Industria y Comercio

SUPERINTENDENCIA

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. EXPEDIENTE Nº 03-7961 1

54. TÍTULO COMPUESTOS QUIMICOS.

NUEVO TITULO: Compuestos Químicos agonistas A1 de la adenosina.

51. CLASIFICACIÓN INTERNACIONAL A61K31/70 ; C07D473/18

71. SOLICITANTE GLAXO GROUP LIMITED

DOMICILIO Glaxo Wellcome House, Berkeley Avenue Greenford Middlesex UB6 ONN.

74. APODERADO CARLOS R. OLARTE

22. BOGOTÁ, D. C. SEPTIEMBRE 10, 2003

QP

FORMA P 10)

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PETITORIO

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Industria y Comercio
SUPERINTENDENCIA

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Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2029 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE :

[X]	Patente de Invención	[ ]	Patente de Modelo de Utilidad
[ ]	Capítulo I.	[X]	Capítulo II.

(2) SOLICITANTE (71)

Nombre: GLAXO GROUP LIMITED

Dirección: Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN

Nacionalidad o Domicilio:

Lugar de Constitución: INGLATERRA.

Teléfono: Fax:

E-Mail

IDENTIFICACION

C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número

(3) REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: World Trade Center Torre C, Calle 100 No. 8A-55 Piso 10.

Teléfono: 6386200 Fax: 6386201

E-Mail: filings@olarteraisbeck.com

IDENTIFICACION

C.C. [X] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número 79.782.747 Bta TP 74.295

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Nacionalidad o Domicilio: BRITANICA

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(6) Título (54) COMPUESTOS QUIMICOS NUEVO TITULO:

Compuestos químicos agonistas A1 de la adenosina

(7) Clasificación Internacional (51) A61K31/70 ; C07D 473/18

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GB	Marzo 20, 2001	0106877.4
GB	Marzo 20, 2001	0106875.8
GB	Marzo 20, 2001	0106871.7

(9) Comprobante de pago No. 61.691 **Fecha** 09-01-03

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

(10) **ANEXOS**

2

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredita la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: BUSQUEDA INTERNACIONAL

(11) **FIGURA CARATERISTICA**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 74.782.747 de Btá T.P. 74.295

Instrucciones para la presentación de los anexos, ver reverso de esta página

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3

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Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 61,691
FECHA : SEPTIEMBRE 1 DE 2003

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
FREDERICK TORRES	CONSIGNACION	BANCO POPULAR	050-00110-6	14578066	29/08/2003	3,870,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
		TOTAL : $	400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

GLAXO GROUP LIMITED.

PODER DE REPRESENTACION

Bilingüe inglés- español otorgado en Brentford, Middlesex, Inglaterra el 13 de agosto de 2003 y firmado por Peter John Giddings, Apoderado y Funcionario autorizado.

Certificado de Notario De Pinna en español firmado por James Kerr Milligan

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
   - Este documento Público
2. ha sido firmado por James Kerr Milligan
3. Quien ejerce funciones de Notario público
4. Lleva el sello del Notario público

CERTIFICADO

5. En Londres
6. El 14 agosto 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la Mancomunidad
8. No. G229474
9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
10. Firma legible de J. Garbrah- Por el Secretario de Estado

Si el documento se usa en un país que no pertenece a la Convención de la Haya del 5 de octubre de 1961 debe pasar por la sección consular de la Misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 21 agosto 03.

26 AGO 2003

Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Ofi.
Inglés - Español - Inglé
Resolución No. 2117 del 7 O.

Yo, el infrascrito **JAMES KERR MILLIGAN**, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

C E R T I F I C O:

QUE es auténtica la firma suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **PETER JOHN GIDDINGS**, cuya identidad me consta, Apoderado de la Sociedad inglesa denominada **"GLAXO GROUP LIMITED"**, Sociedad legalmente constituída y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número **305979**, con domicilio social en Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN, Inglaterra;

QUE el citado Señor Don **PETER JOHN GIDDINGS** está debiday suficientemente autorizado para firmar documentos de esta clase en nombre y representación de dicha Sociedad en virtud de un Poder otorgado por la referida Sociedad fechado 3 de julio de 2002.

Y QUE los objetos para los cuales se otorgó dicho Poder se encuentran dentro de los objetos o actividades de la citada Sociedad, de acuerdo con la Escritura Constitutiva y los Estatutos Sociales, los cuales he tenido a la vista.

Y PARA QUE CONSTE donde y como convenga y fuere necesario expido el presente Certificado que firmo y sello en dicha Ciudad de Londres, el día de hoy ece de agosto del año dos mil tres.

COMO NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
28 AGO 2003
BOGOTA, D.C. - COLOMBIA
NOTARIA ONCE (11)

JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra

SCRIVENER NOTARIES

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by — James Kerr Milligan
   a été signé par

3. Acting in the capacity of — Notary Public
   agissant en qualité de

4. Bears the seal/stamp of — The Said Notary Public
   est revêtu du sceau/timbre de

Certified/Attesté

5. at London/à Londres

6. the/le 14 August 2003

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
   par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No — G229474

9. Stamp:
   timbre:

10. Signature: J. Garbrah

FOREIGN AND COMMONWEALTH OFFICE LONDON

For the Secretary of State / Pour le Secrétaire d'Etat

DMO NOTARIO ONCE DE BOTE
RCULO HAGO CONSTAR QUE ESTA
OTOCOPIA COINCIDE CON EL
IGINAL QUE HE TENIDO A LA VISTA.
29 AGO 2003
BOGOTA, D.C., COLOMBIA
NARIO DE BAUTISTA
A ONCE (11)

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country.

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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BOGOTA, COLOMBIA
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FAX: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned,

Glaxo Group Limited

domiciled in

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents, Utility Models and Industrial Designs** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

Glaxo Group Limited

domiciliado en

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB

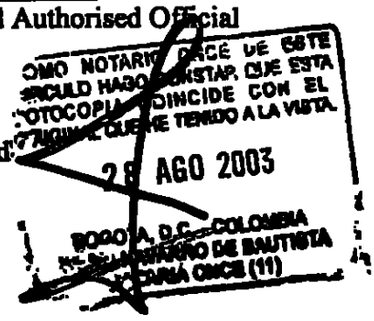
por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad y Diseños Industriales** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: _____

Peter John GIDDINGS as Attorney and Authorised Official

Date/Fecha: 13 August 2003

City,Country/Ciudad,País: Brentford, Middlesex, England



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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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)*: HALL, Adrian [GB/GB]; GlaxoSmithKline, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). JANDU, Karamjit, Singh [GB/GB]; GlaxoSmithKline, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). LUNNIS, Christopher, James [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). VINADER, Maria, Victoria [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). WEST, Robert, Ian [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(74) Agent: GIDDINGS, Peter, John; GlaxoSmithKline, Corporate Intellectual Property, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, 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, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, 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, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CHEMICAL COMPOUNDS

(57) Abstract: The present invention is concerned with pharmaceutical compositions containing certain adenosine derivatives having an acetylene group in the 4' position, which are adenosine A1 agonists, and to their use in therapy.

WO 02/074780 A1

CHEMICAL COMPOUNDS

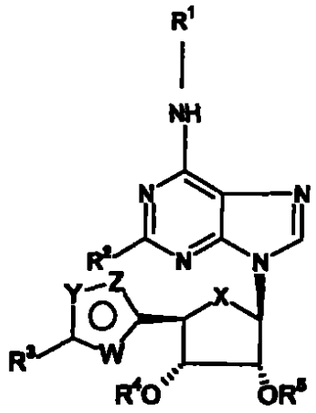
Field of the Invention

The present invention is concerned with pharmaceutical compositions containing certain adenosine derivatives having an acetylene group in the 4' position, which are adenosine A1 agonists, and to their use in therapy. In particular, it is concerned with the use of these adenosine derivatives in treating conditions 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, sleep apnoea or emesis.

Background of the Invention

A variety of compounds which are agonists at the adenosine A1 receptor have been described in the art. These include compounds described in published patent applications WO99/24449, WO99/24450, WO99/24451, WO97/43300, WO98/16539, WO98/04126, WO98/01459, EP0322242, GB2226027, EP222330, WO98/08855, WO94/0707, WO99/67262 and WO00/23447.

For example, WO 99/67262 (Glaxo Group Limited) discloses compounds of formula (I) which are agonists at the adenosine A1 receptor and their use in 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:



(I)

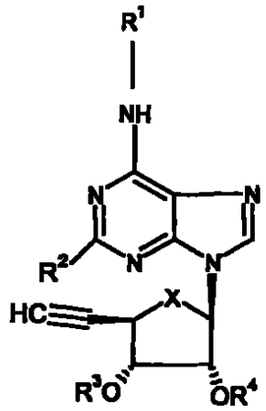
wherein Y and Z represent O, N, CH, N(C_{1-6} alkyl);
W represents CH, O, N, S, N(C_{1-6} alkyl);
and wherein at least one of W and Z represents a heteroatom (and when Y, Z and/or W is N, the presence or absence of an additional H would be apparent to a person skilled in the art);
with the proviso that when W represents CH, Z represents N and Y represents O, R^3 cannot be H.

The compounds disclosed in WO99/67262 (Glaxo Group Limited) are made, for example, via intermediates which have an acetylene group in the 4' position.

The present inventors have surprisingly found that adenosine derivatives with an acetylene group in the 4' position exhibit Adenosine A1 agonist activity.

Summary of the Invention

The present invention provides compounds of formula (Ia):



(Ia)

wherein X represents O or CH_2;

R^1 represents:

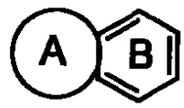
(i) -(alk)$_n$-(C_{3-8})cycloalkyl or -(alk)$_n$-(C_{3-8})cycloalkenyl, said cycloalkyl or cycloalkenyl group being optionally substituted by one or more substituents selected from OH, halogen, C_{1-6}alkyl, -C_{1-6}alkoxy, C_{2-6}alkenyloxy-, C_{2-6}alkynyloxy- and phenyl, wherein (alk) represents C_{1-3}alkyl and n represents 0 or 1, and said (alk) group may be optionally substituted by a C_{3-8}cycloalkyl group;

(ii) a phenyl group optionally substituted by one or more substituents selected from: halogen, CF_3, cyano, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, C_{1-6}alkoxy-, -C_{1-6}alkylOH, -CO_2H and -CO_2C_{1-6} alkyl;

(iii) a C_{4-7}heterocyclic group containing at least one heteroatom selected from O, N or S, and optionally substituted by one or more substituents selected from: OH, -C_{1-6}alkyl, -C_{1-6}alkoxy, -CO_2C_{1-4}alkyl, -COC_{1-4}alkyl, -CO_2aryl or -CO_2(alk)$_n$(C_{3-8})cycloalkyl, wherein (alk) represents C_{1-3}alkyl and n represents 0 or 1;

(iv) a straight or branched C_{1-12}alkyl group optionally substituted by one or more groups selected from phenyl, halogen, hydroxy, and C_{3-7} cycloalkyl, wherein one or more carbon atoms of the C_{1-12}alkyl group may be optionally replaced by a group independently selected from S(=O)$_n$ (where n is 0, 1 or 2) and N;

(v) a fused bicyclic ring



wherein A represents C_{4-6}cycloalkyl or phenyl and B represents phenyl optionally substituted by C_{1-3}alkyl, and the bicyclic ring is attached to the purine-6-amino moiety via a ring atom of ring A;

R^2 represents -C_{1-3}alkyl, halogen, hydrogen or C_{1-3}alkoxy group;

R^3 and R^4 independently represent H or a -C_{1-6}alkyl group;

or pharmaceutically acceptable derivatives thereof.

Further aspects of the invention are:

- A pharmaceutical composition comprising a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof together with a pharmaceutical carrier and/or excipient.

- Use of a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof 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.

- Use of a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a patient suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke or which subject is suffering pain, a CNS disorder, sleep apnoea or emesis.

- 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 comprising administering a therapeutically effective amount of a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof.

- A method of treating a patient suffering or susceptible to ischaemic heart disease, peripheral vascular disease or stroke or which subject is suffering

pain, a CNS disorder, sleep apnoea, or emesis comprising administering a therapeutically effective amount of a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof.

Detailed Description of the Invention

The compounds useful in the invention are agonists at the adenosine A1 receptor. Preferably they are selective agonists at the adenosine A1 receptor. By selective is meant that the affinity for the A1 receptor is at least 2 times, preferably 5 times and more preferably 10 times greater than the other adenosine receptor subtypes, particularly A3. Agonist selectivity of compounds against other human adenosine receptors can be 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, KV. and Spevak, W. (1994) *Biochem. Biophys. Res. Commun.* 198, 626-631. The CHO cells are also transfected with cyclic AMP response elements promoting the gene for secreted placental alkaline phosphatase (SPAP) (Wood, KV. (1995) *Curr. Opinion. Biotechnology*, 6, 50-58). The effect of test compounds is 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 are determined as a ratio to that of the non-selective agonist N-ethyl carboxamidoadenosine (NECA). "Adenosine receptors: New opportunities for future drugs" (S.A. Poulsen *et al*, *Bioorg. Med. Chem*,. 1998, 6, 619-641) summarises disease conditions that may be treated with adenosine A1 agonists.

The compounds of formula (Ia) contain chiral (asymmetric) centres. The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are within the scope of the present invention.

As used herein, the terms "alkyl" and "alkoxy" mean both straight and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl, ethyl, propyl and butyl groups. Examples of alkoxy groups include methoxy and ethoxy groups. Other examples include propoxy and butoxy. Alkyl groups may

be unsubstituted, or substituted with one to four substituents, preferably one to three substituents as defined hereinabove.

One to three, preferably one or two, carbon atoms of an alkyl chain may be replaced by a group independently selected from $S(=O)_n$ (where n is 0, 1 or 2) and N. When the heteroatom N replaces a carbon atom in a C_{1-12}alkyl group the N atom will, where appropriate be substituted by one or two substituents selected from hydrogen and C_{1-6}alkyl.

As used herein, the terms "alkenyl", "alkenyloxy", "alkynyl" and "alkynyloxy" mean both straight and branched chain unsaturated hydrocarbon groups. Examples of alkenyl groups include ethylene and propylene. Examples of alkynyl groups include ethynyl and propynyl. Examples of alkenyloxy groups include propenyloxy and ethenyloxy. Examples of alkynyloxy groups include propynyloxy and ethylyloxy.

As used herein, the term "halogen" means fluorine, chlorine, bromine or iodine.

As used herein, the term "aryl" means monocyclic or bicyclic aromatic carbocyclic groups such as phenyl and naphthyl, especially phenyl.

As used herein, the term "cycloalkyl" means an aliphatic group having 3 to 9 carbon atoms in the ring system unless otherwise defined. The cycloalkyl group can be monocyclic or bicyclic. A bicyclic group may be fused or bridged. Examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl and cyclopentyl. Other examples of monocyclic cycloalkyl groups are cyclohexyl, cycloheptyl and cyclooctyl. Examples of bicyclic cycloalkyl groups include bicyclo[2.2.1]hept-2-yl. Preferably, the cycloalkyl group is monocyclic. Cycloalkyl groups may be unsubstituted, or substituted with one to four substituents, preferably one or two substituents as defined hereinabove.

As used herein, the term "cycloalkenyl" means a partially unsaturated aliphatic group having 3 to 9 carbon atoms in the ring system. The cycloalkenyl group can be monocyclic or bicyclic. Preferably, the cycloalkyl group is monocyclic. Examples of monocyclic cycloalkenyl groups include cyclopentenyl and

cyclohexenyl. Cycloalkenyl groups may be unsubstituted, or substituted with one to four substituents, preferably one or two substituents.

As used herein, the term "heterocyclic" means a cyclic group of 4 to 7 carbon atoms wherein one or more of the carbon atoms is/are replaced by heteroatoms independently selected from nitrogen, oxygen or sulfur. The heterocycle may be aromatic or non-aromatic, i.e., may be saturated (i.e. aliphatic), partially or fully unsaturated. This group may optionally be substituted as defined hereinabove. The heteroatom is preferably O or N. The heterocycle is preferably non-aromatic. Examples of heterocyclyl groups include piperidinyl, tetrahydrofuranyl and tetrahydropyranyl. Cycloalkyl groups may be unsubstituted, or substituted with one to four substituents, preferably one or two substituents. Heterocyclyl groups may be unsubstituted, or substituted with one to four substituents, preferably one or two substituents.

As used herein, the term "pharmaceutically acceptable derivative", means any pharmaceutically acceptable salt, solvate, ester or amide, or salt or solvate of such ester or amide, of the adenosine A1 agonist, or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) the adenosine A1 agonist or an active metabolite or residue thereof, e.g. a prodrug. Preferred pharmaceutically acceptable derivatives according to the invention are any pharmaceutically acceptable salts, solvates and prodrugs, more preferably pharmaceutically acceptable salts and solvates.

As used herein, the term "pharmaceutically acceptable" means a compound which is suitable for pharmaceutical use.

Pharmaceutically acceptable salts of the compounds of formula (Ia) include those derived from pharmaceutically acceptable inorganic and organic acids. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful as

intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of the compound of formula (Ia) are within the scope of the invention.

As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, *Prodrugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series; and in Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

In an alternative aspect R^1 represents:

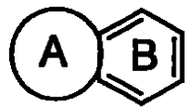
(i) -(alk)$_n$-(C_{3-9})cycloalkyl, including bridged cycloalkyl, optionally substituted by one or more substituents selected from OH, halogen, C_{1-3}alkoxy- and phenyl, wherein (alk) represents C_{1-6}alkyl and n represents 0 or 1;

(ii) a phenyl group optionally substituted by one or more substituents selected from: halogen, CF_3, cyano, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, C_{1-6} alkoxy-, -C_{1-6}alkylOH, -CO_2H and -CO_2C_{1-6} alkyl;

(iii) a C_{4-7}heterocyclic group containing at least one heteroatom selected from O, N or S, and optionally substituted by one or more substituents selected from: OH, -C_{1-6}alkyl, -C_{1-6}alkoxy, -$CO_2(C_{1-4})$alkyl, -$CO(C_{1-4})$alkyl or -CO_2aryl;

(iv) a straight or branched C_{1-12}alkyl substituted by one or more groups selected from: $S(=O)_n$ (where n is 0, 1 or 2) substituted within the alkyl chain, N substituted within the alkyl chain, phenyl, halogen, hydroxy or C_{3-7} cycloalkyl;

(v) a fused bicyclic ring



wherein A represents C_{4-6}cycloalkyl or phenyl and B represents phenyl optionally substituted by C_{1-3}alkyl, and the bicyclic ring is attached to the nitrogen atom of formula (I) via a ring atom of ring A.

In a further aspect R^1 represents:

(i) -$(alk)_n$-(C_{3-9})cycloalkyl, said cycloalkyl group being optionally substituted by one or more substituents selected from: OH, halogen, -C_{1-6} alkyl, C_{1-6} alkoxy-, and phenyl, wherein (alk) represents C_{1-3}alkyl and n represents 0 or 1;

(ii) a C_{4-7}aliphatic heterocyclic group containing at least one heteroatom selected from O, N or S, optionally substituted by one or more substituents selected from: -C_{1-6}alkyl, -$CO(C_{1-4})$alkyl, -$CO_2(C_{1-4})$alkyl, and -CO_2phenyl;

(iii) a straight or branched C_{1-12}alkyl group optionally substituted by one or more groups selected from: phenyl, $S(=O)_n$ (where n is 0, 1 or 2) and N wherein each $S(=O)_n$ or N replaces a carbon of the alkyl group.

In a further aspect R^1 represents a phenyl group optionally substituted by one or more substituents selected from: halogen, CF_3, cyano, -C_{1-6}alkyl, -C_{2-6}alkenyl, -(C_{2-6})alkynyl, (C_{1-6})alkoxy-, -(C_{1-6})alkylOH, -CO_2H and -$CO_2(C_{1-6})$alkyl.

In a yet further aspect R^1 represents phenyl optionally substituted by one or more substituents selected from: halogen and –C_{1-6}alkyl; R^2 represents hydrogen or halogen; and R^3 and R^4 independently represent H or –C_{1-6}alkyl.

Conveniently, R^1 may represent $(alk)_n$-(C_{3-9})cycloalkyl wherein n is 0 or 1 and the said cycloalkyl is either unsubstituted or substituted by at least one substituent selected from -C_{1-6}alkyl, C_{1-6}alkoxy-, phenyl and OH. Alternative substituents include at least one substituent selected from halogen, and C_{2-6} alkenyloxy-. Preferably the cycloalkyl group is unsubstituted or monosubstituted by C_{1-3}alkyloxy-, C_{2-3}alkenyloxy-, -C_{3-6}cycloalkyl, C_{1-3} alkyl, phenyl or OH, or is mono- or disubstituted by halogen, for example fluorine. Alternatively the cycloalkyl

group is unsubstituted or substituted with OH or C_{1-3} alkyl. Preferably n is zero. Preferably the cycloalkyl ring has 3 to 8 carbon atoms, more preferably 5 or 6 carbon atoms. Cycloalkyl groups include hydroxycyclopentyl or methoxycyclohexyl. Other cycloalkyl groups include propenyloxycyclohexyl, difluorocyclohexyl, ethoxycyclohexyl, dicyclopropylmethyl, cyclooctyl and cycloheptyl. When n is 1, the (alk) group may be substituted, for example by cyclopropyl.

R^1 may represent $(alk)_n$-(C_{3-8})cycloalkenyl wherein n is 0 or 1 and the said cycloalkenyl is either substituted by at least one substituent selected from -C_{1-8}alkyl, C_{1-8}alkoxy-, phenyl and OH or is unsubstituted. Alternative substituents include at least one substituent selected from halogen, -C_{2-8} alkenyloxy, and -C_{3-8} cycloalkyl. Preferably n is zero. More preferably, the cycloalkenyl group is unsubstituted. Preferably the cycloalkenyl ring has 5 or 6 carbon atoms, more preferably the ring is cyclohexenyl.

Alternatively, R^1 may represent a substituted or unsubstituted aliphatic heterocyclic group, the substitutent being selected from C_{1-8}alkyl, -$CO_2(C_{1-4})$alkyl or -CO_2phenyl. The substituent may also be -$CO_2(alk)_n(C_{3-8})$cycloalkyl. Preferably the heterocyclic ring is 6 membered and more preferably contains only one O or N heteroatom. Conveniently, the aliphatic heterocyclic group is unsubstituted or, when substituted, the substituent is -$CO_2(C_{1-4})$alkyl or -$CO_2(alk)_n(C_{3-8})$cycloalkyl, the heteroatom is N and the substituent is directly attached to said ring nitrogen atom. Preferably when the heterocycle is substituted the substituent is -$CO_2(C_{1-4})$alkyl, the heteroatom is N and the substituent is directly attached to said ring nitrogen atom. Most preferably when the heterocyclic ring is unsubstituted the heteroatom is O. Most preferably when the heterocyclic ring is substituted the heteroatom is N.

Alternatively, R^1 may represent a straight or branched alkyl of 1-6 carbon atoms including one or more $S(=O)_n$ groups (where n is 0, 1 or 2) each replacing a carbon atom of the alkyl group, optionally substituted with N replacing a carbon atom at a position adjacent to the $S(=O)_n$ group. Preferably n is 1 or 2, more preferably n is 2.

Alternatively, R^1 may represent phenyl optionally substituted one or two substitutents selected from halogen or C_{1-6}alkyl. More preferably, R^1 preferably represents phenyl optionally substituted one or two substitutents selected from halogen or methyl. Preferably the halogen is fluorine, chlorine or bromine, more preferably fluorine or chlorine. Preferably the phenyl is disubstituted. Preferably the phenyl is disubstituted in the 2,3 or 2,4 or 2,5 positions. In an alternative aspect the phenyl is monosubstituted by C_{1-6} alkyl, for example methyl.

In a preferred aspect of the invention, R^1 represents:

(i) -$(alk)_n(C_{3-9})$ cycloalkyl, said cycloalkyl group being optionally substituted by one or more substituents selected from OH, halogen, C_{1-6}alkyl, -C_{1-6}alkoxy, C_{2-6}alkenyloxy- and phenyl, wherein (alk) represents C_{1-3}alkyl and n represents 0 or 1, and said (alk) group may be optionally substituted by a C_{3-6}cycloalkyl group; or R^1 represents $(alk)_n$-(C_{3-9})cycloalkenyl;

(ii) a C_{4-7}heterocyclic group containing at least one heteroatom selected from O or N, optionally substituted by -C_{1-6}alkyl, -CO_2C_{1-4}alkyl, or -$CO_2(alk)_n(C_{3-6})$cycloalkyl; or

(iii) phenyl optionally substituted by halogen or C_{1-6}alkyl.

In an alternative aspect of the invention, R^1 represents:

(i) -$(alk)_n(C_{3-9})$ cycloalkyl, including bridged cycloalkyl, said cycloalkyl group being optionally substituted by one or more substituents selected from OH, C_{1-6} alkyl, C_{1-6} alkoxy, and phenyl, wherein (alk) represents C_{1-3}alkyl and n represents 0 or 1;

(ii) a C_{4-7} heterocyclic group containing at least one heteroatom selected from O or N, optionally substituted by -C_{1-6}alkyl, or -CO_2C_{1-4}alkyl; or

(iii) phenyl optionally substituted by halogen or C_{1-6}alkyl.

In another aspect of the invention, R^1 represents:

(i) -$(alk)_n$-(C_{3-9})cycloalkyl, including bridged cycloalkyl, said cycloalkyl group optionally substituted by one or more substituents selected from OH, -C_{1-6}alkyl, -C_{1-6}alkoxy, and phenyl; wherein (alk) represents C_{1-3}alkyl and n represents 0 or 1; or

(ii) a C_{4-7} aliphatic heterocyclic group containing at least one heteroatom selected from O or N, optionally substituted by $-C_{1-6}$alkyl or $-CO_2C_{1-4}$alkyl.

R^2 preferably represents hydrogen or halogen. More preferably, R^2 represents hydrogen or chlorine. Most preferably, R^2 represents hydrogen.

R^3 and R^4 preferably both represent hydrogen.

X preferably represents O.

When R^1 is C_{1-12}alkyl, the group is preferably substituted.

It is to be understood that the present invention covers all combinations of particular and preferred groups mentioned above.

Preferred compounds of the invention include:
(2R,3R,4S,5R)-2-{6-[(4-chloro-2-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{2-chloro-6-[(4-chloro-2-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(2-chloro-4-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(4-fluoro-2-methylphenyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(2,4-difluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(3-fluoro-2-methylphenyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(3-chloro-2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(4-chloro-2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(5-chloro-2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6-[(2-bromo-4-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{2-chloro-6-[(3-fluoro-2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(3,4-difluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
N-ethyl-2-({9-[(2R,3R,4S,5R)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)ethanesulfonamide;
ethyl 4-({9-[(2R,3R,4S,5R)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate;
(2R,3R,4S,5R)-5-ethynyl-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-[6-indan-2-ylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-[6-(cyclobutylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(2-phenylethyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-[6-(cyclohexylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-(6-{[(1S*,2S*,3S*,4R*)-3-methylbicyclo[2.2.1]hept-2-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-(6-{[(1R*,*2S)-2-methoxy-2-phenylcyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-[6-(cyclopropylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(cyclopropylmethyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-[6-(cyclopentylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-(6-{[(2R,3R)-2-methyltetrahydrofuran-3-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-(6-{[(2S,3S)-2-methyltetrahydrofuran-3-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;

(2R,3R,4S,5R)-5-ethynyl-2-{6-[(trans-4-methoxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
2R,3R,4S,5R)-5-ethynyl-2-{6-[(trans-4-ethoxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
2R,3R,4S,5R)-5-ethynyl-2-{6-[(trans-4-propenyloxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(1R*,5R*,6S*)-bicyclo[3.2.0]hept-6-ylamino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(2,2-dimethylcyclopropyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(trans-4-hydroxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(4-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(3-chloro-2-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(2-fluoro-5-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
butyl 4-({9-[(2R,3R,4S,5R)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate;
cyclopropylmethyl 4-({9-[(2R,3R,4S,5R)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate;
(2R,3R,4S,5R)-5-ethynyl-2-{(6-[(1S,2S)-2-methoxycyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(4,4-difluoro)cyclohexyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(cyclohex-3-enyl)amino]}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-[6-(dicyclopropylmethyl)amino]-9H-purin-9-yl)tetrahydrofuran-3,4-diol;

(2R,3R,4S,5R)-5-ethynyl-2-[6-(cyclooctyl)amino]-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-[6-(cycloheptyl)amino]-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(1R*,4S*)-4-methoxy-cyclohept-2-enylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol; or
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(1S*,4R*)-4-methoxy-cyclohept-2-enylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol.

Particularly preferred compounds of the invention include:
(2R,3R,4S,5R)-2-{6-[(2-chloro-4-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(4-fluoro-2-methylphenyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(3-fluoro-2-methylphenyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(3-chloro-2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(4-chloro-2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
ethyl 4-({9-[(2R,3R,4S,5R)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate;
(2R,3R,4S,5R)-5-ethynyl-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(trans-4-methoxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
2R,3R,4S,5R)-5-ethynyl-2-{6-[(trans-4-ethoxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
2R,3R,4S,5R)-5-ethynyl-2-{6-[(trans-4-propenyloxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(1R*,5R*,6S*)-bicyclo[3.2.0]hept-6-ylamino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol; or

(2R,3R,4S,5R)-2-{6-[(2,2-dimethylcyclopropyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol.

Compounds according to the invention have applicability as inhibitors of lipolysis i.e. they decrease plasma free fatty acid concentrations. The compounds may thus be used in the treatment of hyperlipidaemias. Furthermore, as a consequence of their anti-lipolytic activity, the compounds have the ability to lower elevated blood glucose, insulin and ketone body levels and therefore may be of value in the therapy of diabetes. Since anti-lipolytic agents have hypolipidaemic and hypofibrinogenaemic activity, the compounds may also show anti-atherosclerotic activity. The assay described by P. Strong *et al.* in *Clinical Science* (1993), 84, 663-669 may be used to determine the anti-lipolytic activity of compounds of the invention by their ability to lower the concentration of non-esterified fatty acids (NEFA) in starved rats.

In addition to their anti-lipolytic effect, the compounds of the invention may independently affect cardiac function by reducing heart rate and conduction. The compounds may thus be used in the therapy of a number of cardiovascular disorders, for example cardiac arrythmias, particularly following myocardial infarction, and angina. The compounds may also inhibit renin release and thus be of use in the therapy of hypertension and heart failure.

Furthermore, the compounds of the invention are useful as cardioprotective agents, having applicability in the treatment of ischaemic heart disease. As used herein the term "ischaemic heart disease" includes damage associated with both myocardial ischaemia and reperfusion, for example, associated with coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), cardioplegia, acute myocardial infarction, thrombolysis, stable and unstable angina and cardiac surgery including in particular cardiac transplantation. The compounds of the invention additionally are useful for treating ischaemic damage to other organs. The compounds of the invention may also be valuable in the treatment of other disorders arising as a result of widespread atheromatous disease, for example, peripheral vascular disease (PVD) and stroke.

The compounds of the invention may also be useful as CNS agents (e.g. as hypnotics, sedatives, analgestics and/or anti-convulsants particularly finding use in the treatment of epilepsy). They are therefore useful in treating or preventing pain. They may be used to improve the condition of a host, typically of a human being, suffering from pain. They may be employed to alleviate pain in a host. Thus, a compound of formula (Ia) and its pharmaceutically acceptable acid addition salts may be used as a preemptive analgesic to treat acute pain such as musculoskeletal pain, post operative pain and surgical pain, chronic pain such as chronic inflammatory pain (e.g. rheumatoid arthritis and osteoarthritis), neuropathic pain (e.g. post herpetic neuralgia, diabetic neuropathies associated with diabetes, trigeminal neuralgia, pain associated with functional bowel disorders, e.g. irritable bowel syndrome, non cardiac chest pain and sympathetically maintained pain) and pain associated with cancer and fibromyalgia. The compound of formula (Ia) may also be used in the treatment or prevention of migraine or of pain associated with migraine, tension headache and cluster headaches, pain associated with functional bowel disorders (e.g. IBS), non cardiac chest pain and non ulcer dyspepsia. The compound of formula (Ia) may also be used in the treatment of nociceptive pain (e.g. headaches, labour pain, menstrual pain and early post-operative pain).

In addition, the compounds of the invention may find use in the treatment of sleep apnoea.

In addition, the compounds of the invention may find use in the treatment of emesis. Treatment of emesis includes treatment of nausea, retching and vomiting. Emesis includes acute emesis, delayed emesis and anticipatory emesis.

Accordingly, the invention provides a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof for use in therapy, and in particular in the treatment of human or animal subjects suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or whereby the therapy involves the treatment of ischaemic heart disease, peripheral vascular disease

or stroke or which subject is suffering from a pain, a CNS disorder, sleep apnoea or emesis.

In another aspect, the invention provides a method of treatment of a human or animal subject suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke, or which subject is suffering from pain, a CNS disorder, sleep apnoea or emesis, which method comprises administering to the subject an effective amount of a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof.

In another aspect the invention also provides for the use of a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of human or animal subjects suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease (PVD) or stroke, or which patient is suffering from pain, a CNS disorder, sleep apnoea or emesis.

In respect of the above mentioned ischaemic treatment, the methods of the present invention are applicable not only where ischaemia is planned or expected, for example in cardiac surgery, but also in cases of sudden or unexpected ischaemia, for example in heart attack and unstable angina.

In a preferred aspect, the invention provides a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof for use in therapy, and in particular in the treatment of human or animal subjects of conditions associated with pain including acute pain, chronic pain, inflammatory pain, neuropathic pain, nociceptive pain and pain associated with migraine, tension headaches, cluster headaches and functional bowel disorder. In an alternative embodiment, the invention provides a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof for use in therapy, and in particular in the treatment of human or animal subjects of conditions associated with pain including acute pain,

chronic pain, inflammatory pain, neuropathic pain and pain associated with migraine, tension headaches, cluster headaches and functional bowel disorder.

In another aspect, the invention provides a method of treatment of a human or animal subject suffering from a condition associated with pain including acute pain, chronic pain, inflammatory pain, neuropathic pain, nociceptive pain and pain associated with migraine, tension headaches, cluster headaches and functional bowel disorder; alternatively acute pain, chronic pain, inflammatory pain, neuropathic pain and pain associated with migraine, tension headaches, cluster headaches and functional bowel disorder; which method comprises administering to the subject an effective amount of a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof.

In another aspect the invention also provides for the use of a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of human or animal subjects suffering from a condition associated with pain including acute pain, chronic pain, inflammatory pain, neuropathic pain, nociceptive pain and pain associated with migraine, tension headaches, cluster headaches and functional bowel disorder. In an alternative embodiment the invention provides for the use of a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of human or animal subjects suffering from a condition associated with pain including acute pain, chronic pain, inflammatory pain, neuropathic pain and pain associated with migraine, tension headaches, cluster headaches and functional bowel disorder.

It will be appreciated that reference to treatment includes acute treatment or prophylaxis as well as the alleviation of established symptoms.
While it is possible that compounds of the invention may be administered as the raw material, it is preferable to present the active ingredient as a pharmaceutical formulation.

In a further aspect, the invention provides a pharmaceutical composition comprising at least one compound of formula (Ia) or a pharmaceutically acceptable derivative thereof in association with a pharmaceutically acceptable

carrier and/or excipient. The carrier and/or excipient must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the receipient thereof.

In another aspect, the invention provides a pharmaceutical composition comprising, as active ingredient, at least one compound of formula (Ia) or a pharmaceutically acceptable derivative thereof in association with a pharmaceutically acceptable carrier and/or excipient for use in therapy, and in particular in the treatment of human or animal subjects suffering from a condition in which there is an advantage in decreasing plasma free fatty acid concentration, or reducing heart rate and conduction, or which subject is suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke, or which subject is suffering from a CNS disorder, sleep apnoea, pain or emesis.

There is further provided by the present invention a process of preparing a pharmaceutical composition, which process comprises mixing at least one compound of formula (Ia) or a pharmaceutically acceptable derivative thereof, together with a pharmaceutically acceptable carrier and/or excipient.

Compositions according to the invention may be formulated for topical, oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation. Oral administration is preferred. The compositions may be adapted for sustained release.

For topical administration, the pharmaceutical composition may be given in the form of a transdermal patch.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, microcrystalline cellulose or maize-starch; lubricants, for example, magnesium stearate or stearic acid; 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, or carboxymethyl cellulose; emulsifying agents, for example, sorbitan mono-oleate; non-aqueous vehicles (which may include edible oils), for example, propylene glycol or ethyl alcohol; and preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and 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 of formula (Ia) or pharmaceutically acceptable derivatives thereof may be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing 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 compounds of formula (Ia) or pharmaceutically acceptable derivatives thereof may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

A proposed dose of the compounds of the invention for administration to man (of approximately 70kg body weight) is 0.1mg to 2g, preferably 1mg to 2g, more preferably 1mg to 100mg, of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient. The dosage will also depend on the route of administration.

The compounds of formula (Ia) may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a

combination comprising a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent.

When a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Suitable second therapeutic agents for the treatment of pain include, for example, COX-2 inhibitor e.g. celecoxib, rofecoxib, valdecoxib, parecoxib, 4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluorobenzenesulfonamide (JTE-522), MK663, nimesulide, DFP, 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine; 5HT1 agonists e.g. sumatriptan, naratriptan, zolmitriptan, eletriptan, rizatriptan, frovatriptan, almotriptan, alniditan, dihydroergotamine, donitriptan, PNU-142633, ALX-0646, LY334370, U1092291, IS159, PNY142633; sodium channel blockers e.g. lamotrigine, R(-)-2,4-diamino-5-(2,3-dichlorophenyl)-6-fluoromethyl pyrimidine, 2,6-diamino-3-(2,3,5-trichlorophenyl)pyrazine, 5-amino-6-[2,3,5-trichlorophenyl]-1,2,4-triazine; 5HT3 antagonists e.g. alosetron; gabapentin; pregabalin; EP1 antagonists e.g. ZD6416, ZD6804; and opioids e.g. alfentanil, buprenorphine, codeine, dextropropoxyphene, diamorphine, dihydrocodeine, fentanyl, methadone, morphine, oxycodone, levorphanol, pentazocine, pethidine.
The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise 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 by any convenient route.

When administration is sequential, either the adenosine A1 agonist or the second therapeutic agent may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition.

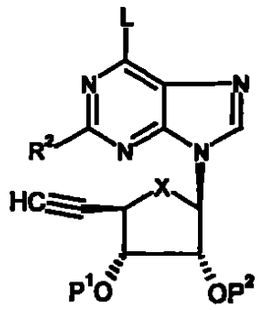
When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other

components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

When a compound of formula (Ia) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian.

The compounds of formula (Ia) and pharmaceutically acceptable derivatives thereof may be prepared by the processes described hereinafter, said processes constituting a further aspect of the invention. In the following description, the groups X, R^1, R^2 and R^3 are as defined for compounds of formula (Ia) unless otherwise stated.

According to a first general process (A), a compound of formula (Ia) may be prepared by reacting a compound of formula (II):



(II)

wherein L represents a leaving group such as a halogen atom (e.g. chlorine), HOBT or a linker group capable of binding to a solid phase polymeric support (e.g. a polystyrene resin) and for example may be $-SO_2C_{1-4}$alkylene and P^1 and P^2 represent hydrogen, C_{1-6} straight chain or branched alkyl or a suitable protecting group (e.g. acetyl or a protecting group wherein P^1 and P^2 together

form an alkylidene group) with a compound of formula R^1NH_2 or a salt thereof under basic or buffered conditions, where R^1, R^2 and X are as defined for compounds of formula (Ia).

Compounds of formula (II) may be used to produce compounds of formula (Ia) directly by reaction with the group R^1NH_2, where R^1 is as defined for compounds of formula (Ia), either in the absence or presence of a solvent such as an alcohol (e.g. a lower alkanol such as isopropanol, t-butanol or 3-pentanol), an ether (e.g. tetrahydrofuran or dioxan), a substituted amide (e.g. dimethylformamide), a halogenated hydrocarbon (e.g. chloroform), an aromatic hydrocarbon (.g. toluene), dimethyl sulfoxide (DMSO) or acetonitrile, preferably at an elevated temperature (e.g. up to the reflux temperature of the solvent), in the presence of a suitable acid scavanger, for example, inorganic bases such as sodium, cesium or potassium carbonate, or organic bases such as triethylamine, diisopropylethylamine or pyridine, optionally in the presence of a palladium catalyst (e.g. palladium acetate) and phosphine ligand (e.g. R-(+/-)-2,2'-bis(diphenylphosphino)-1-1' binaphthyl).

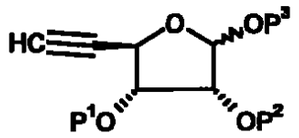
Alternatively, compounds of formula (II) may be used to produce compounds of formula (Ia) by reaction with the group R^1NH_2, where R^1 is as defined for compounds of formula (Ia), in the presence of $CaCO_3$ and an appropriate solvent, e.g. ethanol or acetic acid. Preferably when the solvent is ethanol the reaction is heated, for example at reflux. In an alternative aspect the reaction may be carried out in acetic acid in the absence of $CaCO_3$, preferably the reaction is heated.

The above reactions may be preceded or followed where appropriate by in situ removal of the P^1 and P^2 protecting groups. For example when P^1 and P^2 represent acetyl, this may be effected with an amine such as ammonia or tert-butylamine or an alkoxide such as sodium methoxide in a solvent such as methanol or when P^1 and P^2 represent an alkylidene by acid hydrolysis, e.g. with trifluoroacetic acid (TFA). Interconversion of P^1 and P^2 protecting groups may occur at any stage in the preparation of the compounds of formula (II), for example when P^1 and P^2 represent acetyl, compounds of formula (II) may be prepared from compounds wherein P^1 and P^2 together represent an alkylidene

protecting group by acid catalysed removal of the alkylidene protecting group, e.g. with hydrogen chloride in methanol followed by *in situ* acylation, for example with acetic anhydride in the presence of a base such as pyridine, in a solvent such as dichloromethane.

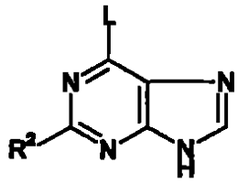
Otherwise, interconversion of P^1 and P^2 protecting groups may occur at any stage during the preparation of compounds of formula (II).

Compounds of formula (II) may be prepared by methods described in WO99/67262. For example, compounds of formula (II) where X = O may be prepared by reacting compounds of formula (III):



(III)

wherein P^3 represents a suitable protecting group, for example acetyl, or a substituent such as C_{1-3} alkyl, and P^1 and P^2 are as defined above, with compounds of formula (IV):



(IV)

wherein L and R^2 are as defined above.

The reaction is conveniently carried out in a suitable solvent, such as acetonitrile in the presence of a silylating agent such as trimethylsilyl trifluoromethane sulfonate and a base such as diazabicyclo[5.4.0]undec-7-ene (DBU). Alternatively the compound of formula (IV) may first be silylated with a suitable silylating agent e.g. hexamethyldisilazane followed by reaction of the silylated intermediate with a compound of formula (III) and a suitable Lewis acid, e.g. trimethylsilyl trifluoromethanesulfonate in a suitable solvent such as acetonitrile.

Compounds of formula (IV) are either known in the art or may be prepared from known compounds using methods analogous to those used to prepare the known compounds of formula (IV).

As described above, the compounds of formula (III) may be prepared from alternative protected compounds by replacement of the alternate P^1 and P^2 protecting groups with other P^1 and P^2 groups. These represent an exchanging of one protecting group for another and will be apparent to those skilled in the art.

Compounds of formula (III) may be prepared by methods known in the art.

Specific optical isomers of a compound of formula (Ia) may be obtained by conventional methods for example, by synthesis from an appropriate asymmetric starting material using any of the processes described herein, or where appropriate by separation of a mixture of isomers of a compound of formula (Ia) by conventional means e.g. by fractional distillation, fractional crystallisation or chromatography.

In the general processes described above, the compound of formula (Ia) obtained may be in the form of a salt, conveniently in the form of a pharmaceutically acceptable salt. Where desired, such salts may be converted into the corresponding free bases using conventional methods.

Pharmaceutically acceptable acid addition salts of the compounds of formula (Ia) may be prepared by reacting a compound of formula (Ia) with an appropriate acid in the presence of a suitable solvent such as acetonitrile, acetone, chloroform, ethyl acetate or an alcohol (e.g. methanol, ethanol or isopropanol). Pharmaceutically acceptable base addition salts may be obtained in an analogous manner by treating a solution of a compound of formula (Ia) with a suitable base. Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts of the compounds of formula (Ia), using conventional methods.

The present invention will now be further illustrated by the accompanying examples which should not be construed as limiting the scope of the invention in any way.

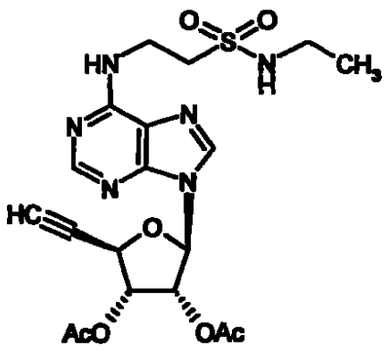
Examples

Definitions of abbreviations used herein: N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), dichloromethane (DCM), tetrahydrofuran (THF), trifluoroacetic acid (TFA) and diazabicyclo[5.4.0]undec-7-ene (DBU).

On occasions (denoted by #) during the reaction some deprotection of the acetate intermediates may occur to give the mono and di-deprotected compounds.

Example 1: N-Ethyl-2-({9-[(2R,3R,4S,5R)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)ethanesulfonamide

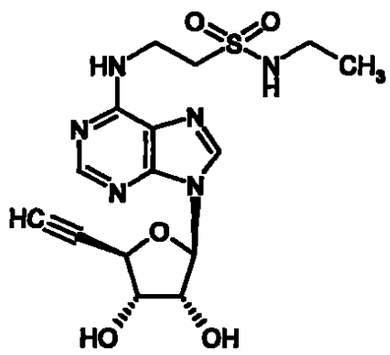
Intermediate 1: (2R,3R,4R,5R)-4-(Acetyloxy)-2-[6-({2-[(ethylamino)sulfonyl]ethyl}amino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate



A solution containing (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate (0.050g), propan-2-ol (1-5ml), diisopropyethylamine(0.095ml) and 2-amino-N-ethylethanesulfonamide (0.041g) was heated to 80°C for 3 to 18 hours. The solvent was removed *in vacuo* to give a gum. (Optional purification) Purification by automated preparative HPLC to give the title compound (0.023g) as a gum. Note on occasions (denoted by #) during the reaction some deprotection of the acetates does occur to give the mono and di-deprotected compounds.
LC/MS Rt 2.76 min.

Mass spectrum *m/z* 481 [MH^+].

Example 1: N-Ethyl-2-({9-[(2R,3R,4S,5R)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)ethanesulfonamide



To a solution of (2R,3R,4R,5R)-4-(acetyloxy)-2-[6-({2-[(ethylamino)sulfonyl]ethyl}amino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate (0.02g) in methanol (2ml) stirred at 5°C(ice bath) was added t-butylamine (0.1ml) and the mixture was stirred for 1 hour at 5°C. The solvent was removed *in vacuo*. Purification by automated preparative HPLC to give the title compound (0.012g) as a white solid
LC/MS Rt 2.29 min.
Mass spectrum *m/z* 397 [MH^+].

The following compounds were made using an analogous route to the above procedure using the appropriate starting materials:

Example 2: Ethyl 4-({9-[(2R,3R,4S,5R)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate

Intermediate 2: Ethyl 4-({9-[(2R,3R,4R,5R)-3,4-bis(acetyloxy)-5-ethynyltetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and ethyl-4-amino-1-piperidine carboxylate.

Example 2: (from Intermediate 2) Ethyl 4-({9-[(2R,3R,4S,5R)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate

^{1}H NMR(MeOD) δ 8.15,8.14 (2H,br.s+s,2xCH), 6.0 (1H,d,CH) ,4.70(1H,t,CH) 4.60(1H,dd,CH), 4.31(1H,dd,CH), 4.23(1H,vbr.m,CH), 4.07-3.98(4H,q+br.m,CH2 + 2xCH eq), 3.16(1H,d,CH), 2.98(2H,br.t, 2xCH ax), 1.96(2H,br.dd, 2xCH eq), 1.45(2H,br.dq, 2xCH ax), 1.17(3H,t,CH_3).
LC/MS(Red) Rt = 2.44min.
Mass Spectrum *m/z* 417 [MH+].

Example 3: (2R,3R,S,5R)-5-Ethynyl-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol

Intermediate 3: (2R,3R,4R,5R)-4-(Acetyloxy)-5-ethynyl-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and (1S, 2S)-2-aminocyclopentanol.

Example 3: (from Intermediate 3) (2R,3R,4S,5R)-5-Ethynyl-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol
^{1}H NMR (MeOD) δ 8.29(1H,s,CH), 8.22(1H,brs,CH), 7.72(1H,br.d,NH), 5.94(1H,d,CH), 5.78 (1Hv.br.s -OH),4.78(1H,br.m,CH) ,4.55(1H,dd,CH), 4.38(1H,t,CH), 4.25(1H,br.m, CH), 4.05(1H,br.m, CH) ,3.75(1H,d,CH) ,3.35(2H, [H_2O],vr.br.s, 2xOH), 2.12-1.43(6H,4xm,3xCH_2).
LC/MS(Blue) Rt = 2.30min.
Mass Spectrum m/z 346 [MH+].

Example 4: (2R,3R,4S,5R)-2-[6-(2,3-Dihydro-1H-inden-2-ylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol

Intermediate 4: (2R,3R,4R,5R)-4-(Acetyloxy)-2-[6-(2,3-dihydro-1H-inden-2-ylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 2-aminoindan.

Example 4: (from Intermediate 4) (2R,3R,4S,5R)-2-[6-(2,3-Dihydro-1H-inden-2-ylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol
LC/MS Rt=2.65min.
m/z 378 [MH+], 376 [MH-].

Example 5: (2R,3R,4S,5R)-2-[6-(Cyclobutylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol

Intermediate 5: (2R,3R,4R,5R)-4-(Acetyloxy)-2-[6-(cyclobutylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(Acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and cyclobutylamine.

Example 5: (from Intermediate 5) (2R,3R,4S,5R)-2-[6-(cyclobutylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol
LC/MS Rt=2.24min.
m/z 318 [MH+].

Example 6: (2R,3R,4S,5R)-5-Ethynyl-2-{6-[(2-phenylethyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol

Intermediate 6: (2R,3R,4R,5R)-4-(acetyloxy)-5-ethynyl-2-{6-[(2-phenylethyl)amino]-9H-purin-9-yl}tetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 2-phenylethylamine.

Example 6: (from Intermediate 6)
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(2-phenylethyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol
LC/MS Rt=2.58min.
m/z 366 [MH+].

Example 7: (2R,3R,4S,5R)-2-[6-(Cyclohexylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol

Intermediate 7: (2R,3R,4R,5R)-4-(Acetyloxy)-5-ethynyl-2-[6-((cyclohexyl)amino]-9H-purin-9-yl]tetrahydrofuran-3-yl acetate

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and cyclohexylamine.

Example 7: (from Intermediate 7) (2R,3R,4S,5R)-2-[6-(Cyclohexylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol

LC/MS Rt=2.73min.

m/z 344 [MH+].

Example 8:# (2R,3R,4S,5R)-5-Ethynyl-2-(6-[[(1S,2S,3S,4R)-3-methylbicyclo[2.2.1]hept-2-yl]amino)-9H-purin-9-yl)tetrahydrofuran-3,4-diol

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and bicyclo [2.2.1]heptan-2-amine.

LC/MS Rt=2.76min.

m/z 370 [MH+].

Example 9:# (2R,3R,4S,5R)-5-Ethynyl-2-(6-[[(1R*,2S*)-2-methoxy-2-phenylcyclopentyl]amino)-9H-purin-9-yl)tetrahydrofuran-3,4-diol

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and (1R*,2S*)-2-methoxy-2-phenyl cyclopentylamine.

(1R*,2S*)-2-Methoxy-2-phenylcyclopentylamine was prepared using the following method: To a solution of 1-pheny-6-azabicyclo[3.1.0]hexane(1.2g) in methanol (30ml) was added conc. sulphuric acid (1ml) and the mixture stirred at 20°C for 5 hours. Mixture was diluted with1N sodium hydroxide (180ml) and extracted with dichloromethane (3 x 25ml). The organic phases were combined, and dried using sodium sulphate. The solvent was removed *in vacuo* to give a pale yellow oil (1.8g). (This was isolated as the maleate salt). mpt. 132-134°C.

LC/MS Rt=2.72min.

m/z 436 [MH+].

Example 10:# (2R,3R,4S,5R)-2-[6-(Cyclopropylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and cyclopropylamine.
LC/MS Rt=2.15min.
m/z 302 [MH+].

Example 11:# (2R,3R,4S,5R)-2-{6-[(Cyclopropylmethyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and (aminomethyl)cyclopropylamine.
LC/MS Rt=2.40min.
m/z 316 [MH+].

Example 12:# (2R,3R,4S,5R)-2-[6-(Cyclopentylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and cyclopentylamine.
LC/MS (blue) Rt=2.54min.
m/z 330 [MH+].

Example 13:# (2R,3R,4S,5R)-5-Ethynyl-2-(6-{[(2R,3R)-2-methyltetrahydrofuran-3-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol

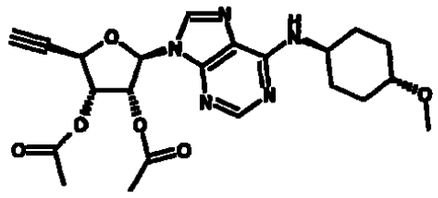
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and (2R,3R)-2-methyl-3-aminotetrahydrofuran.
LC/MS Rt=2.27min.
m/z 346 [MH+].

Example 14:# (2R,3R,4S,5R)-5-Ethynyl-2-(6-{[(2S,3S)-2-methyltetrahydrofuran-3-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and (2S, 3S)-2-methyl-3-amino tetrahydrofuran.
LC/MS Rt=2.27min.
m/z 346 [MH+].

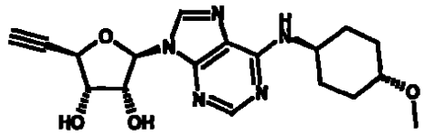
Example 15: (2R,3R,4S,5R)-5-Ethynyl-2-{6-[(trans-4-methoxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol

Intermediate 8: (2R,3R,4R,5R)-4-(Acetyloxy)-5-ethynyl-2-{6-[(trans-4-methoxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3-yl acetate



A mixture of (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate (6.0189g, 16.51 mmol), *N,N*-di-isopropylethylamine (5ml, 28.70mmol) and *trans*-4-methoxy-cyclohexylamine hydrochloride (3.0011g, 18.13 mmol) was heated at reflux in iso-propanol (33ml) for 3.5hrs. The mixture was cooled to room temperature, diluted with ethyl acetate and washed with saturated ammonium chloride and saturated sodium bicarbonate then dried (sodium sulfate), filtered and concentrated. The residue was purified by chromatography using Biotage with cyclohexane containing ethyl acetate (50-100%). Evaporation gave the desired compound (4.6293g, 61%) as a white solid.
^{1}H NMR ($CDCl_3$)δ 8.38 (s, 1H), 8.06 (s, 1H), 6.35(d, 1H), 5.97(dd, 1H) 5.68(dd, 1H) 5.58, (brs, 1H), 4.89(t, 1H) 3.37 (s, 3H), 3.2 (m, 1H), 2.84(d, 1H), 2.25-2.1 (m, 7H), 2.06 (s, 3H), 1.3-1.5 (m, 4H).

Example 15: (2R,3R,4S,5R)-5-ethynyl-2-{6-[(trans-4-methoxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol



tert-Butylamine (5.3 ml) was added to a stirred solution of (2R,3R,4R,5R)-4-(acetyloxy)-5-ethynyl-2-[6-[(trans-4-methoxycyclohexyl)amino]-9H-purin-9-yl]tetrahydrofuran-3-yl acetate (intermediate 8) (4.6293g, 10.13 mmol) in methanol (50 ml) at room temperature. A precipitate formed. After 1 hour, the solvent was evaporated. Diethyl ether was added and decanted-off four times to leave the diol (3.5720g, 95%) as a white solid.

^{1}H NMR ($CDCl_3$) δ 8.33(s, 1H), 8.04 (s, 1H), 6.08 (d, 1H), 5.97 (brs, 1H), 5.62 (brs, 1H), 4.82(t, 1H), 4.71dd, 1H), 4.48(brm, 1H), 3.37(s, 3H), 3.21(m, 1H), 2.73(d, 1H), 2.59(m, 1H) 2.1-2.22(m, 4H), 1.3-1.5(m, 4H).

LC/MS ([MH+] = 373, t =2.26).

Example 16: (2R,3R,4S,5R)-5-Ethynyl-2-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol

Intermediate 9: (2R,3R,4R,5R)-4-(acetyloxy)-2-prop-1-ynyl-5-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3-yl acetate

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 4-aminotetrahydro-2H-pyran.

Example 16: (from Intermediate 9) (2R,3R,4S,5R)-5-ethynyl-2-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol

^{1}H NMR (MeOD) δ 8.30d(2H,s,2xCH) 6.14d(1H,d,CH) 4.84d(1H,t,CH) 4.75d(1H,dd,CH) 4.40d(1Hv.br.m,CH) 4.06d(2H,brdt,2xCHeq) 3.63d(2H,dt,2xCHax) 3.31d(1H, d,CH) 2.08d(2H,v.br, d,2xCHeq) 1.73d(2H,br.dq,2xCHax).

LC/MS Rt = 2.12min.

Mass Spectrum *m/z* 346 [MH+].

Example 17:# (2R,3R,4S,5R)-2-[6-[(1R*,5R*,6S*)-Bicyclo[3.2.0]hept-6-ylamino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and bicyclo[3.2.0]heptan-6-amine (Compt Rend., Ser. C, vol 263(1), 90-92 (1966)).
LC/MS Rt = 2.81min.
Mass Spectrum *m/z* 356 [MH+].

Example 18:# (2R,3R,4S,5R)-2-{6-[(2,2-Dimethylcyclopropyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol

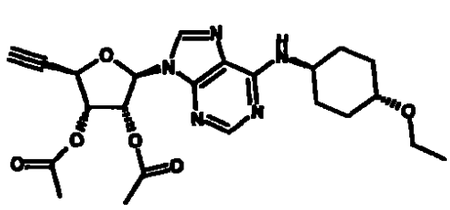
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 2,2-dimethoxycyclopropylamine.
LC/MS Rt = 2.5min.
Mass Spectrum *m/z* 330 [MH+].

Example 19:# (2R,3R,4S,5R)-5-Ethynyl-2-{6-[(trans-4-hydroxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and trans-4- hydroxycyclohexylamine.
LC/MS Rt = 2.22min.
Mass Spectrum *m/z* 330 [MH+].

Example 20: (2R,3R,4S,5R)-5-Ethynyl-2-{6-[(trans-4-ethoxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol

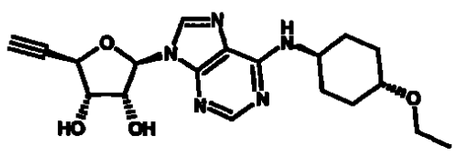
Intermediate 10: (2R,3R,4R,5R)-4-(acetyloxy)-5-ethynyl-2-{6-[(trans-4-ethoxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3-yl acetate



A mixture (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate (0.2079g 0.57 mmol), *N,N*-diisopropylethylamine (0.5ml, 2.87 mmol) and *trans*-4-ethoxycyclohexylamine hydrochloride (prepared according to JP 06329674,Takenochi *et al*), 0.1091g, 0.67 mmol) was heated in 2-propanol (1.2ml) in a reacti-vial at 90°C for 5hrs. The mixture was cooled to room temperature and evaporated. The residue was dissolved in ethyl acetate and washed with saturated ammonium chloride and saturated sodium bicarbonate then dried (sodium sulfate), filtered and concentrated. The residue was purified by chromatography using biotage with cyclohexane containing ethyl acetate (60-80%) to give the desired compound as a white solid (0.1385g, 52%).

^{1}H NMR ($CDCl_3$) δ 8.4 (brs, 1H), 8.1 (brs, 1H), 6.35(d, 1H), 6.0(dd, 1H) 5.7(dd, 1H) 5.58, (brs, 1H), 4. 9(t, 1H) 3.55 (q, 3H), 3.3 (m, 1H), 2.85(d, 1H), 2.25-2.1 (m, 5H), 2.05-2.0 (m, 5H), 1.3-1.5 (t, 2H).

Example 20: (2R,3R,4S,5R5-Ethynyl-2-{6-[(trans-4-ethoxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol



(2R,3R,4R,5R)-4-(acetyloxy)-5-ethynyl-2-{6-[(trans-4-ethoxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3-yl acetate (intermediate 22) (0.1385g, 0.29mmol) was dissolved in methanol (2.4ml) and treated with *tert*-butylamine (0.16ml) (a precipitate formed after 5 minutes). After 1 hour, the solvent was evaporated and the residue purified by Biotage with cyclohexane containing ethyl acetate (60-80%) to furnish the desired compound as a white solid ((0.1385g, 52%).

^{1}H NMR ($CDCl_3$) δ 8.33(s, 1H), 8.04 (s, 1H), 6.08 (d, 1H), 5.97 (brs, 1H), 5.62 (brs, 1H), 4.82(t, 1H), 4.71dd, 1H), 4.48(brm, 1H), 3.37(q, 3H), 3.21(m, 1H), 2.73(d, 1H), 2.59(m, 1H) 2.1-2.22(m, 4H), 1.3-1.5(t, 4H).

LC-MS t=2.87

Example 21: (2R,3R,4S,5R)-5-Ethynyl-2-{6-[(trans-4-propenyl xycyclohexyl)amin]-9H-purin-9-yl}tetrahydrofuran-3,4-diol

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and trans-4-propenyloxycyclohexylamine (intermediate 11)

Intermediate 11:
(4-Hydroxy-cyclohexyl)-carbamic acid *tert*-butyl ester (1.0143g, 4.72mmol) was dissolved in THF (19 mL) and a 60% w/w suspension of sodium hydride in mineral oil (397mg, 9.94mmol) was added in portions at room temperature. Stirring was continued for 2 hours then allyl bromide (0.41mL, 4.73mmol) was added. The mixture was stirred for a further 27 hours before quenching with 2M sodium hydroxide and extraction with ethyl acetate. The organic extracts were washed with saturated ammonium chloride then dried (Na_2SO_4), filtered and concentrated to give an oil which was purified by chromatography on Biotage with cyclohexane containing a gradient of ethyl acetate (5-15%) to yield the title compound (637mg, 53%) as a white solid.

Tlc: R_f 0.50 (cyclohexane-ethyl acetate 1:1)

4M Hydrochloric acid in dioxane (4mL) was added to solid (4-allyloxy-cyclohexyl)-carbamic acid *tert*-butyl ester (637mg) at room temperature and stirred for 7 hours. The solvent was evaporated to give the title compound (455mg, 95%) as a white solid .
^1H NMR ($CDCl_3$) δ 5.75(m, 1H), 5.2-5.0(m, 2H), 3.9 (m, 2H), 3.2 (m, 2H), 3.0 (m, 1H), 2.1-1.9(m, 4H), 1.4-1.1(m, 4H).

Example 21: (from intermediate 11) (2R,3R,4S,5R)-5-ethynyl-2-[6-[(trans-4-propenyloxycxcyclohexyl)amino]-9H-purin-9-yl]tetrahydrofuran-3,4-diol

LC/MS Rt = 2.57min.
m/z 399 [MH+].

Example 22#: Butyl-4-({9-[(2R,3R,4S,5R)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and butyl-4-amino-1-pipridine carboxylate
LC/MS Rt = 2.74min.
Mass Spectrum *m/z* 445 [MH+].

Example 23#: Cyclopropylmethyl 4-({9-[(2R,3R,4S,5R)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and cyclopropylmethyl-4-amino-1-piperidine carboxylate
LC/MS Rt = 2.61min.
Mass Spectrum *m/z* 442 [MH+].

Example24#: (2R,3R,4S,5R)-5-Ethynyl-2-{(6-[(1S,2S)-2-methoxycyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-ylacetate and (1S,2S)-2-methoxycyclopentylamine
LC/MS Rt = 2.26min.
Mass Spectrum *m/z* 359 [MH+].

Example25#: (2R,3R,4S,5R)-5-Ethynyl-2-{6-[(4,4-difluoro)cyclohexyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-ylacetate and 4,4-difluorocyclohexylamine
LC/MS Rt = 2.54min.
Mass Spectrum *m/z* 380[MH+].

Example26#: (2R,3R,4S,5R)-5-Ethynyl-2-{6-[(cyclohex-3-enyl)amino]}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-ylacetate and cyclohex-3-enylamine

LC/MS Rt = 3.05min.
Mass Spectrum *m/z* 341[MH+].

Example27#: (2R,3R,4S,5R)-5-Ethynyl-2-[6-(dicyclopropylmethyl)amino]-9H-purin-9-yl)tetrahydrofuran-3,4-diol;

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-ylacetate and dicyclopropylmethylamine
LC/MS Rt = 2.61min.
Mass Spectrum *m/z* 355[MH+].

Example28#: (2R,3R,4S,5R)-5-ethynyl-2-[6-(cyclooctyl)amino]-9H-purin-9-yl)tetrahydrofuran-3,4-diol

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-ylacetate and cyclooctylamine
LC/MS Rt = 2.80min.
Mass Spectrum *m/z* 371[MH+].

Example29#: (2R,3R,4S,5R)-5-ethynyl-2-[6-(cycloheptyl)amino]-9H-purin-9-yl)tetrahydrofuran-3,4-diol

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-ylacetate and cycloheptylamine
LC/MS Rt = 2.80min.
Mass Spectrum *m/z* 357[MH+].

Example 30: (2R,3R,4S,5R)-5-ethynyl-2-{6-[(1R*,4S*)-4-methoxycyclohept-2-enylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and (1R*,4S*)-4-methoxy-cyclohept-2-enylamine.

Cycloheptadiene (5ml, 46mmol) was added to tetrabutylammonium periodate (20g, 46mmol) dissolved in DCM (200ml), and the mixture was cooled to 0°C. *Tert*-butyl-*N*-hydroxycarbamate (6.14g, 46mmol) was added in small portions with stirring, and the mixture was left overnight under nitrogen. The reaction mixture was washed with 10% aqueous sodium thiosulfate and saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$) and concentrated to give a black oil. It was heated to reflux in 4% MeOH/EtOAc. On cooling tan crystals appeared which were removed by filtration. The filtrate was concentrated and purified by chromatography on silica (gradient elution EtOAc/cyclohexane, 20% to 30%). The fractions containing product were concentrated to give an oil, which was redissolved in EtOAc, washed with 10% aqueous sodium thiosulfate, dried ($MgSO_4$) and concentrated to give *tert*-butyl 6-oxa-7-azabicyclo[3.2.2]non-8-ene-7-carboxylate as a yellow oil (8.89g, 39.5mmol, 89%).
LC/MS Rt=2.95min.
m/z 226 [MH^+].

tert-Butyl 6-oxa-7-azabicyclo[3.2.2]non-8-ene-7-carboxylate (1g, 4.44mmol) was dissolved in 10M aqueous acetic acid (15ml) and zinc dust (2.9g, 44.4mmol) was added slowly with stirring. The mixture was heated to 70°C for six hours. The cooled reaction mixture was diluted with water and ethyl acetate, filtered, and the layers separated. The aqueous layer was extracted with further ethyl acetate. The combined organic extracts were dried ($NaSO_4$) and concentrated to yield *cis-N-(tert*butyloxycarbonyl)-4-hydroxy-cyclohept-2-enylamine as a white solid (0.22g, 0.97mmol, 22%).
m/z 171 (M H^+– *t*Bu).

Sodium hydride (66mg, 1.65mmol) was added to *cis-N-(tert*-butyloxycarbonyl)-4-hydroxycyclohept-2-enylamine (0.178g, 0.78mmol) dissolved in THF (3ml), and the mixture was stirred under nitrogen for one hour. Methyl iodide (48µl, 0.78mmol) was added and the mixture was stirred overnight. 2M aqueous

sodium hydroxide was added to the reaction mixture it was extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride, dried ($MgSO_4$) and concentrated to give an orange oil. Purification by chromatography on silica (gradient elution EtOAc/cyclohexane, 10% to 50%) gave *cis*-*N*-(*tert*butyloxycarbonyl)-4-methoxy-cyclohept-2-enylamine as a white solid (79mg, 0.33mmol, 42%).
m/z 242 (MH^+).

cis-*N*-(*tert*-Butyloxycarbonyl)-4-methoxy-cyclohept-2-enylamine (175mg, 0.73mmol) was treated with 4M hydrochloric acid in dioxane (3ml, 12mmol) and stirred at room temperature for three hours. The mixture was concentrated *in vacuo* to give a quantitative yield of the hydrochloride salt of *cis*-4-methoxycyclohept-2-enylamine as a light brown solid.
m/z 142 (MH^+).

Intermediate 12: (2R,3R,4R,5R)-4-(acetyloxy)-2-[6-[(1R*,4S*)-4-methoxy-cyclohept-2-enylamino)9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-ylacetate

Starting materials:(2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and *cis*-4-methoxy-cyclophept-2-enylamine
LC/MS Rt=2.98min.
m/z 470 [MH^+].

Example 30: (from intermediate 12) (2R,3R,4S,5R)-5-ethynyl-2-[6-[(1R*,4S*)-4-methoxy-cyclohept-2-enylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol

^{1}H NMR (MeOD) δ 8.14(2H,s,2xCH), 5.99(1H,d,CH), 5.76 and 5.67(2x1H, 2xbr.d, CH=CH), 4.70(1H,t,CH), 4.60(1H,dd,CH), 4.31(1H,t,CH), 3.93(1H,br.d, CH), 3.28(3H,s,OCH_3), 3.17(1H, d, CH), 1.93-1.33(6H,4xm,3xCH_2).
LC/MS Rt = 2.80min.
Mass Spectrum *m/z* 357[MH+].

Example 31: (2R,3R,4S,5R)-5-ethynyl-2-[6-[(1S*,4R*)-4-methoxy-cyclohept-2-ylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol

Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-ylacetate and (1R*,4S*)-4-methoxycycloheptylamine

tert-Butyl 6-oxa-7-azabicyclo[3.2.2]non-8-ene-7-carboxylate (3g, 13.3mmol) was dissolved in ethanol (135ml) and added to palladium hydroxide on activated charcoal (300mg). The reaction mixture was stirred under a hydrogen atmosphere until *ca.* 300ml of hydrogen had been absorbed. The catalyst was removed by filtration through celite, and the organic layer was concentrated to yield *tert*-butyl 6-oxa-7-azabicyclo[3.2.2]nonane-7-carboxylate as an oil (2.98g, 13.1mmol, 98%).
m/z 228 (MH^+).

A solution of *tert*butyl 6-oxa-7-azabicyclo[3.2.2]nonane-7-carboxylate (1.81g, 8mmol) in dry THF (25ml) under nitrogen was treated with a 0.1M samarium diiodide in THF (250ml, 25mmol). The dark blue reaction mixture was stirred at room temperature for five hours, then diluted with DCM and quenched with 10% aqueous sodium thiosulfate (150ml). The layers were separated and the aqueous solution was extracted with DCM. The combined DCM solutions were washed with brine, and dried ($NaSO_4$) to give a brown solid. Purification by silica chromatography (50% EtOAc/cyclohexane) gave *cis-N*-(*tert*butyloxycarbonyl)-4-hydroxy-cycloheptylamine as a white solid (0.9g, 3.9mmol, 49%).
m/z =174 (MH^+– *t*Bu).

Sodium hydride (332mg, 8.30mmol) was added slowly to *N*-(*tert*-butyloxycarbonyl)-4-hydroxy-cycloheptylamine (905 mg, 3.95mmol) dissolved in dry THF (16ml) under nitrogen. The mixture was stirred at room temperature for one hour. Methyl iodide (243 µl, 3.91mmol) was added and the mixture was stirred overnight at room temperature. 2.0M aqueous sodium hydroxide was added, and the aqueous layer was extracted with ethyl acetate. The organic phase was washed with saturated aqueous ammonium chloride, dried ($MgSO_4$) and concentrated. The resulting oil was purified by silica chromatography (gradient elution EtOAc/cyclohexane, 15% to 50%) to yield cis-*N*-(*tert*-butyloxycarbonyl)-4-methoxy-cycloheptylamine as a white solid (290mg, 1.19mmol, 30%).

The cis-*N*-(*tert*-butyloxycarbonyl)-4-methoxy-cycloheptylamine (288mg, 1.19mmol) was dissolved in 4M hydrochloric acid in dioxane (2ml, 8mmol) and stirred at room temperature for three hours. The mixture was concentrated *in vacuo* to give a quantitative yield of the hydrochloride salt of *cis*-4-methoxyheptylamine as a yellow solid.
m/z 144 (MH^+).

Intermediate 13: (2R,3R,4R,5R)-4-(acetyloxy)-2-{6-[(1R*,4S*)-4-methoxy-cycloheptylamino)9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-ylacetate

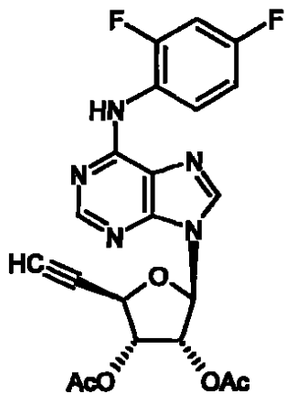
starting materials:(2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and *cis*-4-methoxy-cyclopheptylamine

Example 31: (from intermediate 13) (2R,3R,4S,5R)-5-ethynyl-2-{6-[(1S*,4R*)-4-methoxy-cyclohept-2-ylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol)

^{1}H NMR (MeOD) δ 8.13(2H,s,2xCH), 5.99(1H,d,CH), 4.69(1H,t,CH), 4.60(1H,dd,CH), 4.30(1H,t,CH), 4.20(1H, vbr.s, NH), 3.37-3.44(1H,m, CH), 3.23(3H,s,OCH_3), 3.16(1H,d,CH), 2.05-1.30(10H,4xm,5xCH_2).
MS *m/z* 359[MH+]

Example 32: (2R,3R,4S,5R)-2-{6-[(2,4-Difluorophenyl)amino]-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3,4-diol

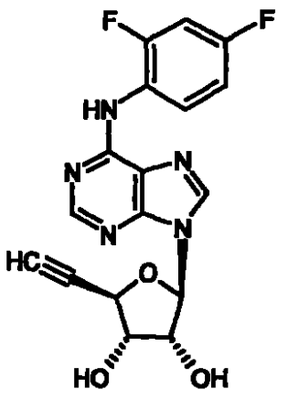
Intermediate 14: (2R,3R,4R,5R)-4-(Acetyloxy)-2-{6-[(2,4-difluorophenyl)amino]-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate



To a solution of (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate (0.050g) in ethanol (2ml) was added 2,4-difluoroaniline (0.041ml) and calcium carbonate (0.027g). The mixture was heated to 90°C for 18 hours in a sealed vessel. The solvent was removed in vacuo. Purification by automated preparative HPLC to give the title compound (0.014 g) as a gum.

Note on some occasions deprotection of the acetates does occur to give the mono and di-deprotected compounds.
LC/MS Rt 3.25 min.
Mass spectrum *m/z* 457 [MH^+].

Example 32: (from Intermediate 14) (2R,3R,4S,5R)-2-[6-[(2,4-Difluorophenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol



To a solution of (2R,3R,4R,5R)-4-(acetyloxy)-2-[6-[(2,4-difluorophenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate (0.012g) in methanol (2ml) stirred at 5°C (ice bath) was added t-butylamine (0.1ml) and the mixture was stirred for 1 hour at 5°C. The solvent was removed *in vacuo*. Purification by automated preparative HPLC to give the title compound (0.007g) as a gum.
LC/MS Rt =2.75 min.
Mass spectrum *m/z* 374 [MH^+].

The following compounds were made using an analogous route to the above procedure for Example 20 using the appropriate starting materials:

Example 33: (2R,3R,4S,5R)-2-[6-[(4-Cloro-2-fluorophenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol

Intermediate 15: (2R,3R,4R,5R)-4-(Acetyloxy)-2-[6-(4-chloro-2-fluoroanilino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 4-chloro-2-fluoroaniline.

Example 33: (from Intermediate 15) (2R,3R,4S,5R)-2-[6-[(4-Chloro-2-fluorophenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol
LC/MS Rt = 3.01min.
Mass Spectrum *m/z* 390 [MH+].

Example 34: (2R,3R,4S,5R)-2-{2-Chloro-6-[(4-chloro-2-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol

Intermediate 16: (2R,3R,4R,5R)-4-(acetyloxy)-2-{2-chloro-6-[(4-chloro-2-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3-yl acetate
Starting materials(2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 4-chloro-2-fluoroaniline.

Example 34: (from Intermediate 16) (2R,3R,4S,5R)-2-{2-chloro-6-[(4-chloro-2-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol
LC/MS Rt = 3.34min.
Mass Spectrum *m/z* 425 [MH+].

Example 35: (2R,3R,4S,5R)-2-{6-[(2-Chloro-4-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol

Intermediate 17: (2R,3R,4R,5R)-4-(acetyloxy)-2-{6-[(2-chloro-4-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 2-chloro-4-fluoroaniline.

Example 35: (from Intermediate 17) (2R,3R,4S,5R)-2-{6-[(2-chloro-4-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol
LC/MS Rt = 2.87min.
Mass Spectrum *m/z* 390 [MH+].

Example 36: (2R,3R,4S,5R)-5-Ethynyl-2-{6-[(4-fluoro-2-methylphenyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol

Intermediate 18: (2R,3R,4R,5R)-4-(Acetyloxy)-5-ethynyl-2-{6-[(4-fluoro-2-methylphenyl)amino]-9H-purin-9-yl}tetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 4-fluoro-2-methylaniline.

Example 36: (from Intermediate 18) (2R,3S,4R,5R)-5-Ethynyl-2-{6-[(4-fluoro-2-methylphenyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol
LC/MS Rt = 2.69min.
Mass Spectrum *m/z* 370 [MH+].

Example 37: (2R,3R,4S,5R)-5-Ethynyl-2-{6-[(3-fluoro-2-methylphenyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol

Intermediate 19: (2R,3R,4R,5R)-4-(Acetyloxy)-5-ethynyl-2-{6-[(3-fluoro-2-methylphenyl)amino]-9H-purin-9-yl}tetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 3-fluoro-2-methylaniline.

Example 37: (from Intermediate 19) (2R,3R,4S,5R)-5-ethynyl-2-{6-[(3-fluoro-2-methylphenyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol
^{1}H NMR (DMSO) δ 9.72 (1H,s,NH); 8.42 (1H,s,CH); 8.26 (1H,s,CH); 7.26-7.20 (2H,m,2xCH); 7.07 (1H,m,CH); 5.99 (1H,d,CH); 5.75 (2H,vr.s.,2xOH); 4.82 (1H,t,CH); 4.58 (1H,dd,CH); 4.39 (1H,t,CH); 3.77 (1H,d,CH); 2.09 (3H,d,CH_3).
LC/MS Rt = 2.64min.
Mass Spectrum *m/z* 370 [MH+].

Example 38: (2R,3R,4S,5R)-2-{6-[(3-Chloro-2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol

Intermediate 20: (2R,3R,4R,5R)-4-(Acetyloxy)-2-{6-[(3-chloro-2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 3-chloro-2-methylaniline.

Example 38: (from Intermediate 20) (2R,3R,4S,5R)-2-{6-[(3-Chloro-2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol
^{1}H NMR (DMSO) δ 9.70 (1H,s,NH); 8.42 (1H,s,CH); 8.25 (1H,s,CH); 7.35-7.32 (2H,m,2xCH); 7.25 (1H,t,CH); 5.99 (1H,d,CH); 5.78 (0.5H,d,OH); 5.74 (0.5H,d,OH); 4.82 (1H,m,CH); 4.58 (1H,dd,CH); 4.38 (1H,q,CH); 3.76 (1H,d,CH); 2.21 (3H,s,CH_3).

LC/MS Rt = 2.80min
Mass Spectrum *m/z* 386 [MH+]

Example 39: (2R,3R,4S,5R)-2-[6-[(4-Chloro-2-methylphenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol

Intermediate 21: (2R,3R,4R,5R)-4-(Acetyloxy)-2-[6-[(4-chloro-2-methylphenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 4-chloro-2-methylaniline.

Example 39: (from Intermediate 21) (2R,3R,4S,5R)-2-[6-[(4-Chloro-2-methylphenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol
^{1}H NMR (DMSO) δ9.69 (1H,s,NH); 8.61(1H,s,CH); 8.45 (1H,s,CH); 7.61 (1H,d,CH); 7.58 (1H,d,CH); 7.48d (1H,dd,CH); 6.19 (1H,d,CH); 5.98 (1.2H, v.br.s.,2xOH); 5.03 (1H,t,CH); 4.78 (1H,dd,CH); 4.59 (1H,t,CH); 3.96 (1H,d,CH); 2.40 (3H,s,CH_3).
LC/MS Rt = 2.85min.
Mass Spectrum *m/z* 386 [MH+].

Example 40: (2R,3R,4S,5R)-2-[6-[(5-Chloro-2-methylphenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol

Intermediate 22: (2R,3R,4R,5R)-4-(acetyloxy)-2-[6-[(5-chloro-2-methylphenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 5-chloro-2-methylaniline.

Example 40: (from Intermediate 22) (2R,3R,4S,5R)-2-[6-[(5-chloro-2-methylphenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol
LC/MS Rt = 2.86min.
Mass Spectrum m/z 386 [MH+].

Example 41: (2R,3R,4S,5R)-2-[6-[(2-Bromo-4-fluorophenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol

Intermediate 23: (2R,3R,4R,5R)-4-(acetyloxy)-2-[6-[(2-bromo-4-fluorophenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 2-bromo-4-fluoroaniline.

Example 41: (from Intermediate 23) (2R,3R,4S,5R)-2-[6-[(2-bromo-4-fluorophenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol
LC/MS Rt = 2.79min.
Mass Spectrum m/z 435 [MH+].

Example 42: (2R,3R,4S,5R)-2-[2-chloro-6-[(3-fluoro-2-methylphenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol

Intermediate 24:
(2R,3R,4R,5R)-4-(Acetyloxy)-2-[2-chloro-6-[(3-fluoro-2-methylphenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 3-fluoro-2-methylaniline.

Example 42: (from Intermediate 24) (2R,3R,4S,5R)-2-[2-chloro-6-[(3-fluoro-2-methylphenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol
LC/MS Rt = 3.17min.
Mass Spectrum m/z 405 [MH+].

Example 43: (2R,3R,4S,5R)-2-[6-[(3,4-Difluorophenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol

Intermediate 25: (2R,3R,4R,5R)-4-(acetyloxy)-2-[6-[(3,4-difluorophenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 3,4-difluoroaniline.

Example 43: (from Intermediate 25) (2R,3R,4S,5R)-2-[6-[(3,4-Difluorophenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol

^{1}H NMR (MeOH) δ 8.5 (1H,s,CH); 8.41 (1H,s,CH); 8.14 (1H,m,CH); 7.52 (1H,m,CH); 7.4 (1H,m,CH); 6.2 (1H,d,CH); 4.91 (1H,m,CH); 4.78 (1H,m,CH); 4.49 (1H,t,CH); 3.31 (1H,d,CH).
LC/MS Rt = 2.85min.
Mass Spectrum m/z 374 [MH+].

Example 44: (2R,3R,4S,5R)-2-{6-[(2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol

Intermediate26: (2R,3R,4R,5R)-4-(Acetyloxy)-2-{6-[(2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 2-methyl aniline

Example 44: (from intermediate26): (2R,3R,4S,5R)-2-{6-[(2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol

LC/MS Rt = 3.05 min.
Mass Spectrum m/z 352 [MH+].

Example 45: (2R,3R,4S,5R)-2-{6-[(4-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol

Intermediate 27: (2R,3R,4R,5R)-4-(acetyloxy)-2-{6-[(4-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 4-methyl aniline

Example 45: (from intermediate 27) (2R,3R,4S,5R)-2-{6-[(4-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol
LC/MS Rt = 3.26 min.
Mass Spectrum m/z 352 [MH+].

Example 46: (2R,3R,4S,5R)-2-{6-[(3-Chloro-2-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol

Intermediate28: (2R,3R,4R,5R)-4-(acetyloxy)-2-[6-[(3-chloro-2-fluorophenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 3-chloro-2-fluoro aniline

Example 46 (from intermediate 28) (2R,3R,4S,5R)-2-[6-[(3-chloro-2-fluorophenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol
LC/MS Rt = 2.83min.
Mass Spectrum *m/z* 390 [MH+].

Example 47:(2R,3R,4S,5R)-2-[6-[(2-Fluoro-5-methylphenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol;

Intermediate 29: (2R,3R,4R,5R)-4-(Acetyloxy)-2-[6-[(2-fluoro-5-methylphenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3-yl acetate
Starting materials: (2R,3R,4R,5R)-4-(acetyloxy)-2-(6-chloro-9H-purin-9-yl)-5-ethynyltetrahydrofuran-3-yl acetate and 2-fluoro-5-methyl aniline

Example 47: (from intermediate 29) (2R,3R,4S,5R)-2-[6-[(2-fluoro-5-methylphenyl)amino]-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol
LC/MS Rt = 2.72min.
Mass Spectrum *m/z* 369 [MH+].

LC/MS System

- Column: 3.3cm x 4.6mm ID, 3um ABZ+PLUS
- Flow Rate: 3ml/min
- Injection Volume: 5µl
- Temp: RT

Solvents: A: 0.1% Formic Acid + 10mMolar Ammonium Acetate.
B: 95% Acetonitrile + 0.05% Formic Acid

Gradient:	Time	A%	B%
	0.00	100	0
	0.70	100	0
	4.20	0	100
	5.30	0	100
	5.50	100	0

Automated preparative HPLC.

- Column: 10cm x 21.2mm ID, 5um ABZ+PLUS
- Flow Rate: 4ml/min
- Temp: RT

Solvents: A: HPLC water + 0.1% Formic Acid
B: Acetonitrile + 0.05% Formic Acid

Gradient:	Time	A%	B%
	0.00	95	5
	1.45	95	5
	20	10	90
	30	10	90
	32	95	5

Reporter Gene Experiments in yeast

Agonist activity at human adenosine A1 receptors was measured in yeast cell lines expressing the adenosine A1 receptor together with a chimeric G-protein

which linked receptor stimulation to the expression of the enzyme β-galactosidase. Cells were plated out in 96-well plates in culture medium to which was added 2mM 3-AT (3-aminotriazole) to limit basal growth in the absence of agonist stimulation, and FDG (fluorescein di-β-D-galactopyranoside) as substrate for β-galactosidase, which converts FDG to fluorescein. For measurement of potency, agonists were added to the appropriate wells at a concentration range of approximately 10^{-10} - 10^{-5}M and incubated at 30°C for 18 hours. At this point the amount of fluorescein generated was measured in a spectrophotometer. From these readings, the concentration-dependence of the stimulation by the agonist can be calculated. One of the agonists tested on each 96-well plate was the standard non-selective agonist, N-ethylcarboxamidoadenosine (NECA), and the potency of all test agonists is expressed relative to that of the NECA standard.

(ECR = equipotent concentration ratio relative to NECA = 1)

<u>Reporter Gene Experiments in CHO cells</u>

Agonist activity at human adenosine A3 receptors was measured in Chinese hamster ovary (CHO) cells containing the CRE/SPAP/HYG (CRE = cyclic AMP response element; HYG = hygromycin resistance; SPAP = secreted placental alkaline phosphatase) reporter gene elements, which upon stimulation of cAMP levels produced SPAP. A cell line was used which was stably transfected with the human adenosine A3 receptor in addition to the above elements. Cells were plated out in 96-well plates in culture medium and incubated at 37°C for 1 hour. For measurement of potency, agonists were added to the appropriate wells at a concentration range of approximately 10^{-10} - 10^{-5}M. 15Min later, cAMP levels were stimulated by addition of a maximal concentration of forskolin. All cells were then incubated for a further 5 hours at 37°C, and cooled to room temperature, after which a substrate for the phosphatase (para-nitrophenol phosphate, pNPP), which is converted by SPAP to a coloured reagent) was then added and the 96-well plates were read in a plate reader. From these readings, the concentration-dependence of the inhibition by the agonist for forskolin-stimulated SPAP production can be calculated. As with the yeast assays, one of the agonists tested on each 96-well plate was the standard non-selective

agonist, N-ethylcarboxamidoadenosine (NECA), and the potency of all test agonists is expressed relative to that of the NECA standard.

Table 2: Potencies in the reporter gene assay

Example No.	Adenosine A1 receptor ECR*	Adenosine A3 receptor ECR*
33	26.31	>215
34	39	>607
1	9.95	>1070
2	10	>3580
3	6.48	>823
35	6.48	>974
36	7.15	>1117
32	7.94	>1070
37	4.79	>145
38	5.45	>145
39	7.36	>168
40	16.94	>505
41	5.92	>505
4	27.96	>407
5	3	>196
6	24.6	>1059
42	9.17	>220
7	11.4	>178
8	7.94	>178
9	23.81	>165

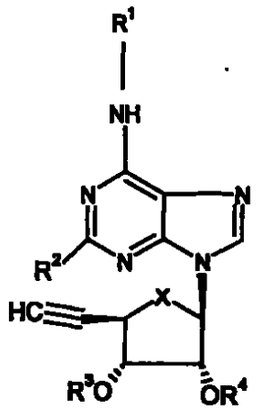
43	34.9	>188
10	6.89	>1066
11	5	>210
12	4.47	>80.2
13	18.86	>386
14	14.86	>502
15	18.79	>778
17	2.88	>416
19	8.57	>3208
18	6.81	>3208

*ECR = equipotent concentration ratio relative to NECA = 1 (see description in Reporter Gene Assay).

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.

Claims

1. A compound of formula (Ia):



(Ia)

wherein X represents O or CH_2;

R^1 represents:

(i) -(alk)$_n$-(C_{3-9})cycloalkyl or -(alk)$_n$-(C_{3-9})cycloalkenyl, said cycloalkyl or cycloalkenyl group being optionally substituted by one or more substituents selected from OH, halogen, C_{1-6}alkyl, -C_{1-6}alkoxy, C_{2-6}alkenyloxy-, C_{2-6}alkynyloxy- and phenyl, wherein (alk) represents C_{1-3}alkyl and n represents 0 or 1, and said (alk) group may be optionally substituted by a C_{3-6}cycloalkyl group;

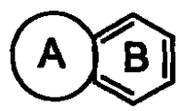
(ii) a phenyl group optionally substituted by one or more substituents selected from: halogen, CF_3, cyano, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, C_{1-6}alkoxy-, -C_{1-6}alkylOH, -CO_2H and -CO_2C_{1-6} alkyl;

(iii) a C_{4-7}heterocyclic group containing at least one heteroatom selected from O, N or S, and optionally substituted by one or more substituents selected from: OH, -C_{1-6}alkyl, -C_{1-6}alkoxy, -CO_2C_{1-4}alkyl, -COC_{1-4}alkyl, -CO_2aryl or -CO_2(alk)$_n$(C_{3-6})cycloalkyl, wherein (alk) represents C_{1-3}alkyl and n represents 0 or 1;

(iv) a straight or branched C_{1-12}alkyl group optionally substituted by one or more groups selected from phenyl, halogen, hydroxy, and C_{3-7} cycloalkyl, wherein one or more carbon atoms of the C_{1-12}alkyl group may be

optionally replaced by a group independently selected from $S(=O)_n$ (where n is 0, 1 or 2) and N;

(v) a fused bicyclic ring



wherein A represents C_{4-6}cycloalkyl or phenyl and B represents phenyl optionally substituted by C_{1-3}alkyl, and the bicyclic ring is attached to the purine-6-amino moiety via a ring atom of ring A;

R^2 represents -C_{1-3}alkyl, halogen, hydrogen or -C_{1-3}alkoxy group;

R^3 and R^4 independently represent H or a -C_{1-6}alkyl group;

or a pharmaceutically acceptable salt and/or solvate thereof.

2. A compound according to claim 1 wherein R^2 represents hydrogen or halogen.

3. A compound according to claim 1 or claim 2 wherein R^3 and R^4 each represent hydrogen.

4. A compound according to any one of claims 1 to 3 wherein X represents O.

5. A compound selected from:

(2R,3R,4S,5R)-2-{6-[(4-chloro-2-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{2-chloro-6-[(4-chloro-2-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6-[(2-chloro-4-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;

(2R,3R,4S,5R)-5-ethynyl-2-{6-[(4-fluoro-2-methylphenyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6-[(2,4-difluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;

(2R,3R,4S,5R)-5-ethynyl-2-{6-[(3-fluoro-2-methylphenyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(3-chloro-2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(4-chloro-2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(5-chloro-2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(2-bromo-4-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{2-chloro-6-[(3-fluoro-2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(3,4-difluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
N-ethyl-2-({9-[(2R,3R,4S,5R)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)ethanesulfonamide;
ethyl 4-({9-[(2R,3R,4S,5R)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate;
(2R,3R,4S,5R)-5-ethynyl-2-(6-{[(1S,2S)-2-hydroxycyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-[6-indan-2-ylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-[6-(cyclobutylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(2-phenylethyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-[6-(cyclohexylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-(6-{[(1S*,2S*,3S*,4R*)-3-methylbicyclo[2.2.1]hept-2-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-(6-{[(1R*,*2S)-2-methoxy-2-phenylcyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-[6-(cyclopropylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6-[(cyclopropylmethyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-[6-(cyclopentylamino)-9H-purin-9-yl]-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-(6-{[(2R,3R)-2-methyltetrahydrofuran-3-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-(6-{[(2S,3S)-2-methyltetrahydrofuran-3-yl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(trans-4-methoxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
2R,3R,4S,5R)-5-ethynyl-2-{6-[(trans-4-ethoxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
2R,3R,4S,5R)-5-ethynyl-2-{6-[(trans-4-propenyloxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-[6-(tetrahydro-2H-pyran-4-ylamino)-9H-purin-9-yl]tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(1R*,5R*,6S*)-bicyclo[3.2.0]hept-6-ylamino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(2,2-dimethylcyclopropyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(trans-4-hydroxycyclohexyl)amino]-9H-purin-9-yl}tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(2-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(4-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(3-chloro-2-fluorophenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-2-{6-[(2-fluoro-5-methylphenyl)amino]-9H-purin-9-yl}-5-ethynyltetrahydrofuran-3,4-diol;
butyl 4-({9-[(2R,3R,4S,5R)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate;
cyclopropylmethyl 4-({9-[(2R,3R,4S,5R)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl]-9H-purin-6-yl}amino)piperidine-1-carboxylate;

(2R,3R,4S,5R)-5-ethynyl-2-{(6-[(1S,2S)-2-methoxycyclopentyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(4,4-difluoro)cyclohexyl]amino}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(cyclohex-3-enyl)amino]}-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-[6-(dicyclopropylmethyl)amino]-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-[6-(cyclooctyl)amino]-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-[6-(cycloheptyl)amino]-9H-purin-9-yl)tetrahydrofuran-3,4-diol;
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(1R*,4S*)-4-methoxy-cyclohept-2-enylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol; and
(2R,3R,4S,5R)-5-ethynyl-2-{6-[(1S*,4R*)-4-methoxy-cyclohept-2-enylamino)-9H-purin-9-yl]-tetrahydrofuran-3,4-diol.

6. A pharmaceutical composition comprising a compound of formula (Ia) or a pharmaceutically acceptable salt and/or solvate thereof together with a pharmaceutical carrier and/or excipient.

7. Use of a compound of formula (Ia) or a pharmaceutically acceptable salt and/or solvate thereof 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.

8. Use of a compound of formula (Ia) or a pharmaceutically acceptable salt and/or solvate thereof for the manufacture of a medicament for the treatment of a patient suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke or which subject is suffering pain, a CNS disorder, sleep apnoea or emesis.

9. 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 comprising administering a therapeutically effective amount of a compound of formula (Ia) or a pharmaceutically acceptable salt and/or solvate thereof.

10. A method of treating a patient suffering from or susceptible to ischaemic heart disease, peripheral vascular disease or stroke or which subject is suffering pain, a CNS disorder, sleep apnoea or emesis, comprising administering a therapeutically effective amount of a compound of formula (Ia) or a pharmaceutically acceptable salt and/or solvate thereof.

COMPUESTOS QUÍMICOS

Campo de la Invención.

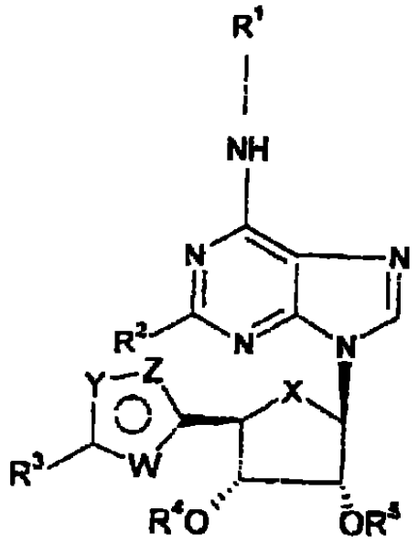
La presente invención se refiere a composiciones farmacéuticas que contienen ciertos derivados de adenosina, que tienen un grupo acetileno en la posición 4', que son agonistas A1 de la adenosina, y a su uso en terapias. En particular, se refiere al uso de estos derivados de adenosina en el tratamiento de condiciones en donde hay una ventaja en la disminución de la concentración de ácidos grasos libres en el plasma, o la reducción del ritmo cardiaco o en el cual el sujeto padece de o es susceptible a, una enfermedad isquémica del corazón, enfermedad vascular periférica o apoplejía o en donde el sujeto padece de dolor, un trastorno del SNC, apnea del sueño o emesis.

Antecedentes de la Invención.

Se han descrito en el arte una variedad de compuestos que son agonistas en el receptor A1 de la adenosina. Estos incluyen los compuestos descritos en las solicitudes de patentes publicadas WO99/24449, WO99/24450, WO99/24451, WO97/43300, WO98/16539, WO98/04126, WO98/01459, EP0322242, GB2226027, EP222330, WO98/08855, WO94/0707, WO99/67262 Y WO00/23447.

Por ejemplo, la WO 99/67262 (Glaxo Group Limited), describe compuestos de fórmula (I) que son agonistas en

el receptor A1 de la adenosina, y su uso en el tratamiento de un paciente que padece de una condición en donde hay una ventaja en la disminución de la concentración de ácidos grasos libres en el plasma, o la reducción del ritmo cardiaco o cuyo sujeto padece de, o es susceptible a, enfermedad isquémica del corazón, enfermedad vascular periférica o apoplejía, o que el sujeto padece de dolor, un trastorno del SNC o apnea del sueño.



(I)

en donde Y y Z representan O, N, CH, N(alquilo C_{1-5});

W representa CH, O, N, S, N(alquilo C_{1-6});

y en donde al menos uno de W y Z representa un heteroátomo (y cuando Y, Z y/o W es N, la presencia o ausencia de un H adicional sería aparente para una persona hábil en el arte);

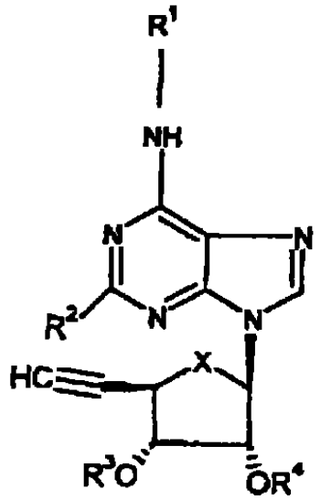
con la condición de que cuando W representa CH, Z representa N e Y representa O, R^3 no puede ser H.

Los compuestos descritos en WO99/67262 (Glaxo Group Limited) se hacen por ejemplo, por medio de intermediarios que tienen un grupo acetileno en la posición 4'.

Los inventores actuales han encontrado, sorprendentemente, que los derivados de la adenosina con un grupo acetileno en la posición 4' muestran una actividad agonista A1 de adenosina.

Sumario de la Invención.

La presente invención proporciona compuestos de fórmula (Ia):



(Ia)

en donde X representa O ó CH_2;

R^1 representa:

(i) cicloalquilo-(C_{3-9})-$(alq)_n$ o cicloalquenilo-(C_{3-9})-$(alq)_n$, tal grupo cicloalquilo o cicloalquenilo está opcionalmente substituido por uno o más substituyentes seleccionados de OH, halógeno,

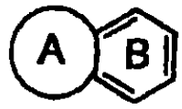
alquilo C_{1-6}, alcoxi C_{1-6}, alqueniloxi C_{2-6}, alquiniloxi C_{2-6} y fenilo, en donde (alq) representa alquilo C_{1-3} y n representa 0 ó 1, y el grupo (alq) puede substituirse opcionalmente por un grupo cicloalquilo C_{3-6};

(ii) un grupo fenilo opcionalmente substituido por uno o más substituyentes seleccionados de: halógeno, CF_3, ciano, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, alquilOH C_{1-6}, $-CO_2H$ y alquilo C_{1-6} CO_2;

(iii) un grupo heterocíclico C_{4-7} que contiene al menos un heteroátomo seleccionado de O, N o S, y substituido opcionalmente por uno o más substituyentes seleccionados de: OH, alquilo C_{1-6}, alcoxi C_{1-6}, alquilo C_{1-4} CO_2, alquilo C_{1-4} CO, arilo CO_2 o cicloalquil $(C_{3-6})CO_2(alq)_n$, en donde (alq) representa alquilo C_{1-3}, y n representa 0 ó 1;

(iv) un grupo alquilo C_{1-12} recto o ramificado substituido opcionalmente por uno o más grupos seleccionados de fenilo, halógeno, hidroxi, y cicloalquilo C_{3-7}, en donde uno o más átomos de carbono del grupo alquilo C_{1-12} pueden reemplazarse opcionalmente por un grupo seleccionado independientemente de $S(=O)_n$ (donde n es 0, 1 ó 2) y N;

(v) un anillo bicíclico fundido



en donde A representa cicloalquilo C_{4-6} o fenilo y B representa fenilo opcionalmente substituido por alquilo C_{1-3}, y el anillo bicíclico se enlaza a la porción de la purina-6-amino por medio de un átomo de anillo del anillo A;

R^2 representa alquilo C_{1-3}, halógeno, hidrógeno o un grupo alcoxi C_{1-3};

R^3 y R^4 representan independientemente H o un grupo alquilo C_{1-6};

o derivados farmacéuticamente aceptables de los mismos.

Aspectos adicionales de la invención son:

- Una composición farmacéutica que comprende un compuesto de fórmula (Ia) o un derivado farmacéuticamente aceptable de la misma junto con un portador y/o excipiente farmacéutico.
- El uso de un compuesto de fórmula (Ia) o un derivado farmacéuticamente aceptable del mismo para la fabricación de un medicamento, para el tratamiento de un paciente que padece de una condición en donde hay una ventaja en la disminución de la concentración de ácidos grasos libres en el plasma, o la reducción del corazón.

- El uso de un compuesto de fórmula (Ia), o un derivado farmacéuticamente aceptable del mismo, para la fabricación de un medicamento, para el tratamiento de un paciente que padece de, o es susceptible a, enfermedad isquémica del corazón, enfermedad vascular periférica o apoplejía o cuyo sujeto padece de dolor, una enfermedad del SNC, apnea del sueño o emesis.
- Un método para el tratamiento de un paciente que padece de una condición en donde hay una ventaja en la disminución de la concentración de los ácidos grasos libres en el plasma, o la reducción del ritmo cardiaco, que comprende administrar una cantidad terapéuticamente efectiva de un compuesto de fórmula (Ia) o un derivado farmacéuticamente aceptable del mismo.
- Un método para el tratamiento de un paciente que padece de, o es susceptible a, enfermedad isquémica del corazón, enfermedad vascular periférica o apoplejía o en donde el sujeto padece de dolor, un trastorno del SNC, apnea del sueño o emesis, que comprende la administración de una cantidad terapéuticamente efectiva de un compuesto de fórmula (Ia) o un derivado farmacéuticamente aceptable del mismo.

Descripción Detallada de la Invención.

Los compuestos útiles en la invención son agonistas en el receptor A1 de la adenosina. Preferiblemente son agonistas selectivos en el receptor A1 de la adenosina. Por selectivo se quiere decir que la afinidad por el receptor A1 es de al menos 2 veces, preferiblemente 5 veces y más preferiblemente 10 veces superior a otros subtipos del receptor de la adenosina, particularmente A3. La selectividad del agonista de compuestos contra otros receptores humanos de la adenosina, se puede determinar usando células de ovario de hámster chino (CHO) transfectadas con el gen para el receptor relevante de la adenosina humana, siguiendo un método basado en aquel de Castanon, KV. y Spevak, W. (1994) Biochem. Biophys. Res. Commun. 198, 626-631. Las células CHO se transfectan también con elementos de respuesta del AMP cíclico que promueven el gen para la fosfatasa alcalina placental secretada (SPAP) (Wood, KV. (1995) Curr. Opinion. Biotechnology, 6, 50-58). El efecto de los compuestos de prueba se determina por sus efectos en los niveles basales del cAMP (A2a) o en el cAMP enriquecido con forscolina (A1 y A3) como se refleja por los cambios en los niveles de SPAP. Los valores EC_{50} para los compuestos se determina como una relación a aquella de un agonista no selectivo N-etil carboxamidoadenosina (NECA).

"Adenosine receptors: New opportunities for future drugs" (S.A. Poulsen y colaboradores, Bioorg. Med. Chem., 1998, 6, 619-641), resume condiciones de enfermedades que se pueden tratar con los agonistas A1 de la adenosina.

Los compuestos de fórmula (Ia) contienen centros quirales (asimétricos). Los estereoisómeros individuales (enantiómeros y diastereoisómeros) y mezclas de estos, se encuentran dentro del alcance de la presente invención.

Como se usa aquí, los términos "alquilo" y "alcoxi", significan grupos hidrocarburos saturados de cadena recta y ramificada. Ejemplos de los grupos alquilo incluyen grupos metilo, etilo, propilo y butilo. Ejemplos de los grupos alcoxi incluyen grupos metoxi y etoxi. Otros ejemplos incluyen propoxi y butoxi. Los grupos alquilo pueden estar substituidos, o no substituidos con uno hasta cuatro substituyentes, preferiblemente de uno a tres substituyentes como se define hasta aquí.

De uno a tres, preferiblemente de uno o dos, átomos de carbono de una cadena de alquilo se pueden reemplazar por un grupo seleccionado independientemente de $S(=O)_n$ (donde n es 0, 1 ó 2) y N. Cuando el heteroátomo N reemplaza un átomo de carbono en el grupo alquilo C_{1-12}, el átomo N se substituirá, donde sea apropiado, por uno o dos substituyentes seleccionados de hidrógeno y alquilo C_{1-6}.

Como se usa aquí, los términos "alquenilo", "alqueniloxi", "alquinilo" y "alquiniloxi" significan grupos hidrocarburo no saturados de cadena recta y ramificada. Los ejemplos de los grupos alquenilo incluyen etileno y propileno. Los ejemplos de grupos alquinilo incluyen etinilo y propinilo. Los ejemplos de grupos alqueniloxi incluyen propeniloxi y eteniloxi. Los ejemplos de los grupos alquiniloxi incluyen propiniloxi y etililoxi.

Como se usa aquí, el término "halógeno" significa flúor, cloro, bromo o yodo.

Como se usa aquí, el término arilo, significa grupos carbocíclicos aromáticos, monocíclicos o bicicliclos tales como fenilo y naftilo, especialmente fenilo.

Como se usa aquí, el término "cicloalquilo" significa un grupo alifático que tiene de 3 hasta 9 átomos de carbono en el sistema de anillos, a menos que se defina de otra manera. El grupo cicloalquilo puede ser monocíclico o bicíclico. Un grupo bicíclico se puede fundir o puentear. Ejemplos de los grupos cicloalquilo monocíclicos incluyen ciclopropilo, ciclobutilo y ciclopentilo. Otros ejemplos de los grupos monocíclicos de cicloalquilo son ciclohexilo, cicloheptilo y ciclooctilo. Ejemplos de los grupos cicloalquilo bicíclicos incluyen biciclo[2.2.1]hept-2-ilo.

Preferiblemente, el grupo cicloalquilo es monocíclico. Los grupos cicloalquilo pueden estar no substituidos, o substituidos con uno hasta cuatro substituyentes, preferiblemente uno o dos substituyentes como se define hasta aquí.

Como se usa aquí, el término "cicloalquenilo" significa un grupo alifático parcialmente insaturado, que tiene de 3 a 9 átomos de carbono en el sistema de anillos. El grupo cicloalquenilo puede ser monocíclico ó bicíclico. Preferiblemente, el grupo cicloalquilo es monocíclico. Ejemplos de los grupos cicloalquenilo monocíclicos incluyen ciclopentenilo y ciclohexenilo. Los grupos cicloalquenilo pueden estar no substituidos, ó substituidos con uno hasta cuatro substituyentes, preferiblemente de uno o dos substituyentes.

Como se usa aquí, el término "heterocíclico" significa un grupo cíclico de 4 hasta 7 átomos de carbono en donde uno o más de los átomos de carbono se reemplaza o reemplazan por heteroátomos seleccionados independientemente de nitrógeno, oxígeno o azufre. El heterociclo puede ser aromático o no aromático, esto es, puede estar saturado (esto es, alifático), parcialmente o completamente insaturado. Este grupo puede estar opcionalmente substituido como se define hasta aquí. El heteroátomo es preferiblemente O ó N. El heterociclo es

preferiblemente no aromático. Ejemplos de grupos heterociclilo incluyen piperidinilo, tetrahidrofuranilo y tetrahidropiranilo. Los grupos cicloalquilo pueden estar no substituidos ó substituidos con uno hasta cuatro substituyentes, preferiblemente uno o dos substituyentes. Los grupos heterociclilo pueden estar no substituidos, o substituidos con uno hasta cuatro substituyentes, preferiblemente uno o dos substituyentes.

Como se usa aquí, el término "derivado farmacéuticamente aceptable", significa cualquier sal farmacéuticamente aceptable, solvato, éster o amida, o sal o solvato de tal éster o amida del agonista A1 de la adenosina, o cualquier otro compuesto que con la administración al receptor es capaz de proporcionar (directamente ó indirectamente) el agonista A1 de la adenosina o un metabolito activo o residuo del mismo, por ejemplo un profármaco. Los derivados preferidos farmacéuticamente aceptables de conformidad con la invención, son cualesquiera sales, solvatos y profármacos farmacéuticamente aceptables, más preferiblemente sales y solvatos farmacéuticamente aceptables.

Como se usa aquí, el término "farmacéuticamente aceptable", significa un compuesto que es apropiado para uso farmacéutico.

Las sales farmacéuticamente aceptables de los compuestos de fórmula (Ia) incluyen aquellas derivadas de ácidos orgánicos e inorgánicos farmacéuticamente aceptables. Ejemplos de los ácidos apropiados incluyen ácidos clorhídrico, bromhídrico, sulfúrico, nítrico, perclórico, fumárico, maléico, fosfórico, glicólico, láctico, salicílico, succínico, toluen-p-sulfónico, tartárico, acético, cítrico, metansulfónico, fórmico, benzoico, malónico, naftalen-2-sulfónico, y bencensulfónico. Otros ácidos tales como oxálico, aunque no son en sí mismos farmacéuticamente aceptables, pueden ser útiles como intermediarios en la obtención de compuestos de la invención y sus sales de adición ácidas farmacéuticamente aceptables.

Aquellos hábiles en el arte de la química orgánica, apreciarán que muchos compuestos orgánicos pueden formar complejos con solventes en los cuales reaccionan, o a partir de los cuales se precipitan o cristalizan. Estos complejos se conocen como "solvatos". Por ejemplo, un complejo con agua se conoce como un "hidrato". Los solvatos de compuestos de la fórmula (Ia) están dentro del alcance de la invención.

Como se usa aquí, el término "profármaco" significa un compuesto que se convierte dentro del cuerpo, por ejemplo, por hidrólisis en la sangre, en su forma activa

que tiene efectos médicos. Los profármacos farmacéuticamente aceptables se describen en T. Higuchi y V. Stella, Prodrugs as Novel Delivery systems, vol. 14 del A.C.S. Symposium Series; y en Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, ambas de las cuales se incorporan en la presente como referencia.

En un aspecto alternativo, R^1 representa:

(i) cicloalquilo-(C_{3-9})-$(alq)_n$, incluyendo cicloalquilo puenteado, opcionalmente substituido por uno o más substituyentes seleccionados de OH, halógeno, alcoxi C_{1-3}, y fenilo, en donde (alq) representa alquilo C_{1-6} y n representa 0 ó 1;

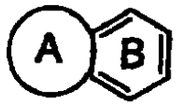
(ii) un grupo fenilo opcionalmente substituido por uno o más substituyentes seleccionados de: halógeno, CF_3, ciano, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, alcoxi C_{1-6}, alquilOH C_{1-6}, $-CO_2H$ y alquilo C_{1-6} CO_2;

(iii) un grupo heterocíclico C_{4-7} que contiene al menos un heteroátomo seleccionado de O, N o S, y substituido opcionalmente por uno o más substituyentes seleccionados de: OH, alquilo C_{1-6}, alcoxi C_{1-6}, alquilo $(C_{1-4})CO_2$, alquilo $(C_{1-4})CO$, o arilo CO_2;

(iv) alquilo C_{1-12} recto o ramificado substituido por uno o más grupos seleccionados de: $S(=O)_n$ (donde n es 0,

1 ó 2) substituido dentro de la cadena alquilo, N substituido dentro de la cadena alquilo, fenilo, halógeno, hidroxi o cicloalquilo C_{3-7};

(v) un anillo bicíclico fundido



en donde A representa cicloalquilo C_{4-6} o fenilo y B representa fenilo opcionalmente substituido por alquilo C_{1-3}, y el anillo bicíclico se enlaza al átomo de nitrógeno de fórmula (I) por medio de un átomo de anillo del anillo A.

En un aspecto adicional, R^1 representa:

(i) cicloalquilo-(C_{3-9})-$(alq)_n$, el grupo cicloalquilo estando opcionalmente substituido por uno o más substituyentes seleccionados de: OH, halógeno, alquilo C_{1-6}, alcoxi C_{1-6}, y fenilo, en donde (alq) representa alquilo C_{1-3} y n representa 0 ó 1;

(ii) un grupo heterocíclico alifático C_{4-7} que contiene al menos un heteroátomo seleccionado de O, N o S, opcionalmente substituido por uno o más substituyentes seleccionados de: alquilo C_{1-6}, alquilo $(C_{1-4})CO$, alquilo$(C_{1-4})CO_2$, y fenilo CO_2;;

(iii) un grupo alquilo C_{1-12} recto o ramificado substituido por uno o más grupos seleccionados de: fenilo, $S(=O)_n$ (donde n es 0, 1 ó 2) y N, en donde cada uno

de $S(=O)_n$ o N reemplaza un carbono del grupo alquilo.

En un aspecto adicional R^1 representa un grupo fenilo opcionalmente substituido por uno o más substituyentes seleccionados de: halógeno, CF_3, ciano, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo (C_{2-6}), alcoxi (C_{1-6}), alquilo(C_{1-6})OH, $-CO_2H$ y $-CO_2(C_{1-6})$alquilo.

Todavía en otro aspecto adicional, R^1 representa fenilo opcionalmente substituido por uno o más substituyentes seleccionados de: halógeno y alquilo C_{1-6}; R^2 representa hidrógeno ó halógeno, y R^3 y R^4 representan independientemente H ó alquilo C_{1-6}.

Convenientemente, R^1 puede representar $(alq)_n$-cicloalquilo (C_{3-9}) en donde n es 0 ó 1 y el cicloalquilo está no substituido o substituido por al menos un substituyente seleccionado de alquilo C_{1-6}, alcoxi C_{1-6}, fenilo y OH. Los substituyentes alternativos incluyen al menos un substituyente seleccionado de halógeno y alqueniloxi C_{2-6}. Preferiblemente, el grupo cicloalquilo está no substituido o monosubstituido por alquiloxi C_{1-3}, alqueniloxi C_{2-3}, cicloalquilo C_{3-6}, alquilo C_{1-3}, fenilo o OH, o está mono o disubstituido por halógeno, por ejemplo flúor. Alternativamente, el grupo cicloalquilo está no substituido o substituido por OH o alquilo C_{1-3}. Preferiblemente n es cero. Preferiblemente, el anillo de

cicloalquilo tiene de 3 hasta 8 átomos de carbono, más preferiblemente 5 ó 6 átomos de carbono. Los grupos cicloalquilo incluyen hidroxiciclopentilo ó metoxiciclohexilo. Otros grupos cicloalquilo incluyen propeniloxiciclohexilo, difluorociclohexilo, etoxiciclohexilo, diciclopropilmetilo, ciclooctilo, y cicloheptilo. Cuando n es 1, el grupo (alq) puede estar substituido, por ejemplo por ciclopropilo.

R^1 puede representar $(alq)_n$-cicloalquenilo (C_{3-9}), en donde n es 0 ó 1 y el cicloalquenilo está substituido por al menos un substituyente seleccionado de alquilo C_{1-6}, alquiloxi C_{1-6}, fenilo y OH, o está no substituido. Los substituyentes alternativos incluyen al menos un substituyente seleccionado de halógeno, alqueniloxi C_{2-6}, y cicloalquilo C_{3-6}. Preferiblemente n es cero. Más preferiblemente, el grupo cicloalquenilo está no substituido. Preferiblemente, el anillo de cicloalquenilo tiene 5 ó 6 átomos de carbono, más preferiblemente el anillo es ciclohexenilo.

Alternativamente, R^1 puede representar un grupo heterocíclico, substituido o no substituido, alifático, el substituyente se selecciona de alquilo C_{1-6}, $-CO_2$ alquilo (C_{1-4}) ó CO_2fenilo. El substituyente puede también ser $-CO_2(alq)_n$cicloalquilo (C_{3-6}). Preferiblemente, el anillo heterocíclico es de 6 miembros, y más

preferiblemente contiene solamente un heteroátomo O ó N. Convenientemente, el grupo alifático heterocíclico está no substituido o, cuando se substituye, el substituyente es $-CO_2(C_{1-4})$alquilo ó $CO_2(alq)_n(C_{3-6})$cicloalquilo, el heteroátomo es N y el substituyente se enlaza directamente al átomo de nitrógeno del anillo. Preferiblemente, cuando el heterociclo está substituido, el substituyente es $-CO_2(C_{1-4})$alquilo, el heteroátomo es N y el substituyente se coloca directamente al átomo de nitrógeno del anillo. Más preferiblemente cuando el anillo heterocíclico no está substituido el heteroátomo es O. Más preferiblemente, cuando el anillo heterocíclico está substituido el heteroátomo es N.

Alternativamente, R^1 puede representar un alquilo recto o ramificado de 1-6 átomos de carbono incluyendo uno ó más grupos $S(=O)_n$ (en donde n es 0, 1 ó 2), cada uno reemplazando un átomo de carbono del grupo alquilo, opcionalmente substituido con N, reemplazando un átomo de carbono en una posición adyacente al grupo $S(=O)_n$. Preferiblemente n es 1 ó 2, más preferiblemente n es 2.

Alternativamente, R^1 pueden representar fenilo opcionalmente substituido, uno o dos substituyentes seleccionados de halógeno ó alquilo C_{1-6}. Más preferiblemente, R^1 representa preferiblemente fenilo opcionalmente substituido, uno o dos substituyentes

seleccionados de halógeno o metilo. Preferiblemente, el halógeno es flúor, cloro ó bromo, más preferiblemente flúor o cloro. Preferiblemente el fenilo está disubstituido. Preferiblemente el fenilo está disubstituido en las posiciones 2,3 ó 2,4 ó 2,5. En un aspecto alternativo, el fenilo está monosubstituido por alquilo C_{1-6}, por ejemplo metilo.

En un aspecto preferido de la invención, R^1 representa:

(i) cicloalquilo-(C_{3-9})-$(alq)_n$, el grupo cicloalquilo estando opcionalmente substituido por uno o más substituyentes seleccionados de: OH, halógeno, alquilo C_{1-6}, alcoxi C_{1-6}, alqueniloxi C_{2-6} y fenilo, en donde (alq) representa alquilo C_{1-3} y n representa 0 ó 1, y el grupo (Alq) puede opcionalmente substituirse por un grupo cicloalquilo C_{3-6}; o R^1 representa cicloalquenilo-(C_{3-9})-$(alq)_n$;

(ii) un grupo heterocíclico C_{4-7} que contiene al menos un heteroátomo seleccionado de O, ó N, opcionalmente substituido por alquilo C_{1-6}, alquilo $C_{1-4}CO_2$, o cicloalquilo$(C_{3-6})CO_2(alq)_n$; o

(iii) fenilo opcionalmente substituido por halógeno o alquilo C_{1-6}.

En un aspecto alternativo de la invención, R^1 representa:

(i) cicloalquilo-(C_{3-9})-(alq)$_n$, incluyendo el cicloalquilo en puente, el grupo cicloalquilo estando opcionalmente substituido por uno o más substituyentes seleccionados de: OH, alquilo C_{1-6}, alcoxi C_{1-6}, y fenilo, en donde (alq) representa alquilo C_{1-3} y n representa 0 ó 1;

(ii) un grupo heterocíclico C_{4-7} que contiene al menos un heteroátomo seleccionado de O, ó N, opcionalmente substituido por alquilo C_{1-6}, alquilo $C_{1-4}CO_2$; o

(iii) fenilo opcionalmente substituido por halógeno o alquilo C_{1-6}.

En otro aspecto de la invención, R^1 representa:

(i) cicloalquilo-(C_{3-9})-(alq)$_n$, incluyendo el cicloalquilo en puente, el grupo cicloalquilo estando opcionalmente substituido por uno o más substituyentes seleccionados de OH, alquilo C_{1-6}, alcoxi C_{1-6}, y fenilo; en donde (alq) representa alquilo C_{1-3} y n representa 0 ó 1; o

(ii) un grupo heterocíclico alifático C_{4-7} que contiene al menos un heteroátomo seleccionado de O, ó N, opcionalmente substituido por alquilo C_{1-6}, o alquilo $C_{1-4}CO_2$.

R^2 representa preferiblemente hidrógeno o halógeno. Más preferiblemente, R^2 representa hidrógeno o cloro. Más preferiblemente, R^2 representa hidrógeno.

R^3 y R^4 preferiblemente representan ambos hidrógeno.

X representa preferiblemente O.

Cuando R^1 es alquilo C_{1-12}, el grupo está preferiblemente substituido.

Se entenderá que la presente invención cubre todas las combinaciones de grupos particulares y preferidos mencionados arriba.

Los compuestos preferidos de la invención incluyen:

(2R,3R,4S,5R)-2-{6-[(4-cloro-2-fluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{2-cloro-6[(4-cloro-2-fluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6-[(2-cloro-4-fluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-{6-[(4-fluoro-2-metilfenil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-[6-[(2,4-difluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-{6-[(3-fluoro-2-metilfenil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6-[(3-cloro-2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6-[(4-cloro-2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2{6-[(5-cloro-2-metilfenil)amino]-9H-purin-9-il)-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6-[(2-bromo-4-fluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{2-cloro-6-[(3-fluoro-2-metilfenil)amino]-9H-purin-9-il)}-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-[6-[(3,4-difluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

N-etil-2-({9-[(2R,3R,4S,5R)-5-etinil-3,4-dihidroxitetrahidrofuran-2-il]-9H-purin-6-il}amino)etansulfonamida;

etil 4-({9-(2R,3R,4S,5R)-5-etinil-3,4-dihidroxitetrahidrofuran-2-il]-9H-purin-6-il}amino)piperidin-1-carboxilato;

(2R,3R,4S,5R)-5-etinil-2-(6-([(1S,2S)-2-hidroxiciclopentil]amino}-9H-purin-9-il)tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-[6-indan-2-ilamino)-9H-purin-9-il]-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-[6-(ciclobutilamino)-9H-purin-9-il]-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-(6-[(2-feniletil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-[6-(ciclohexilamino)-9H-purin-9-il]-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-(6-{[(1S*,2S*,3S*,4R*)-3-metilbiciclo[2,2,1]hept-2-il]amino}-9H-purin-9-il)tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-(6-{[(1R*,*2S)-2-metoxi-2-fenilciclopentil]amino}-9H-purin-9-il)tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-[6-(ciclopropilamino)-9H-purin-9-il]-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6-[(ciclopropilmetil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-[6-(ciclopentilamino)-9H-purin-9-il]-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-(6{[(2R,3R)-2-metiltetrahidrofuran-3-il]amino}-9H-purin-9-il)tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-(6-{[(2S,3S)-2-metiltetrahidrofuran-3-il]amino}-9H-purin-9-il)tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-[6-{(trans-4-metoxiciclohexil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-{6-[(trans-4-etoxiciclohexil)amino]-9H-purin-9-

il}tetrahidrofuran-3,4-diol;

2R,3R,4S,5R)-5-etinil-2-{6-[(trans-4-propeniloxiciclohexil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-[6-(tetrahidro-2H-piran-4-ilamino)-9H-purin-9-il]tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-[6-[(1R*,5R*,6S*)-biciclo[3.2.0]hept-6-ilamino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6-[(2,2-dimetilciclopropil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-{6-[(trans-4-hidroxiciclohexil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6-[(2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6[(4-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6-[(3-cloro-2-fluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6-[(2-fluoro-5-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

butil4-({9-[(2R,3R,4S,5R}-5-etinil-3,4-dihidroxitetrahidrofuran-2-il]-9H-purin-6-il}amino)piperidin-1-carboxilato;

ciclopropilmetil 4-({9-[(2R,3R,4S,5R)-5-etinil-3,4-dihidroxitetrahidrofuran-2-il}-9H-purin-6-il}amino)piperidin-1-carboxilato;

(2R,3R,4S,5R)-5-etinil-2-{(6-[(1S,2S)-2-metoxiciclopentil]amino}-9H-purin-9-il)tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2{6-[(4,4-difluoro)ciclohexil]amino}-9H-purin-9-il)tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2{6-[(ciclohex-3-enil)amino]}-9H-purin-9-il)tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-[6-(diciclopropilmetil)amino]-9H-purin-9-il)tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-[6-(cicloctil)amino]-9H-purin-9-il)tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-[6-(cicloheptil)amino]-9H-purin-9-il)tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2{6-[(1R*,4S*)-4-metoxi-cicloept-2-enilamino)-9H-purin-9-il]-tetrahidrofuran-3,4-diol; o

(2R,3R,4S,5R)-5-etinil-2{6-[(1S*,4R*)-4-metoxi-cicloept-2-enilamino)-9H-purin-9-il]-tetrahidrofuran-3,4-diol.

Los compuestos particularmente preferidos de la invención incluyen:

(2R,3R,4S,5R)-2-{6-[(2-cloro-4-fluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2{6-[(4-fluoro-2-metilfenil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2{6-[(3-fluoro-2-metilfenil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6-[(3-cloro-2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6-[(4-cloro-2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol;

etil 4-({9-[(2R,3R,4S,5R)-5-etinil-3,4-dihidroxitetrahidrofuran-2-il]-9H-purin-6-il}amino)piperidin-1-carboxilato;

(2R,3R,4S,5R)-5-etinil-2-(6{[(1S,2S)-2-hidroxiciclopentil]amino}-9H-purin-9-il)tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-[6-(tetrahidro-2H-piran-4-ilamino)-9H-purin-9-il]tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-{6-[(trans-4-metoxiciclohexil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-5-etinil-2-{6-[(trans-4-etoxiciclohexil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol;

2R,3R,4S,5R)-5-etinil-2{6-[(trans-4-propeniloxiciclohexil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol;

(2R,3R,4S,5R)-2-{6-[(1R*,5R*,6S*)-biciclo[3.2.0]hept-6-ilamino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol; o

(2R,3R,4S,5R)-2-{6-[(2,2-dimetilciclopropil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol.

Los compuestos de conformidad con la invención, tiene aplicabilidad como inhibidores de la lipólisis, esto es, disminuyen las concentraciones de ácidos grasos libres en plasma. Los compuestos pueden así usarse en el tratamiento de hiperlipidemias. Adicionalmente, como consecuencia de su actividad anti-lipolítica, los compuestos tienen la capacidad de disminuir niveles elevados de glucosa en la sangre, insulina y cetona en el cuerpo, y por lo tanto son de valor en la terapia de la diabetes. Ya que los agentes anti-lipolíticos tienen una actividad hipolipidémica e hipofibrinogenémica, los compuestos pueden también mostrar actividad anti-ateroesclerótica. El ensayo descrito por P. Strong y colaboradores en Clinical Science (1993), 84, 663-669, se puede usar para determinar la actividad anti-lipolítica de los compuestos de la invención por su capacidad de disminuir la concentración de ácidos grasos no esterificados (NEFA) en ratas en ayuno.

Además de su efecto anti-lipolítico, los compuestos de la invención pueden afectar independientemente la

función cardiaca al reducir el ritmo cardiaco y la conducción. Los compuestos pueden así usarse en la terapia de diversos trastornos cardiovasculares por ejemplo, arritmias cardiacas, particularmente las que siguen al infarto al miocardio y la angina. Los compuestos pueden también inhibir la liberación de la renina y ser así de uso en la terapia de la hipertensión y falla cardiaca.

Adicionalmente, los compuestos de la invención son útiles como agentes cardioprotectores, que tienen aplicación en el tratamiento de la enfermedad isquémica del corazón. Como se usa aquí, el término "enfermedad isquémica del corazón" incluye el daño asociado con la isquemia del miocardio y la reperfusión, por ejemplo, asociada con el injerto con derivación de la arteria coronaria (CABG), angioplastia coronaria translumenal percutánea (PTCA), cardioplejía, infarto agudo al miocardio, trombolisis, angina estable e inestable y cirugía cardiaca incluyendo transplante cardiaco particular. Los compuestos de la invención son adicionalmente útiles para el tratamiento del daño isquémico a otros órganos. Los compuestos de la invención también pueden ser de valor en el tratamiento de otros trastornos que aparecen como resultado de la enfermedad

ateromatosa esparcida, por ejemplo, enfermedad vascular periférica (PVD) y apoplejía.

Los compuestos de la invención pueden también ser útiles como agentes del SNC (por ejemplo como hipnóticos, sedantes, analgésico y/o anti-convulsivos encontrando uso particularmente en el tratamiento de la epilepsia). Son por lo tanto útiles en el tratamiento o prevención del dolor. Se pueden usar para mejorar la condición de un huésped típicamente un ser humano que padece de dolor. Se pueden emplear para aliviar el dolor en un huésped. Así, un compuesto de fórmula (1a) y sus sales de adición ácidas farmacéuticamente aceptables, se pueden usar como un analgésico preventivo para tratar el dolor agudo tal como el dolor músculo esquelético, dolor post operatorio y dolor quirúrgico, dolor crónico tal como dolor crónico inflamatorio (por ejemplo artritis reumatoide y osteoartritis), dolor neuropático (por ejemplo neuralgia post herpética, neuropatías diabéticas asociadas con la diabetes, neuralgia trigeminal, dolor asociado con trastornos funcionales del intestino, por ejemplo, síndrome del intestino irritable, dolor de pecho no cardiaco y dolor mantenido en el sistema simpático) y dolor asociado con el cáncer y la fibromialgia. El compuesto de fórmula (1a) se puede también usar en el tratamiento o prevención de la migraña o de dolor

asociado con la migraña, dolor de cabeza por tensión y dolores de cabeza en grupo, dolor asociado con trastornos funcionales del intestino (por ejemplo dolor de pecho no cardiaco y dispepsia no de úlcera). El compuesto de fórmula (1a) se puede también usar en el tratamiento de dolor nociceptor (por ejemplo dolores de cabeza, dolor de parto, dolor menstrual y dolor temprano post-operatorio).

Además, los compuestos de la invención pueden encontrar uso en el tratamiento de la apnea del sueño.

Además, los compuestos de la invención pueden encontrar uso en el tratamiento de la emesis. El tratamiento de la emesis incluye tratamiento de náusea, vómito, bascas. La emesis incluye emesis aguda, emesis retardada y emesis anticipatoria.

De conformidad, la invención proporciona un compuesto de fórmula (1a) o un derivado farmacéuticamente aceptable del mismo para su uso en terapia, y en particular, en el tratamiento de sujetos humanos o animales que padecen de una condición en la cual hay una ventaja en la disminución de la concentración de ácidos grasos libres del plasma, o la reducción del ritmo cardiaco y la conducción, o por lo cual la terapia involucra el tratamiento de enfermedad isquémica del corazón, enfermedad vascular periférica o apoplejía o en

la cual el sujeto padece de un dolor, trastorno del SNC apnea del sueño o emesis.

En otro aspecto de la invención proporciona un método de tratamiento de un sujeto humano o animal que padece de una condición en la cual hay una ventaja en la disminución de la concentración de ácidos grasos libres del plasma, o la reducción del ritmo cardiaco y la conducción, o cuyo sujeto padece de una enfermedad isquémica del corazón o es susceptible a la misma, enfermedad vascular periférica o apoplejía, o cuyo sujeto padece de un dolor, un trastorno del SNC, apnea del sueño o emesis, cuyo método comprende administrar al sujeto una cantidad efectiva de un compuesto de fórmula (Ia) o un derivado farmacéuticamente aceptable del mismo.

En otro aspecto, la invención también proporciona el uso de un compuesto de fórmula (Ia) o un derivado farmacéuticamente aceptable del mismo, para la fabricación de un medicamento para el tratamiento de sujetos humanos o animales, que padecen de una condición en la cual hay una ventaja en la disminución de la concentración de ácidos grasos libres en plasma o la reducción del ritmo cardiaco y la conducción, o cuyo sujeto padece de enfermedad isquémica del corazón, enfermedad vascular periférica (PVD) o apoplejía, o cuyo

paciente padece de dolor, o trastorno del SNC, apnea del sueño o emesis.

Con respecto al tratamiento isquémico arriba mencionado, los métodos de la presente invención son aplicables no solamente en donde se planea o espera isquemia, por ejemplo en cirugía cardiaca, sino también en casos de isquemia repentina o inesperada por ejemplo en ataque del corazón y angina inestable.

En un aspecto preferido, la invención proporciona un compuesto de fórmula (Ia) o un derivado farmacéuticamente aceptable del mismo para su uso en terapia, y en particular en el tratamiento de sujetos humanos ó animales, de condiciones asociadas con el dolor incluyendo dolor agudo, dolor crónico, dolor inflamatorio, dolor neuropático, dolor nociceptivo, y dolor asociado con migraña, dolores de cabeza por tensión, dolores de cabeza en grupo y trastorno funcional del intestino. En una modalidad alternativa, la invención proporciona un compuesto de fórmula (Ia) o un derivado farmacéuticamente aceptable del mismo para su uso en terapia, y en particular en el tratamiento de sujetos humanos o animales de condiciones asociadas con dolor, incluyendo dolor agudo, dolor crónico, dolor inflamatorio, dolor neuropático, y dolor asociado con

migraña, dolores de cabeza por tensión, dolores de cabeza en grupo y trastorno funcional del intestino.

En otro aspecto, la invención proporciona un método de tratamiento de un humano o un animal que padece de una condición asociada con el dolor incluyendo dolor agudo, dolor crónico, dolor inflamatorio, dolor neuropático, dolor nociceptivo, y dolor asociado con migraña, dolores de cabeza por tensión, dolores de cabeza en grupo y trastorno funcional del intestino; alternativamente con dolor incluyendo dolor agudo, dolor crónico, dolor inflamatorio, dolor neuropático, y dolor asociado con migraña, dolores de cabeza por tensión, dolores de cabeza en grupo y enfermedad funcional del intestino, cuyo método comprende administrar al sujeto una cantidad de efectiva de un compuesto de fórmula (Ia) o un derivado farmacéuticamente aceptable del mismo.

En otro aspecto la invención también proporciona el uso de un compuesto de fórmula (Ia) o un derivado farmacéuticamente aceptable del mismo para la manufactura de un medicamento para el tratamiento de sujetos humanos ó animales, que sufren de una condición asociada con dolor que incluye dolor agudo, dolor crónico, dolor inflamatorio, dolor neuropático, dolor nociceptivo, y dolor asociado con la migraña, dolores de cabeza por tensión, dolores de cabeza en grupo, y desorden funcional

del intestino. En una modalidad alternativa, la invención se proporciona para el uso de un compuesto de la fórmula (Ia) o un derivado farmacéuticamente aceptable del mismo para la manufactura de un medicamento para el tratamiento de sujetos humanos o animales que sufren de una condición asociada con el dolor que incluye dolor agudo, dolor crónico, dolor inflamatorio, dolor neuropático, dolor nociceptivo, y dolor asociado con la migraña, dolores de cabeza por tensión, dolores de cabeza en grupo, y trastorno funcional del intestino.

Se apreciará que la referencia al tratamiento incluye tratamiento agudo o profilaxis así como el alivio de síntomas establecidos. Aunque es posible que los compuestos de la invención puedan administrarse como el material puro, se prefiere que se presente el ingrediente activo como una formulación farmacéutica.

En un aspecto adicional, la invención proporciona una composición farmacéutica que comprende al menos un compuesto de la fórmula (Ia) o un derivado farmacéuticamente aceptable del mismo en asociación con un portador o excipiente farmacéuticamente aceptable. El portador y/o excipiente debe ser "aceptable" en el sentido de ser compatible con los otros ingredientes de la formulación, y no perjudicar al receptor del mismo.

En otro aspecto, la invención proporciona una composición farmacéutica que comprende como ingrediente activo, al menos un compuesto de la fórmula (Ia) o un derivado farmacéuticamente aceptable del mismo, en asociación con un portador o excipiente farmacéuticamente aceptable, para usarse en la terapia, y en particular en el tratamiento de sujetos humanos o animales que sufren de una condición en la cual hay una ventaja en la reducción de concentración de ácidos grasos libres en plasma, o reducir el ritmo y conducción cardiaca, o en la cual el sujeto sufre de, o es susceptible a, una enfermedad cardiaca isquémica, enfermedad vascular periférica o infarto, o en la cual el sujeto sufre de un desorden del SNC, apnea del dormir, dolor o emesis.

Se proporciona además por la presente invención, un proceso para preparar un composición farmacéutica, cuyo proceso comprende mezclar al menos un compuesto de la fórmula (Ia) o un derivado farmacéuticamente aceptable del mismo, junto con un portador y/o excipiente farmacéuticamente aceptable.

Las composiciones de conformidad con la presente invención pueden formularse para administración tópica oral, bucal, parenteral, o rectal, o en una forma apropiada para la administración por inhalación o

insuflación. Se prefiere la administración oral. Las composiciones pueden adaptarse para liberación sostenida.

Para la administración tópica, la composición farmacéutica puede darse en forma de un parche transdérmico.

Las tabletas y cápsulas para la administración oral pueden contener excipientes convencionales tales como agentes de enlace, por ejemplo el mucílago de almidón ó polivinilpirrolidona; rellenos por ejemplo, lactosa, celulosa microcristalina ó almidón de maíz; lubricantes, por ejemplo, estearato de magnesio ó ácido esteárico; desintegrantes por ejemplo, almidón de papa, croscarmelosa de sodio ó glicolato de almidón de sodio; o agentes humectantes tales como lauril sulfato de sodio. Las tabletas pueden recubrirse de conformidad con los métodos bien conocidos en el arte. Las preparaciones liquidas orales pueden estar en la forma de por ejemplo, suspensiones acuosas o aceitosas, soluciones, emulsiones, jarabes o elixires, o pueden presentarse como un producto seco para su constitución con agua u otro vehículo apropiado antes de usarse. Tales preparaciones pueden contener aditivos convencionales tales como agentes de suspensión, por ejemplo, jarabe de sorbitol, metil celulosa, o carboximetil celulosa; agentes emulsificantes, por ejemplo mono-oleato de sorbitan;

vehículos no acuosos (que pueden incluir agentes comestibles), por ejemplo propilen glicol o alcohol de etilo; y conservadores, por ejemplo, metil o propil-p-hidroxibenzoatos o ácido sórbico. Las preparaciones también pueden contener sales amortiguadoras, saborizantes, colorantes, y agentes educlorantes, (por ejemplo manitol) como sea apropiado.

Para la administración bucal, las composiciones pueden tomar la forma de tabletas o pastillas formuladas de manera convencional.

Los compuestos de la fórmula (Ia) o derivados farmacéuticamente aceptables de los mismos, pueden formularse para administración parenteral por inyección de bolo o infusión continua, y pueden presentarse en forma de dosis unitaria en ampolletas, o en recipientes de dosis múltiples con un conservador agregado. Las composiciones pueden tomar formas tales como suspensiones, soluciones, o emulsiones en vehículos acuosos o aceitosos, y pueden tener agentes de formulación tales como agentes de suspensión, estabilizantes y/o dispersantes. Alternativamente, el ingrediente activo puede estar en forma de polvo para su constitución con un vehículo apropiado, por ejemplo agua, estéril libre de pirógenos, antes de usarse.

Los compuestos de la fórmula (Ia) o derivados farmacéuticamente aceptables de los mismos, también pueden formularse como supositorios, por ejemplo, conteniendo bases de supositorio convencionales tales como manteca de cacao u otros glicéridos. Una dosis propuesta del compuesto de la invención para administrarse al hombre (de aproximadamente de 70 kg de peso corporal) es de 0.1 mg hasta 2g, preferiblemente de 1mg hasta 2g, más preferiblemente 1mg hasta 100 mg, del ingrediente activo por dosis unitaria, que podrá administrarse, por ejemplo, de 1 hasta 4 veces por día. Se apreciará que puede ser necesario hacer variaciones de rutina a la dosis, dependiendo de la edad y condición del paciente. Las dosis también dependen de la vía de administración.

Los compuestos de la fórmula (Ia) también pueden usarse en combinación con otros terapéuticos. La invención proporciona de esta manera en un aspecto adicional, una combinación que comprende un compuesto de la fórmula (Ia) o un derivado farmacéuticamente aceptable del mismo junto con un agente terapéutico adicional.

Cuando un compuesto de la fórmula (Ia) o un derivado farmacéuticamente aceptable del mismo se usa en combinación con un segundo agente terapéutico activo contra el mismo estado de enfermedad, la dosis de cada

uno de los compuestos puede diferir de la que se usaba cuando el compuesto estaba solo. Los segundos agentes terapéuticos apropiados para el tratamiento del dolor incluyen, por ejemplo, inhibidor COX-2, por ejemplo celecoxib, rofecoxib, valdecoxib, parecoxib, 4-(4-ciclohexil-2-metil-5-oxazolil)-2-fluorobencensulfonamida (JTE-552), MK663, nimesulida, DFP, 2-(4-etoxi-fenil)-3-(4-metansulfonil-fenil)-pirazolo[1,5-b]piridazina; agonistas del 5HT1, por ejemplo sumatriptan, naratriptan, zolmitriptan, eletriptan, rizatriptan, frovatriptan, almotriptan, alniditan, dihidroergotamina, donitriptan, PNU-142633, ALX-0646, LY334370, U1092291, IS159, PNY 142633; bloqueadores del canal de sodio, por ejemplo, lamotrigina, R(-)-2,4-diamino-5-(2,3-diclorofenil)-6-fluorometil pirimidina, 2,6-diamino-3-(2,3,5-triclorofenil)pirazina, 5-amino-6-[2,3,5-triclorofenil]-1,2,4-triazina; antagonistas de 5HT3, por ejemplo alosetron, gabapentin, pregabalin; antagonistas de EP1, por ejemplo ZD6416, ZD6804; y opioides, por ejemplo, alfentanil, buprenorfina, codeína, dextropropoxifeno, diamorfina, dihidrocodeína, fentanil, metadona, morfina, oxicodona, levorfanol, pentazocina, petidina. Las combinaciones referidas arriba, pueden convencionalmente presentarse para usarse en forma de una formulación farmacéutica, y de esta manera las formulaciones

farmacéuticas comprenden una combinación como se define arriba junto con un portador o excipiente farmacéuticamente aceptable que comprende un aspecto adicional de la invención. Los componentes individuales de tales combinaciones pueden administrase ya sea secuencialmente o simultáneamente en formulaciones farmacéuticas separadas o combinadas por cualquier ruta conveniente.

Cuando la administración es secuencial, tanto el agonista A1 de la adenosina o el segundo agente terapéutico, pueden administrarse primero. Cuando la administración es simultánea, la combinación puede administrarse en la misma o diferente composición farmacéutica.

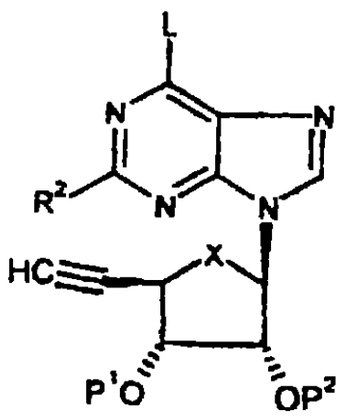
Cuando se combinan en la misma formulación, se apreciará que los dos compuestos deberán ser estables y compatibles el uno con el otro, y con los otros componentes de la formulación. Cuando se formulan separadamente, estos pueden proporcionarse en cualquier formulación conveniente, apropiadamente en una manera tal como las que se conocen para tales compuestos en el arte.

Cuado un compuesto de la fórmula (Ia) o un derivado farmacéuticamente aceptable del mismo se usa en combinación con un segundo agente terapéutico activo contra el mismo estado de enfermedad, la dosis de cada

uno de los compuestos puede diferir de la del compuesto cuando se usa solo. Las dosis apropiadas deberán apreciarse fácilmente por aquellos con habilidad en el arte. Se apreciará que la cantidad de un compuesto de la invención requerido para usarse en el tratamiento, variará con la naturaleza de la condición a ser tratada y la edad y la condición del paciente, y deberá finalmente ser a discreción del médico o veterinario que atiende.

Los compuestos de la fórmula (Ia) y derivados farmacéuticamente aceptables de los mismos pueden preparase por los procesos descritos posteriormente, tales procesos constituyen un aspecto adicional de la invención. En la siguiente descripción, los grupos X, R^1, R^2, y R^3 son como se define por los compuestos de la fórmula (1a) salvo que se establezca lo contrario.

De conformidad con un primer proceso general (A), un compuesto de fórmula (Ia) puede prepararse haciendo reaccionar un compuesto de la fórmula (II):



(II)

en donde L representa un grupo de partida tal como un átomo de halógeno (por ejemplo cloro), HOBT o un grupo de enlace capaz de enlazarse a un soporte polimérico de fase sólida (por ejemplo una resina de poliestireno) y por ejemplo puede ser $-SO_2$ alquilenoC_{1-4} y P^1 y P^2 representan hidrógeno, alquilo C_{1-6} de cadena recta o ramificada, o un grupo protector apropiado (por ejemplo acetilo o un grupo protector donde P^1 y P^2 juntos forman un grupo alquilideno) con un compuesto de la fórmula R^1NH_2 o una sal del mismo bajo condiciones amortiguadas o básicas, donde R^1, R^2 y X son como se define por los compuestos de la fórmula (Ia).

Los compuestos de fórmula (II) pueden usarse para producir compuestos de la fórmula (Ia) directamente por la reacción con el grupo R^1NH_2, donde R^1 es como se define para los compuestos de la fórmula (Ia), ya sea en ausencia o presencia de un solvente tal como alcohol (por ejemplo un alcanol inferior tal como isopropanol, t-butanol ó 3-pentanol), y éter (por ejemplo, tetrahidrofurano o dioxano), una amida sustituida (por ejemplo, dimetilformamida), un hidrocarburo halogenado (por ejemplo, cloroformo), un hidrocarburo aromático (por ejemplo, tolueno), dimetil sulfóxido (DMSO) ó acetonitrilo, preferiblemente a una temperatura elevada (por ejemplo, hasta la temperatura de reflujo del

solvente), en presencia de un eliminador ácido apropiado, por ejemplo, bases inorgánicas tales como carbonato de sodio, cesio ó potasio, o bases orgánicas tales como trietilamina, diisopropiletilamina ó piridina, opcionalmente en presencia de un catalizador de paladio (por ejemplo acetato de paladio) y un ligando de fosfina (por ejemplo, R-(+/-)-2,2'-bis(difenilfosfino)-1-1' binaftilo).

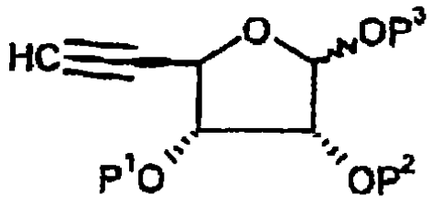
Alternativamente, los compuestos de la fórmula (II) pueden usarse para producir compuestos de la fórmula (Ia) por la reacción con el grupo R^1NH_2, donde R^1 es como se define por los compuestos de la fórmula (Ia), en presencia de $CaCO_3$ y un solvente apropiado, por ejemplo, etanol ó ácido acético. Preferiblemente, cuando el solvente es etanol la reacción se calienta, por ejemplo a reflujo. En un aspecto alternativo, la reacción puede llevarse a cabo en ácido acético en ausencia de $CaCO_3$, preferiblemente la reacción se calienta.

Las reacciones de arriba pueden precederse o continuarse, donde sea apropiado, por la remoción in situ de los grupos protectores P^1 y P^2. Por ejemplo, cuando P^1 y P^2 representan acetilo, esto se puede efectuar con una amina tal como amoniaco o tert-butil amina o un alcóxido tal como metóxido de sodio en un solvente tal como metanol, o cuando P^1 y P^2 representan un alquilideno por

hidrólisis ácida, por ejemplo con ácido trifluoroacético (TFA). La interconversión de los grupos protectores P^1 y P^2 puede ocurrir a cualquier etapa en la preparación de los compuestos de la fórmula (II), por ejemplo cuando P^1 y P^2 representan acetilo, los compuestos de la fórmula (II) pueden prepararse a partir de los compuestos en donde P^1 y P^2 juntos representan un grupo protector alquilideno por la remoción catalizada por ácido del grupo protector alquilideno, por ejemplo con cloruro de hidrógeno en metanol seguido por acilación in situ, por ejemplo con anhidrido acético en presencia de una base tal como piridina, en un solvente tal como diclorometano.

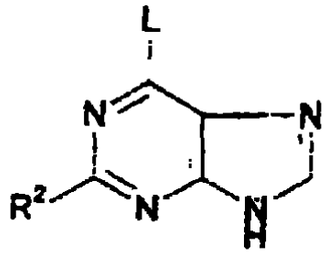
Por otro lado, la interconversión de los grupos protectores P^1 y P^2 puede ocurrir a cualquier etapa durante la preparación de los compuestos de la fórmula (II).

Los compuestos de la fórmula (II) pueden prepararse por los métodos descritos en WO99/67262. Por ejemplo, los compuestos de la fórmula (II) donde X=0, pueden preparase por la reacción de los compuestos de fórmula (III):



(III)

en donde P^3 representa un grupo protector apropiado, por ejemplo acetilo, o un substituyente tal como alquilo C_{1-3}, y P^1 y P^2 son como se define arriba, con los compuestos de la fórmula (IV):



(IV)

en donde L y R^2 son como se define arriba.

La reacción se lleva a cabo convenientemente en un solvente apropiado, tal como acetonitrilo en presencia de un agente sililante tal como trimetilsilil trifluorometansulfonato y una base tal como diazabiciclo[5.4.0]undec-7-eno (DBU). Alternativamente, el compuesto de la fórmula (IV) puede primero sililarse con un agente sililante apropiado, por ejemplo, hexametildisilazano seguido por la reacción del intermediario sililante con un compuesto de la fórmula (III) y un ácido Lewis apropiado, por ejemplo, trimetilsilil trifluorometansulfonato en un solvente apropiado tal como acetonitrilo.

Los compuestos de la fórmula (IV) son, ya sea, conocidos en el arte o pueden prepararse a partir de compuestos conocidos usando métodos análogos a aquellos

usados para preparar los compuestos conocidos de la fórmula (IV).

Como se describe arriba, los compuestos de la fórmula (III) pueden preparase a partir de compuestos protegidos alternativos, reemplazando los grupos protectores alternativos P^1 y P^2 con otros grupos P^1 y P^2. Esto representa un intercambio de un grupo protector por otro, y será aparente para aquellos con habilidad en el arte.

Los compuestos de la fórmula (III) pueden preparase por métodos conocidos en el arte.

Los isómeros específicos ópticos de un compuesto de la fórmula (Ia), pueden obtenerse por métodos convencionales, por ejemplo, por síntesis a partir de un material de partida asimétrico apropiado usando cualesquiera de los procesos descritos en la presente, o donde sea apropiado, por la separación de una mezcla de isómeros de un compuesto de la fórmula (Ia) por medios convencionales, por ejemplo, por destilación fraccionada, cristalización fraccionada ó cromatografía.

En el proceso general descrito arriba, el compuesto de la fórmula (Ia) obtenido puede estar en la forma de una sal, convenientemente en la forma de una sal farmacéuticamente aceptable. Donde se desea, tales sales

pueden convertirse en las bases libres correspondientes usando métodos convencionales.

Las sales de adición ácida farmacéuticamente aceptables de los compuestos de la fórmula (Ia), pueden preparase haciendo reaccionar un compuesto de la fórmula (Ia) con un ácido apropiado en presencia de un solvente apropiado tal como acetonitrilo, acetona, cloroformo, acetato de etilo o un alcohol (por ejemplo metanol, etanol o isopropanol). Las sales de adición base farmacéuticamente aceptables, pueden obtenerse de una manera análoga tratando una solución de un compuesto de la fórmula (Ia) con una base apropiada. Las sales farmacéuticamente aceptables también pueden prepararse a partir de otras sales, incluyendo otras sales farmacéuticamente aceptables de los compuestos de fórmula (Ia), usando métodos convencionales.

La presente invención se ilustrará adicionalmente ahora por los ejemplos acompañantes que no deberían construirse como limitantes del alcance de la invención de ninguna manera.

Ejemplos.

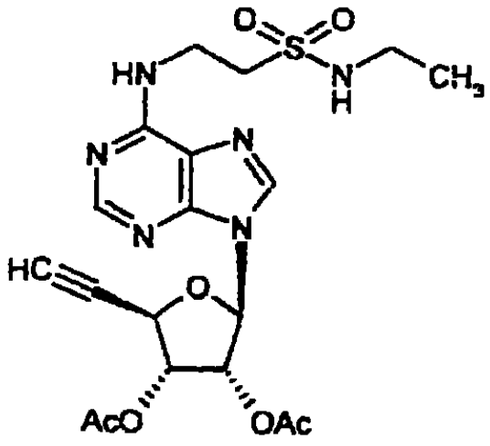
Definiciones de las abreviaturas usadas en la presente: N,N-dimetilformamida (DMF), dimetilsulfóxido (DMSO), diclorometano (DCM), tetrahidrofurano (THF),

ácido trifluoroacético (TFA) y diazabiciclo[5.4.0]undec-7-eno (DBU).

En ocasiones (denotado por #) durante la reacción, puede ocurrir alguna desprotección de los intermediarios de acetato para dar los compuestos mono y di-desprotegidos.

Ejemplo 1: N-etil-2-({9-[(2R,3R,4S,5R)-5-etinil-3,4-dihidroxitetrahidrofuran-2-il]-9H-purin-6-il}amino)etansulfonamida.

Intermediario 1: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-[6-({2-[(etilamino)sulfonil]etil}amino)-9H-purin-9-il]-5-etiniltetrahidrofuran-3-ilo.



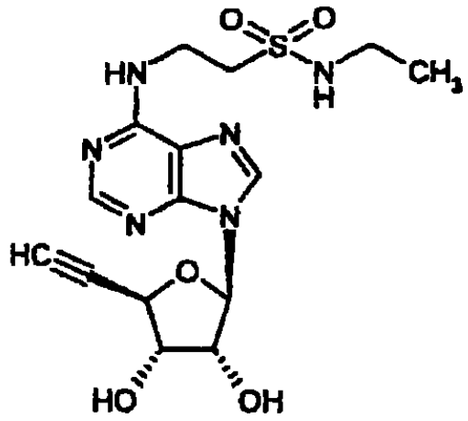
Una solución que contiene el acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo (0.050g), propan-2-ol (1-5ml), diisopropiletilamina (0.095ml) y 2-amino-N-etiletansulfonamida (0.041g), se calentó hasta 80°C durante 3 hasta 18 horas. Se removió el solvente in vacuo

para dar una goma. (Purificación opcional) Purificación por HPLC preparativa automatizada para dar el compuesto del título (0.023g) como una goma. Notar que en ocasiones (denotado por #) durante la reacción, ocurre alguna desprotección de los acetatos para dar los compuestos mono y di-desprotegidos.

LC/MS Tr 2.76 minutos.

Espectro de masa m/z 481 [MH^+].

Ejemplo 1: N-etil-2-({9-[(2R,3R,4S,5R)-5-etinil-3,4-dihidroxitetrahidrofuran-2-il]-9H-purin-6-il}amino)etansulfonamida.



A una solución del acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-[6-({2-[(etilamino)sulfonil]etil}amino)-9H-purin-9-il]-5-etiniltetrahidrofuran-3-ilo (0,02g) en metanol (2ml) agitada a 5°C (baño de hielo), se le agregó t-butilamina (0.1 ml) y la mezcla se agitó durante 1 hora a 5°C. El solvente se removió in vacuo. Purificación por

HPLC preparativa automatizada para dar el compuesto del título (0.012g) como un sólido blanco.

LC/MS Tr 2.29 min.

Espectro de masa m/z 397 [MH^+].

Los siguientes compuestos se hicieron usando una ruta análoga al procedimiento anterior usando los materiales de partida apropiados:

Ejemplo 2: 4-({9-[(2R,3R,4S,5R)-5-etinil-3,4-dihidroxitetrahidrofuran-2-il]-9H-purin-6-il}amino)piperidin-1-carboxilato de etilo.

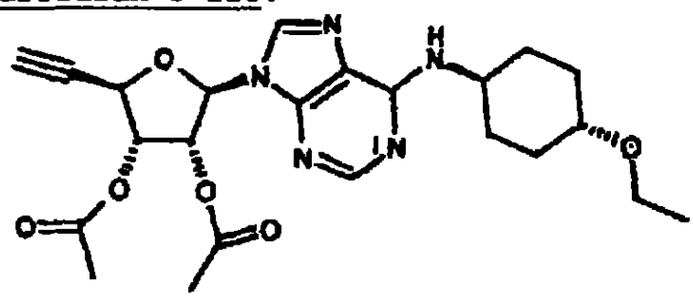
Intermediario 2: 4-({9-[(2R,3R,4R,5R)-3,4-bis(acetiloxi)-5-etiniltetrahidrofuran-2-il]-9H-purin-6-il}amino)piperidina-1-carboxilato de etilo.

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y etil-4-amino-1-piperidin carboxilato.

Ejemplo 2: (a partir del intermediario 2) 4-({9-[(2R,3R,4S,5R)-5-etinil-3,4-dihidroxitetrahidrofuran-2-il]-9H-purin-6-il}amino)piperidin-1-carboxilato de etilo.

^{1}H RMN (MeOD) δ 8.15, 8.14 (2H,br.s+s,2xCH), 6.0 (1H, d, CH), 4.70 (1H, t, CH), 4.60 (1H, dd, CH), 4.31 (1H, dd, CH), 4.23 (1H, vbr.m, CH), 4.07-3.98 (4H, q+br.m, CH2 + 2xCH eq), 3.16 (1H, d, CH), 2.98 (2H, br.t, 2xCH ax),

Intermediario 10: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-5-etinil-2-{6-[(trans-4-etoxiciclohexil)amino]-9H-purin-9-il}tetrahidrofuran-3-ilo.

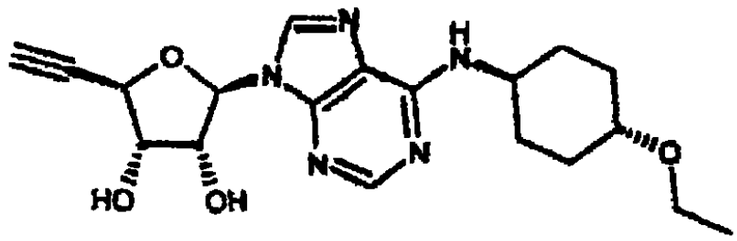


Una mezcla del acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo (0.2079g 0.57 mmol), N,N-diisopropiletilamina (0.5ml, 2.87 mmol) y clorohidrato de trans-4-etoxiciclohexilamina (preparado de conformidad con la JP 06329674, Takenochi y colaboradores), (0.1091g, 0.67 mmol), se calentó en 2-propanol (1.2ml) en un vial reactivo a 90°C durante 5 horas. La mezcla se enfrió hasta temperatura ambiente y se evaporó. El residuo se disolvió en acetato de etilo y se lavó con cloruro de amonio saturado y bicarbonato de sodio saturado, después se secó (sulfato de sodio), se filtró y se concentró. El residuo se purificó por cromatografía usando Biotage con ciclohexano que contenia acetato de etilo (60-80%) para dar el compuesto deseado como un sólido blanco (0.1385g, 52%).

^{1}H RMN ($CDCl_3$) δ 8.4 (brs, 1H), 8.1 (brs, 1H), 6.35 (d, 1H), 6.0 (dd,1H), 5.7 (dd, 1H), 5.58 (brs, 1H), 4.9(t,

1H) 3.55 (q, 3H), 3.3 (m, 1H), 2.85 (d, 1H), 2.25-2.1 (m, 5H), 2.05-2.0 (m, 5H), 1.3-1.5 (t, 2H).

Ejemplo 20: (2R,3R,4S,5R5-Etinil-2-{6-(trans-4-etoxiciclohexil)amino]-9H-purin-9-il}-tetrahidrofuran-3,4-diol.



Se disolvió el acetato de (2R,3R,4R,5R)-4-(acetiloxi)-5-etinil-2-{6-[(trans-4-etoxiciclohexil)amino]-9H-purin-9-il}tetrahidrofuran-3-il (Intermediario 22) (0.1385g, 0.29mmol) en metanol (2.4ml), y se trató con tert-butilamina (0.16ml) (se formó un precipitado después de 5 minutos). Después de una hora, se evaporó el solvente y el residuo se purificó por Biotage con ciclohexano que contenía acetato de etilo (60-80%) para dar el compuesto deseado como un sólido blanco (0,1385g, 52%).

^{1}H RMN ($CDCl_3$) δ 8.33(s, 1H), 8.04 ,(s, 1H), 6.08 (d, 1H), 5.97 (brs, 1H), 5.62 (brs, 1H), 4.82 (t, 1H), 4.71 (dd, 1H), 4.48 (brm, 1H), 3.37 (q, 3H), 3.21 (m, 1H), 2.73(d, 1H), 2.59(m, 1H) 2.1-2.22(m, 4H), 1.3-1.5(t, 4H).

LC-MS t=2.87

Ejemplo 21: (2R,3R,4S,5R)-5-Etinil-2-{6-[(trans-4-

propenil xiciclohexil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol.

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y trans-4-propeniloxiciclohexilamina (Intermediario 11).

Intermediario 11:

Se disolvió éster tert-butilo del ácido (4-hidroxi-ciclohexil)-carbámico (1.0143g, 4.72mmol) en THF (19 mL), y se agregó una suspensión al 60% p/p de hidruro de sodio en aceite mineral (397mg, 9.94mmol) en porciones a temperatura ambiente. La agitación continuó durante 2 horas, después se agregó bromuro de alilo (0.41 mL, 4.73mmol). La mezcla se agitó durante 27 horas adicionales antes de apagar con hidróxido de sodio 2M y extraer con acetato de etilo. Los extractos orgánicos se lavaron con cloruro de amonio saturado, después se secaron (Na_2SO_4), se filtraron y se concentraron para dar un aceite que se purificó por cromatografía en Biotage con ciclohexano que contenía un gradiente de acetato de etilo (5-15%) para producir el compuesto del título (637mg, 53%) como un sólido blanco.

Tlc: R_f 0.50 (ciclohexano-acetato de etilo 1:1).

Se agregó ácido clorhídrico en dioxano (4mL) al éster de tert-butilo del ácido (4-aliloxi-ciclohexil)-carbámico (637mg) a temperatura ambiente, y se agitó durante 7 horas. El solvente se evaporó para dar el compuesto del título (455mg, 95%) como un sólido blanco.

^{1}H RMN ($CDCl_3$) δ 5,75(m, 1H), 5.2-5.0 (m, 2H), 3.9 (m, 2H), 3.2 (m, 2H), 3.0 (m, 1H), 2.1-1.9(m,4H), 1.4-1.1 (m,4H).

Ejemplo 21: (a partir del Intermediario 11) (2R,3R,4S,5R)-5-etinil-2-6-{(trans-4-propeniloxiciclohexil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol

LC/MS Tr= 2.57min.

m/z 399 [MH+].

Ejemplo 22#: Butil-4-({9-[(2R,3R,4S,5R)-5-etinil-3,4-dihidroxitetrahidrofuran-2-il}-9H-purin-6-il}amino)piperidin-1-carboxilato

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y butil-4-amino-1-piperidin carboxilato

LC/MS Tr= 2.74min.

Espectro de masa m/z 445 [MH+].

Ejemplo 23#: Ciclopropilmetil 4-({9-[(2R,3R,4S,5R)-5-etinil-3,4-dihidroxitetrahidrofuran-2-il]-9H-purin-6-il)amino)piperidin-1-carboxilato

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y ciclopropilmetil-4-amino-1-piperidin carboxilato

LC/MS Tr =2.61min.

Espectro de masa m/z 442 [MH+].

Ejemplo24#: (2R,3R,4S,5R)-5-Etinil-2-{[6-(1S,2S)-2-metoxiciclopentil]amino-9H-purin-9-il)tetrahidrofuran-3,4-diol

Materiales de partida: acetato de(2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y (1S,2S)-2-metoxiciclopentilamina

LC/MS Tr= 2.26min.

Espectro de masa m/z 359 [MH+].

Ejemplo 25#: (2R,3R,4S,5R)-5-Etinil-2-[6-[(4,4-difluoro)ciclohexil]amino-9H-purin-9-il)tetrahidrofuran-3,4-diol

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-il y 4,4-difluorociclohexilamina

LC/MS Tr= 2.54min.

Espectro de masa m/z 380[MH+].

Ejemplo26#: (2R,3R,4S,5R)-5-Etinil-2-{6-[(ciclohex-3-enil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol;

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y ciclohex-3-enilamina

LC/MS Tr= 3.05min.

Espectro de masa m/z 341[MH+].

Ejemplo27#: (2R,3R,4S,5R)-5-Etinil-2-[6-diciclopropilmetil)amino]-9H-purin-9-il)tetrahidrofuran-3,4-diol

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y diciclopropilmetilamina

LC/MS Tr =2.61 min.

Espectro de masa m/z 355[MH+].

Ejemplo28#: (2R,3R,4S,5R)-5-etinil-2-[6-(ciclooctil)amino]-9H-purin-9-il)tetrahidrofuran-3,4-diol

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y ciclooctilamina

LC/MS Tr= 2.80min.

Espectro de masa m/z 371[MH+].

Ejemplo29#: (2R,3R,4S,5R)-5-etinil-2-[6-(cicloheptil)amino]-9H-purin-9-il)tetrahidrofuran-3,4-diol

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y cicloheptilamina

LC/MS Tr= 2.80min.

Espectro de masa m/z 357[MH+].

Ejemplo30: (2R,3R,4S,5R)-5-etinil-2-{6-[(1R*,4S*)-4-metoxiciclohept-2-enilamino)-9H-purin-9-il]-tetrahidrofuran-3,4-diol

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y (1R*,4S*)-4-metoxi-ciclohept-2-enilamina.

Se agregó cicloheptadieno (5ml, 46mmol) al peryodato de tetrabutilamonio (20g, 46mmol) disuelto en DCM, y la mezcla se enfrío hasta 0°C. Se agregó ter-butil-N-hidroxi carbamato (6.14g, 46 mmol) en pequeñas porciones con agitación y la mezcla se dejó durante la noche bajo nitrógeno. La mezcla de reacción se lavó con tiosulfato de sodio acuoso al 10% y bicarbonato de sodio acuoso saturado. La capa orgánica se secó ($MgSO_4$) y se concentró para dar un aceite negro. Éste se calentó hasta reflujo en MeOH/EtOAc al 4%. Al enfriar aparecieron cristales

color marrón que se removieron por filtración. El filtrado se concentró y se purificó por cromatografía en sílice (gradiente de elución EtOAc/ ciclohexano, 20 hasta 30%). Las fracciones que contenían el producto se concentraron para dar un aceite, que se volvió a disolver en EtOAc, se lavó con tiosulfato de sodio acuoso al 10%, se secaron ($MgSO_4$) y se concentraron para dar el 6-oxa-7-azabiciclo[3.2.2]non-8-en-7-carboxilato de tert-butilo como un aceite amarillo (8.89g, 39.5mmol, 89%).

LC/MS Tr =2.95min.

m/z 226 [MH^+].

Se disolvió el 6-oxa-7-azabiciclo[3.2.2]non-8-eno-7-carboxilato de ter-butilo (1g, 4.44 mmol) en ácido acético acuoso 10M (15 ml) y se agregó lentamente con agitación polvo de zinc (2.9g, 44.4 mmol). La mezcla se calentó hasta 70°C durante 6 horas. La mezcla de reacción enfriada se diluyó con agua y acetato de etilo, se filtró, y las capas se separaron. La capa acuosa se extrajo con acetato de etilo adicional. Los extractos orgánicos combinados se secaron ($NaSO_4$) y se concentraron para producir la cis-N-(terbutiloxicarbonil)-4-hidroxi-ciclohept-2-enilamina como un sólido blanco (0.22g, 0.97mmol, 22%).

m/z 171 (MH^+-tBu).

Se agregó hidruro de sodio (66mg, 1,65mmol)a la cis-N-(tert-butiloxicarbonil)-4-hidroxiciclohept-2-enilamina (0.178 g, 0.78 mmol) disuelta en THF (3ml), y la mezcla se agitó bajo nitrógeno durante una hora. Se agregó yoduro de metilo (48µl, 0.78mmol) y la mezcla se agitó durante la noche. Se agregó hidróxido de sodio acuoso 2M a la mezcla de reacción que se extrajo con acetato de etilo. La capa orgánica se lavó con cloruro de amonio acuoso saturado, se secó ($MgSO_4$) y se concentró para dar un aceite naranja. La purificación por cromatografía en sílice (gradiente de EtOAc / ciclohexano, 10% hasta 50%) dio la cis-N-(tert-butiloxicarbonil)-4-hidroxiciclohept-2-enilamina como un sólido blanco (79mg, 0.33 mmol, 42%). m/z 242 (MH^+).

Se trató la cis-N-(tert-butiloxicarbonil)-4-hidroxiciclohept-2-enilamina (175mg, 0.73mmol) con ácido clorhídrico 4M en dioxano (3 ml, 12 mmol) y se agitó a temperatura ambiente durante 3 horas. La mezcla se concentró in vacuo para dar un rendimiento cuantitativo de la sal de clorohidrato de cis-4-metoxiciclohept-2-enilamina como un sólido café brillante.
m/z 142 (MH^+).

<u>Intermediario 12: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-[6-[(1R*-4S*)-4-metoxi-ciclohept-2-enilamino)9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo</u>

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y cis-4-metoxi-ciclohept-2-enilamina

LC/MS Tr =2.98 min.

m/z 470 [MH^+].

Ejemplo 30: (a partir del Intermediario 12) (2R,3R,4S,5R)-5-etinil-2-{6-[(1R*,4S*)-4-metoxi-ciclohept-2-enilamino)-9H-purin-9-il]tetrahidrofuran-3,4-diol.

^{1}H RMN (MeOD) δ 8.14(2H,s,2xCH), 5.99 (1H,d,CH), 5.76 and 5.67 (2x1H, 2xbr.d, CH=CH), 4,70(1H,t,CH), 4.60(1H,dd,CH), 4.31 (1H,t,CH), 3.93 (1H, br, d, CH), 3.28(3H,s,OCH_3), 3.17(1H, d, CH), 1.93-1.33(6H,4xm,3xCH_2).

LC/MS Tr= 2.80min.

Espectro de masa m/z 357[MH+].

Ejemplo 31: (2R,3R,4S,5R)-5-etilnil-2-{6-[(1S*,4R*)-4-metoxi-ciclohept-2-ilamino)-9H-purin-9-il-tetrahidrofuran-3,4-diol

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y (1R*,4S*)-4-metoxicicloheptilamina

Se disolvió 6-oxa-7-azabiciclo[3.2.2]non-8-en-7-carboxilato de tert-butilo (3g, 13.3 mmol) en etanol

(135ml), y se agregó a hidróxido de paladio en carbón mineral activado (300mg). La mezcla de reacción se agitó bajo una atmósfera de hidrógeno hasta que casi 300 ml de hidrógeno se habían absorbido. El catalizador se removió por filtración a través de celite, y la capa orgánica se concentró para producir el 6-oxa-7-biciclo[3.2.2]nonan-7-carboxilato de tert-butilo como un aceite (2.98g, 13,1 mmol, 98%)

m/z 228 (MH^+).

Una solución del 6-oxa-7-azabiciclo[3.2.2]nonan-7-carboxilato de tert-butilo (1.81g, 8mmol) en THF seco (25ml) bajo nitrógeno, se trató con diyoduro de samario 0.1M en THF (250ml, 25mmol). La mezcla de reacción azul obscuro se agitó a temperatura ambiente durante 5 horas, después se diluyó con DCM y se apagó con tiosulfato de sodio acuoso al 10% (150ml). Las capas se separaron y la solución acuosa se extrajo con DCM. Los soluciones de DCM combinadas se lavaron con salmuera, y se secaron ($NaSO_4$) para dar un sólido café. La purificación por cromatografía en sílice 50% EtOAc/ ciclohexano) dio la cis-N-(tert-butiloxicarbonil)-4-hidroxi-cicloheptilamina como un sólido blanco (0.9g, 3.9 mmol, 49%).

m/z =174 (MH^+—tBu).

Se agregó hidruro de sodio (332mg, 8.30 mmol) lentamente a la N-(tert-butiloxicarbonil)-4-hidroxi-

ciclohepTilamina (905mg, 3.95 mol) disuelta en THF seco (16ml) bajo nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 1 hora. Se agregó yoduro de metilo (243 µl, 3.91 mmol) y la mezcla se agitó durante la noche a temperatura ambiente. Se agregó hidróxido se sodio acuoso:2.0M y la capa acuosa se extrajo con acetato de etilo. La fase orgánica se lavó con cloruro de amonio acuoso saturado, se secó ($MgSO_4$) y se concentró. El aceite resultante se modificó por cromatografía en gel de sílice (gradiente de elución EtOAc/ciclohexano, 15% hasta 50%) para producir cis-N-(tert-butiloxicarbonil)-4-hidroxicicloheptilamina como un sólido blanco (290 mg, 1.19 mmol, 30%).

Se disolvió la cis-N-(tert-butiloxicarbonil)-4-metoxi-cicloheptilamina (228 mg, 1.19 mmol) en ácido clorhídrico en dioxano. (2ml, 8mmol) y se agitó a temperatura ambiente durante 3 horas. La mezcla se concentró in vacuo para dar un rendimiento cuantitativo de la sal de clorohidrato de cis-4-metoxiheptilamina como un sólido amarillo.

m/z 144 (MH^+).

<u>Intermediario 13: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-[(1R*-4S*)-4-metoxi-Cicloheptilamino)9H-purin-9-ilo)-5-etiniltetrahidrofuran-3-ilo</u>

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y cis-4-metoxi-cicloheptilamina

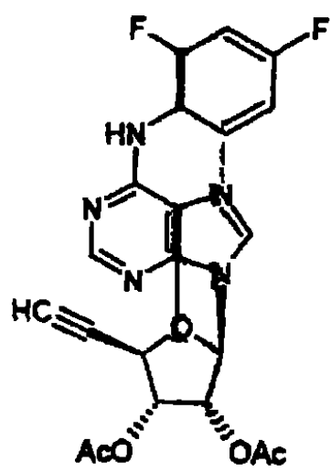
Ejemplo31: (a partir del Intermediario 13) (2R,3R,4S,5R)-5-etinil-2-[6-(1S*,4R*)-4-metoxi-cicloept-2-ilamino)-9H-purin-9-il]-tetrahidrofuran-3,4-diol)

^{1}H RMN (MeOD) δ 8.13(2H,s,2xCH), 5.99 (1H, d, CH), 4.69 (1H, t, CH), 4.60(1H,dd,CH), 4.30(1H,t,CH), 4.20 (1H, vbr.s, NH), 3.37-3.44 (1H,m ,CH), 3.23(3H,s,OCH3), 3.16(1H,d,CH), 2.05-1.30 (10H, 4xm, 5xCH_2).

MS m/z 359[MH+].

Ejemplo 32: (2R,3R,4S,5R)-2-{6-{(2,4-difluorofenil) amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

Intermediario 14: acetato de (2R,3R,4R,5R)-4-(Acetiloxi)-2-{6-[(2,4-difluorofenil)amino]-9H-purin-9-ilo}-5-etiniltetrahidrofuran-3-il



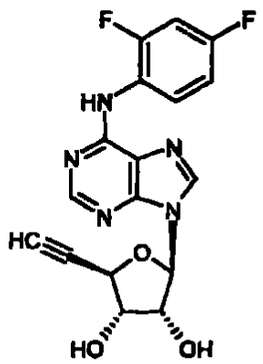
A una solución de acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-il (0.050g) en etanol (2ml), se le agregó 2,4-difluoroanilina (0.041 ml) y carbonato de calcio (0.027g). La mezcla se calentó hasta 90°C durante 18 horas en un recipiente sellado. El solvente se removió in vacuo. La purificación por HPLC preparativa automatizada para dar el compuesto del título (0.014g) como una goma.

Notar que en algunas ocasiones la desprotección de los acetatos ocurre para dar los compuestos mono y di desprotegidos.

LC/MS Tr 3.25 min.

Espectro de masa m/z 457 [MH^+].

Ejemplo 32: (a partir del Intermediario 14) (2R,3R,4S,5R)-2-{6-[(2,4-Difluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol



A una solución de acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-{6-[(2,4-difluorofenil)amino]-9H-purin-9-

il}-5-etiniltetrahidrofuran-3-ilo (0.012g) en metanol (2ml), se agitó a 5°C (baño de hielo), y se le agregó t-butilamina (0.1ml), y la mezcla se agitó durante 1 hora a 5°C. El solvente se removió in vacuo. La purificación por HPLC preparativa automatizada para dar el compuesto del título (0.007g) como una goma.

LC/MS Tr =2.75 min.

Espectro de masa m/z 374 [MH+].

Los siguientes compuestos se elaboraron usando una ruta análoga al procedimiento anterior del ejemplo 20 usando los materiales de partida apropiados.

Ejemplo 33: (2R,3R,4S,5R)-2-{6[(4-Cloro-2-fluorofenil)amino]9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

Intermediario 15: acetato de (2R,3R,4R,5R)-4-(Acetiloxi)-2-[6-(4-cloro-2-fluoroanilino)-9H-purin-9-ilo]-5-etiniltetrahidrofuran-3-ilo

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y 4-cloro-2-fluororanilina.

Ejemplo 33: (a partir del Intermediario 15)

(2R,3R,4S,5R)-2-{6-[(4-cloro-2-fluorofenil)amino]9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

LC/MS Tr =3.01min.

Espectro de masa m/z 390 [MH+].

Ejemplo34: (2R,3R,4S,5R)-2{2-Clor -6-[(4-cl ro-2-fluorofenil)amino]-9H-purin-9-il}-etiniltetrahidrofuran-3,4,-diol

Intermediario 16: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(2-cloro-6-[(4-cloro-2-fluorofenil)amino]-9H-Purin-9-il}-5-etiniltetrahidrofuran-3-ilo

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y 4-cloro-2-fluoroanilina.

Ejemplo 34: (a partir del Intermediario 16) (2R,3R,4S,5R)-2-{2-cloro-6-[(4-cloro-2-fluorofenil)amino]-9H-purin-9-il)-5-etiniltetrahidrofuran-3,4-diol

LC/MS Tr= 3.34 min.

Espectro de masa m/z 425 [MH+].

Ejemplo 35: (2R,3R,4S,5R)-2-[6-[(2-cloro-4-fluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

Intermediario 17: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-[6[(2-cloro-4-fluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3-ilo

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y 2-cloro-4-fluoroanilina.

Ejemplo 35: (a partir del Intermediario 17) (2R,3R,4S,5R)-2-{6-[(2-cloro-4-fluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

LC/MS Tr= 2.87 min.

Espectro de masa m/z 390 [MH+].

Ejemplo 36: (2R,3R,4S,5R)-5-Etinil-2-{6-[(4-fluoro-2-metilfenil)amino1-9H-purin-9-il}tetrahidrofuran-3,4-diol

Intermediario 18: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-5-etinil-2-{6-[(4-fluoro-2-metilfenil)amino]-9H-purin-9-il}tetrahidrofuran-3-ilo

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y 4 fluoro-2-metilanilina.

Ejemplo 36: (a partir del Intermediario 18) (2R,3S,4R,5R)-5-etinil-2-{6-[(4-fluoro-2-Metilfenil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol

LC/MS Tr= 2.69 min.

Espectro de masa m/z 370 [MH+].

Ejemplo 37: (2R,3R,4S,5R)-5-Etinil-2-(6-[(3-fluoro-2-metilfenil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol

Intermediario 19: acetato de (2R,3R,4R,5R)-4-(Acetiloxi)-5-etinil-2-{6-[(3-fluoro-2-metilfenil)amino]-9H-Purin-9-il}tetrahidrofuran-3-ilo

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y 3-fluoro-2-metilanilina.

Ejemplo 37; (a partir del Intermediario 19) (2R,3R,4S,5R)-5-etinil-2-{6-[(3-fluoro-2-Metilfenil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol

^{1}H RMN (DMSO) δ 9.72 (1H, s, NH), 8.42 (1H, s, CH), 8.26 (1H,s,CH), 7.26-7.20 (2H, m, 2xCH), 7.07 (1H, m, CH), 5.99 (1H,d,CH); 5.75 (2H, vr.s, 2xOH), 4.82 (1H,t,CH); 4.58 (1H, dd, CH); 4.39(1H, t, CH); 3.77 (1H, d, CH); 2.09 (3H,d,CH_3).

LC/MS Tr= 2.64 min.

Espectro de masa m/z 370 [MH+].

Ejemplo 38: (2R,3R,4S,5R)-2-{6-[(3-cloro-2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

Intermediario 20: acetato de (2R,3R,4R,5R)-4-(Acetiloxi)-2-{6-[(3-cloro-2-Metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3-ilo

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-ilo y 3-cloro-2-metilanilina.

Ejemplo 38: (a partir del Intermediario 20)(2R,3R,4S,5R)-2-{6-[(3-cloro-2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

^{1}H RMN (DMSO) δ 9.70 (1H,s,NH); 8.42 (1H,s,CH); 8.25 (1H,s,CH); 7.35-7.32 (2H,m,2xCH); 7.25 (1H,t,CH); 5.99 (1H,d,CH); 5.78 (0.5H,d,OH); 5.74 (0.5H,d,OH); 4.82 (1H,m,CH); 4,58 (1H,dd,CH); 4.38 (1H,q,CH);3.76 (1H,d,CH); 2.21(3H,s,CH_3).

LC/MS Tr= 2.80min

Espectro de masa m/z 386 [MH+].

Ejemplo 39: (2R,3R,4S,5R)-2-[6-[(4-Cloro-2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

Intermediario 21: acetato de (2R,3R,4R,5R)-4-(Acetiloxi)-2-{6-[(4-cloro-2-metilfenil)amino-9H-purin-9-ilo}-5-etiniltetrahidrofuran-3 ilo

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9il)-5-etiniltetrahidrofuran-3-ilo y 4-cloro-2-metilanilina.

Ejemplo 39: (a partir del Intermediario 21) (2R,3R,4S,5R)-2-{6-[(4-cloro-2-Metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

^{1}H RMN (DMSO) δ 9.69 (1H,s,NH); 8.61 (1H,s,CH); 8.45 (1H,s,CH); 7.61 (1H,d,CH); 7.58 (1H,d,CH); 7.48d (1H,dd,CH); 6.19 (1H,d,CH); 5.98 (1.2H,v.br.s.,3xOH); 5.03 (1H,t,CH); 4.78 (1H,dd,CH); 4.59 (1H,t,CH); 4.59 (1H,t,CH); 3.96 (1H,d,CH); 2.40 (3H,s,CH3).

LC/MS Tr= 2.85 min.

Espectro de masa m/z 386 [MH+].

Ejemplo 40: (2R,3R,4S,5R)-2-{6-[(5-cloro-2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

Intermediario 22: acetato de (2R,3R,4R,5R)4-(acetiloxi)-2-{6-[(5-cloro-2-metilfenil)amino]-9H-purin-9-ilo}-5-etiniltetrahidrofuran-3-ilo

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-ilo)-5-etiniltetrahidrofuran-3-ilo y 5-cloro-2-metilanilina

Ejemplo 40: (a partir del Intermediario 22) (2R,3R,4S,5R)-2-{6-[(5-cloro-2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

LC/MS Tr= 2.86 min.

Espectro de masa m/z 386 [MH+].

Ejemplo 41: (2R,3R,4S,5R)-2-{6-[(2-Bromo-4-fluorofenil)amino]-9H-purin-9-il}5-etiniltetrahidrofuran-3,4-diol

Intermediario 23: acetato de (2R,3R,4R,5R)-4-acetiloxi)-2-{6-[(2-bromo-4-fluorofenil)amino]-9H-Purin-9-ilo]-5-etiniltetrahidrofuran-3-ilo

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-ilo)-5-etiniltetrahidrofuran-3-il y 2-bromo-4-fluoroanilina.

Ejemplo 41: (a partir del Intermediario 23) (2R,3R,4S,5R)-2-[6-[(2-bromo-4-fluorofenil)amino]-9H-Purin-9-il]-5-etiniltetrahidrofuran-3,4-diol

LC/MS Tr= 2.79min.

Espectro de masa m/z 435 [MH+].

Ejemplo 42: (2R,3R,4S,5R)-2-{2-cloro-6-[(3-fluoro-2-metilfenil)amino]-9H-purin-9-il)-5-etiniltetrahidrofuran-3,4-diol

Intermediario 24: acetato de (2R,3R,4R,5R)-4-(Acetiloxi)-2[2-cloro-6-[(3-fluoro-2-metilfenil)amino]-9H-purin-9-ilo}-5-etiniltetrahidrofuran-3-ilo.

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-ilo)-5-etiniltetrahidrofuran-3-ilo y 3-fluoro-2-metilanilina.

Ejemplo 42: (a partir del Intermediario 24) (2R,3R,4S,5R)-2-{2-cloro-6-[(3-fluoro-2-metilfenil)amino]-9H-purin-9-il}-5-tetrahidrofuran-3,4-diol

LC/MS Tr =3.17 min.

Espectro de masa m/z 405 [MH+].

Ejemplo 43: (2R,3R,4S,5R)-2-{6-[(3,4-Difluorofenil)amino]-9H-Purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

Intermediario 25: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-{6-[(3,4-difluorofenil)amino]-9H-purin-9-ilo}-5-etiniltetrahidrofuran-3-ilo

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-il)-5-etiniltetrahidrofuran-3-il y 3,4-difluoroanilina.

Ejemplo 43: (a partir del Intermediario 25) (2R, 3R, 4S, 5R)-2-{6-[(3,4-Difluorofenil)amino1-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

^{1}H RMN (MeOH) δ 8,5 (1H,s,CH); 8.41 (1H,s,CH); 8.14 (1H,m,CH); 7.52(1H,m,CH); 7.4(1H,m,CH); 6.2 (1H,d,Ch); 4.91 (1H,m,CH); 4.78 (1H,m,CH); 4.49 (1H,t,CH); 3,31 (1H,d,CH).

LC/MS Tr= 2.85 min.

Espectro de masa m/z 374 [MH+].

Ejemplo 44: (2R,3R,4S,5R)-2-{6-[(2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

Lntermediario 26: acetato de (2R,3R,4R,5R)-4-(Acetiloxi)-2-{6-[(2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3-ilo

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-ilo)-5-etiniltetrahidrofuran-3-ilo y 2-metil anilina

Ejemplo 44: (a partir del Intermediario 26): (2R,3R,4S,5R)-2-{6-[(2-metilfenil)amino]-9H-purin-9-il}5-etiniltetrahidrofuran-3,4-diol

LC/MS Tr= 3.05 min.

Espectro de masa m/z 352 [MH+].

Ejemplo 45: (2R,3R,4S,5R)-2{6-[(4-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

Intermediario 27: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-{6-[(4-metilfenil)amino]-9H-purin-9-ilo}-5-etiniltetrahidrofuran-3-ilo

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-ilo)-5-etiniltetrahidrofuran-3-ilo y 4-metil anilina

Ejemplo 45: (a partir del Intermediario 27) (2R,3R,4S,5R)-2-{6-[(4-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

LC/MS Tr= 3.26 min.

Espectro de masa m/z 352 [MH+].

Ejemplo 46: (2R,3R,4S,5R)-2-{6-[(3-Cloro-2-fluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

Intermediario 28: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-{6-[(3-cloro-2-fluorofenil)amino]-9H-Purin-9-ilo}-5-etiniltetrahidrofuran-3-ilo

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-ilo)-5-etiniltetrahidrofuran-3-ilo y 3-cloro-2-fluoro anilina

Ejemplo 46 (a partir del Intermediario 28)

(2R,3R,4S,5R)-2-{6-[(3-cloro-2-fluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofuran-3,4-diol

LC/MS Tr= 2.83 min.

Espectro de masa m/z390 [MH+].

Ejemplo 47: (2R,3R,4S,5R)-2-{6-[(2-fluoro-5-metilfenil)amino]-9H-purin-9-il)-5-etiniltetrahidrofuran-3,4-diol:

Intermediario 29: acetato de (2R,3R,4R,5R)-4-(Acetiloxi)-2-{6-[(2-fluoro-5-metilfenil)amino]-9H-Purin-9-ilo]-5-etiniltetrahidrofuran-3-ilo

Materiales de partida: acetato de (2R,3R,4R,5R)-4-(acetiloxi)-2-(6-cloro-9H-purin-9-ilo)-5-etiniltetrahidrofuran-3-ilo y 2-fluoro-5-metil anilina

Ejemplo 47: (a partir del Intermediario 29)

(2R,3R,4S,5R)-2-{6-[(2-fluoro-5-metilfenil)amino]-9H-purin-9-il]-5-etiniltetrahidrofuran-3,4-diol

LC/MS Tr= 2.72min.

Espectro de masa m/z 369 [MH+].

Sistema LC/MS

- Columna: 3.3cm x 4.6mm ID, 3um ABZ+PLUS
- Relación de Flujo: 3ml/min

- Volumen de inyección: 5µl
- Temperatura: temperatura ambiente

Solventes: A: ácido fórmico 0.1% + acetato de amonio 10m Molar.

B: acetonitrilo 95% + ácido fórmico 0.05%

Gradiente:	Tiempo	A%	B%
	0.00	100	0
	0.70	100	0
	4.20	0	100
	5.30	0	100
	5.50	100	0

HPLC preparativa automatizada.

- Columna: 10cm x 21.2 mm ID, 5um ABZ + PLUS
- Relación de flujo: 4ml/min
- Temperatura: temperatura ambiente

Solventes: A: agua de HPLC + ácido fórmico 0.1%

B: acetonitrilo + ácido fórmico 0.05%

Gradiente:	Tiempo	A%	B%
	0.00	95	5
	1.45	95	5
	20	10	90
	30	10	90
	32	95	5

Experimentos del gen reportero en levadura.

La actividad agonista en los receptores A1 de adenosina humanos se midió en líneas de célula de levadura que expresan el receptor A1 de adenosina, junto con una proteína G quimérica que enlaza la estimulación del receptor a la expresión de la enzima de β-galactosidasa. Las células se sembraron en placas de 96-pozos en un medio de cultivo al cual se le agregó 3-AT 2mM (3-aminotriazol) para limitar el crecimiento basal en ausencia de estimulación agonista, y FDG (di-β-D-galactopiranosida de fluoresceína) como sustrato para la β-galactosidasa, que convirtió la FDG a fluoresceína. Para medir la potencia, se agregaron agonistas a los pozos apropiados a un rango de concentración de aproximadamente 10^{-10} - 10^{-5}M y se incubaron a 30°C por 18 horas. En este punto, la cantidad de fluoresceína se midió en un espectrofotómetro. De estas lecturas, se puede calcular la concentración-dependencia de la estimulación por el agonista. Uno de los agonistas probados en cada una de las placas de 96-pozos fue el agonista no selectivo estándar, N-etilcarboxamido adenosina (NECA), y la potencia de todos los agonistas probados se expresa con relación al estándar NECA. (ECR= relación de concentración equipotente relativa a NECA=1)

Experimentos del gen reportero en células CHO.

La actividad agonista en receptores A3 de adenosina humanos se midió en células de ovario de Hámster Chino (CHO) que contenían los elementos del gen reportero CRE/SPAP/HYG (CRE= elemento de repuesta cíclico AMP; HYG= resistencia a la higromicina; SPAP= fosfatasa alcalina de placenta secretada) que durante la estimulación de niveles cAMP produce SPAP. Se usó una línea de célula que se transfectó establemente con el receptor A3 de adenosina humano, además de los elementos anteriores. Las células se sembraron en placas de 96-pozos en un medio de cultivo y se incubaron a 37°C durante 1 hora. Para medir la potencia, se agregaron agonistas a los pozos apropiados a un rango de concentración de aproximadamente 10^{-10} - 10^{-5}M. Después de 15 minutos, se estimularon los niveles de cAMP por la adición de una concentración máxima de forskolina. Todas las células se incubaron después durante 5 horas adicionales a 37°C, y se enfriaron hasta temperatura ambiente, después de lo cual un sustrato para la fosfatasa (fosfato de para-nitrofenol, pNPP), que se convirtió por SPAP a un reactivo de color) se agregó después, y las placas de 96-pozos se leyeron en una placa lectora. De estas lecturas, puede calcularse la concentración-dependiente de la inhibición por el agonista para la producción de SPAP

estimulada por forskolina. Como en los ensayos de levadura, uno de los agonistas probados en cada una de las placas de 96-pozos fue el agonista no selectivo estándar, N-etilcarboxamidoadenosina (NECA), y la potencia de todos los agonistas probados se expresa con relación al estándar NECA.

Tabla 2: Potencias en los ensayos de gen reportero.

Ejemplo No.	Receptor de Adenosina A1 ECR*	Receptor de Adenosina A3 ECR*
33	26.31	>215
34	39	>607
1	9.95	>1070
2	10	>3580
3	6.48	>823
35	6.48	>974
36	7.15	>1117
32	7.94	>1070
37	4.79	>145
38	5.48	>145
39	7.36	>168
40	16.94	>505
41	5.92	>505
4	27.96	>407

5	3	>196
6	24.6	>1059
42	9.17	>220
7	11.4	>178
8	7.94	>178
9	23.81	>165
43	34.9	>188
10	6.89	>1066
11	5	>210
12	4.47	>80.2
13	18.86	>386
14	14.86	>502
15	18.79	>778
17	2.88	>416
19	8.57	>3208
18	6.81	>3208

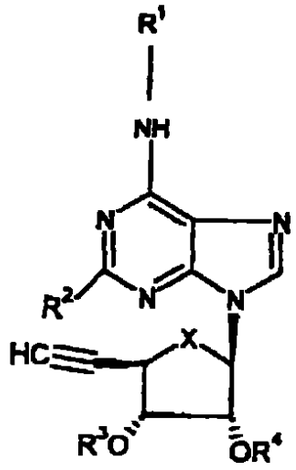
*ECR= la relación de concentración equipotente relativa a NECA=1 (ver descripción en el ensayo Gen reportero).

A través de la especificación y las reivindicaciones que siguen, salvo que el contexto requiera otra cosa, la palabra "comprende", y variaciones tales como "que comprende" y "comprendiendo", se entenderá que implican la inclusión de entidades completas declaradas o etapa o grupo de entidades completas pero no la exclusión de

cualquier otra entidad completa o etapa o grupo de entidades completas o etapas.

Reivindicaciones

1. Un compuesto de fórmula (Ia):



(Ia)

en donde X representa O o CH_2;

R^1 representa:

(i) cicloalquilo (C_{3-9}) -$(alq)_n$- o cicloalquenilo (C_{3-9}) -$(alq)_n$-, el grupo cicloalquilo o cicloalquenilo estando substituido opcionalmente por uno o más substituyentes seleccionados de OH, halógeno, alquilo C_{1-6}, -alcoxi C_{1-6}, alqueniloxi C_{2-6}-, alquiniloxi C_{2-6}- y fenilo, en donde (alq) representa alquilo C_{1-3} y n representa 0 ó 1, y el grupo (alq) puede opcionalmente substituirse por el grupo cicloalquilo C_{3-6};

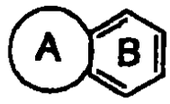
(ii) un grupo fenilo opcionalmente substituido por uno o más substituyentes seleccionados de: halógeno, CF_3,

ciano, -alquilo C_{1-6}, -alquenilo C_{2-6}, -alquinilo C_{2-6}, alcoxi C_{1-6}-, -alquil OH C_{1-6}, $-CO_2H$ y $-CO_2$ alquil C_{1-6};

(iii) un grupo heterocíclico C_{4-7} que contiene al menos un heteroátomo seleccionado de O, N, o S, y substituido opcionalmente por uno o más substituyentes seleccionados de OH, -alquilo C_{1-6}, -alcoxi C_{1-6}, $-CO_2$ alquil C_{1-4}, -CO alquil C_{1-4}, $-CO_2$ arilo o cicloalquil (C_{3-6}) $-CO_2(alq)_n$, en donde (alq) representa alquilo C_{1-3} y n representa 0 ó 1;

(iv) un grupo alquilo C_{1-12} de cadena recta o ramificada substituido opcionalmente por uno o más grupos seleccionados de fenilo, halógeno, hidroxi, y cicloalquilo C_{3-7}, donde uno o más átomos de carbono del grupo alquilo C_{1-12} puede reemplazarse opcionalmente por un grupo independiente seleccionado de $S(=O)_n$ (donde n es 0, 1 ó 2) y N;

(v) un anillo bicíclico fundido



en donde A representa cicloalquilo C_{4-6} o fenilo y B representa fenilo substituido opcionalmente por alquilo C_{1-3}, y el anillo bicíclico se enlaza a la porción purina-6-amino por medio de un átomo de anillo del anillo A;

R^2 representa un grupo -alquilo C_{1-3}, halógeno, hidrógeno o -alcoxi C_{1-3};

R^3 y R^4 independientemente representan H o un grupo -alquilo C_{1-6};

o una sal farmacéuticamente aceptable y/o solvato del mismo.

2. Un compuesto de conformidad con la reivindicación 1 en donde R^2 representa hidrógeno o halógeno.

3. Un compuesto de conformidad con la reivindicación 1 ó 2 en donde R^3 y R^4 cada uno representa hidrógeno.

4. Un compuesto de conformidad con alguna de las reivindicaciones 1 a 3 en donde X representa O.

5. Un compuesto seleccionado de:

(2R, 3R, 4S, 5R)-2-{6-[(4-cloro-2-fluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-{2-cloro-6-[(4-cloro-2-fluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-{6-[(2-cloro-4-fluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-{6-[(4-fluoro-2-metilfenil)amino]-9H-purin-9-il}tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-{6-[(2,4-difluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-{6-[(3-fluoro-2-metilfenil)amino]-9H-purin-9-il}tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-{6-[(3-cloro-2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-{6-[(4-cloro-2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-{6-[(5-cloro-2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-{6-[(2-bromo-4-fluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-{2-cloro-6-[(3-fluoro-2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-{6-[(3,4-difluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

N-etil-2-({9-[(2R,3R,4S,5R)-5-etinil-3,4-dihidroxitetrahidrofurano-2-il]-9H-purin-6-il}amino)etanosulfonamida;

Etil 4-({9-[(2R,3R,4S,5R)-5-etinil-3,4-dihidroxitetrahidrofurano-2-il]-9H-purin-6-il}amino)piperidin-1-carboxilato;

(2R, 3R, 4S, 5R)-5-etinil-2-(6-{[(1S,2S)-2-hidroxiciclopentil]amino}-9H-purin-9-il)tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-[6-indan-2-ilamino)-9H-purin-9-il]-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-[6-(ciclobutilamino)-9H-purin-9-il]-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-{6-[(2-feniletil)amino]-9H-purin-9-il}tetrahidrofuran-3,4-diol;

(2R, 3R, 4S, 5R)-2-[6-(ciclohexilamino)-9H-purin-9-il]-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-(6-{[(1S*,2S*,3S*,4R*)-3-metilbiciclo[2.2.1]hept-2-il]amino}-9H-purin-9-il)tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-(6-{[(1R*,*2S)-2-metoxi-2-fenilciclopentil]amino}-9H-purin-9-il)tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-[6-(ciclopropilamino)-9H-purin-9-il]-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-{6-[(ciclopropilmetil)amino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-[6-(ciclopentilamino)-9H-purin-9-il]-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-(6-{[(2R,3R)-2-metiltetrahidrofurano-3-il]amino}-9H-purin-9-il)tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-(6-{[(2S,3S)-2-metiltetrahidrofurano-3-il]amino}-9H-purin-9-il)tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-{6-[(trans-4-metoxiciclohexil)amino]-9H-purin-9-il}tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-{6-[(trans-4-etoxiciclohexil)amino]-9H-purin-9-il}tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-{6-[(trans-4-propeniloxiciclohexil)amino]-9H-purin-9-il}tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-[6-(tetrahidro-2H-piran-4-ilamino)-9H-purin-9-il]tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-{6-[(1R*,5R*,6S*)-biciclo[3.2.0]hept-6-ilamino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-{6-[(2,2-dimetilciclopropil)amino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-{6-[(trans-4-hidroxiciclohexil)amino]-9H-purin-9-il}tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-{6-[(2-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-{6-[(4-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-{6-[(3-cloro-2-fluorofenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-2-{6-[(2-fluoro-5-metilfenil)amino]-9H-purin-9-il}-5-etiniltetrahidrofurano-3,4-diol;

butil 4-({9-[(2R, 3R, 4S, 5R)-5-etinil-3,4-dihidroxitetrahidrofurano-2-il]-9H-purin-6-il}amino)piperidina-1-carboxilato;

ciclopropilmetil 4-({9-[(2R, 3R, 4S, 5R)-5-etinil-3,4-dihidroxitetrahidrofurano-2-il]-9H-purin-6-il}amino)piperidina-1-carboxilato;

(2R, 3R, 4S, 5R)-5-etinil-2-{(6-[(1S,2S)-2-metoxiciclopentil]amino}-9H-purin-9-il)tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-{6-[(4,4-difluoro)ciclohexil]amino}-9H-purin-9-il)tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-{6-[(ciclohex-3-enil)amino]}-9H-purin-9-il)tetrahidrofuran-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-[6-(diciclopropilmetil)amino]-9H-purin-9-il)tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-[6-(ciclooctil)amino]-9H-purin-9-il)tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-[6-(cicloheptil)amino]-9H-purin-9-il)tetrahidrofurano-3,4-diol;

(2R, 3R, 4S, 5R)-5-etinil-2-{6-[(1R*,4S*)-4-metoxi-ciclohept-2-enilamino)-9H-purin-9-il]-tetrahidrofurano-3,4-diol; y

(2R, 3R, 4S, 5R)-5-etinil-2-{6-[(1S*,4R*)-4-metoxi-ciclohept-2-enilamino)-9H-purin-9-il]-tetrahidrofurano-3,4-diol.

6. Una composición farmacéutica que comprende un compuesto de fórmula (Ia) o una sal farmacéuticamente aceptable y/o solvato del mismo junto con un portador farmacéutico y/o excipiente.

7. El uso de un compuesto de fórmula (Ia) o una sal farmacéuticamente aceptable y/o solvato del mismo, para la manufactura de un medicamento para el tratamiento de un paciente que sufre de una condición donde es una ventaja reducir la concentración de ácido graso libre en plasma o reducir el ritmo cardiaco.

8. El uso de un compuesto de fórmula (Ia) o una sal farmacéuticamente aceptable y/o solvato del mismo para la manufactura de un medicamento para el tratamiento de un paciente que sufre de, o es susceptible a enfermedad isquémica del corazón, enfermedad vascular periférica o apoplejía o cuyo sujeto padece de dolor, un trastorno del SNC, apnea del sueño o emesis.

9. Un método para el tratamiento en un paciente que sufre de una condición donde es una ventaja reducir la concentración de ácido graso libre en plasma o reducir el ritmo cardiaco, que comprende administrar una cantidad terapéuticamente efectiva a un compuesto de fórmula (Ia) o una sal farmacéuticamente aceptable y/o solvato del mismo.

10. Un método para el tratamiento en un paciente que sufre de, o es susceptible a enfermedad isquémica del corazón, enfermedad vascular periférica o apoplejía o cuyo sujeto padece de dolor, un trastorno del SNC, apnea del sueño o emesis, que comprende administrar una cantidad terapéuticamente efectiva de un compuesto de fórmula (Ia) o una sal y/o solvato farmacéuticamente aceptable del mismo.

Resumen.

La presente invención se refiere a composiciones farmacéuticas que contienen ciertos derivados de la adenosina que tienen un grupo acetileno en la posición 4', que son agonistas A1 de la adenosina, y a su uso en terapia.

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Applicant's or agent's file reference PG4423	Date of mailing (day/month/year) 10.06.2003
	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB02/01317	19/03/2002	20/03/2001

Applicant
GLAXO GROUP LIMITED

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27(5), 33(5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Cardenas, C Tel.+31 70 340-3370

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PG4423		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB02/01317	19/03/2002	20/03/2001
International Patent Classification (IPC) or national classification and IPC C07H19/16		
Applicant GLAXO GROUP LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/09/2002	10.06.2003
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Fitz, W Telephone No. +31 70 340 4359

Form PCT/IPEA/409 (cover sheet) (January 1994)

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB02/01317

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-56 as originally filed

Claims, No.:

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-10
	No:	Claims	1-4
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-8
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 99 38877 A (COUSINS RICHARD PETER CHARLES ;COX BRIAN (GB); CHAN CHUEN (GB); GL) 5 August 1999 (1999-08-05)

D2: WO 99 24449 A (COUSINS RICHARD PETER CHARLES ;COX BRIAN (GB); GLAXO GROUP LTD (GB) 20 May 1999 (1999-05-20) cited in the application

1.) The subject-matter of claims 1-4 is not new. The reasons for this are the following:
D1 discloses 5'-ethynyladenosine derivatives (see p. 24, l.4-20, formula (XI)) for use as synthesis intermediates.
In view of the definitions of the variables "L" and "R1" in formula (XI) of D1 ["L" is halogen; "R1": see p.5, l.15-p.6,l.15, and p.10, l.27] it has to be concluded that the compounds of formula XI of D1 anticipate the compounds of formula (Ia) of the application wherein R2 is halogen.

The subject-matter of claim 5 is considered to be new, because none of the available prior art documents discloses the specific compounds recited in claim 5.

The subject-matter of claims 6-10 is considered to be new, because none of the available prior art documents discloses pharmaceutical compositions or pharmaceutical uses of a compound of formula (Ia) of claim 1.

2.) The subject-matter of claims 1-10 is considered to involve an inventive step. The reasons for this are the following:

D2 (cited by the Applicant) is considered to be the closest prior art document.

D2 describes adenosine derivatives with a fluorinated alkyl group at the 4'-position for use as adenosine A1 receptor agonists.

The difference between the application and D2 is that the adenosine derivatives of the application have an acetylene-group in the 4'-position whereas the adenosine derivatives of D2 have a fluorinated alkyl group at the 4'-position.

The problem to be solved is considered to be the provision of further adenosine derivatives for use as adenosine A1 receptor agonists.

The problem is solved by replacing the fluorinated alkyl group of D2 with 4'-acetylene.

Neither D2 alone, nor D2 in combination with another of the available prior art documents, would direct the skilled practioner towards replacing the fluorinated alkyl group of D2 with acetylene.
Thus the subject-matter of claims 1-10 is considered to be non-obvious and to involve an inventive step.

3.) Claims 9 and 10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/01317

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H19/16 C07D473/18 C07D473/34 A61K31/70 A61P9/10
A61P25/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 334 361 A (MERRELL DOW PHARMA) 27 September 1989 (1989-09-27) claim 3, examples	1-6
X	WO 99 38877 A (COUSINS RICHARD PETER CHARLES ;COX BRIAN (GB); CHAN CHUEN (GB); GL) 5 August 1999 (1999-08-05) the whole document, in particular page 24, lines 4-24	1-5
A	WO 99 67262 A (BAYS DAVID EDMUND ;COUSINS RICHARD PETER CHARLES (GB); JUDKINS BRI) 29 December 1999 (1999-12-29) cited in the application abstract	1,6-10

-/--

[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
19 June 2002	27/06/2002

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	Fitz, W

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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/01317

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 24449 A (COUSINS RICHARD PETER CHARLES ;COX BRIAN (GB); GLAXO GROUP LTD (GB) 20 May 1999 (1999-05-20) cited in the application abstract	1,6-10

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/01317

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

Although claims 9,10 are 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

Information on patent family members

International Application No
PCT/GB 02/01317

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0334361 A	27-09-1989	US 4996308 A	26-02-1991
		AT 121415 T	15-05-1995
		AU 3173789 A	28-09-1989
		CA 1322195 A1	14-09-1993
		CN 1036579 A ,B	25-10-1989
		DE 68922235 D1	24-05-1995
		DE 68922235 T2	31-08-1995
		DK 145289 A	26-09-1989
		EP 0334361 A2	27-09-1989
		ES 2074060 T3	01-09-1995
		FI 891339 A ,B,	26-09-1989
		HU 49367 A2	28-09-1989
		IE 67543 B1	17-04-1996
		JP 1283285 A	14-11-1989
		JP 2829737 B2	02-12-1998
		KR 135529 B1	23-04-1998
		NO 891248 A ,B,	26-09-1989
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		PH 26776 A	13-10-1992
		PT 90080 A ,B	10-11-1989
		ZA 8902105 A	29-11-1989
WO 9938877 A	05-08-1999	AU 2719799 A	16-08-1999
		BG 104729 A	30-04-2001
		BR 9907270 A	24-10-2000
		CA 2318278 A1	05-08-1999
		CN 1289338 T	28-03-2001
		EE 200000441 A	17-12-2001
		WO 9938877 A2	05-08-1999
		EP 1051425 A2	15-11-2000
		HR 20000511 A1	31-12-2000
		JP 2002501928 T	22-01-2002
		NO 20003867 A	28-07-2000
		PL 342670 A1	02-07-2001
		SK 11192000 A3	11-06-2001
		TR 200002218 T2	21-12-2000
		TW 434250 B	16-05-2001
		ZA 9900689 A	28-07-2000
WO 9967262 A	29-12-1999	AU 4514699 A	10-01-2000
		BG 105155 A	28-09-2001
		BR 9911498 A	20-03-2001
		CN 1314910 T	26-09-2001
		EE 200000784 A	15-04-2002
		WO 9967262 A1	29-12-1999
		EP 1090019 A1	11-04-2001
		HR 20000896 A1	31-12-2001
		NO 20006520 A	14-02-2001
		PL 345089 A1	03-12-2001
		SK 19582000 A3	06-11-2001
		TR 200100449 T2	21-08-2001
WO 9924449 A	20-05-1999	AU 2048399 A	31-05-1999
		BR 9813976 A	26-09-2000
		CA 2309200 A1	20-05-1999
		CN 1285843 T	28-02-2001
		EE 200000285 A	15-08-2001
		WO 9924449 A2	20-05-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 02/01317

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9924449 A		EP 1030857 A2	30-08-2000
		HR 20000275 A1	31-12-2000
		HU 0004082 A2	28-04-2001
		JP 2001522857 T	20-11-2001
		NO 20002361 A	05-07-2000
		PL 340921 A1	12-03-2001
		SK 6722000 A3	18-01-2001
		TR 200002131 T2	22-01-2001
		ZA 9810125 A	05-05-2000

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 03079611 00000000
Fecha (AMD): 2003-09-10 17:05:44 Folios: 129
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN X MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.	( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
- Descripción de la invención.	( )	( )
- Dibujos de ser estos pertinentes.	( )	( )
- Comprobante de Pago de las tasas establecidas.		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solcitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable: ANDREA ROSSE

Fecha:

Industria y Comercio
SUPERINTENDENCIA

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2020
Bogotá, D.C.,

Doctor:
Carlos R. Olarte
Apoderado
Glaxo Group Limited

Oficio N° 09541

ASUNTO:

Radicación N°	03 079611
Solicitud internacional	PCT/GB02/01317
Fecha Inicio fase nacional	20/10/03
Trámite	011
Evento	379
Actuación	430
Folios	001

Como resultado del examen de forma, realizado con fundamento el el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).
- El solicitante debe presentar un nuevo título que permita identificar la materia de la cual trata la solicitud, ya que el título relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular unica 5.2.9).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha 31 OCT. 2003.

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