Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

PCT

21. **EXPEDIENTE No.** 04-52218

54. **TÍTULO** forma de farmaco cristalina

51. **CLASIFICACIÓN INTERNACIONAL** A 61 K 3/70

71. **SOLICITANTE** Pfizer Inc

DOMICILIO 235 East 42nd Street, new York. NY 10017. E.U.A.

74. **APODERADO** Carlos E. Olarte

22. **BOGOTÁ, D. C.,** Junio 4- de 2004

(FORMA P-10)

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04052218 [illegible] Folios: 113
Fecha (AMD): 2004-06-04 09:43:38
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Consecutivo: 2020 DIVISION DE NUEVAS CREACIONES

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

SOLICITUD DE:

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

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**	**Nombre:** PFIZER INC **Dirección:** 235 East 42nd Street, New York, NY 10017 E.U.A. **Nacionalidad o Domicilio:** ESTADOUNIDENSE **Lugar de Constitución:** Delaware, Estados Unidos de América. **Teléfono:** _____ **Fax:** _____ **E-mail:** _____	**IDENTIFICACIÓN** C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] Cual _____ Número _____
REPRESENTANTE APODERADO	**Nombre:** CARLOS R. OLARTE **Dirección:** Wold Trade Center Torre A, Calle 100 No. 8A-37 Piso 10 **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olarteraisbeck.com	**IDENTIFICACIÓN** C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual _____ Número 79782747Bta TP 74.295
INVENTOR (ES) (72)	**Nombre:** TERENCE VERNON SILK, JULIAN DUNCAN SMITH **Dirección:** Ramsgate Road, Sandwich, Kent CT13 9NJ Reino Unido. **Nacionalidad o Domicilio:** BRITANICA	

(3) **PCT (86)**

Solicitud Internacional No. PCT/IB02/04979 Fecha Noviembre 27, 2002

Publicación Internacional No. WO 03/048180 Fecha Junio 12, 2003

(4) **Título (54)** FORMA DE FARMACO CRISTALINA

Clasificación Internacional (51) C07H, 19/16 // A61K31/70

Prioridad SI [X] N [ ]	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	GB	Diciembre 6, 2001	0129273.9

(5) **Comprobante de pago No.** 43,982 **Fecha** Junio 3, 2004

(10) **ANEX S**

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

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

3

SUPERINDUSTRIA Y COMERCIO

Radicacion : 04052218 00000000 Folios: 113

Fecha (AMD): 2004-06-04 09:43:39

Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 01 - 43,982
FECHA : JUNIO 3 DE 2004

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
FREDERICK TORRES	CONSIGNACION	BANCO POPULAR	050-00110-6	21261189	02/03/2004	3,865,000.00

***** 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	422,000.00
		TOTAL : $	422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

4

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

PFIZER INC.

Bilingüe inglés- español otorgado en Nueva York, Estados Unidos el 14 de julio de 2003 y firmado por J. Trevor Lumb, Vicepresidente de Pfizer Products Inc.

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 14 de julio de 2003 el suscrito notario Kenneth Greenwood certifica que J. Trevor Lumb, domiciliado en Nueva York ejercía funciones de Asistente General Consejero de Patentes la Compañía Pfizer Inc., con sede en Nueva York, Nueva York, Estados Unidos.

Firma del notario: Kenneth Greenwood

Sello notarial: certificado, verificado y autenticado en la Localidad de Egham en Surrey, 14 julio, 2003 por el Notario Kenneth Greenwood-Horne Engall & Freeman

Sello Notario Público en alto relieve rojo.

APOSTILLA

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País :Reino Unido de Gran Bretaña e Irlanda del Norte
   Este documento Público
2. ha sido firmado por K. Greenwood
3. ejerce funciones de Notario Público
4. Lleva el sello de dicho Notario Público

CERTIFICADO

5. En Londres 6. El 17 de julio de 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos Exteriores y de la mancomunidad
8. No. G210434
9. Sello del Secretario de Estado Principal de su Majestad para Asuntos Exteriores y de la mancomunidad
10. Firma de R. Bawden - Por Secretario de Estado

Si este documento se usa en un país que no es parte de la convención de la Haya del 5 de octubre 1961, debe presentarse en sección consular de la misión que representa el país.

BOGOTÁ, D.C. COLOMBIA XIMENA BAUTISTA NAVARRO NOTARIA ONCE (11)E

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 25 de julio-2003. Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 de [illegible]

5

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned,

Pfizer Inc.

domiciled in

235 East 42nd Street, New York, NY 10017 USA

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

Poder

El suscrito,

Pfizer Inc.

domiciliado en

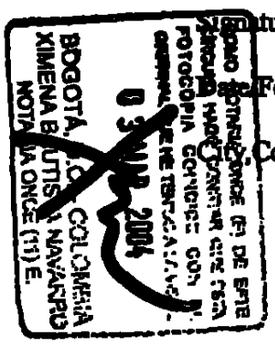
235 East 42nd Street, New York, NY 10017 USA

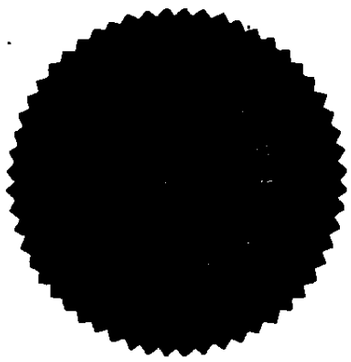
por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia,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

Signature/Firma: _____

Date/Fecha: July 14, 2003

City, Country/Ciudad,País: New York, USA





OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

Notarial Certification

On this date,
July 14, 2003
The undersigned Notary Public certifies:

1. That J. Trevor Lumb
of legal age and domiciled in New York, USA
signed the foregoing document.

2. That the grantor has executed the foregoing document as Assistant General Patent Counsel of Pfizer Inc.

3. That Pfizer Inc.,
having its principal place of business located in New York, New York, U.S.A.
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. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que
J. Trevor Lumb
mayor de edad y domiciliado
New York
suscribió el documento que antecede.

2. Que el otorgante ha suscrito el referido documento en su carácter de
de

4. Que
con sede principal ubicada en

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature):

BOGOTÁ, D.C. COLOMBIA
XIMENA BUTTIS NAVARRO
NOTARIA ONCE (11) E.

EXECUTION
Certified, Verified and Authenticated
In The Town Of Egham, In Surrey
This 16 Day Of July 2003

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGLAND AND FREEMAN

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

   This public document / Le présent acte public

2. Has been signed by — K Greenwood
   a été signé par

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

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

   Certified/Attesté
5. at London/à Londres — 6. the/le 17 July 2003

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

8. Number/sous No **G210434**

9. Stamp:
   timbre:

10. Signature: R. Bawden

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

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

NOTARIA ONCE (11) E. BOGOTA, D.C. - COLOMBIA
XIMENA BAUTISTA NAVARRO
NOTARIA ONCE (11) E.
COPIAS NOTARIA ONCE (11) DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
0 MAR 2004

PCS22056AAJR

CESION

Por contraprestación valiosa pagada a nosotros por PFIZER LIMITED., sociedad constituida en virtud de las leyes del Inglaterra cuya dirección postal completa es Ramsgate Road, Sándwich, Kent CT13 9NJ, Reino Unido, por el presente vendemos y traspasamos a la citada PFIZER LIMITED, todo nuestro derecho, titulo e interés en y sobre nuestro invento de una nueva y útil mejora en FORMA DE FARMACO CRISTALINA, en cuanto respecta a la República de Colombia, tal como se indica y describe plenamente en la especificación y por el presente autorizamos y solicitamos al Comisionado de Patentes de Colombia expedir dicha patente a nombre de la citada PFIZER LIMITED, de conformidad con esta Cesión.

En fe de lo cual, firmamos de nuestro puño y letra,

(Fdo) Terence Vernon Silk

Lugar, fecha y firma - Terence Vernon Silk

Sándwich, Kent, England - 24 Septiembre 2002

(Fdo) Julian Duncan Smith

Lugar, fecha y firma - Julian Duncan Smith

Sándwich, Kent, England - 24 Septiembre 2002

Certificado, verificado y autenticado
En la ciudad de Egham en Surrey

A los 26 días del mes de septiembre de 2002

(Fdo) Kenneth Greenwood

KENNETH GREENWOOD
NOTARIO PUBLICO
HORNE ENGALL AND FREEMAN

(Adherido, sello notarial)

8

APOSTILLA

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

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte

   Este es documento público

2. Ha sido firmado por K. Greenwood

3. Actuando en calidad de Notario Público

4. Lleva el sello/estampilla de El antedicho Notario Público

   Certificado

5. En Londres 6. El 27 de Septiembre de 2002

7. Por el Secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Mancomunidad.

8. Número G029559

9. Sello/Estampilla 10. Firma

(Sello de la Oficina de Asuntos Exteriores y de la Mancomunidad

(Fdo) E.Sharman
Por el secretario de Estado.

PC22056AAJR

CESION

Por contraprestación valiosa pagada a nosotros por PFIZER INC, sociedad constituida en virtud de las leyes del Estado de Delaware, Estados Unidos de América, cuya dirección postal completa es 235 East 42nd Street, NewYork, New Cork 10017, Estados Unidos de América, por el presente vendemos y traspasamos a la citada PFIZER INC, todo nuestro derecho, titulo e interés en y sobre nuestro invento de una nueva y útil mejora en FORMA DE FARMACO CRISTALINA, en cuanto respecta a la República de Colombia, tal como se indica y describe plenamente en la especificación y por el presente autorizamos y solicitamos al Comisionado de Patentes de Colombia expedir dicha patente a nombre de la citada PFIZER INC, de conformidad con esta Cesión.

En fe de lo cual, firmamos de nuestro puño y letra,

PFIZER LIMITED

(Fdo) David J. Wood

Lugar, fecha y firma – DAVID J. WOOD Director Departamento de Patentes UK

Sándwich, Kent, England – 24 Septiembre 2002

Certificado, verificado y autenticado
En la ciudad de Egham en Surrey

A los 26 días del mes de septiembre de 2002

(Fdo) Kenneth Greenwood

KENNETH GREENWOOD
NOTARIO PUBLICO
HORNE ENGALL AND FREEMAN

(Adherido, sello notarial)

10

APOSTILLA

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

2. País: Reino Unido de Gran Bretaña e Irlanda del Norte

   Este es documento público

2. Ha sido firmado por **K. Greenwood**

3. Actuando en calidad de **Notario Público**

4. Lleva el sello/estampilla de **El antedicho Notario Público**

   Certificado

5. En Londres

6. El 27 de Septiembre de 2002

7. Por el Secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Mancomunidad.

8. Número G029560

9. Sello/Estampilla

10. Firma

(Sello de la Oficina de Asuntos Exteriores y de la Mancomunidad

(Fdo) E. Sharman
Por el secretario de Estado.

PCS22056AAJR

CO-1

ASSIGNMENT

For valuable consideration paid to me (us) by **PFIZER LIMITED** a corporation organized under the laws of **England** whose full post office address is **Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom,** I (we) do hereby sell and assign to the said **PFIZER LIMITED,** all my (our) right, title and interest in and to my (our) invention for a new and useful Improvement in **CRYSTALLINE DRUG FORM** so far as the Republic of Colombia is concerned, as fully set forth and described in the specification, and I (we) do hereby authorize and request the Commissioner of Patents of Colombia to issue said patent to the said **PFIZER LIMITED** in accordance with this assignment.

In witness whereof I (we) have hereunto set my (our) hand(s) this

Terence Vernon Silk

Sandwich, Kent, England, 24 September 2002 - Terence Vernon SILK

Julian Duncan Smith

Sandwich, Kent, England, 24 September 2002 - Julian Duncan SMITH

EXECUTION
Certified Witnessed and Authenticated
In the Town Of Epsom In Surrey
This 26th Day Of September 2002

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

9426

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

   This public document / Le présent acte public

2. Has been signed by — K Greenwood
   a été signé par

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

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

   Certified/Attesté
5. at London/à Londres — 6. the/le 27 September 2002

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

8. Number/sous No — **G029559**

9. Stamp:
   timbre:

10. Signature: E. Sharman

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

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

PCS22056AAJR 12

CO-1X

ASSIGNMENT

For valuable consideration paid to me (us) by **PFIZER INC., a corporation organized under the laws of the State of Delaware, United States of America of 235 East 42nd Street, New York, New York 10017, United States of America,** I (we) do hereby sell and assign to the said **PFIZER INC.**, all my (our) right, title and interest in and to my (our) invention for a new and useful Improvement in

CRYSTALLINE DRUG FORM

so far as the Republic of Colombia is concerned, as fully set forth and described in the specification, and I (we) do hereby authorize and request the Commissioner of Patents of Colombia to issue said patent to the said **PFIZER INC.** in accordance with this assignment.

In witness whereof I (we) have hereunto set my (our) hand(s) this

PFIZER LIMITED

D.J. Wood

Sandwich, Kent, England 4 September 2002 - **DAVID J. WOOD, EXECUTIVE DIRECTOR, UK PATENT DEPARTMENT**

EXECUTION
Certified Duly Authenticated
I, the undersigned Notary
This 26th day of September 2002

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

   This public document / Le présent acte public

2. Has been signed by — K Greenwood
   a été signé par

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

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

   Certified/Attesté

5. at London/à Londres — 6. the/le 27 September 2002

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

8. Number/sous No — **G029560**

9. Stamp:
   timbre:

10. Signature: E. Sharman

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

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

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 June 2003 (12.06.2003)

PCT

(10) International Publication Number
WO 03/048180 A1

(51) International Patent Classification[7]: C07H 19/16, A61K 31/70

(21) International Application Number: PCT/IB02/04979

(22) International Filing Date:
27 November 2002 (27.11.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0129273.9 6 December 2001 (06.12.2001) GB

(71) Applicant *(for GB only)*: PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(71) Applicant *(for all designated States except GB, US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SILK, Terence, Vernon [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). SMITH, Julian, Duncan [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(74) Agents: WOOD, David, J. et al.; Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

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

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

Published:
— *with international search report*

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

WO 03/048180 A1

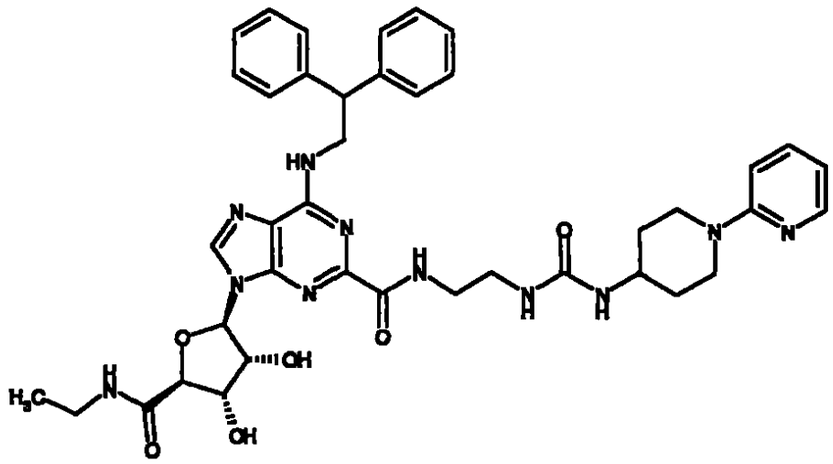
(54) Title: CRYSTALLINE FORM OF A RIBOFURANOSYLURONAMIDE DERIVATIVE; A HUMAN ADENOSINE A2A RECEPTOR AGONIST

(57) Abstract: The present invention relates to a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N* (2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide and to a process for the preparation of, compositions containing and the uses of such a crystalline form.

CRYSTALLINE FORM OF A RIBOFURANOSYLURONAMIDE DERIVATIVE; A HUMAN ADENOSINE A2A RECEPTOR AGONIST

The present invention relates to a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide and to a process for the preparation of, compositions containing and the uses of such a crystalline form.

6-[(2,2-Diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide (also known as 6-[(2,2-diphenylethyl)amino]-9-[(2R,3R,4S,5S)-5-[(ethylamino)carbonyl]-3,4-dihydroxytetrahydro-2-furanyl]-N-{2-[({[1-(2-pyridinyl)-4-piperidinyl]amino}carbonyl)amino]ethyl}-9H-purine-2-carboxamide) has the structure shown in formula (I) and its preparation is disclosed in International Patent Application number PCT/IB01/00973, published as WO-A-01/94368.



(I)

As described in PCT/IB01/00973, 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide is a selective, functional agonist of the human adenosine A2a receptor and may be used as an anti-inflammatory agent in the treatment of, *inter alia*, diseases of the respiratory tract. It may therefore be used to treat any

disease for which an adenosine A2a receptor agonist is indicated. It can be used to treat a disease where leukocyte (e.g. neutrophil, eosinophil, basophil, lymphocyte, macrophage) -induced tissue damage is implicated. It is useful as an anti-inflammatory agent in the treatment of diseases of the respiratory tract such as adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis. It may also be used in the treatment of septic shock, male erectile dysfunction, male factor infertility, female factor infertility, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, dermatitis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Helicobacter pylori* gastritis, non-*Helicobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing.

Examples 8 and 35 of PCT/IB01/00973 both describe the preparation of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide. These methods provide a solid, amorphous form of the compound (see comparative examples 1 and 2 below).

Before a drug compound can be commercialised, a process for its bulk manufacture must be developed that reliably provides a uniform and highly pure grade of the compound. Further, the process must deliver a form of the compound that can be suitably formulated for convenient dosage to patients and which is chemically and physically stable over long periods in that formulation.

A crystalline form of a drug compound has advantages over an amorphous form in several respects. For example, the compound can be easily purified by crystallisation and recrystallisation. Crystallisation is a much cheaper and more convenient method of purification to perform on a large scale than other known methods of purification such as chromatography. Further, a crystalline form is usually more stable than an amorphous form, both before and during formulation

and during subsequent storage. Further, when formulating a drug for delivery by inhalation, it is generally easier to mill or micronise a crystalline form to a respirable size (generally considered as particles less than 5 microns in diameter) than an amorphous form.

There is no generally applicable method for preparing a crystalline form of an amorphous material. Indeed, it is impossible to know, from the outset, whether any crystalline form of a given compound exists. Where it turns out that a compound can be crystallised, extensive experimentation is usually required before a process is identified from which the crystalline form can be isolated. The correct combination of several independently variable conditions (for example, solvent concentration, solvent composition, temperature, cooling rate) must be identified empirically through trial and error with no guarantee of success.

Many efforts to crystallise 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide were unsuccessful. Slurrying the compound in a range of solvents (e.g. methanol, ethanol, tetrahydrofuran, acetonitrile, dichloromethane, toluene) at ambient temperature, with and without added water was fruitless. Similarly, heating such slurries to obtain a solution and allowing them to cool in a conventional fashion did not provide a satisfactory crystalline form.

It has now been surprisingly found that a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide exists and may be prepared using the processes outlined below.

The invention thus provides a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide.

The invention further provides a process for the preparation of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide which comprises

the steps of:

(a) dissolving amorphous 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide in an organic solvent which contains at least 2% w/w dissolved water; and

(b) heating the solution so obtained to a temperature of at least 50°C until crystallisation occurs.

This process is unusual in several respects. The solvent system developed (a solution of least 2%w/w water in an organic solvent) is not conventional. Further, crystallisation is initiated by maintaining the solution of amorphous compound in this solvent at an elevated temperature whereas in conventional crystallisation techniques, crystallisation is initiated by cooling such a solution. Thus, the process presented provides a unique and unconventional set of conditions that unexpectedly solve the problem of preparing a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide.

The crystalline form provided by the above process has a further unexpected advantage in that it leads to a higher resistivity than the amorphous form at an equivalent concentration in solution. This is of particular benefit in preparing a formulation for use in an atomiser that operates by the principles of electrohydrodynamics (see below) since it is possible to lower the resistivity in such a formulation by the addition of, for example, sodium chloride, but it is currently not possible to raise it. Thus, the higher the resistivity of a compound when formulated in solution, the more flexibility exists in the choice of a final resistivity for the formulation.

Any organic solvent may be used in the process which is capable of dissolving both amorphous 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide and at least 2% w/w water. Examples of such a suitable solvent include 2-butanone, ethyl acetate, acetonitrile, isopropyl acetate, isopropanol, methyl acetate, butan-2-ol and methyl acetate. Preferred organic

solvents are 2-butanone, methyl acetate and ethyl acetate. Methyl acetate and ethyl acetate are particularly preferred.

The water content of an organic solvent may conveniently be measured using the Karl-Fischer method.

A temperature of at least 50°C is necessary to induce crystallisation at a practicable rate. Preferably, a temperature of from 50°C to 80°C is used.

Crystallisation will usually be complete within 24 to 72 hours but longer and shorter periods are possible depending on the choice of organic solvent and temperature.

The crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide (henceforth referred to as 'the compound of the invention') can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, it can be administered orally, buccally or sublingually in the form of tablets, capeules, multi-particulates, gels, films, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications. It may also be administered as fast-dispersing or fast-dissolving dosage forms or in the form of a high energy dispersion or as coated particles. Suitable formulations may be in coated or uncoated form, as desired.

Such solid pharmaceutical compositions, for example tablets, may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine and starch (preferably corn, potato or tapioca starch), disintegrants such as sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC),

hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium stearyl fumarate, sodium lauryl sulphate, stearic acid, glyceryl behenate and talc may be included.

General Example

A formulation of the tablet could typically contain from 0.01mg to 500mg of active compound whilst tablet fill weights may range from 50mg to 1000mg. An example of a formulation for a 10mg tablet is illustrated below:

Ingredient	%w/w
Compound of the invention	10.000*
Lactose	64.125
Starch	21.375
Croscarmellose sodium	3.000
Magnesium Stearate	1.500

* Quantity adjusted in accordance with drug activity.

The tablets can be manufactured by a standard process, for example, direct compression or a wet or dry granulation process. The tablet cores may be coated with appropriate overcoats.

Solid compositions of a similar type may also be employed as fillers in gelatin or HPMC capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or a high molecular weight polyethylene glycol. For aqueous suspensions and/or elixirs, the compound of the invention may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol or glycerin, and combinations thereof.

The compound of the invention can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or

subcutaneously, or they may be administered by infusion or needleless injection techniques. For such parenteral administration, it is best used in the form of a sterile aqueous solution which may contain other substances, for example, a co-solvent and/or enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level of the compound of the invention will usually be from 0.00001 to 100 mg/kg, preferably from 0.0001 to 100 mg/kg (in single or divided doses).

Thus tablets or capsules of the compound of the invention may contain from 0.01 to 500 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

The compound of invention can also be administered intranasally or by inhalation and is conveniently delivered in the form of a dry powder (either alone or as a mixture, for example a mixture with lactose) from a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist) or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide, a further perfluorinated hydrocarbon such as Perflubron (trade mark) or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised

container, pump, spray, atomiser or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol (optionally, aqueous ethanol) or a suitable agent for dispersing, solubilising or extending release and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules, blisters and cartridges (made, for example, from gelatin or HPMC) for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as l-leucine, mannitol or magnesium stearate.

Prior to use in a dry powder formulation or suspension formulation for inhalation the compound of the invention will be reduced to a particle size suitable for delivery by inhalation (typically considered as less than 5 microns). Production of particles in a suitable size range could be achieved by the use of a range of destructive methods, for example spiral jet milling or fluid bed jet milling or by use of a range of constructive methods such as supercritical fluid crystallisation or spray drying.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1μg to 10mg of the compound of the invention per actuation and the actuation volume may vary from 1 to 100μl. A typical formulation may comprise the compound of the invention, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents may be used in place of propylene glycol, for example glycerol or polyethylene glycol. A specific example of a formulation for use in an atomiser using electrohydrodynamics is illustrated below:

Ingredient	Quantity
Compound of the invention	14.6mg
Propylene glycol	0.08ml
Sterile water	0.02ml
Ethanol	to 1ml
Sodium chloride	as required to adjust resistivity to 1100 Ohm-m

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 1 to 4000 µg of the compound of the invention for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 1µg to 20mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

Alternatively, the compound of the invention can be administered in the form of a suppository or pessary, or it may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. The compound of the invention may also be dermally or transdermally administered, for example, by the use of a skin patch. It may also be administered by the pulmonary, vaginal or rectal routes.

For application topically to the skin, the compound of the invention can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, it can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compound of the invention may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

The crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide provided by the present invention may optionally be formulated in combination with other pharmacologically active compounds. Preferred combinations for use in the treatment of obstructive airways and other inflammatory diseases include (a) a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide and (b) a corticosteroid, an adrenergic β2 agonist or an anticholinergic compound. Examples of preferred adrenergic β2 agonists are salmeterol and formoterol. Examples of preferred anticholinergic compounds are tiotropium, ipratropium and oxitropium salts.

Thus the invention provides:

(i) a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide;

(ii) a process for the preparation of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide;

(iii) a pharmaceutical composition including a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide together with a pharmaceutically acceptable excipient, diluent or carrier;

(iv) a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide for use as a medicament;

(v) a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide for use as a medicament having A2a receptor agonist activity;

(vi) a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide for use as an anti-inflammatory agent;

(vii) a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide for use as a medicament for the treatment of a respiratory disease;

(viii) a crystalline form as in (vii) where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis;

(ix) a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide for use as a medicament for the treatment of

septic shock, male erectile dysfunction, male factor infertility, female factor infertility, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, dermatitis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Helicobacter pylori* gastritis, non-*Helicobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing;

(x) the use of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide for the manufacture of a medicament having A2a receptor agonist activity;

(xi) the use of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide for the manufacture of an anti-inflammatory agent;

(xii) the use of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide for the manufacture of a medicament for the treatment of a respiratory disease;

(xiii) use as in (xii) where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis;

(xiv) the use of a crystalline form of compound of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide for the manufacture of a medicament for the treatment of septic shock, male erectile dysfunction, male factor infertility, female factor infertility, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, dermatitis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Helicobacter pylori* gastritis, non-*Helicobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced

damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing;

(xv) a method of treatment of a mammal, including a human being, with an A2a receptor agonist including treating said mammal with an effective amount of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide;

(xvi) a method of treatment of a mammal, including a human being, to treat an inflammatory disease including treating said mammal with an effective amount of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide;

(xvii) a method of treatment of a mammal, including a human being, to treat a respiratory disease including treating said mammal with an effective amount of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide;

(xviii) a method as in (xvii) where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis; and

(xix) a method of treatment of a mammal, including a human being, to treat septic shock, male erectile dysfunction, male factor infertility, female factor infertility, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, dermatitis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Helicobacter pylori* gastritis, non-*Helicobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing, including treating said mammal with an effective amount of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide.

The following Examples illustrate the invention.

Example 1

Amorphous 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide (5.0 g, 0.0064 moles) was charged to a vessel equipped with a Teflon(Trade Mark)-covered magnetic stirrer bar, a thermometer and a condenser. A solution of 2%v/v water in 2-butanone (50 ml) was then added, and the resultant mixture was heated to 69-71°C with stirring under an atmosphere of nitrogen to give an initially clear solution. After 24 hours at this temperature, a mobile white suspension had formed. The temperature of the mixture was then reduced to 59-61°C and stirring was continued for an additional 24 hours. The mixture was then cooled to ambient temperature over 30 minutes and was stirred at this temperature for 1 hour. The solid was then collected by filtration and the filter cake was washed with 2-butanone (50ml). The solid was then dried at 50°C under reduced pressure for 48 hours to give the title compound as colourless crystals (3.99g) that contained approximately 1% by weight of 2-butanone by ^{1}H-NMR. Prior to obtaining further characterisation data, the material so formed was dried further at 50°C under reduced pressure for 5 days to give 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide that contained approximately 0.5% by weight of 2-butanone. Measurement of the water content of this material showed that it also contained 1.6% by weight of water. Further drying at elevated temperature further reduced the levels of 2-butanone present, thereby demonstrating that residual 2-butanone is probably not an intrinsic part of the crystal lattice but is trapped within the channels of the crystal lattice.

The crystalline form produced by the process described above has the following characteristics:

Low resolution mass spectrometry

Positive atmospheric pressure chemical ionisation: m/z [MH^+] 778.

Proton NMR spectroscopy

(300 MHz, d_6-DMSO, 30°C) δ : 8.80 (0.8H, br t), 8.67 (0.2H, br s), 8.53 (0.2H, br s), 8.48 (0.8H, s), 8.28 (1H, br t), 8.10-8.02 (1.8H, m), 7.84 (0.2H, br s), 7.50-7.30 (5H, m), 7.28 (4H, t), 7.14 (2H, t), 6.75 (1H, d), 6.58 (1H, dd), 6.11-5.82 (3H, m), 5.65 (1H, m), 5.60-5.45 (1H, m), 4.80-4.50 ((2.4H, m), 4.40-3.95 (5.6H, m), 3.67-3.55 (1H, m), 3.40-3.10 (6H, m (partly obscured by water peak)), 3.00-2.65 (2H, m), 1.74 (2H, br d), 1.30-1.16 (2H, br q), 0.98 (3H, t).

Acquiring the ^{1}H-NMR spectrum at 70°C results in the disappearance of signals attributable to the observation of more than one conformer at 30°C.

Infra-red spectroscopy

The infrared spectrum was acquired using a Nicolet 360 Avatar FT-IR spectrometer fitted with a d-TGS detector and a single reflection diamond ATR accessory (Golden Gate™). The sample was prepared by placing ca. 0.5 mg of sample on the diamond ATR crystal and ensuring good crystal sample contact by applying pressure through an anvil with a built-in pressure control mechanism. The spectrum was recorded at 4cm^{-1} resolution using 32 background and 32 sample scans with a Happ Genzel apodisation function.

Major peaks were recorded at 3478, 3395, 3375, 3301, 3080, 3024, 2971, 2943, 1657, 1639, 1597, 1552, 1527, 1494, 1475, 1468, 1456, 1434, 1405, 1374, 1351, 1324, 1310, 1300, 1233, 1220, 1163, 1150, 1123, 1113, 1102, 1078, 1054, 1000, 976, 947, 932, 909, 864, 813, 777, 759, 734, 699, 683 and 667 cm^{-1}.

Powder X-Ray diffraction (PXRD)

The powder X-ray diffraction pattern was determined using a SIEMENS D5000 powder X-ray diffractometer fitted with an automatic sample changer, a theta-theta goniometer, automatic beam divergence slits, a secondary monochromator

and a scintillation counter. The sample was prepared for analysis by packing the powder on to a silicon wafer specimen mount. The specimen was rotated whilst being irradiated with copper K-alpha$_1$ X-rays (wavelength = 1.5406 Angstroms) with the X-ray tube operated at 40kV/40mA. The analysis was performed with the goniometer running in step-scan mode set for a 5 second count per 0.02° step over a two theta range of 4° to 45°.

The diffraction pattern obtained is shown in Figure 1

The peak intensities of greater than 5% are summarised in Table 1. In Table 1, "Angle 2-Theta" is related to the interplanar spacing of the crystal, and the intensity is given as a percentage of the greatest peak (I/I_1).

Table 1

Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %
5.185	22.9	17.099	27.4	24.861	29.5	33.177	13.8
6.647	96.0	17.369	23.8	24.966	29.5	33.596	18.3
8.232	23.7	17.908	35.6	25.795	26.9	34.484	18.2
9.131	11.3	18.517	35.8	26.214	24.4	35.048	16.2
9.794	15.4	18.753	29.0	26.570	21.4	35.399	13.7
10.702	10.1	19.414	62.3	26.949	40.8	35.704	14.2
11.370	16.1	20.079	35.3	27.054	38.5	36.797	17.1
12.495	6.3	20.418	100	27.308	28.3	37.819	15.4
13.494	30.1	21.357	36.0	27.776	21.2	38.667	16.6
14.393	7.8	21.696	77.7	28.718	25.1	39.568	12.8
14.536	6.8	22.455	28.3	28.991	24.4	40.463	12.9
14.899	8.1	23.187	65.2	29.854	43.7	40.929	17.6
15.148	10.1	23.697	27.0	30.581	16.7	41.473	16.2
15.369	9.9	24.030	15.0	31.142	15.6	42.455	14.5
16.111	33.5	24.755	28.5	32.517	17.2	43.347	14.5
16.439	30.2						

As will be appreciated by the skilled crystallographer, the relative intensities of the various peaks within Table 1 may vary due to a number of factors such as for example orientation effects of crystals in the X-ray beam or the purity of the material being analysed or the degree of crystallinity of the sample. The peak

positions may also shift for variations in sample height but the peak positions will remain substantially as defined in Table 1.

The skilled crystallographer will also appreciate that measurements using a different wavelength will result in different shifts according to the Bragg equation - $n\lambda = 2d \sin\theta$.

Such further PXRD patterns generated by use of alternative wavelengths are considered to be alternative representations of the PXRD pattern of the crystalline material of the present invention and as such are within the scope of the present invention.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry was performed using a Perkin Elmer DSC-7 instrument fitted with an automatic sample changer. Approximately 3mg of the sample was accurately weighed into a 50 microlitre aluminium pan and crimp sealed with a perforated lid. The samples were heated at 20°C/minute over the range 40°C to 250°C with a nitrogen gas purge.

The results are shown in Figure 2. The melting range is approximately 185-195°C.

Thermal gravimetric analysis (TGA)

Thermal gravimetric analysis was performed using a Perkin Elmer Pyris1 TGA instrument fitted with an automatic sample changer. Approximately 8mg of the sample was accurately weighed into a ceramic pan. The sample was heated at 20°C/minute over the range 25°C to 350°C with a nitrogen gas purge.

The results are shown in Figure 3.

Example 2

To amorphous 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide (66.1g, 0.085 moles) was added a 2%v/v solution of water in 2-butanone (660ml) and the resultant mixture was heated at 69-71°C for 18 hours. After this time, a seed of crystalline 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide (0.149g) was added to the mixture and stirring at 69-71°C was continued for 8 hours. The temperature of the mixture was then lowered to 59-61°C and stirring at this temperature was continued for 64 hours. The resultant slurry was then cooled to ambient temperature and the solid was collected by filtration. The filter cake was washed with 2-butanone (2 x 100ml) and the resultant solid was dried at 60°C under vacuum for 60 hours, then at 80°C under vacuum for 72 hours to give a crystalline solid (35.72g) that contained traces of 2-butanone. Analytical data collected on the product, including characterisation by Powder X-Ray Diffraction, were consistent with the data described in Example 1.

Example 3

Ethyl acetate (25ml) was shaken with deionised water (10ml) at ambient temperature and the organic phase was collected to give a solution of ethyl acetate that was saturated with water. Amorphous 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide (1.0 g, 0.0013 moles) was charged to a vessel equipped with a Teflon® -covered magnetic stirrer bar and a condenser. A solution of ethyl acetate that was saturated with water as prepared above (10ml) was then added to the amorphous solid, and the resultant mixture was heated to 55-60°C under an atmosphere of nitrogen. A seed (approximately 0.005g) of crystalline 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide was then added and the resultant mixture was stirred at

55-60°C for 3 days after which time a slurry had formed. The mixture was then cooled to ambient temperature and the solid was collected by filtration. The filter cake was then washed with ethyl acetate (2 x 5ml) and the resultant solid was dried at 50°C for 24 hours to give a crystalline solid (0.898g) that contained traces of sodium chloride (inadvertently present in the starting material and subsequently filtered off with the product) and ethyl acetate. Analytical data collected on the product, including characterisation by Powder X-Ray Diffraction, were consistent with the data described in Example 1 except that a trace of sodium chloride was present.

Example 4

A 2%v/v solution of water in acetonitrile was prepared by dissolving deionised water (2.0ml) in acetonitrile and then making the volume up to 100ml with acetonitrile. Amorphous 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide (1.0 g, 0.0013 moles) was charged to a vessel equipped with a teflon®-covered magnetic stirrer bar and a condenser. A 2%v/v solution of water in acetonitrile as prepared above (10ml) was then added to the amorphous solid, and the resultant mixture was heated to 55-60°C under an atmosphere of nitrogen. A seed (approximately 0.005g) of crystalline 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide was then added and the resultant mixture was stirred at 55-60°C for 3 days after which time a thick slurry had formed. The mixture was then cooled to ambient temperature and additional acetonitrile (10ml) was added. The solid was then collected by filtration. The filter cake was then washed with acetonitrile (2 x 5ml) and dried at 50°C for 24 hours to give a crystalline solid (0.868g) that contained traces of sodium chloride (inadvertently present in the starting material and subsequently filtered off with the product) and acetonitrile. Analytical data collected on the product, including characterisation by Powder X-Ray Diffraction, were consistent with the data described in Example 1 except that a trace of sodium chloride was present.

Example 5

Isopropyl acetate (25ml) was shaken with deionised water (10ml) at ambient temperature and the organic phase was collected to give a solution of isopropyl acetate that was saturated with water. Amorphous 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide (1.0 g, 0.0013 moles) was charged to a vessel equipped with a teflon®-covered magnetic stirrer bar and a condenser. A solution of isopropyl acetate that was saturated with water as prepared above (10ml) was then added to the amorphous solid, and the resultant mixture was heated to 55-60°C under an atmosphere of nitrogen. A seed (approximately 0.005g) of crystalline 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide was then added and the resultant mixture was stirred at 55-60°C for 3 days after which time a slurry had formed. The mixture was then cooled to ambient temperature and the solid was collected by filtration. The filter cake was then washed with isopropyl acetate (2 x 5ml) and dried at 50°C for 24 hours to give a colourless crystalline solid (0.445g) that contained traces of sodium chloride (inadvertently present in the starting material and subsequently filtered off with the product) and isopropyl acetate. Analytical data collected on the product, including characterisation by Powder X-Ray Diffraction, were consistent with the data described in Example 1, except that a trace of sodium chloride was present.

Example 6

A 2%v/v solution of water in isopropanol was prepared by dissolving deionised water (2.0ml) in isopropanol and then making the volume up to 100ml with isopropanol. Amorphous 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide (1.0 g, 0.0013 moles) was charged to a vessel equipped

with a teflon®-covered magnetic stirrer bar and a condenser. A 2%v/v solution of water in isopropanol as prepared above (10ml) was then added to the amorphous solid, and the resultant mixture was heated to 55-60°C under an atmosphere of nitrogen. A seed (approximately 0.005g) of crystalline 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide was then added and the resultant mixture was stirred at 55-60°C for 8 days over which time a slurry formed. The mixture was then cooled to ambient temperature and the solid was then collected by filtration. The filter cake was then washed with isopropanol (2 x 5ml) and dried at 50°C for 24 hours to give a colourless crystalline solid (0.866g) that contained traces of sodium chloride (inadvertently present in the starting material and subsequently filtered off with the product) and isopropanol. Analytical data collected on the product, including characterisation by Powder X-Ray Diffraction, were consistent with the data described in Example 1 except that a trace of sodium chloride was present.

Example 7

Amorphous 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide (1.0 g, 0.0013 moles) was charged to a vessel equipped with a teflon®-covered magnetic stirrer bar and a condenser. To this amorphous solid was then added methyl acetate (10ml) and deionised water (0.20ml), and the resultant mixture was heated to 55-60°C under an atmosphere of nitrogen. A seed (approximately 0.005g) of crystalline 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide was then added and the resultant mixture was stirred at 55-60°C for 24 hours over which time a slurry formed. The mixture was then cooled to ambient temperature and the solid was then collected by filtration. The filter cake was then washed with methyl acetate (2 x 5ml) and dried at 50°C for 24 hours to give a colourless crystalline solid (0.860g) that contained traces of sodium chloride (inadvertently present in the starting material and subsequently filtered off with the product) and methyl acetate. Analytical data collected on the

product, including characterisation by Powder X-Ray Diffraction, were consistent with the data described in Example 1 except that a trace of sodium chloride was present.

Example 8

Amorphous 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide (1.0 g, 0.0013 moles) was charged to a vessel equipped with a teflon®-covered magnetic stirrer bar and a condenser. To this amorphous solid was then added butan-2-ol (10ml) and deionised water (0.20ml), and the resultant mixture was heated to 55-60°C under an atmosphere of nitrogen. A seed (approximately 0.005g) of crystalline 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide was then added and the resultant mixture was stirred at 55-60°C for approximately 3 weeks over which time a slurry slowly formed. The mixture was then cooled to ambient temperature and the solid was then collected by filtration. The filter cake was then washed with butan-2-ol (2 x 5ml) and dried at 50°C for several days to give a colourless crystalline solid (0.860g) that contained traces of sodium chloride (inadvertently present in the starting material and subsequently filtered off with the product). Analytical data collected on the product, including characterisation by Powder X-Ray Diffraction, were consistent with the data described in Example 1 except that a trace of sodium chloride was present.

Example 9

To a stirred suspension of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-2,3-*O*-isopropylidene-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide (200g, 0.245 moles) (see WO-A-01/94368) in deionised water (1000ml) was added methanesulfonic acid (17.5ml, 0.269 moles) under an atmosphere of nitrogen. The resultant mixture was then heated at temperatures up to 95°C and was stirred within this

temperature range for approximately 5 hours during which time all the starting material was consumed. The reaction was then stopped by the addition of a 10%w/w aqueous solution of disodium hydrogen phosphate heptahydrate (82ml) and the resultant solution was then cooled to ambient temperature after which time methyl acetate (2000ml) was added. To the resultant mixture was then slowly added a 10%w/w aqueous solution of disodium hydrogen phosphate heptahydrate (1300ml) with vigorous stirring. The phases were then allowed to separate, and the organic phase was washed with a 2%w/w aqueous solution of disodium hydrogen phosphate heptahydrate (2000ml). After allowing the phases to separate, the organic layer was collected and additional methyl acetate (1000ml) was added. The resultant mixture was then azeotropically dried by distillation at atmospheric pressure until the amount of water left in the mixture was approximately 2%w/w by Karl-Fischer analysis. This required the addition of more methyl acetate (3000ml, added in portions over the duration of the distillation), and a total of approximately 3000ml of distillate was collected. This gave a water level of 1.8%w/w in the mixture, which was then heated at reflux for 18 hours. Deionised water (4ml) was then added to adjust the water content of the mixture to 2.0%w/w and reflux was continued for an additional 24 hours after which time a slurry had formed. The mixture was then cooled to ambient temperature and the solid was collected by filtration. The filter cake was washed with a 2%w/w solution of water in methyl acetate (200ml then 400ml), and dried at 50°C under reduced pressure for 20 hours to give a crystalline material (155.6g) that was contaminated with traces of inorganic salts. A suspension of this material (153.6g) in a mixture of ethyl acetate (1070ml) and ethanol (460ml) was heated to reflux for 10 minutes to give a slightly cloudy solution. After cooling to ambient temperature, the mixture was filtered to give a clear filtrate which was then distilled at atmospheric pressure. During the course of the distillation additional ethyl acetate (2900ml) was added in portions and a total of 2900ml of distillate was collected. Towards the end of the distillation, it was necessary to a deionised water (60ml, added in 2 portions) in order to keep the product in solution and to create the conditions necessary for crystallisation to occur. At the end point of the distillation, there was approximately 2mol% of ethanol remaining and approximately 2.3%w/w of water present in the mixture. For convenience, the mixture was held at this point at ambient temperature for

60 hours. The mixture was then heated at approximately 60°C for 30 hours during which time a slurry was formed. The mixture was then cooled to ambient temperature and the solid was collected by filtration. The filter cake was then washed with a 2%v/v solution of water in ethyl acetate (150ml then 300ml), and dried *in vacuo* at 70°C to give a colourless crystalline solid (134g) that contained traces of residual ethyl acetate. Analytical data collected on the product, including characterisation by Powder X-Ray Diffraction, were consistent with that described in Example 1.

Comparative Example 1

A sample of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide that had been prepared using the process described in Example 8 of WO-A-01/94368 was examined by Powder X-Ray Diffraction, and was found to be non-crystalline. The respective X-ray diffraction pattern is shown in Figure 4. The powder X-ray diffraction pattern was determined using a SIEMENS D5000 powder X-ray diffractometer fitted with an automatic sample changer, a theta-theta goniometer, automatic beam divergence slits, a secondary monochromator and a scintillation counter. The sample was prepared for analysis by packing the powder on to a silicon wafer specimen mount. The specimen was rotated whilst being irradiated with copper K-alpha$_1$ X-rays (wavelength = 1.5406 Angstroms) with the X-ray tube operated at 40kV/40mA. The analysis was performed with the goniometer running in step-scan mode set for a 5 second count per 0.02° step over a two theta range of 4° to 55°.

Comparative Example 2

A sample of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide that had been prepared using the process described in Example 35 of WO-A-01/94368 was examined by Powder X-Ray Diffraction, and was found to be non-crystalline. The respective X-ray diffraction pattern is shown in Figure 5. The powder X-ray diffraction pattern was determined using a

SIEMENS D5000 powder X-ray diffractometer fitted with an automatic sample changer, a theta-theta goniometer, automatic beam divergence slits, a secondary monochromator and a scintillation counter. The sample was prepared for analysis by packing the powder on to a silicon wafer specimen mount. The specimen was rotated whilst being irradiated with copper K-alpha$_1$ X-rays (wavelength = 1.5406 Angstroms) with the X-ray tube operated at 40kV/40mA. The analysis was performed with the goniometer running in step-scan mode set for a 5 second count per 0.02° step over a two theta range of 4° to 55°.

Claims

1. A crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide.

2. A crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide, as claimed in claim 1, characterised by a solid state infra-red spectrum which shows significant absorption bands at ν = 3478, 3395, 3375, 3301, 3060, 3024, 2971, 2943, 1657, 1639, 1597, 1552, 1527, 1494, 1475, 1468, 1456, 1434, 1405, 1374, 1351, 1324, 1310, 1300, 1233, 1220, 1163, 1150, 1123, 1113, 1102, 1078, 1054, 1000, 976, 947, 932, 909, 864, 813, 777, 759, 734, 699, 683 and 667 cm^{-1} and a powder X-ray diffraction pattern, obtained using copper K-alpha$_1$ X-rays (wavelength = 1.5406 Angstroms), showing main peaks at 5.185, 6.647, 8.232, 9.131, 9.794, 10.702, 11.370, 12.495, 13.494, 14.393, 14.536, 14.899, 15.148, 15.369, 16.111, 16.439, 17.099, 17.369, 17.908, 18.517, 18.753, 19.414, 20.079, 20.418, 21.357, 21.696, 22.455, 23.187, 23.697, 24.030, 24.755, 24.861, 24.966, 25.795, 26.214, 26.570, 26.949, 27.054, 27.308, 27.776, 28.718, 28.991, 29.854, 30.581, 31.142, 32.517, 33.177, 33.596, 34.484, 35.048, 35.399, 35.704, 36.797, 37.819, 38.667, 39.568, 40.463, 40.929, 41.473, 42.455 and 43.347 degrees 2θ.

3. A pharmaceutical composition comprising a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide, as defined in claim 1 or claim 2, together with a pharmaceutically acceptable excipient, diluent or carrier.

4. A crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide, as defined in claim 1 or claim 2, for use as a medicament.

5. The use of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-

9*H*-purine-2-carboxamide, as defined in claim 1 or claim 2, for the manufacture of a medicament having A2a receptor agonist activity.

6. The use of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide, as defined in claim 1 or claim 2, for the manufacture of an anti-inflammatory agent.

7. The use of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide, as defined in claim 1 or claim 2, for the manufacture of a medicament for the treatment of a respiratory disease.

8. The use as claimed in claim 7, wherein the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis.

9. The use of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide, as defined in claim 1 or claim 2, for the manufacture of a medicament for the treatment of septic shock, male erectile dysfunction, male factor infertility, female factor infertility, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, dermatitis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Helicobacter pylori* gastritis, non-*Helicobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing.

10. A method of treatment of a mammal, including a human being, with an A2a receptor agonist including treating said mammal with an effective amount of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide, as defined in claim 1 or claim 2.

11. A method of treatment of a mammal, including a human being, to treat an inflammatory disease including treating said mammal with an effective

amount of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide, as claimed in claim 1 or claim 2.

12. A method of treatment of a mammal, including a human being, to treat a respiratory disease including treating said mammal with an effective amount of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide, as claimed in claim 1 or claim 2.

13. A method as claimed in claim 12, wherein the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis.

14. A method of treatment of a mammal, including a human being, to treat septic shock, male erectile dysfunction, male factor infertility, female factor infertility, hypertension, stroke, epilepsy, cerebral ischaemia, peripheral vascular disease, post-ischaemic reperfusion injury, diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, dermatitis, allergic dermatitis, eczema, ulcerative colitis, Crohns disease, inflammatory bowel disease, *Helicobacter pylori* gastritis, non-*Helicobacter pylori* gastritis, non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract or a psychotic disorder, or for wound healing, including treating said mammal with an effective amount of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide, as defined in claim 1 or claim 2.

15. A process for the preparation of a crystalline form of 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide, as defined in claim 1 or claim 2, comprising the steps of:

(a) dissolving amorphous 6-[(2,2-diphenylethyl)amino]-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-*N*-(2-{*N*'-[1-(2-pyridyl)-4-piperidyl]ureido}ethyl)-9*H*-purine-2-carboxamide in an organic solvent which contains at least 2%

w/w dissolved water; and

(b) heating the solution so obtained to a temperature of at least 50°C until crystallisation occurs.

16. A process as claimed in claim 15 wherein the organic solvent is 2-butanone, ethyl acetate, acetonitrile, isopropyl acetate, isopropanol, methyl acetate, butan-2-ol or methyl acetate.

17. A process as claimed in claim 15 wherein the organic solvent is 2-butanone, methyl acetate or ethyl acetate.

18. A process as claimed in any one of claims 15 to 17 wherein the water content of the organic solvent is 2% v/v.

19. A process as claimed in any one of claims 15 to 18 wherein the solution is heated to from 50°C to 80°C.

Figure 1

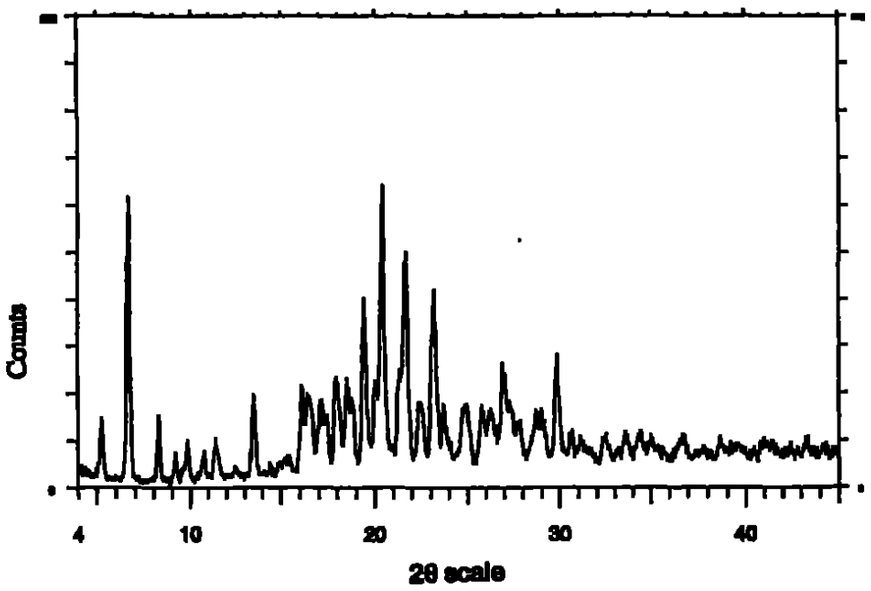
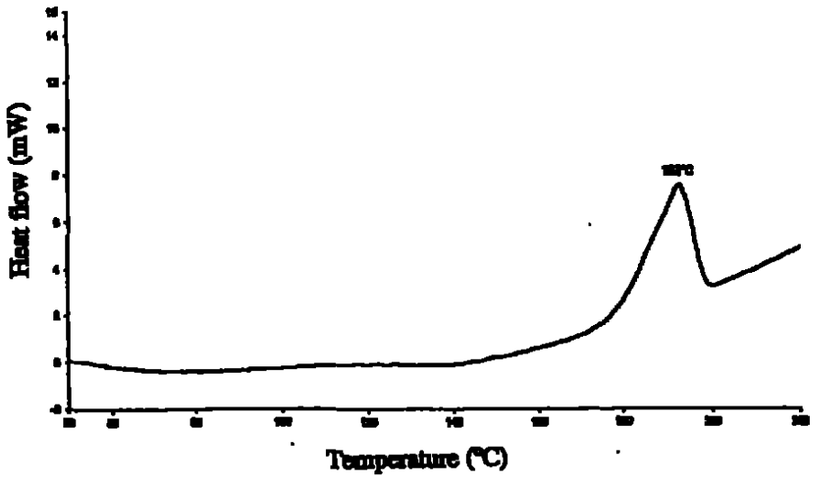


Figure 2



44

Figure 3

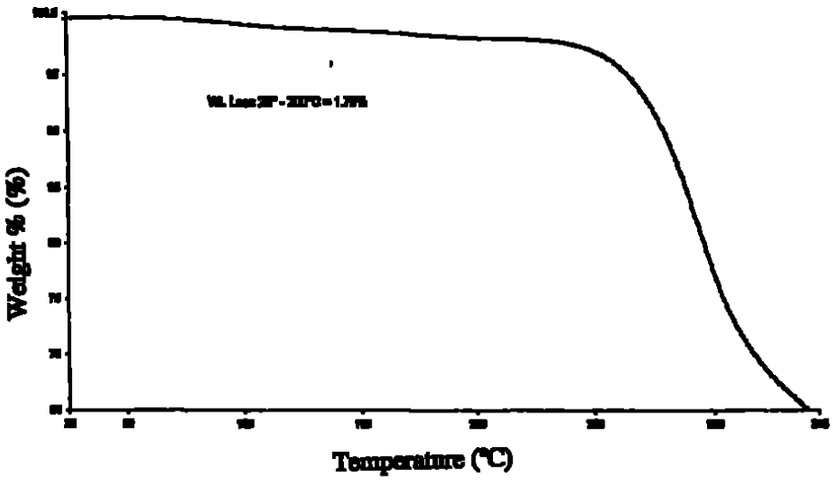
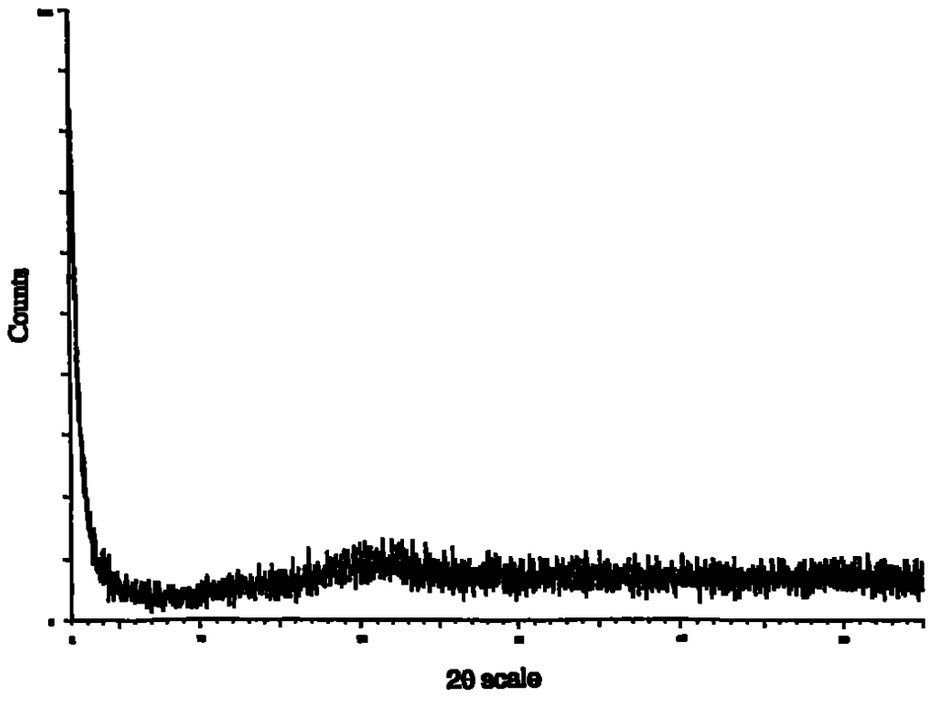
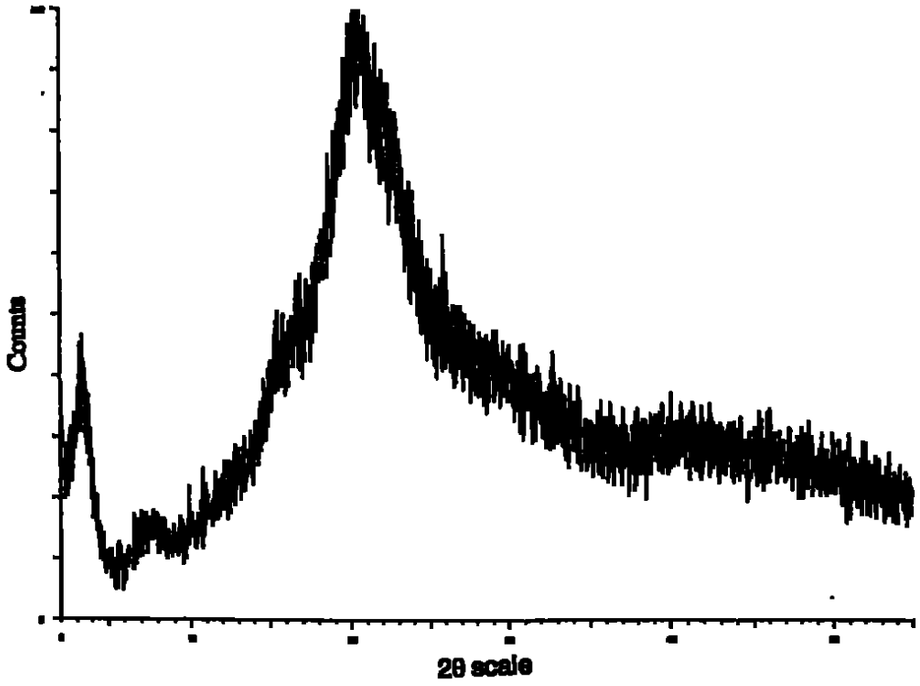


Figure 4



45

Figure 5

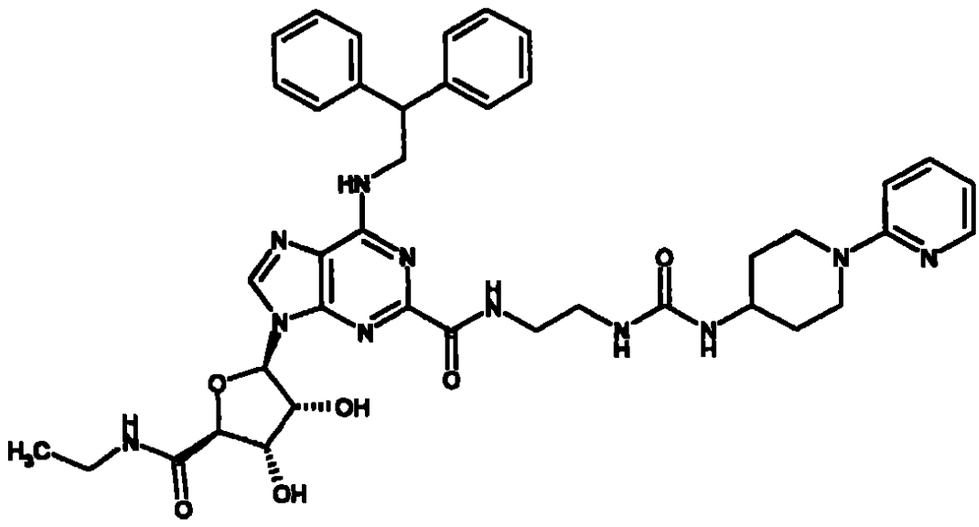


PC22056AAJR

FORMA DE FÁRMACO CRISTALINA

La presente invención se refiere a una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosil-uronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida y a un procedimeinto para la preparación de composiciones que los contienen y a los usos de tal forma cristalina.

La 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida (también conocida como 6-[(2,2-difeniletil)amino]-9-{2R,3R,4S,5S)-5-[(etilamino)carbonil]-3,4-dihidroxitetrahidro-2-furanil}-N-{2-[({[1-(2-piridinil)-4-piperidinil]amino}carbonil)amino]etil}-9H-purin-2-carboxamida) tiene la estructura que se muestra en la fórmula (I) y su preparación se describe en la solicitud de patente internacional número PCT/IB01/00973, publicada como WO-A-01/94368.



(I)

Como se describe en el documento PCT/IB01/00973, la 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida es un agonista funcional selectivo del receptor A2a de adenosina humano y puede usarse como agente antiinflamatorio en el tratamiento de, entre otras, enfermedades del trato respiratorio. Por lo tanto, puede usarse para tratar cualquier enfermedad para la que esté indicado un agonista del receptor A2a de adenosina. Puede usarse para tratar una enfermedad en la que están implicadas lesiones de tejidos inducidas por leucocitos (por ejemplo neutrófilos, eosinófilos, basófilos, linfocitos o macrófagos). Es útil como agente antiinflamatorio en el tratamiento de enfermedades del tracto respiratorio tales como el síndrome de insuficiencia

respiratoria en adultos (ARDS), bronquitis, bronquitis crónica, enfermedad pulmonar obstructiva crónica, fibrosis quística, asma, enfisema, bronquiectasia, sinusitis crónica y rinitis. También se puede usar en el tratamiento del choque séptico, la disfunción eréctil masculina, la infertilidad de factor masculino, la infertilidad de factor femenino, la hipertensión, la apoplejía, la epilepsia, la isquemia cerebral, la enfermedad vascular periférica, la lesión de reperfusión post-isquémica, la diabetes, la artritis reumatoide, la esclerosis múltiple, la psoriasis, la dermatitis, la dermatitis alérgica, eccemas, la colitis ulcerosa, la enfermedad de Crohn, la enfermedad inflamatoria del intestino, la gastritis producida por *Heliobacter pylori*, la gastritis no producida por *Heliobacter pylori*, lesiones en el tracto gastrointestinal inducidas por fármacos antiinflamatorios no esteroideos o un trastorno psicótico, o para la curación de heridas.

Los Ejemplos 8 y 35 del documento PCT/IB01/00973 describen la preparación de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida. Estos procedimientos proporcionan una forma sólida y amorfa del compuesto (véanse los ejemplos comparativos 1 y 2 mostrados más adelante).

Antes de que pueda comercializarse un compuesto farmacológico, tiene que desarrollarse un procedimiento para su

fabricación a granel que proporcione de forma fiable una calidad uniforme y de alta pureza del compuesto. Además, el procedimiento debe proporcionar una forma del compuesto que pueda formularse adecuadamente para la dosificación conveniente a pacientes y que sea química y físicamente estable durante largos períodos en dicha formulación.

Una forma cristalina de un compuesto farmacológico presenta ventajas sobre una forma amorfa en varios aspectos. Por ejemplo, el compuesto puede purificarse fácilmente por recristalización. La recristalización es un procedimiento de purificación mucho más barato y conveniente de realiar a gran escala que otros procedimientos de purificación conocidos tal como cromatografía. Además, una forma cristalina normalmente es más estable que una forma amorfa, tanto antes como durante la formación y durante el almacenamiento posterior. Además, cuando se formula un fármaco para suministrarse por inhalación, generalmente es más fácil triturar o micronizar una forma cristalina hasta un tamaño respirable (considerado generalmente como partículas con un diámetro inferior a 5 micrómetros) que una forma amorfa.

No existe ningún procedimiento que se pueda aplicar de forma general para preparar una forma cristalina de un material amorfo. De hecho, es imposible saber desde el principio si existe algunaββ forma cristalina de un compuesto dado. Cuando resulta que un compuesto puede cristalizar-

se, normalmente se requiere una amplia experimentación antes de que se identifique un procedimiento a partir del cual pueda aislarse la forma cristalina. La combinación correcta de varias condiciones independientemente variables (por ejemplo, concentración del disolvente, composición del disolvente, temperatura y velocidad de refrigeración) debe identificarse empíricamente por medio de ensayo y error sin garantía de éxito.

Muchos esfuerzos para cristalizar la 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida fueron insatisfactorios. La suspensión del compuesto en una diversidad de disolventes (por ejemplo metanol, etanol, tetrahidrofurano, acetonitrilo, diclorometano o tolueno) a temperatura ambiente, con o sin agua añadida, fue infructuosa. De forma similar, el calentamiento de dichas suspensiones para obtener una solución y su refrigeración de una forma convencional no proporcionó una forma cristalina satisfactoria.

Ahora, se ha descubierto que, sorprendentemente, existe y se puede preparar una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida usando los procedimientos indicados más adelante.

La invención proporciona una forma cristalina de 6-

[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida.

La invención además proporciona un procedimeinto para la preparación de una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida que comprende las etapas de:

(a) disolver 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida amorfa en un disolvente orgánico que contiene al menos un 2% p/p de agua disuelta; y

(b) calentar la solución obtenida de esta forma a una temperatura de al menos 50°C hasta que se produzca la cristalización.

Este proceso es inusual en varios aspectos. El sistema disolvente desarrollado (agua al 2% v/v en un disolvente orgánico) no es convencional. Además, la cristalización se inicia manteniendo la solución del compuesto amorfo en este disolvente a una temperatura elevada, mientras que en las técnicas de cristalización convencional, la cristalización se inicia enfriando dicha solución. De esta forma, el procedimiento presentado proporciona una serie única y poco convencional de condiciones que, inesperadamente, resuelve

el problema de preparar una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida.

La forma cristalina proporcionada por el procedimiento anterior tiene una ventaja adicional inesperada, ya que tiene una mayor resistividad que la forma amorfa a una concentración equivalente en solución. Esto es particularmente beneficioso para la preparación de una formulación para uso en un atomizador que funciona por los principios de la electrohidrodinámica (véase más adelante), ya que es posible reducir la resistividad en dicha formulación por la adición de, por ejemplo, cloruro sódico, pero actualmente no es posible aumentarla. De esta forma, cuanto mayor sea la resistividad de un compuesto cuando se formula en una solución, mayor flexibilidad existirá en la elección de una resistividad final para la formulación.

En el procedimiento puede usarse cualquier disolvente orgánico que sea capaz de disolver tanto la 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida amorfa como al menos un 2% p/p en agua. Los ejemplos de tal disolvente adecuado incluyen 2-butanona, acetato de etilo, acetonitrilo, acetato de isopropilo, isopropanol, acetato de metilo, butan-2-ol y acetato de metilo. Los disolventes orgánicos preferidos son 2-

butanona, acetato de metilo y acetato de etilo. Son particularmente preferidos el acetato de metilo y acetato de etilo.

El contenido de agua de un disolvente orgánico puede medirse usando el procedimiento de Karl-Fischer.

Para inducir la cristalización a una velocidad práctica es necesaria una temperatura de al menos 50°C.

Habitualmente, la cristalización se completará en un periodo de 24 a 72 horas, pero pueden ser necesarios periodos mayores o menores dependiendo de la elección del disolvente y la temperatura.

Una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida (mencionada en este documento como "el compuesto de la invención") pueden administrarse sola, pero generalmente se administrarán en mezcla con un excipiente, diluyente o vehículo farmacéuticamente adecuados seleccionados con respecto a la ruta de administración pretendida y a la práctica farmacéutica convencional.

Por ejemplo, puede administrarse por vía oral, bucal o sublingual en forma de comprimidos, cápsulas, multiparticulados, geles, películas, óvulos, elixires, soluciones o suspensiones, que pueden contener agentes aromatizantes o colorantes, para aplicaciones de liberación inmedia-

ta, retrasada, modificada, sostenida, por pulsos o controlada. También puede administrarse como formas de dosificación de dispersión rápida o de disolución rápida o en forma de una dispersión de alta energía o como partículas recubiertas. Las formulaciones adecuadas pueden estar en forma recubierta o no recubierta, según se desee.

Tales composiciones farmacéuticas sólidas, por ejemplo, comprimidos, pueden contener excipientes tales como celulosa microcristalina, lactosa, citrato sódico, carbonato cálcico, fosfato cálcico dibásico, glicina y almidón (preferiblemente almidón de maíz, patata o tapioca), disgregantes tales como almidón glicolato sódico, croscarmelosa sódica y ciertos silicatos complejos, y ligantes de granulación tales como polivinilpirrolidona, hidroxipropilmetilcelulosa (HPMC), hidroxipropilcelulosa (HPC), sacarosa, gelatina y goma arábiga. Adicionalmente, pueden incluirse agentes lubricantes tales como estearato de magnesio, estearil fumarato sódico, lauril sulfato sódico, ácido esteárico, behenato de glicerilo y talco.

Ejemplo General

Típicamente, una formulación de comprimido podría contener de 0,01 mg a 500 mg de compuesto activo, mientras que los pesos de relleno del comprimido pueden variar de 50 mg a 1000 mg. A continuación se ilustra un ejemplo de una formulación para un comprimido de 10 mg:

Ingrediente	% p/p

Compuesto de la invención	10,000*
Lactosa	64,125
Almidón	21,375
Croscarmelosa sódica	3,000
Estearato de Magnesio	1,500

* Cantidad ajustada de acuerdo con la actividad del fármaco.

Los comprimidos pueden fabricarse mediante un procedimiento convencional, por ejemplo, por compresión directa o por un procedimiento de granulación en húmedo o en seco. Los núcleos de los comprimidos pueden recubrirse con recubrimientos apropiados.

También pueden emplearse composiciones sólidas de un tipo similar como cargas en cápsulas de gelatina o de HPMC. Los excipientes preferidos a este respecto incluyen lactosa, almidón, una celulosa, azúcar de la leche o un polietilenglicol de alto peso molecular. Para las suspensiones acuosas y/o elixires, el compuesto de la invención puede combinarse con diversos agentes edulcorantes o aromatizantes, materiales colorantes o tintes, con agentes emulsionantes y/o de suspensión, y con diluyentes tales como agua, etanol, propilenglicol o glicerina, y combinaciones de los mismos.

El compuesto de la invención también puede administrarse por vía parenteral, por ejemplo, por vía intravenosa, intra-arterial, intraperitoneal, intratecal, intraven-

tricular, intrauretral, intraesternal, intracraneal, intramuscular o subcutánea, o puede administrarse por infusión o por técnicas de inyección sin aguja. Para tal administración parenteral, se usa de la mejor manera en forma de una solución acuosa estéril que puede contener otras sustancias, por ejemplo, un co-disolvente y/o suficientes sales o glucosa para hacer que la solución sea isotónica con la sangre. Las soluciones acuosas deben tamponarse adecuadamente (preferiblemente a un pH de 3 a 9), si es necesario. La preparación de formulaciones parenterales adecuadas en condiciones estériles se consigue fácilmente por técnicas farmacéuticas convencionales bien conocidas para los especialistas en la técnica.

Para la administración oral o parenteral a pacientes humanos, el nivel de dosificación diario del compuesto de la invención normalmente será de 0,00001 a 100 mg/kg, preferiblemente de 0,0001 a 100 mg/kg (en una sola dosis o en dosis divididas).

De esta forma, los comprimidos o cápsulas del compuesto de la invención pueden contener de 0,01 a 500 mg de compuesto activo para la administración individual o de dos o más de una vez, según sea apropiado. En cualquier caso, el médico determinará la dosificación real más adecuada para cualquier paciente individual, y ésta variará con la edad, el peso y la respuesta del paciente particular. Las dosificaciones anteriores son ilustrativas del caso medio.

Por supuesto, puede haber casos individuales en los que se requieran intervalos de dosificación superiores o inferiores, y tales intervalos están dentro del alcance de esta invención.

El compuesto de la invención también puede administrarse por vía intranasal o por inhalación y convenientemente se suministra en forma de un polvo seco (solo o como una mezcla, por ejemplo, una mezcla con lactosa) desde un inhalador de polvo seco o una presentación de pulverizador de aerosol desde un recipiente a presión, bomba, pulverizador, atomizador (preferiblemente un atomizador que use la electrohidrodinámica para producir una niebla fina) o nebulizador, con o sin el uso de un propelente adecuado, por ejemplo, diclorodifluorometano, triclorofluorometano, diclorotetrafluoroetano, un hidrofluoroalcano tal como 1,1,1,2-tetrafluoroetano (HFA 134A [marca comercial]) o 1,1,1,2,3,3,3-heptafluoropropano (HFA 227EA [marca comercial]), dióxido de carbono, un hidrocarburo perfluorado adicionalmente tal como Perflubron (marca comercial) u otro gas adecuado. En el caso de un aerosol a presión, la unidad de dosificación puede determinarse proporcionando una válvula para suministrar una cantidad medida. El recipiente a presión, bomba, pulverizador, atomizador o nebulizador puede contener una solución o suspensión del compuesto activo, por ejemplo, usando una mezcla de etanol (opcionalmente, etanol acuoso) o un agente adecuado para dispersar,

solubilizar o extender la liberación, y el propelente como disolvente, que puede contener además un lubricante, por ejemplo, trioleato de sorbitán. Las cápsulas, ampollas y cartuchos (fabricados, por ejemplo, de gelatina o HPMC) para uso en un inhalador o insuflador, pueden formularse para contener una mezcla de polvo del compuesto de la invención, una base de polvo adecuada tal como lactosa o almidón y un modificador del rendimiento tal como l-leucina, manitol o estearato de magnesio.

Antes de usarse en una formulación de polvo seco o en una formulación de suspensión para inhalación, el compuesto de la invención se micronizará hasta un tamaño adecuado para suministrarse por inhalación (considerado típicamente como inferior a 5 micrómetros). La producción de partículas en un intervalo de tamaños adecuado puede conseguirse por una serie de procedimientos destructivos, por ejemplo, trituración con chorro en espiral, trituración con chorro en lecho fluido o por el uso de una serie de procedimientos constructivos tales como cristalización supercrítica de fluidos o secado por pulverización.

Una formulación de solución adecuada para uso en un atomizador que usa la electrohidrodinámica para producir una niebla fina puede contener de 1 µg a 10 mg del compuesto de la invención por actuación, y el volumen de actuación puede variar de 1 a 100 µl. Una formulación típica puede comprender el compuesto de la invención, propilenglicol,

agua estéril, etanol y cloruro sódico. Pueden usarse disolventes alternativos en lugar de propilenglicol, por ejemplo, glicerol o polietilenglicol. A continuación se ilustra un ejemplo específico de una formulación para uso en un atomizador que usa la electrohidrodinámica:

Ingrediente	Cantidad
Compuesto de la invención	14,6 mg
Propilenglicol	0,08 ml
Agua estéril	0,02 ml
Etanol	hasta 1 ml
Cloruro sódico	cantidad necesaria para ajustar la resistividad a 1100 Ohm-m

Las formulaciones de aerosol o de polvo seco preferiblemente se disponen de forma que cada dosis medida o "presión" contenga de 1 a 4000 µg del compuesto de la invención para suministrarse al paciente. La dosis diaria total con un aerosol estará en el intervalo de 1 µg a 20 mg, que pueden administrarse en una sola dosis o, más habitualmente, en dosis divididas a lo largo del día.

Como alternativa, el compuesto de la invención puede administrarse en forma de un supositorio o supositorio vaginal, o puede aplicarse tópicamente en forma de una loción, solución, crema, pomada o polvo fino. El compuesto de la invención también puede administrarse por vía dérmica o transdérmica, por ejemplo, por el uso de un parche

cutáneo. También puede administrarse por vía pulmonar, vaginal o rectal.

Para la aplicación tópica en la piel, el compuesto de la invención puede formularse como una pomada adecuada que contiene el compuesto activo suspendido o disuelto en, por ejemplo, una mezcla con uno o más de los siguientes: aceite mineral, vaselina líquida, vaselina blanca, propilenglicol, compuesto de polioxietileno y polioxipropileno, cera emulsionante y agua. Como alternativa, puede formularse como una loción adecuada o crema, suspendida o disuelta en, por ejemplo, una mezcla de uno o más de los siguientes: aceite mineral, monoestearato de sorbitán, un polietilenglicol, parafina líquida, polisorbato 60, ceras de ésteres cetílicos, alcohol cetearílico, 2-octildodecanol, alcohol bencílico y agua.

El compuesto de la invención también puede usarse en combinación con una ciclodextrina. Se sabe que las ciclodextrinas forman complejos de inclusión y complejos que no son de inclusión con moléculas de fármacos. La formación de un complejo de fármaco-ciclodextrina puede modificar las propiedades de solubilidad, velocidad de disolución, biodisponibilidad y/o estabilidad de una molécula de fármaco. Los complejos de fármaco-ciclodextrina generalmente son útiles para la mayoría de las formas de dosificación y vías de administración. Como alternativa a la formación directa de complejos con el fármaco, la ciclodextrina puede usarse

como aditivo auxiliar, por ejemplo, como un vehículo, diluyente o solubilizante. Las ciclodextrinas usadas más comúnmente son las ciclodextrinas alfa, beta y gamma, y se describen ejemplos adecuados en los documentos WO-A-91/11172, WO-A-94/02518 y WO-A-98/55148.

Se apreciará que todas las referencias en este documento al tratamiento incluyen el tratamiento curativo, paliativo y profiláctico.

La forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida proporcionada por la presente invención, opcionalmente puede formularse en combinación con otros compuestos farmacológicamente activos. Las combinaciones preferidas para uso en el tratamiento de la enfermedad obstructiva de las vías respiratorias y otras enfermedades inflamatorias incluyen (a) una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida y (b) un corticosteroide, un agonista β2 adrenérgico o un compuesto anticolinérgico. Los ejemplos de agonistas β2 adrenérgicos preferidos son el salmeterol y el formoterol. Son ejemplos de compuestos anticolinérgicos preferidos las sales de tiotropio, ipratropio y oxitropio.

De esta forma, la invención proporciona:

(i) una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purina-2-carboxamida;

(ii) un proceso para la preparación de una forma de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida;

(iii) una composición farmacéutica que incluye una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida junto con un excipiente, diluyente o vehículo farmacéuticamente aceptable;

(iv) una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida para uso como un medicamento;

(v) una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida para uso como un medicamento que tiene actividad

agonista del receptor A2a;

(vi) una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida para uso como un agente antiiflamatorio;

(vii) una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida para uso como un medicamento para el tratamiento de una enfermedad respiratoria;

(viii) una forma cristalina como en (vii), donde la enfermedad se selecciona entre el grupo compuesto por el síndrome de insuficiencia respiratoria en adultos (ARDS), bronquitis, bronquitis crónica, enfermedad pulmonar obstructiva crónica, fibrosis quística, asma, enfisema, bronquiectasia, sinusitis crónica y rinitis;

(ix) una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida para uso como un medicamento para el tratamiento del choque séptico, la disfunción eréctil mascu-

lina, la infertilidad de factor masculino, la infertilidad de factor femenino, la hipertensión, la apoplejía, la epilepsia, la isquemia cerebral, la enfermedad vascular periférica, la lesión de reperfusión post-isquémica, la diabetes, la artritis reumatoide, la esclerosis múltiple, la psoriasis, la dermatitis, la dermatitis alérgica, el eccema, la colitis ulcerosa, la enfermedad de Crohn, la enfermedad inflamatoria del intestino, la gastritis producida por *Heliobacter pylori*, la gastritis no producida por *Heliobacter pylori*, lesiones en el tracto gastrointestinal inducidas por fármacos antiinflamatorios no esteroideos o un trastorno psicótico, o para la curación de heridas;

(x) el uso de una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida para la fabricación de un medicamento que tiene actividad agonista del receptor A2a;

(xi) el uso de una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida

para la fabricación de un agente antiinflamatorio;

(xii) el uso de una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida para la fabricación de un medicamento para el tratamiento de una enfermedad respiratoria;

(xiii) uso como en (xii), donde la enfermedad se selecciona entre el grupo compuesto por el síndrome de insuficiencia respiratoria en adultos (ARDS), bronquitis, bronquitis crónica, enfermedad pulmonar obstructiva crónica, fibrosis quística, asma, enfisema, bronquiectasia, sinusitis crónica y rinitis;

(xiv) el uso de una forma cristalina del compuesto de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida para la fabricación de un medicamento para el tratamiento del choque séptico, la disfunción eréctil masculina, la infertilidad de factor masculino, la infertilidad de factor femenino, la hipertensión, la apoplejía, la epilepsia, la isquemia cerebral, la enfermedad vascular periféri-

ca, la lesión de reperfusión post-isquémica, la diabetes, la artritis reumatoide, la esclerosis múltiple, la psoriasis, la dermatitis, la dermatitis alérgica, el eccema, la colitis ulcerosa, la enfermedad de Crohn, la enfermedad inflamatoria del intestino, la gastritis producida por *Heliobacter pylori*, la gastritis no producida por *Heliobacter pylori*, lesiones en el tracto gastrointestinal inducidas por fármacos antiinflamatorios no esteroideos o un trastorno psicótico, o para la curación de heridas;

(xv) un procedimiento de tratamiento de un mamífero, incluyendo un ser humano, con un agonista del receptor A2a, que incluye el tratamiento de dicho mamífero con una cantidad eficaz de una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida;

(xvi) un procedimiento de tratamiento de un mamífero, incluyendo un ser humano, para tratar una enfermedad inflamatoria, que incluye el tratamiento de dicho mamífero con una cantidad eficaz de una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-

(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida;

(xvii) un procedimiento de tratamiento de un mamífero, incluyendo un ser humano, para tratar una enfermedad respiratoria, que incluye el tratamiento de dicho mamífero con una cantidad eficaz de una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida;

(xviii) un procedimiento como en (xvii), donde la enfermedad se selecciona entre el grupo compuesto por el síndrome de insuficiencia respiratoria en adultos (ARDS), bronquitis, bronquitis crónica, enfermedad pulmonar obstructiva crónica, fibrosis quística, asma, enfisema, bronquiectasia, sinusitis crónica y rinitis; y

(xix) un procedimiento de tratamiento de un mamífero, incluyendo un ser humano, para tratar el choque séptico, la disfunción eréctil masculina, la infertilidad de factor masculino, la infertilidad de factor femenino, la hipertensión, la apoplejía, la epilepsia, la isquemia cerebral, la enfermedad vascular periférica, la lesión de reperfusión post-isquémica, la diabetes, la artritis reumatoide, la esclerosis múltiple, la psoriasis,

la dermatitis, la dermatitis alérgica, el eccema, la colitis ulcerosa, la enfermedad de Crohn, la enfermedad inflamatoria del intestino, la gastritis producida por *Heliobacter pylori*, la gastritis no producida por *Heliobacter pylori*, lesiones en el tracto gastrointestinal inducidas por fármacos antiinflamatorios no esteroideos o un trastorno psicótico, o para la curación de heridas, que incluye el tratamiento de dicho mamífero con una cantidad eficaz de una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida.

Los siguientes Ejemplos ilustran la invención:

Ejemplo 1

Se cargó cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida amorfa (5,0 g, 0,0064 mol) en un recipiente equipado con una varilla agitadora recubierta de Teflon (marca comercial), un termómetro y un condensador. Después se añadió una solución de agua al 2% p/p en 2-butanona (50 ml) y la mezcla resultante se calentó a 69-71°C con agitación en una atmósfera de nitrógeno, dando una solución inicialmente transparente. Después de 24 horas a esta temperatura, se

había formado una suspensión blanca móvil. La temperatura de la mezcla después se redujo a 59-61°C y se continuó agitando durante 24 horas más. Después, la mezcla se enfrió a temperatura ambiente durante 30 minutos y se agitó a esta temperatura durante 1 hora. Después, el sólido se recogió por filtración y después la torta de filtro se lavó con 2-butanona (50 ml). Después, el sólido se secó a 50°C a presión reducida durante 48 horas, dando el compuesto del título en forma de cristales incoloros (3,99 g) que contenían aproximadamente un 1% en peso de 2-butanona según indicó el análisis por ^{1}H-RMN. Antes de obtener los datos de caracterización adicionales, el material formado de esta forma se secó adicionalmente a 50°C a presión reducida durante 5 días, dando cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida. que contenía aproximadamente un 0,5% en peso de 2-butanona. La medida del contenido de agua de este material mostró que también contenía un 1,6% en peso de agua. El secado adicional a una temperatura elevada redujo adicionalmente los niveles de 2-butanona presente, demostrando así que probablemente la 2-butanona no es una parte intrínseca de la estructura cristalina, sino que se queda atrapada en los canales de la estructura del cristal.

La forma cristalina producida por los procedimientos

descritos anteriormente tiene las siguientes características:

Espectrometría de masas de baja resolución

Ionización química a presión atmosférica positiva: m/z [MH^+] 778.

Espectroscopía de RMN de protón

(300 MHz, d_6-DMSO, 30°C) δ: 8,80 (0,8H, t a), 8,67 (0,2H, s a), 8,53 (0,2H, s a), 8,48 (0,8H, s), 8,28 (1H, t a), 8,10-8,02 (1,8H, m), 7,84 (0,2H, s a), 7,50-7,30 (5H, m), 7,26 (4H, t), 7,14 (2H, t), 6,75 (1H, d), 6,56 (1H, dd), 6,11-5,82 (3H, m), 5,65 (1H, m), 5,60-5,45 (1H, m), 4,80-4,50 (2,4H, m), 4,40-3,95 (5,6H, m), 3,67-3,55 (1H, m), 3,40-3,10 (6H, m (parcialmente oscurecido por el pico de agua)), 3,00-2,65 (2H, m), 1,74 (2H, d a), 1,30-1,16 (2H, q a), 0,98 (3H, t).

La adquisición de espectro de ^{1}H-RMN a 70°C ocasiona la desaparición de señales atribuibles a la observación de más de un confórmero a 30°C.

Espectroscopía infrarroja

El espectro infrarrojo se adquirió usando un espectrómetro Nicolet 360 Avatar FT-IR equipado con un detector d-TGS y un accesorio ATR de un sólo diamante de reflexión (Golden Gate™). La muestra se preparó poniendo aprox. 0,5 mg de muestra sobre el cristal ATR de diamante y asegurando un buen contacto entre la muestra y el cristal aplicando

presión a través de un yunque con un mecanismo de control de la presión acumulada. El espectro se registró a una resolución de 4 cm^{-1} usando 32 barridos de fondo y 32 barridos de muestra con una función de apodización Happ Genzel.

Los picos principales se registraron a 3478, 3395, 3375, 3301, 3060, 3024, 2971, 2943, 1657, 1639, 1597, 1552, 1527, 1494, 1475, 1468, 1456, 1434, 1405, 1374, 1351, 1324, 1310, 1300, 1233, 1220, 1163, 1150, 1123, 1113, 1102, 1078, 1054, 1000, 976, 947, 932, 909, 864, 813, 777, 759, 734, 699, 683 y 667 cm^{-1}.

Difracción de rayos X de cristales finos (PXRD)

El patrón de difracción de rayos x de cristales finos se determinó usando un difractómetro de rayos x de cristales finos SIEMENS D5000 equipado con un cambiador de muestras automático, un goniómetro theta-theta, ranuras de divergencia de haces automáticas, un monocromador secundario y un contador de centelleo. La muestra se preparó para el análisis empaquetando el polvo en un soporte de muestra de disco de silicio. La muestra se hizo girar mientras se irradiaba con rayos X K-alfa$_1$ de cobre (longitud de onda = 1,5406 Ángstrom), funcionando el tubo de rayos X a 40 kV/40 mA. El análisis se realizó con el goniómetro funcionando en un modo de exploración por etapas fijado para un recuento de 5 segundos por etapa 0,02° sobre un intervalo dos theta de 4° a 45°.

El patrón de difracción obtenido se muestra en la Figura 1.

En la Tabla 1 se resumen las intensidades de los picos superiores al 5%. En la Tabla 1, "Ángulo 2-Theta" se refiere a la distancia interplanar del cristal, y a la intensidad se proporciona como un porcentaje del pico mayor (I/I_1).

Tabla 1

Ángulo 2-Theta°	Intensidad %	Ángulo 2-Theta°	Intensidad %	Ángulo 2-Theta°	Intensidad %	Ángulo 2-Theta°	Intensidad %
5,185	22,9	17,099	27,4	24,861	29,5	33,177	13,8
6,647	96,0	17,369	23,8	24,966	29,5	33,596	18,3
8,232	23,7	17,908	35,6	25,795	26,9	34,484	18,2
9,131	11,3	18,517	35,8	26,214	24,4	35,048	16,2
9,794	15,4	18,753	29,0	26,570	21,4	35,399	13,7
10,702	10,1	19,414	62,3	26,949	40,8	35,704	14,2
11,370	16,1	20,079	35,3	27,054	38,5	36,797	17,1
12,495	6,3	20,418	100	27,308	28,3	37,819	15,4
13,494	30,1	21,357	38,0	27,776	21,2	38,667	16,6
14,393	7,8	21,696	77,7	28,718	25,1	39,568	12,8
14,536	6,8	22,455	28,3	28,991	24,4	40,463	12,9
14,899	8,1	23,187	65,2	29,854	43,7	40,929	17,6
15,148	10,1	23,697	27,0	30,581	16,7	41,473	16,2
15,369	9,9	24,030	15,0	31,142	15,6	42,455	14,5

16,111	33,5	24,755	28,5	32,517	17,2	43,347	14,5
16,439	30,2						

Como apreciará el cristalógrafo especializado, las intensidades relativas de los diversos picos indicados en la Tabla 1 pueden variar debido a varios factores tales como, por ejemplo, los efectos de orientación de los cristales en el haz de rayos X, la pureza del material a analizar o el grado de cristalinidad de la muestra. Las posiciones de los picos también pueden cambiar por variaciones en la altura de la muestra, pero las posiciones de los picos permanecerán sustancialmente como se define en la Tabla 1.

El cristalógrafo especializado también apreciará que las mediciones realizadas usando una longitud de onda distinta producirán cambios diferentes de acuerdo con la ecuación de Bragg

$-n\lambda = 2d \sin \theta.$

Se considera que tales patrones de PXRD adicionales generados por el uso de longitudes de onda alternativas son representaciones alternativas del patrón de PXRD del material cristalino de la presente invención y que, como tales, están dentro del alcance de la presente invención.

Calorimetría de Exploración Diferencial (DSC)

La calorimetría de exploración diferencial se realizó usando un instrumento Perkin Elmer DSC-7 equipado con un cambiador de muestras automático. Se introdujeron aproxima-

damente 3 mg de muestra pesados de manera precisa en un recipiente de aluminio de 50 microlitros y el recipiente se cerró herméticamente con una tapa perforada. Las muestras se calentaron a 20°C/minuto a una temperatura dentro del intervalo de 40°C a 250°C purgando con gas nitrógeno.

Los resultados se muestran en la Figura 2. El intervalo de fusión es de aproximadamente 185-195°C.

Análisis termogravimétrico (TGA)

El análisis termogravimétrico se realizó usando un instrumento Perkin Elmer Pyris1 TGA equipado con un cambiador de muestras automático. Se introdujeron aproximadamente 8 mg pesados de manera precisa en unrecipiente cerámico. La muestra se calentó a 20°C/minuto a una temperatura en el intervalo de 25 a 350°C purgando con gas nitrógeno.

Los resultados se muestran en la Figura 3.

Ejemplo 2

A 6-[(2,2-difeniletil)amino[-9-(N-etil-β-D-ribofuranosiluronamida)-N-(2-{*N'*-[1-(2-piridil)-4-piperidil]-ureido]etil)-9*H*-purin-2-carboxamida amorfa (66,1 g, 0,85 moles) se le añadió una solución de agua al 2% v/v en 2-butanona (660 ml) y la mezcla resultante se calentó a 69-71°C durante 18 horas. Después de este tiempo, se añadió a la mezcla un cristal seminal de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-N-

(2-{*N*'-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida (0,149 g) y se continuó agitando a 69-71°C durante 8 horas. La temperatura de la mezcla después se redujo a 59-61° y se continuó agitando a esta temperatura durante 64 horas. Después, la suspensión resultante se enfrió a temperatura ambiente y el sólido se recogió por filtración. La torta de filtro se lavó con 2-butanona (2 x 100 ml) y el sólido resultante se secó a 60°C al vacío durante 60 horas y después a 80°C al vacío durante 72 horas, dando un sólido cristalino (35,72 g) que contenía pequeñas cantidades de 2-butanona. Los datos analíticos recogidos para el producto el producto, incluyendo la caracterización por difracción de rayos x de cristales finos fueron consistentes con los datos descritos en el Ejemplo 1.

Ejemplo 3

Se agitó acetato de etilo (25 ml) con agua desionizada (10 ml) a temperatura ambiente y la fase orgánica se recogió, dando un solución de acetato de etilo que se saturó con agua. Se cargó 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-N-(2-{*N*'-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida amorfa en un recipiente equipado con una barrilla de agitación magnética cubierta con Teflon® y un condensador. Después se añadió una solución de acetato de etilo que se había saturado con

agua como se ha preparado anteriormente (10 ml) al sólido amorfo y la mezcla resultante se calentó a 55-60°C en una atmósfera de nitrógeno. Después se añadió un cristal seminal (aproximadamente 0,005 g) de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-N-(2-{*N*'-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida cristalina y la mezcla resultante se agitó a 55-60°C durante 3 días, tiempo durante el cual se formó una suspensión. Después, la mezcla se enfrió a temperatura ambiente y el sólido se recogió por filtración. Después, la torta de filtro se lavó con acetato de etilo (2 x 5 ml) y el sólido resultante se secó a 50°C durante 24 horas, dando un sólido cristalino (0,898 g) que contenía pequeñas cantidades de cloruro sódico (presente inadvertidamente en el material de partida y posteriormente retirado por filtración con el producto) y acetato de etilo. Los datos analíticos recogidos para el producto, incluyendo la caracterización por difracción de rayos x de cristales finos fueron consistentes con los datos descritos en el Ejemplo 1, con la excepción se que había una pequeña cantidad de cloruro sódico.

Ejemplo 4

Una solución de agua al 2% v/v en acetonitrilo se preparó por disolución de agua desionizada (2,0 ml) en acetonitrilo y después llevando el volumen hasta 100 ml con

acetonitrilo. Se cargó 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-N-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida amorfa (1,0 g, 0,0013 mol) en un recipiente equipado con una varilla de agitación magnética cubierto con Teflon® y un condensador. Después, se añadió una solución de agua en acetonitrilo preparada como anteriormente (10 ml) al sólido amorfo y la mezcla resultante se calentó a 55-60°C en una atmósfera de nitrógeno. Después se añadió un cristal seminal (aproximadamente 0,005 g) de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-N-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida cristalina y la mezcla resultante se agitó a 55-60°C durante 3 días, tiempo durante el cual se formó una suspensión espesa. Después, la mezcla se enfrió a temperatura ambiente y se añadió más acetonitrilo (10 ml). Después, el sólido se recogió por filtración. Después, la torta de filtro se lavó con acetonitrilo (2 x 5 ml) y se secó a 50°C durante 24 horas, dando un sólido cristalino (0,866 g) que contenía pequeñas cantidades de cloruro sódico (presente inadvertidamente en el material de partida y posteriormente retirado por filtración con el producto) y acetonitrilo. Los datos analíticos recogidos para el producto, incluyendo la caracterización por difracción de rayos x de cristales finos fueron consistentes con los

datos descritos en el Ejemplo 1 con la excepción de que había una pequeña cantidad de cloruro sódico.

Ejemplo 5

Se agitó acetato de isopropilo (25 ml) con agua desionizada (10 ml) a temperatura ambiente y la fase orgánica se recogió, dando una solución de acetato de isopropilo que se saturó con agua. Se cargó 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-N-(2-{*N*'-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida amorfa en un recipiente equipado con una barrilla de agitación magnética cubierta con Teflon® y un condensador. Después se añadió una solución de acetato de isopropilo, que se saturó con agua como se ha preparado anteriormente (10 ml) al sólido amorfo y la mezcla resultante se calentó a 55-60°C en una atmósfera de nitrógeno. Después se añadió un cristal seminal (aproximadamente 0,005 g) de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-N-(2-{*N*'-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida cristalina y la mezcla resultante se agitó a 55-60°C durante 3 días, tiempo durante el cuales formó una suspensión. Después, la mezcla se enfrió a temperatura ambiente y el sólido se recogió por filtración. Después, la torta de filtro se lavó con acetato de isopropanol (2 x 5 ml) y se secó a 50°C durante 24 horas, dando un sólido

cristalino incoloro (0,455 g) que contenía pequeñas cantidades de cloruro sódico (presente inadvertidamente en el material de partida y posteriormente retirado por filtración con el producto) y acetato de isopropanol. Los datos analíticos recogidos para el producto, incluyendo la caracterización por difracción de rayos x de cristales finos fueron consistentes con los datos descritos en el Ejemplo 1, con la excepción de que había pequeñas cantidades de cloruro sódico.

Ejemplo 6

Se preparó una solución de agua al 2% v/v en isopropanol por disolución de agua desionizada (2,0 ml) en isopropanol y después llevando el volumen hasta 100 ml con isopropanol. Se cargó 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-N-(2-{*N*'-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida amorfa (1,0 g, 0,0013 moles) en un recipiente equipado con una barrilla de agitación magnética cubierta con Teflon® y un condensador. Después se añadió una solución de agua al 2% en isopropanol preparada como anteriormente (10 ml) al sólido amorfo y la mezcla resultante se calentó a 55-60°C en una atmósfera de nitrógeno. Después se añadió un cristal seminal (aproximadamente 0,005 g) de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-N-(2-{*N*'-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-

carboxamida cristalina y la mezcla resultante se agitó a 55-60°C durante 8 días, tiempo durante el cual se formó una suspensión. Después, la mezcla se enfrió a temperatura ambiente y el sólido se recogió por filtración. Después, la torta de filtro se lavó con isopropanol (2 x 5 ml) y se secó a 50°C durante 24 horas, dando un sólido cristalino incoloro (0,866 g) que contenía pequeñas cantidades de cloruro sódico (presente inadvertidamente en el material de partida y posteriormente retirado por filtración con el producto) e isopropanol. Los datos analíticos recogidos para el producto, incluyendo la caracterización por difracción de rayos x de cristales finos fueron consistentes con los datos descritos en el Ejemplo 1, con la excepción de que había una pequeña cantidad de cloruro sódico.

Ejemplo 7

Se cargó 6-[(2,2-difeniletil)amino[-9-(N-etil-β-D-ribofuranosiluronamida)-N-(2-{*N'*-[1-(2-piridil)-4-piperidil]-ureido]etil)-9*H*-purin-2-carboxamida amorfa (1,0 g, 0,0013 moles) en un recipiente equipado con una barrilla de agitación magnética cubierta con Teflon® y un condensador. Después, a este sólido amorfo se le añadió acetato de metilo (10 ml) y agua desionizada (0,20 ml) y la mezcla resultante se calentó a 55-60°C en una atmósfera de nitrógeno. Después se añadió un cristal seminal

(aproximadamente 0,005 g) de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-N-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida cristalina y la mezcla resultante se agitó a 55-60°C durante 24 horas, tiempo durante el cual se formó una suspensión. Después, la mezcla se enfrió a temperatura ambiente y el sólido se recogió por filtración. Después, la torta de filtro se lavó con acetato de metilo (2 x 5 ml) y se secó a 50°C durante 24 horas, dando un sólido cristalino incoloro (0,860 g) que contenía pequeñas cantidades de cloruro sódico (presente inadvertidamente en el material de partida y posteriormente retirado por filtración con el producto) y acetato de metilo. Los datos analíticos recogidos para el producto, incluyendo la caracterización por difracción de rayos x de cristales finos fueron consistentes con los datos descritos en el Ejemplo 1, con la excepción de que había una pequeña cantidad de cloruro sódico.

Ejemplo 8

Se cargó 6-[(2,2-difeniletil)amino[-9-(N-etil-β-D-ribofuranosiluronamida)-N-(2-{*N'*-[1-(2-piridil)-4-piperidil]-ureido]etil)-9*H*-purin-2-carboxamida amorfa (1,0 g, 0,0013 moles) en un recipiente equipado con una barrilla de agitación magnética cubierta con Teflon® y un condensador. Después, a este sólido amorfo se la añadió

butan-2-ol (10 ml) y agua desionizada (0,20 ml) y la mezcla resultante se calentó a 55-60°C en una atmósfera de nitrógeno. Después se añadió un cristal seminal (aproximadamente 0,005 g) de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-N-(2-{*N*'-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida cristalina y la mezcla resultante se agitó a 55-60°C durante 3 semanas, tiempo durante el cual se formó lentamente una suspensión. Después, la mezcla se enfrió a temperatura ambiente y el sólido se recogió por filtración. Después, la torta de filtro se lavó con butan-2-ol (2 x 5 ml) y se secó a 50°C durante varios días, dando un sólido cristalino incoloro (0,860 g) que contenía pequeñas cantidades de cloruro sódico (presente inadvertidamente en el material de partida y posteriormente retirado por filtración con el producto) y acetato de metilo. Los datos analíticos recogidos para el producto, incluyendo la caracterización por difracción de rayos x de cristales finos fueron consistentes con los datos descritos en el Ejemplo 1, con la excepción de que había una pequeña cantidad de cloruro sódico.

Ejemplo 9

A una suspensión agitada de 6-[(2,2-difeniletil)amino]-9-(N-etil-2,3-O-isopropilideno-β-D-ribofuranosiluronamida)-N-(2-{N'-[1-(2-piridil)-4-

piperidil]ureido}etil)-9*H*-purin-2-carboxamida (200 g, 0,245 moles) (véase el documento WO-A- 01/94368) en agua desionizada (1000 ml) se le añadió ácido metanosulfónico (17,5 ml, 0,269 moles) en una atmósfera de nitrógeno. Después, la mezcla resultante se calentó a temperaturas de hasta 95°C y se agitó a este intervalo de temperatura durante aproximadamente 5 horas, tiempo durante el cual se consumió todo el material de partida. Después, la reacción se interrumpió por la adición de una solución acuosa al 10% p/p de fosfato ácido disódico heptahidrato (82 ml) y después la solución resultante se enfrió a temperatura ambiente, después de lo cual se añadió acetato de metilo (2000 ml). Después, a la mezcla resultante se le añadió lentamente una solución acuosa al 10% p/p de fosfato ácido disódico heptahidrato (1300 ml) con agitación vigorosa. Después, las fases se dejaron separar y la fase orgánica se lavó con una solución acuosa al 2% p/p de fosfato diácido sódico heptahidrato (200 ml). Después de dejar que las fases se separaran, la capa orgánica se recogió y se añadió acetato de metilo adicional (1000 ml). La mezcla resultante después se destiló azeotrópicamente, se secó por destilación a presión atmosférica en una pequeña cantidad de agua hasta que la cantidad de agua que quedaba en la mezcla fue e aproximadamente del 2% p/p por el análisis de Karl-Fischer. Esto requirió la adición de más acetato de metilo (3000 ml, añadido en porciones durante la

destilación) y se recogió un total aproximadamente 3000 ml de destilado. Esto dio agua un total de 1,8% p/p en la mezcla, que después se calentó a reflujo durante 18 horas. Después se añadió agua desionizada (4 ml) hasta ajustar el contenido de agua de la mezcla a 2,0% p/p y se continuo calentando a reflujo durante 24 horas, tiempo tras el cual se formó una suspensión. La mezcla después se enfrió a temperatura ambiente y el sólido se recogió por filtración. La torta de filtro se lavó con una solución al 2% p/p de agua en acetato de metilo (200 ml después 400 ml) y se secó a 50°C al vacío durante 20 horas, dando material cristalino (155,6 g) que estaba contaminado con pequeñas cantidades de sales inorgánicas. Una suspensión de este material (153,6 g) en una mezcla de acetato de etilo (1070 ml) y etanol (460 ml) se calentó a reflujo durante 10 minutos, dando una solución ligeramente turbia. Después del enfriamiento a temperatura ambiente, la mezcla se filtró, dando un filtrado transparente que después se destiló a presión atmosférica. Durante el curso de la destilación se añadió en porciones acetato de etilo adicional (2900 ml) y se recogieron un total de 2900 ml de destilado. Hacia el final de la destilación, se necesitó agua desionizada (se añadió en 2 porciones 60 ml) para mantener el producto en solución y crear las condiciones necesarias para que se produjera la cristalización. Al final de la destilación, había aproximadamente un 2% en moles de etanol y aproximadamente

un 2,3% p/p de agua presente en la mezcla. Por fines de conveniencia, la mezcla se dejó en este momento a temperatura ambiente durante 60 horas. Después, la mezcla se calentó a aproximadamente 60°C durante 30 horas, tiempo durante el cual se formó una suspensión. Después la mezcla se enfrió a temperatura ambiente y el sólido se recogió por filtración. Después, la torta de filtro se lavó con una solución de agua al 2% v/v en acetato de etilo (150 ml y después 300 ml) y se secó al vacío a 70°C, dando un sólido cristalino incoloro (134 g) que contenía pequeñas cantidades de acetato de etilo residual. Los datos analíticos recogidos para el producto, incluyendo la caracterización por difracción de rayos x de cristales finos fueron consistentes con los datos descritos en el Ejemplo 1.

Ejemplo Comparativo 1

Una muestra de 6-[(2,2-difeniletil)amino]-9-(N-etil-2,3-O-isopropilideno-β-D-ribofuranosiluronamida)-N-(2-{N'-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida que se había preparado usando el procedimiento descrito en el Ejemplo 8 del documento WO-A-01/94368 se examinó por difracción de rayos-X de polvo y se encontró que no era cristalina. El patrón de difracción de rayos x de cristales finos se determinó usando un difractómetro de rayos x de cristales finos SIEMENS D5000 equipado con un cambiador de muestras automático, un goniómetro theta-

theta, ranuras de divergencia de haces automáticas, un monocromador secundario y un contador de centelleo. La muestra se preparó para el análisis empaquetando el polvo en un soporte de muestra de disco de silicio. La muestra se hizo girar mientras se irradiaba con rayos X K-alfa$_1$ de cobre (longitud de onda = 1,5406 Ángstrom), funcionando el tubo de rayos X a 40 kV/40 mA. El análisis se realizó con el goniómetro funcionando en un modo de exploración por etapas fijado para un recuento de 5 segundos por etapa de 0,02° sobre un intervalo dos theta de 4° a 45°.

Ejemplo Comparativo 1

Una muestra de 6-[(2,2-difeniletil)amino]-9-(N-etil-2,3-O-isopropilideno-β-D-ribofuranosiluronamida)-N-(2-{N'-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida que se había preparado usando el procedimiento descrito en el Ejemplo 35 del documento WO-A-01/94368 se examinó por difracción de rayos-X de polvo y se encontró que no era cristalina. El patrón de difracción de rayos x de cristales finos se determinó usando un difractómetro de rayos x de cristales finos SIEMENS D5000 equipado con un cambiador de muestras automático, un goniómetro theta-theta, ranuras de divergencia de haces automáticas, un monocromador secundario y un contador de centelleo. La muestra se preparó para el análisis empaquetando el polvo en un soporte de muestra de disco de silicio. La muestra se

hizo girar mientras se irradiaba con rayos X K-alfa$_1$ de cobre (longitud de onda = 1,5406 Ángstrom), funcionando el tubo de rayos X a 40 kV/40 mA. El análisis se realizó con el goniómetro funcionando en un modo de exploración por etapas fijado para un recuento de 5 segundos por etapa de 0,02° sobre un intervalo dos theta de 4° a 45°.

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en la siguientes:

REIVINDICACIONES

1. Una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(N-etil-2,3-O-isopropilideno-β-D-ribofuranosiluronamida)-N-(2-{N'-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida.

2. Una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(N-etil-2,3-O-isopropilideno-β-D-ribofuranosiluronamida)-N-(2-{N'-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida de acuerdo con la reivindicación 1, caracterizada por un espectro de infrarrojo de estado sólido que muestra bandas de absorción significativas a ν = 3478, 3395, 3375, 3301, 3060, 3024, 2971, 2943, 1657, 1639, 1597, 1552, 1527, 1494, 1475, 1468, 1456, 1434, 1405, 1374, 1351, 1324, 1310, 1300, 1233, 1220, 1163, 1150, 1123, 1113, 1102, 1078, 1054, 1000, 976, 947, 932, 909, 864, 813, 777, 759, 734, 699, 683 y 667 cm^{-1}. y un patrón de difracción de rayos-X de polvo obtenido usando rayos X K-alfa$_1$ de cobre (longitud de onda = 1,5406 Ángstrom) que mostraba picos principales a 5,185, 6,647, 8,232, 9,131, 9,794, 10,702, 11,370, 12,495, 13,949, 14,393, 14,536, 14,899, 15,148, 15,369, 16,111, 16,439, 17,099, 17,369, 17,908, 18,517, 18,753, 19,414,

20,079, 20,418, 21,357, 21,696, 22,455, 23,187, 23,697, 24,030, 24,755, 24,861, 24,966, 25,795, 26,214, 26,570, 26,949, 27,054, 27,308, 27,776, 28,718, 28,991, 29,854, 30,581, 31,142, 32,517, 33,177, 33,596, 34,484, 35,048, 35,399, 35,704, 36,797, 37,819, 38,667, 39,568, 40,463, 40,929, 41,473, 42,455 y 43,347 grados 2θ.

3. Una composición farmacéutica que comprende una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida, como se define en la reivindicación 1 o la reivindicación 2, junto con un excipiente, diluyente o vehículo farmacéuticamente aceptable.

4. Una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida, como se define en la reivindicación 1 o la reivindicación 2, para uso como un medicamento.

5. El uso de una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida, como se define en la reivindicación 1 o la

reivindicación 2, para la fabricación de un medicamento que tiene actividad agonista del receptor de A2a.

6. El uso de forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida, como se define en la reivindicación 1 o la reivindicación 2, para la fabricación de un agente antiinflamatorio.

7. El uso de una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida, como se define en la reivindicación 1 o la reivindicación 2, para la fabricación de un medicamento para el tratamiento de una enfermedad respiratoria.

8. El uso de acuerdo con la reivindicación 7, en el que la enfermedad se selecciona entre el grupo compuesto por el síndrome de insuficiencia respiratoria en adultos (ARDS), bronquitis, bronquitis crónica, enfermedad pulmonar obstructiva crónica, fibrosis quística, asma, enfisema, bronquiectasia, sinusitis crónica y rinitis.

9. El uso de una forma cristalina de 6-[(2,2-

difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida, como se define en la reivindicación 1 o la reivindicación 2, para la fabricación de un medicamento para el tratamiento del choque séptico, la disfunción eréctil masculina, la infertilidad de factor masculino, la infertilidad de factor femenino, la hipertensión, la apoplejía, la epilepsia, la isquemia cerebral, la enfermedad vascular periférica, la lesión de reperfusión postisquémica, la diabetes, la artritis reumatoide, la esclerosis múltiple, la psoriasis, la dermatitis, la dermatitis alérgica, el eccema, la colitis ulcerosa, la enfermedad de Crohn, la enfermedad inflamatoria del intestino, la gastritis producida por *Heliobacter pylori*, la gastritis no producida por *Heliobacter pylori*, lesiones en el tracto gastrointestinal inducidas por fármacos antiinflamatorios no esteroideos o un trastorno psicótico, o para la curación de heridas.

10. Un procedimiento de tratamiento de un mamífero, incluyendo un ser humano, con un agonista del receptor A2a, que incluye el tratamiento de dicho mamífero con una cantidad eficaz de una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-

carboxamida , como se define en la reivindicación 1 o la reivindicación 2.

11. Un procedimiento de tratamiento de un mamífero, incluyendo un ser humano, para tratar una enfermedad inflamatoria, que incluye el tratamiento de dicho mamífero con una cantidad eficaz de una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida, como se define en la reivindicación 1 o la reivindicación 2.

12. Un procedimiento de tratamiento de un mamífero, incluyendo un ser humano, para tratar una enfermedad respiratoria, que incluye el tratamiento de dicho mamífero con una cantidad eficaz de una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida, como se define en la reivindicación 1 o la reivindicación 2.

13. Un procedimiento de acuerdo con la reivindicación 12, donde la enfermedad se selecciona entre el grupo compuesto por el síndrome de insuficiencia respiratoria en adultos (ARDS), bronquitis, bronquitis crónica, enfermedad pulmo-

nar obstructiva crónica, fibrosis quística, asma, enfisema, bronquiectasia, sinusitis crónica y rinitis.

14. Un procedimiento de tratamiento de un mamífero, incluyendo un ser humano, para tratar el choque séptico, la disfunción eréctil masculina, la infertilidad de factor masculino, la infertilidad de factor femenino, la hipertensión, la apoplejía, la epilepsia, la isquemia cerebral, la enfermedad vascular periférica, la lesión de reperfusión post-isquémica, la diabetes, la artritis reumatoide, la esclerosis múltiple, la psoriasis, la dermatitis, la dermatitis alérgica, el eccema, la colitis ulcerosa, la enfermedad de Crohn, la enfermedad inflamatoria del intestino, la gastritis producida por *Heliobacter pylori*, la gastritis no producida por *Heliobacter pylori*, lesiones en el tracto gastrointestinal inducidas por fármacos antiinflamatorios no esteroideos o un trastorno psicótico, o para la curación de heridas, que incluye el tratamiento de dicho mamífero con una cantidad eficaz de una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida, como se define en la reivindicación 1 o la reivindicación 2.

15. Un procedimiento para la preparación de una forma

cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida que comprende las etapas de:

(a) disolver 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida amorfa en un disolvente orgánico que contiene al menos un 2% p/p de agua disuelta; y

(b) calentar la solución obtenida de esta forma a una temperatura de al menos 50°C hasta que se produzca la cristalización.

16. Un procedimiento de acuerdo con la reivindicación 15, en el que el disolvente orgánico es 2-butanona, acetato de etilo, acetonitrilo, acetato de isopropilo, isopropanol, acetato de metilo, butan-2-ol o acetato de metilo.

17. Un procedimiento de acuerdo con la reivindicación 15, en el que el disolvente orgánico es 2-butanona, acetato de metilo o acetato de etilo.

18. Un procedimiento de acuerdo con una cualquiera de las reivindicaciones 15 a 17, en el que el contenido de agua del disolvente orgánico es del 2% v/v.

19. Un procedimiento de acuerdo con una cualquiera de las reivindicaciones 15 a 18, en el que la solución se calienta a 50-80°C.

FORMA DE FÁRMACO CRISTALINA

Resumen de la invención

La presente invención se refiere a una forma cristalina de 6-[(2,2-difeniletil)amino]-9-(*N*-etil-β-D-ribofuranosiluronamida)-*N*-(2-{*N'*-[1-(2-piridil)-4-piperidil]ureido}etil)-9*H*-purin-2-carboxamida y a un procedimiento para la preparación de la misma, a composiciones que la contienen y a los usos de dicha forma cristalina.

Figura 1

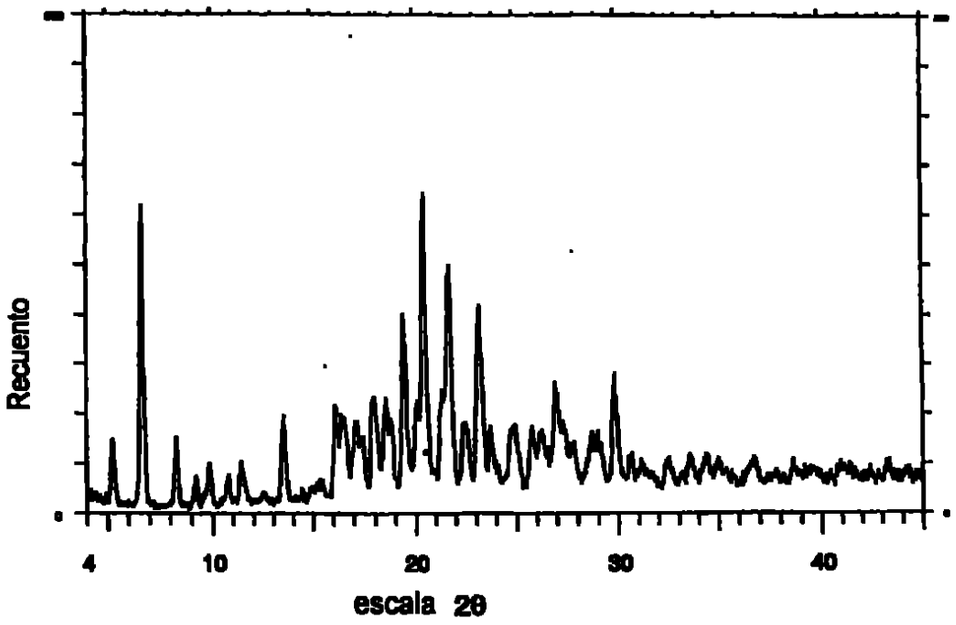


Figura 2

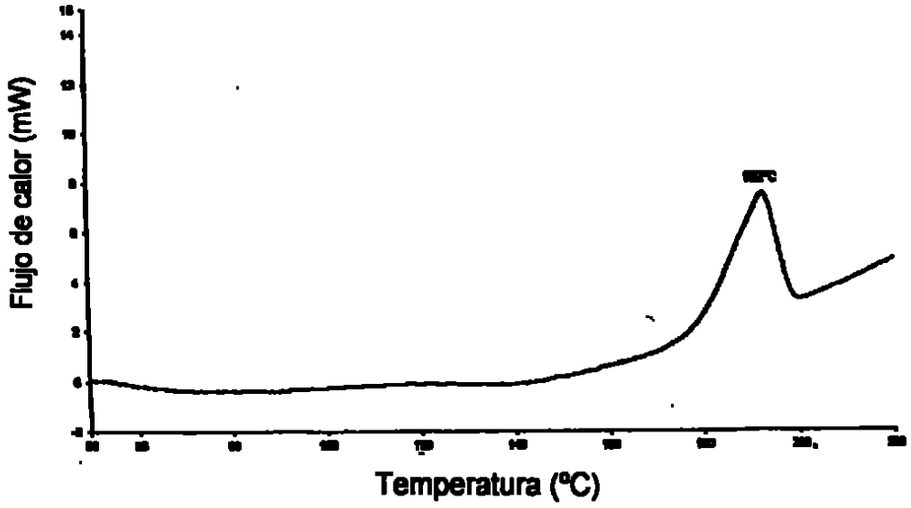


Figura 3

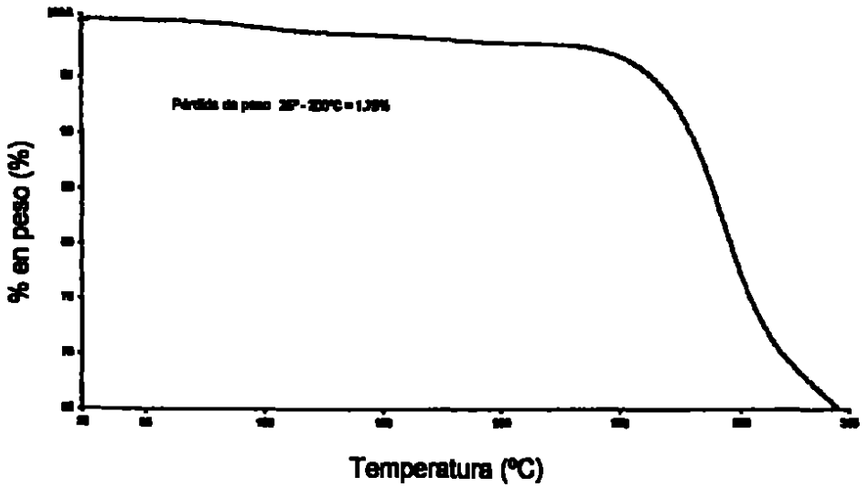


Figura 4

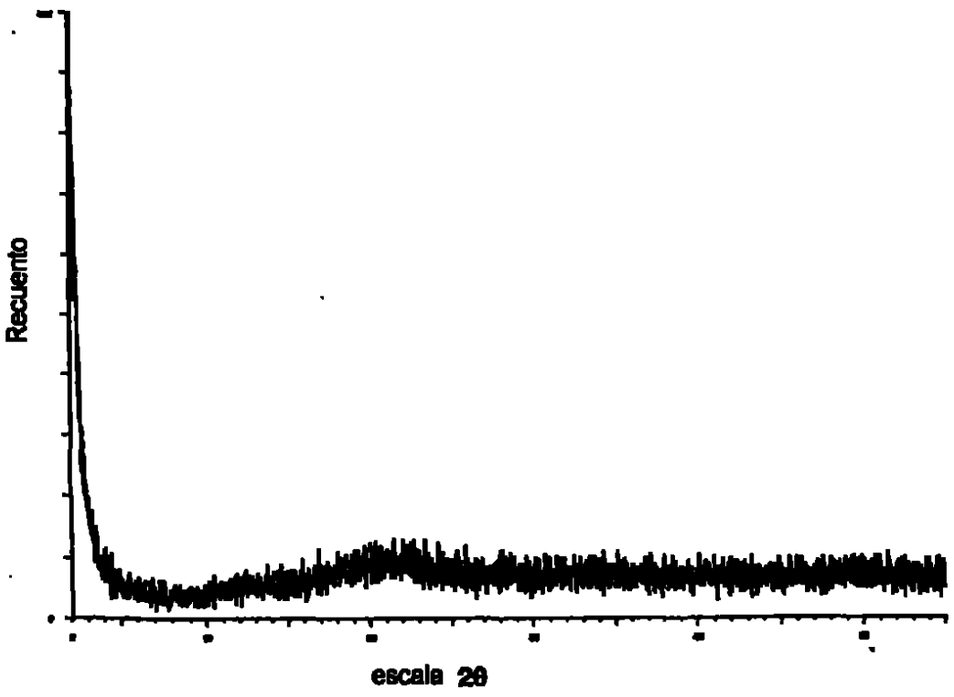
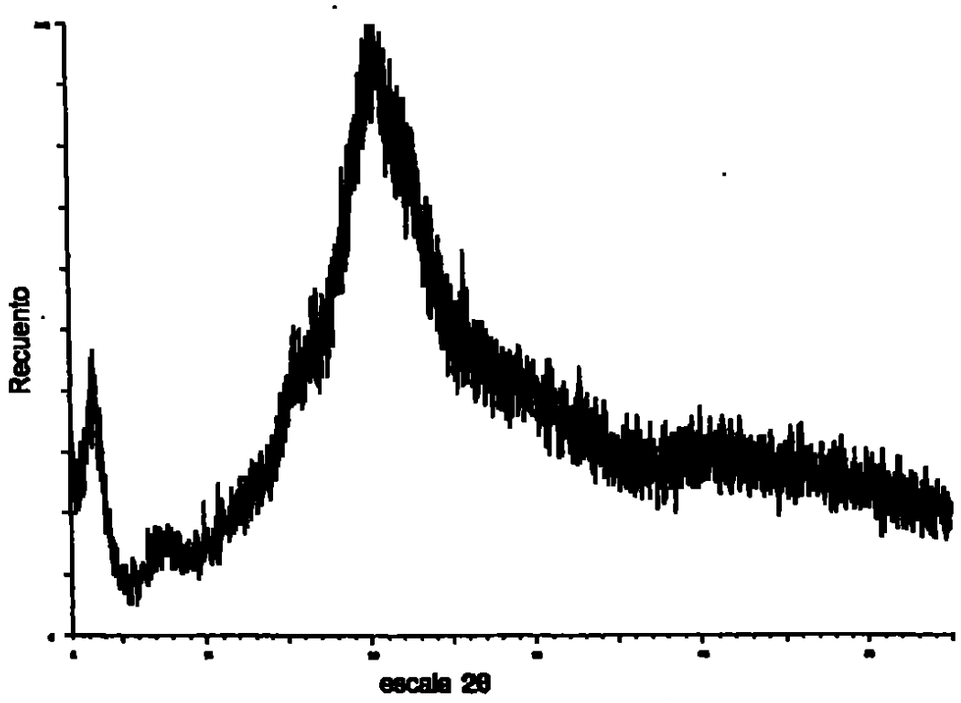


Figura 5



PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

UK PATENT DEPARTMENT
09 FEB 2004

PCT

To:

RUDDOCK, Keith S.
PFIZER LIMITED
Ramsgate Road
Sandwich, Kent CT13 9NJ
GRANDE BRETAGNE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	05.02.2004
Applicant's or agent's file reference PCS22056AAJR	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB 02/04979	27.11.2002	06.12.2001

Applicant
PFIZER LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

   The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/901).

   Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

   For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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

FILING	✓
DEBIT NOTE	
RENEWALS	
RECORDABLE	

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer
Digiusto, M
Tel. +49 89 2399-8162

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATI N REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCS22058AAJR	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 02/04979	International filing date (day/month/year) 27.11.2002	Priority date (day/month/year) 06.12.2001
International Patent Classification (IPC) or both national classification and IPC C07H19/16		
Applicant PFIZER LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

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

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.12.2002	05.02.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Hennard, C Telephone No. +49 89 2399-7355

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

102

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/IB 02/04979

I. **Basis of the report**

1. With regard to the elements of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-28 as originally filed

Claims, Numbers

1-19 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/IB 02/04979

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 10-14

   because:

   ☒ the said international application, or the said claims Nos. 10-14 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

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

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	none
Inventive step (IS)	Yes:	Claims	1-19
	No:	Claims	none
Industrial applicability (IA)	Yes:	Claims	1-9 and 15-19
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 10-14 of the present application relate to a method of treatment of humans related to a disease. For this type of claims, according to rule 67.1(iv) PCT, no opinion is required. Nevertheless, an opinion concerning the novelty and the inventiveness of the claim is given considering that the claim is interpreted as if it would have been formulated as follows: "Use of the compounds ... for the preparation of a medicament for the treatment of ..." or any related form. It is clear that for claims 10-14 to be acceptable, a reformulation of the claims is necessary.

Re item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. Reference is made to the following documents:
   D1: WO 01 094368 A, cited in the application
   D2: WO 02 096462 A
   D3: WO 01 60835 A
   D4: US 2001/0020089
   D1 which is an intermediate document, filed on 05.06.2001, published on 13.12.2001 and D2 which is a document filed 24.05.2002, published on 05.12.2002 and claiming a priority right on 25.02.2001, are not prior art according to the Chap II PCT proceedings.
   The extensive examination of these documents, on the question whether they constitute prior art or not, will depend essentially on the analysis of the claimed priority rights of the present application and will only be performed in the regional European proceedings to come (Rules 64.3 and 70.10 PCT). Nevertheless the following comments are made with regards to D2 and the novelty of claims 1-14 of the present application: D2 (page 24, line 30 - page 28, line 19) discloses the compound of the present application as a preferred embodiment of D2. Furthermore, D2 clearly discloses that the compounds of D2 are separated by fractional crystallisation. It is therefore considered that D2 discloses crystals of the compound claimed in the application. The infra-red and X-ray diffraction parameters even if not disclosed in D2 are considered implicitly present in the document since these features are linked to the compound crystal itself. D2 further discloses the use of this

compound to treat diseases.

3. **Novelty and inventive step (Articles 33(2) and 33(3) PCT):**
D3, which can be considered to represent the closest prior art concerns adenosine derivatives and their use as adenosine A2a receptor agonists. The compound of the present application distinguishes itself from the compounds of D3 by the substituent in position 2 of the purine moiety. Further, the compound of the application is claimed under the crystalline form.
Since there is no indication for substituting the position 2 of the purine by a (2-pyridyl-4-piperidyl)-ureido containing moiety in the prior art D3 or D4, the compound of the present application is considered as an non-obvious alternative to the compounds known from D3 and D4. This compound is therefore novel and involves an inventive merit over the prior art. It is concluded that claims 1-19 of the present application fulfil the requirements of Articles 33(2) and 33(3) PCT.

4. Due to the nature of the claims, an industrial applicability of claims 1-9 and 15-19 is obvious and these claims are considered to fulfil the requirements of Article 33(4) PCT.

5. A brief description of the figures is missing and these should be numbered separately.

Saisi le 4.04.03 NSR

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

17/04/03

To:
PFIZER LIMITED
Attn. Wood, David J.
Ramsgate Road
Sandwich, Kent CT13 9NJ
UNITED KINGDOM

	Date of mailing (day/month/year) 21/03/2003
Applicant's or agent's file reference PCS22056AAJR RP	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/IB 02/04979	International filing date (day/month/year) 27/11/2002
Applicant PFIZER LIMITED	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet. 24.3.03

   Where? Directly to the International Bureau of WIPO
   34, chemin des Colombettes
   1211 Geneva 20, Switzerland
   Facsimile No.: (41-22) 740.14.35 21.4.03

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

   Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

   Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	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	Sandrine Polenzani

Form PCT/ISA/220 (July 1998)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PCS22056AAJR		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB 02/04979	27/11/2002	06/12/2001
Applicant		
PFIZER LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 05 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] Certain claims were found unsearchable (See Box I).

3. [ ] Unity of invention is lacking (see Box II).

4. With regard to the title,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   CRYSTALLINE FORM OF A RIBOFURANOSYLURONAMIDE DERIVATIVE; A HUMAN ADENOSINE A2A RECEPTOR AGONIST

5. With regard to the abstract,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority..

6. The figure of the drawings to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REP RT

International Application No
PCT/IB 02/04979

108

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H19/16 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K

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

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

CHEM ABS Data, EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 2001 094368 A (PFIZER LIMITED, UK;PFIZER INC.) 13 December 2001 (2001-12-13) cited in the application examples 8 and 35	1-19
E	WO 2002 096462 A (PFIZER INC., USA) 5 December 2002 (2002-12-05) page 24, line 30 - page 28, line 19	1-14
A	WO 01 60835 A (STEPHENSON PETER THOMAS ;PFIZER LTD (GB); MANTELL SIMON JOHN (GB);) 23 August 2001 (2001-08-23) the whole document	1-19
A	US 2001/020089 A1 (STEPHENSON PETER THOMAS ET AL) 6 September 2001 (2001-09-06) the whole document	1-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 March 2003	21/03/2003

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	Hennard, C

Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 10-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 28, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 48.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 02/04979

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 02/04979

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2001094368 A		NONE	
WO 2002096462 A		NONE	
WO 0160835 A	23-08-2001	AU 3044001 A	27-08-2001
		BR 0108408 A	26-11-2002
		EP 1255764 A1	13-11-2002
		WO 0160835 A1	23-08-2001
		NO 20023894 A	01-10-2002
		US 2001020089 A1	06-09-2001
US 2001020089 A1	06-09-2001	AU 3044001 A	27-08-2001
		BR 0108408 A	26-11-2002
		EP 1255764 A1	13-11-2002
		WO 0160835 A1	23-08-2001
		NO 20023894 A	01-10-2002

114

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04052218 00000000 Folios: 113
Fecha (AMD): 2004-06-04 09:43:39
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ MODELO DE UTILIDAD	( )	(✓)
- Indicación de que se solicita la concesión de una patente.	( )	(✓)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	(✓)
- Descripción de la invención.	( )	(✓)
- Dibujos de ser estos pertinentes.	( )	(✓)
- Comprobante de Pago de las tasas establecidas.		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solcitante o de la persona que presenta		
La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable: Claudia M Neva

Fecha:

Industria y Comercio
SUPERINTENDENCIA

115

Folio 115

2020
Bogotá D C

Doctor(a)
CARLOS R. OLARTE
Apoderado(a)
PFIZER INC.

REFERENCIA:	Radicación N°	04-052218
	Solicitud internacional	PCT/IB02/04979
	Fecha inicio fase nacional	06/07/2004
	Trámite	011
	Evento	379
	Actuación	416
	Oficio N°	994
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486, de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la Decisión 486.

Cúmplase
Dado en Bogotá D C,

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe División de Nuevas Creaciones.

202044