



OK



Industria y Comercio
SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

08-31044

SOLICITUD DE PATENTE DE
INVENCION

TITULO: DERIVADOS DE PIRAZOLO[1,5-ALFA]PIRIMIDILO UTILES COMO
ANTAGONISTAS DE RECEPTOR DE FACTOR LIBERADOR DE
CORTICOTROPINA

SOLICITANTE: SB PHARMCO PUERTO RICO INC., Y NEUROCRINE
BIOSCIENCES INC.

DIRECCIÓN: BBV Tower, 8th Floor, 254 Munoz Rivera Avenue, San Juan,
Puerto Rico 00918. Puerto Rico; 10555 Science Center Drive, San Diego,
California 92121 E.U.A.

CO7D 487104; A61K 31/519; A61P 25/00.

APODERADO: CARLOS R. OLARTE

BOGOTÁ 28 de Marzo de 2008



No. 08-031044-00000-0000

Fecha: 2008-03-28 17:27:06

Dep. 2020 NUECREACION

Tra. 11 PATENTEIYII

Eve: 378 FASENACIONAL

Act. 411 PRESENTACION

Folios: 119

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD

PATENTE PCT

ENTRADA EN FASE NACIONAL

P2008/000058

SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☒

Capítulo I.

☐

Capítulo II.

2

SOLICITANTE
(71)Nombre: SB PHARMCO PUERTO RICO INC.
NEUROCRINE BIOSCIENCES INC.Dirección: BBV Tower 8th Floor, 254 Munoz
Rivera Avenue, San Juan, 00918 Puerto Rico

Nacionalidad o Domicilio: Estadounidense

Lugar de Constitución: Estados Unidos de
America

Teléfono: _____

Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual _____

Número _____

REPRESENTANTE
O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: World Trade Center Torre A,
Calle 100 No. 8A-37 Piso 10

Teléfono: 601-7700 Fax: 601-7799

E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN

C.C.

☒

NIT

☐

C.E.

☐

Otro

☐

Cual _____

Número 79782747Bta

TP 74.295

INVENTOR (ES)
(72)

Nombre: Frank Hossner

Dirección: Third Avenue, Harlow Essex CM19 5AW Gran Bretaña

Nacionalidad o Domicilio: Británico

5

PCT (86)

Solicitud Internacional No. PCT/EP2006/009531

Fecha

Septiembre 28, 2006

Publicación Internacional No. WO 2007/039264

Fecha

Abril 12, 2007

6

Título (54) DERIVADOS DE PIRAZOLO[1,5-ALFA]PIRIMIDILO UTILES COMO
ANTAGONISTAS DE RECEPTOR DE FACTOR LIBERADOR DE CORTICOTROPINA

Clasificación Internacional (51) C07D 487/04, A61K 31/519, A61P 25/00

Prioridad

SI

☒

NO

☐

(33) País de Origen

GB

GB

(32) Fecha

Septiembre 30, 2005

Octubre 19, 2005

(31) Número de Solicitud

0519957.5

PCT/US2005/037576

9

Comprobante de pago No. 08-23,264

Fecha

Marzo 17 de 2008

10

ANEXOS☒

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.

☒

Poderes, si fuere el caso. Adjunto copias simples.

☐

Documento de cesión del inventor al solicitante o a su causante.

☐

Declaraciones.

☒

Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).

☒

Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).

☐

Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).

☐

Traducción del examen preliminar internacional efectuado por la IPEA.

☐

De ser el caso, copia del contrato de acceso.

☐

De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.

☐

De ser el caso, certificado de depósito del material biológico.

☐

Arte final 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.

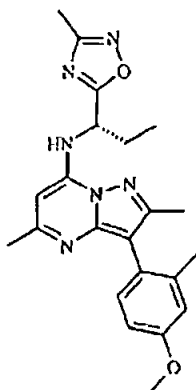
☐

De ser el caso, modificaciones efectuadas a la solicitud internacional.

☒

Otros. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 79.782.747 Bta T.P. 74.295

2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176087-2

RECIBO OFICIAL DE CAJA : 08 - 23,264
FECHA : MARZO 17 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-031044- -00000-0000

Fecha: 2008-03-28 17:27:06 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eje: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 119

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VF. PAGO
OLARTE RAISDEK	CONSIGNACION	BANCO DE BOGOTA	062754387	106976	17/03/2008	6,487,000.00
OLARTE RAISDEK	CONSIGNACION	BANCO DE BOGOTA	062754387	106999	17/03/2008	10,000.00
OLARTE RAISDEK	CONSIGNACION	BANCO DE BOGOTA	062754387	1482919	17/03/2008	2,556,000.00

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

CANT. HISTORICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
	TOTAL :	\$ 501,000.00

CON: QUINIENTOS UN 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 SB PHARMCO PUERTO RICO INC.

Certificado de Notario De Pinna en español sobre funciones de Peter John Giddings, apoderado de SB Pharmco Puerto Rico Inc., quien firma el poder. Firmado el 20 noviembre 2003 por el Notario Público de Londres, Inglaterra: James Kerr Milligan

APOSTILLA

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

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

CERTIFICADO

5. En Londres
6. El 21 noviembre 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la Mancomunidad
8. No. G293253
9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
10. Firma legible de L.D. Wait- Por el Secretario de Estado

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

PODER DE REPRESENTACIÓN

Bilingüe inglés- español firmado por Peter John Giddings, apoderado de SB Pharmco Puerto Rico Inc., el 19 noviembre 2003, en Brentford, Middlesex, Gran Bretaña

CERTIFICACION NOTARIAL

Bilingüe inglés- español, El notario certifica las funciones de Peter John Giddings, apoderado de SB Pharmco Puerto Rico Inc., con sede principal ubicada en Hato Rey, Puerto Rico, y que el otorgante tiene facultad para suscribir el poder.

Es traducción fiel del inglés, con copia para confrontación. Bogotá, 19-12-03.


MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

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

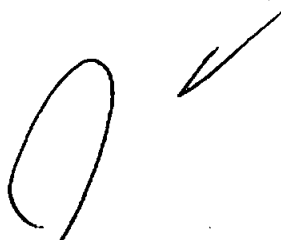
CERTIFICO:

QUE es auténtica la firma suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **PETER JOHN GIDDINGS**, cuya identidad me consta, Apoderado de la Sociedad denominada "**SB PHARMCO PUERTO RICO INC**", Sociedad legalmente constituida y existente de acuerdo con las leyes de Pensilvania, e inscrita bajo el número **66-0489427**, con domicilio social en **105 Ponce de Leon Avenue, Hato Rey, Puerto Rico 00917, Estados Unidos de América;**

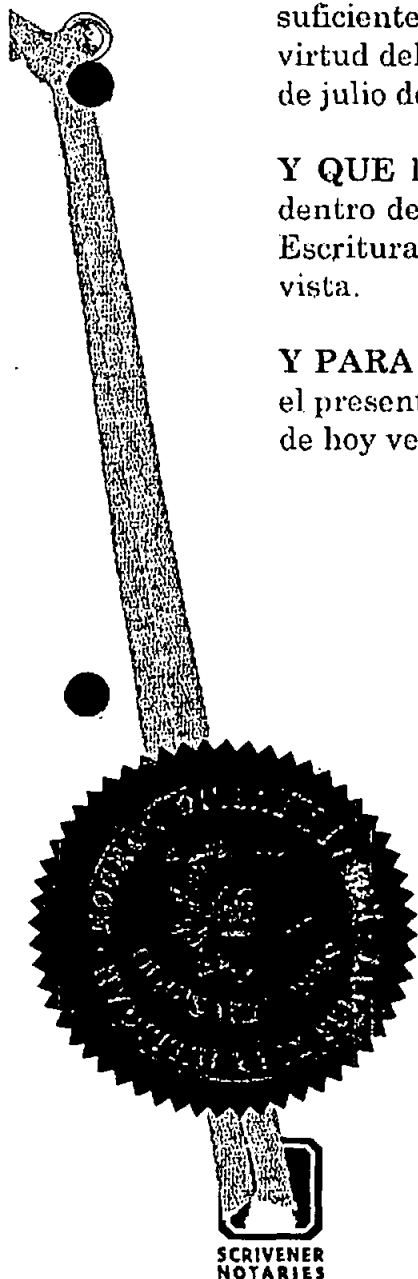
QUE el citado Señor Don **PETER JOHN GIDDINGS** está debida y suficientemente autorizado para firmar documentos de esta clase, en virtud del Poder otorgado en su favor por la referida Sociedad fechado el **11 de julio de 2002**, copia del cual he tenido a la vista;

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

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



JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra



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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

This public document / Le présent acte public

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

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

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

5. at London/à Londres

Certified/Attesté
6. the/le 21 November 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 **G293253**

9. Stamp:
timbre:

10. Signature: **L. D. Wait**



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.

OLARTE RAISBECK

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

PI4826

Power of Attorney

The undersigned,

domiciled in

CSC, The United States Corporation Company, 105 Ponce de Leon Avenue, One Comptroller Plaza, Hato Rey, Puerto Rico 00917, USA

by means of these presents hereby grants to Carlos R. Olarte, and/or Ana Maria Frieri full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models, Industrial Designs and Obtainer's Certificates 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.

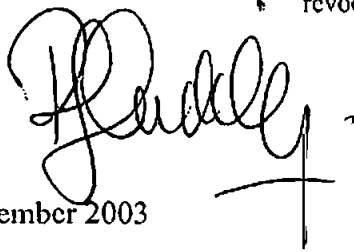
Poder

El suscrito,

domiciliado en

por medio del presente otorga a Carlos R. Olarte, y/o Ana Maria Frieri poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad, Diseños Industriales y Certificados de Obtentor 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: 19 November 2003

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

OLARTE RAISBECK

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,

The undersigned Notary Public certifies:

1. That

of legal age and domiciled in

980 Great West Road, Brentford, Middlesex, TW8 9GS, GB
signed the foregoing document.

2. That the grantor has executed the foregoing
document as attorney
of SB Pharmco Puerto Rico Inc.

3. That SB Pharmco Puerto Rico Inc.
having its principal place of business located in
Hato Rey, Puerto Rico
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):

LIST EACH DOCUMENT SEPARATELY
PROVIDING DATE OF EXECUTION AND ITS
ORIGIN OR SOURCE (e.g. Minutes of 02 July 2003
Board Meeting, Amended Bylaws 01 February 1996)

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

Peter John GIDDINGS
mayor de edad y domiciliado

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
suscibir 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):

Name and Particulars (e.g. Notary's name, Jurisdiction, Date of Licence Expiration)

SEAL (optional)

1

TRADUCCIÓN OFICIAL No. 003-148

Efectuada el día 5 de abril de 2004, de un documento escrito en Inglés, al cual para su identificación se le estampa el sello de Sergio Andrés Rueda Iglesias, Traductor e Intérprete Oficial según consta en el Certificado de Idoneidad Profesional No. 0068 expedido por la Universidad Nacional de Colombia el 26 de febrero del 2001 y en la Resolución No. 0138 expedida por el Ministerio de Justicia y del Derecho el 11 de febrero de 2002.

En Inglés y en Español viene poder otorgado en San Diego, California, Estados Unidos de América el 28 de enero de 2004 por **Neurocrine Biosciences Inc.** a Carlos R. Olarte, y/o Ana Maria Frieri, el cual se explica por sí solo.

Viene certificación notarial que confirma el cargo de la otorgante, Margaret Valeur-Jensen, quien actuó en calidad de Vicepresidente Principal y Asesor Legal General de Neurocrine Biosciences Inc.

RECONOCIMIENTO

Estado de California - Condado de San Diego.

Declaración Juramentada

El 1/28/04 ante mí, Dierde A McCall, Notario Público, compareció personalmente Margaret E. Valeur-Jensen, a quien conozco personalmente y quien reconoció haber firmado el documento precedente en su calidad autorizada, y que mediante tal firma, la persona o entidad en nombre de la cual actuó, firmó el Instrumento.

EN FE DE LO CUAL firmo y estampo mi sello oficial.


SERGIO ANDRÉS RUEDA IGLESIAS
C. C. 83 24.773
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLÉS / INGLÉS - ESPAÑOL
RESOLUCION No. 0138 DE FEBRERO 11.2002
MINISTERIO DE JUSTICIA Y DEL DERECHO

6

(Fdo.) Dierdre A. McCall, Notario Público, cuyo cargo expira el 17 de abril de 2006, según consta en su correspondiente sello notarial.

Estado de California

APOSTILLA

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

1. País: Estados Unidos de América

El presente documento público

2. Fue firmado por Dierdre A. McCall

3. Que actuó en su calidad de Notario Público de California

4. Lleva el sello de dicho Notario Público

Se certificó:

5. En Sacramento, California

6. El 15 de marzo de 2004

7. Por parte del Secretario de Estado Encargado de California

8. Bajo el Número 186724

9. Aparece Gran Sello del Estado de California

10. Kevin Shilley, Secretario de Estado.

Por: (Fdo.) Oatha

Es traducción fiel y completa efectuada por:


Sergio Rueda Iglesias
C.C. 80.424.773 de Bogotá

SERGIO ANDRES RUEDA IGLESIAS
C. C. 80.424.773
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLÉS / INGLÉS - ESPAÑOL
RESOLUCION No. 0138 DE FEBRERO 11, 2002
MINISTERIO DE JUSTICIA Y DEL DERECHO

PI4826

03/16
X

OLARTE RAISBECK

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

Poder

The undersigned,

El suscrito,

domiciled in

Neurocrine Biosciences Inc,
domiciliado en

10555 Science Center Drive, San Diego, CA 92121, USA.

by means of these presents hereby grants to **Carlos R. Olarte, and/or 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, Industrial Designs and Obtainer's Certificates 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.

por medio del presente otorga a **Carlos R. Olarte, y/o Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad, Diseños Industriales y Certificados de Obtentor 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: Margaret Valeur-Jensen,
Senior VP and General Counsel

Date/Fecha: DAY/MONTH (SPELL OUT) YEAR 28 JANUARY 2004

City/Country/Ciudad, País: San Diego, USA

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER - TORRE C
CALLE 100 No. 8A-55 Piso 10
BOGOTÁ, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

Notarial Certification

Certificación Notarial

On this date,

DATE (SPELL OUT MONTH)

The undersigned Notary Public certifies:

En esta fecha,

el Notario Público suscrito certifica:

1. That

Margaret Valeur-Jensen

of legal age and domiciled in

10555 Science Center Drive, San Diego, CA 92121, USA;

signed the foregoing document.

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

2. That the grantor has executed the foregoing document as Señor VP and General Counsel of Neurocrine Biosciences Inc.

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

3. That Neurocrine Biosciences Inc. having its principal place of business located in

San Diego, USA

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. 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. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

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

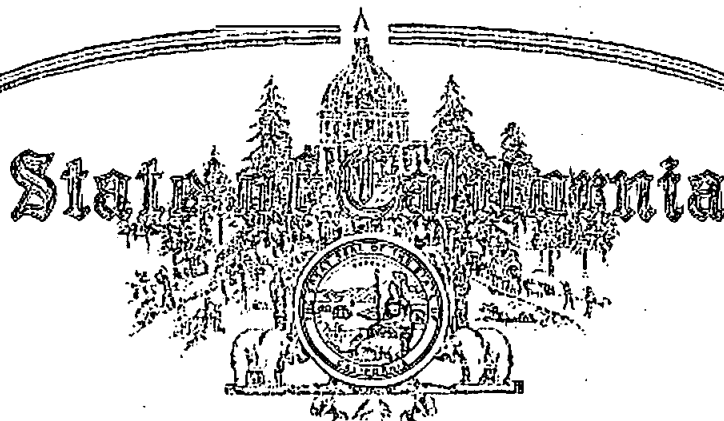
5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):

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):

LIST EACH DOCUMENT SEPARATELY, PROVIDING DATE OF EXECUTION AND ITS ORIGIN OR SOURCE (e.g. Minutes of 02 July 2003 Board Meeting, Amended Bylaws of February 1996)

NOTARY PUBLIC (Signature):

Name and Particulars (e.g. Notary's name, Jurisdiction, Date of Licence Expiration)
SEAL (optional)



SECRETARY OF STATE

APOSTILLE

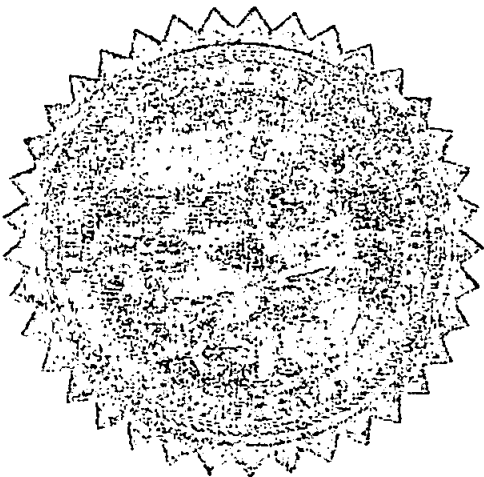
(Convention de La Haye du 5 octobre 1961)

1. Country: *United States of America*
This public document
2. *has been signed by Dierdre A. Mc Call*
3. *acting in the capacity of Notary Public, State of California*
4. *bears the seal/stamp of Dierdre A. Mc Call, Notary Public, State of California*

CERTIFIED

5. *At Sacramento, California*
6. *the 15th day of March 2004*
7. *by Deputy Secretary of State, State of California*
8. *No. 186724*
9. *Seal/Stamp:*

10. Signature



Kevin Shelley
KEVIN SHELLEY
Secretary of State

BY *Oatha*

12

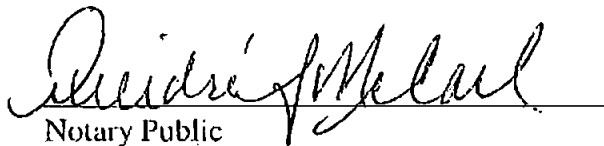
ACKNOWLEDGMENT

STATE OF CALIFORNIA)
) ss.
COUNTY OF SAN DIEGO)

On 1/28/04, before me, Dierdre A. McCall, Notary Public, personally appeared Margaret E. Valeur-Jensen, personally known to me to be the person whose name is subscribed to the within instrument, and acknowledged to me that she executed the same in her authorized capacity and that by her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

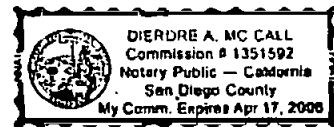
WITNESS my hand and official seal.

(Seal)


Notary Public

Printed Name: Dierdre A. McCall

My Commission Expires April 17, 2006



(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 April 2007 (12.04.2007)

PCT

(10) International Publication Number
WO 2007/039264 A1

(51) International Patent Classification:
C07D 487/04 (2006.01) A61P 25/00 (2006.01)
A61K 31/519 (2006.01)

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(21) International Application Number:
PCT/EP2006/009531

(22) International Filing Date:
28 September 2006 (28.09.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0519957.5 30 September 2005 (30.09.2005) GB
PCT/US2005/037576
19 October 2005 (19.10.2005) US

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

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

Published:
— with international search report

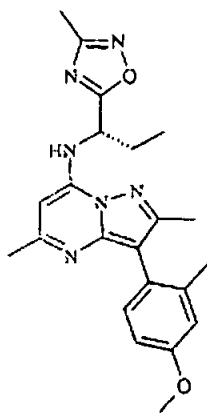
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: PYRAZOLO [1,5 -ALPHA] PYRIMIDINYL DERIVATIVES USEFUL AS CORTICOTROPIN-RELEASING FACTOR (CRF) RECEPTOR ANTAGONISTS



(1)

(57) Abstract: The present invention generally relates to the polymorph Form 2 of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-{(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl}-amine. The present invention also relates to pharmaceutical compositions comprising the same and methods of using the same.

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**PYRAZOLO[1,5-ALPHA] PYRIMIDINYL DERIVATIVES USEFUL AS
CORTICOTROPIN-RELEASING FACTOR (CRF) RECEPTOR ANTAGONISTS**

5 The present invention generally relates to the polymorph Form 2 of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxa-diazol-5-yl)-propyl]-amine. The present invention also relates to pharmaceutical compositions comprising the same and methods of using the same.

10 Corticotropin releasing factor (CRF) is a 41 amino acid peptide that coordinates the overall response of the body to stress. As an agonist of CRF receptors (e. g., CRF1 and CRF2), CRF is well known as the primary physiological secretagogue controlling hypothalamic-pituitary-adrenal (HPA) axis activity which mediates the endocrine stress response. CRF also plays a central role in the autonomic and behavioural responses to stress. Variation in physiological levels of CRF has been correlated with various disorders
15 including depression and anxiety.

Antagonists of CRF receptors have been shown to effectively ameliorate behavioural stress responses in animal models. It is well established that systemic administration of CRF1 receptor antagonists leads to anxiolytic and antidepressant effects in rodents.
20 Animal model evidence also shows that CRF1 antagonists can help alleviate the symptoms of drug withdrawal, stress-induced seizures, and certain inflammations. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy, and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the
25 central nervous system. Eating disorders, such as anorexia nervosa, have also been linked to elevated levels of CRF.

Though widely dispersed throughout the central nervous system, CRF receptors are also found in peripheral systems including glandular, vascular, gastrointestinal, and immune
30 system tissues. Accordingly, CRF antagonists are believed to have potential in treating numerous other disorders outside the central nervous system.

Some CRF-related disorders of peripheral systems include, for example, hypertension, tachycardia, congestive heart failure, stroke, irritable bowel syndrome, post-operative ileus, and colonic hypersensitivity. Studies have indicated that CRF1 antagonists may also
35 be useful as hair growth stimulators.

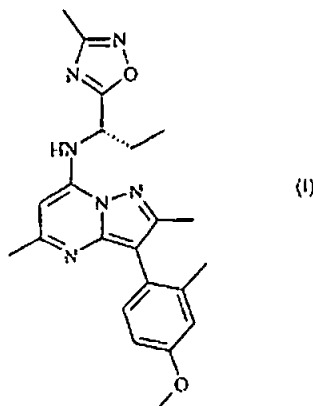
The compound [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine has been identified as an effective
40 CRF receptor antagonist that can be useful in treating, for example, the above-named disorders.

This compound is reported in the International Patent Application WO2006/044958, which is incorporated herein by reference in its entirety.

While numerous CRF receptor antagonists have been discovered, like the above
5 compound, few typically possess the characteristics that are satisfactory for the preparation of stable pharmaceutical compositions. Melting point, hygroscopicity, stability, solubility, crystallinity, bioavailability, and handling characteristics are among the numerous properties that need to be considered in preparing medicaments that can be effectively administered. Accordingly, there is an ongoing need to prepare compounds
10 with physical and chemical properties that are both physiologically acceptable and suitable for preparing reproducible pharmaceutical formulations. The polymorph of the present invention helps fulfill this and other needs. The polymorph of the present invention is the most thermodynamically stable between the two Forms of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-((S)-1-(3-methyl-[1,2,4]-
15 oxadiazol-5-yl)-propyl)-amine of Formula (I). In the Experimental Section an experiment of conversion of a mixture of the two forms to the more stable Form 2 and a calculation of the transition temperature will be provided.

The present invention provides the polymorph Form 2 of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-((S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl)-
20 amine.

[3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-((S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl)-amine may be also designated from now on as compound of Formula (I).



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The polymorph Form 2 of the compound of Formula (I) of the present invention is a free base.

30 The polymorph Form 2 of the compound of Formula (I) of the present invention has been characterised as reported below in the Examples.

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The present invention additionally provides compositions comprising the compound of the present invention and a pharmaceutically acceptable carrier.

5 Further embodiments include methods of treating a disorder in a mammal characterized by abnormal levels of CRF, comprising administering to the mammal a therapeutically effective amount of the compound of the present invention. Accordingly, the present invention further provides methods of treating anxiety or depression or irritable bowel syndrome in a mammal comprising administering to the mammal a therapeutically effective amount of the compound of the present invention.

10 Accordingly, the present invention further provides pharmaceutical compositions comprising polymorph Form 2 of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine of Formula (I) and a pharmaceutically acceptable carrier.

15 A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals.

20 Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and, the therapeutic indication being targeted. Pharmaceutically acceptable carriers include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, e. g. , stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources such as, for example, Remington's Pharmaceutical Sciences, 17th ed. , Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference in its entirety

35 The present invention also includes methods of treating a disorder characterized by abnormal levels of corticotropin releasing factor in a mammal by administering to the mammal a therapeutically effective amount of the compound of the present invention, or a composition containing the compound of the present invention. According to some embodiments, the disorder can be characterized by elevated levels of corticotropin releasing factor. In some embodiments, the disorder affects the central nervous system. Example disorders of the central nervous system that can be treated according to the methods described herein include anxiety or depression.

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In other embodiments, the disorder affects peripheral systems. Accordingly, an example of a treatable disorder of the peripheral systems according to the methods described herein is irritable bowel syndrome.

- 5 CRF receptor antagonists of the present invention may demonstrate activity at the CRF receptor site, and may be used as therapeutic agents for the treatment of a wide range of disorders or illnesses including endocrine, psychiatric, and neurological disorders or illnesses. More specifically, CRF receptor antagonists of the present invention may be useful in treating physiological conditions or disorders arising from the hypersecretion of
- 10 CRF. Because CRF is believed to be an important neurotransmitter that activates and coordinates the endocrine, behavioral and automatic responses to stress, CRF receptor antagonists of the present invention may be useful in the treatment of neuropsychiatric disorders. Neuropsychiatric disorders which may be treatable by the CRF receptor antagonists of this invention include affective disorders such as depression; anxiety-related disorders such as generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, cardiovascular abnormalities such as unstable angina and reactive hypertension; and feeding disorders such as anorexia nervosa, bulimia, and irritable bowel syndrome. CRF antagonists may also be useful in treating stress-induced immune suppression associated with various diseases states, as well as
- 20 stroke. Other uses of the CRF antagonists of this invention include treatment of inflammatory conditions (such as rheumatoid arthritis, uveitis, asthma, inflammatory bowel disease and G.I. motility), pain, Cushing's disease, infantile spasms, epilepsy and other seizures in both infants and adults, and various substance abuse and withdrawal (including alcoholism).
- 25 Within the context of the present invention, the following terms describing the indications used herein are classified in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association (DSM-IV) and/or the International Classification of Diseases, 10th Edition (ICD-10). The various subtypes of the disorders mentioned herein are contemplated as part of the present invention.
- 30 Numbers in brackets after the listed diseases below refer to the classification code in DSM-IV.

Within the context of the present invention, the term "psychotic disorder" includes :-

- 35 Schizophrenia including the subtypes Paranoid Type (295.30), Disorganised Type (295.10), Catatonic Type (295.20), Undifferentiated Type (295.90) and Residual Type (295.60); Schizophreniform Disorder (295.40); Schizoaffective Disorder (295.70) including the subtypes Bipolar Type and Depressive Type; Delusional Disorder (297.1) including the subtypes Erotomantic Type, Grandiose Type, Jealous Type, Persecutory Type, Somatic
- 40 Type, Mixed Type and Unspecified Type; Brief Psychotic Disorder (298.8); Shared Psychotic Disorder (297.3); Psychotic Disorder Due to a General Medical Condition including the subtypes With Delusions and With Hallucinations; Substance-Induced

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Psychotic Disorder including the subtypes With Delusions (293.81) and With Hallucinations (293.82); and Psychotic Disorder Not Otherwise Specified (298.9).

The compounds of the present invention including salts and pharmaceutically acceptable solvates thereof may also be of use in the treatment of the following disorders:-

5 Depression and mood disorders including Major Depressive Episode, Manic Episode, Mixed Episode and Hypomanic Episode; Depressive Disorders including Major Depressive Disorder, Dysthymic Disorder (300.4), Depressive Disorder Not Otherwise Specified (311); Bipolar Disorders including Bipolar I Disorder, Bipolar II Disorder
10 (Recurrent Major Depressive Episodes with Hypomanic Episodes) (296.89), Cyclothymic Disorder (301.13) and Bipolar Disorder Not Otherwise Specified (296.80); Other Mood Disorders including Mood Disorder Due to a General Medical Condition (293.83) which includes the subtypes With Depressive Features, With Major Depressive-like Episode, With Manic Features and With Mixed Features), Substance-Induced Mood Disorder
15 (including the subtypes With Depressive Features, With Manic Features and With Mixed Features) and Mood Disorder Not Otherwise Specified (296.90):

Anxiety disorders including Social Anxiety Disorder, Panic Attack, Agoraphobia, Panic Disorder, Agoraphobia Without History of Panic Disorder (300.22), Specific Phobia
20 (300.29) including the subtypes Animal Type, Natural Environment Type, Blood-Injection-Injury Type, Situational Type and Other Type), Social Phobia (300.23), Obsessive-Compulsive Disorder (300.3), Posttraumatic Stress Disorder (309.81), Acute Stress Disorder (308.3), Generalized Anxiety Disorder (300.02), Anxiety Disorder Due to a General Medical Condition (293.84), Substance-Induced Anxiety Disorder and Anxiety
25 Disorder Not Otherwise Specified (300.00):

Substance-related disorders including Substance Use Disorders such as Substance Dependence, Substance Craving and Substance Abuse; Substance-Induced Disorders
30 such as Substance Intoxication, Substance Withdrawal, Substance-Induced Delirium, Substance-Induced Persisting Dementia, Substance-Induced Persisting Amnesic Disorder, Substance-Induced Psychotic Disorder, Substance-Induced Mood Disorder, Substance-Induced Anxiety Disorder, Substance-Induced Sexual Dysfunction, Substance-Induced Sleep Disorder and Hallucinogen Persisting Perception Disorder (Flashbacks); Alcohol-Related Disorders such as Alcohol Dependence (303.90), Alcohol Abuse
35 (305.00), Alcohol Intoxication (303.00), Alcohol Withdrawal (291.81), Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnesic Disorder, Alcohol-Induced Psychotic Disorder, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder and Alcohol-Related Disorder Not Otherwise
40 Specified (291.9); Amphetamine (or Amphetamine-Like)-Related Disorders such as Amphetamine Dependence (304.40), Amphetamine Abuse (305.70), Amphetamine Intoxication (292.89), Amphetamine Withdrawal (292.0), Amphetamine Intoxication Delirium, Amphetamine Induced Psychotic Disorder, Amphetamine-Induced Mood

Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder and Amphetamine-Related Disorder Not Otherwise Specified (292.9); Caffeine Related Disorders such as Caffeine Intoxication (305.90), Caffeine-Induced Anxiety Disorder, Caffeine-Induced Sleep Disorder and Caffeine-Related Disorder Not Otherwise Specified (292.9); Cannabis-Related Disorders such as Cannabis Dependence (304.30), Cannabis Abuse (305.20), Cannabis Intoxication (292.89), Cannabis Intoxication Delirium, Cannabis-Induced Psychotic Disorder, Cannabis-Induced Anxiety Disorder and Cannabis-Related Disorder Not Otherwise Specified (292.9); Cocaine-Related Disorders such as Cocaine Dependence (304.20), Cocaine Abuse (305.60), Cocaine Intoxication (292.89), Cocaine Withdrawal (292.0), Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder and Cocaine-Related Disorder Not Otherwise Specified (292.9); Hallucinogen-Related Disorders such as Hallucinogen Dependence (304.50), Hallucinogen Abuse (305.30), Hallucinogen Intoxication (292.89), Hallucinogen Persisting Perception Disorder (Flashbacks) (292.89), Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder and Hallucinogen-Related Disorder Not Otherwise Specified (292.9); Inhalant-Related Disorders such as Inhalant Dependence (304.60), Inhalant Abuse (305.90), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium, Inhalant-Induced Persisting Dementia, Inhalant-Induced Psychotic Disorder, Inhalant-Induced Mood Disorder, Inhalant-Induced Anxiety Disorder and Inhalant-Related Disorder Not Otherwise Specified (292.9); Nicotine-Related Disorders such as Nicotine Dependence (305.1), Nicotine Withdrawal (292.0) and Nicotine-Related Disorder Not Otherwise Specified (292.9); Opioid-Related Disorders such as Opioid Dependence (304.00), Opioid Abuse (305.50), Opioid Intoxication (292.89), Opioid Withdrawal (292.0), Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder, Opioid-Induced Mood Disorder, Opioid-Induced Sexual Dysfunction, Opioid-Induced Sleep Disorder and Opioid-Related Disorder Not Otherwise Specified (292.9); Phencyclidine (or Phencyclidine-Like)-Related Disorders such as Phencyclidine Dependence (304.60), Phencyclidine Abuse (305.90), Phencyclidine Intoxication (292.89), Phencyclidine Intoxication Delirium, Phencyclidine-Induced Psychotic Disorder, Phencyclidine-Induced Mood Disorder, Phencyclidine-Induced Anxiety Disorder and Phencyclidine-Related Disorder Not Otherwise Specified (292.9); Sedative-, Hypnotic-, or Anxiolytic-Related Disorders such as Sedative, Hypnotic, or Anxiolytic Dependence (304.10), Sedative, Hypnotic, or Anxiolytic Abuse (305.40), Sedative, Hypnotic, or Anxiolytic Intoxication (292.89), Sedative, Hypnotic, or Anxiolytic Withdrawal (292.0), Sedative, Hypnotic, or Anxiolytic Intoxication Delirium, Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium, Sedative-, Hypnotic-, or Anxiolytic-Persisting Dementia, Sedative-, Hypnotic-, or Anxiolytic- Persisting Amnesic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Psychotic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorder Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction, Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep Disorder and Sedative-, Hypnotic-, or

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Anxiolytic-Related Disorder Not Otherwise Specified (292.9); Polysubstance-Related Disorder such as Polysubstance Dependence (304.80); and Other (or Unknown) Substance-Related Disorders such as Anabolic Steroids, Nitrate Inhalants and Nitrous Oxide:

5 Sleep disorders including primary sleep disorders such as Dyssomnias such as Primary Insomnia (307.42), Primary Hypersomnia (307.44), Narcolepsy (347), Breathing-Related Sleep Disorders (780.59), Circadian Rhythm Sleep Disorder (307.45) and Dyssomnia Not Otherwise Specified (307.47); primary sleep disorders such as Parasomnias such as
10 Nightmare Disorder (307.47), Sleep Terror Disorder (307.46), Sleepwalking Disorder (307.46) and Parasomnia Not Otherwise Specified (307.47); Sleep Disorders Related to Another Mental Disorder such as Insomnia Related to Another Mental Disorder (307.42) and Hypersomnia Related to Another Mental Disorder (307.44); Sleep Disorder Due to a General Medical Condition; and Substance-Induced Sleep Disorder including the
15 subtypes Insomnia Type, Hypersomnia Type, Parasomnia Type and Mixed Type:

Eating disorders such as Anorexia Nervosa (307.1) including the subtypes Restricting Type and Binge-Eating/Purging Type; Bulimia Nervosa (307.51) including the subtypes Purging Type and Nonpurging Type; Obesity; Compulsive Eating Disorder; and Eating
20 Disorder Not Otherwise Specified (307.50):

Autistic Disorder (299.00); Attention-Deficit /Hyperactivity Disorder including the subtypes Attention-Deficit /Hyperactivity Disorder Combined Type (314.01), Attention-Deficit /Hyperactivity Disorder Predominantly Inattentive Type (314.00), Attention-Deficit
25 /Hyperactivity Disorder Hyperactive-Impulse Type (314.01) and Attention-Deficit /Hyperactivity Disorder Not Otherwise Specified (314.9); Hyperkinetic Disorder; Disruptive Behaviour Disorders such as Conduct Disorder including the subtypes childhood-onset type (321.81), Adolescent-Onset Type (312.82) and Unspecified Onset (312.89), Oppositional Defiant Disorder (313.81) and Disruptive Behaviour Disorder Not Otherwise
30 Specified; and Tic Disorders such as Tourette's Disorder (307.23):

Personality Disorders including the subtypes Paranoid Personality Disorder (301.0), Schizoid Personality Disorder (301.20), Schizotypal Personality Disorder (301.22), Antisocial Personality Disorder (301.7), Borderline Personality Disorder (301.83), Histrionic Personality Disorder (301.50), Narcissistic Personality Disorder (301.81),
35 Avoidant Personality Disorder (301.82), Dependent Personality Disorder (301.6), Obsessive-Compulsive Personality Disorder (301.4) and Personality Disorder Not Otherwise Specified (301.9):

Enhancement of cognition including the treatment of cognition impairment in other
40 diseases such as schizophrenia, bipolar disorder, depression, other psychiatric disorders and psychotic conditions associated with cognitive impairment, e.g. Alzheimer's disease: and

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Sexual dysfunctions including Sexual Desire Disorders such as Hypoactive Sexual Desire Disorder (302.71), and Sexual Aversion Disorder (302.79); sexual arousal disorders such as Female Sexual Arousal Disorder (302.72) and Male Erectile Disorder (302.72); orgasmic disorders such as Female Orgasmic Disorder (302.73), Male Orgasmic Disorder (302.74) and Premature Ejaculation (302.75); sexual pain disorder such as Dyspareunia (302.76) and Vaginismus (306.51); Sexual Dysfunction Not Otherwise Specified (302.70); paraphilias such as Exhibitionism (302.4), Fetishism (302.81), Frotteurism (302.89), Pedophilia (302.2), Sexual Masochism (302.83), Sexual Sadism (302.84), Transvestic Fetishism (302.3), Voyeurism (302.82) and Paraphilia Not Otherwise Specified (302.9); gender identity disorders such as Gender Identity Disorder in Children (302.6) and Gender Identity Disorder in Adolescents or Adults (302.85); and Sexual Disorder Not Otherwise Specified (302.9).

All of the various forms and sub-forms of the disorders mentioned herein are contemplated as part of the present invention.

The term "therapeutically effective amount" refers to an amount of the compound of the present invention effective to reduce or eliminate at least one symptom of a disorder that the compound was used to treat.

The compound of the present invention can be administered to treat the above disorders by any suitable means that allows the compound to contact the site of action, such as a CRF receptor, in the body of a mammal. The compound can be administered by any conventional means available for use in conjunction with pharmaceuticals either as an individual therapeutic agent or in combination with other therapeutic agents. The compound of the present invention can be administered alone, or in combination with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage of the compound of the present invention for administration varies depending on several factors such as the pharmacodynamic character of the particular compound, and its mode and route of administration; the recipient's age, weight, and health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of the above diseases or conditions, the salts of this invention can be orally administered daily at a dosage of the active ingredient (e. g. a salt of Formula I) of about 0.002 to about 200 mg/kg of body weight. For example, a dose of about 0.01 to about 10 mg/kg can be divided into smaller doses and administered one to four times a day. Alternatively, sustained release formulations can be effective in obtaining the desired pharmacological effect.

Dosage forms (compositions) suitable for administration can contain from about 1 mg to about 200 mg of active ingredient per dosage unit. In these pharmaceutical compositions,

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the active ingredient (e. g. polymorph Form 2 of formula (I)) can be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

5 The active ingredient (e. g., polymorph Form 2 of formula (I)) can be administered orally in solid dosage forms such as capsules, tablets and powders, or in liquid forms such as elixirs, syrups, and/or suspensions. The compound of this invention can also be administered parenterally in sterile liquid dose formulations

10 Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as, but not limited to, lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to mask any unpleasant taste, or used to protect the active ingredients from
15 the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can also contain colouring or flavouring agents to increase patient acceptance.

20 Typically, water, pharmaceutically acceptable oils, saline; aqueous dextrose, and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral solutions. Solutions for parenteral administration can contain, for example, a water soluble salt of the active ingredient and suitable stabilizing agents.
25 Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, can act as suitable stabilizing agents.

Also suitable as stabilizing agents are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as, for example, benzalkonium chloride, methyl-or propyl-paraben, and chlorobutanol.
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EXAMPLE

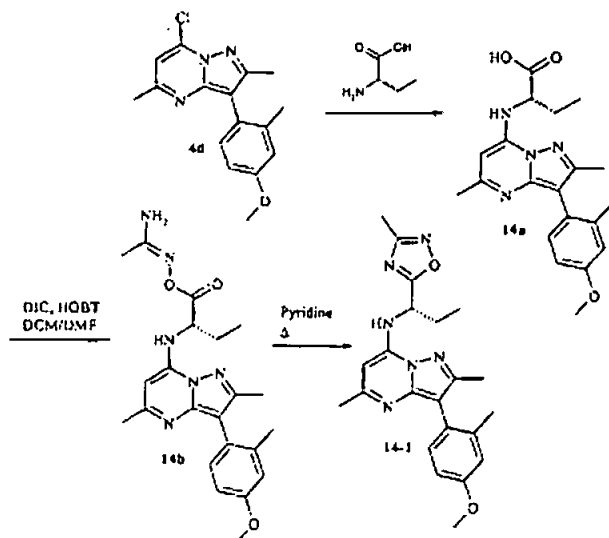
Abbreviations:

35 DCM: Dichloromethane
DIC: N,N'-Diisopropylcarbodiimide
DMF: Dimethylformamide
HOBT: 1-Hydroxybenzotriazole
40 DM water: demineralised water

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Intermediate 1**Preparation and characterisation of polymorph Form 1 of the compound of Formula (I)**

- 5 Polymorph Form 1 of the compound of Formula (I) may be prepared according to the following Scheme, as reported in WO 2006/044958:

**Step 14A:**

10

A suspension of sodium bicarbonate (28.7 g) and (S)-2-aminobutyric acid (21.7 g) in water (250 mL) was added to a solution of **4d** (prepared according to the method disclosed in WO 2006/044958) (39.7 g) in dioxane (250 mL). The mixture was stirred and heated to reflux (102 °C bath) for 14 hr. The mixture was cooled to RT, then concentrated HCl (16 mL) was added over 10 min to final pH 4.5. A copious white precipitate formed. The mixture was concentrated to a weight of about 250 g, then the residue was subjected to co-evaporation with several portions of ethyl acetate, resulting in a thick, pasty aqueous slurry. The mixture was filtered, and the filter cake was washed with water (350 mL). The filter cake was then dried under vacuum at 35 °C, yielding compound **14a** (45.2 g) as a white solid.

20

Step 14B:

Cmpd **14a** (10 g) was suspended in toluene (50 mL) and evaporated to dryness. Dry DCM (100 mL) was added followed by HOBT (4.8 g) and acetamide oxime (2.7 g.) Anhydrous DMF (11 mL) was added, then the reaction mixture was stirred and cooled in an ethylene glycol/dry ice bath to an internal temperature of -15.5 °C under a nitrogen atmosphere. DIC (5.3 mL) was then added via syringe. The reaction mixture was stirred and allowed to warm over 2 hr, at which time the internal temperature was +16.5 °C. The solvents were evaporated, then ethyl acetate (150 mL) was added and the mixture was

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washed twice with saturated aq. sodium bicarbonate, once with 10% aq. potassium dihydrogen phosphate, and finally with brine. The ethyl acetate layer was dried over sodium sulfate, filtered, and concentrated to provide crude Cmpd 14b.

5 Step 14C:

Pyridine (50 mL) was added to Cmpd 14b from Step 14B, then the mixture was heated under nitrogen at 100 °C for 4 hr. The resulting solution was allowed to cool, the solvent was evaporated, and the residue was co-evaporated twice with ethyl acetate and once
10 with heptane. The residue was taken up in 50 mL ether, then filtered to remove DIU, rinsing with several portions of ether. The filtrate was evaporated, then the residue was chromatographed on silica gel, eluting with 2:1 hexane/ethyl acetate to provide the partially purified Cmpd 14-1 as a slightly yellow foam. The foam was co-evaporated once with heptane, then 5:1 heptane/ethyl acetate (60 mL) was added, and the resulting slurry
15 was stirred at RT for 24 hr. The solid was filtered and rinsed with 10:1 heptane/ethyl acetate, providing 14-1 free base (7.3 g) as a white solid. The filtrate was concentrated and a second crop of 14-1 free base (0.7 g) was collected, also as a white solid.

The free base 14-1 (6.0 g) was dissolved in 80 mL acetone and cooled in an ethylene glycol/dry ice bath to -12 °C (internal). Hydrogen chloride (8.9 mL of a 2.0 M solution in ether) was added in one portion. The clear yellow solution was stirred for 1 min, then the solvent was evaporated. The residue was co-evaporated with two portions of acetone, then dried under vacuum to produce an amber foam. The foam was pulverized and then dried under vacuum at RT for 24 hr, providing the hydrochloride salt 14-1 (6.7 g) as an
20 amorphous tan powder.
25

Characterisation of polymorph Form 1 of the compound of Formula (I)

Free Base 14-1 prepared as before shows the XPRD pattern (Figure 4) and it was
30 identified as Form 1 of [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine.

Table 1: XRPD angles and d spacings for [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine. **Form 1.**
35

29

Table 1

Angle 2-Theta °	d value Angstrom
6.721	13.1397
8.361	10.5663
10.698	8.26247
11.757	7.52055
13.323	6.64016
15.112	5.85779
15.492	5.71491
15.959	5.54892
18.222	4.86461
18.965	4.67554
20.291	4.37294
21.428	4.14338
21.974	4.04163
22.664	3.92018
24.002	3.70457
25.082	3.54736
26.268	3.38993
26.941	3.30677
30.544	2.92437
31.289	2.85642

Description of Figures:

5

Figure 4 shows X-Ray powder diffraction data obtained for **Form 1** of [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine as described before. **Form 1** is characterised by having an XRPD pattern with signals substantially as listed in Table 1.

10

Figure 5 shows the Raman spectrum of **Form 1** of [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine.

15

Figure 6 shows a Differential Scanning Calorimetry (DSC) thermogram of **Form 1** of [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine.

20

It will be recognised that spectra and diffraction data will vary slightly according to various factors such as the temperature, concentration and instrumentation used. The skilled person will recognise that XRPD peak positions are affected by differences in sample height. The peak positions quoted herein are thus subject to a variation of +/- 0.15 degrees 2-theta.

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X-Ray Powder Diffraction

X Ray Powder Diffraction (XRPD) analysis was performed on Bruker D5005, using Sol-X detector. The acquisition conditions were: radiation: Cu K α , generator tension: 40 kV, generator current: 50mA, start angle: 2.0 °2 θ , end angle: 45.0 °2 θ , step size: 0.02 °2 θ , time per step: 0.5 seconds. The sample was prepared on zero background sample holder.

Raman Spectroscopy

Instrument Configuration: Kaiser RXN1 Kaiser Optical System Micro Raman. Sample on Al sample pan, laser λ = 785nm.

Differential Scanning Calorimetry (DSC)

Instrument configuration: PE DSC 7, not ermetic sample pan, run @10K/min to 150 °C, sample 1.5-5 mg.

EXAMPLE 1

Synthesis and characterisation of polymorph Form 2 of the compound of Formula (I)

HPLC method

Column	Zorbax SB-C18(150x4.6 mm), 3.5 micron
Mobile Phase-A	0.05% TFA(Aqueous)
Mobile Phase -B	0.025% TFA(Acetonitrile)
Column temperature:	40 °C
Flow rate	1.0 ml/min
Wavelength of detection	225nm
Injection volume	5 μ l
Run time	30 mins
Concentration	0.3 mg/ml
Gradient program	Linear gradient

<u>Time in min</u>	<u>Mobile phase-A(%)</u>	<u>Mobile phase-B (%)</u>
0	75	25
25	5	95
29	5	95
30	75	25
Post run time	5 min	
Retention time	<u>Form 2</u>	about 9 min
Diluent	Mobile Phase-A: Mobile Phase-B (1:1)	

Form 2 of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine was prepared as follows:

5 [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine **Form 1** (0.74 g) was slurried in 50% aqueous isopropanol (4 mL). The temperature was cycled between 0 and 40 °C for 24 hours, then the mixture stirred at ambient temperature for 3 days, then the temperature was cycled between 0 and 40 °C for 24 hours. The residual solid was filtered off and dried at ambient temperature to give 0.70 g of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine **Form 2**.

Preparation of **Form 2** of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine was then repeated on large scale as follows.

15 Free Base **14-1** was prepared in an analogous way as described before, except for the lack of the chromatographic purification present in **Step 14C**. The formation and successive liberation of the mesylate salt afforded a desired compound with an high purity without the necessity of a chromatography.

20 Free Base **14-1** (2.48 kg, 6.10 Mol, chemical purity 90%) was stirred with n-Butyl acetate (12.5 L) for 30 to 45 minutes then Methane sulphonic acid (1.2eq, 7.32 Mol, 703g) was added. After stirring for 2-3 hrs at 25-30°C the mixture was filtered. The solid was slurry washed with n-Butyl acetate (5 L) followed by Heptane (7.5 L). Then dried for 4-6hrs at 25 ± 5 ° C under vacuum to give Mesylate salt (2.48 kg, chemical purity 97.37%).

25 The mesylate salt was stirred with DM water (12.5 L) for 15 to 30 minutes. Aq. ammonia was added to a pH of 9.0-10. The suspension was extracted with ethyl acetate (3 x 7.5 L), then the combined extracts were washed with DM water (5 L) and 20% Brine solution (5 L). The organic solution was concentrated under vacuum at below 50 ± 5 ° C, removing 85 to 90 % of the solvent, then the residue cooled to 30 ± 5 ° C. Heptane (15 L) was added and the mixture stirred for 2 to 3 hrs at 25-30°C then 80 to 70 % of the solvent was distilled off under vacuum at below 50 ± 5 ° C. The mixture was cooled to 30 ± 5 ° C, stirred for 1 to 2 hours, then filtered. The solid was slurry washed with Heptane (5 L) then dried under vacuum at below 50 ± 5 ° C to give **Form 1** of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine (1.70kg, chemical purity 99.34%).

35 40 A mixture of **Form 1** (1.37 kg, 3.37 Mol, purity by HPLC 99.34%) of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine and ethyl acetate (2.05 L) were heated up to 40 to 45 °C (a clear solution was observed). The solution was then cooled to 30 ± 5 °C and Heptane (6.85 L) added before heating to 60 ± 2.5 °C. **Form 2** of [3-(4-methoxy-2-methyl-phenyl)-

2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine seed material prepared as described above (0.5% w/w) was added at 60±2.5 °C then the mixture was cooled to 40±2.5 °C, then heated back to 50±2.5 °C when further seed material (0.5% w/w) was added. The resulting slurry was cooled to 30±5 °C and stirred for 12 hrs at 30±5 °C. Heptane (2.74 L) was added and the mixture stirred for a further 12 hrs at 30±5 °C. The slurry was filtered and the solid slurry washed with heptane (2.74 L). The solid was dried under vacuum at 50±5 °C for 8 hrs to give 0.97 kg of **Form 2** of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine (HPLC purity 99.58%), which has been characterised as follows.

Characterisation of polymorph **Form 2** of the compound of Formula (I)

Form 2 of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine shows the XPRD pattern (Figure 1).

Table 2: XRPD angles and d spacings for [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine, **Form 2**.

Table 2

Angle (2-Theta °)	d value (Angstrom)
10.415	8.48651
12.125	7.29347
12.36	7.15526
13.177	6.7136
13.527	6.5406
15.121	5.85426
16.045	5.51918
16.331	5.42339
19.457	4.55852
20.133	4.40682
20.941	4.2386
21.28	4.1718
22.239	3.99412
22.823	3.89318
23.51	3.78098
24.714	3.59933
25.488	3.49186
26.261	3.39074
29.537	3.02169
27.858	3.19988

Description of Figures:

Figure 1 shows X-Ray powder diffraction data obtained for **Form 2** of [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine as described before. **Form 2** is characterised by having an XRPD pattern with signals substantially as listed in Table 1.

Figure 2 shows the Raman spectrum of **Form 2** of [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine.

Figure 3 shows a Differential Scanning Calorimetry (DSC) thermogram of **Form 2** of [3-(4-Methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine.

It will be recognised that spectra and diffraction data will vary slightly according to various factors such as the temperature, concentration and instrumentation used. The skilled person will recognise that XRPD peak positions are affected by differences in sample height. The peak positions quoted herein are thus subject to a variation of ± 0.15 degrees 2-theta.

X-Ray Powder Diffraction

X Ray Powder Diffraction (XRPD) analysis was performed on Bruker D5005, using Sol-X detector. The acquisition conditions were: radiation: Cu K α , generator tension: 40 kV, generator current: 50mA, start angle: 2.0 °2 θ , end angle: 45.0 °2 θ , step size: 0.04 °2 θ , time per step: 1 second. The sample was prepared on zero background sample holder.

Raman Spectroscopy

Instrument Configuration: Kaiser RXN1 Kaiser Optical System Micro Raman. Sample on Al sample pan, laser λ = 785nm.

Differential Scanning Calorimetry (DSC)

Instrument configuration: Q 1000 TA, not emetic sample pan, run @10K/min to 150°C, N2 Flow =50mL/min, sample 1.5-5 mg.

EXAMPLE 2

Thermodynamic relationship between Form 1 and Form 2 of the compound of Formula (I)

For a polymorphic substance, a property of particular interest is the relative thermodynamic stability of the polymorphs. The questions to be answered are the following:

- a) whether two polymorphs are monotropic (one is more stable than the other at any temperature or enantiotropic (a transition temperature (T_i) exists, below and above which the stability order is reversed; and
- b) for an enantiotropic system, where (T_i) lies.

The thermodynamic relationship between **Form 1** and **Form 2** of compound of Formula (I) was calculated using the melting data of polymorphs measured by DSC, according to what disclosed in: Lian Yu, *Journal of Pharmaceutical Science*, Vol. 84, No. 8, August 1995.

Based on DSC data (see reference article), **Form 1** and **Form 2** have a monotropic relationship and **Form 2** may be considered the stable form (thermodynamically).

Taking samples of **Form 1** and **Form 2** as pure forms 1 and 2 respectively, and using the melting point and the ΔH obtainable by DSC data, it was possible to calculate the thermodynamic relationship and the transition temperature.

Form 1: $T=100.09^\circ\text{C}$ & $\Delta H=75.46\text{ J/g}$

Form 2: $T=110.35^\circ\text{C}$ & $\Delta H=83.43\text{ J/g}$

By solving the equation present in the cited article, the transition temperature corresponds to $T=356^\circ\text{C}$ and it is greater than the previous two for **Form 1** and **Form 2** and $\Delta H_0 < 0$, $\Delta S_0 < 0$, then the conclusion is that the two polymorphic forms have a monotropic relationship.

The above calculation has been performed using DSC data for a different sample of polymorph **Form 1** of compound of Formula (I), showing the Differential Scanning Calorimetry (DSC) thermogram of Figure 7, obtained by the same method discussed above.

It should be recognized that the endotherm peak as measured is dependent under a number of factors including the machine employed, the rate of heating, the calibration standard, humidity and the purity of the sample used.

A similar calculation has been performed using the DSC data of polymorph **Form 1** of compound of Formula (I) showed in Figure 6, prepared according to the process described above.

Form 1: $T=102.44^\circ\text{C}$ & $\Delta H=71.18\text{ J/g}$

Form 2: $T=110.35^\circ\text{C}$ & $\Delta H=83.43\text{ J/g}$

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The transition temperature is now corresponding to $T = 177^{\circ}\text{C}$, greater than the previous two for Form 1 and Form 2, and $\Delta H_0 < 0$, $\Delta S_0 < 0$, confirming again the monotropic relationship between the two polymorphic forms.

5 **EXAMPLE 3**

Conversion of mixture of the two polymorphs of the compound of Formula (I) to Form 2

10 A saturated solution in ethyl acetate / heptane = 1 / 2 of Form 1 of compound of Formula (I) (25 mg in 400 μL) was prepared.

20.4 mg of solid Form 1 of compound of Formula (I) were mixed with 21.3 mg of solid Form 2 of compound of Formula (I). That solid mixture was added to the above saturated solution. The slurry so obtained was stirred at RT one day long. The day after, the solid and liquid phase were separated by centrifugation, and the solid was simply left on air in order to dry and then examined by XPRD.

The analysis showed that the solid was only constituted by Form 2 of compound of Formula (I).

20 **EXAMPLE 4**

Alternative preparation of Form 2 of the compound of Formula (I)

Free Base 14-1 was prepared using a slightly modified process from 14a. The revised reactions conditions led to the formation of lower amounts of related impurities so, instead of mesylate salt formation and successive liberation, the desired compound was obtained directly from the work-up of the reaction from 14b without the need for additional purification. The crude purity was sufficient to provide Form 2 of acceptable chemical purity when using a direct seeded crystallisation procedure. The advantage of this alternative crystallisation is that the desired Form 2 can be prepared direct from solution by seeding with material of the appropriate form, thus allowing for better control of the physical characteristics of the final material if required in the future.

To a mixture of DCM (278 L) and 14a (55.5 kg) were added: HOBt (26.5 kg), acetamidooxime (15.1 kg) and DMF (55.5 L) under nitrogen atmosphere. After stirring for 5 minutes the reaction mass was cooled to $0 - 5^{\circ}\text{C}$. A solution of DCC (40.5 kg) in DCM (278 L) was added over 4 hours at below 25°C . After completion of the addition, the reaction mass was stirred for 1.5 to 2 hrs at below 25°C . The reaction temperature was raised to $25-35^{\circ}\text{C}$ and the reaction mixture was filtered, washing the residue with DCM (111 L). The combined DCM layer was washed with 5 % bicarbonate solution (3 x 280 L) followed by DM water (166.5 L) and finally with 5% Brine solution (166.5 L). The organic layer was concentrated under vacuum below 50°C . Toluene (278 L) was added and the reaction temperature was raised to reflux for 3 to 4 hrs. The reaction was cooled to $30-35^{\circ}\text{C}$ and extracted with 5N HCl (3 x 111 L). The combined aqueous were treated with

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Charcoal (5 kg) and stirred for 15 to 30 minutes then the reaction mixture was filtered through Celite and washed with 5N HCl (111 L). The combined aqueous layers from the Celite filtration were added to aqueous ammonia (500 L) and ethyl acetate (278 L) cooled to 0-10 °C. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 278 L). The combined organic layers were washed with DM water (278 L) followed by 20 % brine solution (278 L). 80 to 85 % solvent was distilled from the reaction mixture under vacuum at below 55 °C. The reaction mass was cooled to 30±5 °C and heptane (555 L) was added. After stirring for 1 to 2 hrs, 75 to 85 % of solvent was distilled from the reaction mixture under vacuum at below 55 °C. The reaction mass was cooled to 30±5 °C and the reaction mass was filtered, washing with Heptane (100 L). The material was dried under vacuum for 4-6 hrs to give free base **14.1** (50.7 kg).

Free base **14.1** (50.7 kg) was dissolved with ethyl acetate (253.5 L). Heptane was added (1116 L) and the mixture was stirred for 15-20 hrs. The reaction mixture was then filtered through a Nutsche filter and washed with ethyl acetate / heptane mixture (1:5) (36 L). The filtrate was then concentrated under vacuum at below 50±5 °C until removal of 85 to 90% of the solvent. The reaction was then cooled at 30±5 °C and Heptane (278 L) was added. After stirring for 1 to 2 hrs at 25-30°C, 75-85% of the solvent was removed under vacuum below 50±5 °C. Then the temperature is kept at 30±5 °C and heptane (167 L) was added and the reaction mass was stirred for 15 to 30 minutes and then filtered. The final solid was washed with Heptane (167 L) and dried to give **Form 1** of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]-oxadiazol-5-yl)-propyl]-amine (41.1kg, chemical purity 93.6 %).

A mixture of **Form 1** (41.1 kg) and isopropyl alcohol (123.5L) was heated to 45-55 °C, producing a clear solution. The solution was filtered then the temperature was kept at 30-40 °C and seeds of **Form 2** of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine were added. The stirring was continued for 5-6 hrs, then the suspension was cooled to 5-15 °C and stirred for 1-2 hrs. The suspension is then filtered and washed with cold isopropyl alcohol and dried under vacuum at 50±5 °C to give 30.2 kg of **Form 2** of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine (HPLC purity 98.63%).

EXAMPLE 5

Recrystallisation of **Form 2** of the compound of Formula (I)

If the purity of the **Form 2** prepared by the process described in Example 4 does not meet the required specification, a further seeded recrystallisation to give **Form 2** can be carried out.

3 kg of **Form 2** of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine (prepared according to Example

4, HPLC purity 98.63%,) was added to isopropyl alcohol (9 L) and stirred for 5 to 10 minutes. The reaction mixture temperature was then raised to 52.5±2.5 °C and a clear solution was obtained. The temperature was reduced to 35±5 °C and seeds of **Form 2** of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine were added. The reaction mixture was then stirred for 2-3 hrs. at 30±5 °C. Then the reaction mixture was cooled to 0 °C±5 °C and stirred for 1-2 hrs. The suspension was then filtered and washed with cold isopropyl alcohol and dried under vacuum at 50 °C to give 2.4 kg of **Form 2** of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]-oxadiazol-5-yl)-propyl]-amine (HPLC purity 99.73%), which shows the DSC of Figure 8.

EXAMPLE 6

Comparison of XRPD data of polymorphs **Form 1** and **Form 2** of the compound of Formula (I)

Form 1		Form 2	
2θ	d value	2θ	d value
6.721	13.1397		
8.361	10.5663		
		10.415	8.48651
10.698	8.26247		
11.757	7.52055		
		12.126	7.29347
		12.36	7.15526
		13.177	6.7136
13.323	6.64016		
		13.527	6.5406
15.112	5.85779		
		15.121	5.85426
15.492	5.71491		
15.959	5.54892		
		16.045	5.51918
		16.331	5.42339
18.222	4.86461		
18.965	4.67554		
		19.457	4.55852
		20.133	4.40682
20.291	4.37294		
		20.941	4.2386
21.428	4.14338		
		21.28	4.1718
		22.239	3.99412
21.974	4.04163		
22.664	3.92018		
		22.823	3.89318
		23.51	3.78098
24.002	3.70457		
		24.714	3.59933
25.082	3.54736		
		25.488	3.49186
		26.261	3.39074
26.268	3.38993		
26.941	3.30677		
		27.858	3.19988
		29.537	3.02169
30.544	2.92437		
31.289	2.85642		

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It is well known in the crystallography art that, for any given polymorph, the relative intensities of the diffraction peaks may vary due to preferred orientation resulting from factors such as crystal morphology. Where the effects of preferred orientation are present peak intensities are altered, but the characteristic peak positions of the polymorph are unchanged.

The X-ray powder diffraction pattern of polymorph **Form 2** as shown in Figure 1 exhibits predominant peaks (expressed in degrees 2θ +/- 0.15 degrees 2θ) at the following positions: 10.415, 12.125, 19.457, 20.941 and 23.51.

The X-ray powder diffraction pattern of polymorph **Form 1** as shown in Figure 4 exhibits predominant peaks (expressed in degrees 2θ +/- 0.15 degrees 2θ) at the following positions: 6.721, 11.757, 13.323, 18.222, 21.426 and 21.974.

EXAMPLE 7

Comparison Raman data of polymorphs Form 1 and Form 2 of the compound of Formula (I)

The Raman spectrum of polymorph **Form 2** as shown in Figure 2 exhibits predominant peaks (expressed in cm^{-1}) at the following positions: 1606, 1561, 1506, 1323, 1301, 1279, 1271, 1253, 889 and 720.

The Raman spectrum of polymorph **Form 1** as shown in Figure 5 exhibits predominant peaks (expressed in cm^{-1}) at the following positions: 1619, 1611, 1581, 1574, 1555, 1525, 1502, 1319, 1311, 1264, 882 and 728.

EXAMPLE 8

DSC data of polymorphs Form 1 and Form 2 of the compound of Formula (I)

It should be recognized that the endotherm peak as measured is dependent under a number of factors including the machine employed, the rate of heating, the calibration standard, humidity and the purity of the sample used.

As shown in Figure 3, the polymorph **Form 2** exhibits a predominant endotherm peak at about 115.1 °C and an onset at about 110.35 °C.

As shown in Figure 6, the polymorph **Form 1** exhibits a predominant endotherm peak at about 108.3 °C and an onset at about 102.44 °C.

As shown in Figure 7, a different sample of the polymorph **Form 1** exhibits a predominant endotherm peak at about 106.3 °C and an onset at about 100.09 °C.

As shown in Figure 8, a different sample of the polymorph **Form 2** exhibits a predominant endotherm peak at about 115.08 °C and an onset at about 110.72 °C.

EXAMPLE 9

- 5 **Illustrative example of a formulation containing polymorph Form 2 of the compound of Formula (I)**

The development of tablets containing polymorph **Form 2** of compound of Formula (I) have been performed introducing a wet-granulation step to obtain granules with increased
10 flow properties. This step involves the wet granulation of one or more components of the tablet formulation by means of a High Shear Granulator followed by drying phase and calibration.

The tablet was then formulated taking into account the technological properties of the
15 granules (size, flowability, disintegrating and binding capacity of the final powder blend) and trying to assure a rapid dissolution of the drug, as final stage tablet was also coated by applying an aqueous film coating.

The excipients used were Mannitol and Microcrystalline cellulose (Avicel®) as diluent,
20 Croscarmellose Sodium (AcDisol®) as disintegrant, Magnesium Stearate as lubricant, Sodium Lauryl Sulphate as wettability enhancer (surfactant), HPMC as binder and Opadry OY-S-28876 as coating agent.

The final composition of both granules and tablets are below reported

25 200mg dose AFC (aqueous film coated) Tablets

COMPONENT	AMOUNT (mg)/UNIT	% w/w
Form 2 64.0% Granule	312.50	83.33
Correspond to:		
Form 2: 200.00		
HPMC: 46.88		
Sodium Lauryl Sulphate: 3.13		
Sodium Croscarmellose: 9.38		
Mannitol powder: 53.11		
MCC Avicel PH102	47.50	12.67
Sodio Croscarmellose	11.25	3.00
Magnesium Stearate	3.75	1.00
Total core weight:	375.00	100.00
Opadry OY-S-28876	11.25	3.00
Total weight:	386.25	103.00

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5 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

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

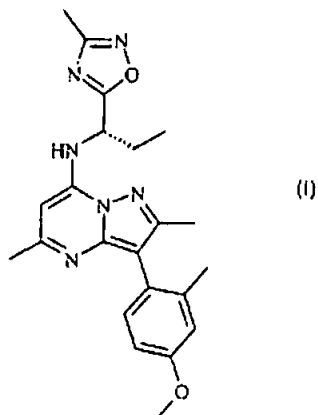
10 The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

15

X
C

Claims

1. A compound which is polymorph Form 2 of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine of Formula (I).



2. The compound of claim 1 having a differential scanning calorimetry thermogram substantially as shown in Figure 2, wherein the DSC was performed at a scan rate of 10K per minute.
3. The compound of claim 1 or claim 2 having a differential scanning calorimetry thermogram with an onset at about $T=110.35^{\circ}\text{C}$.
4. The compound of any of claims 1-3 having an X-ray powder diffraction spectrum substantially as shown in Figure 1, wherein the XRPD pattern is expressed in terms of 2 theta angles and obtained with a diffractometer using copper $K\alpha$ -radiation.
5. The compound of any of claims 1-4 having an X-ray powder diffraction spectrum having peaks comprising the 2-theta values listed below in Table 2, obtained with a diffractometer using copper $K\alpha$ -radiation:

Angle (2-Theta °)	d value (Angstrom)
10.415	8.48651
12.125	7.29347
12.36	7.15526
13.177	6.7136
13.527	6.5406
15.121	5.85426
16.045	5.51918
16.331	5.42339
19.457	4.55852
20.133	4.40682
20.941	4.2386
21.28	4.1718
22.239	3.99412
22.823	3.89318
23.51	3.78098
24.714	3.59933
25.488	3.49186
26.261	3.39074
29.537	3.02169
27.858	3.19988

6. The compound of any of claims 1-5 having an X-ray powder diffraction spectrum which comprises the following peaks expressed in 2-theta values: 10.415 +/- 0.15, 12.125 +/- 0.15, 19.457 +/- 0.15, 20.941 +/- 0.15 and 23.51 +/- 0.15; and obtained with a diffractometer using copper K α -radiation.
7. A composition comprising the compound of any of claims 1-6 and a pharmaceutically acceptable carrier.
8. A method of treating a disorder in a mammal, wherein said disorder is characterized by abnormal levels of CRF, comprising administering to said mammal a therapeutically effective amount of the compound of any of claims 1-6.
9. A method of treating anxiety or depression in a mammal comprising administering to said mammal a therapeutically effective amount of the compound any of claims 1-6.
10. A method of treating irritable bowel syndrome in a mammal comprising administering to said mammal a therapeutically effective amount of the compound of any of claims 1-6.

9/9

FIGURE 1:

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(501)

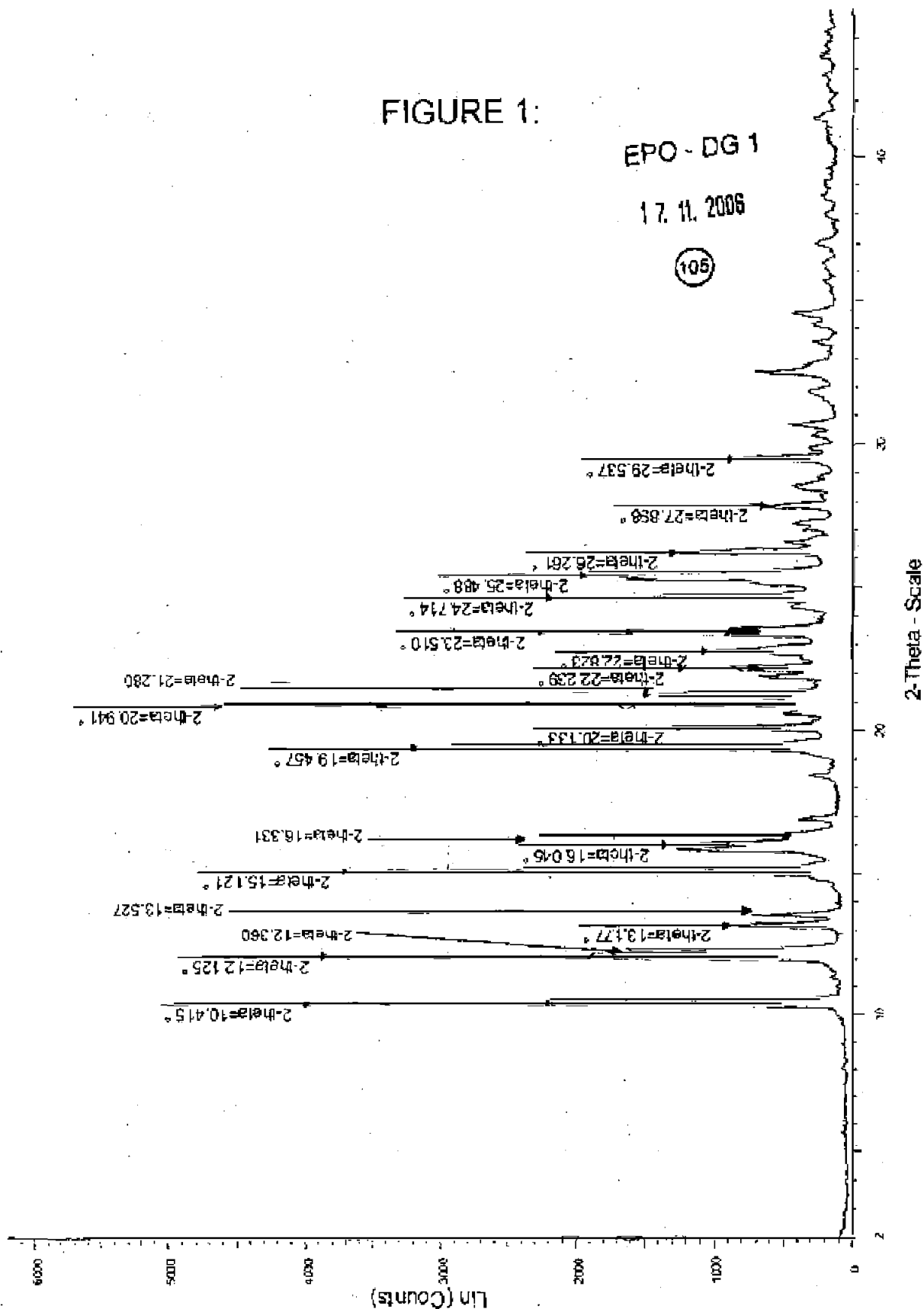
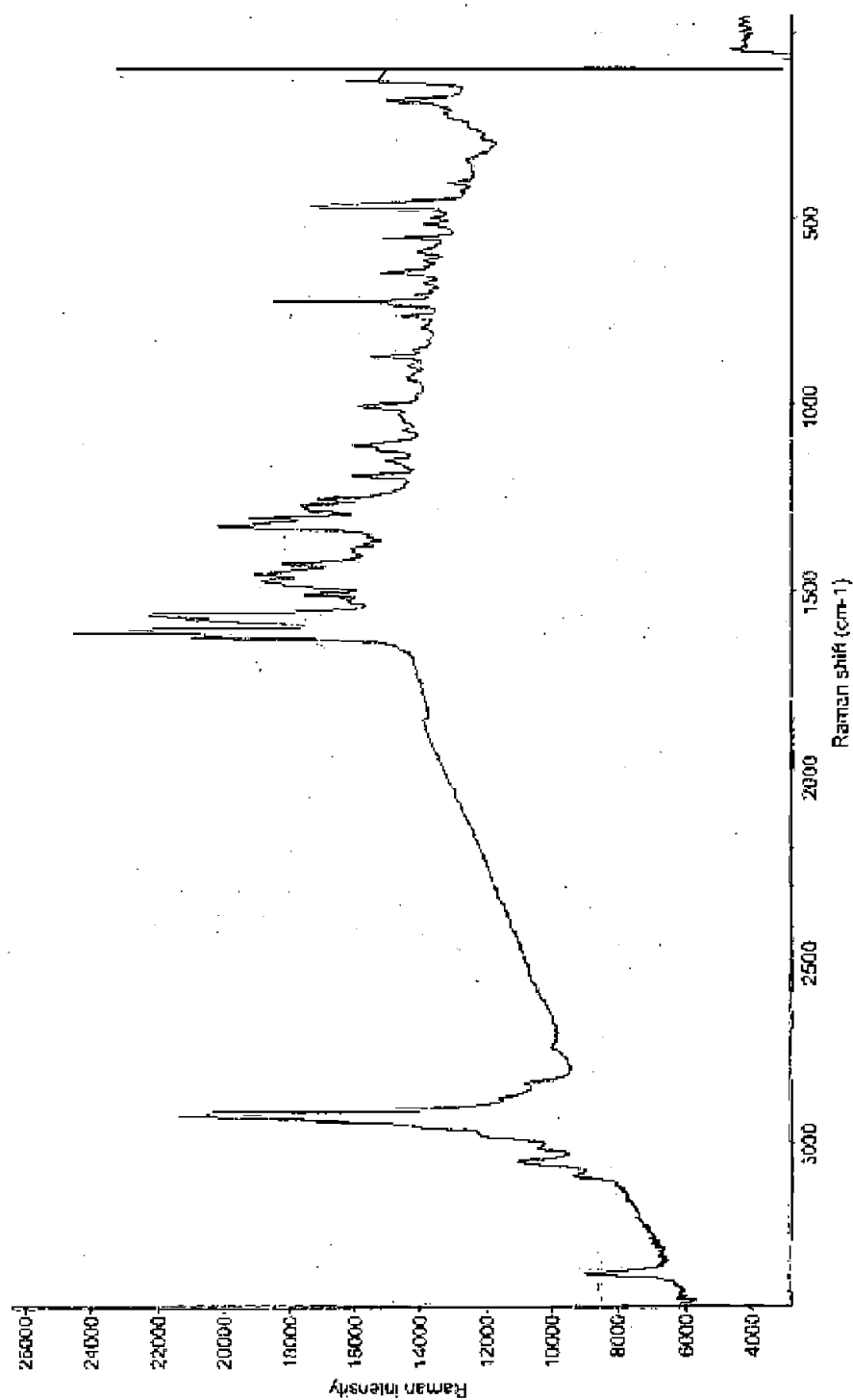
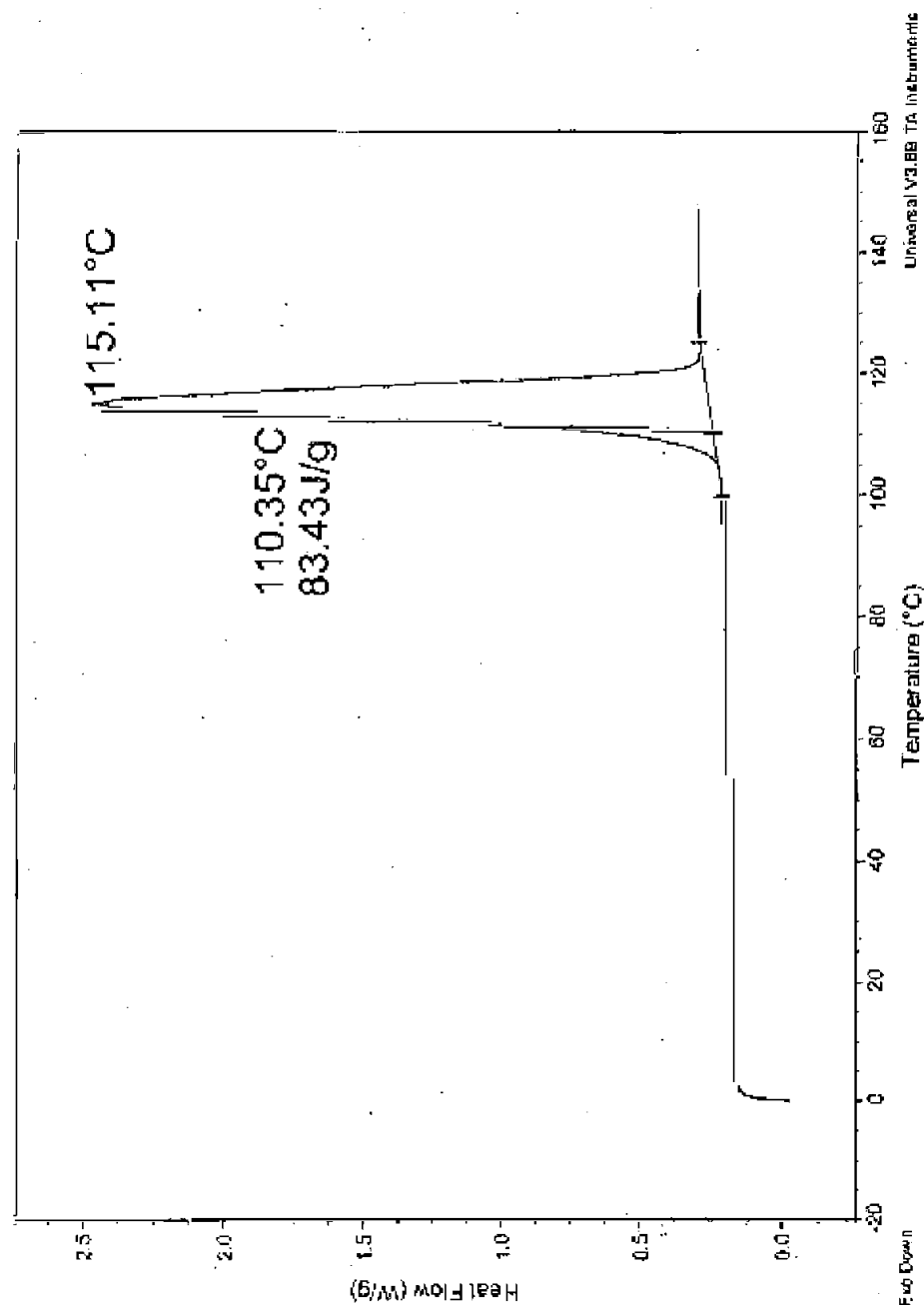


FIGURE 2:



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FIGURE 3:



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FIGURE 4:

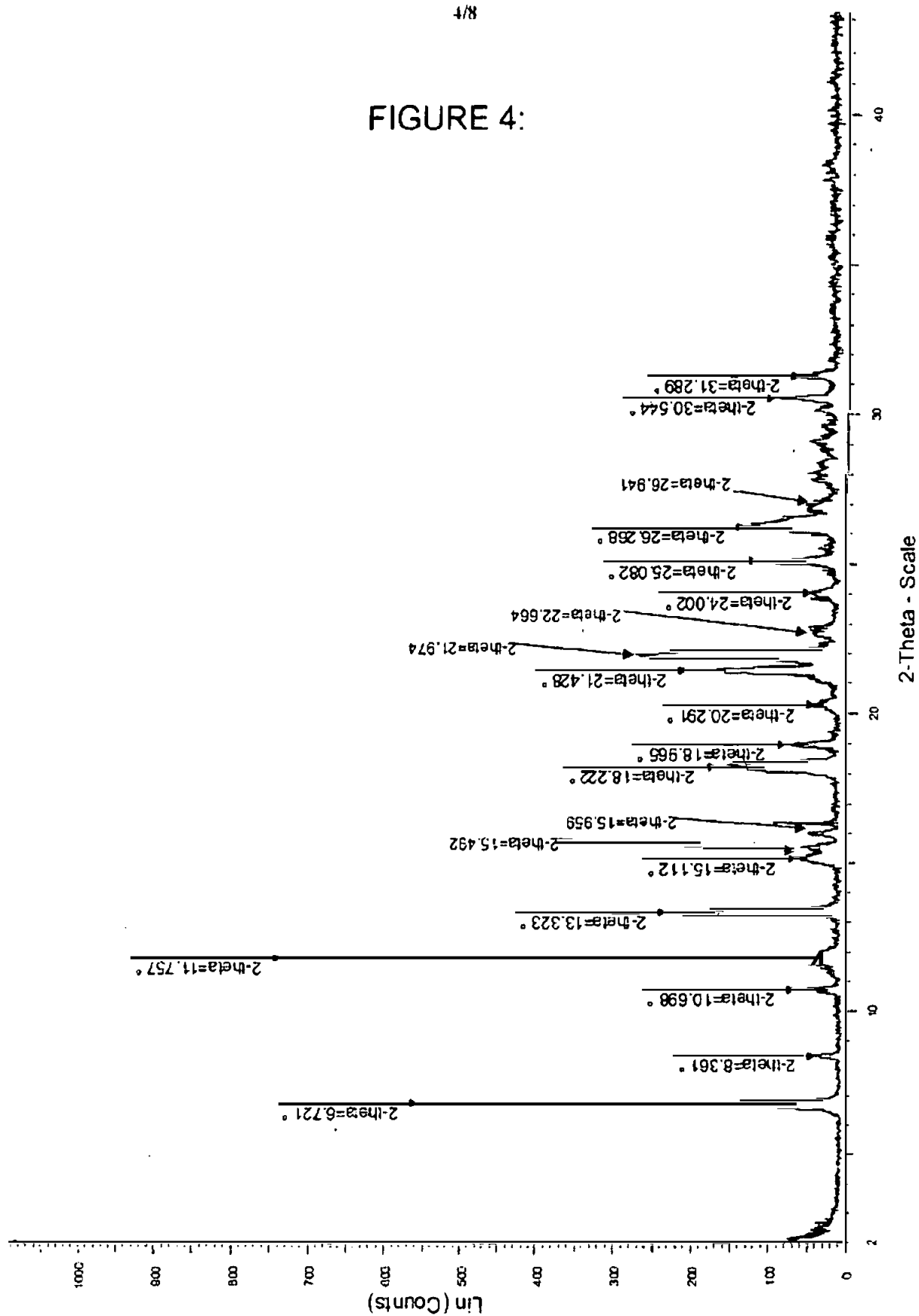
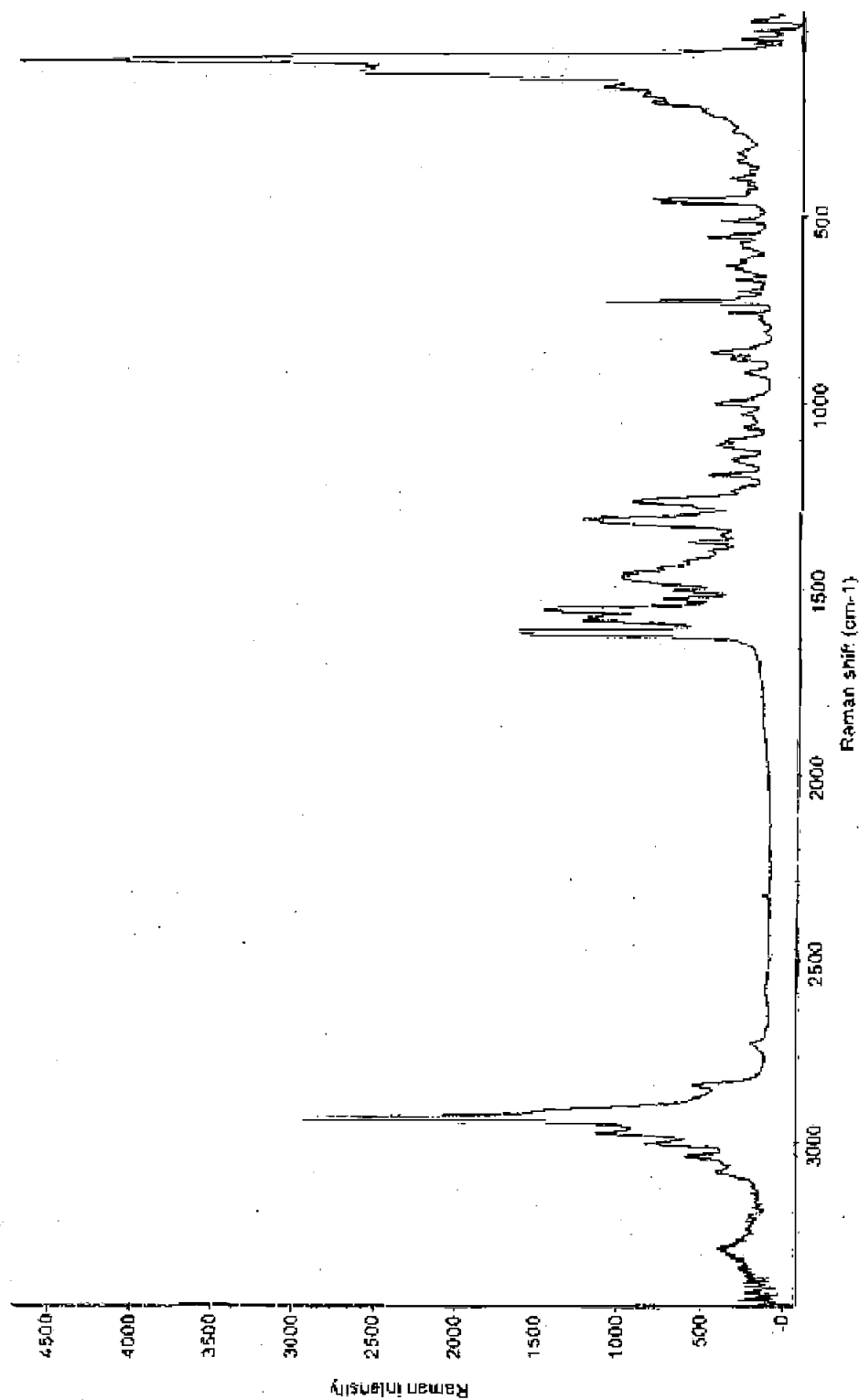
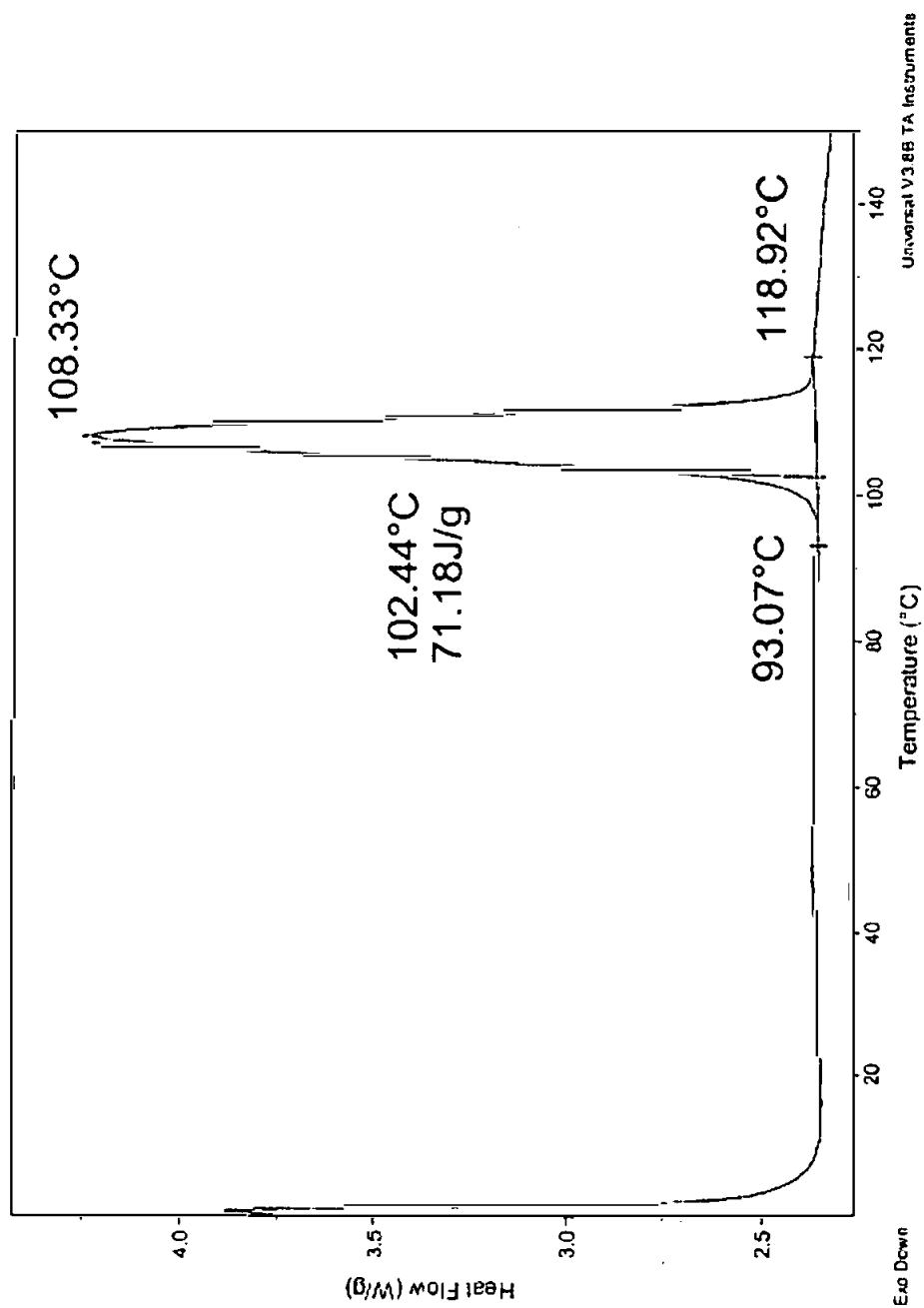


FIGURE 5:



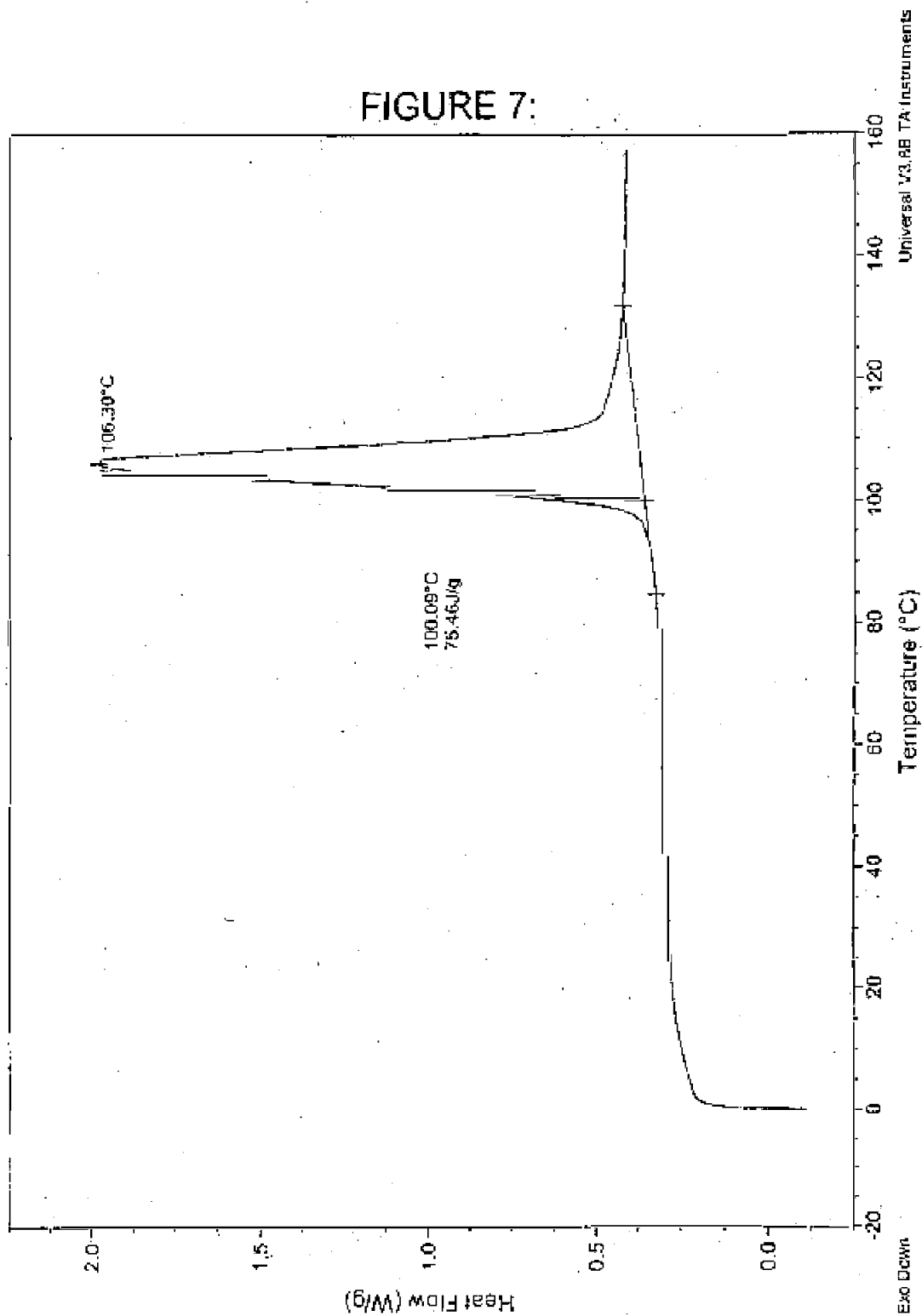
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FIGURE 6:



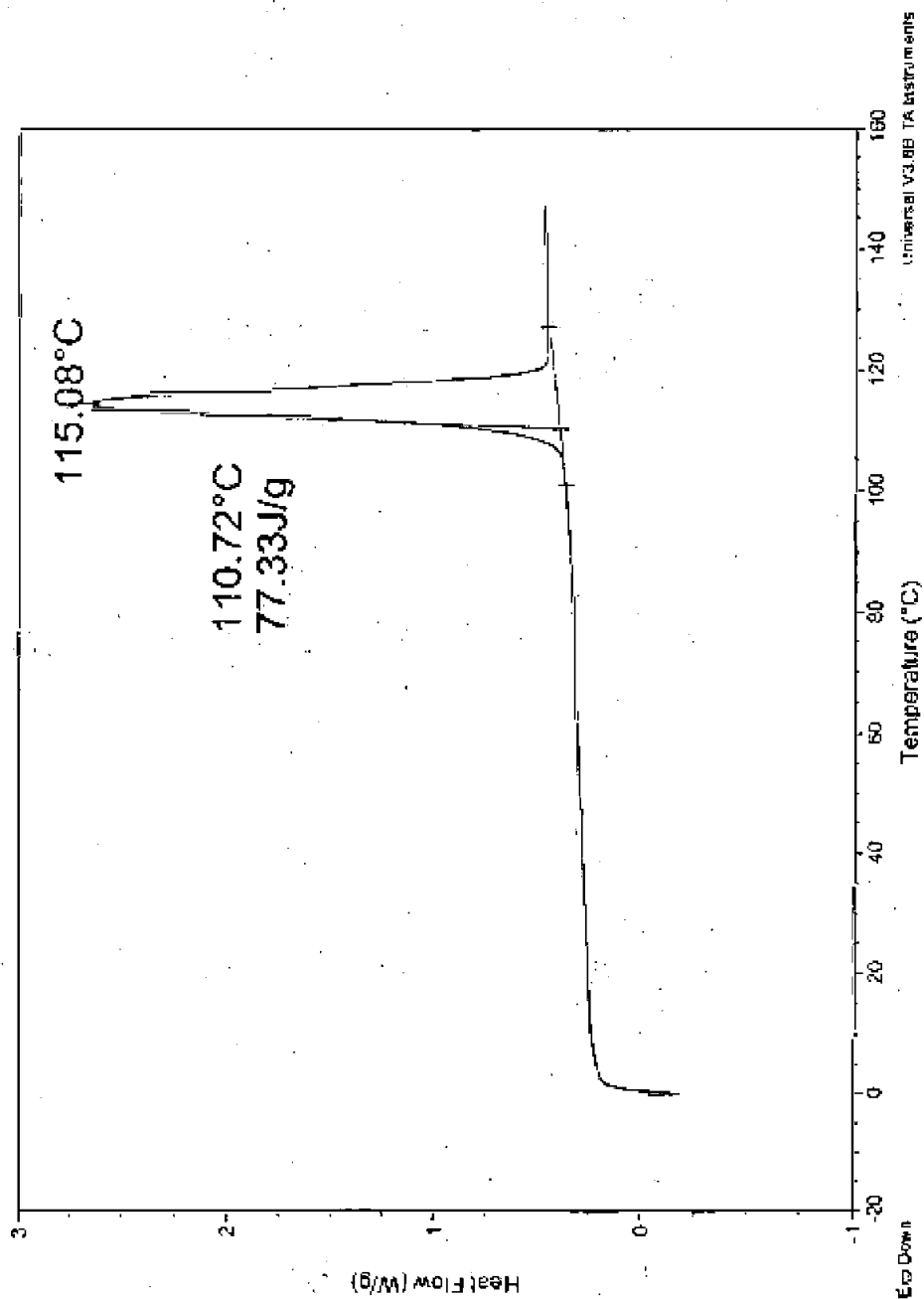
45

FIGURE 7:



alt

FIGURE 8:



DERIVADOS DE PIRAZOLO[1,5-ALFA]PIRIMIDINILO UTILES COMO
ANTAGONISTAS DE RECEPTOR DE FACTOR LIBERADOR DE
CORTICOTROPINA

5

MEMORIA DESCRIPTIVA

La presente invención generalmente se refiere a la forma 2 del polimorfo de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxa-diazol-5-il)-propil]-amina. La presente invención
10 también se refiere a composiciones farmacéuticas que comprenden el mismo y métodos para usar el mismo.

El factor liberador de corticotropina (CRF) es un péptido de 41 aminoácidos que coordina la respuesta global del cuerpo al estrés. Como un agonista de receptores de CRF (v.gr., CRF1 y CRF2), CRF es bien conocido
15 como el secretagogo fisiológico primario que controla la actividad del eje hipotalámico-pituitaria-suprarrenal (HPA) que media la respuesta de estrés endocrina. CRF también juega un papel central en las respuestas autónomas y conductual al estrés. La variación en los niveles fisiológicos de CRF se ha correlacionado con varios trastornos incluyendo depresión y ansiedad.

20 Los antagonistas de receptores de CRF se ha mostrado que alivian de manera efectiva las respuestas de estrés conductual en modelos animales. Está bien establecido que la administración sistémica de antagonistas de receptor de CRF1 conduce a efectos ansiolíticos y

antidepresivos en roedores. La evidencia de modelo animal también muestra que los antagonistas de CRF1 pueden ayudar a aliviar los síntomas de abstinencia a fármacos, ataques inducidos por estrés y ciertas inflamaciones. Un papel para CRF también se ha postulado en la etiología y fisiopatología de enfermedad Alzheimer, enfermedad de Parkinson, enfermedad de Huntington, parálisis supranuclear progresiva y esclerosis lateral amiotrófica ya que se relacionan con la disfunción de neuronas de CRF en el sistema nervioso central. Trastornos de la alimentación, tales como anorexia nerviosa, también se han relacionado con niveles elevados de CRF.

10 Aunque ampliamente dispersos en todo el sistema nervioso central, los receptores de CRF también se encuentran en sistemas periféricos incluyendo tejidos de sistemas glandular, vascular, gastrointestinal e inmune. Por consiguiente, se cree que los antagonistas de CRF tienen potencial en el tratamiento de muchos otros trastornos fuera del sistema nervioso central.

15 Algunos trastornos relacionados con CRF de sistemas periféricos incluyen, por ejemplo, hipertensión, taquicardia, insuficiencia cardíaca congestiva, accidente vascular cerebral, síndrome de intestino irritable, íleo post-operatorio e hipersensibilidad colónica. Los estudios han indicado que los antagonistas de CRF1 también pueden ser útiles como estimuladores de crecimiento del cabello.

20 El compuesto [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina se ha identificado como un antagonista de receptor de CRF efectivo que puede ser

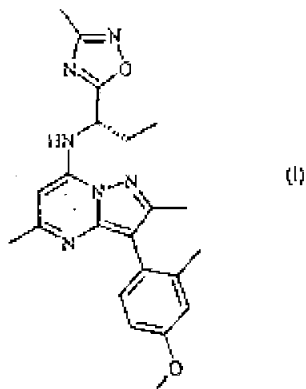
útil en el tratamiento, por ejemplo, de los trastornos anteriormente nombrados.

El compuesto se reporta en la solicitud de patente internacional WO2006/044958, que se incorpora aquí por referencia en su totalidad.

Aunque se han descubierto muchos antagonistas de receptor de
5 CRF, como el compuesto anterior, típicamente poseen las características que son satisfactorias para la preparación de composiciones farmacéuticas estables. El punto de fusión, carácter higroscópico, estabilidad, solubilidad, cristalinidad, biodisponibilidad y características de manejo están entre las numerosas propiedades que necesitan ser consideradas en la preparación de
10 medicamentos que pueden administrarse de manera efectiva. Por consiguiente, existe una necesidad en curso de preparar compuestos con propiedades físicas y químicas que sean tanto fisiológicamente aceptables como adecuados para preparar formulaciones farmacéuticas reproducibles. El polimorfo de la presente invención ayuda a satisfacer esta y otras
15 necesidades. El polimorfo de la presente invención es el más termodinámicamente estable entre las dos formas de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]-oxadiazol-5-il)-propil]-amina de la fórmula (I). En la sección experimental, se proveerá un experimento de conversión de una mezcla de las dos formas a la forma 2 más
20 estable y un cálculo de la temperatura de transición.

La presente invención provee la forma 2 del polimorfo de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]- amina.

[3-(4-Metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-
[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina también se puede designar
de ahora en adelante como compuesto de la fórmula (I).



10 La forma 2 del polimorfo del compuesto de la fórmula (I) de la presente invención es una base libre.

La forma 2 del polimorfo del compuesto de la fórmula (I) de la presente invención se ha caracterizado como se reporta más adelante en los ejemplos.

15 La presente invención además provee composiciones que comprenden el compuesto de la presente invención y un vehículo farmacéuticamente aceptable.

Modalidades adicionales incluyen métodos de tratamiento de un trastorno en un mamífero caracterizado por niveles anormales de CRF, que
20 comprende administrar al mamífero una cantidad terapéuticamente efectiva del compuesto de la presente invención. Por consiguiente, la presente invención además provee métodos de tratamiento de ansiedad o depresión o síndrome de intestino irritable en un mamífero que comprende administrar al

mamífero una cantidad terapéuticamente efectiva del compuesto de la presente invención.

Por consiguiente, la presente invención además provee composiciones farmacéuticas que comprenden la forma 2 del polimorfo de [3-
5 (4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il)-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina de la fórmula (I) y un vehículo farmacéuticamente aceptable.

Un "vehículo farmacéuticamente aceptable" se refiere a medios generalmente aceptados en la técnica para el suministro de agentes
10 biológicamente activos a animales, en particular, mamíferos.

Los vehículos farmacéuticamente aceptables se formulan de conformidad con un número de factores dentro del alcance de los expertos en la técnica. Esos incluyen, sin limitación: el tipo y naturaleza del agente activo que está siendo formulado; el sujeto al cual la composición que contiene
15 agente se ha de administrar; y la vía de administración pretendida de la composición; y la indicación terapéutica que está siendo dirigida. Los vehículos farmacéuticamente aceptables incluyen tanto medio líquido acuoso como no acuoso, así como una variedad de formas de dosis sólidas y semisólidas. Dichos vehículos pueden incluir un número de diferentes
20 ingredientes y aditivos además del agente activo, tales como ingredientes adicionales que se incluyen en la formulación por una variedad de razones, v.gr., estabilización del agente activo, aglutinantes, etc. bien conocidos por los expertos en la técnica. Descripciones de vehículos farmacéuticamente

aceptables adecuados y factores implicados en su selección, se encuentran en una variedad de fuentes fácilmente disponibles tales como, por ejemplo, Remington's Pharmaceutical Sciences, 17a ed., Mack Publishing Company, Easton, PA, 1985, que se incorpora aquí por referencia en su totalidad.

5 La presente invención también incluye métodos de tratamiento de un trastorno caracterizado por niveles anormales de factor liberador de corticotropina en un mamífero al administrar al mamífero una cantidad terapéuticamente efectiva del compuesto de la presente invención, o una composición que contiene el compuesto de la presente invención. De
10 conformidad con algunas modalidades, el trastorno se puede caracterizar por niveles elevados de factor liberador de corticotropina. En algunas modalidades, el trastorno afecta al sistema nervioso central. Trastornos ilustrativos del sistema nervioso central que se pueden tratar de conformidad con los métodos descritos aquí incluyen ansiedad o depresión.

15 En otras modalidades, el trastorno afecta los sistemas periféricos. Por consiguiente, un ejemplo de un trastorno tratable de los sistemas periféricos de conformidad con los métodos descritos aquí es el síndrome de intestino irritable.

 Antagonistas de receptor de CRF de la presente invención
20 pueden demostrar actividad en el sitio receptor de CRF, y se pueden usar como agentes terapéuticos para el tratamiento de una amplia gama de trastornos o enfermedades incluyendo trastornos o padecimientos endocrinos, psiquiátricos y neurológicos. De manera más específica, los antagonistas de

receptor de CRF de la presente invención pueden ser útiles en el tratamiento de condiciones o trastornos fisiológicos que surgen de la hipersecreción de CRF. Puesto que se cree que CRF es un nuevo transmisor importante que activa y coordina las respuestas al estrés endocrinas, conductuales y autónomas, los antagonistas de receptor de CRF de la presente invención pueden ser útiles en el tratamiento de trastornos neuropsiquiátricos. Los trastornos neuropsiquiátricos que pueden ser tratables por los antagonistas de receptor de CRF de la invención incluyen trastornos afectivos tales como depresión; trastornos relacionados con ansiedad tales como trastorno de ansiedad generalizado, trastorno de pánico, trastorno obsesivo-compulsivo, agresión anormal, anormalidades cardiovasculares tales como angina inestable de hipertensión reactiva; y trastornos de la alimentación tales como anorexia nerviosa, bulimia y síndrome de intestino irritable. Los antagonistas de CRF también pueden ser útiles en el tratamiento de supresión inmune inducida por estrés asociada con varios estados de enfermedad, así como accidente vascular cerebral. Otros usos de los antagonistas de CRF de esta invención incluyen tratamiento de condiciones inflamatorias (tales como artritis reumatoide, uveitis, asma, enfermedad intestinal inflamatoria y motilidad G.I); dolor, enfermedad de Cushing, espasmos infantiles, epilepsia y otros ataques en niños pequeños y adultos, y abuso de sustancias y abstinencia a sustancias (incluyendo alcoholismo).

Dentro del contexto de la presente invención, los siguientes términos que describen las indicaciones usadas aquí se clasifican en el

Diagnostic and Statistical Manual of Mental Disorders, 4a Edición, publicada por the American Psychiatric Association (DSM-IV) y/o the International Classification of Diseases, 10a Edición (ICD-10). Los diversos subtipos de los trastornos mencionados aquí se contemplan como parte de la presente invención. Los números entre paréntesis después de las enfermedades listadas a continuación se refieren al código de clasificación en DSM-IV.

Dentro del contexto de la presente invención, el término "trastorno psicótico" incluye:

Esquizofrenia incluyendo los subtipos tipo paranoide (295.30), tipo desorganizado (295.10), tipo catatónico (295.20), tipo indiferenciado (295.90) y tipo residual (295.60); trastorno esquizofreniforme (295.40); trastorno esquizoafectivo (295.70) incluyendo los subtipos tipo bipolar y tipo depresivo; trastorno de delirio (297.1) incluyendo los subtipos tipo erotomaniaco, tipo grandioso, tipo celoso, tipo de persecución, tipo somático, tipo mixto y tipo no especificado; trastorno sicótico breve (298.8); trastorno psicótico compartido (297.3); trastorno psicótico debido a una condición médica general incluyendo los subtipos con ilusiones falsas y con alucinaciones; trastorno psicótico inducido por sustancias incluyendo los subtipos con ilusiones falsas (293.81) y con alucinaciones (293.82); y trastorno psicótico no especificado de otra manera (298.9). Los compuestos de la presente invención incluyendo sales y solvatos farmacéuticamente aceptables de los mismos también se pueden usar en el tratamiento de los siguientes trastornos:

Trastornos de depresión y del estado de ánimo incluyendo episodio depresivo mayor, episodio maniaco, episodio mixto y episodio hipomaniaco; trastorno depresivos incluyendo trastorno depresivo mayor, trastorno distímico (300.4), trastorno depresivo no especificado de otra manera (311); trastornos bipolares incluyendo trastorno bipolar I, trastorno bipolar II (episodios depresivos mayores recurrentes con episodios hipomaniacos) (296.89), trastorno ciclotímico (301.13) y trastorno bipolar no especificado de otra manera (296.80); otros trastornos del estado de ánimo incluyendo trastorno del estado de ánimo debido a una condición médica general (293.83) que incluye los subtipos con características depresivas, con episodio similar al depresivo mayor, con características maniacas y con características mixtas), trastorno del estado de ánimo inducido por sustancias (incluyendo los subtipos con características depresivas, con características maniacas y con características mixtas) y trastornos del estado de ánimo no especificado de otra manera (296.90):

Trastornos de ansiedad incluyendo trastorno de ansiedad social, ataque de pánico, agorafobia, trastorno de pánico, agorafobia sin historia de trastorno de pánico (300.22), fobia específica (300.29) incluyendo los subtipos tipo animal, tipo ambiente natural, tipo sangre-inyección-lesión, tipo situacional y otro tipo), fobia social (300.23), trastorno obsesivo-compulsivo (300.3), trastorno de estrés postraumático (309.81), trastorno de estrés agudo (308.3), trastorno de ansiedad generalizado (300.02), trastorno de ansiedad debido a la condición médica general (293.84), trastorno de ansiedad inducido por

sustancias y trastorno de ansiedad no especificado de otra manera (300.00):

Trastornos relacionados con sustancias incluyendo trastornos de uso de sustancias tales como dependencia de sustancias, anhelo de sustancias y abuso de sustancias; trastornos inducidos por sustancias tales como intoxicación por sustancias, abstinencia a sustancias, delirio inducido por sustancias, demencia persistente inducida por sustancias, trastorno amnésico persistente inducido por sustancias, trastorno psicótico inducido por sustancias, trastorno del estado de ánimo inducido por sustancias, trastorno de ansiedad inducido por sustancias, disfunción sexual inducida por sustancias, trastorno del sueño inducido por sustancias y trastorno de percepción persistente alucinógeno (recuerdos momentáneos); trastornos relacionados con el alcohol tales como dependencia del alcohol (303.90), abuso del alcohol (305.00), intoxicación por alcohol (303.00), abstinencia al alcohol (291.81), delirio por intoxicación con alcohol, delirio por abstinencia al alcohol, demencia persistente inducida por alcohol, trastorno amnésico persistente inducido por alcohol, trastorno psicótico inducido por alcohol, trastornos del estado de ánimo inducido por alcohol, trastorno de ansiedad inducido por alcohol, disfunción sexual inducida por alcohol, trastorno del sueño inducido por alcohol y trastorno relacionado con el alcohol no especificado de otra manera (291.9); trastornos relacionados con anfetaminas (o similares a anfetaminas) tales como dependencia de anfetaminas (304.40), abuso de anfetaminas (305.70), intoxicación con anfetaminas (292.89), abstinencia a anfetaminas (292.0), delirio por intoxicación por anfetaminas,

trastorno psicótico inducido por anfetaminas, trastorno del estado de ánimo inducido por anfetaminas, trastorno de ansiedad inducido por anfetaminas, disfunción sexual inducida por anfetaminas, trastorno del sueño inducido por anfetaminas y trastorno relacionado con anfetaminas no especificado de otra manera (292.9); trastorno relacionados con cafeína tales como intoxicación con cafeína (305.90), trastorno de ansiedad inducido por cafeína, trastorno del sueño inducido por cafeína y trastorno relacionado con cafeína no especificado de otra manera (292.9); trastornos relacionado con *Cannabis* tales como dependencia de *Cannabis* (304.30), abuso de *Cannabis* (305.20), intoxicación por *Cannabis* (292.89), delirio por intoxicación con *Cannabis*, trastorno psicótico inducido por *Cannabis*, trastorno de ansiedad inducido por *Cannabis* y trastorno relacionado con *Cannabis* no especificado de otra manera (292.9); trastorno relacionados con cocaína tales como dependencia de cocaína (304.20), abuso de cocaína (305.60), intoxicación con cocaína (292.89), abstinencia a cocaína (292.0), delirio por intoxicación con cocaína, trastorno psicótico inducido por cocaína, trastorno del estado de ánimo inducido por cocaína, trastorno de ansiedad inducido por cocaína, disfunción sexual inducida por cocaína, trastorno del sueño inducido por cocaína y trastorno relacionado con cocaína no especificado de otra manera (292.9); trastornos relacionados con alucinógenos tales como dependencia de alucinógenos (304.50), abuso de alucinógenos (305.30), intoxicación con alucinógenos (292.89), trastorno de percepción persistente por alucinógenos (recuerdos momentáneos) (292.89), delirio por intoxicación con alucinógenos,

trastorno psicótico inducido por alucinógenos, trastorno del estado de ánimo inducido por alucinógenos, trastorno de ansiedad inducido por alucinógenos y trastorno relacionado con alucinógenos no especificado de otra manera (292.9); trastorno relacionados con inhalantes tales como dependencia de inhalantes (304.60), abuso de inhalantes (305.90), intoxicación con inhalantes (292.89), delirio de intoxicación con inhalantes, demencia persistente inducida por inhalantes, trastorno psicótico inducido por inhalantes, trastorno del estado de ánimo inducido por inhalantes, trastorno de ansiedad inducido por inhalantes y trastorno relacionado con inhalantes no especificado de otra manera (292.9); trastornos relacionados con nicotina tales como dependencia de nicotina (305.1), abstinencia a nicotina (292.0) y trastorno relacionado con nicotina no especificado de otra manera (292.9); trastornos relacionados con opioides tales como dependencia de opioides (304.00), abuso de opioides (305.50), intoxicación con opioides (292.89), abstinencia a opioides (292.0), delirio por intoxicación con opioides, trastorno psicótico inducido por opioides, trastorno del estado de ánimo inducido por opioides, disfunción sexual inducida por opioides, trastorno del sueño inducido por opioides y trastorno relacionado con opioides no especificado de otra manera (292.9); trastornos relacionados con fenciclidina (o similar a fenciclidina)- tales como dependencia de fenciclidina (304.60), abuso de fenciclidina (305.90), intoxicación con fenciclidina (292.89), delirio por intoxicación con fenciclidina, trastorno psicótico inducido por fenciclidina, trastorno del estado de ánimo inducido por fenciclidina, trastorno de ansiedad inducido por fenciclidina y

trastorno relacionado con fenciclidina no especificado de otra manera (292.9);
 trastornos relacionados con sedantes, hipnóticos o ansiolíticos tales como
 dependencia de sedantes, hipnóticos o ansiolíticos (304.10), abuso de
 sedantes, hipnóticos o ansiolíticos (305.40), intoxicación con sedantes,
 5 hipnóticos o ansiolíticos (292.89), abstinencia a sedantes, hipnóticos o
 ansiolíticos (292.0), delirio por intoxicación con sedantes, hipnóticos o
 ansiolíticos, delirio por abstinencia a sedantes, hipnóticos o ansiolíticos,
 demencia persistente por sedantes, hipnóticos o ansiolíticos, trastorno
 amnésico persistente por sedantes, hipnóticos o ansiolíticos, trastorno
 10 psicótico inducido por sedantes, hipnóticos o ansiolíticos, trastorno del estado
 de ánimo inducido por sedantes, hipnóticos o ansiolíticos, trastorno de
 ansiedad inducido por sedantes, hipnóticos o ansiolíticos, disfunción sexual
 inducida por sedantes, hipnóticos o ansiolíticos, trastorno del sueño inducido
 por sedantes, hipnóticos o ansiolíticos y trastorno relacionado con sedantes,
 15 hipnóticos o ansiolíticos no especificado de otra manera (292.9); trastorno
 relacionado con polisustancia tales como dependencia de polisustancia
 (304.80); y otros trastornos relacionados con sustancias (o desconocidos)
 tales como esteroides anabólicos, inhalantes de nitrato y óxido nitroso;

Trastornos del sueño incluyendo trastornos del sueño primarios
 20 tales como disomnias tales como insomnio primario (307.42), hipersomnia
 primaria (307.44), narcolepsia (347), trastornos del sueño relacionados con la
 respiración (780.59), trastornos del sueño del ritmo circadiano (307.45) y
 disomnia no especificada de otra manera (307.47); trastornos del sueño

primarios tales como parasomnias tales como trastornos de pesadillas (307.47), trastorno de terror de sueño (307.46), trastornos de sonambulismo (307.46) y parasomnia no especificada de otra manera (307.47); trastornos del sueño relacionados con otro trastorno mental tal como insomnio relacionado con otro trastorno mental (307.42) e hipersomnia relacionada con otro trastorno mental (307.44); trastorno del sueño debido a una condición médica general; y trastorno el sueño inducido por sustancias incluyendo los subtipos tipo de insomnio, tipo de hipersomnia, tipo de parasomnia y tipo mixto;

Trastornos de la alimentación tales como anorexia nerviosa (307.1) incluyendo los subtipos tipo de restricción y tipo de atascón/purga; bulimia nerviosa (307.51) incluyendo los subtipos tipo purga y tipo sin purga; obesidad; trastorno de alimentación compulsiva y trastorno de alimentación no especificado de otra manera (307.50):

Trastorno autístico (299.00); trastorno de déficit de atención/hiperactividad incluyendo los subtipos tipo combinado de trastorno de déficit de atención/hiperactividad (314.01), tipo predominantemente inatento de trastorno de déficit de atención/hiperactividad (314.00), tipo hiperactivo/impulsivo de trastorno de déficit de atención/hiperactividad (314.01) y trastorno de déficit de atención/hiperactividad no especificado de otra manera (314.9); trastorno hipercinético; trastornos de conducta perturbadora tales como trastorno de la conducta que incluye los subtipos de tipo de inicio en la niñez (321.81), tipo de inicio en la adolescencia (312.82) y e inicio no especificado (312.89), trastorno desafiante opositor (313.81) y

trastorno de conducta perturbadora no especificado de otra manera; y trastornos de tic tales como trastorno de Tourette (307.23):

Trastornos de personalidad incluyendo los subtipos trastorno de personalidad paranoide (301.0), trastorno de personalidad esquizoide (301.20), 5 trastorno de personalidad esquizotípica (301.22), trastorno de personalidad antisocial (301.7), trastorno de personalidad límite (301.83), trastorno de personalidad histriónico (301.50), trastorno de personalidad narcisista (301.81), trastorno de personalidad de evitación (301.82), trastorno de personalidad dependiente (301.6), 10 trastorno de personalidad obsesivo-compulsivo (301.4) y trastorno de personalidad no especificado de otra manera (301.9):

Mejora de la cognición incluyendo el tratamiento de alteración de cognición en enfermedades tal esquizofrenia, trastorno bipolar, depresión, otros trastornos psiquiátricos y condiciones psicóticas asociadas con 15 alteración cognitiva, v.gr., enfermedad de Alzheimer y

Disfunciones sexuales incluyendo trastornos de deseo sexual tales como trastorno de deseo sexual hipoactivo (302.71), y trastorno de aversión sexual (302.79); trastornos de estimulación sexual tales como 20 trastorno de estimulación sexual femenina (302.72) y trastorno eréctil masculino (302.72); trastornos orgásmicos tales como trastorno orgásmico femenino (302.73), trastorno orgásmico masculino (302.74) y eyaculación prematura (302.75); trastornos de dolor sexual tales como Dispareunia (302.76) y Vaginismo (306.51); disfunción sexual no especificada de otra

manera (302.70); parafilias tales como exhibicionismo (302.4), Fetichismo (302.81), Froteurismo (302.89), Pedofilia (302.2), masoquismo sexual (302.83), sadismo sexual (302.84), fetichismo transvéstico (302.3), Voyeurismo (302.82) y Parafilia no especificada de otra manera (302.9);

5 trastornos de identidad de género tales como trastorno de identidad de género en niños (302.6) y trastorno de identidad de género en adolescentes y adultos (302.85); y trastorno sexual no especificado de otra manera (302.9).

Todas las diversas formas y subformas de los trastornos mencionados aquí se contemplan como parte de la presente invención.

10 El término "cantidad terapéuticamente efectiva" se refiere a una cantidad del compuesto de la presente invención efectiva para reducir o eliminar por lo menos un síntoma de un trastorno para el cual se usó el compuesto.

El compuesto de la presente invención se puede administrar

15 para tratar los trastornos anteriores por cualesquiera medios adecuados que permiten que el compuesto haga contacto con el sitio de acción, tal como un receptor de CRF en el cuerpo de un mamífero. El compuesto se puede administrar por cualesquiera medios convencionales disponibles para usarse junto con compuestos farmacéuticos ya sea como un agente terapéutico

20 individual o en combinación con otros agentes terapéuticos. El compuesto de la presente invención se puede administrar solo o en combinación con un vehículo farmacéutico seleccionado sobre la base de la vía de administración escogida y la práctica farmacéutica estándar.

La dosis del compuesto de la presente invención para administración varía dependiendo de varios factores tales como el carácter farmacodinámico del compuesto particular, y su modo y vía de administración; la edad, peso y salud del receptor; naturaleza y grado de los síntomas; tipo de tratamiento concurrente; frecuencia de tratamiento; y efecto deseado. Para usarse en el tratamiento de las enfermedades o condiciones anteriores, las sales de esta invención se pueden administrar por vía oral diariamente a una dosis del ingrediente activo (v.gr., una sal de la fórmula I) de aproximadamente 0.002 a aproximadamente 200 mg/kg de peso corporal. Por ejemplo, una dosis de aproximadamente 0.01 a aproximadamente 10 mg/kg se puede dividir en dosis más pequeñas y administrar de una a cuatro veces al día. Alternativamente, las formulaciones de liberación sostenida pueden ser efectivas para obtener el efecto farmacológico deseado.

Las formas de dosis (composiciones) adecuadas para administración pueden contener de aproximadamente 1 mg a aproximadamente 200 mg de ingrediente activo por unidad de dosis. En estas composiciones farmacéuticas, el ingrediente activo (v.gr., forma 2 del polimorfo de la fórmula (I)) puede estar presente en una cantidad de aproximadamente 0.5 a 95% en peso basada en el peso total de la composición.

El ingrediente activo (v.gr., forma 2 del polimorfo de la fórmula (I)) se puede administrar por vía oral en formas de dosis sólidas tales como cápsulas, tabletas y polvos, o en formas líquidas tales como elixires, jarabes,

y/o suspensiones. El compuesto de la invención también se puede administrar parenteralmente en formulaciones de dosis líquidas estériles.

Se pueden usar cápsulas de gelatina para contener el ingrediente activo y un vehículo adecuado tal como, pero sin limitarse a, lactosa, almidón, estearato de magnesio, ácido esteárico o derivados de celulosa. Se pueden usar diluyentes similares para hacer tabletas comprimidas. Tanto las tabletas como las cápsulas se pueden fabricar como productos de liberación sostenida para proveer liberación continua del medicamento durante un periodo. Las tabletas comprimidas pueden ser revestidas con azúcar o revestidas con película para cubrir cualquier sabor desagradable, o usar para proteger los ingredientes activos de la atmósfera, o para permitir la desintegración selectiva de la tableta en el tracto gastrointestinal.

Las formas de dosis líquidas para administración oral también pueden contener agentes colorantes o saborizantes para incrementar la aceptación por el paciente.

Típicamente, agua, aceites farmacéuticamente aceptables, solución salina, dextrosa acuosa y soluciones de azúcar relacionadas y glicoles, tales como propilenglicol o polietilenglicol, son vehículos adecuados para soluciones parenterales. Las soluciones para administración parenteral pueden contener, por ejemplo, sal soluble en agua del ingrediente activo y agentes estabilizadores adecuados. Agentes antioxidantes, tales como bisulfito de sodio, sulfito de sodio o ácido ascórbico, ya sea solos o en

combinación, pueden actuar como agentes estabilizadores adecuados.

También adecuados como agentes estabilizadores son ácido cítrico y sus sales, y EDTA. Además, las soluciones parenterales pueden contener conservadores tales como, por ejemplo, cloruro de benzalconio, metil- o propil-parabeno y clorobutanol

EJEMPLOS

Abreviaturas:

- 10 DCM: Diclorometano
DIC: N,N'-Diisopropilcarbodiimida
DMF: Dimetilformamida
HOBT: 1-Hidroxibenzotriazol
Agua DM: agua desmineralizada

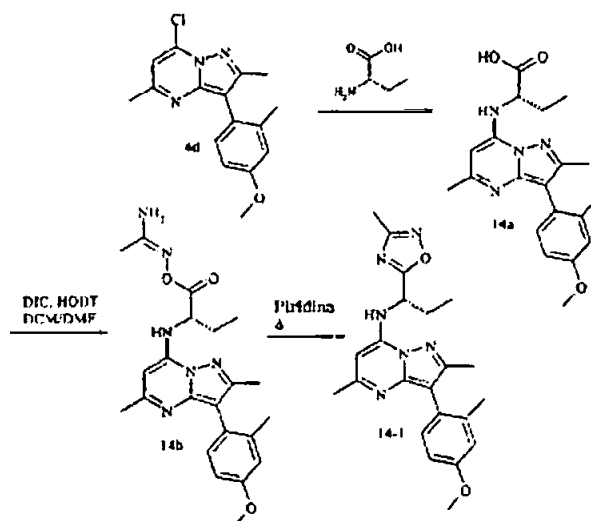
15

INTERMEDIARIO 1

Preparación y caracterización de forma 1 del polimorfo del compuesto de la fórmula (I)

- 20 La forma 1 del polimorfo del compuesto de la fórmula (I) se puede preparar de conformidad con el siguiente esquema, como se reporta en WO 2006/044958:

5



10

Paso 14A:

Una suspensión de bicarbonato de sodio (28.7 g) y ácido (S)-2-aminobutírico (21.7 g) en agua (250 ml) se añadió a una solución de 4d (preparada de conformidad con el método descrito en WO 2006/044958) (39.7 g) en dioxano (250 ml). La mezcla se agitó y se calentó a reflujo (baño a 102°C) durante 14 hr. La mezcla se enfrió a TA, después HCl concentrado (16 ml) se añadió durante 10 min a un pH final de 4.5. Se formó un precipitado blanco copioso. La mezcla se concentró a un peso de aproximadamente 250 g, después el residuo se sometió a co-evaporación con varias porciones de acetato de etilo, dando por resultado una suspensión acuosa, pastosa, espesa. La mezcla se filtró, y la torta de filtro se lavó con agua (350 ml). La torta de filtro después se secó bajo vacío a 35°C, dando el compuesto 14a (45.2 g) como un sólido blanco.

20

Paso 14B:

El compuesto 14a (10 g) se suspendió en tolueno (50 ml) y se evaporó a sequedad. DCM seco (100 ml) se añadió seguido por HOBt (4.8 g) y oxima de acetamida (2.7 g). Se añadió DMF anhidro (11 ml), después la
5 mezcla de reacción se agitó y se enfrió en un baño de etilenglicol/hielo seco a una temperatura interna de -15.5°C bajo una atmósfera de nitrógeno. DIC (5.3 ml) se añadió después mediante jeringa. La mezcla de reacción se agitó y se dejó calentar durante 2 hr, tiempo en el cual la temperatura interna era de +16.5°C. Los solventes se evaporaron, después se añadió acetato de etilo
10 (150 ml) y la mezcla se lavó dos veces con bicarbonato de sodio acuoso saturado, una vez con fosfato diácido de potasio acuoso al 10%, y finalmente con salmuera. La capa de acetato de etilo se secó sobre sulfato de sodio, se filtró y se concentró para proveer el compuesto 14b crudo.

Paso 14C:

15 Se añadió piridina (50 ml) al compuesto 14b del paso 14B, después la mezcla se calentó bajo hidrógeno a 100°C durante 4 hr. La solución resultante se dejó enfriar, el solvente se evaporó, y el residuo se co-evaporó dos veces con acetato de etilo y una vez con heptano. El residuo se
20 recogió en 50 ml de éter, después se filtró para remover DIU, enjuagando con varias porciones de éter. El filtrado se evaporó, después el residuo se sometió a cromatografía sobre gel de sílice, eluyendo con 2:1 de hexano/acetato de etilo para proveer el compuesto 14-1 parcialmente purificado como una

espuma ligeramente amarilla. La espuma se co-evaporó una vez con heptano, después 5:1 de heptano/acetato de etilo (60 ml) se añadió, y la suspensión resultante se agitó a TA durante 24 hr. El sólido se filtró y se enjuagó con 10:1 de heptano/acetato de etilo, dando base libre 14-1 (7.3 g) como un sólido blanco. El filtrado se concentró y una segunda cosecha de base libre 14-1 (0.7 g) se recogió, también como un sólido blanco.

La base libre 14-1 (6.0 g) se disolvió en 80 ml de acetona y se enfrió en un baño de etilenglicol/hielo seco a -12°C (interna). Se añadió cloruro de hidrógeno (8.9 ml de una solución 2.0 M en éter) en una porción. La solución amarilla clara se agitó durante 1 min, después el solvente se evaporó. El residuo se co-evaporó con dos porciones de acetona, después se secó bajo vacío para producir una espuma color ámbar. La espuma se pulverizó y después se secó bajo vacío a TA durante 24 hr, dando la sal de clorhidrato 14-1 (6.7 g) como un polvo color canela amorfo.

15

Caracterización de la Forma 1 del polimorfo del compuesto de la fórmula (I)

La base libre 14-1 se preparó como muestra el patrón de XPRD anterior (figura 4) y se identificó como forma 1 de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina.

20

Cuadro 1: ángulos y separaciones d de XRPD para [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]

oxadiazol-5-il)-propil]-amina, Forma 1.

CUADRO 1

Angulo (2-theta °)	Valor de d, Ångstrom
6.721	13.1397
8.361	10.5663
10.698	8.26247
11.757	7.52055
13.323	6.64016
15.112	5.85779
15.492	5.71491
15.959	5.54892
18.222	4.86461
18.965	4.67554
20.291	4.37294
21.428	4.14338
21.974	4.04163
22.664	3.92018
24.002	3.70547
25.082	3.54736
26.268	3.38993
26.941	3.30677
30.544	2.92437
31.289	2.85642

Descripción de las figuras

La figura 4 muestra datos de difracción en polvo de rayos X obtenidos para la forma 1 de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il)]-(S)-1-(3-metil-[1,2,4]oxa-diazol-5-il)-propil]-amina como se describió antes. La forma 1 se caracteriza por tener un patrón de XRPD con señales sustancialmente como se lista en el cuadro 1.

La figura 5 muestra el espectro de Raman de la forma 1 de [3-(4-

metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il)-[(S)-1-(3-metil-[1,2,4] oxadiazol-5-il)-propil]-amina.

La figura 6 muestra un termograma de calorimetría de escudriñamiento diferencial (DSC) de la Forma 1 de [3-(4-metoxi-2-metil-fenil)-
5 2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il)-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina.

Se reconocerá que los datos de espectro y difracción variarán ligeramente de acuerdo a varios factores tales como temperatura, concentración e instrumentación usados. Los expertos en la técnica
10 reconocerán que las posiciones pico de XRPD son afectadas por diferencias en la altura de la muestra. Las posiciones pico mencionadas aquí por lo tanto son sometidas a una variación de +/- 0.15 grados 2-theta.

Difracción en polvo de rayos X

15 El análisis de la difracción en polvo de rayos X (XRPD) se realizó sobre Bruker D5005, usando un detector Sol-X. Las condiciones de adquisición fueron: radiación: Cu K α , tensión de generador: 40 kV, corriente del generador: 50 mA, ángulo de inicio: 2.0 °2 θ , ángulo de terminación: 45.0 °2 θ , tamaño del paso: 0.02 °2 θ , tiempo por paso: 0.5 segundos. La muestra
20 se preparó sobre un contenedor de muestra de antecedente cero.

Espectroscopia de Raman

Configuración del instrumento: Kaiser RXN 1 Kaiser Optical System Micro Raman. Muestra sobre una charola de Al para muestras, láser I = 785 nm.

5

Calorimetría de escudriñamiento diferencial (DSC)

Configuración del instrumento: PE DSC 7, charola de muestras no hermética, operación a 10 K/min a 150°C, muestra 1.5-5 mg.

10

EJEMPLO 1

Síntesis y caracterización de la forma 2 del polimorfo del compuesto de la fórmula (I)

Método CLAR

15	Columna	Zorbax SB-C18 (150x4.6mm), 3.5 micras
	Fase móvil-A	0.05% TFA(Acuoso)
	Fase móvil-B	0.025% TFA(Acetonitrilo)
	Temperatura de la columna:	40°C
	Velocidad de flujo	1.0 ml/min
20	Longitud de onda de detección:	225 nm
	Volumen de inyección:	5 µl
	Tiempo de operación	30 min
	Concentración	0.3 mg/ml

72

Programa de gradiente

gradiente lineal

	<u>Tiempo en minutos</u>	<u>fase móvil-A(%)</u>	<u>fase móvil-B (%)</u>
	0	75	25
5	25	5	95
	29	5	95
	30	75	25

Tiempo de post-operación

5 min

10 Tiempo de retención

Forma 2 aproximadamente 9 min

Diluyente

Fase móvil-A: Fase móvil-B (1:1)

La forma 2 de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina se preparó como sigue:

15 [3-(4-Metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina Forma 1 (0.74 g) se suspendió en isopropanol acuoso al 50% (4 ml). La temperatura se cicló entre 0 y 40°C durante 24 horas, después la mezcla se agitó a temperatura ambiente durante 3 días, después la temperatura se cicló entre 0 y 40°C

20 durante 24 horas. El sólido residual se filtró y se secó a temperatura ambiente para dar 0.70 g de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina Forma 2.

La preparación de Forma 2 de [3-(4-metoxi-2-metil-fenil)-2,5-

dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina después se repitió a gran escala como sigue.

La base libre 14-1 se preparó de una manera análoga a como se describió antes, excepto por la falta de purificación cromatográfica presente en el paso 14C. La formación y liberación sucesiva de la sal de mesilato dio un compuesto deseado con una alta pureza sin la necesidad de una cromatografía.

La base libre 14-1 (2.48 kg, 6.10 moles, pureza química 90%) se agitó con acetato de n-butilo (12.5 l) durante 30 a 45 minutos, después se añadió ácido metansulfónico (1.2 eq, 7.32 Moles, 703 g). Después de agitación durante 2-3 hr a 25-30°C, la mezcla se filtró. El sólido se lavó en suspensión con acetato de n-butilo (5 l) seguido por heptano (7.5 l). Después se secó durante 4-6 hr a 50±5°C bajo vacío para dar sal de mesilato (2.48 kg, pureza química 97.37%).

La sal de mesilato se agitó con agua DM (12.5 l) durante 15 a 30 minutos. Se añadió amoníaco acuoso a un pH de 9.0-10. La suspensión se extrajo con acetato de etilo (3 x 7.5 l). Después los extractos combinados se lavaron con Agua DM (5 l) y solución de salmuera al 20% (5 l). La solución orgánica se concentró bajo vacío por debajo de 50±5°C, removiendo 85 a 90% del solvente, después el residuo se enfrió a 30±5°C. Se añadió heptano (15 l) y la mezcla se agitó durante 2 a 3 hr a 25-30°C, después se destiló 60 a 70% del solvente bajo vacío por abajo de 50±5°C. La mezcla se enfrió a 30±5°C, se agitó durante 1 a 2 horas, después se filtró. El sólido se lavó en

suspensión con heptano (5 l) después se secó bajo vacío por abajo de $50\pm 5^{\circ}\text{C}$ para dar la forma 1 de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina (1.70 kg, pureza química 99.34%).

- 5 Una mezcla de la forma 1 (1.37 kg, 3.37 moles, pureza por CLAR 99.34%) de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxa-diazol-5-il)-propil]-amina y acetato de etilo (2.05 l) se calentaron a 40 a 45°C (se observó una solución clara). La solución después se enfrió a $30\pm 5^{\circ}\text{C}$ y se añadió heptano (6.85 l) antes de calentamiento a
- 10 $60\pm 2.5^{\circ}\text{C}$. El material de siembra de la forma 2 de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina preparado como se describió antes (0.5% p/p) se añadió a $60\pm 2.5^{\circ}\text{C}$, después la mezcla se enfrió a $40\pm 2.5^{\circ}\text{C}$, después se volvió a calentar a $50\pm 2.5^{\circ}\text{C}$ cuando se añadió material de siembra adicional (0.5%
- 15 p/p). La suspensión resultante se enfrió a $30\pm 5^{\circ}\text{C}$ y se agitó durante 12 hr a $30\pm 5^{\circ}\text{C}$. Se añadió heptano (2.74 l) y la mezcla se agitó durante 12 hr adicionales a $30\pm 5^{\circ}\text{C}$. La suspensión se filtró y la suspensión sólida se lavó con heptano (2.74 l). El sólido se secó bajo vacío a $50\pm 5^{\circ}\text{C}$ durante 8 hr para dar 0.97 kg de la forma 2 de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-
- 20 a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina (pureza por CLAR 99.58%), que se había caracterizado como sigue.

Caracterización de la forma 2 del polimorfo del compuesto de la fórmula (I)

La forma 2 de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina muestra el patrón de XPRD (figura 1).

Cuadro 2: ángulos y separaciones d de XRPD para [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina, forma 2.

10

CUADRO 2

15

20

Angulo (2-theta °)	Valor de d, Ångstrom
10.415	8.48651
12.125	7.29347
12.36	7.15526
13.177	6.7136
13.527	6.5406
15.121	5.85426
16.045	5.51918
16.331	5.42339
19.457	4.55852
20.133	4.40682
20.941	4.2386
21.28	4.1718
22.239	3.99412
22.823	3.89318
23.51	3.78098
24.714	3.59933
25.488	3.49186
26.261	3.39074
29.537	3.02169
27.858	3.19988

Descripción de figuras:

La figura 1 muestra los datos de difracción en polvo de rayos X obtenido para la forma 2 de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxa-diazol-5-il)-propil]-amina como se describió antes. La forma 2 se caracteriza por tener un patrón de XRPD con
5 señales sustancialmente como se lista en el cuadro 1.

La figura 2 muestra el espectro de Raman de la forma 2 de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4] oxadiazol-5-il)-propil]-amina.

10 La figura 3 muestra un termograma de calorimetría de escudriñamiento diferencial (DSC) de la forma 2 de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina.

Se reconocerá que los datos de espectro y difracción variarán
15 ligeramente de acuerdo a varios factores tales como temperatura, concentración e instrumentación usados. Los expertos en la técnica reconocerán que las posiciones pico de XRPD son afectadas por diferencias en la altura de la muestra. Las posiciones pico mencionadas aquí por lo tanto son sometidas a una variación de +/- 0.15 grados 2-theta.

20

Difracción en polvo de rayos X

El análisis de la difracción en polvo de rayos X (XRPD) se realizó sobre Bruker D5005, usando un detector Sol-X. Las condiciones de

adquisición fueron: radiación: Cu K α , tensión de generador: 40 kV, corriente del: 50 mA, ángulo de inicio: 2.0 °2 θ , ángulo de terminación: 45.0 °2 θ , tamaño del paso: 0.02 °2 θ , tiempo por paso: 1 segundo. La muestra se preparó sobre un contenedor de muestra de antecedente cero.

5

Espectroscopía de Raman

Configuración del instrumento: Kaiser RXN1 Kaiser Optical System Micro Raman. Muestra sobre charola de Al para muestras, láser I = 785 nm.

10

Calorimetría de escudriñamiento diferencial (DSC)

Configuración del instrumento: Q 1000 TA, charola para muestras no hermética, operación a 10 K/min a 150°C, Flujo de N₂ =50 ml/min, muestra 1.5-5 mg.

15

EJEMPLO 2

Relación termodinámica entre la forma 1 y la forma 2 del compuesto de la fórmula (I)

20

Para una sustancia polimórfica, una propiedad de particular interés es la estabilidad termodinámica relativa de los polimorfos. Las preguntas a ser respondidas son las siguientes:

a) que dos polimorfos sean monotrópicos (uno es más estable

que el otro a cualquier temperatura) o enantiotrópicos (existe una temperatura de transición (T_t), por abajo y por arriba de la cual el orden de estabilidad es revertido; y

b) para un sistema enantiotrópico, en donde (T_t) se mantiene.

5 La relación termodinámica entre la forma 1 y la forma 2 del compuesto de la fórmula (I) se calculó usando los datos de fusión de polimorfos medidos por DSC, de conformidad con lo descrito en: *Lian Yu, Journal of Pharmaceutical Science, Vol. 84, No. 8, Agosto de 1995.*

10 Con base en los datos de DSC (véase artículo de referencia), la forma 1 y forma 2 tienen una relación monotrópica y la forma 2 se puede considerar la forma estable (termodinámicamente).

15 Tomando muestras de la forma 1 y forma 2 como formas puras 1 y 2 respectivamente, y usando el punto de fusión y el ΔH obtenible por datos de DSC, es posible calcular la relación termodinámica y la temperatura de transición.

Forma 1: $T = 100.09^\circ\text{C}$ y $\Delta H = 75.46 \text{ J/g}$

Forma 2: $T = 110.35^\circ\text{C}$ y $\Delta H = 83.43 \text{ J/g}$

20 Resolviendo la ecuación presentada en el artículo citado, la temperatura de transición corresponde a $T = 356^\circ\text{C}$ y es mayor que el dos anterior para la forma 1 y forma 2 y $\Delta H_0 < 0$, $\Delta S_0 < 0$, después la conclusión es que las dos formas polimórficas tienen una relación monotrópica.

 El cálculo anterior ha sido realizado usando datos de DSC para una muestra diferente de forma 1 del polimorfo del compuesto de la fórmula

79

(I), mostrando el termograma de calorimetría de escudriñamiento diferencial (DSC) de la figura 7, obtenido por el mismo método antes descrito.

Se reconocerá que el pico endotérmico como se midió depende de un número de factores incluyendo la maquinaria empleada, la velocidad de calentamiento, la calibración estándar, humedad y pureza de la muestra usada.

Un cálculo similar se ha realizado usando los datos de DSC de la forma 1 del polimorfo del compuesto de la fórmula (I) mostrado en la figura 6, preparado de conformidad al procedimiento descrito anteriormente.

10 Forma 1: $T=102.44^{\circ}\text{C}$ y $\Delta H = 71.18 \text{ J/g}$

Forma 2: $T=110.35^{\circ}\text{C}$ y $\Delta H = 83.43 \text{ J/g}$

La temperatura de transición ahora corresponde a $T= 177^{\circ}\text{C}$, mayor que las dos anteriores para la forma 1 y forma 2, y $\Delta H_0 < 0$, $\Delta S_0 < 0$, confirmando nuevamente la relación monotrópica entre las dos formas polimórficas.

15

EJEMPLO 3

Conversión de la mezcla de los dos polimorfos del compuesto de la fórmula (I) a la forma 2

20

Se preparó una solución saturada en acetato de etilo/heptano = 1/2 de la forma 1 del compuesto de la fórmula (I) (25 mg en 400 μl).

20.4 mg de la forma 1 sólida del compuesto de la fórmula (I) se

mezclaron con 21.3 mg de la forma sólida 2 del compuesto de la fórmula (I). Esa mezcla sólida se añadió a la solución saturada anterior. La suspensión así obtenida se agitó a TA todo un día. El siguiente día, la fase sólida y líquida se separaron por centrifugación, y el sólido simplemente se dejó al aire para secarse y después se examinaron por XPRD.

El análisis mostró que el sólido únicamente estaba constituido por la forma 2 del compuesto de la fórmula (I).

EJEMPLO 4

Preparación alternativa de la forma 2 del compuesto de la fórmula (I)

La base libre 14-1 se preparó usando un procedimiento ligeramente modificado de 14a. Las condiciones de reacción revisadas permitieron la formación de cantidades menores de impurezas relacionadas por lo que, en lugar de la formación y liberación sucesiva de sal de mesilato, el compuesto deseado se obtuvo directamente del tratamiento de la reacción a partir de 14b sin la necesidad de purificación adicional. La pureza del crudo fue suficiente para proveer la forma 2 de pureza químicamente aceptable cuando se usó un procedimiento de cristalización sembrada directo. La ventaja de esta cristalización alternativa es que la forma 2 deseada se puede preparar directamente a partir de la solución al sembrar con material de la forma apropiada, permitiendo así un mejor control de las características físicas del material final si se requiere en el futuro.

A una mezcla de DCM (278 l) y 14a (55.5 kg) se añadieron: HOBT (26.5 kg), acetamidooxima (15.1 kg) y DMF (55.5 l) bajo atmósfera de hidrógeno. Después de agitarse durante 5 minutos, la masa de reacción se enfrió a 0 - 5°C. Una solución de DCC (40.5 kg) en DCM (278 L) se añadió durante 4 horas por abajo de 25°C. Después de completarse la adición, la masa de reacción se agitó durante 1.5 a 2 hr por abajo de 25°C. La temperatura de reacción se elevó a 25-35°C y la mezcla de reacción se filtró, lavando el residuo con DCM (111 l). La capa de DCM combinada se lavó con solución de bicarbonato al 5% (3 x 280 L) seguido por agua DM (166.5 l) y finalmente con solución de salmuera al 5% (166.5 l). La capa orgánica se concentró bajo vacío por debajo de 50°C. Se añadió tolueno (278 l) y la temperatura de reacción se elevó a reflujo durante 3 a 4 hr. La reacción se enfrió a 30-35°C y se extrajo con HCl 5N (3 x 111 l). Las capas acuosas combinadas se trataron con carbón (5 kg) y se agitaron durante 15 a 30 minutos, después la mezcla de reacción se filtró a través de Celite y se lavó con HCl 5N (111 l). Las capas acuosas combinadas de la filtración de Celite se añadieron a amoníaco acuoso (500 l) y acetato de etilo (278 l), y se enfriaron a 0-10°C. Las capas se separaron y la capa acuosa se extrajo con acetato de etilo (2 x 278 L). Las capas orgánicas combinadas se lavaron con agua DM (278 L) seguido por solución de salmuera al 20% (278 l). 80 a 85% del solvente se destiló de la mezcla de reacción bajo vacío por abajo de 55°C. La masa de reacción se enfrió a 30±5°C y se añadió heptano (555 l). Después de agitarse durante 1 a 2 hr, 75 a 85% del solvente se destiló de la mezcla de

reacción bajo vacío por abajo de 55°C. La masa de reacción se enfrió a 30±5°C y la masa de reacción se filtró, lavando con heptano (100 l). El material se secó bajo vacío durante 4-6 hr para dar base libre 14.1 (50.7 kg).

- La base libre 14.1 (50.7 kg) se disolvió con acetato de etilo (253.5 l). Se añadió heptano (1116 l) y la mezcla se agitó durante 15-20 hr. La mezcla de reacción después se filtró a través de un filtro de Nutsche y se lavó con mezcla de acetato de etilo/heptano (1:5) (36 l). El filtrado después se concentró bajo vacío por abajo de 50±5°C hasta la remoción del 85 a 90% del solvente. Después la reacción se enfrió a 30±5°C y se añadió heptano (278 l).
- 10 Después de agitarse durante 1 a 2 hr a 25-30°C, 75-85% del solvente se removió bajo vacío por debajo de 50±5°C. Después, la temperatura se mantuvo a 30±5°C y se añadió heptano (167 l) y la masa de reacción se agitó durante 15 a 30 minutos y después se filtró. El sólido final se lavó con heptano (167 l) y se secó para dar la forma 1 de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]-oxadiazol-5-il)-propil]-amina
- 15 (41.1 kg, pureza química 93.6 %).

- Una mezcla de la forma 1 (41.1 kg) y alcohol isopropílico (123.5 l) se calentó a 45-55°C, produciendo una solución clara. La solución se filtró, después la temperatura se mantuvo a 30-40°C y se añadieron las semillas de
- 20 la forma 2 de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina. La agitación se continuó durante 5-6 hr, después la suspensión se enfrió a 5-15°C y se agitó durante 1-2 hr. Después la suspensión se filtró y se lavó con alcohol isopropílico frío y se

secó bajo vacío a $50 \pm 5^\circ\text{C}$ para dar 30.2 kg de la forma 2 de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina (Pureza por CLAR 98.63%).

5

EJEMPLO 5

Recristalización de la forma 2 del compuesto de la fórmula (I)

Si la pureza de la forma 2 preparada mediante el procedimiento descrito en el ejemplo 4 no cumple con la especificación requerida, se puede
10 llevar a cabo una recristalización sembrada adicional para dar la forma 2.

3 kg de la forma 2 de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina (preparada de conformidad con el ejemplo 4, pureza por CLAR 98.63%) se añadió a alcohol isopropílico (9 l) y se agitó durante 5 a 10 minutos. La
15 temperatura de la mezcla de reacción se elevó después a $52.5 \pm 2.5^\circ\text{C}$ y se obtuvo una solución clara. La temperatura se redujo a $35 \pm 5^\circ\text{C}$ y se añadieron semillas de la forma 2 de metil-[1,2,4]oxadiazol-5-il)-propil]-amina. La mezcla de reacción después se agitó durante 2-3 hr a $30 \pm 5^\circ\text{C}$. Después la mezcla de reacción se enfrió a $0^\circ\text{C} + 5^\circ\text{C}$ y se agitó durante 1-2 hr. La suspensión
20 después se filtró y se lavó con alcohol isopropílico frío y se secó bajo vacío a 50°C para dar 2.4 kg de la forma 2 de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]- oxadiazol-5-il)-propil]-amina (pureza por CLAR 99.73%), la cual muestra la DSC de la figura 8.

EJEMPLO 6

Comparación de datos de XRPD de la forma 1 y la forma 2 del polimorfo
del compuesto de la fórmula (I)

Forma 1		Forma 2	
2θ	Valor de d	2θ	Valor de d
6.721	13.1397		
8.361	10.5663		
		10.415	8.48651
10.698	8.26247		
11.757	7.52055		
		12.125	7.29347
		12.36	7.15526
		13.177	6.7136
13.323	6.64016		
		13.527	6.5406
15.112	5.85779		
		15.121	5.85426
15.492	5.71491		
15.959	5.54892		
		16.045	5.51918
		16.331	5.42339
18.222	4.86461		
18.965	4.67554		
		19.457	4.55852
		20.133	4.40682
20.291	4.37294		
		20.941	4.2386
21.428	4.14338		
		21.28	4.1718
		22.239	3.99412
21.974	4.04163		
22.664	3.92018		
		22.823	3.89318
		23.51	3.78098
24.002	3.70457		
		24.714	3.59933
25.082	3.54736		
		25.488	3.49186
		26.261	3.39074

26.268	3.38993		
26.941	3.30677		
		27.858	3.19988
		29.537	3.02169
30.544	2.92437		
31.289	2.85642		

- 5 Es bien conocido en la técnica de cristalografía que, para cualquier polimorfo dado, las intensidades relativas de los picos de difracción pueden variar debido a la orientación preferida que resulta de factores tales como morfología de cristal. En donde están presentes los efectos de la orientación preferida, las intensidades de pico se alteran, pero las posiciones
- 10 pico características del polimorfo no cambian.

El patrón de difracción en polvo de rayos X de la forma 2 del polimorfo como se muestra en la figura 1 presenta picos predominantes (expresados en grados $2\theta \pm 0.15$ grados 2θ) en las siguientes posiciones: 10.415, 12.125, 19.457, 20.941 y 23.51.

- 15 El patrón de difracción en polvo de rayos X de la forma 1 del polimorfo como se muestra en la figura 4 presenta picos predominantes (expresados en grados $2\theta \pm 0.15$ grados 2θ) en las siguientes posiciones: 6.721, 11.757, 13.323, 18.222, 21.426 y 21.974.

EJEMPLO 7

Comparación de datos de Raman de la forma 1 y forma 2 de polimorfos del compuesto de la fórmula (I)

5 El espectro de Raman de la forma 2 del polimorfo como se muestra en la figura 2 presenta picos predominantes (expresados en cm^{-1}) en las siguientes posiciones: 1606, 1561, 1506, 1323, 1301, 1279, 1271, 1253, 889 y 720.

10 El espectro de Raman de la forma 1 de polimorfo como se muestra en la figura 5 presenta picos predominantes (expresados en cm^{-1}) en las siguientes posiciones: 1619, 1611, 1581, 1574, 1555, 1525, 1502, 1319, 1311, 1264, 882 y 728.

EJEMPLO 8

15 **Datos de DSC de la forma 1 y forma 2 de polimorfos del compuesto de la
fórmula (I)**

20 Cabe reconocer que el pico endotérmico como se midió depende de un número de factores incluyendo la maquinaria empleada, la velocidad de calentamiento, la calibración estándar, humedad y pureza de la muestra usada.

 Como se muestra en la figura 3, la forma 2 del polimorfo presenta un pico endotérmico predominante a aproximadamente 115.1°C y un

inicio a aproximadamente 110.35°C.

Como se muestra en la figura 6, la forma 1 del polimorfo presenta un pico endotérmico predominante a aproximadamente 108.3°C y un inicio a aproximadamente 102.44°C.

5 Como se muestra en la figura 7, una muestra diferente de la forma 1 del polimorfo presenta un pico endotérmico predominante a aproximadamente 106.3°C y un inicio a aproximadamente 100.09°C.

 Como se muestra en la figura 8, una muestra diferente de la forma 2 del polimorfo presenta un pico endotérmico predominante a
10 aproximadamente 115.08°C y un inicio a aproximadamente 110.72°C.

EJEMPLO 9

Ejemplo ilustrativo de una formulación que contiene la forma 2 del polimorfo del compuesto de la fórmula (I)

15

El desarrollo de tabletas que contienen la forma 2 del polimorfo del compuesto de la fórmula (I) se han realizado introduciendo un paso de granulación en húmedo para obtener gránulos con propiedades de flujo incrementadas. Este paso implica la granulación en húmedo de uno o más
20 componentes de la formulación en tabletas por medio de un granulador de alto esfuerzo cortante seguido por fase de secado y calibración.

La tableta después se formuló tomando en cuenta las propiedades tecnológicas de los gránulos (tamaño, capacidad de flujo,

capacidad de desintegración y unión de la mezcla de polvo final) y tratando de asegurar una disolución rápida del fármaco, ya que la tableta de la etapa final también se revistió aplicando un revestimiento de película acuoso.

Los excipientes usados fueron manitol y celulosa microcristalina (Avicel®) como diluyentes, croscarmelosa sódica (AcDisol®) como desintegrante, estearato de magnesio como lubricante, laurilsulfato de sodio como incrementador de humedad (agente tensioactivo), HPMC como aglutinante y Opadry OY-S-28876 como agente de revestimiento.

La composición final tanto de gránulos como de tabletas se reporta a continuación

Tabletas AFC (revestidas con película acuosa), dosis de 200 mg

Componente	Cantidad (mg)/unidad	% p/p
Forma 2, 64.0% gránulo Corresponde a:	312.5	83.33
Forma 2: 200.00		
HPMC: 46.88		
Laurilsulfato de sodio: 3.13		
Croscarmelosa sódica: 9.38		
Manitol en polvo: 53.11		
MCC Avicel PH102	47.50	12.67
Croscarmelosa sódica	11.25	3.00
Estearato de magnesio	3.75	1.00
Peso total del núcleo:	375.00	100.00
Opadry OY-S-28876	11.25	3.00
Peso total:	386.25	103.00

Todas las publicaciones, incluyendo pero sin limitarse a patentes y publicaciones de patente, citadas en esta especificación se incorporan aquí por referencia como si cada publicación individual fuera específicamente e

individualmente indicada para ser incorporada aquí por referencia como si se expusiera en su totalidad.

Se entenderá que la presente invención cubre todas las combinaciones de grupos particulares y preferidos descritos aquí antes.

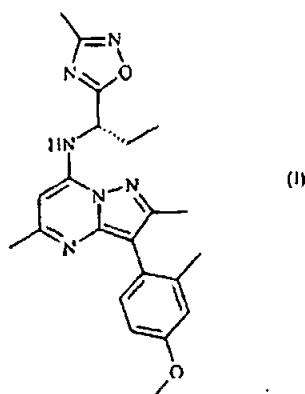
- 5 La solicitud de la cual está descripción y reivindicaciones forman parte se puede usar como una base para prioridad con respecto a cualquier solicitud subsecuente. Las reivindicaciones de dicha solicitud subsecuente pueden estar dirigidas a cualquier característica o combinación de características descritas aquí. Pueden adoptar la forma de reivindicaciones de
- 10 producto, composición, procedimiento o uso, y pueden incluir, a manera de ejemplo y sin limitación, las siguientes reivindicaciones.

NOVEDAD DE LA INVENCIÓN

REIVINDICACIONES

- 5 1.- Un compuesto que es la forma 2 del polimorfo de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-[(S)-1-(3-metil-[1,2,4]oxa-diazol-5-il)-propil]-amina de la fórmula (I).

10



- 15 2.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque tiene un termograma de calorimetría de escudriñamiento diferencial sustancialmente como se muestra en la figura 2, en donde el DSC se realizó a una velocidad de escudriñamiento de 10K por minuto.

- 20 3.- El compuesto de conformidad con la reivindicación 1 o la reivindicación 2, caracterizado además porque tiene un termograma de calorimetría de escudriñamiento diferencial con un inicio a aproximadamente $T = 110.35^{\circ}\text{C}$.

- 4.- El compuesto de conformidad con cualquiera de las

reivindicaciones 1-3, caracterizado además porque tiene un espectro de difracción en polvo de rayos X sustancialmente como se muestra en la figura 1, en donde el patrón de XRPD se expresa en términos de ángulos 2 theta y se obtiene con un difractómetro usando radiación de $K\alpha$ en cobre.

- 5 5.- El compuesto de conformidad con cualquiera de las reivindicaciones 1-4, caracterizado además porque tiene un espectro de difracción en polvo de rayos X que tiene picos que comprenden los valores 2 theta listados a continuación en el cuadro 2, obtenidos con un difractómetro usando radiación de $K\alpha$ en cobre:

	Angulo 2-theta °	Valor de d (Ångstrom)
10	10.415	8.48651
	12.125	7.29347
	12.36	7.15526
	13.177	6.7136
	13.527	6.5406
	15.121	5.85426
	16.045	5.51918
	16.331	5.42339
	19.457	4.55852
15	20.133	4.40682
	20.941	4.2386
	21.28	4.1718
	22.239	3.99412
	22.823	3.89318
	23.51	3.78098
	24.714	3.59933
	25.488	3.49186
	26.261	3.39074
	29.537	3.02169
20	27.858	3.19988

- 6.- El compuesto de conformidad con cualquiera de las reivindicaciones 1-5, caracterizado además porque tiene un espectro de

difracción en polvo de rayos X que comprende los siguientes picos expresados en valores 2-theta: 10.415 +/- 0.15, 12.125 +/- 0.15, 19.457 +/- 0.15, 20.941 +/- 0.15 y 23.51 +/- 0.15; y obtenidos con un difractómetro usando radiación de $K\alpha$ en cobre.

5 7.- Una composición que comprende el compuesto de cualquiera de las reivindicaciones 1-6 y un vehículo farmacéuticamente aceptable.

8.- Un método de tratamiento de un trastorno en un mamífero, en donde dicho trastorno es caracterizado por niveles anormales de CRF, que comprende administrar al mamífero una cantidad terapéuticamente efectiva
10 del compuesto de cualquiera de las reivindicaciones 1-6.

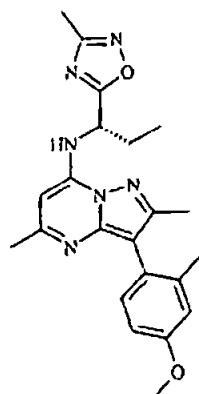
9.- Un método de tratamiento de ansiedad o depresión en un mamífero que comprende administrar al mamífero una cantidad terapéuticamente efectiva del compuesto de cualquiera de las reivindicaciones 1-6.

15 10.- Un método de tratamiento de síndrome de intestino irritable en un mamífero que comprende administrar al mamífero una cantidad terapéuticamente efectiva del compuesto de cualquiera de las reivindicaciones 1-6.

RESUMEN DE LA INVENCION

La presente invención se refiere generalmente a la forma 2 del polimorfo de [3-(4-metoxi-2-metil-fenil)-2,5-dimetil-pirazolo[1,5-a]pirimidin-7-il]-
5 [(S)-1-(3-metil-[1,2,4]oxadiazol-5-il)-propil]-amina; la presente invención también se refiere a composiciones farmacéuticas que comprenden el mismo y métodos de uso del mismo.

10



(I)

15

20 JJ

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94

FIGURE 1:

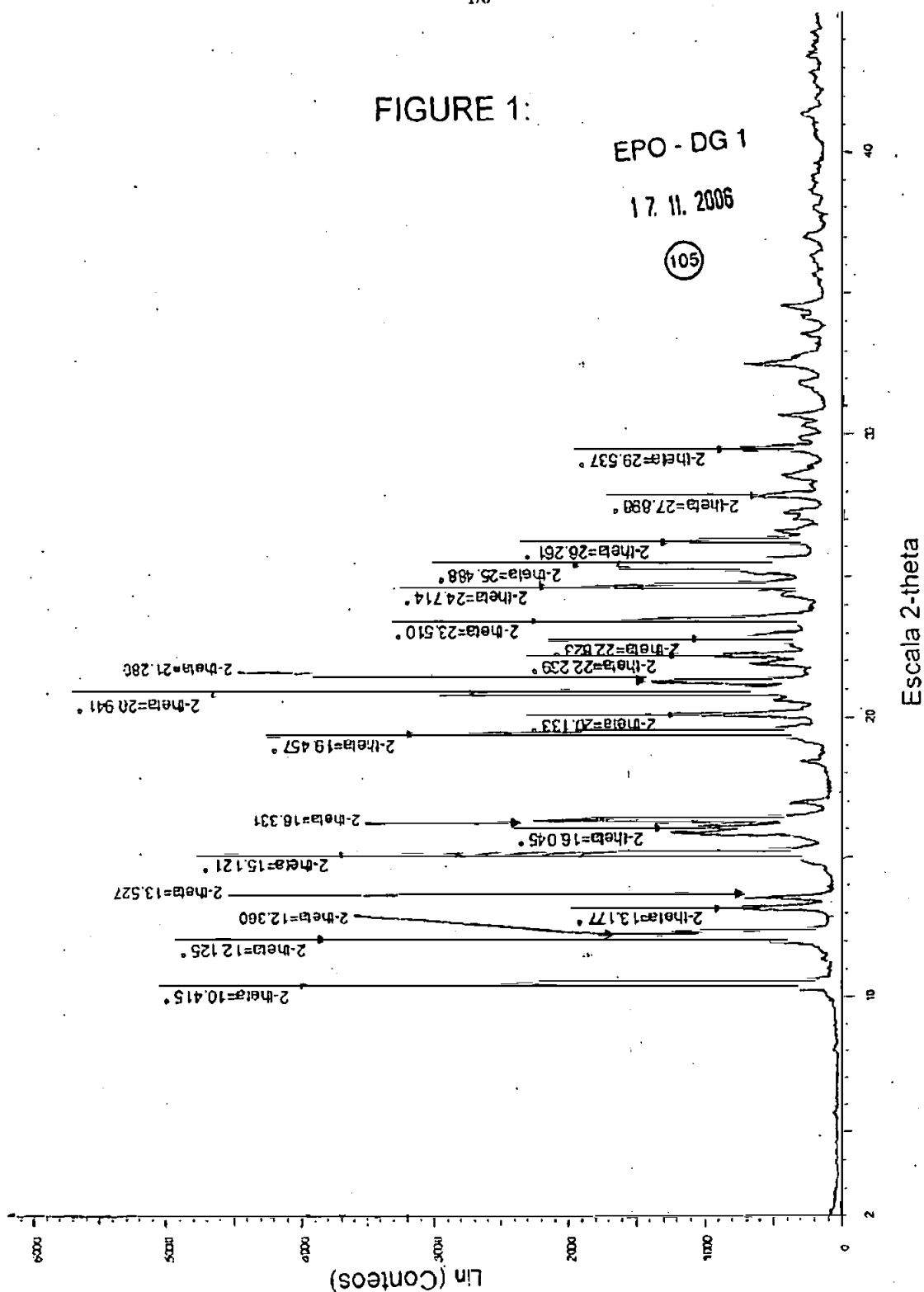


FIGURE 2:

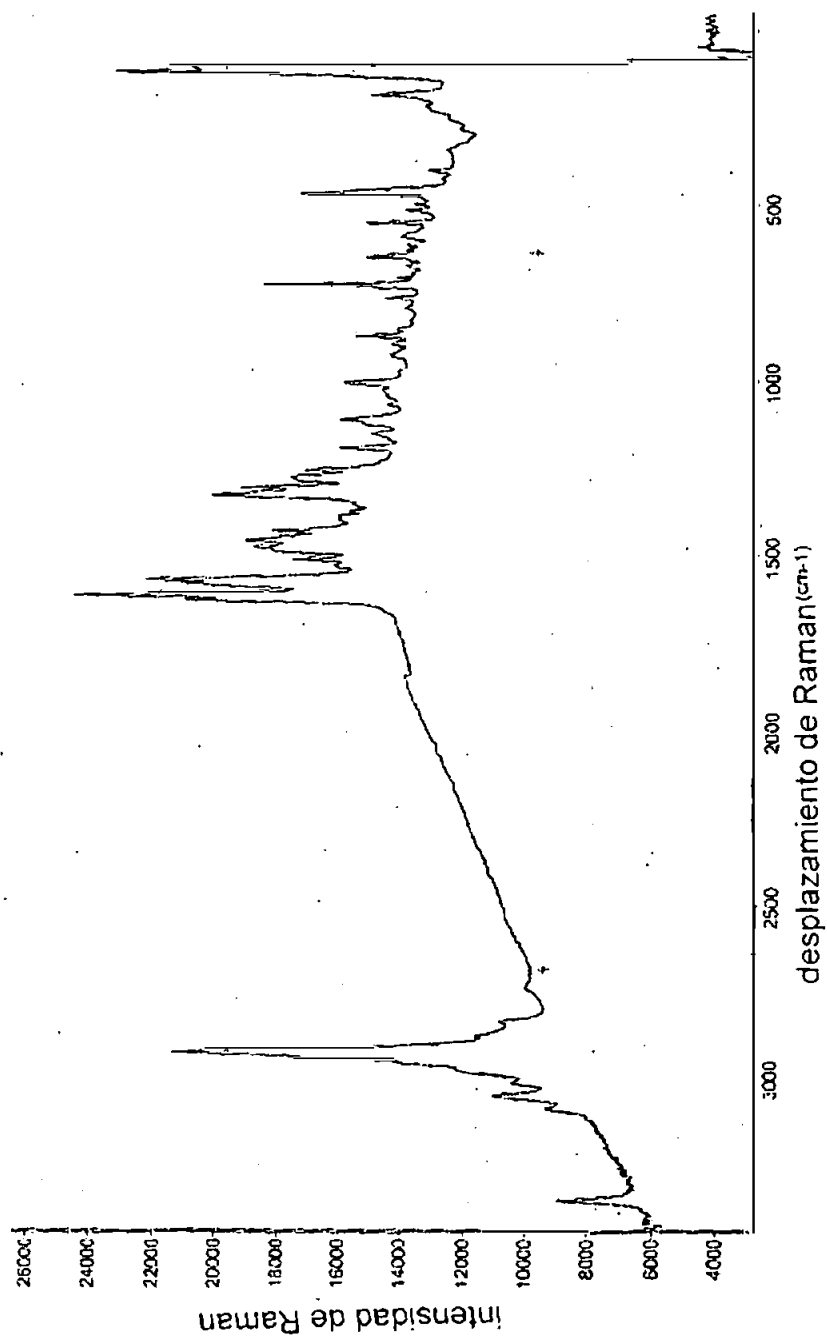
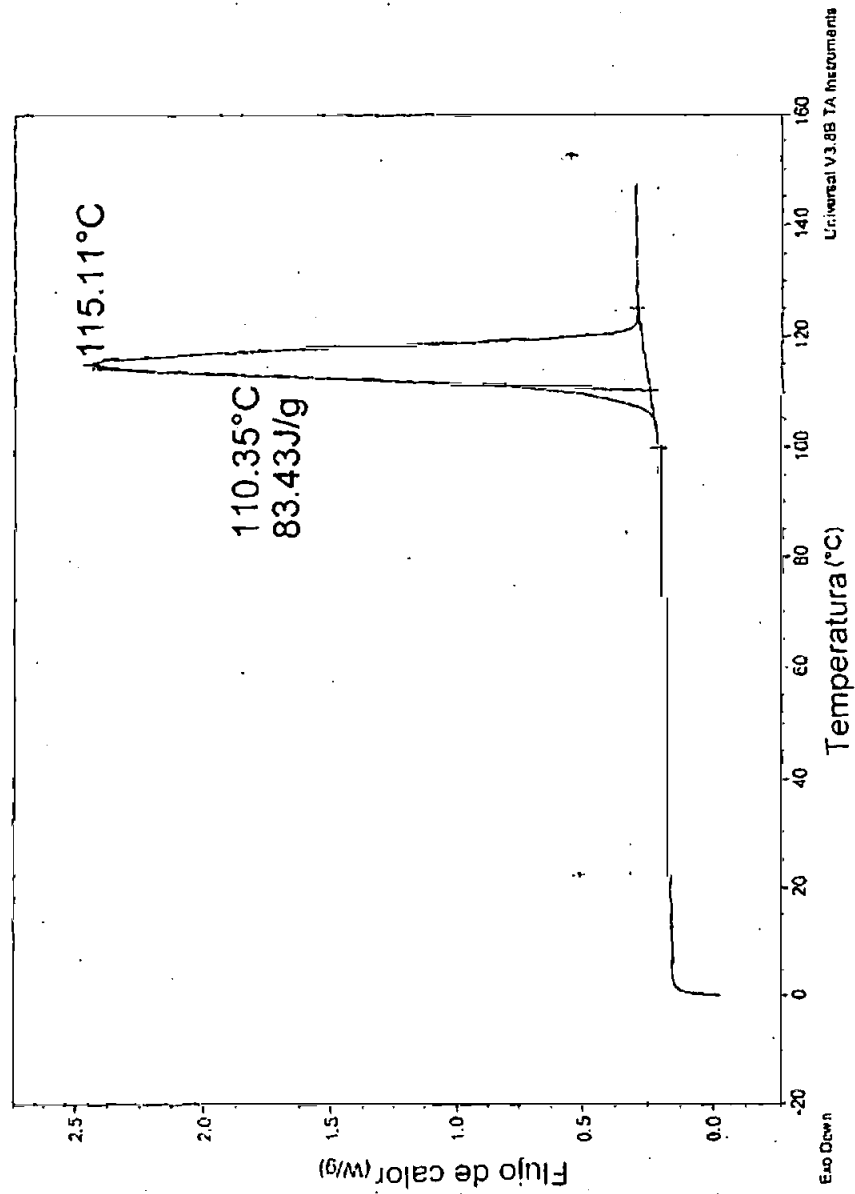


FIGURE 3:



96

FIGURE 4:

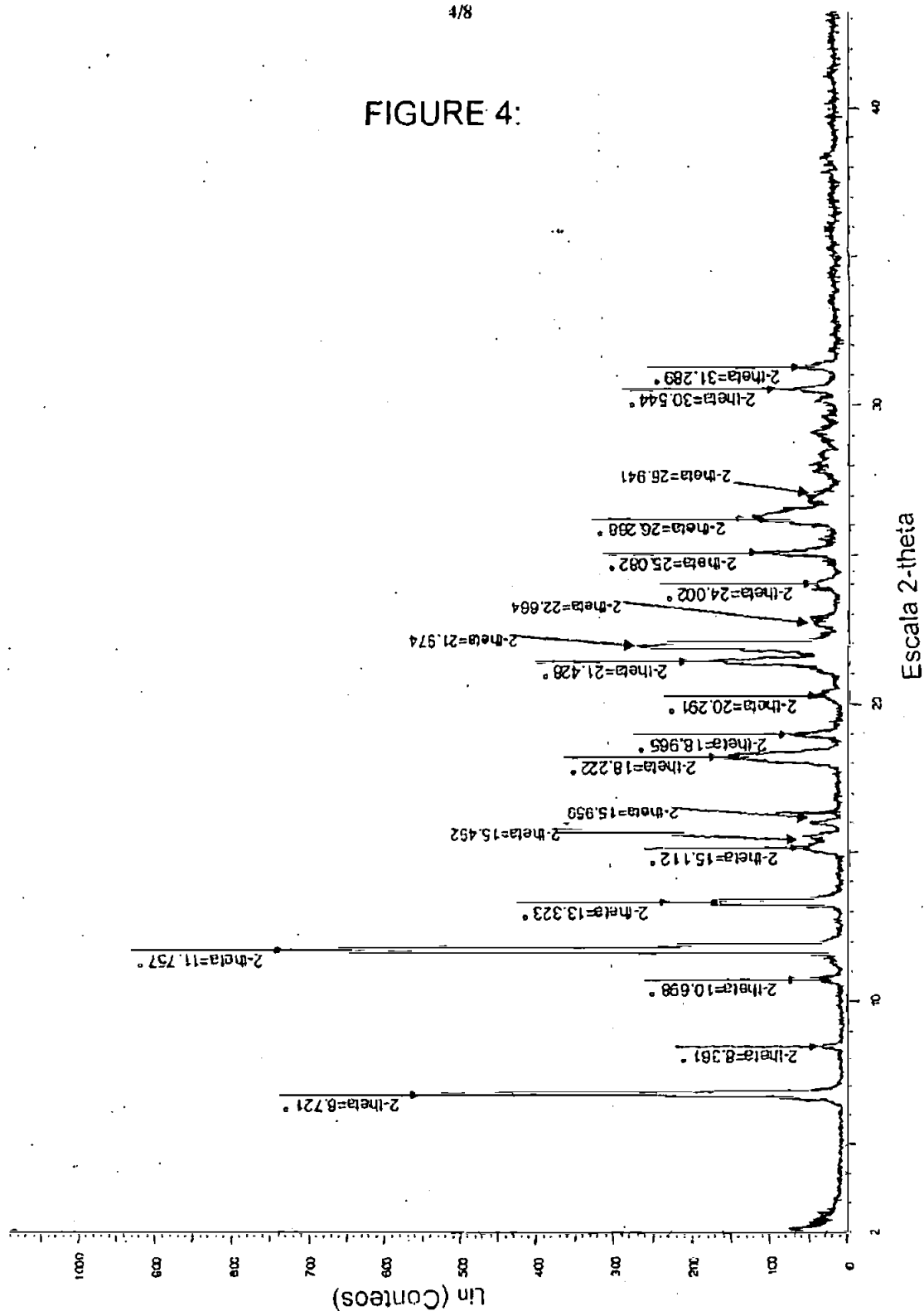
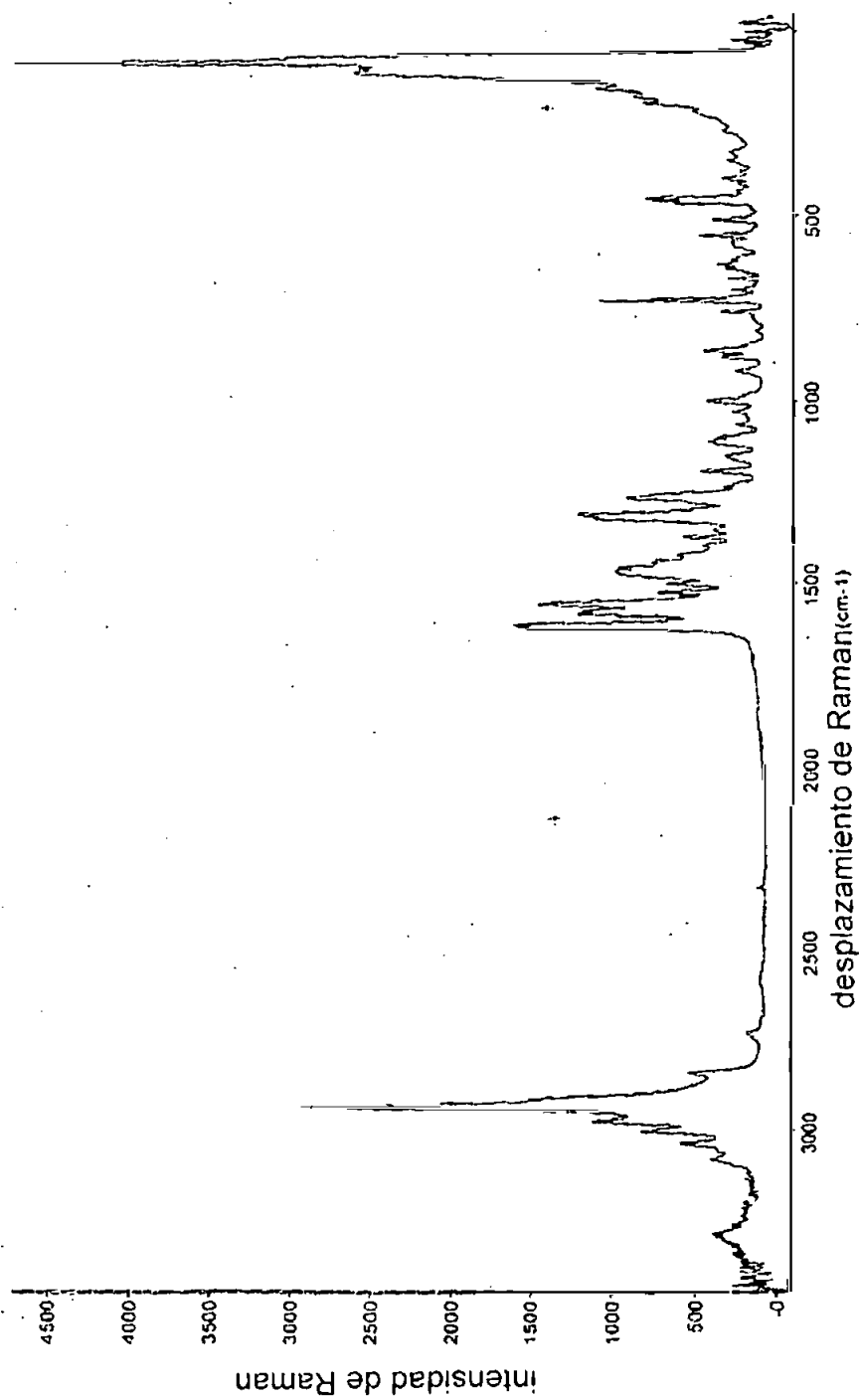
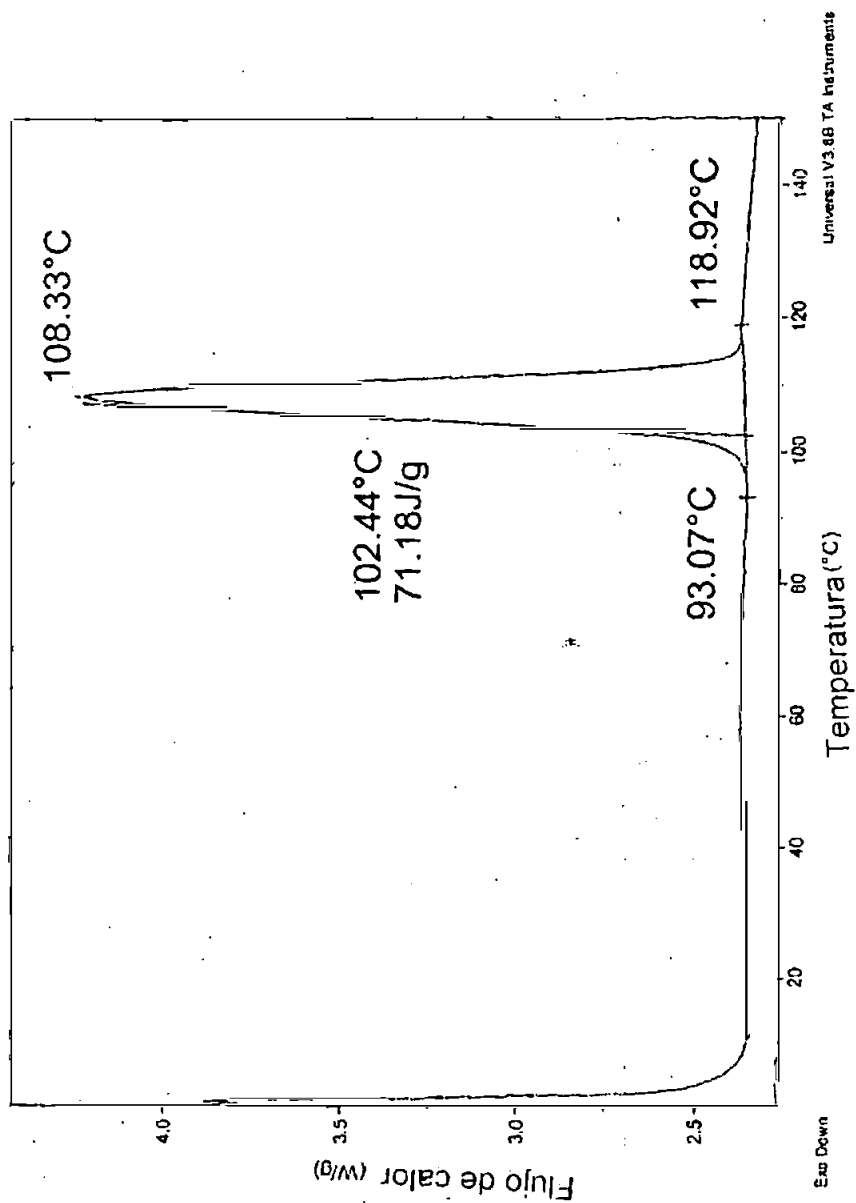


FIGURE 5:



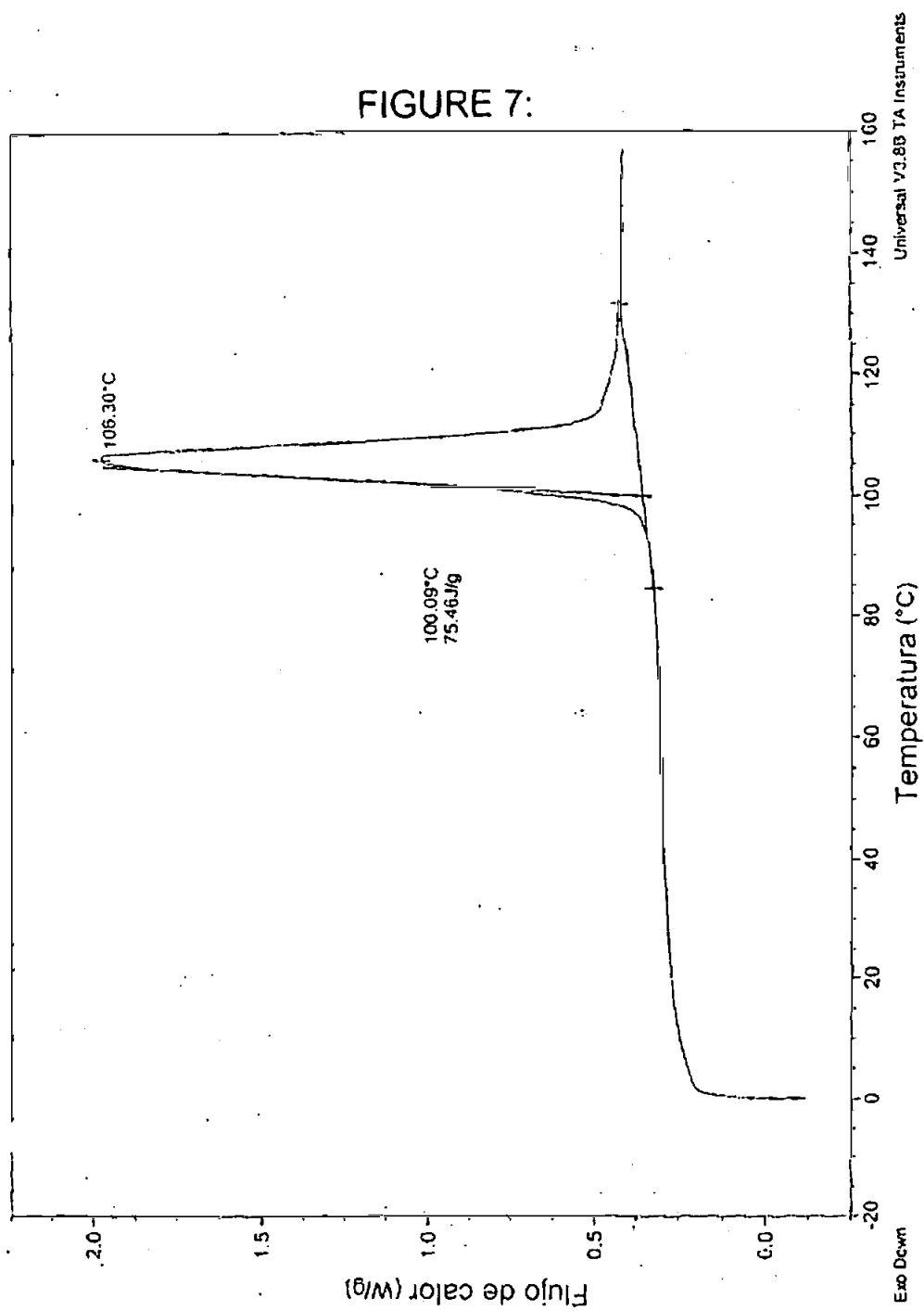
HOJA SUSTITUTA (RÈGLA 26)

FIGURE 6:



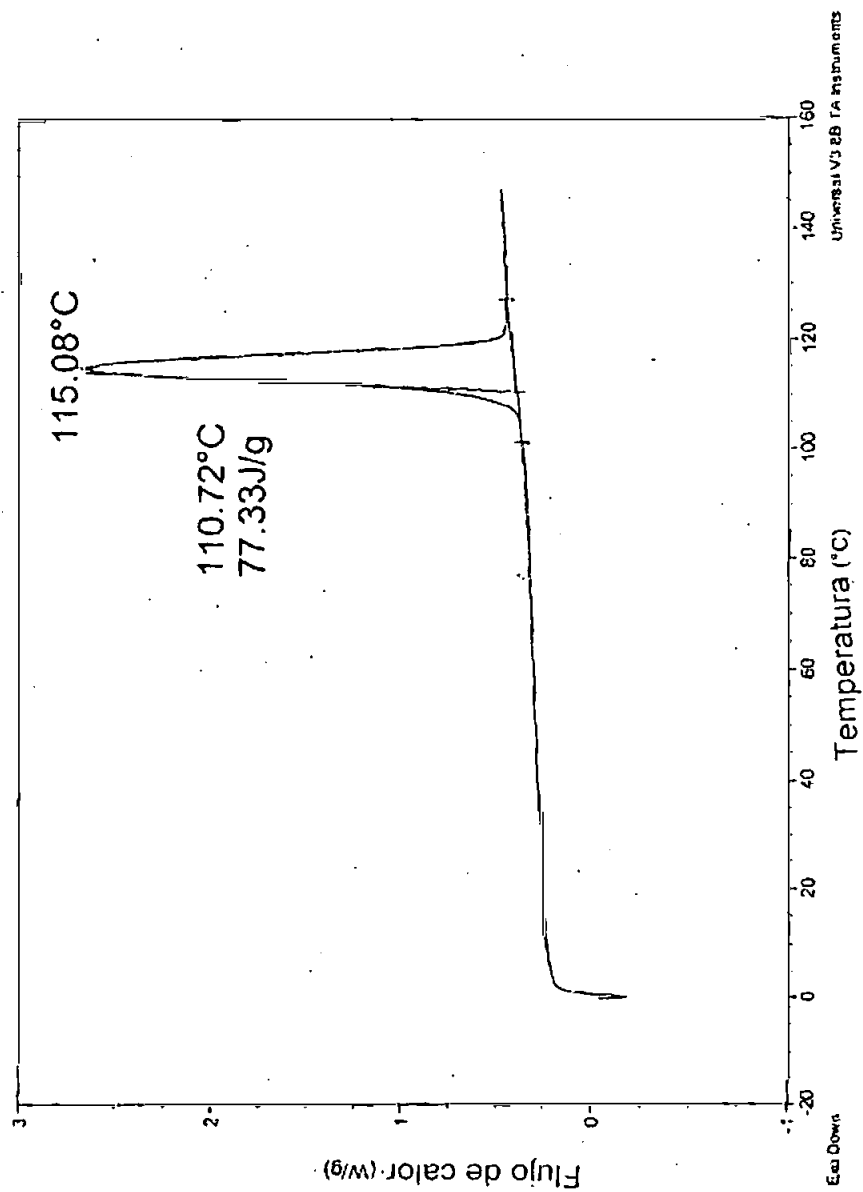
99

FIGURE 7:



101

FIGURE 8:



PATENT COOPERATION TREATY

102

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
GLAXO SMITH KLINE
Attn: Bolton, Peter
CN925.1
980 Great West Road
Brentford, Middlesex TW8
GRANDE BRETAGNE

GLAXO SmithKline
Corporate IP
Received BRENTFORD

23 NOV 2006

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

ATTY: MMV ADMIN:
IPM: N/A ON UPDATED ON: 23/11
ATTY CHECKED: FILE

(PCT Rule 44.1)

Date of mailing
(day/month/year)

23/11/2006

CORPORATE INTELLECTUAL PROPERTY

Applicant's or agent's file reference

MMV/PB61626

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/EP2006/009531

Received 24 NOV 2006

International filing date
(day/month/year)

28/09/2006

Applicant

VERONA File

SB PHARMCO PUERTO RICO INC

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the international Searching Authority have been established and are 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 two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

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 and the written opinion of the International Searching Authority are 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. Reminders

Shortly after the expiration of **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 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, 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); otherwise, the applicant must, within **20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



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

Authorized officer

Jaap Hurenkamp

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 and the written opinion of the International Searching Authority, 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 (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

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 46.1).

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 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 (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.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference MMV/PB61626	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2006/009531	International filing date (day/month/year) 28/09/2006	(Earliest) Priority Date (day/month/year) 30/09/2005
Applicant SB PHARMCO PUERTO RICO INC		

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 4 sheets.

☒ 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
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☐ the text is approved as submitted by the applicant
☒ the text has been established by this Authority to read as follows:

PYRAZOLO [1, 5-ALPHA] PYRIMIDINYL DERIVATIVES USEFUL AS CORTICOTROPIN-RELEASING FACTOR (CRF) RECEPTOR ANTAGONISTS

5. With regard to the **abstract**,

- ☒ 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 No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
- b. ☒ none of the figures is to be published with the abstract

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 A61K31/519 A61P25/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 060 478 A (GILLIGAN ET AL) 9 May 2000 (2000-05-09) claims 1,21-25	1-10
A	US 2003/139426 A1 (WILDE RICHARD G ET AL) 24 July 2003 (2003-07-24) claims; table 1	1-10
X,P	WO 2006/044958 A1 (SB PHARMCO PUERTO RICO INC., P. R.; NEUROCRINE BIOSCIENCES INC.) 27 April 2006 (2006-04-27) cited in the application claims; figures 4-6; examples 14,14A,14B; table 2	1-10

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *I* 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.
- *8* document member of the same patent family

Date of the actual completion of the international search

13 November 2006

Date of mailing of the international search report

23/11/2006

Name and mailing address of the ISA/

European Patent Office, P.O. 5610 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo.nl
Fax: (+31-70) 340-3016

Authorized officer

Bosma, Peter

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/009531

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 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. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 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.

10A

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6060478	A	09-05-2000	US 6136809 A	24-10-2000
			US 6124289 A	26-09-2000
US 2003139426	A1	24-07-2003	NONE	
WO 2006044958	A1	27-04-2006	NONE	

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day:month:year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2006/009531

International filing date (day:month:year)
28.09.2006

Priority date (day:month:year)
30.09.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07D487/04 A61K31/519 A61P25/00

Applicant
SB PHARMCO PUERTO RICO INC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patonilaag 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Bosma, Peter

Telephone No. +31 70 340-3665



WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2006/009531

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

Re Item III.

Claims 8-10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

For the assessment of the present claims 8-10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V.

1 Reference is made to the following document:

D1 : US 6 060 478 A (GILLIGAN ET AL) 9 May 2000

D2: WO 2006/044958 A1 (SB PHARMCO PUERTO RICO INC., P. R.; NEUROCRINE BIOSCIENCES INC.) 27 April 2006 cited in the application

2 The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-10 is new in the sense of Article 33(2) PCT:
Document D1 covers (see claims 1,21-25) pyrazolo[1,5-a]pyrimidine derivatives of the formula depicted in the present claim 1, in which the moiety "Het" represents an heteroaryl or heterocyclyl group in general.

The present oxadiazolyl group for "Het" has not been specifically disclosed in D1. The [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-[(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl]-amine (I) compound in general (irrespective of the polymorphic form) as regarded as a novel selection from the compounds disclosed by D1.

Please note that the subject matter of the present claims 1-10 is also covered by the subject matter described in D2 (see Section VI).

3 The present claims 1-10 meet the requirements of the PCT in respect of inventive step (Article 33(3) PCT), because the present **polymorph Form 2** of (I) has not been described nor suggested by D1 or any of the available prior art documents, **which were published in time.**

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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. 8-10 (with respect to industrial applicability)

because:

- ☒ the said international application, or the said claims Nos. 8-10 relate to the following subject matter which does not require an international search (*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 (*specify*):
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2006/009531

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-10
	No: Claims	
Inventive step (IS)	Yes: Claims	1-10
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-7
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

(19) World Intellectual Property Organization
International Bureau



PCT

(43) International Publication Date
12 April 2007 (12.04.2007)

(10) International Publication Number
WO 2007/039264 A1

(51) International Patent Classification:
C07D 487/04 (2006.01) A61P 25/00 (2006.01)
A61K 31/519 (2006.01)

(74) Agent: DOLTON, Peter; GlaxoSmithKline, Corporate Intellectual Property, CN925.1, 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

(21) International Application Number:
PCT/EP2006/009531

(22) International Filing Date:
28 September 2006 (28.09.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0519957.5 30 September 2005 (30.09.2005) GB
PCT/US2005/037576
19 October 2005 (19.10.2005) US

(71) Applicants (for all designated States except US): SII PHARMCO PUERTO RICO INC [US/US]; The Prentice Hall Corp System, c/o FGR Corporate Services Inc, BBV Tower 8th Floor, 254 Munoz Rivera Avenue, San Juan, 00918 (PR); NEUROCRINE BIOSCIENCES INC [US/US]; 10555 Science Center Drive, San Diego, California 92121 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): HOSSNER, Frank [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB).

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

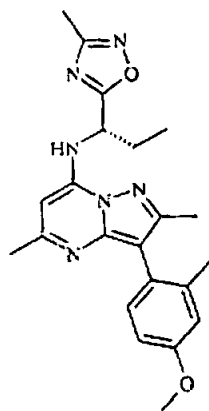
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT,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

Published:

— with international search report

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

(54) Title: PYRAZOLO [1, 5 -ALPHA] PYRIMIDINYL DERIVATIVES USEFUL AS CORTICOTROPIN-RELEASING FACTOR (CRF) RECEPTOR ANTAGONISTS



(I)

(57) Abstract: The present invention generally relates to the polymorph Form 2 of [3-(4-methoxy-2-methyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-{(S)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-propyl}-amine. The present invention also relates to pharmaceutical compositions comprising the same and methods of using the same.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/009531

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 A61K31/519 A61P25/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 060 478 A (GILLIGAN ET AL) 9 May 2000 (2000-05-09) claims 1,21-25	1-10
A	US 2003/139426 A1 (WILDE RICHARD G ET AL) 24 July 2003 (2003-07-24) claims; table 1	1-10
X,P	WO 2006/044958 A1 (SB PHARMCO PUERTO RICO INC., P. R.; NEUROCRINE BIOSCIENCES INC.) 27 April 2006 (2006-04-27) cited in the application claims; figures 4-6; examples 14,14A,14B; table 2	1-10

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

A document member of the same patent family

Date of the actual completion of the international search

13 November 2006

Date of mailing of the international search report

23/11/2006

Name and mailing address of the ISA/

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NL - 2280 HV Rijswijk
Tel.: (+31-70) 340-2040, Tx. 31 851 600 nl,
Fax: (+31-70) 340-3216

Authorized officer

Bosma, Peter

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/009531

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

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

Although claims 8-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 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/EP2006/009531

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6060478	A	09-05-2000	US 6136809 A	24-10-2000
			US 6124289 A	26-09-2000
US 2003139426	A1	24-07-2003	NONE	
WO 2006044958	A1	27-04-2006	NONE	

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/009531

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519 A61P25/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

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- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *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
- *B* document member of the same patent family

Date of the actual completion of the international search

13 November 2006

Date of mailing of the international search report

23/11/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 6818 Patentlaan 2
NL - 2230 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 epo nl
Fax: (+31-70) 340-3016

Authorized officer

Bosma, Peter

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/009531

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

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1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 8-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

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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.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/009531

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6060478	A	09-05-2000	US 6136809 A	24-10-2000
			US 6124289 A	26-09-2000
US 2003139426	A1	24-07-2003	NONE	
WO 2006044958	A1	27-04-2006	NONE	



No. 08-031044- -00000-0000

Fecha: 2008-03-28 17:27:08 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eva: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 119

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION

☒

MODELO DE UTILIDAD

☐

- ◆ Indicación de que se solicita la concesión de una patente
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ◆ Descripción de la invención
- ◆ Dibujos de ser estos pertinentes
- ◆ Comprobante de pago de las tasas establecidas

☒
☒
☒
☒
☒

COMPLETA ☒

INCOMPLETA ☐

DISEÑO INDUSTRIAL

☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño
- ◆ Comprobante de pago de las tasas establecidas

☐
☐
☐
☐

COMPLETA ☐

INCOMPLETA ☐

ESQUEMA DE TRAZADO

☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ◆ Representación gráfica del esquema trazado
- ◆ Comprobante de pago de las tasas establecidas

☐
☐
☐
☐

COMPLETA ☐

INCOMPLETA ☐

Fdo B

Firma Responsable

Fecha 28-Mar-8

Carrera 13 No. 27-00 Piso 5, 7 y 10
Teléfono: 3 82 08 40
Fax: 360 62 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

121

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
SB PHARMCO PUERTO RICO INC.
NEUROCRINE BIOSCIENCES INC.

REFERENCIA	Radicación No.	8 31044
	Solicitud internacional	PCT/EP2006/009531
	Fecha inicio fase nacional	30/04/2008
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	5948

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 19 Mayo 2008
adpall