1-4}alkyl, C_{1-5}alkyl and C_{1-8}alkyl may be interpreted similarly.

References to aryl include references to mono- and bicyclic carbocyclic aromatic rings (e.g. phenyl, naphthyl) and heterocyclic aromatic rings 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.

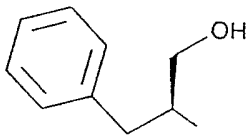
Examples of C_{1-8}alkyl for R^1 and R^2 include $-(CH_2)_2C(Me)_3$, $-CH(Et)_2$ and $CH_2=C(Me)CH_2CH_2$-.

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 or this group in which imidazolyl 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 $PhCH_2CH(CH_2OH)$- especially

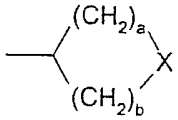


Examples of aryl C_{1-5}alkyl-$C(CH_2OH)_2$- for R^1 and R^2 include $PhCH_2C(CH_2OH)_2$-.

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

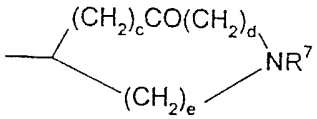


for R^1 and R^2 include pyrrolidin-3-yl, piperidin-3-yl, piperidin- 4-yl or a derivative in which the ring nitrogen is substituted by C_{1-6}alkyl (e.g. methyl) or benzyl, tetrahydro- 1,1-dioxide thiophen-3-yl, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl and 1,1-dioxo-hexahydro-1.lamda.6-thiopyran-4-yl.

Examples of -C_{1-6}alkyl-OH groups for R^1 and R^2 include $-CH_2CH_2OH$.

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-oxo-pyrrolidin-5-yl or a derivative in which the ring nitrogen is substituted by C_{1-6}alkyl (e.g. methyl) or benzyl.

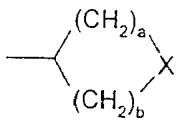
Examples of aryl for R^1 and R^2 include phenyl optionally substituted by halogen (e.g. fluorine, especially 4-fluorine).

Examples of C_{1-6}alkyl for R^7 include methyl and C_{1-6}alkylaryl for R^7 include benzyl.

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

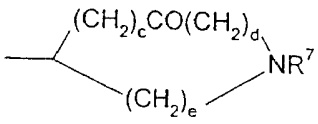
A preferred group of compounds are those compounds of formula I in which: R^1 and R^2 independently represent a group selected from:

(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



;

(xiv) a group of formula



and

(xv) aryl;

R^4 and R^5 independently represent hydrogen, C_{1-6}alkyl, aryl or NR^4R^5 together may represent pyrrolidinyl, piperidinyl, morpholinyl, azetidinyl, azepinyl, piperazinyl or N-methylpiperazinyl;
R^6 represents OH or NH_2;
X represents NR^7 or SO_2; and
a and b independently represent an integer 0 to 4 provided that a + b is in the range 3 to 4.

We prefer R^1 to represent Ph_2CHCH_2-, arylC_{1-6}alkyl-, C_{1-8}alkyl- , arylC_{1-5}alkyl $CH(CH_2OH)$-, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl-, R^4R^5N-C_{1-6}alkyl- or hydrogen.

We may also prefer R^1 to represent tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl and 1,1-dioxo-hexahydro-1.lamda.6-thiopyran-4-yl.

We particularly prefer R^1 to represent Ph_2CHCH_2-, $PhCH_2$-, $(CH_3)_3C(CH_2)_2$-, $Ph[illegible]CH_2$-, arylCH_2- (especially wherein aryl represents optionally substituted phenyl, particularly phenyl or phenyl substituted by halogen most especially iodine in the meta position), $PhCH_2CH(CH_2OH)$-, cyclopentyl, Et_2CH-, (cyclohexyl)$(CH_2)_2$-, (pyrrolidin-1-yl)$(CH_2)_2$-, (morpholin-1-yl)$(CH_2)_2$- or hydrogen.

We more particularly prefer R^1 to represent Ph_2CHCH_2-, $PhCH_2CH_2$-, $PhCH_2CH(CH_2OH)$-, cyclopentyl, Et_2CH-, $(CH_3)_3C(CH_2)_2$-, (cyclohexyl)$(CH_2)_2$-, and hydrogen.

We prefer R^2 to represent $R^4R^5NC_{1-6}$alkyl-, aryl, C_{3-8}cycloalkylC_{1-6}alkyl-, -C_{1-6}alkyl-OH, arylC_{1-5}alkylCH(CH_2OH)-, tetrahydro-1,1-dioxide thiophen-3-yl, C_{3-8}cycloalkyl, $H_2NC(=NH)NHC_{1-6}$alkyl-, C_{3-8}cycloalkyl independently substituted by one or more (e.g. 1, 2 or 3) -$(CH_2)_pR^6$ groups, C_{1-6}alkyl-CH(CH_2OH)-, arylC_{1-6}alkyl- or pyrrolidin-3-yl, 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-5yl, piperidin-3-yl or piperidin-4-yl in which the ring nitrogen is optionally substituted by C_{1-6}alkyl or aryl C_{1-6}alkyl (e.g. benzyl).
We also prefer R^2 to represent tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl and 1,1-dioxo-hexahydro-1.lamda.6-thiopyran-4-yl.