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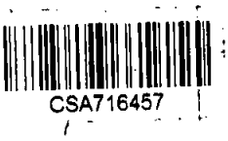
OF

Industria y Comercio

SUPERINTENDENCIA



Organizacion y Digitalizacion CSA Ltda

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

09.1737

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: DERIVADOS DE PURINA COMO AGONISTAS DE A_{2A}

SOLICITANTE: NOVARTIS AG

DIRECCIÓN: Lichtstrasse 35, CH- 4056 Basel, Suiza

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 09 Enero de 2009

P2008/000234

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-001737- -00000-0000
Fecha: 2009-01-09 16:29:24 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 289

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2008/000234**

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: NOVARTIS AG
Dirección: Lichtstrasse 35, CH-4056 Basel
Nacionalidad o Domicilio: Suiza
Lugar de Constitución: Suiza
Teléfono: **Fax:**
E-mail:

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual
Número

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual
Número 79782747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: **1) Robin Alec FAIRHURST, 2) Roger John TAYLOR,**
Dirección: Novartis Horsham Research Centre, Wimblehurst Road, Horsham, West Sussex RH12 5AB Gran Bretaña
Nacionalidad o Domicilio: Británicos

(5) **PCT (86)**

Solicitud Internacional No. PCTEP2007/006156 Fecha Julio 11, 2007

Publicación Internacional No. WO 2008/006563 Fecha Enero 17, 2008

(6) **Título (54)** **DERIVADOS DE PURINA COMO AGONISTAS DE A_{2A}**

Clasificación Internacional (51) C07D 473/16, C07H 19/167, A61K 31/52, A61P 11/00

Prioridad
SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
EP	Julio 13, 2006	06117168.2

(9) **Comprobante de pago No.** 09- **Fecha** Enero 9, de 2009

(10) **ANEXOS**

X	Comprobante de pago de la tasa de presentación de la solicitud.
X	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
X	Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 07-026.397.
X	Documento de cesión del inventor al solicitante o a su causante. Declaración Regla 4.17
	Declaraciones.
X	Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
X	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 12 x 12.
	De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
	De ser el caso, modificaciones efectuadas a la solicitud internacional.
X	Otros. Búsqueda Internacional, Secuencias.

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 1,930
FECHA : ENERO 9 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-001737- -00000-0000
Fecha: 2009-01-09 16:29:24 Dep: 2020 NUECREACIONE
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 289

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14449455	09/01/2009	3,615,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN		540,000.00
		TOTAL :	$	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Nota del traductor: ...

El documento adjunto de poder de Novartis AG a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro lleva los siguientes datos en inglés.

CERTIFICACIÓN NOTARIAL

1. En esta fecha, día 30 de Agosto de 2006, yo, el suscrito Notario Público certifico por medio del presente la autenticidad de las firmas del señor Arthur Canonica, ciudadano de Corticiasca, Suiza, residente en Wisen/SO, Suiza, y del Sr. Pascal Traub, ciudadano de Riehen, Suiza, residente en Basilea, Suiza, ambos personas mayores de edad y con dirección comercial en Lichstrasse 35, 4056, Basilea, Suiza. La autenticidad de la firmas fue establecida por medio de la comparación.
2. Además, yo, el Notario Público, certifico por el presente que las anteriores personas han ejecutado el anterior documento como apoderados de Novartis AG.
3. Además, yo, el Notario Público certifico por el presente que Novartis AG, con su principal lugar de negocios en Basilea, Suiza, está debidamente constituida, está actualmente vigente y que los propósitos para los cuales se otorgó el Documento de Poder están dentro del alcance de sus propósitos corporativos.

Traductor Ofi
JORGE E. SIERRA
Licencia 376 - 1993

5

4. Además, yo, el Notario Público, certifico por el presente que las anteriores personas tienen la autoridad para ejecutar el documento de Poder y que por este instrumento, su representación es legal.

La base para mis certificaciones de los puntos 2, 3 y 4 fue la exhibición de los siguientes documentos auténticos:

- Documento de Poder de Novartis AG fechado el 19 de junio de 2006 y
- Extracto del Registro de Comercio del Cantón de la ciudad de Basilea para Novartis AG, en Basilea, fechado el 25 de enero de 2006.

Basilea, Suiza, este día 30 de Agosto de 2006.

(Firmado) Dr. Matthias Staehelin, Notario Público del Cantón de la ciudad de Basilea, Suiza.

Mi licencia vence el 11 de Marzo de 2009.

Hay una Apostilla de Suiza, firmada por Heidi Fischer, bajo el No. 8049/13584.

Traductor Ofici
JORGE E. SIERRA
Licencia RTA

6

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Novartis"

Fecha: 12 de Septiembre de 2006.

Traductor: Jorge Enrique Sierra Reyes.

Licencia No. 376 de 1993, del Ministerio de Justicia.

Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.

Teléfono: (57-1) 2182308, (57-1) 6232925.

E-mail: treseser1@yahoo.com. No. 8346

Traductor Of
JORGE E. SIERRA
Licencia 376 - 1993

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayde Chahín
Jacqueline Chaparro
José Luis Londoño
Felipe Mendoza
Simón Salina

Of Counsel
Guillermo Chahín
Graciela Mel

Power of Attorney

The undersigned,

domiciled in

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

NOVARTIS AG

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las **Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:

Arthur Cannon

Pascal Traub

Date/Fecha: June 27, 2006

City,Country/Ciudad,País: Basel, Switzerland

Attestation

1 On this date, the 30th (thirtieth) day of August 2006 (two thousand and six), I, the undersigned Notary Public certify herewith the authenticity of the signatures of **Mr. Arthur Canonica**, citizen of Corticiasca, Switzerland, residing in Wisen/SO, Switzerland and of **Mr. Pascal Traub**, citizen of Riehen, Switzerland, residing in Basel, Switzerland, both of legal age and with business address at, Lichtstrasse 35, 4056 Basel, Switzerland. The authenticity of the signatures was established by means of comparison.

2 Further, I, the Notary Public certify herewith that the foregoing persons have executed the foregoing document as proxy holders for Novartis AG.

3 Further, I, the Notary Public certify herewith that Novartis AG, having its principal place of business located in Basel / Switzerland, is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4 Further, I, the Notary Public certify herewith that the foregoing persons have the authority to execute the Power of Attorney and that for this instrument their representation is legal.

The foundation for my certifications contained in points 2 (two), 3 (three) and 4 (four) was the exhibition of the following authentic documents:

- Power of Attorney by Novartis AG dated June 19 (nineteen), 2006 (two thousand and six); and
- Extract from the Register of Commerce of the Canton of Basel-City for Novartis AG, in Basel, dated January 25 (twenty-five), 2006 (two thousand and six).

BASEL, Switzerland, this 30th (thirtieth) day of August 2006 (two thousand and six)

Dr. Matthias Staehelin, Notary Public
in the Canton of Basel-City, Switzerland

My license expires on March 11 (eleven), 2009 (two thousand and nine).

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)
   This official document
2. is signed by .....
   .....
3. in his/her function as .....
4. and certified by the seal of the .....
   .....

Certified 24. AUG. 2015

5. in Basel (Bâle) 6. on .....
7. by the State Chancery of the Canton of Basel-Stadt .....
8. no. .....
9. Seal / stamp: 10. Signature:
   .....
   Heidi Fischer

STATE CHANCERY BASEL-CITY

Box No. VIII (ii) **DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT**

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (ii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

in relation to this international application,

Novartis AG is entitled to apply for and be granted a patent by virtue of the following:

an assignment from:

FAIRHURST Robin Alec, Novartis Horsham Research Centre, Wimblehurst Road, Hosrham, West Sussex RH12 5 AB, GB
TAYLOR Roger John, Novartis Horsham Research Centre, Wimblehurst Road, Horsham, West Sussex RH12 5AB, GB

to Novartis AG, dated 18.04.2007.

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (ii)".

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 January 2008 (17.01.2008)

PCT

(10) International Publication Number
WO 2008/006563 A1

(51) International Patent Classification:
C07D 473/16 (2006.01) *A61K 31/52* (2006.01)
C07H 19/167 (2006.01) *A61P 11/00* (2006.01)

(21) International Application Number:
PCT/EP2007/006156

(22) International Filing Date: 11 July 2007 (11.07.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
06117168.2 13 July 2006 (13.07.2006) EP

(71) Applicant *(for all designated States except AT, US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant *(for AT only)*: **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **FAIRHURST, Robin, Alec** [GB/GB]; Novartis Horsham Research Centre, Wimblehurst Road, Horsham, West Sussex RH12 5AB (GB). **TAYLOR, Roger, John** [GB/GB]; Novartis Horsham Research Centre, Wimblehurst Road, Horsham, West Sussex RH12 5AB (GB).

(74) Agent: **VOEGELI-LANGE, Regina**; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

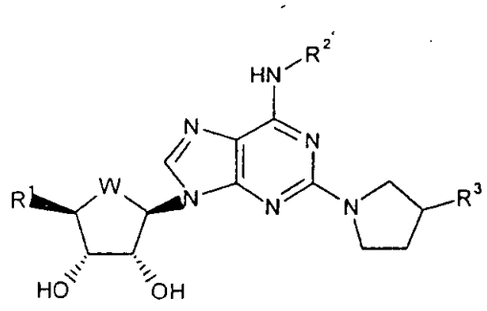
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report*

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

(54) Title: PURINE DERIVATIVES AS A2A AGONISTS



(I)

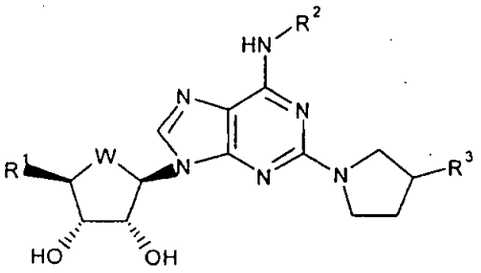
(57) Abstract: Compounds of formula (I):or stereoisomers or pharmaceutically acceptable salts thereof, wherein W, R^1,R^2 and R^3 have the meanings as indicated in the specification, are useful for treating conditions mediated by activation of the adenosine A_{2A} receptor, especially inflammatory or obstructive airways diseases. Pharmaceutical compositions that contain the compounds and a process for preparing the compounds are also described.

WO 2008/006563 A1

PURINE DERIVATIVES AS A2A AGONISTS

This invention relates to organic compounds, their preparation and use as pharmaceuticals.

An aspect of the present invention provides compounds of formula (I)



(I)

or stereoisomers or pharmaceutically acceptable salts thereof,

wherein

W is CH_2 or O, with the proviso that when W is O, then R^1 is not a N-bonded substituent;

R^1 is a 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from 1 to 4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by oxo, C_1-C_8-alkoxy, C_6-C_{10}-aryl, R^{1a} or by C_1-C_8-alkyl optionally substituted by hydroxyl;

R^{1a} is a 3- or 12-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said 3- or 12-membered heterocyclic ring being optionally substituted by halo, cyano, oxo, hydroxy, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl or C_1-C_8-alkoxy optionally substituted by aminocarbonyl;

R^2 is C_1-C_8-alkyl substituted by OH, halogen C_6-C_{10}-aryl optionally substituted by OH, SO_2R^5, SC_1-C_8-alkyl, CN, halogen, O-C_7-C_{14}-aralkyl, or O-C_1-C_8-alkyl, a C_3-C_{15}-carbocyclic group optionally substituted by O-C_7-C_{14} aralkyl, C_3-C_{15}-carbocyclic group, O-C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl or C_1-C_8-alkyl, O-C_1-C_8-alkyl, -SO_2-C_1-C_8-alkyl, a 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from 1 to 4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from 1 to 4 other heteroatoms selected

from the group consisting of oxygen and sulfur, C_7-C_{14}-aralkyl, or C_6-C_{14}-aryl optionally substituted by O-C_7-C_{14}-aralkyl, or

R^2 is a C_3-C_{15}-carbocyclic group optionally substituted by O-C_7-C_{14}-aralkyl, C_3-C_{15}-carbocyclic group, O-C_1-C_8-alkyl, or C_1-C_8-alkyl, or

R^2 is a 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from 1 to 4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from 1 to 4 other heteroatoms selected from the group consisting of oxygen and sulfur, C_7-C_{14}-aralkyl, or C_6-C_{14}-aryl optionally substituted by O-C_7-C_{14}-aralkyl;

R^3 is selected from $NR^{3a}R^{3b}$, $NR^3C(O)NR^{3g}R^{3h}$, $NHC(O)R^{3q}$, and $NHC(=NR^{3m})N(R^{3n})R^{3o}$;

R^{3a}, R^{3f} and R^{3h} are, independently, H, C_1-C_8-alkyl or C_6-C_{10}-aryl;

R^{3b} is H, C_1-C_8-alkyl a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^4 or C_6-C_{10}-aryl;

R^{3g} is C_1-C_8-alkyl optionally substituted by a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted with SO_2R^5, CN, or 0-3R^4, or

R^{3g} is a C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl, CN, -C(=NH)NH_2, SO_2R^5, -halogen, or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^4, or

R^{3g} is a C_7-C_{14}-aralkyl optionally substituted by OH, O-C_1-C_8-alkyl, halogen, C_6-C_{10}-aryl, SO_2R^5, CN, -C(=NH)NH_2 or O-C_6-C_{10}-aryl, or

R^{3g} is a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^4;

R^{3m} is CN;

R^{3n} is H or C_1-C_8-alkyl;

R^{3o} is H, C_1-C_8-alkyl optionally substituted by OH or by a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted with SO_2R^5, CN, or 0-3R^4, C_1-C_8-alkoxy, C_7-C_{14}-aralkyl optionally substituted with OH,

O-C_1-C_8-alkyl, halogen C_6-C_{10}-aryl, or O-C_6-C_{10}-aryl, C_1-C_8-alkoxy, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl SO_2R^5 or -halogen;

R^{3p} is H, C_1-C_8-alkyl or C_7-C_{14}-aralkyl;

R^{3q} is a C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, C_1-C_8-alkoxy, SO_2R^5 or –halogen, or

R^{3q} is a C_7-C_{14}-aralkyl optionally substituted by OH, C_1-C_8-alkyl, C_1-C_8-alkoxy, SO_2R^5 or –halogen, or

R^{3q} is a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur optionally substituted by 0-3 R^4 or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3 R^4;

R^4 is selected from OH, C_1-C_8-alkyl optionally substituted by OH, CN, SO_2R^5 or halogen, C(O)NHR^{3a}, O-C_1-C_8-alkyl optionally substituted by halogen, $NR^{4a}R^{4b}$, $NHC(O)R^{4c}$, a C(O)-C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl, -halogen, or SO_2R^5;

R^{4a}, R^{4b} and R^{4c} are, independently, H, C_1-C_8-alkyl or C_6-C_{10}-aryl; and

R^5 is C_1-C_8-alkyl optionally substituted by halogen, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl, or $NR^{3a}R^{3b}$.

Definitions

Terms used in the specification have the following meanings:

"Optionally substituted" or "substituted" means the group referred to can be substituted at one or more positions by any one or any combination of the radicals listed thereafter.

"Halo" or "halogen", as used herein, may be fluorine, chlorine, bromine or iodine.

"C_1-C_8-Alkyl", as used herein, denotes straight chain or branched alkyl having 1 to 8 carbon atoms.

"C_1-C_8-Alkoxy", as used herein, denotes straight chain or branched alkoxy having 1 to 8 carbon atoms.

"C_3-C_8-Cycloalkyl", as used here in, denotes cycloalkyl having 3 to 8 ring carbon atoms, e.g., a monocyclic group, such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl, any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups; or a bicyclic group, such as bicycloheptyl or bicyclooctyl.

"C_1-C_8-Alkylamino" and "di(C_1-C_8-alkyl)amino", as used herein, denote amino substituted respectively by one or two C_1-C_8-alkyl groups as hereinbefore defined, which may be the same or different.

"C_1-C_8-Alkylcarbonyl" and "C_1-C_8-alkoxycarbonyl", as used herein, denote C_1-C_8-alkyl or C_1-C_8-alkoxy, respectively, as hereinbefore defined attached by a carbon atom to a carbonyl group.

"C_6-C_{10}-Aryl", as used herein, denotes a monovalent carbocyclic aromatic group that contains 6 to 10 carbon atoms and which may be, e.g., a monocyclic group, such as phenyl; or a bicyclic group, such as naphthyl.

"C_7-C_{14}-Aralkyl", as used herein, denotes alkyl, e.g., C_1-C_4-alkyl, as hereinbefore defined, substituted by C_6-C_{10}-aryl as hereinbefore defined.

"C_1-C_8-Alkylaminocarbonyl" and "C_3-C_8-cycloalkylaminocarbonyl", as used herein, denote C_1-C_8-alkylamino and C_3-C_8-cycloalkylamino respectively as hereinbefore defined attached by a carbon atom to a carbonyl group.

"C_3-C_{15}-Carbocyclic group", as used herein, denotes a carbocyclic group having 3 to 15 ring carbon atoms, e.g., a monocyclic group, either aromatic or non-aromatic, such as a cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or phenyl; or a bicyclic group, such as bicyclooctyl, bicyclononyl, bicyclodecyl, indanyl or indenyl, again any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups.

"3- to 12-Membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur", as used herein, may be, e.g., furan, pyrrole, pyrrolidine, pyrazole, imidazole, triazole, isotriazole, tetrazole, thiadiazole, isothiazole, oxadiazole, pyridine, piperidine, pyrazine, oxazole, isoxazole, pyrazine, pyridazine, pyrimidine, piperazine, pyrrolidine, morpholino, triazine, oxazine or thiazole.

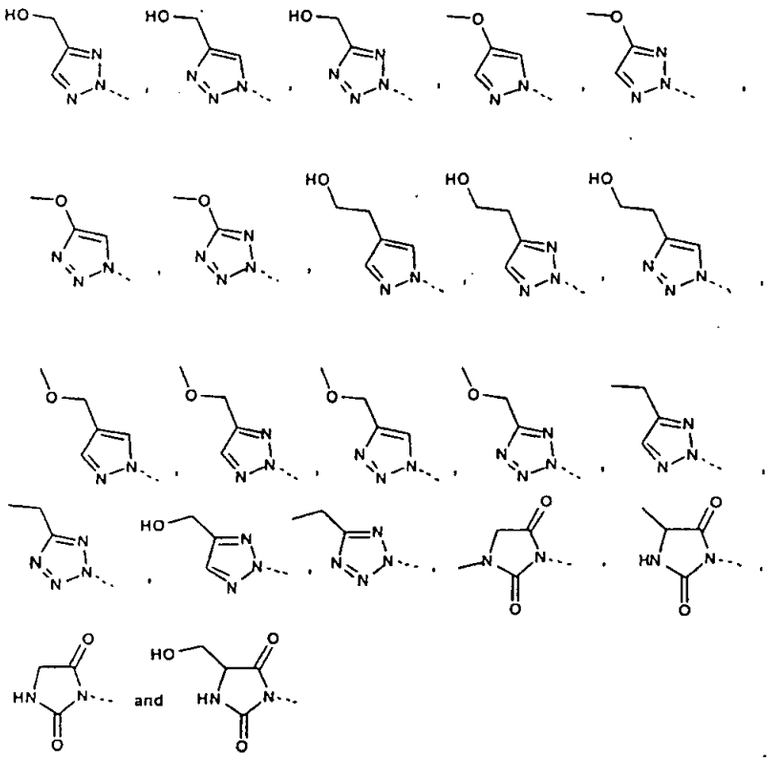
"5- or 6-Membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur" as used herein may be, e.g., a saturated or unsaturated heterocyclic group, such as furanyl, pyrrolyl, pyrrolidinyl, pyrazolyl, imidazolyl, triazolyl, isotriazolyl, tetrazolyl, thiadiazolyl, isothiazolyl, oxadiazolyl, pyridinyl, piperidinyl, pyrazinyl, oxazolyl, isoxazolyl, pyrazinyl, pyridazinyl, pyrimidinyl, piperazinyl, pyrrolidinyl, morpholinyl, triazinyl, oxazinyl or thiazolyl.

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations, such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

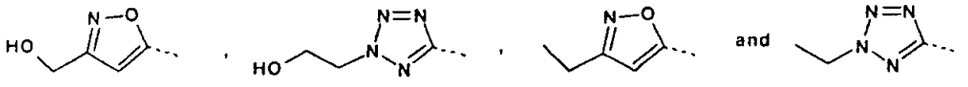
Throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations, such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps. As understood by one skilled in the art only combinations of substituents that are chemically possible are embodiments of the invention.

According to formula (I), R^1 is suitably a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur. Preferably R^1 is a 5-membered heterocyclic group, such as pyazole, triazole, tetrazole, isoxazole and imidazole-2,4-dione. These heterocyclic groups are suitably substituted by a C_1-C_6-alkyl optionally substituted by OH.

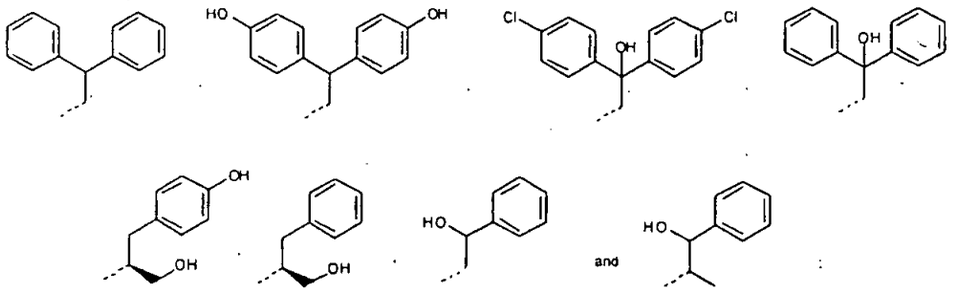
The heterocyclic groups can be either N-bonded or C-bonded. For example, the heterocyclic groups pyrazole, triazole, tetrazole and imidazole-2,4-dione are suitably N-bonded when attached to a cyclopentane group (e.g., when W is CH_2). These N-bonded heterocyclic groups can alsobe suitably substituted by groups such as methanol, methyl, ethyl, methoxy and methoxy-methyl. Preferably, the R^1 groups attached to the cyclopentane group are



The heterocyclic groups isoxazole and tetrazole are C-bonded when attached to a furan group (e.g. when W is O). These C-bonded heterocyclic groups are suitably substituted by C_1-C_6-alkyl optionally substituted by OH such as hydroxymethyl, hydroxyethyl, an ethyl group or a methyl group. Preferably, The R^1 groups attached to the furan group are



According to formula (I), R^2 is suitably selected from C_1-C_8-alkyl optionally substituted by OH, halogen or C_6-C_{10}-aryl optionally substituted by OH, halogen, such as Cl or O-C_1-C_8-alkyl, preferably C_6-C_{10}-aryl is phenyl. Also, preferably, the C_1-C_8-alkyl is substituted by two phenyl rings and the phenyl rings are unsubstituted or substituted by OH. Preferred R^2 groups are



According to formula (I), R^3 is suitably $NR^{3f}C(O)NR^{3g}R^{3h}$. R^{3f} and R^{3h} are suitably H.

R^{3g} is suitably C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl, SO_2R^5, -halogen, CN, -C(=NH)NH_2, or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^4. Preferably this 3- to 12-membered heterocyclic group is a 5-membered heterocyclic group, such as tetrazole.

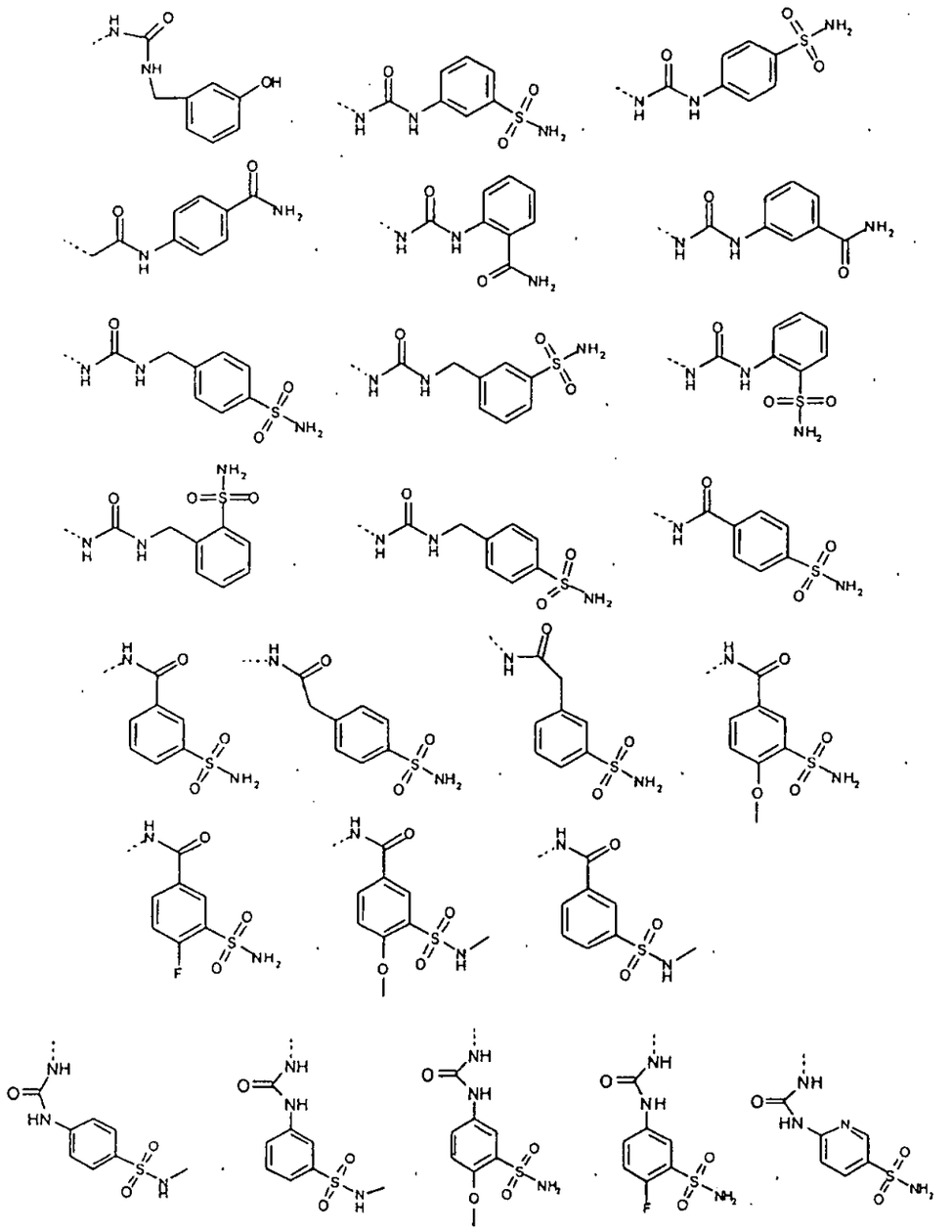
According to formula (I), R^{3g} is also suitably C_7-C_{14}-aralkyl optionally substituted by OH, O-C_1-C_8-alkyl, halogen, C_6-C_{10}-aryl, SO_2R_5, CN, -C(=NH)NH_2, or O-C_6-C_{10}-aryl.

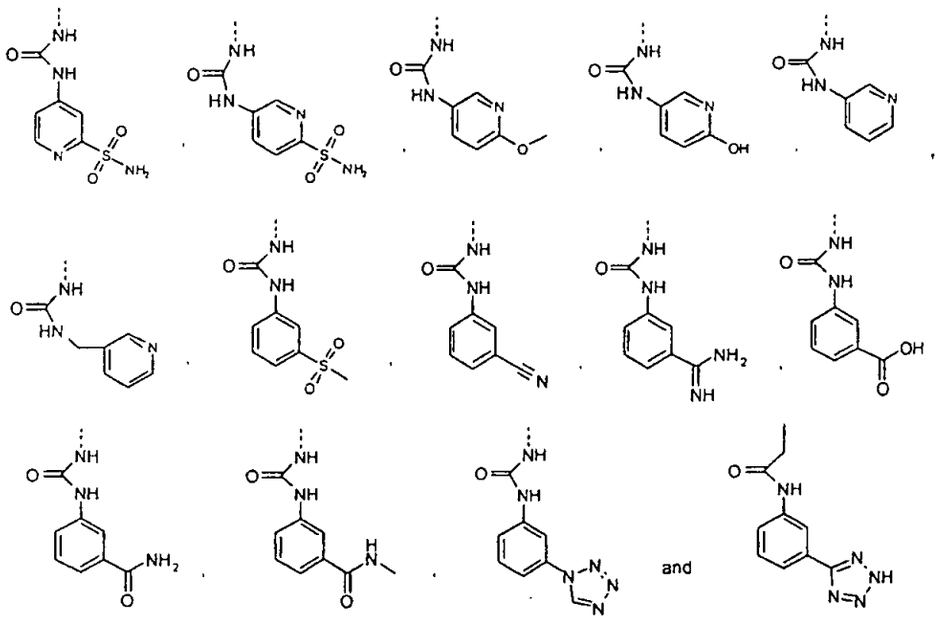
According to formula (I), R^{3g} is also suitably 3- to 12-membered heterocyclic group, preferably a pyridine, containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^4.

According to formula (I), R^3 is also suitably $NHC(O)R^{3q}$, where R^{3q} is a C_6-C_{10}-aryl optionally substituted b y OH, C_1-C_8-alkyl, C_1-C_8-alkoxy, SO_2R^5 or -halogen.

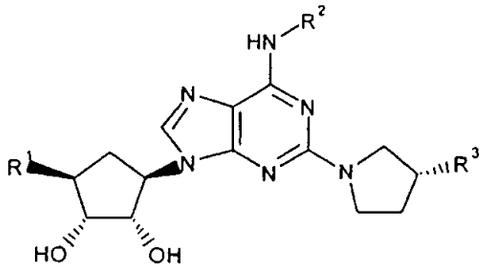
R^{3q} is also suitably a C_7-C_{14}-aralkyl optionally substituted by OH, C_1-C_8-alkyl, C_1-C_8-alkoxy, SO_2R_5 or -halogen.

Preferred R^3 groups are





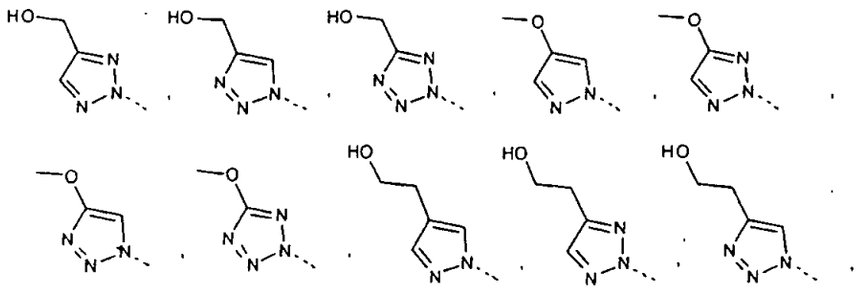
Another aspect of the invention provides compounds of formula (I) wherein the compound is of formula (Ia)

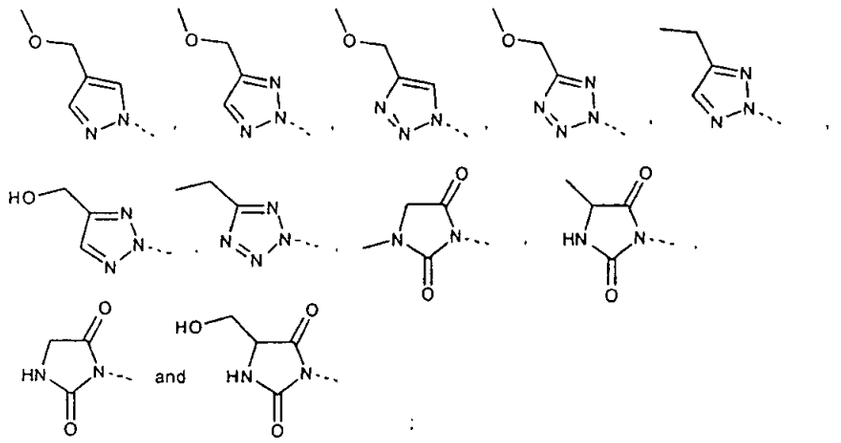


(Ia)

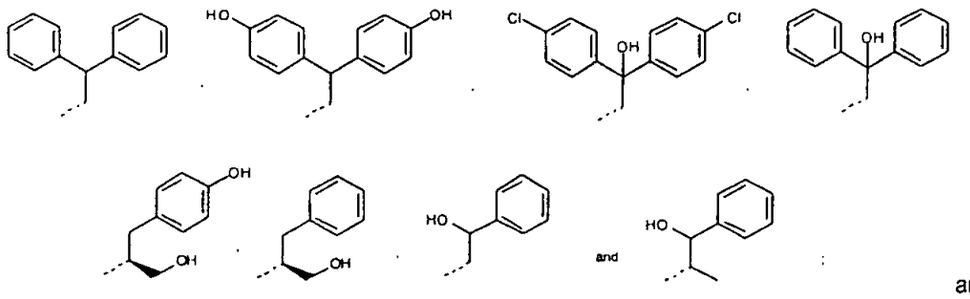
where

R^1 is selected from



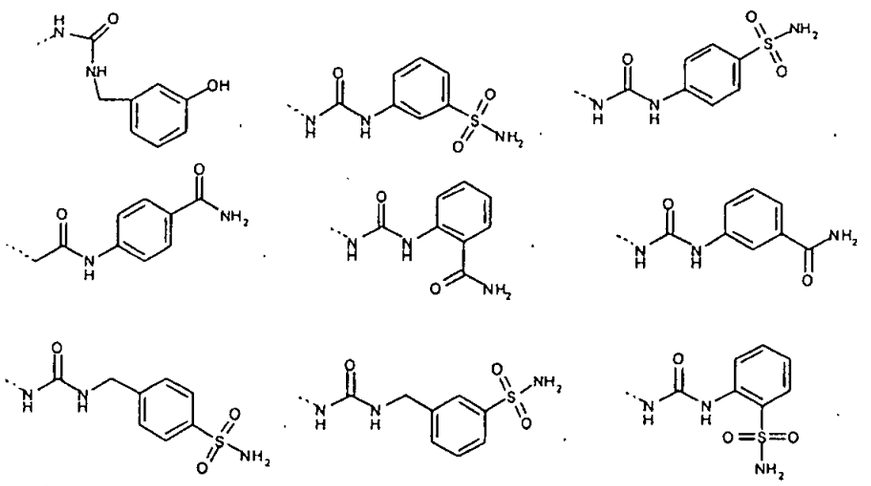


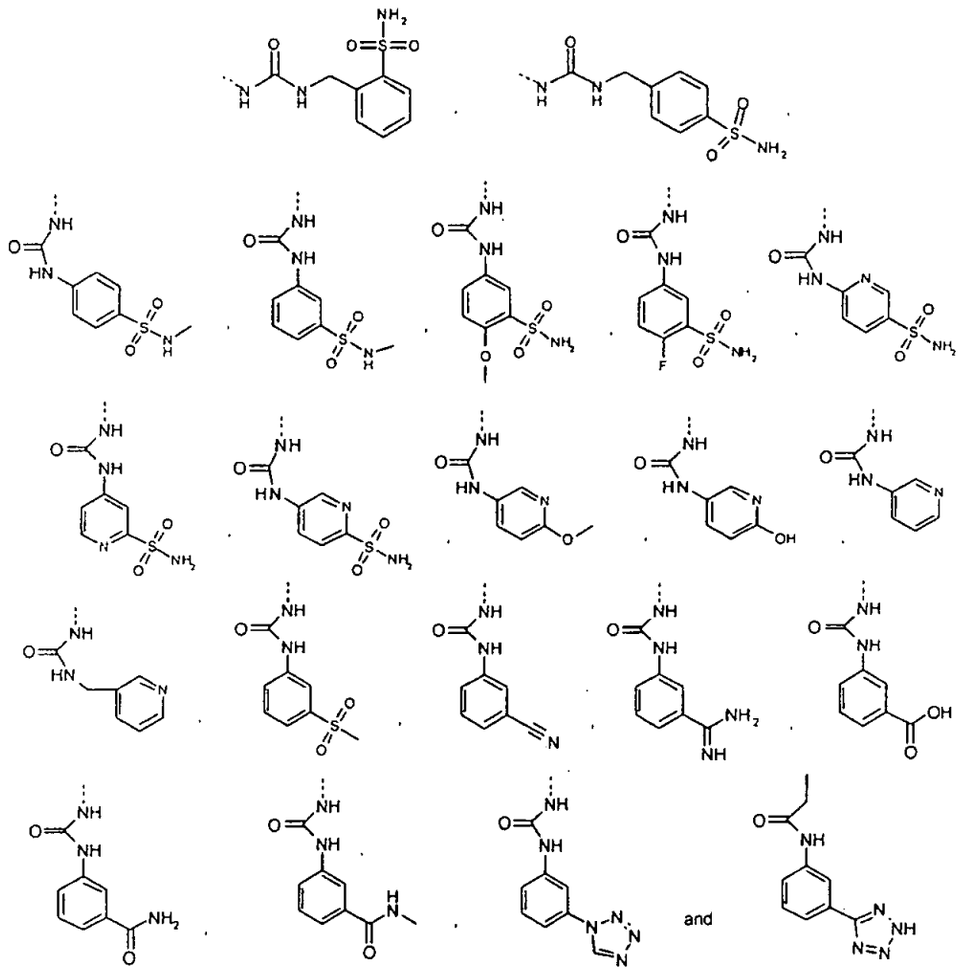
R^2 is selected from



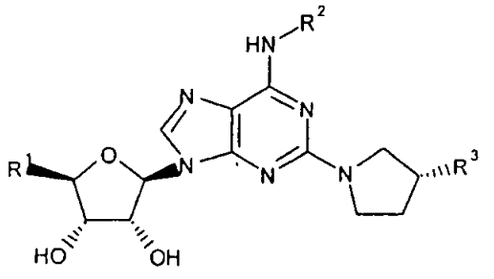
and

R^3 is selected from





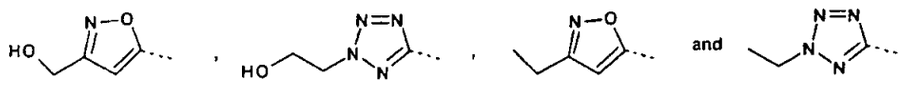
Another aspect of the invention provides compounds of formula (I) wherein the compound is of formula (Ib)



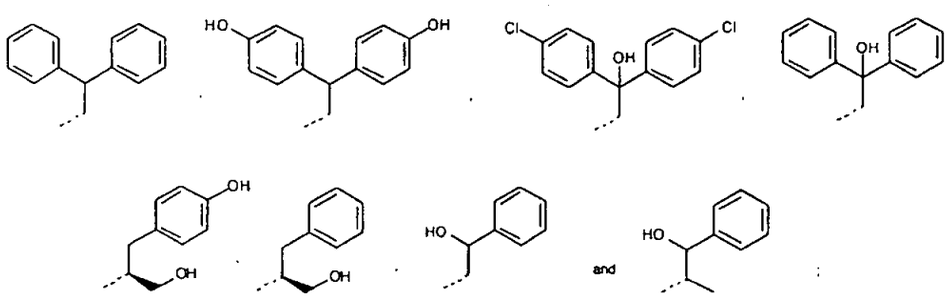
(Ib)

where

R^1 is selected from

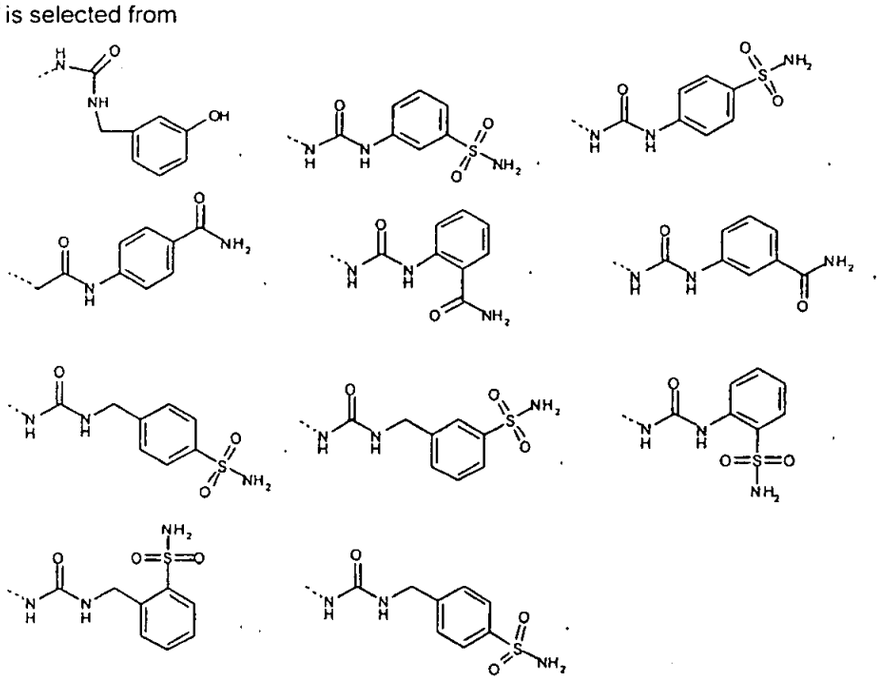


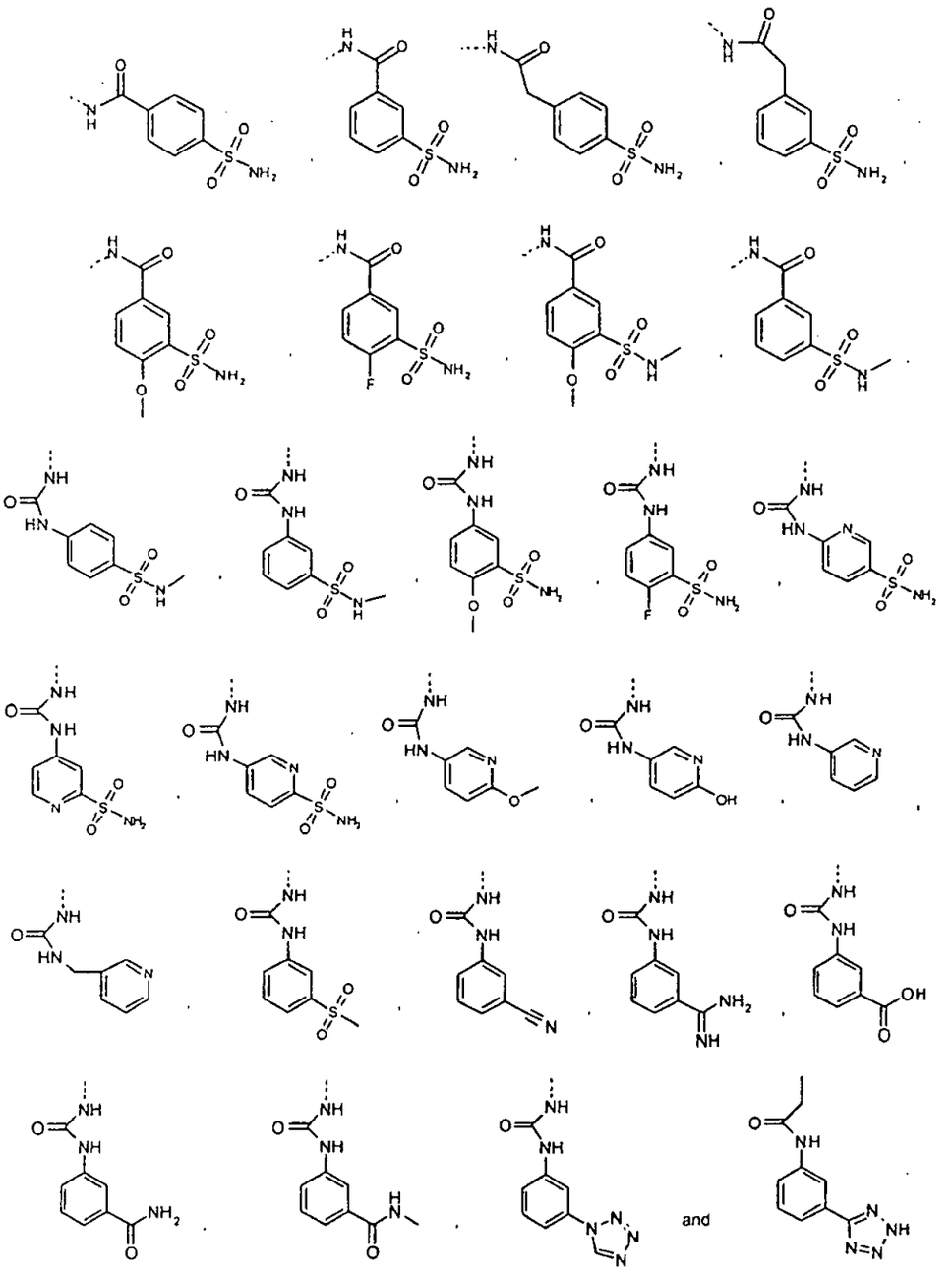
R^2 is selected from



and

R^3 is selected from





Especially preferred specific compounds of formula (I) are those described hereinafter in the Examples.

Stereoisomers are those compounds where there is an asymmetric carbon atom. The compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g., as diastereomeric mixtures. The present invention embraces both individual optically active *R* and *S* isomers, as well as mixtures thereof. Individual isomers can be separated by methods well-known to those skilled in the art, e.g. chiral high performance liquid chromatography (HPLC).

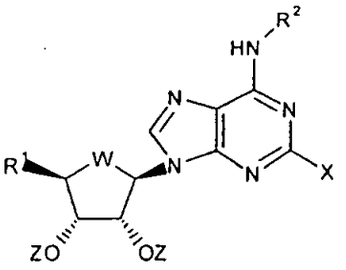
Tautomers are one of two or more structural isomers that exist in equilibrium and are readily converted from one isomeric form to another.

The compounds of the invention may exist in both unsolvated and solvated forms. The term "solvate" is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, e.g., ethanol. The term "hydrate" is employed when said solvent is water.

Synthesis

Another embodiment of the present invention provides a process for the prepara tion of compounds of formula (I) in free or pharma ceutically acceptable salt form, which comprises the steps of:

(i) reacting a compound of formula (Ic)



(Ic)

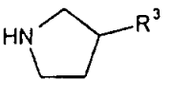
wherein

R^1, W and R^2 are a s defined hereinbefore ;

Z is H or a protecting group; and

X is a leaving group,

with a compound of formula (Id)



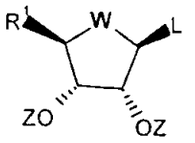
(Id)

wherein

R^3 is as defined in hereinbefore ; and

removing any protecting groups and recovering the resultant compound of formula (I), in free or pharmaceutically acceptable salt form.

The compound of formula (Ic) may be prepared by reacting a compound of formula (Ie)



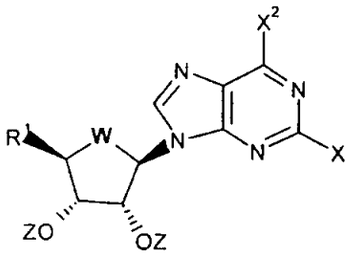
(Ie)

wherein

R^1 and Z are as defined hereinbefore; and

L represents a leaving group or a protected derivative thereof with a 2,6-dihalopurine, e.g., 2,6-dichloropurine,

to provide a compound of formula (If)



(If)

wherein

R^1 and Z are defined hereinbefore; and

X and X^2 are halogen.

Compound of formula (If) can be reacted with R^2NH_2 under conventional conditions to provide compound of formula (Ic).

The compounds of formula (I) can be prepared, e.g., using the reactions and techniques described below and in the Examples. The compounds of formula (I) can be prepared analogously to the preparations described in Applicant's patent applications PCT/EP2005/011344, GB 0500785.1, and GB 0505219.6. The reactions may be performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic

synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

The various substituents on the synthetic intermediates and final products shown in the following reaction schemes can be present in their fully elaborated forms, with suitable protecting groups where required as understood by one skilled in the art, or in precursor forms which can later be elaborated into their final forms by methods familiar to one skilled in the art. The substituents can also be added at various stages throughout the synthetic sequence or after completion of the synthetic sequence. In many cases, commonly used functional group manipulations can be used to transform one intermediate into another intermediate, or one compound of formula (I) into another compound of formula (I). Examples of such manipulations are conversion of an ester or a ketone to an alcohol; conversion of an ester to a ketone; interconversions of esters, acids and amides; alkylation, acylation and sulfonylation of alcohols and amines; and many others. Substituents can also be added using common reactions, such as alkylation, acylation, halogenation or oxidation. Such manipulations are well-known in the art, and many reference works summarize procedures and methods for such manipulations. Some reference works which gives examples and references to the primary literature of organic synthesis for many functional group manipulations, as well as other transformations commonly used in the art of organic synthesis are *March's Organic Chemistry*, 5th Edition, Wiley and Chichester, Eds. (2001); *Comprehensive Organic Transformations*, Larock, Ed., VCH (1989); *Comprehensive Organic Functional Group Transformations*, Katritzky et al. (series editors), Pergamon (1995); and *Comprehensive Organic Synthesis*, Trost and Fleming (series editors), Pergamon (1991). It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. Multiple protecting groups within the same molecule can be chosen such that each of these protecting groups can either be removed without removal of other protecting groups in the same molecule, or several protecting groups can be removed using the same reaction step, depending upon the outcome desired. An authoritative account describing many alternatives to the trained practitioner is T. W. Greene and P. G. M. Wuts, *Protective Groups In Organic Synthesis*, Wiley and Sons (1999). It is understood by those skilled in the art that only

combinations of substituents that are chemically possible are embodiments of the present invention.

Compounds of formula (I) in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallization. Compounds of formula (I) can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as stereoisomers, may be obtained in a conventional manner, e.g., by fractional crystallization or asymmetric synthesis from correspondingly asymmetrically substituted, e.g., optically active, starting materials.

Compounds of formula (I) and their pharmaceutically acceptable salts are useful as pharmaceuticals. In particular, they activate the adenosine A_{2A} receptor, i.e., they act as A_{2A} receptor agonists. Their properties as A_{2A} agonists may be demonstrated using the method described by L. J. Murphree *et al* in *Mol Pharmacol*, Vol. 61, pp. 455-462 (2002).

Compounds of the Examples herein below have K_i values below 1.0 μM in the above assay. For example, the compounds of Examples C1 and C2 have K_i values of 0.089μM and 0.033μM respectively.

Having regard to their activation of the adenosine A_{2A} receptor, compounds of formula (I), in free or pharmaceutically acceptable salt form, hereinafter alternately referred to as "agents of the invention", are useful in the treatment of conditions which respond to the activation of the adenosine A_{2A} receptor, particularly inflammatory or allergic conditions. Treatment in accordance with the invention may be symptomatic or prophylactic.

Accordingly, agents of the invention are useful in the treatment of inflammatory or obstructive airways diseases, resulting, e.g., in reduction of tissue damage, airways inflammation, bronchial hyperreactivity, remodelling or disease progression. Inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), adult/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular, other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further

inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis including, e.g., aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Other inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g., of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g., of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e., therapy for or intended to restrict or abort symptomatic attack when it occurs, e.g., anti-inflammatory (e.g., cortico-steroid) or bronchodilatory. Prophylactic benefit in asthma may, in particular, be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognized asthmatic syndrome, common to a substantial percentage of asthmatics and characterized by asthma attack, e.g., between the hours of about 4 to 6 am, i.e. at a time normally substantially distant from any previously administered symptomatic asthma therapy.

Having regard to their anti-inflammatory activity, in particular, in relation to inhibition of eosinophil activation, agents of the invention are also useful in the treatment of eosinophil related disorders, e.g., eosinophilia, in particular, eosinophil-related disorders of the airways (e.g., involving morbid eosinophilic infiltration of pulmonary tissues) including hypereosinophilia as it effects the airways and/or lungs, as well as, e.g., eosinophil-related disorders of the airways consequential or concomitant to Löffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome),

eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction.

Agents of the invention are also useful in the treatment of inflammatory or allergic conditions of the skin, e.g., psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphisus, epidermolysis bullosa acquisita, and other inflammatory or allergic conditions of the skin.

Agents of the invention may also be used for the treatment of other diseases or conditions, in particular, diseases or conditions having an inflammatory component, e.g., treatment of diseases and conditions of the eye, such as conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or aetiology, including autoimmune haematological disorders (e.g., haemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g., ulcerative colitis and Crohn's disease), endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary billiary cirrhosis, uveitis (anterior and posterior), keratoconjunct-ivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g., including idiopathic nephrotic syndrome or minal change nephropathy).

Further, agents of the invention may also be used for the treatment of cystic fibrosis, pulmonary hypertension, pulmonary fibrosis, inflammatory bowel syndrome, wound healing, diabetic nephropathy as described in WO 05/107463, reduction of inflammation in transplanted tissue as described in US 2005/182018, inflammatory diseases caused by pathogenic organisms as described in WO 03/086408, and cardiovascular conditions as described in WO 03/029264.

Also, the agents of the invention may be used to assess the severity of coronary artery stenosis as described in WO 00/078774 and useful in conjunction with radioactive imaging agents to image coronary activity and useful in adjunctive therapy with angioplasty as described in WO 00/78779.

Agents of the invention are also useful in combination with a protease inhibitor for prevention of organ ischemia and reperfusion injury as described in WO 05/003150, and in combination with an integrin antagonist for treating platelet aggregation as described in WO 03/090733.

Agents of the invention are also useful in promoting wound healing in bronchial epithelial cells as described in *AJP-Lung*, Vol. 290, pp. 849-855.

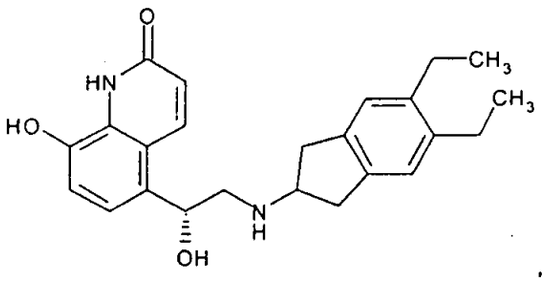
Other diseases or conditions which may be treated with agents of the invention include diabetes, e.g., diabetes mellitus type I (juvenile diabetes) and diabetes mellitus type II, diarrheal diseases, ischemia/reperfusion injuries, retinopathy, such as diabetic retinopathy or hyperbaric oxygen-induced retinopathy, conditions characterised by elevated intraocular pressure or secretion of ocular aqueous humor, such as glaucoma, ischemic tissue/organ damage from reperfusion and bedsores.

The effectiveness of an agent of the invention in inhibiting inflammatory conditions, for example in inflammatory airways diseases, may be demonstrated in an animal model, e.g., a mouse or rat model, of airways inflammation or other inflammatory conditions, e.g., as described by Szarka et al, *J Immunol Methods*, Vol. 202, pp. 49-57 (1997); Renzi et al, *Am Rev Respir Dis*, Vol. 148, pp. 932-939 (1993); Tsuyuki et al., *J Clin Invest*, Vol. 96, pp. 2924-2931 (1995); Cernadas et al., *Am J Respir Cell Mol Biol*, Vol. 20, pp. 1-8 (1999); and Fozard et al, *Eur J Pharmacol*, Vol. 438, pp. 183-188 (2002).

The agents of the invention are also useful as co-therapeutic agents for use in combination with other drug substances such as anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance.

Accordingly the invention includes a combination of an agent of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substance, said agent of the invention and said drug substance being in the same or different pharmaceutical composition.

Suitable anti-inflammatory drugs include steroids, in particular, glucocorticosteroids such as budesonide, beclamethasone dipropionate, fluticasone propionate, cidesonide or mometasone furoate, or steroids described in WO 02/88167, WO 02/12266, WO 02/100879, WO 02/00679 (especially those of Examples 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 73, 90, 99 and 101), WO 03/35668, WO 03/48181, WO 03/62259, WO 03/64445, WO 03/72592, WO 04/39827 and WO 04/66920; non-steroidal glucocorticoid receptor agonsts, such as those described in DE 10261874, WO 00/00531, WO 02/10143, WO 03/82280, WO 03/82787, WO 03/86294, WO 03/104195, WO 03/101932, WO 04/05229, WO 04/18429, WO 04/19935 and WO 04/26248; LTB4 antagonists, such as BIIL 284, CP-195543, DPC11870, LTB4 ethanolamide, LY 293111, LY 255283, CGS025019C, CP-195543, ONO-4057, SB 209247, SC-53228 and those described in US 5451700; LTD4 antagonists include montelukast, pranlukast, zafirlukast, accolate, SR2640, Wy-48,252, ICI 198615, MK-571, LY-171883, Ro 24-5913 and L-648051; PDE4 inhibitors such as cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 / PD168787 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene), SelCID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo) and those disclosed in WO 92/19594, WO 93/19749, WO 93/19750, WO 93/19751, WO 98/18796, WO 99/16766, WO 01/13953, WO 03/104204, WO 03/104205, WO 03/39544, WO 04/000814, WO 04/000839, WO 04/005258, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/018431, WO 04/018449, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/019944, WO 04/019945, WO 04/045607 and WO 04/037805; adenosine A_{2B} receptor antagonists, such as those described in WO 02/42298; and beta-2 adrenoceptor agonists, such as albuterol (salbutamol), metaproterenol, terbutaline, salmeterol fenoterol, procaterol, and especially, formoterol, carmoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula (I) of WO 0075114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof, as well as compounds (in free or salt or solvate form) of formula (I) of WO 04/16601, and also compounds of EP 1440966, JP 05025045, WO 93/18007, WO 99/64035, US 2002/0055651, US 2005/0133417, US 2005/5159448, WO 01/42193, WO 01/83462, WO 02/66422, WO 02/70490, WO 02/76933, WO 03/24439, WO 03/42160, WO 03/42164, WO 03/72539, WO 03/91204, WO 03/99764, WO 04/16578, WO 04/22547, WO 04/32921, WO 04/33412, WO 04/37768, WO 04/37773, WO 04/37807, WO 04/39762, WO 04/39766, WO 04/45618 WO 04/46083, WO 04/80964, EP1460064, WO 04/087142, WO 04/089892, EP 01477167, US 2004/0242622, US 2004/0229904, WO 04/108675, WO 04/108676, WO 05/033121, WO 05/040103, WO 05/044787, WO 05/058867, WO 05/065650, WO 05/066140 and WO 05/07908.

Suitable bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular, ipratropium bromide, oxitropium bromide, tiotropium salts and CHF 4226 (Chiesi), and glycopyrrolate, but also those described in EP 424021, US 3714357, US 5171744, US 2005/171147, US 2005/182091, WO 01/04118, WO 02/00652, WO 02/51841, WO 02/53564, WO 03/00840, WO 03/33495, WO 03/53966, WO 03/87094, WO 04/018422, WO 04/05285 and WO 05/077361.

Suitable dual anti-inflammatory and bronchodilatory drugs include dual beta-2 adrenoceptor agonist/muscarinic antagonists such as those disclosed in US 2004/0167167, US 2004/0242622, US 2005/182092, WO 04/74246 and WO 04/74812.

Suitable antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride, activastine, astemizole, azelastine, ebastine, epinastine, mizolastine and tefenadine, as well as those disclosed in JP 2004107299, WO 03/099807 and WO 04/026841.

Other useful combinations of agents of the invention with anti-inflammatory drugs are those with antagonists of chemokine receptors, e.g., CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists, such as Schering-Plough antagonists SC-351125, SCH-55700 and SCH-D, Takeda antagonists, such as *N*-[[4-[[[6,7-dihydro-2-(4-methylphenyl)-5*H*-benzo-cyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-*N,N*-dimethyl-2*H*-pyran-4-amin-ium chloride (TAK-770), and CCR-5 antagonists described in US 6166037 (particularly claims 18 and 19), WO 00/66558 (particularly claim 8), WO 00/66559 (particularly claim 9), WO 04/018425 and WO 04/026873.

In accordance with the foregoing, the invention also provides a method for the treatment of a condition responsive to activation of the adenosine A_{2A} receptor, e.g., an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease, which comprises administering to a subject, particularly a human subject, in need thereof a compound of formula (I) in free form or in the form of a pharmaceutically acceptable salt. In another aspect the invention provides a compound of formula (I), in free form or in the form of a pharmaceutically acceptable salt, for use in the manufacture of a medicament for the treatment of a condition responsive to activation of the adenosine A_{2A} receptor, particularly an inflammatory or obstructive airways disease.

The agents of the invention may be administered by any appropriate route, e.g., orally, e.g., in the form of a tablet or capsule; parenterally, e.g., intravenously; by inhalation, e.g., in the treatment of inflammatory or obstructive airways disease; intranasally, e.g., in the treatment of allergic rhinitis; topically to the skin, e.g., in the treatment of atopic dermatitis; or rectally, e.g., in the treatment of inflammatory bowel disease.

In a further aspect, the invention also provides a pharmaceutical composition comprising a compounds of formula (I) in free form or in the form of a pharmaceutically acceptable salt, optionally together with a pharmaceutically acceptable diluent or carrier therefor. The composition may contain a co-therapeutic agent, such as an anti-inflammatory, broncho-dilatory, antihistamine or anti-tussive drug as hereinbefore described. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g., patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

When the composition comprises an aerosol formulation, it preferably contains, e.g., a hydro-fluoro-alkane (HFA) propellant such as HFA134a or HFA227 or a mixture of these, and may contain one or more co-solvents known in the art, such as ethanol (up to 20% by weight), and/or one or more surfactants, such as oleic acid or sorbitan trioleate, and/or one or more bulking agents, such as lactose. When the composition comprises a dry powder formulation, it preferably contains, e.g., the compounds of formula (I) having a particle diameter up to 10 microns, optionally together with a diluent or carrier, such as lactose, of the desired particle size distribution and a compound that helps to protect against product performance deterioration due to moisture, e.g., magnesium stearate. When the composition comprises a nebulised formulation, it preferably contains, e.g., the compound of formula (I) either dissolved, or suspended, in a vehicle containing water, a co-solvent, such as ethanol or propylene glycol and a stabilizer, which may be a surfactant.

The invention includes:

(a) a compounds of formula (I) in inhalable form, e.g., in an aerosol or other atomisable composition or in inhalable particulate, e.g., micronized, form;

(b) an inhalable medicament comprising a compounds of formula (I) in inhalable form;

(c) a pharmaceutical product comprising a compounds of formula (I) in inhalable form in association with an inhalation device; and

(d) an inhalation device containing a compounds of formula (I) in inhalable form.

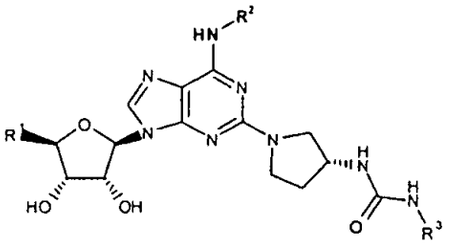
Dosages of compounds of formula (I) employed in practicing the present invention will of course vary depending, e.g., on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of 0.005-10 mg, while for oral administration suitable daily doses are of the order of 0.05-100 mg.

The invention is illustrated by the following Examples.

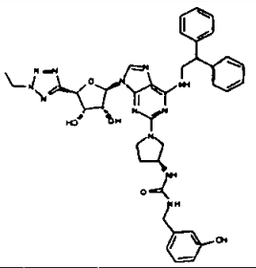
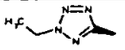
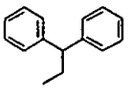
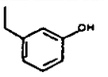
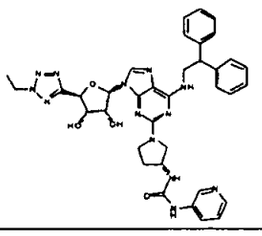
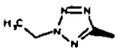
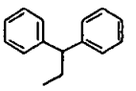
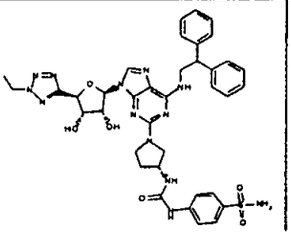
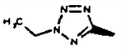
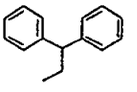
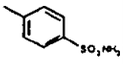
EXAMPLES

Examples 1-48

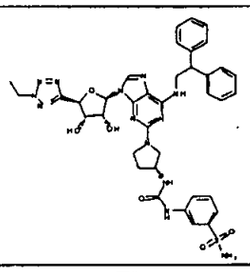
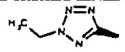
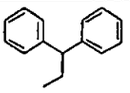
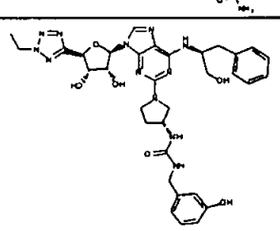
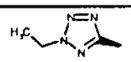
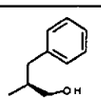
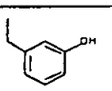
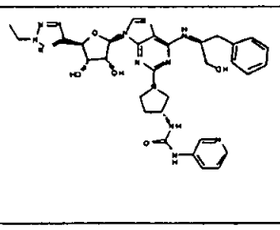
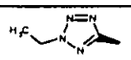
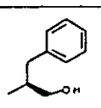
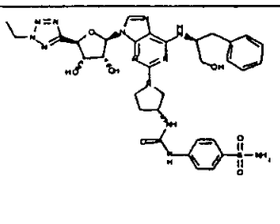
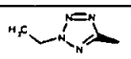
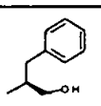
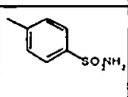
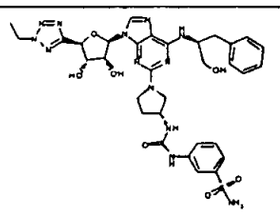
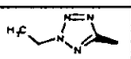
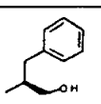
Compounds of formula (I)



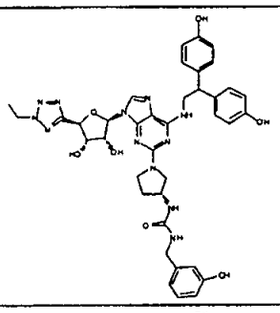
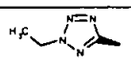
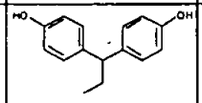
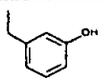
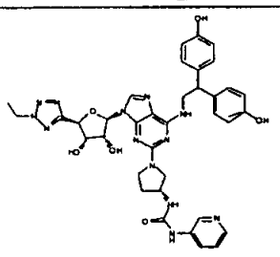
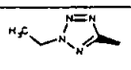
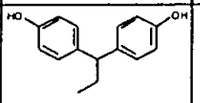
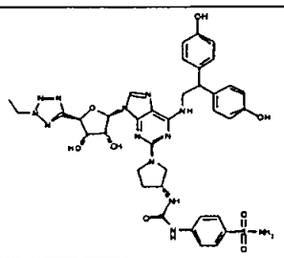
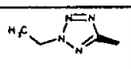
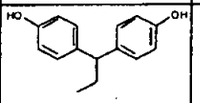
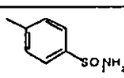
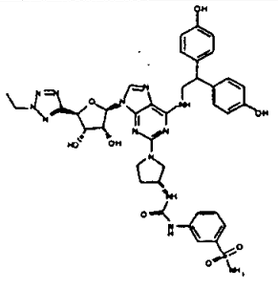
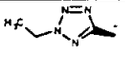
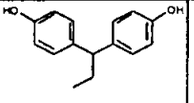
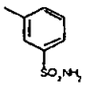
are shown in the following table. Methods for preparing such compounds are described hereinafter.

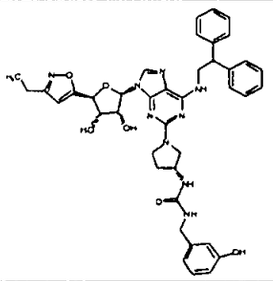
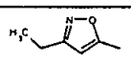
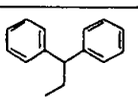
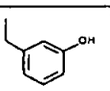
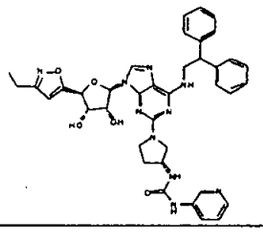
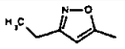
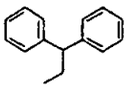
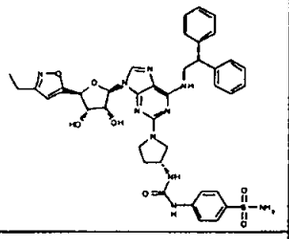
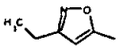
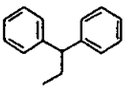
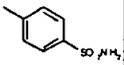
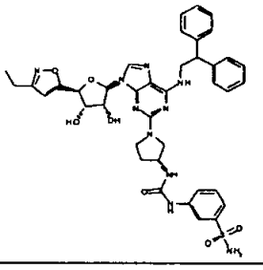
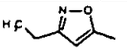
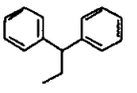
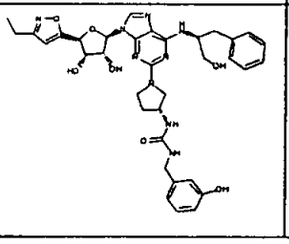
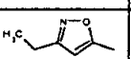
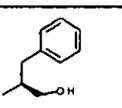
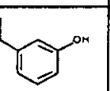
Ex.	Structure	R^1	R^2	R^3	Name
1					1-((R)-1-{6-(2,2-Diphenyl-ethylamino)-9-(2R,3R,4S,5R)-5-(2-ethyl-2H-tetrazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea
2					1-((R)-1-{6-(2,2-Diphenyl-ethylamino)-9-[(2R,3R,4S,5R)-5-(2-ethyl-2H-tetrazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-pyridin-3-yl-urea
3					4-{3-((R)-1-{6-(2,2-Diphenyl-ethylamino)-9-[(2R,3R,4S,5R)-5-(2-ethyl-2H-tetrazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide

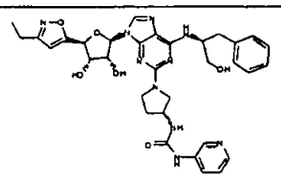
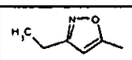
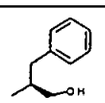
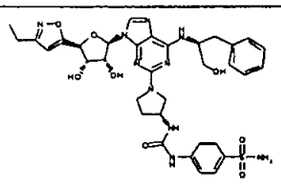
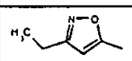
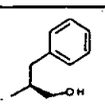
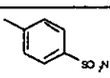
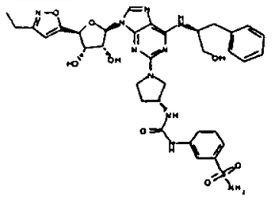
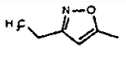
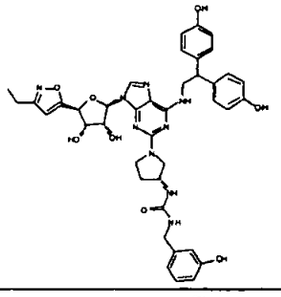
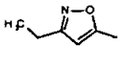
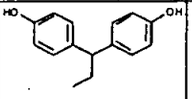
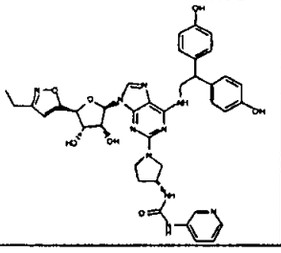
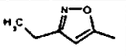
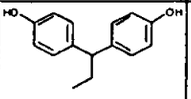
37

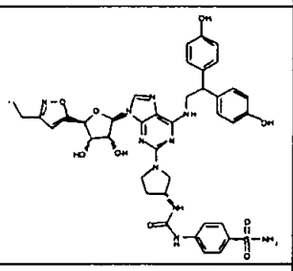
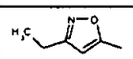
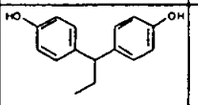
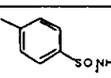
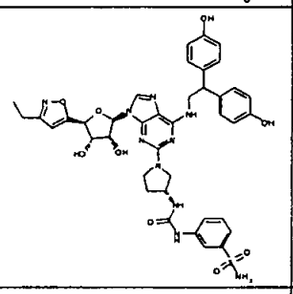
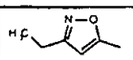
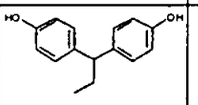
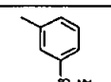
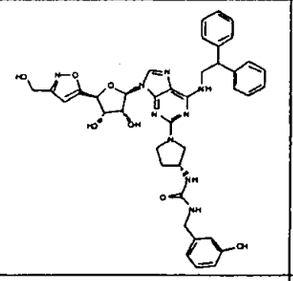
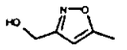
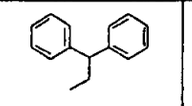
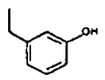
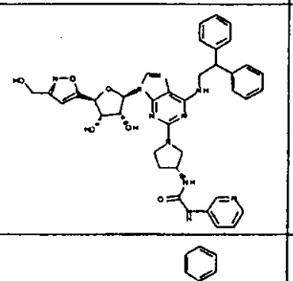
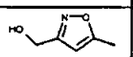
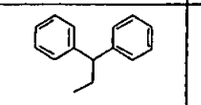
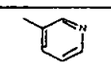
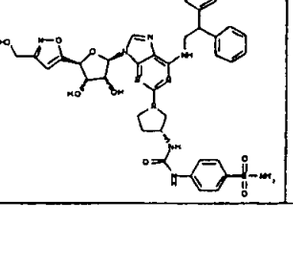
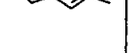
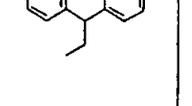
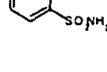
Ex.	Structure	R^1	R^2	R^3	Name
4					3-[3-((R)-1-{6-(2,2-Diphenyl-ethylamino)-9-[(2R,3R,4S,5R)-5-(2-ethyl-2H-tetrazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
5					1-{(R)-1-[9-[(2R,3R,4S,5R)-5-(2-Ethyl-2H-tetrazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea
6					1-{(R)-1-[9-[(2R,3R,4S,5R)-5-(2-Ethyl-2H-tetrazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea
7					4-(3-{(R)-1-[9-[(2R,3R,4S,5R)-5-(2-Ethyl-2H-tetrazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
8					3-(3-{(R)-1-[9-[(2R,3R,4S,5R)-5-(2-Ethyl-2H-tetrazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-6-((S)-1-ydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide

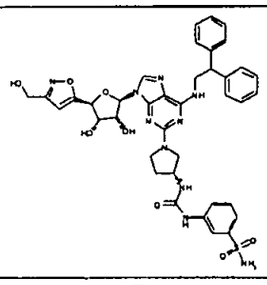
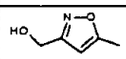
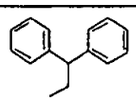
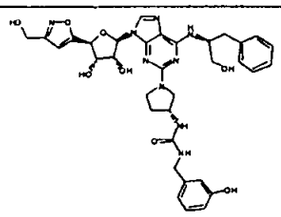
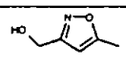
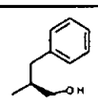
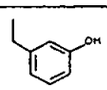
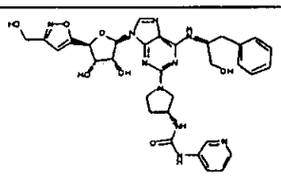
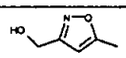
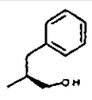
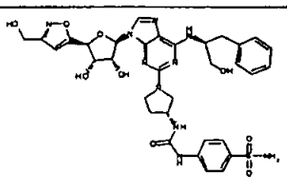
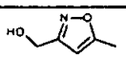
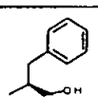
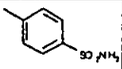
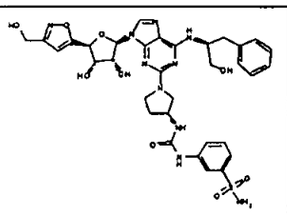
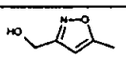
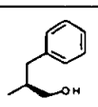
38

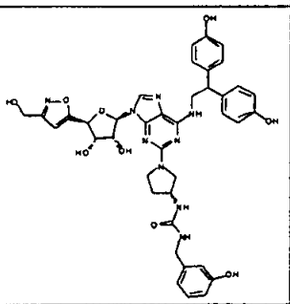
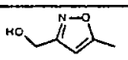
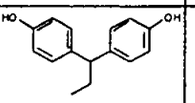
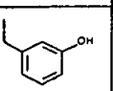
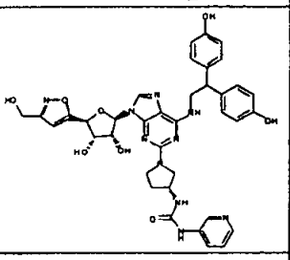
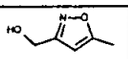
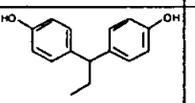
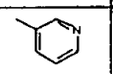
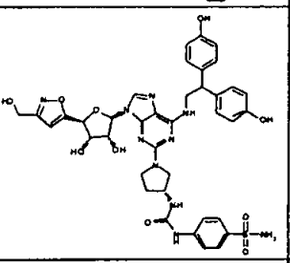
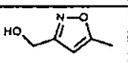
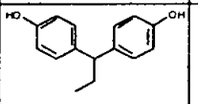
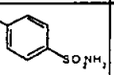
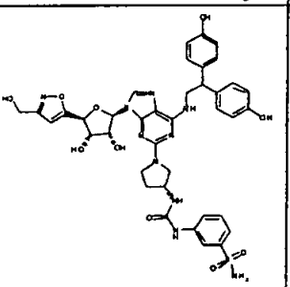
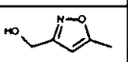
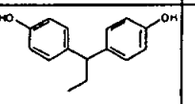
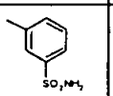
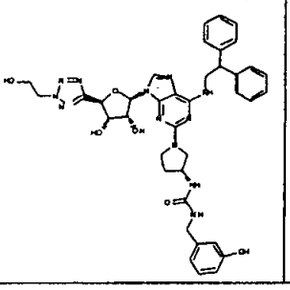
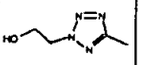
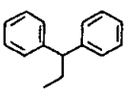
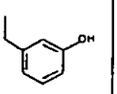
Ex.	Structure	R^1	R^2	R^3	Name
9					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(2R,3R,4S,5R)-5-(2-ethyl-2H-tetrazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea
10					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(2R,3R,4S,5R)-5-(2-ethyl-2H-tetrazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-pyridin-3-yl-urea
11					4-{3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(2R,3R,4S,5R)-5-(2-ethyl-2H-tetrazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
12					3-{3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(2R,3R,4S,5R)-5-(2-ethyl-2H-tetrazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide

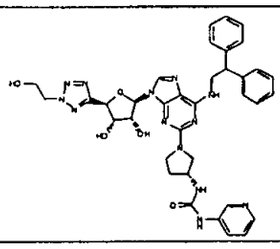
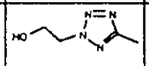
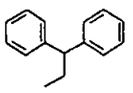
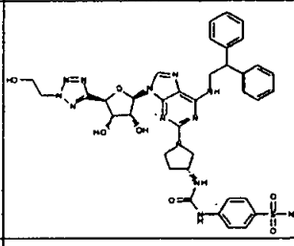
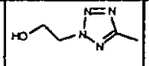
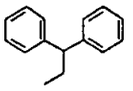
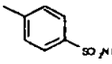
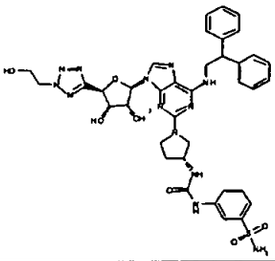
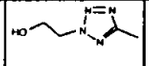
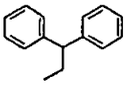
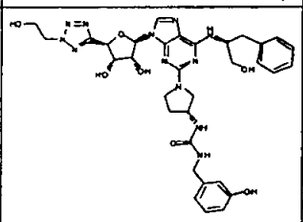
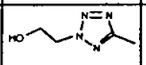
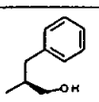
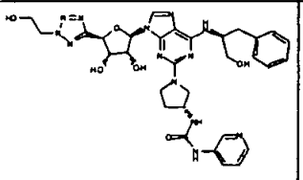
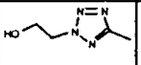
Ex.	Structure	R^1	R^2	R^3	Name
13					1-((R)-1-{6-(2,2-Diphenyl-ethylamino)-9-[(2R,3R,4S,5S)-5-(3-ethyl-isoxazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea
14					1-((R)-1-{6-(2,2-Diphenyl-ethylamino)-9-[(2R,3R,4S,5S)-5-(3-ethyl-isoxazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-pyridin-3-yl-urea
15					4-[3-((R)-1-{6-(2,2-Diphenyl-ethylamino)-9-[(2R,3R,4S,5S)-5-(3-ethyl-isoxazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
16					3-[3-((R)-1-{6-(2,2-Diphenyl-ethylamino)-9-[(2R,3R,4S,5S)-5-(3-ethyl-isoxazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
17					1-((R)-1-[9-[(2R,3R,4S,5S)-5-(3-Ethyl-isoxazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea

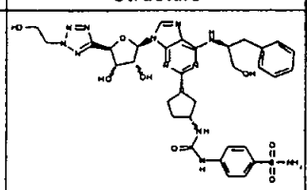
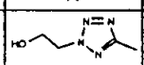
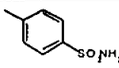
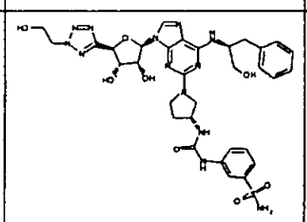
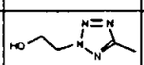
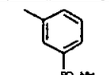
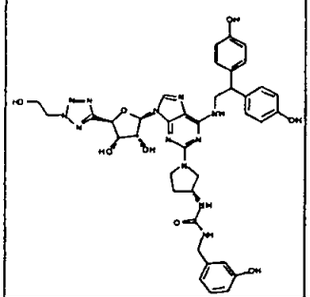
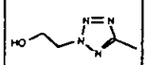
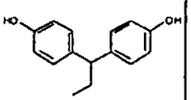
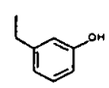
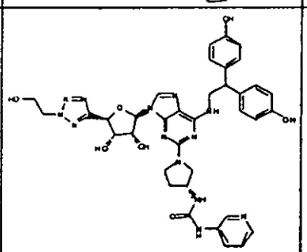
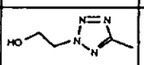
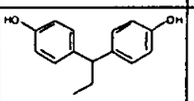
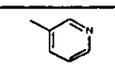
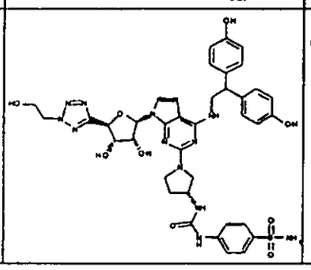
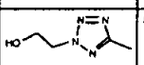
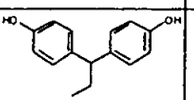
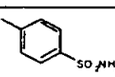
Ex.	Structure	R^1	R^2	R^3	Name
18					1-{(R)-1-[9-[(2R,3R,4S,5S)-5-(3-Ethyl-isoxazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea
19					4-{3-{(R)-1-[9-[(2R,3R,4S,5S)-5-(3-Ethyl-isoxazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
20					3-{3-{(R)-1-[9-[(2R,3R,4S,5S)-5-(3-Ethyl-isoxazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
21					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(2R,3R,4S,5S)-5-(3-ethyl-isoxazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea
22					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(2R,3R,4S,5S)-5-(3-ethyl-isoxazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-pyridin-3-yl-urea

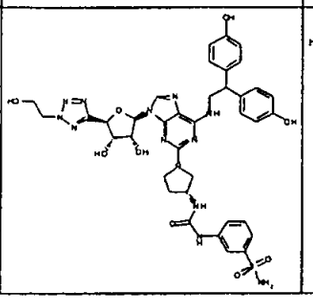
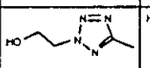
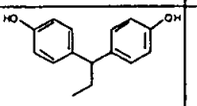
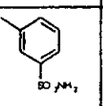
Ex.	Structure	R^1	R^2	R^3	Name
23					4-{3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(2R,3R,4S,5S)-5-(3-ethyl-isoxazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
24					3-{3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(2R,3R,4S,5S)-5-(3-ethyl-isoxazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
25					1-{(R)-1-[9-[(2R,3R,4S,5S)-3,4-Dihydroxy-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-2-yl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea
26					1-{(R)-1-[9-[(2R,3R,4S,5S)-3,4-Dihydroxy-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-2-yl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea
27					4-(3-{(R)-1-[9-[(2R,3R,4S,5S)-3,4-Dihydroxy-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-2-yl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide

Ex.	Structure	R^1	R^2	R^3	Name
28					3-(3-{(R)-1-[9-[(2R,3R,4S,5S)-3,4-Dihydroxy-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-2-yl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
29					1-{(R)-1-[9-[(2R,3R,4S,5S)-3,4-Dihydroxy-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-2-yl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea
30					1-{(R)-1-[9-[(2R,3R,4S,5S)-3,4-Dihydroxy-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-2-yl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrdidin-3-yl}-3-pyridin-3-yl-urea
31					4-(3-{(R)-1-[9-[(2R,3R,4S,5S)-3,4-Dihydroxy-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-2-yl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
32					3-(3-{(R)-1-[9-[(2R,3R,4S,5S)-3,4-Dihydroxy-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-2-yl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide

Ex.	Structure	R^1	R^2	R^3	Name
33					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea
34					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino}-9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-pyridin-3-yl-urea
35					4-[3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
36					3-[3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(2R,3R,4S,5S)-3,4-dihydroxy-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-2-yl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
37					1-{(R)-1-[9-{(2R,3R,4S,5R)-3,4-Dihydroxy-5-[2-(2-hydroxy-ethyl)-2H-tetrazol-5-yl]-tetrahydro-furan-2-yl}-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea

Ex.	Structure	R^1	R^2	R^3	Name
38					1-{(R)-1-[9-{(2R,3R,4S,5R)-3,4-Dihydroxy-5-[2-(2-hydroxy-ethyl)-2H-tetrazol-5-yl]-tetrahydro furan-2-yl}-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea
39					4-(3-{(R)-1-[9-{(2R,3R,4S,5R)-3,4-Dihydroxy-5-[2-(2-hydroxy-ethyl)-2H-tetrazol-5-yl]-tetrahydro furan-2-yl}-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
40					3-(3-{(R)-1-[9-{(2R,3R,4S,5R)-3,4-Dihydroxy-5-[2-(2-hydroxy-ethyl)-2H-tetrazol-5-yl]-tetrahydro furan-2-yl}-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
41					1-{(R)-1-[9-{(2R,3R,4S,5R)-3,4-Dihydroxy-5-[2-(2-hydroxy-ethyl)-2H-tetrazd-5-yl]-tetrahydro furan-2-yl}-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea
42					1-{(R)-1-[9-{(2R,3R,4S,5R)-3,4-Dihydroxy-5-[2-(2-hydroxy-ethyl)-2H-tetrazol-5-yl]-tetrahydro furan-2-yl}-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea

Ex.	Structure	R^1	R^2	R^3	Name
43					4-(3-{(R)-1-[9-{(2R,3R,4S,5R)-3,4-Dihydroxy-5-[2-(2-hydroxy-ethyl)-2H-tetrazol-5-yl]-tetrahydro furan-2-yl}-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
44					3-(3-{(R)-1-[9-{(2R,3R,4S,5R)-3,4-Dihydroxy-5-[2-(2-hydroxy-ethyl)-2H-tetrazol-5-yl]-tetrahydro furan-2-yl}-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
45					1-{(R)-1-(6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-{(2R,3R,4S,5R)-3,4-dihydroxy-5-[2-(2-hydroxy-ethyl)-2H-tetrazol-5-yl]-tetrahydro furan-2-yl}-9H-purin-2-yl)-pyrrolidin-3-yl]-3-(3-hydroxy-benzyl)-urea
46					1-{(R)-1-(6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-{(2R,3R,4S,5R)-3,4-dihydroxy-5-[2-(2-hydroxy-ethyl)-2H-tetrazol-5-yl]-tetrahydro furan-2-yl}-9H-purin-2-yl)-pyrrolidin-3-yl]-3-pyridin-3-yl-urea
47					4-{3-[(R)-1-(6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-{(2R,3R,4S,5R)-3,4-dihydroxy-5-[2-(2-hydroxy-ethyl)-2H-tetrazol-5-yl]-tetrahydro furan-2-yl}-9H-purin-2-yl)-pyrrolidin-3-yl]-ureido}-benzenesulfonamide

Ex.	Structure	R^1	R^2	R^3	Name
48					3-{3-[(R)-1-(6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-{(2R,3R,4S,5R)-3,4-dihydroxy-5-[2-(2-hydroxy-ethyl)-2H-tetrazol-5-yl]-tetrahydro-furan-2-yl}-9H-purin-2-yl)-pyrrolidin-3-yl]-ureido}-benzenesulfonamide

Preparation of intermedia te compounds

Intermediate A **4,4'-(2-Aminoethylidene)*bis*-phenol**

This compound is prepared by the procedure of R.M.Schelkun et al., *Bioorg Med Chem Lett*, Vol. 9,p p. 2447-2452 (1999).

Intermediate BA **(3-Hydroxy-benzyl)-carbamic acid phenyl ester**

3-Hydroxybenzylamine (200 mg, 1.62 mmol) and sodium hydrogen carbonate (273 mg, 3.25 mmol) suspended in water/DCM (4 mL, 1:1) is treated with phenyl chloroformate (0.204 mL, 1.62 mmol). After stirring at RT overnight, the reaction mixture is diluted with more DCM/water and the organic phase is separated. The organic portion is concentrated *in vacuo* to afford the titled compound. (MH+ 244)

Intermediate BB **Pyridin-3-yl-carbamic acid phenyl ester**

Phenyl chloroformate (0.733 mL, 5.84 mmol) is suspended in pyridine/DCM (3 mL, 2:1). The solution is stirred at 0°C, and 3-aminopyridine (500 mg, 5.31 mmol) dissolved in DCM (1 mL) is added dropwise. The reaction mixture is at 0 °C for 1 hour. The solvent is removed *in vacuo* and the residue is dissolved in ethyl acetate. This organic portion is washed with 0.1 M HCl and then concentrated *in vacuo* to afford the titled compound. (MH+ 215)

Intermediates BC and BD

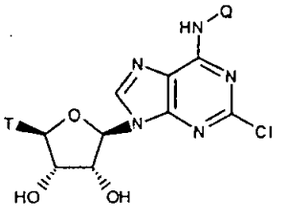
These compounds namely,

- (3-Sulfamoyl-phenyl)-carbamic acid phenyl ester (Intermediate **BC**); and

- (4-Sulfamoyl-phenyl)-carbamic acid phenyl ester (Intermediate **BD**),

are prepared analogously to Intermediate **BB** by replacing 3-aminopyridine with the appropriate amine.

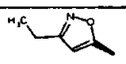
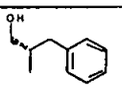
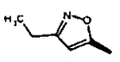
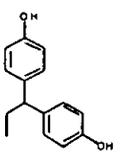
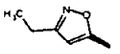
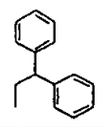
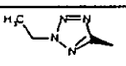
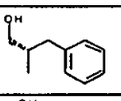
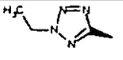
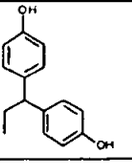
The following intermediates of formula (C)

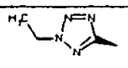
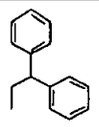
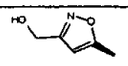
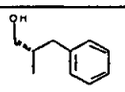
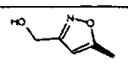
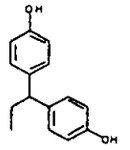
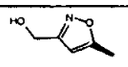
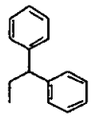
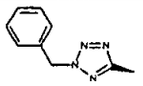
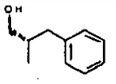
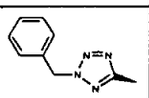
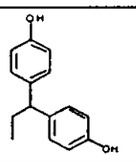


(C)

are shown below in Table 1a, the methods of preparation being described hereinafter.

TABLE 1

Intermediate	T	Q
CA		
CB		
CC		
CD		
CE		

Intermediate	T	Q
CF		
CG		
CH		
CI		
CJ		
CK		

***Intermediate CA* (2*R*,3*R*,4*S*,5*S*)-2-[6-((*S*)-1-Benzyl-2-hydroxy-ethylamino)-2-chloro-purin-9-yl]-5-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3,4-diol**

Step CA1: Acetic acid (2*R*,3*R*,4*R*,5*S*)-4-acetoxy-2-[6-((*S*)-1-benzyl-2-hydroxy-ethyl amino)-2-chloro-purin-9-yl]-5-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3-yl ester hydrochloride

A mixture comprising acetic acid (2*R*,3*R*,4*R*,5*S*)-4-acetoxy-2-(2,6-dichloro-purin-9-yl)-5-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3-yl ester (WO 99/38877) (1 g, 2.13 mmol), (*S*)-2-amino-3-phenyl-propan-1-ol (0.321 g, 2.13 mmol) and DIPEA (0.275 g, 2.13 mmol) in DCE (5 mL) is stirred under an inert atmosphere of argon overnight. After cooling to room temperature (RT), 1 M HCl is added, the organic portion is separated and concentrated

in vacuo to afford the title compound which is used in the next step without further purification. (MH+ 585.1)

Step CA2: (2*R*,3*R*,4*S*,5*S*)-2-[6-((*S*)-1-Benzyl-2-hydroxy-ethylamino)-2-chloro-purin-9-yl]-5-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3,4-diol

A solution of acetic acid (2*R*,3*R*,4*R*,5*S*)-4-acetoxy-2-[6-((*S*)-1-benzyl-2-hydroxy-ethyl amino)-2-chloro-purin-9-yl]-5-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3-yl ester hydrochloride (Step *AC1*) (1.194 g, 2.02 mmol) in MeOH/chloroform (4 mL, 3:1 MeOH/ chloroform) is treated with saturated potassium carbonate solution (10 mL). After stirring at RT overnight, the reaction mixture is diluted with DCM/water and the organic portion is separated. The organic portion is concentrated *in vacuo* to afford the title compound. (MH+ 501)

Intermediate CB-CC

These intermediates namely,

- (2*R*,3*R*,4*S*,5*S*)-2-{6-[2,2-*bis*-(4-Hydroxy-phenyl)-ethylamino]-2-chloro-purin-9-yl}-5-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3,4-diol (Intermediate **CB**); and

- (2*R*,3*R*,4*S*,5*S*)-2-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3,4-diol (Intermediate **CC**),

are prepared analogously to Intermediate **CA** by replacing (*S*)-2-amino-3-phenyl-propan-1-ol with the appropriate amine.

***Intermediate CD* (2*R*,3*R*,4*S*,5*R*)-2-[6-((S)-1-Benzyl-2-hydroxy-ethylamino)-2-chloro-purin-9-yl]-5-(2-ethyl-2*H*-tetrazol-5-yl)-tetrahydro-furan-3,4-diol**

Step CD1: Acetic acid (2*R*,3*R*,4*R*,5*R*)-4-acetoxy-2-[6-((*S*)-1-benzyl-2-hydroxy-ethyl amino)-2-chloro-purin-9-yl]-5-(2-ethyl-2*H*-tetrazol-5-yl)-tetrahydro-furan-3-yl ester

The title compound is prepared analogously to acetic acid (2*R*,3*R*,4*R*,5*S*)-4-acetoxy-2-[6-((*S*)-1-benzyl-2-hydroxy-ethyl amino)-2-chloro-purin-9-yl]-5-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3-yl ester hydrochloride (Step *CA1*) by replacing acetic acid (2*R*,3*R*,4*R*,5*S*)-

4-acetoxy-2-(2,6-dichloro-purin-9-yl)-5-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3-yl ester (WO 99/38877) with acetic acid (2*R*,3*R*,4*R*,5*R*)-4-acetoxy-2-(2,6-dichloro-purin-9-yl)-5-(2-ethyl-2*H*-tetrazol-5-yl)-tetrahydro-furan-3-yl ester (WO 98/28319).

Step CD2: (2*R*,3*R*,4*S*,5*R*)-2-[6-((*S*)-1-Benzyl-2-hydroxy-ethylamino)-2-chloro-purin-9-yl]-5-(2-ethyl-2H-tetrazol-5-yl)-tetrahydro-furan-3,4-diol

The title compound is prepared from acetic acid (2*R*,3*R*,4*R*,5*R*)-4-acetoxy-2-[6-((*S*)-1-benzyl-2-hydroxy-ethylamino)-2-chloro-purin-9-yl]-5-(2-ethyl-2*H*-tetrazol-5-yl)-tetrahydro-furan-3-yl ester (Step *CD1*) analogously to (2*R*,3*R*,4*S*,5*S*)-2-[6-((*S*)-1-benzyl-2-hydroxy-ethylamino)-2-chloro-purin-9-yl]-5-(3-ethyl-isoxazol-5-yl)-tetrahydro-furan-3,4-diol (Step *CA2*).

Intermediates CE and CF

These intermediates namely,

- (2*R*,3*R*,4*S*,5*R*)-2-[6-[2,2-*bis*-(4-Hydroxy-phenyl)-ethylamino]-2-chloro-purin-9-yl]-5-(2-ethyl-2*H*-tetrazol-5-yl)-tetrahydro-furan-3,4-diol (Intermediate **CE**); and

- (2*R*,3*R*,4*S*,5*R*)-2-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(2-ethyl-2*H*-tetrazol-5-yl)-tetrahydro-furan-3,4-diol (Intermediate **CF**),

are prepared analogou sly to Intermediate **CD** by replacing (*S*)-2-amino-3-phenyl-propan-1-ol with the appropriate amine.

Intermediate CG **(2*R*,3*R*,4*S*,5*S*)-2-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-3,4-diol**

Step CG1: Acetic acid (2*R*,3*R*,4*R*,5*S*)-4-acetoxy-5-(3-acetoxymethyl-isoxazol-5-yl)-2-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-tetrahydro-furan-3-yl ester

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A mixture containing acetic acid (2*R*,3*R*,4*R*,5*S*)-4-acetoxy-5-(3-acetoxymethyl-isoxazol-5-yl)-2-(2,6-dichloro-purin-9-yl)-tetrahydro-furan-3-yl ester (WO 99/38877), 2,2-diphenylethylamine and DIPEA in DCE is stirred under an inert atmosphere of argon at 50°C overnight. After cooling to RT, 0.1 M HCl is added, the organic portion separated and concentrated *in vacuo* to afford the titled compound which is used in the next step without further purification.

Step CG2: (2*R*,3*R*,4*S*,5*S*)-2-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-3,4-diol

A solution of acetic acid (2*R*,3*R*,4*S*,5*S*)-4-acetoxy-5-(3-acetoxymethyl-isoxazol-5-yl)-2-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-tetrahydro-furan-3-yl ester (Step *CG1*) in MeOH/chloroform (3:1 MeOH/chloroform) is treated with saturated potassium carbonate solution. After stirring at RT overnight, the reaction is diluted with DCM/water and the organic portion is separated. The organic portion is concentrated *in vacuo* to afford the titled compound.

Intermediate CH **(2*R*,3*R*,4*S*,5*S*)-2-{6-[2,2-*bis*-(4-Hydroxy-phenyl)-ethylamino]-2-chloro-purin-9-yl}-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydrofuran-3,4-diol**

The title compound is prepared from acetic acid (2*R*,3*R*,4*R*,5*S*)-4-acetoxy-5-(3-acetoxymethyl-isoxazol-5-yl)-2-(2,6-dichloro-purin-9-yl)-tetrahydro-furan-3-yl ester (WO 99/38877) analogously to (2*R*,3*R*,4*S*,5*S*)-2-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-3,4-diol (Intermediate **CG**) by replacing 2,2-diphenylethylamine with 4,4'-(2-aminoethylidene)bis-phenol (Intermediate **A**).

Intermediate CI **(2*R*,3*R*,4*S*,5*S*)-2-[2-Chloro-6-((*S*)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-3,4-diol**

The title compound is prepared from acetic acid (2*R*,3*R*,4*R*,5*S*)-4-acetoxy-5-(3-acetoxymethyl-isoxazol-5-yl)-2-(2,6-dichloro-purin-9-yl)-tetrahydro-furan-3-yl ester (WO 99/38877) analogously to (2*R*,3*R*,4*S*,5*S*)-2-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(3-hydroxymethyl-isoxazol-5-yl)-tetrahydro-furan-3,4-diol (Intermediate **CG**) by replacing 2,2-diphenylethylamine with (*S*)-2-amino-3-phenyl-propan-1-ol.

Intermediate CJ **(2R,3R,4S,5R)-2-[6-((S)-1-Benzyl-2-hydroxy-ethylamino)-2-chloro-purin-9-yl]-5-(2-benzyl-2H-tetrazol-5-yl)-tetrahydro-furan-3,4-diol**

The title compound is prepared in an analogous fashion to (2*R*,3*S*,4*R*,5*R*)-2-(2-benzyl-2*H*-tetrazol-5-yl)-5-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol (WO 99/38877) by replacing 2,2-diphenylethylamine with (*S*)-2-amino-3-phenyl-propan-1-ol.

Intermediate CK **(2R,3S,4R,5R)-2-(2-Benzyl-2H-tetrazol-5-yl)-5-{6-[2,2-bis-(4-hydroxy-phenyl) ethylamino]-2-chloro-purin-9-yl}-tetrahydro-furan-3,4-diol**

The title compound is prepared in an analogous fashion to (2*R*,3*S*,4*R*,5*R*)-2-(2-benzyl-2*H*-tetrazol-5-yl)-5-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol (WO 99/38877) by replacing 2,2-diphenylethylamine with 4,4'-(2-aminoethylidene)bis-phenol (Intermediate **A**).

Preparation of Examples

Example 1 **1-((*R*)-1-{6-(2,2-Diphenyl-ethylamino)-9-[(2*R*,3*R*,4*S*,5*R*)-5-(2-ethyl-2*H*-tetrazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9*H*-purin-2-yl}-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea trifluoroacetate**

Step 1: (2*R*,3*R*,4*S*,5*R*)-2-[6-(2,2-Diphenyl-ethylamino)-2-((*R*)-3-BOC-amino-pyrrolidin-1-yl)-purin-9-yl]-5-(2-ethyl-2*H*-tetrazol-5-yl)-tetrahydro-furan-3,4-diol

(2*R*,3*R*,4*S*,5*R*)-2-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(2-ethyl-2*H*-tetrazol-5-yl)-tetrahydro-furan-3,4-diol (Intermediate **CF**) (1 g, 1.82 mmol), (3*R*)-3-(BOC-amino)pyrrolidine (1.02 g, 5.47 mmol) and sodium iodide (273 mg, 1.82 mmol) are dissolved in acetonitrile (10 mL) and NMP (0.5 mL). The reaction mixture is heated using microwave radiation at 160 °C for 30 minutes in the Personal Chemistry Emrys™ Optimizer microwave reactor. The reaction mixture is concentrated *in vacuo* and purified by C-18 reverse phase column chromatography eluting with acetonitrile:water (0.1% TFA) (gradient 0-100% acetonitrile) to afford the titled compound.

Step 2: (2*R*,3*R*,4*S*,5*R*)-2-[2-((*R*)-3-Amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(2-ethyl-2*H*-tetrazol-5-yl)-tetrahydro-furan-3,4-diol trifluoroacetate

(2*R*,3*R*,4*S*,5*R*)-2-[6-(2,2-Diphenyl-ethylamino)-2-((*R*)-3-BOC-amino-pyrrolidin-1-yl)purin-9-yl]-5-(2-ethyl-2*H*-tetrazol-5-yl)-tetrahydro-furan-3,4-diol (Step *AA1*) is dissolved in DCM and TFA and stirred at RT overnight. The reaction mixture is concentrated *in vacuo* to afford the titled compound.

Step 3: 1-((*R*)-1-{6-(2,2-Diphenyl-ethylamino)-9-[(2*R*,3*R*,4*S*,5*R*)-5-(2-ethyl-2*H*-tetrazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-9*H*-purin-2-yl}-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea trifluoroacetate

(2*R*,3*R*,4*S*,5*R*)-2-[2-((*R*)-3-Amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(2-ethyl-2*H*-tetrazol-5-yl)-tetrahydro-furan-3,4-diol trifluoroacetate and (3-hydroxy-benzyl)-carbamic acid phenyl ester (Intermediate **BA**) are dissolved in methanol and TEA. The reaction mixture is heated using microwave radiation at 100°C for 30 minutes in the Personal Chemistry Emrys™ Optimizer microwave reactor. The reaction mixture is concentrated *in vacuo* and purified by C-18 reverse phase column chromatography eluting with acetonitrile:water (0.1% TFA) (gradient 0-100% acetonitrile) to afford the titled compound.

Examples 2-36

These are prepared analogously to Example1 by combining the appropriate starting compound from Table 1a (Intermediates **CA-CI**) with the appropriate phenyl esters (Intermediates **BA-BD**).

Example 37 **1-{(*R*)-1-[9-{(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-[2-(2-hydroxy-ethyl)-2*H*-tetrazol-5-yl]-tetrahydro-furan-2-yl}-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea**

Step 1: 1-{(*R*)-1-[9-[(2*R*,3*R*,4*S*,5*R*)-6-(2-Benzyl-2*H*-tetrazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea

This compound is prepared from (2*R*,3*S*,4*R*,5*R*)-2-(2-benzyl-2*H*-tetrazol-5-yl)-5-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol (WO 99/38877) and pyridin-3-yl-carbamic acid phenyl ester (Intermediate **BB**) analogously to Example 1.

Step 2: 1-{(*R*)-1-[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(2*H*-tetrazol-5-yl)-tetrahydro-furan-2-yl]-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl}-pyrrolidin-3-yl}-3-pyridin-3-yl-urea

A solution of 1-{(*R*)-1-[9-[(2*R*,3*R*,4*S*,5*R*)-5-(2-Benzyl-2*H*-tetrazol-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea in EtOH under an inert atmosphere of argon is treated with 10% palladium on carbon followed by ammonium formate. The reaction mixture is heated to 50°C for 4 hours and then filtered through celite®. The filtrate is concentrated *in vacuo* to afford the title compound.

Step 3: 1-{(*R*)-1-[9-{(2*R*,3*R*,4*S*,5R)-3,4-Dihydroxy-5-[2-(2-hydroxy-ethyl)-2*H*-tetrazol-5-yl]-tetrahydro-furan-2-yl}-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea

A solution of 1-{(*R*)-1-[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(2*H*-tetrazol-5-yl)-tetrahydro-furan-2-yl]-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea in DMF is treated with potassium carbonate followed by 3-bromoethanol and stirred at RT for 18 hours. The mixture is then filtered and the filtrate is concentrated *in vacuo*. Purification of the crude product by C-18 reverse phase column chromatography eluting with acetonitrile:water (0.1% TFA) (gradient 0-100% acetonitrile) to affords the titled compound.

Examples 38-40

These compounds are prepared analogously to Example 37 by replacing pyridin-3-yl-carbamic acid phenyl ester (Intermediate **BB**) with Intermediates **BA**, **BD** and **BC**, respectively.

Examples 41-44

These examples are prepared analogously to Examples 37-40 by replacing (2*R*,3*S*,4*R*,5*R*)-2-(2-benzyl-2*H*-tetrazol-5-yl)-5-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol (WO 99/38877) with (2R,3R,4S,5R)-2-[6-((S)-1-Benzyl-2-

hydroxy-ethylamino)-2-chloro-purin-9-yl]-5-(2-benzyl-2H-tetrazol-5-yl)-tetrahydro-furan-3,4-diol (Intermediate CJ).

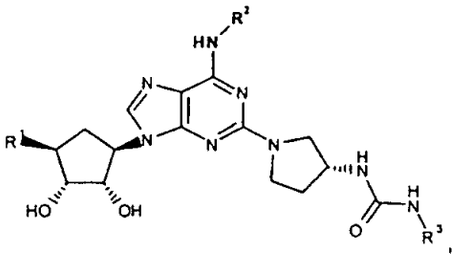
Examples 45-48

These examples are prepared analogously to Examples 37-40 by replacing (2*R*,3*S*,4*R*,5*R*)-2-(2-benzyl-2*H*-tetrazol-5-yl)-5-[2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-tetrahydro-furan-3,4-diol (WO 99/38877) with (2R,3S,4R,5R)-2-(2-Benzyl-2H-tetrazol-5-yl)-5-{6-[2,2-bis-(4-hydroxy-phenyl) ethylamino]-2-chloro-purin-9-yl}-tetrahydro-furan-3,4-diol (Intermediate CK)

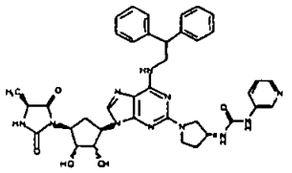
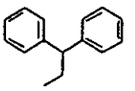
Carbocyclic Examples

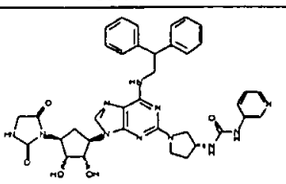
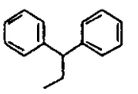
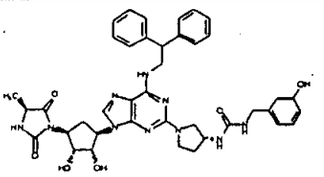
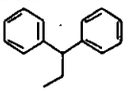
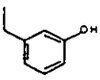
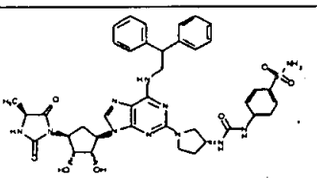
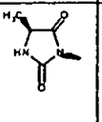
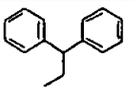
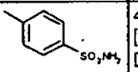
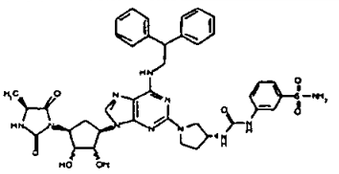
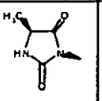
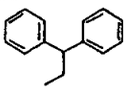
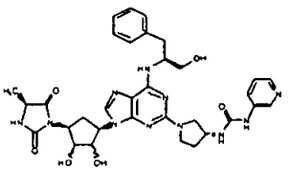
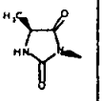
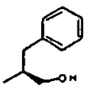
Examples C1-C84

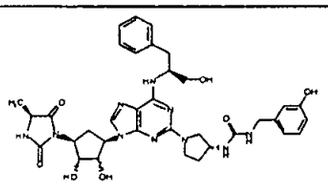
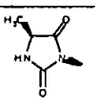
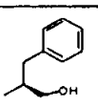
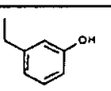
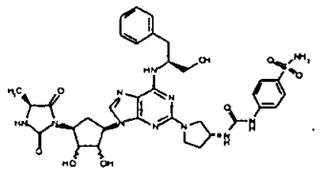
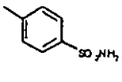
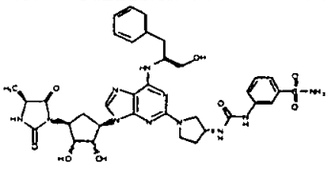
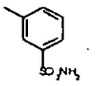
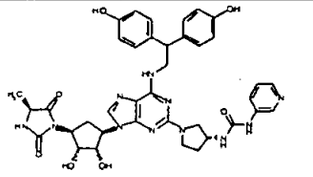
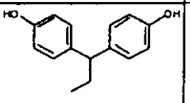
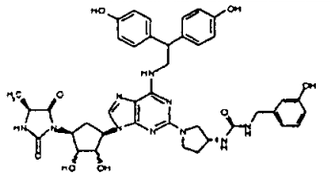
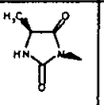
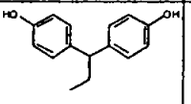
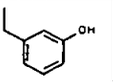
Compounds of formula (I)

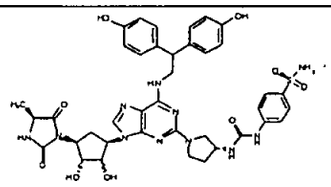
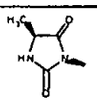
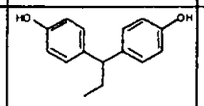
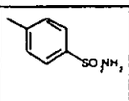
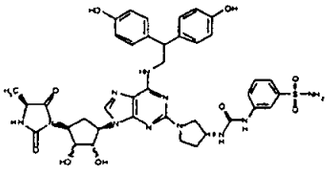
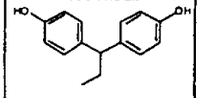
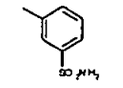
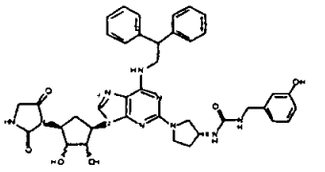
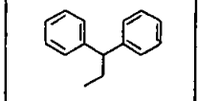
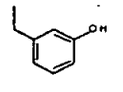
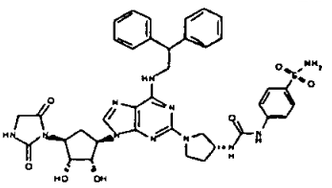
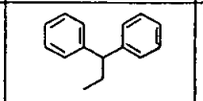
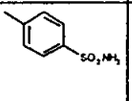
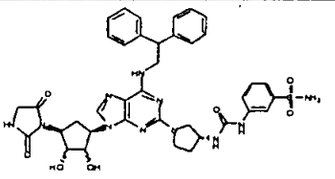
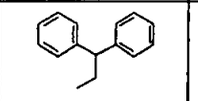
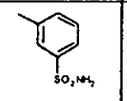


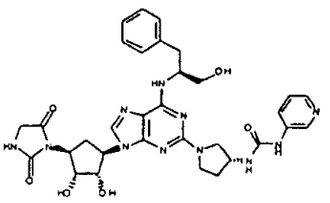
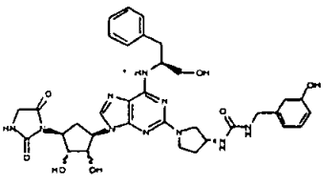
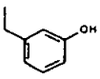
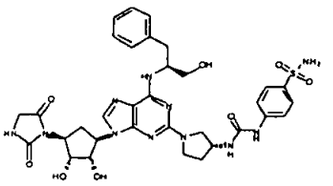
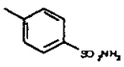
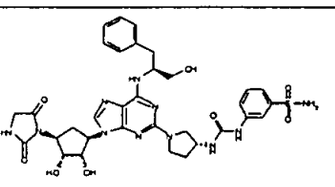
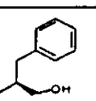
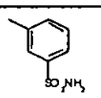
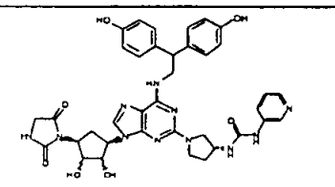
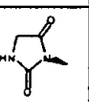
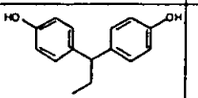
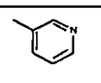
are shown in the following table. Methods for preparing such compounds are described hereinafter. The table also shows mass spectrometry, MH^+ {ESMS), data. The Examples are trifluoroacetate salts.

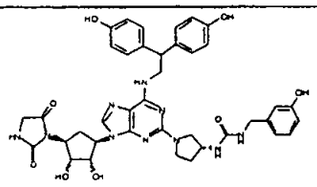
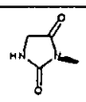
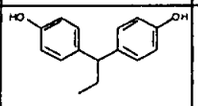
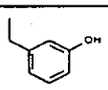
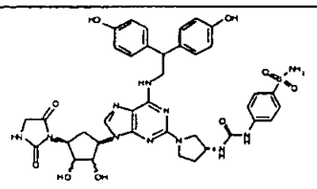
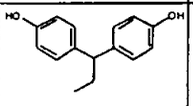
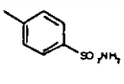
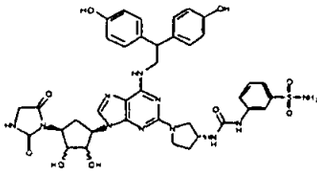
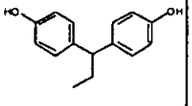
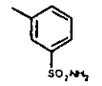
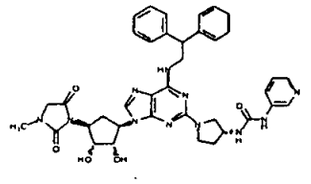
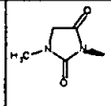
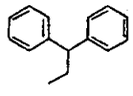
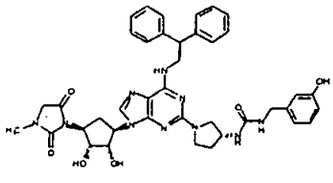
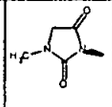
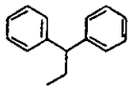
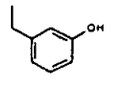
Ex.	Structure	R^1	R^2	R^3	Name
C1					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-((S)-4-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl)-3-pyridin-3-yl-urea

Ex.	Structure	R^1	R^2	R^3	Name
C2					1-{(R)-1-[9-[(1R,2S,3R,4S)-4-(2,5-Dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl}-yrrolidin-3-yl}-3-pyridin-3-yl-urea
C3					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-((S)-4-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl }-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea
C4					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-((S)-4-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C5					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-((S)-4-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C6					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-((S)-4-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-3-pyridin-3-yl-urea

Ex.	Structure	R^1	R^2	R^3	Name
C7					1-((R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-((S)-4-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea
C8					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-((S)-4-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C9					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-((S)-4-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C10					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-((S)-4-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-pyridin-3-yl-urea
C11					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-((S)-4-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea

Ex.	Structure	R^1	R^2	R^3	Name
C12					4-[3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-((S)-4-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
C13					3-[3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-((S)-4-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
C14					1-((R)-1-[9-[(1R,2S,3R,4S)-4-(2,5-Dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-6-(2,2-diphenylethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea
C15					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-4-(2,5-Dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-6-(2,2-diphenylethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C16					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-4-(2,5-Dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-6-(2,2-diphenylethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide

Ex.	Structure	R^1	R^2	R^3	Name
C17					1-{(R)-1-[9-[(1R,2S,3R,4S)-4-(2,5-Dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-3-pyridin-3-yl-urea
C18					1-{(R)-1-[9-[(1R,2S,3R,4S)-4-(2,5-Dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea
C19					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-4-(2,5-Dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C20					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-4-(2,5-Dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C21					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-4-(2,5-dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-pyridin-3-yl-urea

Ex.	Structure	R^1	R^2	R^3	Name
C22					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-4-(2,5-dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea
C23					4-[3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-4-(2,5-dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
C24					3-[3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-4-(2,5-dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
C25					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(3-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-3-pyridin-3-yl-urea
C26					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(3-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea

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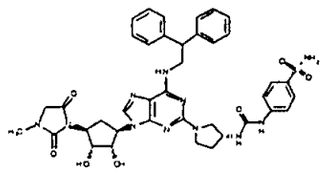
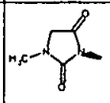
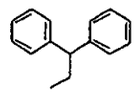
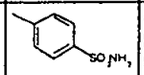
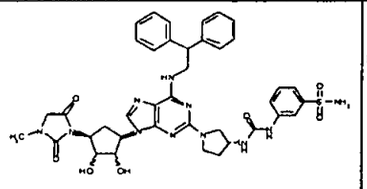
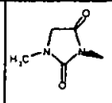
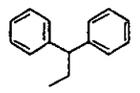
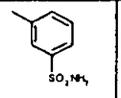
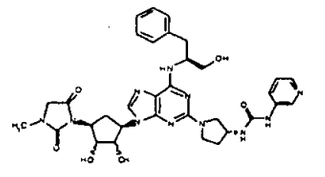
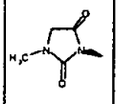
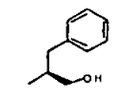
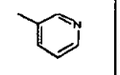
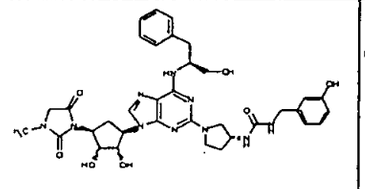
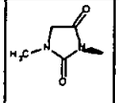
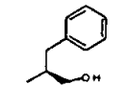
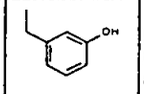
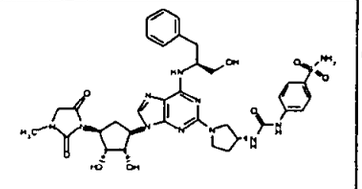
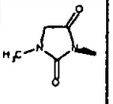
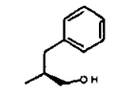
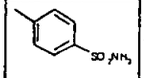
Ex.	Structure	R^1	R^2	R^3	Name
C27					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(3-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C28					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(3-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C29					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(3-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-3-pyridin-3-yl-urea
C30					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(3-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea
C31					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(3-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide

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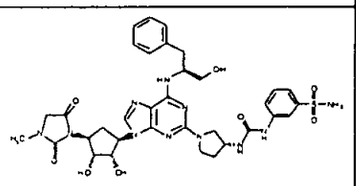
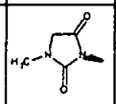
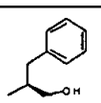
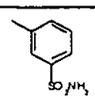
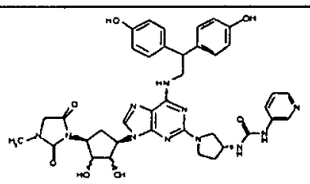
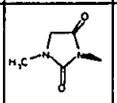
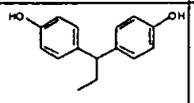
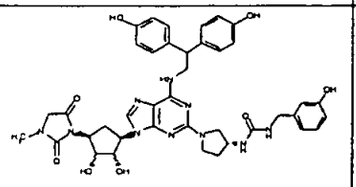
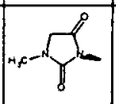
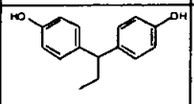
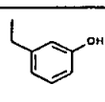
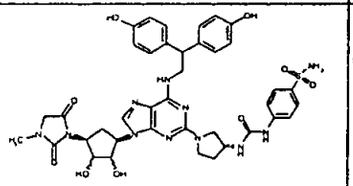
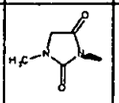
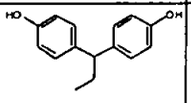
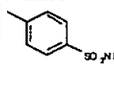
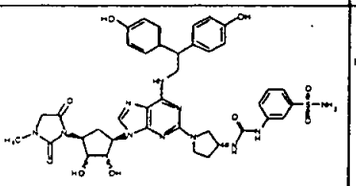
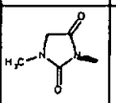
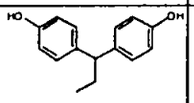
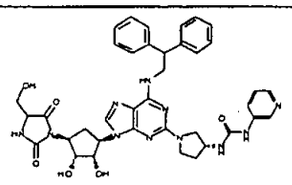
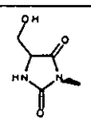
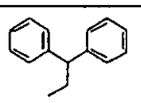
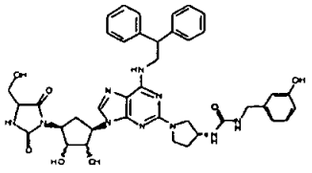
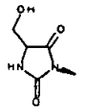
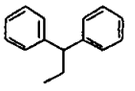
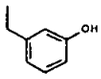
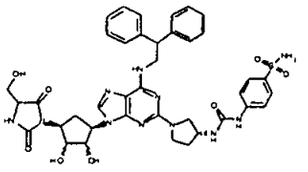
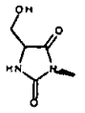
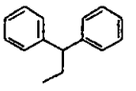
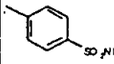
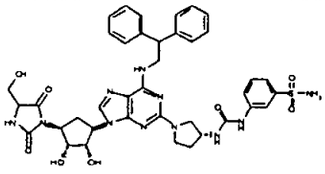
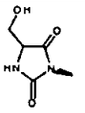
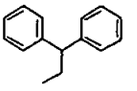
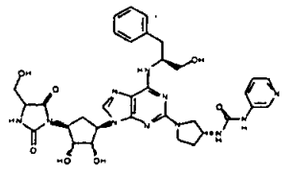
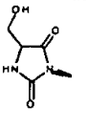
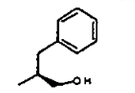
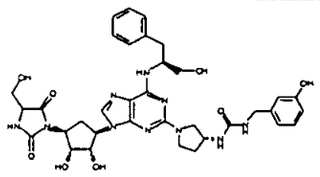
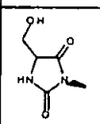
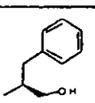
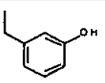
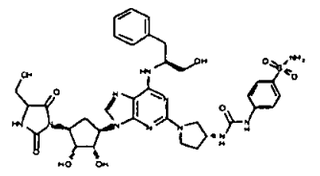
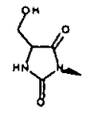
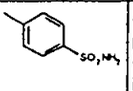
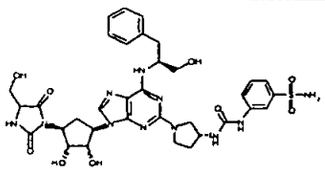
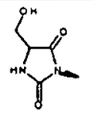
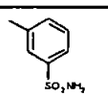
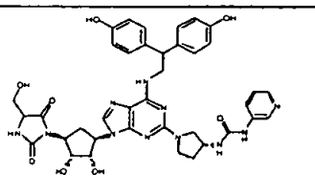
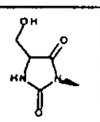
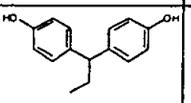
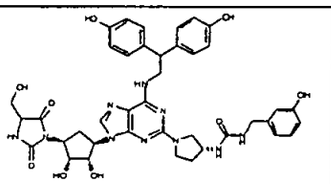
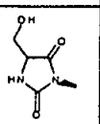
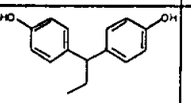
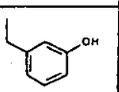
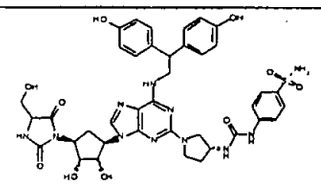
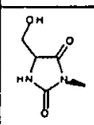
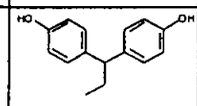
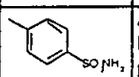
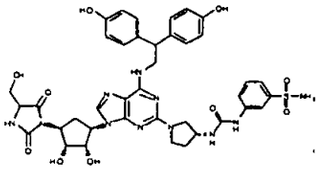
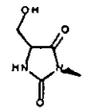
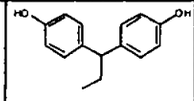
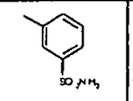
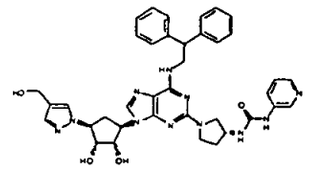
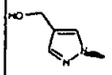
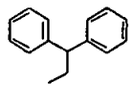
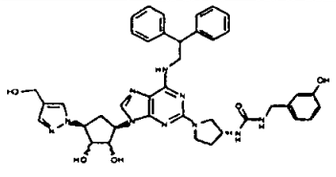
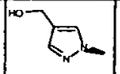
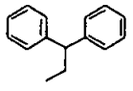
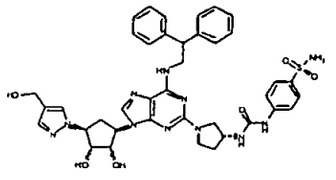
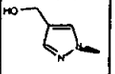
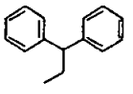
Ex.	Structure	R^1	R^2	R^3	Name
C32					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(3-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C33					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(3-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-pyridin-3-yl-urea
C34					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-{(1R,2S,3R,4S)-2,3-dihydroxy-4-(3-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl}-9H-purin-2-yl}-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea
C35					4-[3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(3-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
C36					3-[3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(3-methyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide

Ex.	Structure	R^1	R^2	R^3	Name
C37					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea
C38					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea
C39					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C40					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C41					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea

Ex.	Structure	R^1	R^2	R^3	Name
C42					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea
C43					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C44					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C45					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(4-hydroxymethyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-pyridin-3-yl-urea
C46					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(4-hydroxymethyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea

65

Ex.	Structure	R^1	R^2	R^3	Name
C47					4-[3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(4-hydroxymethyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-9H-purin-2-yl}-yrrolidin-3-yl)-ureido]-benzenesulfonamide
C48					3-[3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(4-hydroxymethyl-2,5-dioxo-imidazolidin-1-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
C49					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-pyrazol-1-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea
C50					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-pyrazol-1-yl)-cyclopentyl]-6-(2,2-diphenylethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea
C51					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-pyrazd-1-yl)-cyclopentyl]-6-(2,2-diphenylethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide

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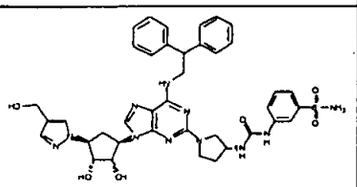
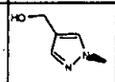
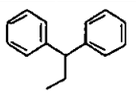
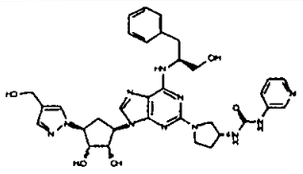
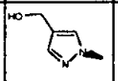
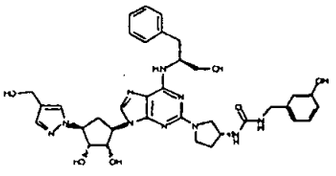
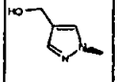
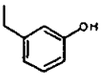
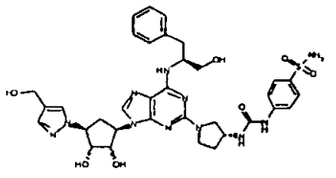
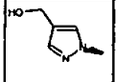
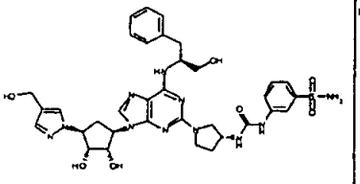
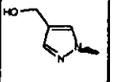
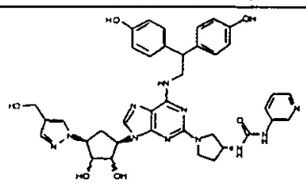
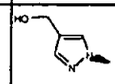
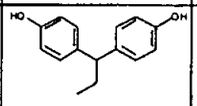
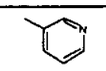
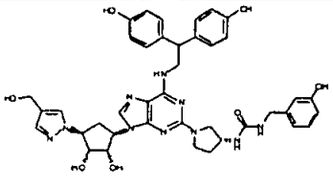
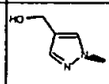
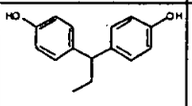
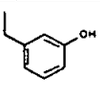
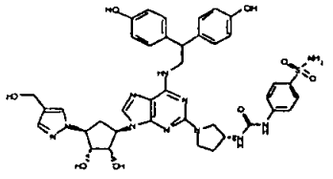
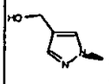
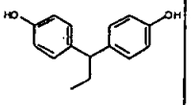
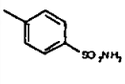
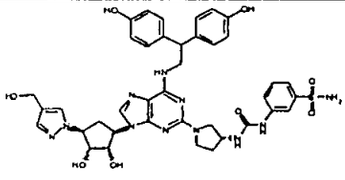
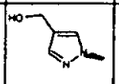
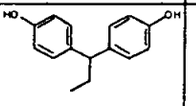
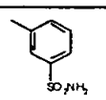
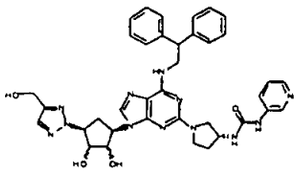
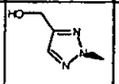
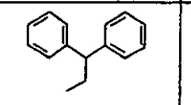
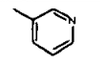
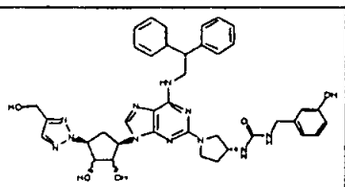
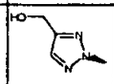
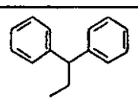
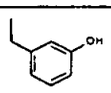
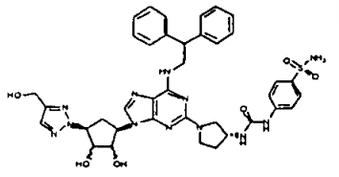
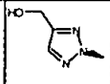
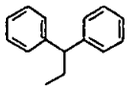
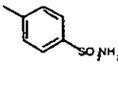
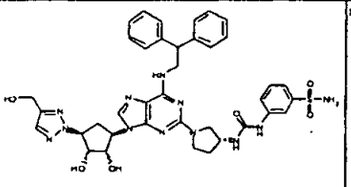
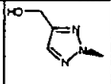
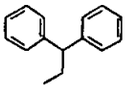
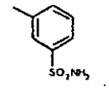
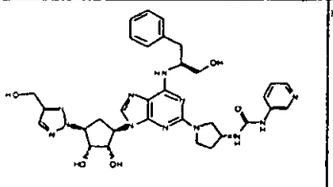
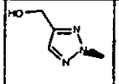
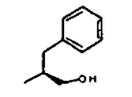
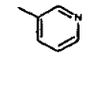
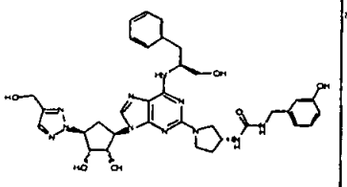
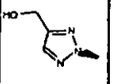
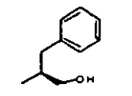
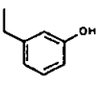
Ex.	Structure	R^1	R^2	R^3	Name
C52					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-pyrazol-1-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C53					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-pyrazol-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-3-pyridin-3-yl-urea
C54					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-pyrazol-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea
C55					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-pyrazol-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C56					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-pyrazol-1-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide

Ex.	Structure	R^1	R^2	R^3	Name
C57					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(4-hydroxymethyl-pyrazol-1-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-pyridin-3-yl-urea
C58					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(4-hydroxymethyl-pyrazol-1-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea
C59					4-[3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(4-hydroxymethyl-pyrazol-1-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
C60					3-[3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(4-hydroxymethyl-pyrazol-1-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
C61					1-((R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentyl]-6-(2,2-diphenylethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl)-3-pyridin-3-yl-urea

Ex.	Structure	R^1	R^2	R^3	Name
C62					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea
C63					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C64					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C65					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-3-pyridin-3-yl-urea
C66					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea

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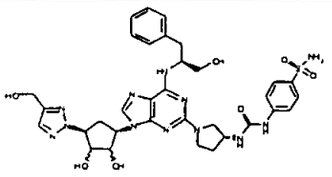
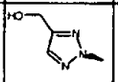
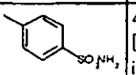
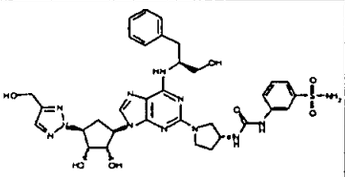
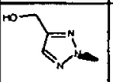
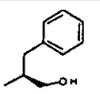
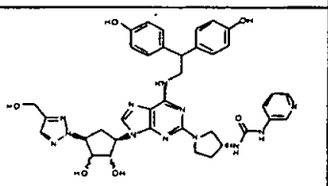
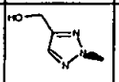
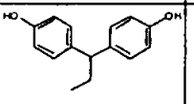
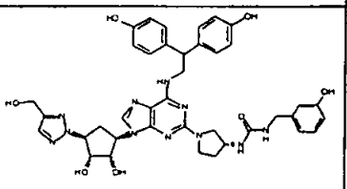
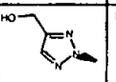
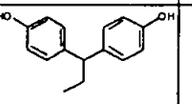
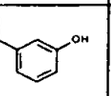
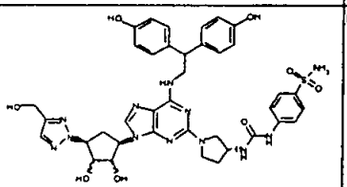
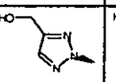
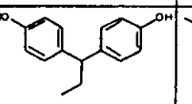
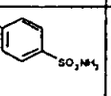
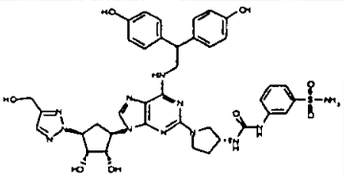
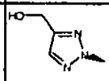
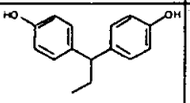
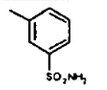
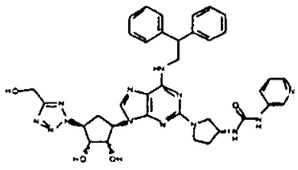
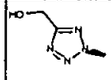
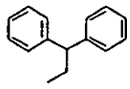
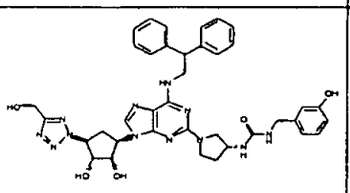
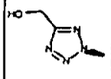
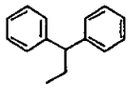
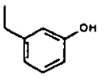
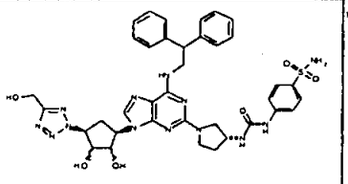
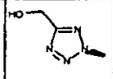
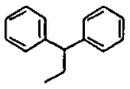
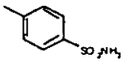
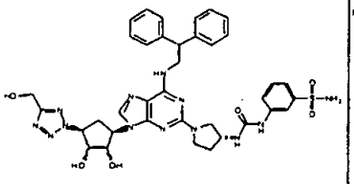
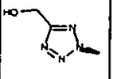
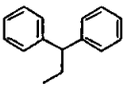
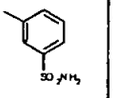
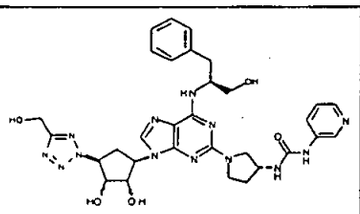
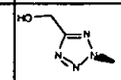
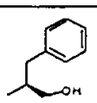
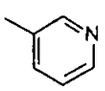
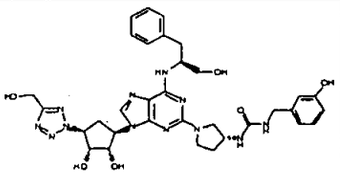
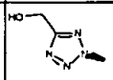
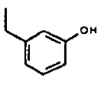
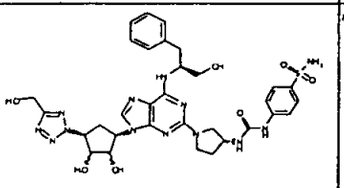
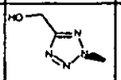
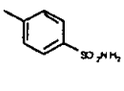
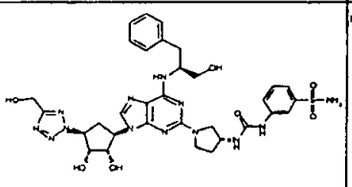
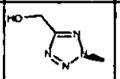
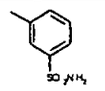
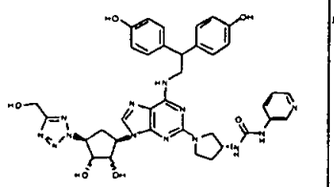
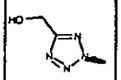
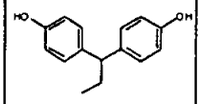
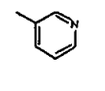
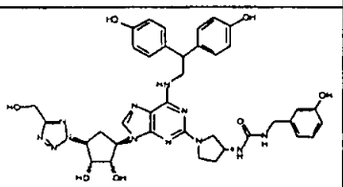
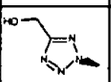
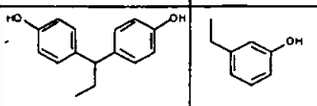
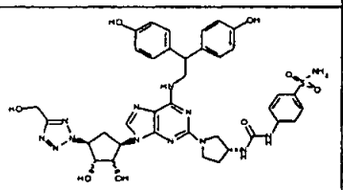
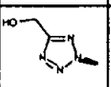
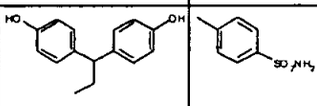
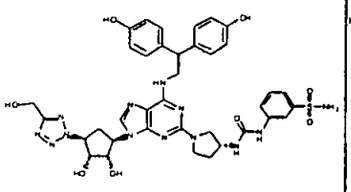
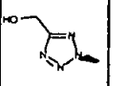
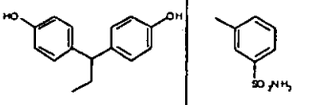
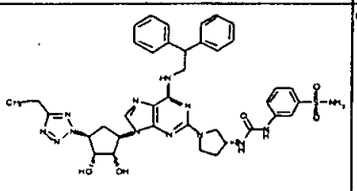
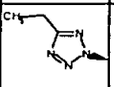
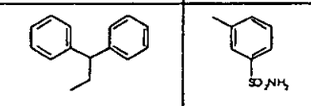
Ex.	Structure	R^1	R^2	R^3	Name
C67					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C68					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C69					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-pyridin-3-yl-urea
C70					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea
C71					4-[3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide

Ex.	Structure	R^1	R^2	R^3	Name
C72					3-[3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
C73					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(5-hydroxymethyl-tetrazol-2-yl)-cyclopentyl]-6-(2,2-diphenylethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl)-3-pyridin-3-yl-urea
C74					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(5-hydroxymethyl-tetrazol-2-yl)-cyclopentyl]-6-(2,2-diphenylethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea
C75					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(5-hydroxymethyl-tetrazol-2-yl)-cyclopentyl]-6-(2,2-diphenylethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido)-benzenesulfonamide
C76					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(5-hydroxymethyl-tetrazol-2-yl)-cyclopentyl]-6-(2,2-diphenylethylamino)-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido)-benzenesulfonamide

Ex.	Structure	R^1	R^2	R^3	Name
C77					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(5-hydroxymethyl-tetrazol-2-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea
C78					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(5-hydroxymethyl-tetrazol-2-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-3-(3-hydroxy-benzyl)-urea
C79					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(5-hydroxymethyl-tetrazol-2-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C80					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihydroxy-4-(5-hydroxymethyl-tetrazol-2-yl)-cyclopentyl]-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl}-ureido)-benzenesulfonamide
C81					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(5-hydroxymethyl-tetrazol-2-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-pyridin-3-yl-urea

Ex.	Structure	R^1	R^2	R^3	Name
C82					1-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(5-hydroxymethyl-tetrazol-2-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-3-(3-hydroxy-benzyl)-urea
C83					4-[3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(5-hydroxymethyl-tetrazol-2-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
C84					3-[3-((R)-1-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(5-hydroxymethyl-tetrazol-2-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide
C85					3-[3-((R)-1-{6-[2,2-Bis-phenyl-ethylamino]-9-[(1R,2S,3R,4S)-2,3-dihydroxy-4-(5-ethyl-tetrazol-2-yl)-cyclopentyl]-9H-purin-2-yl}-pyrrolidin-3-yl)-ureido]-benzenesulfonamide

Preparation of intermediate compounds

Intermediate 1 **Carbonic acid (1 *S*,4*R*)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl ester ethyl ester**

Step a: (1 *S*,4*R*)-4-(2,6-Dichloro-purin-9-yl)-cyclopent-2-enol

2,6-Dichloropurine (10 g, 52.90 mmol), (1*S*,4*R*)-*cis*-4-acetoxy-2-cyclopenten-1-ol (10 g, 70.40 mmol), *tris*(dibenzylideneacetone)dipalladium(0) (3.20 g, 3.50 mmol) and polymer supported triphenylphosphine (3 mmol/g, 11.60 g, 35.00 mmol) are placed in an oven-dried flask under an atmosphere of argon. Dry deoxygenated THF (80 mL) is added and the reaction mixture is stirred gently for 5 minutes. Triethylamine (20 mL) is added and the reaction mixture is stirred at 50°C. The reaction is shown to be complete by LCMS after 1 hour. The reaction mixture is allowed to cool, filtered and the solvent is removed *in vacuo*. The title compound is obtained after purification by flash column chromatography (silica, dichloromethane/methanol 25:1).

^{1}H NMR ($CDCl_3$, 400 MHz); 8.30 (s, 1H), 6.40 (m, 1H), 5.90 (m, 1H), 5.50 (m, 1H), 4.95 (m, 1H), 3.05 (m, 1H), 2.10 (m, 1H). (MH^+) [MH+ 271]

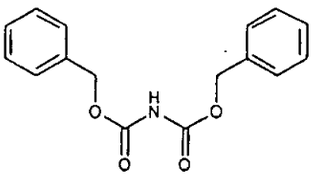
Step b: Carbonic acid (1*S*,4*R*)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl ester ethyl ester

(1*S*,4*R*)-4-(2,6-Dichloro-purin-9-yl)-cyclopent-2-enol [step1](9.5 g, 35.05 mmol) is placed in an oven-dried flask under an atmosphere of argon. Dry THF (200 mL) is added followed by dry pyridine (5.54 g, 70.1 mmol). Ethyl chloroformate (15.21 g, 140.2 mmol) is added slowly so that the temperature does not rise above 40 °C and the reaction mixture is stirred at RT. The reaction is shown to be complete by LCMS after 2 hours. The solvent is removed *in vacuo* and the residue is partitioned between dichloromethane (200 mL) and water (200 mL). The organic layer is washed with water (150 mL) and brine (150 mL), dried over $MgSO_4$, filtered and the solvent is removed *in vacuo*. The title compound is obtained after crystallization from methanol.

^{1}H NMR ($CDCl_3$, 400 MHz); 8.20 (s, 1H), 6.45 (m, 1H), 6.25 (m, 1H), 5.75 (m, 1H), 5.70 (m, 1H), 4.25 (q, 2H), 3.20 (m, 1H), 2.05 (m, 1H), 1.35 (t, 3H). [MH+ 343]

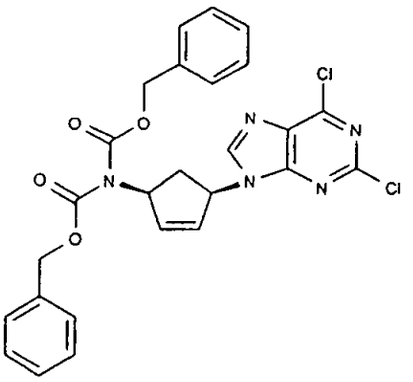
Intermediate 2 **{(1*S*,2*R*,3*S*,4*R*)-4-[2-((*R*)-3-Amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-carbamic acid benzyl ester**

Step a: Preparation of Intermediate **2a** Imidodicarbonic acid, bis(phenylmethyl) ester *(Chemical Abstracts nomenclature)*



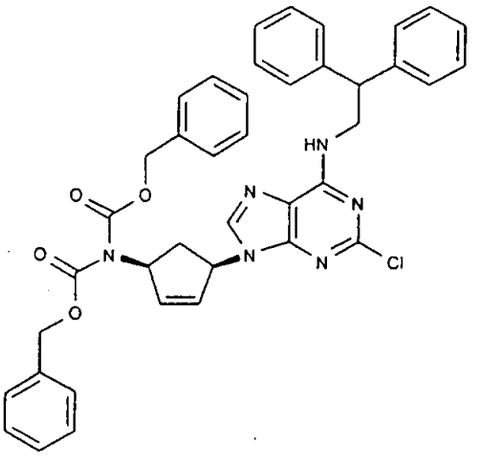
A cooled (0°C) solution of benzyl carbamate (4.0 g, 27 mmol) in THF (100 mL) under an inert atmosphere of argon is treated with potassium iodide (3.2 g of a 35% w/w dispersion in oil, 28 mmol) portionwise over 10 minutes. The reaction mixture is allowed to warm to RT over 30 minutes after which time benzyl chloroformate (5.0 g, 29 mmol) is added. After stirring at RT for 2 hours, the reaction is quenched with water (20 mL). The THF is removed *in vacuo* and the resulting mixture is partitioned between EtOAc and 2 M HCl. The organic portion is separated and washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil is purified by chromatography on silica eluting with 1:3 EtOAc/*iso*-hexane to yield a product which is recrystallized from DCM/*iso*-hexane to afford the title product.

Step b: Preparation of Intermediate **2b**



A solution comprising carbonic acid (1*S*,4*R*)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl ester ethyl ester (Intermediate **1**) (2.0 g, 5.83 mmol), Intermediate **2a** (2.2 g, 7.58 mmol) and triphenyl phosphine (229 mg, 0.9 mmol) in THF (20 mL) is stirred at RT for 30 minutes. *Tris*(dibenzylideneacetone)dipalladium (0) (238 mg, 0.3 mmol) is added and the resulting mixture is stirred at RT for 1.5 hours. The solvent is removed *in vacuo* and the crude product is purified by chromatography on silica eluting with MeOH/DCM (gradient of 0-1% MeOH) to yield the title compound.

Step c: Preparation of Intermediate **2c**



A solution comprising Intermediate **2b** (0.68 g, 1.26 mmol), 1-amino-2,2-diphenylethane (0.37 g, 1.90 mmol) and TEA (190 mg, 1.90 mmol) in THF (10 mL) is stirred at 50°C for 2 hours. The solvent is removed *in vacuo* the resulting oil/solid is partitioned between EtOAc and 0.2 M HCl. The organic portion is separated and washed with saturated sodium bicarbonate solution, water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. [MH+ 699.37]

Step d: Preparation of Intermediate **2d**

A solution comprising Intermediate **2c** (2.0 g, 2.86 mmol) and NMO (0.67 g, 5.7 mmol) in THF (20 mL) is treated with osmium tetroxide (2 mL of a 4% solution in water) and stirred at RT overnight. The solvent is removed *in vacuo* and the crude residue is partitioned between DCM and water. The organic portion is separated, washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting solid is titurated with MeCN to afford the title product. [MH+ 733.40]

Step e: {(*R*)-1-[9-((1*R*,2*S*,3*R*,4*S*)-4-Benzyloxycarbonylamino-2,3-dihydroxy-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-carbamic acid tert-butyl ester

A suspension of Intermediate **2d** (1.03 g, 1.4 mmol) and (3*R*)-(+)-3-(Boc-amino)pyrrolidine (1.03 g, 5.5 mmol) in acetonitrile (2 mL) is treated with sodium iodide (ca. 2 mg) and then heated using microwave radiation at 160°C. After 1 hour, the solvent is

removed *in vacuo* and the crude residue is partitioned between DCM and 0.2 M HCl. The organic layer is separated and the aqueous portion is extracted with DCM. The combined organic extracts are washed with saturated sodium bicarbonate solution, water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a brown oil. [MH+ 745]

Step f: {(1*S*,2*R*,3*S*,4*R*)-4-[2-((*R*)-3-amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-carbamic acid benzyl ester

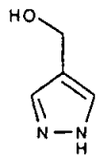
A solution of {(*R*)-1-[9-((1*R*,2*S*,3*R*,4*S*)-4-benzyloxycarbonylamino-2,3-dihydroxy-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (1.24 g, 1.7 mmol) in MeOH (3 mL) is treated with 4 M HCl in dioxane (5 mL) and stirred at RT for 2 hours. The solvent is removed *in vacuo* and purification is carried out by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water – 0.1% HCl). The fractions are collected and the MeCN is removed *in vacuo*. The remaining aqueous portion is basified with saturated sodium bicarbonate solution and extracted with DCM. The combined organic extracted are dried ($MgSO_4$) and concentrated *in vacuo* to afford the title product. [MH+ =649]

Intermediate 3 **(1*R*,2*S*,3*R*,5*S*)-3-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(4-hydroxymethyl-pyrazol-1-yl)-cyclopentane-1,2-diol**

Step a: {1-[(1*S*,4*R*)-4-(2,6-Dichloro-purin-9-yl)-cyclopent-2-enyl]-1*H*-pyrazol-4-yl}-methanol

A mixture comprising carbonic acid (1*S*,4*R*)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl ester ethyl ester (Intermediate **1**) (1.00 g, 2.92 mmol), (1*H*-pyrazol-4-yl)-methanol (preparation shown below) (0.34 g, 3.50 mmol) and triphenyl phosphine (0.115 g, 0.44 mmol) in deoxygenated THF (10 mL) under an inert atmosphere of argon is treated with *tris*(dibenzylideneacetone)dipalladium (0) (0.13 g, 0.15 mmol) and stirred at 50°C for 1 hour. The solvent is removed *in vacuo* and the crude product is purified by chromatography on silica eluting with MeOH/DCM (1:25) to yield the title compound.

Preparation of (1*H*-pyrazol-4-yl)-methanol



4-Ethylpyrazole carboxylate (10 g, 71.40 mmol) is placed in an oven-dried flask under an atmosphere of argon. Dry THF (100 mL) is added followed by the dropwise addition of lithium aluminium hydride (1 M in THF, 100 mL, 100 mmol). Once the addition is complete the reaction mixture is stirred at 50°C. The reaction is shown to be complete by NMR after 4 hours. The reaction mixture is cooled on an ice-bath and the reaction mixture is quenched with water (3.8 mL) then 15% sodium hydroxide (3.8 mL) and finally water again (11.4 mL). The solvent is removed *in vacuo* and the solid is placed in a Soxhlet apparatus. THF is refluxed through the system for 24 hours. The solvent is removed *in vacuo* to give the title compound.

^{1}H NMR (MeOD, 400 MHz); 7.60 (s, 2H), 4.55 (s, 2H).

Step b: (1-{(1*S*,4*R*)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-cyclopent-2-enyl}-1*H*-pyrazol-4-yl)-methanol

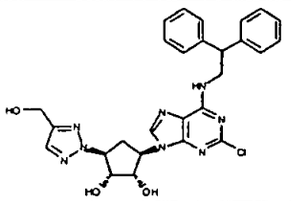
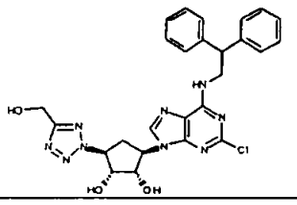
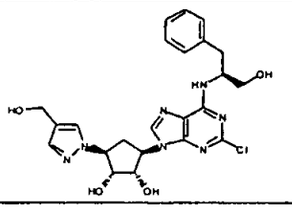
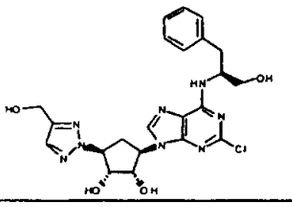
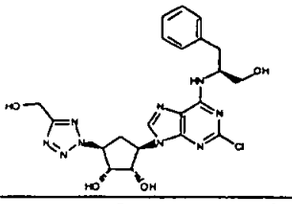
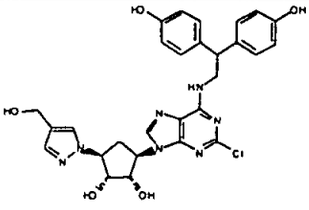
A mixture comprising {1-[(1S,4R)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl]-1H-pyrazol-4-yl}-methanol (0.675 g, 1.92 mmol), diphenylethylamine (0.398 g, 2.02 mmol) and DIPEA (0.298 g, 2.31 mmol) in dry THF (20 mL) is stirred at 35°C for 3 days. The solvent is removed *in vacuo* and the resulting crude residue is partitioned between DCM and 0.1 M HCl. The organic portion is separated, washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title product.

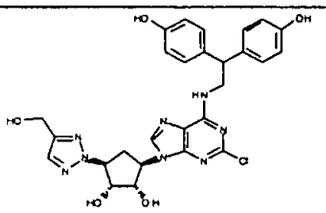
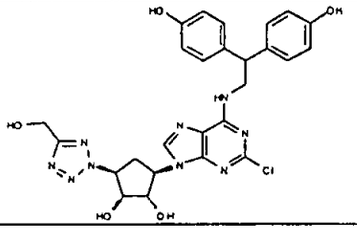
Step d: (1*R*,2*S*,3*R*,5*S*)-3-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(4-hydroxymethyl-pyrazol-1-yl)-cyclopentane-1,2-diol

(1-{(1*S*,4*R*)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-cyclopent-2-enyl}-1*H*-pyrazol-4-yl)-methanol (0.84 g, 1.64 mmol) and NMO (0.39 g, 3.28 mmol) in THF (20 mL) is treated with osmium tetroxide (2 mL of a 4% solution in water) and stirred at RT overnight. The solvent is removed *in vacuo* and the resulting crude residue is partitioned between DCM and 0.1 M HCl (a small amount of MeOH added to improve solubility). The organic portion is dried ($MgSO_4$) and concentrated *in vacuo*. The crude product is dissolved in hot DCM to form the title product as a precipitate on cooling.

Intermediates 4a-4h

Table 1

Intermediate	Structure	Name
4a		(1R,2S,3R,5S)-3-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentane-1,2-diol
4b		(1R,2S,3R5S)-3-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-5-(5-hydroxymethyl-tetrazol-2-yl)-cyclopentane-1,2-diol
4c		(1R,2S,3R,5S)-3-[2-Chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(4-hydroxymethyl-pyrazol-1-yl)-cyclopentane-1,2-diol
4d		(1R,2S,3R,5S)-3-[2-Chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentane-1,2-diol
4e		(1R,2S,3R,5S)-3-[2-Chloro-6-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(5-hydroxymethyl-tetrazol-2-yl)-cyclopentane-1,2-diol
4f		(1R,2S,3R,5S)-3-(6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-2-chloro-purin-9-yl)-5-(4-hydroxy methyl-pyrazol-1-yl)-cyclopentane-1,2-diol

Intermediate	Structure	Name
4g		(1R,2S,3R,5S)-3-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-2-chloro-purin-9-yl}-5-(4-hydroxymethyl-[1,2,3]triazol-2-yl)-cyclopentane-1,2-diol
4h		(1R,2S,3R,5S)-3-{6-[2,2-Bis-(4-hydroxy-phenyl)-ethylamino]-2-chloro-purin-9-yl}-5-(5-hydroxy methyl-tetrazol-2-yl)-cyclopentane-1,2-diol

The intermediates shown in the Table 1 are prepared analogously to Intermediate **3** by using the appropriate 5-membered heterocyclic alcohol in Step *3a* and by using the appropriate amine in Step *3c*.

Intermediate 5 **3-Isocyanato-benzenesulfonamide**

To a vigorously stirred solution of 3-aminobenzenesulphonamide (1 g, 5.8 mmol) in dry 1,4-dioxane (25 mL) is added trichloromethyl chloroformate (1.72 g, 8.7 mmol) and the reaction mixture is heated to reflux for 3 hours. The solvent is removed *in vacuo* to yield the title compound which is used without further purification.

Intermediate 6 **4-Isocyanato-benzenesulfonamide**

This compound is prepared from 4-aminobenzenesulphonamide using a procedure analogous to that of 3-isocyanato-benzenesulfonamide (Intermediate *5*) by replacing 3-aminobenzenesulphonamide with 4-aminobenzenesulphonamide.

Intermediates 7 and 8

These compounds namely,

- ((1*S*,2*R*,3*S*,4*R*)-4-{2-((*R*)-3-Amino-pyrrolidin-1-yl)-6-[2,2-*bis*-(4-hydroxy-phenyl)-ethylamino]-purin-9-yl}-2,3-dihydroxy-cyclopentyl)-carbamic acid benzyl ester (Intermediate **7**); and

- {(1*S*,2*R*,3*S*,4*R*)-4-[2-((*R*)-3-Amino-pyrrolidin-1-yl)-6-((*S*)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-carbamic acid benzyl ester (Intermediate **8**),

are prepared analogously to Intermediate **2** by replacing 1-amino-2,2-diphenylethane (Step *2c*) with the appropriate amine.

Preparation of Examples

Example C1 **1-{(*R*)-1-[9-[(1*R*,2*S*,3*R*,4*S*)-4-(2,5-Dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea**

Step 1: ((1*S*,2*R*,3*S*,4*R*)-4-{6-(2,2-Diphenyl-ethylamino)-2-[(*R*)-3-(3-pyridin-3-yl-ureido)-pyrrolidin-1-yl]-purin-9-yl}-2,3-dihydroxy-cyclopentyl)-carbamic acid benzyl ester trifluoroacetate

A solution comprising {(1*S*,2*R*,3*S*,4*R*)-4-[2-((*R*)-3-amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-carbamic acid benzyl ester (Intermediate **2**) (0.1 g, 0.15 mmol), pyridine-3-isocyanate (0.02 g, 0.17 mmol) and TEA (0.017 g, 0.17 mmol) in THF (2 mL) is stirred at RT overnight. The solvent is removed *in vacuo* and purification is carried out by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water – 0.1% TFA). The fractions are collected and the MeCN is removed *in vacuo*. The remaining aqueous portion is basified with saturated sodium bicarbonate solution and extracted with DCM. The combined organic extracted are dried ($MgSO_4$) and concentrated *in vacuo* to afford the title product. [MH+ 769]

Step 2: 1-{(*R*)-1-[9-((1*R*,2*S*,3*R*,4*S*)-4-Amino-2,3-dihydroxy-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea

To a solution of ((1*S*,2*R*,3*S*,4*R*)-4-{6-(2,2-diphenyl-ethylamino)-2-[(*R*)-3-(3-pyridin-3-yl-ureido)-pyrrolidin-1-yl]-purin-9-yl}-2,3-dihydroxy-cyclopentyl)-carbamic acid benzyl ester trifluoroacetate (35 mg, 46 µmol) in ethanol (1 mL) under an inert atmosphere of argon is added 10% palladium on carbon (10 mg). The reaction mixture is purged with argon and placed under a positive atmosphere of hydrogen overnight after which time, the mixture is

filtered through celite and the catalyst washed with ethanol. The organic portions are combined and concentrated *in vacuo* to yield the title compound. [MH+635]

Step 3: 1-{(*R*)-1-[9-[(1*R*,2*S*,3*R*,4*S*)-4-(2,5-Dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea hydrochloride

To a solution of 1-{(*R*)-1-[9-((1*R*,2*S*,3*R*,4*S*)-4-amino-2,3-dihydroxy-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea (17 mg, 26 µmol) in THF (1 mL) is added Z-L-alanine hydroxysuccinimidyl ester (9 mg, 29 µmol) and the reaction mixture is stirred at RT overnight. The solvent is removed *in vacuo* and the crude residue is dissolved in EtOH (1 mL) and purged with argon. Palladium on carbon (approximately 5 mg) is added and the reaction mixture is placed under a constant pressure of hydrogen (0.35 bar) and stirred at room temperature overnight. The resulting mixture is filtered through celite and concentrated *in vacuo*. Purification of the crude residue by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water– 0.1% HCl) affords the title compound. [MH+732.72].

Example C2 **1-{(*R*)-1-[9-[(1*R*,2*S*,3*R*,4*S*)-4-(2,5-Dioxo-imidazolidin-1-yl)-2,3-dihydroxy-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-3-pyridin-3-yl-urea trifluoroacetate**

This compound is prepared analogously to Example 1 by replacing Z-L-alanine hydroxysuccinimidyl ester (Step *3*) with Z-glycine-*N*-succinimidyl ester. Purification is carried out by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water – 0.1% TFA). [MH+718.68].

Examples C3-C48

These examples can be prepared analogously to Example 1 by using the appropriate starting compound (either Intermediate **2**,**7** or **8**) and isocyanate in Step *1* and by using the appropriate succinimidyl ester in Step *3*.

Those examples containing 3-hyroxybenzyl groups are prepared as follows: (3-hydroxy-benzyl)-carbamic acid phenyl ester (Intermediate **BA**) and (Intermediate **2**, **7** or **8**) are dissolved in MeOH and TEA. The reaction mixture is heated using microwave radiation at 100°C for 30 minutes and then the solvent is removed *in vacuo*. Purification of the crude

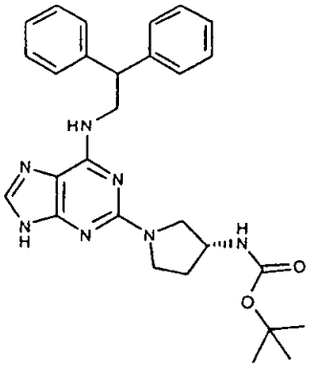
product by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water – 0.1% TFA) affords the product which is taken through Steps *2* and *3* (using the appropriate succinimidyl ester) to afford the final compound.

Examples C49-C84

These compounds are prepared analogously to Example 1 by combining the appropriate starting compound (Intermediates **3** or **4a-4h**) with the appropriate phenyl esters (Intermediates **BA-BD**).

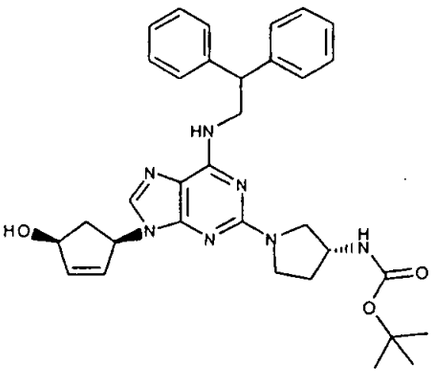
Example C85

Step 1: {(*R*)-1-[6-(2,2-Diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-carbamic acid tert-butyl ester



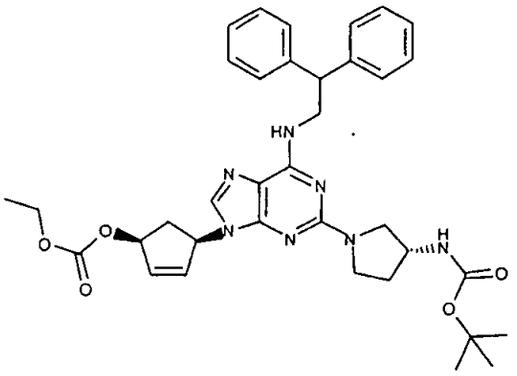
(2-Chloro-9*H*-purin-6-yl)-(2,2-diphenyl-ethyl)-amine (2.5 g) is added to Boc(R)-3-aminopyrrolidine (2.677 g). This is suspended in acetonitrile (10 mL) and put to microwave at 160 °C. Analysis by LCMS shows reaction to be complete after 30 minutes. The reaction mixture is then suspended in acetonitrile and filtered. The resulting precipitate is then dried to give the title compound. MS (ES+) m/e 498 (MH+)

Step 2: {(*R*)-1-[6-(2,2-Diphenyl-ethylamino)-9-((1*R*,4*S*)-4-hydroxy-cyclopent-2-enyl)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-carbamic acid tert-butyl ester



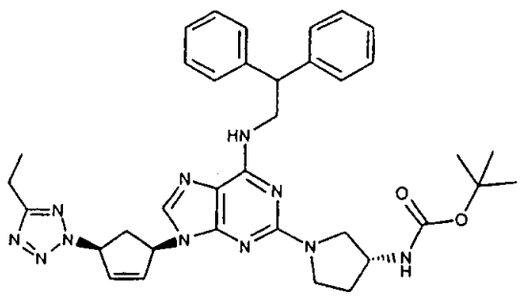
{(*R*)-1-[6-(2,2-Diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (2.5 g) is suspended in THF (15 mL) under an inert atmosphere and oven dried glassware. Sodium hydride (130 mg) is added to the stirring suspension. This is stirred until dissolution has occurred. (1*S*,4*R*)-*cis*-4-Acetoxy-2-cyclopentan-1-ol (865 mg) and triphenylphosphine (236 mg) are placed in an oven-dried flask under an inert atmosphere, this is dissolved in THF (15 mL). This solution is added to the solution of {(*R*)-1-[6-(2,2-diphenyl-ethylamino)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-carbamic acid tert-butyl ester and sodium hydride via syringe. *tris*-(Dibenzylideneacetone)-dipalladium (275 mg) is then added and the reaction is stirred at 50 °C. The reaction is shown to be complete after 1 hour by LCMS. The reaction is allowed to cool and the solvent is removed *in vacuo*. The residue is purified by flash column chromatography (silica, dichloromethane/methanol 25:1), giving the title compound. MS (ES+) m/e 582.62 (MH+)

Step 3: Carbonic acid (1 *S*,4*R*)-4-[2-((*R*)-3-tert-butoxycarbonylamino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-cyclopent-2-enyl ester ethyl ester



{(*R*)-1-[6-(2,2-Diphenyl-ethylamino)-9-((1*R*,4*S*)-4-hydroxy-cyclopent-2-enyl)-9*H*-purin-2-yl]-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (500 mg) is dissolved in dry deoxygenated THF (10 mL). Pyridine (416 µL) is added to the solution. Ethyl chloroformate (492 µL) is pre-dissolved in THF (2.5 mL) and added dropwise to the solution at 0°C. The reaction is stirred at RT. Analysis by LCMS shows reaction completion after 2 hours. The solvent is removed *in vacuo*. The residue is dissolved in dichloromethane (10 mL) and portioned against 0.1 M HCl (10 mL). The organic layer is then washed with water (20 mL) and brine (10 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The title compound is obtained after purification by flash column chromatography (silica, dichloromethane/methanol 40:1).
MS (ES+) m/e 655.46 (MH+).

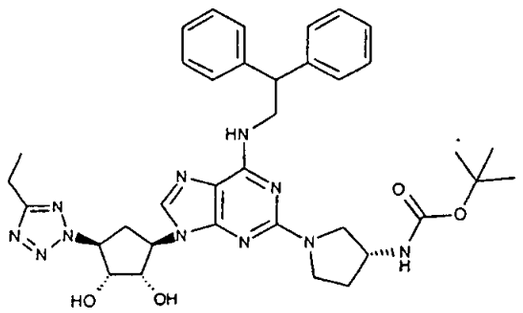
Step 4: ((*R*)-1-{6-(2,2-Diphenyl-ethylamino)-9-[(1*R*,4*S*)-4-(5-ethyl-tetrazol-2-yl)-cyclopent-2-enyl]-9*H*-purin-2-yl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester



Carbonic acid (1*S*,4*R*)-4-[2-((*R*)-3-tert-butoxycarbonylamino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-cyclopent-2-enyl ester ethyl ester (760 mg) is added to ethyl tetrazole (125 mg) and triphenylphosphine (46 mg) in an oven-dried flask under argon. This

is dissolved in anhydrous THF (10 mL). *tris*-(Dibenzylideneacetone)-dipalladium (53 mg) is added to the stirring solution. The reaction is stirred at 50 °C. Analysis by LCMS shows reaction completion after 1 hour. The solvent is removed *in vacuo*. The title compound is obtained by flash column chromatography (silica, dichloromethane/methanol 50:1). MS (ES+) m/e 662.4 (MH+).

Step 5: ((*R*)-1-{6-(2,2-Diphenyl-ethylamino)-9-[(1*R*,4*S*)-4-(5-ethyl-tetrazol-2-yl)-2,3-dihydroxy-cyclopentyl]-9*H*-purin-2-yl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester



((*R*)-1-{6-(2,2-Diphenyl-ethylamino)-9-[(1*R*,4*S*)-4-(5-ethyl-tetrazol-2-yl)-cyclopent-2-enyl]-9*H*-purin-2-yl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester (500 mg) along with *N*-methylmorpholine-*N*-oxide (178 mg) is dissolved in THF (5 mL). Osmium tetroxide 4% in water (500 µL) is added to the stirring solution. The reaction is stirred at RT. Analysis by LCMS showed reaction completion after 72 hours. The solvent is removed *in vacuo* and the residue is portioned between dichloromethane and 0.1 M HCl. The organic layer is washed with water and brine, dried over $MgSO_4$, filtered and the solvent is removed *in vacuo*. The title compound is obtained by Flash column chromatography (silica, dichloromethane/methanol 100:1 - 50:1 – 25:1). MS (ES+) m/e 696.43 (MH+)

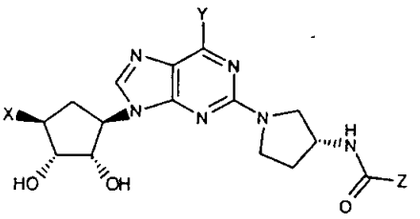
Step 6: 3-[3-((*R*)-1-{6-[bisphenyl-ethylamino]-9-[(1*R*,2*S*,3*R*,4*S*)-2,3-dihydroxy-4-(5-ethyl-tetrazol-2-yl)-cyclopentyl]9*H*-purin-2-yl}-[yrrolidin-3-yl)-ureido]-benzenesulphonamide

((*R*)-1-{6-(2,2-Diphenyl-ethylamino)-9-[(1*R*,4*S*)-4-(5-ethyl-tetrazol-2-yl)-2,3-dihydroxy-cyclopentyl]-9*H*-purin-2-yl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester is deprotected in methanolic HCl to give the corresponding amine hydrochloride salt. The free amine is obtained by neutralization with aqueous sodium hydrogencarbonate followed by elution from a C18 column with water/methanol gradient. The title compound is then prepared in an analogous manner to Example **C1**, Step *1* by replacing {(1*S*,2*R*,3*S*,4*R*)-4-[2-((*R*)-3-amino-

pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-carbamic acid benzyl esterwith the above free amine and replacing pyridine-3-isocyanate with Intermediate **5**.

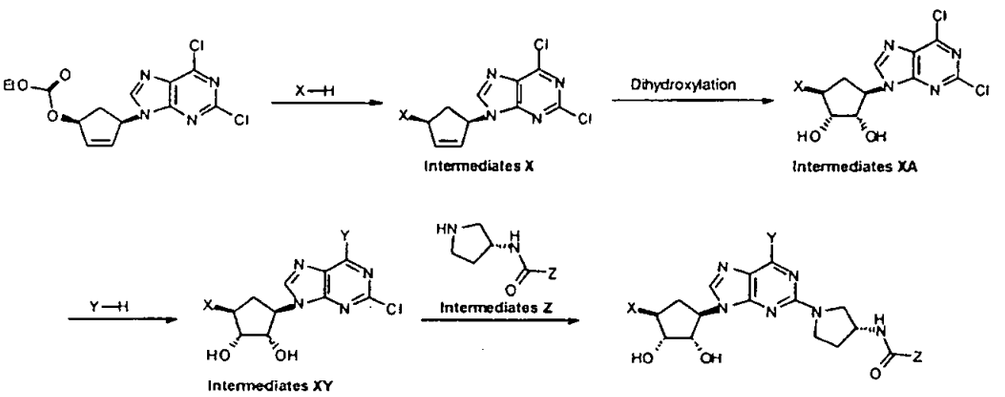
Examples XYZ

Examples of the structure XYZ are prepared in a multiparallel sequence of reactions as described below.



Examples XYZ

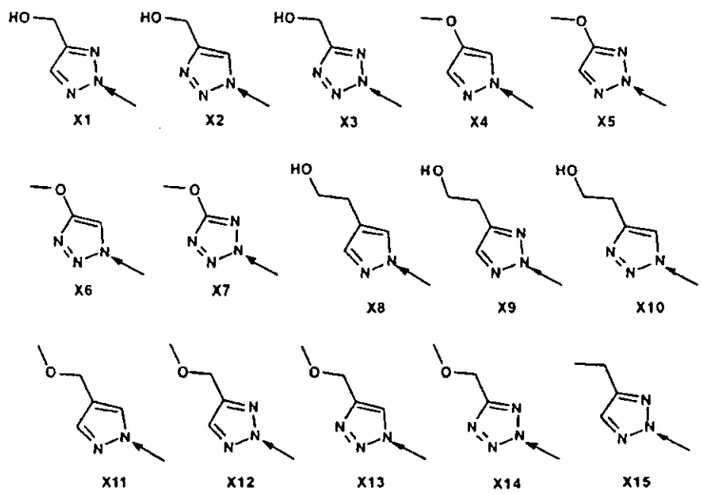
Overall scheme:



Parallel step 1

Reaction of Intermediate **1**, in an analogous manner to that used in the preparation of Intermediate **3**, Step *a* by replacing 4-hydroxymethylpyrazole with the appropriate heterocycle, individually, with the heterocycles X-H gives the Intermediates **X**.

Heterocycles X-H



Heterocycles X-H are prepared as follows:

- X1-X8 and X15 are prepared following literature procedures.
- X11, X12 and X13 are prepared by O-methylation of the corresponding alcohols.
- X14 is prepared by reduction of the corresponding ester to the alcohol followed by O-methylation.
- X9 and X10 are prepared from the corresponding formyl derivatives following standard homologation procedures.

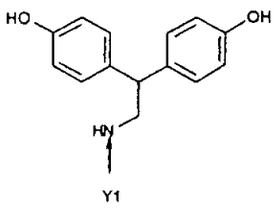
Parallel step 2

Reaction of Intermediates **X**, individually, with either the dihydroxylating agent osmium tetroxide or ruthenium tetroxide gives the Intermediates **XA**.

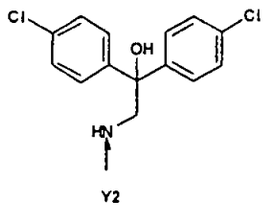
Parallel step 3

Reaction of Intermediates **XA**, in an analogous manner to that used in the preparation of Intermediate **3** Step *b* by replacing 2,2-diphenyethylamine with the appropriate amine, individually with the amines Y-H gives the Intermediates **XY**.

Amines Y-H



Y1



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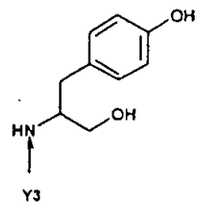

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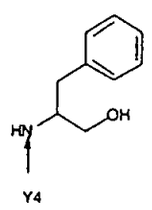

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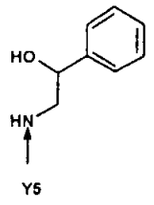

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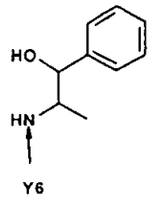


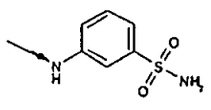
Y6

Parallel step 4

Intermediates **XY** are reacted in ethanol at reflux, or in DMSO at 90-110°C, for 18-24 hours, individually, with a 3-fold excess of the appropriate Intermediate **Z**. The Examples **XYZ** are isolated following purification by mass directed reversed phase chromatography.

Intermediates Z

Where Z =



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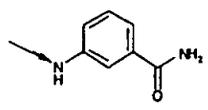

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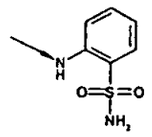

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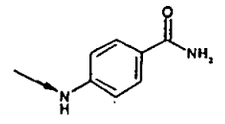

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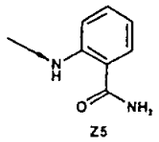

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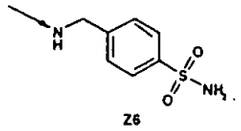

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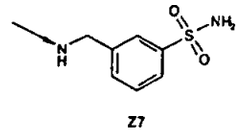

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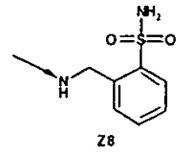

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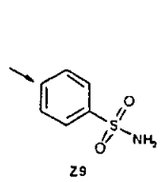
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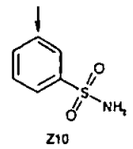
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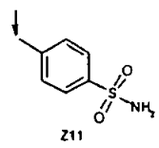
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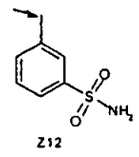
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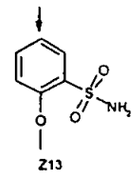
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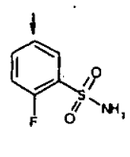
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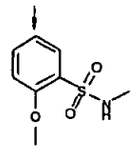
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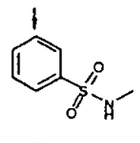
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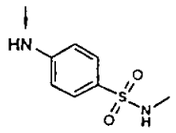
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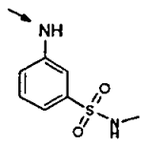
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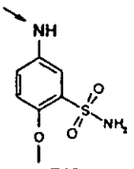
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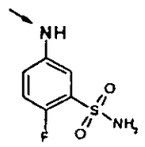
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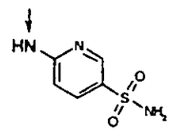
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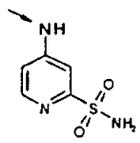
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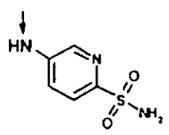
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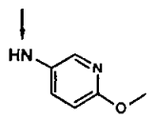
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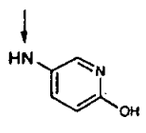
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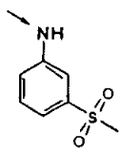
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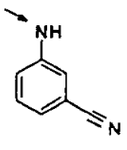
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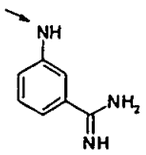
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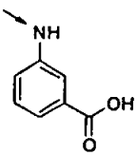
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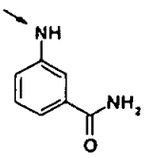
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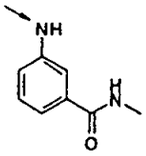
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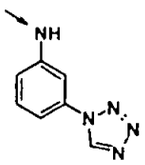
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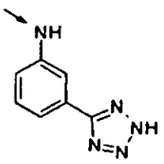
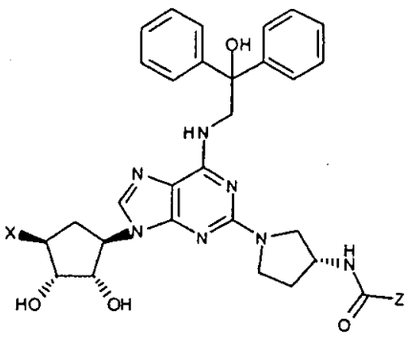

Z33

Examples W

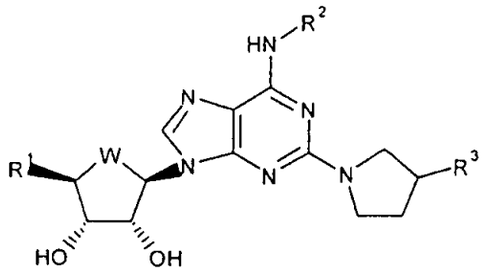


Examples W

For the Examples **XYZ**, where X = X2 a further hydrogenolysis of the aryl chlorides, individually, by transfer hydrogenation using ammonium formate with a palladium on carbon catalyst in ethanol gives a further series of Examples **W**.

Claims

1. A compound of formula (I)



(I)

or stereoisomers or pharmaceutically acceptable salts thereof,
wherein

W is CH_2 or O, with the proviso that when W is O, then R^1 is not a N-bonded substituent;

R^1 is a 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from 1 to 4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by oxo, C_1-C_8-alkoxy, C_6-C_{10}-aryl, R^{1a} or by C_1-C_8-alkyl optionally substituted by hydroxyl;

R^{1a} is a 3- or 12-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, said 3- or 12-membered heterocyclic ring being optionally substituted by halo, cyano, oxo, hydroxy, carboxy, amino, nitro, C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, aminocarbonyl, C_1-C_8-alkylcarbonyl or C_1-C_8-alkoxy optionally substituted by aminocarbonyl;

R^2 is C_1-C_8-alkyl substituted by OH, halogen C_6-C_{10}-aryl optionally substituted by OH, SO_2R^5, SC_1-C_8-alkyl, CN, halogen, O-C_7-C_{14}-aralkyl, or O-C_1-C_8-alkyl, a C_3-C_{15}-carbocyclic group optionally substituted by O-C_7-C_{14} aralkyl, C_3-C_{15}-carbocyclic group, O-C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl or C_1-C_8-alkyl, O-C_1-C_8-alkyl, -SO_2-C_1-C_8-alkyl, a 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from 1 to 4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from 1 to 4 other heteroatoms selected from the group consisting of oxygen and sulfur, C_7-C_{14}-aralkyl, or C_6-C_{14}-aryl optionally substituted by O-C_7-C_{14}-aralkyl, or

R^2 is a C_3-C_{15}-carbocyclic group optionally substituted by O-C_7-C_{14}-aralkyl, C_3-C_{15}-carbocyclic group, O-C_1-C_8-alkyl, or C_1-C_8-alkyl, or

R^2 is a 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from 1 to 4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from 1 to 4 other heteroatoms selected from the group consisting of oxygen and sulfur, C_7-C_{14}-aralkyl, or C_6-C_{14}-aryl optionally substituted by O-C_7-C_{14}-aralkyl;

R^3 is selected from $NR^{3a}R^{3b}$, $NR^3C(O)NR^{3g}R^{3h}$, $NHC(O)R^{3q}$, and $NHC(=NR^{3m})N(R^{3n})R^{3o}$;

R^{3a}, R^{3f} and R^{3h} are, independently, H, C_1-C_8-alkyl or C_6-C_{10}-aryl;

R^{3b} is H, C_1-C_8-alkyl a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^4 or C_6-C_{10}-aryl;

R^{3g} is C_1-C_8-alkyl optionally substituted by a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted with SO_2R^5, CN, or 0-3R^4, or

R^{3g} is a C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl, CN, -C(=NH)NH_2, SO_2R^5,- halogen, or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^4, or

R^{3g} is a C_7-C_{14}-aralkyl optionally substituted by OH, O-C_1-C_8-alkyl, halogen, C_6-C_{10}-aryl, SO_2R^5, CN, -C(=NH)NH_2 or O-C_6-C_{10}-aryl, or

R^{3g} is a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^4;

R^{3m} is CN;

R^{3n} is H or C_1-C_8-alkyl;

R^{3o} is H, C_1-C_8-alkyl optionally substituted by OH or by a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted with SO_2R^5, CN, or 0-3R^4, C_1-C_8-alkoxy, C_7-C_{14}-aralkyl optionally substituted with OH, O-C_1-C_8-alkyl, halogen C_6-C_{10}-aryl, or O-C_6-C_{10}-aryl, C_1-C_8-alkoxy, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl SO_2R^5 or –halogen;

R^{3p} is H, C_1-C_8-alkyl or C_7-C_{14}-aralkyl;

R^{3q} is a C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, C_1-C_8-alkoxy, SO_2R^5 or –halogen, or

R^{3q} is a C_7-C_{14}-aralkyl optionally substituted by OH, C_1-C_8-alkyl, C_1-C_8-alkoxy, SO_2R^5 or –halogen, or

R^{3q} is a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur optionally substituted by 0-3 R^4 or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3 R^4;

R^4 is selected from OH, C_1-C_8-alkyl optionally substituted by OH, CN, SO_2R^5 or halogen, $C(O)NHR^{3a}$, O-C_1-C_8-alkyl optionally substituted by halogen, $NR^{4a}R^{4b}$, $NHC(O)R^{4c}$, a $C(O)$-C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl, -halogen, or SO_2R^5;

R^{4a}, R^{4b} and R^{4c} are, independently, H, C_1-C_8-alkyl or C_6-C_{10}-aryl; and

R^5 is C_1-C_8-alkyl optionally substituted by halogen, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl, or $NR^{3a}R^{3b}$.

2. A compound of formula (I) according to Claim 1 or stereoisomers or pharmaceutically acceptable salts thereof,

wherein

W is CH_2 or O, with the proviso that when W is O, then R^1 is not a N-bonded substituent;

R^1 is a 3- to 12-membered heterocyclic group containing from 1 to 4 ring nitrogen atoms and optionally containing from 1 to 4 other heteroatoms selected from the group consisting of oxygen and sulfur, that group being optionally substituted by oxo or by C_1-C_8-alkyl optionally substituted by hydroxyl;

R^2 is selected from C_1-C_8-alkyl optionally substituted by OH, halogen and C_6-C_{10}-aryl optionally substituted by OH, halogen, or O-C_1-C_8-alkyl;

R^3 is selected from $NR^{3f}C(O)NR^{3g}R^{3h}$, $NR^{3a}NR^{3b}$, $NHC(O)R^{3q}$ and $NHC(=NR^{3m})N(R^{3n})R^{3o}$;

R^{3a} is selected from H and C_1-C_8-alkyl;

R^{3b} is selected from H, C_1-C_8-alkyl and 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3 R^4;

R^{3f} and R^{3n} are H;

R^{3g} is C_1-C_8-alkyl optionally substituted by a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted with SO_2R^5, CN, or 0-3R^4, or

R^{3g} is a C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl, CN, -C(=NH)NH_2, SO_2R^5, -halogen, or a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^4, or

R^{3g} is a C_7-C_{14}-aralkyl optionally substituted by OH, O-C_1-C_8-alkyl, halogen, C_6-C_{10}-aryl, SO_2R^5, CN, -C(=NH)NH_2 or O-C_6-C_{10}-aryl, or

R^{3g} is a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^4;

R^{3m} is CN;

R^{3n} is H or C_1-C_8 alkyl;

R^{3o} is H, C_1-C_8-alkyl optionally substituted by OH or by a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted with SO_2R^5, CN, or 0-3R^4, C_1-C_8-alkoxy, C_7-C_{14}-aralkyl optionally substituted with OH, O-C_1-C_8-alkyl, halogen C_6-C_{10}-aryl, or O-C_6-C_{10}-aryl, C_1-C_8-alkoxy, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl SO_2R^5 or –halogen;

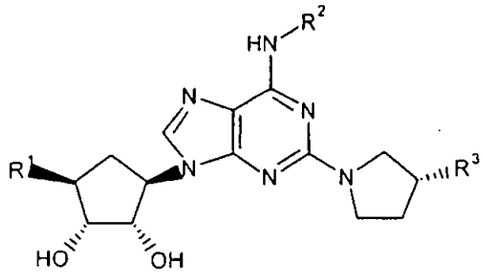
R^{3q} is a 3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur optionally substituted by a3- to 12-membered heterocyclic group containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, optionally substituted by 0-3R^4;

R^4 is selected from OH, C_1-C_8-alkyl optionally substituted by OH, CN, SO_2R^5 or halogen, C(O)NHR^{3a}, O-C_1-C_8-alkyl optionally substituted by halogen, $NR^{4a}R^{4b}$, $NHC(O)R^{4c}$, a C(O)-C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl, -halogen, or SO_2R^5;

R^{4a}, R^{4b} and R^{4c} are, independently, H, C_1-C_8-alkyl or C_6-C_{10}-aryl; and

R^5 is C_1-C_8-alkyl optionally substituted by halogen, C_6-C_{10}-aryl optionally substituted by OH, C_1-C_8-alkyl, O-C_1-C_8-alkyl or –halogen, or $NR^{3a}R^{3b}$.

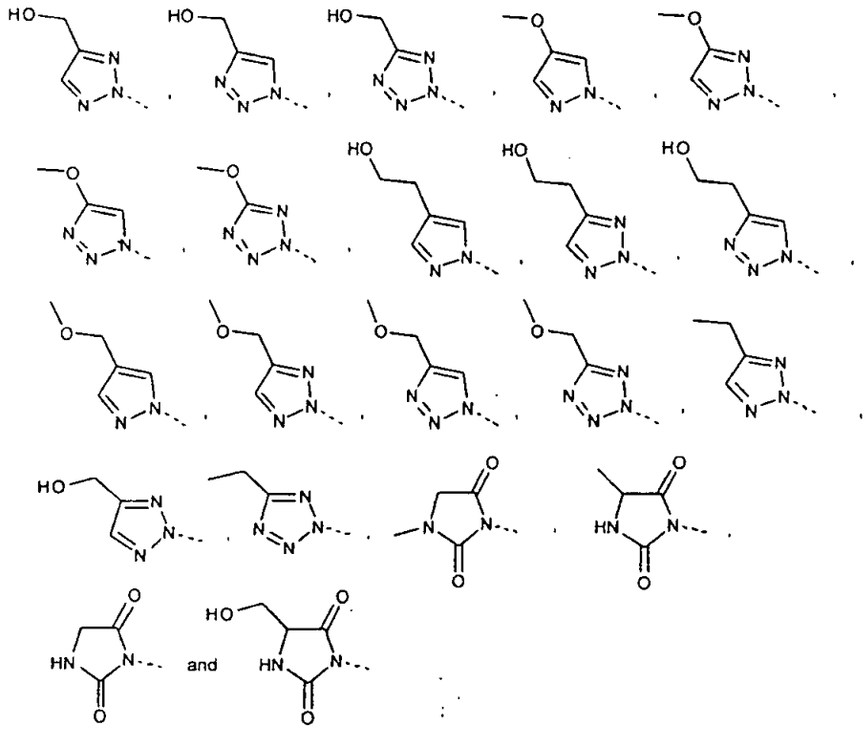
3. A compound according to Claim 1, wherein the compound is of formula (Ia)



(Ia)

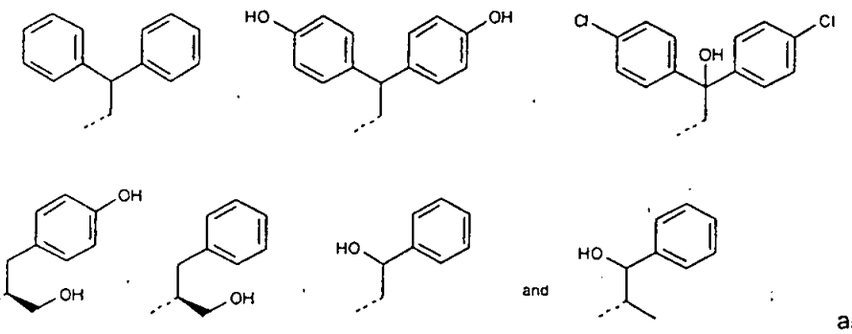
where

R^1 is selected from



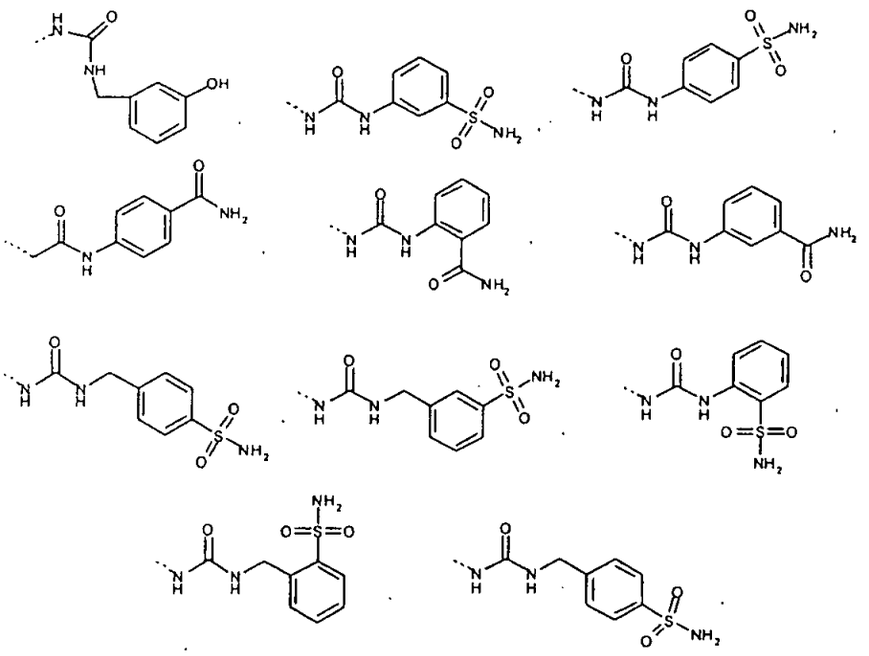
and

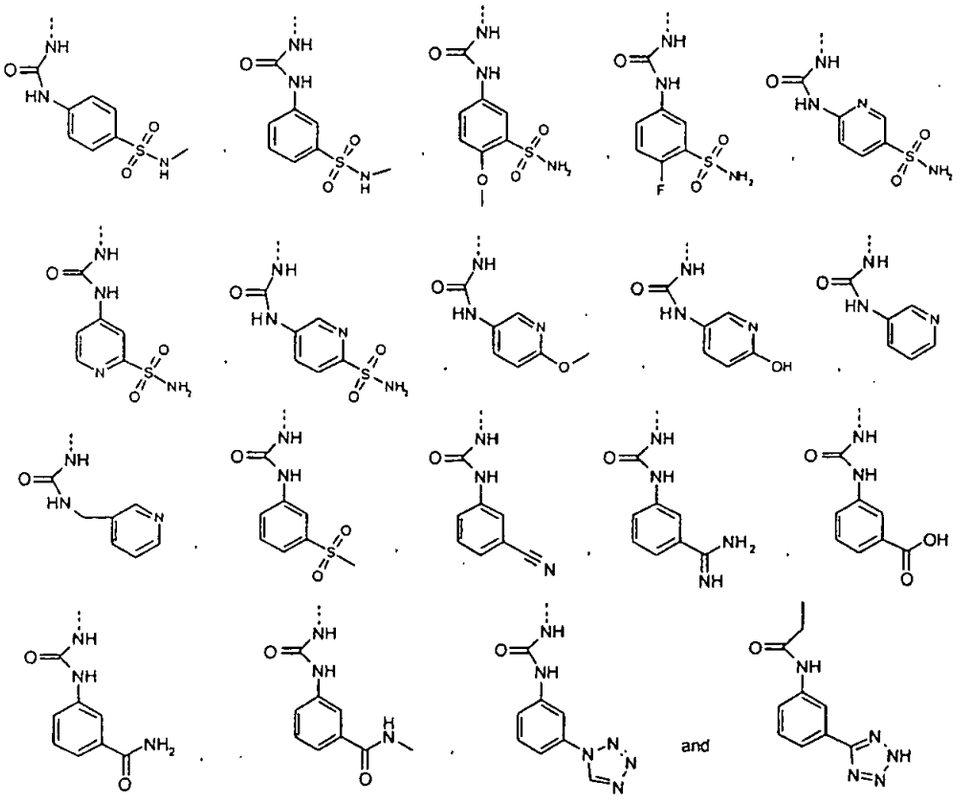
R^2 is selected from



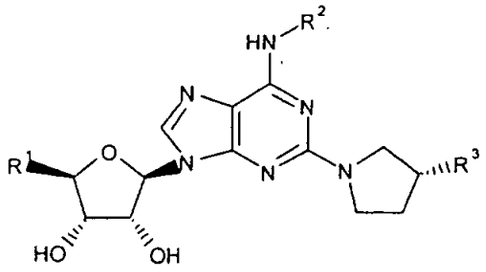
and

R^3 is selected from





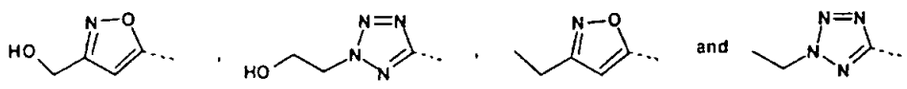
4. A compound according to Claim 1, wherein the compound is of formula (Ib)



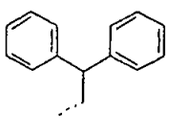
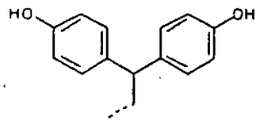
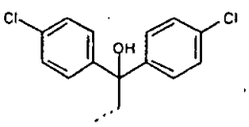
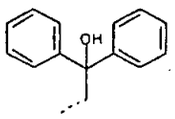
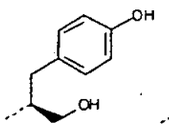
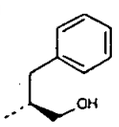
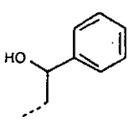
(Ib)

where

R^1 is selected from



R^2 is selected from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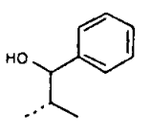
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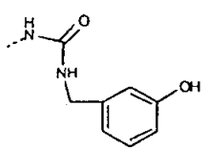
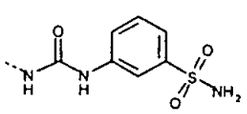
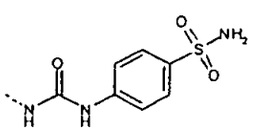
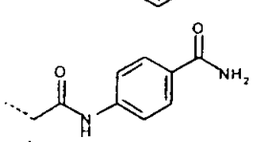
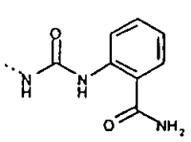
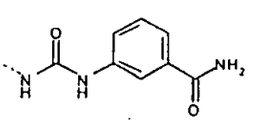
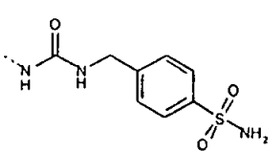
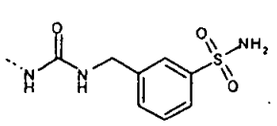
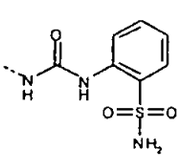
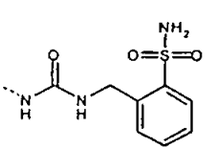
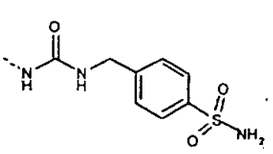
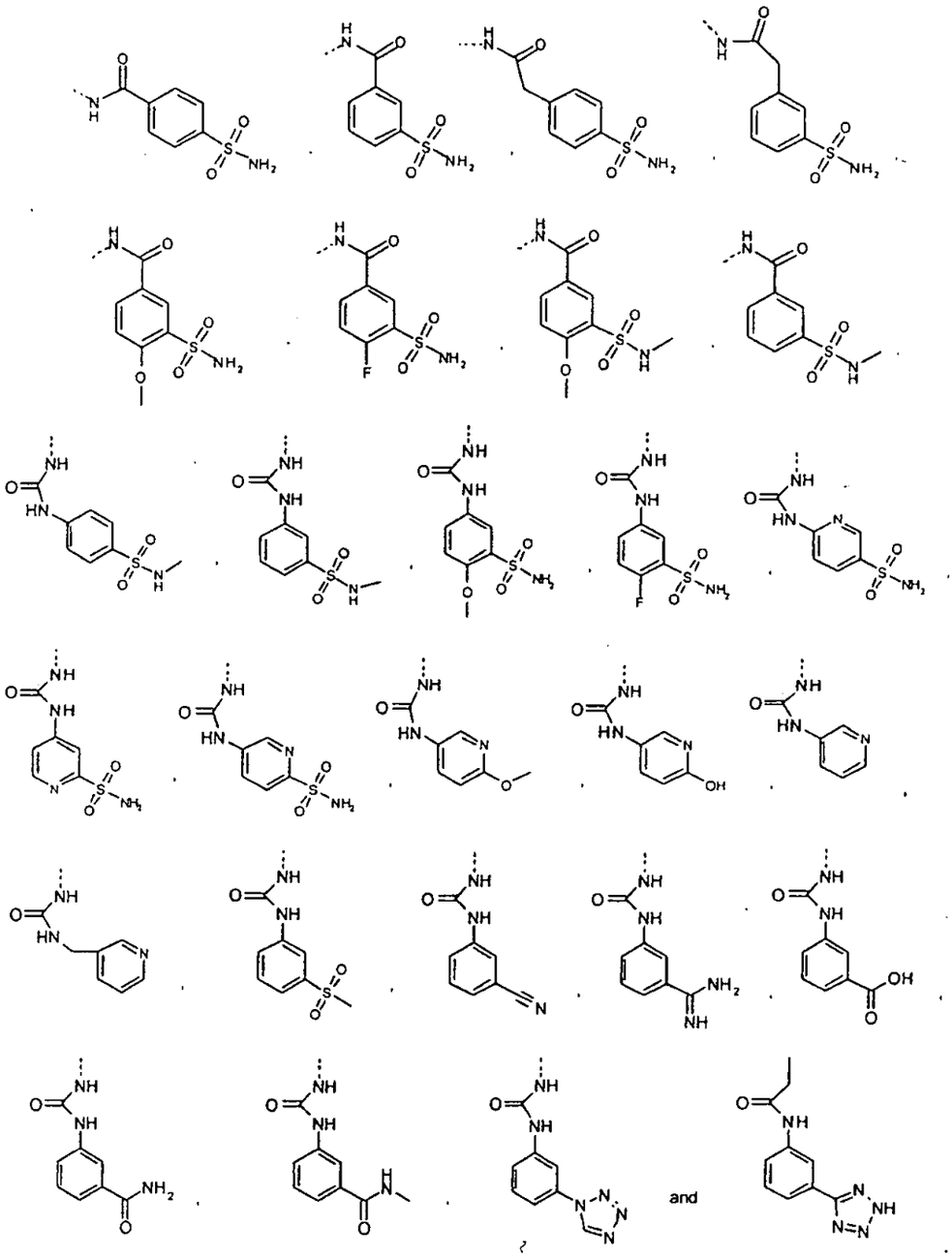
R^3 is selected from



5. A compound according to Claim 1, substantially as herein described with reference to any one of the Examples.

6. A compound according to any one of the preceding claims for use as a pharmaceutical.

7. A compound according to any one of Claims 1-5, in combination with an anti-inflammatory, bronchodilatory, anti-histamine or anti-tussive drug substance, said compound and said drug substance being in the same or different pharmaceutical composition.

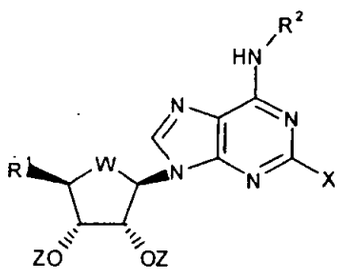
8. A pharmaceutical composition comprising as active ingredient a compound according to any one of Claims 1-5, optionally together with a pharmaceutically acceptable diluent or carrier.

9. Use of a compound according to any one of Claims 1-5, for the manufacture of a medicament for the treatment of a condition mediated by activation of the adenosine A2A receptor.

10. Use of a compound according to any one of Claims 1-5, for the manufacture of a medicament for the treatment of an inflammatory or obstructive airways disease.

11. A process for the preparation of compounds of formula (I) as defined in Claim 1, or stereoisomers or pharmaceutically acceptable salts thereof, which comprises the steps of:

(i) reacting a compound o f formula (Ic)



(Ic)

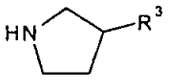
wherein

R^1, W and R^2 are as defined in Claim 1;

Z is H or a protecting group; and

X is a leaving group,

with a compound of formula (Id)



(Id)

wherein

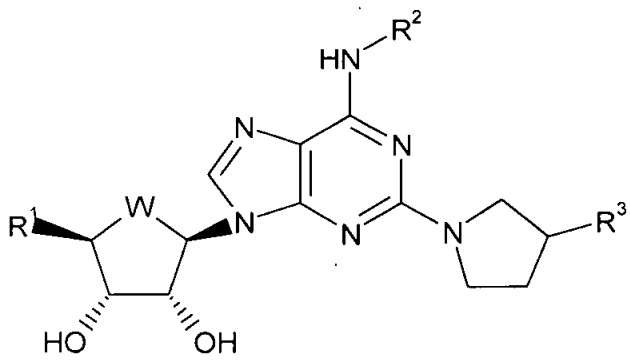
R^3 is as defined in Claim 1; and

removing any protecting groups and recovering the resultant compound of formula (I), in free or pharmaceutically acceptable salt form.

DERIVADOS DE PURINA COMO AGONISTAS DE A_{2A}

Esta invención se refiere a compuestos orgánicos, a su preparación, y a su uso como productos farmacéuticos.

Un aspecto de la presente invención proporciona los compuestos de la fórmula (I):



(I)

o estereoisómeros o sales farmacéuticamente aceptables de los mismos,

en donde:

W es CH_2 u O, con la condición de que, cuando W es O, entonces R^1 no es un sustituyente enlazado con nitrógeno;

R^1 es un grupo heterocíclico de 3 a 12 miembros que contiene de 1 a 4 átomos de nitrógeno del anillo y que contiene opcionalmente de 1 a 4 heteroátomos diferentes seleccionados a partir del grupo que consiste en oxígeno y azufre, estando ese grupo opcionalmente sustituido por oxo, alcoxilo de 1 a 8 átomos de carbono, arilo de 6 a 10 átomos de carbono, R^{1a} o por alquilo de 1 a 8 átomos de carbono

opcionalmente sustituido por hidroxilo;

R^{1a} es un anillo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, estando este anillo heterocíclico de 3 a 12 miembros opcionalmente sustituido por halógeno, ciano, oxo, hidroxilo, carboxilo, amino, nitro, alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, amino-carbonilo, alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono opcionalmente sustituido por amino-carbonilo;

R^2 es alquilo de 1 a 8 átomos de carbono sustituido por OH, halo-arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, SO_2R^5, S-alquilo de 1 a 8 átomos de carbono, CN, halógeno, O-aralquilo de 7 a 14 átomos de carbono, u O-alquilo de 1 a 8 átomos de carbono, un grupo carbocíclico de 3 a 15 átomos de carbono opcionalmente sustituido por O-aralquilo de 7 a 14 átomos de carbono, grupo carbocíclico de 3 a 15 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, o alquilo de 1 a 8 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, $-SO_2$-alquilo de 1 a 8 átomos de carbono, un grupo heterocíclico de 3 a 12 miembros que contiene de 1 a 4 átomos de nitrógeno del anillo y que contiene opcionalmente de 1 a 4 heteroátomos diferentes seleccionados a partir del grupo que consiste en oxígeno y azufre, estando ese grupo opcionalmente sustituido por un grupo heterocíclico de 3 a 12

miembros que contiene de 1 a 4 átomos de nitrógeno del anillo y que contiene opcionalmente de 1 a 4 heteroátomos diferentes seleccionados a partir del grupo que consiste en oxígeno y azufre, aralquilo de 7 a 14 átomos de carbono, o arilo de 6 a 14 átomos de carbono opcionalmente sustituido por O-aralquilo de 7 a 14 átomos de carbono, o

R^2 es un grupo carbocíclico de 3 a 15 átomos de carbono opcionalmente sustituido por O-aralquilo de 7 a 14 átomos de carbono, grupo carbocíclico de 3 a 15 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, o alquilo de 1 a 8 átomos de carbono, o

R^2 es un grupo heterocíclico de 3 a 12 miembros que contiene de 1 a 4 átomos de nitrógeno del anillo y que contiene opcionalmente de 1 a 4 heteroátomos diferentes seleccionados a partir del grupo que consiste en oxígeno y azufre, estando ese grupo opcionalmente sustituido por un grupo heterocíclico de 3 a 12 miembros que contiene de 1 a 4 átomos de nitrógeno del anillo y que contiene opcionalmente de 1 a 4 heteroátomos diferentes seleccionados a partir del grupo que consiste en oxígeno y azufre, aralquilo de 7 a 14 átomos de carbono, o arilo de 6 a 14 átomos de carbono opcionalmente sustituido por O-aralquilo de 7 a 14 átomos de carbono;

R^3 se selecciona a partir de $NR^{3a}R^{3b}$, $NR^{3f}C(O)NR^{3g}R^{3h}$, $NHC(O)R^{3q}$, y $NHC(=NR^{3m})N(R^{3n})R^{3o}$;

R^{3a}, R^{3f} y R^{3h} son independientemente H, alquilo de 1 a 8 átomos de carbono, o arilo de 6 a 10 átomos de carbono;

R^{3b} es H, alquilo de 1 a 8 átomos de carbono, un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido por 0 a 3 R^4 o arilo de 6 a 10 átomos de carbono;

R^{3g} es alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido con SO_2R^5, CN, o de 0 a 3 R^4, o

R^{3g} es un arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, CN, -C(=NH)NH_2, SO_2R^5, -halógeno, o un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido por 0 a 3 R^4, o

R^{3g} es un aralquilo de 7 a 14 átomos de carbono opcionalmente sustituido por OH, O-alquilo de 1 a 8 átomos de carbono, halógeno, arilo de 6 a 10 átomos de carbono, SO_2R^5, CN, -C(=NH)NH_2, u O-arilo de 6 a 10 átomos de carbono, o

R^{3g} es un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido por 0 a 3 R^4;

R^{3m} es CN;

R^{3n} es H o alquilo de 1 a 8 átomos de carbono;

R^{3o} es H, alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por OH o por un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido con SO_2R^5, CN, o de 0 a 3 R^4, alcoxilo de 1 a 8 átomos de carbono, aralquilo de 7 a 14 átomos de carbono opcionalmente sustituido con OH, O-alquilo de 1 a 8 átomos de carbono, halo-arilo de 6 a 10 átomos de carbono, u O-arilo de 6 a 10 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, SO_2R^5 o -halógeno;

R^{3p} es H, alquilo de 1 a 8 átomos de carbono, o aralquilo de 7 a 14 átomos de carbono;

R^{3q} es un arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, SO_2R^5 o –halógeno, o

R^{3q} es un aralquilo de 7 a 14 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, SO_2R^5 o –halógeno, o

R^{3q} es un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre opcionalmente

sustituido por 0 a 3 R^4 o un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido por 0 a 3 R^4;

R^4 se selecciona a partir de OH, alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por OH, CN, SO_2R^5 o halógeno, $C(O)NHR^{3a}$, O-alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por halógeno, $NR^{4a}R^{4b}$, $NHC(O)R^{4c}$, un C(O)-arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, -halógeno, o SO_2R^5;

R^{4a}, R^{4b} y R^{4c} son independientemente H, alquilo de 1 a 8 átomos de carbono, o arilo de 6 a 10 átomos de carbono; y

R^5 es alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por halógeno, arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, o $NR^{3a}R^{3b}$.

Definiciones

Los términos empleados en la memoria descriptiva tienen los siguientes significados:

"Opcionalmente sustituido" o "sustituido" significa que el grupo referido puede estar sustituido en una o más posiciones por cualquiera o cualquier combinación de los radicales enlistados posteriormente.

"Halo" o "halógeno", como se utiliza en la presente, puede ser

flúor, cloro, bromo o yodo.

"Alquilo de 1 a 8 átomos de carbono", como se utiliza en la presente, denota alquilo de cadena recta o ramificada que tiene de 1 a 8 átomos de carbono.

"Alcoxilo de 1 a 8 átomos de carbono", como se utiliza en la presente, denota alcoxilo de cadena recta o ramificada que tiene de 1 a 8 átomos de carbono.

"Cicloalquilo de 3 a 8 átomos de carbono", como se utiliza en la presente, denota cicloalquilo que tiene de 3 a 8 átomos de carbono del anillo, por ejemplo, un grupo monocíclico, tal como un ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo o ciclo-octilo, cualquiera de los cuales puede estar sustituido por uno o más, usualmente uno o dos grupos alquilo de 1 a 4 átomos de carbono; o un grupo bicíclico, tal como biciclohéptilo o biciclo-octilo.

"Alquilo de 1 a 8 átomos de carbono-amino" y "di-(alquilo de 1 a 8 átomos de carbono)-amino", como se utilizan en la presente, denotan amino sustituido respectivamente por uno o dos grupos alquilo de 1 a 8 átomos de carbono como se definen anteriormente en la presente, los cuales pueden ser iguales o diferentes.

"Alquilo de 1 a 8 átomos de carbono-carbonilo" y "alcoxilo de 1 a 8 átomos de carbono-carbonilo", como se utilizan en la presente, denotan alquilo de 1 a 8 átomos de carbono, o alcoxilo de 1 a 8 átomos de carbono, respectivamente, como se definen anteriormente en la presente, unidos por un átomo de carbono a un grupo carbonilo.

"Arilo de 6 a 10 átomos de carbono", como se utiliza en la presente, denota un grupo aromático carbocíclico monovalente que contiene de 6 a 10 átomos de carbono, y el cual puede ser, por ejemplo, un grupo monocíclico, tal como fenilo; o un grupo bicíclico, tal como naftilo.

"Aralquilo de 7 a 14 átomos de carbono", como se utiliza en la presente, denota alquilo, por ejemplo, alquilo de 1 a 4 átomos de carbono, como se define anteriormente en la presente, sustituido por arilo de 6 a 10 átomos de carbono como se define anteriormente en la presente.

"Alquilo de 1 a 8 átomos de carbono-amino-carbonilo" y "cicloalquilo de 3 a 8 átomos de carbono-amino-carbonilo", como se utilizan en la presente, denotan alquilo de 1 a 8 átomos de carbono-amino y cicloalquilo de 3 a 8 átomos de carbono-amino, respectivamente, como se definen anteriormente en la presente, unidos por un átomo de carbono a un grupo carbonilo.

"Grupo carbocíclico de 3 a 15 átomos de carbono", como se utiliza en la presente, denota un grupo carbocíclico que tiene de 3 a 15 átomos de carbono del anillo, por ejemplo, un grupo monocíclico, ya sea aromático o no aromático, tal como un ciclopentilo, ciclohexilo, cicloheptilo, ciclo-octilo o fenilo; o un grupo bicíclico, tal como biciclo-octilo, biciclononilo, biciclodecilo, indanilo o indenilo, nuevamente cualquiera de los cuales puede estar sustituido por uno o más, usualmente uno o dos grupos alquilo de 1 a 4 átomos de carbono.

"Anillo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre", como se utiliza en la presente, puede ser, por ejemplo, furano, pirrol, pirrolidina, pirazol, imidazol, triazol, isotriazol, tetrazol, tiadiazol, isotiazol, oxadiazol, piridina, piperidina, pirazina, oxazol, isoxazol, pirazina, piridazina, pirimidina, piperazina, pirrolidina, morfolino, triazina, oxazina o tiazol.

"Grupo heterocíclico de 5 ó 6 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre", como se utiliza en la presente, puede ser, por ejemplo, un grupo heterocíclico saturado o insaturado, tal como furanilo, pirrolilo, pirrolidinilo, pirazolilo, imidazolilo, triazolilo, isotriazolilo, tetrazolilo, tiadiazolilo, isotiazolilo, oxadiazolilo, piridinilo, piperidinilo, pirazinilo, oxazolilo, isoxazolilo, pirazinilo, piridazinilo, pirimidinilo, piperazinilo, pirrolidinilo, morfolinilo, triazinilo, oxazinilo o tiazolilo.

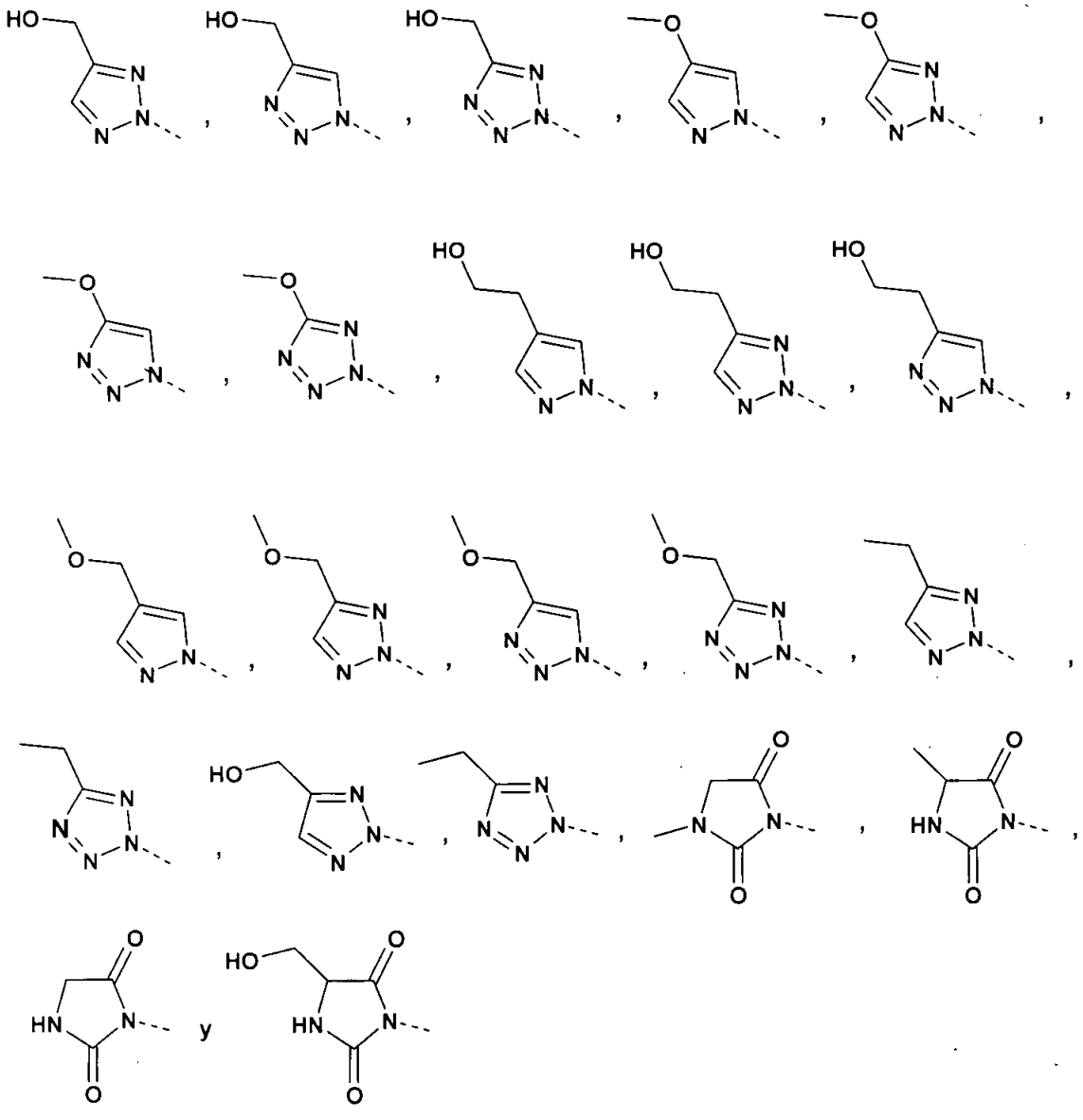
A través de toda esta memoria descriptiva y en las reivindicaciones que siguen, a menos que el contexto lo requiera de otra manera, la palabra "comprenden", o variaciones, tales como "comprende" o "comprendiendo", se entenderán para implicar la inclusión de un entero o paso o grupo de enteros o pasos mencionado, pero no la exclusión de cualquier otro entero o paso o grupo de enteros o pasos.

A través de toda esta memoria descriptiva y en las

reivindicaciones que siguen, a menos que el contexto lo requiera de otra manera, la palabra "comprenden", o variaciones, tales como "comprende" o "comprendiendo", se entenderán para implicar la inclusión de un entero o paso o grupo de enteros o pasos mencionado, pero no la exclusión de cualquier otro entero o paso o grupo de enteros o pasos. Como es entendido por un experto en la materia, solamente las combinaciones de sustituyentes que sean químicamente posibles son modalidades de la invención.

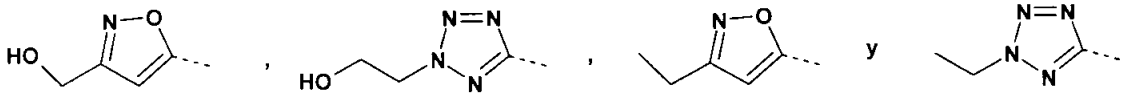
De acuerdo con la fórmula (I), R^1 es adecuadamente un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre. De preferencia R^1 es un grupo heterocíclico de 5 miembros, tal como pirazol, triazol, tetrazol, isoxazol, e imidazol-2,4-diona. Estos grupos heterocíclicos están adecuadamente sustituidos por un alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por OH.

Los grupos heterocíclicos pueden estar ya sea enlazados por nitrógeno o bien enlazados por carbono. Por ejemplo, los grupos heterocíclicos pirazol, triazol, tetrazol e imidazol-2,4-diona están adecuadamente enlazados por nitrógeno cuando están unidos a un grupo ciclopentano (por ejemplo, cuando W es CH_2). Estos grupos heterocíclicos enlazados por nitrógeno también puede estar adecuadamente sustituidos por grupos tales como metanol, metilo, etilo, metoxilo y metoxi-metilo. De preferencia, los grupos R^1 unidos al grupo ciclopentano son:

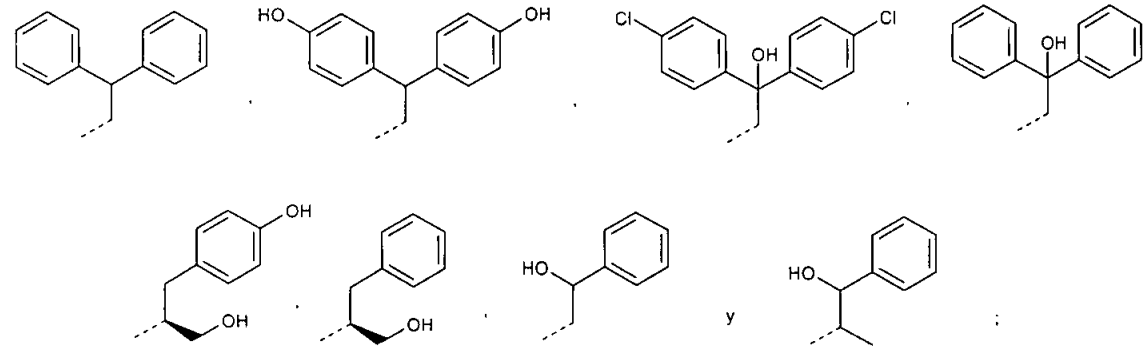


Los grupos heterocíclicos de isoxazol y tetrazol están enlazados por carbono cuando están unidos a un grupo furano (por ejemplo, cuando W es O). Estos grupos heterocíclicos enlazados por carbono están adecuadamente sustituidos por alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por OH, tal como hidroxi-metilo, hidroxi-etilo, un grupo etilo o un grupo metilo. De

preferencia, Los grupos R^1 unidos al grupo furano son:



De acuerdo con la fórmula (I), R^2 se selecciona adecuadamente a partir de alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por OH, halógeno o arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, halógeno, tal como Cl u O-alquilo de 1 a 8 átomos de carbono, de preferencia arilo de 6 a 10 átomos de carbono es fenilo. También, de preferencia, el alquilo de 1 a 8 átomos de carbono está sustituido por dos anillos de fenilo, y los anillos de fenilo están insustituidos o sustituidos por OH. Los grupos R^2 preferidos son:



De acuerdo con la fórmula (I), R^3 es adecuadamente $NR^{3f}C(O)NR^{3g}R^{3h}$. R^{3f} y R^{3h} son de una manera adecuada H.

R^{3g} es adecuadamente arilo de 6 a 10 átomos de carbono

opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, SO_2R^5, -halógeno, CN, $-C(=NH)NH_2$, o un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido por 0 a 3 R^4. De preferencia este grupo heterocíclico de 3 a 12 miembros es un grupo heterocíclico de 5 miembros, tal como tetrazol.

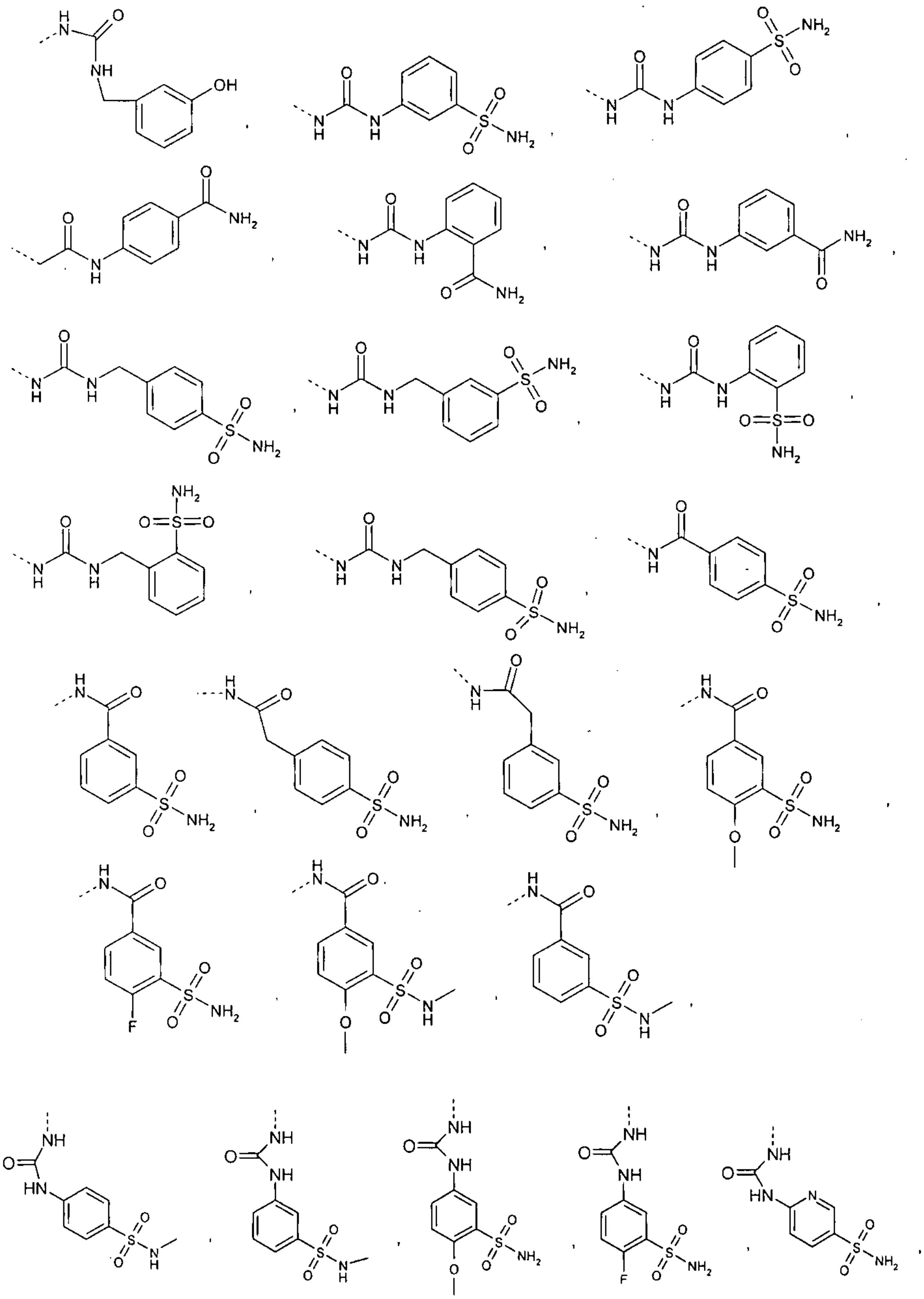
De acuerdo con la fórmula (I), R^{3g} también es adecuadamente aralquilo de 7 a 14 átomos de carbono opcionalmente sustituido por OH, O-alquilo de 1 a 8 átomos de carbono, halógeno, arilo de 6 a 10 átomos de carbono, SO_2R_5, CN, $-C(=NH)NH_2$, u O-arilo de 6 a 10 átomos de carbono.

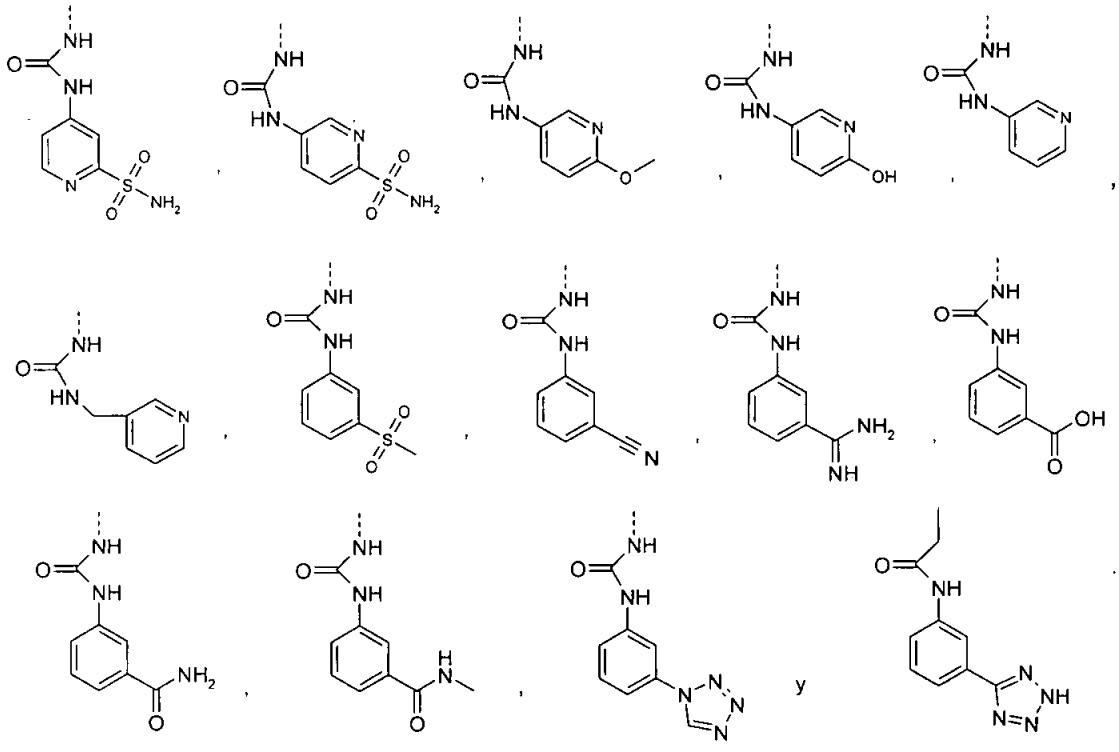
De acuerdo con la fórmula (I), R^{3g} también es adecuadamente un grupo heterocíclico de 3 a 12 miembros, de preferencia a piridina, que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido por 0 a 3 R^4.

De acuerdo con la fórmula (I), R^3 también es adecuadamente $NHC(O)R^{3q}$, en donde R^{3q} es un arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, SO_2R^5 o -halógeno.

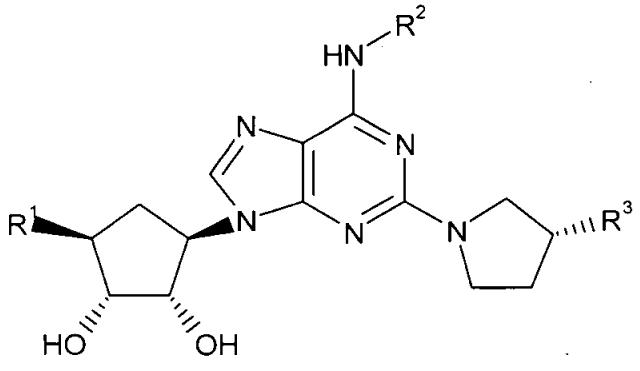
R^{3q} también es adecuadamente un aralquilo de 7 a 14 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, SO_2R_5 o -halógeno.

Los grupos R^3 preferidos son:





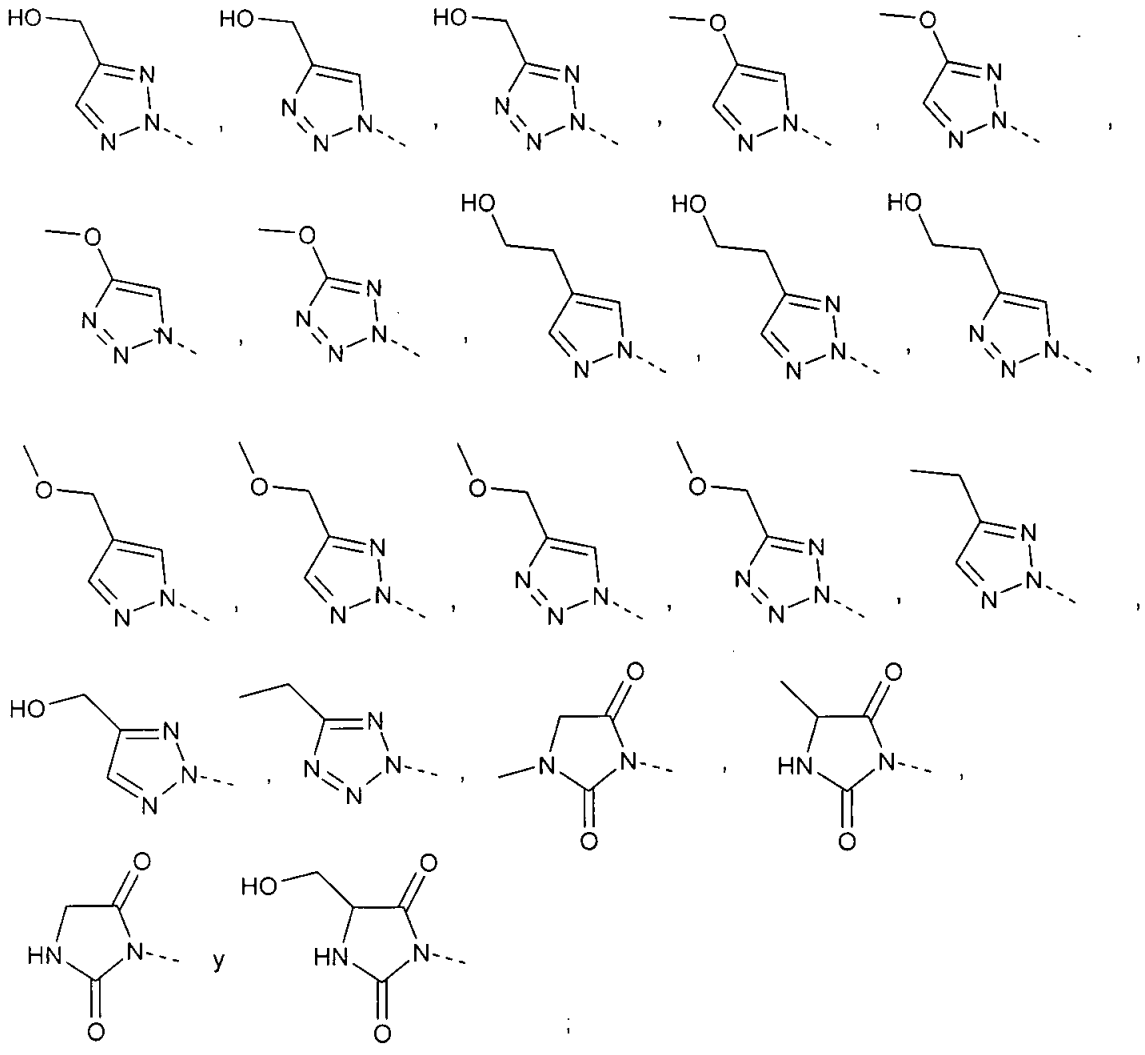
Otro aspecto de la invención proporciona los compuestos de la fórmula (I) en donde el compuesto es de la fórmula (Ia):



(Ia)

en donde:

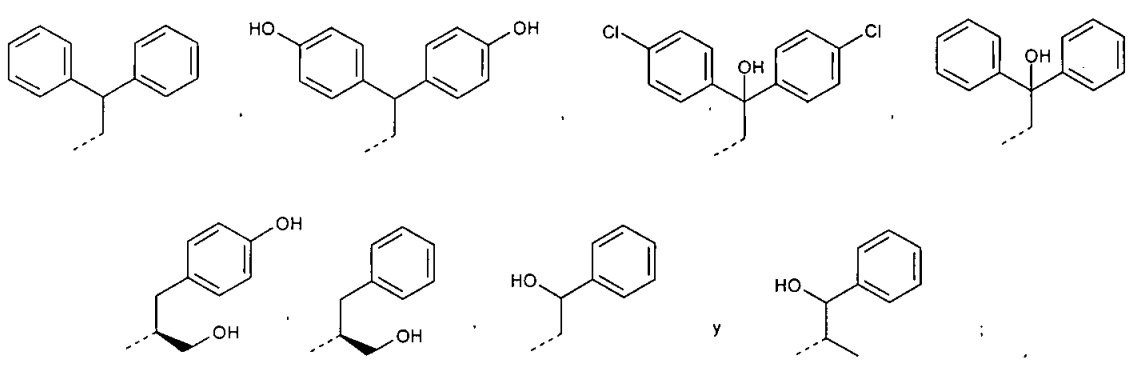
R^1 se selecciona a partir de:



y

;

R^2 se selecciona a partir de:

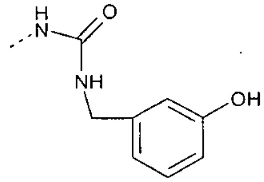
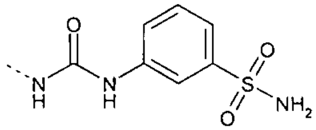
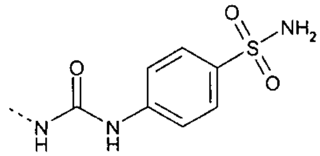


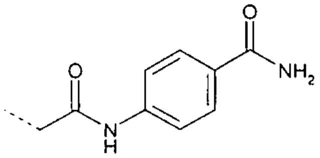
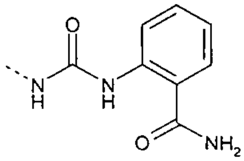
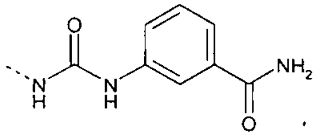
y

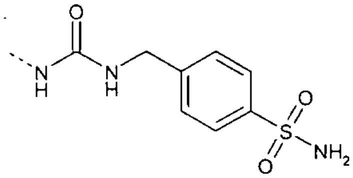
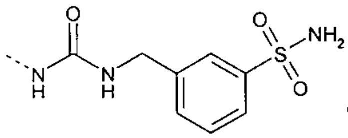
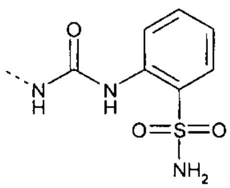
;

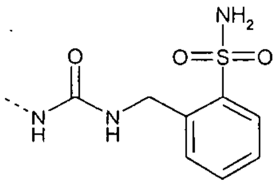
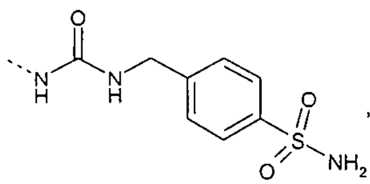
y

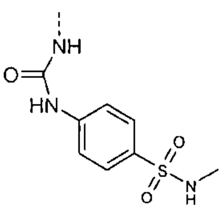
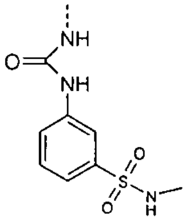
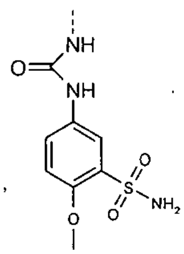
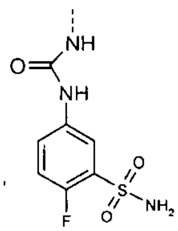
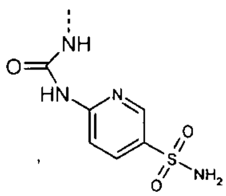
R^3 se selecciona a partir de:

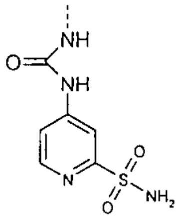
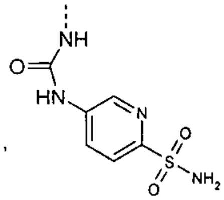
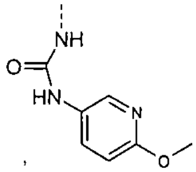
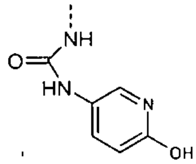
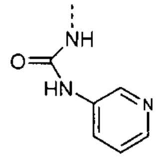
 ,  ,  ,

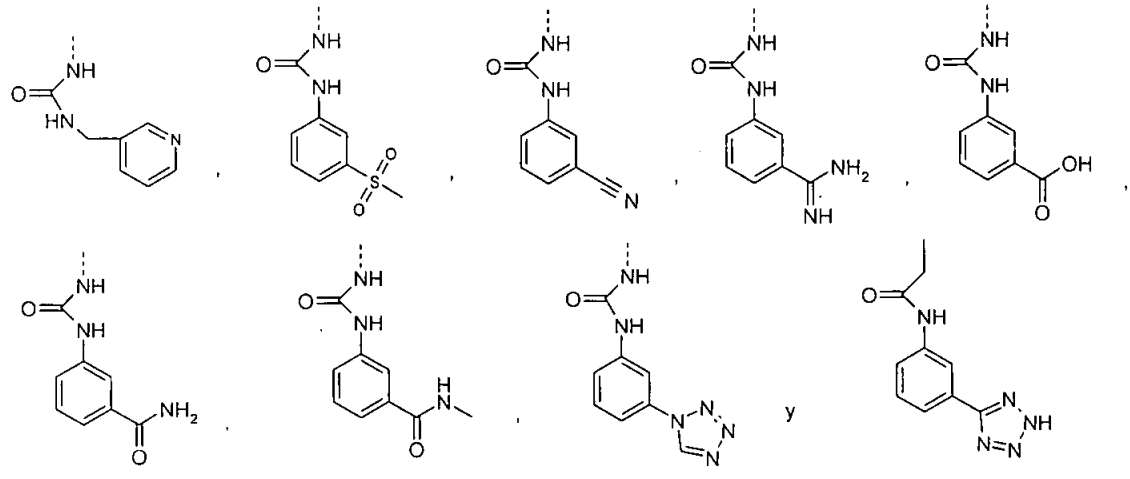
 ,  ,  ,

 ,  ,  ,

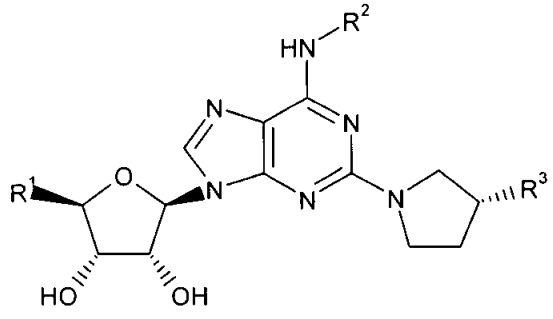
 ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,



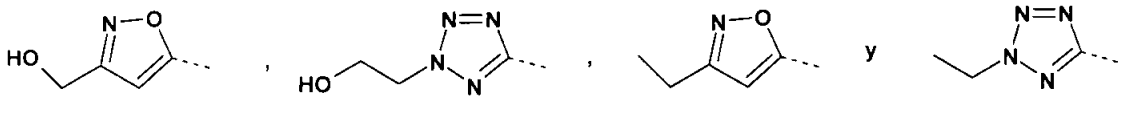
Otro aspecto de la invención proporciona los compuestos de la fórmula (I) en donde el compuesto es de la fórmula (Ib):



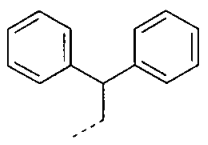
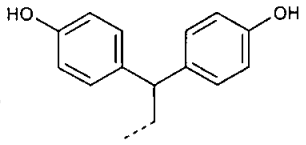
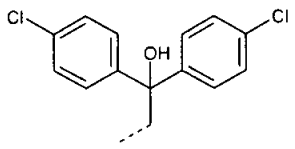
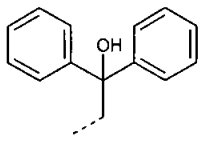
(Ib)

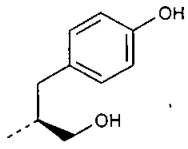
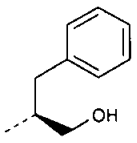
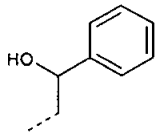
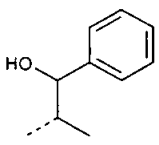
en donde

R^1 se selecciona a partir de:



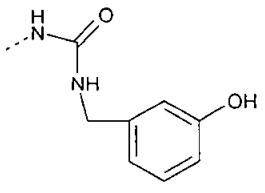
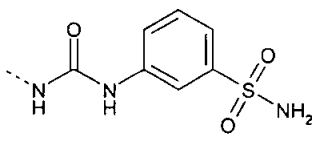
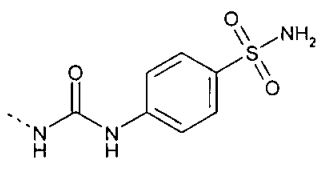
R^2 se selecciona a partir de:

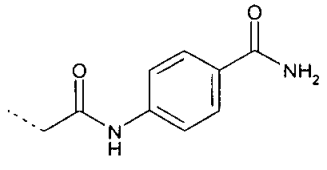
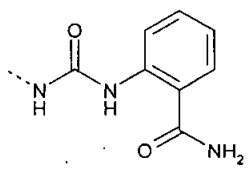
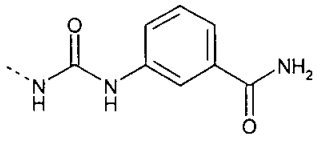





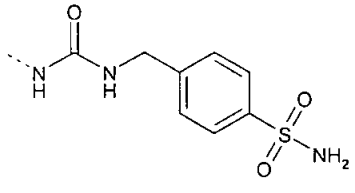
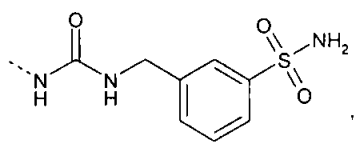
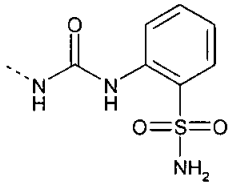



y


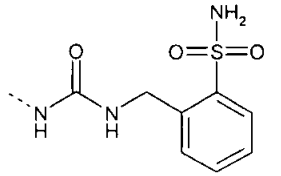
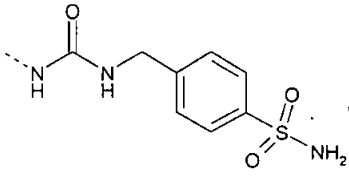
y

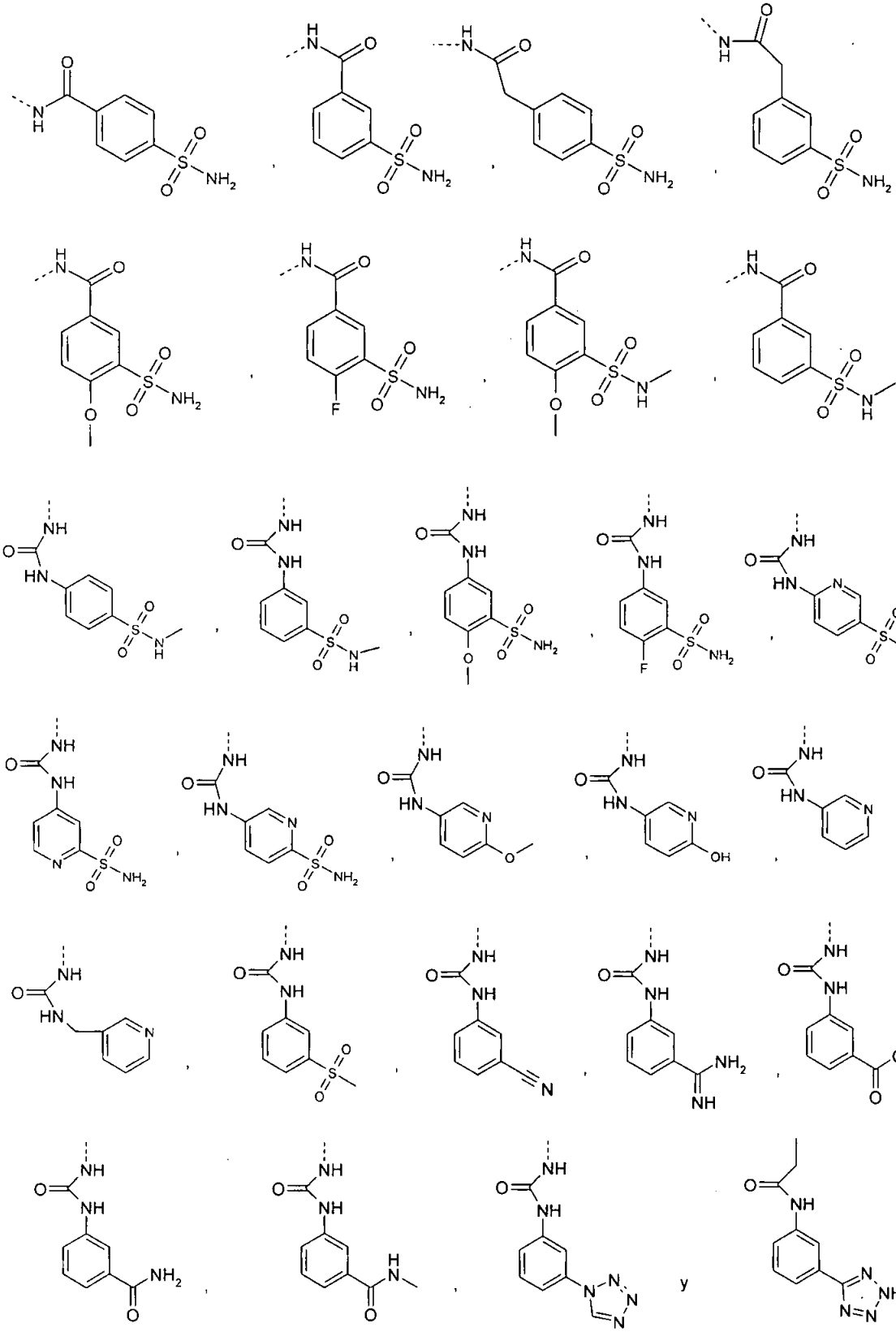
R^3 se selecciona a partir de:



Los compuestos específicos especialmente preferidos de la fórmula (I) son aquéllos descritos posteriormente en la presente en los Ejemplos.

Los estereoisómeros son los compuestos en donde hay un átomo de carbono asimétrico. Los compuestos existen en formas isoméricas ópticamente activas individuales, o como mezclas de las mismas, por ejemplo, como mezclas diaestereoméricas. La presente invención abarca ambos isómeros R y S ópticamente activos individuales, así como mezclas de los mismos. Los isómeros individuales se pueden separar mediante métodos bien conocidos por los expertos en este campo, por ejemplo, cromatografía de líquidos de alto rendimiento quiral (HPLC).

Los tautómeros son uno de dos o más isómeros estructurales que existen en equilibrio y se convierten fácilmente de una forma isomérica a otra.

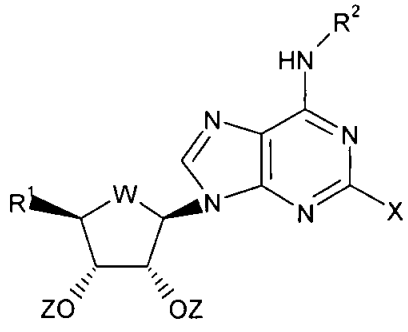
Los compuestos de la invención pueden existir en formas tanto no solvatadas como solvatadas. El término "solvato" se utiliza en la presente para describir un complejo molecular que comprende el compuesto de la invención y una o más moléculas de solvente farmacéuticamente aceptables, por ejemplo, etanol. El término "hidrato" se emplea cuando el solvente mencionado es agua.

Síntesis

Otra modalidad de la presente invención proporciona un proceso para la preparación de los compuestos de la fórmula (I) en forma libre o de sal farmacéuticamente aceptable, el cual comprende

los pasos de:

(i) hacer reaccionar un compuesto de la fórmula (Ic):



(Ic)

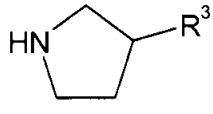
en donde:

R^1, W y R^2 son como se definen anteriormente en la presente;

Z es H o un grupo protector; y

X es un grupo saliente,

con un compuesto de la fórmula (Id):



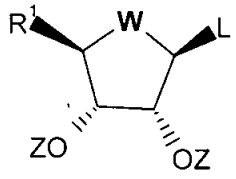
(Id)

en donde:

R^3 es como se define en anteriormente en la presente; y

remover cualesquiera grupos protectores, y recuperar el compuesto resultante de la fórmula (I), en forma libre o de sal farmacéuticamente aceptable.

El compuesto de la fórmula (Ic) se puede preparar mediante la reacción de un compuesto de la fórmula (Ie):

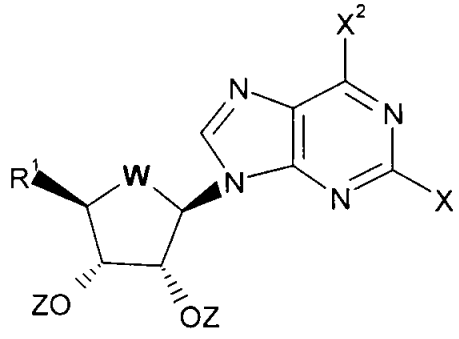


(Ie)

en donde:

R^1 y Z son como se definen anteriormente en la presente; y

L representa un grupo saliente o un derivado protegido del mismo, con una 2,6-dihalo-purina, por ejemplo, 2,6-dicloro-purina, para proporcionar un compuesto de la fórmula (If):



(If)

en donde:

R^1 y Z se definen anteriormente en la presente; y

X y X^2 son halógeno.

El compuesto de la fórmula (If) se puede hacer reaccionar con R^2NH_2 bajo condiciones convencionales para proporcionar el compuesto de la fórmula (Ic).

Los compuestos de la fórmula (I) se pueden preparar, por ejemplo, empleando las reacciones y técnicas descritas más adelante y en los Ejemplos. Los compuestos de la fórmula (I) se pueden preparar de una manera análoga a las preparaciones descritas en las solicitudes de patente de la Solicitante Números

PCT/EP2005/011344, GB 0500785.1, y GB 0505219.6. Las reacciones se pueden llevar a cabo en un solvente apropiado para los reactivos y materiales empleados, y adecuado para las transformaciones que se estén efectuando. Será entendido por los expertos en la técnica de la síntesis orgánica, que la funcionalidad presente sobre la molécula debe ser consistente con las transformaciones propuestas. Esto algunas veces requerirá de un juicio para modificar el orden de los pasos sintéticos o para seleccionar un esquema de proceso particular sobre otro, con el objeto de obtener un compuesto deseado de la invención.

Los diferentes sustituyentes sobre los Intermediarios sintéticos y los productos finales mostrados en los siguientes esquemas de reacción pueden estar presentes en sus formas completamente elaboradas, con grupos protectores adecuados en donde se requieran, como será entendido por un experto en este campo, o en formas precursoras que posteriormente se puedan elaborar en sus formas finales mediante métodos familiares para un experto en la materia. También se pueden agregar sustituyentes en diferentes etapas a través de toda la secuencia sintética o después de completar la secuencia sintética. En muchos casos, se pueden emplear las manipulaciones de grupos funcionales comúnmente empleadas para transformar un intermediario en otro intermediario, o un compuesto de la fórmula (I) en otro compuesto de la fórmula (I). Los ejemplos de estas manipulaciones son la conversión de un éster o de una cetona hasta un alcohol; la conversión de un éster hasta

una cetona; interconversiones de ésteres, ácidos y amidas; alquilación, acilación y sulfonilación de alcoholes y aminas; y muchas otras. También se pueden agregar sustituyentes empleando reacciones comunes, tales como alquilación, acilación, halogenación u oxidación. Estas manipulaciones son bien conocidas en este campo, y muchos trabajos de referencia resumen los procedimientos y métodos para estas manipulaciones. Algunos trabajos de referencia que dan ejemplos y referencias a la literatura primaria de la síntesis orgánica para muchas manipulaciones de grupos funcionales, así como otras transformaciones comúnmente empleadas en la técnica de la síntesis orgánica son *March's Organic Chemistry*, 5a. Edición, Wiley y Chichester, Editores (2001); *Comprehensive Organic transformations*, Larock, Ed., VCH (1989); *Comprehensive Organic Functional Group transformations*, Katritzky y colaboradores, (editores de series), Pergamon (1995); y *Comprehensive Organic Synthesis*, Trost y Fleming (editores de series), Pergamon (1991). También se reconocerá que otra consideración importante en la planeación de cualquier ruta sintética en este campo, es la elección juiciosa del grupo protector utilizado para la protección de los grupos funcionales reactivos presentes en los compuestos descritos en esta invención. Se pueden seleccionar múltiples grupos protectores dentro de la misma molécula, de tal manera que cada uno de estos grupos protectores pueda ser removido sin la remoción de otros grupos protectores en la misma molécula, o que se puedan remover varios grupos protectores empleando el mismo paso de reacción,

dependiendo del resultado deseado. Un informe con autoridad que describe muchas alternativas para el profesional capacitado es T. W. Greene y P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley and Sons (1999). Es entendido por los expertos en este campo que solamente las combinaciones de los sustituyentes que sean químicamente posibles son modalidades de la presente invención.

Los compuestos de la fórmula (I) en forma libre se pueden convertir en forma de sal, y viceversa, de una manera convencional. Los compuestos en forma libre o de sal se pueden obtener en la forma de hidratos o solvatos conteniendo un solvente utilizado para la cristalización. Los compuestos de la fórmula (I) se pueden recuperar de las mezclas de reacción, y se purifican de una manera convencional. Se pueden obtener isómeros, tales como estereoisómeros, de una manera convencional, por ejemplo, mediante cristalización fraccionaria o síntesis asimétrica a partir de los materiales de partida correspondientemente sustituidos asimétricamente, por ejemplo, ópticamente activos.

Los compuestos de la fórmula (I) y sus sales farmacéuticamente aceptables son útiles como productos farmacéuticos. En particular, activan el receptor de adenosina A_{2A}, es decir, actúan como agonistas del receptor A_{2A}. Sus propiedades como agonistas de A_{2A} se pueden demostrar empleando el método descrito por L. J. Murphree y colaboradores en *Mol Pharmacol*, Volumen 61, páginas 455-462 (2002).

Los compuestos de los Ejemplos de la presente, que se

encuentran más adelante, tienen valores Ki debajo de 1.0 μM en el ensayo anterior. Por ejemplo, los compuestos de los Ejemplos C1 y C2 tienen valores Ki de 0.089μM y 0.033μM respectivamente.

Considerando su activación del receptor de adenosina A_{2A}, los compuestos de la fórmula (I), en forma libre o de sal farmacéuticamente aceptable, referidos posteriormente en la presente de una manera alternativa como los "agentes de la invención", son útiles en el tratamiento de condiciones que respondan a la activación del receptor de adenosina A_{2A}, en particular condiciones inflamatorias o alérgicas. El tratamiento de acuerdo con la invención puede ser sintomático o profiláctico.

De conformidad con lo anterior, los agentes de la invención son útiles en el tratamiento de enfermedades inflamatorias u obstructivas de las vías respiratorias, que dan como resultado, por ejemplo, la reducción del daño del tejido, de la inflamación de las vías respiratorias, de la híper-reactividad bronquial, de la remodelación, o del progreso de la enfermedad. Las enfermedades y condiciones inflamatorias u obstructivas de las vías respiratorias a las que es aplicable la presente invención incluyen lesión pulmonar aguda (ALI), síndrome de insuficiencia respiratoria de adultos/aguda (ARDS), enfermedad obstructiva crónica pulmonar, de las vías respiratorias, o del pulmón (COPD, COAD o COLD), incluyendo bronquitis crónica o disnea asociada con la misma, enfisema, así como exacerbación de híper-reactividad de las vías respiratorias a consecuencia de otra terapia con fármacos, en particular, otra terapia con fármacos

inhalados. La invención también es aplicable al tratamiento de bronquitis de cualquier tipo o génesis, incluyendo, por ejemplo, bronquitis aguda, araquídica, catarral, cruposa, crónica, o ftinoide. Otras enfermedades inflamatorias u obstructivas de las vías respiratorias a las que es aplicable la presente invención incluyen neumoconiosis (una enfermedad inflamatoria, comúnmente ocupacional, de los pulmones, con frecuencia acompañada por obstrucción de las vías respiratorias, ya sea crónica o aguda, y ocasionada por la inhalación repetida de polvos) de cualquier tipo o génesis, incluyendo, por ejemplo, aluminosis, antracosis, asbestosis, calicosis, ptilosis, siderosis, silicosis, tabacosis y bisinosis.

Otras enfermedades inflamatorias u obstructivas de las vías respiratorias a las que es aplicable la presente invención incluyen asma de cualquier tipo o génesis, incluyendo tanto asma intrínseco (no alérgico) como asma extrínseco (alérgico), asma leve, asma moderado, asma severo, asma bronquítico, asma inducido por ejercicio, asma ocupacional, y asma inducido en seguida de infección bacteriana. También se debe entender que el tratamiento de asma abarca el tratamiento de sujetos, por ejemplo, de menos de 4 ó 5 años de edad, que exhiban síntomas de jadeo y sean diagnosticados o diagnosticables como "bebés jadeantes", una categoría de paciente establecida de importante preocupación médica y ahora identificada con frecuencia como asmáticos incipientes o en fase temprana. (Para mayor conveniencia, esta condición asmática particular es referida como "síndrome de bebé jadeante").

La eficacia profiláctica en el tratamiento de asma será evidenciada por una frecuencia o severidad reducida del ataque sintomático, por ejemplo, del ataque asmático agudo o broncoconstrictor, mejora en la función pulmonar, o mejor híper-reactividad de las vías respiratorias. Además puede ser evidenciada por un requerimiento reducido de otra terapia sintomática, es decir, terapia para, o pretendida para, restringir o abortar el ataque sintomático cuando se presente, por ejemplo, anti-inflamatoria (por ejemplo, corticosteroide) o broncodilatadora. El beneficio profiláctico en asma puede ser evidente, en particular, en los sujetos susceptibles al "ahogamiento matutino". El "ahogamiento matutino" es un síndrome asmático reconocido, común a un porcentaje sustancial de asmáticos, y caracterizado por ataque de asma, por ejemplo, entre las horas de aproximadamente las 4 a 6 am, es decir, en un tiempo normalmente distante sustancialmente de cualquier terapia sintomática de asma previamente administrada.

Teniendo consideración de su actividad anti-inflamatoria, en particular, en relación con la inhibición de la activación de los eosinófilos, los agentes de la invención son también útiles en el tratamiento de los trastornos relacionados con los eosinófilos, por ejemplo, eosinofilia, en particular, trastornos relacionados con los eosinófilos de las vías respiratorias (por ejemplo, que involucren infiltración eosinofílica patológica de los tejidos pulmonares) incluyendo híper-eosinofilia cuando afecta a las vías respiratorias y/o a los pulmones, así como, por ejemplo, trastornos relacionados con

los eosinófilos de las vías respiratorias a consecuencia de, o concomitantes con, síndrome de Löffler, neumonía eosinofílica, infestación parasitaria (en particular de metazoarios) (incluyendo eosinofilia tropical), aspergilosis broncopulmonar, poliarteritis nodosa (incluyendo síndrome de Churg-Strauss), granuloma eosinofílico, y trastornos relacionados con los eosinófilos que afecten a las vías respiratorias, ocasionados por reacción a fármacos.

Los agentes de la invención son también útiles en el tratamiento de condiciones inflamatorias o alérgicas de la piel, por ejemplo, soriasis, dermatitis por contacto, dermatitis atópica, alopecia areata, eritema multiforme, dermatitis herpetiforme, esclerodermia, vitiligo, angiitis por hipersensibilidad, urticaria, penfigoide buloso, lupus eritematoso, pénfigo, epidermólisis bulosa adquirida, y otras condiciones inflamatorias o alérgicas de la piel.

Los agentes de la invención también se pueden utilizar para el tratamiento de otras enfermedades o condiciones, en particular, enfermedades o condiciones que tengan un componente inflamatorio, por ejemplo, el tratamiento de enfermedades y condiciones de los ojos, tales como conjuntivitis, queratoconjuntivitis sicca, y conjuntivitis vernal, enfermedades que afecten a la nariz, incluyendo rinitis alérgica, y enfermedad inflamatoria en donde estén implicadas reacciones autoinmunes o que tenga un componente o etiología autoinmune, incluyendo trastornos hematológicos autoinmunes (por ejemplo, anemia hemolítica, anemia aplásica, anemia de glóbulos

rojos puros, y trombocitopenia idiopática), lupus eritematoso sistémico, policondritis, esclerodoma, granulomatosis de Wegener, dermatomiositis, hepatitis activa crónica, miastenia gravis, síndrome de Steven-Johnson, prurito idiopático, enfermedad inflamatoria autoinmune del intestino (por ejemplo, colitis ulcerativa y enfermedad de Crohn), oftalmopatía endocrina, enfermedad de Graves, sarcoidosis, alveolitis, neumonitis de hipersensibilidad crónica, esclerosis múltiple, cirrosis biliar primaria, uveítis (anterior y posterior), queratoconjuntivitis sicca y queratoconjuntivitis vernal, fibrosis pulmonar intersticial, artritis soriática, y glomerulonefritis (con y sin síndrome nefrótico, por ejemplo, incluyendo síndrome nefrótico idiopático o nefropatía de cambio mínimo).

Además, los agentes de la invención también se pueden utilizar para el tratamiento de fibrosis quística, hipertensión pulmonar, fibrosis pulmonar, síndrome inflamatorio del intestino, sanado de heridas, nefropatía diabética como se describe en la Publicación Internacional Número WO 05/107463, reducción de inflamación en el tejido trasplantado como se describe en la Patente de los Estados Unidos de Norteamérica Número US 2005/182018, enfermedades inflamatorias causadas por organismos patogénicos como se describen en la Publicación Internacional Número WO 03/086408, y condiciones cardiovasculares como se describen en la Publicación Internacional Número WO 03/029264.

También, los agentes de la invención se pueden utilizar para evaluar la severidad de la estenosis de arterias coronarias, como se

describe en la Publicación Internacional Número WO 00/078774, y son útiles en conjunto con agentes radioactivos de toma de imágenes, para la toma de imágenes de la actividad coronaria, y son útiles en la terapia auxiliar con angioplastía como se describe en la Publicación Internacional Número WO 00/78779.

Los agentes de la invención son también útiles en combinación con un inhibidor de proteasa para la prevención de isquemia de órganos y de lesión por reperfusión, como se describe en la Publicación Internacional Número WO 05/003150, y en combinación con un antagonista de integrina para el tratamiento de la acumulación de plaquetas, como se describe en la Publicación Internacional Número WO 03/090733.

Los agentes de la invención son también útiles para promover el sanado de heridas en las células epiteliales bronquiales, como se describe en *AJP-Lung*, Volumen 290, páginas 849-855.

Otras enfermedades o condiciones que se pueden tratar con los agentes de la invención incluyen diabetes, por ejemplo, diabetes mellitus tipo I (diabetes juvenil) y diabetes mellitus tipo II, enfermedades diarreicas, isquemia/lesiones por reperfusión, retinopatía, tal como retinopatía diabética o retinopatía inducida por oxígeno hiperbárico, condiciones caracterizadas por una presión intraocular elevada o secreción del humor acuoso ocular, tales como glaucoma, daño isquémico de tejidos/órganos por reperfusión, y llagas por la cama.

La efectividad de un agente de la invención en la inhibición de

las condiciones inflamatorias, por ejemplo en las enfermedades inflamatorias de las vías respiratorias, se pueden demostrar en un modelo animal, por ejemplo, un modelo de ratón o de rata, de inflamación de las vías respiratorias u otras condiciones inflamatorias, por ejemplo, como es descrito por Szarka y colaboradores, *J Immunol Methods*, Volumen 202, páginas 49-57 (1997); Renzi y colaboradores, *Am Rev Respir Dis*, Volumen 148, páginas 932-939 (1993); Tsuyuki y colaboradores, *J Clin Invest*, Volumen 96, páginas 2924-2931 (1995); Cernadas y colaboradores, *Am J Respir Cell Mol Biol*, Volumen 20, páginas 1-8 (1999); y Fozard y colaboradores, *Eur J Pharmacol*, Volumen 438, páginas 183-188 (2002).

Los agentes de la invención también son útiles como co-agentes terapéuticos para utilizarse en combinación con otras sustancias de fármaco, tales como sustancias de fármaco anti-inflamatorias, broncodilatadoras, anti-histamínicas, o anti-tusivas, en particular en el tratamiento de enfermedades obstructivas o inflamatorias de las vías respiratorias, tales como aquéllas mencionadas anteriormente en la presente, por ejemplo como potenciadores de la actividad terapéutica de tales fármacos o como un medio para reducir la dosificación requerida o los efectos secundarios potenciales de estos fármacos. Un agente de la invención se puede mezclar con la otra sustancia de fármaco en una composición farmacéutica o se puede administrar por separado, antes, de una manera simultánea con, o después de la otra sustancia

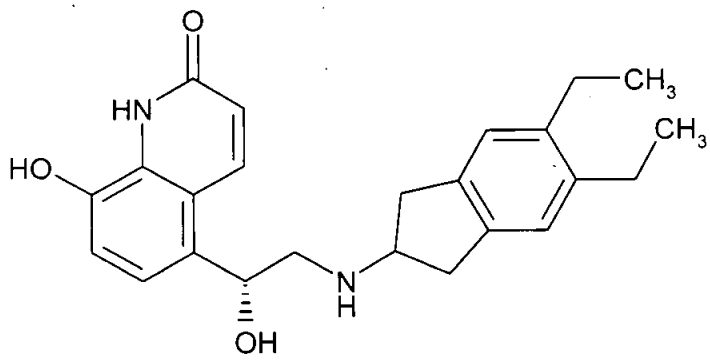
de fármaco.

De conformidad con lo anterior, la invención incluye una combinación de un agente de la invención como se describe anteriormente en la presente, con una sustancia de fármaco anti-inflamatoria, broncodilatadora, anti-histamínica, o anti-tusiva, estando este agente de la invención y la sustancia de fármaco mencionada en la misma o diferente composición farmacéutica.

Los fármacos anti-inflamatorios adecuados incluyen esteroides, en particular, glucocorticosteroides tales como budesonida, dipropionato de beclametasona, propionato de fluticasona, ciclesonida o furoato de mometasona, o los esteroides descritos en las Publicaciones Internacionales Números WO 02/88167, WO 02/12266, WO 02/100879, WO 02/00679 (en especial aquéllos de los Ejemplos 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 73, 90, 99 y 101), WO 03/35668, WO 03/48181, WO 03/62259, WO 03/64445, WO 03/72592, WO 04/39827 y WO 04/66920; agonistas del receptor glucocorticoide no esteroideos, tales como aquéllos descritos en las Patentes Números DE 10261874, WO 00/00531, WO 02/10143, WO 03/82280, WO 03/82787, WO 03/86294, WO 03/104195, WO 03/101932, WO 04/05229, WO 04/18429, WO 04/19935 y WO 04/26248; antagonistas de LTB4, tales como BIIL 284, CP-195543, DPC11870, LTB4 etanolamida, LY 293111, LY 255283, CGS025019C, CP-195543, ONO-4057, SB 209247, SC-53228 y aquéllos descritos en la Patente de los Estados Unidos de Norteamérica Número US 5451700; los antagonistas de LTD4 incluyen montelukast, pranlukast,

zafirlukast, accolato, SR2640, Wy-48,252, ICI 198615, MK-571, LY-171883, Ro 24-5913 y L-648051; los inhibidores de PDE4, tales como cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden), V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofilina (Almirall Prodesfarma), PD189659 / PD168787 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene), SelCID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo) y aquéllos que se dan a conocer en las Publicaciones Internacionales Números WO 92/19594, WO 93/19749, WO 93/19750, WO 93/19751, WO 98/18796, WO 99/16766, WO 01/13953, WO 03/104204, WO 03/104205, WO 03/39544, WO 04/000814, WO 04/000839, WO 04/005258, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/018431, WO 04/018449, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/019944, WO 04/019945, WO 04/045607 y WO 04/037805; antagonistas del receptor de adenosina A_{2B}, tales como aquéllos descritos en la Publicación Internacional Número WO 02/42298; y agonistas del adreno-receptor beta-2, tales como albuterol (salbutamol), metaproterenol, terbutalina, salmeterol, fenoterol, procaterol, y en especial, formoterol, carmoterol y las sales farmacéuticamente aceptables del mismo, y los compuestos (en forma libre o de sal o de solvato) de la fórmula (I) de la Publicación Internacional Número WO 0075114, cuyo documento se incorpora a la presente como referencia, de preferencia los compuestos de los Ejemplos del mismo, en especial

un compuesto de la fórmula:



y las sales farmacéuticamente aceptables del mismo, así como los compuestos (en forma libre o de sal o de solvato) de la fórmula (I) de la Publicación Internacional Número WO 04/16601, y también los compuestos de las Patentes Números EP 1440966, JP 05025045, WO 93/18007, WO 99/64035, US 2002/0055651, US 2005/0133417, US 2005/5159448, WO 01/42193, WO 01/83462, WO 02/66422, WO 02/70490, WO 02/76933, WO 03/24439, WO 03/42160, WO 03/42164, WO 03/72539, WO 03/91204, WO 03/99764, WO 04/16578, WO 04/22547, WO 04/32921, WO 04/33412, WO 04/37768, WO 04/37773, WO 04/37807, WO 04/39762, WO 04/39766, WO 04/45618 WO 04/46083, WO 04/80964, EP1460064, WO 04/087142, WO 04/089892, EP 01477167, US 2004/0242622, US 2004/0229904, WO 04/108675, WO 04/108676, WO 05/033121, WO 05/040103, WO 05/044787, WO 05/058867, WO 05/065650, WO 05/066140 y WO 05/07908.

Los fármacos broncodilatadores adecuados incluyen a los agentes anticolinérgicos o antimuscarínicos, en particular, bromuro de ipratropio, bromuro de oxitropio, sales de tiotropio y CHF 4226

(Chiesi), y glicopirrolato, pero también aquéllos descritos en las Patentes Números EP 424021, US 3714357, US 5171744, US 2005/171147, US 2005/182091, WO 01/04118, WO 02/00652, WO 02/51841, WO 02/53564, WO 03/00840, WO 03/33495, WO 03/53966, WO 03/87094, WO 04/018422, WO 04/05285 y WO 05/077361.

Los fármacos anti-inflamatorios y broncodilatadores dobles adecuados incluyen los agonistas del adreno-receptor beta-2 / antagonistas muscarínicos dobles, tales como aquéllos que se dan a conocer en las Patentes Números US 2004/0167167, US 2004/0242622, US 2005/182092, WO 04/74246 y WO 04/74812.

Las sustancias de fármaco anti-histamínicas adecuadas incluyen clorhidrato de cetirizina, acetaminofeno, fumarato de clemastina, prometazina, loratidina, desloratidina, difenhidramina y clorhidrato de fexofenadina, activastina, astemizol, azelastina, ebastina, epinastina, mizolastina y tefenadina, así como aquéllas que se dan a conocer en las Patentes Números JP 2004107299, WO 03/099807 y WO 04/026841.

Otras combinaciones útiles de agentes de la invención con fármacos anti-inflamatorios son aquéllas con antagonistas de los receptores de quimiocina, por ejemplo, CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 y CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, en particular los antagonistas de CCR-5, tales como los antagonistas Schering-Plough SC-351125, SCH-55700 y SCH-D, los antagonistas Takeda, tales como cloruro de N-[[4-[[[6,7-dihidro-2-(4-metil-fenil)-5H-benzo-ciclohepten-8-il]-carbonil]-

amino]-fenil]-metil]-tetrahidro-N,N-dimetil-2H-piran-4-aminio (TAK-770), y los antagonistas de CCR-5 descritos en la Patente de los Estados Unidos de Norteamérica Número US 6166037 (en particular en las reivindicaciones 18 y 19), y en las Publicaciones Internacionales Números WO 00/66558 (en particular en la reivindicación 8), WO 00/66559 (en particular en la reivindicación 9), WO 04/018425 y WO 04/026873.

De acuerdo con lo anterior, la invención también proporciona un método para el tratamiento de una condición que responda a la activación del receptor de adenosina A_{2A}, por ejemplo, una condición inflamatoria o alérgica, en particular una enfermedad inflamatoria u obstructiva de las vías respiratorias, el cual comprende administrar a un sujeto, en particular a un sujeto humano, que lo necesite, un compuesto de la fórmula (I) en forma libre o en la forma de una sal farmacéuticamente aceptable. En otro aspecto, la invención proporciona un compuesto de la fórmula (I), en forma libre o en la forma de una sal farmacéuticamente aceptable, para utilizarse en la fabricación de un medicamento para el tratamiento de una condición que responda a la activación del receptor de adenosina A_{2A}, en particular una enfermedad inflamatoria u obstructiva de las vías respiratorias.

Los agentes de la invención se pueden administrar por cualquier vía apropiada, por ejemplo, oralmente, por ejemplo, en la forma de una tableta o cápsula; parenteralmente, por ejemplo, intravenosamente; mediante inhalación, por ejemplo, en el

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tratamiento de una enfermedad inflamatoria u obstructiva de las vías respiratorias; intranasalmente, por ejemplo, en el tratamiento de rinitis alérgica; tópicamente a la piel, por ejemplo, en el tratamiento de dermatitis atópica; o rectalmente, por ejemplo, en el tratamiento de enfermedad inflamatoria del intestino.

En un aspecto adicional, la invención también proporciona una composición farmacéutica, la cual comprende un compuesto de la fórmula (I) en forma libre o en la forma de una sal farmacéuticamente aceptable, opcionalmente junto con un diluyente o vehículo farmacéuticamente aceptable para el mismo. La composición puede contener un agente co-terapéutico, tal como un fármaco anti-inflamatorio, broncodilatador, anti-histamínico, o anti-tusivo como se describe anteriormente en la presente. Estas composiciones se pueden preparar utilizando diluyentes o excipientes convencionales y técnicas conocidas en el campo galénico. Por consiguiente, las formas de dosificación oral pueden incluir tabletas y cápsulas. Las formulaciones para administración tópica pueden tomar la forma de cremas, ungüentos, geles, o sistemas de suministro transdérmico, por ejemplo, parches. Las composiciones para inhalación pueden comprender formulaciones en aerosol u otras formulaciones atomizables, o formulaciones en polvo seco.

Cuando la composición comprende una formulación en aerosol, de preferencia contiene, por ejemplo, un propelente de hidro-fluoro-alcano (HFA), tal como HFA134a o HFA227 o una mezcla de los mismos, y puede contener uno o más co-solventes conocidos en la

técnica, tales como etanol (hasta el 20 por ciento en peso), y/o uno o más tensoactivos, tales como ácido oleico o trioleato de sorbitán, y/o uno o más agentes de volumen, tales como lactosa. Cuando la composición comprende una formulación en polvo seco, de preferencia contiene, por ejemplo, los compuestos de la fórmula (I) que tienen un diámetro de partículas de hasta 10 micras, opcionalmente junto con un diluyente o vehículo, tal como lactosa, de la distribución de tamaños de partículas deseada, y un compuesto que ayude a proteger contra el deterioro del desempeño del producto debido a la humedad, por ejemplo, estearato de magnesio. Cuando la composición comprende una formulación nebulizada, de preferencia contiene, por ejemplo, al compuesto de la fórmula (I), ya sea disuelto o suspendido en un vehículo que contenga agua, un co-solvente, tal como etanol o propilenglicol, y un estabilizante, el cual puede ser un tensoactivo.

La invención incluye:

(a) un compuesto de la fórmula (I) en una forma inhalable, por ejemplo, en una composición en aerosol o atomizable, o en una forma particulada inhalable, por ejemplo, micronizada;

(b) un medicamento inhalable que comprende un compuesto de la fórmula (I) en una forma inhalable;

(c) un producto farmacéutico que comprende un compuesto de la fórmula (I) en una forma inhalable en asociación con un dispositivo para inhalación; y

(d) un dispositivo para inhalación que contiene un compuesto

de la fórmula (I) en una forma inhalable.

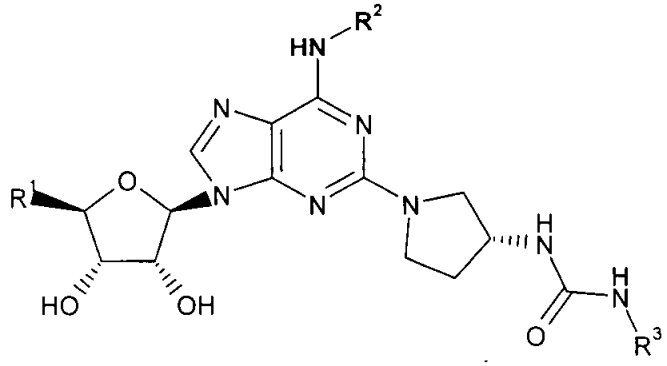
Las dosificaciones de los compuestos de la fórmula (I) empleadas en la práctica de la presente invención, desde luego, variarán dependiendo, por ejemplo, de la condición particular que se vaya a tratar, del efecto deseado, y del modo de administración. En general, las dosificaciones diarias adecuadas para la administración mediante inhalación son del orden de 0.005 a 10 miligramos, mientras que para administración oral, las dosis diarias adecuadas son del orden de 0.05 a 100 miligramos.

La invención se ilustra mediante los siguientes ejemplos.

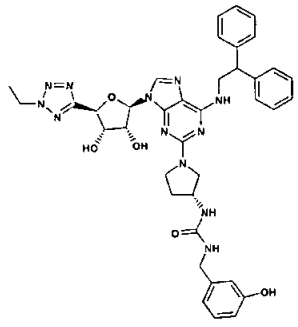
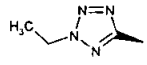
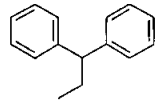
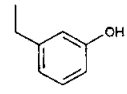
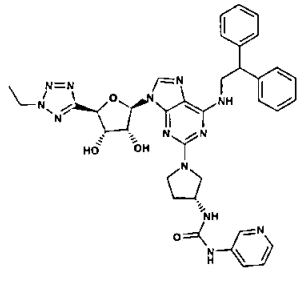
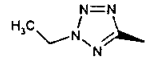
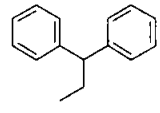
EJEMPLOS

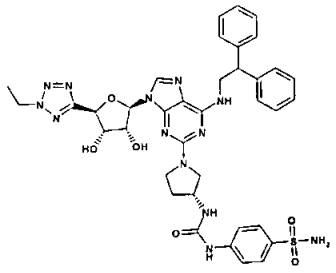
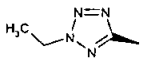
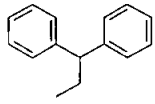
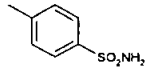
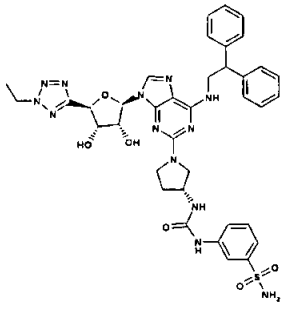
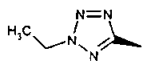
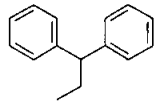
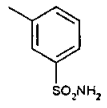
Ejemplos 1 a 48

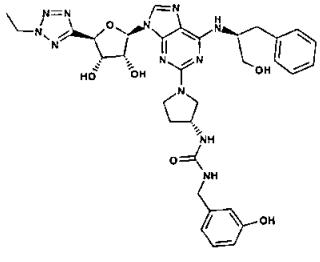
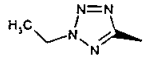
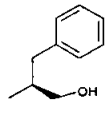
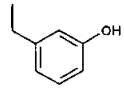
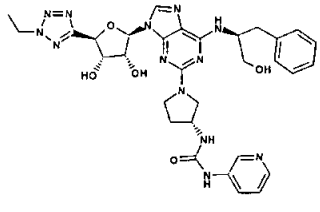
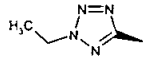
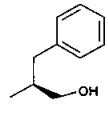
Los compuestos de la fórmula (I):



se muestran en la siguiente Tabla. Los métodos para la preparación de estos compuestos se describen posteriormente en la presente.

Ej.	Estructura	R^1	R^2	R^3	Nombre
1					1-((R)-1-{6-(2,2-difenil-etil-amino)-9-(2R,3R,4S,5R)-5-(2-etil-2H-tetrazol-5-il)-3,4-dihidroxi-tetrahidrofuran-2-il]-9H-purin-2-il}-pirrolidin-3-il)-3-(3-hidroxi-bencil)-urea
2					1-((R)-1-{6-(2,2-difenil-etil-amino)-9-[(2R,3R,4S,5R)-5-(2-etil-2H-tetrazol-5-il)-3,4-dihidroxi-tetrahidrofuran-2-il]-9H-purin-2-il}-pirrolidin-3-il)-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					3-piridin-3-il-urea
3					4-[3-((R)-1-{6-(2,2-difenil-etilamino)-9-[(2R,3R,4S,5R)-5-(2-etil-2H-tetrazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida
4					3-[3-((R)-1-{6-(2,2-difenil-etil-amino)-9-[(2R,3R,4S,5R)-5-(2-etil-2H-tetrazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-9H-purin-2-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida
5					1-{(R)-1-[9-[(2R,3R,4S,5R)-5-(2-etil-2H-tetrazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea
6					1-{(R)-1-[9-[(2R,3R,4S,5R)-5-(2-etil-2H-tetrazol-5-il)-3,4-dihidroxi-tetrahidro-furan-

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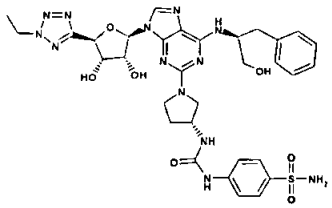
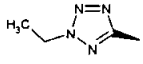
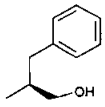
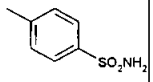
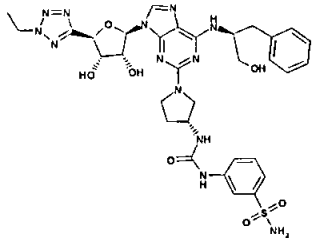
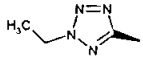
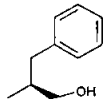
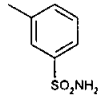
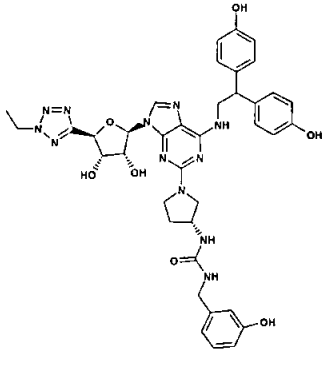
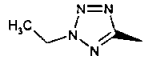
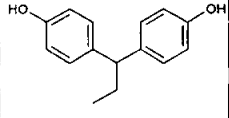
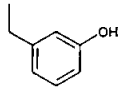
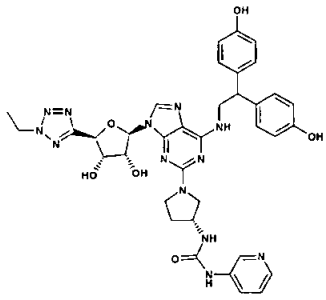
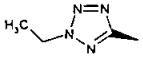
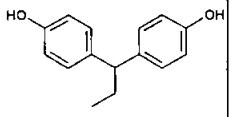
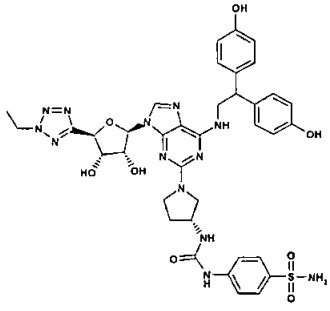
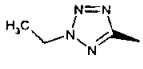
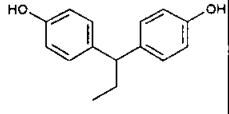
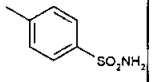
Ej.	Estructura	R^1	R^2	R^3	Nombre
					2-il]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea
7					4-(3-{(R)-1-[9-[(2R,3R,4S,5R)-5-(2-etil-2H-tetrazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida

Ej.	Estructura	R^1	R^2	R^3	Nombre
8					3-(3-{(R)-1-[9-[(2R,3R,4S,5R)-5-(2-etil-2H-tetrazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
9					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(2R,3R,4S,5R)-5-(2-etil-2H-tetrazol-5-il)-3,4-dihidroxi-tetrahidro-furan-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					2-il]-9H-purin-2-il}-pirrolidin-3-il)-3-(3-hidroxi-bencil)-urea
10					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(2R,3R,4S,5R)-5-(2-etil-2H-tetrazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-9H-purin-2-il}-pirrolidin-3-il)-3-piridin-3-il-urea
11					4-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(2R,3R,4S,5R)-5-(2-etil-2H-

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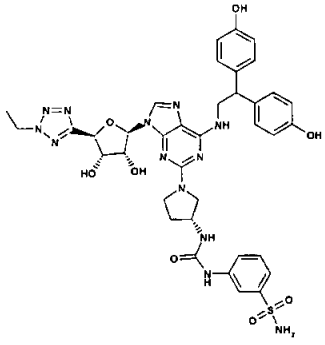
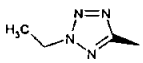
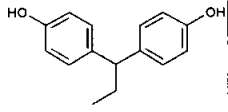
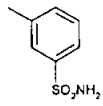
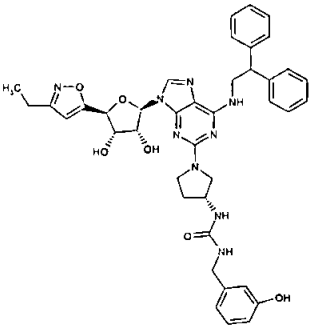
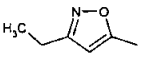
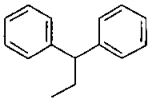
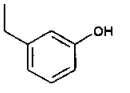
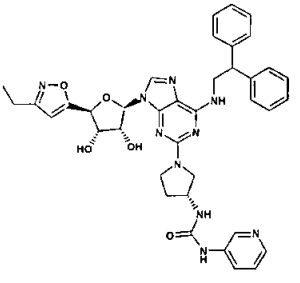
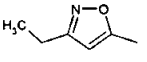
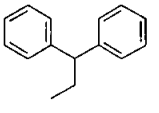
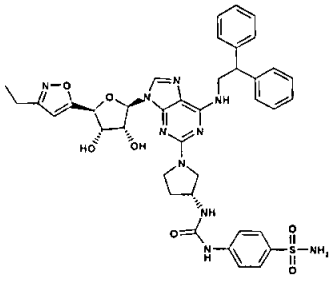
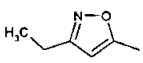
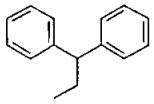
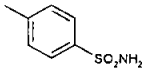
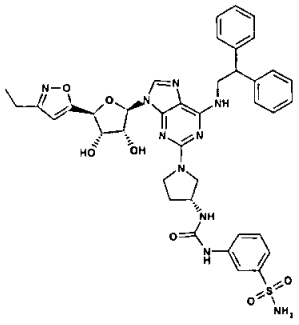
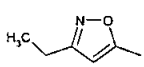
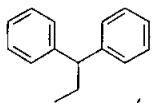
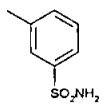
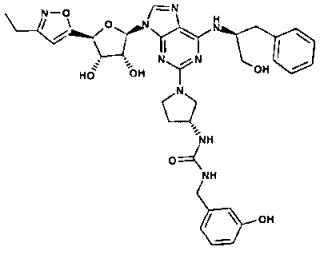
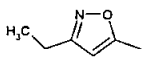
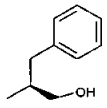
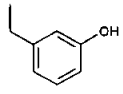
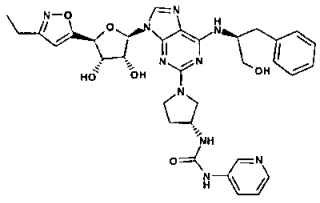
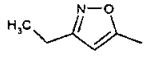
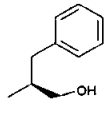
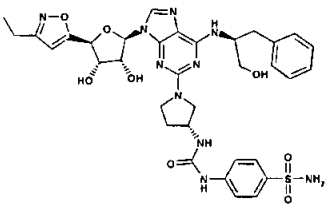
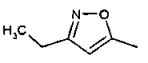
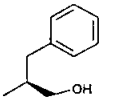
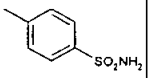
Ej.	Estructura	R^1	R^2	R^3	Nombre
					tetrazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida
12					3-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(2R,3R,4S,5R)-5-(2-etil-2H-tetrazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida

Ej.	Estructura	R^1	R^2	R^3	Nombre
13					1-((R)-1-{6-(2,2-difenil-etil-amino)-9-[(2R,3R,4S,5S)-5-(3-etil-isoxazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-9H-purin-2-il}-pirrolidin-3-il)-3-(3-hidroxi-bencil)-urea
14					1-((R)-1-{6-(2,2-difenil-etil-amino)-9-[(2R,3R,4S,5S)-5-(3-etil-isoxazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-9H-purin-2-il}-pirrolidin-3-il)-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					3-piridin-3-il-urea
15					4-[3-((R)-1-{6-(2,2-difenil-etil-amino)-9-[(2R,3R,4S,5S)-5-(3-etil-isoxazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida
16					3-[3-((R)-1-{6-(2,2-difenil-etil-amino)-9-[(2R,3R,4S,5S)-5-(3-etil-isoxazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-9H-purin-2-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida
17					1-{(R)-1-[9-[(2R,3R,4S,5S)-5-(3-etil-isoxazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea
18					1-{(R)-1-[9-[(2R,3R,4S,5S)-5-(3-etil-isoxazol-5-il)-3,4-dihidroxi-tetrahidro-furan-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					2-il]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea
19					4-(3-{(R)-1-[9-[(2R,3R,4S,5S)-5-(3-etil-isoxazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida

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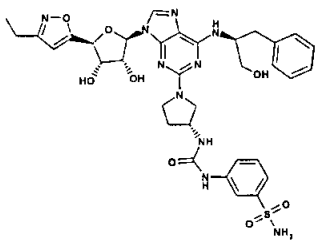
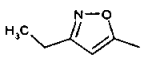
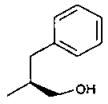
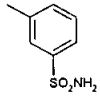
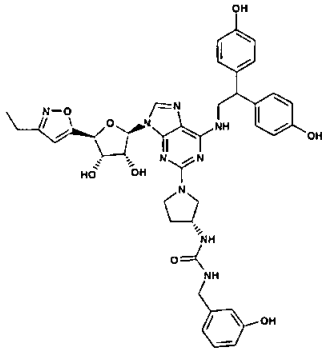
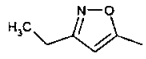
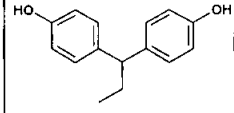
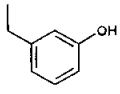
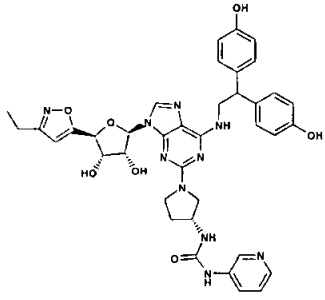
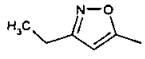
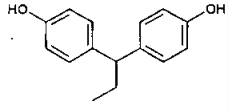
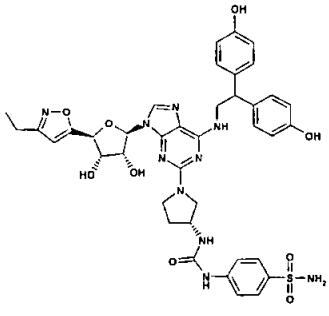
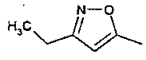
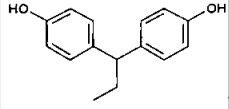
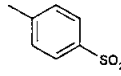
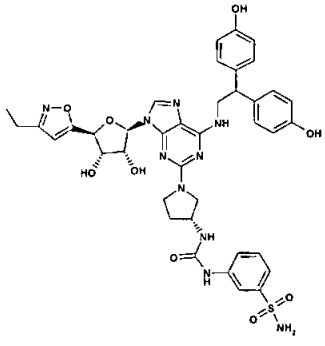
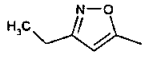
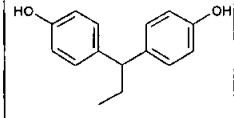
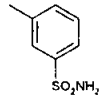
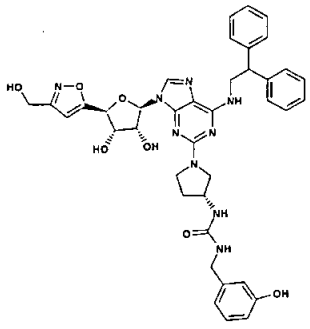
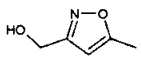
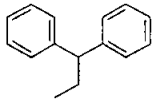
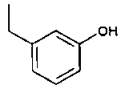
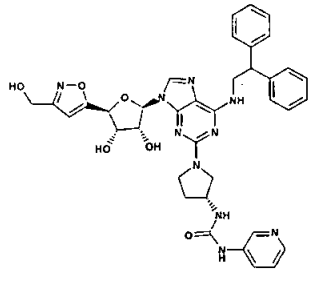
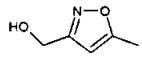
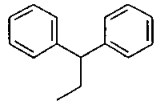
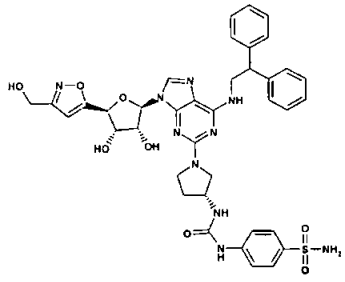
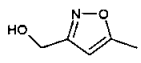
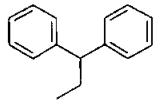
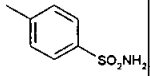
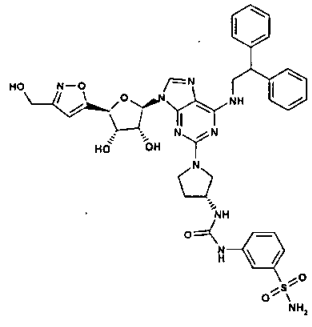
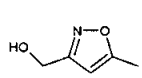
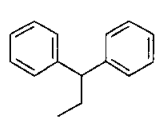
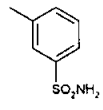
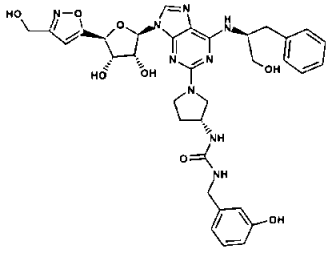
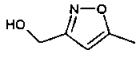
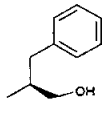
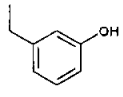
Ej.	Estructura	R^1	R^2	R^3	Nombre
20					3-(3-{(R)-1-[9-[(2R,3R,4S,5S)-5-(3-etil-isoxazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
21					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(2R,3R,4S,5S)-5-(3-etil-isoxazol-5-il)-3,4-dihidroxi-tetrahidrofuran-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					2-il]-9H-purin-2-il}-pirrolidin-3-il)-3-(3-hidroxi-bencil)-urea
22					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(2R,3R,4S,5S)-5-(3-etil-isoxazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-9H-purin-2-il}-pirrolidin-3-il)-3-piridin-3-il-urea
23					4-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(2R,3R,4S,5S)-5-(3-etil-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					isoxazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida
24					3-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(2R,3R,4S,5S)-5-(3-etil-isoxazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida

Ej.	Estructura	R^1	R^2	R^3	Nombre
25					1-{(R)-1-[9-[(2R,3R,4S,5S)-3,4-dihidroxi-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidro-furan-2-il]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea
26					1-{(R)-1-[9-[(2R,3R,4S,5S)-3,4-dihidroxi-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidro-furan-2-il]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					il}-3-piridin-3-il-urea
27					4-(3-{(R)-1-[9-[(2R,3R,4S,5S)-3,4-dihidroxi-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidro-furan-2-il]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
28					3-(3-{(R)-1-[9-[(2R,3R,4S,5S)-3,4-dihidroxi-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidrofuran-2-il]-6-(2,2-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
29					1-{(R)-1-[9-[(2R,3R,4S,5S)-3,4-dihidroxi-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidrofuran-2-il]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea

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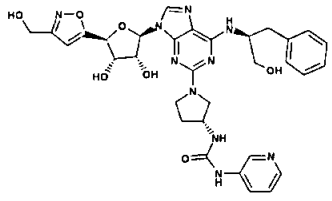
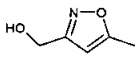
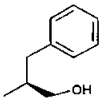
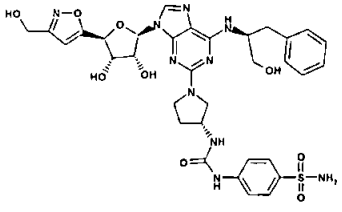
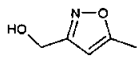
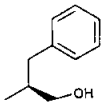
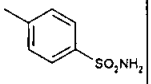
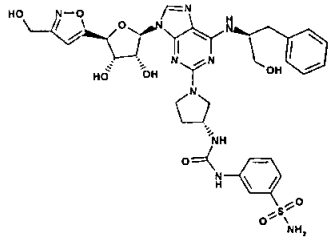
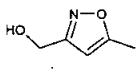
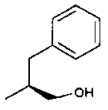
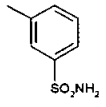
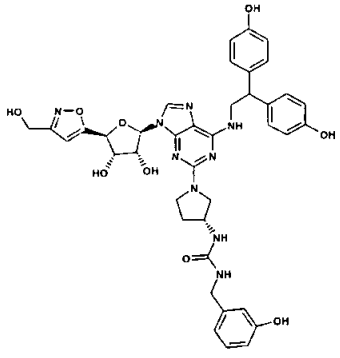
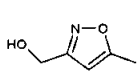
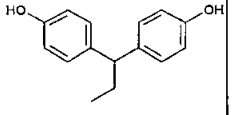
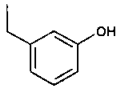
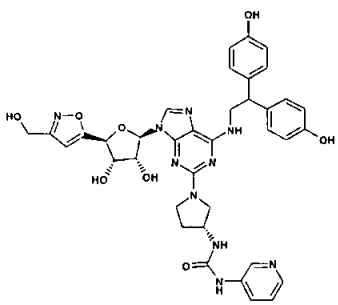
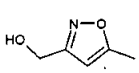
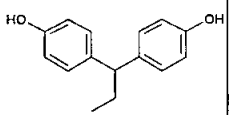
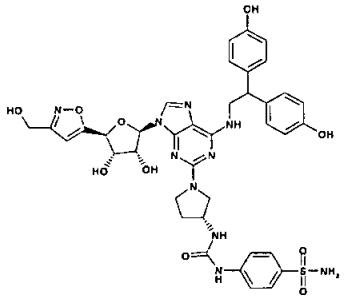
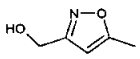
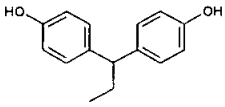
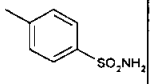
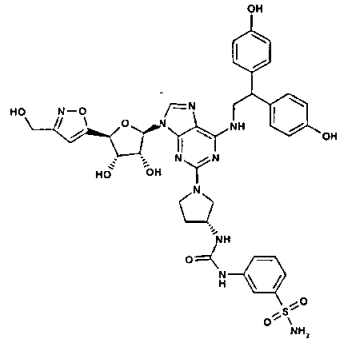
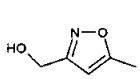
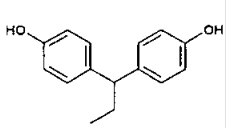
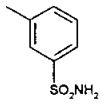
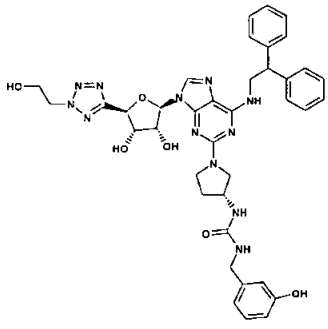
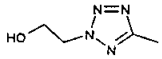
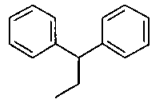
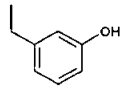
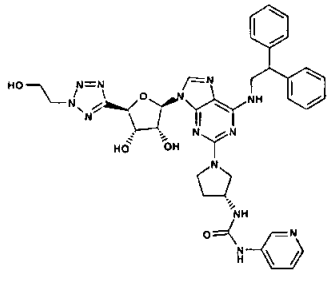
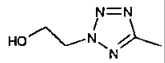
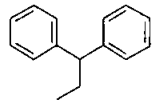
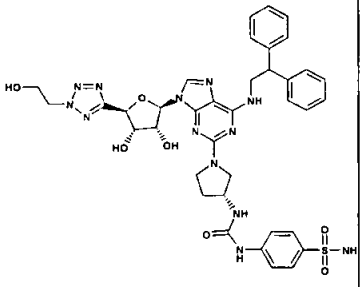
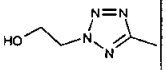
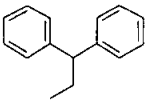
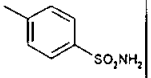
Ej.	Estructura	R^1	R^2	R^3	Nombre
30					1-{(R)-1-[9-[(2R,3R,4S,5S)-3,4-dihidroxi-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidrofuran-2-il]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea
31					4-(3-{(R)-1-[9-[(2R,3R,4S,5S)-3,4-dihidroxi-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidro-furan-2-il]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					pirrolidin-3-il}-ureido)-bencen-sulfonamida
32					3-(3-{(R)-1-[9-[(2R,3R,4S,5S)-3,4-dihidroxi-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidro-furan-2-il]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
33					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(2R,3R,4S,5S)-3,4-dihidroxi-5-

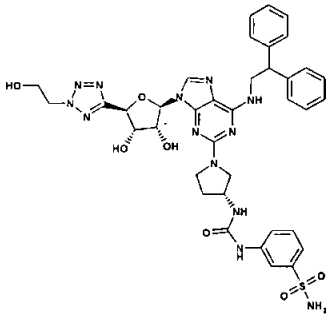
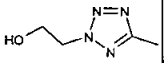
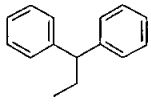
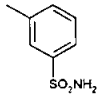
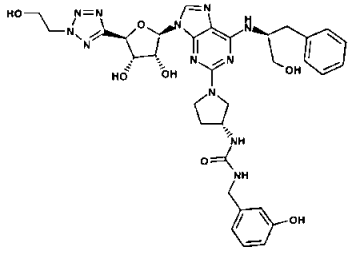
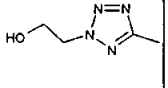
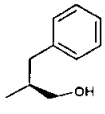
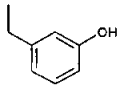
Ej.	Estructura	R^1	R^2	R^3	Nombre
					(3-hidroxi-metil-isoxazol-5-il)-tetrahidro-furan-2-il]-9H-purin-2-il}-pirrolidin-3-il)-3-(3-hidroxi-bencil)-urea
34					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(2R,3R,4S,5S)-3,4-dihidroxi-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidrofuran-2-il]-9H-purin-2-il}-pirrolidin-3-il)-3-piridin-3-il-urea

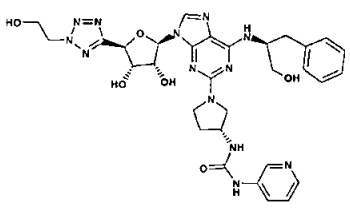
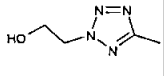
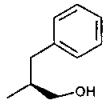
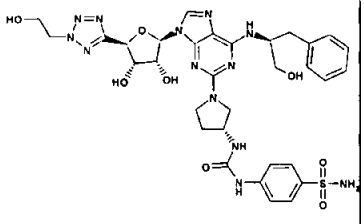
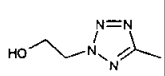
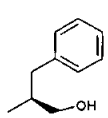
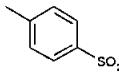
Ej.	Estructura	R^1	R^2	R^3	Nombre
35					4-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(2R,3R,4S,5S)-3,4-dihidroxi-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidrofuran-2-il]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida
36					3-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(2R,3R,4S,5S)-3,4-dihidroxi-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidro-furan-

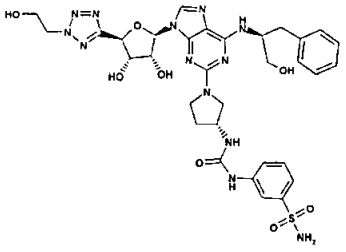
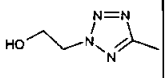
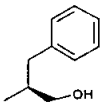
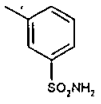
Ej.	Estructura	R^1	R^2	R^3	Nombre
					2-il]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida
37					1-{(R)-1-[9-{(2R,3R,4S,5R)-3,4-dihidroxi-5-[2-(2-hidroxi-etil)-2H-tetrazol-5-il]-tetrahidro-furan-2-il}-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea
38					1-{(R)-1-[9-{(2R,3R,4S,5R)-3,4-dihidroxi-5-[2-(2-hidroxi-etil)-2H-tetrazol-5-il]-tetrahidro-

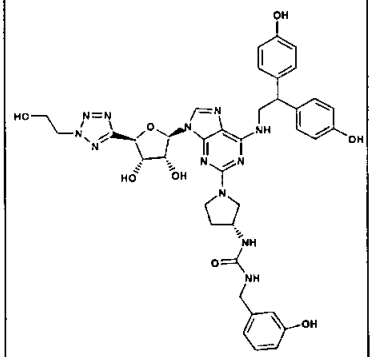
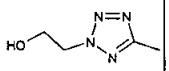
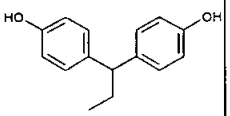
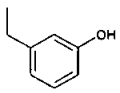
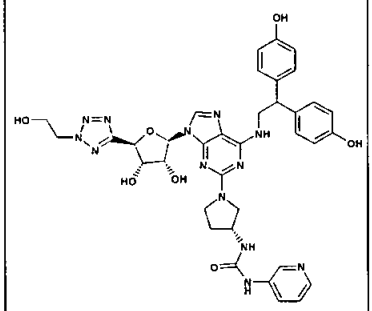
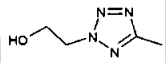
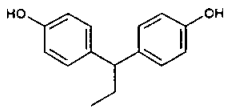
Ej.	Estructura	R^1	R^2	R^3	Nombre
					furan-2-il}-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea
39					4-(3-{(R)-1-[9-{(2R,3R,4S,5R)-3,4-dihidroxi-5-[2-(2-hidroxi-etil)-2H-tetrazol-5-il]-tetrahidro-furan-2-il}-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida

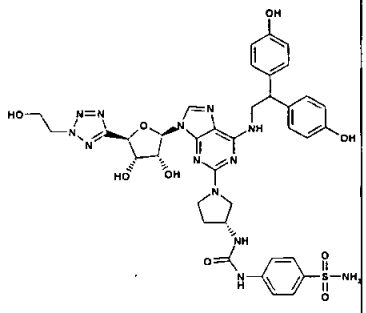
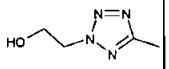
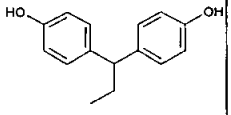
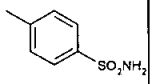
166

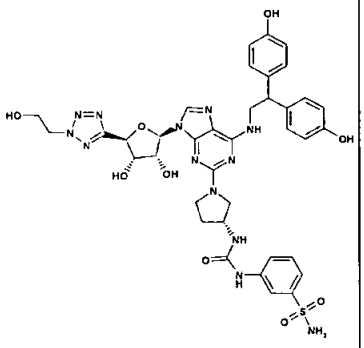
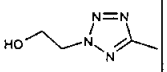
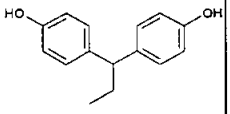
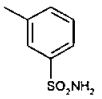
Ej.	Estructura	R^1	R^2	R^3	Nombre
40					3-(3-{(R)-1-[9-{(2R,3R,4S,5R)-3,4-dihidroxi-5-[2-(2-hidroxi-etil)-2H-tetrazol-5-il]-tetrahidro-furan-2-il}-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
41					1-{(R)-1-[9-{(2R,3R,4S,5R)-3,4-dihidroxi-5-[2-(2-hidroxi-etil)-2H-tetrazol-5-il]-tetrahidro-furan-2-il}-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea
42					1-{(R)-1-[9-{(2R,3R,4S,5R)-3,4-dihidroxi-5-[2-(2-hidroxi-etil)-2H-tetrazol-5-il]-tetrahidro-furan-2-il}-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea
43					4-(3-{(R)-1-[9-{(2R,3R,4S,5R)-3,4-dihidroxi-5-[2-(2-hidroxi-etil)-2H-tetrazol-5-il]-tetrahidro-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					furan-2-il}-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
44					3-(3-{(R)-1-[9-{(2R,3R,4S,5R)-3,4-dihidroxi-5-[2-(2-hidroxi-etil)-2H-tetrazol-5-il]-tetrahidro-furan-2-il}-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida

Ej.	Estructura	R^1	R^2	R^3	Nombre
45					1-[(R)-1-(6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-{(2R,3R,4S,5R)-3,4-dihidroxi-5-[2-(2-hidroxi-etil)-2H-tetrazol-5-il]-tetrahidro-furan-2-il}-9H-purin-2-il)-pirrolidin-3-il]-3-(3-hidroxi-bencil)-urea
46					1-[(R)-1-(6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-{(2R,3R,4S,5R)-3,4-dihidroxi-5-[2-(2-hidroxi-etil)-2H-tetrazol-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					5-il]-tetrahidro-furan-2-il}-9H-purin-2-il)-pirrolidin-3-il]-3-piridin-3-il-urea
47					4-{3-[(R)-1-(6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-{(2R,3R,4S,5R)-3,4-dihidroxi-5-[2-(2-hidroxi-etil)-2H-tetrazol-5-il]-tetrahidro-furan-2-il}-9H-purin-2-il)-pirrolidin-3-il]-ureido}-bencen-sulfonamida

Ej.	Estructura	R^1	R^2	R^3	Nombre
48					3-{3-[(R)-1-(6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-{(2R,3R,4S,5R)-3,4-dihidroxi-5-[2-(2-hidroxi-etil)-2H-tetrazol-5-il]-tetrahidro-furan-2-il}-9H-purin-2-il)-pirrolidin-3-il]-ureido}-bencen-sulfonamida

Preparación de Compuestos Intermediarios

Intermediario A **4,4'-(2-amino-etiliden)-bis-fenol**

Este compuesto se prepara mediante el procedimiento de R.M.Schelkun y colaboradores, *Bioorg Med Chem Lett*, Volumen 9, páginas 2447-2452 (1999).

Intermediario BA **Fenil-éster del ácido (3-hidroxi-bencil)-carbámico**

La 3-hidroxi-bencil-amina (200 miligramos, 1.62 milimoles), y el

carbonato ácido de sodio (273 miligramos, 3.25 milimoles) se suspenden en agua/dicloro-metano (4 mililitros, 1:1), y se tratan con cloroformato de fenilo (0.204 mililitros, 1.62 milimoles). Después de agitar a temperatura ambiente durante la noche, la mezcla de reacción se diluye con más dicloro-metano/agua, y la fase orgánica se separa. La porción orgánica se concentra al vacío, para proporcionar el compuesto del título. (MH+ 244)

Intermediario BB **Fenil-éster del ácido piridin-3-il-carbámico**

El cloroformato de fenilo (0.733 mililitros, 5.84 milimoles) se suspende en piridina/dicloro-metano (3 mililitros, 2:1). La solución se agita a 0°C, y se agrega por goteo la 3-amino-piridina (500 miligramos, 5.31 milimoles) disuelta en dicloro-metano (1 mililitro). La mezcla de reacción está a 0°C durante 1 hora. El solvente se remueve al vacío, y el residuo se disuelve en acetato de etilo. Esta porción orgánica se lava con HCl 0.1 M y entonces se concentra al vacío, para proporcionar el compuesto del título. (MH+ 215)

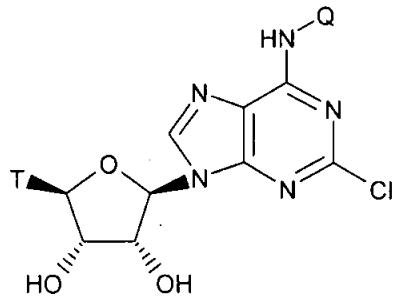
Intermediarios BC y BD

Estos compuestos, es decir,

- Fenil-éster del ácido (3-sulfamoil-fenil)-carbámico (Intermediario **BC**); y
- Fenil-éster del ácido (4-sulfamoil-fenil)-carbámico (Intermediario **BD**),

se preparan de una manera análoga al Intermediario **BB**, mediante el reemplazo de la 3-amino-piridina con la amina apropiada.

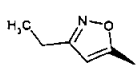
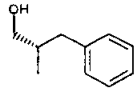
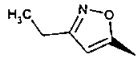
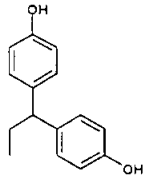
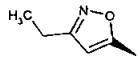
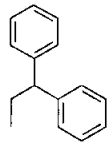
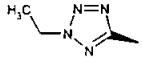
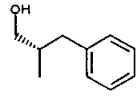
Los siguientes intermediarios de la fórmula (C):

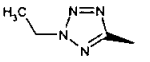
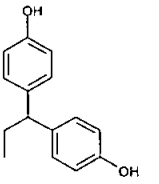
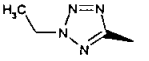
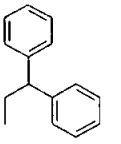
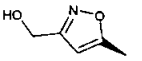
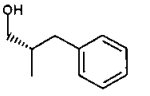
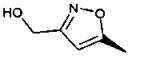
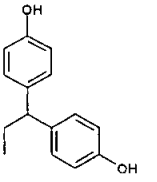
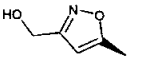
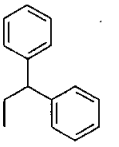
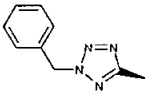
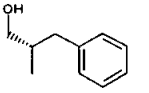
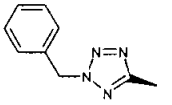
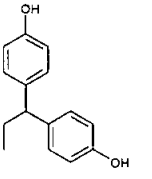


(C)

se muestran más adelante en la Tabla 1a, describiéndose los métodos de preparación posteriormente en la presente.

TABLA 1

Interme-diario	T	Q
CA		
CB		
CC		
CD		

Interme-diario	T	Q
CE		
CF		
CG		
CH		
CI		
CJ		
CK		

Intermediario CA **(2*R*,3*R*,4*S*,5*S*)-2-[6-((*S*)-1-bencil-2-hidroxi-etil-amino)-2-cloro-purin-9-il]-5-(3-etil-isoxazol-5-il)-tetrahidro-furan-3,4-diol**

Paso CA1: Clorhidrato de (2R,3R,4R,5S)-4-acetoxi-2-[6-((S)-1-bencil-2-hidroxi-etil-amino)-2-cloro-purin-9-il]-5-(3-etil-isoxazol-5-il)-tetrahidro-furan-3-il-éster del ácido acético

Una mezcla que comprende (2R,3R,4R,5S)-4-acetoxi-2-(2,6-dicloro-purin-9-il)-5-(3-etil-isoxazol-5-il)-tetrahidro-furan-3-il-éster del ácido acético (Publicación Internacional Número WO 99/38877) (1 gramo, 2.13 milimoles), (*S*)-2-amino-3-fenil-propan-1-ol (0.321 gramos, 2.13 milimoles), y di-isopropil-etil-amina (0.275 gramos, 2.13 milimoles) en dicloro-etano (5 mililitros), se agita bajo una atmósfera inerte de argón durante la noche. Después de enfriar a temperatura ambiente (RT), se agrega HCl 1M, la porción orgánica se separa y se concentra al vacío, para proporcionar el compuesto del título, el cual se utiliza en el siguiente paso sin mayor purificación. (MH+ 585.1)

Paso CA2: (2*R*,3*R*,4*S*,5*S*)-2-[6-((*S*)-1-bencil-2-hidroxi-etil-amino)-2-cloro-purin-9-il]-5-(3-etil-isoxazol-5-il)-tetrahidro-furan-3,4-diol

Una solución de clorhidrato de (2R,3R,4R,5S)-4-acetoxi-2-[6-((S)-1-bencil-2-hidroxi-etil-amino)-2-cloro-purin-9-il]-5-(3-etil-isoxazol-5-il)-tetrahidro-furan-3-il-éster del ácido acético (paso *AC1*) (1.194 gramos, 2.02 milimoles) en MeOH/cloroformo (4 mililitros, 3:1 MeOH/cloroformo), se trata con una solución saturada de carbonato de potasio (10 mililitros). Después de agitar a temperatura

ambiente durante la noche, la mezcla de reacción se diluye con dicloro-metano/agua, y la porción orgánica se separa. La porción orgánica se concentra al vacío, para proporcionar el compuesto del título. (MH+ 501)

Intermediario CB-CC

Estos intermediarios, es decir,

- (2*R*,3*R*,4*S*,5*S*)-2-{6-[2,2-*bis*-(4-hidroxi-fenil)-etil-amino]-2-cloro-purin-9-il}-5-(3-etil-isoxazol-5-il)-tetrahidro-furan-3,4-diol (Intermediario **CB**); y
- (2*R*,3*R*,4*S*,5*S*)-2-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-5-(3-etil-isoxazol-5-il)-tetrahidro-furan-3,4-diol (Intermediario **CC**),

se preparan de una manera análoga al Intermediario **CA**, mediante el reemplazo del (*S*)-2-amino-3-fenil-propan-1-ol con la amina apropiada.

Intermediario CD **(2*R*,3*R*,4*S*,5*R*)-2-[6-((S)-1-bencil-2-hidroxi-etil-amino)-2-cloro-purin-9-il]-5-(2-etil-2*H*-tetrazol-5-il)-tetrahidro-furan-3,4-diol**

Paso CD1: (2R,3R,4R,5R)-4-acetoxi-2-[6-((S)-1-bencil-2-hidroxi-etil-amino)-2-cloro-purin-9-il]-5-(2-etil-2H-tetrazol-5-il)-tetrahidro-furan-3-il-éster del ácido acético

El compuesto del título se prepara de una manera análoga al clorhidrato de (2R,3R,4R,5S)-4-acetoxi-2-[6-((S)-1-bencil-2-hidroxi-etil-amino)-2-cloro-purin-9-il]-5-(3-etil-isoxazol-5-il)-tetrahidro-furan-3-il-éster del ácido acético (paso *CA1*), mediante el reemplazo del

(2R,3R,4R,5S)-4-acetoxi-2-(2,6-dicloro-purin-9-il)-5-(3-etil-isoxazol-5-il)-tetrahidro-furan-3-il-éster del ácido acético (Publicación Internacional Número WO 99/38877) con el (2R,3R,4R,5R)-4-acetoxi-2-(2,6-dicloro-purin-9-il)-5-(2-etil-2H-tetrazol-5-il)-tetrahidro-furan-3-il-éster del ácido acético (Publicación Internacional Número WO 98/28319).

Paso CD2: (2*R*,3*R*,4*S*,5*R*)-2-[6-((*S*)-1-bencil-2-hidroxi-etil-amino)-2-cloro-purin-9-il]-5-(2-etil-2H-tetrazol-5-il)-tetrahidro-furan-3,4-diol

El compuesto del título se prepara a partir del (2R,3R,4R,5R)-4-acetoxi-2-[6-((S)-1-bencil-2-hidroxi-etil-amino)-2-cloro-purin-9-il]-5-(2-etil-2H-tetrazol-5-il)-tetrahidro-furan-3-il-éster del ácido acético (paso *CD1*) de una manera análoga al (2*R*,3*R*,4*S*,5*S*)-2-[6-((*S*)-1-bencil-2-hidroxi-etil-amino)-2-cloro-purin-9-il]-5-(3-etil-isoxazol-5-il)-tetrahidro-furan-3,4-diol (paso *CA2*).

Intermediarios CE y CF

Estos intermediarios, es decir,

- (2*R*,3*R*,4*S*,5*R*)-2-{6-[2,2-*bis*-(4-hidroxi-fenil)-etil-amino]-2-cloro-purin-9-il}-5-(2-etil-2*H*-tetrazol-5-il)-tetrahidro-furan-3,4-diol (Intermediario **CE**); y
- (2*R*,3*R*,4*S*,5*R*)-2-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-5-(2-etil-2*H*-tetrazol-5-il)-tetrahidro-furan-3,4-diol (Intermediario **CF**),

se preparan de una manera análoga al Intermediario **CD**, mediante el reemplazo del (*S*)-2-amino-3-fenil-propan-1-ol con la

amina apropiada.

Intermediario CG **(2*R*,3*R*,4*S*,5*S*)-2-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidro-furan-3,4-diol**

Paso CG1: (2*R*,3*R*,4*R*,5*S*)-4-acetoxi-5-(3-acetoxi-metil-isoxazol-5-il)-2-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-tetrahidro-furan-3-il-éster del ácido acético

Una mezcla que contiene (2*R*,3*R*,4*R*,5*S*)-4-acetoxi-5-(3-acetoxi-metil-isoxazol-5-il)-2-(2,6-dicloro-purin-9-il)-tetrahidro-furan-3-il-éster del ácido acético (Publicación Internacional Número WO 99/38877), 2,2-difenil-etil-amina, y di-isopropil-etil-amina en dicloro-etano, se agita bajo una atmósfera inerte de argón a 50°C durante la noche. Después de enfriar a temperatura ambiente, se agrega HCl 0.1 M, la porción orgánica se separa y se concentra al vacío, para proporcionar el compuesto del título, el cual se utiliza en el siguiente paso sin mayor purificación.

Paso CG2: (2*R*,3*R*,4*S*,5*S*)-2-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidro-furan-3,4-diol

Una solución del (2*R*,3*R*,4*S*,5*S*)-4-acetoxi-5-(3-acetoxi-metil-isoxazol-5-il)-2-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-tetrahidro-furan-3-il-éster del ácido acético (paso *CG1*) en metanol/cloroformo (3:1 de MeOH/cloroformo), se trata con una solución saturada de carbonato de potasio. Después de agitar a temperatura ambiente durante la noche, la reacción se diluye con dicloro-metano/agua, y la porción orgánica se separa. La porción

orgánica se concentra al vacío, para proporcionar el compuesto del título.

Intermediario CH **(2*R*,3*R*,4*S*,5*S*)-2-{6-[2,2-*bis*-(4-hidroxi-fenil)-etil-amino]-2-cloro-purin-9-il}-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidro-furan-3,4-diol**

El compuesto del título se prepara a partir del (2*R*,3*R*,4*R*,5*S*)-4-acetoxi-5-(3-acetoxi-metil-isoxazol-5-il)-2-(2,6-dicloro-purin-9-il)-tetrahidro-furan-3-il-éster del ácido acético (Publicación Internacional Número WO 99/38877) de una manera análoga al (2*R*,3*R*,4*S*,5*S*)-2-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidro-furan-3,4-diol (Intermediario **CG**), mediante el reemplazo de la 2,2-difenil-etil-amina con el 4,4'-(2-amino-etiliden)-bis-fenol (Intermediario **A**).

Intermediario CI **(2*R*,3*R*,4*S*,5*S*)-2-[2-cloro-6-((*S*)-1-hidroxi-metil-2-fenil-etil-amino)-purin-9-il]-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidro-furan-3,4-diol**

El compuesto del título se prepara a partir del (2*R*,3*R*,4*R*,5*S*)-4-acetoxi-5-(3-acetoxi-metil-isoxazol-5-il)-2-(2,6-dicloro-purin-9-il)-tetrahidro-furan-3-il-éster del ácido acético (Publicación Internacional Número WO 99/38877) de una manera análoga al (2*R*,3*R*,4*S*,5*S*)-2-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-5-(3-hidroxi-metil-isoxazol-5-il)-tetrahidro-furan-3,4-diol (Intermediario **CG**), mediante el reemplazo de la 2,2-difenil-etil-amina con el (*S*)-2-amino-3-fenil-propan-1-ol.

Intermediario CJ **(2R,3R,4S,5R)-2-[6-((S)-1-bencil-2-hidroxi-**

etil-amino)-2-cloro-purin-9-il]-5-(2-bencil-2H-tetrazol-5-il)-tetrahidro-furan-3,4-diol

El compuesto del título se prepara de una forma análoga al (2*R*,3*S*,4*R*,5*R*)-2-(2-bencil-2*H*-tetrazol-5-il)-5-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-tetrahidro-furan-3,4-diol (Publicación Internacional Número WO 99/38877), mediante el reemplazo de la 2,2-difenil-etil-amina con el (*S*)-2-amino-3-fenil-propan-1-ol.

Intermediario CK **(2R,3S,4R,5R)-2-(2-bencil-2H-tetrazol-5-il)-5-{6-[2,2-bis-(4-hidroxi-fenil)-etil-amino]-2-cloro-purin-9-il}-tetrahidro-furan-3,4-diol**

El compuesto del título se prepara de una forma análoga al (2*R*,3*S*,4*R*,5*R*)-2-(2-bencil-2*H*-tetrazol-5-il)-5-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-tetrahidro-furan-3,4-diol (Publicación Internacional Número WO 99/38877), mediante el reemplazo de la 2,2-difenil-etil-amina con el 4,4'-(2-amino-etiliden)-bis-fenol (Intermediario **A**).

Preparación de Ejemplos

Ejemplo 1 **trifluoro-acetato de 1-((R)-1-{6-(2,2-difenil-etil-amino)-9-[(2R,3R,4S,5R)-5-(2-etil-2H-tetrazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-9H-purin-2-il}-pirrolidin-3-il)-3-(3-hidroxi-bencil)-urea**

Paso 1: (2*R*,3*R*,4*S*,5*R*)-2-[6-(2,2-difenil-etil-amino)-2-((*R*)-3-BOC-amino-pirrolidin-1-il)-purin-9-il]-5-(2-etil-2*H*-tetrazol-5-il)-tetrahidro-furan-3,4-diol

El (2*R*,3*R*,4*S*,5*R*)-2-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-

il]-5-(2-etil-2*H*-tetrazol-5-il)-tetrahidro-furan-3,4-diol (Intermediario **CF**) (1 gramo, 1.82 milimoles), (3*R*)-3-(BOC-amino)-pirrolidina (1.02 gramos, 5.47 milimoles), y yoduro de sodio (273 miligramos, 1.82 milimoles), se disuelven en acetonitrilo (10 mililitros) y NMP (0.5 mililitros). La mezcla de reacción se calienta utilizando radiación de microondas a 160°C durante 30 minutos en el reactor de microondas Personal Chemistry Emrys^{MR} Optimizer. La mezcla de reacción se concentra al vacío y se purifica mediante cromatografía en columna de fase inversa C-18, eluyendo con acetonitrilo:agua (ácido trifluoro-acético al 0.1 por ciento) (gradiente del 0 al 100 por ciento de acetonitrilo), para proporcionar el compuesto del título.

Paso 2: Trifluoro-acetato de (2R,3R,4S,5R)-2-[2-((R)-3-amino-pirrolidin-1-il)-6-(2,2-difenil-etil-amino)-purin-9-il]-5-(2-etil-2H-tetrazol-5-il)-tetrahidro-furan-3,4-diol

El (2*R*,3*R*,4*S*,5*R*)-2-[6-(2,2-difenil-etil-amino)-2-((*R*)-3-BOC-amino-pirrolidin-1-il)-purin-9-il]-5-(2-etil-2*H*-tetrazol-5-il)-tetrahidro-furan-3,4-diol (paso *AA1*) se disuelve en dicloro-metano y ácido trifluoro-acético, y se agita a temperatura ambiente durante la noche. La mezcla de reacción se concentra al vacío, para proporcionar el compuesto del título.

Paso 3: Trifluoro-acetato de 1-((R)-1-{6-(2,2-difenil-etil-amino)-9-[(2R,3R,4S,5R)-5-(2-etil-2H-tetrazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-9H-purin-2-il}-pirrolidin-3-il)-3-(3-hidroxi-bencil)-urea

El trifluoro-acetato de (2R,3R,4S,5R)-2-[2-((R)-3-amino-pirrolidin-1-il)-6-(2,2-difenil-etil-amino)-purin-9-il]-5-(2-etil-2H-

tetrazol-5-il)-tetrahidro-furan-3,4-diol y el fenil-éster del ácido (3-hidroxi-bencil)-carbámico (Intermediario **BA**) se disuelven en metanol y trietil-amina. La mezcla de reacción se calienta utilizando radiación de microondas a 100°C durante 30 minutos en el reactor de microondas Personal Chemistry Emrys^{MR} Optimizer. La mezcla de reacción se concentra al vacío y se purifica mediante cromatografía en columna de fase inversa C-18, eluyendo con acetonitrilo:agua (ácido trifluoro-acético al 0.1 por ciento) (gradiente del 0 al 100 por ciento de acetonitrilo), para proporcionar el compuesto del título.

Ejemplos 2 a 36

Éstos se preparan de una manera análoga al Ejemplo 1 mediante la combinación del compuesto de partida apropiado a partir de la Tabla 1a (Intermediarios **CA-CI**) con los fenil-ésteres apropiados (Intermediarios **BA-BD**).

Ejemplo 37 **1-{(*R*)-1-[9-{(2*R*,3*R*,4*S*,5*R*)-3,4-dihidroxi-5-[2-(2-hidroxi-etil)-2*H*-tetrazol-5-il]-tetrahidro-furan-2-il}-6-(2,2-difenil-etil-amino)-9*H*-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea**

Paso 1: 1-{(*R*)-1-[9-[(2*R*,3*R*,4*S*,5*R*)-5-(2-bencil-2*H*-tetrazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-6-(2,2-difenil-etil-amino)-9*H*-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea

Este compuesto se prepara a partir del (2*R*,3*S*,4*R*,5*R*)-2-(2-bencil-2*H*-tetrazol-5-il)-5-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-tetrahidro-furan-3,4-diol (Publicación Internacional Número WO 99/38877) y el fenil-éster del ácido piridin-3-il-carbámico (Intermediario **BB**) de una manera análoga al Ejemplo 1.

Paso 2: 1-{(*R*)-1-[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihidroxi-5-(2*H*-tetrazol-5-il)-tetrahidro-furan-2-il]-6-(2,2-difenil-etil-amino)-9*H*-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea

Una solución de la 1-{(*R*)-1-[9-[(2*R*,3*R*,4*S*,5*R*)-5-(2-bencil-2*H*-tetrazol-5-il)-3,4-dihidroxi-tetrahidro-furan-2-il]-6-(2,2-difenil-etil-amino)-9*H*-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea en EtOH bajo una atmósfera inerte de argón, se trata con paladio al 10 por ciento sobre carbón, seguido por formato de amonio. La mezcla de reacción se calienta a 50°C durante 4 horas, y entonces se filtra a través de Celite®. El filtrado se concentra al vacío, para proporcionar el compuesto del título.

Paso 3: 1-{(*R*)-1-[9-{(2*R*,3*R*,4*S*,5R)-3,4-dihidroxi-5-[2-(2-hidroxi-etil)-2*H*-tetrazol-5-il]-tetrahidro-furan-2-il}-6-(2,2-difenil-etil-amino)-9*H*-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea

Una solución de la 1-{(*R*)-1-[9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihidroxi-5-(2*H*-tetrazol-5-il)-tetrahidro-furan-2-il]-6-(2,2-difenil-etil-amino)-9*H*-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea en N,N-dimetil-formamida se trata con carbonato de potasio, seguido por 3-bromo-etanol, y se agita a temperatura ambiente durante 18 horas. La mezcla entonces se filtra, y el filtrado se concentra al vacío. La purificación del producto crudo mediante cromatografía en columna de fase inversa C-18, eluyendo con acetonitrilo:agua (ácido trifluoro-acético al 0.1 por ciento) (gradiente del 0 al 100 por ciento de acetonitrilo) proporciona el compuesto del título.

Ejemplos 38 a 40

Estos compuestos se preparan de una manera análoga al Ejemplo 37, mediante el reemplazo del fenil-éster del ácido piridin-3-il-carbámico (Intermediario **BB**) con los Intermediarios **BA**, **BD** y **BC**, respectivamente.

Ejemplos 41 a 44

Estos ejemplos se preparan de una manera análoga a los Ejemplos 37 a 40, mediante el reemplazo del (2*R*,3*S*,4*R*,5*R*)-2-(2-bencil-2*H*-tetrazol-5-il)-5-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-tetrahidro-furan-3,4-diol (Publicación Internacional Número WO 99/38877) con el (2R,3R,4S,5R)-2-[6-((S)-1-bencil-2-hidroxi-etil-amino)-2-cloro-purin-9-il]-5-(2-bencil-2H-tetrazol-5-il)-tetrahidro-furan-3,4-diol (Intermediario **CJ**).

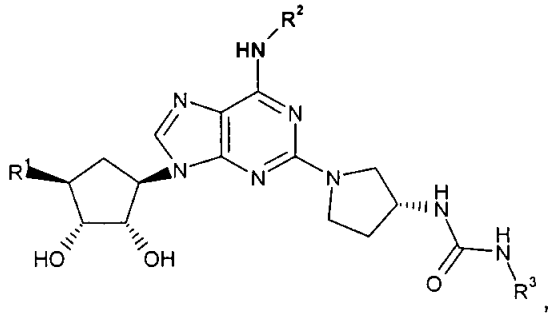
Ejemplos 45 a 48

Estos ejemplos se preparan de una manera análoga a los Ejemplos 37 a 40, mediante el reemplazo del (2*R*,3*S*,4*R*,5*R*)-2-(2-bencil-2*H*-tetrazol-5-il)-5-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-tetrahidro-furan-3,4-diol (Publicación Internacional Número WO 99/38877) con el (2R,3S,4R,5R)-2-(2-bencil-2H-tetrazol-5-il)-5-{6-[2,2-bis-(4-hidroxi-fenil)-etil-amino]-2-cloro-purin-9-il}-tetrahidro-furan-3,4-diol (Intermediario **CK**)

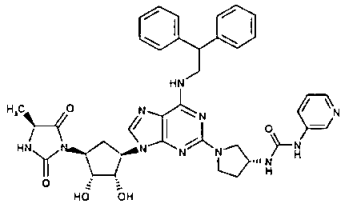
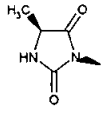
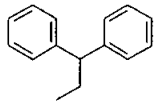
Ejemplos Carbocíclicos

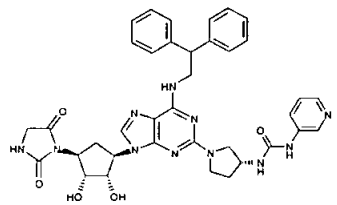
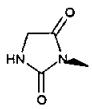
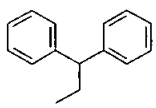
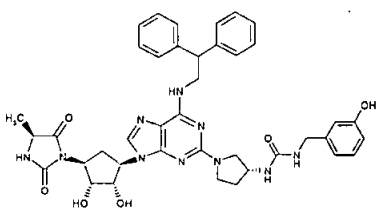
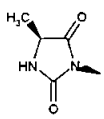
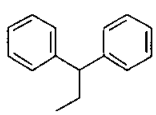
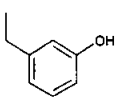
Ejemplos C1 a C84

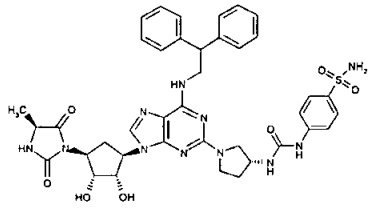
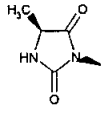
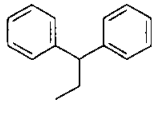
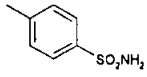
Los compuestos de la fórmula (I):

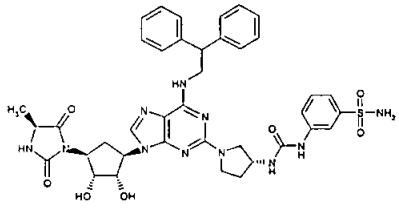
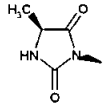
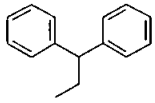
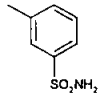
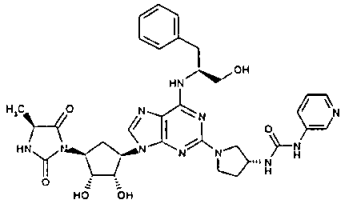
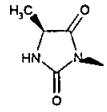
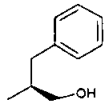


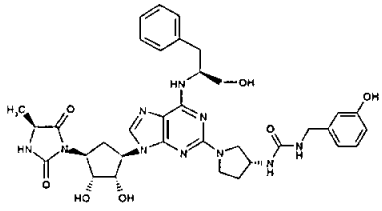
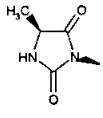
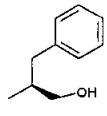
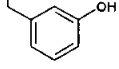
se muestran en la siguiente Tabla. Los métodos para la preparación de estos compuestos se describen posteriormente en la presente. La Tabla también muestra los datos de espectrometría de masas, MH+ {ESMS). Los Ejemplos son sales de trifluoro-acetato.

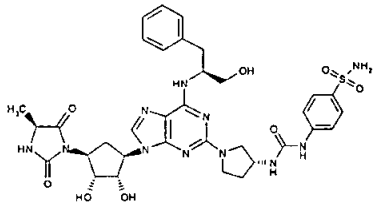
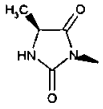
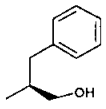
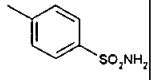
Ej.	Estructura	R^1	R^2	R^3	Nombre
C1					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-((S)-4-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-

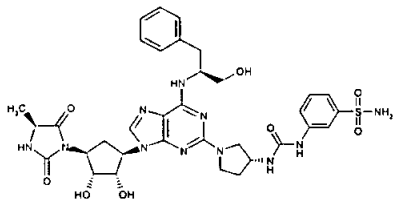
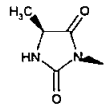
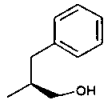
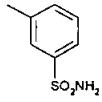
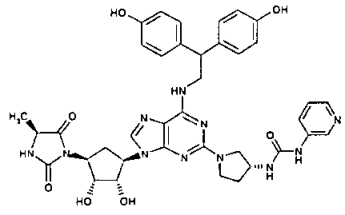
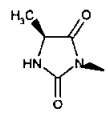
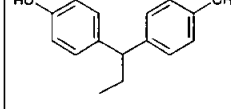
Ej.	Estructura	R^1	R^2	R^3	Nombre
					urea
C2					1-{(R)-1-[9-[(1R,2S,3R, 4S)-4-(2,5-dioxo-imidazolidin-1-il)-2,3-dihidroxi-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea
C3					1-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-((S)-4-metil-2,5-dioxo-imidazolidin-1-

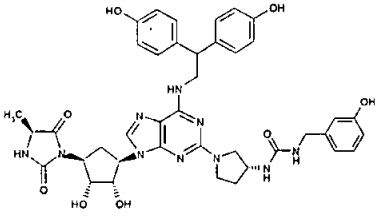
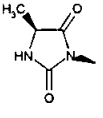
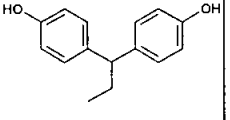
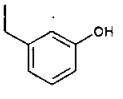
Ej.	Estructura	R^1	R^2	R^3	Nombre
					il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea
C4					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-((S)-4-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida

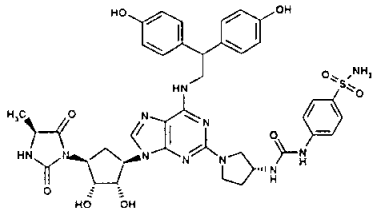
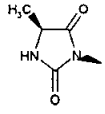
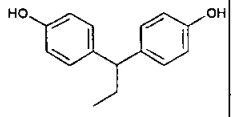
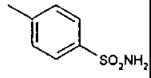
Ej.	Estructura	R^1	R^2	R^3	Nombre
C5					3-(3-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-((S)-4-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C6					1-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-((S)-4-metil-2,5-dioxo-imidazolidin-1-

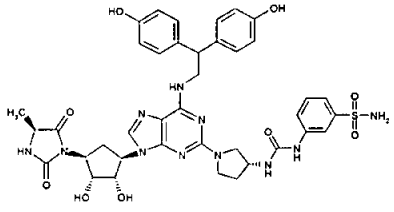
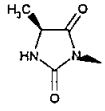
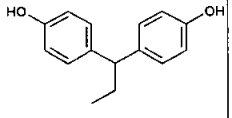
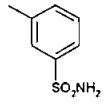
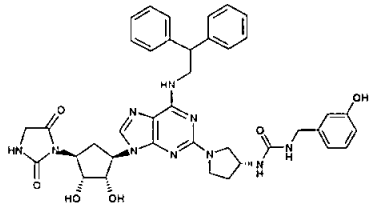
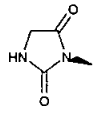
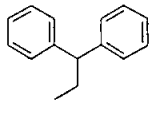
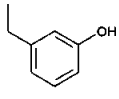
Ej.	Estructura	R^1	R^2	R^3	Nombre
					il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea
C7					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-((S)-4-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-

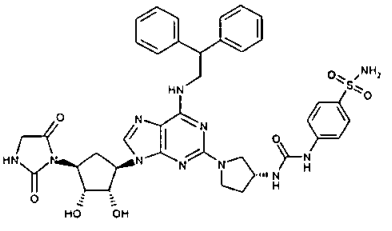
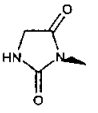
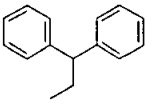
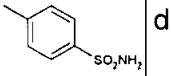
Ej.	Estructura	R^1	R^2	R^3	Nombre
					pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea
C8					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-((S)-4-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida

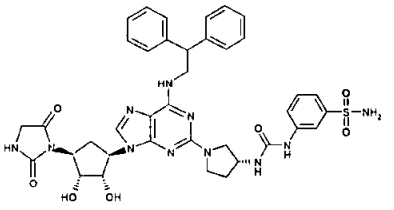
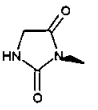
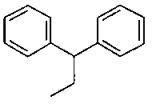
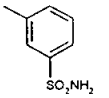
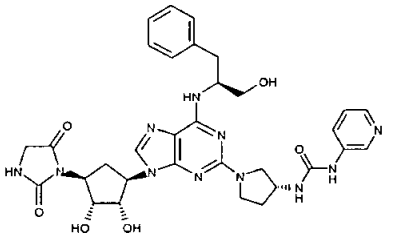
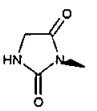
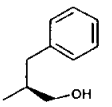
Ej.	Estructura	R^1	R^2	R^3	Nombre
C9					3-(3-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-((S)-4-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C10					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,

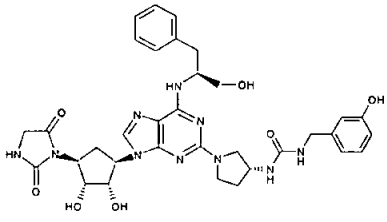
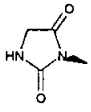
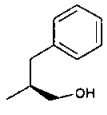
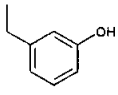
Ej.	Estructura	R^1	R^2	R^3	Nombre
					4S)-2,3-dihidroxi-4-((S)-4-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-3-piridin-3-il-urea
C11					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-((S)-4-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-9H-purin-2-il}-

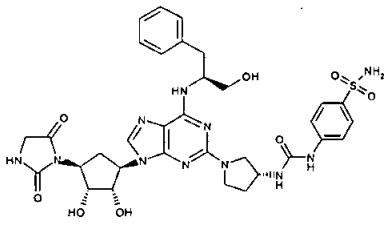
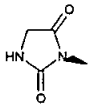
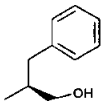
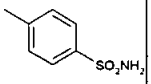
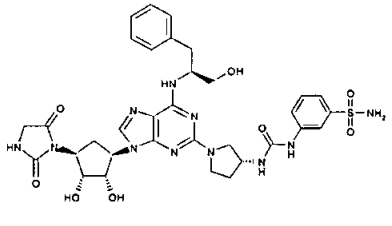
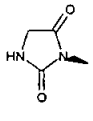
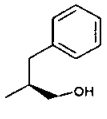
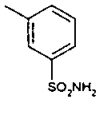
Ej.	Estructura	R^1	R^2	R^3	Nombre
					pirrolidin-3-il)-3-(3-hidroxi-bencil)-urea
C12					4-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-((S)-4-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida

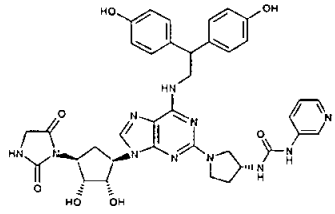
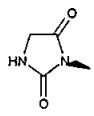
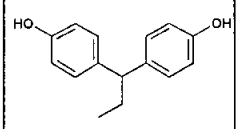
Ej.	Estructura	R^1	R^2	R^3	Nombre
C13					3-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-((S)-4-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida
C14					1-{(R)-1-[9-[(1R,2S,3R, 4S)-4-(2,5-dioxo-imidazolidin-1-il)-2,3-

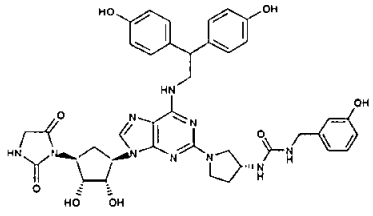
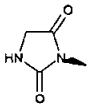
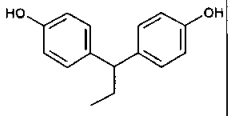
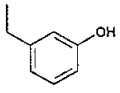
Ej.	Estructura	R^1	R^2	R^3	Nombre
					dihidroxi-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea
C15					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-4-(2,5-dioxo-imidazolidin-1-il)-2,3-dihidroxi-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-

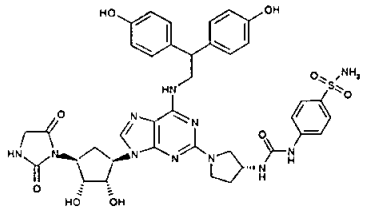
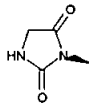
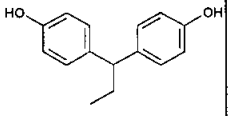
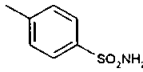
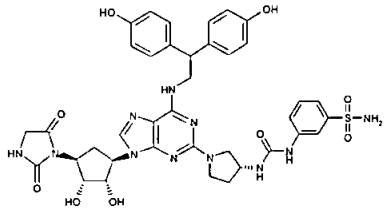
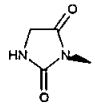
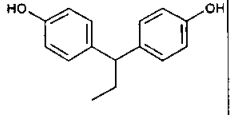
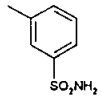
Ej.	Estructura	R^1	R^2	R^3	Nombre
					sulfonamida
C16					3-(3-{(R)-1-[9-[(1R,2S,3R, 4S)-4-(2,5-dioxo-imidazolidin-1-il)-2,3-dihidroxi-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C17					1-{(R)-1-[9-[(1R,2S,3R, 4S)-4-(2,5-dioxo-imidazolidin-1-il)-2,3-

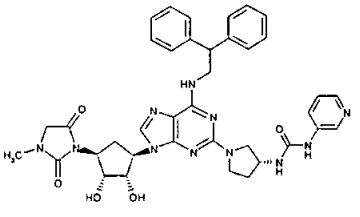
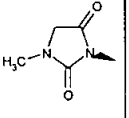
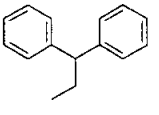
Ej.	Estructura	R^1	R^2	R^3	Nombre
					dihidroxi-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea
C18					1-{(R)-1-[9-[(1R,2S,3R,4S)-4-(2,5-dioxo-imidazolidin-1-il)-2,3-dihidroxi-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-

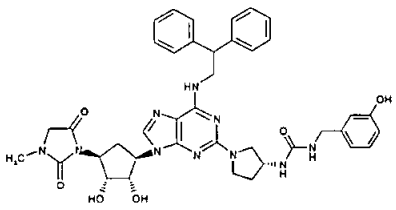
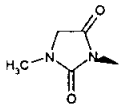
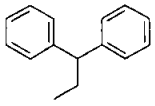
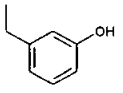
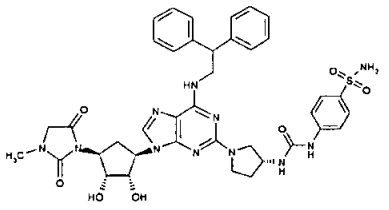
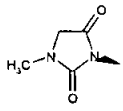
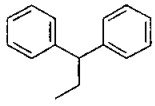
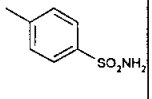
Ej.	Estructura	R^1	R^2	R^3	Nombre
					3-(3-hidroxi-bencil)-urea
C19					4-(3-{(R)-1-[9-[(1R,2S,3R, 4S)-4-(2,5-dioxo-imidazolidin-1-il)-2,3-dihidroxi-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C20					3-(3-{(R)-1-[9-[(1R,2S,3R, 4S)-4-(2,5-dioxo-

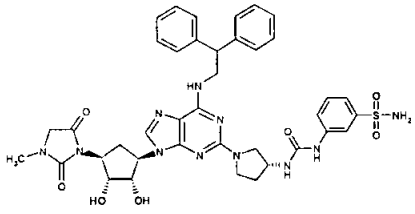
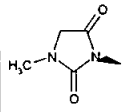
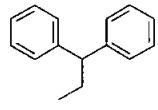
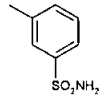
Ej.	Estructura	R^1	R^2	R^3	Nombre
					imidazolidin-1-il)-2,3-dihidroxi-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C21					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-4-(2,5-dioxo-imidazolidin-1-il)-2,3-dihidroxi-

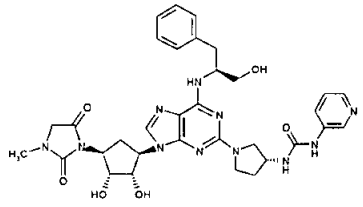
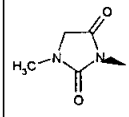
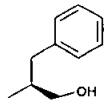
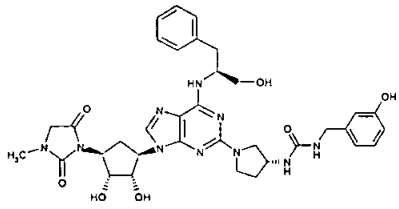
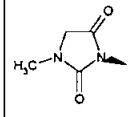
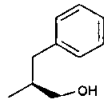
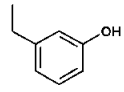
Ej.	Estructura	R^1	R^2	R^3	Nombre
					ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-3-piridin-3-il-urea
C22					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-4-(2,5-dioxo-imidazolidin-1-il)-2,3-dihidroxi-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-3-(3-hidroxi-bencil)-urea

Ej.	Estructura	R^1	R^2	R^3	Nombre
C23					4-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-4-(2,5-dioxo-imidazolidin-1-il)-2,3-dihidroxi-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida
C24					3-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-4-(2,5-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					dioxo-imidazolidin-1-il)-2,3-dihidroxi-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida
C25					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(3-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					3-piridin-3-il-urea
C26					1-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(3-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea
C27					4-(3-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(3-metil-2,5-dioxo-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					imidazolidin-1-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C28					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(3-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					bencen-sulfonamida
C29					1-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(3-metil-2,5-dioxo-imidazo-lidin-1-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea
C30					1-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(3-metil-2,5-

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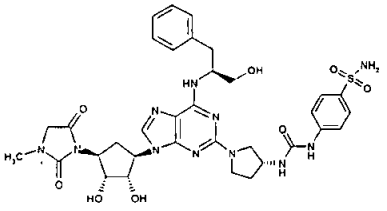
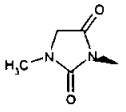
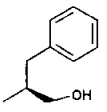
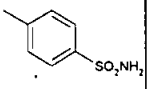
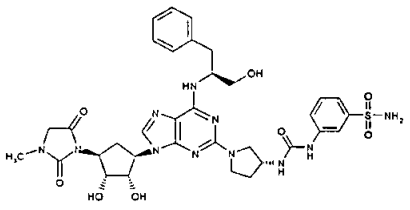
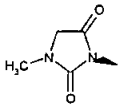
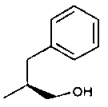
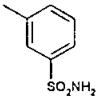
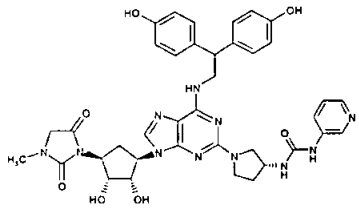
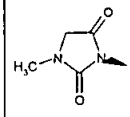
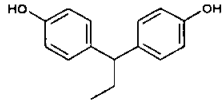
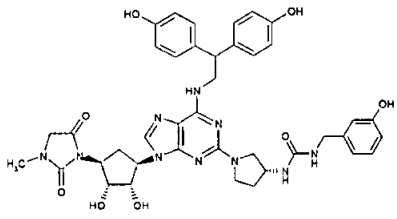
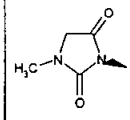
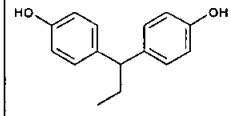
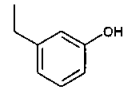
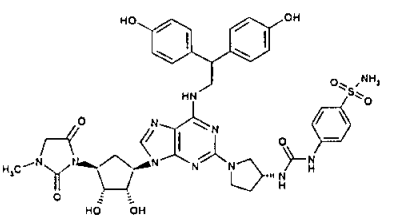
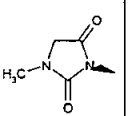
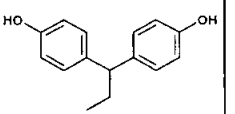
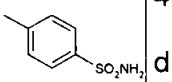
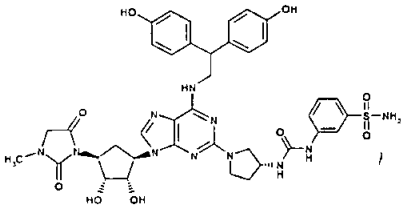
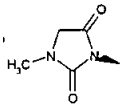
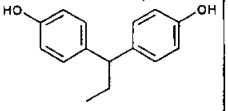
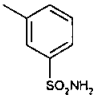
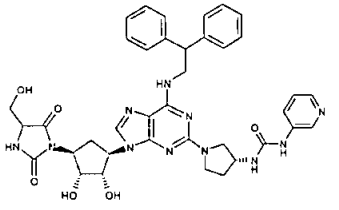
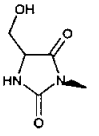
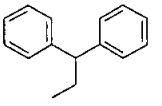
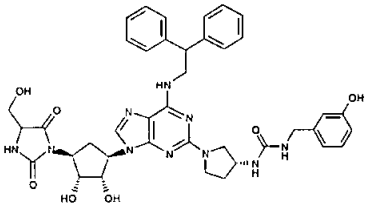
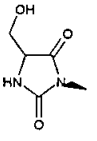
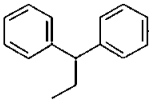
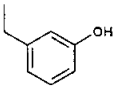
Ej.	Estructura	R^1	R^2	R^3	Nombre
					dioxo-imidazolidin-1-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea
C31					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(3-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-

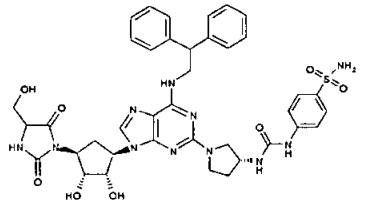
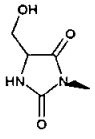
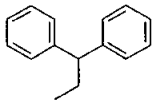
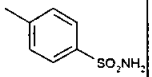
Ej.	Estructura	R^1	R^2	R^3	Nombre
					amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C32					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(3-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-

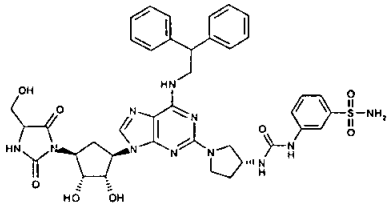
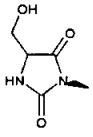
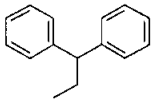
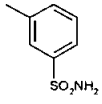
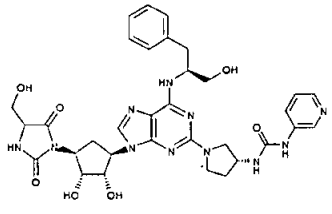
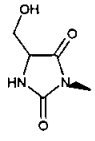
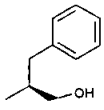
Ej.	Estructura	R^1	R^2	R^3	Nombre
					sulfonamida
C33					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(3-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-3-piridin-3-il-urea
C34					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-2,3-

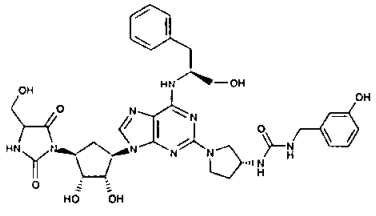
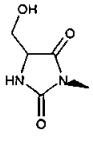
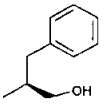
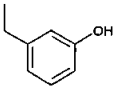
Ej.	Estructura	R^1	R^2	R^3	Nombre
					dihidroxi-4-(3-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-3-(3-hidroxi-bencil)-urea
C35					4-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(3-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-

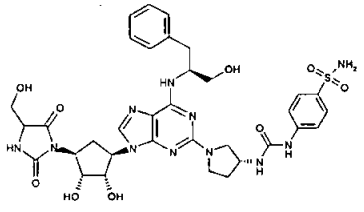
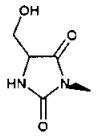
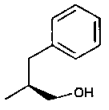
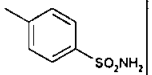
Ej.	Estructura	R^1	R^2	R^3	Nombre
					ureido]-bencen-sulfonamida
C36					3-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(3-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida

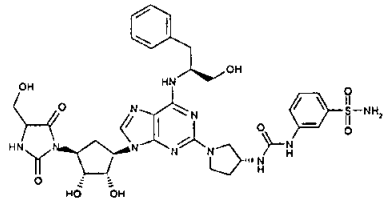
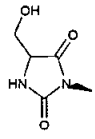
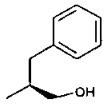
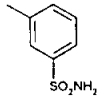
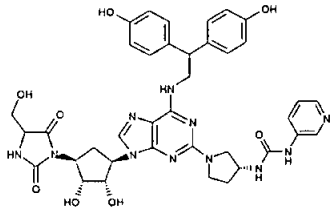
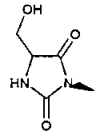
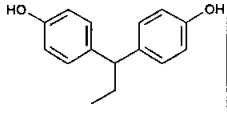
Ej.	Estructura	R^1	R^2	R^3	Nombre
C37					1-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(4-hidroxi-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea
C38					1-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(4-hidroxi-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-

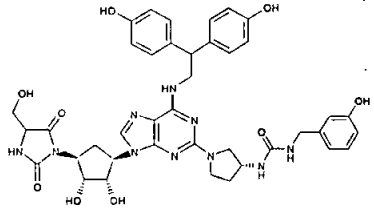
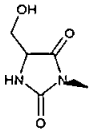
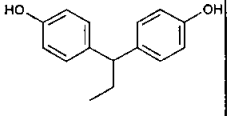
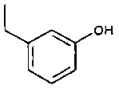
Ej.	Estructura	R^1	R^2	R^3	Nombre
					6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea
C39					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(4-hidroxi-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida

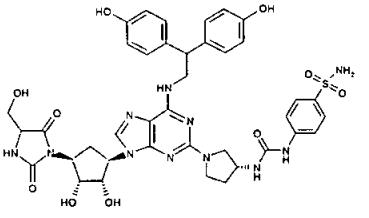
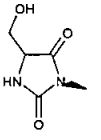
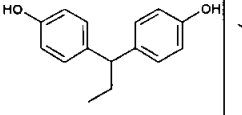
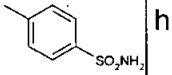
Ej.	Estructura	R^1	R^2	R^3	Nombre
C40					3-(3-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(4-hidroxi-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C41					1-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(4-hidroxi-metil-2,5-dioxo-imidazolidin-1-

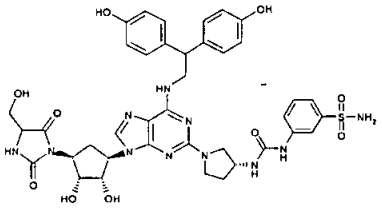
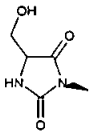
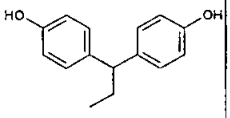
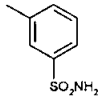
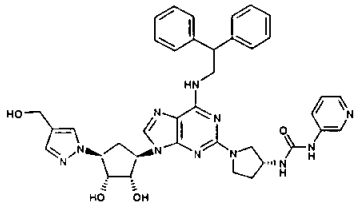
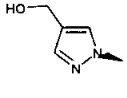
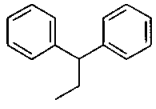
Ej.	Estructura	R^1	R^2	R^3	Nombre
					il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea
C42					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(4-hidroxi-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-

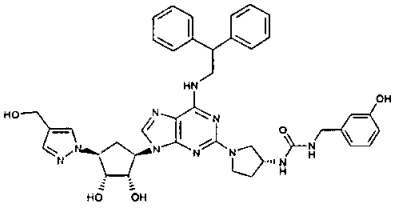
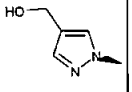
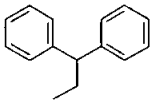
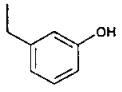
Ej.	Estructura	R^1	R^2	R^3	Nombre
					pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea
C43					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(4-hidroxi-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida

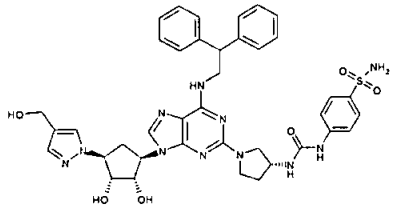
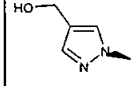
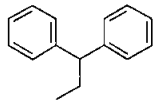
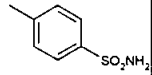
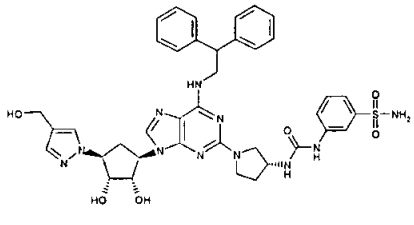
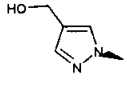
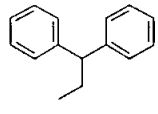
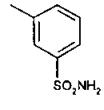
Ej.	Estructura	R^1	R^2	R^3	Nombre
C44					3-(3-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(4-hidroxi-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C45					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,

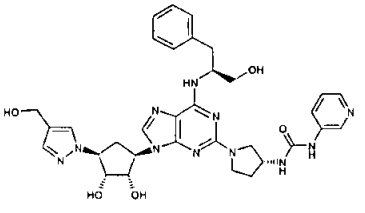
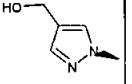
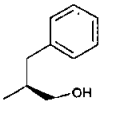
Ej.	Estructura	R^1	R^2	R^3	Nombre
					4S)-2,3-dihidroxi-4-(4-hidroxi-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-3-piridin-3-il-urea
C46					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(4-hidroxi-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-9H-purin-2-il}-

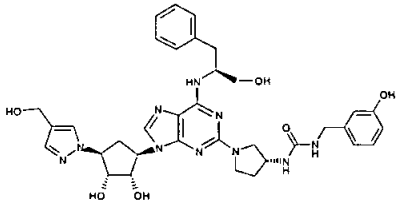
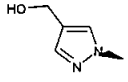
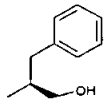
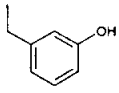
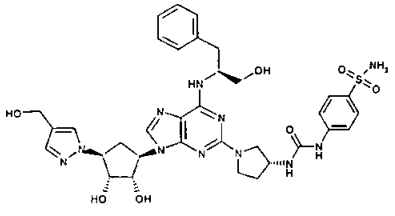
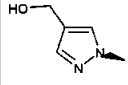
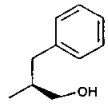
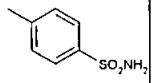
Ej.	Estructura	R^1	R^2	R^3	Nombre
					pirrolidin-3-il)-3-(3-hidroxi-bencil)-urea
C47					4-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(4-hidroxi-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida

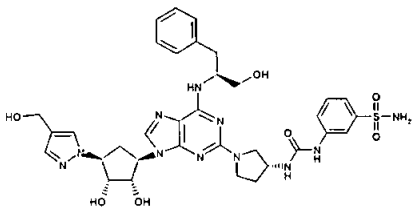
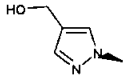
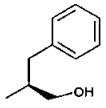
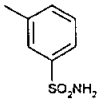
Ej.	Estructura	R^1	R^2	R^3	Nombre
C48					3-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(4-hidroxi-metil-2,5-dioxo-imidazolidin-1-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida
C49					1-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(4-hidroxi-metil-pirazol-1-il)-

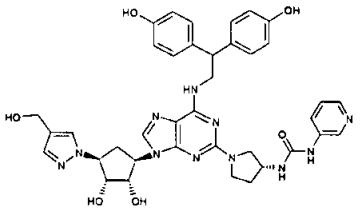
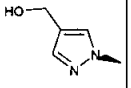
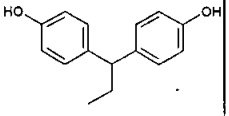
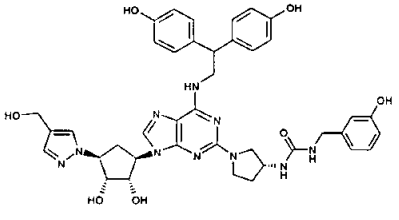
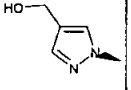
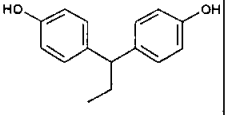
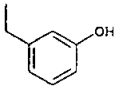
Ej.	Estructura	R^1	R^2	R^3	Nombre
					ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea
C50					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(4-hidroxi-metil-pirazol-1-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea

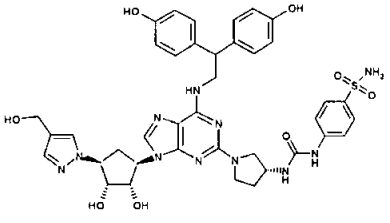
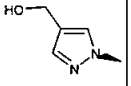
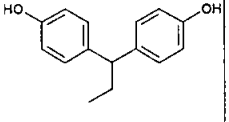
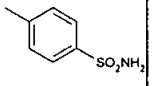
Ej.	Estructura	R^1	R^2	R^3	Nombre
C51					4-(3-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-Dihidroxi-4-(4-hidroxi-metil-pirazol-1-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C52					3-(3-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-Dihidroxi-4-(4-hidroxi-metil-pirazol-1-il)-ciclopentil]-6-(2,2-difenil-

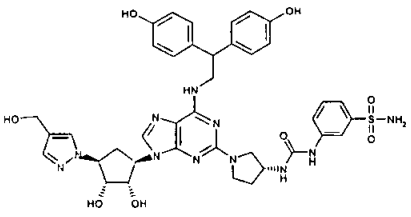
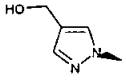
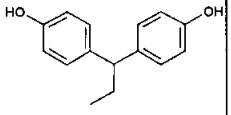
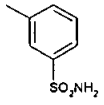
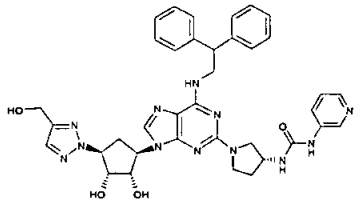
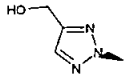
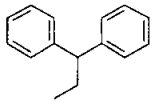
Ej.	Estructura	R^1	R^2	R^3	Nombre
					etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C53					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(4-hidroxi-metil-pirazol-1-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea

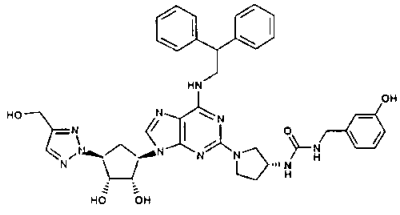
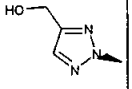
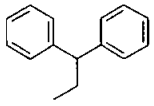
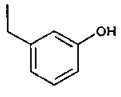
Ej.	Estructura	R^1	R^2	R^3	Nombre
C54					1-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(4-hidroxi-metil-pirazol-1-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea
C55					4-(3-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-Dihidroxi-4-(4-hidroxi-metil-pirazol-1-il)-ciclopentil]-6-((S)-1-hidroxi-

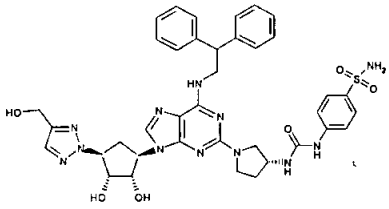
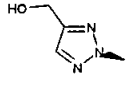
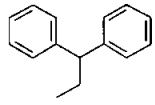
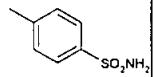
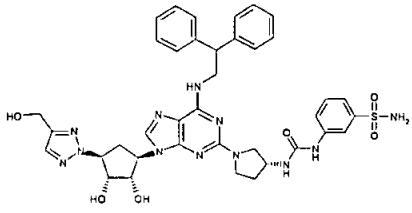
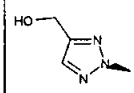
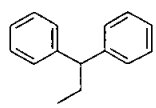
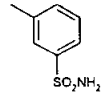
Ej.	Estructura	R^1	R^2	R^3	Nombre
					metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C56					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihidroxi-4-(4-hidroxi-metil-pirazol-1-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida

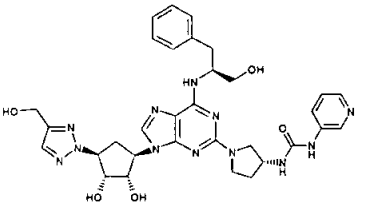
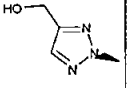
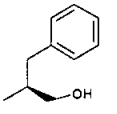
Ej.	Estructura	R^1	R^2	R^3	Nombre
C57					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(4-hidroxi-metil-pirazol-1-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-3-piridin-3-il-urea
C58					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(4-hidroxi-metil-

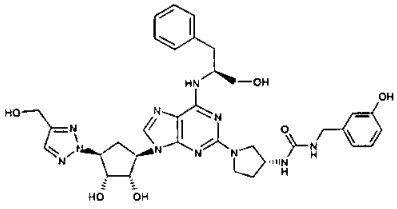
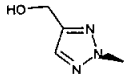
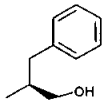
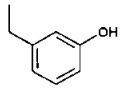
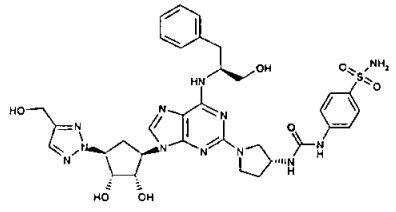
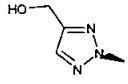
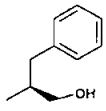
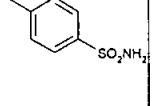
Ej.	Estructura	R^1	R^2	R^3	Nombre
					pirazol-1-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-3-(3-hidroxi-bencil)-urea
C59					4-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(4-hidroxi-metil-pirazol-1-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida

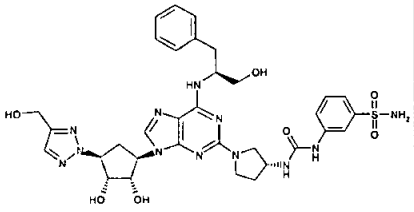
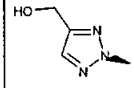
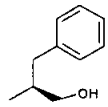
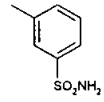
Ej.	Estructura	R^1	R^2	R^3	Nombre
C60					3-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(4-hidroxi-metil-pirazol-1-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida
C61					1-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(4-hidroxi-metil-[1,2,3]-triazol-2-il)-

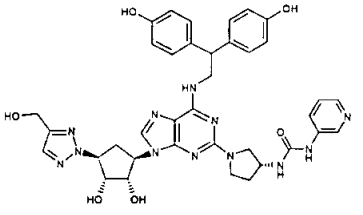
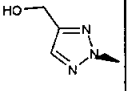
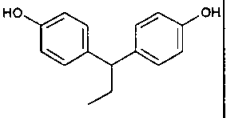
Ej.	Estructura	R^1	R^2	R^3	Nombre
					ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea
C62					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(4-hidroxi-metil-[1,2,3]-triazol-2-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea

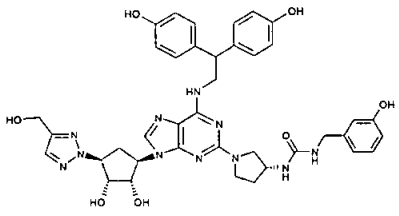
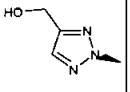
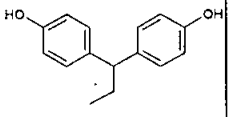
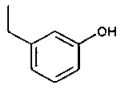
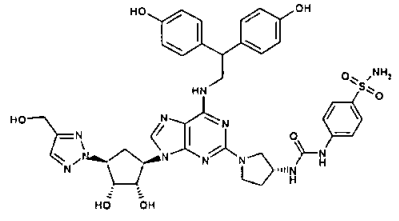
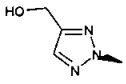
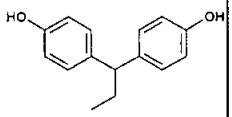
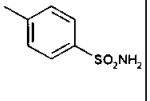
Ej.	Estructura	R^1	R^2	R^3	Nombre
C63					4-(3-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-Dihidroxi-4-(4-hidroxi-metil-[1,2,3]-triazol-2-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C64					3-(3-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-Dihidroxi-4-(4-hidroxi-metil-[1,2,3]-triazol-2-il)-

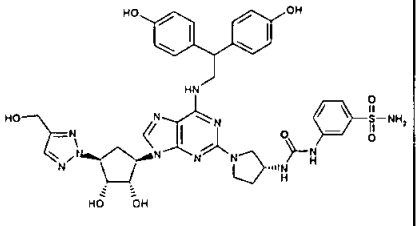
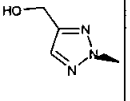
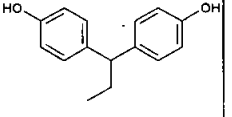
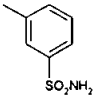
Ej.	Estructura	R^1	R^2	R^3	Nombre
					ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C65					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(4-hidroxi-metil-[1,2,3]-triazol-2-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-

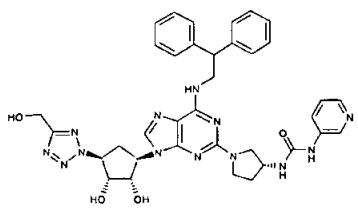
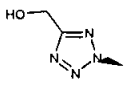
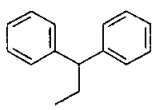
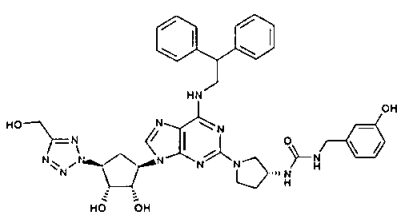
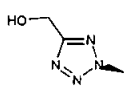
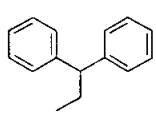
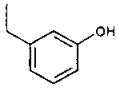
Ej.	Estructura	R^1	R^2	R^3	Nombre
					urea
C66					1-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(4-hidroxi-metil-[1,2,3]-triazol-2-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea
C67					4-(3-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-Dihidroxi-4-(4-hidroxi-metil-[1,2,3]-triazol-

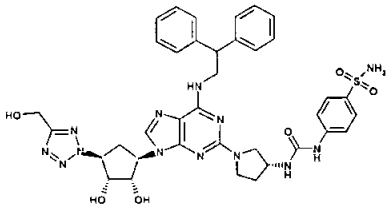
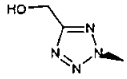
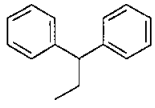
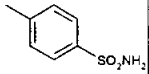
Ej.	Estructura	R^1	R^2	R^3	Nombre
					2-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C68					3-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihidroxi-4-(4-hidroxi-metil-[1,2,3]-triazol-2-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-

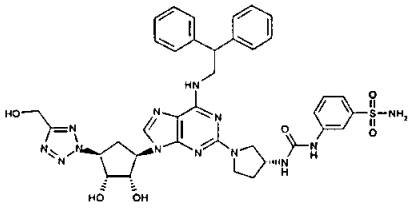
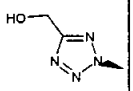
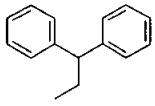
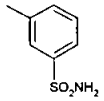
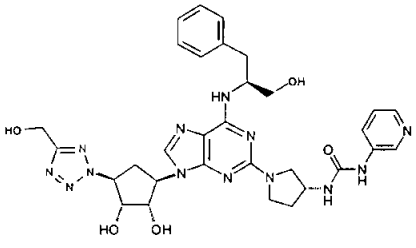
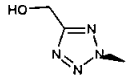
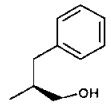
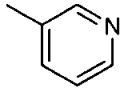
Ej.	Estructura	R^1	R^2	R^3	Nombre
					pirrolidin-3-il}-ureido)-bencen-sulfonamida
C69					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(4-hidroxi-metil-[1,2,3]-triazol-2-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-3-piridin-3-il-urea

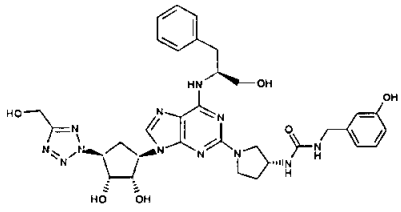
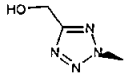
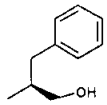
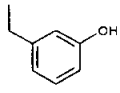
Ej.	Estructura	R^1	R^2	R^3	Nombre
C70					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(4-hidroxi-metil-[1,2,3]-triazol-2-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-3-(3-hidroxi-bencil)-urea
C71					4-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(4-

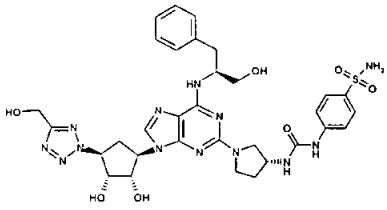
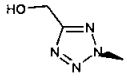
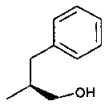
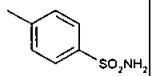
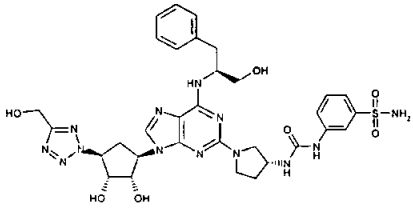
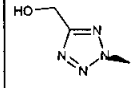
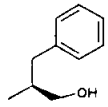
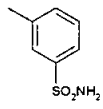
Ej.	Estructura	R^1	R^2	R^3	Nombre
					hidroxi-metil-[1,2,3]-triazol-2-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida
C72					3-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(4-hidroxi-metil-[1,2,3]-triazol-2-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-

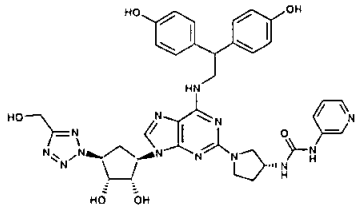
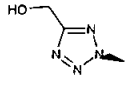
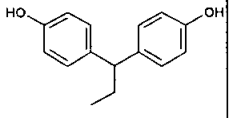
Ej.	Estructura	R^1	R^2	R^3	Nombre
					ureido]-bencen-sulfonamida
C73					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(5-hidroxi-metil-tetrazol-2-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea
C74					1-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(5-hidroxi-metil-tetrazol-2-il)-

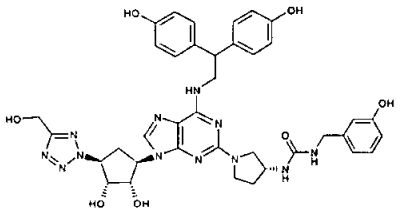
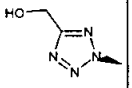
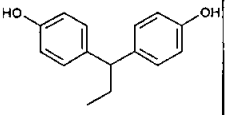
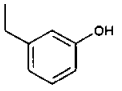
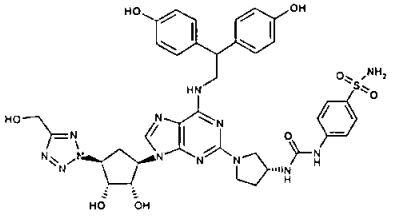
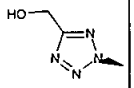
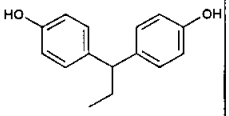
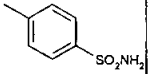
Ej.	Estructura	R^1	R^2	R^3	Nombre
					ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea
C75					4-(3-{(R)-1-[9-[(1R,2S,3R,4S)-2,3-Dihidroxi-4-(5-hidroxi-metil-tetrazol-2-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida

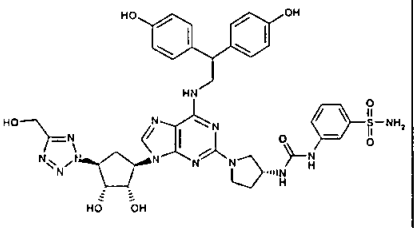
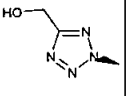
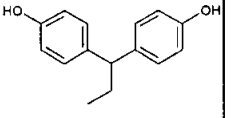
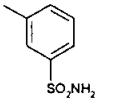
Ej.	Estructura	R^1	R^2	R^3	Nombre
C76					3-(3-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-Dihidroxi-4-(5-hidroxi-metil-tetrazol-2-il)-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C77					1-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-Dihidroxi-4-(5-hidroxi-metil-tetrazol-2-il)-ciclopentil]-6-((S)-1-

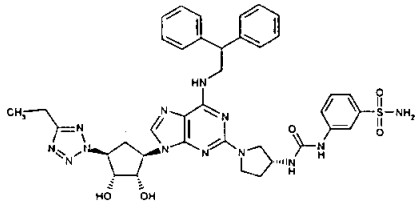
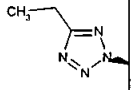
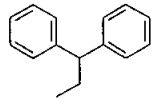
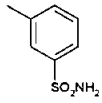
Ej.	Estructura	R^1	R^2	R^3	Nombre
					hidroximetil-2-fenil-etil-amino)-9H-purin -2-il]-pirrolidin-3-il}-3-piridin-3-il-urea
C78					1-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(5-hidroxi-metil-tetrazol-2-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-(3-hidroxi-bencil)-urea

Ej.	Estructura	R^1	R^2	R^3	Nombre
C79					4-(3-{(R)-1-[9-[(1R;2S,3R, 4S)-2,3-Dihidroxi-4-(5-hidroxi-metil-tetrazol-2-il)-ciclopentil]-6-((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C80					3-(3-{(R)-1-[9-[(1R,2S,3R, 4S)-2,3-Dihidroxi-4-(5-hidroxi-metil-tetrazol-2-il)-ciclopentil]-6-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					((S)-1-hidroxi-metil-2-fenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-ureido)-bencen-sulfonamida
C81					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(5-hidroxi-metil-tetrazol-2-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-3-piridin-3-il-urea

Ej.	Estructura	R^1	R^2	R^3	Nombre
C82					1-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(5-hidroxi-metil-tetrazol-2-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-3-(3-hidroxi-bencil)-urea
C83					4-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R; 4S)-2,3-dihidroxi-4-(5-hidroxi-metil-

Ej.	Estructura	R^1	R^2	R^3	Nombre
					tetrazol-2-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida
C84					3-[3-((R)-1-{6-[2,2-Bis-(4-hidroxi-fenil)-etil-amino]-9-[(1R,2S,3R,4S)-2,3-dihidroxi-4-(5-hidroxi-metil-tetrazol-2-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida

Ej.	Estructura	R^1	R^2	R^3	Nombre
C85					3-[3-((R)-1-{6-[2,2-Bis-fenil-etil-amino]-9-[(1R,2S,3R, 4S)-2,3-dihidroxi-4-(5-etil-tetrazol-2-il)-ciclopentil]-9H-purin-2-il}-pirrolidin-3-il)-ureido]-bencen-sulfonamida

Preparación de Compuestos Intermediarios

Intermediario 1 **Etil-éster de (1S,4R)-4-(2,6-dicloro-purin-9-il)-ciclopent-2-enil-éster del ácido carbónico**

Paso a: (1*S*,4*R*)-4-(2,6-dicloro-purin-9-il)-ciclopent-2-enol

La 2,6-dicloro-purina (10 gramos, 52.90 milimoles), (1*S*,4*R*)-cis-4-acetoxi-2-ciclopenten-1-ol (10 gramos, 70.40 milimoles), tris-(dibenciliden-acetona)-dipaladio(0) (3.20 gramos, 3.50 milimoles), y trifenil-fosfina soportada por polímero (3 milimoles/gramo, 11.60 gramos, 35.00 milimoles), se colocan en un matraz secado al horno

bajo una atmósfera de argón. Se agrega tetrahidrofurano desoxigenado seco (80 mililitros), y la mezcla de reacción se agita suavemente durante 5 minutos. Se agrega trietil-amina (20 mililitros), y la mezcla de reacción se agita a 50°C. Se muestra que la reacción está completa mediante LCMS después de 1 hora. La mezcla de reacción se deja enfriar, se filtra, y el solvente se remueve al vacío. Se obtiene el compuesto del título después de la purificación mediante cromatografía en columna por evaporación instantánea (sílice, dicloro-metano/metanol, 25:1).

^{1}H RMN ($CDCl_3$, 400 MHz); 8.30 (s, 1H), 6.40 (m, 1H), 5.90 (m, 1H), 5.50 (m, 1H), 4.95 (m, 1H), 3.05 (m, 1H), 2.10 (m, 1H). (MH^+) [MH+ 271]

Paso b: Etil-éster de (1S,4R)-4-(2,6-dicloro-purin-9-il)-ciclopent-2-enil-éster del ácido carbónico

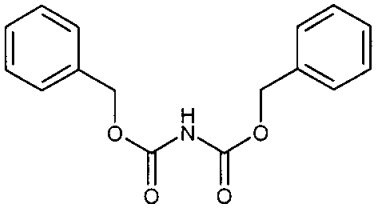
El (1*S*,4*R*)-4-(2,6-dicloro-purin-9-il)-ciclopent-2-enol [paso1] (9.5 gramos, 35.05 milimoles) se coloca en un matraz secado al horno bajo una atmósfera de argón. Se agrega tetrahidrofurano seco (200 mililitros), seguido por piridina seca (5.54 gramos, 70.1 milimoles). Se agrega lentamente cloro-formato de etilo (15.21 gramos, 140.2 milimoles), de tal manera que la temperatura no se eleve arriba de 40°C, y la mezcla de reacción se agita a temperatura ambiente. Se muestra que la reacción está completa mediante LCMS después de 2 horas. El solvente se remueve al vacío, y el residuo se divide entre dicloro-metano (200 mililitros) y agua (200 mililitros). La capa orgánica se lava con agua (150 mililitros) y salmuera (150

mililitros), se seca sobre $MgSO_4$, se filtra, y el solvente se remueve al vacío. Se obtiene el compuesto del título después de la cristalización a partir de metanol.

^{1}H RMN ($CDCl_3$, 400 MHz); 8.20 (s, 1H), 6.45 (m, 1H), 6.25 (m, 1H), 5.75 (m, 1H), 5.70 (m, 1H), 4.25 (q, 2H), 3.20 (m, 1H), 2.05 (m, 1H), 1.35 (t, 3H). [MH+ 343]

Intermediario 2 **Bencil-éster del ácido {(1S,2R,3S,4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-(2,2-difenil-etil-amino)-purin-9-il]-2,3-dihidroxi-ciclopentil}-carbámico**

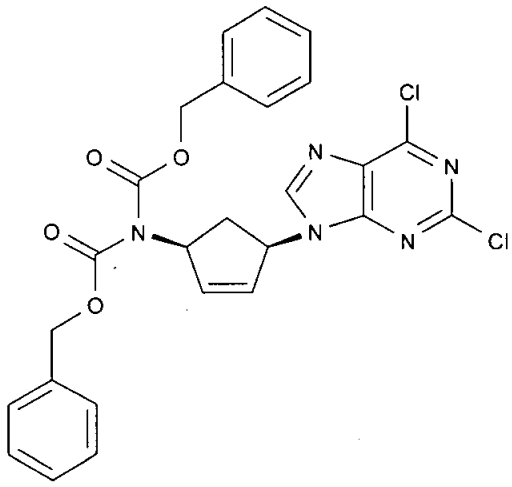
Paso a: Preparación del Intermediario **2a**, bis-(fenil-metil)-éster del ácido imido-dicarbónico, *(*nomenclatura de *Chemical Abstracts):*



Una solución enfriada (0°C) de carbamato de bencilo (4.0 gramos, 27 milimoles) en tetrahidrofurano (100 mililitros), bajo una atmósfera inerte de argón, se trata con yoduro de potasio (3.2 gramos de una dispersión al 35 por ciento en peso/peso en aceite, 28 milimoles) en porciones, durante 10 minutos. La mezcla de reacción se deja calentar a temperatura ambiente durante 30 minutos, después de cuyo tiempo, se agrega cloroformato de bencilo (5.0 gramos, 29 milimoles). Después de agitar a temperatura ambiente durante 2 horas, la reacción se apaga con agua (20 mililitros). El tetrahidrofurano se remueve al vacío, y la mezcla

resultante se divide entre EtOAc y HCl 2 M. La porción orgánica se separa y se lava con salmuera, se seca ($MgSO_4$) y se concentra al vacío. El aceite resultante se purifica mediante cromatografía sobre sílice, eluyendo con 1:3 de EtOAc/*iso*-hexano, para proporcionar un producto, el cual se recristaliza a partir de dicloro-metano/*iso*-hexano, para proporcionar el producto del título.

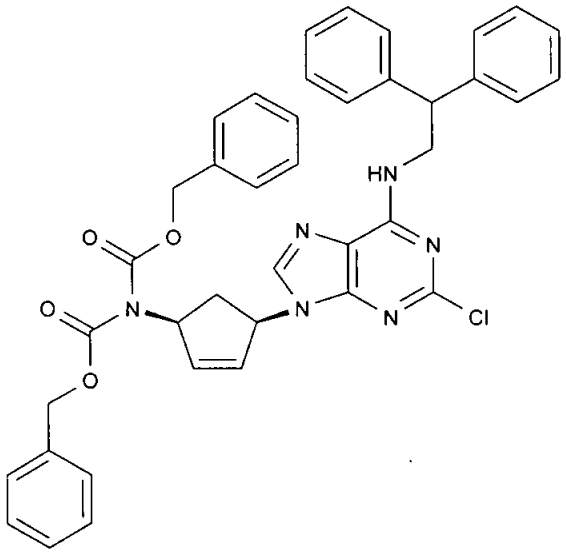
Paso b: Preparación del Intermediario **2b**:



Una solución que comprende el etil-éster de (1S,4R)-4-(2,6-dicloro-purin-9-il)-ciclopent-2-enil-éster del ácido carbónico (Intermediario **1**) (2.0 gramos, 5.83 milimoles), el intermediario **2a** (2.2 gramos, 7.58 milimoles), y trifenil-fosfina (229 miligramos, 0.9 milimoles) en tetrahidrofurano (20 mililitros), se agita a temperatura ambiente durante 30 minutos. Se agrega tris-(dibenciliden-acetona)-dipaladio (0) (238 miligramos, 0.3 milimoles), y la mezcla resultante se agita a temperatura ambiente durante 1.5 horas. El solvente se remueve al vacío, y el producto crudo se purifica mediante cromatografía sobre sílice, eluyendo con metanol/dicloro-metano

(gradiente del 0 al 1 por ciento de MeOH), para proporcionar el compuesto del título.

Paso c: Preparación del Intermediario **2c**:



Una solución que comprende el Intermediario **2b** (0.68 gramos, 1.26 milimoles), 1-amino-2,2-difenil-etano (0.37 gramos, 1.90 milimoles), y trietil-amina (190 miligramos, 1.90 milimoles) en tetrahidrofurano (10 mililitros), se agita a 50°C durante 2 horas. El solvente se remueve al vacío, y el aceite/sólido resultante se divide entre EtOAc y HCl 0.2 M. La porción orgánica se separa y se lava con una solución saturada de bicarbonato de sodio, agua, salmuera, se seca ($MgSO_4$), y se concentra al vacío, para proporcionar el compuesto del título. [MH+ 699.37].

Paso d: Preparación del Intermediario **2d**

Una solución que comprende el Intermediario **2c** (2.0 gramos, 2.86 milimoles), y NMO (0.67 gramos, 5.7 milimoles) en tetrahidrofurano (20 mililitros), se trata con tetróxido de osmio (2

mililitros de una solución al 4 por ciento en agua), y se agita a temperatura ambiente durante la noche. El solvente se remueve al vacío, y el residuo crudo se divide entre dicloro-metano y agua. La porción orgánica se separa, se lava con agua, salmuera, se seca ($MgSO_4$), y se concentra al vacío. El sólido resultante se tritura con MeCN para proporcionar el producto del título. [MH+ 733.40].

Paso e: terbutil-éster del ácido {(R)-1-[9-((1R,2S,3R,4S)-4-benciloxi-carbonil-amino-2,3-dihidroxi-ciclopentil)-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-carbámico

Una suspensión del Intermediario **2d** (1.03 gramos, 1.4 milimoles), y (3*R*)-(+)-3-(Boc-amino)-pirrolidina (1.03 gramos, 5.5 milimoles) en acetonitrilo (2 mililitros), se trata con yoduro de sodio (aproximadamente 2 miligramos), y entonces se calienta utilizando radiación de microondas a 160°C. Después de 1 hora, el solvente se remueve al vacío, y el residuo crudo se divide entre dicloro-metano y HCl 0.2 M. La capa orgánica se separa, y la porción acuosa se extrae con dicloro-metano. Los extractos orgánicos combinados se lavan con una solución saturada de bicarbonato de sodio, agua, salmuera, se seca ($MgSO_4$), y se concentra al vacío, para proporcionar el compuesto del título como un aceite color café. [MH+ 745]

Paso f: Bencil-éster del ácido {(1S,2R,3S,4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-(2,2-difenil-etil-amino)-purin-9-il]-2,3-dihidroxi-ciclopentil}-carbámico

Una solución del terbutil-éster del ácido {(R)-1-[9-

((1R,2S,3R,4S)-4-benciloxi-carbonil-amino-2,3-dihidroxi-ciclopentil)-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-carbámico (1.24 gramos, 1.7 milimoles) en metanol (3 mililitros), se trata con HCl 4M en dioxano (5 mililitros), y se agita a temperatura ambiente durante 2 horas. El solvente se remueve al vacío, y la purificación se lleva a cabo mediante cromatografía en columna de fase inversa (Isolute^{RM} C18, del 0 al 100 por ciento de acetonitrilo en agua – HCl al 0.1 por ciento). Las fracciones se recolectan, y el MeCN se remueve al vacío. La porción acuosa restante se basifica con una solución saturada de bicarbonato de sodio, y se extrae con dicloro-metano. Los orgánicos combinados extraídos se secan ($MgSO_4$) y se concentran al vacío, para proporcionar el producto del título. [MH+ =649]

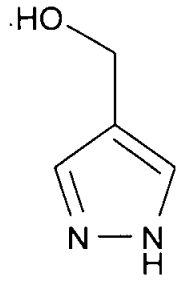
Intermediario 3 **(1*R*,2*S*,3*R*,5*S*)-3-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-5-(4-hidroxi-metil-pirazol-1-il)-ciclopentano-1,2-diol**

Paso a: {1-[(1*S*,4*R*)-4-(2,6-dicloro-purin-9-il)-ciclopent-2-enil]-1*H*-pirazol-4-il}-metanol

Una mezcla que comprende el etil-éster de (1S,4R)-4-(2,6-dicloro-purin-9-il)-ciclopent-2-enil-éster del ácido carbónico (Intermediario **1**) (1.00 gramos, 2.92 milimoles), (1*H*-pirazol-4-il)-metanol (la preparación se muestra más adelante) (0.34 gramos, 3.50 milimoles), y trifenil-fosfina (0.115 gramos, 0.44 milimoles) en tetrahidrofurano desoxigenado (10 mililitros), bajo una atmósfera inerte de argón, se trata con tris-(dibenciliden-acetona)-dipaladio (0)

(0.13 gramos, 0.15 milimoles), y se agita a 50°C durante 1 hora. El solvente se remueve al vacío, y el producto *crudo* se purifica mediante cromatografía sobre sílice, eluyendo con metanol/dicloro-metano (1:25), para proporcionar el compuesto del título.

Preparación de (1*H*-pirazol-4-il)-metanol



El carboxilato de 4-etil-pirazol (10 gramos, 71.40 milimoles) se coloca en un matraz secado al horno bajo una atmósfera de argón. Se agrega tetrahidrofurano seco (100 mililitros), seguido por la adición por goteo de hidruro de litio y aluminio (1 M en tetrahidrofurano, 100 mililitros, 100 milimoles). Una vez que se completa la adición, la mezcla de reacción se agita a 50°C. Se muestra que la reacción está completa mediante RMN después de 4 horas. La mezcla de reacción se enfría en un baño de hielo, y la mezcla de reacción se apaga con agua (3.8 mililitros), luego con hidróxido de sodio al 15 por ciento (3.8 mililitros), y finalmente de nuevo con agua (11.4 mililitros). El solvente se remueve al vacío, y el sólido se coloca en un aparato Soxhlet. El tetrahidrofurano se pone a reflujo a través del sistema durante 24 horas. El solvente se remueve al vacío para dar el compuesto del título.

^{1}H RMN (MeOD, 400 MHz); 7.60 (s, 2H), 4.55 (s, 2H).

Paso b: (1-{(1*S*,4*R*)-4-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-ciclopent-2-enil}-1*H*-pirazol-4-il)-metanol

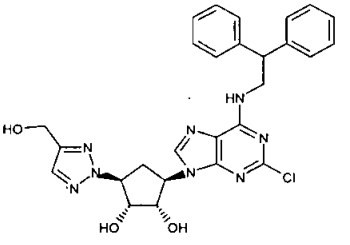
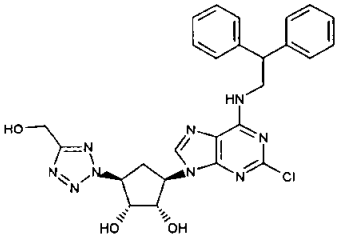
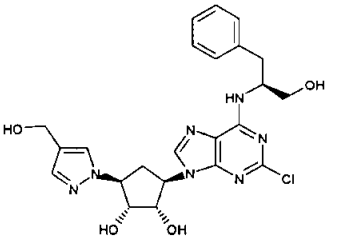
Una mezcla que comprende {1-[(1S,4R)-4-(2,6-dicloro-purin-9-il)-ciclopent-2-enil]-1H-pirazol-4-il}-metanol (0.675 gramos, 1.92 milimoles), difenil-etil-amina (0.398 gramos, 2.02 milimoles), y di-isopropil-etil-amina (0.298 gramos, 2.31 milimoles) en tetrahidrofurano seco (20 mililitros), se agita a 35°C durante 3 días. El solvente se remueve al vacío, y el residuo crudo resultante se divide entre dicloro-metano y HCl 0.1 M. La porción orgánica se separa, se lava con agua, salmuera, se seca ($MgSO_4$), y se concentra al vacío, para proporcionar el producto del título.

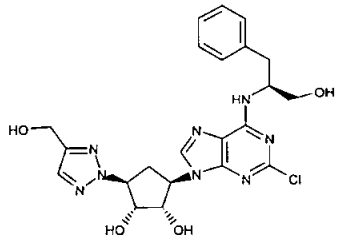
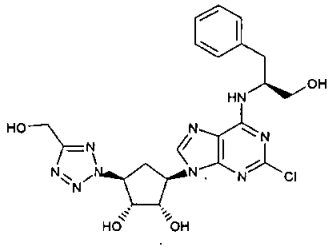
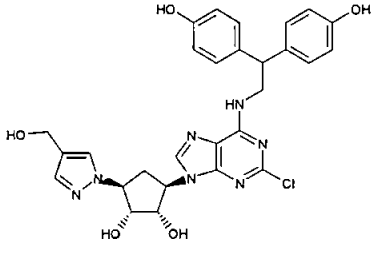
Paso d: (1*R*,2*S*,3*R*,5*S*)-3-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-5-(4-hidroxi-metil-pirazol-1-il)-ciclopentano-1,2-diol

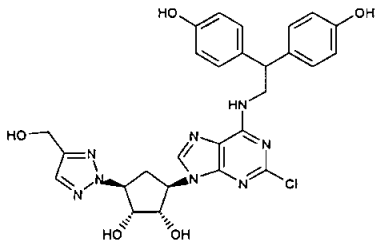
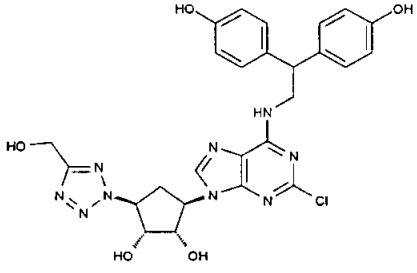
El (1-{(1*S*,4*R*)-4-[2-cloro-6-(2,2-difenil-etil-amino)-purin-9-il]-ciclopent-2-enil}-1*H*-pirazol-4-il)-metanol (0.84 gramos, 1.64 milimoles), y NMO (0.39 gramos, 3.28 milimoles) en tetrahidrofurano (20 mililitros), se trata con tetróxido de osmio (2 mililitros de una solución al 4 por ciento en agua), y se agita a temperatura ambiente durante la noche. El solvente se remueve al vacío, y el residuo crudo resultante se divide entre dicloro-metano y HCl 0.1 M (se agrega una pequeña cantidad de metanol para mejorar la solubilidad). La porción orgánica se seca ($MgSO_4$) y se concentra al vacío. El producto crudo se disuelve en dicloro-metano caliente para formar el producto del título como un precipitado después de enfriarse.

Intermediarios 4a a 4h

Tabla 1

Intermediario	Estructura	Nombre
4a		(1R,2S,3R,5S)-3-[2-Cloro-6-(2,2-difenil-etilamino)-purin-9-il]-5-(4-hidroximetil-[1,2,3]triazol-2-il)-ciclopentano-1,2-diol
4b		(1R,2S,3R,5S)-3-[2-Cloro-6-(2,2-difenil-etilamino)-purin-9-il]-5-(5-hidroximetil-tetrazol-2-il)-ciclopentano-1,2-diol
4c		(1R,2S,3R,5S)-3-[2-Cloro-6-((S)-1-hidroximetil-2-fenil-etilamino)-purin-9-il]-5-(4-hidroximetil-pirazol-1-il)-ciclopentano-1,2-diol

Intermediario	Estructura	Nombre
4d		(1R,2S,3R,5S)-3-[2-Cloro-6-((S)-1-hidroximetil-2-fenil-etilamino)-purin-9-il]-5-(4-hidroximetil-[1,2,3]triazol-2-il)-ciclopentano-1,2-diol
4e		(1R,2S,3R,5S)-3-[2-Cloro-6-((S)-1-hidroximetil-2-fenil-etilamino)-purin-9-il]-5-(5-hidroximetil-tetrazol-2-il)-ciclopentano-1,2-diol
4f		(1R,2S,3R,5S)-3-{6-[2,2-Bis-(4-hidroxi-fenil)-etilamino]-2-cloro-purin-9-il}-5-(4-hidroxi-metil-pirazol-1-il)-ciclopentano-1,2-diol

Intermediario	Estructura	Nombre
4g		(1R,2S,3R,5S)-3-{6-[2,2-Bis-(4-hidroxi-fenil)-etilamino]-2-cloro-purin-9-il}-5-(4-hidroximetil-[1,2,3]triazol-2-il)-ciclopentano-1,2-diol
4h		(1R,2S,3R,5S)-3-{6-[2,2-Bis-(4-hidroxi-fenil)-etilamino]-2-cloro-purin-9-il}-5-(5-hidroxi-metil-tetrazol-2-il)-ciclopentano-1,2-diol

Los intermediarios mostrados en la Tabla 1 se preparan de una manera análoga al Intermediario **3,** utilizando el alcohol heterocíclico de 5 miembros apropiado en el paso *3a,* y utilizando la amina apropiada en el paso *3c*.

Intermediario 5 **3-isocianato-bencen-sulfonamida**

A una solución vigorosamente agitada de la 3-amino-bencen-sulfonamida (1 gramo, 5.8 milimoles) en 1,4-dioxano seco (25 mililitros), se le agrega cloroformato de tricloro-metilo (1.72 gramos,

8.7 milimoles), y la mezcla de reacción se calienta a reflujo durante 3 horas. El solvente se remueve al vacío, para proporcionar el compuesto del título, el cual se utiliza sin mayor purificación.

Intermediario 6 **4-isocianato-bencen-sulfonamida**

Este compuesto se prepara a partir de la 4-amino-bencen-sulfonamida empleando un procedimiento análogo a aquél de la 3-isocianato-bencen-sulfonamida (Intermediario *5*), mediante el reemplazo de la 3-amino-bencen-sulfonamida con la 4-amino-bencen-sulfonamida.

Intermediarios 7 y 8

Estos compuestos, es decir,

- bencil-éster del ácido ((1S,2R,3S,4R)-4-{2-((R)-3-amino-pirrolidin-1-il)-6-[2,2-bis-(4-hidroxi-fenil)-etil-amino]-purin-9-il}-2,3-dihidroxi-ciclopentil)-carbámico (Intermediario **7**); y
- bencil-éster del ácido {(1*S*,2*R*,3*S*,4*R*)-4-[2-((*R*)-3-amino-pirrolidin-1-il)-6-((*S*)-1-hidroxi-metil-2-fenil-etil-amino)-purin-9-il]-2,3-dihidroxi-ciclopentil}-carbámico (Intermediario **8**),

se preparan de una manera análoga al Intermediario **2**, mediante el reemplazo del 1-amino-2,2-difenil-etano (paso *2c*) con la amina apropiada.

Preparación de Ejemplos

Ejemplo C1 **1-{(*R*)-1-[9-[(1*R*,2*S*,3*R*,4*S*)-4-(2,5-dioxo-imidazolidin-1-il)-2,3-dihidroxi-ciclopentil]-6-(2,2-difenil-etil-amino)-9*H*-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea**

Paso 1: Trifluoro-acetato de bencil-éster del ácido ((1*S*,2*R*,3*S*,

4*R*)-4-{6-(2,2-difenil-etil-amino)-2-[(*R*)-3-(3-piridin-3-il-ureido)-pirrolidin-1-il]-purin-9-il}-2,3-dihidroxi-ciclopentil)-carbámico

Una solución que comprende bencil-éster del ácido {(1S,2R,3S,4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-(2,2-difenil-etil-amino)-purin-9-il]-2,3-dihidroxi-ciclopentil}-carbámico (Intermediario **2**) (0.1 gramos, 0.15 milimoles), piridin-3-isocianato (0.02 gramos, 0.17 milimoles), y trietil-amina (0.017 gramos, 0.17 milimoles) en tetrahidrofurano (2 mililitros), se agita a temperatura ambiente durante la noche. El solvente se remueve al vacío, y la purificación se lleva a cabo mediante cromatografía en columna de fase inversa (Isolute^{MR} C18, del 0 al 100 por ciento de acetonitrilo en agua – ácido trifluoro-acético al 0.1 por ciento). Las fracciones se recolectan, y el MeCN se remueve al vacío. La porción acuosa restante se basifica con una solución saturada de bicarbonato de sodio, y se extrae con dicloro-metano. Los orgánicos combinados extraídos se secan ($MgSO_4$) y se concentran al vacío, para proporcionar el producto del título. [MH+769].

Paso 2: 1-{(*R*)-1-[9-((1*R*,2*S*,3*R*,4*S*)-4-amino-2,3-dihidroxi-ciclopentil)-6-(2,2-difenil-etil-amino)-9*H*-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea

A una solución del trifluoro-acetato de bencil-éster del ácido ((1*S*,2*R*,3*S*,4*R*)-4-{6-(2,2-difenil-etil-amino)-2-[(*R*)-3-(3-piridin-3-il-ureido)-pirrolidin-1-il]-purin-9-il}-2,3-dihidroxi-ciclopentil)-carbámico (35 miligramos, 46 micromoles) en etanol (1 mililitro), bajo una atmósfera inerte de argón, se le agrega paladio al 10 por ciento

sobre carbón (10 miligramos). La mezcla de reacción se purga con argón, y se coloca bajo una atmósfera positiva de hidrógeno durante la noche, después de cuyo tiempo, la mezcla se filtra a través de Celite, y el catalizador se lava con etanol. Las porciones orgánicas se combinan y se concentran al vacío, para proporcionar el compuesto del título. [MH+635].

Paso 3: Clorhidrato de 1-{(R)-1-[9-[(1R,2S,3R,4S)-4-(2,5-dioxo-imidazolidin-1-il)-2,3-dihidroxi-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea

A una solución de la 1-{(*R*)-1-[9-((1*R*,2*S*,3*R*,4*S*)-4-amino-2,3-dihidroxi-ciclopentil)-6-(2,2-difenil-etil-amino)-9*H*-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea (17 miligramos, 26 micromoles) en tetrahidrofurano (1 mililitro), se le agrega hidroxi-succinimidil-éster de Z-L-alanina (9 miligramos, 29 micromoles), y la mezcla de reacción se agita a temperatura ambiente durante la noche. El solvente se remueve al vacío, y el residuo crudo se disuelve en EtOH (1 mililitro) y se purga con argón. Se agrega paladio sobre carbón (aproximadamente 5 miligramos), y la mezcla de reacción se coloca bajo una presión constante de hidrógeno (0.35 bar), y se agita a temperatura ambiente durante la noche. La mezcla resultante se filtra a través de Celite, y se concentra al vacío. La purificación del residuo crudo mediante cromatografía en columna de fase inversa (Isolute^{MR} C18, del 0 al 100 por ciento de acetonitrilo en agua – HCl al 0.1 por ciento), proporciona el compuesto del título. [MH+732.72].

Ejemplo C2 **Trifluoro-acetato de 1-{(R)-1-[9-[(1R,2S,3R,4S)-4-(2,5-dioxo-imidazolidin-1-il)-2,3-dihidroxi-ciclopentil]-6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-3-piridin-3-il-urea**

Este compuesto se prepara de una manera análoga al Ejemplo 1, mediante el reemplazo del hidroxi-succinimidil-éster de Z-L-alanina (paso *3*) con el *N*-succinimidil-éster de Z-glicina. La purificación se lleva a cabo mediante cromatografía en columna de fase inversa (Isolute^{MR} C18, del 0 al 100 por ciento de acetonitrilo en agua – ácido trifluoro-acético al 0.1 por ciento). [MH+718.68].

Ejemplos C3 a C48

Estos ejemplos se pueden preparar de una manera análoga al Ejemplo 1, utilizando el compuesto de partida apropiado (ya sea el Intermediario **2**,**7** o bien el **8**) e isocianato en el paso *1*, y utilizando el succinimidil-éster apropiado en el paso *3*.

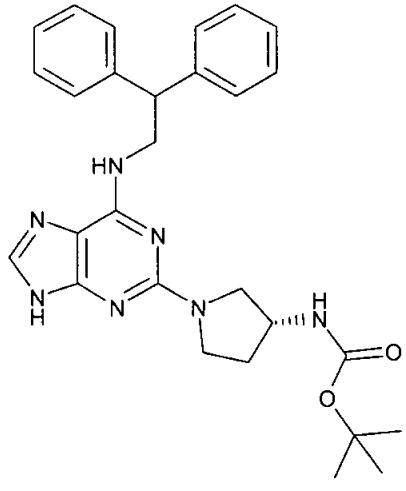
Los ejemplos que contienen grupos 3-hidroxi-bencilo se preparan como sigue: el fenil-éster del ácido (3-hidroxi-bencil)-carbámico (Intermediario **BA**) y el (Intermediario **2**, **7**, **u** **8**), se disuelven en metanol y trietil-amina. La mezcla de reacción se calienta utilizando radiación de microondas a 100°C durante 30 minutos, y entonces el solvente se remueve al vacío. La purificación del producto crudo mediante cromatografía en columna de fase inversa (Isolute^{MR} C18, del 0 al 100 por ciento de acetonitrilo en agua – ácido trifluoro-acético al 0.1 por ciento), proporciona el producto, el cual es lleva a través de los Pasos 2 y 3 (utilizando el succinimidil-éster apropiado), para proporcionar el compuesto final.

Ejemplos C49 a C84

Estos compuestos se preparan de una manera análoga al Ejemplo 1, mediante la combinación del compuesto de partida apropiado (Intermediarios **3 ó 4a-4h**) con los fenil-ésteres apropiados (Intermediarios **BA-BD**).

Ejemplo C85

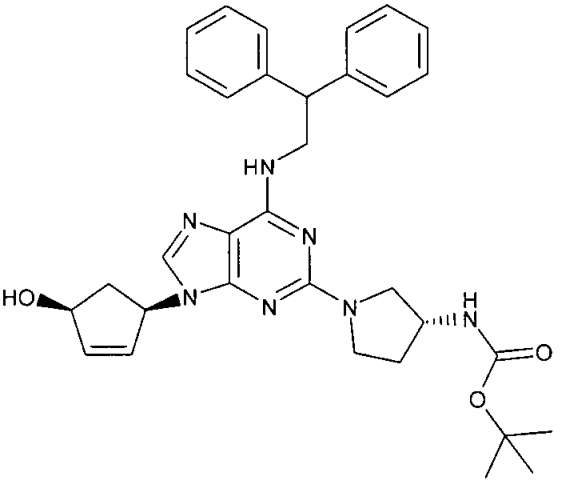
Paso 1: Terbutil-éster del ácido {(R)-1-[6-(2,2-difenil-etil-amino)-9H-purin-2-il]-pirrolidin-3-il}-carbámico



Se agrega (2-cloro-9*H*-purin-6-il)-(2,2-difenil-etil)-amina (2.5 gramos) a la Boc-(R)-3-amino-pirrolidina (2.677 gramos). Esto se suspende en acetonitrilo (10 mililitros), y se pone en microondas a 160°C. El análisis mediante LCMS muestra que la reacción está completa después de 30 minutos. La mezcla de reacción se suspende entonces en acetonitrilo y se filtra. El precipitado resultante se seca entonces para dar el compuesto del título. MS (ES+) m/e 498 (MH+).

Paso 2: Terbutil-éster del ácido {(*R*)-1-[6-(2,2-difenil-etil-amino)-

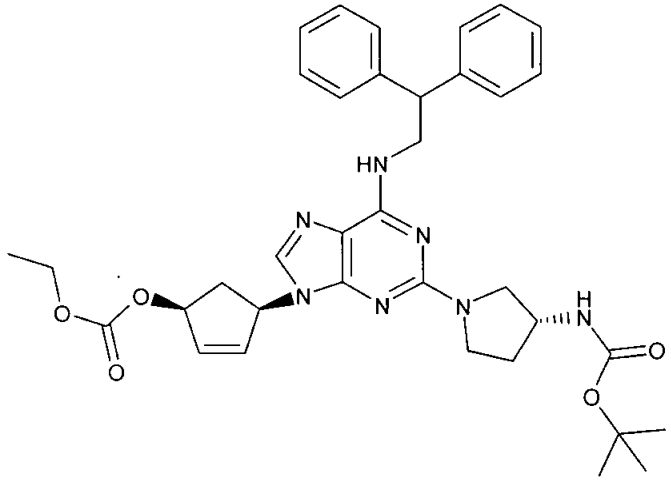
9-((1*R*,4*S*)-4-hidroxi-ciclopent-2-enil)-9*H*-purin-2-il]-pirrolidin-3-il}-carbámico



El terbutil-éster del ácido {(*R*)-1-[6-(2,2-difenil-etil-amino)-9*H*-purin-2-il]-pirrolidin-3-il}-carbámico (2.5 gramos) se suspende en tetrahidrofurano (15 mililitros) bajo una atmósfera inerte, y se seca en un recipiente de vidrio al horno. Se agrega hidruro de sodio (130 miligramos) a la suspensión en agitación. Ésta se agita hasta que se haya presentado la disolución. El (1*S*,4*R*)-cis-4-acetoxi-2-ciclopentan-1-ol (865 miligramos) y trifenil-fosfina (236 miligramos) se colocan en un matraz secado al horno bajo una atmósfera inerte, y esto se disuelve en tetrahidrofurano (15 mililitros). Esta solución se agrega a la solución del terbutil-éster del ácido {(*R*)-1-[6-(2,2-difenil-etil-amino)-9*H*-purin-2-il]-pirrolidin-3-il}-carbámico e hidruro de sodio mediante una jeringa. Entonces se agrega tris-(dibenciliden-acetona)-dipaladio (275 miligramos), y la reacción se agita a 50°C. Se muestra que la reacción está completa después de 1 hora mediante LCMS. La reacción se deja enfriar, y el solvente se

remueve al vacío. El residuo se purifica mediante cromatografía en columna por evaporación instantánea (sílice, dicloro-metano/metanol, 25:1), dando el compuesto del título. MS (ES+) m/e 582.62 (MH+).

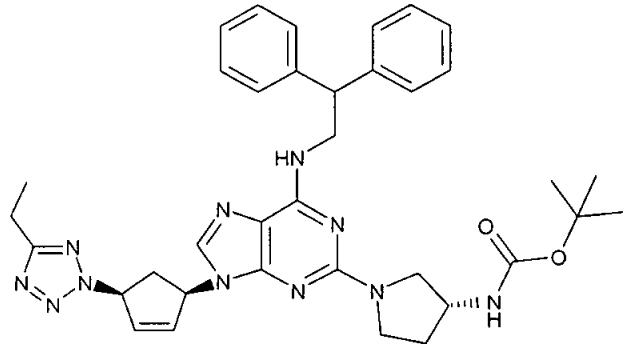
Paso 3: Etil-éster de (1S,4R)-4-[2-((R)-3-terbutoxi-carbonil-amino-pirrolidin-1-il)-6-(2,2-difenil-etil-amino)-purin-9-il]-ciclopent-2-enil-éster del ácido carbónico



El terbutil-éster del ácido {(*R*)-1-[6-(2,2-difenil-etil-amino)-9-((1*R*,4*S*)-4-hidroxi-ciclopent-2-enil)-9*H*-purin-2-il]-pirrolidin-3-il}-carbámico (500 miligramos) se disuelve en tetrahidrofurano desoxigenado seco (10 mililitros). Se agrega piridina (416 microlitros) a la solución. El cloro-formato de etilo (492 microlitros) se disuelve previamente en tetrahidrofurano (2.5 mililitros), y se agrega por goteo a la solución a 0°C. La reacción se agita a temperatura ambiente. El análisis mediante LCMS muestra que la reacción está completa después de 2 horas. El solvente se remueve al vacío. El residuo se disuelve en dicloro-metano (10 mililitros), y se pone en porciones contra HCl 0.1 M (10 mililitros). La capa orgánica

se lava entonces con agua (20 mililitros) y salmuera (10 mililitros), se seca sobre $MgSO_4$, se filtra, y el solvente se remueve al vacío. Se obtiene el compuesto del título después de la purificación mediante cromatografía en columna por evaporación instantánea (sílice, dicloro-metano/metanol, 40:1). MS (ES+) m/e 655.46 (MH+).

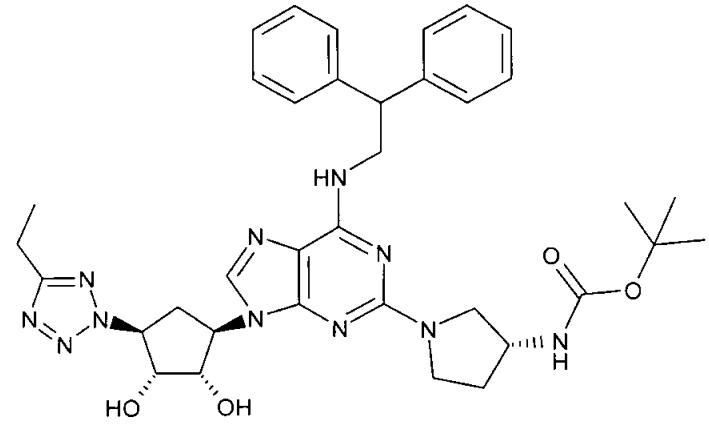
Paso 4: Terbutil-éster del ácido ((*R*)-1-{6-(2,2-difenil-etil-amino)-9-[(1*R*,4*S*)-4-(5-etil-tetrazol-2-il)-ciclopent-2-enil]-9*H*-purin-2-il}-pirrolidin-3-il)-carbámico



El etil-éster de (1S,4R)-4-[2-((R)-3-terbutoxi-carbonil-amino-pirrolidin-1-il)-6-(2,2-difenil-etil-amino)-purin-9-il]-ciclopent-2-enil-éster del ácido carbónico (760 miligramos) se agrega a etil-tetrazol (125 miligramos) y trifenil-fosfina (46 miligramos) en un matraz secado al horno bajo argón. Esto se disuelve en tetrahidrofurano anhidro (10 mililitros). Se agrega tris-(dibenciliden-acetona)-dipaladio (53 miligramos) a la solución en agitación. La reacción se agita a 50°C. El análisis mediante LCMS muestra que la reacción está completa después de 1 hora. El solvente se remueve al vacío. Se obtiene el compuesto del título mediante cromatografía en columna por evaporación instantánea (sílice, dicloro-metano/metanol,

50:1). MS (ES+) m/e 662.4 (MH+).

Paso 5: Terbutil-éster del ácido ((*R*)-1-{6-(2,2-difenil-etil-amino)-9-[(1*R*,4*S*)-4-(5-etil-tetrazol-2-il)-2,3-dihidroxi-ciclopentil]-9*H*-purin-2-il}-pirrolidin-3-il)-carbámico



El terbutil-éster del ácido ((*R*)-1-{6-(2,2-difenil-etil-amino)-9-[(1*R*,4*S*)-4-(5-etil-tetrazol-2-il)-ciclopent-2-enil]-9*H*-purin-2-il}-pirrolidin-3-il)-carbámico (500 miligramos) junto con *N*-óxido de *N*-metil-morfolina (178 miligramos) se disuelve en tetrahidrofurano (5 mililitros). Se agrega tetróxido de osmio al 4 por ciento en agua (500 microlitros) a la solución en agitación. La reacción se agita a temperatura ambiente. El análisis mediante LCMS muestra que la reacción está completa después de 72 horas. El solvente se remueve al vacío, y el residuo se pone en porciones entre dicloro-metano y HCl 0.1 M. La capa orgánica se lava con agua y salmuera, se seca sobre $MgSO_4$, se filtra, y el solvente se remueve al vacío. Se obtiene el compuesto del título mediante cromatografía en columna por evaporación instantánea (sílice, dicloro-metano/metanol, 100:1 - 50:1 – 25:1). MS (ES+) m/e 696.43 (MH+).

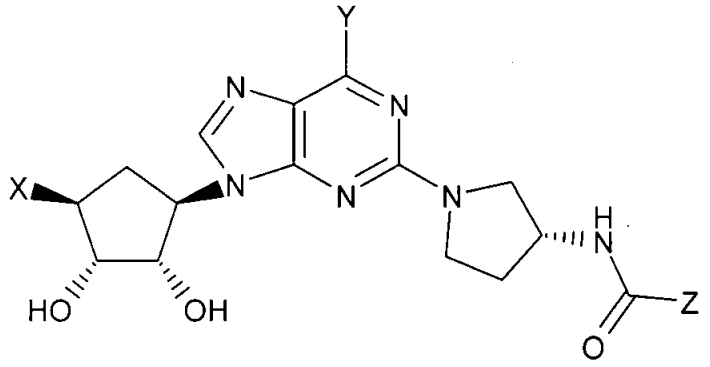
964

Paso 6: 3-[3-((*R*)-1-{6-[bisfenil-etil-amino]-9-[(1*R*,2*S*,3*R*,4*S*)-2,3-dihidroxi-4-(5-etil-tetrazol-2-il)-ciclopentil]-9H-purin-2-il}-[pirrolidin-3-il)-ureido]-bencen-sulfonamida

El terbutil-éster del ácido ((*R*)-1-{6-(2,2-difenil-etil-amino)-9-[(1*R*,4*S*)-4-(5-etil-tetrazol-2-il)-2,3-dihidroxi-ciclopentil]-9*H*-purin-2-il}-pirrolidin-3-il)-carbámico se desprotege en HCl metanólico, para dar la sal de clorhidrato de amina correspondiente. La amina libre se obtiene mediante neutralización con carbonato ácido de sodio acuoso, seguida por elución a partir de una columna C18 con un gradiente de agua/metanol. El compuesto del título se prepara entonces de una manera análoga al Ejemplo **C1**, Paso *1*, mediante el reemplazo del bencil-éster del ácido {(1S,2R,3S,4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-(2,2-difenil-etil-amino)-purin-9-il]-2,3-dihidroxi-ciclopentil}-carbámico con la amina libre anterior, y el reemplazo del piridin-3-isocianato con el Intermediario **5**.

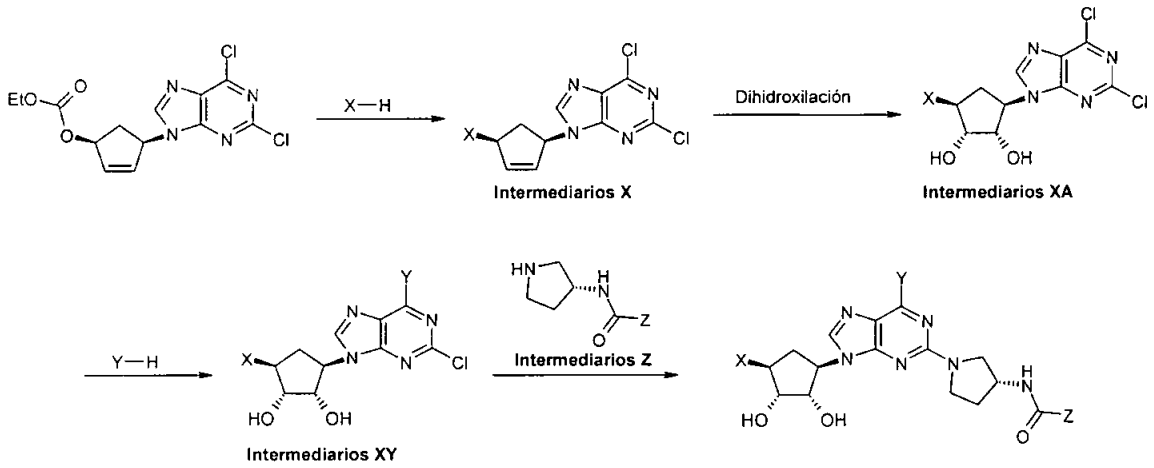
Ejemplos XYZ

Los ejemplos de la estructura XYZ se preparan en una secuencia de reacciones multi-paralelas como se describe en seguida.



Ejemplos XYZ

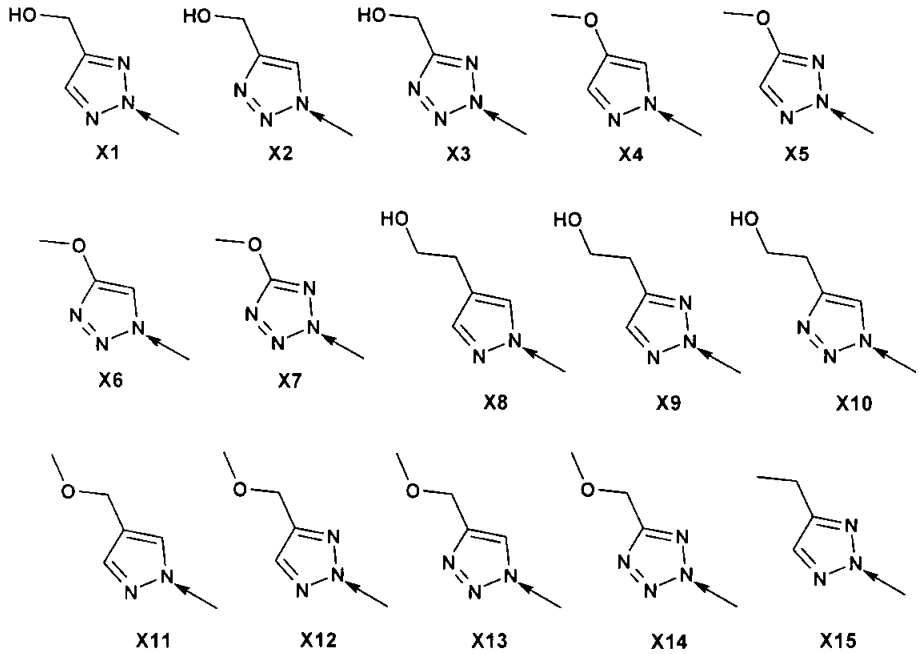
Esquema Global:



Paso Paralelo 1

La reacción del Intermediario **1**, de una manera análoga a la empleada en la preparación del Intermediario **3**, Paso *a*, mediante el reemplazo del 4-hidroxi-metil-pirazol con el heterociclo apropiado, individualmente, con los heterociclos X-H, da los Intermediarios **X**.

Heterociclos X-H:



Los heterociclos X-H se preparan como sigue:

- X1-X8 y X15 se preparan siguiendo los procedimientos de la literatura.
- X11, X12 y X13 se preparan mediante la O-metilación de los alcoholes correspondientes.
- X14 se prepara mediante la reducción del éster correspondiente hasta el alcohol, seguida por O-metilación.
- X9 y X10 se preparan a partir de los derivados de formilo correspondientes siguiendo procedimientos de homologación convencionales.

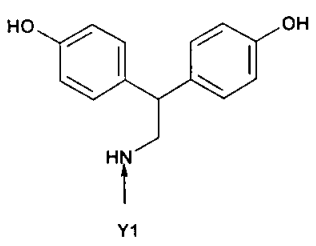
Paso Paralelo 2

La reacción de los Intermediarios **X**, individualmente, con cualquier agente hidroxilante de tetróxido de osmio o de tetróxido de rutenio, da los Intermediarios **XA**.

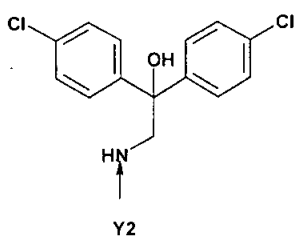
Paso Paralelo 3

La reacción de los Intermediarios **XA**, de una manera análoga a la empleada en la preparación del Intermediario **3**, Paso *b*, mediante el reemplazo de la 2,2-difenil-etil-amina con la amina apropiada, individualmente con las aminas Y-H, para dar los Intermediarios **XY**.

Aminas Y-H:



Y1



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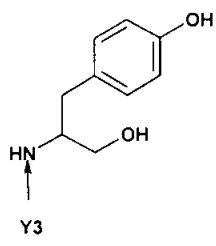

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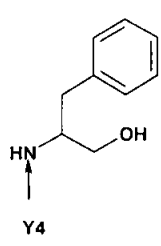

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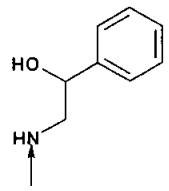

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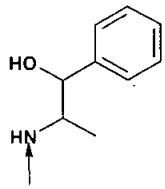


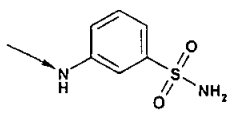
Y6

Paso Paralelo 4

Los Intermediarios **XY** se hacen reaccionar en etanol a reflujo, o en sulfóxido de dimetilo a 90-110°C, durante 18 a 24 horas, individualmente, con un exceso del Intermediario Z triple apropiado. Los Ejemplos **XYZ** se aíslan en seguida de la purificación mediante cromatografía en fase inversa dirigida a la masa.

Intermediarios Z

En donde Z =



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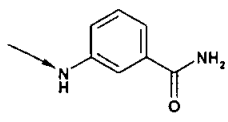

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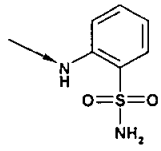

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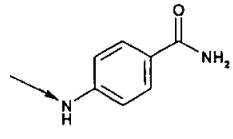

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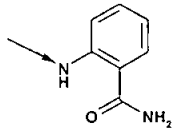

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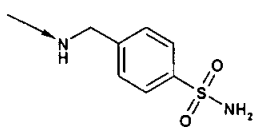

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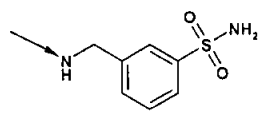

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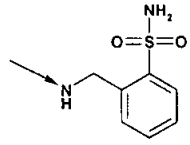

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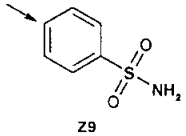

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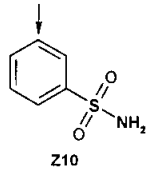

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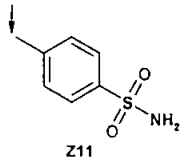

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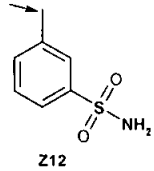

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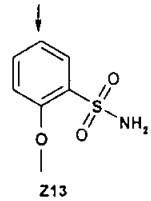

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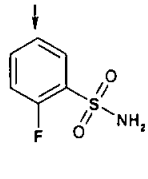

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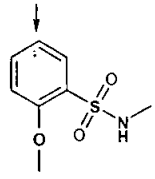

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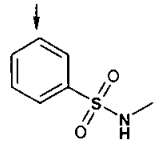

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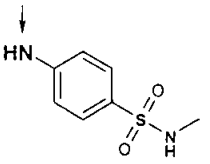
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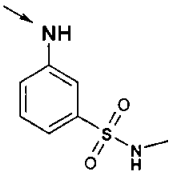
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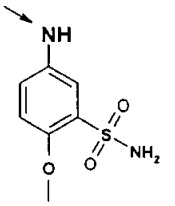
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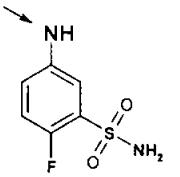
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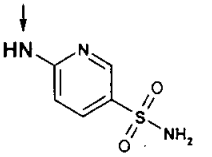
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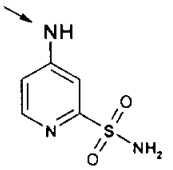
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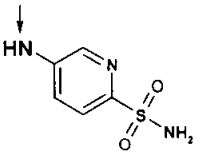
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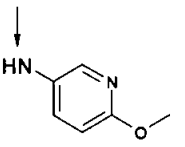
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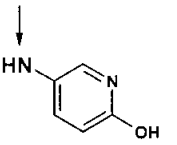
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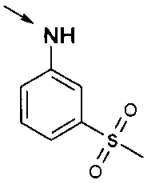
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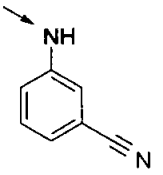
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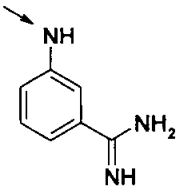
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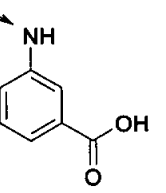
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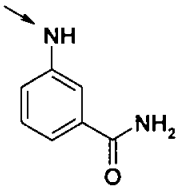
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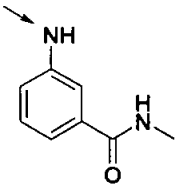
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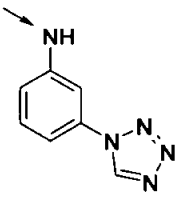
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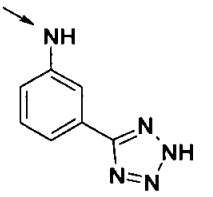
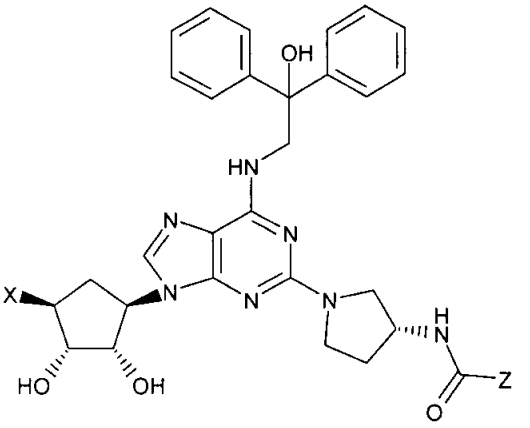

Z33

Ejemplos W

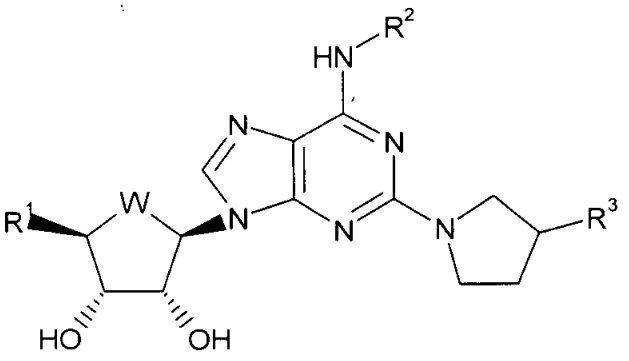

Ejemplos W

Para los Ejemplos **XYZ**, en donde X = X2, una hidrogenólisis

adicional de los cloruros de arilo, individualmente, mediante hidrogenación de transferencia utilizando formato de amonio con un catalizador de paladio sobre carbón en etanol, da una serie adicional de los Ejemplos **W**.

REIVINDICACIONES

1. Un compuesto de la fórmula (I):



(I)

o estereoisómeros o sales farmacéuticamente aceptables del mismo,

en donde:

W es CH_2 u O, con la condición de que, cuando W es O, entonces R^1 no es un sustituyente enlazado con nitrógeno;

R^1 es un grupo heterocíclico de 3 a 12 miembros que contiene de 1 a 4 átomos de nitrógeno del anillo y que contiene opcionalmente de 1 a 4 heteroátomos diferentes seleccionados a partir del grupo que consiste en oxígeno y azufre, estando ese grupo opcionalmente sustituido por oxo, alcoxilo de 1 a 8 átomos de carbono, arilo de 6 a 10 átomos de carbono, R^{1a}, o por alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por hidroxilo;

R^{1a} es un anillo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, estando este anillo heterocíclico de 3 a 12 miembros opcionalmente

sustituido por halógeno, ciano, oxo, hidroxilo, carboxilo, amino, nitro, alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, amino-carbonilo, alquilo de 1 a 8 átomos de carbono-carbonilo, o alcoxilo de 1 a 8 átomos de carbono opcionalmente sustituido por amino-carbonilo;

R^2 es alquilo de 1 a 8 átomos de carbono sustituido por OH, halo-arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, SO_2R^5, S-alquilo de 1 a 8 átomos de carbono, CN, halógeno, O-aralquilo de 7 a 14 átomos de carbono, u O-alquilo de 1 a 8 átomos de carbono, un grupo carbocíclico de 3 a 15 átomos de carbono opcionalmente sustituido por O-aralquilo de 7 a 14 átomos de carbono, grupo carbocíclico de 3 a 15 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, o alquilo de 1 a 8 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, $-SO_2-$ alquilo de 1 a 8 átomos de carbono, un grupo heterocíclico de 3 a 12 miembros que contiene de 1 a 4 átomos de nitrógeno del anillo y que contiene opcionalmente de 1 a 4 heteroátomos diferentes seleccionados a partir del grupo que consiste en oxígeno y azufre, estando ese grupo opcionalmente sustituido por un grupo heterocíclico de 3 a 12 miembros que contiene de 1 a 4 átomos de nitrógeno del anillo y que contiene opcionalmente de 1 a 4 heteroátomos diferentes seleccionados a partir del grupo que consiste en oxígeno y azufre, aralquilo de 7 a 14 átomos de carbono, o arilo de 6 a 14 átomos de carbono opcionalmente sustituido por O-

aralquilo de 7 a 14 átomos de carbono, o

R^2 es un grupo carbocíclico de 3 a 15 átomos de carbono opcionalmente sustituido por O-aralquilo de 7 a 14 átomos de carbono, grupo carbocíclico de 3 a 15 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, o alquilo de 1 a 8 átomos de carbono, o

R^2 es un grupo heterocíclico de 3 a 12 miembros que contiene de 1 a 4 átomos de nitrógeno del anillo y que contiene opcionalmente de 1 a 4 heteroátomos diferentes seleccionados a partir del grupo que consiste en oxígeno y azufre, estando ese grupo opcionalmente sustituido por un grupo heterocíclico de 3 a 12 miembros que contiene de 1 a 4 átomos de nitrógeno del anillo y que contiene opcionalmente de 1 a 4 heteroátomos diferentes seleccionados a partir del grupo que consiste en oxígeno y azufre, aralquilo de 7 a 14 átomos de carbono, o arilo de 6 a 14 átomos de carbono opcionalmente sustituido por O-aralquilo de 7 a 14 átomos de carbono;

R^3 se selecciona a partir de $NR^{3a}R^{3b}$, $NR^{3f}C(O)NR^{3g}R^{3h}$, $NHC(O)R^{3q}$, y $NHC(=NR^{3m})N(R^{3n})R^{3o}$;

R^{3a}, R^{3f} y R^{3h} son independientemente H, alquilo de 1 a 8 átomos de carbono, o arilo de 6 a 10 átomos de carbono;

R^{3b} es H, alquilo de 1 a 8 átomos de carbono, un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido por 0 a 3 R^4 o arilo de 6 a 10 átomos de carbono;

R^{3g} es alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido con SO_2R^5, CN, o de 0 a 3 R^4, o

R^{3g} es un arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, CN, $-C(=NH)NH_2$, SO_2R^5, -halógeno, o un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido por 0 a 3 R^4, o

R^{3g} es un aralquilo de 7 a 14 átomos de carbono opcionalmente sustituido por OH, O-alquilo de 1 a 8 átomos de carbono, halógeno, arilo de 6 a 10 átomos de carbono, SO_2R^5, CN, $-C(=NH)NH_2$, u O-arilo de 6 a 10 átomos de carbono, o

R^{3g} es un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido por 0 a 3 R^4;

R^{3m} es CN;

R^{3n} es H o alquilo de 1 a 8 átomos de carbono;

R^{3o} es H, alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por OH o por un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo

seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido con SO_2R^5, CN, o de 0 a 3 R^4, alcoxilo de 1 a 8 átomos de carbono, aralquilo de 7 a 14 átomos de carbono opcionalmente sustituido con OH, O-alquilo de 1 a 8 átomos de carbono, halo-arilo de 6 a 10 átomos de carbono, u O-arilo de 6 a 10 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, SO_2R^5 o –halógeno;

R^{3p} es H, alquilo de 1 a 8 átomos de carbono, o aralquilo de 7 a 14 átomos de carbono;

R^{3q} es un arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, SO_2R^5 o –halógeno; o

R^{3q} es un aralquilo de 7 a 14 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, SO_2R^5 o –halógeno, o

R^{3q} es un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre opcionalmente sustituido por 0 a 3 R^4 o un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido por 0 a 3 R^4;

R^4 se selecciona a partir de OH, alquilo de 1 a 8 átomos

de carbono opcionalmente sustituido por OH, CN, SO_2R^5 o halógeno, $C(O)NHR^{3a}$, O-alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por halógeno, $NR^{4a}R^{4b}$, $NHC(O)R^{4c}$, un C(O)-arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, -halógeno, o SO_2R^5;

R^{4a}, R^{4b} y R^{4c} son independientemente H, alquilo de 1 a 8 átomos de carbono, o arilo de 6 a 10 átomos de carbono; y

R^5 es alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por halógeno, arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, o $NR^{3a}R^{3b}$.

2. Un compuesto de la fórmula (I) de acuerdo con la reivindicación 1, o estereoisómeros o sales farmacéuticamente aceptables del mismo,

en donde:

W es CH_2 u O, con la condición de que, cuando W es O, entonces R^1 no es un sustituyente enlazado con nitrógeno;

R^1 es un grupo heterocíclico de 3 a 12 miembros que contiene de 1 a 4 átomos de nitrógeno del anillo y que contiene opcionalmente de 1 a 4 heteroátomos diferentes seleccionados a partir del grupo que consiste en oxígeno y azufre, estando ese grupo opcionalmente sustituido por oxo o por alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por hidroxilo;

R^2 se selecciona a partir de alquilo de 1 a 8 átomos de

carbono opcionalmente sustituido por OH, halógeno y arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, halógeno, o O-alquilo de 1 a 8 átomos de carbono;

R^3 se selecciona a partir de $NR^{3f}C(O)NR^{3g}R^{3h}$, $NR^{3a}NR^{3b}$, $NHC(O)R^{3q}$ y $NHC(=NR^{3m})N(R^{3n})R^{3o}$;

R^{3a} se selecciona a partir de H y alquilo de 1 a 8 átomos de carbono;

R^{3b} se selecciona a partir de H, alquilo de 1 a 8 átomos de carbono, y un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido por 0 a 3 R^4;

R^{3f} y R^{3h} son H;

R^{3g} es alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido con SO_2R^5, CN, o de 0 a 3 R^4, o

R^{3g} es un arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, CN, $-C(=NH)NH_2$, SO_2R^5, -halógeno, o un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido por 0 a 3 R^4, o

R^{3g} es un aralquilo de 7 a 14 átomos de carbono opcionalmente sustituido por OH, O-alquilo de 1 a 8 átomos de carbono, halógeno, arilo de 6 a 10 átomos de carbono, SO_2R^5, CN, $-C(=NH)NH_2$, u O-arilo de 6 a 10 átomos de carbono, o

R^{3g} es un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido por 0 a 3 R^4;

R^{3m} es CN;

R^{3n} es H o alquilo de 1 a 8 átomos de carbono;

R^{3o} es H, alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por OH o por un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido con SO_2R^5, CN, o de 0 a 3 R^4, alcoxilo de 1 a 8 átomos de carbono, aralquilo de 7 a 14 átomos de carbono opcionalmente sustituido con OH, O-alquilo de 1 a 8 átomos de carbono, halo-arilo de 6 a 10 átomos de carbono, u O-arilo de 6 a 10 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, SO_2R^5 o –halógeno;

R^{3q} es un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre

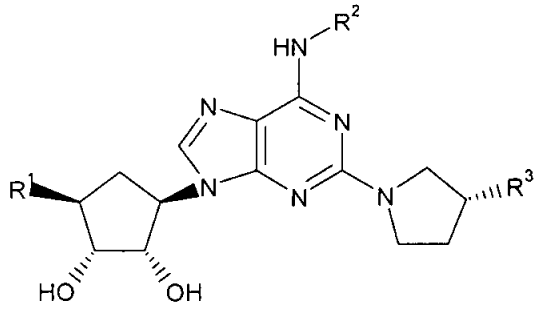
opcionalmente sustituido por un grupo heterocíclico de 3 a 12 miembros que contiene cuando menos un heteroátomo del anillo seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre, opcionalmente sustituido por 0 a 3 R^4;

R^4 se selecciona a partir de OH, alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por OH, CN, SO_2R^5 o halógeno, $C(O)NHR^{3a}$, O-alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por halógeno, $NR^{4a}R^{4b}$, $NHC(O)R^{4c}$, un C(O)-arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, -halógeno, o SO_2R^5;

R^{4a}, R^{4b} y R^{4c} son independientemente H, alquilo de 1 a 8 átomos de carbono, o arilo de 6 a 10 átomos de carbono; y

R^5 es alquilo de 1 a 8 átomos de carbono opcionalmente sustituido por halógeno, arilo de 6 a 10 átomos de carbono opcionalmente sustituido por OH, alquilo de 1 a 8 átomos de carbono, O-alquilo de 1 a 8 átomos de carbono, o –halógeno, o $NR^{3a}R^{3b}$.

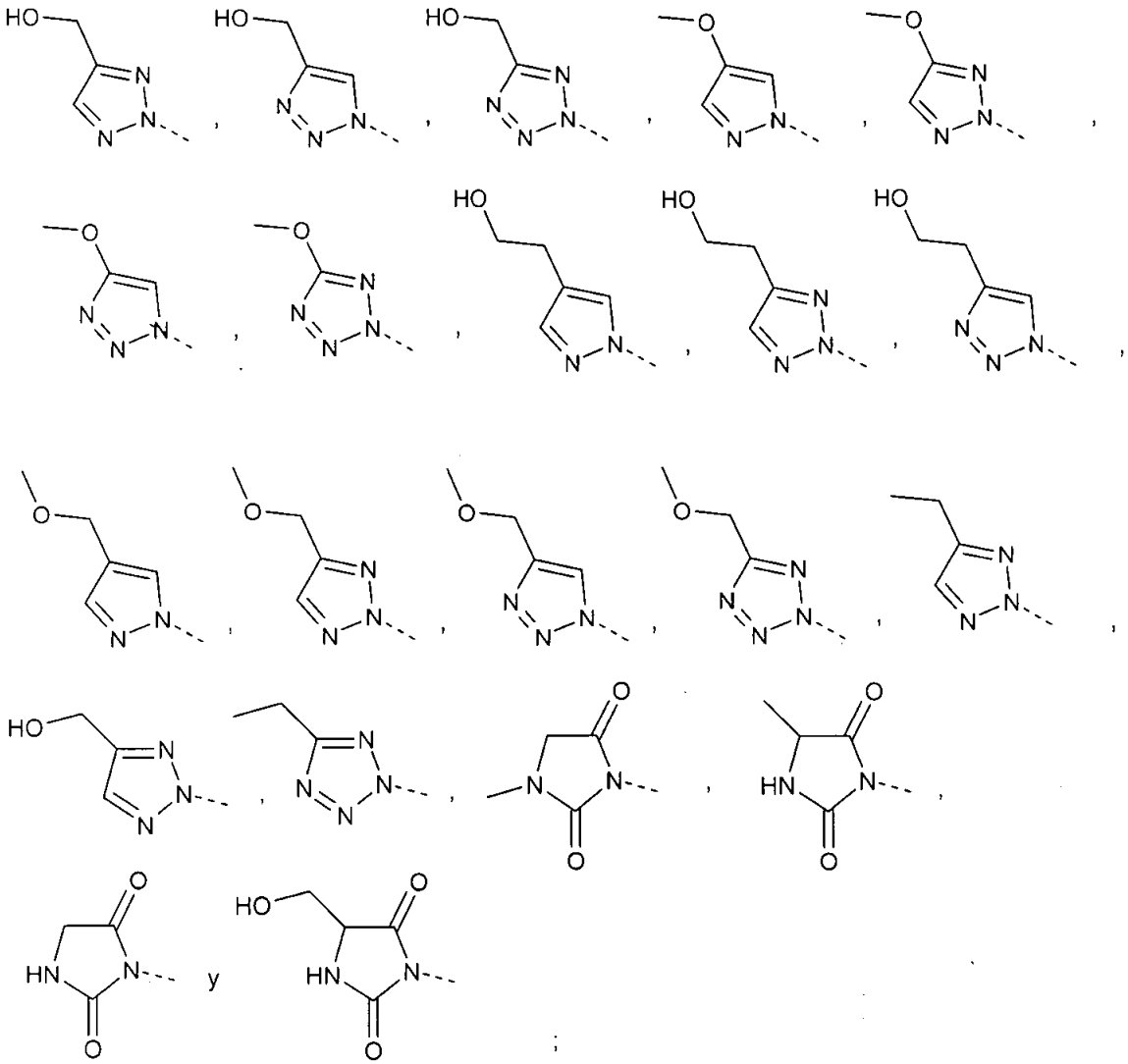
3. Un compuesto de acuerdo con la reivindicación 1, en donde el compuesto es de la fórmula (Ia):



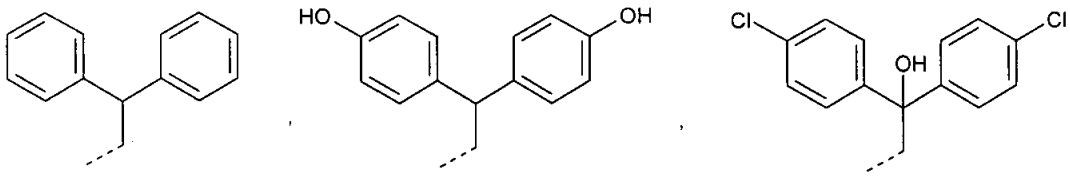
(Ia)

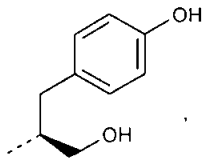
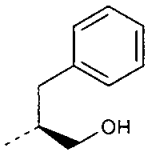
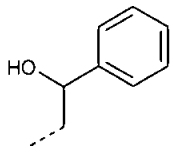
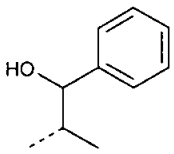
en donde:

R^1 se selecciona a partir de:

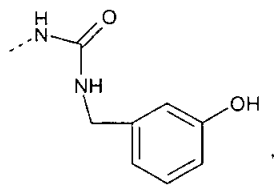
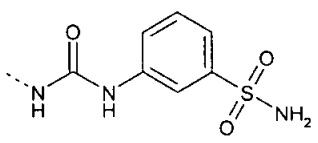
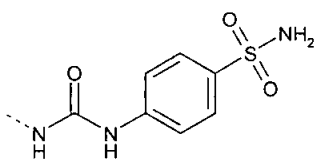
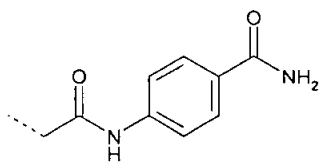
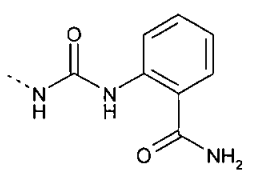
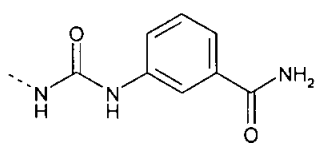
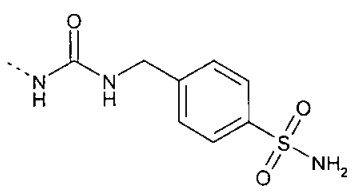
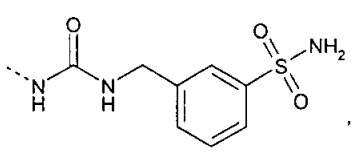
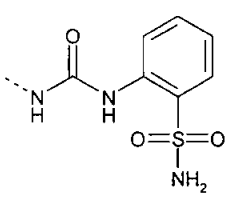
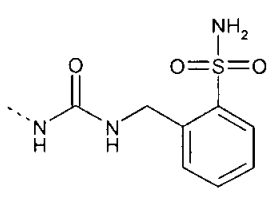
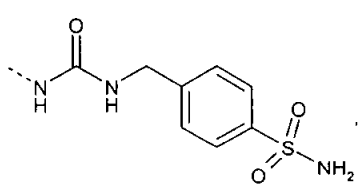


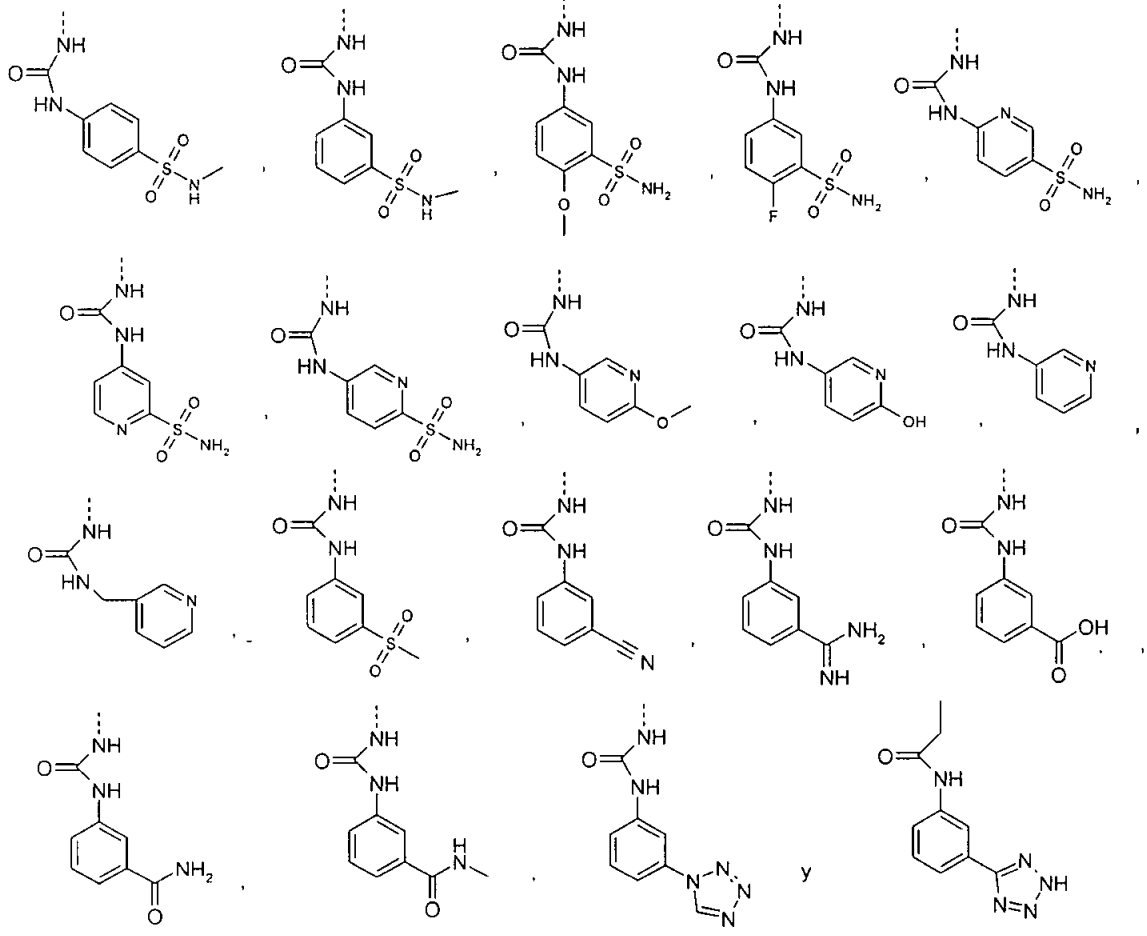
R^2 se selecciona a partir de:



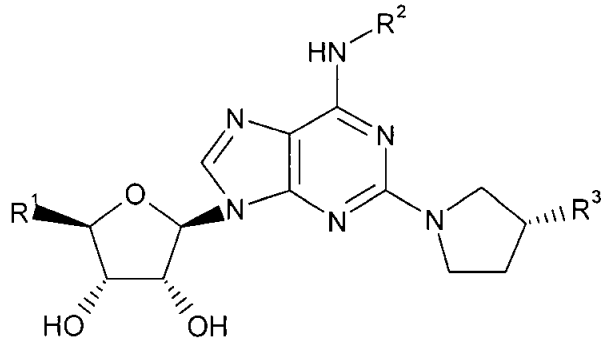



y

y

R^3 se selecciona a partir de:



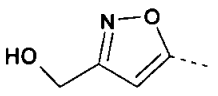
4. Un compuesto de acuerdo con la reivindicación 1, en donde el compuesto es de la fórmula (Ib):



(Ib)

en donde:

R^1 se selecciona a partir de: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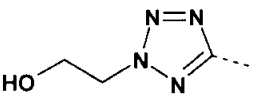
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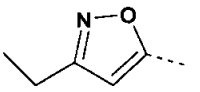
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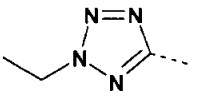

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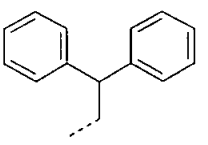
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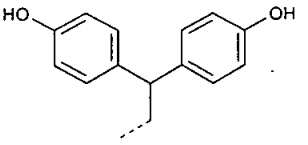
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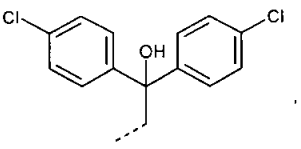
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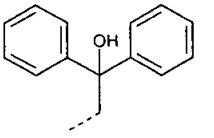

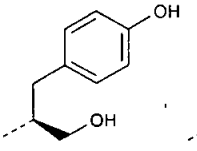
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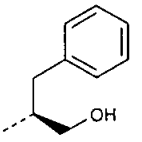
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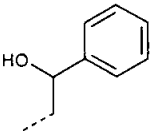
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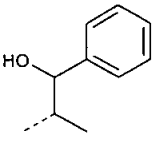
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y

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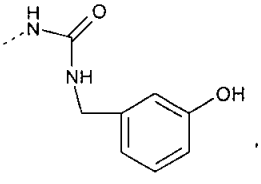
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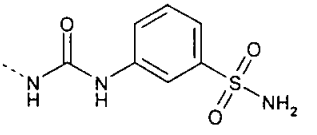
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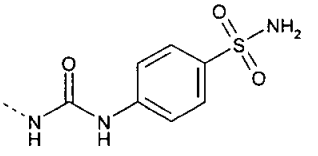
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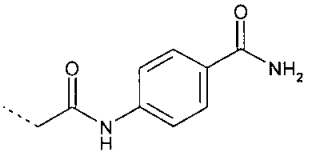
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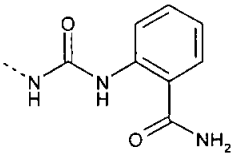
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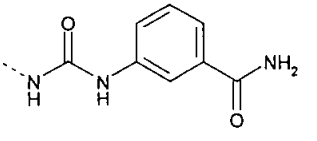
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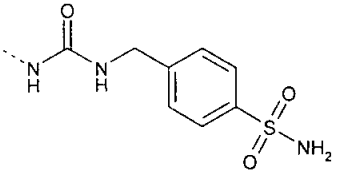
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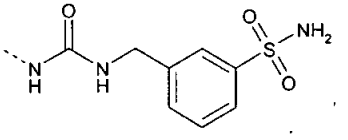
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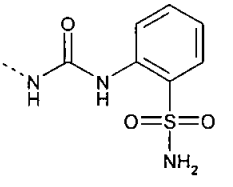
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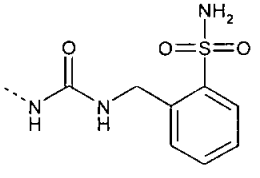
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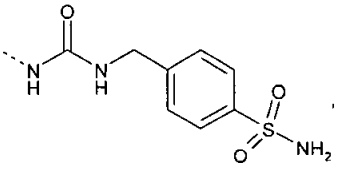
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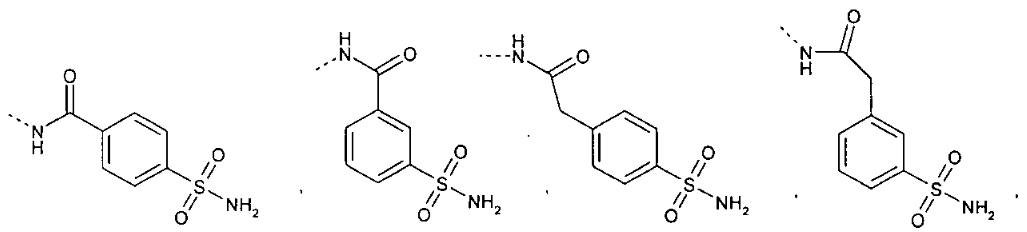
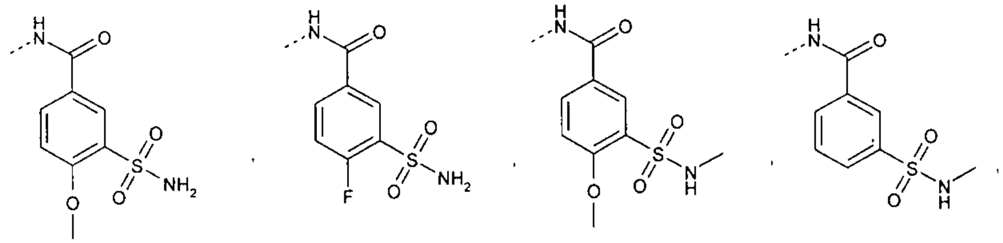
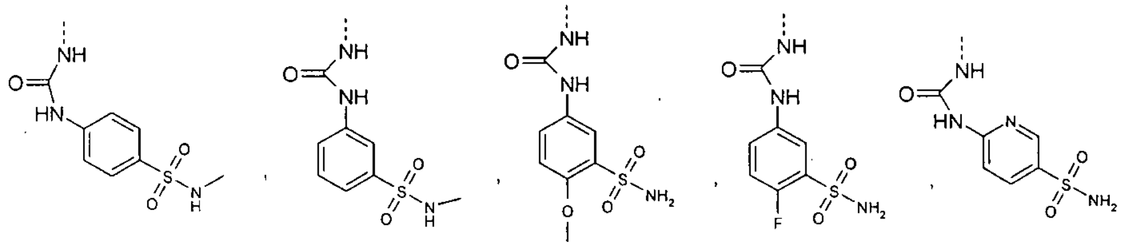
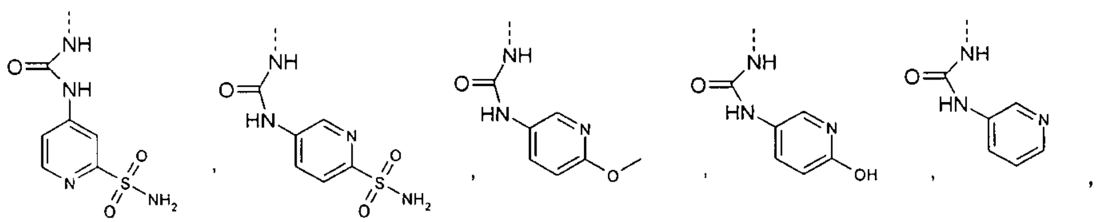
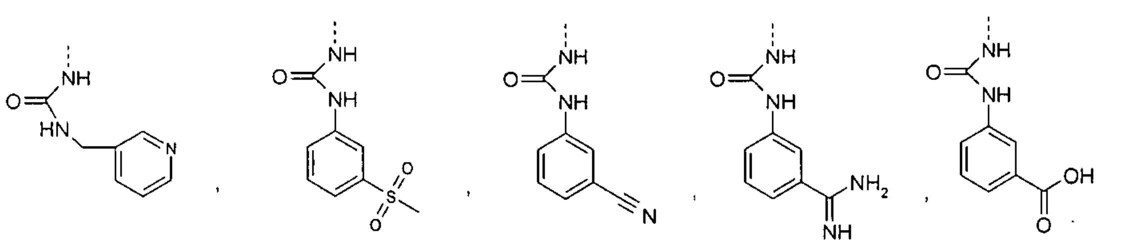
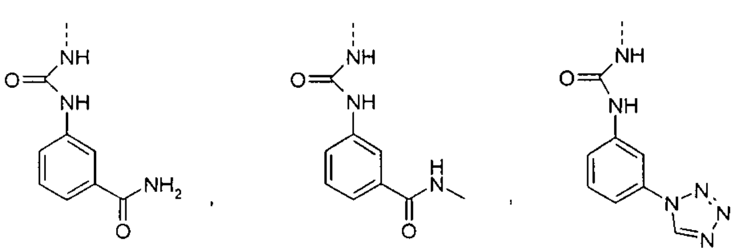
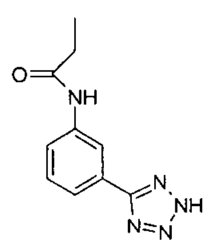










 and 

5. Un compuesto de acuerdo con la reivindicación 1,

sustancialmente como se describe en la presente con referencia a cualquiera de los Ejemplos .

6. Un compuesto de acuerdo con cualquiera de las reivindicaciones anteriores, para utilizarse como un producto farmacéutico.

7. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5, en combinación con una sustancia de fármaco anti-inflamatoria, broncodilatadora, anti-histamínica, o anti-tusiva, estando este compuesto y la sustancia de fármaco mencionada, en la misma o diferente composición farmacéutica.

8. Una composición farmacéutica, la cual comprende, como ingrediente activo, un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5, opcionalmente junto con un diluyente o vehículo farmacéuticamente aceptable.

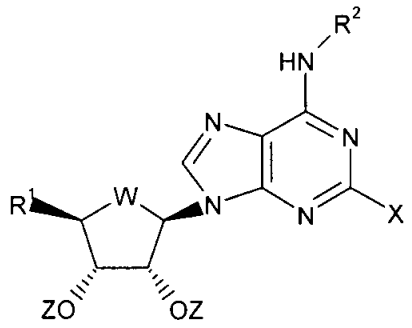
9. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5, para la fabricación de un medicamento para el tratamiento de una condición mediada por la activación del receptor de adenosina A2A.

10. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5, para la fabricación de un medicamento para el tratamiento de una enfermedad inflamatoria u obstructiva de las vías respiratorias.

11. Un proceso para la preparación de los compuestos de la fórmula (I) como se define en la reivindicación 1, o los estereoisómeros o sales farmacéuticamente aceptables de los

mismos, el cual comprende los pasos de:

(i) hacer reaccionar un compuesto de la fórmula (Ic):



(Ic)

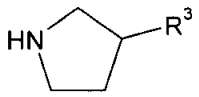
en donde:

R^1, W, y R^2 son como se definen en la reivindicación 1;

Z es H o un grupo protector; y

X es un grupo saliente,

con un compuesto de la fórmula (Id)



(Id)

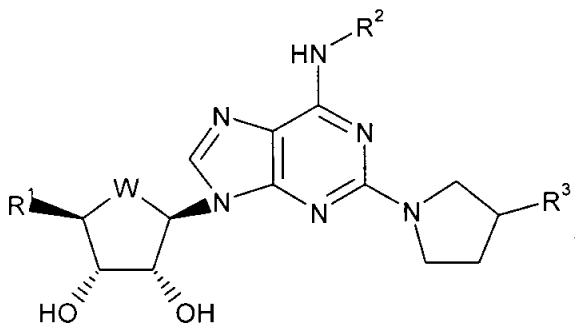
en donde:

R^3 es como se define en la reivindicación 1; y

remover cualesquiera grupos protectores, y recuperar el compuesto resultante de la fórmula (I), en forma libre o de sal farmacéuticamente aceptable.

RESUMEN

Los compuestos de la fórmula (I):



(I)

o los estereoisómeros o sales farmacéuticamente aceptables de los mismos,

en donde W, R^1, R^2 y R^3 tienen los significados indicados en la memoria descriptiva, son útiles para el tratamiento de las condiciones mediadas por la activación del receptor de adenosina A_{2A}, en especial las enfermedades inflamatorias u obstructivas de las vías respiratorias. También se describen composiciones farmacéuticas que contienen los compuestos, y un proceso para la preparación de los compuestos.

* * * * *

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/006156

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D473/16 C07H19/167 A61K31/52 A61P11/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/67263 A (GLAXO GROUP LTD [GB]; ALLEN DAVID GEORGE [GB]; CHAN CHUEN [GB]; COOK C) 29 December 1999 (1999-12-29) page 4, line 26 - page 6, line 24	1-11
Y	WO 99/67265 A (GLAXO GROUP LTD [GB]; ALLEN DAVID GEORGE [GB]; CHAN CHUEN [GB]; COUSIN) 29 December 1999 (1999-12-29) page 4, line 26 - page 7, line 24	1-11
Y	WO 2006/045552 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; FAIRHURST ROBIN ALEC [GB]) 4 May 2006 (2006-05-04) page 1, line 1 - page 2, line 7 page 29, line 8 - page 29, line 11	1-11

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 2007	12/10/2007

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

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2006/097260 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; FAIRHURST ROBIN ALEC [GB]) 21 September 2006 (2006-09-21) page 1 - page 2 page 16, line 8 - page 16, line 16	1-11
P,X	WO 2006/074925 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; FAIRHURST ROBIN ALEC [GB]) 20 July 2006 (2006-07-20) page 1, line 1 - page 2, line 18 page 32, line 10 - page 32, line 18	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/006156

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WO 2006074925 A	20-07-2006	AR 052659 A1	28-03-2007
		AU 2006205878 A1	20-07-2006

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

VOEGELI-LANGE, Regina
Novartis AG
Corporate Intellectual Property
CH-4002 Basel
SUISSE

Date of mailing *(day/month/year)*
21 January 2008 (21.01.2008)

Applicant's or agent's file reference
50311-WO-PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP2007/006156

International filing date *(day/month/year)*
11 July 2007 (11.07.2007)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address
NOVARTIS PHARMA GMBH
Brunner Strasse 59
A-1230 Vienna
Austria

State of Nationality: AT
State of Residence: AT
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
NOVARTIS AG
Lichtstrasse 35
CH-4056 Basel
Switzerland

State of Nationality: CH
State of Residence: CH
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:
NOVARTIS PHARMA GMBH has assigned all its rights to NOVARTIS AG. NOVARTIS AG is now recorded as applicant for all designated States except the United States of America.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

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

Facsimile No. +41 22 338 82 70

Authorized officer
Nissen Diana.
e-mail Diana.Nissen@wipo.int
Telephone No. +41 22 338 80 54

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-001737- -00000-0000
Fecha: 2009-01-09 16:29:24 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 289

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [X]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Claudia M Neva Cortes
Firma Responsable

Fecha_____

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