



Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCION

21. EXPEDIENTE No.

03-100204

54. TÍTULO

El uso de Adenosine y análogos para producir medicinas para el tratamiento del síndrome de resistencia a la Insulina y Diabetes

51. CLASIFICACIÓN INTERNACIONAL

AG/K 31/S2

71. SOLICITANTE

Aventis Pharma Deutschland GmbH

DOMICILIO

Frankfurt am Main, Alemania.

74. APODERADO

Gustavo Hollmann Restrepo

22. BOGOTÁ, D. C.,

12 de Noviembre de 2003

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

03 100204 00

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03100204 00000000 Folios: 156
Fecha (AMD): 2003-11-12 17:32:57
Tramite : 011 PCT-PATENT 379 FASE NNCI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

①

SOLICITUD DE:

☒ Patente de Invención.

☐ Patente de Modelo de Utilidad.

☐ Capítulo I.

☒ Capítulo II.

②

SOLICITANTE
(71)

Nombre: **AVENTIS PHARMA DEUTSCHLAND GmbH**

Dirección: **Brüningstrasse 50,
65926 Frankfurt am Main, Alemania**

Nacionalidad o Domicilio: **Frankfurt am Main,
Alemania**

Lugar de Constitución: **Alemania**

Teléfono: **1111** Fax: **1111**

E-mail:

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

③

REPRESENTANTE
O APODERADO

Nombre: **GUSTAVO HOLLMANN RESTREPO**

Dirección: **Cra. 11A No. 94-76-Of. 308**

Teléfono: **6161948** Fax: **6163976**

E-mail:

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☒

Cual _____

Número **2.878.023** TP **5903**

④

INVENTOR (ES)
(72)

Nombre: **HERLING, Andreas**

Dirección: **Am Walberstück 5,**

Nacionalidad o Domicilio **65520 Bad Camberg, Alemania**

⑤ PCT (86)

Solicitud Internacional No. **PCT/EP02/05301**

Fecha **Mayo 14 de 2002**

Publicación Internacional No. **WO 02/092093 A1**

Fecha **Noviembre 21 de 2002**

⑥

Título (54) **EL USO DE ADENOSINA Y ANALOGOS PARA PRODUCIR MEDICINAS PARA EL TRATAMIENTO DEL SÍNDROME DE RESISTENCIA A LA INSULINA Y DIABETES".**

⑦

Clasificación Internacional (51) **A61K 31/52**

⑧

Prioridad

SI ☒ NO ☐

(33) Pais de Origen

Europa

(32) Fecha

Mayo 14, 2001

(31) Número de Solicitud

01111651.4

⑨

Comprobante de pago No. _____

Fecha _____

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

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☒ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ 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 acredite 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 12x12.
- ☐ 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.
- ☒ Otros Reporte de Búsqueda Internacional.

11 FIGURA CARACTERÍSTICA:



12

Solicito la concesión de la patente,

NOMBRE: GUSTAVO HOLLMANN RESTREPO

FIRMA:

Gustavo Hollmann Restrepo

C.C. 4.878.023 B/t. T.P. 5903

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

Continuación enumeración del nombre de los Inventores, con su correspondiente dirección, código postal y domicilio:

<u>Nombre</u>	<u>Dirección</u>	<u>Domicilio</u>
JÄHNE, Gerhard ✓	Seebachstrasse 22,	65929 Frankfurt am Main, Alemania
MYERS, Michael, R. ✓	205 Lincoln Drive,	Reading, PA 19606 Estados Unidos
MAGUIRE, Martin, P. ✓	8861 Deer Path Circle,	Louisville, KT 40220, Estados Unidos
SPADE, Alfred, P. ✓	473 Painter Way,	Lansdale, PA 19446 Estados Unidos
EWING, William, R.	805 Graystone Lane,	Downington, PA 19335 Estados Unidos
PAULS, Henry, W. ✓	3770 Worthington Circle,	Collegeville, PA 19426 Estados Unidos
CHOI-SLEDESKI, Yong-Mi ✓	5 Dana Drive,	Collegeville, PA 19426 Estados Unidos

Otros anexos que se acompañan a la solicitud.

Forma PCT/IB/304 correspondientes a la notificación y transmisión del documento de prioridad.

Nuevo capítulo Reivindicatorio tal como fue presentado en el Examen Preliminar Internacional, el cual reemplaza al inicialmente presentado.

Forma PCT/IB/308 correspondiente a la nota de información al solicitante de la comunicación de la solicitud internacional a las oficinas designadas.

Forma PCT/IPEA/402 correspondiente a la notificación de recibo de la solicitud por la autoridad competente de Examen Preliminar Internacional.

Forma PCT/IB/332 referente a la información concerniente a las oficinas elegidas notificadas de su elección.

Otros documentos que se acompañan a la solicitud 55274

4

SUPERINDUSTRIA Y COMERCIO

Radicacion : 03100204 00000000 Folios: 158
Fecha (AMB): 2003-11-12 17:32:57
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

NIT : 300176089-2

RECIBO OFICIAL DE CAJA : 03 - 82,174
FECHA : NOVIEMBRE 11 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
GUSTAVO HOLLMAN	CONSIGNACION	BANCO POPULAR.	050-00110-6	10365707	10/11/2003	640,000.00

***** CONCEPTO *****

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

Solicitud patente PET
Ref. 55274

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

G. HOLLMANN RESTREPO

ABOGADOS LTDA.

PARA PATENTES, MARCAS Y LICENCIAS FARMACEUTICAS
FOR PATENTS, TRADE MARKS AND PHARMACEUTICAL LICENSES

The undersigned

Dr. Markus Jacobi
Dr. Hans-Jürgen Fischer

acting on behalf of and representing

Company's
Name

Aventis Pharma
Deutschland GmbH

Company's
Domicile

domiciled in
D-65926 Frankfurt am Main
Germany

hereby appoint/s

G. Hollmann Restrepo

Leave blank

domiciled in Bogotá, Republic of Colombia.

as our true and legal attorneys with the necessary powers; 1) to apply to the administrative, judicial and police authorities of the Republic of Colombia, in any instance or appeal, for obtaining letter patents, industrial designs and models, trademark registrations, registration of commercial names as well as their assignments, extensions, renewals and changes of name; 2) to prepare, apply for, obtain, execute and register contracts, licenses, authorizations and registrations of any kind; 3) intervene as plaintiffs or defendants, in any instance or appeal, before any judge, court, tribunal, corporation, public offices or authority in any judicial, administrative or police action, such as: actions dealing with commercial names; oppositions against trademark registrations; caducity and nullity actions; recovery actions, actions arising from obtainment and exploitations of licenses; actions dealing with unfair competition; criminal actions; actions claiming indemnity for damages; claims or remarks on patent applications, industrial designs and models; the performance of precautionary measures, and in any other similar action, measures or appeals related to industrial property matters.

To this effect, I (we) hereby authorize him (them) to file applications, make descriptions, amendments, protests, declarations, oppositions, cancellations, appeals and claims; to pay taxes, quotas and liens as provided by law; to waive or abandon granted rights or rights in process of being granted, to receive all kind of documents and securities; to issue the respective releases and, in general, to take, before said authorities, pertinent steps to the above mentioned purposes and take all measures he (they) may deem convenient to protect my (our) interests, with all other necessary legal faculties, and I (we) hereby declare as good and valid whatever the attorneys should do to my (our) benefit.

This power comprises the authority to ratify or confirm on my (our) behalf any actions, as well as the faculty of receiving, desisting, transacting, compromising, substituting and revoking substitutions, taking notifications and appointing judicial or extrajudicial attorneys.

Signed in Frankfurt..am Main

On this 11th day of February 2000

(Dr. Markus Jacobi)
- Prokurist -

Signature(s)
Firma(s)

To(nosotros)

Dr. Markus Jacobi y
Dr. Hans-Jürgen Fischer

obrando a nombre y representación de

AVENTIS PHARMA DEUTSCHLAND GmbH

con domicilio en

Frankfurt am Main, Alemania

nombre(amos) a

GUSTAVO HOLLMANN RESTREPO

domiciliado(s) en Bogotá, República de Colombia, en
la Cra. 11A No. 94-76 - Of. 308.

apoderados verdaderos y legales con poder especial amplio y suficiente: 1) Para recabar de las oficinas y autoridades colombianas, administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, de dibujos y modelos industriales, registro de marcas, depósito de nombres comerciales y enseñanzas, así como sus traspaños, prórrogas, renovaciones y cambios de nombre; 2) elaborar, tramitar, solicitar, obtener, realizar, ejecutar y registrar contratos, licencias, autorizaciones y registros de cualesquiera clases; 3) intervenir como demandante o como demandado en cualquier instancia y recurso y ante cualquier juez, entidad, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía, tales como acciones derivadas del nombre comercial, oposición al registro de marcas; acciones de caducidad y nulidad; acciones reivindicatorias; acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales y civiles; acciones de indemnización de perjuicios, reclamos u observaciones a solicitudes de patentes, modelos y dibujos industriales; en el ejercicio de medidas cautelares y en otras acciones, medidas o recursos similares relacionados con la propiedad industrial.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren convenientes al resguardo de mis (nuestros) intereses, con todas las demás facultades necesarias, y por este documento hago ahora declarar(amos) válido y bueno todo cuanto los poderados hicieren en mi (nuestro) beneficio.

Este poder comprende la facultad de ratificar o confirmar en mi(nuestro) nombre lo actuado, así como la facultad de desistir, transigir, comprometer, sustituir y revocar sustituciones, recibir notificaciones y nombrar apoderados judiciales o extrajudiciales.

Firmado en Frankfurt am Main

el 11 de Febrero

de 2000

(Dr. Hans-Jürgen Fischer)
- Authorized Signatory -

CONSULAR CERTIFICATION

COMPANIES

The undersigned Consul certifies: that the preceding signature(s) reading

Dr. Markus Jacobi
Dr. Hans-Jürgen Fischer

is (are) authentic; that the signer(s) at present fills (fill) the position of

Prokurist
Authorized Signatory

of Aventis Pharma Deutschland GmbH

Corporation
Company's

that he (they) is (are) empowered to grant this power; and that said company exists and is organized in

D-65926 Frankfurt am Main
Fed. Rep. of Germany
in accordance with the laws of

Fed. Rep. of Germany

All the foregoing facts are known to the Consul due to his having examined the respective documents to which he, the Consul, attests.

Signed in
Frankfurt am Main

On this day of

CERTIFICACION CONSULAR

SOCIEDADES

El infrascrito Cónsul certifica: que la(s) firma(s) que antecede(n) y dice(n)

es(son) auténtica(s); que el(los) signatario(s) desempeña(n) actualmente el(los) cargo(s) de

de

que tiene(n) facultad para otorgar este poder; y que dicha compañía existe y está organizada en

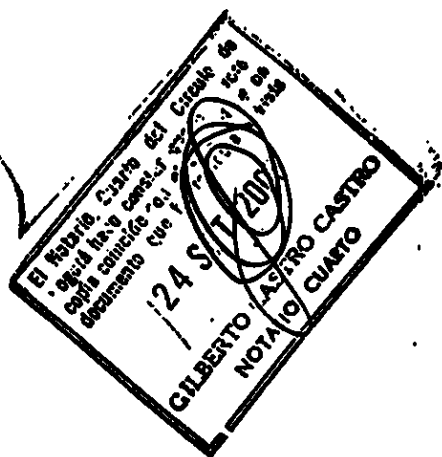
conforme a las leyes de

Todos los hechos anteriores le constan, por haber examinado los documentos respectivos y de todo ello da fe.

Firmado en

El de

de 19



No. 10 of the Urkundenrolle 2000

It is officially certified
hereby that

Die umstehenden heute vor
mir anerkannten Unterschrif-
ten der

1. Dr. Markus Jacobi, D-60385 Frankfurt am Main
2. Dr. Hans-Jürgen Fischer, D-64297 Darmstadt

- personally known to me -
have signed this document.

- persönlich bekannt -
werden hiermit beglaubigt.

At the same time it is
confirmed, that the person
mentioned sub 1. according
to the Commercial Register
which has been inspected
by the Notary Public today
as Prokurist is entitled
to jointly with an other
authorized person sign for
and represent in legally
binding manner the

Gleichzeitig wird bestätigt,
daß die zu 1. genannte
Person laut Eintragung im
Handelsregister, das vom
Notar heute eingesehen
wurde, als Prokurist mit
einem anderen Zeichnungsbe-
rechtigten zeichnungs- und
vertretungsberechtigt ist
für die

Aventis Pharma Deutschland GmbH, D-65926 Frankfurt am Main

and the person mentioned
sub 2. is authorized accord-
ing to the Authorization
of June 2, 1997 to act as
proxy and to represent
said company in legally
binding manner together
with an other authorized
person of this company.

und der zu 2. Genannte
aufgrund der vorliegenden
Handlungsvollmacht vom
Juni 1997 handlungsbevollmäch-
tigt und zugleich mit einem
anderen Zeichnungsberechtig-
ten der Firma zur Ver-
tretung dieser Firma berech-
tigt ist.

Frankfurt am Main, den 11. Februar 2000

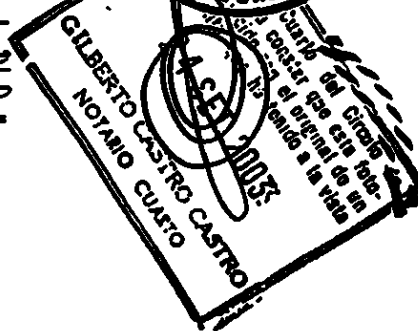
Notary Public
Notar

Kostenberechnung

Geschäftswert: DM 10.000,--
Gebühr §§ 141, 32, 45 KostO
Gebühr § 150 I KostO
15% Mehrwertsteuer

DM 20,--
DM 20,--
DM 6,40
DM 46,40

Notar



Die Echtheit vorstehender Unterschrift des
Notars Dr. Hans Christoph Beil

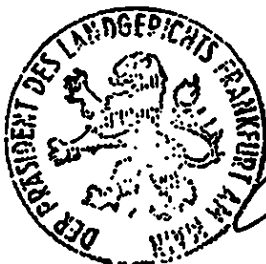
und die Echtheit des beigedruckten Dienst-
siegels wird hiermit bestätigt.

Eugleich wird bescheinigt, daß der Vor-
genannte zur Vornahme der Amtshandlung
befugt war.

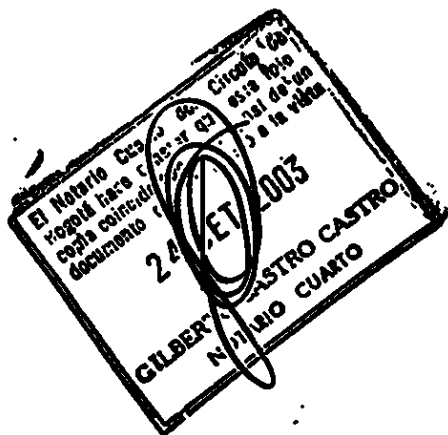
Frankfurt am Main, den 17. 2. 09

DER PRÄSIDENT DES LANDGERICHTS

In Vertretung



Schlitz





CONSULADO GENERAL DE COLOMBIA

Furstenberger Str. 223, 60323 Frankfurt am Main, R.F.A.
Teléfono: 49-69-5963050 * Fax: 49-69-5962080

1139

LA SUSCRITA VICE-CONSUL DE COLOMBIA EN FRANKFURT AM MAIN

CERTIFICA

Que el señor Schlitz ejercía las funciones de Representante del Presidente del Tribunal Regional en Frankfurt am Main en la fecha indicada y su firma corresponde a la registrada en esta Oficina Consular.

Que la empresa Aventis Pharma Deutschland GmbH con sede en Frankfurt am Main, es una sociedad constituida de acuerdo con las leyes de la República Federal de Alemania y cumple su objeto conforme a las mismas:

Que los señores Dr. Markus Jacobi y Dr. Hans-Jürgen Fischer, quienes en su calidad de apoderados, y cuyas firmas fueron autenticadas ante el señor Notario Dr. Hans Christoph Beil, son sus representantes legales en este país.

Frankfurt am Main, Marzo 10, 2000


MARCELA RODRIGUEZ
VICE-CONSUL DE COLOMBIA



Derechos cancelados:
Impuesto de Timbre:
Fondo Rotatorio:

US\$ 7 00
US\$ 100 00



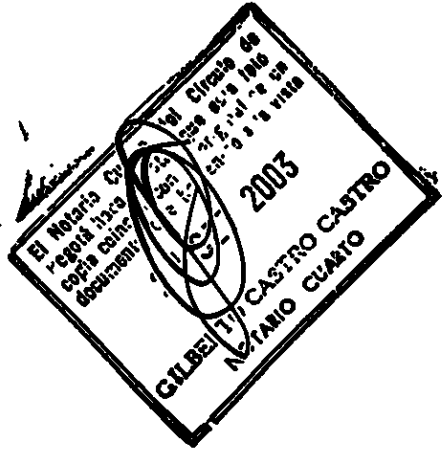
MINISTERIO DE RELACIONES
EXTERIORES

Revela
87357
2003
FOLIO 149
REPUBLICA DE GUATEMALA

RECONSTRUCCION DEL TEXTO

2000 MAR 21 APO 20

Revela
OFICINA DE LEGALIZACIONES



Traducción oficial del alemán de la autenticación y legalización de firmas del poder que AVENTIS PHARMA DEUTSCHLAND GMBH domiciliada en Frankfurt am Main, República Federal de Alemania, otorga a Gustavo Hollmann Restrepo.

Registro Notarial No. 10 para el año 2000

Se autentican oficialmente las firmas que aparecen anteriormente, reconocidas en presencia mía como propias por:

1. Dr. Markus Jakobi, D-60385 Frankfurt am Main,
 2. Dr. Hans-Jürgen Fischer, D-64297 Darmstadt,
- a quienes yo, el suscrito Notario, conozco personalmente.

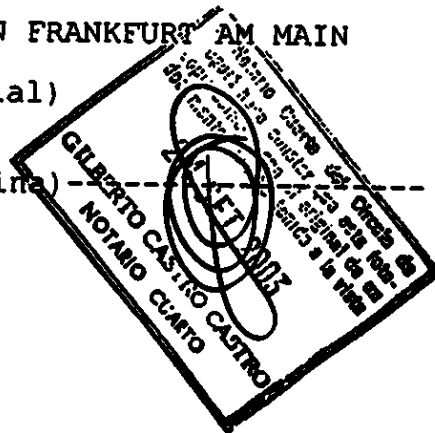
Al mismo tiempo se confirma que, de conformidad con el correspondiente Registro Comercial revisado el día de hoy por el Notario, la persona señalada en 1. está autorizada en su calidad de Apoderado para representar conjuntamente con otro Apoderado a la compañía Aventis Pharma Deutschland GmbH domiciliada en D-65926 Frankfurt am Main,

y que, de conformidad con el poder fechado el 2 de Junio de 1997 que me ha sido presentado, la persona señalada en 2. Está autorizada para representar conjuntamente con otro Apoderado a la mencionada compañía

Frankfurt am Main, 11 de Febrero del 2000

DR. HANS CHRISTOPH BEIL, NOTARIO EN FRANKFURT AM MAIN
(Firma y Sello Oficial)

----- (continúa en la 2ª página) -----



Nota de gastos:

Valor del negocio = DM 10.000,--

Impuesto Artículos 141, 32, 45 Disp. Impuestos DM 20,--

Impuesto Artículo 150 I Disposición Impuestos DM 20,--

16% Impuesto sobre el Valor Agregado DM 6,40

Total DM 46,40

DR. HANS CHRISTOPH BEIL, NOTARIO (firma)

Se confirma mediante este documento la autenticidad de la firma que aparece anteriormente, la cual pertenece al Notario Dr. Hans Christoph Beil en Frankfurt am Main, también la autenticidad del sello oficial que aparece a lado de dicha firma.

Al mismo tiempo se certifica que la persona mencionada se encontraba legalmente autorizada para la ejecución de ese acto oficial.

Frankfurt am Main, 17.2.2000

Schlitz, Representante del Presidente Tribunal Regional
(Firma y Sello Oficial)

El documento traducido del alemán fue legalizado bajo el No. 137357 el día 21 de Marzo del 2000 en la Oficina de Legalizaciones del Ministerio de Relaciones Exteriores



Adolf Watzke

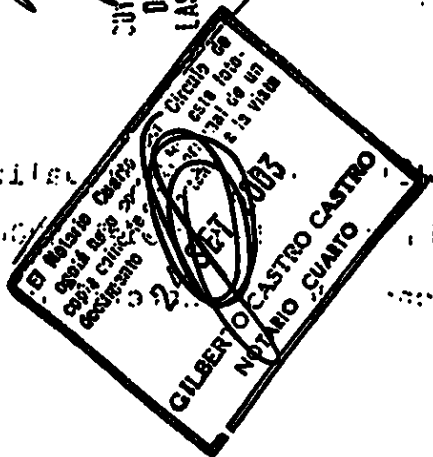
ADOLF WATZKE
Traductor Oficial
Res. 2493 Minjusticia

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2000 MAR 23 14:04
JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTÁ D.C.

MINISTERIO DE RELACIONES
EXTERIORES

139938
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS



RECIBO DE LA
SECRETARIA DE
ESTADO

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 November 2002 (21.11.2002)

PCT

(10) International Publication Number
WO 02/092093 A1

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(21) International Application Number: PCT/EP02/05301

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(30) Priority Data:
01111651.4 14 May 2001 (14.05.2001) EP

(71) Applicant: AVENTIS PHARMA DEUTSCHLAND GMBH/DE/DE; Brüningstrasse 50, 65926 Frankfurt am Main (DE).

(72) Inventors: HERLING, Andreas, Am Walberstück 5, 65520 Bad Camberg (DE); JÄHNE, Gerhard, Seebachstrasse 22, 65929 Frankfurt am Main (DE); MYERS, Michael, R., 205 Lincoln Drive, Reading, PA 19606 (US); MAGUIRE, Martin, P., 8861 Deer Path Circle, Louisville, KY 40220 (US); SPADE, Alfred, P., 473 Painter Way, Lansdale, PA 19446 (US); EWING, William, R., 805 Graystone Lane, Downingtown, PA 19335 (US); PAULS, Henry, W., 3770 Worthington Circle, Collegeville, PA 19426 (US); CHOI-SLEDESKI, Yong-Mi, 5 Dana Drive, Collegeville, PA 19426 (US).

(74) Agent: ISENBRUCK, Günter, Patent- und Rechtsanwälte, Bardhile Pagenberg Dost, Altenburg Geissler Isenbruck Theodor-Heuss-Anlage 12, 68165 Mannheim (DE).

(81) Designated States (national): AE, AG, AI, 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, UZ, VN, YU, ZA, ZM, ZW.

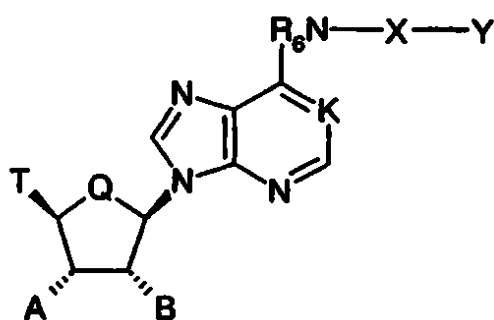
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

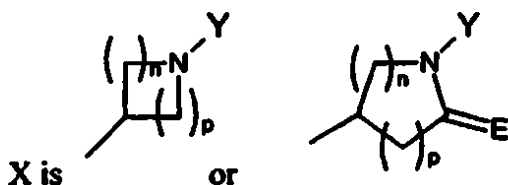
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette

(54) Title: ADENOSINE ANALOGUES FOR THE TREATMENT OF THE INSULIN RESISTANCE SYNDROME AND DIABETES



(I)

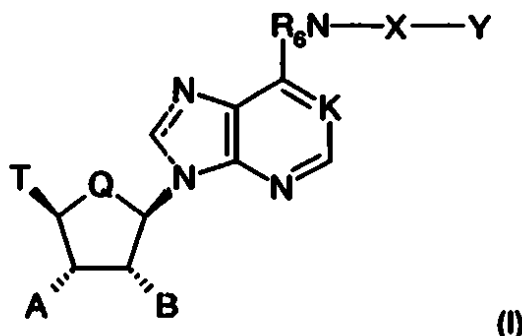
(57) Abstract: The invention relates to the use of adenosine compounds described by formula (I) and certain derivatives thereof for producing a medicine for the treatment of the insulin resistance syndrome and diabetes. In formula (I), K is N, NO, or CH; Q is CH₂ or O; R₆ is hydrogen, alkyl, allyl, 2-methylallyl, 2-butenyl, or cycloalkyl; X is (a) or (b); E is O or S; Y is e.g. hydrogen, alkyl, aralkyl, aryl; n and p are independently 0, 1, 2 or 3 provided that n + p is at least 1; T is e.g. hydrogen, alkyl, acyl, thioacyl, halo, carboxyl, R₁, R₂ and R₃ are independently H, alkyl, or cycloalkyl; A is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or OR'; B is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or OR"; R' and R" are e.g. independently hydrogen, alkyl, aralkyl or carbamoyl.



X is or

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This invention relates to the use of compounds derived from adenosine and analogues thereof according to the general formula (I) as insulin resistance agents.



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Adenosine has a wide variety of physiological and pharmacological actions including a marked alteration of cardiovascular and renal function. In animals and man, intravenous injection of the adenosine nucleotide causes hypotension.

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The physiological and pharmacological actions of adenosine are mediated through specific receptors located on cell surfaces. Four adenosine receptor subtypes, designated as A₁, A_{2A}, A_{2B}, and A₃ receptors, have been identified. The A₁ receptor inhibits the formation of cAMP by suppressing the activity of adenylate cyclase, while stimulation of A₂ receptors increases adenylate cyclase activity and intracellular cAMP. Each receptor appears to mediate specific actions of adenosine in different tissues: for example, the vascular actions of adenosine appears to be mediated through stimulation of A₂ receptors, which is supported by the positive correlation between cAMP generation and vasorelaxation in adenosine-treated isolated vascular smooth muscle; while stimulation of the cardiac A₁ receptors reduces cAMP generation in the heart which contributes to negative dromotropic, inotropic and chronotropic cardiac effects. Consequently, unlike most vasodilators, adenosine administration does not produce a reflex tachycardia.

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Adenosine also exerts a marked influence on renal function. Intrarenal infusion of adenosine causes a transient fall in renal blood flow and an increase in renal vascular resistance. With continued infusion of adenosine, renal blood flow returns to control levels and renal vascular resistance is reduced. The initial renal vasoconstrictor responses to

adenosine are not due to direct vasoconstrictor actions of the nucleotide, but involve an interaction between adenosine and the renin-angiotensin system.

Adenosine is widely regarded as the primary physiological mediator of reactive hyperemia and autoregulation of the coronary bed in response to myocardial ischemia. It has been reported that the coronary endothelium possesses adenosine A₂ receptors linked to adenylate cyclase, which are activated in parallel with increases in coronary flow and that cardiomyocyte receptors are predominantly of the adenosine A₁ subtype and associated with bradycardia. Accordingly, adenosine offers a unique mechanism of ischemic therapy.

Cardiovascular responses to adenosine are short-lived due to the rapid uptake and metabolism of the endogenous nucleotide. In contrast, the adenosine analogues are more resistant to metabolic degradation and are reported to elicit sustained alterations in arterial pressure and heart rate.

Adenosine compounds according to the general formula (I) useful as anti-hypertensive, cardioprotective, anti-ischemic and antilipolytic agents are known from EP A 0 912 520.

Several potent metabolically-stable analogues of adenosine have been synthesized which demonstrate varying degrees of selectivity for the two receptor subtypes. Adenosine agonists have generally shown greater selectivity for A₁ receptors as compared to A₂ receptors. Cyclopentyladenosine (CPA) and R-phenylisopropyl-adenosine (R-PIA) are standard adenosine agonists which show marked selectivity for the A₁ receptor (A₂/A₁ ratio = 780 and 106, respectively). In contrast, N-5'-ethyl- carboxamido adenosine (NECA) is a potent A₂ receptor agonist (K_i-12 nM) but has equal affinity for the A₁ receptor (K_i-6.3 nM; A₂/A₁ ratio = 1.87). Until recently, CV-1808 was the most selective A₂ agonist available (A₂/A₁ = 0.19), even though the compound was 10-fold less potent than NECA in its affinity for the A₂ receptor. In recent developments, newer compounds have been disclosed which are very potent and selective A₂ agonists (K_i=3-8 nM for A₁; A₂/A₁ ratio=0.027-0.042) (C.E. Müller and T. Scior, *Pharmaceutica Acta Helvetica* 68 (1993) 77-111).

Various N6-aryl and N6-heteroarylalkyl substituted adenosines, and substituted-(2-amino and 2-hydroxy)adenosines, have been reported in the literature as possessing varied pharmacological activity, including cardiac and circulatory activity. See, for example, British Patent Specification 1,123,245, German Offen. 2,136,624, German Off 2,059,922, U.S. Patent No. 4,501,735, EP Publication No. 0139358 (disclosing N6-[geminal diaryl substituted alkyl]adenosines), EP-A-0 305 643 (disclosing that N6-heterocyclic-substituted adenosine derivatives exhibit cardiac vasodilatory activity), German Offen. 2,131,938 (disclosing aryl and heteroaryl alkyl hydrazinyl adenosine derivatives), German Offen. 2,151,013 (disclosing

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N6-aryl and heteroaryl substituted adenosines) and German Offen. 2,205,002 (disclosing adenosines with N6-substituents comprising bridged ring structures linking the N6-nitrogen to substituents including thienyl).

5 U.S. Patent No. 4,954,504 and EP Publication No. 0267878 disclose generically that carbocyclic ribose analogues of adenosine, and pharmaceutically acceptable esters thereof, substituted in the 2- and/or N6- positions by aryl lower alkyl groups including thienyl, tetrahydropyranyl, tetrahydrothiopyranyl, and bicyclic benzo fused 5- or 6- membered saturated heterocyclic lower alkyl derivatives exhibit adenosine receptor agonist properties.
10 Adenosine analogues having thienyl-type substituents are described in EP Publication No. 0277917 (disclosing N6-substituted-2-heteroarylalkylamino substituted adenosines including 2-[(2-[thien-2-yl]ethyl)amino] substituted adenosine), German Offenlegung 2,139,107 (disclosing N6-[benzothienylmethyl]-adenosine), PCT WO 85/04882 (disclosing that N6-heterocyclicalkyl-substituted adenosine derivatives, including N6-[2-(2-thienyl)ethyl]amino-9-
15 (D-ribofuranosyl)-9H-purine, exhibit cardiovascular vasodilatory activity and that N6-chiral substituents exhibit enhanced activity), EP Published Application No. 0232813 (disclosing that N6-(1-substituted thienyl)cyclopropylmethyl substituted adenosines exhibit cardiovascular activity), U.S. Patent No. 4,683,223 (disclosing that N6-benzothiopyranyl substituted adenosines exhibit antihypertensive properties), PCT WO 88/03147 and
20 WO 88/03148 (disclosing that N6-[2-aryl-2-(thien-2-yl)]ethyl substituted adenosines exhibit antihypertensive properties), U.S. Patent Nos. 4,636,493 and 4,600,707 (disclosing that N6-benzothienylethyl substituted adenosines exhibit antihypertensive properties).

Adenosine-5'-carboxylic acid amides are disclosed as having utility as anti-hypertensive and
25 anti-anginal agents in U.S. Patent No. 3,914,415, while U.S. Patent No. 4,738,954 discloses that N6-substituted aryl and arylalkyl-adenosine 5'-ethyl carboxamides exhibit various cardiac and antihypertensive properties.

N⁶-alkyl-2'-O-alkyl adenosines are disclosed in EP Publication No. 0,378,518 and UK
30 Patent Application No. 2,226,027 as having antihypertensive activity. N⁶-alkyl-2',3'-di-O-alkyl adenosines are also reported to have utility as antihypertensive agents, U.S. Patent 4,843,066.

Adenosine-5'-(N-substituted)carboxamides and carboxylate esters and N1-oxides thereof
35 are reported to be coronary vasodilators, Stein, et al., *J. Med. Chem.* 1980, 23, 313-319 and *J. Med. Chem.* 19 (10), 1180 (1976). Adenosine-5'-carboxamides and N1-oxides thereof are also reported as small animal poisons in U.S. Patent No. 4,167,565.

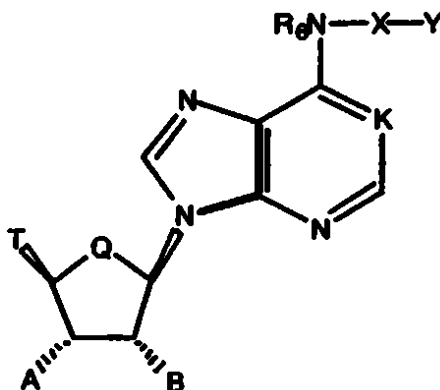
N6-substituted adenosines and analogues, useful in treating gastrointestinal motility disorders, have been reported in EP Published Applications Nos. 0423776, and 0423777.

5 N6-heterocyclyl-alkyl compounds derived from adenosine and analogues thereof, and their use in treating hypertension and myocardial ischemia, their use as cardioprotective agents which ameliorate ischemic injury or myocardial infarct size consequent to myocardial ischemia, their use as antilipolytic agents which reduce plasma lipid levels, serum triglyceride levels, and plasma cholesterol levels, are disclosed in EP-A 0 758 897. N6-heterocyclyl compounds derived from adenosine and analogues thereof, and their use in
10 treating myocardial ischemia and hypertension, are also disclosed in U.S. Patent No. 5,364,862, filed October 2, 1992.

It is believed that the reported toxicity, CNS properties and heart rate elevation associated with adenosine analogues have contributed to the difficulties preventing the development
15 of a commercial adenosine analogue antihypertensive/antiischemic agent. The present invention relates to a class of metabolically stable adenosine analogues, and derivatives thereof, possessing unexpectedly desirable pharmacological properties, i.e. they are antilipolytic agents having a unique therapeutic profile.

20 Surprisingly it has been found that adenosine compounds by stimulating adenosine receptor A₁ on adipocytes can inhibit the peripheral lipolysis of stored triglycerides and thus can cause an immediate fall in plasma free fatty acids. This antilipolytic effect caused an immediate onset of improvement of insulin sensitivity in insulin resistant mammals, including man. Therefore adenosine agonists are useful as therapeutics to treat the insulin
25 resistant syndrome as well as antidiabetics in insulin resistant diabetics.

The invention relates to the use of adenosine compounds described by Formula I



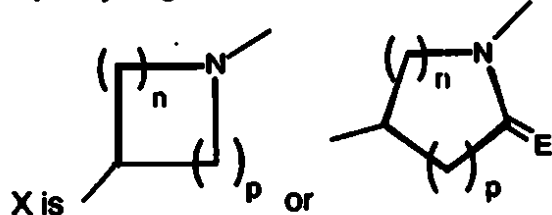
Formula I

30 wherein:

K is N, N→O, or CH;

Q is CH₂ or O;

R₆ is hydrogen, alkyl, allyl, 2-methylallyl, 2-butenyl, or cycloalkyl;



5 where the nitrogen of the ring of X is substituted by Y;

E is O or S;

Y is hydrogen, alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, or substituted heterocyclylalkyl;

n and p are independently 0, 1, 2, or 3, provided that n + p is at least 1;

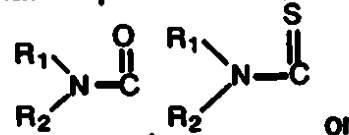
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T is hydrogen, alkyl, acyl, thioacyl, halo, carboxyl, R₃O-CH₂;

R₁, R₂, and R₃ are independently H, alkyl, or cycloalkyl;

A is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or OR';

B is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or OR'';



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R' and R'' are independently hydrogen, alkyl, aralkyl, carbamoyl, alkyl carbamoyl, dialkylcarbamoyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, aryloxycarbonyl, or, when A and B are OR' and OR'', respectively, R' and R'' together may form



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and R_e are independently hydrogen, alkyl, or together with the carbon atom to which they are attached may form a 1,1-cycloalkyl group;

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or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof for producing a medicine for the treatment of the insulin resistance syndrome and diabetes.

As used above and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

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"Acyl" means a straight or branched alkyl-C=O group. "Thioacyl" means a straight or branched alkyl-C=S group. Preferred acyl and thioacyl groups are lower alkanoyl and lower thioalkanoyl having from 1 to about 6 carbon atoms in the alkyl group.

"Alkyl" means a saturated aliphatic hydrocarbon group which may be straight or branched and having about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups may be straight or branched and have about 1 to about 10 carbon atoms in the chain. Branched means that a lower alkyl group such as methyl, ethyl or propyl is attached to a linear alkyl chain.

"Lower alkyl" means an alkyl group having 1 to about 6 carbons.

"Cycloalkyl" means an aliphatic ring having 3 to about 10 carbon atoms in the ring. Preferred cycloalkyl groups have 4 to about 7 carbon atoms in the ring.

"Carbamoyl" means an $\text{H}_2\text{N}-\text{C}(=\text{O})$ group. Alkylcarbamoyl and dialkylcarbamoyl means that the nitrogen of the carbamoyl is substituted by one or two alkyl groups, respectively.

"Carboxyl" means a COOH group.

"Alkoxy" means an alkyl-O group in which "alkyl" is as previously described. Lower alkoxy groups are preferred. Exemplary groups include methoxy, ethoxy, n-propoxy, i-propoxy and n-butoxy.

"Alkoxyalkyl" means an alkyl group, as previously described, substituted by an alkoxy group, as previously described.

"Alkoxycarbonyl" means an alkoxy-C=O group.

"Aralkyl" means an alkyl group substituted by an aryl radical, wherein "aryl" means a phenyl or naphthyl. "Substituted aralkyl" and "substituted aryl" means that the aryl group, or the aryl group of the aralkyl group is substituted with one or more substituents which include alkyl, alkoxy, amino, nitro, carboxy, carboalkoxy, cyano, alkyl amino, halo, hydroxy, hydroxyalkyl, mercaptyl, alkylmercaptyl, trihaloalkyl, carboxyalkyl or carbamoyl.

"Aralkoxycarbonyl" means an aralkyl-O-C=O group.

"Aryloxycarbonyl" means an aryl-O-C=O group.

"Carbalkoxy" means a carboxyl substituent esterified with an alcohol of the formula $\text{C}_n\text{H}_{2n+1}\text{OH}$, wherein n is from 1 to about 6.

"Halogen" (or "halo") means chlorine (chloro), fluorine (fluoro), bromine (bromo) or iodine (iodo).

- 5 "Heterocyclyl" means about a 4 to about a 10 membered ring structure in which one or more of the atoms in the ring is an element other than carbon, e.g., N, O or S. Heterocyclyl may be aromatic or non-aromatic, i.e., may be saturated, partially or fully unsaturated.

10 Preferred heterocyclyl groups include pyridyl, pyridazinyl, pyrimidinyl, isoquinolinyl, quinolinyl, quinazolinyl, imidazolyl, pyrrolyl, furanyl, thienyl, thiazolyl, benzothiazolyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, and morpholinyl groups.

15 "Substituted heterocyclyl" means that the heterocyclyl group is substituted by one or more substituents wherein the substituents include alkoxy, alkylamino, aryl, carbalkoxy, carbamoyl, cyano, halo, heterocyclyl, trihalomethyl, hydroxy, mercaptyl, alkylmercaptlyl or nitro.

20 "Hydroxyalkyl" means an alkyl group substituted by a hydroxy group. Hydroxy lower alkyl groups are preferred. Exemplary preferred groups include hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl and 3-hydroxypropyl.

"Prodrug" means a compound which is rapidly transformed *in vivo* to yield the parent peptide compound, for example by hydrolysis in blood. "Pharmaceutically acceptable prodrug" means a compound which is, within the scope of sound medical judgement, 25 suitable for pharmaceutical use in a patient without undue toxicity, irritation, allergic response, and the like, and effective for the intended use, including a pharmaceutically acceptable ester as well as a zwitterionic form, where possible, of the peptide compounds of the invention. Pharmaceutically acceptable prodrugs according to the invention are described in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the 30 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.

35 "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable

solvates. Representative solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule(s) is/are H₂O.

The compounds of Formula I contain chiral (asymmetric) centers. The invention includes the individual stereoisomers and mixtures thereof. The individual isomers are prepared or isolated by methods well known in the art or by methods described herein.

The compounds described herein may be used in the form of the free base, in the form of acid addition salts or as hydrates. All such forms are within the scope of the invention. Acid addition salts are simply a more convenient form for use. In practice, use of the salt form inherently amounts to use of the base form. The acids which may be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the recipient in pharmaceutical doses of the salts, so that the beneficial anti-hypertensive, cardioprotective, anti-ischemic, and antilipolytic effects produced by the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of the compounds of the invention are preferred, all acid addition salts are useful as sources of the free base form, even if the particular salt, per se, is desired only as an intermediate product as, for example, when the salt is formed only for purposes of purification and identification, or when it is used as an intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures. Pharmaceutically acceptable salts within the scope of the invention are those derived from the following acids: mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid, and sulfamic acid; and organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, fumaric acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid and the like. The corresponding acid addition salts comprise the following: hydrochloride, sulfate, phosphate, sulfamate, acetate, citrate, lactate, tartarate, methanesulfonate, fumarate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfonate and quinate, respectively.

The acid addition salts of the compounds of the invention are conveniently prepared either by dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

Included within the scope of Formula I are classes of compounds which may be characterized generally as N6 -substituted adenosines; N6- substituted carbocyclic adenosines (or, alternatively, dihydroxy[N6- substituted-9-adenyl]cyclopentanes) and N-

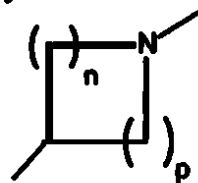
oxides thereof; and N6 -substituted-N'-1-deazaaristeromycins (or, alternatively, dihydroxy[N7 -substituted[4,5-b]imidazopyridyl]-cyclopentanes). Also within the scope of Formula I are the 5'-alkylcarboxamide derivatives of the adenosines, the carbocyclic adenosines and the 1-deazaaristeromycins, the derivatives of compounds of the above classes in which one or both of the 2- or 3- hydroxyl groups of the cyclopentane ring or, in the cases of classes of compounds containing the ribose moiety, the 2'- or 3'- hydroxyl groups of the ribose ring are substituted. Such derivatives may themselves comprise the biologically active chemical entity useful in the treatment of hypertension and myocardial ischemia, and as cardioprotective and antilipolytic agents, or may act as pro-drugs to such biologically active compounds which are formed therefrom under physiological conditions.

Representative compounds to use include: (2R,3R,4S,5R)- 5-hydroxymethyl- 2-[6-[1-(5-chloropyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]- tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(R)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(4-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R) 5-hydroxymethyl -2-[6-[1-(5-bromopyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]- tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl -2-(6-(1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino) -purin-9-yl) tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']-bipyridinyl-3-ylamino)-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(phenylpyrrolidin-3(S)-ylamino)-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(1-pyridin-2-ylpyrrolidin-3(S)-ylamino)-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl -2-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]- tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-methylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-thiophen-2-ylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-methylmercaptopyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl -2-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]- tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl -2-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3-ylamino]-purin-9-yl]- tetrahydrofuran-3,4-diol, (2R,3R,4S,5R) -5-methoxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentanecarboxylic acid ethylamide, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)piperidin-4-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-

hydroxymethyl-3-[6-((3S)-pyrrolidin-3-ylamino)-purin-9-yl] cyclopentane-1,2-diol
dihydrochloride, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)pyrrolidin-3-
ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-
trifluoromethylpyridin-2-yl)pyrrolidin-3(R)-ylamino]-purin-9-yl]cyclopentane-1,2-diol,
5 (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3R)-pyrrolidin-3-ylamino)-purin-9-yl] cyclopentane-
1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-
3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, 4(R)-1-benzyl-4-[9-((1R,2S,3R,5R)-1,2-
dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-purin-6-ylamino] pyrrolidin-2-one hydro-
chloride, (1R,2S,3R,5S)-5-methyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-
10 ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-
yl)pyrrolidin-3(S)-ylamino]-purin-9-yl] -5-hydroxymethylcyclopentane-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-
hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoro-
methylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-
15 5-hydroxymethyl-3-[6-[1-(pyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-
diol, 4(S)-1-benzyl-4-[9-((1R,2S,3R,5R)-1,2-dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-
purin-6-ylamino]pyrrolidin-2-one hydrochloride, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-
(quinolin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-
hydroxymethyl-3-[6-[1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-
20 diol, (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluoropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-
hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoro-
methylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-
5-hydroxymethyl-3-[6-[1-(phenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol,
4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-purin-6-
25 ylamino]pyrrolidin-1-yl]benzonitrile, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(isoquinolin-1-
yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-
bromoquinolin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-
diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-
hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chloro-5-trifluoro-
30 methylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-
diol, (1R,2S,3R,5R)-5-isopropoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-
ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-isopropoxymethyl-3-[6-[1-(4-
trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-
35 hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-
yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-
3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethyl-
cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-
ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-

methoxymethyl-3-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-([6-[1-(4-trifluoromethylphenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylphenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-phenylpyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1S,2R,3S,4R)-2,3-dihydroxy-4-{6-[1-(5-trifluoromethyl-pyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl}-cyclopentanecarboxylic acid-1(S)-methylpropylamide, and (1S,2R,3S,4R)-2,3-dihydroxy-4-{6-[1-(5-trifluoromethyl-pyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl}-cyclopentanecarboxylic acid-1(R)-methylpropylamide.

A preferred class of compounds to use is described by Formula I wherein K is N, T is



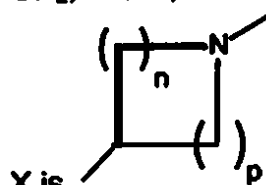
hydroxymethyl or methoxymethyl, A and B are hydroxy, X is or 4, or pharmaceutically acceptable salts thereof. Representative compounds of this preferred class of compounds include (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-chloropyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(R)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(4-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-bromopyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-(6-(1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino)-purin-9-yl)tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']-bipyridinyl-3-ylamino)-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(phenylpyrrolidin-3(S)-ylamino)-purin-9-

yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(1-pyridin-2-ylpyrrolidin-3(S)-ylamino)-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-methylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-thiophen-2-ylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-methylmercaptopyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-methoxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)piperidin-4-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3S)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol dihydrochloride, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(R)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3R)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(pyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(quinolin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluoropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(phenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-purin-6-ylamino]pyrrolidin-1-yl]benzonitrile, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(isoquinolin-1-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chloro-5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-

9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-([6-[1-(4-trifluoromethylphenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylphenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-phenylpyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, and (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol.

Another preferred class of compounds to use is described by Formula I wherein Q is

25 CH_2 , K is N, T is $\begin{array}{c} \text{R}_1 \\ | \\ \text{N} \\ | \\ \text{R}_2 \end{array} \text{C}=\text{O}$, wherein R₁ is H and R₂ is lower alkyl, A and B are hydroxy,

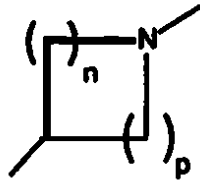


X is $\begin{array}{c} \text{X} \\ | \\ \text{C} \end{array}$, and n + p is 3 or 4, or pharmaceutically acceptable salts thereof.

Representative compounds of this other preferred class of compounds include ,

(1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentanecarboxylic acid ethylamide, (1S,2R,3S,4R)- 2,3-dihydroxy-4-[6-[1-(5-trifluoromethyl-pyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]- cyclopentanecarboxylic acid-1(S)-methylpropylamide, and (1S,2R,3S,4R)- 2,3-dihydroxy-4-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]- cyclopentanecarboxylic acid-1(R)-methylpropylamide.

A more preferred class of compounds to use is described by Formula I wherein Q is CH₂, K is N, T is hydroxymethyl or methoxymethyl, A and B are hydroxy, X is



, and n + p is 3 or 4, or pharmaceutically acceptable salts thereof.

Representative compounds of this more preferred class of compounds include

- 5 (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)piperidin-4-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3S)-pyrrolidin-3-ylamino)-purin-9-yl] cyclopentane-1,2-diol dihydrochloride, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(R)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3R)-pyrrolidin-3-ylamino)-purin-9-yl] cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(pyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(quinolin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluoropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(phenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-purin-6-ylamino]pyrrolidin-1-yl]benzonitrile, (1R,2S,3R,5R)-5-hydroxymethyl-5-[6-[1-(isoquinolin-1-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chloro-5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-

ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-trifluoromethylphenyl) -
 5 pyrrolidin-3(S)-ylamino]-purin-9-yl] -5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylphenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol,
 10 (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino] -purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl) -pyrrolidin-3(S)-ylamino] -purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino] -purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-phenylpyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, and (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol.

Most preferred compound to use in the present invention include (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol and (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol.

The amount of a compound of formula (I) which is necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. In
 30 general, the daily dose is in the range from 0.3 mg to 100 mg (typically from 3 mg to 50 mg) per day and per kilogram of body weight, for example 3-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.3 mg to 1.0 mg/kg, which can most suitably be administered as infusion of from 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg,
 35 typically from 1 ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active ingredient. It is thus possible for ampoules for injections to contain, for example, from 1 mg to 100 mg, and single-dose formulations which can be administered orally, such as, for example, tablets or capsules, to contain, for example, from 1.0 to 1000 mg, typically from 10 to 600 mg. In the case of pharmaceutically acceptable salts, the

aforementioned weight data are based on the weight of the salt of the compound of formula (I). For the prophylaxis or therapy of the above-mentioned conditions, the compounds of formula (I) can be used as the compound itself, but they are preferably in the form of a pharmaceutical composition with an acceptable carrier. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not hazardous for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as single dose, for example as tablet which may contain from 0.05% to 95% by weight of the active ingredient. Further pharmaceutically active substances may likewise be present, including other compounds of formula (I). The pharmaceutical compositions according to the invention can be produced by one of the known pharmaceutical methods which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Pharmaceutical compositions according to the invention are those suitable for oral, rectal, topical, peroral (for example sublingual) and parenteral (for example subcutaneous, intramuscular, intradermal or intravenous) administration although the most suitable mode of administration in each individual case depends on the nature and severity of the condition to be treated and on the nature of the compound of formula (I) used in each case. Coated formulations and coated slow-release formulations also lie within the scope of the invention. Formulations resistant to acid and gastric fluid are preferred. Suitable coatings resistant to gastric fluid comprise cellulose acetate phthalate, polyvinyl acetate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical compounds for oral administration may be in the form of separate units such as, for example, capsules, cachets, suckable tablets or tablets, each of which contain a defined amount of the compound of formula (I); as powders or granules; as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact. In general, the compositions are produced by uniform and homogeneous mixing of the active ingredient with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or molding a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets can be produced by tableting the compound in free-flowing form, such as, for example, a powder or granules, where appropriate mixed with a binder, lubricant, inert diluent and/or a (plurality of) surface-active/dispersing agent(s) in a suitable machine. Molded tablets can be produced by molding the compound which is in powder form and is moistened with an inert liquid diluent in a suitable machine.

Pharmaceutical compositions suitable for peroral (sublingual) administration comprise suckable tablets which contain a compound of formula (I) with a flavoring, normally sucrose and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

Suitable pharmaceutical compositions for parenteral administration comprise preferably sterile aqueous preparations of a compound of formula (I), which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions according to the invention generally contain from 0.1 to 5% by weight of the active compound.

Suitable pharmaceutical compositions for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing a compound of formula (I) with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

Suitable pharmaceutical compositions for topical application to the skin are preferably in the form of ointment, cream, lotion, paste, spray, aerosol or oil. Carriers which can be used are petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active ingredient is generally present in a concentration of from 0.1 to 15% by weight of the composition, for example from 0.5 to 2%.

Transdermal administration is also possible. Suitable pharmaceutical compositions for transdermal uses can be in the form of single plasters which are suitable for long-term close contact with the patient's epidermis. Such plasters suitably contain the active ingredient in an optionally buffered aqueous solution, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active ingredient concentration is about 1% to 35%, preferably about 3% to 15%. As a special possibility, the active ingredient can be released as described, for example, in *Pharmaceutical Research*, 2(6): 318 (1986) by electrotransport or iontophoresis.

The following preparations serve to illustrate the invention without restricting it, however.

Example A

Soft gelatin capsules containing 100 mg of active ingredient per capsule:

5		per capsule
	Active ingredient	100 mg
	Triglyceride mixture fractionated from coconut fat	400 mg
	Capsule contents	500 mg

10

Example B

Emulsion containing 60 mg of active ingredient per 5 ml:

		per 100 ml emulsion
	Active ingredient	1.2 g
15	Neutral oil	q.s.
	Sodium carboxymethylcellulose	0.6 g
	Polyoxyethylene stearate	q.s.
	Glycerol, pure	0.2 to 2.0 g
	Flavoring	q.s.
20	Water (deionized or distilled)	ad 100 ml

Example C

Rectal pharmaceutical form containing 40 mg of active ingredient per suppository:

		per suppository
25	Active ingredient	40 mg
	Suppository base	ad 2 g

Example D

Tablets containing 40 mg of active ingredient per tablet:

30		per tablet
	Lactose	600 mg
	Corn starch	300 mg
	Soluble starch	20 mg
	Magnesium stearate	40 mg
35		1000 mg

Example E

Coated tablets containing 50 mg of active ingredient per coated tablet:

	per coated tablet
Active ingredient	50 mg
Corn starch	100 mg
5 Lactose	60 mg
Sec. calcium phosphate	30 mg
Soluble starch	5 mg
Magnesium stearate	10 mg
Colloidal silica	5 mg
10	
	260 mg

Example F

The following formulas are suitable for producing the contents of hard gelatin capsules:

15	a)	Active ingredient	100 mg
		Corn starch	<u>300 mg</u>
			400 mg
	b)	Active ingredient	140 mg
		Lactose	180 mg
20		Corn starch	<u>180 mg</u>
			500 mg

Example G

Drops can be produced in accordance with the following formula (100 mg of active ingredient in 1 ml = 20 drops):

25	Active ingredient	10 g
	Methyl benzoate	0.07 g
	Ethyl benzoate	0.03 g
	Ethanol 96% pure	5 ml
30	Demineralized water	ad 100 ml

Compounds of this invention may be prepared by known methods or in accordance with the reaction sequences described in EP- A 0 912 520.

35 Following synthesis, compounds of the invention are typically purified by medium pressure liquid chromatography (MPLC), on a chromatotron, radially accelerated thin layer chromatography, flash chromatography or column chromatography through a silica gel or Florisil matrix, followed by crystallization. For compounds of Formula I wherein K is N, Q is

O and T is R_3O-CH_2 , typical solvent systems include chloroform:methanol, ethyl acetate:hexane, and methylene chloride:methanol. Eluates may be crystallized from methanol, ethanol, ethyl acetate, hexane or chloroform, etc.

- 5 For compounds of Formula I, wherein K is N, Q is O, and T is $R_1R_2N-C=O$, typical solvent systems include chloroform:methanol. For example, eluates may be crystallized from 50-100% ethanol (aqueous).

- 10 For compounds of Formula I, wherein Q is CH_2 , K is N or CH, and T is $R_1R_2N-C=O$, typical solvent systems include methylene chloride:methanol. For example, eluates may be crystallized from ethyl acetate with or without methanol, ethanol or hexane.

- 15 Compounds requiring neutralization may be neutralized with a mild base such as sodium bicarbonate, followed by washing with methylene chloride and brine. Products which are purified as oils are sometimes triturated with hexane/ethanol prior to final crystallization.

The method of the present invention is further illustrated and explained by the following Examples.

20 **EXAMPLE 1**

Preparation of 5'-N-Ethyl-2',3'-isopropylidene- N^6 -chloroadenosine-5'-uronamide

Step 1: N^6 -Chloro-2',3'-isopropylideneadenosine

- 25 6-Chloropurine riboside (31.5 g), triethylorthoformate (73 mL) and TsOH (19.8 g) are stirred in 600 mL acetone for 2 hours at RT. The reaction mixture is concentrated in vacuo, combined with ethyl acetate and washed with saturated $NaHCO_3$ solution, and brine, dried (Na_2SO_4) and concentrated to yield N^6 -Chloro-2',3'-isopropylideneadenosine as a white solid.

- 30 Step 2: N^6 -Chloro-2',3'-Isopropylideneadenosine-5'-carboxylic acid

- N^6 -Chloro-2',3'-isopropylideneadenosine (4.5 g, 13.8 mmol) and 4-hydroxy-2,2,6,6-tetramethylpiperidinyloxy benzoate (4-hydroxy-TEMPO benzoate) (0.0381 g, 0.14 mmol) are combined in acetonitrile, 5% $NaHCO_3$ (87%) is added to the reaction mixture and sodium bromite hydrate (10.41 g, 55.1 mmol) is added portionwise at 0-5 °C. The reaction mixture is then allowed to warm to room temperature, and the solution was stirred vigorously for about 3 hours. 10 % tartaric acid solution is added and the aqueous layer is separated and extracted with ethyl acetate (3x). The combined organic layers are washed with 5% sodium bicarbonate solution (3x). The basic layers are combined and reacidified to

pH 3 with concentrated hydrochloric acid. The aqueous layers are extracted with ethyl acetate (3x). The combined organic layers are then washed with brine and dried over magnesium sulfate. The filtrate is concentrated to an amorphous white solid, co-evaporated with 3 portions of toluene and dried in vacuo to give N⁶-chloro-2',3'-isopropylideneadenosine-5'-carboxylic acid.

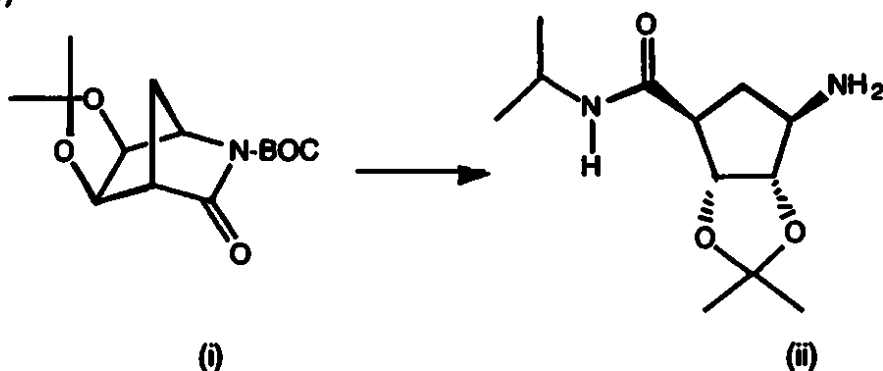
Step 3: 5'-N-Ethyl-2',3'-isopropylidene-N⁶-chloroadenosine-5'-uronamide

N⁶-chloro-2',3'-isopropylideneadenosine-5'-carboxylic acid (4.4 g, 12.9 mmol), triethylamine (1.64 mL, 11.7 mmol) isopropenyl chloroformate (1.28 mL, 11.7 mmol), and methylene chloride (50 mL) are combined under argon at -10 °C and stirred for about 2 minutes. Ethylamine (0.77 mL, 11.7 mmol) is added to the reaction mixture and stirring continued for an additional 1 minute. The reaction mixture is partitioned between methylene chloride and saturated sodium bicarbonate. The aqueous layers are washed with methylene chloride (3X). The combined organic layers are washed with brine and dried over sodium sulfate, filtered, evaporated in vacuo and the residue purified by flash chromatography on silica gel, eluting with 3% MeOH/CHCl₃, to give 5'-N-ethyl-2',3'-isopropylidene-N⁶-chloroadenosine-5'-uronamide, ¹H NMR (300 MHz, (CDCl₃) δ 8.75 (s, 1H), 8.23 (s, 1H), 6.20 (d, 1H), 5.50 (dd, 2H), 4.73 (d, 1H), 3.01 (m, 2H), 1.63 (s, 1H), 1.41 (s, 3H), 0.77 (t, 3H).

EXAMPLE 2

Preparation of (1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]purin-9-yl]cyclopentanecarboxylic acid isopropylamide

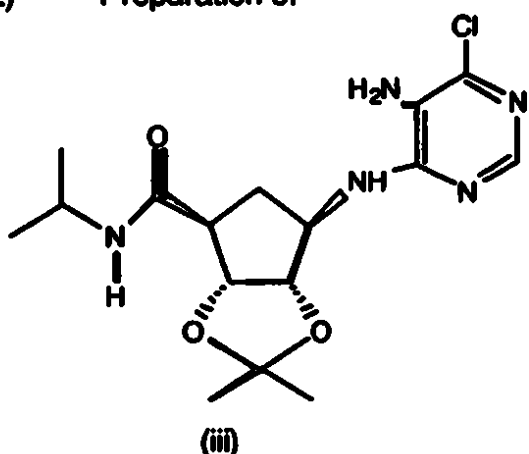
Step (1)



15.5 g (54.6 mmol) N-BOC-5,6-Dimethylenedioxy-2-azabicyclo[2.2.1]heptan-3-one (i) (prepared as in Step (6) of Example 3, below) is dissolved in 16 mL isopropyl amine and the mixture stirred at room temperature for about 2 hours. The mixture is evaporated in vacuo, and the residue azeotroped with chloroform to give a white solid. This solid is

dissolved in 250 mL ethyl acetate, the solution cooled to 0°C, and hydrogen chloride gas is bubbled into the solution, with cooling for about 15 minutes. The solution is then stirred at room temperature for about 4 hours. The solution is evaporated in vacuo, and azeotroped with methanol, then chloroform, to give the amine product as the hydrochloride salt. The hydrochloride salt is partitioned between chloroform and sodium bicarbonate solution, and the organic layer washed with brine, dried, filtered and one equivalent of benzoic acid is added. The solvent is removed in vacuo and the residue triturated in ether to give the desired amine (ii) depicted above as the benzoate salt, m.p. 183-184°C.

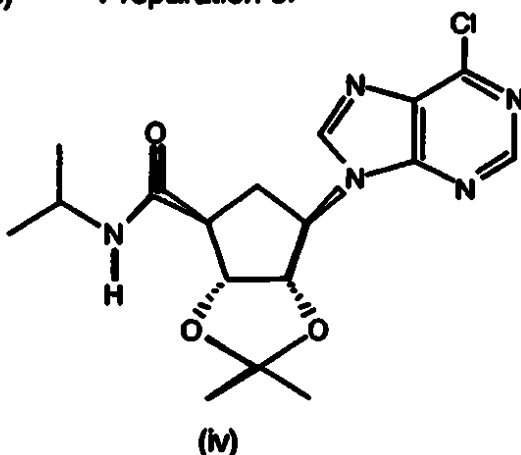
10 Step (2) Preparation of



54 mmol of the product (ii) from Example 2 Step (1) above is dissolved in 110 mL n-butanol and 9.7g 5-amino-4,6-dichloropyrimidine, then 23 mL triethylamine were added and the mixture heated at reflux for about 18 hours. The mixture is cooled, diluted with chloroform and saturated ammonium chloride solution. The aqueous layer is extracted three times chloroform, then twice with 10% isopropyl alcohol/chloroform. The organic layers are combined, dried over sodium sulfate, filtered, concentrated to an oil (iii) which is used, without further treatment for the next step.

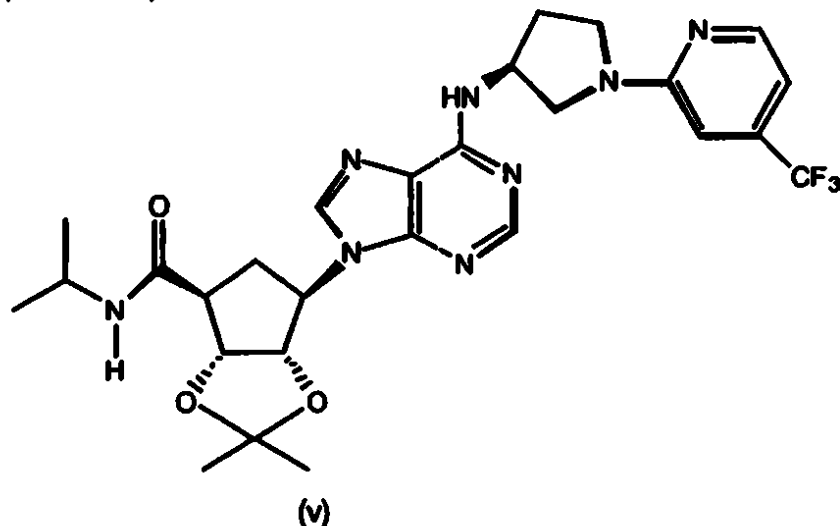
20

Step (3) Preparation of



The product (iii) from Example 2 Step (2) above is taken up in 150 mL n-butyl acetate and 11.2 g formamidine acetate is added. The mixture is heated at reflux under argon for about 9 hours, adding three 5.56 g portions of formamidine acetate at two, four, and six hours. The mixture is cooled, diluted with ethyl acetate, washed with brine, water, brine, dried over sodium sulfate, filtered, concentrated in vacuo, and the residue purified by flash chromatography, eluting with 40-80 % ethyl acetate in hexane, to give the desired chloropurine product (iv) depicted above.

Step (4) Preparation of



400 mg (1.05 mmol) of the product (iv) from Example 2 Step (3) above, 0.22 mL (1.57 mmol) triethylamine, and 270 mg (1.16 mmol) 2-[(3S)-3-aminopyrrolidin-1-yl]-4-trifluoromethylpyridine (prepared as in Example 3, Steps 1 to 5, below) were dissolved together in 3 mL ethanol, and the solution heated at reflux, under argon, for about 20 hours. The mixture is evaporated in vacuo and the residue partitioned between chloroform and saturated sodium bicarbonate solution. The aqueous layer is extracted with 4 portions of chloroform and the combined organic dried over sodium sulfate, filtered, evaporated in vacuo. The residue is purified by flash chromatography, applying the sample in methylene chloride/ethyl acetate (1:1), and eluting with 0 to 3% methanol in ethyl acetate, to give the above-depicted product (v).

Step (5) The product from Example 2 Step (4) above is dissolved in 2 mL methanol/tetrahydrofuran (1:1), and 3.3 mL 1.5 N aqueous hydrochloric acid is added, and the solution stirred at room temperature for about 20 hours. The mixture is evaporated in vacuo. This resulting residue is taken up in 10 mL 15% isopropyl alcohol/chloroform, 1 mL 1 N sodium hydroxide solution, and 9 mL saturated sodium bicarbonate solution. The layers are separated and the aqueous extracted with 4 x 5 mL portions of 15% isopropyl alcohol/chloroform. The combined organic layer is dried over sodium sulfate, filtered, evaporated in vacuo to give (1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(4-trifluoromethylpyridin-2-

yl)pyrrolidin-3(S)-ylamino]purin-9-yl]cyclopentanecarboxylic acid isopropylamide, m.p. 227-228°C.

EXAMPLE 3

- 5 Preparation of (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol

Step (1) 20g (232 mmol) of (3S)-(-)-3 aminopyrrolidine and 26 mL (255 mmol, 1.1 eq) benzaldehyde are combined in 250 mL toluene and refluxed, removing water with a Dean-Stark trap, for about 4.5 hours. The mixture is cooled to 0°C and 55.7g (255.2 mmol, 1.1 eq) di-tert-butyl dicarbonate added, then stirred at room temperature. The mixture is concentrated in vacuo, stirred with KHSO₄ solution, extracted 3 times with ether. The aqueous layer is made alkaline and extracted with CH₂Cl₂. The organic layer is washed with brine and dried over MgSO₄, filtered, and evaporated in vacuo to give N1-BOC-(3S)-(-)-3 aminopyrrolidine.

Step (2) 34.25 g (183.9 mmol) of the product from Example 3 Step (1) above is dissolved in 200 mL CH₂Cl₂ and 25 mL (183.9 mmol, 1 eq) of triethylamine is added. Under a nitrogen atmosphere, 34.7 mL (367.8 mmol, 2 eq) of acetic anhydride is added dropwise, the mixture stirred at room temperature, partitioned with NaHCO₃ solution/CH₂Cl₂. The organic layer is washed with brine, dried over MgSO₄, filtered, evaporated in vacuo, and the product purified by flash chromatography, eluting with 2-8% methanol in methylene, to give N1-BOC-(3S)-(-)-3-acetylamino pyrrolidine.

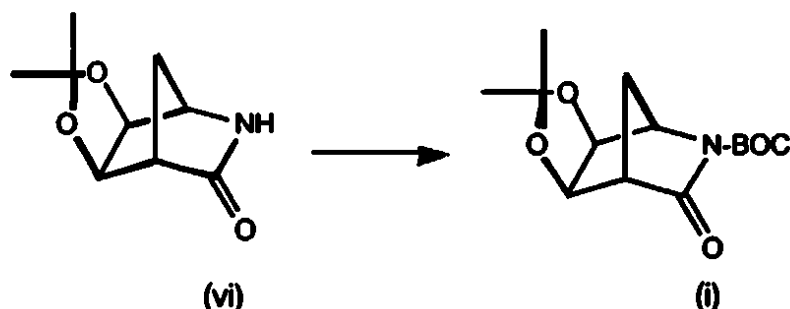
Step (3) 39.2 g (171.7 mmol) of the product from Example 3 Step (2) above is dissolved in 400 mL CH₂Cl₂ and 26.46 mL (343.4 mmol 2 eq) trifluoroacetic acid (hereinafter "TFA") is dropwise at 0°C under a nitrogen atmosphere. The mixture is heated to reflux, adding another 26 mL, then another 10 mL of TFA, refluxed for about an additional 3 hours, then evaporated under high vacuum to remove TFA. The residue was stirred with Amberlite IRA-400 basic resin (hereinafter "basic resin"), filtered, the filtrate dissolved in methanol, filtered slowly through basic resin, and the filtrate evaporated to give (3S)-(-)-3-acetylamino pyrrolidine.

Step (4) 4g (31.2 mmol) of the product from Example 3 Step (3) above and 5.19 (40.6 mmol) 2-chloro-5-trifluoromethylpyridine are combined in 50 mL ethanol and 13 mL (93.6 mmol, 3 eq) triethylamine are added. The mixture is refluxed for about 18 hours, concentrated in vacuo and the residue partitioned between methylene chloride and sodium bicarbonate solution. The organic layer is washed with brine, dried over magnesium sulfate, filtered, evaporated in vacuo, and the residue purified by flash chromatography, eluting with

2-5% methanol in methylene chloride, to give 2-[(3S)-3-acetylamino-1-pyrrolidin-1-yl]-5-trifluoromethylpyridine, as a solid.

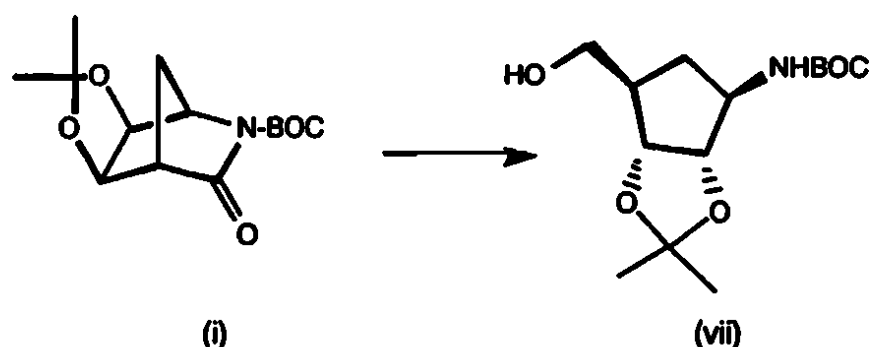
Step (5) 7.52 g (27.5 mmol) of the product from Example 3 Step (4) above is combined with 75 mL 6N aqueous hydrochloric acid and the mixture refluxed for about 18 hours. The mixture is cooled to room temperature, neutralized with solid sodium bicarbonate, partitioned between dilute sodium hydroxide solution and methylene chloride. The organic layer is washed with brine, dried over magnesium sulfate, filtered, evaporated in vacuo to give 2-[(3S)-3-aminopyrrolidin-1-yl]-5-trifluoromethylpyridine.

Step (6)



22.5 g (0.123 mol) (-)-5,6-Dimethylenedioxy-2-azabicyclo[2.2.1]heptan-3-one (vi), 1.5 g 4-dimethylaminopyridine (hereinafter "DMAP"), 12.4 g triethylamine, and 37.5 g di-tert-butyl dicarbonate are combined in methylene chloride and stirred at room temperature for about 18 hours. The mixture is washed with 1N hydrochloric acid, 5% sodium bicarbonate solution, brine, dried over sodium sulfate, filtered, concentrated in vacuo and the residue recrystallized from isopropyl alcohol to give N-BOC-5,6-Dimethylenedioxy-2-azabicyclo[2.2.1]heptan-3-one (i).

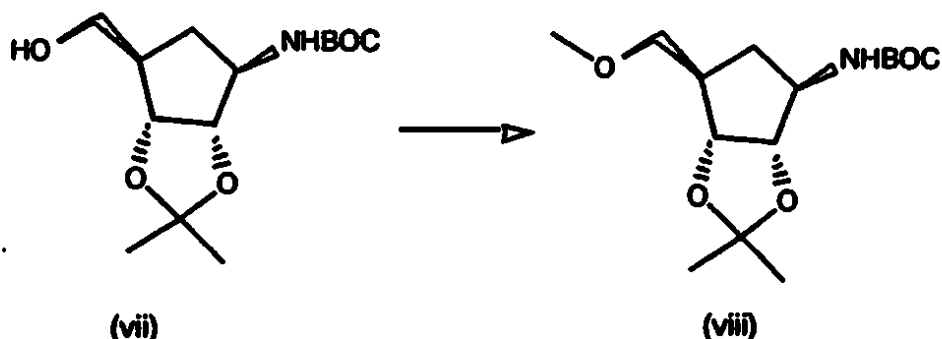
Step (7)



35.6g (0.125 mol) of the product (i) from Example 3 Step (6) above is combined with 400 mL methanol. With rapid stirring and cooling, under argon purge, a total of 23.8g (0.63 mol) sodium borohydride is added in three equal portions over a period of about 2 hours.

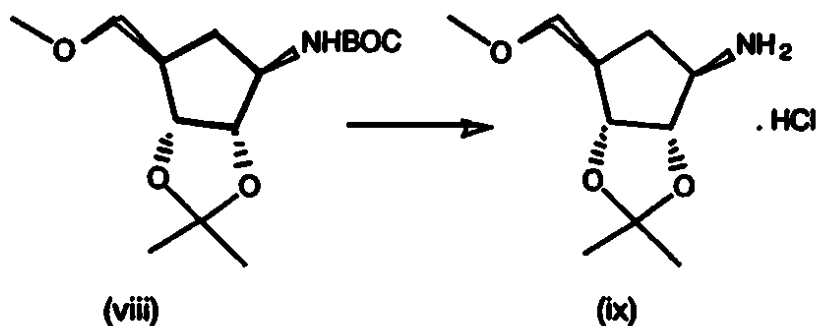
The mixture is concentrated in vacuo and partitioned between 200 mL water and 300 mL ethyl acetate. The aqueous layer is extracted twice more with ethyl acetate and the combined organic solution washed with water, brine, dried over sodium sulfate, filtered, concentrated in vacuo to give N-BOC-1-amino-2,3-dimethylenedioxy-4-hydroxymethylcyclopentane (vii).

Step (8)



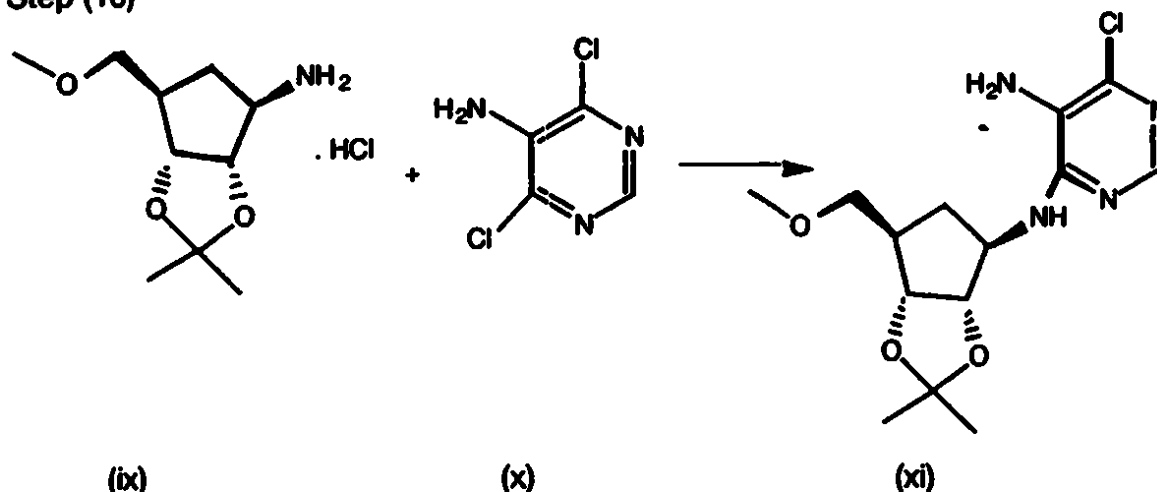
50 g of the product (vii) from Example 3 Step (7) above is placed in 150 mL benzene. 8.8 ml methyl iodide and 33 g silver oxide are added and the mixture refluxed for about 18 hours. Another 25 g of silver oxide and another 50 mL of methyl iodide are added portionwise over about 6 hours and the mixture refluxed for about 18 hours. The mixture is filtered through Celite and the filter cake washed with ethyl acetate. The combined filtrate is concentrated in vacuo and the residue crystallized from hexane to give the desired methoxymethyl compound (viii) depicted above.

Step (9)



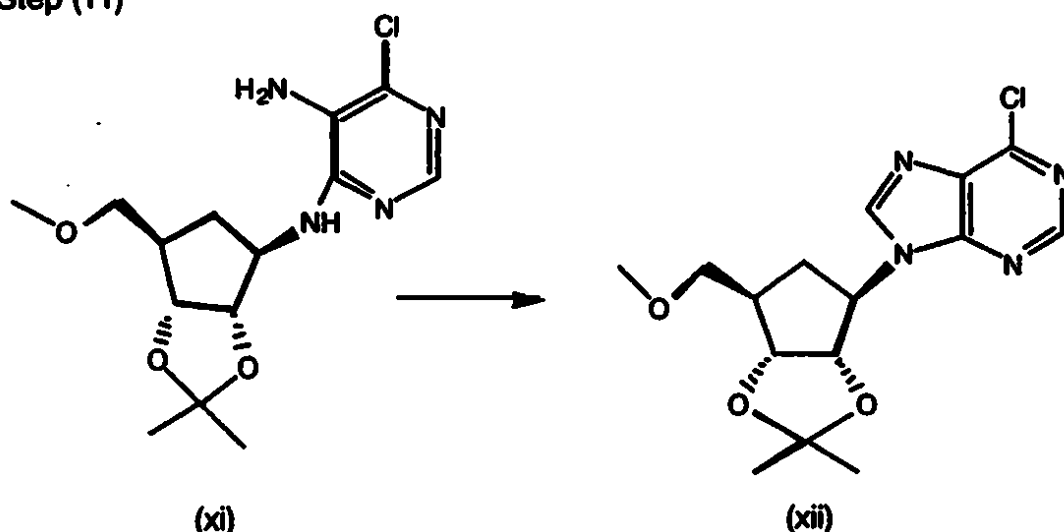
Under argon, 31.6g of the product (viii) from Example 3 Step (8) above is dissolved in 250 mL warm anhydrous ethyl acetate. The solution is cooled in an ice bath and hydrogen chloride gas is bubbled through the solution for about 6 minutes. The mixture is allowed to warm to room temperature and stirred for about 3 hours, then concentrated in vacuo to give the desired amine hydrochloride (ix) depicted above.

Step (10)



- 5 24.2 g of the product from (ix) Example 3 Step (9) above and 42.8 g sodium bicarbonate are combined in 100 mL n-butanol, under argon, and 20.1 g 5-amino-4,6-dichloro pyrimidine is added. The mixture is heated at reflux for about 20 hours, then concentrated in vacuo. The residue is partitioned between ethyl acetate and water and the ethyl acetate layer washed with brine, dried over magnesium sulfate, filtered, concentrated
- 10 in vacuo. The residue in 30% ethyl acetate in hexane, passed through a large flash silica gel wash column, and the column is washed with 50% ethyl acetate/hexane and the combined filtrates concentrated in vacuo to give the desired pyrimidinylaminocyclopentane product (xi) depicted above.

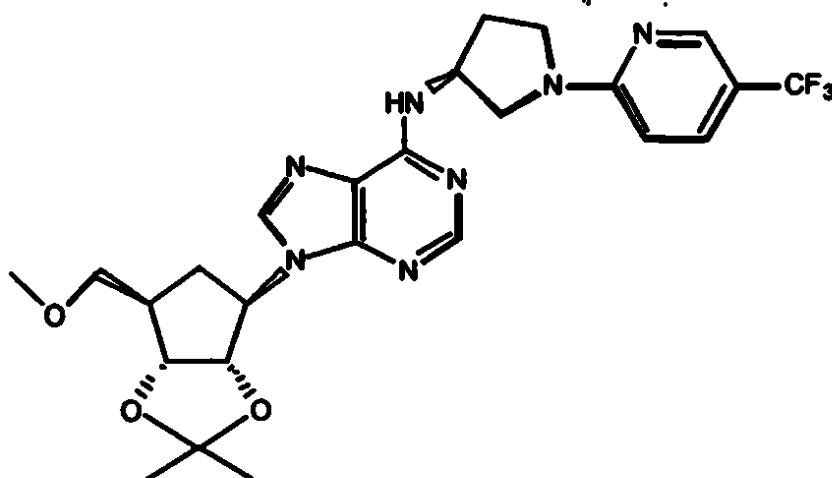
15 Step (11)



- 20 26.7 g of the product (xi) from Example 3 Step (10) above is combined with 125 mL n-butyl acetate under argon. 33.5g formamidine acetate added and mixture heated at reflux for about 3 hours, until thin layer chromatography shows reaction is complete. The mixture is cooled, partitioned between ethyl acetate and brine and the ethyl acetate layer dried over

magnesium sulfate, filtered, concentrated in vacuo. The residue was purified by flash chromatography, eluting with 30-50% ethyl acetate in hexane, to give the chloropurine product (xii) depicted above.

5 Step (12) Preparation of



(xiii)

7.75 g (22.9 mmol) of the product (xii) from Example 3 Step (11) above and 6.35 g
 10 (27.4 mmol) 2-[(3S)-3-aminopyrrolidin-1-yl]-5-trifluoromethylpyridine are combined in 20 mL ethanol and 6.33 mL triethylamine added. The mixture is heated in a sealed vessel at 105°C for about 4 hours. The mixture is cooled, evaporated in vacuo, partitioned between methylene chloride and sodium bicarbonate solution. The organic layer is dried over magnesium sulfate, filtered, concentrated in vacuo, and the residue purified by flash
 15 chromatography, eluting with 4% methanol in methylene chloride, to give the product (xiii) indicated.

Step (13) 10.81g (20.3 mmol) of the product (xiii) from Example 3 Step (12) above is combined with 90 mL trifluoroacetate and 10 mL water, and the mixture stirred at room
 20 temperature for about 30 minutes. The TFA is evaporated off at high vacuum and the residue partitioned between methylene chloride and sodium bicarbonate solution. The methylene chloride solution is washed with sodium bicarbonate solution, brine, isopropyl alcohol is added and the solution dried over magnesium sulfate, filtered, concentrated in vacuo, and the residue flash chromatographed, eluting with 5-10% methanol in methylene
 25 chloride. The appropriate fractions are collected, concentrated, and the residue crystallized from acetonitrile to give (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, m.p. 166-168°C.

EXAMPLE 4

Preparation of (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(R)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol

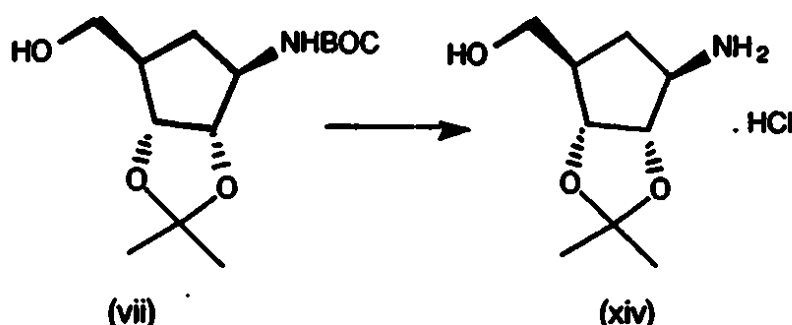
267 mg 2-[(3R)-3-aminopyrrolidin-1-yl]-5-trifluoromethylpyridine, 331 mg 6-chloropurineriboside, 233 mg triethylamine, and 0.5 mL ethanol are combined and heated in a sealed vessel at 100°C for about 5 hours. The mixture is cooled, partitioned between methylene chloride (with some isopropyl alcohol added) and sodium bicarbonate. The organic layer is washed with brine, dried over magnesium sulfate, evaporated, and the residue purified by flash chromatography, eluting with 5% methanol in methylene chloride, to give (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(R)-ylamino]purin-9-yl]tetrahydrofuran-3,4-diol, as the hemihydrate, m.p. 166-170°C.

EXAMPLE 5

Preparation of (1R,2S,3R,5R)-3-[6-[1-(4-trifluoromethylphenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol

Step (1) 1.00 g (11.6 mmol) 3(S)-(-)-3-aminopyrrolidine, 1.35 mL (9.66 mmol) 4-bromobenzotrifluoride, 2.69 g (29 mmol) sodium tert-butoxide, and 1.01g (1.16 mmol) $\text{PdCl}_2(\text{P}[o\text{-tolyl}]_3)_2$ (prepared as in U.S. Patent No. 4,196,135) are combined in 30 mL toluene, and the mixture heated in a sealed vessel at 100°C for about 40 hours. The mixture was cooled, filtered, evaporated in vacuo and the residue purified by flash chromatography, eluting with 10:1 to 7:1 methylene chloride/ethanol, to give 1-(4-trifluoromethyl)phenyl-(3S)-pyrrolidin-3-ylamine.

Step (2)

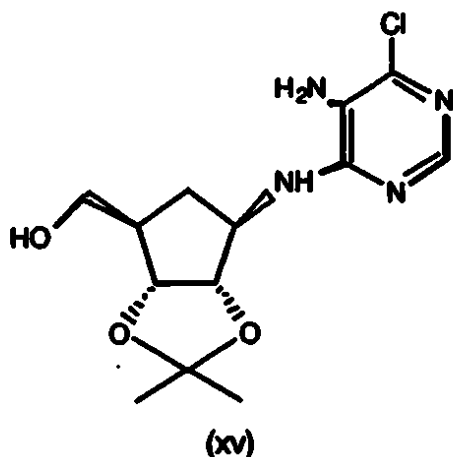


A solution of 24.7 mL (0.61 mol) methanol and 50 mL ethyl acetate is cooled to 0°C, under argon. 43.3 mL (0.61 mol) acetyl chloride is added portionwise and the solution allowed to come to room temperature over about 45 minutes. This solution is again cooled

in ice and a solution of 50.0g N-BOC-1-amino-2,3-dimethylenedioxy-4-hydroxymethyl cyclopentane (vii) in 100 mL ethyl acetate is added over a period of about 45 minutes. The solution is allowed to come to room temperature, then evaporated in vacuo to give the desired amine hydrochloride (xiv) depicted above.

5

Step (3) Preparation of

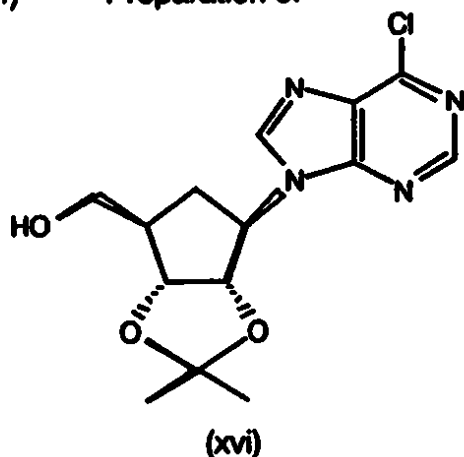


10

38.9g of the product (xiv) from Example 5 Step (2) above and 73 g sodium bicarbonate are combined in 150 mL n-butanol under argon, and the mixture stirred at room temperature for about 30 minutes. 34.2 g 5-amino-4,6-dichloropyrimidine is added and the mixture stirred at reflux for about 19 hours. The mixture is concentrated in vacuo, and the residue taken up in ethyl acetate and water. The aqueous layer is extracted with ethyl acetate and the combined organic washed with brine, filtered, concentrated in vacuo. The residue is purified by flash chromatography, eluting with a gradient of 30% to 100% ethyl acetate in hexane, to give the desired substituted chloropyrimidine (xv) depicted above.

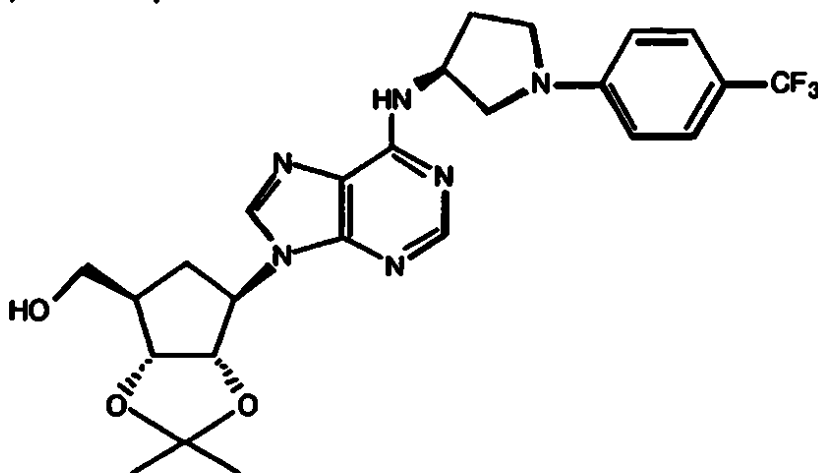
15

20 Step (4) Preparation of



37.9 g of the product (xv) from Example 5 Step (3) above and 25.1 g formamidine acetate are combined in 250 mL n-butyl acetate and the mixture heated at reflux, under argon, for about 2 hours, adding an additional 12.5 g formamidine acetate after about 1 hour, and an additional 10 g after about 1.5 hours. The mixture is cooled, partitioned between ethyl acetate and brine, the brine extracted with 3 portions of ethyl acetate, and the combined organic dried over magnesium sulfate, filtered, evaporated in vacuo. The residue is purified by crystallization from ethyl acetate/hexane to give the above-depicted chloropurine (xvi). The residue from concentration of the mother liquor can be purified by flash chromatography, eluting with 80 to 100% ethyl acetate in hexane to improve recovery.

Step (5) Preparation of



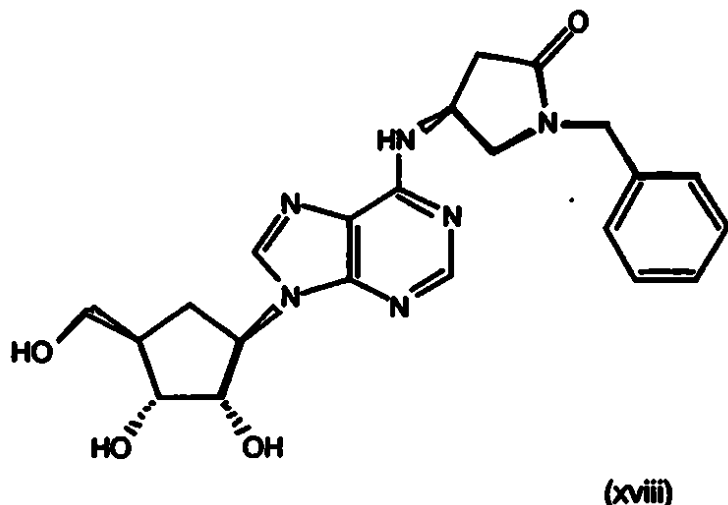
(xvii)

0.225 g (0.693 mmol) of the product (xvi) from Example 5 Step (4) above, 0.239 g (1.04 mmol) 1-(4-trifluoromethyl)phenyl-(3S)-pyrrolidin-3-ylamine, from Step (1) above, and 0.582 g (6.93 mmol) sodium bicarbonate are combined in 20 mL ethanol and heated at reflux for about 60 hours. The mixture is filtered, concentrated in vacuo, and the residue purified by flash chromatography, eluting with a gradient of methylene chloride/ethanol, 30:1 to 10:1, to give the pyrrolidinylamine (xvii) depicted above.

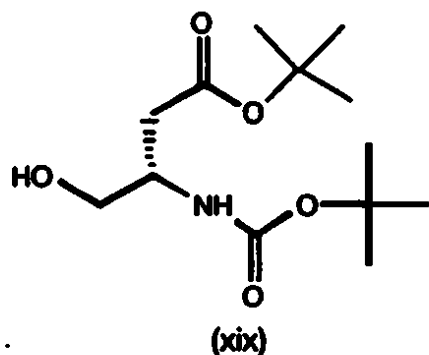
Step (6) 0.234 g of the product from Example 5 Step (5) above is dissolved in 10 mL trifluoroacetic acid and the solution stirred at room temperature overnight. The solution is evaporated in vacuo, and the residue purified by flash chromatography, eluting with methylene chloride/ethyl acetate (10:1) to give (1R,2S,3R,5R)-3-[6-[1-(4-trifluoromethylphenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, m.p. 111-114°C.

EXAMPLE 6

Preparation of 4(S)-1-benzyl-4-[9-((1R,2S,3R,5R)-1,2-dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-purin-6-ylamino]pyrrolidin-2-one



Step (1) Preparation of

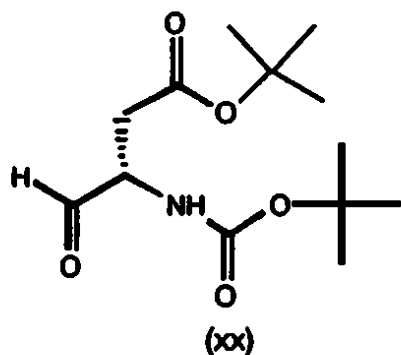


7.1 g (24.5 mmol) N-t-BOC-L- aspartic acid β -t-butyl ester is dissolved in 120 mL tetrahydrofuran. The solution is cooled to 0°C and 2.73 g (27 mmol) triethylamine, then 2.66 g (24.5 mmol) ethyl chloroformate is added. The solution is stirred for about 30 minutes, and a solution of 3.71 g (98.2 mmol) sodium borohydride in water is added. The mixture is stirred at room temperature for about 17 hours, concentrated in vacuo and the residue diluted with ethyl acetate, and the organic layer washed with 1 N hydrochloric acid, 10% sodium carbonate, brine, then dried over magnesium sulfate, filtered, concentrated in vacuo and the residue purified by flash chromatography, eluting with 30% to 50% ethyl acetate in hexane, to give 3(S)-t-butyl-3-BOC-amino-4-hydroxy-n-butanoate (xix).

15

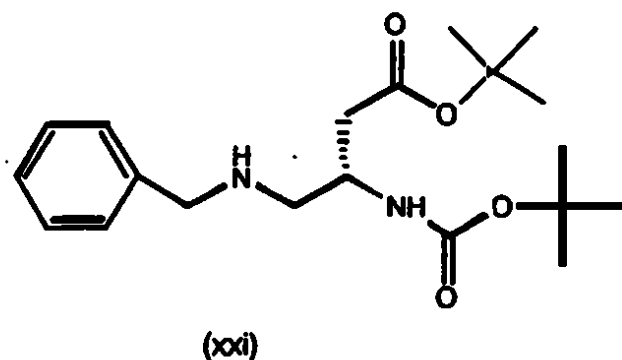
20

Step (2) Preparation of



A solution of 0.73 g of dimethylsulfoxide in 9 mL of methylene chloride is cooled to -70°C and 31 mL of a 2M solution of oxalyl chloride in methylene chloride is added dropwise. The solution is stirred for about 15 minutes and a solution of 0.85 g of 3(S)-t-butyl-3-BOC-amino-4-hydroxy-n-butanoate (xix) in 5 mL methylene chloride is added. After stirring for about 45 minutes, 1.88g triethylamine is added. The solution is allowed to warm to room temperature, stirred for about 30 minutes, then diluted with ethyl acetate. The solution is washed with 1N hydrochloric acid, 10% sodium carbonate, brine, dried over magnesium sulfate, filtered, concentrated in vacuo, to give give 3(S)-t-butyl-3-BOC-amino-4-oxo-n-butanoate (xx).

Step (3)



The product (xx) from Example 6 Step (2) above is dissolved in 9 mL methanol and 1.34g benzyl amine hydrochloride, then 0.94 g triethylamine, then 200 mg 3 Å molecular sieves. The solution is stirred for about 45 minutes and a solution of 0.23 g zinc chloride and 0.22 g sodium cyanoborohydride in 5 mL methanol is added. The solution is stirred for about 4 hours, 2 mL 1N sodium hydroxide, then 10 mL water are added, the mixture concentrated to about one-half volume, and extracted with ethyl acetate. The ethyl acetate solution is washed with 10% sodium carbonate solution, brine, dried over magnesium sulfate, filtered, concentrated in vacuo, and the residue purified by flash chromatography,

eluting with 30% to 40% ethyl acetate in hexane, to give the benzyl amine (xvi) depicted above.

Step (4) 0.90 g of the product from Example 6 Step (3) above is dissolved in 12 mL of toluene/acetic acid (10:1), and the solution refluxed for about 1.5 hours. The mixture is concentrated in vacuo, and the residue purified by flash chromatography, eluting with 25%-35% ethyl acetate in methylene chloride, to give 1-benzyl-4(S)-BOC-amino-2-pyrrolidinone.

Step (5) 0.64g of the product from Example 6 Step (4) above is dissolved in 20 mL ethyl acetate and the solution cooled to 0°C. Hydrogen chloride gas is bubbled into the solution for about 5 minutes, and the mixture stirred at room temperature for about 18 hours. Ether is added to the mixture and the solid collected by filtration to give 1-benzyl-4(S)-amino-2-pyrrolidinone hydrochloride.

Step (6) 0.33 g of the protected chloropurine from Example 5, Step (4) above, 0.26 g 1-benzyl-4(S)-amino-2-pyrrolidinone hydrochloride, and 0.29 g triethylamine are combined in 10 mL ethanol and the mixture heated at reflux for about 50 hours. The mixture is concentrated in vacuo and the residue dissolved in 20 mL 1 N hydrochloric acid and stirred at room temperature for about 1 hour. The mixture is concentrated in vacuo and the residue purified by preparative HPLC, eluting with a gradient of 10% acetonitrile to 60% acetonitrile in water, containing 0.1% trifluoroacetic acid. The appropriate fractions were combined, concentrated, and the residue dissolved in 20 mL 1N hydrochloric acid, the solvent evaporated in vacuo, and this repeated twice more. This residue was dissolved in methanol, the solvent evaporated in vacuo, and the residue triturated in ether to give 4(S)-1-benzyl-4-[9-((1R,2S,3R,5R)-1,2-dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-purin-6-ylamino]pyrrolidin-2-one as the hydrochloride trihydrate, m.p. 100°C (dec.)

EXAMPLE 7

Preparation of (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentane-1,2-diol

Step (1) 4-nitrophenol (1.0g, 7.19 mmol) and triethylamine (3 mL, 21.6 mmol) were dissolved together in anhydrous methylene chloride (10 mL), and the solution cooled to -15°C. Trifluoromethanesulfonic anhydride (1.81 mL, 10.8 mmol) is added and the mixture stirred at -15°C for about 30 minutes. The mixture is diluted with methylene chloride, washed with sodium bicarbonate solution and brine, the organic layer dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified by flash

chromatography, eluting with methylene chloride, to give 4-nitrophenyl trifluoromethanesulfonate as a light yellow solid.

Step (2) 3(S)-amino-1-benzylpyrrolidine (3.0g, 17.0 mmol) and triethylamine (2.50 mL, 17.9 mmol) are dissolved together in anhydrous methanol (17 mL), under nitrogen, and ethyl trifluoroacetate (2.53 mL, 21.3 mmol) is added dropwise. The solution is stirred for about 18 hours, evaporated in vacuo, and the residue taken up in methylene chloride. The solution is washed with sodium bicarbonate solution, brine, dried over magnesium sulfate, filtered, concentrated in vacuo to give 1-benzyl-3(S)-trifluoroacetylaminopyrrolidine.

Step (3) Under nitrogen, 1-benzyl-3(S)-trifluoroacetylaminopyrrolidine (4.59g, 16.7 mmol) is dissolved in anhydrous methanol (50 mL) and di-tert-butyl dicarbonate (3.68g, 16.7 mmol) and 10% palladium on carbon (0.90g) are added. The mixture is then stirred under hydrogen under atmospheric pressure for about 5 hours. The mixture is filtered through Celite®, rinsing with methanol, and the filtrate evaporated in vacuo. The residue was purified by flash chromatography, eluting with 5% methanol in methylene chloride to give 1-BOC-3(S)-trifluoroacetylaminopyrrolidine.

Step (4) 1-BOC-3(S)-trifluoroacetylaminopyrrolidine (4g) is dissolved in methylene chloride (130 mL) and trifluoroacetic acid (19 mL) is added. The solution is stirred at room temperature for about 1 hour, then concentrated in vacuo. The residue is partitioned between methylene chloride and saturated sodium bicarbonate solution. The layers are separated and the aqueous extracted with ethyl acetate. The combined organic is dried over magnesium sulfate, filtered, evaporated in vacuo to give 3(S)-trifluoroacetylaminopyrrolidine.

Step (5) 4-Nitrophenyl trifluoromethanesulfonate (0.423g, 1.56 mmol) and triethylamine (0.217 mL, 1.56 mmol) are dissolved together in anhydrous acetonitrile (15 mL) and 3(S)-trifluoroacetylaminopyrrolidine (0.852g, 4.68 mmol) is added and the mixture heated at reflux for about 18 hours. The mixture is cooled, concentrated in vacuo and the residue purified by flash chromatography, eluting with a gradient of 25% to 50% ethyl acetate in hexane to give 1-(4-nitro)phenyl-3(S)-trifluoroacetylaminopyrrolidine.

Step (6) 1-(4-Nitro)phenyl-3(S)-trifluoroacetylaminopyrrolidine (0.334g, 1.10 mmol) is combined with a saturated solution of potassium carbonate in methanol/water (2:3) (20 mL), and the mixture heated at 55°C for about two hours, then at room temperature for about 18 hours. The mixture is concentrated in vacuo and the residue taken up in water (10 mL). The aqueous is extracted with ethyl acetate, and the organic dried over magnesium sulfate, filtered, evaporated in vacuo to give 3(S)-amino-1-(4-nitro)phenylpyrrolidine.

Step (7) Using essentially the procedures of Example 3, Steps 12 and 13, and Example 5, Steps 5 and 6, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentane-1,2-diol, m.p. 119-120°C, is prepared from 3(S)-amino-1-(4-nitro)phenylpyrrolidine.

Using essentially the procedures of the Reaction Schemes and Examples as described hereinabove, the following compounds for use of the invention are prepared from the appropriate starting materials:

Example 8

(2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-chloropyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, m.p. 154-156°C;

Example 9

(2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, m.p. 153-156°C;

Example 10

(2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(4-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, m.p. 187-190°C;

Example 11

(2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-bromopyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, 153-154°C;

Example 12

(2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, m.p. 230-232°C;

Example 13

(2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']-bipyridinyl-3-ylamino)-purin-9-yl]tetrahydrofuran-3,4-diol, m.p. 113-116°C;

Example 14

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

Example 15

(2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(1-pyridin-2-ylpyrrolidin-3(S)-ylamino)-purin-9-yl]tetrahydrofuran-3,4-diol, m.p. 193-195°C;

5 Example 16

(2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, m.p. 121-124°C;

Example 17

10 (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-methylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, m.p. 164-166°C;

Example 18

15 (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-thiophen-2-ylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, 190-192°C;

Example 19

(2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-methylmercaptopyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, m.p. 231-233°C;

20

Example 20

(2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, m.p. 251-253°C;

25 Example 21

(2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, 154-156°C;

Example 22

30 (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, m.p. 130°C (dec.);

Example 23

35 (2R,3R,4S,5R)-5-methoxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, m.p. 198-200°C;

Example 24

(1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentanecarboxylic acid ethylamide, m.p. 135-138°C;

Example 25

(1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)piperidin-4-ylamino]-purin-9-yl]cyclopentane-1,2-diol, m.p. 126-128°C;

5

Example 26

(1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3S)-pyrrolidin-3-ylamino)-purin-9-yl] cyclopentane-1,2-diol dihydrochloride, m.p. 160°C (dec);

10 **Example 27**

(1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(R)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, 175-177°C;

Example 28

15 (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3R)-pyrrolidin-3-ylamino)-purin-9-yl] cyclopentane-1,2-diol, m.p. 166°C (dec);

Example 29

20 (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, m.p. 110-111°C;

Example 30

4(R)-1-benzyl-4-[9-((1R,2S,3R,5R)-1,2-dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-purin-6-ylamino] pyrrolidin-2-one hydrochloride, m.p. 110°C (dec);

25

Example 31

(1R,2S,3R,5S)-5-methyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, m.p. 114-116°C;

30 **Example 32**

(1R,2S,3R,5R) -3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl] -5-hydroxymethylcyclopentane-1,2-diol, m.p. 169-171°C;

Example 33

35 (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, m.p. 118-121°C;

Example 34

(1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, m.p. 135-137°C;

5 Example 35

(1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(pyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, m.p. 110-112°C;

Example 36

10 (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(quinolin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, m.p. 135-138°C;

Example 37

15 (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol;

Example 38

20 (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluoropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, m.p. 123-126°C;

Example 39

(1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(phenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, m.p. 97-99°C;

25 Example 40

4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-purin-6-ylamino]pyrrolidin-1-yl]benzonitrile, m.p. 140°C;

Example 41

30 (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(isoquinolin-1-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, m.p. 119-122°C;

Example 42

35 (1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol;

Example 43

(1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol;

Example 44

(1R,2S,3R,5R)-3-[6-[1-(3-chloro-5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, m.p. 140-143°C;

5

Example 45

(1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, m.p. 180-182°C;

10 **Example 46**

(1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol;

Example 47

15 (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol;

Example 48

20 (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, m.p. 118-120°C;

Example 49

(1R,2S,3R,5R)-5-isopropoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, m.p. 157-158°C;

25

Example 50

(1R,2S,3R,5R)-5-isopropoxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, 160-161°C;

30 **Example 51**

(1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, m.p. 122-124°C;

Example 52

35 (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, m.p. 110-111°C;

Example 53

(1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, m.p. 110-112°C;

5 Example 54

(1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylphenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, m.p. 128°C;

Example 55

10 (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, m.p. 122-125°C;

Example 56

15 (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, m.p. 127-130°C;

Example 57

(1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, m.p. 131-133°C; and

20

Example 58

(1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-phenylpyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentan-1,2-diol, m.p. 106°C.

25 Example 59

(1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, m.p. 100-102°C;

Example 60

30 (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, m.p. 95-96°C.

Example 61

35 (1S,2R,3S,4R)-2,3-dihydroxy-4-{6-[1-(5-trifluoromethyl-pyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl}-cyclopentanecarboxylic acid-1(S)-methylpropylamide, m.p. 215°C (dec.); and

Example 62

(1S,2R,3S,4R)- 2,3-dihydroxy-4-{6-[1-(5-trifluoromethyl-pyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl}- cyclopentanecarboxylic acid-1 (R)-methylpropylamide, m.p. 206-212°C (dec.).

Aspects of the pathophysiology of insulin resistance and type 2 diabetes

Insulin resistance, which is defined as a state of reduced responsiveness to normal circulating concentrations of insulin, is a characteristic trait of type 2 diabetes and contributes to abnormalities in muscle, fat tissue and liver. Insulin resistance precedes the onset of type 2 diabetes, which develops when additional defects exist at the level of the pancreatic beta-cell. As long as the peripheral insulin resistance can be compensated by increased insulin production glucose homeostasis is balanced. Even in the absence of type 2 diabetes, insulin resistance is a key feature of other human disease states. Impaired insulin action coupled with hyperinsulinemia leads to a variety of abnormalities, including elevated triglycerides, low levels of HDL, enhanced secretion of VLDL, disorders of coagulation, increased vascular resistance, changes in steroid hormone levels, attenuation of peripheral blood flow and weight gain. Thus, insulin resistance is often associated with central obesity, hypertension, polycystic ovarian syndrome, dyslipidemia, and atherosclerosis (JCI 106, 163-164, 2000).

Insulin resistance is characterized in the adipose tissue by increased lipolysis, which results in increased levels of free fatty acids, which by itself contributes to reduced glucose utilisation in the muscle, to increased flux of fatty acids to the liver, with subsequent increased VLDL production, and to impairment of insulin secretion from the beta-cell in the liver by increased hepatic glucose production, and VLDL secretion, which result in hyperglycemia and hypertriglyceridemia, respectively. in the muscle by reduced glucose utilisation rates, which contributes to hyperglycemia,

Inhibition of peripheral lipolysis by TGL 749 (adenosine A1 receptor agonist) results in reduction of plasma free fatty acids (primary pharmacological effect). Reduced availability of free fatty acids to the muscle increased glucose utilisation and reduced VLDL production in

the liver which is paralleld by reduced plasma triglycerides (secondary pharmacological effect).

Measurement of the antilipolytic effect

- 5 The antilipolytic effect of compounds according to the general formula (I) is shown in Table 1.

Example No.	Lipo ec ₅₀ [nm]
2	10,88
3	5,62
5	2
6	267
7	2,82
18	2,24
20	1,37
21	2,43
22	3,07
26	178,0
29	3,57
31	247,0
32	8,0
33	4,2
34	3,3
35	48,0
37	2,8
38	114,0
39	17,6
40	10,5
41	182,0
42	30,0
44	226,0
46	92,5
47	129,0
50	365,0
51	18,6

52	17,0
53	18,6
54	27,8
55	3,3
56	2,4
57	63,5
61	18,0

Measurement of plasma lipdis (free fatty acids, triglycerides, cholesterol) in anaesthetized rats.

5

Plasma lipid levels were assayed in anaesthetized rats. Briefly, rats were anaesthetized with an intraperitoneal injection of pentobarbital sodium (60 mg/kg), tracheotomized, and one jugular vein per rat was cannulated for intravenous administration (bolus injection or infusion). Anesthesia was maintained for up to 7 hours by subcutaneous infusion of pentobarbital sodium (adjusted to the anesthetic depth of the individual animal; about 24 mg/kg/h). Body temperature was monitored with a rectal probe thermometer, and temperature was maintained at 37° C by means of a heated surgical plate. The rats were allowed to stabilize their blood levels after surgery for up to 2 hours, after which the test compound was injected intraperitoneally. Blood samples for glucose analysis (10 µl) were obtained from the tip of the tail every 15 minutes. For analysis of plasma lipids blood samples (0.3 ml) were obtained from the jugular vein either every 10 to 15 minutes for up to 2 hours, or every hour for up to 5 hours after compound administration. Standard enzymatic procedures were used to determine blood glucose (Bergmeyer, 1974).

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15

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Table 2
Effect of Compound of Example 3 on plasma free fatty acids in anaesthetized starved male Wistar rats
(Animal Study: 00-009

	Control		Example 3 (10 mg/kg i.p.)		Example 3 (30 mg/kg i.p.)	
minutes	Mean	SEM	mean	SEM	mean	SEM
-60	0,57	0,04	0,61	0,03	0,52	0,02

10	0,55	0,04	0,42	0,03	0,24	0,02
20	0,59	0,02	0,26	0,07	0,14	0,01
30	0,52	0,04	0,19	0,05	0,13	0,01
40	0,50	0,04	0,19	0,06	0,10	0,01
60	0,48	0,07	0,13	0,05	0,09	0,01
Values are mean +/- SEM, n= 4 rats						

Measurement of insulin sensitivity in conscious rats.

- 5 Insulin resistant Zucker Fatty rats or Zucker Diabetic Fatty (ZDF) rats were treated for up to 3 weeks with the test compound orally once daily. Plasma parameters were obtained by retroorbital bleeding during inhalation anaesthesia on respective study days. At the end of the study rats were starved overnight and they received an insulin bolus injection (3 U/kg s.c.) and blood glucose reduction was monitored up to 6 hours. In the case of improvement of insulin sensitivity by the test compound the blood glucose reduction was much more pronounced and prolonged compared to that of the control group.
- 10

Table 3

Insulin tolerance test (3 U/kg s.c.) in insulin resistant Zucker Fatty Rats after pretreatment with Compound of Example 3 for 3 weeks with 1 and 10 mg/kg po
(Animal Study: 00-027)

minutes after insulin		0	60	120	180	240	300	360	420
control	mean	5,28	2,38	2,92	5,87	6,89	6,20	5,24	4,93
	SEM	0,14	0,10	0,21	0,35	0,46	0,33	0,26	0,16
Example 3 (1 mg/kg p.o.)		4,60	1,96	1,59	1,72	3,02	5,13	4,98	4,04
		0,16	0,07	0,09	0,12	0,25	0,47	0,26	0,24
Example 3 (10 mg/kg p.o.)		5,17	1,99	1,57	1,44	2,54	4,35	5,63	6,09
		0,22	0,17	0,16	0,09	0,27	0,42	0,47	0,31

Values are mean +/- SEM, n = 9									

Compounds within the scope of this invention exhibit activity in standard A₁/A₂ receptor binding assays for the determination of adenosine receptor agonist activity in mammals. Exemplary test procedures which are useful in determining the receptor binding affinity of compounds of the present invention are described below.

A. IN VITRO ADENOSINE RECEPTOR BINDING AFFINITY DETERMINATION

A₁ Receptor Binding Affinity was determined by competition assay based on ligand displacement of ³H-CHA (cyclohexyl adenosine) [Research Biochemicals Inc., Natick, Mass.] from receptor using a membrane preparation of whole rat brain, according to the procedure of R. F. Bruns et al., Mol. Pharmacol., 29:331 (1986). Non-specific binding was assessed in the presence of 1 mM theophylline.

A₂ receptor binding affinity was determined by a similar assay technique, based on ligand displacement of ³H-CGS 21680, a known A₂ receptor-specific adenosine agonist, from receptor, using membranes from rat brain striatum. Non-specific binding was assessed in the presence of 20 μM 2-chloroadenosine.

The assays were run in glass test tubes in duplicate at 25°C. Once the membranes were added, the tubes were vortexed and incubated at 25°C for 60 minutes (A₁ assay) or 90 minutes (A₂ assay) on a rotary shaker. The assay tubes were vortexed halfway through the incubation and again near the end. The assays were terminated by rapid filtration through 2.4 cm GF/B filters using a Brandel Cell Harvester. The test tubes were washed three times with cold 50 mM tris-HCl (pH 7.7 or 7.4), with filtration being completed within 15 seconds. The damp filter circles were placed in glass scintillation vials filled with 10 mL of Aquasol II (New England Nuclear). The vials were allowed to shake overnight on a rotary shaker and were placed into a liquid scintillation analyzer for two minute counts. IC₅₀ values for receptor binding, i.e. the concentration at which a compound of the invention displaced the radiolabeled standard, were obtained using a curve-fitting computer program (RS/1, Bolt, Beranek and Newman, Boston, MA).

A₁ Receptor Binding Affinity was determined also using a preparation of rat epididymal fat pad membranes.

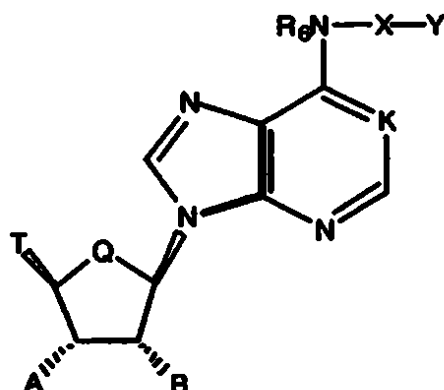
Membrane Preparation: Rat epididymal fat pads are homogenized in buffer containing 0.25 M Sucrose, 10 mM Tris, 2 mM EDTA, 0.1 M phenylmethylsulfonylfluoride, and 1 μ g/mL Leupeptin (200 mg wet tissue weight/mL buffer). This homogenate is placed into 50 mL centrifuge tubes and centrifuged at 1000 g (3000 RPM) for 1 minute, the intermediate supernatant is removed and centrifuged at 38,000 g for 15 minutes. The pellets are resuspended pellets in assay buffer (50 mM Tris and 1 mM EDTA) (300 mg original tissue weight/mL assay buffer), and 2 μ l/ ml of a solution of adenosine deaminase (10 mg/ml) is added to the suspension and the suspension incubated for 30 minutes at 37°C. The suspension is centrifuged at 38,000 g for 10 minutes, the pellet washed once with 20 ml assay buffer, the resuspended in assay buffer (1.2 g original wet tissue weight / mL buffer).

Assay and Counting: Tubes are prepared as follows: Totals (total counts bound) tubes, 100 μ L membrane suspension (prepared as described above), 50 μ L ^{3} H-cyclohexyladenosine solution (prepared by diluting a solution of approximately 1 mCi/mL, with a specific activity of approximately 29.9 Ci/mmol, with assay buffer to 100nM, hereinafter "CHA solution"), 350 μ L assay buffer; Non-specific binding tubes, 100 μ L membrane suspension, 50 μ L CHA solution, 50 μ L 100 μ M 2-chloroadenosine in assay buffer, 300 μ L assay buffer; Sample tubes, 100 μ L membrane suspension, 50 μ L CHA solution, 50 μ L of a solution of the compound to be tested (which may be prepared from serial dilution in assay buffer of a DMSO solution), 300 μ L assay buffer; Blank tubes, 50 μ L CHA solution, 450 μ L assay buffer. Each tube is vortexed for 10 seconds, incubated at 23°C for two hours, and filtered using a Brandel Filtration Unit, using Whatman GF/B Filter Paper, washing twice with 5 mL 50mM Tris. The filter discs are placed in 7 mL scintillation vials, which are then filled with approximately 5 mL Ready Safe Scintillation Cocktail, and counted.

WHAT IS CLAIMED IS:

1. Use of a compound of the formula

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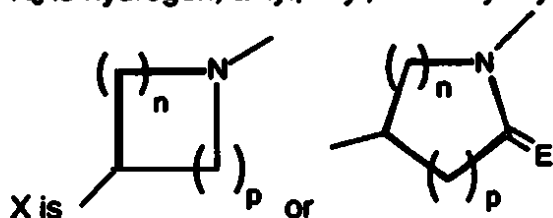
wherein:

K is N, N→O, or CH;

10

Q is CH₂ or O;

R₆ is hydrogen, alkyl, allyl, 2-methylallyl, 2-butenyl, or cycloalkyl;



X is

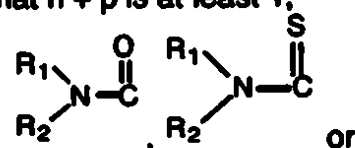
where the nitrogen of the ring of X is substituted by Y;

15

E is O or S;

Y is hydrogen, alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, or substituted heterocyclylalkyl;

n and p are independently 0, 1, 2, or 3, provided that n + p is at least 1;



20

R₃O-CH₂;

R₁, R₂, and R₃ are independently H, alkyl, or cycloalkyl;

A is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or OR';

B is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or OR'';

R' and R'' are independently hydrogen, alkyl, aralkyl, carbamoyl, alkyl carbamoyl,

25 dialkylcarbamoyl, acyl, alkoxy carbonyl, aralkoxy carbonyl, aryloxy carbonyl, or, when A and B are OR' and OR'', respectively,

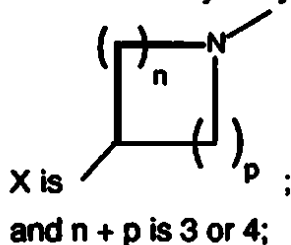
R' and R'' together may form



- 5 where R_d and R_e are independently hydrogen, alkyl, or together with the carbon atom to which they are attached may form a 1,1-cycloalkyl group;

10 or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof for producing a medicine for the treatment of the insulin resistance syndrome and diabetes.

2. The use of a compound according to claim 1 wherein K is N;
T is hydroxymethyl or methoxymethyl;
15 A and B are hydroxy;



20 or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

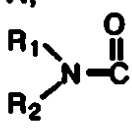
3. The use of a compound according to claim 1 or 2 which is (2R,3R,4S,5R)- 5-hydroxymethyl- 2-[6-[1-(5-chloropyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-
25 tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(R)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(4-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R) 5-
30 hydroxymethyl -2-[6-[1-(5-bromopyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl -2-(6-(1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino) -purin-9-yl) tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']-bipyridinyl-3-ylamino)-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(phenylpyrrolidin-3(S)-ylamino)-purin-9-

y]]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(1-pyridin-2-ylpyrrolidin-3(S)-ylamino)-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-methylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-thiophen-2-ylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-methylmercaptopyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-methoxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)piperidin-4-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3S)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol dihydrochloride, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(R)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3R)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(pyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(quinolin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluoropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(phenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-purin-6-ylamino]pyrrolidin-1-yl]benzonitrile, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(isoquinolin-1-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol,

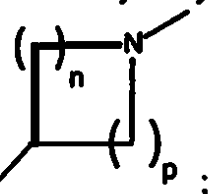
(1R,2S,3R,5R)-3-[6-[1-(3-chloro-5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-trifluoromethylphenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylphenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-phenylpyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, and (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol; or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

4. The use of a compound according to claims 1 to 3 wherein Q is CH₂;

K is N;

T is , wherein R₁ is H and R₂ is lower alkyl;

A and B are hydroxy;

X is  ;

and n + p is 3 or 4;

or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

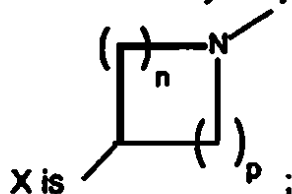
5. The use of a compound according to claim 4 which is (1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentanecarboxylic acid ethylamide, (1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(5-trifluoromethyl-pyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-cyclopentanecarboxylic acid-1(S)-methylpropylamide, and (1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(5-trifluoromethyl-pyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-cyclopentanecarboxylic acid-1(R)-methylpropylamide; or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

6. The use of a compound according to claim 1 wherein Q is CH₂;

K is N;

T is hydroxymethyl or methoxymethyl;

A and B are hydroxy;



and $n + p$ is 3 or 4;

or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

7. The use of a compound according to claim 6 which is (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)piperidin-4-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3S)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol dihydrochloride, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(R)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3R)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(pyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-

24
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hydroxymethyl-3-[6-[1-(quinolin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluoropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol,
5 (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(phenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-purin-6-ylamino]pyrrolidin-1-yl]benzonitrile, (1R,2S,3R,5R)-5-hydroxymethyl-5-[6-[1-(isoquinolin-1-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chloro-5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol,
15 (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-trifluoromethylphenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol,
25 (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylphenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-phenylpyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol,
35 (1R,2S,3R,5R)-3-[6-[1-benzylpyrrolidin-3(S)-ylamino]purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, and (1R,2S,3R,5R)-3-[6-[1-benzylpyrrolidin-3(S)-ylamino]purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol; or a pharmaceutically

acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

8. The use of a compound according to claim 6 which is (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

9. The use of a compound according to claim 6 which is (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/05301

27
38**A. CLASSIFICATION OF SUBJECT MATTER**
IPC 7 A61K31/52 A61P3/10

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 A61K

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 24451 A (GLAXO GROUP LTD ; ELDRED COLIN DAVID (GB); PENNELL ANDREW MICHAEL K) 20 May 1999 (1999-05-20)	1,2
Y	claims 1,23 page 31, line 19-21 page 3, line 17-20 page 7, line 24-26 page 8, line 34 * See compound RN= 223756-98-7, page 35, line 19-20 *	1-9
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☒ Further documents are listed in the continuation of box C.☒ 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

5 September 2002

Date of mailing of the international search report

23/09/2002

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Authorized officer

Veronese, A

INTERNATIONAL SEARCH REPORT

International Application No.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 01426 A (CHOI SLEDESKI YONG MI ; PAULS HENRY W (US); EWING WILLIAM R (US); M) 15 January 1998 (1998-01-15) page 60, line 30-36 claims; examples ---	1-9
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T	WO 01 40244 A (BELARDINELLI LUIZ ;CV THERAPEUTICS INC (US); PALLE VENKATA P (US);) 7 June 2001 (2001-06-07) page 3, paragraphs * See page 5, diabetic disorders * -----	1

37
39

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/05301

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:

- ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
- ☒ 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:
see FURTHER INFORMATION sheet PCT/ISA/210
- ☐ 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:

- ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
- ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
- ☐ 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.:
- ☐ 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.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

The expression "prodrug" in claims 1-9 relates to an extremely large number of possible compounds/products/apparatus/methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds defined by the Markush formula in claim 1, with particular regard to the compounds specifically indicated in claims 3,5,7-9.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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National Application No

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412

**(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL
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(19) Organización Mundial de la Propiedad Intelectual
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21 Noviembre 2002 (21.11.2002)

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(74) Agente: ISENDRUCK, Günter; Patent-und Rechtsanwälte, Bardehle Pagenberg Dost, Altenburg geissler Isenbruck Tjeodor-Heuss-Anlage 12, 68165 Mannheim (DE).

(81) Estados Designados (nacional): 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, UZ, VN, YU, ZA, ZM, ZW

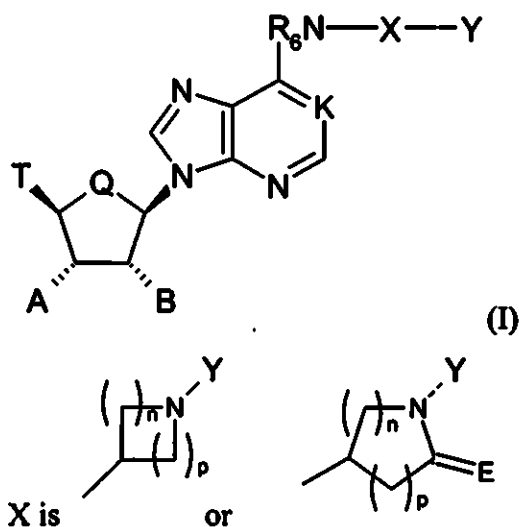
(84) Estados Designados (regional): ARIPO patente (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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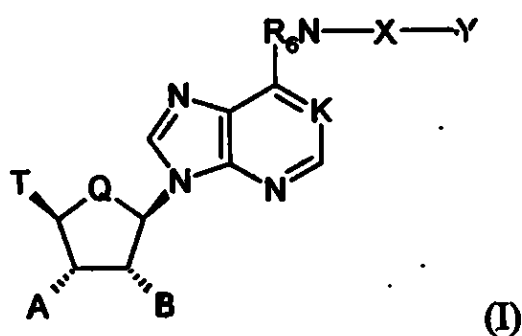
(54) Título: ANÁLOGOS DE ADENOSINA PARA EL TRATAMIENTO DEL SÍNDROME DE RESISTENCIA A LA INSULINA Y DIABETES



(57) Extracto: La invención se relaciona con el uso de compuestos de adenosina descritos por la fórmula I y algunos derivados de ellos para producir una medicina para el tratamiento del síndrome de resistencia a la insulina y diabetes. En la fórmula I K es N, N→ O, o CH; Q es CH₂ o O; R₆ es hidrógeno, alquil, alil, 2-metallil, 2-butenil, o cicloalquil; X es (a) o (b); E es O ó S; Y es por ejemplo, hidrógeno, alquil, aralquil, aril; n y p son independientemente 0, 1, 2, o 3, teniendo en cuenta que n + p es por lo menos 1; T es por ejemplo hidrógeno, alquil, acil, tioacil, halo, carboxil; R₁, R₂ y R₃ son independientemente H, alquil, o cicloalquil; A es hidrógeno, alquil, hidroxialquil, alcoxialquil, o OR'; B es hidrógeno, alquil, hidroxialquil, alcoxialquil, o OR"; R' y R" son por ejemplo independientemente hidrógeno, alquil, aralquil o carbamoil.

El uso de adenosina y análogos para producir medicinas para el tratamiento del síndrome de resistencia a la insulina y diabetes

Esta invención se relaciona con el uso de compuestos derivados de adenosina y sus análogos de acuerdo con la fórmula general (I) como agentes con resistencia a la insulina.



- 10 La adenosina tiene una amplia variedad de acciones fisiológica y farmacológica que incluyen una marcada alteración de la función cardiovascular y renal. En animales y el hombre, la inyección intravenosa del nucleótido de adenosina causa hipotensión.
- 15 Las acciones fisiológica y farmacológica de adenosina son mediadas a través de receptores específicos localizados sobre las superficies de células. Cuatro subtipos receptores de adenosina, designados como receptores A_1 , A_{2A} , A_{2B} , y A_3 , han sido identificados. El receptor A_1 inhibe la formación de cAMP suprimiendo la actividad de ciclazo
- 20 adenilata, mientras que el estímulo de receptores A_2 incrementa la actividad de ciclazo adenilata y cAMP intracelular. Cada receptor parece mediar acciones específicas de adenosina en diferentes tejidos: por ejemplo, las acciones vasculares de adenosina parecen estar mediadas a través del estímulo de receptores A_2 , lo cual está soportado por la
- 25 correlación positiva entre la generación cAMP y vaso dilatación en el músculo blando vascular aislado tratado con adenosina; mientras que el

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estímulo de los receptores A₁ cardiacos reduce la generación cAMP en el corazón lo cual contribuye con los efectos cardiacos negativos dromotrópico, inotrópico y cronotrópico. Consecuentemente, a diferencia de la mayoría de vasodilatadores, la administración de adenosina no produce una taquicardia refleja.

La adenosina también ejerce una marcada influencia sobre la función renal. La infusión intrarenal de adenosina causa una caída transiente en el flujo de sangre renal y un incremento en la resistencia vascular renal. Con continuada infusión de adenosina, el flujo de sangre renal retorna a niveles de control y la resistencia vascular renal se reduce. Las respuestas vasoconstrictoras renales iniciales a adenosina no se deben a directas acciones vasoconstrictoras de los nucleótidos, sino que involucran una interacción entre adenosina y el sistema renin-angiotensin.

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La adenosina se considera ampliamente como el mediador fisiológico primario de hiperemia reactiva y auto regulación del lecho coronario en respuesta a isquemia miocárdica. Se ha reportado que el endotelio coronario posee receptores A₂ adenosina enlazados a ciclazo adenilata, que son activados en paralelo con incrementos en flujo coronario y que los receptores cardiomiocitos son predominantemente del subtipo de A₁ adenosina y asociados con bradicardia. De acuerdo con lo anterior, la adenosina ofrece un mecanismo único de terapia isquémica.

25 Las respuestas cardiovasculares a la adenosina son de corta vida debido a la toma rápida y al metabolismo del nucleótido endógeno. En contraste, los análogos de adenosina son más resistentes a la degradación metabólica y son reportados para extraer las alteraciones sostenidas en la presión arterial y el ritmo cardiaco.

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Los compuestos de adenosina de acuerdo con la formula general (I) útiles como agentes anti-hipertensivos, cardio-protectores, anti-isquémicos y anti-lipolíticos se conocen de EP A 0 912 520.

5 Varios análogos potentes metabólicamente estables de adenosina han sido sintetizados los cuales demuestran grados variables de selectividad para los dos subtipos receptores. Los agonistas de adenosina tienen generalmente mayor selectividad para receptores A₁ en comparación con los receptores A₂. Ciclopentiladenosina (CPA) y R-fenilisopropil-
10 adenosina (R-PIA) son agonistas estándares de adenosina que muestran marcada selectividad para el receptor A₁ (relación A₂/A₁ = 780 y 106, respectivamente). En contraste, N-5'-etil-carboxamido adenosina (NECA) es un potente agonista receptor A₂ (K_i-12 nM) pero tiene afinidad igual para el receptor A₁ (K_i-6.3 nM; relación A₂/A₁ = 1.87). Hasta
15 recientemente, CV-1808 fue el agonista más selectivo A₂ disponible (A₂/A₁ = 0.19), aún si el compuesto fue 10 veces menos potente que NECA en su afinidad para el receptor A₂. En recientes desarrollos, compuestos más nuevos se han divulgado que son agonistas A₂ muy potentes y selectivos (K_i = 3-8 nM para A₁; relación A₂/A₁ = 0.027-
20 0.042) (C.E. Müller y T. Scior, *Pharmaceutica Acta Hevetiae* 68 (1993) 77-111).

Varias adenosinas sustituidas N6-aril y N6-heteroarilalquil, y adenosinas sustituidas-(2-amino y 2-hidroxi), se han reportado en la literatura que
25 poseen variada actividad farmacológica, incluyendo actividad cardiaca y circulatoria. Ver, por ejemplo, la Especificación de Patente Británica 1,123,245, Especificación Alemana 2,136,624, Especificación Alemana 2,059,922, Patente U. S. No. 4,501,735, Publicación EP No. 0139358 (que divulga N6-[geminal diaril sustituidas alquil]adenosinas), EP-A-0 305
30 643 (que divulga que los derivados de adenosina N6-heterocíclicos-

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sustituidos exhiben actividad vaso dilatante cardiaca), Especificación Alemana 2,131,938 (que divulga derivados de adenosina aril y heteroaril alquil hidrazinil), Especificación Alemana 2,151,013 (que divulga adenosinas sustituidas 6-aril y heteroaril) y Especificación Alemana 2,205,002 (que divulga adenosinas con N6-sustituyentes que comprenden estructuras de anillo en puente que enlazan el nitrógeno N6 a sustituyentes que incluyen tienil).

La Patente U. S. No. 4,954,504 y Publicación EP No. 0267878 divulgan genéricamente que los análogos de ribosa carbocíclicos de adenosina, y sus ésteres farmacéuticamente aceptables, sustituidos en las posiciones 2-y/o N6- por grupos aril inferior alquil que incluyen tienil, tetrahidropiranyl, tetrahidrotiopiranyl, y derivados benzo bicíclicos de alquil inferior heterocíclicos saturados fundidos de 5- o 6- miembros exhiben propiedades agonistas de receptor de adenosina. Los análogos de adenosina que tienen sustituyentes tipo tienil se describen en la Publicación EP No. 0277917 (que divulgan adenosinas sustituidas N6-sustituido-2-heteroarilalquilamina que incluyen 2-[(2-[tien-2-il]etil) amino] adenosina sustituida), Especificación Alemana 2,139,107 (que divulga N6-[benzotienilmetil]-adenosina), PCT WO 85/04882 (que divulga que los derivados de adenosina N6-heterocíclico-alquil-sustituidos, incluyendo N6-[2-(2-tienil)etil]amino-9-(D-ribofuranosil)-9H-purina, exhiben actividad cardiovascular vaso dilatante y que los sustituyentes N6-quirales exhiben mejorada actividad), Solicitud Publicada EP No. 0232813 (que divulga que las adenosinas N6-(1-sustituidas tienil)ciclopropilmetil exhiben actividad cardiovascular), la Patente U. S. No. 4,683,223 (que divulga que las adenosinas sustituidas N6-benzotiopiranyl exhiben propiedades antihipertensivas), PCT WO 88/03147 y WO 88/03148 (que divulgan que las adenosinas sustituidas N6-[2-aril-2-(tien-2-il)]etil exhiben propiedades antihipertensivas), las Patentes U. S. Nos. 4,636,493 y 4,600,707 (que

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divulgan que las adenosinas sustituidas N6-benzotieniletil exhiben propiedades antihipertensivas).

Se divulgan amidas adenosina-5'-ácido carboxílico que tienen utilidad
5 como agentes anti-hipertensivos y anti-anginas en la Patente U. S. No. 3,914,415, mientras que la Patente U. S. No. 4,738,954 divulga que las carboxamidas N6-sustituidas aril y arilalquil-adenosina 5'-etil exhiben varias propiedades cardiacas y antihipertensivas.

10 N⁶-alquil-2'-O-alquil adenosinas se divulgan en la Publicación EP No. 0,378,518 y Solicitud de Patente UK No. 2,226,027 que tienen actividad antihipertensiva. Adenosinas N⁶-alquil-2',3'-di-O-alquil también se reportan con utilidad como agentes antihipertensivos, Patente U. S. 4,843,066.

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Las adenosina-5'-(N-sustituidas) carboxamidas y ésteres de carboxilato y sus N1-óxidos se reportan como los vaso dilatadores coronarios, Stein, y otros, *J. Med. Chem.* 1980, 23, 313-319 y *J. Med. Chem.* 19 (10), 1180 (1976). Las adenosina-5'-carboxamidas y sus N1-óxidos también se
20 reportan como venenos de pequeños animales en la Patente U. S. No. 4,167,565.

Las N6-sustituidas adenosinas y análogos, útiles en el tratamiento de los desordenes de movilidad gastrointestinal, han sido reportadas en las
25 Solicitudes EP Publicadas Nos. 0423776, y 0423777.

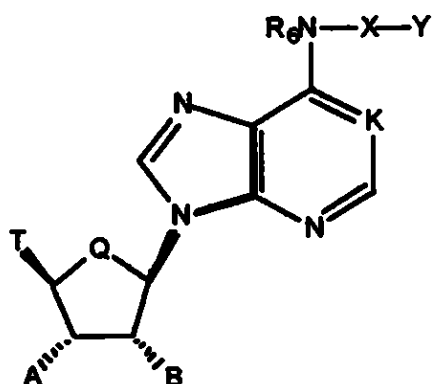
Los compuestos N6-heterociclicil-alquil derivados de adenosina y sus análogos, y su uso en el tratamiento de la hipertensión e isquemia miocardial, su uso como agentes protectores cardiacos que mejoran el
30 daño isquémico o el tamaño del infarto miocardial consecuente con la

isquemia miocardial, su uso como agentes antilipolíticos que reducen los niveles de lípidos en plasma, niveles de triglicéridos en suero, y niveles de colesterol en plasma, se divulgan en EP-A 0 758 897. los compuestos N6-heterociclil derivados de adenosina y sus análogos, y su uso en el
5 tratamiento de la isquemia miocardial e hipertensión, también se divulgan en la Patente U. S. No. 5,364,862, presentada en Octubre 2, 1992.

Se considera que la toxicidad reportada, las propiedades CNS y la elevación del ritmo cardiaco asociada con los análogos de adenosina han
10 contribuido a las dificultades que previenen el desarrollo de un agente antihipertensivo/antiisquémico análogo de adenosina. La presente invención se relaciona con una clase de análogos de adenosina estables metabólicamente, y sus derivados, que poseen propiedades farmacológicas inesperadamente deseables, es decir, son agentes antilipolíticos que tienen
15 un único perfil terapéutico.

Sorpresivamente se ha encontrado que los compuestos de adenosinum que estimulan el receptor de adenosina A₁ en adipositos pueden inhibir la lipólisis periférica de triglicéridos almacenados y así puede causar una
20 caída inmediata en los ácidos grasos libres en plasma. Este efecto antilipolítico causa un establecimiento inmediato de mejora de la sensibilidad a la insulina en mamíferos resistentes a la insulina, incluyendo el hombre. Consecuentemente los agonistas de adenosina son útiles como terapéuticos para tratar el síndrome de resistencia a la insulina así como en
25 diabéticos resistentes a la insulina.

La invención se relaciona con el uso de compuestos de adenosinum descritos por la Formula I



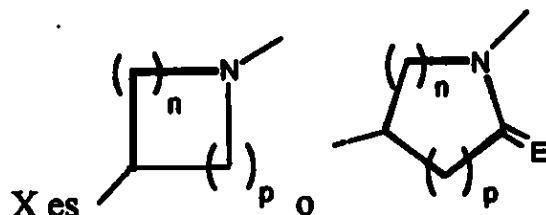
Formula I

donde:

K es N, N→O, o CH;

5 Q es CH₂ ó O;

R₆ es hidrógeno, alquil, alil, 2-metilalil, 2-butenil, o cicloalquil;



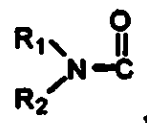
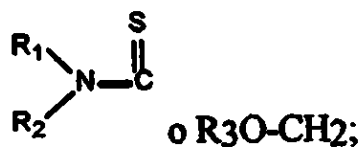
donde el nitrógeno del anillo de X es sustituido por Y;

10 E es O ó S;

Y es hidrógeno, alquil, aralquil, aralquil sustituido, aril, aril sustituido, heterociclil, heterociclil sustituido, heterociclilalquil, o heterociclilalquil sustituido;

15 n y p son independientemente 0, 1, 2, o 3, teniendo en cuenta que n + p es por lo menos 1;

T es hidrógeno, alquil, acil, tioacil, halo, carboxil,

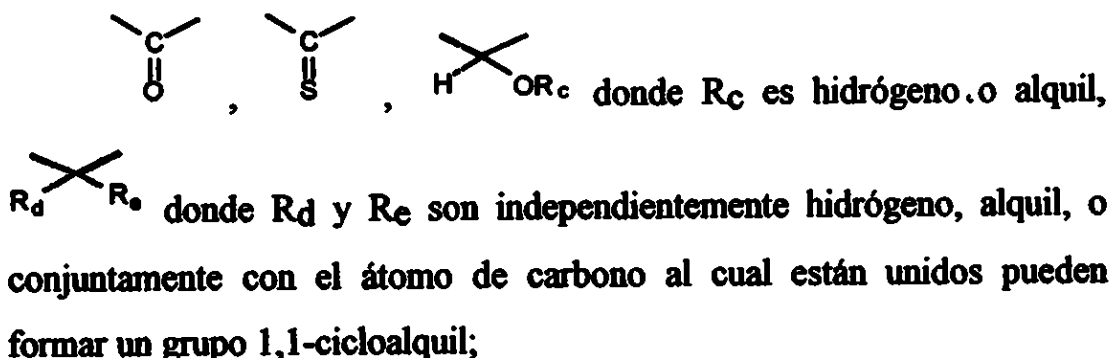


R₁, R₂, y R₃ son independientemente H, alquil, o cicloalquil;

A es hidrógeno, alquil, hidroxialquil, alcoxialquil, o OR';

B es hidrógeno, alquil, hidroxialquil, alcoxialquil, o OR";

R' y R" son independientemente hidrógeno, alquil, aralquil, carbamoil, alquil carbamoil, dialquilcarbamoil, acil, alcoxicarbonil, aralcoxicarbonil, ariloxycarbonil, o, cuando A y B son OR' y OR",
5 respectivamente, R' y R" conjuntamente pueden formar



o su sal farmacéuticamente aceptable, su pro-droga farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de ellos o un solvato de ellos para producir una medicina para el tratamiento del
 15 síndrome de resistencia a la insulina y diabetes.

Como se usa arriba y a todo el través de la descripción de la invención, los siguientes términos, a menos que se indique de otra forma, debe entenderse que tienen los siguientes significados:

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"Acil" significa un grupo recto o ramificado alquil-C=O. "Tioacil" significa un grupo recto o ramificado alquil-C=S. Grupos preferidos acil y tioacil son alcanoil inferior y tioalcanoil inferior que tienen desde 1 hasta alrededor de 6 átomos de carbono en el grupo alquil.

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"Alquil" significa un grupo hidrocarburo alifático saturado que puede ser recto o ramificado y que tiene alrededor de 1 hasta alrededor de 20 átomos de carbono en la cadena. Grupos alquil preferidos pueden ser

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rectos o ramificados y tener alrededor de 1 hasta alrededor de 10 átomos de carbono en la cadena. Ramificado significa que un grupo alquil inferior tal como metil, etil o propil está unido a una cadena alquil lineal.

- 5 "Alquil inferior" significa un grupo alquil que tiene 1 a alrededor de 6 carbonos.

"Cicloalquil" significa un anillo alifático que tiene 3 hasta alrededor de 10 átomos de carbono en el anillo. Grupos cicloalquil preferidos tienen 4 hasta alrededor de 7 átomos de carbono en el anillo.

"Carbamoil" significa un grupo $\text{H}_2\text{N}-\overset{\text{O}}{\parallel}{\text{C}}$. Alquilcarbamoil y dialquilcarbamoil significa que el nitrógeno del carbamoil es sustituido por uno o dos grupos alquil, respectivamente.

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"Carboxil" significa un grupo COOH .

"Alcoxi" significa un grupo alquil-O donde "alquil" es como se describió previamente. Se prefieren los grupos alcoxi inferior. Grupos de ejemplo incluyen metoxi, etoxi, n-propoxi, i-propoxi y n-butoxi.

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"Alcoxialquil" significa un grupo alquil, como se describió previamente, sustituido por un grupo alcoxi, como se describió previamente.

25 "Alcoxycarbonil" significa un grupo alcoxycarbonil C=O .

"Aralquil" significa un grupo alquil sustituido por un radical aril, donde "aril" significa un fenil o naftil. "Aralquil sustituido" y "aril sustituido" significa que el grupo aril, o el grupo aril del grupo aralquil es sustituido

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con uno o más sustituyentes que incluyen alquil, alcoxi, amino, nitro, carboxi, carboalcoxi, ciano, alquil amino, halo, hidroxil, hidroxialquil, mercaptil, alquilmercaptil, trihaloalquil, carboxialquil o carbamoil.

5 "Aralcoxicarbonil" significa un grupo aralquil-O-C=O.

"Arioxycarbonil" significa un grupo aril-O-C=O.

10 "Carbalcoxi" significa un sustituyente carboxil esterificado con un alcohol de la fórmula $C_nH_{2n+1}OH$, donde n es desde 1 hasta alrededor de 6.

"Halógeno" (o "halo") significa cloro, flúor, bromo o iodo.

15 "Heterociclil" significa una estructura de anillo de 4 hasta alrededor de 10 miembros donde uno o más de los átomos en el anillo es un elemento diferente a carbono, es decir, N, O ó S. Heterociclil puede ser aromático o no-aromático, es decir puede ser saturado, parcial o completamente no saturado.

20 Grupos heterociclil preferidos incluyen grupos piridil, piridazinil, pirimidinil, isoquinolinil, quinolinil, quinazolinil, imidazolil, pirrolil, furanil, tienil, tiazolil, benzotiazolil, piperidinil, pirrolidinil, tetrahidrofuranil, tetrahidropiranil, y morfonilil.

25 "Heterociclil sustituido" significa que el grupo heterociclil es sustituido por uno o más sustituyentes donde los sustituyentes incluyen alcoxi, alquilamina, aril, carbalcoxi, carbamoil, ciano, halo, heterociclil, trihalometil, hidroxil, mercaptil, alquilmercaptil o nitro.

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"Hidroxialquil" significa un grupo alquil sustituido por un grupo hidroxil. Se prefieren los grupos hidroxil alquil inferior. Grupos de ejemplo preferidos incluyen hidroximetil, 2-hidroxietil, 2-hidroxipropil y 3-hidroxipropil.

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"Prodroga" significa un compuesto que es transformado rápidamente *in vivo* para lograr el compuesto péptido padre, por ejemplo por hidrólisis en sangre. "Prodroga farmacéuticamente aceptable" significa un compuesto que es, dentro del alcance del juicio médico sonoro, adecuado para uso farmacéutico en un paciente sin indebida toxicidad, irritación, respuesta alérgica, y similar, y efectivo para el uso pretendido, incluyendo un éster farmacéuticamente aceptable así como una forma zwitteriónica, donde sea posible, de los compuestos péptidos de la invención. Las pro-drogas farmacéuticamente aceptables de acuerdo con la invención se describen en

10 T. Higuchi y V. Stella, Pro-drogas como Novedosos Sistemas de Suministro, Vol. 14 de la Serie del Simposio A.C.S., y en Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association y Pergamon Press, 1987, los cuales se incorporan ambos aquí a modo de referencia.

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"Solvato" significa una asociación física de un compuesto de esta invención con una o más moléculas de solvente. Esta asociación física involucra grados variables de enlace iónico y covalente, incluyendo enlace de hidrógeno. En algunas instancias el solvato será capaz de aislamiento,

25 por ejemplo cuando una o más moléculas de solvente se incorporan en la estructura de cristal del sólido cristalino. "Solvato" comprende solvatos tanto en fase de solución como aislado. Los solvatos representativos incluyen etanolatos, metanolatos, y similares. "Hidrato" es un solvato donde la(las) molécula(s) de solvente es/son H₂O.

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Los compuestos de Fórmula I contienen centros quirales (asimétricos). La invención incluye los estéreo-isómeros individuales y sus mezclas. Los isómeros individuales se preparan o aíslan por métodos bien conocidos en el arte aquí descritos.

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Los compuestos descritos aquí pueden usarse en la forma de la base libre, en la forma de sales de adición de ácido o como hidratos. Todas estas formas están dentro del alcance de la invención. Las sales de adición de ácido son simplemente una forma más conveniente para uso. En la práctica, el uso de la forma de sal aumenta inherentemente el uso de la forma de base. Los ácidos que pueden usarse para preparar las sales de adición de ácido incluyen preferiblemente aquellos que producen, cuando se combinan con la base libre, sales farmacéuticamente aceptables, es decir, sales cuyos aniones no son tóxicos para el recipiente en dosis farmacéuticas de las sales, en forma tal que los efectos benéficos anti-hipertensivos, protector cardíaco, anti-isquémico, y antilipolítico producidos por la base libre no son viciados por los efectos laterales atribuibles a los aniones. Aunque se prefieren las sales farmacéuticamente aceptables de los compuestos de la invención, todas las sales de adición de ácido son útiles como fuentes de la forma de base libre, aún si la sal particular, per se, se desea únicamente como un producto intermediario como, por ejemplo, cuando la sal se forma únicamente con propósito de purificación e identificación, o cuando se usa como un intermediario en la preparación de una sal farmacéuticamente aceptable mediante procedimientos de intercambio de iones. Las sales farmacéuticamente aceptables dentro del alcance de la invención son aquellas derivadas de los siguientes ácidos: ácidos minerales tales como ácido clorhídrico, ácido sulfúrico, ácido fosfórico, y ácido sulfámico; y ácidos orgánicos tales como ácido acético, ácido cítrico, ácido láctico, ácido tartárico, ácido malónico, ácido metanosulfónico, ácido fumárico, ácido etanosulfónico,

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ácido bencenosulfónico, ácido, p-toluenosulfónico, ácido ciclohexilsulfámico, ácido quínico, y similares. Las correspondientes sales de adición de ácido comprenden lo siguiente: hidrocloruro, sulfato, fosfato, sulfamato, acetato, citrato, lactato, tartarato, metanosulfonato, fumarato, etanosulfonato, bencenosulfonato, p-toluenosulfonato, ciclohexil-sulfonato y quinato, respectivamente.

Las sales de adición de ácido de los compuestos de la invención se preparan convenientemente ya sea disolviendo la base libre en solución acuosa o acuosa-alcohol u otros solventes adecuados que contienen el ácido apropiado y aislando la sal evaporando la solución, o reaccionando la base libre y el ácido en un solvente orgánico, en cuyo caso la sal se separa directamente o puede obtenerse por concentración de la solución.

Incluidas dentro del alcance de la Fórmula I están clases de compuestos que pueden caracterizarse generalmente como N6-adenosinas-sustituidas; N6-adenosinas carbocíclicas sustituidas (o, alternativamente, dihidroxi[N6-sustituidos-9-adenil]ciclopentanos) y sus N-óxidos; y N6-sustituidas-N'-1-deazaristeromicinas (o, alternativamente, dihidroxi[N7-sustituidos[4,5-b]imidazopiridil]-ciclopentanos). También dentro del alcance de la Fórmula I están los derivados 5'-alquilcarboxamida de las adenosinas, las adenosinas carbocíclicas y las 1-deazaristeromicinas, los derivados de compuestos de las anteriores clases donde uno o ambos de los grupos 2- o 3- hidroxil del anillo ciclopentano o, en los casos de clases de compuestos que contienen la fracción ribosa, los grupos 2'- o 3'- hidroxil del anillo de ribosa están sustituidos. Dichos derivados pueden ellos mismos comprender la identidad química biológicamente activa útil en el tratamiento de la hipertensión y la isquemia miocárdial, y como agentes protectores cardíacos y antilipolíticos, o pueden actuar como pro-

drogas para dichos compuestos biológicamente activos que se forman a partir de ello bajo condiciones fisiológicas.

Compuestos representativos para uso incluyen:

- 5 (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-cloropiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-pirrolidin-3(R)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-
10 pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(4-trifluorometilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-bromopiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
15 (2R,3R,4S,5R)-5-hidroximetil-2-(6-(1-(4-nitrofenil)-pirrolidin-3(S)-ilamina)-purin-9-il)tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-(5'-trifluorometil-3,4,5,6-tetrahidro-2H-[1,2']-bipiridinil-3-ilamina)-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-(fenilpirrolidin-3(S)-ilamina)-purin-9-
20 il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-(1-piridin-2-ilpirrolidin-3(S)-ilamina)-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(4-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
25 (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-metilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-tiofen-2-ilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-metilmercaptopiridin-2-il)-
30 pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,

- (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-metoxipirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
- (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
- 5 (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
- (2R,3R,4S,5R)-5-metoximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol, (1S,2R,3S,4R)-2,3-dihidroxi-4-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3-ilamina]-purin-9-il]ciclopentano ácido carboxílico etilamida,
- 10 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)piperidin-4-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- (1R,2S,3R,5R)-5-hidroximetil-3-[6-((3S)-pirrolidin-3-ilamina)-purin-9-il]ciclopentano-1,2-diol dihidrocloruro,
- 15 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)pirrolidin-3-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(R)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- (1R,2S,3R,5R)-5-hidroximetil-3-[6-((3R)-pirrolidin-3-ilamina)-purin-9-il]ciclopentano-1,2-diol,
- 20 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- 4(R)-1-bencil-4-[9-((1R,2S,3R,5R)-1,2-dihidroxi-5-hidroximetilciclopent-3-il)-9H-purin-6-ilamina]pirrolidin-2-ona hidrocloruro,
- 25 (1R,2S,3R,5S)-5-metil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- (1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-3-[6-[1-(5-cloropiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
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- (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(piridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- 5 4(S)-1-bencil-4-[9-((1R,2S,3R,5R)-1,2-dihidroxi-5-hidroximetilciclopent-3-il)-9H-purin-6-ilamina]pirrolidin-2-ona hidrocioruro,
- (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(quinolin-3-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- 10 (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluorpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- 15 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(fenil)-pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihidroxi-5-hidroximetilciclopent-3-il)-9H-purin-6-ilamina]pirrolidin-1-il]benzonitrilo,
- (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(isoquinolin-1-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- 20 (1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
- 25 (1R,2S,3R,5R)-3-[6-[1-(3-cloro-5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol, (1R,2S,3R,5R)-5-isopropoximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- (1R,2S,3R,5R)-5-isopropoximetil-3-[6-[1-(4-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- 30

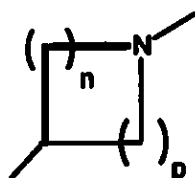
- (1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
- 5 (1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-metoximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(6-metoxipirimidin-4-il)pirrolidin-
10 3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- (1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-metoximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-3-([6-[1-(4-trifluorometilfenil)-pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
- 15 (1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-metoximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-3-[6-[1-(5-clorpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-
il]-5-metoximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(4-trifluorometilfenil)pirrolidin-
20 3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- (1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-
5-metoximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-
5-metoximetilciclopentano-1,2-diol,
- 25 (1R,2S,3R,5R)-3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-
5-hidroximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-fenilpirrolidin-3-(S)-ilamina]-purin-
9-il]ciclopentano-1,2-diol,
- (1R,2S,3R,5R)-3-[6-(1-bencil-pirrolidin-3(S)-ilamina)purin-9-il]-5-
30 hidroximetilciclopentano-1,2-diol,

(1R,2S,3R,5R)-3-[6-(1-bencil-pirrolidin-3(S)-ilamina)purin-9-il]-5-metoximetilciclopentano-1,2-diol,

(1S,2R,3S,4R)-2,3-dihidroxi-4-{6-[1-(5-trifluorometil-piridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il}-ciclopentano-ácido carboxílico-1(S)-metilpropilamida, y

(1S,2R,3S,4R)-2,3-dihidroxi-4-{6-[1-(5-trifluorometil-piridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il}-ciclopentano-ácido carboxílico-1(R)-metilpropilamida.

- 10 Una clase preferida de compuestos para uso se describe por la Fórmula I donde K es N, T es hidroximetil o metoximetil, A y B son hidroxi, X es



, y $n + p$ es 3 o 4, o sus sales farmacéuticamente aceptables.

Compuestos representativos de esta clase preferida de compuestos incluyen (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-cloropiridin-2-il)-

- 15 pirrolidin-3(S)-ilamina]-purin-9-il]-tetrahydrofuran-3,4-diol,

(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-pirrolidin-3(R)-ilamina]-purin-9-il]tetrahydrofuran-3,4-diol,

(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahydrofuran-3,4-diol,

- 20 (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(4-trifluorometilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahydrofuran-3,4-diol,

(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-bromopiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]-tetrahydrofuran-3,4-diol,

- 25 (2R,3R,4S,5R)-5-hidroximetil-2-(6-(1-(4-nitrofenil)-pirrolidin-3(S)-ilamina)-purin-9-il)tetrahydrofuran-3,4-diol,

(2R,3R,4S,5R)-5-hidroximetil-2-[6-(5'-trifluorometil-3,4,5,6-tetrahydro-2H-[1,2']-bipiridinil-3-ilamina)-purin-9-il]tetrahydrofuran-3,4-diol,

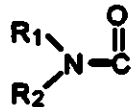
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- (2R,3R,4S,5R)-5-hidroximetil-2-[6-(fenilpirrolidin-3(S)-ilamina)-purin-9-il]tetrahidrofuran-3,4-diol,
- (2R,3R,4S,5R)-5-hidroximetil-2-[6-(1-piridin-2-ilpirrolidin-3(S)-ilamina)-purin-9-il]tetrahidrofuran-3,4-diol,
- 5 (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(4-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
- (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-metilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
- (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-thiopen-2-ilpiridin-2-il)-
- 10 pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
- (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-metilmercaptopiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
- (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-metoxipirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
- 15 (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
- (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
- (2R,3R,4S,5R)-5-metoximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-
- 20 pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
- (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)piperidin-4-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- (1R,2S,3R,5R)-5-hidroximetil-3-[6-((3S)-pirrolidin-3-ilamina)-purin-9-il]ciclopentano-1,2-diol dihidrocloruro,
- 25 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)pirrolidin-3-ilamina]-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(R)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- (1R,2S,3R,5R)-5-hidroximetil-3-[6-((3R)-pirrolidin-3-ilamina)-purin-9-il]
- 30 ciclopentano-1,2-diol,

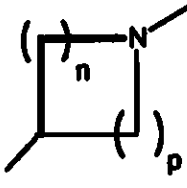
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- (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
 5 (1R,2S,3R,5R)-3-[6-[1-(5-cloropiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(piridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 10 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(quinolin-3-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 15 (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluorpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(fenil)-pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 20 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(isoquinolin-1-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihidroxi-5-hidroximetilciclopent-3-il)-9H-purin-6-ilamina]pirrolidin-1-il]benzonitrilo,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(6-bromoquinolin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
 25 (1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(3-cloro-5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,
 30

- (1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
5 (1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(6-metoxipirimidin-4-il)pirrolidin-
10 3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-(-[6-[1-(4-trifluorometilfenil)-pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
15 (1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(5-clorpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-
il]-5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(4-trifluorometilfenil)pirrolidin-
20 3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-
5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(3-clorofenil) -pirrolidin-3(S)-ilamina]-purin-9-il]-
5-metoximetilciclopentano-1,2-diol,
25 (1R,2S,3R,5R)-3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-
5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-fenilpirrolidin-3-(S)-ilamina]-purin-
9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-(1-bencil-pirrolidin-3(S)-ilamina)purin-9-il]-5-
30 hidroximetilciclopentano-1,2-diol, y

(1R,2S,3R,5R)-3-[6-(1-bencil-pirrolidin-3(S)-ilamina)purin-9-il]-5-metoximetilciclopentano-1,2-diol.

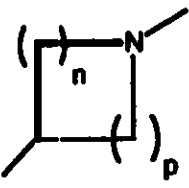
Otra clase preferida de compuestos para uso se describe por la Fórmula I

5 donde Q es CH₂, K es N, T es , donde R₁ es H y R₂ es alquil inferior, A y B son hidroxí,

X es , y n + p es 3 o 4, o sus sales farmacéuticamente aceptables. Compuestos representativos de esta otra clase preferida de compuestos incluyen,

- 10 (1S,2R,3S,4R)-2,3-dihidroxi-4-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3-ilamina]-purin-9-il]ciclopentano ácido carboxílico etilamida,
(1S,2R,3S,4R)-2,3-dihidroxi-4-{6-[1-(5-trifluorometil-piridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il}-ciclopentano ácido carboxílico-1(S)-metilpropilamida, y
15 (1S,2R,3S,4R)-2,3-dihidroxi-4-{6-[1-(5-trifluorometil-piridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il}-ciclopentano ácido carboxílico-1(R)-metilpropilamida.

Una clase más preferida de compuestos para uso se describe por la
20 Fórmula I donde Q es CH₂, K es N, T es hidroximetil o metoximetil, A y

B son hidroxí, X es , y n + p es 3 o 4, o sus sales farmacéuticamente aceptables. Compuestos representativos de esta clase más preferida de compuestos incluyen

- (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)piperidin-4-ilamina]-
purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-((3S)-pirrolidin-3-ilamina)-purin-9-il]
ciclopentano-1,2-diol dihidrocloruro,
5 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)pirrolidin-3-ilamina]-
purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-
il)pirrolidin-3(R)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-((3R)-pirrolidin-3-ilamina)-purin-9-il]
10 ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-
il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
15 (1R,2S,3R,5R)-3-[6-[1-(5-cloropiridin-2-il)pirrolidin-3(S)-ilamina]-purin-
9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-trifluorometilpiridin-2-
il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(piridin-2-il)pirrolidin-3(S)-
20 ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(quinolin-3-il)pirrolidin-3(S)-
ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)-pirrolidin-3(S)-
ilamina]-purin-9-il]ciclopentano-1,2-diol,
25 (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluorpiridin-2-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(5-trifluorometilpiridin-2-
il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(fenil)-pirrolidin-3(S)-ilamina]-
30 purin-9-il]ciclopentano-1,2-diol,

- 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihidroxi-5-hidroxi metilciclopent-3-il)-9H-purin-6-ilamina]pirrolidin-1-il]benzonitrilo,
(1R,2S,3R,5R)-5-hidroxi metil-5-[6-[1-(isoquinolin-1-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
5 (1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroxi metilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroxi metilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(3-cloro-5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoxi metilciclopentano-1,2-diol,
10 (1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroxi metilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroxi metilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoxi metilciclopentano-1,2-diol,
15 (1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroxi metilciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-metoxi metil-3-[6-[1-(6-metoxipirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
20 (1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoxi metilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(4-trifluorometilfenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroxi metilciclopentano-1,2-diol,
25 (1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoxi metilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(5-clorpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoxi metilciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-metoxi metil-3-[6-[1-(4-trifluorometilfenil)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
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- (1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,
5 (1R,2S,3R,5R)-3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-fenilpirrolidin-3-(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-(1-bencil-pirrolidin-3(S)-ilamina)purin-9-il]-5-
10 hidroximetilciclopentano-1,2-diol, y
(1R,2S,3R,5R)-3-[6-(1-bencil-pirrolidin-3(S)-ilamina)purin-9-il]-5-metoximetilciclopentano-1,2-diol.

- Compuestos más preferidos aún para uso en la presente invención
15 incluyen (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]cicloentano-1,2-diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-
20 1,2-diol y (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(4-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol.

- La cantidad de un compuesto de fórmula (I) que es necesaria para lograr el deseado efecto biológico depende de un número de factores, por ejemplo
25 el compuesto específico escogido, el uso pretendido, el modo de administración y la condición clínica del paciente. En general, la dosis diaria está en el rango de desde 0,3 mg a 100 mg (típicamente desde 3 mg hasta 50 mg) por día y por kilogramo de peso corporal, por ejemplo 3-10 mg/kg/día. Una dosis intravenosa puede estar, por ejemplo, en el rango de
30 desde 0,3 mg a 1,0 mg/kg, la cual puede administrarse más

adecuadamente como infusión de desde 10 ng a 100 ng por kilogramo y por minuto. Adecuadas soluciones de infusión para estos propósitos pueden contener, por ejemplo, desde 0,1 ng a 10 mg, típicamente desde 1 ng a 10 mg, por mililitro. Las dosis unitarias pueden contener, por ejemplo, desde 1 mg a 10 g de ingrediente activo. Es consecuentemente posible para ampollas para inyecciones que contengan, por ejemplo, desde 1 mg a 100 mg, y las formulaciones de una sola dosis que pueden administrarse oralmente, tal como, por ejemplo, tabletas o cápsulas, para contener, por ejemplo, desde 1,0 a 1 000 mg, típicamente desde 10 a 600 mg. En el caso de sales farmacéuticamente aceptables, los datos de peso anteriormente mencionados están basados en el peso de la sal del compuesto de fórmula (I). Para la profilaxis o terapia de las condiciones anteriormente mencionadas, los compuestos de fórmula (I) pueden usarse como el compuesto mismo, pero están preferiblemente en forma de una composición farmacéutica con un portador aceptable. El portador debe, por supuesto, ser aceptable en el sentido en que sea compatible con los otros ingredientes de la composición y no sea peligroso para la salud de los pacientes. El portador puede ser un sólido o un líquido o ambos y se formula preferiblemente con el compuesto como una sola dosis, por ejemplo como tableta que puede contener desde 0,05% a 95% en peso del ingrediente activo. Adicionales sustancias farmacéuticamente activas pueden similarmente estar presentes, incluyendo otros compuestos de fórmula (I). Las composiciones farmacéuticas de acuerdo con la invención pueden producirse mediante uno de los métodos farmacéuticos conocidos que consisten esencialmente en mezclar los ingredientes con portadores y/o excipientes farmacológicamente aceptables.

Las composiciones farmacéuticas de acuerdo con la invención son aquellas adecuadas para administración oral, rectal, tópica, peroral (por ejemplo sublingual) y parenteral (por ejemplo subcutánea, intramuscular,

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intradérmica o intravenosa) aunque el modo de administración más adecuado en cada caso individual depende de la naturaleza y severidad de la condición a ser tratada y de la naturaleza del compuesto de fórmula (I) usado en cada caso. Las formulaciones recubiertas y las formulaciones recubiertas de lenta liberación también se encuentran dentro del alcance de la invención. Las formulaciones resistentes al ácido y al fluido gástrico se prefieren. Adecuados recubrimientos resistentes al fluido gástrico comprenden ftalato acetato de celulosa, acetato de polivinilo, ftalato hidroxipropilmetilcelulosa y polímeros aniónicos de ácido metacrílico y metil metacrilato.

Adecuados compuestos farmacéuticos para administración oral pueden estar en forma de unidades separadas tales como, por ejemplo, cápsulas, bolsitas, tabletas remojables o tabletas, cada una de las cuales contiene una cantidad definida del compuesto de fórmula (I); como polvos o gránulos; como solución o suspensión en un líquido acuoso o no acuoso; o como una emulsión de aceite en agua o agua en aceite. Estas composiciones pueden, como se mencionó anteriormente, prepararse mediante cualquier método farmacéuticamente adecuado que incluye un paso donde el ingrediente activo y el portador (el cual puede consistir de uno o más ingredientes adicionales) se llevan en contacto. En general, las composiciones se producen mediante mezcla uniforme y homogénea del ingrediente activo con un líquido y/o portador sólido finamente dividido, después de lo cual el producto es conformado si es necesario. Así, por ejemplo, una tableta puede producirse comprimiendo o moldeando un polvo o gránulos del compuesto, donde sea apropiado con uno o más ingredientes adicionales. Las tabletas comprimidas pueden producirse tableteando el compuesto en forma de flujo libre, tal como, por ejemplo, un polvo o gránulos, donde sea apropiado mezclado con un enlazante, lubricante, diluyente inerte y/o un (pluralidad de) agente(s) activo(s) de

superficie/dispersante(s) en una máquina adecuada. Tabletas moldeadas pueden producirse moldeando el compuesto que está en forma de polvo y es humedecido con un diluyente líquido inerte en una máquina adecuada.

- 5 Las composiciones farmacéuticas adecuadas para administración peroral (sublingual) comprenden tabletas remojables que contienen un compuesto de fórmula (I) con un saborizante, normalmente sacarosa y goma arábica o tragacanto, y pastillas que comprenden el compuesto en una base inerte tal como gelatina y glicerol o sacarosa y goma arábica.

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- Adecuadas composiciones farmacéuticas para administración parenteral comprenden preferiblemente preparaciones acuosas estériles de un compuesto de fórmula (I), que son preferiblemente isotónicas con la sangre del recipiente pretendido. Estas preparaciones se administran
- 15 preferiblemente en forma intravenosa, aunque la administración puede también tener lugar mediante inyección subcutánea, intramuscular o intradérmica. Estas preparaciones pueden producirse preferiblemente mezclando el compuesto con agua y haciendo la solución resultante estéril e isotónica con la sangre. Las composiciones inyectables de acuerdo con
- 20 la invención generalmente contienen desde 0,1 a 5% en peso del compuesto activo.

- Adecuadas composiciones farmacéuticas para administración rectal están preferiblemente en forma de supositorios de una sola dosis. Estos pueden
- 25 producirse mezclando un compuesto de fórmula (I) con uno o más portadores sólidos convencionales, por ejemplo mantequilla de cacao, y conformando la mezcla resultante.

- Adecuadas composiciones farmacéuticas para aplicación tópica a la piel
- 30 están preferiblemente en forma de ungüento, crema, loción, pasta,

atomizado, aerosol o aceite. Portadores que pueden usarse son el petrolato, lanolina, polietilenglicoles, alcoholes y combinaciones de dos o más de estas sustancias. El ingrediente activo está generalmente presente en una concentración de desde 0,1 a 15% en peso de la composición, por ejemplo desde 0,5 a 2%.

La administración transdérmica también es posible. Adecuadas composiciones farmacéuticas para usos transdérmicos pueden estar en forma de emplastos solos que son adecuados para contacto cerrado a largo término con la epidermis del paciente, dichos emplastos contienen adecuadamente el ingrediente activo en una solución acuosa opcionalmente amortiguada, disuelta y/o dispersa en un adhesivo o dispersa en un polímero. Una adecuada concentración de ingrediente activo es de alrededor de 1% a 35%, preferiblemente alrededor de 3% a 15%. Como una posibilidad especial, el ingrediente activo puede liberarse como se describió, por ejemplo, en Investigación Farmacéutica, 2(6): 318 (1986) mediante electrotransporte o iontoforesis.

Las siguientes preparaciones sirven para ilustrar la invención sin restringirla, sin embargo.

Ejemplo A

Cápsulas de gelatina blanda que contienen 100 mg de ingrediente activo por cápsula:

	por cápsula
Ingrediente activo	100 mg
Mezcla de triglicéridos fraccionada de grasa de coco	400 mg
Contenido de cápsula	500 mg

Ejemplo B

Emulsión que contiene 60 mg de ingrediente activo por 5 ml:

	por emulsión
	100 ml
5 Ingrediente activo	1,2 g
Aceite neutro	cantidad suficiente
Carboximetilcelulosa de sodio	0,6 g
Estearato de polioxietileno	cantidad suficiente
Glicerol, puro	0,2 a 2,0 g
10 Saborizante	cantidad suficiente
Agua (desionizada o destilada)	ad 100 ml

Ejemplo C

Forma farmacéutica rectal que contiene 40 mg de ingrediente activo por

15 supositorio:	por supositorio
Ingrediente activo	40 mg
Base de supositorio	ad 2 g

20 **Ejemplo D**

Tabletas que contienen 40 mg de ingrediente activo por tableta:

	por tableta
	600 mg
25 Lactosa	300 mg
Almidón de maíz	20 mg
Almidón soluble	40 mg
Estearato de magnesio	
	1 000 mg

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Ejemplo E

Tabletas recubiertas que contienen 50 mg de ingrediente activo por tableta recubierta:

	por tableta recubierta
5 Ingrediente activo	50 mg
Almidón de maíz	100 mg
Lactosa	60 mg
Sec. Fosfato de calcio	30 mg
Almidón soluble	5 mg
10 Estearato de magnesio	10 mg
Sílice coloidal	5 mg
	260 mg

15 Ejemplo F

Las siguientes formulas son adecuadas para producir el contenido de cápsulas de gelatina dura:

a)	Ingrediente activo	100 mg
	Almidón de maíz	<u>300 mg</u>
20		400 mg
b)	Ingrediente activo	140 mg
	Lactosa	180 mg
	Almidón de maíz	<u>180 mg</u>
		500 mg

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Ejemplo G

Se pueden producir gotas de acuerdo con la siguiente formula (100 mg de ingrediente activo en 1 ml = 20 gotas):

	Ingrediente activo	10 g
30	Benzoato de metil	0,07 g

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Benzoato de etil	0,03 g
Etanol 96% puro	5 ml
Agua desmineralizada	ad 100 ml

- 5 Los compuestos de esta invención pueden prepararse mediante métodos conocidos o de acuerdo con las secuencia de reacción descritas en EP- A 0 912 520.

Después de síntesis, los compuestos de la invención se purifican típicamente mediante cromatografía de líquido de presión media (MPLC),
 10 en un cromatógrafo, cromatografía de capa delgada radialmente acelerada, cromatografía de destello o cromatografía de columna a través de una matriz de gel de sílice o Florisil, seguida por cristalización. Para compuestos de Fórmula I donde K es N, Q es O y T es R_3O-CH_2 , típicos
 15 sistemas solventes incluyen cloroformo: metanol, acetato de etilo: hexano, y cloruro de metileno: metanol. Los levigados pueden cristalizarse a partir de metanol, etanol, acetato de etilo, hexano o cloroformo, etc.

Para compuestos de Fórmula I, donde K es N, Q es O, y T es
 20 $R_1R_2N-C=O$, típicos sistemas solventes incluyen cloroformo: metanol. Por ejemplo, los levigados pueden cristalizarse a partir de 50-100% etanol (acuoso).

Para compuestos de Fórmula I, donde Q es CH_2 , K es N o CH, y T es
 25 $R_1R_2N-C=O$, típicos sistemas solventes incluyen cloruro de metileno: metanol. Por ejemplo, los levigados pueden cristalizarse a partir de acetato de etilo con o sin metanol, etanol o hexano.

Los compuestos que requieren neutralización pueden neutralizarse con una
 30 base suave tal como bicarbonato de sodio, seguido por lavado con cloruro

de metileno y salmuera. Los productos que son purificados como aceites se trituran algunas veces con hexano/etanol antes de cristalización final.

El método de la presente invención se ilustra adicionalmente y se explica
5 mediante los siguientes Ejemplos.

EJEMPLO 1

Preparación de 5'-N-Etil-2',3'-isopropilideno-N⁶-cloroadenosina-5'-uronamida

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Paso 1: N⁶-Cloro-2',3'-isopropilideneadenosina

6-Cloropurina ribosida (31,5 g), trietilortoformato (73 mL) y TsOH (19,8 g) se agitan en 600 mL acetona durante 2 horas a temperatura ambiente. La mezcla de la reacción se concentra in vacuo, se combina con acetato de etilo y se lava con solución saturada de NaHCO₃, y salmuera, se seca
15 (Na₂SO₄) y concentra para lograr N⁶-Cloro-2',3'-isopropilidenoadenosina como un sólido blanco.

Paso 2: N⁶-Cloro-2',3'-Isopropilidenoadenosina-5'-ácido carboxílico

20 N⁶-Cloro-2',3'-isopropilideneadenosina (4,5 g, 13,8 mmol) y 4-hidroxi-2,2,6,6-tetrametilpiperidiniloxi benzoato (4-hidroxi-TEMPO benzoato) (0,0381 g, 0,14 mmol) se combinan en acetonitrilo, 5% NaHCO₃ (87%) se agrega a la mezcla de la reacción e hidrato de bromita de sodio (10,41 g, 55,1 mmol) se agrega en porciones a 0-5 °C. La mezcla de la reacción
25 se deja tibia entonces a temperatura ambiente, y la solución se agitó vigorosamente durante alrededor de 3 horas. 10 % de solución de ácido tartárico se agregó y la capa acuosa se separó y extrajo con acetato de etilo (3x). Las capas orgánicas combinadas se lavaron con 5% de solución de bicarbonato de sodio (3x). Las capas básicas se combinaron y
30 volvieron a acidificar a pH 3 con ácido clorhídrico concentrado. Las capas

34

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acuosas se extrajeron con acetato de etilo (3x). Las capas orgánicas combinadas se lavaron entonces con salmuera y se secaron sobre sulfato de magnesio. El filtrado es concentrado a un sólido blanco amorfo, co-evaporado con 3 porciones de tolueno y se secaron in vacuo para dar N⁶-cloro-2',3'-isopropilidenoadenosina-5'-ácido carboxílico.

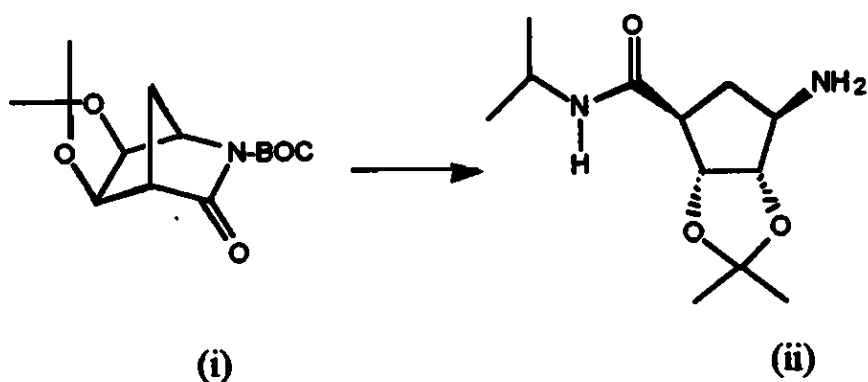
Paso 3: 5'-N-Etil-2',3'-isopropilideno-N⁶-cloroadenosina-5'-uronamida

N⁶-cloro-2',3'-isopropilidenoadenosina-5'-ácido carboxílico (4,4 g, 12,9 mmol), trietilamina (1,64 mL, 11,7 mmol) isopropenil cloroformato (1,28 mL, 11,7 mmol), y cloruro de metileno (50 mL) se combinaron bajo argón a -10 °C y se agitó durante alrededor de 2 minutos. Etilamina (0,77 mL, 11,7 mmol) se agregó a la mezcla de la reacción y continuó la agitación durante 1 minuto adicional. La mezcla de la reacción se partió entre cloruro de metileno y bicarbonato de sodio saturado. Las capas acuosas se lavaron con cloruro de metileno (3X). Las capas orgánicas combinadas se lavaron con salmuera y se secaron sobre sulfato de sodio, se filtraron, evaporaron in vacuo y el residuo se purificó mediante cromatografía de destello sobre gel de sílice, se levigó con 3% MeOH/CHCl₃, para dar 5'-N-etil-2',3'-isopropilideno-N⁶-cloroadenosina-5'-uronamida, ¹H NMR (300 MHz, (CDCl₃) d 8,75 (s, 1H), 8,23 (s, 1H), 6,20 (d, 1H), 5,50 (dd, 2H), 4,73 (d, 1H), 3,01 (m, 2H), 1,63 (s, 1H), 1,41 (s, 3H), 0,77 (t, 3H).

EJEMPLO 2

Preparación de (1S,2R,3S,4R)-2,3-dihidroxi-4-[6-[1-(4-trifluormetil-piridin-2-il)pirrolidin-3(S)-ilamina]purin-9-il]ciclopentanoácido carboxílico isopropilamida

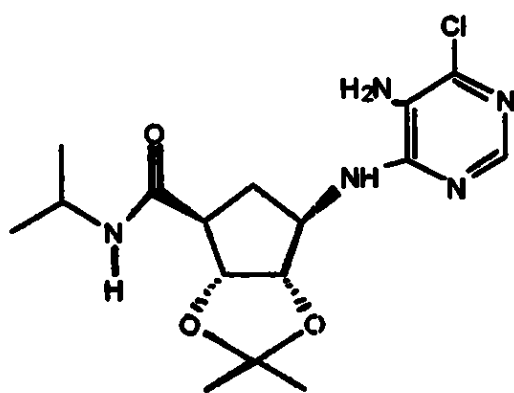
Paso (1)



15,5 g (54,6 mmol) N-BOC-5,6-Dimethylenedioxi-2-azabicyclo[2.2.1]heptan-3-ona (i) (preparado como en el Paso (6) del Ejemplo 3, abajo) se disolvió en 16 mL isopropil amina y la mezcla se agitó a temperatura ambiente durante alrededor de 2 horas. La mezcla se evaporó in vacuo, y el residuo azeotropó con cloroformo para dar un sólido blanco. Este sólido se disolvió en 250 mL de acetato de etilo, la solución se enfrió a 0°C, y gas de cloruro de hidrógeno se burbujeó dentro de la solución, con enfriamiento durante alrededor de 15 minutos. La solución se agitó entonces a temperatura ambiente durante alrededor de 4 horas. La solución se evaporó in vacuo, y azeotropó con metanol, luego cloroformo, para dar el producto amina como la sal de hidrocloreuro. La sal de hidrocloreuro se partió entre cloroformo y solución de bicarbonato de sodio, y la capa orgánica se lavó con salmuera, se secó, se filtró y un equivalente de ácido benzoico se agregó. El solvente se removió in vacuo y el residuo se trituró en éter para dar la amina deseada (ii) ilustrado arriba como la sal de benzoato, punto de fusión 183-184°C.

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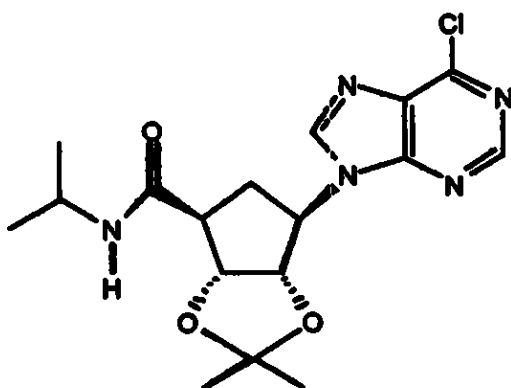
Paso (2) Preparación de



(iii)

54 mmol del producto (ii) del Ejemplo 2 Paso (1) de arriba se disuelve en 110 mL n-butanol y 9,7g 5-amino-4,6-dicloropirimidina, entonces 23 mL trietilamina se agregaron y la mezcla se calentó a reflujo durante alrededor de 18 horas. La mezcla se enfrió, diluyó con cloroformo y solución saturada de cloruro de amonio. La capa acuosa se extrajo tres veces con cloroformo, entonces dos veces con 10% isopropil alcohol/cloroformo. Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio, se filtraron, se concentraron a un aceite (iii) el cual se usó, sin adicional tratamiento para el siguiente paso.

Paso (3) Preparación de



(iv)

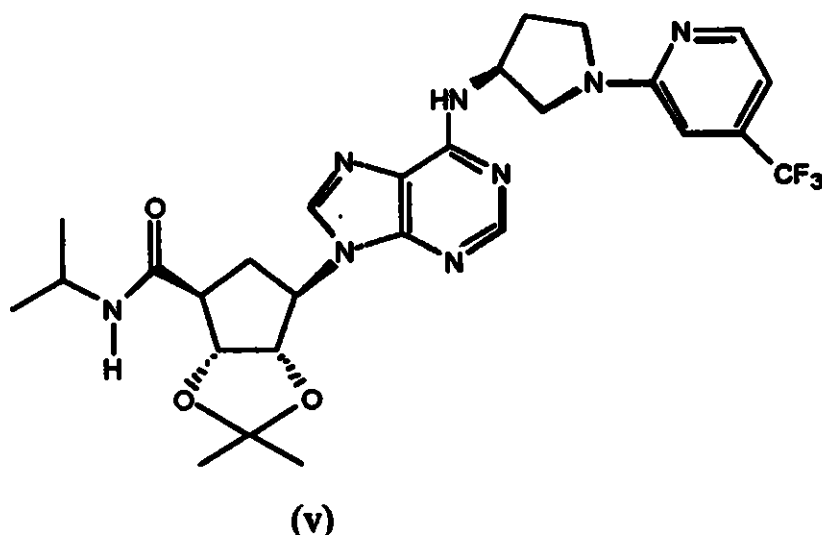
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El producto (iii) del Ejemplo 2 Paso (2) de arriba se desarrolló en 150 mL n-butil acetato y 11,2 g acetato formamidina se agregó. La mezcla se calentó a reflujo bajo argón durante alrededor de 9 horas, agregando tres porciones de 5,56 g de acetato formamidina a dos, cuatro, y seis

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horas. La mezcla se enfrió, diluyó con acetato de etilo, se lavó con salmuera, agua, salmuera, se secó sobre sulfato de sodio, se filtró, se concentró in vacuo, y el residuo se purificó mediante cromatografía de destello, levigando con 40-80 % de acetato de etilo en hexano, para dar el
5 deseado producto de cloropurina (iv) ilustrado arriba.

Paso (4) Preparación de



10 400 mg (1,05 mmol) del producto (iv) del Ejemplo 2 Paso (3) de arriba, 0,22 mL (1,57 mmol) trietilamina, y 270 mg (1,16 mmol) 2-[(3S)-3-aminopirrolidin-1-il]-4-trifluorometilpiridina (preparado como en el Ejemplo 3, Pasos 1 a 5, arriba) se disolvió conjuntamente en 3 mL de etanol, y la solución se calentó a reflujo, bajo argón, durante alrededor de
15 20 horas. La mezcla se evaporó in vacuo y el residuo se partió entre cloroformo y solución saturada de bicarbonato de sodio. La capa acuosa se extrajo con 4 porciones de cloroformo y el orgánico combinado se secó sobre sulfato de sodio, se filtró, se evaporó in vacuo. El residuo se purificó mediante cromatografía de destello, aplicando la muestra en cloruro de metileno/acetato de etilo (1:1), y levigando con 0 a 3% de metanol en acetato de etilo, para dar el producto (v) arriba ilustrado.
20

Paso (5) El producto del Ejemplo 2 Paso (4) de arriba se disolvió en 2 mL metanol/tetrahidrofuran (1:1), y 3,3 mL 1,5 N de ácido clorhídrico

acuoso se agregó, y la solución se agitó a temperatura ambiente durante alrededor de 20 horas. La mezcla se evaporó in vacuo. Este residuo resultante se desarrolló en 10 mL 15% isopropil alcohol/cloroformo, 1 mL de solución 1 N de hidróxido de sodio, y 9 mL de solución de bicarbonato de sodio saturado. Las capas se separaron y el acuosos se extrajo con 4 x 5 mL porciones de 15% isopropil alcohol/cloroformo. La capa orgánica combinada se secó sobre sulfato de sodio, se filtró, se evaporó in vacuo para dar (1S,2R,3S,4R)-2,3-dihidroxi-4-[6-[1-(4-trifluormetilpiridin-2-il)pirrolidin-3(S)-ilamina]purin-9-il]ciclopentano-ácido carboxílico isopropilamida, punto de fusión 227-228°C.

EJEMPLO 3

Preparación de (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol

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Paso (1) 20g (232 mmol) de (3S)-(-)-3 aminopirrolidina y 26 mL (255 mmol, 1,1 eq) benzaldehído se combinaron en 250 mL tolueno y se sometió a reflujo, retirando agua con una trampa Dean-Stark, durante alrededor de 4,5 horas. La mezcla se enfrió a 0°C y 55,7g (255,2 mmol, 1,1 eq) di-tert-butil dicarbonato se agregó, luego se agitó a temperatura ambiente. La mezcla se concentró in vacuo, se agitó con solución de KHSO₄, se extrajo 3 veces con éter. La capa acuosa se hizo alcalina y se extrajo con CH₂Cl₂. La capa orgánica se lavó con salmuera y se secó sobre MgSO₄, se filtró, y evaporó in vacuo para dar N1-BOC-(3S)-(-)-3 aminopirrolidina.

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Paso (2) 34,25 g (183,9 mmol) del producto del Ejemplo 3 Paso (1) de arriba se disolvió en 200 mL CH₂Cl₂ y 25 mL (183,9 mmol, 1 eq) de trietilamina se agregó. Bajo una atmósfera de nitrógeno, 34,7 mL (367,8 mmol, 2 eq) de anhídrido acético se agregó gota a gota, la mezcla se agitó

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a temperatura ambiente, se partió con solución de $\text{NaHCO}_3/\text{CH}_2\text{Cl}_2$. La capa orgánica se lavó con salmuera, se secó sobre MgSO_4 , se filtró, se evaporó *in vacuo*, y el producto se purificó mediante cromatografía de destello, levigando con 2-8% de metanol en metileno, para dar N1-BOC-

5 (3S)-(-)-3-acetilaminapirrolidina.

Paso (3) 39,2 g (171,7 mmol) del producto del Ejemplo 3 Paso (2) de arriba se disolvió en 400 mL CH_2Cl_2 y 26,46 mL (343,4 mmol 2 eq) de ácido trifluoroacético (de aquí en adelante "TFA") se goteó a 0°C bajo una

10 atmósfera de nitrógeno. La mezcla se calentó a reflujo, agregando otros 26 mL, entonces otros 10 mL de TFA, se sometió a reflujo durante alrededor de 3 horas adicionales, luego se evaporó bajo alto vacío para retirar TFA. El residuo se agitó con Amberlite IRA-400 resina básica (de aquí en adelante "resina básica"), se filtró, el filtrado se disolvió en metanol, se

15 filtró lentamente a través de resina básica, y el filtrado se evaporó para dar (3S)-(-)-3-acetilaminapirrolidina.

Paso (4) 4g (31.2 mmol) del producto del Ejemplo 3 Paso (3) de arriba y 5,19 (40,6 mmol) 2-cloro-5-trifluorometilpiridina se combinó en

20 50 mL de etanol y 13 mL (93,6 mmol, 3 eq) de trietilamina se agregó. La mezcla se sometió a reflujo durante alrededor de 18 horas, se concentró in vacuo y el residuo se partió entre cloruro de metileno y solución de bicarbonato de sodio. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró, se evaporó in vacuo, y el residuo se

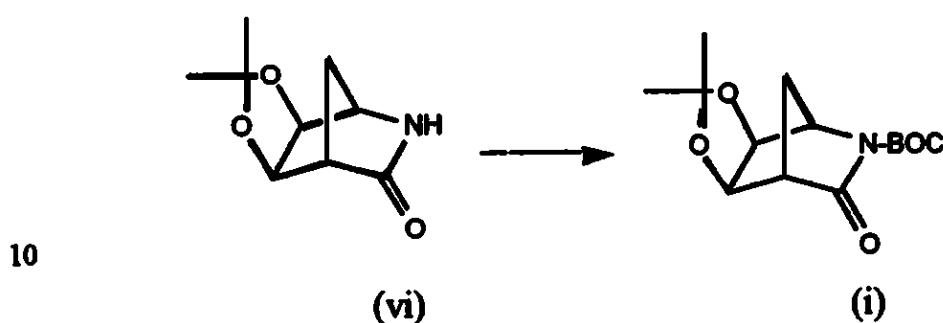
25 purificó mediante cromatografía de destello, levigando con 2-5% de metanol en cloruro de metileno, para dar 2-[(3S)-3-acetilaminapirrolidin-1-il]-5-trifluorometilpiridina, como un sólido.

Paso (5) 7,52 g (27,5 mmol) del producto del Ejemplo 3 Paso (4) de

30 arriba se combinó con 75 mL 6N de ácido de hidrocioruro acuoso y la

mezcla se sometió a reflujo durante alrededor de 18 horas. La mezcla se enfrió a temperatura ambiente, se neutralizó con bicarbonato de sodio sólido, se partió entre solución diluida de hidróxido de sodio y cloruro de metileno. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró, se evaporó in vacuo para dar 2-[(3S)-3-aminopirrolidin-1-il]-5-trifluorometilpiridina.

Paso (6)

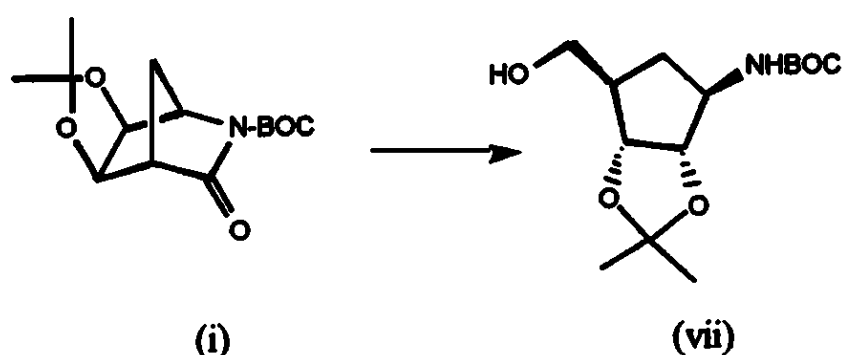


22.5 g (0.123 mol) (-)-5,6-Dimetilenodioxi-2-azabicyclo[2.2.1]heptan-3-ona (vi), 1,5 g 4-dimetilaminapiridina (de aquí en adelante "DMAP"), 12,4 g trietilamina, y 37,5 g di-tert-butil dicarbonato se combinaron en cloruro de metileno y se agitó a temperatura ambiente durante alrededor de 18 horas. La mezcla se lavó con 1N de ácido clorhídrico, 5% de solución de bicarbonato de sodio, salmuera, se secó sobre sulfato de sodio, se filtró, se concentró in vacuo y el residuo se recristalizó a partir de alcohol isopropil para dar N-BOC-5,6-Dimetilenodioxi-2-azabicyclo[2.2.1]heptan-3-ona (i).

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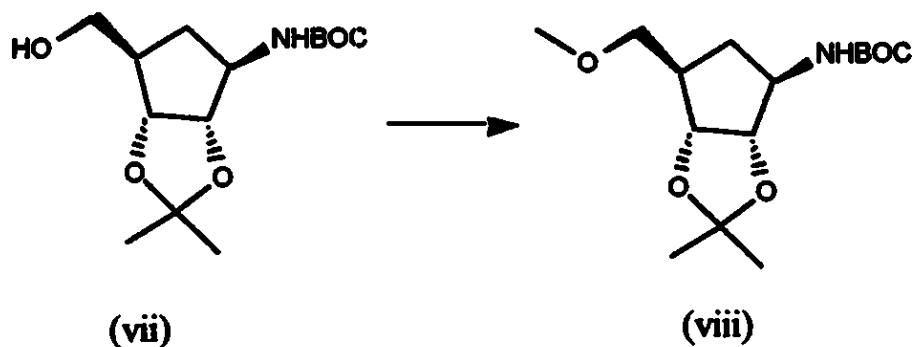
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Paso (7)



35,6g (0,125 mol) del producto (i) del Ejemplo 3 Paso (6) de arriba se combinó con 400 mL de metanol con rápida agitación y enfriamiento, bajo purga de argón, un total de 23,8g (0,63 mol) de boro hidrido de sodio se agregó en tres porciones iguales durante un periodo de alrededor de 2 horas. La mezcla se concentró in vacuo y partió entre 200 mL de agua y 300 mL de acetato de etilo. La capa acuosa se extrajo dos veces más con acetato de etilo y la solución orgánica combinada se lavó con agua, salmuera, se secó sobre sulfato de sodio, se filtró, se concentró in vacuo para dar N-BOC-1-amino-2,3-dimetilenodioxi-4-hidroximetilciclopentano (vii).

Paso (8)

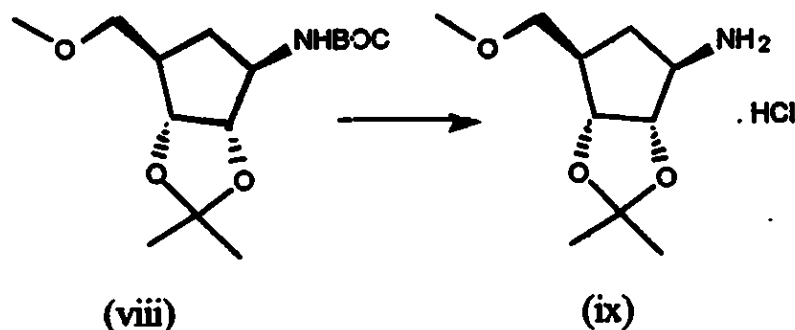


50 g del producto (vii) del Ejemplo 3 Paso (7) de arriba se colocó en 150 mL de benceno. 8,8 ml de ioduro de metil y 33 g de óxido de plata se agregó y la mezcla se sometió a reflujo durante alrededor de 18 horas. Otros 25 g de óxido de plata y otros 50 mL de ioduro de metil se agregaron en porciones durante alrededor de 6 horas y la mezcla se sometió a reflujo durante alrededor de 18 horas. La mezcla se filtró a

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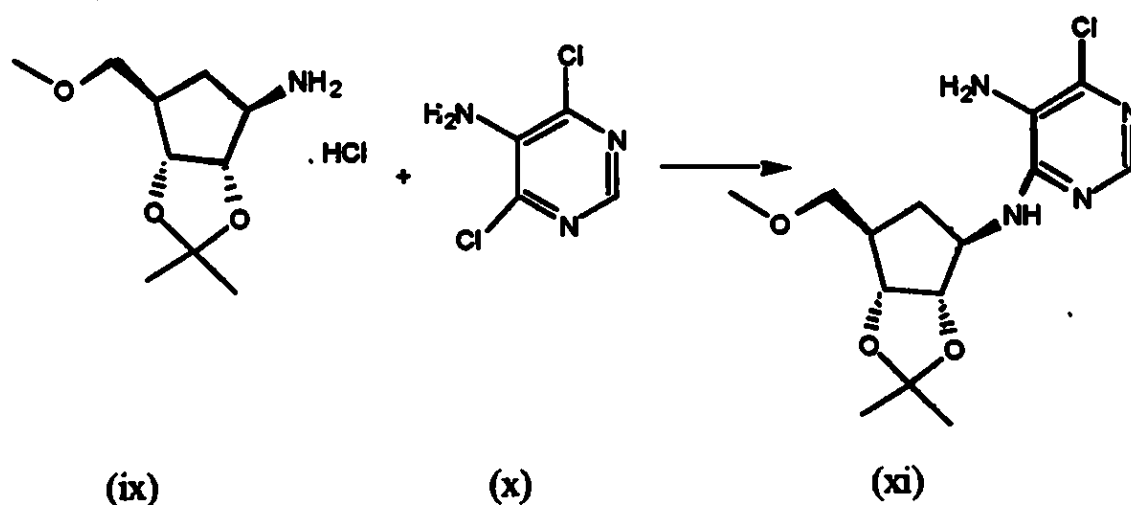
través de Celite y la torta del filtro se lavó con acetato de etilo. El filtrado combinado se concentró in vacuo y el residuo se cristalizó a partir de hexano para dar el deseado compuesto metoximetil (viii) ilustrado arriba.

5 Paso (9)



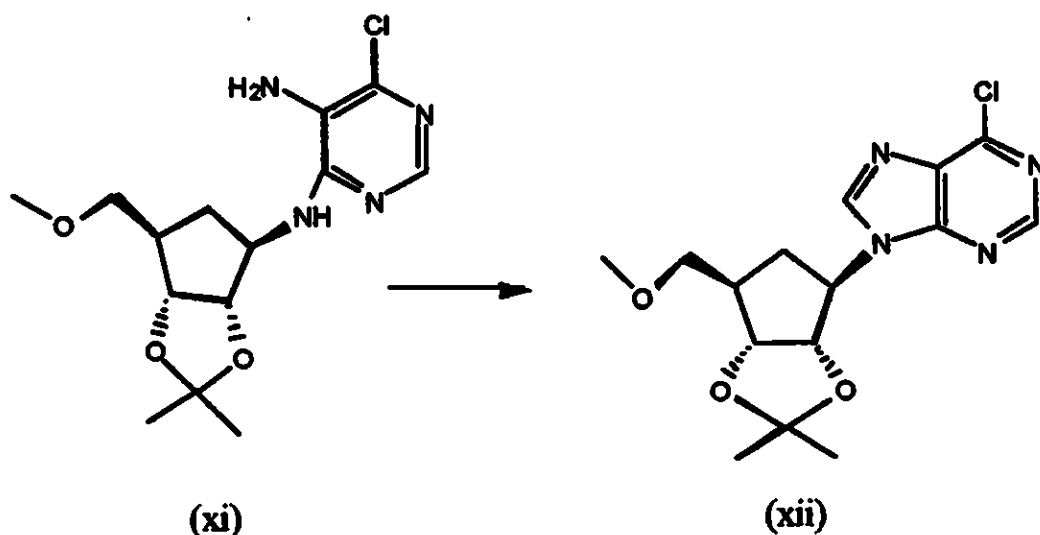
10 Bajo argón, 31,6g del producto (viii) del Ejemplo 3 Paso (8) de arriba se disolvió en 250 mL de acetato de etilo anhidro tibio. La solución se enfrió en un baño de hielo y gas de cloruro de hidrógeno se burbujeó a través de la solución durante alrededor de 6 minutos. La mezcla se dejó tibia a temperatura ambiente y se agitó durante alrededor de 3 hors,
15 entonces se concentró in vacuo para dar el deseado hidrocloreuro de amina (ix) ilustrado arriba.

Paso (10)



24,2 g del producto (ix) del Ejemplo 3 Paso (9) de arriba y 42,8 g de bicarbonato de sodio se combinaron en 100 mL de n-butanol, bajo argón, y 20,1 g 5-amino-4,6-dicloro pirimidina se agregó. La mezcla se calentó a reflujo durante alrededor de 20 horas, entonces se concentró in vacuo. El residuo se partió entre acetato de etilo y agua y la capa de acetato de etilo se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró, se concentró in vacuo. El residuo en 30% de acetato de etilo en hexano, pasó a través de una columna de lavado de gel de sílice de frasco grande, y la columna se lavó con 50% acetato de etilo/hexano y los filtrados combinados se concentraron in vacuo para el deseado producto pirimidinilaminaciclopentano (xi) ilustrado arriba.

Paso (11)



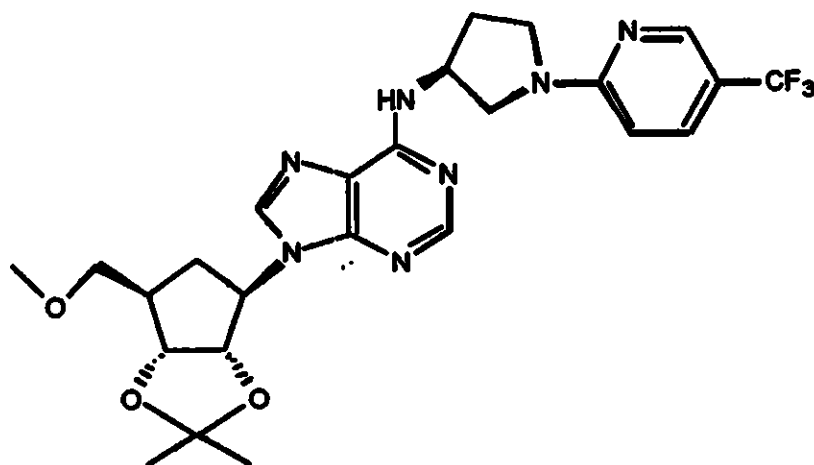
26,7 g del producto (xi) del Ejemplo 3 Paso (10) de arriba se combinó con 125 mL de n-butil acetato bajo argón. 33,5g de acetato de formamida se agregó y la mezcla se calentó a reflujo durante alrededor de 3 horas, hasta que la cromatografía de capa delgada mostró que la reacción es completa. La mezcla se enfrió, partió entre acetato de etilo y salmuera y la capa de acetato de etilo se secó sobre sulfato de magnesio, se filtró, se concentró in vacuo. El residuo se purificó mediante

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cromatografía de destello, levigando con 30-50% de acetato de etilo en hexano, para dar el producto de cloropurina (xii) ilustrado arriba.

Paso (12) Preparación de

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(xiii)

7,75 g (22,9 mmol) del producto (xii) del Ejemplo 3 Paso (11) de arriba y 6,35 g (27,4 mmol) 2-[(3S)-3-aminopirrolidin-1-il]-5-trifluorometilpiridina se combinaron en 20 mL de etanol y 6,33 mL de trietilamina se agregó. La mezcla se calentó en un recipiente sellado a 105°C durante alrededor de 4 horas. La mezcla se enfrió, se evaporó in vacuo, se partió entre cloruro de metileno y solución de bicarbonato de sodio. La capa orgánica se secó sobre sulfato de magnesio, se filtró, se concentró in vacuo, y el residuo se purificó mediante cromatografía de destello, levigando con 4% de metanol en cloruro de metileno, para dar el producto (xiii) indicado.

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Paso (13) 10,81g (20,3 mmol) del producto (xiii) del Ejemplo 3 Paso (12) de arriba se combinó con 90 mL de trifluoroacetato y 10 mL de agua, y la mezcla se agitó a temperatura ambiente durante alrededor de 30 minutos. El TFA se sacó por evaporación a alto vacío y el residuo se partió entre cloruro de metileno y solución de bicarbonato de sodio. La solución de cloruro de metileno se lavó con solución de bicarbonato de

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sodio, salmuera, alcohol isopropil se agregó y la solución se secó sobre sulfato de magnesio, se filtró, se concentró in vacuo, y el residuo se sometió a cromatografía de destello, levigando con 5-10% de metanol en cloruro de metileno. Las fracciones apropiadas se recogieron, se
5 concentraron, y el residuo se cristalizó a partir de acetonitrilo para dar (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol, punto de fusión 166-168°C.

10 EJEMPLO 4

Preparación de (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-trifluoro-metilpiridin-2-il)-pirrolidin-3(R)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol

267 mg 2-[(3R)-3-aminopirrolidin-1-il]-5-trifluorometilpiridina, 331
15 mg 6-cloropurinaribosida, 233 mg trietilamina, y 0,5 mL de etanol se combinaron y calentaron en un recipiente sellado a 100°C durante alrededor de 5 horas. La mezcla se enfrió, partió entre cloruro de metileno (con algo de alcohol isopropil agregado) y bicarbonato de sodio. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, se
20 evaporó, y el residuo se purificó mediante cromatografía de destello, levigando con 5% de metanol en cloruro de metileno, para dar (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-pirrolidin-3(R)-ilamina]purin-9-il]tetrahidrofuran-3,4-diol, como el hemihidrato, punto de fusión 166-170°C.

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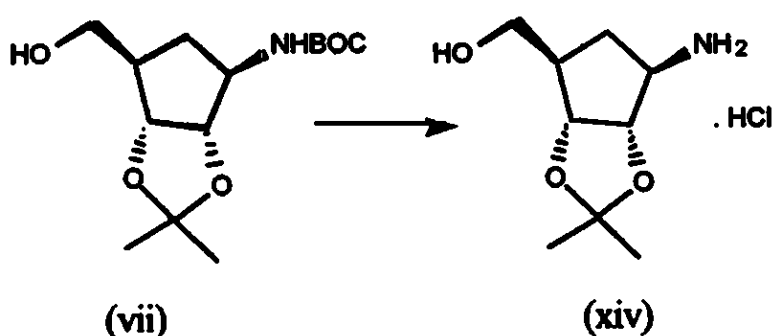
EJEMPLO 5

Preparación de (1R,2S,3R,5R)-3-[6-[1-(4-trifluorometilfenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol

Paso (1) 1,00 g (11,6 mmol) 3(S)-(-)-3-aminopirrolidina, 1,35 mL (9,66 mmol) 4-bromobenzotrifluoruro, 2,69 g (29 mmol) de tert-butoxido de sodio, y 1,01g (1,16 mmol) $\text{PdCl}_2(\text{P}[\text{o-tolil}]_3)_2$ (preparado como en la Patente U.S. No. 4,196,135) se combinaron en 30 mL de tolueno, y la
 5 mezcla se calentó en un recipiente sellado a 100°C durante alrededor de 40 horas. La mezcla se enfrió, se filtró, se evaporó in vacuo y el residuo se purificó mediante cromatografía de destello, levigando con 10:1 a 7:1 de cloruro de metileno/etanol, para dar 1-(4-trifluorometil)fenil-(3S)-pirrolidin-3-ilamina.

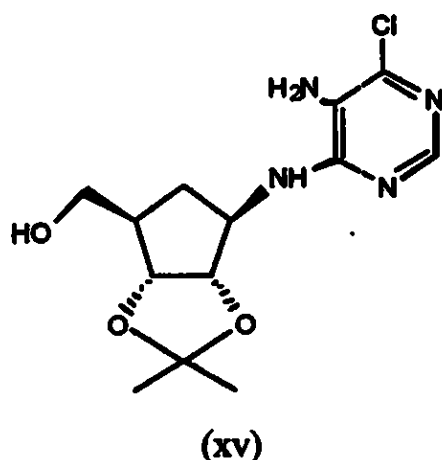
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Paso (2)



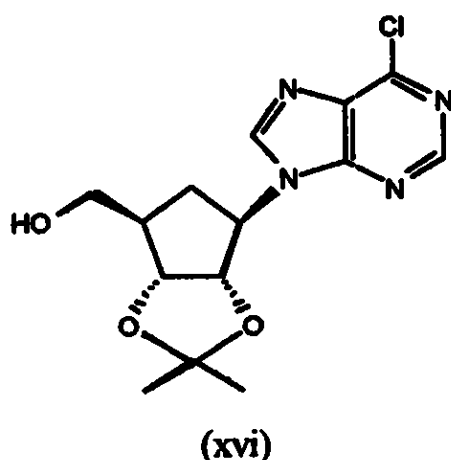
15 Una solución de 24,7 mL (0,61 mol) metanol y 50 mL acetato de etilo se enfrió a 0°C, bajo argón. 43,3 mL (0,61 mol) de cloruro acetyl se agregó en porciones y la solución se dejó llevar a temperatura ambiente durante alrededor de 45 minutos. Esta solución se enfrió nuevamente en hielo y una solución de 50,0g N-BOC-1-amino-2,3-dimetilenodioxi-4-
 20 hidroximetil ciclopentano (vii) en 100 mL de acetato de etilo se agregó durante un periodo de alrededor de 45 minutos. La solución se dejó llevar a temperatura ambiente, luego se evaporó in vacuo para dar el deseado amina hidrocloreuro (xiv) ilustrado arriba.

25 Paso (3) Preparación de



38,9g del producto (xiv) del Ejemplo 5 Paso (2) de arriba y 73 g de bicarbonato de sodio se combinaron en 150 mL de n-butanol bajo argón, y la mezcla se agitó a temperatura ambiente durante alrededor de 30 minutos. 34,2 g de 5-amino-4,6-dicloropirimidina se agregó y la mezcla se agitó a reflujo durante alrededor de 19 horas. La mezcla se concentró in vacuo, y el residuo se desarrolló en acetato de etilo y agua. La capa acuosa se extrajo con acetato de etilo y el orgánico combinado se lavó con salmuera, se filtró, se concentró in vacuo. El residuo se purificó mediante cromatografía de destello, levigando con un gradiente de 30% a 100% de acetato de etilo en hexano, para dar la deseada cloropirimidina sustituida (xv) ilustrada arriba.

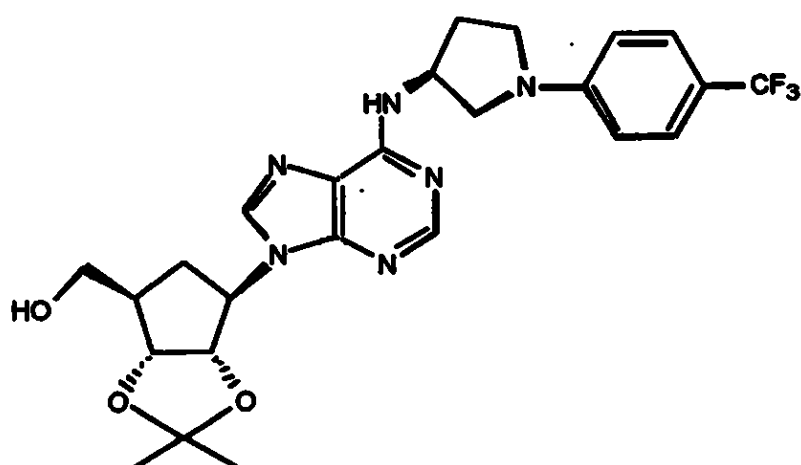
Paso (4) Preparación de



37,9 g del producto (xv) del Ejemplo 5 Paso (3) de arriba y 25,1 g de acetato de formamidina se combinaron en 250 mL de n-butil acetato y

la mezcla se calentó a reflujo, bajo argón, durante alrededor de 2 horas, agregando adicionales 12,5 g de acetato de formamidina después de alrededor de 1 hora, y adicionales 10 g después de alrededor de 1,5 horas. La mezcla se enfrió, partió entre acetato de etilo y salmuera, la salmuera se extrajo con 3 porciones de acetato de etilo, y el orgánico combinado se secó sobre sulfato de magnesio, se filtró, se evaporó in vacuo. El residuo se purificó mediante cristalización a partir de acetato de etilo/hexano para dar la arriba ilustrada cloropurina (xvi). El residuo de la concentración del licor madre puede purificarse mediante cromatografía de destello, levigando con 80 a 100% de acetato de etilo en hexano para mejorar la recuperación.

Paso (5) Preparación de



(xvii)

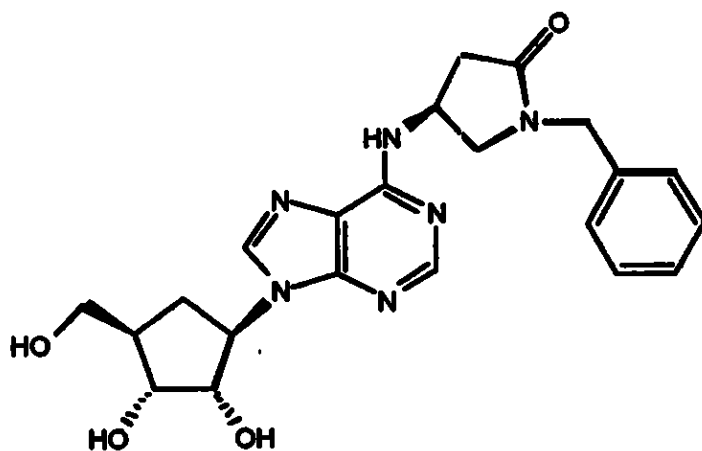
0,225 g (0,693 mmol) del producto (xvi) del Ejemplo 5 Paso (4) de arriba, 0,239 g (1,04 mmol) 1-(4-trifluorometil)fenil-(3S)-pirrolidin-3-ilamina, del Paso (1) de arriba, y 0,582 g (6,93 mmol) de bicarbonato de sodio se combinaron en 20 mL de etanol y se calentó a reflujo durante alrededor de 60 horas. La mezcla se filtró, se concentró in vacuo, y el residuo se purificó mediante cromatografía de destello, levigando con un gradiente de cloruro de metileno/etanol, 30:1 a 10:1, para dar la pirrolidinilamina (xvii) ilustrada arriba.

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Paso (6) 0,234 g del producto del Ejemplo 5 Paso (5) de arriba se disolvió en 10 mL de ácido trifluoroacético y la solución se agitó a temperatura ambiente durante la noche. La solución se evaporó in vacuo, y el residuo se purificó mediante cromatografía de destello, levigando con
5 cloruro de metileno/acetato de etilo (10:1) para dar (1R,2S,3R,5R)-3-[6-[1-(4-trifluorometilfenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol, punto de fusión 111-114°C.

EJEMPLO 6

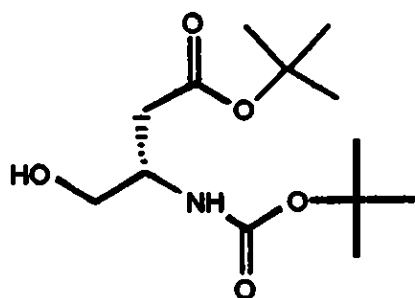
10 Preparación de 4(S)-1-bencil-4-[9-((1R,2S,3R,5R)-1,2-dihidroxi-5-hidroximetilciclopent-3-il)-9H-purin-6-ilamina]pirrolidin-2-ona



(xviii)

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Paso (1) Preparación de



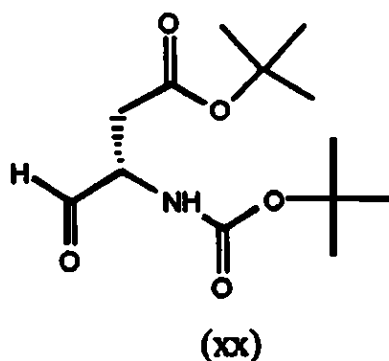
(xix)

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7,1 g (24,5 mmol) N-t-BOC-L-ácido aspártico β -t-butil éster se disolvió en 120 mL de tetrahidrofurano. La solución se enfrió a 0°C y 2,73 g (27 mmol) trietilamina, entonces 2,66 g (24.5 mmol) etil cloroformato se agregó. La solución se agitó durante alrededor de 30 minutos, y una
5 solución de 3,71 g (98,2 mmol) de boro hidrido de sodio en agua se agregó. La mezcla se agitó a temperatura ambiente durante alrededor de 17 horas, se concentró in vacuo y el residuo se diluyó con acetato de etilo, y la capa orgánica se lavó con 1 N de ácido clorhídrico, 10% de carbonato de sodio, salmuera, entonces se secó sobre sulfato de magnesio, se filtró,
10 se concentró in vacuo y el residuo se purificó mediante cromatografía de destello, levigando con 30% a 50% de acetato de etilo en hexano, para dar 3(S)-t-butil-3-BOC-amino-4-hidroxi-n-butanoato (xix).

Paso (2) Preparación de

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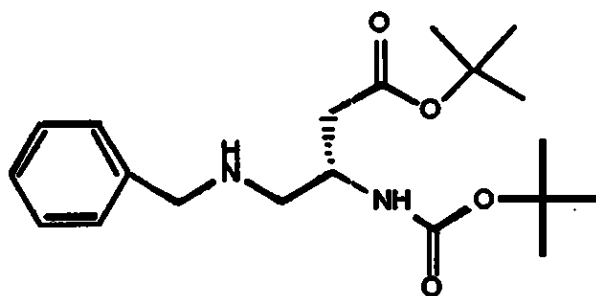
Una solución de 0,73 g de dimetilsulfóxido en 9 mL de cloruro de metileno se enfrió a -70°C y 31 mL de una solución 2M de cloruro de oxalil en cloruro de metileno se agregó gota a gota. La solución se agitó durante alrededor de 15 minutos y una solución de 0,85 g de 3(S)-t-butil-3-BOC-amino-4-hidroxi-n-butanoato (xix) en 5 mL de cloruro de metileno se agregó. Después de agitación durante alrededor de 45 minutos, 1,88g
20 de trietilamina se agregó. La solución se dejó tibia a temperatura ambiente, se agitó durante alrededor de 30 minutos, luego se diluyó con

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51 ✓ 94

acetato de etilo. La solución se lavó con ácido clorhídrico 1N, 10% de carbonato de sodio, salmuera, se secó sobre sulfato de magnesio, se filtró, se concentró in vacuo, para dar 3(S)-t-butil-3-BOC-amino-4-oxo-n-butanoato (xx).

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Paso (3)



(xxi)

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El producto (xx) del Ejemplo 6 Paso (2) de arriba se disolvió en 9 mL de metanol y 1,34g bencil amina hidrocloreto, entonces 0,94 g de trietilamina, entonces 200 mg de tamices 3 Å molecular. La solución se agitó durante alrededor de 45 minutos y una solución de 0m23 g de cloruro de zinc y 0,22 g de ciano borohidrido de sodio en 5 mL fr metanol se agregó. La solución se agitó durante alrededor de 4 horas, 2 mL de hidróxido de sodio 1N, entonces 10 mL de agua se agregaron, la mezcla se concentró hasta alrededor de medio volumen, y se extrajo con acetato de etilo. La solución de acetato de etilo se lavó con 10% de solución de carbonato de sodio, salmuera, se secó sobre sulfato de magnesio, se filtró, se concentró in vacuo, y el residuo se purificó mediante cromatografía de destello, levigando con 30% a 40% acetato de etilo en hexano, para dar la bencil amina (xxi) ilustrada arriba.

25 Paso (4) 0,90 g del producto del Ejemplo 6 Paso (3) de arriba se disolvió en 12 mL de tolueno/ácido acético (10:1), y la solución se

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sometió a reflujo durante alrededor de 1,5 horas. La mezcla se concentró in vacuo, y el residuo se purificó mediante cromatografía de destello, levigando con 25%-35% acetato de etilo en cloruro de metileno, para dar 1-bencil-4(S)-BOC-amino-2-pirrolidinona.

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Paso (5) 0,64g del producto del Ejemplo 6 Paso (4) de arriba se disolvió en 20 mL de acetato de etilo y la solución se enfrió a 0°C. Gas de cloruro de hidrógeno se burbujó dentro de la solución durante alrededor de 5 minutos, y la mezcla se agitó a temperatura ambiente durante
10 alrededor de 18 horas. Se agregó éter a la mezcla y el sólido se recogió mediante filtración para dar 1-bencil-4(S)-amino-2-pirrolidinona hidrocloreto.

Paso (6) 0,33 g de la cloropurina protegida del Ejemplo 5, Paso (4)
15 de arriba, 0,26 g 1-bencil-4(S)-amino-2-pirrolidinona hidrocloreto, y 0,29 g de trietilamina se combinaron en 10 mL de etanol y la mezcla se calentó a reflujo durante alrededor de 50 horas. La mezcla se concentró in vacuo y el residuo se disolvió en 20 mL de ácido clorhídrico 1 N y se agitó a temperatura ambiente durante alrededor de 1 hora. La mezcla se concentró
20 in vacuo y el residuo se purificó mediante HPLC preparativa, levigando con un gradiente de 10% de acetonitrilo a 60% de acetonitrilo en agua, que contiene 0,1% de ácido trifluoroacético. Las fracciones apropiadas se combinaron, se concentraron, y el residuo se disolvió en 20 mL de ácido clorhídrico 1N, el solvente se evaporó in vacuo, y esto se repitió dos veces
25 más. Este residuo se disolvió en metanol, el solvente se evaporó in vacuo, y el residuo se trituró en éter para dar 4(S)-1-bencil-4-[9-((1R,2S,3R,5R)-1,2-dihidroxi-5-hidroximetilciclopent-3-il)-9H-purin-6-ilamina]pirrolidin-2-ona como el trihidrato de hidrocloreto, punto de fusión 100°C (dec.)

30 EJEMPLO 7

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Preparación de (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)pirrolidin-3-ilamina]-purin-9-il]ciclopentano-1,2-diol

Paso (1) 4-nitrofenol (1,0g, 7,19 mmol) y trietilamina (3 mL, 21,6 mmol) se disolvieron conjuntamente en cloruro de metileno anhidro (10 mL), y la solución se enfrió a -15°C. Anhídrido trifluorometano sulfónico (1,81 mL, 10,8 mmol) se agregó y la mezcla se agitó a -15°C durante alrededor de 30 minutos. La mezcla se diluyó con cloruro de metileno, se lavó con solución de bicarbonato de sodio y salmuera, la capa orgánica se secó sobre sulfato de magnesio, se filtró, y se concentró in vacuo. El residuo se purificó mediante cromatografía de destello, levigando con cloruro de metileno, para dar 4-nitrofenil trifluorometanosulfonato como un sólido amarillo brillante.

Paso (2) 3(S)-amino-1-bencilpirrolidina (3,0g, 17,0 mmol) y trietilamina (2,50 mL, 17,9 mmol) se disolvieron conjuntamente en metanol anhidro (17 mL), bajo nitrógeno, y trifluoro acetato de etilo (2,53 mL, 21,3 mmol) se agregó gota a gota. La solución se agitó durante alrededor de 18 horas, se evaporó in vacuo, y el residuo se desarrolló en cloruro de metileno. La solución se lavó con solución de bicarbonato de sodio, salmuera, se secó sobre sulfato de magnesio, se filtró, se concentró in vacuo para dar 1-bencil-3(S)-trifluoroacetilaminapirrolidina.

Paso (3) Bajo nitrógeno, 1-bencil-3(S)-trifluoroacetilaminapirrolidina (4,59g, 16,7 mmol) se disolvió en metanol anhidro (50 mL) y di-tert-butil dicarbonato (3,68g, 16,7 mmol) y 10% de paladio sobre carbono (0,90g) se agregó. La mezcla se agitó entonces bajo hidrógeno bajo presión atmosférica durante alrededor de 5 horas. La mezcla se filtró a través de Celite®, enjuagando con metanol, y el filtrado se evaporó in vacuo. El residuo se purificó mediante cromatografía de destello, levigando con 5%

de metanol en cloruro de metileno para dar 1-BOC-3(S)-trifluoroacetilaminapirrolidina.

Paso (4) 1-BOC-3(S)-trifluoroacetilaminapirrolidina (4g) se disolvió
5 en cloruro de metileno (130 mL) y ácido trifluoroacético (19 mL) se agregó. La solución se agitó a temperatura ambiente durante alrededor de 1 hora, luego se concentró in vacuo. El residuo se partió entre cloruro de metileno y solución saturada de bicarbonato de sodio. Las capas se separaron y el acuoso se extrajo con acetato de etilo. El orgánico combinado se secó
10 sobre sulfato de magnesio, se filtró, se evaporó in vacuo para dar 3(S)-trifluoroacetilaminapirrolidina.

Paso (5) 4-Nitrofenil trifluorometanosulfonato (0,423g, 1,56 mmol) y trietilamina (0,217 mL, 1,56 mmol) se disolvieron conjuntamente en
15 acetonitrilo anhidro (15 mL) y 3(S)-trifluoroacetilaminapirrolidina (0,852g, 4,68 mmol) se agregó y la mezcla se calentó a reflujo durante alrededor de 18 horas. La mezcla se enfrió, se concentró in vacuo y el residuo se purificó mediante cromatografía de destello, levigando con un gradiente de 25% a 50% de acetato de etilo en hexano para dar 1-(4-
20 nitro)fenil-3(S)-trifluoroacetilaminapirrolidina.

Paso (6) 1-(4-Nitro)fenil-3(S)-trifluoroacetilaminapirrolidina (0,334g, 1,10 mmol) se combinó con una solución saturada de carbonato de potasio en metanol/agua (2:3) (20 mL), y la mezcla se calentó a 55°C durante
25 alrededor de dos horas, entonces a temperatura ambiente durante alrededor de 18 horas. La mezcla se concentró in vacuo y el residuo se desarrolló en agua (10 mL). El acuoso se extrajo con acetato de etilo, y el orgánico se secó sobre sulfato de magnesio, se filtró, se evaporó in vacuo para dar 3(S)-amino-1-(4-nitro)fenilpirrolidina.

9.6
9.8
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Paso (7) Usando esencialmente los procedimientos del Ejemplo 3, Pasos 12 y 13, y el Ejemplo 5, Pasos 5 y 6, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)pirrolidin-3-ilamina]-purin-9-il]ciclopentano-1,2-diol, punto de fusión 119-120°C, se preparó a partir de 3(S)-amino-1-(4-nitro)fenilpirrolidina.

Usando esencialmente los procedimientos de los Esquemas de Reacción y los Ejemplos como se describió aquí anteriormente, los siguientes compuestos para uso de la invención son preparados a partir de los apropiados materiales de partida:

EJEMPLO 8

(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-cloropiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]- tetrahidrofuran-3,4-diol, punto de fusión 154-156°C;

EJEMPLO 9

(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol, punto de fusión 153-156°C;

EJEMPLO 10

(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(4-trifluorometilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol, punto de fusión 187-190°C;

EJEMPLO 11

(2R,3R,4S,5R) 5-hidroximetil -2-[6-[1-(5-bromopiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]- tetrahidrofuran-3,4-diol, punto de fusión 153-154°C;

56 97
99

EJEMPLO 12

(2R,3R,4S,5R)-5-hidroximetil-2-(6-(1-(4-nitrofenil)-pirrolidin-3(S)-ilamina)-purin-9-il) tetrahidrofuran-3,4-diol, punto de fusión 230-232°C;

5 **EJEMPLO 13**

(2R,3R,4S,5R)-5-hidroximetil-2-[6-(5'-trifluorometil-3,4,5,6-tetrahidro-2H-[1,2']-bipiridinil-3-ilamina)-purin-9-il]tetrahidrofuran-3,4-diol, punto de fusión 113-116°C;

10 **EJEMPLO 14**

(2R,3R,4S,5R)-5-hidroximetil-2-[6-(fenilpirrolidin-3(S)-ilamina)-purin-9-il]tetrahidrofuran-3,4-diol;

EJEMPLO 15

15 (2R,3R,4S,5R)-5-hidroximetil-2-[6-(1-piridin-2-ilpirrolidin-3(S)-ilamina)-purin-9-il]tetrahidrofuran-3,4-diol, punto de fusión 193-195°C;

EJEMPLO 16

20 (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(4-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]- tetrahidrofuran-3,4-diol, punto de fusión 121-124°C;

EJEMPLO 17

(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-metilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol, punto de fusión 164-166°C;

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EJEMPLO 18

(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-thiophen-2-ilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol, punto de fusión 190-192°C;

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EJEMPLO 19

(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-metilmercaptopiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol, punto de fusión 231-233°C;

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EJEMPLO 20

(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-metoxipirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol, punto de fusión 251-253°C;

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EJEMPLO 21

(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]- tetrahidrofuran-3,4-diol, 154-156°C;

15 **EJEMPLO 22**

(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol, punto de fusión 130°C (dec.);

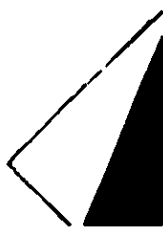
EJEMPLO 23

20 (2R,3R,4S,5R)-5-metoximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol, punto de fusión 198-200°C;

EJEMPLO 24

25 (1S,2R,3S,4R)-2,3-dihidroxi-4-[6-[1-(5-trifluormetilpiridin-2-il)pirrolidin-3-ilamina]-purin-9-il]ciclopentano-ácido carboxílico etilamida, punto de fusión 135-138°C;

EJEMPLO 25



(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)piperidin-4-ilamina]-
purin-9-il]ciclopentano-1,2-diol, punto de fusión 126-128°C;

EJEMPLO 26

5 (1R,2S,3R,5R)-5-hidroximetil-3-[6-((3S)-pirrolidin-3-ilamina)-purin-9-il]
ciclopentano-1,2-diol dihidrocloruro, punto de fusión 160°C (dec);

EJEMPLO 27

10 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)
pirrolidin-3(R)-ilamina]-purin-9-il]ciclopentano-1,2-diol, punto de fusión
175-177°C;

EJEMPLO 28

15 (1R,2S,3R,5R)-5-hidroximetil-3-[6-((3R)-pirrolidin-3-ilamina)-purin-9-il]
ciclopentano-1,2-diol, punto de fusión 166°C (dec);

EJEMPLO 29

20 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)
pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol, punto de fusión
110-111°C;

EJEMPLO 30

25 4(R)-1-bencil-4-[9-((1R,2S,3R,5R)-1,2-dihidroxi-5-hidroximetilciclopent-
3-il)-9H-purin-6-ilamina] pirrolidin-2-ona hidrocloreto, punto de fusión
110°C (dec);

EJEMPLO 31

(1R,2S,3R,5S)-5-metil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-
ilamina]-purin-9-il]ciclopentano-1,2-diol, punto de fusión 114-116°C;

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702

EJEMPLO 32

(1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol, punto de fusión 169-
171°C;

5

EJEMPLO 33

(1R,2S,3R,5R)-3-[6-[1-(5-cloropiridin-2-il)pirrolidin-3(S)-ilamina]-purin-
9-il]-5-hidroximetilciclopentano-1,2-diol, punto de fusión 118-121°C;

10 **EJEMPLO 34**

(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-trifluorometilpiridin-2-
il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol, punto de fusión
135-137°C;

15 **EJEMPLO 35**

(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(piridin-2-il)pirrolidin-3(S)-
ilamina]-purin-9-il]ciclopentano-1,2-diol, punto de fusión 110-112°C;

EJEMPLO 36

20 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(quinolin-3-il)pirrolidin-3(S)-
ilamina]-purin-9-il]ciclopentano-1,2-diol, punto de fusión 135-138°C;

EJEMPLO 37

(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)-pirrolidin-3(S)-
25 ilamina]-purin-9-il]ciclopentano-1,2-diol;

EJEMPLO 38

(1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluorpiridin-2-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol, punto de fusión 123-
30 126°C;

EJEMPLO 39

(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(fenil)-pirrolidin-3(S)-ilamina]-
purin-9-il]ciclopentano-1,2-diol, punto de fusión 97-99°C;

5 **EJEMPLO 40**

4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihidroxi-5-hidroximetilciclopent-3-il)-9H-
purin-6-ilamina]pirrolidin-1-il]benzonitrilo, punto de fusión 140°C;

EJEMPLO 41

10 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(isoquinolin-1-il)pirrolidin-3(S)-
ilamina]-purin-9-il]ciclopentano-1,2-diol, punto de fusión 119-122°C;

EJEMPLO 42

15 (1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol;

EJEMPLO 43

(1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)pirrolidin-3(S)-ilamina]-purin-9-il]-5-
hidroximetilciclopentano-1,2-diol;

20

EJEMPLO 44

(1R,2S,3R,5R)-3-[6-[1-(3-cloro-5-trifluorometilpiridin-2-il)pirrolidin-3(S)-
ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol, punto de fusión
140-143°C;

25

EJEMPLO 45

(1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol, punto de fusión 180-
182°C;

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EJEMPLO 46

**(1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-metoximetilciclopentano-1,2-diol;**

5 EJEMPLO 47

**(1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol;**

EJEMPLO 48

**10 (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(6-metoxipirimidin-4-il)pirrolidin-
3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol, punto de fusión 118-120°C;**

EJEMPLO 49

**15 (1R,2S,3R,5R)-5-isopropoximetil-3-[6-[1-(5-trifluorometilpiridin2-
il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol, punto de fusión
157-158°C;**

EJEMPLO 50

**20 (1R,2S,3R,5R)-5-isopropoximetil-3-[6-[1-(4-trifluorometilpiridin2-
il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol, 160-161°C;**

EJEMPLO 51

**25 (1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-metoximetilciclopentano-1,2-diol, punto de fusión 122-
124°C;**

EJEMPLO 52

**30 (1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-metoximetilciclopentano-1,2-diol, punto de fusión 110-
111°C;**

EJEMPLO 53

(1R,2S,3R,5R)-3-[6-[1-(5-clorpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol, punto de fusión 110-112°C;

5 EJEMPLO 54

(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(4-trifluorometilfenil)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol, punto de fusión 128°C;

EJEMPLO 55

10 (1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol, punto de fusión 122-125°C;

EJEMPLO 56

15 (1R,2S,3R,5R)-3- [6-[1-(3-clorofenil) -pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol, punto de fusión 127-130°C;

EJEMPLO 57

(1R,2S,3R,5R)-3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol, punto de fusión 131-133°C; y

20

EJEMPLO 58

(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-fenilpirrolidin-3-(S)-ilamina]-purin-9-il]ciclopentan-1,2-diol, punto de fusión 106°C.

25 EJEMPLO 59

(1R,2S,3R,5R)-3-[6-(1-bencil-pirrolidin-3(S)-ilamina)purin-9-il]-5-hidroximetilciclopentano-1,2-diol, punto de fusión 100-102°C;

EJEMPLO 60

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206

(1R,2S,3R,5R)-3-[6-(1-bencil-pirrolidin-3(S)-ilamina)purin-9-il]-5-metoximetilciclopentano-1,2-diol, punto de fusión 95-96°C.

EJEMPLO 61

- 5 (1S,2R,3S,4R)-2,3-dihidroxi-4-{6-[1-(5-trifluorometil-piridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il}-ciclopentano-ácido carboxílico-1(S)-metilpropilamida, punto de fusión 215°C (dec.); y

EJEMPLO 62

- 10 (1S,2R,3S,4R)-2,3-dihidroxi-4-{6-[1-(5-trifluorometil-piridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il}-ciclopentano-ácido carboxílico-1(R)-metilpropilamida, punto de fusión 206-212°C (dec.).

Aspectos de la fisiología de resistencia a la insulina y diabetes tipo 2

15

- La resistencia a la insulina, la cual se define como un estado de capacidad de respuesta reducida a las concentraciones de circulación normal de insulina, es un rasgo característico de la diabetes tipo 2 y contribuye a sub-normalidades en el músculo, tejido graso e hígado. La resistencia a la
- 20 insulina precede al establecimiento de la diabetes tipo 2, la cual se desarrolla cuando existen defectos adicionales al nivel de la beta-célula pancreática. En la medida en que la resistencia periférica a la insulina pueda ser compensada por incrementada producción de insulina la homeostasis de glucosa es balanceada. Aún en ausencia de la diabetes tipo
- 25 2, la resistencia a insulina es una característica clave de otros estados de enfermedad humana. La acción de insulina dispareja acoplada con hiperinsulinemia lleva a una variedad de anormalidades, incluyendo elevados triglicéridos, bajos niveles de HDL, elevada secreción de VLDL, desórdenes de coagulación, incrementada resistencia vascular, cambios en
- 30 los niveles de hormona esteroide, atenuación del flujo de sangre periférica

120
107

y ganancia de peso. Consecuentemente, la resistencia a insulina está a menudo asociada con obesidad central, hipertensión, síndrome policístico de ovarios, dislipidemia, y aterosclerosis (JCI 106, 163-164, 2000).

5 La resistencia a insulina está caracterizada en el tejido adiposo por incrementada lipólisis, lo cual resulta en incrementados niveles de ácidos grasos libres, lo cual por sí mismo contribuye a la reducida utilización de glucosa en el músculo, al incrementado flujo de ácidos grasos al hígado, con subsecuente incrementada producción de VLDL y disparidad de
10 secreción de insulina de la beta-célula en el hígado por incrementada producción de glucosa hepática, y secreción de VLDL, lo cual resulta en hiperglicemia e hipertrigliceridemia, respectivamente en el músculo por reducidas velocidades de utilización de glucosa, lo cual contribuye a la hiperglicemia.

15

La inhibición de lipólisis periférica por TGL 749 (agonista receptor A1 adenosina) resulta en reducción de ácidos grasos libres en plasma (efecto farmacológico primario). La reducida disponibilidad de ácidos grasos libres a la utilización de glucosa incrementada en el músculo y reducida
20 producción de VLDL en el hígado que es sostenido por reducidos triglicéridos en plasma (efecto farmacológico secundario).

Medición del efecto antilipolítico

El efecto antilipolítico de los compuestos de acuerdo con la fórmula
25 general (I) se muestra en la Tabla 1.

Ejemplo No.	Lipo ec_{50} [nm]
2	10,88
3	5,62
5	2

65 206
708

6	267
7	2,82
18	2,24
20	1,37
21	2,43
22	3,07
26	178,0
29	3,57
31	247,0
32	8,0
33	4,2
34	3,3
35	48,0
37	2,8
38	114,0
39	17,6
40	10,5
41	182,0
42	30,0
44	226,0
46	92,5
47	129,0
50	365,0
51	18,6
52	17,0
53	18,6
54	27,8
55	3,3
56	2,4
57	63,5
61	18,0

La medición de plasma lipdis (ácidos grasos libres, triglicéridos, colesterol) en ratas anestesiadas.

Los niveles de lipidos en plasma se ensayaron en ratas anestesiadas. En forma breve, las ratas se anestesiaron con una inyección intraperitoneal de sodio de pentobarbital (60 mg/kg), traquea atomizada, y una vena yugular por rata se tomo con cánula para administración intravenosa (inyección de bolo o infusión). La anestesia se mantuvo hasta 7 horas por infusión subcutánea de sodio de pentobarbital (ajustada a la profundidad anestésica del animal individual; alrededor de 24 mg/kg/h). La temperatura corporal se vigiló con un termómetro de sonda rectal, y la temperatura se mantuvo a 37° C por medio de una placa quirúrgica calentada. Las ratas se dejaron estabilizar en sus niveles de sangre después de cirugía hasta 2 horas, después de lo cual el compuesto de prueba se inyectó intra peritonealmente. Las muestras de sangre para análisis de glucosa (10 µl) se obtuvieron desde la punta de la cola cada 15 minutos. Para análisis de las muestras de sangre de lipidos en plasma (0,3 ml) se obtuvieron de la vena yugular ya sea cada 10 a 15 minutos durante hasta 2 horas, o cada hora durante hasta 5 horas después de la administración del compuesto. Se utilizaron procedimientos enzimáticos estándares para determinar la glucosa de la sangre (Bergmeyer, 1974).

Tabla 2
Efecto del Compuesto del Ejemplo 3 en los ácidos grasos libres de plasma en ratas Wistar machos cultivados anestesiados
(Estudio Animal: 00-009)

Minutos	Control		Ejemplo 3 (10 mg/kg i.p.)		Ejemplo 3 (30 mg/kg i.p.)	
	Media	SEM	Media	SEM	Media	SEM
-60	0,57	0,04	0,61	0,03	0,52	0,02
10	0,55	0,04	0,42	0,03	0,24	0,02

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 92 7.10

20	0,59	0,02	0,26	0,07	0,14	0,01
30	0,52	0,04	0,19	0,05	0,13	0,01
40	0,50	0,04	0,19	0,06	0,10	0,01
60	0,48	0,07	0,13	0,05	0,09	0,01
Valores son media +/- SEM, n = 4 ratas						

Medición de sensibilidad a la insulina en ratas conscientes.

Las ratas Grasas Zucker resistentes a la insulina o ratas Zucker Grasas Diabéticas (ZDF) se trataron hasta 3 semanas con el compuesto de prueba oralmente una vez diaria. Los parámetros del plasma fueron obtenidos mediante sangrado retro-orbital durante inhalación de anestesia en los respectivos días de estudio. Al final del estudio las ratas se alimentaron durante la noche y recibieron una inyección en bolo de insulina (3 U/kg s.c.) y la reducción de glucosa en la sangre se vigiló hasta horas. En el caso de mejora de la sensibilidad a la insulina por el compuesto de prueba la reducción de la glucosa en sangre fue mucho más pronunciada y prolongada comparada con la del grupo de control.

Tabla 3
Prueba de tolerancia a la insulina (3 U/kg s.c.) en Ratas Grasas Zucker resistentes a la insulina después de tratamiento previo con el Compuesto del Ejemplo 3 durante 3 semanas con 1 y 10 mg/kg po
(Estudio Animal: 00-027)

minutos después de la insulina		0	60	120	180	240	300	360	420
control	mean	5,28	2,38	2,92	5,87	6,89	6,20	5,24	4,93
	SEM	0,14	0,10	0,21	0,35	0,46	0,33	0,26	0,16
Ejemplo 3 (1 mg/kg p.o.)		4,60	1,96	1,59	1,72	3,02	5,13	4,98	4,04
		0,16	0,07	0,09	0,12	0,25	0,47	0,26	0,24
Ejemplo 3 (10 mg/kg p.o.)		5,17	1,99	1,57	1,44	2,54	4,35	5,63	6,09

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		0,22	0,17	0,16	0,09	0,27	0,42	0,47	0,31
Valores son media +/- SEM, n = 9									

Los compuestos dentro del alcance de esta invención exhiben actividad en ensayos de enlace de receptor estándar A1/A2 para la determinación de actividad de agonista de receptor de adenosina en mamíferos. Los procedimientos de prueba de ejemplo que son útiles en la determinación de la afinidad de enlace del receptor de los compuestos de la presente invención se describen abajo.

10 A. DETERMINACIÓN DE AFINIDAD DE ENLACE DE RECEPTOR DE ADENOSINA IN VITRO

La afinidad de Enlace del Receptor A1 se determinó por ensayo de competición basado en el desplazamiento de ligando de ³H-CHA (ciclohexil adenosina) [Research Biochemicals Inc., Natick, Mass.] a partir del receptor usando una preparación de membrana del completo cerebro de la rata, de acuerdo con el procedimiento de R. F. Bruns y otros, 15 Mol. Pharmacol., 29:331 (1986). Se accedió a enlace no específico en presencia de 1 mM de teofilina.

La afinidad de enlace del receptor A2 se determinó mediante una 20 técnica de ensayo similar, basada en el desplazamiento del ligando de ³H-CGS 21680, un agonista de adenosina conocido específico receptor A2, del receptor, usando membranas del estrito de cerebro de rata. No se obtuvo enlace no específico en presencia de 20 µM 2-cloroadenosina.

25 Los ensayos corrieron en tubos de prueba de vidrio en duplicado a 25°C. Una vez que las membranas se agregaron, los tubos se sometieron a vórtice e incubaron a 25°C durante 60 minutos (ensayo A1) o 90 minutos

(ensayo A2) en un agitador rotativo. Los tubos de ensayo se sometieron a vórtice en la vía media a través de la incubación y nuevamente cerca al final. Los ensayos se terminaron por rápida filtración a través de filtros de 2,4 cm GF/B usando un Brandel Cell Harvester. Los tubos de prueba se lavaron tres veces con 50 mM tris-HCl frío (pH 7,7 o 7,4), completandose la filtración dentro de 15 segundos. Los círculos de filtro se colocaron en recipientes de cintilleo de vidrio llenos con 10 mL de Aquasol II (New England Nuclear). Los recipientes se dejaron agitar durante la noche en un agitador rotativo y se colocaron en un analizador de cintilleo líquido durante conteos de dos minutos. Los valores IC₅₀ para el enlace de receptor, es decir, la concentración a la cual un compuesto de la invención desplazó el estándar radio etiquetado. Se obtuvieron usando un programa de computador de ajuste de curva (RS/1, Bolt, Beranek y Newman, Boston, MA).

15

La Afinidad de Enlace Receptor A₁ se determinó también usando una preparación de membranas de almohadilla grasa epididimal de rata.

Preparación de Membrana: Almohadillas grasas epididimal de ratas se homogenizaron en un amortiguador que contiene 0,25 M Sucrosa, 10 mM Tris, 2 mM EDTA, 0.1 M fenilmetilsulfonilfluoruro, y 1 µg/mL Leupeptin (200 mg peso de tejido húmedo/mL amortiguador). Este homogenizado se colocó en tubos centrífugos de 50 mL y se centrifugó a 1 000 g (3 000 RPM) durante 1 minuto, el sobre nadante intermediario se retiró y se centrifugó a 38 000 g durante 15 minutos. Las pellets se resuspendieron en un amortiguador de ensayo (50 mM Tris y 1 mM EDTA) (300 mg peso de tejido original/mL amortiguador de ensayo), y 2 µl/ml de una solución de deaminasa adenosina (10 mg/ml) se agregó a la suspensión y la suspensión se incubó durante 30 minutos a 37°C. La suspensión se centrifugó a 38 000 g durante 10 minutos, la pellet se lavó una vez con 20 ml de

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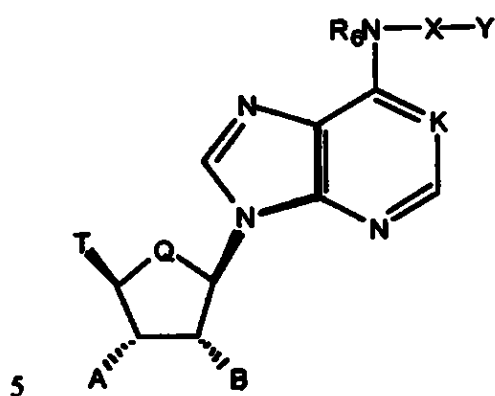
amortiguador de ensayo, se resuspendió en amortiguador de ensayo (1,2 g de pero de tejido húmedo original / mL amortiguador).

Ensayo y Conteo: Se prepararon tubos como sigue: Tubos totales (unión
5 de conteos totales), 100 μL de suspensión de membrana (preparada como
se describió arriba), 50 μL ^3H -ciclohexil adenosina en solución (preparada
diluyendo una solución de aproximadamente 1 mCi/mL, con una actividad
específica de aproximadamente 29,9 Ci/mmol, con amortiguador de
ensayo a 100nM, de aquí en adelante "solución CHA"), 350 μL de
10 amortiguador de ensayo; Tubos de enlace no específicos, 100 μL de
suspensión de membrana, 50 μL de solución CHA, 50 μL 100 μM 2-
cloroadenosina en amortiguador de ensayo, 300 μL de amortiguador de
ensayo; Tubos de muestra, 100 μL de suspensión de membrana, 50 μL de
solución CHA, 50 μL de una solución del compuesto a ser probado (el
15 cual puede prepararse a partir de dilución en serie en un amortiguador de
ensayo de una solución DMSO), 300 μL de amortiguador de ensayo;
Tubos vacíos, 50 μL de solución CHA, 450 μL de amortiguador de
ensayo. Cada tubo se sometió a vórtice durante 10 segundos, se incubó a
23°C durante dos horas, y se filtró usando una Unidad Brandel de
20 Filtración, usando Papel de Filtro Whatman GF/B, se lavó dos veces con 5
mL 50mM Tris. Los discos de filtro se colocaron en 7 mL de recipientes
de cintilleo, los cuales son llenados entonces con aproximadamente 5 mL
de Cóctel de Cintilleo Listo Seguro, y se contó.

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LO QUE SE REIVINDICA ES:

1. El uso de un compuesto de la fórmula

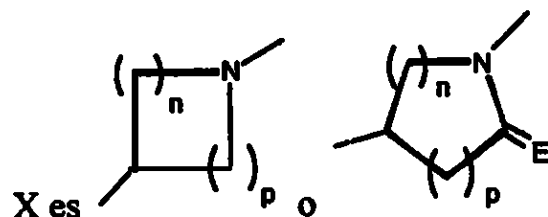


donde:

K es N, N→O, o CH;

Q es CH₂ u O;

- 10 R₆ es hidrógeno, alquil, alilil, 2-metilalil, 2-butenil, o cicloalquil;



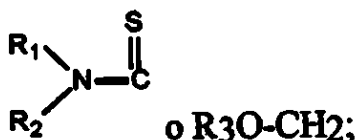
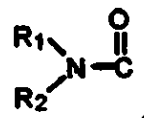
donde el nitrógeno del anillo de X es sustituido por Y;

E es O ó S;

- 15 Y es hidrógeno, alquil, aralquil, aralquil sustituido, aril, aril sustituido, heterociclil, heterociclil sustituido, heterociclilalquil, o heterociclilalquil sustituido;

n y p son independientemente 0, 1, 2, o 3, teniendo en cuenta que n + p es por lo menos 1;

T es hidrógeno, alquil, acil, tioacil, halo, carboxil,



R₁, R₂, y R₃ son independientemente H, alquil, o cicloalquil;

A es hidrógeno, alquil, hidroxialquil, alcoxialquil, o OR';

5 B es hidrógeno, alquil, hidroxialquil, alcoxialquil, o OR'';

R' y R'' son independientemente hidrógeno, alquil, aralquil, carbamoil, alquil carbamoil, dialquilcarbamoil, acil, alcoxicarbonil, aralcoxicarbonil, ariloxicarbonil, o, cuando A y B son OR' y OR'', respectivamente,

10 R' y R'' conjuntamente pueden formar



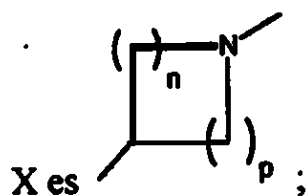
donde R_d y R_e son independientemente hidrógeno, alquil, o
15 conjuntamente con el átomo de carbono al cual están unidos pueden formar un grupo 1,1-cicloalquil;

o una sal de ellos farmacéuticamente aceptable, una pro-droga de ellos farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de
20 ellos o un solvato de ellos para producir una medicina para el tratamiento del síndrome de resistencia a la insulina y diabetes.

2. El uso de un compuesto de acuerdo con la reivindicación 1 donde K es N;

25 T es hidroximetil o metoximetil;

A y B son hidroxil;



y $n + p$ es 3 o 4;

o una sal de ellos farmacéuticamente aceptable, una pro-droga de
5 ellos farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de
ellos o un solvato de ellos.

3. El uso de un compuesto de acuerdo con la reivindicación 1 o 2 que
es (2R,3R,4S,5R)- 5-hidroximetil- 2-[6-[1-(5-cloropiridin-2-il)-pirrolidin-
10 3(S)-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-
pirrolidin-3(R)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-
pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
15 (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(4-trifluorometilpiridin-2-il)-
pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R) 5-hidroximetil-2-[6-[1-(5-bromopiridin-2-il)-pirrolidin-
3(S)-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-(6-(1-(4-nitrofenil)-pirrolidin-3(S)-
20 ilamina)-purin-9-il-tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-(5'-trifluorometil-3,4,5,6-tetrahidro-
2H-[1,2']-bipiridinil-3-ilamina)-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-(fenilpirrolidin-3(S)-ilamina)-purin-9-
il]tetrahidrofuran-3,4-diol,
25 (2R,3R,4S,5R)-5-hidroximetil-2-[6-(1-piridin-2-ilpirrolidin-3(S)-ilamina)-
purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(4-clorofenil)-pirrolidin-3(S)-
ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,

- (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-metilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-thiophen-2-ilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
5 (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-metilmercaptopiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-metoxipirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-cloropirimidin-4-il)pirrolidin-10 3(S)-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-metoximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
15 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)piperidin-4-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-((3S)-pirrolidin-3-ilamina)-purin-9-il]ciclopentano-1,2-diol dihidrocloruro, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)pirrolidin-3-ilamina]-purin-9-il]ciclopentano-1,2-diol,
20 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(R)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-((3R)-pirrolidin-3-ilamina)-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)
25 -3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(5-cloropiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,

- (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(piridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
5 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(quinolin-3-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluorpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
10 (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(fenil)-pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
15 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihidroxi-5-hidroximetilciclopent-3-il)-9H-purin-6-ilamina]pirrolidin-1-il]benzonitrilo,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(isoquinolin-1-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
20 (1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(3-cloro-5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,
25 (1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,
30

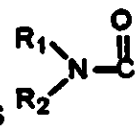
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- (1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(6-metoxipirimidin-4-il)pirrolidin-
3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
5 (1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(4-trifluorometilfenil)-pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamina]-
10 purin-9-il]-5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(5-clorpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-
il]-5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(4-trifluorometilfenil)pirrolidin-
3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
15 (1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-
5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-
5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-
20 5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-fenilpirrolidin-3-(S)-ilamina]-purin-
9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-(1-bencil-pirrolidin-3(S)-ilamina)purin-9-il]-5-
hidroximetilciclopentano-1,2-diol, y
25 (1R,2S,3R,5R)-3-[6-(1-bencil-pirrolidin-3(S)-ilamina)purin-9-il]-5-
metoximetilciclopentano-1,2-diol;

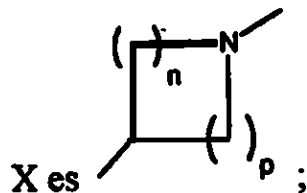
o una sal de ellos farmacéuticamente aceptable, una pro-droga de ellos
farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de ellos o un
solvato de ellos.

4. El uso de un compuesto de acuerdo con las reivindicaciones 1 a 3
donde Q es CH₂;

K es N;

T es , donde R₁ es H y R₂ es alquil inferior;

5 A y B son hidroxi;



y n + p es 3 o 4;

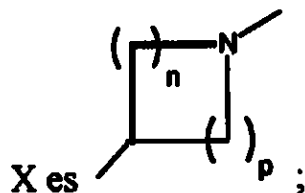
o una sal de ellos farmacéuticamente aceptable, una pro-droga de
ellos farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de
ellos o un solvato de ellos.

5. El uso de un compuesto de acuerdo con la reivindicación 4 que es
(1S,2R,3S,4R)-2,3-dihidroxi-4-[6-[1-(5-trifluormetilpiridin-2-il)pirrolidin-
3-ilamina]-purin-9-il]ciclopentano ácido carboxílico etilamida,
(1S,2R,3S,4R)-2,3-dihidroxi-4-{6-[1-(5-trifluorometil-piridin-2-il)-
pirrolidin-3(S)-ilamina]-purin-9-il}-ciclopentano ácido carboxílico-1(S)-
metilpropilamida, y (1S,2R,3S,4R)- 2,3-dihidroxi-4-{6-[1-(5-
trifluorometil-piridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il}-
ciclopentano ácido carboxílico-1(R)-metilpropilamida; o una sal de ellos
farmacéuticamente aceptable, una pro-droga de ellos farmacéuticamente
aceptable, un N-óxido de ellos, un hidrato de ellos o un solvato de ellos.

6. El uso de un compuesto de acuerdo con la reivindicación 1 donde
Q es CH₂;
K es N;
T es hidroximetil o metoximetil;

119
78 77-1

A y B son hidroxí;



y $n + p$ es 3 o 4;

o una sal de ellos farmacéuticamente aceptable, una pro-droga de
5 ellos farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de
ellos o un solvato de ellos.

7. El uso de un compuesto de acuerdo con la reivindicación 6 que es
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)piperidin-4-ilamina]-
10 purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-((3S)-pirrolidin-3-ilamina)-purin-9-il]
ciclopentano-1,2-diol dihidrocloruro,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)pirrolidin-3-ilamina]-
purin-9-il]ciclopentano-1,2-diol,
15 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-
il)pirrolidin-3(R)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-((3R)-pirrolidin-3-ilamina)-purin-9-il]
ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-
20 il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(5-cloropiridin-2-il)pirrolidin-3(S)-ilamina]-purin-
9-il]-5-hidroximetilciclopentano-1,2-diol,
25 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-trifluorometilpiridin-2-
il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(piridin-2-il)pirrolidin-3(S)-
ilamina]-purin-9-il]ciclopentano-1,2-diol,

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- (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(quinolin-3-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- 5 (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluorpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(fenil)-pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- 10 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihidroxi-5-hidroximetilciclopent-3-il)-9H-purin-6-ilamina]pirrolidin-1-il]benzonitrilo,
- (1R,2S,3R,5R)-5-hidroximetil-5-[6-[1-(isoquinolin-1-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
- 15 (1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-3-[6-[1-(3-cloro-5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,
- 20 (1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,
- 25 (1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
- (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(6-metoxipirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
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123
- (1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(4-trifluorometilfenil)-pirrolidin-3(S)-ilamina]-
purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
5 (1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamina]-
purin-9-il]-5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(5-clorpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-
il]-5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(4-trifluorometilfenil)pirrolidin-
10 3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-
5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-
5-metoximetilciclopentano-1,2-diol,
15 (1R,2S,3R,5R)-3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-
5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-fenilpirrolidin-3(S)-ilamina]-purin-
9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-(1-bencil-pirrolidin-3(S)-ilamina)purin-9-il]-5-
20 hidroximetilciclopentano-1,2-diol, y
(1R,2S,3R,5R)-3-[6-(1-bencil-pirrolidin-3(S)-ilamina)purin-9-il]-5-
metoximetilciclopentano-1,2-diol;
o una sal de ellos farmacéuticamente aceptable, una pro-droga de ellos
farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de ellos o un
25 solvato de ellos.

8. El uso de un compuesto de acuerdo con la reivindicación 6 que es
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-
il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol o

122
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(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol o

una sal de ellos farmacéuticamente aceptable, una pro-droga de ellos farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de ellos o un solvato de ellos.

9. El uso de un compuesto de acuerdo con la reivindicación 6 que es

(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol o

10 (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(4-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol o

una sal de ellos farmacéuticamente aceptable, una pro-droga de ellos farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de ellos o un solvato de ellos.

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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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BARDEHLE PAGENBERG DÖST
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PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

B1	IB
B2	AEW
B3	
Sekr	
EDV	

Date of mailing
(day/month/year)

29.08.2003

Applicant's or agent's file reference
APD61931PC/rg

IMPORTANT NOTIFICATION

International application No.
PCT/EP02/05301

International filing date (day/month/year)
14.05.2002

Priority date (day/month/year)
14.05.2001

Applicant

AVENTIS PHARMA DEUTSCHLAND GMBH

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.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

125
126

Applicant's or agent's file reference APD61931PC/tg	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP0205301	International filing date (day/month/year) 14.05.2002	Priority date (day/month/year) 14.05.2001
International Patent Classification (IPC) or both national classification and IPC A61K31/52, A61P3/10		
Applicant AVENTIS PHARMA DEUTSCHLAND GMBH		

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 4 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 7 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- 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 Rule 63.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting 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 13.12.2002	Date of completion of this report 29.08.2003
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Veronese, A Telephone No. +49 89 2399-7824 

126
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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP02/05301**

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

1-47 as originally filed

Claims, Numbers

1-9 received on 03.06.2003 with letter of 02.06.2003

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:

127
128

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP02/05301**

**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	3-7
	No: Claims	1-2
Inventive step (IS)	Yes: Claims	3-7
	No: Claims	-
Industrial applicability (IA)	Yes: Claims	1-7
	No: Claims	

2. Citations and explanations

see separate sheet

128
129

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty

The present application does not meet the requirements of Article 33(2) PCT, because the subject-matter of claims 1,2 is not new.

WO9924451 discloses (see formula (I-(2)) in claim 1, when R1 is a nitrogen containing heterocycle), adenosine derivatives as defined in the Markush formula of claims 1 and 2 of the present application, X being an heterocycle comprising a nitrogen atom and Y being a C1-3 alkyl. These compounds, which are agonists on the A receptors of adenosine are disclosed in relation to the treatment of diabetes (see page 7, line 25-26). A partial overlap exists between the subject matter disclosed in the prior art and the one claimed in claims 1 and 2 of the present application.

Since the problem underlying the present invention is the same already solved in the prior art, and no new technical effects over the prior art can be identified, the subject matter of claims 1-2 can not be considered new in the sense of Art.33(2) PCT as far as it relates to the compounds defined by the overlapping part of the Markush formula.

Novelty is acknowledged for the compounds defined in claims 1-2 not overlapping with the formula in WO9924451 and for claims 3-9.

Inventive step

Inventive step is acknowledged for the compounds defined in claims 1-2 not overlapping with the formula of WO9924451, and for claims 3-9.

Industrial application.

The subject matter of the application is industrially applicable.

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48

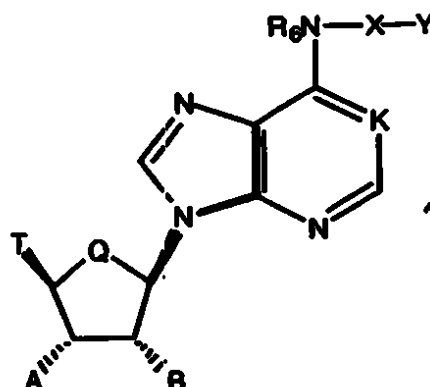
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WHAT IS CLAIMED IS:

NEW SET OF CLAIMS

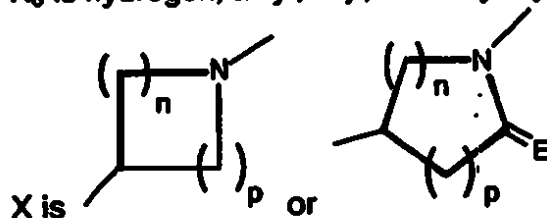
1. Use of a compound of the formula

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wherein:

K is N, N→O, or CH;

Q is CH₂ or O;R₆ is hydrogen, alkyl, allyl, 2-methylallyl, 2-butenyl, or cycloalkyl;

X is

or

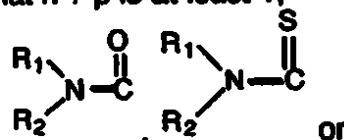
where the nitrogen of the ring of X is substituted by Y;

E is O or S;

Y is hydrogen, alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, or substituted heterocyclylalkyl;

n and p are independently 0, 1, 2, or 3, provided that n + p is at least 1;

T is hydrogen, alkyl, acyl, thioacyl, halo, carboxyl,



or

R₃O-CH₂;R₁, R₂, and R₃ are independently H, alkyl, or cycloalkyl;

A is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or OR';

B is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or OR'';

R' and R'' are independently hydrogen, alkyl, aralkyl, carbamoyl, alkyl carbamoyl,

dialkylcarbamoyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, aryloxycarbonyl, or, when A and B are OR' and OR'', respectively,

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49

137

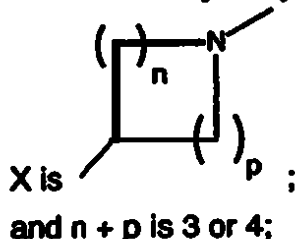
R' and R'' together may form



- 5 where R_d and R_e are independently hydrogen, alkyl, or together with the carbon atom to which they are attached may form a 1,1-cycloalkyl group;

10 or a pharmaceutically acceptable salt thereof, ~~a pharmaceutically acceptable prodrug thereof~~, an N-oxide thereof, a hydrate thereof or a solvate thereof for producing a medicine for the treatment of the insulin resistance syndrome and diabetes.

2. The use of a compound according to claim 1 wherein K is N;
T is hydroxymethyl or methoxymethyl;
15 A and B are hydroxy;



20 or a pharmaceutically acceptable salt thereof, ~~a pharmaceutically acceptable prodrug thereof~~, an N-oxide thereof, a hydrate thereof or a solvate thereof.

3. The use of a compound according to claim 1 or 2 which is (2R,3R,4S,5R)- 5-hydroxymethyl- 2-[6-[1-(5-chloropyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-
25 tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(R)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(4-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R) 5-
30 hydroxymethyl -2-[6-[1-(5-bromopyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl -2-(6-(1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino) -purin-9-yl) tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']-bipyridinyl-3-ylamino)-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(phenylpyrrolidin-3(S)-ylamino)-purin-9-

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50

yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(1-pyridin-2-ylpyrrolidin-3(S)-ylamino)-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-methylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-thiophen-2-ylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-methylmercaptopyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-methoxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)piperidin-4-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3S)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol dihydrochloride, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(R)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3R)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(pyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(quinolin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluoropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(phenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-purin-6-ylamino]pyrrolidin-1-yl]benzonitrile, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(isoquinolin-1-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol,

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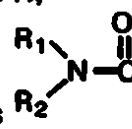
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133

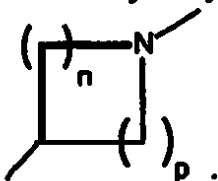
- (1R,2S,3R,5R)-3-[6-[1-(3-chloro-5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-trifluoromethylphenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylphenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-phenylpyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, and (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol; or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

4. The use of a compound according to claims 1 to 3 wherein Q is CH₂;

K is N;

T is , wherein R₁ is H and R₂ is lower alkyl;

A and B are hydroxy;

; and n + p is 3 or 4;

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52

134

or a pharmaceutically acceptable salt thereof, ~~a pharmaceutically acceptable prodrug thereof~~, an N-oxide thereof, a hydrate thereof or a solvate thereof.

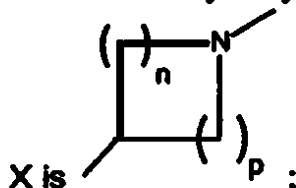
5. The use of a compound according to claim 4 which is (1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentanecarboxylic acid ethylamide, (1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(5-trifluoromethyl-pyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-cyclopentanecarboxylic acid-1(S)-methylpropylamide, and (1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(5-trifluoromethyl-pyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-cyclopentanecarboxylic acid-1(R)-methylpropylamide; or a pharmaceutically acceptable salt thereof, ~~a pharmaceutically acceptable prodrug thereof~~, an N-oxide thereof, a hydrate thereof or a solvate thereof.

6. The use of a compound according to claim 1 wherein Q is CH₂;

K is N;

T is hydroxymethyl or methoxymethyl;

A and B are hydroxy;



and $n + p$ is 3 or 4;

- or a pharmaceutically acceptable salt thereof, ~~a pharmaceutically acceptable prodrug thereof~~, an N-oxide thereof, a hydrate thereof or a solvate thereof.

7. The use of a compound according to claim 6 which is (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)piperidin-4-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3S)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol dihydrochloride, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(R)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3R)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(pyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-

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135

hydroxymethyl-3-[6-[1-(quinolin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluoropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol,
5 (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(phenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-purin-6-ylamino]pyrrolidin-1-yl]benzonitrile, (1R,2S,3R,5R)-5-hydroxymethyl-5-[6-[1-(isoquinolin-1-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chloro-5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol,
10 (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol,
20 (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-trifluoromethylphenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol,
25 (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylphenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol,
30 (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-phenylpyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol,
35 (1R,2S,3R,5R)-3-[6-[1-benzylpyrrolidin-3(S)-ylamino]purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, and (1R,2S,3R,5R)-3-[6-[1-benzylpyrrolidin-3(S)-ylamino]purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol; or a pharmaceutically

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136

acceptable salt thereof, ~~a pharmaceutically acceptable prodrug thereof~~, an N-oxide thereof, a hydrate thereof or a solvate thereof.

8. The use of a compound according to claim 6 which is (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or a pharmaceutically acceptable salt thereof, ~~a pharmaceutically acceptable prodrug thereof~~, an N-oxide thereof, a hydrate thereof or a solvate thereof.

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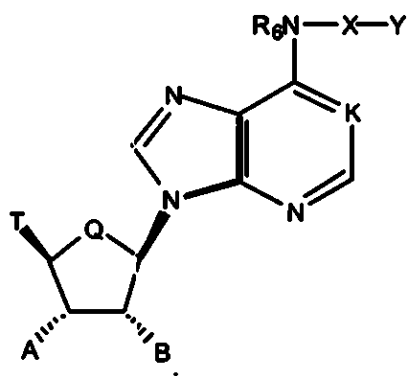
9. The use of a compound according to claim 6 which is (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or a pharmaceutically acceptable salt thereof, ~~a pharmaceutically acceptable prodrug thereof~~, an N-oxide thereof, a hydrate thereof or a solvate thereof.

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AS ENCLOSED TO IPER

WHAT IS CLAIMED IS:

1. Use of a compound of the formula

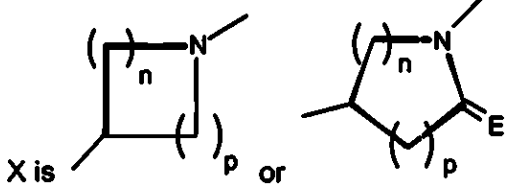


wherein:

K is N, N→O, or CH;

Q is CH₂ or O;

R₆ is hydrogen, alkyl, allyl, 2-methylallyl, 2-butenyl, or cycloalkyl;



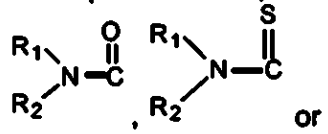
where the nitrogen of the ring of X is substituted by Y;

E is O or S;

Y is hydrogen, alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, or substituted heterocyclylalkyl;

n and p are independently 0, 1, 2, or 3, provided that n + p is at least 1;

T is hydrogen, alkyl, acyl, thioacyl, halo, carboxyl, R₃O-CH₂;



R₁, R₂, and R₃ are independently H, alkyl, or cycloalkyl;

A is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or OR';

B is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or OR'';

R' and R'' are independently hydrogen, alkyl, aralkyl, carbamoyl, alkyl carbamoyl, dialkylcarbamoyl, acyl, alkoxy-carbonyl, aralkoxy-carbonyl, aryloxy-carbonyl, or, when A and B are OR' and OR'', respectively,

R' and R'' together may form



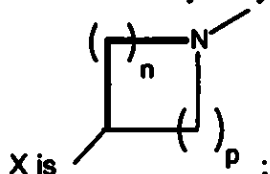
where R_d and R_e are independently hydrogen, alkyl, or together with the carbon atom to which they are attached may form a 1,1-cycloalkyl group;

or a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof for producing a medicine for the treatment of the insulin resistance syndrome and diabetes.

2. The use of a compound according to claim 1 wherein K is N;

T is hydroxymethyl or methoxymethyl;

A and B are hydroxy;



and $n + p$ is 3 or 4;

or a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

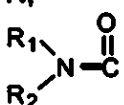
3. The use of a compound according to claim 1 or 2 which is (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-chloropyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(R)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(4-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-bromopyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']-bipyridinyl-3-ylamino)-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(phenylpyrrolidin-3(S)-ylamino)-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-

hydroxymethyl-2-[6-(1-pyridin-2-ylpyrrolidin-3(S)-ylamino)-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-methylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-thiophen-2-ylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-methylmercaptopyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-methoxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)piperidin-4-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3S)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol dihydrochloride, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(R)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3R)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(pyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(quinolin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluoropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(phenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-purin-6-ylamino]pyrrolidin-1-yl]benzonitrile, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(isoquinolin-1-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-

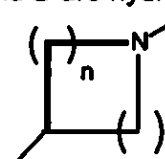
hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chloro-5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-trifluoromethylphenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylphenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-phenylpyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-benzylpyrrolidin-3(S)-ylamino]purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, and (1R,2S,3R,5R)-3-[6-[1-benzylpyrrolidin-3(S)-ylamino]purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol; or a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

4. The use of a compound according to claims 1 to 3 wherein Q is CH₂;

K is N;

T is , wherein R₁ is H and R₂ is lower alkyl;

A and B are hydroxy;

X is ;

and n + p is 3 or 4;

or a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

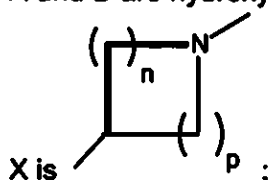
5. The use of a compound according to claim 4 which is (1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentanecarboxylic acid ethylamide, (1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(5-trifluoromethyl-pyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-cyclopentanecarboxylic acid-1(S)-methylpropylamide, and (1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(5-trifluoromethyl-pyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-cyclopentanecarboxylic acid-1(R)-methylpropylamide; or a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

6. The use of a compound according to claim 1 wherein Q is CH₂;

K is N;

T is hydroxymethyl or methoxymethyl;

A and B are hydroxy;



or a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

7. The use of a compound according to claim 6 which is (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)piperidin-4-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3S)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol dihydrochloride, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(R)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3R)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(pyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-

5-hydroxymethyl-3-[6-[1-(quinolin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluoropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(phenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-purin-6-ylamino]pyrrolidin-1-yl]benzonitrile, (1R,2S,3R,5R)-5-hydroxymethyl-5-[6-[1-(isoquinolin-1-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chloro-5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-trifluoromethylphenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylphenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-phenylpyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, and (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]-5-

methoxymethylcyclopentane-1,2-diol; or a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

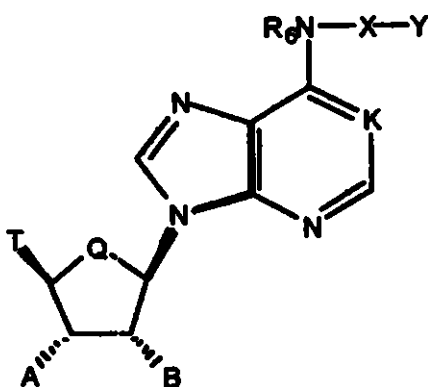
8. The use of a compound according to claim 6 which is (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

9. The use of a compound according to claim 6 which is (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

COMO SE PRESENTÓ A IPER

LO QUE SE REIVINDICA ES:

1. Uso de un compuesto de la fórmula

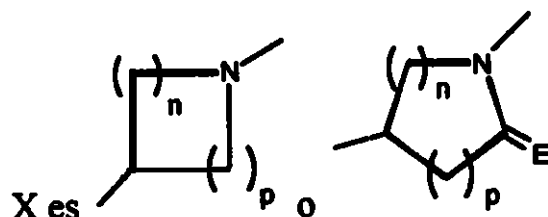


donde:

K es N, N→O, o CH;

Q es CH₂ ó O;

R₆ es hidrógeno, alquil, alilil, 2-metilalilil, 2-butenil, o cicloalquil;



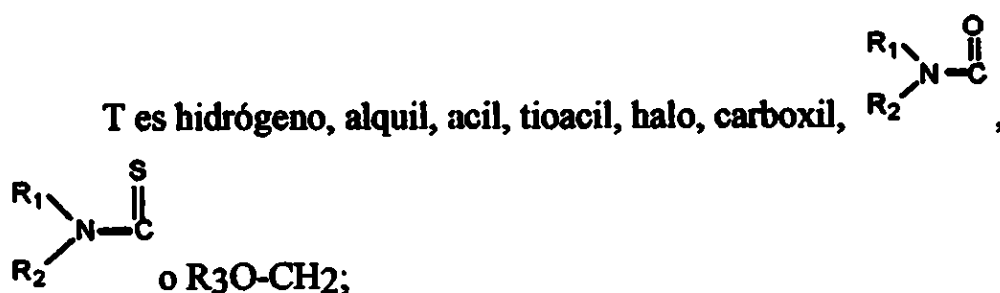
donde el nitrógeno del anillo de X es sustituido por Y;

E es O ó S;

Y es hidrógeno, alquil, aralquil, aralquil sustituido, aril, aril sustituido, heterociclil, heterociclil sustituido, heterociclilalquil, o heterociclilalquil sustituido;

n y p son independientemente 0, 1, 2, o 3, teniendo en cuenta que n + p es por lo menos 1;

144
2
7.45



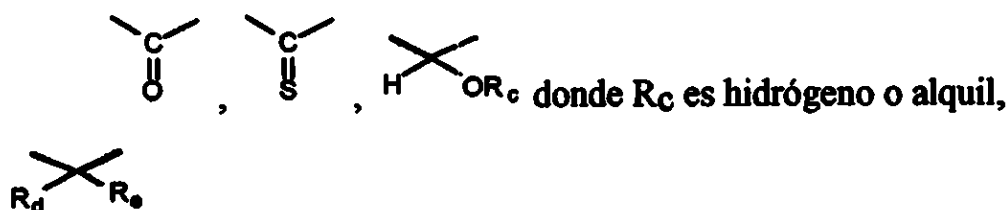
R_1 , R_2 , y R_3 son independientemente H, alquil, o cicloalquil;

A es hidrógeno, alquil, hidroxialquil, alcoxialquil, o OR' ;

B es hidrógeno, alquil, hidroxialquil, alcoxialquil, o OR'' ;

R' y R'' son independientemente hidrógeno, alquil, aralquil, carbamoil, alquil carbamoil, dialquilcarbamoil, acil, alcoxicarbonil, aralcoxicarbonil, ariloxycarbonil, o, cuando A y B son OR' y OR'' , respectivamente,

R' y R'' conjuntamente pueden formar

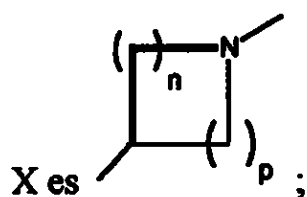


donde R_d y R_e son independientemente hidrógeno, alquil, o conjuntamente con el átomo de carbono al cual están unidos pueden formar un grupo 1,1-cicloalquil;

o una de sus sales farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de ellos o un solvato de ellos para producir una medicina para el tratamiento del síndrome de resistencia a la insulina y diabetes.

2. El uso de un compuesto de acuerdo con la reivindicación 1 donde
 K es N ;
T es hidroximetil o metoximetil;
A y B son hidroxil;

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3
746



y $n + p$ es 3 o 4;

o una de sus sales farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de ellos o un solvato de ellos.

3. El uso de un compuesto de acuerdo con la reivindicación 1 o 2 que es (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-cloropiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-pirrolidin-3(R)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(4-trifluorometilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-bromopiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-(6-(1-(4-nitrofenil)-pirrolidin-3(S)-ilamina)-purin-9-il)-tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-(5'-trifluorometil-3,4,5,6-tetrahidro-2H-[1,2']-bipiridinil-3-ilamina)-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-(fenilpirrolidin-3(S)-ilamina)-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-(1-piridin-2-ilpirrolidin-3(S)-ilamina)-purin-9-il]tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(4-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-metilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,

(2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-tiofen-2-ilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
 (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-metilmercaptopiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
 (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-metoxipirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
 (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
 (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3-ilamina]-purin-9-il]-tetrahidrofuran-3,4-diol,
 (2R,3R,4S,5R)-5-metoximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]tetrahidrofuran-3,4-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)piperidin-4-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-((3S)-pirrolidin-3-ilamina)-purin-9-il]ciclopentano-1,2-diol dihidrocloruro,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)pirrolidin-3-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(R)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-((3R)-pirrolidin-3-ilamina)-purin-9-il]-ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(5-cloropiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,

(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(piridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(quinolin-3-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluorpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(fenil)-pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihidroxi-5-hidroximetilciclopent-3-il)-9H-purin-6-ilamina]pirrolidin-1-il]benzonitrilo,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(isoquinolin-1-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(3-cloro-5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,

148
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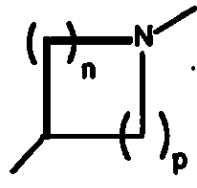
(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(6-metoxipirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(4-trifluorometilfenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(5-chlorpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(4-trifluorometilfenil)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-fenilpirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-(1-bencil-pirrolidin-3(S)-ilamina)purin-9-il]-5-hidroximetilciclopentano-1,2-diol, y
 (1R,2S,3R,5R)-3-[6-(1-bencil-pirrolidin-3(S)-ilamina)purin-9-il]-5-metoximetilciclopentano-1,2-diol;
 o una sal de ellos farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de ellos o un solvato de ellos.

4. El uso de un compuesto de acuerdo con las reivindicaciones 1 a 3 donde Q es CH₂;

K es N;

T es $\begin{array}{c} R_1 \\ \diagup \\ N-C=O \\ \diagdown \\ R_2 \end{array}$, donde R_1 es H y R_2 es alquil inferior;

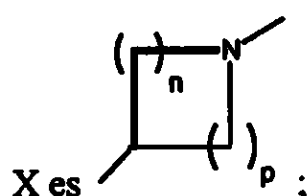
A y B son hidroxi;

X is  ;
and $n + p$ is 3 o 4;

o una sal de ellos farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de ellos o un solvato de ellos.

5. El uso de un compuesto de acuerdo con la reivindicación 4 que es (1S,2R,3S,4R)-2,3-dihidroxi-4-[6-[1-(5-trifluormetilpiridin-2-il)pirrolidin-3-ilamina]-purin-9-il]ciclopentano-ácido carboxílico etilamida, (1S,2R,3S,4R)-2,3-dihidroxi-4-{6-[1-(5-trifluorometil-piridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il}-ciclopentano-ácido carboxílico-1(S)-metilpropilamida, y (1S,2R,3S,4R)-2,3-dihidroxi-4-{6-[1-(5-trifluorometil-piridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il}-ciclopentano-ácido carboxílico-1(R)-metilpropilamida; o una sal de ellos farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de ellos o un solvato de ellos.

6. El use de un compuesto de acuerdo con la reivindicación 1 donde Q es CH_2 ;
K es N;
T es hidroximetil o metoximetil;
A y B son hidroxi;



y $n + p$ es 3 o 4;

o una sal de ellos farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de ellos o un solvato de ellos.

7. El uso de un compuesto de acuerdo con la reivindicación 6 que es
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)piperidin-4-ilamina]-
 purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-((3S)-pirrolidin-3-ilamina)-purin-9-
 il]-ciclopentano-1,2-diol dihidrocloruro,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)pirrolidin-3-ilamina]-
 purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-
 il)pirrolidin-3(R)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-((3R)-pirrolidin-3-ilamina)-purin-9-
 il]-ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-
 il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamina]-
 purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(5-cloropiridin-2-il)pirrolidin-3(S)-ilamina]-
 purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-trifluorometilpiridin-2-
 il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(piridin-2-il)pirrolidin-3(S)-
 ilamina]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(quinolin-3-il)pirrolidin-3(S)-
 ilamina]-purin-9-il]ciclopentano-1,2-diol,

9-447
152

(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluorpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(fenil)-pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihidroxi-5-hidroximetilciclopent-3-il)-9H-purin-6-ilamina]pirrolidin-1-il]benzonitrilo,
(1R,2S,3R,5R)-5-hidroximetil-5-[6-[1-(isoquinolin-1-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(3-cloro-5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(6-metoxipirimidin-4-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,
(1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,

(1R,2S,3R,5R)-3-[6-[1-(4-trifluorometilfenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,

(1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,

(1R,2S,3R,5R)-3-[6-[1-(5-clorpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,

(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(4-trifluorometilfenil)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,

(1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,

(1R,2S,3R,5R)-3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-5-metoximetilciclopentano-1,2-diol,

(1R,2S,3R,5R)-3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamina]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,

(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-fenilpirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol,

(1R,2S,3R,5R)-3-[6-(1-bencil-pirrolidin-3(S)-ilamina)purin-9-il]-5-hidroximetilciclopentano-1,2-diol, y

(1R,2S,3R,5R)-3-[6-(1-bencil-pirrolidin-3(S)-ilamina)purin-9-il]-5-metoximetilciclopentano-1,2-diol;

o una sal de ellos farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de ellos o un solvato de ellos.

8. El uso de un compuesto de acuerdo con la reivindicación 6 que es (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol o

(1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-trifluorometilpiridin-2-il)-pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol

o una de sus sales farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de ellos o un solvato de ellos.

103
154

9. El uso de un compuesto de acuerdo con la reivindicación 6 que es
(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol o
(1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(4-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamina]-purin-9-il]ciclopentano-1,2-diol
o una de sus sales farmacéuticamente aceptable, un N-óxido de ellos, un hidrato de ellos o un solvato de ellos.

PATENT COOPERATION TREATY

154
195

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

ISENBRUCK, Günter
Patent- und Rechtsanwälte
Bardehle Pagenberg & Co. Rechtsanwälte
Altenburg Geissler Isenbrück
Theodor-Heuss-Anlage 12
68165 Mannheim
Germany

Frist:
Bear:

Date of mailing (day/month/year)

25 September 2002 (25.09.02)

Applicant's or agent's file reference

APD6193PC

IMPORTANT NOTIFICATION

International application No.

PCT/EP02/05301

International filing date (day/month/year)

14 May 2002 (14.05.02)

International publication date (day/month/year)

Not yet published

Priority date (day/month/year)

14 May 2001 (14.05.01)

Applicant

AVENTIS PHARMA DEUTSCHLAND GMBH

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date

Priority application No.

Country or regional Office
or PCT receiving Office

Date of receipt
of priority document

14 May 2001 (14.05.01)

01111651.4

EP

27 June 2002 (27.06.02)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Annick TOUSSAINT (Fax : 338 89 75)

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

WO 02/092093
PCT/EP02/05301

156

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

ISENBRUCK, Günter
Patent- und Rechtsanwälte
Bardehle Pagenberg Dost
Altenburg Geissler Isenbruck
Theodor-Heuss-Anlage 12
68165 Mannheim
Germany

Date of mailing (day/month/year) 21 November 2002 (21.11.02)		IMPORTANT NOTICE	
Applicant's or agent's file reference APD6193PC			
International application No. PCT/EP02/05301	International filing date (day/month/year) 14 May 2002 (14.05.02)	Priority date (day/month/year) 14 May 2001 (14.05.01)	
Applicant AVENTIS PHARMA DEUTSCHLAND GMBH			

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:
KP, KR

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 21 November 2002 (21.11.02) under No. WO 02/092093

4. **TIME LIMITS** for filing a demand for international preliminary examination and for entry into national phase

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of the designated Office. For further details, see PCT Gazette No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette, the PCT Newsletter and the PCT Applicant's Guide, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the PCT Applicant's Guide, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II.)

It is the applicant's sole responsibility to monitor all these limits.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.91.11

Continuation of Form PCT/IB/308

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF
THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

154

Date of mailing (day/month/year) 21 November 2002 (21.11.02)	IMPORTANT NOTICE
Applicant's or agent's file reference APD6193PC	International application No. PCT/EP02/05301

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

PATENT COOPERATION TREATY

158

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

ISENBRUCK, Günter
BARDEHLE PAGENBERG DOST
ALTENBURG GEISSLER
Theodor-Heuss-Anlage 12
D-68165 Mannheim
ALLEMAGNE

Patent- u. Rechtsanwälte
Mannheim

23. Dez. 2002

Frist
Beiro.

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year)

20-12-2002

Applicant's or agent's file reference

APD61931PC/rg

IMPORTANT NOTIFICATION

International application No.

PCT/EP 02/ 05301

International filing date (day/month/year)

14/05/2002

Priority date (day/month/year)

14/05/2001

Applicant

AVENTIS PHARMA DEUTSCHLAND GMBH

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

13/12/2002

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide, Volume II*.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

LODOLO F

Tel. (+49-89) 2399-2039



PATENT COOPERATION TREATY

159

PCT

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION(PCT Rule 61.3)
Isenbruck, Günter
Wichmann, Huhn, Patentanwälte
Theodor-Heuss-Anlage 12
68165 Mannheim
Germany

From the INTERNATIONAL BUREAU

To:

ISENBRUCK, Günter
Patent- und Rechtsanwälte
Bardehle Pagenberg Dost
Altenburg Geissler Isenbruck
Theodor-Heuss-Anlage 12
68165 Mannheim
Germany

B1

B2

B3

Sekt

EDV

Abg.

Date of mailing (day/month/year)

25 March 2003 (25.03.03)

Applicant's or agent's file reference

APD6193PC

IMPORTANT INFORMATION

International application No.

PCT/EP02/05301

International filing date (day/month/year)

14 May 2002 (14.05.02)

Priority date (day/month/year)

14 May 2001 (14.05.01)

Applicant

AVENTIS PHARMA DEUTSCHLAND GMBH

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

National : AU, BG, CA, CN, DE, GB, IL, JP, KP, KR, MN, NO, PL, RO, RU, SK

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG

National : AE, AG, AL, AM, AT, AZ, BA, BB, BR, BY, BZ, CH, CO, CR, CU, CZ, DK, DM, DZ, EC, EE,

ES, FI, GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,

MK, MW, MX, MZ, NZ, OM, PH, PT, SD, SE, SG, SI, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU,

ZA, ZM, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.89.75

Authorized officer:

Rosana REYES (Fax : 338 89 75)

Telephone No. (41-22) 338 8471



2020
Bogotá, D.C.,

Doctor:
GUSTAVO HOLLMANN RESTREPO
Apoderado
AVENTIS PHARMA DEUTSCHLAND GmbH

Oficio N° 11432

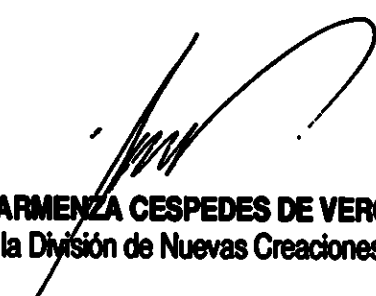
ASUNTO:	Radicación N°	03-100204
	Solicitud internacional	PCT/EP02/05301
	Fecha inicio fase nacional	14/12/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en 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).

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.

26 DIC. 2003

El anterior requerimiento fue notificado por fijación en lista de fecha, _____.

G. HOLLMANN RESTREPO

ABOGADOS LTDA.

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1671

Radicación : 03100204 00000001
Fecha (AMD): 2003-11-26 16:27:26
Trámite : 011 PCI-PATENT 379 FASE MACI 329 COMPLEMEN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Folios: 27

55274

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E.

S.

D.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

B1	JB
B2	AEW
B3	
Sekr	
EDV	

Date of mailing
(day/month/year)

29.08.2003

Applicant's or agent's file reference
APD61931PC/rq

IMPORTANT NOTIFICATION

International application No.
PCT/EP0205301

International filing date (day/month/year)
14.05.2002

Priority date (day/month/year)
14.05.2001

Applicant
AVENTIS PHARMA DEUTSCHLAND GMBH

- 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.
- A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- 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.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the International
preliminary examining authority:



European Patent Office
D-80298 Munich
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Authorized Officer

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference APD61931PC/tg	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP02/05301	International filing date (day/month/year) 14.05.2002	Priority date (day/month/year) 14.05.2001
International Patent Classification (IPC) or both national classification and IPC A61K31/52, A61P3/10		
Applicant AVENTIS PHARMA DEUTSCHLAND GMBH		

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 4 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 7 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- 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 Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting 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 13.12.2002	Date of completion of this report 29.08.2003
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Veronese, A Telephone No. +49 89 2399-7824 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP02/05301**

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

1-47 as originally filed

Claims, Numbers

1-9 received on 03.06.2003 with letter of 02.06.2003

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:

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165

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP02/05301**

**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	3-7
	No: Claims	1-2
Inventive step (IS)	Yes: Claims	3-7
	No: Claims	-
Industrial applicability (IA)	Yes: Claims	1-7
	No: Claims	

2. Citations and explanations

see separate sheet

165
x
166

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty

The present application does not meet the requirements of Article 33(2) PCT, because the subject-matter of claims 1,2 is not new.

WO9924451 discloses (see formula (I-(2)) in claim 1, when R1 is a nitrogen containing heterocycle), adenosine derivatives as defined in the Markush formula of claims 1 and 2 of the present application, X being an heterocycle comprising a nitrogen atom and Y being a C1-3 alkyl. These compounds, which are agonists on the A receptors of adenosine are disclosed in relation to the treatment of diabetes (see page 7, line 25-26). A partial overlap exists between the subject matter disclosed in the prior art and the one claimed in claims 1 and 2 of the present application.

Since the problem underlying the present invention is the same already solved in the prior art, and no new technical effects over the prior art can be identified, the subject matter of claims 1-2 can not be considered new in the sense of Art.33(2) PCT as far as it relates to the compounds defined by the overlapping part of the Markush formula.

Novelty is acknowledged for the compounds defined in claims 1-2 not overlapping with the formula in WO9924451 and for claims 3-9.

Inventive step

Inventive step is acknowledged for the compounds defined in claims 1-2 not overlapping with the formula of WO9924451, and for claims 3-9.

Industrial application.

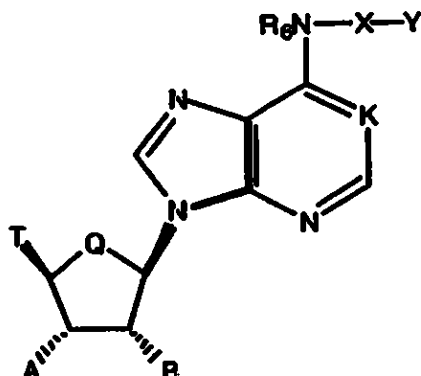
The subject matter of the application is industrially applicable.

WHAT IS CLAIMED IS:

NEW SET OF CLAIMS

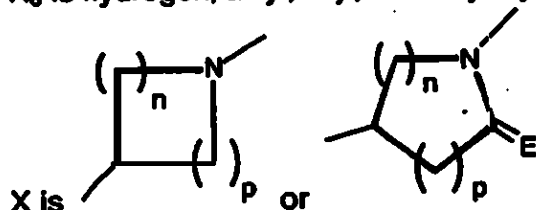
1. Use of a compound of the formula

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wherein:

K is N, N→O, or CH;

Q is CH₂ or O;R₆ is hydrogen, alkyl, allyl, 2-methylallyl, 2-butenyl, or cycloalkyl;

X is

or

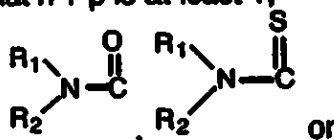
where the nitrogen of the ring of X is substituted by Y;

E is O or S;

Y is hydrogen, alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, or substituted heterocyclylalkyl;

n and p are independently 0, 1, 2, or 3, provided that n + p is at least 1;

T is hydrogen, alkyl, acyl, thioacyl, halo, carboxyl,



or

R₃O-CH₂;R₁, R₂, and R₃ are independently H, alkyl, or cycloalkyl;

A is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or OR';

B is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or OR'';

R' and R'' are independently hydrogen, alkyl, aralkyl, carbamoyl, alkyl carbamoyl, dialkylcarbamoyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, aryloxycarbonyl, or, when A and B are OR' and OR'', respectively,

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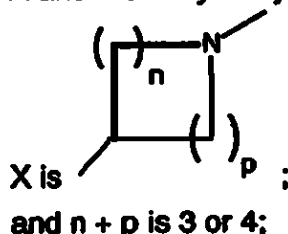
R' and R'' together may form



where R_d and R_e are independently hydrogen, alkyl, or together with the carbon atom to which they are attached may form a 1,1-cycloalkyl group;

or a pharmaceutically acceptable salt thereof, ~~a pharmaceutically acceptable prodrug thereof~~, an N-oxide thereof, a hydrate thereof or a solvate thereof for producing a medicine for the treatment of the insulin resistance syndrome and diabetes.

2. The use of a compound according to claim 1 wherein K is N;
T is hydroxymethyl or methoxymethyl;
A and B are hydroxy;



or a pharmaceutically acceptable salt thereof, ~~a pharmaceutically acceptable prodrug thereof~~, an N-oxide thereof, a hydrate thereof or a solvate thereof.

3. The use of a compound according to claim 1 or 2 which is (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-chloropyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(R)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(4-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-bromopyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-(6-(1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino)-purin-9-yl) tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']-bipyridinyl-3-ylamino)-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(phenylpyrrolidin-3(S)-ylamino)-purin-9-

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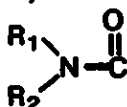
yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-(1-pyridin-2-ylpyrrolidin-3(S)-ylamino)-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-methylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-thiophen-2-ylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(5-methylmercaptopyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-hydroxymethyl-2-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-5-methoxymethyl-2-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)piperidin-4-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3S)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol dihydrochloride, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(R)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3R)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(pyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(quinolin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluoropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(phenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-purin-6-ylamino]pyrrolidin-1-yl]benzonitrile, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(isoquinolin-1-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol,

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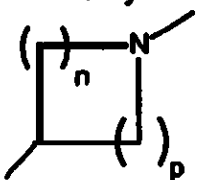
- (1R,2S,3R,5R)-3-[6-[1-(3-chloro-5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-trifluoromethylphenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylphenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-phenylpyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, and (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol; or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

4. The use of a compound according to claims 1 to 3 wherein Q is CH₂;

K is N;

T is , wherein R₁ is H and R₂ is lower alkyl;

A and B are hydroxy;

X is ; and n + p is 3 or 4;

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771

or a pharmaceutically acceptable salt thereof, ~~a pharmaceutically acceptable prodrug thereof~~, an N-oxide thereof, a hydrate thereof or a solvate thereof.

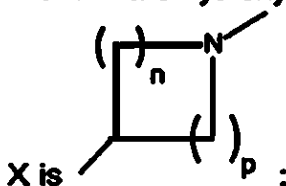
5. The use of a compound according to claim 4 which is (1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentanecarboxylic acid ethylamide, (1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-cyclopentanecarboxylic acid-1(S)-methylpropylamide, and (1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-cyclopentanecarboxylic acid-1(R)-methylpropylamide; or a pharmaceutically acceptable salt thereof, ~~a pharmaceutically acceptable prodrug thereof~~, an N-oxide thereof, a hydrate thereof or a solvate thereof.

6. The use of a compound according to claim 1 wherein Q is CH₂;

K is N;

T is hydroxymethyl or methoxymethyl;

A and B are hydroxy;



and $n + p$ is 3 or 4;

or a pharmaceutically acceptable salt thereof, ~~a pharmaceutically acceptable prodrug thereof~~, an N-oxide thereof, a hydrate thereof or a solvate thereof.

7. The use of a compound according to claim 6 which is (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)piperidin-4-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3S)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol dihydrochloride, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(R)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-((3R)-pyrrolidin-3-ylamino)-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(pyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-

AMENDED SHEET

hydroxymethyl-3-[6-[1-(quinolin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluoropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol,
5 (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(phenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihydroxy-5-hydroxymethylcyclopent-3-yl)-9H-purin-6-ylamino]pyrrolidin-1-yl]benzonitrile, (1R,2S,3R,5R)-5-hydroxymethyl-5-[6-[1-(isoquinolin-1-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-bromoquinolin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chloro-5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol,
20 (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-trifluoromethylphenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol,
25 (1R,2S,3R,5R)-3-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylphenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol,
30 (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-phenylpyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-benzylpyrrolidin-3(S)-ylamino]purin-9-yl]-5-hydroxymethylcyclopentane-1,2-diol, and (1R,2S,3R,5R)-3-[6-[1-benzylpyrrolidin-3(S)-ylamino]purin-9-yl]-5-methoxymethylcyclopentane-1,2-diol; or a pharmaceutically

AMENDED SHEET

acceptable salt thereof, ~~a pharmaceutically acceptable prodrug thereof~~, an N-oxide thereof, a hydrate thereof or a solvate thereof.

8. The use of a compound according to claim 6 which is (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or (1R,2S,3R,5R)-5-hydroxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or a pharmaceutically acceptable salt thereof, ~~a pharmaceutically acceptable prodrug thereof~~, an N-oxide thereof, a hydrate thereof or a solvate thereof.

10

9. The use of a compound according to claim 6 which is (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or (1R,2S,3R,5R)-5-methoxymethyl-3-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or a pharmaceutically acceptable salt thereof, ~~a pharmaceutically acceptable prodrug thereof~~, an N-oxide thereof, a hydrate thereof or a solvate thereof.

AMENDED SHEET

TRATADO DE COOPERACION EN PATENTES

PCT

REPORTE DEL EXAMEN INTERNACIONAL PRELIMINAR

(Artículo 36 y Norma 70 PCT)

Referencia del solicitante o abogado: APD61931PC/rg

PROCEDIMIENTO ADICIONAL: Ver Notificación sobre el envío del reporte de examen internacional provisional (Formulario PCT/IPEA/416)

No. de referencia internacional: PCT/EP02/05301

Fecha de solicitud internacional: 14.05.2002

Fecha de prioridad: 14.05.2001

Clasificación Internacional de Patentes (IPC) o Clasificación Nacional e IPC: A61K31/52, A61P3/10

Solicitante: AVENTIS PHARMA DEUTSCHLAND GMBH

1. La autoridad encargada del examen internacional provisional elaboró el reporte del examen internacional provisional y lo envió al solicitante de conformidad con el Artículo 36.

2. Este REPORTE comprende en total 4 hojas incluyendo esta hoja de cubierta

X Además se adjuntan a este reporte ANEXOS; se trata de hojas con descripciones, reivindicaciones y/o dibujos que fueron modificados y son fundamento de este reporte, y/u hojas con correcciones efectuadas por esta autoridad (ver Norma 70.16 y Sección 607 de las Pautas Administrativas del PCT).

Estos Anexos comprenden en total 7 hojas.

3. Este reporte contiene informaciones y las correspondientes páginas respecto a los siguientes puntos:

I X Base del reporte

II _ Prioridad

III _ Ninguna elaboración de un reporte sobre la novedad, la actividad inventiva y la aplicabilidad industrial

IV _ Falta de unidad de la invención

V X Verificación fundamentada conforme el artículo 35(2) respecto a la novedad, la actividad inventiva y la aplicabilidad industrial; documentos y explicaciones para apoyar dicha verificación

- VI _ Determinados documentos citados
- VII _ Determinadas deficiencias de la solicitud internacional
- VIII _ Determinadas observaciones a la solicitud internacional

Fecha de entrega de la solicitud de examen preliminar internacional:
13.12.2002

Fecha de terminación de este reporte:
29.08.2003

Nombre y dirección postal de la autoridad encargada del examen internacional de provisional:

Oficina Europea de Patentes
D-80298 Munich

Funcionario autorizado:
Veronese, A

REPORTE DEL EXAMEN INTERNACIONAL PROVISIONAL

No. de referencia internacional PCT/EP02/05301

I. Base del reporte**1. Respecto a los elementos de la solicitud internacional:**

Descripción, Páginas

1-47, tal cual fue presentada

Reivindicaciones, Números

1-9, recibidas el 03.06.2003 con comunicación del 02.06.2003

2. Respecto al idioma, todos los elementos marcados arriba fueron suministrados a esta Autoridad en el idioma en que fue presentada la solicitud internacional, a menos que se indique otra cosa distinta en este punto.

Estos elementos fueron suministrados a esta Autoridad en el idioma _____ que es:

- ☐ el idioma de una traducción suministrado para fines de la búsqueda internacional (Norma 23.1(b))
 - ☐ el idioma de publicación de la solicitud internacional (Norma 48.3(b))
 - ☐ el idioma de la traducción entregada para fines de el examen preliminar internacional (Norma 55.2 y/o 55.3)
3. Respecto a la secuencia nucleótida y/o de aminoácidos revelada en la solicitud internacional, el examen internacional provisional se llevó a cabo sobre la base del protocolo de secuencia que:
- ☐ está contenido en forma escrita en la solicitud internacional.
 - ☐ fue entregado junto con la solicitud internacional en forma legible por computadora.
 - ☐ fue entregado posteriormente a la autoridad en forma escrita.
 - ☐ fue entregado posteriormente a la autoridad en forma legible por computadora.
 - ☐ Se presentó la declaración de que el protocolo de secuencia escrito entregado posteriormente no va más allá del contenido revelado en la solicitud internacional.
 - ☐ Se presentó la declaración de que las informaciones registradas en forma legible por computadora corresponden al protocolo de secuencia escrito.

4. ☐ Las enmiendas han resultado en la cancelación de:

- ☐ la descripción, páginas
- ☐ las reivindicaciones, No.
- ☐ los dibujos, hojas

5. ☐ Este reporte se ha establecido como si (algunas de) las enmiendas no se hubieran hecho, ya que se considera que ellas van más allá de la revelación presentada, como se indica en la Casilla Suplementaria (Norma 70.2(c)).

6. Observaciones adicionales, si fueren necesarias: -

V. Verificación fundamentada de conformidad con el Artículo 35(2) respecto a novedad, actividad inventiva y aplicabilidad industrial; documentos y explicaciones para sustentar esta verificación

1. Verificación

Novedad	Sí: Reivindicaciones	3-7
	No: Reivindicaciones	1-2
Actividad inventiva	Sí: Reivindicaciones	3-7
	No: Reivindicaciones	-
Aplicabilidad industrial	Sí: Reivindicaciones	1-7
	No: Reivindicaciones	

2. Documentos y explicaciones

Ver Hoja Separada

HOJA SEPARADAPunto V

Verificación fundamentada de conformidad con el Artículo 35(2) respecto a novedad, actividad inventiva y aplicabilidad industrial; documentos y explicaciones para sustentar esta verificación

Novedad

La presente solicitud no cumple con los requisitos del Artículo 33(2) PCT porque el asunto de las reivindicaciones 1, 2 no es nuevo. WO9924451 revela (ver fórmula (I-(2) en reivindicación 1, cuando R1 es un heterociclo que contiene nitrógeno) derivados de adenosina según ellos son definidos en la fórmula de Markush de las reivindicaciones 1 y 2 de la presente solicitud, siendo X un heterociclo que comprende un átomo de nitrógeno y siendo Y un alquilo C1-3. Estos compuestos, que son agonistas en los receptores A de adenosina son revelados en relación con el tratamiento de diabetes (ver página 7, línea 25-26). Existe un traslapamiento parcial entre el asunto revelado en la técnica anterior y el reivindicado en las reivindicaciones 1 y 2 de la presente solicitud.

Como el problema subyacente a la presente invención es el mismo ya resuelto en la técnica anterior, y como no se pueden identificar ningunos efectos técnicos nuevos en comparación con la técnica anterior, entonces el asunto de las reivindicaciones 1-2 no se puede considerar nuevo en el sentido del Artículo 33(2) PCT ya que se refiere a los compuestos definidos por la parte traslapante de la fórmula de Markush.

Se reconoce novedad para los compuestos definidos las reivindicaciones 1-2 que no se traslapan con la fórmula de WO9924451 y para las reivindicaciones 3-9.

Actividad inventiva

Se reconoce actividad inventiva para los compuestos definidos en las reivindicaciones 1-2 que no se traslapan con la fórmula de WO9924451 y para las reivindicaciones 3-9.

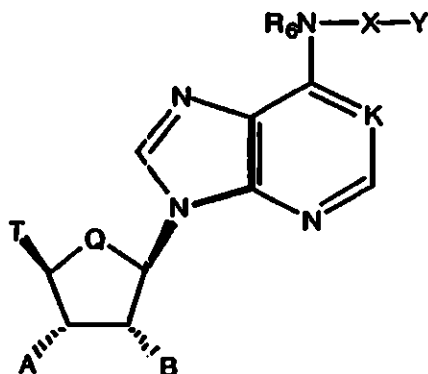
Aplicabilidad industrial

El asunto de la solicitud es aplicable industrialmente.

HOJAS ENMENDADAS

NUEVAS REIVINDICACIONES

1. Uso de un compuesto de la fórmula

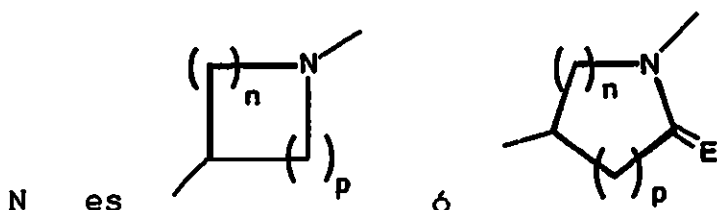


en donde

K es N, N-O ó CH;

Q es CH₂ u O;

R₆ es hidrógeno, alquilo, alilo, 2-metilalilo, 2-butenilo ó cicloalquilo;



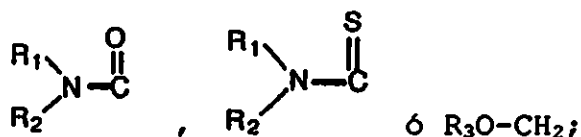
donde el nitrógeno del anillo de X está substituido por Y;

E es O ó S;

Y es hidrógeno, alquilo, aralquilo, aralquilo substituido, arilo, arilo substituido, heterociclilo, heterociclilo substituido, heterociclilalquilo o heterociclilalquilo substituido;

n y p son independientemente 0, 1, 2 ó 3, a condición de que n + p es por lo menos 1;

T es hidrógeno, alquilo, acilo, tioacilo, halo, carboxilo



R₁, R₂ y R₃ son independientemente H, alquilo, cicloalquilo;

A es hidrógeno, alquilo, hidroxialquilo, alcoxialquilo ó OR';

R' y R" son independientemente hidrógeno, alquilo, aralquilo, carbamoilo, alquilcarbamoilo, dialquilcarbamoilo, acilo, alcoxycarbonilo, aralcoxycarbonilo, ariloxycarbonilo, ó cuando A y B son respectivamente OR' y OR" entonces R' y R" conjuntamente pueden formar



o una sal farmacéuticamente aceptable de dicho compuesto, de un N-óxido de éste, de un hidrato de éste o de un solvato de éste para producir una medicina para el tratamiento del síndrome de resistencia a la insulina y de la diabetes.

A y B son hidroxí;



3. El uso de un compuesto de acuerdo con la reivindicación 1 o 2, el cual es (2R,3R,4S,5R)-5-hidroxi metil-2-[6-[1-(5-cloropiridin-2-il)-pirrolidin-3(S)-ilamino]-purin-9-il]-

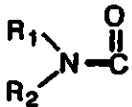
tetrahidrofuran-3,4-diol, (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-pirrolidin-3(R)-ilamino]-purin-9-il]tetrahidrofuran-3,4-diol, (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-pirrolidin-3(S)-ilamino]-purin-9-il]tetrahidrofuran-3,4-diol, (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(4-trifluorometilpiridin-2-il)-pirrolidin-3(S)-ilamino]-purin-9-il]tetrahidrofuran-3,4-diol, (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-bromopiridin-2-il)-pirrolidin-3(S)-ilamino]-purin-9-il]-tetrahidrofuran-3,4-diol, (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(4-nitrofenil)-pirrolidin-3(S)-ilamino]-purin-9-il]-tetrahidrofuran-3,4-diol, (2R,3R,4S,5R)-5-hidroximetil-2-[6-(5'-trifluorometil-3,4,5,6-tetrahidro-2H[1,2']-bipiridinil-3-ilamino)-purin-9-il]tetrahidrofuran-3,4-diol, (2R,3R,4S,5R)-5-hidroximetil-2-[6-(fenilpirrolidin-3(S)-ilamino)-purin-9-il]tetrahidrofuran-3,4-diol, (2R,3R,4S,5R)-5-hidroximetil-2-[6-(1-piridinil-2-ilpirrolidin-3(S)-ilamino)-purin-9-il]tetrahidrofuran-3,4-diol, (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(4-clorofenil)-pirrolidin-3(S)-ilamino]-purin-9-il]tetrahidrofuran-3,4-diol, (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-metilpiridin-2-il)-pirrolidin-3(S)-ilamino]-purin-9-il]tetrahidrofuran-3,4-diol, (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-tiofen-2-ilpiridin-2-il)-pirrolidin-3(S)-ilamino]-purin-9-il]tetrahidrofuran-3,4-diol, (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(5-metilmercaptopiridin-2-il)-pirrolidin-3(S)-ilamino]-purin-9-il]tetrahidrofuran-3,4-diol, (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-metoxipirimidin-4-il)-pirrolidin-3(S)-ilamino]-purin-9-il]tetrahidrofuran-3,4-diol, (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-cloropirimidin-4-il)-pirrolidin-3(S)-ilamino]-purin-9-il]tetrahidrofuran-3,4-diol, (2R,3R,4S,5R)-5-hidroximetil-2-[6-[1-(6-cloropiridazin-3-il)-pirrolidin-3(S)-ilamino]-purin-9-il]tetrahidrofuran-3,4-diol, (2R,3R,4S,5R)-5-metoximetil-2-[6-[1-(5-trifluorometilpiridin-2-il)-pirrolidin-3(S)-ilamino]-purin-9-il]tetrahidrofuran-3,4-diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)piperidin-4-ilamino]-purin-9-

il]ciclopentano-1,2-diol, dihidrocloruro de (1R,2S,3R,5R)-5-
 hidroximetil-3-[6-((3S)-pirrolidin-3-ilamino)-purin-9-
 il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-
 [1-(4-nitrofenil)pirrolidin-3-ilamino]-purin-9-il]ciclopentano-
 1,2-diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-
 trifluorometilpiridin-2-il)pirrolidin-3(R)-ilamino]-purin-9-
 il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-
 ((3R)-pirrolidin-3-ilamino)-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-
 2-il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-
 diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-
 3(S)-ilamino]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(5-cloropiridin-2-il)pirrolidin-3(S)-
 ilamino]-purin-9-il]5-hidroximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-trifluorometilpiridin-
 2-il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-
 diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(piridin-2-
 il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(quinolin-3-il)pirro-
 lidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)-pirroli-
 din-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluoropiridin-2-il)pirro-
 lidin-3(S)-ilamino]-purin-9-il]-5-hidroximetilciclopentano-
 1,2-diol, (1R,2S,3R,5R)-5-metoxi-metil-3-[6-[1-(5-trifluoro-
 metilpiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclo-
 pentano-1,2-diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-
 (fenil)-pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-
 diol, 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihidroxi-5-hidroximetil-
 ciclopent-3-il)-9H-purin-6-ilamino]-pirrolidin-1-il]benzo-
 nitrilo, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(isoquinolin-1-
 il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(bromquinolin-2-il)pirrolidin-3(S)-
 ilamino]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol,
 (1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)pirrolidin-3(S)-ilamino]-

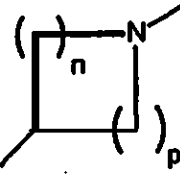
purin-9-il]-5-hidroximetilciclopentano-1,2-diol, (1R, 2S, 3R, 5R)-3-[6-[1-(3-cloro-5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-metoximetilciclopentano-1,2-diol, (1R, 2S, 3R, 5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol, (1R, 2S, 3R, 5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol, (1R, 2S, 3R, 5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-metoximetilciclopentano-1,2-diol, (1R, 2S, 3R, 5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol, (1R, 2S, 3R, 5R)-5-metoxi-metil-3-[6-[1-(metoxipirimidin-4-il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol, (1R, 2S, 3R, 5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-metoximetilciclopentano-1,2-diol, (1R, 2S, 3R, 5R)-3-[6-[1-(4-trifluorometilfenil)pirrolidin-3(S)-ilamino-purin-9-il]-5-hidroximetilciclopentano-1,2-diol, (1R, 2S, 3R, 5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-metoximetilciclopentano-1,2-diol, (1R, 2S, 3R, 5R)-3-[6-[1-(5-clorpiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-metoximetilciclopentano-1,2-diol, (1R, 2S, 3R, 5R)-5-metoximetil-3-[6-[1-(4-trifluorometilfenil)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol, (1R, 2S, 3R, 5R)-3-[6-[1-(4-clorofenil)-pirrolidin-3(s)-ilamino]- purin-9-il]-5-metoximetilciclopentano-1,2-diol, (1R, 2S, 3R, 5R)-3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamino]-purin-9-il]-5-metoximetilciclopentano-1,2-diol, (1R, 2S, 3R, 5R)- 3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamino]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol, (1R, 2S, 3R5R)-5-metoximetil-3-[6-[1-fenilpirrolidin-3-(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol, (1R, 2S, 3R, 5R)-3-[6-(1-benzil-pirrolidin-3(S)-ilamino)purin-9-il]-5-hidroximetilciclopentano-1,2-diol y (1R, 2S, 3R, 5R)-3-[6-(1-benzil-pirrolidin-3(S)-ilamino)purin-il]-5-metoximetilciclopentano-1,2-diol;

o una sal farmacéuticamente aceptable de dicho compuesto, un N-óxido de éste, un hidrato de éste o un solvato de éste.

4. El uso de un compuesto de acuerdo con las reivindicaciones 1 a 3, en donde Q es CH₂; K es N;

T es , en donde R₁ es H y R₂ es alquilo inferior;

A es hidroxil;

X es ; n + p es 3 ó 4;

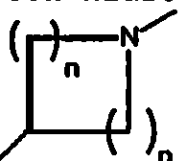
o una sal farmacéuticamente aceptable de dicho compuesto, un N-óxido de éste, un hidrato de éste o un solvato de éste.

5. El uso de un compuesto de acuerdo con la reivindicación 4, el cual es etilamida de ácido (1S,2R,3S,4R)-2,3-dihidroxi-4-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3-ilamino]-purin-9-il]ciclopentanocarboxílico, 1(S)-metilpropilamida de ácido (1S,2R,3S,4R)-2,3-dihidroxi-4-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentanocarboxílico y 1(R)-metilpropilamida de ácido (1S,2R,3S,4R)-2,3-dihidroxi-4-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-carboxílico;

o una sal farmacéuticamente aceptable de dicho compuesto, un N-óxido de éste, un hidrato de éste o un solvato de éste.

6. El uso de un compuesto de acuerdo con la reivindicación 1, en donde Q es CH₂; K es N; T es hidroximetil o metoximetil;

A y B son hidroxil;

X es ; y n + p es 3 ó 4;

o una sal farmacéuticamente aceptable de dicho compuesto, un N-óxido de éste, un hidrato de éste o un solvato de éste.

184 25
185

7. El uso de un compuesto de acuerdo con la reivindicación 6, el cual es (1R,2S,3R,5R)-5-hidroximetil-3-[6-1-(4-nitrofenil)-piperidin-4-ilamino]-purin-9-il]ciclopentano-1,2-diol, dihidrocloruro de (1R,2S,3R,5R)-5-hidroximetil-3-[6-((3S)-pirrolidin-3-ilamino)-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)pirrolidin-3-ilamino]-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(R)-ilamino]-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-((3R)-pirrolidin-3-ilamino)-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-cloropiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]5-hidroximetilciclopentano-1,2-diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(piridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(quinolin-3-il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-nitrofenil)-pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4,5-bistrifluoropiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol, (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(fenil)-pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol, 4-[3(S)-[9-((1R,2S,3R,5R)-1,2-dihidroxi-5-hidroximetilciclopent-3-il)-9H-purin-6-ilamino]-pirrolidin-1-il]benzonitrilo, (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(isoquinolin-1-il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-

(bromoquinolin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)pirrolidin-3(S)-ilamino]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol, (1R, 2S,3R,5R)-3-[6-[1-(3-cloro-5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-metoximetilciclopentano-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-cloropirimidin-4-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-metoximetilciclopentano-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol, (1R,2S,3R,5R))-5-metoximetil-3-[6-[1-(metoxipirimidin-4-il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(6-cloropiridazin-3-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-metoximetilciclopentano-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-trifluorometilfenil)pirrolidin-3(S)-ilamino-purin-9-il]-5-hidroximetilciclopentano-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-bromopiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-metoximetilciclopentano-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(5-clorpiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]-5-metoximetilciclopentano-1,2-diol, (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(4-trifluorometilfenil)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(4-clorofenil)-pirrolidin-3(s)-ilamino]- purin-9-il]-5-metoximetilciclopentano-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamino]-purin-9-il]5-metoximetilciclopentano-1,2-diol, (1R,2S,3R,5R)- 3-[6-[1-(3-clorofenil)-pirrolidin-3(S)-ilamino]-purin-9-il]-5-hidroximetilciclopentano-1,2-diol, (1R,2S,3R5R)-5-metoximetil-3-[6-[1-fenil-pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol, (1R,2S,3R,5R)-3-[6-(1-benzil-pirrolidin-3(S)-ilamino)purin-9-il]-5-hidroximetilciclopentano-1,2-diol y (1R,2S,3R,5R)-3-[6-(1-

benzil-pirrolidin-3(S)-ilamino)purin-il]-5-metoximetilciclopentano-1,2-diol; o una sal farmacéuticamente aceptable de dicho compuesto, un N-óxido de éste, un hidrato de éste o un solvato de éste.

8. El uso de un compuesto de acuerdo con la reivindicación 6, el cual es (1R,2S,3R,5R)-5-hidroximetil-3-[6-1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-purin-9-il]ciclopentano-1,2-diol o (1R,2S,3R,5R)-5-hidroximetil-3-[6-[1-(4-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamino]purin-9-il]ciclopentano-1,2-diol o una sal farmacéuticamente aceptable de dicho compuesto, un N-óxido de éste, un hidrato de éste o un solvato de éste.

9. El uso de un compuesto de acuerdo con la reivindicación 6, el cual es (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(5-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol o (1R,2S,3R,5R)-5-metoximetil-3-[6-[1-(4-trifluorometilpiridin-2-il)pirrolidin-3(S)-ilamino]-purin-9-il]ciclopentano-1,2-diol o una sal farmacéuticamente aceptable de dicho compuesto, un N-óxido de éste, un hidrato de éste o un solvato de éste.