



82



Industria y Comercio
SUPERINTENDENCIA

10-1885

DE LA TITULATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

**SOLICITUD DE PATENTE DE
INVENCION**

TITULO: FORMULACIONES ESTABLES DE DERIVADO DE TIADIAZOL

SOLICITANTE: ELI LILLY AND COMPANY Y KYOWA HAKKO KIRIN CO.,LTD

DIRECCIÓN: Lilly Corporate Center, Indianapolis, Indiana 46285 E.U.A. y 1-6-1 Ohtemachi, Chiyoda-ku Tokyo 100-8185

APODERADO: CARLOS R. OLARTE

BOGOTÁ 08 de Enero de 2010

OLARTE RAISBECK

OLARTE RAISBECK MOURE

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-001885- -00000-0000

Fecha: 2010-01-08 16:51:07 Dep: 2020 DIR.NUEVASOR
Tra. 11 PATENTEIYII Eva: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 65

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

P2009/000199

SOLICITUD DE:

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☐

Capítulo I.

☒

Capítulo II.



**SOLICITANTE
(71)**

Nombre: ELI LILLY AND COMPANY Y
KYOWA HAKKO KIRIN CO.,LTD

Dirección: Lilly Corporate Center,
Indianápolis, Indiana 46285 y 1-6-1
Ohtemachi, Chiyoda-ku Tokyo 100-8185

Nacionalidad o Domicilio: Estadounidense y
Japonesa

Lugar de Constitución: Estados Unidos de
América y Japón

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 79.782.747Bta
TP 74.295

**INVENTOR (ES)
(72)**

Nombre: VER PAGINA ADJUNTA

Dirección: VER PAGINA ADJUNTA

Nacionalidad o Domicilio: VER PAGINA ADJUNTA



PCT (86)

Solicitud Internacional No. PCT/US2008/069301 Fecha Julio 7, 2008

Publicación Internacional No. WO 2009/009470 Fecha Enero 15, 2008



Título (54) FORMULACIONES ESTABLES DE DERIVADO DE TIADIAZOL

Clasificación Internacional (51) A61K 9/19, A61K 31/433

Prioridad

SI ☒ NO ☐

(33) País de Origen

US

(32) Fecha

Julio 12, 2007

(31) Número de Solicitud

60/949,268



Comprobante de pago No. 10-

Fecha Enero 7 de 2010

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 copia simple ver expediente No. 07-128.249.

☐

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.

☒

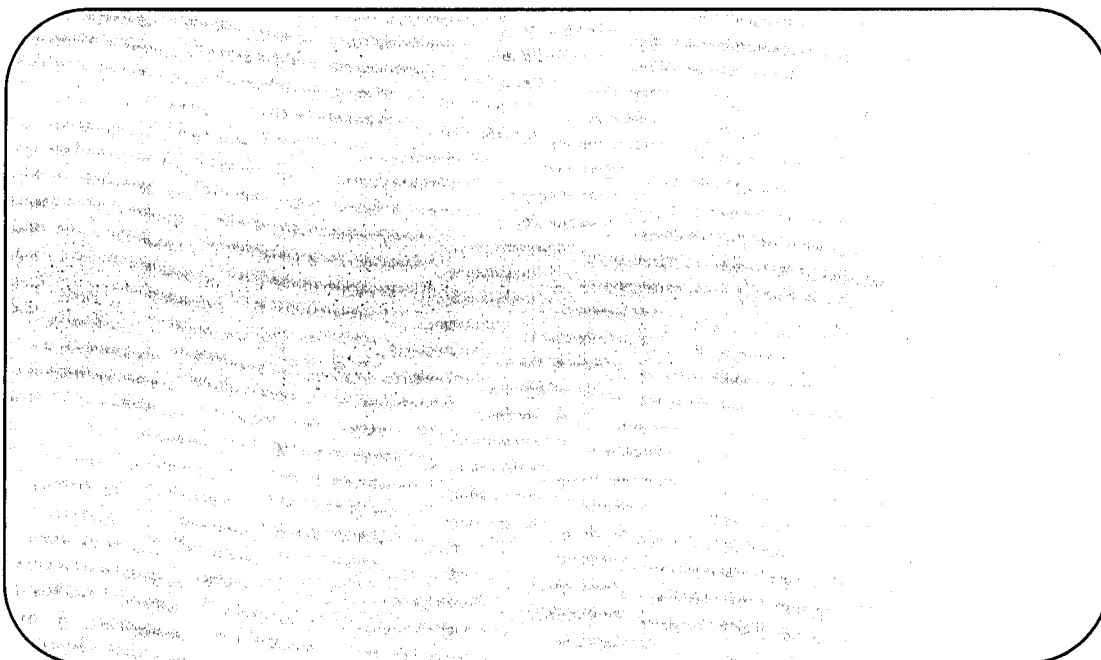
De ser el caso, modificaciones efectuadas a la solicitud internacional.

☒

Otros. Búsqueda Internacional.

11

FIGURA CARACTERÍSTICA:



12

Solicito la concesión de la patente,

NOMBRE: CARLOS E. OLARTE

FIRMA:

C.C. 19.752.747 B13 T.P. 14.295

LISTA DE INVENTORES

PCT/US2008/069301

1. Hiroko **KUSANO**,
Kyowa Hakko Kirin Co., Ltd,
1-6-1, Ohtemachi, Chicoda-ku,
Tokyo 100-8185
Japón
Nacionalidad: Japonés
2. Dinesh Shiamdeo **MISHRA**,
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Carmel, Indiana 46032
Estados Unidos
Nacionalidad: Estadounidense
3. Yoshikazu **TASHIRO**,
Kyowa Hakko Kirin Co., Ltd,
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Tokyo 100-8185
Japón
Nacionalidad: Japonés
4. Yosuke **WATANABE**,
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Tokyo 100-8185
Japón
Nacionalidad: Japonés
5. Hong **ZHUANG**,
3887 Branch Creek Court, Zionsville,
Indiana, Indianápolis,
Indiana 46077
China
Nacionalidad: Estadounidense

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 1,932
FECHA : ENERO 7 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



Nº. 10-001885- -00000-0000

Fecha: 2010-01-08 16:51:07 Dep. 2020 DIR.NUEVASCR
Fra. 11 PATENTEIYII Eve 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 65

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
CLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	131167820	07/01/2010	5.130.000.00

***** CONCEPTO *****

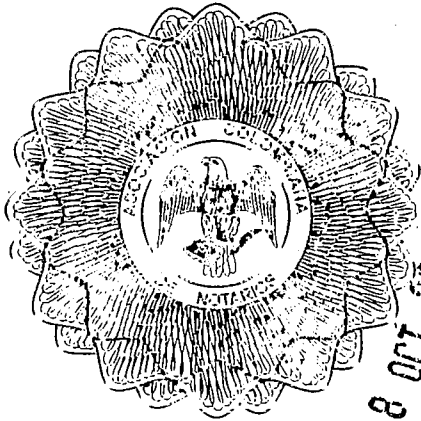
CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	554.000.00
TOTAL :			\$ 554.000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE Nº. _____

WK 9397304



28 OCT. 2008

ESCRITURA PUBLICA NUMERO : (1 2 2 7)

MIL DOSCIENTOS VEINTISIETE -----

En la ciudad de Bogotá, Distrito
Capital, República de Colombia, a los
Veintiocho -- (28) días del mes de
Octubre -- -- del año dos mil ocho
(2008), ante mi MARIA EUGENIA

ROJAS DE URUETA NOTARIA(O) VEINTISIETE (27) DEL
CIRCULO DE BOGOTA, se otorgó la escritura pública que se
consigna en los siguientes términos:-----

CLASE DE ACTO: PROTOCOLIZACION DE PODER.-----

JAMES IAN RAISBECK LLÍNAS Y CARLOS REINALDO
OLARTE GARCIA.-----

C.C. No. 79.376.996 Y 79.782.747.-----

Comparecieron JAMES IAN RAISBECK LLÍNAS, mayor de edad,
vecino de ésta ciudad, identificado con la cédula de ciudadanía
número 79.376.996 de estado civil casado con sociedad conyugal
vigente y CARLOS REINALDO OLARTE GARCIA, mayor de
edad, vecino de Bogotá, identificado con la cédula de
ciudadanía número 79.782.747, de estado civil casado con
sociedad conyugal vigente, obrando en sus propios nombres y
dijeron: -----

PRIMERO.- Que presentan para su protocolización y custodia en
los archivos de ésta notaría, bajo el número y lugar que a ésta
escritura corresponda, en cinco (5) folios autenticados, un poder y
sus traducciones los cuales son del siguiente tenor:-----

PODER-----

El suscrito ELI LILLY AND COMPANY, domiciliado en Lilly
Corporate Center, Indianápolis, Indiana 46285 US por medio del

NOTARIA VEINTISIETE

Maria Eugenia Rojas de Urqueta

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

Firma (ilegible) -----

Fecha 17 July 2003-----

City, Country/ Ciudad, País: Indianápolis, Indiana, United Status of America.- -----

Traduccion oficial del Inglés por Marlén Neira Castro resolución 2117 del Ministerio de Justicia de Colombia.- -----

APOSTILLA EN PODER DE DE REPRESENTACION DE ELI LILLY
AND COMPANY.

Bilingüe inglés- español otorgado en Indianapoles, Indiana, Estados Unidos el 17 de julio de 2003 y firmado por Meter G. Stringer, Director Ejecutivo y patentes Internacionales de Ely Lilly & Company.- -----

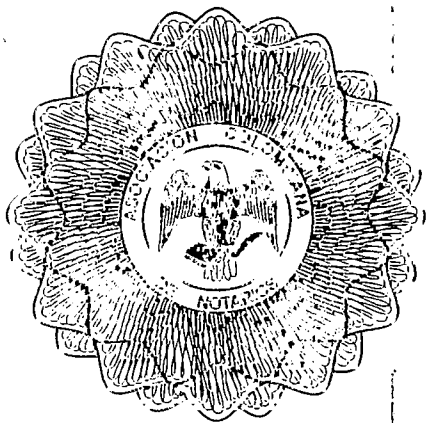
Todd Rokita Secretario de Estado-----

Secretario de Estado de Indiana Estado de Indiana-----

APOSTILLA

(Convencion de la Haya del 5 octubre 1961)

6
WK 9397305



- 1. Pais: Estados Unidos de América-
este documento público -----
- 2. Ha sido firmado por: Catherine Michel
- 3. Quien ejerce funciones de Secretario
de la Corte del Circuito en y para el
condado Jonson -----
- 4 Lleva el sello del Secretario de la Corte

del Circuito en y para el estado de Indiana -----

Certificado

- 5. En: Indianapoles, Indiana -----
- 6. El: 22 de julio de 2003.-----
- 7. Por el Secretario de Estado de Indiana 3 No. A2003-1279-----
- 9. Gran Sello del Estado de Indiana -----
- 10. Firma ilegible de Todd Rokita- Secretario de Estado de Indiana
- * Vigente desde el 1 de mayo de 2003, todas las apostillas del
Secretario y de Estado de Indiana tienen el sello impreso
electrónicamente.-----
- The Statehouse, Indianapoles, Indiana 46204, (307) 232-6531, fax
(317) 233-3283-----

NOTARIA VENTURA
NOTARIA VENTURA
Maria Eugenia Rojas de Urueña

CEPTIFICACION NOTARIAL

Bilingüe inglés- español, el 17 de julio de 2003 el suscrito notario
Catherine Michel certifica que Meter G. Stringer, domiciliado en
7620 Castleton Faros, West Drive Indianápolis, Indiana- 46256
Estados Unidos ejercía funciones de Director Ejecutivo y Patentes
Internacionales de Ely Lilly & Company, con sede en Indianápolis,
Indiana, Estados Unidos.-----
MAPLEN NEIPA CASTPO Traductor e Intérprete Oficial inglés-
Español- Inglés-----
Resolución No. 2117 del 7 Oct 1987.- -----
El otorgante fundamenta sus certificaciones en este documento:
Delegación de Autoridad concerniente a Ciertas Materias de
Patentes, suscrito el 20 de enero de 2003: conforme al poder

otorgado al Asesor General de la Compañía por el Comité Ejecutivo de la Junta Directiva de Eli Lilly and Company.-----

Firma del notario público Catherine Michel certifica sus funciones vencen el 21 de octubre de 2008- residente en el condado Johnson

Sello de notario público de Indiana.-----

Es traducción fiel de inglés, con copia archivo para confrontación, Bogotá 28 de julio-2003.-----

MARLEN NEIRA CASTRO Traductor e Intérprete Oficial Inglés-Español- Inglés -----

Resolución No. 2117 del 7 Oct 1987.- -----

SEGUNDO.- Que solicita a la señora Notaria la incorporación de dichos documentos al protocolo de ésta notaría para que de su tenor se expidan las copias que más adelante se soliciten -----

Se advierte que la protocolización de documentos no da mayor fuerza o autenticidad de la que tienen dichos documentos.-----

Esta escritura pública fue firmada fuera del Despacho Notarial, de conformidad con el artículo 12 del Decreto 2.148 de 1.983. -----

Se advirtió a los otorgantes de esta escritura de la obligación que tienen de leer la totalidad de su texto, a fin de verificar la exactitud de todos los datos en ella consignados, con el fin de aclarar, modificar o corregir lo pertinente antes de firmarla, la firma de la misma demuestra su aprobación total del texto, en consecuencia, la notaria no asume ninguna responsabilidad por errores o inexactitudes establecidas con posterioridad a la firma de (el, los) otorgante(s) y de la notaría, en tal caso, este (os) debe(n) ser corregidos mediante el otorgamiento de una nueva escritura, suscrita por todos los que intervinieron en la inicial y sufragada por los mismos (artículo 35, decreto ley 960 de 1970).-----

2

1

Todd Rokita	Secretario de Estado
Secretario de Estado de Indiana	Estado de Indiana

(Convención de la Haya del 5 de octubre de

- 1
C
to en y para el estado
ulio de 2003
3- 11270
de In
Secretario
A 051
E

5. En Indianapolis, Indiana 6. El 22 de julio de 2003

7. Por el Secretario de Estado de Indiana 8. No. A2003- 11270

9. Gran Sello del Estado de Indiana

10. Firma legible de Todd Rokita- Secretario de Estado de Indiana

1270
15-11-51
10-51
10-51

ESTADO DE SANTA CATARINA

Bilingüe inglés- español, el 17 de julio de 2003 el suscrito notario Catherine Michel certifica que Peter G. Stringer, domiciliado en 7620 Castleton Farms, West Drive, Indianapolis, Indiana - 46256 Estados Unidos ejercía funciones de Director Ejecutivo y Patentes Internacionales de Ely Lilly & Company, con sede en Indianapolis, Indiana, Estados Unidos.

Marlen Neira Castro
MARLEN NEIRA CASTRO
Productor e Intérprete Oficial
inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

El otorgante fundamenta sus certificaciones en este documento: Delegación de Autoridad concerniente a Ciertas Materias de Patentes, suscrito el 20 de enero de 2003: conforme al poder otorgado al Asesor General de la Compañía por el Comité ejecutivo de la Junta Directiva de Eli Lilly and Company.

Firma del notario público Catherine Michel certifica

Sus funciones vencen el 21 de octubre de 2008 - residente en el condado Johnson

Sello de notario público de Indiana

--

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 28 de julio-2003.

Marlen Neira C



MARLEN NEIRA CASTRO

Traductor e Intérprete Oficial

Inglés - Español - Inglés

Resolución No. 2117 del 7 Oct 1987

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

The undersigned,

domiciled in

Lilly Corporate Center, Indianapolis, Indiana 46285 US

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

Signature/Firma

Date/Fecha: / 7 July 2003

City/Country/Ciudad,País: Indianapolis, Indiana, United States of America

Poder

El suscrito,

ELI LILLY AND COMPANY
domiciliado en

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María**

Frieri poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad y Diseños Industriales** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, repuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, decidir 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.

NOTARIA VERIFICADA
Not. - Agencia Bojca de Cúcuta



Todd Rokita
Secretary of State

SECRETARY OF STATE
STATE OF INDIANA

APOSTILLE

(Convention de la Haye du 5 Octobre 1961)

1. Country: United States of America
2. This public document has been signed by *Catherine Michel*
3. acting in the capacity of circuit court clerk in & for *Johnson County*
4. and bears the seal/stamp of circuit court clerk in & for the State of Indiana

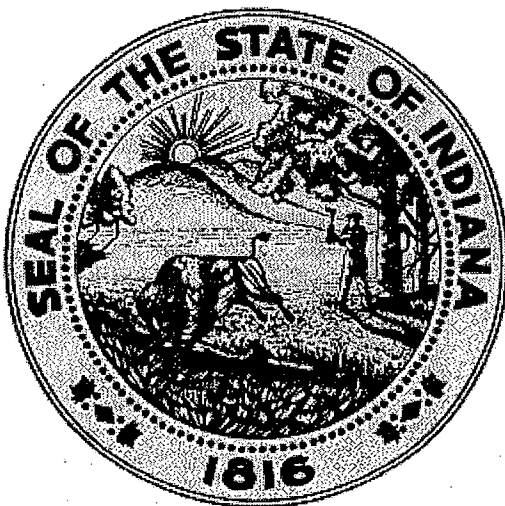
Certified

5. at Indianapolis, Indiana
6. this *Twenty-second day of July, 2003*
7. by Secretary of State of Indiana
8. No. *A2003- 11279*
9. Seal/Stamp:

10. Signature:

Todd Rokita

Indiana Secretary of State



*Effective May 1, 2003 all apostilles from the Indiana Secretary of State will have an electronically printed seal.

The Statehouse, Indianapolis, Indiana 46204, (317) 232-6531, Fax (317) 233-3283

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER - TORRE C
CALLE 100 No. 3A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
Fax: +57-1 638-6201

www.olarteraisbeck.com

Notarial Certification

On this date,

/ 7 July 2003

The undersigned Notary Public certifies:

1. That

of legal age and domiciled in

7620 Castleton Farms, West Drive,
signed the foregoing document.

2. That the grantor has executed the foregoing
document as Executive Director, International
Patents
of ELI LILLY AND COMPANY

3. That ELI LILLY AND COMPANY
having its principal place of business located in
Indianapolis, Indiana, United States of
America

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):

Delegation of Authority Concerning Certain
Patent Matters, executed January 20, 2003;
pursuant to the authority granted to the
General Counsel of the Company by the
executive Committee of the Board of
Directors of Eli Lilly and Company

NOTARY PUBLIC (Signature):



Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

Peter G. Stringer

mayor de edad y domiciliado
Indianapolis, Indiana 46256 US
suscribió el documento que antecede.

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

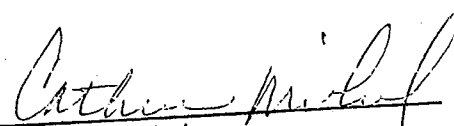
de

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 encuentran dentro de los que
comprenden su objeto social.

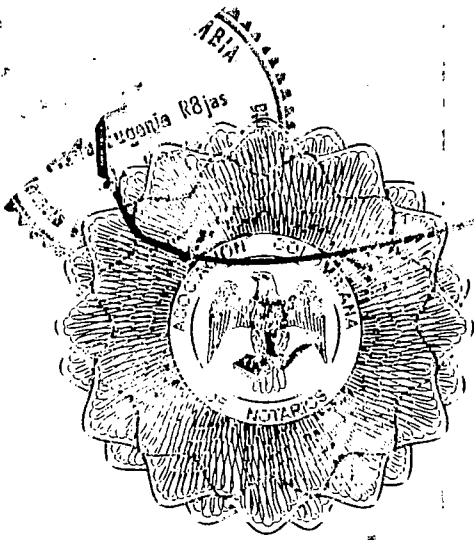
4. Que el otorgante tiene la representación para
suscribir el poder, y que ésta es legítima.

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


Catherine Michel
My Commission Expires October 21, 2008
Resident of Johnson County

NOTARIO PUBLICO
MARIO EUGENIO ROJAS DE ALMEIDA

WK 9397306



ADVERTENCIA, OTORGAMIENTO Y
AUTORIZACION.- Leído el presente
instrumento por el (los) compareciente
(s) y advertido (s) sobre las
formalidades legales, lo aprueban y
firman conmigo y ante mí la(el)
Notaria(o) quién lo autoriza. ---Se/

utilizaron las hojas de papel Notarial Nos. WK 9397304, WK 9397305 Y
WK 9397306 . /-----

DERECHOS LEGALES: \$ 39.630,00 /-----

RESOLUCION 8850 DE 2007 -----

IVA \$ 10.781,00 /-----

James Ian Raisbeck Llínas

JAMES IAN RAISBECK LLÍNAS

C.C.No. 79.376.996 BOGOTÁ

TEL: 601-7700



Carlos Reinaldo Olarte García

CARLOS REINALDO OLARTE GARCIA

C.C.No. 79.782.747 BOGOTÁ.

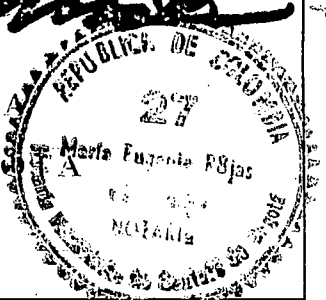
TEL: 601-7700



Maria Eugenia Rojas de Urqueta

MARIA EUGENIA ROJAS DE URUETA
NOTARIA(O) VENTISIETE (27) DE BOGOTÁ

redb.



Es fiel y Segunda (2ª)
fotocopia de la Escritura Pública No. 1-227
de fecha 28 de Octubre de 2008
tomada de su original que expido en
Seis (6) hojas útiles de papel
común autorizado (Decreto 1343 de 1970) con destino a
Interesado

Dado en Santafé de Bogotá D.C., a 28 OCT 2008

El Notario Veintisiete de Santafé de Bogotá



ESPACIO EN BLANCO

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
15 January 2009 (15.01.2009)

PCT

(10) International Publication Number
WO 2009/009470 A1

(51) International Patent Classification:
A61K 9/19 (2006.01) A61K 31/433 (2006.01)

(74) Agents: HOSTETTLER, Danica et al.; Eli Lilly and Company, Patent Division, P.O. Box 6288, Indianapolis, Indiana 46285 (US).

(21) International Application Number:

PCT/US2008/069301

(22) International Filing Date: 7 July 2008 (07.07.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/949,268 12 July 2007 (12.07.2007) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BP, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GE, GR, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LE, LG, LS, LT, LU, LV, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TH, 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): AFIPO (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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report

(54) Title: STABLE FORMULATIONS OF THIADIAZOLE DERIVATIVE

(57) Abstract: The present invention provides formulation parameters and manufacturing conditions for stable pharmaceutical compositions comprising N-[4-(2,2-dimethyl-propionyl)-(5R)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-1,5-dihydro-[1,3,4]thiadiazol-2-yl)]-2,2-dimethyl-propionamide that minimize undesirable chiral conversion to the less active S enantiomeric form.

WO 2009/009470 A1

STABLE FORMULATIONS OF THIADIAZOLE DERIVATIVE

The present invention provides formulation parameters and manufacturing conditions for stable pharmaceutical compositions comprising a thiadiazole derivative. In particular, the present invention provides chirally stable pharmaceutical compositions comprising *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide. Stable manufacturing conditions for this compound and intermediates are also provided.

10

Background of the Invention

The compound *N*-(4-(2,2-dimethyl-propionyl)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide was first described in PCT International Publication Number WO 03/051854. A formulation containing the compound *N*-(4-(2,2-dimethyl-propionyl)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide is described in PCT International Publication Number WO 2004/092147. A formulation containing the compound *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide is described in PCT International Publication Number WO 2006/101102. This compound is useful, for example, for therapeutic treatment of a human malignant tumor.

Stable formulations of the compound *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide which minimize chiral conversion to the less active *S* enantiomeric form are desired for reproducible and efficient manufacturing and commercial scale preparation, long-term storage of a lyophilized form, and stability when the lyophilized form is reconstituted and delivered to a patient. Surprisingly, formulation parameters and manufacturing conditions were discovered that provide stable pharmaceutical compositions comprising *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide that minimize undesirable chiral conversion to the less active *S* enantiomeric form.

Summary of the Invention

The present invention provides a pharmaceutical composition comprising *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide, and a pharmaceutically acceptable carrier, diluent, or excipient in solution wherein the pH of said composition is less than 6.4 and greater than 2.0, less than 6.2 and greater than 2.0, less than 5.4 and greater than 2.0, or less than 4.2 and greater than 2.0.

The present invention further provides a lyophilized pharmaceutical composition comprising *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide, and a pharmaceutically acceptable carrier, diluent, or excipient wherein the pH of said composition when diluted with aqueous diluent is less than 6.4 and greater than 2.0, less than 6.2 and greater than 2.0, less than 5.4 and greater than 2.0, or less than 4.2 and greater than 2.0.

The present invention also provides a lyophilized pharmaceutical composition comprising *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide, and a pharmaceutically acceptable carrier, diluent, or excipient wherein the pH of said composition is less than 6.4 and greater than 2.0, less than 6.2 and greater than 2.0, less than 5.4 and greater than 2.0, or less than 4.2 and greater than 2.0.

The present invention provides a pharmaceutical composition comprising *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide, and a pharmaceutically acceptable carrier, diluent, or excipient in solution wherein the pH of said composition is less than 6.2 and greater than 2.0, less than 5.4 and greater than 2.0, or less than 4.2 and greater than 2.0 and the temperature of said composition is less than 40 °C and greater than 25 °C.

The present invention also provides a pharmaceutical composition comprising *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide, and a

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pharmaceutically acceptable carrier, diluent, or excipient in solution wherein the pH of said composition is less than 8.4 and greater than 2.0 and the temperature of said composition is less than 25°C and greater than 5°C or equal to 5°C.

The present invention further provides a lyophilized pharmaceutical composition comprising *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide, and a pharmaceutically acceptable carrier, diluent, or excipient wherein the pH of said composition when diluted with aqueous diluent is less than 6.2 and greater than 2.0, less than 5.4 and greater than 2.0, or less than 4.2 and greater than 2.0 and the temperature of said composition is less than 40 °C and greater than 25 °C.

Detailed Description of the Invention

The present invention provides a chirally stable pharmaceutical composition comprising *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide, and a pharmaceutically acceptable carrier, diluent, or excipient that has reduced or no conversion to the *S* enantiomeric form. Pharmaceutical compositions for the present invention include both lyophilized forms and solution forms. Examples of solution forms include a solution form ready for lyophilization and a solution form reconstituted after lyophilization and ready for administration to a patient.

A "pharmaceutically acceptable carrier, diluent or excipient" used herein is a medium generally accepted in the art for the delivery of biologically active agents to patients. Such carriers, diluents, or excipients are generally formulated according to a number of factors well within the purview of those of ordinary skill in the art to determine. One skilled in the art of preparing formulations can readily select the proper processes for preparing the pharmaceutical compositions provided in the present invention. See, e.g., Remington: The Science and Practice of Pharmacy (A. Gennaro, et. Al., eds., 19th ed., Mack Publishing Co., 1995).

As used herein, the term "patient" refers to a mammal that is afflicted with, for example, a malignant tumor. The most preferred patient is a human.

As used herein, the term "stable" refers to a pharmaceutical formulation containing *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide that has reduced or no conversion to the *S*-enantiomeric form and meets defined, regulatory shelf life specifications for this compound as a marketed product.

Compounds of the present invention may be administered systemically, such as intravenously.

In order to improve the chiral stability of *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide, preferred pharmaceutical compositions involve particular formulation parameters, including particular pH and/or temperature conditions. Preferably, one embodiment of the present invention involves a pH range from less than about 6.4 to greater than about 2.0. More preferably, the pH range is from less than about 6.2 to greater than about 2.0. Even more preferably, the pH range is from less than about 5.4 to greater than about 2.0. Still more preferably, the pH range is from less than about 4.2 to greater than about 2.0. Various buffers and/or salts are available to maintain or control the pH range. Such buffers and/or salts are preferably tartrate, phosphate, citrate, mesylate, sodium sulfate, sodium chloride, and the like. One such preferable buffer and/or salt is phosphate. More preferably, the buffers and/or salts are sodium phosphate, tartrate, and citrate. Even more preferably, the buffer and/or salt is sodium phosphate. Still more preferably, the buffer and/or salt is tartrate. When using these pH ranges, buffers, and/or salts, the temperature preferably is less than 40 °C and greater than 25 °C.

Preferably, when the pH range for a pharmaceutical composition of the present invention is from less than about 8.4 to greater than about 2.0, the temperature is from less than about 25 °C to greater than about 5 °C. More preferably, the temperature of a pharmaceutical composition with a pH range of less than about 8.4 to greater than about 2.0 is about 5 °C.

Pharmaceutical compositions that are in solution prior to lyophilization, lyophilized, and/or diluted with aqueous diluent after lyophilization containing *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-

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dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide preferably contain no more than 2.0% of the less active S enantiomer. More preferably, the pharmaceutical composition contains no more than 1.5% of the S enantiomer. Even more preferably, the pharmaceutical composition contains no more than 1.0% of the S enantiomer. Still more preferably, the pharmaceutical composition contains no more than 0.5% of the S enantiomer. Even still more preferably, the pharmaceutical composition contains no more than 0.3% of the S enantiomer. Most preferably, the pharmaceutical composition contains no more than 0.2% of the S enantiomer.

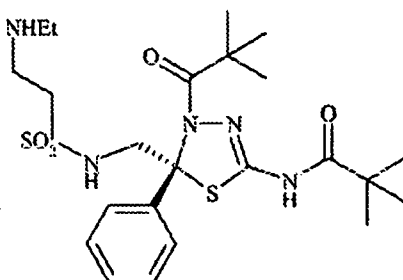
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Formulation Example

The following formulation example is illustrative and is not intended to limit the scope of the present invention.

In one vial, combine 10 mg *N*-[4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide, 60 mg tartaric acid, and 30 mg mannitol. Using water for injection, q.s. to 5.0 mL. Lyophilize the formulation. When ready for use, reconstitute the vial's contents with 5.0 mL water for injection. For this formulation, the concentration of *N*-[4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide is 2 mg/mL. The pH of the formulation is about 3.0 prior to lyophilization and about 3.1 to 3.2 after reconstitution.

Pharmaceutical Composition and Manufacturing Studies



N-{4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl}-2,2-dimethyl-propionamide is isolated, for example, as provided in PCT International Publication Number WO 2006/101102 or by utilizing the chiral HPLC assay noted *infra*.

- 5 Stability for *N*-{4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl}-2,2-dimethyl-propionamide (the compound) is assessed at 0.1 mg/mL in various buffers adjusted from pH 2 through 8 with various pH adjusting agents (e.g. 0.1 and 1 N HCl; 0.1, 1, and 5 N NaOH) and at different storage conditions (e.g. 5 °C, 25 °C, and 40 °C at
- 10 75% relative humidity). Hereinafter, the 40 °C at 75% relative humidity storage condition will be referred to as 40 °C. These buffers include 10 mM and 50 mM tartrate (40 °C), 10 mM phosphate (25 and 40 °C), 50 mM phosphate (40 °C), and 10 mM citrate (25 and 40 °C). Additional solution stability studies include 10 mM citrate (pH 8; 5 °C, 25 °C, and 40 °C) and 10 mM NaCl, 10 mM sodium sulfate, 10 mM mesylate, 10 mM
- 15 tartrate, 10 mM phosphate, and 10 mM citrate (pH 8, 40 °C). Lyophilized stability studies for *N*-{4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl}-2,2-dimethyl-propionamide involve solutions containing 10 mM tartrate buffer at pH 3 which are lyophilized and subjected to storage at 5 °C, 25 °C, and 40 °C for 1, 3, and 6 months. Finally, the enantiomeric
- 20 stability for *N*-{4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl}-2,2-dimethyl-propionamide is assessed when dissolved in various organic solvents and aqueous/solvent mixtures, including methanol, ethanol, acetonitrile, acetone, ethyl acetate, and 50% ethanol / 50% water (all at 25 °C and 40 °C) and in 1-octanol (25 °C).
- 25 The achiral stability of the compound is measured using standard reversed-phase HPLC assays. The analytical operating conditions for achiral stability analyses are as follows: Column: Waters XTerra C18 column, 150 x 4.6 mm, 3.5 micron; Detector: UV, 290 nm; Flow: 0.75 mL/min.; Injection: 10 µL; Column Temperature: 50 °C; Mobile Phase: 50% water with 0.1% TFA / 50% acetonitrile with 0.1% TFA.

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The enantiomeric stability is measured with a chiral HPLC assay employing polar ionic separation conditions. Those conditions include Column: Chirobiotic T, 150 x 4.6 mm; Detector: UV, 290nm; Flow: 0.225 – 0.35mL/min., adjust to optimize chiral separation; Injection: 2µL - 10µL; Column Temperature: 45°C; Mobile Phase: 0.01%

- 5 TEA, 1.0% HOAc, 1.0% water (DIW) in methanol. Enantioselectivity is very sensitive to mobile phase composition, specifically the acid:base ratio. For this reason, the TEA and HOAc additives are accurately measured and then delivered by pipette into the mobile phase while stirring.

- 10 In 10 mM and 50 mM tartrate buffers, no chiral conversion of the compound is observed at pH 4.1, 3.1, and 2.1 for at least 96 hours at 40 °C and at pH 3.9, 2.9, and 2.0 for at least 120 hours at 40 °C, respectively. Furthermore, for this study in 10 mM tartrate buffer, 97.5% of the compound remains after pH 6.2 at 96 hours at 40 °C and 60.3% of the compound remains after pH 8.7 at 96 hours at 40 °C.

- 15 In 10 mM sodium phosphate buffer, no chiral conversion of the compound is observed at pH 5.4, 3.4, and 2.3 for at least 120 hours at 40 °C and at pH 5.4, 3.4, and 2.3 for at least 120 hours at 25 °C. In 50 mM phosphate buffer, no chiral conversion of the compound is observed at pH 5.0, 3.3, and 2.2 for at least 96 hours at 40 °C.

- 20 In 10 mM citrate buffer, no chiral conversion of the compound is observed at pH 4.2, 3.3, and 2.1 for at least 96 hours at 40 °C and for at least 120 hours at 25 °C. In citrate buffer at pH 6.2, 98.2% of the compound remains after 96 hours at 40 °C and 99.9% of the compound remains after 120 hours at 25 °C.

In 10 mM citrate buffer at pH 8.4, 95.8 % of the compound remains after 24 hours at 25 °C and 99.3% of the compound remains after 120 hours at 5 °C.

- 25 For lyophilized formulations at pH 3.0, no chiral conversion of the compound is observed at 1, 3, and 6 months for 5 °C, 25 °C, or 40 °C storage conditions.

- 30 In general, N-{4-(2,2-dimethyl-propionyl)-(5R)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide is less stable and, thus, converts more readily to the S enantiomeric form in acetonitrile, ethyl acetate, and 50% ethanol / 50% water than in the other solvents that are tested.

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We claim:

1. A pharmaceutical composition comprising *N*-{4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl}-2,2-dimethyl-propionamide, and a pharmaceutically acceptable carrier, diluent, or excipient in solution wherein the pH of said composition is less than 6.4 and greater than 2.0.
2. The pharmaceutical composition of Claim 1 wherein the pH of said composition is less than 6.2 and greater than 2.0.
3. The pharmaceutical composition of Claim 2 wherein the pH of said composition is less than 5.4 and greater than 2.0.
4. The pharmaceutical composition of Claim 3 wherein the pH of said composition is less than 4.2 and greater than 2.0.
5. A lyophilized pharmaceutical composition comprising *N*-{4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl}-2,2-dimethyl-propionamide, and a pharmaceutically acceptable carrier, diluent, or excipient wherein the pH of said composition when diluted with aqueous diluent is less than 6.4 and greater than 2.0.
6. The lyophilized pharmaceutical composition of Claim 5 wherein the pH of said composition when diluted with aqueous diluent is less than 6.2 and greater than 2.0.
7. The lyophilized pharmaceutical composition of Claim 6 wherein the pH of said composition when diluted with aqueous diluent is less than 5.4 and greater than 2.0.
8. The lyophilized pharmaceutical composition of Claim 6 wherein the pH of said composition when diluted with aqueous diluent is less than 4.2 and greater than 2.0.

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9. A lyophilized pharmaceutical composition comprising *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide, and a pharmaceutically acceptable carrier, diluent, or excipient wherein the pH of said composition is less than 6.4 and greater than 2.0.

10. The lyophilized pharmaceutical composition of Claim 9 wherein the pH of said composition is less than 6.2 and greater than 2.0.

11. The lyophilized pharmaceutical composition of Claim 10 wherein the pH of said composition is less than 5.4 and greater than 2.0.

12. The lyophilized pharmaceutical composition of Claim 11 wherein the pH of said composition is less than 4.2 and greater than 2.0.

FORMULACIONES ESTABLES DE DERIVADO DE TIADIAZOL**CAMPO DE LA INVENCION**

La presente invención proporciona parámetros de
5 formulación y condiciones de manufacturación para
composiciones farmacéuticas que comprenden un derivado
tiadiazol. En particular, la presente invención proporciona
composiciones quiralmemente estables que comprenden, N-{4-(2,2-
dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-
10 metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-
dimetil-propionamida. También se proporcionan condiciones de
manufacturación estables para este compuesto e
intermediarios.

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ANTECEDENTES DE LA INVENCION

El compuesto N-{4-(2,2-dimetil-propionil)-(5-[(2-
etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-
[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida, fue primero
descrito en la Publicación Internacional de PCT Número WO
20 03/051854. Una formulación que contiene el compuesto N-{4-
(2,2-dimetil-propionil)-5-[(2-etilamino-etansulfonilamino)-
metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-
dimetil-propionamida, se describe en el Número de Publicación
Internacional de PCT WO 2004/092147. Una formulación que
25 contiene el compuesto N-{4-(2,2-dimetil-propionil)-(5R)-5-

[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida, se describe en el Número de Publicación Internacional de PCT WO 2006/101102. Este compuesto es empleado por ejemplo, para el
5 tratamiento terapéutico de un tumor maligno humano.

Formulaciones estables del compuesto N-(4-(2,2-dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida, los cuales minimizan la conversión
10 quiral a la forma enantiomérica S menos activa, son deseados para manufacturación reproducible y eficiente y preparación a escala comercial, almacenamiento de término largo de una forma liofilizada, y estabilidad cuando la forma liofilizada es reconstituida y suministrada a un paciente. De manera
15 sorprendente, los parámetros de formulación y condiciones de manufacturación, son descubiertos que proporcionan composiciones farmacéuticas estables que comprenden N-(4-(2,2-dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-
20 [1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida que minimiza la conversión quiral indeseable a la forma enantiomérica S menos activa.

BREVE DESCRIPCIÓN DE LA INVENCION

25 La presente invención proporciona una composición

farmacéutica que comprende N-(4-(2,2-dimetil-propionil)-(5R)-
5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-
dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida, y un
portador, diluyente o excipiente farmacéuticamente aceptable
5 en solución, en donde el pH de dicha composición es menos de
6.4 y mayor de 2.0, menos de 6.2 y mayor de 2.0, menos de 5.4
y mayor de 2.0, o menos de 4.2 y mayor de 2.0.

La presente invención además proporciona una
composición farmacéutica liofilizada que comprende N-(4-(2,2-
10 dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-
metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-
dimetil-propionamida, y un portador, diluyente o excipiente
farmacéuticamente aceptable, en donde el pH de dicha
composición cuando se diluye con diluyente acuoso es menos de
15 6.4 y mayor de 2.0, menos de 6.2 y mayor de 2.0, menos de 5.4
y mayor de 2.0 o menos de 4.2 y mayor de 2.0.

La presente invención también proporciona una
composición farmacéutica liofilizada que comprende N-(4-(2,2-
dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-
20 metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-
dimetil-propionamida, y un portador, diluyente o excipiente
farmacéuticamente aceptable, en donde el pH de dicha
composición es menos de 6.4 y mayor de 2.0, menos de 6.2 y
mayor de 2.0, menos de 5.4 y mayor de 2.0, o menos de 4.2 y
25 mayor de 2.0.

La presente invención proporciona una composición farmacéutica que comprende N-(4-(2,2-dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida, y un portador, diluyente o excipiente farmacéuticamente aceptable en solución, en donde el pH de dicha composición es menos de 6.2 y mayor de 2.0, menos de 5.4 y mayor de 2.0, o menos de 4.2 y mayor de 2.0 y la temperatura de dicha composición es menos de 40°C y mayor de 25°C.

La presente invención también proporciona una composición farmacéutica que comprende N-(4-(2,2-dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida, y un portador, diluyente o excipiente farmacéuticamente aceptable en solución, en donde el pH de dicha composición es menos de 8.4 y mayor de 2.0 y la temperatura de dicha composición es menos de 25°C y mayor de 5°C o igual a 5°C.

La presente invención además proporciona una composición farmacéutica liofilizada que comprende N-(4-(2,2-dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida, y un portador, diluyente o excipiente farmacéuticamente aceptable, en donde el pH de dicha composición cuando se diluye con diluyente acuoso es menos de

6.2 y mayor de 2.0, menos de 5.4 y mayor de 2.0, o menos de 4.2 y mayor de 2.0 y la temperatura de dicha composición es menos de 40°C y mayor de 25°C.

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DESCRIPCIÓN DETALLADA DE LA INVENCION

La presente invención proporciona una composición farmacéutica quiralmente estable que comprende N-{4-(2,2-dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida, y un portador, diluyente o excipiente farmacéuticamente aceptable, que tiene reducida o no la conversión a la forma enantiomérica S. Las composiciones farmacéuticas para la presente invención incluyen, formas tanto liofilizadas como formas en solución. Ejemplos de formas de solución incluyen una forma de solución lista para liofilización y una forma de solución reconstituida después de la liofilización y lista para administración a un paciente.

Un "portador, diluyente o excipiente farmacéuticamente aceptable" usado aquí, es un medio en general aceptado en la técnica para el suministro de agentes biológicamente activos a pacientes. Tales portadores, diluyentes o excipientes son en general, formulados de conformidad con un número de factores también dentro del punto de vista de aquellos de habilidad ordinaria en la

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técnica a determinar. Un experto en la técnica para preparar formulaciones, puede seleccionar fácilmente los procesos apropiados para la preparación de las composiciones farmacéuticas proporcionadas en la presente invención. Véase, 5 por ejemplo, Remington: The Science and Practice of Pharmacy (A. Gennaro, et. Al., eds., 19th ed., Mack Publishing Co., 1995).

Como se usa aquí, el término "paciente", se refiere a un mamífero que es afligido con, por ejemplo, un tumor 10 maligno. El paciente más preferido es un humano.

Como se usa aquí, el término "estable", se refiere a una formulación farmacéutica que contiene N-{4-(2,2-dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2- 15 dimetil-propionamida que tiene reducida o no conversión a la forma enantiomérica S y cubre las especificaciones de vida de anaquel regulatorias, definidas para este compuesto como un producto comercializado.

Compuestos de la presente invención pueden ser 20 administrados sistémicamente, tal como intravenosamente.

Para mejorar la estabilidad quiral de N-{4-(2,2-dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida, composiciones farmacéuticas involucran 25 parámetros de formulación particular, que incluyen pH

particular y/o condiciones de temperatura. Preferiblemente, una modalidad de la invención involucra un intervalo de pH de menos de aproximadamente 6.4 a mayor de aproximadamente 2.0. Más preferiblemente, el intervalo de pH es desde menos de aproximadamente 6.2 a mayor de aproximadamente 2.0. Aún más preferiblemente, el intervalo de pH es de menos de aproximadamente 5.4 a mayor de aproximadamente 2.0. Todavía más preferiblemente, el intervalo de pH es de menos de aproximadamente 4.2 a mayor de aproximadamente 2.0. Varios amortiguadores y/o sales son disponibles para mantener o controlar el intervalo de pH. Tales amortiguadores y/o sales son preferiblemente tartrato, fosfato, citrato, mesilato, sulfato de sodio, cloruro de sodio y similares. Un amortiguador y/o sal preferible es fosfato. Más preferiblemente, los amortiguadores y/o sales son fosfato, tartrato y citrato de sodio. Aún más preferiblemente, el amortiguador y/o sal es fosfato de sodio. Todavía más preferiblemente, el amortiguador y/o sal es tartrato. Cuando se usan estos intervalos de pH, amortiguadores y/o sales, la temperatura preferiblemente es menos de 40°C y mayor de 25°C.

Preferiblemente, cuando el intervalo de pH para una composición farmacéutica de la presente invención es de menos de aproximadamente 3.4 a mayor de aproximadamente 2.0, la temperatura es desde menos de aproximadamente 25°C a mayor de aproximadamente 5°C. Más preferiblemente, la temperatura de

una composición farmacéutica con un intervalo de pH de menos de aproximadamente 3.4 a más de aproximadamente 2.0 es aproximadamente 5°C.

Las composiciones farmacéuticas que están en
5 solución antes de la liofilización, liofilizadas y/o diluidas con diluyente acuoso después de la liofilización, que contiene N-(4-(2,2-dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida,
10 preferiblemente no contiene más de 2.0% de enantiómero S menos activo. Más preferiblemente, la composición farmacéutica no contiene más de 1.5% de enantiómero S. Aún más preferiblemente, la composición farmacéutica no contiene más de 1.0% del enantiómero S. Todavía más preferiblemente,
15 la composición farmacéutica no contiene más de 0.5% del enantiómero S. Aún todavía más preferiblemente, la composición farmacéutica no contiene más de 0.3% del enantiómero S. Más preferiblemente, la composición farmacéutica no contiene más de 0.2% del enantiómero S.

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Ejemplo de Formulación

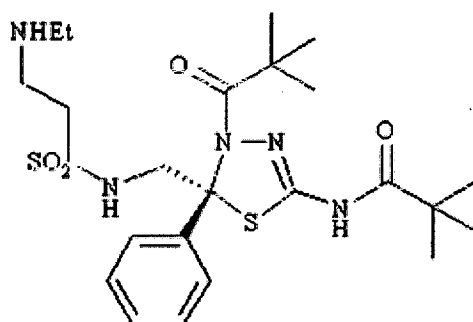
El siguiente ejemplo de formulación es ilustrativo y no pretende limitar el campo de la presente invención.

En un vial, se combinan 10 mg de N-(4-(2,2-dimetil-
25 propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-

fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida, 6.0 mg de ácido tartárico y 30 mg de manitol. Se usa agua para inyección, c.s. a 5.0 ml. Se liofiliza la formulación. Cuando está lista para usar, se reconstituyen los contenidos del vial con 5.0 ml de agua para inyección. Para esta formulación, la concentración de N-{4-(2,2-dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida es 2 mg/ml. El pH de la formulación es aproximadamente 3.0 antes de la liofilización y aproximadamente 3.1 a 3.2 después de la reconstitución.

Composición Farmacéutica y Estudios de Manufacturación

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N-{4-(2,2-dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida se aísla por ejemplo, como se proporciona en el Número de Publicación Internacional de PCT WO 2006/101102 o utilizando el ensayo CLAR quiral notado *infra*.

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La estabilidad para *N*-{4-(2,2-dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida (el compuesto), se valora a 0.1 mg/ml en varios amortiguadores ajustados desde pH 2 hasta 8 con varios agentes ajustadores de pH (por ejemplo, 0.1 y 1N HCl; 0.1, 1 y 5N NaOH) y a condiciones de almacenaje diferentes (por ejemplo, 5°C, 25°C y 40°C a 75% de humedad relativa). Posteriormente, la condición de almacenaje de 40°C a 75% de humedad relativa, será referida como 40°C. Estos amortiguadores incluyen 10 mM y 50 mM de tartrato (40°C), 10 mM de fosfato (25 y 40°C), 50 mM de fosfato (40°C) y 10 mM de citrato (25 y 40°C). Estudios de estabilidad de solución adicional incluyen 10 mM de citrato (pH 8; 5°C, 25°C y 40°C) y 10 mM de NaCl, 10 mM de sulfato de sodio, 10 mM de mesilato, 10 mM de tartrato, 10 mM de fosfato y 10 mM de citrato (pH 8, 40°C). Los estudios de estabilidad liofilizada para *N*-{4-(2,2-dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida, involucran soluciones que contienen 10 mM de amortiguador de tartrato a pH 3, las cuales son liofilizadas y sometidas a almacenaje a 5°C, 25°C y 40°C por 1, 3 y 6 meses. Finalmente, la estabilidad enantiomérica para *N*-{4-(2,2-dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-

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propionamida, es valorada cuando se disuelve en varios
solvente orgánicos y/o mezclas de solvente/acuosas, que
incluyen metanol, etanol, acetonitrilo, acetona, acetato de
etilo y 50% de etanol/50% de agua (todos a 25°C y 40°C) y en
5 1-octanol (25°C).

La estabilidad quiral del compuesto es medida
usando ensayos de CLAR de fase inversa estándares. Las
condiciones de operación analíticas para análisis de
estabilidad quiral son como sigue: Columna: Columna Waters
10 XTerra C18, 150 x 4.6 mm, 3.5 micrones; Detector: UV, 290 nm,
Flujo: 0.75 ml/min; inyección: 10 µl; Temperatura de Columna:
50°C; Fase Móvil: 50% de agua con 1% de TFA/50% de
acetonitrilo con 0.1% de TFA.

La estabilidad enantiomérica es medida con un
15 ensayo CLAR quiral que emplea condiciones de separación
iónica polar. Estas condiciones incluyen Columna: Chirobiotic
T, 150 x 4.6 mm; Detector: UV, 290 nm; Flujo: 0.225-0-35
ml/min, ajustado para optimizar la separación quiral;
Inyección: 2 µl-10 µl; Temperatura de Columna; 45°C; Fase
20 Móvil: 0.01% de TEA, 1.0% de HOAc, 1.0% de agua (DIW) en
metanol. La enantioselectividad es muy sensible a la
composición de fase móvil, específicamente la relación
ácido:base. Por esta razón, los aditivos TEA y HOAc son
exactamente medidos y después suministrados por pipeta en la
25 fase móvil con agitación.

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En amortiguadores de tartrato de 10 mM y 50 mM, no se observa conversión quiral del compuesto a pH 4.1, 3.1 y 2.1 por al menos, 96 horas a 40°C y a pH 3.9, 2.9 y 2.0 por al menos 120 horas a 40°C, respectivamente. Además, para este estudio en amortiguador de tartrato de 10 mM, 97.5% del compuesto permanece después del pH 6.2 a 96 horas a 40°C y 60.3% del compuesto permanecen después de pH 8.7 a 96 horas a 40°C.

En amortiguador de fosfato de sodio de 10 mM, no se observa conversión quiral del compuesto a pH 5.4, 3.4 y 2.3 por al menos 120 horas a 40°C y a pH 5.4, 3.4 y 2.3 por al menos 120 horas a 25°C. En amortiguador de fosfato de 50 mM, no se observa conversión quiral del compuesto a pH 5.0, 3.3 y 2.2 por al menos 96 horas a 40°C.

En amortiguador de citrato de 10 mM, no se observa conversión quiral del compuesto a pH 4.2, 3.3 y 2.1 por al menos 96 horas a 40°C y por al menos 120 horas a 25°C. En amortiguador de citrato a pH 6.2, 98.2% del compuesto permanecen después de 96 horas a 40°C y 99.9% del compuesto permanecen después de 120 horas a 25°C.

En 10 mM de amortiguador de citrato a pH 8.4, 95.8% del compuesto permanecen después de 24 horas a 25°C y 99.3% del compuesto permanecen después de 120 horas a 5°C.

Para formulaciones liofilizadas a pH 3.0, no se observa conversión quiral del compuesto a condiciones de

almacenaje a 1, 3 y 6 meses, por 5°C, 25°C, o 40°C.

En general, N-[4-(2,2-dimetil-propionil)-(5R)-5-
[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-
[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida es menos
5 estable y, de este modo, se convierte más fácilmente a la
forma enantiomérica S en acetonitrilo, acetato de etilo y 50%
de etanol/50% de agua que en los otros solventes que son
probados.

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REIVINDICACIONES

Habiéndose descrito la invención como antecede, se reclama como propiedad lo contenido en las siguientes.

- 5 1. Una composición farmacéutica, caracterizada porque comprende *N*-(4-(2,2-dimetil-propionil)-(5*R*)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida, y un portador, diluyente o excipiente farmacéuticamente aceptable
10 en solución, en donde el pH de dicha composición es menos de 6.4 y mayor de 2.0.
2. La composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque el pH de dicha composición es menos de 6.2 y mayor de 2.0.
- 15 3. La composición farmacéutica de conformidad con la reivindicación 2, caracterizada porque el pH de dicha composición es menos de 5.4 y mayor de 2.0.
4. La composición farmacéutica de conformidad con la reivindicación 3, caracterizada porque el pH de dicha
20 composición es menos de 4.2 y mayor de 2.0.
5. Una composición farmacéutica liofilizada, caracterizada porque comprende *N*-(4-(2,2-dimetil-propionil)-(5*R*)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida, y un
25 portador, diluyente o excipiente farmacéuticamente aceptable,

en donde el pH de dicha composición cuando se diluye con diluyente acuoso es menos de 6.4 y mayor de 2.0.

5 6. La composición farmacéutica liofilizada de conformidad con la reivindicación 5, caracterizada porque el pH de dicha composición cuando se diluye con diluyente acuoso es menos de 6.2 y mayor de 2.0.

7. La composición farmacéutica liofilizada de conformidad con la reivindicación 6, caracterizada porque el pH de dicha composición cuando se diluye con diluyente acuoso
10 es menos de 5.4 y mayor de 2.0.

8. La composición farmacéutica liofilizada de conformidad con la reivindicación 6, caracterizada porque el pH de dicha composición cuando se diluye con diluyente acuoso es menos de 4.2 y mayor de 2.0.

15 9. Una composición farmacéutica liofilizada, caracterizada porque comprende N-{4-(2,2-dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida, y un portador, diluyente o excipiente farmacéuticamente aceptable
20 en donde el pH de dicha composición es menos de 6.4 y mayor de 2.0.

10. La composición farmacéutica liofilizada de conformidad con la reivindicación 9, caracterizada porque el pH de dicha composición es menos de 6.2 y mayor de 2.0.

25 11. La composición farmacéutica liofilizada de

RESUMEN DE LA INVENCIÓN

La presente invención se refiere parámetros de formulación y condiciones de manufacturación para composiciones farmacéuticas estables que comprenden N-(4-(2,2-dimetil-propionil)-(5R)-5-[(2-etilamino-etansulfonilamino)-metil]-5-fenil-4,5-dihidro-[1,3,4]tiadiazol-2-il)-2,2-dimetil-propionamida que minimiza la conversión quiral estable a la forma enantiomérica S menos activa.

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conformidad con la reivindicación 10, caracterizada porque el pH de dicha composición es menos de 5.4 y mayor de 2.0.

12. La composición farmacéutica liofilizada de conformidad con la reivindicación 11, caracterizada porque el
5 pH de dicha composición es menos de 4.2 y mayor de 2.0.

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PATENT COOPERATION TREATY

RECEIVED

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT MAY 27 2009

ELI LILLY AND COMPANY
Patent Division

To:

HOSTETTLER, Danica et al.
ELI LILLY AND COMPANY
Patent Division
P.O. Box 6288
Indianapolis IN 46206-6288
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year) 18-05-2009

Applicant's or agent's file reference
X17500 ✓

IMPORTANT NOTIFICATION

International application No.

PCT/US2008/063301 ✓

International filing date (day/month/year)

7 July 2008 (07-07-2008) ✓

Priority date (day/month/year)

12 July 2007 (12-07-2007) ✓

Applicant

ELI LILLY AND COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

8 May 2009 (08-05-2009)

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/402), received the required corrections.

3. ☒ **ATTENTION:** That date of receipt is **after** the expiration of 19 months from the priority date. Consequently, in respect of some Offices, the demand does not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)) and the date for entry into the national phase must therefore be performed within 30 months from the priority date (or later in some Offices). However, in respect of some other Offices, the time limit of 30 months (or later) may nevertheless apply. 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.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

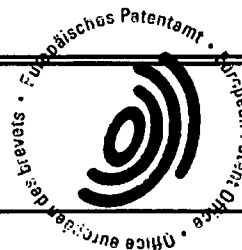
4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/

 European Patent Office
D-80295 Munich
Tel. (+49-89) 2399-0
Fax: (+49-89) 2399-4365

Authorized officer

Lafitte-de Jong, Sandrine
Tel. (+31-70) 340-4827



PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

RECEIVED

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

To:

ELI LILLY AND COMPANY
Patent Division
P.O. Box 6288
Indianapolis IN 46206-6288
ETATS-UNIS D'AMERIQUE

Date of mailing
(day/month/year)

14.10.2009

Applicant's or agent's file reference
X17500

IMPORTANT NOTIFICATION

International application No.
PCT/US2008/069301

International filing date (day/month/year)
07.07.2008

Priority date (day/month/year)
12.07.2007

Applicant

ELI LILLY AND COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

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

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

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

Name and mailing address of the international
preliminary examining authority:



European Patent Office P.B. 5318 Patentlaan 2
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Authorized Officer

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X17500		FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/US2008/069301		International filing date (day/month/year) 07.07.2008	Priority date (day/month/year) 12.07.2007	
International Patent Classification (IPC) or national classification and IPC INV. A61K9/19				
Applicant ELI LILLY AND COMPANY				
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 7 sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ sent to the applicant and to the International Bureau) a total of 2 sheets, as follows: ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 807 of the Administrative Instructions). ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).				
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ 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 Article 35(2) 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				
Date of submission of the demand 2009-05-08		Date of completion of this report 14.10.2009		
Name and mailing address of the international preliminary examining authority:  European Patent Office P.B. 5313 Patentlaan 2 NL-2260 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016		Authorized officer Gómez Gallardo, S Telephone No. +31 70 340-3546		



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2008/069301

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ 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 (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-7 as originally filed

Claims, Numbers

1-9 filed with telefax on 08.05.2009

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☒ the claims, Nos. 1-9
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
5. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 70.2 (e)).
6. ☐ Supplementary international search report(s) from Authority(ies) have been received and taken into account in drawing up this report (Rule 45bis.8(b) and (c)).

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**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2008/069301

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>3-9</u>
	No: Claims	<u>1,2</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-9</u>
Industrial applicability (IA)	Yes: Claims	<u>1-9</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the report

The attention of the applicant is drawn to the fact that some of the amendments introduced in the new claims, as filed with telefax on 8 May 2009, go beyond the disclosure in the application as originally filed. More particularly, said amendments are as follows:

(a) in claims 1 and 5, the following statement has been introduced "*and contains no more than 2.5% N-[4-(2,2-dimethyl-propionyl)-(5S)-5-((2-ethylamino-ethanesulfonylamino)-methyl)-5-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl]-2,2-dimethyl-propionamide*". However, in the originally filed application, there is only basis for the pharmaceutical composition containing no more than 2% N-[4-(2,2-dimethyl-propionyl)-(5S)-5-((2-ethylamino-ethanesulfonylamino)-methyl)-5-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl]-2,2-dimethyl-propionamide (cf. page 5, lines 1 and 2).

(b) following a lack of clarity objection, the pH feature has been removed from claim 9. However, it is to be noted that, throughout the description of the invention, it is apparent that, in order to solve the instability problem of the R enantiomer, it is necessary that the pH is controlled in a range from less than 6.4 to greater than 2 when diluting the lyophilized formulation with an aqueous diluent. The deletion of the pH range in claim 9, instead of the rewording of the pH statement so that it reads that the pH value refers to the diluted lyophilized formulation, leads, therefore, to an undue generalisation according to which any pH is possible upon dilution.

The present examination report is established as if the above-mentioned amendments would not have been made (Rule 70.2(c) PCT).

Re Item V

**Reasoned statement with regard to novelty, inventive step and industrial applicability;
citations and explanations supporting such statement**

1. CITED DOCUMENTS

Reference is made to the following documents:

- D1: EP 1 616 866 A (KYOWA HAKKO KOGYO KK [JP]; FUJI PHOTO FILM CO LTD [JP])
18 January 2006 (2006-01-18), of the same family as WO 2004/092147 A (KYOWA
HAKKO KOGYO KK [JP]; FUJI PHOTO FILM CO LTD [JP]) 28 October 2004 (2004-10-
28) (cited in the application)
- D2: CA 2 602 397 A (KYOWA HAKKO KOGYO KK [JP]; FUJI PHOTO FILM CO LTD [JP])
28 September 2006 (2006-09-28), of the same family as WO 2006/101102 A (KYOWA
HAKKO KOGYO KK [JP]; FUJI PHOTO FILM CO LTD [JP]; MURAKATA CHIKA) 28
September 2006 (2006-09-28) (cited in the application)

2. NOVELTY (Art. 33(2) PCT)

2.1. It is to be noted that, in claim 5, the statement "*affording a solution formulation when diluted with aqueous diluent having a pH less than 6.4 and greater than 2*" is a **result to be achieved**. This merely amounts to a statement of the underlying problem, **without providing the technical features necessary for achieving this result (i.e. the formulation components, e.g. the particular buffers and/or salts used (tartrate, phosphate, citrate, mesylate, sodium sulfate or sodium chloride (cf. page 4, lines 17 and 18)))**. Furthermore, the nature of the aqueous diluent may have a strong influence on the final pH obtained upon dilution. In view of this, the above-mentioned statement is, at present, considered as not limiting when assessing the novelty of the present application.

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

Document D1 discloses (cf. page 37, table 9, compound 176; page 50 - page 51, example 9) an injection composition comprising (A) N-[4-(2,2-dimethyl-propionyl)-5-((2-ethylamino-ethanesulfonylamino)-methyl)-5-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl]-2,2-dimethyl-propionamide, (B) D-mannitol, (C) HCl, (D) NaOH and (E) distilled water for injection. HCl and NaOH are known to produce NaCl, which is one of the possible buffers and/or salts mentioned in the present application. The pH of the composition of D1 is adjusted to 6. It is construed that said composition comprises at least a fraction of the

R enantiomer of the thiadiazole derivative. Furthermore, it is stated in the description of D1 that optical isomers also fall within the scope of the family of compounds claimed (cf. page 22, paragraph 82). Therefore, the subject-matter of claims 1 and 2 is not new in view of D1.

3. INVENTIVE STEP (Art. 33(3) PCT)

3.1. Claims 1 and 2 being not new are also not inventive (Art. 33(3) PCT).

3.2. Dependent claims 3 and 4 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step. The reason for this is that no unexpected effect seems to be related to the pH being as defined in these claims (Art. 33(3) PCT).

3.3. Due to the reasoning disclosed in section 2.1., the statement "*affording a solution formulation when diluted with aqueous diluent having a pH less than 6.4 and greater than 2*", in claim 5, is, at present, considered as not limiting when assessing the inventive step of the present application (Art. 33(3) PCT).

3.4. The document D2 is regarded as being the closest prior art to the subject-matter of claims 5 and 9, and discloses (cf. page 37, table 1, compound 9; page 38, table 2, compound I; page 56, example 5; page 60 - page 61, example 13) an injection composition comprising (A) N-[4-(2,2-dimethyl-propionyl)-(5R)-5-((2-ethylamino-ethanesulfonylamino)-methyl)-5-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl]-2,2-dimethyl-propionamide, (B) D-mannitol, (C) HCl, (D) NaOH and (E) distilled water for injection. HCl and NaOH are known to produce NaCl, which is one of the possible buffers and/or salts mentioned in the present application.

The subject-matter of claims 5 and 9, therefore, differs from D2 in that the thiadiazole derivative composition is lyophilized. This comes, however, within the scope of the customary practice followed by persons skilled in the art of formulating injectable compositions and the advantages thus achieved can readily be foreseen. Consequently, the subject-matter of claims 5-9 also lacks an inventive step (Art. 33(3) PCT).

4. INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

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**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/US2008/069301

Claims 1-9 satisfy the criterion of industrial applicability set forth in Article 33(4) PCT.

Re Item VIII

Certain observations on the international application

CLARITY (Art. 6 PCT)

Although claims 5 and 9 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT. In the telefax received on 8 May 2009, the applicant alleges that claims 5 and 9 are directed to different subject-matter because claim 5 refers to a lyophilized formulation that is later diluted with an aqueous diluent and claim 9 refers to a lyophilized formulation. It is to be noted that even if the lyophilized formulation of claim 5 is later diluted, claim 5 still refers to a lyophilized formulation. Therefore, claims 5 and 9 indeed relate to the same subject-matter.

X-17500

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We claim:

1. A pharmaceutical composition comprising *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide, a buffer and/or salt, and a pharmaceutically acceptable carrier, diluent, or excipient in solution wherein the pH of said composition is less than 6.4 and greater than 2.0 and contains no more than 2.5% *N*-(4-(2,2-dimethyl-propionyl)-(5*S*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide.
2. The pharmaceutical composition of Claim 1 wherein the pH of said composition is less than 6.2 and greater than 2.0.
3. The pharmaceutical composition of Claim 1 wherein the pH of said composition is less than 5.4 and greater than 2.0.
4. The pharmaceutical composition of Claim 1 wherein the pH of said composition is less than 4.2 and greater than 2.0.
5. A lyophilized pharmaceutical composition comprising *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide, a buffer and/or salt, and a pharmaceutically acceptable carrier, diluent, or excipient affording a solution formulation when diluted with aqueous diluent having a pH less than 6.4 and greater than 2.0 and contains no more than 2.5% *N*-(4-(2,2-dimethyl-propionyl)-(5*S*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide.
6. The lyophilized pharmaceutical composition of Claim 5 wherein the pH is less than 6.2 and greater than 2.0.

AMENDED SHEET

X-17500

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7. The lyophilized pharmaceutical composition of Claim 5 wherein the pH is less than 5.4 and greater than 2.0.

8. The lyophilized pharmaceutical composition of Claim 5 wherein the pH is less than 4.2 and greater than 2.0.

9. A lyophilized pharmaceutical composition comprising *N*-(4-(2,2-dimethyl-propionyl)-(5*R*)-5-[(2-ethylamino-ethanesulfonylamino)-methyl]-5-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-2,2-dimethyl-propionamide, a buffer and/or salt, and a pharmaceutically acceptable carrier, diluent, or excipient.

AMENDED SHEET

PATENT COOPERATION TREATY

PCT/US2003/069301

From the INTERNATIONAL BUREAU

PCTNOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

HOSTETTLER, Danica
Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46285
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)

29 May 2003 (29.05.2003)

Applicant's or agent's file reference

X17500

IMPORTANT NOTIFICATION

International application No.

PCT/US2003/069301

International filing date (day/month/year)

07 July 2003 (07.07.2003)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

KYOWA HAKKO KOGYO CO., LTD.
1-6-1 Ohtemachi
Chiyoda-ku, Tokyo 100-8185
Japan

State of Nationality

JP

State of Residence

JP

Telephone No.

Facsimile No.

E-mail address

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

KYOWA HAKKO KIRIN CO., LTD.
1-6-1 Ohtemachi
Chiyoda-ku, Tokyo 100-8185
Japan

State of Nationality

JP

State of Residence

JP

Telephone No.

Facsimile No.

E-mail address

☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Sanvincenti Guido

Facsimile No. +41 22 338 87 40

e-mail pt01.pct@wipo.int

Telephone No. +41 22 338 74 01

PATENT COOPERATION TREATY

RECEIVED

SEP 29 2008

From the INTERNATIONAL SEARCHING AUTHORITY

PCT LILLY AND COMPANY
Patent Division

To:

ELI LILLY AND COMPANY
Attn: Hestettler, Danica
P.O. Box 6092
Indianapolis IN 46206-6092
ETATS-UNIS D'AMERIQUENOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year) 24/09/2008	
Applicant's or agent's file reference X17500 ✓	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US2008/069301 ✓	International filing date (day/month/year) 07/07/2009
Applicant ELI LILLY AND COMPANY	

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) 838.62.70**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 49.2, 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/IS/A/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. 5518 Patentlaan 2 NL-6360 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 apo nl, Fax: (+31-70) 340-3916	Authorized officer Almudena Montalvillo
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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 IA, 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(C), that no international search report would be established (see *PCT Applicant's Guide*, Volume IA, 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 29 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/is filed, see below.

How?

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

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

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (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 X17500	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/US2008/069201	International filing date (day/month/year) 07/07/2008	(Earliest) Priority Date (day/month/year) 12/07/2007
Applicant ELI LILLY AND COMPANY		

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. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ 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:

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

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 35.2(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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/069301

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/19 A61K31/433		
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) A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the International search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, EMBASE, BIOSIS, 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.
X	✓ EP 1 616 866 A (KYOWA HAKKO KOGYO KK [JP]; FUJI PHOTO FILM CO LTD [JP]) 18 January 2006 (2006-01-18) page 3, line 48 - page 6, line 49 page 22, paragraph 82 page 37; table 9; compound 176 page 50 - page 51; example 9 page 95, paragraph 462	1-12
X	& WO 2004/092147 A (KYOWA HAKKO KOGYO KK [JP]; FUJI PHOTO FILM CO LTD [JP]; MURAKATA CHIKA) 28 October 2004 (2004-10-28) cited in the application ----- -/-	1-12
☒ 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 "Z" document member of the same patent family		
Date of the actual completion of the international search 17 September 2008		Date of mailing of the international search report 24/09/2008
Name and mailing address of the ISA/ European Patent Office, P.O. 5310 Patentplan 2 NL - 2200 HV Rijswijk Tel: (+31-70) 340-2040, Tx: 31 651 eps nl, Fax: (+31-70) 340-3016		Authorized officer Gómez Gallardo, S

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/069301

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2 602 397 A1 (KYOWA HAKKO KOGYO KK [JP]; FUJIFILM CORP [JP]) 28 September 2006 (2006-09-28) page 8; compound L page 35, paragraph 53 page 37; table 1; compound 9 page 38; table 2; compound L page 56; example 5 page 60 - page 61; example 13 page 73; example 26	1-12
X	& WO 2006/101102 A (KYOWA HAKKO KOGYO KK [JP]; FUJI PHOTO FILM CO LTD [JP]; MURAKATA CHIKA) 28 September 2006 (2006-09-28) cited in the application -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/069301

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1616866	A	18-01-2006	AU 2004230799 A1 CA 2522594 A1 WO 2004092147 A1 KR 20060008903 A US 2007155804 A1	28-10-2004 28-10-2004 28-10-2004 27-01-2006 05-07-2007
WO 2004092147	A	28-10-2004	AU 2004230799 A1 CA 2522594 A1 EP 1616866 A1 KR 20060008903 A US 2007155804 A1	28-10-2004 28-10-2004 18-01-2006 27-01-2006 05-07-2007
CA 2602397	A1	28-09-2006	AU 2006225636 A1 CN 101193878 A EP 1867640 A1 WO 2006101102 A1 KR 20070113300 A US 2008194653 A1	28-09-2006 04-06-2008 19-12-2007 28-09-2006 28-11-2007 14-08-2008
WO 2006101102	A	28-09-2006	AU 2006225636 A1 CA 2602397 A1 CN 101193878 A EP 1867640 A1 KR 20070113300 A US 2008194653 A1	28-09-2006 28-09-2006 04-06-2008 19-12-2007 28-11-2007 14-08-2008

PATENT COOPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

X 17500

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

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

12 MAY 2009

Applicant's or agent's file reference see form PCT/ISA/220		FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/US2008/069301	International filing date (day/month/year) 07.07.2008	Priority date (day/month/year) 12.07.2007	
International Patent Classification (IPC) or both national classification and IPC INV. A61K9/19 A61K31/433			
Applicant ELI LILLY AND COMPANY			

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 65.1bis(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:	Date of completion of this opinion	Authorized Officer
 European Patent Office - P.B. 5318 Patentlaan 5 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tlx. 31 651 epc nl Fax: +31 70 340 - 3016	See form PCT/ISA/210	Gomez Gallardo, S Telephone No. +31 70 340-9548 

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2008/069301

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. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. 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.
4. ☐ 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.
5. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2008/069301

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	<u>5-12</u>
	No: Claims	<u>1-4</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-12</u>
Industrial applicability (IA)	Yes: Claims	<u>1-12</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step and industrial applicability;
citations and explanations supporting such statement

1. CITED DOCUMENTS

Reference is made to the following documents:

- D1: EP 1 616 866 A (KYOWA HAKKO KOGYO KK [JP]; FUJI PHOTO FILM CO LTD [JP])
18 January 2006 (2006-01-18), of the same family as WO 2004/092147 A (KYOWA
HAKKO KOGYO KK [JP]; FUJI PHOTO FILM CO LTD [JP]) 28 October 2004 (2004-10-
28) (cited in the application)
- D2: CA 2 602 397 A (KYOWA HAKKO KOGYO KK [JP]; FUJI PHOTO FILM CO LTD [JP])
28 September 2006 (2006-09-28), of the same family as WO 2006/101102 A (KYOWA
HAKKO KOGYO KK [JP]; FUJI PHOTO FILM CO LTD [JP]; MURAKATA CHIKA) 28
September 2006 (2006-09-28) (cited in the application)

2. CLARITY (Art. 6 PCT)

2.1. Claim 5 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the composition in terms of a **result to be achieved**, namely as having a certain pH when diluted with an aqueous diluent. This merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result (i.e. the formulation components). In view of this, the statement "*wherein the pH of said composition when diluted with aqueous diluent is less than 6.4 and greater than 2.0*", in claim 5, is, at present, considered as not limiting when assessing the novelty of the present application.

2.2. Claim 9 refers to the pH of a lyophilized composition. Since a lyophilized composition is a solid composition and no pH can be defined for a solid composition, claim 9 is considered to be unclear and, therefore, it is not compliant with Article 6 PCT. As a consequence, the statement "*wherein the pH of said composition is less than 6.4 and greater than 2.0*", in claim 9, is, at present, considered as not limiting when assessing the novelty of the present

application.

2.3. As a general rule, a feature which is described and highlighted in the application as being an **essential feature** of the invention must be a part of the independent claims defining the invention. Essential features are, in particular, those which are necessary for achieving the technical effect or, expressed differently, for solving the technical problem with which the application is concerned. In the present case, the main technical effect of the application is described as being to provide a more stable composition of the R enantiomer of the thiadiazole derivative in which the undesirable chiral conversion to the less active S enantiomeric form is minimized (cf. page 1, last paragraph). According to the description of the present application, this technical effect is achieved by formulating the composition at a certain pH. This is achieved by including a buffer and/or salt (eg. tartrate, phosphate, citrate, mesylate, sodium sulfate or sodium chloride) as a formulation component (cf. page 4, lines 16-18). The wording of claims 1, 5 and 9, however, does not specify the above-mentioned technical feature (i.e. the buffer and/or salt component) as being part of the claimed composition. Since said technical feature is essential for achieving the intended effect of providing a more stable composition of the R enantiomer of the thiadiazole derivative, the above-mentioned claims are considered to lack essential features (Art. 6 PCT and Rule 6.3(b) PCT). The attention of the applicant is also drawn to the fact that the pH depends on the experimental conditions under which its determination is carried out (eg. temperature during the measurement and type of pH meter which is utilized). In view of the arguments given above, the compositions disclosed in D1 and D2 can at present be construed as novelty destroying against the whole range of pH values claimed in the application.

3. NOVELTY (Art. 33(2) PCT)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-4 is not new in the sense of Article 33(2) PCT.

Document D1 discloses (cf. page 37, table 9, compound 176; page 50 - page 51, example 9) an injection composition comprising (A) N-[4-(2,2-dimethyl-propionyl)-5-((2-ethylamino-ethanesulfonylamino)-methyl)-5-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl]-2,2-dimethyl-propionamide and (B) D-mannitol. The pH of the composition is

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2008/069301

adjusted to 6. It is construed that said composition comprises at least a fraction of the R enantiomer of the thiadiazole derivative. Furthermore, it is stated in the description that optical isomers also fall within the scope of the family of compounds claimed in D1 (cf. page 22, paragraph 82). Therefore, the subject-matter of claims 1-4 is not new in view of D1.

Document D2 discloses (cf. page 37, table 1, compound 9; page 38, table 2, compound I; page 56, example 5; page 60 - page 61, example 13) an injection composition comprising (A) N-[4-(2,2-dimethyl-propionyl)- 5 -((2-ethylamino - ethanesulfonylamino)-methyl)- 5 -phenyl-4,5-dihydro-1,3,4-thiadiazol-2 -yl]-2,2-dimethyl-propionamide and (B) D-mannitol. The pH of the composition is adjusted to 7. It is construed that said composition comprises at least a fraction of the R enantiomer of the thiadiazole derivative. Furthermore, it is stated in the description that optical isomers also fall within the scope of the family of compounds claimed in D2 (cf. page 35, paragraph 53). Therefore, the subject-matter of claims 1-4 is not new in view of D2.

4. INVENTIVE STEP (Art. 33(3) PCT)

4.1. Claims 1-4 being not new are also not inventive (Art. 33(3) PCT).

4.2. Claims 5-12 merely refer to the thiadiazole derivative composition being lyophilized. This comes within the scope of the customary practice followed by persons skilled in the art and the advantages thus achieved can readily be foreseen. Consequently, the subject-matter of claims 5-12 also lacks an inventive step (Art. 33(3) PCT).

5. INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

Claims 1-12 satisfy the criterion of industrial applicability set forth in Article 33(4) PCT.

Re Item VIII

Certain observations on the international application

CLARITY (Art. 6 PCT)

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

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PCT/US2008/069301

Although claims 1, 5 and 9 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/069301

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/19 A61K31/433		
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) A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data bases consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, EMBASE, BIOSIS, 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.
X	EP 1 616 866 A (KYOWA HAKKO KOGYO KK [JP]; FUJI PHOTO FILM CO LTD [JP]) 18 January 2006 (2006-01-18) page 3, line 48 - page 6, line 49 page 22, paragraph 82 page 37; table 9; compound 176 page 50 - page 51; example 9 page 95, paragraph 462	1-12
X	& WO 2004/092147 A (KYOWA HAKKO KOGYO KK [JP]; FUJI PHOTO FILM CO LTD [JP]; MURAKATA CHIKA) 28 October 2004 (2004-10-28) cited in the application	1-12
-/-		
☒ 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 claims 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, each contribution being obvious to a person skilled in the art *S* document member of the same patent family		
Date of the actual completion of the international search 17 September 2008		Date of mailing of the international search report 24/09/2008
Name and mailing address of the ISA European Patent Office, P.O. 5516 Patentien 2 NL - 3200 HW Rijswijk Tel. (+31-70) 510-5516, Tx. 51 631 spa nl, Fax (+31-70) 510-5516		Authorized officer Gómez Gallardo, S

Form PCT/ISA/210 (second entry) (April 2005)

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/069301

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2 602 397 A1 (KYOWA HAKKO KOGYO KK [JP]; FUJIFILM CORP [JP]) 28 September 2006 (2006-09-28) page 8; compound I page 35; paragraph 53 page 37; table 1; compound 9 page 38; table 2; compound L page 56; example 5 page 60 - page 61; example 13 page 73; example 26	1-12
X	& WO 2006/101102 A (KYOWA HAKKO KOGYO KK [JP]; FUJI PHOTO FILM CO LTD [JP]; MURAKATA CHIKA) 28 September 2006 (2006-09-28) cited in the application	1-12

Form PCT/ISA/210 (continuation of PCT/ISA/210) (April 2005)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2008/069301

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1616866	A	18-01-2006	AU 2004230799 A1	28-10-2004
			CA 2522594 A1	28-10-2004
			WO 2004092147 A1	28-10-2004
			KR 20060008903 A	27-01-2006
			US 2007155804 A1	05-07-2007
WO 2004092147	A	28-10-2004	AU 2004230799 A1	28-10-2004
			CA 2522594 A1	28-10-2004
			EP 1616866 A1	18-01-2006
			KR 20060008903 A	27-01-2006
			US 2007155804 A1	05-07-2007
CA 2602397	A1	28-09-2006	AU 2006225636 A1	28-09-2006
			CN 101193878 A	04-06-2008
			EP 1867640 A1	19-12-2007
			WO 2006101102 A1	28-09-2006
			KR 20070113300 A	28-11-2007
			US 2008194653 A1	14-08-2008
WO 2006101102	A	28-09-2006	AU 2006225636 A1	28-09-2006
			CA 2602397 A1	28-09-2006
			CN 101193878 A	04-06-2008
			EP 1867640 A1	19-12-2007
			KR 20070113300 A	28-11-2007
			US 2008194653 A1	14-08-2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-001885- -00000-0000

Fecha: 2010-01-08 16:51:07 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 411 PRESENTACION Folios: 65



ADMISIÓN A TRÁMITE - NUEVAS CREACIONES

PATENTE DE INVENCION ☐

MODELO DE UTILIDAD ☐

Art 33 Decisión 486/00

☐	Indicación que se solicita 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 (De ser el caso formato de descuento)
Completa ☐	Incompleta ☐

FATENTE DE INVENCION PCT ☒

MODELO DE UTILIDAD PCT ☐

Art.33 Decisión 486/00, Circular Única

☒	Indicación que se solicita una PCT
☒	Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
☐	Dibujos de ser estos pertinentes
☒	Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)
Completa ☐	Incompleta ☐

DISEÑO INDUSTRIAL ☐

(Art. 119 Decisión 486/00)

☐	Indicación que se solicita 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 ☐

(Art. 92 Decisión 486/00)

☐	Indicación que se solicita un esquema de trazado
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Representación gráfica de un esquema de trazado
☐	Comprobante de pago de las tasas establecidas
Completa ☐	Incompleta ☐



Bogotá,
2020

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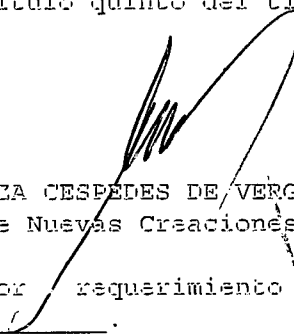
Doctor(a)
OLARTE GARCIA CARLOS PEYNALDO
Apoderado(a) y/o Representante de
ELI LILLY AND COMPANY
KYOWA HAKKO KIRIN CO., LTD.

REFERENCIA	Radicación No.	10 1885
	Solicitud internacional	PCT/US2008/069301
	Fecha inicio fase nacional	12/02/2010
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de
fecha _____
adpall

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Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO

REFERENCIA	Radicación No.	10 1885
	Solicitud internacional	PCT/US2008/069301
	Fecha inicio fase nacional	12/02/2010
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	3009

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 traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT.

2. La solicitud no contiene el poder debidamente otorgado por la sociedad KYOWA HAKKO KIRIN CO., LTD., con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante.

3. El solicitante debe presentar un nuevo título que permita identificar la materia de la cual trata la solicitud, ya que el título relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular Única 5.2.9)

4. 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, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

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

Continúa en la página siguiente...

Al contestar favor indique el número de radicación consignado en el rótulo

Sede Centro: Carrera 12 No. 27-00 pisos 2, 5, 7 y 10 PBX: 5870000
Sede CAN: Av. Carrera 50 No. 26 - 55 int. 3. Tel 5830070
Call Center 6513240. Línea 01800-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. Colombia



Radicación No.: 10 1885



Industria y Comercio
SUPERINTENDENCIA

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considerará abandonada y perderá su prelación.

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

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de
fecha 05 MAR. 2010
adpall

Al contestar favor indique el número
de radicación consignado en el rótulo

Sede Centro: Carrera 13 No. 27-00 pisos 2, 5, 7 y 10 PBX: 5870000
Sede CAN: Av. Carrera 50 No. 26 - 55 int.2. Tel 5880070
Call Center 6512240. Línea 01800-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. Colombia