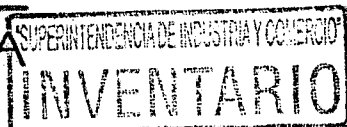




PCT

Industria y Comercio

SUPERINTENDENCIA



SOLICITUD PATENTE DE INVENCION

10-55387

21. EXPEDIENTE N°

54. TÍTULO PROCEDIMIENTO MEJORADO PARA PREPARAR 2-

(FENIL SUSTITUIDO)-2-HIDROXI-ETIL CARBAMATOS.

51. CLASIFICACIÓN INTERNACIONAL C07C 29/147

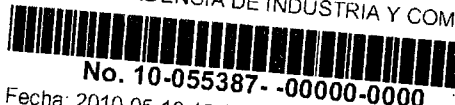
71. SOLICITANTE JANSSEN PHARMACEUTICA N.V.

DOMICILIO Beerse, Bélgica.

74. APODERADO DILIA MARIA RODRIGUEZ D'ALEMAN

22. BOGOTÁ, D.C. _____

Can
18-05-2010



**FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL**

SOLICITUD DE:

1

☒

Patente de Invención

☐

Patente de Modelo de Utilidad

☒

Capítulo I

☐

Capítulo II

2

**SOLICITANTE
(71)**

Nombre: **JANSSEN PHARMACEUTICA
N.V.**

Dirección: Turnhoutseweg 30, B-2340
Beerse, Bélgica.

Nacionalidad o Domicilio: Beerse, Bélgica.

Lugar de Constitución : Bélgica

Teléfono:

Fax:

E-mail

IDENTIFICACIÓN

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Número

3

**REPRESENTANTE
O APODERADO
(74)**

Nombre: **DILIA MARIA RODRIGUEZ
D'ALEMAN**

Dirección: Cra. 11 No. 86-53 piso 6

Teléfono: 6 162051/61 Fax: 6 161889

E-mail: clarkemodet@clarkemodet.com.co

IDENTIFICACIÓN

C.C.

☒

NIT

☐

C.E.

☐

Otro

☐

Número 41.654.882

T.P 20824 CSJ

4

**INVENTOR (ES)
(72)**

Nombre: **PORSTMANN, Frank y
MEIER, Thomas**

Dirección: Tubackackerstr. 34, ch-8234 Stetten, Suiza y
Feldstrasse 9, CH-8200 Schaffhausen, Suiza

Nacionalidad o domicilio: Suizos

5

PCT (86)

Solicitud Internacional No. PCT/IB2008/003300 Fecha 18 de octubre de 2008

Publicación Internacional No. WO 2009/050587 A1 Fecha 23 de abril de 2009

6 TÍTULO (54) PROCEDIMIENTO MEJORADO PARA PREPARAR 2-(FENIL SUSTITUIDO)-2-HIDROXI-ETIL CARBAMATOS.

7 Clasificación Internacional (51)

C07C 29/147

8 Prioridad

SI ☒ NO ☐

(33) País de Origen

Estados Unidos de América

(32) Fecha

18 de octubre de 2007

(31) Número de Solicitud

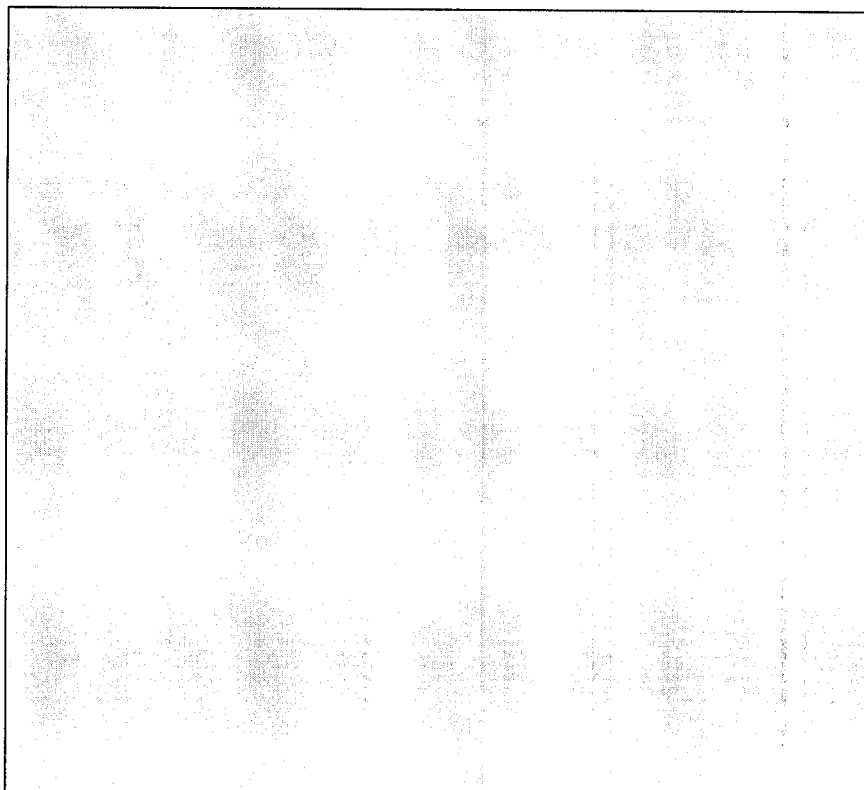
60/980,877

9 Comprobante de pago No. 10 - 24,885

Fecha 5 de abril de 2010

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona
- ☒ Poderes si fuere el caso
- ☐ 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 de 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 deposito 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 *Opinión escrita.

11 FIGURA CARACTERÍSTICA



12 Solicito la concesión de la patente

NOMBRE: DILIA MARIA RODRIGUEZ D'ALEMAN

FIRMA: [Signature]

C.C. 41.654.882

T.P. 20824 CSJ

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 24,885
FECHA : ABRIL 5 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-055387- -00000-0000

Fecha: 2010-05-10 15:15:44 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 63

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO DE BOGOTA	062754387	353190121	31/03/2010	84,780,000.00

***** 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. _____

P-2546
2

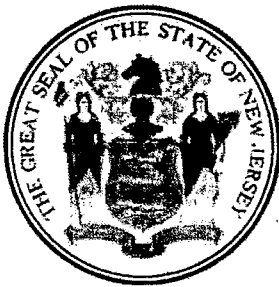
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
AMANDA LIN HAYNES
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
AMANDA LIN HAYNES, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 24TH DAY OF JUNE 2009
7. BY: R. David Rousseau, NEW JERSEY TREASURER
8. NO: A367051
9. SEAL/STAMP:
10. SIGNATURE

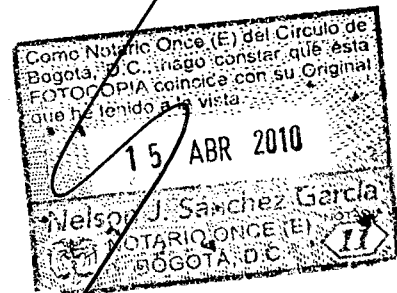


Certificate Number: 1146991910

Verify this certificate at

https://www1.state.nj.us/TYTR_StandingCert/JSP/Verify_Cert.jsp

A handwritten signature in black ink, appearing to be "R. David Rousseau", written over a horizontal line.



COLOMBIA

Carrera 11 N° 86-53 Piso 6 Bogotá Colombia Tel: (57 1) 6181088 Fax: (57 1) 6350824 Email: info@clarkemodet.com.co

PODER

Yo (nosotros), abajo firmante(s)

en mi (nuestro) carácter de representante(s) legales de JANSSEN
PHARMACEUTICA NV

una sociedad organizada y existente de acuerdo con las leyes de

y en actual cumplimiento de su objeto social, con domicilio en Turnhout-
seweg 30, B-2340 Beerse, Bélgica.

por el presente instrumento confiero (conferimos) poder especial a favor de
DILIA MARIA RODRIGUEZ D'ALEMAN, con Cédula de Ciudadanía
No. 41.654.882 de Bogotá, y tp. 20824 y CLAUDIA LUCIA CARO
RAMIREZ, con Cédula de Ciudadanía No. 40.017.374 de Tunja, y tp.
36448, con domicilio en Bogotá, Colombia, para que actuando en su orden
en nombre del (de la) otorgante le (la) representen ante cualquier entidad,
autoridad y/o persona, especialmente ante las del orden Administrativo,
Contencioso Administrativo, Judicial, Tribunales de Arbitramento y/o
cualquier otro en lo referente a los siguientes asuntos:

- 1) Solicitar, tramitar, obtener y/o registrar cualquiera de las modalidades de
Propiedad Industrial, tales como: patentes de invención, modelos de
utilidad; diseños industriales, variedades vegetales; marcas, lemas, nombres
y enseñanzas comerciales y denominaciones de origen; así como sus renovacio-
nes, prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y
licencias.
- 2) Solicitar, tramitar, obtener y/o registrar derechos de autor, en cualquiera
de sus presentaciones así como la protección de secretos industriales y
know-how.
- 3) Solicitar, tramitar, obtener y/o registrar registros sanitarios, permisos y/o
licencias de funcionamiento; así como sus renovaciones o prórrogas,
transferencias, cambios de nombre y/o domicilio, contratos y licencias.
- 4) Ejercer acciones de oposición, observación, reclamos, reconsideración,
reposición, apelación, cancelación administrativa o judicial, nulidad,
protección al consumidor, concesión de licencias, protección de secretos
industriales y demás acciones y recursos relacionados con derechos
derivados de los asuntos arriba indicados y en contra de la competencia
desleal, acciones derivadas de la obtención o explotación de licencias,
acciones de indemnización de perjuicios. También podrá(n) intervenir en
juicios civiles, comerciales, penales, contencioso-administrativos, tutelas y
de policía; en acciones o juicios promovidos por el (la) mandante o en
contra el (ella).
- 5) Registrar nombres de dominio ante la entidad competente.
- 6) En el ejercicio de este mandato los mandatarios arriba mencionados
quedan facultados para: conciliar, cancelar, transigir, comprometer en
árbitros, desistir, recibir y tomar posesión de la cosa objeto de litigio y
renunciar o desistir a derechos concedidos o en curso de concesión, admitir
los hechos del proceso.
- 7) Ratificar o no la agencia oficiosa.
- 8) Así mismo faculta (facultamos) a los mencionados apoderados para
recibir notificaciones y designar apoderados judiciales o extrajudiciales,
sustituir el presente poder y revocar las sustituciones que hicieren.

Dado y firmado en

a los días de

on this 27TH

Firma / signature

PETER L HERRIDGE, POWER OF ATTORNEY

POWER OF ATTORNEY

I (we), the undersigned PETER L HERRIDGE

legal representative(s) of de JANSSEN PHARMACEUTICA NV

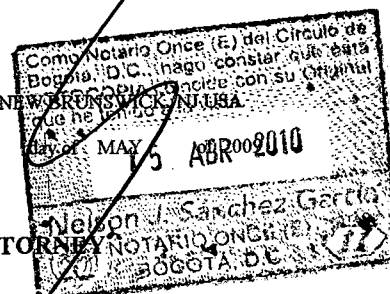
an organization existing under the laws of BELGIUM

and in present execution of its business activity, domiciled Turnhoutseweg 30,
B-2340 Beerse, Belgium.

do hereby grant POWER OF ATTORNEY to DILIA MARIA RODRIGUEZ
D'ALEMAN, identification card No. 41.654.882 of Bogotá, and tp. 20824 and
CLAUDIA LUCIA CARO RAMIREZ, tp. 36448, identification card No.
40.017.374 of Tunja, residing in Bogotá, Colombia, to act in the order of their
appointment in behalf of grantor before any entity, authority and/or natural or
juridical person, specially before those Administrative, Administrative-
Contentious, Judicial, arbitration courts, and/or any other, in all matters
concerning the following:

- 1) To apply, process, obtain and/or register any of the modalities of Industrial
Property, such as: Patents of Invention, Utility Models; Designs, plant varieties;
Marks, Slogans, Trade Names and emblems and appellations of Origin; as well as
their renewals, assignments, changes of name and/or domicile, agreements and
licenses.
- 2) To apply, process, obtain and/or register copyrights of any kind as well as
protection of industrial secrets or know-how.
- 3) To apply, process, obtain and/or register sanitary registrations, operating
authorizations and/or licenses; as well as their renewals or assignments, changes
of name and/or domicile, agreements and licenses.
- 4) To bring actions of opposition, observations, claims, reconsideration, appeal or
legal remedies, cancellations, nullity, protection to the consumer, granting of
licenses, protection of trade secrets and other actions related with rights derived
from the above-mentioned matters and against the unfair competition, actions
resulting from the obtaining or exploitation of licenses, recovering damages
actions. They can also intervene or participate in Civil, Commercial, Criminal or
Contentious-Administrative Trials; the actions for writ mandamus, police
actions; in actions, lawsuits or litigations instituted by the grantor or against him.
- 5) To register domain names before the competent entity.
- 6) To the effect of this mandate the above-named proxy are empowered to:
conciliate, cancel, settle, submit to arbitration, withdraw and to receive and take
possession of the litigation related object and waive or renounce the rights granted
or in process of granting, admit the facts of the case.
- 7) To ratify or not the officious agency.
- 8) I (we) hereby appoint the afore mentioned attorneys with powers to receive
notifications and to designate judicial and extrajudicial attorneys, substitute this
Power of Attorney and to revoke such substitutions.

Granted and signed at NEW YORK, N.Y. USA



CERTIFICADO NOTARIAL

(Cuando el solicitante es SOCIEDAD)

(Poderes otorgados en: El Salvador, Estados Unidos, México y Venezuela)

A los _____ días del mes de _____ de _____
el Notario que suscribe DA FE de que:

1. _____
(nombre de la persona que firma el poder)

mayor de edad y domiciliado en _____
_____ firmó de su puño
y letra el documento que antecede.

2. Conoce al (a la) otorgante y que este (a) está legalmente capacitado para el otorgamiento.

3. El otorgante ha firmado el referido documento en su carácter de _____
de la persona jurídica de de JANSSEN PHARMACEUTICA NV

4. La citada persona jurídica con sede en Turnhoutseweg 30, B-2340 Beerse, Belgium, está legalmente constituida, que tiene actualmente existencia legal y que el acto para el cual se ha otorgado este poder está comprendido entre los que constituyen su objeto social.
5. El otorgante tiene efectivamente la representación que ostenta, que esta es legítima y que está facultado para otorgar este poder.
6. las anteriores certificaciones de los puntos 3, 4 y 5, me constan porque he tenido a la vista los documentos auténticos.

AMANDA LIN HAYNES
NOTARY PUBLIC OF NEW JERSEY
Commission Expires 10/28/2013

NOTA: A continuación de lo anterior, el Cónsul de Colombia debe autenticar la firma del Notario Público.

CERTIFICADO NOTARIAL (Cuando el solicitante es INDIVIDUO)

A los _____ días del mes de _____ de _____
el Notario que suscribe DA FE de que:

1. _____
(nombre de la persona que firma el poder)

mayor de edad y domiciliado en _____
_____ firmó en su presencia

el documento que antecede, conoce al otorgante y que este está legalmente capacitado para el otorgamiento.

Notario Público

NOTA: A continuación de lo anterior, el Cónsul de Colombia debe autenticar la firma del Notario Público.

Para todos los demás países el Señor Cónsul de Colombia o ante quien se otorgue, debe expedir una certificación dejando constancia 1) de la existencia legal de la sociedad, 2) de que esta ejerce actualmente su objeto social, y 3) de que la persona o personas que otorgan el poder están facultadas para hacerlo, dejando constancia así mismo de que tuvo a la vista las pruebas que acrediten tales circunstancias.

**LEGALIZACIÓN POR EL CONSUL DE COLOMBIA
O POR APOSTILLA**

NOTARIAL CERTIFICATE

(When the applicant is a CORPORATION)

(Powers of attorney granted in: El Salvador, Mexico, U.S.A. and Venezuela)

This 27 day of MAY, 2009
the undersigned Notary CERTIFIES that:

1. PETER L. HERRIDGE
(name of the person who signs the power of attorney)

of legal age and domiciled in NEW BRUNSWICK, NJ USA set his hand on the foregoing document.

2. The grantor is to him personally known and that he/she has legal capacity to execute the document.

3. The grantor has executed the foregoing document in his capacity of POWER OF ATTORNEY
of the juridical JANSSEN PHARMACEUTICA NV

4. The mentioned juridical person with place of Turnhoutseweg 30, B-2340 Beerse, Belgium, is duly organized, has actual legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. The grantor has in fact the referred quality and that his/her representation is legal and that he/she is empowered to grant this power of attorney.

6. I have based the above certifications 3, 4 and 5, on the authentic documents which for such purpose were exhibited to me.


Notary Public

NOTA: Then the Colombian Consul must legalize the signature of the Notary Public.

NOTARIAL CERTIFICATE (When the applicant is an INDIVIDUALS)

On this _____ day of _____
the undersigned Notary CERTIFIES that:

1. _____
(name of the person who signs the Power of Attorney)

of legal age and domiciled at _____

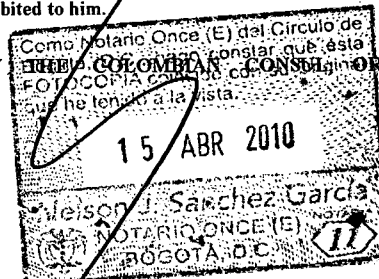
signed in his presence the foregoing document, the grantor is to him personally known and that he/she has legal capacity to execute the document.

Notary Public

NOTA: Then the Colombian Consul must legalize the signature of the Notary Public.

For all other countries the Colombian Consul or before who it is granted must issue a certification stating 1) the legal existence of the corporation, 2) that the corporate purposes are actually being accomplished, 3) that the person or persons who grant this Power of Attorney are empowered to do it. The Consul will certify also that the documents evidencing those circumstances were exhibited to him.

**LEGALIZATION BY _____ BY _____
APOSTILLE.**



5

Traducción oficial hecha por Jimena Escobar Uribe, traductora e intérprete oficial según resolución No. 0369 del Ministerio de Justicia, del documento legalizado mediante la **APOSTILLA** No. A-367051 de 24 de junio de 2009 expedida en Estados Unidos de América (Nueva Jersey) correspondiente a un documento de poder y una certificación notarial en inglés con su correspondiente traducción al español (razón por la cual no se hace su traducción), otorgado a la sociedad **JANSSEN PHARMACEUTICA NV.**, domiciliada en Beerse, Bélgica

Documento de poder firmado el 27 de mayo de 2009 por Peter L. Herridge, con poder de Abogado.

Sello notarial: Amanda Lin Haynes, Notario Público de Nueva Jersey, comisión termina el 10/28/2013.

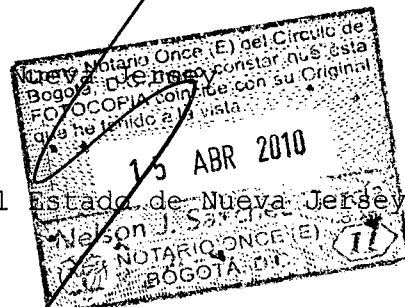
APOSTILLA

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

1. País: Estados Unidos de América
2. Este documento público ha sido firmado por AMANDA LIN HAYNES
3. Actuando en su calidad de Notario Público de Nueva Jersey
4. Lleva el sello/estampilla de AMANDA LIN HAYNES, notario

CERTIFICADO

5. En Trenton, Nueva Jersey
6. El 24 de junio de 2009
7. Por R. David Rousseau, Tesorero de
8. Certificado No. A367051
9. Sello/Estampilla: El Gran Sello del Estado de Nueva Jersey



Jimena Escobar Uribe
JIMENA ESCOBAR URIBE
Traductor e Intérprete Oficial
Resolución No. 0369 Min. Justicia 1995

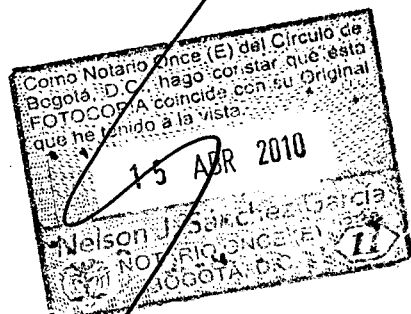
10. Firma: Firma ilegible

Número de certificado: 1146991910

Verifique este certificado en línea:

<https://www1.state.nj.us/TYTR StandingCert/JSP/Verify Cert.jsp>

Jimena
JIMENA ESCOBAR URIBE
Traductor e Intérprete Oficial
Resolución No. 0369 Min. Justicia 1995



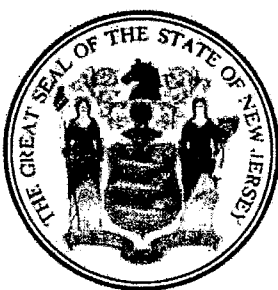
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
GERALDINE A BAILEY
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
GERALDINE A BAILEY, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 13TH DAY OF JULY 2009
7. BY: R. David Rousseau, NEW JERSEY TREASURER
8. NO: A368604
9. SEAL/STAMP:
10. SIGNATURE

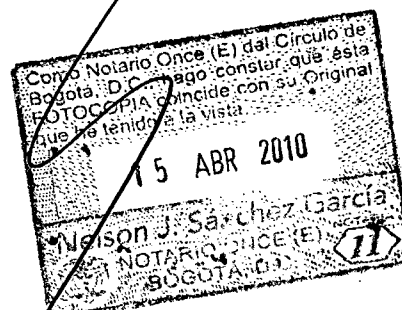


Certificate Number: 1148251010

Verify this certificate at

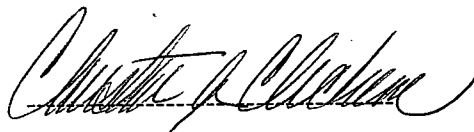
https://www1.state.nj.us/TYTR_StandingCert/JSP/Verify_Cert.jsp

A handwritten signature in ink, appearing to read "Nelson J. Sanchez Garcia", written over a horizontal line.



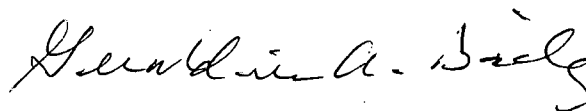
CERTIFICATION

I certify that **Peter L. Herridge**, Power of Attorney of **Janssen Pharmaceutica NV**, a corporation existing, duly organized and complying with its corporate purposes in conformity with the laws of **Belgium**, whose home office is located in **Beerse, Belgium**. I further certify that said individual is duly authorized to sign any and all instruments in his capacity as officer of the company and that the purposes for which are within the scope of the objects or activities of said corporation.



Sworn to and subscribed
before me this

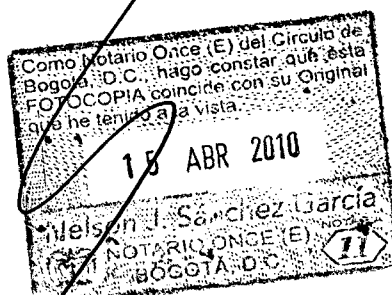
18th day of July, 2009



GERALDINE A. BAILEY
NOTARY PUBLIC OF NEW JERSEY
Commission Expires 1/14/2014

**Esta certificación notarial debe ser llenada en su totalidad y legalizarse por
Apostilla**

This notarial certification must be filled in completely and be legalized by Apostille



Traducción oficial hecha por Jimena Escobar Uribe, traductora e intérprete oficial según resolución No. 0369 del Ministerio de Justicia, del documento legalizado mediante la **APOSTILLA** No. A-368604 de 13 de julio de 2009 expedida en Estados Unidos de América (Nueva Jersey) correspondiente a una certificación notarial relacionada con la sociedad **JANSSEN PHARMACEUTICA.**, domiciliada en Beerse, Bélgica.

CERTIFICACIÓN

Yo certifico que Peter L. Herridge, con Poder de Abogado de Janssen Pharmaceutica NV, una sociedad existente, debidamente constituida y cumpliendo con sus objetos corporativos de acuerdo con las leyes de Bélgica, cuya casa matriz está localizada en Beerse, Bélgica. Además certifico que dicho individuo está debidamente autorizado para firmar cualquier y todos los instrumentos en su capacidad como funcionario de la sociedad y que los propósitos para los cuales están dentro del espectro de los objetivos o actividades de dicha sociedad.

Firmado: Firma ilegible

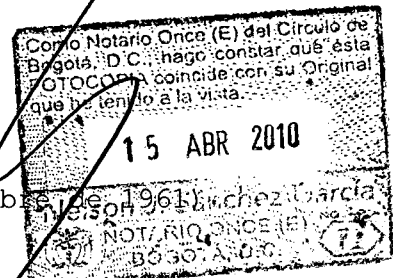
Sello: Juramentado y suscrito ante mí este día 10 de julio de 2009.

Firmado: Geraldine A. Bailey, notario público de Nueva Jersey, comisión termina 1/14/2014.

APOSTILLA

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

1. País: Estados Unidos de América



Jimena Escobar Uribe
JIMENA ESCOBAR URIBE
Traductor Intérprete Oficial
Resolución No. 0369 Min. Justicia 1995

2. Este documento público ha sido firmado por GERLADINE A. BAILEY

3. Actuando en su calidad de Notario Público de Nueva Jersey

4. Lleva el sello/estampilla de GERLADINE A. BAILEY, notario

CERTIFICADO

5. En Trenton, Nueva Jersey

6. El 13 de julio de 2009

7. Por R. David Rousseau, Tesorero de Nueva Jersey

8. Certificado No. A368604

9. Sello/Estampilla: El Gran Sello del Estado de Nueva Jersey

10. Firma: Firma ilegible

Número de certificado: 1148251010

Verifique este certificado en línea:

<https://www1.state.nj.us/TYTR StandingCert/JSP/Verify Cert.jsp>

Monder
JIMENA ESCOBAR URBEL
Traductor - Intérprete Oficial
Resolución No. 0369 Min. Justicia 1998

RECEIVED
REGISTRATION
DIVISION
JUL 14 2009

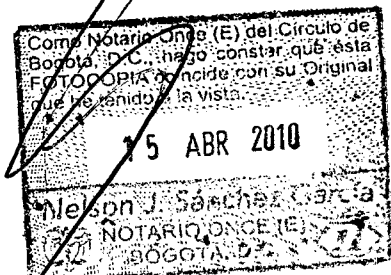
018434

JIMENA ESCOBAR
JUL 14 2009

MINISTERIO DE
RELACIONES EXTERIORES

2009 AGO -6 A 10:27

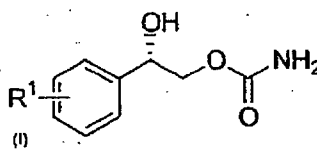
BOGOTÁ, D.C.



11

RESUMEN

La presente invención se refiere a un procedimiento de preparación de un compuesto de Fórmula I:



Fórmula I

en la que R se define en la memoria descriptiva. Los compuestos de Fórmula I son útiles para tratar trastornos del sistema nervioso central, incluyendo la epilepsia. El procedimiento incluye un nuevo uso del reactivo borohidruro de

10 litio.

**PROCEDIMIENTO MEJORADO PARA PREPARAR 2-(FENIL SUSTITUIDO)-
2-HIDROXI-ETIL CARBAMATOS**

Referencia Cruzada con las Solicitudes Relacionadas

- 5 Esta solicitud reivindica la prioridad de los beneficios de la presentación de la Solicitud Provisional de Estados Unidos con N° de Serie 60/980.877, presentada el 18 de octubre de 2007. Las divulgaciones completas de la solicitud de patente de Estados Unidos relacionada mencionada anteriormente se incorporan en el presente documento por referencia para todos los
- 10 propósitos.

Breve Descripción de la Invención

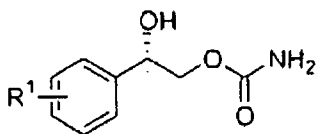
La presente invención se refiere a un nuevo procedimiento para preparar (S)-(+)-2-(fenil sustituido)-2-hidroxi-etil carbamatos y a nuevos intermedios usados en este procedimiento.

15 Antecedentes de la Invención

- Los 2-(fenil sustituido)-2-hidroxi-etil carbamatos y sus isómeros se han descrito en los documentos US 5.698.588, US 5.854.283, US 6.127.412, US 6.103.759, WO 97/26241 y WO 03/053916 como compuestos útiles para tratar trastornos del sistema nervioso central. Estos trastornos incluyen convulsiones,
- 20 epilepsia, ictus, espasmos musculares, dolor neuropático y migraña. Un trastorno preferido es la epilepsia.

Sumario de la Invención

La presente invención se refiere a un procedimiento de preparación de un compuesto de Fórmula I:

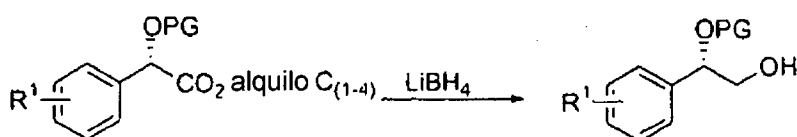


Fórmula I

en la que:

R¹ se selecciona entre el grupo constituido por Cl, F y Br;

- 5 comprendiendo dicho procedimiento el uso de borohidruro de litio para reducir el intermedio de éster de Fórmula II para dar un alcohol de Fórmula III, que se lleva a reacciones posteriores para convertirlo en un compuesto de Fórmula I.



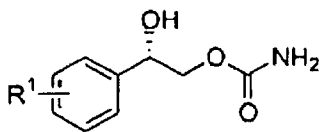
Fórmula II

Fórmula III

- en las que PG es un grupo protector obtenido a partir de un éter,
10 seleccionándose dicho éter entre el grupo constituido por 2-metoxi-1-propeno, dihidropirano, metil vinil éter, etil vinil éter y 5,6-dihidro-4-metoxi-2H-pirano.

Descripción Detallada de la Invención

La presente invención se refiere a un procedimiento de preparación de un compuesto de Fórmula I:



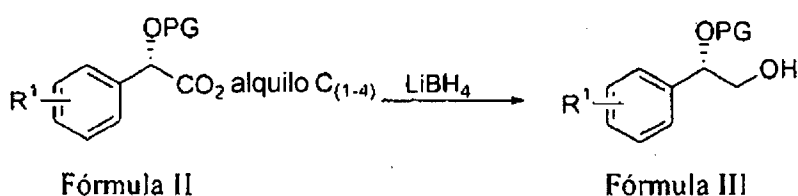
15

Fórmula I

en la que:

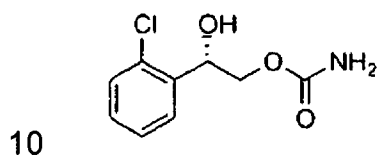
R¹ se selecciona entre el grupo constituido por Cl, F y Br;

comprendiendo dicho procedimiento el uso de borohidruro de litio para reducir el intermedio de éster de Fórmula II para dar un alcohol de Fórmula III, que se lleva a reacciones posteriores para convertirlo en un compuesto de Fórmula I.

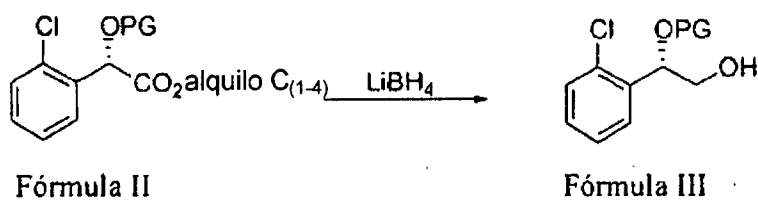


- 5 en las que PG es un grupo protector obtenido a partir de un éter, seleccionándose dicho éter entre el grupo constituido por 2-metoxi-1-propeno, dihidropirano, metil vinil éter, etil vinil éter y 5,6-dihidro-4-metoxi-2H-pirano.

En otra realización, la presente invención se refiere a un procedimiento de preparación de 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico:

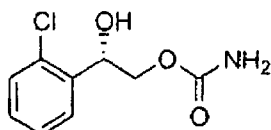


- 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico, comprendiendo dicho procedimiento el uso de borohidruro de litio para reducir el intermedio de éster de Fórmula II para dar un alcohol de Fórmula III, que se lleva a reacciones posteriores para que se convierta en 2-(2-cloro-fenil)-2-hidroxi-etil
- 15 éster del ácido (S)-carbámico.



en las que R¹ es 2-cloro y PG es como se ha definido en la Fórmula II.

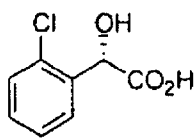
En otra realización, la presente invención se refiere a un procedimiento de preparación de 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico:



2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico

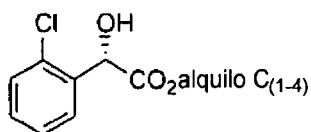
- 5 comprendiendo dicho procedimiento el uso de las etapas a, b y c que se describen a continuación:

a) esterificación de ácido (S)-(2-cloro-fenil)-hidroxi-acético,



ácido (S)-(2-cloro-fenil)-hidroxi-acético

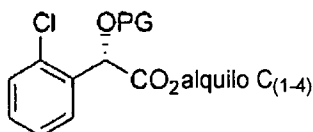
- 10 con un alcohol $C_{(1-4)}$, seleccionado entre el grupo constituido por: metanol, etanol, n-propanol, iso-propanol, n-butanol, iso-butanol, sec-butanol y terc-butanol: caracterizándose dicha esterificación por el uso de: de 0,025 a 0,4 equivalentes de oxiclورو de fósforo para obtener un éster de Fórmula IV.



- 15 Fórmula IV

b) protección del resto alcohol de un compuesto de Fórmula IV, en la que dicha protección se caracteriza por el uso de catálisis ácida controlada por dejar el ácido del oxiclورو de fósforo de la reacción anterior y un éter seleccionado entre el grupo constituido por: 2-metoxi-1-propeno, dihidropirano, metil vinil

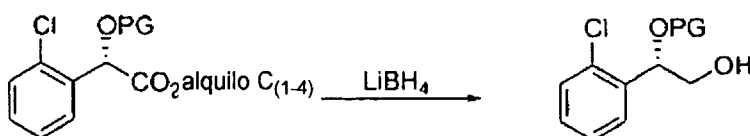
éter, etil vinil éter y 5,6-dihidro-4-metoxi-2H-pirano para obtener un compuesto de Fórmula II,



Fórmula II

5 en la que R¹ es 2-cloro y PG es como se ha definido en Formula II.

c) Uso de borohidruro de litio para reducir el intermedio de éster de Fórmula II para dar un alcohol de Fórmula III, que se lleva a reacciones posteriores para convertirlo en 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico.

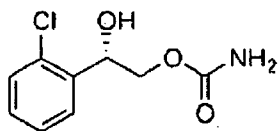


Fórmula II

Fórmula III

10 en las que R¹ es 2-cloro y PG es como se ha definido en la Fórmula II.

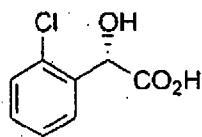
En otra realización, la presente invención se refiere a un procedimiento de preparación de 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico



2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico

15 comprendiendo dicho procedimiento el uso de las etapas a, b, c, d, e, f y g que se describen a continuación:

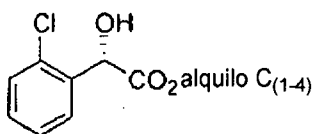
a) esterificación de ácido (S)-(2-cloro-fenil)-hidroxi-acético,



ácido (S)-(2-cloro-fenil)-hidroxi-acético

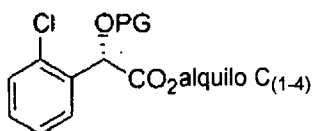
con un alcohol $C_{(1-4)}$, seleccionado entre el grupo constituido por: metanol, etanol, n-propanol, iso-propanol, n-butanol, iso-butanol, sec-butanol y terc-

- 5 butanol: caracterizándose dicha esterificación por el uso de: de 0,025 a 0,4 equivalentes de oxiclورو de fósforo para obtener un éster de Fórmula IV.



Fórmula IV

- b) protección del resto alcohol de un compuesto de Fórmula IV, en la que dicha
- 10 protección se caracteriza por el uso de catálisis ácida controlada por dejar el ácido del oxiclورو de fósforo de la reacción anterior y un éter seleccionado entre el grupo constituido por: 2-metoxi-1-propeno, dihidropirano, metil vinil éter, etil vinil éter y 5,6-dihidro-4-metoxi-2H-pirano para obtener un compuesto de Fórmula II

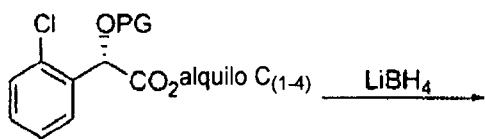


15

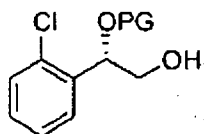
Fórmula II

en la que R^1 es 2-cloro y PG es como se ha definido en la Fórmula II.

- c) Uso de borohidruro de litio para reducir el intermedio de éster de Fórmula II para dar un alcohol de Fórmula III.



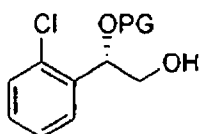
Fórmula II



Fórmula III

en las que R¹ es 2-cloro y PG es como se ha definido en la Fórmula II.

d) Reacción de un alcohol de Fórmula III



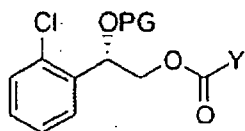
5 Fórmula III

con un compuesto de carbonilo,



en el que X e Y son grupos salientes seleccionados independientemente entre el grupo constituido por bromo, cloro, imidazolilo y fenoxi;

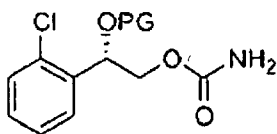
10 caracterizándose dicha reacción por una temperatura de la reacción: de -10 a 65°C, para producir un compuesto de carbonilo de Fórmula V.



Fórmula V

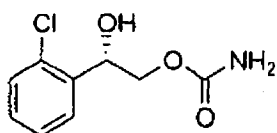
e) Reacción de un compuesto de Fórmula V con hidróxido de amonio o

15 amoníaco, caracterizándose dicha reacción por temperatura de la reacción: de 0 a 55°C para formar el carbamato de Fórmula VI.



Fórmula VI

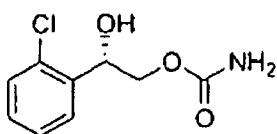
- f) La desprotección del carbamato de Fórmula VI, caracterizándose dicha desprotección por el uso de un ácido seleccionado entre el grupo constituido por ácido fosfórico, ácido clorhídrico y ácido sulfúrico para formar 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico



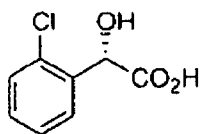
2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico

- g) Recristalización del 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico, caracterizándose dicha recristalización por un gradiente de refrigeración controlada.

En otra realización, la presente invención se refiere a un procedimiento de preparación de 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico



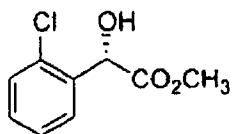
- 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico comprendiendo dicho procedimiento el uso de las etapas a, b y c que se describen a continuación:
- a) Metilesterificación de ácido (S)-(2-cloro-fenil)-hidroxi-acético,



ácido (S)-(2-cloro-fenil)-hidroxi-acético

caracterizándose dicha esterificación por el uso de 0,1 equivalentes de oxicloruro de fósforo para obtener éster metílico del ácido (S)-(2-cloro-fenil)-

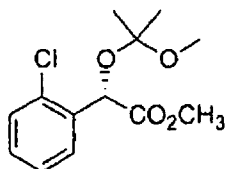
5 hidroxi-acético.



éster metílico del ácido (S)-(2-cloro-fenil)-hidroxi-acético

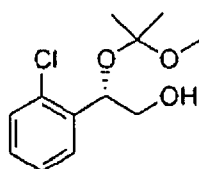
b) protección de éster metílico del ácido (S)-(2-cloro-fenil)-hidroxi-acético, caracterizándose dicha protección por el uso de catálisis ácida controlada por

10 dejar el ácido del oxicloruro de fósforo de la reacción anterior y 2-metoxi-1-propeno, para obtener éster metílico del ácido (S)-(2-cloro-fenil)-(1-metoxi-1-metil-etoxi)-acético.



éster metílico del ácido (S)-(2-cloro-fenil)-(1-metoxi-1-metil-etoxi)-acético

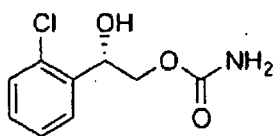
15 c) reducción de éster metílico del ácido (S)-(2-cloro-fenil)-(1-metoxi-1-metil-etoxi)-acético, caracterizándose dicha reducción por el uso de LiBH_4 , para obtener (S)-2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etanol, que se lleva a reacciones posteriores para convertirlo en 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico.



(S)-2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etanol

En otra realización de la invención, la presente invención se refiere a un procedimiento de preparación de 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido

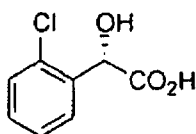
5 (S)-carbámico:



2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico

comprendiendo dicho procedimiento el uso de las etapas a, b, c, d, e, f y g que se describen a continuación:

10 a) metilesterificación de ácido (S)-(2-cloro-fenil)-hidroxi-acético:

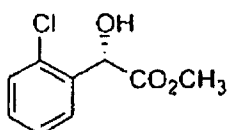


ácido (S)-(2-cloro-fenil)-hidroxi-acético

caracterizándose dicha metilesterificación por el uso de:

- 10 equivalentes de metanol,
- 15 0,1 equivalentes de oxiclورو de fósforo,
- temperatura de la reacción: de 40 a 50°C,
- concentración parcial, y
- co-disolvente de tolueno;

para obtener éster metílico del ácido (S)-(2-cloro-fenil)-hidroxi-acético.



éster metílico del ácido (S)-(2-cloro-fenil)-hidroxi-acético

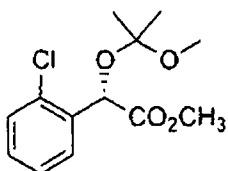
b) protección de éster metílico del ácido (S)-(2-cloro-fenil)-hidroxi-acético,

5 caracterizándose dicha protección por el uso de:

catálisis ácida controlada por dejar el ácido del oxicloruro de fósforo de la etapa anterior, adición de 1,6 equivalentes de isopropenil metil éter a la mezcla de reacción, y

1 extracción con agua;

10 para obtener éster metílico del ácido (S)-(2-cloro-fenil)-(1-metoxi-1-metil-etoxi)-acético.



éster metílico del ácido (S)-(2-cloro-fenil)-(1-metoxi-1-metil-etoxi)-acético

c) reducción de éster metílico del ácido (S)-(2-cloro-fenil)-(1-metoxi-1-metil-

15 etoxi)-acético, caracterizándose dicha reducción por el uso de:

LiBH_4 ,

disolventes: disolventes apróticos tales como éteres, por ejemplo, THF, éter dietílico y similares,

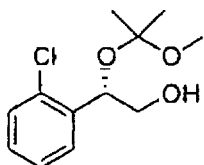
hidrocarburos tales como, por ejemplo, tolueno,

20 tratamiento con cetonas tales como, por ejemplo, acetona,

temperatura de la reacción: de 40 a 50°C,

destilación de THF y acetona, e isopropanol (el último formado durante el procedimiento de trabajo por reducción de acetona)

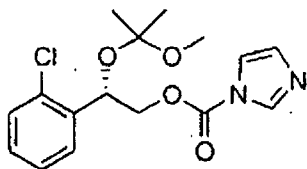
2 extracciones con solución de hidróxido sódico y solución de NaCl; para obtener (S)-2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etanol.



5

(S)-2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etanol

e) reacción de 2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etil éster del ácido (S)-imidazol-1-carboxílico



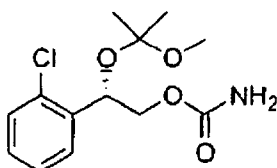
10 2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etil éster del ácido (S)-imidazol-1-carboxílico

con hidróxido de amonio, caracterizándose dicha reacción por

1,60 equivalentes de hidróxido de amonio, y

temperatura de la reacción: de 40 a 50°C

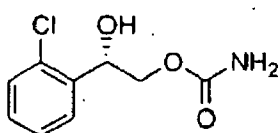
15 para formar 2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etil éster del ácido (S)-carbámico.



2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etil éster del ácido (S)-carbámico

f) desprotección de 2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etil éster del ácido (S)-carbámico, caracterizándose dicha desprotección por adición de 2 equivalentes de ácido sulfúrico ac., y temperatura de la reacción: de 40 a 50°C

5 para formar 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico.



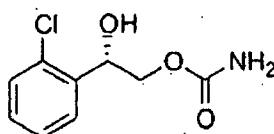
2-(2-cloro-fenil)-2-hidroxi-etil éster de ácido (S)-carbámico

g) recristalización de 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico, caracterizándose dicha recristalización por

10 metanol/agua 1:4, y uso de un gradiente de temperatura controlada.

Ejemplos:

Los siguientes ejemplos ilustran las realizaciones de la invención, y

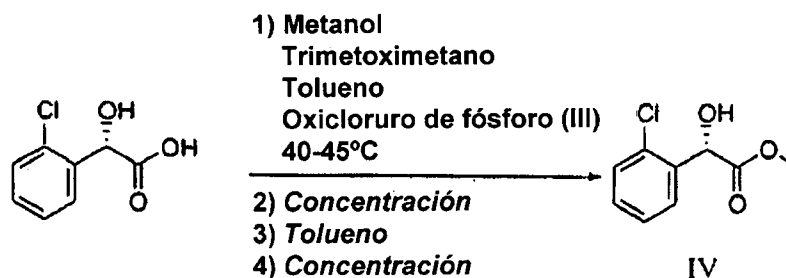


como se aplican a la síntesis de

se puede usar 2-(2-cloro-

15 fenil)-2-(1-metoxi-1-metil-etoxi)-etil éster del ácido (S)-carbámico en lugar de la fórmula del texto.

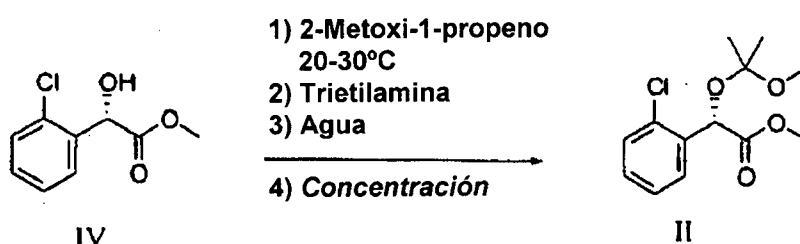
Ejemplo 1



Un recipiente de reacción se cargó con 300 kg (1607,8 mol) de ácido (S)-2-cloromandélico, 519 kg (16199 mol) de metanol, 24,6 kg (160,4 mol) de tricloruro fosfórico, 190 kg (1790,4 mol) de trimetoximetano y 672 kg de tolueno y se calentó de 40 a 50°C, después de lo cual se formó una solución transparente. La solución se concentró parcialmente al vacío hasta que se retiraron aproximadamente 708 kg de disolventes. Se añadieron 708 kg más de tolueno y la destilación al vacío se repitió hasta que se retiraron de nuevo 708 kg de disolventes. El éster IV se transfirió a la siguiente etapa de reacción en forma de una solución en tolueno.

La concentración parcial de la solución de tolueno, a diferencia de la retirada total del metanol en forma de reactivo/disolvente y tolueno como disolvente, proporcionó el beneficio de evitar la reacción inversa y, por lo tanto, de aumentar el rendimiento de la reacción. Además, se descubrió que pueden usarse cantidades menores que las equimolares, tal como 0,025-0,4 equivalentes de POCl_3 en forma de un ácido, en lugar de 2,8 equivalentes de HCl . El uso de una cantidad subestequiométrica de POCl_3 tiene ventajas que incluyen: aumento de la seguridad evitando la necesidad de destruir una gran cantidad de ácido después de la destilación, reducción del tiempo del ciclo, disminución del uso de reactivos y una simplificación global del procedimiento (sin adición de HCl gaseoso).

Ejemplo 2



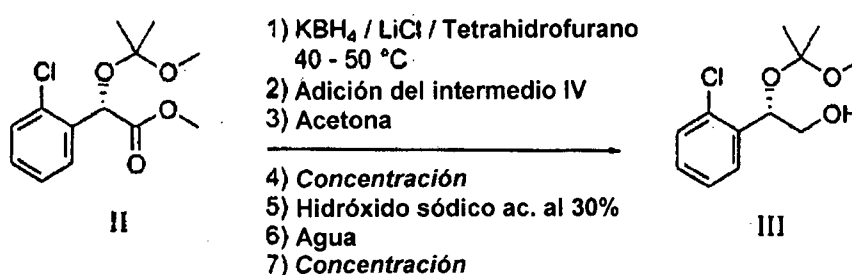
La mezcla de reacción se enfrió de 5 a 15°C. Se añadió lentamente una masa de 184 kg (2552 mol) de 2-metoxi-1-propeno de 5 a 30°C. La solución
 5 resultante se agitó durante 30 a 120 min de 20 a 30°C antes de añadir 24,6 kg (243,1 mol) de trietilamina anhidra. Después de que se comprobara que el pH estaba en el intervalo de 8 a 11, se añadieron 270 kg de agua, después de lo cual se formó una mezcla bifásica. La emulsión se agitó durante 10 a 30 min, antes de que las fases se separaran. La fase acuosa inferior se descartó
 10 (aproximadamente 305 kg). La fase orgánica se concentró parcialmente al vacío hasta que se retiraron aproximadamente 300 kg de disolventes. El éster II se transfirió a la siguiente etapa de reacción en forma una solución.

El descubrimiento de que puede usarse el control de pH para la catálisis ácida controlada por el ácido sobrante del oxiclورو de fósforo de la etapa
 15 anterior en lugar de POCl_3 nuevo dio como resultado varias simplificaciones del procedimiento, incluyendo las que se indican a continuación: evitar la necesidad de añadir más cantidad de oxiclورو de fósforo, evitar la necesidad de supervisar y controlar el pH para una formación cetel óptima y eliminar la necesidad de cambiar el reactor, que da como resultado la reducción del
 20 tiempo del ciclo.

Además, se descubrió que esta reacción no requería múltiples lavados y

secados sobre Na_2SO_4 ; en su lugar, se descubrió que era suficiente un único lavado de agua con secado azeotrópico.

Ejemplo 3

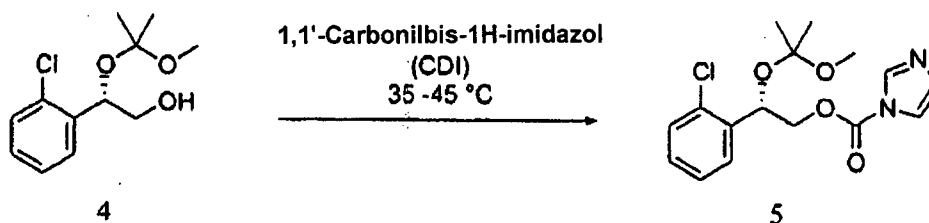


- 5 Un recipiente seco se cargó con 91,8 kg (1702,2 mol) de borohidrato potásico, 72,0 kg (1698,9 mol) de cloruro de litio y 516 kg de tetrahidrofurano. La suspensión resultante se agitó de 40 a 50°C durante 1 a 2 h antes de añadir la solución del éster II durante 90 a 180 min de 40 a 50°C. Después de la adición, la mezcla de reacción se agitó de 40 a 50°C durante 2,5 a 3,5 h más. A
- 10 la misma temperatura, se añadieron lentamente 271 kg de acetona durante 60 a 120 min, seguido de 240 kg de tolueno, y la mezcla se agitó durante 30 a 60 min más de 40 a 50°C. Después, se usó destilación al vacío para retirar 786 kg de disolventes. Se añadió una solución de hidróxido sódico (aproximadamente al 30% (p/p), 278 kg, 2085 mol) seguido de 557 kg de agua purificada. La
- 15 emulsión resultante se agitó durante 20 a 40 min de 40 a 50°C, y las fases se separaron. La fase acuosa inferior se descartó (aproximadamente 997 kg). La fase orgánica se diluyó con 240 kg de tolueno, se trató con 300 kg de agua purificada y 30 kg de cloruro sódico. La emulsión se agitó de 40 a 50°C durante 10 a 30 min y las fases se separaron de nuevo. La fase acuosa
- 20 (aproximadamente 360 kg) se descartó. La fase orgánica se concentró parcialmente al vacío hasta que se retiraron aproximadamente 600 kg de

disolventes. El alcohol III se transfirió a la siguiente etapa de reacción en forma una solución.

El uso de LiBH_4 en forma de un reactivo sólido o en forma una solución en un disolvente apropiado o formado *in situ* a partir de borohidruro potásico y cloruro de litio como agente reductor dio como resultado varias mejoras del procedimiento, incluyendo; eliminar la necesidad de usar el disolvente de dimetil éter de tetraetilenglicol -que puede ser difícil de retirar, reducir la temperatura de la reacción, aumentar el rendimiento en volumen y eliminar la necesidad del secado sobre Na_2SO_4 y la filtración. Además, el uso de LiBH_4 dio como resultado una selectividad de reducción excelente e inesperada. Las reacciones secundarias indeseables que se evitan incluyen la retirada del grupo protector y/o deshalogenación.

Ejemplo 4

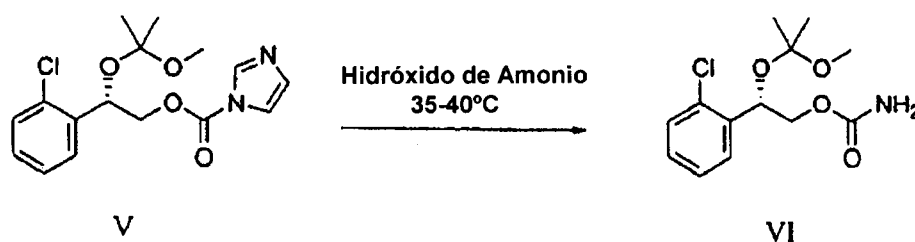


Un recipiente de reacción se cargó con 326 kg (2010,5 mol) de 1,1'-carbonylbis-1H-imidazol y 540 kg de tolueno. La suspensión se agitó vigorosamente durante 10 a 30 min antes de añadir lentamente la solución del alcohol III durante 30 min de 15 a 45°C, formando una solución casi transparente. La imidazolida V se transfirió a la siguiente etapa de reacción en forma de una solución en tolueno.

El uso de un intervalo de temperatura de 15 a 45°C dio como resultado una conversión sistemáticamente completa y un aumento del rendimiento en

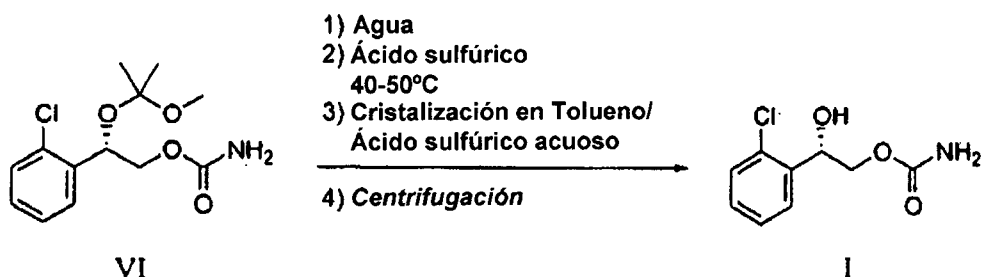
volumen, en comparación con la misma realización realizada a un intervalo de temperatura de 0 a 20°C.

Ejemplo 5



- 5 La solución de la etapa anterior se agitó de 35 a 45°C durante 30 a 60 min antes de añadir lentamente 175 kg de una solución de hidróxido de amonio (al 25% (p/v), 1,6 equiv.) en 90 a 180 min de 35 a 45°C. La mezcla de reacción bifásica se agitó de 35 a 45°C durante 45 a 75 min más. El carbamato VI se transfirió a la siguiente etapa en la mezcla de reacción bifásica.
- 10 El uso de 1,6 (1,44-1,77) equivalentes de hidróxido de amonio en lugar de 10 equivalentes permitió transferir la mezcla de reacción directamente a la siguiente etapa sin extracciones acuosas. El nuevo procedimiento tenía los beneficios de la conversión completa con una baja incidencia de reacciones secundarias, no hubo pérdidas de producto en las fases acuosas y el
- 15 rendimiento en volumen aumentó.

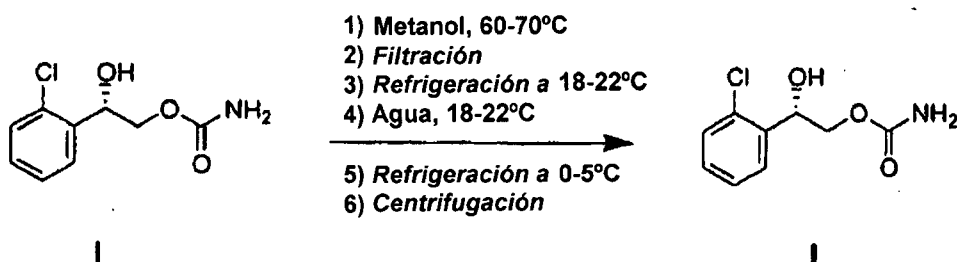
Ejemplo 6



La mezcla de reacción bifásica que contenía el carbamato VI se trató con 392 kg de agua purificada seguido de la adición de 311 kg (3171,2 mol, 2 equivalentes) de ácido sulfúrico de 15 a 50°C seguido de 43,5 kg más de agua purificada. La emulsión se agitó de 40 a 50°C durante 45 a 75 min después de lo cual el carbamato I en bruto precipitó. La suspensión se enfrió de 10 a 20°C seguido de centrifugación. El producto húmedo (aproximadamente 360 kg) se lavó con 360 kg de agua purificada en varias porciones y se secó en un secador de bandejas (cabina de secado) o un secador mecánico al vacío de 65 a 75°C durante 0,5 a 24 h.

El uso de 2 equivalentes de ácido sulfúrico permitió la combinación de la formación de carbamato en el ejemplo 5 con el procedimiento en el ejemplo 6. Además, el uso de 2 equivalentes de ácido sulfúrico de 40 a 50°C en lugar de 0,73 equivalentes de HCl de 20 a 30°C dio como resultado un aumento del rendimiento del 83,7% al 91,6%. El rendimiento en volumen aumentó de 70 g/l a 146 g/l y el tiempo del ciclo se redujo.

Ejemplo 7



El carbamato I se disolvió en metanol a la temperatura de reflujo (~65°C) y se filtró por un cartucho de filtro de 0,45 µm en un reactor precalentado. La solución se enfrió con un gradiente de refrigeración determinado de 18 a 22°C durante el cual el producto comenzó a cristalizar.

A la suspensión se le añadió agua, hasta que la proporción metanol/agua fue de 1:4. La suspensión se enfrió adicionalmente con un gradiente determinado a 0-5°C. La suspensión se filtró y la torta resultante se lavó con agua. El producto húmedo se secó al vacío a 48-52°C en una cabina
5 de secado o en un secador mecánico.

El uso de un gradiente de refrigeración controlado dio como resultado un ligero aumento del rendimiento en volumen de 118 g/l a 123 g/l y el control de los polimorfos.

Aunque la memoria descriptiva anterior muestra los principios de la
10 presente invención, con ejemplos proporcionados para propósitos de ilustración, se apreciará que la práctica de la invención incluye todas las variaciones, adaptaciones y/o modificaciones habituales que se encuentran dentro del alcance de las siguientes reivindicaciones y sus equivalentes.

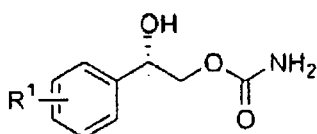
Todas las publicaciones que se describen en la memoria descriptiva
15 anterior se incorporan en este documento como referencia en su totalidad.

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

REIVINDICACIONES

5

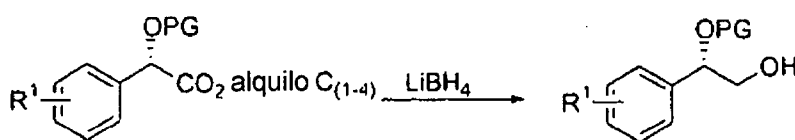
1. Un procedimiento de preparación de un compuesto de Fórmula I:



Fórmula I

en la que:

- 10 R¹ se selecciona entre el grupo constituido por Cl, F y Br; comprendiendo dicho procedimiento el uso de borohidruro de litio para reducir el intermedio de éster de Fórmula II para dar un alcohol de Fórmula III, que se lleva a reacciones posteriores para convertirlo en un compuesto de Fórmula I.



Fórmula II

Fórmula III

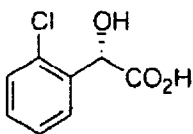
- 15 en las que PG es un grupo protector obtenido a partir de un éter, seleccionándose dicho éter entre el grupo constituido por 2-metoxi-1-propeno, dihidropirano, metil vinil éter, etil vinil éter y 5,6-dihidro-4-metoxi-2H-pirano.

2. El procedimiento de la reivindicación 1, en el que R¹ es 2-cloro.

20

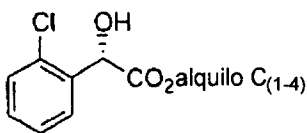
3. El procedimiento de la reivindicación 2, que comprende adicionalmente las siguientes etapas a y b.

a) esterificación de ácido (S)-(2-cloro-fenil)-hidroxi-acético,



5 ácido (S)-(2-cloro-fenil)-hidroxi-acético

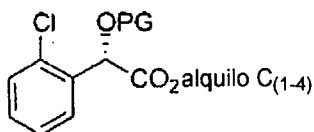
con un alcohol $C_{(1-4)}$, seleccionado entre el grupo constituido por: metanol, etanol, n-propanol, iso-propanol, n-butanol, iso-butanol, sec-butanol y terc-butanol: caracterizándose dicha esterificación por el uso de: de 0,025 a 0,4 equivalentes de oxiclورو de fósforo para obtener un éster de Fórmula IV.



10

Fórmula IV

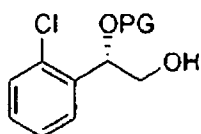
b) protección del resto alcohol de un compuesto de Fórmula IV, en la que dicha protección se caracteriza por el uso de catálisis ácida controlada por dejar el ácido del oxiclورو de fósforo de la reacción anterior y un éter seleccionado entre el grupo constituido por: 2-metoxi-1-propeno, dihidropirano, metil vinil éter, etil vinil éter y 5,6-dihidro-4-metoxi-2H-pirano para obtener un compuesto de Fórmula II,



Fórmula II

4. El procedimiento de la reivindicación 3 que comprende adicionalmente las etapas d, e, f y g que se muestran a continuación:

d) Reacción de un alcohol de Fórmula III



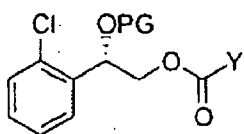
5 Fórmula III

con un compuesto de carbonilo,



en el que X e Y son grupos salientes seleccionados independientemente entre el grupo constituido por bromo, cloro, imidazolilo y fenoxi;

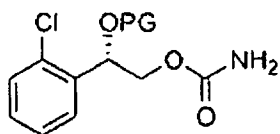
10 caracterizándose dicha reacción por una temperatura de la reacción: de -10 a 65°C, para producir un compuesto de carbonilo de Fórmula V.



Fórmula V

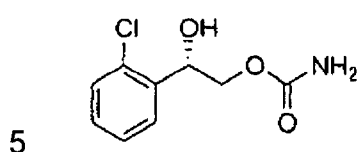
e) Reacción de un compuesto de Fórmula V con hidróxido de amonio o

15 amoniaco, caracterizándose dicha reacción por temperatura de la reacción: de 0 a 55°C para formar el carbamato de Fórmula VI.



Fórmula VI

f) La desprotección del carbamato de Fórmula VI, caracterizándose dicha desprotección por el uso de un ácido seleccionado entre el grupo constituido por ácido fosfórico, ácido clorhídrico y ácido sulfúrico para formar 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico

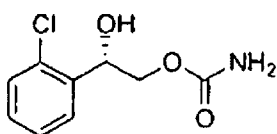


2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico

g) Recristalización del 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico, caracterizándose dicha recristalización por un gradiente de refrigeración controlada.

10

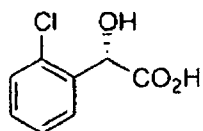
5. Un procedimiento de preparación de 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico



2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico

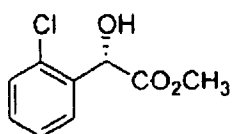
15 comprendiendo dicho procedimiento el uso de las etapas a, b y c que se describen a continuación:

a) Metilesterificación de ácido (S)-(2-cloro-fenil)-hidroxi-acético,



ácido (S)-(2-cloro-fenil)-hidroxi-acético

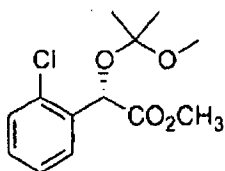
caracterizándose dicha esterificación por el uso de 0,1 equivalentes de oxiclورو de fósforo para obtener éster metílico del ácido (S)-(2-cloro-fenil)-hidroxi-acético.



5 éster metílico del ácido (S)-(2-cloro-fenil)-hidroxi-acético

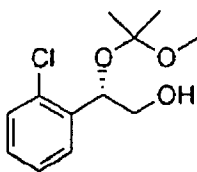
b) protección de éster metílico del ácido (S)-(2-cloro-fenil)-hidroxi-acético, caracterizándose dicha protección por el uso de catálisis ácida controlada por dejar el ácido del oxiclورو de fósforo de la reacción anterior y 2-metoxi-1-propeno, para obtener éster metílico del ácido (S)-(2-cloro-fenil)-(1-metoxi-1-

10 metil-etoxi)-acético.



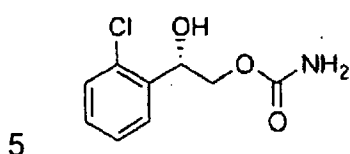
éster metílico del ácido (S)-(2-cloro-fenil)-(1-metoxi-1-metil-etoxi)-acético

c) reducción de éster metílico del ácido (S)-(2-cloro-fenil)-(1-metoxi-1-metil-etoxi)-acético, caracterizándose dicha reducción por el uso de LiBH_4 , para
15 obtener (S)-2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etanol, que se lleva a reacciones posteriores para convertirlo en 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico.



(S)-2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etanol

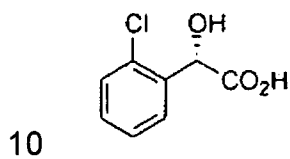
6. Un procedimiento de preparación de 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico:



2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico

comprendiendo dicho procedimiento el uso de las etapas a, b, c, d, e, f y g que se describen a continuación:

a) metilesterificación de ácido (S)-(2-cloro-fenil)-hidroxi-acético:

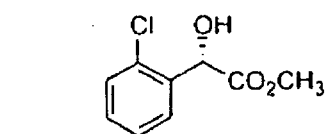


ácido (S)-(2-cloro-fenil)-hidroxi-acético

caracterizándose dicha metilesterificación por el uso de:

- 10 equivalentes de metanol,
- 0,1 equivalentes de oxiclورو de fósforo,
- 15 temperatura de la reacción: de 40 a 50°C,
- concentración parcial, y
- co-disolvente de tolueno;

para obtener éster metílico del ácido (S)-(2-cloro-fenil)-hidroxi-acético.



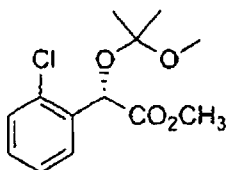
éster metílico del ácido (S)-(2-cloro-fenil)-hidroxi-acético

b) protección de éster metílico del ácido (S)-(2-cloro-fenil)-hidroxi-acético, caracterizándose dicha protección por el uso de:

catálisis ácida controlada por dejar el ácido del oxiclورو de fósforo de la etapa anterior, adición de 1,6 equivalentes de isopropenil metil éter a la
5 mezcla de reacción, y

1 extracción con agua;

para obtener éster metílico del ácido (S)-(2-cloro-fenil)-(1-metoxi-1-metil-etoxi)-acético.



10 éster metílico del ácido (S)-(2-cloro-fenil)-(1-metoxi-1-metil-etoxi)-acético

c) reducción de éster metílico del ácido (S)-(2-cloro-fenil)-(1-metoxi-1-metil-etoxi)-acético, caracterizándose dicha reducción por el uso de:

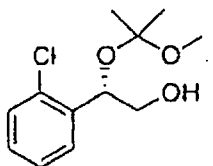
LiBH_4 ,

temperatura de la reacción: de 40 a 50°C,

15 destilación de THF y acetona, e isopropanol (el último formado durante el procedimiento de trabajo por reducción de acetona)

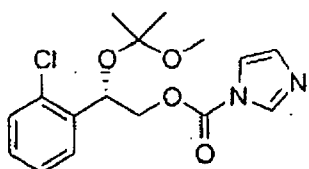
2 extracciones con solución de hidróxido sódico y solución de NaCl;

para obtener (S)-2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etanol.



20 (S)-2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etanol

e) reacción de 2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etil éster del ácido (S)-imidazol-1-carboxílico



2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etil éster del ácido (S)-imidazol-1-carboxílico

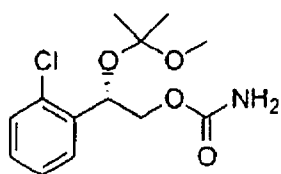
con hidróxido de amonio, caracterizándose dicha reacción por

1,60 equivalentes de hidróxido de amonio, y

temperatura de la reacción: de 40 a 50°C

para formar 2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etil éster del ácido (S)-

carbámico.



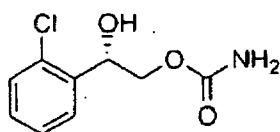
2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etil éster del ácido (S)-carbámico

f) desprotección de 2-(2-cloro-fenil)-2-(1-metoxi-1-metil-etoxi)-etil éster del ácido (S)-carbámico, caracterizándose dicha desprotección por

15 adición de 2 equivalentes de ácido sulfúrico ac., y

temperatura de la reacción: de 40 a 50°C

para formar 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico.



2-(2-cloro-fenil)-2-hidroxi-etil éster de ácido (S)-carbámico

g) recristalización de 2-(2-cloro-fenil)-2-hidroxi-etil éster del ácido (S)-carbámico, caracterizándose dicha recristalización por metanol/agua 1:4, y uso de un gradiente de temperatura controlada.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) P051931WO

Box No. I TITLE OF INVENTION

IMPROVED PROCESS FOR PREPARING 2-(SUBSTITUTED PHENYL)-2-HYDROXY-ETHYL CARBAMATES

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

JANSSEN PHARMACEUTICA, N.V.
Turnhoutseweg 30
B-2340 Beerse
Belgium

Telephone No.

Facsimile No.

Applicant's registration No. with the Office

☐ E-mail authorization: Marking this check-box authorizes the receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority to use the e-mail address indicated in this Box to send, if the Office or Authority so wishes, advance copies of notifications in respect of this international application. (See also the Notes to Boxes Nos. II and III.)

E-mail address

State (that is, country) of nationality:

BE

State (that is, country) of residence:

BE

This person is applicant for the purposes of:

☐ all designated States

☒ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

WARNER, James Alexander

CARPMAELS & RANSFORD
43-45 BLOOMSBURY SQUARE
LONDON, WC1A 2RA
GB

Telephone No.

020 7242 8692

Facsimile No.

020 7405 4166

Agent's registration No. with the Office

☐ E-mail authorization: Marking this check-box authorizes the receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority to use the e-mail address indicated in this Box to send, if the Office or Authority so wishes, advance copies of notifications in respect of this international application. (See also the Notes to Boxes Nos. II and III.)

E-mail address

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

PORSTMANN, Frank
Tubackackerstr. 34
8234 Stetten
Switzerland

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality: CH

State (that is, country) of residence: CH

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

MEIER, Thomas
Feldstrasse 9
CH-8200 Schaffhausen
Switzerland

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality: CH

State (that is, country) of residence: CH

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Supplemental Box

If the Supplemental Box is not used, this sheet should not be included in the request.

1. If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:
 - (i) if more than one person is to be indicated as applicant and/or inventor and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
 - (ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
 - (iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
 - (iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
 - (v) if, in Box No. VI, there are more than four earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.
2. If the applicant intends to make an indication of the wish that the international application be treated, in certain designated States, as an application for a patent of addition, certificate of addition, inventor's certificate of addition or utility certificate of addition: in such a case, write the name or two-letter code of each designated State concerned and the indication "patent of addition," "certificate of addition," "inventor's certificate of addition" or "utility certificate of addition," the number of the parent application or parent patent or other parent grant and the date of grant of the parent patent or other parent grant or the date of filing of the parent application (Rules 4.11(a)(i) and 49bis.1(a) or (b)).
3. If the applicant intends to make an indication of the wish that the international application be treated, in the United States of America, as a continuation or continuation-in-part of an earlier application: in such a case, write "United States of America" or "US" and the indication "continuation" or "continuation-in-part" and the number and the filing date of the parent application (Rules 4.11(a)(ii) and 49bis.1(d)).

CONTINUATION BOX NO. IV

HOWICK, Nicholas Keith
 FISHER, Adrian John
 MERCER, Christopher Paul
 HALLYBONE, Huw George
 HOWARD, Paul Nicholas
 JACKSON, Richard Eric
 JAMES, Anthony Christopher W.P.
 COCKERTON, Bruce Roger
 MARSHALL, Cameron John
 GOODFELLOW, Hugh Robin
 TUNSTALL, Christopher Stephen
 KIRSCH, Susan Edith
 SMALL, Gary James
 WARNER, James Alexander
 BULLETT, Rachel Margaret

All of Carpmiels & Ransford
 43 - 45 Bloomsbury Square
 London WC1A 2RA
 United Kingdom

Tel: 0207 242 8692

Fax: 0207 405 4166

Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a) the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

- ☐ DE Germany is **not designated** for any kind of national protection
- ☐ JP Japan is **not designated** for any kind of national protection
- ☐ KR Republic of Korea is **not designated** for any kind of national protection
- ☐ RU Russian Federation is **not designated** for any kind of national protection

(The check-boxes above may only be used to exclude (irrevocably) the designations concerned if, at the time of filing or subsequently under Rule 26bis.1, the international application contains in Box No. VI a priority claim to an earlier national application filed in the particular State concerned, in order to avoid the ceasing of the effect, under the national law, of this earlier national application.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application: regional Office	international application: receiving Office
item (1) 18th October 2007 (18/10/2007)	60/980877	US		
item (2)				
item (3)				
item (4)				

☐ Further priority claims are indicated in the Supplemental Box.

Transmit certified copy: the receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ other, see Supplemental Box

Restore the right of priority: the receiving Office is requested to restore the right of priority for the earlier application(s) identified above or in the Supplemental Box as item(s) (_____). *(See also the Notes to Box No. VI; further information must be provided to support a request to restore the right of priority.)*

Incorporation by reference: where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if more than one International Searching Authority is competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA/ EP

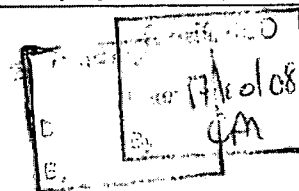
Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:	This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):	Number of items
(a) on paper , the following number of sheets:	1. ☒ fee calculation sheet	: 1
request (including declaration and supplemental sheets) : 5	2. ☐ original separate power of attorney	:
description (excluding sequence listing and/or tables related thereto) : 19	3. ☐ original general power of attorney	:
claims : 8	4. ☐ copy of general power of attorney; reference number, if any:	:
abstract : 1	5. ☐ statement explaining lack of signature	:
drawings :	6. ☐ priority document(s) identified in Box No. VI as item(s):	:
Sub-total number of sheets : 33	7. ☐ translation of international application into (language):	:
sequence listing :	8. ☐ separate indications concerning deposited microorganism or other biological material	:
tables related thereto :	9. ☐ sequence listing in electronic form (indicate type and number of carriers)	:
(for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below)	(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) :	:
Total number of sheets : 33	(ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter :	:
(b) ☐ only in electronic form (Section 801(a)(i))	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column :	:
(i) ☐ sequence listing	10. ☐ tables in electronic form related to sequence listing (indicate type and number of carriers)	:
(ii) ☐ tables related thereto	(i) ☐ copy submitted for the purposes of international search under Section 802(b-quarter) only (and not as part of the international application) :	:
(c) ☐ also in electronic form (Section 801(a)(ii))	(ii) ☐ (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quarter) :	:
(i) ☐ sequence listing	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :	:
(ii) ☐ tables related thereto	11. ☐ copy of results of earlier search(es) (Rule 12bis.1(a)) :	:
Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the	12. ☐ other (specify): :	:
☐ sequence listing:		
☐ tables related thereto:		
(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)		
Figure of the drawings which should accompany the abstract:	Language of filing of the international application: English	

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

WARNER, James Alexander



For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 April 2009 (23.04.2009)

PCT

(10) International Publication Number
WO 2009/050587 A1

(51) International Patent Classification:

C07C 29/147 (2006.01) C07C 271/12 (2006.01)
C07C 269/00 (2006.01) C07C 33/46 (2006.01)

(21) International Application Number:

PCT/IB2008/003300

(22) International Filing Date: 18 October 2008 (18.10.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/980,877 18 October 2007 (18.10.2007) US

(71) Applicant (for all designated States except US):

JANSSEN PHARMACEUTICA, N.V. [BE/BE];
Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): PORSTMANN,
Frank [CH/CH]; Tubackackerstr. 34, ch-8234 Stet-
ten (CH). MEIER, Thomas [CH/CH]; Feldstrasse 9,
CH-8200 Schaffhausen (CH).

(74) Agents: WARNER, James, Alexander et al.; Carpmals

& Ransford, 43-45 Bloomsbury Square, London WC1A
2RA (GB).

(81) Designated States (unless otherwise indicated, for every

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

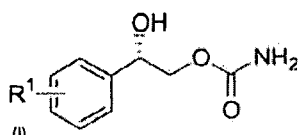
(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, 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).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(54) Title: IMPROVED PROCESS FOR PREPARING 2-(SUBSTITUTED PHENYL)-2-HYDROXY-ETHYL CARBAMATES



(57) Abstract: The present invention relates to a process of preparing a compound of Formula I: (I) Formula I Wherein R¹ is defined in the specification. Compounds of Formula I are useful for treating disorders of the central nervous system, including epilepsy. The process includes a novel use of the reagent lithium borohydride.

WO 2009/050587 A1

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P051931WO	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/IB2008/003300	International filing date (day/month/year) 18/10/2008	(Earliest) Priority Date (day/month/year) 18/10/2007
Applicant JANSSEN PHARMACEUTICA, N.V.		

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 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

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

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

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2008/003300

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C29/147 C07C269/00 C07C271/12 C07C33/46

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)

C07C

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

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

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 127 412 A (CHOI YONG MOON [US] ET AL) 3 October 2000 (2000-10-03) cited in the application the whole document	1-6
Y	DE 31 45 436 A1 (BASF AG [DE]) 26 May 1983 (1983-05-26) page 2, line 20 page 8, lines 21-34	1-6
Y	US 4 156 791 A (CHILDS WILLIAM V [US]) 29 May 1979 (1979-05-29) column 2, lines 15-27 claim 1	1-6
Y	US 5 250 744 A (JOHNSON FRANCIS [US] ET AL) 5 October 1993 (1993-10-05) claims 1,4	1-6
	----- -/--	



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.

"&" document member of the same patent family

Date of the actual completion of the international search

2 March 2009

Date of mailing of the international search report

10/03/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Götz, Gerhard

INTERNATIONAL SEARCH REPORT

International application No PCT/IB2008/003300

(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 237 138 A (CAMPBELL SIMON F ET AL) 2 December 1980 (1980-12-02) page 24, line 56 - page 25, line 10 -----	1-6

50

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2008/003300

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6127412	A	03-10-2000	US 6103759 A	15-08-2000
			US 2001034365 A1	25-10-2001
DE 3145436	A1	26-05-1983	NONE	
US 4156791	A	29-05-1979	NONE	
US 5250744	A	05-10-1993	CA 2105411 A1	17-03-1994
			EP 0588652 A1	23-03-1994
US 4237138	A	02-12-1980	NONE	

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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

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

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

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/IB2008/003300

International filing date (day/month/year)
18.10.2008

Priority date (day/month/year)
18.10.2007

International Patent Classification (IPC) or both national classification and IPC
INV. C07C29/147 C07C269/00 C07C271/12 C07C33/46

Applicant
JANSSEN PHARMACEUTICA, N.V.

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

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

2. FURTHER ACTION

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

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

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

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

Name and mailing address of the ISA:



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

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Götz, Gerhard

Telephone No. +49 89 2399-8105



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2008/003300

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/IB2008/003300

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>1-6</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-6</u>
Industrial applicability (IA)	Yes: Claims	<u>1-6</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

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

International application No.

PCT/IB2008/003300

- D1: US-A-6 127 412 (CHOI YONG MOON [US] ET AL) 3 October 2000 (2000-10-03) cited in the application
D2: DE 31 45 436 A1 (BASF AG [DE]) 26 May 1983 (1983-05-26)
D3: US-A-4 156 791 (CHILDS WILLIAM V [US]) 29 May 1979 (1979-05-29)
D4: US-A-5 250 744 (JOHNSON FRANCIS [US] ET AL) 5 October 1993 (1993-10-05)
D5: US-A-4 237 138 (CAMPBELL SIMON F ET AL) 2 December 1980 (1980-12-02)

Re Item V

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

1. The claimed process according to present claims 1 to 6 differs from the closest prior art process disclosed in D1 in particular by the reduction step of present claim 1.
The process of D1 starts already from the alcohol of formula III and gives no information as to how this alcohol has been prepared.
The subject matter of present claim 1 as well as of claims 2 to 6 is thus novel over said prior art (Article 33(2) PCT).
2. Having regard to the prior art of D1 the underlying problem can be defined by the provision of an alternative process for preparing the compounds of formula I of present claim 1.
The solution consists in particular in the reduction step of present claim 1 whereby lithium borohydride is used as reducing agent to provide the starting compound of the process of D1.
This solution, however, is regarded as not being based on an inventive step: it is well-known in the art (see D2 to D5) that lithium borohydride is widely used as reducing agent in particular for the reduction of an ester to the corresponding alcohol.
furthermore, since the further process steps have to be regarded as mere routine measures to modify the alcohol to get the wanted carbamates of present formula I

no surprising nor inventive step in the whole process can be identified.
The claimed process is thus regarded as being an obvious non-inventive process having regard to the prior art disclosed in D1 to D5 and to the general knowledge.

The present application does therefore not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 6 does not involve an inventive step in the sense of Article 33(3) PCT.

3. The industrial applicability is not in question (Article 33(4) PCT).

Re Item VII

Certain defects in the international application

1. The first paragraph as well as the whole page 19 contains irrelevant subject matter and renders the scope of the claims unclear (Article 6 PCT).
2. Contrary to the statement on page 1, second paragraph, intermediates are not part of the invention as claimed in claims 1 to 6 (Article 6 PCT).
3. Claims 1, 5 and 6 are drafted as independent claims and lack therefore conciseness and as such do not meet the requirements of Article 6 PCT.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information

For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.

Amending claims under Art. 19 PCT

Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.

Filing a demand for international preliminary examination

In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/ WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT).

If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).

Filing informal comments

After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.

End of the international phase

At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).

Relevant PCT Rules and more information

Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

PATENT COOPERATION TREATY

WO 2009/050587
PCT/IB2008/003300

From the INTERNATIONAL BUREAU

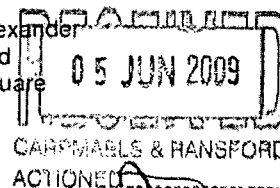
PCT

FIRST NOTICE INFORMING THE APPLICANT OF
THE COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES WHICH
DO NOT APPLY THE 30 MONTH TIME LIMIT
UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

WARNER, James, Alexander
Carpmaels & Ransford
43-45 Bloomsbury Square
London WC1A 2RA
ROYAUME-UNI



Date of mailing (day/month/year) 28 May 2009 (28.05.2009)		
Applicant's or agent's file reference P051931WO		IMPORTANT NOTICE
International application No. PCT/IB2008/003300	International filing date (day/month/year) 18 October 2008 (18.10.2008)	Priority date (day/month/year) 18 October 2007 (18.10.2007)
Applicant JANSSEN PHARMACEUTICA, N.V. et al		

- ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does apply**, please see Form PCT/IB/308(Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date).
- Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
23 April 2009 (23.04.2009)

None

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

- The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1 :

LU, TZ, UG

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. TIME LIMITS for entry into the national phase

For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of 19 months from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, **subject to what is said in the following paragraph**, be 20 MONTHS from the priority date.

In practice, time limits other than the 20-month time limit will continue to apply, for various periods of time, in respect of certain of the designated Offices listed above. For regular updates on the applicable time limits (20 or 21 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Cecile Chatel
Facsimile No. +41 22 338 82 70	e-mail: ro.ib@wipo.int

PATENT COOPERATION TREATY

WO 2009/050587
PCT/IB2008/003300

From the INTERNATIONAL BUREAU

PCT

SECOND AND SUPPLEMENTARY NOTICE
INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES
WHICH APPLY THE 30 MONTH TIME
LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

WARNER, James, Alexander
Carpmaels & Ransford
43-45 Bloomsbury Square
London WC1A 2RA
ROYAUME-UNI

RSN, ns

WAM

Date of mailing (day/month/year) 18 February 2010 (18.02.2010)		IMPORTANT NOTICE	
Applicant's or agent's file reference P051931WO			
International application No. PCT/IB2008/003300	International filing date (day/month/year) 18 October 2008 (18.10.2008)	Priority date (day/month/year) 18 October 2007 (18.10.2007)	
Applicant JANSSEN PHARMACEUTICA, N.V. et al			

- ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does not apply**, please see Form PCT/IB/308(First Notice) issued previously.
- Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
23 April 2009 (23.04.2009)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MY, MZ, NA, NG, PG, RU, SY, TM, US

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

- The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1 :

AE, AG, AL, AM, AO, AP, AT, BA, BB, BG, BH, BR, BW, BZ, CA, CH, CR, CU, CZ, DE, DK, DM, DO, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, ID, IL, IN, IS, JP, KE, KM, KN, KZ, LA, LC, LK, LR, LS, LT, LY, MA, ME, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, RS, SC, SD, SE, SG, SK, SL, SM, ST, SV, TJ, TN, TR, TT, UA, UZ, VC, VN, ZA, ZM, ZW

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

- TIME LIMITS for entry into the national phase**

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, **subject to what is said in the following paragraph**, be **30 MONTHS** from the priority date.

In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For **regular updates on the applicable time limits** (30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's **sole responsibility** to monitor all these time limits.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Cecile Chatel
Facsimile No. +41 22 338 82 70	e-mail: ro.ib@wipo.int

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

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

To:

CARPMAELS & RANSFORD
Attn. Warner, James Alexander
43-45 Bloomsbury Square
London WC1A 2RA
GRANDE BRETAGNE

(PCT Rule 44.1)

Date of mailing
(day/month/year)

10/03/2009

Applicant's or agent's file reference
P051931W0

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/IB2008/003300

International filing date
(day/month/year) 18/10/2008

Applicant

JANSSEN PHARMACEUTICA, N.V.

1. ☒ The applicant is hereby notified that the International search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

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

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

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

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

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

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

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

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

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

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

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Susan Roche

NOTES TO FORM PCT/ISA/220

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

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

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

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

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

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

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

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

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

Where a demand for international preliminary examination has been/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.

NOTES TO FORM PCT/ISA/220 (continued)

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

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

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

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

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

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

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

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

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

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

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

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

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1bis(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion 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 (Rule 43bis.1(c)).

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

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

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

PATENT COOPERATION TREATY

PCT/IB2008/003300

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

WARNER, James, Alexander
Carpmaels & Ransford
43-45 Bloomsbury Square
London WC1A 2RA
ROYAUME-UNI

Date of mailing (day/month/year) 12 March 2009 (12.03.2009)	
Applicant's or agent's file reference P051931WO	IMPORTANT NOTIFICATION
International application No. PCT/IB2008/003300	International filing date (day/month/year) 18 October 2008 (18.10.2008)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 18 October 2007 (18.10.2007)
Applicant JANSSEN PHARMACEUTICA, N.V. et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
18 October 2007 (18.10.2007)	60/980,877	US	06 March 2009 (06.03.2009)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Cecile Chatel

e-mail RO.IB@WIPO.INT

Telephone No. +41 22 338 92 22

Facsimile No. +41 22 338 82 70

Form PCT/IB/304 (October 2005)

1/DZKYHI400

63



No. 10-055387- -00000-0000

Fecha: 2010-05-10 15:15:44 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 63

PATENTE DE INVENCION ☐

MODELO DE L

☐

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 ☐

PATENTE 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 D.C.,
2020

Doctor(a)
RODRIGUEZ D' ALEMAN DILIA MARIA
Apoderado(a) y/o Representante de
JANSSEN PHARMACEUTICA N.V.

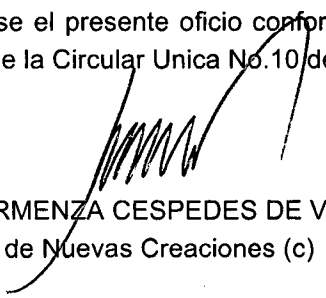
REFERENCIA	Radicación No.	10 055387
	Solicitud internacional	PCT/IB2008/003300
	Fecha inicio fase nacional	18/05/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	0 6 6 4 6

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

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, 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 considerará abandonada y perderá su prelación.

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


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

El anterior requerimiento fue notificado por fijación en lista de fecha **21 MAYO 2013**
adpa11