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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: Expediente 07 039.105

TÍTULO SOLICITADO: DERIVADOS DE PURINA PARA USARSE COMO
AGONISTAS DE RECEPTORES DE A-2A DE
ADENOSIN.

PUBLICACIÓN: Gaceta 599 de 31/12/2008, N° de publicación 1241.

PRIORIDAD: GB 0423551.1 de 22/10/2004.

SOLICITANTE: NOVARTIS AG.

APODERADO: CARLOS R. OLARTE.

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar la oposición presentada oportunamente ante ese Despacho, en los siguientes términos:

I. COMPLEMENTO DE INFORMACIÓN

Comedidamente me permito presentar los argumentos que demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 16 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario, veamos:

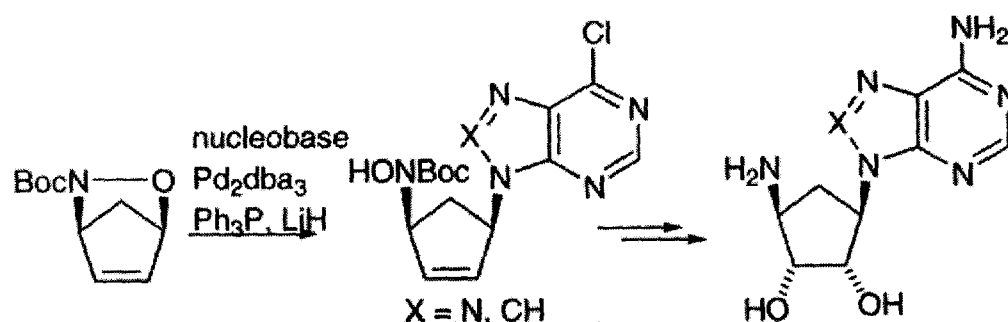
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En primer lugar, y ante la revelación textual del uso de un compuesto de la formula (I) solo o en combinación con otros agentes farmacológicos para el tratamiento de trastornos inflamatorios u obstructivos de las vías respiratorias, es relevante señalar que dichas revelaciones, explícitamente mencionadas en las reivindicaciones 12 a 13, son inaceptables a la luz de la Decisión 486.

En efecto, a la luz de la normativa subregional resulta inaceptable pretender atribuirse exclusiva sobre un "Uso", categoría no incluida en el concepto de "Productos o Procedimientos" que establece el artículo 14 de la Decisión 486 de 2000. Lo anterior, además, en consonancia con la reiterada interpretación de la SIC sobre este punto.

Sin perjuicio de lo anterior me permito hacer notar que aún si los usos o métodos terapéuticos fueran permitidos en nuestro medio, éstos deberían cumplir necesariamente con los requisitos materiales de patentabilidad, novedad, nivel Inventivo y Aplicación Industrial. Cabe entonces desde ahora anotar que el último resulta de imposible cumplimiento, en tanto la reproducción industrial del uso separado, combinado o secuencial de medicamentos para tratar ciertas patologías es del resorte de la profesión médica y no de las actividades industriales.

En otro aspecto, y sin perjuicio de lo anteriormente expuesto, también se puede demostrar la falta de nivel inventivo de la solicitud colombiana en trámite. En efecto, la publicación científica "Synthesis of Novel Carbocyclic Adenosine Analogues as Inhibitors of Adenosine Kinase"¹ revela:



Several new 4'-amino substituted carbocyclic adenosine analogues (6, 7, 31) were prepared as potential inhibitors of the enzyme adenosine kinase. Three different heterocyclic base moieties (adenine, 8-azaadenine, and pyrazolo[3,4-d]pyrimidine)

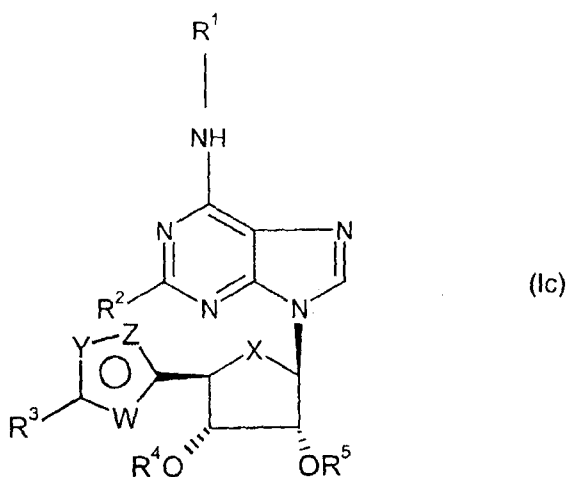
¹ Marlon Cowart,* Michael J. Bennett, and James F. Kerwin, Jr. J. Org. Chem., 1999, 64 (7), pp 2240-2249.

were incorporated into carbocyclic nucleoside analogues through the use of two different synthetic strategies. In both strategies, bicyclic isoxazolidine 9 (prepared through a hetero Diels-Alder reaction with cyclopentadiene) was used as the starting material. In one route, the N-O bond was reductively cleaved, and the hydroxyl group (after inversion and ring functionalization) was used as a leaving group to incorporate the heterocyclic base moiety as the key bond-forming step. A second, more efficient and higher yielding synthetic route was developed as a general solution to the synthesis of the target 4'-amino substituted carbocyclic adenosine analogues. In this methodology, the allylic C-O bond in the bicyclic isoxazolidine 9 was cleaved with double stereoinversion under palladium(0) catalysis as the key bond-forming step to stereospecifically incorporate the heterocyclic base moiety into the cyclopentane ring. The regioselectivity of key bond-forming steps was established principally by NMR methods, especially through ^{13}C NMR shifts and by NOE effects seen in the analogues, as well as by HMBC/HMQC experiments.

Como se puede apreciar, en esta anterioridad se revelan métodos de obtención para la misma clase de compuestos que los reivindicados por la solicitud colombiana en trámite, refiriendose específicamente a los compuestos del mismo tipo que sirven como intermediarios, es decir a los compuestos de formula II, IV, VI, VIII, IX, XIIa, XIIc, XIId y XIIe.

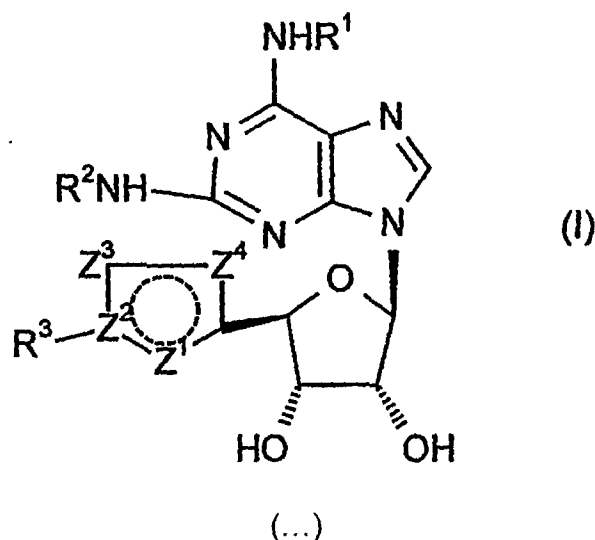
En el mismo sentido, la publicación internacional WO 99/67262 publicada el 29 de Diciembre de 1999 y titulada "ADENOSINE DERIVATIVES" expone compuestos que son estrechamente relacionados a la estructura y a la actividad farmacológica de los compuestos reivindicados por la solicitud en cuestión, en otras palabras son derivados de purina y a la vez son agonistas de los receptores de adenosina del subtipo A2a, veamos:

A compound of formula (Ic) which is an agonist at the adenosine A1 receptor



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De la misma manera en la publicación internacional WO 02/067909 publicada el 06 de Septiembre de 2002 y titulada "NEW METHOD OF BRONCHODILATORY THERAPY" se exponen nuevamente compuestos del mismo tipo (derivados de purina) y con la misma actividad farmacológica, veamos:



1. A method of inducing bronchodilation in a human patient which comprises administering to that patient an effective amount of a selective A2a receptor agonist.

En este caso es relevante señalar que estos compuestos revelados con anterioridad también son útiles en el tratamiento de trastornos respiratorios inflamatorios u obstructivos.

Respecto a la utilización de agonistas de receptor de adenosina A2a para el tratamiento de trastornos inflamatorios, específicamente trastornos inflamatorios obstructivos de las vías respiratorias, también es relevante señalar que dicha utilidad terapéutica también esta relacionada con anterioridad a dicho agonismo A2a en el estado de la técnica, tal y como nos lo revelan las siguientes publicaciones de carácter científico, veamos:

Adenosine A2a Receptor Agonists As Anti-Inflammatory Agents².

Stressed or injured tissues release endogenous adenosine, which blocks potentially destructive inflammatory cascades by binding to A2A adenosine receptors (ARs) and decreasing activation of platelets, leukocytes and endothelial

² Sullivan GW. Curr Opin Investig Drugs. 2003 Nov;4(11):1313-9.

cells. In these tissues, adenosine acts by reducing expression of adhesion molecules and release of pro-inflammatory mediators (e.g., reactive oxygen species, elastase and tumor necrosis factor-alpha). Synthetic A2A selective AR agonists are currently undergoing preclinical testing for the treatment of allergen-induced inflammation, ischemia-reperfusion injury, sepsis and autoimmune diseases. This review discusses potential disease targets for A2A AR agonist treatment, mechanisms of A2A AR agonist action and considerations for synthetic A2A AR agonist design.

Therapy For Chronic Obstructive Pulmonary Disease In The 21st Century³.

Chronic obstructive pulmonary disease (COPD) is a common, smoking-related, severe respiratory condition characterised by progressive, irreversible airflow limitation. Current treatment of COPD is symptomatic, with no drugs capable of halting the relentless progression of airflow obstruction. Better understanding of the airway inflammation, oxidative stress and alveolar destruction that characterise COPD has delineated new disease targets, with consequent identification of novel compounds with therapeutic potential. These new drugs include aids to smoking cessation (e.g. bupropion) and improvements to existing therapies, for example long-acting rather than short-acting bronchodilators, as well as combination therapy. New antiproteases include acyl-enzyme and transition state inhibitors of neutrophil elastase (e.g. sivelestat and ONO-6818), matrix metalloprotease inhibitors (e.g. batimastat), cathepsin inhibitors and peptide protease inhibitors (e.g. DX-890 [EPI-HNE-4] and trappin-2). New antioxidants include superoxide dismutase mimetics (e.g. AEOL-10113) and spin trap compounds (e.g. N-tert-butyl-alpha-phenylnitrone). New anti-inflammatory interventions include phosphodiesterase-4 inhibitors (e.g. cilomilast), inhibitors of tumour necrosis factor-alpha (e.g. humanised monoclonal antibodies), adenosine A(2a) receptor agonists (e.g. CGS-21680), adhesion molecule inhibitors (e.g. bimosiamose [TBC1269]), inhibitors of nuclear factor-kappaB (e.g. the naturally occurring compounds hypoxanthine and (-)-epigallocatechin-3-gallate) and activators of histone deacetylase (e.g. theophylline). There are also selective inhibitors of specific extracellular mediators such as chemokines (e.g. CXCR2 and CCR2 antagonists) and leukotriene B(4) (e.g. SB201146), and of intracellular signal transduction molecules such as p38 mitogen activated protein kinase (e.g. RWJ67657) and phosphoinositide 3-kinase. Retinoids may be one of the few potential treatments capable of reversing alveolar destruction in COPD, and a number of compounds are in clinical trial (e.g. all-trans-retinoic acid). Talmiflumate (MSI-1995), an inhibitor of human calcium-activated chloride channels, has been developed to treat mucous hypersecretion. In addition, the purinoceptor P2Y(2) receptor agonist diquafosol (INS365) is undergoing clinical trials to increase mucus clearance. The challenge to transferral of these new compounds from preclinical research to disease management is the design of effective clinical trials. The current scarcity of well characterised surrogate markers predicts that long-term studies in large numbers of patients will be needed to monitor changes in disease progression.

Para finalizar, y si bien es cierto que dentro de esta información anteriormente expuesta no se involucran directamente los compuestos de la solicitud colombiana

³ Donnelly LE, Rogers DF. Drugs. 2003;63(19):1973-98.

en trámite, también es cierto que cualquier persona medianamente versada en la materia reconocería como una clara guía para la obtención y utilización de dichos compuestos, el hecho que otros compuestos que comparten una relación estrecha en su estructura química (derivados de purina) así como el mismo mecanismo de acción (agonistas de receptor de adenosina A2a) sean terapéuticamente efectivos para los mismos tipos de trastornos.

En conclusión la solicitud colombiana en trámite carece de los requisitos fundamentales para otorgársele el privilegio de patente de invención, en primer lugar porque incurre en una improcedencia directa de patentabilidad al reivindicar el uso de compuestos para un tratamiento terapéutico, y en segundo lugar porque carece de nivel inventivo al reivindicar compuestos cuya estructura química (derivados de purina) se encuentran estrechamente relacionados a compuestos del mismo tipo señalados con anterioridad en el mismo estado de la técnica y que a su vez comparten el mismo mecanismo de acción y utilidad en terapéutica.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales, y que en consecuencia el Despacho decrete, además de la negación de la solicitud en comento, el archivo del expediente que lo contiene.

III. ANEXOS

- ↓ Abstracts de todas las publicaciones científicas mencionadas en el acápite de Complemento de Información.
- ↓ La publicación internacional WO 99/67262 publicada el 29 de Diciembre de 1999 y titulada "ADENOSINE DERIVATIVES" capítulo reivindicatorio.
- ↓ La publicación internacional WO 02/067909 publicada el 06 de Septiembre de 2002 y titulada "NEW METHOD OF BRONCHODILATORY THERAPY" página 7 y capítulo reivindicatorio.

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Article

Synthesis of Novel Carbocyclic Adenosine Analogues as Inhibitors of Adenosine Kinase

Marlon Cowart, Michael J. Bennett, and James F. Kerwin, Jr.
Neurological and Urological Diseases Research,
Pharmaceutical Products Division, Abbott Laboratories,
Abbott Park, Illinois 60064-3500

J. Org. Chem., 1999, 64 (7), pp 2240-2249

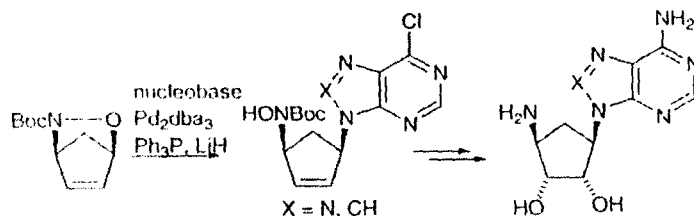
DOI: 10.1021/jo981658m

Publication Date (Web): March 18, 1999

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*In papers with more than one author, the asterisk indicates the name of the author to whom inquiries about the paper should be addressed.

Abstract



Several new 4'-amino substituted carbocyclic adenosine analogues (**6**, **7**, **31**) were prepared as potential inhibitors of the enzyme adenosine kinase. Three different heterocyclic base moieties (adenine, 8-azaadenine, and pyrazolo[3,4-d]pyrimidine) were incorporated into carbocyclic nucleoside analogues through the use of two different synthetic strategies. In both strategies, bicyclic isoxazolidine **9** (prepared through a hetero Diels-Alder reaction with cyclopentadiene) was used as the starting material. In one route, the N-O bond was reductively cleaved, and the hydroxyl group (after inversion and ring functionalization) was used as a leaving group to incorporate the heterocyclic base moiety as the key bond-forming step. A second, more efficient and higher yielding synthetic route was developed as a general solution to the synthesis of the target 4'-amino substituted carbocyclic adenosine analogues. In this methodology, the allylic C-O bond in the bicyclic isoxazolidine **9** was cleaved with double stereoinversion under palladium(0) catalysis as the key bond-forming step to stereospecifically incorporate the heterocyclic base moiety into the cyclopentane ring. The regioselectivity of key bond-forming steps was established principally by NMR methods, especially through ¹³C NMR shifts and by NOE effects seen in the analogues, as well as by HMBC/HMQC experiments.

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Enzymatic Resolution of Aminocyclopentane as Precursors to *trans*- and *cis*-Carbocyclic Nucleosides.
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Revised February 1, 1999

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1: Curr Opin Invest Drugs. 2003 Nov;4(11):1313-9.

Adenosine A2A receptor agonists as anti-inflammatory agents.

Sullivan GW.

Cardiovascular Research Center, University of Virginia Health Sciences Center, MR-5 Room
1314, 415 Lane Rd, Box 801394, Charlottesville, VA 22908, USA. gws3u@virginia.edu

Stressed or injured tissues release endogenous adenosine, which blocks potentially destructive inflammatory cascades by binding to A2A adenosine receptors (ARs) and decreasing activation of platelets, leukocytes and endothelial cells. In these tissues, adenosine acts by reducing expression of adhesion molecules and release of pro-inflammatory mediators (e.g., reactive oxygen species, elastase and tumor necrosis factor- α). Synthetic A2A selective AR agonists are currently undergoing preclinical testing for the treatment of allergen-induced inflammation, ischemia-reperfusion injury, sepsis and autoimmune diseases. This review discusses potential disease targets for A2A AR agonist treatment, mechanisms of A2A AR agonist action and considerations for synthetic A2A AR agonist design.

PMID: 14758770 [PubMed - indexed for MEDLINE]

Related articles

Adenosine A2A receptor agonists inhibit lipopolysaccharide-induced (Vet Immunol Immunopathol. 2008)

Review Adenosine A2A agonists in development for the treatment of inflammation [Expert Opin Invest Drugs. 2005]

Adenosine inhibits tumor necrosis factor- α release from mouse peritoneal macrophages [J Pharmacol Exp Ther. 2006]

A selective adenosine A2A receptor agonist, ATL-146e, prevents concanavalin A-induced (Biochem Biophys Res Commun. 2006)

Review Treating lung inflammation with agonists of the adenosine A2A receptor: promise [Br J Pharmacol. 2008]

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Therapy for chronic obstructive pulmonary disease in the 21st century.

Donnelly LE, Rogers DF.

Thoracic Medicine, National Heart & Lung Institute, Imperial College, London, UK.

Chronic obstructive pulmonary disease (COPD) is a common, smoking-related, severe respiratory condition characterised by progressive, irreversible airflow limitation. Current treatment of COPD is symptomatic, with no drugs capable of halting the relentless progression of airflow obstruction. Better understanding of the airway inflammation, oxidative stress and alveolar destruction that characterise COPD has delineated new disease targets, with consequent identification of novel compounds with therapeutic potential. These new drugs include aids to smoking cessation (e.g. bupropion) and improvements to existing therapies, for example long-acting rather than short-acting bronchodilators, as well as combination therapy. New antiproteases include acyl-enzyme and transition state inhibitors of neutrophil elastase (e.g. sivelestat and ONO-6818), matrix metalloprotease inhibitors (e.g. batimastat), cathepsin inhibitors and peptide protease inhibitors (e.g. DX-890 [EPI-HNE-4] and trappin-2). New antioxidants include superoxide dismutase mimetics (e.g. AEOL-10113) and spin trap compounds (e.g. N-tert-butyl-alpha-phenylnitron). New anti-inflammatory interventions include phosphodiesterase-4 inhibitors (e.g. cilomilast), inhibitors of tumour necrosis factor-alpha (e.g. humanised monoclonal antibodies), adenosine A(2a) receptor agonists (e.g. CGS-21680), adhesion molecule inhibitors (e.g. bimosiamose [TBC1269]), inhibitors of nuclear factor-kappaB (e.g. the naturally occurring compounds hypoxanthine and (-)-epigallocatechin-3-gallate) and activators of histone deacetylase (e.g. theophylline). There are also selective inhibitors of specific extracellular mediators such as chemokines (e.g. CXCR2 and CCR2 antagonists) and leukotriene B(4) (e.g. SB201146), and of intracellular signal transduction molecules such as p38 mitogen activated protein kinase (e.g. RWJ67657) and phosphoinositide 3-kinase. Retinoids may be one of the few potential treatments capable of reversing alveolar destruction in COPD, and a number of compounds are in clinical trial (e.g. all-trans-retinoic acid). Tadalafil (MSI-195), an inhibitor of human calcium-activated chloride channels, has been developed to treat mucous hypersecretion. In addition, the purinoceptor P2Y(2) receptor agonist diquafosol (INS365) is undergoing clinical trials to increase mucus clearance. The challenge to transferral of these new compounds from preclinical research to disease management is the design of effective clinical trials. The current scarcity of well characterised surrogate markers predicts that long-term studies in large numbers of patients will be needed to monitor changes in disease progression.

PMID: 12962514 [PubMed - indexed for MEDLINE]

Related articles

Review COPD: current therapeutic interventions and future approaches. [Eur Respir J. 2005]

Review Prospects for new drugs for chronic obstructive pulmonary disease. [Lancet. 2004]

Review Treatment of airway mucus hypersecretion. [Ann Med. 2006]

Review Future Advances in COPD Therapy. [Respiration. 2001]

Review Emerging targets for COPD therapy. [Curr Drug Targets Inflamm Allergy. 2005]

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Theophylline (Bronkodyl®, Elixophyllin®, Slo-bid®, ...) Theophylline is used to prevent and treat wheezing, shortness of breath, and difficulty breathing caused by

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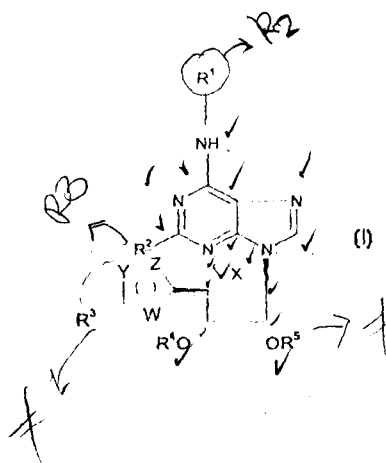
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07H 19/16, A61K 31/70		A1	(11) International Publication Number: WO 99/67262
			(43) International Publication Date: 29 December 1999 (29.12.99)
(21) International Application Number: PCT/EP99/04182		Michael, Kenneth [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).	
(22) International Filing Date: 21 June 1999 (21.06.99)		(74) Agent: LEAROYD, Stephanie, Anne; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).	
(30) Priority Data: 9813554.4 23 June 1998 (23.06.98) GB		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(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		Published	
(75) Inventors/Applicants (for US only): BAYS, David, Edmund [GB/GB]; 9 Windmill Field, Ware, Hertfordshire SG12 9PE (GB). COUSINS, Richard, Peter, Charles [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). ELDRED, Colin, David [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). JUDKINS, Brian, David [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). PASS, Martin [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). PENNELL, Andrew,		With international search report.	

(54) Title: ADENOSINE DERIVATIVES

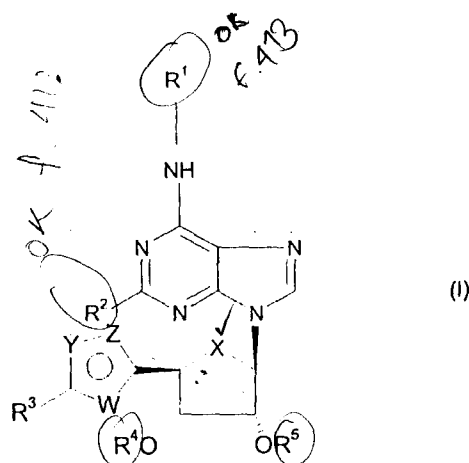


(57) Abstract

A compound of formula (I) which is an agonist at the adenosine A1 receptor, wherein Y, Z and W represent heteroatoms, and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof for use in therapy.

Claims

1. A compound of formula (I) which is an agonist at the adenosine A1 receptor



wherein X represents O or CH₂;

R² represents C₁₋₃alkyl, C₁₋₃alkoxy, halogen or hydrogen;

R³ represents H, phenyl (optionally substituted by halogen), a 5 or 6 membered heteroaryl group, C₁₋₆ alkoxy, C₁₋₆ alkylO(CH₂)_n where n is 0-6, C₃₋₇ cycloalkyl, C₁₋₆ hydroxyalkyl, halogen or a C₁₋₆ straight or branched alkyl, C₁₋₆ alkenyl or C₁₋₆ alkynyl group optionally substituted by one or more halogens.

Y and Z represent O, N, CH, N(C₁₋₆ alkyl)

W represents CH, O, N, S, N(C₁₋₆ alkyl)

and wherein at least one of W and Z represents a heteroatom (and when Y, Z and/or W is N, the presence or absence of an additional H would be apparent to a person skilled in the art)

with the proviso that when W represents CH, Z represents N and Y represents O, R³ cannot be H.

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 329

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✓ ✓

✓
 R^4 and R^5 independently represent H or a C_{1-6} straight chain or branched alkyl group.

5 R^1 represents hydrogen or a group selected from

10 (1) $-(alk)_n - (C_{3-7})$ cycloalkyl, including bridged cycloalkyl, said cycloalkyl group optionally substituted by one or more substituents selected from OH, halogen, $-(C_{1-3})$ alkoxy, wherein (alk) represents C_{1-3} alkylene and n represents 0 or 1.

15 (2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S, optionally substituted by one or more substituents selected from the group consisting of $-(C_{1-3})$ alkyl, $-CO_2-(C_{1-4})$ alkyl, $-CO(C_{1-3})$ alkyl, $-S(=O)_n-(C_{1-3})$ alkyl, $-CONR^aR^b$ (wherein R^a and R^b independently represent H or C_{1-3} alkyl) or $=O$; where there is a sulfur atom in the heterocyclic ring, said sulfur is optionally substituted by $(=O)_n$, where n is 1 or 2.

20 (3) Straight or branched C_{1-12} alkyl, optionally including one or more O, ✓
 $S(=O)_n$ (where n is 0, 1 or 2) and N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy, C_{3-7} cycloalkyl or NR^aR^b wherein R^a and R^b independently represent hydrogen, C_{3-7} cycloalkyl or a C_{1-6} straight chain or branched alkyl optionally substituted by C_{3-7} cycloalkyl.

25 (4) a fused bicyclic aromatic ring



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wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms, wherein the bicyclic ring is

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B
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attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted by $-\text{CO}_2-(\text{C}_{1-3}\text{alkyl})$.

- (5) a phenyl group optionally substituted by one or more substituents selected from:

5 -halogen, $-\text{SO}_3\text{H}$, $-(\text{alk})_n\text{OH}$, $-(\text{alk})_n$ -cyano, $-(\text{O})_n$ $-(\text{C}_{1-6}\text{alkyl})$ (optionally substituted by one or more halogens), $-(\text{alk})_n$ -nitro, $-(\text{O})_m$ $-(\text{alk})_n-\text{CO}_2\text{R}^c$,
10 $-(\text{alk})_n-\text{CONR}^c\text{R}^d$, $-(\text{alk})_n-\text{COR}^c$, $-(\text{alk})_n-\text{SOR}^e$, $-(\text{alk})_n-\text{SO}_2\text{R}^e$, $-(\text{alk})_n-\text{SO}_2\text{NR}^c\text{R}^d$, $-(\text{alk})_n\text{OR}^c$, $-(\text{alk})_n-(\text{CO})_m-\text{NHSO}_2\text{R}^e$, $-(\text{alk})_n-\text{NHCOR}^c$, $-(\text{alk})_n-\text{NR}^c\text{R}^d$ wherein m and n are 0 or 1 and alk represents a C_{1-6} alkylene group or C_{2-6} alkenyl group.

- (6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by $\text{C}_{1-3}\text{alkyl}$ or NR^cR^d .

15 R^c and R^d may each independently represent hydrogen, or C_{1-3} alkyl or when part of a group NR^cR^d , R^c and R^d together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally containing other heteroatoms, which heterocyclic ring may optionally be substituted further by one or more C_{1-3} alkyl groups.

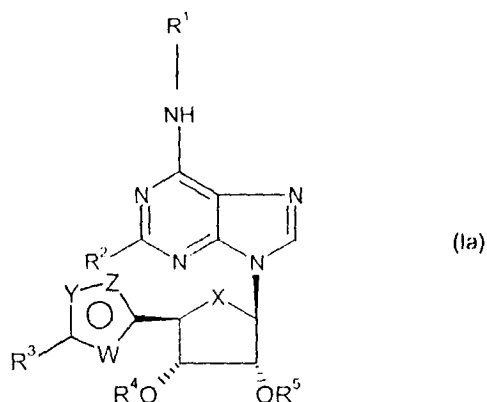
R^e represents $\text{C}_{1-3}\text{alkyl}$

25 and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof for use in therapy.

2. A compound of formula (Ia) which is an agonist at the adenosine A1 receptor

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wherein X represents O or CH₂;

R² represents C₁₋₃alkyl, C₁₋₃alkoxy, halogen or hydrogen;

R³ represents H, phenyl (optionally substituted by halogen), a 5 or 6 membered heteroaryl group, C₁₋₆ alkoxy, C₁₋₆ straight or branched alkyl optionally substituted by one or more halogens, C₃₋₇ cycloalkyl, C₁₋₆ hydroxyalkyl or halogen.

Y and Z represent O, N, CH

W represents CH, O, N, S

and wherein at least one of W and Z represents a heteroatom (and when Y, Z and/or W is N, the presence or absence of an additional H would be apparent to a person skilled in the art)

with the proviso that when W represents CH, Z represents N and Y represents O, R³ cannot be H.

R⁴ and R⁵ independently represent H or a C₁₋₆ straight chain or branched alkyl group.

R¹ represents a group selected from

- (1) $-(\text{alk})_n$ - (C_{3-7}) cycloalkyl, including bridged cycloalkyl, said cycloalkyl group optionally substituted by one or more substituents selected from OH, halogen, $-(\text{C}_{1-3})$ alkoxy, wherein (alk) represents C_{1-3} alkylene and n represents 0 or 1.
- (2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S, optionally substituted by one or more substituents selected from the group consisting of $-(\text{C}_{1-3})\text{alkyl}$, $-\text{CO}_2-(\text{C}_{1-4})\text{alkyl}$, $-\text{CO}(\text{C}_{1-3}\text{alkyl})$, $-\text{S}(=\text{O})_n-(\text{C}_{1-3}\text{alkyl})$, $-\text{CONR}^a\text{R}^b$ (wherein R^a and R^b independently represent H or $\text{C}_{1-3}\text{alkyl}$) or $=\text{O}$; where there is a sulfur atom in the heterocyclic ring, said sulfur is optionally substituted by $(=\text{O})_n$, where n is 1 or 2.
- (3) Straight or branched C_{1-12} alkyl, optionally including one or more O, $\text{S}(=\text{O})_n$ (where n is 0, 1 or 2) and N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy, C_{3-7} cycloalkyl or NR^aR^b wherein R^a and R^b independently represent hydrogen, C_{3-7} cycloalkyl or a C_{1-6} straight chain or branched alkyl optionally substituted by C_{3-7} cycloalkyl.
- (4) a fused bicyclic aromatic ring



wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms, wherein the bicyclic ring is attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted by $-\text{CO}_2-(\text{C}_{1-3}\text{alkyl})$.

- (5) a phenyl group optionally substituted by one or more substituents selected from:

$-\text{halogen}$, $-\text{SO}_3\text{H}$, $-(\text{alk})_n\text{OH}$, $-(\text{alk})_n$ -cyano, $-(\text{O})_n$ $-(\text{C}_{1-6})\text{alkyl}$ (optionally substituted by one or more halogens), $-(\text{alk})_n$ -nitro, $-(\text{O})_m$ $-(\text{alk})_n$ - CO_2R^c ,

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-(alk)_n- CONR^cR^d -(alk)_n-COR^c, -(alk)_n-SOR^e, -(alk)_n-SO₂R^e, -(alk)_n-SO₂NR^cR^d, -(alk)_nOR^c, -(alk)_n-(CO)_m-NHSO₂R^e, -(alk)_n-NHCOR^c, -(alk)_n-NR^cR^d wherein m and n are 0 or 1 and alk represents a C₁₋₆alkylene group or C₂₋₆ alkenyl group.

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- (6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by C₁₋₃alkyl or NR^cR^d.

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R^c and R^d may each independently represent hydrogen, or C₁₋₃ alkyl or when part of a group NR^cR^d, R^c and R^d together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally containing other heteroatoms, which heterocyclic ring may optionally be substituted further by one or more C₁₋₃ alkyl groups.

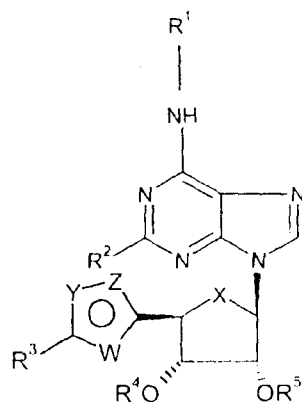
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R^e represents C₁₋₃alkyl

and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof for use in therapy.

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3. A compound of formula (Ib) which is an agonist at the adenosine A1 receptor



(Ib)

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wherein X represents O or CH₂;

R² represents C₁₋₃alkyl, C₁₋₃alkoxy, halogen or hydrogen;

5 R³ represents H, phenyl (optionally substituted by halogen), a 5 or 6 membered heteroaryl group, C₁₋₆ alkoxy, C₁₋₆ alkylO(CH₂)_n where n is 0-6, C₃₋₇ cycloalkyl, C₁₋₆ hydroxyalkyl, halogen or a C₁₋₆ straight or branched alkyl, C₁₋₆ alkenyl or C₁₋₆ alkynyl group optionally substituted by one or more halogens.

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Y and Z represent O, N, CH, N(C₁₋₆ alkyl)

W represents CH, O, N, S, N(C₁₋₆ alkyl)

and wherein at least one of W and Z represents a heteroatom (and when Y, Z or W is N, the presence or absence of an additional H would be apparent to a person skilled in the art)

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with the proviso that when W represents CH, Z represents N and Y represents O, R³ cannot be H.

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R⁴ and R⁵ independently represent H or a C₁₋₆ straight chain or branched alkyl group.

R¹ represents hydrogen or a group selected from

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(1) -(alk)_n - (C₃₋₇) cycloalkyl, including bridged cycloalkyl, said cycloalkyl group optionally substituted by one or more substituents selected from OH, halogen, -(C₁₋₃) alkoxy, wherein (alk) represents C₁₋₃ alkylene and n represents 0 or 1.

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(2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S, optionally substituted by one or more substituents selected from the group consisting of -(C₁₋₃)alkyl, -CO₂-(C₁₋₄)alkyl, -CO(C₁₋₃alkyl), -S(=O)_n-(C₁₋₃alkyl), -CONR^aR^b (wherein R^a and R^b independently represent H or C₁₋₃alkyl) or =O; where there is a sulfur atom in the heterocyclic ring, said sulfur is optionally substituted by (=O)_n, where n is 1 or 2.

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(3) Straight or branched C₁₋₁₂ alkyl, optionally including one or more O, S(=O)_n (where n is 0, 1 or 2) and N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy, C₃₋₇ cycloalkyl or NR^aR^b wherein R^a and R^b independently represent hydrogen, C₃₋₇ cycloalkyl or a C₁₋₆ straight chain or branched alkyl optionally substituted by C₃₋₇ cycloalkyl.

(4) a fused bicyclic aromatic ring



wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms, wherein the bicyclic ring is attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted by -CO₂ -(C₁₋₃alkyl).

(5) a phenyl group optionally substituted by one or more substituents selected from:

-halogen, -SO₃H, -(alk)_nOH, -(alk)_n -cyano, -(O)_n -(C₁₋₆)alkyl (optionally substituted by one or more halogens), -(alk)_n -nitro, -(O)_m -(alk)_n-CO₂R^c,

-(alk)_n- CONR^cR^d -(alk)_n -COR^c, -(alk)_n -SOR^e, -(alk)_n -SO₂R^e, -(alk)_n- SO₂NR^cR^d, -(alk)_nOR^c, -(alk)_n -(CO)_m- NHSO₂R^e, -(alk)_n- NHCOR^c, -(alk)_n- NR^cR^d wherein m and n are 0 or 1 and alk represents a C₁₋₆alkylene group or C₂₋₆ alkenyl group.

(6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by C₁₋₃alkyl or NR^cR^d.

R^c and R^d may each independently represent hydrogen, or C₁₋₃ alkyl or when part of a group NR^cR^d, R^c and R^d together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally

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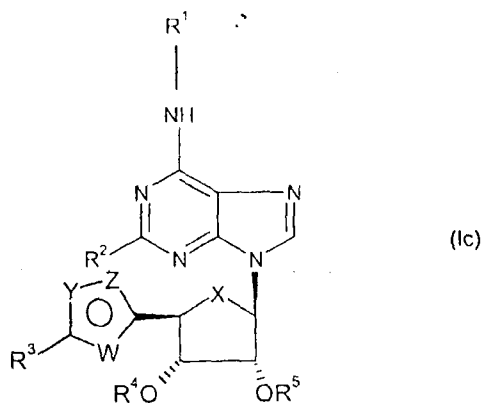
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containing other heteroatoms, which heterocyclic ring may optionally be substituted further by one or more C₁₋₃ alkyl groups.

R^e represents C₁₋₃alkyl with the proviso that when R⁴ and R⁵ both represent halogen, R³ cannot represent methyl, ethyl, n-propyl, isopropyl, cyclopropyl, CH(OH)CH₃, C₁₋₃alkoxy.

and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof.

4. A compound of formula (Ic) which is an agonist at the adenosine A1 receptor



wherein X represents O or CH₂;

R² represents C₁₋₃alkyl, C₁₋₃alkoxy, halogen or hydrogen;

R³ represents H, phenyl (optionally substituted by halogen), a 5 or 6 membered heteroaryl group, C₁₋₆ alkoxy, C₁₋₆ straight or branched alkyl optionally substituted by one or more halogens, C₃₋₇ cycloalkyl, C₁₋₆ hydroxyalkyl or halogen.

Y and Z represent O, N, CH

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W represents CH, O, N, S

and wherein at least one of W and Z represents a heteroatom (and when Y, Z and/or W is N, the presence or absence of an additional H would be apparent to a person skilled in the art)

5 with the proviso that when W represents CH, Z represents N and Y represents O, R³ cannot be H.

R⁴ and R⁵ independently represent H or a C₁₋₆ straight chain or branched alkyl group.

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R¹ represents a group selected from

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(1) -(alk)_n - (C₃₋₇) cycloalkyl, including bridged cycloalkyl, said cycloalkyl group optionally substituted by one or more substituents selected from OH, halogen, -(C₁₋₃) alkoxy, wherein (alk) represents C₁₋₃ alkylene and n represents 0 or 1.

20

(2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S, optionally substituted by one or more substituents selected from the group consisting of -(C₁₋₃)alkyl, -CO₂-(C₁₋₄)alkyl, -CO(C₁₋₃alkyl), -S(=O)_n-(C₁₋₃alkyl), -CONR^aR^b (wherein R^a and R^b independently represent H or C₁₋₃alkyl) or =O; where there is a sulfur atom in the heterocyclic ring, said sulfur is optionally substituted by (=O)_n, where n is 1 or 2.

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(3) Straight or branched C₁₋₁₂ alkyl, optionally including one or more O, S(=O)_n (where n is 0, 1 or 2) and N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy, C₃₋₇ cycloalkyl or NR^aR^b wherein R^a and R^b independently represent hydrogen, C₃₋₇ cycloalkyl or a C₁₋₆ straight chain or branched alkyl optionally substituted by C₃₋₇ cycloalkyl.

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(4) a fused bicyclic aromatic ring



wherein B represents a 5 or 6 membered heterocyclic aromatic group containing 1 or more O, N or S atoms, wherein the bicyclic ring is attached to the nitrogen atom of formula (I) via a ring atom of ring A and ring B is optionally substituted by $-\text{CO}_2-(\text{C}_{1-3}\text{alkyl})$.

- (5) a phenyl group optionally substituted by one or more substituents selected from:

-halogen, $-\text{SO}_3\text{H}$, $-(\text{alk})_n\text{OH}$, $-(\text{alk})_n$ -cyano, $-(\text{O})_n-(\text{C}_{1-6})\text{alkyl}$ (optionally substituted by one or more halogens), $-(\text{alk})_n$ -nitro, $-(\text{O})_m-(\text{alk})_n-\text{CO}_2\text{R}^c$, $-(\text{alk})_n-\text{CONR}^c\text{R}^d$, $-(\text{alk})_n-\text{COR}^c$, $-(\text{alk})_n-\text{SOR}^e$, $-(\text{alk})_n-\text{SO}_2\text{R}^e$, $-(\text{alk})_n-\text{SO}_2\text{NR}^c\text{R}^d$, $-(\text{alk})_n\text{OR}^c$, $-(\text{alk})_n-(\text{CO})_m-\text{NHSO}_2\text{R}^e$, $-(\text{alk})_n-\text{NHCOR}^c$, $-(\text{alk})_n-\text{NR}^c\text{R}^d$ wherein m and n are 0 or 1 and alk represents a C_{1-6} alkylene group or C_{2-6} alkenyl group.

- (6) A phenyl group substituted by a 5 or 6 membered heterocyclic aromatic group, said heterocyclic aromatic group optionally being substituted by $\text{C}_{1-3}\text{alkyl}$ or NR^cR^d .

R^c and R^d may each independently represent hydrogen, or C_{1-3} alkyl or when part of a group NR^cR^d , R^c and R^d together with the nitrogen atom may form a 5 or 6 membered heterocyclic ring optionally containing other heteroatoms, which heterocyclic ring may optionally be substituted further by one or more C_{1-3} alkyl groups.

R^e represents $\text{C}_{1-3}\text{alkyl}$ with the proviso that when R^4 and R^5 both represent halogen, R^3 cannot represent methyl, ethyl, n-propyl, isopropyl, cyclopropyl, $\text{CH}(\text{OH})\text{CH}_3$, $\text{C}_{1-3}\text{alkoxy}$.

and salts and solvates thereof, in particular, physiologically acceptable solvates and salts thereof.

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5. A compound according to claims 1-4 which exhibits little or no agonist activity at the the A3 receptor.
- 5 6. A compound according to claims 1-5 wherein the W, Y and Z containing heterocyclic groups include isoxazoles, oxadiazoles, pyrazoles, oxazoles, triazoles, thiadiazoles.
- 10 7. A compound according to claims 1-6 wherein the W, Y and Z containing heterocyclic groups are isoxazoles, and 1,2,4- and 1,3,4- oxadiazoles.
8. A compound according to claims 1-7 wherein R² represents hydrogen, methyl, methoxy or halogen, more preferably hydrogen or chlorine.
- 15 9. A compound according to claims 1-8 wherein R¹ may represent (alk)_n- C₃₋₆ cycloalkyl wherein n is 0 or 1 and the said cycloalkyl is either substituted by at least one substituent selected from halogen, particularly fluorine, and OH or is unsubstituted and n is zero.
- 20 10. A compound according to claim 9 wherein the cycloalkyl group is unsubstituted or monosubstituted with OH.
11. A compound according to claim 10 wherein the cycloalkyl group is 5-membered.
- 25 12. A compound according to claims 1-8 wherein R¹ may represent a substituted or unsubstituted aliphatic heterocyclic group, the substituent being selected from the group consisting of -CO₂ -(C₁₋₄)alkyl
- 30 13. A compound according to claim 12 wherein the aliphatic heterocyclic group is unsubstituted or when the substituent is -CO₂(C₁₋₄)alkyl, the heteroatom is N and the substituent is directly attached to said ring nitrogen atom.
- 35 14. A compound according to claims 12-13 wherein the heterocyclic ring is 6 membered.

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15. A compound according to claim 14 wherein the heterocyclic ring contains only one O, N or S heteroatom.
- 5 16. A compound according to claims 1-8 wherein R¹ may represent a straight or branched alkyl of 1-6 carbon atoms optionally with at least one S(=O)_n and/or N substituted in the chain; where there is an S(=O)_n in the chain, preferably n is 1 or 2 and is unsubstituted or substituted by at least one OH group.
- 10 17. A compound according to claims 1-8 wherein R¹ may represent a phenyl group which is substituted by one or two substituents selected from OH, alkyl, particularly C₁₋₄ alkyl and halogen.
- 15 18. A compound according to claim 17 wherein the phenyl is disubstituted in the 2,4 positions.
19. A compound according to claims 16 and 17 wherein both substituents are halogen.
- 20 20. A compound according to any preceding claim wherein R⁴ and R⁵ both represent hydrogen.
21. A compound selected from:
- 25 (2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
4-[9-[5S-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-3R,4S-dihydroxy-tetrahydro-furan-2R-yl]-9H-purin-6-ylamino}-piperidine-1-carboxylic acid ethyl ester;
(2S,3S,4R,5R)-2-(5-Isopropyl-[1,3,4]oxadiazol-2-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
30 4-[9-[5S-(5-Cyclopropyl-[1,3,4]oxadiazol-2-yl)-3R,4S-dihydroxy-tetrahydro-furan-2R-yl]-9H-purin-6-ylamino}-piperidine-1-carboxylic acid ethyl ester;
(2S,3S,4R,5R)-2-(5-tert-Butyl-[1,3,4]oxadiazol-2-yl)-5-[6-(4-chloro-2-fluoro-phenylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
35 (2S,3S,4R,5R)-2-(5-Ethyl-oxazol-2-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;

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- (2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
(2S,3S,4R,5R)-2-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-5-[6-(2S-hydroxy-cyclopent-(S)-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
5 (2S,3S,4R,5R)-2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
(2S,3S,4R,5R)-2-(3-tert-Butyl-isoxazol-5-yl)-5-[6-(tetrahydro-pyran-4-ylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol;
ethyl 4-({9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(3-methyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate;
10 (2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-[(cyclopropylmethyl)amino]-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-(isobutylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
15 (2R,3R,4S,5S)-2-[6-(cyclopropylamino)-9H-purin-9-yl]-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol;
2-({9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-2-yl]-9H-purin-6-yl}amino)-N-methylethanesulfonamide;
(2R,3R,4S,5S)-2-[6-(3,4-difluoroanilino)-9H-purin-9-yl]-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol;
20 (2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol;
(2R,3S,4R,5R)-2-[5-(tert-butyl)-4H-1,2,4-triazol-3-yl]-5-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
25 (2R,3R,4S,5R)-2-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-(5-isopropyl-4H-1,2,4-triazol-3-yl)tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
30 (2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
2-[(9-[(2R,3R,4S,5S)-5-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl)amino]-N-ethylethanesulfonamide;

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- 2-[(9-[(2R,3R,4S,5S)-5-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl)amino]-N-(3-methylphenyl)ethanesulfonamide;
- 5 2-[(9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(5-methyl-1,3-oxazol-2-yl)tetrahydrofuran-2-yl]-9H-purin-6-yl)amino]-N-methylethanesulfonamide;
- (2R,3R,4S,5S)-2-[6-(cyclopentylamino)-9H-purin-9-yl]-5-[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]tetrahydrofuran-3,4-diol;
- (2S,3S,4R,5R)-2-(5-ethyl-1,3,4-oxadiazol-2-yl)-5-[6-(isopropylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
- 10 (2R,3R,4S,5S)-2-(6-[(1S,2S)-2-hydroxycyclopentyl]amino)-9H-purin-9-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol;
- (2R,3R,4S,5S)-2-[2-chloro-6-[(1-ethylpropyl)amino]-9H-purin-9-yl]-5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)tetrahydrofuran-3,4-diol formate (1:2);
- (2R,3R,4S,5S)-2-[2-Chloro-6-(1-ethyl-propylamino)-purin-9-yl]-5-(3-cyclopropyl-1,2,4)oxadiazol-5-yl)-tetrahydro-furan-3,4-diol diformate;
- 15 (2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
- (2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-(6-[(1S,2S)-2-hydroxycyclopentyl]amino)-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
- 20 ethyl 4-[(9-[(2R,3R,4S,5S)-5-(3-ethylisoxazol-5-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl)amino]piperidine-1-carboxylate;
- (2R,3S,4R,5R)-2-[5-(tert-butyl)-4H-1,2,4-triazol-3-yl]-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
- (2R,3S,4R,5R)-2-(5-isopropyl-4H-1,2,4-triazol-3-yl)-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
- 25 (2R,3R,4S,5S)-2-[2-chloro-6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-(5-methyl-1,3-oxazol-2-yl)tetrahydrofuran-3,4-diol;
- (2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-methylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
- 30 (2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-propylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
- (2R,3R,4S,5S)-2-[2-chloro-6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
- 35 ethyl 4-[(2-chloro-9-[(2R,3R,4S,5S)-5-(3-ethylisoxazol-5-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl)amino]piperidine-1-carboxylate;

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(2R,3R,4S,5S)-2-(2-chloro-6-(((1S,2S)-2-hydroxycyclopentyl)amino)-9H-purin-9-yl)-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;

(2R,3R,4S,5S)-2-(2-chloro-6-([2-(ethylsulfonyl)ethyl]amino)-9H-purin-9-yl)-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;

5 (2R,3R,4S,5S)-2-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;

(2R,3R,4S,5S)-2-[2-chloro-6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;

10 (2R,3R,4S,5S)-2-[2-chloro-6-(2-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;

(2R,3R,4S,5S)-2-[2-chloro-6-(2-chloroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;

(2R,3R,4S,5S)-2-(6-(((1S,2S)-2-hydroxycyclopentyl)amino)-9H-purin-9-yl)-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;

15 ethyl 4-[(9-((2R,3R,4S,5S)-3,4-dihydroxy-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-2-yl)-9H-purin-6-yl)amino]piperidine-1-carboxylate;

(2S,3S,4R,5R)-2-[3-(hydroxymethyl)isoxazol-5-yl]-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;

20 (2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;

(2R,3R,4S,5S)-2-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;

(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-[6-(2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;

25 (2R,3R,4S,5S)-2-[6-(2-chloroanilino)-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;

(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-[6-(piperidin-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;

30 (2R,3R,4S,5R)-2-[2-chloro-6-[(1-ethylpropyl)amino]-9H-purin-9-yl]-5-(5-ethylisoxazol-3-yl)tetrahydrofuran-3,4-diol formate;

(2S,3S,4R,5R)-2-(3-bromoisoxazol-5-yl)-5-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;

(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-[[1-(methylsulfonyl)piperidin-4-yl]amino]-9H-purin-9-yl)tetrahydrofuran-3,4-diol;

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- (2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(propylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
- (2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(isopropylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
- 5 (2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-{[1-(ethylsulfonyl)piperidin-4-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
- (2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
- (2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[2-chloro-6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
- 10 2-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl)-2-chloro-9H-purin-6-yl]amino]-N-ethylethanesulfonamide;
- 2-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl)-2-chloro-9H-purin-6-yl]amino]-N-isopropylethanesulfonamide;
- 15 (2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-[2-chloro-6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
- (2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-pyridin-3-ylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
- (2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-[3-(4-hydroxybutyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
- 20 2-[(9-{(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl)-9H-purin-6-yl]amino]-N-ethylethanesulfonamide;
- (2R,3R,4S,5S)-2-[6-(cyclopentylamino)-9H-purin-9-yl]-5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]tetrahydrofuran-3,4-diol;
- 25 (2R,3R,4S,5S)-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)-5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]tetrahydrofuran-3,4-diol;
- ethyl 4-[(9-{(2R,3R,4S,5S)-3,4-dihydroxy-5-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]tetrahydrofuran-2-yl)-9H-purin-6-yl]amino]piperidine-1-carboxylate;
- (2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(5-methyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol;
- 30 (2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(3-cyclopropylisoxazol-5-yl)tetrahydrofuran-3,4-diol;
- (2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-{6-{[1-(butyrylpiperidin-4-yl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;

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- isopropyl 4-[(9-[(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl)amino]piperidine-1-carboxylate;
(2S,3S,4R,5R)-2-[3-(tert-butyl)isoxazol-5-yl]-5-(6-[[1-(2,2,2-trifluoroacetyl)piperidin-4-yl]amino]-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
- 5 methyl 4-[(9-[(2R,3R,4S,5S)-5-[3-(tert-butyl)isoxazol-5-yl]-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl)amino]piperidine-1-carboxylate;
(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
- 10 (2R,3R,4S,5S)-2-[6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[6-(2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
- 15 (2R,3R,4S,5S)-2-[6-(2-chloroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-(2-chloro-6-[(1S,2S)-2-hydroxycyclopentyl]amino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
- 20 (2R,3R,4S,5S)-2-[2-chloro-6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
2-[(2-chloro-9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-2-yl]-9H-purin-6-yl)amino]-N-ethylethanesulfonamide;
- ethyl 4-[(2-chloro-9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-2-yl]-9H-purin-6-yl)amino]piperidine-1-carboxylate;
(2R,3R,4S,5S)-2-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
- 25 (2R,3R,4S,5S)-2-[2-chloro-6-(2-chloro-4-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5S)-2-[2-chloro-6-(2-fluoroanilino)-9H-purin-9-yl]-5-[3-(hydroxymethyl)isoxazol-5-yl]tetrahydrofuran-3,4-diol;
- 30 (2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-[2-methoxy-6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
ethyl 4-[(9-[(2R,3R,4S,5S)-5-(3-ethylisoxazol-5-yl)-3,4-dihydroxytetrahydrofuran-2-yl]-2-methoxy-9H-purin-6-yl)amino]piperidine-1-carboxylate;
(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-(6-[(1S,2S)-2-hydroxycyclopentyl]amino)-2-methoxy-9H-purin-9-yl)tetrahydrofuran-3,4-diol;

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(2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-(6-[[2-(ethylsulfonyl)ethyl]amino]-2-methoxy-9H-purin-9-yl)tetrahydrofuran-3,4-diol;

(2R,3R,4S,5S)-2-[6-(2-chloro-4-fluoroanilino)-2-methoxy-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;

5 (2S,3S,4R,5R)-2-(3-ethylisoxazol-5-yl)-5-[6-(2-fluoroanilino)-2-methoxy-9H-purin-9-yl]tetrahydrofuran-3,4-diol;

(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-2-methoxy-9H-purin-9-yl]-5-(3-ethylisoxazol-5-yl)tetrahydrofuran-3,4-diol;

10 (2S,3S,4R,5R)-2-[3-(tert-butyl)-1,2,4-oxadiazol-5-yl]-5-[6-(cyclopropylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;

(2S,3S,4R,5R)-2-[5-(tert-butyl)-1,3,4-oxadiazol-2-yl]-5-[2-chloro-6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;

(2R,3R,4S,5S)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-(5-isopropyl-1,3,4-oxadiazol-2-yl)tetrahydrofuran-3,4-diol.

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22. A pharmaceutical composition comprising compounds of claims 1-21 together with a pharmaceutically acceptable diluent or carrier.

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23. Use of a compound according to claims 1-21 for the manufacture of a medicament for the treatment of a patient suffering from a condition where there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke or which

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24. A method of treating a patient suffering from a condition where there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke or which subject is suffering pain, a CNS disorder or sleep apnoea comprising administration of a therapeutically effective amount of a compound of claims 1-21.

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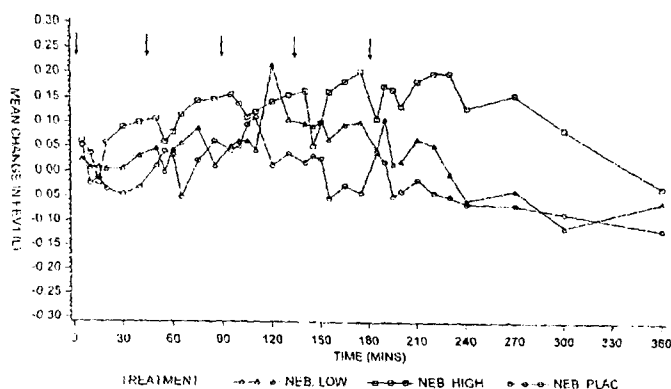
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(72) Inventor; and

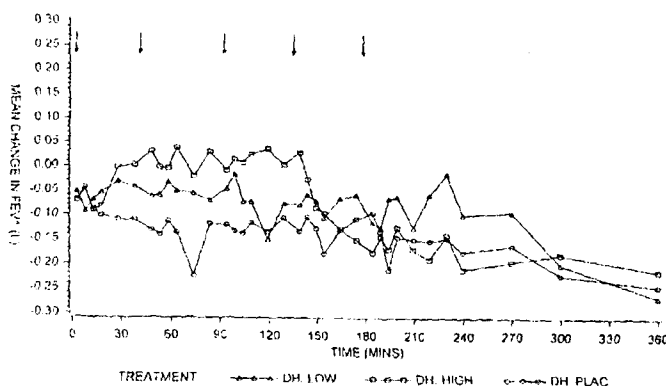
(75) Inventor/Applicant (for US only): **VENTRESCA,**

[Continued on next page]

(54) Title: NEW METHOD OF BRONCHODILATORY THERAPY

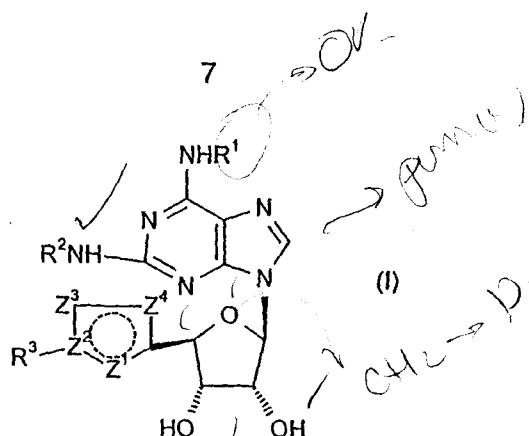


(57) Abstract: As a first aspect of the invention we provide a method of inducing bronchodilation in a human patient which comprises administering to that patient an effective amount of a selective A2a receptor agonist.



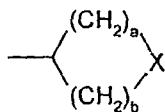
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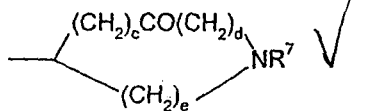
wherein R¹ and R² independently represent a group selected from:

- (i) C₃₋₈cycloalkyl-; ✓
- (ii) hydrogen; ✓
- 5 (iii) aryl₂CHCH₂-;
- (iv) C₃₋₈cycloalkylC₁₋₆alkyl-;
- (v) C₁₋₈alkyl-; ✓
- (vi) arylC₁₋₆alkyl-;
- (vii) R⁴R⁵N-C₁₋₆alkyl-; ✓
- 10 (viii) C₁₋₆alkyl-CH(CH₂OH)-;
- (ix) arylC₁₋₅alkyl-CH(CH₂OH)-;
- (x) arylC₁₋₅alkyl-C(CH₂OH)₂-;
- (xi) C₃₋₈cycloalkyl independently substituted by one or more (e.g. 1, 2 or 3)
-(CH₂)_pR⁶ groups;
- 15 (xii) H₂NC(=NH)NHC₁₋₆alkyl-;
- (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;

- 20 (xiv) -C₁₋₆alkyl-OH;
- (xv) -C₁₋₈haloalkyl;
- (xvi) a group of formula



- (xvii) aryl; and

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X
399Claims

- 5 1. A method of inducing bronchodilation in a human patient which comprises administering to that patient an effective amount of a selective A2a receptor agonist.
2. A method of inducing bronchodilation in a human patient suffering from an inflammatory disorder (eg asthma or COPD) which comprises administering to that patient an effective amount of a selective A2a receptor agonist.
- 10 3. A method of relieving bronchoconstriction in a human patient which comprises administering to that patient an effective amount of a selective A2a receptor agonist.
- 15 4. A method of relieving bronchoconstriction in a human patient suffering from an inflammatory disorder (eg asthma or COPD) which comprises administering to that patient an effective amount of a selective A2a receptor agonist.
- 20 5. A pharmaceutical composition for the inducing of bronchodilation in a human patient which comprises an effective amount of a selective A2a receptor agonist.
6. A pharmaceutical composition for inducing bronchodilation in a human patient suffering from an inflammatory disorder (eg asthma or COPD) which comprises an effective amount of a selective A2a receptor agonist.
- 25 7. A pharmaceutical composition for the relief of bronchoconstriction in a human patient which comprises an effective amount of a selective A2a receptor agonist.
8. A pharmaceutical composition for the relief of bronchoconstriction in a human patient suffering from an inflammatory disorder (eg asthma or COPD) which comprises an effective amount of a selective A2a receptor agonist.
- 30 9. The use of a selective A2a receptor agonist in the manufacture of a medicament for the induction of bronchodilation in a human patient.
10. The use of a selective A2a receptor agonist in the manufacture of a medicament for the induction of bronchodilation in a human patient suffering from an inflammatory disorder (eg asthma or COPD).
11. The use of a selective A2a receptor agonist in the manufacture of a medicament for the relief of bronchoconstriction in a human patient.

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12. The use of a selective A2a receptor agonist in the manufacture of a medicament for the relief of bronchoconstriction in a human patient suffering from an inflammatory disorder (eg asthma or COPD).
- 5 13. A composition, method or use according to any one of claims 1-12 wherein the selective A2a agonist is also an A3 antagonist.
14. A composition, method or use according to any one of claims 3, 4, 7, 8, 11 or 12 wherein the relief is acute relief.
15. A composition, method or use according to any one of claims 1-12 wherein the selective A2a agonist is a derivative of adenosine.
- 10 16. A composition, method or use according to claim 15 wherein the A2a agonist is (2R,3R,4S,5R)-2-[6-Amino-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(2-ethyl-2H-tetrazol-5-yl)-tetrahydro-furan-3,4-diol or a salt thereof.
- 15 17. A composition, method or use according to claim 15 wherein the A2a agonist is (2S,3S,4R,5R)-2-(3-Ethyl-isoxazol-5-yl)-5-{6-(1-ethyl-propylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-tetrahydro-furan-3,4-diol or a salt thereof.
- 20 18. A composition, method or use according to any one of claims 1 to 12 wherein the selective A2a agonist is administered in combination with a beta-2 agonist.
19. A composition, method or use according to any one of claims 1 to 12 wherein the selective A2a agonist is administered by inhalation.