Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISION DE NUEVAS CREACIONES

07. 39105

SOLICITUD DE PATENTE DE INVENCION

TITULO DERIVADOS DE PURINA PARA USARSE COMO ANTAGONISTAS DE RECEPTORES DE A-2A DE ADENOSIN

SOLICITANTE NOVARTIS AG

DIRECCION Lichtstrasse 35 CH-4056 Basel Suiza

C07D 473/40, 473/16, 473/32, A61K 31/52, A61P 29/00

APODERADO CARLOS R OLARTE

BOGOTA 19 de Abril de 2007

P2007/000060

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OlarteRaisbeck

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No 07 039105- -00000-0000
Fecha 2007 04 19 16 35 44 Dep 2020 NUECREACIONE
Tra 11 PATENTEIYII Eve 378 FASENACIONALI
Act 411 PRESENTACION Folios 329

PETITORIO - FORMULARIO UNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE

(1) [X] Patente de Invencion [ ] Patente de Modelo de Utilidad

[X] Capitulo I [ ] Capitulo II

(2) SOLICITANTE (71)

Nombre NOVARTIS AG
Direccion Lichtstrasse 35, CH-456 Basel
Nacionalidad o Domicilio Suiza
Lugar de Constitución Suiza
Telefono _____ **Fax** _____
E-mail _____

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

REPRESENTANTE 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 _____
Numero 79782747Bta
TP 74 295

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Nombre VER PAGINA ADJUNTA
Direccion VER PAGINA ADJUNTA
Nacionalidad o Domicilio VER PAGINA ADJUNTA

(5) PCT (86)

Solicitud Internacional No PCT/EP2005/011344 Fecha Octubre 21 2005

Publicacion Internacional No WO 2006/045552 Fecha Mayo 4 2006

(6) Titulo (54) **DERIVADOS DE PURINA PARA USARSE COMO AGONISTAS DE RECEPTORES DE A-2A DE ADENOSIN**

Clasificación Internacional (51) C07D 473/16 C07D 473/32 C07D 473/40 A61K 31/52 A61P 29/00

Prioridad SI [X] NO [ ]

(33) Pais de Origen	(32) Fecha	(31) Numero de Solicitud
GB	Octubre 22 2004	0423551 1
GB	Julio 15 2005	0514619 6

(9) Comprobante de pago No **07-29 608** **Fecha** **13 de Abril de 2007**

(0) **ANEX S**

- [x] Comprobante de pago de la tasa de presentacion de la solicitud
- [ ] Documento que acredita la existencia y representacion legal cuando el solicitante sea persona juridica
- [x] Poderes, si fuere el caso Adjunto copia simple ver expediente No 06 076 505
- [ ] Documento de cesion del inventor al solicitante o a su causante
- [ ] Declaraciones
- [x] Copia de la solicitud internacional (Resumen, descripcion, reivindicaciones, dibujos)
- [x] Traduccion de la solicitud internacional al castellano (Resumen, descripcion, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- [ ] Traduccion 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 autorizacion de uso de conocimientos tradicionales de las comunidades indigenas
- [ ] De ser el caso, certificado de deposito del material biologico
- [ ] Arte final 12 x 12
- [ ] De ser el caso, informacion sobre otras solicitudes de patente o titulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invencion de esta solicitud
- [x] De ser el caso, modificaciones efectuadas a la solicitud internacional
- [x] Otros Busqueda Internacional

(1) **FIGURA CARACTERISTICA**

(2) Solicito la concesion de la patente,

NOMBRE CARLOS R OLARTE FIRMA

C C 79 782 747 Bta T P 74 295

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

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RECIBO DE CAJA ANEXADO AL EXPEDIENTE No _____

9

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No 07 039105- -00000-0000

Fecha 2007 04 19 16 35 44 Dep 2020 NUECREACIONI
Tra 11 PATENTEIYII Eve 378 FASENACIONALI
Act 411 PRESENTACION Folios 329

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT 800176089-2

RECIBO OFICIAL DE CAJA 07 29,608
FECHA ABRIL 13 DE 2007

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PGO	Vr PAGO
OLARTE RAISBEGR	CONSIGNACION	BANCO POPULAR	050 00110-6	58562732	12/04/2007	3,856,000 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	482,000 00
		TOTAL $	482,000 00

SON CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE _____

TRADUCCION OFICIAL DE UN DOCUMENTO QUE ESTA ORIGINALMENTE EN INGLES

Nota del traductor

El documento adjunto de poder de Novartis AG a Carlos R Olarte y/o J Ian Raisbeck y/o Ana Maria Friem y/o Juan Cuillermo Moure y/o Natalia Castro lleva los siguientesdatos en ingles

CERTIFICACION NOTARIAL

1 En esta fecha, dia 30 de Agosto de 2006, yo, el suscrito Notario Publico 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 direccion comercial en Lichstrasse 35, 4056, Basilea, Suiza La autenticidad de la firmas fue estabiecida por medio de la comparacion

2 Ademas, yo, el Notario Publico, certifico por el presente que las anteriores personas han ejecutado el anterior documento como apoderados de Novartis AG

3 Ademas, yo, el Notario Publico certifico por el presente que Novartis AG, con su principal lugar de negocios en Basilea, Suiza, esta debidamente constituida, esta actualmente vigente y que los propositos para los cuales se otorgó el Documento de Poder estan dentro del alcance de sus propositos corporativos

Traductor Oficial
JORGE E. SIERRA PEREZ
Licencia 376 1993 Ministerio

Notaria Veintisiete del Circulo de Bogotá D.C.
Para constancia se autentica el presente documento
30 NOV 2006

4 Ademas yo, el Notario Publico, certifico por el presente que las anteriores personas tienen la autoridad para ejecutar el anexo de Poder, que por este instrumento su representacion es legal

La base para mis certificaciones de los puntos 2, 3 y 4 fue la exhibicion de los siguientes documentos autenticos

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

Basilea, Suiza, este dia 30 de Agosto de 2006

(Firmado) Dr Matthias Staehelin, Notario Publico del Canton 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

10 NOV. 2006

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 176 1006

7

Certificacion

Certifico que la presente es una traduccion verdadera y completa del documento adjunto 'Novartis'

Fecha 12 de Septiembre de 2006

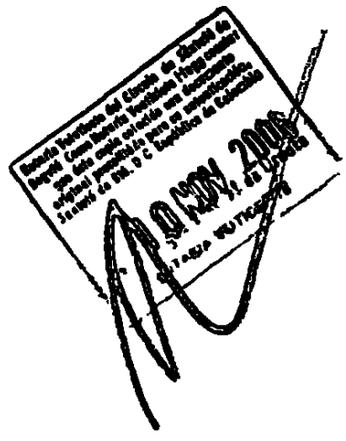
Traductor Jorge Enrique Sierra Reyes

Licencia No 376 de 1993, del Ministerio de Justicia

Direccion Carrera 15 No 99-13 Oficina 411 Bogota, Colombia

Telefono (57-1) 2182303, (57-1) 6232925

E-mail treseser1@yahoo.com No 834€



Traductor Oficial
JORGE E. SIEPRA REYES
Licencia 376 1993 Minis

OLARTERAISBECK
OLARTE RAISBECK & FRIEDI LTDA

C de s R Ol rte
J Ian Raisbeck
A n Ma fa F ied
Juan Guillermo Moure
N talia Castro

Zayde Chalum
Jacq eline Chaparro
Jose Luis Londoño
Felipe Mendoza
Si non S luis

Of Cou sel
C uillermo Cl I ur
C ociela 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 Maria Friedi and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file prosecute obtain defend and enforce in / 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 notification 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 like wise 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 Friedi 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 Invencion, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales Marcas, Lemas Comerciales Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Proteccion 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 Republica 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 dandoles asimismo facultad para sustituir el presente y revocar dichas sustituciones

Signature/Firma

Date/Fecha June 27, 2006

City,Country/Ciudad Pais Basel Switzerland

Esther Concepcion

Pascal Frech

World Trade Center Torre A Calle 100 No 8A – 37 Piso 10 Bogotá D C Colombia
Tel + 57 1 601 7700 Fax + 57 1 601 7799 office@olarteraisbeck.com www.olarteraisbeck.com

Attestation

1 On this date, the 0th (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

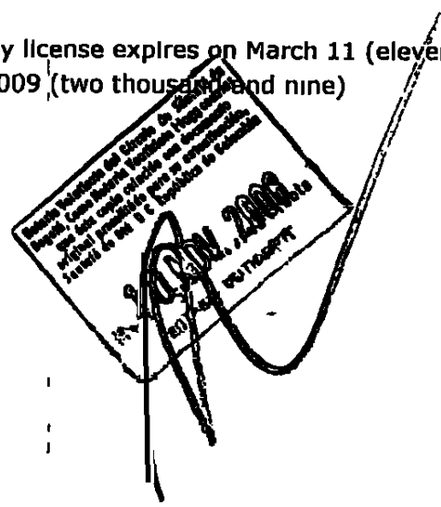
Extract from the Register of Commerce of the Canton of Basel-City for Novartis AG, in Basel, dated January 25 (twenty-five), 2006 (two thousand and six)

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

M. Staehelin Not

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

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



Leg Prot Nr 1117 /2006

10

APOSTILLE

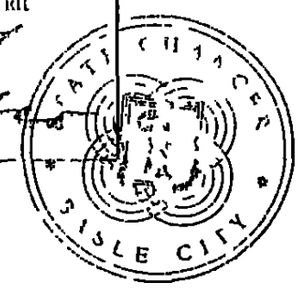
(Hague Convention of 5 October 1961)

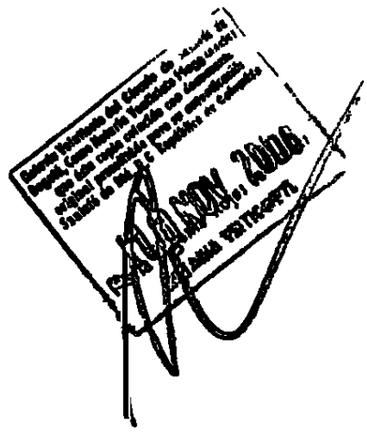
1. Country: Switzerland (Confoederatio Helvetica)
   This official document
2. has been signed by
3. in his/her function as
4. and is clothed with the authority of the

Certified

5. in Basel (Basle)
6. on
7. by the Attorney General of the Canton of Basel-Stadt
8. no
9. Seal/Stamp
10. Signature

Ueli Fischer





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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 May 2006 (04 05 2006)

PCT

(10) International Publication Number
WO 2006/045552 A1

(51) International Patent Classification
C07D 473/16 (2006 01) *A61K 31/52* (2006 01)
C07D 473/32 (2006 01) *A61P 29/00* (2006 01)
C07D 473/40 (2006 01)

(21) International Application Number
PCT/EP2005/011344

(22) International Filing Date 21 October 2005 (21 10 2005)

(25) Filing Language English

(26) Publication Language English

(30) Priority Data
0423551 1 22 October 2004 (22 10 2004) GB
0514619 6 15 July 2005 (15 07 2005) GB

(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, Alex [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) SINGH, Paul [GB/GB] Novartis Horsham Research Centre Wimblehurst Road Horsham West Sussex RH12 5AB (GB)

(74) Agents DE WEERD, Peter et al Novartis AG Corporate Intellectual Property CH-4002 Basel (CH)

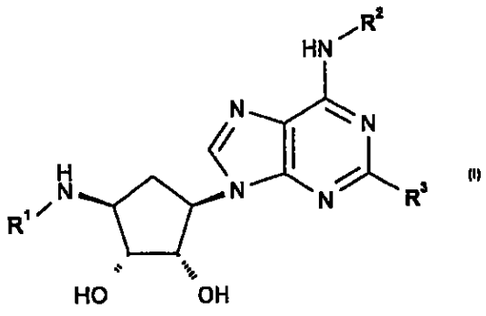
(81) Designated States *(unless otherwise indicated for every kind of national protection available)* AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NG NI NO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

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 FOR USE AS ADENOSIN A 2A RECEPTOR AGONISTS



(I)

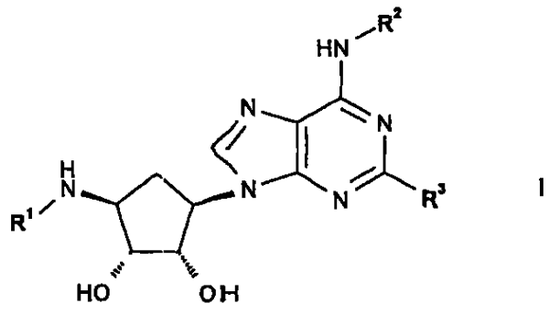
(57) Abstract Compounds of formula (I) in free or salt form wherein R^1 R^2 and R^3 have the meanings as indicated in the specification are useful for treating conditions mediated by activation of the adenosine A_{2A} receptor especially inflammatory or obstructive airways diseases Pharmaceutical compositions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

WO 2006/045552 A1

PURINE DERIVATIVES FOR USE AS ADENOSIN A-2A RECEPTOR AGONISTS

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

In one aspect, the present invention provides compounds of formula I



I

in free or salt form, wherein

R^1 is hydrogen, C_1 C_8 alkylcarbonyl, C_3-C_8-cycloalkylcarbonyl, -SO_2-C_1-C_8-alkyl, C_7-C_{14} aralkylcarbonyl or C(=O)-C(=O)-NH C_1-C_8 alkyl optionally substituted by R^4,

R^2 is hydrogen or C_1 C_8-alkyl optionally substituted by C_6-C_{10} aryl,

R^3 is hydrogen, halo, C_2-C_8-alkenyl or C_2-C_8 alkynyl,
or R^3 is amino optionally substituted by C_3-C_8-cycloalkyl optionally substituted by amino,
or R^3 is C_1 C_8 alkylamino optionally substituted by hydroxy, C_6 C_{10}-aryl or by R^5,
or R^3 is R^6 optionally substituted by amino or –NH-C(=O)-NH-R^7,
or R^3 is –NH-R^6 optionally substituted –NH C(=O)-NH-R^7,
or R^3 is C_1-C_8 alkylaminocarbonyl or C_3 C_8-cycloalkylamino-carbonyl optionally substituted by amino, C_1-C_8 alkylamino, di(C_1-C_8 alkyl)amino or -NH C(=O) NH R^8,

R^4, R^5 and R^6 are independently a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5 or 6-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, and

R^7 and R^8 are independently a 5 or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5- or 6

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, C_1-C_8 alkoxy optionally substituted by aminocarbonyl, or a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said ring also 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, C_1-C_8 alkoxy optionally substituted by aminocarbonyl

Terms used in the specification have the following meanings

"Optionally substituted" means the group referred to can be substituted at one or more positions, preferably one or two 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 Preferably halo is chlorine When R^3 is halo it is preferably chloro When R^3 is R^6 substituted by –NH C(=O)-NH R^7, where R^7 is a 5 or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur substituted by halo, that heterocyclic ring is substituted at two positions by chloro

"C_1 C_8 alkyl" as used herein denotes straight chain or branched alkyl having 1 to 8 carbon atoms Preferably C_1 C_8-alkyl is C_1-C_6-alkyl When R^2 is C_1-C_8 alkyl optionally substituted by C_6-C_{10}-aryl, R^2 is preferably either unsubstituted C_1 C_6 alkyl, especially pentyl or hexyl, more especially -$CH(C_2H_5)_2$ or -$CH_2CH_2C(CH_3)_3$, or R^2 is C_1-C_5 alkyl substituted by C_6 C_{10}-aryl, especially C_2 C_5-alkyl (more especially pentyl) substituted at one position by naphthyl or at two positions by phenyl

"C_2-C_8 alkenyl" as used herein denotes straight chain or branched hydrocarbon chains that contain 2 to 8 carbon atoms and one or more carbon-carbon double bonds Preferably C_2 C_8-alkenyl is C_2 C_4-alkenyl"

C_2 C_8 alkynyl" as used herein denotes straight chain or branched hydrocarbon chains that contain 2 to 8 carbon atoms and one or more carbon-carbon triple bonds and optionally one or more carbon carbon double bond Preferably C_2–C_8-alkynyl is C_2-C_6-alkynyl When R^3 is C_2-C_8 alkynyl it is preferably C_2 C_6-alkynyl, especially hexynyl, more especially -C≡C-C_4H_9

"C_1 C_8 alkoxy" as used herein denotes straight chain or branched alkoxy having 1 to 8 carbon atoms Preferably C_1-C_8 alkoxy is C_1 C_4 alkoxy

"C_3 C_8 cycloalkyl" as used herein denotes cycloalkyl having 3 to 8 ring carbon atoms, for example 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 Preferably C_3 C_8-cycloalkyl" is C_3-C_6-cycloalkyl When R^3 is amino substituted by C_3 C_8-cycloalkyl, C_3-C_8 cycloalkyl is preferably C_3-C_6-cycloalkyl, more especially cyclohexyl

"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 Preferably C_1 C_8 alkylamino and di(C_1 C_8 alkyl)amino are respectively C_1-C_4 alkylamino and di(C_1 C_4 alkyl)amino When R^3 is optionally substituted by C_1-C_8-alkylamino, C_1 C_8 alkylamino is preferably C_1-C_4-alkylamino, especially ethylamino or propylamino

"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 Preferably C_1 C_8-alkylcarbonyl and C_1 C_8 alkoxycarbonyl are C_1-C_4 alkylcarbonyl and C_1-C_4-alkoxycarbonyl respectively

"C_3 C_8 cycloalkylcarbonyl" as used herein denotes C_3-C_8 cycloalkyl as hereinbefore defined attached by a carbon atom to a carbonyl group Preferably C_3 C_8-cycloalkylcarbonyl is C_3-C_5-cycloalkylcarbonyl When R^1 is C_3 C_7 cycloalkylcarbonyl, it is preferably C_3-C_5-cycloalkyl-carbonyl, especially cyclopropylcarbonyl or cyclobutylcarbonyl

"C_3 C_8 cycloalkylamino" as used herein denotes C_3-C_8-cycloalkyl as hereinbefore defined attached by a carbon atom to the nitrogen atom of an amino group Preferably C_3 C_8-cycloalkylamino is C_3-C_5-cycloalkylamino

"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, for example, a monocyclic group such as phenyl or a bicyclic group such as naphthyl Preferably C_6-C_{10}-aryl is phenyl or naphthyl When R^2 is C_1-C_8-alkyl substituted by C_6 C_{10}-aryl, C_6 C_{10} aryl is preferably phenyl or naphthyl

"C_7 C_{14} aralkyl" as used herein denotes alkyl, for example C_1 C_4 alkyl as hereinbefore defined, substituted by C_6-C_{10} aryl as hereinbefore defined Preferably C_7-C_{14} aralkyl is C_7 C_{10}-aralkyl such as phenyl-C_1-C_4 alkyl, especially benzyl

"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 Preferably C_1-C_8 alkylaminocarbonyl and C_3-C_8 cycloalkyl aminocarbonyl are C_1 C_4-alkylaminocarbonyl and C_3 C_8 cycloalkylaminocarbonyl respectively When R^3 is C_1-C_8 alkylaminocarbonyl it is preferably C_1 C_3 alkylaminocarbonyl, especially propylaminocarbonyl

"C_6-C_{10} arylcarbonyl" and "C_7 C_{14} arylkylcarbonyl" as used herein denote C_6-C_{10}-aryl and C_7 C_{14} arylkyl respectively as hereinbefore defined attached by a carbon atom to a carbonyl group Preferably C_6-C_{10} arylcarbonyl and C_7-C_{14} arylkylcarbonyl are C_6-C_8 arylcarbonyl and C_7-C_{10} arylkylcarbonyl respectively When R^1 is C_7 C_{14} aralkylcarbonyl it is preferably C_7-C_{10} aralkylcarbonyl, especially benzylcarbonyl i e phenylacetamido

"5- or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur" as used herein may be, for example, 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 Preferred heterocyclic rings include piperazine, pyrrolidine, morpholino, imidazole, isotriazole, pyrazole, tetrazole, thiazole, thiadiazole, pyridine, piperidine, pyrazine, furan, oxazole, isoxazole, oxadiazole and azetidine The 5- or 6-membered heterocyclic ring can be unsubstituted or it can be substituted at one or more positions, preferably one or two positions, 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 at one or more positions, preferably one or two positions, by aminocarbonyl Especially preferred substituents include methyl, ethyl, d propyl) and amino When R^3 is C_1 C_8-alkylamino optionally substituted by R^5, R^5 is preferably unsubstituted imidazolyl, unsubstituted piperidinyl, or imidazolyl substituted at one position by C_1 C_3-alkyl When R^3 is R^6 optionally substituted by –NH C(=O)-NH R^7, R^6 is preferably pyrrolidinyl, piperidinyl or piperazinyl and, where relevant, R^7 is preferably unsubstituted thiophenyl, unsubstituted pyridinyl, unsubstituted pyrrolidinyl pyridinyl disubstituted by chloro, piperazinyl substituted

at one position by methyl, piperidinyl substituted at one position by pyridinyl, or piperidinyl substituted at one position by pyridinyl When R^3 is –NH R^6 optionally substituted –NH C(=O)-NH-R^7, R^6 is preferably unsubstituted pyrrolidinyl or R^6 is pyrrolidinyl substituted at one position by –NH-C(=O) NH-R^7 where R^7 is unsubstituted pyridinyl When R^3 is C_1 C_8-alkylaminocarbonyl substituted by -NH-C(=O) NH R^8, R^8 is preferably unsubstituted piperidinyl, piperidinyl substituted at one position by methylsulfonyl, piperidinyl substituted at one position by pyridinyl, or pyrrolidinyl substituted at one position by pyridinyl

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

Preferred compounds of formula I in free or salt form include those where
R^1 is C_1 C_8-alkylcarbonyl, C_3-C_8-cycloalkylcarbonyl, SO_2-C_1 C_8-alkyl, C_7-C_{14}-aralkylcarbonyl or C(=O)-C(=O)-NH C_1 C_8 alkyl optionally substituted by R^4,
R^2 is hydrogen or C_1-C_8 alkyl optionally substituted by C_6-C_{10} aryl,
R^3 is halo or C_2 C_8 alkynyl,
or R^3 is amino optionally substituted by C_3 C_8 cycloalkyl optionally substituted by amino,
or R^3 is C_1 C_8-alkylamino optionally substituted by hydroxy, C_6-C_{10}-aryl or by R^5,
or R^3 is R^6 optionally substituted by amino or –NH-C(=O)-NH R^7,
or R^3 is –NH R^6 optionally substituted –NH C(=O)-NH R^7,
or R^3 is C_1 C_8 alkylaminocarbonyl optionally substituted by NH-C(=O) NH R^8,
R^4, R^5 and R^6 are independently a 5 or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5 or 6 membered heterocyclic ring being optionally substituted by C_1 C_8-alkyl, and
R^7 and R^8 are independently a 5 or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5- or 6 membered heterocyclic ring being optionally substituted by halo, C_1-C_8-alkyl, C_1 C_8-alkyl sulfonyl, or a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur

Especially preferred compounds of formula I in free or salt form include those where
R^1 is C_1 C_4 alkylcarbonyl, C_3-C_5 cycloalkylcarbonyl, SO_2 C_1-C_4-alkyl, C_7 C_{10} aralkylcarbonyl or C(=O) C(=O)-NH C_1 C_4-alkyl optionally substituted at one position by R^4,

17

R^2 is hydrogen, unsubstituted C_1-C_6-alkyl or C_1-C_5-alkyl substituted at one position by C_6-C_{10}-aryl,
R^3 is halo or C_2-C_6 alkynyl,
or R^3 is amino optionally substituted at one position by C_3 C_6 cycloalkyl optionally substituted at one position by amino,
or R^3 is C_1-C_4 alkylamino substituted at one or two positions by hydroxy, phenyl or by R^5,
or R^3 is R^6 optionally substituted at one position by amino or –NH C(=O) NH-R^7,
or R^3 is –NH R^6 optionally substituted at one position by –NH C(=O)-NH R^7,
or R^3 is C_1 C_4 alkylaminocarbonyl substituted at one position by -NH-C(=O)-NH-R^8,
R^4, R^5 and R^6 are independently a 5 or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5 or 6 membered heterocyclic ring being optionally substituted at one position by C_1 C_4 alkyl, and
R^7 and R^8 are independently a 5- or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5- or 6 membered heterocyclic ring being optionally substituted at one or two positions by halo, C_1 C_4-alkyl, C_1-C_4-alkylsulfonyl, or a 5- or 6 membered N-heterocyclic ring

In a second aspect, the present invention provides compounds of formula I, in which
R^1 is hydrogen, C_1-C_8-alkylcarbonyl, C_3 C_8-cycloalkylcarbonyl, -SO_2 C_1 C_8 alkyl, C_7-C_{14}-aralkylcarbonyl or -C(=O)-C(=O) NH-C_1 C_8 alkyl optionally substituted by R^4,
R^2 is hydrogen or C_1 C_8-alkyl optionally substituted by C_6-C_{10}-aryl,
R^3 is hydrogen, halo, C_2 C_8-alkenyl or C_2 C_8 alkynyl,
or R^3 is amino optionally substituted by C_3-C_8 cycloalkyl optionally substituted by amino,
or R^3 is C_1-C_8 alkylamino optionally substituted by hydroxy, C_6-C_{10} aryl or by R^5,
or R^3 is R^6 optionally substituted by amino or –NH C(=O)-NH-R^7,
or R^3 is C_1-C_8 alkylaminocarbonyl or C_3 C_8-cycloalkylamino carbonyl optionally substituted by amino, C_1 C_8-alkylamino, di(C_1-C_8-alkyl)amino or -NH-C(=O)-NH R^8,
R^4, R^5 and R^6 are independently a 5 or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, and
R^7 and R^8 are independently a 5- or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5 or 6-membered heterocyclic ring being optionally substituted by a 5 or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur

Preferred compounds of formula I in free or salt form include those where

R^1 is C_1-C_8 alkylcarbonyl, C_3 C_8 cycloalkylcarbonyl, SO_2-C_1 C_8 alkyl, C_7 C_{14} aralkylcarbonyl or -C(=O) C(=O)-NH C_1 C_8 alkyl optionally substituted by R^4,

R^2 is hydrogen or C_1 C_8 alkyl optionally substituted by C_6 C_{10}-aryl,

R^3 is halo or C_2 C_8-alkynyl,

or R^3 is amino optionally substituted by C_3 C_8 cycloalkyl optionally substituted by amino,

or R^3 is C_1 C_8 alkylamino optionally ubstituted by hydroxy, C_6 C_{10} aryl or by R^5,

or R^3 is R^6 optionally substituted by amino or –NH-C(=O) NH R^7,

or R^3 is –NH R^6 optionally substituted –NH C(=O) NH-R^7,

or R^3 is C_1 C_8 alkylaminocarbonyl optionally substituted by -NH C(=O)-NH R^8,

R^4, R^5, and R^6 are independently a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, and

R^7 and R^8 are independently a 5 or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5- or 6-membered heterocyclic ring being optionally substituted by a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur

Especially preferred compounds of formula I in free or salt form include those where

R^1 is C_1 C_4-alkylcarbonyl, C_3-C_6-cycloalkylcarbonyl, SO_2-C_1 C_4 alkyl, C_7 C_{10} aralkylcarbonyl or C(=O) C(=O)-NH-C_1-C_4 alkyl optionally substituted at one position by R^4,

R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by C_6-C_{10}-aryl,

R^3 is halo or C_2 C_5-alkynyl,

or R^3 is amino optionally substituted by C_3-C_8-cycloalkyl optionally substituted by amino,

or R^3 is C_1 C_4 alkylamino optionally substituted by hydroxy, C_6 C_8-aryl or by R^5,

or R^3 is R^6 optionally substituted by amino or –NH-C(=O)-NH-R^7,

or R^3 is –NH-R^6 optionally substituted –NH-C(=O)-NH R^7,

or R^3 is C_1 C_4-alkylaminocarbonyl optionally substituted by -NH-C(=O) NH-R^8;

R^4, R^5, and R^6 are independently a 5 or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, and

R^7 and R^8 are independently a 5 or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5- or 6 membered heterocyclic ring being optionally substituted by a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur

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

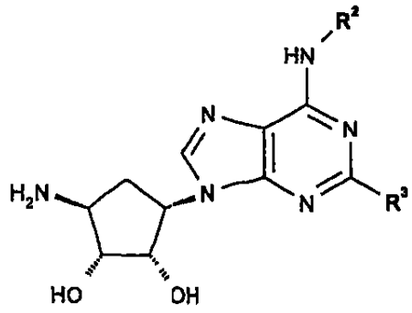
The compounds represented by formula I are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts Pharmaceutically acceptable acid addition salts of the compound of formula Ia include those of inorganic acids, for example, hydrohalic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid, and organic acids, for example aliphatic monocarboxylic acids such as formic acid, acetic acid, trifluoroacetic acid, propionic acid and butyric acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as maleic acid or succinic acid, aromatic carboxylic acids such as benzoic acid, p chlorobenzoic acid, diphenylacetic acid, *para* biphenyl benzoic acid or triphenylacetic acid, aromatic hydroxy acids such as o hydroxybenzoic acid, p hydroxybenzoic acid, 1 hydroxynaphthalene-2-carboxylic acid or 3-hydroxynaphthalene-2 carboxylic acid, cinnamic acids such as 3-(2 naphthalenyl)propenoic acid, *para*-methoxy cinnamic acid or *para*-methyl cinnamic acid, and sulfonic acids such as methanesulfonic acid or benzenesulfonic acid These salts may be prepared from compounds of formula I by known salt-forming procedures

Compounds of formula I which contain acidic, e g carboxyl, groups, are also capable of forming salts with bases, in particular pharmaceutically acceptable bases such as those well known in the art, suitable such salts include metal salts, particularly alkali metal or alkaline earth metal salts such as sodium, potassium, magnesium or calcium salts, or salts with ammonia or pharmaceutically acceptable organic amines or heterocyclic bases such as ethanolamines, benzylamines or pyridine These salts may be prepared from compounds of formula Ia by known salt forming procedures

In 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

The invention provides, in another aspect, a method of preparing a compound of formula Ia in free or salt form which comprises

(i) (A) for the preparation of compounds of formula I, reacting a compound of formula II

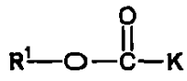


II

wherein R^2 and R^3 are as hereinbefore defined, with a compound of formula III

$$R^1—X^a \qquad \text{III}$$

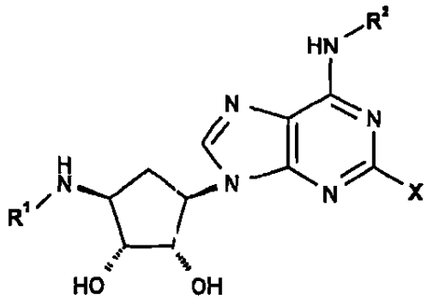
or a formula IIIa



IIIa

wherein R^1 is hydrogen, C_1-C_8 alkylcarbonyl, C_3-C_8 cycloalkylcarbonyl or C_7-C_{14}-aralkylcarbonyl, X^a is a leaving group and K is hydrogen, C_1-C_8-alkyl or C_1-C_8-alkoxy, in the presence of a base,

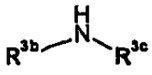
(B) for the preparation of compounds of formula I where R^3 is amino substituted by C_3-C_8 cycloalkyl optionally substituted by amino or R^3 is C_1-C_8 alkylamino optionally substituted by hydroxy, C_6-C_{10} aryl or by R^5, or R^3 is R^6 optionally substituted by amino or NH C(=O)-NH-R^7, reacting a compound of formula IV



IV

wherein R^1 and R^2 are as hereinbefore defined and X is halo, with a compound of formula Va or formula Vb

$$H_2N—R^{3a} \qquad \text{Va}$$

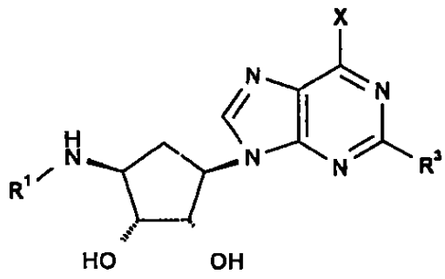


Vb

wherein R^{3a} is C_3-C_8 cycloalkyl optionally substituted by amino or R^3 is C_1-C_8 alkyl optionally substituted by hydroxy, C_6-C_{10}-aryl or by R^5, where R^5 is as hereinbefore defined,

and R^{3b} and R^{3c} together form a 5 or 6 membered heterocyclic ring that contains one or more nitrogen atoms and is optionally substituted amino or -NH C(=O)-NH-R^7, where R^7 is as hereinbefore defined,

(C) for the preparation of compounds of formula I, reacting a compound of formula VI



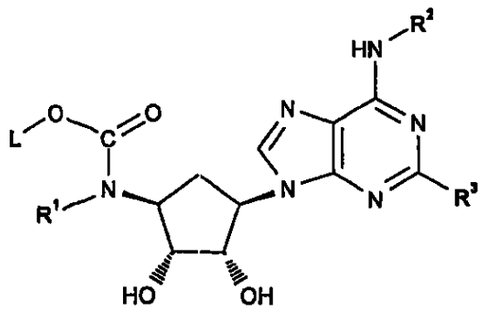
VI

wherein R^1 and R^3 are as hereinbefore defined and X is halo, with a compound of formula VII

$$H_2N—R^2 \qquad \text{VII}$$

wherein R^2 is as hereinbefore defined, in the presence of a base,

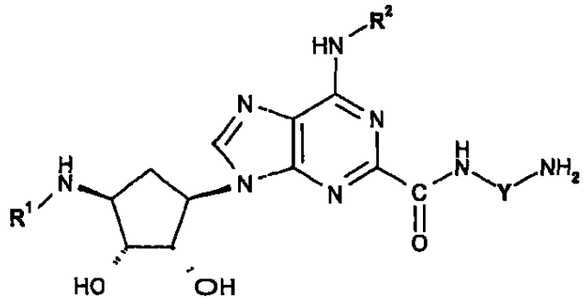
(D) for the preparation of compounds of formula I, deprotecting a compound of formula VIII



VIII

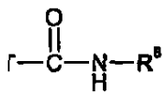
wherein R^1, R^2 and R^3 are as hereinbefore defined and L is C_1-C_8-alkyl,

(E) for the preparation of compounds of formula I wherein R^3 is C_1 C_8 alkylamino-carbonyl or C_3 C_8 cycloalkylaminocarbonyl substituted by NH-C(=O) NH-R^8, where R^8 is as hereinbefore defined, reacting a compound of formula IX



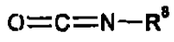
IX

wherein R^1 and R^2 are as hereinbefore defined and Y is C_1 C_8 alkyl or C_3-C_8 cycloalkyl in the presence of a base, with either a compound of formula X



X

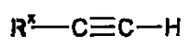
or a compound of formula XI



XI

wherein T is C_6 C_{10}-aryloxy or a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur and R^8 is as hereinbefore defined,

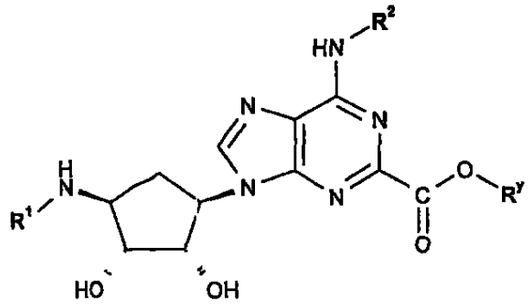
(F) for the preparation of compounds of formula I wherein R^3 is C_2 C_8-alkynyl, reacting a compound of formula IV where R^1 and R^2 are as hereinbefore defined, with a compound of formula XII



XII

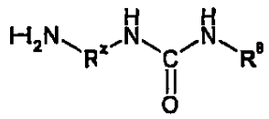
wherein R^x is C_1 C_8 alkyl, in the presence of a base and a catalyst,

(G) for the preparation of compounds of formula I wherein or R^3 is C_1-C_8-alkylaminocarbonyl optionally substituted -NH-C(=O)-NH-R^8, reacting a compound of formula XIIa



XIIa

wherein R^1 and R^2 are as hereinbefore defined and R^y is C_1 C_8-alkyl, optionally in the presence of a base, with a compound of formula XIIb

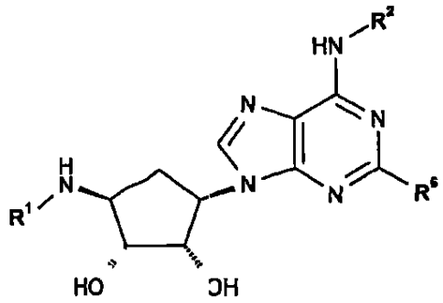


XIIb

wherein R^z is C_1 C_8 alkyl and -NH-C(=O) NH R^8 is as hereinbefore defined, or

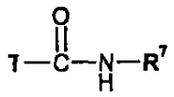
(H) for the preparation of compounds of formula I wherein R^3 is C_1-C_8 alkylamino-carbonyl substituted by -NH C(=O) NH R^8, where R^8 is a 5 or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, that ring being substituted by C_1 C_8 alkylsulfonyl, reacting a compound of formula I wherein R^3 is C_1 C_8 alkylamino-carbonyl substituted by -NH C(=O)-NH-R^8, where R^8 is a 5 or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur with a sulfonylating agent in the presence of a base,

(I) for the preparation of compounds of formula I wherein R^3 is R^6 substituted by – NH C(=O) NH R^7, where R^7 is as hereinbefore defined, reacting a compound of formula XIIc



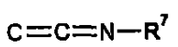
XIIc

where R^1 and R^2 are as hereinbefore defined and R^6 is a 5 or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, substituted at one position by amino, with either a compound of formula Xa



Xa

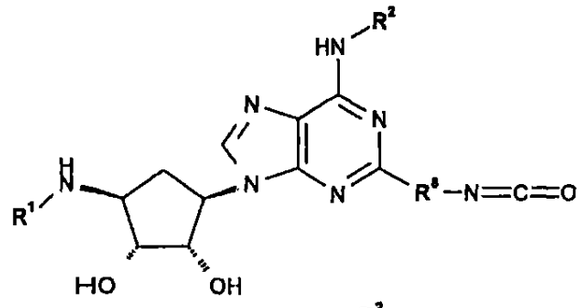
or a compound of formula XIa



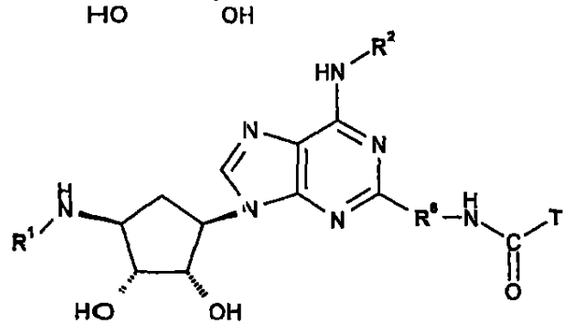
XIa

wherein T is C_6-C_{10}-aryloxy or a 5 or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur and R^1 is as hereinbefore defined,

(J) for the preparation of compounds of formula I wherein R^3 is R^6 substituted by NH C(=O)-NH-R^7, where R^7 is as hereinbefore defined, reacting a compound of formula XIId or XIIe or a protected form thereof

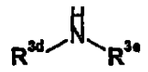


XIId



XIIe

where R^1, R^2 are R^6 are as hereinbefore defined and T is C_6 C_{10} aryloxy or a 5 or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, with a compound of formula XIIf



XIIf

and R^{3d} and R^{3e} together form a 5 or 6-membered N heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5 or 6-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, C_1-C_8-alkoxy optionally substituted by aminocarbonyl, or a 5 or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, or

(K) for the preparation of compounds of formula I wherein R^3 is R^6 substituted by

-NH-C(=O) NH-R^7, where R^7 is as hereinbefore defined, reacting a compound of formula XIId or XIIe, where R^1 R^2 are R^6 are as hereinbefore defined and T is C_6-C_{10} aryloxy or a 5 or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, with a compound of formula XIIg

$$H_2N—R^7 \qquad \text{XIIg}$$

where R^7 is as hereinbefore defined, and

(ii) removing any protecting groups and recovering the resultant compound of formula Ia in free or salt form

Process variant (A) may be carried out using known procedures for reacting amines with acid halides, acid anhydrides or mixed anhydrides e g carboxylic and carbonic anhydrides (or amide forming derivatives thereof such as carboxylic acids) or sulfonyl halides e g mesyl halides, or analogously as hereinafter described in the Examples The leaving group may be any suitable leaving group, for example halo, SO_2-C_1 C_8 alkyl or SO_2-C_6 C_{10}-aryl The reaction is conveniently carried out using an organic solvent, for example tetrahydrofuran (THF), in the presence of a base, for example diisopropylethylamine (DIPEA) Suitable reaction temperatures are from 10° C to 40° C, preferably room temperature

Process variant (B) may be carried out using known procedures for reacting halides, especially aromatic halides, with amines, or analogously as hereinafter described in the Examples The reaction is conveniently carried out using an organic solvent, for example dichlorobenzene, dimethylsulfoxide, acetonitrile or N methyl-pyrrolidone (NMP) or mixtures thereof optionally in the presence of a catalyst, such as sodium iodide, and a base, such as triethylamine Suitable reaction temperatures are from 100° C to 250° C, preferably between 120° C to 220° C, especially about 170° C, for example by heating with microwave radiation

Process variant (C) may be carried out using known procedures for reacting halides with amines, or analogously as hereinafter described in the Examples The reaction is conveniently carried out using an organic solvent, for example tetrahydrofuran, preferably in an inert atmosphere, for example argon, optionally in the presence of a base, for example diisopropyl ethylamine Suitable reaction temperatures from 0° C to 70° C, preferably between 40° C to 60° C, especially about 50° C

Process variant (D) may be carried out using known procedures for cleaving ester bonds, for example using a strong organic acid, such as trifluoroacetic acid The reaction is conveniently carried out using an organic solvent, for example dichloromethane (DCM) Suitable reaction temperatures are from 0° C to 40° C, preferably room temperature

Process variant (E) may be carried out using known procedures for reacting amines with acyl-imidazoles or isocyanates, or analogously as hereinafter described in the Examples T in formula X is preferably imidazolyl The reaction is conveniently carried out using an organic solvent, for example toluene and/or isopropyl alcohol Suitable reaction temperatures are from 0° C to 40° C, preferably room temperature

Process variant (F) may be carried out using known procedures for reacting halides with alkynes, or analogously as hereinafter described in the Examples The catalyst is preferably a palladium catalyst (together with a CuI salt) and the base is preferably butylamine The reaction is conveniently carried out using an organic solvent, such as dimethylformamide (DMF) Suitable reaction temperature are from 40° C to 200° C, preferably 80° C to 160° C, especially about 120° C

Process variant (G) may be carried out using known procedures for reacting carboxylic acid alkyl esters with amines, or analogously as hereinafter described in the Examples The base is preferably is preferably imidazole The reaction is conveniently carried out using an organic solvent, such 1,2-dichloroethane, iso propanol or a mixture thereof Suitable reaction temperatures are from room temperature to 250° C, preferably 50° C to 100° C

Process variant (H) may be carried out using known procedures for sulfonylating heterocycles, or analogously as hereinafter described in the Examples The sulphonylating agent is preferably an alkylsulfonylhalide, for example mesylchloride The base is preferably triethylamine The reaction is conveniently carried out using an organic solvent, such as dimethylformamide (DMF), preferably in an inert atmosphere Suitable reaction temperatures are from 0° C to 40° C, preferably room temperature

Process variant (I) may be carried out using known procedures for reacting amines with acyl imidazoles, isocyanates or arylcarbamates, or analogously as hereinafter described in the Examples T in formula X is preferably imidazolyl The reaction is conveniently carried out using an organic solvent, for example tetrahydrofuran or N-methyl-pyrrolidone (NMP), preferably in the presence of a base, for example triethylamine When the amine is reacted

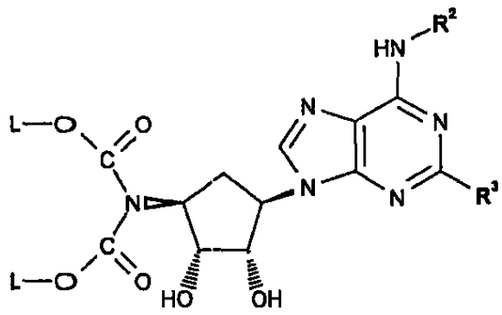
with an acyl-imidazole or an isocyanates suitable reaction temperatures are from 0° C to 40° C, preferably room temperature When the amine is reacted with an arylcarbamate, for example phenyl carbamate, suitable reaction temperatures are from room temperature to 120° C, preferably 80° C to 110° C, especially about 110° C

Process variant (J) may be carried out using known procedures for reacting N-heterocycles with acyl-imidazoles, isocyanates or arylcarbamates, or analogously as hereinafter described in the Examples T in formula XIIe is preferably imidazolyl The reaction is conveniently carried out using an organic solvent, for example tetrahydrofuran or N methyl-pyrrolidone (NMP) When the N heterocycle is reacted with an acyl imidazole or an isocyanates suitable reaction temperatures are from 0° C to 40° C, preferably room temperature When the N heterocycle is reacted with an arylcarbamate, for example phenyl carbamate, suitable reaction temperatures are from room temperature to 120° C, preferably 80° C to 110° C, especially about 110° C

Process variant (K) may be carried out using known procedures for reacting amines with acyl imidazoles, isocyanates or arylcarbamates, or analogously as hereinafter described in the Examples The reaction is conveniently carried out using an organic solvent, for example tetrahydrofuran When the amine is reacted with an acyl-imidazole or an isocyanates suitable reaction temperatures are from 0° C to 40° C, preferably room temperature. When the amine is reacted with an arylcarbamate, for example phenyl carbamate, suitable reaction temperatures are from room temperature to 120° C, preferably 80° C to 110° C, especially about 110° C

Where reference is made herein to protected functional groups or to protecting groups, the protecting groups may be chosen in accordance with the nature of the functional group, for example as described in Protective Groups in Organic Synthesis, T W Greene and P G M Wuts, John Wiley & Sons Inc, Third Edition, 1999, which reference also describes procedures suitable for replacement of the protecting groups by hydrogen

Compounds of formula II may be prepared by deprotecting a compound of formula XIII



XIII

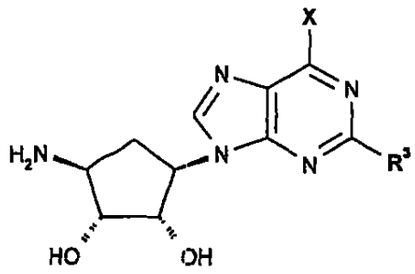
where R^2 and R^3 are as hereinbefore defined, and each L is C_1-C_8-alkyl, using known procedures for cleaving ester bonds, or analogously as herein described in the Examples. Preferably the reaction is carried out using a strong organic acid, such as trifluoroacetic acid. Each L is preferably t-butyl. The reaction is conveniently carried out using an organic solvent, for example dichloromethane. Suitable reaction temperatures from 0° C to 40° C, preferably room temperature.

Compounds of formula III or IIIa are commercially available or may be obtained by known procedures for preparing such compounds, or analogously as herein described in the Examples.

Compounds of formula IV may be prepared by reacting a compound of formula II where R^3 is halo, with a compound of formula III or IIIa wherein R^1 is as hereinbefore defined, X is a leaving group, preferably halo, and K is hydrogen or C_1-C_8-alkyl, in the presence of a base, or analogously as herein described in the Examples. The reaction is conveniently carried out using an organic solvent, for example tetrahydrofuran. The base is preferably diisopropylethylamine. Suitable reaction temperatures from 0° C to 40° C, preferably room temperature.

Compounds of formula Va or formula Vb are either commercially available or may be obtained by known procedures for preparing such compounds, or analogously as herein described in the Examples.

Compounds of formula VI may be prepared by reacting a compound of formula XIV

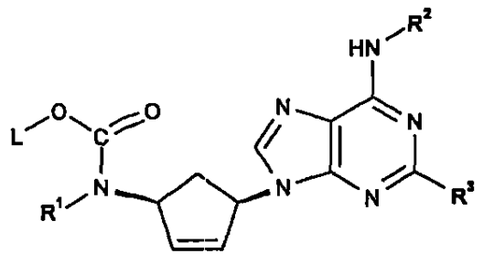


XIV

where R^3 is as hereinbefore defined and X is halo, with a compound of formula III or IIIa, wherein R^1 is as hereinbefore defined, X is a leaving group, preferably halo, and K is hydrogen or C_1 C_8-alkyl, in the presence of a base, wherein R^1 is as hereinbefore defined and X is halo, or analogously as herein described in the Examples The reaction is conveniently carried out using an organic solvent, for example tetrahydrofuran, preferably in the presence of a base, for example diisopropylethylamine Suitable reaction temperatures from 0° C to 40° C, preferably room temperature

Compounds of formula VII are either commercially available or may be obtained by known procedures for preparing such compounds, or analogously as herein described in the Examples

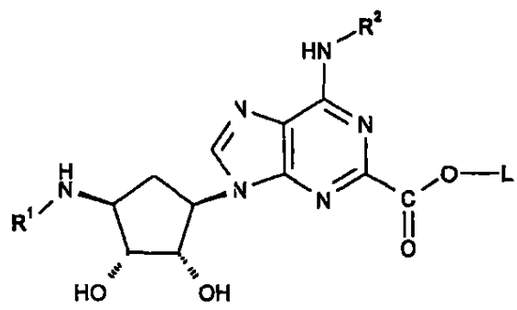
Compounds of formula VIII may be prepared by reacting a compound of formula XV



XV

where R^1, R^2 and R^3 are as hereinbefore defined and L is C_1-C_8 alkyl, with a dihydroxylating agent, such as osmium tetroxide (OsO_4), either in a stoichiometrical amount or a catalytic amount, preferably together with a re oxidant, such as N-methylmorpholine N-oxide (NMO), or alternatively using AD mix-α or AD mix β, or analogously as herein described in the Examples L is preferably t butyl The reaction is conveniently carried out using an organic solvent, for example THF Suitable reaction temperatures from 0° C to 40° C, preferably room temperature

Compounds of formula IX may be prepared by reacting a compound of formula XVI



XVI

where R^1 and R^2 are as hereinbefore de ined and L is C_1-C_8-alkyl, is reacted with a compound of formula XVII



XVII

wherein Y is C_1 C_8 alkyl or C_3-C_8 cyclcalkyl, or analogously as herein described in the Examples Suitable reaction temperatures from 80° C to 130° C, preferably 90° C to 120° C room temperature, especially about 10?° C

Compounds of formula X, Xa, XI or XIa are commercially available or may be obtained by known procedures for preparing such compounds, or analogo usly as herein described in the Examples

Compounds of formula XII are commercially available or may be obtained by known procedures for preparing such compounds, or analogously as herein described in the Examples

Compounds of formula XIIa may be prepared using the process described herein for preparing compounds of formula XVI, or analogously as herein described in the Examples

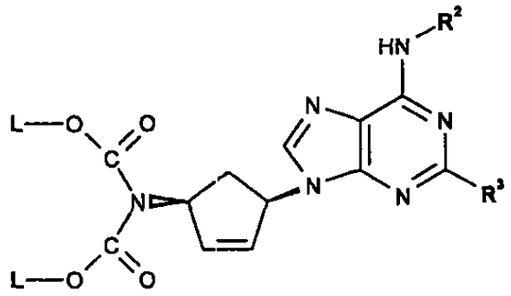
Compounds of formula XIIb are commercially available or may be obtained by known procedures for preparing such compounds, or analogously as herein described in the Examples

Compounds of formula XIIc may be prepared using a process described herein for preparing compounds of formula I when R^3 is R^6, or analogously as herein described in the Examples

Compounds of formula XIId or XIIe may be prepared by reacting a compound of formula I where R^3 is R^6 substituted by amino, with a suitable acylating agent, or analogously as herein described in the Examples

Compounds of formula XIIf of XIIg are commercially available or may be obtained by known procedures for preparing such compounds, or analogously as herein described in the Examples

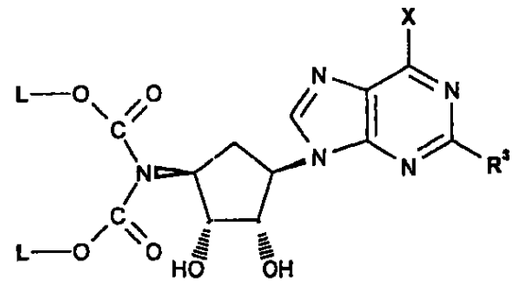
Compounds of formula XIII may be prepared by reacting a compound of formula XVIII



XVIII

where R^2 and R^3 are as hereinbefore defined, and each L is C_1 C_8-alkyl or benzyl, with a hydroxylating agent, such as osmium tetroxide (OsO_4), either in a stoichiometrical amount or a catalytic amount, preferably together with a re oxidant, such as N-methylmorpholine N-oxide (NMO), or alternatively using AD mix α or AD mix β, or analogously as herein described in the Examples L^1 and L^2 are preferably t-butyl The reaction is conveniently carried out using an organic solvent, for example tetrahydrofuran Suitable reaction temperatures from 0° C to 40° C, preferably room temperature

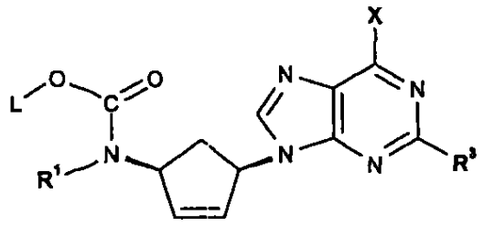
Compounds of formula XIV may be prepared by reacting a compound of formula XIX



XIX

where R^3 and X are as hereinbefore defined, and each L is C_1 C_8-alkyl or benzyl, with a strong organic acid, such as trifluoroacetic acid, or analogously as herein described in the Examples Each L is preferably t-butyl The reaction is conveniently carried out using an organic solvent, for example dichloromethane Suitable reaction temperatures from 0° C to 40° C, preferably room temperature

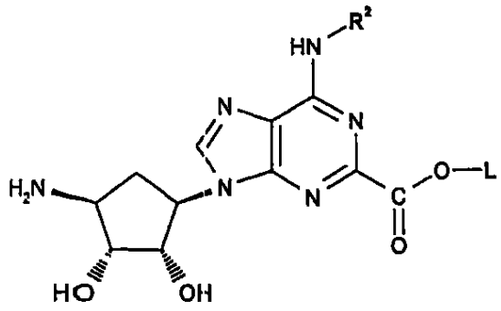
Compounds of formula XV may be prepared by reacting a compound of formula XX



XX

where R^3 is as hereinbefore defined, X is halo and L is C_1-C_8 alkyl or benzyl, with a compound of formula VII, wherein R^2 is as hereinbefore defined, or analogously as herein described in the Examples The reaction is conveniently carried out using an organic solvent, for example tetrahydrofuran, preferably in an inert atmosphere, for example in argon Suitable reaction temperatures from 30° C to 70° C, preferably from 40° C to 60° C, especially about 50° C

Compounds of XVI may be prepared by reacting a compound of formula XXI

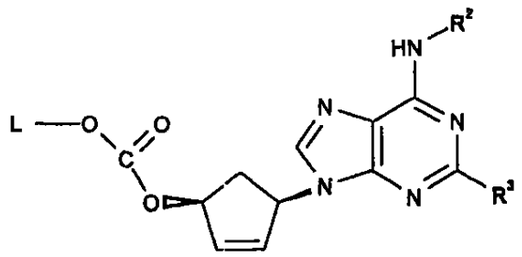


XXI

where R^2 is as hereinbefore defined and L' is C_1-C_8 alkyl or benzyl but preferably methyl, with a compound of formula III or IIIa, wherein R^1 is as hereinbefore defined, X is a leaving group, preferably halo, and K is hydrogen or C_1 C_8 alkyl, or analogously as herein described in the Examples The reaction is conveniently carried out using an organic solvent, for example tetrahydrofuran, preferably in the presence of a base, for example diisopropylethylamine Suitable reaction temperatures from 0° C to 40° C, preferably room temperature

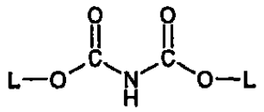
Compounds of formula XVII are commercially available or may be obtained by known procedures for preparing such compounds, or analogously as herein described in the Examples

Compounds of formula XVIII may be prepared by reacting a compound of formula XXII



XXII

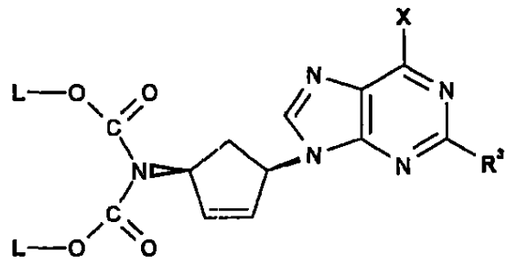
where R^2 and R^3 are as hereinbefore defined, and L'' is C_1 C_8-alkyl preferably methyl or ethyl, with a compound of formula XXIII



XXIII

where each L is C_1 C_8 alkyl or benzyl, preferably benzyl, and preferably in the presence of a catalyst, such as that generated from tetrakis(triphenylphosphine)palladium and triphenylphosphine, or analogously as herein described in the Examples Preferably each L is t butyl or benzyl The reaction is conveniently carried out in an inert environment, for example in argon, using an organic solvent, for example deoxygenated tetrahydrofuran Suitable reaction temperatures from 0° C to 40° C, preferably room temperature

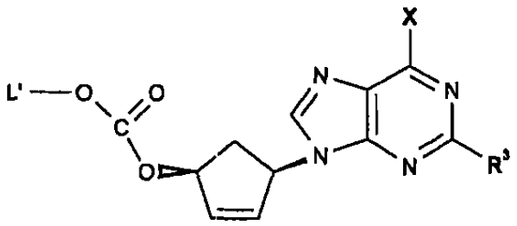
Compounds of formula XIX may be prepared by reacting a compound of formula XXIV



XXIV

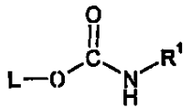
where R^3 and X are as hereinbefore defined, and each L is C_1-C_8 alkyl or benzyl, with a hydroxylating agent, such as osmium tetroxide (OsO_4), either in a stoichiometrical amount or a catalytic amount, preferably together with a re-oxidant, such as N-methylmorpholine N oxide (NMO), or alternatively using AD-mix α or AD-mix-β, or analogously as herein described in the Examples Each L is preferably t-butyl The reaction is conveniently carried out using an organic solvent, for example tetrahydrofuran Suitable reaction temperatures from 0° C to 40° C, preferably room temperature

Compounds of formula XX may be prepared by reacting a compound of formula XXV



XXV

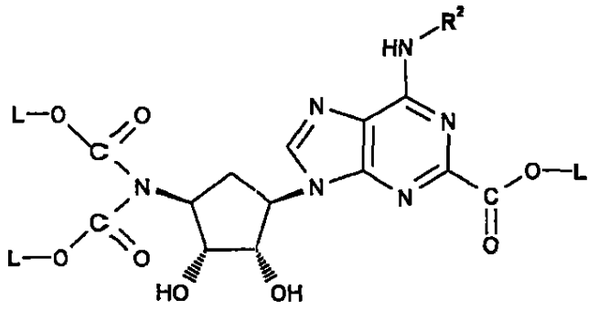
where R^3 is as hereinbefore defined, and L'' is C_1-C_8-alkyl, with a compound of formula XXVa



XXVa

where R^1 is as hereinbefore defined, and L is C_1-C_8-alkyl or benzyl, preferably in the presence of a catalyst, such as that generated from tetrakis(triphenyl-phosphine)palladium and triphenylphosphine, or analogously as herein described in the Examples Preferably L is t-butyl or benzyl The reaction is conveniently carried out in an inert environment, for example in argon, using an organic solvent, for example deoxygenated tetrahydrofuran Suitable reaction temperatures from 0° C to 40° C, preferably room temperature

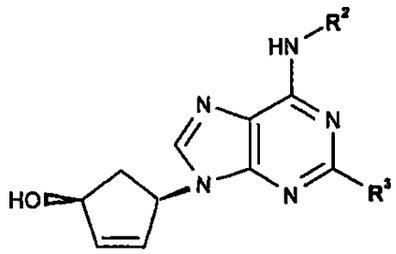
Compounds of XXI may be prepared by reacting a compound of formula XXVI



XXVI

where R^2 is as hereinbefore defined, each L is C_1-C_8-alkyl or benzyl and L' is C_1-C_4-alkyl, is reacted with a strong acid, for example hydrochloric acid using known procedures for cleaving esters bonds, or analogously as herein described in the Examples Preferably each L is t-butyl or benzyl and L' is methyl or ethyl The reaction is conveniently carried out in an inert environment, for example in argon, using an organic solvent, for example dioxane Suitable reaction temperatures from 0° C to 40° C, preferably room temperature

Compounds of formula XXII may be prepared by reacting a compound of formula XXVII

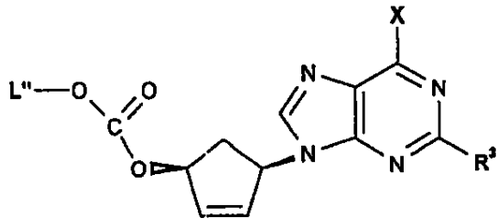


XXVII

where R^2 and R^3 are as hereinbefore defined, with an acylating agent such as a carboxylic acid C_1 C_8 alkyl ester, for example 3-oxy benzotriazole 1 carboxlic acid ethyl ester, in the presence of a base, such as diisoproplylamine, and a catalyst, such as 4-dimethylaminopyridine (DMAP), or analogously as herein described in the Examples The reaction is conveniently carried out in an inert environment, for example in argon, using an organic solvent, for example deoxygenated THF Suitable reaction temperatures from 0° C to 40° C, preferably room temperature

Compounds of formula XXIII are commercially available or may be obtained by known procedures for preparing such compounds, or analogously as herein described in the Examples

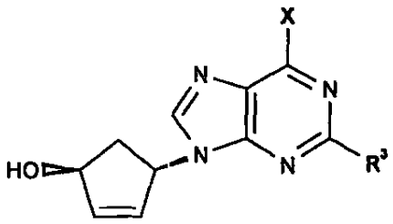
Compounds of formula XXIV may be prepared by reacting a compound of formula XXVIII



XXVIII

where R^3 and X are as hereinbefore defined, and L'' is C_1 C_8 alkyl, with a compound of formula XXIII where each L is C_1-C_8 alkyl or benzyl, preferably in the presence of a catalyst, such as that generated from tetrakis(triphenylphosphine)palladium and triphenylphosphine, or analogously as herein described in the Examples Preferably each L is t-butyl or benzyl The reaction is conveniently carried out in an inert environment, for example in argon, using an organic solvent, for example deoxygenated tetrahydrofuran Suitable reaction temperatures from 0° C to 40° C, preferably room temperature

Compounds of formula XXV may be prepared by reacting a compound of formula XXIX

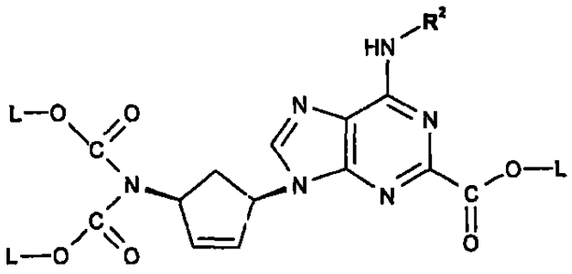


XXIX

where R^3 and X are as hereinbefore def ned, with an acylating agent such as a carboxylic acid C_1 C_8-alkyl ester, for example 3 oxy-benzotriazole 1 carboxlic acid ethyl ester, in the presence of a base, such as diisoproplylamine, ar d a catalyst, such as 4 dimethylaminopyridine (DMAP), or analogously as herein desc ibed in the Examples The reaction is conveniently carried out in an inert environment, for example in argon, using an organic solvent, for example deoxygenated tetrahydrofuran Suitable reaction temperatures from 0° C to 40° C, preferably room temperature

Compounds of formula XXVa are commercially available or may be obtained by known procedures for preparing such compounds, for example as described by Ken ichi Takana et al in *Chem Pharm Bull* 1988, 36, 3125, or analogously as herein described in the Examples

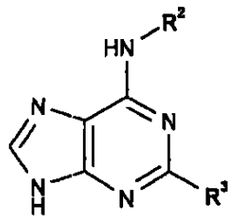
Compounds of XXVI may be prepared by reacting a compound of formula XXX



XXX

where R^2 is as hereinbefore defined, each L is C_1-C_8-alkyl and L' is C_1-C_4-alkyl or benzyl, preferably benzyl, is reacted with a hydroxylating agent, such as osmium tetroxide (OsO_4), either in a stoichiometrical amount or a catalytic amount, preferably together with a re-oxidant, such as N methylmorpholine N-oxide (NMO), or alternatively using AD mix-α or AD-mix β, or analogously as herein described in the Examples Preferably each L is t-butyl and L' is methyl or ethyl The reaction is conveniently carried out using an organic solvent, for example tetrahydrofuran Suitable reaction temperatures from 0° C to 40° C, preferably room temperature

Compounds of formula XXVII may be prepared by reacting a compound of formula XXXI

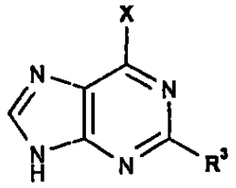


XXXI

where R^2 and R^3 are as hereinbefore defined, with (1S,4R) cis 4 acetoxy-2–cyclopenten-1 ol in the presence of a base, such as sodium hydride, and a catalyst, such as that generated from tetrakis(triphenylphosphine)palladium and triphenylphosphine, or analogously as herein described in the Examples The reaction is conveniently carried out in an inert environment, for example in argon, using an organic solvent, for example deoxygenated tetrahydrofuran or dimethylsulfoxide (DMSO) Suitable reaction temperatures from 40° C to 60° C, preferably about 50° C

Compounds of formula XXVIII may be prepared by reacting a compound of formula XXIX where R^3 and X are as hereinbefore defined, with an acylating agent such as a carboxylic acid C_1-C_8 alkyl ester, for example 3 oxy benzotriazole 1 carboxlic acid ethyl ester, in the presence of a base, such as diisoproplylamine, and a catalyst, such as 4 dimethylaminopyridine (DMAP), or analogously as herein described in the Examples The reaction is conveniently carried out in an inert environment, for example in argon, using an organic solvent, for example THF Suitable reaction temperatures from 0° C to 40° C, preferably room temperature

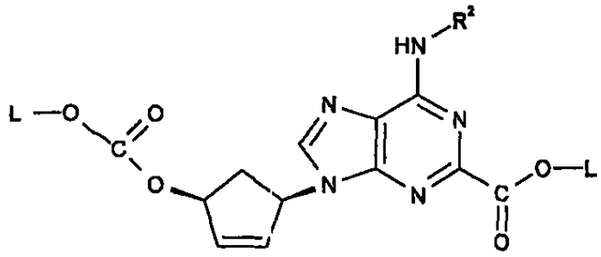
Compounds of formula XXIX may be prepared by reacting a compound of formula XXXII



XXXII

where R^3 and X are as hereinbefore defined, with (1S,4R)-cis 4 Acetoxy-2–cyclopenten 1-ol in the presence of a base, such sodium hydride, and a catalyst, such as that generated from tetrakis(triphenylphosphine)palladium and triphenylphosphine, or analogously as herein described in the Examples The reaction is conveniently carried out in an inert environment, for example in argon, using an organic solvent, for example deoxygenated tetrahydrofuran or dimethylsulfoxide (DMSO) Suitable reaction temperatures from 40° C to 60° C, preferably about 50° C

Compounds of formula XXX may be prepared by reacting a compound of formula XXXIII



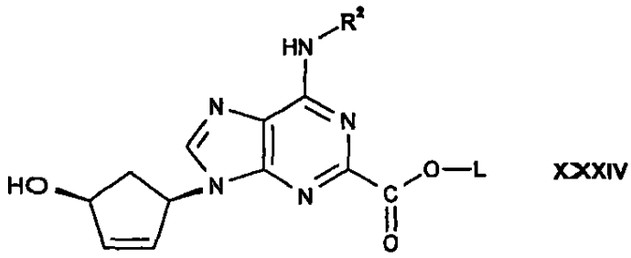
XXXIII

where R^2 is as hereinbefore defined, L'' is C_1-C_8 alkyl or benzyl, and L' is C_1-C_4-alkyl, with a compound of formula XXIII where each L is C_1-C_8 alkyl, preferably in the presence of a catalyst, such as that generated from tetrakis(triphenylphosphine)palladium and triphenylphosphine, or analogously as herein described in the Examples Preferably each L'' is t-butyl or benzyl and L' is methyl or ethyl The reaction is conveniently carried out in an inert environment, for example in argon, using an organic solvent, for example deoxygenated tetrahydrofuran Suitable reaction temperatures from 0° C to 40° C, preferably room temperature

Compounds of formula XXXI may be prepared by reacting a compound of formula XXXII where R^3 is as hereinbefore defined and X is halo, with a compound of formula VII where R^2 is as hereinbefore defined, or analogously as herein described in the Examples The reaction is conveniently carried out in an inert environment, for example in argon, using an organic solvent, for example tetrahydrofuran Suitable reaction temperatures from 40° C to 60° C, preferably about 50° C

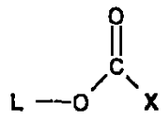
Compounds of formula XXXII are commercially available or may be obtained by known procedures for preparing such compounds, or analogously as herein described in the Examples

Compounds of formula XXXIII may be prepared by reacting a compound of formula XXXIV



XXXIV

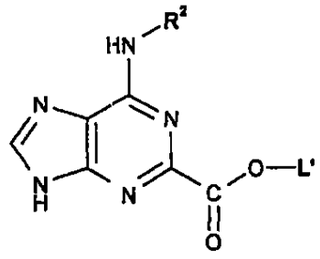
where R^2 and L' are as hereinbefore defined, with a compound of formula XXXV



XXXV

where L'' is C_1 C_8-alkyl, preferably methyl or ethyl, and X is halo, preferably chloro, or analogously as herein described in the Examples The reaction is conveniently carried out in an inert environment, for example in argon, using an organic solvent, for example deoxygenated tetrahydrofuran, preferably in the presence of a base, for example pyridine Suitable reaction temperatures from 0° C to 40° C, preferably room temperature

Compounds of formula XXXIV may be prepared by reacting a compound of formula XXXVI



XXXVI

where R^2 is as hereinbefore defined and L' is C_1 C_4 alkyl, preferably methyl or ethyl, with (1S,4R) cis 4-acetoxy-2-cyclopenten-1 ol in the presence of a base, such sodium hydride, and a catalyst, such as that generated from tetrakis(triphenylphosphine)palladium and triphenylphosphine, or analogously as herein described in the Examples The reaction is conveniently carried out in an inert environment, for example in argon, using an organic solvent, for example deoxygenated tetrahydrofuran or dimethyl sulfoxide Suitable reaction temperatures from 60° C to 100° C, preferably about 80° C

Compounds of formula XXXV are commercially available or may be obtained by known procedures for preparing such compounds, or analogously as herein described in the Examples

Compounds of formula XXXVI may be prepared by reacting a salt compound of formula XXXVI where R^3 is as hereinbefore defined and L is C_1-C_8-alkyl, with a silating agent, for example (N,O bis(trimethylsilyl)acetamide), or analogously as herein described in the Examples The reaction is conveniently carried out in an inert environment, for example in argon, using an organic solvent, for example dry chloroform Suitable reaction temperatures from 60° C to 100° C, preferably about 80° C The silylated intermediate thus formed is treated with methanol to give the free base

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 crystallisation 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 crystallisation 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 *Molecular Pharmacology* 61, 455-462 (2002)

Compounds of the Examples hereinbelow have K_i values below 1 0 µM in the above assay For example, the compounds of Examples 1, 2, 4, 6, 12, 14, 20, 33, 38, 39, 42, 47, 55 and 61 have K_i values of 0 582, 0 018, 0 057 0 008, 0 003, 0 690, 0 008, 0 052, 0 002, 0 003, 0 002, 0 002, 0 004 and 0 009 µM 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, for example, 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, for example, 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, for example 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 recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised 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 hyper-eosinophilia as it effects the airways and/or lungs as well as, for example, eosinophil-related disorders of the airways consequential or concomitant to Loffler'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, for example 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, for example, 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 gavis, 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 minial change nephropathy)
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

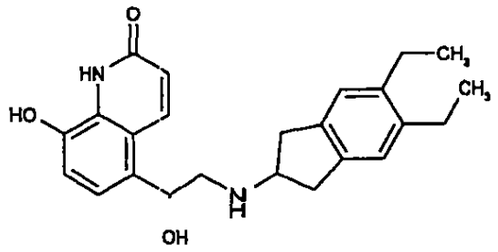
The effectiveness of an agent of the invention in inhibiting inflammatory conditions, for example in inflammatory airways diseases, may be demonstrated in an animal model, e g a mouse or rat model, of airways inflammation or other inflammatory conditions, for example as described by Szarka et al, *J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

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, ciclesonide 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 agonists, 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 such include montelukast, pranlukast, zafirlukast, accolate, SR2640, Wy-48,252, ICI 198615, MK-571, LY-171883, Ro 24-5913 and L-648051, PDE4 inhibitors such 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 adrenocepto 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 02/66412, WO 02/ 70490, WO 02/76933, WO 03/24439, WO 03/42160, WO 03/42164, WO 03/72509, 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 05/013121, 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)-5H benzo cyclohepten-8-yl]carbonyl]amino]phenyl] methyl]tetrahydro-N,N dimethyl-2H-pyran-4 aminium 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, for example 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, for example in the form of a tablet or capsule, parenterally, for example intravenously, by inhalation, for example in the treatment of inflammatory or obstructive airways disease, intranasally, for example in the treatment of allergic rhinitis, topically to the skin, for example in the treatment of atopic dermatitis, or rectally, for example in the treatment of inflammatory bowel disease

In a further aspect, the invention also provides a pharmaceutical composition comprising a compound 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, for example, a hydro fluoro-alkane (HFA) propellan 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, for example, the compound 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, for example, 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 stabiliser, which may be a surfactant

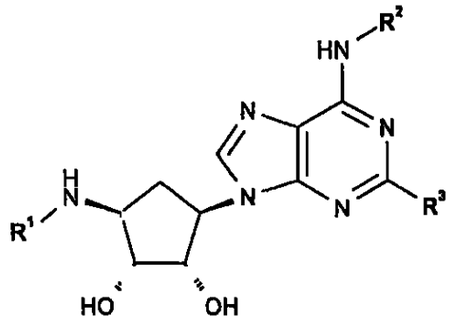
The invention includes (A) a compound of formula I in inhalable form, e g in an aerosol or other atomisable composition or in inhalable particulate, e g micronised, form, (B) an inhalable medicament comprising a compound of formula I in inhalable form, (C) a pharmaceutical product comprising a compound of formula I in inhalable form in association with an inhalation device, and (D) an inhalation device containing a compound of formula I in inhalable form

Dosages of compounds of formula I employed in practising the present invention will of course vary depending, for example, 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 to 10 mg, while for oral administration suitable daily doses are of the order of 0 05 to 100 mg

The invention is illustrated by the following examples

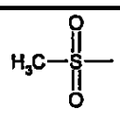
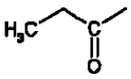
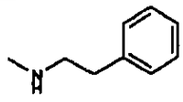
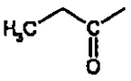
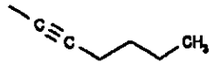
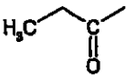
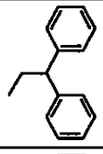
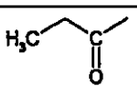
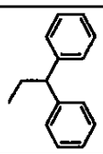
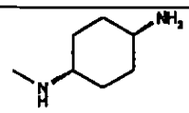
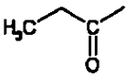
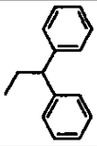
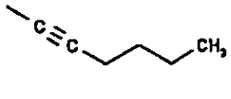
EXAMPLES

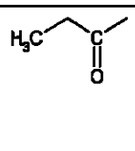
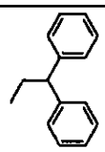
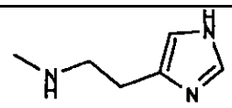
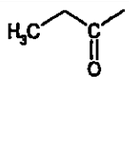
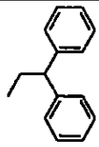
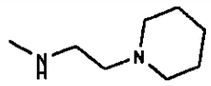
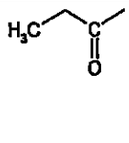
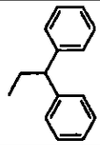
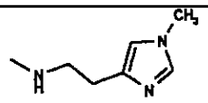
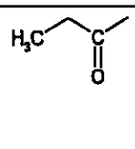
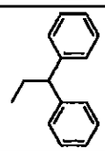
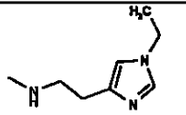
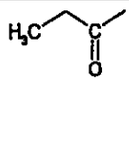
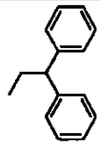
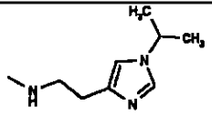
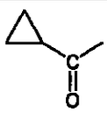
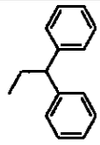
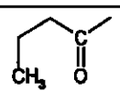
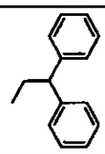
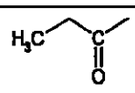
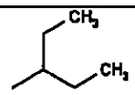
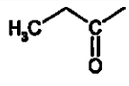
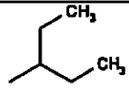
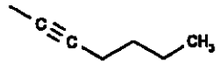
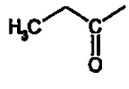
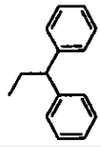
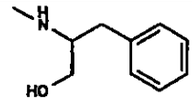
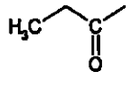
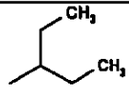
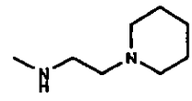
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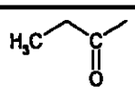
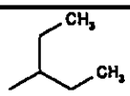
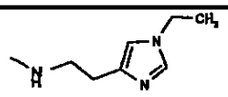
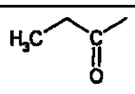
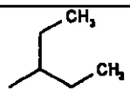
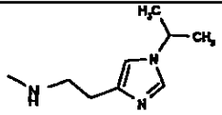
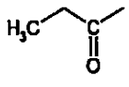
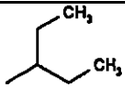
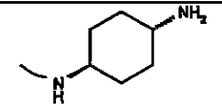
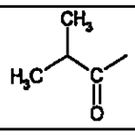
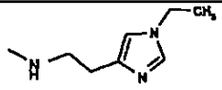
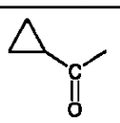
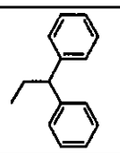
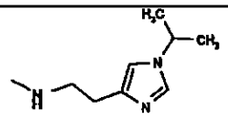
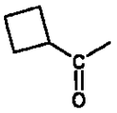
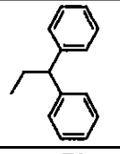
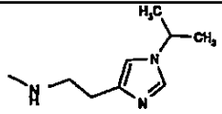
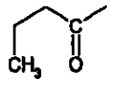
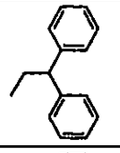
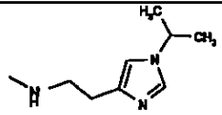
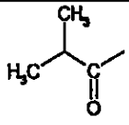
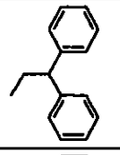
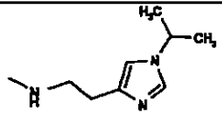
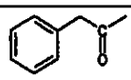
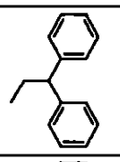
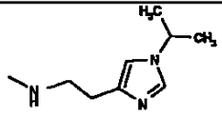
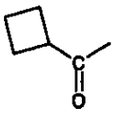
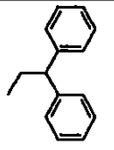
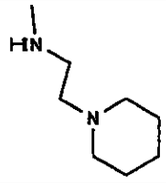
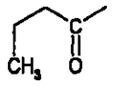
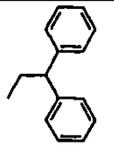
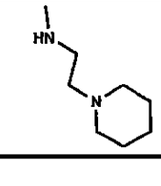


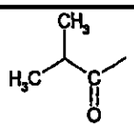
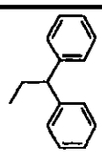
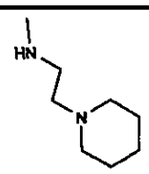
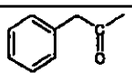
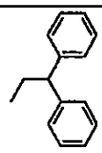
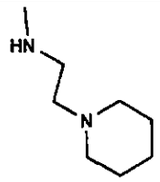
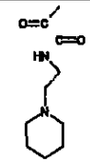
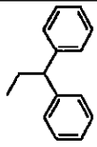
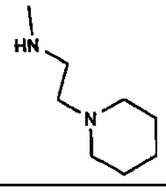
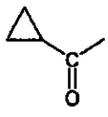
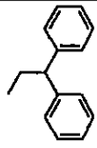
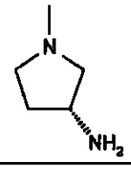
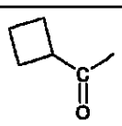
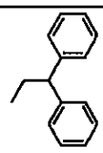
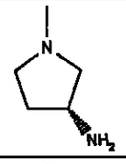
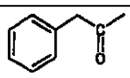
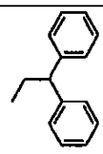
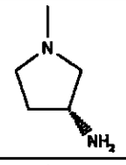
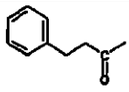
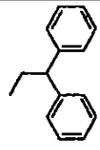
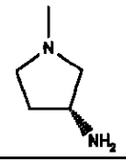
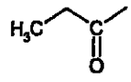
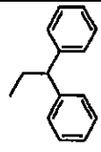
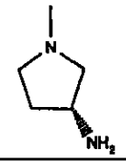
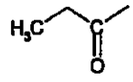
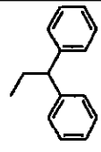
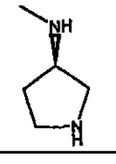
include those shown in Table 1 below Methods for preparing such compounds are described hereinafter The table also shows mass spectrometry, MH^+ (ESMS), data The Examples are in free form, except for Examples 1-3, 7, 9 11 and 17 37, which are trifluoroacetate salts

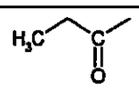
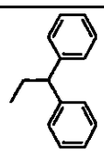
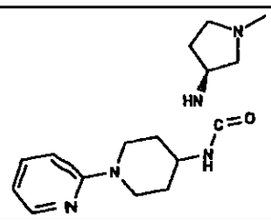
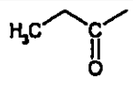
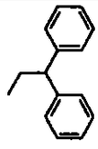
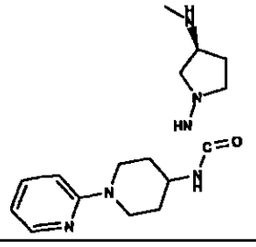
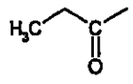
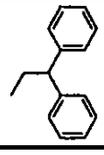
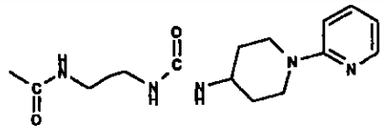
TABLE 1

Ex	R^1	R^2	R^3	MH+ or MH+/2
1		H	Cl	363 10
2		-H		426 27
3		H		387 25
4			Cl	521 30
5				599 28 599 41
6				567 24

7				596 36
8				613 42 613 43
9				610 35
10				624 38
11				638 39
12			-Cl	533 25
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14			Cl	411 21
15				457 30
16				636 37
17				503 34

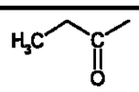
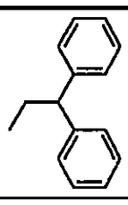
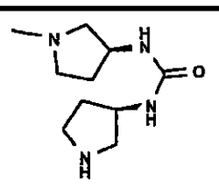
18				514 30
19				528 33
20				489 33
21		H		458 26
22				650 22
23				664 45
24				652 45
25				652 44
26				700 45
27				639 46
28				627 45

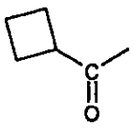
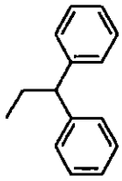
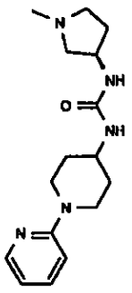
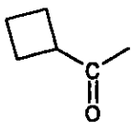
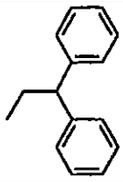
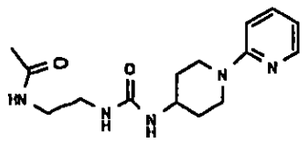
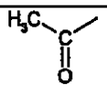
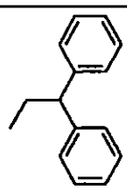
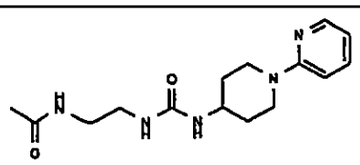
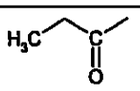
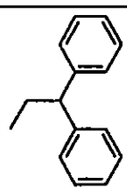
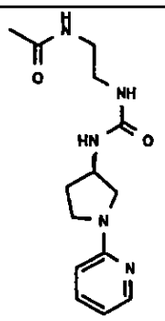
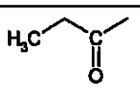
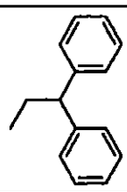
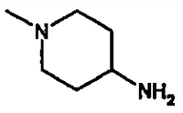
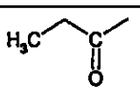
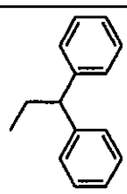
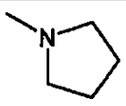
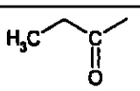
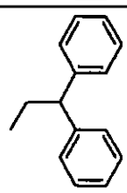
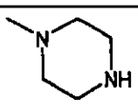
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36b				571 41

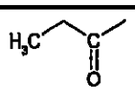
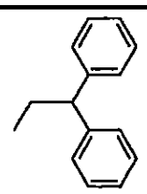
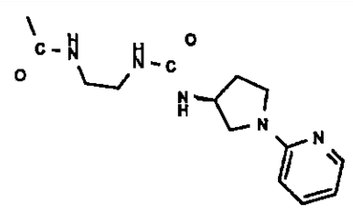
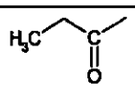
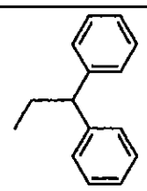
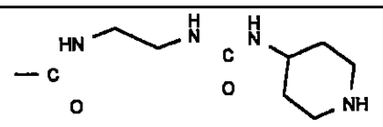
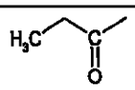
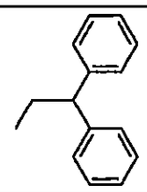
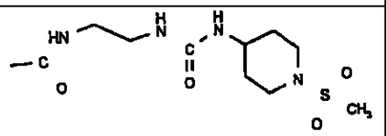
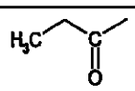
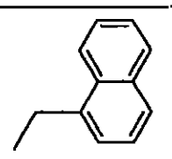
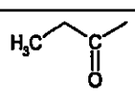
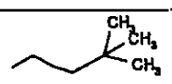
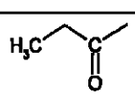
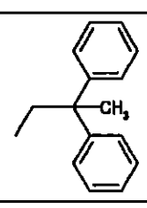
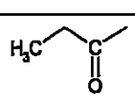
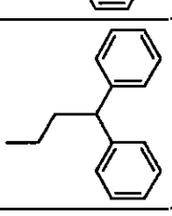
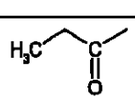
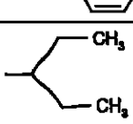
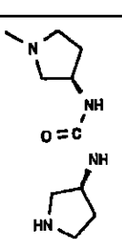
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38				388 7 338 8

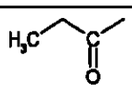
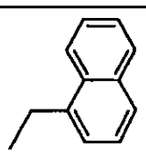
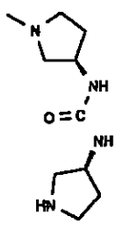
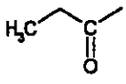
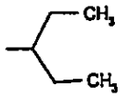
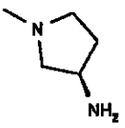
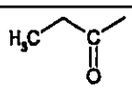
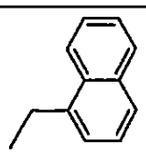
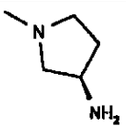
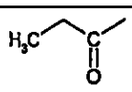
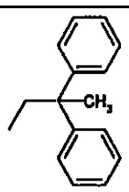
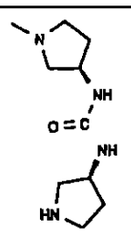
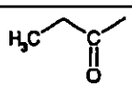
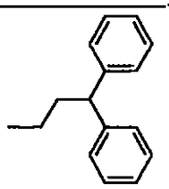
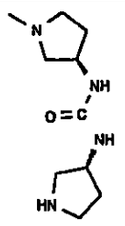
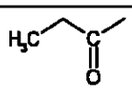
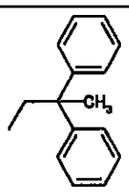
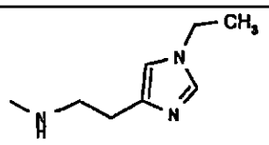
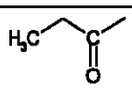
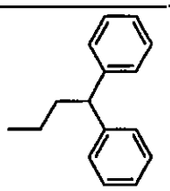
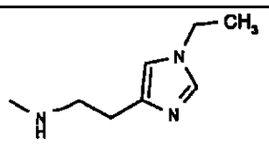
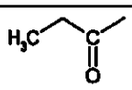
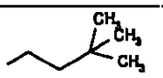
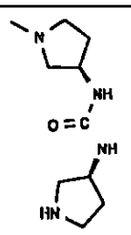
Further preferred examples of compounds of formula I are shown in Table 2 below Methods for preparing such compounds are described hereinafter The table also shows mass spectrometry, MH^+ (ESMS), data The compounds of the examples are trifluoroacetate salts, except for the compounds of Examples 41, 48, 52 and 53 are in free form and the compound of Examples 44 is an hydrochloride sal

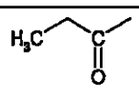
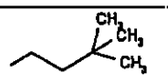
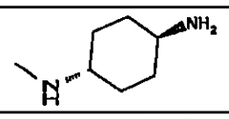
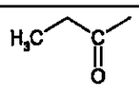
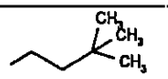
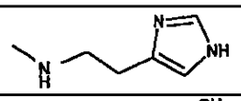
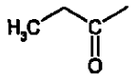
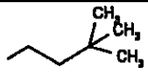
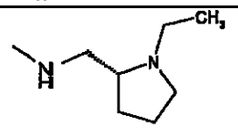
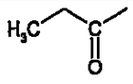
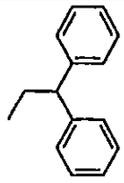
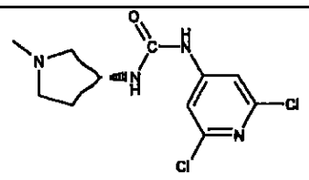
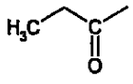
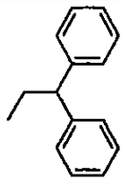
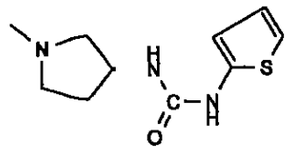
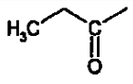
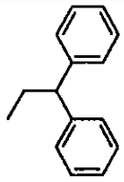
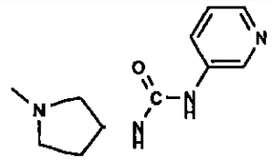
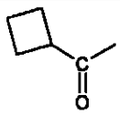
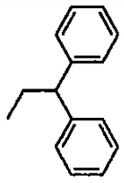
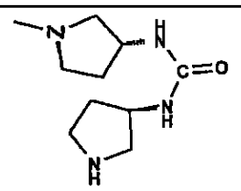
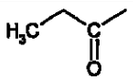
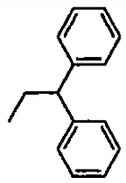
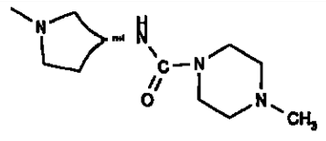
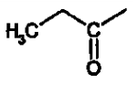
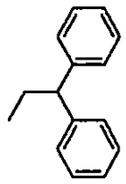
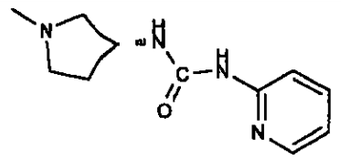
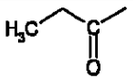
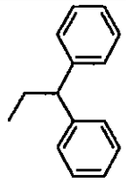
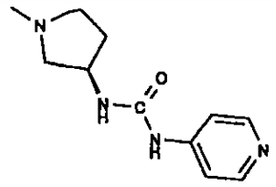
TABLE 2

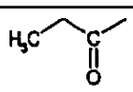
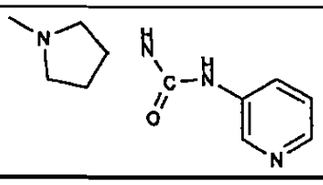
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39				683 6

40				800 6
41				802 6
42				762 6
43				762 5
44				585 5
45				556 5
46				571 5

47				382.9
48				699.6
49				777.6
50			-Cl	481.3
51			-Cl	425.2
52			-Cl	535.3
53			-Cl	535.3
54				573.4

55				643 4
56				461 3
57				531 3
58				697 5
59				697 5
60				638 4
61				638 4
62				587 3

70				503 5
71				500 5
72				517 6
73				759 4
74				696 4
75				691 5
76				709 2
77				697 4
78				691 4
79				705 3

80		-H		-

Preparation of intermediate compounds

Abbreviations used are as follows CDI is 1,1'-carbonyldiimidazole, DCM is dichloromethane, DIPEA is diisopropylethylamine, DMAP is 4 dimethylaminopyridine, DMF is dimethyl formamide, DMSO is dimethylsulfoxide, LCMS is liquid chromatographic mass spectroscopy, TEA is triethylamine, TFA is trifluoroacetic acid, THF is tetrahydrofuran, and TLC is thin-layer chromatography

3 Oxy benzotriazole 1 carboxylic acid ethyl ester

This compound is prepared from 1-hydroxybenzotriazole by the procedure of Wuts, Peter G M et al *Organic Letters* (2003), 5(9), 1483 1485 ^{1}H nmr ($CDCl_3$, 400 MHz), 8 20(d, 1H), 8 00(d, 1H), 7 75(t, 1H), 7 55(t, 1H), 4 60(q, 2H), 1 55(t, 3H)

2 (1 Isopropyl-1H imidazol 4-yl) ethylamine

This compound is prepared from 2 isopropyl-5-oxo-5,6,7,8 tetrahydro-imidazo[1,5-c]pyrimidin 2 ium iodide by the procedure of Rahul Jain and Louis A Cohen *Tetrahedron* 1996, 52, 5363 ^{1}H nmr (MeOD, 400 MHz), 7 60(s, 1H), 6 95(s, 1H), 4 40(m, 1H), 2 90(t, 2H), 2 70(t, 2H), 1 45(d, 6H)

Propionyl carbamic acid tert-butyl ester

The title compound is prepared from propyl carbamic acid tert butyl ester using the procedure described by Ken ichi Takana et al in *Chem Pharm Bull* 1988, 36, 3125 ^{1}H nmr ($CDCl_3$, 400 MHz), 7 25(br s, 1H), 2 75(q, 2H), 1 50(s, 9H), 1 15(t, 3H)

Bis-(4 methoxy-phenyl) methanone oxime

4,4' Dimethoxybenzophenone (25 g, 103 mmol) is suspended in ethanol (150 ml) and pyridine (30 ml) Hydroxylamine hydrochloride (21 50 g, 310 mmol) is added and the reaction mixture is refluxed The reaction is shown to be complete by TLC after 3 hours The reaction mixture is allowed to cool and the solvent is removed *in vacuo* The residue is partitioned between ethyl acetate (500 ml) and water (500 ml) The organic layer dried is over $MgSO_4$, filtered and the solvent removed *in vacuo* The title compound is obtained following crystallisation from

ethylacetate/ cyclohexane ^{1}H nmr ($CDCl_3$, 400 MHz), 7 70(s, 1H), 7 40 (d of d, 4H), 6 95(d, 2H), 6 85(d, 2H), 3 85(s, 3H), 3 80(s, 3H)

C,C Bis (4 methoxy phenyl) methylamine

Bis (4 methoxy-phenyl) methanone oxime (20 g, 77 82 mmol) is suspended in ammonia 880 (450 ml) and ethanol (90 ml) Ammonium acetate (3 00 g, 38 91 mmol) is added followed by the portionwise addition of zinc dust (15 29 g, 389 10 mmol) Once the addition is complete the reaction mixture is slowly heated to 50°C When the effervescence has ceased the reaction mixture is refluxed The reaction is shown to be complete by TLC after 4 hours The reaction mixture is allowed to cool and ethyl acetate is added (250 ml) The reaction mixture is filtered through Celite™ and the phases are separated The organic layer dried is over $MgSO_4$, filtered and the solvent removed *in vacuo* to give the title compound ^{1}H nmr ($CDCl_3$, 400 MHz), 7 25 (d, 4H), 6 80 (d, 4H), 5 10(s, 1H), 3 75(s, 6H)

1 3 Di(R) pyrrolidin-3 yl urea

(a) 1,3 Bis ((R) 1 benzyl pyrrolidin 3 yl)-urea

A solution comprising (R)-1-benzyl pyrrolidin 3-ylamine (5 0 g, 28 4 mmol) in DCM (10 ml) is treated with CDI (2 3 g, 14 2 mmol) and the reaction mixture is stirred at room temperature for 48 hours The solvent is removed *in vacuo* and the resulting residue is dissolved in ethyl acetate This portion is washed with water followed by brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield the titled compound as pale orange solid

(b) 1,3 Di(R) pyrrolidin-3-yl urea

To a solution of 1,3-bis-((R) 1-benzyl pyrrolidin-3-yl)-urea (5 34 g, 14 1 mmol) in ethanol (80 ml) under an inert atmosphere of Argon is added palladium hydroxide on carbon (1 07 g) The reaction mixture is purged with Argon and placed under an atmosphere of hydrogen for two days after which time, the mixture is filtered and the catalyst washed with ethanol The organic portions are combined and concentrated *in vacuo* to yield the titled compound as a white solid

Imidazole 1 carboxylic acid (3,4,5,6 tetrahydro-2H [1 2']bipyridinyl 4-yl) amide

A stirred solution of CDI (1 1 g, 6 77 mmol) in DCM (100 ml) is treated with 3,4,5,6-tetrahydro 2H-[1,2']bipyridinyl 4 ylamine (WO 99/65895, EP 21973) (1 g, 5 64 mmol in 50 ml of DCM) added dropwise over 30 minutes The reaction mixture is stirred at room temperature for 15 minutes to yield the titled compound as a 10 mg/ml solution in DCM

The compound is used in solution in subsequent reactions This solution consists of the imidazole-urea intermediate (C) together with variable amounts of the corresponding isocyanate and imidazole which result from reversible thermal elimination of imidazole under the reaction conditions This solution is used in the subsequent steps since the imidazole-urea intermediate and isocyanate intermedia e are equally suitable as precursors to ureas

1-(2 Amino ethyl) 3 ((S) 1-pyridin 2 yl pyrrolidin 3-yl)-urea

(a) ((S) 1 Pyridin-2 yl pyrrolidin 3 yl) carbamic acid tert butyl ester
A stirred solution comprising (S) pyrrolidin 3 yl carbamic acid tert butyl ester (2 0 g, 10 7 mmol), 2-bromopyridine (1 7 g, 10 7 mmol) and TEA (1 1 g, 10 7 mmol) in DMF (40 ml) is heated to 80 °C for 50 hours The solvent is removed *in vacuo* the purification of the crude residue by chromatography on silica eluting with ethyl acetate hexane (1 9 increasing to 1 4) yields the titled compound as a white solid

(b) (S) 1-Pyridin-2-yl-pyrrolidin 3 ylamine dihydrochloride
To a solution of ((S) 1 pyridin 2 yl pyrrolidin 3 yl)-carbamic acid tert-butyl ester (0 221 g, 0 84 mmol) in dioxane (4 ml) and methanol (1 ml) is added 4M HCl (in dioxane) (0 525 ml, 2 1 mmol) and the reaction mixture is stirred at room temperature overnight The resulting suspension is filtered and washed with dioxane (3 x 1 ml) to yield the titled compound

(c) Imidazole 1-carboxylic acid ((S)-1-pyridin-2-yl pyrrolidin-3-yl)-amide
A mixture comprising ((S)-1 Pyridin-2-yl-pyrrolidin-3-ylamine dihydrochloride (0 242 g, 1 02 mmol), TEA (0 2 ml) in DCM (10 2 ml) is treated with CDI (0 364 g, 2 26 mmol) The reaction mixture is stirred at room temperature for 2 hours to yield the titled compound as 0 1 M solution in DCM This solution consists of the imidazole-urea intermediate together with variable amounts of the corresponding isocyanate and imidazole This solution is used in the subsequent steps since the imidazole-urea intermediate and isocyanate intermediate are equally suitable as precursors to ureas

(d) 1-(2 Amino-ethyl)-3 ((S) 1 pyridin-2 yl pyrrolidin-3-yl)-urea
To a solution of imidazole-1 carboxylic acid ((S)-1-pyridin-2-yl-pyrrolidin 3-yl) amide (9 9 ml of a 0 1 M solution in DCM, 0 99 mmol) in iso-propanol (1 ml) is added ethyl 1,2 diamine (2 ml, 37 mmol) The reaction mixture is stirred at room temperature for 4 hours and then extracted with DCM using a continuous liquid-liquid extraction system to yield the titled compound as 1 4 mole ratio mixture with imidazole

1 (2 Amino ethyl) 3-((R)-1 pyridin-2 y pyrrolidin 3-yl) urea

The titled compound is prepared analogously to Intermediate D by replacing (S) pyrrolidin 3 yl-carbamic acid tert butyl ester with (R) pyrrolidin 3-yl carbamic acid tert-butyl ester and replacing 2 bromopyridine with 2 chloropyridine

[(1S,2R,3S,4R)-4-(2 6-Dichloro purin 9 yl)–2 3 dihydroxy cyclopentyl]-propionyl carbamic acid tert butyl ester

The titled compound is prepared analogously to 9-[(1R,2S,3R,4S) 4-(tert butoxycarbonyl-propionyl amino)-2,3-dihydroxy cyclopentyl] 6-(2,2-diphenyl ethylamino)-9H purine 2 carboxylic acid methyl ester (Example 38) by replacing 9 [(1R,4S)-4 (tert-butoxycarbonyl propionyl amino) cyclopent-2 enyl] 6 (2,2 diphenyl-ethylamino)-9H purine-2-carboxylic acid methyl ester with [(1S,4R)-4 (2,6 dichloro purin-9 yl)-cyclopent 2-enyl] propionyl carbamic acid tert butyl ester

N [(3aR,4S,6R,6aS)-6-[2 ((R) 3 Amino pyrrolidin-1-yl)-6 (2 2-diphenyl-ethylamino)-purin 9 yl] 2,2 dimethyl tetrahydro cyclopenta[1,3]dioxol-4-yl) propionamide

a) {(R) 1 [9-((1R,2S,3R,4S) 2,3 Dihydroxy–4 propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino) 9H-purin-2 yl]-pyrrolidin 3 yl}–carbamic acid benzyl ester

A solution of (R)-pyrrolidin-3-yl carbamic acid benzyl ester hydrochloride (0 88 g, 3 45 mmol) in DCM is free based using sodium hydrogen carbonate solution to yield (R)-pyrrolidin 3-yl carbamic acid benzyl ester (0 487 g, 2 22 mmol) This amine is added to N {(1S,2R,3S,4R)-4 [2-chloro 6 (2,2 diphenyl-ethylamino) purin-9-yl]-2,3-dihydroxy cyclopentyl}-propionamide (Example 4) (0 5 g, 0 96 mmol) and TEA (0 224 g, 2 22 mmol) and then dissolved in NMP (7 ml) The reaction mixture is heated using microwave radiation in a Personal Chemistry Emrys™ Optimizer microwave reactor at 190 °C for 1 hour The resulting mixture is purified by chromatography on silica eluting with 5% MeOH in DCM to yield the titled compound

b) {(R) 1 [9 ((3aS,4R,6S,6aR) 2,2 Dimethyl-6-propionylamino tetrahydro-cy clopenta[1,3]dioxol-4-yl)-6 (2,2 diphenyl-ethylamino) 9H-purin 2 yl]-pyrrolidin 3-yl} carbamic acid benzyl ester

A solution of {(R) 1 [9-((1R,2S,3R,4S) 2,3 dihydroxy-4 propionylamino-cyclopentyl)-6 (2,2-diphenyl ethylamino) 9H-purin 2 yl] pyrrolidin-3-yl} carbamic acid benzyl ester (0 63 g, 0 89 mmol) in acetone (10 ml) and 2,2 dimethyloxypropane (5 ml) is treated with toluenesulfonic

acid (ca 60 mg) and then stirred at room temperature overnight The mixture is basified using ammonium hydroxide and the solvent is removed *in vacuo* The crude product is partitioned between DCM and water and the organic portion is washed with brine, dried over $MgSO_4$, filtered and the solvent is removed *in vacuo* to give the titled compound [MH+ 745]

c) N {(3aR,4S,6R,6aS)-6-[2-((R)-3-Amino-pyrrolidin-1 yl) 6-(2,2-diphenyl-ethylamino) purin 9 yl] 2,2 dimethyl-tetrahydro cyclopenta[1,3]dioxol-4-yl}-propionamide
To a solution of {(R)-1 [9-((3aS,4R,6S,6aR)-2,2-dimethyl 6-propionylamino tetrahydro-cyclopenta[1,3]dioxol-4 yl)-6 (2,2-diphenyl-ethylamino) 9H purin-2-yl] pyrrolidin 3 yl}-carbamic acid benzyl ester (0 598 g, 0 79 mmol) in ethanol (7 5 ml) under an inert atmosphere of Argon is added palladium hydroxide on carbon (10 mg) The reaction mixture is purged with Argon and placed under an atmosphere of hydrogen overnight The mixture is filtered and purified by chromatography on silica eluting with 5 % MeOH in DCM to yield the titled compound [MH+ 611]

Preparation of Specific Examples

Example 1
N-[(1S,2R,3S,4R)-4-(6-Amino-2-chloro purin-9-yl)-2 3-dihydroxy-cyclopentyl]-methane-sulfonamide trifluoroacetate

Bis (4 methoxy-phenyl) methyl] (2 chloro-9H-purin 6-yl)-amine
2,6-Dichloropurine (9 50 g, 50 29 mmol) is dissolved in THF (200 ml) under an atmosphere of argon Diisopropylamine (7 14 g, 55 32 mmol) is added followed by C,C bis-(4-methoxy–phenyl)-methylamine (see preparation of intermediates) (12 22 g, 50 29 mmol) and the reaction mixture is stirred at 50°C The reaction is shown to be complete by LCMS after 5 days The solvent is removed *in vacuo* and replaced with MeOH (250 mL) The resulting precipitate is filtered off and dried to give the title compound ^1H nmr (d_6-DMSO, 400 MHz), 8 20(br s, 1H), 7 25(d, 4H), 6 90(d, 4H), 3 75(s, 6H), 3 15(m, 1H), MS (ES+) *m/e* 396 (MH^+)

(1S,4R) 4 (6-{[Bis-(4-methoxy phenyl) methyl] amino}-2 chloro-purin-9 yl) cyclopent 2 enol
Bis (4 methoxy phenyl)-methyl] (2-chloro-9H-purin 6-yl) amine (13 g, 32 87 mmol) is placed in an oven-dried flask under an atmosphere of argon Dry deoxygenated THF (100 ml) and dry DMSO (2 ml) are added and the suspension is cooled on an ice bath Sodium hydride 95 % (0 79 g, 32 87 mmol) is then slowly added and the solution is stirred at room temperature for

30 minutes (1S,4R)-cis 4 Acetoxy-2 cyclopenten 1 ol (4 9 g 34 5 mmol) and triphenylphosphine (1 36 g, 5 17 mmol) are placed in an oven-dried flask under an atmosphere of argon Dry deoxygenated THF (50 ml) is added This solution is added to the anion solution via syringe Tetrakis(triphenyl phosphine)palladium(0) (2 g, 1 73 mmol) is then added and the mixture is stirred at 50°C The reaction is shown to be complete by LCMS after 2 hours The reaction mixture is allowed to cool and the solvent is removed *in vacuo* The residue is taken up in methanol (50 ml) and the resulting precipitate is filtered off and dried to give the title compound ^{1}H nmr ($CDCl_3$, 400 MHz), 9 10(m, 1H), 8 10(m, 1H), 7 30(d, 4H), 6 90(d, 4H), 6 55(d, 1H), 6 20(m, 1H), 5 95(m, 1H), 5 40(m, 1H), 5 30(d, 1H), 4 70(m, 1H), 3 70(s, 6H), 2 90(m, 1H), 1 70(m, 1H), MS (ES+) *m/e* 478 (MH^+)

Carbonic acid (1S,4R)-4 (6 {[bis (4-methoxy-phenyl)-methyl]-amino}-2 chloro purin 9 yl) cyclopent 2 enyl ester ethyl ester

(1S,4R) 4 (6 {[Bis-(4-methoxy phenyl)-methyl]-amino} 2 chloro purin 9-yl) cyclopent 2 enol (8 00 g, 16 75 mmol) is placed in an oven dried flask under an atmosphere of argon Dry pyridine (80 ml) is added followed by diisopropylamine (16 ml) A catalytic amount of DMAP is added followed by 3 oxy benzotriazole-1 carboxylic acid ethyl ester (6 94 g, 33 50 mmol, see preparation of intermediates) The reaction mixture is stirred at room temperature The reaction is shown to be complete by TLC after 18 hours The solvent is removed *in vacuo* and the residue is partitioned between ethyl acetate (500 ml) and 2M HCl (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 purification by flash column chromatography (silica, dichloromethane / methanol 50 1) ^{1}H nmr ($CDCl_3$, 400 MHz), 7 80(s, 1H), 7 25(d of d, 4H), 6 85(d of d, 4H), 6 65(m, 1H), 6 50(m, 1H), 6 35(m, 1H), 6 15(m, 1H), 5 65(m, 2H), 4 25(q, 2H), 3 80(s, 6H), 3 10(m, 1H), 1 95(m, 1H), 1 35(t, 3H)

[Bis (4 methoxy phenyl)-methyl]-[2-chloro-9-[(1R,4S) 4-(di Boc-amino)-cyclopent 2 enyl] 9H-purin 6 yl]-amine

Carbonic acid (1S,4R)-4 (6-{[bis (4-methoxy phenyl) methyl]-amino}-2 chloro-purin-9-yl) cyclopent 2 enyl ester ethyl ester (2 00 g, 3 64 mmol), di t butyl iminodicarboxylate (0 87 g, 4 00 mmol) and triphenylphosphine (0 14 g, 0 55 mmol) are placed in an oven dried flask under an atmosphere of argon Dry deoxygenated THF (20 ml) is added followed by tetrakis(triphenylphosphine)palladium(0) (0 21 g, 0 18 mmol) and the mixture is stirred at room temperature The reaction is shown to be complete by LCMS after 3 hours The solvent is removed *in vacuo* and the title compound is obtained after purification by flash column chromatography (silica, iso hexane / ethyl acetate 4 1) ^{1}H nmr ($CDCl_3$, 400 MHz), 8 20(s,

1H), 7 25(d, 4H), 6 85(d, 4H), 6 60(m, 1H), 6 35(m, 1H), 6 10(m, 1H), 5 80(m, 1H), 5 65(m, 1H), 5 35(m, 1H), 3 80(s, 6H), 3 15(m, 1H), 2 10(m, 1H), 1 55(s, 18H)

(1R,2S,3R,5S) 3 (6 {[Bis-(4-methoxy-phenyl)-methyl]-amino} 2 chloro purin 9 yl) 5 (di-Boc amino) cyclopentane-1,2-diol

[Bis (4 methoxy phenyl)-methyl] (2-chloro-9-[(1R,4S)-4 (di-Boc amino) cyclopent 2 enyl]-9H purin 6 yl} amine (0 75 g, 1 11 mmol) is dissolved in THF (15 ml) N-Methylmorpholine N-oxide (0 26 g, 2 22 mmol) is added followed by osmium tetroxide (1 5 ml, 4% in water) The reaction mixture is stirred at room temperature The reaction is shown to be complete by LCMS after 18 hours The solvent is removed *in vacuo* and the title compound is obtained after purification by flash column chromatography (silica, dichloromethane / methanol 50 1) ^{1}H nmr ($CDCl_3$, 400 MHz), 7 75(s, 1H), 7 25 (m, 4H), 6 85(m, 4H), 6 60(m, 2H), 5 70(m, 1H), 4 70(m, 2H), 4 60(m, 1H), 4 45(m, 1H), 3 80(s, 6H), 3 70(m, 1H), 3 40(m, 1H), 3 25(m, 1H), 2 65(m, 1H), 2 50(m, 1H), 1 55 (s, 18H)

(1S,2R,3S,5R)-3 Amino-5-(6 amino 2 chloro-purin 9-yl) cyclopentane-1 2-diol trifluoroacetate

(1R,2S,3R,5S)-3 (6 {[Bis-(4-methoxy phenyl)-methyl]-amino}-2 chloro-purin 9-yl) 5 (di-Boc-amino) cyclopentane 1,2 diol (600 mg, 0 84 mmol) is dissolved in dichloromethane (4 ml) TFA (2 ml) is added and the reaction mixture is stirred at room temperature The reaction is shown to be complete by LCMS after 18 hours The solvent is removed *in vacuo* and the title compound is obtained after purification by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water – 0 1% TFA) ^{1}H nmr (MeOD, 400 MHz), 8 10(s, 1H), 4 80(m, 1H), 4 60(m, 1H), 4 30(m, 1H), 3 60(m, 1H), 2 85(m, 1H), 2 30(m, 1H) MS (ES+) *m/e* 285 (MH^+)

N-[(1S,2R,3S,4R)-4-(6-Amino 2-chloro purin-9-yl)-2,3 dihydroxy-cyclopentyl]-methane-sulfonamide trifluoroacetate

(1S,2R,3S,5R)-3 Amino-5-(6 amino-2 chloro-purin-9-yl) cyclopentane-1,2-diol trifluoroacetate (20 mg, 39 µmol) and diisopropylethylamine (25 mg, 190 µmol) are placed in a flask with dry THF (1 ml) Mesyl chloride (4 5 mg, 39 µmol) is added and the reaction mixture is stirred at room temperature The reaction is shown to be complete by LCMS after 3 hours The solvent is removed *in vacuo* and the title compound is obtained after purification by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water – 0 1% TFA) MS (ES+) *m/e* 363 (MH^+)

Example 2

N-[(1S,2R,3S 4R)-4-(6-Amino-2-phenethylamino-purin-9-yl)-2 3-dihydroxy-cyclopentyl]-propionamide trifluoroacetate

N [(1S 2R 3S,4R) 4-(6-Amino-2 chloro purin 9-yl)-2,3 dihydroxy cyclopentyll-propionamide trifluoroacetate

(1S,2R,3S,5R) 3 Amino-5 (6 amino 2 chloro purin-9 yl) cyclopentane-1,2 diol trifluoroacetate (intermediate for preparing Example 1) (20 mg, 39 µmol) and diisopropylethylamine (25 mg, 190 µmol) are placed in a flask with dry THF (1m.l) Propionyl chloride (3 6 mg, 39 µmol) is added and the reaction mixture is stirred at room temperature The reaction is shown to be complete by LCMS after 3 hours The solvent is removed *in vacuo* and the title compound is obtained, which can be purified by reverse phase column chromatography (Isolute™ C1 8, 0 100% acetonitrile in water – 0 1% TFA) ^{1}H nmr (MeOD, 400 MHz), 8 10(s, 1H), 4 75(m, 1H), 4 60(m, 1H), 4 20(m, 1H), 4 00(m, 1H), 3_75(m, 1H), 3 25(m, 1H), 2 85(m, 1H), 2 40(q, 2H), 2 10(m, 1H), 1 20(t, 3H), MS (ES+) *m/e* 341 (MH^+)

N-[(1S,2R,3S,4R) 4-(6 Amino-2 phenethylamino purin 9-yl) 2 3 dihydroxy cyclopentyl] propionamide trifluoroacetate

N-[(1S,2R,3S,4R) 4 (6-Amino-2 chloro-purin 9-yl) 2,3-dihydroxy-cyclopentyl]-propionamide obtained directly in the previous step without purification (10 6 mg, 31 µmol) and phenethyl-amine (19 mg, 150 µmol) are placed in a 0 5-2 5 ml microwave vial Dichlorobenzene (0 5 ml) is added and the reaction mixture is microwaved in a Personal Chemistry Emrys™ Optimizer microwave reactor at 240°C The reaction is shown to be complete by Liquid Chromato graphy-Mass Spectrometry (LCMS) after 1 hour The solvent is removed *in vacuo* and the title compound is obtained after purification by reverse phase column chromatography (Isolute™ C18, 0 100% acetonitrile in water – 0 1% TFA) ^{1}H nmr (MeOD, 400 MHz), 8 05(s, 1H), 7 40 715(m, 5H), 4 70(m, 1H), 4 55(m, 1H), 4 10(m, 2H), 3 70(m, 4H), 3 15(m, 1H), 2 95(m, 4H), 2 70(m, 1H), 2 20(m, 2H), 2 00(m, 1H), 1 20(t, 3H), MS (ES+) *m/e* 426 (MH^+)

Example 3

N-[(1S,2R,3S,4R)-4-(6-Amino-2-hex-1-ynyl-purin-9-yl)-2 3-dihydroxy-cyclopentyl]-propionamide trifluoroacetate

N-[(1S,2R,3S,4R) 4 (6 Amino-2-chlo o purin 9-yl) 2,3 dihydroxy cyclopentyl]-propionamide (10 6mg, 31µmol), 1 hexyne (2.5 4mg, 310µmol), copper (I) iodide (1 5mg, 7 75µmol), dichlorobis(triphenylphosphine)palladium(II) (5 5mg, 7 75µmol), triphenylphosphine (4 0mg, 15 5µmol), diethylamine (0 4mL) and DMF (0 2mL) are placed in a 0 5-2 5mL microwave

vial The reaction mixture is microwaved in a Personal Chemistry Emrys™ Optimizer microwave reactor at 120°C The reaction is shown to be complete by LCMS after 1 hour The solvent is removed *in vacuo* and the title compound is obtained after purification by reverse phase column chromatography (Isolute™ C18, 0 100% acetonitrile in water – 0 1% TFA) MS (ES+) *m/e* 387 (MH+)

Example 4

N-[(1S,2R,3S,4R)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl]-propionamide

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

2,6 Dichloropurine (10 g, 52 90 mmol), (1S,4R) 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), MS (ES+) *m/e* 271 (MH+)

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

(1S,4R)-4 (2,6-Dichloro purin 9-yl)-cyclopent-2-enol (9 5 g, 35 05 mmol) is placed in an oven dried flask under an atmosphere of argon Dry THF (200mL) 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 room temperature The reaction is shown to be complete by LCMS after 1 hour The solvent is removed *in vacuo* and the residue is partitioned between dichloromethane (200mL) and water (200mL) 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 crystallisation 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), MS (ES+) *m/e* 343 (MH+)

Di Boc [(1S,4R)-4-(2,6-dichloro-purin-9-yl)-cyclopent-2-enyl]-amine

Carbonic acid (1S,4R) 4 (2,6 dichloro purin-9-yl) cyclopent 2-enyl ester ethyl ester (2 5 g, 7 29 mmol), di t butyl iminodicarboxylate (1 74 g, 8 02 mmol), tris(dibenzylideneacetone)-dipalladium(0) (0 33 g, 0 36 mmol) and triphenylphosphine (0 29 g, 1 09 mmol) are placed in an oven-dried flask under an atmosphere of argon Dry deoxygenated THF (30ml) is added and the reaction mixture is stirred at room temperature The reaction is shown to be complete by LCMS after 3 hours The solvent is emoved *in vacuo* and the title compound is obtained after purification by flash column chromatography (silica, ethyl acetate / isohexane 4 1) ^{1}H nmr ($CDCl_3$, 400 MHz), 8 70(s, 1H), 6 20(m, 1H), 5 85(m, 1H), 5 80(m, 1H), 5 40(m, 1H), 3 20(m, 1H), 2 15(m, 1H), 1 55(s, 18H), MS (ES+) *m/e* 470 (MH^+)

(1S,2R,3S,5R) 3 (Di Boc amino) 5 (2 6 dichloro purin 9 yl) cyclopentane 1 2 diol

The title compound is prepared from di Boc-[(1S,4R) 4 (2,6 dichloro-purin 9-yl)-cyclopent-2-enyl] amine using a procedure analogous to that use to prepare (1R,2S,3R,5S) 3 (6-[[bis (4-methoxy phenyl) methyl]-amino] 2 chloro-purin-9-yl)-5-(di Boc-amino)-cyclopentane-1,2 diol ^{1}H nmr ($CDCl_3$, 400 MHz), 8 35(, 1H), 4 80(m, 1H), 4 70(m, 1H), 4 50(m, 1H), 3 85(m, 1H), 3 75(m, 1H), 3 10(m, 1H), 2 75(m, 1H), 2 55(m, 1H), 1 55(s, 18H), MS (ES+) *m/e* 504 (MH^+)

(1S,2R,3S,5R) 3 Amino-5 (2,6-dichloro-purin-9-yl) cyclopentane-1 2 diol trifluoroacetate

The title compound is prepared from (1S,2R,3S,5R)-3-(di-Boc-amino)-5 (2,6-dichloro purin 9-yl) cyclopentane-1,2 diol using a procedure analogous to that used to prepare (1S,2R,3S,5R)-3 amino-5-(6-amino-2 chloro-purin 9 yl) cyclopentane-1,2 diol trifluoroacetate in Example 1. MS (ES+) *m/e* 304 (MH^+)

N [(1S,2R,3S,4R)-4 (2 6-Dichloro purin 9-yl) 2,3-dihydroxy-cyclopentyl]-propionamide

The title compound is prepared from (1S,2R,3S,5R) 3-amino-5-(2,6-dichloro-purin 9-yl) cyclopentane-1,2-diol trifluoroacetate and propionyl chloride using a procedure analogous to that used to prepare N-[(1S,2R,3S,4R) 4 (6-amino-2 chloro-purin-9-yl)-2,3 dihydroxy cyclopentyl]-propionamide trifluoroacetate in Example 2 MS (ES+) *m/e* 360 (MH^+)

N [(1S,2R,3S,4R) 4-[2-Chloro-6-(2 2 diphenyl ethylamino)-purin-9 yl] 2 3 dihydroxy cyclopentyl]-propionamide

N [(1S,2R,3S,4R) 4-(2,6 Dichloro purin 9-yl)-2,3 dihydroxy-cyclopentyl] propionamide (160 mg, 0 44 mmol) is dissolved in THF (5 ml) under an atmosphere of argon Diisopropylamine

(69 mg, 0 53 mmol) is added followed by 2,2-diphenylethylamine (96 mg, 0 49 mmol) and the reaction mixture is stirred at 50° C The reaction is shown to be complete by LCMS after 2 hours The solvent is removed *in vacuo* and the title compound is obtained after purification by reverse phase column chromatography (Isolute™ C18, 0 100% acetonitrile in water – 0 1% TFA)) ^{1}H nmr (MeOD, 400 MHz), 8 00(s, 1H), 7 40 7 15(m, 10H), 4 75(m, 1H), 4 60(m, 1H), 4 50(m, 1H), 4 20(m, 3H), 3 95(m, 1H), 2 85(m, 1H), 2 40(q, 2H), 2 10(m, 1H), 1 20 (t, 3H), MS (ES+) *m/e* 521 (MH^+)

The final compound of Example 4 may also be prepared using the following process

(2 Chloro 9 [(1R 4S) 4 (di Boc amino) cyclopent-2-enyl] 9H purin-6 yl) (2 2-diphenyl ethyl) amine

(1S,2R,3S,5R) 3 (Di-Boc amino) 5 (2,6-dichloro purin 9-yl)-cyclopentane-1,2 diol (1 3 0g, 27 66 mmol) is dissolved in THF (250 ml) under an atmosphere of argon Diisopropyl amine (4 28 g, 33 19 mmol) is added followed by 2,2-diphenylethylamine(6 0 g, 30 43 mmol) and the reaction mixture is stirred at 50°C The reaction is shown to be complete by LCMS after 18 hours The solvent is removed *in vacuo* and the reaction mixture is partitioned between dichloromethane (250 ml) and 0 1M HCl (250 ml) The organic layer is washed with water (200 ml) and brine (200 ml), dried over $MgSO_4$, filtered and the solvent is removed *in vacuo* to give the title compound ^{1}H nmr ($CDCl_3$, 400 MHz), 8 05(s, 1H), 7 30-7 10(m, 10H), 6 00(m, 1H), 5 70(m, 2H), 5 60(m, 1H), 5 20(m, 1H), 4 30(m, 1H), 4 20(m, 1H), 3 6 5(m, 1H), 3 05(m, 1H), 2 00(m, 1H), 1 70(m, 1H), 1 40(s, 18H), MS (ES+) *m/e* 631 (MH^+)

(1R,2S,3R,5S) 3 [2-Chloro-6-(2 2-diphenyl ethylamino)-purin-9 yl]-5-(di Boc-amino)-cyclopentane 1,2-diol

The title compound is prepared from (2 -chloro-9 [(1R,4S)-4 (di-Boc-amino)-cyclopent-2-enyl] 9H purin-6-yl]-(2,2 diphenyl-ethyl) amine using a procedure analogous to that of Prep 11 ^{1}H nmr (MeOD, 400 MHz), 8 05(s, 1H), 7.35-7 15(m, 10H), 4 70-4 55(m, 4H), 4 50(m, 1H), 4 35(m, 1H), 4 20(m, 2H), 2 55(m, 1H), 2 45(m, 1H), 1 60(s, 18H)

(1S,2R,3S,5R) 3-Amino 5 [2 chloro 6-(2,2 diphenyl ethylamino)-purin-9-yl]-cyclopentane-1,2 diol trifluoroacetate

(1R,2S,3R,5S) 3-[2-Chloro 6 (2,2 diphenyl-ethylamino) purin-9-yl] 5 (di Boc-amino)-cyclopentane 1,2 diol (10 3 g, 15 50 mmol) is dissolved in dichloromethane (50 ml) TFA (25ml) is added and the reaction mixture is stirred at room temperature The reaction is shown to be complete by LCMS after 2 hours The solvent is removed *in vacuo* to give the title

compound ^{1}H nmr (MeOD, 400 MHz), 7 90(s, 1H), 7 30 7 10(m, 10H), 4 65(m, 1H), 4 50(m, 1H), 4 40(m, 1H), 4 20(m, 1H), 4 10(m, 2H), 3 50(m, 1H), 2 75(m, 1H), 2 15(m, 1H), MS (ES+) *m/e* 465 (MH$^+$)

N [(1S,2R,3S,4R)-4-[2 Chloro-6 (2 2-diphenyl-ethylamino) purin-9 yl] 2,3 dihydroxy-cyclopentyl}-propionamide

(1S,2R,3S,5R)-3-Amino 5 [2-chloro-6-(2,2-diphenyl-ethylamino) purin 9 yl]-cyclopentane-1,2 diol trifluoroacetate (9 50 g, 16 42 mmol) and diisopropylethylamine (6 36 g, 49 27 mmol) are placed in a flask with dry THF (150 ml) Propionyl chloride (1 52 g, 16 42mmol) is added dropwise and the reaction mixture is stirred at room temperature The reaction is shown to be complete by LCMS after 1 hour The solvent is removed *in vacuo* and the residue is partitioned between dichloromethane (250 ml) and water (250 ml) The organic layer is washed with water (200 ml) and brine (200 ml), dried over $MgSO_4$, filtered and the solvent is removed *in vacuo* The solid is recrystallised from 1,2-dichloroethane to give the title compound ^{1}H nmr (MeOD, 400 MHz), 8 00(s, 1H), 7 40 7 15(m, 10H), 4 75(m, 1H), 4 60(m, 1H), 4 50(m, 1H), 4 20(m, 3H), 3 95(m, 1H), 2 85(m, 1H), 2 40(q, 2H), 2 10(m, 1H), 1 20 (t, 3H), MS (ES+) *m/e* 521 (MH$^+$)

Example 5

N [(1S,2R,3S,4R)-4-[2-(4 Amino cyclohexylamino) 6 (2,2-diphenyl ethylamino) purin-9 -yl] 2,3 dihydroxy-cyclopentyl} propionamide trifluoroacetate

N {(1S,2R,3S,4R)-4-[2-Chloro-6-(2,2 diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide (final compound of Example 4) is reacted with cyclohexane 1,4-diamine using a procedure analogous to that used to prepare the compound of Example 2 MS (ES+) *m/e* 599 (MH$^+$)

The free-base is formed as follows N-{ (1S,2R,3S,4R)-4-[2-(4-Amino-cyclohexylamino) 6-(2,2 diphenyl-ethylamino) purin 9-yl] 2,3 dihydroxy-cyclopentyl} propionamide trifluoroacetate (300 mg, 0 50 mmol) is loaded onto DOWEX® 50WX2-200 ion exchange resin (pre washed with water) The resin is eluted with water until neutral pH and then with methanol ammonia 880 (1 1) to elute the free base) ^{1}H nmr (MeOD, 400 MHz), 7 65(s, 1H), 7 40 7 20(m, 10H), 4 60(m, 1H), 4 50(m, 2H), 4 20(m, 3H), 4 05(m, 1H), 3 70(m, 1H), 2 70(m, 2H), 2 30(q, 2H), 2 20(m, 2H), 2 00(m, 1H), 1 95(m, 2H), 1 30 (m, 4H), 1 20 (t, 3H), MS (ES+) *m/e* 599 (MH$^+$)

Example 6

N-[(1S,2R 3S 4R)-4-[6 (2 2-Diphenyl-ethylamino)-2-hex-1-ynyl-purin-9-yl]-2 3-dihydroxy-cyclopentyl]-propionamide

The title compound is prepared from N [(1S,2R,3S,4R)-4-(2,6 Dichloro purin 9 yl) 2,3 - dihydroxy cyclopentyl]-propionamide using a procedure analogous to that used to prepare the compound of Example 3

Example 7

N [(1S,2R,3S 4R)-4-[6-(2 2-Diphenyl-ethylamino)-2-[2-(1H-imidazol-4-yl)-ethylamino] -purin-9-yl]-2,3-dihydroxy-cyclopentyl]-propionamide

This compound is prepared from N-[(1S,2R,3S,4R) 4 (2,6-Dichloro-purin-9 yl)-2,3-dihydroxy cyclopentyl] propionamide using histamine in a procedure analogous to that used to prepare the compound of Example 5

Example 8

N-[(1S,2R,3S,4R)-4-[6 (2 2-Diphenyl-ethylamino)-2-(2-piperidin-1-yl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl]-propionamide

The title compound is prepared using *N*-(aminoethyl)piperidine in a procedure analogous to that used to prepare the compound of Example 5

Example 9

N [(1S,2R,3S,4R)-4-[6-(2 2-Diphenyl-ethylamino)-2-[2-(1-methyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl]-2 3-dihydroxy-cyclopentyl]-propionamide trifluoroacetate

N-[(1S,2R,3S,4R)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino)-purin-9 yl] 2,3-dihydroxy-cyclopentyl] propionamide (compound of Example 4) (20 mg, 38 µmol) and 2-(1 methyl-1H-imidazol 4-yl) ethylamine (24 mg, 190 µmol) are placed in a 0 5 2 5 ml microwave vial Dichlorobenzene (0 5 ml) is added and the reaction mixture is heated using microwave radiation in a Personal Chemistry Emrys™ Optimizer microwave reactor at 200°C The reaction is shown to be complete by LC MS after 2 hours The solvent is removed *in vacuo* and the title compound is obtained after purification by reverse phase column chromatography (Isolute™ C18, 0 100% acetonitrile in water – 0 1% TFA) ^{1}H nmr (MeOD, 400 MHz), * 80(s, 1H), 8 15(s, 1H), 7 40 7 20(m, 11H), 4 75(m, 2H), 4 50(m, 2H), 4 30(m, 1H), 4 10(m, 2H), 3 85(s, 3H), 3 75(m, 2H), 3 10(m, 3H), 2 70(m, 1H), 2 25(q, 2H), 1 95(m, 1H), 1 30(m, 4H), 1 15(t, 3H), MS (ES+) *m/e* 610 (MH^+)

Example 10

N-[(1S,2R,3S,4R)-4-[6-(2 2-Diphenyl-ethylamino)-2-[2-(1-ethyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl]-2 3-dihydroxy cyclopentyl]-propionamide

This compound is prepared from N {(1S,2R,3S,4R)-4-[2 chloro 6-(2,2-diphenyl-ethylamino) purin-9 yl]-2,3-dihydroxy-cyclopentyl} propionamide (compound of Example 4) and 2-(1 ethyl-1H-imidazol 4-yl)-ethylamine using a procedure analogous to that of Example 21 MS (ES+) *m/e* 624 (MH^+)

Example 11

N-{(1S,2R,3S,4R)-4-[6-(2 2-Diphenyl-ethylamino)-2-[2-(1-isopropyl-1H-imidazol -4-yl)-ethylamino]-purin-9-yl]-2 3-dihydroxy-cyclopentyl}-propionamide

This compound is prepared from N-{(1S,2R,3S,4R) 4-[2-chloro-6-(2,2-diphenyl ethylamino)-purin 9 yl]-2,3 dihydroxy cyclopentyl]-propionamide (compound of Example 4) and 2-(1-isopropyl 1H-imidazol-4 yl) ethylamine using a procedure analogous to that of Example 9 for the desired salt MS (ES+) *m/e* 638 (MH^+)

Examples 12 and 13

Cyclopropanecarboxylic acid {(1S,2R,3S,4R)-4-[2 chloro-6-(2,2-diphenyl-ethylamino)-purin-9 yl] 2,3 dihydroxy cyclopentyl} amide and N {(1S,2R,3S,4R)-4-[2 Chloro 6 (2,2-diphenyl ethylamino) purin 9-yl]-2,3 dihydroxy cyclopentyl} butyramide are prepared using a procedure analogous to that of Example 4 in which propionyl chloride is replaces with the appropriate acylating agent

Example 14

N-{(1S,2R,3S,4R)-4-[2-Chloro-6-(1-ethyl-propylamino)-purin-9-yl]-2 3-dihydroxy-cyclopentyl}-propionamide

[(1S,4R) 4-(2,6-Dichloro-purin-9-yl)-cyclopent-2-enyl] propionyl carbamic acid tert-butyl ester

The title compound is prepared from carbonic acid (1S,4R)-4-(2,6 dichloro-purin-9-yl)-cyclopent 2-enyl ester ethyl ester (an intermediate for preparing the compound of Example 4) and propionyl carbamic acid tert-butyl ester (see preparation of intermediates) using a procedure analogous to that of di-Boc [(1S,4R)-4-(2,6-dichloro purin-9-yl)-cyclopent-2-enyl]-amine (another intermediate for preparing the compound of Example 4) ^1H nmr ($CDCl_3$, 400 MHz), 8 70(s, 1H), 6 15(m, 1H), 5 85(m, 1H), 5 80(m, 1H), 5 60(m, 1H), 3 15(m, 1H), 2 75(q, 2H), 2 10(m, 1H), 1 55(s, 9H), 1 15(t, 3H), MS (ES+) *m/e* 426 (MH^+)

[(1S,4R)-4 [2-Chloro-6-(1 ethyl-propylamino) purin 9-yl]-cyclopent 2-enyl] propionyl-carbamic acid tert butyl ester

[(1S,4R)-4-(2,6-Dichloro purin 9-yl)-cyclopent 2-enyl] propionyl carbamic acid tert-butyl ester (700 mg, 1 64 mmol) is dissolved in THF (15 ml) under an atmosphere of argon 3-Pentyl amine (315mg, 3 61 mmol) is added and the reaction mixture is stirred at 50°C The reaction is shown to be complete by LCMS after 18 hours The reaction mixture is partitioned between dichloromethane (50 ml) and 0 1M HCl (50 ml) The organic layer is washed with water (20 ml) and brine (20 ml), dried over $MgSO_4$, filtered and the solvent is removed *in vacuo* to give the title compound ^1H nmr ($CDCl_3$, 400 MHz), 8 10(s, 1H), 6 00(m, 1H), 5 70(m, 1H), 5 60(m, 2H), 5 45(m, 1H), 4 20(m, 1H), 3 65(m, 1H), 3 00(m, 1H), 2 65(m, 3H), 1 95(m, 1H), 1 60(m, 3H), 1 45(s, 9H), 1 10(m, 4H), 0 85(t, 6H), MS (ES+) *m/e* 477 (MH^+)

[(1S,2R,3S,4R) 4-[2-Chloro-6-(1 ethyl propylamino) purin 9-yl] 2 3-dihydroxy cyclopentyl] propionyl carbamic acid tert-butyl ester

The title compound is prepared from [(1S,4R)-4 [2-chloro-6-(1-ethyl propylamino)- purin-9-yl] cyclopent 2-enyl] propionyl-carbamic acid tert butyl ester using a procedure analogous to that of (1R,2S,3R,5S) 3-(6-[[bis-(4-methoxy phenyl) methyl]-amino] 2 chloro purin-9-yl) 5-(di Boc-amino) cyclopentane 1,2-diol (see Example 1) Purification by reverse phase column chromatography (Isolute™ C18, 0 100% acetonitrile in water – 0 1% TFA) ^1H nmr (MeOD, 400 MHz), 8 10(s, 1H), 4 80(m, 1H), 4 65(m, 1H), 4 35(m, 1H), 4 20(m, 1H), 2 85(m, 2H), 2 60(m, 1H), 2 35(m, 1H), 1 70(m, 2H), 1 65(s, 9H), 1 60(m, 2H), 1 15(t, 3H), 0 95(t, 6H)

N [(1S,2R,3S,4R)-4-[2 Chloro-6 (1-ethyl-propylamino)-purin-9 yl]-2 3 dihydroxy cyclopentyl]-propionamide

[(1S,2R,3S,4R)-4-[2 Chloro-6-(1-ethyl-propylamino) purin 9-yl]-2,3 dihydroxy-cyclopentyl]-propionyl-carbamic acid tert-butyl ester (300 mg, 0 59 mmol) is dissolved in dichloromethane (5 ml) TFA (2 ml) is added and the reaction mixture is stirred at room temperature. The reaction is shown to be complete by LCMS after 1 hour The solvent is removed *in vacuo* and the residue is partitioned between dichloromethane (50 ml) and saturated $NaHCO_3$ (50 ml) The organic layer is washed with water (20 ml) and brine (20 ml), dried over $MgSO_4$, filtered and the solvent is removed *in vacuo* to give the title compound ^1H nmr (MeOD, 400 MHz), 8 05(s, 1H), 4 75(m, 1H), 4 60(m, 1H), 4 20(m, 2H), 4 00(m, 1H), 2 90(m, 1H), 2 40(q, 2H), 2 10(m, 1H), 1 70(m, 2H), 1 60(m, 2H), 1 20(t, 3H), 0 95(t, 6H), MS (ES+) *m/e* 411 (MH^+)

Example 15

N-[(1S,2R,3S,4R)-4-[6-(1-ethyl-propylamino)-2-hex-1-ynyl-purin-9-yl]-2 3-dihydroxy-cyclopentyl]-propionamide

72

This compound is prepared from {(1S,'R,3S,4R)-4 [2-chloro-6-(1 ethyl propylamino) purin-9 yl] 2,3 dihydroxy cyclopentyl}-propionyl-carbamic acid tert-butyl ester using a procedure analogous to that of Example 3

Example 16

N-[(1S,2R,3S,4R)-4-[6-(2,2-Diphenyl-ethylamino)-2-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl]-propionamide

N {(1S,2R,3S,4R) 4-[2-Chloro-6-(2,2 diphenyl ethylamino)-purin-9 yl]-2,3 dihydroxy-cyclopentyl}-propionamide (46 8 mg, 90 µmol) of Example 4, L-phenylalaninol (271 mg, 1 80 mmol) and sodium iodide (6 75 mg, 4 1 µmol) are placed in a 0 5-2 5 ml microwave vial Acetonitrile (0 25 ml) and NMP (0 25 ml) are added and the reaction mixture is heated using microwave radiation in a Personal Chemistry Emrys™ Optimizer microwave reactor at 200° C The reaction is shown to be complete by LCMS after 1 hour The title compound is obtained after purification by reverse phase column chromatography (Isolute™ C18, 0–100% acetonitrile in water – 0 1% TFA) MS (ES+) *m/e* 636 (MH^+)

Example 17

N-[(1S,2R,3S,4R)-4-[6-(1 Ethyl-propylamino)-2-(2-piperidin-1-yl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl]-propionamide

N {(1S,2R,3S,4R)-4-[2 Chloro-6-(1-ethyl-propylamino) purin 9 yl] 2,3 dihydroxy-cyclopentyl} propionamide (the compound of Example 14) is reacted with 1 (2 aminoethyl)-piperidine to give the title compound using a procedure analogous to that of Example 9 MS (ES+) *m/e* 503 (MH^+)

Example 18

N-[(1S,2R,3S,4R)-4-[2-[2 (1-Ethyl-1H-imidazol-4-yl)-ethylamino]-6-(1-ethydroxy-cyclopentyl]-propionamide

N {(1S,2R,3S,4R)-4-[2 Chloro-6-(1 ethyl-propylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl} propionamide (the compound of Example 14) is reacted with 2-(1-ethyl-1H-imidazol 4-yl)-ethylamine to give the title compound using a procedure analogous to that of Example 9 MS (ES+) *m/e* 514 (MH^+)

Example 19

N-[(1S,2R,3S 4R)-4-[2-[2 (1-Isopropylthyl-1H-imidazol-4-yl)-ethylamino]-6-(1-ethydroxy-cyclopentyl]-propionamide

N {(1S,2R,3S,4R)-4-[2-Chloro-6-(1-ethyl-propylamino)-purin 9-yl]-2,3 dihydroxy cyclopentyl} propionamide (the compound of Example 14) is reacted with 2-(1-isopropylethyl 1H-imidazol-4 yl) ethylamine to give the title compound using a procedure analogous to that of Example 9 MS (ES+) *m/e* 528 (MH^+)

Example 20

N-[(1S,2R,3S,4R)-4-[2-(4-Amino-cyclohexylamino)-6-(1-ethyl-propylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl]-propionamide

N {(1S,2R,3S,4R) 4-[2-Chloro 6-(1-ethyl-propylamino)-purin 9-yl] 2,3 dihydroxy cyclopentyl} propionamide (the compound of Example 14) is reacted with trans 1 4 diaminocyclohexane to give the title compound using a procedure analogous to that of Example 9 MS (ES+) *m/e* 489 (MH^+)

Example 21

N-((1S,2R,3S,4R) 4-{6-Amino-2-[2-(1 ethyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl} 2,3-dihydroxy-cyclopentyl)-isobutyramide

N-[(1S,2R,3S 4R)-4-(6-Amino 2 chloro purin 9 yl)-2,3 dihydroxy cyclopentyl]-isobutyramide

(1S,2R,3S,5R)-3 Amino 5-(6-amino 2 chloro purin 9-yl)-cyclopentane-1,2-diol trifluoroacetate (an intermediate for preparing the compound of Example 1) is reacted with isopropionyl chloride to give the title compound using a procedure analogous to that of Example 1 MS (ES+) *m/e* 355 (MH^+)

N ((1S,2R,3S 4R) 4-{6 Amino-2-[2-(1-ethyl 1H-imidazol-4-yl) ethylamino]-purin 9 yl} 2,3-dihydroxy-cyclopentyl)-isobutyramide

N-[(1S,2R,3S,4R) 4-(6-Amino-2-chloro-purin 9-yl) 2,3 dihydroxy-cyclopentyl]-isobutyramide is reacted with and 2-(1-ethyl-1H-imidazol-4-yl) ethylamine to give the title compound using a procedure analogous to that of Example 9 MS (ES+) *m/e* 458 (MH^+)

Example 22

Cyclopropanecarboxylic acid ((1S 2R 3S,4R)-4-{6-(2,2-diphenyl-ethylamino)-2-[2-(1-isopropyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-2 3-dihydroxy-cyclopentyl)-amide trifluoroacetate

(2 Chloro-9H-purin-6-yl) (2 2-diphenyl ethyl) amine

2,6 Dichloropurine (2 0 00 g, 106 mmol) is dissolved in THF (250 ml) under an atmosphere of argon Diisopropylamine (16 38 g, 127 mmol) is added followed by 2,2 diphenylethylamine

(2.5 00 g, 1.27 mmol) and the reaction mixture is stirred at 50°C The reaction is shown to be complete by LCMS after 6 hours 50% of the solvent is removed *in vacuo* and replaced with MeOH The resulting precipitate is filtered off and dried to give the title compound ^{1}H nmr (d_6-DMSO, 400 MHz), 8 05(br s, 1H), 7 35 7 10(m, 10H), 4 55(m, 1H), 4 10(m, 2H), MS (ES+) *m/e* 350 (MH^+)

(1S,4R) 4-[2-Chloro-6 (2 2-diphenyl ethylamino)-purin-9-yl] cyclopent-2 enol

(2 Chloro-9H purin-6-yl)-(2,2-diphen /l-ethyl)-amine (12 92 g, 36 97 mmol) is placed in an oven dried flask under an atmosphere of argon Dry deoxygenated THF (100 ml) and dry DMSO (2 ml) are added and the suspension is cooled on an ice bath Sodium hydride 95% (0 89 g, 36 97 mmol) is then slowly added and the solution is stirred at room temperature for 30 minutes (1S,4R)-cis 4-Acetoxy 2-cyclopenten 1 ol (5 00 g 35 20 mmol) and triphenylphosphine (1 38 g, 5 28 mmol) are placed in an oven dried flask under an atmosphere of argon Dry deoxygenated THF (50 ml) is added This solution is added to the anion solution Tetrakis(triphenylpho phine)palladium(0) (2 03 g, 1 76 mmol) is added and the reaction mixture is stirred at 50°C The reaction is shown to be complete by LCMS after 3 hours The reaction mixture is allowed to cool and the solvent is removed *in vacuo* The residue is taken up in dichloromethan (50 ml) and poured into vigorously stirring diethyl ether (300 ml) The precipitate is filtered off, the filtrate is taken and the solvent is removed *in vacuo* to give the title compound ^{1}H nmr ($CDCl_3$, 400 MHz), 7 65(m, 1H), 7 35-7 15(m, 10H), 6 35(m, 1H), 5 90(m, 1H), 5 80(m, 1H), 5 50(m, 1H), 5 25(d, 1H), 4 85(t, 1H), 4 35(t, 1H), 4 25(m, 2H), 2 95(m, 1H), 2 15(d, 1H), MS (ES+) *m/e* 432 (MH^+)

Carbonic acid (1S 4R)-4-[2 chloro-6 (2.2 diphenyl-ethylamino)-purin 9-yl]-cyclopent-2 enyl ester ethyl ester

(1S,4R)-4-[2-Chloro-6-(2,2-diphenyl-ethylamino) purin-9-yl]-cyclopent-2-enol (3 00 g, 6 95 mmol) is placed in an oven-dried flask under an atmosphere of argon Dry THF (100ml) is added followed by dry pyridine (1 10 g, 13 90 mmol) Ethyl chloroformate (3 02 g, 27 80 mmol) is added slowly and the reaction mixture is stirred at room temperature The reaction is shown to be complete by TLC after 4 hours The solvent is removed *in vacuo* and the residue is partitioned between dichloromethane (200 ml) and 10% citric acid (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 purification by flash column chromatography (silica, iso hexane / ethyl acetate 2 1) ^{1}H nmr ($CDCl_3$, 400 MHz), 7 70(br s, 1H), 7 35-7 15(m, 10H), 6 35(m, 1H), 6 15(m, 1H), 5 80(m, 1H), 5 65(m, 2H), 4 35(t, 1H), 4 25(m, 2H), 4 20(q, 2H), 3 10(m, 1H), 1 95(d, 1H), 1 30(t, 3H), MS (ES+) *m/e* 504 (MH^+)

9 ((1R,4S)-4-(Bis (tert butyloxycarbonyl)) amino cyclopent-2 enyl) 2 chloro 9H-purin 6-yl] (2,2-diphenyl ethyl) amine

Carbonic acid (1S,4R)-4 [2-chloro-6-(2,2 diphenyl-ethylamino) purin 9-yl] cyclopent 2-enyl ester ethyl ester (3 2g, 6 3mmol), di-t-butyl imino-dicarboxylate (1 5 g, 7 0 mmol) and triphenyl phosphine (250 mg, 0 95 mmol) are dissolved in degassed THF (30 ml) under an argon atmosphere Tris(dibenzylidene acetone)dipalladium (0) (291 mg,0 32 mmol) is added and the mixture is heated at 40°C for 1 5 hours The reaction mixture is cooled to room temperature and the solvent is removed under reduced pressure The residue is purified by column chromatography on silica gel eluting with a gradient system of ethyl acetate iso-hexane (0 100 by volume) gradually changing to ethyl acetate iso-hexane (20 80 by volume) to afford the title compound LCMS (electrospray) m/z [MH+] 631 32

(1S,2R,3S,5R)-3 (Bis (tert butyloxycarbonyl)) amino-5 [2-chloro 6 (2,2 diphenyl-ethylamino)-purin-9-yl] cyclopentane 1 2-diol

A solution of 9-((1R,4S) 4 (Bis-(tert butyloxycarbonyl))-amino-cyclopent 2-enyl)-2-chloro-9H-purin 6-yl]-(2,2 diphenyl ethyl)-amine (2 9 g, 4 6 mmol) in THF (60 ml) is treated with 4 methyl morpholine N oxide (1 1g, 9 3 mmol) and osmium tetroxide (4% solution in water) (6 ml) and the mixture is stirred at room temperature for 48 hours The solvent is removed under reduced pressure and the residue is purified by column chromatography on silica gel eluting with a gradient system of methanol dichloromethane (0 100 by volume) gradually changing to methanol dichloromethane (4 96 by volume) to afford the title compound LCMS (electrospray) m/z [MH+] 665 34

(1S,2R,3S,5R)-3 Amino 5 [2-chloro-6 (2,2 diphenyl-ethylamino) purin-9-yl]-cyclopentane-1 2 diol hydrochloride

(1S,2R,3S,5R)-3-(Bis-(tert butyloxycarbonyl)) amino 5-[2-chloro 6 (2,2-diphenyl-ethylamino)-purin 9-yl]-cyclopentane-1,2-diol (1 9 g, 2 9 mmol) is dissolved in hydrogen chloride solution (4 M in 1,4–dioxane) (13 ml, 51 2 mmol) and the mixture is stirred at room temperature for 1 hour The solvent is removed under reduced pressure and the residue is purified by reverse phase chromatography eluting with a gradient system of acetonitrile (0 1% HCl) water (0 1% HCl) (0 100 by volume) gradually changing to acetonitrile (0 1% HCl) water (0 1% HCl) (100 0 by volume) to afford the title compound LCMS (electrospray) m/z [MH+] 465 20

Cyclopropanecarboxylic acid {(1S 2R,3S,4R)-4 [2-chloro-6 (2 2 diphenyl ethylamino)-purin 9 yl] 2,3 dihydroxy cyclopentyl}-amide

A solution of (1S,2R,3S,5R) 3-Amino 5-[2 chloro 6-(2,2 diphenyl ethylamino)-purin 9 yl]-cyclopentane-1,2 diol hydrochloride (100 mg, 0 4 mmol) in dry THF (2 5 ml) is treated with diisopropylethylamine (0 35 ml, 2 mmol) and cyclopropanecarboxylic acid chloride (0 036 ml, 0 4 mmol) and the mixture is stirred at room temperature for 48 hours The solvent is removed under reduced pressure and the residue is purified by reverse-phase chromatography eluting with a gradient system of acetonitrile (0 1% TFA) water (0 1% TFA) (0 100 by volume) gradually changing to acetonitrile (0 1% TFA) water (0 1% TFA) (100 0 by volume) to afford the title compound LCMS (electrospray) m/z [MH+] 533 25 ^{1}H nmr (MeOD, 400 MHz), 8 00(s, 1H), 7 40 7 25(m, 8H) 7 25-7 20 (m, 2H), 4 75(m, 1H), 4 60(m, 1H), 4 50(m, 1H), 4 20(m, 2H), 4 00(m, 1H), 2 85(m, 1H), 2 10(m, 1H), 1 85(m, 1H), 0 95-0 80(m, 4H)

Cyclopropanecarboxylic acid ((1S 2R,3S,4R) 4-{6-(2,2-diphenyl ethylamino)-2-[2 (1-isopropyl 1H imidazol-4-yl)-ethylamino] purin-9 yl} 2,3-dihydroxy cyclopentyl) amide trifluoroacetate

A solution of cyclopropanecarboxylic acid {(1S,2R,3S,4R) 4 [2 chloro-6 (2,2–diphenyl-ethylamino) purin 9-yl]-2,3-dihydroxy cyclopentyl} amide (20 mg, 0 04 mmol) in NMP acetonitrile (1 1) (0 5 ml) is treated with 2 (1-isopropyl-1H imidazol-4 yl) ethylamine (30 mg, 0 2 mmol) and sodium iodide (6 mg, 0 04 mmol) and the mixture is heated at 200°C for 30 minutes in a Personal Chemistry Emrys™ Optimizer microwave reactor The reaction mixture is purified by reverse-phase chromatography eluting with a gradient system of acetonitrile (0 1% TFA) water (0 1% TFA) (0 100 by volume) gradually changing to acetonitrile (0 1% TFA) water (0 1% TFA) (100 0 by volume) to afford the title compound LCMS (electrospray) m/z [MH+] 650 22

Example 23

Cyclobutanecarboxylic acid ((1S 2R 3S,4R)-4-{6-(2,2-diphenyl-ethylamino)-2-[2-(1-isopropyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl}-2,3-dihydroxy-cyclopentyl)-amide trifluoroacetate

Cyclobutanecarboxylic acid {(1S,2R,3S,4R)-4-[2 chloro 6-(2,2 diphenyl ethylamino)-purin-9-yl] 2,3-dihydroxy-cyclopentyl}-amide.

A solution of (1S,2R,3S,5R)-3-amino 5 [2-chloro-6-(2,2 diphenyl-ethylamino)-purin-9 yl] cyclopentane-1,2 diol hydrochloride (an intermediate for preparing Example 22) (100 mg, 0 2 mmol) in dry THF (1 ml) is treated with diisopropylethylamine (0 17 ml, 1mmol) and cyclobutanecarboxylic acid chloride (0 023 ml, 0 2 mmol) and the mixture is stirred at room

temperature for 48 hours The solvent is removed under reduced pressure The residue is purified by reverse phase chromatography eluting with a gradient system of acetonitrile (0 1% TFA) water (0 1% TFA) (0 100 by volume) gradually changing to acetonitrile (0 1% TFA) water (0 1% TFA) (100 0 by volume) to afford the title compound (51mg) LCMS (electrospray) m/z [MH+] 547 26 ^{1}H nmr (MeOD, 400 MHz), 8 00(s, 1H), 7 40-7 25(m, 8H), 7 20-7 15 (m, 2H), 4 70(m, 1H), 4 50(m, 2H), 4 20(m, 2H), 3 95(m, 1H), 2 85(m, 1H), 2 30(m, 2H), 2 20(m, 2H), 2 05(m, 2H), 1 90(m, 1H)

Cyclobutanecarboxylic acid ((1S 2R,3S,4R)-4-[6 (2,2 diphenyl-ethylamino)-2-[2 (1 isopropyl 1H-imidazol-4 yl) ethylamino] purin 9 yl] 2,3-dihydroxy cyclopentyl) amide trifluoroacetate

The title compound is prepared using a method that is analogous to that used to prepare the compound of Example 22 using cyclobutanecarboxylic acid {(1S,2R,3S,4R)-4-[2-chloro-6-(2,2 diphenyl-ethylamino) purin-9 yl] 2,3 dihydroxycyclopentyl}-amide, 2-(1-isopropyl 1H imidazol 4-yl) ethylamine (see preparation of intermediates) (30 mg, 0 2 mmol) and sodium iodide (6 mg, 0 04 mmol) LCMS (electrospray) m/z [MH+] 664 44

Example 24

N-((1S,2R,3S 4R)-4-(6-(2 2-Diphenyl-ethylamino)-2-[2-(1-isopropyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl)-2 3-dihydroxy-cyclopentyl)-butyramide trifluoroacetate

N {(1S,2R,3S,4R) 4-[2-Chloro 6-(2 2 diphenyl ethylamino) purin 9 yl] 2,3-dihydroxy cyclopentyl} butyramide

The title compound is prepared by the same method as cyclobutanecarboxylic acid {(1S,2R,3S,4R)-4 [2-chloro-6 (2,2-diphenyl ethylamino)-purin 9 yl] 2,3 dihydroxy-cyclopentyl}-amide from (1S,2R,3S,5R) 3-amino 5-[2-chloro 6-(2,2 diphenyl-ethylamino) purin-9-yl]-cyclopentane-1,2-diol hydrochloride (an intermediate for preparing the compound of Example 22) and butyryl chloride to afford the title compound (48 mg) LCMS (electrospray) m/z [MH+] 535 26 ^{1}H nmr (MeOD, 400 MHz), 8 00(s, 1H), 7 40-7 30(m, 8H), 7 25 7 15 (m, 2H), 4 75(m, 1H), 4 60(m, 1H), 4 50(m, 1H), 4 20(m, 2H), 3 95(m, 1H), 2 85(m, 1H), 2 35(m, 2H), 2 05(m, 1H), 1 70(m, 2H), 1 00(m, 3H)

N-((1S,2R,3S,4R) 4-(6-(2,2-Diphenyl ethylamino) 2 [2-(1-isopropyl-1H-imidazol-4-yl) ethylamino] purin 9-yl) 2 3 dihydroxy cyclopentyl) butyramide trifluoroacetate

The title compound is prepared using a method that is analogous to that used to prepare the compound of Example 22 using N {(1S,2R,3S,4R)-4 [2 chloro-6 (2,2 diphenyl ethylamino)-purin-9-yl] 2,3 dihydroxy-cyclopentyl} butyramide, 2 (1-isopropyl 1H imidazol-4-yl)

ethylamine (see preparation of intermediates) (30 mg, 0 2 mmol) and sodium iodide (6 mg, 0 04 mmol) LCMS (electrospray) m/z [MH+] 652 44

Example 25

N-{(1S,2R,3S,4R)-4-[6-(2 2-Diphenyl ethylamino)-2-[2-(1-isopropyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl]-2 3-dihydroxy-cyclopentyl}-isobutyramide trifluoroacetate

N {(1S,2R,3S,4R)-4-[2-Chloro-6 (2 2 diphenyl-ethylamino) purin 9-yl] 2 3-dihydroxy cyclopentyl}-isobutyramide

The title compound is prepared by the same method as cyclobutanecarboxylic acid {(1S,2R,3S,4R)-4 [2-chloro 6 (2,2 diphenyl ethylamino)-purin 9 yl] 2,3-dihydroxy-cyclopentyl} amide from (1S,2R,3S,5R) 3-amino 5 [2 chloro 6 (2,2 diphenyl-ethylamino)-purin-9 yl] cyclopentane 1,2-diol hydrochloride (an intermediate for preparing the compound of Example 22) and isobutyryl chloride o afford the title compound LCMS (electrospray) m/z [MH+] 535 26 ^{1}H nmr (MeOD, 400 MHz), 8 00(s, 1H), 7 40-7 30(m, 8H), 7 25 -7 15 (m, 2H), 4 75(m, 1H), 4 60(m, 1H), 4 50(m, 1H), 4 20(m, 2H), 3 95(m, 1H), 2 85(m, 1H), 2 70(m, 1H), 2 10(m, 1H), 1 20 (m,6H)

N {(1S,2R,3S 4R)-4-[6-(2 2-Diphenyl ethylamino) 2-[2-(1 isopropyl 1H-imidazol-4-yl)-ethylamino] purin-9-yl]-2 3 dihydroxy cyclopentyl) isobutyramide trifluoroacetate

The title compound is prepared using a method that is analogous to that used to prepare the compound of Example 22 using N {(1S,2R,3S,4R) 4 [2-chloro-6-(2,2-diphenyl-ethylamino)-purin-9 yl] 2,3-dihydroxy-cyclopentyl} isobutyramide, 2 (1 isopropyl 1H imidazol-4-yl) ethylamine (see preparation of intermediates) (30 mg, 0 2 mmol) and sodium iodide (6 mg, 0 04 mmol) LCMS (electrospray) m/z [MH+] 652 44

Example 26

N-{(1S,2R,3S 4R)-4-[6-(2 2-Diphenyl-ethylamino)-2-[2-(1-isopropyl-1H-imidazol-4-yl)-ethylamino]-purin-9-yl]-2 3-dihydroxy-cyclopentyl)-2-phenyl-acetamide trifluoro acetate

N {(1S,2R,3S,4R)-4-[2 Chloro-6-(2 2 diphenyl ethylamino)-purin 9-yl]-2 3 dihydroxy cyclopentyl} 2-phenyl acetamide

A solution of (1S,2R,3S,5R)-3 amino 5 [2 chloro-6-(2,2 diphenyl ethylamino)-purin-9-yl]-cyclopentane-1,2 diol hydrochloride (an intermediate for preparing the compound of Example 22) (100mg, 0 2mmol) in dry THF (1 ml) is treated with diisopropylethylamine (0 17 ml, 1 mmol) and phenylacetyl chloride (0 026 ml, 0 2 mmol) and the mixture is stirred at room

temperature for 18 hours The solvent is removed under reduced pressure and the residue is dissolved in dichloromethane (2 ml) and washed with dilute hydrochloric acid (2 ml) The organic layer is separated and evaporated under reduced pressure to afford the title compound (114 mg) LCMS (electrospray) m/z [MH+] 583 27

N-{(1S,2R,3S,4R) 4-[6-(2,2-Diphenyl-ethylamino)-2-[2-(1 isopropyl 1H-imidazol-4-yl)-ethylamino] purin 9-yl}-2 3-dihydroxy cyclopentyl)-2 phenyl-acetamide trifluoroacetate

The title compound is prepared using a method that is analogous to that used to prepare the compound of Example 22 using N {(1S,2R,3S,4R)-4 [2-chloro-6 (2,2 diphenyl ethylamino)-purin-9-yl] 2,3 dihydroxy-cyclopentyl} 2 phenyl acetamide, 2-(1 isopropyl 1H imidazol-4 yl)-ethylamine (see preparation of intermediates) (30 mg, 0 2 mmol) and sodium iodide (6 mg, 0 04 mmol) LCMS (electrospray) m/z [MH+] 700 45

Example 27

Cyclobutanecarboxylic acid {(1S 2R 3 S,4R)-4-[6-(2,2-diphenyl-ethylamino)-2-(2-piperidin-1-yl-ethylamino)-purin-9-yl]-2 3-dihydroxy-cyclopentyl}-amide trifluoroacetate

The title compound is prepared using a method that is analogous to that used to prepare the compound of Example 22 using cyclobutanecarboxylic acid {(1S,2R,3S,4R)-4-[2-chloro-6 (2,2 diphenyl-ethylamino)-purin-9 yl] 2,3 dihydroxycyclopentyl} amide (an intermediate for preparing Example 23), 1-(2-aminoethyl)piperidine (0 057 ml, 0 4 mmol) and sodium iodide (6 mg, 0 04 mmol) LCMS (electrospray) m/z [MH+] 639 45

Example 28

N-{(1S,2R,3S,4R)-4-[6-(2 2-Diphenyl ethylamino)-2-(2-piperidin-1-yl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-butyramide trifluoroacetate

The title compound is prepared using a method that is analogous to that used to prepare the compound of Example 22 using N-{(1S,2R,3S,4R) 4-[2 chloro 6-(2,2 diphenyl-ethylamino)-purin-9-yl]-2,3 dihydroxy-cyclopentyl}-butyramide (an intermediate for preparing Example 24), 1-(2 aminoethyl)-piperidine (0 057 ml, 0 4 mmol) and sodium iodide (6 mg, 0 04 mmol) LCMS (electrospray) m/z [MH+] 627 44

Example 29

N-{(1S,2R,3S,4R)-4-[6-(2 2-Diphenyl-ethylamino)-2-(2-piperidin-1-yl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-isobutyramide trifluoroacetate

The title compound is prepared using a method that is analogous to that used to prepare the compound of Example 22 using N-{(1S,2R,3S,4R)-4-[2 chloro 6 (2,2-diphenyl-ethylamino) purin 9 yl]-2,3 dihydroxy-cyclopentyl}-isobutyramide (an intermediate for preparing Example

25), 1 (2 aminoethyl) piperidine (0 057 ml, 0 4 mmol) and sodium iodide (6 mg, 0 04 mmol) LCMS (electrospray) m/z [MH+] 627 44

Example 30

N-{(1S,2R,3S,4R)-4-[6-(2,2-Diphenyl ethylamino)-2-(2-piperidin-1-yl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-phenyl-acetamide trifluoroacetate

The title compound is prepared using a method that is analogous to that used to prepare the compound of Example 22 using N-{(1S,2R,3S,4R)-4-[2 chloro 6 (2,2-diphenyl-ethylamino)-purin-9-yl] 2,3-dihydroxy cyclopentyl} 2-phenyl-acetamide (an intermediate of Example 26), 1 (2 aminoethyl)-piperidine (0 057 ml, 0 4 mmol) and sodium iodide (6 mg, O 04 mmol) LCMS (electrospray) m/z [MH+] 675 47

Example 31

N-{(1S,2R 3S 4R)-4-[6-(2 2-Diphenyl ethylamino)-2-(2-piperidin-1-yl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-N'-(2-piperidin-1-yl-ethyl)-oxalamide

Isoxazole-5-carboxylic acid {(1S 2R 3S,4R)-4 [2-chloro-6 (2,2 diphenyl-ethylamino)-purin-9-yl]-2,3 dihydroxy-cyclopentyl} amide

The title compound is prepared by the same method as cyclobutanecarboxylic acid {(1S,2R,3S,4R)-4-[2-chloro-6 (2,2 diphenyl-ethylamino) purin 9-yl]-2,3-dihydroxy-cyclopentyl} amide from (1S,2R,3S,5R)-3 amino-5 [2 chloro-6-(2,2-diphenyl-ethylamino)-purin-9-yl] cyclopentane-1,2-diol hydrochloride (an intermediate for preparing the compound of Example 22) and isoxazole 5-carbonyl chloride to afford the title compound LCMS (electrospray) m/z [MH+] 560 28

N-{(1S,2R 3S 4R)-4-[6-(2 2-Diphenyl ethylamino)-2-(2 piperidin-1 yl-ethylamino)-purin 9-yl]-2,3-dihydroxy cyclopentyl}-N'-(2-piperidin-1 yl-ethyl)-oxalamide

The title compound is prepared using a method that is analogous to that used to prepare the compound of Example 22 using isoxazole-5 carboxylic acid {(1S,2R,3S,4R)-4-[2-chloro-6 (2,2 diphenyl-ethylamino)-purin 9-yl] 2,3 dihydroxy-cyclopentyl} amide, 1-(2-aminoethyl)-piperidine (51 mg, 0 4 mmol) and sodium iodide (6 mg, 0 04 mmol) LCMS (electrospray) m/z [MH+] 739 5 5

Example 32

Cyclopropanecarboxylic acid {(1S 2R,3S,4R)-4-[2-((R)-3-amino-pyrrolidin-1-yl)-6-(2 2-diphenyl-ethylamino)-purin-9-yl]-2 3 dihydroxy-cyclopentyl}-amide

The title compound is prepared using a method that is analogous to that used to prepare the compound of Example 22 using cyclopropanecarboxylic acid {(1S,2R,3S,4R)-4-[2-chloro-6-(2,2-diphenyl ethylamino) purin-9 yl] 2,3 dihydroxy-cyclopentyl}-amide (an intermediate for preparing Example 22), (R)-pyrrolidin 3 ylamine (34 mg, 0 4 mmol) and sodium iodide (6 mg, 0 04 mmol) to give a mixture of two regioisomers which are purified by reverse phase column chromatography (Isolute™ C18, 0 100% acetonitrile in water – 0 1% TFA) to give a product which is predominantly cyclopropanecarboxylic acid {(1S,2R,3S,4R) 4 [2-((R)-3 amino-pyrrolidin-1 yl) 6-(2,2-diphenyl ethyl imino) purin-9 yl]-2,3-dihydroxy cyclopentyl} amide LCMS (electrospray) m/z [MH+] 583 42

Example 33

Cyclobutanecarboxylic acid {(1S 2R 3S,4R)-4-[2-((R)-3-amino pyrrolidin-1-yl)-6-(2 2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl} amide

The title compound is prepared using a method that is analogous to that used to prepare the compound of Example 22 using cyclobutanecarboxylic acid {(1S,2R,3S,4R)–4-[2-chloro-6 (2,2-diphenyl ethylamino)-purin 9-yl] 2,3-dihydroxy-cyclopentyl} amide (an intermediate for preparing Example 23), (R) pyrrolidin-3 ylamine (34 mg, 0 4 mmol) and sodium iodide (6 mg, 0 04 mmol) to give a mixture of two regioisomers which are purified by reverse phase column chromatography (Isolute™ C18, 0 100% acetonitrile in water – 0 1% TFA) to give a product which is predominantly cyclobutanecarboxylic acid {(1S,2R,3S,4R)-4 [2 ((R)-3-amino-pyrrolidin 1-yl) 6-(2,2-diphenyl-ethyl imino)-purin 9 yl]-2,3 dihydroxy-cyclopentyl}-amide LCMS (electrospray) m/z [MH+] 597 45

Example 34

N-{(1S,2R 3S 4R)-4-[2-((R)-3-Amino-pyrrolidin-1-yl)-6-(2 2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-2-phenyl-acetamide

The title compound is prepared using a method that is analogous to that used to prepare the compound of Example 22 using N {(1S,2R,3S,4R)-4-[2 chloro-6-(2,2-diphenyl ethylamino)-purin 9 yl]-2,3 dihydroxy cyclopentyl}-2 phenyl-acetamide (an intermediate for preparing Example 26), (R)-pyrrolidin 3-ylamine (34 mg, 0 4 mmol) and sodium iodide (6 mg, 0 04 mmol) to give a mixture of two regioisomers which are purified by reverse phase column chromatography (Isolute™ C18, 0 100% acetonitrile in water – 0 1% TFA) to give a product which is predominantly N-{(1S,2R,3S,4R) 4 [2 ((R) 3-Amino pyrrolidin-1 yl)-6-(2,2 diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy cyclopentyl}-2-phenyl-acetamide LCMS (electrospray) m/z [MH+] 633 46

82

Example 35

N-[(1S,2R,3S,4R)-4-[2-((R)-3-Amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl]-3-phenyl-propionamide

N-[(1S,2R,3S,4R)-4-[2-Chloro-6 (2 2-diphenyl-ethylamino) purin 9-yl]-2 3-dihydroxy-cyclopentyl] 3 phenyl- propionamide

A solution of (1S,2R,3S,5R)-3-amino 5 [2 chloro 6-(2,2 diphenyl-ethylamino)-purin 9-yl]-cyclopentane-1,2-diol hydrochloride (in intermediate for preparing the compound of Example 22) (100mg, 0 2mmol) in dry THF (1 ml) is treated with diisopropylethylamine (O 17 ml, 1 mmol) and 3-phenyl-propionyl chloride (0 03 ml, 0 2 mmol) and the mixture is stirred at room temperature for 18 hours The solvent is removed under reduced pressure and the residue is dissolved in dichloromethane (2 ml) and washed with dilute hydrochloric acid (2 ml) The organic layer is separated and evaporated under reduced pressure to afford the title compound LCMS (electrospray) m/z [MH+] 597 32

N-[(1S,2R,3S,4R)-4-[2-((R)-3-Amino pyrrolidin-1 yl) 6-(2,2 diphenyl-ethylamino)-purin-9-yl] 2,3-dihydroxy cyclopentyl]-3-phenyl propionamide

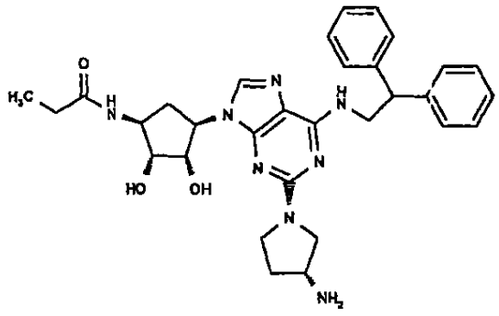
The title compound is prepared using a method that is analogous to that used to prepare the compound of Example 22 using N {(1S,2R,3S,4R)-4-[2 chloro-6-(2,2-diphenyl-ethylamino)-purin 9-yl] -2,3-dihydroxy cyclopentyl]-3-phenyl-propionamide, (R)-pyrrolidin-3 –ylamine (34 mg, 0 4 mmol) and sodium iodide (6 mg, 0 04 mmol) to give a mixture of two regioisomers which are purified by reverse phase column chromatography (Isolute™ C18, 0 1 00% acetonitrile in water – 0 1% TFA) to give a product which is predominantly N {(1S,2R,3S,4R)-4-[2-((R) 3-Amino-pyrrolidin 1-yl) 6 (2,2-diphenyl ethylamino)-purin-9-yl] 2,3-dihydroxy-cyclopentyl]-2 phenyl-acetamide LCMS (electrospray) m/z [MH+] 647 47

Examples 36a and 36b

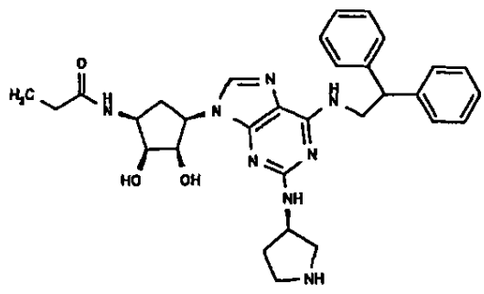
N-[(1S,2R,3S,4R)-4-[2-((1S 3R)-3-Amino-pyrrolidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl]-propionamide and

N-[(1S,2R,3S,4R)-4-[6-(2 2-diphenyl ethylamino)- 2-((R)-pyrrolidin-3-yl-amino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl]-propionamide

83



Example 36a



Example 36b

These compounds are prepared using a method that is analogous to that used to prepare the compound of Example 22 using N-{(1S,2R,3S,4R)-4-[2 chloro 6 (2,2 diphenyl ethylamino)-purin-9 yl] 2,3-dihydroxy cyclopentyl} propionamide (an intermediate for preparing Example 16), (R)-pyrrolidin-3 ylamine (34 mg, 0 4 mmol) and sodium iodide (6 mg, 0 04 mmol) to give a mixture of two regioisomers, namely N {(1S,2R,3S,4R)-4-[2-((1S,3R)-3-Amino-pyrrolidin 1 yl)-6-(2,2-diphenyl ethylamino)-purin-9-yl]-2,3 dihydroxy-cyclopentyl}-propionamide (Example 36a) and N {(1S,2R,3S,4R)-4-[6 (2,2-diphenyl-ethylamino) 2 ((R)-pyrrolidin 3 yl amino) purin 9 yl] 2,3 dihydroxy cyclopentyl}-propionamide (Example 36b), which are purified by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water – 0 1% TFA) to give a product which is predominantly N-{(1S,2R,3S,4R)-4 [2-((R)-3 Amino-pyrrolidin 1-yl) 6-(2,2 diphenyl-ethylamino) purin-9-yl]-2,3-dihydroxy cyclopentyl}-propionamide LCMS (electrospray) m/z [MH+] 571 41

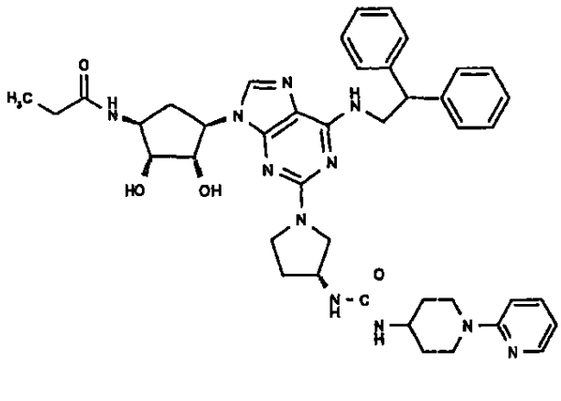
Example 37a and 37b

N-[(1S,2R,3S,4R)-4-(6-(2 2-Diphenyl-ethylamino)-2-[(1S,3R)-3-[3-(3 4 5 6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-ureido]-pyrrolidin-1-yl]-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-propionamide and

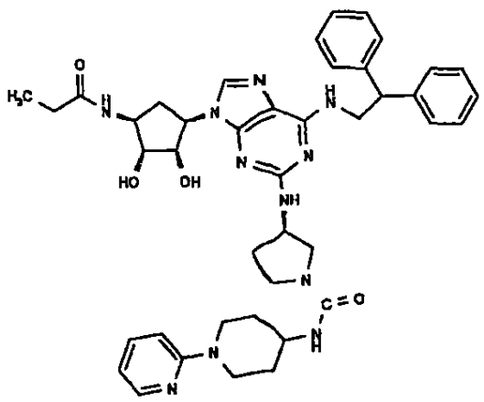
(R)-3-[9-((1R,2S 3R 4S)-2 3-Dihydroxy-4-propionylamino-cyclopentyl)-6-(2 2-diphenyl-ethylamino)-9H-purin-2-ylamino]-pyrrolidine-1-carboxylic acid (3 4 5 6-tetrahydro-2H-[1 2']

84

bipyridinyl-4-yl)-amide



Example 37a



Example 37b

N [(1S,2R,3S,4R)-4-[2 ((R) 3-Amino pyrrolidin 1 yl)-6-(2,2 diphenyl ethylamino)-purin-9-yl] 2,3-dihydroxy-cyclopentyl]-propionamide (30 mg, 0 04 mmol) is dissolved in toluene (2 ml) and ^{i}PrOH (1 ml) *N* [1-(2-Pyridinyl) 4 piperidinyl] 1*H* imidazole-1-carboxamide (prepared using the procedure described in international patent application WO 01/94368) (12 mg, 0 044 mmol) is added as a solution in dichloromethane The reaction mixture is stirred at room temperature The reaction is shown to be complete by LCMS after 24 hours The solvent is removed *in vacuo* The title compounds exist as a mixture of two regioisomers, namely N [(1S,2R,3S,4R)-4-(6-(2,2-Diphenyl ethylamino)-2 [(1S,3R)-3-[3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl 4 yl) ureido] pyrrolidin 1-yl] purin-9 yl)-2,3-dihydroxy-cyclopentyl]-propionamide (Example 37a) and (R) 3-[9 ((1R,2S,3R,4S) 2,3 Dihydroxy-4 propionylamino-cyclopentyl) 6-(2,2-diphenyl ethylamino) 9H purin-2 ylamino]-pyrrolidine 1-carboxylic acid (3,4,5,6 tetrahydro-2H-[1,2']bipyridinyl-4-yl)-amide (Example 37b), and are separated by flash column chromatography (Isolute™ C18, 0-100% acetonitrile in water) LCMS (electrospray) m/z [MH^{+}] 596 42

The structures of the compounds of Example 37a and 37b are assigned using secondary isotope effects in NMR spectroscopy Isotope effects are well established in NMR spectroscopy (B A Bernheim and H Batiz-Hernandez, *Prog Nucl. Magn Reson Spectrosc* 3, 63-85 [1967]) Primary isotope effects have been widely studied (L J Altman et al *J Am Chem Soc* 100, 8264 8266 [1978]), but it is the secondary isotope shift that has provided important structural information These secondary isotope effects are observed in the ^{1}H or X-nucleus (usually ^{13}C) NMR spectra of partially deuterated compounds, a technique known as SIMPLE (*S*econdary *I*sotop*e* *M*ultiplets of *P*artially *L*abelled *E*ntities) Partial

deuteration of exchangeable protons in molecules permits direct observation of the different isotopomers measured under conditions of slow exchange, and the resonance lines separations can be analyzed in terms of two-bond and three-bond isotope effects that contribute to the deuterium induced secondary isotope shift For example, signals from single carbon atoms are observed as a series of multiplets with intensity ratios that vary quantitatively with ^1H ^2H ratios The magnitude of the two- and three-bond effects vary with the configuration of the carbons, and also the substitution and hydrogen bonding of these exchangeable groups It is these signal multiplet formations and magnitude of isotope effects are used to unambiguously assign and confirm the structures of Example 37a and Example 37b

The proton and carbon spectra of the two molecules are assigned by means of standard 1 and 2 D techniques, based on the proposed structures The two urea carbonyls have a shift of 157 38 ppm in Example 37a and 156 34 ppm in Example 37b respectively Both carbonyl moieties are bonded to two nitrogen atoms, however the key difference is that Example 37a is bonded to two NH groups, while the equivalent carbonyl in Example 37b is bonded to one NH group and to the fully substituted nitrogen of the proline ring

Careful titration of deuterium oxide into the two samples results in an approximate 50 50 ratio of protonated and deuterated exchangeable moieties The titration is monitored by means of ^1H NMR, measuring the integrals of the exchangeable protons on addition of 1 µl aliquots of D_2O High resolution ^{13}C spectra are then run on both samples The linkage carbonyl of Example 37a shows a triplet structure, which can only arise from the existence of two partially deuterated groups within two bonds (the triplet consists of NHCONH, [NDCONH/NDCONH] and NDCOND carbon resonances) However, the equivalent carbon in Example 37b consists of a doublet tructure, confirming that this linkage carbonyl is bonded to only one NH grouping thus confirming its structure

Example 38

9-((1R,2S,3R,4S)-2,3-Dihydroxy-4-propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9H-purine-2-carboxylic acid [2-[3-(3,4,5,6-tetrahydro-2H-[1,2]bipyridinyl-4-yl)ureido]-ethyl]-amide

6-(2,2-Diphenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester

6-(2,2-Diphenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester hydrochloride (prepared using the procedure described in international patent application WO 2001/94368) (35 g, 85 3 mmol) is placed in a flask under an atmosphere of argon Dry $CHCl_3$ (300 ml) and

N,O bis(trimethylsilyl)acetamide (61 ml) are added and the reaction mixture is refluxed for 1 hour The reaction mixture is allowed to cool and any volatiles removed *in vacuo* To the resulting oil is added MeOH (300 ml) The resulting white solid is filtered and washed with MeOH (2 x 200 ml) and then dried in a vacuum oven to give the title compound ^{1}H NMR (DMSO, 400 MHz)

6 (2,2 Diphenyl-ethylamino) 9-((1R 4's)-4 hydroxy cyclopent-2 enyl)-9H-purine-2 carboxylic acid methyl ester

To 6 (2,2-diphenyl-ethylamino)-9H purine 2-carboxylic acid methyl ester (5g 13 4mmol) under an atmosphere of argon is added dry deoxygenated tetrahydrofuran (100 ml) and dry dimethyl sulfoxide (2 ml) Sodium hydride 95% (0 32 g, 13 4 mmol) is then added and the solution is stirred at 40 C Separately to (1S,4R)-cis 4 acetoxy-2 cyclopenten 1-ol (1 89 g 13 4 mmol) and triphenylphosphine (0 53 g, 2 0 mmol) in dry deoxygenated tetrahydrofuran (20 ml) is added tris(dibenzylideneacetone)dipalladium(0) (0 69 g, 0 67 mmol) and the mixture stirred at room temperature for 10 minutes This solution is added to the anion solution via syringe and the resulting mixture is then stirred at 80 °C The reaction is shown to be complete by LCMS after 2 hours The reaction mixture is allowed to cool, methanol is added and a solid is filtered The filtrate is concentrated *in vacuo* and the title compound is obtained by precipitation from dichloromethane/hexane ^{1}H NMR (MeOD, 400 MHz), 8 15(s, 1H), 7 40-7 15(m, 10H), 6 20(m, 1H), 5 95(m, 1H), 5 50(m, 2H), 4 75(m, 2H), 4 55(m, 1H), 4 10(m 2H), 3 90(s, 2H), 3 80(s, 1H), 2 9(m, 1H), 1 75(m, 1H)

6-(2,2 Diphenyl-ethylamino) 9 ((1R,4S) 4 ethoxycarbonyloxy cyclopent-2-enyl) 9H-purine 2 carboxylic acid methyl ester

6 (2,2 Diphenyl ethylamino) 9-((1R,4S)-4-hydroxy cyclopent 2 enyl)-9H purine-2 carboxylic acid methyl ester (2 80 g, 6 14 mmol) is placed in an oven-dried flask under an atmosphere of argon Dry tetrahydrofuran (30 ml) is added followed by dry pyridine (0 97 g, 12 3 mmol) Ethyl chloroformate (2 66 g, 24 6 mmol) is added slowly and the reaction mixture is stirred at room temperature The reaction is shown to be complete by LCMS after 3 hours The solvent is removed *in vacuo* and the residue is partitioned between dichloromethane (200 ml) and 1M HCl (2x 200 ml) The organic layer is washed with saturated sodium bicarbonate solution (2 x 200 ml), water (2 x 100 ml), brine (2 x 100 ml), dried over $MgSO_4$, filtered and the solvent is removed *in vacuo* The title compound is obtained after purification by flash column chromatography (silica, 4% MeOH in dichloromethane) MS (ES+) *m/e* 528 3 (MH^+)

9 ((1R,4S)-4 Di-tert-butoxycarbonylamino cyclopent 2 enyl)-6 (2 2 diphenyl ethylamino) 9H purine 2-carboxylic acid methyl ester

6 (2,2-Diphenyl-ethylamino) 9 ((1R,4S) 4 ethoxycarbonyloxy-cyclopent-2-enyl)-9H-purine-2-carboxylic acid methyl ester (2 2 g, 4 2 mmol) is dissolved in deoxygenated tetrahydrofuran The resultant solution is stirred under an atmosphere of argon at room temperature Di-t-butyl iminodicarboxylate (0 9 g, 4 2 mmol), triphenylphosphine (0 16 g, 0 63 mmol) and triethylamine (0 42 g, 4 2 mmol) are added followed by tris(dibenzylideneacetone) dipalladium(0) (0 22 g, 0 21 mmol) The reaction mixture is then stirred at 45 C for 4 hours, allowed to cool to room temperature, methanol is added and the reaction mixture filtered The filtrate is concentrated *in vacuo* The resultant oil is purified by column chromatography (silica, 80% ether in hexane) to yield the title compound, MS (ES+) *m/e* 536 4 (MH^+)

9 ((1R,2S,3R 4S) 4 Di tert-butoxycarbonylamino 2,3-dihydroxy cyclopentyl)-6 (2 2-diphenyl-ethylamino) 9H-purine 2 carboxylic acid methyl ester

The title compound is prepared from 9 ((1R,4S)-4 di-tert-butoxycarbonylamino cyclopent-2-enyl) 6 (2,2 diphenyl-ethylamino)-9H purine-2-carboxylic acid methyl ester using a procedure analogous to that of (1R,2S,3R,5S) 3-[2 chloro 6-(2,2 diphenyl ethylamino)-purin-9-yl]-5 (di Boc amino) cyclopentane-1,2 diol MS (ES+) *m/e* 689 4 (MH^+)

9 ((1R,2S,3R,4S)-4-Amino 2 3 dihydroxy cyclopentyl) 6-(2,2-diphenyl-ethylamino)-9H-purine 2-carboxylic acid methyl ester

9 ((1R,2S,3R,4S)-4-Di-tert butoxycarbonylamino 2,3-dihydroxy cyclopentyl) 6 (2,2 diphenyl-ethylamino)-9H-purine-2 carboxylic acid methyl ester(0 5 g, 0 73 mmol) is dissolved in dioxane and stirred under an atmosphere of argon 4M HCl in dioxane (3 68 ml, 14 5 mmol) is added and the resultant solution is stirred for 20 hours then concentrated *in vacuo* The title compound is obtained by flash column chromatography (Isolute™ C18, 0 100% acetonitrile in water) MS (ES+) *m/e* 489 3 (MH^+)

9-((1R,2S,3R,4S)-2,3-Dihydroxy 4-propionylamino cyclopentyl)-6 (2,2-diphenyl-ethylamino)-9H purine-2-carboxylic acid methyl ester

9 ((1R,2S,3R,4S) ,4-Amino 2,3 dihydroxy cyclopentyl) 6-(2,2-diphenyl-ethylamino)-9H-purine 2-carboxylic acid methyl ester hydrochloride (200 mg, 0 36 mmol) is dissolved in tetrahydrofuran (5 ml) Diisopropylethylamine (0 16 ml, 0 9 mmol) is added and the solution is stirred for 10 minutes Propionyl chloride (33 mg, 0 36 mmol) is added and the reaction mixture is stirred at room temperature for 1 hour The reaction is quenched with methanol

and the title compound is obtained by flash column chromatography (Isolute™ C18, 0-100% acetonitrile in water) MS (ES+) *m/e* 543 (MH+)

9-((1R,2S,3R,4S)-2,3-Dihydroxy-4-propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9H-purine-2-carboxylic acid (2-amino-ethyl)-amide

9-((1R,2S,3R,4S)-2,3-Dihydroxy-4-propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester (62 mg, 1.0 mmol) is dissolved in ethylene diamine (3.4 ml, 51 mmol) and the solution is stirred at 105°C. The reaction is shown to be complete by LCMS after 45 minutes. The reaction mixture is concentrated *in vacuo* and the title compound is obtained after purification by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water) MS (ES+) *m/e* 573.4 (MH+).

9-((1R,2S,3R,4S)-2,3-dihydroxy-4-propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9H-purine-2-carboxylic acid {2-[3-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-ureido]-ethyl}-amide

9-((1R,2S,3R,4S)-2,3-Dihydroxy-4-propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9H-purine-2-carboxylic acid (2-amino-ethyl)-amide (25 mg, 0.044 mmol) is dissolved in toluene (2 ml) and ^{i}PrOH (1 ml). *N*-[1-(2-Pyridinyl)-4-piperidinyl]-1*H*-imidazole-1-carboxamide (prepared using the procedure described in international patent application WO 01/94368) (12 mg, 0.044 mmol) is added as a solution in dichloromethane. The reaction mixture is stirred at room temperature. The reaction is shown to be complete by LCMS after 24 hours. The solvent is removed *in vacuo*. The title compound is obtained by flash column chromatography (Isolute™ C18, 0-100% acetonitrile in water) MS (ES+) *m/e* 388.7 (MH+).

An alternative method for preparing the compound of Example 38 is described below

9-[(1R,4S)-4-(tert-Butoxycarbonyl-propionyl-amino)-cyclopent-2-enyl]-6-(2,2-diphenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester

This compound, which is the trifluoroacetate salt of the final compound of Example 37, is prepared using a method that is analogous to that used to prepare 9-((1R,4S)-4-Di-tert-butoxycarbonylamino-cyclopent-2-enyl)-6-(2,2-diphenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester by replacing di-t-butyl iminodicarboxylate with propionyl carbamic acid tert-butyl ester

9-[(1R,2S,3R,4S)-4-(tert-Butoxycarbonyl-propionyl-amino)-2,3-dihydroxy-cyclopentyl]-6-(2,2-diphenyl-ethylamino)-9H-purine-2-carboxylic acid methyl ester

To a stirred suspension comprising 9 [(1R,4S) 4 (tert butoxycarbonyl propionyl amino) cyclopent 2-enyl] 6-(2,2 diphenyl ethylamino) 9H purine-2-carboxylic acid methyl ester (6 6 g, 10 82 mmol), methane sulphonamide (1 03 g, 10 82 mmol) and AD-mix-α (16 23 g) in t butanol (40 ml) and water (40 ml) is added osmium tetroxide (3 ml of a 4% solution in water) The reaction mixture is stirred vigorously for 36 hours The reaction mixture is partitioned between ethyl acetate and w ter and the organic portion is dried ($MgSO_4$) and concentrated *in vacuo* The titled product is precipitated from methanol Further product is derived from the mother liquor by chromatography on silica eluting with DCM methanol (2S 1)

{(1S,2R,3S,4R) 4-[2-(2 Amino ethylcarbamoyl) 6 (2,2 diphenyl-ethylamin o)-purin 9-yl]-2,3 dihydroxy cyclopentyl} carbamic acid tert butyl ester

This compound is prepared analogously to 9 ((1R,2S,3R,4S)-2,3-dihydroxy-4-propionylamino-cyclopentyl) 6 (2,2 diphenyl ethylamino)-9H-purine 2-carboxylic acid (2-amino-ethyl) amide by replacing 9-((1R,2S,3R,4S) 2,3-dihydroxy-4-propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9H purine 2-carboxylic acid methyl ester with 9-[(1 R,2S,3R,4S) 4 (tert butoxy carbonyl propionyl amino) 2,3-dihydroxy-cyclopentyl]-6-(2,2 diphenyl-ethylamino)-9H purine 2-carboxylic acid methyl ester

(1S,2R,3S,4R)-4 (6 (2,2-Diphenyl ethyl amino) 2 {2 [3 (3 4 5,6 tetrahydro 2H-[1,2']bipyridinyl 4-yl)-ureido]-ethylcarbamoyl}-purin 9-yl) 2 3-dihydroxy-cyclopentyl]-carbamic acid tert butyl ester

This compound is prepared analogously to 9 ((1R,2S,3R,4S) 2,3-dihydroxy-4 propionylamino-cyclopentyl) 6-(2,2 diphenyl ethylamino)-9H-purine 2 carboxylic acid {2-[3 (3,4,5,6 tetra hydro-2H-[1,2]bipyridinyl-4-yl)ureido]-ethyl} amide by replacing 9-((1 R,2S,3R,4S)-2,3 dihydroxy-4-propionylamino-cyclopentyl)-6-(2,2-diphenyl-ethylamino)-9H-purine-2-carboxylic acid (2-amino ethyl)-amide with {(1S,2R,3S,4R) 4-[2-(2-Amino-ethylcarbamoyl)-6-(2,2-diphenyl-ethylamino) purin 9 yl] 2,3 dihydroxy cyclopentyl}-carbamic acid tert butyl ester

9-((1R,2S,3R,4S)-4 Amino 2 3 dihydro cy-cyclopentyl) 6-(2,2-diphenyl-et hylamino) 9H purine-2 carboxylic acid {2 [3-(3,4,5,6 tetrahydro-2H-[1 2']bipyridinyl-4 yl)-ureido]-ethyl} amide dihydrochloride

This compound is prepared analogously to 9 ((1R,2S,3R,4S) 4-Amino-2,3-dihydroxy-cyclopentyl)-6-(2,2-diphenyl ethylamino) 9H purine-2 carboxylic acid methyl ester by replacing 9-((1R,2S,3R,4S)-4-Di tert-butoxycarbonylamino 2,3 dihydroxy cyclopentyl) 6-(2,2

diphenyl-ethylamino)-9H purine 2-carboxylic acid methyl ester with (1S,2R,3S,4R) 4 (6 (2,2-Diphenyl-ethylamino) 2 {2 [3 (3,4,5,6 tetrahydro 2H [1,2']bipyridinyl-4-yl)-ureido] ethylcarbamoyl}-purin-9 yl)-2,3 dihydroxy-cyclopentyl]-carbamic acid tert-butyl ester

9 ((1R,2S,3R 4S)-2 3 Dihydroxy-4-propionylamino cyclopentyl)-6-(2 2-diphenyl-ethylamino) 9H purine 2 carboxylic acid {2 [3 (3,4,5,6 tetrahydro 2H-[1,2]bipyridinyl-4-yl)ureido]-ethyl} amide trifluoroacetate

This compound is prepared analogously to 9 ((1R,2S,3R,4S) 2,3-dihydroxy 4-propionylamino cyclopentyl) 6 (2,2 diphenyl ethylamino)-9H purine-2 carboxylic acid methyl ester by replacing 9 ((1R,2S,3R,4S)-,4 amino-2,3 dihydroxy-cyclopentyl)-6 (2,2-diphenyl-ethylamino)-9H-purine 2 carboxylic acid methyl ester hydrochloride with 9-((1R,2S,3R,4S) 4 Amino-2,3-dihydroxy cyclopentyl) 6 (2,2 diphenyl ethylamino)-9H-purine 2 carboxylic acid {2 [3 (3,4,5,6 tetrahydro 2H [1,2']bipyridinyl 4 yl) ureido] ethyl}-amide dihydrochloride

Example 39

N-{(1S,2R,3S,4R)-4-[6-(2 2-Diphenyl-ethylamino)-2-[(R)-3-((R)-3-pyrrolidin-3-ylureido)-pyrrolidin-1-yl]-purin-9-yl]-2 3-dihydroxy-cyclopentyl}-propionamide trifluoroacetate

This compound is prepared analogously to Example 22 by replacing cyclopropane carboxylic acid {(1S,2R,3S,4R) 4 [2 chloro-6 (2,2 diphenyl-ethylamino) purin-9 yl]-2,3-dihydroxy-cyclopentyl}-amide with N-{(1S,2R,3S,4R) 4-[2-chloro-6 (2,2 diphenyl ethylamino)-purin 9 yl] 2,3-dihydroxy-cyclopentyl}-propionamide and by replacing 2-(1-isopropyl-1H-imidazol-4-yl)-ethylamine with 1,3 di(R) pyrrolidin 3-yl urea

Example 40

Cyclobutanecarboxylic acid {(1S 2R,3S,4R)-4-(6-(2,2-diphenyl-ethylamino)-2-{(R)-3-[3-(3,4,5,6-tetrahydro-2H-[1 2']bipyridinyl-4-yl)-ureido]-pyrrolidin-1 -yl}-purin-9-yl)-2,3-dihydroxy-cyclopentyl]-amide trifluoroacetate

A mixture comprising cyclobutanecarboxylic acid {(1S,2R,3S,4R)-4-[2-((R)-3 amino pyrrolidin-1-yl)-6-(2,2 diphenyl ethyl imino) purin 9-yl]-2,3 dihydroxy-cyclopentyl} amide dihydrochloride (0 02 g, 0 03 mmol), TEA (0 09ml, 0 06 mmol) in iso-propanol (0 5 ml) is treated with imidazole 1 carboxylic acid (3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-amide (0 04 ml of a 10 mg/ml solution in DCM, 0 03 mmol) After the reaction mixture has stirred at room temperature overnight, the solvent is removed *in vacuo* and purification of the crude by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water – 0 1% TFA) yields the titled product

Example 41

9-[(1R,2S,3R 4S)-4-(Cyclobutanecarbonyl-amino)-2,3-dihydroxy-cyclopentyl]-6-(2 2-diphenyl-ethylamino)-9H-purine-2-carboxylic acid {2-[3-(3 ,4,5,6-tetrahydro-2H-[1 2']bipyridinyl-4-yl)-ureido]-ethyl}-amide

This compound is prepared analogously to 9 ((1R,2S,3R,4S)-2,3 Dihydroxy 4-propionyl-amino-cyclopentyl) 6 (2,2-diphenyl ethylamino)-9H-purine-2 carboxylic acid {2-[3-(3,4,5,6-tetrahydro 2H [1,2]bipyridinyl-4-yl)ureido] ethyl }-amide by replacing (1S,2R,3S,5R) 3 amino 5 [2 chloro 6 (2,2-diphenyl ethylamino)-purin-9-yl] cyclopentane-1,2-diol hydrochloride with 9 ((1R,2S,3R,4S) 4 amino-2,3-dihydroxy-cyclopentyl) 6 (2,2-diphenyl ethylamino) 9H purine 2-carboxylic acid {2-[3 (3,4,5,6 etrahydro-2H-[1,2']bipyridinyl 4-yl)-ureido] ethyl}-amide dihydrochloride

Example 42

9 ((1R,2S 3R 4S)-4-Acetylamino-2,3-dihydroxy cyclopentyl)-6-(2 2-diphenyl-ethylamino)-9H-purine-2-carboxylic acid {2-[3-(3 4 5 6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-ureido]-ethyl}-amide trifluoroacetate

A mixture comprising 9 ((1R,2S,3R,4S)-4 amino-2,3-dihydroxy-cyclopentyl) 6-(2,2-diphenyl-ethylamino) 9H purine 2 carboxylic acid {2 [3-(3,4,5,6-tetrahydro-2H [1,2']bipyridinyl-4 yl)-ureido]-ethyl}-amide dihydrochloride (0 02 g, 25 µmol), TEA (0 013 g, 125 µmol) in THF (2 ml) is treated with acetyl chloride (0 003 g, 40 µmol) After the reaction mixture has stirred at room temperature overnight, the solvent is removed *in vacuo* and purification of the crude by reverse phase column chromatography (Isolute™ C18, 0-100% acetonitrile in water – 0 1% TFA) yields the titled product

Example 43

9-((1R,2S 3R 4S)-2 3-Dihydroxy-4-propionylamino-cyclopentyl)-6-(2 2-diphenyl-ethylamino)-9H-purine-2-carboxylic acid {2-[3-((R) 1-pyridin-2-yl-pyrrolidin-3-yl)-ureido]-ethyl}-amide trifluoroacetate

A solution comprising 9 ((1R,2S,3R,4S)-2,3 dihydroxy-4-propionylamino-cyclopentyl) 6-(2,2-diphenyl ethylamino) 9H-purine-2-carboxylic acid methyl ester (0 01 g, 0 018 mmol) and 1-(2 amino-ethyl) 3-((R) 1 pyridin-2-yl-pyrrolidin-3-yl)-urea (0 022 g of a 1 5 mole ratio mixture with imidazole , 0 04 mmol) in 1,2 dichloroethane iso-propanol (0 2 ml of a 1 1 mixture) is heated at reflux for 70 hours The solvent is removed *in vacuo* and purification of the crude by reverse phase column chromatography (Isolute™ C18, 0-65% acetonitrile in water – 0 1% TFA) yields the titled product

Example 44

N-{(1S,2R,3S,4R)-4-[2-(4-Amino-piperidin-1-yl)-6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy-cyclopentyl}-propionamide dihydrochloride

{1 [9-((1R 2S,3R,4S)-2 3 Dihydroxy 4 propionylamino cyclopentyl)-6-(2, 2 diphenyl ethylamino) 9H purin 2 yl] piperidin 4 yl} carbamic acid tert butyl ester trifluoroacetate

This compound is prepared analogously to cyclopropanecarboxylic acid ((1S,2R,3S,4R)-4 {6 (2,2 diphenyl-ethylamino) 2 [2-(1-isopropyl-1H imidazol-4 yl)-ethylamino]-purin-9-yl}-2,3-dihydroxy-cyclopentyl) amide trifluoro acetate by replacing cyclopropanes-carboxylic acid {(1S,2R,3S,4R)-4 [2-chloro 6-(2,2 diphenyl ethylamino)-purin-9-yl] 2,3-dihydroxy cyclopentyl} amide with N-{(1S,2R,3S,4R)-4-[2 chloro 6 (2,2-diphenyl ethylamino)-purin 9 yl] 2,3 dihydroxy-cyclopentyl} propionamide and by replacing 2-(1-isopropyl 1H-imidazol 4 yl) ethylamine with piperidin 4 yl carbamic acid tert-butyl ester

N {(1S,2R,3S,4R)-4 [2-(4-Amino piperidin 1 yl) 6 (2 2-diphenyl-ethylamino) purin-9 yl] 2,3-dihydroxy-cyclopentyl} propionamide dihydrochloride

{1-[9-((1R,2S,3R,4S) 2,3-Dihydroxy-4-propionylamino cyclopentyl) 6-(2,2-diphenyl-ethyl amino)-9H purin-2 yl]-piperidin-4-yl} carbamic acid tert butyl ester trifluoroacetate (0 02 g, 0 03 mmol) is dissolved in HCl (1 ml o a 1 25 M solution in methanol) and allowed to stand at room temperature overnight The solvent is removed *in vacuo* to yield the titled compound

Examples 45 and 46

These compounds, namely N {(1S,2R,3S,4R) 4 [6 (2,2-diphenyl-ethylamino)-2 pyrrolidin 1 yl purin-9-yl]-2,3 dihydroxy-cyclopentyl}-propionamide trifluoroacetate and N-{(1S,2R,3S,4R)-4-[6 (2,2-diphenyl ethylamino) 2 piperazin-1-yl-purin-9-yl]-2,3-dihydroxy cyclopentyl}-propionamide trifluoroacetate, are prepared analogously to cyclopropanecarboxylic acid ((1S,2R,3S,4R)-4 {6-(2,2-diphenyl-ethylamino) 2-[2 (1-isopropyl 1H-imidazol-4-yl)-ethylamino]-purin-9 yl} 2,3 dihydroxy-cyclopentyl)-amide trifluoroacetate by replacing cyclopropanecarboxylic acid {(1S,2R,3S,4R)-4-[2-chloro 6 (2,2-diphenyl-ethylamino) purin-9 yl]-2,3-dihydroxy cyclopentyl} amide with N-{(1S,2R,3S,4R)-4-[2-chloro 6 (2,2-diphenyl-ethylamino)-purin-9-yl]-2,3-dihydroxy cyclopentyl} propionamide and by replacing 2-(1-isopropyl 1H-imidazol 4-yl) ethylamine with the appropriate amine

Example 47

9-((1R,2S 3R 4S)-2 3-Dihydroxy-4-propionylamino-cyclopentyl)-6-(2 2-diphenyl-ethylamino)-9H-purine-2-carboxylic acid {2-[3-((S)-1 pyridin-2-yl-pyrrolidin-3-yl)-ureido]-ethyl}-amide trifluoroacetate

This compound is prepared analogously to 9 ((1R,2S,3R,4S)-2,3-dihydroxy 4 propionylamino cyclopentyl) 6 (2,2 diphenyl ethylamino) 9H-purine 2-carboxylic acid {2-[3-((R) 1-pyridin-2-yl pyrrolidin 3 yl) ureido]-ethyl} amide trifluoroacetate by replacing 1-(2-amino ethyl) 3 ((R) 1 pyridin 2 yl pyrrolidin-3 yl) urea with 1-(2 amino-ethyl)-3-((S)-1 pyridin-2 yl pyrrolidin 3-yl)-urea

Example 48

9-((1R,2S,3R,4S)-2 3-Dihydroxy-4-propionylamino-cyclopentyl)-6-(2 2-diphenyl-ethylamino) 9H-purine-2-carboxylic acid [2-(3-piperidin-4-yl-ureido)-ethyl]-amide

4-[3 (2-{[9-((1R,2S,3R 4S) 2 3 Dihydroxy 4 propionylamino cyclopentyl) 6-(2,2-diphenyl ethylamino) 9H-purine-2 carbonyl] amino}-ethyl) ureido]-piperidine-1-carboxylic acid benzyl ester

To a solution of 9-((1R,2S,3R,4S)-2,3 dihydroxy 4 propionylamino-cyclopentyl)-6 (2,2-diphenyl-ethylamino)-9H-purine 2-carboxylic acid (2-amino-ethyl) amide (0 1 g, 174 mmol) in chloroform (5 ml) is added 4-isocyanato-Z piperidine (0 045 g, 0 174 mmol) in chloroform (5 ml) The reaction mixture is allowed to stir at room temperature overnight and then methanol is added to quench any residual isocyanate The solvent is removed *in vacuo* to yield the titled compound which is used without further purification in the next step

9-((1R,2S,3R 4S) 2 3-Dihydroxy 4 propionylamino-cyclopentyl) 6 (2,2 diphenyl ethylamino) 9H-purine 2-carboxylic acid [2-(3-piperidin-4-yl-ureido)-ethyl]-amide

A solution of 4 [3 (2 {[9-((1R,2S,3R,4S)-2,3-dihydroxy--4-propionylamino-cyclopentyl)-6 (2,2 diphenyl-ethylamino) 9H purine 2 carbonyl]-amino}-ethyl)-ureido] piperidine-1-carboxylic acid benzyl ester (0 145 g, 0 174 mmol) in methanol (1 ml) under an atmosphere of Argon is treated with palladium hydroxide on carbon (0 054 g, 20%w/w carbon) The reaction mixture is placed under an atmosphere of hydrogen and stirred at room temperature for 72 hours and then filtered The filtrate is concentrated *in vacuo* to yield the titled compound as a green oil

Example 49

9-((1R,2S 3R 4S)-2 3-Dihydroxy-4-propionylamino-cyclopentyl)-6-(2 2-diphenyl-ethylamino)-9H purine-2-carboxylic acid [2-[3-(1-methanesulfonyl-piperidin-4-yl)-ureido]-ethyl]-amide trifluoroacetate

To a solution of 9-((1R,2S,3R,4S) 2,3 dihydroxy 4-propionylamino cyclopentyl)-6-(2,2 diphenyl ethylamino) 9H purine-2-carboxylic acid [2 (3-piperidin 4-yl-ureido) ethyl] amide (0 01 g, 0 0143 mmol) in DMF (1 ml) under an inert atmosphere of argon is added triethylamine (TEA) (0 003 g, 0 0286 mmol) followed by mesyl chloride (0 0016 g, 0 0143 mmol) After standing at room temperature overnight, the solvent is removed *in vacuo* and purification of the crude by reverse phase column chromatography (Isolute™ C18, 0 100% acetonitrile in water – 0 1% TFA) yields the titled product

Example 50

N-((1S,2R,3S 4R)-4-[2-Chloro-6-[(naphthalen 1-ylmethyl)-amino] purin-9-yl]-2,3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate

A solution comprising [(1S,2R,3S,4R) 4-(2,6 dichloro-purin-9-yl) 2,3 dihydroxy-cyclopentyl] propionyl carbamic acid tert-butyl ester (0 5 g, 1 1 mmol), DIPEA (0 227 ml, 1 3 mmol), 1 napthalenemethylamine (0 175 ml, 1 2 mmol) in 1,2 dichloro-ethane (3 ml) is heated at 50°C overnight Hydrochloric acid (10 ml of a 0 1 M solution) is added to the reaction mixture and following agitation, the organic portion is separated and treated with TFA (1 ml) After standing at room temperature for 2 hours, the solvent is removed *in vacuo* to yield the titled compound

Example 51-53

These compounds namely,

N [(1S,2R,3S,4R)-4-[2 chloro 6-(3,3-dimethyl butylamino) purin 9-yl] 2,3 dihydroxy cyclopentyl]-propionamide trifluoroacetate (Example 51),

N [(1S,2R,3S,4R)-4-[2-chloro 6 (2,2-diphenyl-propylamino)-purin 9-yl]-2,3-dihydroxy-cyclopentyl]-propionamide (Example 52),

N [(1S,2R,3S,4R) 4-[2-chloro 6 (3,3 diphenyl-propylamino)-purin 9-yl] 2,3-dihydroxy cyclopentyl]-propionamide (Example 53),

are prepared analogously to N-((1S,2R,3S,4R)-4 [2 chloro 6-[(naphthalen 1 ylmethyl) amino]-purin 9-yl]-2,3 dihydroxy cyclopentyl)-propionamide trifluoroacetate by replacing 1 napthalenemethylamine with the appropriate amine Examples 53 and 54 are also treated with potassium carbonate/methanol to afford the product in free form

Example 54

N-{(1S,2R,3S,4R)-4-(6-(1-Ethyl-propylamino)-2-[(R)-3-((R)-3-pyrrolidin-3-ylureido)-pyrrolidin-1-yl] purin-9-yl}-2 3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate

A solution comprising N-{(1S,2R,3S,4R) 4 [2-chloro-6 (1-ethyl-propylamino) purin 9 yl] 2,3-dihydroxy-cyclopentyl}-propionamide (0 02 g, O 03 mmol) and 1,3-di(R)-pyrrolidin-3 yl urea (0 03 g, 0 15 mmol) in DMSO (0 2 ml) is heated to 100°C for 24 hours Purification is carried out using mass directed preparative LC MS eluting with acetonitrile water trifluoroacetic acid to afford the titled compound

Example 55

N-{(1S,2R 3S 4R)-2 3-Dihydroxy-4-[6-[(naphthalen-1-ylmethyl)-amino]-2-[(R)-3-((R)-3-pyrrolidin-3-ylureido)-pyrrolidin-1-yl]-purin-9-yl]-cyclopentyl)-propionamide trifluoroacetate

This compound is prepared analogously to N-((1S,2R,3S,4R)-4-{6 (1 Ethyl-propylamino) 2 [(R) 3-((R)-3-pyrrolidin 3 ylureido)-pyrrolidin 1-yl] purin 9-yl}-2,3-dihydroxy cyclopentyl) propionamide trifluoroacetate by replacing N {(1S,2R,3S,4R) 4 [2 chloro 6 (1-ethyl propylamino) purin 9-yl] 2,3-dihydroxy cyclopentyl}-propionamide with N ((1S,2R,3S,4R) 4 {2-chloro 6-[(naphthalen-1-ylmethyl) amino]-purin-9 yl}-2,3-dihydroxy cyclopentyl) propionamide trifluoroacetate

Example 56

N-{(1S,2R,3S 4R)-4-[2-((R)-3-Amino pyrrolidin-1-yl)-6-(1-ethyl-propylamino)-purin-9-yl]-2 3-dihydroxy-cyclopentyl}-propionamide trifluoroacetate

N-{(1S,2R,3S,4R)-4-[2 chloro-6 (1 ethyl propylamino)-purin-9-yl] 2,3-dihydroxy-cyclopentyl}-propionamide (0 02 g, 0 03 mmol), (3R) 3 (BOC amino)pyrrolidine (0 028 g, 0 15 mmol) and sodium iodide (0 004 g, 0 03 mmol) are placed in a 0 5-2 5 ml microwave vial Acetonitrile (0 25 ml) and NMP (0 25 ml) are added and the reaction mixture is heated using microwave radiation in a Personal Chemistry Emrys™ Optimizer microwave reactor at 160° C for 30 minutes DCM (3 ml) and water (3 ml) are added to the reaction mixture and following agitation, the organic portion is separated and treated with TFA (0 5 ml) After standing at room temperature overnight purification is carried out using mass directed preparative LC MS eluting with acetonitrile water trifluoroacetic acid to afford the titled compound

Example 57

N-{(1S,2R,3S,4R)-4-{2-((R)-3-Amino-pyrrolidin-1-yl)-6-[(naphthalen-1-ylmethyl)-amino]-purin-9-yl}-2,3-dihydroxy-cyclopentyl} propionamide trifluoroacetate

This compound is prepared analogously to N {(1S,2R,3S,4R)-4 [2 ((R)-3 Amino-pyrrolidin-1-yl)-6-(1 ethyl propylamino) purin 9 yl] 2,3-dihydroxy cyclopentyl} propionamide trifluoroacetate by replacing N {(1S,2R,3S,4R) 4-[2-chloro 6 (1-ethyl propylamino)-purin 9 yl]-2,3 dihydroxy-cyclopentyl}-propionamide with N ((1S,2R,3S,4R) 4 {2 chloro-6-[(naphthalen-1 ylmethyl) amino]-purin 9 yl} 2,3-dihydroxy-cyclopentyl) propionamide trifluoroacetate

Examples 58 and 59

These compounds, namely N ((1S,2R 3S,4R)-4-{6 (2,2 diphenyl propylamino)-2-[(R)-3-((R)-3-pyrrolidin-3-ylureido)-pyrrolidin 1-yl purin 9-yl} 2,3-dihydroxy cyclopentyl)–propionamide trifluoroacetate (Example 58) and N ((1S,2R,3S,4R)-4-{6-(3,3 diphenyl propylamino) 2-[(R)-3 ((R) 3 pyrrolidin 3-ylureido)-pyrrolidin-1 yl] purin 9 yl} 2,3 dihydroxy cyclopentyl)-propionamide trifluoroacetate (Example 59), are prepared analogously to N {(1S,2R,3S,4R) 4-{6-(1-ethyl-propylamino)-2 [(R)-3-((R) 3 pyrrolidin-3 ylureido)-pyrrolidin 1 yl]-purin 9-yl} 2,3-dihydroxy-cyclopentyl}-propionamide trifluoroacetate by replacing N {(1S,2R,3S,4R)-4 [2 chloro-6 (1 ethyl-propylamino)-purin 9 yl]-2,3-dihydroxy-cyclopentyl}-propionamide with the appropriate starting materials, the preparations of which are described herein

Examples 60 and 61

These compounds, namely N ((1S,2R,3S,4R) 4 {6 (2,2 diphenyl propylamino)-2-[2 (1-ethyl-1H-imidazol 4 yl) ethylamino]-purin 9 yl] 2,3-dihydroxy cyclopentyl)-propionamide trifluoroacetate (Example 60) and N ((1S,2R,3S,4R)-4-{6-(3,3 diphenyl propyl-amino)-2 [2 (1-ethyl-1H-imidazol-4-yl) ethylamino] purin-9-yl}-2,3 dihydroxy cyclopentyl) propionamide trifluoroacetate (Example 61), are prepared analogously to N-{(1S,2R,3S,4R)–4-[2-((R) 3-amino pyrrolidin 1-yl)-6 (1-ethyl-propylamino)-purin 9 yl] 2,3 dihydroxy-cyclopentyl}-propionamide trifluoroacetate by replacing (3R)-3 (BOC-amino)pyrrolidine with 2 (1 ethyl-1H-imidazol 4 yl) ethylamine and by replacing N-{(1S,2R,3S,4R)-4-[2-chloro–6-(1-ethyl-propylamino)-purin-9-yl] 2,3-dihydroxy cyclopentyl}-propionamide with the appropriate starting materials, the preparations of which are described herein

Example 62

N-{(1S,2R,3S,4R)-4-{6-(3 3-Dimethyl-butylamino)-2-[(R)-3-((R)-3-pyrrolidin–3-ylureido)-pyrrolidin-1-yl]-purin-9-yl}-2 3-dihydroxy cyclopentyl)-propionamide trifluoroacetate

This compound is prepared analogously to N ((1S,2R,3S,4R) 4-{6 (1-ethyl-propylamino) 2-[(R) 3-((R)-3 pyrrolidin-3-ylureido)-pyrrolidin-1 yl] purin 9-yl}-2,3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate by replacing N {(1S,2R,3S,4R)-4 [2 chloro 6 (1-ethyl

propylamino) purin-9-yl] 2,3 dihydroxy-cyclopentyl}-propionamide with N {(1S,2R,3S,4R)-4-[2-chloro 6 (3,3-dimethyl butylamino) purin 9 yl] 2,3 dihydroxy cyclopentyl}-propionamide trifluoroacetate

Example 63

N-{(1S,2R,3S 4R)-4-[6 (1-Ethyl-propylamino)-2-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2 3-dihydroxy-cyclopentyl}-propionamide trifluoroacetate

This compound is prepared analogously to N-{(1S,2R,3S,4R) 4-[6-(2,2-diphenyl-ethylamino) 2 ((S) 1-hydroxymethyl 2 phenyl ethylamino) purin-9-yl]-2,3 dihydroxy cyclopentyl} propionamide (Example 16) by replacing N {(1S,2R,3S,4R)-4 [2 chloro 6-(2,2 diphenyl-ethylamino) purin 9-yl]-2,3 dihydroxy-cyclopentyl}-propionamide (Example 4) with N-{(1S,2R,3S,4R)-4-[2 chloro 6-(1-ethyl propylamino)-purin-9-yl] 2,3 dihydroxy cyclopentyl} propionamide (Example 14)

Example 64

N-((1S,2R,3S,4R)-4-{6-(1-Ethyl-propylamino)-2-[((R)-1-ethyl-pyrrolidin-2-ylmethyl)-amino]-purin-9-yl}-2,3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate

This compound is prepared analogously to N-{(1S,2R,3S,4R)-4-[6-(2,2-diphenyl ethylamino) 2 ((S) 1 hydroxymethyl-2 phenyl ethylamino) purin-9-yl]-2,3 dihydroxy cyclopentyl} propionamide (Example 16) by replacing N-[(1S,2R,3S,4R)-4-[2-chloro 6-(2,2-diphenyl-ethylamino) purin-9-yl] 2,3-dihydroxy-cyclopentyl}-propionamide (Example 4) with N-{(1S,2R,3S,4R)-4 [2 chloro 6-(1-ethyl-propylamino)-purin-9-yl]-2,3 dihydroxy-cyclopentyl} propionamide (Example 14) and by replacing (S)-2-amino 3-phenyl-propan-1-ol with C-((R) 1 ethyl-pyrrolidin 2-yl)-methylamine

Example 65

N-{(1S,2R,3S,4R)-4-[6-Amino-2-((S)-1-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-2 3-dihydroxy-cyclopentyl}-propionamide trifluoroacetate

N {(1S,2R,3S 4R) 4-{2 Chloro-6 [(9H fluoren 9-ylmethyl)-amino]-purin 9 yl}-2,3-dihydroxy cyclopentyl}-propionamide

This compound is prepared analogously to N-((1S,2R,3S,4R)-4 {2-chloro 6-[(naphthalen 1 ylmethyl)-amino] purin 9-yl} 2,3 dihydroxy cyclopentyl)-propionamide trifluoroacetate (Example 50) by replacing 1-napthalene methylamine with C-(9H fluoren 9-yl)-methylamine

N [(1S,2R,3S,4R)-4-[6 Amino-2 ((S) 1 hydroxymethyl 2-phenyl-ethylamino) purin 9 yl] 2 3-dihydroxy-cyclopentyl} propionamide trifluoroacetate

This compound is prepared analogously to N {(1S, 2R,3S,4R) 4 [6 (2,2-diphenyl-ethylamino) 2-((S)-1 hydroxymethyl 2-phenyl ethylamino) purin 9-yl] 2,3 dihydroxy-cyclopentyl}-propionamide (Example 16) by replacing N {(1S,2R,3S,4R) 4 [2 chloro-6 (2,2-diphenyl-ethylamino) purin 9-yl] 2,3 dihydroxy cyclopentyl}-propionamide (Example 4) with N-((1S,2R,3S,4R)-4 {2 chloro-6-[(9H fluoren 9 ylmethyl) amino] purin 9-yl} 2,3-dihydroxy cyclopentyl)-propionamide

Example 66

N-{(1S,2R,3S,4R)-2 3-Dihydroxy-4 [6-[(naphthalen-1-ylmethyl)-amino]-2-(2-piperidin-1-yl-ethylamino)-purin-9-yl]-cyclopentyl} propionamide trifluoroacetate

This compound is prepared analogously to N {(1S, 2R,3S,4R)-4 [6-(2,2 diphenyl-ethylamino) 2-((S)-1 hydroxymethyl 2-phenyl ethylamino) purin-9-yl]-2,3 dihydroxy-cyclopentyl} propionamide (Example 16) by replacing N {(1S,2R,3S,4R)-4 [2-chloro-6 (2,2-diphenyl-ethylamino) purin-9 yl]-2,3-dihydroxy cyclopentyl}-propionamide (Example 4) with N-((1S,2R,3S,4R) 4-[2 chloro 6 [(naphthalen-1 ylmethyl)-amino]-purin-9-yl} 2,3-dihydroxy cyclopentyl) propionamide trifluoroacetate (Example 50) and by replacing (S) 2-amino-3 phenyl-propan 1 ol with 2 piperidin 1 yl ethylamine

Example 67-69

These compounds namely, N-((1S,2R, S,4R) 4-{2-(4 amino-cyclohexylamino) 6 [(naphthalen 1-ylmethyl) amino] purin-9-yl}-2,3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate (Example 67), N-((1S,2R,3S,4R)-2,3 d hydroxy-4-{2-[2-(1H-imidazol 4-yl)-ethylamino]-6 [(naphthalen 1 ylmethyl)-amino]-purin-9 yl} cyclopentyl)-propionamide trifluoroacetate (Example 68) and N ((1S,2R,3S,4R) 4 {2-[((R) 1 Ethyl-pyrrolidin-2-ylmethyl) amino]-6-[(naphthalen 1 ylmethyl) amino]-purin-9-yl} 2,3 dihydroxy-cyclopentyl)-propionamide trifluoroacetate (Example 69) are prepared analogously to N-{(1S,2R,3S,4R) 2,3-dihydroxy 4-[6-[(naphthalen-1-ylmethyl)-amino]-2-(2-piperidin-1-yl-ethylamino)-purin 9-yl] cyclopentyl}-propionamide trifluoroacetate (Example 66) by replacing 2 piperidin 1 yl ethylamine with the appropriate amine

Example 70

These compounds namely, N-{(1S,2R,3S,4R) 4 [2 (4 amino-cyclohexylamino) 6-(3,3 dimethyl butylamino)-purin-9 yl] 2,3 dihydroxy cyclopentyl} propionamide trifluoroacetate (Example 70), N ((1S,2R,3S,4R)-4 {6 (3,3 dimethyl butylamino)-2 [2-(1H-imidazol-4-yl)-ethylamino]-purin-9-yl} 2,3-dihydroxy cyclopentyl)-propionamide trifluoroacetate (Example 71) and

N-((1S,2R,3S,4R)-4-{6-(3,3 Dimethyl butylamino) 2 [((R) 1 ethyl-pyrrolidin 2 ylmethyl)-amino] purin 9-yl}-2,3-dihydroxy cyclopentyl) propionamide trifluoroacetate (Example 72) are prepared analogously to N {(1S,2R,3S,4R) 4-[6 (2,2 diphenyl ethylamino)-2-((S) 1-hydroxy-methyl 2-phenyl-ethylamino) purin-9-yl]-2,3 dihydroxy-cyclopentyl} propionamide (Example 16) by replacing N {(1S,2R 3S,4R)-4 [2 chloro-6 (2,2 diphenyl ethylamino) purin 9 yl]-2,3-dihydroxy-cyclopentyl}-propionamide (Example 4) with N {(1S,2R,3S,4R) 4 [2-chloro-6-(3,3 dimethyl-butylamino) purin 9-yl] 2,3 dihydroxy cyclopentyl}-propionamide trifluoroacetate (Example 51) and by replacing L-phenylalaninol with the appropriate amine

Example 73

N-{(1S 2R 3S 4R)-4-[2-{(R)-3-[3-(2 6 Dichloro-pyridin-4-yl)-ureido]-pyrrolidin-1-yl} 6-(2,2-diphenyl-ethylamino)-purin-9-yl]-2,3 dihydroxy-cyclopentyl}-propionamide trifluoroacetate

A solution of N-{(1S,2R,3S,4R)-4-[2 {(R) 3 amino-pyrrolidin-1-yl)-6 (2,2-diphenyl-ethyl amino) purin-9-yl] 2,3 dihydroxy cyclopentyl} propionamide (Example 36) (23 mg, 40 μmol) in THF (1 ml) is treated with TEA (7 3 mg, 72 μmol) and then added to 2,6-dichloro-4-isocyanato-pyridine (6 8 mg 36 μmol) The reaction mixture is shaken at room temperature and then allowed to stand overnight The solvent is removed *in vacuo* and purification by mass directed preparative LC-MS eluting with acetonitrile water trifluoroacetic acid affords the titled compound

Example 74

N-{(1S,2R,3S,4R)-4-{6-(2 2-Diphenyl-ethylamino)-2-[(R)-3-(3-thiophen-2-yl-ureido)-pyrrolidin-1-yl]-purin-9-yl}-2 3-dihydroxy-cyclopentyl}-propionamide trifluoroacetate

This compound is prepared analogously to N-{(1S,2R,3S,4R)-4-[2 {(R)-3 [3-(2,6-dichloro-pyridin-4 yl)-ureido] pyrrolidin 1 yl} 6-(2,2 diphenyl-ethylamino)-purin-9 yl]-2,3-dihydroxy cyclopentyl}-propionamide trifluoroacetate (Example 73) by replacing 2,6 dichloro-4 isocyanato pyridine with 2 thienyl isocyanate

Example 75

N-{(1S 2R,3S,4R)-4-{6-(2 2-Diphenyl ethylamino)-2-[(R)-3-(3-pyridin-3-yl-ureido)-pyrrolidin-1-yl]-purin-9-yl}-2 3-dihydroxy-cyclopentyl}-propionamide trifluoroacetate

This compound is prepared analogously to 9 ((1R,2S,3R,4S) 4-acetylamino 2,3-dihydroxy cyclopentyl) 6-(2,2-diphenyl ethylamino) 9H purine 2-carboxylic acid {2-[3 (3,4,5,6-tetra hydro 2H [1,2']bipyridinyl 4-yl) ureido] ethyl} amide trifluoroacetate (Ex 42) by replacing 9 ((1R,2S,3R,4S) 4 amino-2,3-dihydroxy cyclopentyl) 6-(2,2 diphenyl ethylamino)-9H-purine 2 carboxylic acid {2 [3-(3,4,5,6 tetrahydro-2H-[1,2']bipyridinyl-4 yl) ureido]-ethyl} amide dihydrochloride (an intermediate for preparing Example 38) with N {(1S,2R,3S,4R) 4 [2 ((R)-3 amino pyrrolidin-1-yl)-6-(2,2 diphenyl ethylamino) purin 9 yl] 2,3 dihydroxy-cyclopentyl} propionamide (Example 36) and by replacing acetyl chloride with 3 isocyanato pyridine

Example 76

Cyclobutanecarboxylic acid {(1S 2R 3S,4R)-4-[6-(2,2-diphenyl-ethylamino)-2-[(R)-3-((R)-3-pyrrolidin-3-ylureido)-pyrrolidin-1 yl] purin-9-yl]-2,3-dihydroxy-cyclopentyl}-amide

This compound is prepared analogously to N ((1S,2R,3S,4R) 4-[6-(1-ethyl-propylamino) 2 [(R) 3 ((R) 3 pyrrolidin 3-ylureido) pyrrolidin 1-yl]-purin 9 yl} 2,3 dihydroxy cyclopentyl} propionamide trifluoroacetate (Example 54) by replacing N {(1S,2R,3S,4R)-4 [2-chloro-6-(1 ethyl propylamino)-purin-9-yl] 2,3 dihydroxy cyclopentyl} propionamide (Example 14) with cyclobutanecarboxylic acid {(1S,2R,3S,4R) 4 [2-chloro-6-(2,2 diphenyl ethylamino)-purin 9-yl] 2,3 dihydroxy cyclopentyl} amide (an intermediate used to prepare Example 23)

Example 77

4-Methyl-piperazine-1-carboxylic acid {(R)-1-[9-((1R,2S,3R 4S)-2 3-dihydroxy-4-propionylamino-cyclopentyl)-6-(2 2-diphenyl-ethylamino)-9H-purin-2-yl]-pyrrolidin-3-yl]-amide trifluoroacetate

Imidazole 1 carboxylic acid {(R) 1 [9-{(3aS,4R,6S,6aR) 2 2 dimethyl 6 propionylamino-tetrahydro cyclopenta[1,3]dioxol 4-yl)-6 (2,2-diphenyl-ethylamino)-9H-purin 2 yl]-pyrrolidin-3-yl}-amide

A mixture comprising N-{(3aR,4S,6R, 6aS)-6-[2 ((R)-3-amino pyrrolidin 1-yl) 6 (2,2 diphenyl-ethylamino) purin-9-yl] 2,2-dimethyl-1 etrahydro-cyclopenta[1,3]dioxol-4-yl} propionamide (see preparation of intermediates) (0 2 4 g, 0 39 mmol) and CDI (0 275 g, 1 7 mmol) in DCM is stirred at room temperature for 3 hours Purification of the resulting mixture by chromatography on silica eluting with 0-5% MeOH in DCM yields the titled compound as a yellow oil The compound exists as a mixture of the imidazole-urea intermediate together with variable amounts of the corresponding isocyanate and imidazole which are equally suitable as precursors to ureas

4 Methyl piperazine-1-carboxylic acid [(R) 1-[9-((1R,2S,3R,4S)-2 3-dihydroxy-4-propionylamino cyclopentyl) 6-(2,2-diphenyl ethylamino) 9H purin-2-yl] pyrrolidin 3-yl] amide trifluoroacetate

A solution of imidazole 1 carboxylic acid [(R)-1-[9-((3aS,4R,6S,6aR) 2,2-dimethyl 6 propionylamino tetrahydro cyclopenta[1,3]dioxol-4-yl)-6 (2,2-diphenyl ethylamino) 9H-purin 2 yl] pyrrolidin-3-yl] amide (25 mg, 40 µmol) in DCM (1 ml) is added to 1-methyl piperazine (4 mg, 40 µmol) and the reaction mixture is stirred at room temperature overnight The solvent is removed *in vacuo* and the crude product is treated with 1 1 TFA/water (1 ml) and stirred at room temperature for 3 hours The resulting mixture is concentrated *in vacuo* and purified by mass directed preparative LC MS eluting with acetonitrile water trifluoroacetic acid to afford the titled compound

Example 78

N-[(1S,2R,3S 4R)-4-[6-(2 2-Diphenyl-ethylamino)-2-[(R)-3-(3-pyridin-2-yl-ureido)-pyrrolidin-1-yl]-purin 9-yl]-2 3-dihydroxy-cyclopentyl)-propionamide trifluoroacetate

This compound is prepared analogously to 4-methyl piperazine-1 carboxylic acid [(R)-1-[9 ((1R,2S,3R,4S)-2,3 dihydroxy-4 propionylamino cyclopentyl)-6-(2,2-diphenyl-ethylamino) 9H purin 2-yl] pyrrolidin-3-yl]-amide trifluoroacetate (Example 77) by replacing 1 methyl piperazine with 2 amino pyridine

Example 79

N-[(1S,2R,3S,4R)-4-[6-(2,2-Diphenyl-ethylamino)-2-[(R)-3-(3-pyridin-4-yl-ureido)-pyrrolidin-1-yl]-purin-9-yl]-2,3-dihydroxy-cyclopentyl)-propionamide hydrochloride

A mixture comprising N-[(1S,2R,3S,4R)-4-[2-((R)-3-amino pyrrolidin-1-yl) 6 (2,2 diphenyl ethylamino)-purin 9 yl]-2,3-dihydroxy cyclopentyl]-propionamide (Example 36) (16 6 mg, 29 µmol) and pyridin-4-yl-carbamic acid phenyl ester [prepared according to the reported procedure in the Journal of Medicinal Chemistry (2005), 48(6), 1857 1872] (6 9 mg, 32 µmol) in NMP (0 5 ml) is heated at 100 °C for 1 hour and then left to stir at room temperature overnight Purification of the product by reverse phase column chromatography (Isolute™ C18, 0 100% acetonitrile in water – 0 1% HCl) affords the titled compound [MH+ 691]

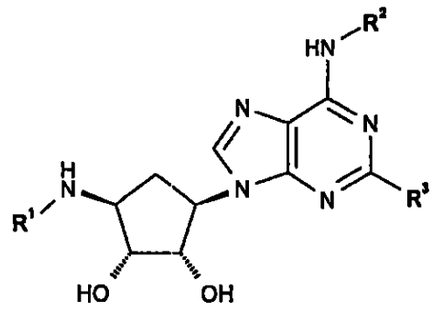
Example 80

N-[(1S,2R,3S,4R)-4-[6-amino-2-[(R)-3 (3-pyridin-3-yl-ureido)-pyrrolidin-1-yl]-purin-9-yl]-2 3-dihydroxy-cyclopentyl)-propionamide

The following compound is prepared analogously to N-((1S,2R,3S,4R)-4-[6 (1-ethyl propylamino) 2 [(R) 3-((R)-3 pyrrolidin-3-ylureido)-pyrrolidin 1-yl] purin 9-yl] 2,3 dihydroxy cyclopentyl) propionamide trifluoroacetate (Example 54)

CLAIMS

1 A compound of formula I



I

in free or salt form, wherein

R^1 is hydrogen, C_1 C_8 alkylcarbonyl, C_3 C_8-cycloalkylcarbonyl, -SO_2-C_1-C_8-alkyl, C_7 C_{14} aralkylcarbonyl or -C(=O)-C(=O) NH-C_1-C_8 alkyl optionally substituted by R^4,

R^2 is hydrogen or C_1-C_8-alkyl optiona ly substituted by C_6-C_{10} aryl,

R^3 is hydrogen, halo, C_2-C_8 alkenyl or C_2 C_8-alkynyl,
or R^3 is amino optionally substituted by C_3-C_8 cycloalkyl optionally substituted by amino,
or R^3 is C_1-C_8-alkylamino optionally substituted by hydroxy, C_6 C_{10}-aryl or by R^5,
or R^3 is R^6 optionally substituted by amino or –NH C(=O) NH-R^7,
or R^3 is –NH R^6 optionally substituted –NH C(=O)-NH R^7,
or R^3 is C_1-C_8-alkylaminocarbonyl or C_3-C_8 cycloalkylamino carbonyl optionally substituted by amino, C_1 C_8 alkylamino, di(C_1-C_8 alkyl)amino or NH C(=O)–NH-R^8,

R^4, R^5 and R^6 are independently a 5 or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5- or 6 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, and

R^7 and R^8 are independently a 5 or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5- or 6 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, C_1-C_8-alkoxy optionally substituted by aminocarbonyl, or a 5 or 6-membered heterocyclic

ring containing at least one ring hetero tom selected from the group consisting of nitrogen, oxygen and sulphur, said ring also 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, C_1 C_8-alkoxy optionally substituted by aminocarbonyl

2 A compound according to claim 1, in which

R^1 is C_1 C_8 alkylcarbonyl, C_3 C_8-cycloalkylcarbonyl, SO_2-C_1 C_8-alkyl, C_7 C_{14}-aralkylcarbonyl or C(=O) C(=O)-NH-C_1 C_8 alkyl optionally substituted by R^4,

R^2 is hydrogen or C_1 C_8-alkyl optionally substituted by C_6 C_{10}-aryl,

R^3 is halo or C_2-C_8-alkynyl,

or R^3 is amino optionally substituted by C_3 C_8 cycloalkyl optionally substituted by amino,

or R^3 is C_1-C_8 alkylamino optionally substituted by hydroxy, C_6-C_{10} aryl or by R^5,

or R^3 is R^6 optionally substituted by amino or –NH-C(=O) NH R^7,

or R^3 is –NH R^6 optionally substituted –NH-C(=O) NH R^7,

or R^3 is C_1 C_8 alkylaminocarbonyl optionally substituted by NH-C(=O) NH-R^8,

R^4, R^5 and R^6 are independently a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5- or 6-membered heterocyclic ring being optionally substituted by C_1-C_8 alkyl, and

R^7 and R^8 are independently a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5- or 6-membered heterocyclic ring being optionally substituted by halo, C_1-C_8-alkyl, C_1-C_8 alkyl-sulfonyl, or a 5 or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur

3 A compound according to claim 1, in which

R^1 is C_1-C_4-alkylcarbonyl, C_3-C_5-cycloalkylcarbonyl, -SO_2 C_1-C_4-alkyl, C_7 C_{10} aralkylcarbonyl or -C(=O) C(=O)-NH-C_1-C_4 alkyl optionally substituted at one position by R^4,

R^2 is hydrogen, unsubstituted C_1-C_6 alkyl or C_1 C_5-alkyl substituted at one position by C_6 C_{10} aryl,

R^3 is halo or C_2-C_6 alkynyl,

or R^3 is amino optionally substituted at one position by C_3-C_6-cycloalkyl optionally substituted at one position by amino,

or R^3 is C_1 C_4 alkylamino substituted at one or two positions by hydroxy, phenyl or by R^5,

or R^3 is R^6 optionally substituted at one position by amino or –NH C(=O) NH-R^7,

or R^3 is –NH R^6 optionally substituted at one position by –NH-C(=O) NH R^7,

or R^3 is C_1 C_4-alkylaminocarbonyl substituted at one position by -NH-C(=O) NH-R^8,

R^4, R^5 and R^6 are independently a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5- or 6 membered heterocyclic ring being optionally substituted at one position by C_1 C_4-alkyl, and R^7 and R^8 are independently a 5 or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5- or 6 membered heterocyclic ring being optionally substituted at one or two positions by halo, C_1-C_4 alkyl, C_1 C_4-alkylsulfonyl, or a 5- or 6 membered N-heterocyclic ring

4 A compound according to claim 1, in which

R^1 is hydrogen, C_1 C_8 alkylcarbonyl, C_1-C_8 cycloalkylcarbonyl, SO_2-C_1 C_8 alkyl, C_7-C_{14} aralkylcarbonyl or C(=O)-C(=O)-NH-C_1 C_8 alkyl optionally substituted by R^4,

R^2 is hydrogen or C_1 C_8 alkyl optionally substituted by C_6 C_{10}-aryl,

R^3 is hydrogen, halo, C_2 C_8-alkenyl or C_2 C_8 alkynyl,

or R^3 is amino optionally substituted by C_3 C_8 cycloalkyl optionally substituted by amino,

or R^3 is C_1-C_8-alkylamino optionally substituted by hydroxy, C_6 C_{10} aryl or by R^5,

or R^3 is R^6 optionally substituted by amino or -NH-C(=O) NH R^7,

or R^3 is C_1 C_8 alkylaminocarbonyl or C_3 C_8-cycloalkylamino-carbonyl optionally substituted by amino, C_1-C_8 alkylamino, di(C_1-C_8 alkyl)amino or NH C(=O) NH-R^8,

R^4, R^5 and R^6 are independently a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, and

R^7 and R^8 are independently a 5- or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5 or 6-membered heterocyclic ring being optionally substituted by a 5- or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur

5 A compound according to claim 4, in which

R^1 is C_1 C_8 alkylcarbonyl, C_3 C_8-cycloalkylcarbonyl, SO_2 C_1 C_8 alkyl, C_7 C_{14} aralkylcarbonyl or C(=O)-C(=O)-NH C_1 C_8-alkyl optionally substituted by R^4,

R^2 is hydrogen or C_1 C_8 alkyl optionally substituted by C_6-C_{10}-aryl,

R^3 is halo or C_2-C_8-alkynyl,

or R^3 is amino optionally substituted by C_3-C_8 cycloalkyl optionally substituted by amino,

or R^3 is C_1-C_8 alkylamino optionally substituted by hydroxy, C_6 C_{10} aryl or by R^5,

or R^3 is R^6 optionally substituted by amino or -NH-C(=O) NH-R^7,

or R^3 is C_1-C_8-alkylaminocarbonyl optionally substituted by NH C(=O) NH R^8,

R^4, R^5, and R^6 are independently a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, and R^7 and R^8 are independently a 5 or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5- or 6 membered heterocyclic ring being optionally substituted by a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur

6 A compound according to claim 5, in which

R^1 is C_1 C_4 alkylcarbonyl, C_3-C_6-cycloalkylcarbonyl, SO_2-C_1-C_4-alkyl, C_7 C_{10} aralkylcarbonyl or -C(=O)-C(=O)-NH C_1 C_4-alkyl optionally substituted by R^4,

R^2 is hydrogen or C_1-C_6 alkyl optionally substituted by C_6 C_{10} aryl,

R^3 is halo or C_2 C_5 alkynyl,

or R^3 is amino optionally substituted by C_3-C_8 cycloalkyl optionally substituted by amino,

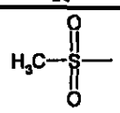
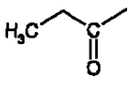
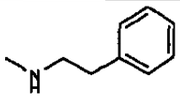
or R^3 is C_1-C_4-alkylamino optionally substituted by hydroxy, C_6-C_8 aryl or by R^5,

or R^3 is R^6 optionally substituted by amino or –NH C(=O)-NH R^7,

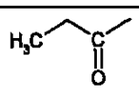
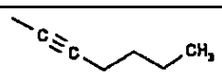
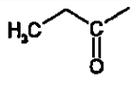
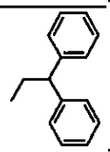
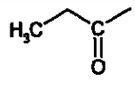
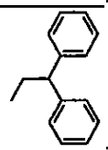
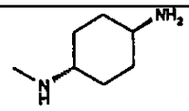
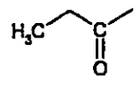
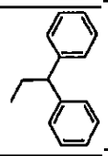
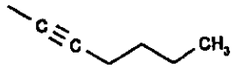
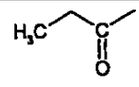
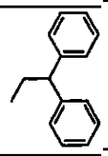
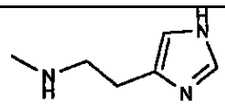
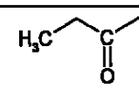
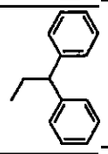
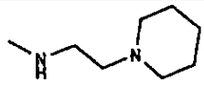
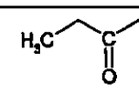
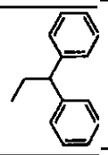
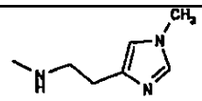
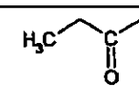
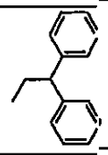
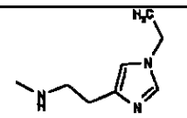
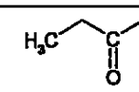
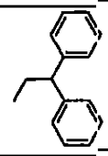
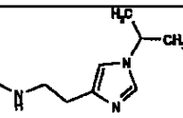
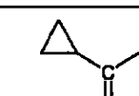
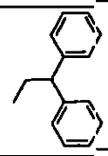
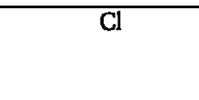
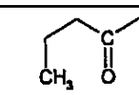
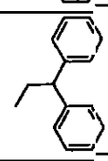
or R^3 is C_1-C_4-alkylaminocarbonyl optionally substituted by NH C(=O) NH-R^8,

R^4, R^5, and R^6 are independently a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, and R^7 and R^8 are independently a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5- or 6 membered heterocyclic ring being optionally substituted by a 5 or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur

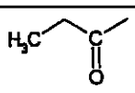
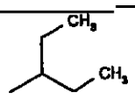
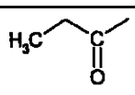
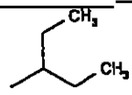
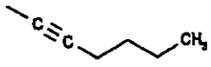
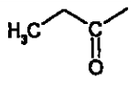
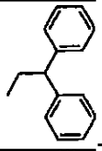
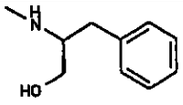
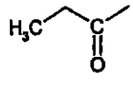
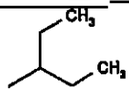
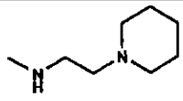
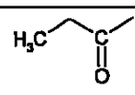
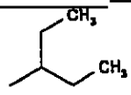
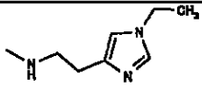
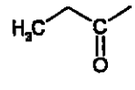
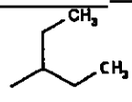
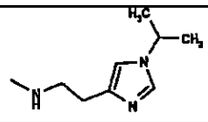
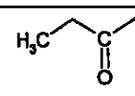
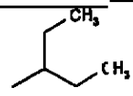
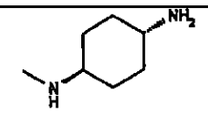
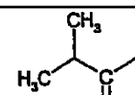
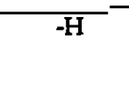
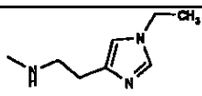
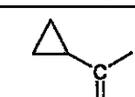
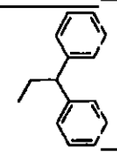
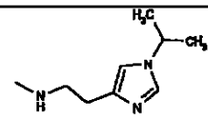
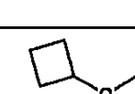
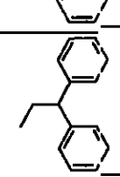
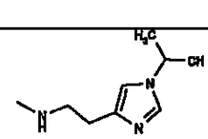
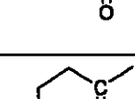
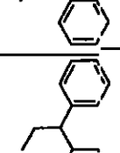
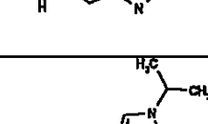
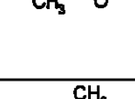
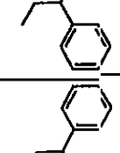
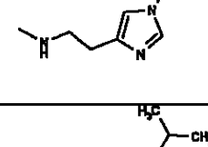
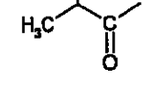
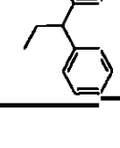
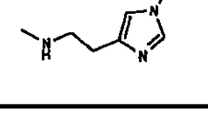
7 A compound of formula I according to claim 1, wherein R^1, R^2 and R^3 are as shown in the following tables

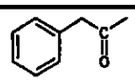
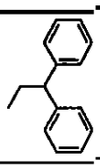
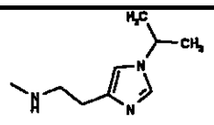
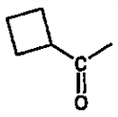
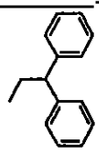
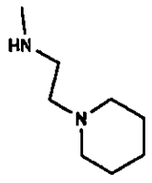
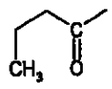
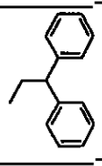
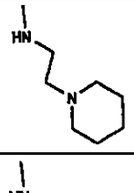
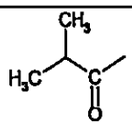
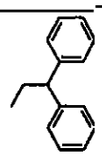
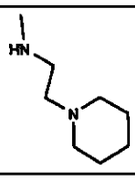
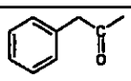
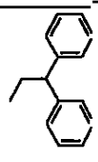
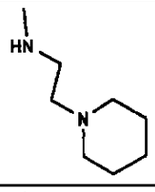
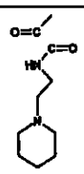
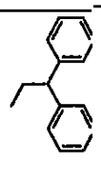
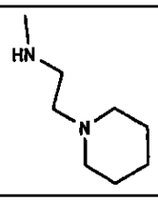
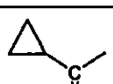
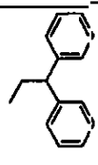
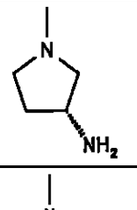
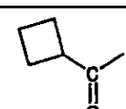
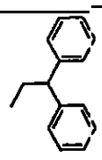
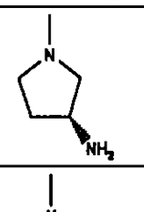
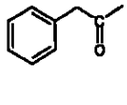
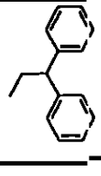
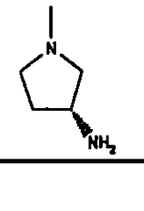
R^1	R^2	R^3
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107

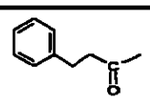
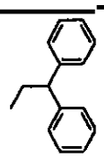
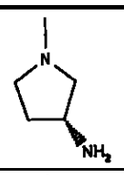
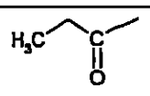
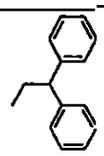
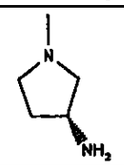
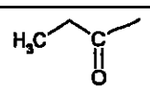
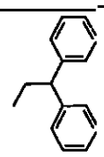
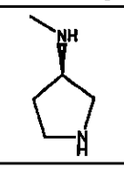
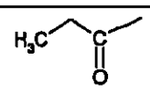
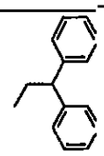
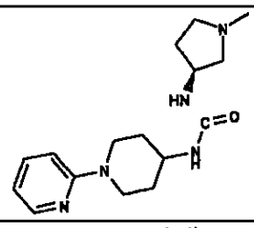
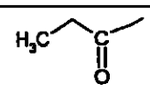
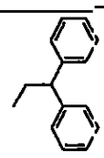
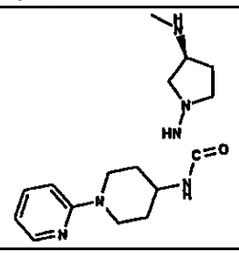
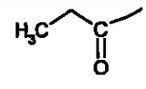
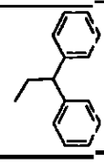
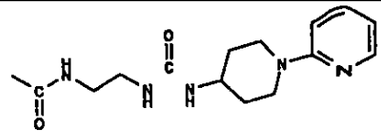
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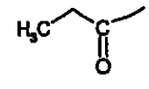
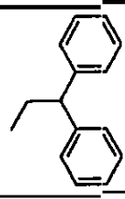
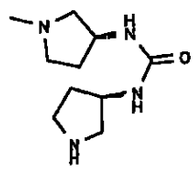
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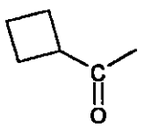
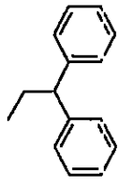
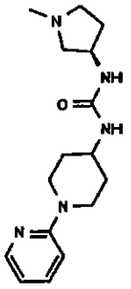
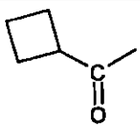
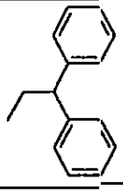
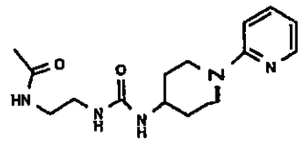
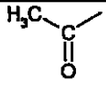
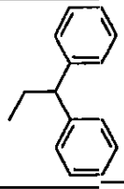
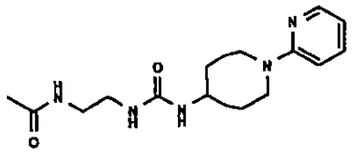
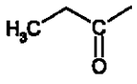
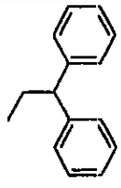
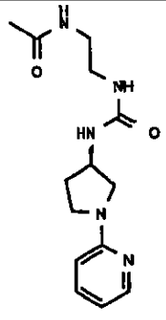
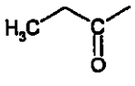
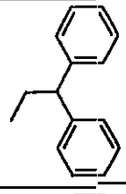
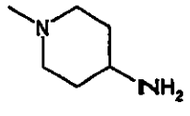
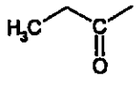
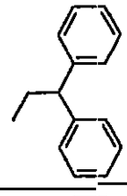
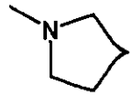
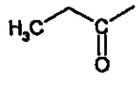
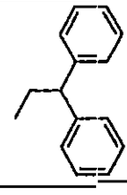
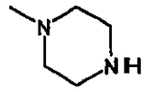
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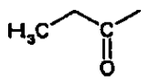
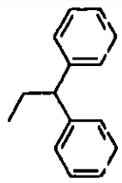
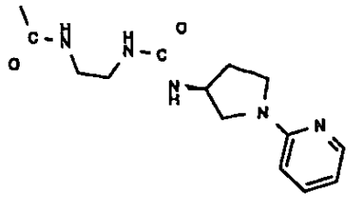
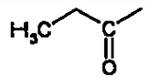
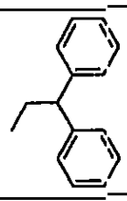
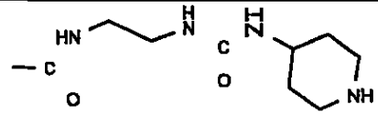
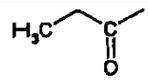
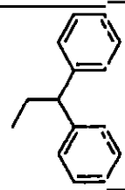
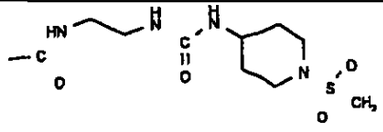
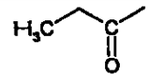
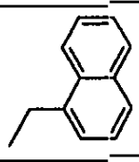
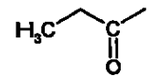
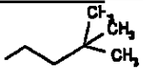
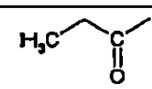
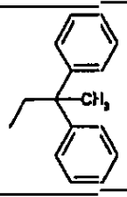
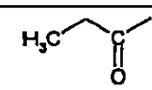
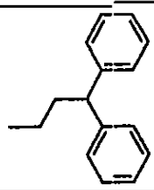
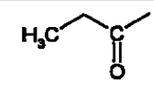
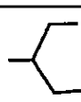
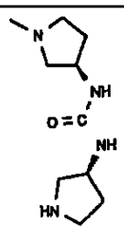
		
		
		
		
		
		
		
		
		

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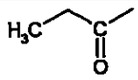
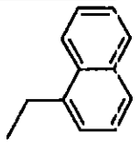
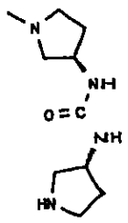
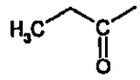
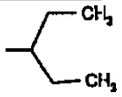
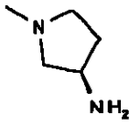
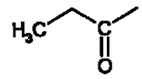
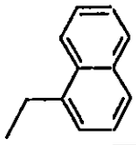
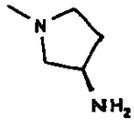
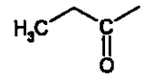
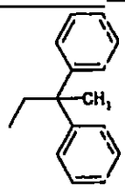
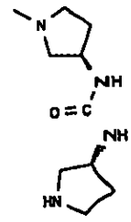
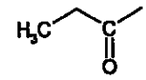
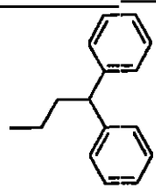
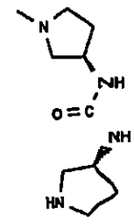
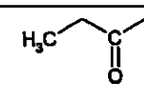
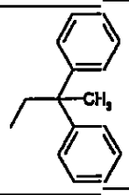
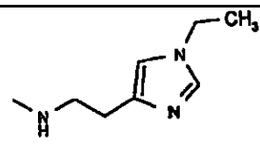
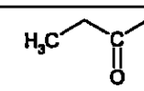
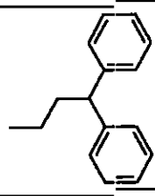
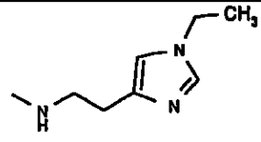
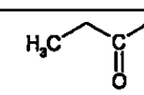
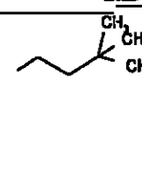
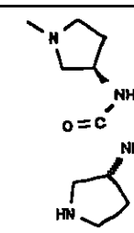
		
		
		
		
		
		

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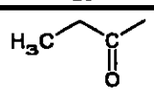
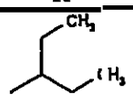
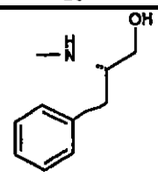
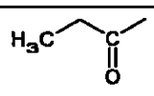
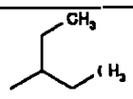
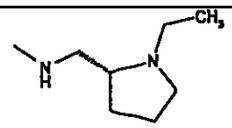
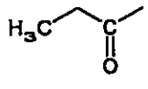
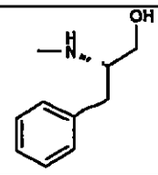
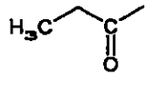
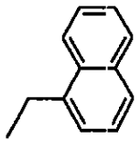
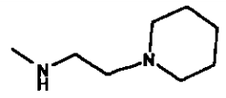
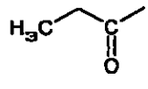
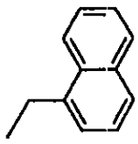
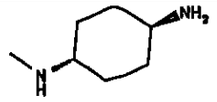
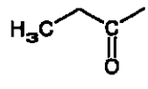
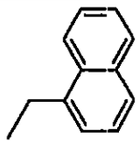
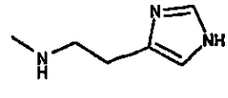
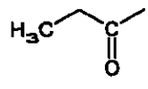
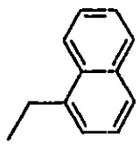
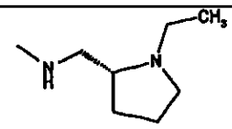
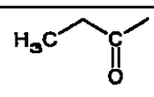
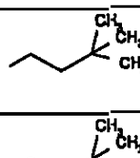
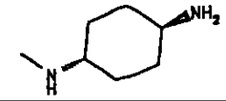
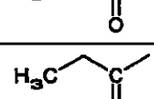
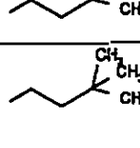
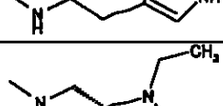
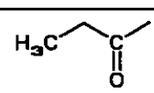
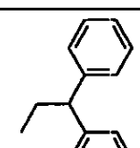
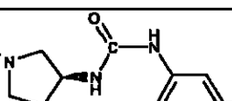
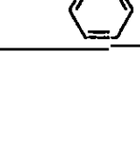
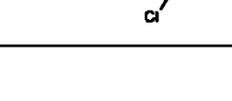
		
		
		
		
		
		
		

		
		
		
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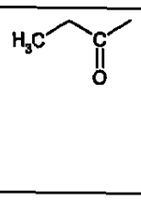
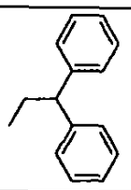
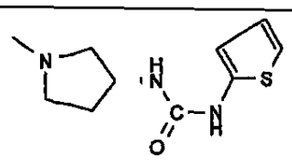
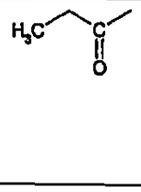
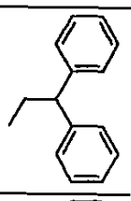
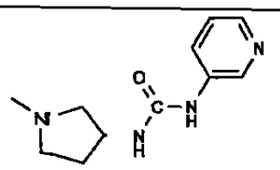
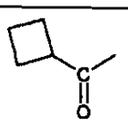
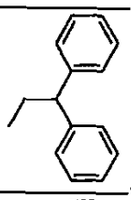
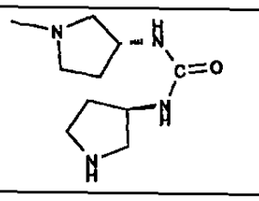
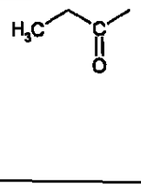
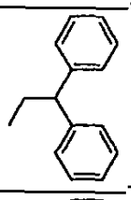
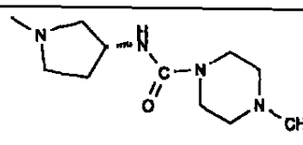
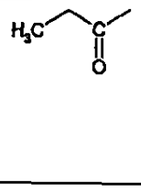
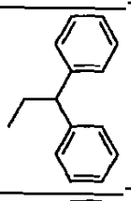
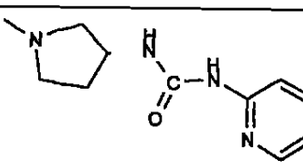
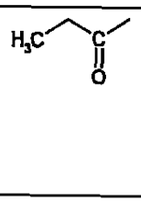
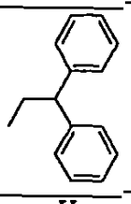
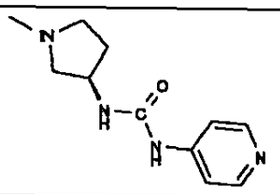
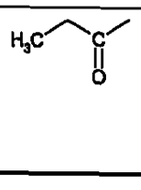
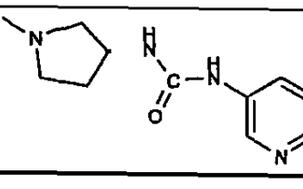
113

114

R^1	R^2	R^3
		
		
		
		
		
		
		
		
		
		
		

115

		
		
		
		
		
		
	-H	

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

9 A compound according to any one of claims 1 to 7 in combination with an anti-inflammatory, bronchodilatory, antihistamine or anti tussive drug substance, said compound

116

and said drug substance being in the same or different pharmaceutical composition

10 A pharmaceutical composition comprising as active ingredient a compound according to any one of claims 1 to 7, optionally together with a pharmaceutically acceptable diluent or carrier

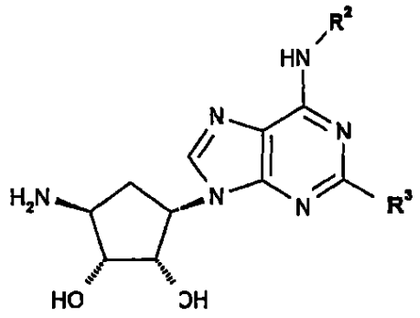
11 A pharmaceutical composition according to claim 10, further comprising an anti inflammatory, bronchodilatory, antihistamine or anti tussive drug substance

12 Use of a compound according to any one of claims 1 to 7 for the manufacture of a medicament for the treatment of a condition mediated by activation of the adenosine A_{2A} receptor

13 Use of a compound according to any one of claims 1 to 7 for the manufacture of a medicament for the treatment of an inflammatory or obstructive airways disease

14 A method of preparing a compound of formula I as defined in claim 1 in free or salt form which comprises

(i) (A) for the preparation of compounds of formula I, reacting a compound of formula II

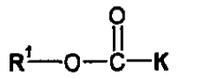


II

wherein R^2 and R^3 are as defined in claim 1, with a compound of formula III

$$R^1—X^a \qquad III$$

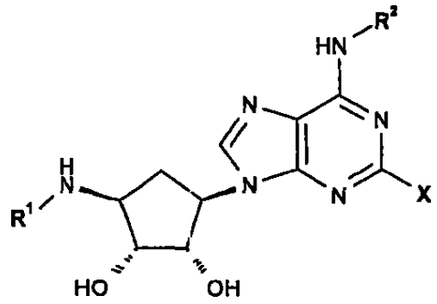
or a formula IIIa



IIIa

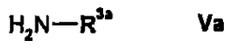
wherein R^1 is hydrogen, C_1 C_8-alkylcarbonyl, C_3 C_8-cycloalkylcarbonyl or C_7 C_{14}-aralkylcarbonyl, X^a is a leaving group and K is hydrogen, C_1 C_8-alkyl or C_1-C_8 alkoxy, in the presence of a base,

(B) for the preparation of compounds of formula I where R^3 is amino substituted by C_3 C_8 cycloalkyl optionally substituted by amino or R^3 is C_1 C_8-alkylamino optionally substituted by hydroxy, C_6 C_{10} aryl or by R^5, or R^3 is R^6 optionally substituted by amino or NH C(=O) NH R^7, reacting a compound of formula IV

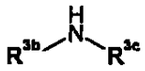


IV

wherein R^1 and R^2 are as defined in claim 1 and X is halo, with a compound of formula Va or formula Vb



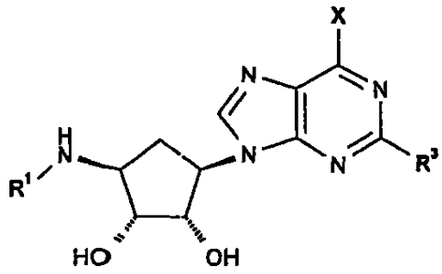
Va



Vb

wherein R^{3a} is C_3 C_8 cycloalkyl optionally substituted by amino or R^3 is C_1 C_8-alkyl optionally substituted by hydroxy, C_6 C_{10}-aryl or by R^5, where R^5 is as defined in claim 1, and R^{3b} and R^{3c} together form a 5- or 6-membered heterocyclic ring that contains one or more nitrogen atoms and is optionally substituted amino or -NH C(=O)-NH-R^7, where R^7 is as defined in claim 1,

(C) for the preparation of compounds of formula I, reacting a compound of formula VI



VI

wherein R^1 and R^3 are as defined in claim 1 and X is halo, with a compound of formula VII

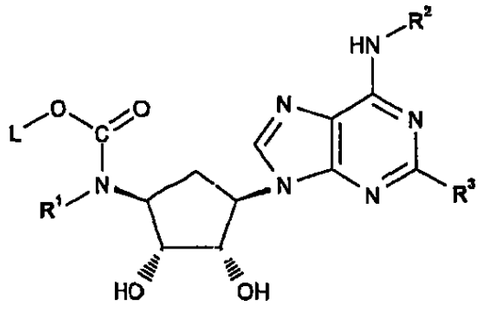


VII

wherein R^2 is as defined in claim 1, in the presence of a base,

11B

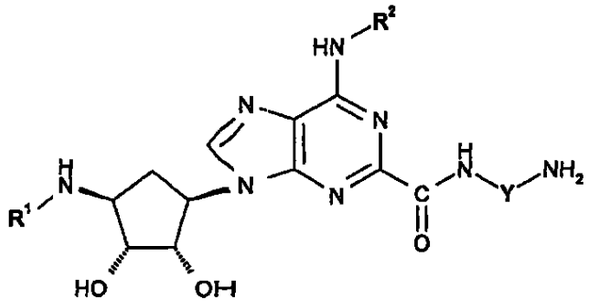
(D) for the preparation of compounds of formula I, deprotecting a compound of formula VIII



VIII

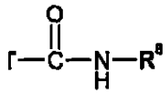
wherein R^1, R^2 and R^3 are as defined in claim 1 and L is C_1-C_8-alkyl,

(E) for the preparation of compounds of formula I wherein R^3 is C_1-C_8-alkylaminocarbonyl or C_3 C_8-cycloalkylaminocarbonyl substituted by NH-C(=O)-NH-R^8, where R^8 is as defined in claim 1, reacting a compound of formula IX



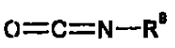
IX

wherein R^1 and R^2 are as defined in claim 1 and Y is C_1-C_8-alkyl or C_3-C_8 cycloalkyl in the presence of a base, with either a compound of formula X



X

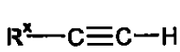
or a compound of formula XI



XI

wherein T is C_6-C_{10}-aryloxy or a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur and R^8 is as defined in claim 1,

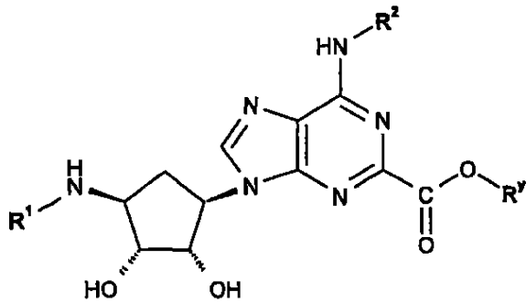
(F) for the preparation of compounds of formula I wherein R^3 is C_2-C_8 alkynyl, reacting a compound of formula IV where R^1 and R^2 are as defined in claim 1, with a compound of formula XII



XII

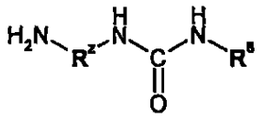
wherein R^x is C_1-C_8-alkyl, in the presence of a base and a catalyst,

(G) for the preparation of compounds of formula I wherein or R^3 is C_1-C_8 alkylamino carbonyl optionally substituted NH-C(=O) NH R^8, reacting a compound of formula XIIa



XIIa

wherein R^1 and R^2 are as defined in claim 1 and R^y is C_1 C_8-alkyl, optionally in the presence of a base, with a compound of formula XIIb



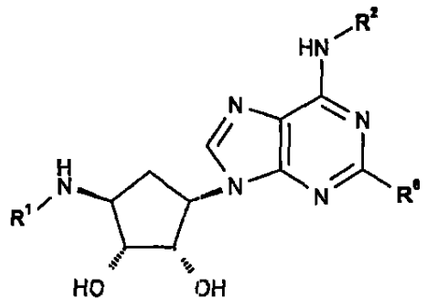
XIIb

wherein R^z is C_1-C_8 alkyl and NH-C(=O)-NH R^8 is as defined in claim 1, or

(H) for the preparation of compounds of formula I wherein R^3 is C_1-C_8-alkylamino-carbonyl substituted by -NH C (=O)-NH-R^8, where R^8 is a 5- or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, that ring being substituted by C_1-C_8-alkylsulfonyl, reacting a compound of formula I wherein R^3 is C_1 C_8 alkylamino-carbonyl substituted by -NH C (=O) NH-R^8, where R^8 is a 5 or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur with a sulfonylating agent in the presence of a base,

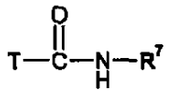
(I) for the preparation of compounds of formula I wherein R^3 is R^6 substituted by –NH-C(=O) NH-R^7, where R^7 is as defined in claim 1, reacting a compound of formula XIIc

120



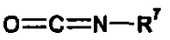
XIIc

where R^1 and R^2 are as defined in claim 1 and R^6 is a 5- or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, substituted at one position by amino, with either a compound of formula Xa



Xa

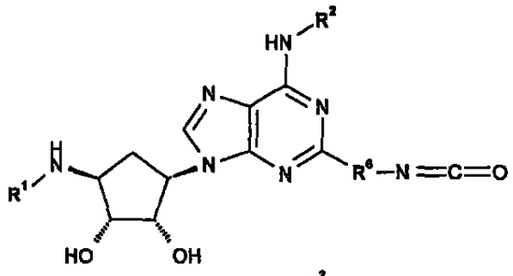
or a compound of formula XIa



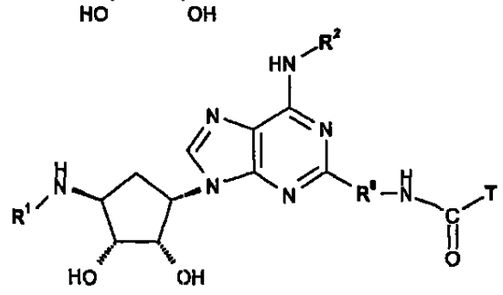
XIa

wherein T is C_6 C_{10}-aryloxy or a 5 or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur and R^8 is as defined in claim 1,

(J) for the preparation of compounds of formula I wherein R^3 is R^6 substituted by -NH C(=O) NH R^7, where R^7 is as defined in claim 1, reacting a compound of formula XIId or XIIe or a protected form thereof



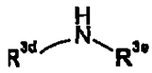
XIId



XIIe

121

where R^1, R^2 are R^6 are as defined in claim 1 and T is C_6-C_{10} aryloxy or a 5- or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, with a compound of formula XIIf



XIIf

and R^{3d} and R^{3e} together form a 5- or 6-membered N heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, said 5 or 6 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, C_1-C_8 alkoxy optionally substituted by aminocarbonyl, or a 5 or 6-membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, or

(K) for the preparation of compounds of formula I wherein R^3 is R^6 substituted by -NH C(=O) NH R^7, where R^7 is as hereinbefore defined, reacting a compound of formula XIId or XIIe, where R^1, R^2 are R^6 are as defined in claim 1 and T is C_6 C_{10}-aryloxy or a 5- or 6 membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, with a compound of formula XIIg



XIIg

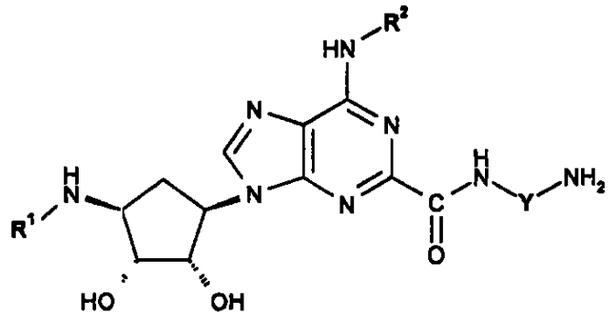
where R^7 is as defined in claim 1, and

(ii) removing any protecting groups and recovering the resultant compound of formula Ia in free or salt form

DERIVADOS DE PURINA PARA USARSE COMO AGONISTAS DE RECEPTORES A-2A DE ADENOSINA

Esta invencion se refiere a compuestos orgánicos a su preparacion y a uso como productos farmaceuticos

En un asoecto la presente invencion proporciona compuestos de la Formula I



I

en forma libre o de sal en donde

R^1 es hidrogeno, alquilcarbonilo de 1 a 8 átomos de carbono cicloalquilcarbonilo de 3 a 8 átomos de carbono SO_2-alquilo de 1 a 8 atomos de carbono, aralquilcarbonilo de 7 a 14 atomos de carbono o -C(=O)-C(=O)-NH-alquilo de 1 a 8 atomos de carbono, opcionalmente sustituido con R^4

R^2 es hidrógeno o alquilo de 1 a 8 atomos de carbono opcionalmente sustituido con arilo de 6 a 10 atomos de carbono,

R^3 es hidrogeno halogeno, alquenilo de 2 a 8 atomos de carbono o alquinilo de 2 a 8 átomos de carbono,

o R^3 es amino opcionalmente sustituido con

123

cicloalquilo de 3 a 8 atomos de carbono opcionalmente sustituido con amino

o R^3 es alquilamino de 1 a 8 átomos de carbono opcionalmente sustituido con hidroxilo arilo de 6 a 10 atomos de carbono o R^5

o R^3 es R^6 opcionalmente sustituido con amino o -NH-C(=O)-NH-R^7

o R^3 es -NH-R^6 opcionalmente sustituido con -NH-C(=O)-NH-R^7,

o R^3 es alquilaminocarbonilo de 1 a 8 átomos de carbono o cicloalquilaminocarbonilo de 3 a 8 átomos de carbono opcionalmente sustituido con amino alquilamino de 1 a 8 atomos de carbono dialquilamino de 1 a 8 atomos de carbono o -NH-C(=O)-NH-R^8

R^4 R^5 y R^6 son independientemente un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrógeno, oxigeno y azufre, estando este anillo heterociclico de 5 ó 6 miembros opcionalmente sustituido con halógeno ciano oxo hidroxilo carboxilo amino nitro alquilo de 1 a 8 átomos de carbono alquilsulfonilo de 1 a 8 atomos de carbono, aminocarbonilo alquilcarbonilo de 1 a 8 atomos de carbono, o alcoxilo de 1 a 8 átomos de carbono opcionalmente sustituido con aminocarbonilo y

R^7 y R^8 son independientemente un anillo

129

heterociclico de 5 o 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrógeno oxigeno y azufre estando este anillo heterociclico de 5 ó 6 miembros opcionalmente sustituido con halogeno ciano oxo, hidroxilo carboxilo amino, nitro, alquilo de 1 a 8 átomos de carbono alquilsulfonilo de 1 a 8 atomos de carbono, aminocarbonilo, alquilcarbonilo de 1 a 8 atomos de carbono alcoxilo de 1 a 8 atomos de carbono opcionalmente sustituido con aminocarbonilo o un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrogeno oxígeno y azufre, estando este anillo también opcionalmente sustituido con halogeno ciano oxo hidroxilo, carboxilo, amino nitro, alquilo de 1 a 8 atomos de carbono alquilsulfonilo de 1 a 8 átomos de carbono aminocarbonilo alquilcarbonilo de 1 a 8 átomos de carbono alcoxilo de 1 a 8 átomos de carbono opcionalmente sustituido con aminocarbonilo

Los terminos utilizados en la presente descripción tienen los siguientes significados

Opcionalmente sustituido significa que el grupo referido puede estar sustituido en una o más posiciones de preferencia una o dos posiciones, con uno o cualquier combinacion de los radicales enlistados posteriormente en la presente

125

Halo o halógeno" como se utiliza en la presente, puede ser fluor cloro, bromo o yodo De preferencia halogeno es cloro Cuando R^3 es halogeno es de preferencia cloro Cuando R^3 es R^6 sustituido con -NH-C(=O)-NH-R^7 en donde R^7 es un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrógeno oxigeno y azufre sustituido con halogeno ese anillo heterociclico esta sustituido en dos posiciones con cloro

'Alquilo de 1 a 8 átomos de carbono", como se utiliza en la presente denota un radical alquilo de cadena recta o ramificada que tiene de 1 a 8 átomos de carbono De preferencia alquilo de 1 a 8 atomos de carbono es alquilo de 1 a 6 atomos de carbono Cuando R^2 es alquilo de 1 a 8 atomos de carbono opcionalmente sustituido con arilo de 6 a 10 átomos de carbono, R^2 es de preferencia alquilo de 1 a 6 atomos de carbono ya sea no sustituido en especial pentilo o hexilo mas especialmente -$CH(C_2H_5)_2$ o -$CH_2CH_2C(CH_3)_3$ o bien R^2 es alquilo de 1 a 5 átomos de carbono sustituido con arilo de 6 a 10 átomos de carbono en especial alquilo de 2 a 5 atomos de carbono (mas especialmente pentilo) sustituido en una posición con naftilo o en dos posiciones con fenilo

Alquenilo de 2 a 8 atomos de carbono como se utiliza en la presente denota cadenas de hidrocarburo de cadena recta o ramificada que contienen de 2 a 8 atomos de

126

carbono y uno o mas dobles enlaces carbono-carbono De preferencia alquenilo de 2 a 8 átomos de carbono es alquenilo de 2 a 4 átomos de carbono

Alquinilo de 2 a 8 atomos de carbono como se utiliza en la presente, denota cadenas de hidrocarburo de cadena recta o ramificada que contienen de 2 a 8 átomos de carbono y uno o mas triples enlaces carbono-carbono y opcionalmente uno o mas dobles enlaces carbono-carbono De preferencia alquinilo de 2 a 8 átomos de carbono es alquinilo de 2 a 6 átomos de carbono Cuando R^3 es alquinilo de 2 a 8 atomos de carbono es de preferencia alquinilo de 2 a 6 atomos de carbono, en especial hexinilo mas especialmente $-C\equiv C-C_4H_8$

Alcoxilo de 1 a 8 atomos de carbono" como se utiliza en la presente denota un radical alcoxilo de cadena recta o ramificada que tiene de 1 a 8 atomos de carbono De preferencia alcoxilo de 1 a 8 atomos de carbono es alcoxilo de 1 a 4 átomos de carbono

"Cicloalquilo de 3 a 8 átomos de carbono", como se utiliza en la presente denota un radical cicloalquilo que tiene de 3 a 8 atomos de carbono en el anillo por ejemplo un grupo monociclico tal como un grupo ciclopropilo, ciclobutilo ciclopentilo ciclohexilo cicloheptilo o ciclooctilo cualquiera de los cuales puede estar sustituido con uno o más usualmente uno o dos grupos alquilo de 1 a 4

177

atomos de carbono o un grupo biciclico tal como bicicloheptilo o biciclooctilo De preferencia cicloalquilo de 3 a 8 atomos de carbono es cicloalquilo de 3 a 6 átomos de carbono Cuando R^1 es amino sustituido con cicloalquilo de 3 a 8 átomos de caroono el cicloalquilo de 3 a 8 átomos de carbono es de preferencia cicloalquilo de 3 a 6 atomos de carbono y más especialmente ciclohexilo

Alquilamino de 1 a 8 atomos de carbono y dialquilamino de 1 a 8 átomos de carbono" como se utilizan en la presente denotan un radical amino sustituido respectivamente ccn uno o dos grupos alquilo de 1 a 8 atomos de carbono tal como se definieron anteriormente los cuales pueden ser iguales o diferentes De preferencia alquilamino de 1 a 8 atomos de carbono y dialquilamino de 1 a 8 atomos de carbono, son respectivamente alquilamino de 1 a 4 atomos de carbono y dialquilamino de 1 a 4 atomos de carbono Cuando R^3 está opcionalmente sustituido con alquilamino de 1 a 8 átomos de carbono el alquilamino de 1 a 8 atomos de carbono de preferencia es alquilamino de 1 a 4 atomos de carbono, en especial etilamino o propilamino

Alquilcarbonilo de 1 a 8 átomos de carbono" y alcoxicarbonilo de 1 a 8 átomos de carbono como se utilizan en la presente denotan un radical alquilo de 1 a 8 atomos de carbono o alcoxilo de 1 a 8 átomos de carbono respectivamente tal como se definieron anteriormente

128

unidos por un atomo de carbono a un grupo carbonilo De preferencia alquilcarbonilo de 1 a 8 atomos de carbono y alcoxicarbonilo de 1 a 8 átomos de carbono son alquilcarbonilo de 1 a 4 átomos de carbono y alcoxicarbonilo de 1 a 4 atomos de carbono respectivamente

Cicloalquilcarbonilo de 3 a 8 atomos de carbono" como se utiliza en la presente denota un radical cicloalquilo de 3 a 8 atomos de carbono como el anteriormente definido unido por un átomo de carbono a un grupo carbonilo De preferencia cicloalquilcarbonilo de 3 a 8 atomos de carbono es cicloalquilcarbonilo de 3 a 5 atomos de carbono Cuando R^1 es cicloalquilcarbonilo de 3 a 8 atomos de carbono es de preferencia cicloalquilcarbonilo de 3 a 5 atomos de carbono en especial ciclopropilcarbonilo o ciclobutilcarbonilo

Cicloalquilamino de 3 a 8 átomos de carbono" como se utiliza en la presente denota un radical cicloalquilo de 3 a 8 átomos de carbono como el anteriormente definido unido por un atomo de carbono al átomo de nitrógeno de un grupo amino De preferencia cicloalquilamino de 3 a 8 atomos de carbono es cicloalquilamino de 3 a 5 átomos de carbono

Arilo de 6 a 10 atomos de carbono como se utiliza en la presente, denota un grupo aromatico carbociclico monovalente que contiene de 6 a 10 átomos de carbono y que puede ser, por ejemplo, un grupo monocíclico

129

tal como fenilo, o un grupo biciclico tal como naftilo De preferencia arilo de 6 a 10 átomos de carbono es fenilo o naftilo Cuando R^2 es alquilo de 1 a 8 atomos de carbono sustituido con arilo de 6 a 10 atomos de carbono el arilo de 6 a 10 atomos de carbono es de preferencia fenilo o naftilo

Aralquilo de 7 a 14 átomos de carbono" como se utiliza en la presente denota un radical alquilo por ejemplo alquilo de 1 a 4 atomos de carbono como el anteriormente definido sustituido con arilo de 6 a 10 atomos de carbono como el anteriormente definido De preferencia, aralquilo de 7 a 14 átomos de carbono es aralquilo de 7 a 10 átomos de carbono, tal como fenilalquilo de 1 a 4 atomos de carbono en especial bencilo

Alquilaminocarbonilo de 1 a 8 atomos de carbono y cicloalquilaminocarbonilo de 3 a 8 atomos de carbono como se utilizan en la presente denotan un radical alquilamino de 1 a 8 atomos de carbono y cicloalquilamino de 3 a 8 átomos de carbono respectivamente tal como se definieron anteriormente unidos por un átomo de carbono a un grupo carbonilo De preferencia alquilaminocarbonilo de 1 a 8 atomos de carbono y cicloalquilaminocarbonilo de 3 a 8 atomos de carbono son alquilaminocarbonilo de 1 a 4 átomos de carbono y cicloalquilaminocarbonilo de 3 a 8 átomos de carbono respectivamente Cuando R^3 es alquilaminocarbonilo de 1 a 8 atomos de carbono es de preferencia

130

alquilaminocarbonilo de 1 a 3 átomos de carbono en especial propilaminocarbonilo

Arilcarbonilo de 6 a 10 átomos de carbono y aralquilcarbonilo de 7 a 14 atomos de carbono , como se utilizan en la presente, denotan un radical arilo de 6 a 10 atomos de carbono y aralquilo de 7 a 14 atomos de carbono respectivamente tal como se definieron anteriormente, unidos por un átomo de carbono a un grupo carbonilo De preferencia arilcarbonilo de 6 a 10 átomos de carbono y aralquilcarbonilo de 7 a 14 atomos de carbono son arilcarbonilo de 6 a 8 atomos de carbono y aralquilcarbonilo de 7 a 10 átomos de carbono respectivamente Cuando R^1 es aralquilcarbonilo de 7 a 14 átomos de carbono es de preferencia aralquilcarbonilo de 7 a 10 átomos de carbono en especial bencilcarbonilo por ejemplo fenilacetamido

'Anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrógeno oxigeno 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 Los anillos heterociclicos preferidos incluyen piperazina pirrolidina morfolino, imidazol

137

isotriazol pirazol tetrazol tiazol tiadiazol, piridina, piperidina pirazina furano oxazol isoxazol, oxadiazol, y acetidina El anillo heterociclico de 5 ó 6 miembros puede estar no sustituido o puede estar sustituido en una o más posiciones de preferencia en una o dos posiciones con halogeno ciano oxo hidroxilo carboxilo amino nitro alquilo de 1 a 8 átomos de carbono, alquilsulfonilo de 1 a 8 atomos de carbono aminocarbonilo alquilcarbonilo de 1 a 8 atomos de carbono o alcoxilo de 1 a 8 átomos de carbono opcionalmente sustituido en una o más posiciones, de preferencia en una o dos posiciones, con aminocarbonilo Los sustituyentes especialmente preferidos incluyen metilo etilo propilo y amino Cuando R^3 es alquilamino de 1 a 8 atomos de carbono opcionalmente sustituido con R^5 R^5 es de preferencia imidazolilo no sustituido piperidinilo no sustituido o imidazolilo sustituido en una posición con alquilo de 1 a 3 átomos de carbono Cuando R^3 es R^6 opcionalmente sustituido con -NH-C(=O)-NH-R^7 R^6 es de preferencia pirrolidinilo piperidinilo o piperazinilo, y cuando sea pertinente R^7 es de preferencia tiofenilo no sustituido piridinilo no sustituido pirrolidinilo no sustituido, piridinilo disustituido con cloro piperazinilo sustituido en una posicion con metilo piperidinilo sustituido en una posicion con piridinilo, o piperidinilo sustituido en una posición con piridinilo Cuando R^3 es -NH-R^6 opcionalmente sustituido con

132

-NH-C(=O)-NH-R^7 R^6 es de preferencia pirrolidinilo no sustituido o R^6 es pirrolidinilo sustituido en una posición con -NH-C(=O)-NH-R^7 en donde R^7 es piridinilo no sustituido Cuando R^3 es alquilaminocarbonilo de 1 a 8 atomos de carbono sustituido con -NH-C(=O)-NH-R^8 R^8 es de preferencia piperidinilo no sustituido piperidinilo sustituido en una posicion con metilsulfonilo piperidinilo sustituido en una posicion con piridinilo o pirrolidinilo sustituido en una posicion con piridinilo

A través de toda la presnete descripcion y en las siguientes reivindicaciones a menos que el contexto lo requiera de otra manera, la palabra "comprenden" o variaciones tales como comprende o comprendiendo se entenderá que implican la inclusión de un numero entero o una etapa o un grupo de numeros enteros o etapas establecidos pero no la exclusión de cualquier otro numero entero o etapa o grupo de numeros enteros o etapas

Los compuestos preferidos de la Formula I en forma libre o de sal incluyen aquellos en donde

R^1 es alquilcarbonilo de 1 a 8 átomos de carbono cicloalquilcarbonilo de 3 a 8 átomos de carbono, -SO_2-alquilo de 1 a 8 átomos de carbono aralquilcarbonilo de 7 a 14 atomos de carbono o -C(=O)-C(=O)-NH-alquilo de 1 a 8 atomos de carbono opcionalmente sustituido con R^4,

R^2 es hicrogeno o alquilo de 1 a 8 atomos de

carbono opcionalmente sustituido con arilo de 6 a 10 átomos de carbono,

R^3 es halógeno o alquinilo de 2 a 8 atomos de carbono

o R^3 es amino opcionalmente sustituido con cicloalquilo de 3 a 8 atomos de carbono opcionalmente sustituido con amino

o R^3 es alquilamino de 1 a 8 átomos de carbono opcionalmente sustituido con hidroxilo, arilo de 6 a 10 átomos de carbono, o R^5,

o R^3 es R^6 opcionalmente sustituido con amino o -NH-C(=O)-NH-R^7,

o R^3 es -NH-R^6 opcionalmente sustituido con -NH-C(=O)-NH-R^7

o R^3 es alquilaminocarbonilo de 1 a 8 atomos de carbono opcionalmente sustituido con -NH-C(=O)-NH-R^8

R^4 R^5 y R^6 son independientemente un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrogeno oxigeno y azufre estando este anillo heterociclico de 5 o 6 miembros opcionalmente sustituido con alquilo de 1 a 8 atomos de carbono y

R^7 y R^8 son independientemente un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que

134

consiste de nitrogeno oxigeno y azufre estando este anillo heterociclico de 5 ó 6 miembros opcionalmente sustituido con halogeno alquilo de 1 a 8 atomos de carbono alquilsulfonilo de 1 a 8 atomos de carbono o un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrogeno oxigeno y azufre

Los compuestos especialmente preferidos de la Formula I en forma libre o de sal incluyen aquéllos en donde

R^1 es alquilcarbonilo de 1 a 4 átomos de carbono, cicloalquilcarbonilo de 3 a 5 atomos de carbono $-SO_2$-alquilo de 1 a 4 atomos de carbono, aralquilcarbonilo de 7 a 10 atomos de carbono o -C(=O)-C(=O)-NH-alquilo de 1 a 4 atomos de carbono opcionalmente sustituido en una posicion con R^4

R^2 es hidrógeno alquilo de 1 a 6 átomos de carbono no sustituido, o alquilo de 1 a 5 atomos de carbono sustituido en una posicion con arilo de 6 a 10 atomos de carbono

R^3 es halogeno o alquinilo de 2 a 6 átomos de carbono

o R^3 es amino opcionalmente sustituido en una posicion con cicloalquilo de 3 a 6 átomos de carbono opcionalmente sustituido en una posición con amino

135

o R^3 es alquilamino de 1 a 4 atomos de carbono sustituido en una o dos posiciones con hidroxilo fenilo o R^5

o R^3 es R^6 opcionalmente sustituido en una posicion con amino o -NH-C(=O)-NH-R^7

o R^3 es -NH-R^6 opcionalmente sustituido en una posicion con -NH-C(=O)-NH-R^7

o R^3 es alquilaminocarbonilo de 1 a 4 atomos de carbono sustituido en una posición con -NH-C(=O)-NH-R^8

R^4 R^5 y R^6 son independientemente un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrogeno, oxigeno y azufre, estando este anillo heterociclico de 5 o 6 miembros opcionalmente sustituido en una posición con alquilo de 1 a 4 átomos de carbono, y

R^7 y R^8 son independientemente un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrógeno oxigeno y azufre estando este anillo heterociclico de 5 ó 6 miembros opcionalmente sustituido en una o dos posiciones con halógeno alquilo de 1 a 4 átomos de carbono alquilsulfonilo de 1 a 4 atomos de carbono o un anillo N-heterociclico de 5 ó 6 miembros

En un segundo aspecto la presente invencion proporciona compuestos de la Formula I en donde

R^1 es hidrógeno alquilcarbonilo de 1 a 8 átomos de

136

carbono cicloalquilcarbonilo de 3 a 8 atomos de carbono -SO_2-alquilo de 1 a 8 átomos de carbono, aralquilcarbonilo de 7 a 14 atomos de carbono o -C(=O)-C(=O)-NH-alquilo de 1 a 8 atomos de carbono opcionalmente sustituido con R^4,

R^2 es hidrógeno o alquilo de 1 a 8 atomos de carbono opcionalmente sustituido con arilo de 6 a 10 átomos de carbono

R^3 es hidrogeno halogeno, alquenilo de 2 a 8 atomos de carbono o alquinilo de 2 a 8 atomos de carbono,

o R^3 es amino opcionalmente sustituido con cicloalquilo de 3 a 8 atomos de carbono opcionalmente sustituido con amino

o R^3 es alquilamino de 1 a 8 atomos de carbono opcionalmente sustituido con hidroxilo arilo de 6 a 10 atomos de carbono o R^5

o R^3 es R^6 opcionalmente sustituido con amino o NH-C(=O)-NH-R^7

o R^3 es alquilaminocarbonilo de 1 a 8 átomos de carbono o cicloalquilaminocarbonilo de 3 a 8 atomos de carbono opcionalmente sustituido con amino alquilamino de 1 a 8 átomos de carbono dialquilamino de 1 a 8 átomos de carbono o -NH-C(=O)-NH-R^8

R^4 R^5 y R^6 son independientemente un anillo heterociclico de 5 o 6 miembros que contiene, cuando menos un heteroatomo del anillo que se selecciona del grupo que

137

consiste de nitrógeno oxigeno y azufre y

R^7 y R^8 son independientemente un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrógeno oxigeno y azufre estando este anillo heterociclico de 5 ó 6 miembros opcionalmente sustituido con un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrogeno oxigeno y azufre

Los compuestos preferidos de la Fórmula I en forma libre o de sal, incluyen aquellos en donde

R^1 es alquilcarbonilo de 1 a 8 átomos de carbono, cicloalquilcarbonilo de 3 a 8 átomos de carbono $-SO_2$-alquilo de 1 a 8 atomos de carbono aralquilcarbonilo de 7 a 14 atomos de carbonc, o -C(=O)-C(=O)-NH-alquilo de 1 a 8 atomos de carbono opcionalmente sustituido con R_4,

R^2 es hidrógeno o alquilo de 1 a 8 atomos de carbono opcionalmente sustituido con arilo de 6 a 10 atomos de carbono

R^3 es halogeno o alquinilo de 2 a 8 atomos de carbono

o R^3 es amino opcionalmente sustituido con cicloalquilo de 3 a 8 átomos de carbono opcionalmente sustituido con amino,

o R^3 es alquilamino de 1 a 8 átomos de carbono

opcionalmente sustituido con hidroxilo arilo de 6 a 10 atomos de carbono, o R^5,

o R^3 es R^6 opcionalmente sustituido con amino o -NH-C(=O)-NH-R^7

o R^3 es -NH-R^6 opcionalmente sustituido con -NH-C(=O)-NH-R^7,

o R^3 es alquilaminocarbonilo de 1 a 8 átomos de carbono opcionalmente sustituido con -NH-C(=O)-NH-R^8

R^4 R^5, y R^6 son independientemente un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrógeno, oxígeno y azufre y

R^7 y R^8 son independientemente un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrógeno oxigeno y azufre estando este anillo heterocíclico de 5 o 6 miembros opcionalmente sustituido con un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrogeno, oxigeno y azufre

Los compuestos especialmente preferidos de la Formula I en forma libre o de sal, incluyen aquellos en donde

R^1 es alquilcarbonilo de 1 a 4 átomos de carbono, cicloalquilcarbonilo de 3 a 6 atomos de carbono -SO_2-alquilo

139

de 1 a 4 atomos de carbono, aralquilcarbonilo de 7 a 10 atomos de carbono o -C(=O)-C(=O)-NH-alquilo de 1 a 4 atomos de carbono opcionalmente sustituido en una posicion con R^4

R^2 es hidrógeno o alquilo de 1 a 6 atomos de carbono opcionalmente sustituido con arilo de 6 a 10 atomos de carbono

R^3 es halógeno o alquinilo de 2 a 5 atomos de carbono

o R^3 es amino opcionalmente sustituido con cicloalquilo de 3 a 8 atomos de carbono opcionalmente sustituido con amino

o R^3 es alquilamino de 1 a 4 átomos de carbono opcionalmente sustituido con hidroxilo arilo de 6 a 8 atomos de carbono o R^5

o R^3 es R^6 opcionalmente sustituido con amino o NH-C(=O)-NH-R^7

o R^3 es -NH-R^6 opcionalmente sustituido con -NH-C(=O)-NH-R^7

o R^3 es alquilaminocarbonilo de 1 a 4 átomos de carbono opcionalmente sustituido con -NH-C(=O)-NH-R^8

R^4 R^5 y R^6 son independientemente un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrógeno oxigeno y azufre y

140

R^7 y R^8 son independientemente un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrógeno oxígeno y azufre, estando este anillo heterociclico de 5 o 6 miembros opcionalmente sustituido con un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrogeno, oxigeno y azufre

Los compuestos especificos especialmente preferidos de la Formula I son aquéllos descritos posteriormente en la presente, en los Ejemplos

Los compuestos representados por la Formula I son capaces de formar sales de adición ácida, en particular sales de adicion acida farmaceuticamente aceptables Las sales de adicion acida farmaceuticamente aceptables del compuesto de la Formula Ia incluyen aquéllas de ácidos inorgánicos por ejemplo ácidos halohídricos tales como acido fluorhidrico ácido clorhidrico ácido bromhídrico, o acido yodhidrico acido nitrico ácido sulfurico ácido fosfórico y de ácidos organicos por ejemplo acidos monocarboxilicos alifaticos tales como ácido fórmico acido acético acido trifluoroacético ácido propionico, y acido butirico hidroxiacidos alifáticos tales como ácido láctico ácido citrico ácido tartárico, o ácido malico, acidos dicarboxílicos tales como acido maleico y ácido succinico acidos

191

carboxílicos aromáticos tales como ácido benzoico ácido p-clorobenzoico ácido difenilacético ácido para-difenilbenzoico o ácido trifenilacético hidroxiácidos aromáticos tales como ácido o-hidroxibenzoico ácido p-hidroxibenzoico ácido 1-hidroxinaftalen-2-carboxílico o ácido 3-hidroxinaftalen-2-carboxílico, ácidos cinámicos tales como ácido 3-(2-naftalenil)-propenoico ácido *para*-metoxicinámico o ácido *para*-metilcinámico, y ácidos sulfónicos tales como ácido metansulfónico o ácido bencensulfónico Estas sales se pueden preparar a partir de los compuestos de la Fórmula I mediante procedimientos de formación de sales conocidos

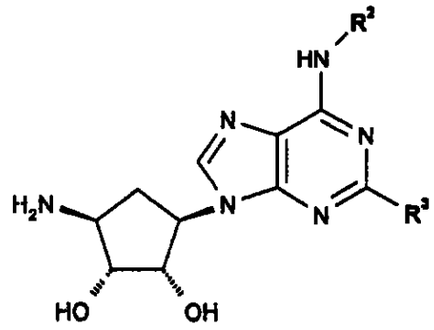
Los compuestos de la Fórmula I que contienen grupos ácidos por ejemplo carboxilo también son capaces de formar sales con bases, en particular bases farmacéuticamente aceptables tales como las que se conocen bien en la técnica las sales adecuadas incluyen las sales de metales en particular las sales de metales alcalinos o de metales alcalinotérreos tales como las sales de sodio potasio magnesio o calcio o las sales con amoníaco o con aminas orgánicas farmacéuticamente aceptables o bases heterocíclicas tales como etanolaminas bencilaminas o piridina Estas sales se pueden preparar a partir de los compuestos de la Fórmula Ia mediante procedimientos de formación de sales conocidos

192

En los compuestos en donde hay un atomo de carbono asimetrico, los compuestos existen en formas isomericas opticamente activas individuales o como mezclas de las mismas por ejemplo como mezclas diaestereoisoméricas La presente invencion abarca los isómeros R y S opticamente activos individuales asi como las mezclas de los mismos

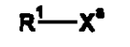
La invención proporciona en otro aspecto un metodo para la preparación de un compuesto de la Fórmula Ia en forma libre o de sal el cual comprende

(i) (A) para la preparación de compuestos de la Fórmula I se hace reaccionar un compuesto de la Formula II



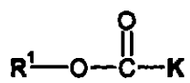
II

en donde R^2 y R^3 son como los anteriormente definidos con un compuesto de la Fórmula III



III

o de la Fórmula IIIa



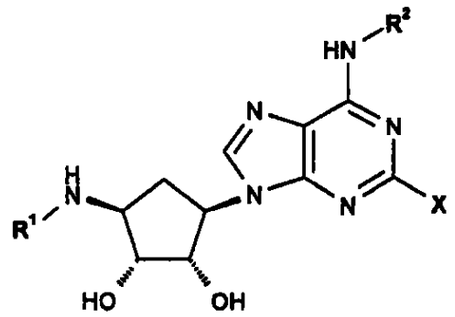
IIIa

en donde R^1 es hidrógeno alquilcarbonilo de 1 a 8 atomos de carbono cicloalquilcarbonilo de 3 a 8 atomos de

193

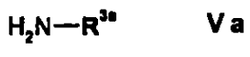
carbono o aralquilcarbonilo de 7 a 14 atomos de carbono X^a es un grupo saliente y K es hidrógeno alquilo de 1 a 8 atomos de carbono, o alcoxilo de 1 a 8 atomos de carbono, en presencia de una base

(B) para la preparación de compuestos de la Formula I en donde R^3 es amino sustituido con cicloalquilo de 3 a 8 atomos de carbono opcionalmente sustituido con amino o R^3 es alquilamino de 1 a 8 atomos de carbono opcionalmente sustituido con hidroxilo arilo de 6 a 10 atomos de carbono o R^5 o R^3 es R^6 opcionalmente sustituido con amino o -NH-C(=O)-NH-R^7, se hace reaccionar un compuesto de la Formula IV

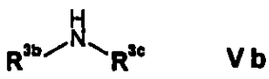


IV

en donde R^1 y R^2 son como los anteriormente definidos, y X es halógeno con un compuesto de la Formula Va o de la Formula Vb



Va



Vb

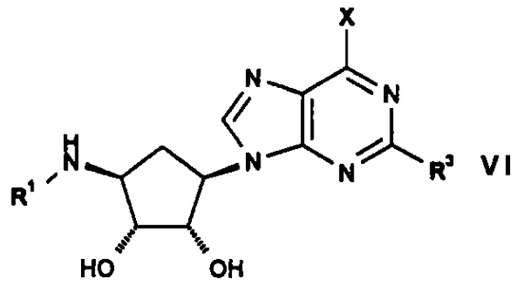
en donde R^{3a} es cicloalquilo de 3 a 8 atomos de

144

carbono opcionalmente sustituido con amino o R^3 es alquilo de 1 a 8 atomos de carbono opcionalmente sustituido con hidroxilo, arilo de 6 a 10 atomos de carbono, o R^5, en donde R^5 es como el anteriormente definido y

R^{3b} y R^{3c} forman juntos un anillo heterociclico de 5 o 6 miembros que contiene uno o más atomos de nitrogeno y esta opcionalmente sustituido con amino o -NH-C(=O)-NH-R^7, en donde R^7 es como el anteriormente definido

(C) para la preparacion de compuestos de la Formula I se hace reaccionar un compuesto de la Formula VI



VI

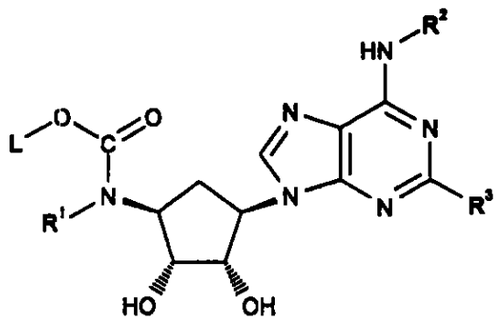
en donde R^1 y R^3 son como los anteriormente definidos y X es halogeno con un compuesto de la Formula VII

$$H_2N—R^2 \qquad \text{VII}$$

en donde R^2 es como el anteriormente definido en presencia de una base

(D) para la preparacion de compuestos de la Fórmula I se desprotege un compuesto de la Formula VIII

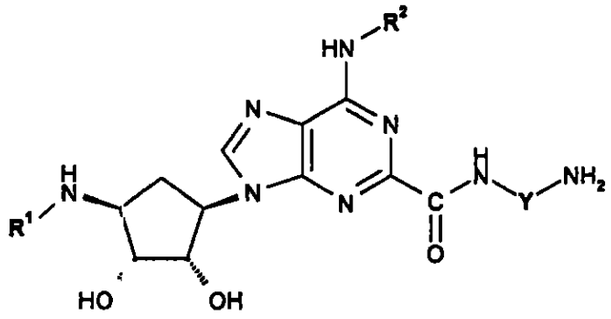
195



VIII

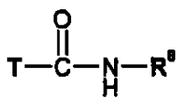
en donde R^1 R^2 y R^3 son como los anteriormente definidos y L es alquilo de 1 a 8 átomos de carbono

(E) para la preparacion de compuestos de la Formula I en donde R^3 es alquilaminocarbonilo de 1 a 8 átomos de carbono, o cicloalquilaminocarbonilo de 3 a 8 atomos de carbono sustituido con -NH-C(=O)-NH-R^8 en donde R^8 es como el anteriormente definido se hace reaccionar un compuesto de la Formula IX



IX

en donde R^1 y R^2 son como los anteriormente definidos e Y es alquilo de 1 a 8 atomos de carbono o cicloalquilo de 3 a 8 atomos de carbono, en presencia de una base ya sea con un compuesto de la Fórmula X



X

146

o bien con un compuesto de la Formula XI

$$O{=}C{=}N{-}R^{8} \qquad \textbf{XI}$$

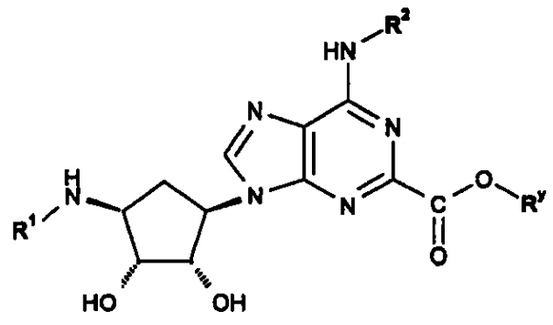
en donde T es ariloxi de 6 a 10 atomos de carbono o un anillo heterocíclico de 5 ó 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrógeno oxigeno y azufre y R^8 es como el anteriormente definido

(F) para la preparacion de compuestos de la Formula I en donde R^3 es alquinilo de 2 a 8 atomos de carbono se hace reaccionar un compuesto de la Formula IV en donde R^1 y R^2 son como los anteriormente definidos con un compuesto de la Formula XII

$$R^{x}{-}C{\equiv}C{-}H \qquad \textbf{XII}$$

en donde R^x es alquilo de 1 a 8 átomos de carbono en presencia de una base y un catalizador

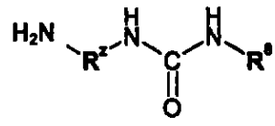
(G) para la preparación de compuestos de la Formula I en donde R^3 es alquilaminocarbonilo de 1 a 8 atomos de carbono opcionalmente sustituido con -NH-C(=O)-NH-R^8 se hace reaccionar un compuesto de la Formula XIIa



XIIa

147

en donde R^1 y R^2 son como los anteriormente definidos y R^y es alquilo de 1 a 8 atomos de carbono opcionalmente en presencia de una base con un compuesto de la Formula XIIb



XIIb

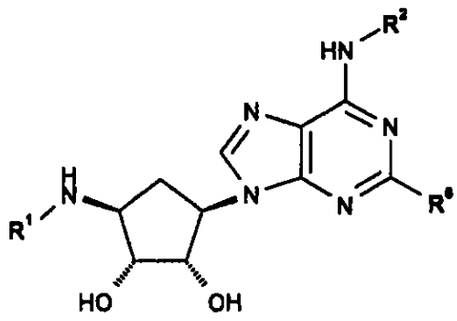
en donde R^z es alquilo de 1 a 8 atomos de carbono y -NH-C(=O)-NH-R^8 es como el anteriormente definido, o

(H) para la preparación de compuestos de la Formula I en donde R^3 es alquilaminocarbonilo de 1 a 8 átomos de carbono sustituido con -NH-C(=O)-NH-R^8 en donde R^8 es un anillo heterocíclico de 5 o 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrogeno, oxigeno y azufre estando ese anillo sustituido con alquilsulfonilo de 1 a 8 atomos de carbono se hace reaccionar un compuesto de la Formula I en donde R^3 es alquilaminocarbonilo de 1 a 8 atomos de carbono sustituido con -NH-C(=O)-NH-R^8 en donde R^8 es un anillo heterocíclico de 5 ó 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrógeno oxígeno y azufre con un agente de sulfonilación en presencia de una base

(I) para la preparación de compuestos de la Formula I en donde R^3 es R^6 sustituido con -NH-C(=O)-NH-R^7

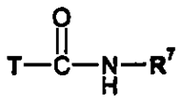
148

en donde R^7 es como el anteriormente definido, se hace reaccionar un compuesto de la Formula XIIc



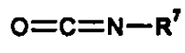
XIIc

en donde R^1 y R^2 son como los anteriormente definidos y R^6 es un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrogeno, oxígeno y azufre sustituido en una posicion con amino, ya sea con un compuesto de la Formula Xa



Xa

o bien con un compuesto de la Formula XIa

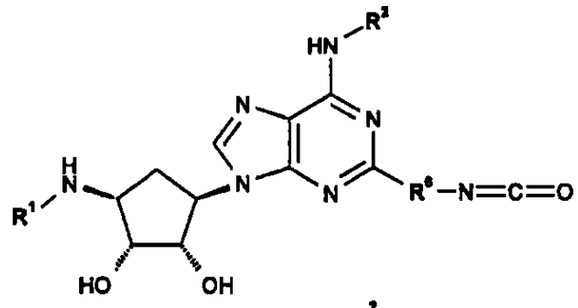


XIa

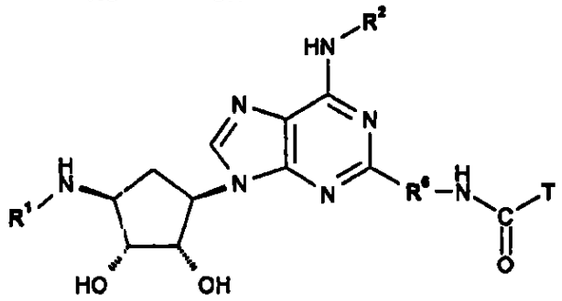
en donde T es ariloxi de 6 a 10 atomos de carbono o un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrógeno, oxigeno y azufre, y R^6 es como el anteriormente definido

(J) para la preparacion de compuestos de la Formula I en donde R^3 es R^6 sustituido con -NH-C(=O)-NH-R^7

en donde R^7 es como el anteriormente definido, se hace reaccionar un compuesto de la Fórmula XIId ó XIIe o una forma protegida del mismo

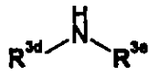


XIId



XIIe

en donde R^1 R^2 y R^6 son como los anteriormente definidos y T es ariloxi de 6 a 10 atomos de carbono o un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrógeno oxigeno y azufre con un compuesto de la Formula XIIf



XIIf

y en donde R^{3d} y R^{3e} forman juntos un anillo N-heterociclico de 5 o 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrógeno oxígeno y azufre estando este anillo

150

heterociclico de 5 o 6 miembros opcionalmente sustituido con halogeno ciano, cxo, hidroxilo, carboxilo amino nitro alquilo de 1 a 8 átomos de carbono, alquilsulfonilo de 1 a 8 atomos de carbono aminocarbonilo alquilcarbonilo de 1 a 8 atomos de carbono, alcoxilo de 1 a 8 átomos de carbono opcionalmente sustituido con aminocarbonilo o un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrogeno, oxigeno y azufre o

(K) para la preparación de compuestos de la Fórmula I en donde R^3 es R^6 sustituido con -NH-C(=O)-NH-R^7 en donde R^7 es como el anteriormente definido se hace reaccionar un compuesto de la Fórmula XIId ó XIIe en donde R^1 R^2, y R^6 son como los anteriormente definidos, y T es ariloxi de 6 a 10 atomos de carbono o un anillo heterocíclico de 5 o 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrogeno oxigeno y azufre con un compuesto de la Formula XIIg

$$H_2N-R^7 \qquad \textbf{XIIg}$$

en donde R^7 es como el anteriormente definido y

(ii) remover cualesquiera grupos protectores y recuperar el compuesto resultante de la Formula Ia, en forma libre o de sal

La variante del proceso (A) se puede llevar a cabo

151

empleando procedimientos conocidos para la reaccion de aminas con haluros de acido, anhídridos de acido, o anhidridos mixtos por ejemplo anhidridos carboxilicos y carbónicos (o derivados formadores de amida de los mismos tales como acidos carboxilicos), o haluros de sulfonilo, por ejemplo haluros de mesilo o de manera análoga a como se describe posteriormente en la presente en los Ejemplos El grupo saliente puede ser cualquier grupo saliente adecuado por ejemplo halogeno -SO_2-alquilo de 1 a 8 átomos de carbono o -SO_2-arilo de 6 a 10 átomos de carbono La reaccion convenientemente se lleva a cabo utilizando un solvente orgánico por ejemplo tetrahidrofurano (THF), en presencia de una base por ejemplo diisopropiletilamina (DIPEA) Las temperaturas de reacción adecuadas son de 10°C a 40°C, de preferencia la temperatura ambiente

La variante del proceso (B) se puede llevar a cabo empleando procedimientos conocidos para la reacción de haluros en especial haluros aromáticos con aminas o de una manera analoga a como se describe posteriormente en la presente en los Ejemplos La reacción convenientemente se lleva a cabo utilizando un solvente organico por ejemplo diclorobenceno dimetilsulfóxido acetonitrilo, o N-metilpirrolidona (NMP), o mezclas de los mismos opcionalmente en presencia de un catalizador tal como yoduro de sodio, y una base tal como trietilamina Las

152

temperaturas de reaccion adecuadas son de 100°C a 250°C de preferencia entre 120°C y 220°C, en especial de aproximadamente 170°C por ejemplo mediante calentamiento con radiacion de microondas

La variante del proceso (C) se puede llevar a cabo empleando procedimientos conocidos para la reacción de haluros con aminas o de una manera análoga a como se describe posteriormente en la presente en los Ejemplos La reacción convenientemente se lleva a cabo utilizando un solvente orgánico, por ejemplo tetrahidrofurano de preferencia en una atmósfera inerte por ejemplo argon opcionalmente en presencia de una base por ejemplo diisopropiletilamina Las temperaturas de reacción adecuadas son de 0°C a 70°C de preferencia entre 40°C y 60°C en especial de aproximadamente 50°C

La variante del proceso (D) se puede llevar a cabo empleando procedimientos conocidos para la disociacion de enlaces de éster por ejemplo utilizando un ácido organico fuerte tal como ácido trifluoroacético La reacción convenientemente se lleva a cabo utilizando un solvente organico por ejemplo diclorometano (DCM) Las temperaturas de reacción adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

La variante del proceso (E) se puede llevar a cabo empleando procedimientos conocidos para la reacción de

163

aminas con acilimidazoles o isocianatos o de una manera análoga a como se describe posteriormente en la presente en los Ejemplos T en la formula X es de preferencia imidazolilo La reacción convenientemente se lleva a cabo utilizando un solvente organico, por ejemplo tolueno y/o alcohol isopropilico Las temperaturas de reaccion adecuadas son de 0°C a 40°C, de preferencia la temperatura ambiente

La variante del proceso (F) se puede llevar a cabo empleando procedimientos conocidos para la reaccion de haluros con alquincs, o de una manera analoga a como se describe posteriormente en la presente en los Ejemplos El catalizador de preferencia es un catalizador de paladio (junto con una sal de CuI) y la base es de preferencia butilamina La reaccion convenientemente se lleva a cabo utilizando un solvente orgánico, tal como dimetilformamida (DMF) Las temperaturas de reaccion adecuadas son de 40°C a 200°C, de preferencia de 80°C a 160°C, en especial de aproximadamente 120°C

La variante del proceso (G) se puede llevar a cabo empleando procedimientos conocidos para la reacción de alquilesteres de acido carboxilico con aminas o de una manera análoga a como se describe posteriormente en la presente en los Ejemplos La base de preferencia es imidazol La reacción convenientemente se lleva a cabo utilizando un solvente orgánico, tal como 1,2-dicloroetano,

154

iso-propanol o una mezcla de los mismos Las temperaturas de reacción adecuadas son desde la temperatura ambiente hasta 250°C de preferencia de 50°C a 100°C

La variante del proceso (H) se puede llevar a cabo empleando procedimientos conocidos para la sulfonilacion de heterociclos o de una manera analoga a como se describe posteriormente en la presente en los Ejemplos El agente de sulfonilacion de preferencia es un haluro de alquilsulfonilo, por ejemplo cloruro de mesilo La base de preferencia es trietilamina La reaccion convenientemente se lleva a cabo utilizando un solvente organico, tal como dimetilformamida (DMF) de preferencia en una atmósfera inerte Las temperaturas de reaccion adecuadas son de 0°C a 40°C, de preferencia la temperatura ambiente

La variante del proceso (I) se puede llevar a cabo empleando procedimientos conocidos para la reacción de aminas con acilimidazoles isocianatos o carbamatos de arilo o de una manera analoga a como se describe posteriormente en la presente en los Ejemplos T en la Fórmula X es de preferencia imidazolilo La reacción convenientemente se lleva a cabo utilizando un solvente orgánico, por ejemplo tetrahidrofurano o N-metilpirrolidona (NMP) de preferencia en presencia de una base por ejemplo trietilamina Cuando la amina se hace reaccionar con un acilimidazol o con un isocianato, las temperaturas de

155

reaccion adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente Cuando la amina se hace reaccionar con un carbamato de arilo por ejemplo carbamato de fenilo, las temperaturas de reaccion adecuadas son desde la temperatura ambiente hasta 120°C de preferencia de 80°C a 110°C en especial de aproximadamente 110°C

La variante del proceso (J) se puede llevar a cabo empleando procedimientos conocidos para la reaccion de N-heterociclos con acilimidazoles, isocianatos, o carbamatos de arilo o de una manera análoga a como se describe posteriormente en la presente en los Ejemplos T en la Formula XIIe es de preferencia imidazolilo La reacción se lleva a cabo convenientemente utilizando un solvente orgánico por ejemplo tetrahidrofurano o N-metilpirrolidona (NMP) Cuando el N-heterociclo se hace reaccionar con un acilimidazol o con un isocianato, las temperaturas de reaccion adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente Cuando el N-heterociclo se hace reaccionar con un carbamato de arilo, por ejemplo carbamato de fenilo las temperaturas de reaccion adecuadas son desde la temperatura ambiente hasta 120°C, de preferencia de 80°C a 110°C en especial de aproximadamente 110°C

La variante del proceso (K) se puede llevar a cabo empleando procedimientos conocidos para la reaccion de aminas con acilimidazoles, isocianatos, o carbamatos de

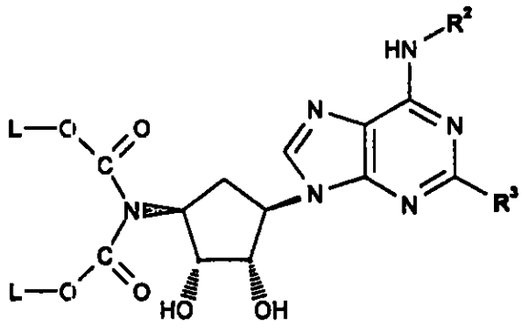
156

arilo, o de una manera análoga a como se describe posteriormente en la presente en los Ejemplos La reacción convenientemente se lleva a cabo utilizando un solvente organico por ejemplo tetrahidrofurano Cuando la amina se hace reaccionar con un acilimidazol o un isocianato las temperaturas de reaccion adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente Cuando la amina se hace reaccionar con un carbamato de arilo por ejemplo carbamato de fenilo las temperaturas de reacción adecuadas son desde la temperatura ambiente hasta 120°C, de preferencia de 80°C a 110°C en especial de aproximadamente 110°C

Cuando se hace referencia en la presente a grupos funciones protegidos o a grupos protectores, los grupos protectores se pueden seleccionar de acuerdo con la naturaleza del grupo funcional, por ejemplo como se describe en *Protecting Groups Inorganic Synthesis*, T W Green y P G M Wuts John Wiley & Sons, Inc , Tercera Edicion 1999 cuya referencia tambien describe los procedimientos adecuados para el reemplazo de los grupos protectores por hidrógeno

Los compuestos de la Fórmula II se pueden preparar mediante la desproteccion de un compuesto de la Formula XIII

157



XIII

en donde R^2 y R^3 son como los anteriormente definidos y cada L es alquilo de 1 a 8 atomos de carbono empleando procedimientos conocidos para la disociacion de enlaces de éster o de una manera analoga a como se describe en la presente en los Ejemplos De preferencia la reaccion se lleva a cabo utilizando un acido organico fuerte tal como acido trifluoroacético Cada L es de preferencia t-butilo La reaccion convenientemente se lleva a cabo utilizando un solvente organico por ejemplo diclorometano Las temperaturas de reaccion adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

Los compuestos de la Fórmula III ó IIIa están disponibles en el comercio o se pueden obtener mediante procedimientos conocidos para la preparación de estos compuestos, o de una manera analoga a como se describe en la presente, en los Ejemplos

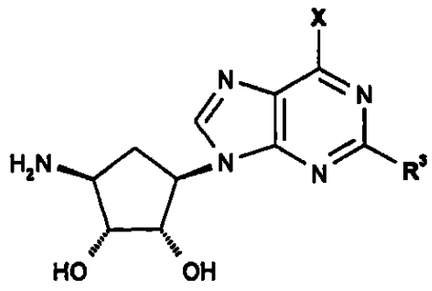
Los compuestos de la Formula IV se pueden preparar mediante la reacción de un compuesto de la Formula II en donde R^3 es halogeno con un compuesto de la Formula III o IIIa, en donde R^1 es como el anteriormente definido X

158

es un grupo saliente, de preferencia halogeno y K es hidrogeno o alquilo de 1 a 8 atomos de carbono en presencia de una base o de una manera análoga a como se describe en la presente en los Ejemplos La reacción convenientemente se lleva a cabo utilizando un solvente orgánico por ejemplo tetrahidrofurano La base de preferencia es diisopropiletilamina Las temperaturas de reaccion adecuadas son de 0°C a 40°C, de preferencia la temperatura ambiente

Los compuestos de la Fórmula Va o de la Formula Vb están disponibles en el comercio o se pueden obtener mediante procedimientos conocidos para la preparación de tales compuestos o de una manera análoga a como se describe en la presente en los Ejemplos

Los compuestos de la Fórmula VI se pueden preparar mediante la reacción de un compuesto de la Fórmula XIV



XIV

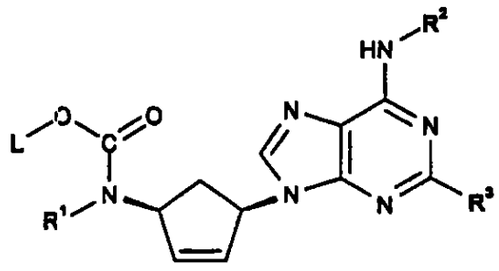
en donde R^3 es como el anteriormente definido y X es halogeno con un compuesto de la Fórmula III ó IIIa en donde R^1 es como el anteriormente definido, X es un grupo saliente, de preferencia halógeno y K es hidrogeno o alquilo

159

de 1 a 8 atomos de carbono en presencia de una base, en donde R^1 es como el anteriormente definido y X es halogeno o de una manera análoga a como se describe en la presente en los Ejemplos La reacción convenientemente se lleva a cabo utilizando un solvente orgánico por ejemplo tetrahidrofurano de preferencia en presencia de una base por ejemplo diisopropiletilamina Las temperaturas de reaccion adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

Los compuestos de la Fórmula VII están disponibles en el comercio o bien se pueden obtener mediante procedimientos conocidos para la preparación de tales compuestos o de una manera análoga a como se describe en la presente en los Ejemplos

Los compuestos de la Fórmula VIII se pueden preparar mediante la reacción de un compuesto de la Formula XV



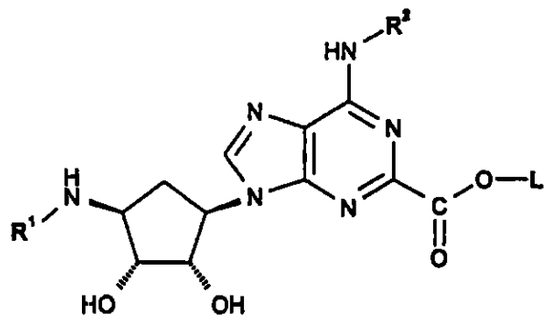
XV

en donde R^1, R^2, y R^3 son como los anteriormente definidos y L es alquilo de 1 a 8 atomos de carbono, con un agente de dihidroxilación tal como tetraoxido de osmio

160

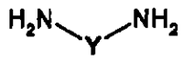
(OsO_4), ya sea en una cantidad estequiométrica o en una cantidad catalítica de preferencia junto con un re-oxidante, tal como N-oxido de N-metilmorfolina (NMO) o de una manera alternativa utilizando AD-mezcla-α o AD-mezcla-β o de una manera analoga a como se describe en la presente en los Ejemplos L es de preferencia t-butilo La reacción convenientemente se lleva a cabo utilizando un solvente organico por ejemplo tetrahidrofurano Las temperaturas de reaccion adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

Los compuestos de la Formula IX se pueden preparar mediante la reaccion de un compuesto de la Formula XVI



XVI

en donde R^1 y R^2 son como los anteriormente definidos y L es alquilo de 1 a 8 atomos de carbono se hace reaccionar con un compuesto de la Fórmula XVII



XVII

en donde Y es alquilo de 1 a 8 atomos de carbono o cicloalquilo de 3 a 8 atomos de carbono o de una manera analoga a como se describe en la presente, en los Ejemplos

Las temperaturas de reaccion adecuadas son de 80°C a 130°C de preferencia de 90°C a 120°C a temperatura ambiente y en especial a aproximadamente 105°C

Los compuestos de las Fórmulas X Xa XI u XIa estan disponibles en el comercio o se pueden obtener mediante procedimientos conocidos para la preparacion de tales compuestos o de una manera análoga a como se describe en la presente, en los Ejemplos

Los compuestos de la Formula XII estan disponibles en el comercio, o se pueden obtener mediante procedimientos conocidos para la preparación de tales compuestos o de una manera analoga a como se describe en la presente en los Ejemplos

Los compuestos de la Formula XIIa se pueden preparar empleando el proceso descrito en la presente para la preparacion de los compuestos de la Fórmula XVI, o de una manera análoga a como se describe en la presente, en los Ejemplos

Los compuestos de la Fórmula XIIb están disponibles en el comercio, o se pueden obtener mediante procedimientos conocidos para preparar tales compuestos o de una manera análoga a como se describe en la presente en los Ejemplos

Los compuestos de la Formula XIIc se pueden preparar empleando un proceso descrito en la presente para

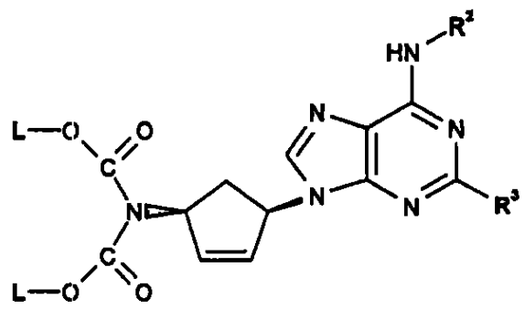
162

la preparacion de los compuestos de la Fórmula I, cuando R^3 es R^6, o de una manera analoga a como se describe en la presente en los Ejemplos

Los compuestos de la Formula XIId o XIIe se pueden preparar mediante la reaccion de un compuesto de la Formula I en donde R^3 es R^6 sustituido con amino, con un agente de acilacion adecuado o de una manera análoga a como se describe en la presente en los Ejemplos

Los compuestos de la Fórmula XIIf ó XIIg están disponibles en el comercio o se pueden obtener mediante procedimientos conocidos para la preparacion de tales compuestos o de una manera analoga a como se describe en la presente en los Ejemplos

Los compuestos de la Formula XIII se pueden preparar mediante la reaccion de un compuesto de la Fórmula XVIII



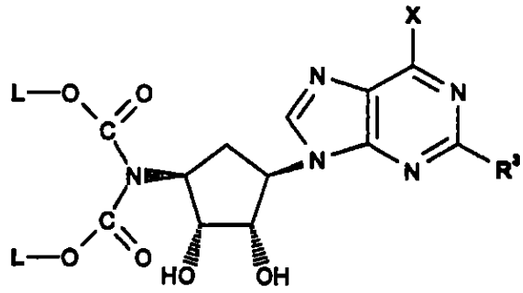
XVIII

en donde R^2 y R^3 son como los anteriormente definidos y cada L es alquilo de 1 a 8 átomos de carbono o bencilo con un agente de hidroxilación tal como tetraóxido de osmio (OsO_4) ya sea en una cantidad estequiométrica, o

163

bien en una cantidad catalitica de preferencia junto con un re-oxidante tal como N-oxido de N-metilmorfolina (NMO) o de manera alternativa, utilizando AD-mezcla-α o AD-mezcla-β o de una manera analoga a como se describe en la presente en los Ejemplos L^1 y L^2 de preferencia son t-butilo La reaccion convenientemente se lleva a cabo utilizando un solvente orgánico por ejemplo tetrahidrofurano Las temperaturas de reaccion adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

Los compuestos de la Formula XIV se pueden preparar mediante la reaccion de un compuesto de la Fórmula XIX

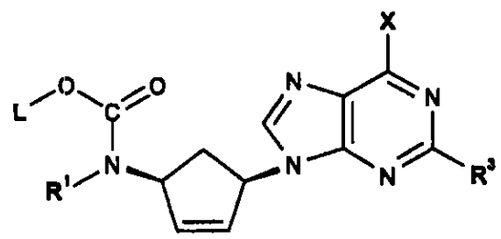


en donde R^3 y X son como los anteriormente definidos y cada L es alquilo de 1 a 8 átomos de carbono o bencilo con un ácido orgánico fuerte, tal como un acido trifluoroacetico o de una manera análoga a como se describe en la presente en los Ejemplos Cada L es de preferencia t-butilo La reaccion convenientemente se lleva a cabo utilizando un solvente organico por ejemplo diclorometano Las temperaturas de reaccion adecuadas son de 0°C a 40°C,

169

de preferencia la temperatura ambiente

Los compuestos de la Fórmula XV se pueden preparar mediante la reacción de un compuesto de la Formula XX

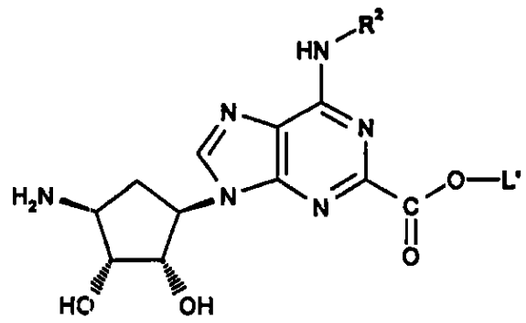


XX

en donde R^3 es como el anteriormente definido X es halogeno y L es alquilo de 1 a 8 atomos de carbono o bencilo, con un compuesto de la Fórmula VII en donde R^2 es como el anteriormente definido o de una manera análoga a como se describe en la presente en los Ejemplos La reaccion convenientemente se lleva a cabo utilizando un solvente organico por ejemplo tetrahidrofurano de preferencia en una atmosfera inerte, por ejemplo en argon Las temperaturas de reaccion adecuadas son de 30°C a 70°C de preferencia de 40°C a 60°C, en especial de aproximadamente 50°C

Los compuestos de la Fórmula XVI se pueden preparar mediante la reacción de un compuesto de la Formula XXI

165



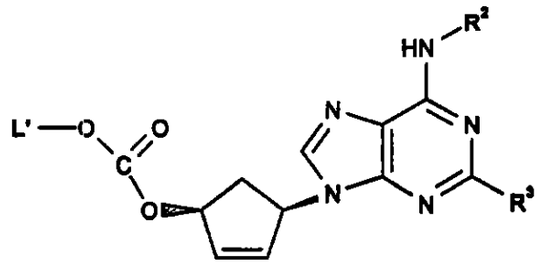
XXI

en donde R^2 es como el anteriormente definido y L es alquilo de 1 a 8 átomos de carbono o bencilo, pero de preferencia metilo con un compuesto de la Fórmula III ó IIIa en donde R^1 es como el anteriormente definido X es un grupo saliente de preferencia halogeno y K es hidrógeno o alquilo de 1 a 8 átomos de carbono o de una manera analoga a como se describe en la presente, en los Ejemplos La reaccion convenien emente se lleva a cabo utilizando un solvente organico, por ejemplo tetrahidrofurano de preferencia en presencia de una base, por ejemplo diisopropiletilamina Las temperaturas de reacción adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

Los compuestos de la Fórmula XVII están disponibles en el comercio, o se pueden obtener mediante procedimientos corocidos para la preparacion de tales compuestos o de una manera análoga a como se describe en la presente, en los Ejemplos

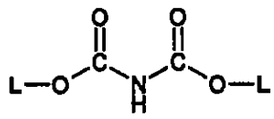
Los compuestos de la Formula XVIII se pueden preparar mediante la reaccion de un compuesto de la Fórmula XXII

166



XXII

en donde R^2 y R^3 son como los anteriormente definidos y L es alquilo de 1 a 8 atomos de carbono de preferencia metilo o etilo con un compuesto de la Fórmula XXIII

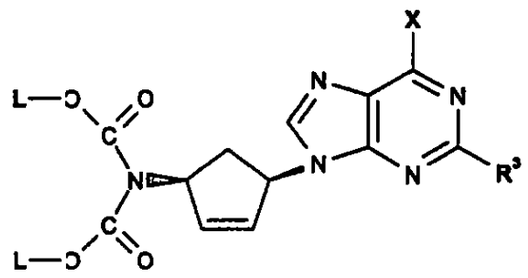


XXIII

en donde cada L es alquilo de 1 a 8 atomos de carbono o bencilo de preferencia bencilo y preferiblemente en presencia de un catalizador tal como aquel generado a partir de tetraquis-(trifenilfosfina)-paladio y trifenilfosfina o de una manera analoga a como se describe en la presente en los Ejemplos De preferencia cada L es t-butilo o bencilo La reaccion convenientemente se lleva a cabo en un medio ambiente inerte por ejemplo en argon, utilizando un solvente orgánico por ejemplo tetrahidrofurano desoxigenado Las temperaturas de reacción adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

Los compuestos de la Formula XIX se pueden preparar mediante la reacción de un compuesto de la Fórmula XXIV

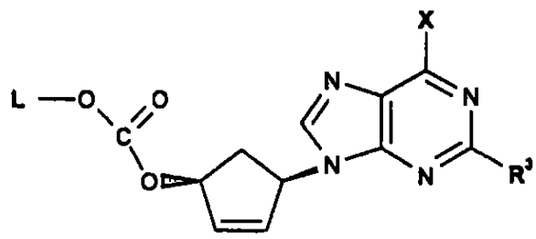
167



XXIV

en donde R^3 y X son como los anteriormente definidos y cada L es alquilo de 1 a 8 átomos de carbono o bencilo con un agente de hidroxilación tal como tetraoxido de osmio (OsO_4), ya sea en una cantidad estequiométrica o bien en una cantidad catalítica de preferencia junto con un re-oxidante tal como N-oxido de N-metilmorfolina (NMO), o de una manera alternativa, utilizando AD-mezcla-α o AD-mezcla-β o de una manera análoga a como se describe en la presente en los Ejemplos Cada L es de preferencia t-butilo La reaccion convenientemente se lleva a cabo utilizando un solvente organico por ejemplo tetrahidrofurano Las temperaturas de reaccion adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

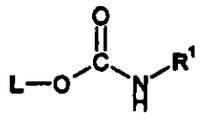
Los compuestos de la Formula XX se pueden preparar mediante la reaccion de un compuesto de la Formula XXV



XXV

168

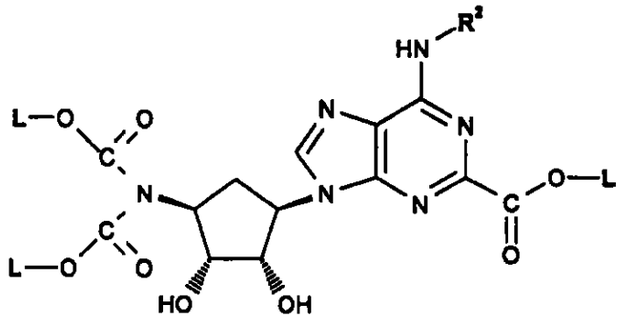
en donde R^3 es como el anteriormente definido y L es alquilo de 1 a 8 átomos de carbono con un compuesto de la Fórmula XXVa



XXVa

en donde R^1 es como el anteriormente definido, y L es alquilo de 1 a 8 átomos de carbono o bencilo de preferencia en presencia de un catalizador, tal como aquel generado a partir de tetraquis-(trifenilfosfina)-paladio y trifenilfosfina, o de una manera análoga a como se describe en la presente en los Ejemplos De preferencia L es t-butilo o bencilo La reacción se lleva a cabo convenientemente en un medio ambiente inerte, por ejemplo en argón utilizando un solvente organico por ejemplo tetrahidrofurano desoxigenado Las temperaturas de reaccion adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

Los compuestos de la Fórmula XXI se pueden preparar mediante la reacción de un compuesto de la Fórmula XXVI

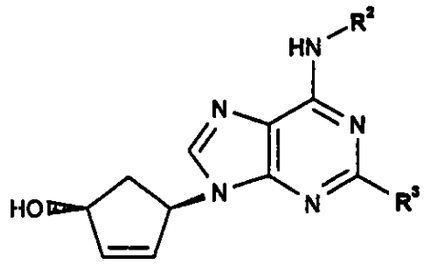


XXVI

169
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en donde R^2 es como el anteriormente definido cada L es alquilo de 1 a 8 atomos de carbono o bencilo y L es alquilo de 1 a 4 atomos de carbono con un ácido fuerte, por ejemplo ácido clorhidrico empleando procedimientos conocidos para la disociacion de los enlaces de ester o de una manera análoga a como se describe en la presente, en los Ejemplos De preferencia cada L es t-butilo o bencilo y L^a es metilo o etilo La reacción convenientemente se lleva a cabo en un medio ambiente inerte por ejemplo en argón utilizando un solvente organico, por ejemplo dioxano Las temperaturas de reacción adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

Los compuestos de la Fórmula XXII se pueden preparar mediante la reacción de un compuesto de la Fórmula XXVII



XXVII

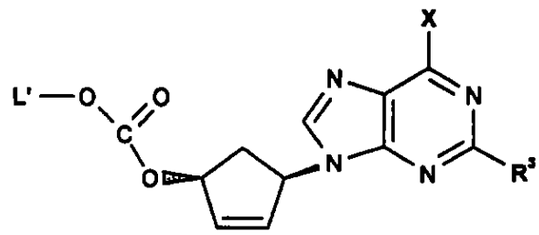
en donde R^2 y R^3 son como los anteriormente definidos con un agente de acilacion, tal como un ester alquilico de 1 a 8 atomos de carbono de ácido carboxilico por ejemplo etilester del acido 3-oxi-benzotriazol-1-carboxilico en la presencia de una base tal como

170
169

diisopropilamina y un catalizador tal como 4-dimetilamino-piridina (DMAP), o de una manera análoga a como se describe en la presente, en los Ejemplos La reaccion convenientemente se lleva a cabo en un medio ambiente inerte por ejemplo en argon utilizando un solvente organico por ejemplo THF desoxigenado Las temperaturas de reaccion adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

Los compuestos de la Fórmula XXIII están disponibles en el comercio, o se pueden obtener mediante procedimientos conocidos para la preparacion de tales compuestos o de una manera analoga a como se describe en la presente en los Ejemplos

Los compuestos de la Formula XXIV se pueden preparar mediante la reacción de un compuesto de la Fórmula XXVIII

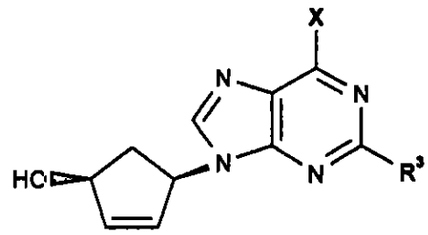


XXVIII

en donde R^3 y X son como los anteriormente definidos y L es alquilo de 1 a 8 atomos de carbono, con un compuesto de la Formula XXIII, en donde cada L es alquilo de 1 a 8 atomos de carbono o bencilo, de preferencia en presencia de un catalizador tal como aquél generado a partir

de tetraquis-(trifenilfosfina)-paladio y trifenilfosfina, o de una manera analoga a como se describe en la presente en los Ejemplos De preferencia, cada L es t-butilo o bencilo La reacción convenientemente se lleva a cabo en un medio ambiente inerte por ejemplo en argón, utilizando un solvente organico, por ejemplo tetrahidrofurano desoxigenado Las temperaturas de reaccion adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

Los compuestos de la Fórmula XXV se pueden preparar mediante la reacción de un compuesto de la Formula XXIX



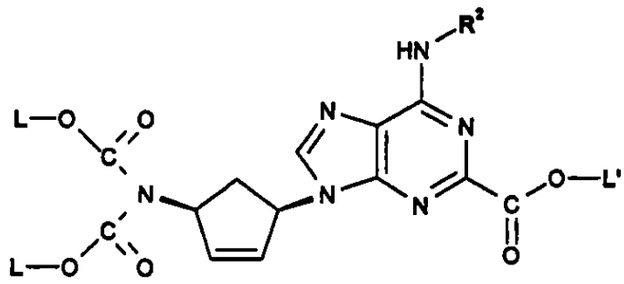
XXIX

en donde R^3 y X son como los anteriormente definidos con un agente de acilación, tal como un alquilester de 1 a 8 atomos de carbono de ácido carboxilico por ejemplo etilester del acido 3-oxibenzotriazol-1-carboxilico en presencia de una base tal como diisopropilamina y un catalizador tal como 4-dimetilaminopiridina (DMAP) o de una manera análoga a como se describe en la presente, en los Ejemplos La reaccion convenientemente se lleva a cabo en un medio ambiente inerte, por ejemplo en argón utilizando un solvente organico, por ejemplo tetrahidrofurano

desoxigenado Las temperaturas de reacción adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

Los compuestos de la Fórmula XXVa están disponibles en el comercio o se pueden obtener mediante los procedimientos conocidos para la preparacion de tales compuestos por ejemplo como es descrito por Ken-ichi Takana *et al* en *Chem Pharm Bull* 1988 36 3125 o de una manera analoga a como se describe en la presente en los Ejemplos

Los compuestos de la Fórmula XXVI se pueden preparar mediante la reacción de un compuesto de la Fórmula XXX

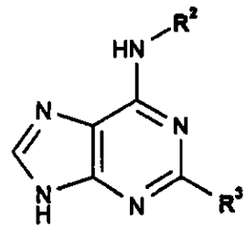


XXX

en donde R^2 es como el anteriormente definido cada L es alquilo de 1 a 8 atomos de carbono y L' es alquilo de 1 a 4 atomos de carbono o bencilo de preferencia bencilo con un agente de hidroxilacion, tal como tetraóxido de osmio (OsO_4) ya sea en una cantidad estequiométrica, o bien en una cantidad catalitica de preferencia junto con un re-oxidante tal como N-oxido de N-metilmorfolina (NMO) o de una manera alternativa utilizando AD-mezcla-α o AD-mezcla-

β o de una manera analoga a como se describe en la presente en los Ejemplos De preferencia cada L es t-butilo, y L^a es metilo o etilo La reaccion convenientemente se lleva a cabo utilizando un solvente organico por ejemplo tetrahidrofurano Las temperaturas de reacción adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

Los compuestos de la Fórmula XXVII se pueden preparar mediante la reacción de un compuesto de la Formula XXXI

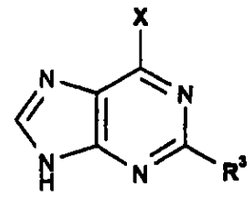


XXXI

en donde R^2 y R^3 son como los anteriormente definidos con (1S 4R)-cis-4-acetoxi-2-ciclopenten-1-ol en presencia de una base tal como hidruro de sodio y un catalizador tal como aquel generado a partir de tetraquis-(trifenilfosfina)-paladio y trifenilfosfina o de una manera analoga a como se describe en la presente, en los Ejemplos La reaccion convenientemente se lleva a cabo en un medio ambiente inerte por ejemplo en argon utilizando un solvente organico por ejemplo tetrahidrofurano desoxigenado o dimetilsulfoxido (DMSO) Las temperaturas de reaccion adecuadas son de 40°C a 60°C, de preferencia de aproximadamente 50°C

Los compuestos de la Fórmula XXVIII se pueden preparar mediante la reacción de un compuesto de la Fórmula XXIX, en donde R^3 y X son como los anteriormente definidos con un agente de acilacion tal como un alquiléster de 1 a 8 átomos de carbono de ácido carboxílico por ejemplo etilester del acido 3-oxi-benzotriazol-1-carboxílico en presencia de una base tal como diisopropilamina, y un catalizador, tal como 4-dimetilaminopiridina (DMAP) o de una manera analoga a como se describe en la presente en los Ejemplos La reacción convenientemente se lleva a cabo en un medio ambiente inerte por ejemplo en argón utilizando un solvente orgánico por ejemplo THF Las temperaturas de reaccion adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

Los compuestos de la Formula XXIX se pueden preparar mediante la reaccion de un compuesto de la Formula XXXII

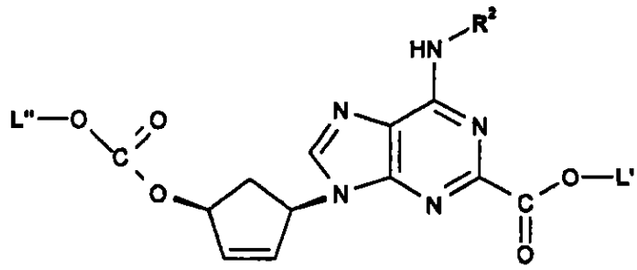


XXXII

en donde R^3 y X son como los anteriormente definidos con (1S,4R)-cis-4-acetoxi-2-ciclopenten-1-ol en presencia de una base, tal como hidruro de sodio y un catalizador tal como aquél generado a partir de tetraquis-(trifenilfosfina)-paladio y trifenilfosfina o de una manera

análoga a como se describe en la presente en los Ejemplos La reaccion convenientemente se lleva a cabo en un medio ambiente inerte, por ejemplo en argon utilizando un solvente organico por ejemplo tetrahidrofurano desoxigenado o dimetilsulfóxido (DMSO) Las temperaturas de reaccion adecuadas son de 40°C a 60°C de preferencia de aproximadamente 50°C

Los compuestos de la Formula XXX se pueden preparar mediante la reacción de un compuesto de la Fórmula XXXIII



XXXIII

en donde R^2 es como el anteriormente definido L es alquilo de 1 a 8 atomos de carbono o bencilo y L es alquilo de 1 a 4 atomos de carbono con un compuesto de la Formula XXIII en donde cada L es alquilo de 1 a 8 átomos de carbono de preferencia en la presencia de un catalizador tal como aquel generado a partir de tetraquis-(trifenilfosfina)-paladio y trifenilfosfina o de una manera analoga a como se describe en la presente en los Ejemplos De preferencia cada L es t-butilo o bencilo, y L es metilo o etilo La reaccion convenientemente se lleva a cabo en un medio

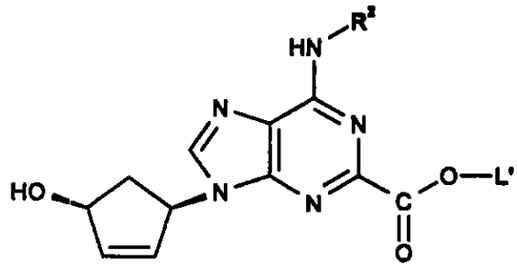
ambiente inerte por ejemplo en argón, utilizando un solvente orgánico, por ejemplo tetrahidrofurano desoxigenado Las temperaturas de reacción adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

Los compuestos de la Formula XXXI se pueden preparar mediante la reacción de un compuesto de la Formula XXXII en donde R^3 es como el anteriormente definido y X es halogeno con un compuesto de la Formula VII, en donde R^2 es como el anteriormente definido, o de una manera análoga a como se describe en la presente en los Ejemplos La reaccion convenientemente se lleva a cabo en un medio ambiente inerte por ejemplo en argon utilizando un solvente orgánico por ejemplo tetrahidrofurano Las temperaturas de reaccion adecuadas son de 40°C a 60°C, de preferencia de aproximadamente 50°C

Los compuestos de la Formula XXXII estan disponibles en el comercio o se pueden obtener mediante los procedimientos conocidos para la preparación de tales compuestos o de una manera analoga a como se describe en la presente en los Ejemplos

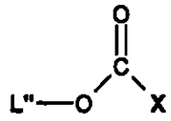
Los compuestos de la Formula XXXIII se pueden preparar mediante la reaccion de un compuesto de la Formula XXXIV

177
176



XXXIV

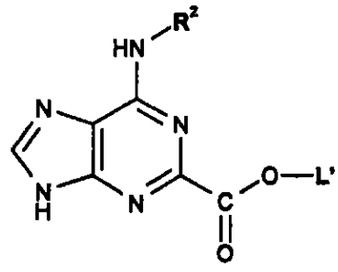
en donde R^2 y L son como los anteriormente definidos con un compuesto de la Fórmula XXXV



XXXV

en donde L' es alquilo de 1 a 8 atomos de carbono, de preferencia metilo o etilo y X es halógeno, de preferencia cloro o de una manera analoga a como se describe en la presente en los Ejemplos La reacción convenientemente se lleva a cabo en un medio ambiente inerte por ejemplo en argon utilizando un solvente organico por ejemplo tetrahidrofurano desoxigenado, de preferencia en la presencia de una base, por ejemplo piridina Las temperaturas de reacción adecuadas son de 0°C a 40°C de preferencia la temperatura ambiente

Los compuestos de la Fórmula XXXIV se pueden preparar mediante la reaccion de un compuesto de la Fórmula XXXVI



XXXVI

en donde R^2 es como el anteriormente definido, y L es alquilo de 1 a 4 átomos de carbono de preferencia metilo o etilo con (1S 4R)-cis-4-acetoxi-2-ciclopenten-1-ol en presencia de una base tal como hidruro de sodio y un catalizador tal como aquel generado a partir de tetraquis-(trifenilfosfina)-paladio y trifenilfosfina o de una manera analoga a como se describe en la presente, en los Ejemplos La reaccion convenientemente se lleva a cabo en un medio ambiente inerte por ejemplo en argón utilizando un solvente organico por ejemplo tetrahidrofurano desoxigenado o dimetilsulfóxido Las temperaturas de reacción adecuadas son de 60°C a 100°C de preferencia de aproximadamente 80°C

Los compuestos de la Fórmula XXXV están disponibles en el comercio o se pueden obtener mediante los procedimientos conocidos para la preparacion de tales compuestos o de una manera analoga a como se describe en la presente en los Ejemplos

Los compuestos de la Formula XXXVI se pueden preparar mediante la reaccion de un compuesto de sal de la Formula XXXVI en donde R^3 es como el anteriormente definido y L es alquilo de 1 a 8 átomos de carbono con un agente de sililación por ejemplo (N O-bis-(trimetil-silil)-acetamida) o de una manera analoga a como se describe en la presente, en los Ejemplos La reacción convenientemente

779
178

se lleva a cabo en un medio ambiente inerte por ejemplo en argon utilizando un solvente orgánico, por ejemplo cloroformo anhidro Las temperaturas de reaccion adecuadas son de 60°C a 100°C de preferencia de aproximadamente 80°C El intermediario sililado así formado se trata con metanol para obtener la base libre

Los compuestos de la Formula I en forma libre se pueden convertir en la forma de sal, y viceversa de una manera convencional Los compuestos en forma libre o de sal se pueden obtenei en la forma de hidratos o solvatos conteniendo un solvente utilizado para la cristalizacion Los compuestos de la Formula I se pueden recuperar de las mezclas de reaccion, y se pueden purificar de una manera convencional Los isómeros tales como los estereoisomeros se pueden obtener de una manera convencional por ejemplo mediante cristalizacion fraccionaria o sintesis asimetrica a partir de las materias primas correspondientemente sustituidas asiméiricamente por ejemplo ópticamente activas

Los compuestos de la Fórmula I y sus sales farmacéuticamente aceptables son utiles como productos farmaceuticos En particular activan el receptor A_{2A} de adenosina es decir actuan como agonistas del receptor A_{2A} Sus propiedades como agonistas de A_{2A} se pueden demostrar empleando el metodo descrito por L J Murphree *et al* res en

Molecular Pharmacology 61 455-462 (2002)

Los compuestos de los Ejemplos que se encuentran mas adelante en la presente tienen valores K_i menores de 1 0 µM en el ensayo anterior Por ejemplo, los compuestos de los Ejemplos 1 2 4 6 12, 14 20 33 38 39 42 47 55 y 61 tienen valores K_i de 0 582, 0 018, 0 057 0 008 0 003 0 690 0 008 0 05? 0 002, 0 003 0 002 0 002 0 004 y 0 009 µM respectivamente

Teniendo consideración de su activacion del receptor A_{2A} de adenosina los compuestos de la Fórmula I en forma libre o de sal farmaceuticamente aceptable referidos posteriormente en la presente de manera alternativa como los agentes de la invención , son utiles en el tratamiento de condiciones que responden a la activacion del receptor A_{2A} de adenosina en particular condiciones inflamatorias o alergicas El tratamiento de acuerdo con la invención puede ser sintomático o profiláctico

De conformidad con lo anterior, los agentes de la invencion son utiles en el tratamiento de enfermedades inflamatorias u obstructivas de las vias respiratorias, que dan como resultado por ejemplo una reducción del daño tisular de la inflamacion de las vias respiratorias de hiperreactividad bronquial, de remodelación o progreso de la enfermedad Las enfermedades y condiciones inflamatorias u obstructivas de las vias respiratorias a las que es aplicable

la presente invención incluyen lesion pulmonar aguda (LPA) sindrome de insuficiencia respiratoria de adultos/aguda (SDRA) enfermedad pulmonar crónica obstructiva o de las vias respiratorias (EPCO o ERCO) incluyendo bronquitis cronica o disnea asociada con la misma, enfisema, asi como exacerbacion de hiperreactividad de las vias respiratorias a consecuencia de otra terapia con farmacos en particular otra terapia con farmacos inhalados La invencion también es aplicable al tratamiento de bronquitis de cualquier tipo u origen, incluyendo por ejemplo, bronquitis aguda, araquidica catarral, cruposa, crónica o tísica Otras enfermedades inflamatorias u obstructivas de las vias respiratorias a las que es aplicable la presente invencion incluyen neumoconiosis (una enfermedad inflamatoria comunmente laboral, de los pulmones, acompañada con frecuencia por obstruccion de las vías respiratorias ya sea cronica o aguda y ocasionada por la inhalacion repetida de polvos) de cualquier tipo u origen incluyendo por ejemplo aluminosis, antracosis asbestosis calicosis ptilosis siderosis, silicosis tabacosis y bisinosis

Otras enfermedades inflamatorias u obstructivas de las vias respiratorias a las que es aplicable la presente invencion incluyen asma de cualquier tipo u origen incluyendo tanto asma intrinseca (no alergica) como asma extrinseca (alergica) asma leve asma moderada asma grave,

182

asma bronquitica, asma inducida por ejercicio, asma laboral, y asma inducida por infeccion bacteriana Se debe entender que el tratamiento del asma también abarca el tratamiento de sujetos, por ejemplo de menos de 4 ó 5 años de edad que exhiban sintomas de jadeo y sean diagnosticados o diagnosticables como bebes jadeantes que es una categoria 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 sindrome de bebé jadeante")

La eficacia profilactica en el tratamiento de asma será evidenciada por una frecuencia o gravedad reducida del ataque sintomatico por ejemplo del ataque asmático agudo o broncoconstrictor mejora en la funcion pulmonar o mejor hiperreactividad de las vias respiratorias Además se puede evidenciar por un requerimiento reducido de otra terapia sintomatica es decir terapia para o pretendida para restringir o abortar el ataque sintomatico cuando se presente por ejemplo antiinflamatoria (por ejemplo corticosteroides) o broncodilatadora El beneficio profilactico del asma puede ser aparente en particular en los sujetos susceptibles al "ahogamiento matutino El ahogamiento matutino es un sindrome asmatico reconocido, comun en un porcentaje sustancial de asmaticos y caracterizado por

183
182

ataque de asma por ejemplo entre las horas de aproximadamente las 4 a 6 am, es decir a una hora a menudo sustancialmente distante de cualquier terapia de asma sintomatica previamente administrada

Teniendo consideracion de su actividad antiinflamatoria, en particular en relacion con la inhibicion de la activacion de los eosinofilos los agentes de la invencion tambien son utiles en el tratamiento de trastornos relacionados con los eosinofilos, por ejemplo eosinofilia en particular trastornos relacionados con los eosinofilos de las vias respiratorias (por ejemplo, que involucren infiltración eosinofilica patologica de los tejidos pulmonares) incluyendo hipereosinofilia en lo que se refiere a sus efectos sobre las vias respiratorias y/o los pulmones asi como por ejemplo trastornos relacionados con los eosinófilos de las vias respiratorias a consecuencia o concomitantes al sindrome de Löffler neumonia eosinofilica infestación parasitaria (en particular de metazoarios) (incluyendo eosinofilia tropical), aspergilosis broncopulmonar poliarteritis nodosa (incluyendo sindrome de Churg-Strauss) granuloma eosinofilico y trastornos relacionados con los eosinófilos que afectan las vias respiratorias, ocasionados por reaccion a farmacos

Los agentes de la invención también son utiles en el tratamiento de condiciones inflamatorias o alergicas de la piel por ejemplo psoriasis dermatitis por contacto

dermatitis atopica, alopecia areata eritema multiforme dermatitis herpetiforme escleroderma vitiligo, angiitis por hipersensibilidad urticaria penfigoide buloso, lupus eritematoso penfigo epidermolisis bulosa adquirida, y otras condiciones inflamatorias o alérgicas de la piel

Los agentes de la invencion 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 del ojo, tales como conjuntivitis queratoconjuntivitis sicca y conjuntivitis vernal enfermedades que afecten a la nariz, incluyen rinitis alergica y enfermedades inflamatorias en las que estén implicadas reacciones autoinmunes o que tengan un componente o etiologia autoinmune incluyendo trastornos hematologicos autoinmunes (por ejemplo anemia hemolitica anemia aplasica, anemia eritrocítica pura y trombocitopenia idiopatica) lupus eritematoso sistemico policondritis esclerodoma granulomatosis de Wegener, dermatomiositis hepatitis activa crónica miastenia grave, sindrome de Steven-Johnson prurito idiopatico, enfermedad inflamatoria autoinmune del intestino (por ejemplo, colitis ulcerativa y enfermedad de Crohn) oftalmopatia endocrina enfermedad de Grave, sarcoidosis alveolitis neumonitis cronica por hipersensibilidad, esclerosis multiple, cirrosis biliar primaria,

uveitis (anterior y posterior) queratoconjuntivitis sicca y queratoconjuntivitis vernal fibrosis pulmonar intersticial artritis psoriatica y glomerulonefritis (con y sin sindrome nefrotico por ejemplo incluyendo síndrome nefrótico idiopatico o nefropa ia de cambio mínimo)

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 lesiones por isquemia/reperfusion, retinopatia tal como retinopatia diabetica o retinopatía inducida por oxigeno hiperbarico condiciones caracterizadas por presión intraocular elevada o secrecion de humor acuoso ocular tales como glaucoma daño isquémico de tejidos/organos por reperfusion, y llagas por la cama

La efectividad de un agente de la invencion para inhibir las condiciones inflamatorias, por ejemplo en las enfermedades inflamatorias de las vias respiratorias se puede demostrar en un modelo animal por ejemplo en un modelo de raton o rata de inflamacion de las vias respiratorias u otras condiciones inflamatorias, por ejemplo como es descrito por Szarka *et al*, *J Immunol Methods* (1997) 202 49-57 Renzi et al, *Am Rev Respir Dis* (1993) 148 932-939 Tsuyuki et al *J Clin Invest* (1995) 96 2924-2931 Cernadas et al (1999) *Am J Respir Cell Mol Biol* 20 1-8,

786
185

y Fozard et al (2002) *European Journal of Pharmacological* 438, 183-188

Los agentes de la invención también son utiles como agentes co-terapeuticos para utilizarse en combinación con otras sustancias medicamentosas, tales como anti-inflamatorios broncodilatadores antihistamínicos, o anti-tusivos, en particular en el tratamiento de enfermedades obstructivas o inflamatorias de las vias respiratorias tales como las mencionadas anteriormente en la presente, por ejemplo como potenciadores de la actividad terapéutica de estos farmacos o como un medio para reducir la dosificación requerida o los efectos secundarios potenciales de estos farmacos Un agente de la invencion se puede mezclar con otro farmaco en una composición farmaceutica fija o se puede administrar por separado, antes, de manera simultanea o despues del otro farmaco

De conformidad con lo anterior la invención incluye una combinacion de un agente de la invención como se describe anteriormente en la presente con un farmaco antiinflamatorio broncodilatador, antihistaminico o anti-tusivo estando el agente de la invención y este fármaco en la misma composicion farmaceutica o en una diferente

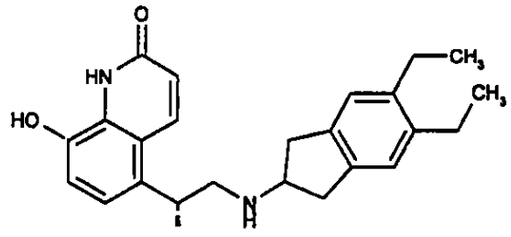
Los fármacos anti-inflamatorios adecuados incluyen esteroides, en particular glucocorticosteroides, tales como budesonida dipropionato de beclametasona propionato de

185
186

fluticasona ciclesonida o furoato de mometasona o los esteroides descritos en WO 02/88167, WO 02/12266, WO 02/100879 WO 02/00679 (en especial aquellos 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 esteroides, tales como los descritos en 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 DCP1187O LTB4 etanolamida LY 293111 LY 255283 CGS025019C, CP-195543 ONO-4057, SB 209247 SC-53228, y los descritos en US 5451700 antagonistas de LTD4 tales como los que incluyen montelukast, pranlukast, zafirlukast, accolato SR2640 Wy-48,252 ICI 198615 MK-571, LY-171883, Ro 24-5913, y L-648051 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 los que se describen en WO 92/19594, WO 93/19749 WO 93/19750, WO

188
187

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 los antagonistas del receptor A_{2B} de adenosina tales como los descritos en WO 02/42298 y los agonistas del adrenoceptor beta-2 tales como albuterol (salbutamol) metaproterenol terbutalina salmeterol, fenoterol procaterol y en especial formoterol, carmoterol, y las sales farmacéuticamente aceptables de los mismos, y los compuestos (en forma libre o de sal o de solvato) de la Formula I de WO 0075114 cuyo documento se incorpora en la presente como referencia de preferencia los compuestos de los Ejemplos de la misma en especial un compuesto de la Formula



y las sales farmaceuticamente aceptables del mismo, asi como los compuestos (en forma libre o de sal o de solvato) de la Fórmula I de la Publicacion WO 04/16601, y también los compuestos de las Patentes 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 los agentes anticolinergicos o antimuscarinicos en particular bromuro de ipratropio bromuro de oxitropio sales de tiotropio y CHF 4226 (Chiesi) y glicopirrolato pero tambien aquellos descritos en las Patentes 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 pares de farmacos antiinflamatorios y broncodilatadores adecuados incluyen el par agonista de adrenorreceptor beta-2/antagonista muscarinico, tales como los que se describen en las Patentes US 2004/0167167 US

190
189

2004/0242622 US 2005/182092 WO 04/74246 y WO 04/74812

Los fármacos antihistamínicos adecuados incluyen clorhidrato de cetirizina, acetaminofen fumarato de clemastina prometazina loratidina desloratidina difenhidramina y clorhidrato de fexofenadina, activastina astemizol azelastina ebastina epinastina misolastina y tefenadina así como las que se dan a conocer en las Patentes JP 200410/299, WO 03/099807 y WO 04/026841

Otras combinaciones utiles de agentes de la invencion con farmacos antiinflamatorios 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 CCR-5 tales como los antagonistas de 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-2-aminio (TAK-770) y los antagonistas CCR-5 descritos en las Patentes US 6166037 (en particular en las reivindicaciones 18 y 19), WO 00/66558 (en particular en la reivindicacion 8) WO 00/66559 (en particular en la reivindicacion 9) WO 04/18425 y WO 04/026873

De conformidad con lo anterior la invencion

197
190

tambien proporciona un método para el tratamiento de una condición que responda a la activación del receptor A_{2A} de adenosina por ejemplo una condición inflamatoria o alérgica en particular una enfermedad inflamatoria u obstructiva de las vias respiratorias el cual comprende administrar a un sujeto, en particular a un sujeto humano que lo necesite, un compuesto de la Formula I en forma libre o en la forma de una sal farmaceutiamente aceptable En otro aspecto, la invencion proporciona un compuesto de la Formula I en forma libre o en la forma de una sal farmaceuticamente aceptable para utilizarse en la fabricación de un medicamento para el tratamiento de una condicion que responda a la activación del receptor A_{2A} de adenosina en particular una enfeimedad inflamatoria u obstructiva de las vias respiratorias

Los agentes de la invención se pueden administrar por cualquier via apropiada por ejemplo oralmente por ejemplo en la forma de una tableta o cápsula parenteralmente, por ejemplo intravenosamente, mediante inhalacion, por ejemplo en el tratamiento de una enfermedad inflamatoria u obstructiva de las vias respiratorias intranasalmente por ejemplo en el tratamiento de rinitis alérgica topicamente en la piel por ejemplo en el tratamiento de dermatitis atopica, o rectalmente, por ejemplo en el tratamiento de una enfermedad intestinal inflamatoria

En un aspecto adicional, la invención tambien proporciona una composicion farmaceutica que comprende un compuesto de la Fórmula I en forma libre o en la forma de una sal farmaceuticamente aceptable opcionalmente junto con un diluyente o vehiculo farmaceuticamente aceptable para el mismo La composición puede contener un agente co-terapeutico tal como un fármaco anti-inflamatorio, broncodilatador anti-histaminico o anti-tusivo como se describe anteriormente en la presente Estas composiciones se pueden preparar utilizando diluyentes o excipientes convencionales y las técnicas conocidas en el campo galenico Por consiguiente, las formas de dosificacion oral pueden incluir tabletas y capsulas Las formulaciones para administración topica pueden tener la forma de cremas, ungüentos geles, o sistemas de administración transdérmica por ejemplo parches Las composiciones para inhalación pueden comprender formulaciones en aerosol u otras formulaciones atomizables, o formulaciones en polvo seco

Cuando la composicion comprende una formulacion en aerosol de preferencia contiene, por ejemplo, un propelente de hidrofluoroalcano (HFA) tal como HFA134a ó HFA227 o una mezcla de los mismos, y puede contener uno o mas cosolventes conocidos en la tecnica tales como etanol (hasta el 20% 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 composicion comprende una formulación en polvo seco de preferencia contiene, por ejemplo al compuesto de la Fórmula I que tiene un diámetro de particulas de hasta 10 micras opcionalmente junto con un diluyente o vehiculo tal como lactosa de la distribución de tamaños de particulas 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 composicion comprende una formulación nebulizada de preferencia contiene por ejemplo al compuesto de la Fórmula I disuelto o suspendido en un vehiculo que contenga agua un cosolvente tal como etanol o propilenglicol y un estabilizante el cual puede ser un tensoactivo

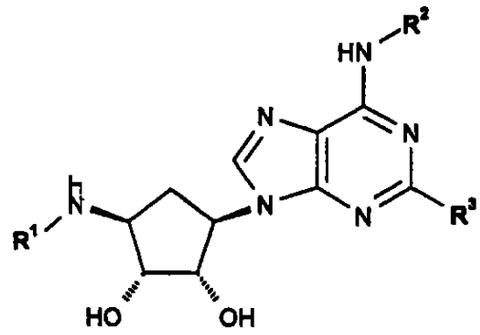
La invencion incluye (A) un compuesto de la Formula I en una forma inhalable por ejemplo en una composicion en aerosol o en otra composicion atomizable, o en un particulado inhalable por ejemplo en una forma micronizada, (B) un medicamento inhalable que comprende un compuesto de la Fórmula I en una forma inhalable (C) un producto farmaceutico que comprende un compuesto de la Formula I en una forma inhalable, en asociación con un dispositivo para inhalación y (D) un dispositivo para inhalacion 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 invencion por supuesto variaran dependiendo por ejemplo de la condición particular que se vaya a tratar, del efecto deseado, y del modo de administiacion En general las dosificaciones diarias adecuadas para administrarse mediante inhalacion son del orden de 0 005 a 10 miligramos mientras que para la administracion oral, las dosis diarias adecuadas son del orden de 0 05 a 100 miligramos

La invención se ilustra mediante los siguientes Ejemplos

EJEMPLOS

Los compuestos preferidos de la Fórmula I

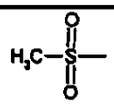
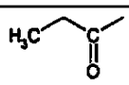
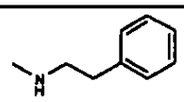
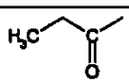
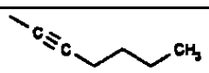
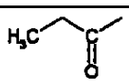
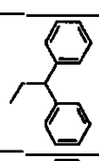
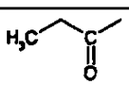
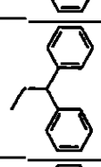
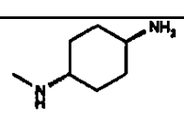
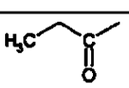
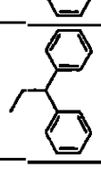
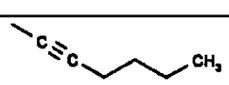


incluyen los mostrados en la siguiente Tabla 1 Los métodos para preparar estos compuestos se describen posteriormente en la presente La tabla tambien muestra la espectrometria de masas y los datos MH^+ (ESMS) Los ejemplos están en forma libre, con la excepción de los Ejemplos 1-3 7 9-11 y 17-37 que son sales de

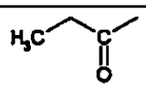
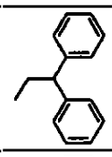
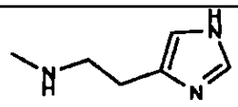
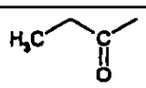
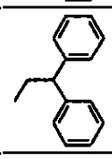
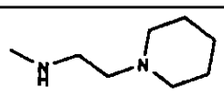
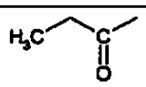
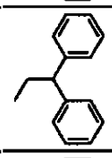
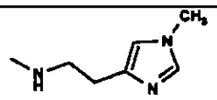
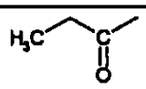
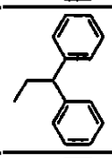
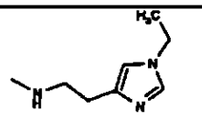
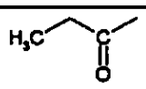
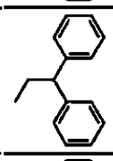
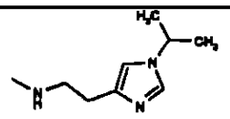
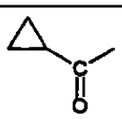
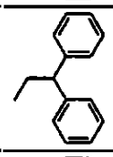
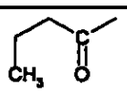
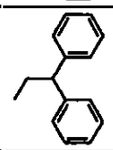
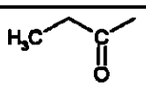
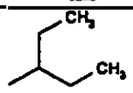
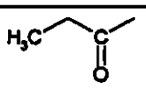
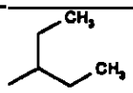
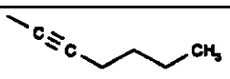
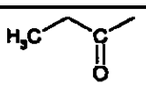
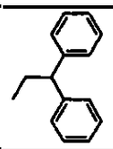
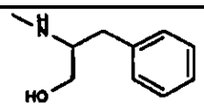
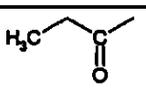
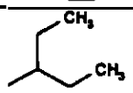
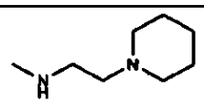
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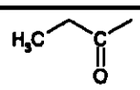
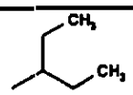
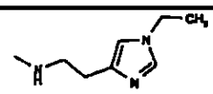
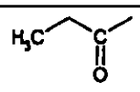
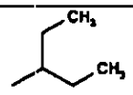
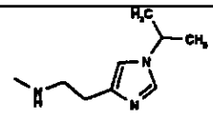
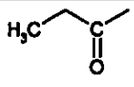
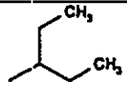
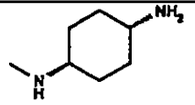
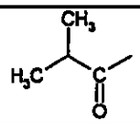
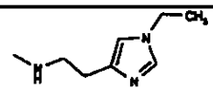
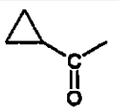
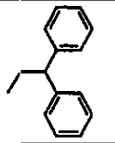
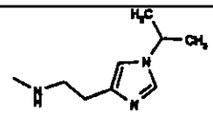
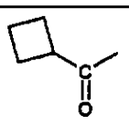
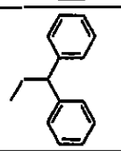
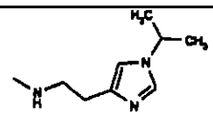
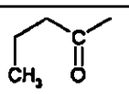
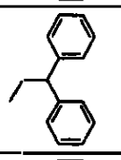
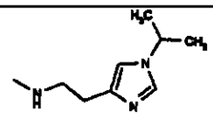
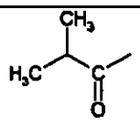
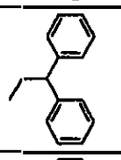
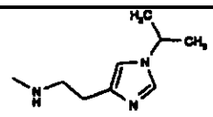
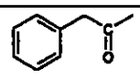
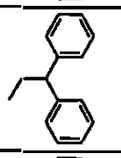
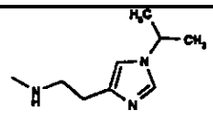
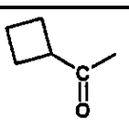
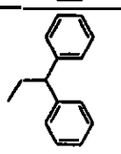
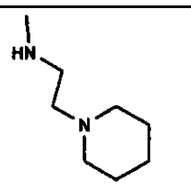
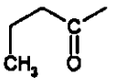
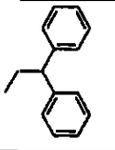
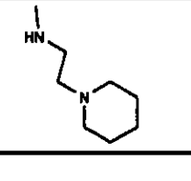
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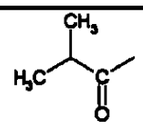
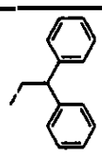
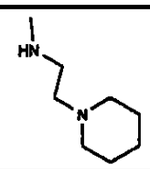
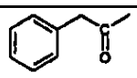
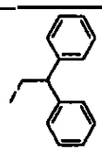
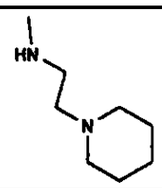
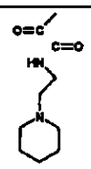
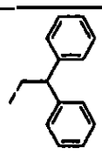
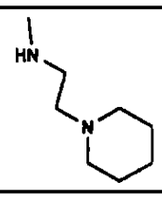
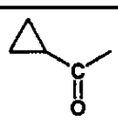
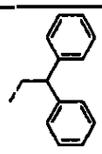
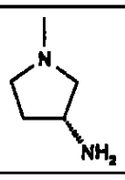
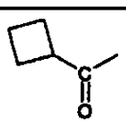
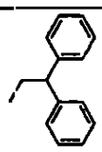
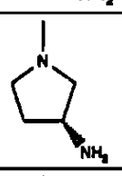
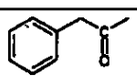
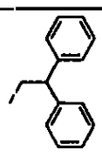
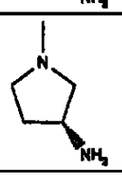
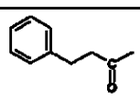
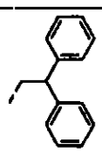
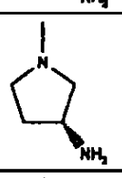
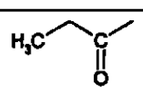
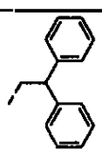
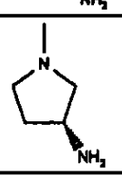
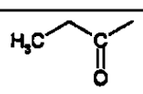
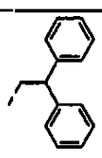
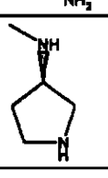
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4			Cl	521 30
5				599 28 599 41
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196
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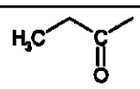
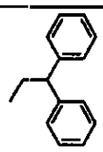
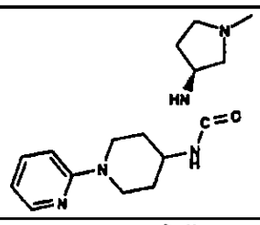
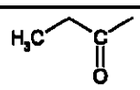
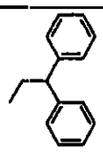
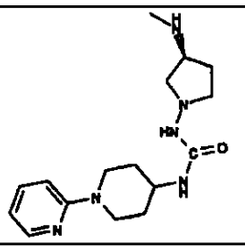
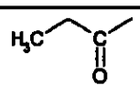
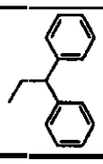
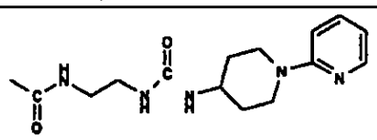
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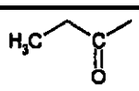
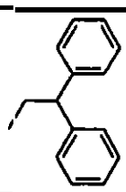
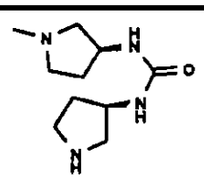
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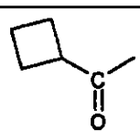
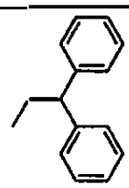
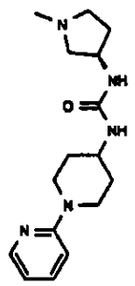
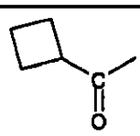
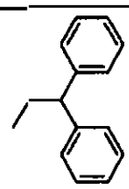
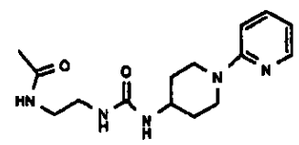
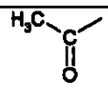
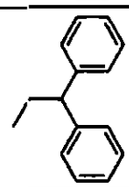
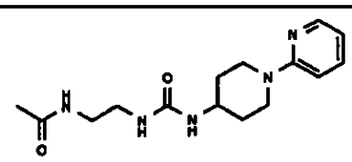
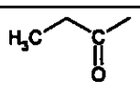
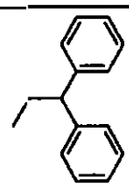
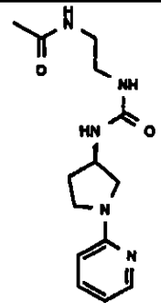
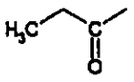
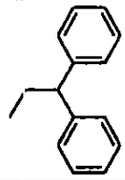
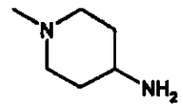
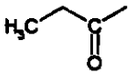
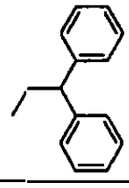
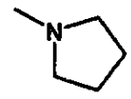
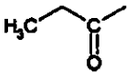
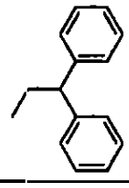
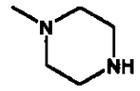
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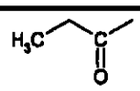
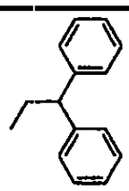
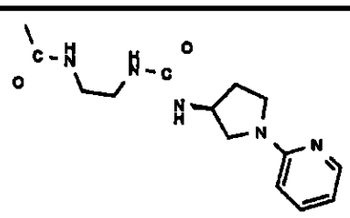
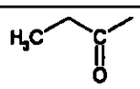
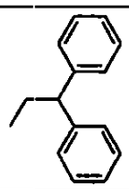
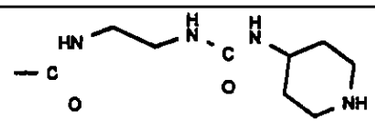
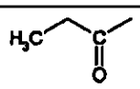
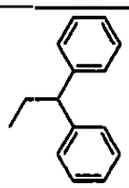
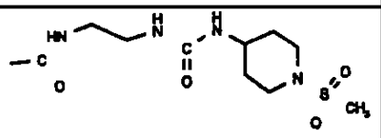
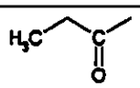
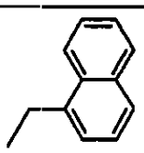
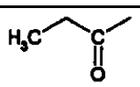
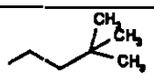
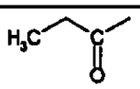
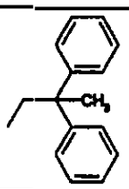
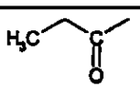
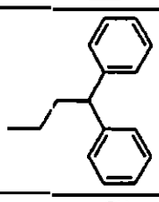
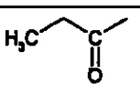
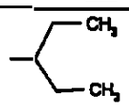
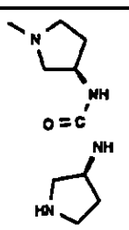
Otros ejemplos preferidos de los compuestos de la Formula I se muestran en la siguiente Tabla 2 Los metodos para preparar estos compuestos se describen posteriormente en la presente La tabla tambien muestra la espectrometria de masas y los datos MH^+ (ESMS) Los compuestos de los ejemplos son las sales de trifluoroacetato con la excepcion de los compuestos de los Ejemplos 41 48 52 y 53 que estan en forma libre, y el compuesto del Ejemplo 44 que es una sal clorhidrato

TABLA 2

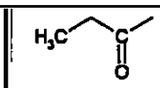
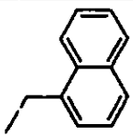
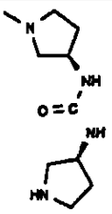
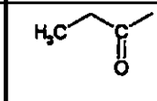
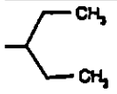
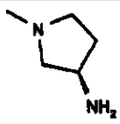
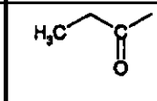
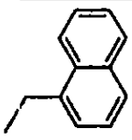
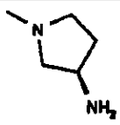
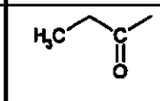
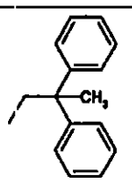
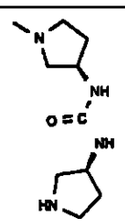
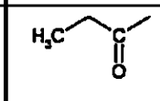
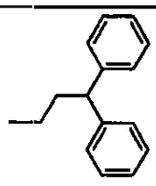
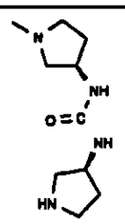
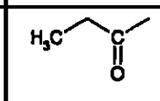
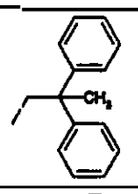
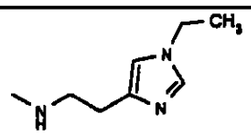
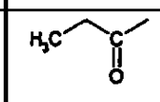
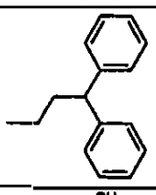
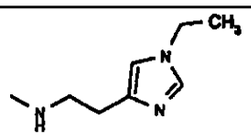
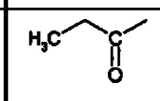
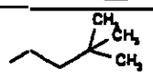
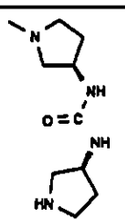
Ex	R¹	R²	R³	MH+ or MH+/2
39				683 6

200
194

40				800 6
41				802 6
42				762 6
43				762 5
44				585 5
45				556 5
46				571 5

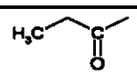
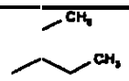
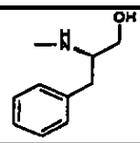
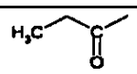
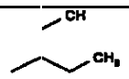
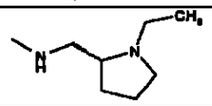
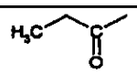
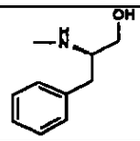
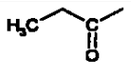
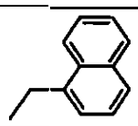
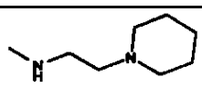
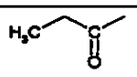
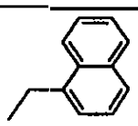
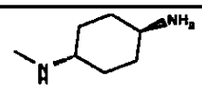
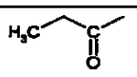
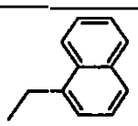
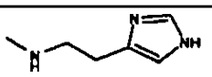
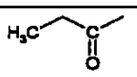
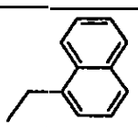
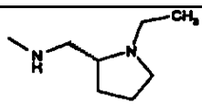
47				382 9
48				699 6
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50			-Cl	481 3
51			-Cl	425 2
52			-Cl	535 3
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54				573 4

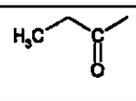
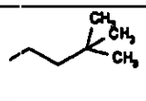
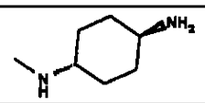
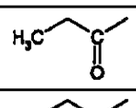
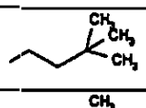
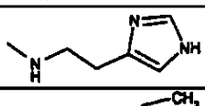
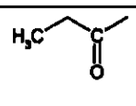
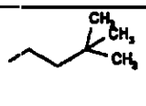
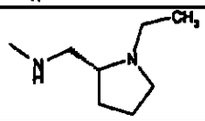
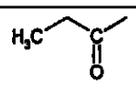
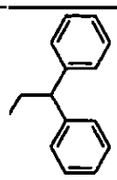
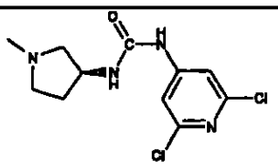
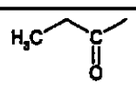
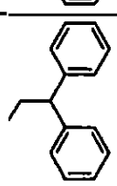
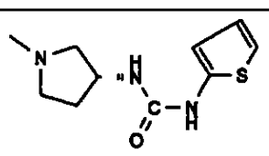
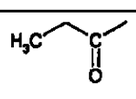
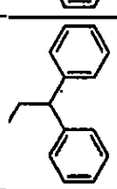
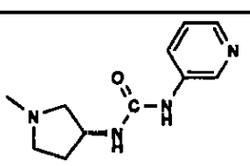
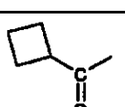
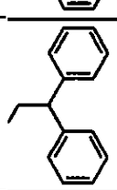
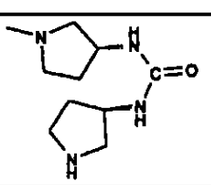
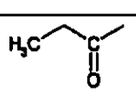
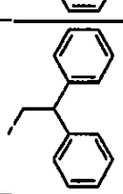
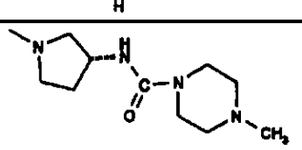
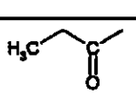
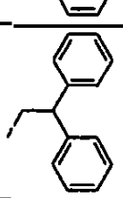
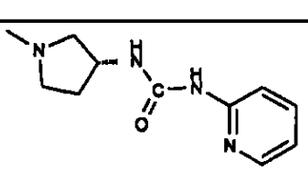
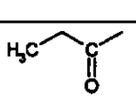
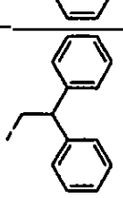
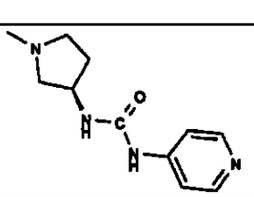
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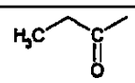
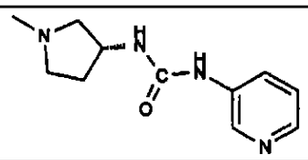
55				643 4
56				461 3
57				531 3
58				697 5
59				697 5
60				638 4
61				638 4
62				587 3

Otros ejemplos preferidos de los compuestos de la Formula I se muestran en la siguiente Tabla 3 Los metodos para preparar estos compuestos se describen posteriormente en la presente La tabla tambien muestra la espectrometría de masas y los datos MH^+ {ESMS} Los compuestos de los ejemplos son sales de trifluoroacetato con la excepcion del compuesto del Ejemplo 76 que está en forma libre y el compuesto del Ejemplo 79, que es una sal clorhidrato

TABLA 3

Ej	R¹	R²	R³	MH+ ó MH+/2
63				526 5
64				503 5
65		-H		456 4
66				573 5
67				559 5
68				556 5
69				573 5

70				503 5
71				500 5
72				517 6
73				759 4
74				696 4
75				691 5
76				709 2
77				697 4
78				691 4
79				705 3

80		H		

Preparacion de compuestos intermediarios

Las abreviaturas utilizadas son como sigue CDI es 1 1 -carbonildiimidazol, DCM es diclorometano DIPEA es diisopropiletilamina DMAP es 4-dimetilaminopiridina DMF es dimetilformamida DMSO es dimetilsulfoxido LCMS es cromatografia liquida-espectroscopia de masas TEA es trietilamina TFA es acido trifluoroacético THF es tetrahidrofurano y TLC es cromatografía en capa fina

Etilester del ácido 3-oxi-benzotriazol-1-carboxilico

Este compuesto se prepara a partir de 1-hidroxi-benzotriazol mediante el procedimiento de Wuts, Peter G M et al *Organic Letters* (2003) 5(9) 1483-1485 ^{1}H RMN ($CDCl_3$ 400 MHz), 8 20 (d 1H) 8 00 (d 1H) 7 75 (t 1H) 7 55 (t 1H) 4 60 (q 2H) 1 55 (t 3H)

2-(1-isopropil-1H-imidazol-4-il)-etilamina

Este compuesto se prepara a partir de yoduro de 2-isopropil-5-oxo-5 6 7 8-tetrahidro-imidazo[1 5-c]-pirimidin-2-io mediante el procedimiento de Rahul Jain y Louis A Cohen *Tetrahedron* 1996 52 5363 ^{1}H RMN (MeOD 400 MHz) 7 60 (s, 1H), 6 95 (s 1H) 4 40 (m, 1H), 2 90 (t, 2H), 2 70 (t 2H) 1 45 (d 6H)

Tert-butiléster del acido propionilcarbámico

El compuesto del titulo se prepara a partir de tert-butilester del acido propil-carbamico empleando el procedimiento descrito por Ken-ichi Takana et al, *Chem Pharm Bull* 1988 36 3125 ^{1}H RMN ($CDCl_3$ 400 MHz) 7 25 (br s 1H) 2 75 (q 2H) 1 50 (s, 9H), 1 15 (t 3H)

Bis-(4-metoxifenil)-metanona oxima

La 4 4 -dimetoxibenzofenona (25 gramos 103 milimoles) se suspende en etanol (150 mililitros) y piridina (30 mililitros) Se agrega clorhidrato de hidroxilamina (21 50 gramos 310 milimoles), y la mezcla de reacción se pone a reflujo Se demuestra que la reacción esta completa mediante TLC despues de 3 horas La mezcla de reacción se deja enfriar y el solvente se remueve al vacio El residuo se somete a extraccion por particion entre acetato de etilo (500 mililitros) y agua (500 mililitros) La fase organica se seca sobre $MgSO_4$ se filtra y el solvente se remueve al vacío El compuesto del titulo se obtiene despues de una cristalizacion a partir de acetato de etilo/ciclohexano ^{1}H RMN ($CDCl_3$ 400 MHz) 7 70 (s 1H) 7 40 (d de d 4H) 6 95 (d 2H) 6 85 (d 2H) 3 85 (s 3H) 3 80 (s 3H)

C,C-bis-(4-metoxifenil)-metilamina

La bis-(4-metoxifenil)-metanona oxima (20 gramos, 77 82 milimoles) se suspende en amoniaco 880 (450 mililitros) y etanol (90 mililitros) Se agrega acetato de amonio (3 00 gramos 38 91 milimoles) seguido por la

206
207

adicion en porciones de polvo de zinc (25 29 gramos 289 10 milimoles) Una vez que se termina la adición la mezcla de reaccion se calienta lentamente a 50°C Cuando cesa la efervescencia la mezcla de reaccion se pone a reflujo Se demuestra que la reaccion esta completa mediante TLC despues de 4 horas La mezcla de reacción se deja enfriar y se agrega acetato de etilo (250 mililitros) La mezcla de reaccion se filtra a través de Celite^{MR} y se separan las fases La fase organica se seca sobre $MgSO_4$ se filtra, y el solvente se remueve al vacío, para obtener el compuesto del titulo ^{1}H RMN ($CDCl_3$ 400 MHz) 7 25 (d 4H) 6 80 (d 4H) 5 10 (s, 1H) 3 75 (s 6H)

1 3-di(R)-pirrolidin-3-il-urea

(a) 1,3-bis-((R)-1-bencil-pirrolidin-3-il)-urea

Una solucion que comprende (R)-1-bencil-pirrolidin-3-il-amina (5 0 gramos, 28 4 milimoles) en DCM (10 mililitros) se trata con CDI (2 3 gramos 14 2 milimoles) y la mezcla de reacción se agita a temperatura ambiente durante 48 horas El solvente se remueve al vacio y el residuo resultante se disuelve en acetato de etilo Esta porcion se lava con agua seguida por salmuera se seca ($MgSO_4$) y se concentra al vacio, para obtener el compuesto del titulo como un solido de color naranja palido

(b) 1 3-di-(R)-pirrolidin-3-il-urea

A una solucion de 1 3-bis-((R)-1-bencil-pirrolidin-3-

il)-urea (5 34 gramos 14 1 milimoles) en etanol (80 mililitros) bajo una atmósfera inerte de argon, se le agrega hidroxido de paladio sobre carbón (1 07 gramos) La mezcla de reaccion se purga con argón y se pone bajo una atmósfera de hidrógeno durante 2 dias después de cuyo tiempo la mezcla se filtra y el catalizador se lava con etanol Las porciones organicas se combinan y se concentran al vacio para obtener el compuesto del titulo como un sólido blanco

(3 4 5 6-tetrahidro-2H-[1 2]-bipiridinil-4-il)-amida del ácido imidazol-1-carboxilico

Una solucion en agitacion de CDI (1 1 gramos 6 77 milimoles) en DCM (100 mililitros) se trata con 3 4 5 6-tetrahidro-2H-[1 2']-bipiridinil-4-il-amina (Patentes WO 99/65895 y EP 2 1973) (1 gramo, 5 64 milimoles en 50 mililitros de DCM) que se agrega por goteo durante 30 minutos La mezcla de reaccion se agita a temperatura ambiente durante 15 minutos para obtener el compuesto del titulo como una solución de 10 miligramos/mililitro en diclorometano

El compuesto se utiliza en solucion en las siguientes reacciones Esta solucion consiste del intermediario de imidazol-urea (C) junto con cantidades variables del correspondiente isocianato e imidazol el cual resulta de la eliminacion termica reversible de imidazol bajo

las condiciones de reacción Esta solucion se utiliza en los siguientes pasos debido a que el intermediario de imidazol-urea y el intermediario de isocianato son igualmente adecuados como precursores para ureas

1-(2-aminoetil)-3-((S)-1-piridin-2-il-pirrolidin-3-il)-urea

(a) Tert-butiléster del ácido ((S)-1-piridin-2-il-pirrolidin-3-il)-carbamico

Una solución en agitacion que comprende tert-butilester del acido (S)-pirrolidin-3-il-carbamico (2 0 gramos, 10 7 milimoles) 2-bromo-piridina (1 7 gramos 10 7 milimoles) y TEA (1 1 gramos, 10 7 milimoles) en DMF (40 mililitros) se calienta a 80°C durante 50 horas El solvente se remueve al vacío, y la purificacion del residuo crudo por cromatografia en gel de silice eluyendo con acetato de etilo/hexano (1 9 aumentando hasta 1 4) produce el compuesto del titulo como un sólido blanco

(b) Diclorhidrato de (S)-1-piridin-2-il-pirrolidin-3-il-amina

A una solución de tert-butiléster del acido ((S)-1-piridin-2-il-pirrolidin-3-il)-carbamico (0 221 gramos 0 84 milimoles) en dioxano (4 mililitros) y metanol (1 mililitro), se le agrega HCl 4M (en dioxano) (0 525 mililitros 2 1 milimoles) y la mezcla de reaccion se agita a temperatura ambiente durante la noche La suspensión resultante se filtra y se lava con dioxano (1 mililitro tres veces), para obtener el compuesto del titulo

(c) ((S)-1-piridin-2-il-pirrolidin-3-il)-amida del acido imidazol-1-carboxílico

Una mezc a que comprende el diclorhidrato de (S)-1-piridin-2-il-pirrolidin-3-ilamina (0 242 gramos 1 02 milimoles) TEA (0 2 mililitros) en DCM (10 2 mililitros) se trata con CDI (0 364 gramos 2 26 milimoles) La mezcla de reaccion se agita a temperatura ambiente durante 2 horas para obtener el compuesto del título como una solucion 0 1 M en DCM Esta solución consiste en el intermediario de imidazol-urea junto con cantidades variables del isocianato y el imidazol correspondientes Esta solucion se utiliza en los siguientes pasos debido a que el intermediario de imidazol-urea y el intermediario de isocianato son igualmente adecuados como precursores para ureas

(d) 1-(2-aminoetil)-3-((S)-1-piridin-2-il-pirrolidin-3-il)-urea

A una solucion de ((S)-1-piridin-2-il-pirrolidin-3-il)-amida del ácido imidazol-1-carboxílico (9 9 mililitros de una solucion 0 1 M en DCM 0 99 milimoles) en isopropanol (1 mililitro) se le agrega etil-1 2-diamina (2 mililitros 37 milimoles) La mezcla de reacción se agita a temperatura ambiente durante 4 horas y luego se extrae con DCM utilizando un sistema de extracción continua de liquido-liquido, para obtener el compuesto del titulo como una mezcla en una relacion molar de 1 4 con imidazol

1-(2-aminoetil)-3-((R)-1-piridin-2-il-pirrolidin-3-il)-urea

El compuesto del titulo se prepara de una manera analoga al Intermediario D, reemplazando el tert-butilester del acido (S)-pirrol din-3-il-carbámico por tert-butiléster del ácido (R)-pirrolidin-3-il-carbamico y reemplazando la 2-bromo-piridina por 2-cloropiridina

Tert-butilester del acido [(1S 2R 3S 4R)-4-(2 6-dicloro-purin-9-il)-2 3-dihidroxiciclopentil]-propionilcarbamico

El compuesto del titulo se prepara de una manera análoga al metiléster del ácido 9-[(1R,2S,3R 4S)-4-terbutoxi-carbonil-propionilamino)-2 3-dihidroxiciclopentil]-6-(2 2-difeniletilamino)-9H purin-2-carboxilico (Ejemplo 38), reemplazando el metiléster del ácido 9-[(1R 4S)-4-(terbutoxi-carbonil-propionilamino)-ciclopent-2-enil]-6-(2,2-difeniletilamino)-9H purin-2-carboxílico por tert-butiléster del acido [(1S 4R)-4-(2 6-dicloro-purin-9-il)-ciclopent-2-enil]-propionilcarbamico

N-{(3aR 4S 6R 6aS) 6-[2-((R)-3-amino-pirrolidin-1-il)-6-(2,2-difeniletilamino)-purin-9-il]-2 2-dimetil-tetrahidro-ciclopenta[1 3]-dioxol-4-il]-propionamida

a) Benciléster del ácido {(R)-1-[9-((1R,2S,3R,4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-il]-pirrolidin-3-il]-carbamico

Una solución del clorhidrato de benciléster del acido (R)-pirrolidin-3-il-carbámico (0 88 gramos 3 45 milimoles) en DCM, se transforma en base libre utilizando

una solucion de carbonato acido de sodio, para obtener el bencilester del acido (R)-pirrolidin-3-il-carbamico (0 487 gramos 2 22 milimoles) Esta amina se agrega a la N-{(1S,2R 3S 4R)-4-[2 cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (Ejemplo 4) (0 5 gramos 0 96 milimoles) y TEA (0 224 gramos 2 22 milimoles) y luego se disuelve en NMP (7 mililitros) La mezcla de reacción se calienta utilizando radiacion de microondas en un reactor de microondas Personal Chemistry Emrys^{MR} Optimizer a 190°C durante 1 hora La mezcla resultante se purifica por cromatografia en gel de silice, eluyendo con MeOH al 5 por ciento en DCM para obtener el compuesto del título

b) Bencilester de ácido {(R)-1-[9-((3aS 4R,6S,6aR)-2 2-dimetil-6-propionilamino-tetrahidro-ciclopenta[1 3]-dioxol-4-il)-6-[2 2-difeniletilamino)-9H-purin-2-il]-pirrolidin-3-il}-carbamico

Una solución del bencilester del acido {(R)-1-[9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-il]-pirrolidin-3-il}-carbamico (0 63 gramos 0 89 milimoles) en acetona (10 mililitros) y 2 2-dimetiloxi-propano (5 mililitros) se trata con acido toluensulfonico (aproximadamente 60 miligramos) y luego se agita a temperatura ambiente durante la noche La mezcla se alcaliniza utilizando hidroxido de amonio, y el solvente se

remueve al vacio El producto crudo se somete a extracción por partición entre DCM y agua y la porción orgánica se lava con salmuera se seca sobre $MgSO_4$, se filtra y el solvente se remueve al vacio, para obtener el compuesto del titulo [MH+ 745]

c) N-{(3aR 4S 6P 6aS)-6-[2-((R)-3-amino-pirrolidin-1-il)-6-(2,2-difeniletilamino)-purin-9-il]-2,2-dimetil-tetrahidro-ciclopenta[1 3]-dioxol-4-il}-propionamida

A una solución de benciléster del ácido {(R)-1-[9-((3aS 4R 6S 6aR)-2 2-dimetil-6-propionilamino-tetrahidro-ciclopenta[1,3]-dioxol-4-il)-6-(2 2-difeniletilamino)-9H-purin-2-il]-pirrolidin-3-il}-carbamico (0 598 gramos 0 79 milimoles) en etanol (7 5 mililitros) bajo una atmósfera inerte de argón se le agrega hidróxido de paladio sobre carbón (10 miligramos) La mezcla de reaccion se purga con argon y se coloca bajo una atmosfera de hidrogeno durante la noche La mezcla se filtra y se purifica por cromatografía en gel de silice eluyendo con MeOH al 5 por ciento en DCM para obtener el compuesto del titulo [MH+ 611]

Preparacion de Ejemplos Especificos

Ejemplo 1

Trifluoroacetato de N-[(1S,2R 3S 4R)-4-(6-amino-2-cloro-purin-9-il)-2 3-dihidroxiciclopentil]-metansulfonamida

Bis-(4-metoxifenil)-metil]-(2-cloro-9H-purin-6-il)-amina

Se disuelve 2 6-dicloropurina (9 50 gramos 50 29

milimoles) en THF (200 mililitros) bajo una atmósfera de argon Se agrega diisopropilamina (7 14 gramos 55 32 milimoles) seguida por C C-bis-(4-metoxifenil)-metilamina (ver la preparación de los intermediarios) (12 22 gramos 50 29 milimoles) y la mezcla de reacción se agita a 50°C Se demuestra que la reacción está completa mediante LCMS despues de 5 dias El solvente se remueve al vacio y es reemplazado con MeOH (250 mililitros) El precipitado resultante se filtra y se seca para obtener el compuesto del titulo ^{1}H RMN (d_6-DMSO 400 MHz) 8 20 (br s 1H) 7 25 (d 4H) 6 90 (d 4H) 3 75 (s 6H) 3 15 (m 1H) MS (ES+) *m/e* 396 (MH+)

(1S 4R)-4-(6-{[bis-(4-metoxifenil)-metil]-amino}-2-cloro-purin-9-il)-ciclopent-2-enol

La bis-(4 metoxifenil)-metil-(2-cloro-9H-purin-6-il)-amina (13 gramos, 32 87 milimoles) se coloca en un matraz secado al horno bajo una atmosfera de argon Se agregan THF desoxigenado anhidro (100 mililitros) y DMSO seco (2 mililitros) y la solución se enfría sobre un baño de hielo Luego se agrega lentamente hidruro de sodio al 95% (0 79 gramos 32 87 milimoles) y la solucion se agita a temperatura ambiente durante 30 minutos Se colocan (1S 4R)-cis-4-acetoxi-2-ciclopenten-1-ol (4 9 gramos 34 5 milimoles) y trifenilfosfina (1 36 gramos, 5 17 milimoles) en un matraz secado al horno bajo una atmosfera de argon Se

agrega THF desoxigenado anhidro (50 mililitros) Esta solucion se agrega a la solucion del anion mediante jeringa Luego se agrega tetraquis-(trifenilfosfina)-paladio(0) (2 gramos 1 73 milimoles), y la mezcla se agita a 50°C Se demuestra que la reaccion esta completa mediante LCMS después de 2 horas La mezcla de reacción se deja enfriar y el solvente se remueve al vacio El residuo se recupera en metanol (50 mililitros), y el precipitado resultante se filtra y se seca para obtener el compuesto del titulo ^{1}H RMN ($CDCl_3$, 400 MHz), 9 10 (m 1H) 8 10 (m 1H) 7 30 (d 4H) 6 90 (d 4H) 6 55 (d 1H) 6 20 (m 1H) 5 95 (m 1H) 5 40 (m, 1H), 5 30 (d, 1H), 4 70 (m, 1H), 3 70 (s, 6H), 2 90 (m 1H) 1 70 (m 1H) MS (ES+) *m/e* 478 (MH^+)

Etilester del (1S 4R)-4-(6-{[bis-(4-metoxifenil)-metil]-amino}-2 cloro-purin-9-il)-ciclopent-2-enil-éster del ácido carbónico

Se coloca el (1S 4R)-4-(6-{[bis-(4-metoxifenil)-metil]-amino}-2-cloro-purin-9-il)-ciclopent-2-enol (8 00 gramos 16 75 milimoles) en un matraz secado al horno bajo una atmosfera de argón Se agrega piridina anhidra (80 mililitros) seguida por diisopropilamina (16 mililitros) Se agrega una cantidad catalitica de 4-dimetilaminopiridina (DMAP) seguida por etiléster del ácido 3-oxi-benzotriazol-1-carboxilico (6 94 gramos 33 50 milimoles) ver la preparación de los intermediarios La mezcla de reaccion se agita a temperatura ambiente Se demuestra que la reacción

276
225

esta completa mediante TLC despues de 18 horas El solvente se remueve al vacío y el residuo se somete a extraccion por particion entre acetato de etilo (500 mililitros) y HCl 2M (200 mililitros) La fase orgánica se lava con agua (150 mililitros) y salmuera (150 mililitros) se seca sobre $MgSO_4$ se filtra y el solvente se remueve al vacio El compuesto del titulo se obtiene despues de la purificacion mediante cromatografia en columna rapida (silice diclorometano/metanol 50 1) ^1H RMN ($CDCl_3$, 400 MHz) 7 80 (s, 1H) 7 25 (d de d 4H) 6 85 (d de d 4H) 6 65 (m 1H) 6 50 (m 1H) 6 35 (m 1H) 6 15 (m, 1H), 5 65 (m 2H) 4 25 (q 2H) 3 80 (s, 6H) 3 10 (m 1H), 1 95 (m 1H) 1 35 (t 3H)

[Bis-(4-metoxifenil)-metil]-{2-cloro-9-[(1R 4S)-4-(di-Boc-amino)-ciclopent-2-enil]-9H-purin-6-il}-amina

El etilester del (1S 4R)-4-(6-{[bis-(4-metoxifenil)-metil]-amino}-2-cloro-purin-9-il)-ciclopent-2-enilester del acido carbonico (2 00 gramos 3 64 milimoles) iminodicarboxilato de ditert-butilo (0 87 gramos 4 00 milimoles) y trifenilfosfina (0 14 gramos 0 55 milimoles) se colocan en un matraz secado al horno bajo una atmósfera de argon Se agrega THF desoxigenado anhidro (20 mililitros) seguido por tetraquis-(trifenilfosfina)-paladio(0) (0 21 gramos 0 18 milimoles) y la mezcla se agita a temperatura ambiente Se demuestra que la reaccion está completa

mediante LCMS después de 3 horas El solvente se remueve al vacio y el compuesto del título se obtiene después de la purificación mediante cromatografia en columna rapida (silice isohexano/acetato de etilo 4 1) ^{1}H RMN ($CDCl_3$ 400 MHz) 8 20 (s 1H) 7 25 (d 4H) 6 85 (d 4H) 6 60 (m 1H) 6 35 (m 1H) 6 10 (m 1H) 5 80 (m 1H) 5 65 (m 1H) 5 35 (m, 1H), 3 80 (s, 6H), 3 15 (m, 1H), 2 10 (m 1H) 1 55 (s 18H)

(1R 2S 3R 5S)-3-(6-[[bis-(4-metoxifenil)-metil]-amino}-2-cloro-purin-9-il)-5-(di-Boc-amino)-ciclopentano-1,2-diol

La [bis-(4-metoxifenil)-metil]-{2-cloro-9-[(1R,4S)-4-(di-Boc-amino)-ciclopent-2-enil]-9H-purin-6-il}-amina (0 75 gramos 1 11 milimoles) se disuelve en THF ((15 mililitros) Se agrega N-oxido de N-metilmorfolina (0 26 gramos 2 22 milimoles) seguida por tetraoxido de osmio (1 5 mililitros al 4 por ciento en agua) La mezcla de reaccion se agita a temperatura ambiente Se demuestra que la reaccion esta completa mediante LCMS despues de 18 horas El solvente se remueve al vacio y el compuesto del titulo se obtiene despues de la purificacion mediante cromatografia en columna rápida (silice diclorometano/metanol 50 1) ^{1}H RMN ($CDCl_3$ 400 MHz), 7 75 (s, 1H), 7 25 (m, 4H) 6 85 (m 4H) 6 60 (m 2H) 5 70 (m 1H) 4 70 (m 2H) 4 60 (m 1H), 4 45 (m 1H) 3 80 (s 6H) 3 70 (m 1H) 3 40 (m 1H), 3 25 (m, 1H) 2 65 (m 1H) 2 50 (m 1H) 1 55 (s 18H)

Trifluoroacetato de (1S,2R,3S,5R)-3-amino-5-(6-amino-2-cloro-purin-9-il)-ciclopentano-1 2-diol

El (1R 2S,3R,5S)-3-(6-{[bis-(4-metoxifenil)-metil]-amino}-2-cloro-purin-9-il)-5-(di-Boc-amino)-ciclopentano-1 2-diol (600 miligramos, 0 84 milimoles) se disuelve en diclorometano (4 mililitros) Se agrega acido TFA (2 mililitros) y la mezcla de reaccion se agita a temperatura ambiente Se demuestra que la reaccion esta completa mediante LCMS después de 18 horas El solvente se remueve al vacio y el compuesto del titulo se obtiene después de la purificacion mediante cromatografia en columna de fase inversa (Isolute^{MR} C18 acetonitrilo del 0 al 100 por ciento en agua-ácido TFA al 0 1 por ciento) ^{1}H RMN (MeOD, 400 MHz) 8 10 (s 1H) 4 80 (m, 1H) 4 60 (m 1H) 4 30 (m 1H) 3 60 (m, 1H) 2 85 (m 1H) 2 30 (m, 1H) MS (ES+) *m/e* 285 (MH+)

Trifluoroacetato de N-[(1S,2R,3S,4R)-4-(6-amino-2-cloro-purin-9-il)-2 3-dihidroxiciclopentil]-metan-sulfonamida

El trifluoroacetato de (1S 2R 3S 5R)-3-amino-5-(6-amino-2-cloro-purin-9-il)-ciclopentano-1 2-diol (20 miligramos, 39 micromoles), y diisopropiletilamina (25 miligramos 190 micromoles) se colocan en un matraz con THF anhidro (1 mililitro) Se agrega cloruro de mesilo (4 5 miligramos 39 micromoles) y la mezcla de reacción se agita a temperatura ambiente Se demuestra que la reacción está

379

completa mediante LCMS despues de 3 horas El solvente se remueve al vacio y el compuesto del titulo se obtiene despues de la purificacion mediante cromatografia en columna de fase inversa (Isolute^{MR} C18, acetonitrilo del 0 al 100 por ciento en agua-ácido TFA al 0 1 por ciento) MS (ES+) *m/e* 363 (MH+)

Ejemplo 2

Trifluoroacetato de N-[(1S,2R,3S,4R)-4-(6-amino-2-fenetilamino-purin-9-il)-2 3-dihidroxiciclopentil]-propionamida

Trifluoroacetato de N-[(1S 2R 3S 4R)-4-(6-amino-2-cloro-purin-9-il)-2 3-dihidroxiciclopentil]-propionamida

El trifluoroacetato de (1S 2R 3S 5R)-3-amino-5-(6-amino-2-cloro-purin-9-il)-ciclopentano-1 2-diol (intermediario para la preparacion del Ejemplo 1) (20 miligramos, 39 micromoles) y diisopropiletilamina (25 miligramos 190 micromoles) se colocan en un matraz con THF anhidro (1 mililitro) Se agrega cloruro de propionilo (3 6 miligramos 39 micromoles), y la mezcla de reaccion se agita a temperatura ambiente Se demuestra que la reacción está completa mediante LCMS despues de 3 horas El solvente se remueve al vacio, y se obtiene el compuesto del título, el cual se puede purificar mediante cromatografia en columna de fase inversa (Isolute^{MR} C18 acetonitrilo del 0 al 100 por ciento en agua-acido TFA al 0 1 por ciento) ^{1}H RMN (MeOD 400 MHz)

8 10 (s 1H) 4 75 (m 1H) 4 60 (m, 1H) 4 20 (m 1H) 4 00 (m 1H) 3 75 (m, 1H),3 25 (m, 1H) 2 85 (m 1H) 2 40 (q 2H), 2 10 (m 1H) 1 20 (t 3H) MS (ES+) *m/e* 341 (MH^+)

Trifluoroacetato de N-[(1S,2R 3S 4R)-4-(6-amino-2-fenetilamino-purin-9 il)-2 3-dihidroxiciclopentil]-propionamida

La N-[(1S,2R 3S 4R)-4-(6-amino-2-cloro-purin-9-il)-2 3-dihidroxiciclopentil]-propionamida obtenida directamente en el paso anterior sin purificación (10 6 miligramos, 31 micromoles), y fenetilamina (19 miligramos 150 micromoles) se colocan en un frasco de microondas de 0 5 a 2 5 mililitros Se agrega diclorobenceno (0 5 mililitros) y la mezcla de reaccion se somete a microondas en un reactor Personal Chemistry Emrys^{MR} Optimizer a 240°C Se demuestra que la reacción está completa mediante cromatografia liquida-espectrometria de masas (LCMS) despues de 1 hora El solvente se remueve al vacio y se obtiene el compuesto del titulo después de la purificacion mediante cromatografia en columna de fase inversa (Isolute^{MR} C18 acetonitrilo del 0 al 100 por ciento en agua-acido TFA al 0 1 por ciento) ^{1}H RMN (MeOD 400 MHz) 8 05 (s, 1H) 7 40-7 15 (m 5H) 4 70 (m 1H) 4 55 (m 1H) 4 10 (m 2H) 3 70 (m 4H) 3 15 (m 1H) 2 95 (m 4H) 2 70 (m 1H) 2 20 (m 2H), 2 00 (m 1H), 1 20 (t 3H) MS (ES+) *m/e* 426 (MH+)

Ejemplo 3

Trifluoroacetato de N-[(1S,2R 3S 4R)-4-(6-amino-2-hex-1-

inil-purin-9-il)-2,3 dihidroxiciclopentil]-propionamida

La N-[(1S 2R 3S 4R)-4-(6-amino-2-cloro-purin-9-il)-2 3-dihidroxiciclopentil]-propionamida (10 6 miligramos, 31 micromoles) 1-hexino (25 4 miligramos 310 micromoles) yoduro de cobre (I) (1 5 miligramos, 7 75 micromoles), dicloro-bis-(trifenil osfina)-paladio(II) (5 5 miligramos 7 75 micromoles) trifenilfosfina (4 0 miligramos, 15 5 micromoles) dietilamina (0 4 mililitros) y DMF (0 2 mililitros) se colocan en un frasco de microondas de 0 5 a 2 5 mililitros La mezcla de reacción se somete a microondas, en un reactor Personal Chemistry Emrys^{MR} Optimizer a 120°C Se demuestra que la reaccion está completa mediante LCMS despues de 1 hora El solvente se remueve al vacio, y se obtiene el compuesto del titulo despues de la purificacion mediante cromatografia en columna de fase inversa (Isolute^{MR} C18 acetonitrilo de 0 al 100% en agua - acido TFA al 0 1%) MS (ES+) *m/e* 387 (MH+)

Ejemplo 4

N-{(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida

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

La 2 6-dicloropurina (10 gramos 52 90 milimoles) (1S 4R)-cis-4-acetoxi-2-ciclopenten-1-ol (10 gramos 70 40 milimoles) tris-(dibencilidenacetona)-dipaladio(0) (3 20 gramos 3 50 milimoles), y trifenilfosfina soportada en un

polímero (3 milimoles/gramo, 11 60 gramos 35 00 milimoles), se colocan en un matraz secado al horno bajo una atmosfera de argon Se agrega THF desoxigenado anhidro (80 mililitros) y la mezcla de reacción se agita suavemente durante 5 minutos Se agrega trietilamina (20 mililitros) y la mezcla de reaccion se agita a 50°C Se demuestra que la reacción está completa mediante LCMS despues de 1 hora La mezcla de reaccion se deja enfriar se filtra y el solvente se remueve al vacio El compuesto del titulo se obtiene después de la purificación mediante cromatografia en columna rapida (silice diclorometano/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) MS (ES+) *m/e* 271 (MH+)

Etiléster de (1S 4R)-4-(2 6-dicloro-purin-9-il)-ciclopent-2-enil-ester del acido carbónico

El (1S 4R)-4-(2,6-dicloro-purin-9-il)-ciclopent-2-enol (9 5 gramos 35 05 milimoles) se coloca en un matraz secado al horno bajo una atmosfera de argón Se agrega THF anhidro (200 mililitros) seguido por piridina anhidra (5 54 gramos 70 1 milimoles) Se agrega lentamente cloroformiato de etilo (15 21 gramos, 140 2 milimoles) de tal manera que la temperatura no se eleve por arriba de 40°C y la mezcla de reaccion se agita a temperatura ambiente Se demuestra que la reaccion está completa mediante LCMS después de 1 hora

El solvente se remueve al vacio, y el residuo se somete a extraccion por partición entre diclorometano (200 mililitros) y agua (200 mililitros) La fase orgánica se lava con agua (150 mililitros) y salmuera (150 mililitros) se seca sobre $MgSO_4$ se filtra y el solvente se remueve al vacio El compuesto del titulo se obtiene después de la cristalizacion a partir de metanol ^1H 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) MS (ES+) *m/e* 343 (MH+)

Di-Boc-[(1S 4R)-4-(2 6-dicloro-purin-9-il)-ciclopent-2-enil]-amina

El etiléster de (1S 4R)-4-(2 6-dicloro-purin-9-il)-ciclopent-2-enil-ester del acido carbónico (2 5 gramos 7 29 milimoles) iminodicarboxilato de ditert-butilo (1 74 gramos 8 02 milimoles), tris-(dibencilidenacetona)-dipaladio(0) (0 33 gramos 0 36 milimoles), y trifenilfosfina (0 29 gramos 1 09 milimoles), se colocan en un matraz secado al horno bajo una atmósfera de argon Se agrega THF desoxigenado anhidro (30 mililitros) y la mezcla de reaccion se agita a temperatura ambiente Se demuestra que la reacción está completa mediante LCMS despues de 3 horas El solvente se remueve al vacio, y se obtiene el compuesto del titulo después de la purificacion mediante cromatografia en columna rapida (silice, acetato de etilo/isohexano, 4 1) ^1H RMN ($CDCl_3$ 400

MHz) 8 70 (s, 1H), 6 20 (m 1H) 5 85 (m, 1H), 5 80 (m 1H) 5 40 (m 1H) 3 20 (m 1H) 2 15 (m 1H) 1 55 (s, 18H), ,S (ES+) *m/e* 470 (MH+)

(1S 2R 3S 5R)-3-(di-Boc-amino)-5-(2 6-dicloro-purin-9-il)-ciclopentano-1 2-diol

El compuesto del titulo se prepara a partir de di-Boc-[(1S 4R)-4-(2,6 dicloro-purin-9-il)-ciclopent-2-enil]-amina empleando un procedimiento analogo al utilizado para preparar el (1R 2S 3R 5S)-3-(6-{[bis-(4-metoxifenil)-metil]-amino}-2-cloro-purin-9-il)-5-(di-Boc-amino)-ciclopentano-1 2-diol ^{1}H RMN ($CDCl_3$ 400 MHz) 8 35 (s 1H) 4 80 (m, 1H) 4 70 (m 1H) 4 50 (m 1H) 3 85 (m 1H) 3 75 (m 1H), 3 10 (m 1H) 2 75 (m 1H) 2 55 (m 1H) 1 55 (s 18H) MS (ES+) *m/e* 504 (MH+)

Trifluoroacetato de (1S 2R 3S 5R)-3-amino-5-(2 6-dicloro-purin-9-il)-ciclopentano-1 2-diol

El compuesto del título se prepara a partir del (1S 2R 3S,5R)-3-(di-Boc-amino)-5-(2 6-dicloro-purin-9-il)-ciclopentano-1,2-diol empleando un procedimiento análogo al utilizado para preparar el trifluoroacetato de (1S,2R,3S 5R)-3-amino-5-(6-amino 2-cloro-purin-9-il)-ciclopentano-1 2-diol del Ejemplo 1 MS (ES+) *m/e* 304 (MH+)

N-[(1S 2R 3S 4R)-4-(2 6-dicloro-purin-9-il)-2 3-dihidroxiciclopentil] propionamida

El compuesto del titulo se prepara a partir del

225
224

trifluoroacetato de (1S,2R,3S,5R)-3-amino-5-(2,6-dicloro-purin-9-il)-ciclopentano-1 2-diol y cloruro de propionilo empleando un procedimiento análogo al utilizado para preparar el trifluoroacetato de N-[(1S 2R 3S 4R)-4-(6-amino-2-cloro-purin-9-il)-2 3-dihidroxiciclopentil]-propionamida del Ejemplo 2 MS (ES+) *m/e* 360 (MH+)

N-{(1S 2R 3S 4R)-4 [2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida

La N-[(1S 2R 3S 4R)-4-(2 6-dicloro-purin-9-il)-2 3-dihidroxiciclopentil]-propionamida (160 miligramos 0 44 milimoles) se disuelve en THF (5 mililitros) bajo una atmósfera de argón Se agrega diisopropilamina (69 miligramos 0 53 milimoles) seguida por 2 2-difeniletilamina (96 miligramos 0 49 milimoles), y la mezcla de reacción se agita a 50°C Se demuestra que la reaccion esta completa mediante LCMS después de 2 horas El solvente se remueve al vacio y se obtiene el compuesto del titulo despues de la purificacion mediante cromatografia en columna de fase inversa (Isolute^{MR} C18 acetonitrilo de 0 a 100% en agua - acido TFA al 0 1%) ^{1}H RMN (MeOD 400 MHz) 8 00 (s 1H) 7 40-7 15 (m, 10H) 4 75 (m 1H) 4 60 (m, 1H) 4 50 (m 1H) 4 20 (m 3H) 3 95 (m 1H) 2 85 (m 1H) 2 40 (q 2H) 2 10 (m 1H) 1 20 (t 3H) MS (ES+) *m/e* 521 (MH+)

El compuesto final del Ejemplo 4 también se puede preparar empleando el siguiente proceso

226
225

{2-cloro-9-[(1R 4S)-4-(di-Boc-amino)-ciclopent-2-enil]-9H-purin-6-il}-2 2-difeniletil)-amina

El (1S,2R 3S,5R)-3-(di-Boc-amino)-5-(2 6-dicloro-purin-9-il)-ciclopentano-1,2-diol (13 0 gramos 27 66 milimoles) se disuelve en THF (250 mililitros) bajo una atmosfera de argón Se agrega diisopropilamina (4 28 gramos 33 19 milimoles), seguida por 2 2-difeniletilamina (6 0 gramos 30 43 milimoles) y la mezcla de reacción se agita a 50°C Se demuestra que la reacción esta completa mediante LCMS despues de 18 horas El solvente se remueve al vacio y la mezcla de reaccion se somete a extraccion por particion entre diclorometano (250 mililitros) y HCl 0 1M (250 mililitros) La fase organica se lava con agua (200 mililitros) y salmuera (200 mililitros), se seca sobre $MgSO_4$ se filtra y el solvente se remueve al vacio para obtener el compuesto del titulo ^{1}H RMN ($CDCl_3$, 400 MHz) 8 05 (s 1H) 7 30-7 10 (m 10H) 6 00 (m 1H), 5 70 (m, 2H) 5 60 (m 1H) 5 20 (m, 1H) 4 30 (m 1H) 4 20 (m 1H) 3 65 (m 1H) 3 05 (m 1H) 2 00 (m 1H) 1 70 'm 1H), 1 40 (s, 18H) MS (ES+) *m/e* 631 (MH+)

(1R 2S 3R 5S)-3-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-5-(di-Boc-amino)-ciclopentano-1 2-diol

El compuesto del titulo se prepara a partir de la {2-cloro-9-[(1R 4S)-4-(di-Boc-amino)-ciclopent-2-enil]-9H-purin-6-il}-(2,2-difeniletil)-amina empleando un procedimiento

227
226

análogo al de la Preparación del Ejemplo 11 ^{1}H RMN (MeOD 400 MHz) 8 05 (s, 1H) 7 35-7 15 (m, 10H), 4 70-4 55 (m, 4H) 4 50 (m 1H), 4 35 (m 1H) 4 20 (m 2H) 2 55 (m 1H) 2 45 (m 1H) 1 60 (s 18H)

Trifluoroacetato de (1S 2R 3S 5R)-3-amino-5-[2-cloro-6-(2 2-difeniletilamino)-pu in-9-il]-ciclopentano-1 2-diol

El (1R,2S 3R 5S)-3-[2-cloro-6-(2,2-difeniletilamino)-pu in-9-il]-5-(di-Boc-amino)-ciclopentano-1 2-diol (10 3 gramos 15 50 milimoles) se disuelve en diclorometano (50 mililitros) Se agrega acido TFA (25 mililitros) y la mezcla de reaccion se agita a temperatura ambiente Se demuestra que la reacción esta completa mediante LCMS despues de 2 horas El solvente se remueve al vacio para obtener el compuesto del titulo ^{1}H RMN (MeOD 400 MHz) 7 90 (5 1H) 7 30-7 10 (m, 10H) 4 65 (m 1H) 4 50 (m 1H) 4 40 (m, 1H), 4 20 (m, 1H) 4 10 (m 2H) 3 50 (m 1H) 2 75 (m 1H) 2 15 (m, 1H) MS (ES+) *m/e* 465 (MH+)

N-{(1S 2R 3S 4R)-4 [2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida

El trifluoroacetato de (1S 2R 3S 5R)-3-amino-5-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-ciclopentano-1 2-diol (9 50 gramos 16 42 milimoles) y diisopropiletilamina (6 36 gramos 49 27 milimoles) se colocan en un matraz con THF anhidro (150 mililitros) Se agrega por goteo cloruro de

propionilo (1 52 gramos 16 42 milimoles) y la mezcla de reaccion se agita a temperatura ambiente Se demuestra que la reaccion está completa mediante LCMS después de 1 hora El solvente se remueve al vacio y el residuo se somete a extraccion por particion entre diclorometano (250 mililitros) y agua (250 mililitros) La fase orgánica se lava con agua (200 mililitros) y salmuera (200 mililitros) se seca sobre $MgSO_4$ se filtra y el solvente se remueve al vacio El solido se recristaliza a partir de 1 2-dicloroetano, para obtener el compuesto del titulo ^{1}H RMN (MeOD 400 MHz) 8 00 (s 1H) 7 40-7 15 (m 0H) 4 75 (m 1H) 4 60 (m 1H) 4 50 (m, 1H) 4 20 (m, 3H) 3 95 (m, 1H) 2 85 (m 1H) 2 40 (q 2H) 2 10 (m 1H) 1 20 (t 3H), MS (ES+) *m/e* 521 (MH+)

Ejemplo 5

Trifluoroacetato de N-{(1S 2R 3S 4R)-4-[2-(4-amino-ciclohexilamino)-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida

La N-{(1S,2R,3S,4R)-4-[2-cloro-6-(2,2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (compuesto final del Ejemplo 4) se hace reaccionar con ciclohexan-1 4-diamina empleando un procedimiento análogo al utilizado para preparar el compuesto del Ejemplo 2 MS (ES+) *m/e* 599 (MH+)

La base libre se forma como sigue Se carga el trifluoroacetato de N-{(1S,2R 3S 4R)-4-[2-(4-amino-

229
230

ciclohexilamino)-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil} propionamida (300 miligramos 0 50 milimoles) se aisla sobre una resina de intercambio ionico DOWEX® 50WX2-200 (previamente lavada con agua) La resina se eluye con agua hasta un pH neutro, y luego con metanol/amoniaco 880 (1 1) para eluir la base libre ^{1}H RMN (MeOD, 400 MHz), 7 65 (s 1H) 7 40-7 20 (m 10H) 4 60 (m 1H) 4 50 (m 2H) 4 20 (m 3H) 4 05 (m, 1H), 3 70 (m, 1H) 2 70 (m, 2H), 2 30 (q, 2H) 2 20 (m 2H) 2 00 (m 1H), 1 95 (m 2H) 1 30 (m 4H) 1 20 (t 3H), MS (ES+) *m/e* 599 (MH+)

Ejemplo 6

N {(1S 2R 3S 4R)-4-[6-(2 2-difeniletilamino)-2-hex-1-inil-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida

El compuesto del titulo se prepara a partir de la N-[(1S 2R 3S 4R)-4-(2 6-dicloro-purin-9-il)-2 3-dihidroxiciclopentil] propionamida, empleando un procedimiento análogo al utilizado para preparar el compuesto del Ejemplo 3

Ejemplo 7

N-{(1S 2R 3S 4R)-4-[6-(2 2-difeniletilamino)-2-[2-(1H-imidazol-4-il)-etilamino]-purin-9-il}-2 3-dihidroxiciclopentil]-propionamida

Este compuesto se prepara a partir de la N-[(1S 2R 3S 4R)-4-(2 6-dicloro-purin-9-il)-2 3-dihidroxiciclopentil] propionamida utilizando histamina en

un procedimiento análogo al utilizado para preparar el compuesto del Ejemplo 5

Ejemplo 8

N-{(1S 2R 3S 4R)-4 [6-(2 2-difeniletilamino)-2-(2-piperidin-1-il-etilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida

El compuesto del titulo se prepara utilizando N-(aminoetil)-piperidina en un procedimiento análogo al utilizado para preparar el compuesto del Ejemplo 5

Ejemplo 9

Trifluoroacetato de N-((1S,2R 3S 4R)-4-{6-(2,2-difeniletilamino)-2 [2-(1-metil-1H-imidazol-4-il)-etilamino]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida

La N-{(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (compuesto del Ejemplo 4) (20 miligramos 38 micromoles) y 2-(1-metil-1H-imidazol-4-il)-etilamina (24 miligramos, 190 micromoles), se colocan en un frasco de microondas de 0 5 a 2 5 mililitros Se agrega diclorobenceno (0 5 mililitros) y la mezcla de reaccion se calienta utilizando radiacion de microondas en un reactor Personal Chemistry Emrys^{MR} Optimizer a 200°C Se demuestra que la reaccion está completa mediante LCMS despues de 2 horas El solvente se remueve al vacio y se obtiene el compuesto del titulo después de la purificacion mediante cromatografia en columna de fase inversa (Isolute^{MR}

C18 acetonitrilo de 0 a 100% en agua - acido TFA al 0 1%) ^{1}H RMN (MeOD 400 MHz), * 80 (s, 1H) 8 15 (s, 1H) 7 40-7 20 (m 11H) 4 75 (m 2H) 4 50 (m 2H) 4 30 (m 1H) 4 10 (m 2H) 3 85 (s 3H) 3 75 (m 2H) 3 10 (m 3H) 2 70 (m, 1H) 2 25 (q 2H) I 95 (m 1H), 1 30 (m, 4H) 1 15 (t 3H) MS (ES+) *m/e* 610 (MH+)

Ejemplo 10

N-((1S 2R 3S 4R)-4-{6-(2 2-difeniletilamino)-2-[2-(1-etil-1H-imidazol-4-il)-etilamino]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida

Este compuesto se prepara a partir de la N-{(1S 2R 3S 4R)-4-[2 cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (compuesto del Ejemplo 4) y 2-(1-etil-1H-imidazol-4-il)-etilamina empleando un procedimiento analogo al del Ejemplo 21 MS (ES+) *m/e* 624 (MH+)

Ejemplo 11

N-((1S 2R 3S 4R)-4-{6-(2 2-difeniletilamino)-2-[2-(1-isopropil-1H-imidazol-4-il)-etilamino]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida

Este compuesto se prepara a partir de la N-{(1S 2R 3S,4R)-4-[2 cloro-6-(2 2-difeniletilamino)-purin-9-il]-2,3-dihidroxiciclopentil}-propionamida (compuesto del Ejemplo 4) y 2-(1-isopropil-1H-imidazol-4-il)-etilamina

empleando un procedimiento análogo al del Ejemplo 9, para la sal deseada MS (ES+) *m/e* 638 (MH+)

Ejemplos 12 y 13

La {(1S 2R,3S 4R)-4-[2-cloro-6-(2,2-difeniletilamino)-purin-9-il]-2,3-dihidroxiciclopentil}-amida del acido ciclopropanocarboxilico y la N-{(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-butiramida se preparan empleando un procedimiento analcgo al del Ejemplo 4 en donde el cloruro de propionilo es reemplazado por el agente de acilación apropiado

Ejemplo 14

N-{(1S 2R 3S 4R)-4 [2-cloro-6-(1-etilpropilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida

Terbutil éster del ácido [(1S 4R)-4-(2 6-dicloro-purin-9-il)-ciclopent-2-enil]-propionilcarbamico

El compuesto del titulo se prepara a partir del etilester de (1S 4R)-4-(2 6-dicloro-purin-9-il)-ciclopent-2-enil ester del acido carbonico (un intermediario para la preparacion del compuesto del Ejemplo 4) y tert-butiléster del acido propionilcarbamico (ver la preparacion de los intermediarios), empleando un procedimiento análogo a aquél de la di-Boc-[(1S 4R)-4-(2 6-dicloro-purin-9-il)-ciclopent-2-enil]-amina (otro intermediario para la preparación del compuesto del Ejemplo 4) ^{1}H RMN ($CDCl_3$ 400 MHz) 8 70 (s 1H) 6 15 (m

1H) 5 85 (m 1H), 5 80 (m 1H) 5 60 (m 1H) 3 15 (m 1H), 2 75 (q 2H) 2 10 (m 1H) 1 55 (s 9H) 1 15 (t 3H) MS (ES+) *m/e* 426 (MH+)

Tert-butilester del ácido {(1S 4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-ciclopent-2-enil}-propionilcarbamico

El tert-butilester del ácido [(1S,4R)-4-(2,6-dicloro-purin-9-il)-ciclopent-2-enil]-propionilcarbámico (700 miligramos 1 64 milimoles) se disuelve en THF (15 mililitros) bajo una atmósfera de argón Se agrega 3-pentilamina (315 miligramos 3 61 milimoles) y la mezcla de reaccion se agita a 50°C Se demuestra que la reaccion esta completa mediante LCMS después de 13 horas La mezcla de reacción se somete a extraccion por particion entre diclorometano (50 mililitros) y HCl 0 1M (50 mililitros) La fase organica se lava con agua (20 mililitros) y salmuera (20 mililitros), se seca sobre $MgSO_4$ se filtra y el solvente se remueve al vacio para obtener el compuesto del titulo ^1H RMN ($CDCl_3$ 400 MHz) 8 10 (s 1H) 6 00 (m 1H) 5 70 (m, 1H) 5 60 (m 2H) 5 45 (m 1H) 4 20 (m 1H) 3 65 (m 1H), 3 00 (m, 1H) 2 65 (m 3H) 1 95 (m 1H) 1 60 (m 3H) 1 45 (s, 9H) 1 10 (m 4H), 0 85 (t 6H) MS (ES+) *m/e* 477 (MH+)

Tert-butilester del acido {(1S 2R 3S 4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionilcarbamico

El compuesto de titulo se prepara a partir del tert-butilester del acido {(1S,4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-ciclopent 2-enil}-propionilcarbámico empleando un procedimiento analcgo a aquél del (1R 2S 3R 5S)-3-(6-{[bis-(4-metoxifenil)-metil]-amino}-2-cloro-purin-9-il)-5-(di-Boc-amino)-ciclopentano-1 2-diol (ver el Ejemplo 1) La purificacion mediante cromatografia en columna de fase inversa (Isolute^{MR} C18 acetonitrilo de 0 a 100% en agua - acido TFA al 0 1%) ^{1}H RMN (MeOD 400 MHz) 8 10 (s 1H) 4 80 (m, 1H), 4 65 (m, 1H), 4 35 (m, 1H), 4 20 (m, 1H), 2 85 (m 2H) 2 60 (m 1H) 2 35 (m 1H) 1 70 (m 2H) 1 65 (s 9H) 1 60 (m, 2H), 1 15 (t, 3H) 0 95 (t, 6H)

N-{(1S 2R 3S 4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida

El tert-butilester del acido {(1S 2R 3S 4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionilcarbamico (300 miligramos 0 59 milimoles) se disuelve en diclorometano (5 mililitros) Se agrega acido TFA (2 mililitros) y la mezcla de reacción se agita a temperatura ambiente Se demuestra que la reaccion esta completa mediante LCMS despues de 1 hora El solvente se remueve al vacio y el residuo se somete a extraccion por particion entre diclorometano (50 mililitros) y $NaHCO_3$ saturado (50 mililitros) La fase organica se lava con agua (20 mililitros) y salmuera (20 mililitros) se seca sobre $MgSO_4$ se filtra y el

solvente se remueve al vacío para obtener el compuesto del título ^{1}H RMN (MeOD 400 MHz) 8 05 (s, 1H), 4 75 (m 1H) 4 60 (m 1H) 4 20 (m 2H) 4 00 (m 1H) 2 90 (m, 1H), 2 40 (q 2H) 2 10 (m 1H) 1 70 (m 2H) 1 60 (m 2H), 1 20 (t 3H) 0 95 (t 6H) MS (ES+) *m/e* 411 (MH+)

Ejemplo 15

N-{(1S 2R 3S 4R)-4 [6-(1-etilpropilamino)-2-hex-1-inil-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida

Este compuesto se prepara a partir del tert-butilester del ácido {(1S 2R 3S 4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-2,3-dihidroxiciclopentil}-propionilcarbamico empleando un procedimiento análogo al del Ejemplo 3

Ejemplo 16

N-{(1S 2R 3S 4R)-4 [6-(2 2-difeniletilamino)-2-((S)-1-hidroximetil-2-fenil-etilamino)-purin-9-il]-2,3-dihidroxiciclopentil}-propionamida

La N-{(1S,2R 3S,4R)-4-[2-cloro-6-(2,2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (46 8 miligramos, 90 micromoles) del Ejemplo 4 L-fenilalaninol (271 miligramos, 1 80 milimoles) y yoduro de sodio (6 75 miligramos, 45 micromoles) se colocan en un frasco de microondas de 0 5 a 2 5 mililitros Se agregan acetonitrilo (0 25 mililitros) y NMP (0 25 mililitros), y la mezcla de reacción se calienta por radiacion de microondas

en un reactor Personal Chemistry Emrys^{MR} Optimizer a 200°C Se demuestra que la reacción está completa mediante LCMS despues de 1 hora El compuesto del titulo se obtiene despues de la purificacion mediante cromatografia en columna de fase inversa (Isolute^{MR} C18 acetonitrilo de 0 a 100% en agua - acido TFA al 0 1%) MS (ES+) *m/e* 636 (MH+)

Ejemplo 17

N-{(1S 2R 3S 4R)-4 [6-(1-etilpropilamino)-2-(2-piperidin-1-il-etilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida

La N-{(1S 2R 3S 4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (el compuesto del Ejemplo 14) se hace reaccionar con 1-(2-aminoetil)-piperidina para obtener el compuesto del título empleando un procedimiento análogo al del Ejemplo 9 MS (ES+) *m/e* 503 (MH+)

Ejemplo 18

N-{(1S,2R 3S 4R)-4-[2-[2-(1-etil-1H-imidazol-4-il)-etilamino]-6-(1-dihidroxiciclopentil}-propionamida

La N-{(1S 2R 3S 4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-2,3-dihidroxiciclopentil}-propionamida (el compuesto del Ejemplo 14) se hace reaccionar con 2 (1-etil-1H-imidazol-4-il)-etilamina para obtener el compuesto del titulo empleando un procedimiento analogo al del Ejemplo 9 MS (ES+) *m/e* 514 (MH+)

Ejemplo 19

N-{(1S 2R 3S 4R)-4 [2-[2-(1-isopropiletil-1H-imidazol-4-il)-etilamino]-6-(1-dihidroxiciclopentil}-propionamida

La N-{(1S,2R 3S 4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (el compuesto del Ejemplo 14) se hace reaccionar con 2-(1-isopropiletil-1H-imidazol-4-il)-etilamina para obtener el compuesto del titulo empleando un procedimiento analogo al del Ejemplo 9 MS (ES+) *m/e* 528 (MH+)

Ejemplo 20

N-{(1S 2R 3S 4R)-4 [2-(4-amino-ciclohexilamino)-6-(1-etilpropilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida

La N-{(1S 2R 3S 4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-2,3-dihidroxiciclopentil}-propionamida (el compuesto del Ejemplo del Ejemplo 14) se hace reaccionar con trans-1 4-diaminociclohexano para obtener el compuesto del titulo empleando un procedimiento analogo al del Ejemplo 9 MS 8ES+) *m/e* 489 (MH+)

Ejemplo 21

N-((1S 2R 3S 4R)-4-{6-amino-2-[2-(1-etil-1H-imidazol-4-il)-etilamino]-purin-9-il}-2 3-dihidroxiciclopentil)-isobutiramida

N-[(1S 2R,3S,4R)-4-(6-amino-2-cloro-purin-9-il)-2 3-

dihidroxiciclopentil]-isobutiramida

El trifluoroacetato de (1S 2R 3S 5R)-3-amino-5-(6-amino-2-cloro-purin 9-il)-ciclopentano-1,2-diol (un intermediario para la preparacion del compuesto del Ejemplo 1) se hace reaccionar con cloruro de isopropionilo para obtener el compuesto del titulo empleando un procedimiento análogo al del Ejemplo 1 MS (ES+) *m/e* 355 (MH+)

N-((1S 2R 3S 4R)-4 {6-amino-2-[2-(1-etil-1H-imidazol-4-il)-etilamino]-purin-9-il}-2 3-dihidroxiciclopentil)-isobutiramida

La N-[(1S,2R,3S,4R)-4-(6-amino-2-cloro-purin-9-il)-2 3-dihidroxiciclopentil]-isobutiramida se hace reaccionar con 2-(1-etil-1H-imidazol-4-il)-etilamina, para obtener el compuesto del titulo empleando un procedimiento análogo al del Ejemplo 9 MS (ES+) *m/e* 458 (MH+)

Ejemplo 22

Trifluoroacetato de ((1S,2R,3S,4R)-4-{6-(2,2-difeniletilamino)-2-[2-(1-isopropil-1H-imidazol-4-il)-etilamino]-purin-9-il}-2 3-dihidroxiciclopentil)-amida del acido ciclopropanocarboxílico

(2-cloro-9H-purin-6-il)-(2 2-difeniletil)-amina

Se disuelve 2 6-dicloropurina (20 00 gramos 106 milimoles) en THF (250 mililitros) bajo una atmosfera de argon Se agrega diisopropilamina (16 38 gramos 127 milimoles) seguida por 2 2-difeniletilamina (25 00 gramos 127 milimoles) y la mezcla de reacción se agita a 50°C Se

demuestra que la reaccion esta completa mediante LCMS después de 6 horas Se remueve el 50% del solvente al vacio y es reemplazado por MeOH El precipitado resultante se filtra y se seca para obtener el compuesto del titulo ^{1}H RMN (d_6-DMSO 400 MHz) 8 05 (br s 1H) 7 35–7 10 (m, 10H) 4 55 (m, 1H), 4 10 (m, 2H), MS (ES+) *m/e* 350 (MH+)

(1S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-ciclopent-2-enol

La (2-cloro-9H-purin-6-il)-(2 2-difeniletil)-amina (12 92 gramos 36 97 milimoles) se coloca en un matraz secado al horno bajo una atmosfera de argon Se agregan THF desoxigenado anhidro (100 mililitros) y DMSO anhidro (2 mililitros) y la suspension se enfria sobre un baño de hielo Luego se agrega lentamente hidruro de sodio al 95% (0 89 gramos 36 97 milimoles) y la solución se agita a temperatura ambiente durante 30 minutos Se colocan (1S 4R)-cis-4-acetoxi-2-ciclopenten-1-ol (5 00 gramos 35 20 milimoles) y trifenilfosfina (1 38 gramos 5 28 milimoles) en un matraz secado al horno bajo una atmósfera de argón Se agrega THF desoxigenado anhidro (50 mililitros) Esta solución se agrega a la solucion del anion Se agrega tetraquis-(trifenilfosfina)-paladio(0) (2 03 gramos, 1 76 milimoles), y la mezcla de reacción se agita a 50°C Se demuestra que la reacción está completa mediante LCMS después de 3 horas La mezcla de reaccion se deja enfriar, y

el solvente se remueve al vacio El residuo se recupera en diclorometano (50 mililitros) y se vierte en eter dietilico con agitación vigorosa (300 mililitros) El precipitado se filtra el filtrado se recupera y el solvente se remueve al vacio para obtener el compues o del titulo ^{1}H RMN ($CDCl_3$ 400 MHz) 7 65 (m 1H), 7 35-7 15 (m 10H) 6 35 (m 1H) 5 90 (m 1H) 5 80 (m 1H) 5 50 (m 1H) 5 25 (d 1H), 4 85 (t 1H) 4 35 (t 1H) 4 25 (m 2H) 2 95 (m 1H) 2 15 (d, 1H) MS (ES+) *m/e* 432 (MH+)

Etilester de (1S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-ciclopent-2-enil-éster del ácido carbonico

El (1S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-ciclopent-2-enol (3 00 gramos 6 95 milimoles) se coloca en un matraz secado al horno bajo una atmosfera de argon Se agrega THF anhidro (100 mililitros) seguido por piridina anhidra (1 10 gramos 13 90 milimoles) Se agrega lentamente clorofolmiato de etilo (3 02 gramos 27 80 milimoles), y la mezcla de reaccion se agita a temperatura ambiente Se demuestra que la reaccion esta completa mediante TLC después de 4 horas El solvente se remueve al vacio y el residuo se somete a extraccion por partición entre diclorometano (200 mililitros) y acido citrico al 10% (200 mililitros) La fase orgánica se lava con agua (150 mililitros) y salmuera (150 mililitros) se seca sobre $MgSO_4$ se filtra y el solvente se remueve al vacio El compuesto del título se

obtiene despues de la purificación mediante cromatografia en columna rapida (sílice isohexano/acetato de etilo 2 1) ^{1}H RMN ($CDCl_3$ 400 MHz) 7 70 (br s 1H) 7 35-7 15 (m 10H) 6 35 (m 1H) 6 15 (m 1H) 5 80 (m 1H) 5 65 (m, 2H), 4 35 (t 1H), 4 25 (m, 2H), 4 20 (q, 2H), 3 10 (m 1H) 1 95 (d 1H) 1 30 (t 3H) MS (ES+) *m/e* 504 (MH+)

9-((1R,4S)-4-(bis-(tert-butiloxicarbonil))-amino-ciclopent-2-enil)-2-cloro-9H-purin-6-il]-(2 2-difeniletil)-amina

El etiléster de (1S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-ciclopent-2-enil-ester del ácido carbónico (3 2 gramos 6 3 milimoles) iminodicarboxilato de di-t-butilo (1 5 gramos 7 0 milimoles) y trifenilfosfina (250 miligramos 0 95 milimoles), se disuelven en THF desgasificado (30 mililitros) bajo una atmosfera de argón Se agrega tris-(dibencilidenacetona)-dipaladio(0) (291 miligramos 0 32 milimoles) y la mezcla se calienta a 40°C durante 1 5 horas La mezcla de reacción se enfria a temperatura ambiente y el solvente se remueve a presion reducida El residuo se purifica mediante cromatografia en columna sobre gel de silice eluyéndose con un sistema de gradiente de acetato de etilo/isohexano (0 100 en volumen), cambiando gradualmente a acetato de etilo/isohexano (20 80 en volumen) para obtener el compuesto del titulo LCMS (electroaspersion) *m/z* [MH+] 631 32

(1S,2R,3S,5R)-3-(bis-(tert-butiloxicarbonil))-amino-5-[2-cloro-

6-(2 2-difeniletilamino)-purin-9-il]-ciclopentano-1 2-diol

Una solución de 9-((1R 4S)-4-(bis-(tert-butiloxicarbonil))-amino-ciclopent-2-enil)-2-cloro-9H-purin-6-il]-(2 2-difeniletil)-amina (2 9 gramos, 4 6 milimoles) en THF (60 mililitros) se trata con N-óxido de 4-metilmorfolina (1 1 gramos 9 3 milimoles) y tetraóxido de osmio (solución al 4% en agua) (6 mililitros), y la mezcla se agita a temperatura ambiente durante 48 horas El solvente se remueve a presión reducida y el residuo se purifica mediante cromatografia en columna sobre gel de silice, eluyendose con un sistema de gradiente de metanol/diclorometano (0 100 en volumen), cambiando gradualmente a metanol/diclorometano (4 96 en volumen), para obtener el compuesto del titulo LCMS (electroaspersion) *m/z* [MH+] 665 34

Clorhidrato de (1S 2R 3S 5R)-3-amino-5-[2-cloro-6-(2,2-difeniletilamino)-purin-9-il]-ciclopentano-1,2-diol

El (1S 2R,3S 5R)-3-(bis-(tert-butiloxicarbonil))-amino-5-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-ciclopentano-1 2-diol (1 9 gramos, 2 9 milimoles), se disuelve en una solucion de cloruro de hidrogeno (4M en 1 4-dioxano) (13 mililitros, 51 2 milimoles), y la mezcla se agita a temperatura ambiente durante 1 hora El solvente se remueve a presion reducida y el residuo se purifica mediante cromatografia de fase inversa eluyéndose con un sistema de gradiente de acetonitrilo (HCl al 0 1%)/agua (HCl al 0 1%)

(0 100 en volumen) cambiando gradualmente a acetonitrilo (HCl al 0 1%)/agua (HCl al 0 1%) (100 0 en volumen) para obtener el compuesto del título LCMS (electroaspersion) *m/z* [MH+] 465 20

{(1S 2R 3S 4R)-4-[2 cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-amida del acido ciclopropanocarboxilico

Una solucion de clorhidrato de (1S 2R,3S 5R)-3-amino-5-[2-cloro-6-(2,2-difeniletilamino)-purin-9-il]-ciclopentano-1,2-diol (200 miligramos 0 4 milimoles) en THF anhidro (2 5 mililitros) se trata con diisopropiletilamina (0 35 mililitros, 2 milimoles), y cloruro de acido ciclopropanocarboxilico (0 036 mililitros 0 4 milimoles) y la mezcla se agita a temperatura ambiente durante 48 horas El solvente se remueve a presión reducida, y el residuo se purifica mediante cromatografia de fase inversa eluyendose con un sistema de gradiente de acetonitrilo (acido TFA al 0 1%) agua (acido TFA al 0 1%) (0 100 en volumen) cambiando gradualmente a (acido TFA al 0 1%) agua (acido TFA al 0 1%) (100 0 en volumen),para obtener el compuesto del titulo LCMS (electroaspersión) *m/z* [MH+] 533 25 ^{1}H RMN (MeOD, 400 MHz), 8 00 (s 1H) 7 40-7 25 (m, 8H) 7 25-7 20 (m 2H) 4 75 (m 1H) 4 60 (m 1H) 4 50 (m 1H) 4 20 (m 2H) 4 00 (m 1H) 2 85 (m 1H) 2 10 (m 1H) 1 85 (m 1H) 0 95-0 80 (m 4H)

244
245

Trifluoroacetato de ((1S 2R 3S 4R)-4-{6-(2 2-difeniletilamino)-2-[2-(1-isopropil-1H-imidazol-4-il)-etilamino]-purin-9-il}-2 3-dihidroxiciclopentil)-amida del ácido ciclopropanocarboxílico

Una solucion de {(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-amida del acido ciclopropanocarboxilico (20 miligramos 0 04 milimoles) en NMP/acetonitrilo (1 1) (0 5 mililitros) se trata con 2-(1-isopropil-1H-imidazol-4-il)-etilamina (30 miligramos, 0 2 milimoles) y yoduro de sodio (6 miligramos 0 04 milimoles) y la mezcla se calienta a 200°C durante 30 minutos en un reactor de microondas Personal Chemistry Emrys^{MR} Optimizer La mezcla de reacción se purifica mediante cromatografía de fase inversa eluyéndose con un sistema de gradiente de acetonitrilo (acido TFA al 0 1%)/agua (acido TFA al 0 1%) (0 100 en volumen) cambiando gradualmente a acetonitrilo (acido TFA al 0 1%)/agua (acido TFA al 0 1%) (100 0 en volumen) para obtener el compuesto del titulo LCMS (electroaspersión) *m/z* 650 22

Ejemplo 23

Trifluoroacetato de ((1S 2R 3S 4R)-4-{6-(2,2-difeniletilamino)-2-[2-(1-isopropil-1H-imidazol-4-il)-etilamino]-purin-9-il}-2 3-dihidroxiciclopentil)-amida del ácido ciclobutanocarboxilico

{(1S,2R,3S 4R)-4-[2 cloro-6-(2 2-difeniletilamino)-purin-9-il]-

2 3-dihidroxiciclopentil}-amida del ácido ciclobutanocarboxílico

Una solución de clorhidrato de (1S,2R 3S 5R)-3-amino-5-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-ciclopentano-1 2-diol (un intermediario para la preparacion del Ejemplo 22) (100 miligramos 0 2 milimoles) en THF anhidro (1 mililitro) se trata con diisopropiletilamina (0 17 mililitros 1 milimol) y cloruro de acido ciclobutanocarboxílico (0 023 mililitros, 0 2 milimoles), y la mezcla se agita a temperatura ambiente durante 48 horas El solvente se remueve a presión reducida El residuo se purifica mediante cromatografia de fase inversa, eluyendose con un sistema de gradiente de acetonitrilo (acido TFA al 0 1%)/agua (acido TFA al 0 1%) (0 100 en volumen) cambiando gradualmente a acetonitrilo (acido TFA al 0 1%)/agua (acido TFA al 0 1%) (100 0 en volumen) para obtener el compuesto del titulo (51 miligramos) LCMS (electroaspersion) *m/z* [MH+] 547 26 ^{1}H RMN (MeOD 400 MHz) 8 00 (s 1H) 7 40-7 25 (m 8H) 7 20-7 15 (m 2H), 4 70 (m 1H) 4 50 (m 2H) 4 20 (m 2H) 3 95 (m 1H) 2 85 (m 1H) 2 30 (m, 2H), 2 20 (m, 2H), 2 05 (m, 2H), 1 90 (m 1H)

Trifluoroacetato de ((1S,2R,3S,4R)-4-{6-(2,2-difeniletilamino)-2-[ ]-(1-isopropil-1H-imidazol-4-il)-

246
245

etilaminol-purin-9-il}-2 3-dihidroxiciclopentil)-amida del acido ciclobutanocarboxilico

El compuesto del titulo se prepara empleando un método que es analogo al utilizado para preparar el compuesto del Ejemplo 22, utilizando {(1S,2R,3S,4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxi-ciclopentil}-amida del acido ciclobutanocarboxilico 2-(1-isopropil-1H-imidazol-4-il)-etilamina (ver la preparacion de los intermediarios) (30 miligramos 0 2 milimoles) y yoduro de sodio (6 miligramos 0 04 milimoles) LCMS (electroaspersión) *m/z* [MH+] 664 44

Ejemplo 24

Trifluoroacetato de N-((1S,2R,3S,4R)-4-{6-(2,2-difeniletilamino)-2-[2-(1-isopropil-1H-imidazol-4-il)-etilaminol-purin-9-il}-2 3-dihidroxiciclopentil)-butiramida

N-{(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-butiramida

El compuesto del título se prepara mediante el mismo metodo que la {(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-amida del acido ciclobutanocarboxílico a partir de clorhidrato de (1S 2R,3S 5R)-3-amino-5-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-ciclopentano-1 2-diol (un intermediario para la preparacion del compuesto del Ejemplo 22) y cloruro de butirilo, para obtener el compuesto del titulo (48 miligramos)

LCMS (electroaspersión) *m/z* [MH+] 535 26 ^{1}H RMN (MeOD, 400 MHz) 8 00 (s, 1H) 7 40-7 30 (m 8H) 7 25-7 15 (m 2H) 4 75 (m 1H) 4 60 (m, 1H) 4 50 (m 1H) 4 20 (m, 2H), 3 95 (m 1H), 2 85 (m 1H) 2 35 (m 2H) 2 05 (m 1H) 1 70 (m 2H) 1 00 (m, 3H)

Trifluoroacetato de N-((1S,2R 3S 4R)-4-{6-(2 2-difeniletilamino)-2-[2-(1-isopropil-1H-imidazol-4-il)-etilamino]-purin-9-il}-2 3-dihidroxiciclopentil)-butiramida

El compuesto del titulo se prepara empleando un metodo que es análogo al utilizado para la preparacion del compuesto del Ejemplo 22 utilizando N-{(1S 2R,3S 4R)-4-[2-cloro-6-(2,2-difeniletilamino)-purin-9-il]-2,3-dihidroxiciclopentil} butiramida, 2-(1-isopropil-1H-imidazol-4-il)-etilamina (ver la preparacion de los intermediarios) (30 miligramos 0 2 milimoles) y yoduro de sodio (6 miligramos 0 04 milimoles) LCMS (electroaspersion) *m/z* [MH+] 652 44

Ejemplo 25

Trifluoroacetato de N-((1S 2R 3S 4R)-4-{6-(2 2-difeniletilamino)-2-[2-(1-isopropil-1H-imidazol-4-il)-etilamino]-purin-9-il}-2,3-dihidroxiciclopentil)-isobutiramida

N-{(1S,2R,3S,4R)-4-[2-cloro-6-(2,2-difeniletilamino)-purin-9-il]-2,3-dihidroxiciclopentil}-isobutiramida

El compuesto del titulo se prepara mediante el mismo metodo que la {(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-

difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-amida del acido ciclobutanocarboxilico a partir de clorhidrato de (1S,2R 3S 5R)-3-amino-5-[2-cloro-6-(2,2-difeniletilamino)-purin-9-il}-ciclopentano-1 2-diol (un intermediario para la preparacion del compuesto del Ejemplo 22) y cloruro de isobutirilo para obtener el compuesto del titulo LCMS (electroaspersion) *m/z* [MH+] 535 26 ^{1}H RMN (MeOD, 400 MHz) 8 00 (s 1H) 7 40-7 30 (m 8H) 7 25-7 15 (m 2H) 4 75 (m 1H) 4 60 (m 1H) 4 50 (m 1H) 4 20 (m 2H) 3 95 (m 1H) 2 85 (m 1H) 2 70 (m 1H) 2 10 (m 1H) 1 20 (m, 6H)

Trifluoroacetato de N-((1S 2R 3S 4R)-4-{6-(2 2-difeniletilamino)-2-[2-(1-isopropil-1H-imidazol-4-il)-etilaminol-purin-9-il}-2 3-dihidroxiciclopentil)-isobutiramida

El compuesto del titulo se prepara empleando un metodo que es analogo al utilizado para la preparacion del compuesto del Ejemplo 22 utilizando N-{(1S 2R,3S,4R)-4-[2-cloro-6-(2 2-difenile ilamino)-purin-9-il]-2,3-dihidroxiciclopentil} isobutiramida 2-(1-isopropil-1H-imidazol-4-il)-etilamina (ver la preparacion de los intermediarios) (30 miligramos 0 2 milimoles) y yoduro de sodio (6 miligramos 0 04 milimoles) LCMS (electroaspersion) *m/z* [MH+] 652 44

Ejemplo 26

Trifluoroacetato de N-((1S 2R 3S 4R)-4-{6-(2,2-

difeniletilamino)-2 [2-(1-isopropil-1H-imidazol-4-il)-etilamino]-purin-9-il}-2,3-dihidroxiciclopentil)-2-fenil-acetamida

N-((1S 2R 3S 4R)-4 [2-cloro-6-(2,2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-2-fenil-acetamida

Una solucion del clorhidrato de (1S 2R 3S 5R)-3-amino-5-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-ciclopentano-1,2-diol (un intermediario para la preparación del compuesto del Ejemplo 22) (100 miligramos 0 2 milimoles) en THF anhidro (1 mililitro) se trata con diisopropiletilamina (0 17 mililitros 1 milimol) y cloruro de fenilacetilo (0 026 mililitros 0 2 milimoles) y la mezcla se agita a temperatura ambiente durante 18 horas El solvente se remueve a presión reducida y el residuo se disuelve en diclorometano (2 mililitros) y se lava con acido clorhídrico diluido (2 mililitros) La fase orgánica se separa y se evapora a presion reducida para obtener el compuesto del titulo (114 miligramos) LCMS (electroaspersión) *m/z* [MH+] 583 27

Trifluoroacetato de N-((1S 2R 3S 4R)-4-{6-(2 2-difeniletilamino)-2-[2-(1-isopropil-1H-imidazol-4-il)-etilamino]-purin-9-il}-2 3-dihidroxiciclopentil)-2-fenil-acetamida

El compuesto del titulo se prepara empleando un método que es analogo al utilizado para preparar el compuesto del Ejemolo 22 utilizando N-{(1S 2R 3S 4R)-4-[2-

cloro-6-(2 2-difeniletilamino)-purin-9-il]-2,3-dihidroxiciclopentil} 2-fenilacetamida 2-(1-isopropil-1H-imidazol-4-il)-etilamina (ver la preparacion de los intermediarios) (30 miligramos 0 2 milimoles) y yoduro de sodio (6 miligramos 0 04 milimoles) LCMS (electroaspersion) *m/z* [MH+] 700 45

Ejemplo 27

Trifluoroacetato de {(1S 2R 3S 4R)-4-[6-(2 2-difeniletilamino)-2-(2-piperidin-1-il-etilamino)-purin-9-il]-2,3-dihidroxiciclopentil}-amida del acido ciclobutanocarboxílico

El compuesto del título se prepara empleando un método que es análogo al utilizado para preparar el compuesto del Ejemplo 22 utilizando {(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil} amida del acido ciclobutanocarboxílico (un intermediario para la preparacion del Ejemplo 23) 1-(2-aminoetil)-piperidina (0 057 mililitros 0 4 milimoles), y yoduro de sodio (6 miligramos 0 04 milimoles) LCMS (electroaspersion) *m/z* [MH+] 639 45

Ejemplo 28

Trifluoroacetato de N-{(1S,2R,3S,4R)-4-[6-(2,2-difeniletilamino)-2-(2-piperidin-1-il-etilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-butiramida

El compuesto del titulo se prepara empleando un

método que es analogo al utilizado para preparar el compuesto del Ejemplo 22 utilizando N-[(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-butiramida (un intermediario para la preparacion del Ejemplo 24), 1-(2-aminoetil)-piperidina (0 057 mililitros 0 4 milimoles) y yoduro de sodio (6 miligramos 0 04 milimoles) LCMS (electroaspersion) *m/z* [MH+] 627 44

Ejemplo 29

Trifluoroacetato de N-{(1S 2R 3S 4R)-4-[6-(2,2-difeniletilamino)-2-(2-piperidin-1-il-etilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-isobutiramida

El compuesto del título se prepara empleando un metodo que es análogo al utilizado para preparar el compuesto del Ejemplo 22, utilizando N-{(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil} isobutiramida (un intermediario para la preparacion del Ejemplo 25), 1-(2-aminoetil)-piperidina (0 057 mililitros 0 4 milimoles) y yoduro de sodio (6 miligramos 0 04 milimoles) LCMS (electroaspersion) *m/z* [MH+] 627 44

Ejemplo 30

Trifluoroacetato de N-{(1S 2R 3S 4R)-4-[6-(2 2-difeniletilamino)-2-(2-piperidin-1-il-etilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-2-fenil-acetamida

El compuesto del título se prepara empleando un metodo que es análogo al utilizado para preparar el compuesto del Ejemplo 22 utilizando N-{(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil} 2-fenil-acetamida (un intermediario del Ejemplo 26) 1-(2-aminoetil-)-piperidina (0 057 mililitros, 0 4 milimoles) y yoduro de sodio (6 miligramos 0 04 milimoles) LCMS (electroaspersion) *m/z* [MH+] 675 47

Ejemplo 31

N-{(1S 2R 3S 4R)-4-[6-(2 2-difeniletilamino)-2-(2-piperidin-1-il-etilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-N'-(2-piperidin-1-il-etil)-oxalamida

{(1S 2R 3S 4R)-4-[2 cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-amida del ácido isoxazol-5-carboxilico

El compuesto del titulo se prepara mediante el mismo metodo que la {(1S,2R,3S,4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-amida del acido ciclobutanocarboxilico, a partir del clorhidrato de (1S 2R 3S 5R)-3-amino-5-[2-cloro-6-(2,2-difeniletilamino)-purin-9-il]-ciclopentano-1,2-diol (un intermediario para la preparacion del compuesto del Ejemplo 22) y cloruro de isoxazol-5-carbonilo para obtener el compuesto del título LCMS (electroaspersión) *m/z* [MH+] 560 28

N-{(1S 2R 3S 4R)-4-[6-(2 2-difeniletilamino)-2-(2-piperidin-1-

il-etilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-N -(2-piperidin-1-il-etil)-oxalamida

El compuesto del titulo se prepara empleando un metodo que es analogo al utilizado para preparar el compuesto del Ejemplo 22 utilizando {(1S,2R,3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil} amida del acido isoxazol-5-carboxilico 1-(2-aminoetil)-piperidina (51 miligramos 0 4 milimoles) y yoduro de sodio (6 miligramos 0 04 milimoles) LCMS (electroaspersion) *m/z* [MH+] 739 55

Ejemplo 32

{(1S 2R 3S 4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-amida del acido ciclopropanocarboxílico

El compuesto del titulo se prepara empleando un metodo que es análogo al utilizado para la preparacion del compuesto del Ejemplo 22, utilizando {(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil} amida del ácido ciclopropanocarboxilico (un intermediario para la preparación del Ejemplo 22) (R)-pirrolidin-3-il-amina (34 miligramos 0 4 milimoles) y yoduro de sodio (6 miligramos, 0 04 milimoles), para obtener una mezcla de 2-regioisomeros, los cuales se purifican mediante cromatografia en columna de fase inversa (Isolute^{MR} C18 acetonitrilo de 0 a 100% en agua-acido TFA al 0 1%) para

obtener un producto que es predominantemente {(1S 2R 3S 4R)-4-[2 ((R)-3-amino-pirrolidin-1-il)-6-(2,2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-amida del acido ciclopropanocarboxilico LCMS (electroaspersion) *m/z* [MH+] 583 42

Ejemplo 33

{(1S 2R 3S 4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-amida del ácido ciclobutanocarboxilico

El compuesto del titulo se prepara empleando un método que es análogo al utilizado para la preparacion del compuesto del Ejemplo 22 utilizando {(1S 2R 3S,4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil} amida del ácido ciclobutanocarboxilico (un intermediario para la preparación del Ejemplo 23), (R)-pirrolidin-3-il-amina (34 miligramos 0 4 milimoles) y yoduro de sodio (6 miligramos 0 04 milimoles), para obtener una mezcla de 2-regioisomeros, los cuales se purifican mediante cromatografia en columna de fase inversa (Isolute^{MR} C18, acetonitrilo de 0 a 100% en agua-acido TFA al 0 1%) para obtener un producto que es predominantemente {(1S 2R 3S 4R)-4-[2 ((R)-3-amino-pirrolidin-1-il)-6-(2,2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-amida del acido ciclobutanocarboxilico LCMS (electroaspersión) *m/z* [MH+] 597 45

254
255

Ejemplo 34

N-{(1S 2R 3S 4R)-4 [2-((R)-3-amino-pirrolidin-1-il)-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-2-fenil-acetamida

El compuesto del titulo se prepara empleando un metodo que es análogo al utilizado para preparar el compuesto del Ejemplo 22 utilizando N-{(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil} 2-fenil-acetamida (un intermediario para la preparacion del Ejemplo 26), (R)-pirrolidin-3-ilamina (34 miligramos 0 4 milimoles) y yoduro de sodio (6 miligramos 0 04 milimoles) para obtener una mezcla de 2-regioisomeros los cuales se purifican mediante cromatografia en columna de fase inversa (Isolute^{MR} C18 acetonitrilo de 0 a 100% en agua-acido TFA al 0 1%), para obtener un producto que es predominantemente N-{(1S 2R 3S 4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-(2 ?-difeniletilamino)-purin-9-il]-2,3-dihidroxiciclopentil} 2-fenil-acetamida LCMS (electroaspersión) *m/z* [MH+] 633 46

Ejemplo 35

N-{(1S 2R 3S 4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-(2,2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-3-fenil-propionamida

N-{(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-3-fenil-propionamida

Una solucion de clorhidrato de (1S 2R 3S 5R)-3-amino-5-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-ciclopentano-1,2-diol (un intermediario para la preparacion del compuesto del Ejemplo 22) (100 miligramos 0 2 milimoles) en THF anhidro (1 mililitro) se trata con diisopropiletilamina (0 17 mililitros 1 milimol) y cloruro de 3-fenil-propionilo (0 03 mililitros 0 2 milimoles), y la mezcla se agita a temperatura ambiente durante 18 horas El solvente se remueve a presión reducida y el residuo se disuelve en diclorometano (2 mililitros), y se lava con acido clorhídrico diluido (2 mililitros) La fase organica se separa y se evapora a presion reducida, para obtener el compuesto del titulo LCMS (electroaspersion) *m/z* [MH+] 597 32

N-{(1S 2R 3S 4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-3-fenil-propionamida

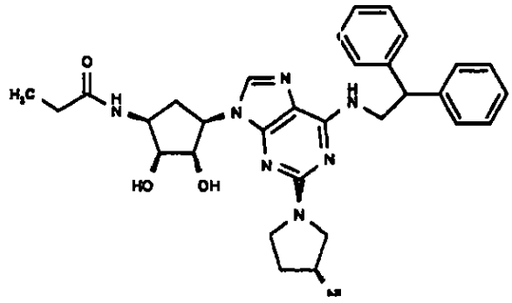
El compuesto del titulo se prepara empleando un método que es análogo al utilizado para preparar el compuesto del Ejemplo 22 utilizando N-{(1S 2R,3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil} 3-fenil-propionamida (R)-pirrolidin-3-il-amina (34 miligramos, 0 4 milimoles) y yoduro de sodio (6 miligramos 0 04 milimoles), para obtener una mezcla de 2-regioisómeros los cuales se purifican mediante cromatografia en columna de fase inversa (Isolute^{MR} C18

acetonitrilo de 0 a 100% en agua-acido TFA al 0 1%) para obtener un producto que es predominantemente N-{(1S 2R 3S 4R)-4-[2 ((R)-3-amino-pirrolidin-1-il)-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-2-fenil-acetamida LCMS (electroaspersión) *m/z* [MH+] 647 47

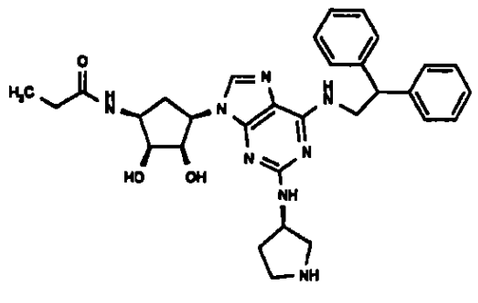
Ejemplos 36a y 36b

N-{(1S 2R 3S 4R)-4-[2-((1S 3R)-3-amino-pirrolidin-1-il)-6-(2 2-difeniletilamino)-purin-9-il]-2,3-dihidroxiciclopentil}-propionamida y

N-{(1S 2R 3S 4R)-4-[6-(2 2-difeniletilamino)-2-((R)-pirrolidin-3-il-amino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida



Ejemplo 36a



Ejemplo 36b

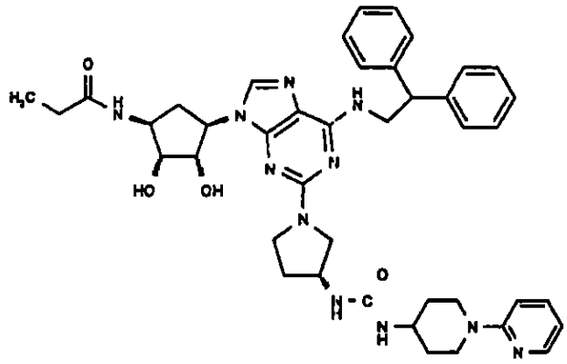
Estos compuestos se preparan empleando un método que es analogo al utilizado para preparar el compuesto del Ejemplo 22 utilizando N-{(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difenile ilamino)-purin-9-il]-2 3-dihidroxiciclopentil} propionamida (un intermediario para la preparacion del Ejemplo 16) (R)-pirrolidin-3-il-amina (34

miligramos 0 4 milimoles), y yoduro de sodio (6 miligramos 0 04 milimoles) para obtener una mezcla de 2-regioisómeros es decir N-{(1S,2R,3S,4R)-4-[2-((1S,3R)-3-amino-pirrolidin-1-il)-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil} propionamida (Ejemplo 36a) y N-{(1S 2R 3S 4R)-4-[6 (2,2-difeniletilamino)-2-((R)-pirrolidin-3-il-amino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (Ejemplo 36b) las cuales se purifican mediante cromatografia en columna de fase inversa (Isolute^{MR} C18 acetonitrilo de 0 a 100% en agua-acido TFA al 0 1%) para obtener un producto que es predominantemente N-{(1S 2R,3S 4R)-4-[2 ((R)-3-amino-pirrolidin-1-il)-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida LCMS (electroaspersión) *m/z* [MH+] 571 41

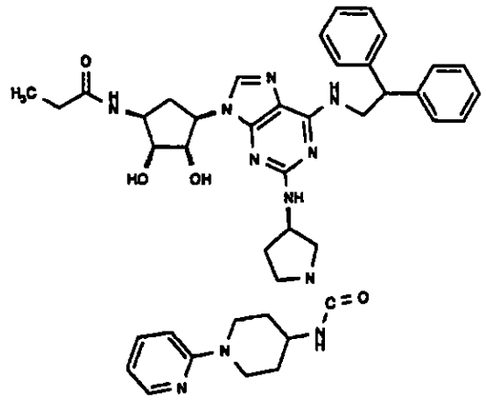
Ejemplos 37a y 37b

N-{(1S 2R 3S 4R)-4-(6-(2 2-difeniletilamino)-2-{(1S 3R)-3-[3-(3 4 5 6-tetrahidro-2H-[1 2']-bipiridinil-4-il)-ureido]-pirrolidin-1-il}-purin-9-il)-2 3-dihidroxiciclopentil]-propionamida y

(3 4 5 6-tetrahidro-2H-[1 2']-bipiridinil-4-il)-amida del acido (R)-3-[9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-il-amino]-pirrolidin-1-carboxilico



Ejemplo 37a



Ejemplo 37b

La N-{(1S 2R 3S 4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil} propionamida (30 miligramos, 0 04 milimoles) se disuelve en tolueno (2 mililitros) e iPrOH (1 mililitros) Se agrega N-[1-(2-piridinil)-4-piperidinil]-1H-imidazol-1-carboxamida (preparada empleando el procedimiento descrito en la Solicitud Internacional de Patente WO 01/94368) (12 miligramos 0 044 milimoles) como una solucion en diclorometano La mezcla de reaccion se agita a temperatura ambiente Se demuestra que la reaccion esta completa mediante LCMS despues de 24 horas El solvente se remueve al vacio Los compuestos del titulo existen como una mezcla de dos regioisomeros, es decir N-[(1S 2R 3S 4R)-4-(6 (2 2-difeniletilamino)-2-{(1S 3R)-3-[3-(3 4 5 6-tetrahidro-2H-[1 2]-bipiridinil-4-il)-ureido]-pirrolidin-1-il}-purin 9-il)-2 3-dihidroxiciclopentil]-propionamida (Ejemplo 37a) y (3,4,5 6-tetrahidro-2H-[1 2]-

bipiridinil-4-il)-amida del acido (R)-3-[9-((1R 2S,3R,4S)-2,3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H purin-2-il-amino]-pirrolidin-1-carboxilico (Ejemplo 37b) y se separan mediante cromatografia en columna rápida (Isolute^{MR} C18 acetonitrilo del 0 al 100 por ciento en agua) LCMS (electroaspersion) *m/z* [MH+] 596 42

Las estructuras de los compuestos de los Ejemplos 37a y 37b se asignan utilizando los efectos del isotopo secundario en la espectroscopia de resonancia magnética nuclear Los efectos del isótopo están bien establecidos en la espectroscopia de RMN (B A Bernheim y H Batiz-Hernandez, *Prog Nucl Magn Reson Spectrosc* 3, 63-85 [1967]) Los efectos del isótopo primario se han estudiado ampliamente (L J Altman et al, *J Am Chem Soc* 100 8264-8266 [1978]), pero es el cambio de isotopo secundario el que ha proporcionado una informacion estructural importante Estos efectos del isotopo secundario se observan en los espectros de RMN ^{1}H o X-nucleo (usualmente ^{13}C) de los compuestos parcialmente deuterados una técnica conocida como SIMPLE (Secondary Isotope Multiplets of Partially Labelled Entities (Multipletes de Isotopo Secundario de Entidades Parcialmente Marcadas)) La deuteracion parcial de los protones intercambiables en las moléculas permite la observación directa de los diferentes isotopómeros medidos bajo condiciones de intercambio lento,

y se pueden analizar las separaciones de las lineas de resonancia en terminos de los efectos del isotopo de dos enlaces y de tres enlaces que contribuyen al cambio del isotopo secundario inducido por deuterio Por ejemplo se observan señales a partir de atomos de carbono individuales como una serie de multipletes con relaciones de intensidad que varían cuantitativamente con las relaciones ^{1}H ^{2}H La magnitud de los efectos de los dos enlaces y de los tres enlaces varia segun la configuracion de los atomos de carbono y tambien segun la sustitución y el enlace de hidrógeno de estos grupos intercambiables Son estas formaciones de multipletes de señales y la magnitud de los efectos del isotopo las que se utilizan para asignar y confirmar sin ambiguedades las estructuras del Ejemplo 37a y del Ejemplo 37b

Los espectros de protones y carbonos de las dos moléculas se asignan por técnicas estándar unidimensionales o bidimensionales basadas en las estructuras propuestas Los dos carbonilos de urea tienen un cambio de 157 38 ppm en el Ejemplo 37a y de 156 34 ppm en el Ejemplo 37b respectivamente Ambas fracciones de carbonilo están enlazadas con dos átomos de nitrógeno, sin embargo, la diferencia clave es que el Ejemplo 37a está enlazado a dos grupos NH mientras que el carbonilo equivalente del Ejemplo 37b está enlazado a un grupo NH y al nitrogeno

completamente sustituido del anillo de prolina

La titulacion cuidadosa del oxido de deuterio en las dos muestras, da como resultado una proporcion aproximada de 50 50 de las fracciones intercambiables protonadas y deuteradas La titulación se monitorea por medio de ^{1}H RMN midiendo las integrales de los protones intercambiables sobre la adicion de alicuotas de 1 microlitro de D_2O Luego se ejecutan los espectros ^{13}C de alta resolución sobre ambas muestras El carbonilo de enlace del Ejemplo 37a muestra una estructura triplete que solamente se puede presentar por la existencia de dos grupos parcialmente deuterados dentro de dos enlaces (el triplete consiste en las resonancias de carbono NHCONH [NDCONH/NDCONH] y NDCOND) Sin embargo el carbono equivalente del Ejemplo 37b consiste en una estructura de doblete confirmando que este enlace carbonilo esta enlazado solamente a un grupo NH confirmando de esta manera su estructura

Ejemplo 38

{2-[3-(3 4 5 6-tetrahidro-2H-[1 2]-bipiridinil]-4-il)-ureido]-etil}-amida del acido 9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxilico

Metiléster el acido 6-(2 2-difeniletilamino)-9H-purin-2-carboxilico

El clorhidrato de metiléster del acido 6-(2 2-

difeniletilamino)-9H-purin-2-carboxilico (preparado empleando el procedimiento descrito en la Solicitud de Patente Internacional WO 2001/94368) (35 gramos 85 3 milimoles) se coloca en un matraz bajo una atmosfera de argón Se agregan $CHCl_3$ anhidro (300 mililitros) y N O-bis-(trimetilsilil)-acetamida (61 mililitros) y la mezcla de reaccion se pone a reflujo durante 1 hora La mezcla de reaccion se deja enfriar y se remueven cualesquiera volatiles al vacio Al aceite resultante se le agrega MeOH (300 mililitros) El sólido blanco resultante se filtra y se lava con MeOH (200 mililitros dos veces) y luego se seca en un horno al vacio para obtener el compuesto del titulo ^{1}H RMN (DMSO 400 MHz)

Metilester del ácido 6-(2 2-difeniletilamino)-9-((1R 4S)-4-hidroxiciclopent-2-enil)-9H-purin-2-carboxilico

Al metilester del acido 6-(2 2-difeniletilamino)-9H-purin-2-carboxilico (5 gramos, 13 4 milimoles) bajo una atmosfera de argon se le agregan THF desoxigenado anhidro (100 mililitros) y dimetilsulfoxido anhidro (2 mililitros) Luego se agrega hidruro de sodio al 95 por ciento (0 32 gramos 13 4 milimoles) y la solucion se agita a 40°C Por separado al (1S,4R)-cis-4-acetoxi-2-ciclopenten-1-ol (1 889 gramos, 13 4 milimoles) y trifenilfosfina (0 53 gramos 2 0 milimoles) en THF desoxigenado anhidro (20 mililitros), se le agrega tris-(dibencilidenacetona)-dipaladio(0) (0 69 gramos 0 67

milimoles) y la mezcla se agita a temperatura ambiente durante 10 minutos Esta solucion se agrega a la solucion del anion por medio de jeringa y luego la mezcla resultante se agita a 80°C Se cemuestra que la reaccion esta completa mediante LCMS despues de 2 horas La mezcla de reaccion se deja enfriar se agrega metanol y se filtra un solido El filtrado se concentra al vacio y se obtiene el compuesto del titulo mediante precipitación a partir de diclorometano/hexano ^{1}H RMN (MeOD 400 MHz) 8 15 (s 1H), 7 40-7 15 (m, 10H) 6 20 (m, 1H), 5 95 (m 1H) 5 50 (m 2H) 4 75 (m 2H) 4 55 (m 1H) 4 10 (m 2H) 3 90 (s 2H) 3 80 (s 1H) 2 9 (m 1H) 1 75 (m 1H)

Metilester del acido 6-(2 2-difeniletilamino)-9-((1R 4S)-4-etoxi-carboniloxi-ciclopent-2-enil)-9H-purin-2-carboxilico

El metilester del acido 6-(2 2-difeniletilamino)-9-((1R 4S)-4-hidroxi-ciclopent-2-enil)-9H-purin-2-carboxilico (2 80 gramos, 6 14 milimoles) se coloca en un matraz secado al horno bajo una atmosfera de argón Se agrega tetrahidrofurano anhidro (30 mililitros) seguido por piridina anhidra (0 97 gramos 12 3 milimoles) Se agrega lentamente cloroformiato de etilo (2 66 gramos 24 6 milimoles) y la mezcla de reacción se agita a temperatura ambiente Se demuestra que la reacción está completa mediante LCMS despues de 3 horas El solvente se remueve al vacio, y el residuo se somete a extracción por particion entre

diclorometano (200 mililitros) y HCl 1M (200 mililitros dos veces) La fase organica se lava con una solucion saturada de bicarbonato de sodio (200 mililitros, dos veces), agua (100 mililitros dos veces) salmuera (100 mililitros dos veces), se seca sobre $MgSO_4$ se filtra y el solvente se remueve al vacio El compuesto del titulo se obtiene despues de una purificacion mediante cromatografia en columna rapida (silice MeOH al 4 por ciento en diclorometano) MS (ES+) *m/e* 528 3 (MH+)

Metilester del acido 9-((1R 4S)-4-diterbutoxi-carbonil-amino-ciclopent-2-enil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxilico

El metilester del acido 6-(2,2-difeniletilamino)-9-((1R 4S)-4-etoxi-carboniloxi-ciclopent-2-enil)-9H-purin-2-carboxilico (2 2 gramos, 4 2 milimoles) se disuelve en tetrahidrofuranodescxigenado La solución resultante se agita bajo una atmósfera de argón a temperatura ambiente Se agregan iminodicarboxilato de di-t-butilo (0 9 gramos 4 2 milimoles) trifenilfosfina (0 16 gramos, 0 63 milimoles) y trietilamina (0 42 gramos 4 2 milimoles), seguidos por tris-(dibencilidenacetona)-dipaladio(0) (0 22 gramos 0 21 milimoles) Luego la mezcla de reaccion se agita a 45°C durante 4 horas, se deja enfriar a temperatura ambiente, se agrega metanol y se filtra la mezcla de reaccion El filtrado se concentra al vacio El aceite resultante se purifica

mediante cromatografia en columna (silice éter al 80 por ciento en hexano) para obtener el compuesto del titulo, MS (ES+) *m/e* 536 4 (MH+)

Metiléster del acido 9-((1R,2S,3R,4S)-4-diterbutoxi-carbonil-amino-2 3-dihidroxiciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxilico

El compuesto del titulo se prepara a partir del metiléster del ácido 9-((1R 4S)-4-diterbutoxi-carbonil-amino-ciclopent-2-enil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxilico empleando un procedimiento análogo al del (1R 2S 3R 5S)-3-[2-cloro-6-(2,2-difeniletilamino)-purin-9-il]-5-(di-Boc-amino)-ciclopentano-1 2-diol MS (ES+) *m/e* 689 4 (MH+)

Metilester del acido 9-((1R 2S,3R,4S)-4-amino-2,3-dihidroxiciclopentil) 6-(2,2-difeniletilamino)-9H-purin-2-carboxilico

El metilester del ácido 9-((1R 2S 3R 4S)-4-diterbutoxi-carbonil-amino-2 3-dihidroxiciclopentil)-6-(2,2-difeniletilamino)-9H-purin-2-carboxílico (0 5 gramos 0 73 milimoles) se disuelve en dioxano, y se agita bajo una atmósfera de argón Se agrega HCl 4M en dioxano (3 68 mililitros 14 5 milimoles) y la solucion resultante se agita durante 20 horas y luego se concentra al vacío El compuesto del titulo se obtiene mediante cromatografia en columna rapida (Isolute^{MR} C18 acetonitrilo del 0 al 100 por

ciento en agua) MS (ES+) *m/e* 489 3 (MH+)

Metilester del ácido 9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxílico

El clorhidrato de metiléster del ácido 9-((1R 2S 3R,4S)-4-amino-2 3-dihidroxiciclopentil)-6-(2 2-difeniletilamino)-9H purin-2-carboxílico (200 miligramos 0 36 milimoles) se disuelve en tetrahidrofurano (5 mililitros) Se agrega diisopropiletilamina (0 16 mililitros 0 9 milimoles) y la solucion se agita durante 10 minutos Se agrega cloruro de propionilo (33 miligramos 0 36 milimoles) y la mezcla de reaccion se agita a temperatura ambiente durante 1 hora La reaccion se para con metanol, y el compuesto del titulo se obtiene mediante cromatografia en columna rapida (Isolute^{MR} C18, acetonitrilo del 0 al 100 por ciento en agua) MS (ES+) *m/e* 545 3 (MH+)

(2-aminoetil)-amida del ácido 9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxílico

El metiléster del acido 9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxílico (62 miligramos 1 0 milimoles) se disuelve en etilendiamina (3 4 mililitros, 51 milimoles) y la solucion se agita a 105°C Se demuestra que la reacción esta completa mediante LCMS después de 45

minutos La mezcla de reaccion se concentra al vacio, y se obtiene el compuesto del titulo despues de la purificacion mediante cromatografia en columna de fase inversa (Isolute^{MR} C18 acetonitrilo del 0 al 100 por ciento en agua) MS (ES+) *m/e* 573 4 (MH+)

{2-[3-(3 4 5 6-tetrahidro-2H-[1 2]-bipiridinil-4-il)-ureido]-etil}-amida del ácido 9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxilico

La (2-aminoetil)-amida del ácido 9-((1R 2S,3R,4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H purin-2-carboxilico (25 miligramos 0 044 milimoles) se disuelve en tolueno (2 mililitros) e iPrOH (1 mililitro) Se agrega N-[1-(2-piridinil)-4-piperidinil]-1H-imidazol-1-carboxamida (preparada empleando el procedimiento descrito en la Solicitud de Patente Internacional WO 01/94368) (12 miligramos 0 044 milimoles) como una solucion en diclorometano La mezcla de reaccion se agita a temperatura ambiente Se demuestra que la reacción esta completa mediante LCMS después de 24 horas El solvente se remueve al vacio El compuesto del título se obtiene mediante cromatografia en columna rapida (Isolute^{MR} C18 acetonitrilo del 0 al 100 por ciento en agua) MS (ES+) *m/e* 388 7 (MH+)

En seguida se describe un metodo alternativo para

la preparacion del compuesto del Ejemplo 38

Metiléster del ácido 9-[(1R 4S)-4-(terbutoxi-carbonil-propionilamino)-ciclopent-2-enil]-6-(2 2-difeniletilamino)-9H-purin-2-carboxilico

Este compuesto que es la sal de trifluoroacetato del compuesto final del Ejemplo 37 se prepara empleando un metodo que es analogo al utilizado para la preparación del metilester del acido 9-((1R,4S)-4-diterbutoxi-carbonil-amino-ciclopent-2-enil)-6-(2,2-difeniletilamino)-9H-purin-2-carboxílico, mediante el reemplazo del iminodicarboxilato de di-t-butilo por tert-butiléster del ácido propionilcarbámico

Metilester del ácido 9-[(1R 2S 3R 4S)-4-(terbutoxi-carbonil-propionilamino)-2 3-dihidroxiciclopentil]-6-(2 2-difeniletilamino)-9H purin-2-carboxilico

A una suspension agitada que comprende metiléster el ácido 9-[(1R 4S)-4-(terbutoxi-carbonil-propionilamino)-ciclopent-2-enil]-6-(2 2-difeniletilamino)-9H-purin-2-carboxilico (6 6 gramos 10 82 milimoles) metansulfonamida (1 03 gramos, 10 82 milimoles), y AD-mezcla-α (16 23 gramos) en t-butanol (40 mililitros) y agua (40 mililitros) se le agrega tetraoxido de osmio (3 mililitros de una solucion al 4 por ciento en agua) La mezcla de reaccion se agita vigorosamente durante 36 horas La mezcla de reaccion se somete a extraccion por particion entre acetato de etilo y agua y la porción orgánica se seca ($MgSO_4$) y se concentra

al vacio El producto del titulo se precipita a partir de metanol Se deriva producto adicional a partir del licor madre por cromatografia en gel de silice eluyendo con DCM/metanol (25 1)

Tert-butilester del acido {(1S 2R 3S 4R)-4-[2-(2-aminoetil-carbamoil)-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil} carbamico

Este compuesto se prepara de una manera analoga a la (2-aminoetil)-amida del ácido 9-((1R,2S,3R,4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2,2-difeniletilamino)-9H purin-2-carboxilico reemplazando el metilester del acido 9-((1R,2S,3R,4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2,2-difeniletilamino)-9H-purin-2-carboxilico por metilester del acido 9-[(1R,2S,3R,4S)-4-(terbutoxi-carbonil-propionilamino)-2 3-dihidroxiciclopentil]-6-(2 2-difeniletilamino)-9H-purin-2-carboxilico

Tert-butilester del acido (1S 2R 3S 4R)-4-(6-(2,2-difeniletilamino)-2-{2-[3-(3 4 5 6-tetrahidro-2H-[1 2]-bipiridinil-4-il)-ureido]-etilcarbamoil}-purin-9-il)-2 3-dihidroxi-ciclopentenil]-carbamico

Este compuesto se prepara de una manera análoga a la {2-[3-(3 4 5,6-tetrahidro-2H-[1,2]-bipiridinil-4-il)-ureido]-etil}-amida del acido 9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxilico reemplazando la (2-aminoetil)-amida del ácido

9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxílico por tert-butilester del acido {(1S 2R,3S 4R)-4-[2-(2-aminoetil-carbamoil)-6-(2 2-difeniletilamino)-purin-9-il]-2,3-dihidroxiciclopentil} carbamico

Diclorhidrato de {2-[3-(3 4 5 6-tetrahidro-2H-[1 2]-bipiridinil-4-il)-ureido]-etil}-amida del ácido 9-((1R 2S 3R 4S)-4-amino-2 3-dihidroxiciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxílico

Este compuesto se prepara de una manera analoga al metilester del acido 9-((1R 2S 3R 4S)-4-amino-2,3-dihidroxiciclopentil) 6-(2 2-difeniletilamino)-9H-purin-2-carboxílico mediante el reemplazo del metiléster del ácido 9-((1R 2S 3R 4S)-4-diterbutoxi-carbonil-amino-2 3-dihidroxiciclopentil) 6-(2 2-difeniletilamino)-9H-purin-2-carboxílico por tert butilester del acido (1S 2R 3S 4R)-4-(6-(2 2-difeniletilamino)-2-{2-[3-(3 4 5 6-tetrahidro-2H-[1 2]-bipiridinil-4-il)-ureido]-etil-carbamoil}-purin-9-il)-2,3-dihidroxiciclopentil] carbamico

Trifluoroacetato de {2-[3-(3 4 5 6-tetrahidro-2H-[1 2]-bipiridinil-4-il)-ureido]-etil}-amida del ácido 9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxílico

Este compuesto se prepara de una manera analoga al metiléster del ácido 9-((1R,2S 3R 4S)-2,3-dihidroxi-4-

propionilamino-ciclopentil)-6-(2,2-difeniletilamino)-9H-purin-2-carboxílico mediante el reemplazo del clorhidrato de metilester del ácido 9-((1R,2S,3R,4S)-4-amino-2 3-dihidroxiciclopentil) 6-(2 2-difeniletilamino)-9H-purin-2-carboxílico por diclorhidrato de {2-[3-(3 4 5 6-tetrahidro-2H-[1 2]-bipiridinil-4-il)-ureido]-etil}-amida del acido 9-((1R 2S 3R,4S)-4-amino-2,3-dihidroxiciclopentil)-6-(2,2-difeniletilamino)-9H purin-2-carboxílico

Ejemplo 39

Trifluoroacetato de N-((1S 2R 3S 4R)-4-[6-(2 2-difeniletilamino)-2-[(R)-3-((R)-3-pirrolidin-3-il-ureido)-pirrolidin-1-il]-purin-9-il]-2 3-dihidroxiciclopentil)-propionamida

Este compuesto se prepara de una manera análoga al Ejemplo 22 mediante el reemplazo de la {(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil} amida del ácido ciclopropanocarboxílico por N-{(1S,2R,3S,4R)-4-[2-cloro-6-(2,2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida, y mediante el reemplazo de la 2-(1-isopropil-1H-imidazol-4-il)-etilamina por 1 3-di(R)-pirrolidin-3-il-urea

Ejemplo 40

Trifluoroacetato de [(1S 2R 3S 4R)-4-(6-(2 2-difeniletilamino)-2-[(R)-3-[3-(3 4 5 6-tetrahidro-2H-[1 2']-bipiridinil-4-il)-ureido]-pirrolidin-1-il}-purin-9-il)-2 3-

dihidroxiciclopentil]-amida del acido ciclobutanocarboxilico

Una mezcla que comprende diclorhidrato de {(1S 2R 3S 4R)-4-[2 ((R)-3-amino-pirrolidin-1-il)-6-(2,2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-amida del acido ciclobutanocarboxilico (0 02 gramos 0 03 milimoles) TEA (0 09 mililitros 0 06 milimoles) en isopropanol (0 5 mililitros) se trata con (3 4 5 6-tetrahidro-2H-[1,2]-bipiridinil-4-il)-amida del acido imidazol-1-carboxilico (0 04 mililitros de una solucion de 10 miligramos/mililitro en DCM 0 03 milimoles) Despues de que se ha agitado la mezcla de reacción a temperatura ambiente durante la noche se remueve el solvente al vacío y la purificacion del producto crudo mediante cromatografia en columna de fase inversa (Isolute^{MR} C18 acetonitrilo de 0 a 100% en agua-acido TFA al 0 1%) se obtiene el producto del titulo

Ejemplo 41

{2-[3-(3 4 5,6-tetrahidro-2H-[1 2']-bipiridinil-4-il)-ureido]-etil}-amida del acido 9-[(1R 2S 3R 4S)-4-(ciclobutanocarbonil-amino)-2 3-dihidroxiciclopentil]-6-(2 2-difeniletilamino)-9H-purin-2-carboxilico

El compuesto se prepara de una manera analoga a la {2-[3-(3 4 5 6-tetrahidro-2H-[1 2]-bipiridinil-4-il)-ureido]-etil}-amida del ácido 9-((1R 2S 3R 4S)-2,3-dihidroxi-4-

propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxilico, mediante el reemplazo del clorhidrato de (1S 2R 3S 5R)-3-amino-5-[2-cloro-6-(2,2-difeniletilamino)-purin-9-il]-ciclopentano-1,2-diol por diclorhidrato de {2-[3-(3 4 5 6-tetrahidro-2H-[1 2]-bipiridinil-4-il)-ureido]-etil}-amida del ácido 9-((1R 2S 3R 4S)-4-amino-2 3-dihidroxiciclopentil) 6-(2,2-difeniletilamino)-9H-purin-2-carboxilico

Ejemplo 42

Trifluoroacetato de {2-[3-(3 4 5 6-tetrahidro-2H-[1 2']-bipiridinil-4-il)-ureido]-etil}-amida del acido 9-((1R 2S 3R 4S)-4-acetilamino-2 3-dihidroxiciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxilico

Una mezcla que comprende diclorhidrato de {2-[3-(3 4,5,6-tetrahidro-2H-[1,2]-bipiridinil-4-il)-ureido]-etil}-amida del acido 9-((1R 2S 3R 4S)-4-amino-2 3-dihidroxiciclopentil) 6-(2,2-difeniletilamino)-9H-purin-2-carboxilico (0 02 gramos 21 micromoles), TEA (0 013 gramos 125 micromoles) en THF (2 mililitros), se trata con cloruro de acetilo (0 003 gramos 40 micromoles) Despues de que se ha agitado la mezcla de reacción a temperatura ambiente durante la noche se remueve el solvente al vacio, y la purificacion del producto crudo mediante cromatografia en columna de fase inversa (Isolute^{MR} C18 acetonitrilo de 0 a 100% en agua-acido TFA al 0 1%) produce el compuesto del

titulo

Ejemplo 43

Trifluoroacetato de {2-[3-((R)-1-piridin-2-il-pirrolidin-3-il)-ureido]-etil}-amida del acido 9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxílico

Una solución que comprende metilester del acido 9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxílico (0 01 gramos 0 018 milimoles) y 1-(2-aminoetil)-3-((R)-1-piridin-2-il-pirrolidin-3-il)-urea (0 022 gramos de una mezcla en una relación molar de 1 5 con imidazol 0 04 milimoles) en 1 2-dicloroetano/isopropanol (0 2 mililitros) de una mezcla de 1 1) se calienta a reflujo durante 70 horas El solvente se remueve al vacío, y la purificación del crudo mediante cromatografía en columna de fase inversa (Isolute^{MR} C18 acetonitrilo del 0 al 65 por ciento en agua-ácido TFA al 0 1%) produce el compuesto del titulo

Ejemplo 44

Diclorhidrato de N-{(1S 2R 3S 4R)-4-[2-(4-amino-piperidin-1-il)-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida

Trifluoroacetato de tert-butiléster del ácido {1-[9-((1R,2S 3R 4S)-2 3-dihidroxi-4-propionilamino)-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-il]-piperidin-4-il}-carbámico

Este compuesto se prepara de una manera analoga al trifluoroacetato de (1S 2R 3S 4R)-4-{6-(2 2-difeniletilamino)-2-[2-(1-isopropil-1H-imidazol-4-il)-etilamino]-purin-9-il}-2 3-dihidroxiciclopentil)-amida del ácido ciclopropanocarboxílico mediante el reemplazo de la {(1S 2R 3S 4R)-4-[2 cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-amida del ácido ciclopropanocarboxilico por N-{(1S,2R,3S,4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2,3-dihidroxiciclopentil}-propionamida y mediante el reemplazo de la 2-(1-isopropil-1H-imidazol-4-il)-etilamina por tert-butilester del acido piperidin-4-il-carbámico

Diclorhidrato de N-{(1S 2R 3S 4R)-4-[2-(4-amino-piperidin-1-il)-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil} propionamida

El trifluoroacetato de tert-butiléster del ácido {1-[9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-il]-piperidin-4-il}-carbámico (0 02 gramos 0 03 milimoles) se disuelve en HCl (1 mililitro de una solucion 1 25 M en metanol) y se deja reposar a temperatura ambiente durante la noche El solvente se remueve al vacio para obtener el compuesto del titulo

Ejemplos 45 y 46

Estos compuestos es decir trifluoroacetato de N-[(1S 2R 3S 4R)-4-[6 (2 2-difeniletilamino)-2-pirrolidin-1-il-

purin-9-il]-2 3-dihid,oxiciclopentil}-propionamida y el trifluoroacetato de N-{(1S,2R,3S,4R)-4-[6-(2,2-difeniletilamino)-2 piperazin-1-il-purin-9-il]-2,3-dihidroxiciclopentil}-propionamida se preparan de una manera analoga al trifluoroacetato de ((1S 2R 3S 4R)-4-{6-(2 2-difeniletilamino)-2-[2-(1-isopropil-1H-imidazol-4-il)-etilamino]-purin-9-il}-2,3-dihidroxiciclopentil)-amida del ácido ciclopropanocarboxilico mediante el reemplazo de la {(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-amida del ácido ciclopropanocarboxilico por N-{(1S,2R,3S,4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida y mediante el reemplazo de la 2-(1-isopropil-1H-imidazol-4-il)-etilamina por la amina apropiada

Ejemplo 47

Trifluoroacetato de {2-[3-((S)-1-piridin-2-il-pirrolidin-3-il)-ureido]-etil}-amida del acido 9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxilico

Este compuesto se prepara de una manera analoga al trifluoroacetato de {2-[3-((R)-1-piridin-2-il-pirrolidin-3-il)-ureido]-etil}-amida del ácido 9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxilico mediante el reemplazo de la 1-(2-aminoetil)-3-((R)-1-piridin-2-il-pirrolidin-3-il)-urea por 1-(2-

aminoetil)-3-((S)-1-piridin-2-il-pirrolidin-3-il)-urea

Ejemplo 48

[2-(3-piperidin-4-il ureido)-etil]-amida del ácido 9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxílico

Bencilester del ácido 4-[3-(2-{[9-((1R 2S 3R 4S)-2,3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H purin-2-carbonil]-amino}-etil)-ureido]-piperidin-1-carboxílico

A una solucion de la (2-aminoetil)-amida del acido 9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxílico (0 1 gramos 174 milimoles) en cloroformo (5 mililitros) se le agrega 4-isocianato-Z-piperidina (0 045 gramos, 0 174 milimoles) en cloroformo (5 mililitros) La mezcla de reaccion se deja agitandose a temperatura ambiente durante la noche, y luego se agrega metanol para inactivar cualquier isocianato residual El solvente se remueve al vacio para obtener el compuesto del titulo el cual se utiliza sin mayor purificacion en el siguiente paso

[2-(3-piperidin-4-il-ureido)-etil]-amida del ácido 9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2,2-difeniletilamino)-9H-purin-2-carboxílico

Una solución del benciléster del ácido 4-[3-(2-{[9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-

(2 2-difeniletilamino)-9H-purin-2-carbonil]-amino}-etil)-ureido]-piperidin-1-carboxilico (0 145 gramos, 0 174 milimoles) en metanol (1 mililitro) bajo una atmosfera de argón se trata con hidróxido de paladio sobre carbón (0 054 gramos 20 por ciento en p/p de carbón) La mezcla de reaccion se pone bajo una atmosfera de hidrógeno, y se agita a temperatura ambiente durante 72 horas y luego se filtra El filtrado se concentra al vacío para obtener el compuesto del titulo como un aceite verde

Ejemplo 49

Trifluoroacetato de {2-[3-(1-metan-sulfonil-piperidin-4-il)-ureido]-etil}-amida del ácido 9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxilico

A una solucion la [2-(3-piperidin-4-il-ureido)-etil]-amida del acido 9-((1R,2S 3R,4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxílico (0 01 gramos 0 0143 milimoles) en DMF (1 mililitro) bajo una atmosfera inerte de argon se le agrega trietilamina (TEA) (0 003 gramos 0 0286 milimoles) seguida por cloruro de mesilo (0 0016 gramos 0 0143 milimoles) Despues de reposar a temperatura ambiente durante la noche el solvente se remueve al vacio y la purificacion del producto crudo mediante cromatografia en columna de fase inversa (Isolute^{MR} C18 acetonitrilo de 0 a 100% en agua-

280

acido TFA al 0 1%) produce el compuesto del título

Ejemplo 50

Trifluoroacetato de N-((1S 2R 3S 4R)-4-{2-cloro-6-[(naftalen-1-il-metil)-amino]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida

Una solucion que comprende tert-butiléster del ácido [(1S 2R 3S 4R)-4-(2 2-dicloro-purin-9-il)-2 3-dihidroxiciclopentil] propionilcarbámico (0 5 gramos 1 1 milimoles), DIPEA (0 227 mililitros 1 3 milimoles) 1-naftalen-metilamina (0 175 mililitros 1 2 milimoles) en 1 2-dicloroetano (3 mililitros) se calienta a 50°C durante la noche Se agrega acido clorhidrico (10 mililitros de una solución 0 1M) a la mezcla de reaccion y despues de la agitacion se separa la porción orgánica y se trata con acido trifluoroacetico (1 mililitro) Después de reposar a temperatura ambiente durante 2 horas el solvente se remueve al vacio, para obtener el compuesto del titulo

Ejemplos 51-53

Estos compuestos, es decir

Trifluoroacetato de N-{(1S 2R 3S 4R)-4-[2-cloro-6-(3 3-dimetil-butil-amino)-purin-9-il]-2,3-dihidroxiciclopentil}-propionamida (Ejemplo 51)

N-{(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difenil-propilamino)-purin-9-il]-2,3-dihidroxiciclopentil}-propionamida (Ejemplo 52)

N-{(1S 2R 3S 4R)-4-[2-cloro-6-(3 3-difenil-propilamino)-purin-

9-il]-2,3-dihidroxiciclopentil}-propionamida (Ejemplo 53) se preparan de una manera análoga al trifluoroacetato de N-((1S 2R 3S 4R)-4-[2-cloro-6-[(naftalen-1-il-metil)-amino]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida mediante el reemplazo de la 1-naftalen-metilamina por la amina apropiada Los Ejemplos 53 y 54 tambien se tratan con carbonato de potasio/metanol para obtener el producto en forma libre

Ejemplo 54

Trifluoroacetato de N-((1S 2R 3S,4R)-4-{6-(1-etilpropilamino)-2-[(R)-3-((R)-3-pirrolidin-3-il-ureido)-pirrolidin-1-il]-purin-9-il}-2,3-dihidroxiciclopentil)-propionamida

Una solución que comprende N-{(1S 2R 3S,4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-2,3-dihidroxiciclopentil} propionamida (0 02 gramos 0 03 milimoles) y 1 3-di(R)-pirrolidin-3-il-urea (0 03 gramos, 0 15 milimoles) en DMSO (0 2 mililitros) se calienta a 100°C durante 24 horas La purificación se lleva a cabo utilizando LC-MS preparativa eluyendo con acetonitrilo/agua/ácido trifluoroacetico para obtener el compuesto del titulo

Ejemplo 55

Trifluoroacetato de N-((1S 2R 3S 4R)-2 3-dihidroxi-4-[6-[(naftalen-1-il-metil)-amino]-2-[(R)-3-((R)-3-pirrolidin-3-il-ureido)-pirrolidin-1-il]-purin-9-il}-ciclopentil)-

propionamida

Este compuesto se prepara de una manera análoga al trifluoroacetato de N-((1S',2R,3S,4R)-4-[6-(1-etilpropilamino)-2-[(R)-3-((R)-3-pirrolidin-3-il-ureido)-pirrolidin-1-il]-purin 9-il}-2 3-dihidroxiciclopentil)-propionamida mediante el reemplazo de la N-{(1S 2R 3S 4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-2 3-dihidroxiciclopentil} propionamida por trifluoroacetato de N-((1S,2R,3S 4R)-4-[2 cloro-6-[(naftalen-1-il-metil)-amino]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida

Ejemplo 56

Trifluoroacetato de N-{(1S 2R 3S 4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-(1-etilpropilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida

La N-{(1S 2R 3S 4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (0 02 gramos 0 03 milimoles) (3R)-3-(Boc-amino)-pirrolidina (0 028 gramos 0 15 milimoles) y yoduro de sodio (0 004 gramos 0 03 milimoles) se colocan en un frasco de microondas de 0 5 a 2 5 mililitros Se agregan acetonitrilo (0 25 mililitros) y NMP (0 25 mililitros) y la mezcla de reacción se calienta por radiación de microondas en un reactor Personal Chemistry Emrys^{MR} Optimizer a 160°C durante 30 minutos Se agregan DCM (3 mililitros) y agua (3 mililitros) a la mezcla de reaccion y despues de la agitacion

la porcion organica se separa y se trata con acido TFA (0 5 mililitros) Despue, de reposar a temperatura ambiente durante la noche se lleva a cabo la purificación utilizando LC-MS preaparativa eluyendo con acetonitrilo/agua/cido trifluoroacetico para obtener el compuesto del titulo

Ejemplo 57

Trifluoroacetato de N-((1S 2R 3S 4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-[(naftalen-1-il-etil)-amino]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida

Este compuesto se prepara de una manera análoga al trifluoroacetato de N-((1S,2R,3S,4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-(1-etilpropilamino)-purin-9-il]-2,3-dihidroxiciclopentil} propionamida mediante el reemplazo de la N-{(1S 2R,3S,4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-2,3-dihidroxiciclopentil}-propionamida por trifluoroacetato de N-((1S 2R 3S 4R)-4-{2-cloro-6-[(naftalen-1-il-metil)-amino]-purin-9-il}-2,3-dihidroxiciclopentil)-propionamida

Ejemplos 58 y 59

Estos compuestos es decir trifluoroacetato de N-((1S 2R 3S 4R)-4-{6-(2,2-difenil-propilamino)-2-[(R)-3-((R)-3-pirrolidin-3-il-ureido)-pirrolidin-1-il]-purin-9-il}-2 3-dihidroxiciclopentil) propionamida (Ejemplo 58) y trifluoroacetato de N-((1S 2R 3S 4R)-4-[6-(3 3-difenil-propilamino)-2-[(R)-3-((R)-3-pirrolidin-3-il-ureido}-pirrolidin-1-il]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida

284

(Ejemplo 59) se preparan de una manera análoga al trifluoroacetato de N-((1S,2R,3S,4R)-4-{6-(1-etilpropilamino)-2-[(R)-3-((R)-3-pirrolidin-3-il-ureido)-pirrolidin-1-il]-purin-9-il}-2 3-dihidroxiciclcpentil)-propionamida mediante el reemplazo de la N-{(1S,2R,3S,4R)-4-[2-cloro-6-(1-etilpropilamino)-pur n-9-il]-2 3-dihidroxiciclopentil}-propionamida por las materias primas apropiadas cuya preparacion se describen en la presente

Ejemplos 60 y 61

Estos compuestos es decir, trifluoroacetato de N-((1S 2R 3S 4R)-4-{6-(2,2-difenil-propilamino)-2-[2-(1-etil-1H-imidazol-4-il)-etilamino]-purin-9-il}-2,3-dihidroxiciclopentil)-propionamida (Ejemplo 60) y trifluoroacetato de N-((1S 2R 3S,4R)-4-{6-(3,3-difenil-propilamino)-2-[2-(1-etil-1H-imidazol-4-il)-etilamino]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida (Ejemplo 61) se preparan de una manera analoga al trifluoroacetato de N-{(1S 2R 3S 4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-(1-etilpropilamino)-purin-9-il]-2 3-dihidroxiciclopentil} propionamida mediante el reemplazo de la (3R)-3-(Boc-amino)-pirrolidina por 2-(1-etil-1H-imidazol-4-il)-etilamina y mediante el reemplazo de la N-{(1S 2R,3S 4R)-4-[2 cloro-6-(1-etilpropilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida por las materias primas apropiadas cuyas preparaciones se describen en la presente

285
284

Ejemplo 62

Trifluoroacetato de N-((1S 2R 3S 4R)-4-{6-(3 3-dimetil-butil-amino)-2-[(R) 3-((R)-3-pirrolidin-3-il-ureído)-pirrolidin-1-il]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida

Este compuesto se prepara de una manera análoga al trifluoroacetato de N-((1S 2R,3S,4R)-4-{6-(1-etilpropilamino)-2-[(R)-3-((R)-3-pirrolidin-3-il-ureido)-pirrolidin-1-il]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida mediante el reemplazo de la N-{(1S 2R 3S 4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-2 3-dihidroxiciclopentil} propionamida por trifluoroacetato de N-{(1S 2R 3S 4R)-4-[2 cloro-6-(3 3-dimetilbutilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida

Ejemplo 63

Trifluoroacetato de N-{(1S,2R,3S,4R)-4-[6-(1-etilpropilamino)-2-((S)-1-hidroximetil-2-fenil-etilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida

Este compuesto se prepara de una manera análoga a la N-{(1S 2R 3S 4R)-4-[6-(2 2-difeniletilamino)-2-((S)-1-hidroximetil-2-fenil-etilamino)-purin-9-il]-2,3-dihidroxiciclopentil} propionamida (Ejemplo 16) mediante el reemplazo de la N-{(1S 2R 3S,4R)-4-[2-cloro-6-(2,2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (Ejemplo 4) por la N-{(1S,2R 3S 4R)-4-[2-cloro-

6-(1-etilpropilamino)-purin-9-il]-2,3-dihidroxiciclopentil}-propionamida (Ejemplo 14)

Ejemplo 64

Trifluoroacetato de N-((1S 2R 3S 4R)-4-{6-(1-etilpropilamino)-2-[((R)-1-etil-pirrolidin-2-il-metil)-amino]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida

Este compuesto se prepara de una manera análoga a la N-{(1S 2R 3S 4R)-4-[6-(2 2-difeniletilamino)-2-((S)-1-hidroximetil-2-fenil-etilamino)-purin-9-il]-2,3-dihidroxiciclopentil} propionamida (Ejemplo 16) mediante el reemplazo de la N-{(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (Ejemplo 4) por N-{(1S 2R 3S 4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (Ejemplo 14), y mediante el reemplazo del (S)-2-amino-3-fenil-propan-1-ol por C-((R)-1-etil-pirrolidin-2-il)-metilamina

Ejemplo 65

Trifluoroacetato de N-{(1S 2R 3S 4R)-4-[6-amino-2-((S)-1-hidroximetil-2-fenil-etilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida

N-((1S 2R 3S 4R)-4-{2-cloro-6-[(9H-fluoren-9-il-metil)-amino]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida

Este compuesto se prepara de una manera analoga al trifluoroacetato de N-((1S 2R 3S 4R)-4-{2-cloro-6-

[(naftalen-1-il-metil)-amino]-purin-9-il}-2 3-dihidroxiciclopentil) propionamida (Ejemplo 50) mediante el reemplazo de la 1-naftalen-metilamina por C-(9H-fluoren-9-il)-metilamina

Trifluoroacetato de N-{(1S 2R 3S 4R)-4-[6-amino-2-((S)-1-hidroximetil-2-fenil-etilamino)-purin-9-il]-2 3-dihidroxiciclopentil} propionamida

Este compuesto se prepara de una manera analoga a la N-{(1S 2R 3S,4R)-4-[6-(2 2-difeniletilamino)-2-((S)-1-hidroximetil-2-fenil-etilamino)-purin-9-il]-2 3-dihidroxiciclopentil} propionamida (Ejemplo 16) mediante el reemplazo de la N-{(1S,2R,3S,4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (Ejemolo 4) por N-((1S 2R 3S 4R)-4-{2-cloro-6-[(9H-fluoren-9-il-metil)-amino]-purin-9-il}-2 3-dihidroxiciclopentil) propionamida

Ejemplo 66

Trifluoroacetato de N-{(1S 2R 3S 4R)-2 3-dihidroxi-4-[6-[(naftalen-1-il-metil)-amino]-2-(2-piperidin-1-il-etilamino)-purin-9-il]-ciclopentil}-propionamida

Este compuesto se prepara de una manera análoga a la N-{(1S 2R,3S,4R)-4-[6-(2,2-difeniletilamino)-2-((S)-1-hidroximetil-2-fenil-etilamino)-purin-9-il]-2 3-dihidroxiciclopentil} propionamida (Ejemplo 16) mediante el reemplazo de la N-{(1S,2R 3S,4R)-4-[2-cloro-6-(2,2-

difeniletilamino)-purin-9-il]-2,3-dihidroxiciclopentil}-propionamida (Ejemplo 4) por trifluoroacetato de N-((1S 2R 3S 4R)-4-{2-cloro-6-[(naftalen-1-il-metil)-amino]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida (Ejemplo 50) y mediante el reemplazo del (S)-2-amino-3-fenil-propan-1-ol por 2-piperidin-1-il-etilamina

Ejemplos 67-69

Estos compuestos es decir trifluoroacetato de N-((1S 2R 3S 4R)-4-{2-(4-amino-ciclohexilamino)-6-[(naftalen-1-il-metil)-amino]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida (Ejemplo 67) trifluoroacetato de N-((1S 2R 3S 4R)-2,3-dihidroxi-4-{2-[2-(1H-imidazol-4-il)-etilamino]-6-[(naftalen-1-il-metil)-amino]-purin-9-il}-ciclopentil)-propionamida (Ejemplo 68) y trifluoroacetato de N-((1S 2R 3S 4R)-4-{2-[((R)-1-etil-pirrolidin-2-il-metil)-amino]-6-[(naftalen-1-il-metil)-amino]-purin-9-il}-2 3-dihidroxiciclopentil) propionamida (Ejemplo 69) se preparan de una manera análoga al trifluoroacetato de N-{(1S 2R 3S 4R)-2 3-dihidroxi-4-[6-[(naftalen-1-il-metil)-amino]-2-(2-piperidin-1-il-etilamino)-purin-9-il]-ciclopentil}-propionamida (Ejemplo 66) mediante el reemplazo de la 2-piperidin-1-il-etilamina por la amina apropiada

Ejemplo 70

Estos compuestos es decir trifluoroacetato de N{(1S 2R 3S 4R)-4-[2-(4-amino-ciclohexilamino)-6-(3,3-

dimetilbutilamino)-purin-9-il]-2,3-dihidroxiciclopentil}-propionamida (Ejemplo 70) trifluoroacetato de N-((1S,2R,3S,4R)-4-[6 (3,3-dimetil-butil-amino)-2-[2-(1H-imidazol-4-il)-etilamino]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida (Ejemplo 71) y trifluoroacetato de N-((1S 2R,3S,4R)-4-[6 (3,3-dimetil-butil-amino)-2-[((R)-1-etil-pirrolidin-2-il-metil) amino]-purin-9-il}-2 3-dihidroxiciclopentil) propionamida (Ejemplo 72) se preparan de una manera analoga a la N-{(1S 2R 3S,4R)-4-[6-(2 2difeniletilamino)-2-((S)-1-hidroximetil-2-fenil-etilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (Ejemplo 16) mediante el reemplazo de la N-{(1S 2R 3S 4R)-4-[2-cloro-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil} propionamida (Ejemplo 4) por trifluoroacetato de N-{(1S 2R 3S 4R)-4-[2-cloro-6-(3 3-dimetilbutilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (Ejemplo 51), y mediante el reemplazo del L-fenilalaninol por la amina apropiada

Ejemplo 73

Trifluoroacetato de N-{(1S 2R 3S 4R)-4-[2-{(R)-3-[3-(2 6-dicloro-piridin-4-il)-ureido]-pirrolidin-1-il}-6-(2 2-difeniletilamino)-purin-9-il]-2,3-dihidroxiciclopentil}-propionamida

Una solucion de N-{(1S,2R 3S 4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-(2 2-difeniletilamino)-purin-9-il],2-3-

290
289

dihidroxiciclopentil} propionamida (Ejemplo 36) (23 miligramos 40 micromoles) en THF (1 mililitro), se trata con TEA (7 3 miligramos 72 micromoles) y luego se agrega a 2 6-dicloro-4-isocianato-piridina (6 8 miligramos 36 micromoles) La mezcla de reacción se agita a temperatura ambiente y luego se deja reposar durante la noche El solvente se remueve al vacio y la purificación mediante LC-MS preparativa eluyendo con acetonitrilo/agua/acido trifluoroacético produce el compuesto del titulo

Ejemplo 74

Trifluoroacetato de N-((1S 2R 3S 4R)-4-{6-(2 2-difeniletilamino)-2-[(R)-3-(3-tiofen-2-il-ureido)-pirrolidin-1-il]-purin-9-il}-2 3 dihidroxiciclopentil)-propionamida

Este compuesto se prepara de una manea analoga al trifluoroacetato de N-{(1S 2R 3S 4R)-4-[2-{(R)-3-[3-(2 6-dicloro-piridin-4-il)-ureido]-pirrolidin-1-il}-6-(2 2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (Ejemplo 73) mediante el reemplazo de la 2 6-dicloro-4-isocianato piridina por isocianato de 2-tienilo

Ejemplo 75

Trifluoroacetato de N-((1S 2R 3S 4R)-4-{6-(2 2-difeniletilamino)-2-[(R)-3-(3-piridin-3-il-ureido)-pirrolidin-1-il]-purin-9-il}-2 3 dihidroxiciclopentil)-propionamida

Este compuesto se prepara de una manera analoga al trifluoroacetato de {2-[3-(3 4 5 6-tetrahidro-2H-[1,2']-

bipiridinil-4-il)-ureido]-etil}-amida del ácido 9-((1R,2S 3R,4S)-4-acetilamino-2 3-dihidroxiciclopentil)-6-(2 2-difeniletilamino)-9H purin-2-carboxílico (Ejemplo 42), mediante el reemplazo del diclorhidrato de {2-[3-(3 4 5 6-tetrahidro-2H-[1 2]-bipiridinil-4-il)-ureido]-etil}-amida del acido 9-((1R 2S 3R 4S)-4-amino-2 3-dihidroxiciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-carboxilico (un intermediario para la preparacion del Ejemplo 38) por la N-{(1S 2R 3S 4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-(2,2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (Ejemplo 36) y mediante el reemplazo del cloruro de acetilo por 3-isocianato-piridina

Ejemplo 76

<u>((1S 2R 3S 4R)-4-{6-(2,2-difeniletilamino)-2-[(R)-3-((R)-3-pirrolidin-3-il-ureido)-pirrolidin-1-il]-purin-9-il}-2,3-dihidroxiciclopentil)-amida del acido ciclobutanocarboxilico</u>

Este compuesto se prepara de una manera analoga al trifluoroacetato de N-((1S 2R 3S 4R)-4-{6-(1-etilpropilamino)-2-[(R)-3-((R)-pirrolidin-3-il-ureido)-pirrolidin-1-il]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida (Ejemplo 54), mediante el reemplazo de la N-{(1S 2R 3S 4R)-4-[2-cloro-6-(1-etilpropilamino)-purin-9-il]-2 3-dihidroxiciclopentil} propionamida (Ejemplo 14) por {(1S 2R,3S,4R)-4-[2 cloro-6-(2 2-difeniletilamino)-purin-9-il]-

2,3-dihidroxiciclopentil}-amida del acido ciclobutanocarboxilico (un intermediario utilizado para preparar el Ejemplo 23)

Ejemplo 77

Trifluoroacetato de {(R)-1-[9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-il]-pirrolidin-3-il}-amida del ácido 4-metil-piperazin-1-carboxilico

{(R)-1-[9-((3aS 4R 6S,6aR)-2,2-dimetil-6-propionilamino-tetrahidro-ciclopenta[1 3]-dioxol-4-il)-6-(2 2-difeniletilamino)-9H-purin-2-il]-pirrolidin-3-il}-amida del acido imidazol-1-carboxilico

Una mezcla que comprende N-{(3aR 4S 6R 6aS)-6-[2-((R)-3-amino-pirrolidin-1-il)-6-(2 2-difeniletilamino)-purin-9-il]-2 2-dimetil-tetrahidro-ciclopenta[1 3]-dioxol-4-il}-propionamida (ver la preparacion de los intermediarios) (0 24 gramos 0 39 milimcles) y CDI (0 275 gramos, 1 7 milimoles) en DCM se agita a temperatura ambiente durante 3 horas La purificacion de la mezcla resultante por cromatografia en gel de silice eluyendo con MeOH al 0-5 por ciento en DCM produce el compuesto del titulo como un aceite amarillo El compuesto existe como una mezcla del intermediario de imidazol-urea junto con cantidades variables del isocianato e imidazol correspondientes que son igualmente adecuados como precursores para ureas

293
292

Trifluoroacetato de {(R)-1-[9-((1R,2S,3R,4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-il]-pirrolidin-3-il}-amida del ácido 4-metil-piperazin-1-carboxilico

Una solución de la {(R)-1-[9-((3aS,4R,6S,6aR)-2,2-dimetil-6-propionilamino-tetrahidro-ciclopenta[1 3]-dioxol-4-il)-6-(2 2-difeniletilamino)-9H-purin-2-il]-pirrolidin-3-il}-amida del acido imidazol-1-carboxilico (25 miligramos, 40 micromoles) en DCM (1 mililitro) se agrega a 1-metil-piperazina (4 miligramos, 40 micromoles), y la mezcla de reaccion se agita a temperatura ambiente durante la noche El solvente se remueve al vacio y el producto crudo se trata con 1 1 de acido trifluoroacetico/agua (1 mililitro) y se agita a temperatura ambiente durante 3 horas La mezcla resultante se concentra al vacio y se purifica mediante LC-MS preparativa eluyendo con acetonitrilo/agua/acido trifluoroacético para obtener el compuesto del título

Ejemplo 78

Trifluoroacetato de N-((1S 2R 3S 4R)-4-{6-(2 2-difeniletilamino)-2-[(R)-3-(3-piridin-2-il-ureido)-pirrolidin-1-il]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida

Este compuesto se prepara de una manera análoga al trifluoroacetato de {(R)-1-[9-((1R 2S 3R 4S)-2 3-dihidroxi-4-propionilamino-ciclopentil)-6-(2 2-difeniletilamino)-9H-purin-2-il]-pirrolidin-3-il}-amida del acido 4-metil-piperazin-1-

294

carboxílico (Ejemplo 77), mediante el reemplazo de la 1-metil-piperazina por 2-amino-piridina

Ejemplo 79

Clorhidrato de N-((1S 2R 3S 4R)-4-{6-(2 2-difeniletilamino)-2 [(R)-3-(3-piridin-4-il-ureido)-pirrolidin-1-il]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida

Una mezcla que comprende N-{(1S 2R,3S 4R)-4-[2-((R)-3-amino-pirrolidin-1-il)-6-(2,2-difeniletilamino)-purin-9-il]-2 3-dihidroxiciclopentil}-propionamida (Ejemplo 36) (16 6 miligramos 29 micromoles) y fenil-ester del ácido piridin-4-il-carbamico [preparado de acuerdo con el procedimiento reportado en *Journal of Medicinal Chemistry* (2005) 48(6) 1857-1872] (6 9 miligramos 32 micromoles) en NMP (0 5 mililitros) se calienta a 100°C durante 1 hora y luego se deja agitándose a temperatura ambiente durante la noche La purificacion del producto mediante cromatografia en columna de fase inversa (Isolute^{MR} C18 acetonitrilo del 0 al 100 por ciento en agua-HCl al 0 1%) produce el compuesto del titulo [MH+ 691]

Ejemplo 80

N-((1S 2R 3S 4R)-4-{6-amino-2-[(R)-3-(3-piridin-3-il-ureido)-pirrolidin-1-il]-purin-9-il}-2 3-dihidroxiciclopentil)-propionamida

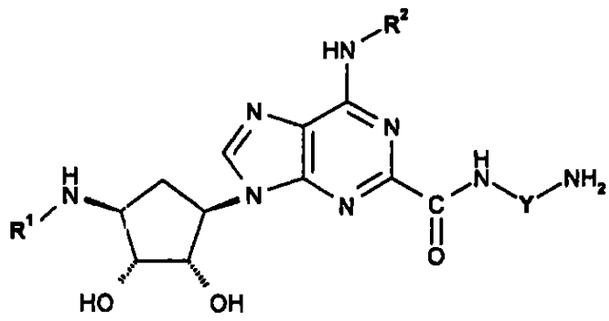
El siguiente compuesto se prepara de una manera análoga al trifluoroacetato de N-((1S 2R,3S,4R)-4-{6-

(1-etil-propionilamino)-2-[(R)-3-((R)-3-pirrolidin-3-il-ureido)-pirrolidin-1-il]-purin 9-il}-2 3-dihidroxiciclopentil)-propionamida (Ejemplo 54)

296
295

REIVINDICACIONES

1 Un compuesto de la Formula I



I

en forma libre o de sal en donde

R^1 es hidrógeno alquilcarbonilo de 1 a 8 átomos de carbono cicloalquilcarbonilo de 3 a 8 atomos de carbono, SO_2-alquilo de 1 a 8 atomos de carbono aralquilcarbonilo de 7 a 14 atomos de carbono o -C(=O)-C(=O)-NH-alquilo de 1 a 8 atomos de carbono opcionalmente sustituido con R^4

R^2 es hidrógeno o alquilo de 1 a 8 atomos de carbono opcionalmente sustituido con arilo de 6 a 10 átomos de carbono

R^3 es hidrogeno halogeno alquenilo de 2 a 8 atomos de carbono o alquinilo de 2 a 8 atomos de carbono

o R^3 es amino opcionalmente sustituido con cicloalquilo de 3 a 8 átomos de carbono opcionalmente sustituido con amino,

o R^3 es alquilamino de 1 a 8 átomos de carbono opcionalmente sustituido con hidroxilo arilo de 6 a 10

297
296

atomos de carbono o R^5

o R^3 es R^6 opcionalmente sustituido con amino o NH-C(=O)-NH-R^7

o R^3 es -NH-R^6 opcionalmente sustituido con -NH-C(=O)-NH-R^7

o R^3 es alquilaminocarbonilo de 1 a 8 átomos de carbono, o cicloalquilaminocarbonilo de 3 a 8 atomos de carbono, opcionalmente sustituido con amino alquilamino de 1 a 8 atomos de carbono dialquilamino de 1 a 8 átomos de carbono o -NH-C(=O)-NH-R^8

R^4 R^5 y R^6 son independientemente un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrógeno oxígeno y azufre, estando este anillo heterociclico de 5 o 6 miembros opcionalmente sustituido con halogeno ciano oxo hidroxilo carboxilo amino nitro, alquilo de 1 a 8 átomos de carbono alquilsulfonilo de 1 a 8 átomos de carbono, aminocarbonilo alquilcarbonilo de 1 a 8 atomos de carbono o alcoxilo de 1 a 8 átomos de carbono opcionalmente sustituido con aminocarbonilo, y

R^7 y R^8 son independientemente un anillo heterociclico de 5 c 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrogeno, oxigeno y azufre, estando este anillo heterociclico de 5 o 6 miembros opcionalmente sustituido con

halogeno ciano, oxo, hidroxilo, carboxilo amino, nitro, alquilo de 1 a 8 átomos de carbono alquilsulfonilo de 1 a 8 atomos de carbono aminocarbonilo alquilcarbonilo de 1 a 8 atomos de carbono, alcoxilo de 1 a 8 atomos de carbono opcionalmente sustituido con aminocarbonilo o un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrógeno oxígeno y azufre estando este anillo tambien opcionalmente sustituido con halogeno ciano oxo hidroxilo carboxilo amino nitro alquilo de 1 a 8 atomos de carbono alquilsulfonilo de 1 a 8 atomos de carbono, aminocarbonilo alquilcarbonilo de 1 a 8 atomos de carbono alcoxilo de 1 a 8 atomos de carbono opcionalmente sustituido con aminocarbonilo

2 Un compuesto de acuerdo con la reivindicacion 1 en donde

R^1 es alquilcarbonilo de 1 a 8 atomos de carbono cicloalquilcarbonilo de 3 a 8 atomos de carbono $-SO_2$-alquilo de 1 a 8 átomos de carbono aralquilcarbonilo de 7 a 14 átomos de carbono o -C(=O)-C(=O)-NH-alquilo de 1 a 8 atomos de carbono opcionalmente sustituido con R^4

R^2 es hicrógeno o alquilo de 1 a 8 átomos de carbono opcionalmente sustituido con arilo de 6 a 10 atomos de carbono

R^3 es halógeno o alquinilo de 2 a 8 atomos de carbono

o R^3 es amino opcionalmente sustituido con cicloalquilo de 3 a 8 átomos de carbono opcionalmente sustituido con amino

o R^3 es alquilamino de 1 a 8 átomos de carbono opcionalmente sustituido con hidroxilo arilo de 6 a 10 atomos de carbono o R^5

o R^3 es R^6 opcionalmente sustituido con amino o -NH-C(=O)-NH-R^7

o R^3 es -NH-R^6 opcionalmente sustituido con -NH-C(=O)-NH-R^7,

o R^3 es alquilaminocarbonilo de 1 a 8 atomos de carbono opcionalmente sustituido con -NH-C(=O)-NH-R^8

R^4, R^5 y R^6 son independientemente un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrogeno oxigeno y azufre, estando este anillo heterociclico de 5 o 6 miembros opcionalmente sustituido con alquilo de 1 a 8 atomos de carbono y

R^7 y R^8 son independientemente un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrogeno oxigeno y azufre estando este anillo heterociclico de 5 ó 6 miembros opcionalmente sustituido con

360
299

halógeno alquilo de 1 a 8 atomos de carbono alquilsulfonilo de 1 a 8 atomos de carbono o un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrógeno oxigeno y azufre

3 Un compuesto de acuerdo con la reivindicación 1 en donde

R^1 es alquilcarbonilo de 1 a 4 átomos de carbono cicloalquilcarbonilo de 3 a 5 atomos de carbono $-SO_2$-alquilo de 1 a 4 atomos de carbono, aralquilcarbonilo de 7 a 10 átomos de carbono, o -C(=O)-C(=O)-NH-alquilo de 1 a 4 atomos de carbono opcionalmente sustituido en una posicion con R^4,

R^2 es hidrogeno alquilo de 1 a 6 atomos de carbono no sustituido o alquilo de 1 a 5 átomos de carbono sustituido en una posición con arilo de 6 a 10 átomos de carbono

R^3 es halógeno o alquinilo de 2 a 6 átomos de carbono

o R^3 es amino opcionalmente sustituido en una posicion con cicloalquilo de 3 a 6 átomos de carbono opcionalmente sustituido en una posición con amino,

o R^3 es alquilamino de 1 a 4 átomos de carbono sustituido en una o dos posiciones con hidroxilo, fenilo, o R^5,

o R^3 es R^6 opcionalmente sustituido en una posicion con amino o -NH-C(=O)-NH-R^7

o R^3 es -NH-R^6 opcionalmente sustituido en una posicion con -NH-C(=O)-NH-R^7

o R^3 es alquilaminocarbonilo de 1 a 4 atomos de carbono sustituido en una posicion con -NH-C(=O)-NH-R^8

R^4, R^5, y R^6 son independientemente un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrógeno, oxígeno y azufre, estando este anillo heterociclico de 5 o 6 miembros opcionalmente sustituido en una posicion con alquilo de 1 a 4 átomos de carbono, y

R^7 y R^8 son independientemente un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrogeno oxigeno y azufre estando este anillo heterociclico de 5 ó 6 miembros opcionalmente sustituido en una o dos posiciones con halogeno, alquilo de 1 a 4 atomos de carbono alquilsulfonilo de 1 a 4 atomos de carbono o un anillo N-heterociclico de 5 ó 6 miembros

4 Un compuesto de acuerdo con la reivindicación 1 en donde

R^1 es hidrogeno alquilcarbonilo de 1 a 8 atomos de carbono cicloalquilcarbonilo de 3 a 8 atomos de carbono

$-SO_2$-alquilo de 1 a 3 atomos de carbono aralquilcarbonilo de 7 a 14 atomos de carbono, o -C(=O)-C(=O)-NH-alquilo de 1 a 8 atomos de carbonc opcionalmente sustituido con R^4,

R^2 es hidrogeno o alquilo de 1 a 8 átomos de carbono opcionalmente sustituido con arilo de 6 a 10 atomos de carbono

R^3 es hicrógeno halogeno alquenilo de 2 a 8 atomos de carbono, o alquinilo de 2 a 8 átomos de carbono

o R^3 es amino opcionalmente sustituido con cicloalquilo de 3 a 8 atomos de carbono opcionalmente sustituido con amino,

o R^3 es alquilamino de 1 a 8 átomos de carbono opcionalmente sustituido con hidroxilo arilo de 6 a 10 atomos de carbono o R^5

o R^3 es R^6 opcionalmente sustituido con amino o -NH-C(=O)-NH-R^7

o R^3 es alquilaminocarbonilo de 1 a 8 atomos de carbono o cicloalquilaminocarbonilo de 3 a 8 átomos de carbono opcionalmente sustituido con amino, alquilamino de 1 a 8 atomos de carbono dialquilamino de 1 a 8 atomos de carbono o -NH-C(=O)-NH-R^8

R^4, R^5, y R^6 son independientemente un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrógeno oxigeno y azufre, y

R^7 y R^8 son independientemente un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrogeno oxígeno y azufre, estando este anillo heterociclico de 5 ó 6 miembros opcionalmente sustituido con un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrógeno, oxígeno y azufre

5 Un compuesto de acuerdo con la reivindicacion 4, en donde

R^1 es alquilcarbonilo de 1 a 8 átomos de carbono cicloalquilcarbonilo de 3 a 8 atomos de carbono $-SO_2$-alquilo de 1 a 8 atomos de carbono aralquilcarbonilo de 7 a 14 atomos de carbono o -C(=O)-C(=O)-NH-alquilo de 1 a 8 átomos de carbono opcionalmente sustituido con R_4,

R^2 es hidrógeno o alquilo de 1 a 8 átomos de carbono opcionalmente sustituido con arilo de 6 a 10 atomos de carbono

R^3 es halogeno o alquinilo de 2 a 8 atomos de carbono

o R^3 es amino opcionalmente sustituido con cicloalquilo de 3 a 8 átomos de carbono opcionalmente sustituido con amino

o R^3 es alquilamino de 1 a 8 átomos de carbono

opcionalmente sustituido con hidroxilo arilo de 6 a 10 atomos de carbono o R^5

o R^3 es R^6 opcionalmente sustituido con amino o -NH-C(=O)-NH-R^7

o R^3 es -NH-R^8 opcionalmente sustituido con -NH-C(=O)-NH-R^7

o R^3 es alquilaminocarbonilo de 1 a 8 átomos de carbono opcionalmente sustituido con -NH-C(=O)-NH-R^8

R^4 R^5 y R^6 son independientemente un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrogeno oxigeno y azufre, y

R^7 y R^8 son independientemente un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrogeno oxigeno y azufre estando este anillo heterociclico de 5 ó 6 miembros opcionalmente sustituido con un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrógeno oxígeno y azufre

6 Un compuesto de acuerdo con la reivindicacion 5 en donde

R^1 es alquilcarbonilo de 1 a 4 atomos de carbono cicloalquilcarbonilo de 3 a 6 atomos de carbono -SO_2-alquilo

de 1 a 4 atomos de carbono aralquilcarbonilo de 7 a 10 átomos de carbono o -C(=O)-C(=O)-NH-alquilo opcionalmente sustituido en con R^4

R^2 es hidrogeno o alquilo de 1 a 6 atomos de carbono opcionalmente sustituido con arilo de 6 a 10 atomos de carbono

R^3 es halógeno o alquinilo de 2 a 5 atomos de carbono

o R^3 es amino opcionalmente sustituido con cicloalquilo de 3 a 8 átomos de carbono opcionalmente sustituido con amino

o R^3 es alquilamino de 1 a 4 átomos de carbono opcionalmente sustituido con hidroxilo arilo de 6 a 8 átomos de carbono o R^5

o R^3 es R^6 opcionalmente sustituido con amino o -NH-C(=O)-NH-R^7

o R^3 es alquilaminocarbonilo de 1 a 4 átomos de carbono opcionalmente sustituido con -NH-C(=O)-NH-R^8

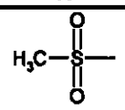
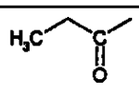
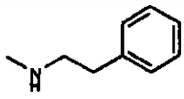
R^4, R^5 y R^6 son independientemente un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrogeno, oxigeno y azufre y

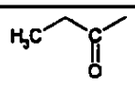
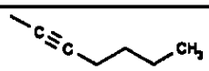
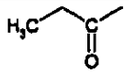
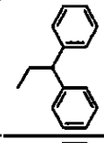
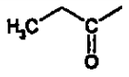
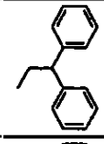
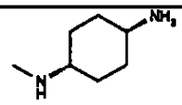
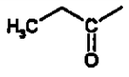
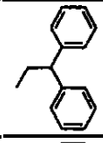
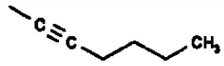
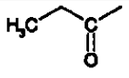
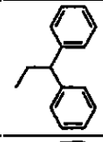
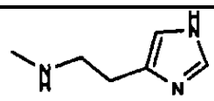
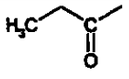
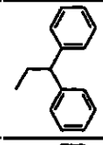
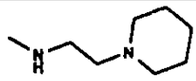
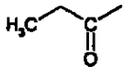
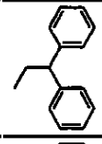
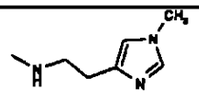
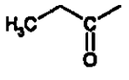
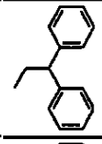
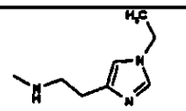
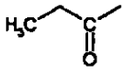
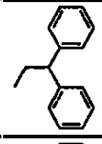
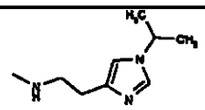
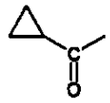
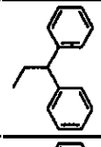
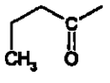
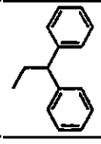
R^7 y R^8 son independientemente un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que

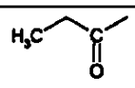
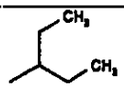
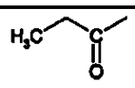
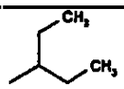
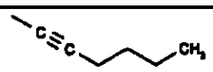
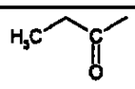
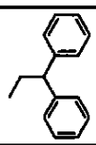
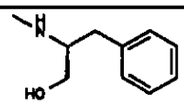
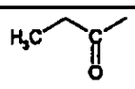
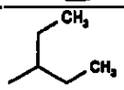
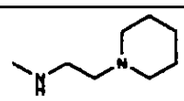
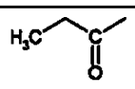
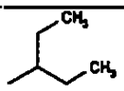
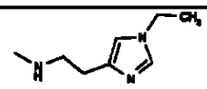
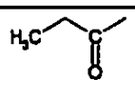
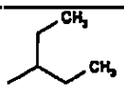
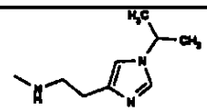
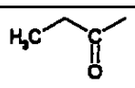
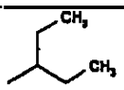
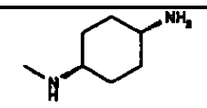
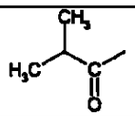
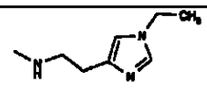
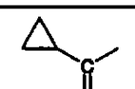
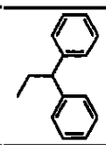
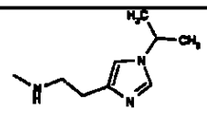
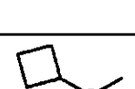
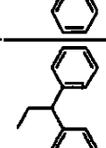
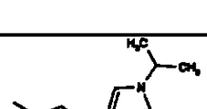
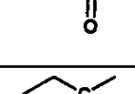
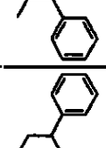
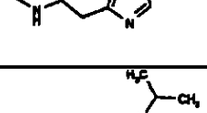
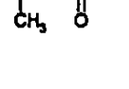
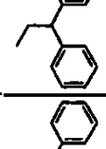
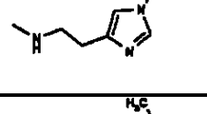
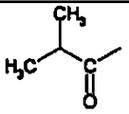
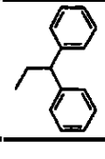
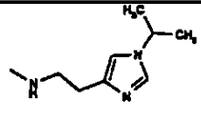
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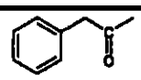
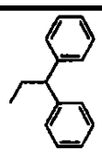
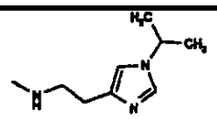
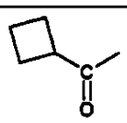
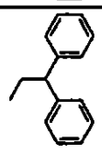
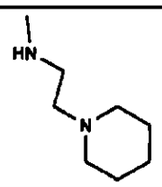
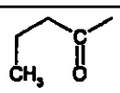
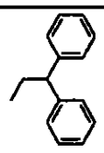
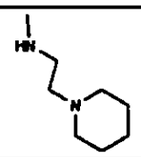
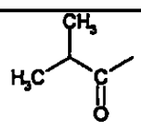
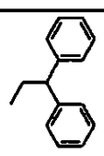
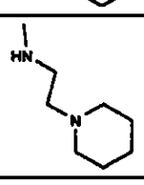
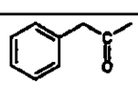
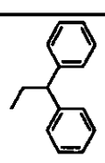
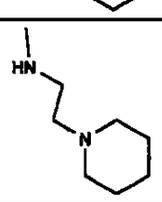
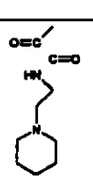
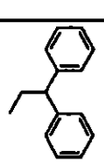
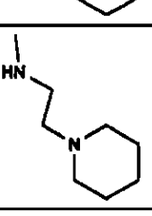
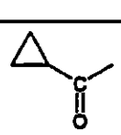
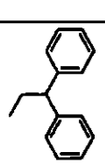
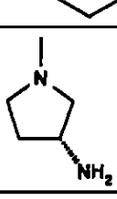
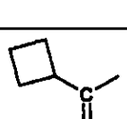
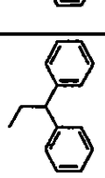
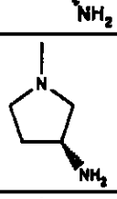
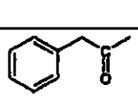
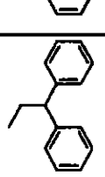
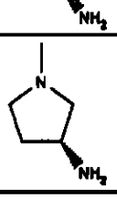
consiste de nitrógeno oxigeno y azufre estando este anillo heterociclico de 5 o 6 miembros opcionalmente sustituido con un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrógeno, oxigeno y azufre

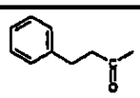
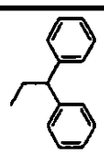
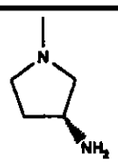
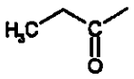
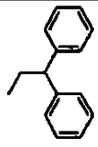
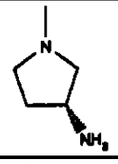
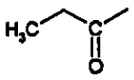
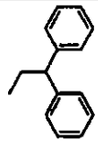
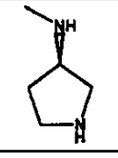
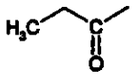
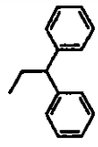
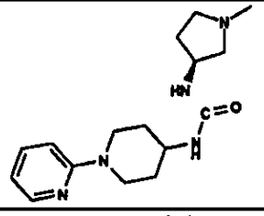
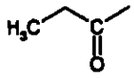
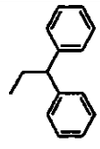
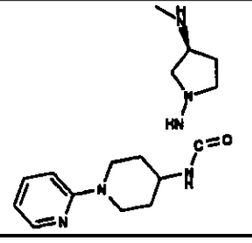
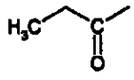
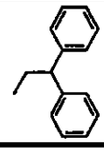
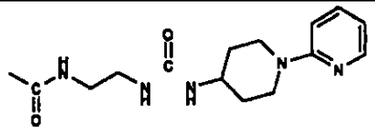
7 Un compuesto de la Formula I de acuerdo con la reivindicacion 1, en donde R^1 R^2 y R^3 son como se muestran en las siguientes tablas

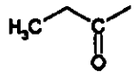
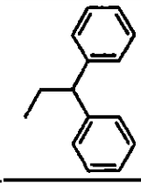
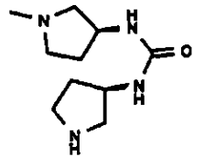
R^1	R^2	R^3
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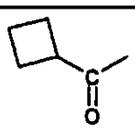
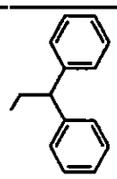
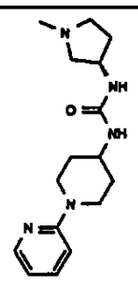
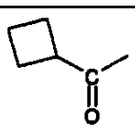
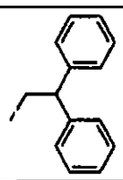
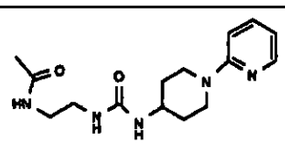
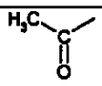
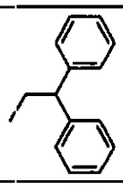
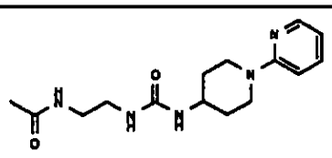
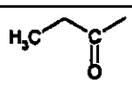
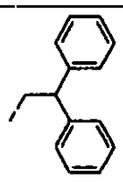
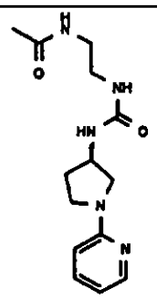
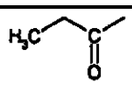
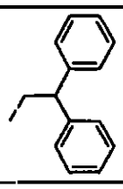
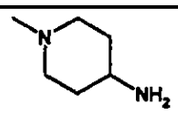
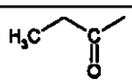
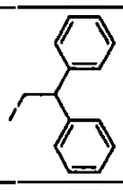
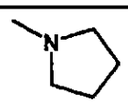
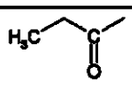
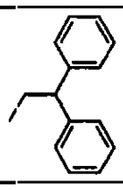
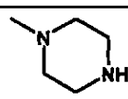
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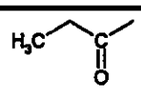
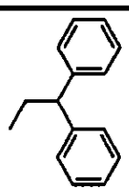
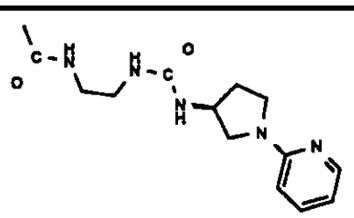
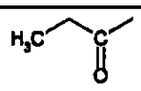
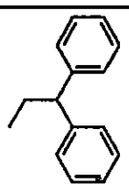
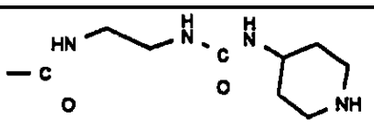
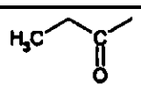
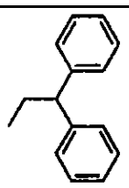
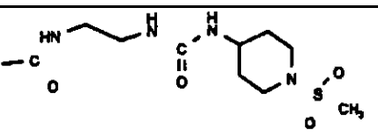
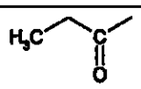
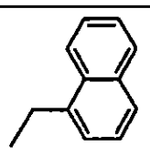
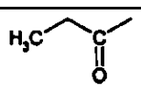
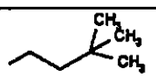
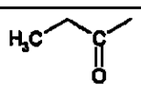
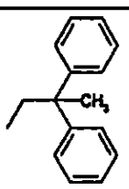
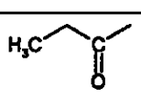
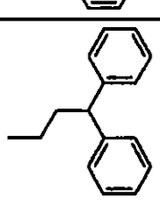
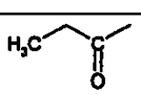
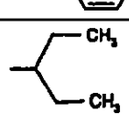
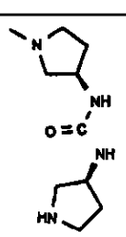
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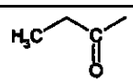
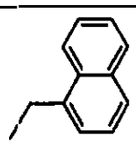
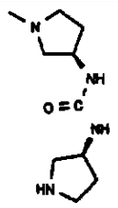
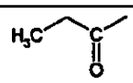
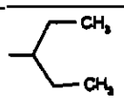
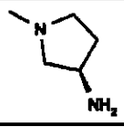
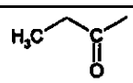
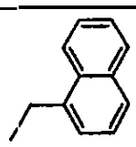
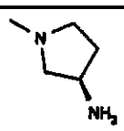
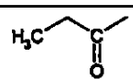
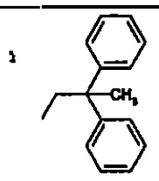
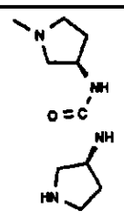
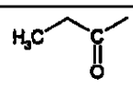
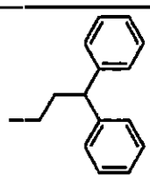
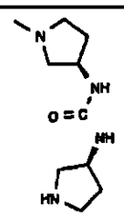
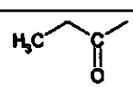
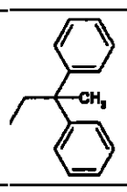
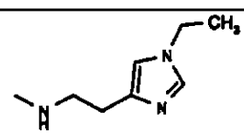
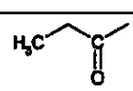
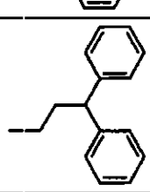
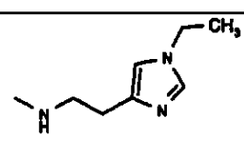
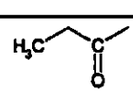
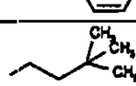
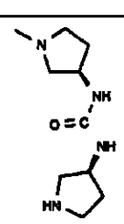
		
		
		
		
		
		
		
		
		

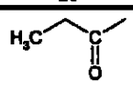
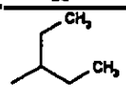
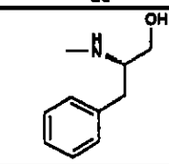
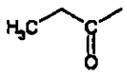
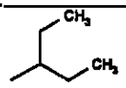
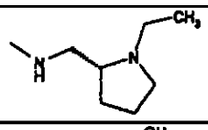
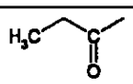
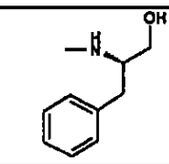
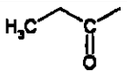
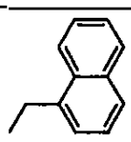
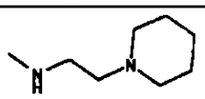
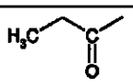
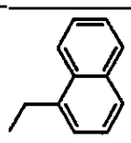
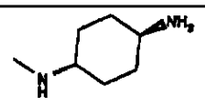
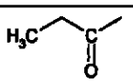
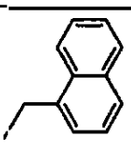
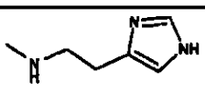
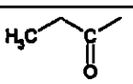
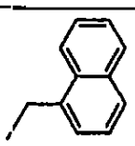
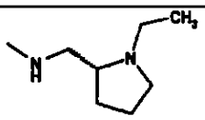
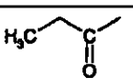
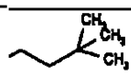
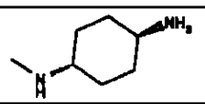
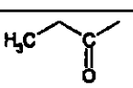
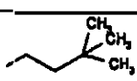
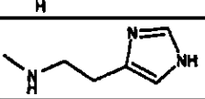
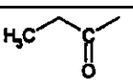
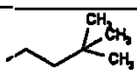
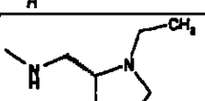
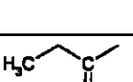
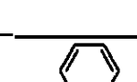
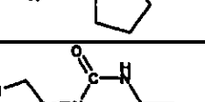
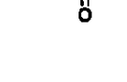
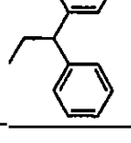
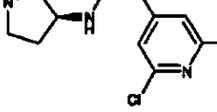
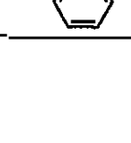
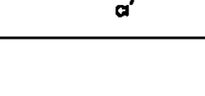
		
		
		
		
		
		

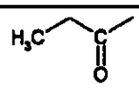
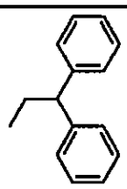
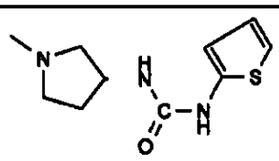
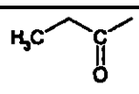
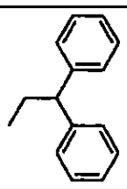
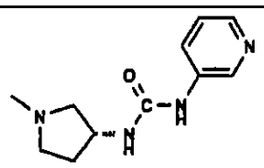
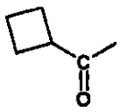
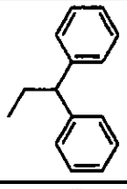
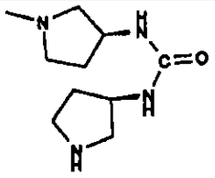
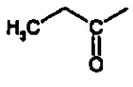
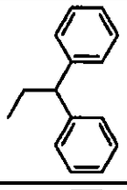
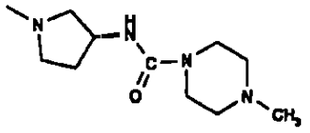
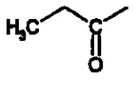
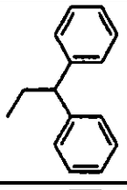
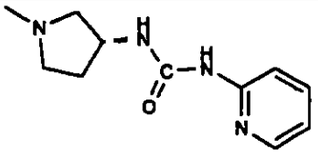
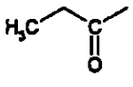
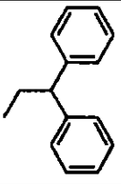
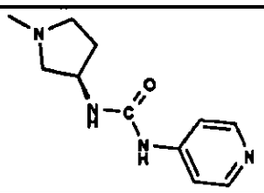
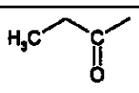
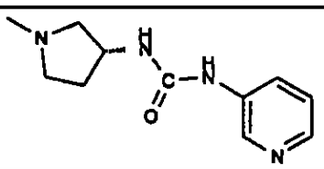
R¹	R²	R³
		

		
		
		
		-Cl
		-Cl
		-Cl
		-Cl
		

R¹	R²	R³
		
		
	H	
		
		
		
		
		
		
		
		
		
		

		
		
		
		
		
		
	H	

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

9 Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 7, en combinación con un farmaco antiinflamatorio broncodilatador, antihistaminico, o antitusivo estando este compuesto y el farmaco en la misma composicion farmacéutica o en una diferente

10 Una composición farmaceutica que comprende como ingrediente activo, un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 7 opcionalmente junto con un diluyente o vehiculo farmacéuticamente aceptable

11 Una composicion farmaceutica de acuerdo con la reivindicación 10 la cual comprende ademas un farmaco antiinflamatorio broncodilatador antihistaminico o antitusivo

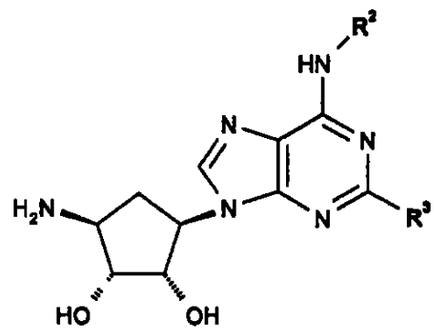
12 El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 7 para la fabricación de un medicamento para el tratamiento de una condicion mediada por la activación del receptor A_{2A} de adenosina

13 El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 7, para la fabricación de un medicamento para el tratamiento de una enfermedad inflamatoria u obstructiva de las vias respiratorias

14 Un metodo para la preparacion de un compuesto de la Formula I como se define en la reivindicacion 1 en forma libre o de sal el cual comprende

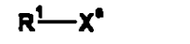
(i) (A) para la preparacion de compuestos de la

Formula I se hace reaccionar un compuesto de la Formula II



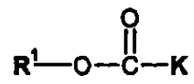
II

en donde R^2 y R^3 son como los definidos en la reivindicacion 1 con un compuesto de la Formula III



III

o de la Formula IIIa

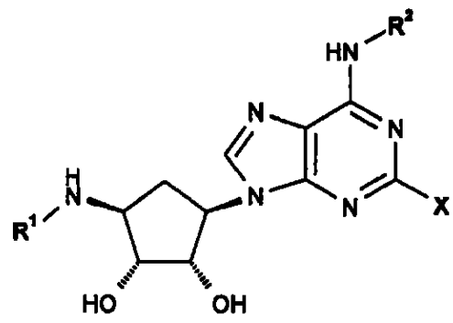


IIIa

en donde R^1 es hidrógeno, alquilcarbonilo de 1 a 8 átomos de carbono, cicloalquilcarbonilo de 3 a 8 átomos de carbono o aralquilcarbonilo de 7 a 14 átomos de carbono X^a es un grupo saliente, y K es hidrógeno alquilo de 1 a 8 atomos de carbono o alcoxilo de 1 a 8 atomos de carbono en presencia de una base,

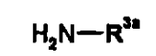
(B) para la preparación de compuestos de la Fórmula I en donde R^3 es amino sustituido con cicloalquilo de 3 a 8 átomos de carbono opcionalmente sustituido con amino o R^3 es alquilamino de 1 a 8 atomos de carbono opcionalmente sustituido con hidroxilo arilo de 6 a 10 atomos de carbono o R^5, o R^3 es R^8 opcionalmente sustituido con amino o -NH-C(=O)-NH-R^7 se hace reaccionar un

compuesto de la Fórmula IV

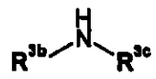


IV

en donde R^1 y R^2 son como los definidos en la reivindicacion 1, y X es halogeno con un compuesto de la Formula Va o de la Formula Vb



Va

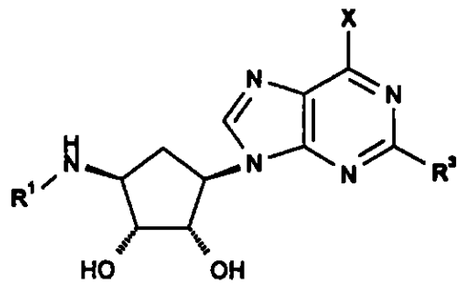


Vb

en donde R^{3a} es cicloalquilo de 3 a 8 atomos de carbono opcionalmente sustituido con amino o R^3 es alquilo de 1 a 8 atomos de carbono opcionalmente sustituido con hidroxilo arilo de 6 a 10 átomos de carbono, o R^5, en donde R^5 es como el definido en la reivindicacion 1 y

R^{3b} y R^{3c} forman juntos un anillo heterociclico de 5 o 6 miembros que contiene uno o mas atomos de nitrogeno y está opcionalmente sustituido con amino o -NH-C(=O)-NH-R^7 en donde R^7 es como el definido en la reivindicación 1

(C) para la preparacion de compuestos de la Formula I se hace reaccionar un compuesto de la Formula VI



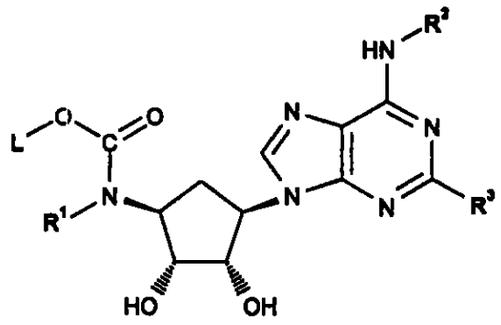
VI

en donde R^1 y R^3 son como los definidos en la reivindicación 1 y X es halogeno con un compuesto de la Formula VII

$$H_2N—R^2 \qquad \text{VII}$$

en donde R^2 es como el definido en la reivindicacion 1 en presencia de una base,

(D) para la preparación de compuestos de la Formula I se desprotege un compuesto de la Fórmula VIII

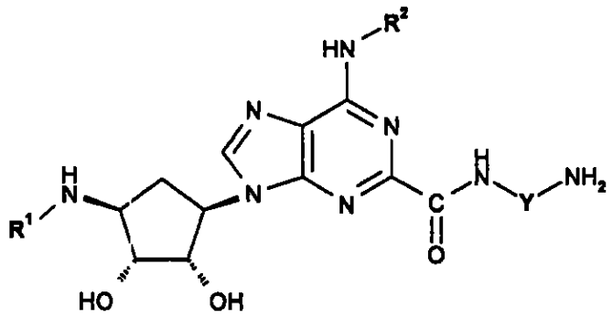


VIII

en donde R^1, R^2 y R^3 son como los definidos en la reivindicacion 1 y L es alquilo de 1 a 8 atomos de carbono

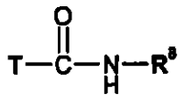
(E) para la preparacion de compuestos de la Formula I en donde R^3 es alquilaminocarbonilo de 1 a 8 atomos de carbono o cicloalquilaminocarbonilo de 3 a 8

átomos de carbono sustituido con -NH-C(=O)-NH-R^8, en donde R^8 es como el definido en la reivindicación 1, se hace reaccionar un compuesto de la Formula IX



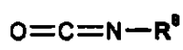
IX

en donde R^1 y R^2 son como los definidos en la reivindicación 1 y Y es alquilo de 1 a 8 atomos de carbono, o cicloalquilo de 3 a 8 atomos de carbono en presencia de una base ya sea con un compuesto de la Fórmula X



X

o bien, con un compuesto de la Formula XI



XI

en donde T es ariloxi de 6 a 10 átomos de carbono o un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrogeno, oxigeno y azufre, y R^8 es como el definido en la reivindicacion 1

(F) para la preparacion de compuestos de la Fórmula I en donde R^3 es alquinilo de 2 a 8 átomos de carbono se hace reaccionar un compuesto de la Formula IV

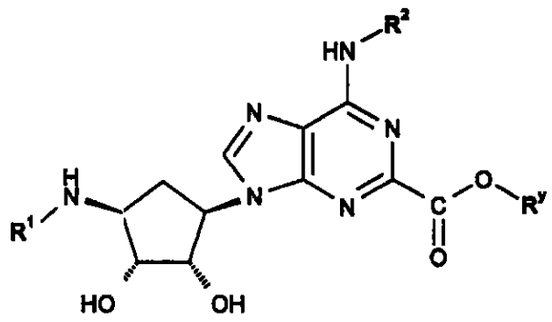
320
321

en donde R^1 y R^2 son como los definidos en la reivindicacion 1 con un compuesto de la Fórmula XII

$$R^x—C\equiv C—H \qquad \textbf{XII}$$

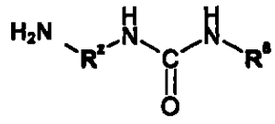
en donde R^x es alquilo de 1 a 8 átomos de carbono en presencia de una base y un catalizador

(G) para la preparacion de compuestos de la Formula I en donde R^3 es alquilaminocarbonilo de 1 a 8 atomos de carbono opcionalmente sustituido con -NH-C(=O)-NH-R^8 se hace reaccionar un compuesto de la Formula XIIa



XIIa

en donde R^1 y R^2 son como los definidos en la reivindicacion 1 y R^y es alquilo de 1 a 8 átomos de carbono opcionalmente en presencia de una base con un compuesto de la Formula XIIb

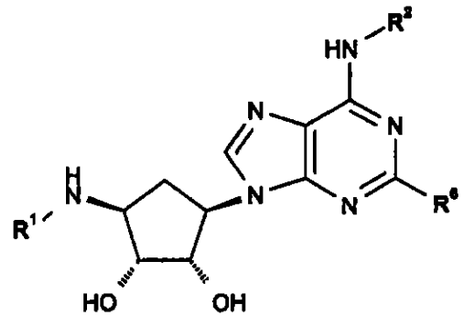


XIIb

en donde R^z es alquilo de 1 a 8 atomos de carbono y -NH-C(=O)-NH-R^8 es como el definido en la reivindicación 1, o

(H) para la preparacion de compuestos de la Formula I en donde R^3 es alquilaminocarbonilo de 1 a 8 atomos de carbono sustituido con -NH-C(=O)-NH-R^8, en donde R^8 es un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrogeno oxigeno y azufre estando ese anillo sustituido con alquilsulfonilo de 1 a 8 átomos de carbono se hace reaccionar un compuesto de la Fórmula I en donde R^3 es alquilaminocarbonilo de 1 a 8 átomos de carbono sustituido con -NH-C(=O)-NH-R^8, en donde R^8 es un anillo heterocíclico de 5 ó 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrogeno, oxigeno y azufre con un agente de sulfonilación en presencia de una base

(I) para la preparacion de compuestos de la Formula I en donde R^3 es R^6 sustituido con -NH-C(=O)-NH-R^7 en donde R^7 es como el definido en la reivindicacion 1, se hace reaccionar un compuesto de la Formula XIIc

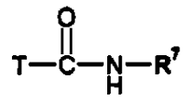


XIIc

en donde R^1 y R^2 son como los definidos en la

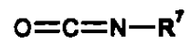
322
323

reivindicación 1 y R^6 es un anillo heterocíclico de 5 o 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrogeno oxigeno y azufre, sustituido en una posicion con amino ya sea con un compuesto de la Fórmula Xa



Xa

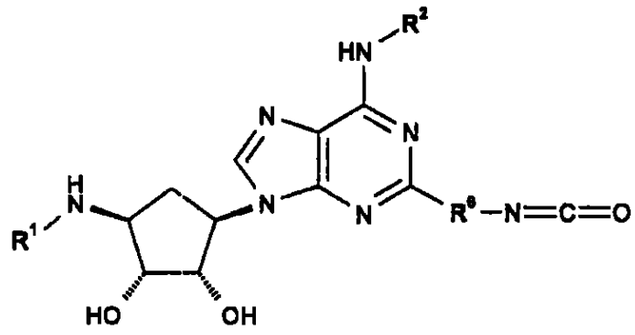
o bien, con un compuesto de la Fórmula XIa



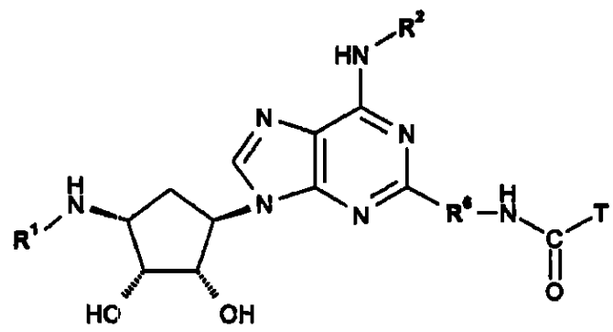
XIa

en donde T es ariloxi de 6 a 10 átomos de carbono o un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrógeno oxígeno y azufre, y R^8 es como el definido en la reivindicacion 1

(J) para la preparacion de compuestos de la Formula I en donde R^3 es R^6 sustituido con -NH-C(=O)-NH-R^7 en donde R^7 es como el definido en la reivindicacion 1 se hace reaccionar un compuesto de la Formula XIId o XIIe o una forma protegida del mismo

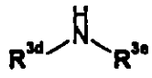


XIId



XIIe

en donde R^1 R^2 y R^6 son como los definidos en la reivindicacion 1 y T es ariloxi de 6 a 10 átomos de carbono o un anillo heterocíclico de 5 o 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrógeno, oxigeno y azufre, con un compuesto de la Formula XIIf



XIIf

y en donde R^{3d} y R^{3e} forman juntos un anillo N-heterociclico de 5 o 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrogeno, oxigeno y azufre, estando este anillo heterociclico de 5 ó 6 miembros opcionalmente sustituido con halógeno ciano oxo hidroxilo, carboxilo amino nitro, alquilo de 1 a 8 átomos de carbono alquilsulfonilo de 1 a 8 atomos de carbono, aminocarbonilo alquilcarbonilo de 1 a 8 atomos de carbono alcoxilo de 1 a 8 átomos de carbono opcionalmente sustituido con aminocarbonilo o un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que

consiste de nitrógeno, oxigeno y azufre, o

(K) para la preparación de compuestos de la Fórmula I en donde R^3 es R^6 sustituido con -NH-C(=O)-NH-R^7 en donde R^7 es como el anteriormente definido, se hace reaccionar un compuesto de la Formula XIId ó XIIe en donde R^1 R^2 y R^6 son como los definidos en la reivindicacion 1 y T es ariloxi de 6 a 10 atomos de carbono o un anillo heterociclico de 5 o 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrogeno, oxigeno y azufre con un compuesto de la Formula XIIg

$$H_2N—R^7 \qquad \textbf{XIIg}$$

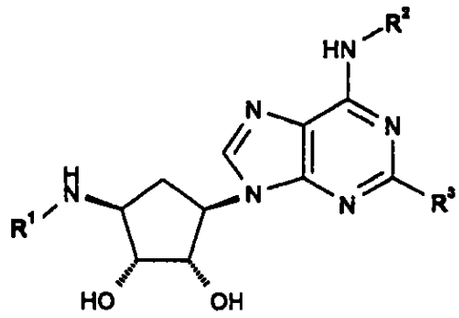
en donde R^7 es como el definido en la reivindicación 1 y

(ii) remover cualesquiera grupos protectores y recuperar el compuesto resultante de la Formula Ia, en forma libre o de sal

325
326

RESUMEN

Los compuestos de la Fórmula I



I

en forma libre o de sal en donde R^1, R^2 y R^3 tienen los significados indicados en la presente descripcion son utiles para el tratamiento de condiciones mediadas por la activación del receptor A_{2A} de adenosina en especial enfermedades inflamatorias u obstructivas de las vias respiratorias Tambien se describen composiciones farmaceuticas que contienen a los compuestos y un proceso para la preparación de los compuestos

* * * * *

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis 1 and Administrative Instructions Section 422)

To

DE WEERD, Peter
Novartis AG
Corporate Intellectual Property
CH 4002 Basel
Switzerland

Date of mailing (day/month/year) 04 April 2006 (04 04 2006)	
Applicant s or agent s file reference PR/4 34005A/HO 1	**IMPORTANT NOTIFICATION**
International application No PCT/EP2005/011344	**International filing date (day/month/year)** 21 October 2005 (21 10 2005)

1 The following indications appeared on record concerning

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No	
	Facsimile No	
	Teleprinter No	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
SINGH Paul Novartis Horsham Research Centre Wimblehurst Road Horsham, West Sussex RH12 5AB United Kingdom	GB	GB
	Telephone No	
	Facsimile No	
	Teleprinter No	

3 Further observations if necessary

The person identified in Box 2 has been recorded as additional applicant for US only and inventor for all designated states

4 A copy of this notification has been sent to

[X] 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**	**Authorized officer** Frédéric SONTAG (Fax 338 8970)
Facsimile No (41 22) 338 89 70	Telephone No (41 22) 338 8391

Form PCT/IB/306 (March 1994) 006930583

INTERNATIONAL SEARCH REPORT

International application No
[redacted]/EP2005/011344

A CLASSIFICATION OF SUBJECT MATTER
C07D473/16 C07D473/32 C07D473/40 A61K31/52 A61P29/00

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, PAJ, WPI Data, CHEM ABS Data

C DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate of the relevant passages	Relevant to claim No
P,X	M YANG ET AL "amino substituted derivatives of 5'-amino-5'-deoxy-5'-noraristeromycin' BIOROGANIC & MEDICINAL CHEMISTRY, vol 13, no 3, 2005, pages 877-882, XP002364403 page 877, compound 5, page 878, chapter "antiviral results"	1,4,10
X	M COWART ET AL "Synthesis of novel carboxyclic adenosine analogs as inhibitors of adenosine kinase" JOURNAL OF ORGANIC CHEMISTRY, vol 64, no 7, 1999, pages 2240-2249, XP002364404 page 2242, figure 2, compound 6, page 2245, chapter "conclusions"	1,4 10

-/--

[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
25 January 2006	17/02/2006

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	Schmid, A

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/011344

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication where appropriate of the relevant passages	Relevant to claim No.
A	EP 1 221 444 A (EISAI CO , LTD) 10 July 2002 (2002-07-10) cited in the application page 3, line 5 - page 3, line 10, claims, examples 1-63	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2005/011344

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1221444 A	10-07-2002	AT 303387 T	15-09-2005
		AU 778450 B2	09-12-2004
		AU 5571700 A	22-01-2001
		CA 2376835 A1	11-01-2001
		CN 1365361 A	21-08-2002
		DE 60022366 D1	06-10-2005
		DK 1221444 T3	14-11-2005
		WO 0102400 A1	11-01-2001
		NZ 516260 A	27-08-2004
		PT 1221444 T	30-11-2005
		US 6841549 B1	11-01-2005

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No 07-039105- -00000-0000
Fecha 2007 04 19 16 35 44 Dep 2020 NUECREACION
Tra 11 PATENTEIYII Eve 378 FASENACIONALI
Act 411 PRESENTACION Folios 329

331

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- ◇ Indicación de que se solicita la concesión de una patente [ ]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◇ Descripción de la invención [ ]
- ◇ Dibujos de ser estos pertinentes [ ]
- ◇ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- ◇ Indicación de que se solicita el registro de Diseño Industrial [ ]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◇ Representacion grafica 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 [ ]

- ◇ Indicacion de que se solicita el registro de un Esquema de Trazado [ ]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◇ Representacion grafica del esquema trazado [ ]
- ◇ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

_____
Firma Responsable

Fecha 19 ABR. 2007

Carrera 13 No 27-00 Piso 5 7 y 10
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332

Industria y Comercio
SUPERINTENDENCIA

[redacted]
No 07 039105- -00000-0000
Fecha 2007-04 19 16 35 44 Dep 2020 NUECREACION
Tra 11 PATENTES Eve 378 FASENACIONALI
Act 411 PRESENTACION Folios 329

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL
SOLICITUD DE

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

[X] Capítulo I [ ] Capítulo II

(2) **SOLICITANTE (71)**

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Lugar de Constitución Suiza
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E-mail _____

IDENTIFICACIÓN
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C E [ ] **Otro** [ ]
Cual _____
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C E [ ] **Otro** [ ]
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Número 79782747Bta
TP 74 295

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Dirección VER PAGINA ADJUNTA
Nacionalidad o Domicilio VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No PCT/EP2005/011344 Fecha Octubre 21, 2005

Publicación Internacional No WO 2006/045552 Fecha Mayo 4 2006

(6) **Título (54)** **DERIVADOS DE PURINA PARA USARSE COMO AGONISTAS DE RECEPTORES DE A-2A DE ADENOSIN**

Clasificación Internacional (51) C07D 473/16, C07D 473/32, C07D 473/40, A61K 31/52 A61P 29/00

Prioridad SI [X] NO [ ]

	(33) País de Origen	(32) Fecha	(31) Numero de Solicitud
	GB	Octubre 22, 2004	0423551 1
	GB	Julio 15 2005	0514619 6

(9) **Comprobante de pago No** 07-29 608 **Fecha** 13 de Abril de 2007

B

LISTA DE INVENTORES PCT/EP2005/011344

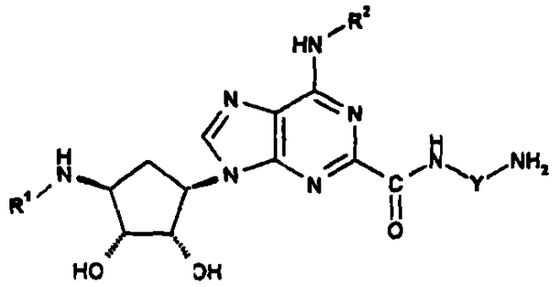
1 **ROBIN ALEC FAIRHURST**
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2 **ROGER JOHN TAYLOR**
Wimblehurst Road, Horsham,
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3 **PAUL SINGH**
Wimblehurst Road, Horsham,
West Sussex RH12 5AB
Gran Bretaña
Nacionalidad Británica

REIVINDICACIONES

1 Un compuesto de la Fórmula I



I

en forma libre o de sal, en donde

R^1 es hidrógeno alquilcarbonilo de 1 a 8 atomos de carbono cicloalquilcarbonilo de 3 a 8 átomos de carbono SO_2 alquilo de 1 a 8 átomos de carbono aralquilcarbonilo de 7 a 14 átomos de carbono, o -C(=O)-C(=O)-NH-alquilo de 1 a 8 atomos de carbono, opcionalmente sustituido con R^4

R^2 es hidrógeno o alquilo de 1 a 8 átomos de carbono opcionalmente sustituido con arilo de 6 a 10 átomos de carbono

R^3 es hidrógero halógeno alquenilo de 2 a 8 átomos de carbono o alquinilo de 2 a 8 atomos de carbono

o R^3 es amino opcionalmente sustituido con cicloalquilo de 3 a 8 átomos de carbono opcionalmente sustituido con amino,

o R^3 es alquilamino de 1 a 8 átomos de carbono opcionalmente sustituido con hidroxilo arilo de 6 a 10

átomos de carbono o R^5

o R^3 es R^6 opcionalmente sustituido con amino o -NH-C(=O)-NH-R^7

o R^3 es NH-R^6 opcionalmente sustituido con NH-C(=O) NH-R^7

o R^3 es alquilaminocarbonilo de 1 a 8 átomos de carbono o cicloalquilaminocarbonilo de 3 a 8 átomos de carbono opcionalmente sustituido con amino alquilamino de 1 a 8 atomos de carbono dialquilamino de 1 a 8 átomos de carbono o NH-C(=O)-NH-R^8

R^4 R^5 y R^6 son independientemente un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroátomo del anillo que se selecciona del grupo que consiste de nitrógeno oxigeno y azufre estando este anillo heterociclico de 5 o 6 miembros opcionalmente sustituido con halogeno ciano oxo hidroxilo carboxilo, amino nitro alquilo de 1 a 8 atomos de carbono alquilsulfonilo de 1 a 8 átomos de carbono, aminocarbonilo alquilcarbonilo de 1 a 8 átomos de carbono, o alcoxilo de 1 a 8 átomos de carbono opcionalmente sustituido con aminocarbonilo y

R^7 y R^8 son independientemente un anillo heterociclico de 5 ó 6 miembros que contiene cuando menos un heteroatomo del anillo que se selecciona del grupo que consiste de nitrógeno oxigeno y azufre estando este anillo heterociclico de 5 ó 6 miembros opcionalmente sustituido con

336

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
NOVARTIS AG

REFERENCIA	Radicación No	7 39105
	Solicitud internacional	PCT/EP2005/011344
	Fecha inicio fase nacional	22/05/2007
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No	10134

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que

1 La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante (Art 26-k) Decisión 486 Cuando se trate de documentos otorgados en el extranjero, deben legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio complete los requisitos anteriormente enunciados En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5 2, literal e), del capítulo quinto del título primero de la Circular Unica No 10 de 2001

ALIX CARMENZA ESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento ue notificado por fijación en lista de fecha 24 AGO 2007
adpa11